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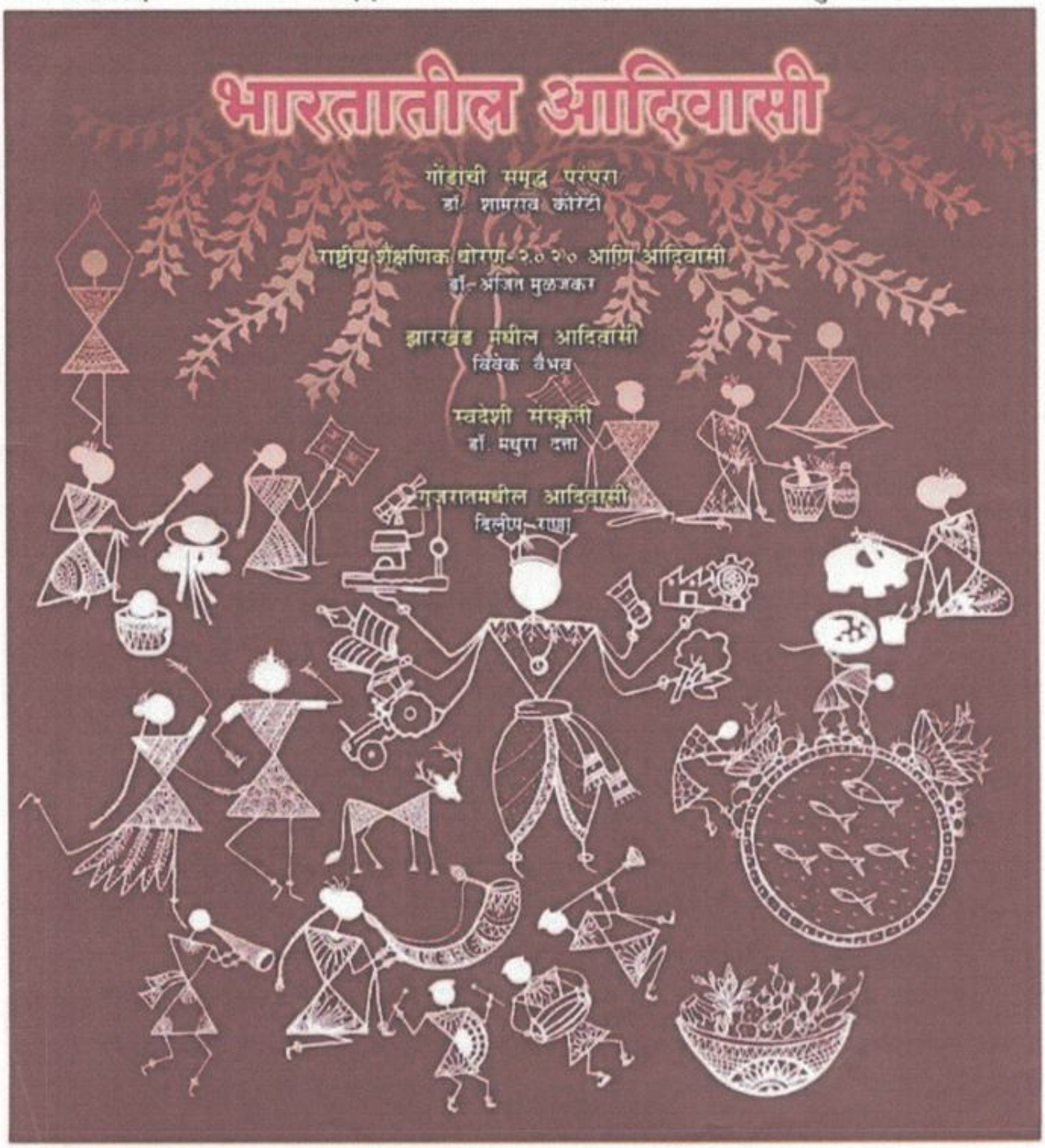
विकास समर्पित मासिक

योजना

वर्ष ४९ अंक ११ पाने ५४ जुलै २०२२

भारतातील आदिवासी



गोंडांची समृद्ध परंपरा
डॉ. शामराव कोरेटी

राष्ट्रीय शैक्षणिक धोरण-२०२० आणि आदिवासी
डॉ.- अजित मुळजकर

झारखंड मधील आदिवासी
विवेक वैभव

स्वदेशी संस्कृती
डॉ. मधुरा दत्ता

गुजरातमधील आदिवासी
दिलीप-रणा

योजना

विकास समर्पित मासिक

❖ वर्ष ४९ ❖ ❖ अंक १२ ❖ ❖ २०२२ ❖

संपादक
उमेश उजगरे

निर्मिती अधिकारी
डॉ. के. सी. हृदयनाथ

मुखपृष्ठ
बिंदू वर्मा

सूचना

'योजना' हे निती आयोगाच्या वतीने, केंद्र सरकारच्या माहिती व प्रसारण मंत्रालयाच्या प्रकाशन विभागातर्फे हिंदी, इंग्रजी, मराठी, गुजराती, कन्नड, तेलुगू, पंजाबी, उर्दू, बंगाली, तमिळ, मल्याळम, उडिया व आसामी भाषांतून प्रकाशित होते. देशाच्या सर्वांगीण विकासाची खुली चर्चा करणारे ते व्यासपीठ आहे. योजना मासिकात प्रसिद्ध झालेल्या लेखातील मते-विचार त्या-त्या लेखकांची असतात. सरकार किंवा लेखक कार्यरत असलेल्या संस्था त्या मतांशी/विचारांशी सहमत असतीलच असे नव्हे. लेखांमध्ये वापरण्यात आलेले नकाशे/भाग हे केवळ प्रातिनिधिक आहेत. राजकीय नकाशा तसेच भारताचा अथवा अन्य देशाचा राष्ट्रध्वज म्हणून ते न्यायालयीन बाबींसाठी ग्राह्य नसतील. स्पर्धा परीक्षा पुस्तक प्रकाशक तसेच मार्गदर्शक संस्थांच्या योजना मासिकातील जाहिरातींमध्ये केलेल्या दाव्यांची वाचकांनी स्वत: खात्री करून घ्यावी. अशा जाहिरातींमधील मजकुराबाबत 'योजना' कुठल्याही प्रकारे जबाबदार असणार नाही. योजना मासिकातील मजकुराचे लेखी अनुमतीशिवाय संपूर्ण अथवा अंशत: पुन: प्रकाशन किंवा पुन: प्रसारण तसेच 'योजना' मासिकाच्या नावाचा वापर व्यावसायिक कारणांसाठी करण्यास मनाई आहे.

■ आदिवासींचे कल्याण – हर्ष चौहान ५

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■ गुजरातमधील आदिवासी – दिलीप राणा ४९

योजना मासिकासाठी लेख, वर्गणी, जाहिरात इ. सर्व पत्रव्यवहारासाठी पत्ता :
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७०१, 'बी' विंग (७वा मजला), केंद्रीय सदन, सेक्टर १०, सी.बी.डी. बेलापूर, नवी मुंबई ४०० ६१४. दुरध्वनी - योजना - ०२२-२७५६६५८२
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राष्ट्रीय शैक्षणिक धोरण-२०२० आणि आदिवासी

– डॉ. अजित मुळजकर

राष्ट्रीय पातळीवर व राज्य पातळीवर आदिवासी समुदायासाठी अनेक योजना शासनाने आणल्या आहेत. एखादी योजना शासन पातळीवर राबवण्याचे ठरवणे आणि प्रत्यक्षात ती योजना राबविण्यासाठी बऱ्याच बाबींचा अंतर्भाव असणे गरजेचे आहे. त्यात ज्या वर्गासाठी किंवा समाजासाठी एखादी योजना तयार करण्यात येते त्या वर्गाची किंवा समाजाची जागृती हा एक अत्यंत महत्त्वाचा घटक असतो. ही सामाजिक जागृती निर्माण करण्यासाठी शिक्षण हे एक अत्यंत प्रभावी साधन आहे. शिक्षणाची कास धरून जो समाज जागरूक होतो त्या समाजाची प्रगती होण्यासाठी वेळ लागत नाही.

राष्ट्रीय शैक्षणिक धोरण २०२० च्या प्रस्तावनेची सुरूवातच मानवाला आपल्या पूर्ण क्षमता वापरता येण्यासाठी, समान आणि न्याय्य समाज विकसित करण्यासाठी तसेच राष्ट्रीय विकासाला चालना देण्यासाठी शिक्षण हा पाया आहे; या विधानापासून करण्यात आलेली आहे. या विधानातून या शैक्षणिक धोरणाचा हेतू किती मोठा आहे ते लक्षात येते. भारताच्या सातत्यपूर्ण प्रगतीचा विचार करत असताना सामाजिक न्याय आणि समता या गोष्टींकडेही विशेष लक्ष देण्यात आलेले आहे. शास्त्रीय प्रगती, राष्ट्रीय एकात्मता आणि संस्कृतीचे जतन या क्षेत्रामध्ये वैश्विक पातळीवर नेतृत्व करण्यासाठी सर्वांना दर्जेदार शिक्षण उपलब्ध करून देणे महत्त्वाचे मानले गेले आहे. आज एकविसाव्या शतकाच्या तिसऱ्या दशकामध्ये भारत जगातील सर्वात मोठी युवकांची लोकसंख्या असलेला देश म्हणून पुढे येत आहे.

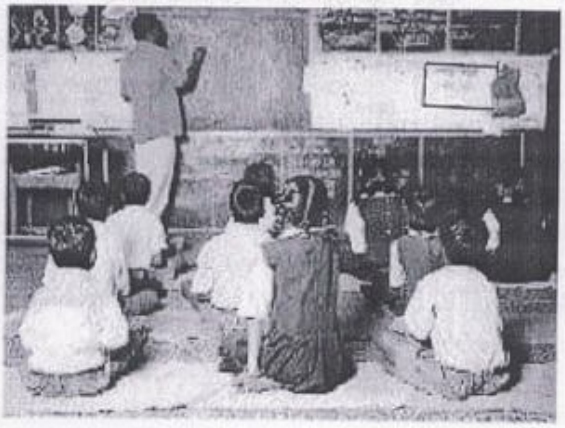
भारताने २०१५ मध्ये स्वीकारलेल्या शाश्वत विकासाच्या २०३० कार्यक्रमाच्या उद्दिष्ट ४ मध्ये जागतिक शिक्षण विकास कृती कार्यक्रम समाविष्ट असून हे उद्दिष्ट २०३० पर्यंत सर्वांसाठी समावेशक आणि समान गुणवत्तेचे शिक्षण सुनिश्चित करणे आणि सर्वांसाठी निरंतर अध्ययनाच्या शिक्षणाच्या संधीना प्रोत्साहन देणे यासाठी प्रयत्न करण्याविषयी आहे.

या उत्तुंग उद्दिष्टाकरता अध्ययनाला पाठिंबा देण्यासाठी आणि चालना देण्यासाठी संपूर्ण शिक्षण प्रणालीची नव्याने रचना करणे आवश्यक होती जेणेकरून शाश्वत विकास कृती कार्यक्रम २०३० ची सर्वात महत्त्वाची लक्ष्ये आणि उद्दिष्टे साध्य करता येतील.

सर्वांना उच्च-गुणवत्तेचे शिक्षण उपलब्ध करून देऊन, त्याद्वारे भारताला एक जागतिक ज्ञान-महासत्ता बनवून भारताचे एका न्याय्य आणि चैतन्यमय ज्ञान-समाजात शाश्वतपणे परिवर्तन करण्यात प्रत्यक्षपणे योगदान देणारी शिक्षण व्यवस्था निर्माण करणे ही अतिउच्च दूरदृष्टी या नवीन शैक्षणिक धोरणाची आहे.

भारतीय असल्याचा अभिमान विद्यार्थ्यांच्या केवळ विचारामध्येच नव्हे तर त्यांच्या व्यवहारात, बुद्धीमध्ये आणि कृतीमध्येदेखील रुजवणे व त्याबरोबरच मानवी हक्क, शाश्वत विकास आणि उत्कृष्ट जीवन जगण्यासाठी आवश्यक असलेले ज्ञान, कौशल्य, मूल्य आणि विशेष म्हणजे स्वभाव विकसित करणे जेणेकरून ते विद्यार्थी ह्या अर्थाने वैश्विक नागरिक बनतील ही दूरदृष्टी या शैक्षणिक धोरणाची आहे.

राष्ट्रीय शैक्षणिक धोरण २०२० म्हणजे जुन्या राष्ट्रीय शैक्षणिक धोरणाची पुनरावृत्ती किंवा नवीन रूप नसून हे एक पूर्णत: राष्ट्राला समर्पित केलेले वैश्विक शैक्षणिक धोरण आहे. माहिती तंत्रज्ञानाच्या द्वारे जगामध्ये अगणित बदल झाले आणि विशेष म्हणजे बदलाची गती ही फार वाढली. त्याचा परिणाम आजच्या समाज जीवनावर पहावयास मिळतो. या बदलांना अनुरूप असलेले कित्येक महत्त्वपूर्ण घटक या नवीन राष्ट्रीय शैक्षणिक धोरण २०२० मध्ये स्वीकारण्यात आलेले आहेत. ज्यायोगे आजची किशोरवयीन पिढी उद्याचे सक्षम व जबाबदार नागरिक बनवून राष्ट्रनिर्मितीमध्ये महत्त्वाचे योगदान देतील. उद्याच्या बलवान भारताची पिढी आज प्राथमिक व माध्यमिक शाळांमध्ये शिक्षण घेत आहे.



कुठल्याही राष्ट्राचा विकासदर वाढवण्या मध्ये त्या राष्ट्राचे शैक्षणिक धोरण अत्यंत महत्त्वाचे असते. त्यामध्ये उच्च शिक्षण हा महत्त्वाचा घटक असला तरी त्याची मुळात पायाभरणी ही प्राथमिक व माध्यमिक शाळांमध्ये होत असते. माणसाच्या सामाजिक व बौद्धिक जडणघडणीसाठी तीन ते सहा वर्षांचा

कालखंड महत्त्वाचा असतो हे सिद्ध झाले आहे. म्हणून नवीन राष्ट्रीय शैक्षणिक धोरण २०२० यामध्ये ३ ते ६ या वयोगटातील विद्यार्थ्यांना अंगणवाडी वा पूर्वप्राथमिक वर्गात प्रवेश निश्चित करून त्यांना सर्वांगीण शिक्षण देऊन जीवनाच्या मुख्य प्रवाहमध्ये आणण्यासाठी प्रयत्न केले आहेत. जुनी १०+२ ही संरचना बदलून, आता नवीन राष्ट्रीय शैक्षणिक धोरण २०२० यामध्ये ५+३+३+४ ही नवीन संरचना स्वीकारण्यात आलेली आहे.

शिक्षण ही एक सार्वजनिक सेवा आहे. शिक्षण व्यवस्थेत सर्व विद्यार्थ्यांना प्रगती करता येईल हे सुनिश्चित करण्यासाठी सर्व शैक्षणिक निर्णयांमध्ये पूर्ण समानता आणि सर्वसमावेशकता ही पायाभूत बाब आहे.

नैतिकता आणि मानवी मूल्य उदाहरणार्थ, सहृदयता, सौजन्य, सेवेची भावना, न्याय विद्यार्थ्यांमध्ये रुजवणे हे या धोरणात अपेक्षित आहे. वास्तविक पाहता आदिवासी समुदायांमध्ये ही मूल्य जन्मजातच पहावयास मिळतात. गरज आहे ती त्यांचे संगोपन करण्याची व त्यावर संस्कार करण्याची. आणि नवीन शैक्षणिक धोरणाच्या माध्यमातून हे कार्य उत्कृष्टरित्या पार पाडले जाईल.

शहरी व ग्रामीण भागातील विद्यार्थ्यांकडे वेगवेगळ्या क्षमता असतात. त्याचप्रमाणे आदिवासी समुदायातील मुलांकडे असलेल्या क्षमताही वैविध्यपूर्ण आहेत. विशेष म्हणजे, नवीन शैक्षणिक धोरण असे मानते की प्रत्येक विद्यार्थ्यांकडे काही वैशिष्ट्यपूर्ण क्षमता असतात. त्या क्षमतांचा शोध घेणे, ओळखणे व त्या विकसित करण्यासाठी जाणीवपूर्वक प्रयत्न करणे हा या शैक्षणिक धोरणाचा महत्त्वाचा भाग आहे. त्या अनुषंगाने हे शैक्षणिक धोरण आदिवासी समुदायांच्या मुलांसाठी फार उपयुक्त ठरेल.

राष्ट्रीय पातळीवर व राज्य पातळीवर आदिवासी समुदायासाठी अनेक योजना शासनाने आणल्या आहेत. एखादी योजना शासन पातळीवर राबवण्याचे ठरवणे आणि प्रत्यक्षात ती योजना राबविण्यासाठी बऱ्याच बाबींचा अंतर्भाव असणे गरजेचे आहे. त्यात ज्या

महाराष्ट्र राज्यात डोंगराळ व दुर्गम भागात राहणाऱ्या अनुसूचित जमातींची सामाजिक व शैक्षणिक प्रगती होण्यासाठी सन १९७२-७३ पासून क्षेत्रविकासाचा दृष्टीकोन स्वीकारण्यात आला. अशा भागाचा मूलभूत विकास व्हावा आणि त्याचा फायदा सर्वांना व्हावा यासाठी तेथे मूळ केंद्रस्थान म्हणून आश्रमशाळा असावी म्हणून शासकीय आश्रम शाळांची निर्मिती करण्यात आली. या शाळेत आदिवासी विद्यार्थ्यांची इ. १० वी पर्यंतच्या शिक्षणाची सोय उपलब्ध आहे.

वर्गासाठी किंवा समाजासाठी एखादी योजना तयार करण्यात येते त्या वर्गाची किंवा समाजाची जागृती हा एक अत्यंत महत्त्वाचा घटक असतो. ही सामाजिक जागृती निर्माण करण्यासाठी शिक्षण हे एक अत्यंत प्रभावी साधन आहे. शिक्षणाची कास धरून जो समाज जागरूक होतो त्या समाजाची प्रगती होण्यासाठी वेळ लागत नाही.

आदिवासी विकास आयुक्तालय, महाराष्ट्र:

आदिवासींच्या कल्याणाच्या अनेक योजना तयार होत असतात. त्या योजनांची परिणामकारक अंमलबजावणी करण्यासाठी सन १९७२ मध्ये समाजकल्याण विभागांतर्गत आदिवासी विकास संचालनालयाची स्थापना करण्यात आली होती. त्यानंतर १९७६ साली आदिवासी विकास आयुक्तालय सुरु करण्यात आले. दि. २२ एप्रिल १९८३ रोजी स्वतंत्र आदिवासी विकास विभागाची स्थापना करण्यात आली आणि १९८४ पासून आदिवासी विकास विभाग स्वतंत्रपणे कार्यरत आहे. आदिवासी विकास विभागाच्या बळकटीकरणाकरिता सन १९९२ मध्ये आदिवासी विकास संचालनालय हे आदिवासी विकास आयुक्तालयात विलीन करण्यात आले.

शासन स्तरावर घेतलेल्या एखाद्या निर्णयाची व्यवस्थित अंमलबजावणी होण्यासाठी विभागीय स्तरावर कार्यालयाची निर्मिती करण्यात येते. त्याचाच एक भाग म्हणून आदिवासी विकास विभागांतर्गत ठाणे, नाशिक, अमरावती व नागपूर येथे चार अपर आयुक्त व २९ एकात्मिक आदिवासी विकास प्रकल्प कार्यालयांची निर्मिती करून; त्यांच्या मार्फत मागासवर्गीय कल्याणाच्या राज्य व केंद्र शासनाच्या योजनांची अंमलबजावणी केली जाते.

संप्रेषणसाठी भाषा अत्यंत आवश्यक आहे. कुठल्याही भाषेच्या उत्पत्तीचा अभ्यास केल्यानंतर असे दिसून येते की, एखाद्या विशिष्ट समुदायाचे लोक ती भाषा बोलतात नंतर त्या भाषेला लिखित रूप प्राप्त होते. म्हणजेच उच्चारण प्रथम व लिखाण द्वितीयक आहे. एखाद्या भाषेची लिपी तयार होण्यासाठी त्यावर जाणीवपूर्वक प्रयत्न केले पाहिजेत. ज्या समाजातील लोकांच्या अन्न, वस्त्र व निवारा या प्रमुख तीन गरजा पूर्ण झाल्या त्या समुदायातील लोकांच्या बोलीभाषेला लिखित स्वरूप प्राप्त

झाले. पण भारतामध्ये आजही काही अशा भाषा आहेत ज्या एखाद्या विशिष्ट समुदायाचे लोक बोलतात मात्र त्या भाषेची लिपी नाही. अशा बोलीभाषा त्या समुदायातील लोकांच्या ओठावरती जगतात. कुठलेच कसलेच प्रमाण नसल्यामुळे उच्चारण व भाषेच्या वापरामध्ये असलेली विविधता ही भाषा अधिक कठीण बनवतात.

'भिलोरी' ही आदिवाशांची भाषा आहे. भिलोरी ही बोलीभाषा प्रामुख्याने नंदुरबार, धुळे व मध्य प्रदेशचा काही भाग याठिकाणी बोलली जाते. विशेष म्हणजे या भाषेची लिपी नाही, ही भाषा आदिवासींच्या ओठावर जगते. भिलोरीवर हिंदी व खान्देशी अर्थात अहिराणी भाषेचा प्रभाव आढळतो. भिलोरी भाषेस लिपिबद्ध करण्याचे कठीण काम राष्ट्रीय पातळीवरून सुरू आहे.

'डांगी' ही भाषादेखील आदिवासी लोक वापरतात. ही भाषा गुजरात मधील डांग जिल्ह्यामध्ये वापरली जाते. या भाषेवर गुजराती भाषेचा प्रभाव दिसून येतो.

आदिवासी बांधवांचा निसर्ग हाच धर्म आहे. महाराष्ट्र, गुजरात व मध्यप्रदेशातील जंगलामध्ये, दऱ्याखोऱ्या मध्ये वस्ती करून ते राहतात. ज्या त्या ठिकाणची भौगोलिक विविधता त्यांच्या जीवनावर खूप प्रभाव टाकते. भौगोलिक बदलाप्रमाणे त्यांचे खानपान, पोषाख, परंपरा व आहार-विहार हेदेखील बदलतात. माणसाने निसर्गाशी नाते जुळवून त्यासोबत मैत्रीपूर्वक संबंध कसे प्रस्थापित केले पाहिजेत हे आदिवासी समाजाकडून शिकले पाहिजे. भौतिक प्रगतीच्या नावाखाली यांत्रिकीकरणाचा अतिरेक करून निसर्गाची लूट करणाऱ्या माणसांनी आदिवासी बांधवाकडून साधेपणाचा धडा घेतला पाहिजे. गरजा कमी करून साधेपणाने सुंदर व सुखी जीवन जगता येऊ शकते हे त्यांच्याकडून आपल्याला समजू शकते. सामाजिक समतेसाठी व निसर्गाची हानी थांबवण्यासाठी गरज आहे ती शहरी भागातील माणसांना थोडे थांबण्याची; व आदिवासी समुदायातील लोकांना थोडे पुढे घेऊन येण्याची. हा सुवर्णमध्य साधण्यासाठी शिक्षण हे एक अत्यंत उपयुक्त आणि प्रभावी साधन आहे.

आदिवासी बांधवांचा निसर्ग हाच धर्म आहे. महाराष्ट्र, गुजरात व मध्यप्रदेशातील जंगलामध्ये, दऱ्याखोऱ्या मध्ये वस्ती करून ते राहतात. ज्या त्या ठिकाणची भौगोलिक विविधता त्यांच्या जीवनावर खूप प्रभाव टाकते. भौगोलिक बदलाप्रमाणे त्यांचे खानपान, पोषाख, परंपरा व आहार-विहार हेदेखील बदलतात. माणसाने निसर्गाशी नाते जुळवून त्यासोबत मैत्रीपूर्वक संबंध कसे प्रस्थापित केले पाहिजेत हे आदिवासी समाजाकडून शिकले पाहिजे. भौतिक प्रगतीच्या नावाखाली यांत्रिकीकरणाचा अतिरेक करून निसर्गाची लूट करणाऱ्या माणसांनी आदिवासी बांधवाकडून साधेपणाचा धडा घेतला पाहिजे.

शासकीय आश्रम शाळा समूह योजनेअंतर्गत डोंगरदऱ्यात व अत्यंत दुर्गम भागात राहणाऱ्या आदिवासी समुदायाच्या विकासासाठी अनेक आश्रम शाळांची निर्मिती करण्यात आली आहे.

शासकीय आश्रम शाळा समूह योजना उद्देश व स्वरूप:

महाराष्ट्र राज्यात डोंगराळ व दुर्गम भागात राहणाऱ्या अनुसूचित जमातीची सामाजिक व शैक्षणिक प्रगती होण्यासाठी सन १९७२-७३ पासून क्षेत्रविकासाचा दृष्टीकोन स्वीकारण्यात आला. अशा भागाचा मूलभूत विकास व्हावा आणि त्याचा फायदा सर्वांना व्हावा यासाठी तेथे मूळ केंद्रस्थान म्हणून आश्रमशाळा असावी म्हणून शासकीय आश्रम शाळांची निर्मिती करण्यात आली. या शाळेत आदिवासी विद्यार्थ्यांची इ. १० वी पर्यंतच्या शिक्षणाची सोय उपलब्ध आहे.

सदर आश्रमशाळेतील विद्यार्थ्यांना निवास, भोजन, वणवेश,अंथरुण-पांघरुण, पुस्तके व इतर लेखन साहित्य इ. सुविधा शासनाकडून मोफत पुरविण्यात येतात. अशा शाळांमध्ये प्रवेशित होण्यासाठी पुढील पात्रता अनिवार्य आहे:

१. आश्रमीय विद्यार्थी हे आदिवासीच असावेत.

२. प्रत्यक्ष प्रवेश देतेवेळी जातीचा दाखला, जन्मतारखेचा दाखला, आई-वडीलांचे प्रतिज्ञापत्र.

३. पहिली व्यतिरिक्त इतर वर्गातील प्रवेशाकरिता पूर्वीच्या शाळेचा शाळा सोडल्याचा दाखला.

४. आश्रमशाळेच्या १ कि.मी. परिसरातील मुले-मुली अनिवासी म्हणून व त्या क्षेत्राच्या बाहेरील निवासी विद्यार्थी म्हणून प्रवेश.

५. आश्रमशाळेत प्रत्येक वर्गात निवासी ४० व बहिस्थ १० विद्यार्थी.

६. आश्रमशाळेमध्ये मुला मुलींचे प्रमाण ५० : ५० प्रमाणे व ५० टक्के मुली मिळाल्या नाहीतर विद्यार्थीनींची क्षमता किमान ३३ टक्के आवश्यक जर सदर टक्केवारी पूर्ण झाली नाही तर आदिवासी विद्यार्थ्यांना प्रवेश देऊन क्षमता पूर्ण करणे.

७. आश्रमशाळांमध्ये प्रत्येक वर्गात शारिरीकदृष्ट्या अपंग विद्यार्थ्यांसाठी ३ टक्के आरक्षण.

बहुचर्चित राष्ट्रीय शैक्षणिक धोरण २०२०च्या अंमलबजावणी प्रक्रियेस आता गती प्राप्त होत आहे. अनेक चर्चासत्रांचे आयोजन, कृती आराखड्याची निर्मिती, विविध समित्यांची निर्मिती व विद्यापीठ अनुदान आयोगापासून गट शिक्षण कार्यालयापर्यंत अनेक स्तरावरून राष्ट्रीय शैक्षणिक धोरण २०२० ची अंमलबजावणी होत आहे. समाजातील सर्व घटकांपर्यंत शिक्षणाची ज्ञानगंगा नेऊन, समूहिक विकासाच्या माध्यमातून, नवीन वैभवशाली आणि बलशाली भारताचे स्वप्न साकार होण्यासाठी सामूहिक प्रयत्नांची आवश्यकता आहे.

■■■

लेखक महाराष्ट्र महाविद्यालय निलंगा येथे सहाय्यक प्राध्यापक तथा इंग्रजी विभाग प्रमुख आहेत.
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३

महर्षि विठ्ठल रामजी शिंदे यांचे स्त्री सुधारणाविषयक विचार व कार्य

डॉ. सुभाष गणपतराव बेंजलवार
महाराष्ट्र महाविद्यालय, निलंगा, जि. लातूर

महर्षि विठ्ठल रामजी शिंदे यांनी आपले जीवितकार्य म्हणून अस्पृश्य सेवेचे कार्य केले असले तरी त्यांनी एवढेच कार्य केले असे नाही. महाराष्ट्रीयन किंबहुना भारतीय प्रबोधन परंपरेच्या परिप्रेक्षात त्यांच्या कार्याचा आणि चिंतनाचा विचार केल्यास त्यांच्या विचार व कार्याची बहुविविधता आणि मौलिकता लक्षात येते. त्यांनी आयुष्यभर केलेले कार्य आणि विविध सामाजिक प्रश्नांसंबंधी केलेले चिंतन यावरून त्यांना 'कर्मवीर' व 'महर्षी' ही दोन विशेषणे लावण्यात आलेली आहेत. ही विशेषणे त्यांच्या कार्यावर व स्वभाव विशेषांवर आणि त्यांच्या चिंतनशील व्यक्तिमत्त्वावर प्रकाश टाकणारी तर आहेतच त्याचबरोबर त्यांच्या कार्याची उंची दर्शविणारी आहेत. महर्षि शिंदे यांचे सबंध जीवनकार्य व चिंतन हे सामाजिक समता आणि राष्ट्रीय स्वातंत्र्य या दोन ध्येयांसाठी समर्पित असेच आहे. त्यांच्या सामाजिक समतेसाठीच्या चिंतनातूनच सामाजिक समतेसाठी महत्त्वाचे असलेले स्त्री सुधारणाविषयक विचार व कार्य प्रस्तुत शोधनिबंधाच्या माध्यमातून मांडण्याचा प्रयत्न केला आहे.

प्रचलित धर्मव्यवस्थेच्या चिंतनातून महर्षि शिंदे यांनी स्त्रियांच्या दुस्थितीसंदर्भात अस्तित्वात असलेल्या सामाजिक प्रश्नांकडे लक्ष दिलेले दिसते. त्यांचा स्त्रियांकडे पाहण्याचा एक उदार आणि व्यापक दृष्टिकोन होता. त्यांनी स्वत: आपल्या आठवणींमध्ये नोंदवून ठेवले आहे की, "माझ्या सुधारणेच्या मताला आणि सामान्यत: स्त्रीजातीसंबंधी कारुण्यालाही पूर येत चालला होता."[१] खरोखर समाजस्थिती सुधारायची असेल तर स्त्रियांना सर्व क्षेत्रांत सहभागी करुन घेतले पाहिजे, असे त्यांचे मत बनत चालले होते. केवळ मत मांडूनच ते स्वस्थ बसले नाहीत तर त्यांची सुरुवात त्यांनी स्वत:पासून केली. तत्कालीन रिवाजानुसार त्यांच्याहून पाच वर्षांच्या लहान असलेल्या बहिणीचे अर्थात

सारांश :

महर्षि विठ्ठल रामजी शिंदे यांनी केलेले स्त्री सुधारणाविषयक कार्य हे त्यांच्या धर्मव्यवस्थेच्या चिंतनातून आणि एकूणच स्त्री जातीबद्दल त्यांच्या मनात असलेला कळवळा यातून आला होता. स्त्रीजीवनाच्या अनुषंगाने समाज जीवनात अस्तित्वात असलेल्या प्रश्नांच्या मुळाशी जाऊन ते सोडवण्याचा प्रयत्न त्यांच्या विचार व कार्याच्या केंद्रवर्ती दिसतो. हा प्रश्न स्वत:च्या कौटुंबिक जीवनाशी संबंधित असो अथवा सार्वजनिक स्वरुपाचा तो समजावून घेऊन सोडविण्याचा प्रयत्न त्यांनी हिरीरीने केलेला दिसतो. त्यांच्या या कार्याचे वेगळेपण म्हणजे त्यांनी प्रचलित पारंपारिक प्रथा, परंपरांना नाकारण्याचे धाडस दाखविले होते. प्रसंगी त्यांना समाजरोषही पत्करावा लागला होता. स्वत:च्या जन्मगावात त्यांना गावकऱ्यांचा विरोध व टीकेला सामोरे जावे जागले होते; परंतु आपले सुधारकी कार्य त्यांनी अर्ध्यात सोडले नाही. त्याचा कायम पाठपुरावा करुन सामाजिक समता प्रस्थापित करण्याच्या अनुषंगाने जी म्हणून भूमिका घेणे आवश्यक होती ती त्यांनी घेतलेली दिसते.

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Stereoselective Synthesis of Euscapholide and Tetraketide via Prins Cyclisation and Ring-Closing Metathesis

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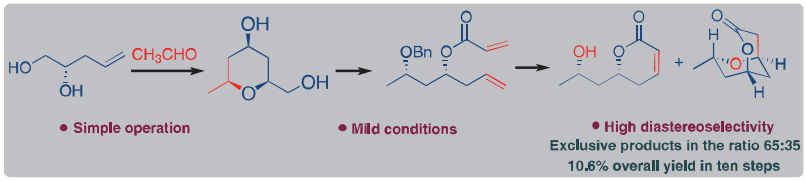

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Abstract A concise and diastereoselective total synthesis of tetraketide and euscapholide is described in ten steps in 10.6% overall yield from acetaldehyde and (*S*)-pent-4-ene-1,2-diol. Jacobsen hydrolytic kinetic resolution, Prins cyclization, ring-closing metathesis and oxa-Michael addition reactions are the key steps involved in the synthesis.

Key words Prins cyclization, euscapholide, tetraketide, ring-closing metathesis

Natural products from terrestrial plant sources have been a source of discovery for numerous biologically active compounds.[1] Along this line, tetraketide (**1**) and euscapholide (**2**) are a dioxabicyclo[3.3.1]nonan-3-one derivative and a α,β-unsaturated δ-lactone that were obtained from the leaves of *Euscaphis japonica*.[2] Natural products containing α,β-unsaturated δ-lactone and bicyclic lactone/pyrone structural motifs have attracted attention because of their unusual structural architecture, electrophilic nature as Michael acceptors, and range of biological properties including analgesic, antibacterial, antifungal, anti-inflammatory, antiparasitic, antidiabetic, and cytotoxic activities (Figure 1).[3,4] In addition, some of them have been used in traditional medicine for treating arthritis, headache, and hepatitis infections,[4h] headaches, morning sickness, cancer, pulmonary diseases, and a variety of other bacterial and fungal infections.[4d] Owing to their interesting chemical framework and promising biological profiles, these compounds have attracted much attention from the chemical synthesis community over the past decade.[5] Recently O'Doherty *et al.* reported the total synthesis of euscapholide (**2**)[6] and Mohapatra *et al.* reported the total synthesis of tetraketide (**1**).[7] The absolute structures of **1** and **2** were assigned based on NMR spectroscopic and circular dichroism analyses. Compound **2** shows anti-inflammatory activity; whereas its analogue, 3,7-dihydroxy-5-octenolide, which lacks the Michael acceptor, does not show any anti-inflammatory activity and the biological activity of **1** remains to be assessed.[4j,k] However, further biological evaluation of compounds **1** and **2** is hindered due to their limited availability from natural sources. Hence, a concise, unified, and efficient approach has been developed toward the total synthesis of **1** and **2**, which can provide sufficient amounts of the target compounds for further biological evaluation.

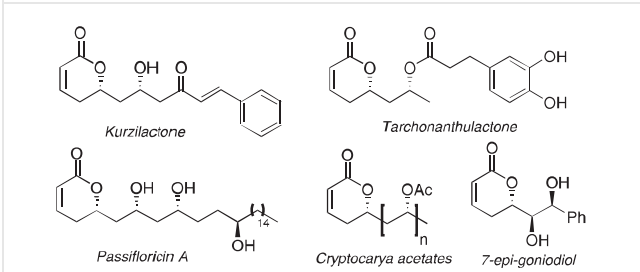
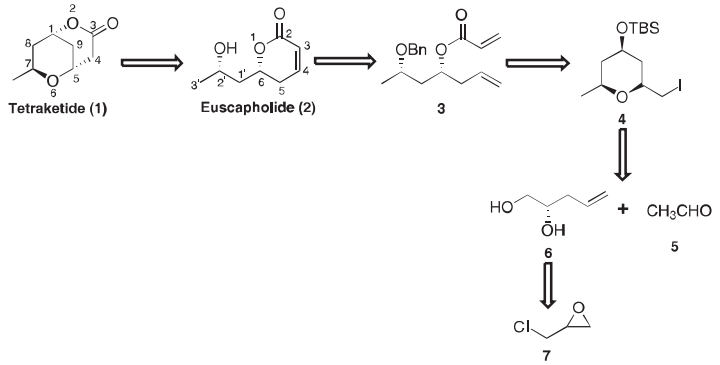


Figure 1 Bioactive natural products bearing the α,β-unsaturated δ-lactone motif[5a,b]

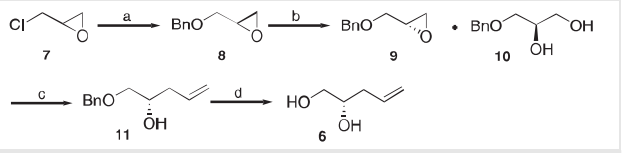
The retrosynthetic analysis of **1** and **2** is illustrated in Scheme 1. An assessment of the structures of tetraketide (**1**) and euscapholide (**2**) showed that bicyclic lactone **1** could be derived from an intramolecular oxa-Michael addition reaction of **2**, which could be accessed from acrylated compound **3** through ring-closing metathesis (RCM). Precursor **3** could be obtained from iodopyran **4**, which could, in turn, be accessed from acetaldehyde **5** and homoallylic alcohol **6**



Scheme 1 Retrosynthetic analysis of tetraketide (**1**) and euscapholide (**2**)

via Prins cyclization. Finally, homoallylic alcohol **6** could be obtained from epichlorohydrin **7** using Jacobsen hydrolytic kinetic resolution.

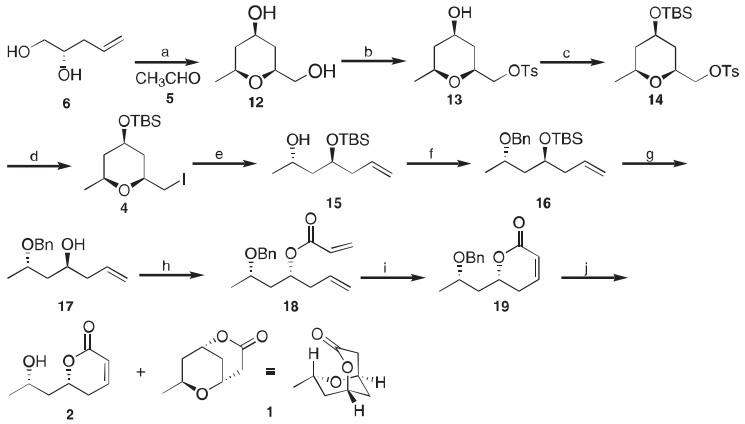
The synthesis of tetraketide (**1**) and euscapholide (**2**) commenced with the synthesis of starting material (*S*)-pent-4-ene-1,2-diol[8] **6** as depicted in Scheme 2. Epichlorohydrin can act as a versatile source of both (*R*)- and (*S*)-homoallylic alcohols **6**. Thus, racemic epichlorohydrin **7** was treated with NaH and BnOH in THF solvent to furnish racemic oxirane **8** in 94% yield. Oxirane **8**, on Jacobsen hydrolytic kinetic resolution using (*R*,*R*)-(salen)Co(II) complex[9] in aqueous acetic acid, afforded (*S*)-oxirane **9** in 46% yield (ee 96%) and (*R*)-1,2-diol **10** in 48% yield (ee 98%). Regioselective ring opening of (*S*)-oxirane **9** using vinyl magnesium bromide[10] in the presence of CuCN afforded (*S*)-1-(benzyloxy)pent-4-en-2-ol (**11**) in 92% yield, which was then subjected to debenzylation[11] by treatment with Li in liquid NH_3 to provide the homoallylic alcohol[8] **6** in 90% yield, being the requisite precursor for the Prins cyclization reaction.



Scheme 2 Reagents and conditions: (a) NaH, BnOH, THF, 0 °C to rt, 12 h, 94%; (b) (*R*,*R*)Co-Salen, AcOH, H_2O, THF, 0 °C to rt, 36 h, 46%; (c) CH_2=CH-Br, Mg, THF, CuCN, 1,2-dibromoethane, −78 to −40 °C, 4 h, 92%; (d) Li, Liq. NH_3, THF, −33 °C, 20 min, 90%.

With quantities of homoallylic alcohol **6** readily available, the key intermolecular Prins cyclization[12,13] reaction was carried out between acetaldehyde **5** and homoallylic alcohol **6** using TFA in CH_2Cl_2 to afford the resultant tetrahydropyran, which, on hydrolysis with K_2CO_3 in MeOH, furnished 2,6-*cis*-tetrahydropyran **12** as the exclusive product in 52% yield. The stereochemical aspects of such Prins cyclisations leading to structurally similar compounds to **12** have been discussed in detail previously.[12,13] Tosylation[14] of the primary hydroxy functionality of **12** furnished **13** in 85% yield. Silylation[15] of the secondary alcohol of **13** produced *tert*-butyldimethylsilyl ether **14** in 94% yield and subsequent nucleophilic substitution of the tosylate group using NaI/acetone[16] afforded the corresponding iodide **4** in 91% yield. Reductive ring opening[17] of iodo-intermediate **4** using Zn/EtOH furnished the key open chain *anti*-1,3-diol **15** in 88% yield (de 97%). Benzylation[18] of the secondary alcohol **15** led to **16** in 85% yield. Desilylation[19] of **16** to its homoallylic alcohol **17** in 84% yield and subsequent acylation[20] under Mitsunobu conditions[20] using acrylic acid, TPP and DEAD afforded ester **18** in 75% yield. Having succeeded in achieving the key intermediate **18** with desired relative and absolute stereochemistry, the bis-olefinic compound **18** was subjected to RCM reaction using Grubbs' second generation catalyst[21] to afford α,β-unsaturated δ-lactone **19** in 70% yield. Debenzylation[22] of α,β-unsaturated δ-lactone **19** using $TiCl_4$ in CH_2Cl_2 afforded euscapholide (**2**) and tetraketide (**1**), through an intramolecular oxa-Michael addition reaction, in a 65:35 ratio, with 89% combined yield, as shown in Scheme 3. A comparison of the ^{1}H NMR spectroscopic and analytical data of synthetic compounds **1** and **2** with those of the natural products showed that they were in agreement. The specific rotation of compound **1** (synthetic $[\alpha]_D^{25}$ −11.5 (*c* 0.8, MeOH); Lit.[7] $[\alpha]_D^{20}$ −12.7 (*c* 0.9, MeOH)) and compound **2** (synthetic $[\alpha]_D^{25}$ +113.8 (*c* 0.24, MeOH); Lit.[23] $[\alpha]_D^{25}$ +115.5 (*c* 1.52 MeOH))[23] were in good agreement with the reported values.

In conclusion, a concise, enantio- and diastereoselective total synthesis of tetraketide (**1**) and euscapholide (**2**) has been accomplished in ten steps with an overall yield of over 10%. Jacobsen hydrolytic kinetic resolution, ring-closing metathesis, Prins cyclisation reaction and oxa-Michael addition reaction are the key steps. The operational expediency, synthetic efficiency, and high diastereoselectivity make the synthetic process practicable. We believe the current strategy provides a reliable route for the synthesis of structural analogues of α,β-unsaturated δ-lactones and α-pyrones for structure–activity studies.



Scheme 3 Reagents and conditions: (a) i. TFA, CH_2Cl_2, 0 °C to rt, 3 h; ii. K_2CO_3, MeOH, r.t., 0.5 h, 52%; (b) TEA, TsCl, CH_2Cl_2, 0 °C to rt, 6 h, 85%; (c) TBSCl, imidazole, DMAP, CH_2Cl_2, 0 °C to rt, 4 h, 94%; (d) NaI, acetone, reflux, 24 h, 91%; (e) Zn, EtOH, reflux, 4 h, 88%; (f) NaH, BnBr, TBAI, THF, 0 °C to rt, 4 h, 85%; (g) CSA, MeOH, 0 °C to rt, 2 h, 84%; (h) Acrylic acid, TPP, DEAD, 0 °C to rt, 6 h, 75%; (i) Grubbs' second generation catalyst, CH_2Cl_2, reflux, 18 h, 70%; (j) $TiCl_4$, DCM, 0 °C, 0.5 h, 89%.

Commercial reagents were used without further purification and all solvents were purified by standard techniques. Infrared spectra were recorded with a Perkin–Elmer 683 spectrometer. Specific rotations were obtained with a Jasco Dip 360 digital polarimeter. NMR spectra were recorded in $CDCl_3$ with Varian Unity 400 and 500 MHz NMR spectrometers. Chemical shifts (δ) are quoted in parts per million and are referenced to tetramethylsilane (TMS) as an internal standard. Coupling constants (*J*) are quoted in Hertz and the resonance multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; q quintet; dt, doublet of triplets; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, double double doublet of doublets; m, multiplet. Column chromatographic separations were carried out on silica gel (60–120 mesh) and flash chromatographic separations were carried out using 230–400 mesh, silica gel. Mass spectra were recorded with Micromass VG-7070H for EI and VG Autospec M FABMS spectrometers.

2-[(Benzyloxy)methyl]oxirane (8)

To a stirred suspension of NaH (8 g, 333 mmol) in anhydrous THF (400 mL) at 0 °C, was added dropwise benzyl alcohol (24 g, 222 mmol) dissolved in anhydrous THF (100 mL). After 30 minutes, epichlorohydrin **7** (20.5 g, 222 mmol) was added and the reaction mixture was allowed to rise to r.t. and stirred for 12 hours. After completion of the reaction (monitored by TLC), the reaction mixture was quenched at 0 °C with saturated aqueous ammonium chloride (100 mL), diluted with EtOAc (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with brine (100 mL) and dried over Na_2SO_4. After filtration and removal of solvent under reduced pressure, the crude oxirane was purified by column chromatography eluting with 5% EtOAc/hexane to give pure product **8** (34.4 g, 94% yield) as a colourless liquid.

IR (neat): 3031, 2999, 2926, 2864, 1725, 1453, 1267, 1096, 742, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 5 H), 4.62–4.46 (m, 2 H), 3.71 (dd, *J* = 11.2, 3.1 Hz, 1 H), 3.41 (dd, *J* = 11.4, 5.7 Hz, 1 H), 3.14 (tt, *J* = 5.9, 3.2 Hz, 1 H), 2.77–2.71 (m, 1 H), 2.58 (dd, *J* = 5.2, 2.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6, 127.2, 127.1, 72.5, 70.1, 50.2, 43.2.

MS-ESIMS: *m*/*z* 165 $[M + H]^+$, 187 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd. for $C_{10}H_{12}O_2Na$: 187.21680, found: 187.21690.

(*S*)-2-[(Benzyloxy)methyl]oxirane (9)

To (*R*,*R*)-(salen)Co(II) precatalyst (604 mg, 1 mmol) in a round-bottom flask were added sequentially racemic oxirane **8** (32.8 g, 200 mmol) and AcOH (0.228 mL, 4 mmol) at r.t. After the reaction mixture turned from a red suspension to a dark-brown solution, the flask was cooled to 0 °C and THF (2 mL) followed by H_2O (1.98 g, 110 mmol, 0.55 equiv) were added over a period of 20 minutes and the reaction mixture was allowed to stir at r.t. for 36 hours. After completion of reaction, monitored by TLC, the mixture was directly purified by column chromatography eluting with 5% EtOAc/hexane to afford epoxide **9** (15.08 g, 46%, 96% ee) as a colorless liquid and enantomerically pure diol **10** (17.05 g, 52%, 98% ee) as a viscous liquid.

$[\alpha]_D^{22}$ +5.2 (*c* 1.1, $CHCl_3$); Lit. $[\alpha]_D^{25}$ + 5.1 (*c* 1.0, $CHCl_3$).

IR (Neat): 3454, 3031, 2999, 2926, 2864, 1725, 1453, 1267, 1096, 742, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.23 (m, 5 H), 4.64–4.48 (m, 2 H), 3.70 (dd, *J* = 11.4, 3.1 Hz, 1 H), 3.41 (dd, *J* = 11.4, 5.7 Hz, 1 H), 3.12 (tt, *J* = 5.8, 3.1 Hz, 1 H), 2.78–2.72 (m, 1 H), 2.57 (dd, *J* = 5.2, 2.6 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.5, 127.2, 127.0, 72.4, 70.2, 50.1, 43.27.

MS-ESIMS: *m*/*z* 165 $[M + H]^+$, 187 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd. for $C_{10}H_{12}O_2Na$: 187.21680; found: 187.21690.

(*S*)-1-(Benzyloxy)pent-4-en-2-ol (11)

To magnesium turnings (6.6 g, 274.4 mmol) in anhydrous THF (35 mL) at r.t. were sequentially added, 1,2-dibromoethane (3 drops) and freshly prepared vinyl bromide (13.1 mL, 182.9 mmol) in a dropwise manner, and CuCN (40.9 mg, 5 mol%). The reaction mixture was stirred for 30 minutes and cooled to –78 °C, then epoxide **9** (15 g, 91.46 mmol) in THF (60 mL) was added, the mixture allowed to warm to –40 °C and stirred for 4 h. The reaction was then quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (2 × 100

mL). The combined organic extracts were washed with brine (120 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography eluting with 12% EtOAc/hexane afforded **11** (16.2 g, 92%) as a colourless liquid.

$[\alpha]_D^{22}$ +2.6 (*c* 1.1, $CHCl_3$); $[\alpha]_D^{25}$ +2.3 (*c* 1.0, $CHCl_3$).

IR (neat): 3426, 3070, 3030, 2910, 2862, 1718, 1640, 1451, 1275, 1103, 997, 915, 741, 698, 608 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.27 (m, 5 H), 5.82 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1 H), 5.18–5.05 (m, 2 H), 4.55 (s, 1 H), 3.88 (dt, *J* = 6.7, 9.9 Hz, 1 H), 3.51 (dd, *J* = 9.5, 3.4 Hz, 1 H), 3.38 (dd, *J* = 9.5, 7.4 Hz, 1 H), 2.38 (s, 1 H), 2.25 (dd, *J* = 17.2, 10.8 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.8, 134.1, 128.2, 127.5, 117.4, 73.7, 73.1, 69.5, 37.7.

MS-ESIMS: *m*/*z* 193 $[M + H]^+$, 215 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd. for $C_{12}H_{16}O_2Na$: 215.21640; found: 215.21650

(*S*)-Pent-4-ene-1,2-diol (6)

To a stirred suspension of lithium (16 g, 250 mmol) in liquid NH_3 (160 mL) was added **11** (16 g, 83.3 mmol) dissolved in anhydrous THF (100 mL). The mixture was stirred for 20 minutes and quenched with solid NH_4Cl (15 g). The ammonia was allowed to evaporate at r.t., ether (100 mL) was added to the residue and the mixture was filtered through Celite®. The filtrate was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography eluting with 70% EtOAc/hexane to afford diol **6** (7.6 g, 90% yield) as a colourless liquid.

$[\alpha]_D^{25}$ –3.5 (*c* 2.5, $CHCl_3$); Lit $[\alpha]_D^{25}$ –3.4 (*c* 2.8, $CHCl_3$).

IR (neat): 3419, 2926, 1840, 1640, 1431, 1073, 915, 848, 765, 654 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.91–5.63 (m, 1 H), 5.20–5.08 (m, 2 H), 3.75–3.55 (m, 1 H), 3.71–3.42 (m, 2 H), 2.93 (s, 1 H), 2.33–2.15 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.1, 117.5, 71.4, 65.9, 37.6.

MS-ESIMS: *m*/*z* 103 $[M + H]^+$, 125 $[M + Na]^+$.

(2*S*,4*R*,6*S*)-Tetrahydro-2-(hydroxymethyl)-6-methyl-2*H*-pyran-4-ol (12)

TFA (21.5 mL) was added slowly to a solution of homoallylic alcohol **6** (2.5 g, 24.5 mmol) and acetaldehyde **5** (3.24 g, 73.5 mmol) in anhydrous CH_2Cl_2 (50 mL) at 25 °C and the reaction mixture was stirred for 6 h at r.t. After completion of reaction, as monitored by TLC, the reaction was quenched with saturated aqueous $NaHCO_3$ (60 mL) and the pH was adjusted to >7 by addition of triethylamine. The two layers were separated, the aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL) and the combined organic layers were concentrated under reduced pressure. The crude residue was dissolved in MeOH (40 mL), potassium carbonate (10.16 g, 73.52 mmol) was added, and the mixture was stirred for 0.5 h. The MeOH was removed under reduced pressure and water (25 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Purification of the crude material by column chromatography eluting with 60% EtOAc/hexane afforded pure **12** (1.86 g, 52%) as a pale-yellow solid.

$[\alpha]_D^{22}$ +15.8 (*c* 1.1, $CHCl_3$).

IR (neat): 3382, 2937, 2872, 1652, 1452, 1375, 1323, 1148, 1115, 1024, 953 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.82–3.72 (m, 1 H), 3.61–3.54 (m, 1 H), 3.53–3.38 (m, 3 H), 2.10 (s, 1 H), 1.95–1.88 (m, 1 H), 1.83–1.76 (m, 1 H), 1.66–1.55 (m, 2 H), 1.22 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 76.1, 71.8, 67.4, 65.3, 42.4, 36.4, 21.5.

MS-ESIMS: *m*/*z* 147 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd. for $C_7H_{15}O_3$: 147.09780; found: 147.09790.

(2*S*,4*R*,6*S*)-Tetrahydro-6-methyl-2-*p*-toluenesulfonyloxymethyl-2*H*-pyran-4-ol (13)

To a stirred solution of alcohol **12** (1.8 g, 12.3 mmol), triethylamine (5.2 mL, 36.9 mmol) and DMAP (cat) in anhydrous dichloromethane (25 mL) at 0 °C was added *p*-toluenesulfonyl chloride (2.8 g, 14.8 mmol) portionwise. After stirring for 2 h at r.t., the resulting mixture was quenched with sat aqueous $NaHCO_3$ and extracted with dichloromethane (2 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered. Removal of solvent under reduced pressure and purification by silica gel chromatography eluting with 20% EtOAc/hexane afforded **13** (3.14 g 85%) as a viscous liquid.

$[\alpha]_D^{22}$ +34.8 (*c* 3, $CHCl_3$).

IR (neat): 3395, 2973, 2859, 1597, 1451, 1358, 1176, 1095, 975, 817 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 4.03–3.87 (m, 2 H), 3.70 (dt, *J* = 15.3, 5.3 Hz, 1 H), 3.53 (dd, *J* = 10.8, 4.9 Hz, 1 H), 3.37 (dd, *J* = 10.9, 6.0 Hz, 1 H), 2.62 (s, 1 H), 2.45 (s, 3 H), 1.86 (dd, *J* = 12.0, 2.5 Hz, 1 H), 1.13 (d, *J* = 6.2 Hz, 3 H), 1.09–0.95 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.0, 133.3, 130.1, 128.4, 73.2, 72.6, 72.2, 68.4, 43.4, 37.5, 21.9, 21.8.

MS-ESIMS: *m*/*z* 323 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd. for $C_{14}H_{20}O_5NaS$: 323.0929; found: 323.0915.

(2*S*,4*R*,6*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-methyltetrahydro-2*H*-pyran-2-yl Methyl *p*-Toluene Sulfonate (14)

To a stirred solution of **13** (3.05 g, 10.2 mmol) in anhydrous CH_2Cl_2 (12 mL) was added DMAP (0.248 g, 2.03 mmol), imidazole (2.1 g, 30.5 mmol) and TBSCl (2.38 g, 15.2 mmol) at 0 °C. The resulting mixture was allowed to stir for 4 h at r.t. After completion of reaction as monitored by TLC, the reaction was quenched with saturated aqueous NH_4Cl (40 mL) and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The resulting crude product on purification with silica gel column chromatography eluting with 10% EtOAc/hexane afforded TBS ether **14** (3.94 g, 94%) as a colourless oil.

$[\alpha]_D^{22}$ +8.1 (*c* 1.0, $CHCl_3$).

IR (neat): 2932, 2856, 1598, 1461, 1363, 1254, 1179, 1121, 1073, 981, 835, 776, 667, 552 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.2 Hz, 2 H), 7.48 (d, *J* = 8.1 Hz, 2 H), 4.19–4.02 (m, 2 H), 3.94–3.79 (m, 1 H), 3.75–3.62 (m, 1 H), 3.59–3.45 (m, 1 H), 2.62 (s, 3 H), 1.90 (ddd, *J* = 8.2, 5.0, 1.9 Hz, 1 H), 1.29 (d, *J* = 6.1 Hz, 3 H), 1.04 (s, 9 H), 0.19 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.7, 129.7, 128.0, 72.8, 72.2, 71.8, 68.0, 42.9, 37.1, 25.7, 21.4, –4.6.

MS-ESIMS: *m*/*z* 437 $[M + Na]^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd. for $C_{20}H_{34}O_5NaSiS$: 437.1793; found: 437.1782.

tert-Butyl (((2*S*,4*R*,6*S*)-2-(Iodomethyl)-6-methyltetrahydro-2*H*-pyran-4-yl)oxy) Dimethylsilane (4)

To a stirred solution of **14** (3.8 g, 9.2 mmol) in acetone (40 mL) was added NaI (20.7 g, 137.7 mmol) and the mixture was heated to reflux for 24 hours. After completion of reaction as monitored by TLC, the acetone was removed under reduced pressure. To the resulting residue was added water and CH_2Cl_2, and the organic layer was extracted, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by silica gel chromatography eluting with 7% EtOAc/hexane to afford **15** (3.1 g, 91%) as a colourless liquid.

$[\alpha]_D^{22}$ +15.10 (*c* 1.0, $CHCl_3$).

IR (neat): 2932, 2855, 1632, 1465, 1381, 1253, 1158, 1120, 1072, 836, 775 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.76–3.61 (m, 1 H), 3.47–3.33 (m, 1 H), 3.32–3.19 (m, 1 H), 3.17–3.00 (m, 2 H), 2.02–1.92 (m, 1 H), 1.72–1.62 (m, 1 H), 1.22 (d, *J* = 6.3 Hz, 3 H), 1.18–1.07 (m, 2 H), 0.88 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 75.1, 72.0, 68.3, 43.0, 41.0, 25.8, 21.6, 9.1, –4.5.

MS-ESIMS: *m*/*z* 393 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd. for $C_{13}H_{27}IO_2SiNa$: 393.16930; found: 393.16922.

(2*S*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)hept-6-en-2-ol (15)

To a stirred solution of iodide **4** (3.0 g, 8.1 mmol) in EtOH (60 mL), zinc dust (10.5 g, 162.16 mmol) was added, the mixture was heated to reflux for 3 h and then cooled to 25 °C. Solid NH_4Cl (6.5 g) and ether (100 mL) were added and the resultant mixture was stirred for 10 min to obtain a grey suspension. The resulting suspension was filtered through a pad of Celite® and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 12% EtOAc/hexane to give pure **15** (1.74 g, 88%, 97% de) as a colourless liquid.

$[\alpha]_D^{22}$ +36.8 (*c* 2.5, $CHCl_3$).

IR (neat): 3444, 2957, 2932, 2858, 1640, 1466, 1370, 1254, 1090, 1063, 1001, 913, 834, 774 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84–5.54 (m, 1 H), 5.11–4.92 (m, 2 H), 4.13–3.78 (m, 2 H), 2.81 (s, 1 H), 2.35–2.16 (m, 2 H), 1.60–1.43 (m, 2 H), 1.11 (d, *J* = 6.2 Hz, 3 H), 0.87 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.6, 117.4, 71.2, 64.4, 43.1, 41.1, 29.7, 25.7, 23.8, –4.5, –4.8

MS-ESIMS: *m*/*z* 245 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{13}H_{28}O_2Si$: 245.19650; found: 245.19510.

(4*S*,6*S*)-(6-(Benzyloxy)hept-1-en-4-yl)oxy(*tert*-butyl)dimethylsilane (16)

To a cooled suspension of NaH (0.4 g, 16.9 mmol, 60% w/w dispersion in paraffin oil) in anhydrous THF (10 mL), was added dropwise a solution of alcohol **15** (1.7 g, 6.7 mmol) in THF (25 mL) at 0 °C and the mixture was stirred for 30 min. To this reaction mixture TBAI (0.124 g, 3.4 mmol) and benzyl bromide (0.96 mL, 8.1 mmol) were added sequentially and stirring was continued for another 15 minutes at the same temperature, followed by 3 hours at reflux. The reaction was quenched with crushed ice until a biphasic solution formed. The reaction mixture was extracted with EtOAc (2 × 25 mL) and the organic extracts were washed with water (25 mL), brine (25 mL), dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent followed by column chromatography eluting with 4% EtOAc/hexane afforded pure **16** (1.92 g, 85%) as a colourless liquid.

$[\alpha]_D^{22}$ +24.72 (*c* 2.8, $CHCl_3$).

IR (neat): 2930, 2857, 1640, 1461, 1371, 1251, 1145, 1068, 998, 913, 833, 773, 734 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.18 (m, 5 H), 5.84 (ddt, *J* = 17.4, 10.4, 7.0 Hz, 1 H), 5.17–5.01 (m, 2 H), 4.69–4.35 (m, 2 H), 4.15–3.99 (m, 1 H), 3.69 (dt, *J* = 10.0, 5.5 Hz, 1 H), 2.37 (dd, *J* = 6.9, 5.7 Hz, 2 H), 1.63–1.56 (m, 2 H), 1.15 (d, *J* = 6.2 Hz, 3 H), 0.92 (s, 9 H), 0.06 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.8, 134.6, 128.2, 127.6, 127.3, 117.1, 75.6, 70.7, 65.4, 44.8, 38.2, 29.6, 25.8, 24.6, 18.1, –3.8, –4.6.

MS-ESIMS: *m*/*z* 335 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{20}H_{35}O_2NaSi$: 335.2406; found: 335.2398.

(4*S*,6*S*)-6-(Benzyloxy)hept-1-en-4-ol (17)

To a stirred solution of **16** (1.8 g, 5.38 mmol) in anhydrous MeOH (25 mL), CSA (0.12 g, 0.05 mmol) was added at 0 °C under a nitrogen atmosphere. The mixture was warmed to r.t. and stirred for 4 h, then the reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with EtOAc (25 mL), washed with brine, dried over (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel eluting with 10% EtOAc/hexane afforded pure **17** (0.99 g, 84%) as a colourless liquid.

$[\alpha]_D^{22}$ +59.75 (*c* 0.25, $CHCl_3$).

IR (neat): 3424, 2966, 2927, 1639, 1495, 1453, 1349, 1093, 1065, 998, 914, 739 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.20 (m, 5 H), 5.87–5.69 (m, 1 H), 5.15–5.02 (m, 2 H), 4.74–4.40 (m, 2 H), 3.98–3.85 (m, 1 H), 3.71 (dt, *J* = 9.8, 4.1 Hz, 1 H), 2.48–2.30 (m, 2 H), 1.74–1.51 (m, 2 H), 1.12 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6, 133.6, 128.3, 127.7, 127.4, 117.6, 78.9, 70.5, 67.4, 42.4, 37.8, 23.3.

MS-ESIMS: *m*/*z* 243 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd. for $C_{14}H_{20}O_2Na$: 243.1360; found: 243.1365.

(4*R*,6*S*)-6-(Benzyloxy)hept-1-en-4-yl Acrylate (18)

To a stirred mixture of **17** (0.9 g, 4 mmol), triphenylphosphine (3.75 g, 14.3 mmol) and acrylic acid (0.70 mL, 10.2 mmol) in anhydrous THF (20 mL) at 0 °C was added diethyl azodicarboxylate (2.2 mL, 14.3 mmol) via syringe. The reaction mixture was then stirred for 6 hours at r.t., diluted with water (50 mL) and extracted with EtOAc (2 × 50 mL). After removing the solvent, water (50 mL) was added and the mixture was extracted with diethyl ether (3 × 30 mL). Separation of the organic solvents, drying over Na_2SO_4, filtering and removal of solvent under reduced pressure followed by flash chromatography eluting with 15% EtOAc/hexane afforded ester **18** (0.84 g, 75%) as a colourless liquid.

$[\alpha]_D^{22}$ +12.66 (*c* 0.42, $CHCl_3$).

IR (neat): 2923, 2853, 1730, 1453, 1369, 1326, 1155, 1082, 1082, 923, 835, 750 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.18 (m, 5 H), 6.40–6.27 (m, 1 H), 6.03 (dd, *J* = 17.3, 10.4 Hz, 1 H), 5.89–5.70 (m, 2 H), 5.15–5.01 (m, 3 H), 4.60–4.40 (m, 2 H), 3.55–3.44 (m, 1 H), 2.38–2.26 (m, 2 H), 1.96 (dt, *J* = 14.1, 7.0 Hz, 1 H), 1.72–1.58 (m, 1 H), 1.21 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 138.4, 134.2, 130.2, 128.8, 128.3, 127.7, 127.5, 117.4, 75.2, 70.5, 68.7, 40.0, 38.0, 20.1.

MS-ESIMS: *m*/*z* 297 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd. for $C_{17}H_{22}O_3NaP$: 297.1466; found: 297.1461.

(*R*)-6-((*S*)-2-(Benzyloxy)propyl)-5,6-dihydro-2*H*-pyran-2-one (19)

A solution of compound **18** (0.70 g, 2.5 mmol) in anhydrous CH_2Cl_2 (500 mL) was degassed and Grubbs' second generation catalyst (0.05 mg, 0.06 mmol) was added at r.t. under nitrogen atmosphere and the resulting pale-purple solution was heated to reflux for 12 hours. After completion of reaction (monitored by TLC), the majority of the solvent was distilled off and the concentrated solution was stirred at r.t. for 2 hours under air bubbling in order to decompose the catalyst. Evaporation to dryness under reduced pressure gave a brown residue that was purified by column chromatography on silica gel eluting with 40% EtOAc/hexane to afford cyclic lactone **19** (0.43 g, 70%) as a colourless oil.

$[\alpha]_D^{22}$ +87.65 (*c* 0.6, $CHCl_3$).

IR (neat): 2938, 1730, 1373, 1217, 977, 746 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.22 (m, 5 H), 6.82–6.72 (m, 1 H), 5.9 (d, *J* = 9.7 Hz, 1 H), 4.64–4.50 (m, 2 H), 4.40 (d, *J* = 11.8 Hz, 1 H), 3.82–3.69 (m, 1 H), 2.38–2.08 (m, 3 H), 1.84–1.70 (m, 1 H), 1.28 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.6, 145.1, 128.4, 127.6, 121.3, 75.3, 70.6, 70.2, 41.4, 29.2, 19.3.

MS-ESIMS: *m*/*z* 247 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{15}H_{19}O_3$: 247.1345; found: 247.1331.

(*R*)-6-((*S*)-2-Hydroxypropyl)-5,6-dihydro-2*H*-pyran-2-one (2)

To a stirred solution of **19** (0.35 g, 14.2 mmol) in CH_2Cl_2 (6 mL), $TiCl_4$ (1.0 mL, 1.80 mmol) was added at 0 °C under a nitrogen atmosphere. The reaction mixture was warmed to r.t. and stirred for 1 h. After completion of reaction (monitored by TLC), the reaction mixture was quenched with 1 M HCl, extracted with CH_2Cl_2 (50 mL), washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with 2% MeOH/chloroform to give euscapholide **2** (15.37 mg, 65%) as a colourless oil and a tetraketide **1** (6.24 mg, 24%) as a white solid.

Euscapholide (2)

$[\alpha]_D^{25}$ +113.8 (*c* 0.24, MeOH); Lit.[23] $[\alpha]_D^{25}$ +115.5 (*c* 1.52 MeOH).

IR (neat): 3427, 2934, 1730, 1370, 1245, 1219, 1172, 1096, 1034, 980, 864, 777 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88 (ddd, *J* = 10.2, 5.1, 3.2 Hz, 1 H), 5.96 (dd, *J* = 9.7, 1.9 Hz, 1 H), 4.70–4.62 (m, 1 H), 4.10–4.00 (m, 1 H), 2.52–2.38 (m, 3 H), 2.22 (br, 1 H), 1.80–1.74 (m, 1 H), 1.24 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 145.1, 121.3, 76.9, 65.4, 43.6, 29.5, 23.8.

MS-ESIMS: *m*/*z* 157 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_8H_{13}O_3$: 157.08592; found: 157.08611.

Tetraketide (1)

$[\alpha]_D^{25}$ –11.5 (*c* 0.8, MeOH); Lit.[7] $[\alpha]_D^{20}$ –12.7 (*c* 0.9, MeOH).

IR (neat): 2925, 2855, 1725, 1504, 1457, 1381, 1252, 1223, 1118, 1066, 1023, 767 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.94–4.89 (m, 1 H), 4.45 (dd, *J* = 5.3, 2.5 Hz, 1 H), 3.93–3.85 (m, 1 H), 2.86 (dtd, *J* = 18.1, 2.5, 0.8 Hz, 1 H), 2.56–2.50 (m, 1 H), 2.32–2.26 (m, 1 H), 2.14 (ddd, *J* = 15.6, 7.8, 5.0 Hz, 1 H), 1.93–1.85 (m, 2 H), (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2, 72.5, 64.6, 64.0, 40.8, 39.4, 25.9, 21.6.

MS-ESIMS: *m*/*z* 157 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_8H_{13}O_3$: 157.08592; found: 157.08594.

Conflict of Interest

The authors declare no conflict of interest.

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Zn/$ZnBr_2$ Catalysed Reaction of Aldehydes with Allylbromide: Synthesis of 2,6-Disubstituted 4-Bromotetrahydropyrans

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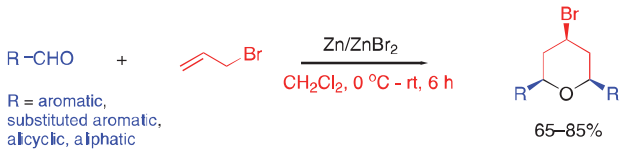

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Abstract An efficient approach for the one-pot synthesis of 4-bromotetrahydropyrans in a highly diastereoselective manner via the alkynylation followed by Prins cyclisation is described. The method employs aldehydes and allyl bromide as reactants, with a Zn/$ZnBr_2$ catalytic system in CH_2Cl_2. A variety of 2,6-disubstituted 4-bromotetrahydropyran derivatives were obtained in good yields.

Key words Prins cyclisation, tetrahydropyrans, aldehydes, allylbromides, one-pot reaction

Tetrahydropyrans (THP) are prominent structural motifs in many natural products showing various biological activities. Examples include diospongin A and B, aza-diospongin A, centolobine, diarylheptanoid, catechola-I and II, the avermectins, aplysiatoxins, oscillatoxins, atrunculins, acutiphycins, kendomycin and phorboxazoles A and B (Figure 1).[1,2] THP rings are also key moieties in molecules demonstrating antiviral, anti-nociceptive, serotonin norepinephrine transporter inhibitory, antimicrobial and anti-proliferative activity.[3–5] Due to their wide ranging presence, there are various synthetic tactics to afford THPs.[6] Among those synthetic protocols, the Prins cyclisation has become a pre-eminent tool for the construction of THPs using acidic catalysts for coupling aldehydes and allyl alcohols.[7]

There are relatively few examples in the literature of one-pot formation of THP rings from aldehydes and allyl bromide via Barbier–Prins reactions,[8] and the reported methods suffer from extended reaction times, low yields and poor stereoselectivity.[9]

Zinc bromide ($ZnBr_2$) is known as a mild, non-toxic, moisture-tolerant, catalyst in organic transformations.[10] Herein, we demonstrate that $ZnBr_2$ can act as an efficient promoter for one-pot synthesis of 2,6-disubstituted 4-bromotetrahydropyrans in a highly diastereoselective manner via Babier–Prins cyclisation, using allyl bromide and aldehydes as reactants.

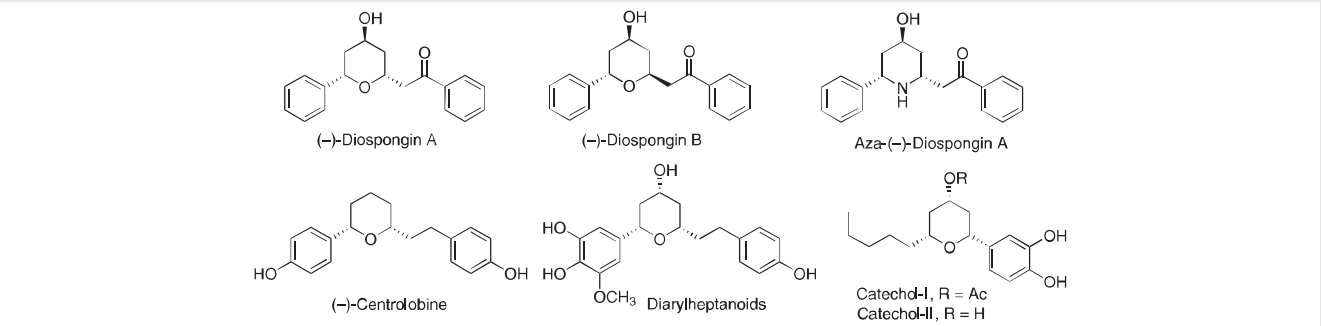
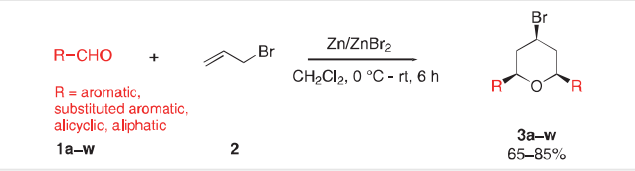


Figure 1 Bioactive compounds featuring a tetrahydropyran moiety

Initial studies were carried out with benzaldehyde (2 mmol) and allyl bromide (1 mmol) in the presence of *p*TSA, at room temperature in CH_2Cl_2. The reaction proceeded smoothly, but gave, 2,6-diphenyl-4-bromotetrahydropyran in low yield. Similarly, we have examined the reaction with CSA and $HClO_4$-SiO_2 catalysts separately and observed that conversions took place but yields were very poor. We then turned our attention to Lewis acid catalyst systems such as $Zn/ZnCl_2$ and $Zn/ZnBr_2$. While, in the case of $Zn/ZnCl_2$ reaction, a mixture of products, 2,6-diphenyl-4-bromotetrahydropyran and 2,6-diphenyl-4-chlorotetrahydropyran were formed, with $Zn/ZnBr_2$, only the desired 2,6-diphenyl-4-bromotetrahydropyran was formed in 85% yield with high diastereoselectivity for the *cis*-product. The predominant formation of this stereoisomer is most likely due to thermodynamic control. Assignment of the stereochemistry was based on the coupling constants of the protons at the C_2 and C_4 positions. The coupling constants of the benzylic proton 2-H_c [δ = 4.5 (J = 11.0 Hz)] and the proton on the carbon bearing the halide group 4-H_c [δ = 4.0 (J = 4.5, 11.0 Hz)] in the ^{1}H NMR spectrum showed a splitting consistent with two phenyl groups and the halide group being in *cis*-equatorial orientations, as shown in Scheme 1.



Scheme 1

To determine the role of solvent, we performed the reaction of benzaldehyde in different solvents such as dichloromethane, toluene, acetonitrile, tetrahydrofuran and found that dichloromethane provided the best results (Table 1).

Table 1 Initial Optimization of Reaction Conditions

Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	pTSA	CH_2Cl_2	25	6	60
2	CSA	CH_2Cl_2	25	6	55
3	$HClO_4$-SiO_2	CH_2Cl_2	25	10	50
4	$ZnCl_2$	CH_2Cl_2	25	8	50
5	$ZnBr_2$	CH_2Cl_2	25	6	85
6	$ZnBr_2$	toluene	25	12	44
7	$ZnBr_2$	CH_3CN	25	8	62
8	$ZnBr_2$	THF	25	9	56

Based on the results obtained with benzaldehyde, we next explored the substrate scope of various substituted aromatic as well as aliphatic aldehydes with allyl bromide to probe the generality of the reaction. Aromatic aldehydes having electron-donating or electron-withdrawing groups on the aromatic ring, reacted readily with allyl bromide to afford the corresponding 2,6-disubstituted 4-bromotetrahydropyrans in 65–85% yield (Figure 2). However, aliphatic aldehydes and aromatic aldehydes bearing electron-withdrawing groups reacted more smoothly than those having

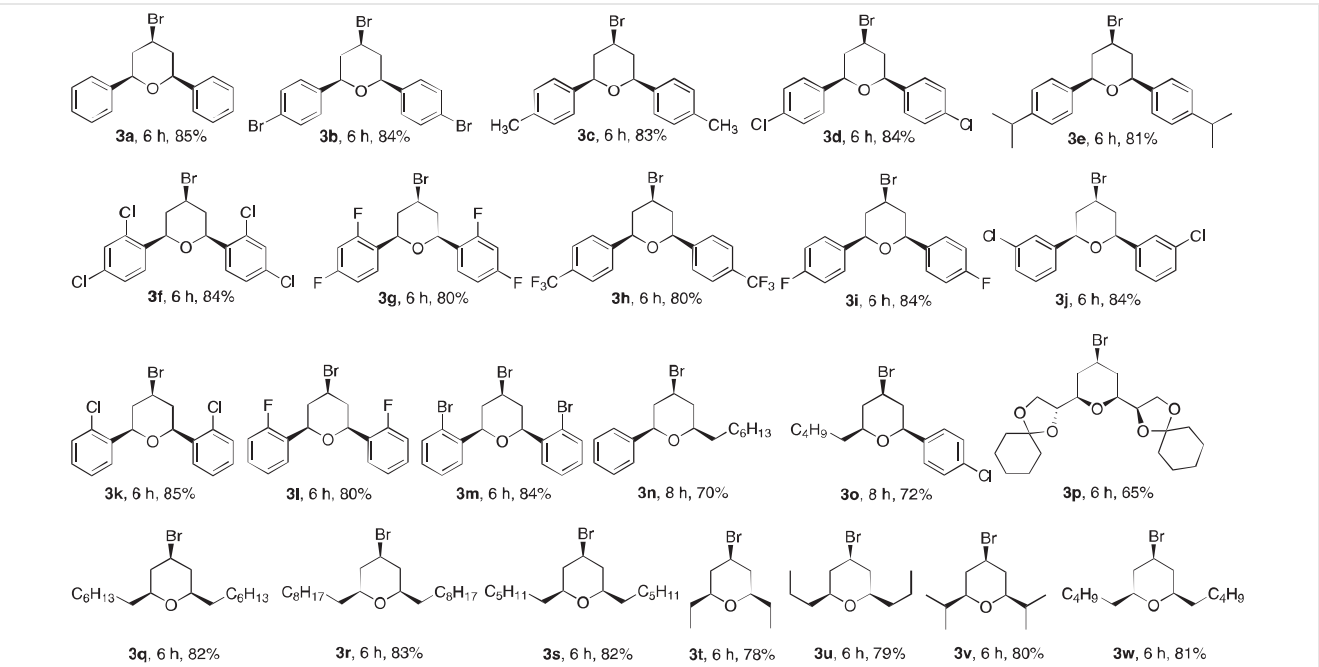
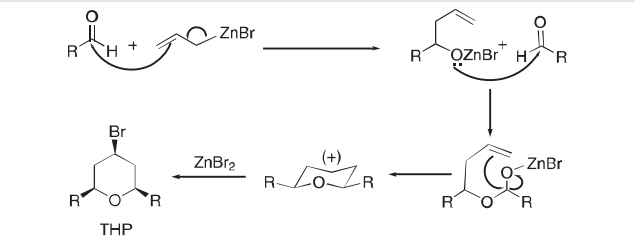


Figure 2 Reaction scope

electron-donating groups. Notably, this protocol was equally applicable to aliphatic, cyclic, and aromatic aldehydes.

On the basis of experimental results and previous reports, a reaction mechanism for the formation of 2,6-disubstituted 4-bromotetrahydropyrans from allyl bromide and aldehydes can be explained by a tandem carbonyl allylation-hemiacetal formation followed by Prins cyclisation and subsequent bromination (Scheme 2). A rationale for the all *cis*-selectivity involves formation of an (*E*)-oxocarbenium ion via a chair-like transition state, which has increased stability relative to the open oxo-carbenium ion due to delocalization. The optimal geometry for this delocalization of hydrogen atom at C_4 in a *pseudo*-axial position favours equatorial attack of the activated π-bond nucleophile.[11]



Scheme 2

In conclusion, we have developed a one-pot synthesis of 2,6-disubstituted 4-bromotetrahydropyrans **3a–w** from aldehydes and allyl bromide in a highly diastereoselective manner via alkenylation followed by Prins cyclisation, catalysed by Zn/$ZnBr_2$.

Solvents, aldehydes, allyl bromide and Zn/$ZnBr_2$ were purchased from a commercial source (Spectrochem) and used as received. Progress of reaction was followed by TLC on silica gel-G plates of 0.5-mm thickness, and spots were visualised by iodine vapour and UV light. Flash column chromatography was performed on silica gel (200–300 mesh). ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded with a Bruker AV 300/400/500 MHz instrument. Chemical shifts are reported in ppm referenced to the residual proton of $CDCl_3$ (7.26 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR). ^{1}H NMR data are reported as chemical shift (ppm), multiplicity (standard abbreviations), coupling constants (Hz), and integration. ^{13}C NMR data are reported as ppm. HRMS analyses were performed with a Micromass Q-TOF apparatus.

Synthesis of 2,6-Disubstituted 4-Bromotetrahydropyrans; General Procedure

To a stirred suspension of aldehyde **1a–w** (2 mmol) and Zn dust (4 mmol) in CH_2Cl_2 was added allyl bromide **2** (1 mmol) and the mixture stirred at r.t. for 30 minutes. Then $ZnBr_2$ was added at 0 °C and the mixture was further stirred for 6–8 hours at r.t., with completion of reaction being confirmed by TLC. The reaction mixture was filtered through a bed of Celite®, the filtrate was evaporated, and the residue was triturated with EtOAc (2 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, evaporated under reduced pressure, and purified by column chromatography on silica gel (60–120 mesh), eluting with EtOAc/hexane to afford the corresponding 2,6-disubstituted 4-bromotetrahydropyrans **3a–w**.

4-Bromo-2,6-diphenyltetrahydro-2*H*-pyran (3a)

Yield: 268 mg (85%); colourless solid; mp 86–87 °C.

IR (neat): 2928, 2850, 1665, 1590, 1376, 1288, 1166, 1090, 1051, 1011, 825, 732 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.20 (m, 10 H), 4.54 (dd, *J* = 11.0, 4.5 Hz, 2 H), 4.40 (tt, *J* = 11.0, 4.5 Hz, 1 H), 2.55 (dd, *J* = 12.8, 4.0 Hz, 2 H), 2.08 (q, *J* = 12.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.4, 128.4, 127.7, 125.7, 79.7, 46.1, 45.0, 29.6.

MS (EIMS): *m*/*z* (%) = 237 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{17}H_{17}O$: 237.45569; found: 237.45570.

4-Bromo-2,6-bis(4-bromophenyl)tetrahydro-2*H*-pyran (3b)

Yield: 399 mg (84%); colourless solid; mp 129–130 °C.

IR (neat): 2958, 2928, 2858, 1901, 1686, 1590, 1486, 1407, 1378, 1290, 1115, 1082, 728 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8.0 Hz, 4 H), 7.26 (d, *J* = 8.2 Hz, 4 H), 4.51 (d, *J* = 11.2, 4.8 Hz, 2 H), 4.39 (tt, *J* = 11.2, 4.8 Hz, 1 H), 2.52 (d, *J* = 13.0 Hz, 2 H), 2.04 (q, *J* = 12.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.9, 131.6, 127.4, 121.7, 78.9, 44.7, 45.2.

MS (EIMS): *m*/*z* (%) = 392 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{17}H_{15}Br_2O$: 392.94897; found: 392.94767.

4-Bromo-2,6-di-*p*-tolyltetrahydro-2*H*-pyran (3c)

Yield: 285 mg (83%); colourless solid; mp 92–93 °C.

IR (neat): 3040, 2930, 2820, 1610, 1515, 1465, 1340, 1165, 1050, 955, 777 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 7.8 Hz, 4 H), 7.22 (d, *J* = 7.8 Hz, 4 H), 4.34 (dd, *J* = 11.2, 4.0 Hz, 2 H,), 4.28 (tt, *J* = 11.2, 4.0 Hz, 1 H), 2.46 (s, 6 H), 2.20 (dd, *J* = 12.4, 3.6 Hz, 2 H), 1.94 (q, *J* = 11.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.2, 138.6, 134.9, 129.0, 128.2, 126.9, 78.9, 45.6, 44.2, 30.0, 21.4.

MS (EIMS): *m*/*z* (%) = 265 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{19}H_{21}O$: 265.26610; found: 265.26580.

4-Bromo-2,6-bis(4-chlorophenyl)tetrahydro-2*H*-pyran (3d)

Yield: 321 mg (84%); colourless solid; mp 111–112 °C.

IR (neat): 2958, 2928, 2858, 1901, 1686, 1590, 1486, 1407, 1378, 1290, 1115, 1052, 728 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 8 H), 4.50 (dd, *J* = 9.7, 1.2 Hz, 2 H), 4.36 (tt, *J* = 12.2, 4.8 Hz, 1 H), 2.54 (dd, *J* = 12.2, 4.8 Hz, 2 H), 2.04 (q, *J* = 12.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.0, 133.5, 130.8, 129.4, 128.6, 127.1, 78.9, 44.7, 45.3, 30.0.

MS (EIMS): *m*/*z* (%) = 305 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{17}H_{15}Cl_2O$: 305.05000; found: 305.04989.

4-Bromo-2,6-bis(4-isopropylphenyl)tetrahydro-2*H*-pyran (3e)

Yield: 324 mg (81%); colourless solid; mp 101–102 °C.

IR (neat): 2950, 2821, 2850, 1908, 1680, 1590, 1485, 1407, 1290, 1164, 1082, 728 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.0 Hz, 4 H), 7.18 (d, *J* = 7.8 Hz, 4 H), 4.50 (dd, *J* = 11.2, 1.2 Hz, 2 H), 4.40 (tt, *J* = 11.2, 1.2 Hz, 1 H), 2.96–2.85 (m, 2 H), 2.54 (dd, *J* = 12.2, 3.2 Hz, 2 H), 2.15 (q, *J* = 12.0, 2 H), 1.24 (d, *J* = 7 Hz, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.4, 138.9, 130.8, 128.4, 127.2, 125.8, 45.2, 44.8, 34.4, 30.2, 21.9.

MS (EIMS): *m*/*z* (%) = 321 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{23}H_{29}O$: 321.40719; found: 321.40740.

4-Bromo-2,6-bis(2,4-dichlorophenyl)tetrahydro-2*H*-pyran (3f)

Yield: 378 mg (84%); colourless solid; mp 125–126 °C.

IR (neat): 3092, 2970, 2864, 1897, 1587, 1560, 1469, 1375, 1293, 1203, 1170, 1108, 1083, 1045, 1004, 864, 818, 784 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8.4 Hz, 2 H), 7.36 (d, *J* = 2.1 Hz, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 4.91 (dd, *J* = 11.2, 1.2 Hz, 2 H), 4.48–4.40 (m, 1 H), 2.72–2.65 (m, 2 H), 1.94–1.84 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1, 134.0, 131.8, 129.1, 128.0, 127.6, 76.2, 44.4, 43.1.

MS (EIMS): *m*/*z* (%) = 373 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{17}H_{13}Cl_4O$: 373.20410; found: 373.20412.

4-Bromo-2,6-bis(2,4-difluorophenyl)tetrahydro-2*H*-pyran (3g)

Yield: 310 mg (80%); colourless solid; mp 104–105 °C.

IR (neat): 3050, 2920, 2853, 1610, 1520, 1456, 1410, 1365, 1170, 835, 760 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.54 (td, *J* = 8.4, 6.7 Hz, 2 H), 6.94–6.88 (m, 2 H), 6.84–6.76 (m, 2 H), 4.54 (dd, *J* = 11.1, 1.5 Hz, 2 H), 4.42 (tt, *J* = 12.0, 4.3 Hz, 1 H), 2.57 (dd, *J* = 12.7, 3.9 Hz, 2 H), 2.06 (dd, *J* = 15.8, 11.9 Hz, 2 H).

^{19}F NMR (500 MHz, $CDCl_3$): δ = –110.7780, –110.7930, –115.4618, –115.4768.

^{13}C NMR (125 MHz, $CDCl_3$): δ = (d, $^1J_{CF}$ = 248.8 Hz), 159.3 (d, $^1J_{CF}$ = 249.0 Hz), 159.2 (d, $^1J_{CF}$ = 249.0 Hz), 128.2 (d, $^3J_{CF}$ = 9.1 Hz), 128.1 (d, $^3J_{CF}$ = 10.0 Hz), 160.2 (d, $^1J_{CF}$ = 246 Hz), 136.8 (d, $^4J_{CF}$ =2.7 Hz), 124.2 (d, $^4J_{CF}$ = 3.6 Hz), 124.1 (d, $^4J_{CF}$ = 3.6 Hz), 111.6 (d, $^2J_{CF}$ = 20.8 Hz), 111.5 (d, $^2J_{CF}$ = 21.7 Hz), 103.7 (d, $^2J_{CF}$ = 25.4 Hz), 103.7 (d, $^2J_{CF}$ = 26.3 Hz), 73.5, 44.6, 43.7.

MS (EIMS): *m*/*z* (%) = 309 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{17}H_{13}F_4O$: 309.09025; found: 309.08858.

4-Bromo-2,6-bis(4-(trifluoromethyl)phenyl)tetrahydro-2*H*-pyran (3h)

Yield: 361 mg (80%); colourless solid; mp 113–114 °C.

IR (neat): 3050, 2920, 2853, 1610, 1520, 1456, 1365, 1170, 835, 760 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.0 Hz, 4 H), 7.22 (d, *J* = 8.0 Hz, 4 H), 4.61–4.57 (m, 2 H), 4.42 (tt, *J* = 12.0, 4.3 Hz, 1 H), 2.60–2.54 (m, 2 H), 2.14–2.04 (m, 2 H).

^{19}F NMR (500 MHz, $CDCl_3$): δ = –57.9030.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.2 (d, $^1J_{CF}$ = 246 Hz), 136.8 (d, $^4J_{CF}$ = 2.7 Hz), 127.5 (d, $^3J_{CF}$ = 2.7 Hz), 115.3 (d, $^2J_{CF}$ = 2.7 Hz), 79.0, 45.5, 44.9.

MS (EIMS):*m*/*zz* (%) = 373 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{19}H_{15}F_6O$: 373.76555; found: 373.76540.

4-Bromo-2,6-bis(4-fluorophenyl)tetrahydro-2*H*-pyran (3i)

Yield: 281 mg (84%); colourless solid; mp 98–99 °C.

IR (neat): 3050, 2920, 2853, 1610, 1520, 1456, 1410, 1365, 1170, 835, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 4 H), 7.08–7.01 (m, 4 H), 4.54 (dd, *J* = 11.2, 1.4 Hz, 2 H), 4.41 (tt, *J* = 11.2, 1.4 Hz, 1 H), 2.55–2.49 (m, 2 H), 2.12–2.03 (m, 2 H).

^{19}F NMR (400 MHz, $CDCl_3$): δ = –118.7734, –119.5223.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2 (d, $^1J_{CF}$ = 246 Hz), 136.8 (d, $^4J_{CF}$ = 2.7 Hz), 127.5 (d, $^3J_{CF}$ = 2.7 Hz), 115.3 (d, $^2J_{CF}$ =2.7 Hz), 79.0, 45.5, 44.9.

MS (EIMS): *m*/*z* (%) = 273 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{17}H_{15}F_2O$: 273.10910; found: 273.10974.

4-Bromo-2,6-bis(3-chlorophenyl)tetrahydro-2*H*-pyran (3j)

Yield: 320 mg (84%); colourless solid; mp 104–105 °C.

IR (neat): 2953, 2948, 2858, 1901, 1686, 1486, 1407, 1368, 1368, 1250, 1122, 1052, 728 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36 (s, 2 H), 7.29–7.22 (m, 6 H), 4.52 (dd, *J* = 10.2, 1.8 Hz, 2 H), 4.42–4.28 (m, 1 H), 2.54 (dd, *J* = 12.6, 4.3 Hz, 2 H), 2.07 (q, *J* = 11.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.8, 134.4, 129.8, 128.0, 125.9, 123.9, 79.0, 45.0, 44.6.

MS (EIMS): *m*/*z* (%) = 305 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{17}H_{15}Cl_2O$: 305.05000; found: 305.04989.

4-Bromo-2,6-bis(2-chlorophenyl)tetrahydro-2*H*-pyran (3k)

Yield: 306 mg (85%); colourless solid; mp 103–104 °C.

IR (neat): 2924, 2866, 1685, 1536, 1448, 1363, 1325, 1274, 1127, 1047, 738 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.70 (tt, *J* = 7.5, 1.4 Hz, 2 H), 7.28–7.23 (m, 2 H), 7.16 (tt, *J* = 7.4, 1.1 Hz, 2 H), 7.05–7.00 (m, 2 H), 4.90 (dd, *J* = 11.1, 1.2 Hz, 2 H), 4.44 (tt, *J* = 12.1, 4.4 Hz, 1 H), 2.60 (dd, *J* = 12.6, 4.0 Hz, 2 H), 2.07 (q, *J* = 11.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9 (d, $^1J_{CF}$ = 245.7 Hz), 128.9 (d, $^3J_{CF}$ = 8.1 Hz), 128.2 (d, $^3J_{CF}$ = 13.2 Hz), 127.5 (d, $^4J_{CF}$ =3.7 Hz), 124.2 (d, $^4J_{CF}$ = 2.2 Hz), 115.9 (d, $^2J_{CF}$ = 21.0 Hz), 73.4, 45.1, 43.6.

MS (EIMS): *m*/*z* (%) = 273 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{17}H_{15}F_2O$: 273.10910; found: 273.10974.

4-Bromo-2,6-bis(2-fluorophenyl)tetrahydro-2*H*-pyran (3l)

Yield: 298 mg (80%); colourless solid; mp 93–94 °C.

IR (neat): 2922, 2855, 1684, 1534, 1445, 1366, 1322, 1284, 1122, 1044, 733 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (dd, *J* = 7.6, 1.4 Hz, 2 H), 7.35–7.31 (m, 4 H), 7.25–7.21 (m, 2 H), 4.99 (dd, *J* = 11.2, 1.5 Hz, 2 H), 4.49 (tt, *J* = 12.0, 4.6 Hz, 1 H, 2.72 (dd, *J* = 12.8, 4.4 Hz, 2 H), 1.95 (q, *J* = 11.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.7, 131.1, 129.3, 128.7, 127.2, 127.1, 76.6, 45.2, 43.3.

MS (EIMS): *m*/*z* (%) = 305 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{17}H_{15}Cl_2O$: 305.05000; found: 305.04989.

4-Bromo-2,6-bis(2-bromophenyl)tetrahydro-2*H*-pyran (3m)

Yield: 395 mg (80%); colourless solid; mp 123–124 °C.

IR (neat): 2954, 2920, 2856, 1686, 1590, 1486, 1407, 1377, 1343, 1280, 1115, 1080, 724 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 7.8 Hz, 2 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.38 (t, *J* = 7.6 Hz, 2 H), 4.95 (dd, *J* = 11.2, 1.5 Hz, 2 H), 4.50 (tt, *J* = 12.2, 4.8 Hz, 1 H), 2.76 (dd, *J* = 12.7, 3.2 Hz, 2 H), 1.92 (q, *J* = 12.1 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2, 132.6, 129.1, 127.8, 127.4, 78.8, 45.1, 43.3.

MS (EIMS): *m*/*z* (%) = 392 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{17}H_{15}Br_2O$: 392.94897; found: 392.94767.

4-Bromo-2-heptyl-6-phenyltetrahydro-2*H*-pyran (3n)

Yield: 182 mg (70%); colourless solid; mp 86–87 °C.

IR (neat): 3028, 2924, 2852, 1648, 1451, 1364, 1140, 1081, 1053, 1010, 752 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.18 (m, 5 H), 4.32 (dd, *J* = 11.3, 2.1 Hz, 1 H), 4.22 (tt, *J* = 11.8., 4.5 Hz, 1 H), 3.50–3.40 (m, 1 H), 2.45 (dd, *J* = 12.8, 4.1 Hz, 1 H), 2.28 (dd, *J* = 12.2, 4.2 Hz, 1 H), 1.94 (q, *J* = 11.9 Hz, 1 H), 1.80 (q, *J* = 12 Hz, 1 H), 1.70–1.57 (m, 1 H), 1.56–1.40 (m, 2 H), 1.38–1.20 (m, 9 H), 0.87 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.5, 128.4, 127.6, 125.7, 77.9, 47.0, 45.2, 43.2, 35.8, 29.5, 29.2, 25.3, 22.6, 14.2.

MS (EIMS): *m*/*z* (%) = 259 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{18}H_{27}O$: 259.20619; found: 259.20580.

4-Bromo-2-(4-chlorophenyl)-6-pentyltetrahydro-2*H*-pyran (3o)

Yield: 247 mg (72%); colourless solid; mp 89–90 °.

IR (neat): 2920, 2820, 1642, 1448, 1362, 1260, 1140, 1082, 1050, 974, 832, 752, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.2 Hz, 2 H), 7.28 (d, *J* = 7.8 Hz, 2 H), 4.34 (dd, *J* = 11.8, 2.2 Hz, 1 H), 4.24 (tt, *J* = 11.8, 4.8 Hz, 1 H), 3.48–3.42 (m, 1 H), 2.40 (dd, *J* = 12.6, 4.1 Hz, 1 H), 2.25 (dd, *J* = 12.2, 3.8 Hz, 1 H), 2.02–1.82 (q, *J* = 11.8 Hz, 1 H), 1.84–1.68 (q, *J* = 11.8 Hz, 1 H), 1.68–1.22 (m, 8 H), 0.86 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.2, 128.6, 128.2, 127.8, 126.5, 79.4, 78.2, 46.8, 45.2, 43.2, 35.1, 31.8, 30.9, 25.3, 22.6, 14.1.

MS (EIMS): *m*/*z* (%) = 266 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{16}H_{22}ClO$: 266.21419; found: 266.21580.

(2*R*,2′*R*)-2,2′-[(2*R*,4*S*,6*S*)-4-Bromotetrahydro-2*H*-pyran-2,6-diyl]bis(1,4-dioxaspiro[4.5]decane) (3p)

Yield: 288 mg (65%); colourless solid; mp 113–114 °C.

IR (neat): 2845, 1260, 1150, 1070, 945, 888, 750 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.37–4.25 (m, 1 H), 4.05 (tt, *J* = 10.8, 2.2 Hz, 2 H), 3.92–3.82 (m, 4 H), 3.41–3.32 (m, 2 H), 2.52 (dd, *J* = 12.4, 3.8 Hz, 2 H), 2.21–1.88 (m, 4 H), 1.78–1.14 (m, 18 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 121.6, 83.4, 79.2, 68.9, 41.4, 34.9, 33.1, 27.2, 24.6.

MS (EIMS): *m*/*z* (%) = 365 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{21}H_{33}O_5$: 365.24064; found: 365.24127.

4-Bromo-2,6-dihepyltetrahydro-2*H*-pyran (3q)

Yield: 282 mg (82%); colourless solid; mp 97–98 °C.

IR (neat): 2925, 2852, 1465, 1325, 1370, 1325, 1258, 1151, 1083, 1024, 961, 781, 566, 1269, 1183, 1014, 718 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.07 (tt, *J* = 11.9, 4.9 Hz, 1 H), 3.22–3.16 (m, 2 H), 2.17 (dd, *J* = 11.9, 4.0 Hz, 2 H), 1.64 (q, *J* = 11.9 Hz, 2 H), 1.56–1.16 (m, 24 H), 0.90 (t, *J* = 6.8 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 77.4, 47.4, 43.6, 35.6, 31.7, 30.0, 29.9, 29.6, 21.9, 14.1.

MS (EIMS): *m*/*z* (%) = 281 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{19}H_{37}O$: 281.28444; found: 281.28534.

4-Bromo-2,6-dinonyltetrahydro-2*H*-pyran (3r)

Yield: 353 mg (83%); colourless solid; mp 104–105 °C.

IR (neat): 2923, 2851, 1467, 1328, 1330, 1297, 1242, 1151, 1151, 1087, 1034, 991, 718 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.08 (tt, *J* = 11.9, 4.9 Hz, 1 H), 3.26–3.12 (m, 2 H), 2.18 (dd, *J* = 12.0, 4.2 Hz, 2 H), 1.65 (q, *J* = 12.2 Hz, 2 H), 1.56–1.16 (m, 2 H), 1.54–1.22 (m, 30 H), 0.92–0.86 (t, *J* = 6.9 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 77.6, 47.5, 43.5, 35.9, 31.8, 29.5, 29.2, 25.5, 22.6, 14.1.

MS (EIMS): *m*/*z* (%) = 337 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{23}H_{45}O$: 337.34704; found: 337.34677.

4-Bromo-2,6-dihexyltetrahydro-2*H*-pyran (3s)

Yield: 282 mg (82%); colourless solid; mp 91–92 °C.

IR (neat): 2925, 2854, 1466, 1365, 1370, 1269, 1225, 1152, 1183, 1014, 718 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.07 (tt, *J* = 11.8, 4.3 Hz, 1 H), 3.30–3.15 (m, 2 H), 2.18 (dd, *J* = 12.4, 4.3 Hz, 2 H), 1.65 (q, *J* = 12.1 Hz, 2 H), 1.54–1.22 (m, 20 H), 0.88 (t, *J* = 6.9 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 77.6, 47.4, 43.6, 35.9, 31.8, 29.2, 25.5, 22.6, 14.08.

MS (EIMS): *m*/*z* (%) = 253 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{17}H_{33}O$: 253.25314; found: 253.25214.

4-Bromo-2,6-diethyltetrahydro-2*H*-pyran (3t)

Yield: 183 mg (78%); colourless solid; mp 61–62 °C.

IR (neat): 2952, 2854, 1440, 1330, 1242, 1150, 1082, 1020, 718, 562 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.10 (tt, *J* = 11.7, 1.4 Hz, 1 H), 3.18–3.10 (m, 1 H), 1.24–1.16 (m, 1 H), 1.70–1.40 (m, 6 H), 0.88 (t, *J* = 8.0 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 78.1, 45.2, 43.8, 29.9, 26.6, 9.4.

MS (EIMS): *m*/*z* (%) = 141 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_9H_{17}O$: 141.13584; found: 141.13687.

4-Bromo-2,6-dipropyltetrahydro-2*H*-pyran (3u)

Yield: 210 mg (79%); colourless solid; mp 68–69 °C.

IR (neat): 2950, 2840, 1365, 1278, 1180, 1070, 1025, 760 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.08 (tt, *J* = 12.0, 3.8 Hz, 1 H), 3.26–3.18 (m, 2 H), 2.16 (dd, *J* = 12.0, 3.8 Hz, 2 H), 1.64 (q, *J* = 12.0, 3.8 Hz, 2 H), 1.56–1.24 (m, 8 H), 0.88 (t, *J* = 6.8 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 76.8, 45.3, 44.2, 36.2, 29.8, 29.2, 21.8, 14.0.

MS (EIMS): *m*/*z* (%) = 169 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{11}H_{21}O$: 169.65464; found: 169.65460.

4-Bromo-2,6-diisopropyltetrahydro-2*H*-pyran (3v)

Yield: 202 mg (80%); colourless solid; mp 66–67 °C.

IR (neat): 2945, 2853, 2460, 1325, 1242, 1151, 1080, 1025, 716, 562 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.08 (tt, *J* = 11.5, 4.4 Hz, 1 H), 2.95–2.90 (m, 2 H), 2.19 (dd, *J* = 12.2, 4.5 Hz, 2 H), 1.72–1.58 (m, 4 H), 0.92 (d, *J* = 6.4 Hz, 6 H), 0.88 (d, *J* = 6.4 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 79.8, 45.4, 44.2, 30.8, 30.1, 19.2.

MS (EIMS): *m*/*z* (%) = 169 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{11}H_{21}O$: 169.64340; found: 169.64321.

4-Bromo-2,6-dipentyltetrahydro-2*H*-pyran (3w)

Yield: 258 mg (81%); colourless solid; mp 82–83 °C.

IR (neat): 2932, 2855, 1465, 1365, 1378, 1280, 1230, 1180, 1160, 1080, 1015, 730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.08 (tt, *J* = 12.40, 4.3 Hz, 1 H), 3.26–3.17 (m, 2 H), 2.20 (dd, *J* = 12.4, 3.6 Hz, 2 H), 1.65 (q, *J* = 12.4, Hz, 2 H), 1.57–1.23 (m, 16 H), 0.88 (t, *J* = 7.3 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 77.6, 47.5, 43.5, 35.8, 30.8, 29.2, 25.5, 22.4, 14.07.

MS (EIMS): *m*/*z* (%) = 225 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{15}H_{29}O$: 225.64632; found: 225.64644.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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First diastereoselective total synthesis of bicyclic styryl lactone: (1*R*,5*R*,7*R*)-7-((*E*)-styryl)-2,6-dioxabicyclo[3.3.1]nonan-3-one

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ABSTRACT

A concise and facile diastereoselective first total synthesis of bicyclic styryl lactone **1** is described in nine steps. This biologically active bicyclic styryl lactone was obtained in 8% overall yield from cinnamaldehyde **2** and (*R*)-3-hydroxyhex-5-enoic acid **3**. Jacobsen resolution, Pinnick oxidation and Prins cyclisation reactions are the key steps involved in the synthesis.

Introduction

2,6-Dioxabicyclo[3.3.1]nonan-3-one (pyranopyrone) skeleton is found in many natural products such as cryptocaryolone, cryptocaryolone diacetate, leiocarpin A and polyrhacitide A & B which were isolated from the bark extract of a South African plant *Cryptocarya latifolia* [1], a Chinese plant *Goniothalamus leiocarpus* [2] and Chinese ant species *Polyrhacis lamellidens* [3] respectively (Fig. 1). These natural products are known to exhibit promising biological activities [4–6]: Cryptocaryolone containing bark extract has been used for the treatment of headaches, morning sickness, cancer, pulmonary diseases, and a variety of other bacterial and fungal infection [4]. Leiocarpin A exhibited excellent anticancer activity against different type of Cancer cells [5]. The ant extract has been used as a folk medicine in the treatment of rheumatoid arthritis and hepatitis in China and the ethanolic extract that contains polyrhacitides A & B was found to display significant analgesic and anti-inflammatory effects [6]. Drewes, *et. al.* have reported the isolation of bicyclic styryl lactone **1** from the bark of South African tree *Cryptocarya wyliei* [1] in the racemic form along with related natural products acetyl and deacetyl-cryptocaryalactones. After three years the same group reported compound **1** prepared from acetyl and deacetyl-cryptocaryalactones by a base induced cyclization [7]. The structure of bicyclic styryl lactone **1** was identified based on exhaustive NMR studies and the absolute configuration was assigned from the X-ray crystal data and correlation of stereogenic centers in the parent cryptocaryalactones to establish the absolute configuration as (*1R,5R,7R*)-pyranopyrone [1,7]. The absolute and relative stereochemistries of pyranopyrone core of leiocarpin A and bicyclic styryl lactone found identical. As these natural products are available in very scarce amounts, total synthesis becomes a viable approach for its availability towards exploring the biological properties. Several synthetic approaches have been developed for the synthesis of natural products having 2,6-dioxabicyclo[3.3.1]nonan-3-one skeleton through oxy-Michael, iodo-lactonization, hetero-Diels-Alder reaction, domino-Aldol reaction, *cis*-Wittig olefination and Baylis-Hillman reaction as key steps [8]. To date no report has been available for the total synthesis of bicyclic styryl lactone **1**.

Results and discussion

Because of the intriguing structural features and inherent biological properties of bicyclic styryl lactone **1**, we were interested in developing an efficient synthetic route to prepare this bicyclic compound. Intermolecular Prins cyclisation is the most effective method for stereoselective synthesis of natural products possessing THP ring, fused/bridged oxacycles and spirocycles [9]. We developed a novel coupling partner **3** that comprises homoallyl alcohol with a carboxylic acid group. This partner is anticipated to undergo Prins cyclization and then intramolecular esterification to produce the complex bicyclic lactone [10]. In this paper, a novel method for the one-step synthesis of bicyclic styryl lactone **1** using tandem Prince cyclization lactonization, involves coupling cinnamaldehyde **2** and (*R*)-3-hydroxyhex-5-enoic acid **3** in the

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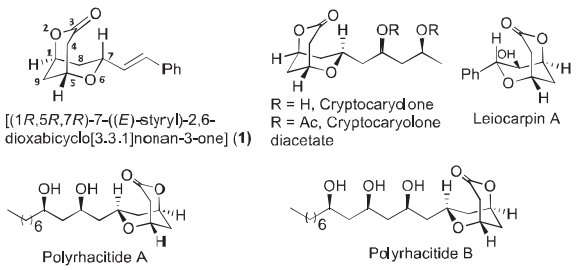


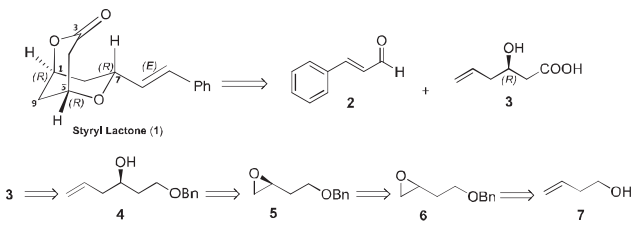
Fig. 1. Natural products harboring a bicyclic lactone (Pyranopyrone) skeleton.

presence of a Lewis acid catalyst, is provided.

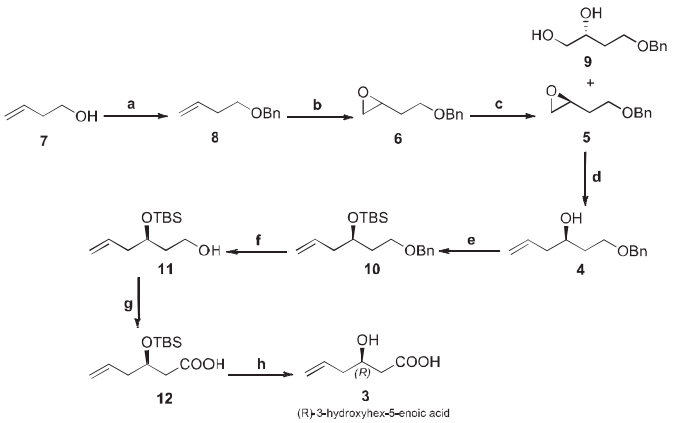
Bicyclic styryl lactone **1** can be synthesized according to the retrosynthetic analysis shown in Scheme 1. Retrosynthetically, it was envisaged that the target compound could be obtained from the key precursor (*R*)-3-hydroxyhex-5-enoic acid **3** which can undergo TMSOTf mediated one-pot Prins cyclisation to give target molecule **1**. The precursor **3** can be synthesized from chiral epoxide **5** following a three-step sequence involving regioselective ring opening of epoxide **5** by vinyl Grignard, secondary hydroxyl group protection, primary hydroxyl group deprotection, Pinnick oxidation and deprotection of secondary hydroxyl group as the key steps. The chiral epoxide **5** in turn can be obtained from Jacobsen resolution of racemate **6**. Racemate **6** can be obtained from homoallylic alcohol **7** following a two-step sequence involving hydroxyl group protection and epoxidation (Scheme 1).

As depicted in Scheme 2 the synthesis of styryl lactone **1** was began from homoallylic alcohol **7**, which was subjected to benzylation using NaH and BnBr in THF to obtain benzyl ether **8** in 90 % yield. The compound **8** was subjected to an epoxidation using MCPBA in CH_2Cl_2 to yield the product **6** as a racemic mixture in 80 % yield. An important element to our synthetic strategy is the utility of asymmetric Jacobsen resolution reaction to establish the initial asymmetry. Thus, Jacobsen hydro kinetic resolution of racemic epoxide **6** using (*S,S*)-(Salen) Co (II) complex [11] in AcOH provided chiral epoxide **5** with desired stereogenic center in 46 % yield (96 % ee) along with side product diol **9** in 48 % yield (98 % ee) Scheme 2. Regioselective ring-opening of compound **5** with vinyl magnesium bromide [12] in THF provided corresponding homoallylic alcohol **4** in 90 % yield. The resulting homoallylic alcohol **4** was then reacted with TBSCl, Imidazole, and a catalytic DMAP in CH_2Cl_2 to get silyl ether **10** in 92 % yield [13]. Chemoselective benzyl ether deprotection of compound **10** was achieved using Li, naphthalene, in THF yielded the primary alcohol **11** in 80 % yield [14]. The alcohol was then converted to corresponding aldehyde by reacting with Dess-Martin periodinane [15]. Subsequently it was subjected for Pinnick oxidation [16] employing $NaClO_2$, 2-Methyl-2-butene in *t*-BuOH-H_2O (3:1) to give the desired carboxylic acid **12** in 85 % yield. Deprotection of secondary hydroxyl group of carboxylic acid **12** utilizing TBAF in THF gave the required starting material **3** in 84 % yield [17].

After, having two coupling fragments (*R*)-3-hydroxyhex-5-enoic acid **3** and cinnamaldehyde **2** in hand we went for the tandem one pot coupling–cyclization reaction. A 10 mol % TMSOTf was added to a mixture of compounds **3** and **2** in CH_2Cl_2 at −40 and stirring at 0 °C for 2 h yielded the bicyclic styryl lactone **1** exclusively as a single diastereomer



Scheme 1. Retrosynthetic Analysis of bicyclic styryl lactones.



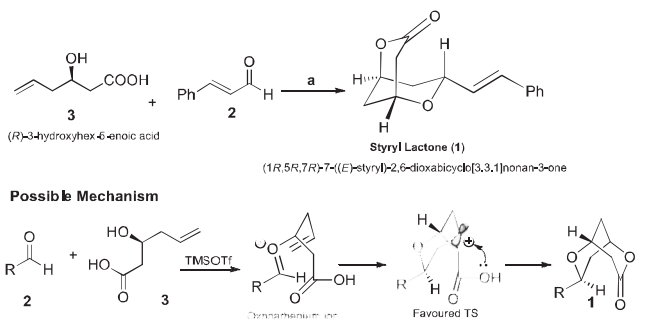
Scheme 2. Reagents and conditions: (a) NaH, BnBr, THF, rt, 1 h, 90 %; (b) MCPBA, CH_2Cl_2, 0 °C-rt, 6 h, 80 %; (c) (S,S) Co-(Salen), AcOH, H_2O, THF, 0 °C-rt, 22 h, 46 %; (d) Vinyl bromide, Mg, THF, 1,2-dibromoethane, CuCN, −78–40 °C, 6 h, 90 %; (e) TBSCl, Imidazole, CH_2Cl_2, DMAP, 0 °C-rt, 1 h, 92 %; (f) Li, Naphthalene, THF, −25 °C, 1 h, 80 %; (g) i) DMP, CH_2Cl_2, 2 h, 80 %; ii) $NaClO_2$, *t*-BuOH-H_2O (3:1), 2-methyl-2-butene, 0 °C-rt, 2 h, 85 %; (h) TBAF, THF, 0 °C-rt, 3 h, 84 %.

in 50 % yield [18,19]. A possible mechanism [20] for the Prins cyclisation and subsequent intramolecular cyclisation was represented in Scheme 3. The structure of bicyclic styryl lactone **1** was derived through NMR experiments such as NOESY, TOCSY, DQFCOSY, HSQC and HMBC. The analytical data was found to be identical and optical rotation was comparable with the reported data of both the natural [1,7] and synthetic product.

The coupling constants $^3J_{H\text{-}1/H\text{-}8a} = 6.0$ Hz, $^3J_{H\text{-}1/H\text{-}8b} = 2.2$ Hz, $^3J_{H\text{-}1/H\text{-}9a} = 4.2$ Hz, $^3J_{H\text{-}1/H\text{-}9b} = 2.0$ Hz indicating that H-1 equitorial to H-9a, H-9b and H-8a, H-8b protons. The large di-axial coupling $^3J_{H\text{-}7/H\text{-}8b} = 11.7$ Hz and di equitorial coupling $^3J_{H\text{-}7/H\text{-}8a} = 2.6$ Hz and strong NOE correlations, H-4a/H-7, H-4b/h-9b and H-8b/H-9a are consistent with the chair conformation of the six membered ring (Fig. 2). The energy minimized structure adequately supports the proposed structure of bicyclic styryl lactone 1.

Conclusion

In conclusion, a concise and stereoselective first total synthesis of bicyclic styryl lactone 1 has been accomplished in nine steps with an 8 % overall yield. Jacobsen hydrolytickinetic resolution of epoxide, selective oxidation using Pinnick oxidation and a tandem Prins cyclisation lactonization reactions are the key steps involved in the synthesis of natural bicyclic styryl lactone. This approach may find wide applications in exploring the synthesis of other bioactive molecules containing pyranopyrone skeleton.



Scheme 3. Plausible mechanism; Reagents and conditions: (a) 10 mol %, TMSOTf, CH_2Cl_2, −40 °C, 2 h, 50 %.

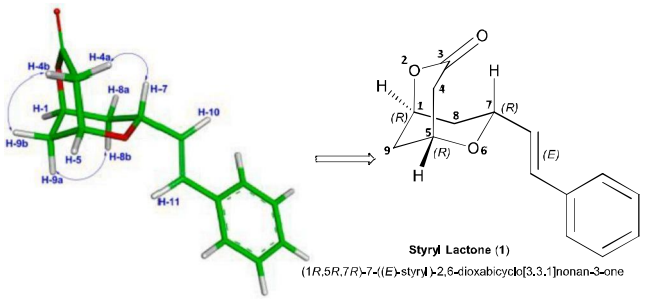


Fig. 2. Energy minimized structure (NOE) of bicyclic styryl lactone **1**.

CRediT authorship contribution statement

Dhanraj O. Biradar: Investigation, Methodology. **Yogesh D. Mane:** Writing – review & editing. **A.V. Narsaiah:** Conceptualization, Supervision. **B.V. Subba Reddy:** Conceptualization, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dhanraj O Biradar reports financial support was provided by CSIR New Delhi.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rechem.2022.100717.

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[17] Spectral data for few selected compounds: (*R*)-2-[2-(Benzyloxy)ethyl]oxirane (**5**): Colorless oil, $[\alpha]_D^{22} = +16.3$ ($c = 1.5$, $CHCl_3$); Lit. + 16.0 ($c = 2$, $CHCl_3$), IR (KBr): ν_{max} 3489, 3031, 2996, 2922, 2860, 1492, 1453, 1260, 1103, 1025, 908, 833, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40-7.26 (m, 5H), 4.52 (s, 2H), 3.62 (dd, J = 9.6, 3.7 Hz, 2H), 3.12-3.02 (m, 1H), 2.78 (t, J = 4.5 Hz, 1H), 2.52 (dd, J = 5.0, 2.7 Hz, 1H), 1.98-1.70 (m, 2H); ^{13}C NMR (124 MHz, $CDCl_3$): δ 138.1, 128.1, 127.3, 72.8, 66.8, 49.8, 46.8, 32.7; MS-ESIMS: *m/z* 178 $[M+H]^-$; HRMS calcd for $C_{12}H_{14}O_2$: $[M+H]^+$ 178.84442, found 178.84460; (*R*)-1-(Benzyloxy)hex-5-en-3-ol (**4**): Colorless liquid, $[\alpha]_D^{22} = -2.0$ ($c = 1.5$, $CHCl_3$), IR (KBr): ν_{max} 3440, 3069, 3030, 2919, 2862, 1640, 1495, 1364, 1206, 1096, 1026, 914, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 5.88-5.78 (m, 1H), 5.14-5.07 (m, 2H), 4.52 (s, 2H), 3.91-3.84 (m, 1H), 3.75-3.62 (m, 2H), 2.90 (s, 1H), 2.27-2.23 (m, 2H), 1.79-1.71 (m, 2H); ^{13}C NMR (124 MHz, $CDCl_3$): δ 137.7, 134.6, 128.1, 127.3, 117.1, 73.0, 69.5, 68.2, 41.6, 35.6; MS-ESIMS: *m/z* 207 $[M+H]^+$, 229 $[M+Na]^-$; HRMS calcd for $C_{13}H_{19}O_2$: $[M+H]^+$ 207.13796, Found 207.13738; (*R*)-3-Hydroxyhex-5-enoic acid (**3**): Colorless oil, $[\alpha]_D^{22} = -112.2$ ($c = 0.48$, $CHCl_3$), IR (KBr): ν_{max} 3404, 3077, 2926, 2855, 1718, 1644, 1404, 1176, 1054, 995, 920 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.81 (ddd, J = 15.0, 11.8, 6.4 Hz, 1H), 5.15 (dd, J = 9.6, 6.6 Hz, 2H), 4.16-4.09 (m, 1H), 2.61-2.43 (m, 2H), 2.37-2.24 (m, 2H); ^{13}C NMR (124 MHz, $CDCl_3$): δ 176.7, 133.6, 118.4, 67.4, 40.8, 40.5, 18.5; MS-ESIMS: *m/z* 131 $[M+H]^+$, 153 $[M+Na]^+$; HRMS calcd for $C_7H_{14}O_2Na$ $[M+Na]^+$ 153.08860, found 153.08826; (1R,5R,7R)-7-((E)-Styryl)-2,6-dioxabicyclo[3.3.1] nonan-3-one (**1**): White solid, mp= 155-157 °C, $[\alpha]_D^{22} = +4.83$ (*c* 0.40, $CHCl_3$), IR (KBr): ν_{max} 3419, 2924, 2853, 1744, 1462, 1377, 1161, 1112, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.34-7.16 (m, 5H), 6.57 (d, J = 15.9 Hz, 1H), 6.08 (dd, J = 15.9, 6.1 Hz, 1H), 5.00-4.94 (m, 1H), 4.50- 4.44 (m, 2H), 2.92 (d, J = 19.3 Hz, 1H), 2.78 (dd, J = 19.3, 5.3 Hz, 1H), 2.31-2.20 (m, 2H), 2.15-2.08 (m, 1H), 2.02 (ddd, J = 11.2, 6.6, 4.6 Hz, 1H), 1.94-1.88 (m, 1H), 1.71 (ddd, J = 13.9, 11.8, 2.0 Hz, 1H); ^{13}C NMR (124 MHz, $CDCl_3$): δ 169.6, 136.2, 131.7, 128.6, 128.1, 128.0, 126.5, 72.8, 66.8, 66.1, 37.1, 36.5, 31.9; MS-ESIMS: *m/z* 245 $[M+H]^+$, 267 $[M+Na]^+$; HRMS calcd for $C_{15}H_{16}O_3Na$: $[M+Na]^+$ 267.09894, found 267.09917.
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Stereoselective total syntheses of dodoneine and its diastereomer, epidodoneine via Prins cyclisation

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ABSTRACT

The diastereoselective total syntheses of dodoneine (**1**) and epidodoneine (**2**) have been accomplished with an overall yield 11.2%. The key steps involved in this approach are Jacobsen hydrolytic kinetic resolution, Prins cyclisation and ring closing metathesis (RCM). The Prins cyclisation has successfully been utilized for the first time to construct *anti*-1,3-diols, which are key precursors for dodoneine and its diastereomer, epidodoneine. This approach is highly diastereoselective to generate the required stereocenters of the natural product.

1. Introduction

Natural products play an important role in the development of novel bioactive substances [1,2]. Due to their remarkable biological activity and fascinating structural features, the lactones are exceptional representatives of secondary metabolites. In particular, α,β-unsaturated δ-lactones, or pyranones are widely distributed in the Nature (Fig. 1). Naturally occurring α,β-unsaturated δ-lactones have recently received a considerable attention from the scientific community due to their impressive architecture and diverse biological activities [3] including apoptosis induction [4] anti-inflammatory [5], anticancer, [6] antituberculosis, [7] antimicrobial, [8–11] and HIV protease inhibition. [12] Besides biological activities, α,β-unsaturated δ-lactones are widely used in perfumes and food industries because of their organoleptic properties. [13] The α,β-unsaturated δ-lactone or pyranone moiety plays an important role in the bioactivity as it can act as a Michael acceptor in the presence of protein functional groups [14]

Dodoneine (**1**), ((*R*)-6-[(*S*)-2-hydroxy-4 (4-hydroxyphenyl) butyl]-5,6-dihydropyran-2-one), is an α,β-unsaturated δ-lactone, isolated from *Tapinunthus dodoneifolius* that grows on the sheanut tree in Loumbila, West Africa, [15] and *Agelanthus dodoneifolius*, a plant that is used in African traditional medicine for the treatment of cardiovascular diseases. [16] *T. dodoneifolius* is a known medicinal plant, which is used in the treatment of respiratory diseases, cholera, diarrhea, abdominal pain and wounds. [17] The structure of the dodoneine (**1**) was determined by spectroscopic methods and X-ray crystallographic analysis of its camphor sulfonate derivative. Dodoneine exhibits diverse biological activities such as HIV protease inhibition, apoptosis induction, anti-leukemic effect and potent vasorelaxant effect with an IC_{50} value of 81.4 ± 0.9 μM. [18] Inspired by its interesting structural features and promising biological activities, many synthetic strategies have developed for its total synthesis. Indeed, several research groups have reported the synthesis of dodoneine (**1**) using asymmetric Keck-allylation, Horner–Wadsworth–Emmons olefination reaction, Sharpless asymmetric epoxidation, Grubbs ring-closing metathesis, Jacobson's hydrolytic kinetic resolution, allylboration, allyltitanation and Still-Gennary modified Horner–Wadsworth–Emmons reaction [19].

Following our interest on the total synthesis of biologically active natural products having α,β-unsaturated δ-lactone motif, we wish to report the total syntheses of dodoneine (**1**) and its diastereomer, epidodoneine (**2**).

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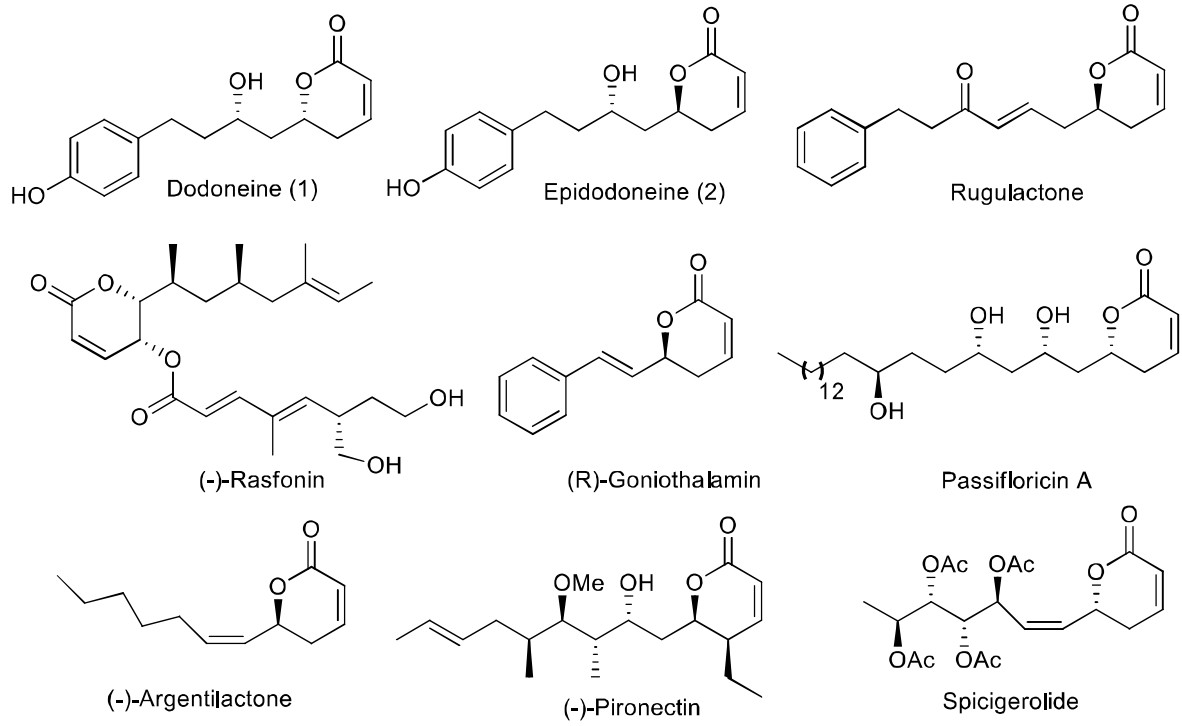


Fig. 1. Examples of 5,6-dihydropyran-2-one containing natural products.

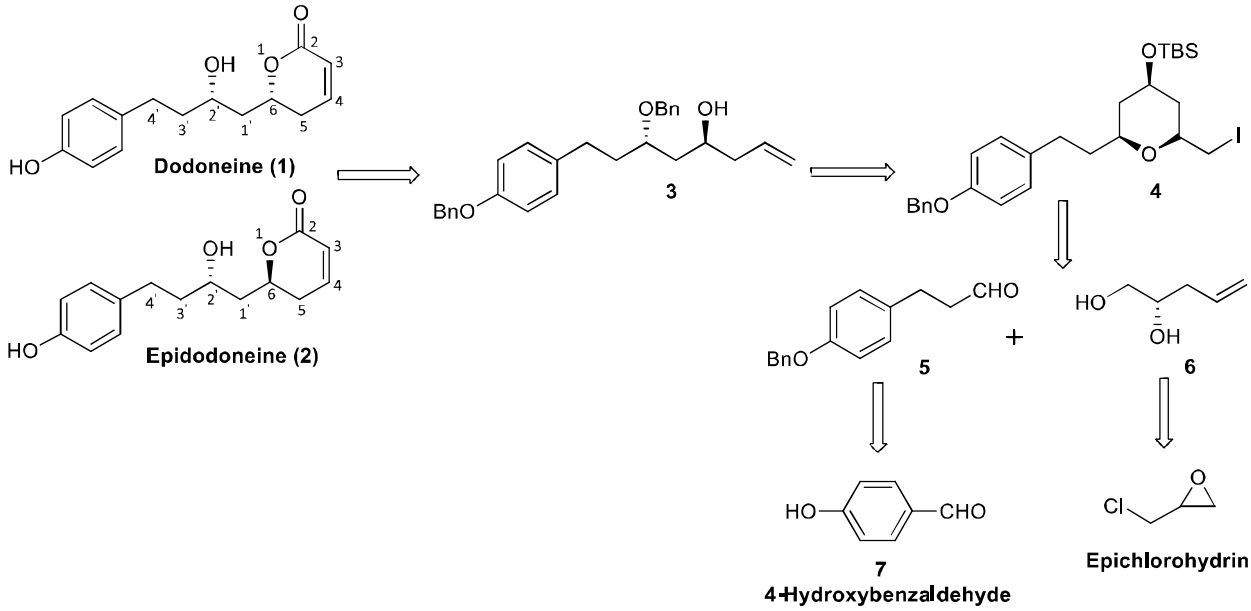
2. Results and discussion

2.1. The retrosynthetic analysis

The retrosynthetic analysis of dodoneine (**1**) and epidodoneine (**2**) is shown in Scheme 1. Dodoneine (**1**) and its diastereomer (**2**) could be synthesized via a Grubb's metathesis from homoallylic alcohol (**3**), which could in turn be accessed from tetrahydropyran (**4**) through a Zn mediated ring opening. Tetrahydropyran (**4**) could be prepared by Prins cyclisation from the aldehyde (**5**) and homoallylic alcohol (**6**), which could be derived from aldehyde (**7**) and epichlorohydrin respectively.

2.2. Synthesis of dodoneine (1) and epidodoneine (2)

The synthesis commenced from a commercially available racemic epichlorohydrin, which was protected as its benzyl ether (**8**) in 94% yield using BnOH and NaH in THF. The Jacobsen



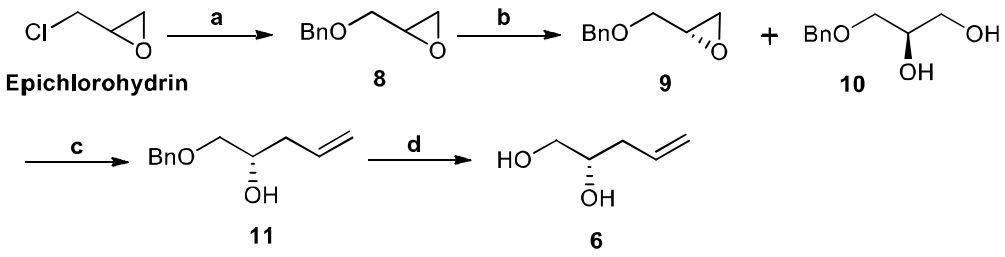
Scheme 1. Retrosynthetic analysis of Dodoneine (**1**)/Epidodoneine (**2**).

hydrolytic kinetic resolution of oxirane (**8**) using (*R*,*R*)-(salen)Co(II) complex [20] in AcOH and H_2O afforded the (*S*)-benzylglycidyl ether (**9**) in 46% yield with 96% ee and (*R*)-diol (**10**) in 48% yield with 98% ee (Scheme 2). Regioselective ring-opening of (*S*)-oxirane (**9**) with vinyl magnesium bromide in the presence of CuCN produced the (*S*)-1-(benzyloxy)pent-4-en-2-ol (**11**) in 92% yield [21]. Debenzylation of the homoallylic alcohol (**11**) using sodium in liquid NH_3 afforded the (*S*)-pent-4-ene-1,2-diol (**6**) in 90% yield [22].

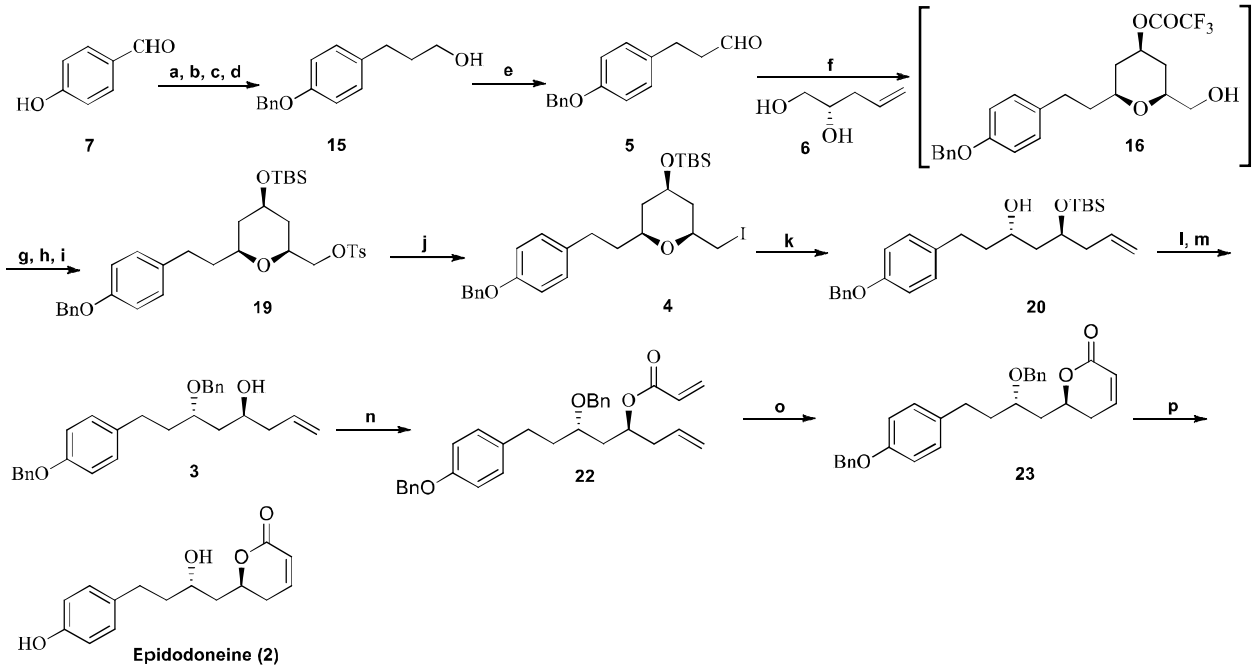
The synthesis begun from *p*-hydroxybenzaldehyde (**7**), which was subjected to benzylation using BnBr and K_2CO_3 in acetone to afford the benzylated aldehyde (**12**) in 95% yield [23]. The C2-Wittig reaction of aldehyde (**12**) gave the α,β-unsaturated ester (**13**) in 90% yield [24]. Reduction of the α,β-unsaturated ester (**13**) using Mg in methanol afforded the saturated methyl ester (**14**) in 85% yield [25]. The ester (**14**) was further reduced with $LiAlH_4$ in dry THF to afford the alcohol (**15**) in 80% yield. [26] Further the oxidation of primary alcohol (**15**) under Swern conditions furnished the corresponding aldehyde (**5**) in 94% yield [27].

An intermolecular Prins cyclisation [28] of the aldehyde (**5**) and (*S*)-pent-4-ene-1,2-diol (**6**) in the presence of TFA afforded the trifluoroacetate (**16**) which up on subsequent hydrolysis with K_2CO_3 in MeOH gave the trisubstituted tetrahydropyran (**17**) in 65% yield. The stereochemical aspects of Prins cyclisation have previously been discussed in detail. [29,30] Regioselective tosylation [31] of tetrahydropyran (**17**) gave the primary tosylate (**18**) in 95% yield. Protection of the secondary alcohol **18** with TBSCl, imidazole, and a catalytic DMAP in CH_2Cl_2 gave the TBS ether (**19**) in 94% yield. [32] Treatment of tosylate (**19**) with NaI in acetone under reflux conditions afforded the corresponding iodide (**4**) in 95% yield. [33] The reductive ring-opening of iodo compound (**4**) using unactivated Zn in refluxing EtOH furnished the key intermediate (**20**) with a required *anti*-1,3-diol in 92% yield [34].

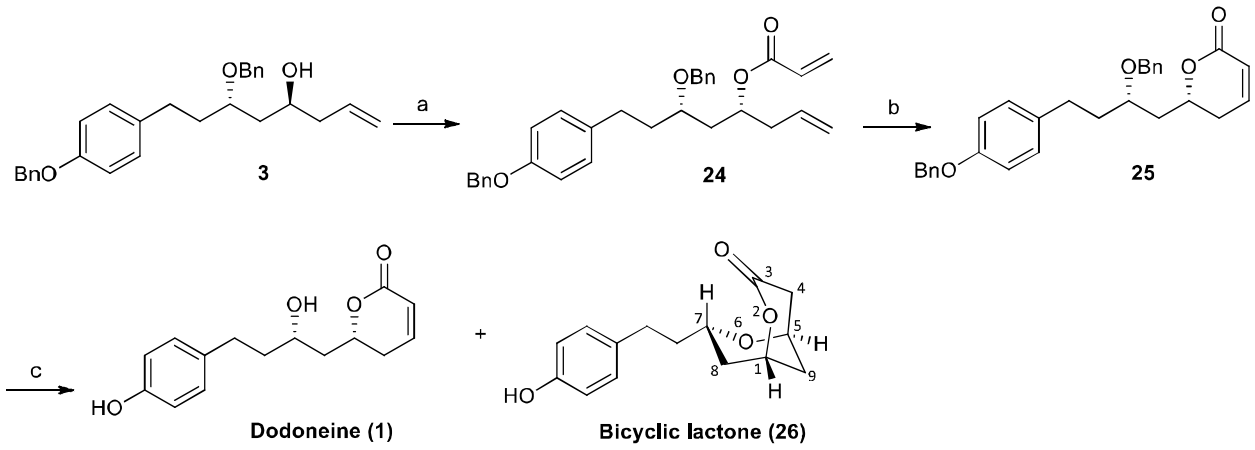
Having a key intermediate **20**, in hand with expected stereochemistry, the newly created secondary hydroxy group of **20** was protected as its benzyl ether (**21**) in 88% yield [35] using sodium hydride, benzyl bromide and a catalytic amount of tetrabutylammonium iodide. Desilylation [36] of TBS ether **21** using CSA in MeOH afforded the alcohol (**3**), as a common intermediate for the synthesis of dodoneine and *epi*-dodoneine, in 90% yield. Esterfication of the alcohol (**3**) [37] with acryloyl chloride using triethyl amine and DMAP in CH_2Cl_2 resulted in the formation of acrylate (**22**) in 85% yield. RCM reaction of the *bis*-olefinic acrylate (**22**) using Grubbs 1st generation catalyst in CH_2Cl_2 afforded the α,β-



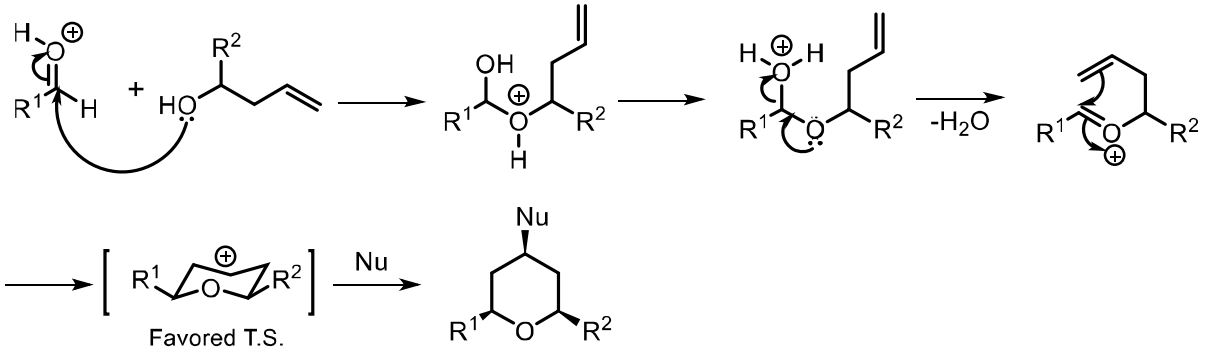
Scheme 2. Reagents and conditions: (a) NaH, BnOH, THF, 0 °C-rt, 12 h, 94%; (b) (*R*,*R*)Co-Salen, AcOH, H_2O, THF, 0 °C-rt, 36 h, 46%; (c) CH_2=CH–MgBr, THF, CuCN, 1,2-dibromoethane, −78 to −40 °C, 4 h, 92%; (d) Na, Liq. NH_3, THF, −30 °C, 20 min, 90%.



Scheme 3. Reagents and conditions: (a) K_2CO_3, BnBr, TBAI, Acetone, reflux, 4 h, 95%; (b) $PPh_3CHCOOEt$, C_6H_6, reflux, 3 h, 90%; (c) Mg, Dry MeOH, 0 °C-rt, 4 h, 85%; (d) LAH, THF, 0 °C-rt, 6 h, 80%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 2 h, 94%; (f) (*S*)-pent-4-ene-1,2-diol (**6**), TFA, CH_2Cl_2, 0 °C-rt, 3 h; (g) K_2CO_3, MeOH, rt, 0.5 h, 65%; (h) TEA, TsCl, CH_2Cl_2, 0 °C-rt, 6 h, 95%; (i) TBSCl, imidazole, DMAP, CH_2Cl_2, 0 °C-rt, 12 h, 94%; (j) NaI, Acetone, reflux, 24 h, 95%; (k) Zn, EtOH, reflux, 4 h, 92%; (l) NaH, BnBr, TBAI, THF, 0 °C-rt, 4 h, 88%; (m) CSA, MeOH, 0 °C-rt, 2 h, 90%; (n) Acryloyl chloride, Et_3N, DMAP, 0 °C-rt, 0.5 h, 85%; (o) Grubbs' first generation catalyst, CH_2Cl_2, reflux, 18 h, 79%; (p) $TiCl_4$, DCM, 0 °C, 0.5 h, 74%.



Scheme 4. Reagents and conditions: (a) Acrylic acid, TPP, DEAD, 0 °C-rt, 4 h, 69%; (b) Grubbs' first generation catalyst, CH_2Cl_2, reflux, 18 h, 75%; (c) $TiCl_4$, DCM, 0 °C, 0.5 h, 56%.



Scheme 5. A plausible reaction pathway.

unsaturated δ-lactone (**23**) in 79% yield. [38] Finally the debenzylation[39] of α,β-unsaturated δ-lactone (**23**) using $TiCl_4$ gave the *Epi*-dodoneine (**2**) in 74% yield with $[\alpha]_D^{20} = -24.8$ (*c* 0.06, $CHCl_3$); Lit. $[\alpha]_D^{25} = -26.7$ (*c* 1, $CHCl_3$) [40] (Scheme 3).

Esterification of the alcohol (**3**) with acrylic acid under Mitsunobu conditions [41] using TPP and DEAD in THF gave the *bis*-olefinic acrylate (**24**) in 69% yield. The *bis*-olefinic acrylate (**24**) on RCM reaction using Grubbs 1st generation catalyst [38] in CH_2Cl_2 afforded the α,β-unsaturated δ-lactone (**25**) in 75% yield. $TiCl_4$-catalyzed debenzylation [39] of α,β-unsaturated δ-lactone (**25**) gave the dodoneine (**1**) with $[\alpha]_D^{22} = +41.3$ (*c* 0.44, $CHCl_3$); Lit. $[\alpha]_D^{25} = +40.2$ (*c* 0.4, $CHCl_3$) [42] in 56% yield and bicyclic lactone (**26**) with $[\alpha]_D^{20} = -34.2$ (*c* 0.42, $CHCl_3$); Lit. $[\alpha]_D^{25} = -33.5$ (*c* 0.45, $CHCl_3$) [43] and Lit. $[\alpha]_D^{25} = -32.9$ (*c* 0.5, $CHCl_3$) [43] in 31% yield (Scheme 4). The spectral data of thus synthesized dodoneine (**1**) and epidodoneine (**2**) were identical with reported natural products.

A plausible reaction pathway and stereochemical outcome of the Prins cyclisation is shown in Scheme 5.

3. Conclusions

In conclusion, we have successfully demonstrated the diastereoselective total syntheses of dodoneine (**1**) and epidodoneine (**2**) in fifteen steps with an overall 11.2% yield. The key steps involved in the total syntheses of dodoneine and its diastereomer are the Jacobsen hydrokinetic resolution, ring closing metathesis (RCM) and Prins cyclisation. The operational expediency, synthetic efficiency and high diastereoselectivity make the synthetic process practicable. We believe that the current strategy would open up a new avenue for the synthesis of structurally variant analogues of α,β-unsaturated δ-lactones.

4. Experimental section

4.1. General experimental details

Commercial reagents were used without further purification, all solvents were purified by standard techniques and Infrared spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. NMR spectra were recorded in CDCl3 solvent on Varian Unity 400 and 500 MHz NMR spectrometers. Chemical shifts (d) are quoted in parts per million and are referenced to tetramethylsilane (TMS) as an internal standard. Coupling constants (J) are quoted in Hertz. and the resonance multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; p, pentuplet; dt, doublet of triplets; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; m, multiplet. Column chromatographic separations were carried out on silica gel (60–120 mesh) and flash chromatographic separations were carried out using 230–400 mesh, silica gel. Mass spectra were recorded on Micromass VG-7070H for EI and VG Autospec M for FABMS.

4.2. Synthetic procedures

2-[(Benzyloxy)methyl]oxirane (8): To a stirred suspension of NaH (8 g, 333 mmol) in anhydrous THF (400 mL) was added a

solution of benzyl alcohol (24 g, 222 mmol) in dry THF (100 mL) dropwise at 0 °C. After 30 min, epichlorohydrin (20.5 g, 222 mmol) was added and the mixture was brought to room temperature and then stirred it for 12 h. After completion of the reaction as monitored by TLC, the mixture was quenched with sat. ammonium chloride (100 mL) and diluted with ethyl acetate (100 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4. After removing the solvent under reduced pressure, the crude benzyl glycidyl ether was purified by column chromatography using (5% ethyl acetate/hexane) to give the pure product **8** (34.4 g, 94% yield) as colourless liquid, IR (Neat): ν_{max} 3031, 2999, 2926, 2864, 1725, 1453, 1267, 1096, 742, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.24 (m, 5H), 4.62–4.46 (m, 2H), 3.71 (dd, J = 11.2, 3.1 Hz, 1H), 3.41 (dd, J = 11.4, 5.7 Hz, 1H), 3.14 (tt, J = 5.9, 3.2 Hz, 1H), 2.77–2.71 (m, 1H), 2.58 (dd, J = 5.2, 2.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 127.2, 127.1, 72.5, 70.1, 50.2, 43.2; MS-ESIMS: m/z 165 $[M+H]^+$, 187 $[M+Na]^+$; HRMS (ESI) m/z Calcd. for $C_{10}H_{12}O_2Na$: $[M+Na]^+$ 187.21680, found: 187.21690.

(*S*)-2-[(Benzyloxy)methyl]oxirane (9): To a (*R*,*R*-(salen)Co(II) catalyst (604 mg, 1 mmol) in a round bottom flask were added (±)-benzyl glycidyl ether **8** (32.8 g, 200 mmol) and AcOH (0.228 mL, 4 mmol) sequentially at room temperature. After the reaction mixture turned from a red suspension into a dark brown solution, the flask was cooled to 0 °C and then THF (2 mL) followed by H_2O (1.98 g, 110 mmol, 0.55 equiv) were added over a period of 20 min. The resulting mixture was allowed to stir at room temperature for 36 h. After completion of the reaction as monitored by TLC, the reaction mass was directly purified by column chromatography using (5% ethyl acetate/hexane) to afford the epoxide **9** (15.08 g, 46%, 96% ee) as a colorless liquid and enantomerically pure diol **10** (17.05 g, 52%, 98%) as a viscous liquid, $[\alpha]_D^{22} = +5.2$ (*c* 1.1, $CHCl_3$); Lit $[\alpha]_D^{25} = +5.1$ (*c* 1.0, $CHCl_3$); IR (Neat): ν_{max} 3454, 3031, 2999, 2926, 2864, 1725, 1453, 1267, 1096, 742, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.36–7.23 (m, 5H), 4.64–4.48 (m, 2H), 3.70 (dd, J = 11.4, 3.1 Hz, 1H), 3.41 (dd, J = 11.4, 5.7 Hz, 1H), 3.12 (tt, J = 5.8, 3.1 Hz, 1H), 2.78–2.72 (m, 1H), 2.57 (dd, J = 5.2, 2.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.5, 127.2, 127.0, 72.4, 70.2, 50.1, 43.27; MS-ESIMS: m/z 165 $[M+H]^+$, 187 $[M+Na]^+$; HRMS (ESI) m/z Calcd. for $C_{10}H_{12}O_2Na$: $[M+Na]^+$ 187.21680 found: 187.21690.

(*S*)-1-(Benzyloxy)pent-4-en-2-ol (11): To a suspension of magnesium turnings (6.6 g, 274.4 mmol) in dry THF (35 mL) at room temperature were added 1,2-dibromoethane (3 drops), a freshly prepared vinyl bromide (13.1 mL, 182.9 mmol) in a dropwise manner and CuCN (40.9 mg, 5 mol%). The mixture was stirred for 30 min and then cooled to −78 °C. A solution of epoxide **9** (15 g, 91.46 mmol) in THF (60 mL) was added and then warmed to −40 °C and stirred it for 4 h. The mixture was quenched with saturated NH_4Cl (50 mL) and extracted with EtOAc (2 × 100 mL). Combined organic layers were washed with brine solution (120 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography using (12% ethyl acetate/hexane) afforded the compound **11** (16.2 g, 92%) as a colourless liquid, $[\alpha]_D^{22} = +2.6$ (*c* 1.1, $CHCl_3$); $[\alpha]_D^{25} = +2.3$ (*c* 1.0, $CHCl_3$); IR (Neat): ν_{max} 3426, 3070, 3030, 2910, 2862, 1718, 1640, 1451, 1275, 1103, 997, 915, 741, 698, 608 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.42–7.27 (m, 5H), 5.82 (ddt, J = 17.2, 10.2, 7.1 Hz, 1H), 5.18–5.05 (m, 2H), 4.55 (s, 1H), 3.88 (td, J = 9.9, 6.7 Hz, 1H), 3.51 (dd, J = 9.5, 3.4 Hz, 1H), 3.38 (dd, J = 9.5, 7.4 Hz, 1H), 2.38 (s, 1H), 2.25 (dd, J = 17.2, 10.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.8, 134.1, 128.2, 127.5, 117.4, 73.7, 73.1, 69.5, 37.7; MS-ESIMS: m/z 193 $[M+H]^+$, 215 $[M+Na]^+$; HRMS (ESI) m/z Calcd. for $C_{12}H_{16}O_2Na$: $[M+Na]^+$ 215.21640 found: 215.21650.

(*S*)-Pent-4-ene-1,2-diol (6): To a stirred suspension of sodium (16 g, 250 mmol) in liquid NH_3 (160 ml) was added a solution of compound **11** (16 g, 83.3 mmol) in dry THF (100 ml). The mixture was stirred for 20 min and then quenched with solid NH_4Cl (15 g). Ammonia was allowed to evaporate at room temperature and then ether (100 mL) was added to this residue and then filtered through Celite bed. The filtrate was dried over Na_2SO_4. Removal of the solvent followed by purification on silica gel column chromatography using 70% ethyl acetate/hexane afforded the diol **6** (7.6 g, 90% yield) as a colorless liquid, $[\alpha]_D^{25} = -3.5$ (*c* 2.5, $CHCl_3$); Lit $[\alpha]_D^{25} = -3.4$ (*c* 2.8, $CHCl_3$); IR (Neat): ν_{max} 3419, 2926, 1840, 1640, 1431, 1073, 915, 848 765, 654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.91–5.63 (m, 1H), 5.20–5.08 (m, 2H), 3.75–3.55 (m, 1H), 3.71–3.42 (m, 2H), 2.93 (s, 1H), 2.33–2.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.1, 117.5, 71.4, 65.9, 37.6; MS-ESIMS: m/z 103 $[M+H]^+$, 125 $[M+Na]^+$

Ethyl-(*E*)-3-[4-(benzyloxy)phenyl]acrylate (13): To a stirred solution of aldehyde **12** (10.5 g, 49.5 mmol) in dry benzene (120 mL) was added $Ph_3P = CHCO_2Et$ (25.9 g, 74.3 mmol) under reflux for 4 h. After completion of the reaction as monitored by TLC, the mixture was concentrated to dryness under reduced pressure and the resultant residue was purified by silica gel column chromatography using (10% ethyl acetate/hexane) to afford the α,β-unsaturated ester **13** (12.5 g, 90%) as a white solid, mp 105–106 °C, IR (Neat): ν_{max} 2986, 2940, 2859, 2338, 1712, 1632, 1602, 1570, 1510, 1457, 1305, 1283, 1167, 1009, 834, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J = 16.0 Hz, 1H), 7.47 (d, J = 1.7 Hz, 2H), 7.42–7.27 (m, 5H), 6.95 (d, J = 8.7 Hz, 1H), 6.28 (d, J = 16 Hz, 2H), 5.10 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 160.5, 144.1, 136.4, 129.7, 128.6, 128.1, 127.4, 115.8, 115.2, 70.0, 60.3, 14.3; MS-ESIMS: m/z 283 $[M+H]^+$, 305 $[M+Na]^+$; HRMS (ESI) m/z Calcd. for $C_{18}H_{18}O_3Na$: $[M+Na]^+$ 305.21684, found: 305.21670.

Methyl-3-[4-(benzyloxy)phenyl]propanoate (14): To a stirred mixture of unsaturated ester **13** (12.4 g, 43.97 mmol) in dry methanol (120 mL) was added Mg turnings (3.2 g, 131.91 mmol) at room temperature and stirred it for 6 h. After completion of the reaction, saturated NH_4Cl (60 mL) was added and the reaction mixture was concentrated under reduced pressure to remove the MeOH and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with 1 N HCl (100 mL), water, brine and dried over Na_2SO_4. Concentration of the solvent afforded the crude product, which was purified by column chromatography on silica gel using (10% ethyl acetate/hexane) to provide the **14** (10 g, 85% yield) as white solid, mp 95–97 °C, IR (Neat): ν_{max} 3029, 2916, 2860, 1893, 1726, 1608, 1512, 1445, 1376, 1297, 1264, 1237, 1180, 1013, 826, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.50–7.26 (m, 5H), 7.10 (d, J = 8.6 Hz, 2H), 6.60 (d, J = 8.6 Hz, 2H), 5.05 (s, 2H), 3.68 (s, 3H), 2.90 (t, J = 7.7 Hz, 2H), 2.58 (t, J = 7.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.3, 157.2, 137.1, 132.8, 129.2, 128.5, 127.8, 127.4, 114.8, 69.9, 51.5, 35.8, 30.1; MS-ESIMS: m/z 271 $[M+H]^+$, 293 $[M+Na]^+$; HRMS (ESI) m/z Calcd. for $C_{17}H_{18}O_3Na$: $[M+Na]^+$ 293.12686, found: 293.12673.

3-[4-(Benzyloxy)phenyl]propan-1-ol (15): To an ice-cold suspension of $LiAlH_4$ (10.1 g, 55 mmol) in dry THF (50 mL) was added slowly a solution of ester **14** (10 g, 37 mmol) in dry THF (40 mL). The mixture was stirred for 4 h at room temperature and the excess reagent was quenched at 0 °C by slow addition of H_2O (2.2 mL) followed by sodium hydroxide solution (15%, 2.2 mL) and water (6.6 mL). Then the mixture was filtered through Celite bed and washed with ether (2 × 50 mL). The filtrate was concentrated to obtain a residue, which was purified by column chromatography on silica gel (20% ethyl acetate/hexane) to afford the alcohol **15** (7.2 g, 80% yield) as white solid, mp 112–113 °C, IR (Neat): ν_{max} 3425, 3277, 2934, 2859, 1633, 1602, 1510, 1456, 1284, 1250, 1167, 1010, 833, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.22 (m, 5H), 7.05 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 5.00 (s, 2H), 3.60 (t, J = 6.3 Hz, 2H), 2.61 (t, J = 7.6 Hz, 2H), 1.87–1.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 137.1, 134.1, 129.3, 128.5, 127.8, 127.4,

114.7, 69.9, 62.1, 34.3, 31.1; MS-ESIMS: *m/z* 243 $[M+H]$,$^+$ 260 $[M + NH_4]$,$^+$ 265 $[M+Na]^+$; HRMS (ESI) *m/z* Calcd. for $C_{16}H_{18}O_2Na$: $[M+Na]^+$ 265.22646, found: 265.22643.

3-[4-(Benzyloxy)phenyl]propanal (5): To a stirred solution of oxalyl chloride (4.6 mL, 54.2 mmol) in dry CH_2Cl_2 (60 mL), was added DMSO (7.9 mL, 108.4 mmol) at −78 °C and stirred it at the same temperature for 15 min. A solution of alcohol **15** (6.5 g, 27.1 mmol) in CH_2Cl_2 (60 mL) was added and the stirring was continued for 3 h. Then the reaction mixture was quenched with Et_3N (22.6 mL, 161.2 mmol) at −78 °C and stirred for an additional 30 min. Then the reaction mixture was diluted with sat. NH_4Cl (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine solution (2 × 100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (10% ethyl acetate/hexane) afforded the aldehyde **5** (5.9 g, 90%) as a white solid, mp 99–100 °C, IR (Neat): ν_{max} 3037, 2828, 2743, 1712, 1689, 1601, 1574, 1504, 1259, 1162, 1019, 826 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.78 (s, 1H), 7.41–7.21 (m, 5H), 7.05 (d, J = 8.6 Hz, 2H), 6.84 (m, J = 8.6 Hz, 2H), 5.01 (s, 1H), 2.87 (t, J = 6.7, 2H), 2.73–2.67 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.4, 156.9, 136.8, 132.4, 129.0, 128.3, 127.7, 127.2, 114.7, 69.8, 45.3, 27.2; MS-ESIMS: *m/z* 241 $[M+H]$,$^+$ 263 $[M+Na]^+$

(2*R*,4*R*,6*R*)-2-[4-(Benzyloxy)phenethyl]-6-(hydroxymethyl) tetrahydro-2*H*-pyran-4-ol (17): To a solution of homoallylic alcohol **6** (2 g, 14.7 mmol) and 3-(4-(benzyloxy)phenyl)propanal **5** (5.2 g, 22 mmol) in CH_2Cl_2 (40 mL) was added trifluoroacetic acid (22.6 mL, 29.4 mmol) slowly at room temperature under nitrogen atmosphere. The mixture was stirred for 3 hours and then sat. $NaHCO_3$ (40 mL) was added and the pH was adjusted to >7 by addition of triethylamine. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x80 mL) and the organic layers were combined, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was dissolved in methanol (80 mL) and treated with potassium carbonate (6.1 g, 44.1 mmol) for 30 minutes. After removing MeOH under reduced pressure, water (40 mL) was added. The mixture was extracted with dichloromethane (3x50 mL) and the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the compound on column chromatography using (40% ethyl acetate / hexane) afforded the pure product **17** (3.4 g, 65% yield) as a yellowish solid, mp 122-124 °C, $[\alpha]_D^{22}$ -6.2 (c =1.4 $CHCl_3$); IR (Neat): ν_{max} 3383, 3031, 2928, 2853, 1665, 1612, 1512, 1450, 1378, 1251, 1160, 1017, 963, 730 cm^{-1}; ^1H-NMR (500 MHz, $CDCl_3$): δ 7.42-7.22 (m, 5H), 7.03 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 5.01 (s, 2H), 3.75 (ddd, J = 15.9, 10.9, 4.8 Hz, 1H), 3.55 (ddd, J = 18.1, 11.4, 5.2 Hz, 2H), 3.44-3.34 (m, 1H), 3.28 (dd, J = 14.1, 7.6 Hz, 1H), 2.75-2.53 (m, 2H), 2.07-1.77 (m, 2H), 1.76-1.62 (m, 1H), 1.61-1.44 (m, 1H), 1.18 (dt, J = 15.7, 10.4 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 156.8, 137.0, 134.1, 129.9, 128.4, 127.8, 127.4, 114.7, 75.8, 74.6, 69.9, 67.6, 65.7, 40.9, 37.7, 36.6, 30.7; MS-ESIMS: *m/z* 343 $[M+H]$,$^+$ 365 $[M+Na]^+$; HRMS (ESI) *m/z* Calcd. for $C_{21}H_{26}O_4Na$: $[M+Na]^+$ 365.1728, Found: 365.1745

{(2*R*,4*R*,6*R*)-6-[4-(Benzyloxy)phenethyl]-4-hydroxytetrahydro-2*H*-pyran-2-yl} methyl-4-methylbenzenesulfonate (18): To solution of diol **17** (3 g, 8.7 mmol) in dry CH_2Cl_2 (15 mL), were added triethylamine (3.6 mL, 26.16 mmol) at 0 °C followed by tosyl chloride (2 g, 10.5 mmol) over 1 hour. The mixture was allowed to warm to room temperature and stirred it for 3 hours. The reaction was treated with aqueous 1N HCl (10 mL) and extracted with CH_2Cl_2 (3x50 mL). The organic layer was washed with sat $NaHCO_3$ (25 mL) and water (25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography of the crude residue using (12% ethyl acetate/hexane) afforded the tosylate **18** (3.9 g, 90%) as a sticky material. Sticky solid, $[\alpha]_D^{22}$ -18.6 (c =1.46 $CHCl_3$); IR (Neat): ν_{max} 3426, 2924, 2855, 1605, 1509, 1457, 1358, 1237, 1176, 1097, 975, 815, 738 cm^{-1}; ^1H-NMR (500 MHz, $CDCl_3$): δ 7.82 (d, J = 8.6. Hz, 2H), 7.45-7.29 (m, 7H), 7.03 (d, J = 9.0, Hz, 2H), 6.84 (d, J = 9.0, Hz, 2H), 5.05 (s, 2H), 4.10-3.95 (m, 2H), 3.81-3.67 (m, 1H), 3.60-3.46 (m, 1H), 3.26-3.12 (m, 1H), 2.69-2.52 (m, 2H), 2.45 (s, 3H), 1.92-1.55 (m, 4H), 1.04 -1.20 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 157.0, 144.8, 137.2, 134.2, 133.0, 129.8, 129.4, 129.0, 128.6, 128.0, 127.9, 127.5, 114.7, 74.5, 72.9, 70.0, 67.6, 40.7, 37.5, 36.9, 30.5, 21.6; MS-ESIMS: *m/z* 514 $[M+NH_4]$,$^+$ 519 $[M+Na]^+$; HRMS (ESI) *m/z* Calcd. for $C_{28}H_{32}O_6NaS$: $[M+Na]^+$ 519.1817, found: 519.1827

{(2*R*,4*R*,6*R*)-6-[4-(Benzyloxy)phenethyl]-4-[(*tert*-butyldimethylsilyl)oxy]tetrahydro-2*H*-pyran-2-yl}methyl 4-methylbenzenesulfonate (19): To a stirred solution of alcohol **18** (3.8 g, 7.6 mmol) in dry CH_2Cl_2 (25 mL) were added DMAP and imidazole (1 g, 15.3 mmol) followed by TBSCl (1.7 g, 11.5 mmol) in three portions at 0 °C and stirred it for 3 h. After completion of the reaction as monitored by TLC, the mixture was quenched with sat. NH_4Cl (30 mL), diluted with CH_2Cl_2 (50 mL). The organic layer was separated and washed with brine (25 mL), dried over Na_2SO_4 and concentrated in *vacuo*. Purification of the crude product by column chromatography on silica gel using (5% ethyl acetate/hexane) afforded the silyl ether **19** (4.1 g, 88%) as a colorless liquid, $[\alpha]_D^{22}$ − 19.6 (c = 1 $CHCl_3$); IR (Neat): ν_{max} 2929, 2856, 1606, 1510, 1458, 1364, 1245, 1178, 1078, 981, 835, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.3 Hz, 2H), 7.41–7.22 (m, 7H), 6.99 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.00 (s, 2H), 4.04–3.90 (m, 2H), 3.73–3.59 (m, 1H), 3.55–3.46 (m, 1H), 3.22–3.12 (m, 1H), 2.64–2.46 (m, 2H), 2.13 (s, 3H), 1.80–1.49 (m, 4H), 1.22–1.02 (m, 2H), 0.84 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 144.7, 137.2, 134.3, 133.1, 129.8, 129.5, 128.6, 128.0, 127.9, 127.5, 114.7, 74.4, 72.9, 70.0, 68.2, 41.4, 37.5, 30.5, 25.8, 21.6, 18.0, −4.5; MS-ESIMS: *m/z* 618 $[M + NH_4]$,$^+$ 633 $[M+Na]^+$; HRMS (ESI) *m/z* Calcd. for $C_{34}H_{46}O_6NaSiS$: $[M+Na]+$ 633.2682, found: 633.2709.

{](2*R*,4*R*,6*R*)-2-(4-(Benzyloxy)phenethyl]-6-(iodomethyl)tetrahydro-2*H*-pyran-4- l)oxy}(*tert*-butyl)dimethylsilane (4): To a stirred solution of **19** (4 g, 6.6 mmol) in acetone (70 mL) was added NaI (19.7 g, 131.2 mmol) and heated it under reflux for 24 h. After completion of the reaction as monitored by TLC, acetone was removed under reduced pressure. The resulting residue was quenched with water and extracted with EtOAc and the organic layer was separated, dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromatography on silica gel using (2% ethyl acetate/hexane) to afford the compound **4** (3.4 g, 90%) as a colorless liquid, $[\alpha]_D^{22}$ +14.86 (c = 1.4 $CHCl_3$); IR (Neat): ν_{max} 3383, 2919, 2850, 1643, 1462, 1363, 1314, 1184, 1134, 1034, 939, 883, 720, 623 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.21 (m, 5H), 7.07 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 4.99 (s, 2H), 3.70–3.62 (m, 1H), 3.60–3.55 (m, 1H), 3.36–3.25 (m, 3H), 2.68 (dd, J = 10.5, 5.6 Hz, 2H), 1.96 (d, J = 7.7 Hz, 1H), 1.88–1.74 (m, 1H), 1.69–1.53 (m, 2H), 1.30–1.01 (m, 2H), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 137.1, 134.4, 129.5, 128.5, 127.8, 127.4, 114.6, 75.1, 74.2, 69.9, 68.3, 41.3, 37.6, 30.6, 25.8, 18.0, 9.1, −4.6; MS-ESIMS: *m/z* 589 $[M+Na]^+$; HRMS (ESI) *m/z* Calcd. for $C_{27}H_{39}O_3NaSiI$: $[M+Na]^+$ 589.1610, found: 589.1585.

(3*S*,5*S*)-1-[4-(Benzyloxy)phenyl]-5-[(tert-butyldimethylsilyl) oxy]oct-7-en-3-ol (20): To a stirred solution of iodide **4** (3.2 g, 5.65 mmol) in ethanol (50 mL) was added zinc dust (7.1 g, 113.1 mmol) and refluxed it for 3 h. After completion as confirmed by TLC, the reaction mixture was cooled to room temperature and then added ammonium chloride (5 g) followed by diethyl ether (50 mL). After stirring for 15 min, a gray suspension was formed, which was filtered through Celite bed and the filtrate was concentrated in *vacuo*. Purification by column chromatography on silica gel using (10% ethyl acetate/hexane) gave the 1,3-*anti*-diol **20**

(2.2 g, 86%) as a colorless liquid, $[\alpha]_D^{22}$ − 2.6 (*c* = 0.68 $CHCl_3$); IR (Neat): ν_{max} 3447, 3383, 3032, 2919, 2850, 1643, 1462, 1363, 1314, 1184, 1134, 1242, 1075, 1026, 834, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46–7.25 (m, 5H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.76–5.61 (m, 1H), 5.07–4.98 (m, 4H), 4.07–3.95 (m, 1H), 3.94–3.84 (m, 1H), 2.90 (s, 1H), 2.76–2.51 (m, 2H), 2.36–2.26 (m, 2H), 1.80–1.54 (m, 4H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 137.2, 134.5, 129.3, 128.5, 127.8, 127.4, 117.4114.7, 71.1, 70.0, 67.5, 41.2, 41.0, 39.7, 30.9, 25.8, −4.5, −4.9; MS-ESIMS: *m/z* 440 [M+H],$^+$ 463 $[M+Na]^+$; HRMS (ESI) *m/z* Calcd. for $C_{27}H_{40}O_3NaSi$: [M+Na]+ 463.2644, found: 463.2633.

{[(4*S*,6*S*)-6-(Benzyloxy)-8-(4-(benzyloxy)phenyl)oct-1-en-4-yl]oxy}(*tert*-butyl)dimethylsilane (21): To a suspension of NaH (0.22 g, 9.09 mmol) in dry THF (12 mL) was added dropwise a solution of alcohol **20** (2 g, 4.5 mmol) in dry THF (8 mL) at 0 °C. To this mixture, TBAI (0.02 g) and benzyl bromide (0.85 mL, 6.8 mmol) were added subsequently and the stirring was continued for 6 h at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with crushed ice until a clear solution is formed. The solvent was then removed and the mixture was extracted with ethyl acetate (2 × 30 mL). The organic extracts were washed with brine (2 × 20 mL) and dried over Na_2SO_4. Evaporation of the solvent followed by column chromatography on silica gel using (2% ethyl acetate/hexane) afforded the pure product **21** (2.02 g, 84% yield) as a colorless liquid, $[\alpha]_D^{22}$ + 23.6 (*c* 0.88 $CHCl_3$); IR (Neat): ν_{max} 2924, 2853, 1715, 1607, 1511, 1461, 1381, 1257, 1217, 915, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 7.3 Hz, 2H), 7.37 (d, *J* = 7.3 Hz, 2H), 7.34–7.23 (m, 6H), 7.08–7.10 (m, 2H), 6.84–6.80 (m, 2H), 5.90–5.78 (m, 1H), 5.18–4.96 (m, 4H), 4.62–4.38 (m, 2H), 3.72–3.58 (m, 1H), 4.00–3.75 (m, 1H), δ 2.68–2.51 (m, 2H), 2.38 (t, *J* = 5.9 Hz, 1H), 2.30–2.16 (m, 1H), 1.95–1.70 (m, 2H), 1.67–1.52 (m, 1H), 1.43–1.25 (m, 1H), 0.87 (s, 9H), 0.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 138.9, 137.2, 135.0, 134.7, 134.5, 129.2, 128.5, 128.3, 127.8, 127.5, 117.2, 114.7, 75.8, 70.6, 70.1, 69.0, 42.5, 41.9, 40.1, 38.3, 30.1, 25.9, −4.0, −4.5; MS-ESIMS: *m/z* 531 [M]+H],$^+$ 553 $[M+Na]^+$; HRMS (ESI) *m/z* Calcd. for $C_{34}H_{46}O_3NaSi$: $[M+Na]^+$ 553.3113, found: 553.3126.

(4*S*,6*S*)-6-(Benzyloxy)-8-[4(benzyloxy)phenyl]oct-1-en-4-ol (3): To a stirred solution of compound **21** (1.8 g 3.4 mmol) in MeOH (20 mL) was added CSA (50 mg) at 0 °C. The reaction was stirred for 1 h. Up on completion, the reaction was quenched with sat. $NaHCO_3$ (15 mL). The methanol was removed *in vacuo* and the residue was diluted with water (25 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography on silica gel using (10% ethyl acetate/hexane) gave the alcohol **3** (1.2 g, 86%) as a colorless oil, $[\alpha]_D^{22}$ + 21.48 (*c* = 1.6 $CHCl_3$); IR (Neat): ν_{max} 3448, 2922, 2852, 1611, 1509, 1459, 1237, 1070, 912, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46–7.24 (m, 10H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6, Hz, 2H), 5.86–5.71 (m, 1H), 5.12–4.98 (m, 4H), 4.79–4.57 (m, 2H), 4.48–4.36 (m, 1H), 3.78–3.58 (m, 1H), 2.76–2.53 (m, 2H), 2.46–2.28 (m, 1H), 1.94–1.84 (m, 1H), 1.79–1.51 (m, 2H), 1.35–1.25 (m, 1H), 1.03–0.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 138.1, 137.2, 134.8, 134.5, 134.3129.3, 129.2, 128.5, 128.4, 128.0, 127.8, 127.7, 127.5, 117.4, 114.7, 76.2, 71.1, 70.0, 67.8, 40.0, 39.4, 37.9, 35.5; MS-ESIMS: *m/z* 417 [M+H],$^+$ 439 $[M+Na]^+$; HRMS (ESI) *m/z* Calcd. for $C_{28}H_{32}O_3Na$: $[M+Na]^+$ 439.2249, found: 439.2270.

(4*S*,6*S*)-6-(Benzyloxy)-8-[4(benzyloxy)phenyl]oct-1-en-4-yl acrylate (22): To a solution of homoallyl alcohol **3** (0.5 g, 1.2 mmol) in CH_2Cl_2 (6 mL) were added acryloyl chloride (0.2 mL, 2.4 mmol) dropwise under N_2 atmosphere followed by Et_3N (0.5 mL, 3.6 mmol) and DMAP at 0 °C. The resulting mixture was allowed to stir for 30 min. Up on completion, the reaction mixture was extracted twice with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine solution, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (5% ethyl acetate/hexane) to give the product **22** as a colorless liquid (0.48 g, 85%), $[\alpha]_D^{22}$ + 41.16 (*c* = 1 $CHCl_3$); IR (Neat): ν_{max} 3031, 2924, 2857, 1719, 1613, 1509, 1239, 1193, 1069, 986, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.36–7.13 (m, 10H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H), 6.29 (dd, *J* = 16.7, 1.2 Hz, 1H), 6.10 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.87–5.74 (m, 1H), 5.36–5.26 (m, 1H), 5.05–4.96 (m, 4H), 5.00 (s, 2H), 4.57–4.35 (m, 2H), 3.20–3.50 (m, 2H), 2.38–2.28 (m, 2H), 1.95–1.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 156.9, 138.3, 137.1, 134.1, 133.7, 130.4, 129.9, 128.7, 128.4, 128.2, 128.0, 127.7, 127.5, 127.3, 117.4, 114.6, 76.9, 74.9, 71.4, 71.3, 39.3, 38.3, 36.9, 30.6; MS-ESIMS: *m/z* 471 [M+H],$^+$ 493 $[M+Na]^+$; HRMS (ESI) *m/z* Calcd. for $C_{31}H_{34}O_4Na$: $[M+Na]^+$ 493.2354, Found: 493.2363.

(*S*)-6-{(*S*)-2-(Benzyloxy)-4-[4-(benzyloxy)phenyl]butyl}-5,6-dihydro-2*H*-pyran-2-one (23): To a stirred solution of *bis*-olefin **22** (0.35 g, 0.75 mmol) in degassed CH_2Cl_2 (500 mL) was added bis(-tricyclohexylphosphine)benzylideneruthenium dichloride (0.06 g, 0.074 mmol) at room temperature under argon atmosphere. The mixture was heated under reflux for 24 h and then the solvent was evaporated *in vacuo*. Thus obtained residue was purified by silica gel column chromatography using (20% ethyl acetate/hexane) to afford the lactone **23** (0.26 g, 79%) as a low melting solid. $[\alpha]_D^{22}$ + 18.26 (*c* = 0.96 $CHCl_3$); IR (Neat): ν_{max} 3031, 2924, 2854, 1944, 1721, 1611, 1510, 1453, 1241, 1071, 1029, 815, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47–7.25 (m, 10H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.5, Hz, 2H), 6.86–6.82 (m, 1H), 6.12 (d, *J* = 8.4 Hz, 1H), 5.04 (s, 2H), 4.67–4.59 (m, 2H), 4.50–4.44 (m, 1H), 3.89 (dtd, *J* = 8.0, 5.6, 2.5 Hz, 1H), 2.60 (t, *J* = 8.2 Hz, 2H), 2.35–2.27 (m, 2H), 2.01–1.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 156.9, 138.3, 137.1, 134.1, 133.7, 130.3, 129.1, 128.7, 128.4, 128.2, 128.0, 127.7, 127.5, 127.3117.4, 114.6, 75.0, 71.4, 71.3, 69.8, 39.3, 38.3, 36.9,30.6, 29.6.74.0, 70.11, 70.0, 38.7, 35.5, 30.4, 29.3; MS-ESIMS: *m/z* 460 [M + NH4],$^+$ 465 $[M+Na]^+$; HRMS (ESI) *m/z* Calcd. for $C_{29}H_{30}O_4Na$: $[M+Na]^+$ 465.2041, found: 465.2049.

(*S*)-6-[(*S*)-2-Hydroxy-4-(4-hydroxyphenyl)butyl]-5,6-dihydro-2*H*-pyran-2-one (2): To a stirred solution of **23** (0.2 g, 0.45 mmol) in CH_2Cl_2 (6 mL) was added $TiCl_4$ (0.17 g, 1 mL, 1 M CH_2Cl_2, 0.9 mmol) at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 30 min and confirmed the completion of the reaction by TLC. Then it was quenched with 1 N HCl and extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic layers were washed with brine solution, dried over Na_2SO_4 and concentrated in *vacuo*. Purification of the compound by chromatography on silica gel using (2% MeOH/$CHCl_3$) afforded the *epi*-dodoneine **2** (88 mg, 74%) as a white solid, mp 158–160 °C, $[\alpha]_D^{20}$ = −24.8 (*c* 0.06, $CHCl_3$); Lit. $[\alpha]_D^{25}$ = −26.7 (*c* 1, $CHCl_3$)[40] IR (Neat): ν_{max} 3417, 2924, 2853, 1715, 1607, 1511, 1461, 1381, 1257, 1217, 1166, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.10–6.90 (m, 2H), 6.65 (d, *J* = 8.5 Hz, 2H), 5.90 (d, *J* = 9.5, Hz, 1H), 4.65–4.75 (m, 1H), 4.60–4.50 (m, 1H), 3.80 (s, 1H), 2.72–2.50 (m, 2H), 2.40–2.27 (m, 2H), 1.80–1.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 154.5, 144.3, 131.6, 128.1, 120.7, 114.5, 74.2, 64.4, 41.0, 39.4, 30.0, 29.5; MS-ESIMS: *m/z* 263 [M+H],$^+$ 285 $[M+Na]^+$; HRMS (ESI) *m/z* Calcd. for $C_{15}H_{18}O_4Na$: $[M+Na]^+$ 285.10999, found: 285.10986.

(4*R*,6*S*)-6-(Benzyloxy)-8-[4(benzyloxy)phenyl]oct-1-en-4-yl acrylate (24): To a stirred solution of **3** (0.6 g, 1.5 mmol) in dry THF (10 mL) were added PPh_3 (0.75 g, 2.9 mmol) and acrylic acid (0.3 mL, 4.3 mmol) at 0 °C followed by diethyl azodicarboxylate (0.8 mL, 5 mmol). The resulting mixture was then stirred for 4 h at room temperature. After completion of the reaction as monitored by TLC, the reaction mixture was diluted with water (10 mL) and then extracted with ether (2 × 25 mL). Removal of the solvent under reduced pressure followed by flash chromatography (5%

ethyl acetate/hexane) afforded the ester **24** (0.47 g, 69%) as a colorless liquid. Colorless liquid, $[\alpha]_D^{22}$ + 16.6 (c = 1.2 $CHCl_3$); IR (Neat): ν_{max} 3031, 2924, 2857, 1719, 1613, 1509, 1239, 1193, 1069, 986, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.18 (m, 10H), 6.99 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6, 2.3 Hz, 2H), 6.80–6.76 (m, 1H), 6.40–6.29 (m, 1H), 6.10–5.96 (m, 1H), 5.84–5.69 (m, 1H), 5.15–4.95 (m, 4H), 4.57–4.35 (m, 2H), 3.51–3.44 (m, 1H), 3.44–3.36 (m, 1H), 2.65–2.44 (m, 2H), 2.38–2.26 (m, 2H), 2.04–1.89 (m, 1H), 1.88–1.75 (m, 2H), 1.77–1.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 157.0, 138.4, 137.2, 134.2, 134.0, 133.4, 130.4, 129.2, 128.8, 128.5, 128.3, 128.0, 127.8, 127.5, 127.4, 117.7, 114.7, 75.1, 71.6, 71.4, 70.0, 39.4, 38.4, 37.0, 30.6; MS-ESIMS: m/z 471 $[M+H]^+$, 493 $[M+Na]^+$; HRMS (ESI) m/z Calcd. for $C_{31}H_{34}O_4Na$: $[M+Na]^+$ 493.2354, found: 493.2363.

(*R*)-6-{(*S*)-2-(Benzyloxy)-4-[4(benzyloxy)phenyl]butyl}-5,6-dihydro-2*H*-pyran-2-one (25): The compound ester **24** (0.4 g, 0.8 mmol) was dissolved in dry CH_2Cl_2 (500 mL) and the Grubbs' catalyst-I (0.07 g, 0.09 mmol) was added at room temperature. Then the mixture was heated under reflux for 48 h under nitrogen atmosphere. After completion of the reaction (as monitored by TLC), the solvent was distilled off and the concentrated solution was stirred at room temperature for 2 h under air bubbling in order to decompose the catalyst. Removal of the solvent under reduced pressure followed by flash chromatography (20% ethyl acetate/hexane) afforded the lactone **25** (0.28 g, 75%) as a low melting solid. $[\alpha]_D^{22}$ + 44.6 (c = 0.84 $CHCl_3$); IR (Neat): ν_{max} 3031, 2924, 2854, 1944, 1721, 1611, 1510, 1453, 1384, 1241, 1071, 1029, 815, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 7.2 Hz, 2H), 7.38 (d, J = 7.2 Hz, 2H), 7.35–7.27 (m, 7H), 7.08 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 6.80–6.75 (m, 1H), 5.99 (dd, J = 9.8, 2.0 Hz, 1H), 4.61–4.39 (m, 3H), 3.68–3.59 (m, 1H), 2.71–2.59 (m, 2H), 2.35–2.09 (m, 3H), 1.96–1.78 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 157.0, 145.1, 138.3, 137.1, 134.1, 129.2, 128.5, 128.4, 127.9, 127.8, 127.6, 127.4, 121.2, 114.8, 75.2, 74.0, 70.11, 70.0, 38.7, 35.5, 30.4, 29.3; MS-ESIMS: m/z 460 $[M + NH4]^+$, 465 $[M+Na]^+$; HRMS (ESI) m/z Calcd. for $C_{29}H_{30}O_4Na$: $[M+Na]^+$ 465.2041,Found: 465.2049.

(*R*)-6-[(*S*)-2-Hydroxy-4-(4-hydroxyphenyl)butyl]-5,6-dihydro-2*H*-pyran-2-one (1): To a stirred solution of **25** (0.24 g, 0.56 mmol) in CH_2Cl_2 (6 mL) was added $TiCl_4$ (0.22 g, 1.1 mL, 1 M, CH_2Cl_2, 1.2 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and stirred for 30 min. It was then quenched with 1 N HCl and extracted with CH_2Cl_2 (2 × 20 mL), washed with brine, dried over Na_2SO_4 and concentrated in *vacuo*. Purification of the compound by column chromatography on silica gel (2% MeOH/$CHCl_3$) afforded the final compound, dodoneine **1** (80 mg, 56%) as a colorless solid and bicyclicclactone **26** (44 mg, 31%) as a white solid, overall in 80% yield. Colourless solid, mp 58–60 °C, $[\alpha]_D^{22}$ = +41.3 (c 0.44, $CHCl_3$); Lit. $[\alpha]_D^{25}$ = +40.2 (c 0.4, $CHCl_3$) [42]; IR (Neat): ν_{max} 3417, 2924, 2853, 1715, 1607, 1511, 1461, 1381, 1257, 1217, 1166, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.81–6.72 (m, 2H), 6.04 (d, J = 9.7 Hz, 1H), 5.68 (s, 1H), 4.66 (td, J = 13.1, 7.7 Hz, 1H), 3.94–3.82 (m, 1H), 2.76–2.58 (m, 2H), 2.42–2.30 (m, 2H), 2.10–1.94 (m, 1H), 1.84–1.69 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 154.0, 145.5, 133.4, 129.4, 121.1, 115.3, 68.6, 42.0, 39.3, 30.8, 29.5; MS-ESIMS: m/z 263 $[M+H]^+$, 285 $[M+Na]^+$; HRMS (ESI) m/z Calcd. for $C_{15}H_{18}O_4Na$: $[M+Na]^+$ 285.10999, found 285.10986.

(1S,5R,7S)-7-(4-hydroxyphenethyl)-2,6-dioxabicyclo[3.3.1]nonan-3-one (26): White solid, mp 174–176 °C, $[\alpha]_D^{20}$ = −34.2 (c 0.42, $CHCl_3$); Lit. $[\alpha]_D^{25}$ = −33.5 (c 0.45, $CHCl_3$) [43] and Lit. $[\alpha]_D^{25}$ = −32.9 (c 0.5, $CHCl_3$) [43]; IR (Neat): ν_{max} 3340, 2958, 2859, 1732, 1682, 1517, 1455, 1342, 1347, 1230, 1084, 1076, 1054, 1004, 821, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.04 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 5.6 Hz, 2H), 4.92–4.87 (m, 1H), 4.42–4.36 (m, 1H), 3.74 (qd, J = 7.4, 3.6 Hz, 1H), 2.86–2.79 (m, 2H), 2.77–2.64 (m, 1H), 2.56 (ddd, J = 13.8, 9.3, 7.2 Hz, 1H), 2.08–1.90 (m, 3H), 1.88–1.65 (m, 2H), 1.60 (ddd, J = 13.8, 11.7, 2.1 z, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 153.5, 133.0, 128.9, 114.9, 72.6, 65.4, 64.4, 37.4, 36.5, 36.0, 30.1, 29.4; MS-ESIMS: m/z 263 $[M+H]^+$, 285 $[M+Na]^+$; HRMS (ESI) m/z Calcd. for $C_{15}H_{18}O_4Na$: $[M+Na]^+$ 285.10999,found: 285.10964.

Compound 26: [42] White solid, mp 173–175 °C; $[\alpha]_D^{25}$ = −32.9 (c 0.50, $CHCl_3$); IR (neat): 3338, 2924, 2856, 1685, 1517, 1451, 1382, 1347, 1230, 1076, 1004, 821, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.53–1.86 (m, 4H), 1.90–2.05 (m, 2H), 2.49–2.59 (m, 1H), 2.64–2.74 (m, 1H), 2.79–2.82 (m, 2H), 3.67–3.76 (m, 1H), 4.38–4.43 (br multiplet, 1H), 4.88–4.93 (br multiplet, 1H), 5.21–5.52 (bs, 1H), 6.75 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.9, 30.7, 36.5, 37.1, 38.0, 65.0, 66.0, 73.3, 115.5, 129.5, 133.6, 154.1, 170.3; MS-ESIMS: m/z 263 $[M+H]^+$; HRMS calcd for $C_{15}H_{19}O_4$: 263.12771, found 263.12779.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dhanraj O Biradar reports financial support was provided by CSIR New Delhi.

Data availability

Data will be made available on request.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2022.133242.

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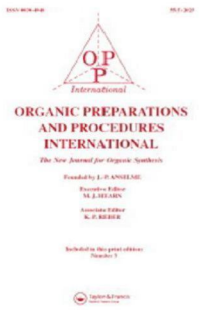

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EXPERIMENTAL PAPER

Facile Synthesis of Substituted Pyrroles Using Silica Supported Catalysis

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The pyrrole unit is a well-known privileged scaffold and widely-used chemical motif.[1] Pyrroles display a broad spectrum of biological activities.[2–5] The pyrrole core is widely distributed in nature in porphyrins, heme, and lamellarin.[6,7] Pyrrole derivatives possess anti-inflammatory,[8–10] anti-oxidant,[11,12] antitumor,[13,14] hypolipidemic,[15] immunosuppressant,[16] antiviral,[17–21] antibacterial,[10,22,23] insecticidal[24] and antifungal[25] properties. Significant pyrrole-containing marketed drugs and drugs under clinical trial include the antihypercholesterolemia drug Atorvastatin,[26–29] Tolmetin,[30,31] Sunitinib,[32,33] Ketorolac,[34,35] Ruxolitinib,[36,37] Vemurafenib,[38–40] Remdesivir, Pemetrexed,[41,42] Ribociclib,[43–45] Tofacitinib,[46] Ondasetron,[47,48] and Indomethacin[49] (Fig. 1).

A number of methods have been established[50–67] for pyrrole synthesis, and each of them has had merit in advancing the field. However, especially for more highly-substituted molecules, some of the methods have deficiencies, so this classic area of heterocyclic synthesis has room for new advances. In the last decade, several transition metal catalysts (such as Ru, Rh, Pd, Cu and Au) have been used for the synthesis of the pyrrole skeleton from alkynes, oximes, enaminones or amines.[68–73] However, these catalysts may suffer from low turnover numbers, high cost or difficulty in catalyst separation and recovery.

Perchloric acid impregnated on silica gel has become well-known as a heterogeneous catalyst, characterized by high efficiency, economic viability and versatility.[74] In this context, we now report the synthesis of substituted pyrroles from internal alkynes and enamides by using silica supported catalysis.

In preparation for our pyrrole synthesis, the *p*-toluenesulfonic acid (PTSA) catalyzed reaction of methyl pyruvate (**1a**) or ethyl pyruvate (**1b**) with acetamide (**2**) gave enamides (**3a**-**b**) in 75% yield. The $Pd(PPh_3)Cl_2$ catalyzed reaction of substituted bromobenzenes (**4a-i**) with propiolic acid (**5**) gave the internal alkynes (**6a-i**) in good yields (60-90%) (Table 1).

When alkyne (**6a**) and enamide (**3a**) were reacted with SiO_2-$HClO_4$ (10 mol%) in 1,2-dichloroethane (DCE) at 90 °C for 12 hours, pyrrole **7a** was obtained in low yield.

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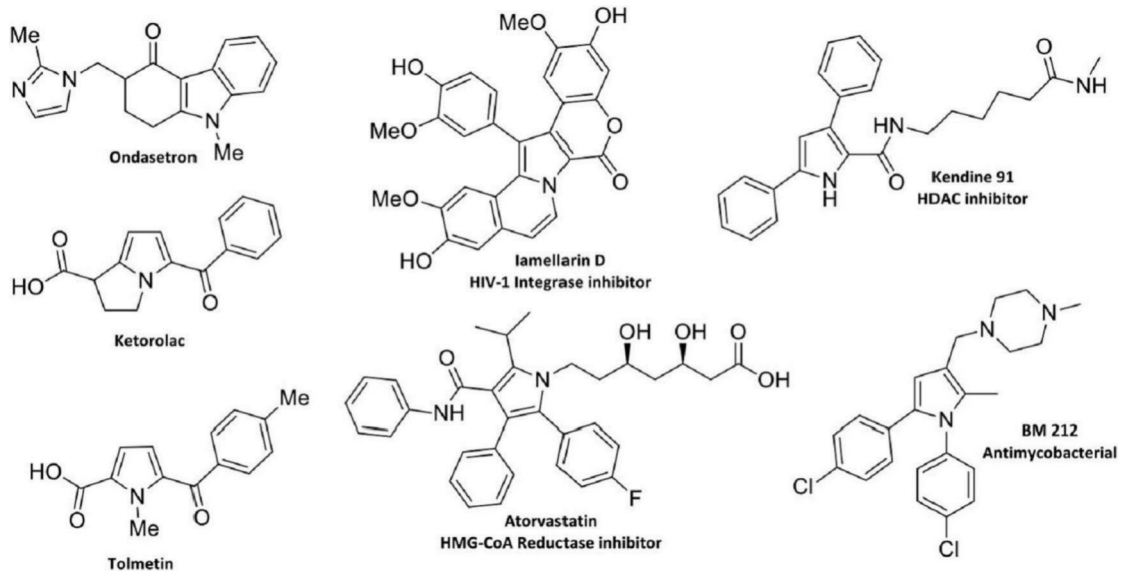


Fig. 1. Pyrrole-containing bioactive molecules.

However, the inclusion of $AgSbF_6$ (20 mol%) as an additive and $Cu(OAc)_2$ (0.5 equiv.) as an oxidant furnished the pyrrole **7a** in 78% yield (Table 2, entry 3). We studied catalysts and solvents (Table 2). We found that the best results were obtained with 10 mol % $HClO_4$-SiO_2 in DCE at 90° C for this cyclization reaction.

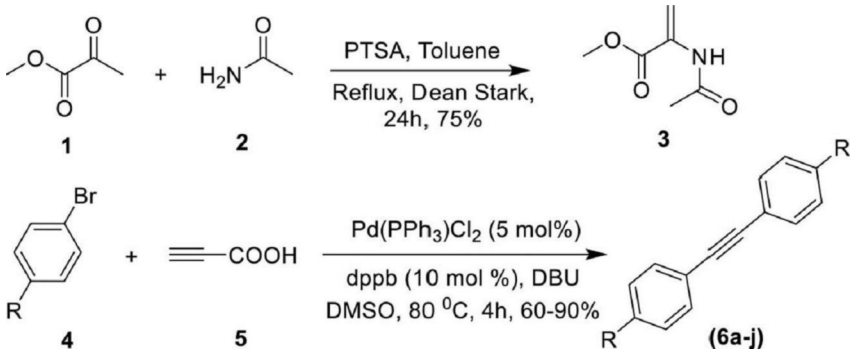
With this encouraging result in hand, we examined the cyclization reactions using differently-substituted alkynes (**6a-i**) with enamides (**3a-b**) (Table 3) to produce pyrroles **7a-i**. In general, yields were good (range 64-82%, mean 73%). The $Pd(PPh_3)Cl_2$ catalyzed reaction of bromobenzene (**4a**) and n-propyl bromide (**4j**) with propiolic acid (**5**) gave the internal alkyne (**6j**) in good yields (69%) (Scheme 1). Cyclization of enamide (**3b**) with alkyne (**6j**) using SiO_2-$HClO_4$ (10 mol%) in 1,2-dichloroethane, $AgSbF_6$ (20 mol%) as an additive and $Cu(OAc)_2$ (0.5 equiv.) as an oxidant afforded the pyrrole **7j** in 72% yield (Scheme 1). Both electron-donating and electron-withdrawing substituents on the internal alkynes were compatible with this reaction process, but the yield was slightly decreased in case of alkynes bearing withdrawing groups (entries **7e**, **7f** and **7i**). Internal alkynes having electron donating groups gave pyrroles in better yield than alkynes having electron withdrawing groups. The reaction did not occur with terminal alkynes.

In conclusion, we have developed an efficient and simple methodology for the one-pot synthesis of multisubstituted pyrroles from internal alkynes and an enamide. This methodology can be applied to the preparation of multi-substituted pyrroles, with a range of substituent groups. Having demonstrated this as an effective method for the preparation of substituted pyrroles, we hope that it will expand the number of complex pyrrole structures available for investigation.

Experimental section

Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Infrared spectra were recorded on Perkin–Elmer 683 spectrometer. Mass spectra were taken on Micromass VG-7070H for EI and VG Autospec M for FABMS. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F254 plates,

Table 1. Synthesis of enamide (**3a-b**) and internal alkynes (**6a-i**).



Entry	R	Time [h]	Yielda [%]
6a	H	04	72
6b	OMe	04	65
6c	Cl	04	79
6d	F	04	66
6e	CF_3	04	85
6f	Ac	04	90
6g	Me	04	60
6h	Br	04	66
6i	NO_2	04	60

[a]Products were purified using silica gel column chromatography.

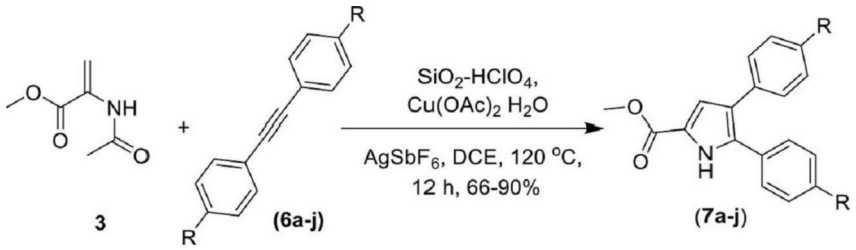
Table 2. Catalysts and solvents.

Entry	**Catalyst 10 Mol%**	Solvent	Time [h]	Yielda [%]
1	Fe_3O_4-SiO_2	DCE	20	48
2	H_2SO_4-SiO_2	DCE	15	56
3	$HClO_4$-SiO_2	DCE	12	78
4	$HClO_4$-SiO_2	CH_3CN	15	65
5	$HClO_4$-SiO_2	THF	14	60
6	$HClO_4$-SiO_2	Toluene	18	52

[a]Products were purified using silica gel column chromatography.

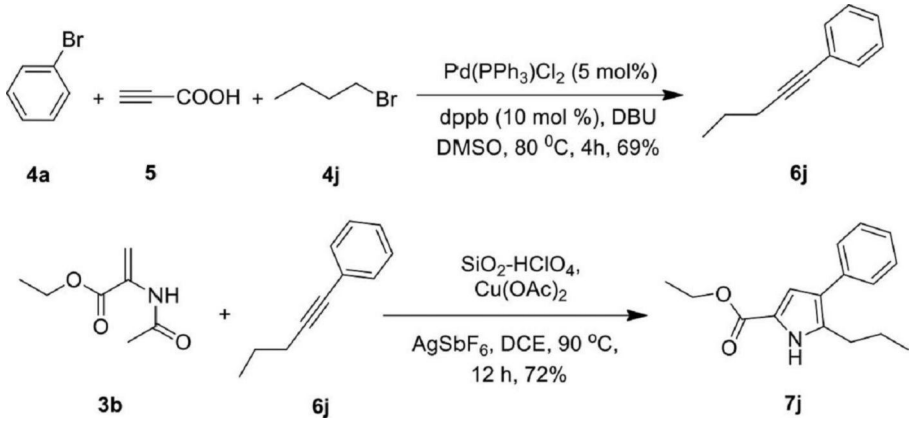
with eluents and R_f values as noted below. Visualization on TLC was achieved by the use of UV light (254 nm). Column chromatography was undertaken on silica gel (100–200 mesh) using the eluents described in individual procedures below. NMR spectra were recorded in chloroform-d and DMSO-d_6 at 300, 400 or 500 MHz for H-NMR spectra and 75, 100 or 125 MHz for C-NMR spectra. Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane. Coupling constants, J, were reported in hertz (Hz).

Table 3. SiO_2-$HClO_4$ catalyzed synthesis of pyrroles (**7a-j**) from enamide (**3**) and internal alkynes (**6a-j**).



Entry	R	Time [h]	Yielda [%]
7a	H	12	78
7b	OMe	12	82
7c	Cl	12	75
7d	F	12	70
7e	CF_3	12	68
7f	Ac	12	66
7g	Me	12	80
7h	Br	12	77
7i	NO_2	12	64

[a]Products were purified using silica gel column chromatography.



Scheme 1. SiO_2-$HClO_4$ catalyzed synthesis of pyrrole (**7j**) from enamide (**3b**) and internal alkyne (**6j**).

Synthesis of methyl 2-acetamidoacrylate (3a)

A round-bottom flask equipped with a Dean-Stark trap was charged successively with acetamide (**2**, 1.5 g, 25.4 mmol), methyl pyruvate (**3a**, 3.27 g, 22.9 mmol, 0.9 equiv), 10 mol% of *p*-TsOH, 4-methoxyphenol (4 mg, 25.4 mmol, 0.001 equiv) and toluene (50 ml). The stirred mixture was heated under reflux for 26 hours then concentrated under vacuum. The resulting yellow oil was taken up in CH_2Cl_2 (100 ml), washed with saturated $NaHCO_3$ (100 ml) and H_2O (100 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum to give methyl 2-acetamidoacrylate (**3a**). Yield 75%; Solid; mp 75-76 °C; R_f = 0.25 (5:1, Hexanes/EtOAc); Infrared (Neat): ν_{max} 3362, 2986, 1693, 1188, 731, 584 cm^{-1}; H-NMR (400 MHz, Chloroform-d) δ: 8.59 (1H, br s), 6.47 (1H, s), 4.40 (s, 3H), 2.28 (3H, s); C-NMR (100 MHz, Chloroform-d) δ: 168.8, 164.0, 131.0, 108.3, 62.1, 24.5, 14.0; Mass: m/z $[M+H]^+$ = 144.

Anal. Calcd. for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.26; H, 6.27; N, 9.71.

In a similar manner, we also prepared the corresponding ethyl 2-acetamidoacrylate (**3b**) for the synthesis of compound **7j**.

General Procedure for the synthesis of alkynes (6a-j)

bis(Triphenylphosphine)palladium (II) chloride ($Pd(PPh_3)_2Cl_2$) (5 mol%), 1,4-bis(diphenylphosphino)butane (dppb) (10 mol %), the appropriate aryl or heteroaryl bromide (20 mmol, 2 eq.) and propiolic acid (10 mmol, 1 eq.) were combined with DBU (20 mmol, 2 eq.) in a 50 ml round bottom flask. DMSO (15 ml) was added and the flask was sealed with a septum. The flask was kept in an oil bath at 80 °C for 4 hours. The reaction mixture was poured into 50 ml of saturated ammonium chloride solution and extracted with ethyl acetate (2 x 30 ml). The organic portion was separated and dried with sodium sulfate, then filtered. The organic layer was concentrated and purified by column chromatography with silica gel and 5% ethyl acetate in hexane as eluent.

1,2-Diphenylethyne (6a)

Yield 72%; Solid; Melting point 170–172 °C; Infrared (Neat): ν_{max} 3063, 1951, 1882, 1599, 1571, 1491, 1442 cm^{-1}; H-NMR (400 MHz, Chloroform-d) δ 7.48 – 7.41 (m, 4H), 6.89 – 6.84 (m, 4H); C-NMR (100 MHz, Chloroform-d) δ 159.41, 132.89, 115.75, 113.99, 87.97; ESI-MS: m/z $[M+H]^+$ 179.

Anal. Calcd. for $C_{14}H_{10}$: C, 94.34; H, 5.66. Found: C, 94.28; H, 5.57.

1,2-bis(4-Methoxyphenyl)ethyne (6b)

Yield 65%; Solid; Melting point 177–179 °C; Infrared (Neat): ν_{max} 3136, 3060, 2947, 1964, 1870, 1583, 1548, cm^{-1}; H-NMR (400 MHz, Chloroform-d) δ 7.48 – 7.41 (m, 4H), 6.89 – 6.84 (m, 4H), 3.82 (s, 6H); C-NMR (100 MHz, Chloroform-d) δ 159.41, 132.89, 115.75, 113.99, 87.97, 55. 32; ESI-MS: m/z $[M+H]^+$ 239.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.55; H, 5.84.

1,2-bis(4-Chlorophenyl)ethyne (6c)

Yield 79%; Solid; Melting point 142–144 °C; Infrared (Neat): ν_{max} 3128, 3052, 2974, 1930, 1865, 1571, 1543 cm^{-1}; H-NMR (400 MHz, Chloroform-d) δ 7.41 (d, J = 8.0 Hz, 4H), 7.17 – 7.12 (m, 4H), 2.36 (s, 6H); C-NMR (100 MHz, Chloroform-d) δ 138.20, 131.46, 129.11, 120.41, 88.90, 21.53; ESI-MS: m/z $[M+H]^+$ 248.

Anal. Calcd. for $C_{14}H_8Cl_2$: C, 68.04; H, 3.26. Found: C, 67.97; H, 3.20.

1,2-bis(4-Fluorophenyl)ethyne (6d)

Yield 66%; Solid; Melting point 132–134 °C; Infrared (Neat): ν_{max} 3146, 3079, 2984, 1948, 1834, 1542, 1570 cm^{-1}; H-NMR (400 MHz, Chloroform-d) δ 7.41 (d, J = 8.0 Hz, 4H), 7.17 – 7.12 (m, 4H), 2.36 (s, 6H); C-NMR (100 MHz, Chloroform-d) δ 138.20, 131.46, 129.11, 120.41, 88.90, 21.53; ESI-MS: m/z $[M+H]^+$ 215.

Anal. Calcd. for $C_{14}H_8F_2$: C, 78.50; H, 3.76. Found: C, 78.59; H, 3.69.

1,2-bis(4-(Trifluoromethyl)phenyl)ethyne (6e)

Yield 85%; Solid; Melting point 130–132 °C; Infrared (Neat): ν_{max} 3126, 3083, 2969, 1967, 1854, 1562, 1540 cm^{-1}; H-NMR (400 MHz, Chloroform-d) δ 7.41 (d, J = 8.0 Hz, 4H), 7.17 – 7.12 (m, 4H); C-NMR (100 MHz, Chloroform-d) δ 138.20, 131.46, 129.11, 120.41, 88.90; ESI-MS: m/z $[M+H]^+$ 315.

Anal. Calcd. for $C_{16}H_8F_6$: C, 61.16; H, 2.57. Found: C, 61.08; H, 2.61.

1, 2-Di-(4-Acetylphenyl)ethyne (6f)

Yield 90%; Solid; Melting point 188–190 °C; Infrared (Neat): ν_{max} 3168, 3054, 2975, 1982, 1863, 1735, 1567, 1526 cm^{-1}; H-NMR (400 MHz, Chloroform-d) δ 7.97 – 7.94 (m, 4H), 7.65 – 7.62 (m, 4H), 2.62 (s, 6H); C-NMR (101 MHz, Chloroform-d) δ 197.26, 136.65, 131.89, 128.35, 127.50, 91.67, 26.68; ESI-MS: m/z $[M+H]^+$ 263.

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.47; H, 5.30.

1,2-Di-p-tolylethyne (6g)

Yield 60%; Solid; Melting point 192–194 °C; Infrared (Neat): ν_{max} 3128, 3074, 2930, 1973, 1893, 1577, 1546 cm^{-1}; H-NMR (400 MHz, Chloroform-d) δ 7.41 (d, J = 8.0 Hz, 4H), 7.17 – 7.12 (m, 4H), 2.36 (s, 6H); C-NMR (100 MHz, Chloroform-d) δ 138.20, 131.46, 129.11, 120.41, 88.90, 21.53; ESI-MS: m/z $[M+H]^+$ 207.

Anal. Calcd. for $C_{16}H_{14}$: C, 93.16; H, 6.84. Found: C, 93.21; H, 6.88.

1,2-bis(4-Bromophenyl)ethyne (6h)

Yield 66%; Solid; Melting point 172–174 °C; Infrared (Neat): ν_{max} 3146, 3070, 2962, 1929, 1847, 1571, 1524 cm^{-1}; H-NMR (400 MHz, Chloroform-d) δ 7.41 (d, J = 8.0 Hz, 4H), 7.17 – 7.12 (m, 4H), 2.36 (s, 6H); C-NMR (100 MHz, Chloroform-d) δ 138.20, 131.46, 129.11, 120.41, 88.90, 21.53; ESI-MS: m/z $[M+H]^+$ 337.

Anal. Calcd. for $C_{14}H_8Br_2$: C, 50.04; H, 2.40. Found: C, 50.09; H, 2.32.

1,2-bis(4-Nitrophenyl)ethyne (6i)

Yield 60%; Solid; Melting point 120–122 °C; Infrared (Neat): ν_{max} 3176, 3054, 2971, 1979, 1883, 1594, 1538 cm^{-1}; H-NMR (400 MHz, Chloroform-d) δ 7.41 (d, J = 8.0 Hz, 4H), 7.17 – 7.12 (m, 4H); C-NMR (100 MHz, Chloroform-d) δ 138.20, 131.46, 129.11, 120.41, 88.90; ESI-MS: m/z $[M+H]^+$ 269.

Anal. Calcd. for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.01; N, 10.44. Found: C, 62.69; H, 3.01; N, 10.44.

Pent-1-yn-1-ylbenzene (6j)

Yield 69%; Solid; Melting point 152–154 °C; Infrared (Neat): ν_{max} 3146, 3059, 2934, 2836, 1584, 1543 cm^{-1}; H-NMR (400 MHz, Chloroform-d) δ 7.52 (dd, 2H), 7.40 – 7.41

(m, 3H), 2.42 (t, 2H), 1,58 (m, 2H), 1.04 (t, 3H); C-NMR (100 MHz, Chloroform-d) δ 126.4, 123.4, 101.6, 80.4, 20.5, 18.2, 10.8; ESI-MS: m/z $[M+H]^+$ 145.

Anal. Calcd. for $C_{11}H_{12}$: C, 91.61; H, 8.39. Found: C, 91.56; H, 8.43.

General Procedure for the synthesis of substituted pyrroles (7a-i)

A mixture of the enamide (**3a**, 0.30 mmol, 1.0 equiv.), the appropriate alkyne (**6a-i**, 0.33 mmol, 1.1 equiv.), $SiO_2{\cdot}HClO_4$ (10 mol %), anhydrous $Cu(OAc)_2$ (0.5 equiv.), and $AgSbF_6$ (20 mol%) (***Safety Note***: silver hexafluoroantimonate(V) is hazardous. All workers must be thoroughly trained on its use before undertaking experiments.), were weighed into a 50 mL Schlenk tube. Dry DCE (2.5 mL) was added, and the reaction mass was stirred at 90 °C for 12 hours under argon. After completion of reaction (monitored by TLC), the reaction mass was diluted with dichloromethane (10 mL) and transferred to a round bottom flask. Silica was added to the flask and volatiles were evaporated under reduced pressure. The purification of product was performed by flash column chromatography on silica gel with ethyl acetate/*n*-hexane (1:20) to afforded pure pyrrole (**7a-i**) in good yield (range 64-82%, mean 73%).

Methyl 4,5-diphenyl-1H-pyrrole-2-carboxylate (7a)

Yield 78%; Solid; Melting point 132–134 °C; Infrared (Neat): ν_{max} 3445, 3059, 2966, 2934, 2836, 2736, 1760 cm^{-1}; H-NMR (500 MHz, Chloroform-d) δ 7.33 – 7.26 (m, 3H), 7.25 – 7.21 (m, 2H), 7.15 – 7.03 (m, 6H), 3.9 (s, 3H); C-NMR (125 MHz, Chloroform-d) δ 173.9, 160.7, 134.4, 134.0, 130.7, 128.9, 128.6, 128.3, 128.0, 126.4, 124.8, 123.4, 118.3, 60.9; ESI-MS: m/z $[M+H]^+$ 278.

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.87; H, 5.49; N, 5.08.

Methyl 4,5-bis(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (7b)

Yield 82%; Solid; Melting point 145–147 °C; Infrared (Neat): ν_{max} 3392, 3059, 2948, 1716, 1598, 1534 cm^{-1}; H-NMR (300 MHz, Chloroform-d) δ 7.15 (d, J = 8.7 Hz, 2H), 7.05 (s, 1H), 7.00 (d, J = 8.7 Hz, (s, 3H), 2H),6.81 (d, J = 8.7 Hz, 2H), 6.67 (d, J = 8.7 Hz, 2H), 3.75(s, 3H), 3.69 (s, 3H),3.6 (s, 3H); C-NMR (75 MHz, Chloroform-d) δ 174.1, 160.8, 159.9, 158.2, 134.0, 132.1, 129.1, 126.7, 124.4, 123.0, 122.9, 118.2, 114.0, 113.7, 60.8, 55.20, 55.15; ESI-MS: m/z $[M+H]^+$ 238.

Anal. Calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.26; H, 5.73; N, 4.19.

Methyl 4,5-bis(4-chlorophenyl)-1H-pyrrole-2-carboxylate (7c)

Yield 75%; Solid; Melting point 160–162 °C; Infrared (Neat): ν_{max} 3380, 3056, 2972, 1701, 1570, 1532 cm^{-1}; H-NMR (300 MHz, Chloroform-d) δ 7.27 (d, J = 8.5 Hz, 2H), 7.17 –7.08 (m, 4H), 7.06 (s, 1H), 6.96 (d, J = 8.5 Hz, 2H), 3.78 (s, 3H); C-NMR (75 MHz, Chloroform-d) δ 173.5, 160.5, 135.3, 133.2, 132.6, 132.3, 132.1, 129.3, 129.0, 128.8, 128.6, 124.1, 123.7, 118.1, 61.1, 29.0; ESI-MS: m/z $[M+H]^+$ 247.

Anal. Calcd. for $C_{18}H_{13}Cl_2NO_2$: C, 62.45; H, 3.78; N, 4.05. Found: C, 62.52; H, 3.70; N, 4.16.

Methyl 4,5-bis(4-fluorophenyl)-1H-pyrrole-2-carboxylate (7d)

Yield 70%; Solid; Melting point 100–102 °C. Infrared (Neat): ν_{max} 3365, 3063, 2968, 1714, 1576, 1562 cm^{-1}; H-NMR (300 MHz, Chloroform-d) δ 7.26 – 7.15 (m, 2H), 7.05 (s, 1H), 7.03 – 6.92 (m, 4H), 6.88 – 6.78 (m, 2H), 3.89 (s, 3H); C-NMR (75 MHz, Chloroform-d) δ 173.7, 162.9 (d, JC-F = 248.2 Hz), 161.6 (d, JC-F = 244.5 Hz), 160.6, 133.3, 132.8 (d, JC-F = 8.3 Hz), 129.9 (d, JC-F = 2.8 Hz), 129.6 (d, JC-F = 7.9 Hz), 126.4 (d, JC-F = 2.6 Hz), 124.2, 123.5, 118.2, 115.8 (d, JC-F = 21.6 Hz), 115.3 (d, JC-F = 21.3 Hz), 61.0; ESI-MS: m/z $[M+H]^+$ 314.

Anal. Calcd. for $C_{18}H_{13}F_2NO_2$: C, 69,01; H, 4.18; N, 4.47. Found: C, 69,12; H, 4.12; N, 4.55.

Methyl 4,5-bis(4-(trifluoromethyl)phenyl)-1H-pyrrole-2-carboxylate (7e)

Yield 68%; Solid; Melting point 206–208 °C; Infrared (Neat): ν_{max} 3382, 3068, 2982, 1724, 1598, 1532 cm^{-1}; H-NMR (400 MHz, Chloroform-d) δ 9.61 (s, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 2.7 Hz, 1H). 3.9 (s, 3H); C-NMR (75 MHz, Chloroform-d) δ 161.2, 138.6, 135.0, 132.1 (q, J_{C-F} = 32.4 Hz), 128.9, 128.6, 128.5, 128.4, 126.1, 125.8 (q, J_{C-F} = 3.8 Hz), 125.5 (q, J_{C-F} = 3.8 Hz), 125.7, 123.6 (d, J_{C-F} = 5.5 Hz), 122.2 (d, J_{C-F} = 23.9 Hz), 116.7, 60.9; ESI-MS: m/z $[M+H]^+$ 414.

Anal. Calcd. for $C_{20}H_{13}F_6NO_2$: C, 58.12; H, 3.17; N, 3.39. Found: C, 58.05; H, 3.11; N, 3.46.

Methyl 4,5-bis(4-acetylphenyl)-1H-pyrrole-2-carboxylate (7f)

Yield 66%; Solid; Melting point 361–363 °C; Infrared (Neat): ν_{max} 3394, 3056, 2969, 1709, 1565, 1528 cm^{-1}; H-NMR (400 MHz, Chloroform-d) δ 7.99 – 7.92 (m, 2H), 7.83 – 7.77 (m, 2H), 7.42 – 7.37 (m, 2H), 7.26 (s, 1H), 7.21 – 7.16 (m, 2H), 3.6 (s, 3H), 2.63 (s, 3H), 2.55 (s, 3H); C-NMR (75 MHz, Chloroform-d) δ 197.5, 197.3, 173.4, 160.5, 138.6, 137.2, 135.3, 135.1, 133.8, 131.0, 128.6, 128.1, 124.4, 124.3, 118.2, 61.3, 29.1, 26.6; ESI-MS: m/z $[M+H]^+$ 362.

Anal. Calcd. for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88. Found: C, 73.19; H, 5.38; N, 3.81.

Methyl 4,5-di-p-tolyl-1H-pyrrole-2-carboxylate (7g)

Yield 80%; Solid; Melting point 341–343 °C; Infrared (Neat): ν_{max} 3386, 3054, 2983, 1718, 1602, 1535 cm^{-1}; H-NMR (400 MHz, Chloroform-d) δ 7.27 – 7.15 (m, 3H), 7.13 – 7.00 (m, 4H), 6.97 (d, J = 7.5 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 3.89 (s, 3H), 2.32 (s, 3H), 2.30 (s, 3H); C-NMR (125 MHz, Chloroform-d) δ 174.0, 160.7, 138.2, 137.7, 134.6, 133.9, 131.2, 130.8, 129.6, 128.7, 128.4, 128.0, 127.8, 127.1, 125.0, 124.6, 123.2, 118.2, 60.8, 28.9, 21.4; ESI-MS: m/z $[M+H]^+$ 306.

Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.59; H, 6.34; N, 4.49.

Methyl 4,5-bis(4-bromophenyl)-1H-pyrrole-2-carboxylate (7h)

Yield 77%; Solid; Melting point 322–324 °C; Infrared (Neat): ν_{max} 3445, 3059, 2947, 1710, 1595, 1529 cm^{-1}; H-NMR (300 MHz, Chloroform-d) δ 7.27 (d, J = 8.5 Hz, 2H), 7.17 – 7.08 (m, 4H), 7.06 (s, 1H), 6.96 (d, J = 8.5 Hz, 2H), 3.78 (s, 3H); C-NMR (75 MHz, Chloroform-d) δ 173.5, 160.5, 128.8, 128.6, 124.1, 123.7, 118.1, 61.1, 29.0; ESI-MS: m/z $[M+H]^+$ 436.

Anal. Calcd. for $C_{18}H_{13}Br_2NO_2$: C, 49.69; H, 3.01; N, 3.22. Found: C, 49.61; H, 3.14; N, 3.15.

Methyl 4,5-bis(4-nitrophenyl)-1H-pyrrole-2-carboxylate (7i)

Yield 64%; Solid; Melting point 311–313 °C; Infrared (Neat): ν_{max} 3420, 3056, 2954, 1713, 1589, 1517 cm^{-1}; H-NMR (300 MHz, Chloroform-d) δ 7.27 (d, J = 8.5 Hz, 2H), 7.17 – 7.08 (m, 4H), 7.06 (s, 1H), 6.96 (d, J = 8.5 Hz, 2H), 3.78 (s, 3H); C-NMR (75 MHz, Chloroform-d) δ 173.5, 160.5, 135.3, 133.2, 132.6, 132.3, 132.1, 129.3, 129.0, 128.8, 128.6, 124.1, 123.7, 118.1, 61.1, 28.0; ESI-MS: m/z $[M+H]^+$ 368.

Anal. Calcd. for $C_{18}H_{13}N_3O_6$: C, 58.86; H, 3.57; N, 11.44. Found: C, 58.77; H, 3.51; N, 11.36.

Ethyl 4-phenyl-5-propyl-1H-pyrrole-2-carboxylate (7j)

A mixture of the enamide (**3b**, 0.30 mmol, 1.0 equiv.), alkyne (**6j**, 0.33 mmol, 1.1 equiv.), $SiO_2{\cdot}HClO_4$ (10 mol %), anhydrous $Cu(OAc)_2$ (0.5 equiv.), and $AgSbF_6$ (20 mol%) (**Safety Note**: silver hexafluoroantimonate (V) is hazardous. All workers must be thoroughly trained on its use before undertaking experiments), were weighed into a 50 ml Schlenk tube. Dry DCE (2.5 ml) was added, and the reaction mass was stirred at 90 °C for 12 hours under argon. After completion of reaction (monitored by TLC), the reaction mass was diluted with dichloromethane (10 mL) and transferred to a round bottom flask. Silica was added to the flask and volatiles were evaporated under reduced pressure. The purification of product was performed by flash column chromatography on silica gel with ethyl acetate/*n*-hexane (1:20) to afford the pure pyrrole (**7j**). Yield 72%; Solid; Melting point 248–250 °C; Infrared (Neat): ν_{max} 3384, 3058, 2948, 1713, 1584, 1526 cm^{-1}; H-NMR (300 MHz, Chloroform-d) δ 9.21 (s, 1H), 7.37 (m, 5H), 7.34 (s, 1H), 4.28 (q, 2H), 2.57 (t, 2H), 1.70 (m, 2H),1.65 (t, 3H), 0.95 (t, 3H); C-NMR (75 MHz, Chloroform-d) δ 161.3, 135.9, 133.6, 127.9, 125.9, 123.7, 120.7, 116.5, 77.2, 60.3, 28.6, 24.0, 14.0; ESI-MS: m/z $[M+H]^+$ 258.

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: 74.60; H, 7.49; N, 5.35.

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समीचीन

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पीयर रिव्यूड व यू. जी. सी. केयर लिस्ट में सम्मिलित जर्नल

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वर्तमान के बिगड़े सांप्रदायिक परिवेश का यथार्थ चित्रण : हमारा शहर उस बरस

डॉ. गोविंद गुंडप्पा शिवमोग्गा

गीतांजलि श्री का हमारा शहर उस बरस बेहद लोकप्रिय औपन्यासिक कृति है। इस कृति में सांप्रदायिकता के बौद्धिक विमर्श को केंद्र में रखकर धार्मिक हिंसा और सांप्रदायिकता की जड़ों को टटोलते हुए इंसानों और उनकी आस्थाओं को भी पकड़ने की कोशिश की गई। आलोच्य कृति की बुनियाद बाबरी मस्जिद विध्वंस के बाद देश के अलग-अलग शहरों में सांप्रदायिक तनाव, दंगे-फसाद की घटना है। उपन्यास में किसी प्रकार के काल और स्थान को परिभाषित नहीं किया गया है क्योंकि कोई भी शहर, किसी भी स्थान विशेष से उपन्यास जुड़ पाएगा। शहर यहाँ जले या वहाँ, लोग इधर के मरें या उधर के, तसल्ली न इनको मिल पाती है और न उनको। बेहद रोचक ढंग और बौद्धिकता के स्तर से दंगों की मानसिकता को उकेरती हुई इस कृति ने मानवता के आगे कई दहला देने वाले सवाल खड़े कर दिए हैं।

देश आजादी का अमृत महोत्सव मना रहा है। जिस देश की रीढ़ की हड्डी है धर्मनिरपेक्षता, वही आज दरअसल खतरे में है। आजादी के 75 साल बाद देश में सांप्रदायिकता इतनी क्यों बढ़ी और क्या कारण हैं, इस पर बहस करवाता है यह उपन्यास। सांप्रदायिक विवाद कोई मामूली सवाल नहीं है। इस विवाद को भारतवर्ष ने विभाजन की विभिषिका के रूप में झेला है। 21 वीं सदी के आरंभ होने से पहले जो सपने देखे थे, उनमें यह भी था कि आधुनिक यंत्रों से लैस मनुष्य दुनिया की सारी नियामतों को पा सकने में समर्थ होगा और दुनिया को देखने की मानवीय दृष्टि का विस्तार होगा। यह शताब्दी पूरी तरह से मानव विकास और मानवीयता की होगी किंतु ऐसा नहीं हुआ। हम पीछे लौट रहे हैं। हमारी आँखें आगे हैं लेकिन पैर पीछे हैं। राजनीति में धर्म, शैक्षिक संस्थानों में धर्म, हर जगह धर्म का बढ़ता उग्र रुप आनेवाले खतरों की चेतावनी दे रहा है। गीतांजलि श्री ने सन् 1998 में इस कृति का लेखन कर वर्तमान की सांप्रदायिक तनाव की स्थितियों की यथार्थ तस्वीर उपस्थित की है।

लेखिका ने उपन्यास हमारा शहर उस बरस में साम्प्रदायिक दंगों और अशांत वातावरण को पूरी शिद्दत से अभिव्यक्त किया है। उपन्यास में एक शहर है, जहाँ एक मठ है, एक विश्वविद्यालय है। ये दोनों ही संस्थाएँ समय-समय पर साम्प्रदायिक गतिविधियों को बढ़ावा देती है। इन दोनों संस्थाओं को बढ़ावा अखबार देता है। अखबार साम्प्रदायिकता की हवा को ओर तेज करने में अहम् भूमिका निभाता है। सांप्रदायिक दंगों का भय उपन्यास में आरम्भ से लेकर अंत तक बना रहता है। लेखिका ने प्रस्तुत उपन्यास में सांप्रदायिक दंगों के भय को उपन्यास का

मूल कथ्य बनाया है। प्रस्तुत उपन्यास के फ्लैप पर दिए गये वाक्य समीचीन लगते हैं- बात उस बरस की है, जब हमारा शहर आए दिन सांप्रदायिक दंगों से ग्रस्त हो जाता था। आगजनी, मारकाट और तद्जनित दहशत रोजमर्रा का जीवन बनकर एक भयावह सहजता पाते जा रहे थे। कृत्रिम जीवन शैली का यों सहज होना शहरवासियों की मानसिकता व व्यक्तित्व ही नहीं बल्कि पूरे वजूद पर चोट कर रहा था। बात दरअसल उस बरस भर की नहीं है, उस बरस को हम आज में भी घसीट लाए हैं। न ही बात सिर्फ हमारे शहर की। और शहरों जैसा ही है हमारा शहर.... सुलगता खदकता- स्रोत और प्रतिबिम्ब दोनों ही मौजूदा स्थिति का।...अभी भी जो समझ रहे हैं कि दंगे उधर हैं दूर, उस पार। उन लोगों में पाते हैं कि उधर इधर बढ़ आया है और वे लोग हम लोग भी। दंगे जहाँ हो रहे हैं, वहाँ खून बह रहा है। ...अपनी ही खाल के नीचे छिड़े दंगे से दरपेश होने की कोशिश है इस गाथा का मूल।[1]

इसमें कोई शक नहीं की हमारा शहर उस बरस नहीं था बल्कि कई वर्षों पूर्व उस से लेकर आज तक सैदव विद्यमान है। शहर पुल, नाले, गली दीवार के इस पार और उस पार है। जैसा कि लेखिका ने उपन्यास में लिखा है हमारा शहर देश की दंगों का स्रोत और प्रतिबिम्ब दोनों बना हुआ है। देवी मठ यहीं है और उसकी शाखाएँ दूसरे शहरों में फूटती जा रही हैं। यहाँ घूम लो तो मान लो भारत भ्रमण हो गया।[2] वर्तमान समय की यह सबसे बड़ी विडम्बना है कि, जो लोग विवेकवान और बुद्धिजीवी हैं, उन्होंने भी अन्याय के खिलाफ आवाज उठानी बंद कर दी है तो फिर उन लोगों से संघर्ष की उम्मीद कैसे कर सकते हैं? वर्तमान दौर में भी देखिए सत्ता की तानशाही के आगे बुद्धिजीवी सिर झुकाए से बैठे हैं। गीतांजलि श्री ने अपने उपन्यास में भी कुछ ऐसे ही पात्रों का चित्रण किया है, जिनके पास विवेक तो होता है लेकिन या तो वो चुप्पी साधे हुए हैं या फिर अपना स्वार्थ साधने के लिए कोई कुचक्र रचते हैं। लेखिका इस उपन्यास में ऐसे छद्म व्यक्तियों के चेहरे को बेनकाब करती हैं। प्रस्तुत उपन्यास में लेखिका मैं कथा वाचक के रूप में शहर की हर घटनाओं का विवरण देती है। लेखिका उपन्यास के आरम्भ से लेकर अंत तक हर जगह उपस्थित है। उपन्यास के शुरुआत में ही इस बात का अहसास पाठकों को होने लगता है कि जरुर कुछ ऐसा घट चुका है जिससे आने वाला वक्त बुरी तरह उससे प्रभावित होने वाला है।

हनीफ, शरद और श्रुति उपन्यास के प्रमुख पात्र हैं। तीनों मित्र हैं। साथ ही अपनी सामाजिक जिम्मेदारी के प्रति सचेत हैं। तीनों शहर के अंदर होने वाले साम्प्रदायिक तनाव के प्रति चिंतित भी हैं। जिस समय शहर में दंगे, फसाद, मारकाट होती है, उस समय दूसरे विवेकवान बुद्धिजीवी अपने घरों में दुबके रहना पसंद करते हैं। वहीं हनीफ, शरद और श्रुति तीनों दंगों से प्रभावित इलाकों का दौरा करने जाते हैं। साम्प्रदायिक दंगों से सम्बन्धित रिपोर्ट को अखबार में प्रकाशित करवाते हैं, जिसका नुकसान भी इन्हें सहन करना पड़ता है। सारा शहर मानों उनका दुश्मन बन जाता है। बढ़ते हुए साम्प्रदायिक तनाव के कारण शहर में अफवाहों की भी अहम् भूमिका होती

है। वास्तव में सांप्रदायिक तनाव के क्षणों में किसी पर विश्वास करना आसान नहीं होता। सामान्य हालत पर विश्वास किया जा सकता है, पर असामान्य हालत पर संदेह, भय की स्थिति ही उभरती है। उस बरस एक बार सड़कों पर ऐसी ही नदियाँ बहने लगी थीं, पर वह बारिश का नहीं था, टंकियों का पानी था, जो मुहल्लों के मुहल्लों ने जहर के डर से खोलकर बहा दिया था।[3] उस बरस सड़कों पर उन्माद की नदियाँ बहने लगी थीं। शहर दो हिस्से में बँट गया था, पुल के इस पार और उस पार। लोग पुल के इस पार वाले इलाके को हिंदुस्तान और उस पार वाले इलाके को पाकिस्तान कहने लगे थे। दोनों ही हिस्से में कभी इस पार तो कभी उस पार दंगे, हत्याएँ, लूटपाट, बलात्कार, लाशों के ढेर लग जाते थे। शहर के हालातों पर काबू पाने के लिए एक बार नहीं बल्कि अनेक बार कर्फ्यू लगाया जाता है- कहीं दूर पुल के उस पार शहर में कुछ घट गया। एक संप्रदाय के चार युवकों ने दूसरे संप्रदाय के इक्के चालक को जबरन नीचे खींचकर उसकी आँखें फोड़ दीं, भीड़ जमा हुई तो पुलिस को आँसू गैस छोडनी पड़ी, कुल मिलाकर दो मरे, छः घायल। अब स्थिति पूरी तरह से नियंत्रण में हैं। एहतियातन कर्फ्यू लगा दिया गया है।[4] शहर में संदेह और डर हमेशा लोगों के मन में बना रहता है। ये इस धर्म का, वह उस धर्म का। ये हमारे धर्म का नहीं है, इसे मारो-पीटो। उस तरफ भीड़ ने ट्रक रोककर उसके ट्रक ड्राइवर को मार दिया।[5] इस प्रकार की घटनाएँ उस बरस अखबारों के पन्नों में आम खबर बन जाती है। सांप्रदायिक तनाव के माहौल में लोग अपने आप को असुरक्षित महसूस करते हैं। पुल के इस पार और उस पार, हिन्दू हो या मुस्लिम आम इंसान कहीं पर भी महफूज नहीं है। न घरों में और न ही सड़कों पर। साम्प्रदायिक दंगाई मौका मिलते ही अपना शिकार उन लोगों को बनाते हैं, जिनका इन दंगों से कोई लेना देना भी नहीं होता। शहर में आतंक का माहौल हर जगह छाया हुआ है। अखबार में खबर और तस्वीर छपी है कि स्वरूपनगर की बड़ी कोठियों को जलाने की कोशिश हुई है। शहर का तनाव स्थानीय पुलिस द्वारा नियंत्रित न होने के कारण सी.आर.पी.एफ. को हटा कर वहाँ बी.एस.एफ. को बुलाया जाता हैक उग्र साम्प्रदायिकों ने शहर का वातावरण असहनीय बना रखा है। बार - बार कर्फ्यू लगने और स्थिति सामान्य होने के बाद फिर थोड़ी ढील होने पर या किसी प्रकार का विवादी भाषण या कोई लेख अखबार में छपने पर वैसा ही माहौल वापिस आ जाता है। शहर में तनाव और बढ़ जाता है। सांप्रदायिक दंगों से तंग आकर कई लोग अपने-अपने घरों को छोड़ कर भागने लगे हैं। जिनके पास जाने के ठिकाने हैं, वो वहाँ जा रहे हैं। बहुत से ऐसे भी लोग हैं जो शहर को छोड़कर जाना चाहते हैं। पर जा नहीं सकतें, उनके पास जाने के ठिकाने नहीं हैं। शहर में तनाव कम करने के लिए बी.एस.एफ. को हटा कर गोरखा रेजीमेंट बुलायी जाती है। पहले खबर आती थी, उस पार किसी को जला दिया, किसी को चोट लग गई, किसी को मार दिया गया, सामूहिक बलात्कार हुए, किसी का घर लूट लिया जैसी खबर पहले दूसरे स्थान के लिए दूसरे वक्त में होती थी। अब ये खबरें, उसी शहर के, उसी

समय में, रोज के अखबारों में, उन्हीं की जगहों के बारे में होती है।

नेताओं के साथ भारी भीड़, मस्जिद में नमाज अदा करने के लिए, चल देती है। पुलिस भीड़ को रास्ते में ही रोक देती है। हवा में चार गोलियाँ चलाई जाती हैं। गोलियों की आवाज से भीड़ बेकाबू हो कर इधर-उधर भागने लगती है। कुछ लोग जमीन पर गिर जाते हैं। लोग उन्हीं पर चढ़ कर भागने लगते हैं। भीड़ उन्हें अपने पैरों के नीचे कुचल देती है। अखबार में खबर आती है- सब बुरी तरह से घबरा गए हैं। पचास से ज्यादा लोग तीसेक मिनट के अंदर ही अंदर मर गए हैं और उनमें बच्चे भी थे। अधिकांश पैरों तले रौंद दिए गए, बाकी अखबारों का कहना है- मेडिकल ओपिनियन है कि डिस्फिक्सिएशन से गए। शहर में आतंक का साया छा जाता है। पुल के उस पार के लोग, इस पार नहीं आना चाहते और न ही इस पार के लोग उस पार जाना चाहते हैं। एक ही शहर सांप्रदायिक दंगों के कारण दो अलग-अलग शहरों में विभाजित हो गया है।

शरद, हनीफ और श्रुति के साथ कुछ विद्यार्थी इन दंगों के बारे में आपस में वाद-विवाद करते हैं। एक विद्यार्थी अपने प्राध्यापक से कहता है- मैं आप लोगों की बात नहीं कर रहा, उन लोगों की कर रहा हूँ, उस पार रहने वाले। उधर सर, मुसलमानों के मोहल्ले में जाने से डर लगता है।' इन सब बातों को सुन कर, हनीफ को थोड़ा दुःख होता है। उस समय आम धारणा बन गई कि मुसलमानों में साम्प्रदायिकता भरी है।' हनीफ एक मुसलमान है परन्तु वह अपने आप को हिन्दू भी मानता है- मैं हूँ, मगर वैसा नहीं। कैसा नहीं? उनके जैसा। जो उधर रहते हैं। दंगे करवाते हैं। खून बहाते हैं। दंगे का मतलब जानते हो? श्रुति उठ गई। असल दंगे वहाँ है जहाँ खून बह रहा है।' श्रुति का कथन बिल्कुल सही है। वास्तव में दंगे तो वहाँ है जहाँ निर्दोष लोगों का खून बह रहा है, दंगे करने वाले इंसानों का कोई मजहब नहीं होता, न ही कोई इमान होता है। वे तो केवल सांप्रदायिक मानसिक बीमारी से ग्रस्त होते हैं। अचानक एक लड़का दौड़ कर आता है और जोर से चीखता है-हाय-हाय मार डाला मुसल्लों ने मारा। उस बरस शहर में सही जानकारी लिए बिना ही चाकू-छुरियाँ हवा में लहराने लगते हैं। परिणाम स्वरूप तीन लोगों के शव गली में मिलते है। एक शव तो उस बेकसूर भिखारी फकीर का है। न जाने क्यों उन साम्प्रदायिक उग्र लोगों को उस बेचारे भिखारी से किस प्रकार का डर था कि उसे मार दिया, उस पर अपनी विजय हासिल कर ली। साम्प्रदायिकता की आग में बेकसूर लोग जलते हैं। कपाड़िया, शरद, दद्दू, हनीफ और श्रुति को शहर के दंगों के बारे में बताता है कि दंगों में बेकसूर लोगों को, जो अपने आप को मुसलमान भी नहीं मानते दंगाइयों ने उन्हें भी अपना शिकार बनाया है। वे लोग अपनी सफाई भी देते हैं कि हम मुसलमान नहीं हैं, हम तो मैमन हैं। लोग तंग आ चुके हैं। दोनों तरफ के गुंडों के खुलकर नाम बता रहे है-जो खुद को पूरी तरह मुसलमान मानते नहीं, वे भी पार लग गए। क्रूर से क्रूर आदमी भी रो पड़ेगा। निहत्थे लोगों को मारा है और वे कह रहे है

कि हमें क्यों मार रहे हो, हम तो मैमन हैं...।[10]

अखबार में एक और हिन्दू और मुसलमानों को आपस में भड़काने वाली खबर आती है कि- मस्जिद में जो बम फूटा है, उसके बारे में यह माना जा रहा है कि इसमें हिन्दुओं का हाथ है ही नहीं कि मुसलमानों ने जो बम हथियार छिपा रखे थे, उन्हीं में गलती से एक फट गया।[11] खबर का मकसद लोगों को बताना है कि मुसलमान अपने ही पवित्र स्थानों पर गोलियाँ और बारूद छिपाये रखते हैं और मुसलमानों का आक्रामक चेहरा दिखाना चाहे हकीकत कुछ और ही क्यों न हो? शहर में जहाँ दोनों सम्प्रदायों के बीच शांति है। वहाँ भी गैर और बेगैर सांप्रदायिक उग्र तत्त्व शांत माहौल को तोड़ने की कोशिश करते हैं। उनकी गतिविधियों द्वारा किसी को कितना भी नुकसान क्यों न हो? सुख, चैन को खत्म कर के उन्हें तो सिर्फ आतंक ही फैलाना है- एक मुसलमान की फैक्टरी में आग लगाई गई। आग फैलकर बगल की पोलिथीन फैक्टरी को भी भस्म कर गई, जो हिन्दू की है। दोनों पड़ोसी और उनके पीछे ढेर सारे हिन्दू और मुसलमान गमगीन खड़े हैं। हमारे यहाँ कोई दुश्मनी नहीं है बाहर वालों की कारस्तानी है।[12] हनीफ, श्रुति और शरद तीनों दंगों के खिलाफ अपना लेख अखबार में छपवाते हैं। अखबार का संपादक बड़ी ही चालाकी से तीनों के नाम में से केवल हनीफ का नाम अखबार में छापता है। शहर के उग्र साम्प्रदायिक तत्त्वों का सारा गुस्सा हनीफ की ओर मुड़ जाता है। हनीफ को हर तरह से मानसिक पीड़ा देने लगते हैं। आए दिन अखबार में खबरें छपती रहती हैं। खबरों में हनीफ से माफी माँगने और धमकी देनी की खबरें आती रहती हैं। वहीं दूसरी तरफ मुसलमान भी अपने अखबार, पर्चों के द्वारा शांति की आड में साम्प्रदायिकता की भावनाओं को बढ़ावा देते हैं- मकबूल हक अपने अखबार में मुसलमानों की अलग अदालतें होने जैसी खबरें छापता है क्योंकि सरकारी अदालतों ने उनकी रक्षा नहीं की है।[13] एक तरफ वह मुसलमानों को पकड़ता है और दूसरी तरफ शांति बनाए रखने के लिए पर्चे छपवाता है।

शहर के लोगों में एक - दूसरे के प्रति संदेह, भय और गलतफहमियों को दूर करने और आपसी समीपता लिए एक सभा आयोजित की जाती है। इस सभा में शरद और हनीफ, हिन्दू और मुसलमान के संबंधों पर अपने विचार को प्रस्तुत करने जाते हैं। सभा में शरद को सभी ध्यान से सुनते हैं क्योंकि वह हिन्दू है। शरद के अनुसार मैं सुधार की माँग कर रहा हूँ, मुसलमानों में भी, औरों में भी। सारे धर्मों के कट्टर तत्वों को बढ़ने देने के खिलाफ बोल रहा हूँ। जिन हिन्दुओं ने और जिन मुसलमानों ने मजहब को इतना घिनौना बना दिया है, उन दोनों के खिलाफ बोल रहा हूँ।[14] परन्तु जैसे ही हनीफ बोलने वाला होता है, सभा में खुसर- फुसर होने लगती है क्योंकि हनीफ मुसलमान है। हनीफ अपना भाषण नहीं दे पाता। साम्प्रदायिक मानसिकता से ग्रसित लोग हनीफ के बोल को समझने की बजाय चुप बे गैर हिन्दू तेज आवाज करके पत्थर मारता है जो शरद के कपाल पर लगता है। शरद घायल हो जाता है। पत्थर मार रहे हैं उग्र तत्त्व जै

- जगदम्बे का नारा भी लगाते हैं। दूसरे दिन अखबार में घायल हुए शरद को हीरो बना दिया जाता है। कुछ साम्प्रदायिक युवक, हनीफ को मारने के लिए उसके घर पर हमला करते हैं। उसे गाली देते हैं, जिसे सुनकर दद्दू गुस्सा होते हैं। वे भी उन युवकों को गालियाँ देते हैं। घर से चले जाने के लिए कहते हैं। दंगाई युवक और अधिक गुस्से में आकर दद्दू को ऊपर उछाल कर दूर फेंक देते है- दद्दू मुँह के बल गिर पड़े थे। उनकी धोती जांघों के ऊपर तक उलट गई थी और उनकी पतली नंगी टाँगे बेइज्जत होकर धूल में पड़ी थीं।'[15] मानवता का पतन सरेआम होता है। यह घटना इस ओर इशारा करती है कि भारत में न तो जनतंत्र है, न ही मानवीय मूल्य। सारा वातावरण दमघोंटू बनने की राह पर है। इसे बचाया जा सकता है- यदि हम हिन्दू और मुसलमान दोनों ईमानदारी के साथ पारस्परिक सम्मान और स्नेह का वातावरण पैदा करने का सक्रिय प्रयत्न करें तो कोई कारण नहीं कि इस समस्या का समाधान न हो सके।'[16]

शशिकला राय अपने विचार प्रकट करते हुए कहती हैं- जब धीरे-धीरे आजादी... स्वर्ण जयंती की ओर सरक रही थी... तब भारत भर में नर-पिशाचों का घोर धर्म विध्वंसी तांडव हो रहा था। मस्जिद गिरिजाघर के साथ-साथ मंदिरों की भी नींव हिली। लेखिका की वेदना है कि चाहे कुछ भी कह लें हम, नींव तो राष्ट्र की ही हिली। जिस तरह मुल्क में ईंटें टूटीं, उसमें सच तो यह है कि नींव तो मुल्क की हिली। एक बार जो नींव हिल गई तो उसी मजबूती को लेकर न तो हम निःशंक रह सकते हैं न ही आश्वस्त। सदा दहशत का साया हमारे ऊपर मंडराता है। हमारे मुल्क में धर्म लाउस्पीकरों में बँटता है अब। शरद, हनीफ भी नाम होकर मुहिम बन गए। वे जो धर्म के पाखंडों का विद्रोह करते थे, वे एक-दूसरे के साथ सहज नहीं रह पाते। साम्प्रदायिकता का तूफान गुजर चुका है, तूफान का खौफ बाकी है। उस साल की बदहवास सरगोशियाँ बीत रहे सालों के साथ लिपटी हैं।'[17]

जिस देश में इतिहास को भी सांप्रदायिक रंग दे दिया जाए उस देश को कौन बचा सकता है? आज सारे मुल्क में राष्ट्रवाद, देशभक्ति के नाम पर सांप्रदायिक सौहार्द को बिगाड़ने की कोशिशें जोर शोर से जारी है किंतु हम इस शाश्वत सत्य को क्यों नकार रहे हैं कि जिस तरह हिंदू और मुसलमान होना किसी आदमी के अपने बस की बात नहीं है, जहाँ उसका जन्म हो गया, वह वही हो गया लेकिन है तो इसी देश के हम सभी। धार्मिक सहिष्णुता हमारी पहचान है। इस बात को कभी ना भूलें हम।

संदर्भ :

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२. हमारा शहर उस बरस, गीतांजलि श्री- पृ.सं १७
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