NJC

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: S. vedachalam, N. Murugesh, P. Chakraborthy, R. Karvembu and X. Liu, *New J. Chem.*, 2017, DOI: 10.1039/C7NJ04057A.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/njc

ROYAL SOCIETY OF CHEMISTRY
View Article Online
DOI: 10.1039/C7NJ04057A

Journal Name

ARTICLE

NHC catalyzed enantioselective Coates-Claisen rearrangement : A rapid access to the dihydropyran core for Oleuropein based Secoiridoids

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Seenuvasan Vedachalam,*[a] Nithya Murugesh,[a] Priyanka Chakraborty,[a] Ramasamy Karvembu[a] and Xue-Wei Liu*[b]

"We present a short synthesis of a suitably functionalized enantioselective dihydropyran core of Secoiridoids using N-heterocyclic carbene (NHC) catalyzed Coates-Claisen rearrangment mechanism. Key steps of the synthesis are (i) the highly enantioselective NHC catalyzed Coates-Claisen rearrangment for dihydropyran core (ii) the highly diastereoselective exocyclic *trans* alkene for the assembly of the target dihydropyran core structure of Oleuropein (iii) highly stereoselective assembly of monoterpene elenolide core structure."

Introduction

Secoiridoids are monoterpenoid based natural products, they have a unique dihydropyran based structural skeleton. Their novel structures and potent biological activity makes these scarcely available Secoiridoids acts as an attractive synthetic target for the medicinal chemistry community. Oleuropein based Secoiridoid natural products have a characteristic dihydropyran ring with an unique stereo structural analogy (Figure 1).[1] Similar natural products have also been identified, consolidating to over 250 members in this family.[2] This unprecedented dihydropyran based structure of these molecules have attracted considerable attention as it shows similar structural skeleton with each other Secoiridoids. Also Oleuropein and their analogues are biogenetically related to each other by an oxidative ring contraction and functional group modification to generate other Secoiridoids and Iridoids.[3] Oleuropein (**1a**) possesses a wide spectrum of biological activities such as antioxidant,[4] anti-inflammatory,[5] anti-atherogenic,[6] anti-cancer,[7] antimicrobial,[8] antiviral[9] and anti-HIV[10] properties. Also it has enormous application towards neurodegenerative diseases.[11] Oleuropein has a prime dihydropyran-3-methylcarboxylate ring like structure with 1,1'-glycosidic bond. In addition, it has an exo-cyclic *trans* alkene bond and an ester linkage with the tyrosyl group (Figure 1, **1a**). Recently, we are interested in developing various bio-active organic molecules for medicinal applications.[12] The fascinating and challenging structures of the Oleuropein based Secoiridoid natural products immediately caught our attention and lead us to initiate a program aiming to the total synthesis of Oleuropein and its structural analogues. However, no one has been reported the total synthesis of Oleuropein yet. This can lead us to the design of new synthetic strategy for the acquirement of derivatives of Oleuropein analogues or other Secoiridoids (Figure 1) by utilising a common key intermediate approach. Recently, N-Heterocyclic carbene (NHC) catalysis has emerged as one of the most promising areas of research and has undergone significant developments and application in complex molecule synthesis.[13] NHC catalysis provides efficient routes to access a variety of nucleophilic species such as acyl anion, homoenolate, enolate which are more attractive tactics for carbon-carbon bond-formation.[14]

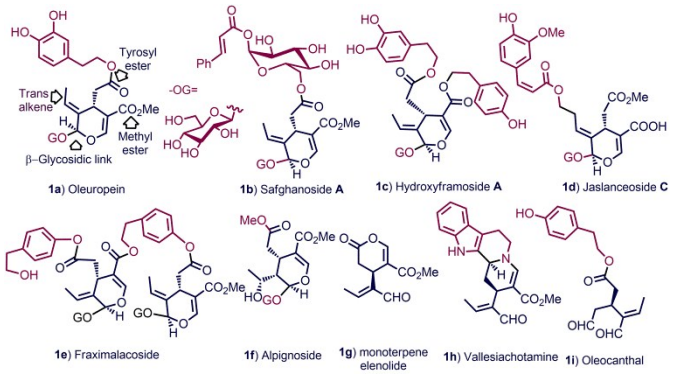


Figure 1. Examples of Secoiridoids based natural products.

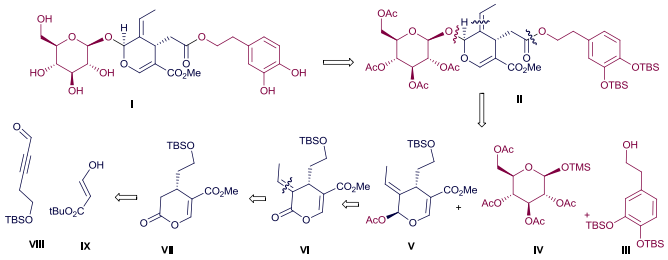
In addition, generation of an activated carboxylate species is another attractive area for the delivery of ester and amide bonds.[15] Zeitler introduced redox esterification on alkynyl aldehydes by providing an α,β-unsaturated ester.[16] Later Bode, developed NHC-catalyzed Coates-Claisen rearrangement

[a] *Department of Chemistry, National Institute of Technology, Tiruchirappalli-620015, India, E-mail: vseenu@nitt.edu, seenuvasanv@gmail.com; Fax: +91-4312500133; Tel: +91-4312503636.*
[b] *21 Nanyang Link, Division of Chemistry and Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore, 637371. E-mail: xuewei@ntu.edu.sg; Fax: +65-6791 1901; Tel: +65 6316 8901*
Electronic supplementary information (ESI) available: Detailed experimental procedures and characterization data See DOI: 10.1039/x0xx00000x

through one pot redox esterification with electron rich Kojic acid followed by 3,3'-sigmatropic rearrangement reaction.[17] An important aspect of this NHC catalyzed Coates-Claisen rearrangement is that it leads us to design the possible Oleuropein synthetic route and other Secoiridoids from easily accessible starting materials such as **2** and **3** (Table 1) obtained from homopropargyl alcohol and Meldrum acid respectively.[18] Herein, we report a short and efficient formal synthesis of enantioselective Oleuropein and monoterpene elenolide, using an organocatalytic strategy for the construction of the dihydropyran core structure. This approach can produce library of chiral fragment based on Secoiridoids natural compounds

Results and discussion

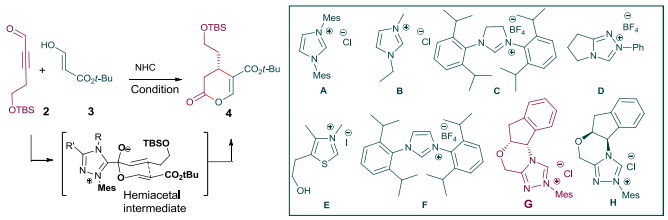
Retrosynthesis: Bode *et al*.[17] discussed the challenges and strategies for facilitating NHC catalyzed Coates-Claisen rearrangement for the construction of dihydropyran based lactone ring which could be a suitable method for Oleuropein synthesis with modified starting materials. The retrosynthetic approach for Oleuropein synthesis is illustrated in **Scheme 1**. From the Oleuropein, dihydropyran based lactone ring (**VII**) is a core structure which could be constructed first and further functionalization can introduced such as alkene construction, lactone reduction, glycosylation and esterification with tyrosyl group. Enantioselective lactone ring can be constructed from two aldehydes **VIII** and **IX** using a chiral NHC catalyst. The lactone ring (**VII)** is further converted in to *trans*-alkene (**VI**) at the ring diastereotropic carbon. Then the lactone ring subsequently reduces to lactol which upon *in situ* acetylation produces aglycon (**V**). This acetyl protected aglycon (**V**) is further subjected to 1,1' glycosylation with glycosyl acceptor (**IV)** and esterification of tyrosyl unit (**III**) leads to formation of protected Oleuropein (**II**) which upon deprotection completes the Oleuropein (**I**) total synthesis.



Scheme 1. Retrosynthetic analysis

NHC-catalyzed enantioselective key dihydropyran based lactone synthesis: To probe the feasibility of Coates-Claisen rearrangement to generate dihydropyran core of Oleuropein Secoiridoid using NHC catalysts (**A**–**H**) orienting the experiments were carried out using two aldehydes **3** and **2** in 1:1.5 equivalent. The initial optimization was carried out using the NHC catalyst precursors (**A**–**H**) (Table 1, entries 1–8) in 0.1 equiv. and 0.1 equiv. of DBU as base in (0.1 M) dry toluene at room temperature for 24 h. Among the tested catalysts, catalyst **G** furnished the dihydropyran based lactone product **4** in 35% yield and 42% enantioselectivity (Entry 7). The catalyst **H** gave similar results with the stereoisomer of **4**.

Table 1 Optimization of key step for dihydropyran based lactone formation.



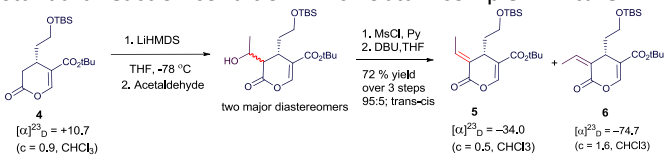
Entry[a]	Catalyst[b]	Base[c]	Solvent (0.1 M)	Temp. / °C	Yield[d] (%)	% of *ee*[e]
1	A	DBU	Toluene	20	Trace	–
2	B	DBU	Toluene	20	–	–
3	C	DBU	Toluene	20	–	–
4	D	DBU	Toluene	20	–	–
5	E	DBU	Toluene	20	–	–
6	F	DBU	Toluene	20	–	–
7	G	DBU	Toluene	20	35	42
8	H	DBU	Toluene	20	33	-41
9	G	DIPEA	Toluene	20	45	50
10	G	No base	Toluene	20	52	79
11	**G**	**No base**	**Toluene**	**40**	**62**	**82**
12	G	No base	Toluene	80	51	79
13	G	No base	THF	40	–	–
14	G	No base	Hexane	40	–	–
15	G	No base	*o*-Xylene	40	32	81
16	G	No base	*p*-Xylene	40	38	77
17	G	No base	$CF_3C_6H_5$	40	35	78

[a]Unless otherwise specified, all of the reactions were carried out with freshly distilled dry solvents at the specified temperature for 24 h. [b,c]0.1 equivalent. was used. [d]Isolated yields. [e]Determined by HPLC (IC column, solvent system: 99:1 hexanes:*i*-PrOH), t_R= 10.2 and 12.1 min. To get a racemic product, 1:1 mixture of G & H was used.

The product obtained using catalyst **G** furnishes the stereochemistry of Oleuropein and it was predicted with the aid of Bode's report (Entry 7).[18] So we chose catalyst **G** for further optimization of the reaction. The racemic compound of **4** is derived from the 1:1 mixture of **G** and **H** as this reaction does not work with any achiral catalyst which was screened here. By exchanging the base from DBU to DIPEA leads to slight increases in the yield and selectivity (Entry 9). Next the reaction is carried out using the catalyst **G** without adding any base which furnishes the lactone product **4** in 52% yield and 79% enantioselectivity at room temperature (Entry 10). The used base plays a dual role; activates the catalyst and generates enol from **3**. Unfortunately, diminished yields and selectivities were obtained from both DBU and DIPEA (Entries 7–9). The counter (Cl) anion present in the catalyst **G** acts as a mild base which performs this dual role as it produces major selectivity (79% ee), hence, the reaction condition was tested without base (Entry 10). In order to improve the yield of the product, reaction was subjected to higher temperatures (Entries 11 and 12) such as 40 °C and 80 °C. It was found that, 40 °C resulted in 62% yield with 82% enantiomeric excess (Entry 11). We expect that the compound **3** is highly unstable

at higher temperature as it needs to be stored at -78 °C. No loss of its composition was noted for a month. Next, the reaction was carried out in different solvents and it was found that the reaction is not feasible in THF, hexane (Entries 13, 14) and the toluene mimic solvents such as o-xylene, p-xylene and trifluro toluene afforded moderate yields (32, 38 & 35% respectively) and selectivities (81, 77 & 78% ee respectively) (Entries 15-17). So the key dihydropyran based lactone synthesis was carried out using catalyst **G** at 40 °C in 0.1 M dry toluene for 24 h. If this reaction is carried out in a large scale, the catalyst can be recovered by column chromatography followed by drying in high vacuum and reused for 3 to 4 times. The possible transition state for stereoselective-outcome can be obtained through hemiacetal chair transition state (Shown in Table 1) adduct which undergoes 3, 3'-sigmatropic rearrangement followed by ring closure to obtain **4**.

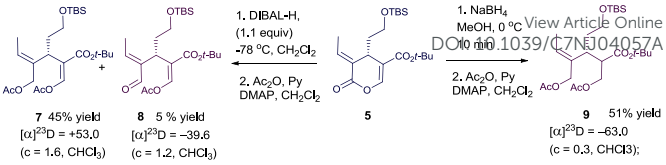
Alkene construction: *Trans* alkene construction on diastereotropic ring carbon of **4** is an another key step due to the presence of various functional groups such as alkene, lactone and *tert*-butyl ester. The initial approach was to construct *trans* alkene by using Horner-Wadsworth-Emmons (HWE) reaction by preparing phosphate diastereomeric mixtures in ring diastereotopic carbon using Lithium Diisopropylamide (LDA) as a base and acetaldehyde as a counter substrate.[19] It leads to formation of complex mixtures even at both –78 and –40 °C in dry THF which is unlike the expected *trans* alkene product (**5**). Furthermore, the reaction was subjected to Mukiyama aldol reaction and aldol condensation with acetaldehyde using LDA as a base under standard reaction condition which obtain complex mixture.[20]



Scheme 2. *Trans* alkene construction through aldol reactions

Next, we turned our attention to carry out aldol reaction with acetaldehyde using Lithium hexamethyldisilane (LiHMDS) as a base that resulted in a diastereomeric mixture of aldol products which is similar in core structure of Alpignoside and was isolated as a diastereomeric mixtures.[21] This diastereomeric mixture was then subjected to mesylation followed by elimination using DBU as a base to obtain the requisite alkenes **5** and **6** in 72% yield (*trans*:*cis*-95:5). *Trans* (**5**) and *Cis* (**6**) alkenes were separated *via* column chromatography. The obtained major *trans* alkene was subjected to one pot protocol of lactone to lactol reduction followed by acetyl protection that leads to the formation of expected glycosyldonor (**V**) (Scheme 1).

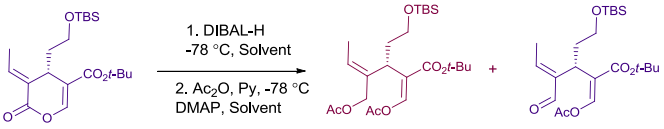
Lactone reduction: The vast number of reports have been devised from lactone to lactol at lower temperature using DIBAL-H as a reducing agent followed by one pot acetyl protection. For this we have subjected Rychnovsky method's for one pot DIBAL-H reduction of lactone (**5**) to lactol followed by acetylation at -78 °C using dry dichloromethane as a



Scheme 3. Reduction of lactone **5**

solvent.[22] The result consisted of two major products **7** (ring opened primary alcohol, 45% yield) and **8** (ring opened *α,β*-unsaturated aldehyde, 5 % yield) which is unlikely to be the expected products based on the retrosynthetic analysis (Scheme 1). But it resembles the core structural skeleton of Oleocanthal (**1i**) (Scheme 3). If the acetylation is not carried out in one pot protocol, it leads to the allylic primary alcohol which further reacts with terminal aldehyde intramolecularly to form undesired lactol which further protected with an acetyl group, it produces an undesired dihydropyran alkene compound.[18] Another significant reported procedure from Lupton group for the reduction of lactone to lactol using sodium borohydride in methanol produces over-reduced product which was isolated as acetyl protected compound **9** in 51% yield (Scheme 3).[13h-i] Then we decided to carry out the controlled DIBAL-H reduction reactions that needs to optimize selectively one product as the major one with good chemical yield (Table 2). Initially reaction was carried out using 1.1 equiv of DIBAL-H at –78 °C in dichloromethane to form the reduced product which upon subsequent acetylation, produced **7** and **8**

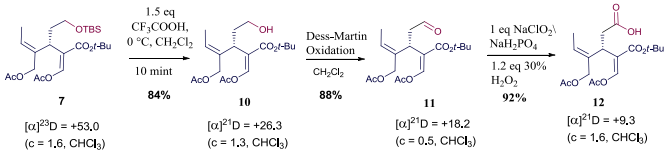
Table 2 Optimization of lactone reduction and one pot acetylation.



Entry[a]	DIBAL-H (equiv)	Time/h	solvent [0.1 M]	Yield **7**[b,c](%)	Yield **8**[b,c](%)	Recv **5**[b,c](%)
1	1.1	2	CH_2Cl_2	45	5	25
2	0.5	2	CH_2Cl_2	20	10	50
3	1.5	2	CH_2Cl_2	70	5	10
4	**2.0**	**2**	**CH_2Cl_2**	**80**	**5**	**5**
5	2.5	2	CH_2Cl_2	79	0	0
6	1.1	2	Toluene	52	15	10
7	1.1	2	THF	51	10	15
8	2.0	2	Toluene	72	5	5
9	2.0	4	CH_2Cl_2	76	5	5
10	1.1	4	CH_2Cl_2	46	5	10

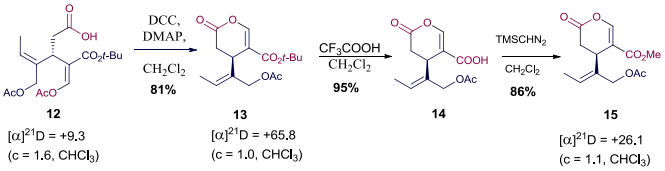
[a]Unless otherwise specified, all of the reactions were carried out with freshly distilled dry solvents at –78 °C and used 1 M DIBAL-H in toluene as a reducing agent. [b]Isolated yield. [c]After the mentioned reduction time the following reagents were added at the same temperature (–78 °C) in the following order 2 equiv of pyridine, 1.1 equiv of DMAP in dichloromethane, 4 equiv of acetic anhydride and stirred for 12 h.

in 45% & 5% yields respectively (Table 2, Entry 1). If the DIBAL-H quantity was reduced to 0.5 equiv, **7** was obtained in 20% yield indicating that, after the formation of lactol subsequently it undergoes ring opening forms of α,β- unsaturated aldehyde which further undergoes reduction instead of reducing another molecule of lactone (**5**) (Entry 2). Also it provides 50% unreacted lactone which emphasises the reaction with lower amount of reducing agent also leads to ring opened over reduced product **7** as a major product which is unlike the expected lactol product from the retro-synthetic analysis (Scheme 1). If the DIBAL-H quantity was increased to 1.5, 2 and 2.5 equiv, it results in increasing yields of 70, 80, 79% respectively (Entries 3-5). From that we concluded more than 2 equiv. of DIBAL-H leads to slight decrease in the product yield, so we chose 2 equiv which is an ideal amount of reducing agent for getting compound **7** as the major product. Next, reactions were carried out in different solvents such as THF and toluene that yielded similar ring opened product were obtained with diminished yield of **7** (Entries 6–8). Furthermore, reduction reaction time was increased to 4 h producing similar results which was obtained from 2 and 1.1 equiv of DIBAL-H in 2 h period (Entries 9 and 10). In conclusion, the detail obtained from optimization table for reduction of lactone (**5**) to lactol followed by one pot acetylation leads to ring opened product **7** as a major one which is unlike the result obtained from the retrosynthetic analysis. Part of our aim of this project is to develop the synthesis of other Secoiridoids (Figure 1) which can be compatible with this method. So we decided to use the over reduced acetyl protected compound **7** as a key starting material for the synthesis of diastereoselective monoterpene elenolide core. The compound **7** was subjected to TBS deprotection by using Tetrabutyl ammonium fluoride (TBAF) leads to the acetyl group deprotection which further undergoes an undesired lactol formation with allylic primary alcohol and terminal aldehyde.[18] So, the deprotection of TBS group of **7** was carried out in acidic condition using 1.5 equiv of Trifluroacetic acid at 0 °C for 10 min. to obtain the selective TBS deprotected alcohol (**10**) (Scheme 4) in 84% yield. Furthermore, compound **10** was oxidized to aldehyde **11** using Desmartin periodide and acid **12** using Pinnick oxidation, that delivered 88% and 92% yields respectively (Scheme 4).



Scheme 4. Synthesis of acid (**12**)

The compound **12** was further subjected to intramolecular DCC coupling in the presence of DMAP that leads to compound **13** in 81% yield (Scheme 5). In this case, acetyl protected vinyl group of **12** was selectivley deprotected and *in situ* intramolecular lactonization produces compound **13** which is the structural skeleton of monoterpene elenolide[23] (Figure 1, **1i**). Next, *tert*-butyl ester of **13** was converted into corresponding methyl ester. *Tert*-butyl ester of **13** was treated with excess amount of Trifluoroacetic acid (10 equiv) in dichloromethane at 0 °C to form corresponding acid **14** in 30 mins which further undergoes methylation using Timethylsilydiazomethane to obtain **15** in 95 and 86% yields. In both the reaction, the products were obtained in quantitative yield and the obtained acid **14** reaction mixture was subjected to remove the excess trifluroaceticacid followed by tituration with hexane and high vacuum drying before methylation. In this functional group interconversion, we could use the corresponding methyl 3-oxopropanoate as a starting material for the initial lactone formation instead of *tert*-butyl 3-oxopropanoate (**3**), but the synthesis and stability of this aldehyde is very poor. Compound **15** shows similar core structural analogues for monoterpene elenolide (**1g)** and Vallesiachotamine (**1h)**. Furthermore, the compound **15** was subjected to NaOMe/MeOH that delivers deprotection of acetate group as well as ring opened methyl ester product was obtained.[18] In this protocol, we find the resulting chiral intermediates shows interesting structural features which allows anyone can develop other Secoiridoids.



Scheme 5. Synthesis of monoterpene elenolide core

Conclusions

In conclusion, we have developed a novel chemical approach for the synthesis of Oleuropein based Secoiridoids core using NHC catalyzed Coates-Claisen rearrangement reaction. Furthermore, an aldol reaction with acetaldehyde that takes place at the diastereotropic ring carbon using LiHMDS which resulted in an exocyclic *trans* ethyleneic double bonded product (major). This approach can produce a library of compounds by using diverse aldehydes. Although the selective reduction of lactone to lactol by DIBAL-H leads to formation of over reduced ring opened product instead of the anticipated lactol product creates a new type of chiral fragment which can further be used by other synthetic organic community. The ring opened product is successfully exploited for functional group transformation which produces diastereoselective monoterpene elenolide core structure. The synthetic strategy developed here is flexible and can be extended towards the synthesis of numerous stereochemical analogues of the Secoiridoid natural products or medicinally active fragments.

Experimental

General methods: All the reactions were carried out in a flame or oven dried glassware under an argon or nitrogen atmosphere with freshly distilled dry solvents under anhydrous conditions unless otherwise indicated. Evaporation of organic solutions was achieved by rotary evaporation with a water bath temperature below 40 °C. Product purification by flash

column chromatography was accomplished using silica gel 60 (0.010–0.063 nm). Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using base solution of potassium permanganate. Technical grade solvents were used for chromatography and were distilled prior to use. NMR spectra were recorded at room temperature on 300 MHz Bruker ACF 300, 400 MHz Bruker DPX 400, 500 MHz Bruker AMX 500, and 400 MHz JEOL ECA 400 NMR spectrometers. The residual solvent signals were taken as the reference (7.26 ppm for ^{1}H NMR spectra and 77.0 ppm for ^{13}C NMR spectra in $CDCl_3$, 2.5 ppm for ^{1}H NMR spectra and 39.5 ppm for ^{13}C NMR spectra in DMSO-d_6. Sometimes the TMS signal at 0.0 ppm was used an internal standard for ^{1}H NMR spectra. Chemical shift (δ) is reported in ppm, coupling constants (J) are given in Hz. The following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal. HR-MS (ESI) spectra were recorded on a Waters Q-Tof premier™ mass spectrometer.

Materials: All solvents were distilled under argon from the following drying agents immediately before use: tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl; dichloromethane was distilled from calcium hydride. All the starting materials were purchased from commercial suppliers and used without further purification. All the NHC catalyses were purchased from commercial suppliers and catalyst **G** and **H** was prepared from standard literature procedure.

(*S*)-*tert*-Butyl-4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-oxo-3,4-dihydro-2H-pyran-5-carboxylate (4):

In an oven dried 10.0 mL round bottom flask, *tert*-butyl formylacetate (**3**) (100 mg, 0.69 mmol, 1.0 equiv) and (*R,S*) triazolium precatalyst (**G**) (26.7 mg, 0.10 equiv) were added, followed by 4.0 mL of toluene (0.1 M) and ((*tert*-Butyldimethylsilyl)oxy)pent-2-ynal (**2**) (220.0 mg, 1.04 mmol, 1.50 equiv) in a nitrogen atmosphere. The resulting solution was heated to 40 °C and stirred for 24 h. Toluene was evaporated and the residue was purified by column chromatography to obtained (**4)** as a viscous oil. (Note: In higher scale, catalyst was recovered by column chromatography and reused) (153 mg, 62%). $[\alpha]^{23}_D$ = +10.7 (*c* = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 3.71–3.66 (m, 2H), 3.09–3.03 (m, 1H), 2.88 (dd, J_1 = 16.0 Hz, J_2 = 1.6 Hz, 1H), 2.66 (dd, J_1 = 16.0 Hz, J_2 = 7.2 Hz, 1H), 1.80–1.76 (m, 12H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 164.3, 149.7, 117.2, 81.4, 60.5, 35.9, 33.0, 28.2, 25.9, 18.3, –5.3, –5.3; HRMS (ESI) m/z $[M+H]^+$: calcd. for $C_{18}H_{33}O_5Si$: 357.2097, found: 357.2102. 82% *ee* as determined by HPLC (IC, 99:1 hexanes:*i*-PrOH), t_R = 9.3 min. (major) and 12.1 min. (minor).

(*S,E*)-*tert*-Butyl-4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-ethylidene-2-oxo-3,4-dihydro-2H-pyran-5-carboxylate (5):

(i) $LiN(SiMe_3)_2$ (1.68 mL, 1.68 mmol, 1M in hexane) was added to the solution of (**4)** (0.5 g, 1.4 mmol) in dry THF (5 mL) at -78 °C with stirring under nitrogen atmosphere. After 10 min. a solution of acetaldehyde (0.78 mL, 14.0 mmol) in dry THF (5 mL) was added to this mixture, and stirred for 15 min. The reaction mixture was quenched with a solution of saturated NH_4Cl (2 mL) at room temperature, diluted with EtOAc, washed with sat. $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuum to give a residue, which was passed through a silica gel column (Hexane–EtOAc; 3:2) gave a mixture of diastereomers (0.42 g, 75%) which was used for next steps. (ii) The above obtained mixture of alcohols (0.42 g, 10.5 mmol) was dissolved in pyridine (8 mL), and to this solution methane sulfonyl chloride (0.16 mL, 21.0 mmol) was added at room temperature with vigorous stirring. After 1 h, the reaction mixture was concentrated in high vacuum distillation, diluted with EtOAc (20 mL), washed with H_2O (2x10 mL), and brine (10 mL), dried over $MgSO_4$, and concentrated in vacuum to gave a crude mixture of diastereomers (0.46 g, 85%). (iii) The mixture of mesylates (0.46 g, 0.97 mmol) was dissolved in THF (5 mL) and added DBU (0.29 mL, 1.95 mmol) and stir at room temperature. After 10 min. stirring, the reaction mixture was diluted with EtOAc, washed with sat. NH_4Cl, sat. $NaHCO_3$, brine and dried over $MgSO_4$, and concentrated in vacuum to give a mixture of *E* and *Z*-geometrical isomers as viscous oil. The mixture was chromatographed on a silica gel column. Elution with Hexane-EtOAc (98:2); (0.26 g, 72%); $[\alpha]^{23}_D$ = –34.0 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (s, 1H), 7.05 (qd, J_1 = 7.2 Hz, J_2 = 0.9 Hz, 1H), 3.86 (dd, J_1 = 7.4 Hz, J_2 = 4.9 Hz, 1H), 3.62–3.47 (m, 2H), 1.91 (d, J = 7.3 Hz, 3H), 1.82–1.61 (m, 2H), 1.50 (s, 9H), 0.86 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 162.9, 148.7, 143.1, 127.3, 115.6, 81.3, 59.5, 37.4, 30.1, 28.1, 25.9, 18.3, 14.5, –5.3; HRMS (ESI) m/z $[M+H]^+$: calcd. for $C_{20}H_{35}O_5Si$: 383.2260, found: 383.2256.

(*S,Z*)-*tert*-Butyl-4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-ethylidene-2-oxo-3,4-dihydro-2H-pyran-5-carboxylate (6): $[\alpha]^{23}_D$ = –74.7 (*c* = 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (s, 1H), 6.35 (q, J = 7.2 Hz, 1H), 3.65-3.51 (m, 3H), 2.11 (d, J = 7.2 Hz, 3H), 1.94–1.82 (m, 1H), 1.51 (s, 9H), 1.51–1.46 (m, 1H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 161.0, 148.3, 144.9, 125.3, 117.2, 81.2, 59.0, 37.2, 36.9, 28.1, 25.9, 18.2, 16.2, –5.3; HRMS (ESI) m/z $[M+H]^+$: calcd. for $C_{20}H_{35}O_5Si$: 383.2260, found: 383.2274.

DIBAL-H reduction: (*S,1E,4E*)-2-(*tert*-Butoxycarbonyl)-3-(2-((*tert*butyldimethylsilyl) oxy)ethyl)-4-ethylidene pent-1-ene-1,5-diyldiacetate (7):

To a 10 mL flame-dried round bottom flask (**5**) (0.1 g, 0.26 mmol) was placed and dissolved in 3 mL of dry CH_2Cl_2 under nitrogen atmosphere. After the mixture was cooled to –78 °C cool bath, DIBAL-H (1.0 M in toluene, 0.52 mL, 0.52 mmol, 2 equiv) was added drop wise. After being stirred for 2 h the reaction mixture was treated with pyridine (62 mg, 0.063 mL, 0.78 mmol, 3.0 equiv), and then a solution of DMAP (35 mg, 0.28 mmol, 1.1 equiv) in 1 mL of dry CH_2Cl_2 was slowly added. Finally, aceticanhydride (26 mg, 0.025 mL, 1.0 mmol, 4.0 equiv) was added drop wise, and the mixture was stirred under nitrogen atmosphere for 12 h. The reaction vessel was packed in a Dewar flask containing dry ice-acetone mixture was warmed to –20 °C and the reaction was quenched by adding saturated NH_4Cl (5 mL) solution. The reaction mixture was stirred for 30 mins, allowed to warm to room temperature,

and then extracted with dichloromethane (3 x 5 mL). Aluminum salts formed emulsions, they were disrupted by adding a saturated solution of Rochelle's salt (10 mL) with vigorous stirring. The combined dichloromethane extracts were washed with ice-cold 1 N $NaHSO_4$ (2 x 5 mL), saturated $NaHCO_3$ (3 mL), and brine (1 mL). After drying (anhydrous Na_2SO_4) and evaporation of dichloromethane extracts, the residue obtained was purified by flash chromatography on silica gel to give compound (**7)** as a viscous oil. Yield (0.1 g, 80%); $[\alpha]^{23}_D$ = +53.0 (*c* = 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.17 (s, 1H), 5.69 (q, *J* = 6.8 Hz, 1H), 4.58 (s, 2H), 4.24 (t, *J* = 7.8 Hz, 1H), 3.60–3.50 (m, 2H), 2.22 (s, 3H), 2.21–2.11 (m, 1H), 2.05 (s, 3H), 2.02–1.94 (m, 1H), 1.77 (d, *J* = 6.8 Hz, 3H) 1.51 (s, 9H), 0.86 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 170.8, 166.5, 166.2, 144.2, 135.0, 127.8, 119.2, 80.9, 66.7, 60.8, 34.1, 32.4, 28.1, 25.8, 21.1, 20.7, 18.1, 13.4, –5.1; HRMS (ESI) m/z $[M+H]^+$: calcd. for $C_{24}H_{42}O_7SiNa$: 493.2598, found: 493.2608.

(*S*,2*E*,4*E*)-*tert*-Butyl-2-(acetoxymethylene)-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-formylhex-4-enoate (8):

Obtained from Table 5.2, entry 4 condition (6 mg, 5% not able to isolate in pure form); $[\alpha]^{22}_D$ = –39.6 (*c* = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 9.41 (s, 1H), 8.10 (s, 1H), 6.63 (q, *J* = 7.2 Hz, 1H), 4.20 (t, *J* = 7.8 Hz, 1H), 3.62–3.50 (m, 2H), 2.23 (s, 3H), 2.22–2.11 (m, 1H), 2.05 (d, *J* = 7.2 Hz, 3H), 2.03–2.01 (m, 1H), 1.49 (s, 9H), 0.90 (s, 9H), 0.04 (s, 6H); HRMS (ESI) m/z $[M+H]^+$: calcd. for $C_{22}H_{38}O_6SiNa$: 449.2245, found: 449.2233.

(3*R*,*E*)-2-(*tert*-Butoxycarbonyl)-3-(2-((*tert*-butyldimethylsilyl) oxy)ethyl)-4-ethylidene pentane-1,5-diyl diacetate (9):

A magnetically stirred solution of **(5)** (0.1 g, 0.26 mmol) in CH_3OH (1 mL) was cooled to 0 °C then treated with $NaBH_4$ (1 ml of a 0.1 M solution in CH_3OH). The reaction was stirred at 0 °C for 10 min. then quenched with H_2O (1 ml) and extracted with CH_2Cl_2 (3 x 3 ml). The combined organic layers were dried (Na_2SO_4) and concentrated in high vacuum. The crude reaction mixture was used for acetylation step. The crude reaction mixture was dissolved in CH_2Cl_2 treated with pyridine (62 mg, 0.63 mL, 0.78 mmol, 3.0 equiv), and then a solution of DMAP (35 mg, 0.28 mmol, 1.1 equiv) in 2 mL of dry CH_2Cl_2 was slowly added by syringe at 0 °C. Finally, Ac_2O (0.1 mg, 0.1 mL, 1.0 mmol, 4.0 equiv) was added drop wise and stir for 2 h. After 2 h, the reaction mixture was quenched by adding saturated NH_4Cl (5 mL) solution and extract with dichloromethane (5 x 3 mL). The combined organic layer was dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography to give (**9**) as a viscous liquid. Yield: (62 mg, 51%); $[\alpha]^{23}_D$ = –63.0 (*c* = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.85 (q, *J* = 7.2 Hz, 1H), 4.54–4.46 (m, 2H), 4.25 (dd, J_1 = 10.4 Hz, J_2 = 4.4 Hz, 1H), 4.0 (t, *J* = 10.4 Hz, 1H), 3.56–3.41 (m, 2H), 3.13–3.11 (m, 1H), 2.75–2.71 (m, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.73 (d, *J* = 6.8 Hz, 3H), 1.68–1.61 (m, 2H), 1.51 (s, 9H), 0.86 (s, 9H), 0.06 (s, 6H); HRMS (ESI) m/z $[M+H]^+$: calcd. for $C_{24}H_{44}O_7SiNa$: 495.2723, found: 495.2719.

(*S*,1*E*,4*E*)-2-(*tert*-Butoxycarbonyl)-4-ethylidene-3-(2-hydroxyethyl)pent-1-ene-1,5-diyl diacetate (10):

In an oven dried 10 mL round bottom flask (**7**) (1g, 2.12 mmol, 1 equiv) was taken and dissolved in dichloromethane (10 mL). Trifluoroacetic acid (0.36 g, 3.19 mmol, 244 µL, 1.5 equiv) was added slowly at 0 °C. Then the mixture was stirred for 10 min. and then removed the solvents using low temperature rota-vapour and the residue was neutralized with saturated solution of sodium bicarbonate (10 ml) and extract with dichloromethane (3x30 mL). The residue was purified by flash silica gel column chromatography using a mixture of hexane and EtOAc (20:1 to 6:1) to afford corresponding compound (**10**). Yield (0.64 g, 84%); $[\alpha]^{21}_D$ = +26.3 (*c* = 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.16 (s, 1H), 5.71 (q, *J* = 6.8 Hz, 1H), 4.69 (d, *J* = 12.4 Hz, 1H), 4.59 (d, *J* = 12.4 Hz, 1H), 4.16 (t, *J* = 7.6 Hz, 1H), 3.64–3.58 (m, 2H), 2.24 (s, 3H), 2.19–2.08 (m, 1H), 2.05 (s, 3H), 2.04–2.02 (m, 1H), 1.85 (bs, 1H), 1.73 (d, *J* = 6.8 Hz, 3H) 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 170.8, 166.8, 166.4, 144.1, 135.0, 128.3, 119.5, 81.4, 66.7, 60.8, 33.5, 32.7, 28.1 (3C), 21.1, 20.7, 13.4; HRMS (ESI) m/z $[M+H]^+$: calcd. for $C_{18}H_{28}O_7Na$: 379.1733, found: 379.1716.

(*S*,1*E*,4*E*)-2-(*tert*-Butoxycarbonyl)-4-ethylidene-3-(2-oxoethyl)pent-1-ene-1,5-diyldiacetate (11):

In an oven dried 10 mL round bottom flask (**10**) (1 g, 2.6 mmol, 1 equiv) was taken and dissolved in dichloromethane (10 mL), Dess-martin periodide (1.68 g, 3.9 mmol, 1.5 equiv) was added slowly and then stirred for 3 h. Then the reaction mixtures passed though celite bed and wash the celite bed with dichloromethane (3x10 mL). The filtrate was concentrated and purified by flash silica gel column chromatography using a mixture of hexane and EtOAc (20:1 to 6:1) to afford corresponding compound (**11**) as a viscous liquid. Yield (0.87 g, 88%); $[\alpha]^{21}_D$ = +18.2 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 9.69 (s, 1H), 8.13 (s, 1H), 5.70 (q, *J* = 6.8 Hz, 1H), 4.59-4.49 (m, 3H), 3.07 (dd, *J* = 17.2 Hz, 8.4 Hz, 1H), 2.88 (dd, *J* = 17.2 Hz, 7.6 Hz, 1H), 1.77 (s, 3H), 1.75 (s, 3H), 1.71 (d, *J* = 6.8 Hz, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 201.1, 170.6, 166.2, 165.8, 144.3, 133.8, 129.3, 118.0, 81.5, 66.9, 45.0, 30.7, 28.1, 21.0, 20.7, 13.5; HRMS (ESI) m/z $[M+H]^+$: calcd. for $C_{18}H_{27}O_7$: 355.1757, found: 355.1757.

(*S*,*E*)-3-((*E*)-1-Acetoxy-3-(*tert*-butoxy)-3-oxoprop-1-en-2-yl)-4-(acetoxymethyl)hex-4-enoic acid (12):

A solution of of $NaClO_2$ (432 mg, 4.80 mmol) in 1 mL of water was added drop wise in 2 h to a stirred mixture of (**11**) (1 g, 2.82 mmol) in 2 mL of acetonitrile and NaH_2PO_4 (67 mg, 0.56 mmol) of in 0.5 mL of water and 35% H_2O_2 (283 µL, 4.23 mmol) of keeping the temperature at 10 °C with ice-water cooling. Oxygen evolved from the solution was monitored until the end of the reaction (about 1h) with a bubbler connected to the apparatus. A small amount (~0.05 g) of Na_2SO_3 was added to destroy the unreacted HOCl and H_2O_2. Acidification with 10% aqueous ammonium chloride (20 mL) which was extracted with ethylacetate (3x10 mL) and evaporate the organic layer to afforded of (**12**) 960 mg (92%), as viscous liquid. The acid was used for next step without purification. $[\alpha]^{21}_D$ = +9.3 (*c* = 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.16 (s, 1H), 5.73 (q, *J* = 6.8 Hz, 1H), 4.61–4.46 (m, 3H), 3.03 (dd, *J* = 16.4 Hz, 8.4 Hz, 1H), 2.87 (dd, *J* = 16.4 Hz, 7.8 Hz, 1H), 2.22 (s, 3H), 2.03 (s, 3H), 1.78 (d, *J* = 6.8 Hz, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 177.6, 170.6, 166.3, 165.8, 144.3, 133.6, 129.9, 118.2, 81.4,

67.1, 35.9, 32.7, 28.1, 21.1, 20.6, 13.5; HRMS (ESI) m/z $[M+H]^+$: calcd. for $C_{18}H_{27}O_8$: 371.1706, found: 371.1706.

(*R*,*E*)-*tert*-Butyl-4-(1-acetoxybut-2-en-2-yl)-2-oxo-3,4-dihydro-2H-pyran-5-carboxylate (13) :

To a mixture of (**12**) (800 mg, 2.16 mmol) and DMAP (290 mg, 2.37 mmol) in dichloromethane (8 mL), DCC (467 mg, 2.27 mmol) was added in one portion. The reaction mixture stirred at room temperature for 24 h. Evaporate dicholoromethane and then add water (10 mL) and extract with diethylether (3X30 mL). The combined organic layer was dried and purified by flash column chromatography (10% Ethylacetate and Hexane) to obtained **13** as viscous oil. Yield (0.54 g, 81%); $[\alpha]^{21}_D$ = +65.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (s, 1H), 5.80 (q, *J* = 6.8 Hz, 1H), 4.40 (d, *J* = 12 Hz, 1H), 4.32 (d, *J* = 12 Hz, 1H), 4.10 (d, *J* = 9.6 Hz, 1H), 2.91 (dd, *J* = 16.4 Hz, 9.6 Hz, 1H), 2.67 (d, *J* = 16.4 Hz, 1H), 2.03 (s, 3H), 1.80 (d, *J* = 6.8 Hz, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 165.6, 164.2, 150.9, 134.5, 130.1, 112.6, 81.6, 68.0, 34.3, 30.2, 28.1, 20.8, 13.2; HRMS (ESI) m/z $[M+H]^+$: calcd. for $C_{16}H_{23}O_6$: 311.1495, found: 311.1502.

(*R*,*E*)-4-(1-Acetoxybut-2-en-2-yl)-2-oxo-3,4-dihydro-2H-pyran-5-carboxylic acid (14):

To a stirred solution of (**13**) (500 mg, 1.61 mmol) in dichloromethane (5 mL) at 0 °C, trifluoaceticacid (5 mL) was added slowly, the reaction mixture was stirred for another 1 h at room temperature. Evaporated the reaction mixture and the obtained acid was washed with hexane for several times and then dry to give (**14**) which was used further step without purification. Yield (389 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 5.83 (q, *J* = 6.8 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.37 (d, *J* = 11.9 Hz, 1H), 4.15 (d, *J* = 9.6 Hz, 1H), 2.95 (dd, *J* = 16.4 Hz, 9.6 Hz, 1H), 2.73 (d, *J* = 16 Hz, 1H), 2.04 (s, 3H), 1.81 (d, *J* = 6.8 Hz, 3H).

(*R*,*E*)-Methyl-4-(1-acetoxybut-2-en-2-yl)-2-oxo-3,4-dihydro-2H-pyran-5-carboxylate (15):

To a stirred solution of crude (**14**) (200 mg, 0.78 mmol) in dichloromethane (5 mL) at 0 °C, Trimethylsilyldiazomethane (0.39 mL 2M solution in hexane, 0.86 mmol, 1.1 equiv,) was added slowly and the reaction mixture stirred for another 2 h at room temperature. Quench the reaction mixture with saturated solution of sodium bicarbonate (10 mL) and extract with dicholormethane (3X20 mL). The combined organic layer was dried and purified by flash column chromatography (15% Ethylacetate and Hexane) to obtain **15** as a viscous liquid. Yield (181 mg, 86%) $[\alpha]^{21}_D$ = +26.1 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 5.82 (q, *J* = 6.8 Hz, 1H), 4.40 (d, *J* = 12.4 Hz, 1H), 4.34 (d, *J* = 12 Hz, 1H), 4.17 (d, *J* = 9.2 Hz, 1H), 3.77 (s, 3H), 2.92 (dd, *J* = 16.8 Hz, 9.6 Hz, 1H), 2.71 (dd, *J* = 16.6 Hz, 1.2 Hz, 1H), 2.03 (s, 3H), 1.82 (dd, *J* = 7.2 Hz, 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 165.5, 165.3, 151.5, 133.8, 130.8, 111.2, 67.8, 52.0, 34.1, 30.1, 20.8, 13.3; HRMS (ESI) m/z $[M+H]^+$: calcd. for $C_{13}H_{17}O_6$: 269.1025, found: 269.1019.

Acknowledgements

We thank Department of Science and Technology, DST-INSPIRE faculty award (DST/INSPIRE/04/2015/000328), New Delhi, India for financial support and gratefully acknowledged. We also thank Department of chemistry, National Institute of Technology-Tiruchirappalli for providing Infrastructure and Instrumentation facilities.

View Article Online
DOI: 10.1039/C7NJ04057F

Notes and references

1 M. Guiso and C. Marra, *Nat. Prod. Res.,* 2005, **19**, 105.
2 (a) B. Dinda, D. R. Chowdhury and B. C. Mohanta, *Chem. Pharm. Bull.,* 2009, **57**, 765; (b) B. Dinda, S. Debnath and Y. Harigaya, *Chem. Pharm. Bul.,* 2007, **55**, 159; (c) B. Dinda, S. Debnath and Y. Harigaya, *Chem. Pharm. Bull.,* 2007, **55**, 689; (d) C. A. Boros and F. R. Stermitz, *J. Nat. Prod.,* 1991, **54**, 1173. (e) L. J. El-Naggar and J. L. Beal, *J. Nat. Prod.* 1980, **43**, 649; (f) B. Shasha and J. Leibowitz, *J. Org. Chem.,* 1961, **26**, 1948.
3 (a) K. Miettinen, L. Dong, N. Navrot, T. Schneider, V. Burlat, J. Pollier, L. Woittiez, S. van der Krol, R. Lugan, T. Ilc, R. Verpoorte, K.-M. Oksman-Caldentey, E. Martinoia, H. Bouwmeester, A. Goossens, J. Memelink and D. Werck-Reichhart, *Nat. Commun.*, 2014, **5**, 3606; (b) S. Brown, M. Clastre, V. Courdavault and S. E. O'Connor, *PNAS*, 2015, **112**, 3205.
4 F. Visioli, A. Poli and C. Gall, *Med. Res. Rev.,* 2002, **22**, 65.
5 F. Visioli, S. Bellosta and C. Galli, *Life Sci.,* 1998, **62**, 541.
6 M. A. Carluccio, L. Siculella, M. A. Ancora, M. Massaro, E. Scoditti, C. Storelli, F. Visioli, A. Distante and R. De Caterina, *Arterioscler. Thromb. Vasc. Biol.,* 2003, **23**, 622.
7 R. W. Owen, A. Giacosa, W. E. Hull, R. Haubner, G. Wartele, B. Spiegelhalder and H. Bartsch, *Lanc. Oncol.* 2000, **1**, 107.
8 E. Tripoli, M. Giammanco, G. Tabacchi, D. Di Majo, S. Giammanco and M. La Guardia, *Nutr. Res. Rev.,* 2005, **18**, 98.
9 W. R. Fredrickson, *U.S. Patent.,* 2000, **117**, 884.
10 S. Lee-Huang, P. L. Huang, D. Zhang, J. W. Lee, J. Bao, Y. Sun, Y.-T. Chang, J. Zhang and P. L. Huang, *Biochem. Biophys. Res. Commun.*, 2007, **354**, 879.
11 (a) W. Li, J. B. Sperry, A. Crowe, J. Q. Trojanowski, A. B. Smith III and V. M. Y. Lee, *J. Neurochem.,* **2009**, *110*, 1339; (b) M. C. Monti, L. Margarucci, A. Tosco, R. Riccio and A. Casapullo, *Food Funct.,* **2011**, *2*, 423; (c) M. C. Monti, L. Margarucci, R. Riccio and A. Casapullo, *J. Nat. Prod.,* **2012**, *75*, 1584–1588.
12 (a) F. Ding, R. William, S. M. Kock, M. Leow and X.-W. Liu, *Chem. Commun.,* 2015, **51**, 4639; (b) F. Ding, M. Leow, J. Ma, R. William, H. Liao and X.-W. Liu, *Chem. Asian J.,* 2014, **9**, 2548; (c) J. Zeng, Y. J. Tan, J. Ma, M. L. Leow, D. Tirtorahardjo and X.-W. Liu, *Chem. Eur. J.,* 2014, **20**, 405; (d) F. Ding, R. William, M. L. Leow, H. Chai, J. Z. M. ong and X.-W. Liu, *Org. Lett.,* 2014, **16**, 26; (e) R. Lorpitthaya, S. B. Suryawanshi, S. Wang, K. K. Pasunooti, S. Cai, J. Ma and X.-W. Liu, *Angew. Chem. Int. Ed.,* 2011, **50**, 12054; (f) S. Vedachalam, B.-H. Choi, K. K. Pasunooti, K. M. Ching, K. Lee, H. S. Yoon and X.-W. Liu, *Med. Chem. Commun.,* 2011, **2**, 371; (g) F. Ding, R. William, F. Wang, J. Ma, L. Ji and X.-W. Liu, *Org. Lett.*, 2011, **13**, 652; (h) J. Zeng, S. Vedachalam, S. Xiang and X.-W.Liu, *Org. Lett.*, 2011, **13**, 42; (i) J. Ma, Y. Zhao, S. Ng, J. Zhang, J. Zeng, A. Than, P. Chen and X.-W. Liu, *Chem. Eur. J.*, 2010, **16**, 4533.
13 (a) B. M. Trost, C. D. Shuey and F. DiNinno, *J. Am. Chem. Soc.*, 1979, **101**, 1284; (b) B. D. Roth, C. J. Blankley, A. W. Chucholowski, E. Ferguson, M. L. Hoefle, D. F. Ortwine, R. S. Newton, C. S. Sekerke, D. R. Sliskovic and M. Wilson, *J. Med. Chem.*, 1991, **34**, 357; (c) K. L. Baumann, D. E. Butler, C. F. Deering, K. E. Mennen, A. Millar, T. N. Nanninga, C. W. Palmer and B. D. Roth, *Tetrahedron Lett.*, 1992, **33**, 2283; (d) C. C. Galopin, *Tetrahedron Lett.*, 2001, **42**, 5589; (e) P. E. Harrington and M. A. Tius, *Org. Lett.*, 1999, **1**, 649; (f) P. E. Harrington and M. A. Tius, *J. Am. Chem. Soc.*, 2001, **123**,

8509-8514; (g) H. Takikawa, Y. Hachisu, J. W. Bode and K. Suzuki, *Angew. Chem. Int. Ed.*, 2006, **45**, 3492; (h) L. Candish and D. W. Lupton, *Org. Lett.,* 2010, **12**, 4836; (i) L. Candish and D. W. Lupton, *Org. Biomol. Chem.,* 2011, **9**, 8182.

14 (a) D. M. Flanigan, F. Romanov-Michailidis, N. A. White and T. Rovis, *Chem. Rev.*, 2015, **115**, 9307; (b) M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, *Nature,* 2014, **510**, 485; (c) V. Nair, S. Vellalath and B. P. Babu, *Chem. Soc. Rev.*, 2008, **37**, 2691; (d) N. Marion, S. Diez-Gonzalez and S. P. Nolan, *Angew. Chem. Int. Ed.*, 2007, **46**, 2988; (e) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606; (f) K. Zeitler, *Angew. Chem. Int. Ed.*, 2005, **44**, 7506; Our group contribution: (g) B. Maji, J. Li, W. Siming, S. Vedachalam, R. Ganguly and X-W. Liu. *Angew. Chem. Int. Ed.* 2012, **51**, 8276; (h) S. Vedachalam, S. M. Tan, H. P. Teo and X-W. Liu, *Org. Lett.* 2012, **14**, 174; (i) B. Maji, S. Vedachalam, X. Ge, S. Cai and X-W. Liu, *J. Org. Chem.* 2011, **76**, 3016; (j) S. Vedachalam, Q.-L. Wong, B. Maji, J. Zeng, J. Ma and X-W. Liu, *Adv. Synth. Cata.* 2011, **353**, 219; (k) S. Vedachalam, J. Zeng, B. K. Gorityala, M. Antonio and X-W. Liu, *Org. Lett.* 2010, **12**, 352.

15 (a) G. A. Grasa, R. M. Kissling and S. P. Nolan, *Org. Lett.*, 2002, **4**, 3583; (b) N. T. Reynolds, J. R. de Alaniz and T. Rovis, *J. Am. Chem. Soc.*, 2004, **126**, 9518; (c) M. Movassaghi and M. A. Schmidt, *Org. Lett.*, 2005, **7**, 2453.

16 K. Zeitler, *Org. Lett.*, 2006, **8**, 637.

17 (a) J. Kaeobamrung, J. Mahatthananchai, P. Zheng and J. W. Bode, *J. Am. Chem. Soc.,* 2010, **132**, 8810; (b) J. Mahatthananchai, P. Zheng and J. W. Bode, *Angew. Chem. Int. Ed.,* 2011, **50**, 1673; (c) E. Lyngvi, J. W. Bode, F. Schoenebeck, *Chem. Sci.,* 2012, **3**, 2346. (d) J. Mahatthananchai, J. W. Bode, *Chem. Sci.,* 2012, **3**, 192; (e) J. Mahatthananchai, J. Kaeobamrung and J. W. Bode, *ACS Catal.,* 2012, **2**, 494; Other groups: (f) L. Yang, F. Wang, P. J. Chua, Y. Lv, L.-J. Zhong and G. Zhong, *Org. Lett.,* 2012, **14**, 2894; (g) Y. Lin, L. Yang, Y. Deng and G. Zhong, *Chem. Commun.,* 2015, 51, 8330; (h) D. Xie, L. Yang, Y. Lin, Z. Zhang, D. Chen, X. Zeng and G. Zhong, *Org. Lett.,* 2015, **17**, 2318.

18 See the supporting information for the detail and experimental procedures.

19 J. S. Yu and D. F. Wiemer, *J. Org. Chem.,* 2007, **72**, 6263.

20 I. Paterson, *Tetrahedron,* 1988, **44**, 4207.

21 (a) S. Hanessian, Y. Hou, M. Bayrakdarian and M. Tintelnot-Blomley, *J. Org. Chem.,* 2005, **70**, 6735; (b) M. Shiozaki, Y. Kobayashi, T. Hata and Y. Furukawa, *Tetrahedron,* **1991**, *47*, 2785.

22 V. H. Dahanukar and S. D. Rychnovsky, *J. Org. Chem.,* 1996, **61**, 8317.

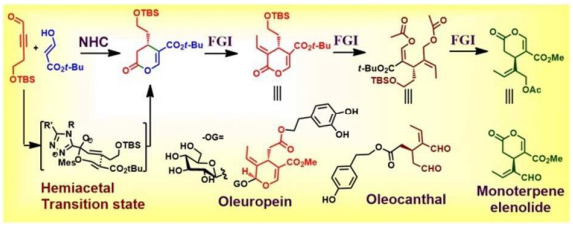
23 R. T. Brown and M. F. Jones, *J. Chem. Soc. Chem. Commun.,* 1986, 1818.

View Article Online
DOI: 10.1039/C7NJ04057A

Table of Content:

NHC catalyzed enantioselective Coates-Claisen rearrangement : A rapid access to the dihydropyran core for Oleuropein based Secoiridoids

Seenuvasan Vedachalam,*[a] Nithya Murugesh,[a] Priyanka Chakraborty,[a] Ramasamy Karvembu[a] and Xue-Wei Liu[b]*



A simple protocol for the synthesis of dihydropyran core structure of Secoiridoid using NHC catalyzed Coates-Claisen rearrangement is described. Further functional group conversion was carried out to generate monoterpene elenolide core structure