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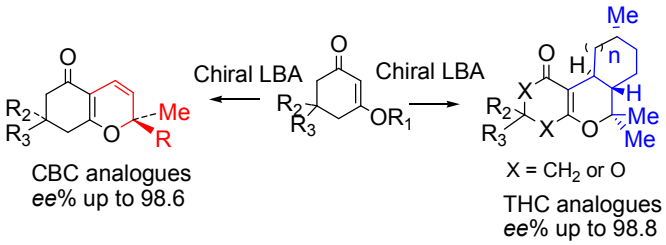
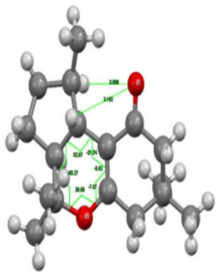
Graphical Abstract

Efficient catalyst for tandem solvent free enantioselective Knoevenagel-formal [3+3] cycloaddition and Knoevenagel-Hetero-Diels-Alder Reactions

Sylvia Fernandes,[a] P. Rajakannu[b] and Sujata V. Bhat*[a]





In this study highly efficient catalyst has been observed for one-pot solvent free enantioselective *Knoevenagel*-[3+3] cycloaddition and *Knoevenagel*-Hetero-Diels-Alder reactions. Thus, the synthesis of bicyclic tetrahydro-2*H*-chromen-5(6*H*)-one and tricyclic octahydro-2*H*-benzo[*c*]-chromen-1(6*H*)-one derivatives with enantioselectivity up to *ee* 98.8% has been achieved in the presence of chiral LBA, titanium-isopropoxy-(*S*)-BINOLate under a solvent free condition. The stereochemistry of tricyclic product **10** has been further supported by single crystal X-ray analysis.

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Efficient catalyst for tandem solvent free enantioselective Knoevenagel-formal [3+3] cycloaddition and Knoevenagel-Hetero-Diels-Alder Reactions

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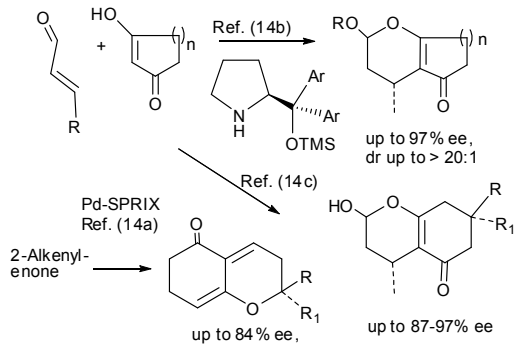
In this study highly efficient catalyst has been observed for tandem solvent free enantioselective Knoevenagel-formal [3+3] cycloaddition and Knoevenagel-Hetero-Diels-Alder reactions. Thus, the synthesis of bicyclic tetrahydro-2*H*-chromen-5(6*H*)-one and tricyclic octahydro-2*H*-benzo[*c*]-chromen-1(6*H*)-one derivatives with enantioselectivity up to *ee* 99% has been achieved in the presence of chiral Lewis acid assisted Brønsted acid, (LBA), titanium-isopropoxy-(*S*)-BINOLate under a solvent free condition. The stereochemistry of tricyclic product **10** has been further supported by single crystal X-ray analysis.This domino powerful strategy combines both the economic and environmental aspects of organic chemistry, which are necessary for academic and industrial applications.

Introduction

Several bioactive natural products contain tetrahydro-benzopyran moiety,[1] some examples being forskolin,[2] hongoquercin A,[3a] zanthosimuline,[3b] chromazonarol,[3c] Δ^9-tetrahydrocannabinol (THC),[4] cannabichromene (CBC).[5a] etc. Asymmetric catalysis of organic reactions to provide enantiomerically enriched products is of central importance to modern synthetic and pharmaceutical chemistry. Therefore, the need for truly efficient and practical asymmetric synthesis has been one of the greatest challenges for synthetic chemists.[6]

A common approach for the synthesis of bicyclic tetrahydro-2*H*-chromen-5(6*H*)-one and tricyclic octahydro-2*H*-benzo[*c*]-chromen-1(6*H*)-one rings utilizes *Knoevenagel*-[3+3] cycloaddition and *Knoevenagel*-Hetero-Diels-Alder reactions. Several catalysts have been reported for these reactions.[7-13] In previous reports, the reactions between 1,3-dicarbonyls (**2** or **3**) and olefinic aldehydes **4a** or **4b** were evaluated in the presence of catalysts such as $InCl_3$,[7] EDDA,[8] *p*-TSA,[9] BF_3OEt_2,[9] $TiCl_4$,[9] $In(OTf)_3$,[9] phosphoric acid,[10] EDDA/$ZnCl_2$,[11] water,[12] NaOMe/MeOH[13a] etc. A recent report utilizes a new hollow-structured ZIF-8-H nanosphere as a catalyst for [3+3] cycloaddition reactions.[13b]

In previous reports, enantioselective cyclization of 2-alkenyl-1,3-diones promoted by Pd-SPRIX catalyst was evaluated, where isomeric 2,2-dialkyl-6,7-dihydro-2*H*-chromen-5(3*H*)-ones were formed in *ee* up to 88%.[14a] Similarly, the enantioselective addition of conjugated aldehyde to 1,3-cyclohexadione and cyclopentadione in the presence of organo-catalyst (trimethylsilyl-1,1-diaryl-prolinol) has been achieved, which yielded 4-substituted-2-hydroxy or 2-acyloxy-chromenones[14b,c] in *ee* up to 97% (Scheme 1).



Scheme 1 Reported asymmetric syntheses of chromanonesin the presence of chiral catalysts

We report herein a highly efficient tandem solvent free enantioselective K*noevenagel*-formal[3+3] cycloaddition and *Knoevenagel*-Hetero-Diels-Alder reactions in the presence of the chiral LBA titanium-isopropoxy-(*S*)-BINOLate (**1**) (Figure 1).

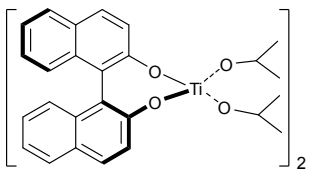


Figure 1 [(*S*)-(-)-BINOLate]$_2$Ti$_2$(O-*i*-Pr)$_4$ **1** (LBA)

[a] *Laboratory for Advanced Research in Natural and Synthetic Chemistry, V. G Vaze College, Mumbai University,Mithagar Road, Mulund East, Mumbai 400 081, India. E mail: Sujata8b@gmail.com*
[b] *Department of Chemistry, Indian Institute of Technology, Powai, Mumbai 400 o76, India*

† Electronic Supplementary Information (ESI) available: Experimental procedures, characterisation data for new compounds, X-ray crystal structure details, copies of NMR , GCMS spectra and chiral GC analysis . See DOI: 10.1039/x0xx00000x

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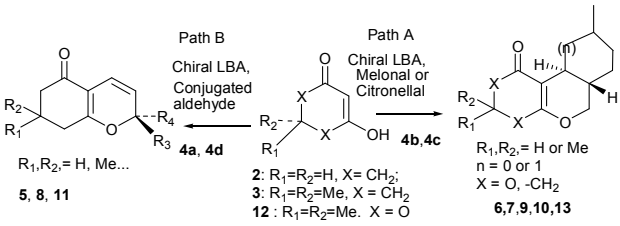
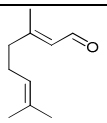
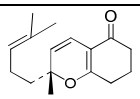
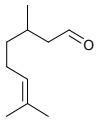
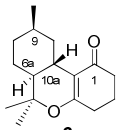
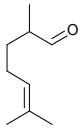
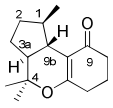
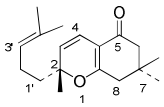
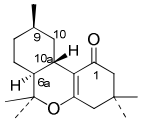
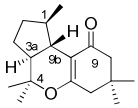
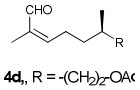
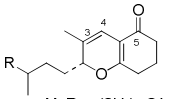
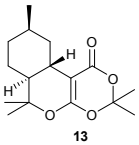
Table 1 Products of enantioselective reactions in the presence of $[(S)\text{-}(-)\text{-BINOLate}]_2Ti_2(O\text{-}i\text{-}Pr)_4$[a,b,c]



Entry	Aldehydes	Product	Yield %, (*ee*%)
1.	 4a	 **5**	80 (99)
2.	 4b	 **6**	76 (97)
3.	 4c	 **7**	77 (88)
4.	**4a**	 **8**	77 (89)
5.	**4b**	 **9**	76 (89)
6.	**4c**	 **10**	77 (99)
7.	 **4d**, R = -$(CH_2)_2$-OAc	 **11**, R = -$(CH_2)_2$-OAc	75 (98)
8	**4b**	 **13**	72 (83)

[a] Reaction conditions: catalyst **1** (3 mol%) at 0 °C, N_2 atmosphere
[b] Isolated yield
[c] Enantiomeric excess (*ee*%) was obtained in GC analysis using chiral Beta Dex column

Thus, the synthesis of bicyclic tetrahydro-2*H*-chromen-5(6*H*)-one and tricyclic octahydro-2*H*-benzo[*c*]-chromen-1(6*H*)-one derivatives with enantioselectivity up to 98.8% has been achieved in the presence of chiral LBA, under a solvent free condition (Scheme 2, Table 1).

Results and discussion

The chiral catalyst **1** was prepared according to the reported procedure.[15] Initially, the reaction of 1,3-cyclohexadienone (**2**) and citral (**4a**) in CH_2Cl_2 at 0 °C under N_2 atmosphere was attempted, which went to completion in ½ h, with 79% yield. A similar reaction of 1,3-cyclohexadienone (**2**) and citral (**4a**) in the presence of chiral catalyst **1** under solvent free condition gave similar yield in the same duration of time. Hence we carried further reactions under solvent free condition.

The reaction between α,β-unsaturated aldehyde such as citral (**4a**) (17.90 mmol) and 1,3-cyclohexadienone (**2**) or dimedone (**3**) (17.90 mmol) was achieved in the presence of **1** (3 mol %) at 0 °C under solvent free condition. The reaction was monitored by GC and TLC analyses and was completed within ½ h to give the bicyclic tetrahydro-2*H*-chromen-5(6*H*)-one derivatives **5** (80% yield and 99% *ee*) and **8** (77% yield and 89% *ee* respectively (Table 1, entries 1 and 4).

Additional reactions of 1,3-dicarbonyl compounds **2** or **3** with terpenic olefinic aldehydes such as (*R*)-citronellal (**4b**), (*R*)-melonal (**4c**) were also evaluated on the same reaction scale, which yielded tricyclic octahydro-2*H*-benzo[*c*]-chromen-1(6*H*)-one derivatives **6, 7**, **9** and **10** respectively in ~77% yields and *ee* in the range of 88-98% (Table 1, entries 2, 3, 5, 6). Similarly, the reaction of cyclohexa-1,3-dione (**2**) with conjugated aldehyde (*E)*-7-formyl-3-methyl-oct-6-enyl acetate (**4d**) yielded bicyclic chromenone adduct **11** (75% yield and 98% *ee)*. The reaction of Meldrum's acid (**12**) with (*R*)-citronellal (**4b**) gave tricyclic [1,3]dioxino[4,5-*c*]isochromen-1(6*H*)-one derivative **13** . The reaction of cyclopenta-1,3-dione) with (*R*)-citronellal (**4b)** did not yield tricyclic product. Apparently Knoevenagel adduct intermediate in case of cyclopenta-1,3-dione does not undergo hetero-Diels-Alder reaction under present reaction condition.

The required aldehydes (*R*)-melonal (**4c**) and **(***R*)-(*E)*-7-formyl-3-methyl-oct-6-enyl acetate (**4d**) were synthesised with minor modifications of reported procedures.[16]

The structures of compounds **5-11, 14** and **15** were identified with IR, ^{1}H NMR, ^{13}C NMR, GC/MS and HRMS data. In ^{1}H-NMR spectrum, the olefinic protons of **5** absorbed at δ 6.45 (*d*, *J* = 10.12 Hz, 1 H), 5.18 (*d*, *J* = 10.12 Hz, 1 H). ^{13}C NMR spectrum of compound **5** showed peaks at δ 194.9 and 172.1 due to C-5 carbonyl and C-8a enol carbon respectively. The olefinic carbons absorbed at δ 131.9, 123.6, 121.6, 116.4, 110.3 and ethereal carbon at δ 82.4. ^{1}H-NMR compound **6** showed absence of olefinic protons. The ^{13}C NMR spectrum of compound **6** showed peaks at δ 197.8 and 170.5 due to carbonyl and enol carbon respectively. The ^{1}H-NMR and ^{13}C-NMR of remaining molecules were also in agreement with their structures.

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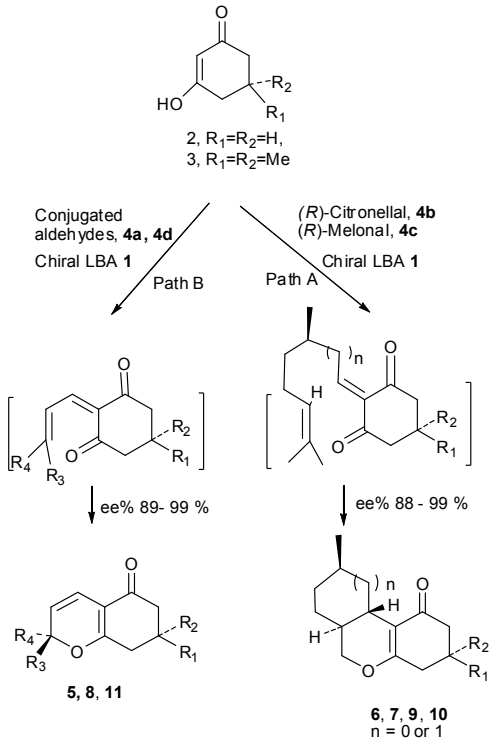

Scheme 2 Stereoselective reactions of cyclohexa-1,3-dienones with Aldehydes in the presence of [(*S*)-(-)-BINOLate]$_2$Ti$_2$(O-*i*-Pr)$_4$ (Chiral LBA, **1**)

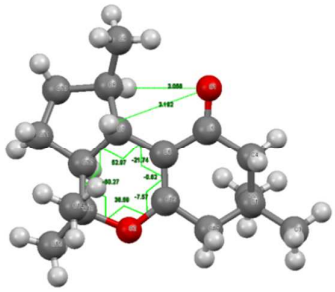

Figure 2 ORTEP diagram of compound **10**

The enantiomeric excess (*ee%)* of compounds **5-11, 14, 15** was obtained in GC analysis using chiral Beta-Dex column. High stereoselectivity was observed, *ee*% ranging from 88.1-98.8%, for both bicyclic (**5**, **8**, **11**) and tricyclic (**6**, 7, **9**, **10**) molecules (Table 1). The structure and stereochemistry of tricyclic compound **10** was further supported by single crystal X-ray analysis,[17-19] which is shown in Figure **1**. It is noteworthy, that the stereochemistry at ring junction positions 3a and 9b of analogue **10** is opposite to that of natural (*R*,*R*)-THC. [4] In view of strong analgesic activity of (*S*,*S*)-daxanabinol[5b] the present report has more significance.

The 2-(*R*)-stereochemistry of 7,8-dihydro-2*H*-chromen-5(6*H*)-one derivatives **5, 8** and **11** was assigned based on (-)-optical rotation and CD spectra.[20,21]

The molecules **7**, **10** and **11** are novel to the best of our knowledge.

The probable mechanism for stereoselective formation of (2*R)*-5,6,7,8-tetrahydro-5-oxo-2*H*-chromene derivatives is shown in Figure 3. In Intermediate **A** the bulky substituent (R-) in aldehyde prefers equatorial position, which is converted to condensation product intermediate **B**. The elimination of water molecule leads to intermediate **C**, subsequent attack by isopropanol releases (2*R)*-5,6,7,8-tetrahydro-5-oxo-2*H*-chromene derivative and the catalyst **1** is regenerated. Similar mechanism for stereospecific formation of tricyclic octahydro-6,6,9-trimethyl-2H-benzo[*c*]-chromen-1(6*H*)-onederivatives is given in scheme 4. The Aldol condensation of Intermediate **A** leads to Intermediate **B,** which undergoes dehydration to give **C,** the hetero-Diels-Alder reaction, subsequent attack by isopropanol and release of tricyclic octahydro-6,6,9-trimethyl-2*H*-benzo[*c*]-chromen-1(6*H*)-one derivative regenerates the catalyst **1**.

The present catalytic system provides an attractive protocol to various optically active derivatives of bicyclic chromen-5(6*H*)-one and tricyclic benzo[*c*]-chromen-1(6*H*)-onein terms of the following features: (i) the catalyst is inexpensive and easily available; (ii) the protocol has a broad scope of substrates; (iii) the reactions show

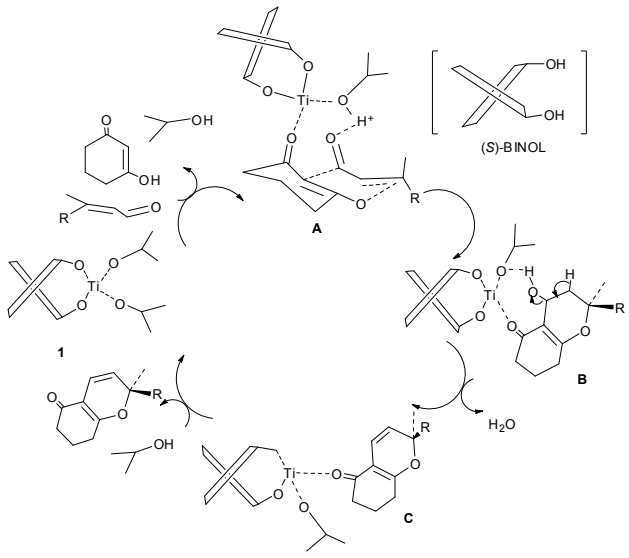

Figure 3 The probable mechanism of formation of (2*R)*-5,6,7,8-tetrahydro-5-oxo-2*H*-chromene derivatives

high enantioselectivity; (iv)short reaction time, reactions are completed within ½ h; (v) the reaction is environmentally benign because of solvent-free condition; and (vi) low catalyst loading (5 mol %) is sufficient to achieve high yield and optical purity of the products. We hope our findings in this research will stimulate further work on practical asymmetric synthesis of more molecules of biological and pharmacological importance.

Conclusions

In summary, highly efficient catalyst has been observed for tandem solvent free enantioselective *Knoevenagel*-formal[3+3] cycloaddition and *Knoevenagel*-Hetero-Diels-Alder Reactions.

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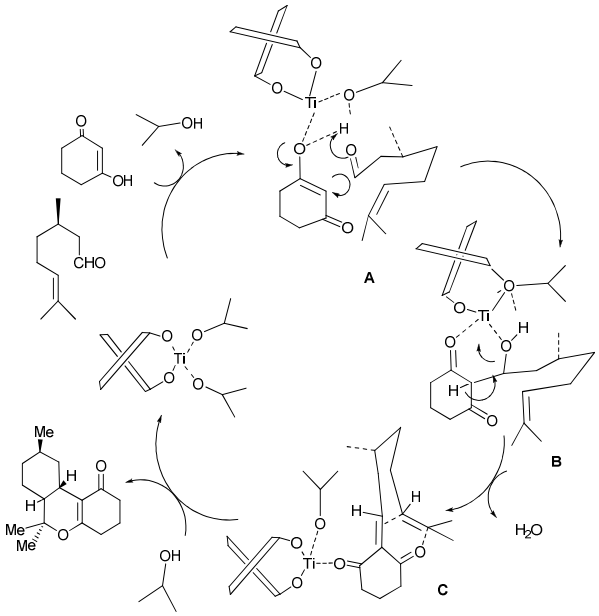

Figure 4 The probable mechanism of formation of octahydro-6,6,9-trimethyl-2*H*-benzo[*c*]-chromen-1(6*H*)-onederivatives

Thus, the synthesis of bicyclic tetrahydro-2*H*-chromen-5(6*H*)-one and tricyclic octahydro-2*H*-benzo[*c*]-chromen-1(6*H*)-one derivatives with enantioselectivity up to *ee* 99% has been achieved in the presence of titanium-isopropoxy-(*S)*-BINOLate under a solvent free condition. The stereochemistry of tricyclic product **10** has been further supported by single crystal X-ray analysis. The methodology reported herein can be used for the synthesis of various natural and non-natural molecules with chromenone moiety. This one-pot powerful strategy combines both the economic and environmental aspects of organic chemistry which are necessary for academic and industrial applications.

Experimental

General procedures

The monitoring of reaction and checking the purity of the products were done using pre-coated silica gel plates (Merck) and visualization using anisaldehyde/ H_2SO_4 reagent. FT-IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer. ^{1}H NMR spectra were recorded on a Varian spectrometer at 400 MHz and ^{13}C-NMR at 100 MHz; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. Multiplicities is reported as follows: s = singlet, d = doublet, dd = doublets of doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet.GC-MS was carried on an Agilent instrument, where GC-6890 was coupled with a mass spectrometer MS-5973 N with quadrapole mass detector, using a HP-5 (5% phenyl methyl siloxane) column. Electrospray ionization and a TOF mass analyser were used for HRMS measurements. The compounds (**5-11**) showed the required m/z: (M^+) values in HR-MS. Enantiomeric excess (*ee*%) was obtained in GC analysis using chiral Beta Dex 120 column (30 m x 0.25µm x 0.25 mm). Silica gel (100-200 mesh), which was used for column chromatography (CC) was activated by heating at 120° for 4 h. All asymmetric reactions were performed under inert atmosphere and at 0 °C.

General procedure for synthesis of compounds 5-11, **14** and **15**

A mixture of cyclohexa-1,3-dione (**2**) or 5,5-dimethyl-cycohexa-1,3-dione (**3**) or Meldrum's acid (**12**), (17.90 mmol), terpenic aldehyde (**4a**-4**d**, 17.90 mmol) and catalyst (**1**) (3 mol %) was stirred at 0 °C under solvent free condition for 30 min under N_2 atmosphere. After completion of the reaction (monitored by TLC/ GC analysis), the reaction mixture was diluted with hexane: CH_2Cl_2 (1:1, 5 mL) and filtered. The filtrate was evaporated and the residue was purified by silica gel column chromatography to afford the pure products.

(*R*)-2-methyl-2-(4-methylpent-3-enyl)-7,8-dihydro-2*H*-chromen-5(6*H*)-one (5). Yellow oil; $[\alpha]_D$ = - 65.2° (*c* = 1 in MeOH), Chiral GC analysis: 33.79 (major), 33.19 (minor) min, *ee* 99%; IR ($CHCl_3$, cm^{-1}): 2939, 1647, 1603, 1428, 1381, 1333, 1285, 1257, 1184, 1111, 1081, 967, 864, 787; ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ (PPM) 6.45 (d, *J* = 10.12 Hz, 1 H), 5.18 (d, *J* = 10.12 Hz, 1 H), 5.09-5.07 (m, 1H), 2.42-2.39 (m, 4H), 2.01-1.94 (m, 4H), 1.74-1.71 (m, 1H), 1.68 (s, 3H), 1.59 (s, 3H),1.68-1.53 (m,1H), 1.36 (s, 3H); ^{13}C NMR (150 MHz, TMS): δ (PPM) 194.9, 172.1, 131.9, 123.6, 121.6, 116.4, 110.3, 82.4, 41.7, 36.4, 28.6, 27.4, 25.7, 22.5, 20.6, 17.6; GC-MS (*m/z*) : 246, 231, 213, 203, 190, 175, 163, 155, 147, 135, 122, 107, 99, 91, 77, 69, 55, 41; HRMS (EI^+) calcd for $C_{16}H_{22}O_2$ 246.1620, found *m/z* 246.1622.

Synthesis of (±)-2-methyl-2-(4-methylpent-3-enyl)-7,8-dihydro-2*H*-chromen-5(6*H*)-one (5)using ethylenediamine diacetate as catalyst. To a mixture of 1,3-cyclohexadione, **2** (2g, 17.9 mmol) and citral **4a** , (2.73g ,17.9 mmol) was added catalyst EDDA (5 mol %) and stirred at room temperature for 1h. After completion of the reaction, the reaction mixture was purified by column chromatography using *n*-hexane/ EtOAc (4:1) as eluent to provide **5** (3.31 g, 75.4%) as a yellow oil. $[\alpha]_D$= 0.

(6a*S*,9*R*,10a*S*)-6,6,9-trimethyl-2,3,4,6,6a,7,8,9,10,10a-dehydro-1*H*-benzo[*c*]chromen-1-one (6). Colourless solid; $[\alpha]_D$ = -100.1° (*c* = 1 in MeOH), Chiral GC analysis 36.61 min (major), 37.78 min (minor), *ee*% 97); IR ($CHCl_3$, cm^{-1}): 2920, 2847, 1649, 1598, 1447, 1379, 1273, 1252, 1192, 1128, 999, 850, 775, 693; ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ (PPM) 2.80-2.77 (ddt, *J*= 11.5,3,1.7 Hz,1H), 2.43-2.18 (m,4 H), 2.13-2.06 (dt, J= 11.08, 2.2 Hz, 1H), 1.92-1.86 (m, 2H), 1.86-1.78 (m, 1H), 1.78-1.72 (m, 1H), 1.61-1.50 (m, 1H), 1.33 (s, 3H), 1.29-1.23 (td, *J* = 11.3,2.6Hz, 1H), 1.05 (s, 3 H), 1.12-0.95 (m,2H), 0.91-0.89 (d, *J* = 6.6 Hz, 3H), 0.49 (q, *J* =11.5 Hz, 1H); ^{13}C NMR (100 MHz, TMS): δ (PPM) 197.8, 170.5, 114.7, 80.3, 48.6, 38.8, 37.5, 35.5, 33.6, 32.3, 29.6, 27.5, 27.2, 22.5, 20.2, 19.4; GCMS (*m/z*) : 248, 233, 219, 205, 192, 177, 163, 150, 137, 123, 109, 95, 81, 68, 55, 41; HRMS (EI^+) calcd for $C_{16}H_{24}O_2$ 248.1776, found *m/z* 248.1774.

(1*R*,3a*S*,9b*S*)-1,4,4-trimethyl-1,2,3,3a,4,7,8,9b-octahydrocyclo-penta[*c*]chromen-6(6*H*)-one (7). Colourless liquid. $[\alpha]_D$ = - 86.6° (*c* = 1, MeOH); Chiral GC analysis 34.23 (major), 33.88 (minor) min, (*ee*% 88); IR ($CHCl_3$, cm^{-1}): 2945, 2869, 1651, 1582, 1455, 1428, 1379, 1334, 1278, 1226, 1192, 1113, 1064, 1004, 991, 848, 629; ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ (PPM) 2.41-2.34 (dt, *J*=11.4,5Hz, 1H), 2.35-2.30 (m, 2H), 2.29-2.26 (m, 2H), 2.04-1.98 (m, 1H), 1.91-1.87 (m,1H), 1.86-1.81 (m, 4H), 1.72-1.55 (m,2H), 1.41-1.39 (d, *J*= 6.16 Hz, 3H), 1.36 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, TMS): δ (PPM) 197.5, 171.2, 115.4, 81.5, 53.5, 42.6, 37.6, 36.6, 34.4, 29.7, 28.4, 24.8, 23.4, 20.4, 20.1; GC purity :

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90.0%; GCMS (*m/z*): 234, 219, 191, 177, 163, 151, 137, 125, 109, 91, 79, 67, 55, 41; HRMS (EI^+) calcd for $C_{15}H_{22}O_2$ 234.1620, found *m/z* 234.1622.

(*R*)-2,7,7-trimethyl-2-(4-methylpent-3enyl)-7,8-dihydro-2*H*-chromen-5(6*H*)-one (8). Yellow oil. $[\alpha]_D$ = - 66.2° (*c* =1, MeOH); Chiral GC analysis) 33.86 (major), 32.39 (minor) min, (*ee*% 89); IR ($CHCl_3$, cm^{-1}): 2961, 1680, 1606, 1449, 1382, 1331, 1287, 1217, 1198, 1165, 1112, 1077, 1034, 936, 889; ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ (PPM) 6.44 (d, *J*= 10Hz,1H), 5.17 (d, *J*= 10Hz, 1H), 5.11-5.07 (m,1H), 2.29-2.23 (m,4H), 2.08-2.01 (m,2H), 1.76-1.69 (m,1H), 1.67 (s,3H), 1.57(s, 3H), 1.56-1.54 (s,1H), 1.37(s,3H), 1.08 (s, 3H), 1.06 (s,3H); ^{13}C NMR (100 MHz, TMS): δ (PPM) 194.4, 170.6, 131.8, 123.6, 121.4, 116.2, 109.0, 82.5, 50.3, 42.4, 41.7, 32.1, 28.6, 28.2, 27.5, 25.7, 22.5 , 17.6; GCMS (*m/z*): 274, 259, 241, 231, 218, 205, 191, 175, 165, 157, 149, 141, 129, 121, 107, 91, 77, 69, 55, 41; HRMS (EI^+) calcd for $C_{18}H_{26}O_2$ 274.1933, found *m/z* 274.1930.

(6a*S*,9*R*,10a*S*)-3,3,6,6,9-pentamethyl-2,3,4,6,6a,7,8,9,10,10a-decahydro-1*H*-benzo[*c*]chromen-1-one(9). Yellow oil. $[\alpha]_D$ = - 101.5° (*c* =1, MeOH); Chiral GC analysis 34.33 (major), 33.78 (minor) min, (*ee*% 89); IR ($CHCl_3$, cm^{-1}): 2957, 2868, 1644, 1606, 1455, 1381, 1360, 1278, 1236, 1165, 1088, 1031, 1013, 941, 865, 665; ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ (PPM) 2.85 (ddt, *J*= 11.2,3,1.7 Hz,1H), 2.22-2.18 (m, 4H), 2.02-2.18 (m,1H), 1.84-1.78 (m,1H), 1.78-1.72 (m,1H), 1.61-1.50 (m,1H), 1.35 (s,3H), 1.26 (td,*J*= 11.2,2.2 Hz, 1H), 1.12-0.98 (m, 2H), 1.05 (s,3H), 1.04 (s, 3H), 1.03 (s,3H). 0.90 (d, *J*=6.5 Hz, 3H), 0.49 (q, *J*= 11.2 Hz,1H);^{13}C NMR (100 MHz, TMS): δ (PPM) 197.9, 175.3, 168.8, 113.2, 80.4, 51.4, 48.8, 45.4, 43.3, 43.2, 38.6, 35.6, 33.5, 32.3, 31.6, 29.3, 28.1, 27.6, 27.3, 27.2, 22.5, 19.5; GCMS (*m/z*) : 276, 261, 243, 220, 205, 192, 177, 165, 153, 134, 123, 109, 91, 81, 69, 55, 41; HRMS (EI^+) calcd for $C_{18}H_{28}O_2$ 276.2089, found *m/z* 276.2091.

(1*R*,3a*S*,9b*S*)-1,4,4,7,7-pentamethyl-1,2,3,3a,4,7,8,9b-octahydrocyclo-penta[*c*]chromen-9(6*H*)-one (10). Yellow oil. $[\alpha]_D$ = - 89.6° (*c* =1, MeOH), Chiral GC analysis 33.55 min (major), 34.23 min (minor), (*ee*% 99); IR ($CHCl_3$, cm^{-1}): 2950, 1728, 1651, 1586, 1468, 1378, 1230, 1118, 1024, 938, 860, 757; ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ (PPM) 2.29-2.10 (m,4H), 2.08-1.99 (m, 1H), 1.99-1.91 (m, 1H), 1.89-1.81 (m,1H), 1.73-1.57 (m,2H), 1.44 (d, *J*=6 Hz, 3H), 1.38 (s,3H), 1.22-1.13 (m,2H), 1.16 (s, 3H), 1.07 (s,3H), 1.04 (s,3H); ^{13}C NMR (100 MHz, TMS): δ (PPM) 198.4, 197.6, 169.4, 167.5, 114.1, 81.6, 78.3, 53.7, 51.8, 43.5, 42.5, 42.8, 36.4, 34.6,31.7, 28.7, 28.5, 27.9, 25.0, 23.7, 20.4; GCMS (*m/z*) : 262, 247, 219, 205, 191, 179, 165, 151, 109, 91, 83, 67, 55, 41; HRMS (EI^+) calcd for $C_{17}H_{26}O_2$ 262.1933, found *m/z* 262.1930.

(*R*)-3-methyl-5-((*R*)-3-methyl-5-oxo-5,6,7,8-tetrahydro-2*H*-chromen-2-yl)pentyl acetate (11). Yellow oil. $[\alpha]_D$ = - 90.5° (*c* =1, MeOH), Chiral GC analysis 33.88 min (major), 32.39 min (minor), (*ee*% 98); IR ($CHCl_3$, cm^{-1}): 2920, 2847, 1729, 1649, 1598, 1447, 1379, 1273, 1252, 1192, 1128, 999, 850, 775, 693; ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ (PPM) 6.21 (s, 1H), 4,75 (dd, *J*= 10.8 Hz,3.5 Hz, 1H), 4.18-4.12 (m, 4H), 2.42-2.35 (m, 4H), 2.05 (s, 3H), 1.99-1.93 (m, 2H), 1.72 (s, 3H), 1.68-1.62 (m, 1 H), 1.62-1.53 (m, 2H), 1.50-1.38 (m, 2H), 0.95-0.90 (dd,*J =6.*4 Hz,3H); ^{13}C NMR (100 MHz, TMS): δ (PPM) 195.1, 171.2, 169.9, 126.1, 112.5, 80.9, 62.7, 36.4, 35.4, 35.1, 31.3, 30.3, 29.7, 27.9, 26.3, 20.9, 19.5, 19.1; GCMS (*m/z*) : 306, 291, 263, 189, 163, 121, 107, 91, 77, 56, 43; HRMS (EI^+) calcd for $C_{18}H_{26}O_4$ 306.1831 found *m/z* 306.1833.

(6a*S*,9*R*,10a*S*)-6a,7,8,9,10,10a-hexahydro-3,3,6,6,9-pentamethyl-[1,3]dioxino[4,5-*c*]isochromen-1(6*H*)-one (13). Yellow oil. $[\alpha]_D$ = -40.2 ° (*c* =1, MeOH), Chiral GC analysis 33.77 min (major), 32.76 min (minor), (*ee*% 83); IR ($CHCl_3$, cm^{-1}): 2925, 2855, 1736, 1726, 1620, 1455, 1390, 1280, 1155, 994, 965, 891, 731; ^{1}H-NMR ($CDCl_3$, 400 MHz, TMS): δ (PPM) 2.65 (dd, *J*= 5.6, 18.4 Hz, 1H), 2.08- 2.01 (m, 1H), 1.85-0.95 (m, 6H), 1.68 (s,3H), 1.60(s,3H), 1.41 (s,3H), 1.26 (s,3H), 0.91 (d,*J*=6.5 Hz ,3H), 0.78-0.62 (m,1H) ^{13}C NMR (100 MHz, TMS): δ (PPM) 171.4, 167.3, 124.4, 85.9, 47.4, 42.3, 37.2, 36.3, 32.0, 31.8, 28.7, 27.6, 25.9, 23.5, 22.3. GCMS (*m/z*) : 280,; HRMS (EI^+) calcd for $C_{16}H_{24}O_4$ 280.1704 found *m/z* 280.1703.

X-ray single crystal structure determination of molecule 10. A suitable crystal of size 0.06 × 0.18 × 0.24 mm^3 was mounted on a diffractometer for unit cell determination and three dimensional intensity data collection. 800 frames in total were collected at 150 K with the exposure time of 16 s per frame. Data integration, indexing and absorption correction were followed by structure solution using the programs in a WinGX module.[17] The structure was solved by direct methods (SIR-92)[18] and the final refinement of the structure was carried out using full least-squares methods on F^2 using SHELXL-97.[19] Unit cell determination using both high and low angle reflections reveals that compound **10** crystallizes in a monoclinic $P2_1/c$ space group. Non-hydrogen atoms were refined anisotropically. C–H hydrogen atoms were placed in geometrically calculated positions by using a riding model.

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Notes and references

‡ Crystallographic data -Unit cell determination using both high and low angle reflections revealed that compound **10, $C_{17}H_{26}O_2$**; 262.38;crystallizes in a, monoclinic $P2_1/c$ space group; Unit cell dimensions a = 5.9897(17), alpha = 90°, b = 12.612(4), beta = 96.062°(5), c = 19.986(6) Å, gamma = 90°; Volume 1501.3(8) A^3

See supporting information for more details. CCDCNumber-1060831

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