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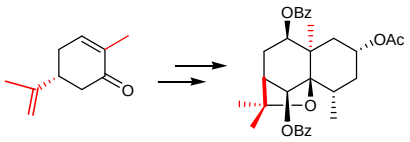

R-(-)-Carvone deacetoxy-*ent*-orbiculin A

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An enantiodivergent protocol from *R*-(-)-carvone: Synthesis of dihydroagarofuran sesquiterpenoid 1-deacetoxy-*ent*-orbiculin A

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ABSTRACT

A strategy for achieving enantiodivergency from *R*-(-)-carvone in the context of synthesis of eudesmanes and dihydroagarofurans is disclosed which involves, among other things, sequential setting of the C10 quaternary centre and recreation of the desired C7 isopropyl stereochemistry to enter the anti-podal series. A synthesis of 1-deacetoxy-*ent*-orbiculin has been achieved as a demonstration of the effectiveness aqnd applicability of this approach.

Introduction

Enantioselective synthesis of a single enantiomer, employing abundantly available, naturally occuring chiral building-blocks (chirons) has been on ascendency for several decades.[1] This approach has found favour and productive applications in the industrial scale preparation of important pharmaceuticals and agrochemicals wherein the desired bioactivity is generally enantiomer specific. In the academic research environment also, chiron based enantioselective synthesis of complex molecules, particularly of natural products, has been a widely pursued creative endeavour. A limiting aspect of the chiral pool (sugars, amino acids, terpenes, alkaloids etc.) based asymmetric synthesis strategies is that by and large Nature's biosynthetic machinery is geared to deliver the chiron in only one absolute configuration, although a few notable exceptions to this are known.[2] Thus, if in the given context of an enantispecific synthesis objective, the requirement is of an anti-pode of the chiron, then either it may not be available at all or command a prohibitive price premium. One way to overcome this problem is through adoption of enantiodivergent strategies wherein a single starting chiral pool enantiomer can be manipulated to eventuate in either of the two enantiomers of the target molecule. Several enantiodivergent approaches to diverse bioactive molecules, particularly to active pharmaceutical intermediates, have been implemented following various modes of asymmetric syntheses employing either chiral pool precursors or achiral starting materials.[1,3]

For quite some time, our group[4] has been involved in enantioselective syntheses of natural products following 'terpenes to terpenes' theme that employed terpenes as chirons. In this context, we have recently outlined a general enantioselective approach to eudesmanes and dihydroagarofurans employing *R*-(-)-carvone **1** as the chiral building block (chiron) and leading to a synthesis of (-)-isocelorbicol **2**, Fig 1.[5] As an interesting extension of this investigation, we decided to explore a strategy for achieving enantiodivergency from *R*-(-)-carvone **1** towards the synthesis of dihydroagarofurans and identified *ent*-orbiculin A **3** (Fig. 1) and siblings, corresponding to the antipodal series of **2**, as possible objectives.[5,6]

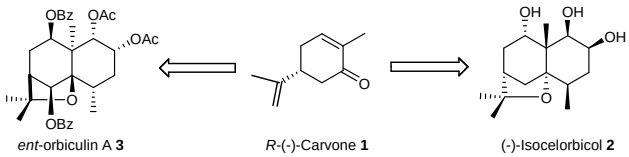


Fig. 1. Enantiodivergence from *R*-(-)-carvone

Eudesmane sesquiterpenoids, embodying bicyclic decalin framework **4** constitute a large, widely occurring and growing family.[7,8] There are many interesting structural variants of eudesmanes present in Nature and one of the more prominent among them is the dihydroagarofuran framework **5** composed of A and B rings of eudesmane with a 1,3-bridged tetrahydrofuran moiety as C ring.[9] While simple agarofurans have been known

for over half a century,[10] it is the densely oxy-functionalized agarofurans that have aroused attention in recent years as many of them could be traced to plant sources prominently mentioned in traditional medicine. Celafolin A **6**, maytol **7**, reissantin D **8** and celastrine A **9** are representative of the degree of oxygenation and variegated hydroxyl group functionalization present in dihydroagarofuran natural products, Fig 2.[9]

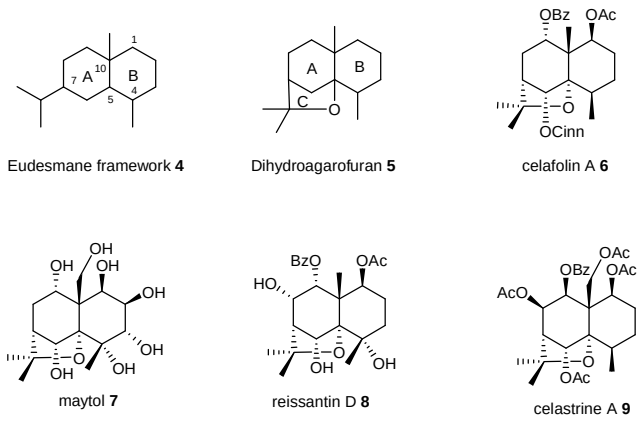


Fig. 2. Representative eudesmane based dihydroagarofuran natural products

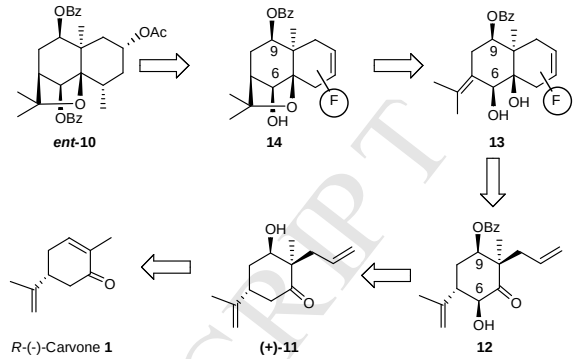
Some of the recently reported dihydroagarofurans have been shown to exhibit exceptional bioactivities that range from cancer and rheumatoid arthritis to efficacy against *Mycobacterium tuberculosis* bacteria and *Leishmania tropica* protozoan parasite in modern screening assays.[11] It is both for the structural complexity and bioactivity that dihydroagarofurans continue to engage the attention of synthetic organic chemistry community.[12]

As already indicated (*vide supra*) bioactivities of natural products strongly correlate, in most cases, with their absolute configuration[2,3] and therefore it was of interest to devise routes that will also make available unnatural *ent*-dihydroagarofurans for evaluation. Since, we had already crafted a viable synthetic route[5] to natural dihydroagarofurans from *R*-(-)-carvone, it was of interst to explore if *ent*-dihydroagarofurans could also be accessed from the same enantiomer of carvone by incorporating elements of enantiodivergency in the scheme while retaining the core strategy. Successful realization of this theme leading to a synthesis of 1-deacetoxy-*ent*-orbiculin A **10** from *R*-(-)-carvone **1** is delineated here.

Results and discussion

From a retrosynthetic perspective, access to 1-deacetoxy-*ent*-orbiculin A **10** from *R*-(-)-carvone **1** required inversion of the pre-existing C7 isopropyl group and setting-up of C10 quaternary methyl group in α-orientation so that C7-C10 substituents have the desired trans disposition, besides building the framework and generation of requisite functionalities in a stereocontrolled manner. The projected plan is depicted in Scheme 1 and its key elements were access to **11** with the desired quaternary methyl bearing centre, stereoselective α-hydroxylation to **12**, construction of the bicyclic framework and destruction of the C7 stereogenic centre to deliver **13**. Recreation of the desired C7 stereochemistry with concomitant installation of the bridged tetrahydrofuran moiety could lead to **14** and finally functional group manipulations on it could deliver **10**, Scheme 1.

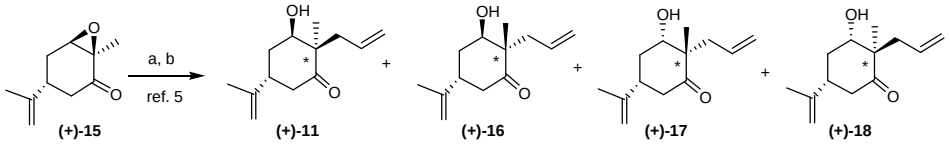
Earlier we have shown[5] that reductive allylation of carvone epoxide **(+)-15** (derived from **1**) in Li/liq. ammonia milieu led to



Scheme 1. Retrosynthetic analysis for enantiodivergent access to dihydroagarofuran

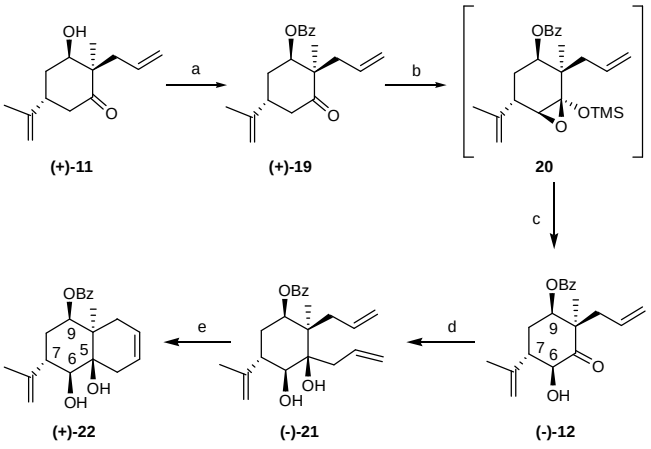
the formation of four diastereomers **(+)-11**, **(+)-16**, **(+)-17** and **(+)-18** in a ratio of ~ 1:10.5:9.5:1, respectively, *via* a process involving retro-aldol and re-aldolisation under the given reaction conditions, Scheme 2. The required diastereomer **(+)-11** as per the projected retrosynthetic perspective, Scheme 1, was present only in meagre amount (4-5%) and if it were to be serviceable for our objective than its availability had to be considerably enhanced. Recognizing that the four diastereomers **(+)-11**, **(+)-16**, **(+)-17** and **(+)-18** and are in all probability generated through the intervention of some equilibrium controlled process; an opportunity presented in terms of re-equilibrating them. After screening a variety of recipes, it was observed that in NaOMe-MeOH milieu, either of the major β-hydroxyl-ketones (+)-**16** or (+)-**17** individually or as a mixture, diastereomers **(+)-11** , **(+)-16**, **(+)-17** and **(+)-18** obtained directly from the reductive allylation of carvone epoxide (+)-**15**, on reconstructive epimerization led to an equilibrium mixture (1:1:1:1) of the four in which the required (+)-**11** was substantially enriched and could be readily separated by column chromatography from the other isomers. This was not an optimal solution to the problem at hand but in practical sense provided access to (+)-**11** in reasonable quantities for further advance toward the target.

The next step was to stereoselectively introduce α-hydroxyl group in (+)-**11** and evolve towards **12**. After some unsuccessful forays towards the direct α-hydroxylation [SeO_2, $Mn(OAc)_3$, $Pb(OAc)_4$ etc] of the methylene group flanking the carbonyl in **(+)-11**, it was found that Rubottom protocol[13] worked well for this purpose. Thus, the hydroxyl group in (+)-**11** was protected as benzoate **19** and the DBU mediated trimethylsilylether obtained from it was directly subjected to epoxidation with *m*-chloroperbenzoic acid to furnish the intermediate epoxide **20** in a regio- and stereoselective manner, Scheme 3. Acid mediated epoxide cleavge in **20** delivered the desired α-hydroxylketone



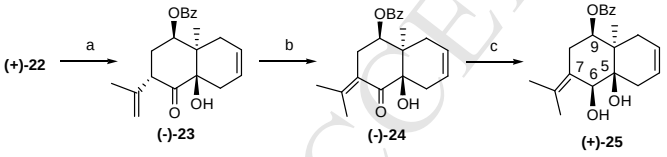
Scheme 2. *Reagents and conditions*: a) Li, liq.NH_3, ether, CH_2=$CHCH_2Br$, - 78 ^oC; b) NaOMe, MeOH, rt, 95%, **(+)-11**, **(+)-16**, **(+)-17**, **(+)-18** in the ratio of 1:1:1:1.

(-)-**12** in decent yield. Stage was now set to generate the decalin framework by annulating a six membered ring employing RCM reaction. Hydroxy directed and indium metal mediated allylation on ketone (-)-**12** delivered bis-allylated (-)-**21** as a single diastereomer. Exposure of (-)-**21** to Grubbs' catalyst (G1) led to noreudesmane framework (+)-**22** quite smoothly and efficiently, Scheme 3. At this stage, the main task was to invert the stereochemistry at the isopropenyl bearing centre (C7). Towards this end, several attempts were made to isomerise the double bond in (+)-**22** to an isopropylidene derivative **23** using acid and metal mediation but these efforts were not successful, Scheme 3. Thus, recourse to a more circuitous route was undertaken to invert the isopropenyl group in (+)-**22**.



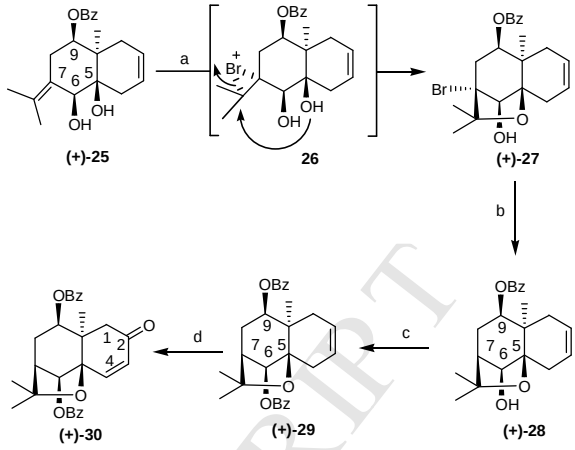
Scheme 3. *Reagents and conditions:* a) BzCl, Et_3N, DMAP, DCM, rt, 92%; b) i. DBU, TMSCl, THF, 70 °C; ii. *m*CPBA, hexane, 0 °C; c) 50% HCl, THF, 0 °C, 78% for three steps; d) CH_2=$CHCH_2Br$, In, THF/H_2O (4:1), 0 °C to rt, 92%; e) 1 mol% Grubbs' cat., C_6H_6, 80 °C, 94%

Chemoselective Swern oxidation of the secondary hydroxyl group in (+)-**22** proved to be straightforeward and led to hydroxyketone (-)-**23** quite uneventfully. Being a β,γ-unsaturated ketone, the double bond in (-)-**23** was considered amenable to ready migration to a conjugated position. Indeed, brief exposure of (-)-**23** to base (DBU) efficiently delivered the requisite α, β-unsaturated enone (-)-**24**. Luche reduction[14] in (-)-**24** was expectedly chelation controlled and delivered the hydride from the α-face to eventuate in allylic alcohol (+)-**25** as a single, required diastereomer, Scheme 4.



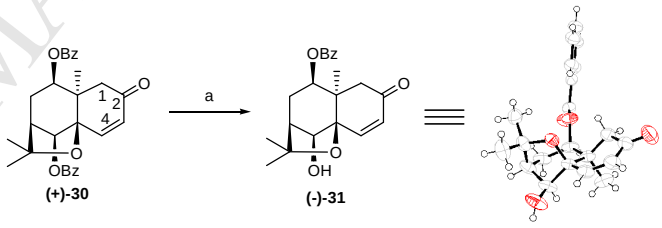
Scheme 4. *Reagents and conditions:* a) $(COCl)_2$, DMSO, Et_3N, DCM, –78 °C, 86%; b) DBU, C_6H_6, 80 °C, 96%; c) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C, 89%.

Stage was now set for the installation of the bridged tetrahydrofuran moiety. Attempted direct acid mediated etherification in (+)-**25** was unproductive but it was gratifying to observe that exposure of (+)-**25** to N-bromosuccinimide (NBS) led stereoselectively to tricyclic bromide (+)-**27** via the intermediacy of bromonium ion (+)-**26**, Scheme 5. This outcome was crucial in our context of achieving enantiodivergency as it led to formal inversion at the isopropyl bearing C7 center. Reductive debromination in (+)-**27** with TBTH delivered (+)-**28** and the free hydroxyl group in it was protected as benzoate derivative to furnish dibenzoate (+)-**29**, as in most dihydroagarofuran natural products, as also in the context of our present target **10**, C6 hydroxyl group is present as a benzoate ester, Scheme 5.

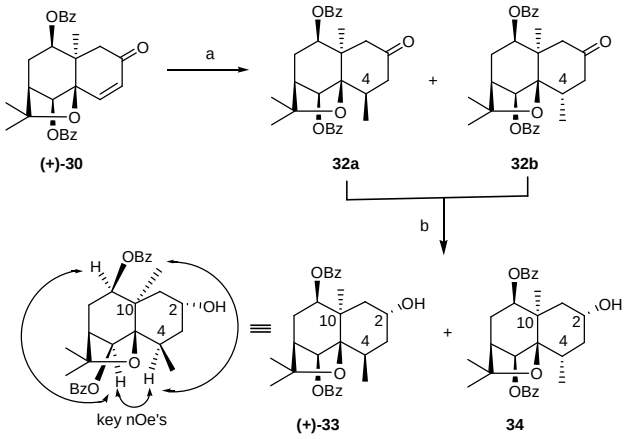


Scheme 5. *Reagents and conditions:* a) NBS, DCM, rt, 78%; b) TBTH, AIBN, C_6H_6, 80 °C, 92%; c) BzCl, Et_3N, $^nBu_4NI$, DMAP, DMF, 80 °C, 90%; d) PDC, ^tBuOOH, C_6H_6, celite, rt, 76%

To carry forward dibenzoate (+)-**29** towards our objective, functionalization of cyclohexene ring and particularly installation of C4 methyl group was mandated. This required amplification of functionality in dibenzoate (+)-**29** employing C2-C3 olefinic moiety. After some exploratory oxidative manoeuvres on dibenzoate (+)-**29**, we found that exposure to PDC-*ter*-butylhydroperoxide milieu[15] transformed it into a transposed α,β-unsaturated ketone (+)-**30**, Scheme 5. At this stage it was



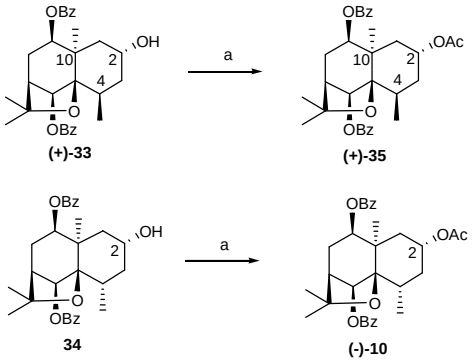
Scheme 6. *Reagents and conditions:* a) 5% NaOH, MeOH, 0 °C, 81%.



Scheme 7. *Reagents and conditions:* a) Me_2CuLi, MeLi, ether, –78 °C to – 35 °C, **32a**,**32b** in a ratio of (5:1), 72%; b) $NaBH_4$, MeOH, 0 °C, 95%.

considered necessary to unambiguously establish the stereostructure of (+)-**30** and thereby also secure all the preceding formulations. Controlled regioselective hydrolysis in dibenzoate (+)-**30** led to a crystalline monobenzoate (-)-**31** and its single crystal X-ray structure was determined (ORTEP diagram is displayed in Scheme 6). The next stage was the introduction of C4-methyl group to complete the acquisition of the dihydroagarofuran framework. This was sought to be achieved

through 1,4-conjugate addition to (+)-**30**. Addition of Gilman reagent (lithium dimethylcopper) to (+)-**30** was not diastereoselective and furnished a mixture of diastereomers **32a** (β-C4-methyl) and **32b** (α-C4-methyl) in a ratio of 5:1 (^{1}H NMR) in which the required isomer was a minor product, Scheme 7. Since chromatographic separation of diastereomers **32a** and **32b** proved unsuccessful, the carbonyl group in the mixture was stereoselectively (β-face selectivity) reduced with sodium borohydride to furnish readily separable hydroxyl-dibenzoated (+)-**33** and **34**, Scheme 7. Stereostructure of the major C4-diastereomer **33** was secured through 2D NMR (COSY and nOe) studies and key nOe's are displayed in Scheme 7. This in turn led to the identification of the minor required isomer as C4- α -methyl isomer **34**. Lastly, the free C2 hydroxyl group in (+)-**33** and **34** were acetylated to furnish (+)-**35** and the targeted 1-deacetoxy-*ent*-orbiculin A (-)-**10**, respectively, Scheme 8.



Scheme 8. *Reagents and conditions:* a) Ac_2O, Et_3N, DMAP, DCM, rt, 68%.

Conclusion

In summary, a flexible strategy for achieving enantiodivergency from *R*-(-)-carvone to access *ent*-eudesmane and *ent*-dihydroagarofuran frameworks has been outlined. This was accomplished by setting-up the requisite C10 quaternary methyl centre and reconstructing the C7 isopropyl stereochemistry to gain entry into the antipodal series. As a demonstrator of what we believe is a generally applicable approach, a short synthesis of 1-deacetoxy-*ent*-orbiculin A has been achieved.

Experimental section

General Information: Melting points reported are uncorrected. Infrared spectra were recorded on JASCO FT-IR 410 spectrometer. The samples were recorded either as thin films or between NaCl plates. Unless otherwise mentioned, NMR spectra were recorded on JEOL JNM-LA 300 or Brucker 400 instruments in $CDCl_3$ solutions. Chemical shifts are reported in parts per million (δ) downfield from Me_4Si as the internal standard (for ^{1}H NMR) and the central line of $CDCl_3$ (for ^{13}C NMR). The standard abbreviations s, d, t, q and m refer to singlet, doublet, triplet, quartet and multiplet, respectively. Mass Spectra were recorded either on Shimadzu, GCMS-QP 5050A or on Q-TOF Micromass mass spectrometers.

The X-ray data were collected on a Bruker AXS SMART APEX CCD diffractometer with graphite monochromated MoKα radiation (λ = 0.7107Å). The data were reduced by SAINTPLUS; an empirical absorption correction was applied using SADABS and space group was determined by XPREP. The structure was solved by direct methods (SIR92). Refinement was done by full-matrix least squares procedures on F^2 using SHELXL-97. The non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were refined isotropically. Molecular and packing diagrams were generated using ORTEP32 in the WINGX program. The crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or deposit@ccdc.cam.ac.uk)

Interconversion of unrequired aldol products to the required ***(+)-11*** *- an equilibration reaction:* To a suspension of NaOMe (650 mg, 12.0 mmol) in dry MeOH (10 mL) was added hydroxyl-ketone **(+)-16** and/or **(+)-17** (1.25 g, 6.0 mmol) in MeOH (10 mL) at room temperature and the reaction was allowed to stir for 24 h. Before quenching the reaction mixture, it was thoroughly cooled and ice-cold water (1 mL) was added dropwise to the mixture. The reaction mixture was diluted and extracted with ethyl acetate (2 x 60 mL). The combined organic extract was subjected to usual workup and after purification furnished 300 mg of **(+)-16**, 300 mg of **(+)-17**, 300 mg of **(+)-11** and 300 mg of **(+)-18** (95%).

(1R,2R,5R)-2-allyl-5-isopropenyl-2-methyl-3-oxocyclohexyl benzoate **(+)-19:** To a dry DCM (5 mL) solution of the alcohol **(+)-11** (208 mg, 1.0 mmol) were added Et_3N (0.42 mL, 3 mmol), DMAP (12 mg, 0.1 mmol) and BzCl (0.17 mL, 1.5 mmol) at 0 ^{o}C. The reaction was stirred at room temperature for 10 h. The reaction was quenched by careful addition of ice-cold water and diluted with DCM (30 mL). The organic extract successively washed with water (10 mL), sodium bicarbonate solution (8 mL) and brine (8 mL). The crude material was purified through silica gel column chromatography (1% EtOAc-hexane) to furnish 285 mg of benzoate **(+)-19** (92%) as a colorless liquid. $[\alpha]_D^{24}$: (+)-3.1 (c 2.6, $CHCl_3$); IR (neat): ν_{max} 1714 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.1 Hz, 2H), 7.58 (t, *J* = 8.1 Hz, 1H), 7.43 (t, *J* = 8.1 Hz, 2H), 5.80-5.66 (m, 1H), 5.32 (t, *J* = 3.0 Hz, 1H), 5.04 (dd, *J* = 10.2, 2.1 Hz, 1H), 4.95 (dd, *J* = 16.8, 2.1 Hz, 1H), 4.81 (s, 1H), 4.75 (s, 1H), 2.78-2.63 (m, 2H), 2.53-2.47 (m, 2H), 2.44 (d, *J* = 7.5 Hz, 1H), 2.26-2.07 (m, 2H), 1.73 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.7, 165.1, 146.4, 133.3, 133.1, 129.7, 129.6 (2C), 128.5 (2C), 119.0, 110.5, 77.5, 50.6, 42.5, 39.9, 37.1, 30.2, 21.2, 20.6; HRMS (ES): *m/z* calcd for $C_{20}H_{24}O_3Na$ (M^+ +Na): 335.1623; found: 335.1619.

(1R,2R,4S,5S)-2-allyl-4-hydroxy-5-isopropenyl-2-methyl-3-oxocyclohexyl benzoate **(-)-12**: To a stirred solution of ketone **(+)-19** (250 mg, 0.80 mmol) in dry THF (4 ml) was added DBU (0.30 mL, 2.0 mmol) at room temperature and the reaction mixture was refluxed for 3-4 h. After that the reaction was brought back to room temperature and TMSCl (0.15 mL, 1.2 mmol) was added drop wise to the reaction mixture. Once the TMSCl addition was over, the reaction was again warmed to 60 ^{o}C for another 10 h. The reaction was quenched with a small piece of ice and extracted with ether (80 ml). The combined organic extract was washed water (4 ml), brine and dried. The crude material was filtered through a neutral alumina column (2% EtOAc-hexane/5% TEA) to afford the silyl enolether as a colorless liquid.

To a solution of silyl enol ether in hexane (5 mL) was added mCPBA (200 mg, 0.80 mmol) at 0 ^{o}C and stirred at the same temperature for 2 h. The unreacted reagent was quenched with saturated solution of Na_2SO_3 and extracted with hexane (50 mL). The combined extract was washed with water (3 mL), sodium bicarbonate solution (5 mL) and brine. The extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure without raising the temperature of the water bath above 30 ^{o}C to deliver the crude material **20**.

The crude material **20** was dissolved in THF (5 mL) and few drops of 50% HCl was added at 0 ^{o}C. The reaction was allowed to stir for 30 min and carefully quenched by the slow addition of solid $NaHCO_3$ and diluted with ethyl acetate (60 mL). The organic extract was washed with water (5 mL), brine and dried. The crude material was purified using silica gel column chromatography (5% EtOAc-hexane) to furnish 205 mg of alcohol **(-)-12** (78% for three steps) as a liquid. $[\alpha]_D$ ^{23}: (-)-7.1 (c 2.4, $CHCl_3$); IR (neat): ν_{max} 3470, 1716 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 5.79-5.65 (m, 1H), 5.31 (t, *J* = 3.0 Hz, 1H), 5.07 (dd, *J* = 9.9, 1.5 Hz, 1H), 4.98-4.96 (m, 1H), 4.93 (s, 1H), 4.88 (s, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 2.64 (dt, *J* = 12.0, 4.5 Hz, 1H), 2.48 (d, *J* = 7.2 Hz, 1H), 2.46 (d, *J* = 7.2 Hz, 1H), 2.27 (dt, *J* = 13.2, 2.4 Hz, 1H), 2.11-2.08 (m, 1H), 1.82 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.0, 165.0, 143.6, 133.4, 132.3, 130.1, 129.6 (2C), 128.6 (2C), 119.6, 113.4, 77.3, 73.1, 50.3, 49.8, 37.2, 29.7, 21.3, 19.2; HRMS (ES): m/z calcd for $C_{20}H_{24}O_4Na$ (M^+ +Na): 351.1572; found: 351.1559.

(1R,2R,3R,4S,5S)-2,3-diallyl-3,4-dihydroxy-5-isopropenyl-2-methylcyclohexyl benzoate **(-)-21**: To a stirred ice-cooled solution of ketone **(-)-12** (195 mg, 0.60 mmol) in THF:H_2O mixture (4:1, 2 mL) were added indium metal (145 mg, 1.26 mmol) and allyl bromide (0.18 mL, 2.1 mmol). The stirring was continued at room temperature for 12 h. The solvent was removed and diluted with ether (40 mL). The ether extract was washed with dil.HCl (5 mL), water (5 mL) and brine. The crude material was loaded on a silica gel column (5% EtOAc-hexane) to afford 202 mg of **(-)-21** (92%) as a viscous liquid. $[\alpha]_D$ ^{23}: (-)-28.0 (c 3.0, $CHCl_3$); IR (neat): ν_{max} 3547, 1713, 1637 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.1 Hz, 2H), 7.59 (t, *J* = 8.1 Hz, 1H), 7.47 (t, *J* = 8.1 Hz, 2H), 6.24-6.10 (m, 1H), 5.78-5.64 (m, 1H), 5.19-4.76 (m, 7H), 3.81 (d, *J* = 10.8 Hz, 1H), 2.97 (br s, -OH), 2.87 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.68-2.52 (m, 3H), 2.28 (dd, *J* = 13.8, 7.2 Hz, 1H), 1.93-1.85 (m, 2H), 1.74 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 145.1, 136.1, 133.2 (2C), 130.1, 129.5 (2C), 128.6 (2C), 119.0, 117.2, 113.8, 77.4, 76.4, 72.9, 44.6, 43.3, 40.4, 36.9, 29.5, 20.4, 19.1; HRMS (ES): *m/z* calcd for $C_{23}H_{30}O_4Na$ (M^+ +Na): 393.2042; found: 393.2032.

(1R,3S,4S,4aR,8aR)-4,4a-dihydroxy-3-isopropenyl-8a-methyl-1,2,3,4,4a,5,8,8a-octahydro-1-naphthalenyl benzoate **(+)-22**: A solution of diene **(-)-21** (190 mg, 0.51 mmol) in dry degassed C_6H_6 (5 mL) was exposed to Grubbs' first generation catalyst (4 mg, 0.005 mmol) at rt. After 10 min, the reaction mixture was refluxed for 3 h. Benzene was removed under reduced pressure and the reaction mixture was directly charged on a silica gel column (20% EtOAc-hexane) to afford 165 mg of **(+)-22** (94%). $[\alpha]_D$ ^{24}: (+)-35.0 (c 3.8, $CHCl_3$); IR (neat): ν_{max} 3557, 1714, 1649 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 5.69 (s, 2H), 5.08 (t, *J* = 2.7 Hz, 1H), 4.94 (s, 1H), 4.89 (s, 1H), 3.66 (d, *J* = 10.8 Hz, 1H), 2.91 (br s, -OH), 2.73-2.59 (m, 2H), 2.49-2.46 (m, 1H), 2.18-2.10 (m, 1H), 2.03 (dt, *J* = 12.9, 2.7 Hz, 1H), 1.91-1.88 (m, 1H), 1.78 (s, 3H), 1.63-1.61 (m, 1H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 145.1, 133.3, 129.9, 129.6 (2C), 128.6 (2C), 124.8, 123.4, 113.6, 77.0, 74.5, 72.0, 43.9, 39.8, 34.1, 31.7, 30.3, 21.2, 19.2; HRMS (ES): *m/z* calcd for $C_{21}H_{26}O_4Na$ (M^+ +Na): 365.1729; found: 365.1709.

(1R,3S,4aR,8aR)-4a-hydroxy-3-isopropenyl-8a-methyl-4-oxo-1,2,3,4,4a,5,8,8a-octahydro-1-naphthalenyl benzoate **(-)-23:** To a dry DCM (1 mL) solution of oxalyl chloride (0.08 mL, 0.90 mmol) at –78 ^{o}C was added slowly DMSO (0.13 mL, 1.8 mmol) and the reaction mixture was allowed to stir at the same temperature for 40 min. Compound **(+)-22** (155 mg, 0.45 mmol) dissolved in DCM (3 mL) was added to the reaction mixture at the same temperature. After 1 h, Et_3N (0.50 mL, 3.6 mmol) was added to the reaction and stirring was continued for another 30 min. The reaction was quenched by careful addition of ice-water and diluted with DCM (40 mL). The DCM extract was washed with water (5 mL), dil. HCl (5 mL) and brine. The crude material was purified through column chromatography (12% EtOAc-hexane) to furnish 132 mg of ketone **(-)-23** (86%) as a brownish liquid. $[\alpha]_D$ ^{25}: (-)-48.0 (c 1.0, $CHCl_3$); IR (neat): ν_{max} 3502, 1718 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.2 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 2H), 5.66 (s, 2H), 5.24 (t, *J* = 3.0 Hz, 1H), 5.01 (s, 1H), 4.77 (s, 1H), 4.15 (dd, *J* = 12.0, 6.9 Hz, 1H), 3.69 (br s, -OH), 2.70-2.67 (m, 1H), 2.59-2.56 (m, 1H), 2.38-2.30 (m, 2H), 2.08-2.05 (m, 1H), 1.80 (s, 3H), 1.78-1.71 (m, 1H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.4, 165.3, 141.9, 133.6, 129.6 (2C), 129.4, 128.8 (2C), 123.6, 123.3, 113.4, 78.6, 76.6, 46.5, 43.1, 32.3, 30.4, 30.0, 21.6, 20.6; HRMS (ES): *m/z* calcd for $C_{21}H_{24}O_4Na$ (M^+ +Na): 363.1572; found: 363.1552.

(1R,4aR,8aR)-4a-hydroxy-8a-methyl-3-(1-methylethylidene)-4-oxo-1,2,3,4,4a,5,8,8a-octahydro-1-naphthalenyl benzoate **(-)-24**: To a solution of ketone **(-)-23** (125 mg, 0.37 mmol) in dry THF (3 mL) was added DBU (0.17 mL, 1.10 mmol) at room temperature and allowed to reflux for 24 h. The reaction was extracted with ether (40 mL). The etheral extract was washed with 10% HCl (4 mL), water (4 mL) and brine. The crude residue was charged on a silica gel column (20% EtOAc-hexane) to deliver 120 mg of enone **(-)-24** (96%) as a colorless liquid. $[\alpha]_D$ ^{26}: (-)-130.3 (c 3.3, $CHCl_3$); IR (neat): ν_{max} 3558, 1722 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.2 Hz, 2H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 2H), 5.74-5.63 (m, 2H), 5.18 (t, *J* = 3.0 Hz, 1H), 3.77 (d, *J* = 1.8 Hz, -OH), 3.24-3.21 (m, 1H), 2.77-2.68 (m, 2H), 2.50-2.47 (m, 1H), 2.20-2.18 (m, 1H), 1.94 (s, 3H), 1.73 (s, 3H), 1.69-1.64 (m, 1H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.0, 165.3, 145.0, 133.6, 129.4 (3C), 128.8 (2C), 125.7, 123.5, 123.4, 78.0, 77.9, 41.4, 31.3, 30.6, 29.5, 22.7, 21.2, 20.5; HRMS (ES): m/z calcd for $C_{21}H_{24}O_4Na$ (M^+ +Na): 363.1572; found: 363.1563.

(1R,4S,4aR,8aR)-4,4a-dihydroxy-8a-methyl-3-(1-methylethylidene)-1,2,3,4,4a,5,8,8a-octahydro-1-naphthalenyl benzoate **(+)-25:** To a stirred solution of the ketone **(-)-24** (110 mg, 0.32 mmol) in MeOH (4 mL) was added $CeCl_3.7H_2O$ (360 mg, 0.96 mmol) at 0 ^{o}C and the reaction was stirred for 10 min. $NaBH_4$ (12 mg, 0.32 mmol) was added to the above reaction and the stirring was continued for another 1 h. The reaction was quenched with few drops of water and MeOH was removed under reduced pressure. The reaction mixture was extracted with ethyl acetate (30 mL) and washed with 5% HCl (5 mL), water (2 mL), brine and dried over anhydrous Na_2SO_4. The crude material was charged on a silica gel column (25% EtOAc-hexane) to obtain 100 mg of **(+)-25** (89%). $[\alpha]_D$ ^{23}: (+)-6.2 (c 0.8, $CHCl_3$); IR (neat): ν_{max} 3442, 1717 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 5.68 (s, 2H), 4.99 (t, *J* = 4.2 Hz, 1H), 4.38 (d, *J* = 10.2 Hz, 1H), 3.02 (dd, *J* = 15.0, 5.1 Hz, 1H), 2.84 (d, -OH), 2.67 (d, *J* = 16.8 Hz, 1H), 2.48-2.37 (m, 2H), 2.30 (d, *J* = 9.9 Hz, 1H), 2.20-2.19 (m, 1H), 2.02 (s, 3H), 1.62 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 133.3, 132.2, 129.9, 129.3 (2C), 128.6 (3C), 124.9, 123.2, 78.8, 77.2, 75.9, 40.2, 33.9, 31.4, 30.2, 22.8, 22.0, 20.9; HRMS (ES): m/z calcd for $C_{21}H_{26}O_4Na$ (M^+ +Na): 365.1729; found: 365.1721.

(1R,6R,7R,9R,12R)-9-bromo-12-hydroxy-6,10,10-trimethyl-11-oxatricyclo [7.2.1.0^{1,6}]dodec-3-en-7-yl benzoate **(+)-27**: To a DCM solution of the alcohol **(+)-25** (90 mg, 0.26 mmol) was

added NBS (69 mg, 0.39 mmol) at room temperature and the stirring was continued for 45 min. The reaction was diluted with DCM (25 mL) and the organic extract was washed with water (2 mL), saturated sodium thio sulphate solution (5 mL) and brine. The concentrated residue was purified (12% EtOAc-hexane) to obtain 86 mg of **(+)-27** (78%). m.p: 114-116 ^{o}C; $[\alpha]_D$ ^{24}: (+)-29.5 (c 3.8, $CHCl_3$); IR: ν_{max} 3424, 1715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 5.65 (s, 2H), 5.15 (d, *J* = 7.2 Hz, 1H), 4.10 (d, *J* = 1.8 Hz, 1H), 2.97-2.77 (m, 3H), 2.49-2.43 (m, 2H), 2.32 (d, *J* = 1.8 Hz, 1H), 1.69 (s, 3H), 1.58 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 133.2, 129.8, 129.7, 128.5 (3C), 124.7, 122.4, 84.8, 84.2, 80.1, 74.9, 72.7, 45.2, 45.0, 30.9, 30.8, 30.1, 25.3, 23.9; HRMS (ES): m/z calcd for $C_{21}H_{25}O_4BrNa$ (M^+ +Na): 443.0834; found: 443.0859.

(1R,6R,7R,9S,12S)-12-hydroxy-6,10,10-trimethyl-11-oxatricyclo[7.2.1.0^{1,6}] dodec-3-en-7-yl benzoate **(+)-28**: To a stirred solution of **(+)-27** (80 mg, 0.19 mmol) in dry C_6H_6 (3 mL) were added TBTH (0.08 mL, 0.29 mmol), along with catalytic amount of AIBN at the room temperature and the reaction mixture was refluxed for 1.5 h. Aqueous ammonia solution was added to the reaction mixture at room temperature and stirred for 20-30 min and then diluted with ethyl acetate (25 mL). The extract was washed with water (2 mL) and brine. The crude material was purified through a silica column (20% EtOAc-hexane) to furnish 60 mg of **(+)-28** (92%). $[\alpha]_D$ ^{22}: (+)-30.4 (c 2.2, $CHCl_3$); IR (neat): ν_{max} 3402, 1713 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 5.66 (s, 2H), 5.12 (d, *J* = 8.4 Hz, 1H), 4.17 (s, 1H), 2.92-2.89 (m, 1H), 2.45-2.37 (m, 3H), 2.20-2.15 (m, 1H), 1.57 (s, 3H), 1.56 (s, 3H), 1.39-1.25 (m, 1H), 1.16 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 133.0, 130.2, 129.7 (2C), 128.5 (2C), 125.6, 122.7, 85.7, 82.6, 79.3, 73.2, 49.4, 45.3, 33.9, 31.2, 30.7, 30.6, 26.5, 25.9; HRMS (ES): m/z calcd for $C_{21}H_{26}O_4Na$ (M^+ +Na): 365.1729; found: 365.1730.

(1R,6R,7R,9S,12S)-12-(benzoyloxy)-6,10,10-trimethyl-11-oxatricyclo[7.2.1.0^{1,6}] dodec-3-en-7-yl benzoate **(+)-29**: To a dry DMF (1 mL) solution of **(+)-28** (50 mg, 0.15 mmol) were added Et_3N (0.10 mL, 0.75 mmol), BzCl (0.05 mL, 0.45 mmol) along with catalytic amount of ^{n}Bu$_4$NI and DMAP at room temperature for 30 min. The reaction was heated at 80 ^{o}C for 12 h. The reaction was quenched with water and diluted with DCM (15 mL). The organic extract was washed successively with water (2 mL), sodium bicarbonate solution (5 mL) and brine. Purification through column chromatography (2% EtOAc-hexane) delivered 59 mg of **(+)-29** (90%). $[\alpha]_D$ ^{23}: (+)-8.0 (c 1.0, $CHCl_3$); IR (neat): ν_{max} 1716 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.8 Hz, 4H), 7.64-7.55 (m, 2H), 7.53-7.44 (m, 4H), 5.68-5.59 (m, 2H), 5.47 (s, 1H), 5.24 (d, *J* = 8.4 Hz, 1H), 2.96-2.93 (m, 1H), 2.67-2.65 (m, 1H), 2.40-2.36 (m, 3H), 2.29-2.26 (m, 1H), 1.64 (s, 3H), 1.58-1.57 (m, 1H), 1.56 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 166.0, 133.3, 133.1, 130.1, 129.9, 129.7 (2C), 129.6 (2C), 128.6 (2C), 128.5 (2C), 125.5, 122.4, 84.9, 82.7, 81.5, 73.0, 47.7 (2C), 45.9, 33.9, 31.0, 30.5, 26.3, 25.7; HRMS (ES): m/z calcd for $C_{28}H_{30}O_5Na$ (M^+ +Na): 469.1991; found: 469.1996.

(1R,6R,7R,9S,12S)-12-(benzoyloxy)-6,10,10-trimethyl-4-oxo-11-oxatricyclo [7.2.1.0^{1,6}]dodec-2-en-7-yl benzoate **(+)-30**: To a stirred solution of olefin **(+)-29** (55 mg, 0.12 mmol) in C_6H_6 (2 mL) were added PDC (135 mg, 0.36 mmol), ^{t}BuOOH (0.04 mL, 0.36 mmol) and celite at room temperature, then stirred for 12-14 h. The reaction mixture was filtered through a celite pad. The filtrate was concentrated and diluted with ethyl acetate (20 mL). The extract was washed with water (2 mL), brine and dried. The crude material was loaded on a silica gel column (18% EtOAc-hexane) to obtain 43 mg of **(+)-30** (76%). $[\alpha]_D$ ^{23}: (+)-24.2 (c 1.2, $CHCl_3$); IR (neat): ν_{max} 1717, 1685 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, *J* = 7.5 Hz, 2H), 8.08 (d, *J* = 7.5 Hz, 2H), 7.68-7.43 (m, 6H), 6.84 (d, *J* = 10.2 Hz, 1H), 6.09 (d, *J* = 10.2 Hz, 1H), 5.70 (s, 1H), 5.22 (d, *J* = 6.9 Hz, 1H), 3.40-3.37 (m, 1H), 2.66 (dd, *J* = 6.9, 3.6 Hz, 1H), 2.62-2.57 (m, 1H), 2.46-2.43 (m, 1H), 2.09-2.06 (m, 1H), 1.65 (s, 3H), 1.63 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.0, 165.8, 165.7, 140.8, 133.8, 133.4, 130.3, 129.8 (2C), 129.7 (2C), 129.6, 129.2, 128.8 (2C), 128.6 (2C), 84.1, 83.2, 80.0, 72.3, 48.9, 48.3, 44.4, 32.2, 30.9, 25.9, 25.6; HRMS (ES): m/z calcd for $C_{28}H_{28}O_6Na$ (M^+ +Na): 483.1784; found: 483.1807.

(1R,6R,7R,9S,12S)-12-hydroxy-6,10,10-trimethyl-4-oxo-11-oxatricyclo[7.2.1.0^{1,6}] dodec-2-en-7-yl benzoate **(-)-31**: To an ice-cooled solution of the enone **(+)-30** (8 mg, 0.02 mmol) in MeOH (1 mL) was added NaOH (2 mg, 0.05 mmol) and water (0.05 mL) which was stirred at the same temperature for 45 min. The solvent was removed under reduced pressure and diluted with ethyl acetate (10 mL). The extract was washed with water (2 mL) and brine. The residue was charged on a silica gel column (60% EtOAc-hexane) to obtain 5 mg of **(-)-31** (81%) as a crystalline solid. m.p: 200-202 ^{o}C; $[\alpha]_D$ ^{26}: (-)-11.7 (c 1.8, $CHCl_3$); IR: ν_{max} 3393, 1715, 1682 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.15 (d, *J* = 9.6 Hz, 1H), 6.12 (d, *J* = 9.6 Hz, 1H), 5.11 (d, *J* = 6.3 Hz, 1H), 4.49 (s, 1H), 3.35-3.33 (m, 1H), 2.41-2.26 (m, 3H), 1.99-1.97 (m, 1H), 1.62 (s, 3H), 1.55 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.0, 165.9, 142.5, 133.3, 129.8, 129.7, 129.6, 128.5 (3C), 84.2, 83.9, 72.6, 76.6, 50.8, 47.4, 44.5, 31.9, 30.7, 26.0, 25.7.

Crystallographic information of **(-)-31**: The compound was crystallized from hexane-DCM solvent system. M_f = $C_{21}H_{24}O_5$, M_W = 356.4, Crystal system: monoclinic, space group: P2(1), cell parameters: a = 8.4839 (15), b = 10.3067 (18), c = 10.5897 (18) Å, β = 94.361 (3), V = 923.29 (3) Å^3, Z = 2, ρ_{calcd} = 1.28 gcm^{-3}, F(000) = 380.0, μ = 0.091 mm^{-1}, T = 293 K; Total number of l.s. parameters = 239, R_1 = 0.032 for 2974 $F_o > 4\sigma(F_o)$ and 0.035 for all 6651 data. wR_2 = 0.082, GOF = 1.034, Restrained GOF = 1.034 for all data (CCDC 602352).

(1R,2S,6R,7R,9S,12S)-12-(benzoyloxy)-2,6,10,10-tetramethyl-4-oxo-11-oxatricyclo[7.2.1.0^{1,6}]dodec-7-yl benzoate and (1R,2R,6R,7R,9S,12S)-12-(benzoyloxy)-2,6,10,10-tetramethyl-4-oxo-11-oxatricyclo [7.2.1.0^{1,6}]dodec-7-yl benzoate **32a,b**: Conjugate addition on the enone **(+)-30** was performed under the typical condition as described below and any change in the reaction conditions failed to deliver the desired conversion. To a suspension of CuI (4 mg, 0.02 mmol) in dry ether (1 mL) at –20 ^{o}C was added the freshly prepared 1.5 M solution of the MeLi-LiI complex in ether (0.04 mL, 0.06 mmol), which initially formed a yellow solution and after the complete addition of MeLi (2 equiv.), the reaction turned to clear colorless solution. To the reaction mixture, MeLi (1 equiv.) was added.

To the above mentioned freshly prepared dimethyl lithium cuprate-MeLi complex was added enone **(+)-30** (40 mg, 0.09 mmol) in dry ether (2 mL) at –78 ^{o}C and the reaction was stirred at the same temperature for 1 h. The reaction temperature was slowly raised to –35 ^{o}C and then stirred for another 1.5 h. The reaction was quenched with saturated NH_4Cl solution and diluted with ether (15 mL). The ethereal extract was washed with saturated NH_4Cl solution (4 mL), water (2 mL) and brine, respectively. The crude material was charged on a silica gel column (8% EtOAc-hexane) to deliver 30 mg of **32a** and **32b** as

an inseparable mixture in a ratio of 5:1 (72%). IR (neat): ν_{max} 1718, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.08-8.01 (m, 4H), 7.65-7.56 (m, 2H), 7.52-7.44 (m, 4H), 5.80 (s, 1H), 5.11 (d, *J* = 8.1 Hz, 1H), 3.28 (d, *J* = 12.9 Hz, 1H), 2.67-2.58 (m, 1H), 2.53-2.42 (m, 1H), 2.37-2.20 (m, 4H), 1.81 (dd, *J* = 12.9, 2.1 Hz, 1H), 1.69 (s, 3H), 1.66 (s, 3H), 1.34 (s, 3H), 1.22 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.6, 166.4, 165.6, 133.5, 133.3, 129.8, 129.7 (4C), 129.6, 128.7 (2C), 128.6 (2C), 86.9, 83.7, 83.3, 73.7, 53.2, 48.4, 47.9, 46.7, 33.5, 33.4, 29.7, 25.9 (2C), 18.2; HRMS (ES): *m/z* calcd for $C_{29}H_{32}O_6Na$ (M^+ +Na): 499.2097; found: 499.2107.

Preparation of **(+)-33** and **34:** To a stirred solution of the ketones **32a,b** (22 mg, 0.05 mmol) in MeOH (1 mL) was added $NaBH_4$ (2 mg, 0.05 mmol) at 0 °C and reaction was allowed to stir at the same temperature for 1 h. The reaction was quenched and solvent was removed under reduced pressure. The reaction mixture was extracted with ethyl acetate (15 mL) and washed with water (2 mL), brine and dried. The crude material was charged on a silica gel column and careful elution with 12% EtOAc-hexane delivered 4 mg of **34**, further elution with 15% EtOAc-hexane yielded 17 mg of **(+)-33** (95%).

(1R,2R,4R,6R,7R,9S,12S)-12-(benzoyloxy)-4-hydroxy-2,6,10,10-tetramethyl-11-oxatricyclo[7.2.1.0^{1,6}]dodec-7-yl benzoate **34**: IR (neat): ν_{max} 3513, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, *J* = 7.2 Hz, 2H), 8.08 (d, *J* = 7.2 Hz, 2H), 7.63-7.56 (m, 2H), 7.52-7.44 (m, 4H), 5.65 (s, 1H), 5.04 (d, *J* = 7.5 Hz, 1H), 4.31 (s, 1H), 2.65-2.40 (m, 4H), 2.32-2.17 (m, 3H), 1.78-1.73 (m, 1H), 1.61 (s, 3H), 1.54 (s, 3H), 1.47 (s, 3H), 1.31 (d, *J* = 7.8 Hz, 3H).

(1R,2S,4R,6R,7R,9S,12S)-12-(benzoyloxy)-4-hydroxy-2,6,10,10-tetramethyl-11-oxatricyclo[7.2.1.0^{1,6}]dodec-7-yl benzoate **(+)-33**: $[\alpha]_D$ ^{23}: (+)-17.3 (c 2.2, $CHCl_3$); IR (neat): ν_{max} 3529, 1714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.12-8.04 (m, 4H), 7.63-7.51 (m, 2H), 7.49-7.26 (m, 4H), 5.91 (s, 1H), 5.09 (d, *J* = 7.5 Hz, 1H), 4.14 (t, *J* = 3.0 Hz, 1H), 2.63-2.60 (m, 1H), 2.49-2.39 (m, 1H), 2.36-2.27 (m, 1H), 2.22-2.20 (m, 2H), 1.84-1.74 (m, 1H), 1.62 (s, 3H), 1.60 (s, 6H), 1.32 (t, *J* = 2.4 Hz, 1H), 1.27 (t, *J* = 2.4 Hz, 1H), 1.14 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 166.0, 133.2, 133.0, 130.3, 130.1, 129.8 (2C), 129.7 (2C), 128.6 (2C), 128.5 (2C), 88.8, 83.2, 82.7, 74.3, 67.1, 49.0, 48.6, 40.6, 36.7, 32.5, 29.9, 29.3, 26.4, 25.9, 18.0; HRMS (ES): *m/z* calcd for $C_{29}H_{34}O_6Na$ (M^+ +Na): 501.2253; found: 501.2264.

(1R,2S,4R,6R,7R,9S,12S)-4-(acetyloxy)-12-(benzoyloxy)-2,6,10,10-tetramethyl-11-oxatricyclo[7.2.1.0^{1,6}]dodec-7-yl benzoate **(+)-35**: To a dry DCM solution of **(+)-33** (4 mg, 0.008 mmol) were added Et_3N (0.008 mL, 0.06 mmol), catalytic amount of DMAP and acetic anhydride (Ac_2O) (0.003 mL, 0.03 mmol) at 0 °C. The reaction was allowed to stir at room temperature for 3 h. The reaction was diluted with DCM (5 mL) and successively washed with water (1 mL), sodium bicarbonate solution (1 mL) and brine. The crude material was purified through silica gel column chromatography (2% EtOAc-hexane) to furnish 3 mg of **(+)-35** (68%) as a colorless liquid. $[\alpha]_D$ ^{26}: (+)-10.0 (c 0.5, $CHCl_3$); IR (neat): ν_{max} 1732, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.09-8.04 (m, 4H), 7.63-7.56 (m, 2H), 7.52-7.44 (m, 4H), 5.91 (s, 1H), 5.07 (s, 1H), 5.04 (s, 1H), 2.62-2.59 (m, 1H), 2.40-2.21 (m, 4H), 2.01 (s, 3H), 1.82-1.72 (m, 1H), 1.64 (s, 3H), 1.60 (s, 3H), 1.51 (s, 3H), 1.50-1.42 (m, 2H), 1.11 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 166.6, 165.9, 133.3, 133.1, 130.2, 130.0, 129.8 (2C), 129.7 (2C), 128.7 (2C), 128.5 (2C), 88.4, 83.0, 82.9, 73.9, 69.9, 48.5, 37.2, 33.6, 32.7, 29.9, 28.4, 27.1, 25.9, 22.3, 21.5, 17.8; HRMS (ES): m/z calcd for $C_{31}H_{36}O_7Na$ (M^+ +Na): 543.2359; found: 543.2384.

(1R,2R,4R,6R,7R,9S,12S)-4-(acetyloxy)-12-(benzoyloxy)-2,6,10,10-tetramethyl-11-oxatricyclo[7.2.1.0^{1,6}]dodec-7-yl benzoate **(-)-10**: Acetylation of the secondary hydroxyl group in **34** (4 mg, 0.008 mmol) was performed using the above mentioned condition. Purification of the crude material through a silica gel column (2% EtOAc-hexane) furnished 3 mg of **(-)-10** (68%) as a colorless liquid. $[\alpha]_D$ ^{26}: (-)-28.0 (c 0.5, $CHCl_3$); IR (neat): ν_{max} 1736, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.09-8.06 (m, 4H), 7.64-7.56 (m, 2H), 7.52-7.44 (m, 4H), 5.64 (s, 1H), 5.22 (s, 1H), 5.01 (d, *J* = 6.9 Hz, 1H), 2.64-2.48 (m, 3H), 2.43-2.41 (m, 1H), 2.35-2.23 (m, 2H), 2.00 (s, 3H), 1.82-1.80 (m, 1H), 1.53 (s, 3H), 1.51 (s, 3H), 1.47 (s, 3H), 1.26-1.23 (m, 1H), 1.22 (d, *J* = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 166.0, 165.8, 133.3, 133.1, 130.2, 130.1, 129.8 (2C), 129.6 (2C), 128.7 (2C), 128.5 (2C), 88.3, 82.4, 80.2, 75.3, 70.4, 49.2, 46.3, 34.1, 33.6, 31.8, 30.9, 26.8, 26.2, 22.3, 21.7, 18.8; HRMS (ES): *m/z* calcd for $C_{31}H_{36}O_7Na$ (M^+ +Na): 543.2359; found: 543.2361.

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References and notes

1. (a) Hannesian, S. *Total synthesis of natural products: The 'chiron' approach*, Pergamon Press, Inc. N. Y. 1983. (b) Hanessian, S.; Giroux, S.; Bradley, M. *Design and Strategy in Organic Synthesis. From the Chiron Approach to Catalysis*, Wiley- VCH, Weinheim, 2013.
2. For a recent relevant review, see: Finefield, J. M.; Sherman, D. H.; Krictman, M.; Williams, R. M. *Angew Chem. Intl. Ed. Engl.* **2012**, *51*, 4802-4836.
3. Selected examples of divergent enantioselective synthesis: (a) Elhalem, E.; Recio, R.; Werner, S.; Lieder, F.; Calderón-Monterio, J. M.; López-Lózaro, M.; Fernández, I.; Khiar, N. *Eur J. Med. Chem.* **2014**, *87*, 552-563. (b) Foschi, F.; Tagliabue, A.; Mihali, T.; Pilati, T.; Pecnikaj, I.; Penso, M. *Org. Lett.* **2013**, *15*, 3686-3689. (c) Nakata, K.; Tokumaru, T.; Iwamato, H.; Nishigaichi, Y.; Shiina, I. *Asian J. Org. Chem.* **2013**, *2*, 920-922. (d) Biswas, T.; Mukherjee, J. P.; Chattopadhyay, S. K. *Tetrahedron: Asymmetry* **2012**, *23*, 1416-1422. (e) Sanyal, I.; Barman, P. D.; Banerjee, A. K. *Synthesis* **2012**, *44*, 1102-1108. (f) Mehta, G.; Samineni, R.; Srihari, P. *Tetrahedron Lett.* **2012**, *53*, 829-832. (g) Dube, A. K.; Chattopadhyay, A. *Tetrahedron: Asymmetry* **2011**, *22*, 1516-1521. (h) Austin, A. K.; Elsworth, J. D.; Banwell, M. G.; Willis, A. C. *Org. Biomol. Chem.* **2010**, *8*, 751-754. (i) Ghosh, M.; Bose, S.; Maity, S. Ghosh, S. *Tetrahedron Lett.* **2009**, *50*, 7102-7104. (j) Khan, F. A.; Sudheer, Ch. *Org. Lett.* **2008**, *10*, 3029-3033. (k) Prasad, K. R.; Anbarasan, P. *J. Org. Chem.* **2007**, *72*, 3155-3157. (l) Popsavin, V.; Krstic, I.; Popsavin, M.; Sreco, B.; Benedekovic, G.; Kojic, V.; Bogdanovic, G. *Tetrahedron* **2006**, *62*, 11044-11053. (m) Demintz, J.; Lavecchia, L.; Bacher, E.; Keller, T. H.; Müller, T.; Schürch, F.; Weber, H.-P. *Molecules* **1998**, *3*, 107-119. (n) Javier Sardina, F.; Howard, M. H.; Morningstar, M.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5025-5033.
4. (a) Mehta, G.; Kapoor, S. K. *Tetrahedron Lett.* **1972**, *13*, 715-716. (b) Mehta, G.; Kapoor, S. K. *J. Org. Chem.* **1974**, *39*, 2618-2624. (c) Mehta, G.; Singh, B. P. *Tetrahedron Lett.* **1975**, *16*, 4495-4498. (d) Mehta, G.; Krishnamurthy, N. *Tetrahedron Lett.* **1987**, *28*, 5945-5948. (e) Mehta, G.; Krishnamurthy, N. *Syn. Commun.* **1988**, *18*, 1267-1274. (f) Mehta, G.; Krishnamurthy, N.; Karra, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 5765-5775. (g) Mehta, G.; Karra, S. R. *J. Chem. Soc. Chem. Commun.* **1991**, 1367-1368. (h) Mehta, G.; Karra, S. R.; Krishnamurthy, N. *Tetrahedron Lett.* **1994**, *35*, 2761-

2762. (i) Mehta, G.; Acharyulu, P. V. R. *J. Chem. Soc. Chem. Commun.* **1994**, 2759-2760. (j) Mehta, G.; Acharyulu, P. V. R.; Reddy, K. S.; Umarye, J. D. *Synlett* **1997**, 1161-1163. (k) Mehta, G.; Acharyulu, P. V. R. *J. Ind. Chem. Soc.* **1998**, *75*, 601-612. (l) Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2004**, *45*, 1113-1116. (m) Mehta, G.; Karmakar, S.; Chattopadhyay, S. K. *Tetrahedron* **2004**, *60*, 5013. (n) Mehta, G.; Kumaran, R. S. *Tetrahedron Lett.* **2005**, *46*, 8831-8835.

5. (a) Mehta, G.; Kumaran, R. S., accompanying paper. (b) Mehta, G.; Kumaran, R. S. *Tetrahedron Lett.* **2003**, *44*, 7055-7059.

6. For an example of enantiodivergent synthesis employing (*R*)-(-)-carvone, see: Lieva de Faria, M.; Magalhães, R. D. A.; Silva, F. C.; Matias, L. G. D. O.; Ceschi, M. A.; Brocksom, U.; Brocksom, T. J. *Tetrahedron Asymmetry* **2000**, *11*, 4093-4103.
7. Fraga, B. M. *Nat. Prod. Rep.*, **2013**, *30*, 1226-1264 and earlier reports in this series by the same author.
8. Review on eudesmanes sesquiterpenoids: Wu, Q-X.; Shi, Y-P.; Jia, Z-J. *Nat. Prod. Rep*. **2006**, *23*, 699-734.
9. Reviews on agarofurans: (a) Spivey, A. C.; Weston, M.; Woodhead, S. *Chem. Soc. Rev.* **2002**, *31*, 43-59. (b) Gao, J. M.; Wu, W. J.; Zhang, J. W.; Konishi, Y. *Nat. Prod. Rep.* **2007**, *24*, 1153-1189 and references cited therein.
10. For the first report on agarofurans, see: a) Maheshwari, M. L.; Jain, T. C.; Bates, R. B.; Bhattacharyya, S. C. *Tetrahedron* **1963**, *19*, 1079-1090. b) Maheshwari, M. L.; Varma, K. R.; Bhattacharyya, S. C. *Tetrahedron* **1963**, *19*, 1519-1525.
11. (a) Torres-Romero, D.; Jiménez, I. A.; Rojas, R.; Gilman, R. H.; López, M.; Bazzocchi, I. L. *Bioorg. Med. Chem.* **2011**, *19*, 2182-2189. (b) Delgado-Méndez, P.; Herrera, N.; Chàvez, H.; Estévez-Braun, A.; Ravelo, A. G.; Cortes, F.; Castanys, S.; Camarro, F. *Bioorg. Med. Chem.* **2008**, *16*, 1425-1430. (c) Jiménez, I. A.; Bazzocchi, I. L.; Núnez, M. J.; Mukainaka, T.; Tokuda, H.; Nishino, H.; Konoshima, T.; Ravelo, A. G. *J. Nat. Prod.* **2003**, *66*, 1047-1050. (d) Takaishi, Y.; Ohshima, S.; Nakano, K.; Tomimatsu, T. *J. Nat. Prod.* **1993**, *56*, 815-824.
12. Lead references on the synthesis of agarofuran natural products: (a) Todoroki, H.; Iwatsu, M.; Urabe, D.; Inoue, M. *J. Org. Chem.* **2014**, *79*, 8835-8849. (b) Webber, M. J.; Warren, S. A.; Grainger, D. M.; Weston, M.; Clark, S.; Woodhead, S. J.; Powell, L.; Stokes, S.; Alanine, A.; Stonehouse, J. P.; Frampton, C. S.; White, A. J.; Spivey, A. C. *Org. Biomol. Chem.* **2013**, *11*, 2514-2533. (c) Ishiyama, T.; Urabe, D.; Fujisawa, H.; Inoue, M. *Org. Lett.* **2013**, *15*, 4488-4491. (d) Jiao, L.; Lin, M.; Zhou, L.-G.; Yu, Z.-X.; *Org. Lett.* **2010**, *12*, 2528-2531. (e) Siwicka, A.; Cuperly, D.; Tadeschi, L.; Vezouet, R. L.; White A. J. P.; Barrett, A. G. M. *Tetrahedron* **2007**, *63*, 5903-5917. (f) Heliwell, M.; Thomas, E. J.; Whitehouse, D. L. *Synthesis* **2005**, *19*, 3235-3238. (g) Lee, C. A.; Floreancig, P. E. *Tetrahedron Lett.* **2004**, *45*, 7193-7196. (h) Boyer, F.-D.; Descoins, C. L.; Descoins, C.; Prangé, T.; Ducrot, P.-H. *Tetrahedron Lett.* **2002**, *43*, 8277-8279. i) Boyer, F.-D.; Prangé, T.; Ducrot, P.-H. *Tetrahedron: Asymmetry* **2003**, *14*, 1153-1159. j) Boyer, F.-D.; Descoins, C. L.; Thanh, G. V.; Descoins, C.; Prangé, T.; Ducrot, P.-H. *Eur. J. Org. Chem.* **2003**, 1172-1183. k) Boyer, F.-D.; Descoins, C.; Ducrot, P.-H. *Eur. J. Org. Chem.* **2003**, 1184-1190. (l) Xia, W. J.; Li, D. R.; Shi, L.; Tu, Y. Q. *Tetrahedron Lett.* **2002**, *43*, 627-630. (m) Li, W. D. Z.; Zhou, Z.; Gao, X.; Li, Y. *Tetrahedron Lett.* **2001**, *42*, 4469-4471. (n) Spivey, A. C.; Woodhead, S.; Weston, M.; Andrews, B. *Angew. Chem. Int. Ed.* **2001**, *40*, 769-771 and earlier references cited therein.
13. Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, *15*, 4319-4322.
14. Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226-2227.
15. Bhaskaran, S.; Islam, I.; Chandrasekaran, S. *J. Org. Chem.* **1990**, *55*, 891-894.