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Asymmetric synthesis of dihydroartemisinic acid through intramolecular Stetter reaction

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ABSTRACT

A short and concise formal synthesis of enantiopure dihydroartemisinic acid from (*R*)-citronellal is described in this article. Intramolecular version of asymmetric Stetter reaction using Rovis aminoindane based NHC catalyst was explored to access the core substituted cyclohexanone framework which on functional group manipulation and late stage ring closing metathesis (RCM) reaction afforded an advanced intermediate for dihydroartemisinic acid.

1. Introduction

Artemisinin (**1**), also called qinghaosu is the most promising and significant anti-malarial agent discovered in the last 50 years.[1] Artemisinin, a sesquiterpene lactone (made up of three isoprene units bound to cyclic organic esters) was distilled from the dried leaves or flower clusters of *Artemisia annua*. The antipyretic properties[2] of that specific plant were first documented in the fourth century by Chinese physicians, who named the plant qinghao and recommended it as a natural remedy in the form of qinghao tea. The active ingredient from this plant was isolated in 1970 by Tu Youyou who was awarded the prestigious Nobel Prize in Medicine (2015) for her excellent work on artemisinin (**1**) and dihydroartemisinin. Malaria is widely known lethal infectious disease caused by four protozoan species of the genus Plasmodium (*Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium vivax*). In the majority of the cases death of the infected people (malaria kills 1–2 million people each year) are caused by *P. falciparum*. According to World Health Organization (WHO), the eradication of malaria from developing countries is a long-term goal that will depend on the success of sustainable research effort to deliver a more robust arsenal of tools than those available today. The growing resistance to existing antimalarial drugs could nullify efforts to eliminate this deadly disease. Unfortunately, there are still very few drugs available that are active against malaria (artemisinin, atovaquone, and chloroquine analogues) and vaccines against malaria are not yet available.[3] Artemisinin (**1**) is effective against all the malaria-causing protozoan organisms of the genus *Plasmodium*. The drug is particularly useful in the treatment of infections involving chloroquine-resistant[4] parasites and infections involving multidrug-resistant *P. falciparum*, which is the deadliest of the malaria protozoans. The WHO has recommended artemisinin combination therapies (ACT) to be the first-line therapy for *P. falciparum* malaria worldwide. Dihydroartemisinic acid (**2**) another natural product isolated from the same species and a metabolite of artemisinin was also known for several years and structurally much simpler. Dihydroartemisinic acid was regarded as one of the potential biogenetic precursor for artemisinin, as researchers shown that spontaneous auto-oxidation of compound **2** yields **1**.[5] In addition artemisinin (**1**) and, dihydroartemisinic acid (**2**) (Fig. 1), can also be useful as anticancer agents,[6] as it disrupts the growth of various types of cancer cells in laboratory research.

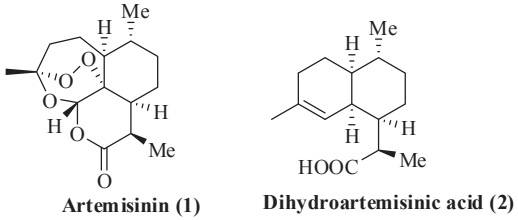

Fig. 1. Structure of artemisinin (**1**) and dihydroartemisinic acid (**2**).

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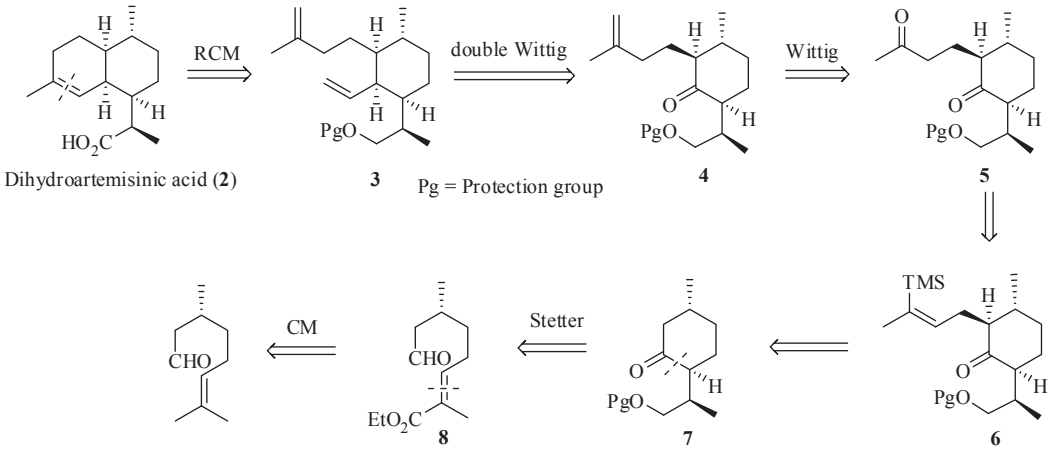
After its disclosure in 1979, artemisinin and dihydroartemisinic acid has been the subject of several elegant syntheses.[7] In pursuit of potentially novel and efficient synthetic strategies for artemisinin and analogues, we would like to report here a short and stereoselective asymmetric synthesis of dihydroartemisinic acid (**2**).

2. Results and discussion

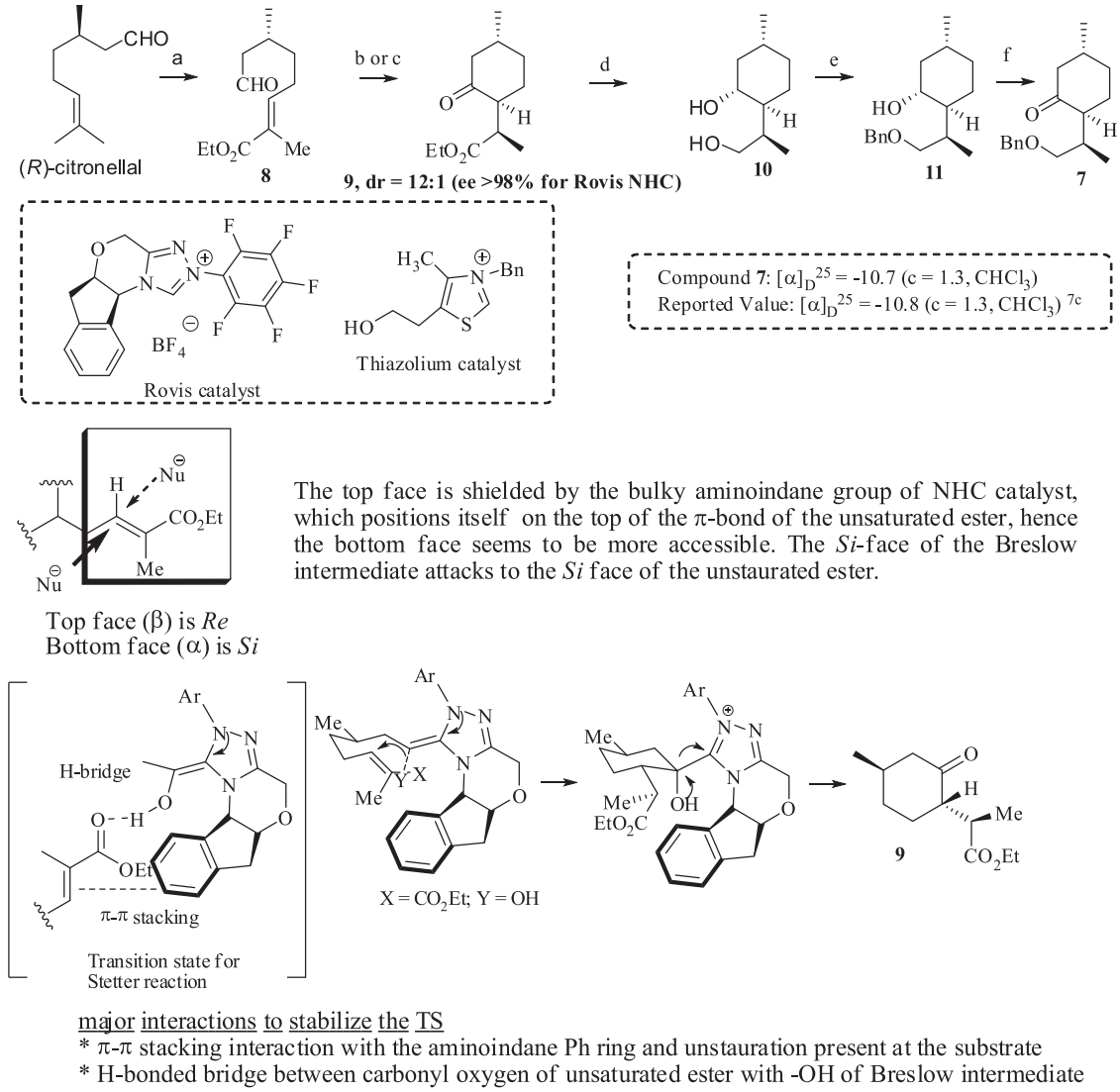
We envisioned that a late stage RCM (ring closing metathesis) reaction of a bis-olefinic precursor (**3**) might be an alternative option to construct the bicyclic ring of dihydroartemisinic acid, as it was never attempted before. The bis-olefinic precursor was planned to be accessed by double Wittig reaction of a properly functionalized cyclohexanone (**4**), which in turn can be synthesized from a 1,5-diketosystem (**5**). The diketo compound was synthesized from a vinyl silane derivative (**6**) which was prepared by alkylation of corresponding cyclohexanone (**7**). The required cyclohexanone was thought to be synthesized by intramolecular asymmetric Stetter reaction from an acyclic precursor (**8**). To the best of our knowledge intramolecular Stetter reaction and ring closing metathesis (RCM) reaction was never used for the synthesis of artemisinin and its analogues (Scheme 1).



Scheme 1. Retrosynthetic analysis of dihydroartemisinic acid.

Compound **8** was earlier synthesized in four steps by a reported procedure starting from (*R*)- citronellal.[8] We have prepared compound **8** from (*R*)-(+)-citronellal via a Ru-catalyzed *E*-selective olefin cross-metathesis (CM) with ethyl methacrylate in 70% yield using G-II catalyst in single step (Scheme 2).[9] With the required α,β-unsaturated ester (**8**) in our hand, the model version of intramolecular Stetter reaction[10] was attempted with the thiazolium catalyst in anhydrous toluene as a solvent as reported by Trost and co-workers for their synthesis of hirsutic acid.[11] To our delight, the reaction proceeded smoothly and furnished compound **9** with overall good diastereoselectivity (12:1) in favor of the conformationally more favorable diastereomer (desired one for our synthetic exercise). The minor diastereomer was also separated and well characterized by standard analytic method (see the ESI for more detail). Inspired by the initial result, next we switched our attention to the enantioselective version of the same reaction. Thus when compound **8** was exposed to Rovis's aminoindane based NHC catalyst (20 mol %) in presence of KHMDS as a base, the intramolecular Stetter reaction went smoothly and furnished compound **9** with excellent diastereoselection and enantioselection (ee≥98%; see the HPLC chromatogram in Supplementary data). The absolute configuration of compound **9** was assigned based on the known model for similar NHC catalyzed Stetter reaction.[10c] It has been speculated that attack from the *Si*-face of the Breslow intermediate (formed between Rovis NHC catalyst and *R*-citronellal) to the more accessible *Si*-face of the α,β-unsaturated carbonyl system yielded the desired stereoisomer (The *Re*-face of the α,β-unsaturated carbonyl system seems to be blocked by the bulky aminoindane moiety of the NHC catalyst, which seems to position itself just above the double bond of the α,β-unsaturated carbonyl system through probably a π−π stacking type of interaction). It was also hypothesized that the transition state for such intramolecular Stetter reaction which seem to be occur through 6-exo-trig pathway and is favored by Baldwin's rule of cyclization. The transition state is further stabilized by bridged H-bonding between carbonyl 'O' (from CO_2Et group) and the −OH moiety of the Breslow intermediate as predicted by Enders et al. and which was later supported by Houk and co-workers.[10e] Similarly a π−π stacking type of interaction also was predicted for intermolecular asymmetric benzoin condensation reaction with NHC. Eventually such π−π stacking type of interaction might also take place in our case, hence the relative positioning of the aminoindane framework with the olefinic unsaturation has a predictive role to block one face of the substrate. In our case we do believe that the *Re*-face (top face or the β-face of the electrophilic carbon where the umpolung attacks) of the α,β-unsaturated carbonyl system seems to be blocked by the bulky aminoindane moiety of the NHC catalyst and thus making the *Si*-face (bottom face or α-face) more accessible for attacking of the nucleophile generated from the Breslow intermediate. In addition the starting substrate **8**, derived from (*R*)-citronellal has its own conformational bias and once it reacts with the Rovis-NHC, the generated Breslow intermediate adopts a more flexible chair like conformational orientation (Scheme 2). The existing stereocenter in substrate **8**, seems to not play any predictive role in the final outcome of the reaction due to its remote location from the reaction center. The intramolecular asymmetric version of Stetter reaction was also attempted with ent-**8** (prepared from *S*-citronellal as described in Scheme 2) by using ent-Rovis aminoindane based NHC catalyst, to afford ent-**9** with excellent enantioselection (refer to ESI for HPLC chromatogram).

Reduction of both the ester and keto functionality of compound **9** was achieved by using $LiAlH_4$ in ether to afford the diol **10**, which on selective benzylation of the primary hydroxyl group forms compound **11**[7b] in 90% overall yield over two steps (Scheme 2). The crystal structure of diol **10** (CCDC-1469107) was presented in Fig. 2, which also confirms the relative stereochemistry of the two newly formed stereocenters in compound **9** after intramolecular Stetter reaction with Rovis's aminoindane based NHC catalyst. Dess-Martin



Scheme 2. Intramolecular asymmetric Stetter reaction; Reagents and conditions: (a) G-II catalyst, ethyl methacrylate, 70%; (b) Thiazolium Catalyst (20 mol %), KHMDS (20 mol %), Toluene, 24 h, 85%; (c) Rovis catalyst (20 mol %), KHMDS (20 mol %), Toluene, 24 h, 87%; (d) LAH, dry ether, 0 °C, 1 h, (e) NaH, dry DMF, BnBr, 0 °C, 3 h, 90% for two steps; (f) DMP, DCM, 2 h, 91%.

periodinane oxidation of compound **11** afforded the known ketone **7** in 91% yield (Scheme 2). Spectral data as well as optical rotation value was also in good agreement with the literature value reported by Zhou's group in their respective synthesis of Arteannuin and deoxyarteannuin,[7b,7c] which also established the absolute configuration of compound **9** obtained after asymmetric intramolecular Stetter reaction. We have also observed that presence of an '*E*' olefinic geometry in the parent α,β-unsaturated ester (**8**) was essential for overall good yield and stereoselection in the final product, which was also noticed by Rovis and co-workers for similar intramolecular Stetter reaction.[10]

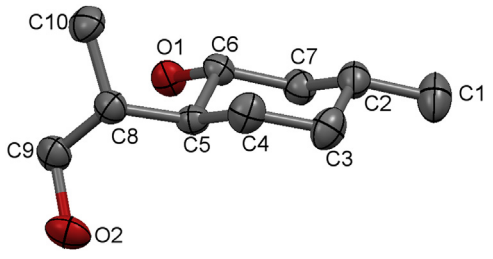
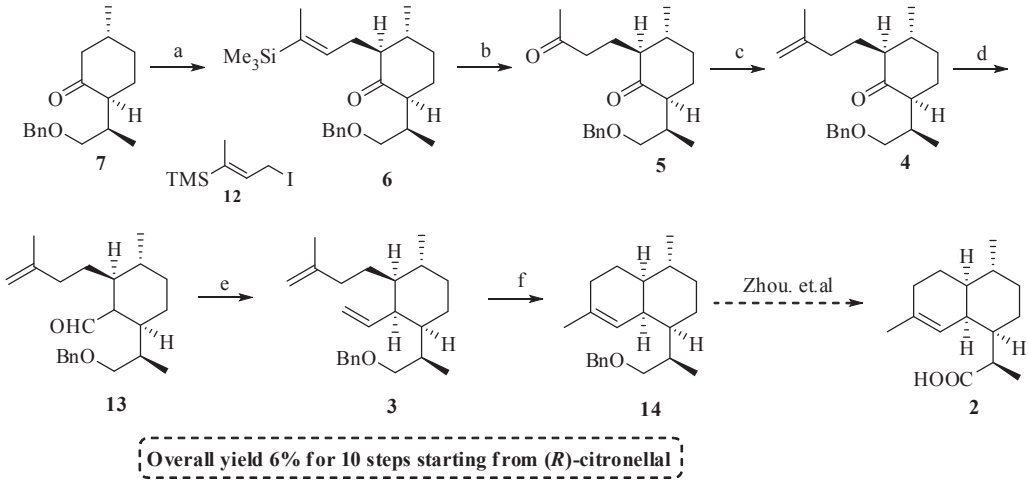


Fig. 2. ORTEP diagram of compound **10** (50% probability, H-atoms are omitted for clarity).

To install the required α-homoallyl appendage in compound **7**, we have relied upon the selective alkylation which was more challenging than may be apparent at first glance.[12] Initial trial with allyl bromide or allyl iodide resulted in the desired compound with poor yield, whereas 4-iodo-2-methylbut-1-ene did not yield any desired alkylated product. Finally kinetic enolate formation of compound **7** was achieved using LDA as base and Et_2Zn as additive, and treatment of the resulting enolate with (*E*)-(3-iodo-1-methyl-1-propenyl)-trimethylsilane (Stork-Jung iodide)[14] (**12**) provided the alkylated product **6** in 75% overall yield (Scheme 3) as a sole product. Similar yield was also obtained on using 3 equiv of HMPA instead of diethyl zinc keeping the other reaction conditions similar.[13] The vinyl silane **6** on treatment with *m*-CPBA afforded 1,5 diketone compound **5** in one pot in 60% yield over two steps. At first the epoxide was formed, which upon in situ Tamao-Fleming oxidation resulted the diketone **5** (Scheme 3). Diketone **5** on regioselective Wittig olefination with $Ph_3P^+CH_3I^-$, afforded the olefin **4** in 80% yield. The keto-olefin **4** was then subjected to Wittig reaction[15a] with methoxymethyl triphenylphosphonium chloride ($MeOCH_2Ph_3P^+Cl^-$) and KHMDS at room temperature afforded a mixture of enone ethers which was subjected to hydrolysis with trichloroacetic acid in DCM[15b] to afford the aldehyde **13** in 60% yield for two steps. Compound **13** was then immediately treated with

$Ph_3P^+CH_3I^-$, to furnish the bis-olefin **3**, which on RCM using Grubbs-II metathesis catalyst in dry dichloromethane furnished the required functionalized bicyclic core of dihydroartemisinic acid (**14**; Scheme 3), in 72% yield.[16] The synthesis of dihydroartemisinic acid (**2**) was reported from compound **14** by Zhou et al.[7b]



Scheme 3. Formal synthesis of dihydroartemisinic acid; Reagents and conditions: (a) LDA, Et_2Zn, compound **12**, 75%; (b) mCPBA, Dry DCM, 8 h, 60%; (c) $Ph_3P^+CH_3I^-$, LiHMDS, THF, 0 °C, 80%, 4 h; (d) i) methoxymethyl triphenylphosphonium chloride, KHMDS, room temperature, 24 h; ii) CCl_3CO_2H, Dry DCM, 60% (for two steps); (e) $Ph_3P^+CH_3I^-$, LiHMDS, THF, 0 °C, 72%; (f) G-II, DCM, reflux, 12 h, 72%.

3. Conclusions

In summary an intramolecular asymmetric version of Stetter reaction using Rovis aminoindane based NHC catalyst was employed to access the fully functionalized enantiopure cyclohexanone from an acyclic precursor. Finally substrate directed alkylation and RCM reaction was successfully exploited to access the required fully functionalized bicyclic core of dihydroartemisinic acid.

4. Experimental section

4.1. General

Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF and diethyl ether were distilled from sodiumbenzophenone ketyl. Dichloromethane (CH_2Cl_2), dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were distilled from CaH_2. Rovis's aminoindane based NHC catalyst (both the enantiomers) was purchased from commercial supplier and used as obtained. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, ethanolic anisaldehyde and phosphomolybdic acid/heat as developing agents. Silica gel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were acquired in $CDCl_3$ unless otherwise mentioned. Chemical shifts are reported in parts per million (ppm, δ), downfield from tetramethylsilane (TMS, δ=0.00 ppm), and are referenced to residual solvent [$CDCl_3$, δ=7.26 ppm (^{1}H), 77.16 ppm (^{13}C)]. Data are presented in the form: chemical shift (multiplicity, coupling constants, and integration). ^{1}H data are reported as though they were first order. The errors between the coupling constants for two coupled protons were less than 0.5 Hz, and the average number was reported. Coupling constants (J) are reported in hertz (Hz) and the resonance multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; dt, doublet of triplets; dd, doublet of doublets; ddd, doublet of doublet of doublets; m, multiplet; comp, overlapping multiplets of magnetically non-equivalent protons. Optical rotations were measured on a digital polarimeter. Mass spectrometric analysis was performed in the CRF, IIT-Kharagpur (TOF analyzer). X-ray crystallographic analysis was performed at IACS, Kolkata.

4.2. (*R*,*E*)-Ethyl 2,6-dimethyl-8-oxooct-2-enoate (8)

To a solution of (*R*)-(+)-citronellal (1.45 mL, 1.23 g, 8.0 mmol) in DCM (150 mL) was added ethyl methacrylate (1.7 mL, 1.6 g, 16.0 mmol) and G-II catalyst (340 mg, 0.4 mmol). The reaction mixture was refluxed for 24 h under argon atmosphere. The reaction mixture was then allowed to cool to room temperature and concentrated under vacuum. The residue was then purified via silica column chromatography (EtOAc:hexane=1:20) to afford compound **8** (1.18 g, 5.6 mmol, 70%) as a pale yellow oil.

R_f=0.4 (EtOAc:hexane=1:20); $[\alpha]_D^{28}$=+14.7 (c=0.5, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H: 9.80 (s, 1H), 6.76 (t, J=7.2 Hz, 1H), 4.22 (q, J=7.2 Hz, 2H), 2.49–2.29 (m, 5H), 1.61 (s, 3H), 1.50–1.40 (m, 2H), 1.33 (t, J=7.0 Hz, 3H), 1.03 (d, J=6.4 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$), δ_C: 202.2, 168.0, 141.3, 127.9, 60.3, 50.6, 35.4, 27.7, 25.9, 19.4, 14.0, 12.0; **HRMS (ESI)** m/z: calcd for $C_{12}H_{20}O_3Na$ $[M+Na]^+$, calcd: 235.1309; found: 235.1302.

$[\alpha]_D^{28}$=−14.5 (c=0.5, $CHCl_3$) for **ent-8**.

4.3. (*R*)-Ethyl 2-((1*S*,4*R*)-4-methyl-2-oxocyclohexyl)propanoate (9)

4.3.1. General procedure for the asymmetric intramolecular Stetter reaction of aliphatic substrates. A flame-dried round bottom flask was charged with Rovis aminoindane based NHC catalyst (0.02 mmol, 0.2 equiv) and toluene (1 mL) under argon atmosphere. To this solution was added KHMDS (0.5 M in toluene) (0.02 mmol, 0.2 equiv) via syringe and the solution was stirred at ambient temperature for 5 min. Substrate **8** (0.1 mmol, 1 equiv) was added in toluene (1 mL) via syringe and allowed to stirred for 24 h at room temperature. The residue was then purified via silica column chromatography (EtOAc:hexane=1:10) to afford compound **9** in 85% yield.

R_f=0.4 (EtOAc:hexane=1:10); **$[\alpha]_D^{28}$**=+27.1 (c=1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 4.10 (q, J=7.2 Hz, 2H), 2.73 (quint,

J=6.8 Hz, 1H), 2.58–2.52 (m, 1H), 2.36 (dd, *J*=2.4, 13.2 Hz, 1H), 2.04–1.96 (m, 2H), 1.89–1.85 (m, 2H), 1.55 (dq, *J*=3.2, 12.8 Hz, 1H), 1.39 (dq, *J*=3.2, 12.8 Hz, 1H), 1.24 (t, *J*=7.2 Hz, 3H), 1.18 (d, *J*=6.8 Hz, 3H), 1.01 (d, *J*=6.8 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ_C: 210.2, 175.4, 60.2, 52.4, 50.5, 39.1, 35.3, 33.8, 30.1, 22.3, 14.8, 14.2; **HRMS (ESI)** *m*/*z*: calcd for $C_{12}H_{21}O_3$ $[M+H]^+$, calcd: 213.1491; found: 213.1491.

4.4. (*S*)-Ethyl 2-((1*R*,4*S*)-4-methyl-2-oxocyclohexyl)propanoate (ent-9)

The compound was synthesized as described earlier by using the enantiomeric Rovis aminoindane based NHC catalyst to furnish **ent-9** in 83% yield.

$[\alpha]_D^{28}$=−26.8 (*c*=1.0, $CHCl_3$) for **ent-9**.

4.5. (2*S*,5*R*)-2-((*R*)-1-(Benzyloxy)propan-2-yl)-5-methylcyclohexanol (11)

LAH (0.5 g, 12 mmol) was taken in 250 mL dry ether followed by addition of the keto ester **9** (2.12 g, 10.0 mmol) at 0 °C. After 1 h saturated solution of Na_2SO_4 was added to quench the reaction mixture. Then the reaction solution was filtered by washing with hot Et_2O for several times and then it was concentrated in vacuo. The product was then purified by flash chromatography (1:1; EtOAc/hexane) to afford the diol compound **10** as a thick liquid, which was crystallized from EtOAc (1.85 g, 87.2% yield) to furnish the diol as long needles. R_f=0.2 (EtOAc:hexane=1:1).

To a suspension of NaH (520 mg, 60%, 13.0 mmol) in DMF (20 mL) was added drop wise a solution of compound **10** (1.6 g, 9.3 mmol) in DMF (16 mL) and further stirred for 45 min. Then $PhCH_2Br$ (1.2 mL, 10.22 mmol) in DMF (5 mL) was added drop wise and stirring was continued for 3 h. The temperature of the reaction solution was kept at 0 °C. The reaction mixture was then poured into ice water (40 mL) and extracted with ether. The ethereal solution was washed to neutrality, dried and concentrated. The residue was then purified by silica gel chromatography (EtOAc:hexane=1:5) to afford **11** as colorless oil (2.19 g, 8.37 mmol, 90%).

R_f=0.4 (EtOAc:hexane=1:5); $[\alpha]_D^{28}$=−13.0 (*c*=1.6, $CHCl_3$); **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H: 7.34 (s, 5H), 4.53 (d, *J*=2.6 Hz, 2H), 3.95 (br s, 1H), 3.52 (br s, 1H), 3.40–3.27 (m, 2H), 1.96–1.80 (m, 5H), 1.50–1.40 (m, 4H), 0.97 (d, *J*=7.2 Hz, 3H), 0.86 (d, *J*=6.2 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ_C: 137.6, 128.4, 127.7, 73.3, 72.7, 69.6, 46.3, 42.4, 36.4, 35.3, 26.0, 22.3, 21.0, 17.4; **HRMS (ESI)** *m*/*z*: calcd for $C_{17}H_{26}O_2Na$ $[M+Na]^+$, calcd: 285.1830; found: 285.1831.

4.6. (2*S*,5*R*)-2-((*R*)-1-(Benzyloxy)propan-2-yl)-5-methylcyclohexanone (7)

Alcohol **11** (930 mg, 3.54 mmol), was taken in dry DCM (10 mL) and cooled to 0 °C. Dess Martin periodinane (DMP) (1.8 g, 4.25 mmol) was then added and warmed to room temperature over 2 h. The reaction mixture was then quenched with $Na_2S_2O_3$ and saturated $NaHCO_3$ solution successively and stirred for further 20 min. The organic solution was then dried with $MgSO_4$, filtered, and the solvent was removed in vacuo. The residue was then purified by silica gel chromatography (EtOAc:hexane=1:10) to furnish compound **7** as colorless oil (828 mg, 3.18 mmol, 91%).

R_f=0.5 (EtOAc:hexane=1:10); $[\alpha]_D^{28}$=−10.7 (*c*=1.3, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H: 7.37–7.33 (m, 4H), 7.30–7.28 (m, 1H), 4.50 (dd, *J*=12.0, 18.0 Hz, 2H), 3.50 (dd, *J*=5.4, 9.0 Hz, 1H), 3.40 (dd, *J*=6.0, 9.0 Hz, 1H), 2.37–2.34 (m, 2H), 2.19–2.17 (m, 1H), 2.05–2.03 (m, 1H), 2.01 (dt, *J*=1.2, 12.6 Hz, 1H), 1.90–1.85 (m, 2H), 1.46–1.38 (m, 2H), 1.04 (d, *J*=2.4 Hz, 3H), 1.03 (d, *J*=6.0 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ_C: 211.9, 138.7, 128.2, 127.5, 73.0, 72.9, 52.2, 51.0, 35.5, 34.1, 32.6, 29.5, 22.3, 15.5; **HRMS (ESI)** *m*/*z*: calcd for $C_{17}H_{25}O_2$ $[M+H]^+$, calcd: 261.1855; found: 261.1851.

4.7. (2*S*,3*R*,6*S*)-6-((*R*)-1-(Benzyloxy)propan-2-yl)-3-methyl-2-((*E*)-3-(trimethylsilyl)but-2-en-1-yl)cyclohexanone (6)

To a THF solution (6 mL) of *n*-BuLi (2.1 mL, 3.38 mmol, 1.6 M) was added diisopropylamine (0.52 mL, 3.68 mmol) at −78 °C under an inert atmosphere. The reaction mixture was held at −78 °C for 15 min then it was allowed to warm to room temperature and stirred for 30 min before being recooled to −78 °C. Next, compound **7** (800 mg, 3.07 mmol) was added dropwise as a solution in THF (2.0 mL). The reaction was held at −78 °C for 40 min before being allowed to warm to 0 °C and stirred for 30 min after which the reaction was recooled to −78 °C. Hexamethylphosphoramide (0.53 mL, 3.07 mmol) was then added and the reaction mixture was stirred for 5 min, and then diethyl zinc (3.07 mL, 3.07 mmol) was added. A solution of **13** (1.19 g, 4.6 mmol) in 2 mL of THF was added drop wise and the reaction mixture was allowed to warm to rt and stirred overnight. Saturated aqueous NH_4Cl solution was added to quench the reaction and the mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified using silica gel column chromatography (EtOAc:hexane=1:20) to furnish **6** as a colorless oil (890 mg, 2.30 mmol, 75%).

R_f=0.6 (EtOAc:hexane=1:10); $[\alpha]_D^{28}$=−16.1 (*c*=0.6, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H: 7.35 (s, 3H), 7.28 (s, 2H), 5.58 (tq, *J*=1.8, 7.2 Hz, 1H), 4.52 (d, *J*=12.0 Hz, 1H), 4.45 (d, *J*=12.0 Hz, 1H),3.45 (dd, *J*=4.2, 9.0 Hz, 1H), 3.27 (t, *J*=9.0 Hz, 1H), 2.54–2.51 (m, 1H), 2.41 (dd, *J*=6.0, 15.6 Hz, 1H), 2.36–2.30 (m, 2H), 2.05 (dd, *J*=10.8, 15.0 Hz, 1H), 1.77–1.75 (m, 1H), 1.67–1.65 (m, 1H), 1.65 (s, 3H), 1.60 (s, 2H), 1.49–1.45 (m, 1H), 0.96 (d, *J*=6.6 Hz, 3H), 0.88 (d, *J*=6.6 Hz, 3H), 0.03 (s, 9H); **^{13}C NMR** (50 MHz, $CDCl_3$), δ_C: 213.4, 138.7, 133.3, 128.2, 127.5, 127.3, 73.2, 72.9, 52.1, 47.5, 35.2, 33.1, 32.5, 29.9, 29.1, 21.6, 14.6, 11.8, −2.13; **HRMS (ESI)** *m*/*z*: calcd for $C_{24}H_{39}O_2Si$ $[M+H]^+$, calcd: 387.2719; found: 387.2712.

4.8. (2*S*,3*R*,6*S*)-6-((*R*)-1-(Benzyloxy)propan-2-yl)-3-methyl-2-(3-oxobutyl)cyclohexanone (5)

To a DCM solution (5.0 mL) of **6** (450 mg, 1.17 mmol) was added mCPBA (0.320 mg, 1.40 mmol) at 0 °C under argon atmosphere. After 8 h the reaction was quenched with aqueous sodium bicarbonate and extracted with DCM. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified using silica gel column chromatography (EtOAc:hexane=1:10) to afford **5** as a colorless oil (230 mg, 0.7 mmol, 60%).

R_f=0.3 (EtOAc:hexane=1:10); $[\alpha]_D^{28}$=−5.7 (*c*=0.8, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ_H: 7.35–7.32 (m, 4H), 7.29–7.27 (m, 1H), 4.52, 4.48 (ABq, J_{AB}=12.0 Hz, 2H), 3.47 (dd, *J*=5.4, 9.0 Hz, 1H), 3.39 (dd, *J*=6.0, 9.0 Hz, 1H), 2.56–2.52 (m, 1H), 2.43–2.40 (m, 1H), 2.37–2.32 (m, 1H), 2.14 (s, 3H), 2.08–2.01 (m, 2H), 1.87–1.70 (m, 4H), 1.53–1.50 (m, 2H), 1.39–1.37 (m, 1H), 1.07 (d, *J*=6.0 Hz, 3H), 1.01 (d, *J*=6.0 Hz, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$), δ_C: 213.0, 209.0, 138.6, 128.2, 127.4, 127.3, 72.9, 72.8, 56.9, 53.3, 41.3, 40.4, 34.7, 31.4, 30.5, 29.7, 20.4, 20.1, 14.0; **HRMS (ESI)** *m*/*z*: calcd for $C_{21}H_{30}O_3Na$ $[M+Na]^+$, calcd: 353.2092; found: 353.2093.

4.9. (2*S*,3*R*,6*S*)-6-((*R*)-1-(Benzyloxy)propan-2-yl)-3-methyl-2-(3-methylbut-3-en-1-yl)cyclohexanone (4)

To a suspension of methyltriphenylphosphonium iodide (242 mg, 0.6 mmol) in dry THF (2 mL) was added LiHMDS (1.0 M solution in THF, 0.6 mL) at 0 °C. The yellow mixture was then stirred at 0 °C for 15 min. A solution of the diketone **5** (132 mg, 0.4 mmol)

in 2 mL of THF was added to the reaction mixture. The yellow suspension was stirred at room temperature for further 4 h. After that the reaction solution was quenched with addition of water, and the layers were separated and extracted with 25 mL of ether, washed with brine. It was then dried with $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude residue was purified by flash column chromatography (EtOAc:hexane=1:30) to afford compound **4** (104 mg, 0.32 mmol) in 80% yield.

R_f=0.3 (EtOAc:hexane=1:20); **$[\alpha]_D^{28}$**=+1.2 (*c*=0.8, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.32–7.21 (m, 5H), 4.58 (dd, *J*=7.8, 15.6 Hz, 2H), 4.44–4.31 (m, 2H), 3.41–3.27 (m, 1H), 3.24 (dd, *J*=2.1, 6.4 Hz, 1H), 2.46–2.25 (m, 2H), 2.12–1.67 (m, 5H), 1.63 (s, 3H), 1.50–1.42 (m, 5H), 0.96 (d, *J*=6.1 Hz, 3H), 0.92 (d, *J*=6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$), δ_C: 213.4, 146.2, 138.8, 128.4, 127.6, 127.5, 110.0, 73.5, 72.9, 57.4, 53.7, 40.9, 36.7, 35.7, 32.5, 31.2, 22.4, 20.7, 16.1, 13.4; **HRMS (ESI)** *m*/*z*: calcd for $C_{22}H_{32}O_2Na$ $[M+Na]^+$, calcd: 351.2299; found: 351.2303.

4.10. (2*S*,3*R*,6*S*)-6-((*R*)-1-(Benzyloxy)propan-2-yl)-3-methyl-2-(3-methylbut-3-en-1-yl)cyclohexanecarbaldehyde (13)

A solution of methoxymethyltriphenylphosponium chloride (296 mg, 0.86 mmol) in THF (1 mL) and HMPA (1 mL) was stirred at 0 °C for 20 min with a solution of 0.5 M potassium bis(-trimethylsilyl)amide (KHMDS) (0.86 mL, 0.86 mmol) in toluene. To this solution was slowly added a solution of ketone **4** (94 mg, 0.289 mmol) in THF (1 mL) and the resulting reaction mixture was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was cooled to 0 °C and saturated NH_4Cl solution was added and extracted with diethyl ether, the combined organic layers were washed with H_2O, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure.

To a stirred solution of crude methylvinylether in dry DCM (3 mL) at 40 °C under N_2 was added trichloroacetic acid (0.16 g, 1.0 mmol) and stirring was continued for 15 min. After cooling to room temperature, saturated aqueous $NaHCO_3$ (7 mL) was added to the reaction mixture and the organic layer separated. The aqueous layer was further extracted with DCM (20 mL) and the combined organic phases washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo to provide as pale yellow oil **13** which was used immediately without further purification.

4.11. (((2*R*)-2-((1*R*,3*S*,4*R*)-4-Methyl-3-(3-methylbut-3-en-1-yl)-2-vinylcyclohexyl)propoxy)methyl)benzene (3)

To a suspension of methyltriphenylphosphonium iodide (121 mg, 0.3 mmol) in dry THF (1 mL) was added LiHMDS (1.0 M solution in THF, 0.3 mL) at 0 °C. The yellow mixture was stirred at 0 °C for 15 min. A solution of compound **13** (68 mg, 0.2 mmol) in 1.0 mL of THF was added to the reaction mixture. The yellow suspension was stirred at room temperature for further 4 h. After that the reaction was quenched with addition of water, and the layers were separated and extracted with 25 mL of ether, washed with brine. It was then dried with $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude residue was purified by flash column chromatography (EtOAc:hexane=1:30) to afford compound **3** (48 mg, 0.15 mmol) in 72% yield.

R_f=0.6 (EtOAc:hexane=1:40); **$[\alpha]_D^{28}$**=−13.7 (*c*=0.8, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.34–7.26 (m, 5H), 5.91–5.85 (m, 1H), 5.10–4.95 (m, 2H), 4.58 (m, 2H), 4.39 (s, 2H), 3.24 (dd, *J*=4.4, 9.2 Hz, 1H), 3.12 (dd, *J*=4.4, 9.2 Hz, 1H), 2.34–2.29 (m, 1H), 2.16–1.96 (m, 4H), 1.7 (s, 3H), 1.62–1.57 (m, 3H), 1.42–1.38 (m, 5H), 1.04 (d, *J*=6.8 Hz, 3H), 1.01 (d, *J*=6.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$), δ_C: 145.8, 137.6, 137.5, 128.4, 127.6, 127.5, 117.6, 110.6, 74.4, 73.4, 46.9, 45.6, 40.1, 39.0, 38.1, 34.3, 30.8, 28.2, 22.5, 18.9, 15.5.

4.12. (1*R*,4*R*,4a*S*,8a*R*)-1-((*R*)-1-(Benzyloxy)propan-2-yl)-4,7-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene (14)

Compound **3** (34 mg, 0.1 mmol) was taken in anhydrous degassed DCM (30 mL). Grubbs second generation metathesis catalyst (G-II, 7 mg, 0.008 mmol) was added and the solution was refluxed for 12 h. The solution was then evaporated and the content of the flask was directly loaded on a silica gel column. Flash chromatography on silica (EtOAc:hexane=1:50) afforded the desired product **14** (22 mg, 0.072 mmol, 72%).

R_f=0.3 (EtOAc:hexane=1:40); **$[\alpha]_D^{28}$**=−15.7 (*c*=0.8, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 7.35–7.32 (m, 4H), 7.29–7.27 (m, 1H), 5.19 (s, 1H), 4.52, 4.48 (ABq, J_{AB}=12.0 Hz, 2H), 3.52 (dd, *J*=3.2, 8.8 Hz, 1H), 3.30 (dd, *J*=6.8, 8.8 Hz, 1H), 2.47 (br s, 1H), 1.93–1.90 (m, 2H), 1.80–1.73 (m, 2H), 1.64 (s, 3H), 1.53–1.50 (m, 4H), 1.27–1.21 (m, 4H), 1.00 (d, *J*=6.4 Hz, 3H), 0.80 (d, *J*=6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$), δ_C: 139.1, 135.1, 128.5, 127.7, 127.5, 121.0, 74.8, 73.2, 43.5, 42.3, 37.7, 35.9, 35.0, 27.9, 26.9, 26.6, 26.0, 24.0, 20.0, 16.0; **HRMS (ESI)** *m*/*z*: calcd for $C_{22}H_{32}ONa$ $[M+Na]^+$, calcd: 335.235; found: 335.2351.

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Supplementary data

Supplementary data (^{1}H, ^{13}C and DEPT spectra for all new compounds, HPLC chromatogram and X-ray crystallographic information for compound **10**) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.06.066.

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