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A novel approach for introduction of C-1 oxygenated group on decalin skeleton: first asymmetric total synthesis of 1α,6α-dihydroxy-eudesm-3-ene

Guojun Zheng, Jinchun Chen, Lijing Fang, Zhiyong Tang and Yulin Li*

State Key Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou 730000, People's Republic of China

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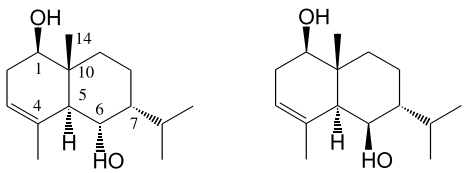
Abstract—This paper describes a novel approach for introduction of C-1 hydroxy on decalin ring system starting from (−)-carvone. Utilizing the substrate controlled Mukaiyama aldol reaction and alkaline cyclization as key steps, the C-1 oxygenated decalin eudesmane skeleton **2′** and its four isomers were synthesized efficiently. What's more, X-ray structural analysis confirmed sufficiently that something was wrong about the structure of natural product: 1β,6β-dihydroxy-7-*epi*-eudesm-3-ene as reported by the literature.

1. Introduction

Although considerable efforts have been devoted to the total synthesis of eudesmane and agarofuran sesquiterpenoids over the past decades, introduction of C-1 oxygenated group on decalin skeleton still represents a significant challenge for synthetic chemist.[1] To our knowledge, many C-1 oxygenated decalin of eudesmane and agarofuran sesquiterpenoids have been isolated in recent years,[2] but there was few report on total synthesis of them. In connection with our ongoing studies on the total synthesis of bioactive sesquiterpenoids,[3–5] we intended to explore a new strategy for the introduction of an oxygenated functional group at the C-1 position in the decalin ring system.

2. Result and discussion

Compounds **1** and **2** (Fig. 1) were first isolated in 1997 from the leaves of *Pluchea dioscoridis*, the structures were confirmed to be 1β,6α-dihydroxy-7-*epi*-eudesm-3-ene and it's C-6 epimer.[6] They both had an oxygenated group in C-1 position. Our first attempt was to synthesize the aimed compounds **1′** and **2′** (the enantiomner of **1** and **2**). Surprisingly, when we accomplished the aimed compounds **1′** and **2′**, we found that the spectral data of two compounds were inconsistent with the literature.



1 **2**

Figure 1.

The total synthesis of compounds **1′** and **2′** is detailed in Scheme 1. Compound **7** could be readily prepared from commercially available (−)-carvone by catalytic hydrogenation and refluxing with *tert*-butyldimethylsilyl chloride (TBSCl) in *N*,*N*-dimethylformamide. After refluxing for 2 days, the silyl enol ether **7** was obtained in 90% yield and the selectivity of thermodynamic and kinetic silyl enol ethers was up to 20:1 when the solvent was tripled the amount of the literature procedure.[7] However, for our substrate, the literature procedure gave less than 10% yield of **7** and we found that high temperature (about 140 °C) was essential for good yield. Mukaiyama aldol reaction[8] of aldehyde **6** and **7** successfully introduced C-1 oxygenated group to give **8** and **9** (2:1 in ratio) which were both key optical intermediates for the synthesis of natural occurring compounds. The stereochemistry of methyl group was determined as α by NOESY due to the steric bulk of the *tert*-butyldimethylsilyl group. After the hydroxy of **8** was protected with *p*-methoxybenzyl group and deprotection of benzoyl group, the resulting compound was oxidized with PCC to afford aldehyde keto **11**.

Keywords: Asymmetric synthesis; C-1 oxygenated; Eudesmane; X-ray structural analysis; Wrong structure.
* Corresponding author. Tel.: +86-931-8912595; fax: +86-931-8912283; e-mail address: liyl@lzu.edu.cn

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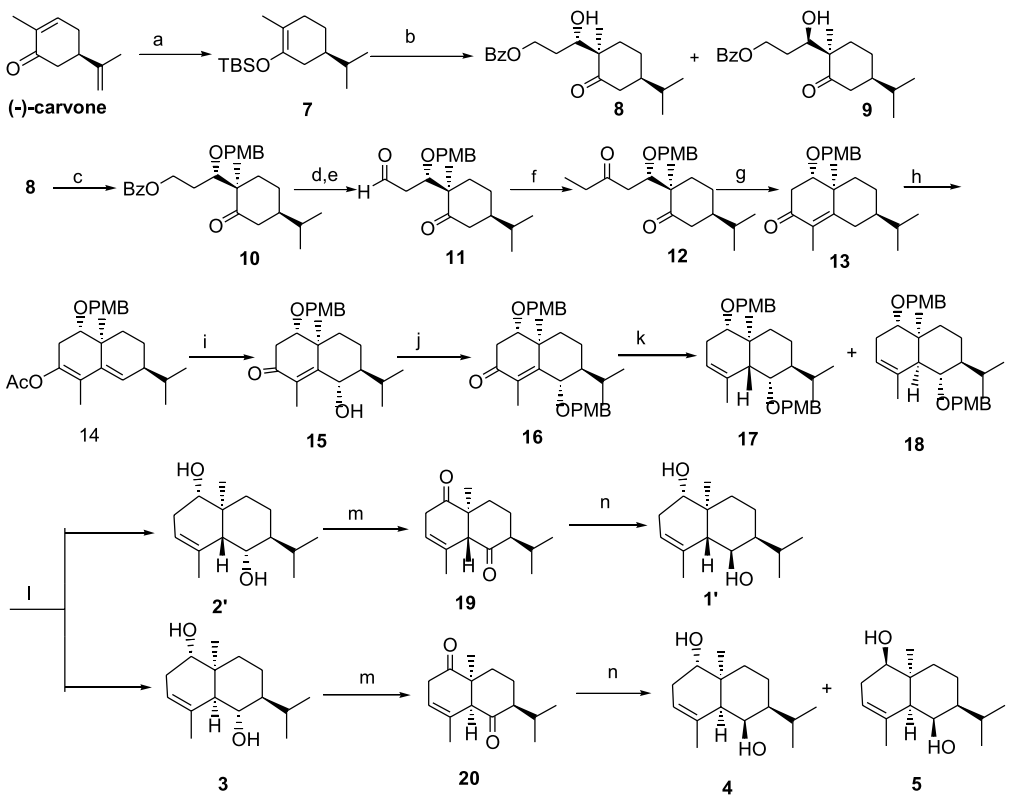

Scheme 1. Reagents and conditions: (a) pd/C/H_2, EtOH; then TBSCl/Et_3N, DMF, reflux 2 days, 90%; (b) **6** ($BzOCH_2CH_2CHO$)/$TiCl_4$, CH_2Cl_2, 60%; (c) PMBOC(=NH)CCl_3, *p*-TsOH, CH_2Cl_2, 85%; (d) 2% NaOH, MeOH, 96%; (e) PCC, Py, CH_2Cl_2, 80%; (f) −78 °C, EtMgBr, THF, 75%; PCC, Py, CH_2Cl_2, 90%; (g) 0.2% NaOMe/MeOH, 98%; MsCl, NEt_3, 89%; (h) AcCl, Ac_2O, DMAP, NaOAc,82%; (i) *m*-CPBA, CH_2Cl_2, 83%; (j) PMBOC(=NH)CCl_3, *p*-TsOH, CH_2Cl_2, 82%; (k) $TsNHNH_2$/HOAc, $NaBH_4$, 80%; (l) DDQ,CH_2Cl_2–H_2O, 87%; (m) Dess–Martin reagent, CH_2Cl_2, 92%; (n) $NaBH_4$/MeOH, 80–90%.

The diketo **12**, obtained by the highly selective reaction of EtMgBr and aldehyde keto **11** at −78 °C and subsequent PCC oxidation, was cyclized and dehydrated under condition of 0.2% CH_3ONa/CH_3OH and $MsCl/NEt_3$ respectively.[9] We have tried many other conditions, such as 10% KOH/MeOH[10] refluxing, NaOMe/MeOH[11] refluxing and TsOH/benzene refluxing, but none of them turned out to be ideal. That is, under such conditions, either the yield is rather low or the product is unwanted (obtaining compound **21**, Fig. 2). Refluxing enone **13** in AcCl and Ac_2O (2:1 in ratio) with the addition of sodium acetate (2 equiv.) to prevent eliminating of C-1 oxygenated group afforded **14**.[12] Oxidation of **14** with 3-chloroperoxybenzoic acid and subsequent deacetylation under acidity condition gave the alcohol **15**. The reaction went on in a highly stereoselective way to give 100% (*S*)-alcohol, which could be deduced from the coupling constants ($J_{6,7}$=2.4 Hz), and also proved by the X-ray structure analysis. The protection of alcohol **15** with *p*-methoxybenzyl group afforded **16**. The reaction of **16** with $TsNHNH_2$ in acetic acid for 10 h followed by addition of $NaBH_4$ generated compounds **17** and **18**,[13] which couldn't be separated by silica gel chromatography. Deprotection of *p*-methoxybenzyl group with DDQ in CH_2Cl_2–H_2O (18:1)[14] afforded **2′** and **3** (1:4 in ratio), which could be easily separated. Oxidation of diol **2′** with Dess–Martin reagent and subsequent reduction with $NaBH_4$ gave diol **1′**. Similarly, we got diol **4** and **5** (6:1 in ratio) from **3**.

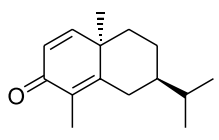

Figure 2.

Unfortunately, the spectral data of **1′** and **2′** were inconsistent with those of **1** and **2** in literature. Based on the inevitability of the reaction (from **16** to **17** and **18**), only one chiral carbon (C-5) was introduced and two compounds were generated. Obviously, they must be epimers of C-5, **17** was *trans*-fused-ring and **18** was *cis*-fused-ring. However, it was difficult to determine which one was the *trans*-fused-ring from the spectral data of ^1H NMR and ^{13}C NMR. For this reason, a single crystal X-ray structural analysis of the compound **3** (relatively more in amount) was performed to confirm the absolute configuration (Fig. 3). Thus, the configuration of **2′** was determined as the just right compound we anticipated. The configurations of compounds **1′**, **4** and **5** could be elucidated according to the stereoselectivity of the reaction and the spectral data of the compounds. However, none of the five isomers was consistent with the two compounds in literature.

What's wrong with the compounds **1** and **2**? In literature, the configuration of compound **1** was determined by the coupling constants ($J_{5,6}$=9.5 Hz, $J_{6,7}$=5 Hz), which were in agreement with an (axial–axial and axial–equatorial) pattern for these protons. So the configuration was assigned as 5α,6α,7β (H). The conclusion seemed plausible. Those configurations were also proved by the NOE 1D. It couldn't

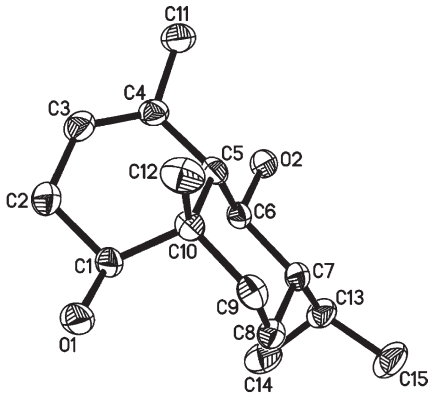

Figure 3. Molecular structure of **3** (CCDC 220322).

be denied that the result of NOE 1D was a very important factor to determine the configuration of the compound, but it could not be the sole evidence.

3. Conclusion

In summary, a novel approach for introduction of C-1 oxygenated group on decalin skeleton was exemplified in synthesis of 1α,6α-dihydroxy-eudesm-3-ene and its four isomers. The strategy is of great potential for the divergent synthesis of complex polyhydroxylated eudesmane and agarofuran sesquiterpenoids. The application of the established method to the further synthesis of a number of C-1 oxygenated natural products is under active investigation.

4. Experimental

4.1. General

IR spectra were recorded on a Nicolet NEXUS 670 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-400 or Varian Mercury Plus-300 spectrometer in $CDCl_3$ using TMS as an internal reference, and *J* values were given in Hertz. Mass spectra were determined on a HP5988A spectrometer by direct inlet at 70 eV. Optical rotation measurements were carried out on a Perkin–Elmer 141 polarimeter. Flash chromatography was performed on silica gel, with petroleum ether (PE) and diethyl ether (Et) mixtures as eluent.

4.1.1. *tert*-Butyl-(5β-isopropyl-2-methyl-cyclohex-1-enyloxy)-dimethyl-silane (7). A mixture of (−)-carvone (9 g) and 10% Pd/C (900 mg) in EtOH 20 mL was stirred under hydrogen for 30 h and the mixture was filtered through a celite gel, which without further purification, was taken in dry DMF (250 mL) and treated with NEt_3 (24 mL, 3 equiv.) and TBSCl (13.1 g, 1.5 equiv.). The resulting mixture was refluxed for 2 days before it was extracted with petroleum ether and dried over $MgSO_4$. After chromatographic purification, the silyl enol ether **7** (14.4 g) was obtained, yielding 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.87–1.00 (m, 15H, $C(CH_3)_3$ and $CH(CH_3)_2$), 1.02–1.19 (m, 2H), 1.32–1.50(m, 2H), 1.57 (s, 3H, CH_3), 1.65–1.75 (m, 2H), 1.76–2.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −3.7, −3.4, 16.4, 18.4, 19.9, 20.2, 25.9, 26.7, 30.7, 32.4, 34.3, 41.9, 111.4, 143.0.

4.1.2. 2β-(3-Benzyloxy-1α(β)-hydroxy-propyl)-5β-isopropyl-2α-methyl-cyclohexanone 8 (9). A mixture of aldehyde **6** (900 mg, 5 mmol) and silyl enol ether **7** (1.33 g, 5 mmol) in 5 mL CH_2Cl_2 was added dropwise to $TiCl_4$ (0.5 mL, 5 mmol) in 20 mL dry CH_2Cl_2 under argon at −78 °C. The mixture was allowed to warm up to −40 °C, stirred for 2 h and quenched with aqueous sodium carbonate at −40 °C then to room temperature. The mixture was extracted with ether and washed successively with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. After chromatographic purification, 332 mg of **9** (yellow oil) and 670 mg of pure **8** (white crystal, mp 84–86 °C) were obtained, yielding 60%. Compound **8** $[\alpha]_D^{25}$=+21° (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, 3H, *J*=4.1 Hz, Me), 0.83 (d, 3H, *J*=4.1 Hz, Me), 1.05 (s, 3H, Me), 1.34–1.49 (m, 2H), 1.62–1.74 (m, 4H), 2.14–2.19 (m, 1H), 2.24–2.28 (m, 1H), 2.39–2.44 (dd, 1H, *J*=4.4, 14 Hz), 2.55 (d, 1H, *J*=5.8 Hz), 4.15–4.19 (m, 1H, CHOH), 4.40–4.45 (m, 1H, OCH_2), 4.56–4.62 (m, 1H, OCH_2), 7.43 (t, 2H, *J*=7.9 Hz, Ar), 7.55–7.57 (t, 1H, *J*=7.6 Hz, Ar), 8.01–8.03 (d, 2H, *J*=8.4 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 19.5, 19.6, 23.5, 30.8, 31.2, 32.9, 42.9, 45.2, 53.1, 62.3, 68.9, 128.4, 129.5, 130.1, 133.1, 166.9, 216.0; MS *m/z* (%): 314 ($M-H_2O$, 0.6), 192 (5), 154 (50), 122 (14), 111 (10), 105 (100), 77 (41), 69 (17), 55 (20), 41 (21); IR (film, cm^{-1}) ν_{max}=3476, 2959, 2931, 1718, 1689, 1272, 1121, 1099, 1070, 974, 710. Compound **9** $[\alpha]_D^{25}$=+55° (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, 3H, *J*=5.1 Hz, Me), 0.84 (d, 3H, *J*=5.1 Hz, Me), 1.06 (s, 3H, Me), 1.46–1.49 (m, 2H), 1.58–1.70 (m, 4H), 1.86–1.89 (m, 2H), 2.40–2.43 (m, 2H), 4.20 (dd, 1H, *J*=8.1, 1 Hz, CHOH), 4.49–4.60 (m, 2H, $BzOCH_2$), 7.42–7.45 (m, 2H, Ar), 7.55–7.58 (m, 1H, Ar), 8.01–8.06 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 19.5, 23.7, 25.6, 30.2, 31.5, 34.9, 42.0, 45.2, 52.2, 62.3, 70.6, 128.3, 129.6, 133.0, 166.7, 216.2.

4.1.3. 2β-[3-Benzyloxy-1α-(4-methoxy-benzyloxy)-propyl]-5β-isopropyl-2α-methyl-cyclohexanone (10). *p*-TsOH (25 mg) was added to alcohol **8** (1.66 g, 5 mmol) in 5 mL dry CH_2Cl_2 under argon. The mixture was cooled to 0 °C, then 2, 2, 2-trichloro-acetimidic acid 4-methoxy-benzyl ester (1.7 g, 6 mmol) in 2 mL dry CH_2Cl_2 was added, the mixture was allowed to warm up to room temperature and stirred for 24 h. The crude was directly chromatographed on silica gel to afford a colorless oil **10** (1.92 g, 85%). $[\alpha]_D^{25}$=+16.5° (*c* 3.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (d, 3H, *J*=3.6 Hz, Me), 0.76 (d, 3H, *J*=3.9 Hz, Me), 0.96 (s, 3H, Me), 1.25–1.27 (m, 1H), 1.41–1.60 (m, 4H), 1.75–1.80 (m, 2H), 2.06–2.10 (m, 2H), 2.22–2.28 (m, 2H), 3.68 (s, 3H, OMe), 4.04 (d, 1H, *J*=9.6 Hz, $CHOCH_2$), 4.28–4.32 (m, 2H, OCH_2), 4.52 (s, 2H, OCH_2Ar), 6.75 (d, 2H, *J*=8.4 Hz, Ar), 7.17 (d, 2H, *J*=8.4 Hz, Ar), 7.35 (t, 2H, *J*=7.5 Hz, Ar), 7.49 (t, 1H, *J*=7.5 Hz, Ar), 7.94 (d, 2H, *J*=8.7 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 19.2, 19.4, 23.9, 30.7, 32.3, 34.6, 43.3, 45.6, 53.9, 55.1, 62.0, 74.7, 75.7, 113.7, 128.4, 130.0, 130.1, 133.0, 159.2, 166.2, 214.9; MS *m/z* (%): 452 (M^+, 0.8), 316 (10), 194 (17), 179 (7), 151 (9), 137 (10), 121 (100), 77 (17), 41 (7); IR (film, cm^{-1}) ν_{max}=2958, 2871, 1718, 1611, 1513, 1456, 1273, 1250, 1176, 1112, 1074, 1033, 823.

4.1.4. 3-(4β-Isopropyl-1α-methyl-2-oxo-cyclohexyl)-3α-(4-methoxy-benzyloxy)-propionaldehyde (11). To a solution of ketone **10** (1.8 g, 4 mmol) in 5 mL MeOH was added 2% NaOH/MeOH (20 mL) at 0 °C and stirred for 3 h. Then MeOH was evaporated under a reduced pressure, diluted with ether, washed with water, brine, and dried over $MgSO_4$. Evaporation of the solvent in vacuum gave the crude product, which without further purification, was taken in CH_2Cl_2 (20 mL) and treated with PCC (1.7 g, 8 mmol), pyridine (0.64 mL, 8 mmol) and SiO_2 (2.4 g). The resulting suspension mixture was stirred over night at room temperature and diluted with ether. The mixture was filtered through a silica gel. The solvent was removed and the residue was purified by chromatography to furnish yellow oil (1.06 g, 77%). $[\alpha]_D^{25}=+100°$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, 6H, *J*=6.3 Hz, Me), 0.93 (s, 3H, Me), 1.17–1.31 (m, 2H), 1.40–1.52 (m, 2H), 2.01–2.09 (m, 1H), 2.20–2.27 (m, 2H), 2.27–2.39 (m, 1H), 2.59–2.68 (m, 1H), 3.73 (s, 3H, OMe), 4.33 (d, 1H, *J*=11.1 Hz, OCH_2Ar), 4.40 (dd, 1H, *J*=3.6, 7.2 Hz, $CHOCH_2$), 4.49 (d, 1H, *J*=10.8 Hz, OCH_2Ar), 6.81 (d, 2H, *J*=14.7 Hz, Ar), 7.18 (d, 2H, *J*=14.7 Hz, Ar), 9.73 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 19.4, 19.6, 23.8, 32.3, 34.3, 43. 6, 45.5, 45.9, 53.5, 55.3, 72.5, 72.8, 113.8, 129.7, 130.0, 159.3, 200.7, 215.1; MS *m*/*z* (%): 346 (M^+, 0.4), 210 (2), 173 (14), 167 (11), 137 (24), 121 (100), 55 (13), 41 (23); IR (film, cm^{-1}) ν_{max}=2957, 2871, 1722, 1702, 1612, 1514, 1462, 1249, 1176, 1081, 1034, 823.

4.1.5. 5β-Isopropyl-2β-[1α-(4-methoxy-benzyloxy)-3-oxo-pentyl]-2α-methyl-cyclohexanone (12). To a solution of aldehyde **11** (1.2 g, 3.46 mmol) in dry THF (5 mL) under argon atmosphere was added dropwise EtMgBr (8 mL, 4 mmol) at −78 °C. The mixture was stirred at −78 °C for 30 min and quenched with aqueous ammonium chloride. The resulting mixture was extracted with ether and washed successively with sodium hydrogencarbonate and brine, and dried over $MgSO_4$. The solvent was removed in vacuum to give the crude product, which without further purification, was taken in CH_2Cl_2 (20 mL) and treated with PCC (1.48 g, 7 mmol), pyridine (0.5 mL, 7 mmol) and SiO_2 (2.22 g). The resulting suspension mixture was stirred for 2 days at room temperature and diluted with ether. The mixture was filtered through a silica gel. The solvent was removed and the residue was purified by chromatography to furnish yellow oil **12** (880 mg, 68%). $[\alpha]_D^{25}=+62°$ (*c* 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, 6H, *J*=1.8 Hz, Me), 0.92 (s, 3H, Me), 0.96 (t, 3H, *J*=7.2 Hz, Me), 1.14–1.21 (m, 2H), 1.43–1.50 (m, 4H), 2.09–2.13 (m, 1H), 2.18–2.34 (m, 2H), 2.30 (q, 2H, *J*=7.5Hz, CH_2), 2.55–2.63 (m, 1H), 3.73 (s, 3H, OMe), 4.33 (d, 1H, *J*=11.1 Hz, OCH_2Ar), 4.45 (m, 2H, OCH_2Ar and $CHOCH_2$), 6.81 (d, 2H, *J*=8.7 Hz, Ar), 7.18 (d, 2H, *J*=8.7 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.6, 17.1, 19.4, 19.5, 23.8, 32.5, 35.0, 36.9, 43.6, 44.0, 46.0, 53.7, 55.2, 72.8, 73.3, 113.7, 129.5, 131.9, 159.2, 210.0, 215.3; MS *m*/*z* (%): 374 (M^+, 0.3), 238 (10), 202 (12), 167 (36), 121 (100), 57 (13); IR (film, cm^{-1}) ν_{max}=2958, 2938, 2872, 1702, 1603, 1513, 1460, 1250, 1161, 1035, 830.

4.1.6. 1α-(4-Methoxy-benzyloxy)-10-*epi*-eudesm-4 (5)-en-3-one (13). To a solution of diketone **12** (500 mg, 1.34 mmol) in dry MeOH 10 mL was added NaOMe (20 mg) under argon at 0 °C. Then the mixture was allowed to warm up to room temperature and stirred for 2 h. The solution was evaporated to dryness in vacuum and the residue was diluted with ether, washed with 5% HCl, sodium hydrogencarbonate, brine, and dried over $MgSO_4$. Evaporation of the solvent in vacuum gave the crude product, which without further purification, was taken in CH_2Cl_2 (5 mL) and treated with NEt_3 (1.8 mL) and MsCl (1.2 mL). The resulting mixture was stirred for 8 h at room temperature and diluted with ether, washed with 5% HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. Purification by flash chromatography gave white crystal **13** (415 mg, 87%, mp 116–118 °C). $[\alpha]_D^{25}=+11°$ (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, 3H, *J*=6.4 Hz, Me), 0.85 (d, 3H, *J*=6.4 Hz, Me), 1.18 (s, 3H, Me), 1.26–1.29 (m, 1H), 1.37–1.38 (m, 1H), 1.41–1.46 (m, 2H), 1.60–1.64 (m, 1H), 1.70 (s, 3H, Me), 1.71–1.74 (m, 1H), 2.16–2.21 (m, 1H), 2.39–2.46 (m, 1H), 2.68–2.75 (m, 2H), 3.45 (dd, 1H, *J*=4.8, 12.8 Hz, $CHOCH_2$), 3.73 (s, 3H, OMe), 4.31 (d, 1H, *J*=11.6 Hz, OCH_2Ar), 4.45 (d, 1H, *J*=11.6 Hz, OCH_2Ar), 6.81 (d, 2H, *J*=11.2 Hz, Ar), 7.19 (d, 2H, *J*=11.2 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 18.2, 20.3, 21.6, 23.4, 28.6, 30.2, 32.5, 39.2, 41.7, 41.8, 55.2, 71.0, 79.8, 113.7, 129.1, 129.8, 130.5, 159.1, 162.8, 197.4; MS *m*/*z* (‰): 356 (M^+, 0.5), 235 (32), 220 (15), 192 (12), 163 (4), 135 (26), 121(1000), 110 (19), 91 (47), 77(57), 43 (55); IR (film, cm^{-1}) ν_{max}=2966, 2889, 1658, 1608, 1512, 1459, 1348, 1309, 1246, 1072, 822.

4.1.7. 1α-(4-Methoxy-benzyloxy)-10-*epi*-eudesm-3-aceyloxy-3 (4), 5 (6)-dien (14). To a solution of enone **13** (350 mg, 0.98 mmol) in Ac_2O (1 mL) was added NaOAc (500 mg), DMAP (10 mg) and AcCl (2 mL) and stirred at 0 °C for 2 min. The resulting mixture was heated to reflux and stirred for 20 min. The reaction was then cooled to 0 °C and diluted with ether before NEt_3 (10 mL) and water (2 mL) was added. The resulting mixture was stirred for a further 0.5 h prior to extraction with ether. The organic phase was washed with water, 5% HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. Evaporation of the solvent followed by flash column chromatography on silica gel afforded compound **14** (320 mg, 82%). $[\alpha]_D^{25}=+141°$ (*c* 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, 3H, *J*=5.1 Hz, Me), 0.92 (d, 3H, *J*=5.1 Hz, Me), 0.98 (s, 3H, Me), 1.29–1.36 (m, 1H), 1.54–1.63 (m, 2H), 1.65 (s, 3H, Me), 1.78–1.83 (m, 1H), 1.91–1.95 (m, 1H), 2.05–2.08 (m, 1H), 2.19 (s, 3H, Me), 2.38–2.42 (m, 1H), 2.52–2.58 (m, 1H), 3.35–3.38 (m, 1H, $CHOCH_2$), 3.80 (s, 3H, OMe), 4.38 (d, 1H, *J*=8.7 Hz, OCH_2Ar), 4.55 (d, 1H, *J*=8.7 Hz, OCH_2Ar), 5.70 (d, 1H, *J*=3.6 Hz, CH=), 6.86 (d, 2H, *J*=6.3 Hz, Ar), 7.25 (d, 2H, *J*=6.3 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 17.5, 20.3, 20.7, 20.8, 31.1, 31.4, 32.9, 37.9, 40.7, 55.3, 71.0, 80.8, 113.7, 113.8, 120.5, 126.7, 129.0, 131.1, 139.5, 141.0, 159.0, 169.0; MS *m*/*z* (‰): 398 (M^+, 2.6), 356 (11), 313 (46), 235 (20), 193 (29), 175 (39), 161 (11), 135 (73), 121 (1000), 107 (24), 91 (44), 77 (56), 43 (145); IR (film, cm^{-1}) ν_{max}=2954, 2870, 1752, 1513, 1366, 1246, 1212, 1173, 1096, 1035, 822.

4.1.8. 1α-(4-Methoxy-benzyloxy)-10-*epi*-eudesm-4 (5)-en-6α-hydroxy-3-one (15). To a solution of **14** (520 mg, 1.3 mmol) in CH_2Cl_2 (15 mL) was added *m*-CPBA (387 mg, 70%, 1.56 mmol) and stirred for 24 h at room temperature. Then saturated aqueous $Na_2S_2O_3$ (5 mL) was

added and stirred for 5 min before extraction. The combined organic layers were washed successively with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give an oil. Flash column chromatography on silica gel yielded alcohol **15** (400 mg, 83%). $[\alpha]_D^{25}=+53°$ (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, 3H, *J*=6.4 Hz, Me), 0.96 (d, 3H, *J*=6.4 Hz, Me), 1.24–1.38 (m, 2H), 1.39 (s, 3H, Me), 1.41–1.48 (m, 2H), 1.51–1.58 (m, 1H), 1.85 (s, 3H, Me), 1.98–2.04 (m, 1H), 2.56 (dd, 1H, *J*=12.8, 16.8 Hz), 2.82 (dd, 1H, *J*=4.8, 16.8 Hz), 3.50 (dd, 1H, *J*=4.8, 12.8 Hz, $CHOCH_2$), 3.81 (s, 3H, OMe), 4.39 (d, 1H, *J*=11.2 Hz, OCH_2Ar), 4.57 (d, 1H, *J*=11.2 Hz, OCH_2Ar), 4.96 (d, 1H, *J*=2.4 Hz, CHOH), 6.88 (d, 2H, *J*=8.8 Hz, Ar), 7.26 (d, 2H, *J*=8.8 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.7, 18.0, 20.3, 20.6, 21.7, 27.0, 31.4, 39.5, 40.7, 48.2, 55.3, 69.5, 71.0, 80.0, 113.7, 129.1, 130.4, 133.2, 159.2, 159.5, 198.5; MS *m/z* (‰): 372 (M^+, 0.4), 354 (0.2), 251 (3), 234 (26), 191 (37), 165 (34), 121 (1000), 107(20), 91 (33), 77 (43), 43 (84); IR (film, cm^{-1}) ν_{max}=3438, 2954, 2872, 1662, 1612, 1513, 1461, 1248, 1175, 1081, 1036, 1005, 820.

4.1.9. 1α,6α-Di-(4-methoxy-benzyloxy)-10-*epi*-eudesm-4 (5)-en-3-one (16). To a mixture of alcohol **15** (400 mg, 1.08 mmol) and *p*-TsOH (8 mg) in dry CH_2Cl_2 (5 mL) was added dropwise 2,2,2-trichloro-acetimidic acid 4-methoxy-benzyl ester (456 mg, 1.61 mmol) in CH_2Cl_2 (2 mL) under argon at 0 °C. The mixture was allowed to warm up to room temperature and stirred for 24 h. The crude was directly chromatographyed on silica gel and afforded colorless oil **16** (434 mg, 82%). $[\alpha]_D^{25}=+21°$ (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, 3H, *J*=6.8 Hz, Me), 0.88 (d, 3H, *J*=6.8 Hz, Me), 1.17–1.31 (m, 2H), 1.38 (s, 3H, Me), 1.50–1.55 (m, 1H), 1.61–1.71 (m, 1H), 1.72 (s, 3H, Me), 1.79–1.95 (m, 2H), 2.60 (dd, 1H, *J*=16.8, 12.8 Hz), 2.83 (dd, 1H, *J*=4.8, 12.8 Hz), 3.53 (dd, 1H, *J*=4.8, 12.8 Hz, $CHOCH_2$), 3.80 (s, 6H, OMe), 4.25 (d, 1H, *J*=7.2 Hz, OCH_2Ar), 4.38–4.41 (m, 2H, OCH_2Ar and $CHOCH_2$), 4.43–4.59 (m, 2H, OCH_2Ar), 6.86–6.89 (m, 4H, Ar), 7.24–7.27 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 19.1, 19.8, 20.2, 21.6, 27.4, 31.3, 39.3, 41.4, 47.7, 55.2, 69.5, 71.1, 76.0, 79.1, 113.7, 128.8, 129.1, 130.4, 130.6, 134.4, 157.8, 159.0, 159.1, 198.5; MS *m/z* (‰): 492 (M^+, 1), 463 (1), 371 (1.6), 235 (10), 191 (10), 177 (2), 121 (1000), 91 (22), 77 (35), 43 (16); IR (film, cm^{-1}) ν_{max}=2952, 2870, 1669, 1612, 1513, 1461, 1248, 1174, 1080, 1038, 821.

4.1.10. 1α,6α-Dihydroxy-5β(α)-*H*−10-*epi*-eudesm-3 (4)-ene 2′ (3). To a solution of **16** (150 mg, 0.3 mmol) in acetic acid (1.5 mL) was added $TsNHNH_2$ (57 mg, 0.45 mmol) and stirred for 10 h at room temperature. Then $NaBH_4$ (342 mg, 9 mmol) was added in batches during 0.5 h. The resulting mixture was diluted with ether and washed successively with 5% HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give an oil. Flash column chromatography on silica gel afforded compound **17** and **18** (117 mg, 80%), which without further purification, was taken in 5 mL $CH_2Cl_2{\cdot}H_2O$ (18:1), and treated with DDQ (82 mg, 0.36 mmol) at 0 °C and stirred for 3 h before it was quenched by saturated aqueous $NaHCO_3$ (1 mL) at 0 °C. After stirring for a further 15 min, the reaction mixture was extraction with ether. The organic phase was washed with water, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. Evaporation of the solvent followed by flash column chromatography on silica gel afforded colorless oil **2′** (10 mg, 17.4%) and white crystal **3** (40 mg, 70%, mp 140–142 °C). Compound **2′** $[\alpha]_D^{26}=-28°$ (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J*=4 Hz, 3H, Me), 0.96 (d, *J*=4 Hz, 3H, Me), 1.05 (s, 3H, Me), 1.17–1.24 (m, 1H), 1.31–1.34 (m, 1H), 1.57–1.66 (m, 4H), 1.80 (s, 3H, Me), 1.94–2.00 (m, 1H), 2.02 (s, br, 1H), 2.26–2.30 (m, 1H), 3.51 (dd, *J*=10.2, 6.4 Hz, 1H, CHOH), 4.25 (s, br, 1H, CHOH), 5.42 (s, br, 1H, CH═); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 20.3, 20.3, 21.4, 21.7, 26.9, 30.1, 32.3, 37.3, 45.0, 48.0, 69.5, 76.7, 122.1, 133.6; MS *m/z* 238 (M^+, 0.5%), 220 (7), 205 (5), 202 (5), 177 (6), 159 (15), 135 (11), 123 (22), 107 (72), 93 (36), 83 (85), 69 (51), 43 (100); IR (film, cm^{-1}) ν_{max}=3272.3, 2951.7, 2887.9, 1456.1, 1427.3, 1367.5, 1289.2, 1048.5, 1028.0, 989.0, 828.3, 804.2. Compound **3** $[\alpha]_D^{26}=+31°$ (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, *J*=6.4 Hz, 3H, Me), 0.85 (s, 3H, Me), 0.94 (d, *J*=6.4 Hz, 3H, Me), 1.09–1.12 (m, 1H), 1.26–1.27 (m, 1H), 1.30–1.37 (m, 1H), 1.46–1.47 (m, 1H), 1.63–1.65(d, *J*=14 Hz, 1H), 1.89 (s, 3H, Me), 1.90–1.95 (m, 1H), 2.03–2.06 (m, 1H), 2.07–2.17 (m, 1H), 2.49–2.53 (m, 1H), 3.46 (d, *J*=9 Hz, 1H, CHOH), 4.02 (t, *J*=8 Hz, 1H, CHOH), 5.34 (s, br, 1H, CH═); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 18.0, 20.2, 21.0, 25.9, 26.3, 33.3, 33.9, 38.9, 51.1, 57.3, 65.9, 75.9, 120.4, 137.0; MS *m/z* 238 (M^+, 1%), 220 (7), 205 (6), 202 (3), 177 (7), 159 (10), 123 (31), 107 (92), 93 (33), 83 (15), 69 (30), 43 (100).

4.1.11. 1α,6β-Dihydroxy-5β-*H*-10-*epi*-eudesm-3 (4)-ene (1′). To a solution of **2′** (5 mg) in CH_2Cl_2 (2 mL) was added Dess–Martin regent (10 mg) at 0 °C and stirred for 8 h before it was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL) at 0 °C. After stirring for a further 15 min, the reaction mixture was extraction with ether. The organic phase was washed with water, saturated aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. Evaporation of the solvent in vacuum gave the crude product, which without further purification, was taken in CH_3OH (2 mL) and treated with $NaBH_4$ (10 mg). The resulting mixture was stirred for 1 h at room temperature and diluted with ether, washed with 5% HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. Purification by flash chromatography gave colorless oil **1′** (4 mg, 80%). $[\alpha]_D^{26}=-21°$ (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 3H, Me), 0.95 (d, *J*=6.8 Hz, 3H, Me), 0.97(d, *J*=6.4 Hz, 3H, Me), 1.26–1.30 (m, 1H), 1.42–1.43 (m, 1H), 1.45–1.55 (m, 2H), 1.64–1.69 (m, 2H), 1.71 (s, 3H, Me), 1.93–1.95 (m, 1H), 2.02–2.03 (m, 1H), 2.12–2.13 (m, 1H), 2.40–2.44 (m, 1H), 3.98 (s, br, 1H, CHOH), 4.44 (t, *J*=8.6 Hz, 1H, CHOH), 5.57 (s, br, 1H, CH═); MS *m/z* 238 (M^+, 1.8%), 220 (57), 205 (45), 202 (5), 177 (25), 159 (17), 135 (13), 123 (47), 107 (66), 93 (25), 84 (100), 69 (21), 43 (47); IR (film, cm^{-1}) ν_{max}=3368, 2957, 2928, 2851, 1456, 1372, 1275, 1154, 1072, 1049, 1025, 835.

4.1.12. 1α(β),6β-Dihydroxy-5α-*H*-10-*epi*-eudesm-3 (4)-ene 4 (5). To a solution of **3** (30 mg) in CH_2Cl_2 (4 mL) was added Dess–Martin regent (60 mg) at 0 °C and stirred for 14 h before it was quenched by saturated aqueous $Na_2S_2O_3$ (2 mL) at 0 °C. After stirring for a further 15 min, the reaction mixture was extraction with ether. The organic phase was washed with water, saturated aqueous $NaHCO_3$

and brine, dried over $MgSO_4$. Evaporation of the solvent in vacuum gave the crude product, which without further purification, was taken in CH_3OH (4 mL) and treated with $NaBH_4$ (50 mg). The resulting mixture was stirred for 1 h at room temperature and diluted with ether, washed with 5% HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. Purification by flash chromatography gave white crystal **4** (18 mg, 60%, mp 174–176 °C) and gave colorless oil **5** (3 mg, 10%). Compound **4** $[\alpha]_D^{26}=+8°$ (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (s, 3H, Me), 0.90 (d, *J*=6.4 Hz, 3H, Me), 0.94 (d, *J*=6.8 Hz, 3H, Me), 1.29–1.37 (m, 2H), 1.56–1.58 (m, 2H), 1.59–1.71(m, 2H), 1.77 (s, 3H, Me), 1.84–1.90 (m, 1H), 2.03–2.08 (m, 1H), 2.37–2.44 (m, 1H), 3.41 (d, *J*=4.2 Hz, 1H, CHOH), 4.12 (s, br, 1H, CHOH), 5.47 (s, br, 1H, CH═); MS *m/z* 238 (M^+, 0.7%), 220 (29), 205 (6), 202 (5), 177 (6), 159 (23), 135 (7), 123 (20), 107 (100), 93 (24), 81 (20), 69 (24), 43 (81); IR (film, cm^{-1}) ν_{max}=3360, 2955, 2916, 2854, 1447, 1372, 1301, 1148, 1062, 854, 788. Compound **5** $[\alpha]_D^{26}=+18°$ (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (s, 3H, Me), 0.95 (d, *J*=6.8 Hz, 3H, Me), 0.97 (d, *J*=6.8 Hz, 3H, Me), 1.19–1.23 (m, 2H), 1.31–1.61 (m, 2H), 1.63–1.69 (m, 1H), 1.71 (s, 3H, Me), 1.75 (s, br, 1H), 1.87–1.94 (m, 1H), 2.07–2.18 (m, 1H), 2.44–2.50 (m, 1H), 3.98 (s, br, 1H, CHOH), 4.44 (s, br, 1H, CHOH), 5.56 (s, br, 1H, CH═); MS *m/z* 238 (M^+, 1.3%), 220 (74), 205 (63), 202 (1.6), 177 (32), 159 (21), 136 (26), 123 (50), 107 (85), 93 (34), 84 (59), 69 (28), 43 (100); IR (film, cm^{-1}) ν_{max}=3351, 2929, 1444, 1372, 1231, 1150, 1069, 1046, 1024, 829.

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