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Synthesis of a key intermediate for the total synthesis of pseudopteroxazole

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ABSTRACT

A facile synthesis of a key intermediate for the total synthesis of *anti*-mycobacterial compound pseudopteroxazole is described employing an intramolecular Diels–Alder cyclization and an iodine-mediated oxidative aromatization step.

1. Introduction

Marine organisms continue to be a tremendous source of natural products exhibiting significant biological properties.[1] Pseudopteroxazole[2] and pseudopterosins A and E,[3] the diterpene class of compounds, isolated from marine soft coral *pseudopterogorgia elisabethae* are recent examples, which share a common backbone skeleton (Fig. 1) and yet display diverse biological activities. Pseudopteroxazole showed inhibitory activity against Mycobacterium tuberculosis H37Rv,[2] whereas pseudopterosins were found to display potent *anti*-inflammatory and analgesic activities.[3]

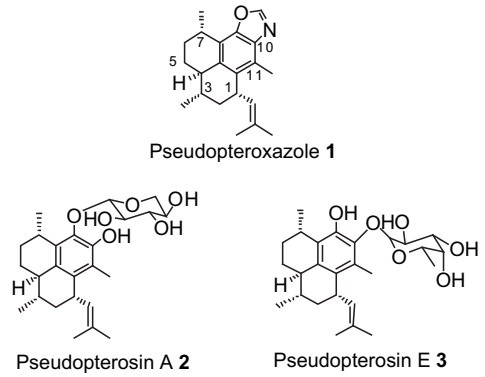

Figure 1.

The presence of four chiral centers without any adjacent functional groups makes this class of compounds a synthetic challenge. While there are several synthetic efforts from various groups on pseudopterosins,[4,5] only two groups have been found to be engaged in the total synthesis of pseudopteroxazole. In Corey's group[6] the structural assignment and first total synthesis was accomplished, while in Harmata's[7] group a chiral benzothiazine was utilized for the total synthesis.

In our long-term programme toward the total synthesis of biologically active natural products,[8] we have recently accomplished the total synthesis of terpene-based natural products artemisinin and erogorgiane.[9] Herein, we wish to report the synthesis of a key intermediate for the total synthesis of pseudopteroxazole.

2. Results and discussion

Our retrosynthetic approach for these compounds relied on a common intermediate **4** with the required tricyclic backbone, which could be obtained by an intramolecular Diels–Alder cyclization reaction (IMDA) of compound **5** followed by an iodine-mediated oxidative aromatization (Scheme 1). IMDA precursor **5** could be obtained by conversion of ketone **6** to the corresponding silyl enol ether followed by coupling with Weinreb amide **27**. Iodo ketone **6** was realized from β-keto ester **7** in five steps. Keto ester **7** was synthesized in three steps from diol **8**, which in turn was obtained by stereoselective manipulation of commercially available (*S*)-(−)-citronellal **9**.

Accordingly, our journey started with the racemic synthesis of key intermediate **4** (starting from (±)-citronellal) and was followed by an enantiopure synthesis following similar strategy as delineated below.

Ring cyclization of (*S*)-(−)-citronellal was achieved by an ene reaction with $ZnBr_2$ following a known procedure[10] to yield **10** and **10a** as the major products. Since the facial selectivity of hydroboration is directed by the neighboring chiral hydroxyl group, it was necessary for us to invert the stereochemistry of the hydroxyl group in compound **10** to get the desired diastereomer. Thus, compound **10** was transformed to the required product **10a** using modified Mitsunobu inversion conditions.[11] Hydroboration of **10a** using $BH_3 \cdot DMS$ followed by oxidative hydrolysis afforded mixture of inseparable diastereomers **8** and **8a** in 8:2 ratio.[12] At this stage,

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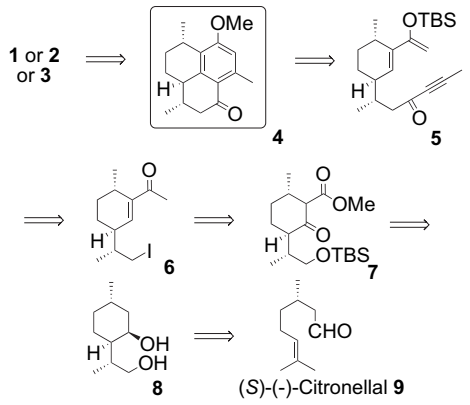
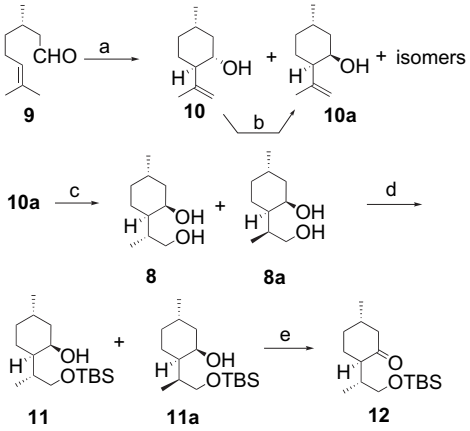
the required stereochemistry at C3 was installed. Selective primary alcohol protection with TBSCl in presence of NaH afforded easily separable (column chromatography) diastereomers **11** and **11a**. The required major diastereomer **11** was oxidized with PCC to get the ketone **12** (Scheme 2).

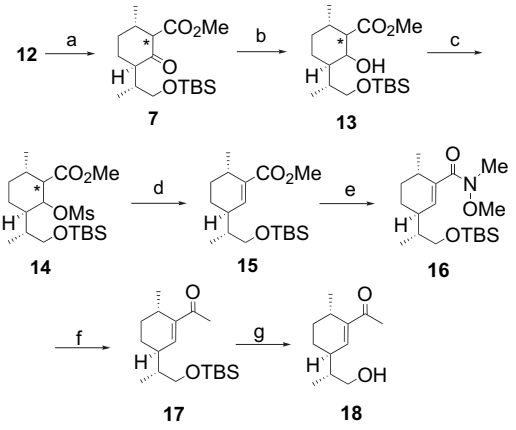


Scheme 1. Retrosynthesis.

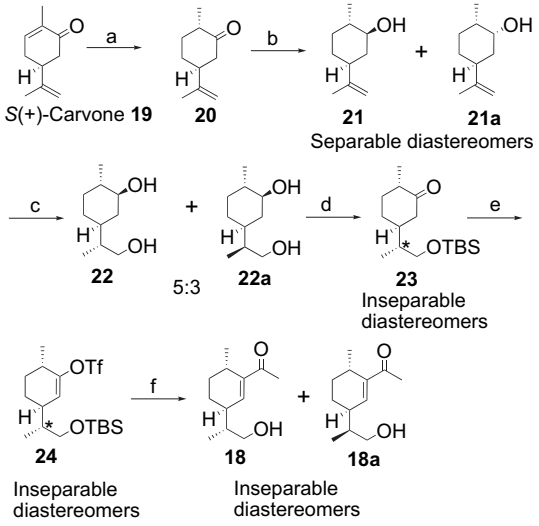


Scheme 2. Synthesis of **12**. Reagents and conditions: (a) $ZnBr_2$, benzene, 5–10 °C, 10 min 70%. **10** (94%), **10a** 4%+other isomers 2% (b) (i).Ph_3P, DIAD, 4-NO_2–C_6H_4COOH, benzene, 0 °C to rt, 3 h, 84%. (ii). NaOMe, MeOH, rt 30 min 97%. (c) BH_3·DMS, THF, 4 h, 0 °C to rt 94%. (d) NaH, TBSCl, THF, 0 °C to rt 2 h, 92%. (e) PCC, NaOAc, DCM, 30 min 0 °C to rt 94%.

Deprotonation of the ketone **12** on treatment with LDA followed by reaction with methyl cyanoformate yielded β-keto ester **7** as an inseparable diastereomeric mixture. As the newly generated chiral center was not a requisite in future steps, we proceeded further with the mixture of diastereomers. The keto functionality in **7** was reduced with $NaBH_4$ to yield **13**, which was mesylated with mesyl chloride and DMAP in pyridine. Attempts to get the α,β-unsaturated ester **15** by known procedures with DBU, *t*-BuOK or NaH yielded mixtures of inseparable regioisomers. Fortunately, the reaction with NaOMe was clean to produce the desired α,β-unsaturated ester **15** exclusively in 94% yield.[13] Ester **15** was converted to Weinreb amide **17** by treatment with Weinreb salt[14] in the presence of LiHMDS and then treated with methyl magnesium iodide to yield ketone **17**. The ketone 17 on desilylation with TBAF afforded alcohol **18** (Scheme 3). Simultaneously, compound **18** was also synthesized in seven steps starting from (*S*)-(+)-carvone **19** as a diastereomeric mixture in our laboratory (Scheme 4). However, since we could not succeed in separating the diastereomers[15] at any stage after the hydroboration reaction, we had to alter our strategy and thus proceeded with (*S*)-(−)-citronellal.

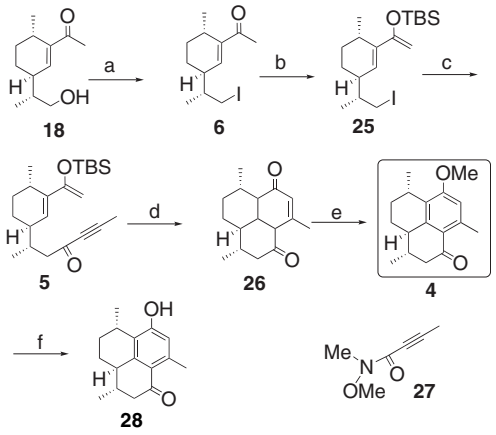


Scheme 3. Synthesis of keto-alcohol **18**. Reagents and conditions: (a) LDA, NCCO2Me, THF, −78 °C, 1.5 h, 87% (9:1 mixture). (b) NaBH4, MeOH, 0 °C, 0.5 h, 88%. (c) MsCl, pyridine (10 equiv), cat. DMAP, CH2Cl2, 0 °C to rt, 6 h, 94%. (d) NaOMe, MeOH, rt, 2 h, 96%. (e) LiHMDS, (MeO)MeNH.HCl, THF, −10 °C to rt 3 h, 86%. (f) MeMgI, Et_2O, THF, −10 °C, rt, 30 min 92%. (g) TBAF, THF, 0 °C to rt 1 h, 90%.



Scheme 4. Synthesis of keto-alcohol from (*S*)-(+)-carvone. Reagents and conditions: (a) K-Selectride, THF, −78 °C, 1 h, NaOH, 30% H_2O_2, 87%. (b) $LiAlH_4$, THF, −78 °C, 5 min 88% for, 7% for. (c) $((-)\text{-ipc})_2BH$, THF, 0 °C to rt 16 h, 98%. (d) NaH, TBSCl, THF, 0 °C to rt, 2 h, 90%. (ii) PCC, NaOAc, DCM, 0 °C to rt, 1 h, 90%. (e) LDA, *N*-phenyltriflimide, THF, −78 °C, 2 h, 0 °C, 3 h, then rt 12 h, 92%. (f) Ethylvinyl ether, LiCl, $Pd(PPh_3)_4$, 3 N HCl, 92%.

The enantiopure alcohol **18** obtained from (*S*)-(−)-citronellal was converted to iodide **6** via its tosyl ester followed by treatment with NaI in acetone under reflux conditions. The methyl ketone functionality in **6** was converted to the corresponding TBS enol ether **25** by treating with TBSOTf in the presence of triethylamine. Having, thus-installed the requisite diene, it was necessary to introduce an appropriate dienophile to set the stage for the envisaged intramolecular Diels–Alder cyclization reaction. Toward this, iodide **6** was lithiated with *tert*-butyllithium[16] and the resulting carbanion was quenched with Weinreb amide **27** to get IMDA cyclization precursor **5**. Treatment with $TiCl_4$[17] afforded thermodynamically preferred enone **26** as a light yellow solid (mp 172–174 °C) whose ^1H NMR spectrum (singlet at 5.97 ppm (proton on C10) and doublet at 3.24 ppm (proton on C12)) was consistent with olefin migration after cycloaddition. Enone **26** was oxidatively aromatized with I_2 in the presence of methanol[18] to give **4**, which possesses most of the attributes of the shared core of the pseudopterosins (Scheme 5).



Scheme 5. Synthesis of tricyclic core intermediate **4**. Reagents and conditions: (a) (i)TsCl, TEA, DMAP, DCM, 0 °C to rt 8 h, 94%. (ii) NaI, acetone, reflux, 12 h, 88%. (b) TEA, TBSOTf, DMAP, DCM, 0 °C, 20 min. 91%. (c)*t*.BuLi, then, Et_2O–hexane, −78 °C, 15 min. (d)$TiCl_4$, Mol. sieves 4 Å, −78 °C to rt. DCM, 6 h, 78% (overall yield for two steps c and d). (e) I_2 (6 equiv), MeOH, reflux, 2 h, 82%. (f) BBr_3, −20 °C to rt, DCM, 4 h, 80%.

The racemic version of compound **4** was recrystallized in EtOH to get colorless needles and suitable for X-ray crystallography, which clearly showed the desired relative stereochemistry at C3, C4, and C7 (Fig. 2).[19] Unfortunately, attempts to grow crystals from enantiopure compound **4** did not succeed.[20] Thus, we have accomplished the synthesis of a key intermediate **4** for the total synthesis of pseudopteroxazole. Further treatment of methyl ether **4** with BBr_3 in DCM yielded compound **28**, a known intermediate for the total synthesis of the aglycone of pseudopterosins A and E.[4b,5a]

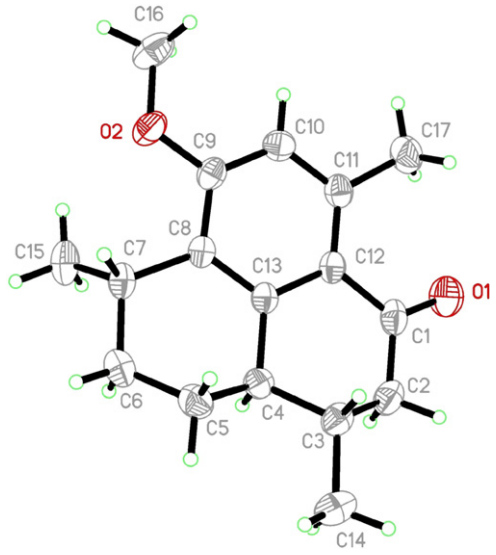


Figure 2. X-ray crystal structure of *rac*-4.

3. Conclusions

In conclusion, we have described the synthesis of a key intermediate for the total synthesis of pseudopteroxazole and pseudopterosins A and E. Our approach relies on an IMDA reaction followed by an iodine-mediated oxidative aromatization reaction, with a Mitsunobu inversion and a hydroxyl-directed hydroboration being employed to establish the required stereochemistry. Further studies toward the total synthesis of pseudopteroxazoles are currently being investigated.

4. Experimental section

4.1. General information

All the reagents employed were obtained commercially from M/s. Aldrich and used without further purifications unless otherwise stated. For anhydrous reactions, solvents were dried following known literature and removal of solvent was performed under reduced pressure using a rotary evaporator. All reactions requiring anhydrous conditions were carried out in oven-dried glassware under a nitrogen atmosphere. Optical rotations were measured using Perkin–Elmer model no.343 digital polarimeter using a 1 mL cell with a 1 dm path length. The ^1H NMR spectra were recorded at 300 or 400 MHz, and the ^{13}C NMR spectra were recorded at 75 MHz/100 MHz at ambient temperature. Chemical shifts of the ^1H NMR spectra are expressed in parts per million relative to the solvent residual signal 7.26 in $CDCl_3$ or to tetramethylsilane (δ=0.00). Chemical shifts of the ^{13}C NMR spectra are expressed in parts per million relative to the solvent signal 77.00 in $CDCl_3$ unless otherwise noted. Mass spectra were recorded on LCQ-Ion trap mass spectrometer (Thermo Finnigan, San Jose, USA) for ESI and Q-TOF mass spectrometer (Q STARXL Hybrid, Applied biosystems, USA) for HRMS. One or more of the following methods were used for visualization: UV absorption by fluorescence quenching; iodine staining; anisaldehyde stain (ethanol (135 mL)/H_2SO_4 (5 mL)/AcOH (1.5 mL)/*p*-anisaldehyde 3.7 mL). Column chromatography was performed using 60–120 mesh silica gel. Ethyl acetate and hexane were the common eluents used unless specified.

4.1.1. (1S,2R,5S)-5-Methyl-2-(prop-1-en-2-yl)cyclohexanol ***10***. To a stirred solution of (*S*)-(−)-citronellal (9 g, 58.4 mmol) in anhydrous benzene (150 mL) was added catalytic amount of $ZnBr_2$ (1.3 g, 5.8 mmol) at ~10 °C. After stirring at ~10 °C for 10 min, the precipitated $ZnBr_2$ was filtered off and washed with Et_2O/hexane (1:1, 150 mL). After concentrating the solvent, the residue was dissolved in water and extracted with Et_2O (3×100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (100–200 mesh, 5% EtOAc/hexane) to afford pure **10** (6.3 g, 70%) followed by **10a** (450 mg, 5%) as colorless oils. R_f=0.35 and 0.3 (5% EtOAc/hexane), respectively. $[\alpha]_D^{25}$ +10.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3419, 2922, 2865, 1644, 1451, 1374, 1051, 1027, 888, 547 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.94–4.83 (m, 2H), 3.46 (td, *J*=4.3, 10.4 Hz, 1H), 2.04 (dm, *J*=12.2 Hz, 1H), 1.99–1.83 (m, 2H), 1.79–1.62 (m, 2H), 1.71 (s, 3H), 1.60–1.42 (m, 1H), 1.41–1.24 (m, 1H), 1.07–0.85 (m, 2H), 0.95 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.5, 112.7, 70.2, 54.0, 42.6, 34.2, 31.3, 29.5, 22.1, 19.1; Mass (ESI-MS) *m/z*: 155 (100, $[M+H]^+$); HRMS (ESI): calcd for $C_{10}H_{19}O$ $(M+H)^+$, 155.1430; found 155.1437.

4.1.2. (1R,2R,5S)-5-Methyl-2-(prop-1-en-2-yl)cyclohexyl-4-nitrobenzoate. To a stirred solution of *iso*-pulegol **10** (6.0 g, 38.9 mmol), triphenylphosphine (20.4 g, 77.9 mmol), and *p*-nitrobenzoic acid (13.0 g, 77.9 mmol) in benzene (40 mL) was added dropwise diisopropylazodicarboxylate (15.7 g, 77.9 mmol) at 0 °C. The clear yellow reaction mixture was stirred at room temperature for 3 h. After filtration and washing, solvent was removed under reduced pressure to furnish a residue, which was purified by column chromatography on silica gel (60–120 mesh, hexane) to afford pure benzoate (9.9 g, 84%) as a yellowish solid. R_f=0.5 (Hexane). Mp 93–95 °C. $[\alpha]_D^{25}$ −52 (*c* 2.0, $CHCl_3$); IR (neat) ν_{max}: 2926, 2863, 1721, 1602, 1520, 1345, 1277, 1108, 1006, 925, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.27 (d, *J*=8.8 Hz, 2H), 8.16 (d, *J*=8.8 Hz, 2H), 5.53 (s, 1H), 4.73 (s, 1H), 4.68 (s, 1H), 2.16–2.05 (m, 2H), 1.99–1.66

(m, 4H), 1.77 (s, 3H), 1.40–1.24 (m, 1H), 1.20–1.02 (m, 1H), 0.94 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7, 150.3, 145.7, 136.2, 130.5 (2C), 123.4 (2C), 111.0, 72.2, 46.8, 39.1, 34.4, 26.9, 25.2, 22.3, 22.0; Mass (ESI-MS) m/z: 304 (100, $[M+H]^+$); HRMS (ESI): calcd for $C_{17}H_{21}O_4NNa$ $(M+Na)^+$, 326.1368; found 326.1357.

4.1.3. (1R,2R,5S)-5-Methyl-2-(prop-1-en-2-yl)cyclohexanol ***10a***. Solid benzoate (9.2 g, 30.3 mmol) obtained above was added to a solution of a freshly prepared MeONa in MeOH [prepared from sodium (2.1 g, 91.0 mmol) and MeOH (100 mL)] at room temperature and the resulting solution was stirred at room temperature. After 30 min, water was added and the reaction mixture was extracted with Et_2O (3×100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (60–120 mesh, 5% EtOAc/hexane) to afford pure neo-isopulegol **10a** (4.55 g, 97%) as a colorless oil. R_f=0.4 (5% EtOAc/hexane). $[\alpha]_D^{25}$ −22.2 (c 2.0, $CHCl_3$); IR (neat) ν_{max}: 3411, 2925, 2862, 1639, 1451, 1374, 1045, 1025, 881, 547 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.94 (s, 1H), 4.78 (s, 1H), 4.02–3.96 (m, 1H), 2.02–1.92 (m, 2H), 1.88–1.63 (m, 3H), 1.78 (s, 3H), 1.60–1.40 (m, 2H), 1.19–1.06 (m, 1H), 1.03–0.85 (m, 1H), 0.88 (d, J=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.2, 111.2, 66.2, 48.3, 40.8, 34.7, 25.7, 23.8, 22.7, 22.1; Mass (ESI-MS) m/z: 155 (100, $[M+H]^+$); HRMS (ESI): calcd for $C_{10}H_{19}O$ $(M+H)^+$, 155.1430; found 155.1434.

4.1.4. (1R,2R,5S)-2-((R)-1-Hydroxypropan-2-yl)-5-methylcyclohexanol ***8***. To a stirred solution of (−)-neo-isopulegol **10a** (3.8 g, 20.7 mmol) in anhydrous THF was added BH_3·DMS (1.58 g, 20.7 mmol) dropwise over a period of 15 min. After complete addition, the reaction was stirred at 0 °C for 3 h and at room temperature for 4 h. The reaction was cooled to 0 °C and basified with 3 N NaOH (15 mL). After 5 min, H_2O_2 (5.6 mL, 30% aq solution) was added slowly (exothermic) and the reaction mixture was stirred at room temperature. After 3 h, water was added and extracted with EtOAc (4×100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (230–400 mesh, 50% EtOAc/hexane) to afford partially separated diastereomers **8** and **8a** (4.0 g, 94%) as a colorless highly viscous oil. R_f=0.4 (40% EtOAc/hexane).

Data for major product (**8**): Highly viscous oil. $[\alpha]_D^{25}$ −6.2 (c 1.0, $CHCl_3$); IR (neat) ν_{max}: 3314, 2919, 1612, 1454, 1373, 1249, 1035, 969, 839 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.07 (s, 1H), 3.84 (br s, 2H, 2OH), 3.61 (dd, J=10.9, 2.8 Hz, 1H), 3.48 (dd, J=10.9, 5.6 Hz, 1H), 1.87–1.36 (m, 6H), 1.25–0.87 (m, 3H), 0.96 (d, J=7.2 Hz, 3H), 0.84 (d, J=6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 66.1, 64.5, 45.9, 42.1, 38.0, 35.3, 26.0, 25.4, 22.3, 15.8; Mass (ESI-MS) m/z: 195 (M^++Na); HRMS (ESI): calcd for $C_{10}H_{20}O_2Na$ $(M+Na)^+$, 195.1360; found 195.1365.

4.1.5. (1R,2R,5S)-2-((R)-1-(tert-Butyldimethylsilyloxy)propan-2-yl)-5-methylcyclohexanol ***11***. To a well-stirred suspension of freshly activated NaH (880 mg, 22.0 mmol, 60% dispersion in mineral oil) in anhydrous THF (100 mL), was added a solution of mixture of diastereomers **8** and **8a** (3.6 g, 20.9 mmol) in THF (30 mL) slowly at 0 °C. After 30 min, added TBSCl (3.15 g, 24.4 mmol) in anhydrous THF (30 mL) at 0 °C and then mixture was allowed to warm up to room temperature. After 2 h, the reaction was quenched with ice flakes and extracted with Et_2O (3×100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (100–200 mesh, 8% EtOAc/hexane) to afford pure compound **11** (5.0 g, 83.7%) followed by **11a** (495 mg, 8.3%) as colorless oils. R_f=0.5 and 0.4 (20% EtOAc/hexane). $[\alpha]_D^{25}$ −9.3 (c 1.0, $CHCl_3$); IR (neat) ν_{max}: 3442, 2926, 2860, 1463, 1390, 1254, 1073, 838, 777, 670 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.07 (br s, 1H), 3.66 (dd, J=10.0, 2.2 Hz, 2H), 3.53 (dd, J=10.2, 6.2 Hz, 1H), 1.95–1.38 (m, 6H), 1.22–0.82 (m, 3H), 0.95 (d, J=6.9 Hz, 3H), 0.91 (s, 9H), 0.86 (d, J=6.4 Hz, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 66.1, 65.9, 46.6, 41.8, 38.2, 35.4, 26.1, 25.8, 25.5, 22.4, 18.2, 16.0, −5.6; Mass (ESI-MS) m/z: 287 (100, $[M+H]^+$); HRMS (ESI): calcd for $C_{16}H_{35}O_2Si$ $(M+H)^+$, 287.2401; found 287.2400.

4.1.6. (2R,5S)-2-((R)-1-(tert-Butyldimethylsilyloxy)propan-2-yl)-5-methylcyclohexanone ***12***. To a stirred suspension of PCC (10.3 g, 48 mmol), NaOAc (7.9 g, 96.5 mmol) in anhydrous CH_2Cl_2 (100 mL) at ∼10 °C, was added alcohol **11** (4.6 g, 16.0 mmol) in CH_2Cl_2 (50 mL) and stirred for 30 min. To the resulting mixture was added silica gel (∼20 g), solvent was removed under reduced pressure and purified on a short path column of silica gel (60–120 mesh, 4% EtOAc/hexane) to afford pure ketone **12** (4.3 g, 94%) as a colorless oil. R_f=0.5 (10% EtOAc/hexane). $[\alpha]_D^{25}$ +20.0 (c 2.0, $CHCl_3$); IR (neat) ν_{max}: 2954, 2859, 1710, 1463, 1364, 1253, 1090, 1041, 839, 776, 668 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.52–3.36 (m, 2H), 2.51–2.20 (m, 3H), 2.08–1.74 (m, 4H), 1.46–1.23 (m, 2H), 1.02 (d, J=6.2 Hz, 3H), 0.87 (s, 9H), 0.80 (d, J=6.9 Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.3, 65.8, 50.7, 49.7, 35.2, 33.9, 33.1, 26.8, 25.8, 22.3, 18.2, 12.7, −5.41, −5.48; Mass (ESI MS) m/z: 285 (100, $[M+H]^+$); HRMS (ESI): calcd for $C_{16}H_{33}O_2Si$ $(M+H)^+$, 285.2244; found 285.2248.

4.1.7. (3R,6S)-Methyl-3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yl)-6-methyl-2-oxocyclohexanecarboxylate **7**. To a stirred solution of diisopropylamine (4.0 mL, 28.2 mmol) in anhydrous THF (40 mL) was added n-BuLi (13.2 mL, 1.6 M solution in hexane, 21.1 mmol) at −10 °C and stirred for 20 min at same temperature. To the resulting mixture at −78 °C was added a solution of ketone **12** (4 g, 14.0 mmol) in anhydrous THF (40 mL). After 30 min, was added methyl cyanoformate (1.25 g, 14.7 mmol) at −78 °C and stirred for 30 min. The reaction mixture was quenched with aq saturated NH_4Cl (30 mL) and extracted with Et_2O (3×75 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (100–120 mesh, 5% EtOAc/hexane) to afford pure keto ester **7** (4.2 g, 87%) as a colorless oil. R_f=0.45 (10% EtOAc/hexane). IR (neat) ν_{max}: 2954, 2931, 2858, 1749, 1710, 1464, 1357, 1254, 1095, 840, 776, 668 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (s, 3H), 3.53–3.31 (m, 2H), 3.04 (d, J=12.0 Hz, 1H), 2.58–2.47 (m, 1H), 2.32–2.15 (m, 2H), 2.08–1.89 (m, 2H), 1.53–1.35 (m, 2H), 1.01 (d, J=6.4 Hz, 3H), 0.86 (s, 9H), 0.79 (d, J=6.9 Hz, 3H), 0.014 (s, 3H), 0.004 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.8, 170.3, 65.5, 51.8, 49.7, 37.3, 33.1, 32.8, 26.2, 25.8, 21.0, 18.2, 12.5, −5.4, −5.5; Mass (ESI-MS) m/z: 343 (100, $[M+H]^+$); HRMS (ESI): calcd for $C_{18}H_{35}O_4Si$ $(M+H)^+$, 343.2299; found 343.2297.

4.1.8. (3R,6S)-Methyl-3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yl)-2-hydroxy-6-methylcyclohexanecarboxylate ***13***. To a stirred solution of keto ester **7** (3.6 g, 10.5 mmol) in MeOH (100 mL) was added $NaBH_4$ (400 mg, 10.5 mmol) portion wise at 0 °C. After 30 min, solvent was removed under reduced pressure and to this was added aq saturated NH_4Cl (20 mL), and extracted with EtOAc (3×75 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (60–120 mesh, 10% EtOAc/hexane) to afford pure alcohol **13** (3.18 g, 88%) as a colorless crystalline solid. R_f=0.5 (10% EtOAc/hexane). Mp 48–50 °C. IR (neat) ν_{max}: 3517, 2953, 2930, 2858, 1715, 1463, 1254, 1200, 1090, 838, 775, 669 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.19 (s, 1H), 3.68 (s, 3H), 3.63–3.49 (m, 2H), 3.41 (d,

J=2.2 Hz, 1H), 2.12–2.00 (m, 2H), 1.82–1.43 (m, 4H), 1.25–1.09 (m, 2H), 0.94–0.85 (m, 15H), 0.04 (s, 3H), 0.034 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.3, 68.0, 66.5, 55.3, 51.4, 45.4, 37.4, 34.4, 27.8, 25.7, 23.9, 20.6, 18.1, 15.8, −5.66, −5.63; Mass (ESI-MS) m/z: 345 (100, $[M+H]^+$); HRMS (ESI): m/z calcd for $C_{18}H_{37}O_4Si$ $(M+H)^+$, 345.2456; found 345.2459.

4.1.9. (3R,6S)-Methyl-3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yl)-6-methyl-2-(methylsulfonyloxy)cyclohexanecarboxylate ***14***. To a solution of alcohol **13** (2.8 g, 8.1 mmol) and pyridine (6.4 g, 81.4 mmol) in anhydrous CH_2Cl_2 (50 mL) at ~5 °C was added methanesulphonylchloride (2.8 g, 24.4 mmol), catalytic amount of DMAP (100 mg, 10 mol %) and allowed to stir at room temperature. After 6 h, the reaction mixture was quenched with aq saturated $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (60–120 mesh, 10% EtOAc/hexane) to afford the pure mesyl-ester **14** (3.2 g, 94%) as a colorless oil. R_f=0.5 (10% EtOAc/hexane). IR (neat) ν_{max}: 2953, 2857, 1740, 1463, 1340, 1253, 1174, 1092, 1021, 901, 838, 777, 539 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.35 (s, 1H), 3.81 (dd, J=3.9, 10.3 Hz, 1H), 3.68 (s, 3H), 3.46 (dd, J=3.2, 10.3 Hz, 1H), 3.03 (s, 3H), 2.16–1.97 (m, 2H), 1.83 (dq, J=3.4, 13.4 Hz, 1H), 1.74–1.49 (m, 3H), 1.36 (qd, J=3.6, 12.6 Hz, 1H), 1.10–0.97 (m, 1H), 0.93 (d, J=6.8 Hz, 3H), 0.91–0.85 (m, 12H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 80.3, 65.1, 54.6, 51.7, 41.9, 39.0, 35.3, 33.6, 27.3, 25.8, 23.0, 20.0, 18.2, 15.3, −5.6, −5.7; Mass (ESI-MS) m/z: 423 (100, $[M+H]^+$); HRMS (ESI): calcd for $C_{19}H_{39}O_6SSi$ $(M+H)^+$, 423.2231; found 423.2230.

4.1.10. (3R,6S)-Methyl-3-((R)-1-(tert-butyldimethylsilyloxy)propan-2-yl)-6-methylcyclohex-1-enecarboxylate ***15***. To a stirred solution of mesyl-ester **14** (2.5 g, 5.9 mmol) in MeOH (50 mL) was added NaOMe (950 mg, 17.7 mmol) at 0 °C and stirred at room temperature for 2 h. Solvent was removed under reduced pressure, and the residue was quenched with aq saturated NH_4Cl, diluted with water and extracted with Et_2O (3×50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (60–120 mesh, 3% EtOAc/hexane) to afford pure α,β-unsaturated ester **15** (1.85 g, 95.8%) as a colorless oil. R_f=0.6 (5% EtOAc/hexane). $[\alpha]_D^{25}$ −20.3 (c 1.0, $CHCl_3$); IR (neat) ν_{max}: 2953, 2859, 1717, 1639, 1465, 1250, 1092, 840, 775, 669 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82–6.76 (m, 1H), 3.72 (s, 3H), 3.50 (d, J=6.2 Hz, 2H), 2.66–2.52 (m, 1H), 2.43–2.31 (m, 1H), 1.89–1.55 (m, 3H), 1.40–1.21 (m, 2H), 1.05 (d, J=6.9 Hz, 3H), 0.87 (s, 9H), 0.82 (s, 3H), 0.028 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 143.2, 135.6, 65.8, 51.3, 39.8, 36.9, 29.9, 29.0, 25.8, 20.9, 20.2, 18.2, 13.6, −5.45, −5.47; Mass (ESI-MS) m/z: 327 (100, $[M+H]^+$); HRMS (ESI): calcd for $C_{18}H_{35}O_3Si$ $(M+H)^+$, 327.2350; found 327.2351.

4.1.11. (3R,6S)-3-((R)-1-(tert-Butyldimethylsilyloxy)propan-2-yl)-N-methyoxy-N,6-dimethylcyclohex-1-enecarboxamide ***16***. To a solution of unsaturated ester **15** (1.5 g, 4.6 mmol) and Me(OMe)NH·HCl (670 mg, 6.9 mmol) in anhydrous THF (30 mL) at −10 °C was added LiHMDS (13.8 mL, 1.0 M in THF, 13.8 mmol) dropwise over 15 min. After stirring further 15 min at −10 °C, the mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with aq saturated NH_4Cl and extracted with Et_2O (3×50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (60–120 mesh, 30% EtOAc/hexane) to afford pure Weinreb amide **16** (1.4 g, 85.9%) as a colorless oil. R_f=0.3 (20% EtOAc/hexane). $[\alpha]_D^{25}$ −13.1 (c 1.0, $CHCl_3$); IR (neat) ν_{max}: 2930, 2856, 1653, 1463, 1409, 1371, 1253, 1092, 988, 841, 776, 669 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.89 (s, 1H), 3.65 (s, 3H), 3.56–3.42 (m, 2H), 3.25 (s, 3H), 2.67–2.52 (m, 1H), 2.48–2.37 (m, 1H), 1.94–1.63 (m, 3H), 1.38–1.17 (m, 2H), 0.99 (d, J=6.9 Hz, 3H), 0.88 (s, 9H), 0.81 (d, J=6.9 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 139.8, 134.1, 65.8, 60.8, 39.6, 37.0, 33.5, 31.4, 31.0, 25.8, 22.9, 19.4, 18.2, 12.8, −5.41, −5.46; Mass (ESI-MS) m/z: 356 (100, $[M+H]^+$); HRMS (ESI): calcd for $C_{19}H_{38}NO_3Si$ $(M+H)^+$, 356.2615; found 356.2614.

4.1.12. 1-((3S,6S)-3-((R)-1-(tert-Butyldimethylsilyloxy)propan-2-yl)-6-methylcyclohex-1-enyl)ethanone ***17***. To a solution of the Weinreb amide **16** (1.2 g, 3.4 mmol) in THF (30 mL) at −20 °C was added MeMgI (10.1 mL, 1.0 M solution in THF, 10.1 mmol) over 10 min. The resulting solution was allowed to warm to room temperature and stirred for 30 min. The reaction mixture was quenched with aq saturated NH_4Cl solution diluted with water (25 mL), and then extracted with Et_2O (3×50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (60–120 mesh, 4% EtOAc/hexane) to afford pure ketone **17** (960 mg, 92%) as a colorless oil. R_f=0.5 (5% EtOAc/hexane). $[\alpha]_D^{25}$ −48.8 (c 1.0, $CHCl_3$); IR (neat) ν_{max}: 2954, 2931, 2859, 1670, 1630, 1466, 1387, 1363, 1251, 1094, 840, 776, 669 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.72 (d, J=3.2 Hz, 1H), 3.59–3.48 (m, 2H), 2.77–2.63 (m, 1H), 2.52–2.41 (m, 1H), 2.28 (s, 3H), 1.84–1.59 (m, 3H), 1.41–1.24 (m, 2H), 1.00 (d, J=6.8 Hz, 3H), 0.90 (s, 9H), 0.84 (d, J=6.9 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.8, 145.2, 144.2, 65.8, 39.9, 36.8, 29.3, 27.8, 26.0, 25.8, 20.3, 20.0, 18.2, 13.7, −5.44, −5.47; Mass (ESI-MS) m/z: 311 (100, $[M+H]^+$); HRMS (ESI): calcd for $C_{18}H_{35}O_2Si$ $(M+H)^+$, 311.2401; found 311.2403.

4.1.13. 1-((3S,6S)-3-((R)-1-Hydroxypropan-2-yl)-6-methylcyclohex-1-enyl)ethanone ***18***. To a stirred solution of ketone **17** (870 mg, 2.8 mmol) in THF (15 mL) at 0 °C was added TBAF (7 mL, 1.0 M solution in THF, 7.0 mmol) over 10 min. After stirring at room temperature for 1 h, the mixture was poured in to saturated NH_4Cl (20 mL) and extracted with Et_2O (3×60 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (60–120 mesh, 30% EtOAc/hexane) to afford the pure alcohol **18** (490 mg, 90%) as a colorless oil. R_f=0.4 (30% EtOAc/hexane). $[\alpha]_D^{25}$ −53.0 (c 1.0, $CHCl_3$); IR (neat) ν_{max}: 3415, 2930, 2873, 1663, 1458, 1387, 1361, 1247, 1033, 942, 880, 605 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (d, J=2.8 Hz, 1H), 3.70–3.53 (m, 2H), 2.79–2.62 (m, 1H), 2.54–2.42 (m, 1H), 2.29 (s, 3H), 2.10 (br s, –O*H*, 1H), 1.91–1.63 (m, 3H), 1.44–1.25 (m, 2H), 1.00 (d, J=6.8 Hz, 3H), 0.89 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.0, 145.4, 143.5, 65.7, 39.9, 37.0, 29.4, 27.9, 26.0, 20.6, 20.0, 13.6; Mass (ESI-MS) m/z: 197 (100, $[M+H]^+$); HRMS (ESI): calcd for $C_{12}H_{21}O_2$ $(M+H)^+$, 197.1536; found 197.1535.

4.1.14. 1-((3S,6S)-3-((R)-1-Iodopropan-2-yl)-6-methylcyclohex-1-enyl)ethanone ***6***. To a stirred solution of alcohol **18** (430 mg, 2.2 mmol) and Et_3N (0.66 g, 6.6 mmol) in anhydrous CH_2Cl_2 (15 mL), was added p-TsCl followed by DMAP (40 mg, 10 mol %) at 0 °C and the resulting mixture was allowed for stirring at room temperature for 8 h. The mixture was poured in to saturated $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic layer were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (60–120 mesh, 10% EtOAc/hexane) to afford pure tosyl-ester (720 mg, 94%) as a colorless oil. R_f=0.5 (10% EtOAc/hexane). $[\alpha]_D^{25}$ −18.0 (c 1.0, $CHCl_3$); IR (neat) ν_{max}: 3417, 2969, 1708, 1495, 1456, 1358, 1176, 1124, 1035, 1007, 816, 684, 565 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d,

J=8.3 Hz, 2H), 7.36 (d, J=7.9 Hz, 2H), 6.53 (d, J=2.8 Hz, 1H), 3.96 (d, J=6.0 Hz, 2H), 2.72–2.58 (m, 1H), 2.46 (s, 3H), 2.43–2.33 (m, 1H), 2.23 (s, 3H), 2.03–1.89 (m, 1H), 1.76–1.50 (m, 2H), 1.32–1.18 (m, 2H), 0.97 (d, J=7.0 Hz, 3H), 0.88 (d, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.7, 146.1, 144.8, 141.1, 132.8, 129.8 (2C), 127.8 (2C), 72.6, 36.9, 36.6, 29.0, 27.8, 26.1, 21.6, 20.5, 19.9, 13.5; Mass (ESI-MS) m/z: 351 (100, $[M+H]^+$); HRMS (ESI): calcd for $C_{19}H_{27}O_4S$ $(M+H)^+$, 351.1625; found 351.1623.

A suspension of tosyl-ester (700 mg, 2 mmol) and NaI (2.4 g, 15.9 mmol) in acetone (30 mL) was heated to reflux for 12 h. The solvent was removed under reduced pressure, and the residue was diluted with water and then extracted with Et_2O (2×40 mL). The combined organic layer were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on neutral alumina (3% EtOAc/hexane) to afford pure iodide **6** (540 mg, 88%) as a colorless oil. R_f=0.6 (5% EtOAc/hexane). $[\alpha]_D^{25}$ −42.0 (c 1.2, $CHCl_3$); IR (neat) ν_{max}: 2929, 1667, 1627, 1454, 1355, 1245, 1197, 600 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.62 (d, J=3.2 Hz, 1H), 3.31–3.21 (m, 2H), 2.76–2.62 (m, 1H), 2.51–2.41 (m, 1H), 2.30 (s, 3H), 1.84–1.64 (m, 3H), 1.40–1.27 (m, 2H), 1.00 [d, J=6.8 Hz, 6H, (two doublets merged with a common 'J' value)]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.7, 146.0, 141.5, 39.6, 39.1, 29.1, 27.8, 26.2, 20.1, 19.9, 17.5, 14.4; Mass (ESI MS) m/z: 329 (80, $[M+Na]^+$); HRMS (ESI): calcd for $C_{12}H_{19}ONaI$ $(M+Na)^+$, 329.0378; found 329.0384.

*4.1.15. tert-Butyl(1-((3S,6S)-3-((R)-1-iodopropan-2-yl)-6-methylcyclohex-1-enyl)vinyloxy)dimethylsilane **25**.* To a stirred solution of iodide **6** (400 mg, 1.3 mmol) and Et_3N (390 mg, 3.9 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 °C was added TBSOTf (410 mg, 1.6 mmol) slowly over a period of 10 min followed by catalytic amount of DMAP (~30 mg). After stirring at 0 °C for 15 min, the reaction mixture was poured into ice water and extracted with CH_2Cl_2 (2×30 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on neutral alumina (Hexane) to afford the pure compound **25** (500 mg, 91%) as a colorless oil. R_f=0.7 (Hexane). $[\alpha]_D^{25}$ −42.1 (c 1.0, $CHCl_3$); IR (neat) ν_{max}: 2955, 2930, 2858, 1593, 1462, 1274, 1194, 1009, 838, 780, 691 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.01 (d, J=3.4 Hz, 1H), 4.37 (s, 1H), 4.25 (s, 1H), 3.34–3.19 (m, 2H), 2.51–2.37 (m, 1H), 2.26–2.15 (m, 1H), 1.84–1.63 (m, 2H), 1.59–1.48 (m, 1H), 1.42–1.29 (m, 2H), 1.07 (d, J=7.0 Hz, 3H), 1.00 (d, J=6.6 Hz, 3H), 0.96 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 140.8, 127.1, 91.3, 39.2, 39.1, 29.3, 28.7, 25.8, 25.6, 20.7, 20.3, 18.1, 16.0, −4.5, −4.6; Mass (ESI-MS) m/z: 443 (60, $[M+Na]^+$); HRMS (ESI): calcd for $C_{18}H_{33}INaOSi$ $(M+Na)^+$, 443.1243; found 443.1250.

*4.1.16. (S)-6-((1R,4S)-3-(1-(tert-Butyldimethylsilyloxy)vinyl)-4-methylcyclohex-2-enyl)hept-2-yn-4-one **5**.* To a well-stirred solution of compound **25** (250 mg, 0.59 mmol) and Weinreb amide **27** (90 mg, 0.71 mmol) dissolved in anhydrous Et_2O/hexane (1:1, 10 mL) at −78 °C was added t-BuLi (0.93 mL, 1.6 M solution in pentane, 1.5 mmol) dropwise with syringe. After stirring for further 15 min at the same temperature, the reaction mixture was quenched with aq saturated NH_4Cl (10 mL), diluted with water and extracted with Et_2O (3×30 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified through short path column chromatography using neutral alumina (5% EtOAc/hexane) to afford the inseparable mixture of Diels–Alder precursor **5** (quantitative yield) and *tert*-butyl propargyl ketone (byproduct) as a colorless oil. R_f=0.3 (5% EtOAc/hexane). The above mixture as such was used for the next step without further purification. IR (neat) ν_{max}: 2951, 2244, 1706, 1521, 1481, 1410, 1270, 1012, 836, 715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.96 (d, J=2.2 Hz, 1H), 4.36 (s, 1H), 4.24 (s, 1H) 2.61 (dd, J=4.9, 15.3 Hz, 1H), 2.51–2.06 (m, 4H), 2.03 (s, 3H), 2.01 (s, 3H of *tert*-butyl propargyl ketone), 1.89–1.62 (m, 2H), 1.38–1.23 (m, 2H), 1.19 (s, 9H of *tert*-butyl propargyl ketone), 1.05 (d, J=6.8 Hz, 3H), 0.95 (s, 9H), 0.91 (d, J=6.6 Hz, 3H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.2, 188.1, 157.0, 141.1, 127.8, 91.3, 90.2, 89.7, 81.6, 80.4, 50.1, 39.4, 34.2, 30.1, 29.0, 25.9, 25.7, 21.8, 20.4, 16.7, 3.9, −4.5, −4.6; Mass (ESI-MS) m/z: 361, $[M+H]^+$; HRMS (ESI): calcd for $C_{22}H_{37}O_2Si$ $(M+H)^+$, 361.2563; found 361.2565.

*4.1.17. (6S,6aR,9S)-3,6,9-Trimethyl-6,6a,7,8,9,9a-hexahydro-3aH-phenalene-1,4(3a^{1}H,5H)-dione **26**.* To a stirred solution of compound **5** (250 mg) and molecular sieves (4 Å, 2 g) in CH_2Cl_2 (10 mL) at −78 °C, was added $TiCl_4$ (0.1 mL, 1.0 M solution in CH_2Cl_2) slowly with syringe. The resulting mixture was stirred at −78 °C for 10 min and allowed to warm to room temperature. After stirring for 6 h, the reaction mixture was poured in to saturated $NaHCO_3$ (10 mL), diluted with water and extracted with CH_2Cl_2 (3×30 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (60–120 mesh, 10% EtOAc/hexane) to afford pure diketone **26** (114 mg, 78% overall yield for two steps) as a pale yellowish solid (tiny granules). R_f=0.4 (20% EtOAc/hexane). Mp 172–174 °C. $[\alpha]_D^{25}$ +30.5 (c 1.0, $CHCl_3$); IR (neat) ν_{max}: 2932, 2217, 1707, 1650, 1446, 1372, 1213, 1105, 874, 613, 528 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.97 (s, 1H), 3.24 (d, J=5.4 Hz, 1H), 2.94–2.78 (m, 1H), 2.71–2.55 (m, 1H), 2.51–2.02 (m, 3H), 1.94 (s, 3H), 1.92–1.54 (m, 4H), 1.46–1.19 (m, 2H), 1.05 (d, J=4.7 Hz, 3H), 0.87 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.5, 198.8, 158.0, 128.5, 56.5, 49.6, 45.2, 42.5, 40.6, 30.8, 27.1, 26.6, 24.4, 20.3, 19.9, 12.8; Mass (ESI-MS) m/z: 269 (M^++Na); HRMS (ESI): calcd for $C_{16}H_{22}O_2Na$ $(M+Na)^+$, 269.1517; found 269.1529.

*4.1.18. (3S,3aR,6S)-7-Methoxy-3,6,9-trimethyl-2,3,3a,4,5,6-hexahydrophenalen-1-one **4**.* To a solution of diketone **26** (30 mg, 0.12 mmol) in MeOH (10 mL) was added iodine granules (177 mg, 0.70 mmol) at room temperature. The resulting dark brown solution was heated to 60 °C and stirred for 2 h. After removing the solvent under reduced pressure, residue was dissolved in $CHCl_3$ (15 mL), stirred along with saturated hypo solution (15 mL) for 30 min and the layer were separated. The aqueous layer was extracted with $CHCl_3$ (2×10 mL). The combined organic layer was washed with brine, dried on anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (100–200 mesh, 8% EtOAc/hexane) to afford the pure aromatized compound **4** (25.8 mg, 82%) as a white solid. R_f=0.4 (10% EtOAc/hexane). Mp 106–108 °C. $[\alpha]_D^{25}$ +54.9 (c 1.0, $CHCl_3$); IR (neat) ν_{max}: 2924, 2859, 1740, 1668, 1584, 1560, 1457, 1320, 1262, 1153, 1098, 1025, 841, 800, 545 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.60 (s, 1H), 3.86 (s, 3H), 3.27–3.12 (m, 1H), 2.64 (s, 3H), 2.61 (dd, J=3.7, 16.8 Hz, 1H), 2.37–2.11 (m, 4H), 1.85–1.68 (m, 1H), 1.45–1.03 (m, 2H), 1.19 (d, J=6.6 Hz, 3H), 1.12 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.5, 160.2, 147.0, 141.0, 128.0, 124.0, 112.3, 55.1, 48.8, 44.3, 35.1, 31.3, 27.8, 27.1, 23.9, 22.8, 19.5; Mass (ESI-MS) m/z: 259 (100, $[M+H]^+$); HRMS (ESI): calcd for $C_{17}H_{22}O_2Na$ $(M+Na)^+$, 281.1517; found 281.1530.

*4.1.19. (3S,3aR,6S)-7-Hydroxy-3,6,9-trimethyl-2,3,3a,4,5,6-hexahydrophenalen-1-one **28**.* To a stirred solution of compound **4** (12 mg, 0.046 mmol) in anhydrous CH_2Cl_2 (3 mL) was added BBr_3 (0.14 mL, 1.0 M solution in CH_2Cl_2, 0.14 mmol) with syringe at −20 °C. The resulting solution was allowed to warm to room temperature and then stirred for 1 h. After quenching the reaction mixture with saturated $NaHCO_3$, extracted with CH_2Cl_2 (3×5 mL), combined organic layer were washed with brine and dried over anhydrous

Na_2SO_4. After removing the solvent under reduced pressure, the crude product obtained was purified by column chromatography on silica gel (100–200 mesh, 12% EtOAc/hexane) to afford the pure phenol **28** (9 mg, 80%) as a colorless crystalline solid. Mp 168–170 °C. $[\alpha]_D^{25}$ +62.4 (*c* 0.5, $CHCl_3$); IR (neat) ν_{max}: 3421, 3110, 2932, 2854, 1712, 1632, 1577, 1450, 1320, 1255, 1169, 1093, 801 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.52 (s, 1H), 5.38 (br s, –OH, 1H), 3.24–3.09 (m, 1H), 2.61 (dd, *J*=4.0, 17.2 Hz, 1H), 2.57 (s, 3H), 2.39–2.13 (m, 4H), 1.87–1.70 (m, 1H), 1.26 (d, *J*=6.8 Hz, 3H), 1.47–1.05 (m, 2H), 1.12 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (150.0 MHz, $CDCl_3$): δ 199.6, 157.2, 148.3, 141.1, 125.7, 124.3, 117.4, 48.7, 44.4, 35.0, 31.4, 27.9, 27.1, 23.4, 22.5. 19.4; Mass (ESI-MS) *m*/*z*: 245 (100, $[M+H]^+$); HRMS (ESI): calcd for $C_{16}H_{21}O_2$ $(M+H)^+$, 245.1536; found 245.1539.

4.1.20. N-Methoxy-N-methylbut-2-ynamide ***27***. To a well-stirred solution of 2-butynoic acid (3 g, 35.6 mmol) and Weinreb salt in CH_2Cl_2 (10 mL) was added Et_3N (3.60 g, 35.6 mmol) followed by CBr_4 (11.84 g, 35.6 mmol) at room temperature and allowed for stirring for 5 min. To the resulting solution was added TPP (9.36 g, 35.6 mmol) in CH_2Cl_2 (60 mL) slowly at ~10 °C and stirred at room temperature for 30 min. After removing the solvent, to the residue was added 1:2 of EtOAc/hexane and filtered off. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (60–120 mesh, 30% EtOAc/hexane) to afford the pure product **27** (4.0 g, 90%) as a colorless viscous oil. R_f=0.3 (30% EtOAc/hexane). IR (neat) ν_{max}: 2977, 2936, 2242, 1706, 1635, 1427, 1385, 1256, 1206, 979, 723, 583 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.76 (s, 3H), 3.21 (br s, 3H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.1, 85.6, 71.9, 61.8, 32.1, 3.8; Mass (ESI-MS) *m*/*z*: 128 (100, $[M+H]^+$). HRMS (ESI): calcd for $C_6H_{10}NO_2$ $(M+H)^+$, 128.0714; found 128.0719.

4.1.21. (2S,5S)-2-Methyl-5-(prop-1-en-2-yl)cyclohexanone ***20***. To a stirred solution (*S*)-(+)-carvone **19** (5 g, 33.3 mmol) in anhydrous THF (100 mL) at −78 °C was added a solution of potassium tri-*sec*-butylborohydride (33.3 mL, 1.0 M solution in THF, 33.3 mmol) dropwise over a period of 20 min. After stirring at −78 °C for 1 h and 15 min at room temperature, the resultant solution was transferred in to an Erlenmeyer flask containing 10% aq NaOH solution. An aq solution of H_2O_2 (30%, 70.8 mL) was carefully added at 0 °C and the mixture was stirred for 3 h at room temperature. The aq phase was extracted with EtOAc/hexane (1:1, 2×100 mL) and combined layer was washed with aq saturated Na_2SO_3 (50 mL) and dried over anhydrous Na_2SO_4. After removing the solvent under vacuo, the residue was purified by column chromatography on silica gel (230–400 mesh, 2% EtOAc/hexane) to afford the pure **20** (4.46 g, 87%) followed by it's diastereomer (0.42 g, 9%) as colorless liquids. $[\alpha]_D^{25}$ −11.2 (*c* 1.2, $CHCl_3$); IR (neat) ν_{max}: 2924, 2860, 1640, 1450, 1370, 1027, 887 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.75–4.68 (m, 2H), 2.45–1.86 (m, 6H), 1.73(s, 3H), 1.67–1.23 (m, 2H), 1.00 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.3, 147.3, 109.3, 46.7, 46.5, 44.4, 34.6, 30.4, 20.1, 14.0; Mass (EI-MS) *m*/*z*: 152 (M^+, 14%).

4.1.22. (1S,2S,5S)-2-Methyl-5-(prop-1-en-2-yl)cyclohexanol ***21***. To a stirred suspension of $LiAlH_4$ (2.28 g, 60.0 mmol) in THF (50 mL) at −78 °C was added a solution of (−)-dihydrocarvone **20** (3.5 g, 23.0 mml) in THF (50 mL) over 10 min. After a further 5 min the reaction was quenched with aq saturated Na_2SO_4 (10 mL) and allowed to warm to room temperature. The resultant solid was filtered through sintered funnel and washed with EtOAc/hexane (1:9, 200 mL). After concentrating the solvent the residue was purified by column chromatography on silica gel (100–200 mesh, 4% EtOAc/hexane) to yield alcohol **21a** (250 mg, 7%) as a colorless oil, and alcohol **21** as a colorless oil (3.12 g, 88%). R_f=0.4 (5% EtOAc/hexane). $[\alpha]_D^{25}$ −26.2 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}: 3345, 2924, 2857, 1645, 1452, 1373, 1049, 887 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.70 (s, 2H), 3.18 (td, *J*=10.5, 3.7 Hz, 1H), 2.08–1.94 (m, 2H), 1.84–1.67 (m, 2H), 1.74 (s, 3H), 1.59 (s, 1H), 1.38–1.08 (m, 4H), 1.06 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.6, 108.7, 76.5, 44.3, 40.7, 40.1, 33.4, 31.2, 21.0, 18.5; Mass (EI-MS) *m*/*z*: 154 (15%, M^+).

4.1.23. (1S,2S,5S)-5-((R)-1-Hydroxypropan-2-yl)-2-methylcyclohexanol ***22***, ***22a***. To a stirred solution of (−)-α-pinene (18.2 mL, 114 mmol) in THF (100 mL) at 0 °C was added BH_3·DMS complex (5.4 mL, 57.3 mmol) over 5 min. After 1 h alkene **21** (8.84 g, 57.3 mmol) in THF (50 mL) was added via syringe over 10 min and the reaction was allowed to warm to room temperature. After 3 h, 10% aq NaOH (22 mL) and H_2O_2 (19 mL, 30% aq solution) were added sequentially and then stirred for 16 h. The reaction mixture was diluted with water (50 mL) and chloroform (100 mL). The phases were separated and the aqueous phase was extracted with chloroform (3×200 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated in vacuo and purified by column chromatography (silica gel, diethyl ether) to give a 5:2 mixture of diols **22** and **22a** (9.63 g, 55.9 mmol, 98%) as a colorless viscous oil. Partial separation of the diastereomers was achieved by column chromatography on silica (230–400 mesh, using a 3:1:1 mixture of diethyl ether, THF, and hexane). The enriched samples were then recrystallized from ether/petrol. After a two recrystallizations **22** was attained as a semisolid contaminated with ~18% of **22a**, while **22a** was partially crystallized out as colorless needles. Data for mixture of diastereomers: IR (neat) ν_{max}: 3314, 2919, 1454, 1373, 1249, 1035, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.61–3.43 (m, 2H), 3.18–3.06 (m, 1H), 1.96–1.80 (m, 3H, 2OH), 1.78–1.70 (m, 1H), 1.65–1.41 (m, 3H), 1.33–0.94 (m, 4H), 1.01 (d, *J*=6.4 Hz, 3H), 0.93–0.87 (m, 3H); Mass (ESI-MS) *m*/*z*: 195 $(M+Na)^+$; HRMS (ESI): calcd for $C_{10}H_{20}O_2Na$ $(M+Na)^+$, 195.1360; found 195.1365.

4.1.24. (1S,2S,5S)-5-((S)-1-(tert-Butyldimethylsilyloxy)propan-2-yl)-2-methylcyclohexanone ***23***. To a well-stirred suspension of freshly activated NaH (976 mg, 24.4 mmol, 60% dispersion in mineral oil) in anhydrous THF (100 mL), was added a solution of mixture of diastereomers (**22**, **22a**) (4 g, 23.2 mmol) in THF (40 mL) at 0 °C. After 30 min TBSCl (3.48 g, 23.2 mmol) in anhydrous THF (4 mL) was added at 0 °C. After two hours, the reaction was quenched with ice pieces and extracted with Et_2O (3×100 mL). The combined organic layer was washed with brine, dried on anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (230–400 mesh, 10–30% Et_2O/hexane) to afford the compound diTBS ether (266 mg, 4%) followed by a mixture of monoTBS ether as inseparable diastereomers (6.0 g, 90%) as colorless viscous oils. R_f=0.8 and 0.3 (30% Et_2O/hexane).

Data for monoTBS ether: IR (neat) ν_{max}: 3440, 2928, 1464, 1262, 1076, 840, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.87–3.81 (m, 1H), 3.60–3.52 (m, 1H), 3.41 (dd, 1H), 1.90–1.58 (m, 4H), 1.54–1.19 (m, 4H), 1.17–0.80 (m, 2H), 0.95 (d, 3H), 0.89 (s, 9H), 0.87–0.83 (m, 3H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.0, 70.9, 66.4, 66.2, 40.1, 37.9, 36.3, 36.0, 32.0, 31.8, 30.1, 28.2, 28.1, 28.0, 25.9, 25.6, 18.3, 13.5, 13.2, −5.4; Mass (ESI MS) *m*/*z*: 287 (100, $[M+H]^+$); HRMS (ESI): calcd for $C_{16}H_{35}O_2Si$ $(M+H)^+$, 287.2401; found 287.2409.

To a solution of monoTBS ether mixture (3.2 g, 11.2 mmol) in CH_2Cl_2 (100 mL) was added NaOAc (5.5 g, 67.1 mmol) in one portion followed by pyridinium chlorochromate (7.2 g, 33.5 mmol) portion wise at ~5 °C and allowed to warm to room temperature. After 1 h, the solvent was concentrated to 1/3 of its volume under reduced pressure and adsorbed on silica gel. Purification by column chromatography using silica gel (230–400 mesh, 5% Et_2O/hexane) afforded the inseparable mixture of ketones **23** (2.86 g, 90%) as

a colorless oil. R_f=0.6 (10% Et_2O/hexane). IR (neat) ν_{max}: 2954, 2929, 1712, 1458, 1250, 1092, 841, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.56–3.42 (m, 2H), 2.40–2.05 (m, 4H), 1.93–1.78 (m, 2H), 1.69–1.22 (m, 3H), 1.01 (d, J=6.4 Hz, 3H), 0.93–0.84 (m, 12H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.2, 213.1, 65.7, 46.2, 44.8, 44.4, 41.7, 41.6, 40.1, 35.0, 29.6, 27.6, 25.8, 18.1, 14.2, 13.2, 13.1, −5.5; Mass (ESI MS) m/z: 285 (100, $[M+H]^+$); HRMS (ESI): calcd for $C_{16}H_{33}O_2Si$ $(M+H)^+$, 285.2244; found 285.2246.

4.1.25. (3R,6S)-3-((S)-1-(tert-Butyldimethylsilyloxy)propan-2-yl)-6-methylcyclohex-1-enyl trifluoromethane sulfonate ***24****.* To a stirred solution of diisopropylamine (1.25 mL, 8.8 mmol) in anhydrous THF (30 mL) was added *n*-BuLi (4.6 mL, 1.6 M solution in hexane, 7.4 mmol) at −10 °C and stirred for 20 min at same temperature. To the resulting mixture at −78 °C was added a mixture of ketones **23** (1.4 g, 4.9 mmol) in anhydrous THF (20 mL) dropwise with syringe. The reaction mixture was stirred at the same temperature for 2 h and to this was added solid *N*-phenyltrifluoromethanesulfonimide (2.63 g, 7.4 mmol) in one portion. The resulting solution was stirred at 0 °C for 3 h and then at room temperature for 16 h. After removing the solvent under reduced pressure, the crude enoltriflate was purified by column chromatography on silica gel (230–400 mesh, 5% Et_2O/hexane) to afford the inseparable mixture of enoltriflate **24** (1.88 g, 92%) as a colorless oil. R_f=0.4 (5% Et_2O/hexane). IR (neat) ν_{max}: 2958, 2933, 1675, 1416, 1211, 1142, 1096, 972, 889, 840, 607 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.68–5.60 (m, 1H), 3.54–3.46 (m, 2H), 2.61–2.43 (m, 2H), 2.28–1.94 (m, 1H), 1.89–1.54 (m, 2H), 1.48–1.22 (m, 2H), 1.13 (d, J=6.6 Hz, 3H), 0.93–0.81 (m, 12H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4, 153.2, 130.9, 129.9, 122.7, 121.0, 65.8, 65.6, 39.5, 39.3, 33.0, 32.0, 31.7, 25.8, 25.5, 17.8, 18.2, 16.5, 13.0, 12.8, −5.5; Mass (ESI-MS) m/z: 417 (80, $M+H)^+$; HRMS (ESI): calcd for $C_{17}H_{32}F_3O_4SSi$ $(M)^+$, 417.1743; found 417.1749.

4.1.26. 1-((3S,6S)-3-(1-Hydroxypropan-2-yl)-6-methylcyclohex-1-enyl)ethanone ***18****,* ***18a****.* To a well-stirred slurry of enoltriflate (1 g, 2.4 mmol), LiCl (713 mg, 16.8 mmol), and $Pd(OAc)_2$ (54 mg, 10 mol %) in anhydrous THF (30 mL), was added ethylvinyl ketone (346 mg, 4.8 mmol) at room temperature. The reaction mixture was heated to reflux for overnight, cooled to 0 °C and treated with 5 M HCl solution under stirring for 15 min. The resultant solution was extracted with EtOAc (3×50 mL) then washed with water, brine and dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (230–400 mesh, 30% EtOAc/hexane) to furnish the inseparable mixture of keto-alcohol **18** and **18a** (433 mg, 92%) as a colorless oil. R_f=0.3 (30% EtOAc/hexane). IR (neat) ν_{max}: 3415, 2930, 2873, 1663, 1458, 1387, 1361, 1247, 1033, 942, 880, 605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.78–6.62 (m, 1H), 3.78–3.53 (m, 2H), 2.87–2.62 (m, 1H), 2.64–2.42 (m, 1H), 2.32 (s, 1H), 2.29 (s, 2H), 2.10 (br s, 1H), 1.92–1.20 (m, 5H), 1.02–0.86 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2, 200.0, 145.4, 145.3, 143.5, 143.2, 65.8, 65.7, 39.9, 37.0, 29.4, 29.3, 27.9, 26.0, 25.9, 20.6, 19.8, 13.6, 13.4.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.01.054.

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20. Attempts in ethanol, methanol, and combination of hexane/diethyl ether solutions did not yield the required crystal.