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Stereoselective synthesis of (+)-sordidin, the male-produced aggregation pheromone of the banana weevil *Cosmopolites sordidus*

J.S. Yadav*, K. Bhaskar Reddy, A.R. Prasad, H. Ur Rehman

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, Andhra Pradesh, India

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Abstract

Stereoselective synthesis of (1*S*,3*R*,5*R*,7*S*)-(+)-sordidin, the natural male-produced aggregation pheromone of the banana weevil *Cosmopolites sordidus* (Germar) starting from 5-benzyloxy-(2*E*)-pentene-1-ol is described. The key transformations employed in the synthesis are Sharpless asymmetric epoxidation, Ueno–Stork cyclization, and Jacobsen kinetic resolution.
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Keywords: Banana weevil; Jacobsen's resolution; Epoxide opening; Intramolecular acetalization

1. Introduction

The banana weevil, *Cosmopolites sordidus* (Germar), is the most devastating insect pest on banana plants and known world over.[1] Budenberg et al. in 1993[2] first reported the release of the aggregation pheromone by male *C. sordidus*. Subsequently, in 1995, Ducrot et al.[3] reported the isolation and identification of the major pheromone compound and gave a trivial name sordidin while reporting the first synthesis. Further syntheses were reported by Ducrot and Beauhaire,[4] Oehlschlager et al.,[5] Mori and Nakayama,[6] Kitching et al.,[7] and Wardrop et al.[8] Recently, Enders et al.[9] reported the first asymmetric synthesis of (+)-sordidin and (−)-7-*epi*-sordidin.

In our attempts to synthesize sordidin, Scheme 1 depicts the retrosynthetic analysis of (1*S*,3*R*,5*R*,7*S*)-(+)-sordidin **1a**. Ketone **22a** is assumed as the key intermediate, which after intramolecular acetalization would lead to the target pheromone. Ketone **22a** could be achieved by alkylative cleavage of (*R*)-propylene oxide **14** with the organolithium reagent obtained from dithiane **12**. Dithiane **12** could be prepared from cyclic acetal **7**. Cyclic acetal **7** would be easily synthesized from alcohol **5**, which in turn would be synthesized from 5-benzyloxy-(2*E*)-pentene-1-ol **2**.

2. Results and discussion

As summarized in Scheme 2, our synthesis of (+)-sordidin **1a** started from 5-benzyloxy-(2*E*)-pentene-1-ol **2**.[10a,b] Utilizing a standard literature procedure,[11] **2** was transformed into known epoxy alcohol **3** in 91% yield. Alcohol **3** was converted into epoxy iodide **4** by treating with I_2, TPP, and imidazole[12] at 0 °C and on treating the iodide **4** with Zn and NaI in MeOH at reflux temperature afforded the secondary alcohol **5**[13] in 84% yield (over two steps). Treatment of alcohol **5** with *N*-bromosuccinimide and ethyl vinyl ether[14a,b] in dichloromethane resulted in bromo acetal **6**, which was converted into cyclic ethyl acetal **7** (96:4 trans–cis mixture) in 89% yield with a preferential trans-geometry[15] of the resulting new stereogenic center by using *n*-tributyltinhydride in refluxing toluene with 2,2′-azobisisobutyronitrile as a radical initiator. Based on the stereochemical outcome, which was believed to be set as trans from our earlier studies and also according to one of the Beckwith guidelines, which states that 2- or 4-substituted radicals give mainly *trans*-disubstituted cyclopentyl derivatives, we proceeded further. Cleavage of benzyl ether **7** with lithium in liquid ammonia gave the primary

* Corresponding author. Tel.: +91 40 27193030; fax: +91 40 27160512.
E-mail address: yadavpub@iict.res.in (J.S. Yadav).

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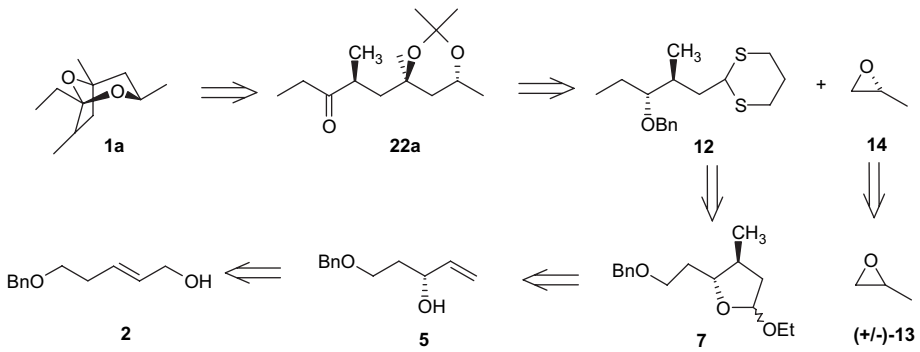


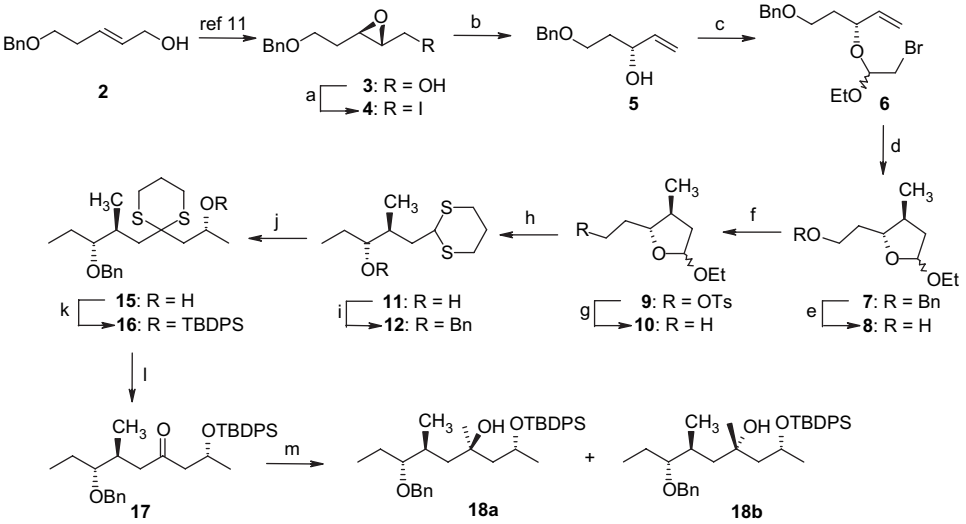
Scheme 1. Retrosynthetic analysis of sordidin **1a**.

alcohol **8**, which was transformed into the corresponding tosylate **9** in 90% yield. Reduction of the tosylate **9** with $LiAlH_4$ in THF furnished the cyclic acetal[14a] **10** in 89% yield. Hydrolysis of cyclic acetal **10** using 1,3-propanedithiol and borontrifluoride diethylether in anhydrous dichloromethane[16] afforded alcohol **11** in 87% yield. Protection of **11** using sodium hydride, *n*-tetrabutylammonium iodide, and benzyl bromide in THF under refluxing conditions furnished benzyl ether **12**.

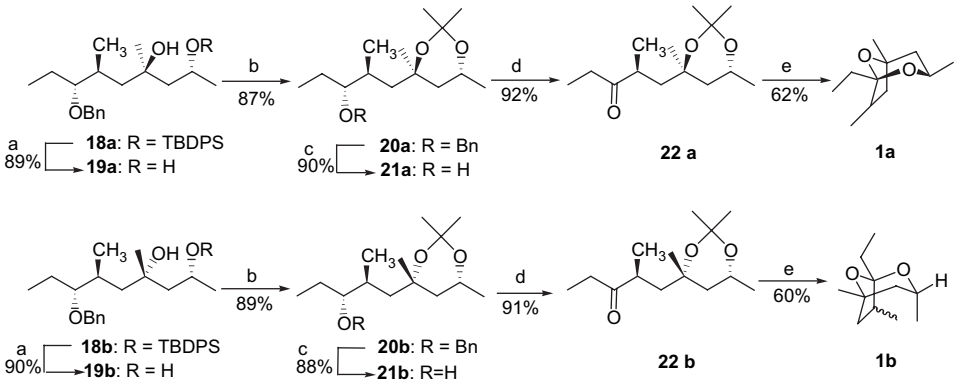
Kinetic resolution of (±)-propylene oxide **13** using Jacobsen's catalyst (*R*,*R*)-(−)-*N*-*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino cobalt(II)[17] and water afforded (*R*)-propylene oxide **14** in 42% yield with 98% ee.

Lithiation of **12** with *n*-butyllithium[18] followed by ring opening of (*R*)-propylene oxide **14** in the presence of $BF_3\cdot OEt_2$ at −78 °C gave alcohol **15** in 88% yield. The secondary hydroxyl group of **15** was protected as the corresponding *tert*-butyldiphenylsilylether **16** and dithiane deprotection of **16** using Dess–Martin periodinane[19] in CH_3CN–CH_2Cl_2–H_2O (8:1:1) furnished ketone **17** in 76% yield (over two steps).

Methylation of ketone **17** with methyllithium at 0 °C afforded the diastereomeric mixture of tertiary alcohols **18a** and **18b** in 65:35 ratio. Both the isomers were subjected to a standard reaction sequence to reach the final target as well as to know the stereochemistry of the isomers. In contrast, reaction of ketone **17** with methylmagnesium iodide (prepared from MeI and Mg) resulted in **18a** and **18b** in 45:55 ratio in 81% yield. The slow running isomer **18a** as observed on thin-layer chromatography was subjected to deprotection with *n*-tetrabutylammonium fluoride in THF[20] and thus furnished **19a** in 89% yield (Scheme 3). Further, **19a** was protected as acetonide **20a** with 2,2-dimethoxy propane and catalytic *para*-toluenesulfonic acid in dry methylenechloride in 87% yield. Benzyl ether in **20a** was cleaved with lithium in liquid ammonia at −33 °C to furnish the alcohol **21a**, which on oxidation with TEMPO free radical[21] afforded the ketone **22a** in 82% yield (over two steps). Finally, ketone **22a** underwent intramolecular acetalization with saturated aqueous oxalic acid in *n*-pentane at 0 °C without epimerization (as monitored by GC–MS analysis), furnishing the (+)-sordidin



Scheme 2. Reagents and conditions: (a) I_2, PPh_3, imidazole, ether–acetonitrile (3:1), 0 °C, 0.5 h, 90%; (b) Zn, NaI, MeOH, reflux, 6 h, 87%; (c) NBS, ethyl vinyl ether, CH_2Cl_2, 0 °C, 5 h, 88%; (d) *n*-Bu_3SnH, AIBN, toluene, reflux, 2 h, 89%; (e) Li, liq. NH_3, THF, −33 °C, 1 h, 91%; (f) *p*-TsCl, TEA, DMAP, CH_2Cl_2, 0 °C→rt, 5 h, 90%; (g) $LiAlH_4$, THF, 0 °C→rt, 7 h, 89%; (h) 1,3-propanedithiol, $BF_3\cdot OEt_2$, CH_2Cl_2, −10 °C→rt, 6 h, 87%; (i) NaH, benzyl bromide, TBAI, THF, reflux, 7 h, 89%; (j) *n*-BuLi, TMEDA, THF, −40 °C, 1 h and then **13**, $BF_3\cdot OEt_2$, −78 °C, 3 h, 88%; (k) TBDPSCl, imidazole, DMAP, CH_2Cl_2, rt, 15 h, 90%; (l) Dess–Martin periodinane, CH_3CN–CH_2Cl_2–H_2O (8:1:1), rt, 2 h, 85%; (m) CH_3Li, diethyl ether, 0 °C→rt, 2 h, 87%.



Scheme 3. Reagents and conditions: (a) TBAF, THF, rt, 4 h; (b) *p*-TsOH, 2,2-dimethoxypropane, 0 °C→rt, 2 h; (c) Li, liq. NH_3, THF, −33 °C, 1 h; (d) TEMPO, NaOCl, NaBr, EtOAc−toluene (1:1), H_2O, rt, 2 h; (e) satd aq oxalic acid, *n*-pentane, 0 °C, 2 days.

1a in 62% yield. Compound **1a** was confirmed based on ^1H and ^{13}C NMR, and optical rotation values.[6,22] The observed optical rotation of compound **1a** was $[\alpha]_D^{25}$ +24.61 (*c* 0.25, Et_2O), lit.[9] $[\alpha]_D^{25}$ +25.1 (*c* 0.94, Et_2O). Next, the faster running isomer **18b** on thin-layer chromatography was subjected to same reaction conditions as described for conversion of **18a** to **1a** to give the mixture of two isomers **1b** in 70:30 ratio based on GC−MS. Formation of two isomers might be due to epimerization at the C-7 position. These two *epimers* could be separated by preparative GC, as previously reported for (+)-sordidin and (−)-7-*epi*-sordidin.[6,22]

3. Conclusion

In summary, we succeeded in accomplishing the synthesis of (1*S*,3*R*,5*R*,7*S*)-(+)-sordidin **1a** from 5-benzyloxy-2(*E*)-pentene-1-ol **2** via Sharpless asymmetric epoxidation, Ueno−stork cyclization, and Jacobsen's kinetic resolution as the key steps.

4. Experimental

4.1. General

All reactions were carried out under inert atmosphere unless mentioned following standard syringe septa techniques. Solvents were dried and purified by conventional methods prior to use. The progress of all the reactions was monitored by thin-layer chromatography (TLC) using glass plates precoated with silica gel-60 F_{254} to a thickness of 0.5 mm (Merck). Column chromatography was performed on silica gel (60−120 mesh) and neutral alumina using diethyl ether, ethyl acetate, and hexane as the eluents. Optical rotation values were measured with a Perkin−Elmer P241 polarimeter and JASCO DIP-360 digital polarimeter at 25 °C and IR spectra were recorded with a Perkin−Elmer FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded with Varian Gemini 200 MHz, Bruker Avance 300 MHz, Varian Unity 400 MHz, or Varian Inova 500 MHz spectrometer using trimethylsilane as an internal standard in $CDCl_3$. Mass spectra were recorded on Micro mass VG-7070H for EI and VG Autospec M for FABMS.

4.2. (2R,3S)-2-(2-Benzyloxy ethyl)-3-(iodomethyl)oxirane (*4*)

To a stirred solution of epoxy alcohol **3** (14.2 g, 68.2 mmol) in dry ether−acetonitrile (3:1, 400 mL) at 0 °C under nitrogen atmosphere were added imidazole (6.97 g, 102.4 mmol), triphenylphosphine (26.82 g, 102.4 mmol), and iodine (25.90 g, 102.4 mmol) successively. The mixture was stirred for 30 min at the same temperature, diluted with cold ether (200 mL), and filtered through a sintered funnel. The residue was washed with ether (3×50 mL) and concentrated in vacuo. Purification of the residue through silica gel column chromatography using 10% ethyl acetate−hexane as eluent resulted in the epoxy iodide **4** (20.3 g, 90%) as a colorless liquid; $[\alpha]_D^{25}$ −1.32 (*c* 5.46, $CHCl_3$); IR (Neat): ν_{max} 2860, 2360, 1453, 1102, 889, 770 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.36−7.21 (m, 5H), 4.51 (s, 2H), 3.57 (t, *J*=6.0 Hz, 2H), 3.29−3.18 (m, 1H), 3.05−2.89 (m, 3H), 1.95−1.73 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.0, 128.3, 127.6, 73.0, 66.6, 60.2, 58.2, 32.1, 4.9; MS (ESI): *m/z* 341 $[M+Na]^+$; ESI-HRMS, *m/z* calcd for $C_{12}H_{15}O_2NaI$ (M^++Na): 341.0014, found: 341.0001.

4.3. (R)-5-(Benzyloxy)pent-1-en-3-ol (*5*)

A mixture of epoxy iodide **4** (20.2 g, 63.7 mmol), NaI (23.89 g, 159 mmol), and freshly activated zinc (12.42 g, 191 mmol) in dry MeOH (120 mL) was refluxed for 6 h under nitrogen atmosphere. The solution was filtered and the residue was washed with MeOH (2×25 mL). The combined filtrates were concentrated and the residue was taken in ethyl acetate (50 mL), washed with water (2×30 mL) and brine (1×20 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification by silica gel column chromatography using 15% ethyl acetate−hexane as eluent furnished the alcohol **5** (10.9 g, 87%) as a colorless oil; $[\alpha]_D^{25}$ −9.60 (*c* 2.08, $CHCl_3$); IR (Neat): ν_{max} 3424, 3031, 2920, 2863, 1454, 1364, 1098, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50−7.20 (m, 5H), 5.93−5.72 (m, 1H), 5.23 (d, *J*=17.0 Hz, 1H), 5.06 (d,

J=10.9 Hz, 1H), 4.49 (s, 2H), 4.37–4.20 (m, 1H), 3.74–3.50 (m, 2H), 2.79 (br s, 1H, –OH), 1.90–1.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.4, 137.8, 128.3, 127.5, 114.2, 73.1, 71.5, 68.1, 36.2; MS (LCMS): *m/z* 215 $[M+Na]^+$; ESI-HRMS, *m/z* calcd for $C_{12}H_{16}O_2Na$ (M^++Na): 215.1047, found: 215.1041.

*4.4. 1-(((R)-3-(2-Bromo-1-ethoxyethoxy)-pent-4-enyloxy)methyl)benzene (**6**)*

Ethyl vinyl ether (10.9 mL, 113.6 mmol) was added to a stirred solution of freshly recrystallized NBS (12.14 g, 68.2 mmol) and allyl alcohol **5** (10.8 g, 56.8 mmol) in anhydrous CH_2Cl_2 (120 mL) at 0 °C. After stirring the reaction mixture for 5 h at the same temperature, the precipitate so-formed was filtered off and washed with hexane. The combined filtrates were washed with water (1×20 mL) and brine (1×20 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by silica gel column chromatography using 5% ethyl acetate–hexane as eluent afforded bromo acetal **6** (17.15 g, 88% yield) as a pale yellow oil; IR (Neat): ν_{max} 2976, 2924, 2867, 1423, 1366, 1106, 1058, 1024, 739 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35–7.19 (m, 5H), 5.84–5.61 (m, 1H), 5.30–5.10 (m, 2H), 4.68–4.56 (m, 1H), 4.52–4.41 (m, 2H), 4.28–4.02 (m, 1H) 3.82–3.35 (m, 4H), 3.35–3.23 (m, 2H), 1.96–1.69 (m, 2H), 1.30–1.14 (m, 3H); MS (FAB): *m/z* 343 (M^+); ESI-HRMS, *m/z* calcd for $C_{16}H_{23}O_3NaBr$ (M^++Na): 365.0728, found: 365.0716.

*4.5. (2R,3S)-2-(2-(Benzyloxy)ethyl)-5-ethoxy-tetrahydro-3-methylfuran (**7**)*

To a solution of bromo acetal **6** (14 g, 40.8 mmol) in dry toluene (75 mL) at reflux temperature under nitrogen atmosphere was added a solution of *n*-Bu_3SnH (13 mL, 49 mmol) and AIBN (5 mg) in toluene (20 mL). After 2 h, the solution was cooled to room temperature, concentrated in vacuo, and purified by silica gel column chromatography using 10% ethyl acetate–hexane as eluent to afford pure cyclic acetal **7** as a colorless oil (9.6 g, 89%); IR (Neat): ν_{max} 2965, 2930, 2868, 1452, 1369, 1100, 985, 738 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35–7.16 (m, 5H), 5.05–4.91 (m, 1H), 4.49 (s, 2H), 3.78–3.48 (m, 4H), 3.45–3.25 (m, 1H), 2.38–1.38 (m, 5H), 1.14 (t, J=7.0 Hz, 3H), 1.04 (d, J=7.0 Hz, 3H); MS (LCMS): *m/z* 219 (M^+–OEt); ESI-HRMS, *m/z* calcd for $C_{16}H_{24}O_3Na$ (M^++Na): 287.1623, found: 287.1620.

*4.6. 2-((2R,3S)-5-Ethoxy-tetrahydro-3-methylfuran-2-yl)ethanol (**8**)*

To a solution of lithium (1.193 g, 170.4 mmol) in liquid NH_3 (200 mL) was added compound **7** (9 g, 34.1 mmol) in dry THF (10 mL) at –33 °C. The reaction mixture was stirred for 1 h at the same temperature and quenched with solid NH_4Cl till blue color disappears. Ammonia was allowed to evaporate and the residual mixture was taken in ethyl acetate (50 mL), washed with water (2×15 mL) and brine (1×15 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by silica gel column chromatography using 20% ethyl acetate–hexane as eluent afforded alcohol **8** (5.45 g, 91%) as a colorless liquid; IR (Neat): ν_{max} 3431, 2930, 1452, 1377, 1343, 1055, 983 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.12–4.96 (m, 1H), 3.87–3.57 (m, 4H), 3.49–3.27 (m, 1H), 2.60 (br s, 1H, –OH), 2.42–2.11 (m, 1H), 2.10–1.97 (m, 1H), 1.96–1.40 (m, 3H), 1.18 (t, J=7.2 Hz, 3H), 1.04 (d, J=6.4 Hz, 3H); MS (LCMS): *m/z* 175 (M^++H); ESI-HRMS, *m/z* calcd for $C_9H_{18}O_3Na$ (M^++Na): 197.1153, found: 197.1157.

*4.7. 2-((2R,3S)-5-Ethoxy-tetrahydro-3-methylfuran-2-yl)ethyl-4-methylbenzenesulfonate (**9**)*

To a stirred solution of alcohol **8** (5.2 g, 29.88 mmol), triethylamine (12.43 mL, 89.65 mmol), and DMAP (0.01 g, 0.08 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C was added *para*-toluenesulfonyl chloride (6.81 g, 35.85 mmol) in portion wise and the mixture was stirred at room temperature for 5 h. The reaction mixture was poured into saturated NH_4Cl solution and extracted with CH_2Cl_2 (3×50 mL). The organic layer was washed with 1 N HCl, saturated $NaHCO_3$ solution, and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by silica gel column chromatography using 12% ethyl acetate–hexane as eluent afforded **9** (8.82 g, 90%) as a pale yellow liquid; IR (Neat): ν_{max} 2976, 1619, 1451, 1361, 1177, 1098, 974, 928 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.77 (d, J=7.5 Hz, 2H), 7.32 (d, J=7.5 Hz, 2H), 5.28–5.13 (m, 1H), 4.23–4.02 (m, 2H), 3.72–3.43 (m, 2H), 3.42–3.30 (m, 1H), 2.46 (s, 3H), 2.18–1.92 (m, 2H), 1.85–1.44 (m, 3H), 1.20 (d, J=6.0 Hz, 3H), 1.02 (t, J=6.8 Hz, 3H); MS (LCMS): *m/z* 351 (M^++Na); ESI-HRMS, *m/z* calcd for $C_{16}H_{24}O_5NaS$ (M^++Na): 351.1242, found: 351.1234.

*4.8. (2R,3S)-5-Ethoxy-2-ethyl-tetrahydro-3-methylfuran (**10**)*

To a magnetically stirred suspension of $LiAlH_4$ (1.86 g, 51.82 mmol) in dry THF (30 mL) at 0 °C was added compound **9** (8.5 g, 25.91 mmol) in dry THF (10 mL) and the mixture was allowed to stir at room temperature for 7 h. The reaction mixture was cooled to 0 °C and quenched with ice-cooled water (2 mL), 10% NaOH solution (2 mL), and again with water (6 mL). The mixture was filtered over a small pad of Celite and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by silica gel column chromatography using 5% ethyl acetate–hexane as eluent furnished ethylacetal[14a] **10** as a colorless liquid (3.5 g, 89% yield); IR (Neat): ν_{max} 2957, 2925, 2858, 1634, 1459, 1373, 1080, 971 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.04–4.92 (m, 1H), 3.78–3.64 (m, 1H), 3.49–3.28 (m, 2H), 2.34–2.22 (m, 1H), 2.17–1.98 (m, 1H), 1.79–1.65 (m, 1H), 1.65–1.35 (m, 2H), 1.17 (dd, J=14.3, 6.8 Hz, 3H), 1.03 (t, J=6.8 Hz, 3H), 0.97 (t, J=7.5 Hz, 3H); MS (EI): *m/z* 158 (M^+).

4.9. (2S,3R)-1-(1,3-Dithian-2-yl)-2-methylpentan-3-ol (**11**)

To a stirred solution of cyclic acetal **10** (3.2 g, 21.05 mmol) and 1,3-propanedithiol (2.32 mL, 23.15 mmol) in dry CH_2Cl_2 (20 mL) at −10 °C under nitrogen atmosphere was added $BF_3\cdot OEt_2$ (0.25 mL, 2 mmol) and allowed to warm to room temperature. After stirring for 6 h at room temperature, the reaction mixture was cooled to 0 °C, quenched with 2 M NaOH solution (10 mL), and extracted with CH_2Cl_2 (2×30 mL). The combined organic extracts were washed with water (1×20 mL) and brine (1×10 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by silica gel column chromatography using 20% ethyl acetate–hexane as eluent afforded alcohol **11** (4.03 g, 87% yield) as a colorless viscous liquid; $[\alpha]_D^{25}$ −16.98 (*c* 1.67, $CHCl_3$); IR (Neat): ν_{max} 3435, 2960, 2931, 2899, 1459, 1421, 1275, 1243, 972, 908, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.05 (dd, *J*=9.8, 5.3 Hz, 1H), 3.40–3.30 (m, 1H), 2.93–2.75 (m, 4H), 2.17–2.05 (m, 1H), 1.97–1.79 (m, 3H), 1.62–1.44 (m, 2H), 1.44–1.33 (m, 1H), 0.97 (t, *J*=7.5 Hz, 3H), 0.96 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 77.1, 45.5, 37.4, 35.1, 30.3, 29.9, 26.4, 25.8, 15.7, 10.1; MS (FAB): *m/z* 220 (M^+); ESI-HRMS, *m/z* calcd for $C_{10}H_{21}OS_2$ (M^++H): 221.1033, found: 221.1034.

4.10. 2-((2S,3R)-3-(Benzyloxy)-2-methylpentyl)-1,3-dithiane (**12**)

To a stirred suspension of NaH (0.878 g, 36.59 mmol, 60% w/v dispersion in mineral oil) in dry THF (40 mL) at 0 °C was added drop wise a solution of alcohol **11** (3.5 g, 15.9 mmol) in dry THF (15 mL). After stirring for 30 min at 0 °C, TBAI (5 mg) and benzyl bromide (2.26 mL, 19.08 mmol) were added drop wise. The reaction mixture was stirred for 7 h at refluxing temperature and quenched with saturated NH_4Cl solution until a clear solution (biphasic) was formed. The reaction mixture was extracted with ethyl acetate (2×50 mL). The combined organic extracts were washed with water (1×10 mL) and brine (1×15 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo and purification of the residue by silica gel column chromatography using 10% ethyl acetate–hexane as eluent afforded **12** (4.39 g, 89% yield) as a colorless viscous liquid; $[\alpha]_D^{25}$ +3.3 (*c* 1.81, $CHCl_3$); IR (Neat): ν_{max} 2960, 2930, 1456, 1421, 1375, 1097, 1067 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.37–7.17 (m, 5H), 4.49 (s, 2H), 4.03 (dd, *J*=9.6, 5.9 Hz, 1H), 3.21–3.09 (m, 1H), 2.94–2.73 (m, 4H), 2.27–2.01 (m, 2H), 1.99–1.73 (m, 2H), 1.63–1.41 (m, 3H), 0.95 (d, *J*=6.7 Hz, 3H), 0.93 (t, *J*=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.9, 128.1, 127.6, 127.2, 84.1, 71.3, 45.7, 38.2, 31.8, 30.3, 30.0, 25.9, 22.6, 15.2, 10.0; MS (FAB): *m/z* 310 (M^+); ESI-HRMS, *m/z* calcd for $C_{17}H_{27}OS_2$ (M^++H): 311.1503, found: 311.1512.

4.11. (R)-1-(2-((2S,3R)-3-(Benzyloxy)-2-methylpentyl)-1,3-dithian-2-yl)propan-2-ol (**15**)

To a stirred solution of dithiane **12** (4.1 g, 13.22 mmol) in dry THF (30 mL) at −40 °C under nitrogen atmosphere were added *n*-butyllithium (9.9 mL, 15.86 mmol, 1.6 M solution in hexane) and dry TMEDA (0.765 g, 6.61 mmol) successively. The reaction mixture was stirred for 1 h at −40 °C and then cooled to −78 °C, $BF_3\cdot OEt_2$ (0.83 mL, 6.61 mmol) was added to the reaction mixture, and stirring was continued for 15 min at −78 °C. Finally, a solution of (*R*)-propylene oxide **14** (2.78 mL, 39.6 mmol) in dry THF (10 mL) was added and after stirring the reaction mixture for 3 h at −78 °C, the reaction was quenched with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (2×25 mL). The combined organic extracts were washed with water and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by silica gel column chromatography using 20% ethyl acetate–hexane as eluent furnished the alcohol **15** (4.28 g, 88% yield) as a colorless viscous liquid; $[\alpha]_D^{25}$ −1.6 (*c* 1.05, $CHCl_3$); IR (Neat): ν_{max} 3446, 3029, 2963, 2929, 1452, 1370, 1275, 1065, 942, 739, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.17 (m, 5H), 4.56 (d, *J*=11.3 Hz, 1H), 4.48 (d, *J*=11.3 Hz, 1H), 4.14–4.0 (m, 1H), 3.46 (br s, 1H, −OH), 3.14–3.04 (m, 1H), 3.04–2.90 (m, 2H), 2.79–2.65 (m, 2H), 2.35 (dd, *J*=15.1, 9.8 Hz, 1H), 2.26–2.13 (m, 1H), 2.10–1.95 (m, 1H), 1.94–1.80 (m, 2H), 1.71 (dd, *J*=15.1, 6.8 Hz, 1H), 1.57–1.40 (m, 3H), 1.11 (d, *J*=6.8 Hz, 3H), 1.06 (d, *J*=6.8 Hz, 3H), 0.95 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 128.2, 128.0, 127.6, 127.2, 126.7, 84.9, 71.2, 64.5, 52.9, 46.9, 43.1, 31.0, 26.4, 26.0, 24.4, 23.5, 22.3, 17.4, 10.2; MS (FAB): *m/z* 368 (M^+); ESI-HRMS, *m/z* calcd for $C_{20}H_{33}O_2S_2$ (M^++H): 369.1921, found: 369.1931.

4.12. ((R)-1-(2-((2S,3R)-3-(Benzyloxy)-2-methylpentyl)-1,3-dithian-2-yl)propan-2-yloxy)-tert-butyldiphenylsilane (**16**)

To a stirred solution of alcohol **15** (4 g, 10.87 mmol), imidazole (2.152 g, 32.6 mmol), and DMAP (65 mg, 0.54 mmol) in dry CH_2Cl_2 (35 mL) at 0 °C under nitrogen atmosphere was added TBDPSCl (3.38 mL, 13 mmol) and stirred for 15 h allowing the mixture to warm to room temperature. The reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (2×25 mL). The combined organic layers were washed with brine (1×10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by silica gel column chromatography using 3% ethyl acetate–hexane as eluent afforded **16** (6.06 g, 90% yield) as a colorless viscous liquid; $[\alpha]_D^{25}$ +25.7 (*c* 1.45, $CHCl_3$); IR (Neat): ν_{max} 3067, 2961, 2932, 2857, 1456, 1426, 1373, 1107, 999, 738, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.78–7.62 (m, 4H), 7.42–7.14 (m, 11H), 4.57 (d, *J*=11.9 Hz, 1H), 4.42 (d, *J*=11.9 Hz, 1H), 4.21–4.05 (m, 1H), 3.15–3.03 (m, 1H), 2.69–2.48 (m, 4H), 2.36–2.20 (m, 2H), 2.06 (dd, *J*=14.8, 6.7 Hz, 1H), 1.87–1.70 (m, 3H), 1.56–1.23 (m, 3H), 1.16 (d, *J*=6.7 Hz, 3H), 1.03 (s, 9H), 0.97 (d, *J*=6.7 Hz, 3H), 0.90 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.2, 135.9, 134.8, 134.2, 129.4, 129.3, 128.1, 127.8, 127.4, 127.3, 127.2, 85.2, 71.2, 67.9, 53.3, 49.5, 43.5, 31.2, 27.0, 26.3, 25.5, 24.7, 23.3, 19.1, 16.9, 10.8; MS (FAB): *m/z* 607 (M^++H); ESI-HRMS, *m/z* calcd for $C_{36}H_{51}O_2SiS_2$ (M^++H): 607.3099, found: 607.3102.

4.13. (2S,6S,7S)-7-(Benzyloxy)-2-[1-(tert-butyl)-1,1-diphenylsilyl]oxy-6-methylnonan-4-one (**17**)

To a stirred solution of dithiane **16** (5.8 g, 9.57 mmol) in 40 mL $CH_3CN-CH_2Cl_2-H_2O$ (8:1:1) was added freshly prepared Dess–Martin periodinane (7.848 g, 19.14 mmol) in one portion. The reaction mixture was stirred at room temperature, exposed to air, for 2 h until complete consumption of starting material was observed by TLC. The reaction mixture was diluted with 50% aq $NaHCO_3$, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel column chromatography using 4% ethyl acetate–hexane as eluent furnished ketone **17** (4.197 g, 85% yield) as a pale yellowish liquid; $[\alpha]_D^{25}$ −1.2 (*c* 3.75, $CHCl_3$); IR (Neat): ν_{max} 3068, 2963, 2932, 2858, 1712, 1458, 1427, 1374, 1108, 993, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.70–7.61 (m, 4H), 7.42–7.30 (m, 6H), 7.30–7.16 (m, 5H), 4.47 (d, *J*=11.0 Hz, 1H), 4.41 (d, *J*=11.0 Hz, 1H), 4.31–4.23 (m, 1H), 3.09–3.01 (m, 1H), 2.56 (dd, *J*=15.4, 5.9 Hz, 1H), 2.40 (dd, *J*=16.2, 4.4 Hz, 1H), 2.35 (dd, *J*=16.2, 5.9 Hz, 1H), 2.29–2.20 (m, 1H), 2.14 (dd, *J*=16.2, 8.1 Hz, 1H), 1.54–1.40 (m, 2H), 1.05 (d, *J*=6.6 Hz, 3H), 1.01 (s, 9H), 0.90 (t, *J*=7.3 Hz, 3H), 0.84 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 135.7, 134.7, 134.3, 129.6, 129.5, 128.1, 127.6, 127.5, 127.4, 127.3, 83.8, 71.4, 66.3, 52.7, 47.1, 31.1, 26.9, 26.5, 23.6, 22.8, 19.1, 16.0, 9.5; MS (ESI): *m/z* 517 (M^++H); ESI-HRMS, *m/z* calcd for $C_{33}H_{45}O_3Si$ (M^++H): 517.3137, found: 517.3148.

4.14. (2S,4S,6S,7S)-7-(Benzyloxy)-2-[1-(tert-butyl)-1,1-diphenylsilyl]oxy-4,6-dimethylnonan-4-ol (**18a**)

To a freshly prepared methyllithium solution [prepared from methyl iodide (0.725 mL, 11.62 mmol) and lithium (0.054 g, 7.75 mmol)] in dry ether (25 mL) under nitrogen atmosphere at 0 °C, ketone **17** (4 g, 7.75 mmol) was added slowly. After the addition was complete, the mixture was allowed to stir at room temperature for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution (15 mL) and extracted with diethyl ether (2×40 mL). The organic extracts were washed with water (2×10 mL) and brine (1×10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica gel column chromatography using 5% ethyl acetate–hexane as eluent resulted in the alcohols **18a** and **18b** (3.546 g, 87% yield) in 65:35 ratio as colorless liquids; **18a**: $[\alpha]_D^{25}$ +2.89 (*c* 1.73, $CHCl_3$); IR (Neat): ν_{max} 3509, 3070, 2964, 2932, 2858, 1454, 1428, 1377, 1111, 1069, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.80–7.65 (m, 4H), 7.44–7.32 (m, 6H), 7.31–7.19 (m, 5H), 4.45 (s, 2H), 4.28–4.10 (m, 1H), 3.83 (br s, 1H, −OH), 3.07–2.95 (m, 1H), 2.04–1.88 (m, 1H), 1.77 (dd, *J*=14.8, 9.0 Hz, 1H), 1.60–1.37 (m, 5H), 1.10 (s, 3H), 1.01 (s, 9H), 0.96 (d, *J*=6.6 Hz, 3H), 0.95 (d, *J*=6.6 Hz, 3H), 0.90 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.0, 135.8, 135.7, 134.4, 133.3, 129.8, 129.5, 128.2, 127.7, 127.3, 85.8, 72.4, 71.5, 68.9, 50.5, 44.4, 31.0, 28.2, 26.9, 24.9, 22.5, 19.0, 17.2, 10.1; MS (ESI): *m/z* 533 (M^++H); ESI-HRMS, *m/z* calcd for $C_{34}H_{49}O_3Si$ (M^++H): 533.3450, found: 533.3444.

4.15. (2S,4R,6S,7S)-7-(Benzyloxy)-2-[1-(tert-butyl)-1,1-diphenylsilyl]oxy-4,6-dimethylnonan-4-ol (**18b**)

$[\alpha]_D^{25}$ −13.54 (*c* 4.34, $CHCl_3$); IR (Neat): ν_{max} 3446, 2961, 2923, 2853, 1462, 1378, 1108, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.80–7.69 (m, 4H), 7.46–7.33 (m, 6H), 7.32–7.15 (m, 5H), 4.48 (s, 2H), 4.28–4.13 (m, 1H), 3.87 (br s, 1H, −OH), 3.15–3.06 (m, 1H), 2.13–1.98 (m, 1H), 1.82 (dd, *J*=14.3, 9.0 Hz, 1H), 1.56–1.44 (m, 3H), 1.39 (dd, *J*=14.3, 3.7 Hz, 1H), 1.28–1.09 (m, 4H), 1.02 (s, 9H), 0.96 (d, *J*=6.8 Hz, 3H), 0.96 (d, *J*=6.8 Hz, 3H), 0.93 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 135.8, 135.7, 134.3, 133.1, 129.8, 129.5, 128.1, 127.7, 127.3, 85.5, 72.3, 71.3, 69.1, 49.7, 46.6, 30.2, 27.0, 26.8, 25.0, 22.2, 19.0, 17.4, 9.9; MS (ESI): *m/z* 533 (M^++H); ESI-HRMS, *m/z* calcd for $C_{34}H_{49}O_3Si$ (M^++H): 533.3450, found: 533.3452.

4.16. (2R,4R,6S,7R)-7-(Benzyloxy)-4,6-dimethylnonane-2,4-diol (**19a**)

To an ice-cooled solution of **18a** (1.6 g, 3.0 mmol) in dry THF (15 mL) was added a 1 M solution of TBAF in THF (6 mL, 6 mmol) and stirred for 4 h at room temperature. After completion of the reaction, water was added to the reaction mixture and extracted with ethyl acetate. The combined organic extracts were washed with water (1×5 mL) and brine (1×5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography using 20% ethyl acetate–hexane as eluent to afford the alcohol **19a** (0.78 g, 89% yield) as a colorless oil; $[\alpha]_D^{25}$ −15.3 (*c* 2.60, $CHCl_3$); IR (Neat): ν_{max} 3365, 2968, 2931, 2875, 1457, 1376, 1275, 1105, 1068, 922, 739, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.21 (m, 5H), 4.56 (d, *J*=11.3 Hz, 1H), 4.44 (d, *J*=11.3 Hz, 1H), 4.16–4.03 (m, 1H), 3.41 (br s, 1H, −OH), 3.05 (dd, *J*=10.5, 6.0 Hz, 1H), 2.01–1.89 (m, 1H), 1.74–1.37 (m, 5H), 1.37–1.19 (m, 1H), 1.15 (s, 3H), 1.10 (d, *J*=6.0 Hz, 3H), 0.99 (d, *J*=7.5 Hz, 3H), 0.94 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5, 128.3, 127.9, 127.5, 85.6, 73.4, 71.6, 65.3, 49.5, 44.1, 31.2, 30.2, 24.3, 22.4, 17.9, 9.3; MS (ESI): *m/z* 295 (M^++H); ESI-HRMS, *m/z* calcd for $C_{18}H_{30}O_3Na$ (M^++Na): 317.2092, found: 317.2102.

4.17. (2R,4S,6S,7R)-7-(Benzyloxy)-4,6-dimethylnonane-2,4-diol (**19b**)

In the same manner as described above for compound **19a**, TBDPS ether **18b** (1.1 g, 2.06 mmol) was converted into diol **19b** (0.547 g, 90% yield) as a colorless liquid; $[\alpha]_D^{25}$ −42.86 (*c* 3.34, $CHCl_3$); IR (Neat): ν_{max} 3377, 2967, 2931, 2875, 1458, 1375, 1065, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.23 (m, 5H), 4.62 (d, *J*=11.3 Hz, 1H), 4.38 (d, *J*=11.3 Hz, 1H), 4.20–4.06 (m, 1H), 3.11–3.02 (m, 1H), 2.05–1.88 (m, 1H), 1.87–1.72 (m, 1H), 1.68–1.41 (m, 3H), 1.31–1.19 (m,

2H), 1.16 (s, 3H), 1.11 (d, J=6.0 Hz, 3H), 0.93 (t, J=8.3 Hz, 3H), 0.92 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6, 128.4, 128.2, 127.8, 85.1, 72.7, 71.5, 64.8, 50.3, 48.9, 29.9, 25.1, 23.9, 22.0, 19.2, 7.8; MS (ESI): *m/z* 295 (M^++H); ESI-HRMS, *m/z* calcd for $C_{18}H_{30}O_3Na$ (M^++Na): 317.2092, found: 317.2094.

*4.18. (4R,6R)-4-((2S,3R)-3-(Benzyloxy)-2-methylpentyl)-2,2,4,6-tetramethyl-1,3-dioxane (**20a**)*

To a stirred solution of diol **19a** (0.720 g, 2.45 mmol) and 2,2-dimethoxy propane (0.36 mL, 2.93 mmol) in dry CH_2Cl_2 at 0 °C, freshly recrystallized *para*-toulenesulfonic acid (23 mg, 0.12 mmol) was added. The reaction mixture was warmed to room temperature, stirred for 2 h, and neutralized with $NaHCO_3$. The organic layer was washed with water (1×5 mL) and brine (1×5 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification by silica gel column chromatography using 7% ethyl acetate–hexane as eluent afforded acetonide **20a** (0.71 g, 87% yield) as a colorless liquid; $[\alpha]_D^{25}$ +3.83 (*c* 1.82, $CHCl_3$); IR (Neat): ν_{max} 2971, 2934, 2874, 1457, 1374, 1195, 1097, 1067, 974, 738, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.17 (m, 5H), 4.47 (s, 2H), 3.93–3.80 (m, 1H), 3.12–3.04 (m, 1H), 1.91–1.77 (m, 1H), 1.71–1.56 (m, 2H), 1.56–1.39 (m, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 1.31–1.23 (m, 1H), 1.21 (s, 3H), 1.05 (d, J=6.0 Hz, 3H), 0.96 (d, J=6.8 Hz, 3H), 0.93 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1, 128.2, 127.7, 127.3, 98.6, 85.3, 73.8, 71.5, 61.9, 44.3, 42.3, 31.6, 31.2, 30.2, 26.5, 22.3, 22.2, 17.1, 10.0; MS (ESI): *m/z* 357 (M^++Na); ESI-HRMS, *m/z* calcd for $C_{21}H_{34}O_3Na$ (M^++Na): 357.2405, found: 357.2402.

*4.19. (4S,6R)-4-((2S,3R)-3-(Benzyloxy)-2-methylpentyl)-2,2,4,6-tetramethyl-1,3-dioxane (**20b**)*

In the same manner as described above for compound **20a**, diol **19b** (0.5 g, 1.70 mmol) was converted into acetonide **20b** (0.505 g, 89% yield) as a colorless liquid (SiO_2, 6% ethyl acetate–hexane as eluent); $[\alpha]_D^{25}$ +25.2 (*c* 0.61, $CHCl_3$); IR (Neat): ν_{max} 2969, 2933, 2874, 1457, 1375, 1196, 1091, 1004 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.17 (m, 5H), 4.54 (d, J=11.3 Hz, 1H), 4.46 (d, J=11.3 Hz, 1H), 4.10–3.96 (m, 1H), 3.25–3.16 (m, 1H), 2.15–1.98 (m, 1H), 1.55–1.42 (m, 3H), 1.41 (s, 3H), 1.37–1.29 (m, 1H), 1.29 (s, 3H), 1.28 (s, 3H), 1.26–1.18 (m, 2H), 1.16 (d, J=6.0 Hz, 3H), 0.94 (d, J=6.8 Hz, 3H), 0.92 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.3, 128.1, 127.6, 127.2, 98.0, 85.0, 73.1, 71.2, 61.4, 48.6, 41.8, 31.8, 30.0, 26.6, 24.8, 22.1, 22.0, 16.7, 10.7; MS (ESI): *m/z* 335 (M^++H); ESI-HRMS, *m/z* calcd for $C_{21}H_{34}O_3Na$ (M^++Na): 357.2405; found: 357.2399.

*4.20. (2S,3R)-2-Methyl-1-((4R,6R)-2,2,4,6-tetramethyl-1,3-dioxan-4-yl)pentan-3-ol (**21a**)*

To a magnetically stirred solution of lithium (0.054 g, 8.98 mmol) in liq. NH_3 (15 mL) was added compound **20a** (0.6 g, 1.79 mmol) in dry THF (5 mL) at −33 °C. The reaction mixture was stirred for 1 h at the same temperature and quenched with solid NH_4Cl till the blue color disappears. Ammonia was allowed to evaporate and the residual mixture was taken in CH_2Cl_2 (20 mL), washed with water (2×10 mL) and brine (1×10 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by silica gel column chromatography using 22% ethyl acetate–hexane as eluent afforded the alcohol **21a** (0.394 g, 90% yield) as a colorless liquid; $[\alpha]_D^{25}$ −19.24 (*c* 1.89, $CHCl_3$); IR (Neat): ν_{max} 3415, 2931, 1458, 1376, 1219, 974, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.04–3.91 (m, 1H), 3.24–3.09 (m, 1H), 1.91–1.80 (m, 2H), 1.70–1.49 (m, 3H), 1.40 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 1.33–1.28 (m, 1H), 1.28–1.23 (m, 1H), 1.20 (d, J=6.8 Hz, 3H), 0.94 (t, J=7.5 Hz, 3H), 0.93 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 99.5, 77.7, 73.6, 62.7, 47.2, 41.0, 34.2, 31.1, 30.7, 27.0, 26.0, 22.5, 19.5, 9.3; MS (ESI): *m/z* 245 (M^++H); ESI-HRMS, *m/z* calcd for $C_{14}H_{29}O_3$ (M^++H): 245.2116, found: 245.2110.

*4.21. (2S,3R)-2-Methyl-1-((4S,6R)-2,2,4,6-tetramethyl-1,3-dioxan-4-yl)pentan-3-ol (**21b**)*

In the same manner as described above for compound **21a**, acetonide **20b** (0.4 g, 1.19 mmol) was converted into alcohol **21b** (0.257 g, 88% yield) as a colorless liquid (SiO_2, 20% ethyl acetate–hexane as eluent); $[\alpha]_D^{25}$ +6.65 (*c* 1.95, $CHCl_3$); IR (Neat); ν_{max} 3415, 1637, 1618, 1352, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.14–4.01 (m, 1H), 3.85 (br s, 1H, –OH), 3.18–3.09 (m, 1H), 1.83–1.68 (m, 1H), 1.68–1.52 (m, 1H), 1.46 (s, 3H), 1.37 (s, 6H), 1.36–1.23 (m, 5H), 1.18 (d, J=6.0 Hz, 3H), 0.95 (t, J=7.3 Hz, 3H), 0.89 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.7, 77.7, 73.2, 61.5, 52.5, 43.4, 34.1, 31.7, 27.1, 25.0, 24.6, 22.0, 19.9, 9.4; MS (ESI): *m/z* 245 (M^++H); ESI-HRMS, *m/z* calcd for $C_{14}H_{29}O_3$ (M^++H): 245.2116, found: 245.2107.

*4.22. (S)-2-Methyl-1-((4R,6R)-2,2,4,6-tetramethyl-1,3-dioxan-4-yl)pentan-3-one (**22a**)*

To a stirred solution of **21a** (0.2 g, 0.82 mmol) in ethyl acetate/toluene mixture (1:1, 2 mL) were added sodium bromide (0.084 g, 0.82 mmol), water (0.3 mL), and TEMPO free radical (2.5 mg, 0.016 mmol) at 0 °C successively. $NaHCO_3$ (0.193 g, 2.29 mmol) dissolved in NaOCl solution (1.46 mL, 0.90 mmol, 4% aqueous solution) was added slowly to the above reaction mixture at 0 °C. After completion of the reaction, the resultant ketone was washed with an aqueous solution of KI (5 mg), 10% $KHSO_4$ (2 mL), and 10% hypo (2 mL) followed by water. The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography using 5% ethyl acetate–hexane as eluent furnished **22a** (0.182 g, 92% yield) as a light yellow oil; $[\alpha]_D^{25}$ +15.15 (*c* 1.13, $CHCl_3$); IR (Neat): ν_{max} 2974, 2934, 1715, 1375, 1196, 1003, 975 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.03–3.91 (m, 1H), 2.84–2.71 (m, 1H), 2.66–2.38 (m, 2H), 2.12 (dd, J=14.3, 9.0 Hz, 1H), 1.62–1.4 (m, 2H), 1.40 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.32–1.21 (m, 1H), 1.15 (d, J=6.0 Hz, 3H), 1.06 (d,

J=7.5 Hz, 3H), 1.05 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.5, 72.4, 61.8, 43.4, 42.9, 41.6, 34.3, 31.6, 30.8, 29.6, 25.4, 22.2, 19.5, 7.8; MS (ESI): m/z 242 (M^+); ESI-HRMS, m/z calcd for $C_{14}H_{29}O_3$ (M^++H): 243.1960, found: 243.1967.

4.23. (S)-2-Methyl-1-((4S,6R)-2,2,4,6-tetramethyl-1,3-dioxan-4-yl)pentan-3-one (**22b**)

In the same manner as described above for compound **22a**, alcohol **21b** (0.090 g, 0.37 mmol) was converted to ketone **22b** (0.08 g, 91% yield) as a light yellow liquid (SiO_2, 4% ethyl acetate–hexane as eluent); $[\alpha]_D^{25}$ +16.9 (c 1.18, $CHCl_3$); IR (Neat): ν_{max} 2975, 2937, 1715, 1375, 1195, 1006, 971 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.07–3.94 (m, 1H), 2.85–2.71 (m, 1H), 2.51 (dd, J=14.3, 6.8 Hz, 2H), 2.01 (dd, J=14.3, 9.0 Hz, 1H), 1.42–1.37 (m, 4H), 1.31 (s, 3H), 1.29–1.22 (m, 4H), 1.22–1.16 (m, 1H), 1.14 (d, J=6.0 Hz, 3H), 1.05 (d, J=6.8 Hz, 3H), 1.03 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.0, 72.1, 61.3, 49.1, 47.7, 41.9, 41.0, 33.8, 31.4, 26.0, 24.6, 21.9, 19.0, 7.5; MS (ESI): m/z 243 (M^++H); ESI-HRMS, m/z calcd for $C_{14}H_{29}O_3$ (M^++H): 243.1960, found: 243.1957.

4.24. (1S,3R,5R,7S)-(+)-Sordidin (**1a**)

To a stirred solution of **22a** (0.04 g, 0.164 mmol) in n-pentane (20 mL) at 0 °C was added saturated aqueous oxalic acid (0.7 mL) in a duration of 20 min time. After stirring the reaction mixture for 48 h at the same temperature (completion of the reaction monitored by TLC), the mixture was neutralized by the addition of saturated $NaHCO_3$ and extracted with diethyl ether (3×5 mL). The combined organic extracts were washed with water (1×5 mL) and brine (1×5 mL), and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure at 0–2 °C and purification over neutral alumina column chromatography using 2% diethyl ether–n-pentane as eluent afforded **1a** (18 mg, 62% yield) as a colorless liquid; $[\alpha]_D^{25}$ +24.61 (c 0.25, Et_2O); IR (Neat): ν_{max} 2971, 2928, 1459, 1377, 1250, 1194, 1131, 1099, 1047, 1003, 940, 911 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.97–3.88 (m, 1H), 2.34–2.26 (m, 1H), 2.13 (dd, J=13.0, 9.2 Hz, 1H), 1.73–1.64 (m, 1H), 1.63–1.54 (m, 1H), 1.39–1.20 (m, 2H), 1.29 (s, 3H), 1.19–1.16 (m, 1H), 1.15 (d, J=6.1 Hz, 3H), 0.97 (d, J=6.9 Hz, 3H), 0.97 (t, J=7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 108.6, 78.8, 64.5, 44.9, 44.1, 40.0, 27.3, 26.4, 21.8, 19.8, 7.9; MS (ESI): m/z 202 (M^++NH_4); ESI-HRMS, m/z calcd for $C_{11}H_{21}O_2$ (M^++H): 185.1541, found: 185.1535.

4.25. (1S,3R,5S,7R/S)-(±)-Sordidin (**1b**)

In the same manner as described above for compound **1a**, ketone **22b** (0.05 g, 0.206 mmol) was converted into **1b** (22.8 mg, 60%) as a colorless liquid (neutral Al_2O_3, 2% ether–n-pentane as eluent); IR (Neat): ν_{max} 2971, 2929, 1457, 1376, 1255, 1172, 1106, 1076, 1041, 997, 947, 916 cm^{-1}; ^{1}H NMR (300 MHz): δ 4.03–3.85 (m, 1H), 2.36–2.12 (m, 1H), 2.0–1.88 (m, 1H), 1.83–1.70 (m, 1H), 1.69–1.50 (m, 1H), 1.50–1.37 (m, 2H), 1.36 (s, 3H), 1.24–1.18 (m, 1H), 1.16 (d, J=6.0 Hz, 3H), 1.01 (d, J=6.0 Hz, 3H), 0.99 (t, J=7.5 Hz, 3H); MS (ESI): m/z 185 (M^++H).

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