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Asymmetric synthesis of both enantiomers of α-methyl-α-methoxyphenylacetic acid from L-(+)-tartaric acid: formal enantioselective synthesis of insect pheromone (−)-frontalin

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Abstract—Both antipodes of α-methyl-α-methoxyarylacetic acid derivatives were prepared from a common chiralpool precursor L-(+)-tartaric acid. The key step involves the addition of Grignard reagents to 1,4-diketones derived from tartaric acid. The utility of this strategy was applied in the formal enantioselective synthesis of pine beetle pheromone (−)-frontalin.

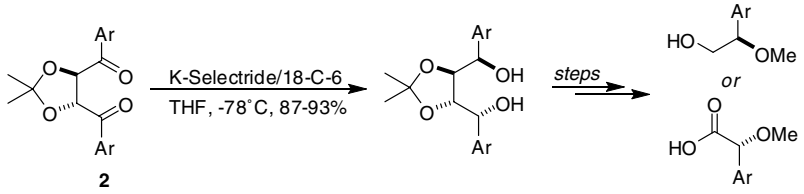
1. Introduction

The construction of chiral building blocks containing a quaternary center is a continuing synthetic challenge in organic chemistry.[1] Synthesis of these compounds from chiral pool precursors is of great advantage because of the low cost and rich source of chirality associated with the chiral pool compounds. It would be even more rewarding to synthesize both antipodes of the chiral quaternary compounds from a single abundant chiral source, thus avoiding the use of unnatural sources. As part of our interest in the synthesis of chiral building blocks from tartaric acid,[2] we herein report the synthesis of α-alkyl-α-methoxyarylacetic acid derivatives in both enantiomeric forms starting from single chiral precursor, that is, L-(+)-tartaric acid. In addition, the utility of this methodology was applied in the synthesis of pine beetle pheromone (−)-frontalin.

2. Results and discussion

We have recently reported the synthesis of α-methoxyarylacetic acids starting from tartaric acid.[3] The synthesis involves the stereoselective reduction of 1,4-diketone, and elaboration of the 1,4-diol to the α-methoxyarylacetic acid derivatives (Scheme 1).

In continuation of our efforts in the extension of this strategy, we envisaged the synthesis of α-methoxyarylacetic acids containing quaternary centers from C_2-symmetric 1,4-diols **4** and **6** containing 1,4-quaternary centers. As shown in the retrosynthesis (Scheme 2), the synthesis of both enantiomers of the α-alkyl, α-methoxyarylacetic acid was envisaged from the corresponding diastereomerically different diols **4a** and **4b** and **6a** and **6b**. It was intended to perform the addition of alkyl Grignard reagents to the 1,4-diphenyldiketone **2** leading to the C_2-symmetric diols



Scheme 1. Asymmetric synthesis of α-methoxyarylacetic acid derivatives.

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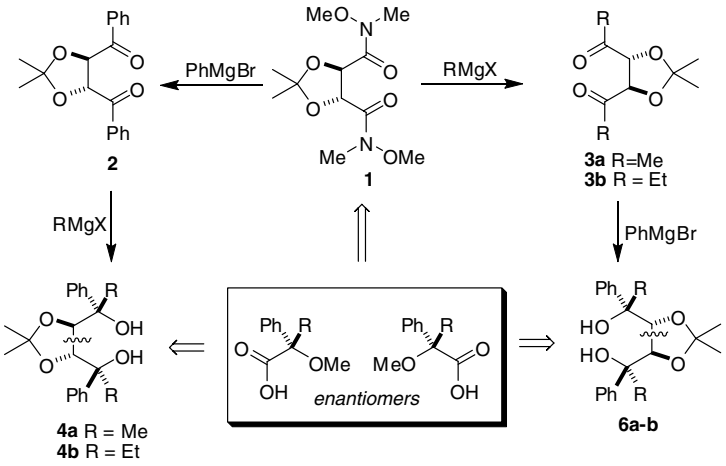


Scheme 2. Retrosynthesis for the synthesis of both antipodes of α-alkyl-α-methoxyarylacetic acids.

4a and **4b**, while, the addition of PhMgBr to diketones **3a** and **3b** leads to the other C_2-symmetric diastereomer **6a** and **6b**.

1,4-Diones **2**, **3a**, and **3b** were synthesized by the addition of Grignard reagents to the bis-Weinreb amide **1** of tartaric acid.[4] Under the conditions previously optimized by us[5] for the nucleophilic addition reactions to diketones **2** and **3**, addition of methylmagnesium bromide and ethylmagnesium bromide to ketone **2** resulted in the formation of diastereomeric alcohols **4a** and **5a** in 84:16 and **4b** and **5b** in 75:25 ratios, respectively. While ether solvents favored higher diastereoselectivity in the addition of MeMgBr to diketone **2**, non-ether solvents, such as dichloromethane, were found to be better for the addition of EtMgBr. The diastereomeric alcohols **4a** and **5a** were separable by column chromatography, while alcohols **4b** and **5b** were inseparable and were isolated as their corresponding methyl ethers. To synthesize the other C_2-symmetric diastereomers **6a** and **6b**, addition of PhMgBr to alkyl diketones **3a** and **3b** was envisaged. Addition of PhMgBr to diketone **3a** proceeded with high diastereoselectivity leading to alcohols **5a**:**6a** in 5:95 ratio, while addition to diketone **3b** led to alcohols **5b**:**6b** in 25:75 ratio (Table 1, Scheme 3).

Protection of alcohols **4a** and **4b** as their methyl ethers **7a** and **7b** was performed under standard conditions using NaH/MeI in DMF. Deprotection of the acetonide[6] was achieved to yield diols **8a** and **8b**, which underwent smooth reaction with $Pb(OAc)_4$ to afford the aldehydes, which were oxidized to the corresponding acids **11a** $[\alpha]_D = -39$ (*c* 1, MeOH) {lit.[7a] $[\alpha]_D = -26$ (*c* 1, MeOH) lit.[7b] $[\alpha]_D = +37.6$ (*c* 8.8, MeOH) for 97% ee of the enantiomer} and **11b** $[\alpha]_D = +52$ (*c* 1, $CHCl_3$). The enantiomeric purity of acid **11b** was found to be >95% as determined by the ^1H NMR of the corresponding menthyl ester within detectable limits.[8] Performing the same transformations on the diastereomeric alcohol **6a** afforded the enantiomer of *ent*-**11a** $[\alpha]_D = +38$ (*c* 1, MeOH) (Scheme 4).[9]

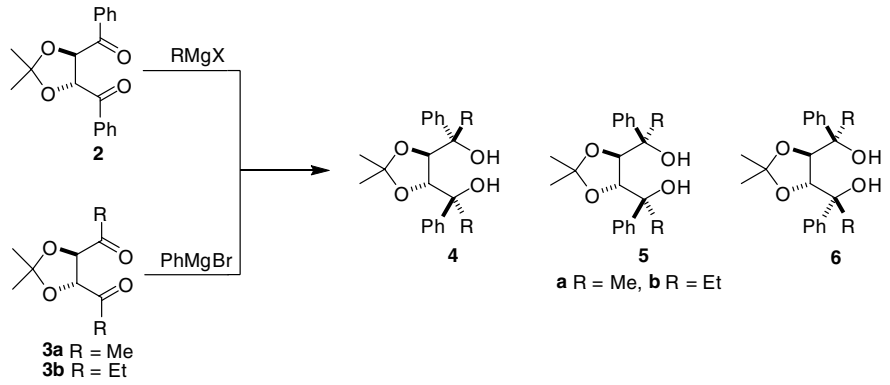
To demonstrate the synthetic utility of this methodology, the synthesis of pine beetle pheromone (−)-frontalin **16**[10] was undertaken. The pheromone frontalin **16** is an aggregation pheromone produced by *Dendroctonus brevicomis*, the western pine beetle, which is a significant pest in the timber regions of the west coast of North America. It was anticipated to synthesize quaternary alcohol **15**, a key intermediate in the synthesis of frontalin from the C_2-symmetric tertiary alcohol **13**, which in turn can be obtained by the addition of MeMgBr to diketone **12**. Diketone **12**[11] was prepared by the addition of 4-pentenylmagnesium bromide to the bis-Weinreb amide **1** derived from tartaric acid (Scheme 5).

Thus, the addition of 4-pentenylmagnesium bromide to bis-Weinreb amide **1** derived from L-(+)-tartaric acid resulted in diketone **12** in 96% yield. The reaction of diketone **12** with MeMgBr in the presence of $MgBr_2{\cdot}OEt_2$ in dichloromethane afforded C_2-symmetric alcohol **13** in 74% yield, along with 20% of C_1-symmetric isomer. Tertiary alcohol **13** was protected as its benzyl ether, which without further purification was treated with $FeCl_3{\cdot}6H_2O$ to yield diol **14** in 40% yield for two steps. Cleavage of the 1,2-diol unit in **14** to the corresponding aldehyde was effected with $Pb(OAc)_4$ and the resultant aldehyde was reduced with $NaBH_4$ to yield alcohol **15** $[\alpha]_D = -4.1$ (*c* 1.1, $CHCl_3$); lit.[12]

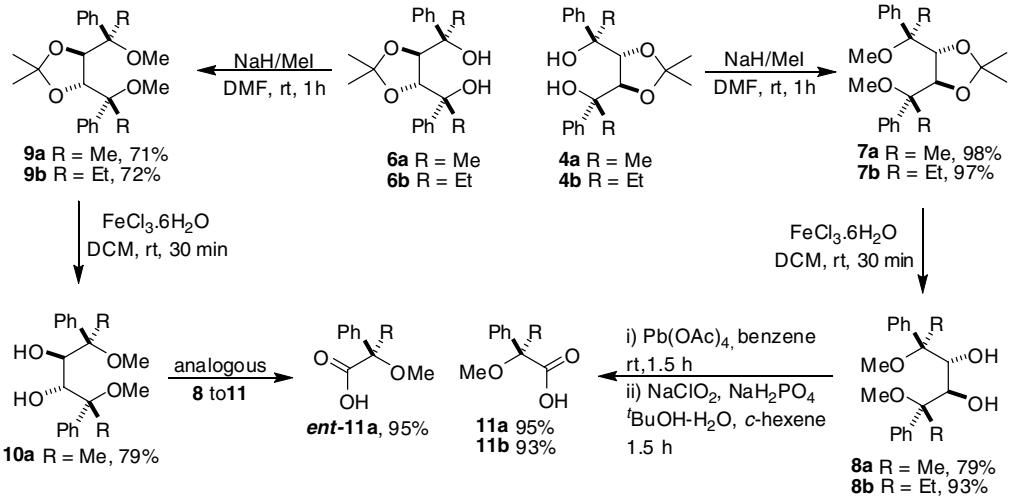
Table 1. Addition of RMgX to 1,4-diketones **2**, **3a**, and **3b** derived from tartaric acid

S. no.	Ketone	RMgX	Solvent	Temperature (°C)	dr (**4**:**5**:**6**)			Yield (%)
1	**2**	MeMgBr	Ether	0	84	16	0	76[a]
2	**2**	EtMgBr	DCM	0	75	25	0	72[b]
3	**3a**	PhMgBr	THF	−78	**0**	**5**	**95**	81[a]
4	**3b**	PhMgBr	THF	−78	0	25	75	71[b]

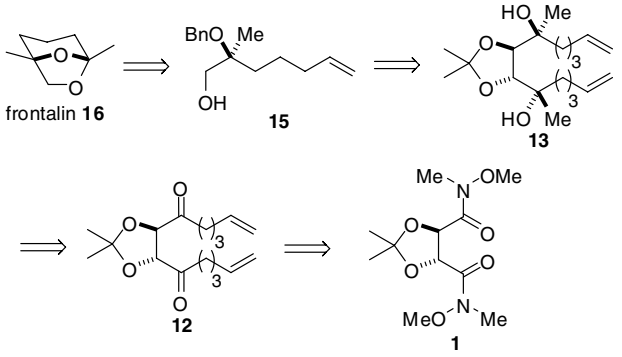
[a] Isolated yield of the major diastereomer.
[b] Isolated as the corresponding dimethyl ether.



Scheme 3. Addition of Grignard reagents to 1,4-diketones derived from tartaric acid.



Scheme 4. Synthesis of both enantiomers of α-alkyl-α-methoxyaryl acetic acids.



Scheme 5. Retrosynthesis for the synthesis of (−)-frontalin.

$[\alpha]_D = -3.6$ (c 1, $CHCl_3$) in 90% yield for two steps (Scheme 6). Conversion of **15** to frontalin is known in the literature[12] using Wacker oxidation and deprotection of the benzyl group. Thus the present sequence constitutes a formal synthesis of (−)-frontalin.

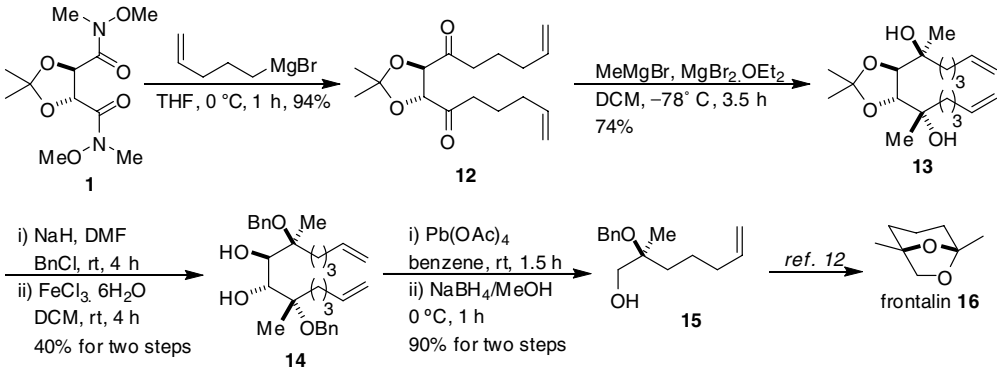
3. Conclusion

In conclusion, an enantioselective approach to both enantiomers of α-alkyl-α-methoxyarylacetic acid derivatives was described from L-(+)-tartaric acid. Key steps include the stereoselective addition of Grignard reagents to 1,4-diketones derived from tartaric acid. Application of these building blocks containing a quaternary carbon center was illustrated in the synthesis of pine beetle pheromone frontalin.

4. Experimental

4.1. General procedures

Column chromatography was performed on silica gel, Acme grade 100–200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray, unless noted otherwise. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points were uncorrected. Unless stated otherwise, all the reactions were performed under inert atmosphere. Compounds **2**, **3a**,**b** were prepared according to the literature procedure.[4b] Preparation of 1,4-diols **4a**,**b** and **6a**,**b** was achieved according to the procedure reported.[5]



Scheme 6. Stereoselective synthesis of (−)-frontalin.

4.2. General procedure for the preparation of 4,5-bis-(1-methoxy-1-phenylalkyl)-2,2-dimethyl-1,3-dioxolanes 7a and 7b, and 9a and 9b

In an oven dried two-neck round-bottom flask equipped with a magnetic stir bar, guard tube and a stopper was placed α,α′,2,2-dialkyl-α,α′-diphenyl-1,3-dioxolane-4,5-dimethanol **4a** or **4b**, **6a** or **6b** (0.5 mmol). This was dissolved in 2 mL of DMF. It was cooled to 0 °C and NaH (0.076 g, 2 mmol, 60% suspension in oil) was introduced portionwise. The reaction mixture was stirred for 1 h at the same temperature and CH_3I (0.2 mL, 3.2 mmol) was added dropwise. The reaction mixture was slowly warmed up to room temperature over the course of 1 h. After the reaction was complete (monitored by TLC), it was cautiously quenched with saturated solution of NH_4Cl and extracted with diethyl ether (3 × 10 mL). The combined ether extract was washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. Silica gel chromatography of the residue yielded 4,5-bis(1-methoxy-1-phenylalkyl)-2,2-dimethyl-1,3-dioxolanes **7** and **9**.

4.2.1. (4*R*,5*R*)-4,5-Bis((*S*)-1-methoxy-1-phenylethyl)-2,2-dimethyl-1,3-dioxolane 7a. Colorless oil, yield 97%; $[\alpha]_D = +25.7$ (*c* 0.7, $CHCl_3$); IR (neat): 3086, 2981, 1494, 1445, 1240, 1160, 1076, 868 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.17–7.06 (m, 10H), 4.31 (s, 2H), 3.01 (s, 6H), 1.44 (s, 6H), 1.38 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.7, 127.9, 126.8, 111.7, 85.0, 50.0, 28.0, 19.5; HRMS for $C_{23}H_{30}O_4$+Na calcd 393.2042; found 393.2054.

4.2.2. (4*R*,5*R*)-4,5-Bis((*R*)-1-methoxy-1-phenylethyl)-2,2-dimethyl-1,3-dioxolane 9a. Colorless oil, yield 98%; $[\alpha]_D = -80$ (*c* 0.5, $CHCl_3$); IR (neat): 2983, 1445, 1376, 1241, 1164, 1103, 1074, 863, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.22 (m, 10H), 4.18 (s, 2H), 3.05 (s, 6H), 1.32 (s, 6H), 1.26 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.6, 128.0, 127.8, 127.2, 111.6, 85.5, 80.4, 50.3, 28.0, 19.4; HRMS for $C_{23}H_{30}O_4$+Na calcd 393.2042; found 393.2045.

4.2.3. (4*R*,5*R*)-4,5-Bis((*S*)-1-methoxy-1-phenylpropyl)-2,2-dimethyl-1,3-dioxolane 7b. Colorless oil, yield 71%; $[\alpha]_D = -38$ (*c* 0.5, $CHCl_3$); IR (neat): 2981, 1446, 1377, 1242, 1213, 1079 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.21 (m, 10H), 4.33 (s, 2H), 3.24 (s, 6H), 1.83–1.71 (m, 2H), 1.57–1.44 (m, 2H), 1.08 (s, 6H), 0.72 (t, 6H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.6, 127.9, 127.6, 126.9, 109.2, 83.2, 81.8, 50.5, 27.6, 24.9, 8.3; HRMS for $C_{25}H_{34}O_4$+Na calcd 421.2355; found 421.2356.

4.2.4. (4*R*,5*R*)-4,5-Bis((*R*)-1-methoxy-1-phenylpropyl)-2,2-dimethyl-1,3-dioxolane 9b. Colorless oil, yield 72%; $[\alpha]_D = -32.5$ (*c* 1.2, $CHCl_3$); IR (neat): 2935, 1493, 1446, 1219, 1082, 887, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41–7.19 (m, 10H), 4.03 (s, 2H), 3.20 (s, 6H), 2.29–2.16 (m, 2H), 2.03–1.89 (m, 2H), 0.89 (t, 6H, $J = 7.2$ Hz), 0.80 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.0, 128.7, 127.2, 126.7, 107.7, 81.6, 79.5, 50.4, 27.3, 26.2, 7.4; HRMS for $C_{25}H_{34}O_4$+Na calcd 421.2355; found 421.2334.

4.2.5. General procedure for the preparation of 1,4-dimethoxy-1,4-diphenyl-1,4-dialkylbutane-2,3-diol. In a single-neck round-bottom flask equipped with a magnetic stirrer bar and a guard tube was placed a solution of 4,5-bis-(1-methoxy-1-phenylalkyl)-2,2-dimethyl-1,3-dioxolane **7** and **9** (0.4 mmol) in CH_2Cl_2 (5 mL). $FeCl_3{\cdot}6H_2O$ (0.38 g, 1.4 mmol) was introduced into the flask at room temperature. The resulting yellow colored suspension was stirred for 30 min and after the reaction was complete (monitored by TLC), it was quenched by the addition of saturated solution of $NaHCO_3$. The aqueous layer was extracted with diethyl ether (3 × 10 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Silica gel column chromatography of the residue afforded 1,4-dimethoxy-1,4-diphenyl-1,4-dialkylbutane-2,3-diol (**8** and **10**).

4.2.6. (2*S*,3*R*,4*R*,5*S*)-2,5-Dimethoxy-2,5-diphenylhexane-3,4-diol 8a. White solid, yield 79%; mp 104.6–105.6 °C; $[\alpha]_D = +70$ (*c* 0.5, $CHCl_3$); IR (neat): 3492, 2941, 1494, 1445, 1372, 1163, 1073, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.25–7.06 (m, 10H), 3.62 (d, 2H, $J = 3.6$ Hz), 3.47 (d, 2H, $J = 3.6$ Hz), 3.20 (s, 6H), 1.55 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.4, 128.1, 126.8, 126.2, 83.2, 74.8, 51.1, 19.5. Anal. Calcd for C, 72.70; H, 7.93. Found C, 72.79; H, 8.00.

4.2.7. (2*R*,3*R*,4*R*,5*R*)-2,5-Dimethoxy-2,5-diphenylhexane-3,4-diol 10a. Viscous mass, yield 79%; $[\alpha]_D = -48$ (*c* 0.5, $CHCl_3$); IR (neat): 3463, 2936, 1558, 1541, 1457, 1373, 1159, 1103, 1071, 761, 700 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$): δ 7.19–7.04 (m, 10H), 3.51 (d, 2H, $J = 3.9$ Hz), 3.03 (d, 2H, $J = 3.9$ Hz), 2.94 (s, 6H), 1.54 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.9, 128.1, 127.2, 127.1, 82.1, 74.5, 50.0, 16.1; HRMS for $C_{20}H_{26}O_4$+Na calcd 353.1729; found 353.1738.

4.2.8. (2*S*,3*R*,4*R*,5*S*)-3,6-Dimethoxy-3,6-diphenyloctane-4,5-diol 8b. Viscous mass, yield 93%; $[\alpha]_D = -16.3$ (*c* 0.8, $CHCl_3$); IR (neat): 3467, 2974, 1446, 1155, 1055, 758, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.29–7.07 (m, 10H), 3.82 (d, 2H, $J = 1.8$ Hz), 3.56 (d, 2H, $J = 1.8$ Hz), 3.54 (s, 6H), 2.49–2.31 (m, 2H), 1.68–1.56 (m, 2H), 0.53 (t, 6H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.6, 128.0, 126.6, 126.2, 84.6, 75.9, 52.8, 25.3, 7.7; HRMS for $C_{22}H_{30}O_4$+Na calcd 381.2042; found 381.2029.

4.2.9. General procedure for the preparation of 2-methoxy-2-phenylalkanoic acid. To a solution of diol **8a** or **10a** or **10b** (0.21 mmol) in 2 mL of benzene at room temperature was added $Pb(OAc)_4$ (0.23 g, 0.52 mmol) under argon atmosphere. The reaction mixture was stirred for 1.5 h at the same temperature and filtered through a short pad of Celite. The Celite pad was washed with ether (15 mL) and the ether layers were combined. After removal of the solvent, the crude residue of the aldehyde was subjected to oxidation without further purification.

A solution of the crude aldehyde (obtained above) dissolved in cyclohexene (1.2 mL) and *tert*-BuOH (12 mL) was added to a solution of $NaClO_2$ (0.15 g, 1.7 mmol) and NaH_2PO_4 (0.20 g, 1.7 mmol) in water (6 mL). The resultant solution was stirred for 3.5 h at room temperature. It was extracted with ethyl acetate (3×10 mL) and the combined extracts were dried over Na_2SO_4, filtered, and concentrated to yield the acid. An analytically pure sample was obtained by $NaHCO_3$ extraction of an organic layer of the crude acid and acidification of the bicarbonate layer and extraction with ethylacetate.

4.2.10. (*S*)-2-Methoxy-2-phenylpropanoic acid 11a. Viscous mass, yield 95% for two steps; $[\alpha]_D = +38$ (*c* 1, MeOH); IR (neat): 3693–3065 (br), 2925, 1726, 1495, 1455, 1104, 989, 721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.49–7.30 (m, 5H), 6.52 (br s, 1H), 3.27 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.7, 138.9, 128.6, 128.4, 126.2, 81.3, 51.7, 20.7; HRMS for $C_{10}H_{12}O_3$+Na calcd 203.0684; found 203.0687.

4.2.11. (*R*)-2-Methoxy-2-phenylpropanoic acid *ent*-11a. Viscous mass, yield 95% for two steps; $[\alpha]_D = -39$ (*c* 1, MeOH) {lit.[7a] $[\alpha]_D = +37.6$ (*c* 8.8, MeOH) for 97% ee of the enantiomer lit.[7b] $[\alpha]_D = -26$ (*c* 1, MeOH)}; IR (neat): 3693–3065 (br), 2942, 1719, 1495, 1447, 1144, 1074, 1046, 721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.49–7.30 (m, 5H), 6.52 (br s, 1H), 3.27 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.8, 138.9, 128.6, 128.4, 126.2, 81.3, 51.7, 20.7; HRMS for $C_{10}H_{12}O_3$+Na calcd 203.0684; found 203.0687.

4.2.12. (*S*)-2-Methoxy-2-phenylbutanoic acid 11b. Viscous mass, yield 93% for two steps; $[\alpha]_D = +52$ (*c* 1, $CHCl_3$); IR (neat): 3222, 2952, 1718, 1448, 1145, 1058, 721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.48–7.30 (m, 5H), 3.20 (s, 3H), 2.56–2.44 (m, 1H), 2.23–2.10 (m, 1H), 0.94 (t, 6H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5, 137.9, 128.6, 128.5, 126.5, 84.5, 51.0, 25.0, 7.4.

4.2.13. Preparation of (4*R*,5*R*)-4,5-bis(hex-5-enoyl)-2,2-dimethyl-1,3-dioxolane 12. In an oven dried two neck 50 mL round-bottom flask equipped with a magnetic stir bar and an argon inlet was placed the bis-Weinreb amide **1** (0.5 g, 1.8 mmol) dissolved in 6 mL of THF. This was cooled to 0 °C and a THF solution of 4-pentenylmagnesium bromide (7 mL of 1 M solution in THF, 7 mmol) was added dropwise under an argon atmosphere. The reaction was stirred for 1 h, quenched with satd NH_4Cl (10 mL) and extracted with ether (2×10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The residue obtained after the evaporation of solvent was purified by column chromatography to yield **12** in 96% (0.51 g) as a colorless oil. $[\alpha]_D = +11.6$ (*c* 1.2, $CHCl_3$); IR (neat): 2937, 1725, 1455, 1375, 1259, 1153, 995, 914, 860 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.77 (ddt, 2H, $J = 17.1$, 10.2, 6.6 Hz), 5.06–4.96 (m, 4H), 4.55 (s, 2H), 2.75–2.56 (m, 4H), 2.12–2.05 (m, 4H), 1.77–1.67 (m, 4H), 1.42 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.4, 137.8, 115.3, 112.4, 81.4, 38.2, 32.9, 26.1, 22.1; HRMS for $C_{17}H_{26}O_4$+Na calcd 317.1729; found 317.1742.

4.2.14. Preparation of (4*R*,5*R*)-4,5-bis((*S*)-2-hydroxyhept-6-en-2-yl)-2,2-dimethyl-1,3-dioxolane 13. In an oven dried two-neck round-bottom flask equipped with a magnetic stir bar, septa and argon inlet were placed diketone **12** (0.5 g, 1.7 mmol) and $MgBr_2{\cdot}Et_2O$ (1.3 g, 5 mmol) in 4mL of DCM. It was stirred for 1 h at −78 °C, and a solution of MeMgBr (2.2 mL of 3 M solution in ether, 6.6 mmol) was introduced dropwise with the aid of a syringe. The reaction mixture was stirred for further 2.5 h at the same temperature, and after the reaction was complete (TLC), it was quenched by the addition of satd NH_4Cl. It was then extracted with ether (2×20 mL) and the combined ethereal layers were washed with brine and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was purified by column chromatography to yield diastereomeric diol **13** in 74% (0.41 g) as a colorless oil. $[\alpha]_D = -5$ (*c* 2.7, $CHCl_3$); IR (neat): 3295, 2981, 1459, 1376, 1240, 1064, 910, 889 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.83 (ddt, 2H, $J = 17.0$, 10.2, 6.6 Hz), 5.06–4.92 (m, 4H), 3.82 (s, 2H), 3.57–3.60 (br s, 2H), 2.12–2.02 (m, 4H), 1.65–1.45 (m, 8H), 1.35 (s, 6H), 1.22 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 114.5, 107.4, 80.4, 72.0, 40.9, 34.1, 27.2, 22.0, 21.9; HRMS for $C_{19}H_{34}O_4$+Na calcd 349.2355; found 349.2356.

4.2.15. Preparation of (6*S*,7*R*,8*R*,9*S*)-6,9-bis(benzyloxy)-6,9-dimethyltetradeca-1,13-diene-7,8-diol 14. In an oven dried 25 mL two-neck round-bottom flask equipped with a guard tube and a stopper was placed a solution of **13** (0.4 g, 1.2 mmol) in 5 mL of DMF. This was cooled to 0 °C and NaH (0.29 g, 7.3 mmol, 60% suspension in mineral oil) was added portionwise. The reaction mixture was stirred for 1 h at room temperature. The mixture was then cooled to 0 °C and benzyl bromide (0.9 mL, 7.5 mmol) added dropwise. The reaction mixture was

warmed up to RT and stirred at room temperature for 3 h. After the reaction was complete (TLC), it was quenched with cautious addition of water (5 mL) and extracted with ether (2×20 mL). The combined ether layer was washed with brine and dried over Na_2SO_4. The residue obtained after the evaporation of solvent was used as such for the next step.

To a DCM (4 mL) solution of crude product obtained above was added $FeCl_3 \cdot 6H_2O$ at room temperature, under argon atmosphere. The reaction mixture was stirred for 4 h during which time the reaction was complete (TLC). It was filtered through a short pad of Celite and the Celite pad washed with ether (10 mL). To the ether layer, solid $NaHCO_3$ and a few drops of water were added and stirred for 10 min, to remove the iron impurities. It was then filtered, and dried over Na_2SO_4. Evaporation of the solvent followed by column chromatography of the crude residue afforded 1,2-diol **14** (0.23 g) in 40% yield as a colorless oil. $[\alpha]_D = -12.2$ (*c* 2.7, $CHCl_3$); IR (neat): 3492, 2940, 1413, 1382, 1106, 1056, 910, 734, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.21 (m, 10H), 5.74 (ddt, 2H, $J = 17.4$, 10.2, 6.6 Hz), 5.03–4.90 (m, 4H), 4.47 (d, 2H, $J = 11.4$ Hz), 4.42 (d, 2H, $J = 11.4$ Hz), 3.88 (d, 2H, $J = 5.4$ Hz), 3.08 (d, 2H, $J = 5.4$ Hz), 2.09–1.95 (m 4H), 1.82–1.20 (m, 8H), 1.30 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.2, 138.7, 128.3, 127.3, 114.6, 80.4, 70.7, 63.6, 34.7, 34.2, 22.6, 19.3; HRMS calcd for $C_{33}H_{42}O_4$+Na 489.2981; found 489.2986.

4.2.16. Preparation of (*S*)-2-(benzyloxy)-2-methylhept-6-en-1-ol 15. To a solution of 1,2-diol **15** (0.2 g, 0.4 mmol) in 3 mL of benzene at room temperature was added $Pb(OAc)_4$ (0.38 g, 0.8 mmol) under argon atmosphere. The reaction mixture was stirred for 1.5 h and filtered through a short pad of Celite. The Celite pad was washed with DCM (10 mL). Evaporation of dichloromethane yielded the crude aldehyde which was dissolved in 2 mL of MeOH. It was cooled to 0 °C and $NaBH_4$ (30 mg, 0.8 mmol) was added at the same temperature. The reaction mixture was stirred for 1 h at 0 °C and was cautiously quenched with water and extracted with ether (2×20 mL). The combined ether layer was washed with brine and dried over Na_2SO_4. Residue obtained after evaporation of the solvent was purified by column chromatography to yield alcohol **15** (0.18 g, 90%) as a colorless oil. $[\alpha]_D = -4.1$ (*c* 1.1, $CHCl_3$); lit.[12] $[\alpha]_D = -3.6$ (*c* 1, $CHCl_3$); IR (neat): 3442, 2973, 2938, 1496, 1380, 1060, 910, 734, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.23 (m, 5H), 5.81 (ddt, 1H, $J = 17.1$, 10.5, 6.6 Hz), 5.07–4.92 (m, 2H), 4.43 (s, 2H), 3.57 (d, 1H, $J = 11.4$ Hz), 3.48 (d, 1H, $J = 11.4$ Hz), 2.12–2.01 (m, 2H), 1.69–1.16 (m, 4H), 1.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1, 138.5, 128.4, 127.4, 114.8, 77.6, 67.3, 63.6, 34.8, 34.2, 22.9, 20.1; HRMS for $C_{15}H_{22}O_2$+Na calcd 257.1517; found 257.1515.

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