Enantiodivergent Formal Total Synthesis of Aspercyclide C from L-(+)-Tartaric Acid

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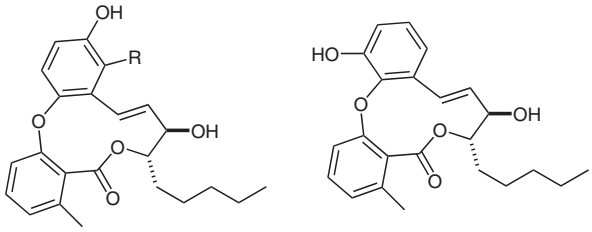
Abstract: The enantiodivergent formal syntheses of both enantiomers of aspercyclide C is accomplished. Starting from L-(+)-tartaric acid, the key protected allylic alcohol, (3*R*,4*R*)-4-(methoxymethoxy)non-1-en-3-ol is prepared, and is then elaborated into both enantiomers of 3-[(4-methoxybenzyl)oxy]non-1-en-4-ol via Mitsunobu inversion. Esterification with a known biaryl acid, followed by ring-closing metathesis and deprotection completes the syntheses.

Key words: aspercyclide C, total synthesis, tartaric acid, Mitsunobu inversion, ring-closing metathesis

Aspercyclides A–C (Figure 1) are 11-membered biaryl ether lactones which were isolated by Singh et al. via extraction of the fermentation broth of *Aspergillus sp.*[1] Aspercyclides are reported to be moderately active in IgE receptor binding, which is key to the understanding of allergic disorders. The total syntheses of aspercyclides A–C have been reported by Fürstner's group,[2a,b] while a total synthesis of aspercyclide A,[2c] and a formal total synthesis of aspercyclide C[2d] have also recently been described. As a part of our program on the synthesis of bioactive natural products starting from chiral pool tartaric acid, we have accomplished the synthesis a number of oxygenated natural products, including macrolactones.[3] Herein, we disclose our efforts on the formal total syntheses of both enantiomers of aspercyclide C starting from L-(+)-tartaric acid.

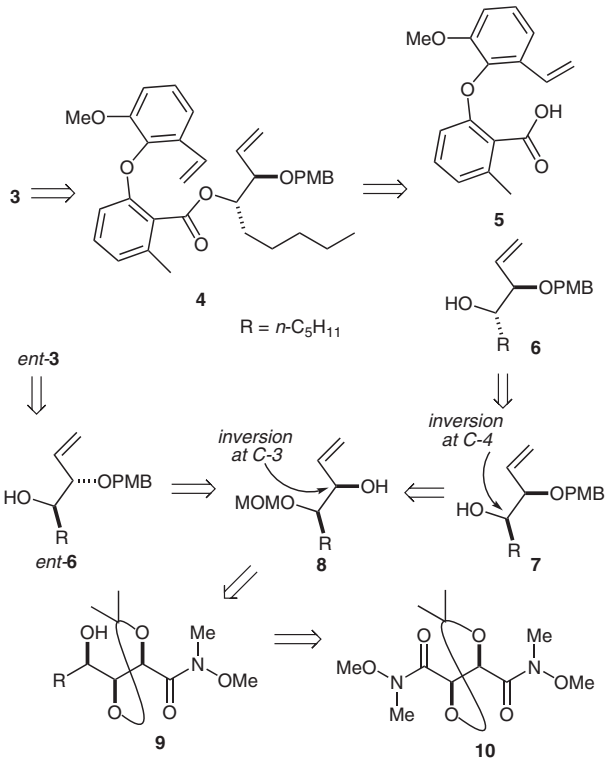


R = CHO: aspercyclide A (**1**)
R = CH_2OH: aspercyclide B (**2**)

aspercyclide C (**3**)

Figure 1 Structures of aspercyclides A–C

Our approach toward the synthesis of aspercyclide C is depicted in Scheme 1. We envisaged formation of the key double bond in aspercyclide C via ring-closing metathesis of a suitably protected diene-ester **4**. Preparation of the ester **4** is anticipated by condensation between the biaryl acid **5** and the homoallylic alcohol **6**. Formation of **6** would be possible through Mitsunobu inversion of the C-4 hydroxy group in **7**, which itself can be obtained from the allylic alcohol **8**. By contrast, inversion of the allylic hydroxy group (C-3) in **8** and further elaboration would enable access to *ent*-**6**. The γ-Hydroxy amide **9** derived from the bis-Weinreb amide of L-(+)-tartaric acid **10**[4] was identified as the appropriate starting material for the synthesis of alcohol **8** (Scheme 1).



Scheme 1 Retrosynthesis of aspercyclide C (**3**) and its enantiomer (*ent*-**3**)

The synthesis of aspercyclide C commenced with the controlled addition of *n*-pentylmagnesium bromide to the bis-Weinreb amide **10**[5] to afford the mono keto amide **11** in 92% yield. Reduction of the keto group in **11** with K-Selectride® furnished the corresponding alcohol **9** as a single diastereomer in 87% yield,[6] which was subsequently protected as the methoxymethyl ether **12** employing standard conditions. Treatment of **12** with sodium borohy-

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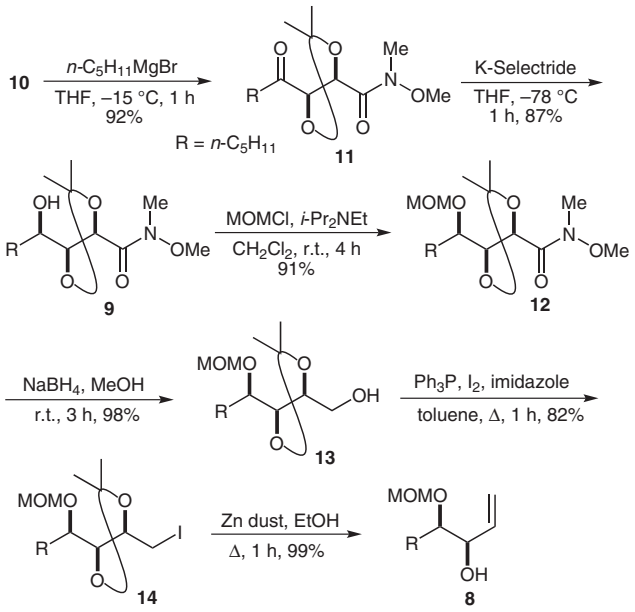
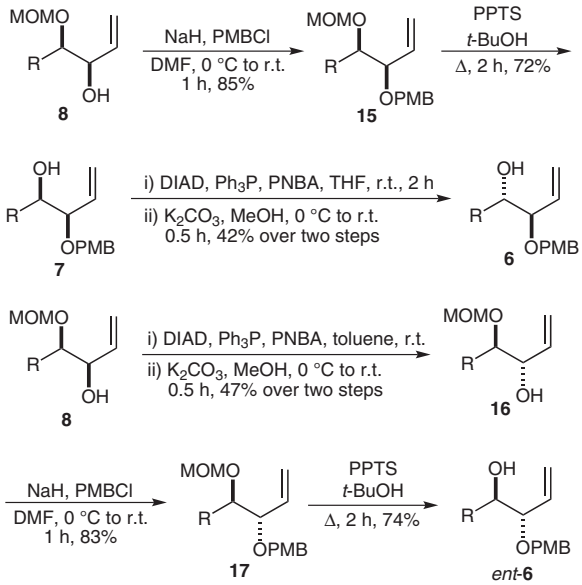
dride afforded the primary alcohol **13** in 98% yield which was converted into the iodide **14** in 82% yield. Zinc-mediated Boord fragmentation[7] of the iodide produced the desired allylic alcohol **8** in an excellent 99% yield (Scheme 2).



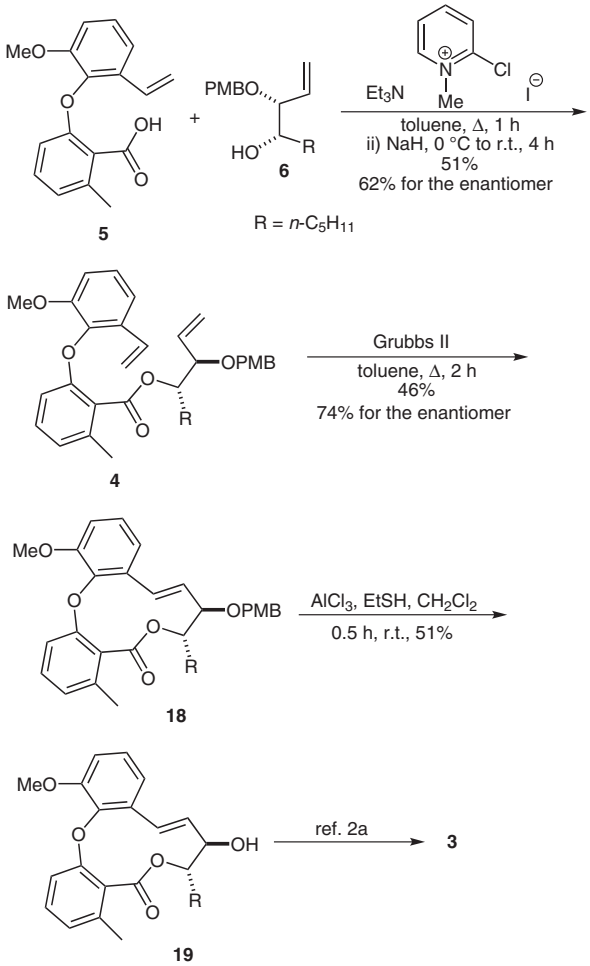
Scheme 2 Synthesis of the key allylic alcohol **8** from bis-Weinreb amide 10

Allylic alcohol **8** represented the point of divergence in the synthesis of both enantiomers of homoallylic alcohol **6** (Scheme 3). Thus, protection of the hydroxy group in **8** as the *p*-methoxybenzyl ether (85% yield) followed by selective deprotection of the methoxymethyl ether with pyridinium *p*-toluenesulfonate[8] in refluxing *tert*-butanol gave the alcohol **7** in 72% yield. Mitsunobu[9] inversion of the free alcohol in **7** afforded homoallylic alcohol **6** in 42% yield. For the synthesis of *ent*-**6**, inversion of **8** was performed under Mitsunobu conditions leading to alkene **16** in 47% yield. Protection of the allylic alcohol group in **16** as the *p*-methoxybenzyl ether gave **17** (83% yield) which underwent selective deprotection of the methoxymethyl ether, as previously described, to afford *ent*-**6** in 74% yield.

Homoallylic alcohol **6** was next coupled with the known biaryl acid **5**[10] to produce the ester **4** in 51% yield following the protocol described by Ramana et al.[2d] Ring-closing metathesis of the ester using Grubbs' second-generation catalyst produced the biaryl lactone **18** in 46% yield. Deprotection of the *p*-methoxybenzyl ether in **18** with aluminum trichloride in the presence of ethanethiol afforded lactone **19**, the conversion of which into aspercyclide C (**3**) by deprotection of the aryl methyl ether was described by Fürstner et al.[2b] Hence this synthetic sequence constitutes a formal synthesis of aspercyclide C (Scheme 4). An analogous reaction sequence employing *ent*-**6** afforded the enantiomer of **19**.



Scheme 3 Enantiodivergent synthesis of both enantiomers of homoallylic alcohol **6**



Scheme 4 Completion of the formal total synthesis of aspercyclide C (**3**)

In conclusion, we have accomplished the formal total syntheses of both enantiomers of the bioactive biaryl ether lactone, aspercyclide C. Key features of the route include the synthesis of both enantiomers of the chiral fragment **6** from a common precursor derived from L-(+)-tartaric acid. Further examination of this approach for the synthesis of other aspercyclide natural products and analogues is underway.

Unless stated otherwise, all reagents were purchased from commercial sources and were used without additional purification. All reactions were performed under an inert atmosphere unless otherwise stated. THF was freshly distilled from Na/benzophenone. Column chromatography was performed on silica gel (Acme grade, 100–200 mesh). Petroleum ether (PE) refers to the fraction boiling in the 60–80 °C range. TLC was accomplished using Merck 60F254 precoated silica gel plates which were made visual using either UV light, an iodine chamber, or with phosphomolybdic acid spray. Melting points were determined using a Büchi M 560 melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP 370 digital polarimeter at 25 °C. IR spectra were obtained on a Perkin-Elmer spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 400 MHz and 100 MHz, respectively. HRMS spectra were obtained on a Micromass Q-TOF apparatus.

(4*R*,5*R*)-5-Hexanoyl-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (11)

Bis-Weinreb amide **10** (1.60 g, 5.8 mmol) was dissolved in THF (20 mL) and cooled to –10 °C. A freshly prepared soln of *n*-pentylmagnesium bromide (24 mL, 0.5 M soln in THF, 12 mmol) was added at such a rate that the internal temperature did not rise above –10 °C. After the reaction was complete (TLC), it was quenched cautiously by the addition of a sat. aq NH_4Cl soln (15 mL), then poured into H_2O (15 mL) and extracted with EtOAc (2 × 35 mL). The combined organic extract was washed with brine (20 mL) and dried over anhyd Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue (PE–EtOAc, 7:3) yielded **11** (1.53 g, 92%) as a colorless oil.

$[\alpha]_D$ +6.3 (*c* 2, $CHCl_3$).

IR (neat): 2937, 2872, 1720, 1674, 1379, 1081, 862 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.04 (d, *J* = 4.9 Hz, 1 H), 4.82 (d, *J* = 5.0 Hz, 1 H), 3.72 (s, 3 H), 3.24 (s, 3 H), 2.76–2.51 (m, 2 H), 1.75–1.55 (m, 2 H), 1.51 (s, 3 H), 1.44 (s, 3 H), 1.39–1.12 (m, 4 H), 0.90 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.4, 169.8, 112.7, 82.3, 73.9, 61.7, 39.3, 32.5, 31.3, 26.7, 26.2, 22.7, 22.4, 13.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{25}NO_5Na$: 310.1630; found: 310.1630.

(4*R*,5*S*)-5-[(1*R*)-1-Hydroxyhexyl]-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (9)

To a soln of **11** (1.43 g, 5.0 mmol) in THF (15 mL) at –78 °C was added K-Selectride® (7.5 mL, 1 M soln in THF, 7.5 mmol), dropwise, over a period of 10 min and the resulting mixture was stirred for 1 h. After the reaction was complete (TLC), it was quenched cautiously by the addition of H_2O (10 mL) at –78 °C and then extracted with EtOAc (2 × 35 mL). The combined organic extract was washed with brine (15 mL) and dried over anhyd Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue (PE–EtOAc, 1:1) yielded carboxamide **9** (1.25 g, 87%) as a colorless oil.

$[\alpha]_D$ –4.6 (*c* 1.3, $CHCl_3$).

IR (neat): 3479, 2936, 2861, 1667, 1382, 728 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.77 (br s, 1 H), 4.37 (br s, 1 H), 3.74 (s, 3 H), 3.68–3.52 (m, 1 H), 3.22 (s, 3 H), 1.96 (d, *J* = 6.4 Hz, 1 H), 1.65–1.21 (m, 14 H), 0.87 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 111.0, 80.9, 73.8, 70.3, 61.7, 34.6, 32.4, 31.7, 27.0, 26.1, 25.5, 22.6, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{27}NO_5Na$: 312.1787; found: 312.1777.

(4*R*,5*S*)-*N*-Methoxy-5-[(1*R*)-1-(methoxymethoxy)hexyl]-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (12)

To a soln of carboxamide **9** (1.20 g, 4 mmol) in anhyd CH_2Cl_2 (8 mL) were added DIPEA (2.2 mL, 12.4 mmol) and MOMCl (0.8 mL, 10.3 mmol) at 0 °C, and the resulting mixture stirred for 10 min at 0 °C. The reaction mixture was warmed to r.t. and then stirred for a further 4 h. After the reaction was complete (TLC), it was poured into ice-cold H_2O (15 mL) and extracted with Et_2O (2 × 30 mL). The combined ethereal extract was washed with brine (15 mL) and dried over anhyd Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue (PE–EtOAc, 7:3) yielded compound **12** (1.24 g, 91%) as a colorless oil.

$[\alpha]_D$ –4.3 (*c* 1.4, $CHCl_3$).

IR (neat): 2987, 2836, 1673, 1462, 1214, 731 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.82–4.49 (m, 4 H), 3.76 (s, 3 H), 3.68 (dd, *J* = 11.7, 5.5 Hz, 1 H), 3.39 (s, 3 H), 3.23 (s, 3 H), 1.75–1.22 (m, 14 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 111.1, 96.6, 79.6, 77.2, 73.2, 61.8, 55.9, 32.4, 31.9, 31.2, 27.0, 26.2, 25.3, 22.6, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{31}NO_6Na$: 356.2049; found: 356.2036.

{(4*S*,5*S*)-5-[(1*R*)-1-(Methoxymethoxy)hexyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methanol (13)

To a round bottomed flask equipped with a $CaCl_2$ guard tube was added a soln of **12** (1.14 g, 3.34 mmol) in MeOH (15 mL). $NaBH_4$ (0.76 g, 20 mmol) was added at 0 °C and the reaction mixture was allowed to warm slowly to r.t. and then stirred for 3 h at this temperature. Following completion (TLC), most of the MeOH was removed under reduced pressure and H_2O (20 mL) was added. The mixture was extracted with EtOAc (2 × 30 mL) and the combined organic layer washed with brine (15 mL) and dried over anhyd Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue (PE–EtOAc, 1:1) furnished primary alcohol **13** (0.90 g, 98%) as a colorless oil.

$[\alpha]_D$ +3.6 (*c* 1.4, $CHCl_3$).

IR (neat): 3463, 2987, 2873, 1457, 1373, 854 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.74 (d, *J* = 6.8 Hz, 1 H), 4.67 (d, *J* = 6.8 Hz, 1 H), 4.25–3.86 (m, 2 H), 3.84–3.51 (m, 3 H), 3.40 (s, 3 H), 2.40 (br s, 1 H), 1.90–1.21 (m, 14 H), 0.88 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 108.8, 96.9, 78.9, 77.3, 77.2, 62.7, 56.0, 31.9, 30.7, 27.1, 27.0, 25.4, 22.6, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{28}O_5Na$: 299.1834; found: 299.1841.

(4*R*,5*S*)-4-(Iodomethyl)-5-[(1*R*)-1-(methoxymethoxy)hexyl]-2,2-dimethyl-1,3-dioxolane (14)

To a soln of alcohol **13** (0.83 g, 3 mmol) in anhyd toluene (10 mL) at r.t. were added Ph_3P (2.33 g, 8.9 mmol), imidazole (0.61 g, 8.9 mmol) and I_2 (1.51 g, 5.94 mmol) under an Ar atm. The reaction mixture was heated at reflux temperature for 1 h. After the reaction was complete (TLC), it was cooled to r.t., poured into H_2O (10 mL) and extracted with Et_2O (2 × 30 mL). The combined ethereal layer

was washed with brine (15 mL), sat. aq $Na_2S_2O_3$ soln (10 mL) and H_2O (15 mL), and then dried over anhyd Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue (PE–Et_2O, 95:5) yielded iodide **14** (1.05 g, 82%) as a colorless oil.

$[\alpha]_D$ –13.6 (*c* 1.1, $CHCl_3$).

IR (neat): 2967, 2933, 1457, 1379, 1216, 889 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.73 (d, *J* = 6.8 Hz, 1 H), 4.68 (d, *J* = 6.8 Hz, 1 H), 3.98–3.79 (m, 2 H), 3.70–3.63 (m, 1 H), 3.46–3.34 (m, 4 H), 3.32–3.21 (m, 1 H), 1.75–1.20 (m, 14 H), 0.90 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.3, 96.6, 82.2, 76.6, 75.7, 56.1, 31.9, 30.9, 27.5, 27.2, 25.4, 22.6, 14.0, 7.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{27}IO_4Na$: 409.0852; found: 409.0849.

(3*R*,4*R*)-4-(Methoxymethoxy)non-1-en-3-ol (8)

To a soln of the iodide **14** (1.00 g, 2.59 mmol) in absolute EtOH (12 mL) was added activated Zn dust (1.35 g, 20.72 mmol) at r.t., and the reaction mixture was then heated at reflux temperature for 1 h. After the reaction was complete (TLC), it was filtered through a short pad of Celite and the residue was washed with Et_2O (2 × 30 mL). Evaporation of the solvent followed by silica gel column chromatography of the crude (PE–EtOAc, 7:3) furnished alcohol **8** (0.51 g, 99%) as a colorless oil.

$[\alpha]_D$ –2.7 (*c* 1.5, $CHCl_3$).

IR (neat): 3449, 3081, 2955, 1466, 1152, 920 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.87 (ddd, *J* = 16.9, 10.4, 6.2 Hz, 1 H), 5.36 (d, *J* = 17.2 Hz, 1 H), 5.22 (d, *J* = 10.4 Hz, 1 H), 4.74 (d, *J* = 6.8 Hz, 1 H), 4.68 (d, *J* = 6.8 Hz, 1 H), 4.03 (t, *J* = 6.2 Hz, 1 H), 3.48–3.28 (m, 4 H), 3.14 (br s, 1 H), 1.62–1.23 (m, 8 H), 0.89 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 116.8, 97.3, 83.6, 74.7, 55.9, 31.9, 31.2, 24.9, 22.6, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{22}O_3Na$: 225.1467; found: 225.1474.

1-{[(3*R*,4*R*)-4-(Methoxymethoxy)non-1-en-3-yloxy]methyl}-4-methoxybenzene (15)

To a cold (0 °C) soln of **8** (0.34 g, 1.69 mmol) in anhyd DMF (3 mL) was added NaH (0.14 g of a 60% suspension in mineral oil, 3.38 mmol) portionwise under an N_2 atm. After stirring for 15 min at 0 °C, PMBCl (0.50 mL, 3.38 mmol) was added dropwise at the same temperature, and the mixture allowed to warm slowly to r.t. and then stirred for 1 h. After the reaction was complete (TLC), it was quenched cautiously with ice-cold H_2O (10 mL) and extracted with Et_2O (2 × 20 mL). The combined ethereal layer was washed with brine (15 mL) and dried over anhyd Na_2SO_4. Evaporation of the solvent followed by careful silica gel column chromatography of the residue (PE–EtOAc, 9:1) afforded **15** (0.45 g, 85%) as a colorless oil.

$[\alpha]_D$ –7.9 (*c* 1.4, $CHCl_3$).

IR (neat): 2953, 2930, 2860, 1613, 1514, 920 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.5 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 5.84 (ddd, *J* = 17.6, 10.5, 7.6 Hz, 1 H), 5.42–5.21 (m, 2 H), 4.75 (d, *J* = 6.9 Hz, 1 H), 4.67 (d, *J* = 6.9 Hz, 1 H), 4.57 (d, *J* = 11.6 Hz, 1 H), 4.30 (d, *J* = 11.6 Hz, 1 H), 3.88–3.70 (m, 4 H), 3.55 (td, *J* = 7.7, 4.9 Hz, 1 H), 3.37 (s, 3 H), 1.74–1.15 (m, 8 H), 0.87 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 135.6, 130.5, 129.4, 118.5, 113.6, 96.9, 81.5, 79.8, 70.0, 55.7, 55.2, 31.9, 30.7, 25.1, 22.6, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{30}O_4Na$: 345.2042; found: 345.2034.

(3*R*,4*R*)-3-[(4-Methoxybenzyl)oxy]non-1-en-4-ol (7)

To a soln of alkene **15** (0.42 g, 1.3 mmol) in *t*-BuOH (5 mL) was added PPTS (3.26 g, 13 mmol) and the reaction mixture was heated at reflux temperature for 2 h. After the reaction was complete (TLC), it was poured into ice-cold H_2O (10 mL) and extracted with Et_2O (2 × 25 mL). The combined ethereal layer was washed with brine (15 mL) and dried over anhyd Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue (PE–EtOAc, 9:1) afforded alcohol **7** (0.26 g, 72%) as a colorless oil.

$[\alpha]_D$ –31.0 (*c* 1.0, $CHCl_3$).

IR (neat): 3470, 2955, 2859, 1614, 1515, 1250 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 5.73 (ddd, *J* = 17.7, 10.4, 7.9 Hz, 1 H), 5.37 (d, *J* = 10.4 Hz, 1 H), 5.33 (d, *J* = 17.2 Hz, 1 H), 4.58 (d, *J* = 11.2 Hz, 1 H), 4.28 (d, *J* = 11.2 Hz, 1 H), 3.81 (s, 3 H), 3.63–3.47 (m, 2 H), 2.70 (br s, 1 H), 1.56–1.12 (m, 8 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 135.4, 130.1, 129.5, 120.0, 113.8, 84.2, 73.4, 70.0, 55.7, 55.2, 32.4, 31.9, 25.2, 22.6, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{26}O_3Na$: 301.1780; found: 301.1776.

(3*R*,4*S*)-3-[(4-Methoxybenzyl)oxy]non-1-en-4-ol (6)

To a soln of alcohol **7** (0.24 g, 0.87 mmol) in anhyd THF (9 mL) were added Ph_3P (0.71 g, 2.61 mmol) and *p*-nitrobenzoic acid (PNBA) (0.6 g, 2.61 mmol) under an N_2 atm. The reaction mixture was stirred for 10 min, cooled to 0 °C, and treated with DIAD (0.75 mL, 2.61 mmol) over a period of 3 min. The mixture was then warmed to r.t. and stirred for 2 h. After the reaction was complete (TLC), the volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (PE–EtOAc, 95:5) to afford the *p*-nitrobenzoate ester of **6** which was used as such in the next step. To a soln of the ester **6** in MeOH (5 mL) was added K_2CO_3 (0.23 g, 1.74 mmol) and the resulting mixture was stirred for 0.5 h at 0 °C. After the reaction was complete (TLC), the mixture was poured into H_2O (5 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layer was washed with brine (10 mL) and dried over anhyd Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue (PE–EtOAc, 7:3) afforded **6** (0.10 g, 42%) as a colorless oil.

$[\alpha]_D$ –33.0 (*c* 1.0, $CHCl_3$).

IR (neat): 3440, 2954, 2859, 1614, 1515, 1249 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 5.84 (ddd, *J* = 18.1, 10.4, 7.9 Hz, 1 H), 5.39 (dd, *J* = 10.5, 1.6 Hz, 1 H), 5.29 (dd, *J* = 17.4, 1.7 Hz, 1 H), 4.56 (d, *J* = 11.4 Hz, 1 H), 4.31 (d, *J* = 11.4 Hz, 1 H), 3.81 (s, 3 H), 3.75–3.64 (m, 2 H), 2.18 (br s, 1 H), 1.58–1.15 (m, 8 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 134.6, 130.3, 129.4, 120.0, 113.8, 83.2, 73.2, 69.9, 55.2, 32.1, 31.8, 25.5, 22.6, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{26}O_3Na$: 301.1780; found: 301.1776.

(3*S*,4*R*)-(4-Methoxymethoxy)non-1-en-3-ol (16)

To a soln of alcohol **8** (0.15 g, 0.75 mmol) in anhyd toluene (8 mL) were added Ph_3P (0.59 g, 2.3 mmol) and *p*-nitrobenzoic acid (0.38 g, 2.3 mmol) under an N_2 atm. The reaction mixture was stirred for 10 min, cooled to 0 °C, and treated with DIAD (0.5 mL, 2.25 mmol) in anhyd THF (1 mL) over a period of 3 min. The mixture was then warmed to r.t. and stirred for 2 h. After the reaction was complete (TLC), the volatiles were removed under reduced pressure and the

crude residue was purified by silica gel column chromatography (PE–EtOAc, 95:5) to yield the corresponding *p*-nitrobenzoate ester. To a soln of the ester in MeOH (3 mL) at 0 °C was added K_2CO_3 (0.23 g, 1.74 mmol) and the resulting mixture was stirred for 15 min at 0 °C. After the reaction was complete (TLC), the mixture was poured into H_2O (3 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layer was washed with brine (5 mL) and dried over anhyd Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue (PE–EtOAc, 7:3) afforded alcohol **16** (0.07 g, 47%) as a colorless oil.

$[\alpha]_D$ −27.0 (*c* 1.0, $CHCl_3$).

IR (neat): 3444, 2955, 2874, 1464, 1037, 921 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.91 (ddd, *J* = 16.9, 10.5, 5.9 Hz, 1 H), 5.32 (d, *J* = 17.2 Hz, 1 H), 5.24 (d, *J* = 10.5 Hz, 1 H), 4.75 (d, *J* = 6.9 Hz, 1 H), 4.66 (d, *J* = 6.9 Hz, 1 H), 4.07 (t, *J* = 6.0 Hz, 1 H), 3.62–3.55 (m, 1 H), 3.43 (s, 3 H), 3.39 (d, *J* = 7.9 Hz, 1 H), 1.58–1.15 (m, 8 H), 0.89 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.3, 116.5, 97.7, 84.8, 73.3, 55.9, 31.7, 31.1, 25.5, 22.5, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{22}O_3Na$: 225.1467; found: 225.1469.

1-{[(3*S*,4*R*)-4-(Methoxymethoxy)non-1-en-3-yloxy]methyl}-4-methoxybenzene (17)

To a cold (0 °C) soln of alcohol **16** (0.06 g, 0.30 mmol) in anhyd DMF (1 mL) was added NaH (0.03 g of a 60% suspension in mineral oil, 0.60 mmol), portionwise, under an N_2 atm. After stirring for 15 min at 0 °C, PMBCl (0.10 mL, 0.60 mmol) was added dropwise at the same temperature, the mixture allowed to warm slowly to r.t., and then stirred for 1 h. After the reaction was complete (TLC), it was quenched cautiously with ice-cold H_2O (5 mL) and extracted with Et_2O (2 × 10 mL). The combined ethereal layer was washed with brine (5 mL) and dried over anhyd Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue (PE–EtOAc, 9:1) afforded **17** (0.10 g, 83%) as a colorless oil.

$[\alpha]_D$ +55.7 (*c* 0.9, $CHCl_3$).

IR (neat): 2953, 2873, 1614, 1515, 1249, 920 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 9.0 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 5.85 (ddd, *J* = 17.7, 10.5, 7.8 Hz, 1 H), 5.35 (d, *J* = 9.7 Hz, 1 H), 5.28 (d, *J* = 17.4 Hz, 1 H), 4.80 (d, *J* = 6.8 Hz, 1 H), 4.64 (d, *J* = 6.8 Hz, 1 H), 4.57 (d, *J* = 11.6 Hz, 1 H), 4.34 (d, *J* = 11.6 Hz, 1 H), 3.82 (s, 3 H), 3.79 (dd, *J* = 7.8, 3.9 Hz, 1 H), 3.68 (dt, *J* = 7.6, 3.9 Hz, 1 H), 3.38 (s, 3 H), 1.58–1.15 (m, 8 H), 0.89 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 135.5, 130.6, 129.2, 119.0, 113.6, 96.4, 82.0, 79.2, 69.8, 55.7, 55.2, 31.8, 30.9, 25.2, 22.6, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{30}O_4Na$: 345.2042; found: 345.2071.

(3*S*,4*R*)-3-[(4-Methoxybenzyl)oxy]non-1-en-4-ol (*ent*-6)

To a soln of alkene **17** (0.08 g, 0.25 mmol) in *t*-BuOH (2 mL) was added PPTS (0.63 g, 2.5 mmol). The reaction mixture was heated at reflux temperature for 2 h, and following completion (TLC), was poured into ice-cold H_2O (2 mL) and extracted with Et_2O (2 × 5 mL). The combined ethereal layer was washed with brine (5 mL) and dried over anhyd Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue (PE–EtOAc, 9:1) afforded *ent*-**6** (0.05 g, 74%) as a colorless oil.

$[\alpha]_D$ +34.6 (*c* 2.4, $CHCl_3$).

IR (neat): 3462, 2955, 2860, 1614, 1515, 821 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.7 Hz, 2 H), 6.90 (d, *J* = 8.6 Hz, 2 H), 5.86 (ddd, *J* = 18.0, 10.4, 8.0 Hz, 1 H), 5.41 (d, *J* = 10.4 Hz, 1 H), 5.32 (d, *J* = 17.3 Hz, 1 H), 4.58 (d, *J* = 11.4 Hz, 1 H), 4.33 (d, *J* = 11.4 Hz, 1 H), 3.82 (s, 3 H), 3.72–3.64 (m, 2 H), 2.13 (br s, 1 H), 1.45–1.29 (m, 8 H), 0.89 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 134.5, 130.2, 129.3, 120.0, 113.7, 83.1, 73.1, 69.8, 55.2, 32.0, 31.8, 25.3, 22.5, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{26}O_3Na$: 301.3814; found: 301.1771.

(3*R*,4*S*)-{3-[(4-Methoxybenzyl)oxy]non-1-en-4-yl} 2-(2-Methoxy-6-ethenylphenoxy)-6-methylbenzoate (4)

To a soln of acid **5**[10] (0.06 g, 0.22 mmol) in toluene (0.5 mL) was added Et_3N (0.1 mL, 0.66 mmol) and 1-methyl-2-chloropyridinium iodide (0.06 g, 0.22 mmol) under an N_2 atm. After stirring for 10 min, a soln of alcohol **6** (0.06 mg, 0.22 mmol) in toluene (0.5 mL) was added and the resulting mixture heated at reflux temperature for 1 h. The mixture was cooled to 0 °C and NaH (0.02 g of a 60% suspension in mineral oil, 0.22 mmol) was added and stirring continued for 4 h at r.t. After the reaction was complete (TLC), it was quenched cautiously with ice-cold H_2O (2 mL) and extracted with EtOAc (2 × 10 mL). The combined organic extract was washed with brine (10 mL) and dried over anhyd Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the residue (PE–EtOAc, 95:5) afforded ester **4** (0.06 g, 51%) as a yellow liquid.

$[\alpha]_D$ –30.0 (*c* 1.0, $CHCl_3$); (*ent*-**4**) $[\alpha]_D$ +31.1 (*c* 1.1, $CHCl_3$).

IR (neat): 2955, 1730, 1611, 1515, 1461, 1273 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.5 Hz, 2 H), 7.21 (d, *J* = 6.5 Hz, 1 H), 7.15 (t, *J* = 8.0 Hz, 1 H), 7.03 (t, *J* = 8.0 Hz, 1 H), 6.98–6.82 (m, 3 H), 6.81 (d, *J* = 8.5 Hz, 2 H), 6.23 (d, *J* = 8.3 Hz, 1 H), 5.89 (ddd, *J* = 17.5, 10.5, 7.5 Hz, 1 H), 5.74 (d, *J* = 17.7 Hz, 1 H), 5.36 (t, *J* = 4.4 Hz, 1 H), 5.34 (d, *J* = 10.4 Hz, 1 H), 5.30 (d, *J* = 10.4 Hz, 1 H), 5.20 (d, *J* = 11.3 Hz, 1 H), 4.52 (d, *J* = 11.5 Hz, 1 H), 4.40 (d, *J* = 11.5 Hz, 1 H), 3.98 (dd, *J* = 7.3, 4.3 Hz, 1 H), 3.79 (s, 3 H), 3.68 (s, 3 H), 2.33 (s, 3 H), 1.74–1.10 (m, 8 H), 0.74 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 158.9, 155.3, 152.8, 140.3, 136.8, 135.1, 132.4, 130.6, 130.5, 129.7, 129.2, 125.6, 123.6, 123.1, 119.2, 117.7, 115.9, 113.5, 112.0, 110.5, 81.3, 76.1, 70.2, 56.0, 55.2, 31.7, 29.8, 29.7, 24.9, 22.4, 19.4, 13.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{34}H_{40}O_6Na$: 567.2723; found: 567.2728.

4-Methoxybenzyl Protected Biaryl Lactone 18

In a two-neck 25 mL round bottom flask fitted with an addition flask was placed a soln of diene **4** (0.05 g, 0.09 mmol) in anhyd toluene (3 mL) under an N_2 atm. The soln was heated to reflux temperature followed by the slow addition of a soln of Grubbs' second-generation catalyst (10 mol%) in anhyd toluene (3 mL) via the addition flask. The mixture was stirred at reflux temperature for 2 h. After the reaction was complete (TLC), the volatiles were evaporated under reduced pressure and the residue was purified by silica gel column chromatography (PE–EtOAc, 95:5) to afford **18** (0.02 g, 46%) as a brown sticky mass.

$[\alpha]_D$ +78.0 (*c* 0.5, $CHCl_3$) {Lit.[2d] $[\alpha]_D$ +148.6 (*c*, 0.4, $CHCl_3$)}; (*ent*-**18**) $[\alpha]_D$ –78.3 (*c* 0.5, $CHCl_3$).

IR (CH_2Cl_2): 2956, 1739, 1612, 1586, 1461, 1251 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 10.1 Hz, 2 H), 7.15 (t, *J* = 7.9 Hz, 1 H), 7.08 (t, *J* = 7.9 Hz, 1 H), 6.94 (d, *J* = 7.9 Hz, 1 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 6.82 (dd, *J* = 11.5, 7.6 Hz, 1 H), 6.59 (d, *J* = 8.4 Hz, 1 H), 6.29 (d, *J* = 16.0 Hz, 1 H), 5.98 (dd, *J* = 16.0, 9.7 Hz, 1 H), 5.36–5.24 (m, 1 H), 4.58 (d, *J* = 11.4 Hz, 1 H), 4.34 (d, *J* = 11.4 Hz, 1 H), 3.91 (s, 3 H), 3.81 (s, 3 H), 3.75 (t, *J* = 9.5 Hz, 1 H), 2.34 (s, 3 H), 2.06–1.98 (m, 1 H), 1.54–1.12 (m, 8 H), 0.90 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 159.2, 154.0, 153.8, 143.0, 136.8, 134.7, 133.7, 130.1, 129.7, 129.6, 129.4, 126.7, 125.4, 123.7, 121.6, 114.3, 113.8, 111.6, 82.9, 75.7, 70.5, 56.0, 55.3, 31.9, 31.7, 25.2, 22.5, 19.3, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{32}H_{36}O_6Na$: 539.2410; found: 539.2408.

Biaryl Lactone 19

To a soln of **18** (0.02 g, 0.03 mmol) in anhyd CH_2Cl_2 (0.5 mL) were added ethanethiol (0.1 mL, 0.13 mmol) followed by anhyd $AlCl_3$ (8 mg, 0.06 mmol) at r.t. under an N_2 atm, and the resulting mixture was stirred for 0.5 h. After the reaction was complete (TLC), it was quenched with $NaHCO_3$ (0.02 g) and then filtered through a Celite pad and the residue rinsed with EtOAc. Evaporation of the solvent followed by silica gel column chromatography of the residue (PE–EtOAc, 7:3) afforded lactone **19** (0.01 g, 51%) as a colorless solid.

Mp 239–240 °C; $[\alpha]_D$ +276.7 (*c* 0.6, CH_2Cl_2) {Lit.[2d] $[\alpha]_D$ +330.5 (*c* 0.8, CH_2Cl_2)}; (*ent*-**19**) $[\alpha]_D$ –277.3 (*c* 0.4, CH_2Cl_2).

IR (KBr): 3522, 2951, 1721, 1600, 1456, 1294 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.05 (m, 2 H), 6.94 (d, *J* = 7.4 Hz, 1 H), 6.84 (d, *J* = 7.5 Hz, 1 H), 6.76 (d, *J* = 7.2 Hz, 1 H), 6.60 (d, *J* = 8.4 Hz, 1 H), 6.30 (d, *J* = 15.9 Hz, 1 H), 6.01 (dd, *J* = 15.8, 9.5 Hz, 1 H), 5.23 (td, *J* = 9.6, 2.2 Hz, 1 H), 4.07 (t, *J* = 9.2 Hz, 1 H), 3.91 (s, 3 H), 2.36 (s, 3 H), 2.22–1.91 (m, 1 H), 1.85–1.11 (m, 8 H), 0.93 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 154.0, 153.8, 143.0, 137.6, 134.7, 133.5, 129.7, 128.0, 126.6, 125.5, 123.8, 121.5, 114.4, 111.7, 56.0, 31.8, 31.6, 29.6, 25.3, 22.5, 19.3, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{28}O_5Na$: 419.1834; found: 419.1809.

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