Asymmetric and Regiospecific Synthesis of Isotopically Labelled Cyclopropane Fatty Acid (9*R*,10*S*)-Dihydrosterculic Acid: Overcoming Spontaneous Protonation During Lithium-Sulfoxide Exchange

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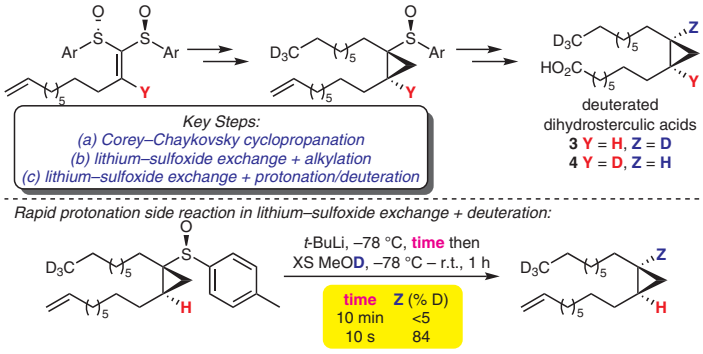

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Abstract The total synthesis of isotopically labelled (9*R*,10*S*)-dihydrosterculic acid, a usual cyclopropane fatty acid with biologically relevant toxicity upon desaturation *in vivo*, is reported. A diastereoselective Corey–Chaykovsky reaction was employed to form the cyclopropane ring. Rapid quenching of a lithium-sulfoxide exchange was required to achieve the requisite high levels of deuterium incorporation.

Key words lithium-sulfoxide exchange, deuterium labelling, asymmetric Corey–Chaykovsky cyclopropanation, cyclopropane fatty acids, mechanistic probes, fatty acid desaturation

Cyclopropane fatty acids, such as (9*R*,10*S*)-dihydrosterculic acid (**1**) are a structurally unique class of fatty acids produced by a variety of organisms.[1] The presence of their cyclopropane ring confers oxidative stability to lipidic ensembles relative to their olefinic counterparts while maintaining favourable biophysical properties, such as membrane fluidity, and greater tolerance of low pH.[2] Interestingly, in some plant species, *cis*-cyclopropane fatty acids are thought to be converted into the corresponding cyclopropene compounds via a unique *syn*-dehydrogenation (desaturation) reaction. Such cyclopropene fatty acids are potent inhibitors of mammalian stearoyl CoA Δ^9 desaturases (SCDs). Humans have two SCD homologues – SCD1 and SCD5. The X-ray structure of both human[3] and murine[4] variants of SCD1 were recently published. Mice deficient in SCD1 demonstrated improved insulin sensitivity and lipid metabolic profiles when fed a high-fat diet[5,6] and dysregulation of SCD1 in humans has implications in diabetes,[7] metabolic syndrome,[8] and cancer;[9] therefore, SCD1 is an active therapeutic target.[10] The proposed mechanism for *cis*-cyclopropane to cyclopropene bioconversion involves stepwise hydrogen removal in a manner similar to that established for the desaturase-mediated dehydrogenation of *cis*-olefinic fatty acids to give acetylenic products;[11] however, further details, including the cryptoregiochemistry of this process (i.e., which hydrogen is removed first), have not been elucidated. The situation is complicated by the fact that the putative cyclopropane fatty acid desaturases have not been isolated or characterised. Nevertheless, as part of our ongoing interest in fatty acid desaturation[12] and cyclopropane fatty acids[13–15] we have undertaken a mechanistic study of the biochemical desaturation of **1** to **2** (Figure 1). Herein, we report the asymmetric synthesis of deuterium-labelled dihydrosterculic acids appropriate for use in evaluating the individual primary kinetic isotope effects on C–H bond cleavage at C9 and C10.

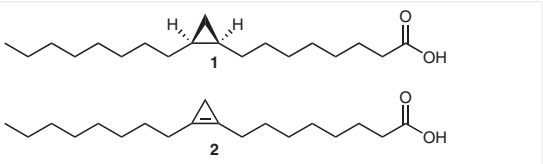
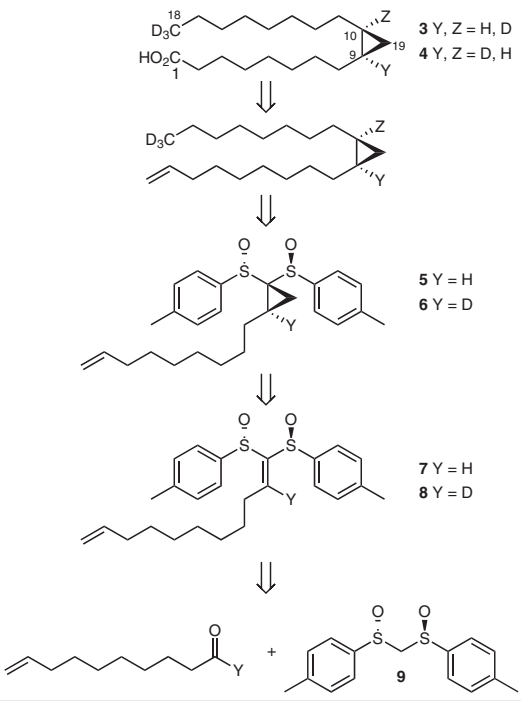


Figure 1 Structures (9*R*,10*S*)-dihydrosterculic acid (**1**) and sterculic acid (**2**)

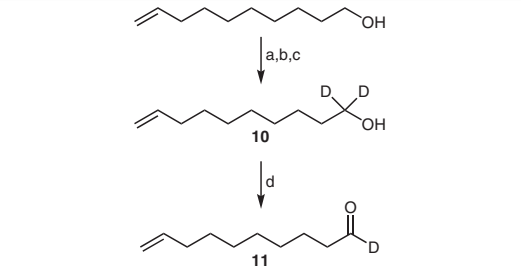
Our synthetic plan for the asymmetric synthesis of deuterium-labelled dihydrosterculic acids **3** and **4** involved preparation of cyclopropyl bis(sulfoxides) **5** and **6** via a diastereoselective cyclopropanation of α,β-unsaturated chiral bis(sulfoxide) (**7**/**8**) derived from readily accessible (S_S,S_S)-1,1-bis(*p*-toluenesulfinyl)methane **9**, followed by regio-

selective lithium-sulfoxide exchange and alkylation.[16] Quenching with a proton or deuteron source would follow a second lithium-sulfoxide exchange (Scheme 1).[14,17]



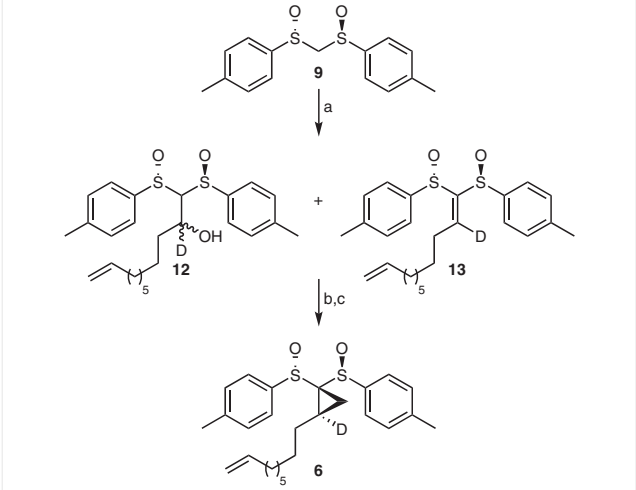
Scheme 1 Retrosynthesis of isotopically labelled dihydrosterculic acids **3** and **4**

Synthesis of our 9-deuterio isotopologue **4** required dec-9-enal-1-*d* (**11**), which was prepared from dec-9-en-1-ol (Scheme 2). Jones oxidation and Fischer esterification were followed by reduction with lithium aluminium deuteride (LAD) to afford dec-9-en-1-ol-1,1-d_2 (**10**), which was transformed into the requisite aldehyde **11** via Swern oxidation.



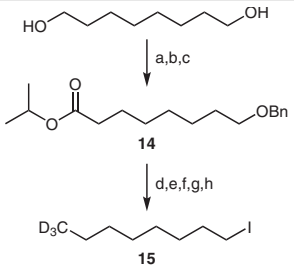
Scheme 2 *Reagents and conditions*: (a) CrO_3, aq H_2SO_4, acetone, 0 °C→r.t., 20 h, 95%; (b) H_2SO_4 (cat.), IPA, Δ, 18 h, 90%; (c) LAD, THF, r.t., 1 h, 96%; (d) $[ClC(O)]_2$, DMSO, TEA, CH_2Cl_2, –78 °C, 1 h, 81%.

Addition of the anion of **9** to **11** afforded the desired alcohol **12** as a mixture of alcohol epimers and a minor amount of alkene **13** (Scheme 3). Excess aldehyde was removed from the crude reaction mixture by rapid filtration through a silica plug, as the unlabelled isotopologue of **13** was known to undergo Mislow–Evans rearrangement upon prolonged exposure to silica gel.[14,18,19] The resultant mixture of **12** and **13** was exposed to a water-soluble carbodiimide to complete the conversion into **13**, which was again passed through a silica plug and immediately exposed to Corey–Chaykovsky cyclopropanation conditions. This produced two cyclopropane diastereomers in an 85:15 ratio, with the major product being the desired diastereomer **6**, which was isolated in 43% yield over three steps, with the final step requiring iterative chromatography to remove the minor diastereomer completely.



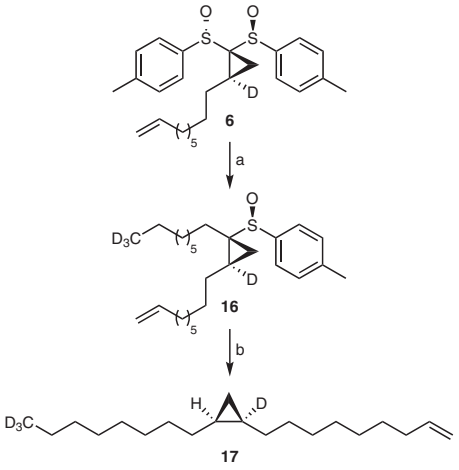
Scheme 3 *Reagents and conditions*: (a) *n*-BuLi, THF, –50 °C to –40 °C, 1 h; –78 °C, 15 min; **11**, –78 °C, 30 min; (b) $CuCl_2$ (cat.), *N*-cyclohexyl-*N*′-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate, MeCN, r.t., 12 h; (c) $Me_3S(O)I$, NaH, DMSO, r.t., 13 h, 43% over three steps (major diastereomer).

As we intend to employ mass spectrometry to analyse the results of our competitive kinetic isotope studies, we required a mass tag to differentiate products derived from D-labelled isotopologues and unlabelled dihydrosterculic acid. Accordingly, we prepared 1-iodooctane-8,8,8-d_3 (**15**)[20] from 1,8-octanediol (Scheme 4). Monobenzylation was followed by oxidation to the corresponding aldehyde. Szpliman's protocol for 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-catalysed oxidation to the mixed anhydride and conversion into the isopropyl ester[21] then provided facile access to ester **14**. Subsequent reduction with LAD, alcohol tosylation,[22] and tosylate reduction with LAD afforded the desired terminal CD_3 group. Hydrogenolysis with Pearlman's catalyst, followed by Appel iodination produced the desired iodide **15** in high yield.



Scheme 4 *Reagents and conditions*: (a) NaH, BnBr, THF/DMF, 0 °C to r.t., 18 h, 51%; (b) TEMPO (1 mol%), KBr (10 mol%), NaOCl, CH_2Cl_2, pH 8.6 buffer, 0 °C, 0.5 h, 99%; (c) TEMPO (5 mol%), pivalic acid, *t*-BuOCl, pyr., MeCN, 0 °C, then IPA, DIPEA, DMAP, r.t., 18 h, 91%; (d) LAD, THF, 0 °C to r.t., 6 h, 84%; (e) TsCl, TEA, Me_3N·HCl (10 mol%), toluene, 0 °C, 1 h, 89%; (f) LAD, THF, 0 °C to r.t., 2.5 h, 77%; (g) H_2 (1 atm.), cat. $Pd(OH)_2/C$, EtOAc, r.t., 48 h, 98%; (h) Ph_3P, I_2, imidazole, CH_2Cl_2, 0 °C to r.t., 0.5 h, 96%.

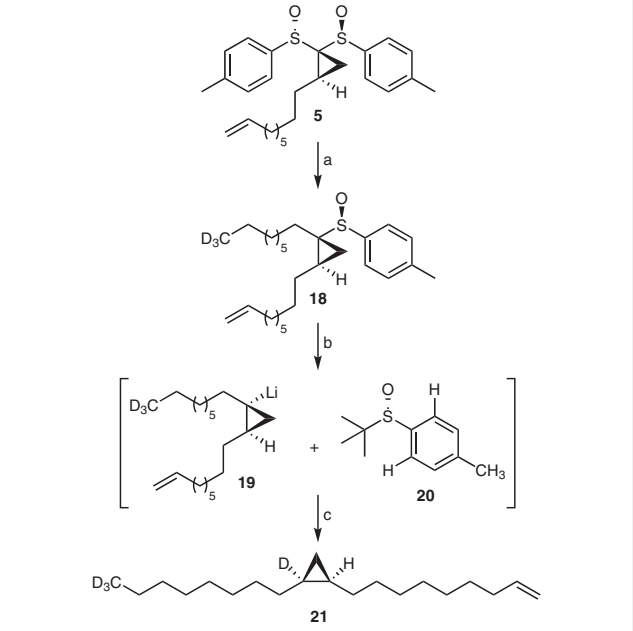
With **15** in hand, we proceeded with the lithium-sulfoxide exchange/alkylation reaction (Scheme 5). Interestingly, the addition of *n*-BuLi to **6** led to contra-steric cleavage of the more hindered sulfoxide;[16,17] subsequent addition of 5 equivalents of iodide **15** afforded the desired dialkylcyclopropane sulfoxide **16** in moderate yield. Addition of *t*-BuLi and quenching with MeOH produced the desired *cis*-cyclopropane **17**.



Scheme 5 *Reagents and conditions*: (a) *n*-BuLi, THF, –78 °C to –40 °C, 1 h; **15**, –78 °C, 3 h, 54%; (b) *t*-BuLi, toluene, –78 °C, 1 min; MeOH, –78 °C to 0 °C, 1 h, 70%.

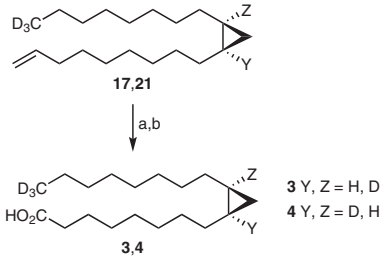
Our 10-deuteriodihydrosterculic acid isotopologue **3** was envisaged to accede from **5** – the variant of **6** lacking the deuterium on the cyclopropane ring. Cyclopropane bis(sulfoxide) **5** was prepared from **9** and 9-decenal in 35% isolated yield over three steps, with the cyclopropanation step producing an 86:14 ratio of diastereomers, which were separated by analogy to **6**.[14,18]

The lithium-sulfoxide exchange/alkylation of **5** proceeded in the expected moderate yield (Scheme 6). The subsequent lithium-sulfoxide exchange/deuteration of **18** afforded some surprising results. Unlike the lithium-sulfoxide exchange reaction of **5**, the reaction of **18** with *t*-BuLi produces an intermediate cyclopropyllithium species **19** that lacks the stabilisation afforded by a residual sulfoxide group.[23] Accordingly, the more reactive *t*-BuLi was used and *t*-butyl *p*-tolyl sulfoxide (**20**) was formed as a byproduct. This sulfoxide lacks acidic protons on the α carbon; nevertheless, when **18** was allowed to stir for 10 minutes at –78 °C after a slow addition of *t*-BuLi followed by the addition of a large excess of MeOD, we observed less than 5% D incorporation on the cyclopropane ring. We hypothesise that even at –78 °C, cyclopropyllithium **19** rapidly deprotonates **20**, most likely via directed orthometallation,[24] though remote deprotonation of the methyl group of the tolyl residue, or E2 elimination via deprotonation of the *t*-butyl group cannot be ruled out. Such a phenomenon may also explain the moderate yields obtained in transformations of substrates similar to **18**.[17] Thus, we surmised that a rapid addition of *t*-BuLi followed by immediate quenching would improve the deuterium labelling efficiency. This supposition proved to be correct, as we obtained a 90% yield of desired cyclopropane **21** with an 84% D incorporation at C10.



Scheme 6 *Reagents and conditions*: (a) *n*-BuLi, THF, –78 °C to –40 °C, 1 h; **15**, –78 °C, 3 h, 64%; (b) *t*-BuLi, toluene, –78 °C, 10 s; (c) MeOD, –78 °C to 0 °C, 1 h, 90%.

Having successfully prepared regioisomeric deuterium-labelled cyclopropane alkenes **17** and **21**, we completed the synthesis of **3** and **4** via Marshall ozonolysis and hydrolysis (Scheme 7).



Scheme 7 *Reagents and conditions*: (a) O_3, NaOH, MeOH, CH_2Cl_2, –78 °C, 1.5 h; (b) LiOH·H_2O, MeOH, Δ, 15 h; (**3**: 54% over two steps; **4**: 85% over two steps).

In conclusion, we have successfully synthesised isotopically labelled and mass-tagged isotopologues of dihydrosterculic acid for use in *in vitro* and *in vivo* studies of the cryptoregiochemistry of desaturation to form sterculic acid. Efforts to isolate and functionally express the putative desaturase gene are ongoing and results will be reported in due course.

All reagents were reagent grade and purchased from Sigma–Aldrich, Fluka, Analar, or Cambridge Isotope Laboratories Inc. and used as received, with the following exceptions: PhMe, CH_2Cl_2, DMSO, DIPA and MeCN were distilled from CaH_2; Et_2O and THF was distilled from $LiAlH_4$ or sodium benzophenone ketyl; and all alkyl halides (commercial or prepared) were purified by elution through a short column of aluminium oxide (activated, basic, Brockman I) prior to use. Ozone was generated by using an A2Z Systems Inc. A2ZS-SGLAB ozone generator with a 0.5 L/min O_2 flow. All reactions involving air- or moisture-sensitive reagents or intermediates were performed under an Ar or N_2 atmosphere in glassware that was flame-dried or oven-dried. Reaction temperatures refer to the temperature of the cooling/heating bath. For the more unusual temperatures, a Neslab Cryotrol cryobath was used with a liquid coolant composed of a mixture of acetone and MeOH (1:1). Volatile solvents were removed under reduced pressure using a Heidolph rotary evaporator at 40 °C (bath temperature). Thin-layer chromatography was performed on glass-backed Extra Hard Layer (60 Å) TLC plates purchased from Silicycle. Spots were visualised by fluorescence quenching under UV light (254 nm) and/or staining with aqueous ceric ammonium molybdate, iodine on silica gel, or $KMnO_4$. Chromatography was performed using forced flow (flash chromatography, FCC) on Silia-P Flash silica gel (40–62 µm) from Silicycle or adsorbed onto Celite 521 from Sigma–Aldrich and was performed using dry column vacuum chromatography (DCVC)[25] with SiliaFlash E60 silica gel (15–40 µm) from Silicycle. Compounds that were dried under high vacuum refer to a reduced pressure of ca. 20 mTorr. FTIR spectra were recorded with a Varian 1000 Scimitar Series or an ABB Bomem MB Series spectrometer and were obtained as thin films on sodium chloride and are reported in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance 300 or Bruker Avance III 400 spectrometer at 300 or 400 MHz for ^1H and 75 or 100 MHz for ^{13}C, respectively, and were obtained at the indicated field as solutions in $CDCl_3$ (stored over activated 4 Å molecular sieves) unless otherwise indicated. Chemical shifts are referenced to tetramethylsilane (δ = 0.00 ppm) as an internal standard and are reported in parts per million (ppm, δ) relative to TMS. Coupling constants (*J*) are reported in Hz, and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Chemical purity of compounds that were used without purification was determined by ^1H NMR spectroscopy. Yields refer to purified compounds unless explicitly indicated otherwise. Deuterium incorporation of deuterated compounds was determined by comparison of peak integrations of the labelled materials versus the integration of the same peak(s) in the ^1H NMR spectrum of the unlabeled compound.

9-Decen-1,1-*d*$_2$-ol (10)[26]

A solution of ester **S2** (8.17 g, 38 mmol) in THF (50 mL) was added to a suspension of $LiAlD_4$ (1.30 g, 31 mmol) in THF (150 mL) at 0 °C by using a cannula over 10 min. The mixture was warmed to ambient temperature and stirred for 1 h. The reaction mixture was re-cooled in an ice/water bath for 10 min before slowly quenching by portionwise addition of solid $Na_2SO_4{\cdot}10H_2O$ (10 g). Acetone (20 mL) was added to ensure the consumption of any residual metal-deuteride species, and the sludgy mixture was vigorously stirred while warming to ambient temperature for 2 h. The now white reaction mixture was filtered over Celite®, washed with saturated aqueous Rochelle's salt (2 × 300 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to give a light-yellow liquid (6.12 g). The crude liquid was purified by DCVC (2.5–10%, EtOAc/hexanes) to afford the product.

Yield: 5.79 g (96%); clear liquid; R_f = 0.09 (5%, EtOAc/hexanes, $KMnO_4$).

FTIR (NaCl plate): 3334, 2926, 2855, 1641, 1465, 1367, 1134, 967, 909 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 5.81 (ddt, ^3J = 17.1, 10.2, 6.6 Hz, 1 H), 5.03–4.92 (m, 2 H), 2.04 (q, ^3J = 7.5 Hz, 2 H), 1.57–1.53 (m, 2 H), 1.40–1.23 (m, 10 H), 1.18 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.2, 114.2, 62.4 (C1, quin, $^1J_{CD}$ = 21.0 Hz, upfield α-deuterium isotope shift[27] (0.1 ppm)), 33.8, 32.6, 29.4, 29.5, 29.1, 28.9, 25.7.

Dec-9-en-1-*d*-al (11)

A –40 °C solution of DMSO (6.6 mL, 93 mmol) in CH_2Cl_2 (30 mL), was added to a solution of $(COCl)_2$ (3.9 mL, 46 mmol) in CH_2Cl_2 (260 mL) at –78 °C by using a cannula over 15 min. The solution was stirred for 15 min. A 0 °C solution of **10** (5.1 g, 34 mmol) in CH_2Cl_2 (58 mL) was then added by using a cannula over 15 min and the mixture was stirred for an additional 15 min. NEt_3 (24 mL, 174 mmol) was then added, and the reaction mixture was allowed to slowly warm to 0 °C over 4 h. The reaction mixture was diluted in H_2O (200 mL). The organic layer was washed with 1 M aqueous HCl (3 × 150 mL) then saturated aqueous NaCl (1150 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered then concentrated *in vacuo* to afford a yellow oil (6.58 g). The crude oil was purified by FCC (5%, Et_2O/hexanes) to afford the product.

Yield: 4.38 g (81%, 99% D); clear liquid; R_f = 0.26 (5%, Et_2O/hexanes, $KMnO_4$).

FTIR (NaCl plate): 3077, 2929, 2856, 2066, 1716, 1641, 1465, 1406, 1095, 995, 910 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 9.77 (t, ^3J = 1.8 Hz, 0.01 H), 5.81 (ddt, ^3J = 17.1, 10.2, 6.6 Hz, 1 H), 5.03–4.91 (m, 2 H), 2.42 (t, ^3J = 7.2 Hz, 2 H), 2.04 (q, ^3J = 7.2 Hz, 2 H), 1.63 (quin, ^3J = 7.2 Hz, 2 H), 1.41–1.23 (m, 10 H).

^{13}C NMR (C_6D_6, 100 MHz): δ = 200.0 (t, ^1J = 26.0 Hz), 138.8, 114.2, 43.2 (t, ^2J = 3.7 Hz), 33.8, 29.1, 28.9, 28.8, 28.7, 21.8.

(S_S,S_S,)-1,1-Bis(*p*-tolylsulfinyl)undec-10-en-2-*d*-2-ol (12)

The protocol was adapted from the procedure reported by Malacria.[28] A solution of *n*-BuLi in hexanes (3.9 mL, 2.91 M, 11.3 mmol) was added dropwise to a solution of bis(sulfoxide) **9** (2.99 g, 10.2 mmol) dissolved in THF (43 mL) at –50 °C (best results were obtained if bis(sulfoxide) was dried under vacuum at 65 °C for 18 h). The light-yellow solution was allowed to warm to –40 °C for 1 h to ensure complete formation of the anion. The solution was then re-cooled to –78 °C in an acetone/dry ice bath for 15 min. Aldehyde **11** (6.51 g, 42 mmol) was chilled to 0 °C and added neat by using a cannula over 10 min. The reaction was allowed to stir at this temperature for 30 min before quenching with saturated aqueous NH_4Cl (60 mL) and subsequent warming to ambient temperature. 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 anhydrous Na_2SO_4, filtered and concentrated to give a yellow oil (9.5 g). This material was semi-purified by FCC (20–80%, EtOAc/hexanes) to afford a mixture of diastereomeric alcohols **12** and dehydrated product **13**.

Yield: 4.06 g; pale-yellow oil; R_f = 0.42 (50%, EtOAc/hexanes, UV, $KMnO_4$). The product was not fully characterised because of its limited shelf-life and complexity of spectra.

(S_S,S_S)-1,1-Bis(*p*-tolylsulfinyl)-2-*d*-oct-1,10-diene (13)

This protocol was adapted from the procedure reported by Malacria.[28] A 500 mL round-bottomed flask was charged with the mixture of diastereomeric alcohols **12** and diene **13** prepared above (4.06 g, 9.10 mmol), MeCN (180 mL), and morpho-CDI (5.80 g, 13.7 mmol). To this solution, anhydrous $CuCl_2$ (193 mg, 1.43 mmol) was added and the mixture was stirred at r.t. for 12 hours. The reaction mixture was diluted in CH_2Cl_2 (160 mL) and filtered through a short pad of Celite® and silica gel; the filter cake was washed with CH_2Cl_2 (200 mL) then EtOAc (100 mL) and concentrated *in vacuo* to afford **13** as a yellow to blue-green oil (3.72 g). This oil was used without further purification because it was unstable to flash chromatography. R_f = 0.56 (40%, EtOAc, UV, $KMnO_4$).

(S_S,S_S,2*R*)-1,1-Bis(*p*-tolylsulfinyl)-2-*d*-2-dec-10-enylcyclopropane (6)

DMSO (68 mL) was cautiously added to a mixture of NaH (1.04 g, 95%, 41.2 mmol) and Me_3SOI (9.55 g, 43.4 mmol) while stirring at r.t. until the mixture became homogeneous (30 min). To this solution was added alkylidene bis-sulfoxide **13** (3.72 g, 8.66 mmol) and the resultant mixture was stirred at r.t. for 12 h, at which point the reaction was quenched with saturated aqueous NH_4Cl (100 mL). The mixture was extracted with Et_2O (3 × 125 mL) and the combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give a viscous yellow oil (3.38 g). The crude oil was exhaustively purified by FCC (toluene/Hexane/EtOAc/3-methyl-2-butanone, 26:10:3:4) to afford **6**.

Yield: 1.97 g (43% over three steps); colourless oil; R_f = 0.14 (20%, EtOAc/toluene, UV, $KMnO_4$); $[\alpha]_D^{26}$ = –114.08 (*c* = 0.233, $CHCl_3$).

FTIR (NaCl plate): 3058, 2976, 2926, 2855, 1640, 1596, 1492, 1454, 1399, 1303, 1209, 1178, 1085, 1048, 1015, 994, 909, 809, 731, 635 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.57 (d, ^3J = 8.1 Hz, 2 H), 7.36 (d, ^3J = 7.8 Hz, 2 H), 7.21 (d, ^3J = 6.6 Hz, 2 H), 7.05 (d, ^3J = 8.4 Hz, 2 H), 5.81 (ddt, ^3J = 17.1, 10.2, 6.6 Hz, 1 H), 5.03–4.92 (m, 2 H), 2.45 (s, 3 H), 2.39 (s, 3 H), 2.04 (q, ^3J = 7.5 Hz, 2 H), 1.78–1.68 (m, 2 H), 1.41–1.19 (m, 10 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 143.1, 142.2, 139.1, 138.9, 138.4, 130.1, 129.8, 126.5, 125.2, 114.2, 62.9, 33.8, 29.6, 29.3, 29.0, 29.0, 28.9, 27.3 (C3, upfield β-deuterium isotope shift[14,18] (0.09 ppm)), 24.7 (C2, t, $^1J_{CD}$ = 23.0 Hz, upfield α-deuterium isotope shift[14,18] (0.3 ppm)), 21.6, 21.5, 13.3.

Isopropyl 8-(Benzyloxy)octanoate (14)

This procedure was adapted from the work of Szpilman et al.[21] Aldehyde **S4** (6.18 g, 26.4 mmol), pivalic acid (3.0 g, 29.4 mmol), TEMPO (207 mg, 1.3 mmol), and pyridine (4.3 mL, 53.2 mmol) were dissolved in MeCN (66 mL) and cooled to 0 °C and flushed with Argon. ^{t}BuOCl (3.22 g, 29.7 mmol) was then added dropwise over 10 min. The solution was allowed to warm to ambient temperature over 15 min, and DIPA (10.1 mL, 58.0 mmol), isopropanol (3.6 mL, 47 mmol) and DMAP (0.32 g, 2.6 mmol) were added sequentially. The reaction was stirred overnight (18 h) at r.t. The reaction was diluted with saturated aqueous $NaHCO_3$ (1.3 L), extracted with EtOAc (3 × 250 mL) and the organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to yield a crude pale-pink oil (7.67 g). The crude oil was purified by FCC (20–30%, EtOAc/hexanes) to give **14**.

Yield: 7.04 g (91%); colourless liquid; R_f = 0.77 (30%, EtOAc/hexanes; UV).

FTIR (NaCl plate): 3064, 3031, 2979, 2934, 2857, 1950, 1730, 1466, 1373, 1309, 1253, 1202, 1179, 1109, 1028, 963, 901, 823, 736 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.35–7.16 (m, 5 H), 5.00 (sep, ^3J = 6.3 Hz, 1 H), 4.50 (s, 2 H), 3.46 (t, ^3J = 6.6 Hz, 2 H), 2.25 (t, ^3J = 7.5 Hz, 2 H), 1.66–1.56 (m, 4 H), 1.45–1.25 (m, 6 H), 1.22 (d, ^3J = 6.3 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.3, 138.8, 128.4, 127.6, 127.6, 127.5, 72.9, 70.4, 67.3, 34.7, 29.8, 29.2, 29.1, 26.1, 25.0, 21.9.

1-Iodo-8,8,8-*d*$_3$-octane (15)[20]

Alcohol **S8** (0.61 g, 4.6 mmol), PPh_3 (1.55 g, 5.9 mmol), imidazole (0.41 g, 5.9 mmol) were dissolved in CH_2Cl_2 (7.5 mL) at ambient temperature, before cooling to 0 °C. I_2 (1.57 g, 5.9 mmol) was added slowly and a vigorous gas evolution was observed. The orange reaction mixture was warmed to ambient temperature and stirred for 30 min. After the reaction was judged to be complete by TLC, saturated aqueous $Na_2S_2O_3$ (10 mL) was added, and the mixture was stirred for 5 min. The layers were separated and aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). Organic layers were combined, dried over anhydrous $MgSO_4$, and filtered over a short pad of silica. After thorough washing of the filter cake with hexanes (30 mL), the solution was concentrated to give a slushy white solid. This solid was suspended in hexanes (10 mL) and cooled to 0 °C without stirring. The suspension was filtered over a short pad of silica, and the filter cake was washed with cold hexanes (50 mL), the filtrate was concentrated to give the product.

Yield: 1.07 g (96%); colourless liquid; R_f = 0.74 (100%, hexanes; UV, $KMnO_4$).

FTIR (NaCl plate): 2923, 2854, 2212, 2121, 2075, 1463, 1196, 1165, 1055, 720 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 3.19 (t, ^3J = 6.8 Hz, 2 H), 1.82 (quin, ^3J = 7.2 Hz, 2 H), 1.45–1.35 (m, 2 H), 1.35–1.14 (m, 8 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 33.6, 31.7, 30.5, 29.1, 28.5, 22.3 (C7, upfield β-deuterium isotope shift[29] (0.2 ppm)), 13.2 (C8, quin, $^1J_{CD}$ = 19.0 Hz, upfield α-deuterium isotope shift[29] (0.9 ppm)), 7.21.

(S_S)-1-*p*-Tolylsulfinyl-(1*R*,2*R*)-2-*d*-2-(non-8-en-1-yl)-1-(8,8,8-d_3-octyl)cyclopropane (16)

This protocol was adapted from the procedure reported by Marek and co-workers.[17] A solution of *n*-BuLi in hexanes (2.15 mL, 2.50 M, 4.7 mmol) was added dropwise to a solution of bis(sulfoxide) **6** (0.92 g, 2.1 mmol) in THF (21 mL) at –78 °C. The solution was then warmed to –40 °C and stirred for 1 h. Labelled iodooctane **15** (3.01 g, 12.4 mmol) was added to the reaction mixture dropwise neat by using a cannula and stirred at 0 °C for 3 h. The reaction was quenched with saturated aqueous NH_4Cl (30 mL); the layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were combined and dried over anhydrous Na_2SO_4, filtered and concentrated to give a pale-yellow liquid (3.45 g). The crude oil was purified by FCC (10–30%, Et_2O in hexanes) to afford **16**.

Yield: 0.48 g (60%); colourless oil; R_f = 0.29 (30%, Et_2O/hexanes, UV, $KMnO_4$); $[\alpha]_D^{25}$ = +62.13 (*c* = 0.235, $CHCl_3$).

FTIR (NaCl plate): 3075, 2925, 2855, 1640, 1463, 1085, 1053, 908, 807, 722 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.50 (d, ^3J = 8.1 Hz, 2 H), 7.29 (d, ^3J = 7.8 Hz, 2 H), 5.81 (ddt, ^3J = 17.1, 10.2, 6.6 Hz, 1 H), 5.03–4.91 (m, 2 H), 2.41 (s, 3 H), 2.03 (q, ^3J = 7.5 Hz, 2 H), 1.65–1.45 (m, 2 H), 1.44–1.05 (m, 25 H), 0.42 (d, ^2J = 5.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 141.4, 140.0, 139.2, 129.5, 125.1, 114.2, 44.2, 33.8, 31.8, 29.7, 29.4, 29.4, 29.3, 29.5, 29.2, 29.0, 28.9, 28.2, 27.4, 26.1, 22.4, 21.4, 18.5 (C2, t, $^1J_{CD}$ = 25.0 Hz, upfield α-deuterium isotope shift[14,18] (0.3 ppm)), 14.6, 13.2 (C8, quin, $^1J_{CD}$ = 19.0 Hz, upfield α-deuterium isotope shift[14,18] (0.9 ppm)).

(1*R*,2*S*)-1-*d*-1-(Non-8-en-1-yl)-2-(8,8,8-d_3-octyl)cyclopropane (17)

A *t*-BuLi solution in pentane (2.15 mL, 1.5 M, 3.2 mmol) was added in one portion (as quickly and safely as possible) to a stirred solution of sulfoxide **15** (438 mg, 1.0 mmol) in toluene (21 mL) at –78 °C. The reaction was stirred for 1 min before quenching with MeOH (3 mL) and allowing it to warm to 0 °C for 1 h. Saturated NH_4Cl (25 mL) was then added, the layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to afford a crude oil (0.65 g). The oil was the purified by FCC (100%, HPLC grade hexanes) to afford **16**.

Yield: 202 mg (70%); colourless oil; R_f = 0.88 (100%, hexanes, I_2, $KMnO_4$); $[\alpha]_D^{25}$ = +2.012 (*c* = 0.400, $CHCl_3$).

FTIR (NaCl plate): 3060, 2989, 2925, 2854, 1641, 1465, 909 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 5.82 (ddt, ^3J = 17.1, 10.2, 6.6 Hz, 1 H), 5.05–4.89 (m, 2 H), 2.04 (q, ^3J = 7.2 Hz, 2 H), 1.45–1.22 (m, 26 H), 0.71–0.58 (m, 1 H), 0.58–0.51 (m, 1 H), –0.34 (t, *J* = 4.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.2, 114.1, 33.8, 31.9, 30.2, 30.2, 29.7, 29.6, 29.6, 29.4, 29.2, 29.0, 28.7, 28.6, 22.4, 15.7 (C2, upfield β-deuterium isotope shift[14,18] (0.1 ppm)), 15.4 (C1, t, $^1J_{CD}$ = 23.0 Hz, upfield α-deuterium isotope shift[14,18] (0.3 ppm)), 13.2 (C8, quin, $^1J_{CD}$ = 19.0 Hz, upfield α-deuterium isotope shift[14,18] (0.9 ppm)), 10.8.

(S_S,S_S,2*R*)-1,1-Bis(*p*-tolylsulfinyl)-2-dec-10-enylcyclopropane (5)[14]

Prepared analogously to **6** except aldehyde **S9** was used.

Yield: 1.61 g (35% over three steps); clear oil; R_f = 0.35 (20%, EtOAc/toluene, $KMnO_4$, UV).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.58 (d, ^3J = 8.0 Hz, 2 H), 7.37 (d, ^3J = 8 Hz, 2 H), 7.23 (d, ^3J = 8 Hz, 2 H), 7.07 (d, ^3J = 8.0 Hz, 2 H), 5.81 (ddt, ^3J = 17.2, 10.4, 6.4 Hz, 1 H), 5.03–4.92 (m, 2 H), 2.49 (s, 3 H), 2.41 (s, 3 H), 2.05 (q, ^3J = 6.8 Hz, 2 H), 1.80–1.62 (m, 2 H), 1.40–1.25 (m, 11 H).

(S_S)-1-*p*-Tolylsulfinyl-(1*R*,2*R*)-2-*d*-2-(non-8-en-1-yl)-1-(8,8,8-d_3-octyl)cyclopropane (18)

Prepared analogously to **16**.

Yield: 1.61 g (64%); clear oil; R_f = 0.29 (30%, Et_2O/hexanes, UV, $KMnO_4$); $[\alpha]_D^{23}$ = +57.27 (*c* = 0.220, $CHCl_3$).

FTIR (NaCl plate): 2925, 2854, 2360, 1640, 1492, 1464 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.50 (d, ^3J = 8.0 Hz, 2 H), 7.29 (d, ^3J = 8.0 Hz, 2 H), 5.81 (ddt, ^3J = 17.2, 10.4, 6.4 Hz, 1 H), 5.04–4.87 (m, 2 H), 2.41 (s, 3 H), 2.03 (q, ^3J = 7.6 Hz, 2 H), 1.65–1.45 (m, 3 H), 1.44–1.05 (m, 25 H), 0.42 (t, ^2J = 6.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 141.4, 139.8, 139.1, 129.5, 125.1, 114.2, 44.4, 33.8, 31.8, 29.8, 29.4, 29.4, 29.3, 29.3, 29.2, 29.0, 28.9, 28.3, 27.4, 26.2, 22.4, 21.4, 18.8, 14.7, 13.2 (C8, quin, $^1J_{CD}$ = 18.0 Hz, upfield α-deuterium isotope shift[14,18] (0.9 ppm)).

(1*R*,2*S*)-1-(Non-8-en-1-yl)-2-2-*d* -(8,8,8-d_3-octyl)cyclopropane (21)

A *t*-BuLi solution in pentane (0.75 mL, 1.5 M, 0.5 mmol) was added in one portion (as quickly and safely as possible) to a stirred solution of sulfoxide **18** (151.3 mg, 0.36 mmol) in toluene (7.1 mL) at –78 °C. The reaction was stirred for 10 seconds before quenching with MeOD (1 mL) in one portion; the mixture was then warmed to 0 °C and stirred for 1 h. Saturated NH_4Cl (10 mL) was then added, the layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated to afford a crude oil (0.30 g). The oil was the purified by FCC (100%, HPLC grade hexanes) to afford **21**.

Yield: 93.1 mg (90%, 84% D at C_{10}); colourless oil; R_f = 0.92 (100% hexanes, I_2, $KMnO_4$); $[\alpha]_D^{22}$ = +2.041 (*c* = 0.392, $CHCl_3$).

FTIR (NaCl plate): 3076, 3060, 2989, 2912, 2856, 1641, 1464, 992, 909 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.82 (ddt, ^3J = 17.2, 10.4, 6.8 Hz, 1 H), 5.05–4.90 (m, 2 H), 2.04 (q, ^3J = 7.6 Hz, 2 H), 1.45–1.10 (m, 26 H), 0.71–0.58 (m, 1 H), 0.58–0.51 (m, 1 H), –0.34 (t, *J* = 4.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 139.3, 114.1, 33.8, 31.8, 30.2, 29.7, 29.6, 29.5, 29.4, 29.2, 29.0, 28.7, 28.6, 22.4, 15.7 (C2, upfield β-deuterium isotope shift[18] (0.1 ppm)), 15.4 (C1, t, $^1J_{CD}$ = 23.0 Hz, upfield α-deuterium isotope shift[18] (0.4 ppm)), 13.2 (C8, t, $^1J_{CD}$ = 19.0 Hz, upfield α-deuterium isotope shift[18] (0.9 ppm)), 10.8.

(9*R*,10*S*)-9-*d*-Dihydrosterculic Acid (4)

This protocol was adapted from the procedure reported by Kitahara.[30] Crude ester **S10** (137.8 mg, 0.44 mmol if pure) and $LiOH{\cdot}H_2O$ (186.3 mg, 4.4 mmol) were dissolved in MeOH (14.5 mL) and heated to reflux for 15 h. The resulting reaction mixture was allowed to cool to ambient temperature before acidifying with 1 M HCl (5 mL) and concentrating under reduced pressure to remove the MeOH. EtOAc (15 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to give a crude pale-brown oil (120.5 mg). The crude oil was purified by FCC (9% EtOAc/1% AcOH/ hexanes) to afford acid **4**.

Yield: 102 mg (85% over two steps, 98% D at C_9); R_f 0.20 (9% EtOAc/1% AcOH/ hexanes, I_2, $KMnO_4$).

FTIR (NaCl plate): 3057, 2924, 2854, 2676, 2213, 1711, 1465, 1413, 1285, 936 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 10.98 (br s, 1 H), 2.35 (t, ^3J = 7.2 Hz, 2 H), 1.64 (quin, ^3J = 7.2 Hz, 2 H), 1.45–1.21 (m, 22 H), 1.19–1.05 (m, 2 H), 0.69–0.61 (m, 1 H), 0.57–0.53 (m, 1 H), –0.34 (t, ^3J = 4.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 179.9, 34.0, 31.9, 30.2, 30.1, 29.7, 29.4, 29.4, 29.3, 29.1, 28.7, 28.5, 24.7, 22.4, 15.7, 15.3 (C9, t, $^1J_{CD}$ = 23.6 Hz, upfield α-deuterium isotope shift[18] (0.4 ppm)), 13.2 (C19, t, $^1J_{CD}$ = 19.0 Hz, upfield α-deuterium isotope shift[18] (0.9 ppm)), 10.8.

(9*R*,10*S*)-10-*d*-Dihydrosterculic Acid (3)

Prepared analogously to **4**.

Yield: 43 mg (54%); light-yellow solid; R_f = 0.20 (9% EtOAc/1% AcOH/hexanes, I_2, $KMnO_4$).

FTIR (NaCl plate): 3057, 2924, 2854, 2676, 2213, 1711, 1465, 1413, 1285, 936 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.98 (br s, 1 H), 2.35 (t, ^3J = 7.2 Hz, 2 H), 1.64 (quin, ^3J = 7.2 Hz, 2 H), 1.45–1.21 (m, 22 H), 1.19–1.05 (m, 2 H), 0.69–0.61 (m, 1 H), 0.57–0.53 (m, 1 H), –0.34 (t, ^3J = 4.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 180.0, 34.0, 31.9, 30.2, 30.1, 29.7, 29.4, 29.4, 29.3, 29.1, 28.7, 28.5, 24.7, 22.4, 15.62, 15.4 (C10, t, ^1J = 23.6 Hz, upfield α-deuterium isotope shift[18] (0.3 ppm)), 13.3 (C19, t, ^1J = 19.0 Hz, upfield α-deuterium isotope shift[18] (0.8 ppm)), 10.8.

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Supporting Information

Experimental procedures, spectral data, copies of ^{1}H NMR and ^{13}C NMR spectra are available.Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591976.

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