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

Samuel W. J. Shields* Peter H. Buist* Jeffrey M. Manthorpe*

*Carleton University, Department of Chemistry, 203 Steacie Building, 1125 Colonel By Drive, Ottawa, Ontario, K1S 5B6, Canada
b Carleton University, Institute of Biochemistry, 209 Nesbitt Building, 1125 Colonel By Drive, Ottawa, Ontario, K1S 5B6, Canada

Received: 12.01.2018
Accepted after revision: 14.03.2018
Published online: 08.06.2018
DOI: 10.1002/sopen.201800004-op
License terms: (C) Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2018

Abstract The total synthesis of isotopically labelled (9R,10S)-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 (9R,10S)-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 cyclopropane fatty acids are potent inhibitors of mammalian stearoyl CoA Δ⁹ desaturases (SCDs). Humans have two SCD homologues – SCD1 and SCD5. The X-ray structure of both human3 and murine4 variants of SCD1 were recently published. Mice deficient in SCD1 demonstrated improved insulin sensitivity and lipid metabolic profiles when fed a high-fat diet5,6 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 products11 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 desaturation12 and cyclopropane fatty acids13–15 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.

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 (S₉,S₉)-1,1-bis(p-toluenesulfinyl)methane 9, followed by regio-
selective lithium-sulfoxide exchange and alkylation. Quenching with a proton or deuteron source would follow a second lithium-sulfoxide exchange (Scheme 1). 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.

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-d₃ (15) from 1,8-octanediol (Scheme 4). Monobenzylation was followed by oxidation to the corresponding aldehyde. Szpli-man’s protocol for 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-catalysed oxidation to the mixed anhydride and conversion into the isopropyl ester then provided facile access to ester 14. Subsequent reduction with LAD, alcohol/tosylation, and tosylate reduction with LAD afforded the desired terminal CD₃ group. Hydrogenolysis with Pearlman’s catalyst, followed by Appel iodination produced the desired iodide 15 in high yield.

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. 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.

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-d₂ (10), which was transformed into the requisite aldehyde 11 via Swern oxidation.

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-d₃ (15) from 1,8-octanediol (Scheme 4). Monobenzylation was followed by oxidation to the corresponding aldehyde. Szpli-man’s protocol for 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-catalysed oxidation to the mixed anhydride and conversion into the isopropyl ester then provided facile access to ester 14. Subsequent reduction with LAD, alcohol/tosylation, and tosylate reduction with LAD afforded the desired terminal CD₃ group. Hydrogenolysis with Pearlman’s catalyst, followed by Appel iodination produced the desired iodide 15 in high yield.

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. 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.
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. According to previously reported results,23 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 only 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-buty1 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.

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

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).
In conclusion, we have successfully synthesised isotopically labelled and mass-tagged isotopologues of dihydros-tercic 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 de-cryptoregiochemistry of desaturation to form sterculic acid.

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, CH2Cl2, DMSO, DIPA and MeCN were distilled from CaH2; Et2O and THF was distilled from LiAlH4 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. Oxygen was generated by using an A2Z Systems Inc. A2ZS-SGLAB oxygen generator with a 0.5 L/min O2 flow. All reactions involving air- or moisture-sensitive reagents or intermediates were performed under an Ar or N2 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 cryostat was used. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual temperatures, a Neslab Cryotrol cryostat was used. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-ing bath. For the more unusual pressures, a Heidolph rotary evaporator at 40 °C (bath temperature). Reaction temperatures refer to the temperature of the cooling/heat-
The protocol was adapted from the procedure reported by Malacria. 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) (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 (651 mg, 4.2 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 NH4Cl (60 mL) and subsequent warming to ambient temperature. The mixture was separated and the aqueous layer was extracted with CH2Cl2 (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na2SO4, 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; Rf = 0.42 (50%, EtOAc/hexanes, UV, KMnO4). The product was not fully characterized because of its limited shelf-life and complexity of spectra.

This protocol was adapted from the procedure reported by Malacria. A 500 mL round-bottomed flask was charged with the mixture of diastereomeric alcohols 12 and dehydrated product 13. To this mixture was added alkylidene bis-sulfoxide (3.72 g, 8.66 mmol) and the reaction mixture was stirred at r.t. for 12 hours. The reaction mixture was diluted in CH2Cl2 (160 mL) and filtered through a short pad of Celite® and silica gel; the filter cake was washed with CH2Cl2 (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. Rf = 0.56 (40%, EtOAc, UV, KMnO4).

This procedure was adapted from the work of Szpilman et al. Aldehyde (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, 33.2 mmol) were dissolved in MeCN (66 mL) and cooled to 0 °C and flushed with Argon. 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 NaHCO3 (1.3 L), extracted with EtOAc (3 × 250 mL) and the organic layers were combined, washed with brine, dried over anhydrous Na2SO4 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; Rf = 0.77 (30%, EtOAc/hexanes, UV).


1H NMR (CDCl3, 400 MHz): δ = 6.37 (d, J = 6.8 Hz, 2 H), 2.59 (t, J = 6.8 Hz, 2 H), 2.33 (t, J = 6.8 Hz, 2 H), 2.17 (t, J = 6.8 Hz, 2 H), 1.82 (quin, J = 6.8 Hz, 2 H), 1.45-1.52 (m, 4 H), 1.22 (d, J = 6.8 Hz, 6 H), 0.81 (d, J = 6.8 Hz, 3 H), 0.74 (100%, hexanes; UV, 1H NMR) ppm). The solution was then filtered through 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 cold hexanes (50 mL), the filtrate was concentrated to give the product.

Yield: 1.07 g (96%); colourless liquid; Rf = 0.74 (100%, hexanes, UV, KMnO4).

FTIR (NaCl plate): 3023, 2854, 2212, 2121, 2075, 1463, 1169, 1165, 1055, 720 cm–1.

1H NMR (CDCl3, 300 MHz): δ = 4.19 (t, J = 6.8 Hz, 2 H), 2.59 (t, J = 6.8 Hz, 2 H), 1.82 (quin, J = 6.8 Hz, 2 H), 1.45-1.52 (m, 4 H), 1.22 (d, J = 6.8 Hz, 6 H), 0.81 (d, J = 6.8 Hz, 3 H), 0.74 (100%, hexanes; UV, 1H NMR) ppm). The solution was then filtered through 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 cold hexanes (50 mL), the filtrate was concentrated to give the product.

Yield: 1.07 g (96%); colourless liquid; Rf = 0.74 (100%, hexanes, UV, KMnO4).

FTIR (NaCl plate): 3023, 2854, 2212, 2121, 2075, 1463, 1169, 1165, 1055, 720 cm–1.
This protocol was adapted from the procedure reported by Marek and co-workers.1 A solution of n-But in hexanes (2.15 mL, 2.50 M, 4.7 mmol) was added dropwise to a solution of bis(sulfite) 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 NH₄Cl (30 mL); the layers were separated and the aqueous layer was extracted with Et₂O (3 × 30 mL). The combined organic layers were combined and dried over anhydrous Na₂SO₄, filtered and concentrated to give a pale-yellow liquid (3.45 g). The crude oil was purified by FCC (10–30%, EtOAc in hexanes) to afford 16.

Yield: 0.48 g (60%); colourless oil; Rf = 0.29 (30%, EtOAc/hexanes, UV, KMnO₄); [α]₁₅ = +62.13 (c = 0.235, CHCl₃).

FTIR (NaCl plate): 3075, 2925, 2854, 1640, 1465, 1085, 1053, 908, 807, 722 cm⁻¹.

1H NMR (CDCl₃, 300 MHz): δ = 7.60 (d, J = 8.1 Hz, 2 H), 7.29 (d, J = 7.8 Hz, 2 H), 5.81 (ddt, J = 17.1, 10.2, 6.6 Hz, 1 H), 5.03–4.91 (m, 2 H), 2.41 (s, 3 H), 2.03 (q, J = 7.5 Hz, 2 H), 1.65–1.45 (m, 2 H), 1.44–1.05 (m, 25 H), 0.42 (d, J = 5.4 Hz, 1 H).

13C NMR (CDCl₃, 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, 29.3, 29.2, 29.0, 28.9, 28.7, 27.4, 26.1, 22.4, 21.4, 18.5 (C₂, t, JCD = 25.0 Hz, upfield α-deuterium isotope shift 16,18 (0.3 ppm)), 14.6, 13.2 (C₈, quin, JCD = 19.0 Hz, upfield α-deuterium isotope shift 16,18 (0.9 ppm)).

(1R,2S)-(−)-1,1-Diisopropylcyclohexane (17) A t-ButI solution in pentane (0.75 mL, 1.5 M, 0.55 mmol) was added in one portion (as quickly and safely as possible) to a stirred solution of sulfite 15 (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 NH₄Cl (10 ml) was then added, the layers were separated and the aqueous layer was extracted with Et₂O (3 × 10 ml). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated to afford a crude oil (0.30 g). The oil was purified by FCC (100%, HPLC grade hexanes) to afford 16.

Yield: 0.202 mg (70%); colourless oil; Rf = 0.88 (100%, hexanes, I₂, KMnO₄); [α]₂⁵ = +2.012 (c = 0.400, CHCl₃).

FTIR (NaCl plate): 3060, 2989, 2925, 2854, 1641, 1465, 909 cm⁻¹.

1H NMR (CDCl₃, 300 MHz): δ = 5.82 (ddt, J = 17.1, 10.2, 6.6 Hz, 1 H), 5.05–4.89 (m, 2 H), 2.04 (q, J = 7.2 Hz, 2 H), 1.45–1.22 (m, 26 H), 0.51–0.38 (m, 1 H), 0.58–0.51 (m, 1 H), −0.34 (t, J = 4.8 Hz, 1 H).

13C NMR (CDCl₃, 75 MHz): δ = 139.3, 141.4, 33.8, 31.9, 30.2, 30.2, 29.7, 29.6, 29.6, 29.4, 29.2, 28.9, 28.7, 28.6, 22.4, 15.7 (C₂, upfield α-deuterium isotope shift 16,18 (0.1 ppm)), 15.4 (C₁, t, JCD = 23.0 Hz, upfield α-deuterium isotope shift 16,18 (0.3 ppm)), 13.2 (C₈, quin, JCD = 19.0 Hz, upfield α-deuterium isotope shift 16,18 (0.9 ppm)).
Funding Information

This research was supported by a Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant (PH.B.), an NSERC Research Tools and Instrument Grant (PH.B. and J.M.M.), the Canada Foundation for Innovation Leaders Opportunity Fund (J.M.M.) and Carleton University (J.M.M.).

Acknowledgment

The authors thank Prof. Jeffrey Smith (Carleton University) for assistance with high-resolution mass spectrometry.

Supporting Information

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

References


(24) Orthometallation as the proton source is supported by non-integral integration of \textit{t}-butyl p-tolyl sulfoxide that was observed in the $^1$H NMR spectrum of the crude reaction products in the conversion of \textbf{18} to \textbf{21} (See Supporting Information, Figure S29). The authors surmise that non-integral integration of the protons ortho to the sulfinyl group arises via formation of \textbf{20} followed by directed orthometallation by excess t-BuLi followed by deuteriation. While this evidence is indirect, a similar phenomenon has been previously reported in the lithium-sulfoxide exchange of paracyclophanyl \textit{p}-tolyl sulfoxides. The authors had experimental evidence for orthometallation of \textit{t}-butyl \textit{p}-tolyl sulfoxide as the proton source; however, these side-products were obtained in low to moderate yields, thus not excluding the other possible proton sources proposed herein. See: Parmar, R.; Coles, M. P.; Hitchcock, P. B.; Rowlands, G. J. \textit{Synthesis} \textbf{2010}, \textit{4177}.


