An alternative stereoselective synthesis of (-)-1-tetrahydropyrenophorol

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Abstract

Macrodilides have become highly attractive target molecules because of their interesting structural features and biological properties, including antibacterial, antifungal, cytotoxic, and phytotoxic activity. A simple and efficient synthesis of the macrocyclic dilactone, (-)-1-tetrahydropyrenophorol, has been accomplished from commercially available compounds. The synthesis utilizes regioselective ring opening of a chiral epoxide, followed by asymmetric dihydroxylation and a Mitsunobu reaction for the construction of the macrolactone.

Keywords: (-)-1-Tetrahydropyrenophorol, macrodiolide, asymmetric dihydroxylation, cyclodimerisation, Mitsunobu reaction
Introduction

Macrodiolides have become highly attractive target molecules to synthetic chemists in recent years because of their biological properties and interesting structural features. In nature, macrodiolides are found as both homodimers, consisting of two identical units and showing C\textsubscript{2} symmetry, and heterodimers, consisting of two different units. Many of these macrodiolides (both homo and hetero) exhibit potent biological activities, such as antibacterial, antifungal, cytotoxic, and phytotoxic activity.\textsuperscript{6,9}

(-)-1-Tetrahydropyrenophorol (Fig. 1) is an example of a C\textsubscript{2}-symmetric macrodiolide. It was isolated from the ethyl-acetate extract of a culture of an endophytic \textit{Phoma} sp. isolated from the plant \textit{Fagonia cretica}. It exhibits good herbicidal and algicidal and moderate fungicidal activities. The relative configuration of (-)-1-tetrahydropyrenophorol (1) was confirmed by X-ray single-crystal analysis. Its absolute configuration was determined by solid-state time-dependent density-functional theory (TDDFT) CD methodology.\textsuperscript{2} Recently, a synthesis of (-)-1-tetrahydropyrenophorol was reported by Pratapareddy \textit{et al.},\textsuperscript{10} while Trost and Quintard\textsuperscript{11} reported the total synthesis of (+)-tetrahydropyrenophorol.

![(-)-1-Tetrahydropyrenophorol](image1)

Figure 1

Results and Discussion

In continuation of our work on the synthesis of biologically-active natural products,\textsuperscript{12} we report herein an efficient straightforward and concise total synthesis of (-)-1-tetrahydropyrenophorol starting from commercially available starting materials.

As depicted in Scheme 1, retrosynthetic analysis of (1) envisioned that it could be obtained from the hydroxy-acid (2) via cyclodimerisation under Mitsunobu reaction conditions, followed by deprotection of the benzyl ether. The hydroxy-acid (2) could easily be prepared from the diol (3), which in turn could be prepared from the known chiral epoxide (4), all by simple chemical transformations.

Synthesis of (-)-1-tetrahydropyrenophorol (1) (Scheme 2) began with the reported chiral \textit{p}-methoxybenzyloxy-epoxide (4).\textsuperscript{13} Regioselective ring-opening of (4) by allyl magnesium chloride in the presence of Cul yielded the alcohol (5) in 87% yield, which, on subsequent benzylaion with NaH and benzyl bromide at 0 °C, gave (6) in 91% yield. The terminal olefin group in (6) was subjected to asymmetric dihydroxylation with AD-mix-β in \textit{t}-BuOH/H\textsubscript{2}O to afford diol (3) in 79% yield (d.r. 9:1).\textsuperscript{14} Selective monotosylation of the diol (3) using TsCl and Et\textsubscript{3}N in CH\textsubscript{2}Cl\textsubscript{2}, followed by cyclization of the resulting monotosylate (3a) in the presence of K\textsubscript{2}CO\textsubscript{3} in MeOH, afforded the chiral epoxide (7) in 77% yield.
Scheme 1. Retrosynthesis model for (-)-1-tetrahydropyrenophorol (1) from p-methoxybenzyloxy-epoxide (4).

Scheme 2. Preparative route to (-)-1-tetrahydropyrenophorol (1). Reagents and conditions: (a) allyl chloride, Mg, Cul, dry ether, -40 ºC to rt, 6 h; (b) BnBr, NaH, THF, 0 ºC to rt, 6 h; (c) AD-mix-β, t-BuOH/H2O, 0 ºC to rt, 48 h; (d) p-TsCl, Et3N, rt, 2 h; (e) K2CO3, MeOH, rt, 1 h; (f) LAH, THF, 0 ºC to rt, 3h; (g) TBSCI, imidazole, CH2Cl2, rt, 4 h; (h) DDQ, CH2Cl2:H2O (19:1), rt, 3 h; (i) TEMPO, [bis(acetoxy)iodo]benzene, aq. CH2Cl2, 0 ºC, 1 h; (j) TBAF, THF, 0 ºC to rt, 3 h; (k) Ph3P, DEAD, toluene:THF (10:1) -20 ºC, 10 h; (l) TiCl4, CH2Cl2, 0 ºC to rt, 1 h.

Regioselective opening of the epoxide (7) with LAH in dry THF furnished the alcohol (8) in 87% yield, which, on subsequent masking with t-butyldimethylsilyl chloride (TBSCI) in the presence of imidazole at 0 ºC, afforded (9) in 91% yield. Next, selective cleavage of the p-methoxybenzyloxy (PMB) ether from compound (9), in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in aq. CH2Cl2, gave alcohol (10) in 86%
yield. The alcohol (10) was then oxidized following treatment with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and [bis(acetoxy)iodo]benzene in aq. CH₂Cl₂, affording the corresponding carboxylic acid (11) in 75% yield, which, on desilylation with tetra-n-butylammonium fluoride (TBAF) in dry THF, gave the hydroxy-acid (2) in 86% yield.

Following the successful synthesis of the hydroxyacid (2), it was subjected to cyclodimerisation under Mitsunobu reaction conditions [Ph₃P and diethyl azodicarboxylate (DEAD)] at -20 °C for 10 h to furnish (12) in 59% yield. Finally, debenzylation of (12) with TiCl₄ in CH₂Cl₂ for 3 h afforded (-)-1-tetrahydropyrenophorol (1) in 77% yield. The spectroscopic data (¹H and ¹³C NMR) and specific optical rotation ([α]D₂⁵ −70.3 (c 0.54, CHCl₃)) of (1) were in good agreement with the reported values ([α]D₂⁵ −68 (c 0.14, CHCl₃)).

Conclusions

A concise stereoselective total synthesis of the macrodiolide, (-)-1-tetrahydropyrenophorol, was accomplished using an efficient combination of regioselective opening of a known chiral epoxide, subsequent asymmetric dihydroxylation, and Mitsunobu reaction.

Experimental Section

General. Solvents were dried over standard drying agents or freshly distilled prior to use. Chemicals were purchased and used without further purification. All column chromatographic separations were performed using silica gel (60-120 mesh). Organic solutions were dried over anhydrous Na₂SO₄ and concentrated below 40 °C in vacuo. ¹H NMR spectra were acquired at 300 MHz, 500 MHz and 600 MHz while ¹³C NMR spectra were acquired at 75 MHz and 125 MHz, both with TMS as internal standard for solutions in CDCl₃. J values are given in Hz. The following abbreviations are used in reporting NMR data: s, singlet; brs, broad singlet; d, doublet; dd, doublet of doublets; m, multiplet; and t, triplet. IR spectra were recorded on an FT IR spectrophotometer with NaCl optics. Optical rotations were measured on a digital polarimeter at 25 °C. Mass spectra were recorded with a direct inlet system or LC by MSD trap SL. The HRMS data were obtained using Q-TOF mass spectrometry.

(5)-1-(4-Methoxybenzyloxy)oct-7-en-4-ol (5). To a stirred solution of epoxide (4) (4.6 g, 20.72 mmol) in dry diethyl ether (100 mL), copper(I) iodide (1.96 g, 10.35 mmol) was added and the mixture was cooled to -40 °C. A solution of allylmagnesium chloride in ether [generated from Mg (1.49 g, 62.16 mmol) and allyl chloride (2.13 mL, 24.86 mmol in 50 mL ether)] was added. After the addition was complete, the mixture was stirred for 6 h and then quenched with aq. NH₄Cl solution (30 mL) dropwise. The residue was filtered through celite and the filtrate was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried (Na₂SO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, 60-120 mesh, 12% EtOAc in pet. ether) to furnish (5) (4.75 g, 87%) as a yellow liquid. [α]D₂⁵ +11.3 (c 1.5, CHCl₃); IR (neat): 3457, 3077, 2988, 2929, 1622, 1375, 1213, 854 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 7.19 (d, 2H, J 8.0 Hz), 6.89 (d, 2H, J 8.0 Hz), 5.83 (m, 1H), 4.99 (m, 2H), 4.47 (s, 2H), 3.79 (s, 3H), 3.68-3.57 (m, 1H), 3.49 (t, 2H, J 8.0 Hz), 2.81 (brs, 1H, -OH), 2.16-2.08 (m, 2H), 1.71-1.59 (m, 2H), 1.41-1.30 (m, 4H); ¹³C NMR (CDCl₃,
with brine, dried (Na$_2$SO$_4$). The reaction mixture was then extracted with ethyl acetate (3 × 20 mL), the combined organic layers were washed (2 × 30 mL) and the aqueous layer was further extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over Na$_2$SO$_4$. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (60-120 silica gel, 8% EtOAc in pet. ether) to give the corresponding diol (3) (4.41 g, 79%) as a colorless oil: [α]$_D^{25}$ +141.7 (c 1.2, CHCl$_3$); IR (neat): 3071, 2989, 2935, 1617, 1516, 1248, 1061 cm$^{-1}$; 1H NMR (CDCl$_3$, 300 MHz): δ 7.41-7.29 (m, 5H), 7.19 (d, 2H, $J$ 8.5 Hz), 6.77 (d, 2H, $J$ 8.4 Hz), 5.79 (m, 1H), 5.01 (m, 2H), 4.59 (d, 1H, $J$ 10.6 Hz), 4.49 (s, 2H), 4.39 (d, 1H, $J$ 10.6 Hz), 3.76 (s, 3H), 3.54 (t, 2H, $J$ 6.8 Hz), 3.46-3.32 (m, 1H), 2.21-2.11 (m, 2H), 1.63-1.31 (m, 6H); 13C NMR (CDCl$_3$, 75 MHz): δ 159.1, 138.2, 130.3, 129.5, 128.1, 114.6, 113.3, 113.1, 79.1, 76.0, 73.1, 72.1, 113.9, 79.1, 76.2, 73.3, 72.4, 68.3, 56.7, 32.2, 31.6, 31.0, 29.8; HRMS (ESI): m/z calcd for C$_{32}$H$_{58}$O$_3$Na: 411.2148; found: 411.2148 [M+Na]$^+$. (S)-1-((4-(Benzyloxy)oct-7-enyloxy)methyl)-4-methoxybenzene (6). To a cooled (0 °C) solution of (5) (4.4 g, 16.66 mmol) in dry THF (15 mL), NaH (1.2 g, 49.98 mmol) was added, stirred for 30 min and treated with a solution of benzyli bromide (2.36 mL, 19.92 mmol) in dry THF (10 mL). After stirring at room temperature for 6 h, the reaction mixture was quenched with sat. NH$_4$Cl solution (15 mL) and extracted with ethyl acetate (2 × 50 mL). The organic layers were washed with water (2 × 30 mL), brine (30 mL) and dried (Na$_2$SO$_4$). The solvent was evaporated under reduced pressure and the residue purified by column chromatography (60-120 silica gel, 8% EtOAc in pet. ether) to furnish (6) (5.25 g, 91%) as a yellow liquid. To the above crude mixture in MeOH at 0 °C, triethylamine (2.2 mL, 16.45 mmol) was added, stirred for 2 h at room temperature, and concentrated. Column chromatography of the crude product using 10% EtOAc in pet. ether gave the epoxide (7) (3.12 g, 77%) as a colorless liquid. [α]$_D^{25}$ -74.8 (c 0.9, CHCl$_3$); 1H NMR (300 MHz, CDCl$_3$): δ 7.33-7.23 (m, 5H), 7.14 (d, 2H, $J$ 8.6 Hz), 6.80 (d, 2H, $J$ 8.6 Hz), 4.52 (d, 1H, $J$ 10.9 Hz), 4.41 (s, 2H), 4.32 (d, 1H, $J$ 10.9 Hz), 3.68 (s, 3H), 3.51 (t, 2H, $J$ 6.8 Hz), 3.42-3.31 (m, 1H), 2.91-2.86 (m, 1H), 2.67 (dd, 1H, $J$ 5.1, 3.2 Hz), 2.44 (dd, 1H, $J$ 5.1, 3.0 Hz), 1.69-1.58 (m, 2H), 1.41-1.21 (m, 6H); 13C NMR (CDCl$_3$, 75 MHz): δ 159.4, 138.2,
130.1, 128.6, 128.4, 128.0, 127.8, 114.1, 78.9, 76.6, 73.4, 72.0, 56.1, 54.7, 45.1, 31.3, 30.8, 30.2, 29.8; ESIMS: 393 (M+ Na)

(2S,5R)-5-(Benzyloxy)-8-(4-methoxybenzoyloxy)octan-2-ol (8). To a stirred suspension of LAH (0.46 g, 12.16 mmol) in dry THF (5 mL), a solution of (7) (3.0 g, 8.10 mmol) in dry THF (10 mL) was added dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature. The reaction mixture was cooled to 0 °C, treated with saturated aq. Na2SO4 solution, filtered, and the filtrate was dried (Na2SO4) and concentrated. The residue was purified by column chromatography (60-120 Silica gel, 18% EtOAc in pet. ether) to give (8) (2.62 g, 87%) as a color less syrup. 

[(2S,5R)-5-(Benzyloxy)-8-(4-methoxybenzoyloxy)octan-2-ol (9). A mixture of the alcohol (8) (2.5 g, 6.72 mmol) and imidazole (1.37 g, 20.16 mmol) in dry CH2Cl2 (20 mL) was treated with TBSCI (1.20 g, 8.06 mmol) at 0 °C under nitrogen atmosphere and stirred at room temperature for 4 h. The reaction mixture was quenched with aq. NH4Cl solution (20 mL) and extracted with CH2Cl2 (2 × 50 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried (Na2SO4) and concentrated. The residue was purified by column chromatography (60-120 silica gel, 12% EtOAc in pet. ether) to furnish (9) (2.97 g, 91%) as a colorless liquid, [α]D25 +57.4 (c 0.49, CHCl3); IR (neat): 3448, 2932, 1611, 1513, 1455, 1374, 1109, 701 cm⁻¹; 1H NMR (300 MHz, CDCl3): δ 7.34-7.22 (m, 5H), 7.19 (d, 2H, J 8.4 Hz), 6.79 (d, 2H, J 8.4 Hz), 4.53 (d, 1H, J 10.6 Hz), 4.43-4.27 (m, 3H), 3.68 (s, 3H), 3.59-3.42 (m, 1H), 3.40-3.27 (m, 3H), 1.70-1.50 (m, 4H), 1.49-1.31 (m, 3H), 1.22 (d, 3H, J 6.6 Hz), 1.18-1.05 (m, 1H), 0.81 (s, 9H), 0.16 (s, 6H). 13C NMR (CDCl3, 75 MHz): δ 158.9, 137.2, 129.8, 128.8, 128.3, 127.9, 127.7, 113.8, 78.7, 75.9, 73.2, 71.6, 67.1, 55.9, 36.2, 33.3, 32.8, 31.6, 26.3, 24.1, 17.3, -4.1; ESIMS: 487 (M+ H)+. HRMS (ESI): m/z calcd for C29H48O5SiNa: 509.3064; found: 509.3055 [M+Na]+.

(4R,7S)-4-(Benzyloxy)-7-(tert-butyl(dimethyl)silyloxy)octan-1-ol (10). To a solution of the silane (9) (2.76 g, 5.67 mmol) in aq. CH2Cl2 (20 mL, 19:1), DDQ (1.54 g, 6.81 mmol) was added and stirred at room temperature for 3 h. The reaction mixture was quenched with sat. NaHCO3 solution (10 mL), filtered, and the filtrate was washed with water (30 mL), brine (30 mL), dried (Na2SO4) and evaporated under reduced pressure. The residue was purified by column chromatography (60-120 Silica gel, 20% EtOAc in pet. ether) to furnish (10) (1.78 g, 86%). [α]D25 +46.1 (c 0.9, CHCl3); IR (neat): 3470, 2983, 2927, 1612, 1513, 1458, 1374, 1248, 1173, 1090, 1042 cm⁻¹; 1H NMR (300 MHz, CDCl3): δ 7.37-7.22 (m, 5H), 4.59 (s, 2H), 3.66-3.54 (m, 1H), 3.48 (t, 2H, J 6.5 Hz), 3.33 (m, 1H), 2.98 (brs, 1H), 1.68-1.49 (m, 5H), 1.47-1.30 (m, 2H), 1.22 (d, 3H, J 6.3 Hz), 1.17-1.09 (m, 1H), 0.83 (s, 9H), 0.12 (s, 3H), 0.01 (s, 3H). 13C NMR (CDCl3, 75 MHz): 139.3, 129.2, 128.8, 128.3, 79.2, 72.4, 67.6, 61.9, 39.2, 33.4, 33.3, 31.2, 26.8, 23.9, 19.3, -4.2, -3.9; ESIMS: 389 (M+ H)+. HRMS (ESI): m/z calcd for C29H38O5SiNa: 389.2486; found: 389.2488 [M+Na]+.

(4S,7S)-4-(Benzyloxy)-7-(tert-butyl(dimethyl)silyloxy)octanoic acid (11). To a stirred solution of the octanol (10) (1.55 g, 4.23 mmol) in CH2Cl2:H2O (1:1, 10 mL), TEMPO (0.19 g, 1.27 mmol) and [bis(acetoxy)iodo]benzene (0.40 g, 1.27 mmol) were added at 0 °C and stirred for 1 h. The reaction mixture was diluted with water (20 mL) and extracted with CH2Cl2 (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried (Na2SO4), evaporated and the residue purified by column chromatography (silica gel, 60–120 mesh, 30% EtOAc in pet. ether) to give acid (11) (1.2 g, 75%) as a colorless gummy oil. [α]D25 = -105.3 (c 0.25, CHCl3); IR
(neat): 3435, 2958, 2855, 1727, 1614, 1520, 1369, 1299, 1174, 1012 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.41-7.36 (m, 5H), 4.46 (d, 1H, J 10.8 Hz), 3.61-3.50 (m, 1H), 3.42-3.37 (m, 1H), 2.36 (t, J 7.1 Hz, 2H), 1.59-1.33 (m, 6H), 1.21 (d, 3H, J 6.8 Hz), 0.91 (s, 9H), 0.13 (s, 3H), 0.06 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): 177.2, 139.8, 129.6, 129.0, 128.7, 79.3, 72.7, 67.6, 38.3, 33.7, 30.3, 29.6, 26.9, 24.4, 19.7, -4.3, -3.9. ESIMS: 403 (M+ Na)⁺. HRMS (ESI): m/z calcd for C₂₁H₃₆O₄SiNa: 403.2283; found: 403.2286 [M+Na]⁺.

(4S,7S)-4-(Benzyloxy)-7-hydroxyoctanoic acid (2). To a cooled (0 °C) solution of the octanoic acid (11) (1.1 g, 2.89 mmol) in dry THF (15 mL) under nitrogen atmosphere, TBAF (4.3 mL, 4.34 mmol) was added and stirred for 3 h. After completion of the reaction, the reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with water (2 × 10 mL), brine (10 mL), dried (Na₂SO₄), evaporated, and the residue was purified by column chromatography (60-120 silica gel, 55% EtOAc in pet. ether) to give (2) (0.66 g, 86%) as a white solid which was used for the next step without purification. [α]D²⁵ = -16.8 (c 0.25, CHCl₃); IR (neat): 3490, 2976, 2840, 1725, 1619, 1520, 1360, 1268, 1175, 1012 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.36-7.26 (m, 5H), 4.47 (s, 2H), 3.77-3.68 (m, 1H), 3.48 (m, 1H), 3.04 (brs, 1H), 2.34 (t, J 6.6 Hz, 2H), 1.71-1.64 (m, 1H), 1.57-1.38 (m, 5H), 1.19 (d, J 6.6 Hz). ¹³C NMR (CDCl₃, 75 MHz): 176.6, 139.3, 129.3, 129.0, 128.6, 80.1, 72.4, 66.6, 36.3, 32.1, 30.4, 29.3, 23.8. ESIMS: 289 (M+ Na)⁺. HRMS (ESI): m/z calcd for C₁₅H₂₂O₄Na: 289.1416; found: 289.1421 [M+Na]⁺.

(5S,8R,13S,16R)-5,13-Bis(benzyloxy)-8,16-dimethyl-1,9-dioxacyclohexadecane-2,10-dione (12). To a solution of the hydroxy acid (2) (0.26 g, 0.97 mmol) and Ph₃P (1.28 g, 4.88 mmol) in toluene:THF (10:1, 260 mL), DEAD (2.76 mL, 17.46 mmol) was added at -20 °C and stirred under N₂ atmosphere for 10 h. Solvent was evaporated under reduced pressure, and the residue purified by column chromatography (60-120 silica gel, 15% EtOAc in pet. ether) to afford (12) (0.14 g, 59%) as a colorless oil. [α]D²⁵ +7.9 (c 1.03, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 7.35-7.22 (m, 10H), 5.03-4.91 (m, 2H), 4.51 (s, 4H), 3.58-3.41 (m, 2H), 2.34 (t, J 6.6 Hz, 2H), 1.79-1.60 (m, 8H), 1.57-1.41 (m, 2H), 1.37-1.29 (m, 2H), 1.19 (d, J 6.1 Hz, 6 H); ¹³C NMR (CDCl₃, 75 MHz): 177.9, 139.4, 129.1, 128.7, 128.3, 128.0, 79.4, 73.1, 69.0, 33.2, 32.4, 29.8, 29.4, 23.2; ESIMS: 519 (M+ Na)⁺. HRMS (ESI): m/z calcd for C₃₀H₄₀O₆Na: 519.2744; found: 519.2751 [M+Na]⁺.

(-)-1-Tetrahydropyrenophorol (1). To a stirred solution of the dilactone (12) (0.090 g, 0.18 mmol) in dichloromethane (2 mL), TiCl₄ (0.04 mL, 0.36 mmol) in dichloromethane was added at 0 °C and stirred under N₂ atmosphere for 1 h. Sat. aq. NaHCO₃ solution (10 mL) was added and the mixture extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with water (15 mL), brine (10 mL), dried (Na₂SO₄) and concentrated. The crude residue was purified by column chromatography (silica gel, 60-120 mesh, 30% EtOAc in pet. ether) to afford the tetrahydropyrenophorol (1) (44 mg) in 77% yield as a white solid. M.p. 126–128 °C; [α]D²⁵ −70.3 (c 0.54, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 5.05-4.99 (m, 2H), 3.59-3.51 (m, 2H), 2.47-2.34 (m, 4H), 1.91-1.78 (m, 4H), 1.75-1.63 (m, 4H), 1.52-1.44 (m, 2H), 1.38-1.33 (m, 2H), 1.22 (d, J 6.1 Hz, 6 H); ¹³C NMR (75 MHz, CDCl₃): δ 173.4, 69.8, 68.1, 32.9, 31.0, 30.8, 30.6, 20.1; ESIMS: 317 (M+ H)⁺. HRMS (ESI): m/z calcd for C₁₆H₂₈O₆Na: 339.1785; found: 339.1788 [M+Na]⁺.

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Supplementary Material

Copies of $^1$H and $^{13}$C NMR spectra associated with this paper can be found in the online version.

References