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A Short Enantioselective Synthesis of *N*-Boc-(2*R*,3*R*)-3-Methyl-3-Hydroxypipecolic Acid from Geraniol

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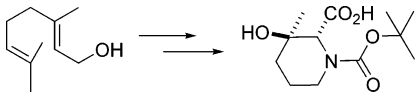
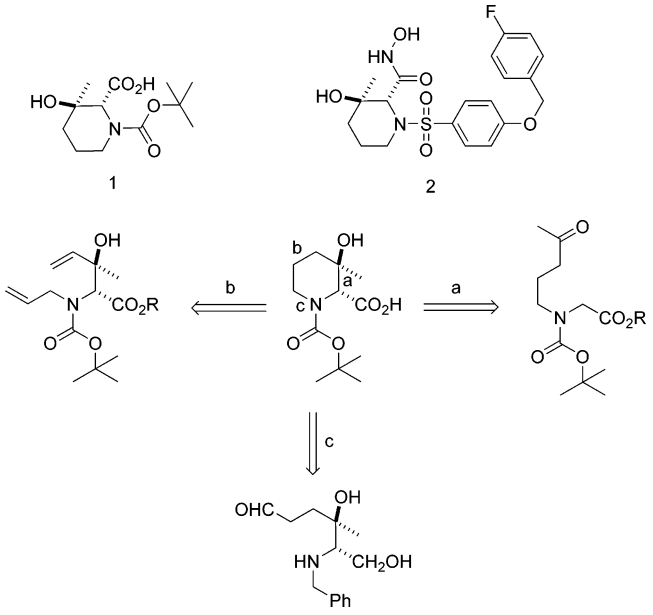


The asymmetric synthesis of (2*R*,3*R*)-3-methyl-3-hydroxypipecolic acid, a key intermediate in the synthesis of dual MMP-13/aggrecanase inhibitors, is described. The title compound is prepared in seven steps with an overall yield of 41% starting from geraniol. Key steps in the synthesis include Sharpless asymmetric epoxidation, which establishes the chiral centers, and a one-pot oxidative olefin cleavage/reductive amination sequence that closes the piperidine ring.

Pipecolic acid derivatives are present in a variety of biologically active compounds, such as the immunosuppresant FK-506[1] and the antitumor antibiotic WF-3161,[2] and methods for their enantioselective synthesis are of considerable interest to the pharmaceutical industry.[3] Functionalized cyclic amino acids have also been used for the construction of conformationally constrained peptides and for further elaboration into stereochemically complex natural products, such as (−)-swainsonine.[4] During the course of our studies on matrix metalloproteinase (MMP) inhibitors as therapeutic agents for the treatment of osteoarthritis and cancer, we desired a short enantioselective synthesis of *N*-Boc-(2*R*,3*R*)-3-methyl-3-hydroxypipecolic acid (**1**). This protected amino acid forms the nucleus for **2**, which was found to be a potent inhibitor of MMP-13, a key mediator of cartilage−collagen breakdown in osteoarthritis.[5] Although several methods have been reported for the enantioselective preparation of 3-hydroxypipecolic acid derivatives, asymmetric methods to prepare simple 3-alkyl-3-hydroxypipecolic acids have not been reported in the literature.[6−10] The lack of readily available chiral piperidines with appropriate substitution for simple functional group manipulation to give rise to **1** forced us to consider methods for stereoselective construction of the piperidine ring. Of the several methods considered, (1) cyclization to form bond *a* through an aldol-type process, (2) ring closure via metathesis and reduction to establish bond *b*, or (3) reductive amination to form bond *c*, the latter was found to be most amenable for development of a short enantioselective synthesis.



The synthesis of **1** began with the known Sharpless asymmetric epoxidation of geraniol to form the epoxy alcohol **3** in 99% yield and 91% ee (Scheme 1).[11] The crude epoxide was directly converted to its carbamate derivative **4** using benzyl isocyanate and triethylamine in methylene chloride solution. The presence of the phenyl chromophore allowed convenient assessment of the enantiomeric purity of the chiral epoxide by chiral HPLC with UV detection. Base-catalyzed cyclization of **4** to establish one of the C−N bonds of the piperidine ring was initially attempted using sodium hydride as base in tetrahydrofuran.[12] We found that large-scale reactions (>10 g) required

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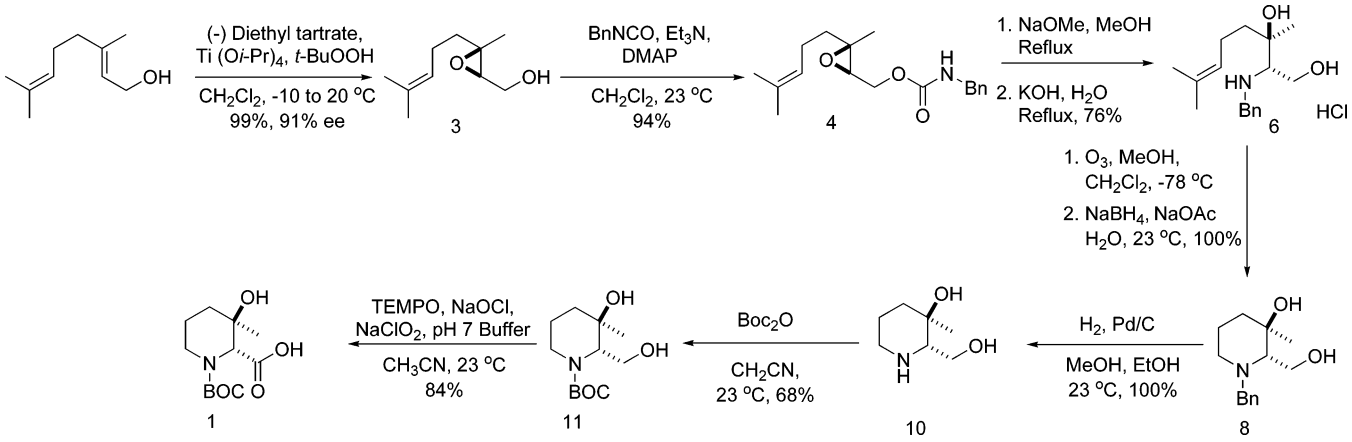
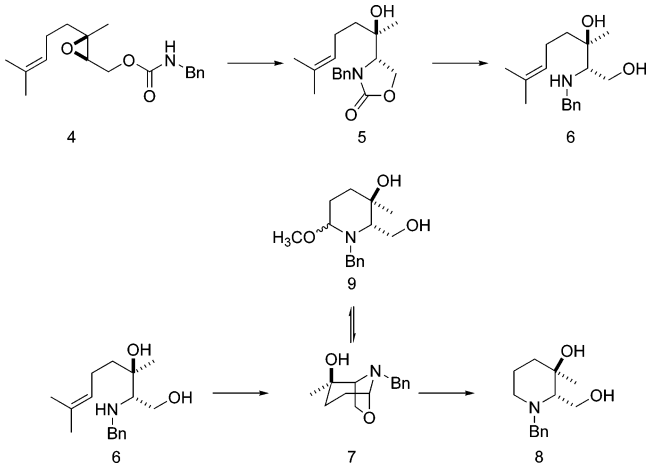
SCHEME 1. Synthesis of *N*-Boc-(2*R*,3*R*)-3-Methyl-3-Hydroxypipecolic Acid from Geraniol



SCHEME 2. Intermediates in the Hydrolysis and Ozonolysis Steps



an induction period of 1−3 h, during which time very little of **5** is formed and after which cyclization proceeds rapidly. The induction period observed in this reaction is likely due to the fact that the reaction mixture is heterogeneous, and the deprotonation of the carbamate nitrogen atom of **4** by sodium hydride is slow. The addition of small amounts of isopropanol to generate sodium isopropoxide resulted in only a modest improvement. Concerned about the adverse safety implications of large-scale exothermic reactions having inductions, we turned to homogeneous reaction conditions to optimize this step. Thus, using sodium methoxide as the base in refluxing methanol resulted in smooth conversion of **4** to **5** and also allowed the subsequent carbamate hydrolysis to be conducted in situ by the addition of water and potassium hydroxide without isolation of **5**.

The oxidative cleavage of double bonds in the presence of unprotected secondary amines is not well precedented due to the propensity of the amine nitrogen to undergo oxidation itself. We reasoned that protonation of the amine nitrogen of **6** via salt formation would protect it from oxidation and facilitate formation of a bicyclic aminal intermediate (Scheme 2). Ganem reported a similar ozonolysis−reductive amination sequence for the synthesis of a chiral piperidine-based hexosaminidase inhibitor.[13] In the event, ozonolysis of **6-HCl** at −78 °C in methanol−methylene chloride solution, followed by an immediate quench with dimethyl sulfide and subsequent workup, afforded the bicyclic aminal **7** in good yield. Prolonged stirring of **7** after the dimethyl sulfide quench resulted in its conversion to the methoxyaminal **9**. The methoxyaminal **9** was found to be very difficult to reduce using borohydride reagents, and catalytic hydrogenation using 10% Pd/C under either neutral or acidic conditions resulted in debenzylation without reduction of the aminal. Fortunately, the reduction of **7** to piperidine **8** was readily accomplished using sodium triacetoxyborohydride in methylene chloride at room temperature and could be performed with concomitant debenzylation using hydrogen and 10% Pd/C. It was subsequently found that oxidative cleavage of the double bond and reduction of the hemiaminal intermediate could be performed in high yield in one pot by quenching the ozonolysis at −78 °C with a solution of sodium borohydride and sodium acetate in water, thereby obviating the concern of formation of **9** during the dimethylsulfide quench. Attempts to effect the transformation of **6** to **7** using OsO_4 and sodium periodate resulted in much lower yields.

The protection of the piperidine nitrogen as its *N*-Boc derivative proceeded uneventfully using di-*tert*-butyldicarbonate and DMAP in acetonitrile. Oxidation of the hydroxymethyl group to the carboxylic acid using sodium chlorite under catalysis by TEMPO and bleach afforded **1** in good yield.[14]

In conclusion, we have developed a short enantioselective synthesis of **1** from geraniol in seven steps with an overall yield of 41%. This synthesis highlights catalytic asymmetric epoxidation, regioselective delivery of nitrogen to the epoxide, and a one-pot oxidative alkene cleavage−intramolecular reductive amination as key steps.

Experimental Section

(2*R*,3*R*)-Epoxygeraniol *N*-Benzylcarbamate (4). A mixture of 21.2 g of crushed 4 Å molecular sieves and 588 mL of methylene chloride at −10 °C was treated with (−)-diethyl tartrate (4.9 mL, 5.9 g, 29 mmol), titanium isopropoxide (5.6 mL, 5.4 g, 19 mmol), and *tert*-butylhydroperoxide (74 mL, 5.5 M in nonane, 0.41 mol). After stirring for 30 min, the mixture was cooled to −30 °C, and a solution of geraniol (50 g, 0.32 mol) in 50 mL of methylene chloride was added dropwise. The mixture was slowly warmed to −10 °C over 1 h. The mixture was diluted with 240 mL of water, warmed to 23 °C, and was treated with 30 mL of 30% aqueous NaOH. After stirring for 1 h, the mixture was filtered through a

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pad of Celite, and the filtrate was transferred to a separatory funnel. The organic phase was separated, and the aqueous phase was extracted twice with methylene chloride. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude (2*R*,3*R*)-epoxygeraniol thus obtained was dissolved in 1 L of methylene chloride and was treated with triethylamine (90 mL, 66 g, 0.65 mol), benzyl isocyanate (42 mL, 46 g, 0.34 mol), and a few crystals of *N*,*N*-dimethylaminopyridine (DMAP). After stirring for 24 h at room temperature, an additional 5 mL of benzyl isocyanate was added, and the mixture was stirred for an additional 24 h. The mixture was washed with saturated aqueous NH_4Cl and 1 M HCl, and the aqueous phase was extracted twice with methylene chloride. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was taken up in 750 mL of hot hexanes, and the supernatant was decanted and diluted with an additional 400 mL of hexanes. The mixture was cooled to 4 °C, allowed to crystallize, and was stored at − 20 °C for 3 h. Filtration of the solids afforded 88 g (94%) of (2*R*,3*R*)-epoxygeraniol *N*-benzylcarbamate (**4**) as a light yellow solid with 91% ee as determined by chiral HPLC analysis (Chiralcel OJ column, 5 cm, 10% *i*-PrOH/hexanes, $\lambda = 214$ nM, 3.45 min (major), 4.37 min (minor)); α^{D}_{23} +15° [$c = 0.61$, MeOH]; mp 49.4−49.6 °C; IR (thin film) 3331, 2967, 2913, 2855, 1685, 1542, 1450, 1254, 1145, 1043, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.28 (m, 5H), 5.09 (br t, 1H, $J = 7.5$ Hz), 4.40 (m, 3H), 4.05 (dd, 1H, $J = 7.0$, 12 Hz), 3.02 (dd, 1H, $J = 4.5$, 7.0 Hz), 2.09 (m, 2H), 1.70 (s, 3H), 1.68 (m, 1H), 1.62 (s, 3H), 1.50 (m, 1H), 1.33 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.5, 138.6, 132.4, 128.9, 127.8 (2C), 123.5, 64.2, 60.8, 60.3, 45.4, 38.6, 25.9, 23.9, 17.9, 17.1 ppm; HRMS calcd for $C_{18}H_{25}NO_3$ 303.1834, observed 303.1827. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Observed: C, 71.23; H, 8.60; N, 4.62.

(2*S*,3*R*)-2-Benzylamino-3,7-dimethyl-oct-6-ene-1,3-diol hydrochloride (6). A mixture of (2*R*,3*R*)-epoxygeraniol *N*-benzylcarbamate (**4**) (100 g, 0.33 mol) and sodium methoxide (90 g, 1.7 mol) in 1.65 L of methanol was refluxed for 1.5 h. After cooling to 23 °C, a solution of potassium hydroxide (320 g, 5.7 mol) in 850 mL of water was added, and the resulting mixture was stirred at reflux for 2 days. The mixture was cooled to 23 °C, concentrated in vacuo, and the aqueous residue was extracted three times with 500 mL of ether. The combined organic layers were dried over magnesium sulfate, filtered, and cooled to 0 °C. The solution was treated with HCl gas, at which point a crystalline solid precipitated, affording 78.5 g (76% yield) of (2*S*,3*R*)-2-benzylamino-3,7-dimethyl-oct-6-ene-1,3-diol hydrochloride (**6**): α^{D}_{23} −1.2° [$c = 0.55$, MeOH]; mp 142 °C; IR (thin film) 3315, 2970, 2928, 1578, 1454, 1384, 1122, 1044, 751, 700, 536 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.58−7.56 (m, 2H), 7.50−7.46 (m, 3H), 5.14−5.10 (m, 1H), 4.49 (d, 1H, $J = 13$ Hz), 4.38 (d, 1H, $J = 13$ Hz), 3.93−3.83 (m, 2H), 3.06−3.04 (m, 1H), 2.16−2.09 (m, 1H), 2.06−2.0 (m, 1H), 1.68 (s, 3H), 1.63 (s, 3H), 1.58−1.39 (m, 2H), 1.23 (s, 3H) ppm; ^{13}C NMR (CD_3OD, 125 MHz) δ 131.6, 131.1, 130.4, 129.5, 129.0, 123.9, 70.9, 67.3, 57.8, 51.2, 36.4, 24.7, 23.5, 21.6, 16.5 ppm. Anal. Calcd for $C_{17}H_{28}ClNO_2$: C, 65.05; H, 8.99; N, 4.46; Cl, 11.30. Observed: C, 64.65; H, 9.02; N, 4.60%; Cl, 11.24.

***N*-Benzyl-(2*S*,3*R*)-3-Methyl-3-hydroxypiperidine-2-methanol (8).** A solution of (2*S*,3*R*)-2-benzylamino-3,7-dimethyl-oct-6-ene-1,3-diol hydrochloride (**6**) (100 g, 319 mmol) in 800 mL of methanol was diluted with 800 mL of methylene chloride and cooled to −78 °C. Ozone was added through a sparge tube until a light blue color persisted. After stirring for 5 min, the mixture was purged with nitrogen until colorless, and a solution of sodium borohydride (60 g, 1.57 mol) and sodium acetate (52.3 g, 650 mmol) in 1.1 L of water was added over 5 min. The mixture was warmed to room temperature and was stirred for 12 h. The mixture was treated with 10 g of solid sodium hydroxide, extracted three times with methylene chloride. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo, affording 75 g (100%) of *N*-benzyl-(2*S*,3*R*)-3-methyl-3-hydroxypiperidine-2-methanol (**8**) as a light yellow solid. An analytically pure sample was obtained by recrystallization from hot isopropyl ether: α^{D}_{23} +14° [$c = 0.60$, MeOH]; mp 88−91 °C; IR (thin film) 3388, 2928, 1451, 1370, 1025, 752, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.29 (m, 4H), 7.27 (m, 1H), 3.91 (m, 3H), 3.69 (dd, 1H, $J = 5.0$, 11 Hz), 3.2 (br s, 2H), 2.73 (app t, 1H, $J = 6.0$ Hz), 3.56−2.50 (m, 2H), 1.89 (m, 1H), 1.59−1.52 (m, 2H), 1.43 (m, 1H), 1.22 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.7, 129.0, 128.7, 127.4, 70.3, 69.9, 59.9, 58.1, 45.2, 34.6, 26.2, 20.0 ppm; HRMS calcd for $[C_{14}H_{21}NO_2 + H]^+$ 236.1650, observed 236.1664. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Observed: C, 71.07; H, 9.26; N, 5.93.

(2*S*,3*R*)-3-Methyl-3-hydroxypiperidine-2-methanol (10). A solution of *N*-benzyl-(2*S*,3*R*)-3-methyl-3-hydroxypiperidine-2-methanol (**8**) (50 g, 0.20 mol) in 630 mL of methanol was charged with a mixture of 10% palladium on carbon (5 g) and ethanol (20 mL) and was shaken under 50 psi of hydrogen for 16 h. The mixture was filtered and concentrated in vacuo to an oil. Residual solvent was removed azeotropically with toluene, and the residue was dried in vacuo, affording 31 g (100%) of (2*S*,3*R*)-3-methyl-3-hydroxypiperidine-2-methanol (**10**) as a colorless oil that subsequently crystallized on standing: α^{D}_{23} −43° [$c = 0.44$, MeOH]; IR (thin film) 3300, 2933, 2857, 1440, 1370, 1322, 1192, 1121, 1067, 1026, 1004, 989, 927, 898, 829, 753, 586, 532 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 4.89 (dd, 1H, $J = 4.2$, 10.8 Hz), 3.43 (dd, 1H, $J = 8.7$, 10.4 Hz), 3.0 (d, 1H, $J = 12$ Hz), 2.59−2.54 (m, 2H), 1.73−1.71 (m, 1H), 1.65−1.62 (m, 1H), 1.57−1.49 (m, 2H), 1.16 (s, 3H) ppm; ^{13}C NMR (CD_3OD, 125 MHz) δ 69.6, 66.6, 61.2, 45.7, 40.5, 23.9, 19.7 ppm; Anal. Calcd for $C_7H_{15}NO_2 + 1/2H_2O$: C, 54.52; H, 10.46; N, 9.08. Observed: C, 55.21; H, 10.94; N, 9.00.

***N*-Boc-(2*S*,3*R*)-3-Methyl-3-hydroxypiperidine-2-methanol (11).** To a solution of (2*S*,3*R*)-3-methyl-3-hydroxypiperidine-2-methanol (**10**) (1 g, 6.9 mmol) in 34 mL of acetonitrile at room temperature was added di-*tert*-butyldicarbonate (1.6 g, 7.5 mmol) in one portion. The mixture was stirred for 24 h, diluted with water, and the mixture was extracted with three portions of ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo, affording 1.1 g (68%) of *N*-Boc-(2*S*,3*R*)-3-methyl-3-hydroxypiperidine-2-methanol (**11**) as a colorless oil that crystallized on standing: α^{D}_{23} +30° [$c = 0.57$, MeOH]; mp 108 °C; FTIR 3409, 2973, 2931, 1663, 1425, 1366, 1151 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.2 (br s, 1H), 4.0 (br s, 1H), 3.75−3.70 (m, 2H), 3.9−3.8 (m, 1H), 2.1−2.2 (m, 1H), 1.9−1.8 (m, 1H), 1.54−1.53 (m, 2H), 1.49 (s, 9H), 1.21 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158, 80.5, 69.1, 63, 59.6, 39, 33.2, 28.6, 27.3, 20.8 ppm; Anal. Calcd for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Observed: C, 59.09; H, 9.91; N, 5.72.

***N*-Boc-(2*R*,3*R*)-3-Methyl-3-hydroxypiperidine-2-carboxylic acid (1).** To a mixture of *N*-Boc-(2*S*,3*R*)-3-methyl-3-hydroxypiperidine-2-methanol (**11**) (1.1 g, 4.4 mmol), acetonitrile (22 mL), and pH 7 phosphate buffer (0.5 M, 16.9 mL) were added $NaClO_2$ (795 mg, 8.8 mmol) and 2,2,6,6-tetramethylpiperidinyloxy free radical (TEMPO) (47 mg, 0.3 mmol). An aqueous solution of NaOCl (4%, 3 mL) was added dropwise, and the mixture was heated to 40 °C for 6 h. After cooling to 23 °C, the mixture was treated with 1 N NaOH and ca. 1 g of Na_2SO_3. The aqueous mixture was poured into ether and was extracted once with 1 M NaOH. The aqueous layer was carefully acidified with 6 M HCl and was extracted three times with ethyl acetate. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo, affording 955 mg (84%) of *N*-Boc-(2*R*,3*R*)-3-methyl-3-hydroxypiperidine-2-carboxylic acid (**1**) as a colorless oil that crystallized on standing: α^{D}_{23} +20° [$c = 0.35$, MeOH]; mp 143 °C; FTIR

3425 (br s), 2977, 2935, 1716, 1670, 1394, 1368, 1282, 1169, 1145,969 cm^{-1}; ^1H NMR (500 MHz, DMSO) δ 4.7−4.5 (m, 2H), 3.97 (m, 1H), 3.12 (m, 1H), 1.8−1.59 (m, 3H), 1.47 (s, 9H), 1.42 (s, 3H) ppm; ^1H NMR at 60 °C (500 MHz, DMSO) δ 4.52 (s, 1H), 4.43 (br s, 1H), 3.81 (d, 1H, J = 8.8 Hz), 3.16 (m, 1H), 1.87−1.78 (m, 1H), 1.58−1.47 (m, 2H), 1.39 (s, 9H), 1.21 (s, 3H) ppm; ^{13}C NMR (DMSO, 125 MHz) δ 173.3, 156.0, 155.7, 79.5, 67.3, 65.3, 64.0, 40.9, 33.4, 29.0, 28.9, 28.7, 20.0, 19.7 ppm. Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.l6; N, 5.40. Observed: C, 55.72; H, 8.39; N, 5.44.

Supporting Information Available: Proton and carbon NMR spectra of reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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