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A Practical Total Synthesis of (+)-Spirolaxine Methyl Ether

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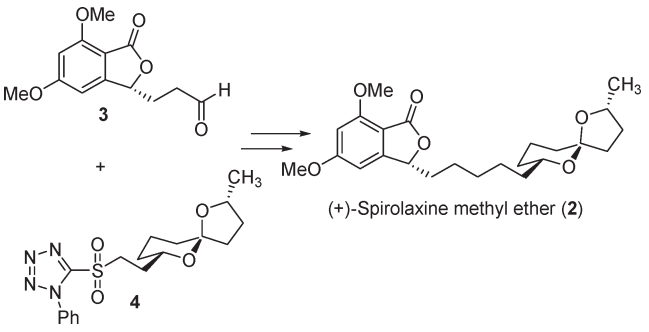

An efficient and practical total synthesis of (+)-spirolaxine methyl ether is described. The phthalide-aldehyde **3** has been prepared via the Diels−Alder reaction between 1,4-unconjugated diene **5** and a long-chain acetylenic dienophile **6**. The carbon framework of spiroketal sulfone **4** has been constructed from monobenzyl protected 1,5-pentanediol and the stereochemistry in both the phthalide portion and the spiroketal portion has been established by the Sharpless asymmetric epoxidation.

Helicobacter pylori (*H. Pylori*) organisms are gram-negative bacteria that infect the gastric mucosa in 20% to 80% of the humans throughout the world.[1] Prevalence of *H. pylori* infection varies depending upon the age and the geographic location.[2a] In most of the cases, infection will persist for the lifetime of an individual without medical intervention.[2b] In most infected persons, *H. pylori* infection is well tolerated with few or no symptoms over the decades.[3] However, infection with this organism is a significant risk factor for the development of peptic ulceration[4] and adenocarcinoma of the distal stomach.[5] Current treatment of *H. pylori* infection involves the prescription of one or more antibiotics in combination with H_2 blockers; however, none of the existing treatments are capable of complete eradication of *H. pylori*.[6]

Spirolaxine **1** and spirolaxine methyl ether **2** (Figure 1) are produced by various strains of white rot fungi belonging to the genera *Sporotrichum* and *Phanerochaete*.

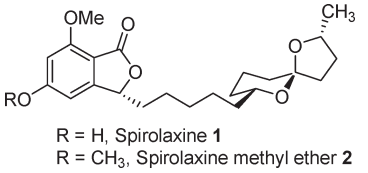

FIGURE 1. Chemical structure of spirolaxine methyl ether.

These are potent helicobactericidal compounds and useful for the treatment of gastroduodenal disorders and the prevention of gastric cancer.[7] Several structurally related phthalide-containing helicobactericidal compounds that contain a 5,5-spiroacetal moiety have also been reported by Dekker et al.,[8] which also provide promising leads for the treatment of *H. pylori*-related diseases.

The spirolaxine and its methyl ether are found to exhibit cholesterol lowering activity.[9a] More recent studies have shown that it has cytotoxic activity toward endothelial cells (BMEC and Huvec) as well as a variety of tumor cell lines (LoVo and HL60).[9b,c] Consequently, there have been some reports on the total synthesis of spirolaxine methyl ether.[10] Due to its fascinating structural features and potent biological activity, we have attempted the total synthesis of spirolaxine methyl ether **2**. Herein we report an efficient and practical total synthesis of biologically active polyketide-derived natural substance, (+)-spirolaxine methyl ether **2**.

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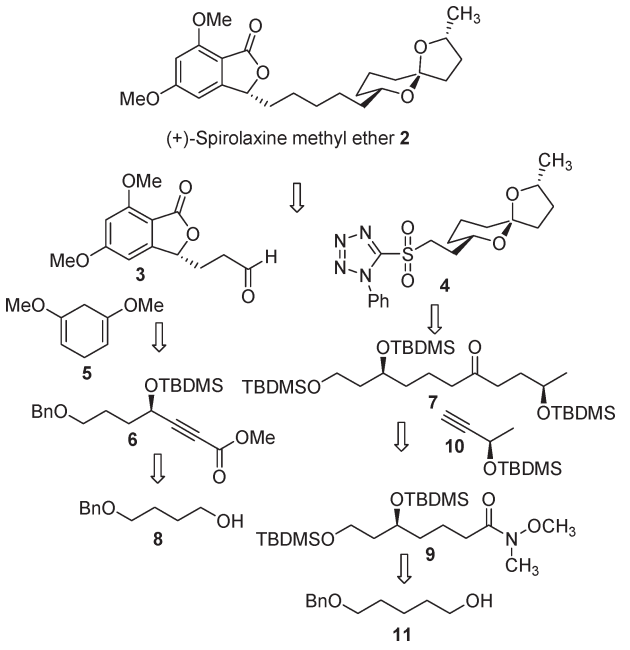
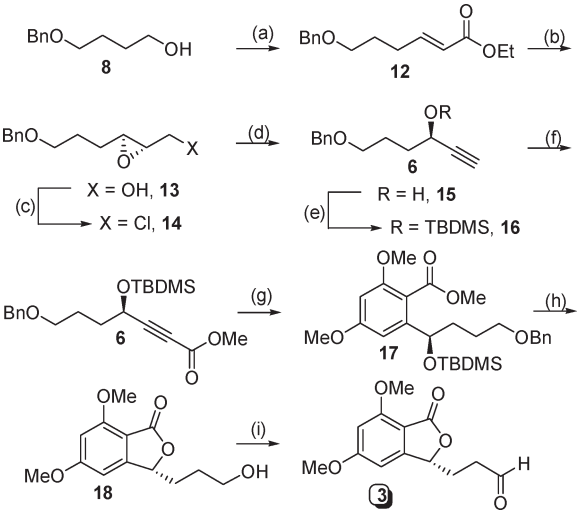
SCHEME 1. Retrosynthetic Analysis of (+)-Spirolaxine Methyl Ether



SCHEME 2. Synthesis of Phthalide Aldehyde (3)[a]



[a]Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C, 89%; (ii) $Ph_3P{=}CH{-}CO_2Et$, benzene, reflux, 84%; (b) (i) $LiAlH_4/AlCl_3$, Et_2O, 0 °C, 89%; (ii) (−)-DIPT, $Ti(O^iPr)_4$, TBHP, DCM, −20 °C 91%; (c) TPP, $NaHCO_3$, CCl_4, reflux, 93%; (d) Li/naphthalene, liquid NH_3, −78 °C, 88%; (e) ^{t}BuMe$_2$Si−Cl, imidazole, DCM, 0 °C to rt 91%; (f) *n*-BuLi, $ClCO_2Me$, THF, −78 °C, 86%; (g) **5**, neat, *N*,*N*-dimethylaniline, 200 °C, 48 h, 45%; (h) (i) TBAF, THF, rt, 6 h, 87%; (ii) Pd/C, H_2, EtOAc, 6 h, 91%; (i) DMP, DCM, 1 h, 84%.

Our retrosynthetic analysis of (+)-spirolaxine methyl ether is shown in Scheme 1.

It was envisioned to proceed via a heterocycle activated modified Julia−Kocienski olefination[10a−d] of phthalide-aldehyde **3** with sulfonyl spiroketal **4**. Phthalide-aldehyde **3** was prepared via the Alder−Rickert reaction between 1,4-unconjugated diene **5** and a long-chain acetylenic dienophile **6**, which in turn was prepared from benzyl-protected 1,4-butanediol **8** by known methods. The stereochemistry of the sulfonyl spiroketal fragment **4** was derived from commercially available (*R*)-3-butyn-2-ol. Sulfonyl spiroketal **4** was prepared via acid-catalyzed cyclization of protected dihydroxyketone **7**, which was synthesized from benzyl-protected 1,5-pentanediol **11**. The phthalide-aldehyde **3** (Scheme 2) was synthesized from a known monobenzyl ether **8**, which was oxidized to the corresponding aldehyde and further homologated by a two-carbon Wittig olefination to afford α,β-unsaturated ester (*E*-isomer) **12** as the sole product. Reduction of compound **12** with $LiAlH_4/AlCl_3$ afforded an allylic alcohol in 87% yield, which on Sharpless asymmetric epoxidation[11] with (−)-DIPT, $Ti(^iPrO)_4$, and TBHP at −20 °C furnished epoxy alcohol **13** in 91% yield with 94% ee (determined by chiral HPLC).

Subsequent reaction of **13** with PPh_3 in CCl_4 in the presence of $NaHCO_3$ (10 mol %) at reflux temperature, followed by base-induced dehydrohalogenation with the methodology developed by us,[12] gave alkynol **15** in 88% overall yield. Treatment of the ^{t}BuMe$_2$Si-ether protected alkyne **16** with *n*-BuLi followed by addition of methyl chloroformate gave a long-chain acetylenic ester **6** in 84% yield. Subsequently we have attempted the Alder−Rickert reaction of diene **5** with acetylenic dienophile **6**.[13] The reaction was carried out by heating 2:1 ratio of diene **5** and acetylenic dienophile **6** in a sealed tube at 200 °C in the presence of a catalytic amount of *N*,*N*-dimethylaniline to give the aromatic precursor **17** in 45% yield. The amount of *N*,*N*-dimethylaniline plays a crucial role in the Diels−Alder reaction, notably the use of a very minute quantity of *N*,*N*-dimethylaniline affords the product in higher yield. Surprisingly no Diels−Alder reaction was observed in the absence of *N*,*N*-dimethylaniline. This cleanly indicates that addition of a trace amount of *N*,*N*-dimethylaniline is essential to facilitate the reaction. It is noteworthy to mention that 2 equiv of diene is required to achieve good yields as it is unstable and susceptible to undergo rearrangement to give the 3-methoxy-cyclohex-2-enone. Deprotection of silyl ether with TBAF in THF gave the benzyl-protected phthalide-alcohol, which on debenzylation followed by oxidation[14] with Dess−Martin periodinane gave the phthalide-aldehyde **3** in 84% yield. The synthesis of fragment **4** (Scheme 3) began with the known monobenzyl ether **11**, which was oxidized to the corresponding aldehyde and further homologated by a two-carbon Wittig olefination to afford α,β-unsaturated ester **19** (*E*-isomer) as the sole product.

Reduction of compound **19** with $LiAlH_4/AlCl_3$ afforded an allylic alcohol in 81% yield, which on Sharpless asymmetric epoxidation[11a−e] with (+)-DIPT, $Ti(O^iPr)_4$, and TBHP at −20 °C

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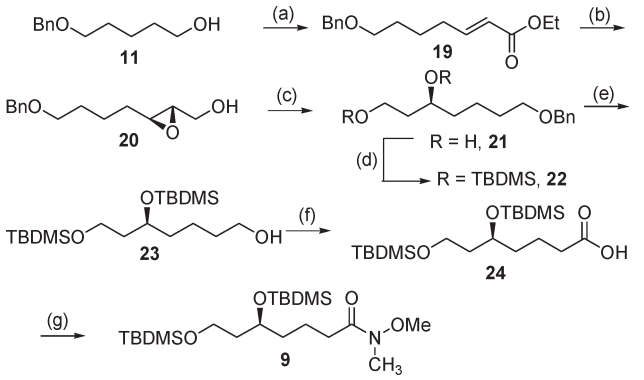
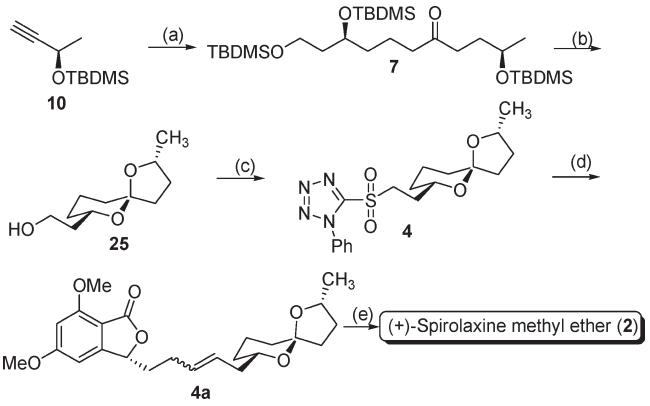
SCHEME 3. Synthesis of Sulfonyl Spiroketal (4)[a]



[a]Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C, 86%; (ii) $Ph_3P{=}CH{-}CO_2Et$, benzene, reflux, 83%; (b) (i) $LiAlH_4$/$AlCl_3$ Et_2O, 0 °C, 81%; (ii) (+)-DIPT, $Ti(O^iPr)_4$, TBHP, DCM, −20 °C, 91%; (c) Red-Al, THF, 88%; (d) ^{t}BuMe$_2$Si−Cl, imidazole, DCM, 0 °C to rt, 90%; (e) (a) Li/naphthalene, THF, −30 °C, 82%; (f) BAIB, TEMPO, CH_3CN:H_2O (2:1), 89%; (vii) DCC/CH_3CN/Pyr, MeO(H)-NMe·HCl, 64%.

SCHEME 4. Synthesis of (+)-Spirolaxine Methyl Ether[a]



[a]Reagents and conditions:(a) (i) LDA, THF, 0 °C to −30 °C then Weinreb amide **9** in THF, 88%; (ii) Lindlar catalyst, H_2, EtOAc, rt, 92%; (b) aq HF, CH_3CN, 89%; (c) (i) 1-phenyl-1*H*-tetrazole-5-thiol, PPh_3, DEAD, 62%; (ii) *m*-CPBA, $NaHCO_3$, DCM, 82%; (d) (a) KHMDS, THF, −78 °C then aldehyde **3**, 75%; (e) PtO_2, H_2, THF, 6 h, 90%.

furnished epoxy alcohol **20** in 89% yield with 94% ee (determined by chiral HPLC). Reductive opening of epoxy alcohol **20** with Red-Al afforded diol **21** in good yield.

The diol **21** was protected as silyl ether and then subjected to debenzylation to give alcohol **23**, which on subsequent oxidation with TEMPO/BAIB gave compound **24**. This was converted into its Weinreb amide **9** by using the Mosset procedure.[15] Treatment of the alkyne **10** with LDA followed by addition of the Weinreb amide **9** and a subsequent hydrogenation with the Lindlar catalyst gave the corresponding ketone **7** in excellent yield without affecting ^{t}BuMe$_2$Si-ether. Next compound **7** was subjected to ^{t}BuMe$_2$Si-ether deprotection and a subsequent spiroketolization by treatment with aqueous HF in acetonitrile to give thermodynamically stable 6,5-spiroketal **25** in 84% yield. Conversion of the side chain alcohol of spiroketal **25** into sulfone **4** proceeded readily in two steps by treatment with 1-phenyl-1*H*-tetrazole-5-thiol, PPh_3, and DEAD followed by oxidation with *m*-CPBA. The key heterocycle-activated modified Julia olefination was carried out with phthalide-aldehyde **3** and sulfone **4** (Scheme 4).[16]

Thus treatment of sulfone **4** with phthalide-aldehyde **3** in the presence of KHMDS at −78 °C gave the olefin as a mixture of trans- and cis-isomers, favoring trans-isomer **4a**. Reduction of olefin **4a** (trans/cis) with PtO_2 under H_2 atmosphere gave the target spirolaxinemethyl ether in 72% yield. The ^{1}H and ^{13}CNMR data and optical rotation of the synthetic (+)-spirolaxine methyl ether **2** were in agreement with data reported in the literature.[7,17]

In conclusion, we have accomplished the total synthesis of (+)-spirolaxine methyl ether through a modified Julia−Kocienski olefination between spiroketal sulfone and phthalide-aldehyde. The stereochemistry in both phthalide and spiroketal portions has been established by the Sharpless asymmetric epoxidation. The carbon framework of spiroketal was constructed from monobenzyl-protected 1,5-pentanediol and the phthalide-aldehyde was prepared from 1,4-butanediol through the Diels−Alder approach. This synthetic strategy may be applicable to the synthesis of other complex natural products as well.

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Experimental Section

5-({2-[(2*R*,5*R*,7*R*)-2-Methyl-1,6-dioxaspiro[4.5]dec-7-yl]ethyl}-sulfonyl)-1- phenyl-1*H*-1,2,3,4-tetraazole (4). To a solution of thioether **25a** (108 mg, 0.309 mmol) in dichloromethane (5 mL) at 0 °C under an atmosphere of nitrogen was added sodium bicarbonate (0.156 g, 1.545 mmol) and a solution of *m*-chloroperoxybenzoic acid (0.106 g, 0.618 mmol) in dichloromethane (5 mL). After the solution was stirred for 6 h, saturated aqueous sodium bicarbonate (2 mL) and saturated aqueous sodium thiosulfate (2 mL) were added. The aqueous layer was extracted with dichloromethane (30 mL), and the combined extracts were dried over Na_2SO_4. Filtration and removal of the solvent under reduced pressure provided an oil that was purified by flash column chromatography, using hexane−ethyl acetate (9:1) as eluent to afford the title compound **4** (96 mg, 82%) as a yellow oil: $[\alpha]^{20}_D$ +20.6 (*c* 2.01 in $CHCl_3$); IR (Neat) υ 2932, 2853, 1498, 1342, 1220, 1152, 1066, 984, 763, and 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73−7.66 (m, 2H), 7.63−7.58 (m, 3H), 4.15 (sextet, J = 6.6 Hz, 1H), 3.95−3.85 (m, 2H), 3.77−3.67 (m, 1H), 2.16−1.59 (m, 11H), 1.47−1.34 (m, 1H), 1.22 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 133.0, 131.4, 129.6, 125.0, 106.2, 74.0, 67.9, 53.0, 37.8, 33.2, 31.3, 30.6, 28.4, 21.1, 19.9; HRMS (ESI) calcd for $C_{18}H_{25}N_4O_4S$ $[M + H]^+$ 393.1596, found 393.1606.

3-((*R*)-1,3-Dihydro-5,7-dimethoxy-1-oxoisobenzofuran-3-yl)-propanal (3). Dess−Martin periodinane (252 mg, 1.0 mmol) was added to an ice-cooled solution of alcohol **18** (520 mg, 1.2 mmol) in dichloromethane (10 mL) under nitrogen atmosphere. After being stirred for 10 min, the reaction mixture was brought to room temperature and the stirring was continued until the completion of the reaction (1 h). The reaction mixture was diluted with ether and the precipitate was filtered off on a pad of Celite, using ether as solvent, then the filtrate was washed with saturated aq $NaHCO_3$ solution. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography with hexane−ethyl acetate (6:4) as a eluent to give the title compound **3** (210 mg, 84%) as viscous liquid: $[\alpha]^{20}_D$ +6.4 (*c* 1.06, $CHCl_3$); IR (KBr) υ 2930, 2848, 1751, 1724, 1608, 1471, 1341, 1218, 1158,

1040, 983, 839, 753, 687, 556 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 6.45 (d, J = 1.7 Hz, 1H), 6.43 (d, J = 1.7 Hz, 1H), 5.36 (dd, J = 3.2, 8.3 Hz, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 2.8−2.7 (m, 1H), 2.65−2.54 (m, 1H), 2.51−2.40 (m, 1H), 1.95−1.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.7, 166.8, 159.5, 154.2, 106.4, 98.9, 97.3, 78.3, 55.9, 38.7, 26.8; HRMS (ESI) calcd for $C_{13}H_{14}O_5Na$ $[M + Na]^+$ 273.0738, found 273.0751.

(*3R*)-5,7-Dimethoxy-3-(*E*)-5-[(*2R*,*5R*,*7S*)-2-methyl-1, 6-dioxaspiro-[4.5]dec-7-yl]-3-pentenyl-1,3-dihydro-1-isobenzofuranone (4a). Sulfone **4** (70 mg, 0.178 mmol) was dissolved in tetrahydrofuran (5 mL) and cooled to −78 °C under an atmosphere of argon. To this stirred solution was added dropwise KHMDS (0.20 mL, 0.5 M in THF). The resultant deep yellow solution was stirred for 0.75 h before a solution of aldehyde **3** (89 mg, 0.357 mmol) in tetrahydrofuran (3 mL) was added dropwise. After being stirred at −78 °C for 4 h, the solution was allowed to slowly warm to room temperature then stirred for 0.75 h. The reaction was quenched by the addition of brine (3 mL) and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined extracts were dried over Na_2SO_4 then filtered, and the solvent was removed in vacuo. The resultant oil was purified by flash column chromatography with hexane−ethyl acetate (6:4) as eluent to give the title compound **4a** (55 mg, 75%, *E*-isomer) as a yellow oil: $[\alpha]^{20}_D$ +58.6 (*c* 1.02 in $CHCl_3$); IR (KBr) υ 2928, 2854, 1749, 1607, 1496, 1460, 1339, 1218, 1158, 1057, 1031, and 978 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.41 (d, 2H, J = 3.9 Hz), 5.56−5.40 (m, 2H), 5.32 (dd, 1H, J = 3.3, 8.6 Hz), 4.18−4.08 (m, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.79−3.68 (m, 1H), 2.31−1.93 (m, 5H), 1.90−1.5 (m, 9H), 1.4−1.22 (m, 2H), 1.21 (d, 3H, J = 6.2 Hz); C (75 MHz, $CDCl_3$) δ 168.4, 166.6, 159.5, 155.2, 155.1, 129.9, 128.9, 127.8, 106.1, 98.6, 97.3, 79.2, 78.9, 70.0, 69.9, 55.9, 55.8, 39.4, 38.0,34.8, 34.0, 33.5, 33.4, 31.3, 30.4, 29.6, 27.9, 22.8, 21.1, 20.2; HRMS (ESI) calcd for $C_{24}H_{32}O_6Na$ $(M + Na)^+$ 439.2096, found 439.2103.

(+)-Spirolaxine Methyl Ether (2). Alkene **4a** (30 mg, 0.072 mmol) was dissolved in tetrahydrofuran (25 mL) and hydrogenated by using a hydrogen-filled double balloon in the presence of platinum(IV) oxide (3 mg) for 6 h. The catalyst was removed by filtration through a pad of Celite and the solvent was removed under reduced pressure. Purification of the resultant oil by flash column chromatography with hexane−ethyl acetate (7:3) as eluent gave the spirolaxine methyl ether **2** (27 mg, 90%) as a yellow oil: $[\alpha]^{20}_D$ +60.7 (*c* 0.58, $CHCl_3$) [lit.[1] +62 (*c* 0.22, $CHCl_3$)]; IR (KBr) υ 2934, 2861, 1755, 1608, 1461, 1338, 1217, 1158, 1053, 1030, 983, 838 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.41 (d, 2H, J = 7.8 Hz), 5.30 (dd, 1H, J = 3.4, 7.8 Hz), 4.18−4.11 (m, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.64−3.69 (m, 1H), 2.06−2.15 (1H, m), 1.92−1.99 (1H, m), 1.59−1.88 (7H, m), 1.50−1.54 (1H, m), 1.30−1.42 (9H, m), 1.21 (d, 3H, J = 6.2 Hz), 1.14 (dddd, 1H, J = 3.9, 13.1, 13.1, 16.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 166.6, 159.5, 155.1, 106.9, 105.9, 98.5, 97.3, 79.8, 73.6, 69.9, 55.9, 55.8, 37.9, 36.0, 34.7, 33.4, 31.3, 30.9, 29.3, 25.4, 24.5, 21.2, 20.3; HRMS (ESI) calcd for $C_{24}H_{34}O_6Na$ $(M + Na)^+$ 441.2253, found 441.2255. These data were in agreement with those reported in the literature.[12]

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Supporting Information Available: Experimental procedures, specific rotation, and spectral data (^1H NMR, ^{13}C NMR, IR, MS, and HRMS) and copies of ^1H NMR and ^{13}C NMR spectra for all compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.