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Synthesis of (+)-Spirolaxine Methyl Ether

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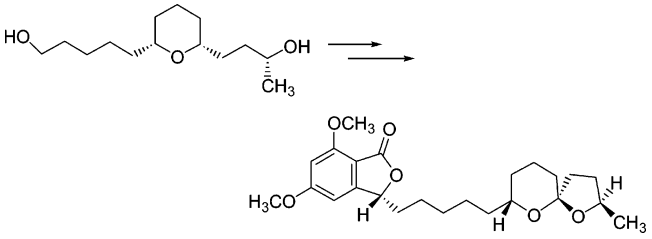
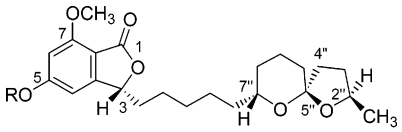


A short and efficient synthesis of (+)-spirolaxine methyl ether, a metabolite of the fungus *Sporotrichum laxum* with inhibitory activity against *Helicobacter pylori*, is described. The synthesis has been carried out by a Prins cyclization, to obtain the [6,5]-spiroketal system, and a Wadsworth−Emmons condensation, applied for the installation of the polymethylene chain on the phthalide moiety.

(+)-Spirolaxine (**1**) and (+)-spirolaxine 5-*O*-methyl ether (**2**) (Chart 1) are polyketide-derived natural substances that were isolated years ago from the cultures of *Sporotrichum laxum*, now *Phanerochaete pruinosum* (Basidiomycetes).[1] They contain a 3-methoxy-5-hydroxyphthalide nucleus linked to a [6,5]-spiroketal group by a five-membered methylene chain. The absolute configuration of (+)-spirolaxine has recently been established to be 3*R*,2″*R*,5″*R*,7″*R* by some of us.[2]

Along with spirolaxine, similar metabolites were isolated from MPGA (malt−peptone−glucose agar) cultures derived from the aforementioned fungus, which included sporotricale[1,3] and phanerosporic acid. Similar compounds recently received attention for their inhibitory activity against the micro-aerophilic Gram-negative bacterium *Helicobacter pylori*, described by Dekker et al.,[4] where compound **1** exhibited the best activity. The interest of this group of derivatives was in its selectivity. In fact, when tested against a panel of different microorganisms,

CHART 1



R = H Spirolaxine (**1**)
R = CH_3 Spirolaxine methylether (**2**)

they did not show any antibacterial activity.[4] There have been recent studies that have shown a strong relationship between the presence of *H. pylori*, which lives beneath the mucus layer of the stomach, and the development of gastric and duodenal ulcers.[5] Presently, none of the existing therapies are capable of completely eradicating *H. pylori*. Therefore, spirolaxine and its derivatives could become potential lead compounds in the development of drugs that treat gastroduodenal disorder and for the prevention of gastric cancer.

Also, spirolaxine has been reported to exhibit cholesterol-lowering activity.[6] Moreover, 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).[7]

Due to the interest shown in such molecules, we have developed a stereoselective synthesis of **2**, which may, in principle, have value in the preparation of spirolaxine itself as well as different analogues. Any strategy for the total synthesis of spirolaxine must conform to the intriguing spiroketal ring system. Development of such methods for the preparation of this moiety gains importance due to the existence of similar fragments in a variety of other natural products, such as monensin A[8] and calyculin.[9]

The retrosynthetic approach was envisioned to proceed via a condensation of phosphonate **3** with the aldehyde **4**, obtained by the oxidation of the corresponding alcohol **5** (Scheme 1). We envisaged that the spiroketal system could be obtained by an oxidative cyclization of a hydroxyalkyl-substituted tetrahydropyran (**6**). One possibility to obtain the latter was a Prins cyclization, which is a powerful synthetic route for the construction of these six-membered tetrahydropyran derivatives.[10] This flexible methodology involves the cross coupling of an aldehyde with an unsaturated alcohol, in the presence of a Lewis acid, to obtain 2,6-disubstituted 4-halotetrahydropyrans. Interestingly, most of the examples reported that a single diastereoisomer was produced with the three substituents occupying equatorial positions.[11] A rationale for the *all-cis* stereoselectivity was set

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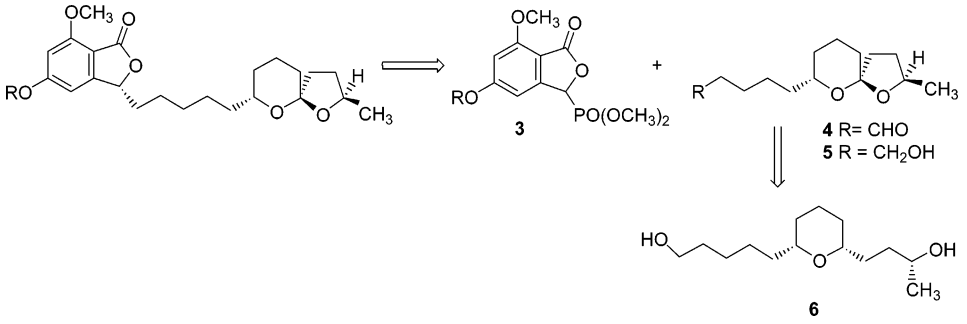
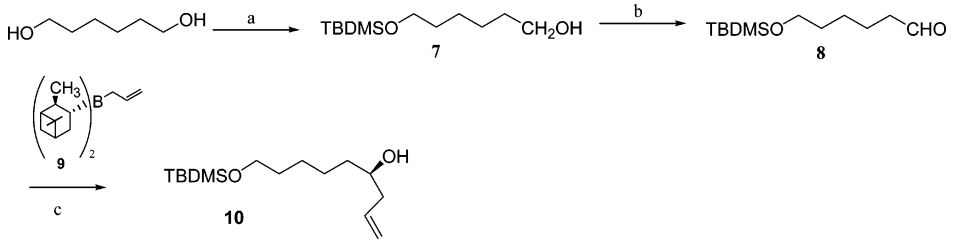
SCHEME 1



SCHEME 2 [a]



[a] Reagents and conditions: (a) (TBDM)SiCl, Et_3N, DMAP, THF, rt, 18 h, 57%; (b) NaOCl, polymer-supported TEMPO, KBr, CH_2Cl_2, rt, 6 h, 100%; (c) (i) **9**, −78 °C, 1 h, then 1 h at rt; (ii) NaOH (3 N), H_2O_2 (35%), 1 h of reflux, 82%.

forth by the computational work of Alder.[12] The reaction was believed to proceed via the formation of an oxocarbenium ion that underwent an intramolecular cyclization. The possibility to obtain the desired tetrahydropyran in a single step and to do so in a stereocontrolled fashion prompted us to exploit this condensation for the purpose of synthesizing the aldehyde **4**.

Since spirolaxine has *R* configuration at C-7″, we needed to perform the reaction from an appropriate, optically pure homoallylic (*R*)-alcohol that carried a substituent that enabled us to link with the phthalide moiety. The asymmetric synthesis of alcohol **10** was successfully accomplished by using the chiral-directing property of *B*-allyldiisopinocamphenylborane, following a well-known procedure, as described by Brown.[13] This method has the advantage of providing access to both enantiomers starting from **8**, by using the appropriate chiral borane. The aldehyde **8**[14] was prepared by protection of 1,6-hexanediol to give the monosilyl derivative **7**,[15] followed by oxidation with polymer-supported TEMPO. The *B*-allyldiisopinocamphenylborane **9** was obtained by treatment of (−)-Ipc_2OCH_3 with allylmagnesium bromide at −78 °C. It was immediately subjected to a condensation with **8** at −78 °C to furnish, after the usual alkaline hydrogen peroxide workup, the secondary homoallylic alcohol **10**, in 82% yield and with enantiomeric purity >96%, as confirmed by ^{1}H NMR in the presence of the chiral shift reagent Eu(hfc)$_3$ (Scheme 2). The absolute configuration of **10** was assumed to be *R*, advocating that, in all the examples reported by Brown or others,[16] the addition of the allyl group took place in the same stereochemical fashion.

With homoallylic alcohol **10** in hand, we needed a chiral aldehyde as a second building block for the introduction of the proper stereochemistry at C-2″. The required aldehyde should incorporate the hydroxyalkane side chain for the oxidative cyclization step to give the spiroketal **5**. The hemiacetal of 4-(*R*)-hydroxypentanal (**11**) was easily obtained by the reduction with *i*-Bu_2AlH of (*R*)-γ-valerolactone,[17] which recently became commercially available. Also, the use of (*S*)-γ-valerolactone allowed access to the opposite stereoisomer.

Prins cyclization was performed by using different Lewis acids, following a procedure described by Taddei.[11] We observed that the use of $TiCl_4$ in dichloromethane at a low temperature afforded better yields and cleaner reaction mixtures, leading to the desired chlorotetrahydropyran **12**, with a 63% yield after chromatographic purification (Scheme 3).

By comparing the spectroscopic data of **12** with the values reported in the literature of similar compounds,[11,18] the major product was identified as the stereoisomer where the two alkyl chains and the chlorine substituents were equatorial. This was represented by the width at half-heigth (W_H) of the ^{1}H NMR multiplets for the protons at the 2, 6, and 4 positions of the tetrahydropyran ring, which showed a value of about 20 Hz, meaning existence of an axial−axial coupling.[11] Furthermore, the ^{1}H NMR chemical shift of the 4-hydrogen was at 3.9 ppm, typical for a H in the axial position.[19] These findings confirmed that the three substituents were all in the equatorial positions, which is in agreement with the *all-cis* stereochemistry.

Flash chromatography allowed the separation of **12** from a diastereoisomer (ca. 10%). The formation of this side product could be explained by invoking a competitive oxo-Cope rearrangement of the intermediate oxocarbenium ion during the intramolecular allylation step. This side reaction, which recently came to light, is associated with the Prins cyclization reaction.

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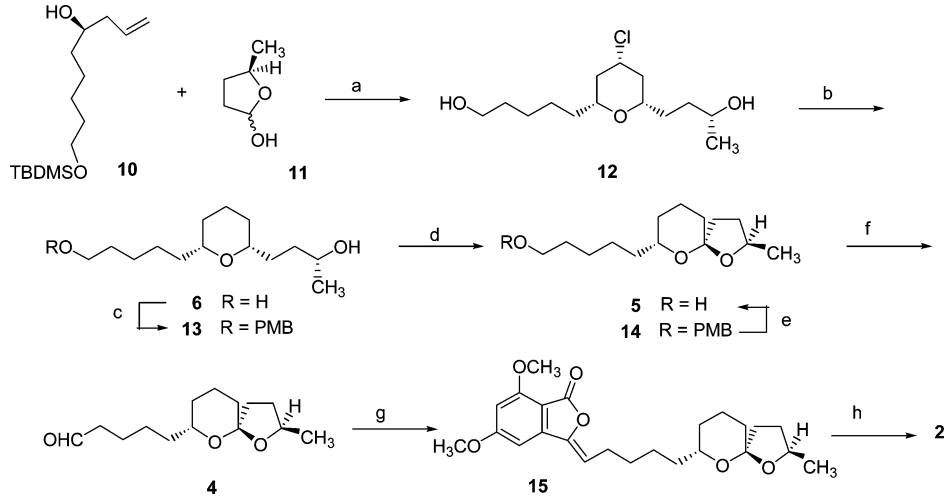
SCHEME 3 [a]



[a] Reagents and conditions: (a) $TiCl_4$, CH_2Cl_2, −70 °C, 4 h, then −20 °C, 1 h, 63%; (b) $NaBH_4$, DMSO, 130 °C, 8 h, 96%; (c) (PMB)Cl, NaH, DMF, rt, 3 days, 50%; (d) HgO, I_2, *hν*, cyclohexane, 9 h, 68%; (e) CAN, CH_3CN/H_2O, rt, 2 h, 68%; (f) TEMPO, KBr, NaOCl, 3 h, 100%; (g) **3**, NaH, THF, rt, 24 h, 62%; (h) 10% Pd/C, AcOH, 4 h, 45%.

Partial inversion of the original C−O stereochemistry of the homoallylic alcohol could result from this kind of reaction.[20,21] The presence of an electron-rich aromatic ring, linked to the alcohol, favors this rearrangement,[22] but there is evidence that shows it may occur also with aliphatic alcohols.[23]

Reductive dechlorination, using the Hutchins[24] protocol ($NaBH_4$ in DMSO), gave tetrahydropyran **6** in good yield (96%). Oxidative cyclization,[25] mediated by HgO/I_2, generated the desired spiroketal **5** in a disappointing yield of 21%. We reasoned that this was due to the presence of a free primary hydroxy group at the end of the methylene chain. Hence, the alcohol was protected as a *p*-methoxybenzyl ether, and the oxidative cyclization was performed using the same conditions described before, leading to an improved yield of 68% after purification by column chromatography. Deprotection of the hydroxyl moiety gave rise to compound **5**. This was oxidized with TEMPO to obtain the desired aldehyde **4**, which was condensed with the phthalide moiety.

The synthesis of the phosphonate **3** was performed, as previously described,[3] by a reaction of *N*,*N*-diethyl-2-formylbenzamide, obtained by *ortho*-lithiation−formylation of *N*,*N*-diethylbenzamide, with chlorotrimethylsilane and triethyl phosphite. This was followed by a desilylation step and then a cyclization step with methanesulfonic acid. The condensation of the aldehyde **4** with **3** afforded the alkene **15** as a mixture of *E*/*Z* stereoisomers.

The complete assignment of the spiroketal structure and stereochemistry was aided by proton homonuclear correlation (COSY) experiments, followed by extensive NOE experiments

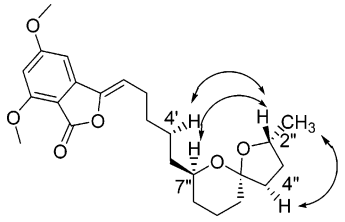


FIGURE 1. Selected NOESY correlations for **15**.

(supported by molecular modeling of the conformational preferences). NOE correlations were found between H-2″ and H-7″, H-4′ and H-2″, and H-4″ and CH_3-2″, which is consistent with the minimal energy conformation of (3*R*,2″*R*,5″*R*,7″*R*)-**15** but not with the C-5″ epimer. Interestingly, we did not find a correlation between H-4′ and H-4″, meaning that the spiroketal epimer was not present. These observations confirmed that the reaction generated the thermodynamically favored spirocycle, as found in the natural product, due to the expected axial (anomerically stabilized) preference of the five-membered-ring oxygen.[26] A summary of the results from NOE experiments, supported by molecular modeling, is reported in Figure 1.

Finally, reduction of the double bond in AcOH, using Pd/C (10%) as a catalyst, led to a mixture of two diastereoisomers from which (+)-spirolaxine methyl ether **2** was separated by preparative HPLC. Its structure was confirmed by HPLC analysis, where it was compared with an authentic sample. All the spectroscopic data of the obtained compound, including the CD spectrum, matched those of an authentic sample.

In summary, a total synthesis of (+)-spirolaxine methyl ether was designed and carried out. Crucial steps for our strategy included a Prins cyclization, to obtain the [6,5]-spiroketal system, and a Wadsworth−Emmons condensation, applied for the installation of the polymethylene chain on the phthalide moiety. When this work was already in its advanced stage, an alternative synthesis of (+)-spirolaxine methyl ether was reported by Robinson and Brimble.[27] The Brimble synthesis

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required 15 steps to prepare the spiroketal moiety and 6 steps for the phthalide moiety. The synthesis had the advantage of coupling two moieties that already contained all the stereocenters, but our synthetic approach proved to be shorter. A combination of the two routes would most likely offer the best pathway, where varied chain lengths could be implemented and a variety of potentially bioactive analogues (e.g., phthalide moiety with other substituents) could be obtained. Moreover, different stereoisomers could be obtained, depending on the different chiral building blocks used as starting materials.

Experimental Section

(*R*)-(*tert*-Butyldimethylsilanyloxy)non-1-en-4-ol (10). (−)-*B*-Methoxydiisopinocamphenylborane (2.02 g, 6.4 mmol) was dissolved in anhydrous diethyl ether (6.4 mL) and cooled to −78 °C. To the borinate was added dropwise 6.4 mL (6.4 mmol) of 1 M allylmagnesium bromide in ethyl ether. The reaction mixture, after being stirred for 15 min at −78 °C, was removed from the dry ice−acetone bath and allowed to warm to 25 °C (∼1 h). The formation of $IpC_2BCH_2CH{=}CH_2$ was indicated by the precipitation of the magnesium salts. The allylborane was cooled to −78 °C, and **8** (1.48 g, 6.4 mmol) was added dropwise. The reaction mixture was stirred for 1 h at −78 °C and then allowed to warm to 25 °C (∼1 h). The mixture was treated with 3 M NaOH (4.7 mL) and 1.8 mL of 35% H_2O_2, and the contents were refluxed for 1 h. The organic layer was separated, washed with water (4 mL) and brine (4 mL), and dried over Na_2SO_4. Flash chromatography of the residue using 95% hexane−5% ethyl acetate as eluent afforded the title compound (1.44 g, 82%) as a colorless oil: $[\alpha]^{20}_D = +2.76$ (c = 1.12, Et_2O); ^{1}H NMR ($CDCl_3$) δ 0.03 (6H, s), 0.88 (9H, s), 1.18−1.67 (8H, m), 2.39−2.02 (2H, m), 3.49−3.74 (3H, m), 5.12 (2H, d, J = 12.65 Hz), 5.81 (1H, m). Anal. Calcd for $C_{15}H_{32}O_2Si$: C, 66.11, H, 11.84. Found: C, 66.26, H, 12.00.

(2′*R*,4′*S*,6′*R*,3″*R*)-5-[4′-Chloro-6′-(3″-hydroxybutyl)tetrahydropyran-2′-yl]pentan-1-ol (12). To a stirred solution of $TiCl_4$ (205 mg, 1.1 mmol) in dry CH_2Cl_2, which was cooled to −78 °C, was added dropwise a solution of (*R*)-γ-valerolactol (100 mg, 0.98 mmol) in CH_2Cl_2 (1.8 mL). After 10 min, a solution of **10** (268 mg, 0.98 mmol) in CH_2Cl_2 (1.8 mL) was added. The mixture was stirred at −78 °C for 4 h and at −20 °C for 1 h and then allowed to warm to 0 °C. The reaction mixture was hydrolyzed with 6 mL of saturated aqueous NH_4Cl solution. The organic phase was separated, washed with brine, and dried over Na_2SO_4. Evaporation of the solvent in vacuo followed by flash chromatography of the residue using 50% hexane−50% ethyl acetate as eluent afforded the title compound (0.17 g, 63%) as a white solid: mp 63−64 °C; $[\alpha]_D^{20} = -15$ (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.17 (3H, d, J = 6.33 Hz), 1.20−1.86 (14H, m), 1.93−2.20 (2H, m), 3.20−3.38 (1H, m), 3.63 (2H, t, J = 6.33 Hz), 3.70−3.85 (1H, m), 3.89−4.06 (1H, m); ^{13}C NMR (150 MHz) ($CDCl_3$) δ 23.4, 24.9, 25.5, 32.5, 32.6, 35.6, 35.9, 42.3, 42.6, 55.6, 62.4, 68.0, 76.7, 77.1; MS (EI) m/z 225 (40), 85 (100), 67 (30), 55 (55). Anal. Calcd for $C_{14}H_{27}ClO_3$: C, 60.31, H, 9.76. Found: C, 60.14, H, 9.87.

(2′*R*,6′*R*,3″*R*)-5-[6′-(3″-Hydroxybutyl)tetrahydropyran-2′-yl]-pentan-1-ol (6). A solution of **12** (870 mg, 3.12 mmol) and $NaBH_4$ (708 mg, 18.72 mmol) in dry DMSO (15 mL) was heated for 15 h at 130 °C, then diluted with water (30 mL), and extracted with diethyl ether (30 mL × 3). The organic phase was washed with water, dried, and concentrated in vacuo to give the title compound (728 mg, 96%) as a colorless oil: $[\alpha]_D^{20} = -1.4$ (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, d, J = 6.33 Hz), 1.26−2.34 (18H, m), 3.25−3.37 (2H, m), 3.63 (2H, t, J = 6.33 Hz), 3.70−3.85 (1H, m); MS (EI) m/z 245 (M^+, 100), 227 (35), 95 (35), 85 (80), 67 (50), 55 (95). Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81, H, 11.55. Found: C, 68.66, H, 11.34.

(2′*R*,5′*R*,7′*R*)-5-(2′-Methyl-1′,6′-dioxaspiro[4,5]dec-7′-yl)pentan-1-ol (5). A solution of HgO (89 mg, 0.41 mmol) and I_2 (104 mg, 0.41 mmol) in cyclohexane (7 mL) was stirred for 10 min, and then **6** (100 mg, 0.41 mmol) in 5 mL of cyclohexane was added. The reaction mixture was stirred at room temperature under a 275 W light. After 9 h, the reaction was quenched with saturated aqueous $Na_2S_2O_5$, and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4. Evaporation of the solvent in vacuo followed by flash chromatography of the residue using 95% CH_2Cl_2−5% acetone as eluent afforded the title compound (21 mg, 21%) as a colorless oil: $[\alpha]_D^{20} = +1.50$ (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, d, J = 5.95 Hz), 1.29−2.15 (18H, m), 3.63 (2H, t, J = 6.33 Hz), 3.65−3.76 (1H, m), 4.07−4.19 (1H, m); MS (EI) m/z 136 (11), 121 (100), 98 (48), 83 (14), 77 (26), 55 (85). Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38, H, 10.81. Found: C, 69.57, H, 10.98.

(2″*R*,5″*R*,7″*R*)-5,7-Dimethoxy-3-[5′-(2″-methyl-1″,6″-dioxaspiro-[4,5]dec-7″-yl)pentylidene]isobenzofuran-1-one (15). To a solution of dimethyl phthalide-3-phosphonate 3 (51 mg, 0.17 mmol) and 4 (48 mg, 0.2 mmol) in dry THF (2.5 mL) was added NaH (10 mg of a 60% dispersion in mineral oil, 0.24 mmol), and the mixture was stirred under nitrogen at room temperature for 24 h. Water was added to react with the excess NaH and to dissolve inorganic materials. The organic layer was separated and evaporated in vacuo to give a residue which was taken up in CH_2Cl_2. The resulting solution was washed with water, dried over Na_2SO_4, and evaporated. Flash chromatography of the residue using 75% hexane−25% ethyl acetate as eluent afforded the pure *Z*-isomer as an oil (26 mg, 36%) and an *E*/*Z* mixture as an oil (18 mg, 26%): ^{1}H NMR ($CDCl_3$) (*Z*) δ 1.19 (3H, d, J = 5.95 Hz), 1.15−1.90 (14H, m), 2.05−2.15 (2H, m), 2.37−2.46 (2H, m), 3.62−3.75 (1H, m), 3.89 (3H, s), 3.92 (3H, s), 4.06−4.18 (1H, m), 5.53 (1H, t, J = 7.82 Hz), 6.40 (1H, d, J = 1.86 Hz), 6.59 (1H, d, J = 1.86 Hz); (*E*) δ 1.12−2.16 (19H, m), 2.45−2.55 (2H, m), 3.73−3.83 (1H, m), 3.91 (3H, s), 3.96 (3H, s), 4.18−4.25 (1H, m), 5.78 (1H, t, J = 8.19 Hz), 6.46 (1H, d, J = 1.86 Hz), 6.79 (1H, d, J = 1.86 Hz). Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21, H, 7.74. Found: C, 69.05, H, 7.56.

(+)-Spirolaxine 5-*O*-Methyl Ether (2). Compound **15** (7.5 mg, 0.018 mmol) dissolved in AcOH (1.2 mL) was hydrogenated at room temperature with 10% Pd/C (13 mg) for 4 h to obtain, after filtration and evaporation of the solvent, 7 mg of a crude. Preparative HPLC of the residue afforded the title compound (45%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.75−2.19 (23H, m), 3.60−3.72 (1H, m), 3.88 (3H, s), 3.94 (3H, s), 4.09−4.18 (1H, m), 5.29 (1H, dd, J = 4.09, 7.44 Hz), 6.39 (1H, d, J = 1.49 Hz), 6.40 (1H, d, J = 1.49 Hz). MS (EI) m/z 241 (18), 197 (12), 155 (25), 136 (41), 121 (100), 111 (48), 98 (100), 77 (67), 57 (66). HPLC comparison: natural **2**, column Chiral Daicel OB, eluent hexane−*i*-PrOH (8:2) t_R = 13.36 min, flow rate 0.6 mL/min; synthetic **2**, column Chiral Daicel OB, t_R = 13.46 (50%), 14.83 (50%) min.

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Supporting Information Available: Full details of the synthetic procedures and characterization data for compounds **7**, **8, 13**, **14**, **5,** and **4,** ^{1}H NMR spectra of compounds **8**, **12,** and **15**, diagnostic region of the COESY and TROESY NMR spectra of compound **15**, molecular model of compound **15**, and CD spectra and ^{13}C NMR spectra of natural and synthetic **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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