A Synthetic Approach to Sporotricale Methylether

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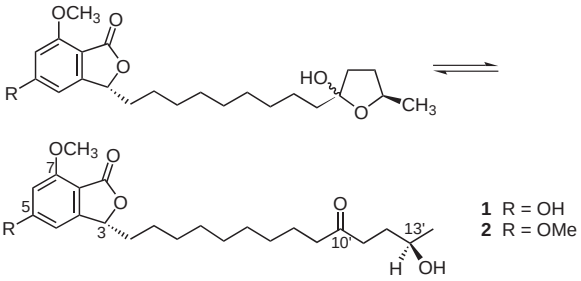
Abstract: A synthetic approach to sporotricale methylether, a metabolite of the fungus *Sporotrichum laxum* with inhibitory activity against *Helicobacter pylori*, is described. The synthesis relies on the condensation of 13-hydroxy-10-oxotetradecanal, prepared via reaction of a sulfone-activated moiety with valerolactone, with diethyl 3,5-dimethoxyphthalide-7-phosphonate.

Key words: natural products, total synthesis, sulfones, condensation, hydrogenation

(+)-Sporotricale [**1**, 5-hydroxy-3-(13′-hydroxy-10′-oxotetradecyl)-7-methoxy-3*H*-isobenzofuran-1-one] and (+)-sporotricale methylether (**2**) are polyketide-derived natural substances that were isolated some years ago from a culture of the fungus *Sporotrichum laxum* (basidiomycetae).[1] They exist as an equilibrium mixture of the two epimeric hemiketals and of the open hydroxy ketone depending on the solvent (Scheme 1).[1]



Scheme 1 Ring–chain equilibrium in sporotricale

Sporotricale and sporotricale methylether belong to a small group of fungal metabolites that have received attention for their inhibitory activity against *Helicobacter pylori*[2] and therefore may become leading compounds for the development of drugs for the treatment of gastroduodenal disorders and prevention of gastric cancer. The members of this group contain the same 5-hydroxy-7-methoxy- or 5,7-dimethoxyphthalide nucleus, but have chains of different length and of different oxidation state, also containing a spiroketal group, with respect to sporotricale.[3] The synthesis of one of these compounds, CJ-13015 (**3**, stereochemistry unknown, Figure 1), where the γ-diketone system derived from a furan nucleus, was reported recently.[4]

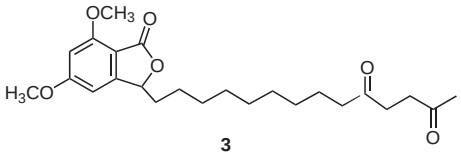


Figure 1

Apart from the activity against *Helicobacter pylori*, sporotricale and sporotricale methylether exhibit hypolipemic activity, compound **1** was showing 158% promotion of LDL uptake by HEP G2 cells.[5]

Herein we report a synthesis of (+)-sporotricale methylether (**2**), hinged on the Horner–Wadsworth–Emmons condensation of diethyl 5,7-dimethoxyphthalide-3-phosphonate (**4**) with 13-hydroxy-10-oxotetradecanal (**5**) followed by hydrogenation of the obtained alkene.

We found that a convenient route to the synthesis of aldehyde **5**, containing a γ-hydroxyketone moiety, is provided by the condensation of a sulfone-activated methylene group[6] onto commercially available γ-valerolactone as a masked 1,4-bifunctional compound (Scheme 2).

Reaction of 9-bromononan-1-ol (**6**) with sodium benzenesulfinate gave the sulfone **7**, that, after silylation of the OH group, was added with 2 equivalents of *n*-butyllithium in THF to give the soluble dilithio-derivative. Addition of a small amount of hexamethylphosphoramide followed by the stoichiometric amount of γ-valerolactone at –78 °C afforded **9** in a 60% yield. Sulfone cleavage was accomplished with Na/Hg amalgam in methanol to give the silylated hydroxyketone **10**. Desilylation of this latter required the use of aqueous HF[7] in order to obtain the primary alcohol that was oxidized to the aldehyde **5** with polymer-supported TEMPO.

Compound **4** was prepared following a procedure described by Watanabe[8] for the synthesis of various diethyl phthalide-3-phosphonates, that requires the reaction of appropriate diethyl-2-formylbenzamides (in our case **12**) with *tert*-butyldimethylsilyldimethylphosphite. However, in our hands the synthesis of *tert*-butyldimethylsilyldimethylphosphite gave variable yields due to unsatisfactory purification of the product by vacuum distillation. Therefore we modified this step of the synthesis, so that the phosphonate **4** could be prepared more easily and with higher yields by direct treatment of **12** with chlorotrimethylsilane and triethylphosphite,[9] followed by desilylation and cyclization using methanesulfonic acid (Scheme 3).

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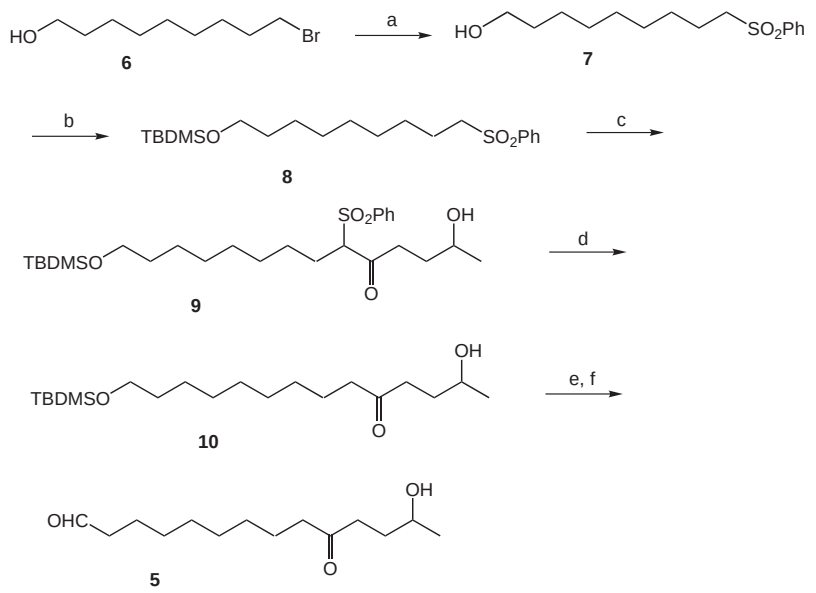

Scheme 2 *Reagents and conditions*: (a) $PhSO_2Na$, NaI, DMF, r.t., 5 h, 82%; (b) TBDMSCl, Et_3N, DMAP, DMF, r.t., 48 h, 87%; (c) THF, 0 °C, *n*-BuLi, 30 min then HMPTA, (±)-γ-valerolactone, –78 °C, 3 h, 60%; (d) Na/Hg 10%, MeOH, r.t., 24 h, 66%; (e) 40% aq HF, MeCN, r.t., 3 h, 52%; (f) NaOCl, KBr, polymer-supported TEMPO, CH_2Cl_2, r.t., 5 h, 50%

The Horner–Wadsworth–Emmons reaction in the presence of NaH[10]gave the expected alkene **13** as a mixture of *E*/*Z* isomers. Hydrogenation of the exocyclic double bond was first attempted in ethyl acetate using Pd/C 10% as a catalyst, but in these conditions also the keto group of the chain was reduced to the corresponding alcohol.

To avoid overreduction, we took advantage of the observed shift of the ring–chain equilibrium of **2** toward the hemiketal in methanol.[1] Thus, the selective catalytic reduction of the double bond was performed successfully in this solvent to give **2**, identical to the natural product in the NMR spectrum[1] (Scheme 3). By HPLC comparison, the isomeric mixture appeared to contain the natural isomer.[11]

In conclusion a simple first total synthesis of the helicobactericidal agent sporotricale methylether has been achieved by condensation of the phthalide phosphonate **4** with aldehyde **5**, on its turn obtained by the use of γ-valerolactone exploiting the mobile activating sulfonyl group.

When this work was already in an advanced stage, the absolute configuration of (+)-sporotricale was established as 3*R*,13′*R*.[12] The present synthetic approach, although the yields have not been optimized, should be amenable to the stereocontrolled synthesis of (+)-sporotricale itself. In fact *R*-stereochemistry at C13 could derive from the use of (*R*)-valerolactone, that has now become commercially available, instead of racemic γ-valerolactone, and asymmetric hydrogenation of the alkene **13** could provide the 3*R*-stereochemistry of the natural metabolite. Indeed, there are examples in the literature of asymmetric hydrogenation of 2-alkylidene-γ-butyrolactones catalyzed by BINAP–Ru (II) complexes with high enantioselectivities.[13]

Moreover, this synthetic approach can be easily extended to the synthesis of analogues with different chain length.

Acknowledgment

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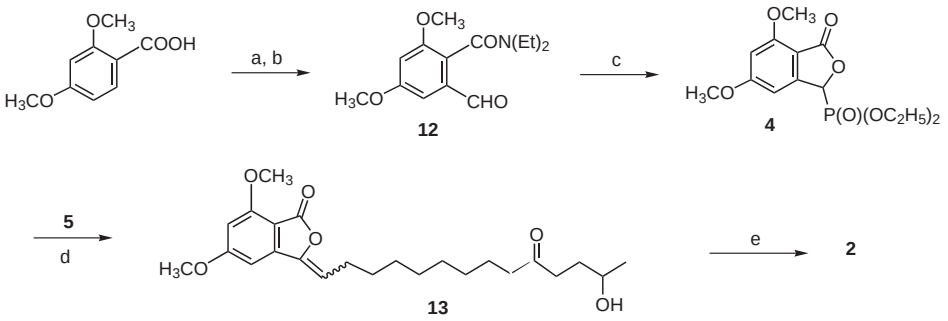

Scheme 3 *Reagents and conditions*: (a) $SOCl_2$, Et_2NH, toluene, reflux, 2 h, 92% (b) *s*-BuLi, TMEDA, DMF, –78 °C to r.t., 2 h, 85%; (c) $(CH_3)_3SiCl$, $P(OEt)_3$, then $MeSO_3H$, MeOH, 53%; (d) NaH 60%, anhyd THF, r.t., 5 d, 42%; (e) H_2/Pd/C, MeOH, 50%

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(11) **Preparation of *E*/*Z* 3-(13-Hydroxy-10-oxo-tridecylidene)-5,7-dimethoxy-3*H*-isobenzofuran-1-one (13).** To a stirred solution of phosphonate **4** (0.024 g, 0.12 mmol) and aldehyde **5** (0.024 g, 0.12 mmol) in dry THF (0.8 mL), NaH (7.4 mg of a 60% dispersion in mineral oil; 0.154 mmol) was added and the mixture stirred under nitrogen at r.t. for 5 d. After addition of H_2O, the organic layer was separated and evaporated in vacuo to give a residue which was purified by preparative layer chromatography (PLC) using 1:1 hexane–EtOAc as eluent to afford the *Z*-isomer **13** as a solid (11 mg, 24%), mp 79–81 °C and the *E*-isomer as an oil, (8 mg, 18%). ^{1}H NMR ($CDCl_3$): δ (*Z*-isomer) = 1.22 (3 H, d, *J* = 6.2 Hz, H-14′), 2.00–1.20 (14 H, m, 7 × CH_2), 2.45 and 2.35 (4 H, m, H-9′ and H-11′), 2.51 (2 H, dt, *J* = 7.8, 7.5 Hz, H-2′), 3.85 (1 H, m, H-13′), 3.92 (3 H, s, OMe), 3.97 (3 H, s, OMe), 5.55 (1 H, t, *J* = 7.8 Hz, H-1′), 6.70 and 6.45 (2 H, br d, *J* = 1.8 Hz, H-4 and H-6); δ (*E*-isomer) = 1.22 (3 H, d, *J* = 6.2 Hz, H-14′), 2.00–1.20 (14 H, m, 7 × CH_2), 2.48 and 2.33 (4 H, m, H-9′ and H-11′), 2.49 (2 H, dt, *J* = 7.8, 7.5 Hz, H-2′), 3.87 (1 H, m, H-13′), 3.93 (3 H, s, OMe), 3.98 (3 H, s, OMe), 5.79 (1 H, t, *J* = 7.8 Hz, H-1′), 6.80 and 6.47 (2 H, br d, *J* = 1.8 Hz, H-4 and H-6). MS (EI): *m*/*z* (%) = 400 (41), 345 (15), 219 (80), 111 (90), 55 (100).
Preparation of (±) Sporotricale Methylether(2). Compound **13** (12 mg) dissolved in MeOH (5 mL) was hydrogenated at r.t. with 10% Pd/C (3 mg) for 20 min. PLC of the residue in 50:50 hexane–EtOAc gave 6 mg (50%) of **2**, mp 94–96 °C. ^{1}H NMR ($CDCl_3$): δ (hemiketal) = 1.22 (3 H, d, *J* = 6.2 Hz, H-14′), 2.50–1.20 (22 H, m, 11 × CH_2), 3.83 (1 H, m, H-13′). 3.90 (3 H, s, OMe), 3.95 (3 H, s, OMe), 5.29 (1 H, br dd, *J* = 7.2, 4.0 Hz, H-7), 6.42 and 6.40 (2 H, br d, *J* = 1.7 Hz, H-4 and H-6); ^{1}H NMR (acetone-d_6): δ (hydroxyketone) = 1.10 (3 H, d, *J* = 7.2 Hz, H-14′), 2.00–1.20 (18 H, m, 9 × CH_2), 2.53 and 2.44 (4 H, t, *J* = 7.5 Hz, H-9′ and H-11′), 3.66 (1 H, m, H-13′), 3.92 (3 H, s, OMe), 3.93 (3 H, s, OMe), 5.35 (1 H, br dd, *J* = 7.6, 3.6 Hz, H-7), 6.71 and 6.59 (2 H, br d, *J* = 1.7 Hz, H-4 and H-6). ^{13}C NMR (acetone-d_6): δ = 210.01 (C-10′), 166.92 (C-1), 166.73, 159.49, 155.30, 106.45, 98.53, 98.02, 79.22 (C-3), 66.06 (C-13′), 55.57 (OMe), 55.30 (OMe), 42.10–23.60 (11 × CH_2), 21.87. MS (EI): *m*/*z* (%) = 403 (75) [MH^+], 402 (44) [M^+], 207 (34), 193 (55), 111 (55), 55 (100).
The ^{1}H NMR spectrum of this product was identical with that of natural sporotricale methylether. HPLC comparison: natural **2**, column LiChroCART 250-4 SiO_2 (Merck), eluent hexane–EtOAc (1:3), retention time (t_R) = 14.72 min; column Chiral Daicel OB, eluent hexane–*i*-PrOH (9:1) t_R = 3.19; synthetic **2**, column LiChroCART 250-4 SiO_2 (Merck), t_R = 14.78, column Chiral Daicel OB, t_R = 3.19 (48.6%); 10.91 (51.4%). Analyses were performed using a Merck-Hitachi L-4000 instrument equipped with a L-6000A pump and a UV detector (250 nm); flow rate 0.5 mL/min.
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