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Stereoselective Synthesis of Spiroketal Moiety of Ionophore Antibiotic Routiennocin

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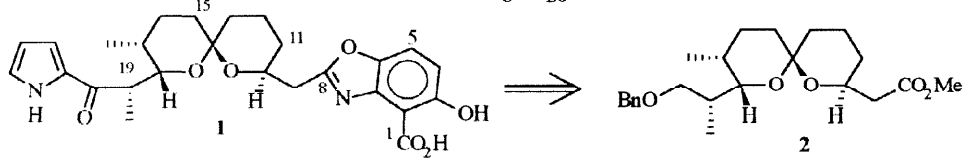
Abstract : A synthetic route to optically pure spiroketal moiety comprising C_8-C_{20} segment of ionophore antibiotic routiennocin is described.

Routiennocin (Cp-61,405) **1** an ionophore antibiotic was isolated[1] from a microbial fermentation of *Streptomyces routiennii*. Ionophore antibiotics are important tools in determining the role of metal ions in many biological processes. The biological importance and structural features of this type of spiroketal ionophore (calcimycin, cezomycin etc) have inspired successful routes to their syntheses.[2] We wish to communicate our strategy for the stereoselective synthesis of the spiroketal moiety, which constitutes the C_8-C_{20} fragment of routiennocin.



1 **2**

The synthesis was initiated with commercially available 2(R)-methyl-3-hydroxypropionate, which was converted to the corresponding alcohol[3] **3**. The epoxy alcohol **4** was prepared from the alcohol **3** by a straightforward sequence as reported by Kishi et al.[4] Enroute to the γ,δ-epoxy acrylate **5**, the epoxy alcohol **4** was subjected to Collins' oxidation to afford the aldehyde, which was subsequently treated with carboethoxytriphenylphosphorane in benzene at room temperature. The γ,δ-epoxy acrylate **5** on treatment with trimethylaluminum[5] in the presence of water in 1,2-dichloroethane at -30°C gave solely *syn* product **6**, which was converted to its corresponding TBDMS ether **7** using TBDMSOTf in the presence of 2,6-lutidine. The olefin present in the acrylate **7** was reduced by treating with magnesium in methanol at room temperature to get the saturated ester.[6] The ester was reduced to the corresponding aldehyde by treating with 1eq of DIBAL-H at -78°C; the resulting aldehyde was further subjected to Grignard reaction to furnish compound **8**. The compound **8** was conveniently oxidised with PCC to furnish keto compound **9**. The olefin compound **9** was subjected to ozonolysis, followed by Wittig olefination with carboethoxytriphenylphosphorane in benzene at room temperature to give α,β-unsaturated ester **10**. The silylether was deprotected by treating compound **10** with HF-pyridine; the resulting alcohol **11** was subjected to base catalysed cyclisation[2c] by treating with NaOMe in

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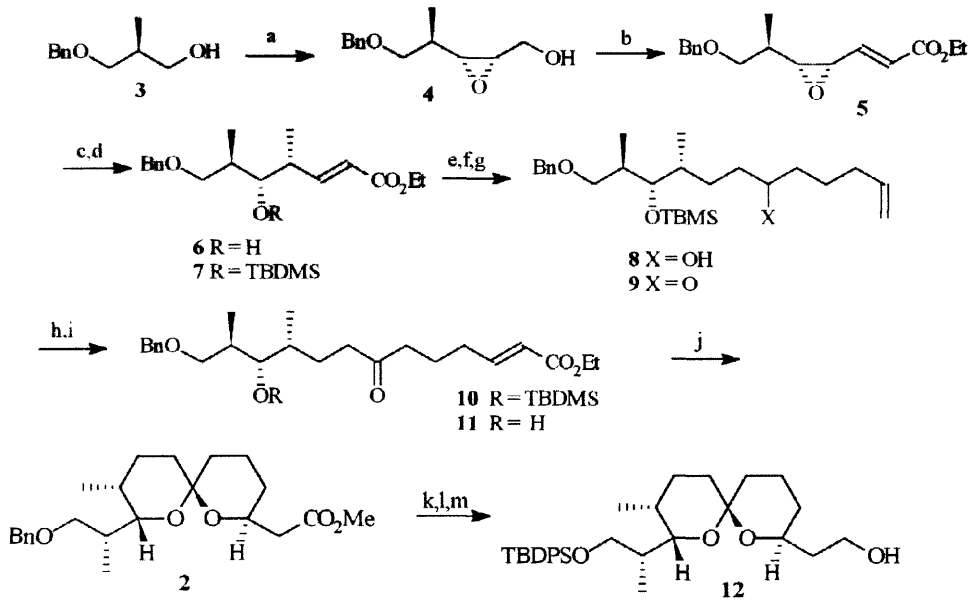

Reagents : a) ref 4; b) (i) CrO_3, py. CH_2Cl_2, 0°C, (ii) $Ph_3P{=}CHCO_2Et$, C_6H_6, r.t, 74%; c) $(CH_3)_3Al$, H_2O, $ClCH_2CH_2Cl$, -30°C, 85%; d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 95%; e) Mg, MeOH, r.t, 95%; f) (i) DIBAL-H, -78°C, CH_2Cl_2, (ii) $CH_2{=}CH(CH_2)_3Br$, Mg, ether, 0°C, 78%; g) PCC, CH_2Cl_2, 0°C, 76%; h) (i) O_3, Ph_3P, CH_2Cl_2, -78°C; (ii) $Ph_3P{=}CHCO_2Et$, C_6H_6, r.t., 72%; i) HF-py., THF, 12h. 71%; j) NaOMe (catalyst), CH_2Cl_2 : CH_3OH (9:1), r.t., 62%; k) Pd-C, H_2, EtOH, 95%, l) TBDPSCl, Im, CH_2Cl_2, 0°C, 85%; m) DIBAL-H, CH_2Cl_2, -78°C, 78%.

CH_2Cl_2:CH_3OH (9:1) at room temperature to afford the spiroketal **2** exclusively. In order to substantiate the structural assignment, the spiroketal **2** was converted to a spiro alcohol **12**, which was an intermediate in the synthesis of routiennocin by Ley et al.,[7] whose spectral data and optical purity were in agreement with literature values.

Thus we have demonstrated a straightforward strategy for the construction of the spiroketal moiety of routiennocin. This route enables the synthesis of related molecules and analogues with ease.

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8. ^1H NMR ($CDCl_3$, 200MHz) **10** : δ 0.05 (m, 6H) 0.80-1.00 (m, 15H), 1.32 (t, 3H, J = 7Hz), 1.40-2.00 (m, 6H), 2.20 (m, 2H), 2.50 (t, 4H, J = 6.7Hz), 3.30-3.60 (m, 3H) 4.20 (q, 2H, J = 7Hz) 4.50 (ABq, J = 12.5, 4.5Hz), 5.86 (d, 1H, J = 16.6Hz), 6.90 (dt, 1H), 7.30 (s, 5H). **2** : δ 0.90 (d, 6H, J = 6.6Hz), 1.10-1.90 (m, 12H), 2.30 (dd, 1H, J = 4.5, 13.5Hz), 2.55 (dd, 1H), J = 7, 13.5Hz), 3.32 (dd, 1H, J = 2.2, 10.3Hz), 3.50-3.70 (m, 5H, includes a singlet corresponding to $COOCH_3$), 4.30 (m, 1H), 4.50 (d, 2H), 7.30 (s, 5H).