Total Synthesis of Furoscrobiculin B

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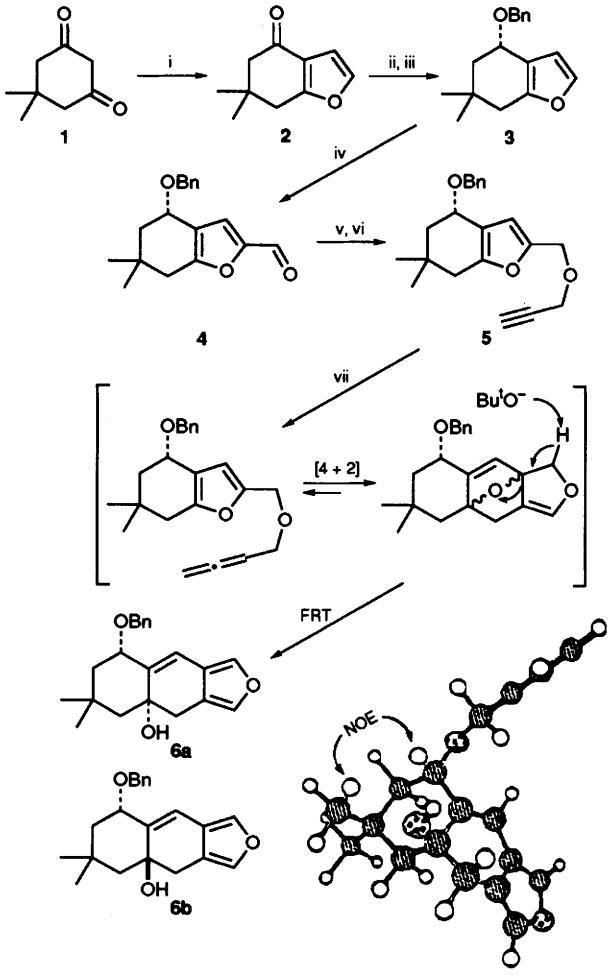
The first total synthesis of Furoscrobiculin B is accomplished by construction of the azuleno[6,7-*c*]furan ring system by base catalysed pinacol-type rearrangement of isonaphthofuran derivative, prepared from suitably functionalized hydrobenzofuran by use of the Furan Ring Transfer (FRT) reaction.

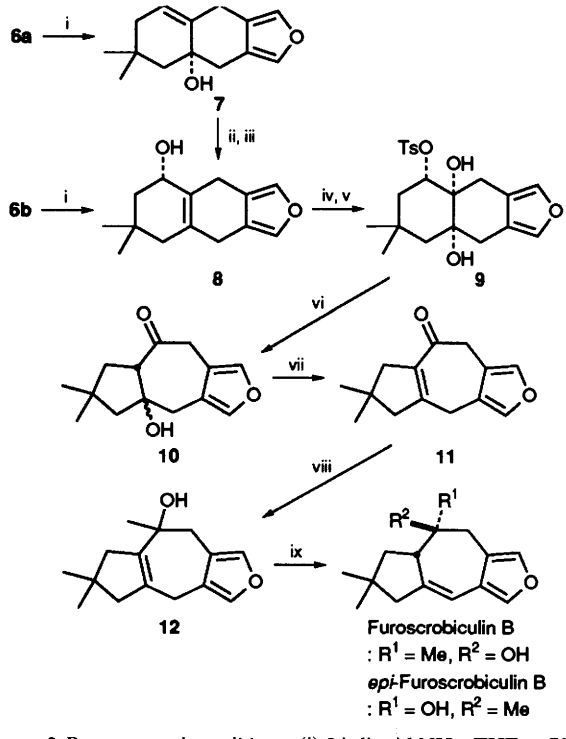
Lactarane sesquiterpenes such as Furoscrobiculin B, Furanether B and Furandiol have been isolated from basidiomycetes of several mushrooms including *Marasmius*, *Lactarius*, and *Russula*.[1] These compounds possess antifungal, antibacterial and antifeedant activities against insect and opossum[2] and their structures comprise a complex hydroazulene framework with 3,4-disubstituted furan ring. Only a limited number of synthetic studies on the lactarane skeleton have been reported.[3] Here, we report a novel methodology for construction of the azuleno[6,7-*c*]furan ring system.

Benzofuran derivative **2** was prepared from dimedone **1** by modified Feist–Beniary furanation of dimedone **1**. Formylation of **2** to **4** was effected by the sequence: (i) reduction of the ketone ($NaBH_4$), (*ii*) protection of hydroxy group (BnBr), (*iii*) formylation according to Vilsmeier method. Compound **4** was cleanly converted to the propynyl ether **5** by reduction with $NaBH_4$ followed by propynylation of the resulting alcohol (prop-2-ynyl bromide, NaOH aq., Bu_4NHSO_4). Treatment of **5** with Bu^tOK (3 equiv.) in Bu^tOH at 60 °C resulted in a smooth Furan ring transfer (FRT) reaction[5] within 30 min to afford a mixture of naphthol[2,3-*c*]furans **6a** and **b** in a ratio of 3:1 determined by HPLC analysis, which were confirmed by the coupling constant and observation of the correlation between *gem*-methyl group and α-proton of benzyl ether by the ^1H NMR inspection including NOESY measurements (Scheme 1).

The diastereoselectivity of the FRT reaction probably arises from the steric interaction between the terminal hydrogen of the allene and the *gem*-dimethyl group in the transition state. Sterically preferred β-face approach of the allenyl ether to the furan leads to the *trans* product **6b**. In addition, intramolecular Diels–Alder reaction of **5** could not occur under the neutral conditions (in toluene, 110 °C, 20 h). The generation of the allene moiety seems to be an essential factor in the Diels–Alder reaction.



Scheme 1 *Reagents and conditions*: (i) $ClCH_2CHO$, $NaHCO_3$ aq., $CHCl_3$, room temp.; H_2SO_4 aq., room temp., 89%; (ii) $NaBH_4$, EtOH, room temp., 94%; (iii) BnBr, NaH, DMF, room temp., 99%; (iv) $POCl_3$, DMF, room temp., 95%; (v) $NaBH_4$, EtOH, room temp., quant.; (vi) propargyl bromide, Bu_4NHSO_4 (cat.), NaOH aq., diethyl ether, room temp., 98%; (vii) Bu^tOK, Bu^tOH, 70 °C, 87% (**6a**:**6b** = 1:3)



Scheme 2 *Reagents and conditions*: (i) Li, liquid NH_3, THF, −78 °C, 80–90%; (ii) PDC, CH_2Cl_2, room temp., 46% (iii) DIBAH, THF, −78 °C, 85% (iv) OsO_4, CH_2Cl_2, Py, room temp., then $NaHSO_3$, 33%; (v) TsCl, DMAP , NEt_3, CH_2Cl_2, 40 °C, 80%; (vi) Bu^tOK, Bu^tOH, room temp., 97%; (vii) Al_2O_3, py, 110 °C, 69% (α,β-enone **11**: β,γ-enone = 4; 1); (viii) MeLi, THF, $CeCl_3$, −78 °C, 79%; (ix) Bu^tOK, DMF, room temp., 68% (Furoscrobiculin B:*epi*-Furoscrobiculin B = 7:2)

Removal of the protecting groups of compounds **6a** and **b** provided the allyl alcohols **7** and **8**, respectively. Compound **7** was converted to the alcohol **8** by rearrangement of its chromium acid ester followed by reduction of the enone. Dihydroxylation of **8**, which was examined with a catalytic amount of OsO_4 and a variety of cooxidants (H_2O_2, TBHP, NMO, TMNO) and various reaction conditions (temperatures, solvent systems), proved unrewarding. However, a stoichiometric amount of OsO_4 gave the triol in the highest yield for this substrate. In contrast, dihydroxylation of both the *tert*-butyldimethylsilyl and benzyl ethers of **8** failed entirely and only slow decomposition occurred. The resulting triol was transformed by selective mono-esterification to the corresponding tosylate **9** as the precursor to the pinacol-type rearrangement. A key step in this synthesis, pinacol-type rearrangment was accomplished rapidly in high yield under mild conditions to give the inseparable diastereoiso mixture (5:2 determined by ^{1}H NMR) of the hydroazuleno[6,7-*c*]-furan derivative **10**.[6] Compound **10** was converted to the hydrazone, from which the major diastereoisomer (4:1 isolated ratio)† was separated by recrystallization. The molecular structure of the major product was determined by X-ray crystallographic analysis, details to be published elsewhere. Dehydration of **10** gave regioisomers of the α,β-enone **11** and β,γ-enone (4:1) as potential key intermediates. Methylation of **11** provided the alcohol **12** in high yield. Successful isomerization of **12** gave diastereoisomer of *epi*-Furoscrobiculin B and Furoscrobiculin B (2:7 isolated ratio),‡ which were determined by NOESY measurements, and its spectral data were essentially identical or comparable to those reported for the natural compound[1] (Scheme 2).

In summary, a total synthetic route to Furoscrobiculin B (overall yield 3.6%, 14 steps from dimedone) was established which will facilitate analogous preparations in search for new biologically active material.

We are grateful to Professor Paola Vita Finzi for providing spectral data on the natural product.

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Footnotes

† Data for major diastereoisomer; yellow crystalline needles; mp 175 °C; R_f = 0.62 [hexane–ethyl acetate (1:1)]; HRMS calcd. for $C_{20}H_{23}O_6N_4$: 415.1621. Found: 415.1608; *Anal.* Calcd. for $C_{20}H_{22}O_6N_4$: C, 57.97; H, 5.35; N, 13.52. Found: C, 57.98; H, 5.39; N, 13.37%.

‡ Furoscrobiculin B; pale yellow viscous oil; R_f = 0.25 [hexane–ethyl acetate (3:1)]; IR ν_{max} ($CHCl_3$) cm^{-1} 3450, 2960, 1380, 1080, 880; ^{1}H NMR ($CDCl_3$; J/Az) δ 7.22 (s, 1H), 7.16 (d, *J* 0.1, 1H), 6.12 (d, *J* 2.3, 1H), 3.10–3.18 (m, 1H), 2.94 (d, *J* 9.9, 1H), 2.90 (d, *J* 9.9, 1H), 2.29 (s, 2H), 1.77 (dd, *J* 11.9, 8.1, 1H), 1.60 (t, *J* 11.9, 1H), 1.12 (s, 3H), 1.11 (s, 3H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 142.35 (s), 140.91(d), 140.17 (d), 123.36 (s), 118.32 (s), 112.15 (d), 71.89 (s), 54.94 (d), 50.19 (t), 43.63 (t), 41.08 (t), 35.94 (s), 29.15 (q), 27.36 (q), 20.69 (q); *m/z* 232 (M^+), 215 (M^+ −OH); HRMS calcd. for $C_{15}H_{20}O_2$: 232, 1464. Found 232.1464. *epi*-Furoscrobiculin B; colourless oil; R_f = 0.53 [hexane–ethyl acetate (3:1)]; IR ν_{max} ($CHCl_3$) cm^{-1} 3450, 2950, 1360, 1120, 890; ^{1}H NMR ($CDCl_3$; *J* Hz) δ 7.29 (s, 1H), 7.18 (m, 1H), 6.30 (d, *J* 2.3, 1H), 3.02–2.97 (m, 1H), 2.96 (d, *J* 15.8, 1H), 2.84 (dd, *J* 15.8, 1.7, 1H), 2.29 (s, 2H), 1.76 (d, *J* 12.5, 1H), 1.66 (dd, *J* 12.5, 8.7, 1H), 1.57 (s, D_2O exchange 1H), 1.33 (s, 3H), 1.09 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 142.22 (s), 141.87 (d), 140.42 (d), 122.86 (s), 118.48 (s), 113.03 (d), 69.00 (s), 53.94 (d), 50.09 (t), 44.13 (t), 39.87 (t), 35.78 (s), 29.02 (q), 27.92 (q), 27.31 (q); *m/z* 233 (M^+ + H); HRMS calcd. for $C_{15}H_{20}O_2$: 232.1464. Found 232.1466.

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