A CONCISE ENANTIO- AND STEREOCONTROLLED SYNTHESIS OF (+)-RAMULOSIN FROM (R)-O-BENZYLGLYCIDOL

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Abstract——Ramulosin, a metabolite of Pestolatia ramulose, has been synthesized in enantio- and stereocontrolled fashion starting from (R)-O-benzylglycidol.

(+)-Ramulosin[1] (**1**), a metabolite of Pestolatia ramulose, is the simplest member of other biogenetically related δ-lactone antibiotics such as actinobolin[2] (**2**) and bactobolin[3] (**3**). We report herewith an efficient enantio- and stereocontrolled synthesis of ramulosin[4] (**1**) from (R)-O-benzylglycidol[5] (**4**) via the α,β-unsaturated δ-lactone intermediate[6] **5**.

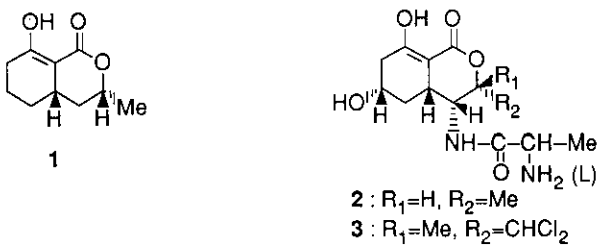
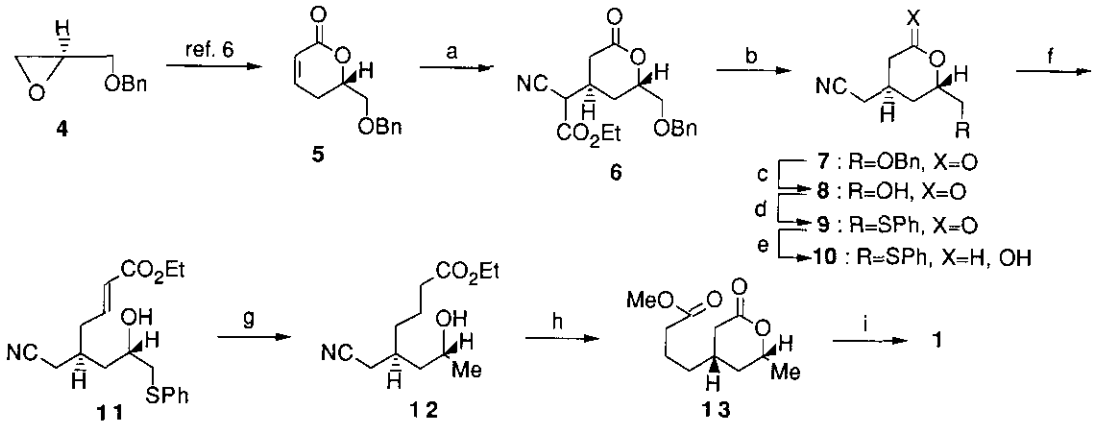


Figure 1

Reaction of the lactone **5**, obtained in 64% overall yield[6] from (R)-O-benzylglycidol (**4**), with ethyl cyanoacetate in the presence of sodium hydride proceeded in a stereoelectronically favorable way[7] to furnish a separable mixture (9:1) of the anti-**7**, $[\alpha]_D^{27}$ +35.8° (c 1.14, $CHCl_3$), and the syn-cyanolactone in isolated yields of 62 and 7% after treating the crude adduct **6** with magnesium chloride in hot dimethylacetamide.[8] Hydrogenolytic removal of the benzyl group of **7** followed by treating the resulted alcohol **8** (96% yield), $[\alpha]_D^{24}$ +51.2° (c 1.04, $CHCl_3$), with diphenyl disulfide and tri-n-butylphosphine[9] afforded the sulfide **9**, $[\alpha]_D^{28}$ +12.8° (c 1.00, $CHCl_3$), in 92% yield. Reduction of **9** with diisobutylaluminum hydride gave the lactol **10** which was immediately treated with ethoxycarbonyltriphenylmethylide to give the α,β-unsaturated ester **11**, in 82% overall yield, which was consisted mostly of E isomers (ca. 8:1). Upon treatment with Raney nickel (W-2) in refluxing ethanol **11** furnished the saturated product **12**, $[\alpha]_D^{27}$ -20.3° (c 0.92, $CHCl_3$), in 63% yield in one step via spontaneous desulfurization and hydroge



Scheme 1

(a) NaH, ethyl cyanoacetate, THF, 0 °C; (b) $MgCl_2 \cdot 6H_2O$, EtOH, reflux; (c) $Pd(OH)_2/H_2$, AcOEt, 10% HCl (cat.); (d) $(PhS)_2$, $^nBu_3P$, pyridine, room temp; (e) diisobutylaluminum hydride, THF, -30 °C; (f) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, room temp; (g) Ra-Ni, EtOH, reflux; (h) i) KOH, EtOH-H_2O, reflux, ii) CH_2N_2; (i) t-BuOK, THF, room temp.

nation. On sequential saponification (KOH, aq. EtOH), acid work-up, and esterification (CH_2N_2), **12** afforded the δ-lactone ester **13**, $[\alpha]_D^{26}$ +3.2° (c 1.00, $CHCl_3$), with 4,6-syn stereochemistry in 82% overall yield. Finally, **13** was treated with potassium tert-butoxide to give (+)-ramulosin (**1**), mp 121-122 °C, $[\alpha]_D^{26}$ +18.1° (c 1.03, EtOH) [lit.: mp 120-121 °C[1], 118-119 °C[4b]; $[\alpha]_D^{25}$ +18° ±2 (c 2.9, EtOH)[1], $[\alpha]_D^{22}$ +18.2° (c 1.15, EtOH)[4b]], in 70% yield. Spectral data (ir, ^{1}H-nmr, and mass) were all identical with those reported.[1,4]

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