

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

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

(+)-Ramulosin¹ (1), a metabolite of *Pestotlatia ramulose*, is the simplest member of other biogenetically related δ -lactone antibiotics such as actinobolin² (2) and bactobolin³ (3). We report herewith an efficient enantio- and stereocontrolled synthesis of ramulosin⁴ (1) from (R)-O-benzylglycidol⁵ (4) via the α,β -unsaturated δ -lactone intermediate⁶ 5.

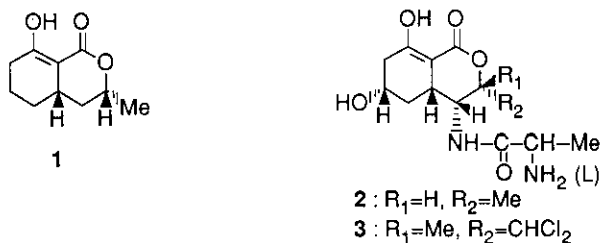
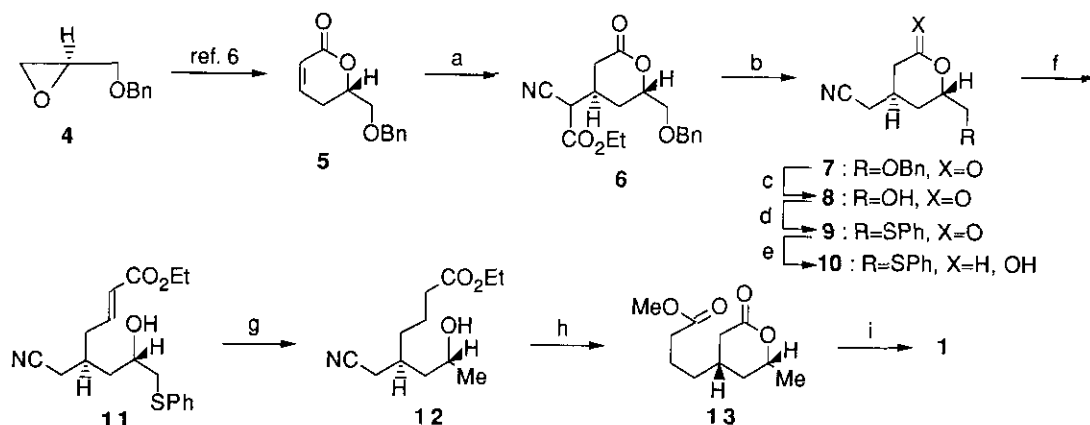


Figure 1

Reaction of the lactone 5, obtained in 64% overall yield⁶ from (R)-O-benzylglycidol (4), with ethyl cyanoacetate in the presence of sodium hydride proceeded in a stereoelectronically favorable way⁷ to furnish a separable mixture (9:1) of the *anti*-7, [α]_D²⁷ +35.8° (c 1.14, CHCl₃), 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), [α]_D²⁴ +51.2° (c 1.04, CHCl₃), with diphenyl disulfide and tri-*n*-butylphosphine⁹ afforded the sulfide 9, [α]_D²⁸ +12.8° (c 1.00, CHCl₃), 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, [α]_D²⁷ -20.3° (c 0.92, CHCl₃), in 63% yield in one step via spontaneous desulfurization and hydroge



Scheme 1

(a) NaH, ethyl cyanoacetate, THF, 0 °C; (b) MgCl₂·6H₂O, EtOH, reflux; (c) Pd(OH)₂/H₂, AcOEt, 10% HCl (cat.); (d) (PhS)₂, ⁿBu₃P, pyridine, room temp; (e) diisobutylaluminum hydride, THF, -30 °C; (f) Ph₃P=CHCO₂Et, CH₂Cl₂, room temp; (g) Ra-Ni, EtOH, reflux; (h) i) KOH, EtOH-H₂O, reflux, ii) CH₂N₂; (i) *t*-BuOK, THF, room temp.

nation. On sequential saponification (KOH, aq. EtOH), acid work-up, and esterification (CH₂N₂), 12 afforded the δ -lactone ester 13, [α]_D²⁶ +3.2° (c 1.00, CHCl₃), 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, [α]_D²⁶ +18.1° (c 1.03, EtOH) [lit.: mp 120-121 °C¹, 118-119 °C^{4b}; [α]_D²⁵ +18° ± 2 (c 2.9, EtOH)¹, [α]_D²² +18.2° (c 1.15, EtOH)^{4b}], in 70% yield. Spectral data (ir, ¹H-nmr, and mass) were all identical with those reported.^{1,4}

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