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TOTAL SYNTHESIS OF (+)-SESBANIMIDE A FROM D-GLUCOSE

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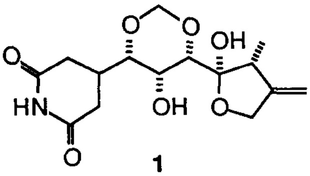
Summary: The title compound was synthesized from D-glucose in 21 steps.

Sesbanimide A (**1**) is known to be endowed with remarkable antitumor activity against experimental tumor cell lines and has been the goal of substantial synthetic studies.[1~4] Using L-sorbitol[4a,c] or D-xylose[4c] as a chiral template, accomplishment of the synthesis of sesbanimide A has been reported by three groups.[4] We report the successful synthesis of (+)-**1** from D-glucose, one of the most inexpensive optically active compounds.

The dithioacetal (**2**),[5] prepared in four steps from D-glucose, was converted to the aldehyde (**3**) according to the procedure reported by Fleet.[3b] Wittig reaction of **3** afforded a 1:1 mixture of *E*- and *Z*-α,β-unsaturated ester (**4**).[6] Glutarimide ring formation was carried out by utilizing the selective 1,4-addition reaction of lithiated trimethylsilylacetonitrile.[3a]



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Treatment of **4** with lithiated trimethylsilylacetonitrile in THF at -78 °C cleanly afforded, after protodesilylation with cesium fluoride in acetonitrile, the desired conjugate addition product (**5**) without contamination of the 1,2-addition product. Selective hydrolysis of the cyano group to the amide followed by cyclization with sodium ethoxide in THF afforded **6**. Hydrolysis of the acetonide protecting group afforded the glycol (**7**). The alcohol (**8**) was obtained by oxidative cleavage of the glycol of **7** with sodium metaperiodate followed by sodium borohydride reduction in ethanol.[7]

The benzyl protecting group of **8** was changed to *tert*-butyldiphenylsilyl group in four steps. Treatment of **8** with pivaloyl chloride in pyridine afforded **9**. Hydrogenolysis of **9** over 10%Pd-C in ethanol gave the corresponding alcohol, which was then treated with *tert*-butyldiphenylsilyl triflate[8]-2,6-lutidine in methylene chloride to give **10**. Selective reduction of **10** with DIBAH in methylene chloride afforded the alcohol (**11**). Melting point (145-148 °C) and optical rotation ($[\alpha]_D^{20}$ -12.6 °(c 1.14, $CHCl_3$)) of **11** were in good agreement with those reported.[4c] Since Schlessinger and Wood reported the synthesis of sesbanimide A (**1**) from **11**,[4c] formal total synthesis of **1** was completed.

In fact, sesbanimide A (**1**) was synthesized in the similar way as reported by Schlessinger.[4c] Collins oxidation of **11** afforded the aldehyde (**12**).[9] Coupling of **12** with **13**, Collins oxidation of the corresponding adducts (**14**), and acidic deprotection afforded **1** (mp 153-155 °C, $[\alpha]_D^{20}$ +53.1 °(c 0.11, $CHCl_3$)). The synthetic **1** was in good agreement by direct comparison with the sample of sesbanimide A of natural configuration.

In conclusion, (+)-sesbanimide A was synthesized from D-glucose in 21 steps.

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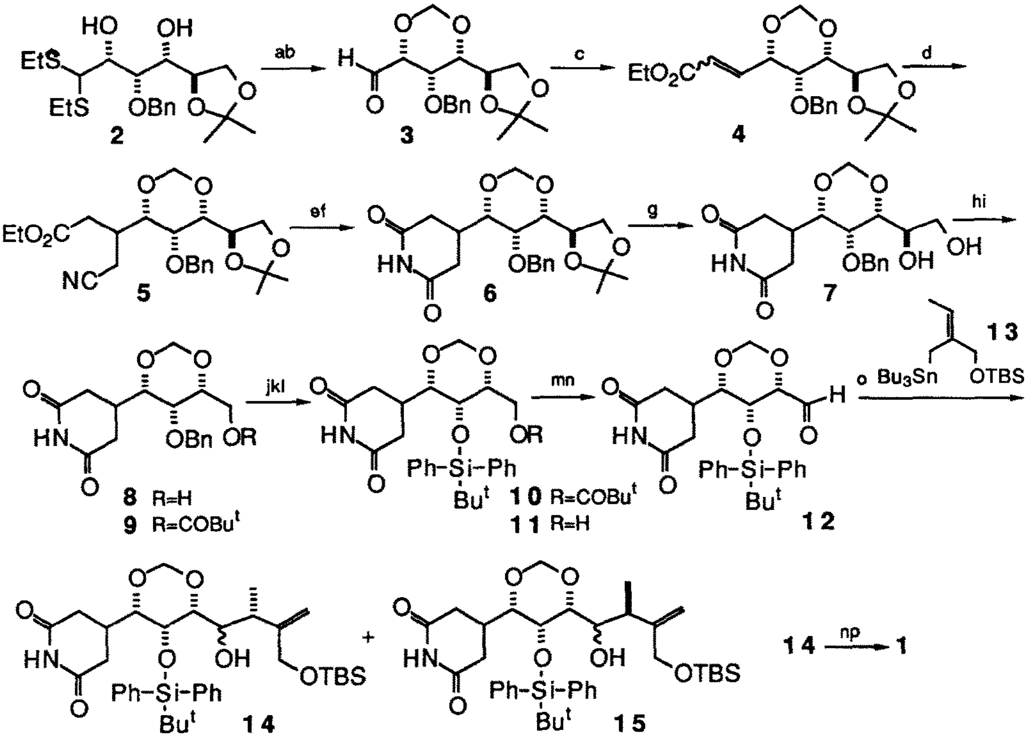

a) $BrCH_2Br$, NaOH, Bu_4NI/aq. dioxane, 69%; b) $HgCl_2$, HgO/aq. CH_3CN, quant; c) $Ph_3P{=}CHCO_2Et$/PhH, 99%; d) i. Li(TMS)CHCN/THF, ii. CsF/CH_3CN, 84%; e) H_2O_2, KOH, aq. EtOH; f) NaOEt/THF, 41% (two steps); g) aq. HCl/THF, quant; h) $NaIO_4$/aq. MeOH, quant; i) $NaBH_4$/EtOH, 89%; j) tBuCOCl/Py, 92%; k) H_2, 10%Pd-C/EtOH, 92%; l) $tBuPh_2SiOTf$, 2,6-lutidine/CH_2Cl_2, 97%; m) DIBAH/CH_2Cl_2, 88%; n) $CrO_3\cdot 2Py/CH_2Cl_2$, 95%; o) **13**, $BF_3\cdot Et_2O/CH_2Cl_2$, 18% for **14**, 17% for **15**; p) AcOH/aq. THF, 91% two-step yield from **14**.

References and Notes

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4. Synthesis of (+)- and (-)-sesbanimide A. a) M. J. Wanner, N. P. Willard, G.-J. Koomen, and U. K. Pandit, *Tetrahedron*, **43**, 2549 (1987). b) F. Matsuda and S. Terashima, *Tetrahedron Lett.*, **27**, 3407 (1986). c) R. H. Schlessinger and J. L. Wood, *J. Org. Chem.*, **51**, 396 (1986).
5. S. Valverde, S. Garcia-Ochoa, and M. Martin-Lomas, *Carbohydr. Res.*, **1986**, 147, C1-C2.
6. Satisfactory spectroscopic and analytical data were obtained for all compounds.
7. Hydrogenolysis of **8** afforded the diol which showed melting point (211-213 °C), optical rotation ($[\alpha]_D^{20}$ -6.7° (c 0.55, DMSO)) and NMR spectra identical with those reported.[4a,b]
8. Prepared from *tert*-butyldiphenylsilyl chloride and silver triflate.
9. Collins oxidation gave better result than Swern oxidation reported by Schlessinger.[4c]

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