SYNTHESIS OF THE AB RING MOIETY OF SESBANIMIDE

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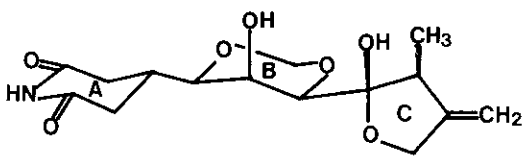
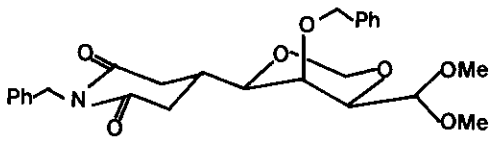
Abstract —— The synthesis of the AB ring moiety of sesbanimide or its enantiomer from D-glucose is described.

Sesbanimide, isolated from seeds of *Sesbania drummondii*, was shown to possess an exceptionally potent antitumor activity against PS leukemia in mice. The structure was elucidated by X-ray crystallographic analysis[1a] and NMR study[1b] as 1 or its enantiomer that is a novel tricyclic structure in which three rings are linked by single bonds. In this communication, we wish to report the preparation of the AB ring system of sesbanimide. Our synthetic strategy toward 1 involves (i) construction of one enantiomer of the AB ring system from some chiral starting material to elucidate the unknown absolute configuration and (ii) stereocontrolled formation of ring C from the above segment. Very recently, Tomioka *et al.* reported the synthesis of the left half of 1 from D-tartaric acid,[2] Fleet *et al.* reported the synthesis of both enantiomers of AB ring system from D-glucose,[3] and independently, Wanner *et al.* reported the synthesis of one enantiomer of the AB ring synthon from D-sorbitol.[4] We here report our own approach for the synthesis of the AB ring synthon 2 from D-glucose.



1

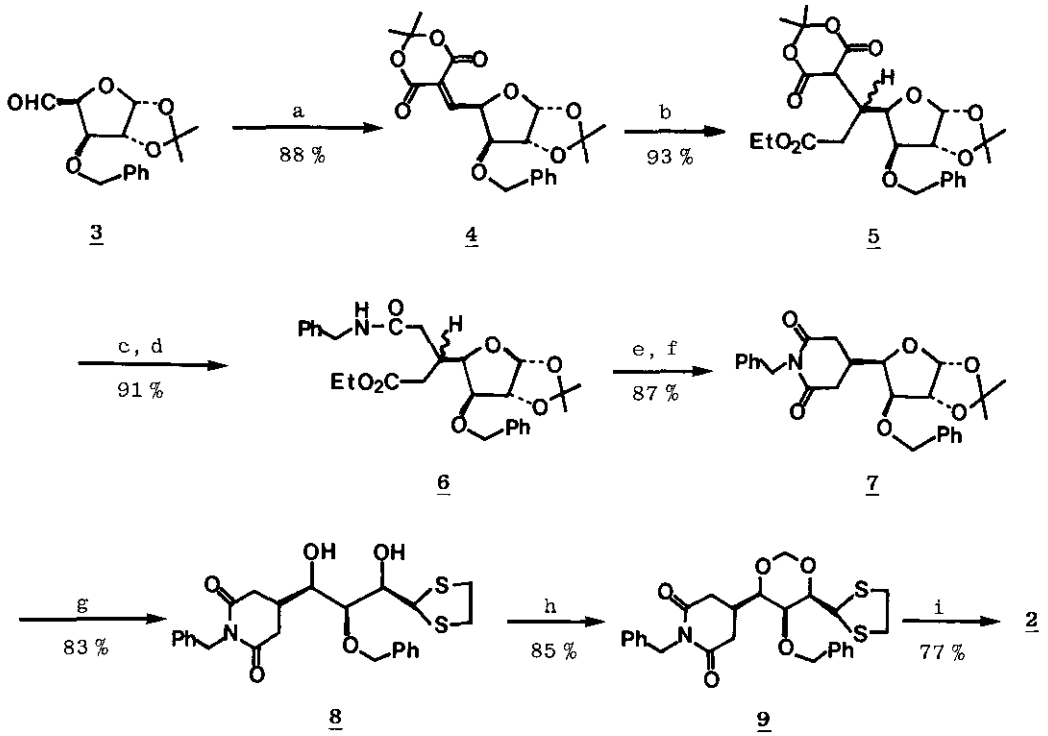


2

The aldehyde 3, prepared from D-glucose in 4 steps according to the established procedure,[5] was condenced with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) in the presence of type 4A molecular sieves, a catalytic amount of piperidine, and acetic acid to give 4. Michael reaction of lithio ethyl acetate with 4 afforded

an enantiomeric mixture of the ethyl ester 5 in good yield. Decarboxylative esterification of 5 with p-nitrophnol in the presence of Cu powder and successive treatment of the resulting p-nitrophenyl ester with benzylamine in one pot gave the amide ester 6. The desired glutarimide derivative 7 was obtained by hydrolysis of 6 followed by thermal dehydration without purification of the intermediate carboxylic acid. Dithioacetalization of the protected aldehyde group of 7 was achieved with ethanedithiol using zinc chloride as a catalyst to give the diol 8. The 1,3-dioxane 9 was obtained by acetalization of 8 with paraformaldehyde in the presence of a catalytic amount of p-toluenesulfonic acid at 100°C. Usual oxidative hydrolysis of dithioacetal group of 9 using $HgCl_2/HgO$ or N-bromosuccimide[6] was unsuccessful. Eventually, the dimethyl acetal 2 was obtained by use of 4 mol equiv of mercuric perchlorate in methanol/chloroform (1:2).[7]

The above work completes the construction of AB ring moiety of sesbanimide or its enantiomer[8] and the work is in progress toward the formation of ring C.



3 4 5 6 7 8 9 2

Reagents: a. Meldrum's acid/4A molecular sieves/piperidine/acetic acid/ CH_2Cl_2/RT. b. 1.2 equiv $LiCH_2COOEt$/THF/-78°C. c. p-nitrophenol/Cu powder/ CH_3CN/reflux. d. $PhCH_2NH_2/NEt_3$/RT. e. 1N NaOH/EtOH/70°C. f. 210°C/20mmHg. g. $HSCH_2CH_2SH/ZnCl_2$/0°C. h. paraformaldehyde/toluene/TsOH/100°C. i. $Hg(ClO_4)_2 \cdot 3H_2O$/MeOH,$CHCl_3$(1:2)/RT.

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8. Selected data: 4: mp 127-128°C; $\nu(CHCl_3)$ 1765 and 1735 cm^{-1}; $\delta(CDCl_3,100MHz)$ 1.32, 1.50, 1.66, 1.69 (4x3H, s), 4.32 (1H, d, J=12), 4.52 (1H, d, J=3), 4.55 (1H, d, J=12), 4.63 (1H, d, J=3), 5.55 (1H, dd, J=3.5 and 6.5), 6.04 (1H, d, J=3.5), 7.23 (5H, m), and 7.86 (1H, d, J=6.5). 5: $\nu(CHCl_3)$ 1745 cm^{-1}. 6: $\nu(CHCl_3)$ 3440, 1720, and 1665 cm^{-1}. 7: $\nu(CHCl_3)$ 1728 and 1675 cm^{-1}. 8: $\nu(CHCl_3)$ 3550, 1725, and 1673 cm^{-1}. 9: mp 197-198°C; $\nu(CHCl_3)$ 1725 and 1675 cm^{-1}; $\delta(CDCl_3,200$ MHz) 2.13-2.57 (4H, m), 2.88-2.98 (1H, m), 3.15 (1H, br.d, J=6.4), 3.19-3.34 (4H, m), 3.32 (1H, dd, J=1.2 and 10.2), 3.71 (1H, br.s), 4.55 (1H, d, J=11.6), 4.62 (1H, d, J=6.2), 4.75 (1H, d, J=10.2), 4.88 (1H, d, J=11.6), 4.90 (2H, s), 5.14 (1H, d, J=6.2), and 7.18-7.37 (10H, m); $[\alpha]_D^{20}$ -38.8° (c,0.49, $CHCl_3$). 2: mp 163-164°C; $\nu CHCl_3$) 1725 and 1675 cm^{-1}; $\delta(CDCl_3,200MHz)$ 2.06-2.55 (4H, m), 2.90 (1H, ddd, J=1.5, 4.2, and 17.1), 3.14 (1H, d, J=7.7), 3.43 (3H, s), 3.46 (3H, s), 3.55 (1H, s), 3.57 (1H, d, J=4.2), 4.47 (1H, d, J=11.7), 4.60 (1H, d, J=7.7), 4.62 (1H, d, J=6.2), 4.82 (1H, d, J=11.7), 4.89 (2H, s), 5.16 (1H, d, J=6.2), and 7.20-7.36 (10H, m); $[\alpha]_D^{20}$ -46.6 (c, 0.39, $CHCl_3$).

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