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EFFICIENT SYNTHESIS AND ANTITUMOR ACTIVITY OF AN ENANTIOMERIC PAIR OF THE SESBANIMIDE AB-RING SYSTEMS[1]

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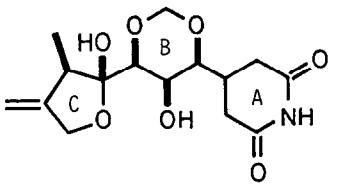
Abstract: An enantiomeric pair of the fully unprotected AB-ring systems of sesbanimide A (1), a potent antitumor alkaloid, was efficiently synthesized from readily available D- and L-xylose. Examination on their in vitro antitumor activity clearly disclosed that the AB-ring system only made a small contribution to the notable cytotoxicity of 1.

Sesbanimide A (1), an antitumor alkaloid isolated from the seeds of Sesbania drummondii and S. punices, has shown notable cytotoxicity against KB cells in vitro, and potent inhibitory activity against P388 murine leukemia in vivo.[2] Although the structure of 1 including its relative stereochemistry has been established by X-ray crystallographic analysis as a unique tricyclic structure in which the three rings are linked by single bonds, its absolute configuration has not been determined.[2] Its remarkable antitumor activity and



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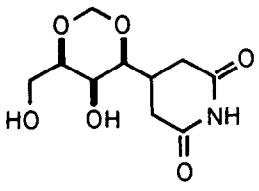

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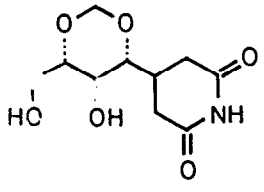

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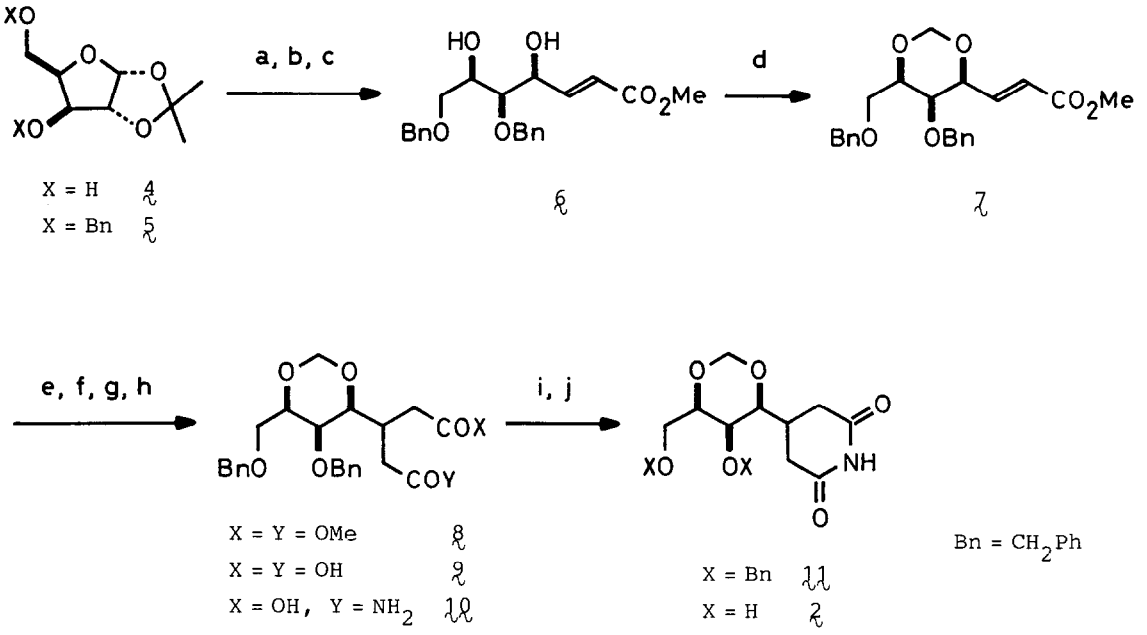
novel structure in addition to the lack of determination of its absolute stereochemistry distinguish this molecule as a very interesting target for the total synthesis.[3] Furthermore, synthetic studies on this unique compound are anticipated to contribute to elucidation of its structure-activity relationships, leading to the new analogues which may show superior antitumor activity to that of the parent compound.

In conjunction with our program directed toward the total syntheses of 1



a) 1) NaH, THF, reflux, 15 min 2) BnCl, Bu_4NBr, reflux, 5 min, 92% (2 steps) b) 12N-HCl, AcOH, rt, 5 min, 73% c) $Ph_3P{=}CHCO_2Me$, PhMe, reflux, 30 sec, 92% d) TMSOTf, 2,6-Lu, $(MeO)_2CH_2$, 0 °C, 15 min, 79% e) $NaCH(CO_2Me)_2$, Bu_4NBr, THF, 40 °C, 12 h f) NaCl, H_2O, DMSO, 160 °C, 1 h, 89% (2 steps) g) 1N-KOH, MeOH, rt, 48 h h) 1) MeOCOCl, Et_3N, THF, -20 °C, 3 h 2) NH_3 (gas), 0 °C, 30 min i) NaOAc, Ac_2O, 100 °C, 20 min, 51% (4 steps) j) H_2 (5 atm), Pd-C, MeOH, rt, 2 h, 95%

and its related compounds, we have developed an efficient and straightforward synthetic route to an enantiomeric pair of the glutarimide diols (2 and 3), which correspond to the AB-ring system of 1, starting from readily available D- and L-xylose, respectively. Although syntheses of the various protected AB-ring systems have been hitherto reported,[3] we have succeeded for the first time in preparing an enantiomeric pair of the AB-ring systems in fully unprotected forms. Moreover, with an aim to elucidate the structure-activity relationships of 1, the antitumor activity of 2 and 3 was examined by subjecting them to P388 murine leukemia in vitro cytotoxicity assay.

Protection of the two hydroxy groups of D-1,2-O-isopropylidene-xylo-furanoside (4), prepared from D-xylose in 2 steps according to the known procedure,[4] as benzyl ether groups afforded D-3,5-di-O-benzyl-1,2-O-isopropylidene-xylo-furanoside (5), caramel, $[\alpha]_D^{20}$ -48.4° (c 1.00, $CHCl_3$).[5] After removal of the acetonide group by acidic hydrolysis, treatment of the obtained lactol with

the stabilized ylide, methoxycarbonylmethylenetriphenylphosphorane, under the strictly defined conditions resulted in simultaneous opening of the furanoside ring and carbon chain elongation, producing the α,β-unsaturated ester (6) in an excellent yield. Exposure of 6 to trimethylsilyl trifluoromethanesulfonate in dimethoxymethane in the presence of 2,6-lutidine as a base effected construction of the dioxane ring, and the 1,3-dioxane (7), mp 103 - 104 °C, $[\alpha]_D^{20}$ -38.4° (c 1.00, $CHCl_3$),[5] was produced in a high yield. Micheal addition of an anion of dimethyl malonate for introducing a C_2-unit cleanly occurred in the presence of a catalytic amount of tetrabutylammonium bromide in tetrahydrofuran. Subsequent demethoxycarbonylation of the resulting Micheal adduct by brine-dimethyl sulfoxide[6] gave the diester (8), mp 49 - 52 °C, $[\alpha]_D^{20}$ -7.80° (c 1.00, $CHCl_3$),[5] in an excellent yield. The diester (8) was converted into the glutarimide (11), caramel, $[\alpha]_D^{20}$ +38.6° (c 1.00, $CHCl_3$),[5] in a good overall yield by the sequence (1) hydrolysis of the two methoxycarbonyl groups, (2) activation of the diacid (9) with methyl chloroformate in a form of the glutaric anhydride and subsequent ammonolysis on the resulting glutaric anhydride, and (3) glutarimide formation by treating the amide acid (10) (a 1:1 diastereoisomeric mixture) with acetic anhydride in the presence of sodium acetate as a buffer. The glutarimide (11) thus obtained was subjected to catalytic hydrogenation to remove the two benzyl ether groups to yield the glutarimide diol (2), mp 214 - 216 °C, $[\alpha]_D^{20}$ -6.00° (c 0.50, DMSO),[5] in an almost quantitative yield. The enantiomeric glutarimide diol (3), mp 214 - 216 °C, $[\alpha]_D^{20}$ +5.60° (c 0.50, DMSO),[5] was prepared from L-xylose following the same route as described above.

Interestingly, P388 murine leukemia in vitro cytotoxicity assay carried out on 2 and 3 cleanly revealed that each of them shows no significant antitumor activity (2; ID_{50} >25 μg/ml: 3; ID_{50} 15 μg/ml). This result may suggest that the AB-ring system of sesbanimide A (1) only makes a small contribution to the cytotoxicity of 1 and that the notable antitumor activity of 1 results from its characteristic C-ring.

As illustrated in this paper, an enantiomeric pair of the fully unprotected AB-ring systems of 1 was efficiently synthesized in a high overall yield. On the basis of this result, the total synthesis of 1 and its related compounds by adding the C-ring system to 2 and 3 are in progress in this laboratory.

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References and Notes

(1) This paper is dedicated to Prof. Shun-ichi Yamada on the occasion of his 70th birthday.

(2) R.G. Powell and C.R. Smith, Jr., U. S. Pat. Appl. US 566569 (1984); R.G. Powell, C.R. Smith, Jr., and D. Weisleder, Phytochemistry, 23, 2789 (1984)

and references cited therein.

(3) Synthetic studies on 1: K. Tomioka and K. Koga, Tetrahedron Lett., 25, 1599 (1984); G.W.J. Fleet and T.K.M. Shing, J. Chem. Soc., Chem. Commun., 835 (1984); M.J. Wanner, G.-K. Koomen, and U.K. Pandit, Heterocycles, 22, 1483 (1984); N. Willard, M.J. Wanner, G.-K. Koomen, and U.K. Pandit, Ibid., 23, 51 (1985); M. Shibuya, Ibid., 23, 61 (1985).

(4) P.A. Levene and A.L. Raymond, J. Bio. Chem., 102, 317 (1933).

(5) Satisfactory spectral and analytical data were obtained for this compound and its enantiomer. Their representative physical data are follows.

5: IR (neat) 1605, 1585, 1500 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.30, 1.47 (each 3H, s), 3.76 (2H, d, 6 Hz), 3.96 (1H, d, 4 Hz), 4.50 (2H, s), 4.52, 4.60 (each 1H, d, 12 Hz), 5.90 (1H, d, 4 Hz), 7.26, 7.30 (each 5H, s); MS m/z 370 (M^+).

7: IR (Nujol) 1720, 1670, 1500 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.78 (3H, s), 4.34 (1H, dt, 4 and 2 Hz), 4.53 (2H, s), 4.54, 4.58 (each 1H, d, 12 Hz), 4.86, 5.26 (each 1H, d, 6 Hz), 6.21 (1H, dd, 2 and 15 Hz), 6.99 (1H, dd, 4 and 15 Hz), 7.29, 7.35 (each 5H, s); MS m/z 398 (M^+).

8: IR (Nujol) 1745, 1730, 1500 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.65, 3.67 (each 3H, s), 4.57 (2H, s), 4.67, 4.71 (each 1H, d, 11 Hz), 4.76, 5.26 (each 1H, d, 6 Hz), 7.33, 7.36 (each 5H, s); MS m/z 473 (M^++H), 472 (M^+).

11: IR (neat) 3250, 1730, 1710, 1505 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.56 (1H, d, 13 Hz), 4.60 (2H, s), 4.75 (1H, d, 6 Hz), 4.81 (1H, d, 13 Hz), 5.16 (1H, d, 6 Hz), 7.33, 7.38 (each 5H, s), 7.70 (1H, bs); MS m/z 426 (M^++H).

2: IR (Nujol) 3300, 1710, 1700 cm^{-1}; ^{1}H-NMR [$(CD_3)_2SO$] δ 4.65 (1H, d, 6.0 Hz), 4.75 (1H, d, 8.2 Hz), 4.97 (1H, d, 6.0 Hz), 10.77 (1H, bs); MS m/z 246 (M^++H). Anal. Calcd. for $C_{10}H_{15}NO_6$: C, 48.97; H, 6.17; N, 5.71%. Found: C, 49.17; H, 6.22; N, 5.69%.

ent-5: caramel; $[\alpha]_D^{20}$ +50.4° (c 1.00, $CHCl_3$).

ent-7: mp 103 - 104 °C; $[\alpha]_D^{20}$ +33.6° (c 1.00, $CHCl_3$).

ent-8: mp 49 - 52 °C; $[\alpha]_D^{20}$ +9.40° (c 1.00, $CHCl_3$).

ent-11: caramel; $[\alpha]_D^{20}$ -38.8° (c 1.00, $CHCl_3$).

3 (ent-2). Anal. Calcd. for $C_{10}H_{15}NO_6$: C, 48.97; H, 6.17; N, 5.71%. Found: C, 49.16; H, 6.34; N, 5.58%.

(6) A.P. Krapcho, E.G.F. Jahngen, and A.J. Lovey, Tetrahedron Lett., 1091 (1974); C.L. Liotta and F.L. Cook, Ibid., 1095 (1974).

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