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TOTAL SYNTHESES OF NATURAL (+)-SESBANIMIDE A AND (-)-SESBANIMIDE B

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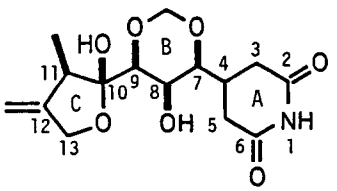
Abstract: Natural (+)-sesbanimide A (1) and (-)-sesbanimide B (2), potent antitumor alkaloids, were efficiently synthesized from the (-)-glutarimide diol (3), corresponding to the AB-ring system of 1 and 2, which had already been derived from readily available D-xylose. Our total synthesis obviously established the absolute configuration of 1.

Potent antitumor alkaloids, sesbanimide A (1) and B (2) were isolated from the seeds of the leguminous plant, Sesbania drummondii. They have shown notable cytotoxicity against KB cells in vitro, and potent inhibitory activity against P388 murine leukemia in vivo.[1] These compounds have unique tricyclic structures in which the three rings are linked by the two single bonds. These remarkable antitumor activity and novel structures distinguished these molecules as unusually attractive targets for total synthesis.[2] Previously, we had reported an efficient



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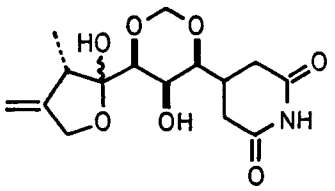

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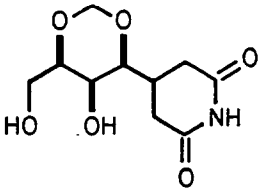
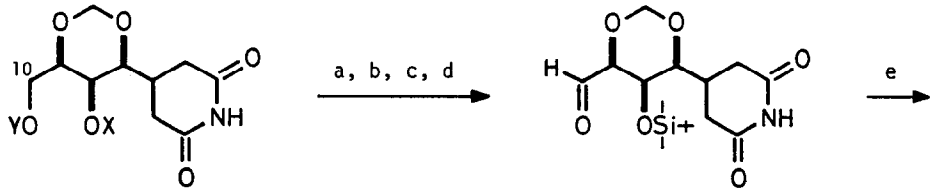


3

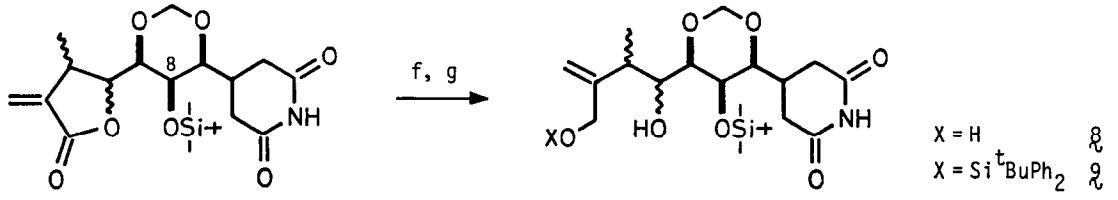
synthesis of the (-)-glutarimide diol (3), corresponding to the AB-ring system of 1 and 2, from readily available D-xylose.[3] In this communication we would like to report on the first total syntheses of natural (+)-sesbanimide A (1) and (-)-sesbanimide B (2) from 3 by forming the characteristic C-ring.

In order to construct the C-ring, it was necessary to introduce a C_5-unit into the C_{10}-carbon. For this purpose, 3 was first converted into the aldehyde (6). Thus, the primary and secondary hydroxyl groups of 3 were successively protected in forms of pivalate ester and t-butyldimethylsilyl ether, respectively, to yield the silyl ether (4).[4] Reductive cleavage of the pivalate ester group cleanly occurred without disruption of the glutarimide ring by treating with diisobutylaluminumhydride, affording the alcohol (5) [mp 176 - 178 °C, $[\alpha]_D^{20}$ -10.4° (0.50, $CHCl_3$)]. Collins oxidation of 5 readily produced 6 as an unstable solid, which without purification was immediately subjected to the next addition reaction.

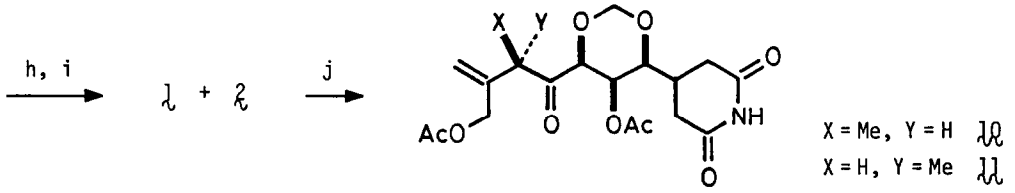
After several experiments for introducing a C_5-unit into 6,[5] it was finally found that Reformatsky reaction employing (Z)-ethyl 2-(bromomethyl)-2-butenoate[6] proceeded smoothly without any loss of the labile t-butyldimethylsilyl ether group attached to the C_8-hydroxyl group[5]



X = Y = H 3
X = Si^{t}BuMe$_2$, Y = CO^{t}Bu 4
X = Si^{t}BuMe$_2$, Y = H 5



X = H 8
X = Si^{t}BuPh$_2$ 9



X = Me, Y = H 10
X = H, Y = Me 11

(a) ^{t}BuCOCl, Py, 0 °C, 2.5 h, 91% (b) ^{t}BuMe$_2$SiOTf, 2,6-Lu, CH_2Cl_2, rt, 10 min, 86% (c) ^{i}Bu$_2$AlH, CH_2Cl_2, -78 °C, 1 h, 87% (d) CrO_3·2Py, CH_2Cl_2, rt, 10 min, 84% (e) MeCH=C(CH_2Br)CO_2Et, Zn, THF, reflux, 6 min, 73% (f) (1) ^{i}Bu$_2$AlH, CH_2Cl_2, -78 °C, 1 h (2) $NaBH_4$, $CeCl_3$·7H_2O, MeOH, 0 °C, 10 min, 73% (2 steps) (g) ^{t}BuPh$_2$SiCl, imidazole, DMF, rt, 40 min (h) CrO_3·2Py, CH_2Cl_2, rt, 30 min (i) Bu$_4$N·F, THF, rt, 10 min, 16% (1, 3 steps), 19% (2, 3 steps) (j) Ac_2O, Py, rt, 12 h, 53% (10), 61% (11).

to give the exo-methylene-γ-lactone (7) as a mixture of stereoisomers.[7] Reduction of 7 to the diol (8) was performed in a stepwise manner, since direct hydride reduction to 8 gave unsatisfactory results. Thus, treatment of 7 with diisobutylaluminumhydride gave the corresponding lactol, which without isolation was further reduced with sodium borohydride in the presence of cerium (III) chloride to afford 8 in a good yield.[7] The diol (8) was converted into an almost 1:1 mixture of 1 and 2 by the sequence of (1) selective protection of the primary hydroxyl group of 8, (2) Collins oxidation of the resulting alcohol (9), and (3) removal of the two silyl groups.[7]

The mixture of 1 and 2 could be separated by silica gel TLC. The less polar epimer [mp

156 - 157 °C, $[\alpha]_D^{20}$ +55.3° (0.17, $CHCl_3$)] and its diacetate [mp 120 - 121 °C, $[\alpha]_D^{20}$ -89.2° (0.13, $CHCl_3$)] were identical with natural sesbanimide A (1) [mp 157 - 158 °C, $[\alpha]_D^{20}$ +56.5° (0.17, $CHCl_3$)] and the authentic diacetate (10) [mp 121 - 122 °C, $[\alpha]_D^{20}$ -87.7° (0.13, $CHCl_3$)] derived from natural 1 by our hands, respectively, in all respects (mp, mmp, $[\alpha]_D$, 400 MHz ^{1}H-NMR, IR, MS, and TLC mobilities with several different solvent systems). Furthermore, synthetic and natural 1 exhibited almost the same magnitude of activity in P388 murine leukemia in vitro cytotoxicity assay (IC_{50}: synthetic 1 1.3×10^{-4} μg/ml; natural 1 0.62×10^{-4} μg/ml). Accordingly, our synthesis of natural sesbanimide A (1) obviously confirmed its absolute configuration that had been suggested by Pandit and coworkers.[2a]

On the other hand, the more polar epimer [caramel, $[\alpha]_D^{20}$ -22.4° (0.17, $CHCl_3$)] and its diacetate [caramel, $[\alpha]_D^{20}$ +55.6° (0.50, $CHCl_3$)] were found to show the 400 MHz ^{1}H-NMR spectra identical with those of natural sesbanimide B (2) and its diacetate (11), respectively. Other spectral data (IR and MS) of the synthetic compounds further supported their structures. Since 2 has been isolated from the same plant as that giving 1, its absolute configuration can be tentatively assigned as shown. Weak cytotoxicity was also observed for synthetic 2 in P388 murine leukemia in vitro assay (IC_{50}: synthetic 2 3.1×10^{-2} μg/ml). Therefore, sesbanimide B (2) synthesized by us was anticipated to be identical with natural 2 even if comparison of the optical rotations could not be carried out due to the lack of the reported rotation value.

As described in this communication, the total syntheses of natural (+)-sesbanimide A (1) and (-)-sesbanimide B (2) was efficiently accomplished starting from readily available D-xylose. Our synthesis of 1 rigorously confirmed its absolute configuration. Our total synthesis of these unique compounds should contribute to the elucidation of their structure-activity relationships,[3] leading to explore new analogues which may show superior antitumor property to those of the parent compounds.

Acknowledgement: We are grateful to Dr. R.G. Powell, U.S. Department of Agriculture, for providing us with an authentic sample and spectral data of 1, 10, and 11. We also thank Prof. U.K. Pandit, University of Amsterdam, for letting us see a copy of his paper[2a] in advance of publication. P388 Murine leukemia in vitro assay was performed by Dr. K. Sakai, Misses K. Yamada and N. Hida, Sagami Chemical Research Center, to whom our thanks are due.

References and Notes

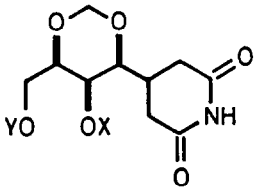
(1) R.G. Powell and C.R. Smith, Jr., U.S. Pat., 4532327 (1985); R.G. Powell, C.R. Smith, Jr., and D. Weisleder, Phytochemistry, 23, 2789 (1984) and references cited therein.

(2) (a) While the relative stereochemistry of 1 had been established by X-ray crystallographic analysis,[1] its absolute configuration was not initially determined. However, the synthesis of the enantiomer of 1 recently achieved by Pandit and coworkers disclosed its absolute configuration as shown. M.J. Wanner, N.P. Willard, G.-J. Koomen, and U.K. Pandit, J. Chem. Soc., Chem. Commun., 396 (1986). (b) Synthetic studies on 1: K. Tomioka and K. Koga, Tetrahedron Lett., 25, 1599 (1984); G.W.J. Fleet and T.K.M. Sing, J. Chem. Soc., Chem. Commun., 835 (1984); M. Shibuya, Heterocycles, 23, 61 (1985); A.V. Rama Rao, J.S. Yadav, A.N. Naik, and A.B. Chaudhary, Tetrahedron Lett., 27, 993 (1986).

(3) F. Matsuda, M. Kawasaki, and S. Terashima, Tetrahedron Lett., 26, 4639 (1985).

(4) Other combinations of protective groups for the primary and secondary hydroxyl groups of 3 were also examined. However, only pivalate ester and t-butyldimethylsilyl ether groups

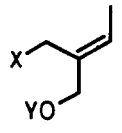
gave the satisfactory result. For examples, methoxymethylation or 2-(trimethylsilyl)-ethoxymethylation of the alcohols (12 and 13) usually afforded low yields of the products,



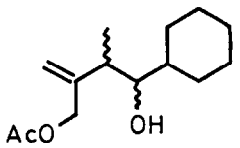
X = H, Y = CO^tBu 12
X = H, Y = CPh_3 13
X = Si^tBuMe_2, Y = CPh_3 14

because the starting materials were unstable under alkylation conditions. Moreover, reductive cleavage of the trityl ether group of the silyl ether (14) met failure because of unexpected lability of the t-butyldimethylsilyl ether group under hydrogenation condition.

(5) Various types of addition reactions were attemped using cyclohexanecarbaldehyde (15) as a model aldehyde. Thus, reactions of the bromide (16) with 15 in the presence of zinc metal, tin metal, or chromium (II) chloride were found to produce no addition product. On the other hand, Lewis acid catalyzed addition of the allylstannane (17) to 15 proceeded smoothly to give the desired alcohol (19) (BF_3·OEt_2, CH_2Cl_2, -78 °C, 2 h, 90%), although



X = Br, Y = Si^tBuPh_2 16
X = $SnBu_3$, Y = Ac 17
X = $SiMe_3$, Y = Ac 18



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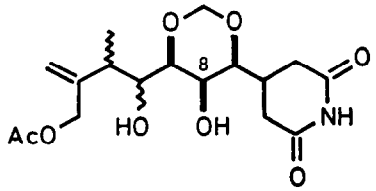

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the same reaction employing the allylsilane (18) in place of 17 did not afford 19. However, addition reaction of 17 to 6 accompanied desilylation, only giving the diol (20) (BF_3·OEt, CH_2Cl_2, -78 °C, 2 h, 65%). As shown in this example, the t-butyldimethylsilyl ether group attached to the C_8-hydroxyl group is very labile under acidic conditions. Such lability required careful treatments of the silylated synthetic intermediates (4, 5, 6, 7, 8, and 9).

(6) Prepared from ethyl acrylate and acetaldehyde according to the known procedure: H.M.R. Hoffmann and J. Rabe, Angew. Chem. Int. Ed. Eng., 22, 795 (1983).

(7) Three diastereomers whose stereostructures could not be determined were detected in a ratio of 1 : 1.3 : 1.5 in 400 MHz ^{1}H-NMR spectrum of 7. These stereoisomers were found to exhibit considerably different reactivity in the reduction of 7 and Collins oxidation of 9. Furthermore, the labile t-butyldimethylsilyl ether group of one isomer of 9 was partly cleaved during purification. Due to these reasons, the rather low yields were obtained for 8, 1, and 2, and the ratio of 1 to 2 being close to 1:1 was observed.

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