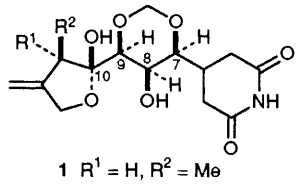
Total Synthesis of (±)-Sesbanimide A and B

Paul A. Grieco,* Kenneth J. Henry, Joseph J. Nunes and James E. Matt, Jr.
Department of Chemistry, Indiana University, Bloomington, Indiana 47405, USA

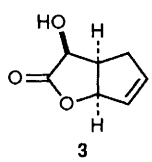
The total synthesis of sesbanimide A (**1**) and B (**2**) is reported which features (*a*) the reaction of cyclopentadiene with glyoxylic acid leading to the useful bicyclic lactone building block **3** and (*b*) the use of 2.5 mol dm^{-3} lithium perchlorate in diethyl ether to promote the conjugate addition of 1-methoxy-1-(*tert*-butyldimethylsiloxy)ethene to unsaturated lactone **11**.

Since the discovery of sesbanimide A (**1**) and sesbanimide B (**2**), rare, potent antitumour compounds isolated from seeds of *Sesbania drummondii* in 1983,[1] considerable attention has been focused on the synthesis of these novel natural products. To date several syntheses of **1** and **2** have been recorded in the literature.[2] We detail below our results in this area which have culminated in syntheses of (±)-sesbanimide A and (±)-sesbanimide B.

The starting point of our synthesis was the crystalline bicyclic lactone **3**, m.p. 67–68 °C, which was prepared in *ca.* 40% yield upon exposure of glyoxylic acid to cyclopentadiene in water. Despite the modest yield of **3**, the reaction between glyoxylic acid and cyclopentadiene can be easily carried out on a mole scale. The hydroxy group in **3** was readily protected (72%) as its methoxymethyl ether employing dimethoxymethane–chloroform, 20:1, (0 °C) containing 5.0 equiv. of phosphorus pentoxide.[3] Sequential reduction of the lactone carbonyl and carbon–carbon double bond[4] in **4** afforded diol **5** (Scheme 1). Selective protection of the primary hydroxy as its *tert*-butyldiphenylsilyl ether and subsequent oxidation of the secondary hydroxy provided the corresponding cyclopentanone which was subjected to a Baeyer–Villiger oxidation giving rise to δ-lactone **6**. Treatment of the silyl ketene acetal derived



1 R^1 = H, R^2 = Me
2 R^1 = Me, R^2 = H



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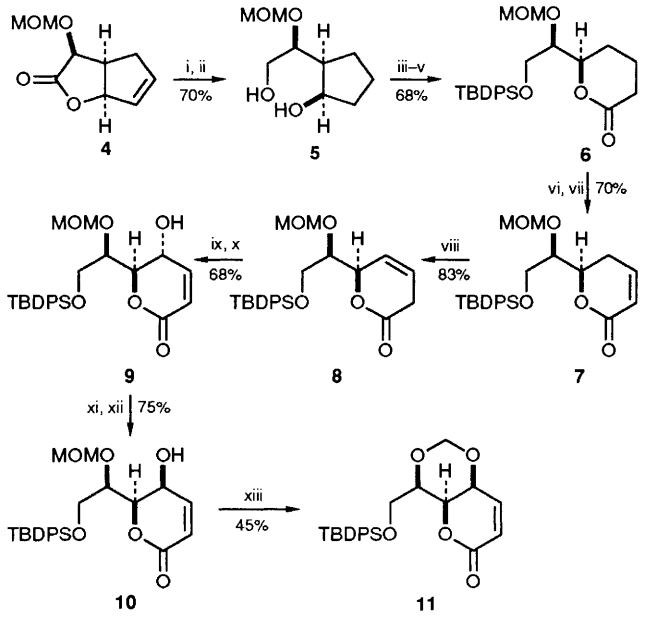
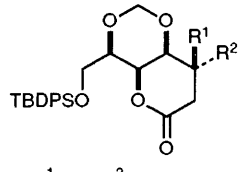
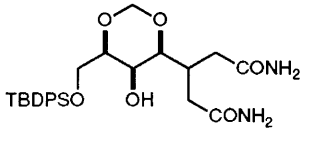


Scheme 1 *Reagents and conditions*: i, Bu^i_2AlH, THF, 0 °C, 12 h; ii, $NiCl_2·6H_2O$, $NaBH_4$, MeOH, −30 °C; iii, TBDPSCl, Et_3N, DMAP, CH_2Cl_2; iv, PCC, CH_2Cl_2, 4 Å sieves, Celite; v, MCPBA, $NaHCO_3$, CH_2Cl_2; vi, LDA, THF, −78 °C; TMSCl, Et_3N; PhSeCl; vii, MCPBA, CH_2Cl_2, −78 °C → room temp.; viii, NaHMDS, THF–Et_2O (1 : 1), −110 °C; 5% HCl, MeOH; ix, 0.1 mol dm^{-3} DMDO in acetone, 3 h; x, Et_3N, CH_2Cl_2, 12 h; xi, Ph_3P, DEAD, HCO_2H, 40 °C, 1 h; xii, $NaHCO_3$, H_2O, MeOH, THF, 20 min; xiii, $BF_3·Et_2O$, CH_2Cl_2, 0 °C, 10 min (MOM = $MeOCH_2^-$; TBDPSCl = *tert*-butyldiphenylsilyl chloride; PCC = pyridinium chlorochromate; MCPBA = *m*-chloroperbenzoic acid; LDA = lithium diisopropylamide; TMS = trimethylsilyl; DMAP = 4-dimethylaminopyridine; NaHMDS = sodium hexamethyldisilazane; DMDO = dimethyldioxirane; DEAD = diethyl azodicarboxylate



12 R^1 = H, R^2 = CH_2CO_2Me
14 R^1 = CH_2CONH_2, R^2 = H



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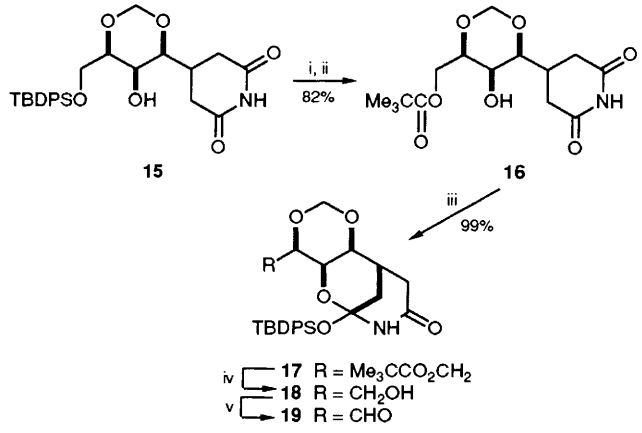
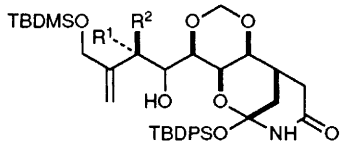
from **6** with phenyl selenenyl chloride followed by oxidation of the resultant selenide provided, in 70% overall yield, unsaturated lactone **7**. Treatment of **7** with sodium hexamethyldisilazane at −110 °C followed by warming to 0 °C and quenching with hydrochloric acid gave β,γ-unsaturated lactone **8** in 83% yield.

Transformation of **8** into lactone **10** necessitated a four-step sequence. Treatment of **8** with 5.0 equiv. of dimethyldioxirane[5] in acetone gave rise to a single epoxide which upon exposure to base afforded in *ca.* 70% yield γ-hydroxy unsaturated lactone **9** possessing the wrong configuration at the eventual C(7) position of **1**. The stereochemistry at C(7) was inverted *via* a Mitsunobu reaction[6] providing, after hydrolysis, lactone **10**. Brief exposure (10 min) of **10** to 3.0 equiv. of boron trifluoride etherate in methylene chloride cooled to 0 °C afforded the crystalline α,β-unsaturated lactone **11**, m.p. 133–135 °C.

Glutarimide formation was realized *via* a novel conjugate addition of a silyl ketene acetal to unsaturated lactone **11** in a lithium perchlorate–diethyl ether medium.[7] Treatment (2 h) of a 0.1 mol dm^{-3} solution of lactone **11** in 2.5 mol dm^{-3} lithium perchlorate–diethyl ether with 3.0 equiv. of 1-methoxy-1-(*tert*-butyldimethylsiloxy)ethene at ambient temperature gave rise to lactone **12**, m.p. 92–94 °C, in 65% yield. Exposure (5 h, pressure tube) of **12** to a saturated solution of ammonia in methanol afforded (87%) bis(amide) **13**, m.p. 170–171 °C, which upon heating (259 °C, 50 min) provided in essentially quantitative yield a 1 : 1 mixture of the amide δ-lactone **14** and glutarimide **15**. The undesired lactone **14** was converted (90%) to bis(amide) **13** upon treatment with ammonia in methanol.



Scheme 2 *Reagents and conditions*: i, NBu_4F, THF; ii, Me_3CCOCl, pyridine (py); iii, TBDPSOTf, 2,6-lutidine, CH_2Cl_2; iv, Bu^i_2AlH, CH_2Cl_2, −78 °C, 88%; v, $CrO_3·2py$, CH_2Cl_2, 30 min, 90% (TBDPSOTf = *tert*-butyldiphenylsilyl triflate)



20 R^1 = H, R^2 = Me
21 R^1 = Me, R^2 = H

Completion of the synthesis of sesbanimide A is outlined in Scheme 2. Cleavage of the *tert*-butyldiphenylsilyl ether in **15** followed by reprotection of the primary hydroxy as a pivaloate ester generated **16**, m.p. 197.5–200.0 °C. Contrary to published reports[2] attempts to silylate the secondary hydroxy in **16** did not give rise to the anticipated silyl ether. Instead a near quantitative yield of the novel tricyclic silyl ether **17**, m.p. 110.5–113.0 °C was obtained whose structure was established by single-crystal X-ray analysis. A similar observation has been recorded by Pandit and co-workers.[8] Cleavage of the pivaloate ester in **17** provided alcohol **18**, m.p. 197.5–200 °C, which set the stage for completion of the synthesis. Oxidation of **18** afforded aldehyde **19** which was transformed into alcohols **20** and **21** in a *ca.* 1 : 1 ratio according to the Schlessinger protocol.[2f]

Collins oxidation of **20** followed by hydrolysis [HOAc : tetrahydrofuran(THF) : H_2O, 3 : 1 : 1] of the silyl ether afforded (±)-sesbanimide A, m.p. 153–156 °C. Similar oxidation of **21** followed by hydrolysis provided (±)-sesbanimide B.† The spectral properties of **1** and **2** were identical to those of the natural products which were kindly provided by Dr Shiro Terashima (Sagama Chemical Research Center).

† For convenience C(10) in sesbanimide B (**2**) is depicted with a clearly defined stereochemistry, however the natural product actually exists as a mixture of isomers about C(10).

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