

## An Approach to the Enantiospecific Syntheses of Sesbanimide and its Enantiomer from D-Glucose

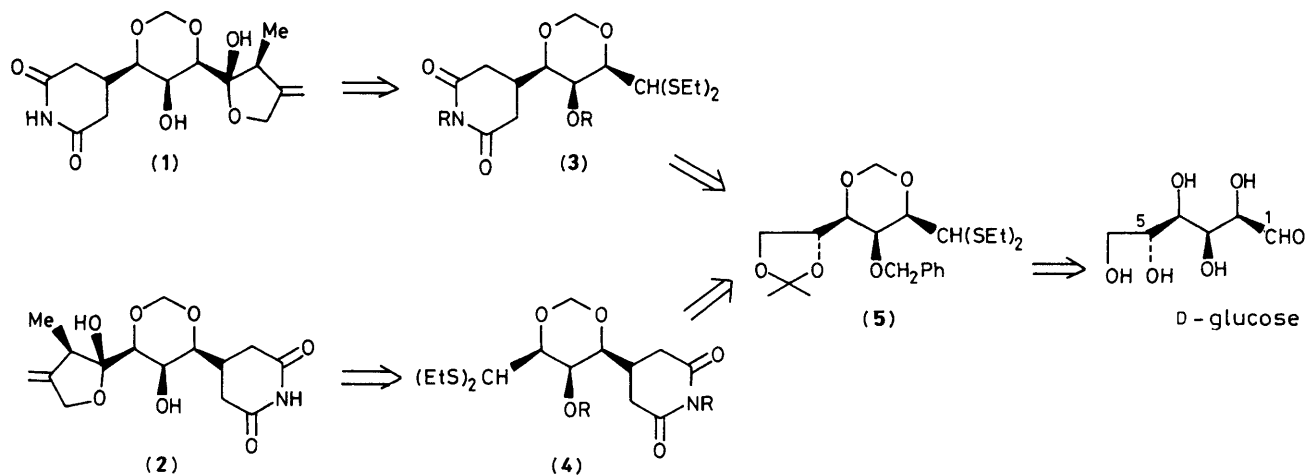
George W. J. Fleet\* and Tony K. M. Shing

Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY, U.K.

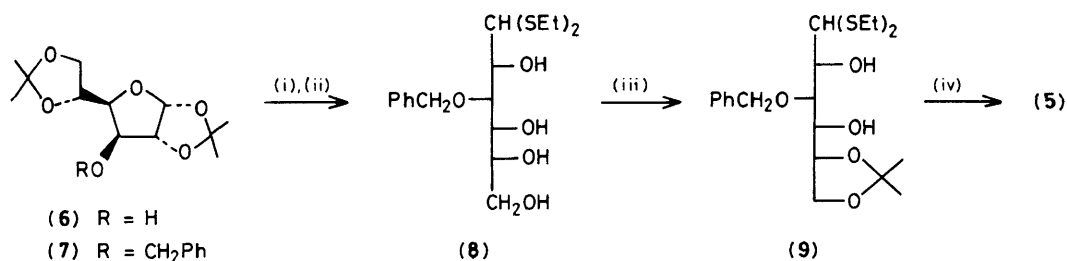
An approach to the enantiospecific syntheses of sesbanimide and its enantiomer is described; enantiomeric intermediates in the syntheses of both compounds possessing the required glutarimide and 1,3-dioxane rings are derived from D-glucose.

Very small quantities of sesbanimide have been isolated from the seeds of *Sesbania drummondii*. Sesbanimide is an exceptionally potent antitumour compound, being substantially

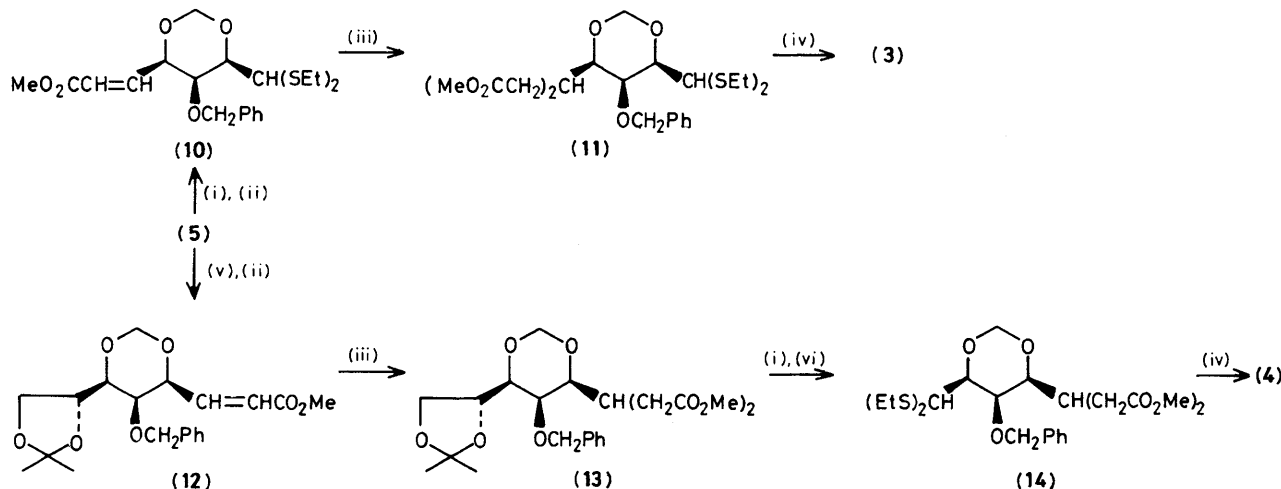
active against P388 lymphocytic leukaemia *in vivo* and causing potent inhibition of the growth of human cancer cells *in vitro*.<sup>1</sup> Although sesbanimide has a structural relationship with



Scheme 1. R = CH<sub>2</sub>Ph



**Scheme 2.** (i) PhCH<sub>2</sub>Br, NaH, Bu<sub>4</sub>NI, tetrahydrofuran; (ii) Dowex-H<sup>+</sup>, then EtSH, conc. HCl; (iii) Me<sub>2</sub>CO, anhydrous CuSO<sub>4</sub>; (iv) CH<sub>2</sub>Br<sub>2</sub>, NaOH, Bu<sub>4</sub>NI, dioxane, water.



**Scheme 3.** (i) MeOH, HCl; then NaIO<sub>4</sub>, aqueous MeOH; (ii) Ph<sub>3</sub>P=CHCO<sub>2</sub>Me; (iii) CH<sub>2</sub>(CO<sub>2</sub>Me)<sub>2</sub>, NaOMe, MeOH; then aqueous NaCl, Me<sub>2</sub>SO; (iv) PhCH<sub>2</sub>NHLi, tetrahydrofuran, -78 °C; (v) HgCl<sub>2</sub>, HgO, Me<sub>2</sub>CO; (vi) EtSH, Et<sub>2</sub>O-BF<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>.

glutarimide antibiotics such as streptovitamin A,<sup>2</sup> the tricyclic structure with the three rings linked by single bonds is unique. The structure of sesbanimide has been shown to be (1) or its enantiomer (2) by X-ray crystallography, although the absolute configuration of sesbanimide has yet to be determined.<sup>1</sup> Because of the extreme sensitivity of sesbanimide to base,<sup>1</sup> any synthetic strategy requires that the lactol ring is formed at a late stage. This paper describes the unambiguous syntheses of the enantiomeric dithioacetals (3) and (4) which possess suitably protected glutarimide and 1,3-dioxane rings; conversion of the dithioacetals into the corresponding aldehydes should allow elaboration of the third lactol ring to complete the syntheses of sesbanimide and its enantiomer, and to determine the absolute configuration of the natural product. The enantiomeric dithioacetals (3) and (4) are synthesised from a common intermediate 1,3-dioxane (5) by construction of the glutarimide ring from an aldehyde derived from either C-5 or C-1 of glucose (Scheme 1).

3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-glucoside (7), prepared in quantitative yield by benzylation<sup>3</sup> of diacetone glucose (6), was hydrolysed and subsequently treated with ethanethiol in the presence of acid to give 3-*O*-benzylglucose diethyl dithioacetal† (8) (92% yield) (Scheme 2). Kinetic acetonation of (8) (acetone, anhydrous CuSO<sub>4</sub>) gave (9) (75% yield) which underwent methylenation<sup>4</sup> with dibromomethane, aqueous sodium hydroxide, dioxane, and tetrabutylammonium iodide to form the key intermediate 1,3-dioxane (5), m.p. 83–84 °C, [α]<sub>D</sub><sup>20</sup> +23.8° (c, 0.9 in CHCl<sub>3</sub>) [84% yield; 58% overall yield from (6)].

† Satisfactory microanalytical and spectral data were obtained for all new compounds referred to in this paper.

An aldehyde derived from C-5 of glucose was obtained by methanolysis of the isopropylidene ring of (5), followed by periodate oxidation, and was immediately treated with the stabilised ylide, methoxycarbonylmethylenetriphenylphosphorane, to form the diastereoisomeric α,β-unsaturated esters (10) [yield from (5) 72%; *Z*:*E* ratio 4:1] (Scheme 3). Michael addition of the anion of dimethyl malonate to (10), followed by demethoxycarbonylation by brine–Me<sub>2</sub>SO,<sup>5</sup> gave the dimethyl glutarate (11), m.p. 75–76 °C, [α]<sub>D</sub><sup>20</sup> -18.3° (c, 0.6 in CHCl<sub>3</sub>) [42% yield; 30% from (5)]. Treatment of (11) with lithium benzylamide in tetrahydrofuran at -78 °C gave the required benzyl glutarimide (3), m.p. 105–107 °C [α]<sub>D</sub><sup>20</sup> -44.3° (c, 0.24 in CHCl<sub>3</sub>) (34% yield). Elaboration of the original C-1 of glucose was achieved by deprotection of the dithioacetal unit in (5), followed by treatment with methoxycarbonylmethylenetriphenylphosphorane to give a mixture of the diastereoisomeric esters (12) [yield from (5), 88%; *Z*:*E* ratio 5:3]. Michael addition of the anion of dimethyl malonate, followed by demethoxycarbonylation,<sup>5</sup> yielded the dimethyl glutarate (13), m.p. 81–82 °C, [α]<sub>D</sub><sup>20</sup> +12.6° (c, 0.7 in CHCl<sub>3</sub>) (55% yield). Removal of the isopropylidene protecting group in (13) by methanolysis, followed by periodate oxidation and subsequent treatment with ethanethiol–boron trifluoride–diethyl ether gave the dithioacetal (14), m.p. 76–77 °C, [α]<sub>D</sub><sup>20</sup> +18.8° (c, 0.6 in CHCl<sub>3</sub>) [73% yield; 40% yield from (5)]. The diester (14) was also converted by lithium benzylamide into the benzylglutarimide (4), m.p. 106–108 °C, [α]<sub>D</sub><sup>20</sup> +45.8° (c, 0.24 in CHCl<sub>3</sub>).

Thus this paper reports the efficient syntheses of the enantiomeric dimethyl glutarates (11) and (14) from glucose. Attempts are now in progress to improve the present moderate yields for the conversion of these esters into the

glutarimides (**3**) and (**4**), and to complete the syntheses of sesbanimide and its enantiomer.

We acknowledge a S.E.R.C. postdoctoral fellowship (to T.K.M.S.) in support of this work.

Received, 2nd April 1984; Com. 450

### References

- 1 R. G. Powell, C. R. Smith, D. Weisleder, G. K. Matsumoto, J. Clardy, and J. Kozlowski, *J. Am. Chem. Soc.*, 1983, **105**, 3739.
  - 2 H. D. Sisler and M. R. Siegel, *Antibiot. (Mech. Action)*, 1967, **1**, 283.
  - 3 S. Czernecki, C. Georgoulis, and C. Provelenghiou, *Tetrahedron Lett.*, 1976, 3535.
  - 4 Low yields of the 1,3-dioxane (**5**) were obtained using the standard methylenation procedure (K. S. Kim and W. A. Szarek, *Synthesis*, 1978, 48); addition of dioxane as a diluent was necessary for a satisfactory yield to be obtained.
  - 5 A. P. Krapcho, E. G. E. Jahngen, and A. J. Lovey, *Tetrahedron Lett.*, 1974, 1091; C. L. Liotta and F. L. Cook, *ibid.*, p. 1095.
-