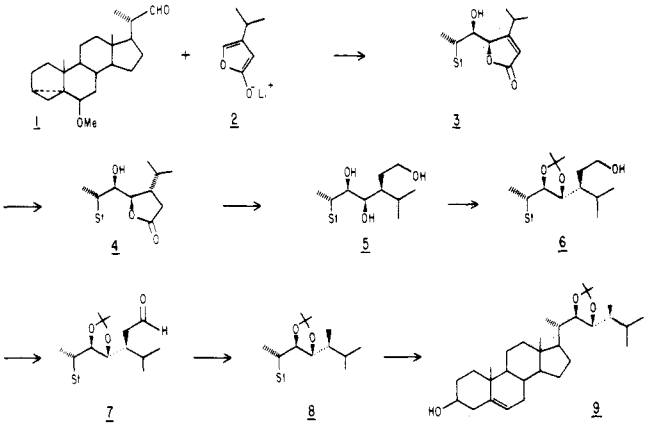
Communications

A Novel Synthesis of Brassinolide

Summary: A stereoselective synthesis of brassinolide which involves construction of the side chain by reaction of (20*S*)-6β-methoxy-3α,5-cyclo-5α-pregnane-20-carboxaldehyde with the anion of 2,3-dimethylbutenolide is described.

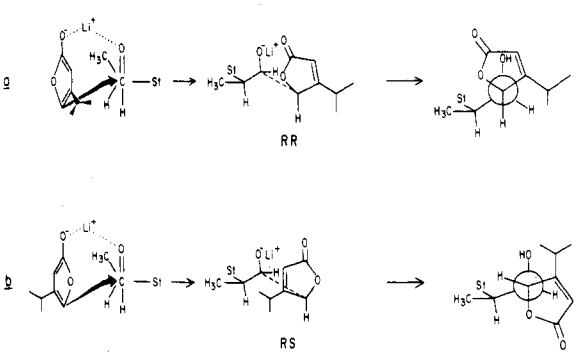
Sir: There has been a great deal of interest in the synthesis of the recently discovered plant growth hormone brassinolide, and several routes to this steroid have been published.[1] We now report a new method for constructing the brassinolide side chain which is quite stereoselective and is higher yielding than any of the published methods.

Stigmasterol was converted to (20*S*)-6β-methoxy-3α,5-cyclo-5α-pregnane-20-carboxaldehyde (**1**) according to well-known procedures.[2] This aldehyde was then used in



an aldol reaction with the anion from 3-isopropylbut-2-enolide (**2**).[3] The anion was generated in tetrahydrofuran from the butenolide and lithium diisopropylamide and was cooled to −78 °C before addition of the aldehyde. The temperature was maintained below −70 °C for 5 h and the reaction was quenched with dilute hydrochloric acid at this temperature. Under these conditions (kinetic) the 22*R*,23*R* intermediate **3** was obtained in 65% yield.[4] The preferred stereochemistry at C-22 (i.e., *R*) is predicted by the Cram or Felkin-Anh models for the transition state.[5] The stereochemistry at C-23 appears to be determined by the approach of the anion as shown in Scheme I. It is seen that path a involves fewer steric interactions and is thus favored over path b, which results in the predominance of the 23*R* stereochemistry. When the aldol reaction mixture was allowed to warm up to 0 °C before quenching, the major product was the 22*R*,23*S* isomer. Apparently,

Scheme I



the reversible nature of the aldol reaction led to the more stable product at higher temperature.[6]

Catalytic hydrogenation of the intermediate butenolide **3** (Pt/activated carbon, freshly distilled dioxane, H_2 at 1 atm) gave a 78:22 mixture of isomers in virtually quantitative yield. The coupling constant for H-23 to H-24 (4.9 Hz) in the major isomer **4**, was smaller than that for H-23 to H-24 (6.8 Hz) in the minor isomer[7] and the stereochemistry at C-24 in **4** was therefore tentatively assigned as 24*S*.

Reduction of lactone **4** with $LiAlH_4$ afforded the trihydroxy derivative **5** in 90% yield, and this compound was heated with 2,2-dimethoxypropane (55–60 °C) and pyridinium *p*-toluenesulfonate to form the 22,23-acetonide and a mixed ketal at C-29. The crude product was refluxed in methanol for 1 h to give the C-29 hydroxy compound **6** in an overall yield of 92%. Oxidation of **6** with pyridinium dichromate gave the aldehyde **7** (94%). This compound was decarbonylated with tris(triphenylphosphine)rhodium chloride to give the 24*S* methyl derivative **8** (78%). The overall yield for the side-chain synthesis starting from the aldehyde **1** was 32%. The stereochemistry of the side chain was confirmed by converting the isomethyl ether **8** to the known 3β-hydroxy derivative **9**, mp 134–135 °C (lit.[1a] mp 130–131 °C) (98% yield), by treatment with *p*-toluenesulfonic acid monohydrate in refluxing acetone–water. The 24*R* isomer obtained in similar fashion had a melting point of 165–167 °C.

A shorter way of constructing the side chain employed a similar sequence of reactions but starting with 2,3-dimethylbutenolide which was readily obtained by reduction of 2,3-dimethylmaleic anhydride with sodium borohydride in tetrahydrofuran.[8] Aldol reaction of the anion **10** of this compound with the aldehyde **1** at −78 °C afforded the hydroxy butenolide **11** in 74% yield. A small amount of the 22*R*,23*S* isomer (6%) and of the 22*S*,23*S* isomer (10%) were also obtained. Catalytic hydrogenation of **11** as for **3** gave the saturated lactone **12** (77%). Reduction of the

(1) (a) Fung, S.; Siddall, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 6580. (b) Ishigure, M.; Takasuto, S.; Morisaka, M.; Ikekawa, N. *J. Chem. Soc., Chem. Commun.* **1980**, 962. (c) Hayami, H.; Sato, M.; Kanemoto, S.; Morizawa, Y.; Oshima, K.; Nosake, H. *J. Am. Chem. Soc.* **1983**, *105*, 4491. (d) Sakakihara, M.; Okada, K.; Ichikawa, Y.; Mori, K. *Heterocycles* **1982**, *17*, 301.

(2) (a) Steele, J. A.; Mosettig, E. *J. Org. Chem.* **1963**, *28*, 571. (b) Pappas, J. J.; Keaveney, W. P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* **1966**, 4273.

(3) McMorris, T. C.; Seshadri, R.; Arunachalam, T. *J. Org. Chem.* **1974**, *39*, 669.

(4) The stereochemistry at C-23 was confirmed by the CD curve, $[\theta]_{215}$ +23 938 (dioxane) which was opposite to that reported for cyclograndisolide, $[\theta]_{220}$ −31 500 (see: Edwards, J. A.; Sundeen, J.; Salmond, W.; Iwadare, T.; Fried, J. H. *Tetrahedron Lett.* **1972**, 791). The values obtained for the 22*R*,23*S* and 22*S*,23*S* isomers were $[\theta]_{215}$ −34 362 and $[\theta]_{215}$ −21 777, respectively.

(5) For a review of nucleophilic additions to chiral carbonyl compounds, see: Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.

(6) NMR evidence is in accord with this since the coupling constant between H-22 and H-23 in the 22*R*,23*R* isomer (~1.5 Hz) indicates the preferred conformation for the side chain shown (Scheme I). For the 22*R*,23*S* isomer the corresponding coupling constant (~7.5 Hz) indicates a preferred conformation for the side chain in which the dihedral angle between H-22 and H-23 is about 180°. There are two gauche interactions in this conformation, and it would be expected to be more stable than the conformation for the 22*R*,23*R* isomer in which there are three gauche interactions.

(7) The coupling constants for H-20 to H-22 and H-22 to H-23 for the major isomer **4** were 6.8 Hz and 5.4 Hz, respectively. In the minor isomer the corresponding values were 1.0 Hz and 2.1 Hz. (Spectra were taken at 360 MHz.)

(8) Bailey, D. M.; Johnson, R. E. *J. Org. Chem.* **1970**, *35*, 3574.

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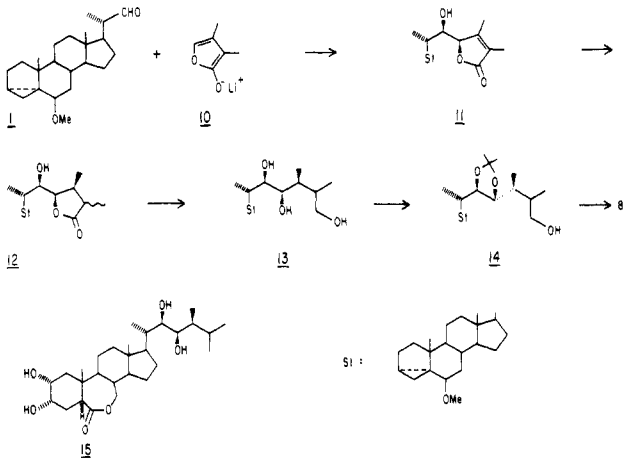

lactone with $LiAlH_4$ gave the triol **13** which was converted to the acetonide **14**. This compound was treated with methanesulfonyl chloride and pyridine, and the product was reduced with lithium aluminum hydride to give the same intermediate **8** (22*R*,23*R*,24*S*) obtained in the earlier sequence. The overall yield for the four steps from the saturated lactone **12** was 70%.

It should be noted that catalytic hydrogenation of **3** and of **11** gave products which had mainly the 24*S* stereochemistry. Initially, we had reasoned that if hydrogenation occurred at the face of the butenolide ring nearest the C-22 hydroxyl, then **3** would yield the 24*S* product while **11** would yield the 24*R* isomer. The fact that hydrogenation of **11** gave mainly the 24*S* isomer suggests that the hydroxyl does not have a directive influence on the course of the hydrogenation.

Conversion of intermediate **9** to brassinolide **15** was achieved in 15% yield by utilizing procedures similar to those described by other workers. Our synthetic brassinolide, mp 273–276 °C (lit.[1a] mp 273–274 °C), had the same biological activity as natural brassinolide in the bean second internode bioassay at all concentrations tested. It was also found to possess identical activity to authentic brassinolide in the rice lamina inclination test. The synthetic route reported here makes available 28-homobrassinolide and also new analogues of brassinolide and 28-homobrassinolide which may be of interest for structure–activity studies of this group of steroids.

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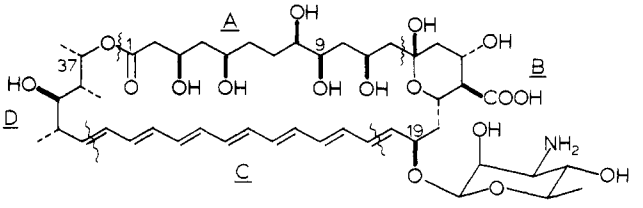
Synthesis of Amphotericin B. 1. Fragment A of the Aglycon

Summary: The C(1)–C(12) unit (fragment A) of the aglycon of amphotericin B has been synthesized with excellent regio- and stereoselection.

Sir: A variety of highly diastereoface-selective chiral reagents and catalysts have been developed for several major organic reactions.[1] The availability of these reagents and catalysts combined with an enriched chiral pool[2] now allows us to design a practical plan for the synthesis of stereochemical complex molecules such as macrolide antibiotics.[3] We have chosen the polyene macrolide amphotericin B (**1**)[4] as our target and record herein the synthesis of its C(1)–C(12) unit, fragment A (**2**). The syntheses of the other fragments B, C, and D shown in **1** and also the assembly of A and these fragments will follow this report shortly.



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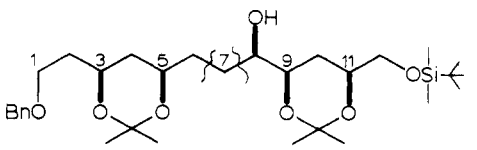

2

At the outset of this project we designed two schemes for the synthesis of **2**. Scheme I involves the coupling of the C(1)–C(6) fragment **3** and the C(7)–C(12) fragment **4**, both of which have a common four-carbon unit, readily derivable from (*S*)-malic acid. This coupling, although expected to be only partially successful (see below), offers the advantage that it will provide after desulfurization only one product which must have the stereostructure shown in **2**. No new chiral center is created in this final process. Alternatively, **2** can be retrosynthetically dissected at the C(7)–C(8) bond, giving the two fragments **5** and **6** (Scheme II). The coupling of these fragments will definitely proceed, but it is not without an anticipated problem. The unpredictable stereochemical outcome[5] of the reaction [which creates the C(8) chiral center] can only be evaluated in comparison with **2** hopefully to be secured in the first approach. A brief outline of the experimental results follows.

(1) For a fundamental strategy for the construction of acyclic systems and also for the principle of multiple asymmetric synthesis, see: (a) Masamune, S. *Heterocycles* **1984**, *21*, 107. Also see: (b) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47.

(2) (a) Seebach, D.; Hungerbühler, E. "Modern Synthetic Methods 1980"; Scheffold, R., Ed.; Salle and Sauerländer-Verlag: Frankfurt and Aarau, 1980. (b) Hanessian, S. "Total Synthesis of Natural Products: The 'Chiron' Approach"; Pergamon Press: New York, 1983.

(3) Masamune, S.; McCarthy, P. A. In "Macrolide Antibiotics"; Omura, S., Ed.; Academic Press: New York, 1984.

(4) (a) Isolation from *Streptomycetes nodosus*: Vandeputte, J.; Wachtel, J. L.; Stiller, E. T. *Antibiot. Annu.* **1956**, 587. (b) Chemical degradation: Borowski, E.; Mechlinski, W.; Falkowski, L.; Ziminski, T.; Dutcher, J. D. *Tetrahedron Lett.* **1965**, 473. Cope, A. C.; Axen, U.; Burrows, E. P.; Weinlich, J. *J. Am. Chem. Soc.* **1966**, *88*, 4228. Dutcher, J. D.; Walters, D. R.; Wintersteiner, O. *J. Org. Chem.* **1963**, *28*, 995. Dutcher, J. D.; Young, M. B.; Sherman, J. H.; Hibbits, W. E.; Walters, D. R. *Antibiot. Annu.* **1957**, 866. von Saltza, M.; Dutcher, J. D.; Reid, J.; Wintersteiner, O. *J. Org. Chem.* **1963**, *28*, 999. (c) X-ray analysis: Ganis, P.; Avitabile, G.; Mechlinski, W.; Schaffner, C. P. *J. Am. Chem. Soc.* **1971**, *93*, 4560. Mechlinski, W.; Schaffner, C. P.; Ganis, P.; Avitabile, G. *Tetrahedron Lett.* **1970**, 3873.

(5) In this coupling reaction, Li^+ may coordinate with oxygen atoms in a number of possible modes. See: (a) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526 and references quoted therein. Also see: (b) Stork, G.; Paterson, I.; Lee, F. K. C. *Ibid.* **1982**, *104*, 4686.

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