Tetrahedron Letters No. 51, pp 4701-4704, 1976. Pergamon Press. Printed in Great Britain.

USEFUL STEREOSELECTIVE AND POSITION-SELECTIVE TRANSFORMATIONS OF BREFELDIN A AND DERIVATIVES AT CARBONS 4, 7 and 15

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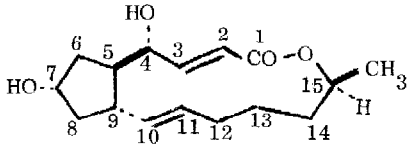
(Received in USA 23 September 1976; received in UK for publication 11 November 1976)

Brefeldin A (cyanein, decumbin) (1)[1] is a fungal metabolite which exhibits a wide range of biological activity including antibiotic, cytostatic, antimitotic and antiviral effects.[2] The structure of this interesting substance was derived by chemical[3] and X-ray crystallographic[4] studies. An effective partial synthesis of brefeldin A which involves the lactonization of the protected 2-pyridinethiol ester 2 (double activation process[5]) has recently been reported.[6] The establishment of this interconversion has removed one of the



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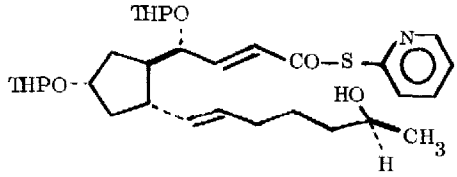

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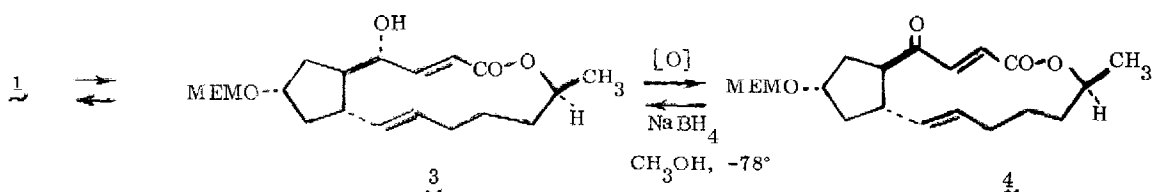
major obstacles to synthesis. This note deals with a further simplification of the synthetic problem with regard to stereochemical aspects, specifically the generation of the required orientation of substituents about C(4) and C(15). A number of selective reactions of brefeldin A are described. The following note outlines a total synthesis of (±)-brefeldin A which takes advantage of this new information.

Reaction of brefeldin A[7] (1) with 1.5 equiv of methoxyethoxymethyl chloride (MEM chloride) and 1.9 equiv of diisopropylethylamine in methylene chloride (180 μl/mg of 1) at 25° for 24 hr led to highly selective formation of the 7-mono MEM ether (3) in 90% isolated yield.[9,10] Oxidation of 3 with 10 equiv of Collins reagent (CrO_3·2 pyridine) in methylene chloride at 0° for 10 min produced the 4-ketone 4 in 99% yield. Alternatively, the conversion 3→4 could also be accomplished using 3 equiv of pyridinium chlorochromate[11] in methylene chloride at 25° for 2.5 hr (95% yield). Reduction of 4 with excess sodium borohydride in methanol at -78° for 3 hr afforded stereospecifically and in > 95% yield the 4α-alcohol 3. Even at higher temperatures the reduction of 4 by sodium borohydride exhibited considerable selectivity (α/β ratio 20:1 at -45° and 3:1 at



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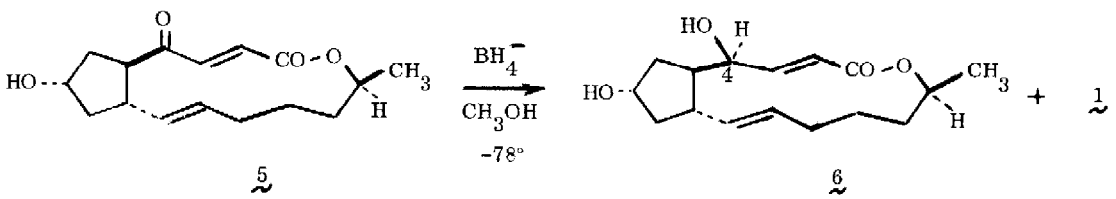
+25°). The 4α- and 4β-epimers could be separated by thin layer chromatography on silica gel (97:3 methylene chloride-methanol) with the former being slightly more polar. Since the deprotection of 3 to form 1 occurs quantitatively ($TiCl_4$ - CH_2Cl_2 at 0°), these interconversions demonstrate a stereospecific method for the generation of the required configuration at C(4) via the 4-ketone 4.[12]

Interestingly the reduction of unprotected 4-keto derivative of brefeldin A (5)[13] with sodium borohydride in methanol at -78° or with potassium tri-sec-butylborohydride in THF at -78° produced mainly 4-epi-brefeldin A (ratio 4-epi-brefeldin A (6)-brefeldin A, 5:1). (Tlc R_f values found for 1 and 6 using silica gel plates with ether acetone (3:1) were 0.38 and 0.53, respectively.) Thus, it is clear that the MEM protecting



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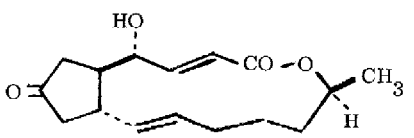
group at the C(7) oxygen exerts a powerful (and remarkable) directing effect on the stereochemistry of carbonyl reduction at C(4).

Still another fascinating example of selectivity was discovered during an investigation of the action of activated MnO_2 on brefeldin A (1) and the 4-epimer 6. Under conditions which oxidize 6 completely to 5, brefeldin A (1) is unchanged. Thus, oxidation of a 1:1 mixture of 1 and 6 with ca. 25-fold excess of MnO_2 in methylene chloride at 0° for 1 hr affords quantitatively a 1:1 mixture of 5 and brefeldin A.

Another interesting oxidation is the reaction of brefeldin A with pyridinium chlorochromate[11] (3.3 equiv) in CH_2Cl_2 at 0° for 12 hr which yields selectively the 7-keto derivative 7 (62% isolated yield).



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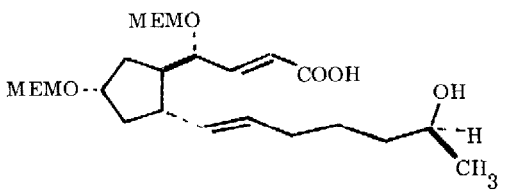
Finally, we describe an important observation on the effect of stereochemistry at C(15) on the rate of lactonization of 2-pyridinethiol esters of brefeldin A 4,7-bis ethers.[5,6] Treatment of the 4,7-bis-MEM ether of brefeldin A with 0.13 N lithium hydroxide in methanol-water (3:1) at 50° for 8 hr effected lactone hydrolysis to give the hydroxy acid 8. Oxidation of 8 with pyridinium chlorochromate[11] in methylene chloride at 25° afforded the corresponding 15-ketone which underwent reduction ($NaBH_4$, CH_3OH, -25°) to give a mixture (approx. 1:1) of 8 and the corresponding C(15)-epimer 9.[14] The hydroxy acid 8 was transformed readily and



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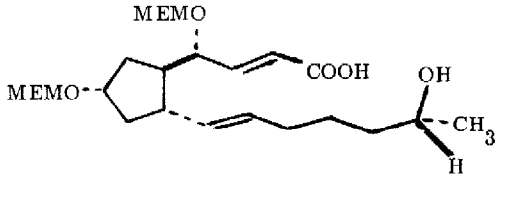

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efficiently into the 4,7-bis-MEM ether of brefeldin A by heating the 2-pyridinethiol ester.[5,6] The lactonization process occurs rapidly in dry xylene at reflux (under argon) and appeared to be complete in only 1 hr. In contrast the mixture of the 2-pyridinethiol esters of 8 and 9 upon heating in xylene at reflux afforded only the 4,7-bis-MEM ether of brefeldin A and unreacted 2-pyridinethiol ester of 9 (even after 8.5 hr reaction time). This experiment demonstrates conclusively still another interesting aspect of stereochemistry in the brefeldin A series and at the same time provides a simplification of the problem of synthesis with respect to configuration at C(15). The relatively slow cyclization of the 2-pyridinethiol ester of 9 (as compared to the ester of 8) can be rationalized in terms of steric repulsion between the 15-methyl group and one of the substituents at C(1) in the tetrahedral intermediate for lactone formation. Inspection of space-filling (CPK) models of the tetrahedral intermediate derived from 9, assuming the ring conformation shown by X-ray analysis of brefeldin itself,[4] indicates a sizable repulsion between methyl at C(15) and either O or S at C(1).[15,16]

References and Notes

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5. E. J. Corey and K. C. Nicolaou, J. Am. Chem. Soc., 96, 5614 (1974).
6. E. J. Corey, K. C. Nicolaou, and L. S. Melvin, Jr., ibid., 97, 654 (1975).
7. A sample of naturally derived brefeldin A was kindly provided by Dr. H. P. Sigg (Sandoz Ltd., Basle) to whom we are most grateful.
8. E. J. Corey, J.-L. Gras and P. Ulrich, Tetrahedron Lett., 809 (1976).

9. Satisfactory infrared, proton magnetic resonance and mass spectrometric data were obtained for all new compounds described herein.
10. It was also observed that the mono-MEM derivative 3 could be obtained selectively in 85% yield from the 4,7-bis-MEM ether of brefeldin under carefully controlled conditions (5 equiv of anhydrous zinc bromide in dry benzene at 40° for 19 hr with rapid stirring).
11. E. J. Corey and J. W. Suggs, Tetrahedron Lett., 2647 (1975).
12. Obviously, mixtures of 3 and the 4β-epimer are convertible to 4.
13. Obtained in quantitative yield by deprotection of 4 using $TiCl_4$ - CH_2Cl_2 at 0°.
14. This mixture was not readily separable by chromatography.
15. Partial spectral data for 4 are: nmr (δ, $CDCl_3$), 7.71 (d, J = 16, H_3, 1H), 6.38 (d, J = 16, H_2, 1H), 5.74 (m, 1H), 5.43 (dd, J = 9 and 16 Hz, 1H), and 4.08 (p, J = 5 Hz, C<u>H</u>-OMEM); ir (CCl_4) 2935, 1730, 1700, 1631, 1250, and 972 cm^{-1}. Partial spectral data for 5 are: nmr (δ, $CDCl_3$), 6.20 (d, J = 13 Hz, 1H), 5.97 (d, J = 13 Hz), and 5.2 (m, 2H). Partial spectral data for 6 are: nmr (δ, $CDCl_3$), 6.04 (dd, J = 9 and 13 Hz, 1H), 5.55 (d, J = 13 Hz, 1H), and 5.3 (m, 2 H); ir (CCl_4) 3400, 2930, 1712, and 1630 cm^{-1}.
16. This research was assisted financially by a grant from the National Institutes of Health.