Tetrahedron Letters No. 26, pp 2243 - 2246, 1977. Pergamon Press. Printed in Great Britain.

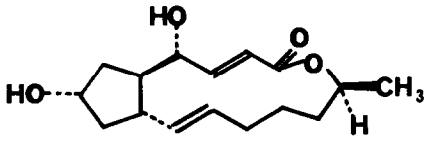
TOTAL SYNTHESIS OF (±)-BREFELDIN A (PART IV)[1]

E. J. Corey, Robert H. Wollenberg and David R. Williams

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

(Received in USA 14 April 1977; received in UK for publication 17 May 1977)

Brefeldin A (1) is a macrocyclic fungal metabolite which exhibits both antibiotic and antiviral activity. A route for the total synthesis of this substance in racemic form has recently been established and reported from these laboratories.[1] This note describes modifications in the synthetic sequence which have allowed a shorter and more efficient synthesis. The methods used in these modifications are expected to be generally useful.



1

The methoxyethoxymethyl (MEM)[2] ether-diacid 2, available by the route described earlier, underwent smooth decarboxylation upon heating with pyridine at reflux under argon for 1 hr to form quantitatively the mono acid 3.[3] Reaction of 3 in tetrahydrofuran solution (under argon) with excess (> 3 equiv) lithium diisopropylamide (initially at -78°, then warming to 0° over 15 min and at 25° for 30 min) generated the α-lithiated lithium salt of 3 which was added over 20 min through a stainless steel cannula to a stirred oxygenated THF solution at 25°. Treatment of this solution with trimethylphosphite (excess) at 25° for 1 hr afforded after work up the hydroxy acid 4 (80% yield).[4] Finally, oxidation of 4 with a small excess of lead tetraacetate in dry benzene at 25° for 10 min produced the aldehyde 5 in 78% yield overall from 2. In previous work[1b] the aldehyde 5 was obtained by a much longer and much less efficient process. The sequence 2 → 5 reported herein represents a welcomed improvement in methodology for the change $RCH(COOH)_2 \rightarrow RCHO$ and should be of general utility. The classical malonic ester anion thus should be considered as an effective synthetic equivalent to the formyl anion.

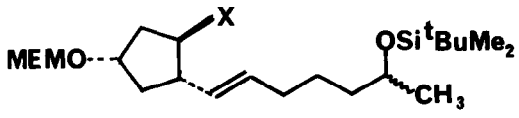
The aldehyde 5 was then converted to a mixture of diastereomers containing both group orientations at C-4 and C-15, i.e., 6 (both C-4 diastereomers) and 7 (both C-4 diastereomers), as described earlier except for protection of the C-4 hydroxyl as the tetrahydropyranyl (THP) ether. Although the use of the THP protecting group doubled the number of diastereomers in the mixture, no difficulties resulted in the execution of the remaining steps in the synthesis. Protection of the C-4 hydroxyl in this way did not excessively complicate chromatographic analysis of reaction products as compared to the use of the MEM protecting group in the original synthesis. As observed previously for the mixture of 4,7-bis-MEM ethers corresponding to 6 and

7.[1b] lactonization by the double activation process[1,5,6] occurred much more rapidly (at least 15 times) for the hydroxy acids 6 than for the C-15 diastereomers 7. Thus the only cyclization product obtained when the mixture of 2-pyridinethiol esters of 6 and 7 was heated in xylene at reflux under argon for 8.5 hr was the mixture of C-4 epimers 8 having the orientation of methyl at C-15 corresponding to brefeldin A and obviously derived from 6. That the 2-pyridinethiol ester of 7 was unchanged could be shown as described below. As indicated earlier[1], the substantial difference in rates of lactonization of the 2-pyridinethiol esters of 6 and 7 can be understood on the basis that steric repulsions involving the methyl group at C-15 are considerably less in the tetrahedral lactonization intermediate derived from 6 as compared to that resulting from 7.

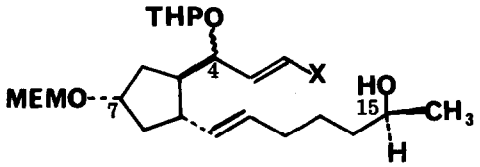
The differentially protected lactone 8 was more simply and reproducibly transformed into (+)-brefeldin A than the 4,7-bis-MEM derivative used in the original synthesis.[1b] The sequence employed was: (1) selective THP cleavage (acetic acid-water-THF, 3:3:1 at 50° for 4 hr), (2) Collins oxidation of the C-4 hydroxyl at 0°, (3) stereospecific[1b] sodium borohydride reduction of the 4-keto function in methanol at -45° and (4) cleavage of the MEM protecting group from the C-4 oxygen (2.5 equiv of titanium tetrachloride in methylene chloride at 0° for 15 min). The overall yield of (+)-brefeldin A for these 4 steps was excellent (85%), but equally important is the ease of execution. The lack of interference by the MEM protecting group during the cleavage of the THP ether is noteworthy.

The mixture of diastereomers which remained uncyclized in the above described lactonization was recovered as methyl ester 9 after hydrolysis of the pyridinethiol ester of 7 (aqueous base at 25°) and esterification with diazomethane. Preparation of the tosylate of 9 (tosyl chloride-pyridine in methylene chloride 18 hr at 25°) followed by displacement with excess potassium superoxide[7] (with ca. 2×10^{-2} M 18-crown-6 in THF-dimethylsulfoxide 10:1 at 25° for 2.5 hr) afforded after esterification with diazomethane and chromatography the methyl ester 11 (80%) and epoxide 12 (15%) as an unwanted by-product. Higher concentrations of 18-crown-6 resulted in the formation of epoxide 12 as the sole product. Saponification of 11 followed by lactonization of the 2-pyridinethiol ester produced additional amounts of 8 and thence, as described above (+)-brefeldin. Thus, all of the C-4/C-15 diastereomers produced in the synthetic sequence can be transformed into (+)-brefeldin A.

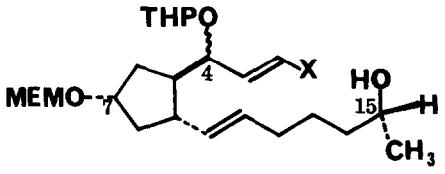
The superoxide displacement method was also used as a key step to prepare a sample of the 4-THP, 7-MEM ether of 15-epi-brefeldin A (13) from (+)-brefeldin A. The optically active hydroxy acid 7 was synthesized by the sequence: 7-MEM ether of brefeldin A[1] → 4-THP, 7-MEM ether of brefeldin A (dihydropyran in CH_2Cl_2 with tosic acid catalyst at 25°, 90% yield) → hydroxy acid 6 (lithium hydroxide in aqueous methanol, 100% yield), → hydroxy ester 11 (CH_2N_2, 100% yield) → 15-tosyl derivative of 11 (tosyl chloride-pyridine, 25°, 96% yield) → 7 (potassium superoxide-18-crown-6 in THF-DMSO, 82% yield). Prolonged heating of the 2-pyridinethiol ester of 7 in xylene at reflux > 30 hrs afforded in ca. 45% yield the 15-epi-lactone 13. Although the 15-epi-lactone 13 and the isomeric synthetic lactone 8 (natural methyl orientation) were chromatographically similar they were readily distinguished by the pmr spectra. In each case the proton at C-3 appears as a doublet of doublets; in the case of intermediate 8 (15-natural config.) the chemical shift for this proton is 7.10δ ($CDCl_3$) whereas for the isomer 13 the chemical shift is observed at 6.50δ ($CDCl_3$).[8]



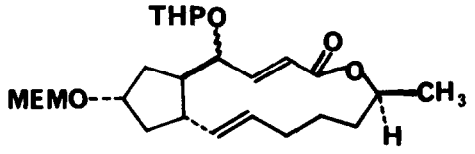
2, X = $CH(COOH)_2$
3, X = CH_2COOH
4, X = CH(OH)COOH
5, X = CHO



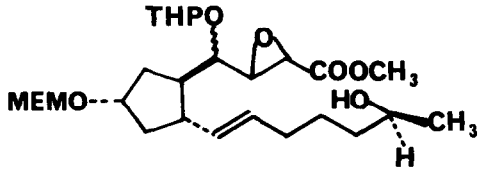
6, X = COOH
11, X = $COOCH_3$



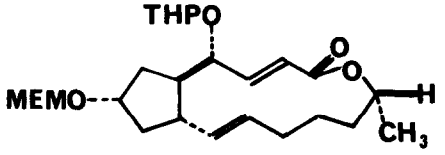
7, X = COOH
9, X = $COOCH_3$



8



12



13

References and Notes

1. For preceding parts see (a) E. J. Corey, K. C. Nicolaou and L. S. Melvin, Jr., J. Am. Chem. Soc., 97, 654 (1975); and (b) E. J. Corey and R. H. Wollenberg, Tetrahedron Lett., 4701, 4705 (1976).
2. E. J. Corey, J.-L. Gras and P. Ulrich, Tetrahedron Lett., 809 (1976).
3. Satisfactory infrared, nmr and mass spectral data were obtained for each synthetic intermediate.
4. See (a) H. H. Wasserman and B. H. Lipschutz, Tetrahedron Lett., 1731 (1975) and (b) P. E. Pfeffer and L. S. Silbert, U.S. Patent, 3,652,612 (March 28, 1972); Chem. Abstr., 76, 1,399,382 (1972), and (c) W. Adams, O. Cueto, and V. Ehrig, J. Org. Chem., 41, 370 (1976).
5. E. J. Corey, D. J. Brunelle and P. J. Stork, Tetrahedron Lett., 3405 (1976).
6. E. J. Corey and D. J. Brunelle, Tetrahedron Lett., 3409 (1976).
7. E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, Tetrahedron Lett., 3183 (1975).
8. This study was assisted financially by the National Institutes of Health.