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TOTAL SYNTHESIS OF (±)-BREFELDIN A

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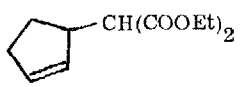
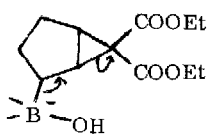
This note outlines a total synthesis of (±)-brefeldin A (1) which is based on the simplifications of the problem which have been described in preceding papers.[1,2] The pathway of synthesis is illustrated in Chart I.

Hydroboration of the known[3] bicyclic ester 2 with borane in tetrahydrofuran (THF) at -50° followed by treatment with alkaline hydrogen peroxide afforded the alcohol 3 (> 50% and up to 80% yield) after separation from the easily removed by-product A, which evidently results from base induced fragmentation of intermediate B.[4,5] Oxidation of 3 with 2 equiv of 8 N chromic acid in ethyl ether gave the ketone 4 (98% yield) which



A



B

was converted to the enone 5 by treatment with triethylamine in ether at 0° for 5 hr (88% yield). Reaction of the enone 5 as the sodio malonate derivative (formed using NaH) with the vinyl Gilman reagent 6 at -78° in THF for 1 hr (for preparation see Chart II and below) produced the required conjugate adduct 7 stereospecifically in 82% yield.

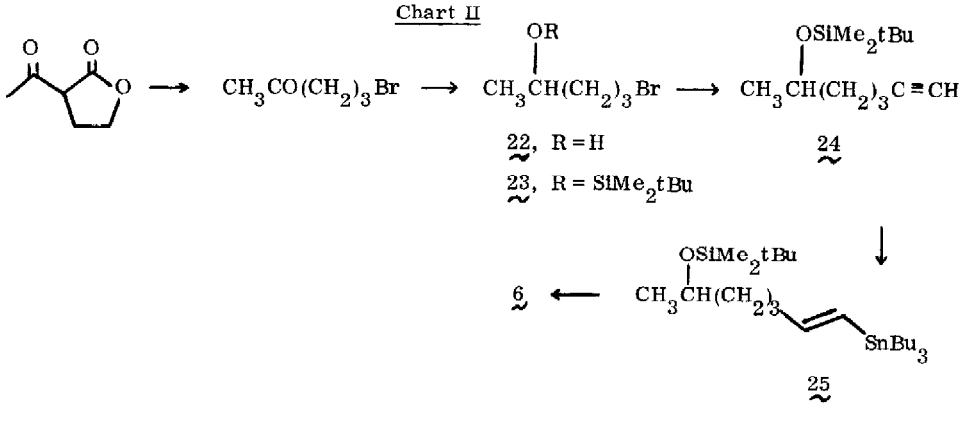
Reduction of ketone 7 using lithium borohydride in methanol at -78° gave a mixture consisting of 80% of the desired alcohol 8 and 20% of the C(7) epimer, readily separated by column chromatography on silica gel with 95:5 chloroform-acetone for elution. The stereochemistry of these isomeric alcohols was readily ascertained from the relative magnitude of the shifts produced in the pmr resonance for the malonate α-hydrogen by the reagent EuFOD. The alcohol 8 was next protected as the methoxyethoxymethyl (MEM) ether,[6] saponified to the corresponding diacid (2N sodium hydroxide in methanol at 25°), α-hydroxylated (8-10 equiv of n-butyllithium in THF at 0° for 2 hr followed by oxygenation with dry O_2-$(MeO)_3P$ at -20°), and oxidatively decarboxylated (aqueous sodium periodate buffered with a little pyridine) to afford after treatment with diazomethane and chromatography the ester 10 in 60% yield. Reduction of ester 10 with excess diisobutylaluminum hydride in THF at -78° for 2 hr gave the primary alcohol 11 (97%) which was oxidized by Collins reagent to corresponding aldehyde 12 (98%). Reaction of 12 with the lithium reagent 13 (prepared by treatment of the organotin compound 14[7] with 1 equiv of n-butyllithium in THF at -78° for 1 hr) resulted in efficient carbonyl addition to form alcohol 15 which was directly converted to the MEM ether 16 (82% from 12) in the usual way.[6] Removal of the methylthiomethylene protecting group from 16 was effected[7b] by the action of mercuric chloride in acetonitrile-water (4:1) in the presence of excess calcium carbonate at 25° for 4 hr to give the alcohol 17 which was

oxidized sequentially by the Collins reagent and silver oxide to form the acid 18 (48% overall). Desilylation of 18 with fluoride ion[8] proceeded quantitatively to give the hydroxy acid 19. Although neither 19 nor the precursors 15-18 could be resolved into more than one spot by analytical thin layer chromatography (tlc) all are obviously mixtures of diastereomers relative to C(4) and C(15). Fortunately, as indicated in the preceding note[1] and also below, this stereochemical complication is easily dealt with. Thus the conversion of 19 to (±)-brefeldin A was accomplished as follows.

The 2-pyridinethiol ester of 19 was subjected to lactonization in xylene at reflux for 8 hr to form preferentially the thirteen membered ring structure 20 having the required β-orientation of methyl at C(15).[1,2,9] The other C(15) diastereomers remain uncyclized and can be recovered as hydroxy acid upon aqueous treatment.[1] The lactone 20 was deprotected ($TiCl_4$ - CH_2Cl_2, 0°, 30 min) to form the 4,7-diol, selectively oxidized (MnO_2 in CH_2Cl_2) to the 4-keto-7-hydroxy lactone and etherified at C(7) with MEM-Cl[6] to form 21. Reduction of 21 at C(4) ($NaBH_4$ in CH_3OH at -78°) led stereospecifically to the required 4α-alcohol[1] which upon deprotection ($TiCl_4$ - CH_2Cl_2 0°) afforded (±)-brefeldin A, indistinguishable from a sample of naturally occurring brefeldin A by pmr, ir, mass spectral and tlc comparison.[10]

The method of synthesis of the Gilman reagent 6 was accomplished as outlined in Chart II. 5-Bromo-2-pentanone, prepared by the action of hot aqueous hydrobromic acid on α-acetyl-γ-butyrolactone, was reduced with lithium aluminum hydride in ether at -78° to form the bromo pentanol 22 (85%) which was silylated

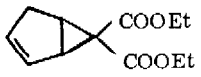
Chart II



in the standard way[8] to give the bromo t-butyldimethylsilyl ether 23. Displacement of bromine in 23 by ethynyl was accomplished by reaction with lithium acetylide-ethylenediamine complex in dimethyl sulfoxide for 17 hr at 25° to give 24 (97%) which was then allowed to react with tri-n-butyltin hydride (using azoisobutyronitrile as initiator) at 90° for 12 hr to form 25 (94%).[7a] Finally treatment of 25 with 1 equiv of n-butyllithium in THF at -78° for 10 min and 25° for 50 min with subsequent cooling to -78°, and addition of 1-pentynylcopper gave after 1 hr at -78° the transoid Gilman reagent 6 as an orange solution.[11]

Further studies on modified approaches to brefeldin A will be described shortly.[12]

Chart I



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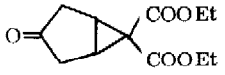

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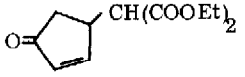

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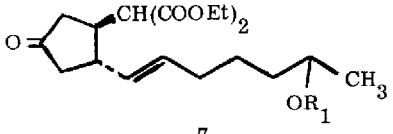

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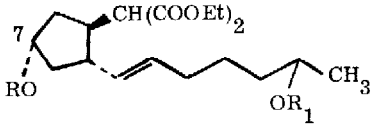
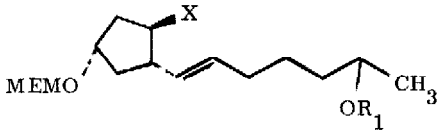
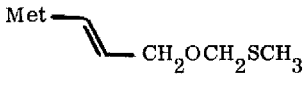


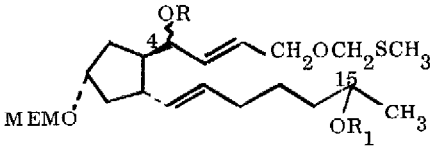
8, R = H
9, R = MEM



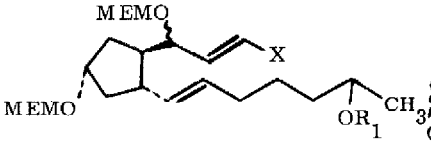
10, X = $COOCH_3$
11, X = CH_2OH
12, X = CHO



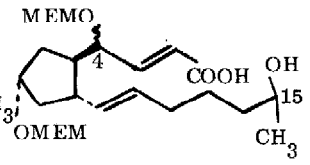
13, Met = Li
14, Met = Bu_3Sn



15, R = H
16, R = MEM



17, X = CH_2OH
18, X = COOH



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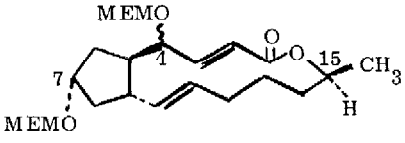

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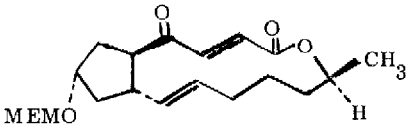

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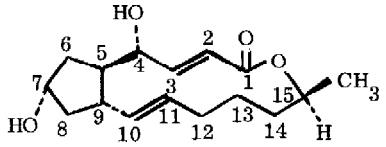

1

$R_1 = Si(CH_3)_2tBu$

References and Notes

1. E. J. Corey and R. H. Wollenberg, preceding paper.
2. E. J. Corey, K. C. Nicolaou and L. S. Melvin, Jr., J. Amer. Chem. Soc., 97, 654 (1975).
3. R. W. Kierstead, R. P. Linstead, and B. C. L. Weedon, J. Chem. Soc., 1803 (1953).
4. Unfortunately, all attempts to attach the vinylic appendage of brefeldin A to the cyclopentane ring at this point by homoconjugate addition of a vinyl Gilman reagent [see, E. J. Corey and P. W. Fuchs, J. Amer. Chem. Soc., 94, 4014 (1972)] using the THP ether of 3 were unsuccessful (experiments performed by J. M. Fitzpatrick).
5. Satisfactory infrared, proton magnetic resonance (pmr) and mass spectrometric data were obtained for each synthetic intermediate unless otherwise indicated.
6. E. J. Corey, J.-L. Gras and P. Ulrich, Tetrahedron Lett., 809 (1976).
7. See, (a) E. J. Corey and R. H. Wollenberg, J. Org. Chem., 40, 2265 (1975), and (b) E. J. Corey and M. G. Bock, Tetrahedron Lett., 3269 (1975) for the preparation of proporgyl methylthiomethyl ether and its conversion to 14.
8. E. J. Corey and A. Venkateswarlu, J. Amer. Chem. Soc., 94, 6190 (1972).
9. The difference in rates of cyclization of the C(15)-diasteromeric hydroxy acid derivatives (see also preceeding paper[1]) is consistent with the severe crowding of methyl exhibited in CPK space-filling models of the tetrahedral intermediate for lactonization of 15-epi-brefeldin A.
10. We are grateful to Dr. H. P. Sigg, Sandoz Ltd., for an authentic sample of brefeldin A.
11. E. J. Corey and D. J. Beames, J. Amer. Chem. Soc., 94, 7210 (1972).

12. This work was assisted financially by grants from the National Institutes of Health. We are also grateful to Dr. J. M. Fitzpatrick for helpful experimental contributions in the early phase of this study. The synthesis of brefeldin A outlined herein was presented at the Bicentennial Meeting of the American Chemical Society, New York, April 1976.