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A SYNTHESIS OF BREFELDIN A[1]

R. Baudouy[2], P. Crabbé, A.E. Greene, C. Le Drian and A.F. Orr[2]
C.E.R.M.O., Université Scientifique et Médicale
38041 Grenoble, France.

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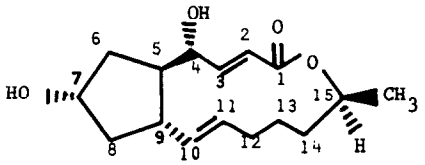
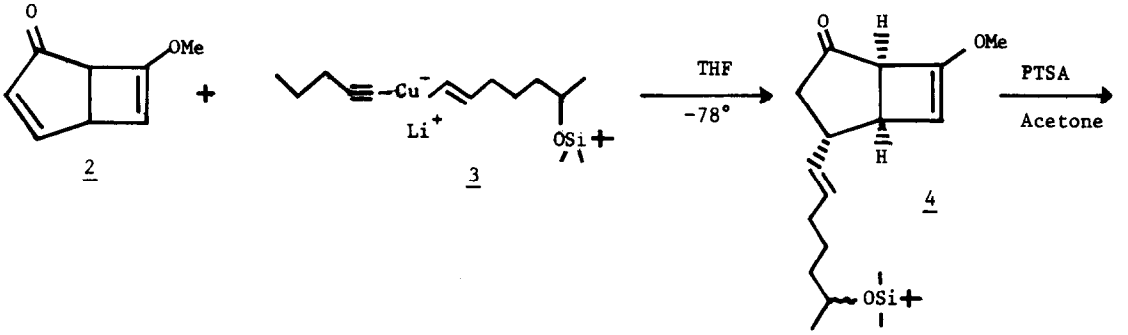
The remarkable range of biological activity exhibited by brefeldin A (1)[3], combined with its structural similarity to the prostaglandins, has made this fungal metabolite a choice target for total synthesis. While our work in this field was in progress a synthesis of (±) brefeldin A (1) was published by Corey and Wollenberg[4]. We now wish to report a direct and efficient preparation of the key intermediate (13), which the Harvard group has shown to be convertible to (±) brefeldin A (1)[4].

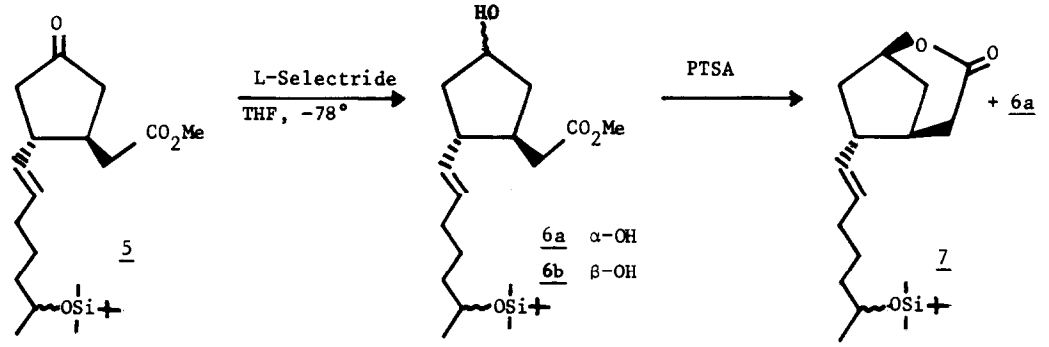
We have previously used the bicyclic ketone (2) (obtained in > 80% yield from the photolysis of α-tropolone methyl ether) as a starting point for the preparation of prostaglandins[5]. This versatile compound (2) also proved to be an excellent starting material for the synthesis of brefeldin A. Thus, the bicycloheptadienone (2) underwent stereoselective addition of the required C_7 side chain by reaction with the mixed cuprate reagent (3)[4,6], to give the cyclopentanone (4) [IR : ν_{max}(film) 1740, 1630 cm^{-1} ; NMR : $\delta(CDCl_3)$ 1.05 (d, J = 6 Hz, 3-H), 3.57 (s, 3-H), 3.7 (m, 1-H), 4.73 (br.s, 1-H), 5.33 ppm (m, 2-H)][9] in 82% yield. Hydrolytic cleavage of the methoxycyclobutene in the bicyclic intermediate (4) was effected quantitatively in moist acetone containing p-toluenesulphonic acid (PTSA) at 20°, and afforded the ester (5) [IR : ν_{max}(film) 1740 cm^{-1} ; NMR : $\delta(CDCl_3)$ 1.07 (d, J = 6 Hz, 3-H), 3.65 (s, 3-H), 3.7 (m, 1-H), 5.40 ppm (m, 2-H)][9].

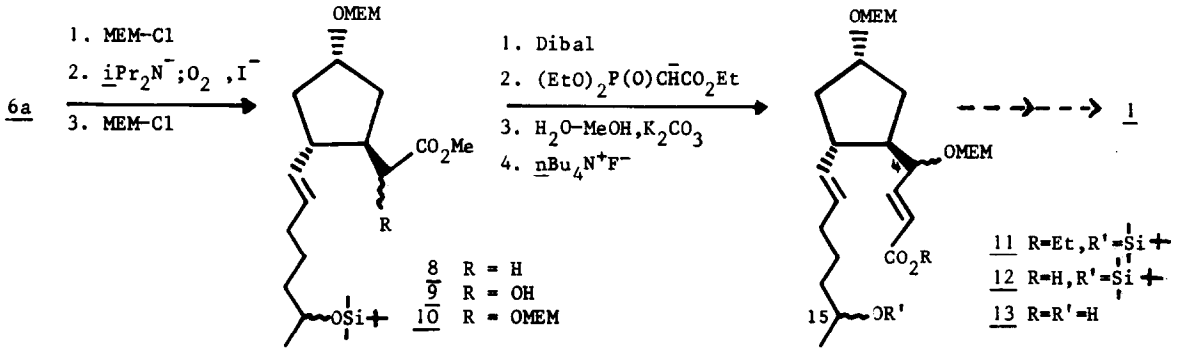
Reduction of the keto group of the cyclopentanone (5) was best effected using L-Selectride in THF at -78°, which provided a ca. 3.5:1 mixture of the epimeric ring alcohols at C-7 (6a and b) in 95% yield. That the required alcohol (6a) predominated was shown by subjecting the mixture to a trace of PTSA in refluxing toluene, which resulted in complete lactonisation of the undesired epimer (6b) to give the bicyclic compound (7) [IR : ν_{max}(film) 1735 cm^{-1} ;



(+)-Brefeldin-A 1







NMR : $\delta(CDCl_3)$ 1.05 (d, J = 6 Hz, 3-H), 3.70 (m, 1-H), 4.77 (m, 1-H), 5.33 ppm (m, 2-H)][9]. The required alcohol (6a) [IR : ν_{max}(film) 3420, 1740 cm^{-1} ; NMR : $\delta(CDCl_3)$ 1.05 (d, J = 6 Hz, 3-H), 3.60 (s, 3-H), 3.70 (m, 1-H), 4.30 (m, 1-H), 5.33 ppm (m, 2-H)][9] remained intact and this provided a convenient method of separation of the diastereomers (6a and b), which could be effected only with difficulty by chromatography. The lactone (7) clearly could be recycled by conversion back to ketone (5) using standard procedures. Further proof of the configurations of the alcohols (6a and b) came from the relative shifts of the ester methyl resonances in the proton NMR using the shift reagent EuFOD.

Protection of the free hydroxyl group in cyclopentanol (6a) was effected in 95% yield using methoxyethoxymethyl chloride and diisopropylethylamine in methylene chloride[10] to afford the MEM ether (8). The introduction of a hydroxyl group adjacent to the ester in (8) proved possible (70%, based on a 72% conversion) by treating the derived lithium enolate (from (8) and lithium diisopropylamide) with dry oxygen at -78° in THF, followed by a mildly reductive work-up[11]. The newly introduced hydroxyl group in the hydroxy-ester (9) [I.R. : ν_{max}(film) 3420, 1740 cm^{-1} ; NMR : $\delta(CDCl_3)$ 1.05 (d, J = 6 Hz, 3-H), 3.67 (s, 3-H), 4.10 (m, 2-H), 5.33 ppm (m, 2-H)][9] was then protected[10] to give the bis-MEM ether (10).

Conversion of the ester group of the intermediate (10) to the required α,β-unsaturated ester (11) was carried out by reduction with diisobutylaluminium hydride in toluene at -78°[12] to give the corresponding aldehyde, which was treated immediately with the sodio derivative of triethyl phosphonoacetate[13] to provide the ethyl ester (11) [IR : ν_{max}(film) 1720, 1650 cm^{-1} ; NMR : $\delta(CCl_4)$ 1.05 (d, J = 6 Hz, 3-H), 1.12 (t, J = 7 Hz, 3-H), 3.7 (m, 1-H), 4.08 (br.q, J = 7 Hz, 4-H), 5.30 (m, 2-H), 5.80 (d, J = 15 Hz, 1-H), 6.67 ppm (dd, J = 6 Hz, 15 Hz 1-H) ; m/e 616 (M^+).][9] in 60% overall yield from (10). Hydrolysis with potassium carbonate in aqueous methanol then afforded the free acid (12), which was desilylated using tetrabutylammonium fluoride in THF[8] to afford the hydroxy acid (13) [IR : ν_{max}(film) 3400, 1710, 1650 cm^{-1} ; NMR : $\delta(CCl_4)$ 1.05 (d, J = 6 Hz, 3-H), 4.06 (m, 2-H), 5.25 (m, 2-H), 5.80 (d, J = 15 Hz, 1-H), 6.65 ppm (dd, J = 7 Hz, 15 Hz, 1-H)][9].

As was the case in the Harvard synthesis[4], the key intermediate (13) clearly exists as diastereomers at carbons 4 and 15. The problem of converting this mixture to stereochemically pure (±) (1) had previously been resolved by studies on natural brefeldin A, therefore the synthesis outlined above represents a formal total synthesis of this substance[4].

The directness of our approach and the ease of stereocontrol at carbons 5, 7 and 9 are both a result of the ideally located functionality and stereochemistry of our starting compound (2). We are currently pursuing further refinements of this synthesis.

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1. Contribution N°21 from the Laboratoire de Chimie Organique, C.E.R.M.O. For N°20, see : J.L. Luche, J.M. Dollat and P. Crabbé, submitted for publication.
2. Post-doctorate Research Fellow.
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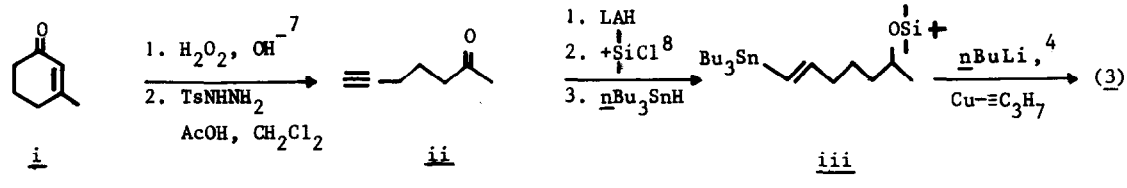
6. The mixed cuprate reagent (3) was prepared as indicated below :



i ii iii

We have also reduced ketone ii microbiologically to the corresponding S(+)-alcohol for use in a planned total synthesis of (+)-brefeldin A.

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