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A SYNTHESIS OF (±)-BREFELDIN A

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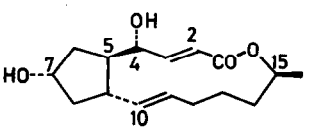
Summary: A macrolide antibiotic, brefeldin A, was synthesized from *trans*-4-oxocyclopentane-1,2-dicarboxylic acid in a stereoselective manner, the intermediary hydroxy acid being lactonized by the mixed 2,4,6-trichlorobenzoic acid anhydride—4-dimethylaminopyridine method.

Brefeldin A (1) is a unique fungal metabolite[1] of a thirteen-membered macrocyclic lactone ring and shows a wide range of interesting biological activities.[2] On the basis of X-ray crystallographic, chemical, and spectroscopic studies, its structure was determined by Sigg et al.[3] including the absolute configurations. The synthesis of (1) has been reported by several groups,[4] while we now wish to report another stereoselective synthesis starting from *dl-trans*-4-oxocyclopentane-1,2-dicarboxylic acid (2)[5] which has also been used by Bartlett et al. in their synthesis.[4d]

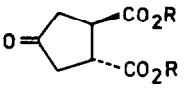
The construction of carbon skeleton was carried out as summarized below: a) fixation of the stereochemistry on cyclopentane ring with a crystalline intermediate (6); b) introduction of *trans*-10-double bond by Claisen rearrangement and subsequent extension of the chain by Wittig reaction; c) introduction of α,β-unsaturated carboxyl function by Wittig reaction.

The acid (2) was methylated with diazomethane to the corresponding methyl ester (3, mp 63-64°C, 99%), which on catalytic hydrogenation with Raney nickel in methanol afforded the alcohol (4, 93%). Partial hydrolysis of 4 with aqueous methanolic potassium hydroxide (0.95 mol eq.) and benzylation of the resulting salt with benzyl bromide in HMPA gave a mixture of esters [5 (95%) and its diastereomer (5%)]. Participation of the hydroxyl group at C-4 seems to be responsible for the stereoselectivity in this saponification. Acetylation with acetic anhydride in pyridine followed by catalytic hydrogenation with palladium on carbon in aqueous 2-propanol gave the crude carboxylic acid. Recrystallization from benzene eliminated the contaminating isomeric acid giving pure 6 [mp 122-123°C, 87% from 4, PMR[6] δ 2.03(s, 3H), 3.74 (s, 3H), 5.19(m, 1H), 10.37(s, 1H)].

Treatment of 6 with oxalyl chloride in dichloromethane and subsequent Rosenmund reduction of the resulting acid chloride in xylene at 140°C gave the aldehyde [7, PMR 1.97(s, 3H), 3.71 (s, 3H), 5.20(m, 1H), 9.68(s, 1H)] which was transformed into the allyl alcohol (8, 65% from 6) with vinylmagnesium bromide in THF at -50°C. 8 was then submitted to transetherification and Claisen rearrangement[7] by heating it with ethyl vinyl ether and mercuric acetate in a sealed tube under nitrogen at 50°C for 1 h and then at 150°C for 2 h, giving the labile aldehyde (9) which was used immediately for the next step without purification. Reaction of 9 with α-methoxyethylidenetriphenylphosphorane[8] in DME at -50°C to 25°C, followed by acid hydrolysis of the product gave the methyl ketone [10, 44% from 8, PMR 2.03(s, 3H), 2.14(s, 3H), 3.68(s, 3H), 5.17(m, 1H), 5.40(m, 2H)]. Sodium borohydride reduction of 10 in methanol led to the alcohol

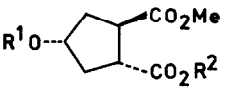


1 Brefeldin A



2 R=H

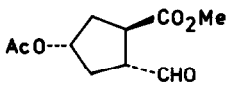
3 R=Me



4 R^1=H, R^2=Me

5 R^1=H, R^2=$CH_2C_6H_5$

6 R^1=Ac, R^2=H



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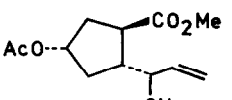

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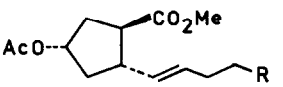
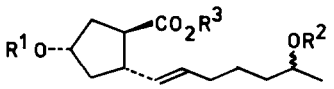


9 R=CHO

10 R=CH_2COCH_3

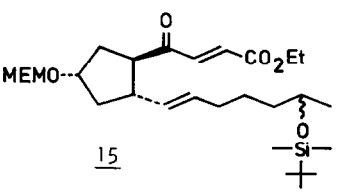


11 R^1=Ac, R^2=H, R^3=Me

12 R^1=Ac, R^2=TBDMS, R^3=Me

13 R^1=MEM, R^2=TBDMS, R^3=Me

14 R^1=MEM, R^2=TBDMS, R^3=H



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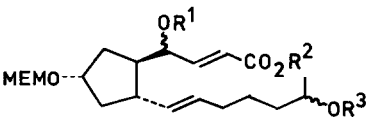
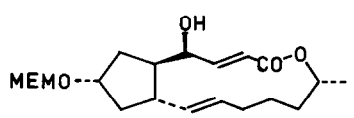


16 R^1=H, R^2=Et, R^3=TBDMS

17 R^1=THP, R^2=Et, R^3=TBDMS

18 R^1=THP, R^2=H, R^3=H



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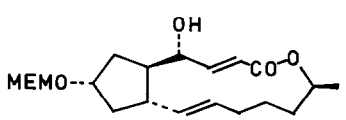

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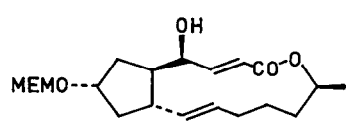

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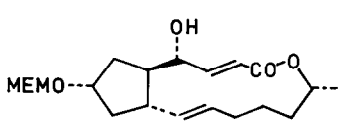

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(11) which was then converted into the corresponding *t*-butyldimethylsilyl ether (12) by the usual procedure.[9] Saponification of 12 with potassium carbonate in methanol and subsequent protection of the hydroxyl group with methoxyethoxymethyl chloride and dicyclohexylethylamine in dichloromethane gave 13 [84% from 10, PMR 0.04(s, 6H), 0.87(s, 9H), 1.11(d, J=6.0 Hz, 3H), 3.49(s, 3H), 3.65(s, 3H), 4.26(m, 1H), 4.69(s, 2H), 5.40(m, 2H)]. 13 has been reported by Corey et al. as an intermediate of their synthesis of brefeldin A.[4b]

Hydrolysis of 13 with potassium carbonate in aqueous methanol gave the acid (14, 99%) which was treated with N,N'-carbonyldiimidazol in THF and then with salt-free methylenetriphenylphosphorane in benzene[10] for 1 h at 40°C. The resulting solution was stirred with ethyl glyoxylate[11] for 17 h at 60°C, giving the enone [15, 69% from 14, PMR 0.03(s, 6H), 0.88(s, 9H), 1.10(d, J=6.1 Hz, 3H), 1.31(t, J=7.0 Hz, 3H), 3.38(s, 3H), 4.25(q, J=7.1 Hz, 2H), 4.72(s, 2H), 5.40(m, 2H), 6.64 and 7.10(ABq, J=16.0 Hz, 2H)]. Reduction of the enone (15) with sodium

borohydride in ethanol at -22°C gave a mixture of four diastereomeric alcohols (16), in which the isomers of unnatural configuration at C-4 relative to C-5 asymmetric center [PMR; 6.91(dd, J=4.9 and 15.6 Hz, 1H at C-3] predominate over those of natural configuration in an approximate ratio of 4:1.[12] Protection of hydroxyl group by the usual procedure led to a mixture of the THP ethers (17, 71% from 15). Saponification with lithium hydroxide in aqueous methanol and subsequent desilylation with tetrabutylammonium fluoride in THF gave the seco-acid mixture [18, 71% from 17. PMR; 1.18(d, J=6.1 Hz, 3H), 3.39(s, 3H), 5.34(m, 2H)], which has been synthesized by Corey et al. from 13 in a different way.[4c] Lactonization of 18 by the mixed anhydride method (TCBA-DMAP method) previously developed by our group,[13] gave a mixture of lactones in 94% yield. The mixture was roughly separated into two zones by TLC (silica gel; benzene-ethyl acetate, 4:1). The upper zone gave 19[14] and 20, after hydrolysis of the elute (AcOH:THF:H_2O= 3:1:3, 50°C) followed by TLC separation (silica gel; benzene-ethyl acetate, 2:1) and the lower zone, 20, 21, and 22 after the similar treatments [PMR; 19, 1.21(d, J=6.6 Hz, 3H), 3.39(s, 3H), 4.74(s, 2H), 6.01(dd, J=2.4 and 15.8 Hz, 1H), 6.95(dd, J=1.9 and 15.6 Hz, 1H); 20, 1.26(d, J= 6.1 Hz, 3H), 3.39(s, 3H), 4.73(s, 2H), 5.91(dd, J=1.9 and 15.6 Hz, 1H), 7.35(dd, J=3.1 and 15.8 Hz, 1H); 21, 1.25(d, J=6.4 Hz, 3H), 3.39(s, 3H), 4.73(s, 2H), 5.76(dd, J=0.8 and 15.9 Hz, 1H), 7.07(dd, J=8.4 and 15.9 Hz, 1H); 22, 1.22(d, J=6.6 Hz, 3H), 3.39(s, 3H), 4.73(s, 2H), 5.81(d, J=15.5 Hz, 1H), 6.75(dd, J=9.6 and 15.5 Hz, 1H)]. The approximate ratio of 19:20:21:22 thus isolated was 4:1:4:1. The result indicated that the lactonization of the seco-acids by TCBA-DMAP method proceeded at approximately the same rate irrespective of the configuration at C-15. Treatment of 20 with titanium tetrachloride in dichloromethane at 0°C gave (±)-brefeldin A (1), mp 175-175.5°C, which was identical with the natural specimen in TLC and UV, IR, PMR, and mass spectra. 21 was also transformed into 1 according to the procedure reported by Corey et al.[4c]

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6) PMR spectra were recorded in $CDCl_3$ solutions unless otherwise specified.

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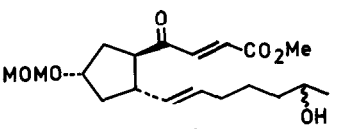
12) Bartlett et al. have reported that reduction of i with sodium borohydride in methanol proceeded stereospecifically, favoring the formation of the unnatural epimer (4β-OH) over the natural epimer (4α-OH) with a ratio of 5:1 (reference 4d).



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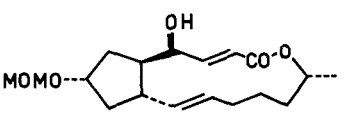
14) The configuration at C-15 was determined from the PMR data of 4-oxo derivative obtained by Collins oxidation [1.26(d, J=6.6 Hz, 3H), 3.39(s, 3H), 4.73(s, 2H), 6.44(d, J=15.8 Hz, 1H), 7.44(d, J=16.0 Hz, 1H)]. The corresponding enone derived from 21 or from natural brefeldin A gave: 1.33(d, J=6.1 Hz, 3H), 3.39(s, 3H), 4.72(s, 2H), 6.44(d, J=16.0 Hz, 1H), 7.77(d, J=16.0 Hz, 1H). The configuration at C-4 was given tentatively from the similarity of the PMR data of 19 to those reported by Bartlett et al. (reference 4d) for the 7-methoxymethoxy derivative, ii.



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