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A TOTAL SYNTHESIS OF (+)-BREFELDIN A

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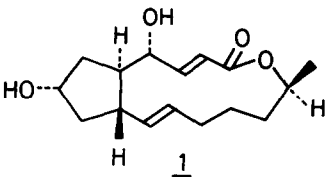
Summary: A key intermediate, a substituted cyclopentanonitrile (10) with correct stereochemistry. was prepared from D-mannitol and converted to the Corey's intermediate (27) without a C_{15}-epimer, which was finally transformed to (+)-brefeldin A.

(+)-Brefeldin A (1), isolated from a variety of fungi by several groups[2], possesses a wide range of biological activity[2c,3], and the complete structure was determined by Sigg et al[4] by X-ray analysis. Because of its wide spectrum of activity and macrocyclic structure, brefeldin A has been an attractive target for the synthetic chemist and up to date the total synthesis of (±)-(1) was achieved by three groups[5], but none of the synthesis of (+)-brefeldin A itself is accomplished yet. Here we wish to report the first total synthesis of (+)-brefeldin A.
Our synthetic planning is to devide (1) into three synthons A,B and C and by retrosynthetic analysis, we selected the known (4R)-2,2-dimethyl-4-iodomethyl-1,3-dioxolane (2)[6], readily available from D-mannitol[7], and D-glutamic acid as starting materials for synthons A and B, respectively.



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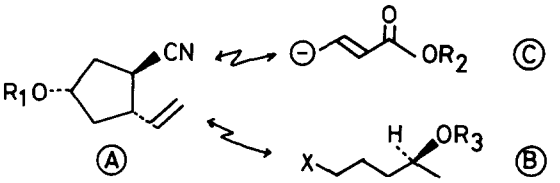
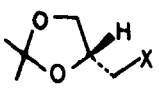
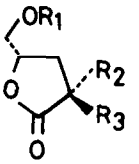


Condensation of (2) with sodiomalonate in THF gave a mono-substituted malonate (3), bp. 115-8°C/0.1 (86%). Subsequent several steps were carried out without isolation to the end, namely the malonate (3) was treated successively with NaOH-MeOHaq, 2N-H_2SO_4, HCHOaq and Et_2NHaq in EtOH[8], excess MeI in THF and with NaCN in DMF to afford a mixture of two hydroxycyanides (4a,b) in a 64/36 ratio (40-71% yield)[9]. Both isomers were converted to their ethoxyethyl derivatives (5a,b) in 89% yield ($EtOCH=CH_2$, PPTS[10]) and the stereochemistry was determined at this stage. In the major isomer both C_2-and C_4-proton signals [δ=3.0, (m) and 4.60 ppm (m)] are located at higher field than those of the minor isomer [δ=3.13 (m) and 4.75 ppm (m)], and therefore we tentatively assigned the desired structure 5a for the major product and 5b for the minor one. DIBAL reduction of 5a, followed by the Wittig reaction with $CH_2=PPh_3$ in DME afforded a vinylcyanide (6) in 52% yield. Protection of secondary OH group as MEM ether[11] (98%), selective acid hydrolysis of ethoxyethyl group (75% AcOH, 35°C, 30 min, 94%) and subsequent tosylation (83%) yielded a desired precursor (9) for cyclization, which was effected by refluxing



2: X= I

3: X=CH(CO$_2$Et)$_2$

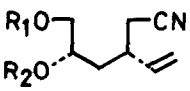


4 a: R$_1$ = H, R$_2$=CH$_2$CN, R$_3$ = H

b: R$_1$ = H, R$_2$= H, R$_3$=CH$_2$CN

5 a: R$_1$ = EE, R$_2$=CH$_2$CN, R$_3$= H

b. R$_1$ = EE, R$_2$= H, R$_3$= CH$_2$CN

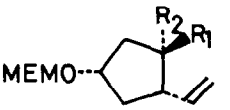


6: R$_1$=EE, R$_2$= H

7: R$_1$=EE, R$_2$=MEM

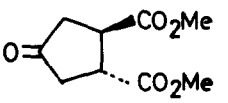
8: R$_1$ = H, R$_2$=MEM

9: R$_1$ =Ts, R$_2$=MEM



10 a· R$_1$ = CN, R$_2$ = H

b: R$_1$ = H, R$_2$ =CN



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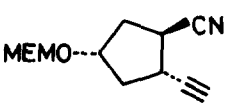

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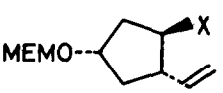
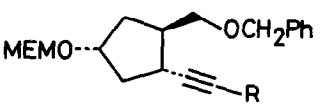


13: X = CO$_2$H

14: X = CO$_2$Me

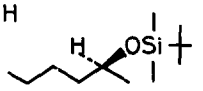
15: X = CH$_2$OH

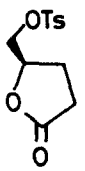
16. X = CH$_2$OCH$_2$Ph



17: R = H

18: R =





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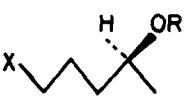


20: R= H, X=OH

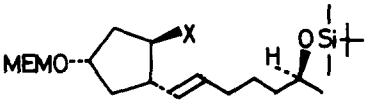
21: R= H, X=OTr

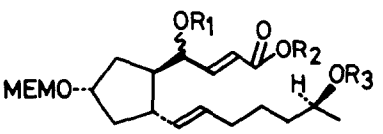
22: R=Me$_2$Bu^{t}Si, X=OTr

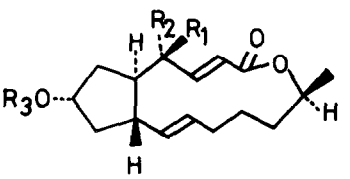
23: R= Me$_2$Bu^{t}Si, X = OH

24: R= Me$_2$Bu^t Si, X = OTs

25: R= Me$_2$Bu^t Si, X = I







26: X = CH$_2$OH

27 X = CHO

28 X = CH(OH)CH(NO$_2$)CH$_2$CO$_2$Me

29: R$_1$= H, R$_2$=Me, R$_3$=Me$_2$Bu^{t}Si

30: R$_1$=THP, R$_2$=Me, R$_3$=Me$_2$Bu^{t}Si

31· R$_1$=THP, R$_2$ = H, R$_3$=Me$_2$Bu^t Si

32: R$_1$ = THP, R$_2$= R$_3$ = H

33: R$_1$, R$_2$=H, OTHP, R$_3$=MEM

34: R$_1$, R$_2$= H, OH, R$_3$=MEM

35: R$_1$, R$_2$= =O, R$_3$=MEM

36: R$_1$ = H, R$_2$= OH, R$_3$=MEM

9 with $NaN(TMS)_2$ in C_6H_6 for 20 min[12] to give a mixture of the expected trans-cyclopentanonitrile (10a) and its cis-isomer (10b) in a 92/8 ratio (81%)[13]. Both isomers afforded a single methyl ester (14) after alkaline hydrolysis, followed by CH_2N_2 treatment (82%). Transformation of the nitrile (10a) to the known keto-diester (11)[14] and the identification by comparing physical data confirmed that the nitrile (10a) possesses the correct configuration. When the same sequence was applied to the minor lactone (4b), surprisingly the same nitrile (10a) was obtained, probably because of equilibration during the Wittig reaction. As the acidic hydrogen is present in the molecule, direct conversion of 10a to an acetylene (12) did not give a satisfactory result, thus the ester (14) was reduced with $LiAlH_4$ to an alcohol (15) and then treated with $PhCH_2Cl$-NaH (96% from 14) to give a benzyl ether (16), $[\alpha]_D^{29}$=-34.5° (c=1, $CHCl_3$), which was transformed to a terminal acetylene (17) by two steps (Pyr.HBr_3-$CHCl_3$, then $NaNH_2$, 81%).

The synthon B (25) was prepared as follows; (R)-(-)-γ-tosyloxymethyl-γ-butyrolactone (19), readily available from D-glutamic acid by the known procedure[15], was reduced with $LiAlH_4$ in THF (76%) to afford (4S)-(+)-pentane-1,4-diol (20), $[\alpha]_D^{21}$=+13.1°, (c=1, MeOH); [lit.[16], (4R)-pentane-1,4-diol, $[\alpha]_D^{20}$=-13.4° (c=1.05, MeOH)] the primary OH group of which was selectively tritylated (TrCl-Pyr) and then the secondary OH group was protected with a dimethyl-t-butylsilyl group[17] (87% overall) to give an ether (22), $[\alpha]_D^{21}$=+6.2°, (c=1, EtOH). Reductive cleavage of the trityl group with Na in liq. NH_3, followed by tosylation gave a tosylate (24), which was refluxed with NaI (2.4 eq) in acetone to give the desired (2S)-(+)-5-iodo-2-dimethyl-t-butylsilyloxypentane (25) (63% from 22); bp. 79-80°C/2mmHg, $[\alpha]_D^{21}$=+14.3° (c=1, EtOH).

Alkylation of the acetylene (17) with this iodide (n-BuLi in HMPA-THF[18], 82%) afforded a disubstituted acetylene (18) which was treated with Na in liq. NH_3 (79%) to give an alcohol (26), $[\alpha]_D^{24}$=+12.7° (c=1, MeOH). PCC-NaOAC oxidation[19] of the alcohol (26) (94%) gave the corresponding aldehyde (27), which was treated with methyl β-nitropropionate[20] (iPr_2NH-DMSO) to give an unexpected nitro-alcohol (28). Elimination of nitrous acid was effected by treating with pyrrolidine in HMPA (54% from 13) to afford a γ-hydroxyacrylate (29), $[\alpha]_D^{24}$=+13.4°, (c=0.65, MeOH)[21], which was converted to a THP-ether[10] (30, 97%).

Remaining steps were elaborated in almost the same manner as reported by Corey et al[5b], thus alkaline hydrolysis, removal of the silyl group and cyclization (47%) gave a macrocyclic lactone (33), $[\alpha]_D^{21}$=+8.4° (c=0.37, EtOH), which was converted to a keto-lactone (35), $[\alpha]_D^{21}$=-15.1° (c=0.30, EtOH), λmax (EtOH) 220 nm (log =3.67). $NaBH_4$ reduction (75% from 33) afforded an C_4-(S)-alcohol (36), $[\alpha]_D^{20}$=+51.5° (c=0.27, EtOH), which was treated with $TiCl_4$ (79%) to give (+)-brefeldin A.

After recrystallization from EtOAc, the synthetic sample was completely indistinguishable with authentic (+)-brefeldin A in all respect (^{1}H-NMR, IR-KBr, mp, mixed mp, TLC), $[\alpha]_D^{21}$=+90.2° (c=0.14, MeOH); authentic, $[\alpha]_D^{25}$=+91.8° (c=17, MeOH), kindly provided by Dr. A.Takatsuki and Dr. A von Wartburg.

Acknowledgement

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References and Footnotes

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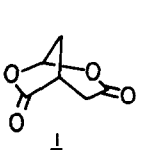
9 The major isomer (11a) is a crystalline compound (mp 59-60°C), $[\alpha]_D^{30}$ =+50.9° (c=1, EtOH), and the minor one (11b) is an oily product, $[\alpha]_D^{30}$ =+20.8° (c=1, EtOH). An attempt to prepare a dilactone (i) failed [a) KOH-$CH_3OCH_2CH_2OH$, b) Ac_2O-AcONa, c) CH_2N_2] and both isomers afforded acetoxy esters (ii) and (iii), thus the configuration at C_2 could not be elucidated at this stage.



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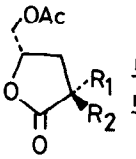

ii : R_1=CH_2CO_2Me, R_2= H
iii : R_1= H R_2=CH_2CO_2Me

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13 trans-Isomer (2), $[\alpha]_D^{28}$=-43.6° (c=1, $CHCl_3$), cis-isomer (14), $[\alpha]_D^{28}$=+55.9° (c=1, $CHCl_3$); spectral data of both isomers supported their structure except for stereochemistry.

14 Ozonization (-78°C/CH_2Cl_2), followed by oxidative cleavage (Jones' reagent, 0°C) and CH N treatment gave an ester. Cleavage of MEM-ether (2% H_2SO_4/MeOH, reflux, 60 min), Jones oxidation and subsequent methanolysis (5% H_2SO_4-MeOH, reflux, 40 hr) afforded (-)-keto-diester (17); $[\alpha]_D^{21}$ =-116° (c=1, $CHCl_3$), CD; negative Cotton effect: Lit. $[\alpha]_D$ =-119° (c=0.55, $CHCl_3$), CD; negative Cotton effect.

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21 Other bases, Et_2NH and piperidine, were also employable for this purpose, but in any case retro-aldol type reaction back to the starting aldehyde (27) occurred in some extent. Of three bases, pyrrolidine gave the best result to give the acrylate(29).

22 Other synthetic approaches to (±)-brefeldin A reported are; a) D. P. Curran, D. Scholz, Monatshefte Chem. 108, 1401 (1977). b) T. Livinghouse, R. V. Stevens, J. Chem. Soc., Chem. Commun., 754 (1978).

** Part of this work was presented at the 21st symposium of the chemistry of the natural products, August, 1978, Sapporo, Hokkaido, and the annual meeting of the agricultural chemical society of Japan. April, 1979, Tokyo.

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