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STEREOSELECTIVE TOTAL SYNTHESIS OF (+)-BREFELDIN A†

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Abstract—A total synthesis of (+)-brefeldin A, an antibiotic fungal metabolite, has been achieved stereoselectively starting from (+)-mannitol and (+)-glutamic acid.

(+)-Brefeldin A (**1**) possesses a wide range of biological activity, including antifungal,[1a-c] antiviral,[1d] antimitotic[1e] and antitumor[1a,f] effects. This fungal metabolite was first isolated in 1958 from *Penicillium decumbens* by Singleton *et al.*[2a] and named decumbin. Because it has been isolated from a variety of microoganisms,[1a,h,2] it was named independently as cyanein[2b] and ascotoxin[1h] in addition to decumbin[2a] and brefeldin A,[1a] before the identity of these compounds was established.[3] The complete structure was determined through a definite X-ray crystallographic analysis by Sigg's group[4b] in 1971 after the extensive efforts on elucidation of the structure had been made by several workers.[1h,2,3,4a]

Because of its diverse spectrum of biological activity and its macrocyclic framework, brefeldin A has been an attractive target for synthetic chemists and various approaches to synthesize this molecule have been reported.[5] Corey and Wollenberg announced the first total synthesis of (±)-**1**[5a-c] in 1976, after the explorative work on the formation of macrocyclic lactone ring.[6] Since then, several additional syntheses of (±)-**1** have been achieved.[5d,e,g-j] In 1979, we reported the first total synthesis of (+)-brefeldin A, naturally occurring antibiotic, in the preliminary communication.[5f] Recently, second total synthesis of (+)-**1** was reported by Greene's group.[5k]

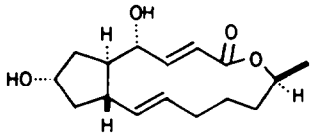

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Fig. 1.

In this paper, we detail the stereoselective synthesis of (+)-brefeldin A from easily available chiral sources.

DISCUSSION

Strategy

Our synthetic planning was based on dividing **1** into three segments **A**, **B** and **C**, where the coupling of **A** and **B** seemed to be rational by alkylation via the acetylene derivative and then the carbanion type segment **C** would be able to add to **A** at the nitrile portion after the functional group modification. Among them, segments **A** and **B** had to be prepared in optically active forms. It seemed to be of no difficulty to obtain (*S*)-**B**, because it has only one asymmetric center, and (+)-glutamic acid was employed as the chiral source.

Therefore, the main problem was how to build the

†Synthesis of macro- and medium-cyclic compounds—Part IV. Part III, T. Kitahara, M. Iwamoto, Y. Takagi, K. Mori and M. Matsui, *Agric. Biol. Chem.* in the press.

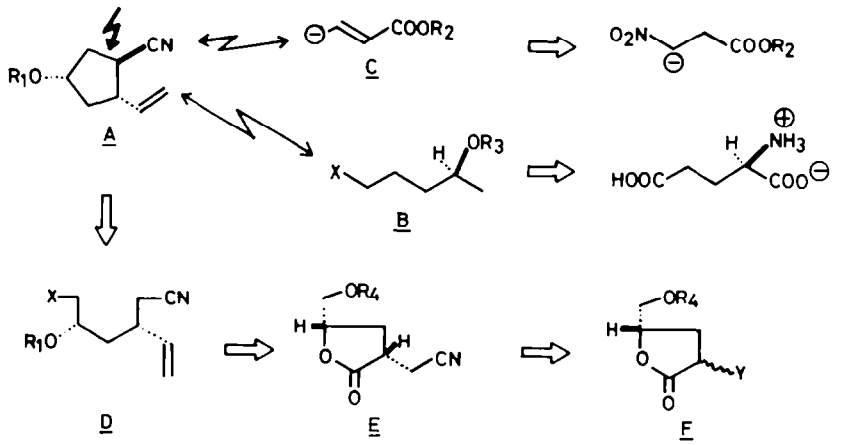


Fig. 2.

segment **A** with correct absolute configuration. We considered that intramolecular alkylation of the substituted nitrile (**D**) with a proper leaving group (halogen or halogen equiv) should be suitable to yield **A**, where the precursor (**D**) seemed to be derivable from the lactone (**E**), which in turn might be obtained by selective alkylation of the chiral lactone (**F**) from α-face. It would be preferable that C_2-position of the lactone (**F**) is activated by the electron withdrawing group Y (–COOH, $-CO_2R$ etc). Accordingly, we selected (*R*)-2,2-dimethyl-4-iodomethyl-1,3-dioxolane (**2**)[7] as starting material which was easily obtained from (+)-mannitol.[8]

Synthesis of segment **A**

Alkylation of diethyl sodiomalonate with the iodide (**2**) in refluxing THF gave a monosubstituted malonate (**3**) in 86% yield based on the consumed **2**. Subsequent several steps were carried out without isolation of the intermediate until the end. The malonate (**3**) was hydrolyzed with KOH in aqueous MeOH, followed by the acidification with cold 2N H_2SO_4 and the resulting crude lactonic acid was treated with 37% aqueous HCHO and 40% aqueous Me_2NH in EtOH.[9] The exothermic Mannich reaction with vigorous CO_2 evolution finished within 20 min. The mixture was concentrated *in vacuo* and the residue was treated with excess MeI in refluxing THF, followed by the treatment with excess NaCN in DMF at room temperature to give two epimeric hydroxycyanides (**4a, b**) in 40–70% (**4a** : **4b** = 64 : 36).† In order to determine the stereochemistry of two isomers, they were separately treated with KOH in refluxing $CH_3OCH_2CH_2OH$, Ac_2O and AcONa at 90° for 3 hr and CH_2N_2 successively to give the corresponding acetoxyesters (**5a, b**) respectively and neither of **4a** nor **4b** yielded the expected dilactone (**7**). Consequently, the stereochemistry of two isomers remained uncertain at this stage.

Both isomers **4a** and **4b** were converted to their 1-ethoxyethyl ether (**6a, b**) in 89% yield ($EtOCH{=}CH_2$, PPTS[10] in CH_2Cl_2) and determination of the stereochemistry was examined by ^{1}H-NMR analysis. Though the coupling constants of C_2- and C_4-protons with adjacent methylene group were not clearly observed, chemical shifts of C_2- and C_4-proton signals [δ = 3.00 (m), and 4.60 ppm (m)] of the major isomer are higher than those of the minor isomer [δ = 3.13 (m) and 4.74 ppm (m)], and therefore we tentatively assigned the desired structure **6a** for the major product and **6b** for the minor isomer based on the conformational analysis as shown in Fig. 3.

DIBAL reduction of **6a** at −75°, followed by the Wittig reaction with excess salt free methylenetriphenylhosphorane in DME[11] (−10° to rt, 30 min) afforded a vinyl cyanide (**9**) in 52% yield. Protection of secondary alcohol as 2-methoxyethoxymethyl (MEM) ether[12] (MEMCl i-Pr_2NEt in CH_2Cl_2, **10**; 98%), selective acid hydrolysis of ethoxyethyl group (75% AcOH, 35°, 30 min, **11**: 94%) and subsequent treatment with p-TsCl in pyridine (83%) yielded the desired precursor (**12**). The cyclization was effected by refluxing **12** with $NaN(TMS)_2$ in benzene for 20 min[13] to give a mixture of the expected *trans*-cyclopentanenitrile (**13a**) and its *cis*-isomer (**13b**) in a 92/8 ratio (81% yield), which afforded a single *trans*-methyl ester (**14**) after the alkaline hydrolysis and subsequent CH_2N_2 treatment.

The absolute configuration of the nitrile (**13a**) was confirmed directly by the transformation to the known (−)-keto diester (**17**). Ozonization of **13a**, followed by oxidative workup with Jones' reagent and successive treatment with CH_2N_2 and then with 2% H_2SO_4 in MeOH (reflux for 60 min) gave a hydroxy cyanide (**15**). Jones oxidation and subsequent methanolysis (5% H_2SO_4 in MeOH, reflux for 40 hr) afforded (−)-keto diester (**17**); [$[\alpha]_D^{21}$ − 116° in $CHCl_3$, CD; negative Cotton effect.] These chiroptical data were identical with those of the known (−)-(3R,4R)-dimethoxycarbonylcyclopentanone (**17**); [lit., $[\alpha]_D$ − 119° in $CHCl_3$,[4b] $[\alpha]_D$ − 130°,[14] CD; negative Cotton effect].[4b] Thus, it was established that the *trans*-nitrile (**13a**) as well as *trans*-methyl ester (**14**) has the correct absolute configuration for the synthesis of (+)-**1**.

The same sequence was applied to the minor lactone (**6b**) as mentioned for the preparation **13a** from **6a**, *surprisingly, the same desired nitriles* (**13a,b**) *were obtained in almost the same yield.* Although it was a little difficult to explain this unexpected phenomenon clearly by the rational scheme, we assumed that the hemiacetal (**8b**) was equilibrated with the other hemiacetal (**8a**) with the desired configuration through their acyclic tautomers (aldehyde form) in the presence of base during the Wittig reaction and methylenation proceeded only *via* **8a** to afford the desired product (**9**) selectively. *In any case, the segment* **A** *was synthesized in a completely stereoselective manner from the iodide* (**2**).

As an acidic hydrogen is present in the molecule, direct conversion of **13a** into an acetylene (**18**) did not give the satisfactory result. Alternatively, the ester (**14**) was reduced with $LiAlH_4$ to give the primary alcohol (**19**), which was treated with benzyl chloride and NaH in DMF to afford a benzyl ether (**20**) in 96% yield from **14**. In this case, transformation of the double bond to the acetylene group was achieved cleanly in two steps, namely, treating the olefin (**20**) with pyridinium bromide perbromide in $CHCl_3$ and then with excess $NaNH_2$ in refluxing ammonia for 40 min to given an acetylene (**21**) in 81% yield.

Synthesis of the segment **B**

The preparation of the segment **B** for the side chain was carried out as follows (*R*)-(−)-γ-Tosyloxymethyl-γ-butyrolactone (**23**),[15] readily available as an optically pure crystalline product from (+)-glutamic acid by the reported procedure,[16] was reduced with $LiAlH_4$ in THF to give (*S*)-(+)-1,4-pentanediol (**24**), $[\alpha]_D^{21}$ + 13.1° in MeOH, which was in good accordance with that of known (*R*)-(−)-1,4-pentanediol,[17] $[\alpha]_D^{20}$ − 13.4° in MeOH.

The primary OH group was selectively tritylated with TrCl in pyridine and then the secondary OH group was protected with dimethyl-t-butylsilyl

†The major isomer (**4a**) was crystalline compound (m.p. 59–60°), and the minor one (**4b**) was an oily product. Because both isomers were extremely soluble in water, workup procedure was different from the normal manner and as it was necessary to remove DMF directly from the reaction mixture *in vacuo*, the yield was varied by reaction scale.

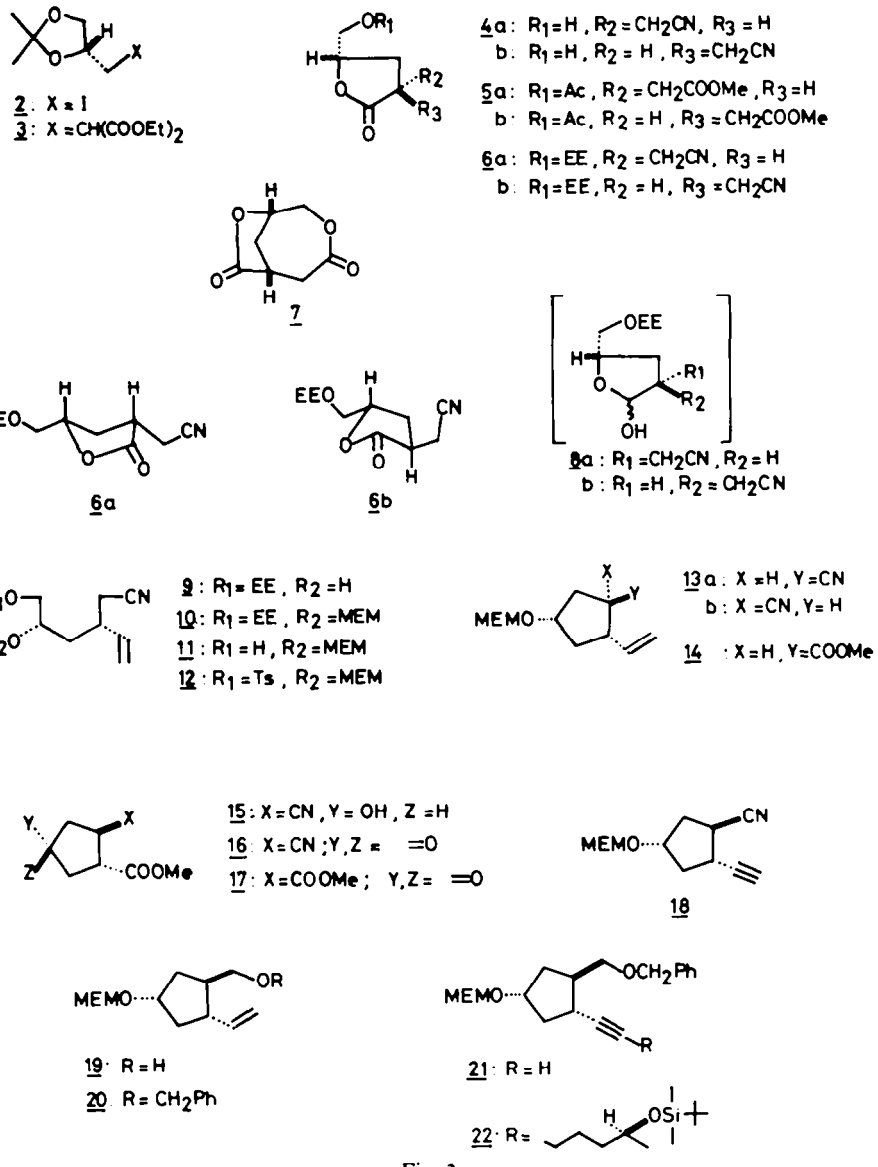


Fig. 3.

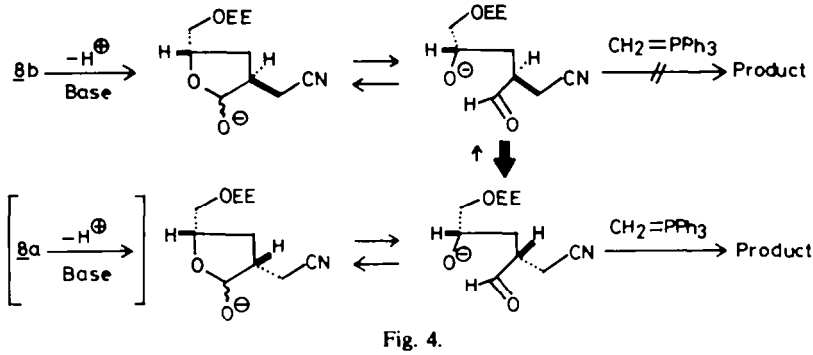


Fig. 4.

group[18] to give an ether (**26**) in 87% yield from **24**. Reductive cleavage of the trityl ether with Na in refluxing ammonia, followed by the treatment with TsCl in pyridine at 0° to give a tosylate (**28**), which was refluxed with NaI in acetone in the presence of $NaHCO_3$ for 40 hr to afford the desired (*S*) - (+) - 5 - iodo - 2 - dimethyl - t - butylsilyloxypentane (**29**), chiral segment **B**, $[\alpha]_D^{21}$ + 14.3° in EtOH in 63% yield from **26** (43% overall yield from the tosylate (**23**)).

Coupling of the segments **A**, **B** *and* **C**, *and completion of the total synthesis*

Alkylation of the acetylene (**21**) with the iodide (**29**) by the procedure reported by Schwarz and Waters[19]

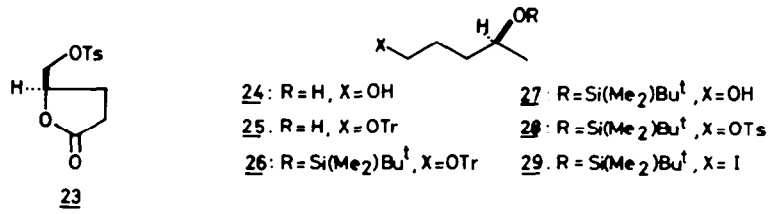
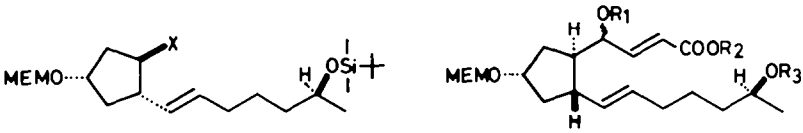


Fig. 5.

afforded the disubstituted acetylene (**22**) in 82% yield, which gave an alcohol (**30**) on treatment with Na in refluxing ammonia for the reductive cleavage of benzyl group as well as the selective reduction of acetylene group to *trans*-double bond. The alcohol (**30**) is the same intermediate as used for the Corey's synthesis of (±)-brefeldin A,[5b] except that our intermediate (**30**) does not contain the other undesired stereoisomer in the side chain and is optically active.

PCC oxidation in the presence of NaOAc[20] gave the labile aldehyde (**31**), which was treated with methyl β-nitropropionate[21a] in the presence of diisopyropylamine in DMSO[21b] at room temperature to give an unexpected nitroalcohol (**32**).† Elimination of nitrous acid was effected by treating **32** with pyrrolidine in HMPA‡ to afford the diastereomeric γ-hydroxycrotonate (**33**) in 54% yield from **30**, which now has whole carbon assembly of brefeldin A in the molecule.

Remaining steps were elaborated similarly according to the Corey's procedure,[5c] namely, protection of secondary alcohol as THP ether,[10] alkaline hydrolysis



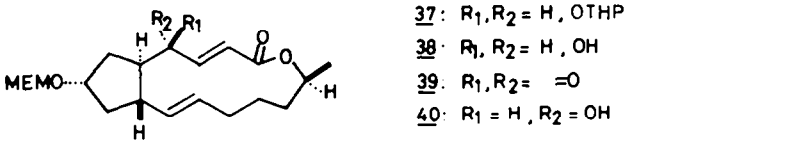


Fig. 6.

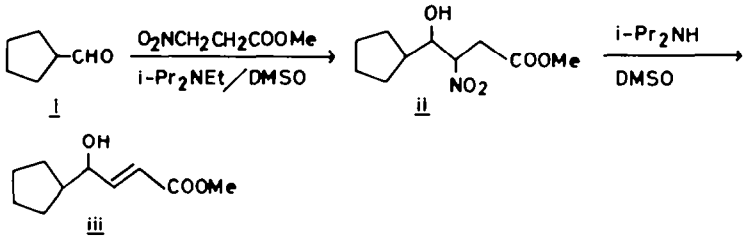


Fig. 7.

†The aldehyde (**i**) was treated with methyl β-nitropropionate according to the procedure reported by Bakuzis *et al.*[21b] except that diisopropylamine was replaced by diisopropylethylamine, we obtained not a γ-hydroxycrotonate (**iii**) but a nitroalcohol (**ii**) in nearly quantitative yield in the model experiment.

Treating (**ii**) with diisopropylamine under the Bakuzis' procedure gave (**iii**). This result indicates that it is better to use hindered base to effect the cross-aldol type reaction in the initial step, but it is necessary to use unhindered base for the elimination of nitrous acid to form the final product in the second step. This information played an important role in elaborating the condensation reaction of **31** to optimize the reaction condition.

‡Other bases, Et_2NH and piperidine, were also useful for this elimination, but in any case retro-aldol type reaction back to the starting aldehyde occurred in some extent (by TLC check). Among three bases, pyrrolidine gave the best result to give the elimination product.

of ester and removal of the silyl group with n-Bu_4NF in THF afforded the hydroxy acid (**36**) whose cyclization was effected under high dilution condition via a pyridinethiol ester to give a macrocyclic lactone (**37**) in 42% overall yield from **33**. THP group was selectively cleaved by mild acid hydrolysis and the resulting diastereomeric alcohol (**38**) was oxidized with PCC–NaOAc in CH_2Cl_2 to give a single ketone (**39**) in 66% yield, which was selectively reduced with $NaBH_4$ in MeOH at $-75°$ to afford an C_4-(*S*)-alcohol (**40**). Finally, deprotection of C_7-alcohol was effected by brief treatment with $TiCl_4$ in CH_2Cl_2 at 0°[12] to give (+)-brefeldin A in 79% yield. After recrystallization from EtOAc, the synthetic **1** was completely indistinguishable from authentic (+)-brefeldin A spectroscopically as well as chromatographically; m.p. 203–4°, $[\alpha]_D^{22} + 92.2°$ in MeOH; authentic m.p. 204–5° $[\alpha]_D^{22} + 92.9°$ in MeOH.

In summary, the first total synthesis of (+)-brefeldin A, naturally occurring antibiotic, has been accomplished from the chiral iodide (**2**) and (+)-glutamic acid with complete stereoselectivity.

EXPERIMENTAL

M.ps and b.ps are uncorrected. IR spectra were recorded on a Shimadzu IRA-400 spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-360 (60 MHz) and Varian HA-100 (100 MHz) spectrometer. Unless otherwise noted, the NMR solvent was $CDCl_3$. Chemical shifts are reported in ppm on the δ scale, relative to TMS as internal standard. MS spectra were obtained by Hitachi RMU-60 mass spectrometer. Optimal rotations were determined on a Perkin–Elmer 141 polarimeter. CD spectrum was obtained with Jasco J-20 circular dichrometer.

TLC was performed on Merck 60 F_{254} (0.25 mm) precoated silica gel plates. Merck silica gel 60 (70–230 mesh) was employed for column chromatography. Unless otherwise noted, reaction workups culminated in drying the solvent over anhydrous $MgSO_4$ and removing the solvent by evaporation under reduced pressure.

Diethyl (4S)-2,2-*dimethyl*-1,3-*dioxolan*-4-*yl*-*methylmalonate* (**3**)

To a stirred suspension of NaH (60%, 28.8 g, 0.72 mol, mineral oil was removed by washing with dry pentane several times) in dry THF (30 ml) was added dropwise diethyl malonate (115 g, 0.72 mol) over 60 min and the mixture was stirred for further 20 min. To the resulting clear soln was added a soln of **2** (145 g, 0.6 mol) in dry THF (100 ml) over 20 min under N_2 and the mixture was stirred with reflux for 70 hr. The mixture was poured into ice water and extracted with ether. The combined extract was washed with brine, dried and concentrated. The residue was distilled under reduced pressure: fraction I, 12 g, b.p. ~ 65°C//7 mmHg; mostly diethyl malonate, fraction II, 61 g, b.p. 66–75°C/7 mmHg; **2** + diethyl malonate (*ca* 1 : 1). (Fraction II could be recycled to use for the alkylation reaction.) Fraction III, 111.9 g, b.p. 115–8°C/0.1 mmHg; **3** (86% based on consumed **2**). $n_D^{23} = 1.4332$. $[\alpha]_D^{25} - 6.31°$ (*c* 3.0, MeOH) IR (film) 1742, 1260 (sh), 1245, 1220, 1180, 1160, 1100, 1065, 1030 cm^{-1}. NMR (CCl_4), 1.24 (6H, t, J = 7 Hz), 1.24 (3H, s), 1.31 (3H, s), 1.85–2.30 (2H, m) 3.2–3.7 (2H, m), 3.80–4.25 (2H, m), 4.14 (4H, q, J = 7 Hz). (Found: C, 56.71; H, 7.99. Calc. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08%.)

(2S,4S) - 2 - *Cyanomethyl* - 5 - *hydroxy* - 4 - *pentanolide* (**4a**) *and* (2R,4S) - *cyanomethyl* - 5 - *hydroxy* - 4 - *pentanolide* (**4b**)

To a soln of 85% KOH (7.9 g, 0.12 mol) in water (50 ml) was added at once to a soln of **3** (13.7 g, 0.05 mol) in MeOH (25 ml) and the mixture was refluxed for 4 hr. After cooling, the mixture was extracted with ether (50 ml) and the extract was washed with water. The combined aqueous layers were acidified (pH 2) with 2N H_2SO_4 and concentrated *in vacuo* to give the semisold residue which was extracted by stirring with the mixture of acetone–EtOH (4 : 1, 200 ml) for 10 min and filtered. The white solid was washed with the same solvent (*ca* 100 ml) and the combined filtrates were concentrated *in vacuo* to give a crude lactonic acid. To a soln of this lactonic acid in EtOH (30 ml) was added dropwise a mixed soln of 37% HCHO aq (6 ml, 0.07 mol) and 40% Me_2NH aq (8 ml, 0.07 mol) in EtOH (10 ml) over 20 min and the mixture was stirred for further 10 min. During this period, vigorous CO_2 evolution revealed 70–80% of the theoretical amount of CO_2 evolved in any run of this process. The solvent was removed *in vacuo* and the residue was dissolved in the mixture of benzene–EtOH (4 : 1, 100 ml) and the mixture was concentrated *in vacuo* to remove water and volatile materials. This operation was repeated again to give the crude Mannich product, which was dissolved in THF (50 ml). To this was added MeI (32 g, 0.25 mol) and the mixture was stirred with reflux for 2 hr. The mixture was concentrated *in vacuo* to remove volatiles thoroughly. The resulting white solid of crude ammonium iodides was suspended with NaCN (4.0 g, 0.082 mol) in DMF (40 ml) and the mixture was stirred at room temp for 40 hr. Solvent was removed under reduced pressure (5 mmHg) with dry ice–acetone trap and with bath temp below 50°. The brown residue was stirred well with CH_2Cl_2 (100 ml) and filtered. The ppt was washed with CH_2Cl_2 and the combined filtrates were concentrated *in vacuo* and chromatographed (SiO_2, 120 g). Elution with CH_2Cl_2–EtOAc (2 : 3–1 : 2) yielded two products : fraction I, **4b** (1.23 g), fraction II, mixture (0.75 g), fraction III, **4a** (2.28 g). Rechromatography of f-II (SiO_2, 20 g) gave further amount of **4b** (0.19 g) and **4a** (0.25 g). Total amount; 3.95 g (51%). **4a**; 2.53 g (33%), **4b**; 1.42 g (18%).

Compound **4a**: m.p. 59–60° (recrystallized from EtOAc–hexane), R_f 0.29 (EtOAc), $[\alpha]_D^{30} + 50.9°$ (*c* 1.0, EtOH), IR (KBr), 3500, 2240, 1770–1735, 1215, 1185, 1040, 1020, 995, 690, 650 cm^{-1}. NMR, 1.80–3.30 (6H, m), 3.55–4.30 (2H, m), 4.40–4.90 (1H, m). (Found: C, 54.22; H, 5.89; N, 9.01. Calc. for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03%.)

Compound **4b**: R_f 0.37 (EtOAc), $[\alpha]_D^{30} + 20.8°$ (*c* 1.0, EtOH), IR (film), 3400, 2240, 1770–1730, 1240, 1220, 1170, 1050, 990 cm^{-1}. NMR, 1.75–3.35 (6H, m), 3.50–4.45 (2H, m), 4.50–4.90 (1H, m). (Found: C, 54.55; H, 5.99; N, 8.95. Calc for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03%.)

(2R,4S) - 2 - *Methoxycarbonylmethyl* - 5 - *acetoxy* - 4 - *pentanolide* (**5a**)

A mixture of **4a** (213 mg, 1.5 mmol) and 85% KOH (488 mg, 7.5 mmol) in water (1 ml) and $CH_3OCH_2CH_2OH$ (4 ml) was stirred under reflux for 18 hr. After cooling, the mixture was stirred with wet Amberlite IR-120 (H^+ type, 10 ml) for 10 min and filtered. The resin was washed with EtOAc (20 ml) and the combined filtrates concentrated *in vacuo*. The residue was dissolved in the mixture of benzene–EtOH (4 : 1, 25 ml) and thoroughly concentrated to remove water. The residual oil (220 mg) was mixed with NaOAc (120 mg) and Ac_2O (2 ml) and the mixture was heated at 90° with vigorous stirring for 3 hr. The mixture was poured into 2N HCl and extracted with EtOAc (× 5). The extract was treated with excess CH_2N_2 in ether for 5 min. After the usual workup, the residue was chromatographed (SiO_2, 6 g, hexane–EtOAc = 2 : 3) to give **5a** (201 mg, 58%): $[\alpha]_D^{25} + 48.2°$ (*c* 1.0, EtOH), IR (film), 1770, 1735, 1260 (sh), 1230, 1170, 1040, 735 cm^{-1}. NMR, 1.65–3.35 (5H, m), 2.10 (3H, s), 3.70 (3H, s), 4.07–5.15 (3H, m).

(2S,4S) - 2 - *Methyloxycarbonylmethyl* - 5 - *acetoxy* - 4 - *pentanolide* (**5b**)

In the same manner, **4b** (213 mg) gave **5b** (211 mg, 61%):

$[\alpha]_D^{25}$ + 33.2° (*c* 1.0, EtOH), IR (film), 1770, 1735, 1260 (sh), 1230, 1170, 1040, 735 cm^{-1}. NMR, 1.60–3.45 (5H, m), 2.10 (3H, s), 3.70 (3H, s), 4.09–5.13 (3H, m).

(2S,4S) - 2 - *Cyanomethyl* - 5 - (1 - *ethoxyethoxy*) - 4 - *pentanolide* (**6a**)

A mixture of **4a** (12.4 g, 80 mmol), ethyl vinyl ether (7.2 g, 100 mmol) and PPTS[10] (1.9 g, 8 mmol) in dry CH_2Cl_2 (125 ml) was stirred at room temp for 18 hr. The mixture was washed with water, dried and concentrated. The residue was chromatographed (SiO_2, 150 g, hexane–EtOAc = 1 : 1 – 1 : 2) to give **6a** (16.2 g, 89%): R_f 0.51 (EtOAc). $[\alpha]_D^{25}$ + 64.5° (*c* 1, $CHCl_3$). IR (film), 2240, 1785, 1460, 1426, 1390, 1345, 1190, 1140, 1090 (br), 1055, 1010, 945, 930 cm^{-1}. NMR 1.20 (3H, t, J = 7 Hz), 1.32 (3H, d, J = 6 Hz), 1.70–2.80 (4H, m), 2.80–3.20 (center at 3.00, 1H, m), 3.25–4.20 (4H, m), 4.39–4.81 (center at 4.60, 1H, m), 4.85 (1H, q, J = 6 Hz). (Found: C, 56.16; H, 8.07; N, 6.39. Calc for $C_{10}H_{17}O_4N$: C, 55.80; H, 7.96; N, 6.51%.)

(2R,4S) - 2 - *Cyanomethyl* - 5 - (1 - *ethoxyethoxy*) - 4 - *pentanolide* (**6b**)

In the same manner starting from **4b** (6.2 g, 40 mmol), **6b** (8.2 g, 90%) was obtained. R_f 0.58 (EtOAc). $[\alpha]_D^{29}$ + 19.2° (*c* 1.0, $CHCl_3$). IR (film), 2240, 1785, 1460, 1425, 1390, 1345, 1190, 1140, 1095 (br), 1055, 1010, 945, 930 cm^{-1}. NMR, 1.20 (3H, t, J = 7 Hz), 1.29 (3H, d, J = 6 Hz), 2.00–2.85 (4H, m), 2.96–3.30 (center at 3.13, 1H, m), 3.33–4.03 (4H, m), 4.58–4.90 (center at 4.74, 1H, m), 4.65–4.95 (1H, m). (Found: C, 56.22; H, 8.09; N, 6.41. Calc for $C_{10}H_{17}O_4N$: C, 55.80; H, 7.96; N, 6.51%.)

(3S,5S) - 6 - (1 - *Ethoxyethoxy*) - 5 - *hydroxy* - 3 - *vinylhexanenitrile* (**9**)

To a soln of **6a** (4.54 g, 20 mmol) in dry toluene (320 ml) was added dropwise 1.74M soln of diisobutylalane in hexane (13.2 ml, 23 mmol) over 5 min at – 75° under N_2 and the mixture was stirred for further 15 min. To this was added 20% NaOH (8 ml) at once and stirring was continued until the temp was raised to 0° (dry ice bath was removed). The mixture was filtered through celite pad and organic phase was dried ($MgSO_4$) and concentrated. The residual crude lactol was dried in vacuum desiccator for 3 hr. Salt free methylenetriphenylphosphorane was prepared in a similar manner as reported.[11]

To a stirred soln of crude **8a** (4.55 g) in dry DME (30 ml) was added 0.36 M soln of the phosphorane in DME (170 ml, 61 mmol) during 5 min at – 10° under N_2 and the mixture was stirred at ambient temp for further 25 min. The reaction was quenched with sat $NaHCO_3$ aq (20 ml) and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and filtered. The filtrate was washed with brine, dried and concentrated. The residue was chromatographed (SiO_2, 180 g, hexane–EtOAc = 3 : 1-3 : 2) to give **9** (2.39 g, 52%) R_f 0.51 (hexane–EtOAc = 1 : 1). $[\alpha]_D^{26}$ – 12.3° (*c* 1.0, $CHCl_3$). IR (film), 3450, 3090, 2250, 1640, 1420, 1380, 1340, 1130, 1120–1080 (br), 1050, 990, 915 cm^{-1}. NMR, 1.20 (3H, t, J = 7 Hz), 1.31 (3H, d, J = 6 Hz), 1.65 (2H, br t), 2.33–2.95 (4H, m), 3.20–4.10 (5H, m), 4.72 (1H, q, J = 6 Hz), 5.00–6.20 (3H, m, vinyl protons). MS *m/z*, 226 (M^+-1), 212, 196, 182, 166, 153, 138, 124, 120, 97, 96, 94, 93, 87, 79, 64, 63 (100), 58, 45, 42. (Found: C, 63.79; H, 9.19; N, 6.08. Calc for $C_{12}H_{21}O_3N$: C, 63.41; H, 9.31; N, 6.16%.)

(3S,5S) - 6 - (1 - *Ethoxyethoxy*) - 5 - (2 - *methoxyethoxymethoxy*) - 3 - *vinylhexanenitrile* (**10**)

To a soln of **9** (2.27 g, 10 mmol) and i-Pr_2NEt (3.9 g, 30 mmol) in dry CH_2Cl_2 (11 ml) was added $CH_3OCH_2CH_2OCH_2Cl$ (1.87 g, 15 mmol) at once and the mixture was stirred at room temp overnight. The mixture was washed with $NaHCO_3$ aq (× 2) and water, dried and concentrated. The residue was chromatographed (SiO_2, 60 g, hexane–EtOAc = 1 : 1 containing 0.5% Et_3N) to give **10** (3.09 g, 98%): R_f 0.36 (hexane–EtOAc = 1 : 1), $[\alpha]_D^{26}$ – 26.4° (*c* 1.0, $CHCl_3$). IR (film), 3090, 2240, 1640, 1450, 1380, 1130, 1120–1080, 1040, 990 (sh), 915 cm^{-1}. NMR, 1.20 (3H, t, J = 7 Hz), 1.31 (3H, d, J = 6 Hz), 1.53–1.90 (2H, m), 2.20–2.95 (3H, m), 3.40 (3H, s), 3.25–4.00 (9H, m), 4.73 (1H, q, J = 6 Hz), 4.80 (2H, m), 5.00–6.20 (3H, m, vinyl protons).

(3S,5S) - 6 - *Hydroxy* - 5 - (2 - *methoxyethoxymethoxy*) - 3 - *vinylhexanenitrile* (**11**)

The ether **10** (2.84 g, 9 mmol) was dissolved in 75% AcOH (14 ml) and stirred at 35° for 30 min. The mixture was poured carefully into cold sat Na_2CO_3 aq and extracted with CH_2Cl_2 (× 5). The extract was washed with $NaHCO_3$ aq and brine, dried and concentrated to give **11** (2.05 g, 94%), analytical sample was obtained by chromatography (hexane–EtOAc = 1 : 2). **11**: R_f 0.13 (hexane–EtOAc = 1 : 1). $[\alpha]_D^{26}$ – 35.5° (*c* 1.1, $CHCl_3$). IR (film), 3450, 3080, 2240, 1635, 1440, 1420, 1380, 1340, 1130, 1120–1080 (br), 1040, 990 (sh), 915 cm^{-1}. NMR, 1.40–1.90 (2H, m), 2.30–2.95 (3H, m), 3.40 (3H, s), 3.10–4.00 (7H, m), 4.86 (2H, m), 5.00–6.20 (3H, m, vinyl protons). (Found: C, 59.38; H, 8.79; N, 5.68. Calc for $C_{12}H_{21}O_4N$: C, 59.24; H, 8.70; N, 5.76%.)

Starting from **6b** (2.27 g, 10 mmol), **11** was obtained in 47% yield through three steps in the same manner as described (*vide supra*). IR and NMR spectra as well as $[\alpha]_D^{26}$ value [– 35.4° (*c* 1.0, $CHCl_3$)] were identical with those of **11** obtained from **6a**.

(3S,5S) - 6 - p - *Toluenesulfonyloxy* - 5 - (2 - *methoxyethoxymethoxy*) - 3 - *vinylhexanenitrile* (**12**)

To a stirred soln of **11** (2.43 g, 10 mmol) in dry pyridine (12 ml) was added *p*-TsCl (2.19 g, 11.5 mmol) at once at – 10° and the mixture was stirred at 0° for 8 hr. The mixture was poured into ice-cold 6N HCl and extracted quickly with CH_2Cl_2 (× 3). The extract was washed with cold water (× 2), $NaHCO_3$ aq (× 2) and brine, dried and concentrated. The residue was chromatographed (SiO_2, 100 g, hexane–EtOAc = 2 : 3) to give **12** (3.3 g, 83%): R_f 0.28 (hexane–EtOAc = 1 : 1). IR (film), 3090, 2240, 1640, 1595, 1450, 1420, 1360, 1240, 1185, 1175, 1090, 1040–1020 (br), 970, 915, 840, 820 cm^{-1}. NMR, 1.40–1.85 (2H, m), 2.45 (3H, s), 2.25–2.95 (3H, m), 3.35 (3H, s), 3.30–3.95 (5H, m), 4.04 (2H, d, J = 4 Hz), 4.68 (2H, br s), 4.90–6.05 (3H, m, vinyl protons), 7.38 (2H, d, J = 9 Hz), 7.81 (2H, d, J = 9 Hz).

(1R,2S,4S) - 4 - (2 - *Methoxyethoxymethoxy*) - 2 - *vinyl* - 1 - *cyclopentanecarbonitrile* (**13a**) *and* (1S,2S,4S) - 4 - (2 - *methoxyethoxymethoxy*) - 2 - *vinyl* - 1 - *cyclopentanecarbonitrile* (**13b**)

To a stirred soln of $NaN(TMS)_2$ (3.22 g, 17.6 mmol) in dry benzene (80 ml) was added a soln of **12** (3.16 g, 8 mmol) in dry benzene (15 ml) in one portion at reflux under N_2 and the mixture was stirred with reflux for 20 min. The mixture was washed with water (× 2), dried and concentrated to give a mixture of **13a** and **13b** (1.82 g). The crude mixture was directly submitted to the next step for the synthesis. In another run, crude product (690 mg) from **12** (1.19 g) was chromatographed (SiO_2, 70 g, hexane–EtOAc = 8 : 1) to give two products (54 mg, 81%).

f-I: **13a** (503 mg, 75%), $[\alpha]_D^{28}$ – 43.6° (*c* 1.0, $CHCl_3$), IR (film), 3090, 2230, 1640, 1445, 1360, 1190, 1100, 1040, 990, 925, 845 cm^{-1}. NMR, 1.20–3.00 (6H, m), 3.40 (3H, s), 3.40–3.83 (4H, m), 4.06–4.55 (1H, m), 4.70 (2H, s), 5.00–6.25 (3H, m, vinyl protons). (Found: C, 64.21; H, 8.63; N, 6.09. Calc for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22%.)

f-II: **13b** (44 mg, 6%), $[\alpha]_D^{28}$ + 55.9° (*c* 1.0, $CHCl_3$). IR (film), 3090, 2225, 1630, 1445, 1365, 1195, 1100, 1040, 990, 920, 845 cm^{-1}. NMR, 1.20–3.25 (6H, m), 3.39 (3H, s), 3.40–3.87 (4H, m), 4.10–4.54 (1H, m), 4.73 (2H, s), 5.00–6.10 (3H, m, vinyl protons). (Found: C, 64.36; H, 8.66; N, 6.12. Calc for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22%.)

Transformation of **13a** *into* (3R,4R)-*dimethoxycarbonylcyclopentanone* (**17**)

Ozone was bubbled into a soln of the **13a** (338 mg, 1.5 mmol) in acetone (17 ml) at – 78° until the color of the

soln turned to pale green. After excess O_3 was flushed with N_2, Jones' reagent (1.5 ml) was added to the resulting ozonide and the mixture was stirred until the temp. was raised to −10°. To this was added MeOH (2 ml) and the mixture was allowed to stand at −10–0° for 20 min. Solvent was removed *in vacuo* and the residue was diluted with water and extracted with ether. The crude extract was treated with excess CH_2N_2. Usual workup gave a crude cyano-methyl ester, which was dissolved in 2% H_2SO_4 in MeOH (15 ml) and refluxed for 60 min. After cooling, the mixture was neutralized with $NaHCO_3$ aq and concentrated *in vacuo*. The residue was dissolved in ether, washed with brine, dried and concentrated to give **15**. IR (film), 3400, 2220, 1720, 1430, 1350 (sh), 1325, 1250, 1200 (br), 1060 (br), 1030, 1000 (sh), 730 cm^{-1}.

The crude **15** in acetone (15 ml) was treated with Jones' reagent (1 ml) at 0° for 10 min and the excess reagent was decomposed with MeOH (2 ml). After removing the solvent, ether was added and the mixture was filtered through celite pad. Ethereal layer was washed with brine, dried and concentrated. The residue was chromatographed (SiO_2, 25 g, hexane–EtOAc = 2 : 1) to give **16** (161 mg). IR (film), 2250, 1755, 1735, 1440, 1410, 1370, 1320, 1260, 1210 (br), 1170, 1140, 1050, 1020, 890, 810 cm^{-1}. NMR, 2.00–2.80 (4H, m), 3.25–3.65 (2H, m), 3.74 (3H, s).

The nitrile, **16** (150 mg) in 5% H_2SO_4 in MeOH (15 ml) was refluxed for 40 hr. The mixture was neutralized with $NaHCO_4$ aq and concentrated *in vacuo*. The residue was dissolved in ether, washed with brine, dried and concentrated. The residual oil was chromatographed (SiO_2, hexane–EtOAc) to give, **17**, (67 mg) and the recovered **16** (89 mg).

Compound **17**. $[\alpha]_D^{21}$ −116.0° (*c* 1.0, $CHCl_3$), CD. maxima in CH_3CN, 313 (−0.90), 303 (−1.81), 294 (−2.02), 285 (−1.97). IR (film), 1750, 1730, 1440, 1405, 1365, 1260, 1205, 1170, 1150, 1130, 1040, 890, 840 cm^{-1}. NMR, 2.35–2.70 (4H, m), 3.25–3.65 (2H, m), 3.85 (6H, s). Lit.[56] $[\alpha]_D$ −119° (*c* 0.55, $CHCl_3$); CD. maxima in CH_3CN, 312 (−0.92), 302 (−1.85), 293 (−2.03), 284 (−1.65), 217 (−0.99).

Methyl (1R,2S,4S) - 4 - (2 - *methoxyethoxymethoxy*) - 2 - *vinyl* - 1 - *cyclopentanecarboxylate* (**14**)

A mixture of 85% KOH (2.08 g, 32 mmol) and the crude mixture of **13a** and **13b** (1.82 g) in water (4 ml) $CH_3OCH_2CH_2OH$ (10 ml) was stirred under reflux for 24 hr. The mixture was diluted with water and extracted with ether. The aqueous layer was acidified with cold 4N HCl (pH 3.5) and extracted with CH_2Cl_2. The extract was washed with brine, dried and concentrated. The residue was dissolved in ether and treated with excess CH_2N_2. The usual workup and chromatography (SiO_2, hexane–EtOAc = 4 : 1) gave **14** (1.59 g, 77%): R_f 0.42 (hexane–EtOAc = 1 : 1), $[\alpha]_D^{25}$ −7.9° (*c* 1.0, $CHCl_3$). IR (film), 3080, 1735, 1640, 1440, 1370, 1260, 1200 (sh), 1160, 1090, 1020, 990 (sh), 915 cm^{-1}. NMR, 1.25–2.95 (6H, m), 3.33 (3H, s), 3.40–3.80 (4H, m), 3.62 (3H, s), 4.00–4.55 (1H, m), 4.67 (2H, s), 4.80–6.10 (3H, m, vinyl protons). (Found: C, 60.61; H, 8.68. Calc for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59%.)

(1R,2S,4S) - 4 - (2 - *Methoxyethoxymethoxy*) - 2 - *vinyl* - 1 - *cyclopentylmethyl benzyl ether* (**20**)

To a stirred suspension of $LiAlH_4$ (247 mg, 6.5 mmol) in dry ether (25 ml) was added dropwise a soln of **14** (1.29 g, 5 mmol) in dry ether (15 ml) at 0° and the mixture was stirred for further 60 min at ambient temp. To this was added water and 10% NaOH aq and white ppt was filtered off. The filtrate was dried and concentrated *in vacuo* to give **19** (1.15 g). IR (film), 3400, 3080, 1635, 1450, 1360, 1280, 1240, 1190, 1100 (br), 1040 (br), 990 (sh), 910, 845 cm^{-1}.

To a stirred suspension of NaH (50%, 360 mg, 7.5 mmol) in dry DMF (12 ml) was added dropwise a soln of crude **19** (1.15 g) in dry DMF (6 ml) and the mixture was stirred for further 15 min. To this was added dropwise benzyl chloride (8885 mg, 7 mmol) at 0° and the mixture was stirred overnight at room temp. The mixture was poured into ice-water and extracted with ether. The extract was washed with brine, dried and concentrated. The residue was chromatographed (SiO_2, 100 g, hexane–EtOAc = 4 : 1) to give **20** (1.53 g, 96%). R_f 0.66 (hexane–EtOAc = 1 : 1), $[\alpha]_D^{29}$ −34.5° (*c* 1.0, $CHCl_3$). IR (film), 3080, 3030, 1635, 1490, 1450, 1360, 1240, 1195, 1100 (br), 1040 (br), 990 (sh), 910, 845, 735, 700 cm^{-1}. NMR, 1.20–2.60 (6H, m), 3.35 (3H, s), 3.10–3.80 (6H, m), 3.96–4.36 (1H, m), 4.47 (2H, s), 4.69 (2H, s), 4.70–4.88 (1H, m), 4.94–5.13 (1H, m), 5.35–6.16 (1H, m), 7.28 (5H, br s). (Found: C, 71.39; H, 8.92. Calc for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81%.)

(1R,2S,4S) - 2 - *Ethynyl* - 4 - (2 - *methoxyethoxymethoxy*) - 1 - *cyclopentylmethyl benzyl ether* (**21**)

A mixture of **20** (960 mg, 3 mmol) and pyridinium bromide perbromide (1.01 g, 3.16 mmol) in $CHCl_3$ (9 ml) was stirred at 0° for 40 min. The mixture was diluted with CH_2Cl_2, washed with $Na_2S_2O_3$ aq, $NaHCO_3$ aq, and brine, dried and concentrated to give a crude dibromide (1.43 g). IR (film), 3030, 1490, 1450, 1430, 1360, 1195, 1100 (br), 1040 (br), 980 (sh), 850, 740, 700 cm^{-1}.

To a soln of $NaNH_2$ (18 mmol) prepared from Na (414 mg, 18 mmol) and $Fe(NO_3)_3$ (catalytic amount) in refluxing ammonia (−80 ml) was added a soln of the crude bromide (1.43 g) in dry THF (15 ml) rapidly and the mixture was stirred for 30 min. To this was added NH_4Cl (5 g) with vigorous stirring and the ammonia was evaporated. The residue was diluted with water and extracted with ether. The extract was washed with brine, dried and concentrated. The residue was chromatographed (SiO_2, 60 g, hexane–EtOAc = 3 : 1) to give **21** (773 mg, 81%). IR (film), 3290, 3060 (sh), 3030, 2120, 1495, 1455, 1365, 1240, 1200, 1100 (br), 1040 (br), 980 (sh), 930 (sh), 845, 740, 700 cm^{-1}. NMR, 1.20–2.95 (6H, m), 2.08 (1H, d, J = 2 Hz), 3.39 (3H, s), 3.37–3.80 (6H, m), 4.07–4.50 (1H, m), 4.56 (2H, s), 4.81 (2H, d), 7.36 (5H, br s).

(S)-(+)-1,4-*Pentanediol* (**24**)

To a stirred suspension of $LiAlH_4$ (6.1 g, 16.1 mmol) in dry THF (100 ml) was added dropwise a soln of (*R*)-**23** (23.0 g, 8.5 mmol), $[\alpha]_D^{27}$ −46.4° (*c* 1.0, $CHCl_3$). M.p. 86–7°: lit.:[15] $[\alpha]_D^{23}$ −46.3° (*c* 1.33, $CHCl_3$). M.p. 85–6°], in dry THF (100 ml) over 60 min below 30°. The mixture was stirred at room temp. for 4 hr. The complex and excess $LiAlH_4$ was decomposed by adding water and 10% NaOH aq carefully below 15°. Solvent was removed and EtOAc (150 ml) was added to the resulting paste with vigorous stirring. The suspension was filtered through a celite pad and the white ppt was washed thoroughly with EtOAc (100 ml). The combined extract was dried and concentrated. The residual oil was distilled under reduced pressure to give **24**. (7.1 g, 77%). B.p. 125–8°/18 mmHg, $[\alpha]_D^{21}$ +13.1° (*c* 1.0, MeOH). [lit.:[17]; (*R*)-isomer, $[\alpha]_D^{20}$ −13.4° (*c* 1.05, MeOH)]. IR (film), 3310, 1440 (br), 1375, 1330 (br), 1190, 1140, 1095, 1060, 1040, 1015, 990, 940, 880, 830 cm^{-1}.

(S)-4-*t*-*Butyldimethylsilyloxy*-1-*trityloxypentane* (**26**)

A mixture of **24** (7.0 g, 6.7 mmol) and trityl chloride (19.5 g, 7.0 mmol) in dry pyridine (50 ml) was stirred at room temp. overnight. The mixture was poured into ice-water and extracted with ether. The extract was washed with $CuSO_4$ aq, water, $NaHCO_3$ aq and brine, dried and concentrated to give crude **25** (23.7 g). IR (film), 3350, 3080 (sh), 3060, 3020, 1595, 1485, 1445, 1370, 1220, 1080 (sh), 1070, 1030, 900, 770 (sh), 760, 745, 705, 695 cm^{-1}.

To a soln of the crude **25** (23.7 g) and immidazole (13.6 g, 20 mmol) in dry DMF (70 ml) was added portionwise t-butylchlorodimethylsilane (12.8 g, 8.0 mmol) at 5–10°. The mixture was stirred at ambient temp. for 16 hr. The mixture was poured into water and extracted with ether. The extract was washed with water, dried and concentrated. The residue was chromatographed (SiO_2, 200 g, hexane–EtOAc = 9 : 1) to give **26** (27.2 g, 87%). R_f 0.83 (hexane–EtOAc = 1 : 1), $[\alpha]_D^{20}$ +6.2° (*c* 1.0, EtOH). IR (film), 3090 (sh), 3050, 3020, 1595, 1490, 1470, 1460, 1445, 1370, 1250, 1210, 1060 (br),

1000, 835, 805, 770, 760 (sh), 740, 705, 695 (sh) cm^{-1}. NMR, 0.03 (6H, s), 0.86 (9H, s), 1.12 (3H, d, J = 6 Hz), 1.40–1.95 (4H, m), 3.06 (2H, br t), 3.45–4.15 (1H, m), 7.10–7.70 (15H, m). MS, *m/z*, 470 (M^+), 412, 393, 383, 321, 281, 207 (100), 167, 133, 102, 96, 91, 73.

(S)-4-t-Butyldimethylsilyloxy-1-pentanol (**27**)

To a soln of **26** (26.8 g, 58.3 mmol) in dry THF (80 ml) and liquid ammonia (200 ml) was added portionwise Na (4.0 g, 175 mmol) at −30 to −35° over 30 min and the mixture was stirred for further 60 min. To this was added portionwise NH_4Cl (10 g) and ammonia was evaporated. The residue was diluted with water and extracted with ether. The extract was washed with brine, dried and concentrated. The residue was chromatographed (SiO_2, 100 g, hexane–EtOAc = 2 : 1) to give **27** (11.0 g, 85%). R_f 0.51 (hexane–EtOAc = 1 : 1), $[\alpha]_D^{20}$ + 11.3° (*c* 1.1, EtOH). IR (film), 3310, 1460, 1370, 1255, 1130, 1090, 1050 (br), 1000, 935, 870, 835, 775 cm^{-1}. NMR, 0.06 (6H, s), 0.90 (9H, s), 1.29 (3H, d, J = 6 Hz), 1.45–1.83 (4H, m), 2.20 (1H, s, –OH), 3.50–4.15 (3H, m).

(S)-(+)-5-Iodo-2-t-butyldimethylsilyloxypentane (**29**)

To a soln of **28** (10.1 g, 46.3 mmol) in dry pyridine (40 ml) was added *p*-TsCl (9.7 g, 51.1 mmol) at 0–5° and the mixture was stirred at 0° for further 8 hr. The mixture was poured into ice-water and extracted with ether. The extract was washed with $CuSO_4$ aq, water, $NaHCO_3$ aq and brine, dried and concentrated to give a tosylate **28** (17 g). NMR, 0.13 (6H, s), 0.98 (9H, s), 1.22 (3H, d, J = 6 Hz), 1.40–2.05 (4H, m), 2.56 (3H, s), 3.70–4.20 (1H, m), 4.16 (2H, t, J = 6 Hz), 7.37 (2H, d, J = 8 Hz), 7.81 (2H, d, J = 8 Hz).

A mixture of **28**, NaI (17.5 g, 115.7 mmol) and $NaHCO_3$ (6.8 g) in acetone (250 ml) was stirred vigorously under reflux for 40 hr. Solvent was removed *in vacuo*. The residue was diluted with cold water and extracted with ether. The extract was washed with $Na_2S_2O_3$ aq, $NaHCO_3$ aq and brine, dried and concentrated. The residue was distilled under reduced pressure to give **29** (10.9 g, 74%). B.p. 79–80°/2 mmHg. $[\alpha]_D^{21}$ + 14.3° (*c* 1.0, EtOH). IR (film), 1470, 1455, 1440, 1370, 1360, 1250, 1225, 1170, 1125, 1080, 1040, 1000, 990, 935, 900, 880, 830, 800, 770, 700 cm^{-1}. NMR, 0.05 (6H, s), 0.88 (9H, s), 1.15 (3H, d, J = 6 Hz), 1.33–3.37 (4H, m), 3.20 (2H, t, J = 7 Hz), 3.83 (1H, sextet, J = 6 Hz). MS, *m/z*, 328 (M^+), 313, 271 (100), 230, 229, 215, 185, 159, 143, 129, 115, 101, 87, 75, 73, 69, 59. (Found: C, 40.22; H, 7.64; I, 38.71. Calc. for $C_{11}H_{25}IOSi$ C, 40.24; H, 7.67; I, 38.65%.)

(1R,2S,4S)-2-[(6S)-t-Butyldimethylsilyloxy-1-heptynyl]-4-(2-methoxyethoxymethoxy)-1-cyclopentylmethyl benzyl ether (**22**)

To a stirred soln of **21** (763 mg, 2.4 mmol) in dry THF (9.6 ml) was added dropwise 1.52 N soln of n-BuLi in hexane (1.9 ml, 2.89 mmol) over 10 min at 0° and the mixture was stirred for 5 min. To this was added dropwise a soln of **29** (945 mg, 2.88 mmol) in dry HMPA (16.5 ml) over 10 min at 0° and the mixture was stirred at ambient temp. for 60 min. The mixture was poured into cold water and extracted with ether. The extract was washed with water and brine, dried and concentrated. The residue was chromatographed (SiO_2, 120 g, hexane–EtOAc = 3 : 1) to give **22** (914 mg, 82% based on consumed **21**) and **21** (92 mg). **22**: $[\alpha]_D^{23}$ + 5.4° (*c* 0.09, EtOH), IR (film), 3080 (sh), 3030, 1470, 1460, 1450, 1365, 1250, 1140, 1090 (br), 1040 (br), 1010 (sh), 920, 840, 810, 780, 740, 700 cm^{-1}. NMR, 0.03 (6H, s), 0.87 (9H, s), 1.12 (3H, d, J = 6 Hz), 1.30–2.90 (12H, m), 3.40 (3H, s), 3.30–3.90 (7H, m), 4.04–4.43 (1H, m), 4.54 (2H, s), 4.70 (2H, br d), 7.34 (5H, br s).

(1R,2S,4S)-2-[(6S,1E)-6-t-Butyldimethylsilyloxy-1-heptenyl]-4-(2-methoxyethoxymethoxy)-1-cyclopentylmethanol (**30**)

To a stirred soln of **22** (898 mg, 1.7 mmol) in dry THF (25 ml) and liquid ammonia (100 ml) was added portionwise Na (469 mg, 20.4 mmol) and the soln was stirred for further 60 min. To this was added NH_4Cl (900 mg) and the ammonia was evaporated off. The residue was diluted with water and extracted with ether. The extract was washed with brine, dried and concentrated. The residue was chromatographed (SiO_2, 70 g, hexane–EtOAc = 1 : 1) to give **30** (588 mg, 79%). R_f 0.37 (hexane–EtOAc = 1 : 1). $[\alpha]_D^{24}$ + 12.7° (*c* 1.0, MeOH), IR (film), 3420, 1465 (sh), 1455, 1365, 1250, 1195, 1130, 1090, 1040, 1000 (sh), 960, 930 (sh), 835, 800, 770, 740 cm^{-1}. NMR, 0.03 (6H, s), 0.88 (9H, s), 1.13 (3H, d, J = 6 Hz), 1.25–2.55 (12H, m), 2.30 (1H, br s, –OH), 3.40 (3H, s), 3.25–4.00 (7H, m), 4.05–4.45 (1H, m), 4.73 (2H, s), 5.23–5.63 (2H, m). MS, *m/z*, 429 (M^+-1), 356, 342, 297, 281, 267, 237, 211, 207, 185, 175, 171, 159, 133, 119, 105, 97, 95, 91, 89, 82, 75, 67, 59, 58, 43, 40 (100). (Found: C, 64.48; H, 10.79. Calc for $C_{23}H_{46}O_5Si$: C, 64.14; H, 10.76%.)

(1R,2S,4S)-2-[(6S,1E)-6-t-Butyldimethylsilyloxy-1-heptenyl]-4-(2-methoxyethoxymethoxy)-1-cyclopentanecarboxaldehyde (**31**)

To a stirred mixture of PCC (pyridinium chlorochromate, 440 mg, 2.0 mmol) and NaOAc (49 mg, 0.6 mmol) in dry CH_2Cl_2 (25 ml) was added at once a soln of **30** (440 mg, 1 mmol) in dry CH_2Cl_2 (25 ml) and the mixture was stirred for 2.5 hr at room temp. To this was added ether (100 ml) with vigorous shaking and the ppt was filtered through florisil pad and washed with ether. The combined filtrate was concentrated *in vacuo* and the residue was dissolved in ether. The mixture was filtered again through florisil pad and the filtrate was concentrated *in vacuo* to give **31** (431 mg) which was used for the next step without further purification. R_f 0.81 (hexane–EtOAc = 1 : 1). IR (film), 2730, 1725, 1460, 1370, 1255, 1160 (sh), 1130 (sh), 1095 (br), 1040 (br), 970 (sh), 835, 805, 775, 730 cm^{-1}.

Methyl 4-[(1R,2S,4S)-2-[(6S,1E)-6-t-butyldimethylsilyloxy-1-heptenyl]-4-(1-methoxyethoxymethoxy)-1-cyclopentyl]-4(R,S)-hydroxy-(2E)-butenoate (**33**)

To a soln of **31** (431 mg) and methyl β-nitropropionate (266 mg, 2 mmol) in dry DMSO (7.5 ml) was added diisopropylamine (253 mg, 2.5 mmol) and the mixture was stirred at room temp. overnight. The mixture was poured into water and extracted with ether. The extract was washed with water and brine, dried and concentrated *in vacuo* to give **32** (570 mg). IR (film), 3450, 1740, 1555, 1460 (sh), 1440, 1370, 1360 (sh), 1255, 1200, 1170, 1130, 1090 (br), 1040 (br), 990 (sh), 835, 810, 775 cm^{-1}.

A mixture of **32** and pyrrolidine (178 mg, 2.5 mmol) in dry HMPA (7 ml) was stirred at room temp. overnight. The mixture was poured into water and extracted with ether. The extract was washed with water, dried and concentrated *in vacuo*. The residue was chromatographed (SiO_2, 50 g, hexane–EtOAc = 1 : 1) to give **33** (289 mg, 54%) as a diastereomeric mixture (*ca* 3/2). $[\alpha]_D^{24}$ + 13.4° (*c* 0.65, MeOH), IR (film), 3400, 3010, 1715, 1645, 1465, 1455, 1430, 1365, 1360, 1300 (sh), 1275 (sh), 1245, 1210, 1190, 1160, 1130, 1090, 1040 (br), 975, 930 (sh), 835, 905, 750 cm^{-1}. NMR (100 MHz), 0.04 (6H, s), 0.88 (9H, s), 1.11 (2H, d, J = 6 Hz), 1.25–2.55 (13H, m), 3.40 (3H, s), 3.45–3.95 (5H, m), 3.76 (3H, s), 4.05–4.55 (2H, m), 4.72 (2H, m), 5.20–5.50 (2H, m), 6.65 and 6.11 (total 1H, each d–d, J = 2 and 16 Hz), 6.90 and 6.94 (total 1H, each d–d, J = 4 and 16 Hz).

Methyl 4-[(1R,2S,4S)-2[(6S,2E)-6-t-butyldimethylsilyloxy-1-heptenyl]-4-(1-methoxyethoxymethoxy)-1-cyclopentyl]-4(R,S)-tetrahydropyranyloxy-(2E)-butenoate (**34**)

To a soln of **33** (262 mg, 0.5 mmol) and dihydropyran (84 mg, 1 mmol) in dry CH_2Cl_2 (5 ml) was added PPTS (63 mg, 0.2 mmol) and the mixture was stirred at room temp. overnight. The mixture was washed with water, dried and concentrated. The residue was chromatographed (SiO_2,

25 g, hexane–EtOAc = 1 : 1) to give **34** (294 mg, 97%). R_f 0.53 (hexane–EtOAc = 1 : 1). $[\alpha]_D^{24}$ + 4.3° (*c* 0.9, $CHCl_3$). IR (film), 3030, 1720, 1655, 1460, 1370, 1250, 1200, 1130 (br), 1070, 1030 (br), 980, 840, 810, 770 cm^{-1}. NMR (100 MHz), 0.04 (6H, s), 0.88 (9H, s), 1.11 (3H, d, J = 6 Hz, 1.20–2.30 (18H, m), 3.39 (3H, s), 3.35–4.00 (7H, m), 3.73 (3H, s), 4.05–4.40 (2H, m), 4.45–4.65 (1H, m), 4.70 (2H, br s), 5.05–5.55 (2H, m), 5.91 and 6.03 (total 1H, each br d, J = 16 Hz), 6.79 and 6.94 (total 1H, each d–d, J = 6 and 16 Hz). (Found: C, 64.43; H, 9.84. Calc for $C_{32}H_{58}O_8Si$. C, 64.18; H, 9.76%.)

4 - [(1R,2S,4S) - 2[(6S,1E) - 6 - *Hydroxy* - 1 - *heptenyl*] - 4 - (2 - *methoxyethoxymethoxy*) - 1 - *cyclopentyl*] - 4(R,S)-*tetrahydropyranyloxy* - (2E) - *butenoic acid* (**36**).

A soln of **34** (260 mg, 0.43 mmol) in 0.13N LiOH in 75% MeOH aq (7.3 ml, 0.94 mmol) was stirred at 50° for 18 hr. The mixture was poured into water and extracted once with ether. The aqueous phase was acidified (pH 3.5) with 2N H_3PO_4 and extracted with ether. The extract was washed with brine, dried and concentrated to give **35** (248 mg, 98%), IR (film), 3600–2300 (br), 1715–1695, 1655, 1460, 1440, 1370, 1255, 1200, 1130 (br), 1070, 1030 (br), 980, 870, 835, 810, 775 cm^{-1}.

A mixture of **35** (248 mg) and n-Bu_4NF (561 mg, 2.15 mmol) in dry THF (5 ml) was stirred at room temp. for 5 hr. The mixture was poured into cold water and pH was adjusted to 3.5 with 2N H_3PO_4. The mixture was extracted with ether (× 5) and the extract was washed with brine, dried and concentrated to give **36** (182 mg, 93%), which was dried completely in vacuum desiccator and used for the cyclization. IR (film), 3350, 3500–2300 (br), 1705, 1655, 1450, 1370, 1255, 1200, 1120 (br), 1075, 1030 (br), 980, 930 (sh), 870, 850, 815, 740 cm^{-1}.

(1RS,2E,6S,10E,11aS,13S,14aR) - 1,6,7,8,9,11a,12,13,14,14a - *Decahydro* - 1 - *tetrahydropyranyloxy* - 13 - (2 - *methoxyethoxymethoxy*) - 6 - *methyl* - 4H - *cyclopent*[*f*] - *oxacyclotridecin* - 4 - *one* (**37**)

A mixture of **36** (115.5 mg, 0.25 mmol), triphenylphosphine (105 mg, 0.4 mmol) and dipryidyl disulfide (80 mg, 0.4 ml) in dry xylene (2 ml) was stirred under N_2 at room temp. overnight. The resulting pyridinethiol ester was diluted with dry xylene (20 ml) and added slowly through a motor driven syringe to the refluxing xylene (110 ml) with stirring over 10 hr under N_2. After the addition was complete, the mixture was stirred for further 1 hr and cooled. The mixture was filtered through a celite pad and the filtrate was concentrated *in vacuo*. The residue was chromatographed (SiO_2, 15 g, hexane–EtOAc = 2 : 3) to give **37** (52.6 mg, 47%). $[\alpha]_D^{21}$ + 8.4° (*c* 0.38, EtOH). IR (film), 1715, 1665, 1450, 1380, 1350, 1255, 1195, 1150 (sh), 1120, 1075, 1035, 1020, 1000, 980, 900, 870, 840, 815 cm^{-1}. NMR, 1.25 (3H, d, J = 6 Hz), 1.35–2.55 (18H, m), 3.38 (3H, s), 3.30–4.30 (8H, m), 4.55–4.95 (2H, m), 4.70 (2H, s), 5.05–5.40 (1H, m), 5.45–6.15 (2H, m), 6.95–7.25 (1H, m).

(2E,6S,10E,11aS,13S,14aR) - 7,8,9,11a,12,13,14,14a - *Octahydro* - 13 - (2 - *methoxyethoxymethoxy*) - 6 - *methyl* - 6H - *cyclopent*[*f*]*oxacyclotridecin* - 1,4 - *dione* (**39**)

A soln of **37** (45.2 mg, 0.10 mmol) in a mixture of AcOH–THF–H_2O (3 : 3 : 1, 2.2 ml) was stirred at 50° for 4 hr. The mixture was poured into cold $NaHCO_3$ aq and extracted with CH_2Cl_2. The extract was washed with $NaHCO_3$ aq and brine, dried and concentrated to give a crude **38** (35 mg). IR (film), 3450, 1705, 1640, 1445, 1350, 1245, 1190, 1150 (sh), 1100 (br), 1050 (br), 980, 925, 840 cm^{-1}.

To a mixture of PCC (57.2 mg, 0.26 mmol) and NaOAc (6.6 mg, 0.08 mmol) in CH_2Cl_2 (4 ml) was added a soln of **38** (35 mg) in CH_2Cl_2 (2 ml) and the mixture was stirred for 4 hr at room temp. The mixture was diluted with ether (40 ml) and filtered through a florisil pad. The ppt was washed with ether and the combined filtrate was concentrated *in vacuo*. The residue was chromatographed (SiO_2, 4 g, hexane–EtOAc = 1 : 2) to give **39** (24.1 mg, 66%). $[\alpha]_D^{21}$ − 15.1° (*c* 0.31, EtOH). IR (film), 1720, 1690, 1625, 1445, 1350, 1250, 1190 (sh), 1165, 1120, 1080 (br), 1040, 1000 (sh), 970, 840 (br) cm^{-1}. NMR, (100 MHz), 1.31 (3H, d, J = 6 Hz), 2.30–2.40 (11H, m), 2.45–3.00 (1H, m), 3.36 (3H, s), 3.40–3.80 (4H, m), 4.00–4.30 (1H, m), 4.70 (2H, s), 4.50–4.85 (1H, m), 5.20–6.00 (2H, m), 6.42 (1H, d, J = 16 Hz), 7.73 (1H, d, J = 16 Hz). UV, λ_{max}^{EtOH} 220 nm (log ϵ = 3.67). (Found: C, 65.94; H, 8.33. Calc for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25%.)

(1R,2E,6S,10E,11aS,13S,14aR) - 1,6,7,8,9,11a,12,13,14,14a - *Decahydro* - 1 - *hydroxy* - 13 - (2 - *methoxyethoxymethoxy*) - 6 - *methyl* - 4H - *cyclopent*[*f*]*oxacyclotridecin* - 4 - *one*[(+) - *Brefeldin A* 7 - *methoxyethoxymethyl ether*] (**40**)

To a stirred soln of **39** (13.0 mg, 0.036 mmol) in dry MeOH (1 ml) was added $NaBH_4$ (4 mg, 0.108 mmol) at − 75° and the mixture was stirred for 90 min. Acetone (0.2 ml) was added and the mixture was allowed to warm up to 0°. The mixture was diluted with CH_2Cl_2, washed with water and brine, dried and concentrated. The residue was chromatographed (SiO_2, 2 g, hexane–EtOAc = 2 : 1) to give **40** (11.9 mg, 91%). $[\alpha]_D^{20}$ + 51.5° (*c* 0.27, EtOH). IR (film), 3430, 1705, 1638, 1445, 1350, 1280 (sh), 1245, 1190, 1150 (sh), 1105 (br), 1040 (br), 1000 (sh), 975, 915, 840, 750, 735 cm^{-1}. NMR (100 MHz), 1.25 (3H, d, J = 6 Hz), 1.35–2.45 (12H, m), 3.38 (3H, s), 3.45–3.80 (4H, m), 3.85–4.30 (2H, m), 4.72 (2H, s), 4.70–5.00 (1H, m), 5.24 (1H, d–d, J = 9.0 and 15.0 Hz), 5.68 (1H, d–d–d, J = 5.0, 15.0 Hz), 5.89 (1H, d–d, J = 2.0 and 16.0 Hz), 7.32 (1H, d–d, J = 3.5 and 16.0 Hz).

(1R,2E,6S,10E,11aS,13S,14aR) - 1,6,7,8,9,11a,12,13,14,14a,- *Decahydro* - 1,13 - *dihydroxy* - 6 - *methyl* - 4H - *cyclopent*[*f*]*oxacyclotridecin* - 4 - *one* [(+) - *Brefeldin A*] (**1**)

A mixture of **40** (10 mg, 0.027 mmol) and $TiCl_4$ (13 mg, 0.068 mmol) in dry CH_2Cl_2 (1 ml) was stirred at 0° for 15 min. The mixture was poured into $NaHCO_3$ aq and extracted with EtOAc. The extract was washed with $NaHCO_3$ aq and brine, dried and concentrated. The residue was triturated with ether–CH_2Cl_2 to give **1** (4.2 mg) and oily residue was chromatographed (SiO_2, 2 g, hexane–EtOAc = 1 : 4) gave further **1** (1.2 mg) and **40** (1.0 mg) (79% total yield). Recrystallization from EtOAc gave analytically pure (+)-Brefeldin A (2.9 mg). M.p. 203–4°. $[\alpha]_D^{22}$ + 92.2° (*c* 0.12, MeOH). [authentic sample; m.p. 204–5°. $[\alpha]_D^{22}$ + 92.9° (*c* 0.51, MeOH)]. IR (KBr), 3360, 1710, 1640, 1445, 1350, 1285, 1250, 1115, 1105, 1075, 1000, 980, 970, 860, 850, 835 cm^{-1}. NMR (100 MHz, DMSO-d_6, $CDCl_3$), 1.22 (3H, d, J = 6.5 Hz), 1.30–2.40 (12H, m), 3.85–4.35 (center at 4.00 and 4.17, 2H, m), 4.52–5.00 (1H, m), 5.28 (1H, d–d, J = 9.0 and 15.0 Hz), 5.68 (1H, d–d–d, J = 5.0, 8.8 and 15.0 Hz), 5.83 (1H, d–d, J = 2.0 and 15.7 Hz), 7.36 (1H, d–d, J = 3.3 and 15.7 Hz).

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