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TOTAL SYNTHESIS OF N-PHTHALOYL ADDA METHYL ESTER : ALL STEREOCENTERS ORIGINATING FROM A SINGLE CHIRAL EPOXYALCOHOL

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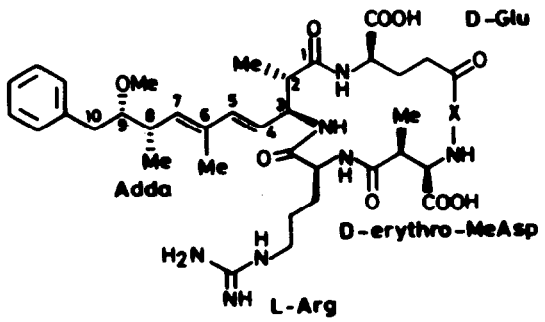
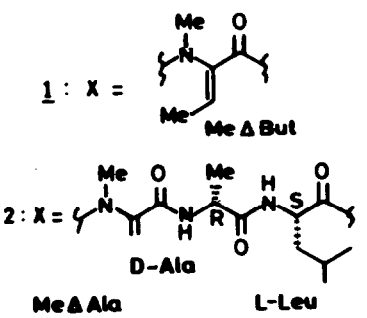
Abstract: Selective ring opening of (2S,3R)-epoxide of 4-benzyloxy-cis-2-buten-1-ol either at 2- or 3-position ensures stereospecific construction of all the chiral centers of Adda.

A unique C_{20} amino acid (2S, 3S, 8S, 9S)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-decadienoic acid (Adda)[1] is present in many closely related toxins produced by cyanobacteria. For example, both nodularin (1), a cyclic pentapeptide from Nodularia spumigena and microcystin-LR (2), a cyclic heptapeptide from Microcystis aeruginosa owe their hepatotoxicity to this characteristic β-aminoacid. Recently stereochemistry of Adda and structural assignment of nodularin were published[1].





The presence of four chiral centers in Adda makes the total synthesis of this unique β-aminoacid a challenging task[2]. Only an efficient synthesis of this aminoacid in multigram quantity will enable one to attempt the synthesis of parent hepatotoxins. Herein we report a short and practical total synthesis of N-phthaloyl Adda methyl ester. A close look at the retrosynthetic analysis of this compound reveals that the route persued by us mainly focuses on the variation of reaction conditions in the ring opening of chiral 2,3-epoxyalcohol (3)[3]. This common starting material gave an easy access to all the stereocenters of Adda. While opening at 2-position with Me_2CuLi establishes syn-relationship between C-2 and C-3 of Adda, a prerequisite for their final anti-relationship achieved by Mitsunobu inversion[4], opening at 3-position will straightway fix the required syn-relationship between C-8 and C-9.

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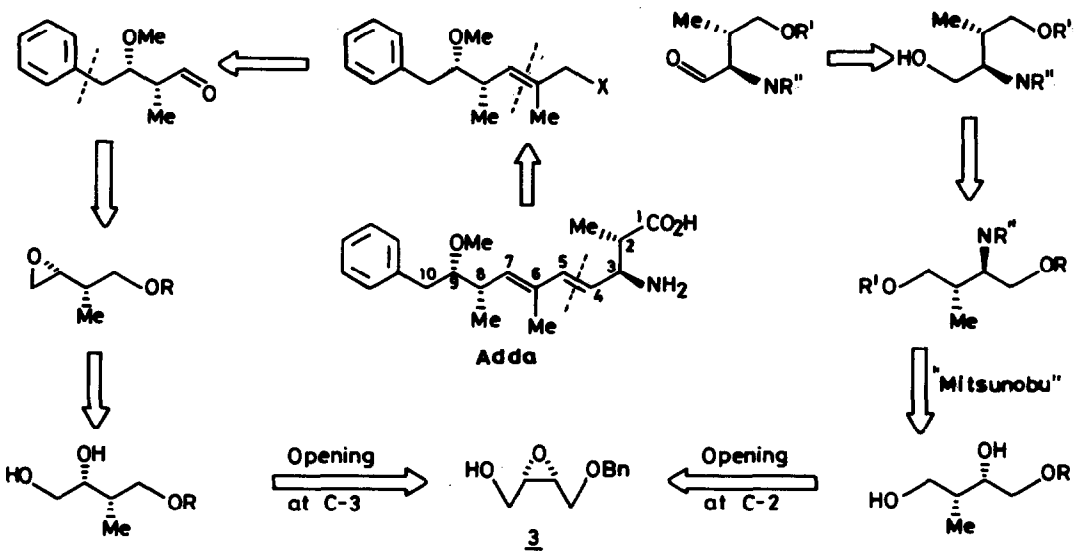
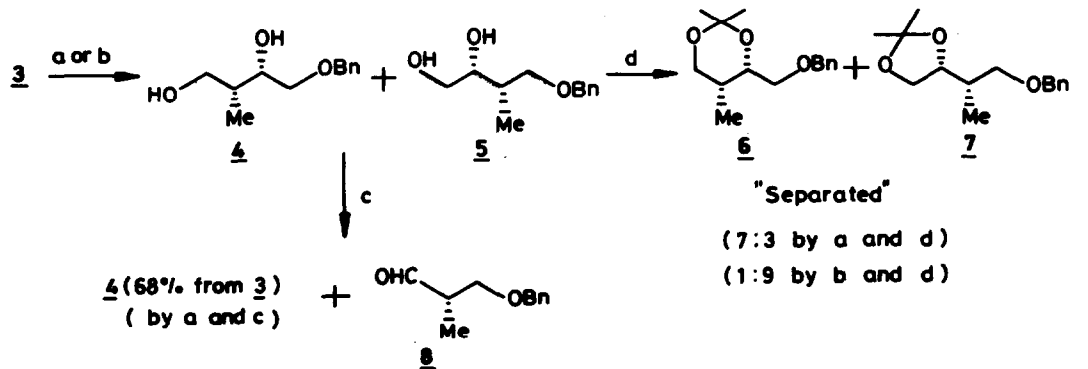
Retrosynthesis of Adda



R , R', R" = Protective groups ; X = halogen

Treatment of 3 with Me_2CuLi in ether at -40°C gave 1,3-diol 4 as the major product (4:5=7:3)[5,6] (scheme I). Oxidative cleavage of 1,2-diol 5 with $NaIO_4$ in $THF:H_2O$ (4:1) allowed an easy chromatographic separation of 1,3-diol. Conversion into acetonides with 2,2-dimethoxypropane and p-toluenesulfonic acid (PTSA, catalytic) also made possible a quick separation of

Scheme - I



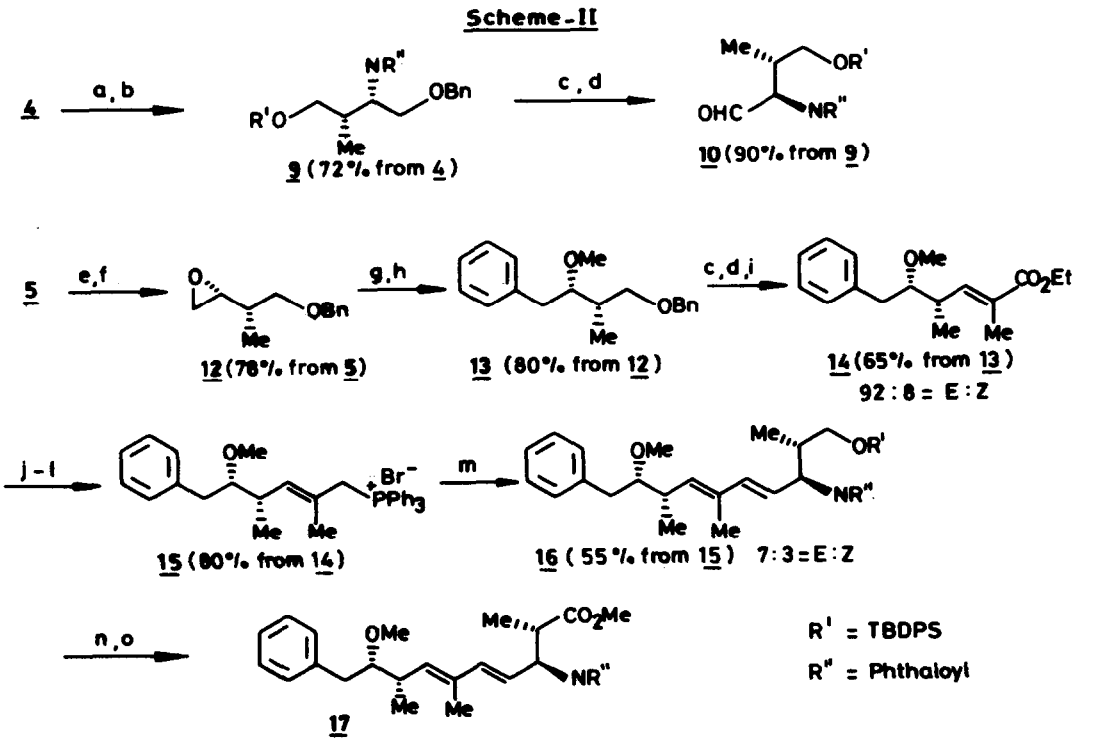
6 —e→ 4 (63% from 3 after a,d and e)

7 —e→ 5 (86% from 3 after b,d and e)

a) Me_2CuLi(4 eq), Et_2O,-40°C, 4 h; b) Me_3Al(4 eq), $C_5H_{12}:CH_2Cl_2$(9:1), 0°C-- r.t, 24 h; c) $NaIO_4$ (2 eq), $THF:H_2O$(4:1), r.t., 4 h; d) $Me_2C(OMe)_2$, PTSA(Cat.), 0°C, r.t., 4 h; e) Et_2O, HCl (1 drop), 0°C, 2 h.

the regioisomers by silica gel column chromatography. Compounds **4**[7] and **5**[7] were then regenerated from their respective acetonides by mild acid treatment. In an alternate way larger amount of 1,2-diol **5** was obtained by treating epoxyalcohol **3** with trimethyaluminium (Me_3Al)[8] at room temperature in C_5H_{12}:CH_2Cl_2 (9:1). This favoured opening at 3-position (4:5=9:1)[5] and here again products were separated in their acetonide stage.

Scheme-II



a) t-$BuPh_2SiCl$(1 eq), imidazole(2.5 eq), DMF, r.t., 5 h; b) Phthalimide(1.1 eq), DEAD(1.1 eq), Ph_3P(1.1 eq), THF, 0°C, r.t., 12 h; c) Pd/C, H_2, EtOH, r.t., 8 h; d) $(COCl)_2$,DMSO,Et_3N,CH_2Cl_2, -78°C, 1h; e) TsCl(1 eq),Py,-20°C, 24 h; f) MeONa,MeOH, r.t., 2 h; g) PhMgBr(3 eq), CuI(0.05 eq), Et_2O, 0°C, 2 h; h) NaH(1.1 eq), MeI(1.1 eq), THF, 0°C, 3 h; i) $Ph_3P{=}C(CH_3)CO_2Et$,C_6H_6, reflux, 4 h; j) DIBAL-H(3 eq), CH_2Cl_2,-78°C, 30 min; k) CBr_4 (2.2 eq), PPh_3 (2 eq), CH_2Cl_2, r.t., 4 h; l) PPh_3 (1.2 eq), CH_3CN, reflux, 24 h; m) **15**, n-BuLi, 0°C, 30 min, then add **10**; n) HF-Py, THF, r.t., 12 h; o) Jones' oxidation followed by CH_2N_2.

Having constructed the stereocenters the next step was to carry out necessary functional group manipulations to build up the target molecule. Selective protection of primary hydroxyl group of **4** as t-butyldiphenylsilyl ether (TBDPS) followed by Mitsunobu inversion of the secondary one with phthalimide, DEAD and Ph_3P[4] gave **9**[7] (scheme II). Swern oxidation of the debenzylated alcohol provided C-1 to C-4 segment of Adda **10**[7].

For the other half **5** was first converted into terminal epoxide **12** which on opening with PhMgBr and subsequent methylation gave **13**[7]. Oxidation of the debenzylated product followed by olefination led to E-α,β-unsaturated ester **14**[7,9] (8% Z- product was also formed which was

separated after the next step). DIBAL-H reduction gave alcohol which was brominated with CBr_4 and Ph_3P. The bromide was then converted to phosphonium salt **15**. Ylid from **15** was reacted with aldehyde **10**. As expected major product was E- isomer **16** which was separated easily from the Z- isomer after the next step by silica gel column chromatography. Finally desilylated primary hydroxyl group on oxidation followed by treatment with CH_2N_2 gave methyl ester of N-phthaloyl Adda **17**[10]. In conclusion, a common chiral epoxy alcohol laid the foundation of all the stereocenters of Adda showing the versatility of this synthon[11].

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4. O. Mitsunobu, M. Wada and T. Sano, J. Am. Chem. Soc., **94**, 679 (1972).
5. Ratio was determined in their acetonide stage from isolated yields.
6. Though much better ratio (4:5=9:1) was observed at even lower temperature (-110°C), the reaction was extremely slow and far from complete even after prolonged reaction time.
7. Satisfactory NMR, Mass and IR spectra were obtained for this compound.
8. K. Mori and Y-B. Seu, Tetrahedron, **44**, 1035 (1988).
9. Ratio of E:Z isomers was determined by HPLC and NMR; see also reference 2.
10. IR(thin film): 1730 (methyl ester), 1705 (phthaloyl) cm^{-1}. $[\alpha]_D$-90.1 (c 1.0, $CHCl_3$). MS(CI, MeOH): m/z 476 (M+1). ^1H NMR($CDCl_3$): δ7.6-7.87 (m, 4H, phthaloyl), 7.21 (s, 5H, phenyl), 6.34 (d, $J_{4,5}$= 15.2 Hz, 1H, H-5), 5.89 (dd, $J_{4,5}$=15.2 Hz, $J_{3,4}$=8.8 Hz, 1H, H-4), 5.42 (broad d, $J_{7,8}$=10.2 Hz, 1H, H-7), 4.86 (dd, $J_{3,2}$=10.8 Hz, $J_{3,4}$=8.8 Hz, 1H, H-3), 3.51 (s, 3H, $COOCH_3$), 3.48 (m, 1H, H-9), 3.24 (s, 3H, OCH_3), 3.27-3.15, 2.77-2.65 (m, 4H, H-10, H-8, H-2), 1.63 (d, J=1.1 Hz, 3H, C_6-CH_3), 1.23 (d, J=7.1 Hz, 3H, CH_3), 0.98 (d, J=7.3 Hz, 3H, CH_3).
11. The same epoxyalcohol **3** is also precursor for the other "unnatural" amino acid, D-erythro-MeAsp of nodularin, a finding which will be reported separately.

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