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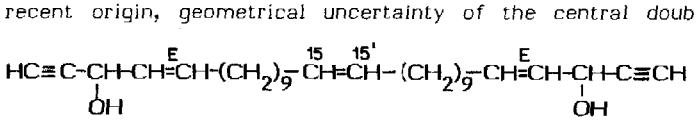
SYNTHESIS OF (±)DURYNE+

V.H. Deshpande*, B.K. Upadhye and R.D. Wakharkar
National Chemical Laboratory, Pune 411 008, India

Summary: Synthesis of cytotoxic metabolite, duryne (1), involving symmetrical synthetic strategy is described.

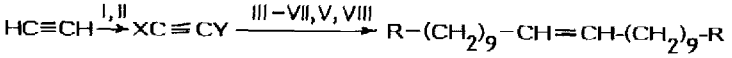
There has been considerable growth in the newly discovered biologically active marine natural products in the last decade[1]. Recently, Wright et al.[2] reported the isolation of duryne (I) from marine sponge Cribrochalina dura which inhibits the growth of a number of in vitro tumour cell lines. The structure of duryne was established on the basis of spectroscopic analysis as a symmetrical C_{30} diol, consisting of two terminal acetylenic groups,two asymmetric centres and three olefinic bonds. Although the geometry of two double bonds at C^4 and $C^{4'}$, is E, the geometry of central double bond (-HC^{15}=$CH^{15'}$-) and absolute configuration remain to be established. Prompted by its symmetry, recent origin, geometrical uncertainty of the central double bond, biological



I

activity and scarce availability via a tedious process of extraction from marine sources, we initiated a research programme which secures an expeditious entry into duryne frame. Based on the use of dialkylated acetylene to obtain both isomers E and Z of C^{15}-$C^{15'}$ double bond, herein we report the first synthesis of **Ia** and **Ib** having E and Z geometry of the central C^{15}-$C^{15'}$ double bond respectively (Scheme-I).

SCHEME - I



3: X=H, Y=$(CH_2)_{10}$-OTHP 5: R=CH_2OTHP

4: X=Y=$(CH_2)_{10}$-OTHP 6: R=CH_2OH

7: R=CHO

8: R=HC=CH-COOEt (E)

9: R=HC=CH-CH_2OH

10: R=HC=CH-CHO

1: R=HC=CH-CH(OH)-C≡CH

a = E isomer b = Z isomer

Reagents:

i. n-BuLi, $Br(CH_2)_{10}$-OTHP(2), THF, HMPA;
ii. n-BuLi, 2, HMPA;
iiia. LAH, Diglyme, 140°
iiib. Pd/$CaCO_3$, H_2,Quinoline (cat.);
iv. MeOH, conc. HCl (cat.);
v. PCC, CH_2Cl_2;
vi. Ph_3P = CHCOOEt, Benzene;
vii. DIBAL-H, Toluene, -78°C;
viii. HC≡CMgBr, THF

1,10-Decanediol was monobrominated[3] with aq. HBr (48%) followed by protection of hydroxyl group as THP-ether [DHP, conc.HCl (cat.)] to give THP-ether of 10-bromodecanol 2 (76%). Lithium acetylide[4] (prepared from acetylene and n-BuLi in THF at 0°C) was alkylated with 2 in HMPA

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to obtain monoalkylated acetylene **3**[5] in 90% yield. It was again alkylated[6] with **2** using n-BuLi in HMPA to give dialkylated acetylene derivative **4**[7] (60%) which was partially reduced[8] (LAH in diglyme, 140°C, 48 h) to obtain E olefin **5a** (80%). The dialkylated acetylene derivative **4** was partially reduced[9] [10% Pd on $CaCO_3$ in n-hexane, H_2, quinoline (cat.)] to obtain Z olefin **5b** (95%). The diols **6a** (m.p. 78-79°C) and **6b** (m.p. 61-62°C) readily prepared in 98 and 96% yield respectively by deprotection of **5a** and **5b** [MeOH, conc.HCl (cat.)], were oxidised[10] (PCC, CH_2Cl_2, 3 h) to dialdehyde **7a** (60%, m.p. 55-56°C) and **7b** (60%, m.p. 30-31°C) respectively. Subsequent Wittig olefination[11] of **7a** and **7b** with triphenylcarbethoxymethylene phosphorane in refluxing benzene (20 h) furnished E olefinic diester **8a** (98%) and **8b** (99%) respectively. The diesters **8a** and **8b** on reduction[12] (DIBAL-H in toluene, -78°C) gave diols **9a** (m.p. 61-62°C, 96%) and **9b** (m.p. 52-54°C, 94%) respectively which on subsequent oxidation (PCC, CH_2Cl_2, 2 h) furnished **10a** (60%) and **10b** (64%) respectively. Finally ethynylation[13] of **10a** and **10b** (H-C≡C-MgBr, THF, room temperature) gave duryne **1a** in 60% yield m.p. 38-40°C and and **1b** in 63% yield m.p. 32-33°C. The spectral data of **1a** and **1b** coincided[14] well with the reported values of natural duryne, however, the geometry of the double bond at C^{15}-$C^{15'}$ in the natural duryne could not be established.

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14. Compound **1a** (E isomer): m.p. 38-40°C; IR (Nujol) ν max cm^{-1}: 3550, 3300, 2110, 1100, 1030, 980 and 670; ^{1}H NMR: 300 MHz ($CDCl_3$): δ 1.28 (28H, m); 1.96 (4H, m); 2.06 (4H, m); 2.28 (2H, bs, 2 x OH, exchangeable with D_2O); 2.56 (2H, d, J = 2.1 Hz); 4.83 (2H, bd, J = 6.1 Hz); 5.37 (2H, m); 5.60 (2H, ddt, J = 15.3, 6.1, 1.3 Hz); 5.91 (2H, ddt, J = 15.3, 1.08, 6.7 Hz). ^{13}C NMR: 75 MHz, ($CDCl_3$): δ (2C each), 28.83, 29.14, 29.18, 29.45, 29.49, 29.53, 29.64, 31.93, 32.59, 62.74, 73.90, 83.42, 128.39, 130.35, 134.50. Compound **1b** (Z isomer): m.p. 32-33°C; IR (neat) ν max cm^{-1}: 3500, 3300, 2110, 1100, 1030, 980 and 670; ^{1}H NMR: 300 MHz ($CDCl_3$): δ 1.28 (28H, m); 1.96 (4H, m); 2.06 (6H, m, 2 x OH, exchangeable with D_2O): 2.56 (2H, d, J = 2.1 Hz); 4.83 (2H, bd, J = 6.1 Hz); 5.37 (2H, m); 5.60 (2H, ddt, J = 15.3, 6.1, 1.4 Hz); 5.91 (2H, ddt, J = 15.3, 1.06 6.7 Hz). ^{13}C NMR: 75 MHz ($CDCl_3$): δ (2C each), 28.98, 29.20, 29.30, 29.38, 29.48, 29.52, 29.59, 31.78, 32.42, 62.44, 73.68, 83.37, 128.32, 130.19, 134.16.

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