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Chiron Approach Towards a Potent Toxin Fumonisin B_1 Backbone : Synthesis of its Hexaacetate Derivative

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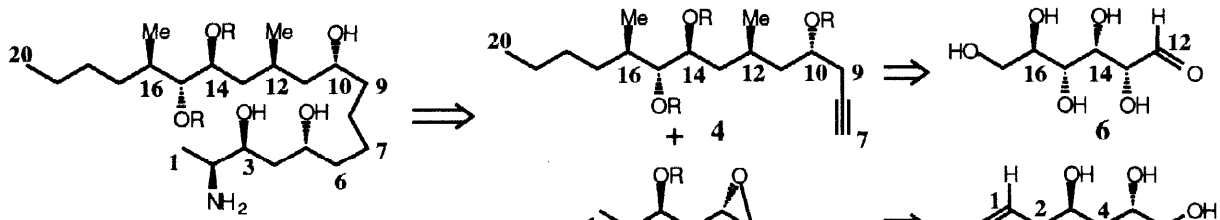
Abstract : Synthesis of a potent toxin fumonisin B_1-AP as an hexaacetate has been described starting from carbohydrates.

Fumonisin B_1 and B_2 (**1** and **3**) are potent toxic materials isolated from *Fusarium moniliforme* produced[1] by plant pathogens in corn and other grains. The human esophageal cancer is a direct consequence of fumonisins contaminated in corn products. Enormous work has been put in to elucidate relative and absolute configurations of fumonisins.[1b] Fumonisins are characterised by the presence of covalently linked propane-1,2,3-tricarboxylic acid (TCA). Ironically, the hydrolysed product fumonisin B_1-AP (**2**) is equally active but more importantly with broader spectrum of activity than the parent natural product. Recently, Kishi *et al*[2] reported the synthesis of fumonisin B_2 (**3**) whereas we summarise in this communication, the first synthesis of hexaacetyl fumonisin B_1-AP. Scheme 1 narrates the retrosynthetic planning and reveals compounds **4** and **5** as advanced intermediates whose synthesis from D-glucose and D-glucosamine respectively were undertaken.

Scheme 1



1. Fumonisin B_1(R=TCA)
2. Fumonisin B_1-AP(R=H)
3. Fumonisin B_2(R=TCA, C_{10}-OH=C_{10}-H)

D-Glucose was converted into the 5-ulose derivative **8** by a sequence of reaction reported earlier.[3] Subsequent olefination with Ph_3P=CH-C_3H_7 and palladium catalysed reduction followed by chromatographic separation of the mixture gave the required diastereomer **9** in 50% yield and the unwanted isomer in 45% yield. The stereochemical identity of the newly formed chiral centre was established by chemical correlation studies.[4] The inversion of configuration at C-3 in **9** was effected in four steps involving oxidation-reduction protocol to give **10**. Under acidic condition (70% aq.AcOH), compound **10** underwent isopropylidene

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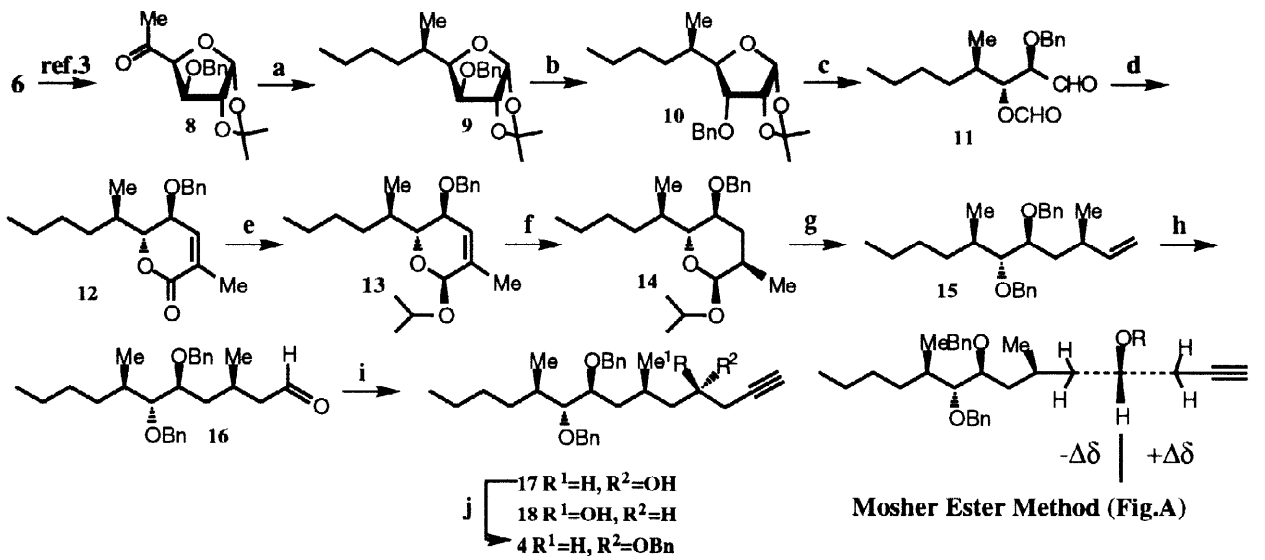
cleavage which was followed by consequent oxidation with $NaIO_4$ to give the aldehyde **11**, its Wittig-Horner reaction with $(MeO)_2P(O)C(Me)CO_2Et$-NaH at -78°C followed by lactonisation using K_2CO_3-MeOH gave **12**. In order to induce maximum stereoselectivity[5] during hydrogenation of the olefin, it was felt necessary to convert **12** into the corresponding isopropyl glycoside derivative **13** by first reducing the lactone to lactol with DIBAL-H at -78°C followed by treatment with isopropanol and CSA. The S-configuration at the anomeric centre was confirmed by proton decoupled ^{13}C-NMR spectrum in which C-1 was located at 95.3 ppm. Indeed the hydrogenation of **13** over Rh-Al_2O_3 in ether at 0 to 5°C under atmospheric pressure gave **14** as an exclusive product in whose ^1H NMR spectrum the characteristic coupling constant for H-1 ($J_{H1\text{-}H2}$=3.01 Hz) at 4.53 ppm was observed. In addition the anomeric carbon in its ^{13}C NMR spectrum was located at 97.12 ppm. The stereochemical assignment at C-2 was proven.

Scheme 2



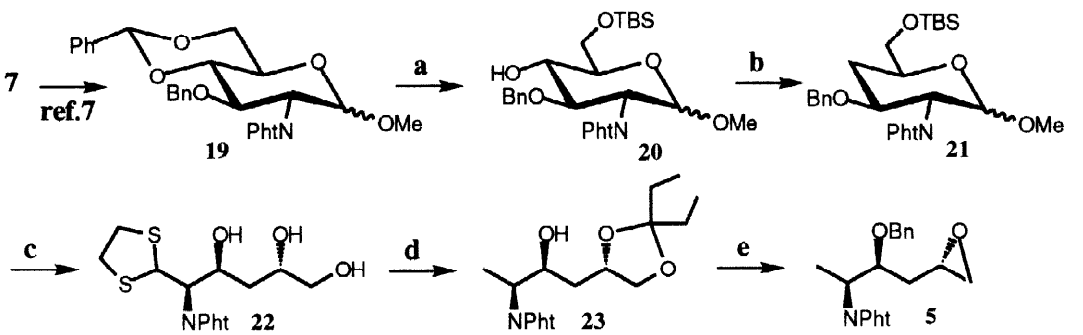
a) i) $C_4H_9P^+Ph_3Br^-$, n-BuLi, THF, -78 → 0°C, 3h, 86%; ii) Pd-C, H_2, EtOAc, 7 h, 50%; b) i) Ca/liq.NH_3, Et_2O, -78°C, 1h; ii) IBX, DMSO, RT, 20h; iii) $NaBH_4$, MeOH, 0°C, 3h; iv) BnBr, NaH, THF, RT, 72%; c) i) 70% aq. CH_3COOH, H_2SO_4 (Cat.), RT, 12 h; ii) $NaIO_4$, MeOH:H_2O(8:2), RT, 3 h, 77%; d) i) $(MeO)_2P(O)CH(CH_3)COOEt$, NaH, THF. -78°C, 5 h; ii) K_2CO_3, MeOH, RT, 1 h, 88%; e) i) DIBAL-H, PhMe, -78°C, 30 min.; ii) ^iPr-OH, CSA, 0°C, 2 h, 98%; f) Rh-Al_2O_3, H_2, 1 atm, Et_2O, 0 → 5°C, 10 min., 98%; g) i) 70% aq.CH_3COOH, (cat.) H_2SO_4, RT, 10 h; ii) $CH_3P^+Ph_3I^-$, n-BuLi, THF,- 78°C → 0°C, 2 h, 78%; iii) BnBr, NaH, THF, RT, 3 h; h) i) 9-BBN, THF, NaOH, H_2O_2, RT, 5 h; ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C, 45 min., 82%; i) C_3H_3Br, Zn dust, aq. NH_4Cl, THF, RT, 12 h, 70%; j) NaH, BnBr, THF, RT, 85%.

Hydrolysis of the O-glycosidic bond with 70% aq. acetic acid and one carbon Wittig olefination with $Ph_3P{=}CH_2$ afforded **15**, its derived benzyl derivative was subjected to hydroboration-oxidation (9-BBN-H_2O_2) and Swern oxidation to provide the aldehyde **16**. Addition of propargyl bromide in presence of Zn dust in aqueous NH_4Cl gave a diastereomeric mixture of alcohols **17** and **18** in equal amounts which were easily separated by silica gel chromatography. The stereochemical identification of the required diastereomer **17** was confirmed by modified Mosher ester method[6] according to which **17** was individually converted into (R)-MTPA- and (S)-MTPA-esters and further analysed by ^1H NMR spectroscopy. The characteristic variations

in (δ_S-δ_R) values (Figure A) were uniformly observed thereby leading to us to assign S-configuration to **17**. Compound **17** was benzylated (NaH-BnBr) to give C_7-C_{20} segment **4** (Scheme 2).

Synthesis of C_1-C_6 segment **5** was investigated from D-glucosamine hydrochloride (**7**). It was converted into the N-phthalimido methylglycoside (**19**).[7] Subsequent cleavage of benzylidene group and selective protection of O-6 with TBS-chloride-Imid. gave **20**. The deoxygenation at C-4 of **20** was accomplished by Barton radical deoxygenation leading to the 4-deoxy product **21**. Treatment of **21** with 1,2-ethanedithiol and $BF_3.OEt_2$ opened the ring to afford **22** which was reductively desulfurised over Ra-Ni and consequently protected with 3-pentanone-CSA to give **23**. Transformation of **23** into the epoxide derivative **5** was realised in four steps as shown in scheme 3.

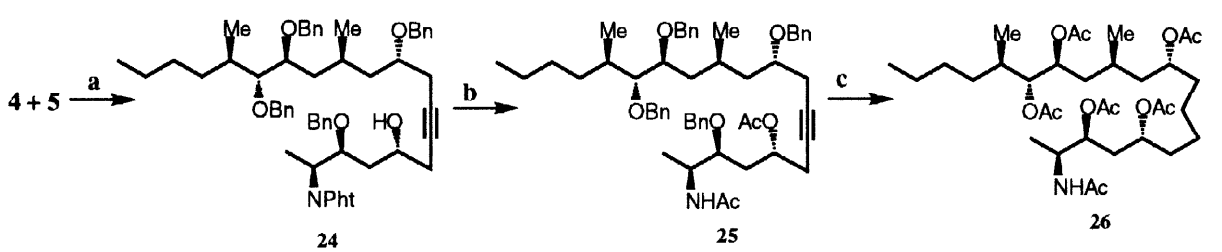
Scheme 3



a) i) 60% aq.CH_3COOH, 50°C, 5h; ii) TBS-Cl, Imidazole, CH_2Cl_2, RT, 3h, 81%; b) i) NaH, CS_2, MeI, THF, RT, 2 h; ii) Bu_3SnH, AIBN (cat.), PhMe, reflux, 3 h, 80%; c) MeOH, pTSA, RT, 1h; ii) $BF_3.Et_2O$, $HSCH_2CH_2SH$, CH_2Cl_2, RT, 3h, 73%; d) Ra-Ni, EtOH, RT, 3 h, 85%; ii) $(CH_3CH_2)_2CO$, CSA, CH_2Cl_2, RT, 1h, 92%; e) i) NaH, BnBr, THF, RT, 3h; ii) MeOH, pTSA, RT, 2h; iii) Ts-Cl, Py, CH_2Cl_2, 0°C, 12 h; iv) NaH, THF, 0°C, 30 min., 52%.

The C-C bond coupling[8] between **4** and **5** was performed with n-BuLi-$BF_3.OEt_2$ as a mediator at -78°C to give **24**. The removal of phthalimido group followed by acetylation afforded **25** which was exhaustively hydrogenolysed over $Pd(OH)_2$-C to afford after acetylation, fumonisin B_1-AP derivative **26** (Scheme 4). This compound was fully characterised by ^1H NMR and Mass spectral data.[9]

Scheme 4



a) n-BuLi, $BF_3.Et_2O$, THF, -78°C, 40 min, 73%; b) i) $MeNH_2$-MeOH, reflux, 2.5 h; ii) Ac_2O, Et_3N, CH_2Cl_2, RT, 1h, 85%; c) i) $Pd(OH)_2$, H_2, MeOH, 12 h; ii) Ac_2O, Et_3N, CH_2Cl_2, 1h, 95%.

In conclusion we have developed an efficient protocol for fumonisin B_1 backbone utilising carbohydrates as chiral raw materials.

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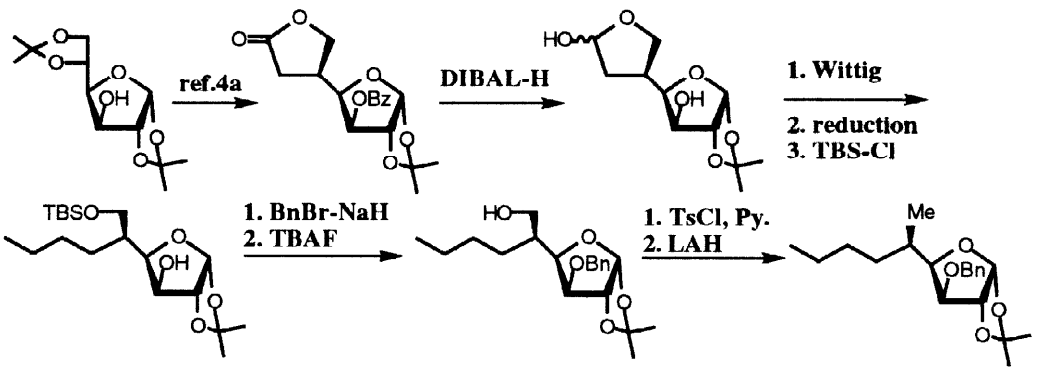

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9. All new compounds were fully characterised by high resolution spectroscopic analysis. Spectral data for selected compounds are described below:

17: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (d, 3H, J=6.5 Hz), 0.92 (t, 3H, J=6.5 Hz), 0.98 (d, 3H, J=6.6 Hz), 1.0-1.9 (m, 12H), 1.96 (t, 1H, J=1.9 Hz), 2.27 (m, 2H), 3.4 (dd, 1H, J=2.2, 7.0 Hz), 3.64 (brd, 1H, J=8.8 Hz), 3.77 (m, 1H), 4.46 (d, 1H, 11.1 Hz), 4.60 (ABq, 2H, J=13.3 Hz), 4.84 (d, 1H, J=11.1 Hz), 7.3 (m, 10 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 16.49, 21.37, 23.0, 26.75, 26.92, 28.92, 32.56, 35.15, 37.11, 42.65, 68.0, 70.82, 71.24, 74.09, 78.94, 80.91`, 83.78, 127.35, 127.55, 127.76, 127.88, 127.89, 128.0, 128.07, 128.17, 128.33, 128.45, 138.50, 138.90; FABMS: m/z 451 (M$^+$+1); **25**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (m, 6H), 0.91 (d, 3H, J=6.8 Hz), 1.16 (d, 3H, J=6.5 Hz), 1.2-1.9 (m, 14H) 1.92, 2.03 (2s, 6H), 2.2-2.55 (m, 4H), 3.4 (dd, 1H, J=2.2, 7.1 Hz), 3.51 (m, 1H), 3.61 (m, 1H), 3.65 (brd, 1H, J=8.8 Hz), 4.13 (m, 1H), 4.4-4.7 (m, 7H), 4.85 (d, 1H, J=14.5 Hz), 5.09 (m, 1H), 5.63 (d, 1H, J=8.7 Hz), 7.3 (m, 20H); **26**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 3H, J=6.8 Hz), 0.93 (d, 6H, J=6.8 Hz), 1.10 (d, 3H, J=6.7 Hz), 1.2-1.65 (m, 20H),1.76 (m, 2H), 1.99 (s, 6H), 2.01, 2.02, 2.07, 2.09 (4s, 12H), 4.17 (m, 1H), 4.8-5.02 (m, 4H), 5.17 (dt, 1H, J= 2.5, 10.1 Hz), 5.58 (d, 1H, J=9.3 Hz), HRFABMS: m/z 658.4176 (M$^+$+1), Calcd. for $C_{34}H_{60}NO_{11}$: 658.4166 (error 1.5 ppm).

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