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A Norbornyl Route to Cyclopentitols *via* Novel Regiospecific Fragmentation of a 2,7-Disubstituted Norbornane

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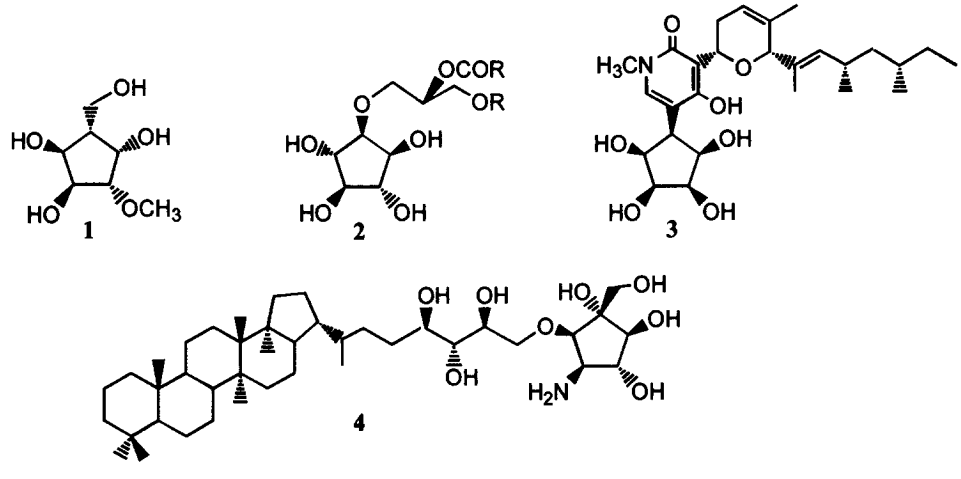
Abstract: A novel fragmentation sequence has been executed within the norbornane system, involving C1-C2 bond scission, to extract a versatile, fully substituted cyclopentanoid moiety. Its further evolution towards a range of cyclopentitols is described.

Keywords: Fragmentation reactions, Cyclitols, Hydroxylation

There is a great deal of current interest in cyclopentitols, polyhydroxylated cyclopentanes, as these structural entities not only constitute important segments of a diverse range of biologically potent natural products but in their own right exhibit promising activity profiles, particularly glycosidase inhibition.[1] Some of the recently reported examples of polyhydroxycyclopentane containing natural products are salpantiol **1**,[2a] keruffarides **2**,[2b] funiculosin **3**[2c] and bacteriohopanetetrol **4**,[2d] each of which display dense and stereochemically varied substitution patterns on their five-membered rings. The cyclopentitol sub-structure present in these and related compounds has attracted widespread attention amongst synthetic chemists. Among the main synthetic strategies that have been explored in this context are: (i) the sequential functionalization of cyclopentanoid precursors like, cyclopentene, 1,3-cyclopentadiene and fulvene, (ii) restructuring of carbohydrates to carbocycles, and (iii) transformation of cyclohexitols like quinic acid and microbially produced *cis*-cyclohexadiene diols *via* ring contraction protocols.[1,3] We visualised a new and general approach to cyclopentitols, based on the bicyclo[2.2.1]heptane (norbornane) framework,



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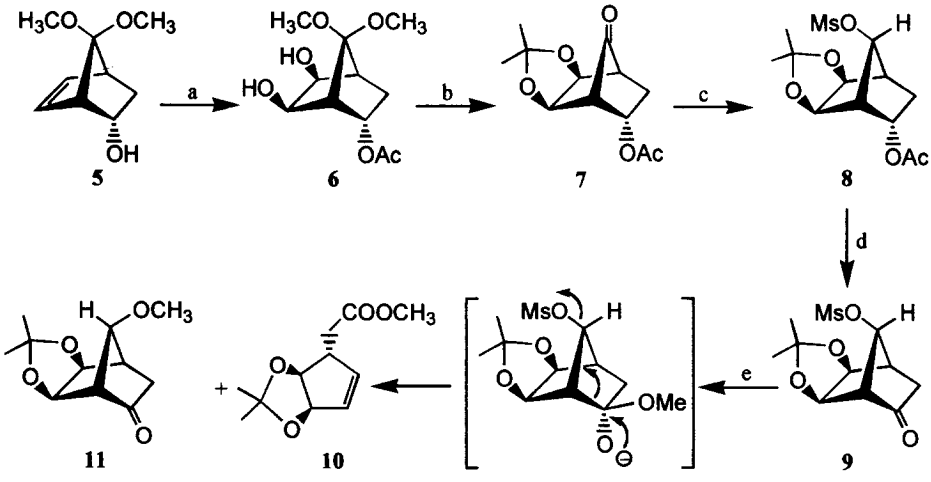
in which the intrinsic stereo- and regioselective proclivities of the norbornyl system are harnessed.[4] The key tactic in this approach is the setting up of a Grob-like fragmentation process in a suitably crafted 2,7-disubstituted norbornane derivative to cleave the C1-C2 bond, and disengage the five-membered ring from the bridged bicyclic frame with its full complement of functionalities. Following this strategy, we have accomplished the syntheses of several interesting and stereochemically well defined cyclopentitols and these results are detailed in this and the accompanying letter.

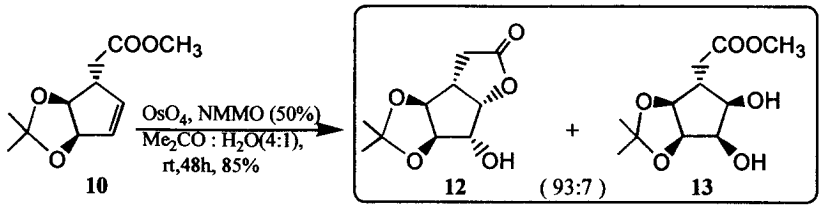
Scheme 1



Reagents and conditions: (a) i. Ac_2O, Py, DMAP (cat.), 6h, 80%, ii. OsO_4, NMMO, Me_2CO:H_2O (4:1), 20 h, 89%; (b) Amberlyst-15, Me_2CO, 6 h, rt, 70 %; (c) i. $NaBH_4$, MeOH, 35 min, 95 %, ii. MsCl, Py, DCM, overnight, 91%; (d) i. KOH, MeOH, 1h, 88%; ii. PCC, DCM, 5°C, 4h, 92%; (e) NaOMe, MeOH, rt, 3h, 40% for **10** & 20% for **11**.

Bicyclic alcohol **5**, readily available from 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and vinyl acetate,[5] on acyl transfer and OsO_4-hydroxylation furnished the *exo*-diol **6**.[6] Amberlyst mediated single-pot protection-deprotection led to the 7-norbornanone derivative **7**. Stereoselective reduction of the carbonyl group from the face opposite to the acetonide group and mesylation gave **8**. Acetate hydrolysis in **8** and oxidation delivered the desired 2,7-disubstituted keto-mesylate **9**. Exposure of **9** to NaOMe resulted in a smooth fragmentation to furnish the olefinic methyl ester **10**[6] along with an interesting product **11** (2:1)[6] derived through S_N2 substitution at the C7 of the norbornyl system, Scheme 1. In the cyclopentanoid **10** of secured stereochemistry, all the five ring carbons had a substitution pattern well poised for further elaboration.

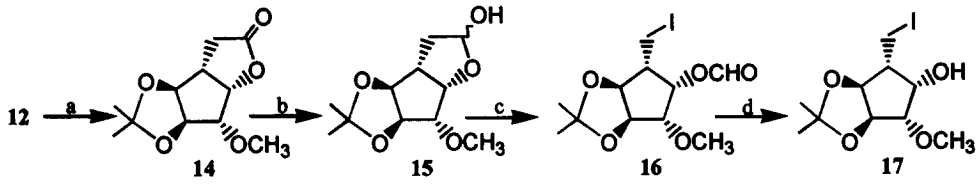
Scheme 2



Osmylation of olefinic ester **10** proceeded with high stereoselectivity (93:7) and furnished a readily separable mixture of lactone **12**[6] and *cis*-diol ester **13**[6] in good yield, Scheme 2. The stereochemical issue among **12** and **13** was settled via formation of the bicyclic lactone **12**, which was

found to be identical with the compound previously synthesised by Enholm and coworkers[7] from a carbohydrate precursor and whose X-ray crystal structure had been determined. While the major product **12** offers many possibilities in complex synthesis, its utility in the context of cyclopentitol preparation requires a one carbon degradation of the lactone moiety.

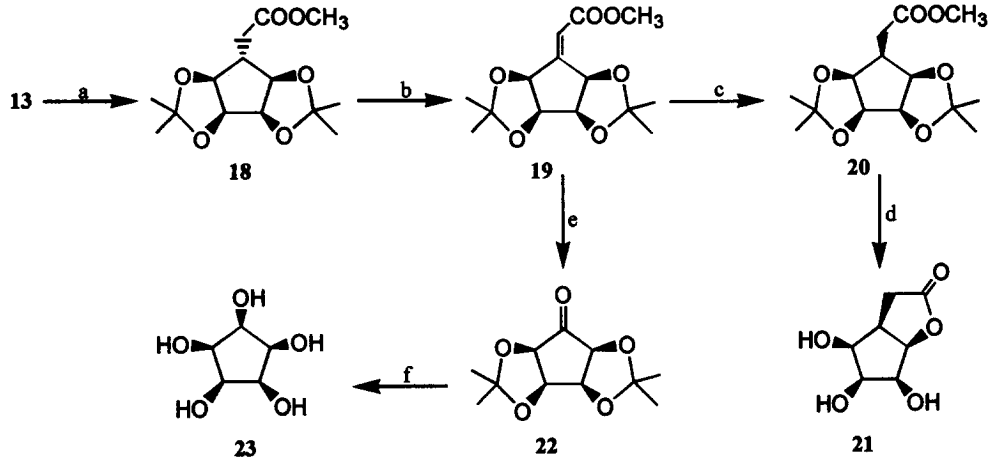
Scheme 3



Reagents and conditions: (a) MeI, Ag_2O, Mol. sieves 4A°, 93%; (b) DIBAL-H, DCM, -78 °C, 40 min, 84%; (c) $PhI(OAc)_2$, I_2, cyclohexane, hv, 500 W, 1h, 61%; (d) aq. Na_2CO_3, MeOH, 6h, 91%

The hydroxyl group in **12** was protected and the resulting methyl ether **14** was reduced to the lactol **15** to set up the hypervalent iodine mediated Suarez alkoxy radical fragmentation step.[8] Exposure of **15** to iodobenzene diacetate, under irradiation, resulted in smooth fragmentation to the iodoformate ester **16**, which was hydrolysed to the hydroxy-iodide **17**[6], Scheme 3. In **17**, all the elements for further elaboration to a range of cyclopentitols are present and some of its transformations are reported in the accompanying paper.

Scheme 4



Reagents and conditions: (a) Amberlyst-15, Me_2CO, Mol. sieves 4A°, 2h, 90%; (b) LiHMDS, THF, PhSeCl, -78°C to rt, 2h; H_2O_2 (30%), Py, DCM, 1h, 60%; (c) H_2, Pd/C(10%), EtOAc, 2h, 95%; (d) HCl (5%), Et_2O:H_2O (1:9), 30h, >95%; (e) O_3, DCM, -78°C, 5 min, 80%; (f) i. $NaBH_4$, MeOH, 0-5°C, 30 min, 89%; ii. HCl (5%), Et_2O: H_2O (1:9), 36h, ~ 100%.

The minor product **13** from the osmylation of **10** was particularly appealing for the generation of the *all cis*-pentasubstitution pattern present in natural products like funiculosin **3**.[2c] Thus, **13** was converted to the bis-acetonide **18** and elaborated to the conjugated ester **19**[6] *via* a phenylselenylation-selenoxide elimination sequence. Stereoselective hydrogenation in **19** from the convex face gave *all*

cis-**20**,[6] which on deprotection furnished the bicyclic lactone **21**,[6] Scheme 4. Substrates **20** and **21** are reminiscent of the advanced intermediates reported by Pattenden[9a] and Williams[9b] in their approaches towards **3**. In another sequence, **19** was subjected to ozonolysis to give cyclopentanone **22** and was further transformed to the *cis*-cyclopentanepentol **23**[10] via stereoselective reduction and deprotection.

In short, we have disclosed here a new and versatile approach towards polyhydroxylated cyclopentanoids from a readily accessible 2,7-disubstituted norbornane precursor, involving a novel Grob-like fragmentation as the pivotal step.

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[6] All new compounds reported here were racemic and characterized on the basis of their spectral data and elemental analyses. Selected spectral data: **9:** δ_H (200 MHz, $CDCl_3$): 5.0-4.85 (1H, m), 4.6 - 4.55 (1H, m), 4.5-4.4 (1H, m),.3.25–3.2(2H, m), 3.07 (3H,s), 2.20–2.03 (1H, m), 1.96–1.86 (1H, m), 1.55 (3H, s), 1.33 (3H, s); δ_c (50 MHz, $CDCl_3$): 205.51, 112.70, 82.13, 81.67, 77.09, 58.40, 43.65, 40.22, 39.06, 24.87, 23.76; **17:** δ_H (300 MHz, $CDCl_3$): 4.58 (1H, dd, J=3.5, 7.5 Hz), 4.45 (1H, dd, J=5.5 7.5 Hz), 4.38 (1H, dd, J=3.5, 7), 3.70 (1H, dd, J=3.5, 4Hz), 3.48 (3H, s), 3.43 (1H, d, J=9.5 Hz), 3.29 (1H, dd, J=7, 9.5 Hz), 2.42-2.38(1H, m), 1.58 (3H, s), 1,30 (3H, s); δ_c (50 MHz, $CDCl_3$): 112.93, 87.06, 83.87, 82.90, 74.97, 57.75, 51.90, 26.99, 24.54, 2.03; **20:** δ_H (300 MHz, $CDCl_3$): 4.63- 4.61 (2H, m), 4.43- 4.41 (2H, m), 3.65 (3H,s), 2.57-2.54 (3H, m), 1.55 (6H, s), 1.27 (6H, s); δ_c (75 MHz, $CDCl_3$): 172.47, 112.58, 87.16, 80.36, 51.78, 45.25, 35.92, 26.28, 24.98; **23:** δ_H (300 MHz, D_2O): 3.87; δ_c (75MHz, D_2O): 71.73.

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