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5-*Exo-dig,* 5-*exo-trig* cascade radical cyclisation on sugar-furanose templates: entry to angularly fused oxa- and dioxa-triquinane skeletons

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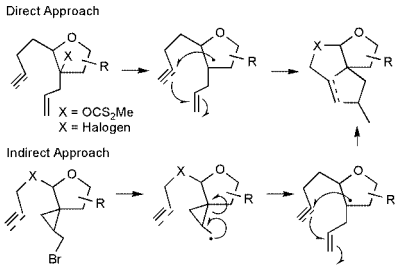
Serial radical cyclisation on sugar-furanose templates to create angularly fused oxa- and dioxa-triquinane skeletons has been described, the salient feature of this approach being to incipiently generate a tertiary radical from cyclopropylmethyl bromide with simultaneous release of allyl group and to subsequently incorporate it in the triquinane system.

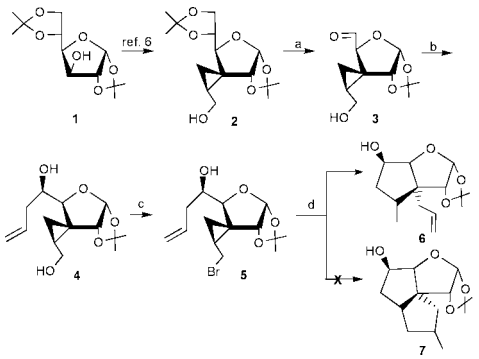
Ever since their isolation, the angularly fused triquinanes have attracted intense attention of synthetic organic chemists as challenging targets.[1] Structural complexity associated with significant biological activity has necessitated development of very many approaches for their synthesis.[2] Among them, the radical cascade reactions are by far the most elegant and efficient approaches as significantly demonstrated by the work of Curran and others.[3] Bis-annulated sugars are also useful synthons for triquinane synthesis. For example, Fraser-Reid and coworkers[4] have performed some novel transformations mediated by serial radical cyclization of pyranose based sugar synthons[5] to create pyranosin diquinanes, elaborated to naturally occurring triquinanes.

We feel that radical cascade reactions on furanose ring systems of sugar derivatives would be interesting to explore primarily to understand the stereo-chemical behavior but more importantly to obtain synthons potentially useful for angularly fused, unknown and structurally novel oxa-triquinanes. The direct approach for oxa-triquinane would be to trigger a cascade of radical reactions by generating tertiary radicals on synthons with prefabricated radical acceptors (Scheme 1). Realistically, formation of a tertiary radical is a difficult proposition because its precursor, namely tertiary halide or tertiary thiocarbamate, is not easily accessible by conventional methods. However, the indirect formation of a tertiary radical with concomitant installation of an allylic side chain as radical acceptor, by our recently developed approach[6] of radical ring opening of spirocyclopropyl methyl bromide, could constitute an elegant and ideal proposition for this endeavor. This study forms the basic premise of this communication.

1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**1**) was converted into the 3,3-spiro cyclopropylmethanol derivative (**2**) in five steps (Scheme 2).[7] It was then exposed to 0.8% sulfuric acid in methanol at rt to give the triol derivative whose oxidative cleavage with $NaIO_4$ absorbed on silica gel[8] in CH_2Cl_2 yielded the aldehyde (**3**). Compound **3** was immediately treated with



Scheme 1

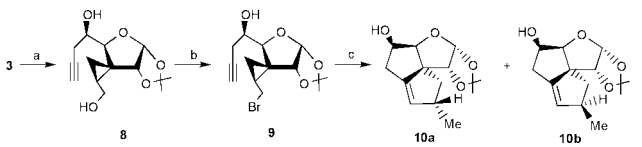


Scheme 2 *Reagents and conditions*: (a) (i) 0.8% H_2SO_4, MeOH, rt, 10 h; (ii) silica gel adsorbed $NaIO_4$, CH_2Cl_2, 15 min, 78% (two steps); (b) allyl bromide, Zn, aq. NH_4Cl, THF, 0 °C, 6 h, 72%; (c) PPh_3, CBr_4, pyridine, CH_2Cl_2, rt, 1 h, 83%; (d) TBTH, AIBN (cat), $C_6H_5CH_3$, 100 °C, 1 h, 70%.

Zn, allyl bromide under aqueous Barbier conditions[9] to give a predominantly (90%) and chromatographically separable allyl addition product (**4**) whose stereochemical assignment was based on literature precedents.[10] Compound **4** upon treatment with CBr_4–PPh_3 in CH_2Cl_2 in the presence of pyridine at rt gave the corresponding bromo derivative (**5**). Treatment of **5** with tri-*n*-butyl tin hydride (TBTH), AIBN in toluene (0.05 M) at 100 °C gave a single product whose fused bicyclic structure (**6**) was assigned on the basis of NMR and MS studies. Presence of compound **7** was not noticed. The formation of **6** indicated premature termination of serial radical cyclisation after the first *exo-trig* addition. This abrupt termination could be attributed to the poor reactivity of the methyl radical.[11] In order to circumvent this problem, we sought to explore the vinyl radical primarily for its pronounced reactivity coupled with the ease with which it could be generated.[12]

Accordingly, **3** was subjected to Barbier reaction in aqueous conditions with Zn and propargyl bromide to afford **8** as an exclusive product. The transformation of **8** into **9** was carried out as described earlier (Scheme 3).

The radical reaction of **9** with TBTH and AIBN (cat.) in dry toluene (0.05 M) at 100 °C gave the angularly fused oxa-triquinane derivatives **10a** and **10b,** whose formation was attributed to 5-*exo-dig*, 5-*exo-trig* serial cyclisations. The structure of the product was thoroughly investigated by high resolution ^1H NMR, ^{13}C NMR, MS and elemental analysis. The ^1H and ^{13}C NMR spectra indicated that it was a 8.5 : 1.5 mixture of diastereomers **10a** and **10b**. However, COSY and NOSY



Scheme 3 *Reagents and conditions*: (a) HC≡C–CH_2Br, Zn, aq. NH_4Cl, THF, 0 °C, 6 h, 74%; (b) PPh_3, CBr_4, pyridine, CH_2Cl_2, rt, 1 h, 80%; (c) TBTH, AIBN (cat), $C_6H_5CH_3$, 100 °C, 1 h, 74%.

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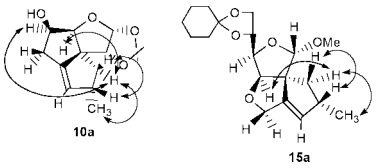
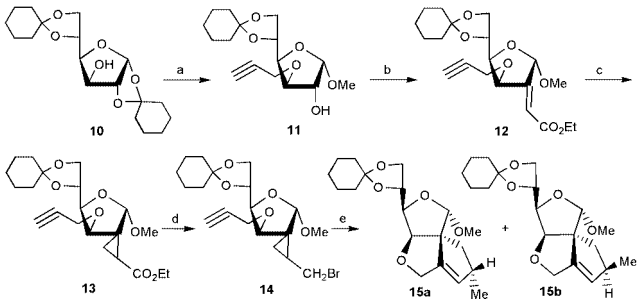


Fig. 1 NOSY studies.

studies (Fig. 1) on the major diastereomer **10a** revealed the absolute stereochemistry of the methyl group as indicated.[12]

We also synthesized starting from 1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose (**10**) the 2,2-spirocyclopropyl methyl bromide derivative **14** *via* intermediates **11**–**13** as shown in Scheme 4. Subsequent radical cascade reaction of **14** with TBTH and AIBN (cat.) in toluene at 100 °C gave the fused ring derivatives **15a** and **15b**. The ^{1}H and ^{13}C NMR spectra of the product showed to be a 8:2 mixture of diastereomers. The COSY and NOSY studies (Fig. 1) predicted the stereochemistry of the methyl group of the major product **15a** as indicated.[13]



Scheme 4 *Reagents and conditions*: (a) (i) NaH, HC≡C–CH_2Br, DMF, 0 °C, 90%; (ii) H_2SO_4, MeOH, Δ, chromatography, 65%; (b) (I) IBX, DMSO, rt, 10 h; (ii) PPh_3=$CHCO_2Et$, C_6H_6, 80 °C, 2 h, 74% (two steps); (c) Me_2SOCH_3I, NaH, DMSO, rt, 3 h, 55%; (d) (i) DIBAL-H, CH_2Cl_2, 78 °C, 0.5 h, 87%; (ii) PPh_3, CBr_4, pyridine, rt, 82%; (e) TBTH, AIBN (cat), $C_6H_5CH_3$, 100 °C, 1 h, 80%.

In conclusion, we have developed a one pot, stereoselective 5-*exo-dig*, 5-*exo-trig* cascade radical cyclization utilizing the incipiently formed *C*-allyl radical leading to useful and structurally novel oxa-triquinane system.

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13 NMR data for **10a**: ^{1}H (500 MHz): δ 0.98 (d, 3 H, J = 7.2 Hz), 1.26 (t, 1 H, J = 10.8 Hz), 1.34, (s, 3 H), 1.47, (s, 3 H), 1.80 (m, 1 H) 2.50 (dd, 1 H, J = 5.4, 12.7 Hz), 2.67 (dd, 1 H, J = 3.6, 10.8 Hz), 2.95 (brs, 1 H), 3.72 (m, 1 H), 4.24 (d, 1 H, J = 4.0 Hz), 4.28 (d, 1 H, J = 3.0), 5.41 (s, 1 H), 5.74 (d, 1 H, J = 3.0 Hz); ^{13}C (125 MHz): δ 19.98, 27.27, 27.59, 33.99, 40.51, 42.70, 65.52, 74.79, 85.75, 87.75, 106.55, 112.59, 132.33, 144.66. NMR data for **15a**: ^{1}H (500 MHz): δ 1.09 (d, 3 H, J = 7.5 Hz), 1.3–1.75 (m, 10 H), 1.49 (t, 1 H, J = 12.7 Hz), 2.72 (dd, 1 H, J = 5.0, 12.7 Hz), 3.41 (brs, 1 H), 3.37 (s, 3 H), 3.90 (dd, 1H, J = 2.6, 7.6 Hz), 3.98 (dd, 1 H, J = 4.5, 7.6 Hz), 4.06 (ddd, 1 H, J = 1.5, 3.0, 11.3 Hz), 4.11–4.17 (m, 2 H), 4.29 (brd, 1 H, J = 10.6 Hz), 4.39 (m, 1 H), 4.69 (s, 1 H), 5.46 (s, 1 H); ^{13}C (125 MHz): δ 20.11, 23.85, 24.04, 25.17, 34.83, 36.55, 40.93, 44.99, 54.88, 65.86, 66.73, 71.34, 73.23, 81.79, 85.14, 108.32, 109.59, 128.59, 148.36.