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A Carbohydrate-Based Synthetic Approach to Quadrone

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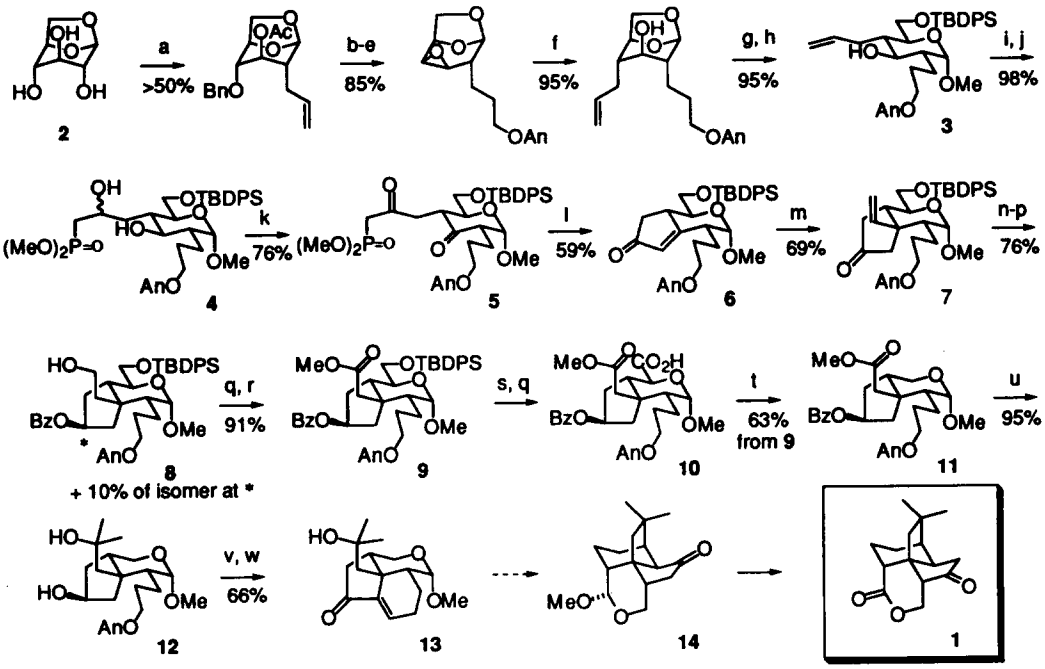
Abstract: *An advanced intermediate* ***13*** *towards the total synthesis of the anti-tumor sesquiterpene (-)-quadrone* ***1*** *has been prepared from levoglucosan.*

Its fascinating structure and anti-tumor activity make the sesquiterpene quadrone **1** an attractive synthetic target. A number of syntheses of quadrone were reported in the past, most of them in racemic form.[1] In this Letter we wish to disclose the preliminary results of our carbohydrate-based approach towards the natural (-)-quadrone.

We felt that the carbocyclic skeleton of **1** might be assembled enantiospecifically on a carbohydrate pyranoside template which later could be transformed into the lactone portion of the molecule. Following the sequence of the Scheme, levoglucosan **2** was transformed into the pyranoside **3** (*cf.* ref. 2) which was further elaborated into dihydroxyphosphonate **4**. Oxidation of **4** to **5** by most of the reagents proved to be extremely inefficient due to the strong tendency of the intermediate mono-oxidation products to form cyclic hemi-acetals. However, making use of the mechanistic feature of fast prior alcohol complexation in Dess-Martin periodinane oxidation,[3] the desired diketo derivative **5** was obtained in good yield by adding **4** in one portion to an excess of the reagent followed by acceleration of the reaction with water.[4] In mild basic conditions[5] the ketophosphonate **5** afforded the annulated cyclopentenone **6** in reasonable 59% yield, together with 5% of its epimer at C-2. With the cyclopentenone **6** in hand, the introduction of an angular carbon chain, a plausible precursor of a tertiary alcohol for the projected radical cyclization step (**13**→**14**), was then addressed. Several attempts to attach a carbalkoxymethyl group in Mukaiyama-Michael conditions or a methallyl group by the Sakurai reaction failed. Methallyl-derived copper and titanium reagents underwent mainly 1,2-addition, even in the presence of the appropriate additives [Me_3SiCl, BF_3, $Ni(acac)_2$], to give the corresponding alcohol which unfortunately resisted the anionic oxy-Cope rearrangement. Eventually, the angular chain, suitable for further elaboration into a tertiary alcohol, was introduced in the form of vinyl group (**7**) by conjugated addition of the higher order mixed cuprate[6] to the enone **6**. Reduction of the carbonyl group of the vinyl derivative **7** with $KBHEt_3$ afforded a mixture of the corresponding alcohols (*ca.* 9:1, by NMR) which were separated after sequential benzoylation and hydroboration.[7] The primary hydroxyl group in **8** was oxidized to give an acid which was isolated as its methyl ester **9**. At this stage of the synthesis, the excessive hydroxymethyl group at C-5 of the pyranose ring, which so far had played a strategically important role,[8] was removed by the Barton's thiohydroxamate radical decarboxylation[9] of the derived acid **10**. The product **11** thus obtained was treated with an excess of MeLi to give the desired tertiary alcohol **12**. The deprotection of the primary hydroxyl group in **12** under the strictly controlled conditions, simultaneous oxidation of both primary and secondary hydroxyls, and, finally, base-catalyzed condensation provided, in good overall yield, the tricyclic enone **13** which possesses sufficient functionalities for its further transformation into the natural (-)-quadrone *via* radical cyclization (→**14**) and carbonyl transposition steps. Further results will be reported in due course.[10]



a. see ref. 2; b. Cy_2BH/THF, rt, then H_2O_2, $NaHCO_3$; c. p-$MeOC_6H_4OH$, DEAD, Ph_3P/CH_2Cl_2, rt; d. H_2, Pd(C)/MeOH; e. MsCl, Et_3N/CH_2Cl_2, -10°C, then MeONa/MeOH; f. $(CH_2{=}CHCH_2)_2Mg/Et_2O$, rt; g. MeOH, Dowex-50($H^+$), separation and recycling of β-anomer; h. TBDPSCl/Py, rt; i. NMO, OsO_4 (cat)/t-BuOH-H_2O, then H_5IO_6; j. $(MeO)_2P(O)CH_2Li$ (2.5 eq)/THF, -78°C; k. Dess-Martin periodinane (3 eq)/CH_2Cl_2, then addition of H_2O (3 eq) as a 10% solution in CH_3CN (for 1 h); l. LiCl, i-Pr_2NEt, MS 4Å/CH_3CN, 60°C; m. $CH_2{=}CHCu(Me)Li{\cdot}LiCN$, $BF_3{\cdot}Et_2O$/THF, -78°C to -40°C; n. $KBHEt_3$/THF, -78°C; o. BzCl, Et_3N, DMAP (cat)/CH_2Cl_2, rt; p. BH_3/THF, rt, then H_2O_2, $NaHCO_3$; q. NMO, TPAP (0.02 eq), MS 4Å/CH_3CN, then $KMnO_4$/t-BuOH-NaH_2PO_4 (aq); r. CH_2N_2; s. Bu_4NF/THF; t. $(COCl)_2$, DMF (cat)/C_6H_6, then Na-salt of N-hydroxypyridine-2-thione , DMAP (cat), then Bu_3SnH, AIBN, Δ; u. MeLi (8 eq)/Et_2O, -78°C to rt; v. CAN (5 eq), Py (7.5 eq)/CH_3CN-H_2O (9:1), 5 min, then immediate neutralization with conc. NaOH (aq); w. NMO, TPAP (0.02 eq), MS 4Å/CH_3CN, then K_2CO_3/MeOH; rt.

References and Notes

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7. Both **8** and its epimer are synthetically useful since the carbinol centre is to be oxidized later on.
8. At first, as an element of the bicyclic skeleton providing the highly stereoselective introduction of the side chains at C-2 and C-4, and later, as an anchor group preserving these centres from easy isomerization (see **5**→**6** above).
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10. All new compounds were characterized by analytical and spectroscopic methods. Specific rotations were measured in $CHCl_3$ solutions. Selected data: **3**: +58 (c 1.0); **5**: +46 (c 1.0); **6**: +27 (c 0.9); **7**: -31 (c 2.0); **8**: +50 (c 1.3); **9**: +41 (c 1.3); **11**: +61 (c 1.5); **12**: +52 (c 0.9); **13**: -30 (c 0.5).

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