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LETTERS

Norbornyl Route to Polyoxygenated Cyclohexanes. A Facile Entry into Carbasugars and Shikimic Acid

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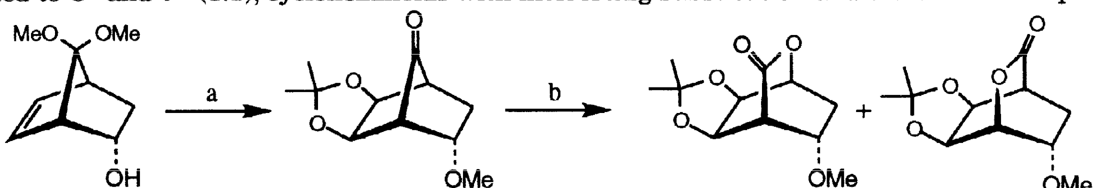
Abstract: A short, stereoselective entry to carbasugars and shikimic acid from a readily available 7-norbornenone is reported.

Polyoxygenated cyclohexanes are not only important sub-structures present in many diverse, complex and biologically important natural products, but in their own right, are known to elicit a variety of biological responses. Consequently, much attention has been bestowed on devising methodologies for gaining rapid entry to polyoxygenated cyclohexanes in a regio- and stereoselective manner.[1] As a result, considerable success has been achieved employing microbial oxidation of aromatics,[1a,g] Diels-Alder cycloadditions to furans[1b,c] and pyrones[1d,e] and restructuring of carbohydrates[1f,g] as the dominant strategies. In the accompanying communication, we have outlined new approach to polyfunctional cyclohexanes from readily available bicyclo[2.2.1]heptane (norbornane) precursors, and herein we amplify this theme for rapidly accessing the shikimic acid and carbasugar frameworks.

Readily available *endo*-hydroxy-7-norbornenone ketal 1[2] was transformed to 2 through a three-step sequence involving O-methylation, dihydroxylation from the *exo*-face and a single-pot deprotection-protection of the 7-keto and dihydroxy functionalities, respectively. Baeyer-Villiger oxidation on 2 furnished a regioisomeric mixture of lactones 3[3] and 4 (80:20)[3] which were separatated, Scheme 1. The more abundant lactone 3, on LAH reduction, acetonide deprotection and acylation furnished the tetraacetate 5,[3] representing a restructured carbasugar moiety. On the other hand, hydrolysis of 3 and acylation led to 6[3] and 7[3] (1:1), cyclohexanoids with interesting substitution and stereochemical pattern.



Scheme 1. Reagents: (a) i. NaH, MeI,DMF, >90%; ii. OsO_4, NMMO, aq.Me_2CO, ~50%; iii. Amberlyst-15, Me_2CO, 85-90%; (b) MCPBA, $NaHCO_3$, DCM, ~90% .

The minor lactone 4 proved to be more productive and on LAH reduction, acetonide deprotection and acylation furnished the tetraacetate 8,[3] a α-talopyranose carbasugar.[4] Quite interestingly, the base mediated hydrolysis of 4 and acylation directly furnished the protected shikimic acid 9[3] as the single isolable product , in a stereoseletive manner through concomitant elimination of one of the functionalities, Scheme 2. The stereostructure of 9 was fully secured on the basis of spectral data, including DEPT and COSY experiments.

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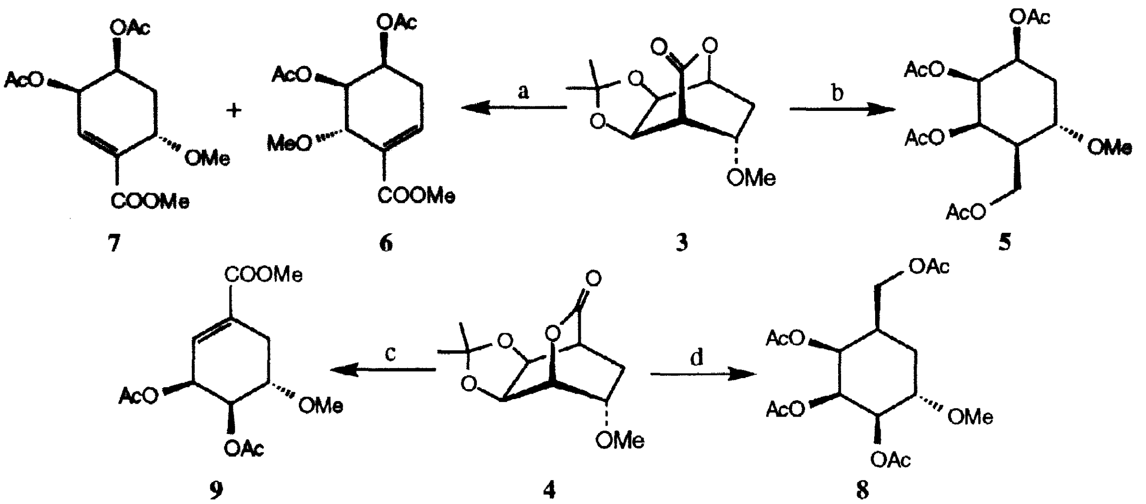

Scheme 2. Reagents : (a) i.KOH, MeOH, 0-5°C; H^+; CH_2N_2, Et_2O; Ac_2O,Py,19% for **6** & 25% for **7**; (b) i.LAH, THF, -18°C → 0°C ,75%; ii. Amberlyst-15, aq.MeOH; Ac_2O,Py,84%; (c) same as (a) yield 48%; (d) same as (b) yield 77%.

Many routes to shikimic acid[5] and carbasugars[1f,4] have been reported in the literature and they continue to engage the attention of synthetic chemists. However, our approach to derivatives **8** and **9** from the same precursor **4** is notable for its brevity and simplicity.

References

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2. Paquette, L.A.; Learn, K.S.; Romine, J.L.; Lin, H-S. *J. Am. Chem. Soc.* **1988**, *110*, 879.
3. All new compounds were duly characterized (IR, ^1H & ^{13}C NMR at 200 and 50 MHz, respectively in $CDCl_3$, MS). Selected spectral data: **5**: δ_H 5.36-5.34 (1H, m), 5.28-5.2 (2H, m), 4.27-4.22 (2H, m), 3.67-3.59 (1H, m), 3.35 (3H, s), 2.46-2.34 (1H, m), 2.07 (3H, s), 2.06 (3H, s), 2.05 (3H, s), 2.03 (3H, s), 2.2-1.8 (2H, m); δ_C 170.98, 169.86(2C), 169.66, 74.19, 70.2, 67.52, 67.36, 61.40, 56.56, 41.76, 27.88, 20.89(4C). **8**: δ_H 5.40 (1H, dd as t, J=2.8Hz), 5.28 (1H, dd as t, J=4Hz), 5.17 (1H, dd , J=3.7,3.2Hz), 4.09-3.94 (2H, m), 3.57 (1H, q, J=3.2Hz), 3.40 (3H, s), 2.5-2.3 (1H, m), 2.09 (3H, s), 2.05 (3H, s), 2.04 (3H, s), 2.0 (3H, s), 1.79-1.68 (2H, m); δ_C 170.92, 170.05, 169.82(2C), 75.80, 68.50, 68.22, 67.61, 63.46, 57.20, 33.96, 32.96, 23.36, 20.44, 20.73(2C). **9**: δ_H 6.73-6.71 (1H, m), 5.75-5.70 (1H, m), 5.35 (1H, dd, J=6.4, 4.0Hz), 3.78 (3H, s) 3.87-3.67 (1H, m), 3.44 (3H, s), 2.76-2.62 (1H, m), 2.54-2.39 (1H, m), 2.18 (3H, s), 2.08 (3H, s); δ_C 170.14, 169.90, 166.36, 133.42, 130.75, 74.29, 67.99, 66.86, 57.40, 52.02, 27.37, 20.86, 20.78.
4. For the synthesis of α-talopyranose and related carbasugars, see: Pingli, L; Vandewalle, M. *Synlett* **1994**, 228 and referenced cited therein.
5. Campbell, M.M.; Sainsbury, M.; Searle, P.A. *Synthesis* **1993**, 179.