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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 6235–6238

Stereoselective syntheses of (+)-*proto*, (−)-*gala* quercitols and carba-L-rhamnose from D-(−)-quinic acid

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Received 13 May 2005; revised 2 July 2005; accepted 14 July 2005

Abstract—Efficient syntheses of (+)-*proto*, (−)-*gala* quercitols and carba-L-rhamnose from D-(−)-quinic acid are described.

Cyclitols have attracted a great deal of attention from the synthetic community due to their glycosidase inhibition activities and their versatility as synthetic intermediates.[1] Quercitols as cyclohexanepentols can exist in 16 diastereomeric forms,[2] of which four are symmetric. Only (+)-*proto*, (−)-*proto* and (−)-*vibo* quercitols are found in Nature.[3] (+)-*proto* Quercitol **1** was discovered initially and its first synthesis was completed in 1968 by McCasland et al.[4] Although there is considerable literature on the synthesis of various quercitols, we felt the need to develop a practical and efficient synthetic route to these compounds in bulk quantities. Besides quercitols, carba-sugars are cyclic monosaccharide analogues in which the endocyclic oxygen atom is replaced by a methylene group.[5] As a consequence of this substitution, carba-sugars are hydrolytically stable analogues of their parent sugars towards degradation by glycosidases.[6] Carba-L-rhamnose **3**, an analogue of L-rhamnose has received little attention from synthetic chemists.[7] Herein, we report efficient syntheses of (+)-*proto* **1**, (−)-*gala* **2** quercitols and carba-L-rhamnose **3** (Fig. 1) from D-(−)-quinic acid.

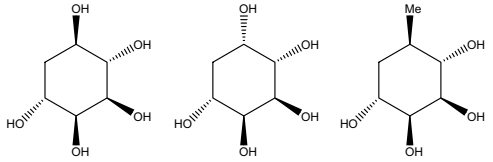

Figure 1.

The synthesis of **1** began with the preparation of (−)-shikimic ester **5** from D-(−)-quinic acid **4** according to the literature procedure.[8] OsO_4 catalyzed NMO oxidation of **5** in *t*-BuOH at reflux for 3 h produced the diol **6** as a single diastereomer. The secondary OH group at C-2 was protected selectively as a MOM-ether and the ester reduced with LAH to afford the triol **7**, which was subjected to oxidative cleavage using silica-supported sodium metaperiodate in DCM to give the β-hydroxy ketone **8** in quantitative yield (Scheme 1).

We envisaged that the presence of the cyclohexylidene protection at C-3, C-4 would direct hydride attack from the *Si* face (Scheme 2) and indeed, sodium borohydride reduction of ketone **8** at −40 °C in methanol gave the diol **9**[9] as a single diastereomer.

It was difficult to establish the stereochemistry at the newly formed chiral centre C-1 due to second order splitting and overlapping of the signals for the H-3, H-4, H-5, H-1 and OMe protons. In order to shift the resonance due to H-1 and H-5, the compound was derivatized as the di-*O*-benzoate **11**[10] by treatment with benzoyl chloride and pyridine in DCM at 0 °C (Scheme 3). The configuration at C-1 was assigned based on the coupling constants of H-1 with H-2 and H-6a ($J = 8.3$ and 12.6 Hz, respectively). This was further confirmed by a COSY experiment.

The deprotection of the diol **9** was carried out with cat. HCl in MeOH at room temperature for 10 h to give

Keywords: (+)-*proto* Quercitol; (−)-*gala* Quercitol; Stereoselectivity; Carba-L-rhamnose; D-(−)-Quinic acid; Cyclohexanepentols.
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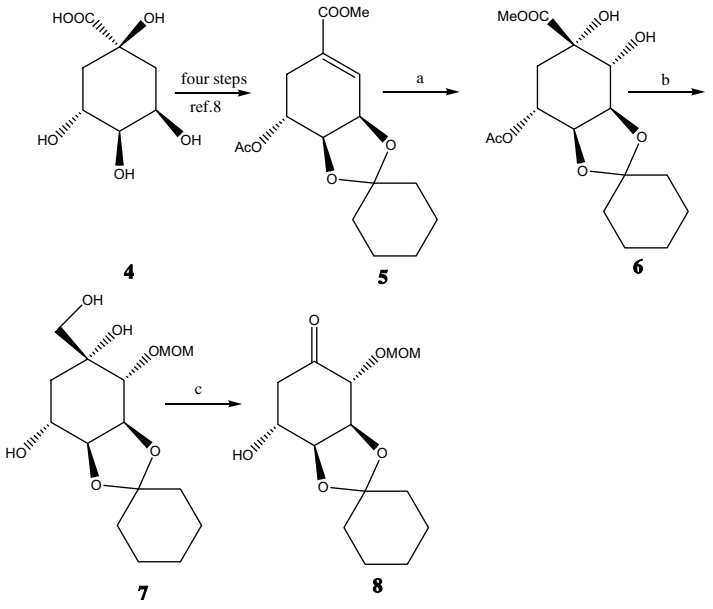
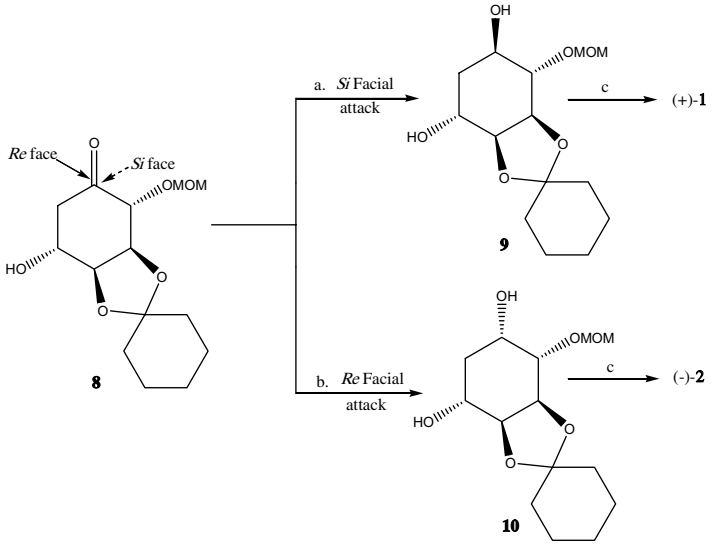
doi:10.1016/j.tetlet.2005.07.052



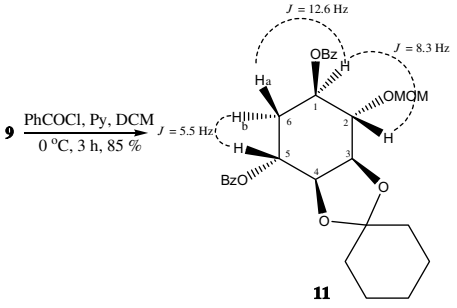
Scheme 1. Reagents and conditions: (a) OsO_4, NMO, *t*-BuOH, reflux, 3 h, 70%; (b) (i) MOMCl, Hünig's base, DCM, 12 h, 87%; (ii) LAH, THF, 60 °C, 2 days, 90%; (c) $NaIO_4$–SiO_2, DCM, rt, 2 h, 100%.



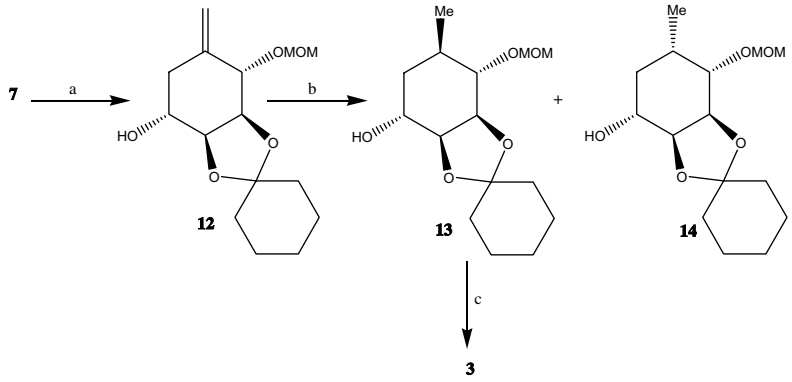
Scheme 2. Reagents and conditions: (a) $NaBH_4$, MeOH, −40 °C, 2 h, 87%; (b) K-Selectride, THF, −78 °C, 1 h, 95%; (c) cat. HCl, MeOH, rt, 10 h, 92%.

(+)-*proto* quercitol **1** with analytical data in excellent agreement with the literature values.[11]

The synthesis of (−)-*gala* quercitol **2**, which is the C-1 epimer of **1**, required the reversal of stereoselectivity during the reduction of ketone **8**. The reduction of **8** with K-Selectride in dry THF at −78 °C afforded the diol **10**[12] as a single diastereomer, no diastereomeric impurity being detected. The selectivity was attributed to chelation of a potassium ion with the C-1 carbonyl oxygen and the C-5 hydroxyl group from the *Si* face, which directed the hydride attack from the *Re* face to produce the diol **10**. Deprotection of **10** with cat. HCl



Scheme 3.



Scheme 4. Reagents and conditions: (a) (i) 1,1′-thiocarbonyldiimidazole, toluene, reflux, 6 h; (ii) trimethyl phosphite, reflux, 9 h, (85%) from (**7**); (b) Pd/C–H_2, MeOH, 8 h, 40 psi, 97%; (c) cat. HCl, MeOH, rt, 10 h, 95%.

in MeOH gave (−)-*gala* quercitol **2** in excellent yield, with analytical data in agreement with reported values.[13]

We next turned our attention to the synthesis of **3** from **7**. The triol **7** was converted in to the *exo*-olefin **12** by employing the Corey–Winter protocol.[14] We anticipated that reduction of the *exo*-olefin would proceed in a manner similar to the carbonyl reduction. Catalytic hydrogenation of **12** with 10% Pd/C at 40 psi in methanol afforded a diastereomeric mixture of **13**[15] and **14** in a ratio of 93:7, which were separated by flash column chromatography. All attempts to improve the selectivity, including changing the catalyst were unsuccessful. Global deprotection of **13** with cat. HCl in methanol gave **3** in excellent yield with analytical data in agreement with the literature values[7a,16] (Scheme 4).

In conclusion, we have successfully synthesized (+)-*proto*, (−)-*gala* quercitols and carba-L-rhamnose from D-(−)-quinic acid in ten linear steps.

Acknowledgements

A.K.Y. thanks CSIR for financial assistance in the form of a fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.07.052.

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9. Compound **9**: White solid. Mp 97 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.83 (s, 2H), 4.26 (dd, $J = 5.0$, 3.7 Hz, 1H), 4.15 (m, 2H), 3.84 (ddd, $J = 14.1$, 9.2, 4.9 Hz, 1H), 3.62 (br s, 1H), 3.45 (br s, 4H), 2.05 (dt, $J = 14.1$, 5.1 Hz, 1H), 1.87 (ddd, $J = 13.2$, 9.5, 3.7 Hz, 1H), 1.75–1.50 (m, 8H), 1.41 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 97.6, 86.0, 78.2, 77.7, 66.7, 66.5, 55.8, 37.8, 35.1, 34.6, 24.9, 23.9, 23.6. Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.32; H, 8.39. Found: C, 58.04; H, 8.51. $[\alpha]_D^{25}$ −12.6 (*c* 0.70, $CHCl_3$).
10. Compound **11**: Clear syrup. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (m, 4H), 7.57 (dd, $J = 7.6$, 6.4 Hz, 2H), 7.45 (m, 4H), 5.69 (m, 1H), 5.46 (ddd, $J = 12.6$, 8.9, 3.7 Hz, 1H), 4.89 (d, $J = 6.6$ Hz, 1H), 4.79 (d, $J = 6.6$ Hz, 1H), 4.35 (t, $J = 5.7$ Hz, 1H), 4.33 (t, $J = 4.2$ Hz, 1H), 4.11 (dd, $J = 8.3$, 5.7 Hz, 1H), 3.33 (s, 3H), 2.29 (dt, $J = 14.0$, 5.5 Hz, 1H), 2.22 (ddd, $J = 14.0$, 12.6, 3.7 Hz, 1H), 1.85 (t, $J = 6.2$ Hz, 2H), 1.7–1.55 (m, 6H), 1.4 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.6, 165.3, 133.3, 133.1, 129.9, 129.8, 129.7, 128.5, 128.4, 110.5, 96.5, 78.5, 77.0, 75.3, 70.0, 69.4, 55.8, 37.9, 35.4, 30.0, 24.9, 23.9, 23.7. $[\alpha]_D^{25}$ +45 (*c* 0.2, $CHCl_3$).
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12. Compound **10**: Clear syrup. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.80 (dd, $J = 16.8$. 6.6 Hz, 2H), 4.30 (m, 2H), 4.40 (br s, 1H), 4.10 (m, 1H), 3.75 (d, $J = 8.9$ Hz, 1H), 3.70 (dd, $J = 5.9$, 2.8 Hz, 1H), 3.40 (s, 3H), 2.95 (br s, 1H), 2.18 (dt, $J = 14.9$, 4.6 Hz, 1H), 1.92 (dt, $J = 14.9$, 3.3 Hz, 1H), 1.75–1.50 (m, 8H), 1.40 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 109.7, 95.7, 78.6, 78.4, 75.6, 69.4, 67.9, 55.6, 38.0, 35.4, 31.3, 24.9, 23.9, 23.6. Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.32: H, 8.39. Found: C, 59.16; H, 8.56. $[\alpha]_D^{25}$ +32.9 (*c* 1.5, $CHCl_3$).

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15. Compound **13**: Clear syrup. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.00 (d, $J = 6.5$ Hz, 1H), 4.66 (d, $J = 6.5$ Hz, 1H), 4.20–4.05 (m, 3H), 3.42 (s, 3H), 3.45–3.30 (m, 1H), 2.05–1.75 (m, 2H), 1.75–1.50 (m, 9H), 1.50–1.35 (m, 2H), 1.05 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 109.4, 96.4, 81.1, 79.3, 78.8, 67.3, 55.9, 37.8, 35.2, 29.1, 25.0, 24.0, 23.7, 18.4. Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 62.71; H, 9.52. $[\alpha]_D^{25}$ −30.4 (*c* 0.85, $CHCl_3$).
16. Optical rotation: $[\alpha]_D^{25}$ +5.9 (*c* 0.65, MeOH). Reported value: $[\alpha]_D^{25}$ +5.9 (*c* 1, MeOH).[7a]