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Synthesis of carba-sugars from (−)-quinic acid

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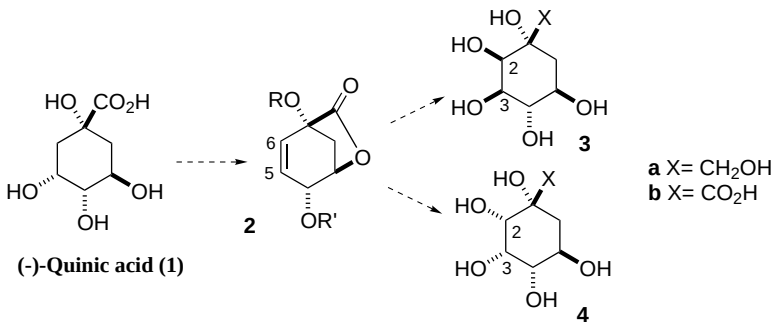
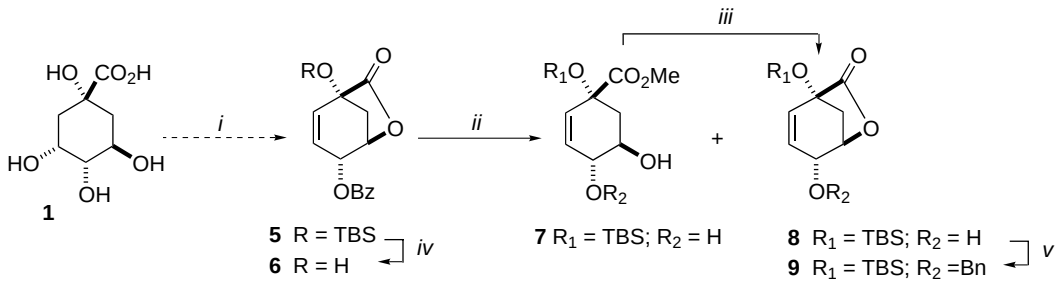
Abstract—(1*S*,2*R*,3*R*,4*S*,5*R*)- (**3a**) and (1*S*,2*S*,3*S*,4*S*,5*R*)-1,2,3,4,5-pentahydroxy-1-hydroxymethylcyclohexane (**4a**), (1*R*,2*R*,3*R*,4*S*,5*R*)- (**3b**) and (1*R*,2*S*,3*S*,4*S*,5*R*)-1,2,3,4,5-pentahydroxycyclohexan-1-carboxylic acid (**4b**) are reported. The syntheses exploit the diastereoselective oxidation of the 5,6-double bond of the quinic acid-derived lactone **2** with osmium tetroxide.

Carba-sugars are cyclic monosaccharide analogues in which the endocyclic oxygen atom is replaced by a methylene group.[1] As a consequence of this substitution, carba-sugars are hydrolytically stable analogues of their parent sugars towards degradation of glycosidases. The discovery of carba-sugars in natural products and their potential in biochemical studies of specific enzyme inhibition, particularly as glycosidase inhibitors,[2] have resulted in considerable attention being focused on their synthesis.



Scheme 1.



Scheme 2. *Reagents and conditions*: (i) Ref. 4; (ii) K_2CO_3, MeOH, rt (94%); (iii) NaH, THF, 0°C (83%); (iv) TBAF, AcOH, THF, rt (94%); (v) (1) NaH, THF, 0°C, (2) BnBr, Bu_4NI, rt (79%).

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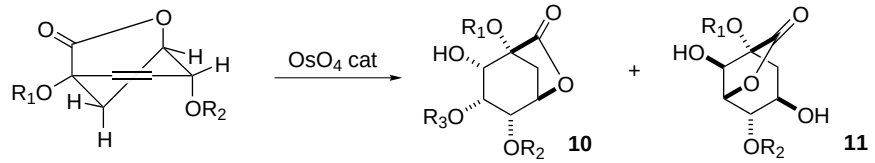


5: R_1= TBS; R_2= Bz
6: R_1= H; R_2= Bz
8: R_1= TBS; R_2= H
9: R_1= TBS; R_2= Bn

a: R_1= TBS; R_2= Bz; R_3= H
b: R_1= TBS; R_2= H; R_3= H
c: R_1= TBS; R_2= Bn; R_3= H
d: R_1= H; R_2= Bz; R_3= H
e: R_1= TBS; R_2= H; R_3= Bz
f: R_1= H; R_2= H; R_3= Bz

a: R_1= TBS; R_2= Bz
b: R_1= TBS; R_2= H
c: R_1= TBS; R_2= Bn
d: R_1= H; R_2= Bz

Scheme 3.

In this communication, we report the synthesis of carba-sugars **3** and **4** starting from a cheap and commercially available (–)-quinic acid (**1**) as a chiral template,[3] by *cis*-hydroxylation of the 5-cyclohexene derivative **2** (Scheme 1).

The cyclohexene derivative **5** was obtained in three steps and 47% overall yield from (–) quinic acid (**1**), as described by Bartlett et al. (Scheme 2).[4] Treatment of the benzolactone **5** with sodium methoxide or potassium carbonate in methanol afforded, in both cases, a mixture of the methyl ester **7**[5] and the hydroxycarbolactone **8**.[5] The main product during the reaction course was the methyl ester **7**; however, after work-up, the reaction mixture was equilibrated to an approximate 1:1 mixture of **7** and **8**. Treatment of diol **7** with an equivalent of sodium hydride yielded lactone **8** in 83% yield.

The key step of the synthesis of **3** and **4** is the introduction of the hydroxyl groups in the 2- and 3-positions using osmium tetroxide (Scheme 3). This paper describes a study of various conditions and reagents. The results are summarized in Table 1.[6] Different co-oxidants for the regeneration of osmium tetroxide were investigated (potassium ferrocyanide, *N*-methylmorpholine oxide, *N*-trimethylamine oxide and sodium periodate). No reaction was observed when potassium ferrocyanide, AD_{mix}-α or AD_{mix}-β was used. Sodium periodate gave cleaner reaction mixtures than both *N*-methylmorpholine oxide and *N*-trimethylamine oxide.

Hydroxylation of the allylic alcohol **8** (entries 7, 8 and 9, Table 1) gave a mixture of two hydroxylated products, **10b** and **11b**, resulting from the reaction of the *Si* and *Re* faces, respectively. When the addition occurs from the *Re* face, migration of the carbolactone from the 1,5- to the 1,3-position was also observed. Surprisingly, the proportional ratio of *Si* and *Re cis*-hydroxylation was very dependent on the co-oxidant. Hydroxylated lactone **11b** was the major diastereoisomer in the OsO_4/$NaIO_4$ oxidation (entry 7, Table 1) proceeding from the sterically more congested face of the molecule, which has been demonstrated to be the more sterically hindered one.[7] In contrast, hydroxylated lactone **10b** was the major diastereoisomer in the OsO_4/NMO oxidation (entry 8, Table 1).

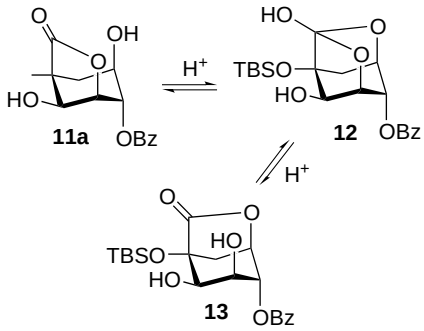
Kishi noted that osmium tetroxide approaches preferentially to the face of the double bond opposite to the pre-existing allylic hydroxyl or alkoxyl group.[8] However, if there is more than one allylic substituent, the stereochemical results are not so easily predicted. In our case, the *cis*-hydroxylation also depends on the reaction conditions. Intrigued by this result, we turned our attention to study the osmylation reaction with a series of alkenes and with different co-oxidants for the regeneration of the osmium tetroxide.

The major product arising from the diprotected benzoylalkene **5** arose from *Si*-hydroxylation when $NaIO_4$ or NMO were the co-oxidants (entries 1 and 2, Table 1), whereas OsO_4/M_3NO oxidation gave predominantly *Re*-hydroxylation. In the latter case, compound **12** was also formed. This is an intermediate in the equilibrium process in acid media between lactones **11a** and **13** (Scheme 4). TBS deprotection of **5** afforded hydroxyalkene **6**, which was subjected to osmylation and gave an approximately 1:1 mixture of *Re*- and *Si*-hydroxylation in low yield (entries 4 and 5, Table 1). Benzylation of **8** afforded **9**. This compound was not hydroxylated with OsO_4/$NaIO_4$, but afforded mainly the *Re*-hydroxylation product using NMO as co-oxidant (entry 11, Table 1). Finally, removal of the lactone bridge, as in **7**,

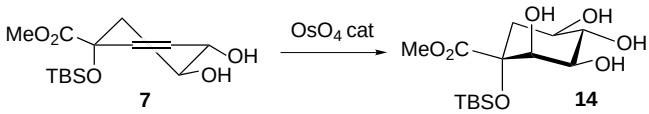
Table 1. Osmium tetroxide oxidation[a]

Entry	Substrate	Method	Hydroxylation	
			Si (%)	*Re* (%)
1	**5**	A	71	26
2	**5**	B	64	<5
3	**5**	C	19	57
4	**6**	A	22	19
5	**6**	B	23	24
6	**6**	C	–[b]	–[b]
7	**8**	A	12	55
8	**8**	B	61	18
9	**8**	C	36	18
10	**9**	A	–[c]	–[c]
11	**9**	B	<5	80

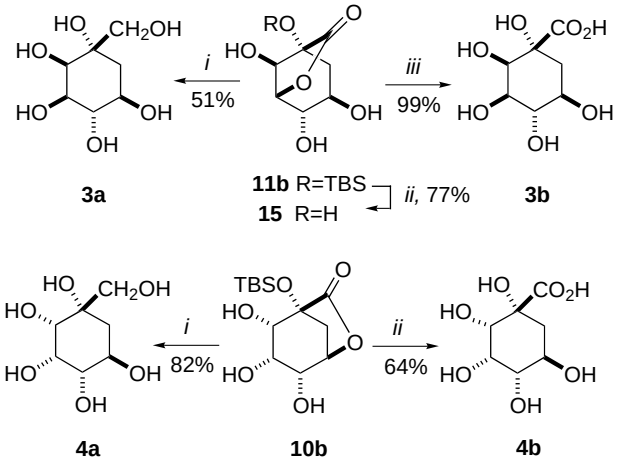
[a] Ratio determined from isolated compounds. Method A: $NaIO_4$; B: NMO; C: Me_3NO.
[b] Complex mixture of products.
[c] No reaction.



Scheme 4.



Scheme 5. *Reagents and yields*: (i) NMO (87%); (ii) $NaIO_4$ (70%); (iii) Me_3NO (89%).



Scheme 6. *Reagents and conditions*: (i) (1) $LiBH_4$, MeOH, THF, Δ, (2) AcOH, H_2O, Δ; (ii) AcOH, H_2O, THF, 40°C; (iii) (1) LiOH, 0°C, (2) Amberlite-IR 120.

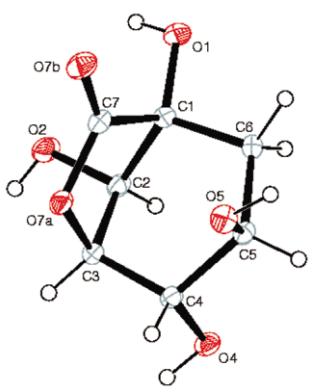


Figure 1. X-Ray structure of **15**.

shows that the osmylation reaction takes place on the olefin face opposite to the allylic oxygen, as in the Kishi model, and with formation in high yield of a sole diastereoisomer **14** independent of the reaction conditions (Scheme 5).

In summary, it was found that the facial selectivity of the hydroxylation with osmium tetroxide could be reversed by changing the protecting groups on C-1 and C-4, or in the case of compounds **5** and **8**, by changing the co-oxidant. It is notable in this comparison that treatment of **5** with $NaIO_4$ gave predominantly *Si*-hydroxylation for **5**, and use of Me_3NO gave predominantly *Re*-hydroxylation, whereas the opposite was observed with **8**.

Reduction of the carbolactones **11b** and **10b** with lithium borohydride followed by deprotection of the hydroxyl group with aqueous acetic acid afforded polyhydroxycyclohexanes **3a** and **4a** in 45 and 63% overall yield, respectively (Scheme 6).[9] Treatment of hydroxycarbolactone **11b** with aqueous acetic acid gave tetraol **15**, whose X-ray structure is shown in Fig. 1.[10] Hydrolysis of lactone **15** under basic conditions afforded the hydroxy quinic acid derivative **3b** in quantitative yield, whereas treatment of hydroxycarbolactone **10b** with aqueous acetic acid gave analogue **4b** directly in 64% yield.

Acknowledgements

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9. Compound **3a**: $[\alpha]_D^{20}$ −2° (*c* 0.7, CH_3OH); ^1H NMR (500 MHz, CH_3OD) δ 3.76 (m, 2H), 3.64 (s, 2H), 3.45 (d, 1H, *J* 11.2), 1.77 (dd, 1H, *J* 13.1 and 4.7) and 1.66 (dd, 1H, *J* 13.1 and 11.8); ^{13}C NMR (125 MHz, DEPT, CH_3OD) δ 86.8 (CH), 84.2 (C), 82.6 (CH), 81.7 (CH), 78.4 (CH), 75.1 (CH_2) and 31.7 (CH_2); MS (+FAB) *m*/*z* (%) 195 (MH^+); HRMS calcd for $C_7H_{15}O_6$: MH^+, 195.0869. Found: MH^+, 195.0875. Compound **3b**: $[\alpha]_D^{20}$ −12° (*c* 0.7, H_2O); ^1H NMR (250 MHz, D_2O) δ 3.59 (d, 1H, *J* 3.0), 3.41 (dd, 1H, *J* 3.0 and 9.5), 3.33 (m, 1H), 3.22 (t, 1H, *J* 9.5) and 1.70 (m, 2H); ^{13}C NMR (63 MHz, DEPT, D_2O) δ 177.5 (C), 76.0 (C), 74.5 (CH), 73.2 (CH), 71.2 (CH), 69.1 (CH) and 34.7 (CH_2); MS (+FAB) *m*/*z* (%) 209 (MH^+); HRMS calcd for $C_7H_{13}O_7$: MH^+, 209.0661. Found: MH^+, 209.0666. Compound **4a**: $[\alpha]_D^{20}$ −20° (*c* 1.1, CH_3OH); ^1H NMR (250 MHz, CD_3OD) δ 4.12 (t, 1H, *J* 3.0), 4.05 (m, 1H), 3.66 (m, 2H), 3.64 (s, 2H), 3.32 (m, 1H), 1.98 (dd, 1H, *J* 13.6 and 4.9) and 1.56 (dd, 1H, *J* 13.6 and 11.7); ^{13}C NMR (63 MHz, DEPT, CD_3OD) δ 78.1 (C), 77.1 (CH), 76.8 (CH), 70.4 (CH), 68.2 (CH), 67.5 (CH_2) and 39.8 (CH_2); MS (+FAB) *m*/*z* (%) 195 (MH^+); HRMS calcd for $C_7H_{13}O_7$: MH^+, 195.0869. Found: MH^+, 195.0875. Compound **4b**: mp 210–212°C [20% ethyl acetate–methanol (Lit.[11] 221°C, 25% aq. ethanol)]; $[\alpha]_D^{20}$ −17° (*c* 2.6, H_2O), Lit.[11] −16° (*c* 1.0, 50% aq. ethanol).
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