Syntheses of (−)-MK7607 and Other Carbasugars from (−)-Shikimic Acid

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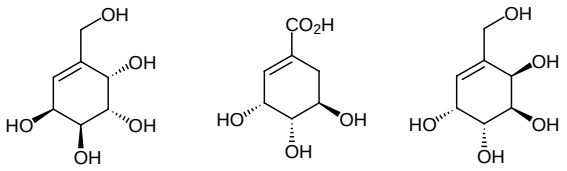
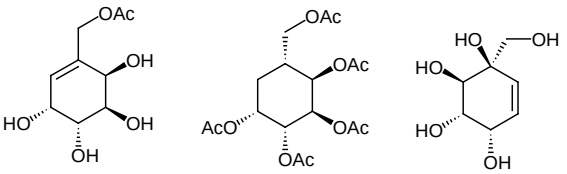
Abstract: (−)-MK7607 (**1**) and other carbasugars **2**, **3**, **4** have been synthesised from (−)-shikimic acid via OsO_4-catalysed dihydroxylation of diene **7**, an unstable key intermediate which was obtained by transient elimination of triflate **6**.

Key words: carbasugars, shikimic acid, carbocycles, dihydroxylations, functionalised cyclohexenes

Carbasugars, or pseudosugars as they were previously called,[1] refer to a broad category of carbocyclic analogues of monosaccharides in which the ring oxygen is replaced by a carbon atom.[2] Carbasugars lack the acetal function which is characteristic of common monosaccharides. As carbohydrate mimics, they are stable to enzymatic hydrolysis in biological systems, and often display a range of biological activities, particularly as glycosidase inhibitors.[3] Some examples of naturally occurring carbasugars include carba-α-D-galactose,[4] streptol,[5] zeylenol,[6] ferrudiol,[7] valienamine[8] and validamine.[9] MK7067 is a recent example of carbasugar which was isolated from the fermentation broth of *Curvularia eragrostidis* D2452 and was found to have an effective herbicidal activity.[10] So far, only a racemic synthesis of MK7607 has been reported.[11] Available synthetic strategies for the synthesis of carbasugars generally fall into two categories. One is the transformation of carbohydrates to carbocycles,[12] and the other the synthetic elaboration of existing carbocycles, such as quinic acid[13] and arene *cis*-dihydrodiols.[14] In connection with our work on the shikimate pathway,[15] we felt that the synthetic utility of shikimic acid as a chiral template has not been fully exploited. This was probably due to its limited availability from the *Illicium* plants. However, an alternative source of shikimic acid has recently been reported from microbial fermentation of glucose using recombinant *E. coli*,[16] and shikimic acid produced by this method has already been used as a raw material for the manufacture of the antiinfluenza drug Tamiflu™ (oseltamivir phosphate).[17] In this communication, we describe the syntheses of (−)-MK7607 (**1**) and other carbasugars **2**, **3** and **4** (Figure), using shikimic acid as the starting material.

(−)-Shikimic acid was esterified in methanol in the presence of camphorsulphonic acid and the resulting methyl ester was treated with 2,2-dimethoxypropane also in the presence of camphorsulphonic acid to give the acetonide





Figure

5[18] in an overall yield of 91% (Scheme 1). The hydroxyl group in acetonide **5** was reacted with trifluoromethanesulfonic anhydride to give the corresponding triflate **6** in almost quantitative yield. Elimination of the triflate group in **6** was effected under Kellogg's conditions[19] with cesium acetate in DMF at room temperature for 2 h to yield the diene **7** (81%),[20] which was unstable and prone to further aromatisation.[21] We have found that use of excessive cesium acetate, higher reaction temperature (40 °C) and prolonged reaction time (12 h) all contributed to the aromatisation with the formation of methyl 3-hydroxybenzoate. In fact, our initial attempts to eliminate the triflate group in **6** had all ended with the aromatised product. Hydroxylation of the diene **7** using *N*-methylmorpholine *N*-oxide and a catalytic amount of osmium tetroxide gave, in equal ratio, the vicinal diols **8**, mp 97−99 °C, $[\alpha]_D$ −31.3 (*c* 0.80 in $CHCl_3$), and **9**, mp 91−92 °C, $[\alpha]_D$ +82.7 (*c* 1.05 in $CHCl_3$), in combined yield of 73%.

Diol **8** was protected with 2,2-dimethoxypropane to form the diacetonide **10** (98%), $[\alpha]_D$ +41.9 (*c* 0.86 in $CHCl_3$), which was further reduced with DIBAL-H in THF to give the alcohol **11**, $[\alpha]_D$ +24.2 (*c* 0.99 in $CHCl_3$), in almost quantitative yield (Scheme 2). Deprotection of **11** with aqueous TFA gave (−)-MK7607 (**1**) (92%) as colourless crystals, mp 158−159 °C, $[\alpha]_D$ −207.0 (*c* 0.55 in MeOH), −239.9 (*c* 0.55 in H_2O) {for the enantiomer, lit.,[10] $[\alpha]_D$ −210 (*c* 1.0 in H_2O)}.

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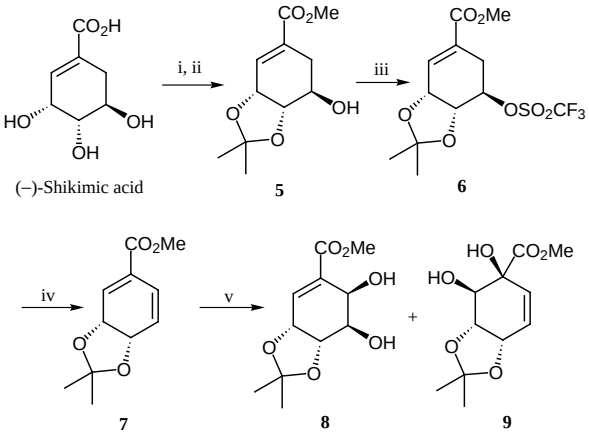
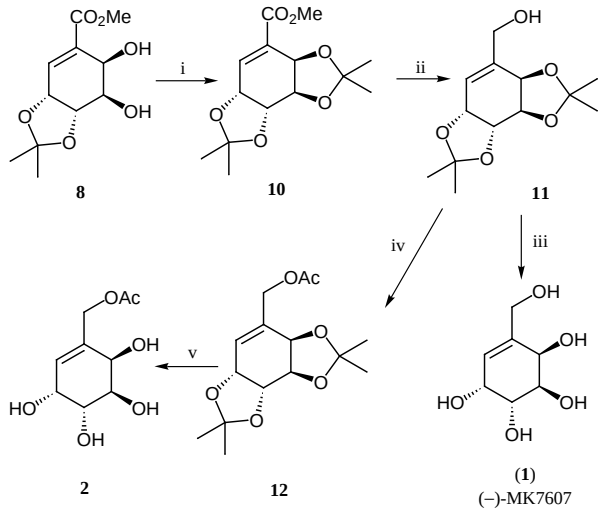


Scheme 1 Reagents and condtions: i, CSA, MeOH, reflux, 10 h, 96%; ii, $CMe_2(OMe)_2$, CSA, r.t., 2 h, 95%; iii, Tf_2O, DMAP, pyridine, CH_2Cl_2, −20 ºC, 40 min, 98%; iv, CsOAc, DMF, r.t., 2 h, 81%; v, OsO_4, NMO, *t*-BuOH−H_2O (10:1), 20 ºC, 8 h, 38% for **8**, 35% for **9**.

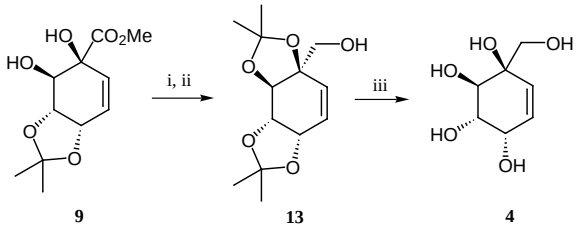
Gabosine K had previously been assigned the structure **2**, which is from a family of carbasugars produced by *Streptomyces*.[22] However, the spectral properties of a racemic **2**, synthesised by Metha and Lakshminath,[11] were found to be different from that of gabosine K. To investigate this, alcohol **11** was treated with acetic anhydride in pyridine to give the acetate **12** (93%), $[\alpha]_D$ +43.1 (*c* 1.16 in $CHCl_3$). Selective removal of the isopropylidene groups in **12** proved to be difficult under a range of reaction conditions, such as 50% aq. TFA, I_2 in methanol, Amberlyst in THF–water, which all produced a mixture of (−)-MK7607 (**1**) and compound **2**. It was later found that treatment of **12** with 80% aqueous acetic acid could selectively take off the isopropylidene groups to give the tetrol **2**, the spectral properties of which are identical with that of the synthesised racemate.[11] Therefore, our synthesis confirmed that gabosine K was incorrectly assigned the structure **2**.



Scheme 2 Reagents and condtions: i, $CMe_2(OMe)_2$, CSA, r.t., 3 h, 98%; ii, DIBAL-H, THF, −10 ºC, 1.5 h, 99%; iii, TFA–H_2O (6:1), r.t., 2 h, 92%; iv, Ac_2O, DMAP, pyridine, r.t., 2.5 h, 93%; v, aq. HOAc (80%), 60 ºC, 4.5 h, 66%.

The diacetonide **10** can be converted to the pentaacetate of carba-β-D-altropyranose **3** following known literature procedures by stereoselective hydrogenation, DIBAL-H reduction, removal of the isopropylidene group and subsequent acetylation.[14]

Following a sequence of reactions similar to that of diol **8**, the diol **9** was also transformed into carbasugar **4** in an overall yield of 73% (Scheme 3).



Scheme 3 Reagents and condtions: i, $CMe_2(OMe)_2$, CSA, r.t., 10 h, 82%; ii, DIBAL–H, THF, −10 ºC, 1 h, 99%; iii, TFA-H_2O (6:1), r.t., 1 h, 90%.

In summary, using (−)-shikimic acid as chiral template we have synthesised the antipode of the naturally occuring herbicide MK 7607 and some other carbasugars. Works are under way to further elaborate the diene **7** into other synthetic targets.

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(20) All new compounds were characterised and had spectroscopic and analytical data in agreement with the assigned structure. *Selected data*: For **7**: δ_H (270 MHz, $CDCl_3$) 1.39 (3 H, s), 3.80 (3 H, s), 4.65 (1 H, ddd, *J* = 9.9, 4.0 and 0.7 Hz), 4.82 (1 H, dddd, *J* = 9.2, 4.0, 2.0 and 0.7 Hz), 6.04 (1 H, dd, *J* = 9.9 and 4.0 Hz), 6.54 (1 H, d, *J* = 9.9 Hz), 6.85−6.87 (1 H, m); δ_C (67.8 MHz, $CDCl_3$) 24.36, 26.38, 51.89, 69.27, 70.43, 105.23, 122.03, 125.27, 126.67, 133.32, 165.40. For compound **2**: mp 148−149 °C, $[\alpha]_D$ −150.0 (*c* 0.50 in MeOH); δ_H (500 MHz, CD_3OD) 2.07 (3 H, s), 3.87–3.88 (2 H, m), 4.24−4.25 (2 H, m), 4.59 (1 H, d, *J* = 13.3 Hz), 4.70 (1 H, d, *J* = 13.3 Hz), 5.79 (1 H, d, *J* = 4.1 Hz); δ_C (125.76 MHz, CD_3OD) 20.75, 65.74, 67.41, 67.96, 70.66, 70.91, 128.20, 137.16, 172.52; [*m/z* HRMS (CI, NH_3) Found: MNH_4^+ 236.1136, $C_9H_{18}NO_6$ requires 236.1134] (Found: C, 49.50; H, 6.53. $C_9H_{14}O_6$ requires C, 49.54; H, 6.47%). For compound **4**: mp 127−128 °C; $[\alpha]_D$ +161.5 (*c* 0.61 in MeOH); δ_H (270 MHz, CD_3OD) 3.53−3.57 (2 H, m), 3.78−3.82 (2 H, m), 4.17−4.20 (1 H, m), 5.79 (1 H, d, *J* = 9.9 Hz), 5.92 (1 H, dd, *J* = 9.9 and 5.3 Hz); δ_C (67.8 MHz, CD_3OD) 67.30, 68.01, 69.66, 70.92, 74.05, 131.03, 133.08; [*m/z* HRMS (CI, NH_3) Found: MNH_4^+ 194.1027, $C_7H_{16}NO_5$ requires 194.1028] (Found: C, 47.45; H, 6.94. $C_7H_{12}O_5$ requires C, 47.73; H, 6.87%).
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