A Direct Entry to Carbasugars: Asymmetric Synthesis of 1-*epi*-(+)-MK7607

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Abstract: A short and flexible synthesis of 5a-carbasugars is presented. The combination of a proline-catalyzed aldol reaction and a ring-closing metathesis affords 1-*epi*-(+)-MK7607 in seven steps with an overall yield of 23%.

Key words: carbasugars, organocatalysis, asymmetric synthesis, aldol reaction, ring-closing metathesis

Carbasugars,[1] also known as pseudosugars,[2] are characterized by the replacement of the ring oxygen of monosaccharides by a methylene group.[3] Not only saturated carbasugars are known, but also unsaturated ones bearing a ring double bond. Interestingly, they are often recognized by enzymes instead of the original sugar. Because of the lack of the acetal moiety, such carbasugars are stable towards hydrolysis.[4] Furthermore, they often show interesting biological properties, for instance, they are glycosidase inhibitors, antibiotics, antivirals or plant growing inhibitors.[5] Typical examples of naturally occurring carbasugars are streptol,[6] valienamine,[7] validamine,[8] cyclophellitol,[9] (+)-MK7607[10] or the family of gabosines.[11] (+)-MK7607 (**2**) has effective herbicidal activity and is the 4-epimer of streptol (**1**), a plant-growth inhibitor. They are two representative examples of eight possible diastereoisomers of the class of the unsaturated 5a-carbasugars characterized by an exocyclic hydroxymethyl moiety (Figure 1).

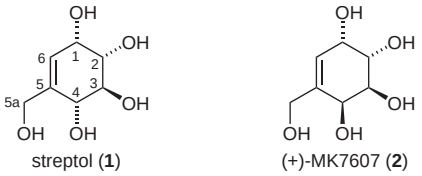
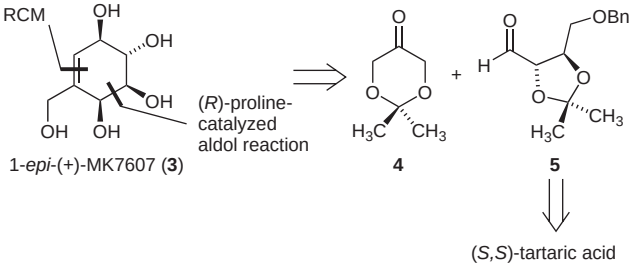


Figure 1 Structures of streptol (**1**) and (+)-MK7607 (**2**)

Altogether, four diastereoisomers are already known, three of them are naturally occuring and the fourth one has been synthesized in racemic form. Most interestingly, all these compounds are bioactive, but unfortunately direct and flexible approaches to synthesize different stereoisomers or derivatives have not been reported yet.[12] We therefore wish to present a modular strategy for the synthesis of carbasugars, which is demonstrated by an efficient and straightforward synthesis of 1-*epi*-(+)-MK7607 (**3**). (+)-MK7607 has been isolated from the fermentation broth of *Curvularia eragrostidis* D2452.[10] So far, only the synthesis of the racemic mixture and a synthesis of the (–)-enantiomer has been reported.[12d,e] A synthesis of the racemic mixture of the epimer **3** is also known and first studies towards its biological activity are very promising. Compound *rac*-**3** was used in a test with the BIAcore system and it was found that it shows a high affinity to galactose-recognizing lectin (ML I).[13] An efficient synthesis of **3** and its stereoisomers would allow for a more systematic evaluation of the biological activities. This may help to shed light on the mode of action involved and pave the way to the development of these compounds as drugs.

The retrosynthetic analysis for **3** is depicted in Scheme 1. Our strategy involves the construction of the cyclohexene core via a ring-closing metathesis. The second disconnection is a (*R*)-proline-catalyzed aldol reaction between 2,2-dimethyl-1,3-dioxan-5-one (**4**, dioxanone) and the aldehyde **5**, which can easily be obtained from (*S*,*S*)-tartaric acid in four steps.[14]



Scheme 1 Retrosynthetic analysis of **3**

Our first attempts towards the total synthesis of **3** were based on the (*R*)-proline-catalyzed aldol reaction between **4** and **5**. We were able to transfer our results of the (*S*)-proline-catalyzed aldol reaction of **4** with various aldehydes for the direct synthesis of carbohydrates and derivatives to the present case.[15] We have carried out both the (*R*)-proline- as well as the (*S*)-proline-catalyzed aldol reaction and we found, that this reaction proceeds to **6** with a good yield (69%) and nearly perfect stereocontrol (de ≥96%, ee >99%) employing (*R*)-proline. The yield decreases to 37% but with an identical diastereocontrol using (*S*)-proline (Scheme 2). The cause for the different reactivity between (*R*)- and (*S*)-proline can be rationalized with the fact that the Si-face of the aldehyde function of **5** is less

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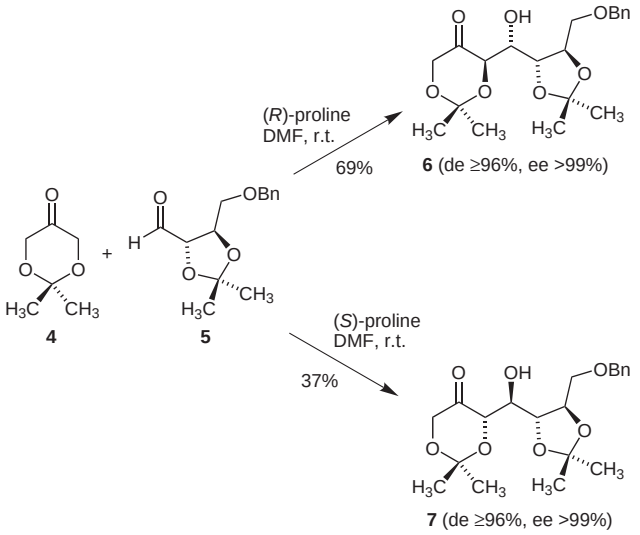
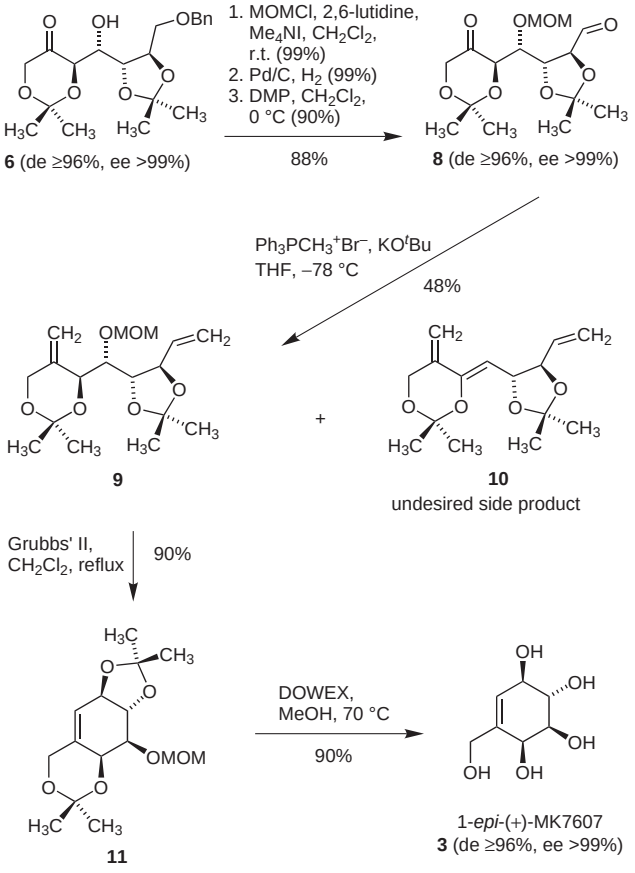


Scheme 2 (*R*)- and (*S*)-proline-catalyzed aldol reaction of **4** and **5**



Scheme 3 Synthesis of the carbasugar **3**

sterically hindered than the Re-face and therefore (*R*)-proline is a better organocatalyst than (*S*)-proline.[16] The aldol products **6** and **7** are inherently interesting because they represent the selectively and orthogonal protected heptuloses D-*gulo*-2-heptulose (**6**) and D-*talo*-2-heptulose (**7**).

For the successful completion of the synthesis of **3** we were able to carry out the (*R*)-proline-catalyzed aldol reaction on a 40 mmol scale obtaining 5.22 g of **6** without a decrease of yield and selectivity. The remaining synthesis requires the right choice for the protection of **6**. Our first attempt was a TBS protecting group but this turned out to be a dead end. We therefore choose the smaller MOM protecting group. The conversion of **6** to the MOM-ether proceeds quantitatively using MOMCl, DIPEA and catalytic amounts of Bu_4NI. After hydrogenolytic debenzylation the aldehyde-ketone **8** was obtained after Dess–Martin oxidation with an overall yield of 88% from **6** over three steps and the need of one chromatographic purification (Scheme 3).

The next goal was the conversion of **8** into the bisolefin **9** which turned out to be fairly difficult, since the elimination to **10** is favored under strong basic condition. This problem could be avoided by a double Wittig reaction using Ph_3PCH_3Br and the base *t*-BuOK. Compound **9** was formed in 48% yield. The bisolefine **9** was then converted into the protected 1-*epi*-(+)-MK7607 **11** via ring-closing metathesis employing Grubbs' second-generation catalyst.[17] To our delight, the desired cyclohexene **11** was smoothly formed with 90% yield after five hours in refluxing CH_2Cl_2, although **11** represents a penta-functionalized cyclohexene and is the part of a tricycle.[18] The relative configuration of **11** was proven by ^1H NMR spectroscopy and NOE measurements and is in agreement with the proposed relative configuration of the aldol product **6**. The final step of our synthesis comprises a complete deprotection of **11** to **3**. We therefore envisaged to carry out the final deprotection with the acidic ion-exchange resin DOWEX, because all protecting group are acetals and should be removable under acidic conditions. The deprotection was carried out in methanol at 70 °C. The reaction was finished after 2.5 hours and the carbasugar **3** could be obtained and in pure form simply by filtration over glass wool.[19]

In conclusion, we have developed a straightforward concept for the asymmetric synthesis of carbasugars containing an exocyclic hydroxymethyl moiety, which is based on a combination of a proline-catalyzed aldol reaction followed by ring-closing metathesis. We have demonstrated the applicability of our approach with the synthesis of 1-*epi*-(+)-MK7607 of high stereoisomeric purity (de ≥96%, ee >99%) in seven steps with an overall yield of 23%. The advantage of this strategy is its flexibility, because (*R*)- and (*S*)-proline can be used. Furthermore, the substitution pattern of the aldehyde as well as the chain length should be variable, which should allow the direct synthesis of various carbasugars and derivatives, which are difficult to access by conventional approaches.

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(19) Analytical Data of **3**.
R_f = 0.15 (EtOAc–MeOH = 6:1); $[\alpha]_D^{22}$ 232.7 (*c* 1.25, H_2O). ^1H NMR (300 MHz, D_2O): δ = 3.49 (dd, *J* = 10.9, 4.2 Hz, 1 H), 3.59 (dd, *J* = 10.9, 7.4 Hz, 1 H), 4.03 (m, 1 H), 4.09 (m, 2 H, CH_2OH), 4.16 (d, *J* = 4.2 Hz, 1 H), 5.66 (m, 1 H, C=CH) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 61.8 (CH_2OH), 66.5, 70.7, 71.7, 72.3 (CHOH), 126.9 (C=CH), 137.5 (C=CH). MS (EI, 70 eV): *m/z* (%) = 140 (7), 122 (10), 116 (47), 111 (28), 99 (17), 98 (100), 97 (21), 83 (11), 81 (13), 71 (11), 72 (14), 69 (27), 55 (15). HRMS: *m/z* calcd for $C_7H_{12}O_5 - 2H_2O$ [$M^+ - 2H_2O$]: 140.04734; found: 140.04735.