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A Unified Strategy for the Synthesis of Enantiomerically Pure Branched-Chain Cyclohexenones and -Cyclopentenones from a Single Progenitor

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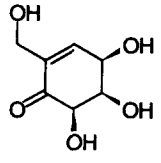
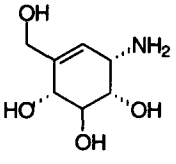
Abstract : Branched-chain cyclohexenones and cyclopentenones were prepared from sugar lactones by amide enolate condensation and subsequent intramolecular Knoevenagel reaction. Depending on the conditions, either the six- or the five-membered rings can be prepared from the same progenitor © 1997 Elsevier Science Ltd.

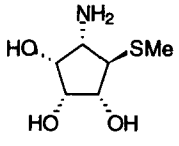
Nature has provided us with a number of highly functionalised five and six-membered carbocyclic structures. Many of these apparently simple structures have itself intesting biological properties or are part of more complex edifices of biological significance. Branched-chain cyclohexanone key structures are present in the recently isolated natural compounds gabosines.[1] Synthetic hydroxylated carbocycles have found wide applications as carbohydrate surrogates. As an example, valienamine which is a component of a natural aminoglycoside antibiotic,[2] may be regarded as a carbocyclic analogue of glucosamine.[3] Mannostatin-A,[4] another natural compound is useful as an inhibitor of glycoprotein processing enzymes. Carbocyclic pentoses analogues are also naturally occuring, the most representative being the nucleoside analogues aristeromycin [5] and its unsaturated derivative neplanocin-A.[6] The importance of these so-called carba-sugars is now well established,[3] and the recognition of sugar analogues as potential drugs and pharmacological tools has prompted the search for new routes to these compounds.[7]



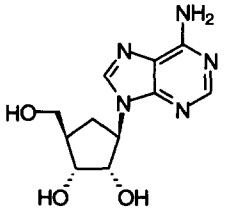
Gabosine C



Valienamine



Mannostatin A



Aristeromycin

The construction of carba-sugars requires the preparation of chiral branched-chain carbocyles. If many solutions for the synthesis of chiral cyclohexanes and cyclopentanes from sugars have been proposed during the last twelve years,[8] the synthesis of chiral branched-chain cyclohexanes from sugar precursors is less documented. Some examples of branched-chain cyclohexene ring synthesis based on intramolecular carbon-carbon double bond formation have been reported. Intramolecular Wittig reactions have been used in the synthesis of shikimate derivatives from D-ribose,[9] and D-mannose.[10] Altenbach *et al.* proposed an alternative route to cyclohexenone-based structures from sugar lactones using an intramolecular Horner olefination.[11]

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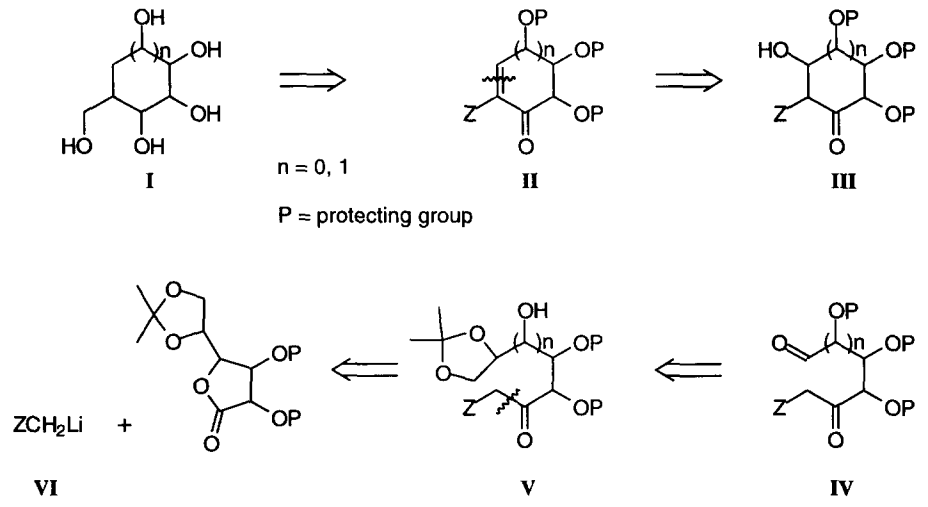
Another elegant approach involving an intramolecular aldol condensation and the use of sugar pseudolactone as the key features has been reported used by Vasella in the synthesis of a glyoxylase I inhibitor.[12]

In connection with our synthetic programme on carbohydrate mimics, we have investigated an efficient route to these basic carbocyclic structures and we found that, en route to six-membered rings, it was also possible to prepare five-membered rings along the same lines by a slight modification of the reaction conditions.



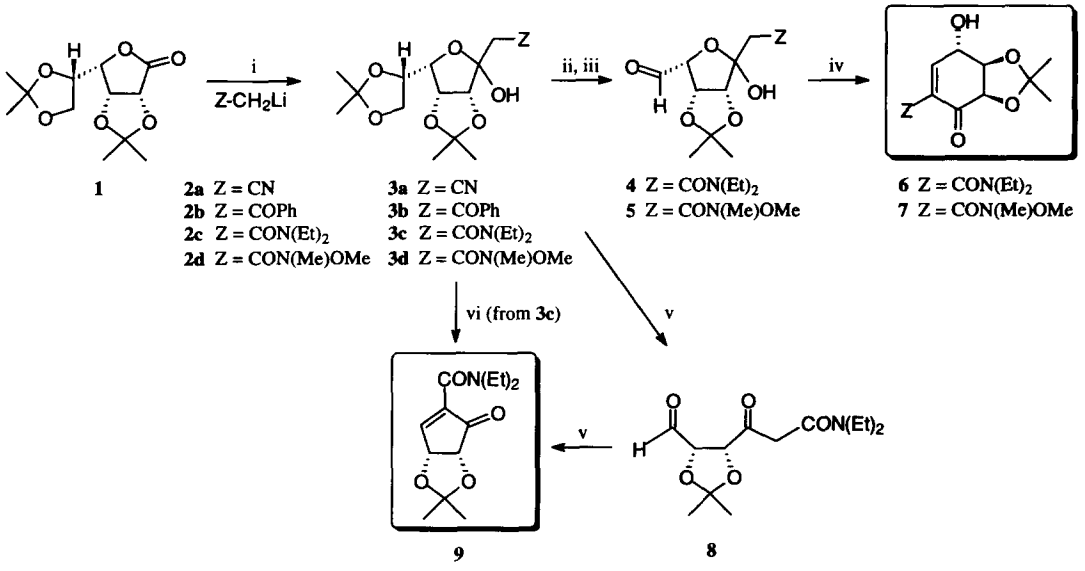
Scheme 1

Assuming that carba-sugar structures of type **I** could be in turn prepared by chemical manipulations of enone **II**, we focused on the preparation of this type of compound according to the strategy delinated on Scheme 1. It relies on an intramolecular Knoevenagel condensation to form **III** from **IV**. The activating Z group required for this latter reaction must be carefully chosen to provide a sufficiently reactive methylene group in **IV** and a reactive anion **VI**. Furthermore it needs to be chemically transformable and to make the starting compound also available in quantities. In a effort to allow large scale preparation of the required carbocyclic structures, we planned to use readily available sugar lactones providing a high level of stereochemical diversity. It should be noted that most of the absolute configurations present in the target compound are deduced from that of the starting lactone.

The first experiments were conducted on readily available 2,3:5,6-di-*O*-isopropylidene-D-gulonolactone **1**. Lithiated anions **2** were prepared by treatment with lithium diisopropylamide of acetonitrile, acetophenone, *N,N*-diethylacetamide, and *N*-(methyl)-*N*-(methoxy)-acetamide and were allowed to react with lactone **1** at 0°C in THF. The expected adducts **3a-d** were obtained in 72, 60, 51, and 40 % yield respectively. The same reaction has been successfuly applied to ***ent*-1** i.e. 2,3:5,6-di-*O*-isopropylidene-L-gulono-1,4-lactone.[13]

The next key step was the formation of the carbocycle, i.e. removal of the 5,6-isopropylidene unit, glycol cleavage and Knoevenagel reaction. The first experiment were conducted with the nitrile **3a** which seemed to be a good candidate for this purpose. The 5,6-acetal group was easily removed upon treatment with aqueous acetic acid (9/1:v/v) at 60°C. The resulting diol, after purification, was treated with one molar equivalent of sodium periodate in a methanol/water mixture to give the expected aldehyde. All attempts to promote the cyclisation reaction under various basic conditions led invariably to decomposition. Adduct **3b** was

also reluctant to cyclisation. We turned then to the adduct **3c** which was also treated under basic conditions. After considerable experimentation, we found that sodium carbonate suspended in dry tetrahydrofuran cleanly transformed the aldehyde **4** into the cyclohexenone **6** *provided that a catalytic amount of DBU* was added to the reaction mixture (60% yield).[14] Use of DBU alone caused extensive decomposition of the starting material. Under these conditions no intermediate aldol product was formed.[15] Almost identical results were obtained using ***ent*-3c** available from ***ent*-1**. The cyclohexenone ***ent*-6** was then obtained in 58% yield. This procedure was also applied to the amide **3d** which was cyclized in 20% yield from **3d** to **7**.



Scheme 2. Reagents: i, ZCH_3, lithium diisopropylamide, 1.2 equ., 0°C, THF, then add to **1**, 40-72%; ii, AcOH, H_2O, 9/1, 60°C; iii, $NaIO_4$ 1.1eq, H_2O, MeOH; iv, Na_2CO_3 3equ., DBU 0.1 equ., THF, rt overnight; v, from the intermediate diol, $NaIO_4$ 2.2eq, H_2O, MeOH; vi, H_5IO_6, ether, rt, sonication.

In several experiments, the oxidative cleavage:cyclisation sequence to **6** was poor yielding. In these cases a minor product was isolated, the structure of which was very similar to that of **6**. ^1H and ^{13}C nmr spectra showed no CHOH, unlike **6**, and led us to the conclusion that cyclopentenone **9** could be formed in this process. Suspecting that the formation of this by-product might be related to the oxidative cleavage conditions. The use of an excess of sodium periodate or extended reaction times resulted after carbocyclisation in the extensive formation of cyclopentenone **9**.[14] This reaction can be easily rationalized. Given its hemiketalic structure, the intermediate aldehyde **4** is in equilibrium with the corresponding open-chain α-hydroxy-aldehyde form which can be further oxidatively cleaved to give **8**. Subsequent treatment of this compound under cyclisation conditions gave **9** in 52% yield for the three steps.

In an effort to shorten our synthesis we applied the methodology proposed by Wu and Wu [16] who described the one pot transformation of the 5,6-O-isopropylidene acetal of some sugars into the corresponding aldehyde with one carbon less, using periodic acid in ether. Applied to amide **3c**, this method gave the over-oxidation product **8** which under cyclisation conditions gave the cyclopentenone **9** in 50% overall yield. Although efficient, Wu's procedure is slow, probably because of the heterogeneous nature of the medium (H_5IO_6 is only sparingly soluble in ether). In order to accelerate the process, the reaction vessel was placed, every four hours, in an ultrasonic bath for 20 minutes to remove solids from the reactor walls. To our surprise, extended reaction times (36h) according to the above procedure led to the formation of **9**. Thus, it became clear that *direct transformation of* **3c** *into cyclopentenone* **9** *can be performed in a single one-pot operation* in the

acceptable yield of 59%. This procedure worked equally well with L-gulonolactone derivative ***ent*-3c** which gave ***ent*-9** in 50% yield.

In conclusion, the four-steps sequence described here allowed us to prepare either a cyclohexenone or a cyclopentenone according to the oxidative cleavage conditions used. These key intermediates can be obtained in two possible enantiomerically pure forms from readily available D- or L- gulono1,4-lactone. Although it was less efficient, this sequence can be performed using Weinreb amide [17] which is most suitable for subsequent transformation into carbasugars and congeners.

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13. This condensation has been also applied to 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone, 5,6-*O*-isopropylidene-2,3-di-*O*-trimethylsilyl-D-galactono-1,4-lactone and 2,3-*O*-isopropylidene-D-ribono-1,4-lactone in 50, 20 and 55 % yield respectively. In the latter case a two fold excess of lithium enolate was used to deprotonate the free 5-OH group.
14. Selected analytical data: Compound **6**: $[\alpha]_D$ +11 (c, 0.7, $CHCl_3$), IR ν_{max} 3340, 1690, 1615, 1340; ^1H nmr (250 MHz, $CDCl_3$) δ: 1.11, (t, 3H, CH_3); 1.18 (t, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 3.0-3.23 (m, 2H, CH_2), 3.3-3.5 (m, 2H, CH_2), 4.5-4.63 (m, 3H, H-2, H-3, H-4), 6.8 (dd, 1H, $J_{4,5}$ 4.5, $J_{3,5}$ 1.5 Hz, H-5); ^{13}C nmr, δ: 12.7, 13.8 (CH_2CH_3), 25.3, 27.0 ($C(CH_3)_2$), 39.2, 43.0 (CH_2CH_3), 64.3, 74.2, 78.6 (*C*-2, *C*-3, *C*-4), 109.5 ($C(CH_3)_2$, 136.2 (*C*-6), 144.5 (*C*-5), 165.8 (*C*=O), 192.0 (*C*=O). Compound **9**: $[\alpha]_D$ -7 (c, 1.5, $CHCl_3$), IR ν_{max} 1731, 1619, 1340; ^1H nmr (250 MHz, $CDCl_3$) δ: 1.16, (t, 3H, CH_3); 1.20 (t, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 3.1-3.24 (m, 2H, CH_2), 3.32-3.57 (m, 2H, *C*H2), 4.63 (d, 1H, $J_{2,3}$ 5Hz, H-2), 5.29 (dd, 1H, $J_{3,4}$ 2.5 Hz, H-3), 7.61 (d, 1H, H-4); ^{13}C nmr, δ: 12.0, 12.6 (CH_2CH_3), 25.8, 27.2 ($C(CH_3)_2$), 39.1, 42.5 (CH_2CH_3), 76.78 (C-2), 77.0 (C-3), 115.3 ($C(CH_3)_2$), 142.3 (*C*-5), 155.4 (*C*-4), 162.6 (*C*=O), 199.1 (*C*=O).
15. No other diastereoisomer which may result from epimerisation of the intermediate keto-aldehyde was detected in the reaction mixture.
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