Acid Promoted Syntheses of New Enantiopure Amino Sugar Derivatives from 3,6-Dihydro-2*H*-1,2-oxazines

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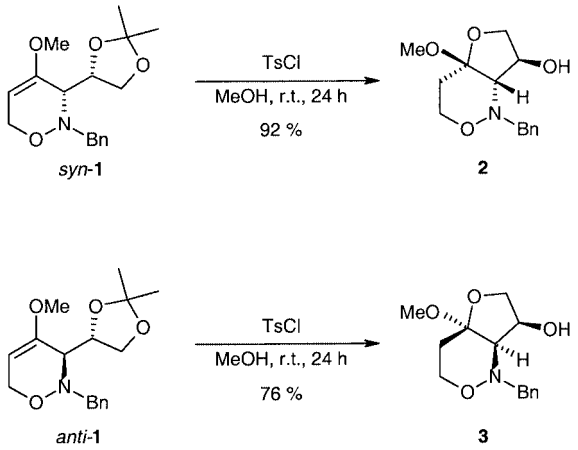
Abstract: The acid promoted rearrangement of *syn*-**1** with HCl led to bicyclic acetal **2** from which enantiopure furan derivative **4** was obtained by hydrogenolysis. The same sequence was applied to *anti*-**1** leading to bicyclus **3** and diastereomeric tetrahydrofuran **5**. Treatment of *syn*-**6** with pyridinium hydrogen fluoride provided either semiacetal **7** or bicyclic acetal **8**, depending on the ratio of HF and pyridine. Lewis acid mediated intramolecular aldol reaction of *syn*-**6** afforded bicyclic 1,2-oxazine **9**. Protection and subsequent stereoselective reduction of **9** led to **10**, which was hydrogenated to yield enantiopure amino substituted pyran derivative **11**.

Key words: 1,2-oxazines, reductions, furans, carbohydrates, aldol reactions

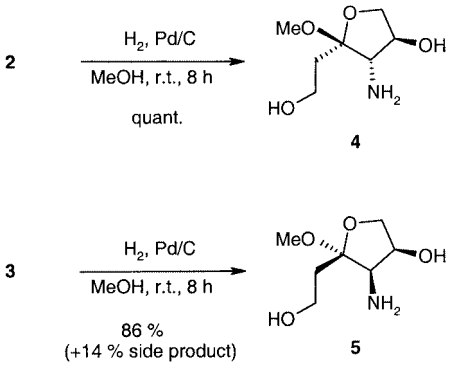
We recently reported[1] that the addition of lithiated methoxyallene to D-glyceraldehyde derived nitrone[2] and subsequent cyclisation of the primary allene adduct furnish new enantiopure 3,6-dihydro-2*H*-1,2-oxazines **1** in high diastereoselectivity.[3] The stereochemistry of this formal [3+3] cyclization is controlled by the reaction conditions: use of THF as solvent leads to *syn*-**1**, precomplexation of the nitrone with Et_2AlCl in diethyl ether furnishes *anti*-**1**. We have also demonstrated that enantiopure 3-methoxypyrrolidine derivatives are easily available in a stereodivergent manner by hydrogenolysis of 1,2-oxazines **1** followed by cyclisation of the intermediate 1,4-amino alcohols.[4] Herein, we wish to present the acid catalysed reactions of these highly functionalised C_6 building blocks *syn*-**1** and *anti*-**1** which afford novel enantiopure amino sugar derivatives.

Treatment of *syn*-**1** with 0.5 equivalents of *p*-toluenesulfonyl chloride in methanol led to bicyclic compound **2**.[5] Under HCl catalysis, the dioxolane ring is cleaved and the primary hydroxyl group attacks the enol ether moiety to form acetal **2** as a single diastereomer. Reaction of *anti*-**1** under the same conditions provided diastereomeric bicyclic 1,2-oxazine **3** in good yield (Scheme 1). In both cases the *cis* fusion of the two rings was proved by NOESY experiments. For this reaction the use of *p*-toluenesulfonyl chloride is advisable since treatment of *syn*-**1** with *p*-toluenesulfonic acid in acetone provided a rather complex mixture of two diastereomers of semiacetal **7** (see below) and other products.[6]



Scheme 1

One valuable property of 1,2-oxazines is the smooth cleavage of the relatively weak N-O bond leading to interesting cyclic and acyclic amino alcohols.[4] Thus, the hydrogenation of **2** using palladium on charcoal as catalyst produced highly functionalised tetrahydrofuran **4** in quantitative yield.[5] Similar treatment of **3** with hydrogen provided the expected enantiopure tetrahydrofuran derivative **5**.[7] Furan derivatives **4** and **5** correspond to diastereomeric acyclic 4-amino 3-keto-hexoses (Scheme 2).



Scheme 2

Bicyclic compounds can also be prepared starting from (trimethylsilyl)ethoxy (TMSE) substituted 2*H*-1,2-oxazine *syn*-**6**. Stereoselective synthesis of *syn*-**6** was smoothly achieved in 76% yield by addition of lithiated (trimethylsilyl)ethoxyallene[8] to the D-glyceraldehyde derived nitrone using our standard procedure.[1,9] Treatment

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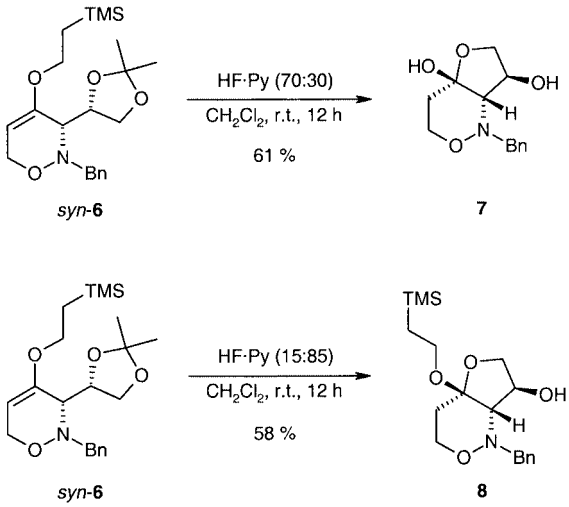
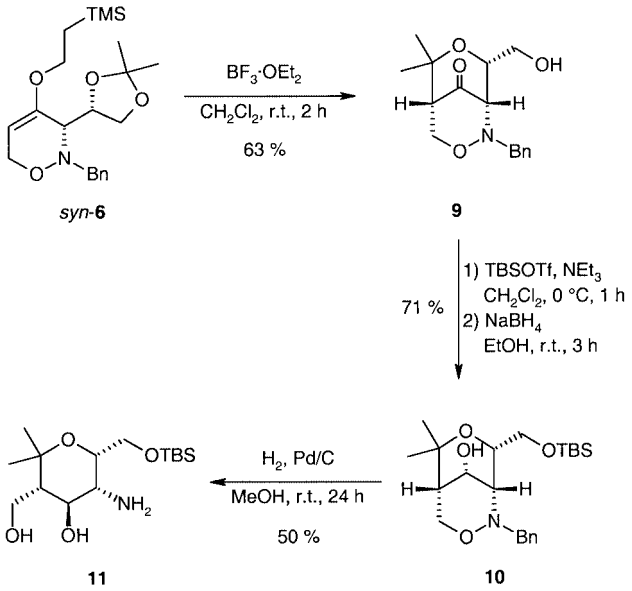
of *syn*-**6** with pyridinium hydrogen fluoride (30% pyridine, 70% HF) in dichloromethane led to semiacetal **7** as a single isomer. Using the same reagent and adding an excess of pyridine (85% pyridine, 15% HF) to reduce the acidity of the solution afforded bicyclic acetal **8** in similar yield (Scheme 3). The mechanism of this reaction is not exactly known, however, it is well known that HF·py cleaves silyl ethers[10] as well as the dioxolane group.[11] Thus, acetal **8** is likely to be an intermediate during the formation of **7**.



Scheme 3

Interestingly, the reaction of *syn*-**6** with boron trifluoride etherate led to a novel bicyclic compound **9** where the 1,2-oxazine ring is bridged by a newly formed pyran ring (Scheme 4). This reaction can be understood as an aldol type reaction between the dioxolane acetal and the enol ether.[12] Related intramolecular reactions between enol ethers and acetals are described in literature.[13] BF_3 probably coordinates to the less hindered oxygen of the dioxolane group and provides an intermediate carbenium ion which attacks the enol ether double bond to form **9** as single diastereomer. However, there must also be a crucial influence of the TMSE group because the treatment of *syn*-**1** with BF_3·OEt_2 under identical conditions afforded only acetal **2** in low yields. Subsequent protection of the primary hydroxy group of **9** with TBSOTf followed by stereoselective reduction of the carbonyl group with sodium borohydride led to bicyclic alcohol **10**, whose structure was proved by NOE experiments. Debenzylation and N–O bond cleavage with hydrogen in the presence of palladium on charcoal produced pyran derivative **11**. This sequence opens a new entry to unnatural and highly functionalised amino sugar derivatives.

In summary, we have shown a new short route to highly functionalised enantiopure amino sugar derivatives, like furan derivatives **4** and **5** and pyran **11**. They are all accessible in a few straightforward steps from 1,2-oxazines **1** and **6**. As these 1,2-oxazines are easy prepared from chiral nitrones and alkoxyallenes, this again demonstrates the



Scheme 4

versatility of these allenes as valuable C_3 building blocks in stereoselective organic synthesis.[14]

Acknowledgement

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(5) **Typical procedure**, *syn*-**1** to **2**: To a stirred solution of *p*-TsCl (0.156 g, 0.819 mmol) in dry methanol (10 mL) at r.t. a solution of *syn*-**1** (0.500 g, 1.64 mmol) in dry methanol (10 mL) was added. The mixture was stirred for 24 h at r.t., then sat. $NaHCO_3$ solution (20 mL) was added. The aqueous layer was extracted with dichloromethane (3 × 20 mL) and the combined extracts were dried with $MgSO_4$. Removal of the solvent in vacuo yielded crude **2** which was purified by column chromatography (silica gel, *n*-hexane–ethyl acetate, 3:2). Compound **2** was obtained as colourless crystals (0.400 g, 92%).
Analytical data of (4a*S*,7*S*,7a*S*)-1-benzyl-4α-methoxyhexahydro-1*H*-furo[3,2-*c*][1,2]oxazin-7-ol(**2**): ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.41–7.25 (m, 5 H, Ph), 4.42 (dd, *J* = 5.6, 9.8 Hz, 1 H, 6-H_A), 4.18, 3.80 (2 d, *J* = 15.2 Hz, each 1 H, CH_2Ph), 4.05 (dd_{br}, *J* ≈ 5.4, 11.7 Hz, 1 H, 7-H), 3.91 (dd, *J* = 1.5, 9.8 Hz, 1 H, 6-H_B), 3.88 (dd_{br}, *J* ≈ 6.3, 11.9 Hz, 1 H, 3-H_A), 3.80 (dt, *J* = 2.7, 11.9 Hz, 1 H, 3-H_B), 3.44 (d, *J* = 11.7 Hz, 1 H, OH), 3.33 (s, 3 H, OMe), 3.13 (s, 1 H, 7a-H), 2.12 (d_{br}, *J* ≈ 12.7 Hz, 1 H, 4-H_A), 1.86 (dt, *J* = 6.3, 12.7 Hz,

1 H, 4-H_B). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 138.2, 128.3, 127.8, 127.1 (s, 3 d, Ph), 105.8 (s, C-4a), 76.3 (d, C-7a), 76.2 (t, C-6), 74.6 (d, C-7), 65.8 (t, C-3), 59.7 (t, *C*H_2Ph), 47.8 (q, OMe), 30.4 (t, C-4). Mp = 27–29 °C. $[\alpha]_D^{20}$ = +100.6 (c = 1.7, $CHCl_3$). IR (CCl_4): ν = 3480 cm^{-1} (OH), 2940–2890 (C-H). $C_{14}H_{19}NO_4$ (265.3) Calcd. C 63.38, H 7.22, N 5.28; found C 63.33, H 7.18, N 5.18.

2 to **4**: A stirred suspension of Pd(10%)/C (0.175 g, 0.164 mmol) in dry methanol (8 mL) was saturated with hydrogen for 1 h. Then a solution of **2** (0.116 g, 0.437 mmol) in dry methanol (3 mL) was added and the mixture was stirred under hydrogen atmosphere at normal pressure for 8 h at r.t. Filtration through a pad of celite and removal of the solvent in vacuo provided **4** (0.077 g, quant.) as colourless oil. Analytical data of (2*S*,3*S*,4*R*)-3-amino-4-hydroxy-2-(2′-hydroxy-1′-ethyl)-2-methoxytetrahydrofuran(**4**): ^{1}H NMR (CD_3OD, 500 MHz): δ = 4.30 (ddd, *J* = 0.5, 6.8, 9.5 Hz, 1 H, 5-H_A), 4.13 (ddd, *J* = 1.7, 4.6, 6.8 Hz, 1 H, 4-H), 3.68–3.60 (m, 2 H, 2′-H), 3.58 (dd, *J* = 4.6, 9.5 Hz, 1 H, 5-H_B), 3.22 (d_{br}, *J* = 1.7 Hz, 1 H, 3-H), 3.19 (s, 3 H, OMe), 2.12 (td, *J* = 4.4, 15.4 Hz, 1 H, 1′-H_A), 1.91 (ddd, *J* = 6.2, 8.7, 15.4 Hz, 1 H, 1′-H_B). ^{13}C NMR (CD_3OD, 125 MHz): δ = 111.0 (s, C-2), 78.7 (d, C-4), 73.6 (t, C-5), 66.1 (d, C-3), 58.0 (t, C-2′), 48.0 (q, OMe), 32.3 (t, C-1′).- $[\alpha]_D^{20}$ = +52.3 (c = 0.41, $CHCl_3$). IR (Film): ν = 3350 cm^{-1} (NH, OH), 2950–2835 (C-H). MS (pos. FAB): *m/z* (%) = 178 (M^+ + H, 37), 160 (M^+ – OH, 32), 146 (M^+ – OMe, 100), 128 (M^+ – OH – OMe, 47), 77 (50). HRMS: calcd. for $C_7H_{14}NO_3$ (M^+ – OH) 160.09737, found 160.09666.

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