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An expeditious approach to tri-substituted chiral thiazolines

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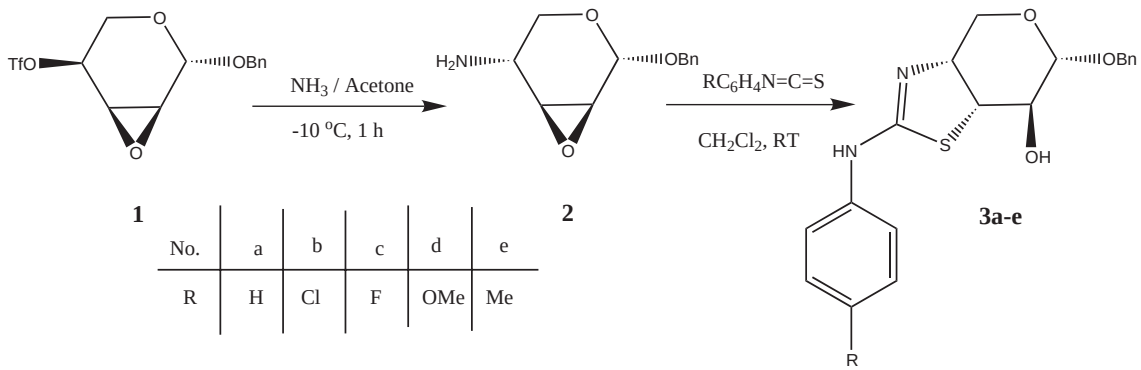
Abstract—A regio- and stereoselective route from the *cis*-oriented epoxytriflate pentoses **1** and **4** via 4-amino-4-deoxy sugars **2** and **5** to chiral thiazoline derivatives **3a–e** and **6a–e** in high yields is described.

Thiazolines have very significant biochemical interest owing to the fact that they represent substructures of a variety of biologically active natural products,[1,2] or they can serve as precursor molecules to other functionalities[3] and are also potent (NAGases) inhibitors.[4]

Starting with the chiral synthons benzyl 2,3-anhydro-4-*O*-trifyl-β-L-ribopyranoside (**1**) and benzyl 2-anhydro-4-*O*-trifyl-α-D-ribopyranoside (**4**) leading to novel chiral heterocyclic systems, is one of our interests in this field.[5] Herein we report for the first time an access to stereochemically pure 2-thiazolines of type **3** and **6** using an arabinose derived chiral auxiliary.

The strategy banks on the introduction of an amino group adjacent to the oxirane ring which upon reaction with *p*-substituted phenylisothiocyanates affords the corresponding thiazoline ring in one step. The reaction of epoxy triflate **1** with gaseous ammonia was carried out in acetone at −10°C to afford benzyl 2,3-anhydro-4-deoxy-α-D-lyxopyranoside (**2**) in 85% yield.[6] The latter amino sugar **2** was allowed to react with *p*-substituted phenyl isothiocyanates in dichloromethane to afford the corresponding thiazoline derivative **3a–e** in 72–81% isolation yields after purification using column chromatography (Scheme 1). The intermediate is presumably a thioureido derivative, which leads to an opening of the epoxy ring by the participation of the sulfur atom. However, the thioureido intermediates could not be isolated despite numerous attempts. The same methodology was applied to the α-D isomer **4**, to afford the corresponding chiral thiazolines **6a–e** in 75–79% yields (Scheme 2).



1 **2** **3a-e**

No.	a	b	c	d	e
R	H	Cl	F	OMe	Me

Scheme 1. Synthesis of thiazoline derivatives from the β-L-anhydro triflate sugar.

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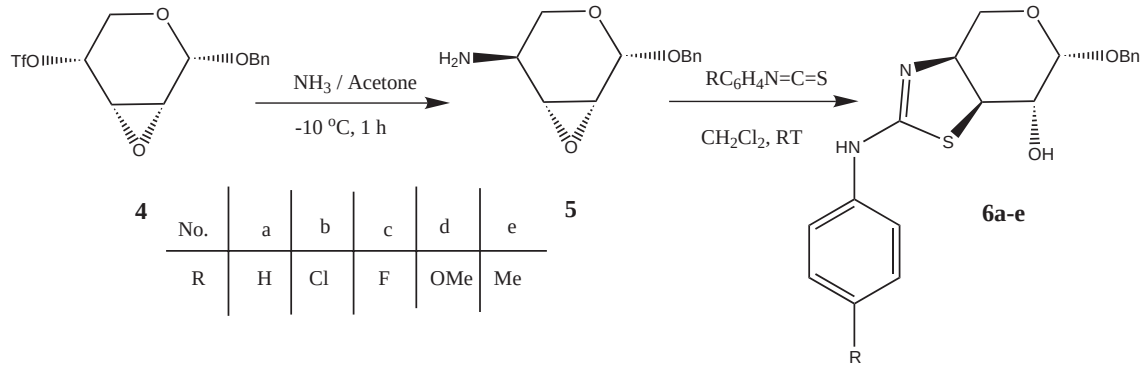

Scheme 2. Synthesis of thiazoline derivatives from the α-D-anhydro triflate sugar.

The ^{13}C NMR of all new compounds show a quaternary carbon resonance at about 161–162 ppm, indicative for the imine bond formation (C=N).[7] The C-3 and C-4 arise at 50–52 and 62–65 ppm, respectively. Furthermore, the two-dimensional experiments (HMBC, HMQC and H/H COSY) for compound **3a** enables us to the exact assignment of the whole skeleton. Thus, H/H COSY shows H-1 ($\delta=4.3$ ppm, $J_{1,2}=7.3$ Hz) coupled to H-2 ($\delta=3.67$ ppm, $J_{1,2}=7.3$ and $J_{2,3}=9.8$ Hz). The latter proton is directly connected to C-2 ($\delta=73.3$ ppm) as shown in the HMQC spectrum, indicating for a C–O bond resonance. Furthermore, H-3 ($\delta=3.43$ ppm, $J_{2,3}=9.8$ and $J_{3,4}=6.1$ Hz) is directly connected to C-3 ($\delta=52.1$ ppm) characteristic chemical shift for C–S bond in similar systems.[8] The structure of compound **3b** was confirmed by single-crystal X-ray analysis.[9]

Extensive ^1H NMR studies enabled the unambiguous conformation of the stereochemistry of the compounds **3a**–**e**. A silent feature of the ^1H NMR spectra of these compounds is their chemical shifts and the coupling constant of H-1 ($\delta=4.24$–4.30 ppm; $J=7.3$ Hz), indicating an axial–axial relationship between H-1 and H-2, $^1C_4$ conformation for these compounds is also supported by the axial–axial relationship between H-2 and H-3 ($J=9.2$–9.8 Hz). In the other series **6a**–**e**, the main factor is the coupling constants between H-2/H-3. In all compounds the $J_{2,3}$ are 9.5–9.8 Hz, indicating axial–axial relationship, therefore $^4C_1$ is the predominant conformation

In summary, the chiral thiazoline derivatives **3a**–**e** and **6a**–**e**, which are key intermediates for the synthesis of natural products,[10–12] can easily be obtained from the corresponding amino sugars **2** and **5**, respectively. These new derivatives are not only of interest for their biological activities, but can also be further modified or integrated into other structural frameworks.[13–15]

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13. Thiazoline preparation: To a stirred solution of the amino sugar **2**[6] (1 mmol) in 20 ml dichloromethane was added a solution of phenyl isothiocyanate (2 mmol) in 5 ml of dichloromethane over a period of 10 min under argon. Stirring at room temperature was continued until the TLC showed no starting material. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, 60, Merk) using 20% ethyl acetate/dichloromethane as eluent to afford **3a** as white solid (73% yield).
14. Data for **3a**; $[\alpha]_D^{20}=-69.4°$ ($c=0.1$, CH_2Cl_2), ^1H NMR (250 MHz, $CDCl_3$): δ_H 7.04–7.36 (m, 10H, C_6H_5, $C_6H'_5$), 5.11 (bs, 1H, N-H), 4.88 (d, $J=11.6$ Hz, 1H, OC*H*HPh), 4.58 (d, $J=11.6$ Hz, 1H, OCH*H*Ph), 4.30 (d, $J=7.3$ Hz,

1H, H-1), 4.25 (dd, $J=2.4$, 12.8 Hz, 1H, H-5), 4.03 (m, 1H, H-4), 3.67 (dd, $J=7.3$, 9.8 Hz, 1H, H-2), 3.62 (dd, $J=3.4$, 12.2 Hz, 1H, H-5′), 3.43 (dd, $J=6.1$, 9.8 Hz, 1H, H-3). δ_C (63 MHz, $CDCl_3$): 52.1 (C-3), 64.7 (C-4), 64.6 (C-5), 70.6 (O*C*H_2Ph), 73.3 (C-2), 102.2 (C-1), 121.4, 124.4, 128.1–129.1, 137.0, 143.3 (C_6H_5, C_6H_5'), 162.2 (C-7). FAB-MS: $m/z=357.1$ [M^++1]. Data for **3b**; $[\alpha]_D^{20}=-60.9°$ ($c=0.14$, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 7.26–7.30 (m, 5H, C_6H_5), [7.08 (d, $J=8.9$ Hz, 2H), 7.16 (d, $J=8.9$ Hz, 2H), (C_6H_4)], 4.85 (d, $J=11.6$ Hz, 1H, OC*H*HPh), 4.53 (d, $J=11.3$ Hz, 1H, OCH*H*Ph), 4.25 (m, 1H, H-5), 4.24 (d, $J=7.3$ Hz, 1H, H-1), 4.10 (m, 1H, H-4), 3.67 (dd, $J=3.1$, 12.8 Hz, 1H, H-5′), 3.62 (dd, $J=7.9$, 9.2 Hz, 1H, H-2), 3.38 (dd, $J=5.8$, 9.8 Hz, 1H, H-3). Data for **3c**; $[\alpha]_D^{20}=-68.6°$ ($c=0.1$, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 7.29–7.36 (m, 5H, C_6H_5), 6.87–7.07 (m, 4H, C_6H_4), 4.89 (d, $J=11.6$ Hz, 1H, OC*H*HPh), 4.59 (d, $J=11.6$ Hz, 1H, OCH*H*Ph), 4.30 (d, $J=7.3$ Hz, 1H, H-1), 4.08 (bd, $J=12.8$ Hz, 1H, H-5), 3.90 (bs, 1H, H-4), 3.68 (dd, $J=7.6$, 9.8 Hz, 1H, H-2), 3.58 (dd, $J=1.8$, 12.5 Hz, 1H, H-5′), 3.38 (dd, $J=5.8$, 9.5 Hz, 1H, H-3). Data for **3d**; $[\alpha]_D^{20}=-80.0°$ ($c=0.05$, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 7.29–7.35 (m, 5H, C_6H_5), [6.74 (d, $J=8.9$ Hz, 2H), 7.01 (d, $J=8.9$ Hz, 2H), C_6H_4], 5.61 (bs, 1H, N-H), 4.86 (d, $J=11.6$ Hz, 1H, OC*H*HPh), 4.58 (d, $J=11.6$ Hz, 1H, OCH*H*Ph), 4.29 (d, $J=7.3$ Hz, 1H, H-1), 4.07 (dd, $J=2.4$, 12.8 Hz, 1H, H-5), 3.90 (m, 1H, H-4), 3.66 (dd, $J=7.3$, 9.5 Hz, 1H, H-2), 3.53 (dd, $J=3.4$, 12.8 Hz, 1H, H-5′), 3.36 (dd, $J=6.1$, 9.5 Hz, 1H, H-3). Data for **3e**; $[\alpha]_D^{20}=-96.8°$ ($c=0.06$, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 7.31–7.36 (m, 5H, C_6H_5), [7.05 (d, $J=8.9$ Hz, 2H), 7.10 (d, $J=8.9$ Hz, 2H), C_6H_4], 4.90 (d, $J=11.6$ Hz, 1H, OCH*H*Ph), 4.59 (d, $J=11.6$ Hz, 1H, OC*H*HPh), 4.31 (d, $J=7.3$ Hz, 1H, H-1), 4.27 (m, 1H, H-5), 4.08 (m, 1H, H-4), 3.69 (m, 2H, H-2, H-5′), 3.43 (dd, $J=5.8$, 9.8 Hz, 1H, H-3).

15. Data for **6a**; $[\alpha]_D^{20}=+135.2°$ ($c=0.16$, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 6.87–7.40 (m, 10H, C_6H_5, C_6H_5), 4.9 (d, $J=3.4$ Hz, 1H, H-1), 4.77 (d, $J=11.9$ Hz, 1H, OC*H*HPh), 4.69 (bs, 1H, N-H), 4.53 (d, $J=11.6$ Hz, 1H, OCH*H*Ph), 4.05 (m, 1H, H-4), 3.92 (m, 2H, H_5, H_5'), 3.76 (dd, $J=3.7$, 9.8 Hz, 1H, H-2), 3.59 (dd, $J=5.5$, 9.8 Hz, 1H, H-3). Data for **6b**; $[\alpha]_D^{20}=+137.1°$ ($c=0.25$, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 7.27–7.38 (m, 5H, C_6H_5), [7.20 (d, $J=8.9$ Hz, 2H), 6.99 (d, $J=8.9$ Hz, 2H), C_6H_4], 5.38 (bs, 1H, N-H), 4.87 (d, $J=3.4$ Hz, 1H, H-1), 4.74 (d, $J=11.6$ Hz, 1H, OC*H*HPh), 4.49 (d, $J=11.6$ Hz, 1H, OCH*H*Ph), 3.91 (bd, $J=4.0$ Hz, 1H, H-4), 3.66–3.84 (m, 3H, H-5, H-5′, H-2), 3.52 (dd, $J=5.2$, 9.8 Hz, 1H, H-3). Data for **6c**; $[\alpha]_D^{20}=+156.8°$ ($c=0.21$, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 7.29–7.39 (m, 5H, C_6H_5), 6.89–7.08 (m, 4H, C_6H_4), 5.09 (bs, 1H, N-H), 4.92 (d, $J=3.4$ Hz, 1H, H-1), 4.77 (d, $J=11.6$ Hz, 1H, OC*H*HPh), 4.52 (d, $J=11.6$ Hz, 1H, OCH*H*Ph), 3.99 (bd, $J=4.6$ Hz, 1H, H-4), 3.81–3.90 (m, 2H, H-5, H-5′), 3.78 (dd, $J=3.4$, 9.8 Hz, 1H, H-2), 3.55 (dd, $J=5.2$, 9.8 Hz, 1H, H-3). Data for **6d**; $[\alpha]_D^{20}=+113.8°$ ($c=0.18$, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 7.21–7.30 (m, 5H, C_6H_5), [6.98 (d, $J=8.9$ Hz, 2H), 6.74 (d, $J=8.8$ Hz, 2H), C_6H_4], 4.85 (d, $J=3.4$ Hz, 1H, H-1), 4.70 (d, $J=11.9$ Hz, 1H, OC*H*HPh), 4.46 (d, $J=11.6$ Hz, 1H, OCH*H*Ph), 3.93 (bd, $J=5.2$ Hz, 1H, H-4), 3.81 (bs, 2H, H-5, H-5′), 3.71 (dd, $J=9.5$, 3.7 Hz, 1H, H-2), 3.70 (s, 3H, $C_6H_4OCH_3$), 3.49 (dd, $J=9.8$, 5.5 Hz, 1H, H-3). Data for **6e**; $[\alpha]_D^{20}=+124.9°$ ($c=0.28$, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ_H 7.27–7.39 (m, 5H, C_6H_5), [7.06 (d, $J=8.2$ Hz, 2H), 6.99 (d, $J=8.4$ Hz, 2H), C_6H_4], 5.01 (bs, 1H, N-H), 4.89 (d, $J=3.4$ Hz, 1H, H-1), 4.75 (d, $J=11.6$ Hz, 1H, OCH*H*Ph), 4.51 (d, $J=11.6$ Hz, 1H, OC*H*HPh), 3.95 (bd, $J=5.2$ Hz, 1H, H-4), 3.83 (bs, 2H, H-5, H-5′), 3.76 (dd, $J=3.4$, 9.8 Hz, 1H, H-2), 3.54 (dd, $J=5.2$, 9.8 Hz, 1H, H-3), 2.29 (s, 3H, $C_6H_4CH_3$).