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A new simple route to deoxyamino sugars from non-sugar material: synthesis of D-tolyposamine and 4-*epi*-D-tolyposamine and formal synthesis of D-vicenisamine

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Abstract—A new, simple strategy has been formulated for the synthesis of deoxyamino sugars from a non-sugar starting material. Starting from the enantiomerically pure diol obtained from ethyl sorbate by Sharpless asymmetric dihydroxylation, the synthesis of two types of 2,3,4,6-tetradeoxy-4-amino sugars—D-tolyposamine and 4-*epi*-D-tolyposamine—, and formal synthesis of 2,4,6-trideoxy-4-amino sugar—D-vicenisamine—were performed.

Amino sugars, especially deoxyamino sugars, are found in clinically important antibiotics such as antimicrobial macrolides and anthracycline antitumor antibiotics.[1] In most instances, the sugar parts of these antibiotics are essential for biological activity; however, the functions of the sugar moieties have not yet been evaluated.[2]

We envisaged that a modification of the sugar moieties of these antibiotics may serve as a tool for investigating the significance of amino sugars and the structure–activity relationship. For this purpose, a versatile and synthetic route for deoxyamino sugars is highly desirable. Furthermore, we expected that such a route would also be beneficial for elucidating the biosynthetic route of antibiotics.[3,4] We were especially interested in developing a new synthetic route for deoxyamino sugars from a non-sugar material.[5]

Our target deoxyamino sugars were tolyposamine and its diastereomers, namely, two types of 2,3,4,6-tetradeoxy-4-aminohexoses—the simplest class among deoxyamino sugars and a kind of 2,4,6-trideoxy-4-aminohexose—D-vicenisamine. Tolyposamine is recognised as an amino sugar moiety of the antibiotic tolypomycin Y[6] and was recently found in P371 A1—a novel angucycline compound that possesses antigastrin and gastric mucosal protective properties in the form wherein its amino group is substituted for an ureido group.[7] Vicenisamine is a novel deoxyamino sugar component of the antitumor antibiotic vicenistatin isolated from *Streptomyces* sp. HC-34.[8]

In this letter, we describe a novel strategy to synthesise methyl *N*-Ts-D-tolyposaminide and methyl *N*-Ts-4-*epi*-D-tolyposaminide, and a formal synthesis of methyl D-vicenisaminide starting from the same chiral diol available in both enantiomers by Sharpless asymmetric dihydroxylation (AD). Methyl *N*-Ac-L-tolyposaminide[9] and methyl *N*-Boc-4-*epi*-D-tolyposaminide[10] were previously synthesised from ethyl (*S*)-3-hydroxybutyrate and L-threonine derivative, respectively, using different approaches.[11] In addition, methyl D-vicenisaminide was previously synthesised from a sugar material[12] and a chiral epoxy alcohol.[5]

Starting chiral diol **1**[13,14] was obtained from commercially available ethyl sorbate[15] by Sharpless asymmetric dihydroxylation using dihydroquinidine phthaladine [$(DHQD)_2PHAL$] as a chiral ligand (AD-mix β) in an 86% yield (Scheme 1). The selective protection of the 5-hydroxyl group of diol **1** by the *tert*-butyldimethylsilyl (TBS) group furnished the ether **2**[16] in a 64% yield. Although, the resulting compound was the desired regioisomer **2** just as anticipated, it was actually confirmed

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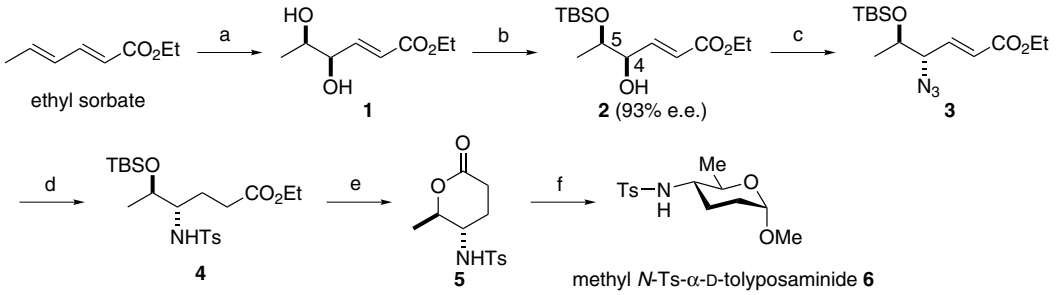
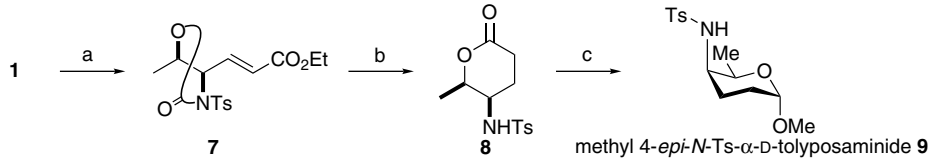


Scheme 1. Reagents and conditions: (a) AD-mix-β, $CH_3SO_2NH_2$, Bu^tOH–H_2O, 0 °C (86%); (b) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt (64%; SM: 7%, 4-isomer: 8%, di-isomer: 20%); (c) (i) *p*-NO_2–$C_6H_4SO_2Cl$, DMAP, pyridine, 0 °C; (ii) NaN_3, DMF, rt (80%, two steps); (d) (i) H_2, cat. 10% Pd–C, EtOAc, rt; (ii) TsCl, Na_2CO_3, toluene–H_2O, rt (80%, two steps); (e) CF_3CO_2H, THF–H_2O, 0 °C–rt (82%); (f) (i) DIBAL, THF–toluene, −78 °C; (ii) PPTS, $CH(OCH_3)_3$, MeOH, rt (91%, two steps).

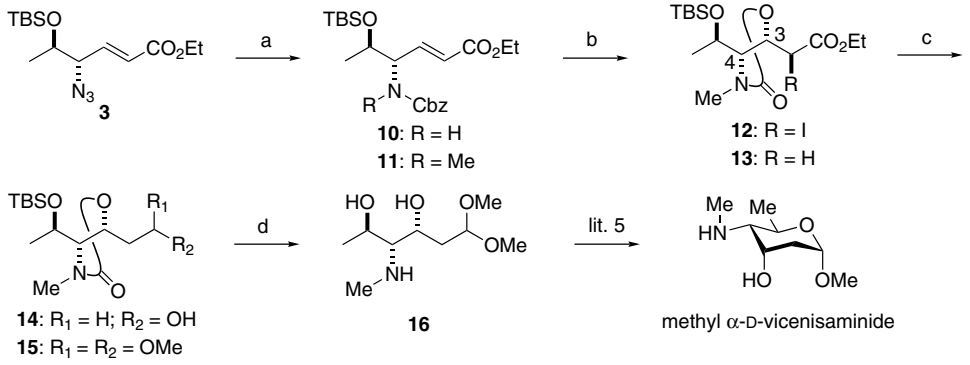
in the next step.[17] The enantiomeric purity of **2** was determined to be 93% ee by ^{1}H NMR analysis of the corresponding ester with (+)/(−)-MTPA (α-methoxy-α-trifluoromethylphenylacetic acid).[18] The next step was the introduction of the nitrogen functional group. Sulfonylation of the hydroxy group of compound **2** followed by azide ion nucleophilic displacement afforded azide **3** (80% yield, two steps). The azide group of **3** was then hydrogenated in the presence of a 10% Pd–C catalyst to produce the amino group, which was successively protected by the *p*-toluenesulfonyl (Ts) group. During the course of the reduction, the double bond was also hydrogenated to obtain **4** (80% yield, two steps). Removal of the TBS protecting group of **4** and spontaneous lactone formation were carried out by treatment with trifluoroacetic acid (TFA) in THF and water to afford δ-lactone **5** (82%). Half reduction of δ-lactone **5** was effected by using diisopropylaluminium hydride (DIBAL) in THF–toluene at −78 °C to produce hemiacetal (lactol). The obtained lactol was immediately dissolved in methanol and treated with pyridinium *p*-toluenesulfonate (PPTS) and trimethyl orthoformate to produce the desired methyl *N*-Ts-D-tolyposaminide as an anomeric mixture, which was converged to an almost single α-anomer **6** during the course of the reaction in an excellent yield (91%, two steps).

Next, a nitrogen functional group was intramolecularly introduced to the diastereomeric isomer 4-*epi*-D-tolyposamine via the intermediary 4,5-di-carbamates from the same starting diol **1** (Scheme 2). The reaction was effectively carried out in the presence of the Pd(0) catalyst to form a cyclic carbamate **7** in an 86% yield.[19] The mechanism involving the S_N2 nucleophilic displacement of the leaving group (4-carbamate) by Pd(0) followed by a second displacement of Pd by the nucleophilic nitrogen of 5-carbamate is commonly known as the palladium-mediated double inversion process. This reaction involving the same substrate using tetrakis(triisopropylphosphite)palladium(0), $Pd[P(OPr^i)_3]_4$ as a palladium(0) catalyst was reported by Xu and Sharpless.[19] However, the use of commercially available tetrakis(triphenylphosphine)palladium(0), $Pd(PPh_3)_4$ improved the chemical yield and availability of the reaction. The double bond of the obtained cyclic carbamate **7** was then hydrogenated in the presence of 10% Pd–C catalyst, and the product was successively subjected to alkaline hydrolysis and treatment with trifluoroacetic acid for a smooth formation of the δ-lactone **8** (72%, two steps). Penultimate half reduction by DIBAL at −78 °C and subsequent final methyl acetal formation were successfully carried out to produce the desired methyl 4-*epi*-*N*-Ts-D-tolyposaminide **9** exclusively as α-anomer in a 94% yield.

Iodocyclisation of the carbamate, so-called iodocyclocarbamation, is a well-documented method for the heterofunctionalisation of alkenes,[20] however, the examples involving electron deficient olefins are rare.[21] In an attempt to expand our strategy to the synthesis of 2,4,6-trideoxy-4-aminosugars, we successfully used the iodocyclisation of the carbamate based on the (*E*)-α,β-unsaturated ester moiety indigenous to the starting materials (Scheme 3). Firstly, the azide group of the intermediate **13** in the tolyposamine synthesis was reduced to primary amine by treatment with triphenylphosphine and water in THF with gentle warming. Thus obtained primary amine was subsequently protected by carbobenzoxy (Cbz) group, which should be used as an origin of the oxygen functional group, namely 3-hydroxy group, to furnish compound **10** (89%, two steps). The methyl group on the amino nitrogen was



Scheme 2. Reagents and conditions: (a) Ts-N=C=O, cat. $Pd(PPh_3)_4$, THF, reflux (86%); (b) (i) H_2, cat. 10% Pd–C, EtOAc, rt; (ii) 4 M NaOH, MeOH, rt; evaporation; CF_3CO_2H, THF, rt (72%, two steps); (c) (i) DIBAL, THF–toluene, −78 °C; (ii) PPTS, $CH(OCH_3)_3$, MeOH, rt (94%, two steps).



Scheme 3. Reagents and conditions: (a) (i) PPh_3, H_2O, THF, 50 °C; (ii) benzyl chloroformate, $NaHCO_3$, dioxane, H_2O, 0 °C (89%, two steps); (b) (i) iodine, $NaHCO_3$, CH_3CN, 0 °C (94%); (ii) $Bu^n{}_3SnH$, AIBN, benzene, reflux (quantitative); (c) (i) $NaBH_4$, LiCl, THF–EtOH, rt (94%); (ii) Dess–Martin periodinane, CH_2Cl_2, 0 °C; (iii) *p*-TsOH·H_2O, $CH(OCH_3)_3$, CH_3OH (77%, two steps); (d) 10% NaOH aq, CH_3OH, reflux (60%).

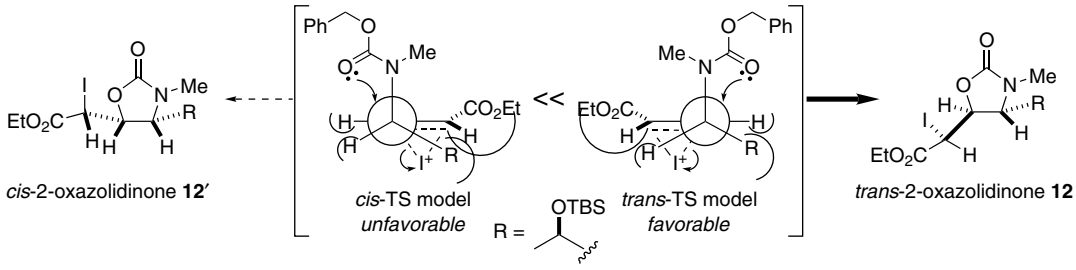


Figure 1. Proposed transition state models for iodocyclocarbamation.

introduced at this point to give compound **11** in excellent yield (98%). The next key iodocyclocarbamation was performed with iodine in acetonitrile at 0 °C in the presence of sodium hydrogen bicarbonate, which was used to prevent TBS protecting group from being removed during the course of the reaction. Consequently, compound **11** underwent a facile cyclisation with extremely high diastereoselective formation of the *trans*-product **12** in 94% yield along with a small amount of the *cis*-product (2%). It was reported that in an oxazolidinone ring the large coupling constant corresponded to cis form and the small one to trans form.[22] Therefore, its small coupling constant ($J_{H\text{-}3,4} = 2.8$ Hz) implied trans stereochemistry of compound **12**. Additionally, the stereochemistry of the *trans*-product **12** was confirmed by nuclear Overhauser enhancement (NOE) experiment as follows: irradiation of H-4 yielded an NOE of ca. 10% on the H-2, whereas a relatively small NOE (3%) was observed on H-3. Stereoselectivity as described above in the cyclisation can be explained using the transition state (TS) models shown in Figure 1. The cyclisation is thought to proceed through the *trans*-TS model to give the *trans*-oxazolidinone product, namely the *trans*-product **12**, since *cis*-TS model is obviously unfavourable than *trans*-TS model due to its steric hindrance between the side chain R and the alkenyl group.[22]

The final manipulation of our work was the transformation to the intermediate compound for the vicenisamine synthesis. To this end, reductive deiodination of compound **12** was first realised with tri-*n*-butyltin hydride in the presence of 2,2′-azobis(isobutyronitrile) (AIBN) in boiling benzene to furnish compound **13** in quantitative yield. Then, the reduction of the ester group of compound **13** was readily achieved by sodium borohydride and lithium chloride to give alcohol **14** in 94% yield. Thus obtained alcohol **14** was oxidised by Dess–Martin periodinane to furnish a corresponding aldehyde, which was spontaneously transformed in dimethyl acetal **15** (77% in two steps). Finally, the cyclic carbonate group along with the silyl protective group of acetal **15** was removed by alkaline hydrolysis to give the advanced intermediate **16**[5] for the synthesis of methyl D-vicenisaminide (60% yield). The spectral data (^1H and ^{13}C NMR, IR) of **16** derived from the chiral diol **1** were identical to those of previously prepared sample.[5]

In conclusion, we have successfully synthesised *N*-Ts-D-tolyposamine and *N*-Ts-4-*epi*-D-tolyposamine as their methyl hexopyranosides,[23] thus demonstrating our synthetic strategy for 2,3,4,6-tetradeoxy-4-amino sugars using easily available non-sugar starting chiral diol **1** in a versatile manner. Furthermore, we have described a formal synthesis of methyl D-vicenisaminide using iodocyclocarbamation, showing our synthetic strategy was applicable to the synthesis of 2,4,6-trideoxy-4-aminosugars.

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16. All new compounds (**2**–**6**, **8**–**15**) were fully characterised with relevant spectroscopic data and elemental analyses.
17. The observed peak shift of the H-4 signal during the next sulfonylation undoubtedly indicates the regioselectivity in the TBS protection [**2**: $\delta_{H\text{-}4}$ 4.05 (ddd, $J = 1.5, 5.8, 5.8$ Hz) and the corresponding *p*-nitrotoluenesulfonate: $\delta_{H\text{-}4}$ 5.95 (ddd, $J = 1.5$, 5.8, 5.8 Hz)].
18. The signals due to the H-2 appeared in distinctly different fields [ester from (+)-MTPA: $\delta_{H\text{-}2}$ 5.82 (dd, $J = 1.7, 16.0$ Hz) and ester from (−)-MTPA: $\delta_{H\text{-}2}$ 5.95 (dd, $J = 1.5$, 15.8 Hz)].
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23. The data for compounds **6** and **9** are listed below. Methyl 2,3,4,6-tetradeoxy-4-(*p*-toluenesulfonylamino)-α-D-*erythro*-hexopyranoside **6**: $[\alpha]_D^{29}$ −60.8 (*c* 1.08, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3512, 2978, 2937, 1344, 1213, 1161, 1093, 1068, 997 and 675; δ_H (270 MHz, $CDCl_3$) 7.70 (d, $J = 8.1$ Hz, 2H), 7.33 (d, $J = 8.1$ Hz, 2H), 5.06 (d, $J = 5.3$ Hz, 1H), 4.15–4.04 (m, 1H), 3.60 (ddd, $J = 1.7$, 8.3, 8.3 Hz, 1H), 3.47 (s, 3H), 2.83 (br d, $J = 3.8$ Hz, 1H), 2.44 (s, 3H), 2.10–1.94 (m, 1H), 1.85–1.62 (m, 2H), 1.27–1.08 (m, 1H), 1.14 (d, $J = 6.4$ Hz, 3H); δ_C (67.8 MHz, $CDCl_3$) 144.0, 153.3, 129.9, 127.3, 93.1, 68.2, 66.7, 55.3, 31.9, 23.1, 21.5 and 18.1. Anal. Calcd for $C_{14}H_{21}NO_4$: C, 56.16; H, 7.07; N, 4.68. Found: C, 56.03; H, 7.13; N, 4.85. Methyl 2,3,4,6-tetradeoxy-4-(*p*-toluenesulfonylamino)-α-D-*threo*-hexopyranoside **9**: $[\alpha]_D^{29}$ +60.2 (*c* 1.01, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3494, 2981, 2937, 1342, 1213, 1161, 1093, 1074, 997 and 675; δ_H (270 MHz, $CDCl_3$) 7.70 (d, $J = 8.1$ Hz, 2H), 7.33 (d, $J = 7.9$ Hz, 2H), 5.13 (d, $J = 5.1$ Hz, 1H), 3.78–3.64 (m, 1H), 3.67 (br s, 1H), 3.48 (t, $J = 7.7$ Hz, 1H), 3.44 (s, 3H), 2.44 (s, 3H), 1.83–1.68 (m, 3H), 1.21–1.03 (m, 1H), 1.17 (d, $J = 6.2$ Hz, 3H); δ_C (67.8 MHz, $CDCl_3$) 144.1, 135.1, 130.0, 127.4, 93.8, 71.4, 66.8, 55.0, 32.0, 26.7, 21.5 and 19.5. Anal. Calcd for $C_{14}H_{21}NO_4$: C, 56.16; H, 7.07; N, 4.68. Found: C, 56.43; H, 7.24; N, 4.89.