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Tetrahedron Letters 45 (2004) 3629–3632
Tetrahedron Letters

# Synthesis of a protected enantiomerically pure 2-deoxystreptamine derivative from D-allylglycine

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Received 14 August 2003; revised 5 March 2004; accepted 10 March 2004

**Abstract**—A diastereoselective synthetic route from D-allylglycine to the enantiopure (protected) 2-deoxystreptamine derivative **14** is presented. Key steps involve two consecutive chain extensions—with crucial stereodirective roles for the amino protective groups, ring closure by olefin metathesis, face selective dihydroxylation, cyclic sulfate formation and finally opening with azide. The resulting 2-deoxystreptamine derivative is ideally protected for the preparation of 4,5- or 4,6-linked aminoglycoside antibiotics.


Since the original discovery of streptomycin in 1944, the family of aminoglycosides has grown steadily into a powerful class of antibiotics with a broad antibacterial spectrum and proven efficacy, particularly in combination with other drugs.[1] Nevertheless, extensive use of the aminoglycosides is limited due to the associated toxicities, most notably nephrotoxicity and ototoxicity, and to a lesser extent neuromuscular blockade.[2] Another, more alarming drawback of the aminoglycosides is the global development of microbial resistance with the most common mechanism being structural modification by bacterial resistance enzymes. These circumstances necessitate the development of new and innovative aminoglycoside antibiotics and several reports on the derivatisation of existing aminoglycosides have appeared in the literature in recent years.[3] To be fully flexible in the design and preparation of novel aminoglycoside-type structures, however, de novo synthesis from individually prepared components is required. Consequently, our research has focused on the synthesis of enantiomerically pure derivatives of 2-deoxystreptamine, an aminocyclitol ring that constitutes the core structure of the majority of clinically useful aminoglycosides (Fig. 1) and, as may well be speculated, is crucial for binding of the aminoglycosides to their target A-site RNA.[4]

Although several synthetic routes towards 2-deoxystreptamine are known in the literature, all require many synthetic steps and offer minimal flexibility in protective groups.[5] Moreover, only two of these routes afford an asymmetric analogue of 2-deoxystreptamine, starting from either D-mannose[6] or D-glucose.[7] The most practical method to obtain this aminocyclitol moiety is by degradation of neomycin,[8–10] but the 'naked' *meso*-compound thus obtained still requires desymmetrisation as well as protective group manipulations before incorporation into new aminoglycoside entities can be ensured. In contrast, we here wish to report a synthesis of an orthogonally protected, enantiopure 2-deoxystreptamine derivative, which is highly suitable to serve as a scaffold for new aminoglycoside entities, either 4,5- or 4,6-linked.

Our synthesis starts from enantiomerically pure D-allylglycine, a non-proteinogenic amino acid that is readily available in our group.[11] Thus, the methyl ester of D-allylglycine[12] was subjected to conditions explored by Dondoni,[13] involving introduction of thiazole as a masked aldehyde. Our first attempt to obtain the thiazolyl β-amino alcohol **2a** (Scheme 1) started with Boc-protected allylglycine methyl ester **1a**, which upon partial reduction and addition of 2-(trimethylsilyl)thiazole (2-TST) gave the *syn*-amino alcohol **2a**. Not unexpectedly, however, alcohol **2a** was obtained[13] with a de of only 70%, which led us to follow a slightly different procedure involving double protection of the amino function (Boc, PMB) as in **1b** and reversal of the sequence of events, that is, first reaction with 2-lithiothiazole (2-LTT) and then $NaBH_4$ reduction of the resulting ketone. To our satisfaction, the *syn*-β-amino

*Keywords*: Aminoglycosides; 2-Deoxystreptamine; D-Allylglycine; Synthesis.

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doi:10.1016/j.tetlet.2004.03.051

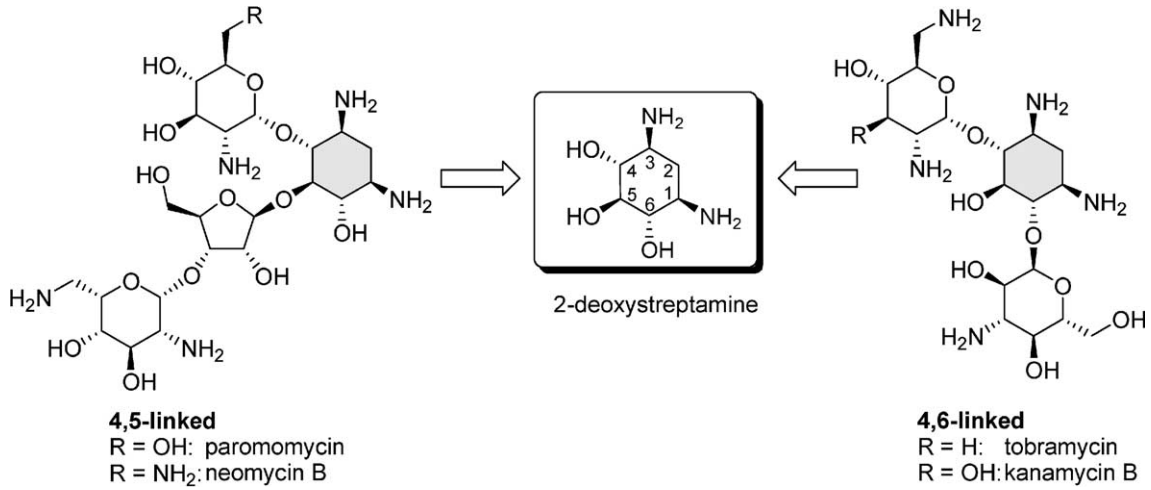
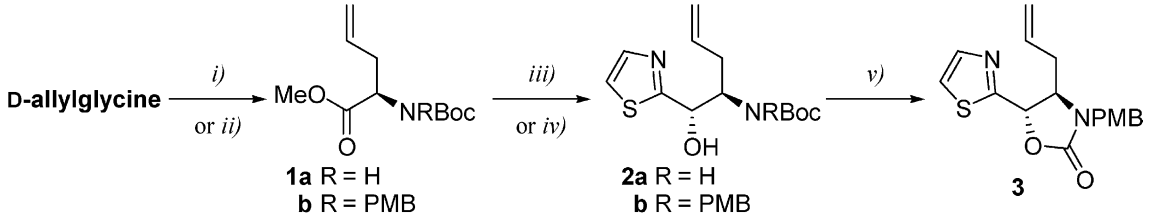
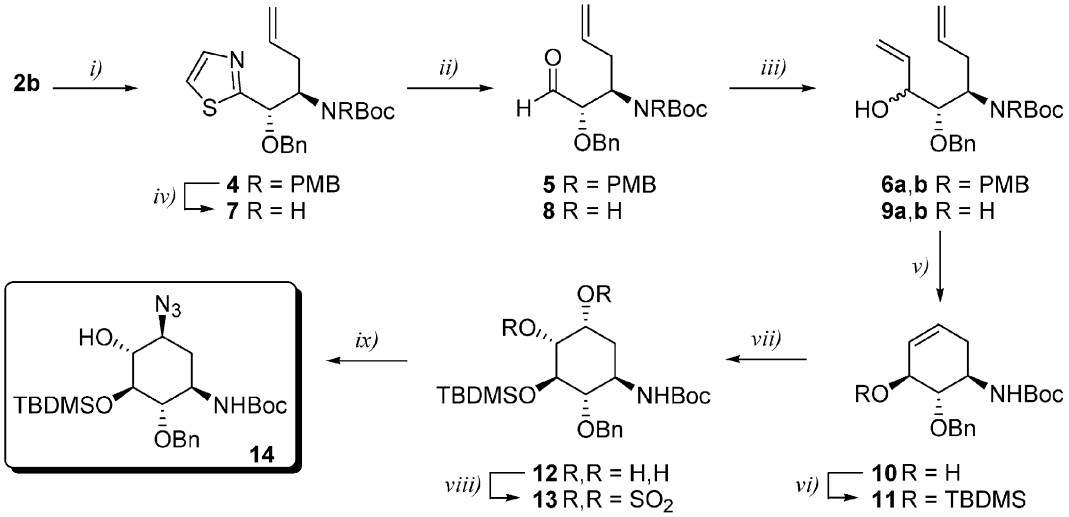



**Figure 1.** Representative aminoglycoside antibiotics, both 4,5- and 4,6-linked to 2-deoxystreptamine.




**Scheme 1.** Reagents and conditions: (i) AcCl, MeOH, 2 h, Δ then $Boc_2O$, dioxane, rt, 18 h; (ii) AcCl, MeOH, Δ, 2 h then $Et_3N$, *p*-$MeOC_6H_4CHO$, $CH_2Cl_2$, rt, 18 h then $NaBH_4$, MeOH, 30 min, 0 °C then $Boc_2O$, dioxane, rt, 18 h (89%); (iii) DIBAL-H, toluene, −78 °C, 2 h, 2-TST, $CH_2Cl_2$, −20 °C, 48 h then $Bu_4NF{\cdot}3H_2O$, THF, rt, 1 h (70% de, 70%); (iv) 2-LTT, $Et_2O$, −78 to −45 °C, 6 h then $NaBH_4$, MeOH, 0 °C, 30 min (89%, de > 95%); (v) NaH, DMF, 0 °C (BnBr).

alcohol **2b** was now obtained with a de of >95%.[13] Next, benzyl protection of the free hydroxyl was investigated but it was found that standard conditions (sodium hydride followed by benzyl bromide) led to 2-oxazolidinone **3** (Scheme 1). However, inverting the order of addition of NaH and BnBr cleanly gave the O-benzylated derivative **4** (Scheme 2), which was subjected to the thiazole deblocking protocol[13] followed by condensation of the resulting aldehyde **5** with vinylmagnesium bromide. Unfortunately, the nucleophilic chain extension




**Scheme 2.** Reagents and conditions: (i) BnBr, DMF, 0 °C then NaH, 1 h (90%); (ii) 4 Å MS, MeOTf, MeCN, rt, 25 min then $NaBH_4$, MeOH, 0 °C, 10 min then $CuCl_2{\cdot}2H_2O$, CuO, $MeCN/H_2O$, 10/1, rt, 15 min (**5**: 78%, **8**: 83%); (iii) vinyl MgBr, THF, −78 °C, 4 h (**6a**: 33%, **9a**: 56%); (iv) CAN, $NaHCO_3$, $MeCN/H_2O$ (4/1), rt, 30 min (67%); (v) second generation Grubbs' catalyst (mono-substituted imidazolylidene ligand), $CH_2Cl_2$, rt, 2 h; (vi) TBDMSOTf, $Et_3N$, $CH_2Cl_2$, rt, 2 h (two steps 82%); (vii) $RuCl_3$, $NaIO_4$, EtOAc/$MeCN/H_2O$ (3/3/1), 0 °C, 3 min (70%); (viii) $SOCl_2$, pyridine, EtOAc, 0 °C, 30 min then $NaIO_4$, $RuCl_3{\cdot}H_2O$, $CH_2Cl_2/MeCN/H_2O$ (2/2/3), 0 °C, 1 h (80%); (ix) $LiN_3$, DMF, Δ, 4 h then $H_2SO_4$, THF, $H_2O$, rt, 30 min (60%).

was characterised by low stereoselectivity revealing a 1:1 mixture of *syn*- and *anti*-diastereomers **6a** and **6b**, which did not improve upon varying the reaction conditions (temperature, solvents, additives). A crucial role of the amino protection was again suspected and therefore it was decided to remove the *p*-methoxybenzyl group of **4** (→**7**) with CAN prior to Grignard addition.[14] Gratifyingly, addition of vinylmagnesium bromide after thiazole unmasking (**7** → **8**) now led to a much improved *syn*/*anti* ratio of 4:1 of compounds **9a** and **9b** (Scheme 2).[15] After silica gel separation of the diastereomers, ring-closing metathesis proceeded smoothly and the free hydroxyl of the cyclic product **10**[16] was protected with a TBDMS group to afford **11** in 82% yield (two steps). Despite the presence of the bulky silyl group, however, epoxidation of compound **11** with several reagents, such as *m*-CPBA, oxone and in situ formed dioxirane[17] led in all cases to inseparable mixtures of diastereomers varying from 1:1 to 3:1 (not depicted). Matters became more complicated when we tried to open the diastereomeric epoxides with sodium azide, leading to the formation of four isomeric azido alcohols. Therefore, it was decided to prepare cyclic sulfate **13**. The reactivity of cyclic sulfates and epoxides towards nucleophiles is similar in nature but differs in selectivity.[18] Another advantage is that the ring opening of five-membered cyclic sulfates proceeds much faster than with epoxides probably due to the better leaving group ability.[19] Thus, the double bond of **11** was dihydroxylated[20] (**11** → **12**),[15] which occurred with exclusive facial selectivity, followed by reaction with thionyl chloride and oxidation to form the cyclic sulfate **13** in 80% yield.[21] Much to our satisfaction, opening of the cyclic sulfate with lithium azide proceeded completely regioselectively to give, after subsequent sulfate hydrolysis, the protected 2-deoxystreptamine **14** in enantiomerically pure form.[15] The latter compound, after glycosylation of the free hydroxyl, is ideally suited for the preparation of either 4,5- or 4,6-linked aminoglycoside analogues after subsequent desilylation or debenzylation, respectively.

In conclusion, we believe that the synthesis described above is a versatile route towards orthogonally protected 2-deoxystreptamine in enantiomerically pure form in 14 steps and an overall yield of 6.1%. The aminocyclitol building block obtained is suitable for incorporation into new aminoglycoside entities. Work along this line is currently in progress in our laboratory.

## Acknowledgement

This research was financially supported by the Netherlands Organisation for Scientific Research (NWO).

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13. Configuration of the *syn*-amino alcohol **2b** was assigned by $^1$H NMR analysis of the corresponding oxazolidinone **3**. See, for example: Dondoni, A.; Perrone, D. *Synthesis* **1993**, 1162–1176.
14. Reaction was performed up to 5 mmol scale. Buffering of the CAN solution with $NaHCO_3$ was required to prevent a drop in yield.
15. Compound identification: **9a**: $[\alpha]_D^{20}$ +27.3 (*c* 1.89, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$, 400 MHz, ppm): $\delta$ 7.48–7.25 (m, 5H, arom), 6.19–6.40 (m, 1H, =CH–), 5.82–5.62 (m, 1H, =CH–), 5.72 (d, 1H, $J = 10.5$ Hz, $=CH_2$), 5.12 (d, 1H, $J = 17.3$ Hz, $=CH_2$), 5.11–5.02 (m, 2H, $=CH_2$), 4.77 (d, 1H, $J = 11.3$ Hz, $CH_2$), 4.66 (d, 1H, $J = 11.0$ Hz, $CH_2$), 4.80 (br s, 1H, CH), 4.23–4.15 (m, 1H, CH), 4.09–3.80 (m, 1H, CH), 3.45 (d, 1H, $J = 6.92$ Hz, NH), 2.55 (d, 1H, $J = 4.68$ Hz, OH), 2.31 (br t, 2H, $J = 7.18$ Hz, $CH_2$), 1.41 (s, 9H, *t*-Bu). $^{13}$C NMR ($CDCl_3$, 75 MHz, ppm): 159.6, 139.6, 135.0, 128.9, 128.8, 118.1, 118.0, 79.9, 75.6, 73.7, 51.0, 38.5, 29.1. HRMS (CI) *m*/*z* calcd for $C_{20}H_{30}O_4N$ $(M+H)^+$: 348.2174, found: 348.2167. IR $\nu_{max}$ film: $cm^{-1}$ 2975, 1706, 1502, 1171.

**12**: $[\alpha]_D^{20}$ +12.8 (*c* 0.44, $CH_2Cl_2$). $^1H$ NMR ($CDCl_3$, 400 MHz, ppm): $\delta$ 7.36–7.12 (m, 5H, arom Bn), 4.71 (d, 1H, $J = 11.6$ Hz, $CH_2$), 4.53 (d, 1H, $J = 11.6$ Hz, $CH_2$), 4.21 (m, 1H, CH), 4.1 (m, 1H, CH), 3.97 (m, 1H, CH), 3.75 (m, 1H, CH), 3.44 (m, 1H, CH), 3.27 (br d, 1H, $J = 9.8$ Hz, NH), 2.02–1.89 (m, 2H, $CH_2$), 1.42 (s, 9H, *t*-Bu), 0.88 (s, 9H, *t*-Bu), 0.03 (s, 6H, $SiMe_2$). $^{13}C$ NMR ($CDCl_3$, 100 MHz, ppm): $\delta$ 154.8, 136.7, 128.3, 79.4, 73.7, 72.8, 72.3, 64.7, 60.6, 48.1, 30.1, 28.7, 26.0, 18.1, 14.6, −4.7. HRMS (CI) *m*/*z* calcd for $C_{24}H_{42}O_6NSi$ $(M+H)^+$: 468.2782, found: 468.2785. IR $\nu_{max}$ film: $cm^{-1}$ 2925, 2358, 1778, 1697, 1508, 1135, 1082.

**14**: $[\alpha]_D^{20}$ −21.0 (*c* 0.10, $CH_2Cl_2$). $^1H$ NMR ($CDCl_3$, 400 MHz, ppm): $\delta$ 7.43–7.24 (m, 5H, arom), 4.75 (d, 1H, $J = 11.4$ Hz, $CH_2$), 4.60 (d, 1H, $J = 11.4$ Hz, $CH_2$), 3.72–3.44 (m, 4H, CH), 3.22–3.11 (m, 1H, CH), 2.62–2.47 (m, 1H, $CH_2$), 2.32–2.26 (m, 1H, $CH_2$), 1.40 (s, 9H, *t*-Bu), 0.93 (s, 9H, *t*-Bu), 0.32 (s, 6H, $SiMe_2$). HRMS (CI) *m*/*z* calcd for $C_{24}H_{41}O_5N_4Si$ $(M+H)^+$: 493.2846, found: 493.2847. IR $\nu_{max}$ film: $cm^{-1}$ 2928, 2103, 1689, 1169, 1069, 610.

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