Pergamon

Tetrahedron Letters 43 (2002) 6451–6455

TETRAHEDRON LETTERS

A stereoselective route towards highly functionalized 4,6-diaminocyclohexene derivatives

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Received 11 June 2002; accepted 28 June 2002

Abstract—A flexible synthetic route towards chirally pure 4,6-diaminocyclohexene derivatives based on palladium catalyzed allylic amination of carbohydrate derived cyclohexenes is presented.

Aminoglycosides, polyamino oligosaccharides often containing the aminocyclitol 2-deoxystreptamine (Fig. 1), show strong binding with a variety of RNA structures, including bacterial 16S ribosomal RNA[1] and the HIV transactivating region.[2] Based on the RNA binding properties, aminoglycosides are widely considered as potential therapeutics in combating bacterial and viral infections.[3] For example, the aminoglycosides tobramycin and neomycin B are presently used as antibiotics in the treatment of some bacterial infections.[4] However, the toxicity of most aminoglycosides limits their use as broad-spectrum therapeutics. The latter may be ascribed to the undesired binding with eukaryotic rRNA.[5] It may therefore be expected that aminoglycoside derivatives with enhanced selectivity towards bacterial/viral RNA would find broader application as clinically useful drugs.

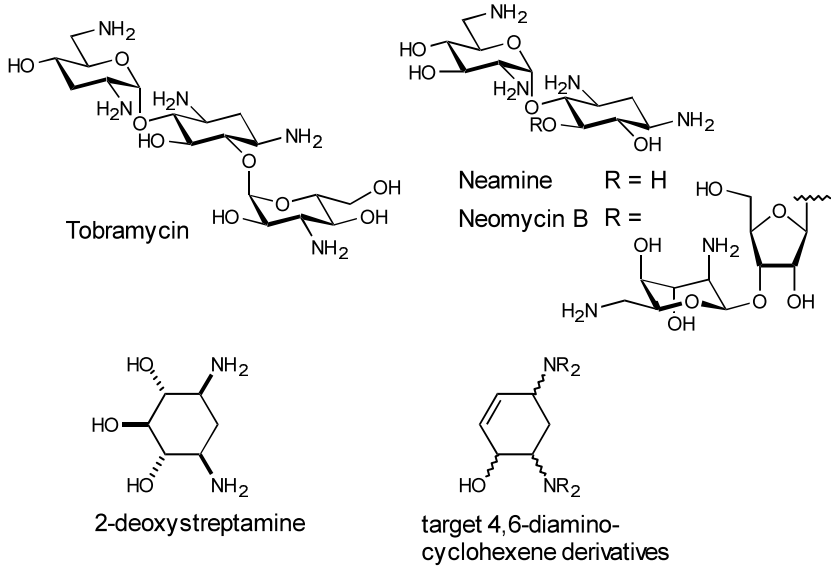

Figure 1.

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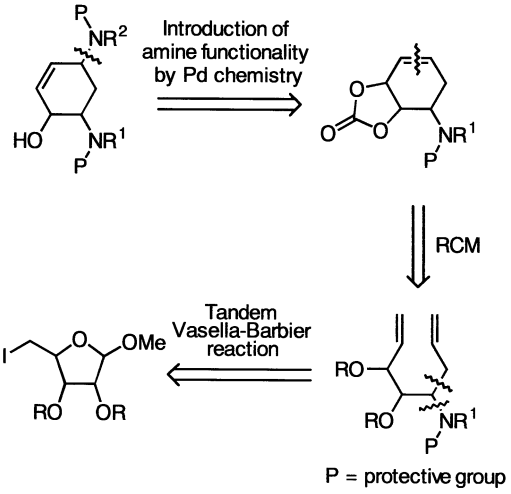
0040-4039/02/$ - see front matter
PII: S0040-4039(02)01364-3

The derivatization of aminoglycoside substructures, such as the pseudo-disaccharide neamine (Fig. 1), is a burgeoning field of research aimed at the preparation of novel and more effective aminoglycosides.[6] This strategy is certainly attractive for the rapid generation of new, functionally diverse RNA-binding ligands. However, the limited stereochemical diversity in this type of ligands is a drawback, as the spatial positioning of the amino groups in aminoglycosides may well be critical for selective recognition of RNA.[7]

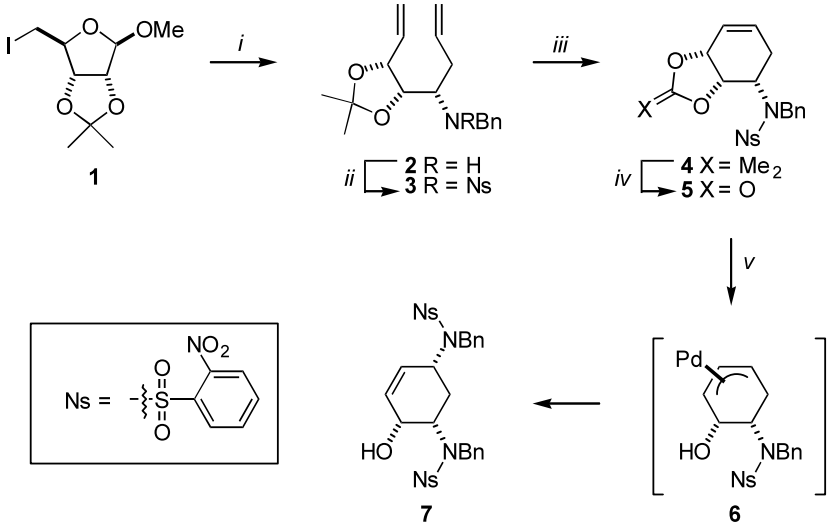
In general, the implementation of stereochemical diversity in aminoglycosides may eventually result in the discovery of new lead compounds with potential selective RNA binding properties. It was envisaged that this objective could be attained by the synthesis of 4,6-diaminocyclohexene derivatives which are structural analogs of 2-deoxystreptamine (Fig. 1). In this paper we report a flexible route towards highly functionalized 4,6-diaminocyclohexene derivatives starting from carbohydrate-derived 1,7-dienes.

Retrosynthetic analysis (Scheme 1) reveals that Vasella fragmentation of a readily available methyl-5-deoxy-5-iodo furanoside in the presence of an alkylamine followed by in situ Barbier-type allylation of the resulting imine affords the required functionalized 1,7-diene.[8] Subsequent ring-closing metathesis (RCM) and further elaboration will give the cyclic carbonate derivative which is amenable to palladium catalyzed allylic amination resulting in the target 4,6-diaminocyclohexene.

In the first instance, the conversion of methyl-5-deoxy-5-iodo-2,3-isopropylidene-ribofuranoside **1** into diaminocyclohexenol **7** was examined (Scheme 2).[9] Vasella–Barbier domino reaction[8] on **1** using zinc in the presence of benzylamine and allyl bromide, led to the isolation of optically pure 1,7-diene **2**. The secondary amine function in **2** was protected, prior to the ensuing RCM reaction, with the *o*-nitrobenzenesulfonyl (Ns) group, the removal of which can be effected under very mild conditions.[10] RCM of fully protected **3** in the presence of Grubbs' catalyst ($Cl_2(PPh_3)_2Ru{=}CHPh$)[11] proceeded smoothly to give cyclohexene derivative **4**. Transformation of **4** into the cyclic carbonate **5**[12] was then followed by a Pd(0) catalyzed allylic amination using *N*-benzyl-nosylamide as the nucleophile.[13] Several palladium complexes, generated in situ from



Scheme 1. Retrosynthetic analysis.



Scheme 2. *Reagents and conditions*: (i) Zn (excess), allyl bromide (2.2 equiv.), benzylamine (2 equiv.), THF, sonication, 70%.[8] (ii) a. NsCl, DCM/sat. Na_2CO_3, 90%. (iii) Grubbs' catalyst (1.5 mol%), 93%. (iv) a. AcOH/H_2O 8/2, reflux, b. carbonyldiimidazole, DMF, 84% (two steps). (v) NsNHBn (1.5 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), PPh_3 (25 mol%), Et_3N (3 equiv.), THF, 80%.

$(dba)_3Pd_2{\cdot}CHCl_3$ and an excess of the respective phosphine ligands (PPh_3, dppb[14] and dppp[14]), were tested for their catalytic activity. It turned out that the triphenylphosphine ligand was superior over the bidentate ligands dppb and dppp in terms of overall yield.[15] The regio- and stereoselective formation of **7** is ensured by the formation of the π-allyl complex **6** and subsequent substitution with overall retention at the less hindered carbon atom.

The synthesis of the enantiomeric and similarly protected 4,6-diaminocyclohexenol **13** (Scheme 3) was readily accomplished starting from methyl-5-deoxy-5-iodo-2,3-isopropylidene-lyxofuranoside (**8**), obtained from D-mannose.[16] Subjection of **8** to the Vasella–Barbier tandem reaction provided 1,7-diene **9**. Execution of the sequence of reactions mentioned above for the conversion of **2** into **7** gave compound **13**[9] in comparable overall yield (Scheme 3).

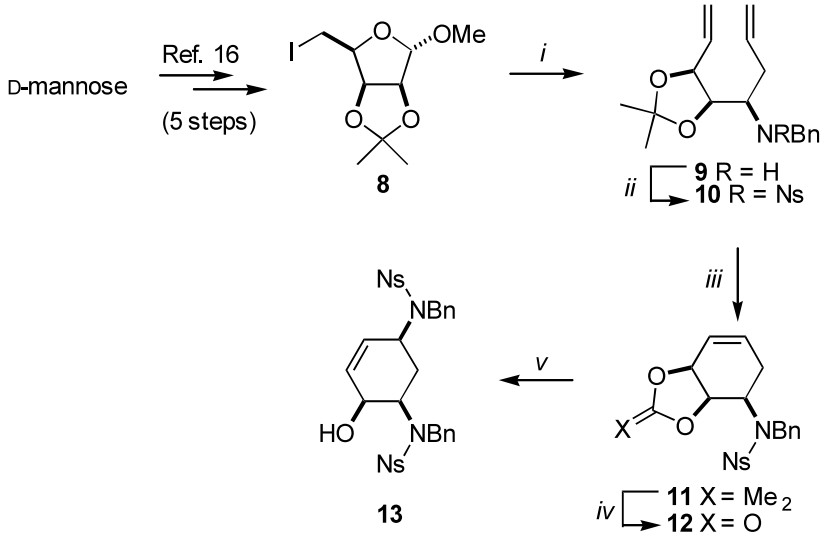
At this stage it was gratifying to find that the scope of the allylic amination of carbocyclic cores **5** or **12** is not limited to the use of *N*-benzyl-nosylamide, but can also be extended to the synthesis of higher functionalized cyclohexenediamines. The results of these substitution reactions are summarized in Table 1.

It can be seen (entry 1) that allylic amination of cyclic carbonate **5** with Ns-glycine methyl ester proceeded as expected to give glycine derivative **14** in a high yield. A similar result was obtained in the case of ε-Ns-α-boc-lysine methyl ester providing compound **15** in 71% (entry 2). Furthermore, amino acid derivatives **16–18** were isolated, although in lower yields, using α-Ns-ε-Z-lysine methyl ester, α-Ns-glutamic acid dimethyl ester and α-Ns-phenylalanine methyl ester as the nucleophiles (entry 3–5). It is also interesting to note that reaction of scaffold **5** with galactose and acridine derivatives featuring a terminal nosylated amine furnished compounds **19** and **20** in satisfactory yields (entry 6 and 7).

The results described in this paper clearly show that chiral 4,6-diaminocyclohexene derivatives can be obtained by palladium catalyzed allylic amination of easily accessible carbocyclic cores **5** and **12** with *o*-nitrobenzenesulfonyl amides. The versatility of the allylic amination was nicely illustrated by the use of structurally diverse nucleophiles including amino acid and carbohydrate derived nosyl amides. The authors firmly believe that the approach presented here gives access to valuable synthons for the future design and synthesis of stereochemically diverse aminoglycoside antibiotics. Further synthetic efforts along these lines are underway and will be reported in due course.

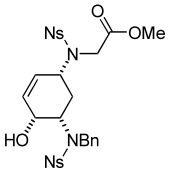
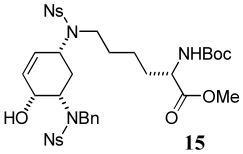
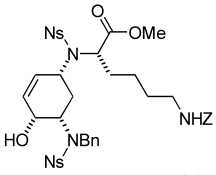
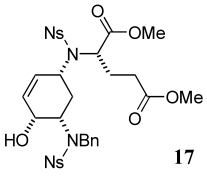
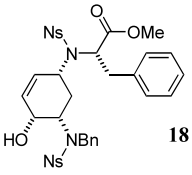
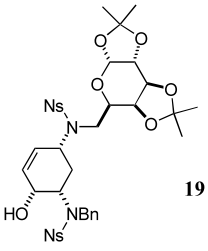
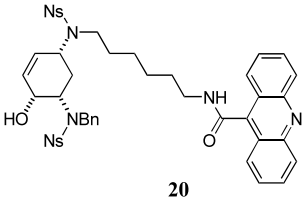
Acknowledgements

The authors thank Fons Lefeber and Cees Erkelens for recording NMR spectra, Hans van den Elst for mass spectrometry, and Organon N.V. for financial support.



Scheme 3. *Reagents and conditions*: (i) Zn (excess), allyl bromide (2.2 equiv.), benzylamine (2 equiv.), THF, sonication, 66–80%. (ii) a. NsCl, DCM/sat. Na_2CO_3, 88%. (iii) Grubbs' catalyst (1.5 mol%), 91%. (iv) a. $AcOH/H_2O$ 8/2, reflux, b. carbonyldiimidazole, DMF 84% (two steps). (v) NsNHBn (1.5 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%), PPh_3 (25 mol%), Et_3N (3 equiv.), THF, 82%.

Table 1. Transformation of **5** into 4,6-diaminocyclohexene derivatives

Entry	Product	Yield (%)
1	 **14**	85
2	 **15**	71
3	 **16**	36
4	 **17**	37
5	 **18**	40
6	 **19**	80
7	 **20**	58

General conditions: NsNHR (1.5 eq.), $Pd_2(dba)_3.CHCl_3$ (2.5 mol%), PPh_3 (25 mol%), Et_3N (3 eq.), THF.

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9. Selected analytical data: **5**: ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.52–7.47 (m, 2H), 7.40–7.39 (d, 1H, $J=8.0$ Hz, $J=1.4$ Hz), 7.27–7.24 (m, 1H), 7.19–7.13 (m, 2H), 7.07–7.04 (m, 3H), 6.04 (ddd, 1H, $J=10.2$ Hz, $J=6.2$ Hz, $J=1.9$ Hz), 5.64–5.61 (m, 1H), 5.25–5.22 (m, 1H), 5.09–5.07 (m, 1H), 4.80 (d, 1H, $J=15.9$ Hz), 5.54 (d, 1H, $J=15.8$ Hz), 4.55–4.52 (m, 1H), 2.47–2.42 (m, 1H), 2.32–2.28 (m, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 154.13, 146.96, 135.73, 134.16, 133.38, 132.66, 131.70, 131.22, 128.30, 128.12, 127.65, 124.01, 121.11, 78.99, 75.09, 54.43, 49.34, 25.20. ESI MS: $m/z=$ 431.2 $(M+H)^+$. $[\alpha]_D^{20}$ −76.4 (c 0.1, $CHCl_3$). **12**: $[\alpha]_D^{20}$ +76.8 (c 0.1, $CHCl_3$). Regio- and stereochemistry of the amination products were ascertained by HH-COSY and H-NOESY (NOE signals were visible between H-4 and H-6). **7**: ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.70–7.79 (m, 1H), 7.56–7.51 (m, 5H), 7.43–7.40 (m, 1H), 7.39–7.36 (m, 1H), 7.19–7.04 (m, 10H), 5.80 (ddd, 1H, $J=10.0$ Hz, $J=5.7$ Hz, $J=2.6$ Hz), 5.56–5.54 (m, 1H), 4.69–4.65 (m, 1H), 4.58 (d, 1H, $J=16.4$ Hz), 4.50 (d, 1H, $J=15.8$ Hz), 4.41 (d, 1H, $J=16.4$ Hz), 4.27 (d, 1H, $J=15.8$ Hz), 4.14 (bs, 1H), 3.96 (dt, 1H, $J=13.1$ Hz, $J=2.9$), 2.04–1.97 (m, 1H), 1.80–1.74 (m, 1H), 1.53 (bs, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 147.49, 147.46, 137.28, 133.84, 133.78, 133.52, 133.39, 131.68, 131.65, 131.37, 131.32, 130.95, 130.92, 128.51, 128.38, 127.73, 127.68, 127.45, 124.12, 124.08, 66.72, 56.97, 56.75, 49.29, 48.79, 27.44. ESI MS: $m/z=701.4$ $(M+Na)^+$. $[\alpha]_D^{20}$ −17.8 (c 0.1, $CHCl_3$). **13**: $[\alpha]_D^{20}$ +17.0 (c 0.1, $CHCl_3$).

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12. Upon substitution, the cyclic carbonate liberates carbon dioxide and generates an allylic alcohol which is not susceptible for further reaction. The corresponding bisacetates did not react in palladium catalyzed allylic aminations.
13. Typical experimental procedure: THF was distilled under argon prior to use. Cyclic carbonate **5** and the *o*-nitrobenzenesulfonyl amide nucleophile (1.5 equiv.) were coevaporated with dioxane and dissolved in THF (final concentration of **5**: 0.1 M). Subsequently triethylamine (3 equiv.), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%) and PPh_3 (25 mol%) were added, and the reaction mixture was stirred under argon for 3 h at ambient temperature. The reaction mixture was concentrated in vacuo and purified by flash chromatography, affording the desired products as slightly yellow foams.
14. Dppb: diphenylphospinobutane; dppp: diphenylphosphinopropane.
15. The reaction of **5** with benzyl-nosylamine catalyzed by $Pd(dppb)_2$ and $Pd(dppp)_2$ proceeded in 22 and 27% yield, respectively. The yield could not be improved by performing the reaction at elevated temperature (50°C).
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