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Asymmetric Syntheses of (−)-1-Deoxymannojirimycin and (+)-1-Deoxyallonojirimycin via a Ring-Expansion Approach

Stephen G. Davies,* Aude L. A. Figuccia, Ai M. Fletcher, Paul M. Roberts, and James E. Thomson

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K.

steve.davies@chem.ox.ac.uk

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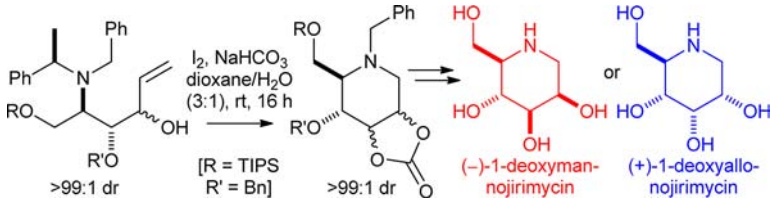
ABSTRACT



The asymmetric syntheses of (−)-1-deoxymannojirimycin and (+)-1-deoxyallonojirimycin are described herein. The ring-closing iodoamination of two epimeric bishomoallylic amines to give the corresponding 5-iodomethylpyrrolidines was followed by in situ ring-expansion to give two diastereoisomerically pure (>99:1 dr) cyclic carbonates. Subsequent deprotection gave (−)-1-deoxymannojirimycin and (+)-1-deoxyallonojirimycin as single diastereoisomers in 7.4 and 3.3% overall yield, respectively, from commercially available starting materials.

The potent biological activity displayed by polyhydroxylated piperidines (iminosugars) has made them very attractive targets for total synthesis;[1] for example, (−)-1-deoxynojirimycin **6** is an effective glycosidase inhibitor and has potential in the treatment of cancer and HIV.[2] As part of our ongoing research program directed toward the de novo preparation of imino- and aminosugars,[3] we recently reported an oxidation and ring-contraction approach for the synthesis of (−)-1-deoxynojirimycin **6** and its stereoisomer (+)-1-deoxyaltronojirimycin.[4] In our synthesis of **6**, chemoselective oxidation[5] of dihydroazepine **1** was followed by resolution via preparative chiral HPLC which gave **2** as a single diastereoisomer (>99:1 dr) in >99% ee. Treatment of **2** with MsCl produced tetrahydropyridine **4**, presumably via the intermediacy of aziridinium **3**. Subsequent elaboration of **4** produced (−)-1-deoxynojirimycin **6** in 10% overall yield (Figure 1).

(1) (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (b) Davis, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 652.

(2) For example, see: (a) Cross, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935. (b) Qian, X.; Moris-Varas, F.; Fitzgerald, M. C.; Wong, C.-H. *Bioorg. Med. Chem.* **1996**, *4*, 2055. (c) Nakagawa, K.; Kubota, H.; Tsuzuki, T.; Kariya, J.; Kimura, T.; Oikawa, S.; Miyazawa, T. *Biosci. Biotechnol. Biochem.* **2008**, *72*, 2210. (d) Winchester, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 645.

(3) For example, see: (a) Bagal, S. K.; Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Roberts, P. M.; Scott, P. M.; Thomson, J. E. *Tetrahedron Lett.* **2011**, *52*, 2216. (b) Csatayová, K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Wilson, D. L. *Org. Lett.* **2011**, *13*, 2606.

(4) (a) Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Thomson, J. E. *Org. Lett.* **2010**, *12*, 136. (b) Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Scott, P. M.; Thomson, J. E. *J. Org. Chem.* **2010**, *75*, 8133.

(5) For example, see: (a) Aciro, C.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3762. (b) Aciro, C.; Claridge, T. D. W.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3751. (c) Bond, C. W.; Cresswell, A. J.; Davies, S. G.; Fletcher, A. M.; Kurosawa, W.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *J. Org. Chem.* **2009**, *74*, 6735. (d) Brennan, M. B.; Claridge, T. D. W.; Compton, R. G.; Davies, S. G.; Fletcher, A. M.; Henstridge, M. C.; Hewings, D. S.; Kurosawa, W.; Lee, J. A.; Roberts, P. M.; Schoonen, A. K.; Thomson, J. E. *J. Org. Chem.* **2012**, *77*, 7241.

(6) (a) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2009**, *20*, 758. (b) Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2011**, *13*, 1594. (c) Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; West, C. J. *Tetrahedron* **2012**, *68*, 4302. (d) Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2012**, *14*, 4278.

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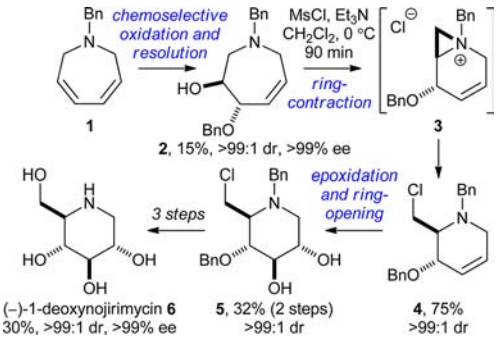
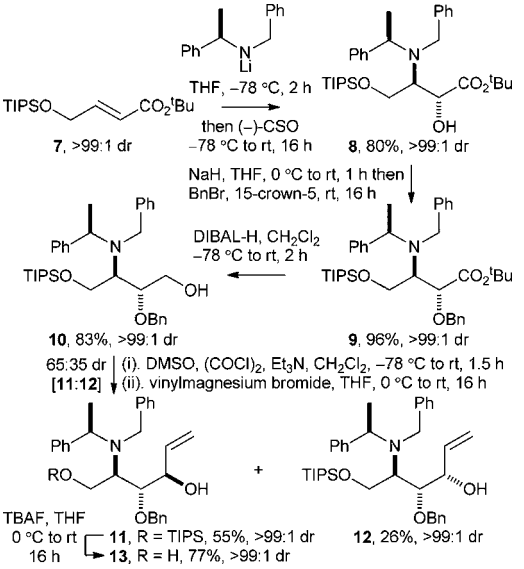


Figure 1. Synthesis of (−)-1-deoxynojirimycin **6** via a ring-contraction approach.

Herein we report an alternative ring-expansion procedure for the preparation of 1-deoxyiminosugars employing our ring-closing iodoamination[6] protocol to effect cyclization of bishomoallylic amines (which can be readily prepared from the corresponding α,β-unsaturated ester using our diastereoselective aminohydroxylation procedure[7] followed by reduction and reaction with vinylmagnesium bromide), followed by ring-expansion of the resultant iodomethylpyrrolidines and deprotection.

Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to **7** (prepared in 61% yield and >99:1 dr over three steps from *cis*-but-2-ene-1,4-diol),[8] followed by oxidation of the resultant enolate with (−)-camphorsulfonyloxaziridine [(−)-CSO], gave β-amino ester **8** in 80% yield and >99:1 dr.[8a] The stereochemical outcome of this reaction was initially assigned by reference to our transition state mnemonic[9] and by analogy to the well established outcome of this aminohydroxylation protocol,[7,10] and was later confirmed unambiguously by single crystal X-ray diffraction analysis of a derivative. Subsequent *O*-benzyl protection of **8** and reduction of the ester moiety within **9** gave alcohol **10** in 80% overall yield (from **8**). Oxidation of the primary hydroxyl functionality within **10**, followed by reaction of the resultant aldehyde with vinylmagnesium bromide, gave a 65:35 mixture of **11** and **12**.[11] After chromatographic purification of the crude reaction mixture, **11** was isolated in 55% yield and >99:1 dr, and **12** was isolated in 26% yield and >99:1 dr. Deprotection of the *O*-silyl group within the major diastereoisomer **11** using TBAF gave **13** in 77% yield (Scheme 1). The relative configuration within **13** was unambiguously established by single crystal X-ray diffraction analysis (Figure 2),[12] with the absolute (*R*,*R*,*R*,*R*)-configuration within **13** following from the known configuration of the *N*-α-methylbenzyl fragment. This analysis therefore also secured the assigned configurations within **8**–**12**.

Scheme 1. Preparation of Cyclization Precursors **11** and **12**



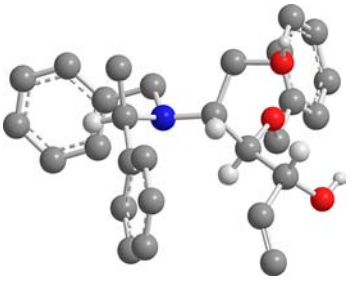


Figure 2. X-ray crystal structure of (*R*,*R*,*R*,*R*)-**13** (selected H-atoms are omitted for clarity).

Ring-closing iodoamination of **11** under our previously optimized conditions[6] produced a mixture of iodomethylpyrrolidine **14** (>99:1 dr) and *N*-(α-methylbenzyl)-acetamide; after purification of the crude reaction mixture **14** was isolated in 20% yield and >99:1 dr. The relative configuration within **14** was tentatively assigned by ^{1}H NMR NOE analysis, and from its ^{13}C NMR spectrum, which displayed a diagnostic peak for the CH_2I carbon atom (δ_C = 3.4 ppm which is indicative of a 4,5-*cis*-relationship);[6a,13]

(7) For reviews of this methodology, see: (a) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833. (b) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2012**, *23*, 1111.

(8) (a) Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655. (b) Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 1665.

(9) Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999.

(10) Bunnage, M. E.; Chernega, A. N.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2373.

(11) Attempts to improve the diastereoselectivity of this process (solvent, temperature, counterion redox, etc.) were not successful.

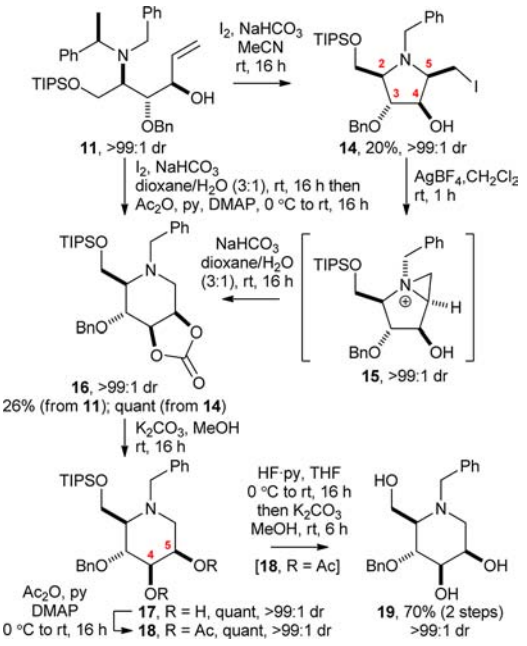
(12) Crystallographic data (excluding structure factors) for the structures of **13**, **19**·$CHCl_3$, and **25** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 926152–926154, respectively.

this stereochemical outcome is also consistent with our previous observations concerning this class of ring-closing iodoamination reaction.[6a] Subsequent treatment of **14** with $AgBF_4$ in CH_2Cl_2 promoted the formation of aziridinium ion **15**, and the relative configuration within **15** was established by ^1H NMR NOESY analysis. Treatment of **15** with $NaHCO_3$ in dioxane/H_2O (3:1) gave ring-expanded, cyclic carbonate **16** in quantitative yield.[14,15] We then developed a procedure for the preparation of carbonate **16** directly from **11** upon treatment with I_2 and $NaHCO_3$ in a mixture of dioxane/H_2O (3:1),[16] followed by treatment with Ac_2O to facilitate the separation of **16** from the 1-phenylethanol by-product. Methanolysis of the carbonate functionality within **16** and acetate protection of the C(4) and C(5) hydroxyl groups within **17** gave **18** in quantitative yield. The relative configurations within **16**–**18** were assigned based on ^1H NMR NOE and ^3J coupling constant analyses. Deprotection of the *O*-silyl group within **18**, which was achieved upon treatment with HF·pyridine, followed by methanolysis produced **19** in 70% yield and >99:1 dr (Scheme 2). The relative configuration within **19** was unambiguously established by single crystal X-ray diffraction analysis (Figure 3);[12] furthermore, the determination of a Flack *x* parameter[17] of −0.09(12) for this crystal structure allowed the assigned absolute (*R*,*R*,*R*,*R*)-configuration within **19**, and hence also the assigned configurations within **14**–**18**, to be confirmed.

Under the optimized conditions, the reaction of **11** with I_2 and $NaHCO_3$ in a mixture of dioxane/H_2O (3:1) followed by immediate *O*-desilylation of **16**, upon treatment with HF·pyridine, and methanolysis of the carbonate functionality within **20** gave triol **19** in 40% isolated yield (from **11**) and >99:1 dr. Subsequent global hydrogenolytic deprotection of **19** was achieved in the presence of Pearlman's catalyst [$Pd(OH)_2$/C] which gave (−)-1-deoxymannojirimycin **21**[18,19] in 87% yield and >99:1 dr (Scheme 3). The spectroscopic data for this sample of **21**, including its specific rotation {$[\alpha]_D^{20}$ −38.6 (*c* 1.0 in H_2O)}, were in excellent agreement with literature data {lit.[20] for sample isolated from a natural source $[\alpha]_D$ −41.4 (*c* 0.74 in H_2O); lit.[18] $[\alpha]_D^{20}$ −40 (*c* 1.35 in H_2O); lit.[19] $[\alpha]_D^{22}$ −36.1 (*c* 0.33 in H_2O)}.

The reaction of the epimeric substrate **12** produced a 73:27 mixture of diol **22** and carbonate **23**;[21] methanolysis of the crude reaction mixture then gave diol **22** exclusively (confirming the homochirality of **22** and **23**), and then acetate protection facilitated the isolation of **24** as a single diastereoisomer in 43% yield (from **12**). The relative

Scheme 2. Ring-Closing Iodoamination of **11**



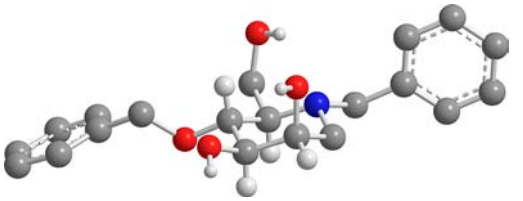
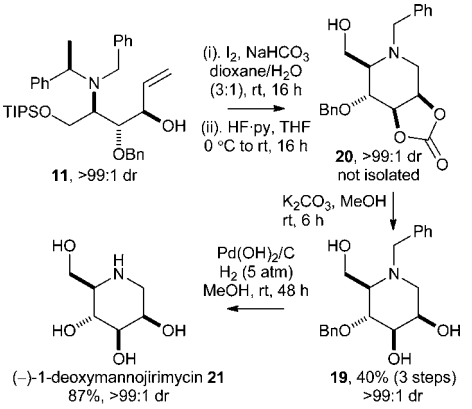


Figure 3. X-ray crystal structure of (*R*,*R*,*R*,*R*)-**19**·$CHCl_3$ ($CHCl_3$ and selected H-atoms are omitted for clarity).

Scheme 3. Synthesis of (−)-1-Deoxymannojirimycin **21**



(13) (a) Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett*. **1984**, *25*, 1063. (b) Palmer, A. M.; Jäger, V. *Synlett* **2000**, 1405.

(14) Cyclic carbonates have previously been prepared upon treatment of *vic*-halohydrins with $(Me_4N)HCO_3$; see: Venturello, C.; D'Aloisio, R. *Synthesis* **1985**, 33.

(15) Direct treatment of **14** with $NaHCO_3$ in dioxane/H_2O (3:1) also gave cyclic carbonate **16** in quantitative yield.

(16) Verhelst, S. H. L.; Paez Martinez, B.; Timmer, M. S. M.; Lodder, G.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *J. Org. Chem*. **2003**, *68*, 9598.

(17) Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876.

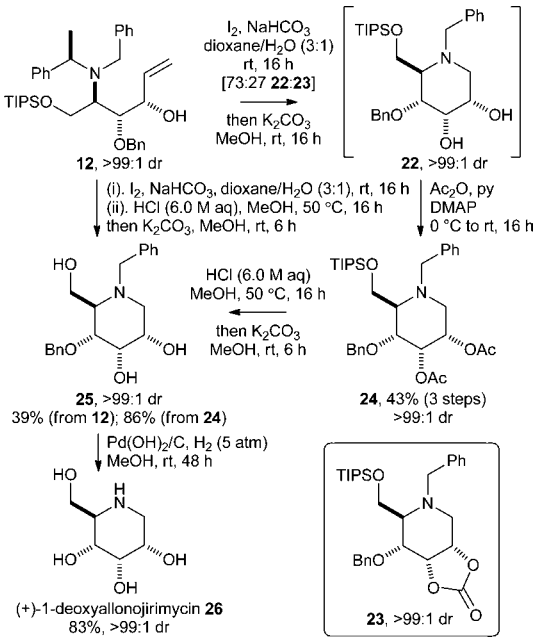
(18) Broxterman, H. J. G.; Neefjes, J. J.; van der Marel, G. A.; Ploegh, H. L.; van Boom, J. H. *J. Carbohydr. Chem*. **1988**, *7*, 593.

(19) Concia, A. L.; Lozano, C.; Castillo, J. A.; Parella, T.; Joglar, J.; Clapés, P. *Chem.—Eur. J*. **2009**, *15*, 3808.

(20) Asano, N.; Oseki, K.; Kizu, H.; Matsui, K. *J. Med. Chem*. **1994**, *37*, 3701.

(21) An authentic sample of diol **22** was prepared in quantitative yield upon transesterification of **24** with K_2CO_3 and MeOH.

Scheme 4. Synthesis of (+)-1-Deoxyallonojirimycin **26**



configurations within **22**−**24** were initially assigned based on a combination of ^{1}H NMR NOE and ^{3}J coupling constant analyses. However, following *O*-silyl deprotection, the relative configuration with **25** was unambiguously established by single crystal X-ray diffraction analysis (Figure 4);[12] furthermore, the determination of a Flack *x* parameter[17] of −0.05(16) for the crystal structure of **25** allowed the assigned absolute (2*R*,3*R*,4*S*,5*S*)-configuration within **25**, and also the assigned configurations within **22**−**24**, to be confirmed. Under optimized conditions, **25** was isolated in 39% overall yield (from **12**) avoiding the formation of **24** and purification of all intermediates. Finally, hydrogenolysis of **25** gave (+)-1-deoxyallonojirimycin **26**[22,23] as a single diastereoisomer which was isolated in 83% yield (Scheme 4). The spectroscopic data for this sample of **26**, including its specific rotation {$[\alpha]_D^{20}$ +28.3 (*c* 1.0 in H_2O)}, were in excellent agreement with literature data {lit.[20] for sample isolated from a natural source $[\alpha]_D$ +25.7 (*c* 0.65 in H_2O); lit.[22] $[\alpha]_D^{25}$ +30.5 (*c* 0.15 in H_2O); lit.[23] $[\alpha]_D^{20}$ +28.1 (*c* 0.8 in H_2O)}.

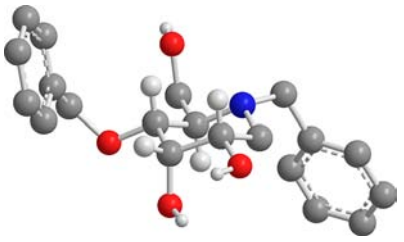


Figure 4. X-ray crystal structure of (2*R*,3*R*,4*S*,5*S*)-**25** (selected H-atoms are omitted for clarity).

In conclusion, the ring-closing iodoamination and ring-expansion of two epimeric bishomoallylic amines were achieved in one pot, generating the corresponding cyclic carbonates as single diastereoisomers. Subsequent deprotection gave (−)-1-deoxymannojirimycin and (+)-1-deoxyallonojirimycin in 7.4 and 3.3% overall yield, respectively, from commercially available starting materials.

Supporting Information Available. Experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra, and crystallographic data (for structures CCDC 926152−926154). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(22) Hong, B.-C.; Chen, Z.-Y.; Nagarajan, A.; Kottani, R.; Chavan, V.; Chen, W.-H.; Jiang, Y.-F.; Zhang, S.-C.; Liaoa, J.-H.; Sarsharb, S. *Carbohydr. Res.* **2005**, *340*, 2457.

(23) Ikota, N.; Hirano, J.-I.; Gamage, R.; Nakagawa, H.; Hama-Inaba, H. *Heterocycles* **1997**, *46*, 637.