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An Oxidation and Ring Contraction Approach to the Synthesis of (±)-1-Deoxynojirimycin and (±)-1-Deoxyaltronojirimycin

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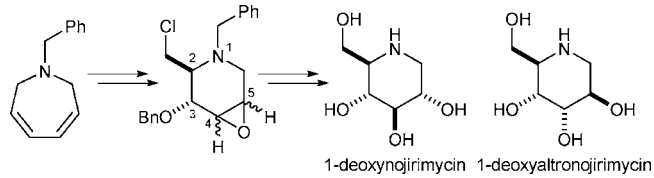
ABSTRACT



A reaction sequence involving the chemoselective olefinic oxidation of *N*(1)-benzyl-2,7-dihydro-1*H*-azepine with *m*-CPBA in the presence of HBF_4 and BnOH followed by ring contraction facilitates the stereoselective preparation of either of the epoxide diastereoisomers of (2*RS*,3*SR*)-*N*(1)-benzyl-2-chloromethyl-3-benzyloxy-4,5-epoxypiperidine by simple modification of the reaction conditions. Epoxide ring opening, functional group interconversion, and deprotection allow the synthesis of (±)-1-deoxynojirimycin and (±)-1-deoxyaltronojirimycin.

Polyhydroxylated piperidines have received considerable attention from the synthetic community due to their glycosidase inhibitory properties,[1] which give them great potential in the treatment of a variety of disorders including cancer and HIV.[2] As part of an ongoing research program directed toward the de novo preparation of imino and amino sugars and their derivatives,[3] we recently reported the ammonium-directed oxidation of 3-(*N*,*N*-dibenzylamino)cyclohex-1-ene **1** upon treatment with *m*-CPBA in the presence of Cl_3CCO_2H.[4] Regioselective in situ ring opening of the intermediate epoxide **2** gave trichloroacetate ester **3**, which underwent transesterification to give diol **4** in quantitative yield and 95:5 dr (Scheme 1). Herein, the application of this methodology to the stereoselective synthesis of (±)-1-deoxynojirimycin (and its diastereoisomer (±)-1-deoxyaltronojirimycin) using a strategy reliant on oxidation of *N*(1)-benzyl-2,7-dihydro-1*H*-azepine and ring contraction is reported.

N(1)-Benzyl-2,7-dihydro-1*H*-azepine **10** was prepared according to a modification of the procedure reported by Walsh and co-workers.[5] Methylation of (*Z*,*Z*)-hexa-2,4-dienedioic

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

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

(3) For selected recent examples, 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) Davies, S. G.; Durbin, M. J.; Goddard, E. C.; Kelly, P. M.; Kurosawa, W.; Lee, J. A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2009**, *7*, 761. (c) Aciro, C.; Davies, S. G.; Kurosawa, W.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 1333. (d) 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.

(4) Aciro, C.; Claridge, T. D. W.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3751.

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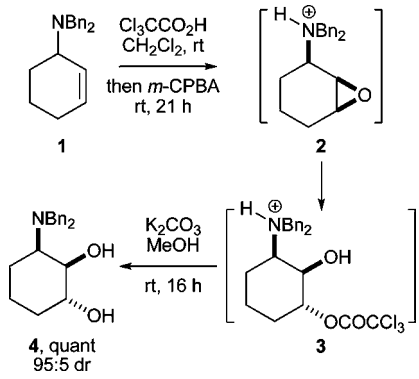
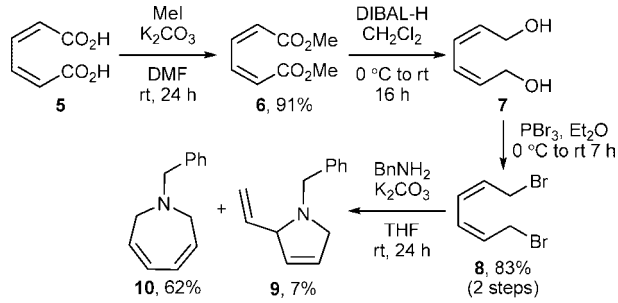
Scheme 1. Ammonium-Directed Dihydroxylation of 3-(*N*,*N*-Dibenzylamino)cyclohex-1-ene **1**



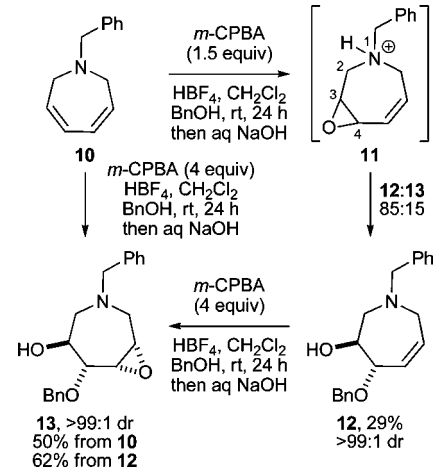
acid **5** (*cis*,*cis*-muconic acid) with MeI and K_2CO_3 gave dimethyl (*Z*,*Z*)-hexa-2,4-dienedioate **6** in 91% yield. DIBAL-H reduction of **6** followed by treatment of the resultant diol **7** with PBr_3 gave dibromide **8** in 83% yield over the two steps. Addition of benzylamine to **8** furnished a chromatographically separable 14:86 mixture of **9** and **10**, which were isolated in 7 and 62% yield, respectively. The overall yield of **10** from **5** (four steps) was 47%[6] (Scheme 2).

Scheme 2. Preparation of *N*(1)-Benzyl-2,7-dihydro-1*H*-azepine **10**



Initial studies into the olefinic oxidation of **10** employing in situ N-protection by treatment with Cl_3CCO_2H in a CH_2Cl_2/BnOH mixture under the previously reported conditions[4] gave incomplete conversion to a chromatographically inseparable mixture of products. However, when the acid protecting agent was changed to HBF_4, complete conversion to a mixture of monobenzyl protected diol **12** and monobenzyl protected diol epoxide **13** was noted. Optimization of the reaction conditions revealed that use of 1.5 equiv of *m*-CPBA gave an 85:15 mixture of **12**:**13** from which **12** was isolated as a single diastereoisomer, albeit in only 29% yield due to its incompatibility with chromatographic media. Employing 4 equiv of

Scheme 3. Oxidation of *N*(1)-Benzyl-2,7-dihydro-1*H*-azepine **10** by *m*-CPBA in the Presence of HBF_4



m-CPBA under analogous conditions gave **13** exclusively, which was isolated in 50% yield (Scheme 3). The relative configuration within **13** was unambiguously established by single-crystal X-ray analysis (Figure 1), and the relative

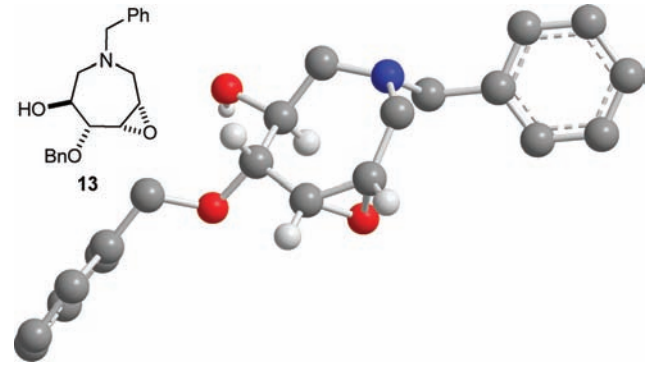


Figure 1. Chem3D representation of the single-crystal X-ray structure of **13** (some H atoms omitted for clarity).

configuration within **12** was established by chemical correlation: resubjection of **12** to the oxidation reaction conditions promoted conversion to **13** as a single diastereoisomer in 62% isolated yield. These results are consistent with a mechanism involving epoxidation of the double bond followed by highly regioselective ring opening of the intermediate epoxide **11** by BnOH at C(4), which is both remote from the destabilizing influence of the electron-withdrawing, protonated nitrogen atom in the late transition state[7] and an activated allylic site.[8] In the presence of excess *m*-CPBA, the intermediate monobenzyl protected diol **12** is further oxidized in a diastereoselective manner to give the monobenzyl protected diol epoxide **13** (Scheme 3).

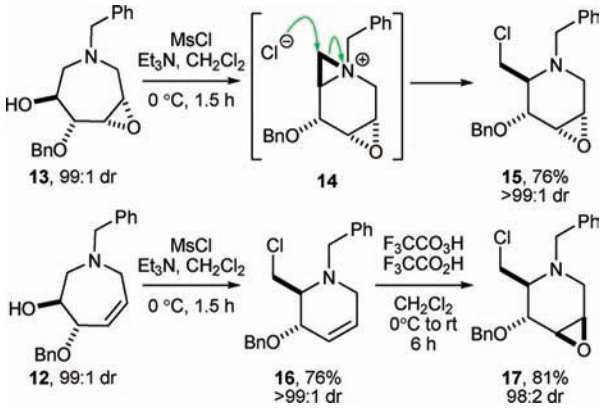
(5) Walsh, J. G.; Furlong, P. J.; Gilheany, D. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3657.

(6) Walsh et al. reported that **10** is unstable and "decomposed too fast to allow for ^{13}C analysis" (see ref 5). In our hands, however, **10** proved stable and could be stored for several months under argon in a freezer without any detectable degradation.

(7) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. Addy, J. K.; Parker, R. E. *J. Chem. Soc.* **1963**, 915.

(8) Smith, M. B.; March, J. *March's Advanced Organic Chemistry - Reactions, Mechanisms, and Structure*, 5th ed.; John Wiley & Sons Inc.: New York, 2001; p 434.

Scheme 4. Ring Contraction of Tetrahydroazepine **12** and Azepane **13**



Treatment of azepane **13** with MsCl promoted ring contraction[9] to give piperidine **15** in 76% isolated yield as a single diastereoisomer (Scheme 4). The relative configuration within **15** was unambiguously established by single-crystal X-ray analysis (Figure 2). This stereochemical outcome is consistent

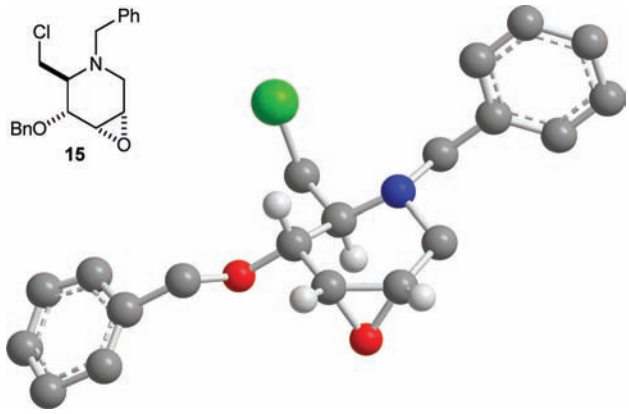


Figure 2. Chem3D representation of the single-crystal X-ray structure of **15** (some H atoms omitted for clarity).

with a mechanism involving initial mesylation of the free hydroxyl group followed by intramolecular S_N2-type displacement of the mesylate by the nitrogen atom to give an intermediate aziridinium ion **14**. Attack of the chloride ion at the least hindered site furnishes the six-membered ring **15** exclusively. Treatment of tetrahydroazepine **12** with MsCl gave tetrahydropyridine **16** as a single diastereoisomer in 76% yield after purification. The relative configuration within **16** was initially assigned on the basis of this transformation proceeding via formation and ring opening of the corresponding aziridium ion. The olefinic oxidation of tetrahydropyridine **16** using *m*-CPBA/Cl_3CCO_2H returned starting material under a range of conditions, although use of F_3CCO_3H/F_3CCO_2H[10] promoted conversion to a 98:2 mixture of the diastereoisomeric expoxides **17**:**15**, with purification giving **17** in 98:2 dr (Scheme 4). The observation of epoxide **15** as the minor diastereoisomeric product of this reaction confirms the stereochemical assignment of tetrahydropyridine **16**.

Treatment of **15** with Cl_3CCO_2H followed by 2 M aq NaOH effected regioselective ring opening of the epoxide and hydrolysis of the resultant trichloroacetate ester to give **19** as a single diastereoisomer. The relative configuration within **19** was unambiguously established by single-crystal X-ray analysis (Figure 3); this analysis also unambiguously

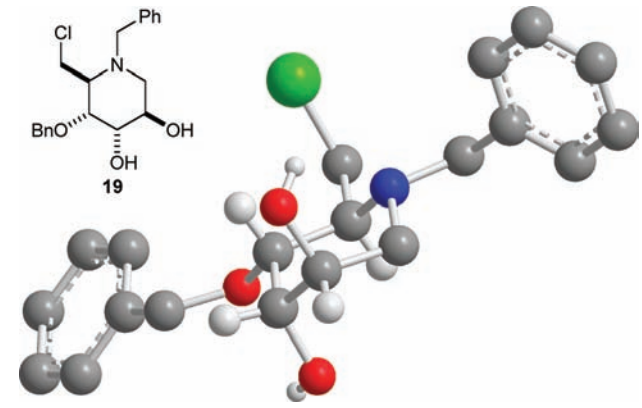


Figure 3. Chem3D representation of the single-crystal X-ray structure of **19** (some H atoms omitted for clarity).

established the regioselectivity of epoxide ring opening [i.e., attack of Cl_3CCO_2H occurs exclusively at C(5)]. ^{1}H NMR ^3J coupling constant analysis of **19** was indicative of an analogous solution phase conformation. Examination of the favored solid-state conformation of **15** revealed that attack of Cl_3CCO_2H at C(5) would give rise to *trans*-diaxial ring opening[11] via a chair-like transition state **18** with the C(2)- and C(3)-substituents in pseudoequatorial sites. Ring opening of epoxide **17** gave an 88:12 mixture of **20**:**19**, and chromatographic purification gave **20** in 60% yield and 99:1 dr. The relative configuration within **20** was assigned by ^{1}H NMR ^3J coupling constant analysis, assuming a chair conformation. This stereochemical outcome is also consistent with ring opening proceeding preferentially via attack of Cl_3CCO_2H at C(5). However, this results in either a disfavored chair-like transition state which places the C(2)-chloromethyl and C(3)-benzyloxy substituents in pseudoaxial sites or a disfavored twist-boat-like transition state, which may therefore account for the lower levels of regioselectivity observed. The regioselectivity of ring opening of epoxides **15** and **17** parallels our previous observations,[3,4] as well as those of Wolinsky[12] and Crotti[13] in related systems, insofar as ring opening occurs preferentially at the carbon atom

(9) Liu, T.; Zhang, Y.; Bleriot, Y. *Synlett* **2007**, *6*, 905.

(10) Gil, L.; Compère, D.; Guilloteau-Bertin, B.; Chiaroni, A.; Marazano, C. *Synthesis* **2000**, 2117.

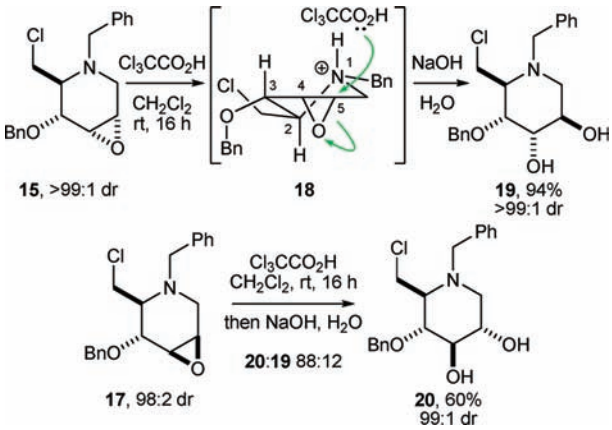
(11) Fürst, A. Plattner, P. A. *12th Internat. Congr. Pure & Appl. Chem.*; New York, 1951; p 409.

(12) Wolinsky, J.; Thorstenson, J. H.; Killinger, T. A. *J. Org. Chem.* **1978**, *43*, 875.

(13) Calvani, F.; Crotti, P.; Gardelli, C.; Pineschi, M. *Tetrahedron* **1994**, *50*, 12999.

remote from the exocyclic heteroatom (in this case oxygen). In the case of **17**, the preferential attack at C(5) may be promoted by both steric[13] and electrostatic[14] effects associated with the exocyclic C(3)-benzyloxy substituent, although hydrogen-bonded delivery of the nucleophile by the endocyclic (protonated) nitrogen atom may also play a role in determining the regioselectivity of attack[15] (Scheme 5).

Scheme 5. Ring Opening Reactions of Epoxides **15** and **17**

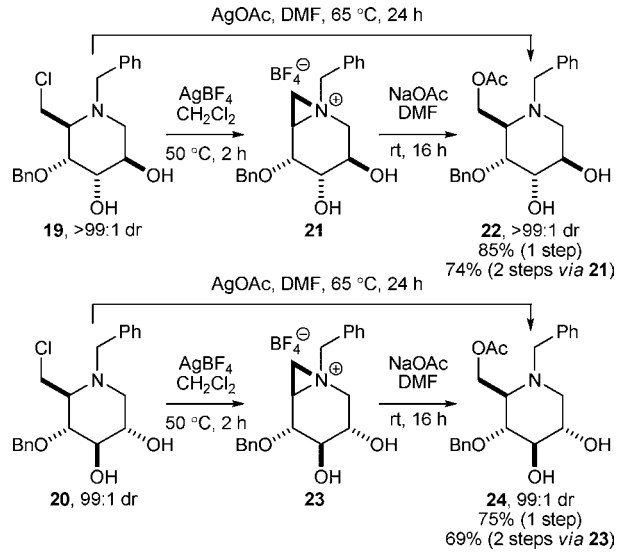


Treatment of **19** with $AgBF_4$ in CH_2Cl_2 promoted ring closure to aziridinium **21**. Treatment of **21** with NaOAc in DMF gave **22** as a single diastereoisomer in 74% yield (two steps) after chromatography. The relative configuration within **22** was assigned on the basis of ^1H NMR ^3J coupling constant analysis. This two-step conversion of **19** to **22** could be effected in one-pot upon treatment of **19** with AgOAc in DMF, giving **22** in 85% isolated yield. An analogous series of transformations applied to **20** (99:1 dr) gave **24** (99:1 dr), either in a single chemical operation or in two steps via the intermediacy of aziridinium **23** (Scheme 6).

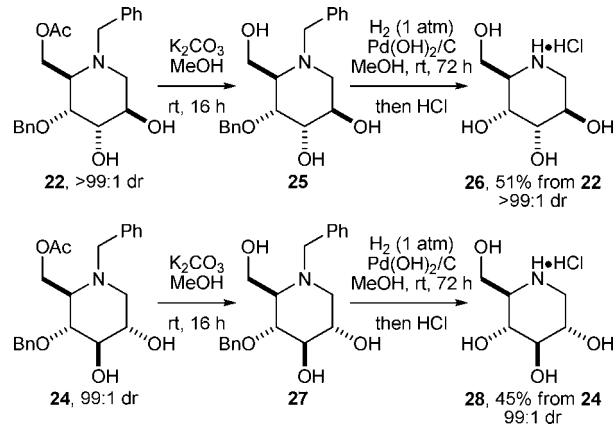
Transesterification of **22** was achieved upon treatment with K_2CO_3 in MeOH and was followed by global hydrogenolytic N- and O-debenzylation mediated by Pearlman's catalyst [$Pd(OH)_2$/C] to give (±)-1-deoxyaltronojirimycin, which was isolated as its hydrochloride salt **26**[16] in 51% yield over the two steps, and in >99:1 dr (Scheme 7). Similar treatment of **24** gave (±)-1-deoxynojirimycin which was isolated as its hydrochloride salt **28**[17] in 45% yield (over two steps) and in 99:1 dr after chromatography (Scheme 7).

In conclusion, the oxidative functionalization of *N*(1)-benzyl-2,7-dihydro-1*H*-azepine on one or both of the olefin moieties and subsequent ring contraction facilitates the preparation of both epoxide diastereoisomers of (2*RS*,3*SR*)-*N*(1)-benzyl-2-chloromethyl-3-benzyloxy-4,5-epoxypiperidine. A further sequence of transformations gives (±)-1-deoxynojirimycin and (±)-1-deoxyaltronojirimycin. This strategy is reliant on N-protection during the oxidative steps being achieved in situ by protonation and demonstrates the utility of our recently reported protocol for the synthesis of molecules with function. Further applications of this useful transformation, as well as studies into the development of an asymmetric variant, are ongoing.

Scheme 6. Functional Group Interconversion of Piperidines **19** and **20**



Scheme 7. Deprotection of Piperidines **22** and **24**



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

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(14) Miljković, M.; Gligorijević, M.; Glišin, D. *J. Org. Chem.* **1974**, 3223.

(15) For a related example, see: Quick, J.; Khandelwal, Y.; Meltzer, P. C.; Weinberg, J. S. *J. Org. Chem.* **1983**, *48*, 5199.

(16) Dhavale, D. D.; Markad, S. D.; Karanjule, N. S.; Reddy, J. P. *J. Org. Chem.* **2004**, *69*, 4760.

(17) Fleet, G. W. J.; Carpenter, N. M.; Petursson, S.; Ramsden, N. G. *Tetrahedron Lett.* **1990**, *31*, 409. Ermert, P.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 2043. Somfai, P.; Marchand, P.; Torsell, S.; Lindström, U. M. *Tetrahedron* **2003**, *59*, 1293.