ORGANIC LETTERS

2006
Vol. 8, No. 14
3069−3072

Stereodivergent Syntheses of Conduramines and Aminocyclitols

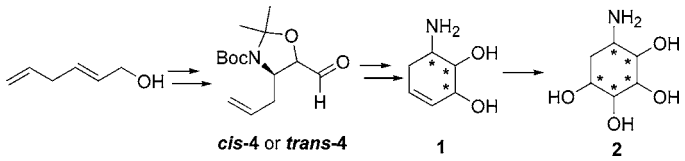
Carlos Alegret,[†] Jordi Benet-Buchholz,[‡] and Antoni Riera*,[†]

Unitat de Recerca en Síntesi Asimètrica (URSA-PCB), Institut de Recerca Biomédica (IRB), and Departament de Química Orgànica, Universitat de Barcelona, Parc Científic de Barcelona, C/ Josep Samitier 1-5, 08028 Barcelona, and Institute of Chemical Research of Catalonia (ICIQ), Avda dels Països Catalans, 16, 43007 Tarragona, Spain

ariera@pcb.ub.es

Received April 28, 2006

ABSTRACT



The diastereomers of 6-amino-cyclohex-3-ene-1,2-diols 1 (4-deoxy-3-conduramines), key building blocks for the syntheses of a large range of natural products, have been enantioselectively prepared. Diastereoselective dihydroxylation of the compounds provided a new family of aminocyclitols 2 (deoxyinosamines). The key reactions of our syntheses are Sharpless catalytic asymmetric epoxidation, diastereoselective addition of vinylmetal reagents to the aldehydes, and ring-closing metathesis (RCM).

Amino alcohols are ubiquitous in nature. Some cyclic polyhydroxylated amines are saccharide-like compounds with diverse biological activities[1] (Figure 1). Diaminocyclitols such as 2-deoxystreptamine[2] are key structural fragments of aminoglycoside antibiotics,[3] a large class of clinically important antibiotics with a broad antibacterial spectrum and proven efficacy in the treatment of serious infections. Owing to their sugar-mimetic structure, aminocyclitols such as deoxyinosamines have garnered interest as key intermediates in aminoglycoside biosynthesis[4] and as potential inhibitors of important metabolic processes such as glycolysis.[5] Noteworthy examples of this family include validamine[6] and valienamine,[6b,7] which are specific α-D-glucosidase inhibitors. Conduramines[8] are purely synthetic aminocyclohexenetriols that also have significant glycosidase inhibitory activity, such as that of the *N*-benzyl derivative of conduramine B-1.[9]

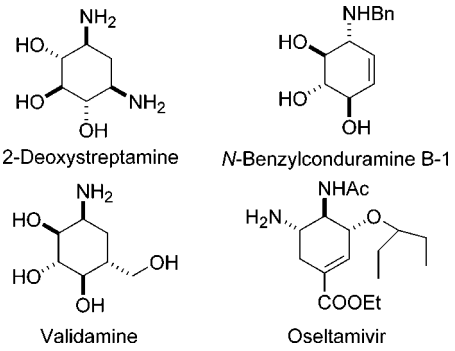


Figure 1. Some conduramines, aminocyclitols, and related compounds with biological interest.

[†] URSA-PCB, IRB.
[‡] ICIQ.

(1) (a) *Iminosugars as glycosidase inhibitors;* Stütz, A., Ed.; Wiley-VHC: Weinheim, 1999. (b) Berecibar, A.; Crandjean, C.; Siriwardena, A. *Chem. Rev.* **1999**, *99*, 779.

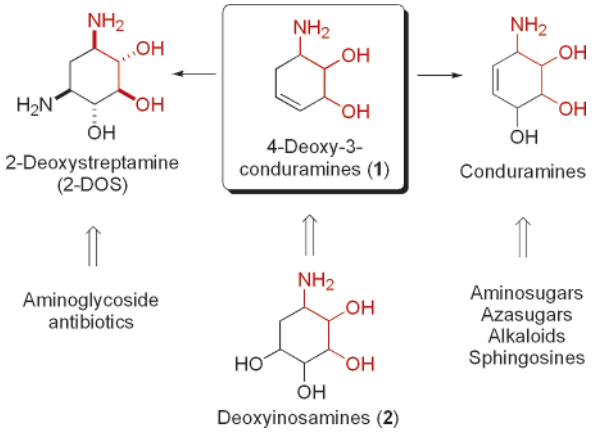
(2) For a recent review about deoxystreptamine, see: Busscher, G. F.; Rutjes, F. P. J. T.; van Delf, F. L. *Chem. Rev.* **2005**, *105*, 775.

(3) (a) Umezawa, W. *Adv. Carbohydr. Chem. Biochem.* **1974**, *30*, 111. (b) Rinehart, K. L.; Stroshane, R. M. *J. Antibiot.* **1976**, *29*, 319. (c) Daniels, P. J. L. *Kirk−Othmer Encycl. Chem. Technol.* **1978**, *2*, 819. (d) Rinehart, K. L.; Suami, T. *Aminocyclitol Antibiotics*; ACS Symposium Series 125; American Chemical Society: Washington, DC, 1980.

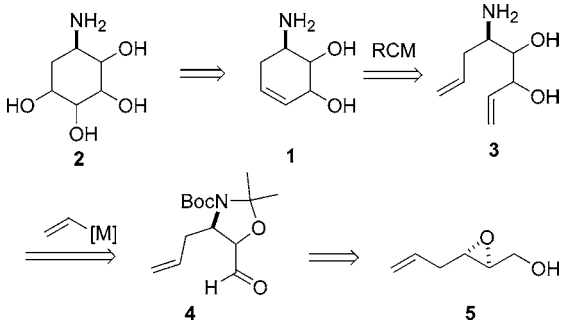
(4) (a) Kakinuma, K.; Ogawa, Y.; Sasaki, T.; Seto, H.; Otake, N. *J. Am. Chem. Soc.* **1981**, *103*, 5614. (b) Kakinuma, K.; Ogawa, Y.; Sasaki, T.; Seto, H.; Otake, N. *J. Antibiot.* **1989**, *42*, 926. (c) Nango, E.; Eguchi, T.; Kakinuma, K. *J. Org. Chem.* **2004**, *69*, 593.

10.1021/ol061022e CCC: $33.50
Published on Web 06/14/2006

Scheme 1. Deoxyconduramines as Key Building Blocks



Scheme 2. Retrosynthetic Analysis of Aminocyclitols **2**



Moreover, these compounds have proven most useful as synthetic precursors of amino- and diaminocyclitols, having been used as intermediates for azasugars, aminosugars, sphingosines, and narcissus alkaloids. Oseltamivir phosphate (Tamiflu), an orally administered drug for the treatment and prevention of influenza infections, is an important example of a clinically useful aminocyclitol.[10] Much effort has been devoted to the development of synthetic routes to these compounds and their derivatives,[9−11] which are normally accessed via functional group manipulation of carbohydrates or other natural products.

Building blocks for carbasugar synthesis can be obtained through manipulation of the double bond of the synthetic 4-deoxy-3-conduramines (**1**). A few strategies have been developed to convert this class of compound or synthetic equivalents into conduramines[11a] and deoxystreptamines.[12] With this in mind, we sought to develop a stereodivergent and practical asymmetric synthesis of 4-deoxy-3-conduramines **1** (Scheme 1). We envisaged that dihydroxylation of deoxyconduramines **1** would be a convenient entry to deoxyinosamines **2**, a new family of aminocyclitols.

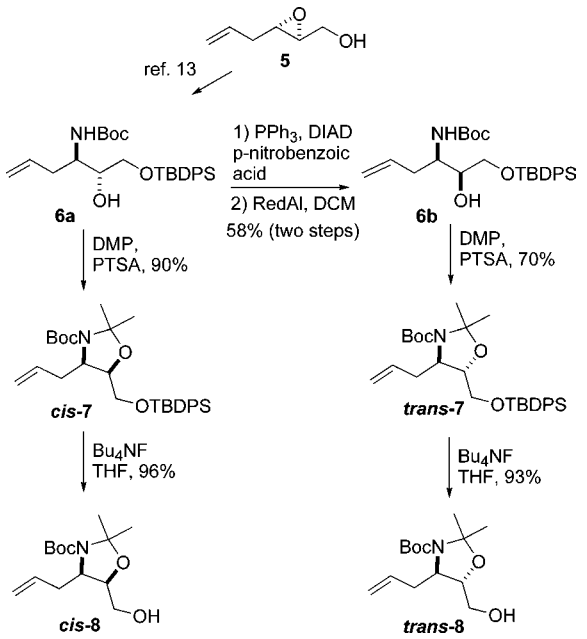
As shown in Scheme 2, in our approach, all of the stereoisomers of deoxyconduramines **1** would be obtained from the ring-closing metathesis (RCM) of dienes **3** which, in turn, would be obtained from the known aldehydes **4** by addition of vinylmetal reagents. Moreover, all of the stereoisomers of aldehyde **4** had already been synthesized in our research group[13] from chiral unsaturated epoxide **5** or its enantiomer.

Our synthesis started from epoxy alcohol **5**, prepared according to a literature procedure[14] in 93% ee by Sharpless epoxidation[15] of 2,5-hexadien-1-ol, which is readily available in multigram quantities from propargyl alcohol and allyl bromide. The product was then subjected to a high-yielding procedure (epoxide ring opening, azide reduction, and protection) developed in our laboratory to yield amino alcohol **6a**[13] with the anti configuration. Protection as the acetal followed by deprotection afforded the cis isomer of alcohol **8** (Scheme 3). Oxidation of the alcohol gave the cis isomer of aldehyde **4**, which could be epimerized[16] in the presence of catalytic base to afford an 84:16 trans/cis mixture of **4**. However, to avoid using a mixture of products in the following steps, the trans isomer of **8** was prepared by a completely stereoselective alternative procedure based on inversion of the secondary alcohol. Compound **6a** was subjected to Mitsunobu conditions[17] (*p*-nitrobenzoic acid and DIAD in toluene, as THF led to lower yields) to give the *p*-nitrobenzoate ester with the syn configuration, which was reduced with RedAl (attempts to use Dibal-H resulted in a decreased yield) to yield **6b**. Alcohol **6b** was then submitted to the same reaction sequence as **6a** to afford the diastereomerically pure trans isomer of **8** (Scheme 3).

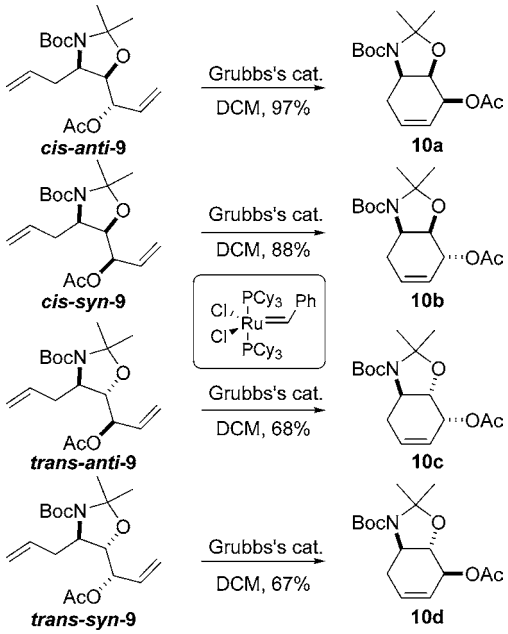
With both isomers of alcohol **8** in hand, we proceeded to study the diastereoselective addition of vinylmetal reagents

(5) Ogawa, S.; Asada, M.; Ooki, Y.; Mori, M.; Itoh, M.; Korenaga, T. *Bioorg. Med. Chem.* **2005**, *13*, 4306.
(6) (a) Horii, S.; Iwasa, T.; Mizuta, E.; Kameda, Y. *J. Antibiot.* **1971**, *24*, 59. (b) Mahmud, T. *Nat. Prod. Rep.* **2003**, *20*, 127.
(7) (a) Horii, S.; Kameda, Y. *J. Chem. Soc., Chem. Commun.* **1972**, 747. (b) Kameda, Y.; Asano, N.; Yoshikawa, M.; Takeuchi, M.; Yamaguchi, T.; Matsui, K.; Horii, S.; Fukase, H. *J. Antibiot.* **1984**, *37*, 1301
(8) (a) Posternack, T. *The Cyclitols;* Holden-Day, Inc.: San Francisco, 1965; pp 211−212. (b) Balci, M.; Sütbeyaz, Y.; Seçen, H. *Tetrahedron* **1990**, *46*, 3715. (c) Lysek, R.; Vogel, P. *Tetrahedron* **2006**, *62*, 1.
(9) Lysek, R.; Schütz, C.; Vogel, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3071.
(10) Harrington, P. J.; Brown, J. D.; Foderaro, T.; Hughes, R. C. *Org. Process Res. Dev.* **2004**, *8*, 86 and references therein.
(11) (a) Toung, R. L.; Liu, Y.; Muchowski, J. M.; Wu, Y. *J. Org. Chem.* **1998**, *63*, 3235 and references therein. (b) McDonough, M. J.; Stick, R. V.; Tilbrook, M. G. *Aust. J. Chem.* **1999**, *52*, 143. (c) Akgün, H.; Hudlicky, T.; *Tetrahedron Lett.* **1999**, *40*, 3081. (d) Spielvogel, D.; Kammerer, J.; Keller, M.; Prinzbach, H. *Tetrahedron Lett.* **2000**, *41*, 7863. (e) Trost, B. M.; Dudash, J.; Hembre, E. J. *Chem.−Eur. J.* **2001**, *7*, 1619. (f) Serrano, P.; Llebaria, A.; Delgado, A. *J. Org. Chem.* **2005**, *70*, 7829.
(12) (a) Tóth, Z. G.; Pelyvás, I. F.; Szegedi, C.; Benke, P.; Magyar, E.; Miklovicz, T.; Batta, G.; Sztaricskai, F. *Carbohydr. Res.* **1997**, *300*, 183. (b) Pelyvás, I. F.; Tóth, Z. G.; Vereb, G.; Balla, A.; Kovacs, E.; Gorzsas, A.; Sztaricskai, F.; Gergely, P. *J. Med. Chem.* **2001**, *44*, 627. (c) Busscher, G. F.; Rutjes, F. P. J. T.; van Delft, F. L. *Tetrahedron Lett.* **2004**, *45*, 3629. (d) Busscher, G. F.; Groothuys, S.; De Gelder, R.; Rutjes, F. P. J. T.; van Delft, F. L. *J. Org. Chem.* **2004**, *69*, 4477. (e) Verhelst, S. H. L.; Wennekes, T.; van der Marel, G. A.; Overkleeft, H. S.; van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron* **2004**, *60*, 2813.
(13) Ginesta, X.; Pastó, M.; Pericàs, M. A.; Riera, A. *Org. Lett.* **2003**, *5*, 3001.
(14) Alcón, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1999**, *10*, 4639.
(15) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(16) Pastó, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1998**, *39*, 1233.
(17) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

Scheme 3. Synthesis of the Cis and Trans Isomers of Oxazolidine Alcohol **8**

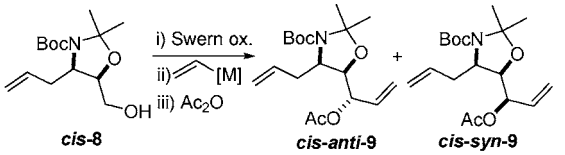


Scheme 4. Syntheses of All Isomers of Deoxyconduramines **10** by RCM of the Corresponding Dienes **9**

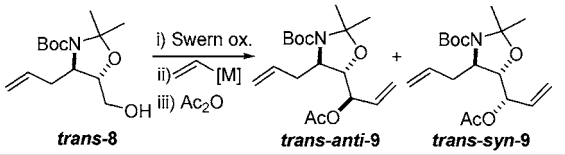


to the corresponding cis and trans aldehydes **4**. The aldehydes were readily obtained via Swern oxidation and subsequently reacted without purification with various vinylmetal reagents. The crude reaction products were acetylated to facilitate workup and chromatography. The most interesting results are shown in Table 1. In close agreement with our previous work,[13] addition of lithium divinylcuprate in diethyl ether afforded the syn diastereomers in good to excellent diastereoselectivity, whereas vinyllithium provided the anti isomer in moderate to good selectivity. As expected, vinylmagnesium bromide reagents afforded a mixture of acetates with poor selectivity. Attempts to use Lewis acids to improve the selectivity resulted in decomposition of the aldehydes. The influence of the stereochemistry at the β-position of the aldehyde is especially noteworthy: if the oxazolidine is cis, a syn addition is favored, whereas the *trans*-oxazolidine increases the proportion of the anti product.[18]

Table 1. Preparation of Dienes **9** from Alcohols **8**



reagent	solvent, temp, time	yield[a]	anti/syn[b]
CH_2=CH-MgBr	THF, -78 → 0 °C, 4.5 h	65%	1 / 2
CH_2=CH -Li	Et_2O, -78 → -40 °C, 2.5 h	66%	**4 / 1**
$(CH_2$=$CH)_2$CuLi	Et_2O, -78 → -33 °C, 2.0 h	55%	**1 / 95**



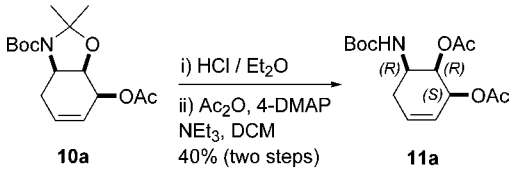
reagent	solvent, temp, time	yield[a]	anti/syn[b]
CH_2=CH MgBr/CuI	Et_2O, -78 → -33 °C, 2.5 h	46%	2 / 1
CH_2=CH-Li	Et_2O, -78 → -25 °C, 2.0 h	31%	**14 / 1**
$(CH_2$=$CH)_2$CuLi	Et_2O, -78 → -40 °C, 2.0 h	41%	**1 / 5**

[a] Overall yield (three steps). [b] Determined by GC.

cis-anti-**9** and *cis-syn*-**9** were easily separated by conventional chromatography; however, the corresponding trans dienes were impossible to separate at this stage. Fortunately, the final aminocyclitol products derived from trans isomers could be easily purified on column. All isomeric dienes **9** were subjected to RCM[19] using the first generation Grubbs catalyst to afford the protected 4-deoxy-3-conduramines **10** in good to excellent yields (Scheme 4).

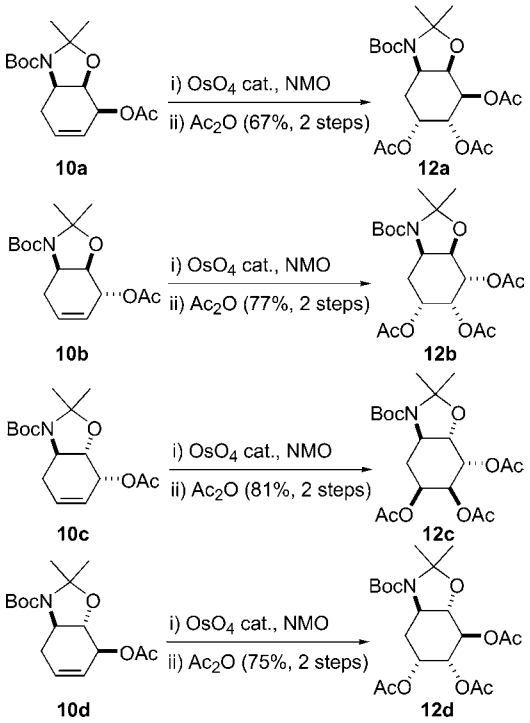
At this point, changing the protecting groups in **10a** allowed us to obtain a crystalline compound **11a** (Scheme 5). Single-crystal X-ray diffraction of this compound confirmed the stereochemistry and facilitated the unambiguous stereochemical assignment of all isomeric dienes **10**.[20]

Scheme 5. Derivatization of Compound **10a**



Finally, deoxyconduramines **10** were subjected to dihydroxylation using catalytic osmium tetraoxide, and the crude

Scheme 6. Syntheses of Aminocyclitols **12**



products were directly protected as acetates yielding the protected aminocyclitols **12** (Scheme 6). In all cases, the diastereoselectivity was very high, yielding a single isomer of **12** in high yields. The stereochemistry of aminocyclitols **12** was established by X-ray analysis of the crystalline product **12d**[20] combined with NOESY spectroscopic experiments. In cis bicyclic acetals **10a** and **10b**, the dihydroxylation takes place anti to the bulky oxazolidine group. Conversely, in trans isomers **10c** and **10d**, dihydroxylation occurs anti to the contiguous acetoxy group. An alternative procedure involved the protecting group cleavage by acidic hydrolysis after the dihydroxylation reaction of **10** to afford aminocyclitols **2**.

(18) For discussions about vinyl addition to the Garner's aldehyde, see: (a) Coleman, R. S.; Carpenter, A. J. *Tetrahedron Lett.* **1992**, *33*, 1697. (b) Williams, L.; Zhang, Z.; Shao, F.; Carroll, P. J.; Joullié, M. *Tetrahedron* **1996**, *52*, 11673.

(19) (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (c) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073.

(20) See Supporting Information for crystallographic data.

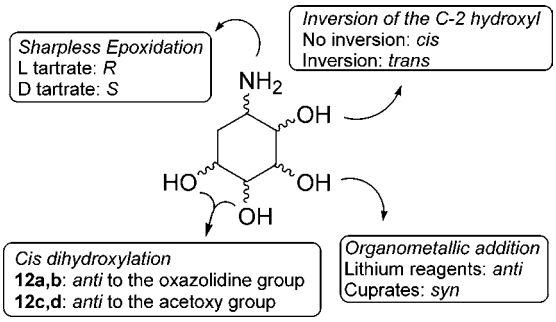


Figure 2. General approach to aminocyclitols **2** featuring full control of the stereogenic centers.

In summary, we have developed a new enantioselective entry to 4-deoxy-3-conduramines **1** with full stereochemical control of the three contiguous stereogenic centers. In addition, the compounds have been derivatized to obtain the new family of aminocyclitols **2** by simple diastereoselective cis dihydroxylation of the double bond (Figure 2).

Acknowledgment. We thank MEC (CTQ2005-00623) for financial support. C.A.M. thanks CIRIT (Generalitat de Catalunya) for a doctoral fellowship. We thank Serveis Científicotècnics (U.B.) for technical support.

Supporting Information Available: Full experimental details and characterization data of all new compounds as well as crystallographic data concerning compounds **11a** and **12d** (CCDC 610276 and 610277). This material is available free of charge via the Internet at http://pubs.acs.org.

OL061022E