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New Stereodivergent Approach to 3-Amino-2,3,6-trideoxysugars. Enantioselective Synthesis of Daunosamine, Ristosamine, Acosamine, and Epi-daunosamine

Xavier Ginesta, Mireia Pastó, Miquel A. Pericàs, and Antoni Riera*

Unitat de Recerca en Síntesi Asimètrica (URSA-PCB), Departament de Química Orgànica/Parc Científic de Barcelona, Universitat de Barcelona, C/Josep Samitier 1-5, 08028 Barcelona, Spain

ariera@pcb.ub.es

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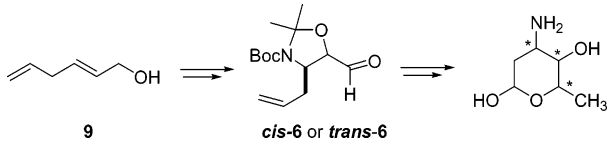
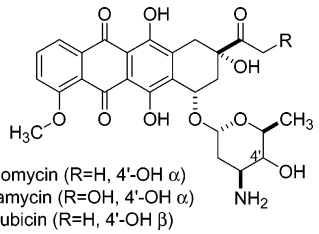
ABSTRACT



9 ***cis*-6** or ***trans*-6**

An enantioselective preparation of the four diastereomeric 3-amino-2,3,6-trideoxy-hexoses, key components of anthracycline antibiotics, has been developed. Sharpless catalytic asymmetric epoxidation of the (2*E*)-2,5-hexadien-1-ol, regioselective ring opening with azide, followed by convenient functional group transformations, afforded the key aldehydes *cis*- or *trans*-6 in any configuration. The diastereoselective addition of methylmetal reagents to these aldehydes followed by ozonolysis gives access in a completely stereocontrolled manner to the four isomeric trideoxyaminosugars.

Anthracycline antibiotics have received much attention because of their bioactivity against a wide range of human tumors.[1] A large number of these clinically important antibiotics, for example, daunomycin (**I**), adriamycin (**II**), or epirubicin (**III**), consist of a tetracyclic chromophore and one amino sugar residue (Figure 1). Clinical studies revealed that the relative stereochemistry of the functional groups in the glycosidic component strongly influences the bioactivity of the drug. It has been reported that changing L-daunosamine (**1**) to the 4-epimer, L-acosamine (**4**), as in adriamycin, nearly suppresses the undesired toxic side effects while maintaining similar antitumor activity.[2] Therefore, the synthetic community has dedicated numerous efforts toward efficient, stereoselective, and stereocontrolled syntheses of the not readily available four diastereomeric 3-amino-2,3,6-trideoxy-L-hexoses (**1**−**4**) (Figure 2). A wide variety of approaches that range from classical sugar chemistry,[3] synthesis from other chiral pool molecules,[4] catalytic asymmetric synthesis,[5] use of chiral auxiliaries,[6] and enzymatic methods[7] have been reported.



I, Daunomycin (R=H, 4'-OH α)
II, Adriamycin (R=OH, 4'-OH α)
III, Epirubicin (R=H, 4'-OH β)

Figure 1. Anthracycline antibiotics with antitumoral activity.

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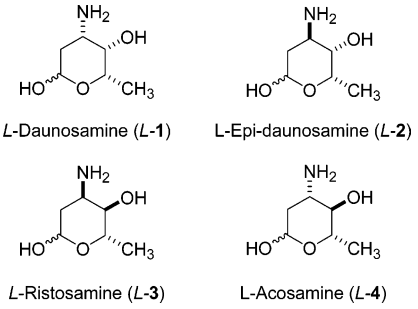


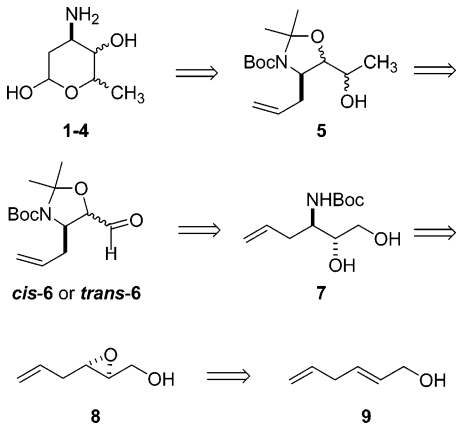
Figure 2. Structures of some natural 3-amino-2,3,6-trideoxysugars.

In a project devoted to the synthesis of different structural types of amino acids and dipeptide isosteres,[8] we have explored the diastereoselective addition of methylmetal reagents to *N*-Boc-2,2,4-trimethyloxazolidine-5-formaldehydes and we have succeeded in generating either the *syn*- or the *anti*-3-amino-1,2-diols products in highly diastereoselective way by simple modification of the organometallic reagent.[9] As an application of this general methodology for the aminodiol fragment, we envisaged the preparation of the four stereoisomeric 3-amino-2,3,6-trideoxyhexoses **1**−**4**.

Our retrosynthetic analysis involves ozonolysis of oxazolidine alcohols **5**, stereoselectively prepared by addition of a methylmetal reagent to oxazolidine aldehydes *cis*-**6** or *trans*-**6** (Scheme 1). These oxazolidine aldehydes would be in turn obtained from the common intermediate *N*-Boc-aminodiol **7** prepared by regioselective ring opening of the enantiomerically enriched epoxy alcohol **8** with an ammonia equivalent.

The synthesis started with the preparation of the known allyl alcohol **9** from propargyl alcohol.[10] The catalytic

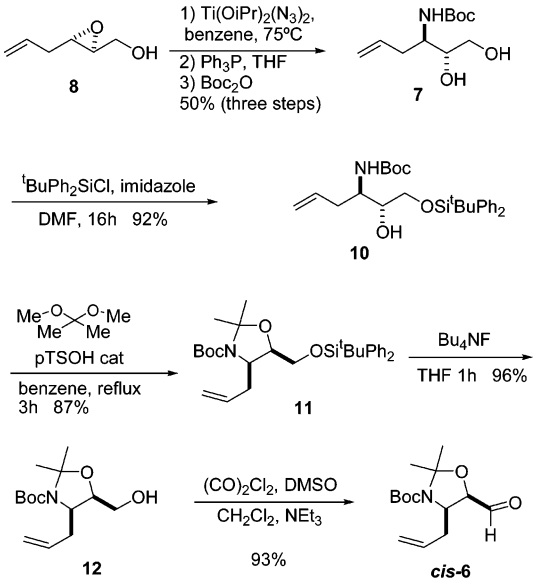
Scheme 1. Retrosynthetic Analysis of 3-Amino-2,3,6-trideoxyhexoses **1**−**4**



Sharpless epoxidation was performed as described[11] using L-(+)-DET to afford epoxy alcohol **8** in 84% yield and 93% ee.[12]

Enantiomerically enriched **8** was subjected to nucleophilic epoxide ring-opening by azide. Using trimethylsilyl azide under Sharpless conditions[13] produced a completely regioselective reaction, although the ring-opening could be performed somewhat more conveniently using titanium diazidodiisopropoxide.[14] The corresponding azido alcohol was then treated with a variety of reducing agents such as $SnCl_2$, Lindlar catalyst, or $LiAlH_4$, but after protection with Boc_2O, very low yields of *N*-Boc-3-amino-5-hexen-1,2-diol (**7**) were obtained. Gratifyingly, conversion of the azide into the *N*-Boc-amine[15] could be performed efficiently by treatment with PPh_3 or PBu_3 and reaction of the iminophosphorane with Boc_2O, affording the protected aminodiol **7** in 50% overall yield (three steps) (Sheme 2).

Scheme 2



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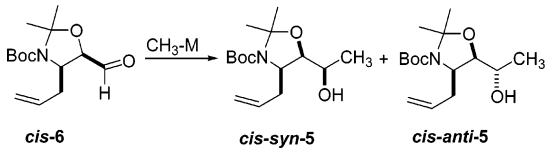
(9) While it was found that lithium dimethyl cuprate in ether solution adds into these aldehydes with high syn diastereoselectivity, an excellent diastereomeric ratio in favor of the anti isomer was obtained with MeLi or MeMgBr in the presence of $TiCl_4$. Pastó, M.; Ginesta, X.; Pericàs, M. A.; Riera, A. Unpublished results.

Aldehyde *cis*-**6** was prepared from *N*-Boc-3-amino-5-hexen-1,2-diol **7** through the following sequence: protection of the primary hydroxyl group, formation of the oxazolidine ring, deprotection, and oxidation. Thus, treatment of **7** with *tert*-butyldiphenylsilyl chloride/imidazole in DMF afforded chemoselectively the *tert*-butyldiphenylsilyl ether **10** in excellent yield. Subsequent treatment with excess 2,2-dimethoxypropane (DMP) in the presence of a catalytic amount of *p*-toluenesulfonic acid[16] in benzene at reflux provided the silyloxymethyloxazolidine **11** also in high yield. The primary hydroxyl group was then selectively deprotected by treatment with tetrabutylammonium fluoride in THF and oxidized under Swern conditions[17] to afford the target aldehyde *cis*-**6** almost quantitatively (Scheme 2).

The results of the diastereoselective addition of methylmetal reagents to aldehyde *cis*-**6** are shown in Table 1. As

Table 1. Methyl Addition to Aldehyde *cis*-**6**



cis-**6** *cis-syn*-**5** *cis-anti*-**5**

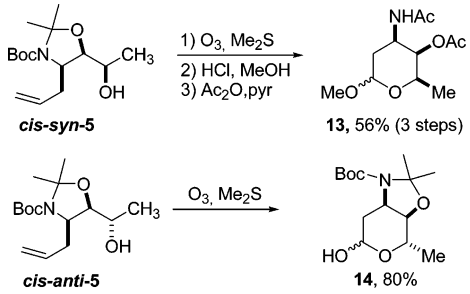
reagent	solvent, *T*, time	yield	syn/anti[a]
Me_2CuLi	Et_2O, −20°C, 5 h	81%	93/7
$MeLi/TiCl_4$	Et_2O, −30°C, 3 h	73%	4/96

[a] Determined by GC.

expected from our previous work,[9] addition of lithium dimethylcuprate in diethyl ether afforded the syn diastereomer in excellent diastereoselectivity, whereas MeLi in the presence of $TiCl_4$ provided almost exclusively the anti isomer.

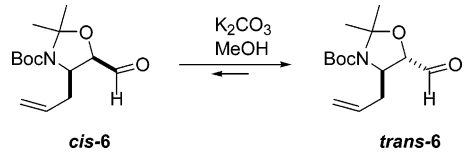
Reductive ozonolysis[18] of *cis-syn*-**5** afforded a mixture of hemiacetals corresponding to a protected form of D-Daunosamine. To facilitate the characterization of the product, it was deprotected with HCl/MeOH and treated with Ac_2O to afford the known derivative **13**[19] as an (8:2) acetalic mixture. Obviously, the corresponding enantiomer with L-configuration would be obtained with the same sequence but performing the Sharpless epoxidation with D-(−)-DET. Ozonolysis of *cis-anti*-**5** afforded the protected L-Ristosamine derivative **14** as a 9:1 epimeric mixture that could be fully characterized (Scheme 3).

Scheme 3



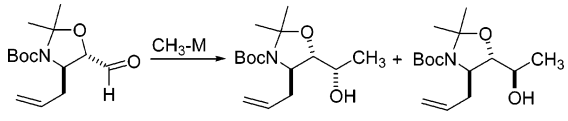
Aminosugars with a trans configuration between the 3-amino and the 4-hydroxyl would be available starting from aldehyde *trans*-**6**. The simplest solution involves a base-catalyzed epimerization of the corresponding cis isomer[8c,20] (Scheme 4).

Scheme 4



Treatment of *cis*-**6** with potassium carbonate in methanol overnight afforded a 5/1 mixture of *trans*-/*cis*-**6** that was submitted to the addition of methylmetal reagents (Table 2).

Table 2. Methyl Addition to Aldehyde *trans*-**6**



trans-**6** *trans-syn*-**5** *trans-anti*-**5**

reagent	solvent, *T*, time	yield	syn/anti
Me_2CuLi	Et_2O, −20°C, 5 h	72%	89/11
$MeLi/TiCl_4$	Et_2O, −30°C, 3 h	81%	6/94

As expected according to our previous study,[9] the reaction with lithium dimethyl cuprate afforded the *trans-syn*-**5** in good yield and selectivity. On the other hand, the reaction with $MeLi/TiCl_4$ afforded *trans-anti*-**5** as the major compound. In both cases, the major isomer was purified by

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(12) Determined by ^1H NMR of the corresponding Mosher ester.
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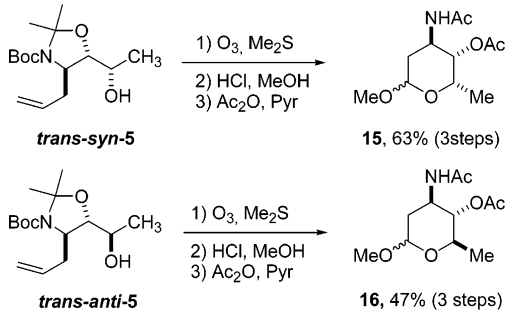
chromatography and submitted to reductive ozonolysis. The trans stereochemistry of the oxazolidine prevented the cyclization of the hydroxy aldehydes, which were consequently submitted to acid hydrolysis in methanol, leading to the corresponding aminosugars. To facilitate characterization, the crude products were acylated with acetic anhydride. Thus, the sequence of ozonolysis, hydrolysis, and acylation of *trans-syn*-**5** afforded, in good overall yield, **15**, a known[21] derivative of L-Epi-daunosamine **2**. Likewise, the same sequence starting with *trans-anti*-**5** led to diacetyl derivative of D-Acosamine **16**[22] (Scheme 5).

Scheme 5



In summary, we have developed a new enantioselective entry to 3-amino-2,3,6-trideoxysugars with complete control of the stereochemistry of the three contiguous stereogenic centers. The configuration at C-3 is controlled by the tartrate used in the Sharpless epoxidation, the configuration at C-4 by the epimerization (or not) of the oxazolidinecarbaldehyde intermediate, and the configuration at C-5 by the organometallic reagent used in the methyl addition (Figure 3).

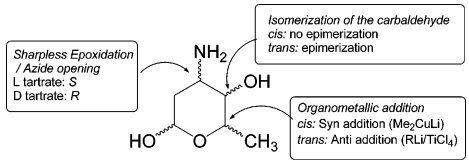


Figure 3. General approach to aminosugars with control of the configuration of the stereogenic centers.

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Supporting Information Available: Experimental details for the synthesis of **13**−**16** and full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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