A stereodivergent access to naturally occurring aminocarbasugars from (Phenylsulfonyl)-7-oxa-bicyclo[2.2.1]heptane derivatives. Total synthesis of (±)-Validamine and its C_1 and C_2 stereoisomers

Un ruta de acceso estereodivergente a carbaazúcares naturales a partir de derivados (Fenilsulfonil)-7-oxabiciclo[2.2.1]heptane. Sintesis total de (±)-Validamina y de sus C_1 y C_2 estereoisómeros

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ABSTRACT

The total syntheses of the antibiotic validamine an its three diastereomers have been acomplished and their racemic penta-N-O-acetates via stereocontrolled nucleophilic epoxidation of polihydroxylated cyclohexenyl sulfones, obtained from (phenylsulphonyl)-7-oxabicyclo[2,2,1]heptanes. The diastereoselectivity of the epoxidation can be readily controlled by careful choice of the hydroxyl protecting group. Ring opening of the resulting epoxisulfones followed by stereocontrolled introduction of an amine precursor led to the four C-1 and C-2 diastereomers of the 1-aminocarbasugars.
Key words: carbasugars, stereocontrolled epoxidation, validamine.

RESUMEN

La epoxidación nucleofílica estereocontrolada de ciclohexenil sulfonas polidroxiladas, obtenidas a partir de (fenilsulfonil)-7-oxabiciclo[2,2,1]heptanos conduce a la síntesis total del antibiótico validamina y sus tres diastereoisómeros. La diastereoselectividad de la epoxidación puede controlarse facilmente mediante la elección del grupo protector del hidroxilo. La apertura del anillo de las epoxisulfonas resultantes, seguida de la introducción estereocontrolada de un precursor del grupo amino, conduce a los cuatro diastereosiómeros en C-1 y C-2 de 1-aminocarbaazúcares.
Palabras clave: Carbaazúcares, pseudoazúcares, epoxidación estéreocontrolada, validamina.

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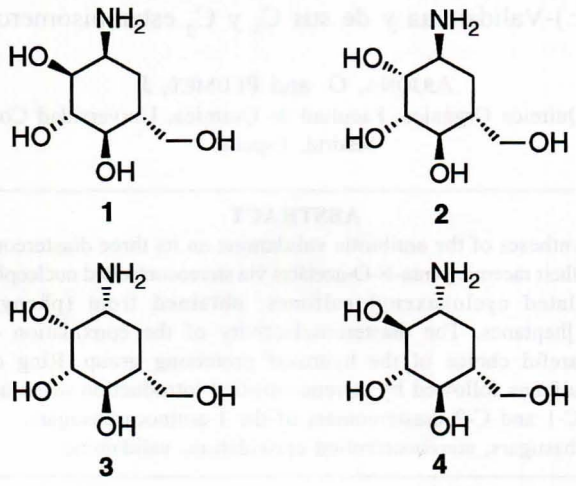
INTRODUCTION

Carbasugars (often called pseudosugars) and related compounds are products of biological relevance because they may act as enzyme inhibitors, sweeteners, antibiotics, etc. (1). Considerable efforts directed towards the development of syntheses of these compounds have been made (1, 2). 1-Aminocarbasugars like validamine **1**[3] (Figure 1) are some of the most important and attractive members of the carbasugars family due to its enzymatic inhibitory activity against various glucose hydrolases (4). 1-Aminocarbasugars are also constituents of the antibiotic validamycin complex (5), isolated from the fermentation broth of *streptomyces hygroscopicus* subsp. *limonenus,* which shows growth inhibition activity against bacterial diseases of rice plants (6).

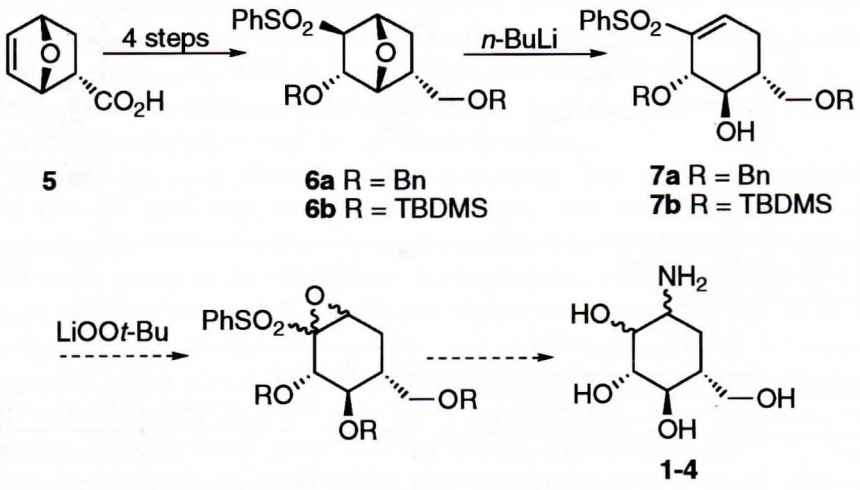
Figure 1



Although there are several syntheses of 1-aminocarbasugars (7), in many cases these methods suffer from a lack of versatility in terms of both regio- and stereocontrol. One of the most widely used intermediates in the syntheses of carbasugars are 7-oxanorbornenic systems (1, 8, 9), which are readily available even enantiomerically pure (10). A crucial transformation in these synthetic sequences employing oxabicyclic intermediates is the cleavage of the oxygen bridge to produce highly functionalized cyclohexenols derivatives (11). In this paper, we describe a short and stereodivergent route of validamine **1** and its C_1 and C_2 stereoisomers **2-4** from the cyclohexenyl sulfones **7** (Scheme 1). These compounds are available by our previously described methodology based on the strain-directed bridge cleavage of 7-oxanorbornanic sulfones **6** with *n*-BuLi and

they have been employed in the total synthesis of carba-α-DL-glucopyranose (8). Sulfones **6** are readily available in four steps from acid **5**[12].

Scheme 1



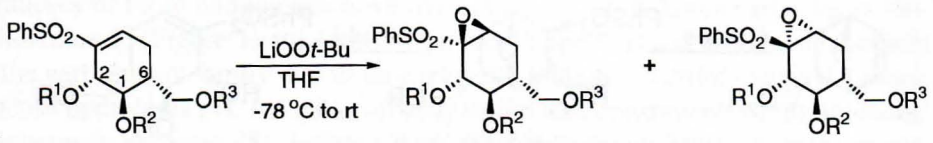
The key step of our synthetic plan involves the diastereoselective nucleophilic epoxidation of sulfones **7.** This kind of epoxidation is a well-known process (13). The reaction has been studied in terms of diastereoselectivity on acyclic (14) and cyclic (15) oxygenated vinyl sulfones. Coordination and/or conformational effects have been invoked in order to explain the diastereoselectivity of the process. With the appropiate α,β-epoxysulfone in our hands, the stereoselective introduction of an amine group precursor by epoxide cleavage would produce the 1-aminocarbasugars **1-4.**

RESULTS AND DISCUSSION

We first examined methylene acetal **7c,** obtained by reaction of sulfone **7a** with $(MeO)_2CH_2$[8] (Scheme 2). This compound, which presents a fixed conformation, by treatment with LiOO*t*-Bu[13b] afforded a 60:40 mixture of epoxides **8c** and **9c** (Table 1, entry 3). In contrast with this disappointing result, dibenzyl ether **7a,** under identical reaction conditions, gave a single α,β-epoxysulfone **8a** (entry 1). In the case of disilyl sulfone **7b,** a high diastereoselectivity (95:5) in the same sense was observed (entry 2) (16). In contrast, sulfones **7d** and **7e,** obtained by silylation (TBDMSOTf, Et_3N, THF, –78 °C) of **7a** and **7b** respectively, displayed high or total diastereoselectivity, but in the opposite direction (entries 4 and 5).

Thus, the diastereoselectivity of the nucleophilic epoxidation of our polyhydroxycyclohexenyl sulfones can be controlled by the choice of the protecting groups.

Scheme 2



7a $R^1 = R^3 = Bn$, $R^2 = H$
7b $R^1 = R^3 = TBDMS$, $R^2 = H$
7c $R^1 = Bn$, $R^2 = R^3 = -CH_2-$
7d $R^1 = R^3 = Bn$, $R^2 = TBDMS$
7e $R^1 = R^2 = R^3 = TBDMS$

8a-d **9b-e**

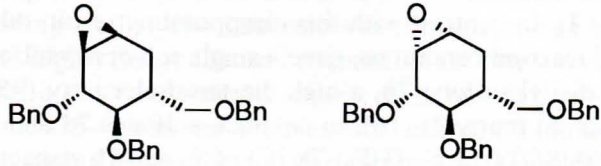
Table 1.—Nucleophilic epoxidation of vinyl sulfones **7a-e.**

entry	*substrate*	$J_{1,2}{}^a J_{1,6}{}^a$	*8*	*9*	*8:9 ratio*[b]	*yield*[c]
1 **7a**	6.8	9.8	**8a**		100:0	92%
2 **7b**	4.9	7.4	**8b**	**9b**	95:5	85%
3 **7c**	7.6	11.0	**8c**	**9c**	60:40	82%
4 **7d**	2.9	2.9	**8d**	**9d**	10:90	88%
5 **7e**	2.7	2.7		**9e**	0:100	80%

[a]In Hz. [b]Measured by integration of the ^1H NMR spectra of the crude reaction mixtures. [c]Overall yield of pure products.

The stereochemistry of the resulting epoxides was tentatively established from their ^1H NMR spectra. The crucial data was the chemical shift of the proton linked at the β-alkoxy substituent to the phenylsulfonyl group, which is more deshielded for compounds **9b-d** due to the *syn* effect of the sulfone. Anyway, to further prove our assignment, we carried out chemical correlations of our sulfonyl oxiranes with the known tribenzyl epoxides **10** and **11**[17] (Figure 2), and thus, the previously proposed stereochemistry was confirmed.

Figure 2



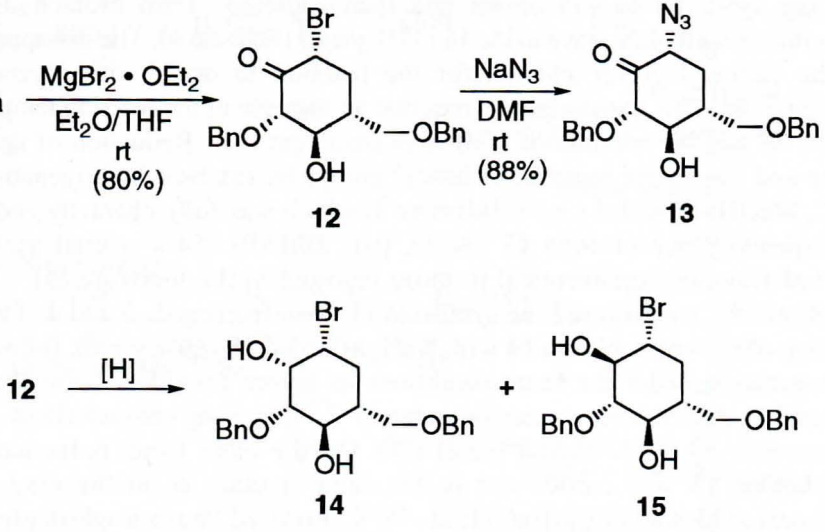
10 **11**

The stereochemical outcome of the nucleophilic epoxidation of our substrates can be rationalized on the basis of the conformational behaviour of the starting polyoxygenated cyclohexenyl sulfones along with coordinative effects of the remote hydroxyl group. Inspection on the $J_{1,2}$ and $J_{1,6}$ coupling constant data (Table 1) shows that **7a-c** present similar ground state conformational equilibria; however, the selectivity of the process is clearly controlled by the free homoallylic hydroxyl group. Finally, the striking reversal of diastereoselectivity found for **7d** and **7e** presumably reflects the intrinsic steric bias of the molecule (15) as a result of its very different conformation (see $J_{1,2}$ and $J_{1,6}$ in Table 1) probably due to the dissappearance of an hydrogen bonding.

The epoxide ring opening with concomitant loss of the phenylsulfonyl group was the next step of our synthetic plan. The introduction of an azide group in the epoxide **9e** would produce an α-azidoketone with the same configuration on the azide group as in validamine. Unfortunately, when **9e** was treated with NaN_3 in DMF at reflux (18), we did not obtain the desired α-azidoketone (19). Therefore, the approach to this product was performed indirectly by means of the reaction of **8a** with $MgBr_2$-OEt_2[20] (Scheme 3) affording α-bromoketone **12** along with its epimer in 89:11 ratio (90% overall yield). After chromatographic separation, **12** was transformed into the related α-azidoketone **13**[21] by halogen displacement with NaN_3 (88% yield). This reaction occured at room temperature and with retention of configuration (22).

Compound **13** could be the intermediate precursor of compounds **3** and **4,** by reduction of the carbonyl group followed by azide hydrogenation. At this

Scheme 3



point, we reasoned that stereocontrolled reduction of the carbonyl group in **12** would produce both diols **14** and **15.** Azide displacement in each case with inversion of configuration and subsequent reduction of the azide to amine would afford validamine **1** and its epimer **2.** Thus, the stereochemistry of the reduction of carbonyl group of **12** was considered.

A wide range of reagents and temperatures were tested for the reduction of ketone **12** (Table 2). Treatment of **12** with $LiAl(t\text{-}BuO)_3H$ at –78 °C gave axial alcohol **14** as single diastereomer (85% yield). Other reducing agents ($NaBH_4$, $LiAlH_4$, DIBAL-H, $NaBH_4/CeCl_3$) afforded mixtures of both diastereomers, but **14** was always the major product due to preferential equatorial attack. Finally, reduction with BH_3-SMe_2 at room temperature yielded the desired equatorial alcohol **15** as the major diastereomer in a 82:18 ratio (94% overall yield). These diols were easily separated by column chromatography.

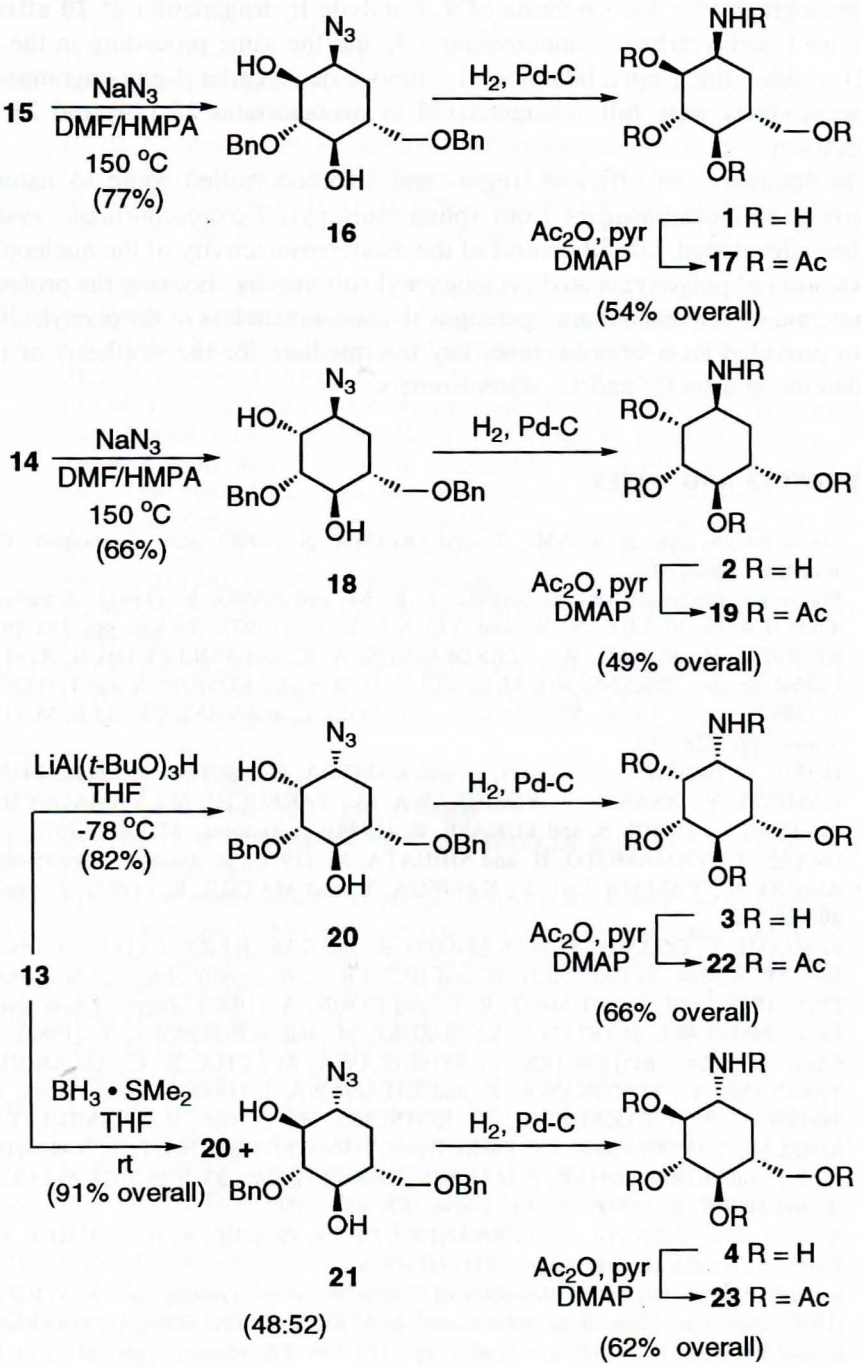
Table 2.—Stereochemistry of the reduction of ketone **12.**

reagent	*temperature*	***14:15** ratio*
$LiAl(t\text{-}BuO)_3H$	–78 °C	100:0
$NaBH_4$	0 °C	91:9
$LiAlH_4$	0 °C	91:9
DIBAL-H	0 °C	91:9
$NaBH_4/CeCl_3$	–78 °C	71:29
$NaBH_4/CeCl_3$	rt	50:50
$BH_3 \cdot SMe_2$	–78 °C	40:60
$BH_3 \cdot SMe_2$	rt	18:82

The synthesis of validamine was then addressed from bromohydrin **15.** Substitution with NaN_3 gave azide **16** (77% yield) (Scheme 4). The dissappearance of the carbonyl group allowed for the reaction to occur with inversion of configuration. This transformation required an increase of the reaction temperature to 150 °C and the addition of HMPA as cosolvent (23). Reduction of the azido group and concurrent removal of benzyl groups by catalytic hydrogenation (H_2, Pd-C, MeOH) provided (±)-validamine **1,** which was fully characterized as the corresponding pentaacetate **17** (Ac_2O, pyr, DMAP) (54% overall yield). Its spectral features were identical to those reported in the literature (3).

Similarly, we achieved the syntheses of diastereomers **2, 3** and **4.** Thus, the reaction of *cis*-bromohydrin **14** with NaN_3 afforded **18** (66% yield), followed by hydrogenation under the same conditions as before provided 2-epivalidamine (1-amino-1-deoxycarba-α-mannopyranose) **2,** that was characterized as the pentaacetate **19** (49% overall yield) (7f). On the other hand, reduction of α-azidoketone **13** was carried out in the same manner as in the case of **12.** Treatment of **13** with $LiAl(t\text{-}BuO)_3H$ at –78 °C produced **20** as a single diastereomer

Scheme 4


15
NaN3
DMF/HMPA
150 °C
(77%)
16
H2, Pd-C
Ac2O, pyr
DMAP
1 R = H
17 R = Ac
(54% overall)
14
NaN3
DMF/HMPA
150 °C
(66%)
18
2 R = H
19 R = Ac
(49% overall)
LiAl(t-BuO)3H
THF
-78 °C
(82%)
20
3 R = H
22 R = Ac
(66% overall)
13
BH3 • SMe2
THF
rt
(91% overall)
20 +
21
(48:52)
4 R = H
23 R = Ac
(62% overall)

(82% yield), whereas in the presence of BH_3-SMe_2, a 48:52 mixture of **20** and **21** was obtained (91% overall yield). Compound **21** was easily separated by chromatography for the synthesis of **4.** Catalytic hydrogenation of **20** afforded 1-amino-1-deoxycarba-β-mannopyranose **3,** and the same procedure in the case of **21** yielded the 1-epivalidamine (1-amino-1-deoxycarba-β-glucopyranose) **4.** These products were fully characterized as pentaacetates **22** (24) and **23** (25) respectively.

In summary, an efficient, regio- and stereocontrolled route to naturally occurring aminocarbasugars from (phenylsulfonyl)-7-oxanorbornanic systems has been developed. Useful control of the diastereoselectivity of the nucleophilic epoxidation of polyoxygenated cyclohexenyl sulfones by choosing the protecting groups, and subsequent oxirane opening with concomitant loss of the phenylsulfonyl group provided an α-bromoketone, key intermediate for the synthesis of (±)-validamine and its C_1 and C_2 stereoisomers.

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