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Hemisynthesis of bistramide D by stereoselective reduction of bistramide A. Partial determination of relative and absolute configurations

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Abstract

The hemisynthesis of bistramide D by stereoselective reduction of bistramide A is reported. The absolute configuration of C4 in bistramide D was also determined and the relative configurations of C6, C9 and C11 in the pyran part, as well as those of C22, C23, C27 and C31 in the spiro moiety of bistramides A and D were also determined by NMR. © 2000 Published by Elsevier Science Ltd.

Bistramides, a family of bioactive macrolides, were isolated from *Lissoclinum bistratum* Sluiter, an ascidian from New Caledonia. Five members (A, B, C, D and K) were identified.[1a,b] Bistramide A was also isolated from the same ascidian collected in Australia and described as bistratene A.[1c] This product has antiparasitic[2] and immunomodulatory[3] properties; it induces atypical differentiation in HL-60[4] and in NSCLC-N6[5] cell lines. However, it is too toxic in vivo for therapeutic purposes. Bistramides D and K, which are far less abundant, have the same activity in the NSCLC-N6 cell line but are less toxic and were evaluated for their in vivo antitumoral activity.[6] We therefore intended to produce large amounts of bistramide D by reduction of bistramide A. The first task was to determine the configurations of the chiral centres. Faced with the noncrystallinity of such compounds, we assigned their absolute and relative configurations by combining NMR spectroscopy and a synthetic correlation of natural bistramide A with bistramide D (bst D).

To transform naturally available bistramide A (**1**) into bistramide D, we investigated the reduction of the C4 carbonyl (Scheme 1) with different reducing agents, as shown in Table 1. The first experiment with L-selectride (entry 1) gave a mixture of diastereomers D_1 and D_2.

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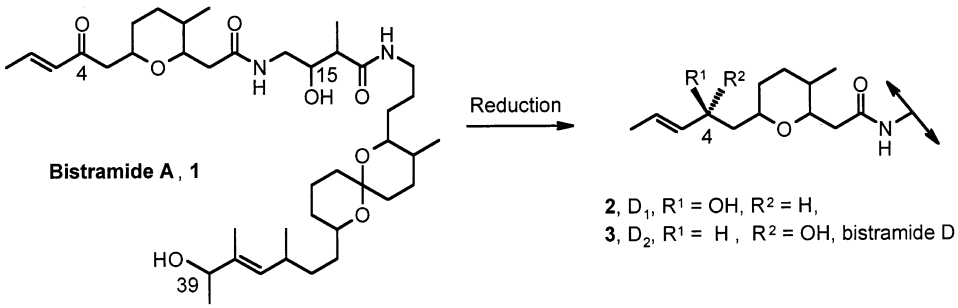


Scheme 1.

Table 1
Reduction conditions of bistramide A to natural bistramide D

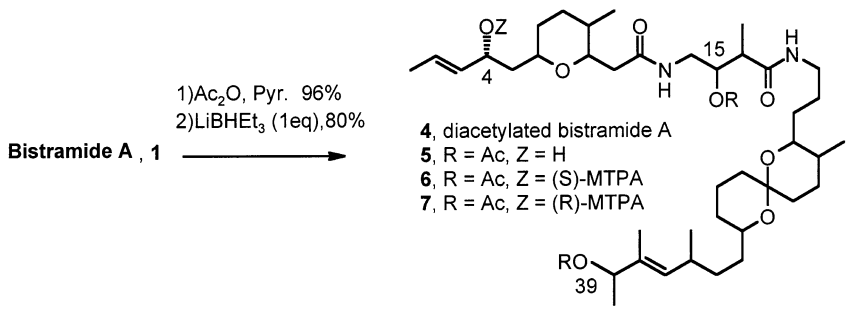
Entry	Reducing agent (equiv.)	Solvent/time (h)	T (°C)	D_1 (%)[a]	D_2 (%)[b]	D_3	Yield[c]
1	L-Selectride (5.3)	THF/0.5	−78	24	76	Yes	Quant.
2	$LiAlH_4$ (6.5)	THF/16	−78	23	77	Yes	93
3	$Zn(BH_4)_2$ (4.6)	Ether/11	−78	22	78	Yes	99
4	**$NaBH_4$ (5.9)**	**THF/4**	**−75**	**73**	**27**	**Yes**	**95**
5	$LiBH_4$ (5.5)	THF/4	−75	65	35	Yes	98
6	**$LiBH(Et)_3$ (3)**	**THF/0.3**	**−75**	**>5**	**95**	**No**	**80[d]**

[a] Diastereomers % determined by ^1H NMR of the crude product; TLC R_f values (acetone/CH_2Cl_2 6:4): D_1 0.7, D_2 0.6.
[b] D_2 corresponds to the natural bst D.
[c] Yield given for the crude product ($D_1+D_2+D_3$).
[d] The isolated yield of a mixture of D_1 and D_2, no side product D_3 detected by NMR.

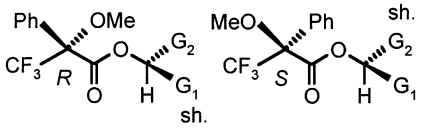
These two epimers were separated and characterized by NMR. We have shown by TLC comparison with natural bistramide D, by ^1H and ^{13}C NMR, as well as by HPLC, that the D_2 isomer was identical to natural bistramide D.

We observed that by changing the reducing agents and the experimental conditions, the diastereoselectivity could be drastically changed. $LiAlH_4$ afforded a similar diastereoselectivity (50%, entry 2), the D_2 isomer being the main product. Zinc borohydride gave a similar result (entry 3), while sodium and lithium borohydride led to the opposite stereoselectivity, D_1 being the main product (entries 4 and 5). In all these cases we observed the formation of an impurity, D_3, which was not identified. We could, however, avoid the formation of the impurity D_3 by using 3 equivalents of superhydride so obtaining D_2 in more than 90% de (entry 6). Alkoxyaluminium hydrides afforded only degradation products and no reduction was observed with DIBAL-H.

In order to assign the absolute configuration of C4 in D_2, we used Mosher's method:[7] esterification of the C4 hydroxyl group with the two enantiomers of 2-methoxy-2-phenyl-2-trifluoromethyl acetyl chloride (MPTA-Cl), followed by an NMR study of the two resulting diastereomers. It was first necessary to protect the two hydroxyl groups on C39 and C15 in bst A (**1**) (Scheme 2) by acetylation (Ac_2O, pyridine, 96% yield) and then to reduce **4** with superhydride to obtain **5** (80% yield). The configuration of the C4 hydroxyl in **5** was shown to be the same as in bistramide D by reduction of the two acetoxy groups with $LiAlH_4$ at low temperature (80% yield), giving a sample identical to the natural product.



Scheme 2.



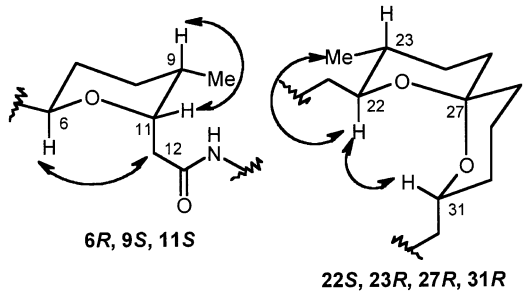
Scheme 3. Mosher's model

Mosher proposed the preferred conformation for MTPA esters in solution shown in Scheme 3.

In the proton NMR, according to this conformation, the aromatic ring would be expected to shield the protons of the G_1 group in one diastereomer and the protons of the G_2 group in the other. By comparing the chemical shift displacements of the hydrogens close to the carbinol in the two diastereomers, it is possible to assign the absolute configuration of the asymmetric center. Many applications of this method have been reported in the literature to assign the absolute configurations of carbinols.[7]

From this model and from the data in Table 2, we can assign the *R* absolute configuration to the carbon C4 of diacetylated bst D **5** and therefore to C4 of bst D **3**.

Furthermore, the relative configurations of several chiral centers were assigned by a 2D 500 MHz ^{1}H NMR analysis of diacetylated bst A **4**. The NOESY spectrum showed, for the cyclic pyran part, a strong long-range correlation between protons H6 and H12, indicating that the H6 proton, as well as the 12-CH_2 methine were both axially oriented (Scheme 4).



Scheme 4.

In addition, a *cis* relationship between H9 and H11 was suggested on the basis of a clear ^{1}H–^{1}H NOESY correlation between these two nuclei. Thus the relative structure of the pyran moiety was established as either (6*R*,9*S*,11*S*) or (6*S*,9*R*,11*R*).

Table 2
^{1}H NMR (500 MHz) chemical shift differences ($\Delta\delta$) for MTPA derivatives **6** and **7**

Protons	(*S*)-MTPA ester **6**	(*R*)-MTPA ester **7**	$\Delta\delta$
Me1	1.59	1.58	+0.01[a]
H2	5.96	5.95	+0.01[a]
H3	**5.41**	**5.53**	**−0.12**
H5	**2.16**	**2.11**	**+0.05**
H5b	1.56	1.57	−0.01[a]
H6	**3.60**	**3.39**	**+0.21**

[a] No significant change.

Further NOESY analysis showed a very clear ^{1}H–^{1}H correlation between H22 and H31 showing the axial orientation of these two protons in the spiran part of the molecule. Moreover, H22 exhibited a long-range ^{1}H–^{1}H correlation with the adjacent methyl group on carbon C23, which must be equatorial. The lack of any NOESY correlation between H22 and H23 indicated that they have the *trans* configuration (Scheme 4). Therefore the two possible relative configurations of the spiran part must be (22*S*,23*R*,27*R*,31*R*) or (22*R*,23*S*,27*S*,31*S*).

In conclusion we have reported a stereoselective transformation of bst A into bst D and determined the absolute configuration of C4. We have also assigned by 2D NMR, the relative configuration of three chiral centers in the pyran part and four in the spiro moiety of bst **4**.

Acknowledgements

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