Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1543–1545

TETRAHEDRON: *ASYMMETRY*

Studies towards the synthesis of superstolide A. Synthesis and stereochemical assignment of the C(21)–C(26) fragment of superstolide A

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Received 25 May 2001; accepted 19 June 2001

Abstract—An asymmetric synthesis of the C(21)–C(26) fragment of superstolide A is described. A fragment, corresponding to a reductive ozonolysis product of superstolide, was also prepared. Comparison of spectroscopic and optical properties of the corresponding fragment obtained by degradation of natural superstolide A allowed the confirmation of the stereochemistry of the natural product.

Superstolides are two novel 16-membered macrolides isolated in our laboratories from the deep water marine sponge *Neosiphonia superstes*.[1,2] These compounds showed marked activity (in the 0.003–0.04 μg/mL range) in cytotoxic assays against various human and murine cancer cell lines.

The gross structure of the major superstolide A **1** was determined by extensive 2D NMR experiments and chemical degradation. The stereostructure of this complex macrolide was deduced by a combination of NMR data and acetonide analysis on an opened derivative.[1] However, the application of the modified Mosher's method on the secondary hydroxyl groups at C(23) and C(25) in the polypropionate-derived side chain left some uncertainty in the assignment of the absolute stereochemical relationship associated with this part of the molecule.

So far no total synthesis of **1** has been reported, although two fragments have been prepared by the groups of Roush[3] and Jin.[4]

En route to a total synthesis of superstolide A, herein we describe an alternative, practical asymmetric synthesis of the C(21)–C(28) fragment **2** of superstolide A,

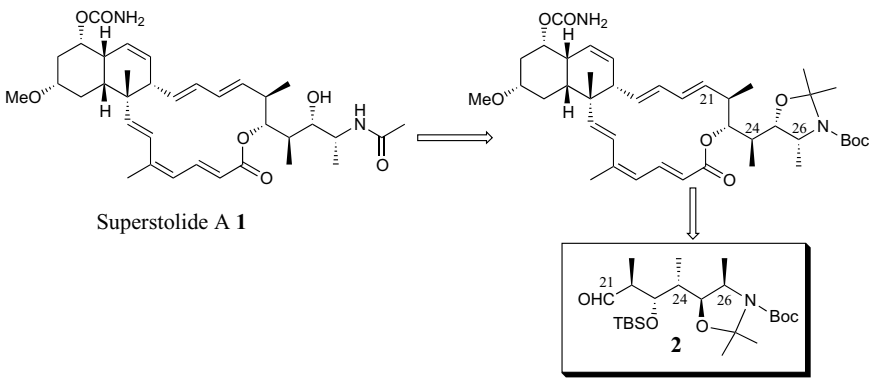

Figure 1.

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0957-4166/01/$ - see front matter
PII: S0957-4166(01)00281-6

which also allowed the unambigous definition of the relative and absolute stereochemistry of the five contigous stereocenters present in this subunit of the natural compound (Fig. 1).

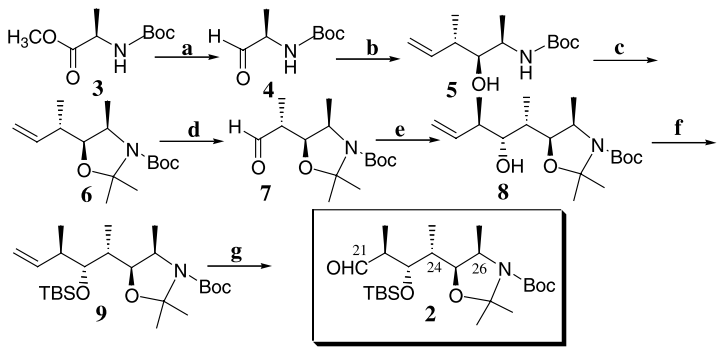
Scheme 1 outlines our stereoselective synthesis of the above fragment. We envisaged that the dipropionate framework present in **2** could be obtained with high stereoselectivity by two consecutive crotylborations[5] using Brown's procedure and starting from D-alanine.

N-Boc-D-alaninal **4**, obtained by DIBAL-H reduction of the commercially available *N*-Boc-D-alanine methyl ester[6] was reacted with (*E*)-crotonyl-diisopinocampheylborane derived from (–)-*B*-methoxydiisopinocampheylborane to give the *anti*-homoallylic alcohol **5**. The stereochemistry of this compound was assigned on the basis of literature precedents.[7]

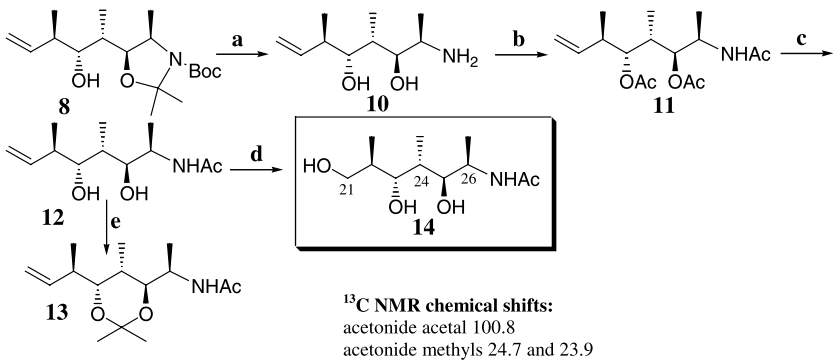
Attempts to obtain the C(25) aldehyde for the successive crotylboronation reaction through oxidative cleavage of the double bond in **5** failed. Many reaction conditions attempted gave either complex mixtures or no reaction occurred. In some cases we isolated the γ-lactam or the hemiaminal arising from intramolecular nucleophilic attack of the NHBoc group on the incoming C(23) electrophilic center. The concomitant protection of C(25) hydroxyl group and NHBoc group as the oxazolidine derivative **6** circumvented the problems encountered in the required transformation. In fact oxidative cleavage of the terminal double bond in **6** with O_3/DMS gave aldehyde **7** in 90% yield. Addition of the allylborane derived from (+)-B-methoxydiisopinocampheylborane and (*E*)-butene to aldehyde **7** at −78°C afforded the homoallylic alcohol **8** as a single distereoisomer in good yield. To confirm the configuration of **8**, we converted **8** to acetonide **13** in four steps (Scheme 2). First, the oxazolidine group was removed by acid hydrolysis, forming **10** that was peracetylated. Selective hydrolysis of the ester groups and acetalization afforded **13**. The ^{13}C chemical shifts assigned to the acetonide methyls and acetal were 24.7, 23.9 and 100.8, respectively, confirming an *anti* 1,3-diol relationship.[8,9]

The requisite aldehyde **2** was obtained from homoallylic alcohol **8** by TBS protection of the hydroxy group and oxidative cleavage of the terminal double bond (90% yield over two steps).[10]

In order to unambigously confirm the absolute configuration of the natural superstolide A **1**, it was subjected to methanolysis,[1] followed by reductive ozonolysis of the double bonds. HPLC separation of the crude reaction mixture afforded the C(21)–C(26) fragment **14**. On the other hand, the same fragment was easily obtained



Scheme 1. (a) DIBAL-H, CH_2Cl_2, −78°C, 2 h; (b) *tert*-BuOK, (*E*)-but-2-ene, BuLi, −78 to −45°C, (–)-B-methoxydiisopinocampheylborane, $BF_3{\cdot}OEt_2$, aldehyde **4**, −78°C, 4 h, 81%, two steps; (c) dimethoxypropane dry, *p*-TsOH (cat.), 25°C, 14 h, 90%; (d) O_3, CH_2Cl_2, −78°C, then DMS, 3 days, 90%; (e) *tert*-BuOK, (*E*)-but-2-ene, BuLi, −78 to −45°C, (+)-B-methoxydiisopinocampheylborane, $BF_3{\cdot}OEt_2$, aldehyde **7**, −78°C, 4 h, 80%; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 1 h, 25°C, 90%; (g) O_3, CH_2Cl_2, −78°C, then DMS, 3 days, quantitative yield.



Scheme 2. (a) MeOH/HCl, 25°C, 12 h; (b) Ac_2O, Pyr, Et_3N, 25°C, 12 h; (c) K_2CO_3/MeOH, 12 h; (d) O_3, CH_2Cl_2, −78°C, then $NaBH_4$ overnight; (e) dimethoxypropane dry, *p*-TsOH (cat.).

from **12** by reductive ozonolysis of the terminal double bond (Scheme 2). ^{1}H and ^{13}C NMR spectra of natural and synthetic **14** were superimposable,[11] confirming the relative stereochemistry. Both natural and synthetic **14** showed a positive value of the optical rotation ($[\alpha]_D$ +3.4; *c* 1, MeOH, for the ozonolysis derivative **14** from natural superstolide; $[\alpha]_D$ +3.8; *c* 0.2, MeOH for the synthetic fragment **14**), therefore the absolute 22*R*,23*R*,24*R*,25*S*,26*R* configuration was determined for C(22)–C(26) portion of superstolide A **1**.

In conclusion, we have described a novel and efficient approach to the superstolide fragment **2** (seven steps, 45% overall yield). A triol **14** of defined absolute stereochemistry was also prepared and compared with a reductive ozonolysis product of superstolide, thus confirming the relative and absolute stereochemistry of the natural product. Further investigations into the total synthesis of superstolide A are under way in our laboratory.

Acknowledgements

This work was supported by grants from MURST (PRIN '99) 'Chimica dei composti organici di interesse biologico' Rome, Italy. The NMR spectra were recorded at CRIAS Centro Interdipartimentale di Analisi Strumentale, Faculty of Pharmacy, University of Naples.

References

1. D'Auria, M. V.; Debitus, C.; Gomez Paloma, L.; Minale, L.; Zampella, A. *J. Am. Chem. Soc.* **1994**, *116*, 6658–6663.
2. D'Auria, M. V.; Gomez Paloma, L.; Minale, L.; Zampella, A.; Debitus, C. *J. Nat. Prod.* **1994**, *57*, 1595–1597.
3. Roush, W. R.; Champoux, J. A.; Peterson, B. C. *Tetrahedron Lett.* **1996**, *37*, 8989–8992.
4. Yu, W.; Zhang, Y.; Jin, Z. *Org. Lett.* **2001**, *3*, 1447–1450.
5. Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570–1576.
6. Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487–1492.
7. Giordano, A.; Spinella, A.; Sodano, G. *Tetrahedron: Asymmetry* **1999**, *10*, 1851–1854.
8. Rychnovsky, S. D.; Skalitsky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948.
9. Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511–3515.
10. The ^{1}H and ^{13}C NMR spectra of aldehyde **2** showed two sets of signals at room temperature due to the presence of a conformational equilibrium, as previously noted for other oxazolidine derivatives.[7] NMR data ($CDCl_3$, 500 MHz) and optical rotation (chloroform) for compound **2**. ^{1}H NMR δ: 9.71 (1H, s, H-21), 4.33 (1H, dd, J=4.3, 10.3 Hz, H-25), 3.99/3.81 (1H, m, H-26), 3.77 (1H, dd, J=4.0, 8.8, H-23), 2.53 (1H, m, H-22), 1.72 (1H, m, H-24), 1.54/1.52, 1.49/1.50 (6H, s's, acetonide Me), 1.46/1.45 (9H, s, N-Boc), 1.08/1.07 (3H, d, J=6.6 Hz, Me-26), 0.88/0.87 (3H, d, J=6.6 Hz, Me-24), 0.86/0.85 (3H, d, J=6.6 Hz, Me-22), 0.87 (9H, s, Si-^{t}Bu), 0.09/0.08, 0.06/0.04 (6H, s's, Si-Me); ^{13}C NMR δ: 204.8/204.5 (C-21), 151.8/151.4 (N-Boc), 93.1/92.7 (acetonide), 80.3/79.4 (N-Boc), 76.9 (C-23), 72.3/71.9 (C-25), 54.9/54.8 (C-26), 52.4/52.1 (C-22), 36.6/36.4 (C-24), 28.6-28.5 (N-Boc), 28.5–27.5, 25.6–24.5 (acetonide Me), 26.1–25.9 (Si-^{t}Bu), 18.4 (Si-^{t}Bu), 14.0/13.1 (Me-26), 11.4/11.2 (Me-24) 10.3/10.1 (Me-22), −3.9/−4.0 (Si-Me); $[\alpha]_D$=−4.2 (c=0.5, $CHCl_3$).
11. ^{1}H NMR data (CD_3OD, 500 MHz) and optical rotation (methanol) for compound **14**. ^{1}H NMR δ: 4.11 (1H, m, H-26), 3.86 (1H, d, J=9.4 Hz, H-23), 3.77 (1H, dd, J=10.3, 5.1 Hz, H-21), 3.55 (1H, d, J=6.0 Hz, H-25), 3.53 (1H, dd, overlapped, H-21), 1.96 (3H, NHCO$\underline{CH_3}$), 1.78 (1H, m, H-22), 1.73 (1H, m, H-24), 1.15 (3H, d, J=6.6 Hz, Me-26), 0.96 (3H, d, J=6.6 Hz, Me-24), 0.84 (3H, d, J=6.6 Hz, Me-22); ^{13}C NMR δ: 169.0 (NH$\underline{C}$OCH$_3$), 74.0 (C-25), 70.9 (C-23), 63.7 (C-21), 44.6 (C-26), 36.7 (C-22), 34.0 (C-24), 19.5 (NHCO$\underline{CH_3}$), 11.5 (Me-26), 10.2 (Me-22), 6.1 (Me-24). $[\alpha]_D$=+3.4 (c=1, MeOH).