ORGANIC LETTERS

2002
Vol. 4, No. 19
3223−3226

Synthesis, Structure Revision, and Absolute Configuration of (+)-Didemniserinolipid B, a Serinol Marine Natural Product from a Tunicate *Didemnum* sp.

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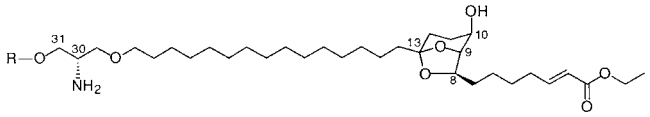
Received June 25, 2002

ABSTRACT



Didemniserinolipid B (**1**)
R = H; proposed structure
R = SO_3Na; revised structure

En route to proving the absolute and relative stereochemistry, through synthesis, of (+)-didemniserinolipid B (1), the first natural serinolipid isolated from a tunicate *Didemnum* sp., it was discovered that the isolated natural product was in fact the 31-sulfate configured 8*R*,9*R*,10*R*,-13*S*,30*S*. This structural reassignment was only possible after the development of a microwave-assisted method for the sulfation of unreactive hydroxyl groups.

Marine tunicates belonging to the genus *Didemnum* have proven to be a particularly rich source of structurally diverse and biologically potent marine metabolites.[1] Recently, González et al. reported the isolation of didemniserinolipids A−C from a methanol extract of *Didemnum* sp., collected along the coast of Sulawesi Island (Indonesia), with the aim of finding new cytotoxic agents against P388, A549, and HT29 tumor cell lines.[2] Although these isolated compounds exhibited no such activity, they were of interest because of their unusual serinolipid structures. More recently, a related cyclodidemniserinol trisulfate was isolated from the Palauan ascidian *Didemnum guttatum* as an HIV-1 integrase inhibitor.[3] All these serinolipids possess a unique serinol component and a 6,8-dioxabicyclo[3.2.1]octane core structure and are attractive targets for synthesis. We have therefore embarked on a study of the synthesis of (+)-didemniserinolipid B. Here we describe this work, which also led to a structural reassignment and determination of the absolute configuration of **1**.

Figure 1 shows our synthetic plan in a broad outline. Since the relative stereochemistry of the 6,8-dioxabicyclo[3.2.1]-octane portion was known to be (8*R**,9*R**,10*R**,13*S**),[2] we devised a route that would allow us to prepare both (8*R*,9*R*,-10*R*,13*S*,30*R*)- and (8*R*,9*R*,10*R*,13*S*,30*S*)-diastereomers to determine the absolute and relative configuration of the natural product. The (8*R*,9*R*,10*R*,13*S*) enantiomeric series was selected because this relative stereochemistry was recognized within the related product (+)-2-hydroxy-*exo*-

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(1) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *15*, 113.
(2) Gonzalez, N.; Rodriguez, J.; Jiminez, C. *J. Org. Chem.* **1999**, *64*, 5705.
(3) Mitchell, S. S.; Rhodes, D.; Bushman, F. D.; Faulkner, D. *Org. Lett.* **2**, 1605.

10.1021/ol026421y CCC: $22.00
Published on Web 08/24/2002

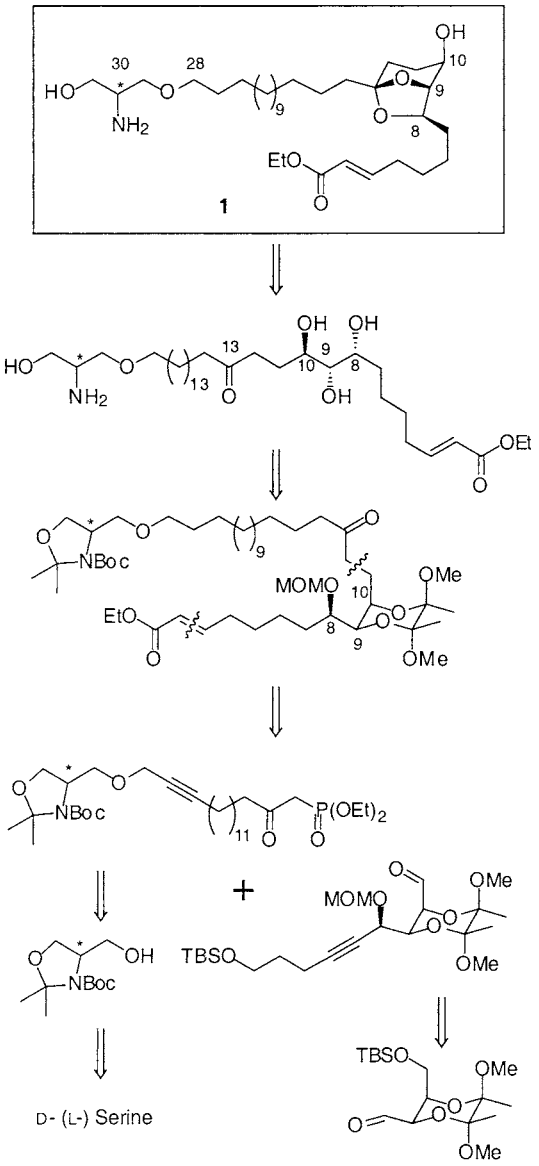
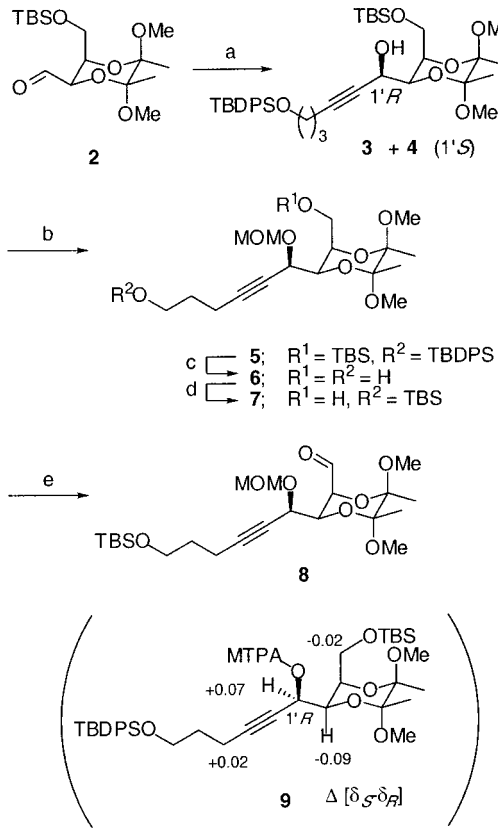


Figure 1. Structure and retrosynthetic analysis of **1**.

brevicomin,[4] which shares the same sign of specific rotation as (+)-didemniserinolipid B.

As illustrated in Scheme 1, the synthesis started from the known butanediacetal (BDA)-protected aldehyde **2**.[5] This compound was coupled with *O*-TBDPS-protected pentynol. Studies on similar systems had shown that selectivity of up to 20:1 was possible using allylic nucleophiles.[5] However, using *n*-BuLi as a base, the ratio of the desired compound **3** to its (1′*S*)-isomer **4** was only 2.5:1. Other bases such as

Scheme 1. Synthesis of the Central Fragment



[a] Reagents and conditions: (a) TBDPSO(CH$_2$)$_3$CCLi, THF; −78 °C (74% for **3** and 22% for **4**). (b) MOMCl, *i*-Pr$_2$NEt, DME; 60 °C (75%). (c) TBAF, THF (quant.). (d) TBSCl, Im, THF (74%). (e) DMSO, (COCl)$_2$, CH$_2$Cl$_2$, −78 °C then Et$_3$N, to room temperature (99%).

MeMgBr or *i*-PrMgCl gave even worse results. Although this ratio was a little disappointing, the diastereoisomers were readily separated by silica gel chromatography. The stereochemistry of the 1′-position in **9** was determined by the modified Mosher method.[6]

The secondary hydroxyl group of **3** was then protected as methoxymethyl (MOM) ether (**5**), and then both the silyl protecting groups were removed to afford diol **6**. This was done because selective removal of the TBS group had failed using HF·Py or TBAF. The less hindered hydroxyl group was selectively reprotected with TBS to give **7**, and the remaining hydroxyl group was oxidized by the Swern reagent to give aldehyde **8** as the central coupling fragment.

The serinol fragment (*S*)-**13** was prepared from the known D-serinol derivative (*S*)-**10** in a series of straightforward steps (Scheme 2).[7] The hydroxyl group was first propargylated to give ether (*S*)-**11**, and the terminal alkyne was further elongated with 1,11-dibromoundecane; the resulting bromide (*S*)-**12** was coupled with the dianion of β-ketophosphonate[8]

(4) Franke, W.; Schroeder, F.; Philipp, P.; Meyer, H.; Sinwell, V.; Gries, G. *Bioorg. Med. Chem.* **1996**, *4*, 363.

(5) (a) Dixon, D. J.; Foster, A. C.; Ley, S. V. *Org. Lett.* **1999**, *2*, 123. (b) Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1631. (c) Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1635. (d) Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Angew. Chem.* **2000**, *39*, 3622. (e) Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Chem. Eur. J.* **2002**, *8*, 1621. (f) Dixon, D. J.; Krause, L.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2516.

(6) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

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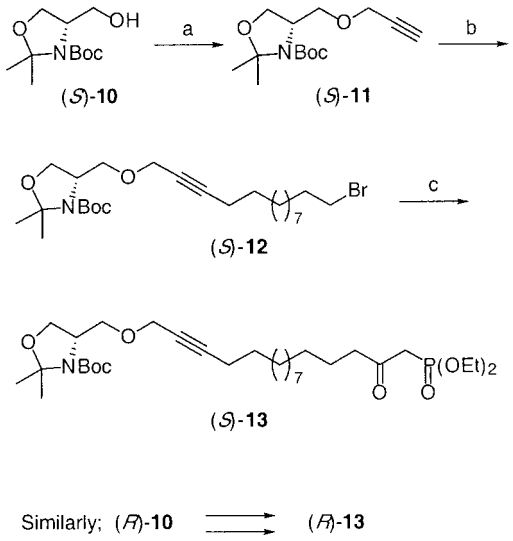
Scheme 2. Synthesis of the Serinol Fragments[a]



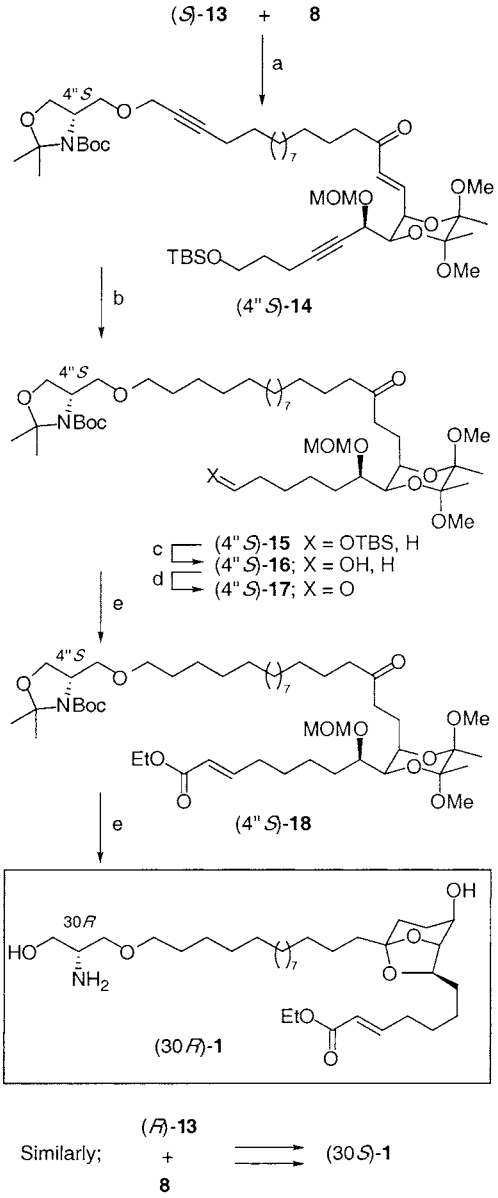
[a] Reagents and conditions: (a) NaH, THF then $HCCCH_2Br$, toluene (49%). (b) *n*-BuLi, THF then $Br(CH_2)_{11}Br$, HMPA (46%). (c) $CH_3C(=O)CH_2P(=O)(OEt)_2$, NaH, *n*-BuLi, THF; −78 °C then (*S*)-**12** (97%).

to give (*S*)-**13**. Following a similar procedure, (*R*)-**13** was prepared from L-serinol derivative (*R*)-**10**.

With both the coupling fragments now available, Wittig−Horner reaction of (*S*)-**13** with **8** gave the enone (4″*S*)-**14** in 46% yield without any epimerization of the initial aldehyde (Scheme 3).[9] The two triple bonds and one double bond in (4″*S*)-**14** were removed by hydrogenation over a Raney-Nickel catalyst to afford (4″*S*)-**15** in 73% yield. Prolonged reaction times caused further reduction of the keto carbonyl group. Removal of the silyl protecting group in (4″*S*)-**15** gave (4″*S*)-**16**, and the resulting hydroxyl group was subsequently oxidized with the Dess−Martin periodinane[10] to give aldehyde (4″*S*)-**17**. This aldehyde was subjected to the Wittig−Horner reaction to give (4″*S*)-**18**. Removal of all the protecting groups (acetonide, Boc, BDA, and MOM) was achieved in one step using 1 N HCl in EtOH at 45 °C to obtain the target compound (30*R*)-**1** in 73% yield. The diastereomer (30*S*)-**1** was also prepared similarly.

The structures of all the synthetic compounds were fully characterized by ^1H, ^{13}C, and two-dimensional NMR spectral data. The relative stereochemistry of dioxabicyclooctane component was confirmed by selected NOE difference spectral analysis. As shown in Figure 2, most peaks in ^1H NMR of (30*R*)-**1** matched the natural peaks except those shifts associated with the serinol unit of the molecule, especially H-31 signals, which are shifted significantly upfield. In view of the fact that related natural products were sulfated on the serinol unit, we therefore believed the structure of the natural product **1** may have been misassigned.

Scheme 3. Synthesis of (+)-Didemniserinolipid B[a]



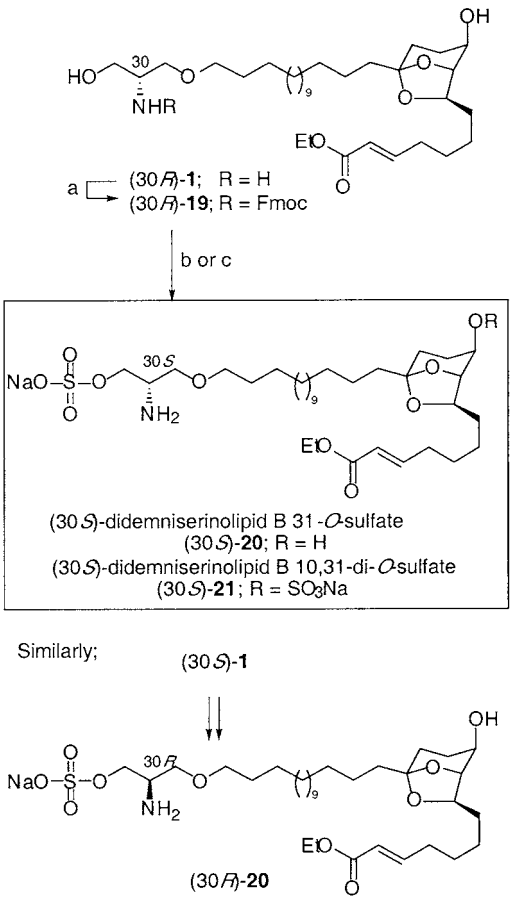
[a] Reagents and conditions: (a) LiCl, *i*-Pr_2NEt, MeCN; 20 °C (46%). (b) Raney-Ni, EtOH, H_2 (73%). (c) TBAF, THF (95%). (d) Dess−Martin periodinane, pyridine, CH_2Cl_2 (79%). (e) triethyl phosphonoacetate, LiCl, *i*-Pr_2NEt, MeCN; 20 °C (96%). (f) 1 N HCl, EtOH; 45 °C (73%).

This assumption was later supported by a private communication from Prof. Jiménez, whose remeasurement of the HR-FAB-MS spectrum of natural **1** with NaCl added to matrix indicated a monosulfate +Na peak. Without added NaCl, no sulfate peak could be observed.

To confirm this suspicion, it was clear that (30*R*)-**1** and (30*S*)-**1** should be derivatized as the monosulfate, presumably at O-31 in line with related natural products (Scheme 4). To achieve monosulfation, it was necessary to first protect the amino group of the serinol unit with the fluorenylmethoxycarbonyl (Fmoc) group. Beginning with (30*R*)-**1**, this was installed in moderate yield using standard conditions and

(8) Grieco, P. A.; Pogonowski, C. S. *J. Am. Chem. Soc.* **1973**, *95*, 3071.
(9) Blanchette, M. A.; Choy, W.; Davis, J. T. Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(10) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

Scheme 4. Synthesis of (+)-Didemniserinolipid B 31-*O*-Sulfate[a]



[a] Reagents and conditions: (a) FmocCl, K_2CO_3, dioxane−H_2O (64%). (b) (i) SO_3·Py (1.2 equiv), Na_2SO_4, DMF; microwave, 110 °C; (ii) Piperidine, DMF; 20 °C (49%). (c) (i) SO_3·Py (10 equiv), Na_2SO_4, DMF; microwave, 110 °C; (ii) piperidine, DMF; 20 °C (84%).

provided the diol (30*R*)-**19**. Standard sulfation conditions (SO_3·Py or SO_3·NMe_3 in DMF, 1,4-dioxane or (and) pyridine at 20−100 °C) failed to derivatize the diol, and only starting material was returned in each trial reaction. This was probably due to hydrogen bonding of the OH group with the adjacent NH group and steric hindrance at 10-axial OH group. However, when a focused microwave system[11,12] was employed as the source of power, treatment of diol (30*R*)-**19** with 1 equiv SO_3·Py at 110 °C for 1 h in the microwave well afforded the desired 31-*O*-sulfate as the major product. Deprotection of the Fmoc group under mild conditions (piperidine in DMF, rt) afforded 31-*O*-sulfate (30*S*)-**20**.[13] The overall yield of (30*S*)-**20** was 1.1% in over 15 steps.

(11) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.

(12) A Smith Synthesizer from Personal Chemistry, Uppsala, Sweden, was used.

(13) The *R*/*S* indication of the serinol part is reversed after sulfation. *sn*-Numbering should be applicable: (30*S*)-**20** for *sn*-serinol-1-sulfate.

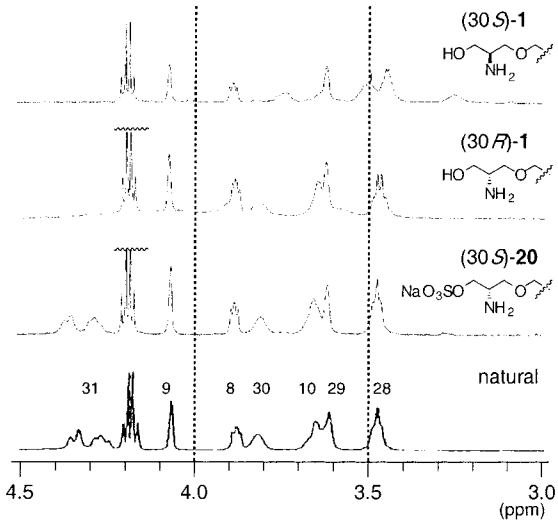


Figure 2. Comparison of ^{1}H NMR spectra taken at 600 MHz for the synthetic compounds and at 500 MHz for the natural one in $CDCl_3$.

For spectral comparison, (30*S*)-10,31-di-*O*-sulfate (30*S*)-**21** was synthesized using excess SO_3·Py (10 equiv). Likewise, the other diastereomer of the monosulfate (30*R*)-**20** was synthesized following the conditions described above. Whereas (30*S*)-**21** and (30*R*)-**20** showed significant spectral differences to the isolated material, the spectroscopic data for synthetic (30*S*)-**20** and the specific rotation $[\alpha]_D^{25}$ +11 (*c* 0.12, $CHCl_3$) [lit.[2] $[\alpha]_D^{24}$ +10.3 (*c* 0.225, $CHCl_3$)] were in excellent agreement. As a result, the structure of natural (+)-didemniserinolipid B was revised to be the corresponding 31-*O*-sulfate, and its absolute configuration was determined to be 8*R*,9*R*,10*R*,13*S*,30*S*.

In summary, the synthesis of two possible diastereomers of (+)-didemniserinolipid B and their 31-*O*-sulfates was achieved starting from D-(or L-)serinol and the BDA-protected chiral building block.[2,5] The structure of natural (+)-didemniserinolipid B was therefore reassigned as the 31-*O*-sulfate, and its absolute configuration was determined to be 8*R*,9*R*,10*R*,13*S*,30*S*. During this synthetic study, we also developed a microwave-assisted sulfation method for α-acylamino- and sterically hindered hydroxyl groups that may find application in other systems.

Acknowledgment. We thank Prof. C. Jiménez (Universidade da Coruña, Spain) for additional information on the FAB-MS spectrum of natural **1** and for helpful discussions.

Supporting Information Available: Experimental procedures and spectroscopic data for **1**, **3**−**8**, and **11**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026421Y