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Diastereospecific formal synthesis of (2*R*,3*S*)-2-amino-tetradeca-5,7-dien-3-ol isolated from *Xestospongia* sp.

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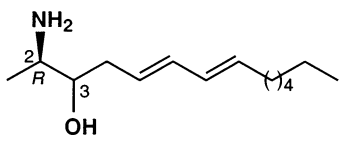
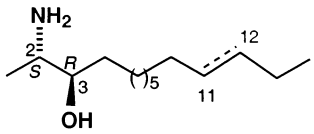
Abstract—Stereospecific synthesis of a common precursor of several acyclic (2*R*,3*S*)-2-amino-3-ols from marine origin, especially of (2*R*,3*S*)-2-amino-tetradeca-5,7-dien-3-ol isolated from *Xestospongia* sp., is described starting from the versatile epoxide **10**.

Several natural 'sphingosine-like' vicinal amino alcohols, isolated from marine sources, exhibit antifungal, antimicrobial or cytotoxic activities.[1–6] Thus, 2-amino-tetradeca-5,7-dien-3-ols **1** and **2**, found as unseparable C-3 epimers in the methanolic extract of a Papua New Guinea sponge *Xestospongia* sp., inhibit the growth of *Candida albicans*,[1] whereas xestoaminols **A 3** and **C 4**, extracted from the same genus, display reverse transcriptase inhibition activity.[2] Other vicinal amino alcohols derived from C-11 and C-15 fatty acids and isolated from *Pseudodistoma* genus, such as crucigasterins **5** and **6**[3] or new obscuraminol **A 7**,[4] were shown to be cytotoxic.

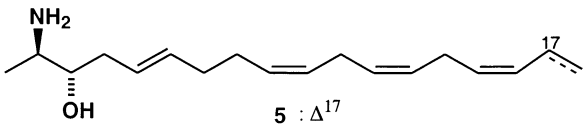
The relative configurations of these amino alcohols have been established by ^{1}H NMR of the corresponding oxazolidinones, but their absolute configurations remain controversial. The 2*S* configuration has been originally attributed to **1** and **2** on the basis of HPLC retention times of degradation products.[1] However, the preparation of their synthetic precursors **8** and **9** (as two mixtures of *anti* and *syn* diastereomers), respectively, from (*S*)- and (*R*)-alanine, allowed to assign the 2*R* configuration of these natural compounds by comparison of the optical rotations.[7] Crucigasterins **5** and **6** were shown to be 2*R*,[3] whereas xestoaminol **C 4**, as well as very recently described obscuraminol **A 7** are



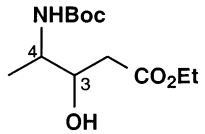
1 : 3*S*
2 : 3*R*



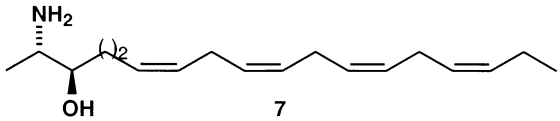
3 : Δ^{11}
4



5 : Δ^{17}
6



8 a : 3*R*, 4*S*
b : 3*S*, 4*S*
9 a : 3*S*, 4*R*
b : 3*R*, 4*R*
11 : 3*S*, 4*R*, methylester



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Keywords: acyclic marine 2-amino-3-ols; samarium diiodide; lactam alcoholysis.
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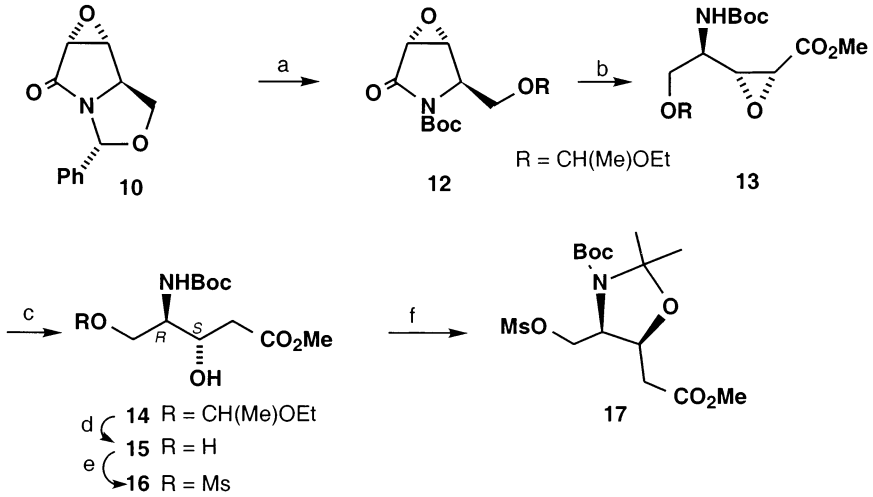
PII: S0040-4039(01)01097-8



Scheme 1. *Reagents and conditions*: (a), (b) see Ref. 10; (c) SmI_2 (2.5 equiv.), HMPA (5 equiv.), DMAE (2 equiv.), 62%; (d) 0.1N HCl, 100%; (e) MsCl, py; 73%; (f) $(Me)_2C(OMe)_2$, TsOH, 82%.

2*S*.[4] In fact, the two configurations at the nitrogen bearing carbon can even co-exist in the products of the same marine organism as illustrated by cyclic amaminols[5] and pseudodistomins.[6]

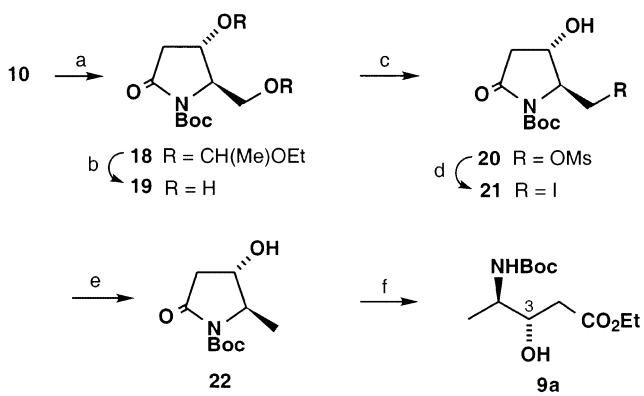
We report here the stereospecific synthesis of the precursor **9a** of definite 3*S*,4*R* configurations common to bioactive **1**, **5** and **6**, from the versatile epoxide **10** derived from (*S*)-pyroglutaminol.[8–10]

A first approach towards the described corresponding methylester **11**[11] is outlined in Scheme 1. It started with the conveniently protected compound **12**, obtained after controlled acidic hydrolysis of **10**, and involved the α,β-epoxyester **13**, already prepared by a very efficient (94%) opening of the lactam ring of **12** with methanol and catalytic potassium cyanide.[10,12]

Owing to the easy opening of oxirane with vicinal *N*-Boc protecting group, the crude α,β-epoxyester **13** was used without purification in the next step of regioselective reduction into the β-hydroxyester **14**. The epoxide **13** in THF–MeOH was inert towards samarium diiodide under the reaction conditions which reduce efficiently epoxyketones[13] and epoxylactam **10**.[14] It is well known that the addition of HMPA can increase the reducing power of SmI_2.[15] With a strong chelating agent such as *N*,*N*-dimethylaminoethanol (DMAE, 2 equiv.) as co-additive with HMPA (5 equiv.), a highly regioselective opening of α,β-epoxyesters was observed with SmI_2 (2.25 equiv.) in THF.[16] Applied to **13** using 2.5 equivalents of SmI_2, this procedure afforded the alcohol **14**, isolated in modest 62% yield, together with the starting epoxide (22%). Quantitative deprotection of the primary alcohol **15**[17] with dilute HCl was followed by selective monomesylation giving rise to **16** (73%). After *O*,*N* protection as oxazolidine **17** (82%), attempts to convert the mesyloxymethyl group into a methyl group failed. Furthermore, the iodomethyl derivative could not be prepared as an alternative intermediate without *N*-Boc participation to oxazolidinone formation.[18]

To circumvent this drawback, the chronology of the main steps was modified according to Scheme 2.

This route started with fully protected dihydroxypyrrolidin-2-one **18** previously used in our laboratory,[19] and involved the early conversion of 5-hydroxymethyl substituent into a methyl group. Accordingly, **18** was fully *O*-deprotected in acidic medium (100% yield), since the attempts to selectively deprotect the primary alcohol were not very efficient. The selective mesylation of diol **19** afforded **20** in 75% yield along with recovered **19** (15%). The iodo derivative **21** was easily prepared (NaI, DMF, 50°C, 78%) and hydrogenolysed into **22** (H_2, Pd/C 10%, EtOH, $NaHCO_3$, 88%).[20] Concomitant formation of some desired ethylester **9a** (ca. 10%) was also observed. The lactam ring of *N*-Boc-4-hydroxy-5-methyl-pyrrolidin-2-one **22** in THF–EtOH (1:1) was slowly but quantitatively opened in the presence of KCN (20 mol%) and converted by alcoholysis to (3*S*,4*R*)-**9a**.[21]



Scheme 2. *Reagents and conditions*: (a) see Ref. 19; (b) 0.1N HCl, 100%; (c) MsCl-py, 0°C, 75%; (d) NaI, DMF, 50°C, 78%; (e) H_2, Pd/C 10%, 88%; (f) EtOH–THF, KCN cat., 100%.

This work constitutes a diastereospecific formal synthesis of *Xestospongia* amino-alkadienol **1**. It could also be useful in the synthesis of 2*R*,3*S* more complex marine vicinal amino alcohols such as crucigasterins **5** and **6**.[3]

References

1. Gulavita, N. K.; Scheuer, P. J. *J. Org. Chem.* **1989**, *54*, 366–369.
2. Jiménez, C.; Crews, P. *J. Nat. Prod.* **1990**, *53*, 978–982.
3. Jares-Erijman, E. A.; Bapat, C. P.; Lithgow-Bertelloni, A.; Rinehart, K. L.; Sakai, R. *J. Org. Chem.* **1993**, *58*, 5732–5737.
4. Garrido, L.; Zubía, E.; Ortega, M. J.; Naranjo, S.; Salvá, J. *Tetrahedron* **2001**, *57*, 4579–4588.
5. Sata, N. U.; Fusetani, N. *Tetrahedron Lett.* **2000**, *41*, 489–492.
6. Kobayashi, J.; Ishibashi, M. *Heterocycles* **1996**, *42*, 943–970.
7. Mori, K.; Matsuda, H. *Liebigs Ann. Chem.* **1992**, 131–137.
8. Griffart-Brunet, D.; Langlois, N. *Tetrahedron Lett.* **1994**, *35*, 119–122.
9. Herdeis, C.; Aschenbrenner, A.; Kierfel, A.; Schwabenländer, F. *Tetrahedron: Asymmetry* **1997**, *8*, 2421–2432.
10. Langlois, N.; Moro, A. *Eur. J. Org. Chem.* **1999**, 3483–3488.
11. Hashiguchi, S.; Kawada, A.; Natsugari, H. *Synthesis* **1992**, 403–408.
12. Preliminary communication: Langlois, N. 'Natural Products from the Plants and Marine Organisms of the Mediterranean and Atlantic Seabord: Isolation, Synthesis and Industrial Applications', April 2–5, 2000, Lisbon (Portugal).
13. Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596–2599.
14. Panday, S. K.; Langlois, N. *Synth. Commun.* **1997**, *27*, 1373–1384.
15. (a) Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2945–2948; (b) Hanessian, S.; Girard, C.; Chiara, J. L. *Tetrahedron Lett.* **1992**, *33*, 573–576; (c) Hasegawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008–5010.
16. Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4437–4440.
17. Selected data of **15**: ^{1}H NMR (300 MHz, $CDCl_3$, $\delta=0$ ppm: TMS): 5.45 (bd, 1H, NH), 4.16 (m, 1H, H-3), 3.95 (dd, 1H, Ha-5), 3.70 (s+m, 4H, OCH_3, Hb-5), 3.58 (m, 1H, H-4), 2.65 and 2.58 (2dd, 2H, H_2-2). ^{13}C NMR (75.0 MHz, $CDCl_3$): 173.39 (C-1), 156.16 (NCO_2), 79.97 (qC, *t*-Bu), 69.38 (C-3), 62.04 (C-5), 54.95 (OCH_3), 52.04 (C-4), 38.64 (C-2), 28.43 (CH_3, *t*-Bu). HRMS (CI, CH_4) calcd for $C_{11}H_{22}NO_6$ $(MH)^+$: 264.1447. Found: 264.1422.
18. (a) Agami, C.; Couty, F.; Hamon, L.; Venier, O. *Tetrahedron Lett.* **1993**, *34*, 4509–4512; (b) Curran, T. P.; Pollastri, M. P.; Abelleira, S. M.; Messier, R. J.; McCollum, T. A.; Rowe, C. G. *Tetrahedron Lett.* **1994**, *35*, 5409–5412; (c) Lee, J. W.; Lee, J. H.; Son, H. J.; Choi, Y. K.; Yoon, G. J.; Park, M. H. *Synth. Commun.* **1996**, *26*, 83–88.
19. Langlois, N.; Calvez, O. *Tetrahedron Lett.* **2000**, *41*, 8285–8288.
20. Kim, Y. J.; Takatsuki, A.; Kogoshi, N.; Kitahara, T. *Tetrahedron* **1999**, *55*, 8353–8364.
21. Selected data of **9a**: Mp: 69–71°C. $[\alpha]_D^{24}=+10$ ($c=0.58$, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): 4.81 (m, 1H, NH), 4.18 (q, 2H, $J=7$ Hz, OCH_2), 4.03 (m, 1H, H-3), 3.70 (m, 1H, H-4), 3.38 (exch. D_2O, OH), 2.46 (2H, H_2-2), 1.44 (s, 9H, *t*-Bu), 1.27 (t, 3H, $J=7$ Hz, $CH_2C\underline{H}_3$), 1.13 (d, 3H, $J=7$ Hz, $CHC\underline{H}_3$). ^{13}C NMR (75.0 MHz, $CDCl_3$): 172.78 (OCO), 155.65 (NCO_2), 79.57 (qC, *t*-Bu), 70.82 (C-3), 60.85 (OCH_2), 49.97 (C-4), 38.11 (C-2), 28.38 (CH_3, *t*-Bu), 15.14 (CH_3), 14.15 (CH_3). HRMS (CI) calcd for $C_{12}H_{24}NO_5$ $(MH)^+$: 262.1654, found: 262.1651.