ORGANIC LETTERS

2003
Vol. 5, No. 16
2821−2824

The Total Synthesis and Stereochemical Revision of Yanucamide A†

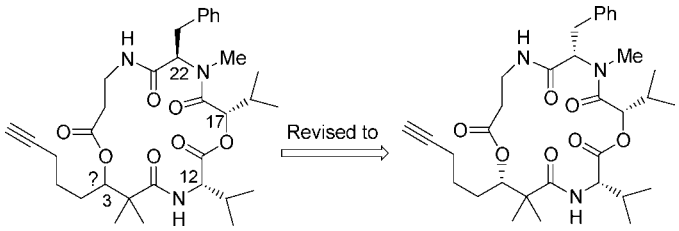
Zhengshuang Xu,‡ Yungui Peng,‡ and Tao Ye*,‡,§

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, China, and Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery & Synthesis and Department of Applied Biology & Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, China

bctaoye@inet.polyu.edu.hk

Received May 11, 2003

ABSTRACT



The first total synthesis of yanucamide A is reported via amide and ester couplings of the key components. This synthesis has established the configuration at the previously ambiguous 3-position, and also revised the stereochemistry at the 22-position, to give 3*S*,12*S*,17*S*,22*S* for the natural product.

There has been much interest recently in natural products from cyanobacteria, including isolation of obyanamide[1] and aeruginosamide,[2] and synthesis of dendroamide A[3] and 7-epicyclindrospermopsin.[4] These compounds, and numerous others, have shown that cyanobacteria produce a wide range of secondary metabolites displaying a broad spectrum of biological activities. Species *Lyngbya majuscula*,[5] a strain of cyanobacterium, has provided many varied metabolites, the biological activity of which ranges from cytotoxic agents to anticancer and antifungal activity. Unusual effects include immunosuppressants and antifeedants. These compounds have potential applications as therapeutic agents and this has driven our group to synthesize a range of these metabolites, with the aim of structure modification for fine-tuning biological activity. One particular target of interest was yanucamide A (**1**),[6] which was isolated by Gerwick and co-workers from an assemblage of *Lyngbya majuscula* and *Schizothrix* species. Both yanucamide A (**1**) and the closely related yanucamide B[7] have shown potent toxicity toward brine shrimp, but full data on their respective biological activities are unknown. The stereochemistry at the C-3 position was unassigned in the isolation paper and our initial aim was to identify the correct configuration at this center.

The true stereochmistry at C-3 was strongly suspected to be (*S*), since the (*S*)-2,2-dimethyl-3-hydroxyoctynoic acid (Dhoya) group has appeared in the natural products kulolide-1 and kulokainalide-1. Although these were not directly extracted from a cyanobacterium, they were taken from a higher organism known to have cyanobacteria in its food chain. Consequently, the origin of the Dhoya is believed

† Dedicated to Professor M. Anthony McKervey on his 65th birthday.
‡ The University of Hong Kong.
§ The Hong Kong Polytechnic University.

(1) Williams, P. G.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2002**, *65*, 29−31.
(2) Lawton, L. A.; Morris, L. A.; Jaspars, M. *J. Org. Chem.* **1999**, *64*, 5329−5332.
(3) Xia, Z.; Smith, C. D. *J. Org. Chem.* **2001**, *66*, 3459−3466.
(4) Heintzelman, G. R.; Fang, W.-K.; Keen, S. P.; Wallace, G. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 3939−3945.
(5) Burja, A. M.; Banaigs, B.; Abou-Mansour, E.; Burgess, J. G.; Wright, P *Tetrahedron* **2001**, *57*, 9347−9377.
(6) Sitachitta, N.; Williamson, R. T.; Gerwick, W. H. *J. Nat. Prod.* **2000**, *63*, 197−200.
(7) For the isolation of yanucamide B, please see ref 6.

10.1021/ol034803d CCC: $25.00
Published on Web 07/12/2003

to be cyanobacterial and the (*S*)-configuration was assumed to be correct when considering appropriate disconnections (Figure 1).

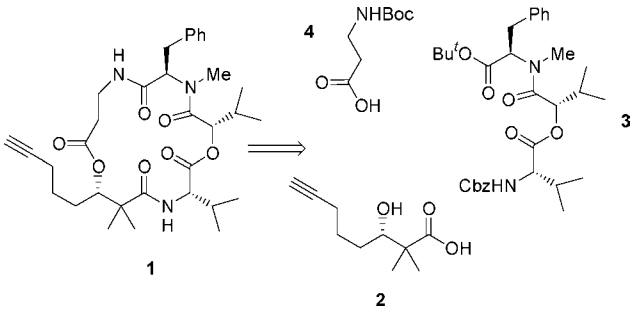
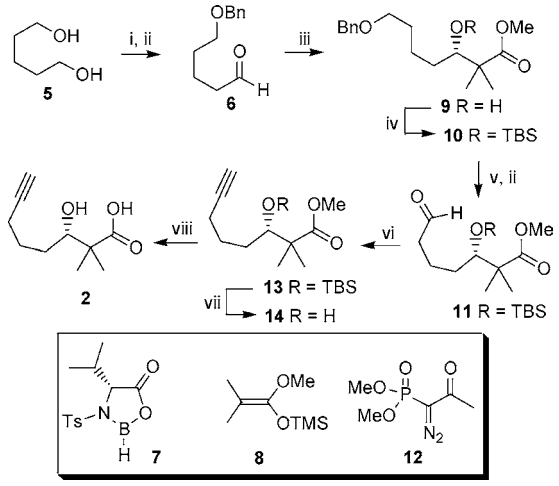


Figure 1. Retrosynthetic analysis of yanucamide A.

Ultimate closure of the depsipeptide was chosen to be a peptide linkage between the β-alanine and phenylalanine units. This is sufficiently unhindered to allow smooth reaction, and should be possible to achieve without any racemization. With this in mind, we set about preparing fragments **2** and **3**.

The Dhoya fragment **2** (Scheme 1) was constructed in eight steps from 1,5-pentanediol (**5**). Benzyl protection and

Scheme 1. Synthesis of Fragment **2**[a]

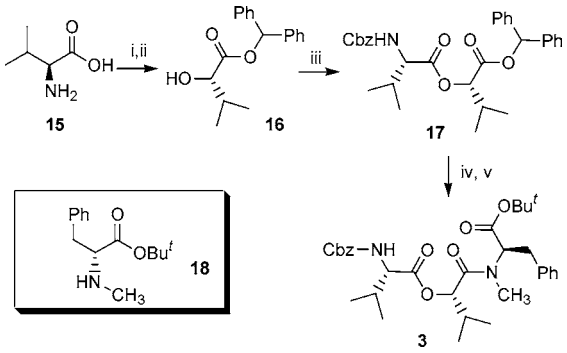


[a] Reagents and conditions: (i) NaH, BnBr; (ii) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C, 71%; (iii) **7**, THF, −78 °C, then **8**, 67%; (iv) TBSOTf, 2,6-lutidine, DCM, −50 °C, 83%; (v) H_2, Pd/C; (vi) **12**, K_2CO_3, MeOH, 71%; (vii) TFA, DCM, 82%; (viii) NaOH (aq), 0 °C, 92%.

Swern oxidation gave the protected aldehyde **6**. This was converted into the (S)-β-hydroxy ester **9** via an asymmetric aldol reaction with methyl trimethylsilyl ketene (**8**), in the presence of oxazaborolidinone **7** (derived from (*R*)-valine), using the method of Kiyooka.[8] Silyl protection of the secondary alcohol with use of TBS-triflate resulted in ester **10**. Hydrogenolysis of the benzyl group, using palladium on charcoal as catalyst, and a further Swern oxidation furnished aldehyde **11**. This was then treated with the Ohira−Bestmann reagent[9] to form the corresponding alkyne in excellent yield. Desilylation with trifluoroacetic acid and saponification yielded, after acidification, (*S*)-acetylenic acid **2**. Palladium-catalyzed hydrogenation of acid **2** afforded the corresponding 2,2-dimethyl-3-hydroxyoctanoic acid. Its negative optical rotation revealed 3*S* configuration of the hydrogenation product by comparison with data for the known compound.[10] Attention now turned to fragment **3**.

This was a straightforward preparation starting from (*S*)-valine **15** (Sheme 2). Diazotization and hydrolysis gave (*S*)-

Scheme 2. Synthesis of Fragment **3**[a]



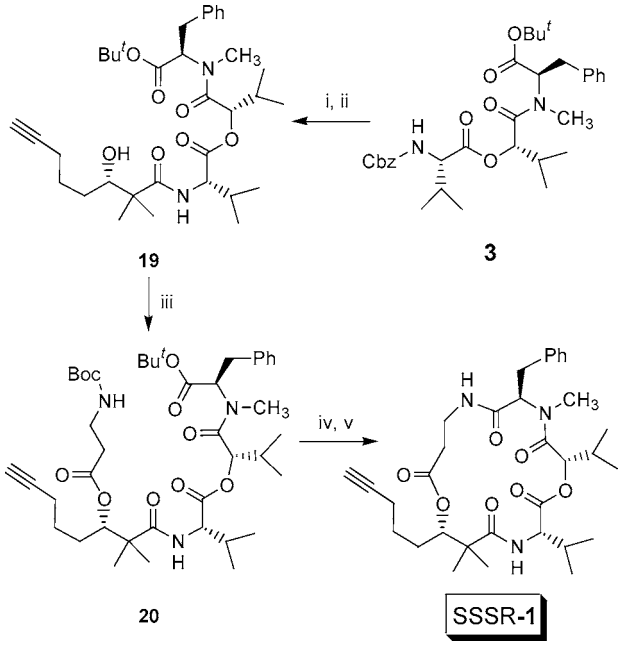
[a] Reagents and conditions: (i) $NaNO_2$, H_2SO_4, H_2O; (ii) $Ph_2CN{=}NH_2$, $PhI(OAc)_2$, I_2, DCM, −10°C, 86%; (iii) Cbz-L-Val-OH, EDC, DMAP, DCM, 84%; (iv) TFA, DCM; (v) **18**, BEP, DIPEA, DCM, −10 °C to rt, 66%.

2-hydroxyisovaleric acid, which was protected as its diphenylmethyl (DPM) ester **16**,[11] allowing a degree of versatility in the choice of the other protecting groups used. The coupling of **16** with Cbz-L-Val-OH, mediated by EDC and DMAP, proceeded smoothly to give **17** in 84% yield. TFA removal of the DPM protecting group, followed by coupling with amino ester **18**, using Xu's conditions for hindered substrates,[12] gave fragment **3** in a reasonable yield.

The construction of yanucamide A from the three fragments was completed with use of standard procedures (Scheme 3). Hydrogenolytic removal of the Cbz group in **3** was achieved by using 10% Pd/C in methanol. The crude product of this reaction, after filtering and concentrating, was combined directly with acetylenic acid **2**, and coupling was mediated by BEP to give a 68% yield of **19** over two steps. Esterification of Boc-protected β-alanine with **19**, facilitated by EDC and DMAP, produced the cyclization precursor **20**

(8) Kiyooka, S.-I.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276−2278.
(9) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561−564. (b) Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521−522.
(10) Nakao, Y.; Yoshida, W. Y.; Szabo, C. M.; Baker, B. J.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3272−3280.
(11) Lapatsanis, L.; Milias, G.; Paraskewas, S. *Synthesis* **1985**, 513−515.
(12) Li, P.; Xu, J. C. *Tetrahedron Lett.* **1999**, *40*, 8301−8302.

Scheme 3. Assembling the Cyclodepsipeptide[a]



[a] Reagents and conditions: (i) $PdCl_2$, H_2, MeOH; (ii) **2**, BEP, DIPEA, DCM, 68%; (iii) **4**, EDC, DMAP, DCM, 98%; (iv) TFA, DCM; (v) BOPCl, NMM, DMF, 24 h, 75%.

in moderate yield. Simultaneous unmasking of amine and acid functions by treatment with TFA allowed the cyclization to be effected via activation with BOPCl and NMM, at high dilution in DMF, in 75% yield.

Unfortunately, on comparison of our spectra and the published data for natural yanucamide A, there were considerable differences. Given that the stereochemistry at C-3 had been ambiguous, our disappointment was not too great. Having established that the published structure was incorrect we wished to verify the correct structure for yanucamide A. With many building blocks already at hand, the next step was to prepare a batch of *ent*-**2**, and this was

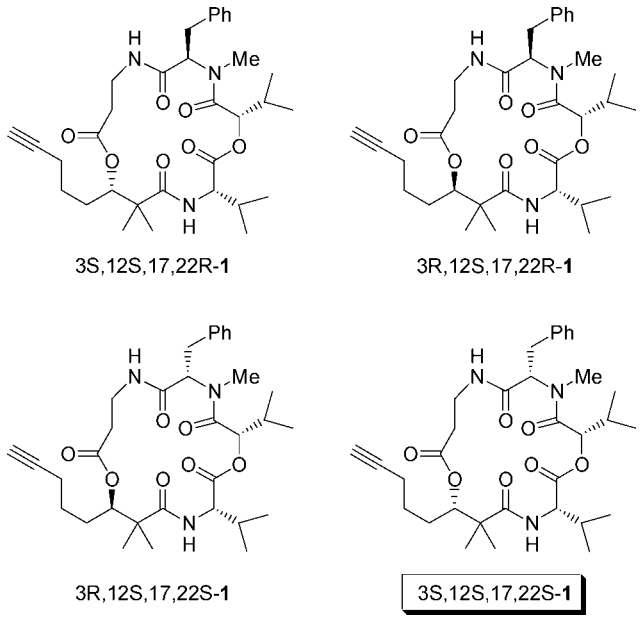


Figure 2. Four stereoisomers of yanucamide A.

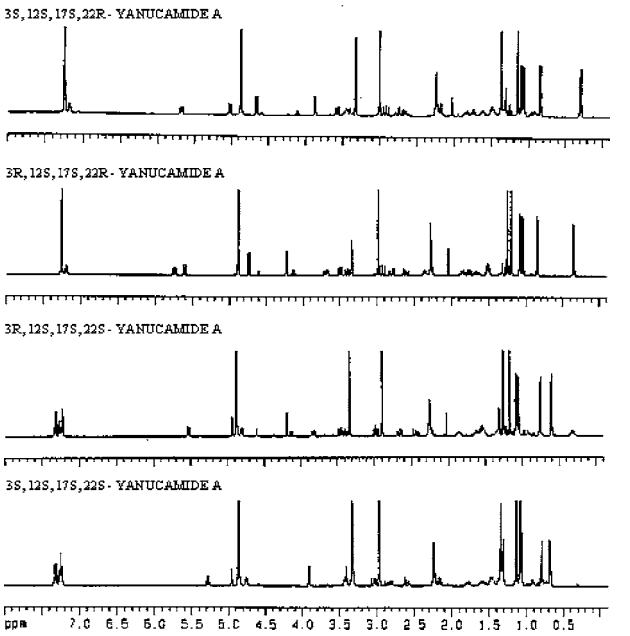


Figure 3. ^1H NMR spectra of four synthetic yanucamide A stereoisomers.

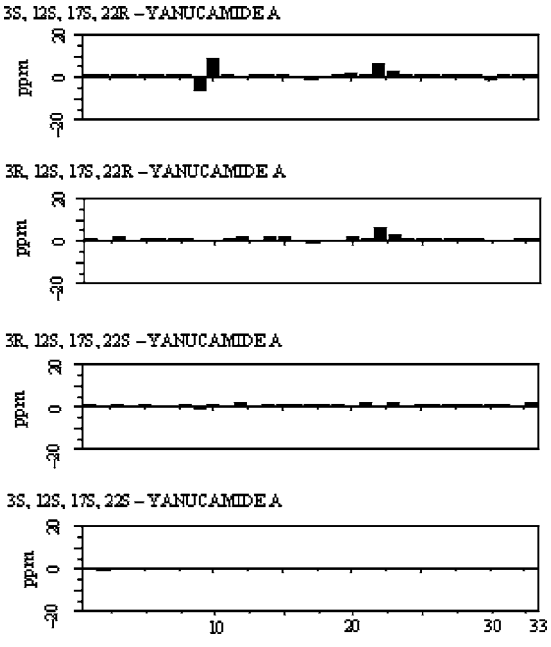


Figure 4. Differences in ^{13}C NMR shifts between natural yanucamide A (**1**) and four synthetic yanucamide A stereoisomers.

readily achieved by following the same synthetic procedure as for **2**, but using the oxazaborolidinone derived from (*S*)- instead of (*R*)-valine. This proceeded smoothly, and the (*R*)-Dhoya fragment was readily incorporated into the synthesis to produce 3*R*,12*S*,17*S*,22*R*-**1**. On examining the analytical information we were disappointed and somewhat confused as to why the authentic data did not match those of our product. To our surprise, we realized that the stereochemistry of the Dhoya fragment may have been (*S*), but there was at least one further incorrect assignment made on the original isolation paper.

On comparing the proton NMR of the natural product with our synthetic isomers, one significant difference was a doublet at δ 0.30 ppm in the synthetic materials, but no signals below δ 0.66 ppm appeared in the authentic sample. The signal appeared to be one of the diastereotopic methyl signals on the Hiv unit. Such a shielded signal could be accounted for by having an aromatic ring in close spatial proximity. Since the only residue with an aromatic portion was the (*R*)-phenylalanine, our attention turned to the stereochemistry that it was exhibiting. The "shielded" signal appeared in both samples of **1** where (*R*)-phenylalanine was used but not in the authentic **1**. It seemed reasonable to repeat the synthesis with (*S*)-phenylalanine, incorporating both isomers of Dhoya. These syntheses proceeded smoothly under the previous conditions, through to cyclization. Four stereoisomers of yanucamide A have been synthesized and their structures are illustrated in Figure 2.

Upon completion, it was clear from comparing analytical data (Figures 3 and 4) that the true configuration of natural yanucamide A was (3*S*,12*S*,17*S*,22*S*).

It is easy to see how the mistake was made in the initial assignment. The configuration of the Dhoya fragment was correctly assumed from related structures within the research area. The configuration of the other fragments, except the phenylalanine unit, was unambiguously assigned on their retention times on HPLC. The problem with the Phe residue was that the difference in retention times between each of the enantiomers was incredibly small. On handling such small amounts of material it is reasonable to accept that certain errors are liable to enter the analysis.

Acknowledgment. We thank the support form the Area of Excellence Scheme (established under the University Grants Committee of the Hong Kong Special Administrative Region), The University of Hong Kong, and The Hong Kong Polytechnic University.

Supporting Information Available: Full details for experimental procedures for compounds **1**−**3**, **6**−**14**, and **16**−**20**, and ^{1}H and ^{13}C NMR spectra for compounds **1**−**3**, **9**−**11**, **13**−**14**, **16**−**17**, **19**−**20**, and *S*-2,2-dimethyl 3-hydroxyoctanoic acid. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034803D