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Total Synthesis of Cyclomarin C

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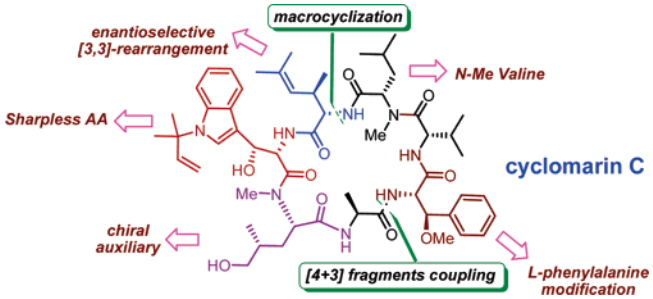
ABSTRACT



The total synthesis of cyclomarin C was accomplished through a convergent strategy from a tetrapeptide fragment and a tripeptide one. The developed methods to prepare the needed noncoded amino acids, the proper protection of peptide fragments, and identification of the optimum macrocylization site can be applied to further synthetic studies on other members of cyclomarins.

A large number of marine-derived cyclopeptides with diverse structures have been isolated and characterized in recent years, among which many contain novel noncoded amino acids and often present unique complex structures, as well as varied biological activities.[1] In 1999, Clardy et al.[2] isolated and characterized for the first time three new antiinflammatory cyclic heptapeptides, cyclomarins A (**1**), B (**2**), and C (**3**) (Figure 1) from a sediment sample in the vicinity of San Diego. Both in vitro and in vivo studies revealed they are potential candidates for further drug research. Recently, several groups,[3] including ours,[4] have reported synthetic studies on key amino acids existing in the cyclomarins. Structurally, cyclomarins show remarkable resemblance to each other. Cyclomarins A and C both contain three common amino acids (Ala, Val, and *N*-MeLeu), two less common ones (*β*-methoxyphenylalanine, *N*-methylleucine), and one novel noncoded amino acid (2-amino-3,5-dimethylhex-4-enoic acid[3]). The only difference between these two lies in an unusual tryptophan derivative, with *N*′-prenyltryptophan[4] being in cyclomarin C, and *N*′-(1,1-dimethyl-2,3-expoxypropyl)-*β*-hydroxytryptophan[3a] being in cyclomarin A. Herein, we wish to report the total synthesis of cyclomarin C (**3**) by

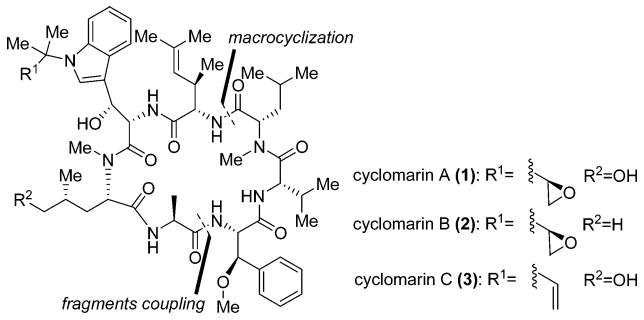


Figure 1. Structure of cyclomarins A, B, and C.

(1) Recent reviews, see: (a) Jimeno, J. M. *Anticancer Drugs* **2002**, *13* (Suppl. 1), S15. (b) Vera, M. D.; Joullie, M. M. *Med. Res. Rev.* **2002**, *22*, 102. (c) Taguchi, T. *Gan to Kagaku Ryoho* **2003**, *30*, 579. (d) Fenical, W. *Chem. Rev.* **1993**, *93*, 1793.

(2) Renner, M. K.; Shen, Y. C.; Cheng, X. C.; Jensen, P. R.; Frankmoelle, W.; Kauffman, C. A.; Fenical, W.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1999**, *121*, 11273.

(3) (a) Sugiyama, H.; Shioiri, T.; Yokokawa, F. *Tetrahedron Lett.* **2002**, *43*, 3489. (b) Tarver, J. E., Jr.; Joullie, M. M. *J. Org. Chem.* **2004**, *69*, 815.

(4) Wen, S.-J.; Zhang, H.-W.; Yao, Z.-J. *Tetrahedron Lett.* **2002**, *43*, 5291.

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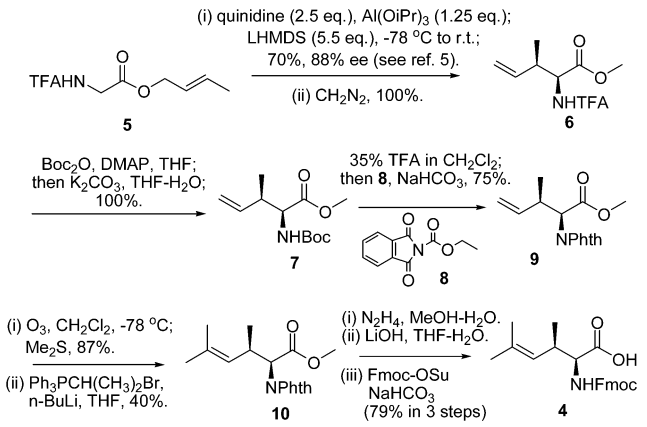
a convergent macrocycle assembly strategy from a tetrapeptide fragment and a tripeptide one. Optimization of the macrocyclization site was achieved through screening of several different ring closure possibilities. The resultant two key amide bonds are indicated in Figure 1.

The various components of cyclomarin C were synthesized in different fashions. Our synthesis of *N*-Fmoc 2-amino-3,5-dimethylhex-4-enoic acid derivative **4** utilized an enantioselective [3,3]-Claisen rearrangement[5] (Scheme 1). *N*-TFA

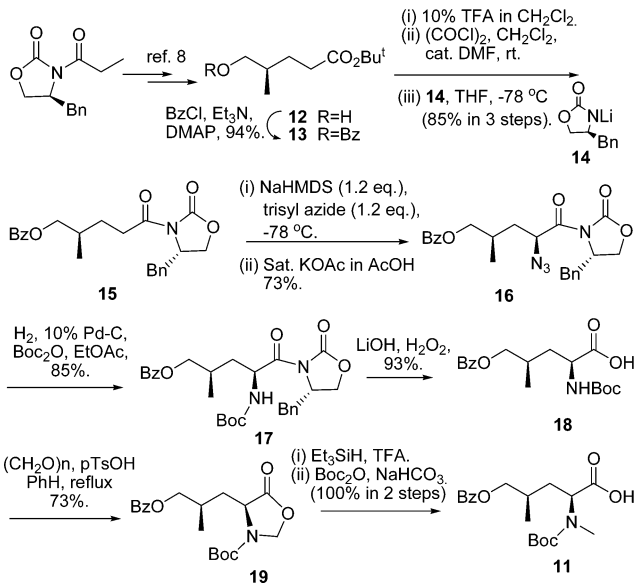
Scheme 1



amino acid methyl ester **6** was immediately converted into *N*-Phth derivative **9** in an indirect fashion through the *N*-Boc derivative **7**. It was found that direct transformation of **6** into **9** was accompanied by partial racemization. Ozonolysis[6] of terminal olefin **9** and subsequent Wittig reaction[7] afforded the desired amino acid derivative **10**. The amino acid derivative **4** was finally obtained in three facile steps.

The second noncoded amino acid derivative, *N*-Boc-*N*-methyl 5-benzoyloxyleucine **11**, was synthesized with use of chiral auxiliary strategies (Scheme 2). The first stereogenic center (**12**) was introduced through an Evans protocol.[8] Following initial protection of alcohol **12** as its benzoic acid ester, cleavage of the *tert*-butyl ester was achieved with 10% TFA in dichloromethane. The resultant acid was then transformed into its acid chloride, which upon treatment with the chiral auxiliary lithium salt **14** yielded **15** (85% for 3 steps). Successive treatment of **15** with NaHMDS, then trisyl azide and quenching with HOAc−KOAc buffer afforded azide **16**.[9] Reduction of azide functionality by hydrogenation and in situ *N*-Boc protection gave **17**. Hydrolysis of the chiral auxiliary was then done in a routine fashion[10] (LiOH, H_2O_2). *N*-Methylation[11] of the resulting *N*-Boc amino acid **18** was

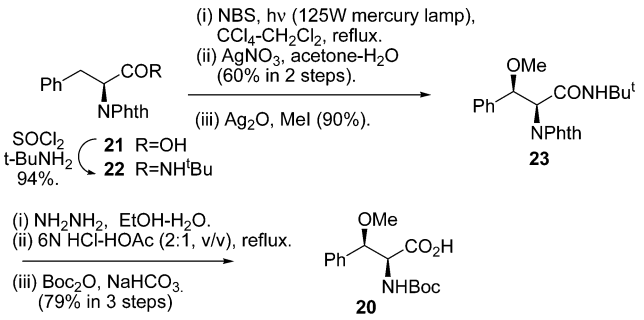
Scheme 2



carried out through a ketalization−reduction sequence to yield the desired *N*-Boc *O*[5]-Bz derivative **11**. An initial attempt to obtain **11** from L-glutamic acid lacked stereoselectivity when introducing a methyl group on its C-4 position.[12]

N-Boc-*β*-methoxyphenylalanine methyl ester **20** was prepared from L-phenylalanine[13] (Scheme 3). Initially, *N*-Phth

Scheme 3



phenylalanine **21** was converted into its *tert*-butyl amide **22**. Subsequently, radical-based bromination[13a] at the benzyl position of **22** followed by substitution with hydroxide gave the syn-*β*-hydroxyl derivative, which was *O*-methylated to **23** with Ag_2O and MeI. Hydrazine-mediated phthaloyl deprotection of **23** followed by acid-catalyzed *tert*-butyl amide hydrolysis and *N*-Boc protection provided the amino acid derivative **20**.

(5) (a) Mues, H.; Kazmaier, U. *Synthesis* **2001**, 487. (b) Bakke, M.; Ohta, H.; Kazmaier, U.; Sugai, T. *Synthesis* **1999**, 1671.

(6) Mooiweer, H. H.; Hiemstra, H.; Spechamp, W. N. *Tetrahedron* **1991**, *47*, 3451.

(7) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(8) Evans, D. A.; Ripin, D. H. B.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816.

(9) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

(10) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987** *28*, 6141.

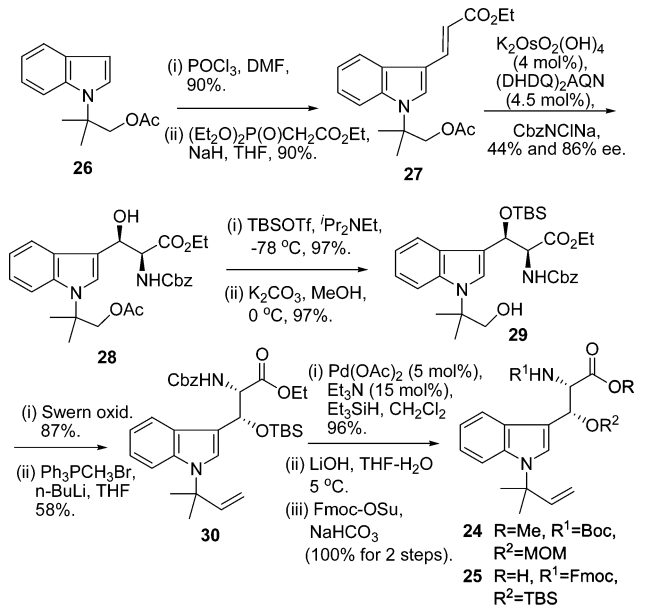
(11) Aurelio, L.; Brownlee, R. T. C.; Hughes, A. B. *Org. Lett.* **2002**, *4*, 3767.

(12) Arda, A.; Jimenez, C.; Rodriguez, J. *Tetrahedron Lett.* **2004**, *45*, 3241.

(13) (a) Easton, C. J.; Hutton, C. A.; Roselt, P. D.; Tiekink, E. R. T. *Tetrahedron* **1994**, *50*, 7327. (b) Sheehan, J. C.; Champman, D. W.; Roth, R. W. *J. Am. Chem. Soc.* **1952**, *74*, 3822.

Previously, we reported the synthesis of the noncoded amino acid derivative **24**[4] bearing *O*-MOM and *N*-Boc protections. Unfortunately, this amino acid derivative proved to be very sensitive to a variety of acidic conditions, which prevented its incorporation into linear peptide precursors of cyclomarin C. To meet requirements imposed by the current total synthesis, the amino acid was resynthesized as its *N*-Fmoc O^3-TBS protected variant, *N*′-prenyl-3-hydroxytryptophan derivative **25** (Scheme 4). Sharpless asymmetric

Scheme 4

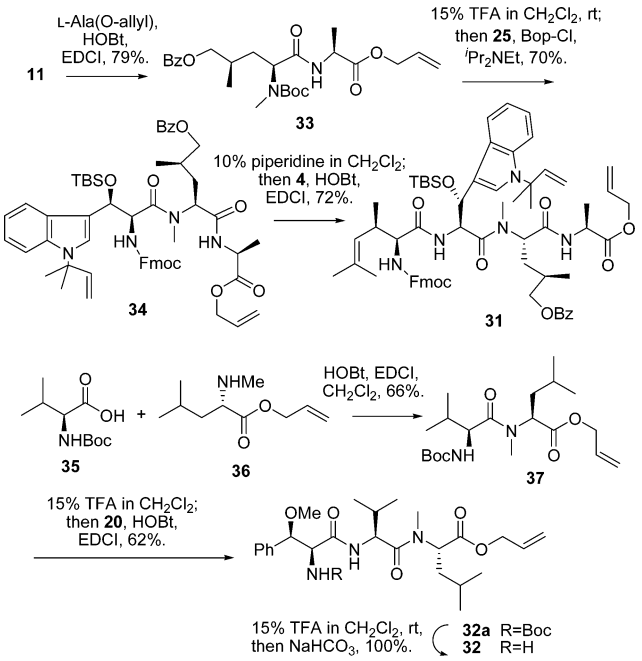


aminohydroxylation[3a,14] served as a key step in the route to **25**. The α,β-unsaturated ester **27**, prepared from a known indole derivative **26**,[4] was treated with CbzNClNa in the presence of $K_2OsO_2(OH)_4$ and $(DHDQ)_2AQN$ to give 3-hydroxytryptophan derivative **28** in 44% isolated yield and 86% ee.[14] Sequential TBS hydroxyl protection and acetate hydrolysis afforded the alcohol **29**. Swern oxidation[15] of **29**, then Wittig reaction[7] yielded intermediate **30**. Final protecting group transformations were achieved by selective *N*-Cbz removal through a Pd-mediated reduction,[16] ethyl ester hydrolysis, and *N*-Fmoc protection, yielding **25**.

With all noncoded amino acid derivatives in hand, several combinations of [4+3] coupling strategies from a tetrapeptide fragment and a tripeptide one were examined (see the Supporting Information). The results of these studies indicated that reliable macrocyclization could be achieved as outlined in Figure 1. According to this protocol, the linear tetrapeptide **31** and the tripeptide **32** were first synthesized respectively as shown in Scheme 5, using typical coupling reagents (EDCI[17] and Bop-Cl[18]) and Boc and Fmoc chemistries.

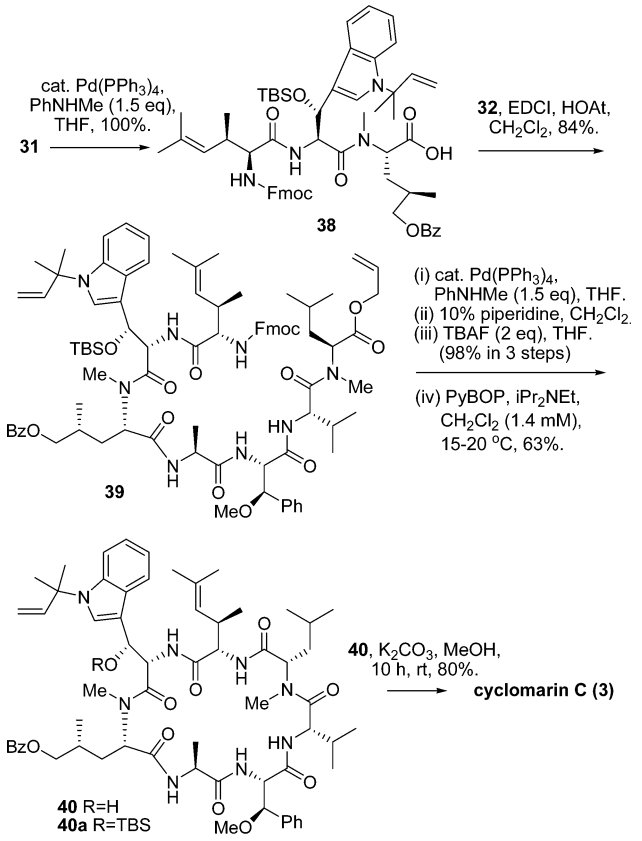
(14) Tao, B.; Schlingloff, G.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507.
(15) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(16) Wipf, P.; Uto, Y. *Tetrahedron Lett.* **1999**, *40*, 5165.
(17) Sheehan, J. C.; Cruickshank, P. A.; Boshart, G. L. *J. Org. Chem.* **1961**, *26*, 2525.

Scheme 5



Coupling of the above two fragments and completion of the total synthesis of cyclomarin C were executed as shown in Scheme 6. The allyl ester of tetrapeptide **31** was cleaved

Scheme 6



by Pd-catalyzed isomerization[19] in quantitative yield. The free acid was immediately coupled with tripeptide **32**, using EDCI and HOAt,[20] to afford the linear heptapeptide **39** in 84% yield. Comparison with the same reaction using HOBt[21] showed that HOAt gave much higher yields. Prior to macrocyclization, three protecting groups were removed by Pd-catalyzed isomerization (for the *C*-terminal allyl ester group), 10% piperidine in dichloromethane (for the *N*-terminal Fmoc group), and TBAF in THF (for the *O*-TBS). It is noteworthy that deprotection of the TBS ether is necessary before macrocyclization, because use of similar TBS deprotection conditions with the macrocycle **40a** resulted in no reaction at room temperature and gave very complex products at higher temperatures. After examining several macrocyclization conditions, we successfully obtained *O*-Bz-protected cyclomarin C in 63% yield, using PyBOP[22] as the condensation reagent in a dilute solution (1.4 mM). This step has been repeated three times, and in all cases, comparable chemical yields were obtained. Final deprotection of the *O*-Bz group with K_2CO_3 in MeOH at room temperature in 10 h gave cyclomarin C (**3**, 38 mg in one batch) in 80% yield. Both ^{1}H NMR and ^{13}C NMR spectra of the synthetic sample (HPLC purity >98%) are identical with those of the natural product[2] (see the Supporting Information), while the optical rotation value of our synthetic sample ($[\alpha]^{20}_D$ −72.8 (*c* 0.75, $CHCl_3$)) is higher than that reported for the natural material ($[\alpha]^{20}_D$ −19.7 (*c* 1.0, $CHCl_3$)).[2] Careful peak-to-peak comparison of the NMR hardcopies (see Supporting Information) shows that the natural product (1 mg as reported)[2] contains a small amount of impurities, which might lead to this discrepancy of rotation values.

In summary, the total synthesis of cyclomarin C was accomplished through a convergent macrocycle assembly strategy from a tetrapeptide fragment and a tripeptide one. The methods developed to prepare the needed noncoded amino acids, the proper protection of peptide fragments, and the optimum macrocylization site are all outcomes of this study that will be expanded to further studies on the remaining cyclomarins. Efforts toward those natural products are currently underway in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental details with full characterization of compounds, description of optimization for the macrocylization site, ^{1}H and ^{13}C NMR spectra of synthetic cyclomarin C (**3**) (PDF), and comparison of NMR spectra hardcopies of synthetic sample with those of natural product. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernandez-Lizarbe, J. R.; Zugaza-Bilbao, A. *Synthesis* **1980**, 547.
(19) Kiho, T.; Nakayama, M.; Yasuda, K.; Miyakoschi, S.; Inukai, M.; Kogen, H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2315.
(20) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397.
(21) Horiki, K. *Tetrahedron Lett.* **1977**, 1897.
(22) Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 205.