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Synthesis of a fully protected (2*S*,3*R*)-*N*-(1′,1′-dimethyl-2′-propenyl)-3-hydroxytryptophan from tryptophan

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Abstract—(2*S*,3*R*)-*N*-(1′,1′-Dimethyl-2′-propenyl)-3-hydroxytryptophan, a key amino acid of the anti-inflammatory cyclic peptide, cyclomarin C, has been synthesized stereoselectively, with full protection, from L-tryptophan for the first time.

In recent years, studies into new bioactive chemical agents from marine microorganisms as new natural resources, although poorly known biologically, have been carried out. Amongst these efforts, three novel cyclic peptides, cyclomarins A, B and C (Fig. 1) were isolated and characterized from a sediment sample collected in the vicinity of San Diego by Clardy et al.[1] These were found to show significant anti-inflammatory activities in both in vivo and in vitro assays, especially in the phorbol ester (PMA)-induced mouse ear edema assay. The structures of cyclomarins contain several unusual amino acids, including two β-hydroxytryptophan derivatives **3** and **4**. During the past 2 years, several groups have developed synthetic studies of these natural products, as well as related methodology to obtain these amino acids.[2] Many bioactive natural products[3] have been found to contain *N*-reversed prenylated indole fragments. However, until the recent work of Shioiri et al.,[2] few studies have been reported on these *N*-reversed prenylated indole compounds. As part of our interest in synthetic studies toward cyclomarins, we would like to report the first stereoselective synthesis of (2*S*,3*R*)-*N*-(1′,1′-dimethyl-2′-propenyl)-3-hydroxytryptophan from readily available L-tryptophan.

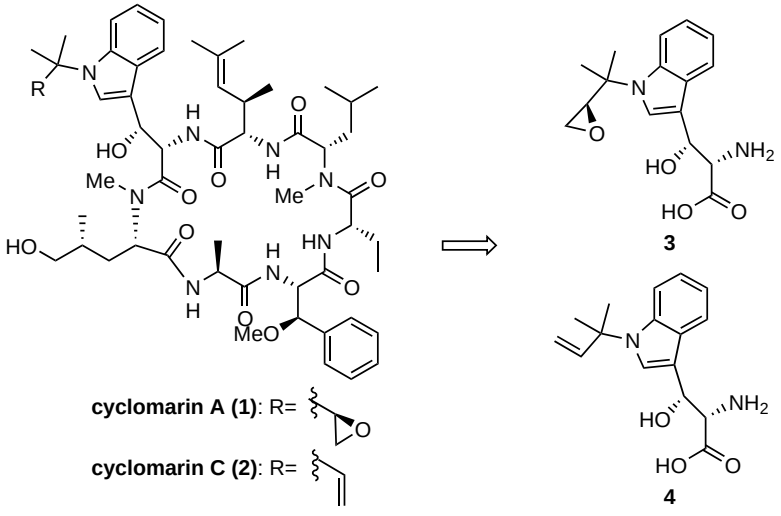

Figure 1. The chemical structures of cyclomarin A and C.

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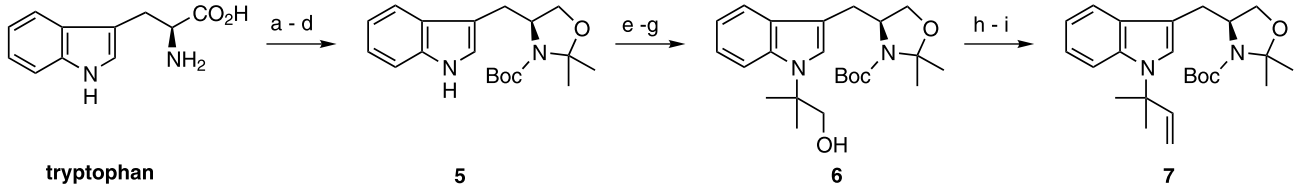
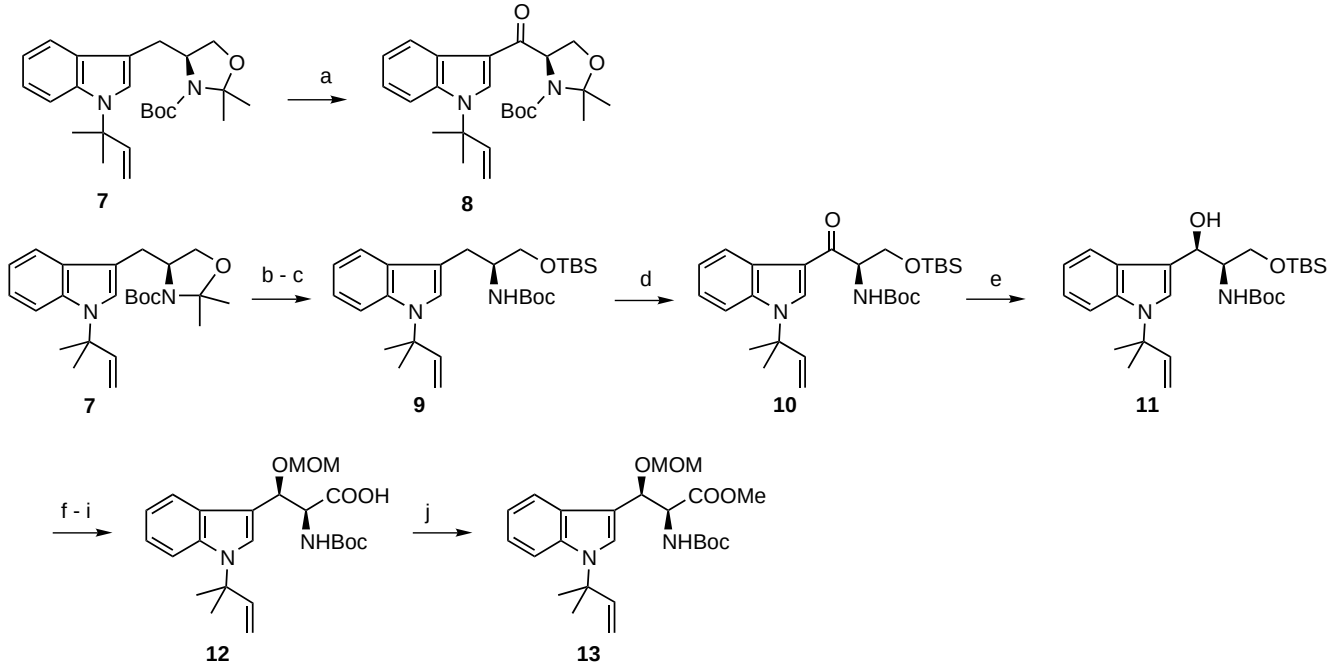
The synthesis started with *N*-alkylation. In order to furnish the *N*-*tert*-alkylation and avoid racemization, L-tryptophan was reduced to the corresponding *N*-Boc amino-alcohol by a routine procedure.[4] The *N*-Boc protected amino-alcohol was then treated with 2,2-dimethoxypropane (DMP) to afford compound **5** in high yield (Scheme 1). Deprotonation of **5** with NaH and then *N*-alkylation of the indole nitrogen with ethyl 2-bromopropionate gave an intermediate which was subjected to further treatment with LDA and methyl iodide to methylate the α-position of the ester. Reduction with $LiAlH_4$ afforded the stable and easy-to-separate alcohol **6**. A Wittig reaction of the aldehyde prepared from alcohol **6** by Swern oxidation gave the terminal olefin **7**. At this stage, the desired *N*-*tert*-alkylation had been achieved. The *S*-configuration of the *N*-functionalized carbon had been retained from the natural L-tryptophan.

A DDQ-based oxidation[5] successfully introduced the new carbonyl group into **7** at the benzylic site (86% yield, Scheme 2). This newly introduced carbonyl was to be the basis for the (3*R*)-hydroxyl group in future transformations. Unfortunately, there were unexpected difficulties encountered in removing the dimethyl acetal from the reduced product of **8** although a wide selection of reagents and conditions were tried to resolve the problem, including TFA, AcOH (aq.), *p*-TsOH, PPTS and others. Finally, we decided to remove the dimethyl acetal from **7** and change it to an alternative protecting group before the DDQ oxidation (Scheme 2).

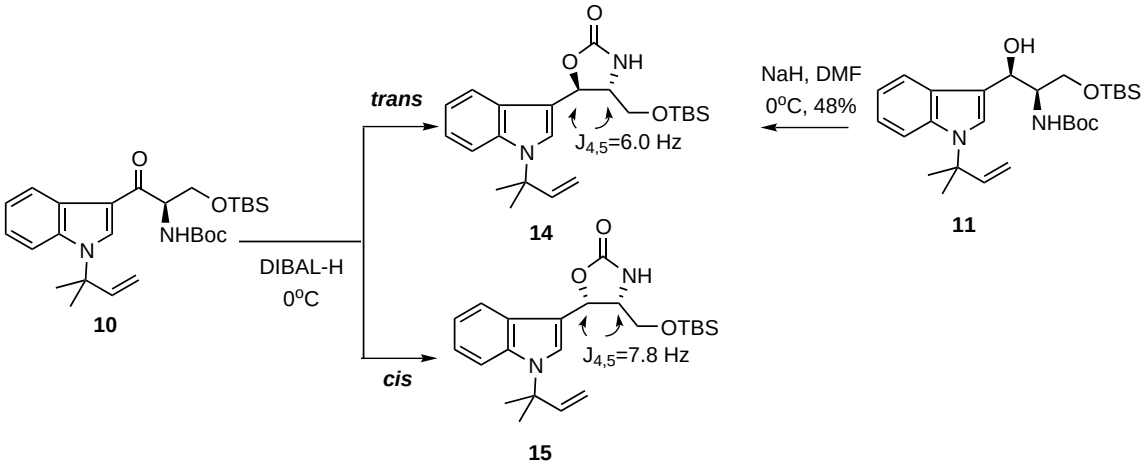
Selective deprotection of the acetal **7** was achieved using methanol with a catalytic amount of *p*-TsOH (92%), and the resultant alcohol was protected quantitatively with TBSCl (Scheme 2). DDQ-based oxidation of **9** afforded the carbonyl compound **10** in 68% yield. A stereoselective reduction of **10** by DIBAL-H was carried out at −78°C to give the alcohol **11** (>19:1 diastereoselectivity). The *threo* configuration of **11** was confirmed using a ^1H NMR method discussed below. It is worth noting that temperature control during the reduction is essential to obtain good diastereoselectivity. If the DIBAL-H reduction was performed at 0°C, almost equal amounts of *threo* and *erythro* products were obtained which cyclized to give the cyclic carba-



Scheme 1. *Reagents and conditions:* (a) AcCl, MeOH; (b) Boc_2O, Et_3N, 97% (two steps); (c) $LiAlH_4$, 96%; (d) DMP, 89%; (e) NaH, $CH_3CHBrCOOEt$, 74%; (f) LDA, MeI; (g) $LiAlH_4$, 92% (two steps); (h) Swern oxidation, 88%; (i) $Ph_3P^+CH_3Br^-$, *t*-BuOK, toluene, 99%.



Scheme 2. *Reagents and conditions:* (a) DDQ, THF/water (9:1), 86%; (b) *p*-TsOH, MeOH, 92%; (c) TBSCl, imidazole, 100%; (d) DDQ, THF/water (9:1), 68%; (e) DIBAL-H, −78°C, 81%; (f) MOMCl, *i*-Pr_2NEt, 91%; (g) TBAF, 100%; (h) Swern oxidation, 68%; (i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, 50%; (j) CH_2N_2, 63%.



Scheme 3.

mates **14** and **15** (Scheme 3), respectively. The hydroxyl group of **11** was protected using MOMCl in the presence of diisopropylethylamine, and then the TBS group was removed with TBAF. The primary alcohol was converted into the corresponding acid **12** by sequential Swern oxidation and $NaClO_2$-based oxidation. The more stable methyl ester **13**[6] was finally prepared by treatment of **12** with CH_2N_2 in situ.

As mentioned above, the stereochemistry of **11** was finally confirmed by ^1H NMR, which has been applied recently to similar cases of vicinal amino alcohols.[7] In order to determine the H–H coupling constants between the β-CH and the α-CH, the cyclic carbamates were prepared. Both *cis*- and *trans*-cyclic oxazolidinones **14** and **15**[8] were obtained by the reduction of **9** with DIBAL-H at 0°C (Scheme 3). In agreement with the literature,[7] the coupling constant $J_{4,5}$ (6.0 Hz) for the *trans*-oxazolidinone **14** (threo configuration) is smaller than the $J_{4,5}$ (7.8 Hz) for the *cis*-oxazolidinone **15** (*erythro* configuration) (Scheme 3). Furthermore, the intermediate **11** could be converted into the *trans*-oxazolidinone **14** using NaH in DMF at 0°C. Based on this evidence, it is clear that the DIBAL-H reduction of **10** preferentially gives the threo product **11** at lower temperatures (−78°C versus 0°C).

In summary, (2*S*,3*R*)-*N*-(1′,1′-dimethyl-2′-propenyl)-3-hydroxytryptophan, a key amino acid component of the anti-inflammatory cyclic peptide cyclomarin C, has been synthesized stereoselectively for the first time from L-tryptophan. Further synthetic studies to incorporate the acid **12** into cyclomarin C are underway in our laboratory.

Acknowledgements

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References

1. 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.
2. (a) Sugiyama, H.; Yokokawa, F.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **2001**, *42*, 7277; (b) Wen, S.-J.; Yao, Z.-J. *Acta Chim. Sinica* **2002**, *60*, 129.
3. (a) Levy, L. M.; Cabrera, G. M.; Wright, J. E.; Seldes, A. M. *Phytochemistry* **2000**, *54*, 941; (b) Fujino, M.; Kamiya, T.; Iwasaki, H.; Ueyanagi, J.; Miyake, A. *Chem. Pharm. Bull.* **1964**, *12*, 1390; (c) Yamamoto, Y.; Nishimura, K. I.; Kiriyama, N. *Chem. Pharm. Bull.* **1976**, *24*, 1853; (d) Arai, K.; Shimizu, S.; Taguchi, Y.; Yamamoto, Y. *Chem. Pharm. Bull.* **1981**, *29*, 991.
4. Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 1921.
5. Kogan, T. P.; Somers, T. C.; Venuti, M. C. *Tetrahedron* **1990**, *46*, 6623.
6. Data for **13**: $[\alpha]_D^{25}$ 89.3 (*c* 0.52, $CHCl_3$). IR (neat): 3444, 3357, 2980, 1718, 1167, 1025, 743 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 9H), 1.72 (s, 6H), 3.38 (s, 3H), 3.65 (s, 3H), 4.54 (d, 1H, $J=6.9$ Hz), 4.14 (d, 1H, $J=6.6$ Hz), 4.82 (m, 1H), 5.14 (d, 1H, $J=17.1$ Hz), 5.15 (m, 1H), 5.22 (d, 1H, $J=11.1$ Hz), 5.28 (d, 1H, $J=6.3$ Hz), 6.12 (dd, 1H, $J=10.8$ Hz, $J=17.1$ Hz), 7.05–7.16 (m, 2H), 7.30 (s, 1H), 7.50 (d, 1H, $J=8.1$ Hz), 7.74 (d, 1H, $J=6.6$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.90, 28.20, 52.02, 55.62, 58.07, 59.20, 72.46, 79.73, 93.74, 109.22, 113.94, 114.18, 119.92, 120.57, 121.83, 124.65, 128.42, 135.87, 143.81, 155.02, 181.49 ppm. EI MS (*m*/*z*): 384 (M^+–62). Anal. calcd for $C_{24}H_{34}N_2O_6$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.51; H, 7.46; N, 6.13.
7. Hoffman, R. V.; Maslouh, N.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045.
8. Data for **14**: ^1H NMR ($CDCl_3$, 300 MHz): δ 0.08 (s, 6H), 0.90 (s, 9H), 1.76 (s, 6H), 3.75 (m, 2H), 4.15 (m, 1H), 5.19

(d, 1H, $J=17.4$ Hz), 5.24 (d, 1H, $J=10.8$ Hz), 5.50 (brs, 1H), 5.57 (d, 1H, $J=6.0$ Hz), 6.12 (dd, 1H, $J_1=10.8$ Hz, $J_2=17.4$ Hz), 7.10–7.20 (m, 2H), 7.36 (s, 1H), 7.53 (m, 1H), 7.66 (m, 1H) ppm. EI MS (m/z): 414 (M^+). Data for **15**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ −0.14 (s, 6H), 0.80 (s, 9H), 1.76 (s, 6H), 3.24 (dd, 1H, $J_1=3.9$ Hz, $J_2=10.5$ Hz), 3.38 (dd, 1H, $J_1=8.4$ Hz, $J_2=10.5$ Hz), 4.18 (td, 1H, $J_1=8.4$ Hz, $J_2=3.9$ Hz), 5.13 (d, 1H, $J=17.1$ Hz), 5.22 (d, 1H, $J=10.8$ Hz), 5.43 (s, 1H), 6.06 (d, 1H, $J=7.8$ Hz), 6.12 (dd, 1H, $J_1=10.8$ Hz, $J_2=17.4$ Hz), 7.08–7.18 (m, 1H), 7.36 (s, 1H), 7.44 (m, 1H), 7.52 (m, 1H) ppm. EI MS (m/z): 414 (M^+).