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Syntheses of four unusual amino acids, constituents of cyclomarin A

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Abstract—The stereoselective syntheses of four unusual amino acids, constituents of cyclomarin A, are described. The protected *N*-methylhydroxyleucine **2** was synthesized using Evans' asymmetric azide-transfer reaction. The unusual amino acid **3** was prepared via diastereoselective methylation of the L-aspartic acid derived lactone **13**. The stereoselective formation of threo-β-methoxyphenylalanine **4** was performed via aldol reaction using Schöllkopf's chiral glycine enolate. The synthesis of *N*-reverse prenylated tryptophane **5** was achieved by the AQN ligand-promoted Sharpless regioreversed asymmetric aminohydroxylation protocol.

Marine organisms are emerging as a significant new chemical resource for drug discovery. Many products having interesting biological activities and structural features have been isolated from this new source.[1] Cyclomarin A (**1**) is a novel cyclic peptide isolated from the marine bacterium *Streptomyces* sp. by Fenical and co-workers.[2] The structure of **1** has been determined from the X-ray crystallographic analysis of its diacetate derivative.[2c] Most importantly, this structure contains four structurally interesting unusual amino acids, which have previously never been reported (Fig. 1). Cyclomarin A (**1**) exhibits significant anti-inflammatory properties in both in vitro and in vivo assays. Furthermore, **1** has been licensed to Phytera Inc. for therapeutic application, where preclinical trials are currently underway.[1,2b] In continuous studies on the syntheses of biologically active aquatic natural products,[3] we have been interested in the synthesis of cyclomarin A due to its unique structure as well as important biological activities. In this paper, we wish to report efficient syntheses of four unusual amino acid components **2**–**5** for the construction of the cyclomarin A molecule (**1**).

We first started the synthesis of *N*-methylhydroxyleucine precursor (**2**) using Evans' asymmetric azide-transfer reaction,[4] as shown in Scheme 1. The half

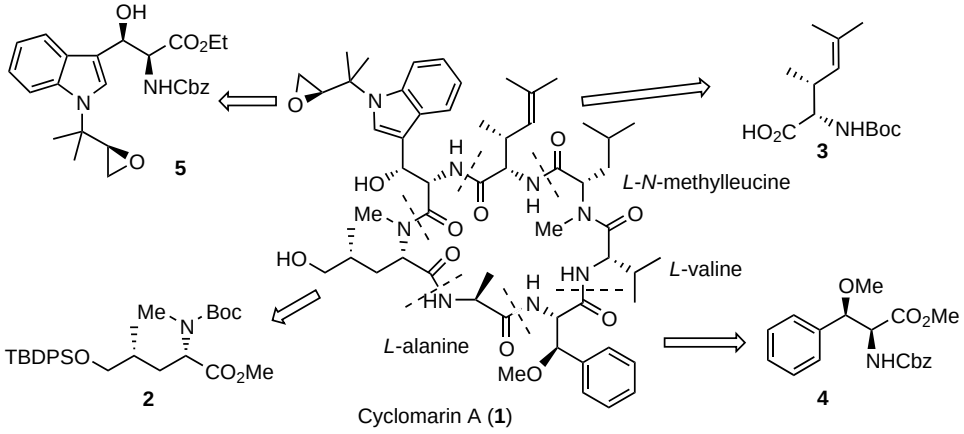

Figure 1.

Keywords: cyclomarin A; Evans' asymmetric azide-transfer reaction; Schöllkopf's aldol reaction; Sharpless aminohydroxylation.
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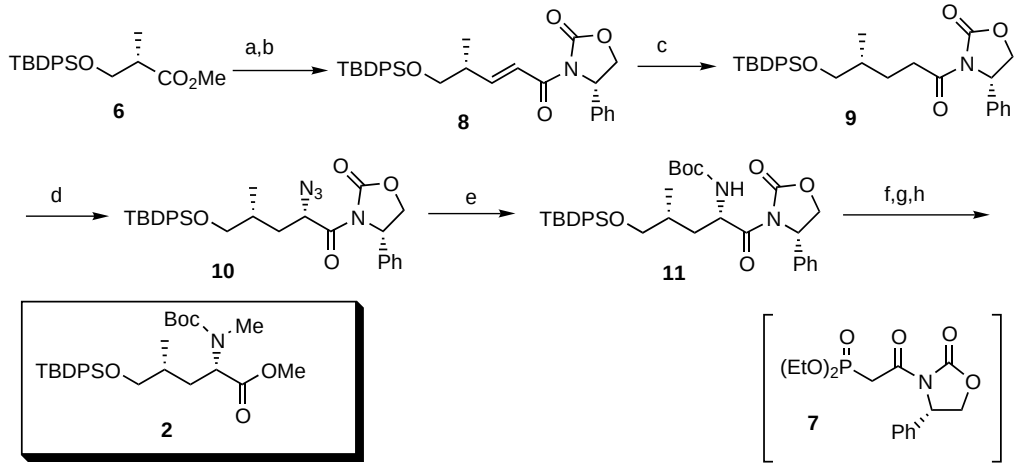
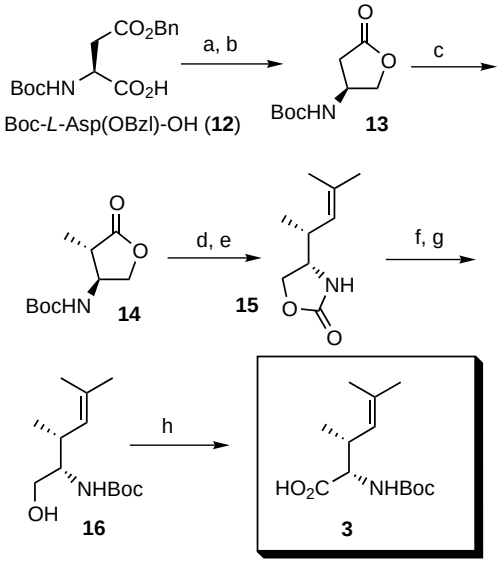


Scheme 1. (a) DIBAL, ether, −78°C. (b) LiCl, *i*-Pr_2NEt, **7**, MeCN, rt, 79% in two steps. (c) H_2, 5% Pd/C, EtOAc, 97%. (d) KHMDS, THF, −78°C; trisyl azide, −78°C, 2 min, AcOH, rt, 82%, single diastereomer. (e) H_2, 5% Pd/C, Boc_2O, EtOAc, 88%. (f) aqueous LiOH, 30% aqueous H_2O_2, THF. (g) NaH, MeI, THF, 0°C to rt. (h) MeI, $KHCO_3$, DMF, 85% in three steps.

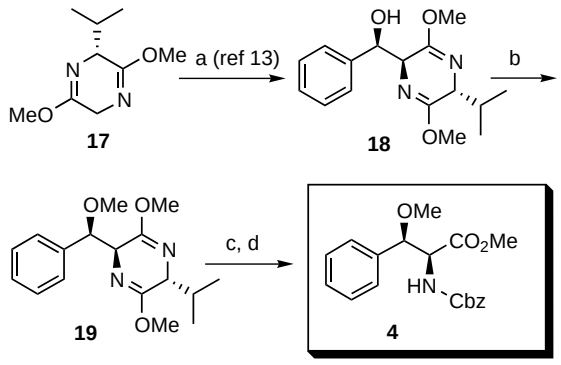
reduction of the methyl ester **6**[5] by DIBAL followed by the Horner–Emmons reaction of the resulting aldehyde with the phosphonate **7**[6] attached to the chiral auxiliary under Masamune–Roush conditions[7] gave the (*E*)-enimide **8** in 79% yield as a single geometric isomer. After the enimido **8** was hydrogenated to the *N*-acyl oxazolidinone **9**, the deprotonation of **9** using KHMDS at −78°C, followed by reaction of the enolate with trisyl azide according to Evans' procedure,[4] afforded the azide derivative **10** in 82% yield. The unwanted azide diastereomer was not detected by the ^1H NMR analysis of the crude reaction mixture. Catalytic hydrogenation over Pd/C in the presence of Boc_2O gave the *N*-Boc imido **11** in good yield. Subsequent cleavage of the chiral auxiliary[8] and *N*-methylation using Benoiton's procedure,[9] followed by methyl esterification provided the desired product **2** in high yield.

The introduction of the β-methyl group of the second unusual amino acid **3** would be achieved by diastereoselective methylation using the lactone **13** having the α-chirality which originally existed in L-aspartic acid.[10a] The requisite lactone **13**[11] was prepared from Boc-L-Asp(OBzl)-OH by reduction of the carboxylic acid via the mixed anhydride, and then acid-catalyzed lactonization. Enolization of **13** with LDA followed by the treatment with methyl iodide gave a diastereomeric mixture in a ratio of 10:1, which was readily separated by silica gel column chromatography to afford **14**[10b] in 67% yield. After the reduction of the lactone to the lactol, the Wittig homologation to introduce the isopropylidene group gave the oxazolidinone **15**, which arose from the attack of the alkoxide on the Boc carbonyl group. Reinstallation of the Boc group followed by the hydrolysis of oxazolidinone afforded the amino alcohol **16** in high yield. Finally, regeneration of the carboxyl group without epimerization was achieved by PDC oxidation of the alcohol[12] to give **3** in 88% yield (Scheme 2).

The *threo*-β-methoxyphenylalanine **4** was synthesized in four steps via the aldol reaction using the Schöllkopf's chiral glycine enolate[13] (Scheme 3). Titanium enolate derived from the bislactim ether **17**[13b] was treated with benzaldehyde to give the known aldol adduct **18**[13c] as a single diastereomer. The *O*-methylation required considerable optimization and was finally accomplished with $Me_3O^+\cdot BF_4^{-}$[14] and a Proton sponge® at 4°C to afford the desired product **19** in 51% yield. Removal of the chiral auxiliary with aqueous TFA followed by protection of the resulting amine as a benzyl carbamate afforded **4** in high yield.

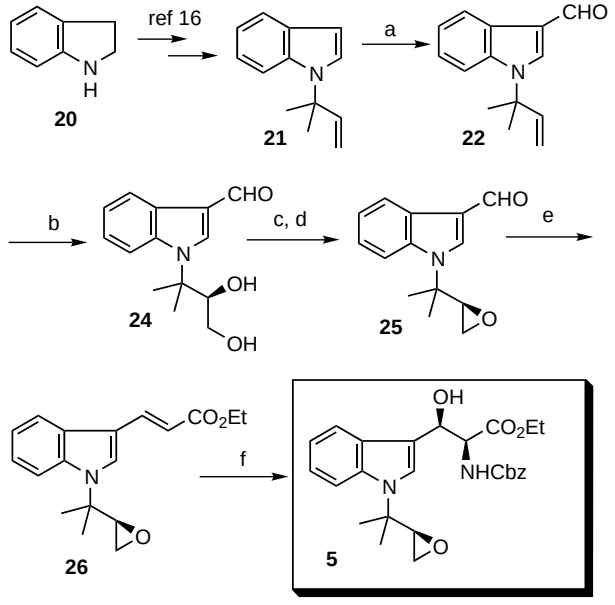


Scheme 2. (a) $ClCO_2Et$, Et_3N, THF, $NaBH_4$, H_2O. (b) cat. TFA, toluene, 52% in two steps. (c) LDA (2.1 equiv.), THF, −78°C; MeI, 67%. (d) DIBAL, CH_2Cl_2, −78°C, 87%. (e) *n*-BuLi, *i*-$PrP^+Ph_3P\cdot I^-$, THF, 85%. (f) Boc_2O, DMAP, THF, 96%. (g) 1N aqueous NaOH, THF–MeOH, 90%. (h) PDC, DMF, rt, 88%.



Scheme 3. (a) *n*-BuLi, THF, −78°C; $ClTi(NEt_2)_3$, *n*-hexane; PhCHO, 78%. (b) $Me_3O{\cdot}BF_4$, Proton sponge®, CH_2Cl_2, 4°C, 51% (11% recovered). (c) 1N aqueous TFA, MeCN–THF. (d) CbzCl, Et_3N, THF, 92% in two steps.

The remaining unusual amino acid, the *N*-reverse prenylated tryptophan **5**, has the same configuration as **4**. However, the above Schöllkopf's aldol method could not be used in the synthesis of **5** because the cleavage of the bislactim ether was not suitable for acid sensitive β-hydroxytryptophan, which has a vinylogous aminal structure. Therefore, we employed the AQN ligand-promoted Sharpless asymmetric aminohydroxylation (AA)[15] of the α,β-unsaturated aryl ester for the synthesis of the β-hydroxy tryptophan derivative. Previously, we reported the efficient synthesis of the unique *N*-reverse prenylated indole **21**[16] from indoline **20**, and we used **21** as a starting material for the synthesis of **5**. Vilsmeier formylation[17] of **21** quantitatively afforded



Scheme 4. (a) $POCl_3$, DMF, rt; 1N aqueous NaOH, 50°C, quantitative. (b) $K_2[OsO_2(OH)_4]$ (4 mol%), $(DHQD)_2PYR$ (5 mol%), $K_3Fe(CN)_6$, K_2CO_3, *tert*-BuOH–H_2O, 4°C. (c) TsCl, Et_3N, cat. $Me_3N{\cdot}HCl$ (0.1 equiv.), CH_2Cl_2, 0°C. (d) K_2CO_3, MeOH, 0°C, 73% in three steps. (e) NaH, triethyl phosphonoacetate, THF, 0°C to rt, 83%. (f) $K_2[OsO_2(OH)_4]$ (8 mol%), $(DHQD)_2AQN$ (10 mol%), *t*-BuOCl (4 equiv.), 1N aqueous NaOH (4 equiv.), $CbzNH_2$ (4 equiv.), *n*-PrOH–H_2O, rt, 36%.

the 3-formylindole **22**. The Sharpless asymmetric dihydroxylation (AD)[18] of the terminal olefin in the reverse prenyl group using $(DHQD)_2PYR$ as a chiral ligand[16,18b] followed by the conversion to the epoxide via tosylation[19] gave the epoxide **25** in 73% yield (three steps). The enantiomeric excess of **25** was 85%, which was determined by chiral HPLC.[20] The epoxide **25** subjected to the Horner–Emmons reaction with triethyl phosphonoacetate gave the requisite *E*-olefin **26** in 83% yield as a single stereoisomer. The pivotal Sharpless AA of **26** proceeded as expected to afford the desired β-hydroxytryptophan fragment **5** in 36% yield (Scheme 4).[21]

In summary, we have accomplished the efficient synthesis of four novel unusual amino acids as appropriate protected forms, which were useful for the total synthesis of cyclomarin A (**1**). Experiments toward this end are actively being carried out in our laboratory.

Acknowledgements

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20. HPLC analysis of **25** was carried out as follows; column: Daicel CHIRALCEL OD; solvent: *n*-hexane:*i*-PrOH = 9:1; flow rate: 1.2 ml/min; detector: 254 nm; retention time: 37.9 ((*S*)-isomer) and 40.8 min ((*R*)-isomer). The enantiomeric purity of **25** was 85% ee. The absolute configuration was assumed from the result of Ref. 16 and the mnemonic model of the Sharpless AD (Ref. 18a).
21. It is likely that this AA methodology regioselectively introduced the α-amino-β-hydroxy acid moiety. However, product **5** was rather unstable under this condition and underwent a retro-aldol reaction to afford the aldehyde **22**. The diastereoselectivity in AA was 95:5 as determined by the ^{1}H NMR of the corresponding MTPA amide of **5**.