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Synthesis of an Oxazoline Analogue of Apratoxin A

Bin Zou, Jingjun Wei, Guorong Cai, and Dawei Ma*

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

madw@pub.sioc.ac.cn

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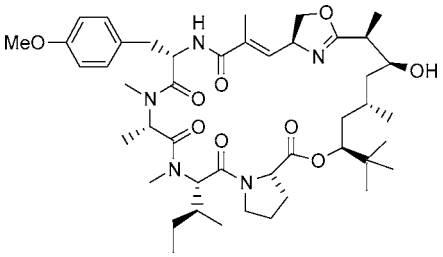
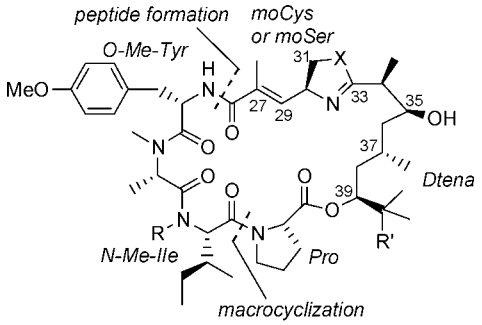
ABSTRACT



Michael addition of $Me_2Cu(CN)Li_2$ to α,β-unsaturated lactone 7 derived from β-hydroxyl ketone 5 provides lactone 8, which is converted to alcohol 11 using Oppolzer's methodology as the key step. Connection of 11 with the L-proline moiety and subsequent installation of an oxazoline ring affords 16, which is coupled with tripeptide 21; subsequent macrocyclization then furnishes 4, an oxazoline analogue of apratoxin A.

Apratoxin A (**1**, Figure 1) is a cyclodepsipeptide bearing both peptide and polyketide moieties isolated from the marine cyanobacterium *Lyngbya majuscula* by Moore and co-workers.[1] One year later, two other analogues, apratoxins B and C (**2** and **3**, Figure 1) were discovered by further organism collections and isolations.[2] Through in vitro studies on cytotoxicity against several human tumor cell lines, apratoxin A was found to have IC_{50} values ranging from 0.36 to 0.52 nM. However, in vivo antitumor investigation indicated that **1** was poorly tolerated in mice mainly due to lack of selectivity for different cell lines.[1] Structure−activity relationship (SAR) studies on this compound might provide a cure for this problem. In fact, the different cytotoxicity pattern displayed by **1**−**3** has already demonstrated that their cytotoxicity is highly dependent on their primary structures. It was reported that **3** possesses almost identical IC_{50} values for in vitro cytotoxicity in comparison with **1**, but **2** is significantly less cytotoxic than **1**.[2] To initiate SAR studies we decided to explore an efficient synthesis of apratoxin A and its analogues. Recently, Forsyth and Chen disclosed an



1: X = S, R = R' = Me, apratoxin A
2: X = S, R = H, R' = Me, apratoxin B
3: X = S, R = Me, R' = H, apratoxin C
4: X = O, R = R' = Me, oxazoline analogue of apratoxin A

Figure 1. Structures of apratoxins A−C and an oxazoline analogue of apratoxin A.

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(2) Leusch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J. *Bioorg. Med. Chem. Lett.* **2002**, *10*, 1973−1978.

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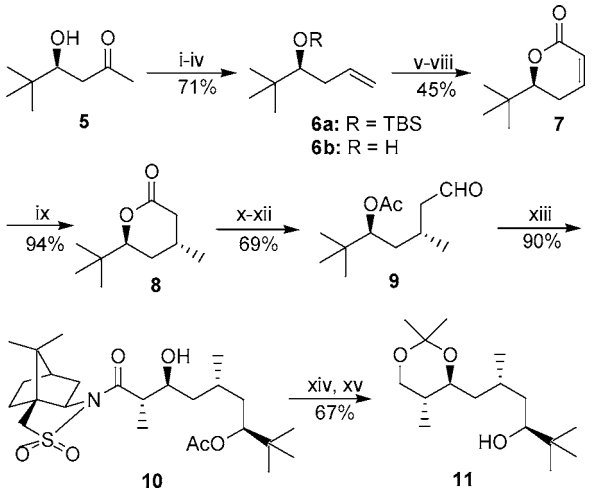
Scheme 1[a]



[a] Reagents and conditions: (i) TBSCl/imidazole, DMF, rt; (ii) $NaBH_4$, MeOH, 0 °C; (iii) MsCl/Et_3N, CH_2Cl_2, rt; (iv) *t*-BuOK, toluene, reflux; (v) O_3/Me_2S; (vi) $LiCH_2CO_2Et$, THF, −78 °C; (vii) 40% HF, MeCN, rt; (viii) MsCl/Et_3N, CH_2Cl_2, 0 °C to rt; (ix) $Me_2(CuCN)Li_2$, ether, −78 °C; (x) LAH, THF, reflux; (xi) AcCl/Py, CH_2Cl_2, 0 °C, then K_2CO_3, MeOH; (xii) Dess−Martin oxidation; (xiii) *N*-propionylsultam/Et_2BOTf/DIPEA, CH_2Cl_2, −15 °C, then **9**, $TiCl_4$, −78 °C; (xiv) LAH, THF, reflux; (xv) DMP/PPTs.

elegant total synthesis of apratoxin A[3] based on their newly developed methodology for preparing thiazoline,[4] which prompted us to report here our result on the synthesis of **4**, an oxazoline analogue of apratoxin A. Obviously, this compound may still have potent cytotoxicity activity as apratoxin A, but its total synthesis may be simpler than that of **1** because there exist more convenient methods to form oxazolines in comparison with thiazolines.[5,6]

Structurally, **4** contains a novel 3,7-dihydroxy-2,5,8,8-tetramethylnonanoic acid (Dtena) unit, which connects with a modified serine moiety (moSer) by an oxazoline ring, and a tetrapeptide unit possessing a high degree of methylation at the L-proline site. We planned to synthesize **4** in a convergent manner as illustrated in Figure 1, that is, peptide formation between the *O*-Me-Tyr and moSer sites and macrocyclization at the *N*-Me-IIe-Pro site.

The synthesis of enantiopure 3,7-dihydroxy-2,5,8,8-tetramethylnonanoic acid (Dtena) precursor **11** is outlined in Scheme 1. *β*-Hydroxyl ketone **5** (>99% ee), an aldol reaction product of trimethylacetaldehyde with acetone catalyzed by D-proline,[7] was employed as the starting material. After protection of **5** with TBSCl, the ketone moiety was reduced with $NaBH_4$ and the resultant alcohol was subjected to elimination through its mesylate to afford allyl ether **6a**. It is notable that we initially attempted asymmetric allylboration of trimethylacetaldehyde according to Brown's procedure in order to obtain allyl alcohol **6b**.[8] However, an inconvenient workup operation *(it was found that the desired product was difficult to separate from the resultant isopinocampheol by either distillation or column chromatography)* made us give up this direct synthesis. Next, ozonolysis of **6a** provided an aldehyde, which was condensed with $LiCH_2CO_2Et$ at −78 °C followed by cyclization and elimination to give the α,*β*-unsaturated lactone **7**. Methylcupration with $Me_2Cu(CN)Li_2$ served as an excellent method[9] for installing the C37 methyl group in a highly diastereoselective fashion to provide **8** in 94% yield as a single diastereomer as detected by ^1H NMR. After LAH reduction of the lactone **8** to produce a diol and then protection of it with acetic chloride, selective deprotection with K_2CO_3 was carried out in methanol. Subsequent Dess−Martin oxidation of the resulting primary alcohol delivered aldehyde **9**.

For the assembly of the C33−C35 unit in the target molecule, Oppolzer's methodology[10] for preparing *anti*-diols from bornanesultam-derived boryl enolates appeared to be particularly attractive. Toward this end, treatment of *N*-propionylsultam with Et_2BOTf resulted in a (*Z*)-enolate, which was reacted with the aldehyde **9** under the action of $TiCl_4$ to afford "*anti*"-aldol **10** in 90% yield as the only detectable diastereomer. It is noteworthy that 8 equiv of $TiCl_4$ was necessary in this case to ensure the high yield. Finally, removal of both the chiral auxiliary and the acyl group by LAH reduction gave a triol, which was protected with DMP to furnish **11** in 67% yield.

With the alcohol **11** in hand, our next task was to connect it with the L-proline unit on the right side followed by subsequent installation of an oxazoline ring bearing an α,*β*-unsaturated ester side chain on the left side. As outlined in Scheme 2, esterification of **11** with *N*-Fmoc-L-proline using Yamaguchi's procedure[11] worked well to produce **12** in 90% yield. Liberation of the diol moiety in **12** with TsOH in methanol followed by selective oxidation of the primary alcohol using hindered chloro oxammonium salt generated from TEMPO/NaClO afforded an aldehyde, which was further oxidized with $NaClO_2$ to provide acid **13**.[12] In a parallel procedure, α,*β*-unsaturated ester **14**, prepared by a Wittig olefination reaction of (*R*)-Garner aldehyde and the corresponding ylide, was treated with 3:1 trifluoroacetic acid and water to give liberated amine. Coupling of this amine with the acid **13** mediated with HATU and DIPEA (diisopropylethylamine) furnished **15** in 90% yield. The oxazoline

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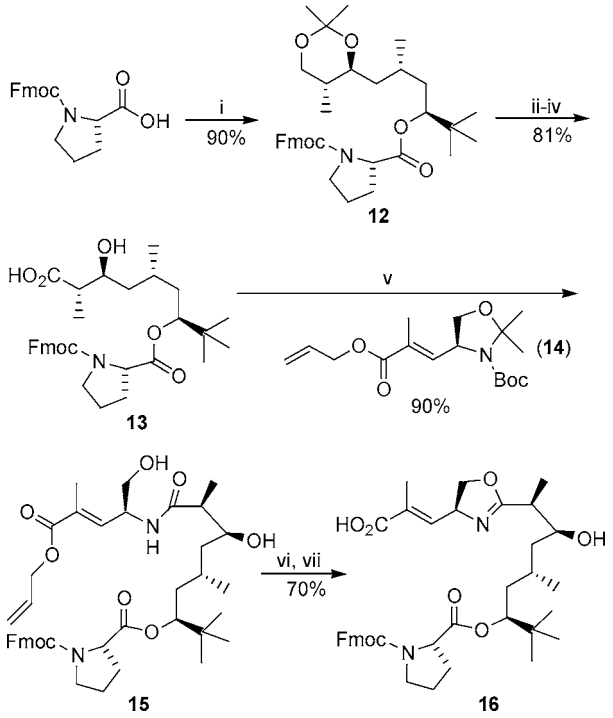
Scheme 2[a]

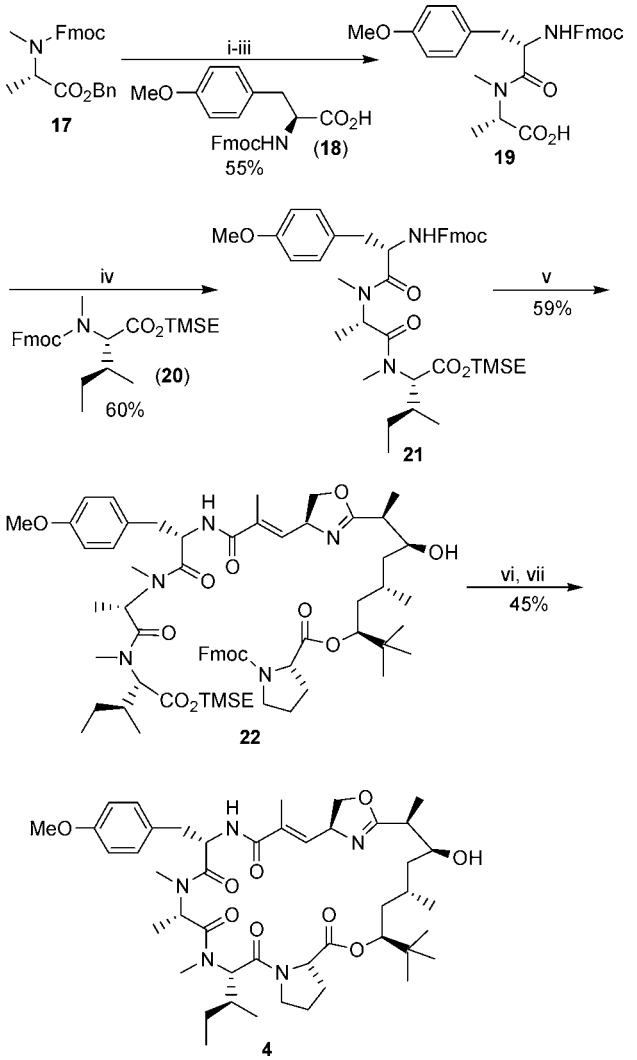


[a] Reagents and conditions: (i) 2,4,6-trichlorobezoyl chloride, DIPEA, benzene then **11**, DMAP, rt; (ii) TsOH, MeOH, rt. (iii) TEMPO, NaClO, aq $NaHCO_3$, CH_2Cl_2, 0 °C; (iv) NaH_2PO_4/$NaClO_2$, *t*-BuOH, H_2O, 2-methylbutene; (v) **14**/TFA/H_2O, then **13**/HATU/DIPEA, CH_2Cl_2, rt. (vi) DAST, CH_2Cl_2, −78 °C; (vii) $Pd(PPh_3)_4$, *N*-methylaniline, THF, rt.

ring formation was achieved through exposure of **15** to 2.5 equiv of DAST in methylene chloride at −78 °C.[13] Subsequent cleavage of allyl ester catalyzed by $Pd(PPh_3)_4$ under the assistance of *N*-methylaniline resulted in acid **16** in 70% yield over two steps.[14] It is notable that the utilization of *N*-methylaniline as the base was essential for this step because other bases employed such as morpholine were found to cause the simultaneous cleavage of the N^{α}-Fmoc protecting group during the above deprotection reaction.

For the synthesis of the highly methylated tripeptide part, 2-bromo-1-ethyl pyridinium tetrafluoroborate (BEP), an efficient coupling reagent for hindered peptide synthesis developed by Xu and Li, was used for peptide formation.[15] As shown in Scheme 3, deprotection of **17** with diethylamine in acetonitrile followed by amide formation with *N*-Fmoc-*O*-methyl-L-tyrosine **18** under the assistance of BEP gave a dipeptide, which was subjected to Pd/C-catalyzed hydrogenolysis to afford acid **19** in 55% yield over three steps. Cleavage of the Fmoc group in **20** and subsequent connection of the liberated amine with **19** mediated with BEP resulted in tripeptide **21**. Next, treatment of **21** with diethylamine in acetonitrile produced a free amine, which was coupled with

Scheme 3[a]



[a] Reagents and conditions: (i) Et_2NH, MeCN, rt; (ii) **18**/BEP/DIPEA, CH_2Cl_2, rt; (iii) Pd/C/H_2, EtOAc; (iv) **20**/Et_2NH, MeCN, then **19**/BEP/DIPEA, CH_2Cl_2, rt; (v) Et_2NH, MeCN, then **16**/HATU/DIPEA; (vi) TBAF, THF; (vii) HATU/DIPEA, CH_2Cl_2 (0.002 M), rt.

the acid **16** to afford **22** in 59% yield. The stage was now set for the crucial macrocyclization. We were gratified to observe that after removal of the Fmoc and TMSE protecting groups with TBAF in one pot, the target molecule **4**[16] was obtained in 45% yield by treatment the resultant amino acid with HATU/DIPEA in a diluted methylene chloride solution.

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(15) Li, P.; Xu, J.-C. *Tetrahedron* **2000**, *56*, 8119−8131.

(16) Selected data for **4**: $[\alpha]^{20}_D$ −117.5 (*c* 0.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.2 Hz, 2H), 6.21 (d, J = 9.3 Hz, 1H), 6.01 (d, J = 9.3 Hz 1H), 5.25 (d, J = 11.5 Hz, 1H), 5.05 (td, J = 10.2, 5.6 Hz, 1H), 4.97 (d, J = 11.6 Hz, 1H), 4.81 (m, 1H), 4.70 (d, J = 10.6 Hz, 1H), 4.38 (m, 1H), 4.20 (m, 1H), 3.78 (s, 3H), 3.70−3.55 (m, 3H), 3.28 (br q, J = 6.7 Hz, 1H), 3.15 (d, J = 3.8 Hz, 1H), 3.10 (d, J = 11.7 Hz, 1H), 2.85 (dd, J = 12.7, 4.6 Hz, 1H), 2.81 (s, 3H), 2.75 (s, 3H), 2.65 (d, J = 13.5 Hz, 1H), 2.33 (m, 1H), 2.25 (m, 1H), 2.15 (m, 1H), 2.05 (m, 1H), 1.92 (s, 3H), 1.90−1.75 (m, 3H), 1.45 (m, 1H), 1.31 (m, 1H), 1.26 (m, 1H), 1.25 (s, 3H), 1.10 (m, 1H), 1.07 (d, J = 6.9 Hz, 3H), 1.01 (t, J = 7.0 Hz, 3H), 0.99 (d, J = 6.4 Hz, 3H), 0.96 (m, 1H), 0.95 (d, J = 7.6 Hz, 3H), 0.87 (s, 9H); ESI-MS *m*/*z* 824 $(M + H)^+$; HRMS calcd for $C_{45}H_{70}N_5O_9$ $(M + H)^+$ 824.5168, found 824.5160.

In conclusion, we have described here an efficient route to synthesize an oxazoline analogue of apratoxin A. Notable elements include a highly diastereoselective assembly of the Dtena moiety and subsequent installation of the oxazoline ring bearing an α,β-unsaturated ester side chain. In addition, the success in macrocyclization at the *N*-Me-IIe-Pro site demonstrates again that this site is a suitable macrolactamization site for synthesizing apratoxins and their analogues.[3] Extension of these investigations to the total synthesis of apratoxin A and other analogues, as well as the biological evaluation of the synthesized compounds, is being actively pursued in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterizations for compounds **6a**, **7**−**13**, **15**, **16**, **19**, **21**, **22**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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