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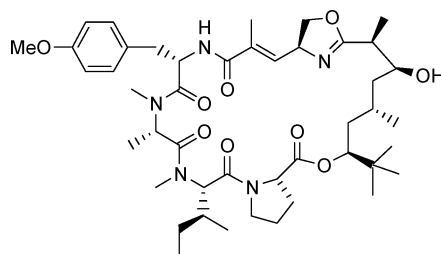
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Received July 18, 2003

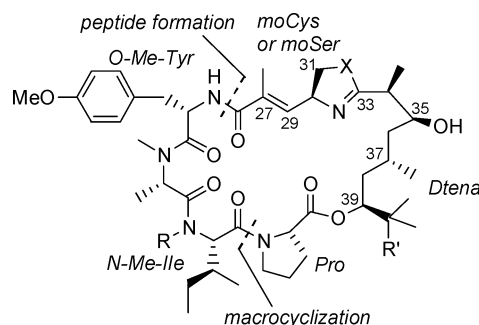
ABSTRACT



Michael addition of $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$ 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

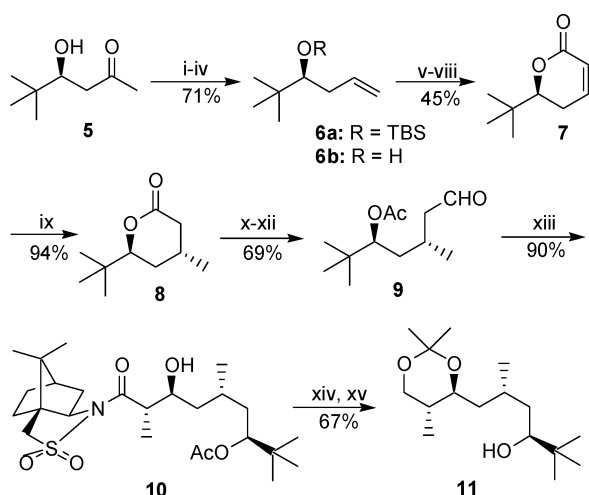


- 1:** X = S, R = R' = Me, apratoxin A
2: X = S, R = H, R' = Me, apratoxin B
3: X = S, R = Me, R' = H, apratoxin C
4: X = O, R = R' = Me, oxazoline analogue of apratoxin A

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

(1) Leusch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J.; Corbett, T. H. *J. Am. Chem. Soc.* **2001**, *123*, 5418–5423.

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

Scheme 1^a

^a Reagents and conditions: (i) TBSCl/imidazole, DMF, rt; (ii) NaBH₄, MeOH, 0 °C; (iii) MsCl/Et₃N, CH₂Cl₂, rt; (iv) *t*-BuOK, toluene, reflux; (v) O₃/Me₂S; (vi) LiCH₂CO₂Et, THF, -78 °C; (vii) 40% HF, MeCN, rt; (viii) MsCl/Et₃N, CH₂Cl₂, 0 °C to rt; (ix) Me₂(CuCN)Li₂, ether, -78 °C; (x) LAH, THF, reflux; (xi) AcCl/Py, CH₂Cl₂, 0 °C, then K₂CO₃, MeOH; (xii) Dess–Martin oxidation; (xiii) *N*-propionylsultam/Et₃BOTf/DIPEA, CH₂Cl₂, -15 °C, then 9, TiCl₄, -78 °C; (xiv) LAH, THF, reflux; (xv) DMP/PPTs.

elegant total synthesis of apratoxin A³ 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 (Dtēna) 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-Ile-Pro site.

The synthesis of enantiopure 3,7-dihydroxy-2,5,8,8-tetramethylnonanoic acid (Dtēna) 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 NaBH₄ 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 LiCH₂CO₂Et at -78 °C followed by cyclization and elimination to give the α,β -unsaturated lactone **7**. Methylcupration with Me₂Cu(CN)-Li₂ served as an excellent method⁹ 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 K₂CO₃ 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 methodology¹⁰ for preparing *anti*-diols from bornanesultam-derived boryl enolates appeared to be particularly attractive. Toward this end, treatment of *N*-propionylsultam with Et₂BOTf resulted in a (*Z*)-enolate, which was reacted with the aldehyde **9** under the action of TiCl₄ to afford "*anti*"-aldol **10** in 90% yield as the only detectable diastereomer. It is noteworthy that 8 equiv of TiCl₄ 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 procedure¹¹ 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 NaClO₂ 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

(3) Chen, J.; Forsyth, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 8734–8735.

(4) Chen, J.; Forsyth, C. J. *Org. Lett.* **2003**, *5*, 1281–1283.

(5) For reviews, see: (a) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115–2134.

(b) Wipf, P.; Venkatraman S. *Synlett* **1997**, 1–10.

(6) For recent leading references on the preparation of thiazoline and oxazoline rings, see: (a) McKeever, B.; Pattenden, G. *Tetrahedron* **2003**, *59*, 2701–2712. (b) Yokokawa, F.; Sameshima, H.; Katagiri, D.; Aoyama, T.; Shioiri, T. *Tetrahedron* **2002**, *58*, 9445–9458. (c) Kedrowski, B. L.; Heathcock, C. H. *Heterocycles* **2002**, *58*, 601–634. (d) Boden, C. D. J.; Norley, M.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 883–888. (e) Boden, C. D. J.; Norley, M.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 875–882.

(7) (a) List, B. *Synlett* **2001**, 1675–1685. (b) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573–575.

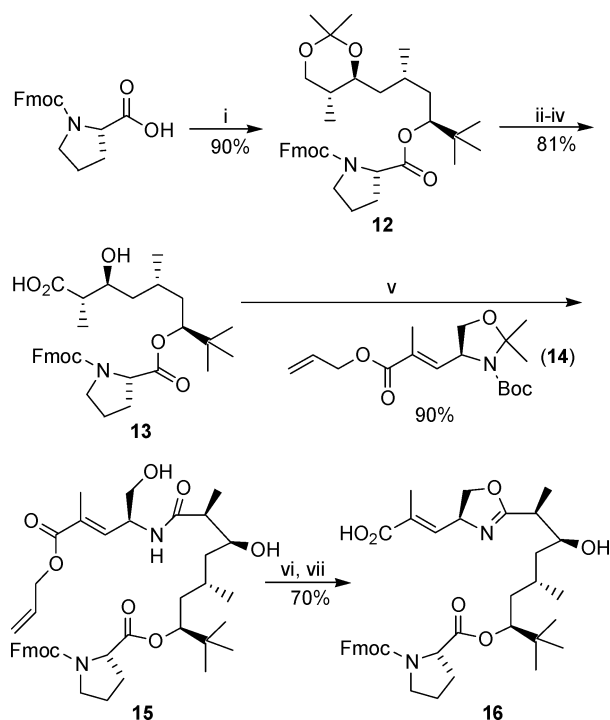
(8) (a) Rachelra, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401–401. (b) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432–439.

(9) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1980**, *45*, 4117–4121.

(10) Oppolzer, W.; Lienard, P. *Tetrahedron Lett.* **1993**, *34*, 4321–4324.

(11) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993. (b) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367–6370.

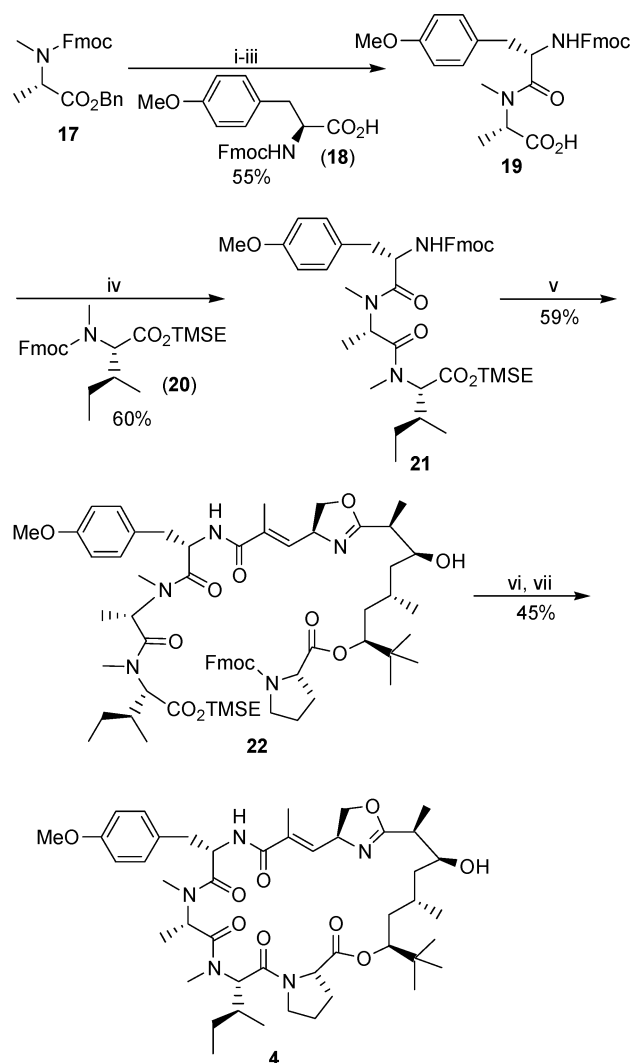
(12) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559–2562.

Scheme 2^a

^a Reagents and conditions: (i) 2,4,6-trichlorobenzoyl chloride, DIPEA, benzene then **11**, DMAP, rt; (ii) TsOH, MeOH, rt. (iii) TEMPO, NaClO, aq NaHCO₃, CH₂Cl₂, 0 °C; (iv) NaH₂PO₄/NaClO₂, *t*-BuOH, H₂O, 2-methylbutene; (v) **14**/TFA/H₂O, then **13**/HATU/DIPEA, CH₂Cl₂, rt. (vi) DAST, CH₂Cl₂, -78 °C; (vii) Pd(PPh₃)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(PPh₃)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) Et₂NH, MeCN, rt; (ii) **18**/BEP/DIPEA, CH₂Cl₂, rt; (iii) Pd/C/H₂, EtOAc; (iv) **20**/Et₂NH, MeCN, then **19**/BEP/DIPEA, CH₂Cl₂, rt; (v) Et₂NH, MeCN, then **16**/HATU/DIPEA; (vi) TBAF, THF; (vii) HATU/DIPEA, CH₂Cl₂ (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.

(16) Selected data for **4**: [α]_D²⁰ -117.5 (c 0.2, CHCl₃); ¹H NMR (500 MHz, CDCl₃) 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 C₄₅H₇₀N₅O₉ (M + H)⁺ 824.5168, found 824.5160.

(13) Lafargue, P.; Guenot, P.; Lellouche, J.-P. *Heterocycles* **1995**, *41*, 947–957.

(14) Ciommer, M.; Kunz, H. *Synlett* **1991**, 593–595.

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

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-Ile-Pro site demonstrates again that this site is a suitable macro-lactamization 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.

Acknowledgment. The authors are grateful to the Chinese Academy of Sciences, National Natural Science Foundation of China (Grant 20242003), and Science and Technology Commission of Shanghai Municipality (Grant 02JC14032) for their financial support. We thank Professor Tao Ye of The Hong Kong Polytechnic University for helpful discussion and for providing information about their results in this field.

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>.

OL035332Y