ORGANIC LETTERS

2000
Vol. 2, No. 26
4169−4172

Total Synthesis of the Antiviral Marine Natural Product (−)-Hennoxazole A

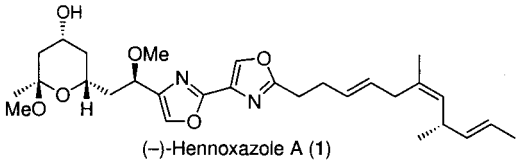
Fumiaki Yokokawa,* Toshinobu Asano, and Takayuki Shioiri

Faculty of Pharmaceutical Sciences, Nagoya City University,Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan

yokokawa@phar.nagoya-cu.ac.jp

Received October 9, 2000

ABSTRACT



(−)-Hennoxazole A (**1**)

The marine natural product hennoxazole A was synthesized by a convergent approach. The diastereoselective Mukaiyama aldol reaction with *β*-alkoxy aldehyde was used to construct the tetrahydropyran segment, and the preparation of the nonconjugated triene moiety was accomplished via S_N2 displacement of allylic bromide with vinyllithium and Takai's iodoolefination followed by palladium-catalyzed cross coupling with MeMgBr. The final steps involve an amide coupling using DEPC and oxazole synthesis via a oxidation/cyclodehydration process.

Hennoxazole A (**1**) was isolated from the marine sponge *Polyfibrospongia* sp. by Scheuer, Higa, and co-workers.[1] It has been found to be active against herpes simplex virus type 1 ($IC_{50} = 0.6\ \mu g/mL$) and displays peripheral analgesic activity. The most unique feature of its structure is a directly linked bisoxazole core, which is only found in the complex polycyclic marine alkaloid diazonamide A−B,[2] cyanobacterium-derived muscoride A,[3] and hennoxazole A.[4] Other unique structural features of hennoxazole A are a highly functionalized tetrahydropyranyl ring moiety and a nonconjugated triene unit. The unique structural features and interesting biological activity of hennoxazole A have attracted the attention of several synthetic research groups. Wipf and Lim have accomplished the total synthesis of the (+)-enantiomer of **1**, and their synthesis has elucidated the absolute configuration of **1** and relative stereochemistries at C_8 and C_{22}.[5] Recently, the total synthesis of (−)-hennoxazole A has been reported by Williams and co-workers.[6] In our program concerning the total synthesis of marine natural products,[7] we have also embarked on the total synthesis of hennoxazole A.[8,9] In this Letter, we wish to report our synthetic studies leading to the total synthesis of (−)-hennoxazole A (**1**).

Our strategy is a convergent approach that combines tetrahydropyran segment **2** and triene unit **3** via Wipf's oxidation/cyclodehydration process. The tetrahydropyran segment **2** could be obtained by acid-catalyzed ketalization of the methyl ketone **4**, which could be synthesized by the diastereoselective Mukaiyama aldol reaction. The triene unit

(1) (a) Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T. *J. Am. Chem. Soc.* **1991**, *113*, 3173−3174. (b) Higa, T.; Tanaka, J.; Kitamura, A.; Koyama, T.; Takahashi, M.; Uchida, T. *Pure Appl. Chem.* **1994**, *66*, 2227−2230.

(2) Lindquist, N.; Fenical, W.; Van Duyne, G. D. *J. Am. Chem. Soc.* **1991**, *113*, 2303−2304.

(3) Nagatsu, A.; Kajitani, H.; Sakakibara, J. *Tetrahedron. Lett.* **1995**, *36*, 4097−4100.

(4) Linked trisoxazole units have been found in some marine macrolides. (a) Ulapualides A and B (Roesener, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 846−847). (b) Halichondramides (Kernan, M. R.; Molinski, T. F.; Faulkner, J. D. *J. Org. Chem.* **1988**, *53*, 5014−5020). (c) Kabiramides A−E (Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Koseki, K.; Noma, M.; Noguchi, H.; Sankawa, U. *J. Org. Chem.* **1989**, *54*, 1360−1363). (d) Jaspisamides A−C (Kobayashi, J.; Murata, O.; Shigemori, H. *J. Nat. Prod.* **1993**, *56*, 787−791). (e) Mycalolides (Matsunaga, S.; Sugawara, T.; Fusetani, N. *J. Nat. Prod.* **1998**, *61*, 1164−1167, and references therein).

(5) (a) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558−559. (b) Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157−167.

(6) Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924−4925.

(7) For recent examples of our work, see: Sugiyama, H.; Yokokawa, F.; Shioiri, T. *Org. Lett.* **2000**, *2*, 2149−2152.

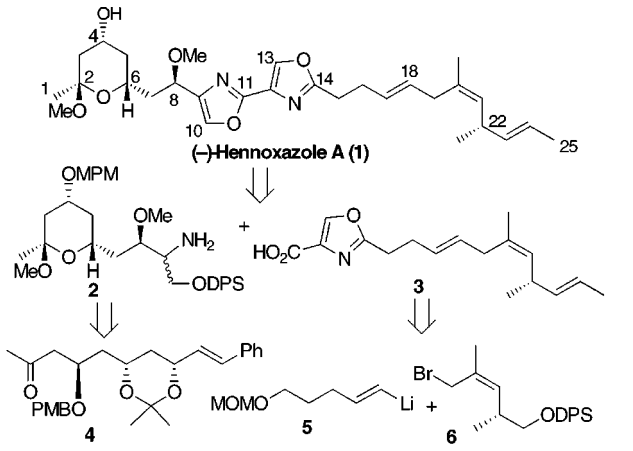
(8) For our preliminary synthetic studies on hennoxazole A, see: (a) Cheng, Z.; Hamada, Y.; Shioiri, T. *Synlett* **1997**, 109−110. (b) Shioiri, T.; McFarlane, N.; Hamada, Y. *Heterocycles* **1998**, *47*, 73−76.

(9) For other synthetic studies on hennoxazole A, see: Barrett, A. G. M.; Kohrt, J. T. *Synlett* **1995**, 415−416.

10.1021/ol000305i CCC: $19.00
Published on Web 12/01/2000

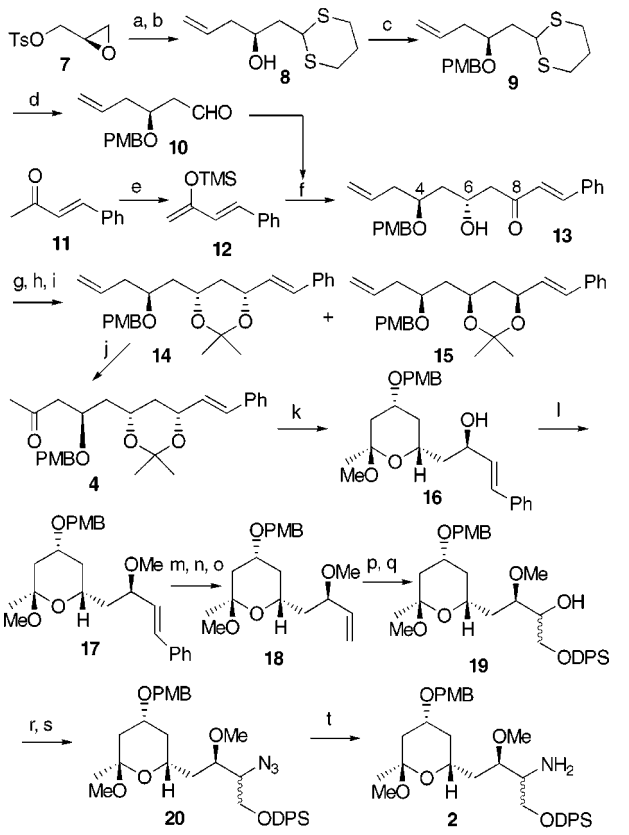
3 could be constructed by S_N2 displacement of allylic bromide **6** with vinyllithium **5** (Scheme 1).

Scheme 1



The synthesis of the tetrahydropyran segment **2** was started (Scheme 2) by treatment of commercially available (*R*)-glycidyl tosylate (**7**) with lithiated 1,3-dithiane followed by copper-catalyzed Grignard addition to afford the alcohol **8** in 63% yield. Protection of the alcohol **8** as its *p*-methoxybenzyl (PMB) ether **9** and removal of the 1,3-dithiane provided the aldehyde **10** in 64% yield. The $BF_3{\cdot}OEt_2$-mediated Mukaiyama aldol reaction between the trimethylsilyl enol ether **12** derived from benzalacetone (**11**) and the aldehyde **10** provided the aldol adduct **13** in 89% yield with good diastereoselectivity (88:12 *anti*:*syn*).[10] This transformation establishes the C_6 stereocenter with a good level of 1,3-*anti* induction.[12] Subsequent chelation-controlled reduction[13] of the C_8 ketones from the aldol reaction afforded the corresponding *syn* diols. Protection of the *syn* diols as acetonides followed by separation on silica gel gave the desired isomer **14** (59%),[14] the minor isomer **15** (9%),[14] and recovered starting diol (31%). The terminal olefin of **14** was converted to the methyl ketone **4** by the modified Wacker oxidation[16] in 77% yield. Mild acidic treatment of **4** caused cleavage of the acetonide and intramolecular ketalization simultaneously to produce the tetrahydropyran **16** in 85%

Scheme 2[a]



[a] (a) *n*-BuLi, 1,3-dithiane, THF; (b) vinylmagnesium bromide, CuI, THF, 63%; (c) KH, PMBCl, *n*-Bu_4NI, THF, 86%; (d) MeI, $CaCO_3$, aq. CH_3CN, 74%; (e) TMSOTf, Et_3N, CH_2Cl_2, 96%; (f) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 89% (88:12); (g) Et_2BOMe, $NaBH_4$, THF; (h) 2,2-dimethoxy propane, PPTs; (i) silica gel column chromatography **14**; 59%, **15**; 9%; (j) $PdCl_2$, $Cu(OAc)_2{\cdot}H_2O$, $AcNMe_2/H_2O$ (7:1), 77%; (k) PPTs, MeOH, 85%; (l) NaH, MeI, THF, 98%; (m) OsO_4, NMO, aq. acetone; (n) $NaIO_4$, pH 7 phosphate buffer, THF; (o) $Cp_2TiCH_2AlClMe_2$, THF, 72%; (p) OsO_4, NMO, aq. acetone; (q) DPSCl, Et_3N, DMAP, CH_2Cl_2, 94%; (r) MsCl, Et_3N, DMAP, CH_2Cl_2; (s) *n*-Bu_4NN_3, DMF, 100 °C, 68%; (*t*) Ph_3P, aq. THF, 55 °C, 68%.

yield. After *O*-methylation of **16**, oxidative cleavage of the styryl group in **17** followed by Tebbe olefination[17] afforded **18** in 71% yield. Dihydroxylation of terminal olefin **18** with osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO) and selective protection of the primary alcohol led to the mono-*tert*-butyldiphenylsilyl (DPS) ether **19** in 94% yield. Treatment of the resulting alcohol with methanesulfonyl chloride (MsCl) and displacement with *n*-Bu_4NN_3 provided the azide **20** in 68% yield. Mild reduction of the azide **20** with Ph_3P/H_2O completed the C_1-C_{10} tetrahydropyran segment **2** in 68% yield.

The synthesis of the triene unit (Scheme 3) was initiated by protection of methyl (*S*)-3-hydroxy-2-methylpropionate (**21**) as its DPS ether to give **22** in 95% yield. Diisobutylaluminum hydride (DIBAL) reduction of **22** afforded the

(10) The configuration of the newly formed hydroxyl stereogenic center of the aldol adduct **13** was established by NOE analysis of the corresponding *p*-methoxybenzylidene acetal, which was produced by treatment of the aldol adduct **13** under anhydrous condition with DDQ (see Supporting Information).[11]

(11) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron. Lett.* **1982**, *23*, 889−892.

(12) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343.

(13) Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923−1926.

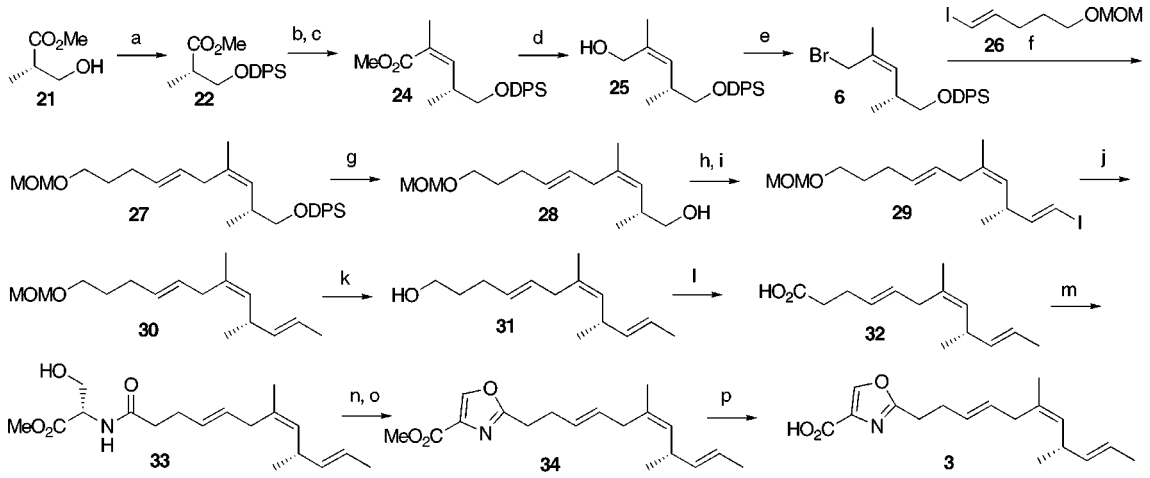
(14) The 1,3-*syn* relationships of the acetonides **14** and **15** were supported by analysis of their ^{13}C NMR spectra.[15]

(15) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron. Lett.* **1990**, *31*, 945−948. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron. Lett.* **1990**, *31*, 7099−7100. (c) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−3515.

(16) Smith, A. B., III; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765−8768.

(17) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611−3613.

Scheme 3[a]



[a] (a) DPSCl, imidazole, DMF, 95%; (b) DIBAL, Et_2O, −78 °C; (c) $(CF_3CH_2O)_2P(O)CH(CH_3)CO_2CH_3$ (**23**), KHMDS, 18-crown-6, THF, −78 °C, 48%; (d) DIBAL, Et_2O, −78 °C, 94%; (e) CBr_4, Ph_3P, CH_3CN, 99%; (f) **26**, *t*-BuLi, HMPA, THF, −78 °C, 53%; (g) TBAF, THF, 90%; (h) Py·SO_3, DMSO, Et_3N, CH_2Cl_2; (i) $CrCl_2$, CHI_3, THF, 68%; (j) MeMgBr, $Pd(Ph_3P)_4$, THF, quant.; (k) aq. HCl, MeOH, THF, 83%; (l) PDC, DMF, 72%; (m) DEPC, HCl·H-(*S*)-Ser-OMe, Et_3N, DMF, 91%; (n) Deoxo-fluor, CH_2Cl_2, −20 to −30 °C; (o) $BrCCl_3$, DBU, CH_2Cl_2, 80%; (p) aq. LiOH, THF, quant.

corresponding aldehyde, which was directly treated with the phosphonate **23** under (*Z*)-selective Still−Horner olefination conditions[18] to provide the (*Z*)-ester **24** in 48% yield as a single isomer. Reduction of the methyl ester **24** with DIBAL and bromination of the resulting allylic alcohol **25** using CBr_4 and Ph_3P gave the allylic bromide **6** in 93% yield.[19] After considerable experimentation,[20] S_N2 displacement of the allylic bromide **6** with vinyllithium derived from the vinyl iodide **26**[21] cleanly afforded the skipped diene **27** in 53% yield.[22] After deprotection of the DPS group, the resulting primary alcohol **28** was oxidized by the Parikh−Doering oxidation[23] to furnish the corresponding aldehyde, which was immediately subjected to the Takai's $CrCl_2$-mediated iodoolefination process[24] to give the (*E*)-vinyl idodide **29** in 61% yield. Cross coupling of the vinyl iodide **29** with MeMgBr in the presence of palladium catalyst[25] constructed the nonconjugated tiene unit **30** in quantitative yield. Removal of the methoxymethyl group (MOM), oxidation using pyridinium dichromate (PDC), followed by coupling with (*S*)-serine methyl ester using diethyl phosphorocyanidate (DEPC)[26] afforded the amide **33** in 54% yield. According to the Wipf and Williams' methodology,[27] dehydrative cyclization of the *β*-hydroxy amide **33** with bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-fluor) to the oxazoline followed by oxidation with $BrCCl_3$ and 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) provided the oxazole **34** in 80%

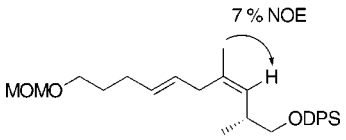
(18) (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408. (b) Hensel, M. J.; Fuchs, P. L. *Synth. Commun.* **1986**, *16*, 1285−1295. (c) Rathke, M. W.; Bouhlel, E. *Synth. Commun.* **1990**, *20*, 869−875.

(19) Cheng, Z.; Nakao, R.; Hamada, Y.; Shioiri, T. Unpublished results. We thank Dr. Z. Cheng and Mr. R. Nakao for their preliminary studies on the preparation of the triene unit.

(20) Stille coupling of allylic bromide or acetate with vinyl stannane caused the loss of the $C_{20}-C_{21}$ double bond stereochemistry to give the inseparable *E*/*Z* mixture.

(21) MOM ether **26** was preparaed by MOMCl, *i*-Pr_2NEt in CH_2Cl_2 from the known alcohol. Yamada, H.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1991**, *65*, 4569−4574.

(22) The *Z*-configuration of the $C_{20}-C_{21}$ double bond in **27** was confirmed by NOE analysis.



(23) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

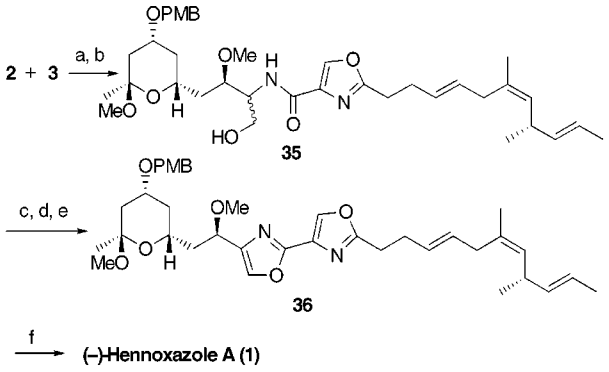
(24) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.

(25) Review: Negishi, E.-I.; Liu, F. *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 1−47.

(26) Takuma, S.; Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 3147−3153, and references therein.

(27) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165−1168.

Scheme 4[a]



[a] (a) DEPC, Et_3N, DMF; (b) TBAF, THF, 86%; (c) Dess−Martin periodinane, CH_2Cl_2; (d) $BrCCl_2CCl_2Br$, Ph_3P, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 0 °C; (e) DBU, CH_3CN, 60%; (f) DDQ, pH 7 phosphate buffer, CH_2Cl_2, 36%.

yield.[28] Saponification of the methyl ester **34** completed the construction of the $C_{11}-C_{25}$ triene unit **3** in quantitative yield.

The final steps of the synthesis (Scheme 4) began with the condensation of **2** and **3** using DEPC,[26] and removal of the DPS group provided the amido alcohol **35** in 86% yield. Oxazole synthesis via the oxidation/cyclodehydration process[5,29] was performed through intermediary bromo-oxazoline under Wipf's conditions to afford the bisoxazole **36** in 60% yield. The final oxidative removal of the C_4 PMB group with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[30] provided (−)-hennoxazole A (**1**) in 36% yield. The synthetic hennoxazole A was identical in all respects with spectra provided for the natural product.

(28) We thank Professor Wipf for physical data of the enantiomer of **34** for our comparisons.

(29) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604−3606.

(30) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885−888.

In summary, we have developed an efficient, convergent strategy for the preparation of the structurally and biologically attractive marine natural product hennoxazole A.

Acknowledgment. This work was financially supported in part by a Grant-in-Aid for Research in Nagoya City University (to F.Y.) and Grant-in-Aids from the Ministry of Education, Science, Sports and Culture, Japan. Helpful comments by Prof. Y. Hamada of Chiba University at the early stage of this work are greatly acknowledged.

Supporting Information Available: Experimental procedures and characterization data for all compounds of the synthesis. This material is available free of charge via the Internet at http://pubs.acs.org.

OL000305I