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Stereoselective Total Synthesis of Antitumor Macrolide (+)-Rhizoxin D†

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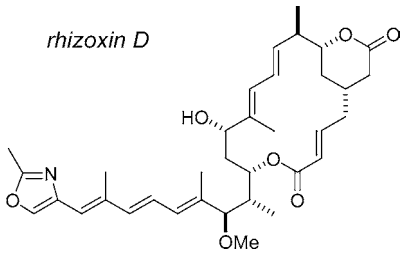
ABSTRACT



A convergent, stereoselective total synthesis of the macrolide antitumor agent rhizoxin D is described. (+)-DIPCl-promoted asymmetric aldol reaction, Evans–Tishchenko 1,3-diol synthesis, modified Julia coupling, and Horner–Wadsworth–Emmons reactions are featured.

Rhizoxin, **1**, (Scheme 1) and its congeners constitute a family of 16-membered macrolactones first isolated in 1984 from the plant pathogenic fungus *Rhizopus chinensis* by Iwasaki and co-workers.[1] Rhizoxin is a tubulin-interactive antimitotic agent that exhibits pronounced antimicrobial and antifungal activity as well as potent in vitro cytotoxicity and in vivo antitumor activity.[2] Rhizoxin (**1**) has undergone extensive clinical trials as a potential drug candidate.[3] Rhizoxin D (**2**), a didesepoxy analogue of rhizoxin, was isolated in 1986 and is thought to be the biogenetic precursor of **1**.[4] Although rhizoxin D is equally potent as **1**, it has been less studied due to limited natural abundance.[5] Because of their significant biological activity, potential as chemotherapeutic agents, and unique structural features, the rhizoxins have attracted substantial interest as synthetic targets. One total synthesis of rhizoxin[6] and six syntheses of rhizoxin D,[7] along with several partial syntheses,[8] have been reported. In a culmination of our previous efforts,[9] we describe herein a total synthesis of rhizoxin D (**2**).

As outlined in Scheme 1, our convergent strategy breaks rhizoxin D into segments **3**−**5**. An asymmetric aldol reaction and an anti-stereoselective Evans−Tishchenko 1,3-diol syn-

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(1) (a) Iwasaki, S.; Kobayashi, H.; Furukawa, J.; Namikoshi, M.; Okuda, S.; Sato, Z.; Matsuda, I.; Noda, T. *J. Antibiot.* **1984**, *37*, 354. (b) Kiyoto, S.; Kawai, Y.; Kawakita, T.; Kino, E.; Okuhara, M.; Uchida, I.; Tanaka, H.; Hashimoto, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1986**, *39*, 762. (c) Takahashi, M.; Iwasaki, S.; Kobayashi, H.; Okuda, S.; Murai, T.; Sato, Y.; Haraguchi-Hiraoka, T.; Nagano, H. *J. Antibiot.* **1987**, *40*, 66.

(2) Hendriks, H. R.; Plowman, J.; Berger, D. P.; Paull, K. D.; Fiebig, H. H.; Fodstad, O.; Dreef-van der Meulen, H. C.; Henrar, R. E. C.; Pinedo, H. M.; Schwartsmann, G. *Ann. Oncol.* **1992**, *3*, 755.

(3) (a) Hanauske, A.-R.; Catimel, G.; Aamdal, S.; ten Bokkel Huinink, W.; Paridaens, R.; Pavlidis, N.; Kaye, S. B.; te Velde, A.; Wanders, J.; Verweij, J. *Br. J. Cancer* **1996**, *73*, 397. (b) Verweij, J.; Wanders, J.; Gil, T.; Schoffski, P.; Catimel, G.; te Velde, A.; de Mulder, P. H. M. *Br. J. Cancer* **1996**, *73*, 400. (c) Kaplan, S.; Hanauske, A. R.; Pavlidis, N.; Bruntsch, U.; te Velde, A.; Wanders, J.; Heinrich, B.; Verweij, J. *Br. J. Cancer* **1996**, *73*, 403. (d) McLeod, H. L.; Murray, L. S.; Wanders, J.; Setanoians, A.; Graham, M. A.; Pavlidis, N.; Heinrich, B.; ten Bokkel Huinink, W. W.; Wagener, D. J. T.; Aamdal, S.; Verweij, J. *Br. J. Cancer* **1996**, *74*, 1944.

(4) (a) Iwasaki, S.; Namikoshi, M.; Kobayashi, H.; Furukawa, J.; Okuda, S. *Chem. Pharm. Bull.* **1986**, *34*, 1387. (b) Kiyoto, S.; Kawai, Y.; Kawakita, T.; Kino, E.; Okuhara, M.; Uchida, I.; Tanaka, H.; Hashimoto, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1986**, *39*, 762.

(5) Kato, Y.; Ogawa, Y.; Imada, T.; Iwasaki, S.; Shimazaki, N.; Kobayashi, T.; Komai, T. *J. Antibiot.* **1991**, *44*, 66.

(6) (a) Nakada, M.; Kobayashi, S.; Iwasaki, S.; Ohno, M. *Tetrahedron Lett.* **1993**, *34*, 1035. (b) Nakada, M.; Kobayashi, S.; Shibasaki, M.; Iwasaki, S.; Ohno, M. *Tetrahedron Lett.* **1993**, *34*, 1039.

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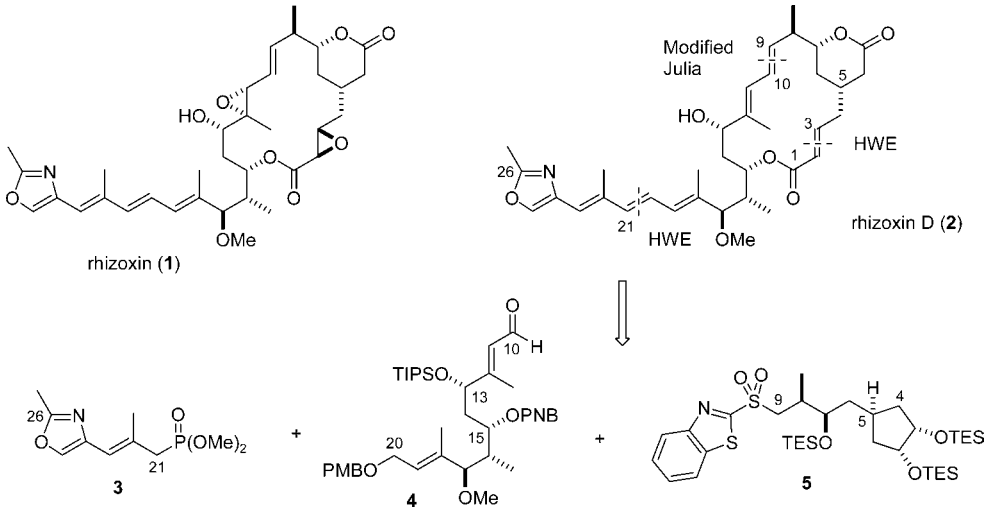
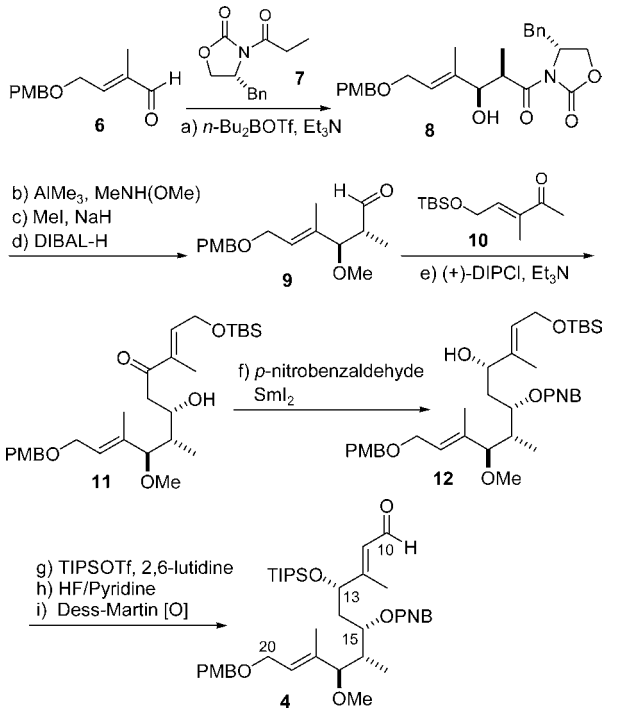
Scheme 1



thesis were envisioned as key steps to establish the C15 and C13 stereocenters in the central C10−C20 subunit. Modified Julia olefination (C9−C10) and intra- and intermolecular Horner−Wadsworth−Emmons (HWE) olefinations (C2−C3 and C20−C21, respectively) were planned for subunit coupling to establish the carbon skeleton of rhizoxin D.

Synthesis of the C10−C20 subunit **4** began from α,β-unsaturated aldehyde **6**[7d] (Scheme 2). Evans aldol reaction with **7** gave the corresponding syn adduct **8** exclusively.[10] Conversion of imide **8** to the Weinreb amide,[11] followed by *O*-methylation and DIBAL-H reduction, provided aldehyde **9**. An aldol reaction between **9** and the enolate of methyl ketone **10**,[12] prepared with (+)-chlorodiisopinocamphenyl borane (DIP-Cl),[13] afforded β-keto alcohol **11** in 65% yield

Scheme 2[a]



[a] Conditions: (a) **7**, *n*-Bu_2BOTf, Et_3N, 0 °C, then add **6**, CH_2Cl_2, −78 °C to room temperature, 85%; (b) $AlMe_3$, MeNH(OMe), CH_2Cl_2, 0 °C to room temperature; (c) MeI, NaH, THF−DMF (3:1), 0 °C, 78% for two steps; (d) DIBAL-H, THF, −78 °C, 98%; (e) **10**, (+)-DIP−Cl, Et_3N, then add **9**, CH_2Cl_2, −78 °C, 65%; (f) *p*-nitrobenzaldehyde, SmI_2, THF, 0 °C, 86%; (g) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78 to 0 °C; (h) HF/Pyridine, THF, 0 °C to room temperature, 83% for two steps; (i) Dess−Martin periodinane, CH_2Cl_2, rt, 81%.

(7) (a) Kende, A. S.; Blass, B. E.; Henry, J. R. *Tetrahedron Lett*. **1995**, *36*, 4741. (b) Williams, D. R.; Werner, K. M.; Feng, B. *Tetrahedron Lett*. **1997**, *38*, 6825. (c) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *Tetrahedron Lett*. **1999**, *40*, 4145. (d) Keck, G. E.; Wager, C. A.; Wager, T. T.; Savin, K. A.; Covel, J. A.; McLaws, M. D.; Krishnamurthy, D.; Cee, V. J. *Angew. Chem., Int. Ed*. **2001**, *40*, 231. (e) Mitchell, I. S.; Pattenden, G.; Stonehouse, J. P. *Tetrahedron Lett*. **2002**, *43*, 493. (f) White, J. D.; Blakemore, P. R.; Green, N. J.; Hauser, E. B.; Holoboski, M. A.; Keown, L. E.; Nylund Kolz, C. S.; Phillips, B. W. *J. Org. Chem*. **2002**, *67*, 7750. (g) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem*. **2003**, *68*, 4215.

(8) (a) Rama Rao, A. V.; Sharma, G. V. M.; Bhanu, M. N. *Tetrahedron Lett*. **1992**, *33*, 3907. (b) Rama Rao, A. V.; Bhanu, M. N.; Sharma, G. V. M. *Tetrahedron Lett*. **1993**, *34*, 707. (c) Boger, D. L.; Curran, T. T. *J. Org. Chem*. **1992**, *57*, 2235. (d) Keck, G. E.; Park, M.; Krishnamurthy, D. *J. Org. Chem*. **1993**, *58*, 3787. (e) Keck, G. E.; Savin, K. A.; Weglarz, M. A.; Cressman, E. N. K. *Tetrahedron Lett*. **1996**, *37*, 3291. (f) Lafontaine, J. A.; Leahy, J. W. *Tetrahedron Lett*. **1995**, *36*, 6029. (g) Provencal, D. P.; Gardelli, C.; Lafontaine, J. A.; Leahy, J. W. *Tetrahedron Lett*. **1995**, *36*, 6033. (h) White, J. D.; Nylund, C. S.; Green, N. J. *Tetrahedron Lett*. **1997**, *38*, 7329. (i) White, J. D.; Holoboski, M. A.; Green, N. J. *Tetrahedron Lett*. **1997**, *38*, 7333. (j) Davenport, R. J.; Regan, A. C. *Tetrahedron Lett*. **2000**, *41*, 7619. (k) N'Zoutani, M.-A.; Pancrazi, A.; Ardisson, J. *Synlett* **2001**, 769. (l) Kim, I. C.; Fuchs, P. L. *Book of Abstracts*, 224th National Meeting of the American Chemical Society, Boston, MA, August 18−22, 2002; ORGN-363.

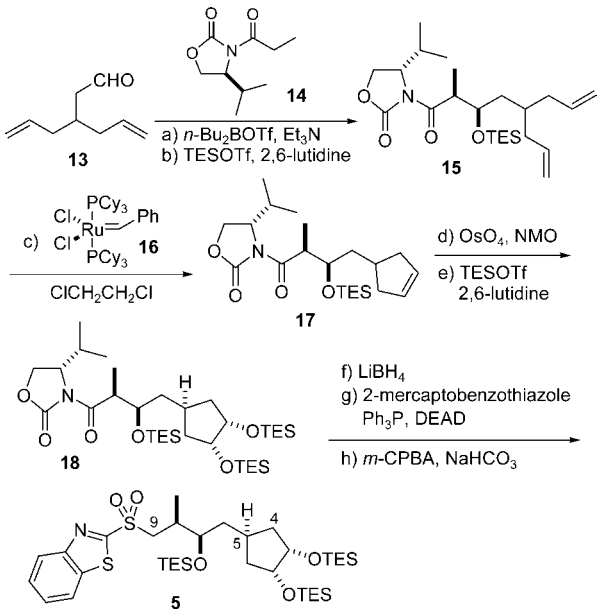
(9) (a) Burke, S. D.; Hong, J.; Mongin, A. P. *Tetrahedron Lett*. **1998**, *39*, 2239. (b) Burke, S. D.; Hong, J.; Lennox, J. R.; Mongin, A. P. *J. Org. Chem*. **1998**, *63*, 6952.

(10) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc*. **1981**, *103*, 2127. (b) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23. (c) Gage, J. R.; Evans, D. A. *Org. Synth*. **1990**, *68*, 83.

(11) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett*. **1977**, *18*, 4171. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun*. **1982**, *12*, 989.

(12) Ketone **10** was prepared in two steps from the known (2*E*)-4-(*tert*-butyldimethylsiloxy)-2-methyl-but-2-enal[7c] by methyl Grignard addition and Swern oxidation.

Scheme 3[a]



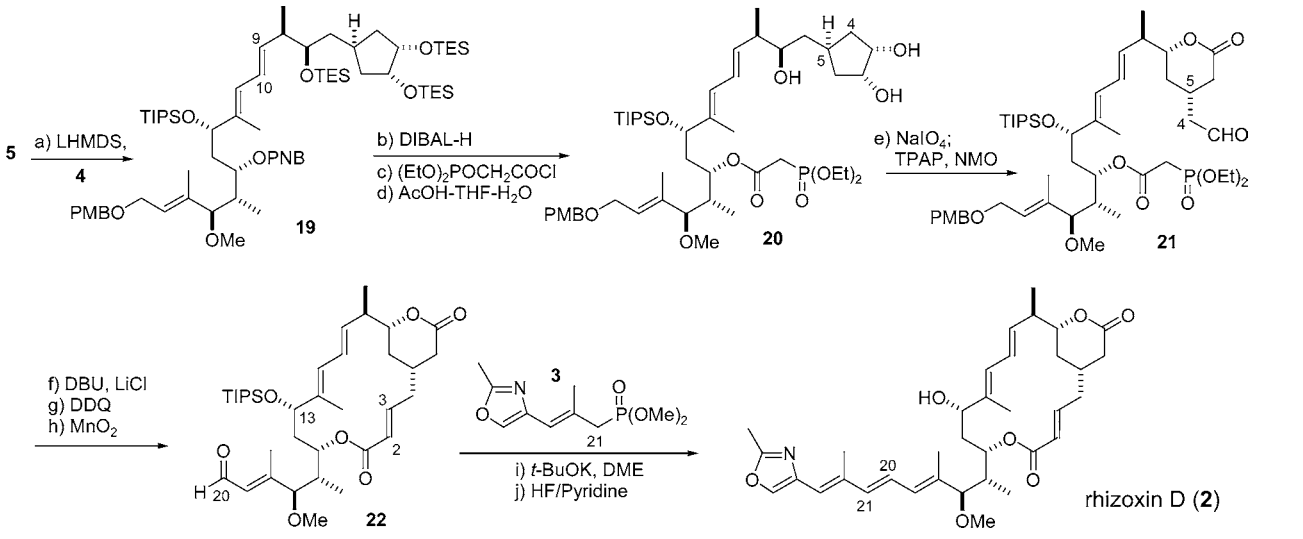
[a] Conditions: (a) *n*-Bu_2BOTf, Et_3N, **14**, CH_2Cl_2, −78 to 0 °C, 88%; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 to 0 °C, 85%; (c) **16** (3.6 mol %), $ClCH_2CH_2Cl$, rt, 91%; (d) OsO_4 (6 mol %), NMO, acetone−H_2O (8:1), rt, 87%; (e) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 to 0 °C, 95%; (f) $LiBH_4$, MeOH, THF, 0 °C to room temperature, 58%; (g) 2-mercaptobenzothiazole, Ph_3P, DEAD, THF, 0 °C to room temperature, 98%; (h) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 97%.

with a 10:1 diastereomeric ratio. An intramolecular Evans−Tishchenko reaction with *p*-nitrobenzaldehyde afforded **12** with the C13 stereocenter installed and the C15 hydroxyl protected as the *p*-nitrobenzoate (PNB) ester.[14] Subsequent alcohol protection (TIPS), selective cleavage of the C10-siloxy group, and Dess−Martin oxidation[15] gave the desired C10−C20 segment **4**.

Synthesis of the C3−C9 subunit **5** started with the known aldehyde **13**[16] (Scheme 3). An Evans aldol condensation[10] of **13** with the boron enolate of **14** afforded the aldol product as a single diastereomer, which was protected as its TES ether **15**. Ring-closing metathesis of the diene using Grubbs' catalyst **16** gave cyclopentene **17** in 91% yield.[17] Dihydroxylation of **17** afforded the cis diol with a diastereomeric ratio of 8:1,[18] which upon silylation gave **18**. Reductive removal of the chiral auxiliary using $LiBH_4$ yielded the primary alcohol, which was converted to the corresponding benzothiazole sulfide under Mitsunobu conditions.[19] Subsequent *m*-CPBA oxidation provided the C3−C9 sulfone subunit **5**.

Coupling of enal **4** and sulfone **5**, utilizing the one-pot modified Julia protocol,[20] selectively gave **19** as the *E*-isomer in 80% yield (Scheme 4). The PNB ester was reductively removed, and the resulting alcohol was esterified with diethylphosphonoacetyl chloride. Subsequent removal of the three TES groups afforded the triol **20**. Differentiation of the C5 diastereotopic groups was achieved by one-pot oxidative cleavage of the vicinal diol and TPAP oxidation to provide lactone aldehyde **21** in 75% overall yield.[21] This tactic for establishing the C5 stereocenter is analogous to those employed by Keck[8d] and Williams,[7b] and relies upon thermodynamic diequatorial deployment of the side chains in the intermediate hemiacetal. An intramolecular Horner−Wadsworth−Emmons coupling reaction established the macrolactone C2−C3 bond in 80% yield.[22] Oxidative removal of PMB group,[23] followed by MnO_2 allylic oxidation,[24] afforded aldehyde **22**. Treatment of **22** and phosphonate **3**[9a,b] with *t*-BuOK in DME gave only (*E*,*E*,*E*)-triene via HWE

Scheme 4[a]



[a] Conditions: (a) LHMDS, THF, −78 °C, 0.5 h, then **4**, THF, −78 °C to room temperature, 80%; (b) DIBAL-H, CH_2Cl_2, −78 °C, 99%; (c) diethylphosphonoacetyl chloride, pyridine, THF, 0 °C to room temperature, 90%; (d) AcOH−THF−H_2O (3:2:1), rt, 88%; (e) $NaIO_4$, THF−H_2O (1:1); TPAP, NMO, 4 Å MS, CH_2Cl_2, 75%; (f) DBU, LiCl, CH_3CN, rt, 5×10^{-4} M, 80%; (g) DDQ, CH_2Cl_2−H_2O (20:1), rt, 92%; (h) MnO_2, CH_2Cl_2, rt, 71%; (i) **3**, *t*-BuOK, DME, 0 °C, 39%; (j) HF/pyridine, THF, 0 °C to room temperature, 70%.

C20−C21 coupling.[25,26] Final deprotection of the C13 TIPS ether afforded rhizoxin D (**2**), $[\alpha]^{23}_{D}$ +271.56 (*c* 0.41, MeOH), with all data (^{1}H NMR, ^{13}C NMR, IR, and $[\alpha]_D$) in agreement with those reported for the natural product.[4a,7f,g] A stereoselective synthesis of rhizoxin D has thus been accomplished with the longest linear sequence requiring 19 steps.

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Supporting Information Available: Detailed experimental procedures and spectral data for all compounds and ^{1}H and ^{13}C NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663. (b) Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997. (c) Paterson, I.; Lister, M. A.; McClure, C. K. *Tetrahedron Lett.* **1986**, *27*, 4787.

(14) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

(15) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(16) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Perkin Trans. 2* **1975**, *71*, 1726.

(17) (a) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039. (c) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(18) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

(19) (a) Besson, T.; Al Neirabeyeh, M.; Viaud, M.-C.; Rollin, P. *Synth. Commun.* **1990**, *20*, 1631. (b) Dancy, I.; Laupichler, L.; Rollin, P.; Thiem, J. *Liebigs Ann. Chem.* **1993**, 343.

(20) (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175. (b) Bellingham, R.; Jarowicki, K.; Kocienski, P.; Martin, V. *Synthesis* **1996**, 285.

(21) (a) Lee, D. G.; Chen, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, pp 541−591. (b) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(22) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(23) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

(24) Cahiez, G.; Alami, M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 5, pp 3229−3235 and references therein.

(25) For applications of the Horner−Wadsworth−Emmons reaction in diene synthesis, see: (a) Roush, W. R.; Peseckis, S. M. *Tetrahedron Lett.* **1982**, *23*, 4879. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(26) As reported by Williams[7b] and Pattenden,[7e] we also observed some hydrolytic opening of the δ-lactone during the reaction. In practice, the crude product was subjected to Yamaguchi lactonization conditions (procedure: Suzuki, K.; Tomooka, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 5221) prior to purification, as suggested by Professor Williams.