ORGANIC LETTERS

2002
Vol. 4, No. 2
253−256

Studies Aimed at the Total Synthesis of the Antitumor Antibiotic Cochleamycin A. An Enantioselective Biosynthesis-Based Pathway to the AB Bicyclic Core

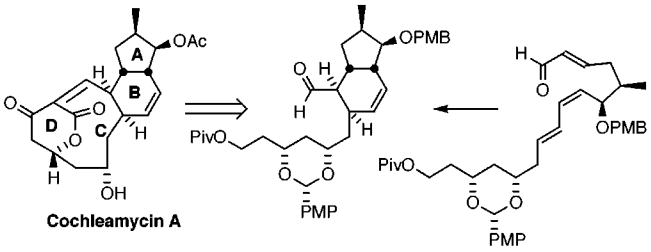
Jiyoung Chang and Leo A. Paquette*

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

paquette.1@osu.edu

Received November 5, 2001

ABSTRACT



A convergent, highly enantioselective synthesis of the fully functionalized AB sector of cochleamycin A is described. A pair of building blocks, crafted from L-malic and L-ascorbic acids, are conjoined in a manner that gives rise to an (*E,Z,E*)-1,6,8-nonatriene. On heating, the latter undergoes stereocontrolled intramolecular Diels–Alder cyclization via an endo transition state.

During the period 1992−1996, a team headed by Shindo and Kawai reported on the isolation and characterization of a small family of architecturally novel antitumor antibiotics named cochleamycins.[1] The structures and relative stereochemistries of these compounds were ascertained by mass spectrometry and a battery of NMR spectroscopic techniques. Of these, cochleamycin A (**1**) demonstrated the highest level of cytotoxicity against P388 leukemia cells, with an IC_{50} of 1.2 μg/mL. Good antimicrobial activity against Gram-positive bacteria was also uncovered.[1] Independent investigations by Abbott researchers led almost simultaneously to the discovery of the macquarimicins.[2,3] Like **1**, these unique microbial metabolites feature a *cis*-tetrahydroindane AB part structure fused to a 10-membered carbocyclic ketone that is bridged in turn with lactone functionality to set the CD ring assembly. In neither series is the absolute configuration yet established.

In light of our longstanding interest in the construction of biologically active natural products characterized by bridgehead unsaturation[4] and the clinical potential of **1**, we have been led to undertake its total synthesis.[5] Retrosynthetically, the intent was to utilize an intramolecular Diels−Alder

(1) (a) Shindo, K.; Kawai, H. *J. Antibiot.* **1992**, *45*, 292. (b) Shindo, K.; Matsuoka, M.; Kawai, H. *J. Antibiot.* **1996**, *49*, 241. (c) Shindo, K.; Iijima, H.; Kawai, H. *J. Antibiot.* **1996**, *49*, 244. (d) Shindo, K.; Sakakibara, M.; Kawai, H. *J. Antibiot.* **1996**, *49*, 249.

(2) (a) Jackson, M.; Karwowski, J. P.; Theriault, R. J.; Rasmussen, R. R.; Hensey, D. M.; Humphrey, P. E.; Swanson, S. J.; Barlow, G. J.; Premachandran, U.; McAlpine, J. B. *J. Antibiot.* **1995**, *48*, 462. (b) Hochlowski, J. E.; Mullally, M. M.; Henry, R.; Whitern, D. M.; McAlpine, J. B. *J. Antibiot.* **1995**, *48*, 467.

(3) For a more recent report disclosing inhibitory activity against membrane-bound neutral sphingomyclinase from rat brain, consult: Tanaka, M.; Nara, F.; Yamasao, Y.; Masuda-Inoue, S.; Doi-Yoshioka, H.; Kumaura, S.; Enokita, R.; Ogita, T. *J. Antibiot.* **1999**, *52*, 670.

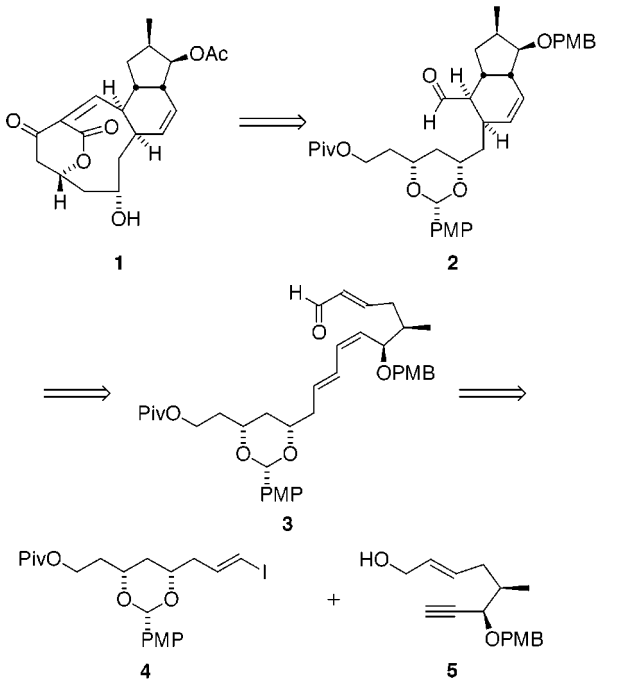
(4) Paquette, L. A. *Chem. Soc. Rev.* **1995**, *24*, 9.

(5) A group headed by Tadano has recently disclosed their preliminary studies toward the synthesis of the macquarimicins: Munakata, R.; Ueki, T.; Katakai, H.; Takao, K.; Tadano, K. *Org. Lett.* **2001**, *3*, 3029.

10.1021/ol0102592 CCC: $22.00
Published on Web 12/19/2001

cycloaddition for construction of the AB ring system in line with the proposed biosynthesis[1c] (Scheme 1). Initial dis-

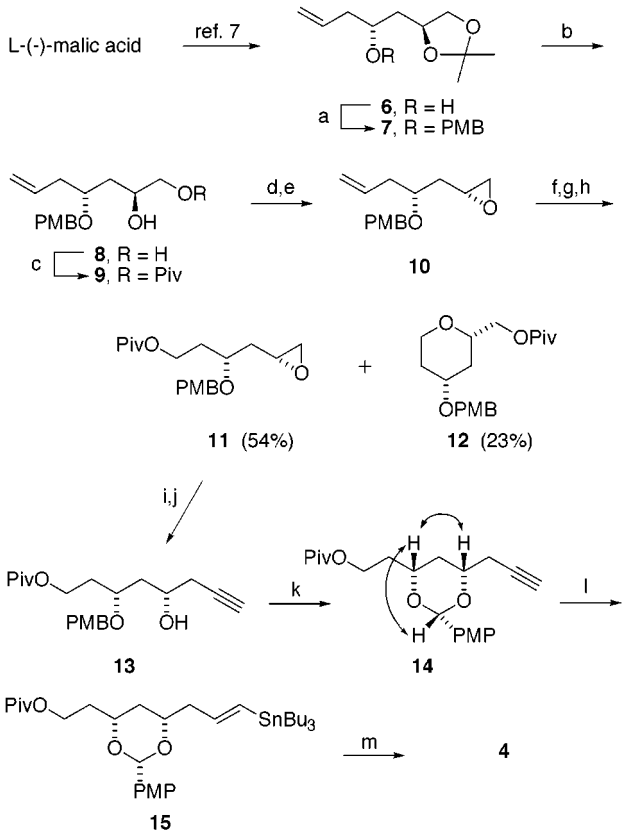
Scheme 1



connection of **1** at the site of its "anti-Bredt" double bond was visualized, thereby targeting aldehyde **2** as an advanced intermediate. Construction of the carbocyclic network in **2** was viewed likely to be feasible by stereoselective [4 + 2] cycloaddition within the (*E*,*Z*,*E*)-1,6,8-nonatriene **3**.[6] A key consideration in this scenario was adherence by **3** to appropriate transition state geometry (see below). Ultimately, triene **3** would arise by Sonogashira coupling of **4** to **5** and subsequent semi-hydrogenation of the alkyne link to secure the *Z*-double bond geometry.

Synthesis of vinyl iodide **4** began with the four-step conversion of L-(−)-malic acid to the hydroxy acetal **6** according to established precedent[7] (Scheme 2). Protection of the secondary hydroxyl as the *p*-methoxybenzyl ether[8] and acidic hydrolysis of acetonide **7** furnished diol **8** in 92% yield for the two steps. Following chemoselective pivaloyl-

Scheme 2[a]



[a] Reagents and conditions: (a) PMBBr, NaH, DMF (100%); (b) HOAc, H_2O, THF (1:1:1), 50−60 °C (92%); (c) PivCl, pyr, CH_2Cl_2 (91%); (d) CH_3SO_2Cl, DMAP, pyr, CH_2Cl_2 (97%); (e) K_2CO_3, MeOH (89%); (f) O_3, EtOAc, −78 °C, then Ph_3P; (g) $NaBH_4$, MeOH, 0 °C; (h) PivCl, pyr, CH_2Cl_2 (77% for 3 steps); (i) $HC{\equiv}CSiMe_3$, *n* -BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C; (j) $(n\text{-}Bu)_4NF$, THF, 0 °C (95% for 2 steps); (k) DDQ, 4 Å MS, CH_2Cl_2 (85%); (l) $(n\text{-}Bu)_3SnH$, AIBN, C_6H_6, Δ (99%); (m) I_2, CH_2Cl_2 (96%).

ation[9] to generate **9**, an epoxide ring was installed[10] as in **10**. Subsequent double bond cleavage via ozonolysis and accompanying reductive workup could be accomplished without excessive intramolecular cyclization. The product composition was defined to be 54% of **11** and 23% of **12** after esterification. The conversion of chromatographically purified major product **11** to **13** entailed highly regioselective nucleophilic opening of the oxirane with lithium trimethylsilylacetylide with subsequent fluoride ion-induced desilylation.[11] This result allowed for DDQ-promoted oxidative cyclization[8c,12] to deliver **14** efficiently. This alkyne, the configuration of which was ascertained by NOESY tech-

(6) For recent examples of intramolecular Diels−Alder reactions involving (*E*,*Z*,*E*)-trienes, see: (a) Back, T. G.; Nava-Salgado, V. O.; Payne, J. E. *J. Org. Chem*. **2001**, *66*, 4361. (b) Back, T. G.; Payne, J. E. *Org. Lett*. **1999**, *1*, 663. (c) Diedrich, M. K.; Klärner, F.-G. *J. Am. Chem. Soc*. **1998**, *120*, 6212. (d) Review: Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 513−550.

(7) (a) Carman, R. M.; Karoli, T. *Aus. J. Chem*. **1998**, *51*, 995. (b) Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *35*, 933. (c) Steel, P. G.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 371. (d) Rodriguez, E. B.; Scally, G. D.; Stick, R. V. *Aust. J. Chem*. **1990**, *43*, 1391. (e) Hayashi, H.; Nakanishi, K.; Brandon, C.; Marmur, J. *J. Am. Chem. Soc*. **1973**, *95*, 8749.

(8) (a) Ruder, S. M.; Ronald, R. C. *Tetrahedron Lett*. **1987**, *28*, 135. (b) Nakata, M.; Ishiyama, T.; Hirose, Y.; Maruoka, H,; Tatsuta, K. *Tetrahedron Lett*. **1993**, *34*, 8439. (c) Kochetkov, N. K.; Sviridov, A F.; Ermolenko, M. S.; Yashunsky, D. V.; Borodkin, V. S. *Tetrahedron* **1989**, *45*, 5109.

(9) (a) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453. (b) Takao, K.; Ochiai, H.; Yoshida, K.; Hashizuka, T.; Koshimura, H.; Tadano, K.; Ogawa, S. *J. Org. Chem*. **1995**, *60*, 8179.

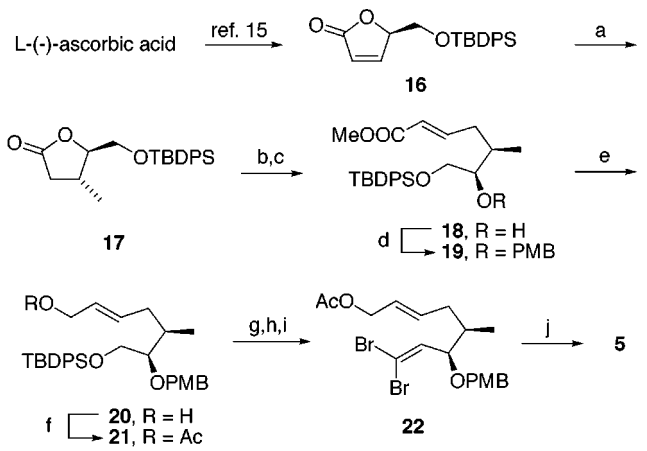
(10) McGarvey, G. J.; Mathys, J. A.; Wilson, K. J. *J. Org. Chem*. **1996**, *61*, 5704.

(11) (a) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett*. **1983**, *24*, 391. (b) Mukai, C.; Kim, J. S.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2903. (c) Sinha, A.; Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem*. **1999**, *64*, 2381. (d) Kittaka, A.; Suhara, Y.; Takayanagi, H.; Fujishima, T.; Kurihara, M.; Takayama, H. *Org. Lett*. **2000**, *2*, 2619.

niques, was readily converted to the (*E*)-vinylstannane **15** by reaction with tri-*n*-butyltin hydride and AIBN in refluxing benzene.[13] Equal success was enjoyed in the generation of iodide **4**,[14] quantities of which were made available in enantiopure form by this pathway.

Acquisition of the second cross-coupling partner took early advantage of the readiness with which L-ascorbic acid can be transformed into butenolide **16**[15] (Scheme 3). In line with

Scheme 3[a]

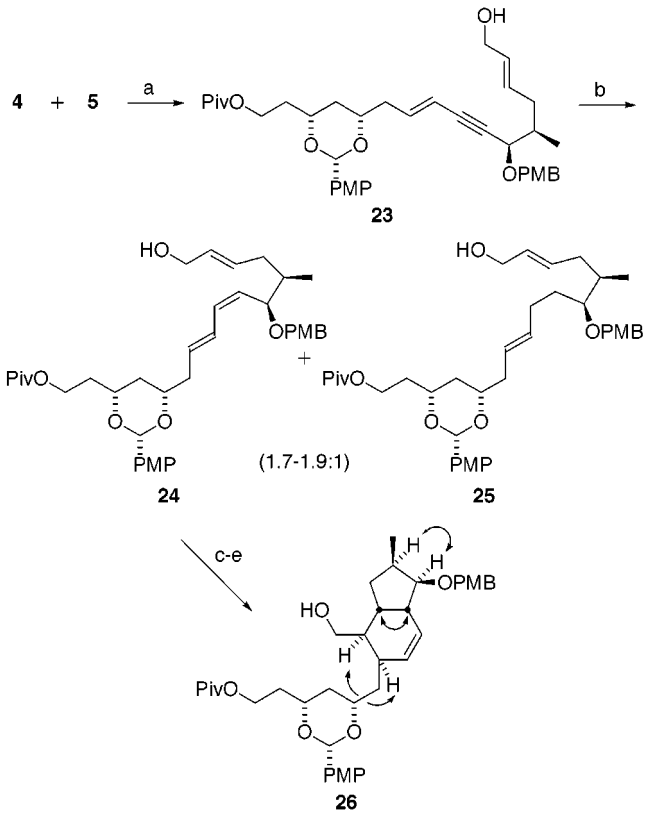


[a] Reagents and conditions: (a) $(CH_3)_2CuLi$, ether, THF, −30 °C (89%); (b) $(i\text{-Bu})_2AlH$, CH_2Cl_2, −78 °C; (c) $Ph_3P{=}CHCO_2Me$, C_6H_6, Δ (100% for 2 steps); (d) PMBOC(=NH)CCl_3, CSA, CH_2Cl_2; (e) $(i\text{-Bu})_2AlH$, CH_2Cl_2, −78 °C (60% for 2 steps); (f) Ac_2O, DMAP, pyr, CH_2Cl_2 (97%); (g) $(n\text{-Bu})_4NF$, THF, 0 °C (100%); (h) IBX, THF/DMSO (9:1) (90%); (i) CBr_4, Ph_3P, CH_2Cl_2, −78 °C (98%); (j) *n*-BuLi, THF, −78 °C (90%).

expectation,[16] the conjugate addition of lithium dimethylcuprate to **16** proceeded to deliver the trans adduct **17** exclusively in 89% yield. Reduction to the lactol was followed by Wadsworth−Emmons chain extension[11c,17] to provide the *E*-configured open-chain α,β-unsaturated ester with unequivocally established relative and absolute configuration at the δ- and ϵ-positions. Protection of the hydroxyl group in **18** was accomplished via the trichloroacetimidate,[18] thereby making it possible to advance to **21** via Dibal-H reduction and acetylation. Following chemoselective desilylation and oxidation with iodoxybenzoic acid (IBX),[19] the resulting aldehyde was homologated via the Corey−Fuchs protocol.[20] Terminal alkyne **5** was formed in 88% yield for the two steps.

The crucial Sonagashira coupling of **4** with **5** was most successfully implemented with $Pd(PPh_3)_2Cl_2$ and CuI in triethylamine as solvent[13a,21] (Scheme 4). The clean semi-

Scheme 4[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N (82%); (b) H_2, Lindlar catalyst, EtOAc/pyr/1-octene (10:1:1) (95%); (c) IBX, THF/DMSO (9:1) (85%); (d) 20% BHT, toluene, sealed tube, 195 °C, 26 h; (e) $NaBH_4$, MeOH, 0 °C (66% for 2 steps).

hydrogenation of the triple bond in **23** proved to be challenging. Irrespective of whether catalytic quantities or several molar equivalents of quinoline were present, mixtures of **24** and **25** were formed. The use of 1-octene as a cosolvent likewise did not effectively curtail the production of **25**. Also, reaction times in excess of 1 day were required. Ultimately, recourse was made to a compromise position involving the

(12) Tsuboi, K.; Ichikawa, Y.; Jiang, Y.; Naganawa, A.; Isobe, M. *Tetrahedron* **1997**, *53*, 5123.

(13) (a) Izzo, I.; De Caro, S.; De Riccardis, F.; Spinella, A. *Tetrahedron Lett.* **2000**, *41*, 3975. (b) Otaka, K.; Mori, K. *Eur. J. Org. Chem.* **1999**, 1795. (c) Deng, Y.; Salomon, R. G. *J. Org. Chem.* **2000**, *65*, 6660.

(14) (a) Drouet, K. E.; Theodorakis, E. A. *Chem. Eur. J.* **2000**, *6*, 1987. (b) Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935. (c) Smith, A. B., III; Wan, Z. *J. Org. Chem.* **2000**, *65*, 3738.

(15) (a) Andrews, G. C.; Crawford, T. C.; Bacon, B. E. *J. Org. Chem.* **1981**, *46*, 2976. (b) Hubschwerlen, C. *Synthesis* **1986**, 962. (c) Fazio, F.; Schneider, M. P. *Tetrahedron: Asymmetry* **2000**, *11*, 1869.

(16) Hanessian, S.; Murray, P. J. *Tetrahedron* **1987**, *43*, 5055.

(17) (a) Van Hijfte, L.; Little, R. D.; Petersen, J. L.; Moeller, K. D. *J. Org. Chem.* **1987**, *52*, 4647. (b) Mehta, G.; Mohal, N. *Tetrahedron Lett.* **1999**, *40*, 5791. (c) Agyei-Aye, K.; Baker, D. C. *Carbohydr. Res.* **1988**, *183*, 261. (d) Okabe, M.; Sun, R.-C.; Tam, S. Y.-K.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1988**, *53*, 4780. (e) Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 7067.

(18) (a) Nakata, M.; Ishiyama, T.; Akamatsu, S.; Hirose, Y.; Maruoka, H.; Suzuki, R.; Tatsuta, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 967. (b) Kawata, S.; Yoshimura, F.; Irie, J.; Ehara, H.; Hirama, M. *Synlett* **1997**, 250.

(19) (a) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272. (b) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.

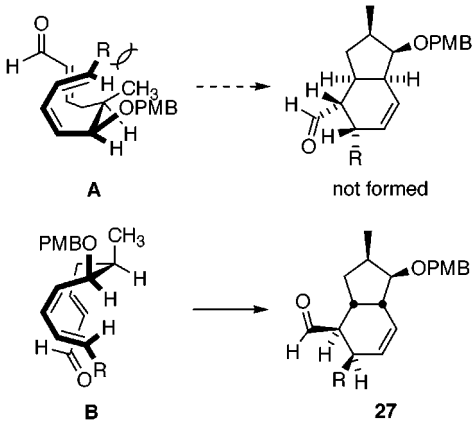
(20) (a) Critcher, D. J.; Connolly, S.; Wills, M. *J. Org. Chem.* **1997**, *62*, 6638. (b) Horita, K.; Oikawa, Y.; Nagato, S.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 5143. (c) Mukai, C.; Kim, J. S.; Sonobe, H.; Hanaoka, M. *J. Org. Chem.* **1999**, *64*, 6822. (d) González, I. S.; Forsyth, C. J. *Org. Lett.* **1999**, *1*, 319.

(21) (a) Yu, Q.; Wu, Y.; Ding, H.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1183. (b) Madec, D.; Férézou, J.-P. *Tetrahedron Lett.* **1997**, *38*, 6661.

use of 10:1:1 ethyl acetate/pyridine/1-octene as the reaction medium.[5,22] These conditions gave rise to a 1.7−1.9:1 mixture of **24** and **25** (ES MS analysis) in 95% yield after only 5.5 h. Since these carbinols coeluted during attempted chromatographic separation, they were carried in admixed form through a three-step sequence involving sequential IBX oxidation, thermal activation in toluene at 195 °C, and reduction with methanolic sodium borohydride. While aldehyde **3** derived from **24** underwent smooth intramolecular Diels−Alder cycloaddition, the oversaturated congener did not share in this capability and did not enter into cyclization. The bicyclic product detected following careful chromatography proved to be **26** (66% from **24**),[23] the relative (and absolute) stereochemistry of which was elucidated by NOESY measurements (see formula).

An (*E*,*Z*,*E*)-1,6,8-nonatriene such as **3** was expected on the basis of precedent to cyclize via an endo transition state, of which only two are possible as defined in **A** and **B**.[5,6d,24]

The two options differ significantly in the level of nonbonded steric interaction that must necessarily be faced in order for diene-dienophile linkup to materialize. In **A**, the methyl and OPMB substituents are projected into the region necessarily reserved for proper positioning of the diene unit, thereby disfavoring this arrangement. Since this level of proximity is completely avoided in **B**, this transition state is adopted in wholesale fashion and generates exclusively **27**.



This excellent π-facial stereoselection, when compared with the results of Tadano,[5] supports the working assumption that the extent of destabilization depends on the steric requirements of the interlinking tetrahedral carbons and their substituents.

In conclusion, the studies reported herein serve to chart an approach to cochleamycin A that is based on the effective use of an intramolecular Diels−Alder reaction to set all six stereogenic centers resident in rings A and B in their proper configuration. Current investigations are underway to determine if **26** can indeed serve as a suitable precursor to **1**.

Acknowledgment. This research was financed by an unrestricted grant from Aventis Pharmaceuticals.

Supporting Information Available: Experimental procedures and spectroscopic characterization (IR, ^{1}H and ^{13}C NMR, HRMS) of all key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0102592

(22) (a) Nicolaou, K. C.; Ladduwahetty, T.; Taffer, I. M.; Zipkin, R. E. *Synthesis* **1986**, 344. (b) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc*. **1988**, *110*, 2248.

(23) While this cycloadduct could not be readily separated from minor nonisomeric impurities, it could be readily characterized as **26** on the basis of confirmatory 1D and 2D NMR measurements. Alternate means for producing **26** are currently under investigation.

(24) Ciganek, E. *Org. React*. **1984**, *32*, 1.