ORGANIC LETTERS

2002
Vol. 4, No. 22
3891−3894

Synthetic and Mechanistic Studies of the Retro-Claisen Rearrangement 4. An Application to the Total Synthesis of (+)-Laurenyne

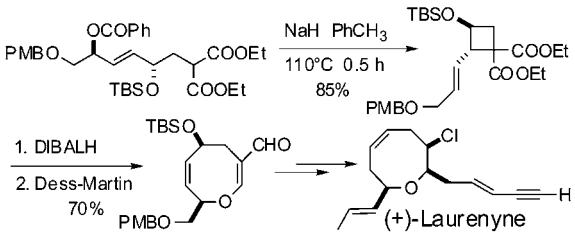
Robert K. Boeckman, Jr.,* Jing Zhang, and Michael R. Reeder

Department of Chemistry, University of Rochester, Rochester, New York 14627-0216

rkb@rkbmac.chem.rochester.edu

Received August 12, 2002

ABSTRACT



A novel asymmetric total synthesis of marine natural product (+)-Laurenyne has been achieved. The key elements of the strategy are the sequential metal ion-templated S_N2' cyclization affording a highly functionalized chiral vinyl cyclobutane and a retro-Claisen rearrangement for the construction of an eight-membered ring ether.

The species of the *Laurencia* genus of red algae produce a plethora of structurally novel C_{15} nonterpenoid metabolites, a number containing a medium-ring ether.[1] In addition to an oxocene or oxepine ring, structural features common to many of these materials include halogen substitution and an enyne side chain. The medium-sized oxocene ring still imposes a notable challenge, and numerous synthetic approaches have been documented.[2] Being the initial member of this class isolated,[3] a number of total[4] and formal syntheses[5] of Laurencin (**1**) have been recorded (Figure 1). Several formal and total syntheses of the structurally related oxepine derivative isolaurepinnacin (**2**) have also been reported.[6] The structure and absolute configuration of the related (+)-Laurenyne (**3**), isolated from *Laurencia obtusa*, had been assigned as 2*S*,7*S*,8*S* by X-ray crystallography.[7] The only total synthesis of **3** reported thus far, by Overman and co-workers,[8] afforded the enantiomer (−)-**3**.[7] This synthesis verified the structure and relative stereochemistry of **3** but required revision of the absolute stereochemistry of natural (+)-Laurenyne (**3**) to 2*R*,7*R*,8*R*.

(1) (a) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1−48. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1−49. (c) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7−55. (d) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 1−6.

(2) (a) Holmes, A. B.; Stephenson, G. R. *Chem. Ind. (London)* **2001**, 187−189. (b) Elliott, M. C. *Contemp. Org. Synth.* **1994**, *1*, 457−474. (c) Moody, C. J.; Davies, M. J. *Stud. Nat. Prod. Chem.* **1992**, *10*, 201−239.

(3) (a) Irie, T.; Susuki, M.; Masumune, T. *Tetrahedron Lett.* **1965**, 1091−1099. (b) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, *24*, 4193−4205.

(4) (a) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029−2032. (b) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483−7498. (c) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958−5966. (d) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345−4348. (e) Masamune, T.; Matsue, H.; Murase, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 127−134. (f) Masamune, T.; Murase, H.; Matsue, H.; Murai, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 135−141.

(5) (a) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653−5660. (b) Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *J. Org. Chem.* **1998**, *63*, 9728−9738. (c) Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Synlett* **1996**, 983−984.

(6) (a) Suzuki, T.; Matsumura, R.; Oku, K. i.; Taguchi, K.; Hagiwara, H.; Hoshi, T.; Ando, M. *Tetrahedron Lett.* **2001**, *42*, 65−67. (b) Berger, D.; Overman, L. E.; Renhowe, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 2446−2452. (c) Berger, D.; Overman, L. E.; Renhowe, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 9305−9306. (d) Davies, M. J.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 9−12. (e) Davies, M. J.; Moody, C. J. *Synlett* **1990**, 95−96. (f) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1989**, *54*, 5153−5161.

10.1021/ol0267174 CCC: $22.00
Published on Web 09/27/2002

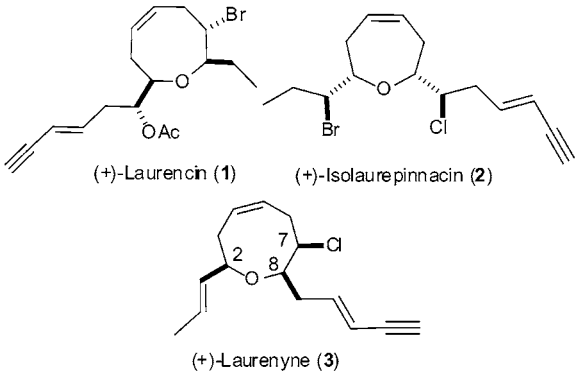
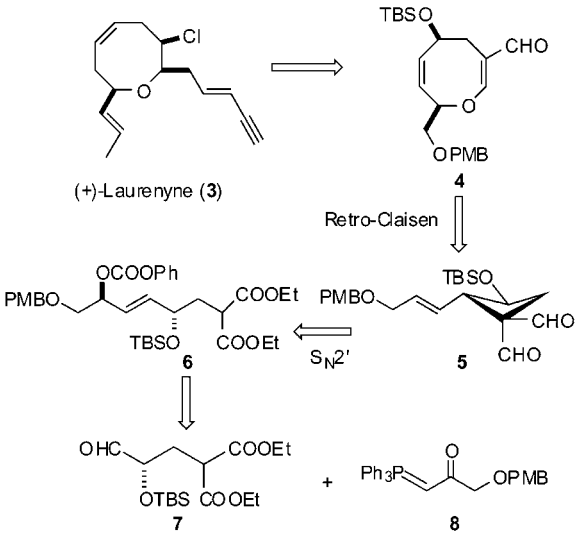


Figure 1.

Here we disclose the first synthesis of the natural enantiomer (+)-Laurenyne (**3**) using a novel approach that applies two key methodologies recently developed in our laboratories: (1) a completely diastereoselective metal-templated S_N2' cyclization and (2) a retro-Claisen rearrangement of the derived homochiral cyclobutane dicarboxaldehyde affording the eight-membered ring ether.[9,10]

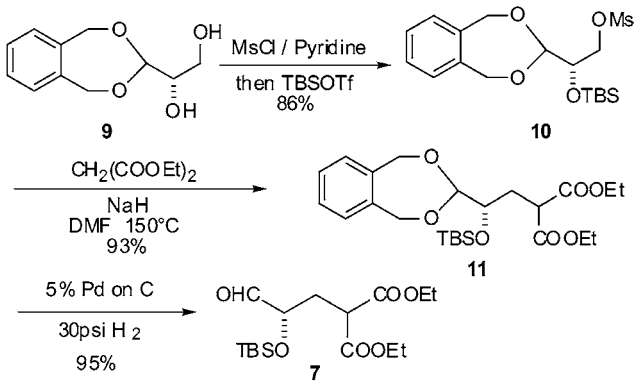
Scheme 1



Our synthetic plan is depicted in Scheme 1. We anticipated that (+)-Laurenyne (**3**) could be elaborated from dihydrooxocene **4**. The allylic silyloxy group was intended to facilitate the required double-bond migration. Dihydrooxocene **4**, in turn, would be derived via a retro-Claisen rearrangement from vinyl cyclobutane **5**. A stereoselective S_N2' cyclization of allyl carbonate **6** would then produce **5**, which is available from enantiomerically pure aldehyde **7** and the known ylide **8**[11] via a Wittig olefination.

Our synthesis of the aldehyde **7** starts from the readily available known (−)-(1*S*)-diol **9** (97% ee) as shown in Scheme 2.[12] A one-pot double protection of **9** was effected

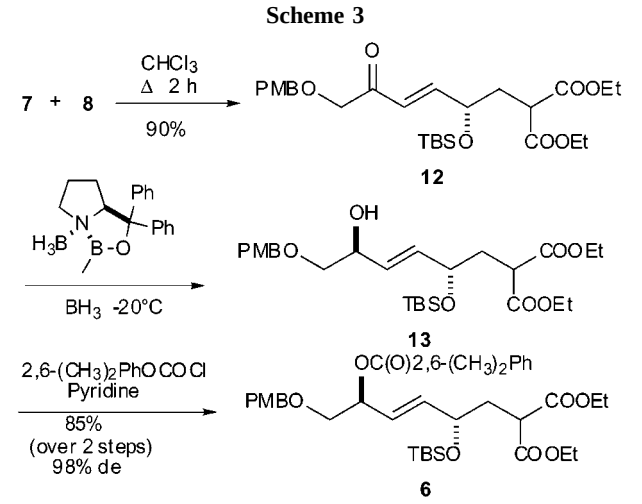
Scheme 2



by selective mesylation of the primary alcohol followed by silylation of the secondary alcohol (TBSOTf) affording mesylate **10** in 86% yield. Alkylation of the sodium anion of diethyl malonate with mesylate **10** in DMF smoothly provided diester acetal **11** in 93% yield. Finally, unmasking the aldehyde function in acetal **11** by catalytic reduction furnished aldehyde **7** in 95% yield.

Condensation of aldehyde **7** and stabilized ylide **8** readily afforded the enone **12** in 90% yield (Scheme 3). A CBS

Scheme 3

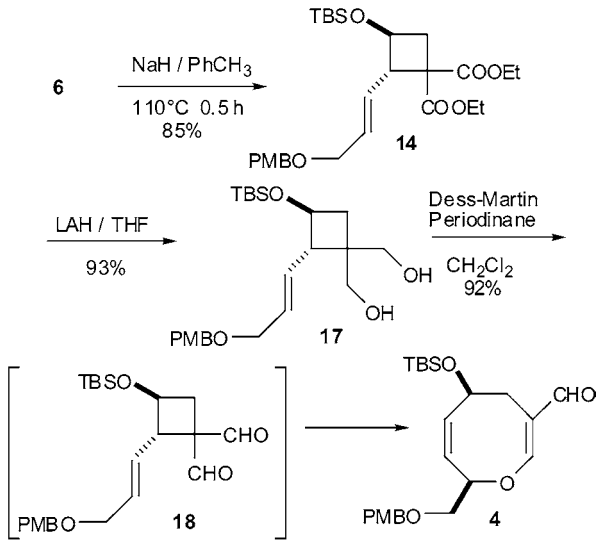


reduction was then employed to introduce the required stereogenic center, from which the chirality at C_2 in **3** will ultimately be derived, affording allylic alcohol **13** in 98% de.[13] Activation of the allylic alcohol via acylation with 2,6-dimethylphenyl chloroformate provided the allylic carbonate **6**, the substrate for the S_N2' cyclization, in 85% yield over two steps.

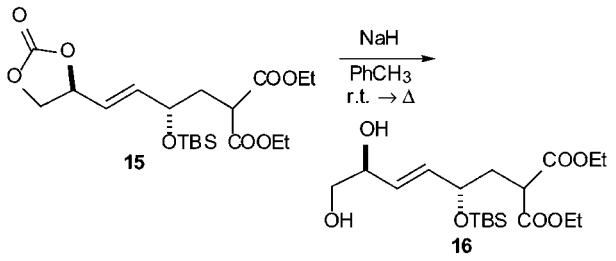
(7) Falshaw, C. P.; King, T. J.; Imre, S.; Islimyeli, S.; Thomson, R. H. *Tetrahedron Lett.* **1980**, *21*, 4951−4954.
(8) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248−2256.
(9) Boeckman, R. K., Jr.; Reeder, M. R. *J. Org. Chem.* **1997**, *62*, 6456−6457.
(10) Boeckman, R. K., Jr.; Shair, M. D.; Vargas, J. R.; Stolz, L. A. *J. Org. Chem.* **1993**, *58*, 1295−1297.

The key syn-S_N2' cyclization, which assembles the required homochiral cyclobutane ring, was then effected by treatment of 2,6-dimethylphenyl carbonate **6** with NaH in toluene at reflux, which efficiently produced the highly functionalized vinyl cyclobutane **14** *as a single diastereomer* in 85% yield (Scheme 4).

Scheme 4



The efficiency and high stereospecificity of this cyclization are critically dependent on several (not readily apparent) variables that shed light on the mechanism of this cyclization. For example, the related cyclic carbonate **15** failed to undergo cyclization under any conditions examined, even after extensive experimentation, affording only the diol precursor **16** resulting from hydrolysis (eq 1). Indeed, deacylation is



the competing side reaction in the conversion of **6** to **14**. In the case of **6**, deacylation could be suppressed by conducting the cyclization at 110 °C rather than 45−50 °C. This dramatic dependence on the activating group is strongly suggestive that the conversion proceeds through a highly organized transition-state involving the counterion as a template for the S_N2' cyclization. In this transition state (Figure 2), the sodium counterion simultaneously coordinates to one of the enolate oxygen atoms and the carbonyl oxygen atom from

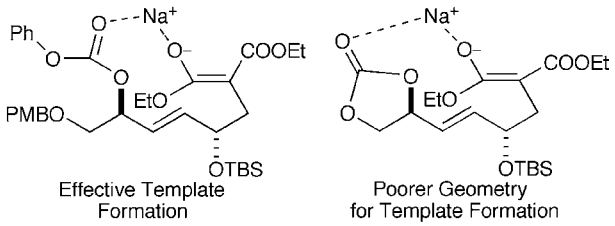


Figure 2.

the carbonate minimizing charge separation in the nonpolar medium.[9,14] Such a counterion-templated transition state accounts for the observed stereoselectivity (syn-S_N2'), the apparent rate acceleration, and the dependence on substrate by enforcing proximity of the two reacting partners. Such a circumstance is not possible for cyclic carbonate **15** due to geometric constraints. The failure of the sodium salt of **6** to cyclize in the presence of 18-C-6 and the failure of Li and K anions derived from **6** to undergo cyclization to **14** to any significant extent provide further evidence for the role of the counterion.

With the vinyl cyclobutane diester **14** in hand, we now addressed the key retro-Claisen rearrangement to construct the oxocene ring. Diester **14** was reduced with LAH under standard conditions affording diol **17** in 93% yield. Upon Dess−Martin periodinane (DMP) oxidation and subsequent thermal equilibration at 45 °C, the desired dihydrooxocene **4** was obtained in 92% yield.[9,15] Interestingly, in this case, dialdehyde **18** could be isolated under carefully controlled conditions. This is the first observation of a dialdehyde intermediate of type **18** in the cyclobutane series.[9,10] Oxocene aldehyde **4** was stable at −10 °C for at least a month with no evidence of rearrangement back to the dialdehyde **18**.

To eliminate complexities arising from the fluxional character of intermediates such as **4**, the disubstituted olefin in **4** was selectively reduced using $(Ph_3P)_3RhCl$ to give aldehyde **19** in 91% yield (Scheme 5).[16] Catalytic decarbonylation of **19**, which was inert to $(Ph_3P)_3RhCl$, proceeded smoothly using the more reactive cationic $Rh(dppp)_2^+Cl^-$ complex in xylenes affording vinyl ether **20** in 90% yield.[17] Epoxidation of **20** with dimethyldioxirane (DMDO) cleanly

(11) Oguri, H.; Hishiyama, S.; Oishi, T.; Hirama, M. *Synlett* **1995**, 1252−1254.

(12) Oi, R.; Sharpless, K. B. *Org. Synth.* **1996**, *73*, 1−12.

(13) (a) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553. (c) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925−7926.

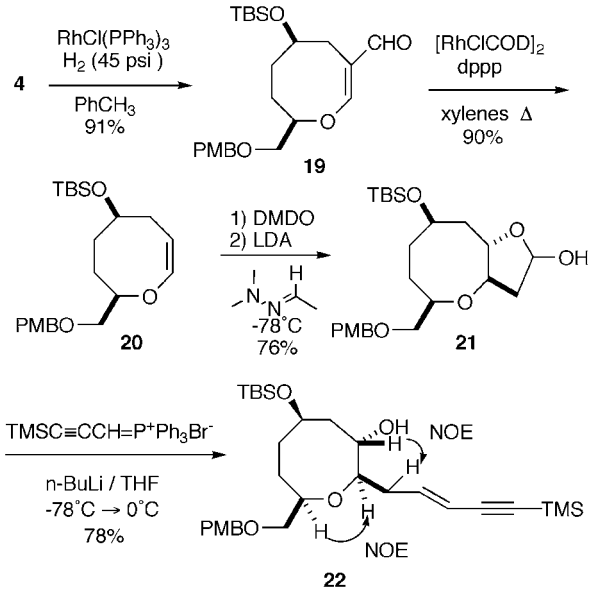
(14) (a) Williams, R. M.; Glinka, T.; Kwast, E. *J. Am. Chem. Soc.* **1988**, *110*, 5927−5929. (b) Martel, J.; Blade-Font, A.; Marie, C.; Vivat, M.; Toromanoff, E.; Buendia, J. *Bull. Soc. Chim. Fr.* **1978**, 131−139. (c) Martel, J.; Toromanoff, E.; Mathieu, J.; Nomine, G. *Tetrahedron Lett.* **1972**, 1491−1496.

(15) (a) Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. *Org. Synth.* **2000**, *77*, 141−152. (b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.

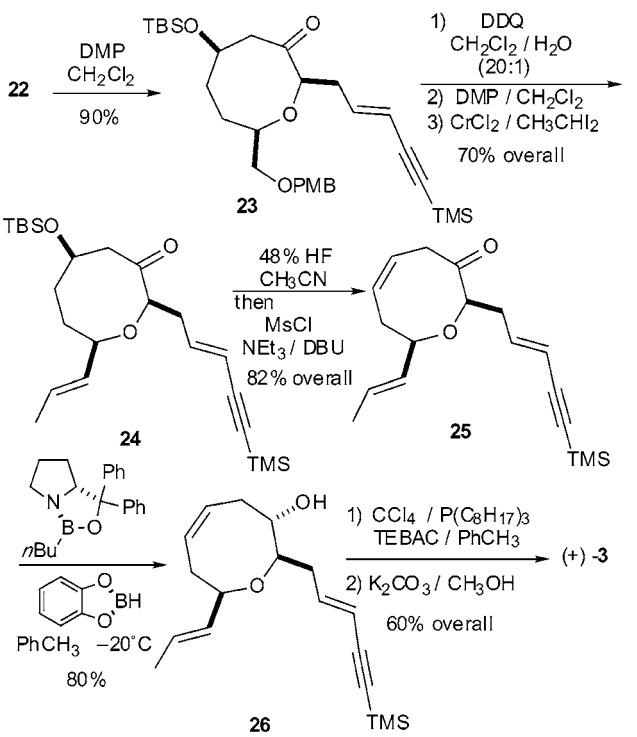
(16) (a) Stolz, L. A., Ph.D. Dissertation, University of Rochester, Rochester, NY, 1992. (b) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711−1732.

(17) (a) Doughty, D. H.; Pignolet, L. H. *J. Am. Chem. Soc.* **1978**, *100*, 7083−7085. (b) Meyer, M. D.; Kruse, L. I. *J. Org. Chem.* **1984**, *49*, 3195−3199.

Scheme 5



Scheme 6



generated a single α-epoxide diastereomer,[18] which was directly opened with the lithium enolate of acetaldehyde *N*,*N*-dimethylhydrazone providing the hemiacetal **21** in 76% overall yield after a mildly oxidative acid hydrolysis.[19] The trans enyne side chain was then introduced via Wittig olefination to provide **22** in 78% yield (>15:1 *E*/*Z* selectivity). The free hydroxyl group in **21** may be the source of the unusually high *E*/*Z* selectivity.[20] NOE studies confirmed the relative stereochemistry of alcohol **22** (Scheme 5).

Conversion of alcohol **22** to (+)-Laurenyne (**3**) was initiated by DMP oxidation of **22** to ketone **23** (Scheme 6). Assembly of the trans propenyl side chain was accomplished by sequential treatment of **23** with DDQ, DMP oxidation, and Takai olefination[21] of the resulting aldehyde affording ketone **24** in 70% yield (three steps). Cleavage of the TBS ether in **24** with 48% HF in CH_3CN followed by in situ mesylation of the resulting alcohol followed by elimination with concomitant deconjugation of the resulting alcohol provided ketone **25**, incorporating the key $\Delta^{4,5}$ double-bond, in 82% yield (overall).[22]

Installation of the C_7 chlorine was initiated by CBS reduction of ketone **25** under reagent control (mismatched case), using (2*R*)-*n*-butyloxazaborolidine, giving the desired C_7 α-alcohol **26** in 80% yield along with 16% of the C_7 epimer. Unexpectedly, conversion of the C_7 α-alcohol **26** to the C_7 *β*-chloride was not trivial. Standard reaction conditions for this conversion (CCl_4/(nC_8H_{17})$_3$P/$PhCH_3$/70 °C) afforded 20% of the desired *β*-chloride together with 80% of the diene from elimination.[4c] However, upon addition of 1 equiv of $BnEt_3NCl$ (TEBAC), (+)-Laurenyne (**3**) was obtained as a white solid in 60% overall yield (after removal of the TMS group with K_2CO_3 in CH_3OH), accompanied by 30% of the diene and 4% of the a epimeric chloride (unoptimized). Synthetic (+)-**3** [mp 78−79 °C, $[\alpha]_D^{25}$ + 17.9 ($CHCl_3$, *c* 0.145)] was identical in all respects (mp, ^{1}H NMR, ^{13}C NMR, IR, $[\alpha]_D^{25}$) to natural (+)-**3**[7] and synthetic (−)-**3** (except for the sign of the optical rotation).[8]

Acknowledgment. We thank the NIH (GM-30345) for generous financial support of this project and Professor Larry Overman for providing NMR data for synthetic (−)-**3**.

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

OL0267174

(18) (a) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377. (b) Adam, W.; Hadjiarapoglou, L. *Chem. Ber.* **1990**, *123*, 2077−2079.

(19) (a) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 11−14. (b) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3−6.

(20) Evans, P. A.; Murthy, V. S.; Roseman, J. D.; Rheingold, A. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 3175−3177.

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

(22) Jeyaraj, D. A.; Kapoor, K. K.; Yadav, V. K.; Gauniyal, H. M.; Parvez, M. *J. Org. Chem.* **1998**, *63*, 287−294.