ORGANIC LETTERS

2007
Vol. 9, No. 13
2537−2540

Domino Metathesis Involving ROM-RCM of Substituted Norbornenes. Rapid Access to Densely Functionalized Tricyclic Bridged and Condensed Ring Systems

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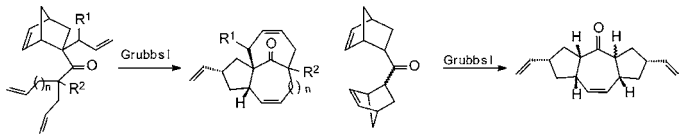
Received April 18, 2007

ABSTRACT



Domino metathesis involving ROM-RCM of appropriately constructed norbornene derivatives having multiple alkene chains leads to direct access of highly functionalized bridged tricyclic compounds while that of a compound having two norbornene units tethered through one carbon produces a linearly arrayed condensed tricyclic system.

Domino processes[1] involving a series of organic transformations are of great significance for rapid assembly of complex molecular structures. Olefin metathesis[2] offers enormous possibilities toward this end as a number of synthetic operations such as ring closing (RCM), ring opening (ROM), and cross metathesis (CM) can be performed under similar reactions conditions. Of the various metathetic processes, RCM has been widely employed in organic synthesis. However, the synthetic potential of ROM or CM has been relatively less explored. Domino processes involving ROM-CM of strained cycloalkenes, especially norbornenes and their aza and oxa analogues, have been investigated[3] mainly to determine the regioselectivity in ring opening. On the contrary, very little attention[4] has been paid to explore the synthetic application of domino processes involving ROM-RCM of norbornenes. This sequence has so far been used to construct fused bicycles only. As part of our continued interest[5] in the application of olefin metathesis in organic synthesis, we became interested in the metathesis of norbornene derivatives having multiple olefinic chains in order

(1) Tietze, L. F.; Beifus, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131.
(2) (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (d) Armstrong, S. K.; *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (e) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (f) Deiters, A.; Martin, S. *Chem. Rev.* **2004**, *104*, 2199. (g) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed*. **2005**, *44*, 4490. (h) Ghosh, S.; Ghosh, S.; Sarkar, N. *J. Chem. Sci.* **2006**, *118*, 223.

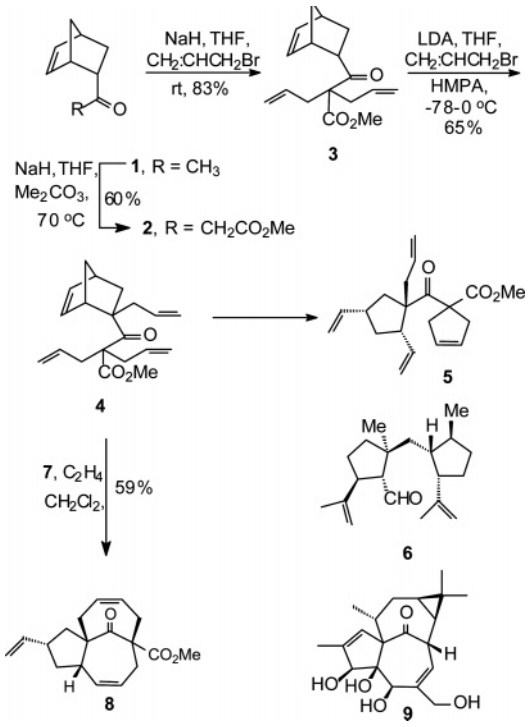
(3) (a) For a recent review on the use of norbornene derivatives in ROM/CM sequences, see: (a) Arjona, O.; Csaky, A. G.; Plumet, J. *Eur. J. Org. Chem.* **2003**, 611. (b) For some recent works see: (i) Schneider, M. F.; Lucas, N.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 257. (ii) Weeresakare, G. M.; Liu, Z.; Rainer, J. D. *Org. Lett.* **2004**, *6*, 1625. (c) Liu, Z.; Rainer. J. D. *Org. Lett.* **2005**, *7*, 131.
(4) (a) Stille, J. R.; Santarsiero, B. D.; Grubbs, R. H. *J. Org. Chem.***1990**, *55*, 843. (b) Stragies, R.; Blechert, S. *Synlett* **1998**, 169. (c) Arjona, O.; Csaky, A. G.; Murcia, M. C.; Plumet, J. *Tetrahedron Lett.* **2000**, *41*, 9777. (d) Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828. (e) Hagiwara, H.; Katsumi, T.; Endou, S.; Hoshi, T.; Suzuki, T. *Tetrahedron*, **2002**, *58*, 6651. (f) Arjona, O.; Csaky, A. G.; Medel, R.; Plumet, J. *J. Org. Chem.* **2002**, *67*, 1380. (g) Arjona, O.; Csaky, A. G.; Leon, V.; Medel, R.; Plumet, J. *Tetrahedron Lett.* **2004**, *45*, 565. (h) Wrobleski, A.; Sahasrabudhe, K.; Aube, J. *J. Am. Chem.* Soc. **2004**, *126*, 5475. (i) Hart, A. C.; Phillips, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 1094. (j) Maechling, S.; Norman, S. E.; Mckendrick, J. E.; Basra, S.; Koppner, K.; Blechert, S. *Tetrahedron Lett.* **2006**, *47*, 189. (k) Liu, Z.; Rainier, J. D. *Org. Lett.* **2006**, *8*, 459. (l) Carreras, J.; Avenoza, A.; Busto, J. H.; Peregrina, J. M. *Org. Lett.* **2007**, *9*, 1235. (m) Calvet, G.; Blanchard, N.; Kouklovsky, C. *Org. Lett.* **2007**, *9*, 1485.

10.1021/ol070906a CCC: $37.00
Published on Web 05/31/2007

to construct a polycyclic carbon network with a high degree of molecular complexity. Herein, we report the results of this investigation culminating in rapid access to densely functionalized tricyclic bridged and condensed ring systems which are otherwise difficult to obtain.

We first chose the norbornene derivative **4**. Metathesis of compound **4** offers interesting possibilities. As RCM of the *gem*-diallyl unit is a facile process,[6] the *gem*-diallyl unit present in **4** may undergo RCM to form cyclopentene with simultaneous ROM of the norbornene unit to produce a novel ring system **5** present in the diterpene dictymal **6**.[7] Alternatively a sequence of metathesis initiated by ROM followed by RCM of the resulting vinyl unit with one of the allyl units of the *gem*-diallyl moiety may take place. The compound **4** was prepared from the Diels−Alder adduct **1** as delineated in Scheme 1. Conversion of **1** to the β-keto

Scheme 1



ester **2** followed by alkylation of its enolate with excess allyl bromide afforded the *gem*-diallyl derivative **3**. Allylation of the lithium enolate generated from **3** with LDA provided the norbornene derivative **4** in overall good yield. Metathesis of this compound was initiated with Grubbs' first generation catalyst $(Cy_3P)_2Cl_2Ru{=}CHPh$ **7** in an atmosphere of ethylene at rt and was complete in 2 h. Interestingly the tricyclo-[7.4.1.$0^{1,5}$]tetradecene **8** was found to be the only product isolated in 59% yield as a crystalline solid, mp 79−80 °C. The structure of this compound was established through X-ray crystallography (Figure 1).[8] Compound **8** having "out−

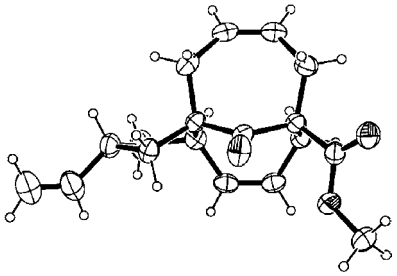


Figure 1. ORTEP plot of compound **8**.

out" bicyclo[4.4.1]undecene represents the tricyclic framework of the anti-cancer and anti-HIV active hightly strained tetracyclic diterpene ingenol **9**.[9] Direct access to this structurally complex bridged tricyclic skeleton of ingenol, which otherwise has been prepared with difficulty mostly through milti-step processes,[10] is the most remarkable feature of the present synthetic protocol. Since norbornene derivatives are easily available through Diels−Alder cycloaddition of cyclopentadiene derivatives, a sequence of Diels−Alder reaction and metathesis thus offers an attractive route for rapid access to highly complex structures.

To determine whether the angular substituent COOMe has any influence on the metathesis reaction course, the decarbomethoxy analogue **14** was chosen. This was obtained from the Diels−Alder adduct **10** (Scheme 2). Thus **10** was converted to the allylated derivative **11** through alkylation of the lithium enolate (LDA) with allyl bromide. The ester **11** was then transformed to the aldehyde **12** through a reduction−oxidation sequence. Addition of 4-butenyl magnesium bromide to the aldehyde **12** followed by oxidation gave the ketone **13**. Allylation of the lithium enolate of the ketone **13** gave the compound **14**. Metathesis of the nor-

(5) (a) Holt, D. J.; Barker, W. D.; Jenkins, P. R.; Davies, D. L.; Garratt, S.; Fawcett, J.; Rusell, D. R.; Ghosh, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3298. (b) Haque, A.; Panda, J.; Ghosh, S. *Indian J. Chem.* **1999**, *38B*, 8. (c) Holt, D. J.; Barker, W. D.; Jenkins, P. R.; Panda, J.; Ghosh, S. *J. Org. Chem.* **2000**, *65*, 482. (d) Nayek, A.; Banerjee, S.; Sinha, S.; Ghosh, S. *Tetrahedron Lett.* **2004**, *45*, 6457. (e) Banerjee, S.; Ghosh, S.; Sinha, S.; Ghosh, S. *J. Org. Chem.* **2005**, *70*, 4199. (f) Banerjee, S.; Nayek, A.; Sinha, S.; Bhaumik, T.; Ghosh, S. *J. Mol. Catal. A: Chem.* **2006**, *254*, 85. (g) Ghosh, S.; Sinha, S.; Drew, M. G. B. *Org. Lett.* **2006**, *8*, 3781. (h) Ghosh, S.; Bhaumik, T.; Sarkar, N.; Nayek, A. *J. Org. Chem.* **2006**, *71*, 9687.

(6) Kirkland, T. K.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.

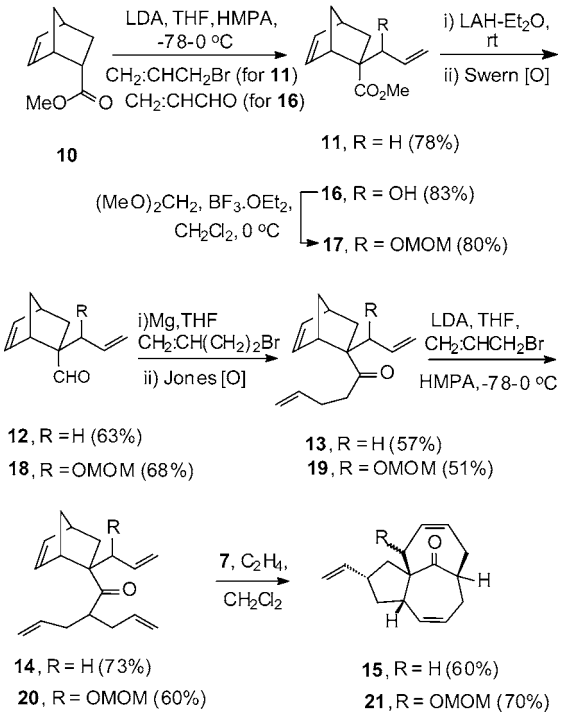
(7) Segawa, M.; Enok, N.; Ikuara, M.; Hikichi, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1987**, *28*, 3703.

(8) Crystallographic data for compound **8** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 602385. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44-1233-336033. E-mail: deposit@ccdc.cam.ac.uk.

(9) Total synthesis of ingenol: (a) Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726. (b) Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi,Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498. (c) Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300. (d) Watanabe, K.; Suzuki, Y.; Aoki, K.; Sakakura, A.; Suenaga, K.; Kigoshi, H. *J. Org. Chem.* **2004**, *69*, 7802.

(10) For a review on synthetic approaches to ingenol see: (a) Kim, S.; Winkler, J. D. *Chem. Soc. Rev.* **1997**, *26*, 387. For a few selected recent works see: (b) Grainger, R. S.; Owoare, R. B. *Org. Lett.* **2004**, *6*, 2961. (c) Epstein, O. L.; Cha, J. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 121. (d) Winkler, J. D.; Lee, E. C. Y.; Nevels, L. T. I. *Org. Lett.* **2005**, *7*, 1489.

Scheme 2



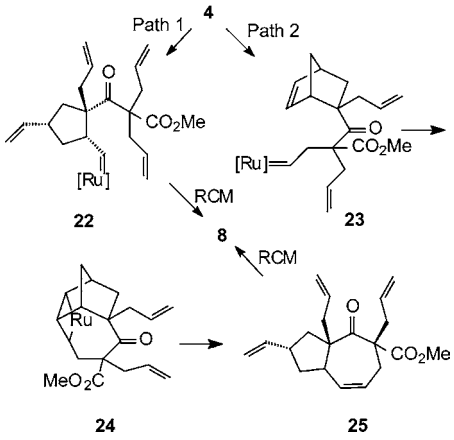
bornene derivative **14** under the same condition gave the tricycle **15** in about the same yield establishing that the angular substituent has little influence on the metathesis reaction course.

This protocol can be extended for the synthesis of the tricyclic analogue with a higher degree of functional complexity as demonstrated in Scheme 2. Reaction of the lithium enolate of the adduct **10** with acrolein provided a 1:1 diastereomeric mixture of the hydroxy-ester **16** in excellent yield. The hydroxyl group in one of the pure diastereoisomers (with unassigned stereochemistry) of **16** was protected to provide the MOM ether **17**, which was converted to the aldehyde **18** through a reduction−oxidation sequence. The aldehyde **18** was then converted to the trienone **19** following the protocol used for transformation of **12** to **13**. Finally allylation of the lithium enolate of **19** provided the norbornene derivative **20**. The metathesis of the norbornene derivative **20** provided the highly functionalized tricycle **21** in 70% yield. The tricycle **21** is particularly interesting as the three olefin units offer possibilities for chemoselective functionalization. Further, the tricycle **21** is functionalized in a way that offers the possibility for conversion of the "out−out" isomer of bicyclo[4.4.1]undecene to its "in−out" isomer present in ingenol derivatives following the protocol developed by Rigby et al.[11]

Two different reaction courses may be envisaged for the formation of the tricyclo[7.4.1.0]tetradecenes (Scheme 3). Metathesis may initiate at the norbornene double bond to produce regioselectively[3] the Ru-carbene intermediate **22**

(11) Rigby, J. H.; Claire, V. S.; Cuisiat, S. V.; Heeg, M. J. *J. Org. Chem.* **1996**, *61*, 7992.

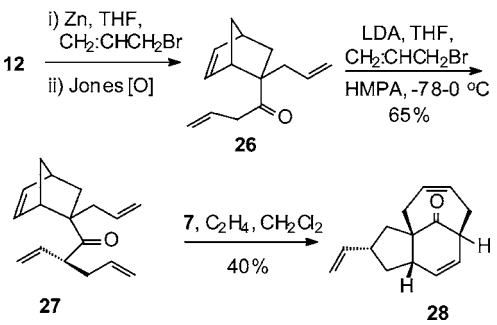
Scheme 3



(path 1), which on two consecutive RCM gives rise to tricycle **8**. This regioselectivity may arise by a keto-directed addition of the catalyst from the less favored endo face. It is also possible that ROM occurs to provide a regioisomer of **22**, which on CM with ethylene followed by two RCM steps provides **8**. Alternatively, metathesis may initiate at one of the allyl units of the *gem*-diallyl moiety to produce the Ru-carbene **23**. An intramolecular cycloaddition of the carbene to the norbornene double bond may give rise to the metallacyclobutane **24**. Cycloreversion of **24** to the Ru-carbene **25** and its CM with ethylene followed by RCM involving the residual allyl units may lead to **8**. If metathesis would proceed through the carbene intermediate **23** (path 2) some cyclopentene derivative **6** would be formed competitively through RCM with the adjacent allyl group. However, no such cyclization product could be isolated from any of the above examples. It is probably the strain associated with the highly sterically crowded norbornene that facilitates ROM leading preferentially to the carbene **22** rather than **23**. Thus metathesis of the above norbornene derivatives probably proceeds through path 1 involving a sequence of ROM-RCM-RCM.

The success of domino metathesis in the above examples led us to extend it for the construction of tricyclo[6.4.1.0^{1,5}] system (Scheme 4). The required norbornene derivative **27** was obtained from the aldehyde **12**. Reaction of the aldehyde

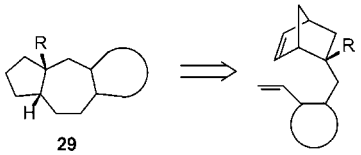
Scheme 4



12 with allyl zinc followed by oxidation of the resulting carbinol gave the ketone **26**. Allylation of the enolate of **26** proceeded from the exo-face giving rise to the norbornene derivative **27**. Metathesis of the norbornene derivative **27** afforded the tricyclic ketone **28** in moderate yield (40%).

The ROM-RCM cascade can be extended for synthesis of the condensed tricyclic system. The linearly arrayed tricyclic skeleton of the general structure **29** is frequently encountered in a large number of natural products such as dolastanes,[12a] clavularanes,[12b] chromophycanes,[12c] guanacastepenes,[12d] etc. We envisaged that metathesis of the norbornene derivatives of the general structure **30** would provide **29** (Scheme 5) through a ROM-RCM sequence. The

Scheme 5



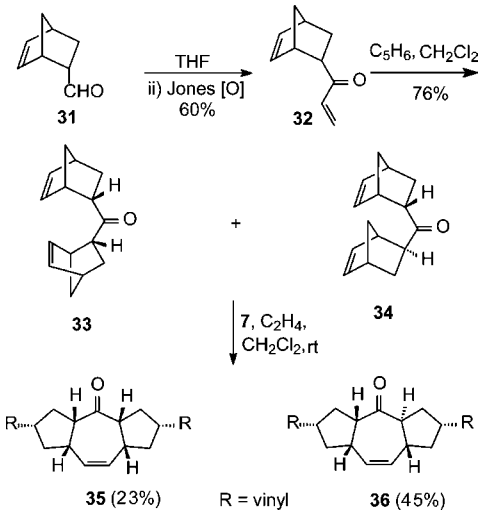
29 **30**

success of such an strategy will be of immense importance for direct entry into a series of natural products with wide ranging biological profile. To test the feasibility of such a sequence we chose compounds **33** and **34** in which two norbornene units are tethered through one carbon unit. Presumably one of the vinyl units generated in situ through ROM of each norbornene unit will undergo RCM to provide tricycles. The compounds **33** and **34** (Scheme 6) were prepared as follows. The endo aldehyde **31** was converted to the enone **32** on reaction with vinylmagnesium bromide followed by oxidation of the resulting carbinol. Diels−Alder reaction of the enone **32** with cyclopentadiene afforded an inseperable mixture of the endo,endo adduct **33** and exo,exo adduct **34** in 1:2 ratio (from integation of the olefinic protons at δ 5.88 and 5.77 in ^{1}H NMR of the mixture) in 76% yield. That the endo,endo adduct **33** was the minor product was ascertained from the ratio of the products obtained after metathesis of this mixture. Metathesis of the mixture of adducts **33** and **34** with Grubbs' catalyst **7** proceeded smoothly to produce the tricyclic compounds **35** (23%) and **36** (45%).[13] The symmetrical nature of the product **35**, which can arise only from the endo,endo adduct **35**, was indicated by the appearance of nine carbon signals as against seventeen carbon signals for compound **36** in their ^{13}C NMR spectra. The stereocontrolled synthesis of linearly arrayed tricyclic structures in a single operation is noteworthy as multiple steps[14] are generally required for their synthesis.

(12) (a) Pettit, G. R.; Ode, R. H.; Herald, C. L.; Von Dreele, R. B.; Michel, C. *J. Am. Chem. Soc.* **1976**, *98*, 4677. (b) Braekman, J. C.; Daloze, D.; Schubert, R.; Albericci, M.; Tursch, B.; Karlson, R.; *Tetrahedron* **1978**, *34*, 1551. (c) Clardy, J.; van Duyne, G.; Gonzalez, A. C.; Manta, E.; Martin, J. D.; Perez, C.; Ravel'o, J. L.; Schulte, G. K. *J. Chem. Soc., Chem. Commun.* **1978**, 767. (d) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900.

(13) A mixture of the ROM products of **33** and **34** was isolated in 10% yield.

Scheme 6



In conclusion we have demonstrated that metathesis of appropriately designed norbornene derivatives can be made to follow the ROM-RCM-RCM or the ROM-ROM-RCM sequence providing an expedient route for the construction of densely functionalized bridged and condensed ring systems with a high degree of molecular complexity. With the availability of numerous efficient routes to enantiopure norbornene derivatives[15] through asymmetric Diels−Alder reactions of cyclopentadiene with a variety of dienophiles, the present strategy offers possibilities for asymmetric synthesis of natural products.

Acknowledgment. S.G. thanks the Department of Science and Technology, Government of India for a Ramanna Fellowship. C.K.M. thanks CSIR, New Delhi for a Senior Research Fellowship.

Supporting Information Available: Experimental procedures with spectroscopic data, X-ray crystal data for compound **8**, and ^{1}H , ^{13}C NMR, and DEPT spectra of compounds **8**, **15**, **21**, 2**8**, **33** and **34**, **35**, and **36**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070906A

(14) (a) Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399. (b) Dudley, G. B.; Tan, D. S.; Kim, G.; Tanski, J. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6789. (c) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2185. (d) Lin, S.; Dudley, G. B.; Tan, D. S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2188. (e) Snider, B. B.; Shi, B. *Tetrahedron Lett.* **2001**, *42*, 9123. (f) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 567. (g) Shipe, W. D.; Sorensen, E. J. *Org. Lett.* **2002**, *4*, 2063. (h) Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030. (i) Mehta, G.; Pallavi, K.; Umarye, J. D. *Chem. Commun.* **2005**, *35*, 4456. (j) Miller, A. K.; Hughes, C. C.; Kennedy-Smith, J. J.; Gradl, S. N.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 17057. (k) Iimura, S.; Overman, L. E.; Paulini, R.; Zakarian, A. *J. Am. Chem. Soc.* **2006**, *128*, 13095. (l) Li, C. C.; Wang, C. H.; Liang, B.; Zhang, X. H.; Deng, L. J.; Liang, S.; Chen, J. H.; Wu, Y. D. *J. Org. Chem.* **2006**, *71*, 6892. (m) Shipe, W. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 7025. (n) Boyer, F. D.; Hanna, I. *Eur. J. Org. Chem.* **2006**, 471.

(15) Maruoka, K. In *Asymmetric Cycloaddition Reactions*; Ojima, I., Ed.; Wiley-VCH: New York, 2002; Chapter 8A, p 467.