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Application of Lewis Acid Catalyzed Tropone [6+4] Cycloadditions to the Synthesis of the Core of CP-225,917

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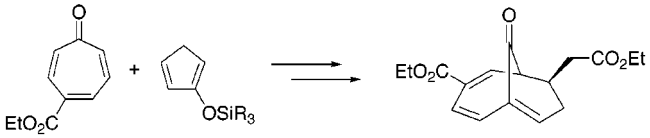
ABSTRACT



The carbocyclic core of CP-225,917 and CP-263,114 is accessible through the [6+4] cycloaddition of a tropone with a 2-substituted cyclopentadiene. Examination of this reaction has revealed for the first time that this cycloaddition process is catalyzed by Lewis acids, including lanthanide triflates. Cycloadditions of several mono-, di-, and trisubstituted tropones with 2-silyloxycyclopentadienes using $ZnCl_2$ catalysis are found to proceed in good yield and, in many cases, with excellent diastereoselectivity. Subsequent transformation to the core of the CP-molecules involves a site-selective Baeyer–Villiger oxidation of a tricyclic diketone, followed by a syn-elimination process.

The [6+4] cycloaddition of tropone with a diene[1] is a potentially powerful tool for natural product synthesis.[2] The reaction can be used to rapidly generate bicyclo[4.4.1]-undecanone structures and, if more complex reacting partners are used in conjunction with selective carbon−carbon cleaving reactions, holds the potential for the synthesis of other ring structures as well as linear molecules.[3] Despite this potential, relatively few synthetic efforts have utilized the tropone cycloaddition strategy.[4] This is mainly due to low yields and poor periselectivities, which are observed with more functionalized tropones and dienes.[2]

CP-225,917 and CP-263,114 (Figure 1) are an interesting set of natural products isolated by the Pfizer research group.[5]

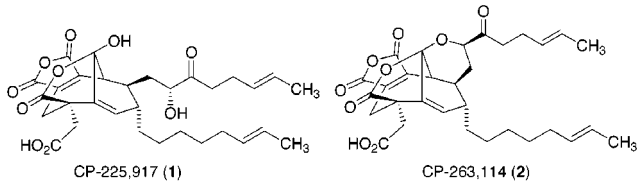


Figure 1. Structure of CP-225,917 and CP-263,114.

These fungal metabolites possess inhibitory activity against squalene synthetase and Ras farnesyl transferase, and they have been the focus of significant synthetic research[6] that has culminated in several recent total syntheses.[7] Our retrosynthetic analysis of this molecule (Scheme 1) indicated that the bicyclo[4.3.1]decadienone core of these molecules

(1) Cookson, R. C.; Drake, B. V.; Hudec, J.; Morrison, A. *J. Chem. Soc., Chem. Commun.* **1966**, 15.

(2) (a) Garst, M. E.; Roberts, V. A.; Prussin, C. *Tetrahedron* **1983**, *39*, 581. (b) Garst, M. E.; Roberts, V. A.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 3882. (c) Rigby, J. H. *Org. React.* **1997**, *49*, 331.

(3) For related modifications of tropylium [6+4] adducts, see: (a) Rigby, J. H.; Fales, K. R. *Tetrahedron Lett.* **1998**, *39*, 1525. (b) Rigby, J. H.; Fales, K. R. *Tetrahedron Lett.* **1998**, *39*, 5717.

(4) Rigby, J. H.; Rege, S. D.; Sandanayaka, V. P.; Kirova, M. *J. Org. Chem.* **1996**, *61*, 842.

(5) (a) Dabrah, T. T.; Kaneko, T.; Massefski, W., Jr.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594. (b) Dabrah, T. T.; Harwood, H. J., Jr.; Huang, L. H.; Jankovich, N. D.; Keneko, T.; Li, J.-C.; Linjdsey, S.; Moshier, P. M.; Subashi, T. A.; Therrien, M.; Watts, P. C. *J. Antibiot.* **1997**, *50*, 1.

(6) For a review, see: Starr, J. T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1415.

(7) (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; He, Y.; Yoon, W. H.; Choi, H.-S. *Angew. Chem, Int. Ed.* **1999**, *38*, 1676. (b) Nicolaou, K. C.; Jung, J.-K.; Yoon, W. H.; He, Y.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1829. (c) Meng, D.; Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3197. (d) Chen, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424. (e) Waizumi, N.; Itoh, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 7825.

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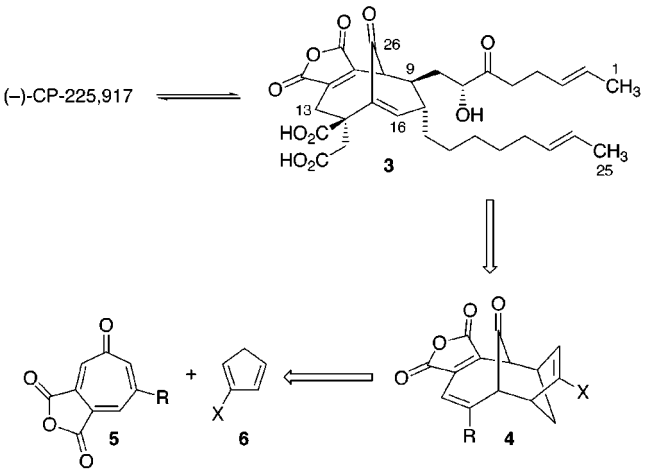
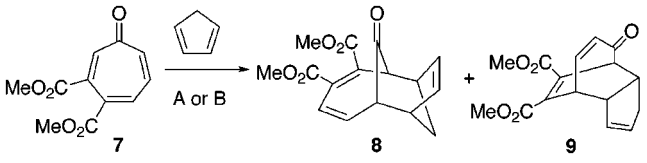
Scheme 1



might be accessed by a [6+4] cycloaddition between a functionalized tropone and an appropriately substituted cyclopentadiene. This cycloaddition would furnish tricyclic structure **4** that, upon selective carbon−carbon bond cleavage in the two-carbon bridge, might produce the desired carbocyclic framework of the natural product. In this letter, we disclose our preliminary examination of [6+4] tropone cycloadditions relevant to the synthesis of the CP-molecules, including the first examples of Lewis acid catalysis in this class of reactions. Furthermore, we demonstrate a highly site-selective Baeyer−Villiger oxidation that allows the cycloadducts to be transformed into the carbocyclic core of the CP-molecules.

Application of a tropone cycloaddition to the synthesis of the CP-ring system would ideally utilize a trisubstituted tropone containing electron-withdrawing groups at the 3- and 4-positions (e.g., **5**). As a model for this system, cycloadditions of diester tropone **7** were studied.[8] Cycloaddition of **7** with cyclopentadiene proceeded rapidly in toluene at reflux (Scheme 2). The reaction was complete in less than 2

Scheme 2[a]



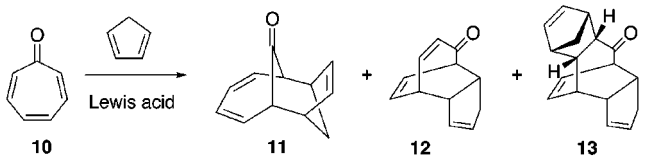
[a] Key: (A) PhMe, reflux, 2 h, 51% **8**, 1.5:1 ratio of **8/9**. (B) 10% $ZnCl_2$, Et_2O, 3 h, 62% **8**, 3:1 ratio of **8/9**.

h, but NMR analysis indicated that a mixture of [6+4] and [4+2] cycloadducts had formed in a 1.5:1 ratio. Although these cycloadducts could not be separated, the [4+2] adduct **9** could be selectively reduced in the presence of the [6+4] cycloadduct **8** with $NaBH_4/CeCl_3$ in methanol at −78 °C. Chromatographic separation then provided the desired [6+4] cycloadduct in 51% yield. The yield of the [6+4] cycloadduct could be improved by running the reaction in the presence of a Lewis acid. When the cycloaddition was conducted in ether in the presence of 10 mol % $ZnCl_2$, the reaction proceeded to completion within 3 h at room temperature and resulted in an improved ratio of cycloadducts (3:1) favoring the desired [6+4] adduct. Selective reduction of the minor product, as described above, allowed the desired adduct to be isolated in an improved 62% yield. As with most tropone [6+4] cycloadditions, both the catalyzed and the uncatalyzed reactions occurred exclusively with exo-stereoselectivity.[9]

The observation of Lewis acid catalysis in tropone [6+4] cycloadditions is noteworthy. Although there is a single report of Brønsted acid catalysis in the cycloaddition of tropone with cyclopentadiene,[10] a study by Garst et al. concluded that Lewis acids were not useful for mediating this reaction.[2a] Rigby has developed related [6+4] cycloadditions of cycloheptatriene η^1-tricarbonylchromium complexes,[11] and Trost has shown that palladium TMM complexes undergo [6+3] cycloadditions with tropone;[12] however, to our knowledge, no examples of Lewis acid catalysis exist for simple tropone [6+4] cycloadditions. In light of this, we chose to study Lewis acid catalyzed cycloadditions of tropone (**10**) with cyclopentadiene.

In the reaction between tropone (**10**) and cyclopentadiene, no acceleration above the background rate was observed when $ZnCl_2$ was employed as a catalyst in ether. Switching to methylene chloride as the solvent afforded a small amount of cycloadduct **11** along with lesser amounts of [4+2] adduct **12**. Examining a range of Lewis acids revealed that several lanthanides as well as Et_2AlCl catalyzed the reaction at significantly higher rates (Table 1). The best results were

Table 1. Lewis Acid Catalysis in Tropone Cycloadditions



entry	Lewis acid[a]	time	11	12	13
1	$ZnCl_2$	24 h	14%	4%	
2	Et_2AlCl	1.5 h	33%	3%	18%
3	$La(OTf)_3$	24 h	44%	25%	2%
4	$Yb(OTf)_3$	19 h	58%	28%	trace
5	$Sc(OTf)_3$	6 h	55%	14%	17%
6	$Sc(OTf)_3$	24 h[b]	59%	38%	

[a] All reactions conducted with 5 equiv of cyclopentadiene in the presence of 10 mol % Lewis acid in CH_2Cl_2 at 21 °C. [b] Reaction contained 1 equiv of H_2O.

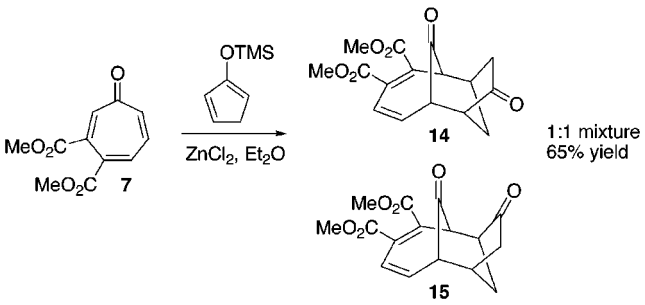
achieved with ytterbium triflate and scandium triflate, the latter of which gave nearly complete consumption of tropone within 6 h, resulting in a 55% yield of **11**. This was accompanied by **12** (14%) and 2:1 adduct **13** (17%), which arises from the Diels−Alder reaction of **12** with cyclopenta-

(8) Tropone **7** was prepared as described: Roberts, V. A.; Garst, M. E. *J. Org. Chem.* **1985**, *50*, 893.

diene. Interestingly, addition of 1 equiv of water moderates the acidity of the scandium triflate, resulting in complete suppression of the 2:1 adduct (Table 1, entry 6).[13] Although the periselectivity in these reactions is not absolute, they represent the first example of Lewis acid catalysis in tropone [6+4] cycloadditions. Employing the scandium triflate conditions in the cycloaddition of **7** with cyclopentadiene afforded a 4:1 ratio of cycloadducts and a 60% isolated yield of **8**.

As indicated in the retrosynthetic analysis depicted in Scheme 1, it was desirable to conduct the cycloaddition with a 2-substituted cyclopentadiene. Cycloaddition of **7** with 2-trimethylsilyloxycyclopentadiene[14] proceeded rapidly in ether in the presence of $ZnCl_2$ (Scheme 3). After aqueous

Scheme 3

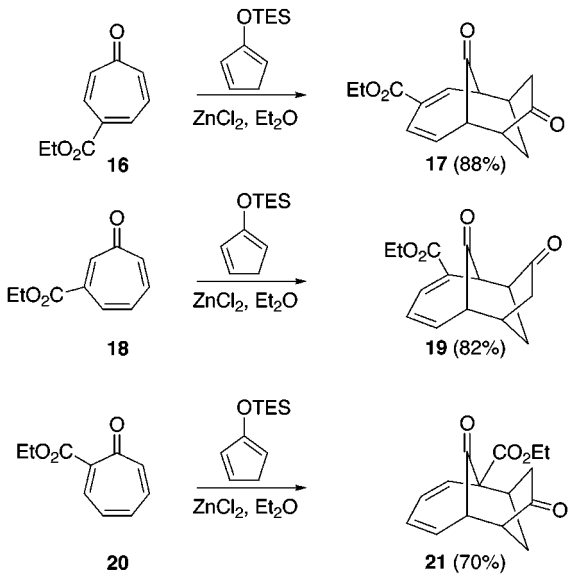


acidic workup to hydrolyze the initially formed silyl enol ether, the product was isolated in 65% yield as a 1:1 mixture of regioisomeric ketones. It has been shown that tropones display "even" regioselectivity when electron-withdrawing groups are placed in the 3- or 4-position.[2b,15] In this example, the two ester groups exert equal and opposite directing influences on the regioselectivity of the reaction, resulting in a poorly selective cycloaddition.

In comparison to the above results, cycloaddition of the 4-substituted tropone **16**[16] with 2-triethylsilyloxy-cyclopentadiene under identical conditions afforded adduct **17** in 88% yield. Similarly, the 3-substituted tropone **18** and the 2-substituted tropone **20** underwent regioselective cycloadditions with excellent yields. In all cases, only the "even" regioisomer is formed in these cycloadditions. The cycloaddition of **20** is particularly noteworthy. In many cases, 2-substituted tropones give predominantly [4+2] cycloadducts.[17] 2-Chlorotropone shows disparate reactivity, giving the [4+2] adduct with cyclopentadiene[18] and the [6+4] adduct with 1,3-cyclohexadiene.[19] Although **20** shows excellent [6+4] selectivity with 2-silyloxycyclopentadiene, reaction with cyclopentadiene resulted in mainly the [4+2] adduct. It is important to note that the cycloaddition reactions using 2-silyloxycyclopentadiene are also efficient in the absence of $ZnCl_2$, proceeding to completion within 24 h at 21 °C (vs instantaneous reaction in the presence of Lewis acid).

For a successful route to the CP-molecules to be realized, it will be necessary to use a 3,4,6-substituted tropone (cf. Scheme 1). To this end, tropone **22** was prepared by rhodium acetate catalyzed reaction of ethyl diazoacetate with 3,5-

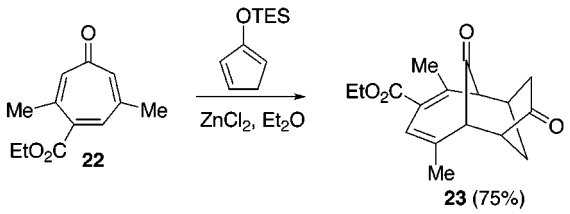
Scheme 4



dimethylanisole, followed by oxidation of the adduct with bromine (see Supporting Information for details). It was expected that **22** would serve as a useful model for the total synthesis, as hydroxymethyl groups in the 3- and 6-positions might eventually be oxidized at a late stage in the synthesis. The reaction of **22** was much slower than that of either the mono- or disubstituted tropones, requiring 18 h for complete reaction. Although the periselectivity of the reaction was slightly reduced, with the [4+2] adduct being isolated in 5% yield, the desired [6+4] cycloadduct could be isolated in good yield (75%). It should be noted that Lewis acid catalysis is crucial to the success of this reaction. In its absence, the

(9) Houk, K. N.; Woodward, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 4145.
(10) Ito, S.; Sakan, K.; Fujise, Y. *Tetrahedron Lett.* **1970**, *11*, 2873. Ito et al. reported that reaction of tropone and cyclopentadiene in the presence of pTsOH afforded a 65% yield of **11** and a 15% yield of a mixture of [4+2] adducts, although the solvent, temperature, and amount of catalyst were not specified. We have found that use of 10% pTsOH in toluene afforded a 40% yield of **11** along with 38% of the [4+2] adduct, **12**.
(11) Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Cuisiat, S. V.; Ferguson, M. D.; Henshilwood, J. A.; Krueger, C.; Ogbu, C. O.; Short, K. M.; Heeg, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 1382. For a thermal version using a catalytic amount of chromium, see: Rigby, J. H.; Fiedler, C. *J. Org. Chem.* **1997**, *62*, 6106.
(12) Trost, B. M.; Seoane, P. R. *J. Am. Chem. Soc.* **1987**, *109*, 615.
(13) Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *24*, 3755.
(14) 2-Trimethylsilyloxycyclopentadiene and 2-triethylsilyloxy-cyclopentadiene were prepared by silylation of 2-cyclopentenone with the corresponding silyl triflates and triethylamine. See: Plenio, H.; Aberle, C. *Organometallics* **1997**, *16*, 5950.
(15) "Even" or "odd" regioselectivity in this case refers to the number of atoms along the shortest path between the functional groups in the cycloadduct.
(16) Tropones **16**, **18**, and **20** were prepared by rhodium acetate catalyzed reaction of ethyl diazoacetate with anisole to give three cycloheptatrienes, which may be separated by chromatography and individually oxidized with bromine to afford the tropones. See: (a) Garst, M. E.; Roberts, V. A. *J. Org. Chem.* **1982**, *47*, 2188. (b) Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. *J. Org. Chem.* **1981**, *46*, 873.
(17) Rigby, J. H.; Moore, T. L.; Rege, S. *J. Org. Chem.* **1986**, *51*, 2400.
(18) Ito, S.; Sakan, K.; Fujise, Y. *Tetrahedron Lett.* **1969**, *10*, 715.
(19) Fujise, Y.; Mazaki, Y.; Shiokawa, T.; Fukazawa, Y.; Ito, S. *Tetrahedron Lett.* **1984**, *25*, 3611.

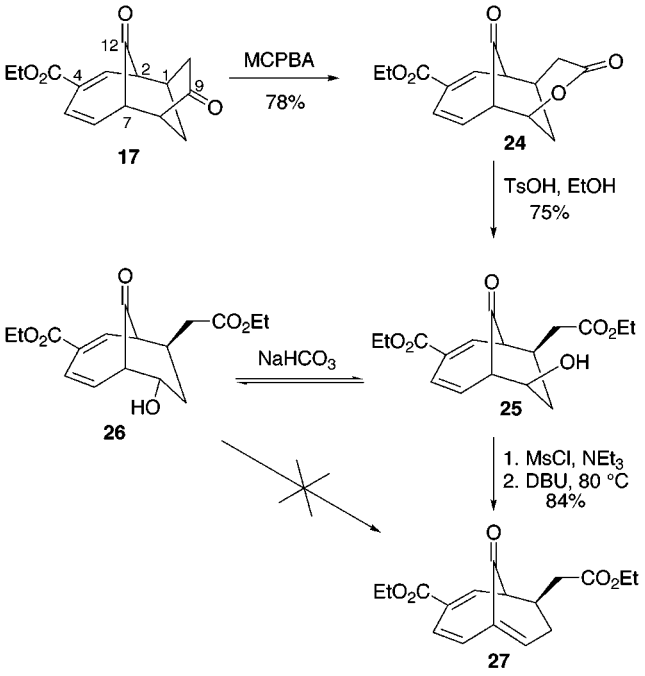
Scheme 5



tropone was not completely consumed and only a 50% yield of cycloadduct was isolated.

The success of the cycloaddition strategy hinges on the ability to effect a selective carbon−carbon bond cleavage to reveal a [4.3.1]bicyclic system. We studied this process using tricyclic diketone **17**. To our delight, treatment of **17** with 1 equiv of MCPBA in methylene chloride results in clean conversion of the diketone into lactone **24** (Scheme 6). The reaction is highly site selective, with no other

Scheme 6



oxidation products being isolated. The site selectivity in the reaction is striking and may be explained by two cooperating factors. First, molecular modeling (MM2 and PM3) calculations indicate that oxidation at C9 should be favored by at least 10 kcal/mol, as oxidation at C12 would be accompanied by a large increase in bond angle strain (See Scheme 6 for numbering). Second, formation of the requisite tetrahedral intermediate at C12 is greatly disfavored as the ketone does not undergo nucleophilic attack readily. One side of this ketone is flanked by the two-carbon bridge, preventing any nucleophile from approaching from that direction. On the opposite face, molecular models indicate that the C4−C5 bond lies almost directly along the Burgi−Dunitz trajectory,[20] thus greatly hindering nucleophilic attack from that side. The C9 ketone, although blocked on one side by the C12 carbonyl group, is completely unhindered on the outer face, thus permitting addition of MCPBA to take place. Similar site selectivity has been observed for $LiAlH_4$ reductions of an analogous diketone.[21]

Hydrolysis of the lactone in **24** was best achieved by treatment with acid in ethanol to provide **25** in 75% yield. Interestingly, the method of workup for the acidic hydrolysis is important. If saturated $NaHCO_3$ is added directly to the reaction mixture, the product is invariably isolated as a mixture of alcohol diastereomers **25** and **26**. A similar result is obtained if pure **25** is treated with a mixture of $NaHCO_3$ in ethanol/water. The stereoisomer in these cases presumably arises by a retro-aldol/aldol sequence. Exposure of the mixture of epimeric alcohols **25** and **26** to acid in ethanol cleanly reconverts the mixture back to a single stereoisomer (**25**). The retro-aldol cleavage problem is exacerbated if stronger base is used. Attempted transesterification of **24** with K_2CO_3/MeOH led to complete decomposition of the starting material.

Installation of the bridgehead olefin turned out to be a straightforward process. Mesylation of **25** under standard conditions followed by heating in toluene in the presence of DBU at 80 °C furnished the alkene **27** in 84% yield via an apparent syn-elimination.[22] If the elimination was carried out for extended reaction times or at higher temperatures (e.g., 150 °C, collidine), deconjugation of the olefin occurred. The stereochemistry of the leaving group is very important in this reaction. When the epimeric alcohol **26** was subjected to identical reaction conditions, no elimination of the intermediate mesylate was observed.

In conclusion, we have developed a tropone cycloaddition route to the core of CP-225,917 and CP-263,114. These studies have for the first time revealed that tropone cycloadditions may be effected using Lewis acid catalysts. The cycloadducts may be further transformed to the desired bridgehead enone by a site-selective Baeyer−Villiger oxidation followed by a straightforward ring-opening and elimination sequence. The application of this method to a total synthesis of the CP-molecules is in progress, and results will be reported in due course.

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

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(20) (a) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. J. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (b) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.

(21) Li, Z.-H.; Mori, A.; Kato, N.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2778.

(22) For related eliminations, see: (a) Warnhoff, E. W.; Wong, C. M.; Tai, W. T. *J. Org. Chem.* **1967**, *32*, 2664. (b) Carruthers, W.; Qureshi, M. I. *J. Chem. Soc. C* **1970**, 2238. (c) Buchanan, G. L.; Jamieson, G. *Tetrahedron* **1972**, *28*, 1129. (d) Meng, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1485.