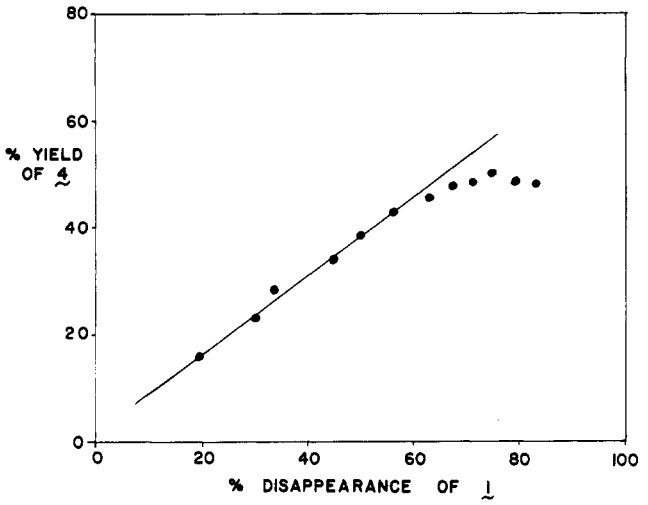


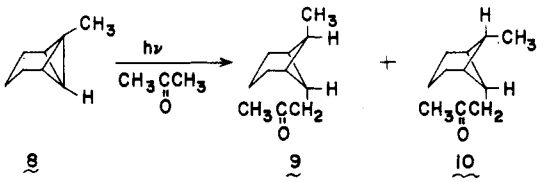

**Figure 1.** Plot of appearance of the photoproduct 4 vs. the disappearance of tricyclo[4.1.0.0$^{2,7}$]heptane (1).

a 34% isolated yield of 7.[5] Analysis of the crude reaction mixture by VPC after 120 h indicated the presence of 46% of 7 and 12% of 1.[6] The structures of 6 and 7 were established through a comparison of their spectral properties with those of 4 and 5.

Mechanistically, we believe that the addition of acetone, acetonitrile, and ethyl acetate across the C1–C7 bond of 1 occurs via a photoinitiated radical chain reaction.[7] Since no reaction occurs in the dark, the addition was certainly photoinitiated. Numerous factors point to the radical nature of the addition. The addition was inhibited by the presence of oxygen. With toluene as solvent, 1,2-diphenylethane was the major product with only trace amounts of acetone adduct being observed.[8] In addition, the formation of the acetonitrile adduct in the presence of small amounts of the photoactive acetone provided convincing evidence for a radical chain process.

The ability to obtain high yields of 4 from 1 was limited by the stability of 4 under the reaction conditions. Figure 1 shows a plot of disappearance of 1 vs. appearance of 4. As can be seen from this plot, a reasonably linear relationship exists for the conversion of 1 into 4 up to about 60% reaction. At this point, the product concentration leveled off, even though the starting material continued to be used up. At 60% reaction, the yield of 4 was 75%, based on unreacted starting material.[9]

Lastly, the photoinduced addition of acetone to 1-methyltricyclo[4.1.0.0$^{2,7}$]heptane (8) was studied. This reaction gave a 42% yield of a 4.3:1 mixture of 9 and 10, respectively.[10] The anti-Markovnikov nature of the addition to 8 is significant in that it is consistent with the intermediacy of a radical chain process.




8 9 10

We are continuing to study photoinitiated additions to strained carbon–carbon $\sigma$ bonds.

**Acknowledgment.** We are indebted to the National Science Foundation for Grant CHE81-14772, which supported this investigation.

**Registry No.** 1, 287-13-8; 4, 87568-92-1; 5, 87568-93-2; 6, 87568-95-4; 7, 87568-94-3; 8, 32348-63-3; 9, 87568-96-5; 10, 87638-00-4; $CH_3C(O)CH_3$, 67-64-1; $CH_3CO_2C_2H_5$, 141-78-6; $CH_3CN$, 75-05-8.

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*Received August 1, 1983*

## A Versatile Synthesis of $\alpha$-Pyrones

*Summary:* The $\alpha$-oxoketene dithioacetal functionality is exploited in a versatile and efficient synthesis of annulated and simple $\alpha$-pyrones. The alkyl substitution pattern about the $\alpha$-pyrone ring can be modified at all four olefinic carbon atoms in a systematic manner.

*Sir:* We report an efficient and versatile synthesis of alkyl-substituted $\alpha$-pyrones from $\alpha$-oxoketene dithioacetals. The $\alpha$-pyrone ring system[1] is found in several types of natural products and is an important synthetic intermediate. Steroidal,[2] nor- and dinorditerpenoid,[3] and monocyclic[4] $\alpha$-pyrones constitute important classes of natural products that exhibit a wide range of biological activity. The steroidal bufadienolides show cardiotonic[2c] and antineoplastic[2b] properties while several nor- and dinorditerpenoid $\alpha$-pyrones isolated from *Podocarpus* plants function as insect larvae toxins[3e] and cytotoxic agents.[3a–c] Synthetically, the Diels–Alder reaction of $\alpha$-pyrones with acetylene[5] or olefin[6] dienophiles affords preparative routes to benzene and cyclohexadiene derivatives, respectively.

The synthesis of $\alpha$-pyrones from $\alpha$-oxoketene dithioacetals requires a sequence of operations involving organocopper conjugate addition, 1,2-nucleophilic addition of ester enolates, and subsequent ester hydrolysis and enol lactonization. The method is applicable for the synthesis of both simple and annulated $\alpha$-pyrones, and, in principle,

(6) Direct irradiation of 1 in ethyl acetate (which contained no acetone) in a quartz cell with a 450-W Hanovia medium-pressure mercury lamp also gave 7, but in lower yield (16%).

(7) Numerous examples of the photoinduced addition of acetone and of other ketones *to olefins* have appeared in the literature. These additions to olefins have been postulated to occur via radical chain processes. For leading references, see: Bartlett, P. D.; Roof, A. A. M.; Winter, W. J. *J. Am. Chem. Soc.* **1981**, *103*, 6520. Reusch, W. *J. Org. Chem.* **1962**, *27*, 1882. deMayo, P. "Advances in Organic Chemistry"; Interscience: New York, 1960; Vol. II; p 367. Elad, D. In "Organic Photochemistry"; Chapman, O., Ed.; Marcel Dekker: New York, 1969, Vol. II, p 190.

(8) Heating of 1 in acetone containing $\alpha,\alpha'$-azobis(isobutyronitrile) gave low yields of 4.

(9) We do not know the nature of the products formed in the photodecomposition of 4.

(10) The structures of 9 and 10 were established on the basis of their 300-MHz $^1$H NMR spectra and their 20-MHz $^{13}$C NMR spectra.[3]

(11) Sohio Fellow, 1979–1980; Amoco Foundation Fellow, 1980–1981.

(1) For a discussion of the chemistry of $\alpha$-pyrones see: Staunton, J. In "Comprehensive Organic Chemistry"; Sammes, P. G., Ed.; Pergamon Press: Oxford, England, 1979; Vol. 4, Part 18.2, pp 629–646. 2*H*-Pyran-2-one and its derivatives are commonly referred to as 2-pyrones or $\alpha$-pyrones.

(2) (a) Goetz, M. A.; Meinwald, J.; Eisner, T. *Experientia* **1981**, *37*, 679 and references cited therein. (b) Kupchan, S. M.; Moniot, J. L.; Sigel, C. W.; Hemingway, R. J. *J. Org. Chem.* **1971**, *36*, 2611 and references cited therein. (c) Chem, K. K.; Kovarikova, A. *J. Pharm. Sci.* **1967**, *56*, 1535.

(3) (a) Hayashi, Y.; Matsumoto, T.; Sakan, T. *Heterocycles* **1978**, *10*, 123. (b) Hayashi, Y.; Yuki, Y.; Matsumoto, T.; Sakan, T. *Tetrahedron Lett.* **1977**, 3637. (c) Hayashi, Y.; Yuki, Y.; Matsumoto, T.; Sakan, T. *Ibid.* **1977**, 2953. (d) Loder, J. W.; Nearn, R. H. *Ibid.* **1975**, 2497. (e) Russell, G. B.; Fenemore, P. G.; Singh, P. *J. Chem. Soc., Chem. Commun.* **1973**, 166.

(4) Adityachaudhury, N.; Das, A. K. *J. Sci. Ind. Res.* **1979**, *38*, 265.

(5) (a) Bryson, T. A.; Donelson, D. M. *J. Org. Chem.* **1977**, *42*, 2930. (b) Reed, J. A.; Schilling, C. L., Jr.; Tarvin, R. F.; Rettig, T. A.; Stille, J. K. *Ibid.* **1969**, *34*, 2188.

(6) Kozikowski, A. P.; Corey, E. J. *Tetrahedron Lett.* **1975**, 2389.

0022-3263/83/1948-4439$01.50/0 

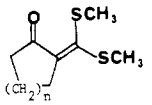
Table I. Synthesis of α-Pyrones from β-(Methylthio) α,β-Enones

| entry | substrate | reagent[a] (rxn cond)[b] | δ-keto ester or acid | yield,[c] % | enol lactonization procedure[d] | α-pyrone[e] | yield,[c] % |
|---|---|---|---|---|---|---|---|
| 1 | 4 | A (1) | **10a** | 88 | X | **16a** | 93 |
| 2 | | B (1) | **10b** | 72 | Y | | 88 |
| 3 | | C (3) | | 46 | | | |
| 4 | | D (1) | **10c** | 87 | Y | | 88 |
| 5 | | E (1) | **10d** | 57 | X | **16b** | 83 |
| 6 | 5 | A (1) | **11** | 71[f] | X | **17** | 99 |
| 7 | 6 | A (2) | **12a** | 74 | X | **18** | 94 |
| 8 | | B (1) | **12b** | 77 | Y | | 70 |
| 9 | 7 | A (2) | **13a** | 76 | | **19** | |
| 10 | | B (1) | **13b** | 69 | Y | | 60 |
| 11 | 8 | A (2) | **14a** | 93[g] | X | **20** | 92 |
| 12 | | B (1) | **14b** | 25 | | | |
| 13 | 9 | A (2) | **15b** | 90 | X | **21** | 90 |
| 14 | | B (1) | | 24 | | | |

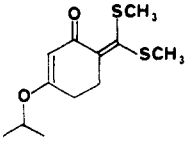
[a] A = $LiCH_2CO_2$-*t*-Bu; B = $LiCH_2CO_2SiMe_3$; C = $LiCH_2CO_2Li$; D = $LiCH_2CO_2CH_3$; E = $CH_3CHLiCO_2$-*t*-Bu. [b] 1 = THF, 2 N HCl −78 °C to room temperature. 2 = THF, −78 °C; 10% aqueous $HBF_4$, −78 °C to room temperature. 3 = THF, 0–40 °C; 2 N NaOH; 10% HCl. [c] All yields are based upon isolated products purified by column chromatography on silica gel. [d] X = 10 equiv of $CF_3COOH$, $(CF_3CO)_2O$, 6–12 h. Y = $(CF_3CO)_2O$, 3–7 h. [e] All α-pyrones gave satisfactory C and H combustion analyses. The assigned structures were in accord with infrared, proton NMR, and carbon NMR spectral data. [f] This is a composite yield of acid (63%) and α-pyrone (8%). [g] This yield includes a small quantity (~5%) of **20** that was present.

a diverse array of C3–C6 alkyl-substituted derivatives can be prepared by simply varying the substitution pattern on the ester and/or ketene dithioacetal component and by choice of organocuprate. Although several synthetic strategies are available for the synthesis of α-pyrones,[1,7,8] the synthetic routes are limited by the substitution patterns that can be generated.[1,9] Annulated α-pyrones, for example, have been prepared from 2-((benzyloxy)-methylene)[10] and 2-((*n*-butylthio)methylene)cyclohexanones,[11] which do not conveniently provide for C6-substitution commonly found in naturally occuring α-pyrones.[4]

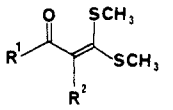
α-Oxoketene dithioacetals **1a,b**, **2** and **3a,b** were pre-



**1a**, *n* = 1
**b**, *n* = 2

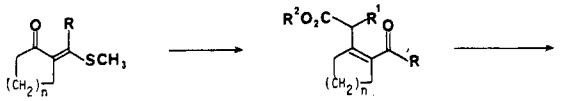


**2**



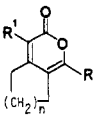
**3a**, $R^1 = i\text{-}C_3H_7$; $R^2$ = H
**b**, $R^1 = C_2H_5$; $R^2 = CH_3$

pared by an established procedure[12] and converted into β-methylthio α,β-enones **4–9** upon reaction with organocuprates.[13] Reaction of **1a**, for example, with lithium methyl(phenylthio)copper[14] in THF afforded enone **4** (80%) in a chemoselective fashion. Nucleophilic addition of *tert*-butyl lithioacetate to **4** followed by quenching with 2 N HCl afforded δ-keto ester **10a** (88%) via an alkylative 1,3-carbonyl transposition process.[15] Treatment of **10a** with trifluoroacetic acid in trifluoroacetic anhydride effected ester hydrolysis and enol lactonization[16] to afford α-pyrone **16a** in 93% yield. α-Pyrones **17–21** (Table I) were prepared according to a similar sequence of operations.



**4**, *n* = 1; R = Me
**5**, *n* = 1; R = *sec*-Bu
**6**, *n* = 2; R = Me

**10a**, *n* = 1; $R^2$ = *t*-Bu; $R^1$ = H; R = Me
**b**, *n* = 1; $R^2 = R^1$ = H; R = Me
**c**, *n* = 1; $R^2$ = R = Me; $R^1$ = H
**d**, *n* = 1; $R^2$ = *t*-Bu; $R^1$ = R = Me
**11**, *n* = 1; $R^2 = R^1$ = H; R = *sec*-Bu
**12a**, *n* = 2; $R^2$ = *t*-Bu; $R^1$ = H; R = Me
**b**, *n* = 2; $R^2 = R^1$ = H; R = Me



**16a**, *n* = 1; $R^1$ = H; R = Me
**b**, *n* = 1; $R^1$ = R = Me
**17**, *n* = 1; $R^1$ = H; R = *sec*-Bu
**18**, *n* = 2; $R^1$ = H; R = Me

In this synthetic approach to α-pyrones, the 1,2-nucleophilic addition must ultimately deliver an acetic acid

(7) For a recent approach to α-pyrones involving the conjugate addition of methyl 2-lithio-2-(phenylthio)acetate to α,β-enones, see: Bornack, W. K., Jr. *Diss. Abstr. Int. B* **1981**, *42*, 208; *Chem. Abstr.* **1981**, *95*, 168918*r*.

(8) For synthesis of the α-pyrone ring of bufadienolides, see: Bauer, P. E.; Kyler, K. S.; Watt, D. S. *J. Org. Chem.* **1983**, *48*, 34 and references cited therein.

(9) The diversity of approaches to α-pyrones reflects varied synthetic objectives. All of the methods exhibit limitations in terms of the number of steps involved, chemical yields, functional group compatibility, and the pattern and type of substituents that can be introduced. The present method, for example, does not constitute a convenient route to bufadienolide α-pyrones (see ref 8) or to 4-hydroxy- and 4-alkoxy-2-pyrones. The reaction of β-keto ester dianions with esters represents the most versatile approach to the important 4-hydroxy-2-pyrones: Huckin, S. N.; Weiler, L. *Tetrahedron Lett.* **1972**, 2405. Harris, T. M.; Harris, C. M. *J. Org. Chem.* **1966**, *31*, 1032.

(10) Plattner, Pl. A.; Treadwell, P.; Scholz, C. *Helv. Chim. Acta* **1945**, *28*, 771.

(11) Peterse, A. J. G. M.; de Groot, Ae.; van Leeuwen, P. M.; Penners, N. H. G.; Koning, B. H. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 124.

(12) Dieter, R. K. *J. Org. Chem.* **1981**, *46*, 5031.

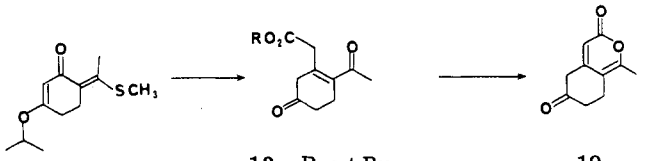
(13) Dieter, R. K.; Fishpaugh, J. R.; Silks, L. A. *Tetrahedron Lett.* **1982**, *23*, 3751.

(14) For the preparation of alkyl(phenylthio)cuprates, see: Posner, G. H.; Whitten, C. E.; Sterling, J. H. *J. Am. Chem. Soc.* **1973**, *95*, 7788.

(15) (a) Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1620. (b) Akiyama, S.; Nakatsuji, S.; Hamamura, T.; Katacka, M.; Nakagawa, M. *Tetrahedron Lett.* **1979**, 2809. (c) Bernstein, P. R. *Ibid.* **1979**, 1015.

(16) (a) For reaction conditions employed to effect enol lactonization, see: Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 4597. (b) Eggelte, T. A.; de Boer, J. J. J.; de Koning, H.; Huisman, H. O. *Synth. Commun.* **1978**, *8*, 353. (c) Marshall, J. A.; Snyder, W. R. *J. Org. Chem.* **1975**, *40*, 1656. (d) Meinwald, J.; Frauenglass, E. *J. Am. Chem. Soc.* **1960**, *82*, 5235. (e) Rosenmund, K. W.; Herzberg, H.; Schutt, H. *Chem. Ber.* **1954**, *87*, 1258.

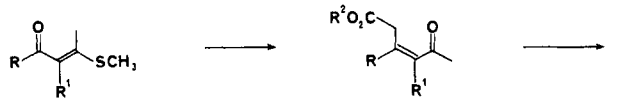
or substituted acetic acid unit and can, in principle, be effected with *tert*-butyl, methyl, and trimethylsilyl ester enolate anions[17,18] or carboxylic acid dianions.[18] These various nucleophiles were examined in an effort to maximize the efficiency of the synthetic sequence. Dilithioacetate[19] afforded low yields of addition products (entry 3) and carboxylic acid dianions were not examined further. Trimethylsilyl lithioacetate underwent smooth addition to cyclic ketones (entries 2, 8, and 10) but afforded poor



7 13a, R = *t*-Bu; b, R = H 19

yields of addition products upon reaction with acyclic ketones (entries 12 and 14). *tert*-Butyl lithioacetate, however, underwent smooth addition[20] to both cyclic and acyclic ketones (entries 1, 6, 7, 9, 11, and 13) although diminished yields were observed for *tert*-butyl lithiopropionate (entry 5). Addition of methyl lithioacetate to **4** (87%) requires subsequent alkaline hydrolysis of the methyl ester and enol lactonization of the resulting δ-keto acid. The alkaline hydrolysis of **10c** [10% aqueous KOH, $CH_3OH$] was quantitative, and the resulting δ-keto acid **10b** was converted to α-pyrone **16a** (88%) upon treatment with trifluoroacetic anhydride. These results indicate that the enolate anions of the *tert*-butyl and methyl esters are generally the more reliable nucleophiles in the 1,2-nucleophilic addition reaction.

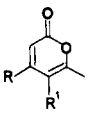
The reaction conditions required to effect *tert*-butyl ester hydrolysis and subsequent enol lactonization were remarkably dependent upon substrate structure. The cyclic δ-keto esters **10a,d**, **12a**, and **13a** were isolated upon quenching the Rathke-type Reformatsky reactions[17] and then converted into the corresponding α-pyrones upon treatment with trifluoroacetic acid in trifluoroacetic anhydride. The acyclic substrates **14a** and **15a** were more susceptible to ester hydrolysis and enol lactonization. α-Pyrones **20** (76%) and **21** (77%) were formed directly



8a, R = *i*-Pr; $R^1$ = H; b, R = Et; $R^1$ = Me

14a, $R^2$ = *t*-Bu; $R^1$ = H; R = *i*-Pr; b, $R^2$ = $R^1$ = H; R = *i*-Pr

15a, $R^2$ = *t*-Bu; $R^1$ = Me; R = Et; b, $R^2$ = H; $R^1$ = Me; R = Et



20, $R^1$ = H; R = *i*-Pr; 21, $R^1$ = Me; R = Et

in a one-pot process when the reaction of **8** and **9**, respectively, with *tert*-butyl lithioacetate was quenched with $HBF_4$ (10% v/v aqueous $HBF_4$/THF, 1:2, v/v) and the resulting solution allowed to stir at room temperature for 12 h.[21] Interestingly, δ-keto ester **10a** was recovered unchanged when treated with $HBF_4$ under the same reaction conditions. Finally, although the acyclic δ-keto esters **14a** and **15a** existed as a mixture of *E* and *Z* geometrical isomers,[22] good yields of α-pyrones were obtained.

In summary, cyclic and acyclic ketones can be efficiently converted into α-pyrones in four steps through the intermediacy of α-oxoketene dithioacetals. The method provides for the systematic introduction of alkyl substituents at all four olefinic carbon atoms of the α-pyrone ring and is the most general synthetic route to alkyl-substituted α-pyrones.

**Acknowledgment.** We are pleased to acknowledge the partial support of this investigation by Research Corporation, NSF (Grant CHE-8219093), and Boston University for seed grants from the Graduate School and Department of Chemistry.

**Supplementary Material Available:** Detailed spectroscopic data (IR and NMR) for compounds **10a,d**, **11**, **12a,b**, and **14a,b** (2 pages). Ordering information is given on any current masthead page.

(17) Rathke, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3222.

(18) For a review, see: Petragnani, N.; Yonashiro, M. *Synthesis* **1982**, 521.

(19) (a) Ellison, R. A.; Bhatnagar, P. K. *Synthesis* **1974**, 719. (b) Lawson, J. A.; Colwell, W. T.; Degraw, J. I.; Peters, R. H.; Dehn, R. L.; Tanabe, M. *Ibid.* **1975**, 729.

(20) Utilization of *tert*-butyl lithioacetate (i) in THF at −78 °C afforded higher yields of addition products than the alternative procedure involving 1 M solutions of i in toluene at 25 °C (e.g., reaction of **4** with i afforded, after quenching with 2 N HCl a 55% yield of **10a** and a 31% yield of unreacted **4**): Rathke, M. W.; Sullivan, D. F. *J. Am. Chem. Soc.* **1973**, *95*, 3050.

(21) Under these reaction conditions trans olefinic δ-keto esters **14a** and **15a** did not undergo ester hydrolysis or isomerization to the cis isomers. Treatment of pure *trans*-**15a** with $HBF_4$ for 24 h afforded only recovered ester. The crude products were a mixture of α-pyrones **20** and **21**, trans δ-keto esters **14a** and **15a**, and uncyclized cis δ-keto acids **14b** and **15b**, respectively. Exposure of the initial 1,2-addition product to $HBF_4$ for shorter periods of time (2–4 h) afforded larger quantities of δ-keto acid **14b**. Attempted separation of these product mixtures by chromatography on silica gel afforded pure α-pyrones **20** and **21** in yields that were unaffected by the quantity of δ-keto acids **14b** and **15b** present in the original mixture. Similarly, δ-keto acid **11** underwent cyclization to α-pyrone **17** when subjected to medium-pressure liquid chromatography (MPLC) on silica gel.

(22) When the reaction of **8** with *tert*-butyl lithioacetate was quenched with 1.2 equiv of 10% $HBF_4$ **14a** was isolated as a 5:1 *Z*/*E* mixture of stereoisomers. The structures of these stereoisomers were assigned on the basis of proton NMR chemical shifts for the methylene protons ($CDCl_3$; *E* δ 3.01, *Z* 3.53). A methyl substituent cis to the carbonyl functionality in β-methyl-α,β-unsaturated carbonyl compounds resonates downfield in the NMR spectrum relative to the trans methyl substituent: Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: London, 1969; pp 222–224.

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*Received June 23, 1983*

## Asymmetric Diels–Alder Reaction: Applications of Chiral Dienophiles

*Summary:* The chiral dienophile recently designed and its related compounds react highly diastereoselectively with a wide variety of both achiral and chiral dienes, and the stereochemical outcome of these Diels–Alder reactions is predictable.

*Sir:* The asymmetric Diels–Alder reaction continues to attract keen attention.[1] Our recent efforts in this area were directed toward the design of new chiral dienophiles

(1) For recent reviews, see: (a) Mori, Y. *J. Synth. Org. Chem., Jpn.* **1982**, *40*, 321. (b) Paquette, L. A. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press; New York, in press.

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