ORGANIC LETTERS

2002
Vol. 4, No. 1
79−82

Construction of Substituted Cyclohexanones by Reductive Cyclization of 7-Oxo-2,8-alkadienyl Esters

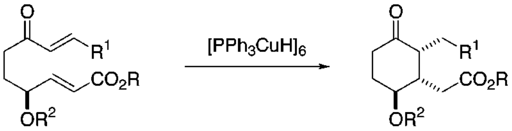
Theodore M. Kamenecka,[†] Larry E. Overman,* and Sylvie K. Ly Sakata[‡]

Department of Chemistry, University of California, Irvine, 516 Rowland Hall,
Irvine, California 92697-2025

leoverma@uci.edu

Received October 18, 2001

ABSTRACT



Cyclization of 7-oxo-2,8-alkadienyl esters upon reaction with triphenylphosphinecopper hydride hexamer stereoselectively yields substituted cyclohexanones having a cis relationship of carbon side chains at C2 and C3. This cyclohexanone construction is particularly useful for preparing 4-alkoxy- or 4-siloxy-2,3-disubstituted cyclohexanones, in which instance stereoselection is ≥20:1.

The preparation of six-membered carbocyclic rings is a fundamental process of organic synthesis. One useful method is to assemble such rings from acyclic precursors by sequential conjugate addition reactions.[1] In one widely investigated variant of this strategy, a 2,7-nonadienyldicarboxylic diester is cyclized by reaction with an external carbon,[2] nitrogen,[3] or hydride[4] nucleophile (eq 1). For ongoing synthesis efforts directed at members of the manzamine alkaloid family, we required an efficient way to prepare cyclohexanones having carbon side chains at C2 and C3 and an oxygen substituent at C4. To achieve this objective, we examined a new tandem Michael sequence in which cyclization of a 7-oxo-2,8-alkadienyl ester would be

---

* To whom correspondence should be addressed.

[†] Current address: Merck Research Laboratories, MRLSDB2-1204, 3535 General Atomics Court, La Jolla, CA 92121.

[‡] Current address: Pfizer Global Research & Development, La Jolla, 3565 General Atomics Court, La Jolla, CA, 92121.

(1) (a) Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *Org. React.* **1995**, *47*, 315−552. (b) Ho, T. L. *Tandem Organic Reactions*; John Wiley: New York, 1992. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131−163.

(2) (a) Saito, S.; Hirohara, Y.; Narahara, O.; Moriwake, T. *J. Am. Chem. Soc.* **1989**, *111*, 4533−4535. (b) Klimko, P. G.; Singleton, D. A. *J. Org. Chem.* **1992**, *57*, 1733−1740. (c) Savchenko, A. V.; Montgomery, J. *J. Org. Chem.* **1996**, *61*, 1562−1563.

(3) Typically a lithium amide: (a) Uyehara, T.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1410−1411. (b) Uyehara, T.; Asao, N.; Yamamoto, Y. *Tetrahedron* **1988**, *44*, 4173−4180. (c) Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 113−114. (d) Uyehara, T.; Asao, N.; Yamamoto, Y. *J. Chem. Soc. Chem. Commun.* **1989**, 753−754. (e) Asao, N.; Uyehara, T.; Yamamoto, Y. *Tetrahedron* **1990**, *46*, 4563−4572. (f) Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 3139−3145. (g) Shida, N.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 5049−5051. (h) Urones, J. G.; Garrido, N. M.; Díez, D.; Dominguez, S. H.; Davies, S. G. *Tetrahedron: Asymmetry* **1999**, *10*, 1637−1641.

(4) LiR_3BH: (a) Hori, K.; Hikage, N.; Inagaki, A.; Mori, S.; Nomura, K.; Yoshii, E. *J. Org. Chem.* **1992**, *57*, 2888−2902. (b) Hori, K.; Kazumo, H.; Nomura, K.; Yoshii, E. *Tetrahedron Lett.* **1993**, *34*, 2183-2186. (c) Yoshii, E.; Hori, K.; Nomura, K.; Yamaguchi, K. *Synlett* **1995**, 568−570. (d) Yoshizaki, H.; Tanaka, T.; Yoshii, E.; Koizumi, T.; Takeda, K. *Tetrahedron Lett.* **1998**, *39*, 47−50. (e) Takeda, K.; Ohkawa, N.; Hori, K.; Koizumi, T.; Yoshii, E. *Heterocycles* **1998**, *47*, 277−282. *n*-Bu_3SnH: (f) Suwa, T.; Nishino, K.; Miyatake, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **2000**, *41*, 3403−3406. $PhSiH_3$: (g) Baik, T.-G.; Luis, A. L.; Wang, L.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112−5113.

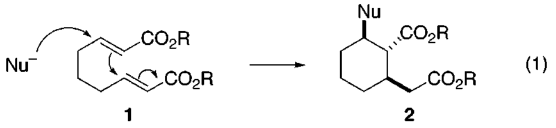
(5) (a) Brief review: Daeuble, J. F.; Stryker, J. M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: New York, 1996; p 2651. (b) Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1988**, *29*, 3749−3752.

(6) A small portion of these studies were disclosed in a 1996 presentation; see: Kamenecka, T. M.; Ly, S. K.; Overman, L. E. *Abstracts of Papers*, 212th National Meeting of the American Chemical Society, Orlando, FL.; American Chemical Society: Washington, DC, 1996: ORGN 010.

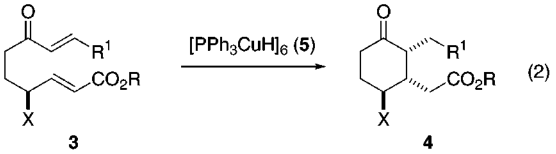
(7) For other sequential reactions that are initiated by conjugate reduction with Stryker's reagent, see: (a) Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* **2001**, *3*, 1901−1903. (b) Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779−2788. (c) Chiu, P.; Chen, B.; Cheng, K.-F. *Tetrahedron Lett.* **1998**, *39*, 9229−9232. (d) Kiyooka, S.; Shimizu, A.; Torii, S. *Tetrahedron Lett.* **1998**, *39*, 5237−5240. (e) ref 5a.

10.1021/ol0169325 CCC: $22.00

promoted by an external hydride reagent. Commercially available triphenylphosphinecopper hydride hexamer $[Ph_3PCuH]_6$ (**5**), Stryker's reagent, was found to be the reagent of choice for this process (eq 2).[5] The scope and limitations of this new stereocontrolled synthesis of substituted cyclohexanones is the subject of this report.[6,7]



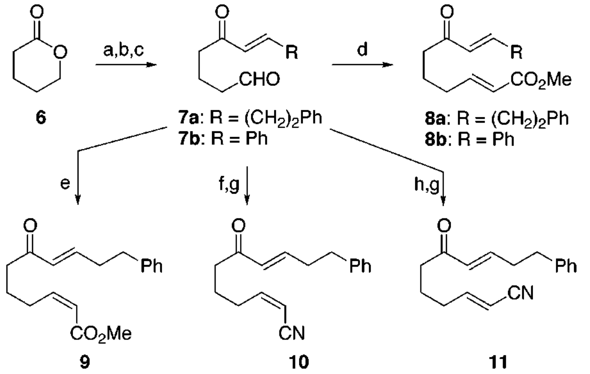
(1)



(2)

Simple 7-oxo-2,8-alkadienoic esters and analogous nitriles were employed in our exploratory studies. They were prepared from δ-valerolactone as summarized in Scheme 1.

Scheme 1[a]



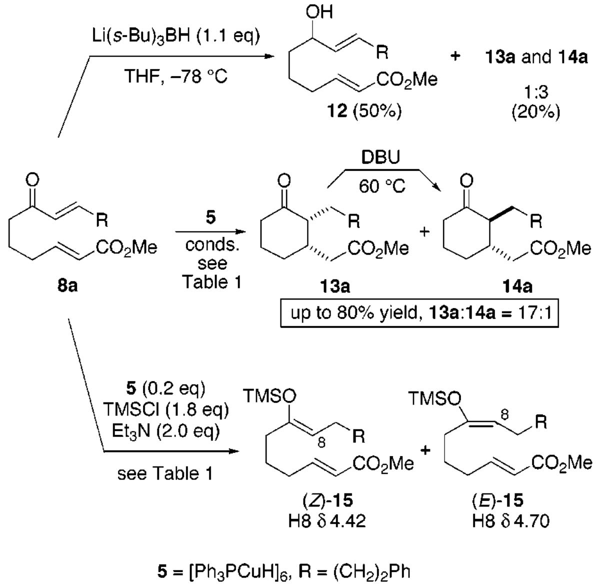
[a] Reagents and yields: (a) $LiCH_2PO(OEt)_2$; (b) RCHO, K_2CO_3; (c) TPAP, NMO; (d) $Ph_3P{=}CHCO_2Me$, **8a**: 50% overall from **6**, **8b**: 60% overall from **6**; (e) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-C-6, **9**: 56% overall from **6**; (f) $(Ph_3PCH_2I)^+I^-$, NaHMDS, HMPA; (g) KCN, $(Ph_3P)_4Pd$, 18-C-6; (h) CHI_3, $CrCl_2$, **10**: 22% overall from **6**, **11**: 43% overall from **6**.

(*E*,*E*)-Oxoalkadienyl esters **8** were obtained from keto aldehydes **7**[8] by reaction with methyl (triphenylphosphoranylidene)acetate, whereas the 2*Z*,8*E* stereoisomer **9** was formed from **7a** by the method of Still and Gennari.[9]

Related oxodienyl nitriles were obtained from their corresponding vinyl iodide precursors[10] by palladium-catalyzed coupling with KCN.[11] After purification by column chromatography, the isomeric purity of **8**−**11** was judged to be ≥95% by ^{1}H NMR analysis.

An issue of chemoselectivity, not involved in reductive cyclizations of dienyl diesters, would be critical for the success of the cyclohexanone construction depicted in eq 2: conjugate reduction of the α,β-unsaturated ketone functional array must be the initial event. Salient results of our investigation of this issue with 7-oxo-2,8-alkadienoic ester **8a** are summarized in Scheme 2. Not surprisingly, attempted cyclization of **8a** with lithium tri(*sec*-butyl)borohydride, the reagent utilized extensively by Yoshii in tandem Michael cyclizations of dienyl diesters **1**,[4a−e] resulted largely in 1,2-reduction of the enone group to yield allylic alcohol **12**. Stryker's reagent **5**, which is known to reduce both α,β-unsaturated esters and α,β-ketones in conjugate fashion,[5] exhibited the requisite chemoselectivity, converting **8a** in good yield to cyclohexanones **13a** and **14a**. The relative configuration of these stereoisomeric products was ascertained by their individual equilibration (DBU, PhH, 60 °C) to give a 3:1 equilibrium mixture of trans (**14a**) and cis (**13a**) stereoisomers.

Scheme 2



The yield (80%) and stereoselectivity (**13a**:**14a** = 17:1) of the reductive cyclization of **8a** were optimal when the reaction was carried out in toluene at −50 °C using 0.2 equiv (1.2 hydride equiv) of **5** (Table 1). Carrying out the reduction at room temperature reduced the yield and stereoselection only slightly. However, stereoselection was solvent dependent, decreasing markedly with increasing solvent polarity (Table 1, entries 3−5). The purity of $[Ph_3PCuH]_6$ (**5**) was also important for realizing high cis stereoselectivity, as stereoselection was reduced if **5** was contaminated with excess Ph_3P.[12]

To pursue the origin of the solvent effect on cyclization stereoselectivity, oxoalkadienyl ester **8a** was allowed to react

---

(8) Prepared by a general method: (a) Ditrich, K.; Hoffmann, R. W. *Tetrahedron Lett.* **1985**, *26*, 6325−6328. (b) Altenbach, H.-J.; Holzapfel, W.; Smerat, G.; Finkler, S. H. *Tetrahedron Lett.* **1985**, *26*, 6329−6332.

(9) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408.

(10) *E* isomer: (a) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173−2174. (b) *Z* isomer: Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.

(11) Yamamura, K.; Murahashi, S.-I. *Tetrahedron Lett.* **1977**, *50*, 4429−4430.

(12) (a) The purity of commercial samples of **5**, which is readily assayed by ^{1}H NMR analysis, differs widely.[5,7b] Stryker's one-pot preparation of **5**[5b] reliably produces material of high purity. (b) Using Schlenk equipment, excess Ph_3P can be removed from **5** by slurrying the reagent with hexane or benzene under an argon or nitrogen atmosphere and filtering and drying residual **5** under vacuum.

Table 1. Reductive Cyclization of **8a**

entry	solvent (ϵ)[b]	temp °C	**15** Z:E[c]	products yield %	**13a**:**14a**[c]
1[d]	PhH (2.3)	23		70	10:1
2	PhMe (2.4)	23		74	17:1
3	PhMe (2.4)	−50	20:1[e]	80[f]	17:1[e]
4	PhCl (5.6)	−50	8:1[e]		7:1[e]
5	CH_2Cl_2 (8.9)	−50	3:1[e]	86	1:1[e]

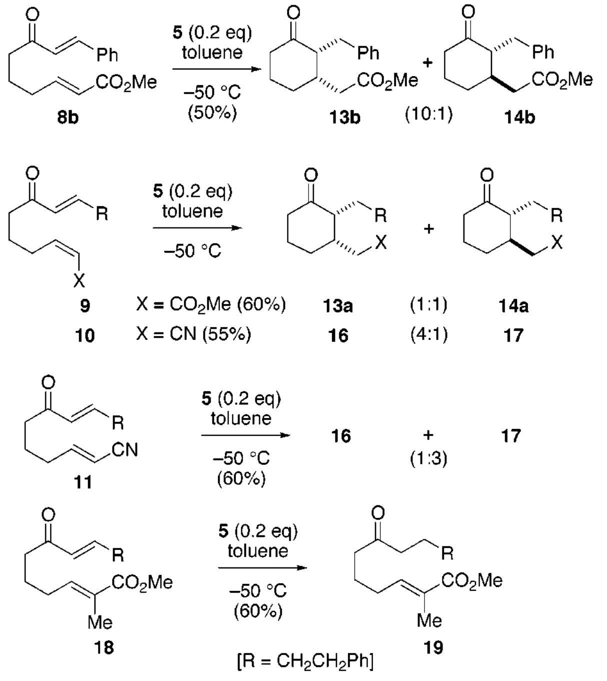
[a] Conditions: 0.2 equiv (1.2 hydride equiv) of $[Ph_3PCuH]_6$, [**8a**] = 0.1 M. [b] Dielectric constant. [c] By ^{1}H NMR analysis. [d] [**8a**] = 0.4 M. [e] Mean values from duplicate experiments. [f] When [**8a**] = 0.07 or 0.2 M, the ratio **13a**:**14a** *was unchanged*; however, the yield was reduced slightly (72−74%).

with **5** in various solvents in the presence of TMSCl and Et_3N.[5a,13] Enoxysilane stereoisomers (*Z*)- and (*E*)-**15** were produced in high yield in these experiments.[14] As summarized in Table 1, stereoselection in forming the (*Z*)-enoxysilane stereoisomer in trapping experiments correlates directly with stereoselection in forming the 2,3-*cis*-cyclohexanone product **13a**.

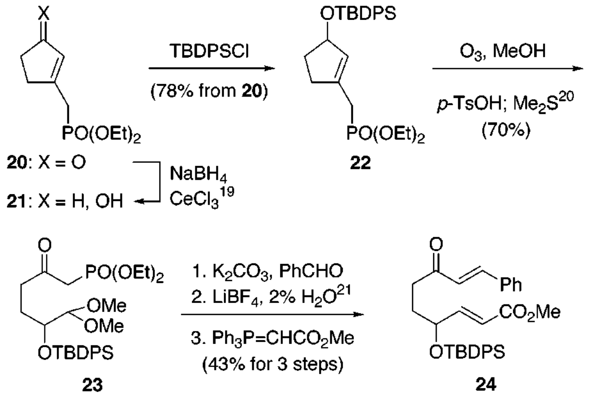
Additional definition of the scope and some insight into the mechanism of this new synthesis of substituted cyclohexanones were provided by the experiments summarized in Scheme 3. Although (*E*)-7-oxo-9-phenyl-2,8-alkadienoic ester **8b** cyclized in the presence of 0.2 equiv of $[Ph_3PCuH]_6$ (**5**) to provide largely the *cis*-2,3-disubstituted cyclohexanone product **13b**, (*Z*)-enoate **9** cyclized stereorandomly under identical conditions. Also cyclizing with low stereoselectivity were the (*Z*)- and (*E*)-7-oxo-2,8-alkadienyl nitriles **10** and **11**. Substitution on the double bonds, even at the α-position of the enoate Michael acceptor, appears not to be tolerated. For example, **18** did not cyclize but upon workup yielded only the product of enone-1,4-reduction **19** in reactions carried out over a range of temperatures (−50 to 50 °C).[15,16]

This cyclohexanone construction is particularly useful for the stereocontrolled synthesis of 4-alkoxy- or 4-siloxy-2,3-disubstituted cyclohexanones (eq 2, X = OR). The acyclic precursors for these reactions can be assembled in a variety of ways, in both racemic and enantiopure form.[16,17] For example, racemic **24** (>15:1 E:Z by ^{1}H NMR analysis) was prepared in 43% overall yield from cyclopentenone phosphonate **20**[18] using a series of standard transformations (Scheme 4).[19−21]

Scheme 3



Scheme 4



A variety of (*E*)-4-alkoxy- and (*E*)-4-siloxy-7-oxo-2,8-alkadienyl esters cyclize upon reaction with 0.2−0.3 equiv of $[Ph_3PCuH]_6$ (**5**) to provide a single cyclohexanone product in high yield (Scheme 5). Diastereoselection in forming **30**−**34** was judged to be ≥20:1 in reactions carried out either at −50 °C or at room temperature.[22] Yields are slightly higher in reactions conducted at room temperature with 0.3 equiv of **5**. A variety of substituents can be incorporated in the CH_2R^1 side chain.[17] For example, the high-yielding cyclization of enantiopure **28** to give enantiopure **34** demonstrates that even a highly bulky tritylamino group is tolerated at the γ-position of the enoate. High stereoselection was not

---

(13) The high stereoselectivity seen in toluene in reductive silylation of **8a** with Stryker's reagent suggests the use of this reagent and solvent for stereocontrolled synthesis of other acyclic (*Z*)-enoxysilanes.

(14) Diagnostic chemical shifts of the C8 vinylic hydrogens of (*Z*)- and (*E*)-**15** readily defined their configurations; see: Saunders, W. H.; Xie, L. F. *J. Am. Chem. Soc.* **1991**, *113*, 3123−3130.

(15) Substitution at the α-position of the enone is also not tolerated.[16]

(16) Ly, S. K. Ph.D. Dissertation, University of California, Irvine, CA, 1998.

(17) Kamenecka, T. M. Ph.D. Dissertation, University of California, Irvine, CA, 1996.

(18) Available in one step and high yield from dimethyl glutarate; see: Wenkert, E.; Schorp, M. K. *J. Org. Chem.* **1994**, *59*, 1943−1944.

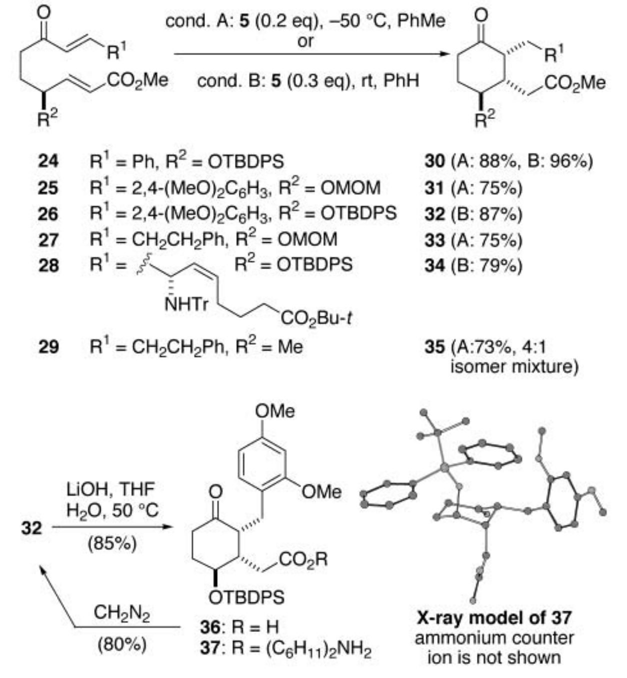
(19) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226−2227.

(20) Claus, R. E.; Schreiber, S. L. *Org. Synth., Coll. Vol. 7* **1990**, 168−171.

(21) Lipshutz, B. H.; Harvey, D. F. *Synth. Commun.* **1982**, *12*, 267−277.

(22) Diagnostic signals for other stereoisomers were not apparent in ^{1}H and ^{13}C NMR spectra of crude reaction products.

Scheme 5



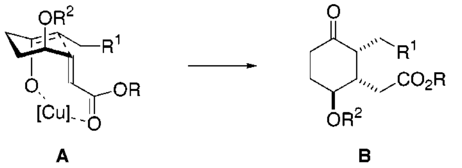


Figure 1. Possible rationale for forming the less stable 2,3 cis stereoisomer.

seen in cyclizations of acyclic precursors having alkyl substituents γ to the ester. For example, **29** cyclized under identical conditions to provide a 4:1 mixture of stereoisomeric products **35**.

Cyclohexanones **30**−**34** showed diagnostic narrow multiplets for their C4 methine hydrogens, suggesting an axial orientation for the alkoxy or siloxy substituents. The broad signal observed for the C2 hydrogen of **30**−**32** established that the C2 side chains of these products are equatorial. These data suggest the configurations of **30**−**34** that are depicted in Scheme 5. Evidence for this conclusion was secured by hydrolysis of **32** to give acid **36**,[23] whose dicyclohexylamine salt **37** was amenable to single-crystal X-ray analysis.[17] As suggested by the NMR data, **37** adopts a chair conformation that places the C3 alkyl and C4 siloxy substituents axial.

A distinctive feature of the reductive cyclizations of (*E*,*E*)-7-oxo-2,8-alkadienyl esters reported herein is preferential formation of cyclohexanone products having a cis relationship of the C2 and C3 side chains. In contrast, cyclizations of (*E*,*E*)-2,7-nonadienyldicarboxylic diesters typically provide trans products (eq 1), an outcome rationalized by chair transition state topographies in which the emerging C2 and C3 side chains adopt quasi-equatorial orientations.[2−4] Although detailed mechanistic analysis is beyond the scope of this initial disclosure, we suggest that chelation between the copper of a (*Z*)-copper enolate intermediate and the enoate is responsible for the stereoselection seen in cyclizations of (*E*,*E*)-7-oxo-2,8-alkadienyl esters (Figure 1). The observed erosion of stereoselectivity when excess Ph_3P is present is consistent with this suggestion,[24] as is the lack of stereoselection seen when **13a** and **14a** are formed by reaction of enoxysilane (*Z*)-**15** with tetrabutylammonium fluoride.[25,26] Preferential formation of the *trans*-2,3-disubstituted cyclohexanone stereoisomer **17** from the (*E*)-α,β-unsaturated nitrile analogue **11** (see Scheme 3) suggests that coordination with the copper enolate in the (*E*)-enoate series might involve the carbonyl oxygen, rather than the C−C π-bond, of the Michael acceptor.

In summary, reaction of (*E*,*E*)-7-oxo-2,8-alkadienyl esters with Stryker's reagent gives the less stable cis stereoisomer of 2,3-disubstituted cyclohexanones in high yield and stereoselectivity. This cyclohexanone construction is particularly useful for preparing 4-alkoxy- or 4-siloxy-2,3-disubstituted cyclohexanones (eq 2, X = OR), in which instance stereoselection is $\geq$20:1. Cyclohexanones of this latter type are readily assembled in high enantiopurity because many convenient methods are available for preparing the allylic alcohol precursors in enantioenriched form.[16,17,27] Although not addressed in this investigation, recent disclosures suggest that the reactions reported herein might well be carried out using catalytic quantities of $[Ph_3PCuH]_6$.[7b,28]

Acknowledgment. We thank the NSF (CHE-9726471) for financial support, Drs. J. Greaves and J. Mudd for mass spectrometric analyses, and Dr. J. Ziller for X-ray analyses. NMR and mass spectra were determined at UCI with instruments purchased with the assistance of the NSF and HIH.

Supporting Information Available: Representative experimental procedures: preparation of **24** and its cyclization to **30** and trapping of the initially formed acyclic enolate derived from **8a** to form (*Z*)-**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0169325

---

(23) That epimerization of the carboxyl substituent did not occur under the basic hydrolysis conditions was confirmed by reaction of acid **36** with diazomethane to return **32**.

(24) In the presence of 2.5 equiv of Ph_3P, cyclization of **8b** by the conditions reported in Scheme 3 gave **13b** and **14b** in a 1:1 ratio.

(25) Several other observations made during this investigation are consistent with this analysis. For example, a cyclization topography related to **A** should be less favorable when the C4 substituent is methyl than when the substituent is alkoxy or siloxy due to the larger A value of the former.[26] As a result of destabilizing steric interactions between C5 and a *Z* ester group, (*Z*)-enoate **9** should also have a reduced propensity to cyclize in the fashion depicted in Figure 1.

(26) Eliel, E. L.; Satici, H. *J. Org. Chem.* **1994**, *59*, 688−689 and related references therein.

(27) *Methoden Org. Chem. (Houben-Weyl, Workbook Edition)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995.

(28) (a) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627−4630. (b) Mori, A.; Fujita, A.; Kajiro, H.; Nishihara, Y.; Hiyama, T. *Tetrahedron* **1999**, *55*, 4573−4582. (c) Chen, J.-X.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2153-2166. (d) Chen, J.-X.; Daeuble, J. F.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2789−2798. See also: (e) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797−6798.