Acknowledgment. We gratefully acknowledge support of this work by the National Institutes of Health (Grant GM 34442).

Supplementary Material Available: Experimental details for the preparation of 3–8 and physical data for 3–8 (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Carbometalation of Cyclopropenes. Stereoselective Synthesis of Divinyl Ketone Acetals by 1,5-Hydrogen Migration of Vinylcyclopropanes

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Summary: Stereoselective vinylcupration of a cyclopropenone acetal (1), followed by in situ electrophilic trapping with an alkylating agent, affords a cis-substituted vinylcyclopropane 2, which stereoselectively rearranges to the acetal of a cross-conjugate dienone 3 upon thermolysis at 60–160 °C.

Conversion of a *cis*-1-alkyl-2-vinylcyclopropane to a 1,4-diene through a 1,5-sigmatropic hydrogen migration has long attracted the attention of organic chemists.[1] Synthetically, however, this reaction is strategically unattractive, since there are few efficient synthetic routes to the starting cis-substituted cyclopropane. We report that stereospecific addition of a vinyl cuprate to a cyclopropene 1 provides a highly effective synthetic entry to the required *cis*-1-alkyl-2-vinylcyclopropane structure 2. The mechanism of the carbocupration and the electrophilic trapping[2] secure the necessary cis-stereochemistry, and mild thermolysis of the cyclopropane 2 produces the diene 3 in two steps from 1 in overall yield of 70–90% (Scheme I). Stereoelectronic and steric control in the transition state of the 1,5-hydrogen migration resulted in excellent stereoselectivity with respect to *both* of the two newly formed double bonds in 3.

The cyclopropene 1 is a stable compound and is available in two steps from 1,3-dichloroacetone on a multigram scale.[3] The use of 1 as a cyclopropene substrate is of particular synthetic benefit,[4] since the product is the acetal of a cross-conjugated dienone (4)—a useful synthetic intermediate, e.g., for Nazarov synthesis of cyclopentenones.[5] Efficiency of the vinylcupration/alkyl trapping sequence (1 to 2) was examined first, and the results are shown in columns 2–4 in Table I. The reaction tolerates a variety of cuprate structures which can be used in nearly equi-

Scheme I

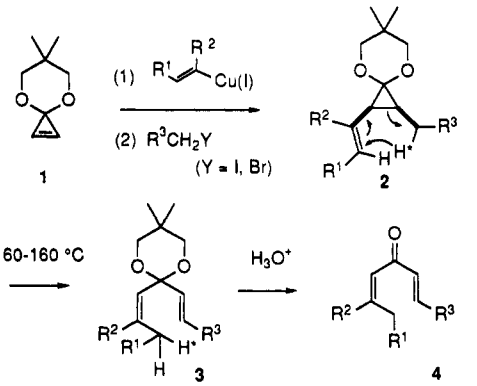
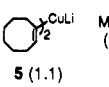
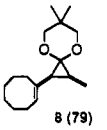
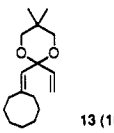
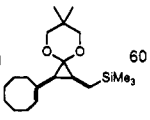
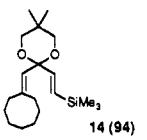
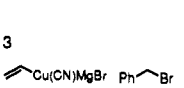
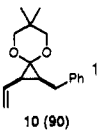
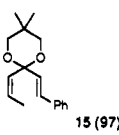
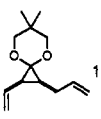
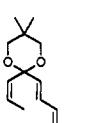
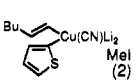
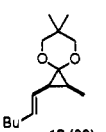
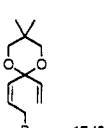


Table I. Vinylcupration and Rearrangement[a]

entry	cuprate (equiv)	R^3CH_2X (equiv)	3 (%yield)	rearrngt condns	4 (%yield)
1		MeI (5)	 8 (79)	120 °C, 11 h	 13 (100)
	5 (1.1)				
2		Me_3SiCH_2I (5)	 9 (84)	60 °C, 54 h	 14 (94)
3		(1.1)	 10 (90)	100 °C, 60 h	 15 (97)
	6 (1.1)				
4		(2)	 11 (68)	100 °C, 29 h	 16 (96)
5		MeI (2)	 12 (89)	160 °C, 70 h	 17 (92)
	7 (1.2)				

[a] The rearrangement was carried out in either benzene, toluene, or mesitylene depending on the required reaction temperature (in some cases, in the presence of BSA). All yields are based on pure isolated product. All olefins in the table are of at least 97% stereochemical purity as determined by ^1H NMR and/or capillary GC analyses.

(1) (a) Ellis, R. J.; Frey, H. M. *J. Chem. Soc., Suppl. 1* **1964**, 5578. Ellis, R. J.; Frey, H. M. *Proc. Chem. Soc., London* **1964**, 221. Roth, W. R.; Konig, J. *Liebigs Ann. Chem.* **1965**, *688*, 28. Glass, D. S.; Boikess, R. S.; Winstein, S. *Tetrahedron Lett.* **1966**, 999. (b) Berson, J. A. *Acc. Chem. Res.* **1991**, *24*, 215. Parziale, P. A.; Berson, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 1650. Getty, S. J.; Berson, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 4607. Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187.

(2) (a) Nakamura, E.; Isaka, M.; Matsuzawa, S. *J. Am. Chem. Soc.* **1988**, *110*, 1297. (b) Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1990**, *112*, 7248.

(3) (a) Isaka, M.; Matsuzawa, S.; Yamago, S.; Ejiri, S.; Miyachi, Y.; Nakamura, E. *J. Org. Chem.* **1989**, *54*, 4727. (b) Isaka, M.; Ando, R.; Morinaka, Y.; Nakamura, E. *Tetrahedron Lett.* **1991**, *32*, 1339. (c) Isaka, M.; Ejiri, S.; Nakamura, E. *Tetrahedron Symposium-in-Print* **1992**, *48*, 2045.

(4) (a) The present sequence may also be applicable to simple cyclopropenes. Cf. Nakamura, E.; Isaka, M. *Organomet. News* **1990**, 194. Moiseenkov, A. M.; Czeskis, B. A.; Semenovsky, A. V. *J. Chem. Soc., Chem. Commun.* **1982**, 109. Lukina, M. Yu.; Rudashevskaya, T. Yu.; Nesmeyanova, O. A. *Dokl. Akad. Nauk SSSR.* **1970**, *190*, 1109. Lehmkuhl, H.; Mehler, K. *Liebigs Ann. Chem.* **1982**, 2244. Stoll, A. T.; Negishi, E.-i. *Tetrahedron Lett.* **1985**, *26*, 5761. (b) We have found that spiro[2.5]oct-1-ene, an all-carbon congener of 1, also serves as a good acceptor of dialkylcuprates.

(5) Reviews: Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429. Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 751–784.

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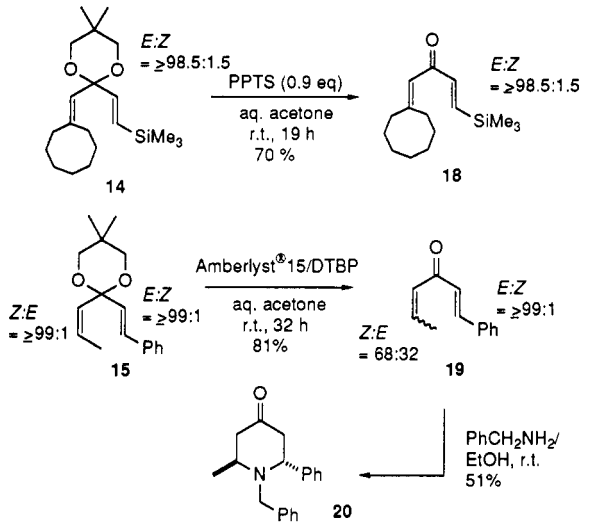
Scheme II



molar quantity and gives the product as a single cis-stereoisomer. Both vinyllithium (cf. **5** and **7**) and vinylmagnesium bromide (cf. **6**) can be employed as a cuprate precursor. In addition to homocuprate **5**, heterocuprate **6** and higher order cuprate **7** with dummy ligands serve as a vinyl donor. The latter two selectively transfer the vinyl group to the cyclopropene, thus allowing the use of nearly stoichiometric amounts of the vinyl metal precursor and the electrophilic trapping agent (cf. entry 3).

1,5-Hydrogen migrations of the vinylcyclopropanes **2** took place at 60–160 °C in 0.2–0.6 M solutions of an aromatic solvent and gave a variety of dienone and trienone structures in quantitative yield (Table I, column 6). Some dienone acetals were found to undergo acid-catalyzed stereochemical isomerization of the olefinic bond during thermolysis, which could be prevented by carrying out the reaction in the presence of BSA. In no case could we observe competitive formation of cyclopentenes via vinylcyclopropane rearrangement involving the rupture of a C–C bond connected to the acetal carbon.[3]

Of the two olefinic bonds produced by the rearrangement, the one which originated from the vinylic side chain was found to be cis and the one from the alkyl side chain to be trans. The selectivity for both olefins was better than 97%. Thus, for instance, the rearrangement of **12** gave the cis-dienone acetal **17** in 92% yield with >98.5% selectivity (entry 5). This stereochemistry translates to the endo orientation of the vinyl group in the transition state of the 1,5-hydrogen shift.[6] The endo preference, which amounts to several kcal/mol,[7] is strong enough to override the steric effects of the neighboring acetal oxygen.

Literature examples[2c,7] indicate that the stereochemistry of the olefin originating from the alkyl group is much more difficult to control. In the present case, however, the rearrangement proceeded with very high trans-selectivity (entries 2–4), which is likely due to the steric effect of the acetal moiety.[8]

Interestingly, there was found considerable rate acceleration by the silyl, phenyl, and vinyl groups on the alkyl side chain (entries 2–4). The effect of the silyl group is remarkable,[9] causing the rearrangement to proceed even at 60 °C.[10] The silyl substitution leads to the formation of a silylated dienone **18**, which is a particularly good substrate for the Nazarov cyclization.[6]

Hydrolysis of the dienone acetals proceeded very smoothly under mild conditions. Thus, treatment of the acetals with either PPTS or Amberlyst 15 treated previously with 2,6-di-*tert*-butylpyridine (Amberlyst/DTBP)[4c] in an aqueous acetone gave the desired dienones **18** and **19** in high yield.[11] The use of the latter mildly acidic resin allows easy isolation of the product. The synthetic utility of the dienones may be illustrated by stereoselective synthesis of 4-ketopiperidine (**20**) by the reaction with an amine.[12] The overall three-step reaction provides a strategically novel heteroannulation sequence.

It may be useful to note that the 1,5-hydrogen migration selectively[1b] places the transferred hydrogen (H* in **2**) onto a single diastereoface of the trigonal carbon connected to R^1 to create a potential stereogenic center in **3** (e.g., if a hydrogen isotope is transferred). Given the high facial selectivity of such hydrogen transfer reported recently[1b] and the ready availability of chiral counterparts of the acetal **2**,[3b] the present sequence would also provide a unique approach to optically active molecules.

In summary, we have established a short stereoselective synthesis of cross-conjugated dienones and their acetals by taking advantage of a stereoselective carbocupration/trapping sequence. The stereochemistry of each step is rigorously controlled, rendering the overall sequence highly efficient despite the fact that two stereogenic centers created in the first step are destroyed in the second.[13]

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Supplementary Material Available: Experimental procedures and physical data for compounds **8–20** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

(6) Daub, J. P.; Berson, J. A. *Tetrahedron Lett.* **1984**, *25*, 4463. Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 2089.

(7) Frey, H. M.; Solly, R. K. *J. Chem. Soc. B* **1970**, 996.

(8) Our speculation is based on force field calculations of the ground-state conformers, which revealed steric interactions disfavoring the formation of a *Z,Z*-diene.

(9) Cf. Piers, E.; Maxwell, A. R. *Can. J. Chem.* **1984**, *62*, 2392.

(10) The overall rate acceleration is in part due to the cyclooctenyl group (compare entries 1 and 5 in Table I).

(11) Our current hydrolysis conditions gave a cis–trans mixture of dienone **19**, whose ratio, however, remained unchanged under the reaction conditions.

(12) Starting with a pure *Z,E*-isomer, the cyclization gave a varying trans/cis isomeric ratio of 7:3 to >9:1 depending on the slight difference of the conditions.

(13) **Typical Procedure.** To a suspension of CuCN (21 mmol) in THF (22 mL) was added a 0.713 M THF solution of vinylmagnesium bromide (21 mmol) at −70 °C over 3 min, and the mixture was stirred for 20 min. The mixture was warmed to 0 °C and then cooled to −70 °C. Cyclopropene **1** (20 mmol) in THF (20 mL) was added to the cuprate solution over 5 min. After stirring for 30 min, HMPA (30 mmol) and benzyl bromide (22 mmol) were added and the mixture was stirred for 3 h. After being warmed to room temperature, water (28 mmol) was added, and the mixture was filtered through a short pad of silica gel. Chromatographic purification on silica gel afforded the cyclopropane **10** as a colorless oil (4.67 g, 90%). Heating of a 0.2–0.6 M toluene solution of the cyclopropane and a small amount of BSA under conditions indicated in Table I gave the dienone acetal in quantitative yield after concentration and purification on silica gel.