In order to extend this methodology to tricyclic fused-ring systems, two examples of dienyne-tethered molybdenum carbene complexes were investigated. Thermolysis (THF, 65 °C, 1.5 h) of **3c** gave the desired divinylcyclopropane **10**, but in only 6% yield. A variety of additional products were observed by TLC but could not be cleanly isolated or characterized. Thermolysis in benzene gave similar results. With this substrate it is anticipated that olefin metathesis and C–H insertion/reductive elimination pathways might compete with the desired cyclopropanation process.[2b] Cycloheptadiene **11**, resulting from the [3,3]-sigmatropic rearrangement of divinylcyclopropane **10**, was not observed during the thermolysis of carbene complex **3c** under the cyclization conditions described above.[11] However, thermolysis of divinylcyclopropane **10** at 100 °C for 4 h in toluene resulted in the smooth conversion of **10** to the tricyclic product **11** in 67% yield.[12]

Ester-substituted 1,3-dienes have been demonstrated to successfully undergo intramolecular cyclopropanation and rearrangement in related systems to give 1,4-cycloheptadienes in excellent yield.[2a] Indeed, thermolysis (65 °C, benzene, 2 h) of dienyne complex **3d**, containing an ester-activated 1,3-diene, gave the tricyclic product **14** in 55% yield as a single diastereomer. As in the previous systems, this product is believed to be produced via in situ generation of vinylcarbene complex **12** which subsequently cyclopropanates the 1,3-diene to give *cis*-divinylcyclopropane **13**. As has been observed in previous cases with donor–acceptor-substituted divinylcyclopropanes, divinylcyclopropane **11** is not isolated.[2a] The [3,3]-sigmatropic rearrangement of **13** smoothly occurs under the reaction conditions to give 1,4-cycloheptadiene **14**. The indicated stereochemistry for **11** and **14** is that expected to arise via the *cis*-divinylcyclopropane rearrangement occurring through a boat transition state.[11]

In summary, molybdenum carbene complexes containing tethered enyne and dienyne moieties have been prepared in excellent yield via the alkylation of the tetramethylammonium salt of molybdenum acylate complex **2**. Thermolysis of these systems leads to the formation of three rings in one step. The further development of this all-intramolecular molybdenum-mediated cyclization pathway, as well as its application to organic synthesis, is currently in progress.

Acknowledgment. Support from the Cancer Research Coordinating Committee of the University of California, the donors of the Petroleum Research Fund, administered by the American Chemical Society, the American Cancer Society (Junior Faculty Research Award to D.F.H.), and the National Institutes of Health (GM41984) is gratefully acknowledged. The 500-MHz NMR spectrometer was purchased with assistance from the NIH (RR04733) and NSF (CHE 8814866).

Supplementary Material Available: Experimental procedures and compound characterization data (12 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.

(10) The enol ether stereochemistry of **8** was assigned based on comparison of ^{1}H NMR spectra with 1,4-dialkoxy-1,3-butadienes prepared in a related fashion (Harvey, D. F.; Neil, D. A., manuscript in preparation).

(11) As determined by TLC comparison versus an authentic sample of **11**.

(12) The [3,3] sigmatropic rearrangement is thought to occur via a boat transition state. See: Piers, E.; Morton, G. E.; Nagakura, I.; Thies, R. W. *Can. J. Chem.* **1983**, *61*, 1226–1238 and references cited therein.

Electrochemically Promoted Cyclocoupling of 1,3-Dienes or Styrenes with Aliphatic Carboxylic Esters[1]

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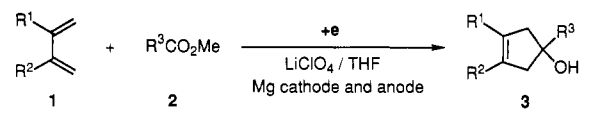
Received May 19, 1992

Summary: The cathodic cyclocoupling of 1,3-dienes **1** with aliphatic esters **2** is promoted by a magnesium electrode and yields homologs of 3-cyclopentenol. Under similar reaction conditions, the coupling of styrenes with **2** affords 2-phenylcyclopropanol derivatives, and this coupling reaction has been successfully applied to the synthesis of *ar*-dihydroturmerone and curcumone.

It is well-known that a 6-membered ring is easily formed by the [2 + 4] cycloaddition of a 1,3-diene **1** with a suitable dienophile, whereas formation of a 5-membered ring from a 1,3-diene is not always straightforward.[2,3]

However, it has been found in the present study that the electroreduction of a solution of **1** and an aliphatic carboxylic ester **2** with a magnesium electrode[4] gives a 3-cyclopentenol type of compound **3** in one step (Scheme I). This novel electroreductive cyclocoupling is the equivalent of a 1,4-addition of a one-carbon unit to **1**[7] and represents one of the simplest methods of formation of a 5-membered ring system from **1**.

Scheme I



1 2 3

The use of Mg as the electrode was one of the most important factors in the formation of **3**, since the elec-

(1) Electroorganic Chemistry. 138. For part 137: Regioselective Synthesis of Substituted Tropones and Azulenes using Anodic Oxidation of Cycloheptatriene Systems as the Key Reaction. Shono, T.; Okada, T.; Furuse, T.; Kashimura, S.; Nozoe, T.; Maekawa, H. *Tetrahedron Lett.*, in press.

(2) Corey, E. J.; Walinsky, S. W. *J. Am. Chem. Soc.* **1972**, *94*, 8932.

(3) Danheiser, R. L.; Martinez-Davila, C.; Auchus, R. J.; Kadonaga, J. T. *J. Am. Chem. Soc.* **1981**, *103*, 2443 and references cited therein.

(4) We have recently found that the Mg electrode promotes a variety of unique reactions such as cathodic coupling of chlorosilanes yielding polysilane[5] and electroreduction of aliphatic esters.[6]

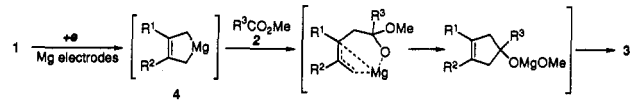
(5) Shono, T.; Kashimura, S.; Ishifune, M.; Nishida, R. *J. Chem. Soc., Chem. Commun.* **1990**, *17*, 1160.

(6) Shono, T.; Masuda, H.; Murase, H.; Shimomura, M.; Kashimura, S. *J. Org. Chem.* **1992**, *57*, 1061.

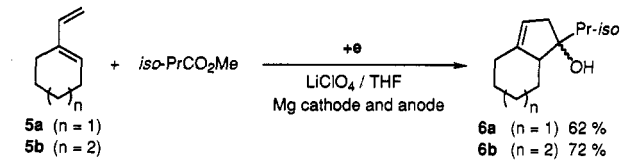
(7) Erker, G.; Engel, K.; Krüger, C.; Chiang, A.-P. *Chem. Ber.* **1982**, *115*, 3311.

0022-3263/92/1957-5561$03.00/0

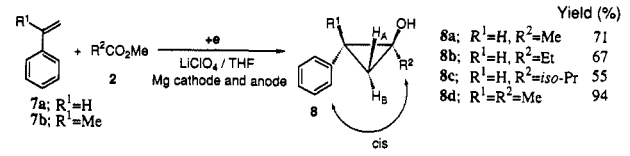
Scheme II



Scheme III



Scheme IV



troreduction of a solution of **1** and **2** with other types of electrode such as Pt, Al, Zn, Cu, Ni, or Pb did not afford **3**. These results indicate that the Mg electrode is not only a donor of electrons; Mg is also involved in the reaction as a chemical reagent. Thus it would seem reasonable that in this cyclocoupling a Mg complex **4** is formed from **1** and then it reacts with **2** to afford **3** (Scheme II). The same coupling product **3** was formed when a solution of diene was electrochemically reduced[8] with a Mg electrode, and an ester was added to the solution after the current was terminated. This result suggests the formation of a Mg–diene complex in the electroreduction step.

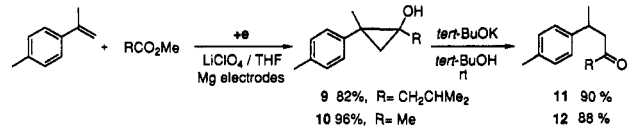
It has been reported that the reaction of chemically activated Mg[11] with **1** gave a complex of **1** with Mg,[15] although reaction of the Mg complex with **2** usually yielded **3** in poor yields (~20%).[16-18] On the other hand, the electroreductively-promoted cyclocoupling gave **3** in reasonable yields. Some typical results are shown in Table I (entries 1–4).[20] It is interesting that 2,3-dimethyl-1,3-butadiene gave the cyclized product (**3e**) in high yield (Table I, entry 5), despite the fact that formation of the Mg complex of 2,3-dimethyl-1,3-butadiene is known to be difficult, as compared to isoprene.[21,22] The reduction of **1** in the presence of aromatic ester, however, did not give the coupling product (entry 6).[23]

Table I. Cathodic Coupling of 1,3-Dienes with Esters

entry	diene 1 R^1	diene 1 R^2	ester 2 R^3	product 3 yield[a] (%)
1	Me	H	*n*-Bu	76, **3a**
2	Me	H	*i*-Pr	71, **3b**
3	Me	H	$PhCH_2CH_2$	56, **3c**
4	$(CH_3)_2C{=}CHCH_2CH_2$	H	Et	63, **3d**
5	Me	Me	*i*-Pr	88, **3e**
6	Me	H	Ph	0

[a] Isolated yields.

Scheme V



The cathodic cyclocoupling reaction of 1-vinylcyclohexene (**5a**) or 1-vinylcycloheptene (**5b**) with **2** also took place under the same reaction conditions and gave the product containing the skeleton of hydroindenol (**6a**) or hydroazulenol (**6b**) in satisfactory yield (Scheme III).

Interestingly, cathodic reduction of a solution of styrene **7** and **2** with the Mg electrode afforded exclusively a single stereoisomer of a 2-phenylcyclopropanol-type compound **8**[25] in which the phenyl and alkyl (R^2) groups were located on the same side of the cyclopropane ring (Scheme IV). The stereochemistry of **8** was determined by ^1H NMR using NOE.[26] In this reaction, the use of the Mg electrode was essential since the cathodic reduction of a solution of **7** and **2** did not afford **8** when Pt was used as the electrode. Although formation of a Mg complex from **7** could not be detected,[27] it seems clear that the anionic intermediate formed by electroreduction of **7**[28] with the Mg electrode has unique reactivity and the same intermediate is not formed by reduction of **7** with a Pt electrode.[30]

Although the reason for the selectivity in the formation of **8** is unclear, some typical results shown in Scheme IV

(8) The reduction potential of **1** (~−2.8 V vs SCE in DME)[9] is more positive than that of **2** (<−3.0 V vs SCE).[10]

(9) Breslow, R.; Johnson, R. W. *Tetrahedron Lett.* **1975**, 3443.

(10) Belotti, D.; Cossy, J.; Pete, J. P.; Portella, C. *J. Org. Chem.* **1986**, *51*, 4196.

(11) Rieke et al. have recently reported[12-14] that highly active Mg prepared by the reduction of anhydrous $MgCl_2$ is applicable to the diene complex formation.

(12) Xiong, H.; Rieke, R. D. *J. Org. Chem.* **1989**, *54*, 3247.

(13) Xiong, H.; Rieke, R. D. *Tetrahedron Lett.* **1991**, *32*, 5269.

(14) Rieke, R. D.; Xiong, H. *J. Org. Chem.* **1991**, *56*, 3109.

(15) For a recent review on 1,3-diene magnesium compounds and their reactions: Dzhemilev, U. M.; Ibragimov, A. G.; Tolstikov, G. A. *J. Organomet. Chem.* **1991**, *406*, 1.

(16) Yang, M.; Ando, M.; Takase, K. *Tetrahedron Lett.* **1971**, 3529.

(17) Baker, R.; Cookson, R. C.; Saunders, A. D. *J. Chem. Soc., Perkin Trans.* 1 **1976**, 1815.

(18) Rieke et al. reported recently that the highly activated Mg was effective for the coupling of 1,2-bis(methylene)cycloalkanes with esters.[19]

(19) Xiong, H.; Rieke, R. D. *J. Am. Chem. Soc.* **1992**, *114*, 4415.

(20) The general procedure is as follows: The electroreduction was carried out in a single-compartment cell equipped with Mg rod electrodes (cathode and anode) (Φ = 7 mm, length = 5 cm) and a dropping funnel. Cathode and anode were alternated at the interval of 15 s using a commutator in order to keep the current at a proper value. Into the cell was added a solution of $LiClO_4$ (1 g) in dry THF (15 mL) and molecular sieves 5A (1 g). A constant current of 0.05 A was passed through the solution under nitrogen atmosphere, and a solution of **1** (5 mmol) and **2** (10 mmol) in dry THF (5 mL) was added dropwise (1 mL/h) into the solution during the electroreduction. After 4 F/mol of electricity (based on **1**) was passed, the usual workup and purification by silica gel chromatography yielded the product **3**.

(21) Yasuda, H.; Kajihara, Y.; Mashima, K.; Nagasuna, K.; Lee, K.; Nakamura, A. *Organometallics* **1982**, *1*, 388.

(22) Rieke et al. reported[12] that reaction of highly activated Mg with 2,3-dimethyl-1,3-butadiene formed the corresponding Mg complex.

(23) The fact that aromatic esters are generally reduced at more positive potential (methyl benzoate, −2.29 V vs SCE in DMF)[24] than dienes is the reason why the coupling did not take place.

(24) Eberson, L.; Utley, J. H. P. In *Organic Electrochemistry*, 2nd ed.; Baizer, M. M., Lund, H., Eds.; Marcel Dekker: New York, 1983; p 381.

(25) Each of the compounds (**8a–8d**) was formed as a single stereoisomer (^1H NMR, GLC, and TLC), and its stereochemistry was clearly determined to be cis by ^1H NMR, NOE, and ^{13}C NMR.

(26) In the case of **8a** (R^1 = H, R^2 = Me), for example, irradiation on the benzylic proton (R^1 = H, δ 2.35) showed NOE at the proton H_A (δ 1.25), and irradiation on the proton H_B (δ 0.98) showed NOE at the methyl protons (R^2 = Me, δ 1.19) and H_A (δ 1.25). These results indicated that phenyl and R^2 groups were located on the same side.

(27) The procedure that **7a** was reduced in the absence of **2** and **2** was added to the solution after the electricity was terminated did not give the coupling product, but the product was the oligomer of **7a**.

(28) The reduction potential of **7a** (−2.34 V vs SCE in DME)[29] is more positive than that of **2** (<−3.0 V vs SCE).[10]

(29) Laitinen, H. A.; Wawzonek, S. *J. Am. Chem. Soc.* **1942**, *64*, 1765.

(30) We have also found that the electroreduction of **7a** with Mg electrode in the presence of chlorotrimethylsilane (no reduction wave at the cathodic range of 0~−3 V vs SCE)[31] gave 1-phenyl-1,2-bis(trimethylsilyl)ethane in 81% yield, whereas the same reduction achieved with Pt electrode gave no bis-trimethylsilylated product but the product was oligomer of **7a**. These results suggest that the electroreduction of **7a** with Mg electrode forms an anionic intermediate which is not generated by the reduction of **7a** with Pt electrode.

(31) Corriu, R. J. P.; Dabosi, G.; Martineau, M. *J. Organomet. Chem.* **1980**, *188*, 63.

indicate that this electroreductive method is effective for stereoselective synthesis of a variety of phenylcyclopropanols 8.

It has been reported that the treatment of 8a with acid or base formed cyclopropane ring-opened products.[32,33] It was found in the present study that 8a yielded similar ring-opened products with much better selectivity under modified reaction conditions.

The base-catalyzed ring-opening reaction of phenylcyclopropanols was successfully applied to the synthesis of *ar*-dihydroturmerone (R = CH_2CHMe_2) (11) and curcumone (R = Me) (12).[34] Specifically, the cathodic cyclocoupling of *p*-methyl-α-methylstyrene with methyl isovalerate and methyl acetate gave phenylcyclopropanol derivatives 9 and 10, respectively. Addition of *t*-BuOK (0.1 equiv based on 9 or 10) to a solution of 9 and 10 in *t*-BuOH gave 11 and 12, respectively (Scheme V).

Supplementary Material Available: Experimental procedures for new compounds (4 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.

(32) DePuy, C. H.; Breitbeil, F. W. *J. Am. Chem. Soc.* **1963**, *85*, 2176.
(33) Gibson, D. H.; DePuy, C. H. *Chem. Rev.* **1974**, *6*, 605.
(34) The structures of 11[35] and 12[36] were determined by comparison of their spectrscopic values with those of authentic samples.
(35) Kashima, C.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1735.
(36) Ho, T. L. *Synth. Commun.* **1981**, *11*, 579.

Enzyme-Mediated Enantioselective Preparation of Pure Enantiomers of the Antiviral Agent 2′,3′-Dideoxy-5-fluoro-3′-thiacytidine (FTC) and Related Compounds

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Received July 8, 1992

Summary: Racemic 2′,3′-dideoxy-3′-thianucleosides were resolved by enzyme-catalyzed hydrolysis of their butyrate ester derivatives.

Recently, we required the enantiomers of the important antiviral agents BCH-189 (2′,3′-dideoxy-3′-thiacytidine, 1) and FTC (2′,3′-dideoxy-5-fluoro-3′-thiacytidine, 2) for biological evaluation.[1] Initial attempts to resolve the enantiomers by either classical techniques or enantioselective synthesis were unsuccessful.[2] Since enzymes have been exploited for biocatalytic resolutions, we examined their potential to resolve the racemates of 1 and 2.[3] Lipases, esterases, and proteases were chosen because of their commercial availability, relatively low cost, and tolerance for a wide class of substrates. Since nucleosides have been typically synthesized from chiral, nonracemic precursors (e.g., carbohydrates or other naturally-occurring nucleosides), little information exists regarding the enantioselective enzyme-catalyzed hydrolysis of racemic nucleosides.[4] The results of our study are presented herein.

Enantioselective Enzyme-Catalyzed Hydrolysis of FTC Esters. *O*-Acyl derivatives of sulfur-containing nucleosides (3b–e and 4a–e) were prepared either by O-acylation of the 5′-hydroxyl group or by tin-mediated coupling of the corresponding acetate precursor 7a–e with the appropriate cytosine base (5 or 6; Scheme I).[5] A

(1) (a) Choi, W.-B.; Wilson, L. J.; Yeola, S.; Liotta, D. C.; Schinazi, R. F. *J. Amer. Chem. Soc.*, **1991**, *113*, 9377. (b) Chu, C. K.; Beach, J. W.; Jeong, L. S.; Choi, B. G.; Comer, F. I.; Alves, A. J.; Schinazi, R. F. *J. Org. Chem.* **1991**, *56*, 6503. (c) Doong, S.-L.; Tsai, C.-H.; Schinazi, R. F.; Liotta, D. C.; Cheng, Y.-C. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 8495. (d) Doong, S.-L.; Tsai, C.-H.; Schinazi, R. F.; Liotta, D.; Cheng, Y. C. *Interscience Conference on Antimicrobial Agents and Chemotherapy*; Chicago, IL, Sept 29–Oct 2, 1991. (e) Schinazi, R. F.; Liotta, D. C.; Choi, W.-B.; Peck, A.; McClure, H. M.; Boudinot, F. D.; Sommadosi, J.-P.; Davis, M.; Furman, P. A.; Painter, G. *National Collaborative Drug Discovery Group, Frontiers in HIV Therapy*; San Diego, CA, Nov 3–7, 1991. (f) Schinazi, R. F.; Chu, C. K.; Peck, A.; McMillan, A.; Mathis, R.; Cannon, D.; Jeong, L.-S.; Beach, J. W.; Choi, W.-B.; Yeola, S.; Liotta, D. C. *Antimicrob. Agents Chemother.* **1992**, *36*, 672.

(2) Formation of chiral salts between various nucleoside derivatives and camphorsulfonic acid or tartaric acid derivatives was examined, but no detectable enrichment was observed in repeated attempts at crystallization. Efforts directed at enantioselective synthesis were thwarted by racemization during a crucial step involving the formation of the nucleoside via a tin-mediated coupling between the acetate 7 and the pyrimidine base.

(3) For reviews of applications of enzymes in organic synthesis, see: (a) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071. (b) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114. (c) Wong, C.-H. *Chemtracts* **1990**, *3*, 91. (d) Zhu, L.; Tedford, M. C. *Tetrahedron* **1990**, *46*, 6587. (e) Whitesides, G. M.; Wong, C. *Aldrichim. Acta* **1983**, *16*, 27. (f) Turner, N. J. *Nat. Prod. Rep.* **1989**, *6*, 625. (g) Sih, C. J.; Wu, S. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley and Sons: New York, 1989; Vol. 19, p 63. (h) Walpole, C. S. J.; Wrigglesworth, R. *Nat. Prod. Rep.* **1989**, 311. (i) Butt, S.; Roberts, S. M. *Chem. Britain* **1987**, 127. (j) Jones, J. B. *Tetrahedron* **1986**, *42*, 3351. (k) Mulzer, J. In *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H., Braun, M., Krohn, K., Reissig, H., Eds.; VCH: New York, 1991; p 216. (l) Mulzer, J. In *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H., Braun, M., Krohn, K., Reissig, H., Eds.; VCH: New York, 1991; p 207.

(4) Of the studies reported, almost all have focused on *regioselective* hydrolyses for differentiating two or more available ester functional groups. For a recent attempt at enantioselective lipase-mediated hydrolysis of carbohydrate-like substrates which can be utilized for the synthesis of C-nucleosides, see: Hultin, P. G.; Mueseler, F.-J.; Jones, J. B. *J. Org. Chem.* **1991**, *56*, 5375. For an example of enantioselective resolution by enzymatic deamination of purine nucleosides, see: Secrist, J. A., III; Montgomery, J. A.; Shealy, Y. F.; O'Dell, C. A.; Clayton, S. J. *J. Med. Chem.* **1987**, *30*, 746.

(5) For the stereoselective preparation of the β-anomer of BCH-189 1, see ref 1a. A detailed process for the preparation of FTC 2 and its 5′-*O*-(acyloxy) derivatives on a multigram scale will be reported elsewhere.

0022-3263/92/1957-5563$03.00/0