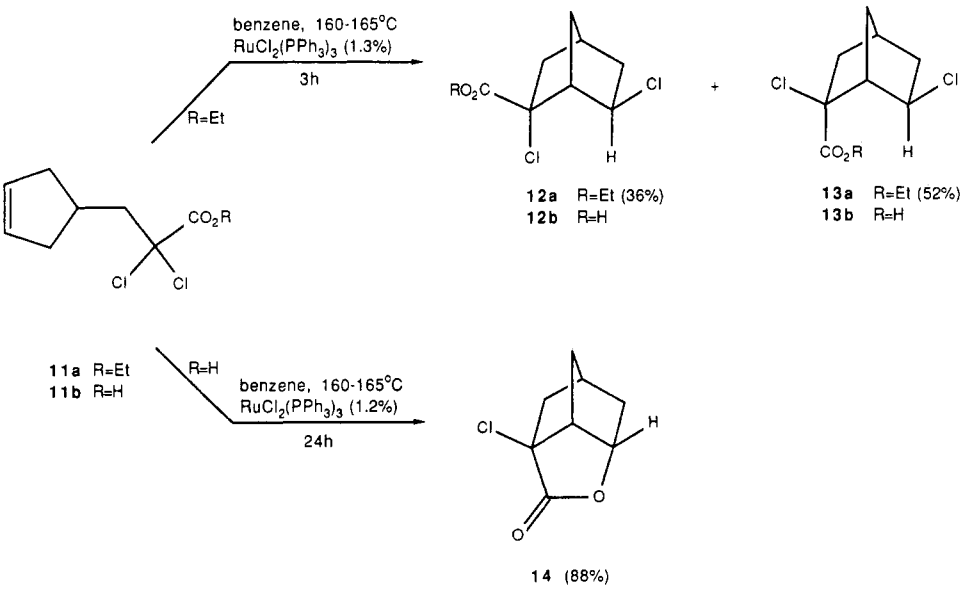
Scheme IV



This cyclization methodology can also be used to produce six-membered carbocycles as shown in Scheme III. Results with α,α-dichloro ester **8a** and acid **8b** closely paralleled those for **3a** and **3b**. Thus, with the ruthenium and iron catalysts, ester **8a** gave primarily **9** as a mixture of epimers. The molybdenum catalyst afforded substantial amounts of lactone **10** (also as a mixture of epimers).[11] Similarly, acid **8b** yielded only the annulated γ-lactone **10** with all catalysts employed. As with the five-membered ring system, epimer ratios were reaction condition dependent.

Bridged carbocyclic compounds are also available by this procedure. Cyclization of dichloro ester **11a** (Scheme IV) with the ruthenium catalyst under the conditions used for **3a** and **8a** gave only two of four possible diastereomeric norbornyl α,γ-dichloro esters **12a** (36%) and **13a** (52%). Very similar results were obtained with $FeCl_2[P(OEt)_3]_3$ as catalyst. The stereochemistry of these products was established by ^1H NMR and by the fact that **13a** cyclizes to lactone **14** with $AgNO_3$, while **12a** can be recovered from similar treatment.

Likewise, acid **11b** cyclized to lactone **14** in high yield under the same reaction conditions. The structure of **14** was firmly established by X-ray crystallography.[12] We have monitored this reaction and found that acid **11b** cyclizes over 3 h to a mixture of exo acid **12b** and endo acid **13b**, which upon further heating (10–12 h) with the ruthenium catalyst is cleanly converted to the γ-lactone. Clearly, the exo α,γ-dichloro acid **12b** must epimerize during the transformation, and we suggest this occurs via reversible α-carboxylate radical formation (cf. **7**).

The methodology described here has several advantages over other free radical cyclizations.[6] Starting α,α-dichloro esters and acids are easily synthesized.[7,8] These cyclizations afford products which are more highly functionalized than those from radical processes terminated by hydrogen atom abstraction.[6,13] Also, only catalytic amounts of transition metal are required, unlike some metal-induced radical reactions requiring stoichiometric quantities of reagents.[14] We are currently investigating the scope of this reaction and its applications in natural product synthesis.

Acknowledgment. We are grateful to the National Institutes of Health (GM-32299) for financial support.

(11) Stereochemistry of the epimers of **9** and **10** has not been unambiguously assigned.
(12) Details of the determination will be given in a full paper.
(13) For an interesting case, see: Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489.
(14) Fristad, W. E.; Peterson, J. R.; Ernst, A. B.; Urbi, G. B. *Tetrahedron* **1986**, *42*, 3429 and references cited therein.
(15) Yields reported were determined by GLC. All compounds were isolated in pure form by preparative TLC in somewhat lower yields and were fully characterized spectroscopically.

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Total Synthesis of (+)-Dihydrocostunolide via Tandem Cope–Claisen Rearrangement[1]

Summary: The total synthesis of (+)-dihydrocostunolide via tandem Cope–Claisen rearrangement has been accomplished.

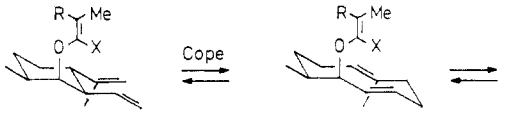
Sir: The total synthesis of germacrane sesquiterpenes[2] presents a formidable challenge.[3] The construction of a 10-membered ring with the control of stereochemistry is of paramount importance in this endeavor. We recently reported that the tandem Cope–Claisen rearrangement of **1a** provides a method for the construction of the cyclo-

(1) Synthesis via Sigmatropic Rearrangements. 12. For previous paper in this series: Raucher, S.; Gustavson, L. M. *Tetrahedron Lett.* **1986**, *27*, 1557.
(2) Review: Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 47.
(3) Syntheses of dihydrocostunolide: (a) Corey, E. J.; Hortmann, A. G. *J. Am. Chem. Soc.* **1965**, *87*, 5736. (b) Grieco, P. A.; Nishizawa, M. *J. Org. Chem.* **1977**, *32*, 1717. (c) Fujimoto, Y.; Shimizu, T.; Tatsuno, T. *Tetrahedron Lett.* **1976**, 2041. (d) Fujimoto, Y.; Shimizu, T.; Ohmori, M.; Tatsuno, T. *Chem. Pharm. Bull.* **1979**, *27*, 923. For a recent list of other syntheses of germacrane sesquiterpene, see: (e) Kitahara, T.; Mori, K. *J. Org. Chem.* **1984**, *49*, 3281, footnote 6. Recent synthesis of (±)-costunolide: (f) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. *J. Org. Chem.* **1986**, *51*, 4315.

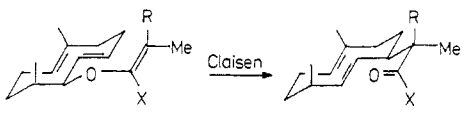
0022-3263/86/1951-5503$01.50/0

decadiene **2a**.[4] We now report the first successful application of this strategy for the total synthesis of the germacrane sesquiterpene (+)-dihydrocostunolide (**13**).[5]

Although the thermolysis of the *tert-butyldimethylsilyl* ketene acetal **1b** is complicated by O- to C-silyl migration,[4] the tandem Cope–Claisen rearrangement of the *triisopropylsilyl* ketene acetal **1c** to **2c** occurs with no evidence for silyl migration. The silyl ketene acetal **1c** was prepared by deprotonation of the corresponding propionate ester[4] with LDA in THF/HMPA at −78 °C followed by treatment with $(i\text{-Pr})_3SiCl$. Thermolysis of a dodecane solution of **1c** at 200 °C for 140 min gave **2c**. Hydrolysis of crude **2c** with $KF{\cdot}2H_2O$ in HMPA followed by esterification with CH_2N_2 provided **3** in 30% overall yield from the propionate ester.[6]



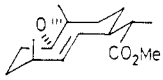
1a R = Me X = t-BuMe$_2$SiO
1b R = H X = t-BuMe$_2$SiO
1c R = H X = i-Pr$_3$SiO



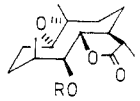
2a R = Me X = t-BuMe$_2$SiO
2c R = H X = i-Pr$_3$SiO
3 R = H X = MeO

Conversion of **3** to (+)-dihydrocostunolide (**13**) requires the selective transposition of the disubstituted double bond and the formation of the γ-butyrolactone. These transformations are made difficult both by the greater reactivity of the trisubstituted double bond of **3** toward electrophilic reagents and by the tendency of cyclodecadienes to undergo transannular cyclizations.[2] The stereochemical outcome for transformations of 10-membered rings is dependent on their preferred conformations.[7] NOE experiments indicate that the preferred conformation of **3** is that depicted.[8] This conclusion is also supported by MM2 molecular mechanics calculations.[9]

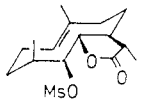
Since it was not possible to selectively functionalize the disubstituted double bond of **3**, the trisubstituted double bond was protected by epoxidation with 1 equiv. of MCPBA to give **4**. Reaction of **4** with OsO_4 afforded the hydroxy lactone **5** (mp 159–161 °C) in 68% overall yield from **3**. Both of these transformations occur diastereo-



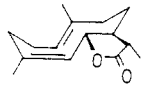
4



5 R = H
6 R = Ms



7



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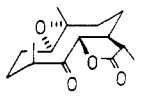
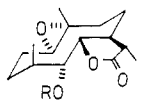
selectively from the outside face[7] of the double bonds for the conformation predicted by MM2 calculations and supported by NOE experiments. It should also be noted that for both cases MM2 calculations indicate that conformations which expose the other diastereotopic face of these double bonds are of considerably higher energy. Although attempts to introduce the requisite *E* double bond by syn elimination of derivatives of **5** were unsuccessful, anti elimination of **7** using tetra-*n*-butylammonium oxalate (TBAO)[10] provided the heliangolide **8** (mp 71–72 °C) in 60% yield.[11] The requisite mesylate **7** (mp 110–111 °C) was prepared by reaction of **5** with MsCl to give **6** (mp 116–118 °C) in 88% yield, followed by deoxygenation of **6** with dimethyl diazomalonate and $[(n\text{-}C_7H_{15}CO_2)_2Rh]_2$[12] in 70% yield.

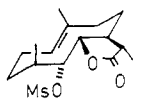
Since syn elimination of derivatives of **5** could not be effected and since anti elimination of **7** produced a *Z* double bond, the epimeric alcohol **10** (mp 179–181 °C) was



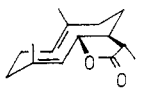
9



10 R = H
11 R = Ms



12



13

prepared in 71% overall yield by PDC oxidation[13] of **5** to **9** (mp 95–96 °C) followed by reduction with $NaBH_4$. MM2 calculations predicted that the preferred conformation of **9** is that depicted. The reduction of **9** to **10** occurs diasteroselectively by attack from the outside face of the carbonyl in the predicted preferred conformation. Treatment of **10** with MsCl gave **11** (mp 139–140 °C) in 92% yield, deoxygenation of **11** with dimethyl diazomalonate and $[(n\text{-}C_7H_{15}CO_2)_2Rh]_2$[12] afforded **12** (mp 128–129 °C) in 66% yield, and anti elimination of **12** by reaction with TBAO[10] provided (+)-dihydrocostunolide (**13**) in 48% yield: mp 76–77 °C (lit.[5] mp 77–78 °C); $[\alpha]^{20}_D$ +112.17° (*c* 0.076, $CHCl_3$) [lit.[5] $[\alpha]^{20}_D$ +113.6° (*c* 3.0 $CHCl_3$)]; HREIMS, *m/e* 234.1605 (calcd M^+ for $C_{15}H_{22}O_2$ 234.1620). The conversion of dihydrocostunolide to cos-

(4) Raucher, S.; Burks, J. E., Jr.; Hwang, K.-J.; Svedberg, D. P. *J. Am. Chem. Soc.* **1981**, *103*, 1853.

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(6) All structures in this paper represent the single enantiomer depicted. All new compounds gave IR, ^1H NMR, and HREIMS data in accord with their assigned structures. Yields refer to isolated compounds purified by flash chromatography.[16]

(7) For discussions of stereochemical control of transformations in medium-sized rings, see: (a) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4186. (b) Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493. (c) Still, W. C.; Galynker, I. *Tetrahedron*, **1981**, *37*, 3981. (d) Still, W. C.; Murata, S.; Revial, G.; Yoshihara, K. *J. Am. Chem. Soc.* **1983**, *105*, 625.

(8) For NOE studies on germacrane sesquiterpenes, see ref. 2. NOE results (germacrane numbering system): irradiation of the C-14 methyl group of **3** gave a 0.7% enhancement of the C-6 hydrogen, and irradiation of the C-5 hydrogen of **3** gave a 3.0% enhancement of the C-1 hydrogen; irradiation of the C-6 hydrogen of **5** gave a 4.2% enhancement of the C-14 methyl signal, and irradiation of the C-5 hydrogen of **5** gave a 11.5% enhancement of the C-5 hydrogen; irradiation of the C-6 hydrogen of **10** gave a 6.8% enhancement of the C-14 methyl signal, and irradiation of the C-5 hydrogen of **10** gave a 2.9% enhancement of the C-4 hydrogen.

(9) MM2 calculations were carried out on a VAX 11/780 using BAKMOD on conformations generated by RINGMAKER.

(10) Corey, E. J.; Terashima, S. *Tetrahedron Lett.* **1972**, *13*, 111.

(11) For other syntheses of the heliangolide skeleton, see: (a) Shimizu, T.; Saito, M.; Ohgoshi, Y.; Fujimoto, Y.; Tatsuno, T. *Heterocycles* **1982**, *17*, 53. (b) Kuroda, C.; Hirota, H.; Takahashi, T. *Chem. Lett.* **1982**, 249.

(12) Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 251. Better yields were obtained by using $[(n\text{-}C_7H_{15}CO_2)_2Rh]_2$ instead of $[(CH_3CO_2)_2Rh]_2$.

(13) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

tunolide has been reported.[14]

This synthesis demonstrates the use of the tandem Cope–Claisen rearrangement[15] for the synthesis of germacrane sesquiterpenes. It also indicates the potential utility of molecular mechanics calculations for stereochemical predictions involving transformations of medium-sized rings. We are now investigating the application of this strategy for the synthesis of more complex germacranolides.

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(15) For other tandem Cope–Claisen rearrangement studies, see: (a) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1979**, *101*, 1611. (b) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 880. (c) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 6576. (d) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1982**, *104*, 7181. (e) Ziegler, F. E.; H. Lim *J. Org. Chem.* **1982**, *47*, 5229. (f) Ziegler, F. E.; Lim, H. *J. Org. Chem.* **1984**, *49*, 3278.

(16) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(17) Recipient of NIH Research Career Development Award (1983–1988) and Fellow of the Alfred P. Sloan Foundation (1980–1984).