Irregular Monoterpene Constituents of *Artemisia tridentata cana*. The Isolation, Characterization, and Synthesis of Two New Chrysanthemyl Derivatives

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Received January 14, 1991

The neutral pentane extract of the leaves and flower heads of *Artemisia tridentata cana* was found to contain two new naturally occurring chrysanthemyl derivatives **21a** and **22a** in addition to several previously characterized monoterpenes. The structures of these compounds have been established by spectral and chemical means including synthesis. In the process of establishing these structures it was found that lavandulyl skeletal artifacts were formed. The structures of these artifacts were also established by chemical and spectral means.

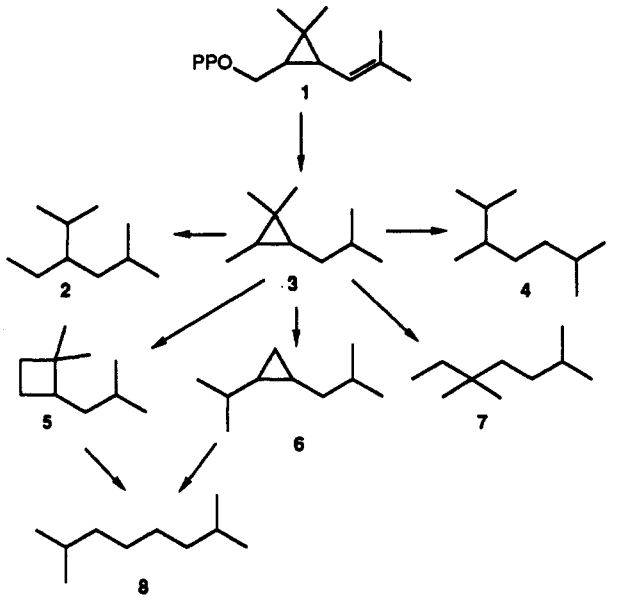
Introduction

We have been interested in the biosynthesis of irregular, non-head-to-tail monoterpenes primarily as a model for the biologically important squalene synthetase reaction.[1] Since the irregular monoterpene chrysanthemic acid is structurally related to presqualene diphosphate, it has been suggested that biosynthesis of irregular terpenes involves ionization of the structurally analogous cyclopropyl compounds followed by rearrangement.[1,2] Thus chrysanthemyl diphosphate **1** would be the precursor to the known irregular skeletal systems santolinyl **2**, chrysanthemyl **3**, lavandulyl **4**, rothrockyl **6**, and artemisyl **7** as well as possible C_{10} systems **5** and **8** as shown in Scheme I.

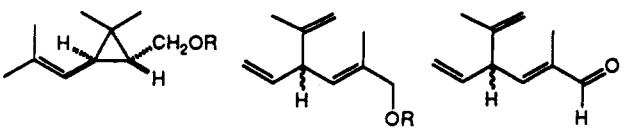
The isolation of monoterpenes possessing these skeletal structures provides support for this pathway. The artemisyl, santolinyl, chrysanthemyl, and rothrockyl[3,4] irregular monoterpene skeletal systems have been found exclusively in plants of the Anthemideae tribe of the Asteraceae family. The lavandulyl carbon skeleton has not been found thus far in the Anthemideae tribe. One explanation involves direct condensation of two dimethylallyl diphosphate (DMAPP) molecules to form lavandulyl diphosphate rather than requiring **1** as an intermediate.

To these ends, we have been screening various species of *Artemisia* (sagebrush), the largest genera in the Anthemideae tribe. This screening has led to the isolation and characterization of numerous new irregular monoterpenes that were consistent with a unified approach to irregular monoterpene biosynthesis.[3-10] We now report our results concerning the volatile oil constituents of *Artemisia tridentata cana*.

Scheme I



Scheme II



9a R = H
9b R = Ac
9c R = TBDMS

10a R = H
10b R = Ac

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Results and Discussion

Artemisia tridentata cana was collected at Brianhead, UT, at an elevation near 10000 ft. The neutral pentane extract was bulb to bulb distilled to afford a fragrant yellow oil. The three major constituents (Scheme II) from preparative GLC were identified as *trans*-chrysanthemol (**9a**),[5] lyratol (**10a**),[11,12] and lyratal (**11**),[11] by comparison of ^{1}H NMR, ^{13}C NMR, and IR spectra with knowns or literature values. Lyratal has never been isolated from a natural source prior to this study.

The second of four chromatographic fractions from a large collection of *A. cana* on GLC gave chrysanthemyl acetate (**9b**) and lyratyl acetate (**10b**) as major constituents and lyratal as a minor constituent. The third fraction contained *trans*-chrysanthemol and lyratol.

The IR spectrum of a previously unidentified constituent isolated from fraction 4 indicated the presence of a terminal olefin with an absorption at 898 cm^{-1} (CH_2=C).

(1) Epstein, W. W.; Poulter, C. D. *Phytochemistry* **1973**, *12*, 737.
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(3) Epstein, W. W.; Gaudioso, L. A. *J. Org. Chem.* **1982**, *47*, 175.
(4) Epstein, W. W.; Gaudioso, L. A.; Brewster, G. B. *J. Org. Chem.* **1984**, *49*, 2748.
(5) Alexander, K.; Epstein, W. W. *J. Org. Chem.* **1975**, *40*, 2576.
(6) Shaw, J.; Noble, T.; Epstein, W. W. *J. Chem. Soc., Chem. Commun.* **1976**, 380.
(7) Noble, T. A.; Epstein, W. W. *Tetrahedron Lett.* **1977**, 3931.
(8) Noble, T. A.; Epstein, W. W. *Tetrahedron Lett.* **1977**, 3933.
(9) Epstein, W. W.; Gaudioso, L. A. *J. Org. Chem.* **1979**, *44*, 3133.
(10) Epstein, W. W.; Gaudioso, L. A. *Phytochemistry* **1984**, *23*, 2257.
(11) Bose, A. K.; Trivedi, G. K.; Chakravarti, K. K. *Tetrahedron* **1969**, *25*, 3217.
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(13) Leopold, M. F. Ph.D. Dissertation, University of Utah, **1990**.

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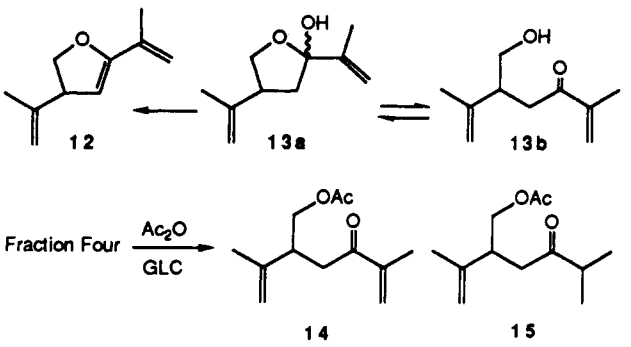
Scheme III



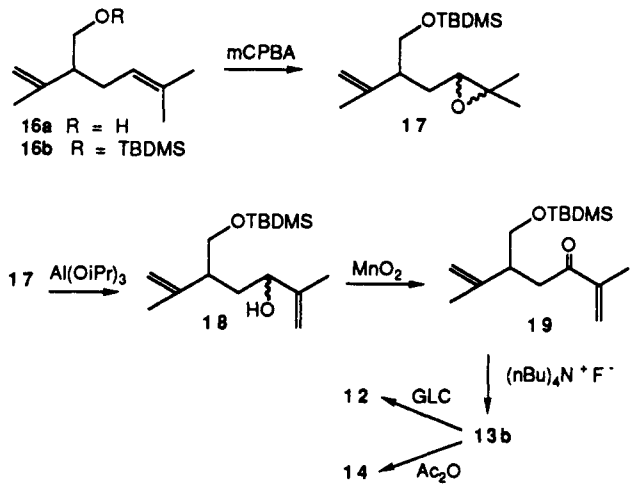
Two methyl groups attached to unsaturated carbons ($CH_3C{=}C$) were indicated by three hydrogen singlets at 1.70 and 1.88 ppm in the ^1H NMR spectrum, which also contained a one-hydrogen doublet of doublets at 4.14 ppm and a one-hydrogen doublet of doublets at 4.45 ppm. These signals can be attributed to methylene hydrogens on carbon adjacent to both a chiral carbon with one hydrogen attached and an oxygen atom ($CHCH_2OH$). The olefinic region of the ^1H NMR spectrum included five hydrogens as one-proton, broad singlets at 4.72, 4.76, 4.92, 4.98, and 5.30 ppm. The final remaining hydrogen appeared as a one-hydrogen multiplet at 3.66–3.72 ppm. Lack of absorptions for either a carbonyl or an alcohol in the IR spectrum suggested an ether functionality. Only one saturated carbon attached to oxygen at 73.9 ppm (doublet) was present in the proton-coupled ^{13}C NMR spectrum, indicating enol ether functionality. The proton-coupled ^{13}C NMR spectrum also contained six carbons in the olefinic region at 101.1 (doublet), 110.8 (triplet), 113.2 (triplet), 133.2 (singlet), 146.3 (singlet), and 157.6 (singlet) ppm, confirming the presence of two terminal methylenes and a trisubstituted olefin (CCH=C). A molecular ion of 151 in the MS (CI) confirmed molecular formula $C_{10}H_{14}O$. Thus the compound possessed four degrees of unsaturation, which required that the compound have one ring. A rigorous analysis of possible structures resulted in unique structure **12** for this compound.

TLC of the new constituent showed a single spot with $R_f = 0.50$ in hexanes/ethyl acetate (90:10) as the solvent. Earlier work on fraction 4 had shown the components to have R_f's ranging from 0.00 to 0.17 in hexanes/ethyl acetate (85:15). The inconsistency of R_f's and the component isolated via preparative GLC could be explained only if **12** was a GLC artifact.

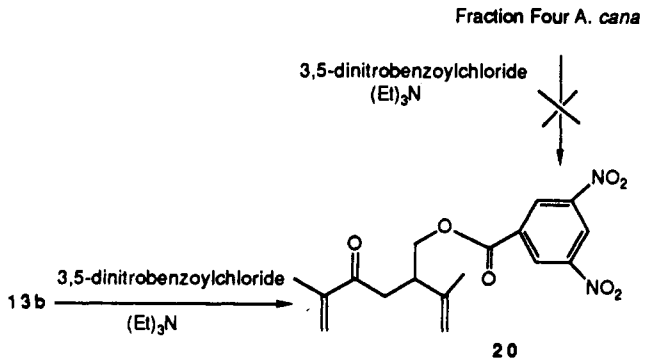
Assignment of structure **12** led to the speculation that keto alcohol **13b**, in equilibrium with its hemiketal form **13a**, could lose water to form the artifact **12** according to Scheme III. In order to establish the possible presence of **13b** as the precursor of **12**, fraction 4 was acetylated to prevent cyclization. Purification of two acetate derivatives was accomplished via preparative GLC. The spectral data for **14** and **15** (the dihydro derivative of **14**) were consistent with corresponding literature data for acetates isolated from *Lavandula officinalis*.[14]

In order to establish the structure of **14** as well as confirm the nature of **12** and **13b**, these compounds were synthesized as shown in Scheme IV. Lavandulol **16a** prepared by a modification of a known literature method[15] was converted to its hydroxy-protected OTBDMS derivative **16b**. Diastereomeric epoxides **17** were obtained by reaction of **16b** with *m*-chloroperbenzoic acid. Isomerization of **17** with aluminum isopropoxide[16] afforded diastereomeric alcohols **18**, which were converted to the α,β-unsaturated ketone **19** with activated manganese dioxide. Deprotection with fluoride ion[17] afforded the desired alcohol **13b**. Preparative GLC of **13b** resulted in the expected rearrangement to artifact **12**. Reaction of **13b** with acetic anhydride[18] and subsequent purification gave a colorless oil whose spectral and chromatographic properties were identical with those of acetate **14**, isolated from the acetylation of *A. cana* fraction 4.

Scheme IV



Scheme V



Identification of the acetates derived from *A. cana* fraction 4 has thus led to the identification of two new lavandulyl skeletal monoterpenes each having keto alcohol functionalities. The isolation of lavandulyl monoterpenes from *A. cana* was interesting since this would be the first reported isolation of lavandulyl monoterpenes from Anthemidae tribe species.

The question of absolute stereochemistry of the novel lavandulyl compounds still needed to be addressed. Analysis of the CD spectrum of the 3,5-dinitrobenzoate derivative of keto alcohol **13b** was the first method considered for establishing the absolute stereochemistry.[19] The 3,5-dinitrobenzoate derivative of synthetic **13b** was prepared, as shown in Scheme V, for comparison to the 3,5-dinitrobenzoates of *A. cana* fraction 4. Surprisingly none of the derivatives of *A. cana* fraction 4 had the same skeletal structure as **20**, derived form keto alcohol **13b**, as evidenced by a consideration of the following data. The synthetic keto alcohol derivative showed the presence of two terminal double bonds in the ^1H NMR spectrum and

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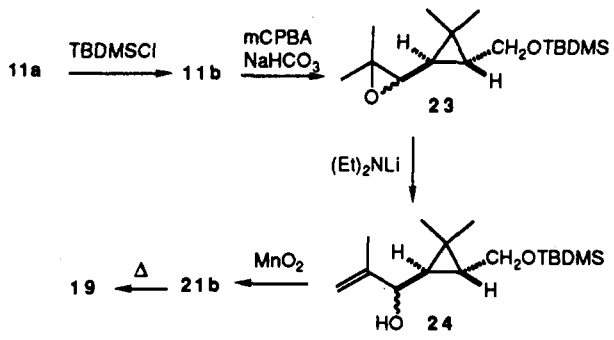
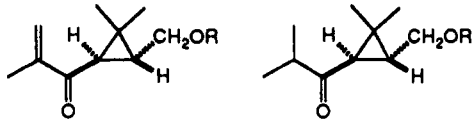
(15) Matsui, M.; Kobayashi, A. *Agric. Biol. Chem.* **1962**, *26*, 705.
(16) Terao, M.; Shiraishi, K. K. *Synthesis* **1979**, 467.
(17) Morton, D. R.; Thompson, J. L. *J. Org. Chem.* **1978**, *43*, 2102.
(18) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *4*, 2069.
(19) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257.

Scheme VI



had the molecular formula $C_{17}H_{18}N_2O_7$, as inferred from the mass spectrum (EI) (m/z, 362). The mixture of derivatives isolated from the reaction of *A. cana* fraction 4 with 3,5-dinitrobenzoyl chloride showed only one terminal double bond in the ^1H NMR spectrum and molecular formulas of $C_{17}H_{18}N_2O_7$ and $C_{17}H_{20}N_2O_7$ as inferred from the mass spectrum (CI) molecular ions (m/e, 363; m/e, 365). From these data it was determined that the skeletal structures of the acetates previously isolated from the acetylation of *A. cana* fraction 4 were in fact thermal rearrangement artifacts. The actual structures must have a ring and one less double bond, leading to speculation that the components of *A. cana* fraction 4 had the structures of keto alcohols **21a** and **22a**. The likelihood of these structures gained support from the previous isolation of chrysanthemol and chrysanthemyl acetate from the same plant. A thermal rearrangement of **21b** to form **19** would explain the observed results, and a literature search showed that similar α-cyclopropyl carbonyl compounds undergo this type of rearrangement.[20,21]



21a R = H
21b R = TBDMS

22a R = H
22b R = TBDMS

In order to confirm the rationalization, the OTBDMS derivative **21b** was synthesized according to Scheme VI and thermally rearranged to **19**. Chrysanthemol **11a** prepared from commercial chrysanthemic acid[22] via esterification and lithium aluminum hydride reduction was converted to its OTBDMS derivative and epoxidized with *m*-chloroperbenzoic acid to give **23**.[23] The diastereomeric epoxide mixture was isomerized to the diastereomeric allylic alcohols **24** with lithium diethylamide[24] and oxidized with manganese dioxide to give the desired α,β-unsaturated ketone **21b**. The ^1H NMR spectrum contained a doublet at 2.04 ppm (J = 5.5 Hz) that is consistent with retention of the trans-substituted cyclopropyl ring. When **21b** was subjected to preparative GLC, it yielded the cyclopropyl ring opened product **19** as predicted.

The *tert*-butyldimethylsilyl ethers of all alcohols in *A. cana* fraction 4 were prepared and separated by preparative TLC to give material with an R_f identical with that of synthetic **21b**. Analysis of the ^1H NMR spectrum established that the isolated material contained identical resonances as compared to the ^1H NMR spectrum of synthetic **21b**, although resonances due to the presence of the dihydro derivative **22b** were also present. The doublet at 2.04 ppm (J = 5.5 Hz) in the ^1H NMR spectrum established the relative stereochemistry of the *trans*-cyclopropane ring. Preparative GLC of this mixture resulted in isolation of the ring-opened product **19**. The optical rotation of the ring-opened product was lower than that of optically pure **19** obtained from (1*R*,3*R*)-chrysanthemic acid, although within experimental error due to the very low rotation of the optically pure material.

Another method of establishing the absolute stereochemistry of the new chrysanthemol derivatives involved use of optically active shift reagents.[25] Because the cyclopropyl ring opened product **19** had been synthesized in both racemic and optically pure forms as well as derived from one of the natural products in question, this compound was considered attractive for NMR spectroscopic studies utilizing optically active shift reagents. The ^1H NMR spectrum of racemic **19** complexed with optically active shift reagent showed nonequivalence at four separate methyl signals. The methyl absorptions at 0.00 and 0.01 ppm were each resolved into two signals in the expected ratio of 1:1, while the methyl absorptions at 1.72 and 1.84 ppm were also resolved into two pairs of signals in a ratio of 1:1. The ^1H NMR spectrum of optically pure synthetic **19** complexed with optically active shift reagent resulted in equivalence of all four methyl signals as expected. The addition of optically active shift reagent to **19** derived from *A. cana* also resulted in a ^1H NMR spectrum that showed equivalence of all four methyl absorptions in question. These data established that the α,β-unsaturated ketone derived from chrysanthemic acid is optically pure, as is the natural product **21a**, which therefore must possess the 1*R*,3*R* absolute configuration as shown. The 1*R*,3*R* configuration is consistent with the isolation of (>95%) optically pure (1*R*,3*R*)-chrysanthemol from this plant.

The isolation of (1*R*,3*R*)-chrysanthemol as a major constituent of the essential oils provides support for the proposed unified approach to irregular monoterpene biosynthesis. Although the presence of naturally occurring lavandulyl compounds in the Anthemideae tribe species would lend support for **1** as an intermediate in the biosynthesis of lavandulyl monoterpenes, the lack of reported occurrences of lavandulyl skeleton monoterpenes in these species leaves this an unanswered question.

Experimental Section

Thin-layer chromatography (TLC) analyses were performed on precoated sheets (0.20 mm thick) of silica gel on aluminum backing with detection by staining with 5% phosphomolybdic acid in ethanol or with a vanillin/H_2SO_4 reagent followed by heating. Preparative GLC purifications involved a 9 m × 6 mm Carbowax 20 M (5%) on silanized 60–80-mesh Chromosorb W column at 170 °C with injector and detector temperatures at 250 °C unless otherwise indicated. Column chromatography was done on 60–200-mesh silica gel. All solvents were distilled prior to LC or TLC use, and spectral grade solvents were used for all spectroscopic measurements.

Large-Scale Extraction of *A. cana* (Brianhead, UT).[26] The whole plants (4 kg) were ground and extracted with pentanes in a large Soxhlet extractor. The combined extracts were concentrated in vacuo and vacuum short path distilled (0.1 mm) to yield 10.6 g of a yellowish oil (0.27% of dry weight of plant). The oil was separated into four fractions by flash chromatography on silica gel with hexane/ethyl acetate (90:10) as eluent. Preparative

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(21) Trost, B. M.; Vladuchick, W. C. *J. Org. Chem.* **1979**, *44*, 148.
(22) We thank the C. D. Poulter group for the *trans*-chrysanthemic acid used in this synthesis.
(23) Mitsuru, I.; Ziffer, H. *J. Org. Chem.* **1979**, *44*, 1351.
(24) Smith, J. *Synthesis* **1984**, 629.
(25) Morrison, J. D. *Asymmetric Synthesis*; Academic Press: London, 1981; Vol. 1.
(26) Plant samples of the material used in this study are on deposit at the University of Utah Herbarium.

GLC analysis of fraction 2 indicated the presence of two major and one minor components, which were identified respectively as chrysanthemyl acetate (**9b**), lyratyl acetate (**10b**), and lyratal (**11**) by analysis of ^{1}H NMR, ^{13}C NMR, and IR spectral data.[12] Preparative GLC analysis of fraction 3 indicated the presence of two major constituents, which were identified as chrysanthemol (**9a**) and lyratol (**10a**) by analysis of ^{1}H NMR, ^{13}C NMR, and IR spectral data. GLC analysis of fraction 4 resulted in the isolation of **12**. Capillary GLC analysis of the crude oil indicated the following composition in order of retention volume as determined by comparison to known samples: lyratal (<1%), (1*R*,3*R*)-chrysanthemyl acetate (3.6%), lyratyl acetate (1.8%), (1*R*,3*R*)-chrysanthemol (10.4%), and lyratol (11.8%).

The GC artifact 12 from fraction 4 was isolated as a colorless oil via preparative GLC: λ_{max} = 256 nm; IR (neat) 3078, 2974, 2951, 2889, 1755, 1647, 1600, 1446, 1369, 1219, 1123, 1068, 933, 898, and 776 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.70 (3 H, s), 1.88 (3 H, s), 3.66–3.72 (1 H, m), 4.14 (1 H, dd, J = 6.9, 8.9 Hz), 4.45 (1 H, dd, J = 8.9, 10.3 Hz), 4.72 (1 H, br s), 4.77 (1 H, br s), 4.79 (1 H, br s), 5.30 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 19.46 (q), 19.80 (q), 50.87 (d), 73.93 (t), 101.10 (d), 110.75 (t), 113.46 (t), 133.24 (s) 146.29 (s), 157.63 (s); MS (EI) 150 (47), 135 (38), 109 (66), 81 (34), 69 (100); HRMS calcd for $C_{10}H_{14}O$ 150.1041, found 150.1044.

Acetylation of Fraction 4 of *A. cana*. A solution of 100 mg of fraction 4 *A. cana*, triethylamine (120 mg, 1.19 mmol), DMAP (7 mg, 0.06 mmol) and acetic anhydride (121 mg, 1.19 mmol) was stirred for 3 h and 250 μL of 10% HCl added. The organic layer was concentrated in vacuo to give acetate derivatives **14** and **15** by preparative GLC.

4-Oxo-2-isopropenyl-5-methylhex-5-enyl acetate (14):[14] IR (neat) 3070, 2950, 1737, 1675, 1645, 1435, 1370, 1232, 1035, 932, and 890 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73 (3 H, s), 1.84 (3 H, s), 2.00 (3 H, s), 2.81–2.84 (2 H, m), 2.94–3.03 (1 H, m), 3.99 (1 H, dd, J = 6.8, 11.0 Hz), 4.07 (1 H, dd, J = 6.3, 11.0 Hz), 4.73 (1 H, br s), 4.81 (1 H, br s), 5.76 (1 H, br s), 5.94 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 17.64, 20.88, 21.09, 38.43, 41.28, 65.82, 112.38, 124.60, 144.36, 144.68, 170.91, 200.03; MS (CI) (isobutane) 69 (100), 151 (54), 107 (17), 122 (10), 150 (8), and (M + 1) 211 (4); HRMS calcd for (M + 1) $C_{12}H_{19}O_3$ 211.1310, found 211.1334.

4-Oxo-2-isopropenyl-5-methylhexyl acetate (15):[14] IR (neat) 3070, 3065, 1735, 1710, 1645, 1455, 1377, 1362, 1230, 970, and 893 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.07 (6 H, d, J = 6.9 Hz), 1.73 (3 H, s), 2.00 (3 H, s), 2.55–2.60 (2 H, m), 2.95 (1 H, m), 3.95 (1 H, dd, J = 6.8, 11.0 Hz), 4.07 (1 H, dd, J = 6.3, 11.0 Hz), 4.73 (1 H, br s), 4.81 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 18.19, 20.98, 21.22, 40.51, 41.13, 41.54, 65.82, 112.21, 144.40, 170.74, 212.30; MS (CI) (isobutane) 153 (100), 213 (55), 152 (15), 71 (8), 135 (5), 195 (4); HRMS calcd for (M + 1) $C_{12}H_{21}O_3$ 213.149 07, found 213.149 01.

Preparation of Lavandulol *tert*-Butyldimethylsilyl Ether (16b). A solution of lavandulol (**16a**, 3.00 g, 19.5 mmol), imidazole (2.24 g, 33.0 mmol) in 7 mL of DMF, and TBDMSCl (3.28 g, 25.3 mmol) was stirred for 2 h and quenched wtih 25 mL of 10% HCl and 15 mL of water. The mixture was extracted [hexane/ethyl acetate (85:15)] and the dried ($MgSO_4$) organic layer concentrated in vacuo and chromatographed on silica gel [hexane/ethyl acetate (95:5)] to yield 3.67 g of **16b** as a colorless oil (70%): IR (neat) 3070, 2920, 2855, 1630, 1435, 1373, 1247, 1090, 933, 882, 830, 767, and 660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.01 (6 H, s), 0.87 (9 H, s), 1.59 (3 H, s), 1.66 (6 H, s), 1.90–1.98 (1 H, m), 2.00–2.27 (2 H, m), 3.48 (1 H, dd, J = 6.5, 9.9 Hz), 3.50 (1 H, dd, J = 6.1, 9.9 Hz), 5.68 (1 H, br s), 5.77 (1 H, br s), 5.05 (1 H, m); ^{13}C NMR ($CDCl_3$) δ −5.23, −5.21, 17.95, 18.41, 20.74, 25.88, 26.02, 28.38, 49.80, 65.58, 111.39, 122.63, 131.85, 146.15; MS (EI) 69 (100), 75 (99), 211 (68), 73 (53), 41 (36), 143 (15). Anal. Calcd for $C_{16}H_{32}OSi$: C, 71.57; H, 12.01. Found: C, 71.89; H, 12.16.

Preparation of Diastereomeric Epoxides 17. A solution of *m*-CPBA (3.88 g, 13.7 mmol) dissolved in a minimal volume of CH_2Cl_2 and lavandulol *tert*-butyldimethylsilyl ether (**16b**) (3.67 g, 13.7 mmol) in 100 mL of CH_2Cl_2 at 0 °C was stirred for 2 h at 0 °C and washed with 50 mL of 10% saturated $NaHCO_3$. The dried ($MgSO_4$) organic layer was concentrated in vacuo to yield 3.26 g of a colorless oil (84%), consisting of a mixture of diastereomers **17** as determined by the ^{1}H NMR spectrum of the mixture. TLC [hexane/ethyl acetate (85:15)] showed a single spot at R_f = 0.66: IR (neat) 3072, 2975, 2925, 2856, 1645, 1460, 1377, 1253, 1100, 890, 835, and 772 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ −0.1 (12 H, s), 0.84 (18 H, s), 1.1 (3 H, s), 1.25 (9 H, br s), 1.50–1.75 (4 H, m), 1.67 (3 H, s), 1.69 (3 H, s), 2.27–2.41 (2 H, m), 2.71 (2 H, dd, J = 5.9, 6.6 Hz), 3.44–3.62 (4 H, m), 4.74 (1 H, s), 4.76 (1 H, s), 4.81 (2 H, br s); ^{13}C NMR ($CDCl_3$) δ −5.25, 18.21, 18.69, 18.98, 20.36, 20.42, 24.80, 24.86, 25.74, 25.84, 29.07, 29.16, 47.27, 47.4, 57.95, 58.47, 62.95, 63.12, 65.68, 65.72, 112.16, 112.23, 145.35, 145.39; MS (EI) 75 (100), 135 (36), 73 (35), 89 (9), 93 (8), 69 (7), (41 (7), 43 6), 197 (4), 227 (2). Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.54; H, 11.34. Found: C, 67.91; H, 11.47.

Preparation of Diastereomeric Allylic Alcohols 18. A solution of **17** (3.00 g, 10.6 mmol) in 17 mL of toluene and aluminum isopropoxide (2.16 g, 10.6 mmol) was stirred and refluxed for 12 h and quenched with 10 mL of 10% HCl. The dried ($MgSO_4$) organic layer was concentrated in vacuo and chromatographed on silica gel to give 2.49 g of a colorless oil (83%), as a 1:1 mixture of diastereomers **18** determined by the ^{1}H NMR spectrum of the mixture. TLC [hexane/ethyl acetate (85:15)] showed two spots at R_f = 0.43 and 0.47. IR (neat) of the mixture of diastereomers: 3350, 3070, 2950, 2930, 2855, 1640, 1250, 1100, 890, 832, and 772 cm^{-1}. A small amount of each diastereomer was separated by chromatography on silica gel [hexane/ethyl acetate (95:5)].

Diastereomer with higher R_f: ^{1}H NMR ($CDCl_3$) δ 0.04 (6 H, s), 0.87 (9 H, s), 1.63–1.71 (8 H, m), 2.37–2.45 (1 H, m), 3.50 (1 H, dd, J = 7.8, 9.9 Hz), 3.62 (1 H, dd, 5.4, 9.9 Hz), 4.02 (1 H, t, J = 6.2 Hz), 4.74 (1 H, s), 4.79 (2 H, s), 4.95 (1 H, s); ^{13}C NMR ($CDCl_3$) δ −5.44, 18.12, 18.28, 20.51, 25.87, 37.48, 46.94, 66.75, 74.26, 110.11, 11.92, 146.46, 148.11.

Diastereomer with lower R_f: ^{1}H NMR ($CDCl_3$) δ 0.03 (6 H, s), 0.87 (9 H, s), 1.61–1.70 (7 H, m), 1.81 (1 H, dt, J = 6.1, 12.2 Hz), 2.23 (1 H, m), 3.47 (1 H, dd, J = 8.1, 9.9 Hz), 3.78 (1 H, dd, J = 5.1, 9.9 Hz), 4.13 (1 H, dd, J = 6.3, 6.5 Hz), 4.73 (1 H, s), 4.78 (1 H, s), 4.82 (1 H, s), 4.93 (1 H, s); ^{13}C NMR ($CDCl_3$) δ −5.47, 17.50, 18.26, 20.81, 25.88, 35.80, 45.83, 66.38, 74.19, 111.55, 111.80, 146.53, 146.99. Anal. Calcd for mixture of diastereomers $C_{16}H_{32}O_2Si$: C, 67.54; H, 11.34. Found: C, 67.32; H, 11.35.

Oxidation of Allyic Alcohols 18. A mixture of **18** (1.47 g, 5.21 mmol) in 50 mL of hexane and 25 g of active MnO_2 was stirred for 5 h, filtered, and concentrated in vacuo to yield 1.35 g of **19** as a colorless oil (92%): IR (neat) 3075, 2080, 2030, 2890, 2058, 1778, 1645, 1630, 1455, 1370, 1360, 1245, 1193, 945, 887, 835, 772; ^{1}H NMR ($CDCl_3$) δ 0.00 (3 H, s), 0.01 (3 H, s) 0.85 (9 H, s), 1.72 (3 H, s), 1.84 (3 H, s), 2.66–2.81 (2 H, m), 3.00 (1 H, m), 3.47 (1 H, dd, J = 7.0, 9.9 Hz), 3.61 (1 H, dd, J = 5.2, 9.9 Hz), 4.68 (1 H, br s), 4.76 (1 H, br s), 5.73 (1 H, br s), 5.95 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ −5.32, 17.77, 18.34, 21.55, 25.94, 38.36, 45.06, 65.31, 111.35, 124.21, 144.60, 145.60, 201.09; MS (EI) 75 (100), 225 (52), 73 (51), 41 (35), 133 (30), 89 (10), 145 (9), 59 (7), 105 (6). Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 68.11; H, 10.70. Found: C, 67.98; H, 11.07.

Deprotection of α,β-Unsaturated Ketone 19. A solution of tetrabutylammonium fluoride (19.5 mL, 1 M in THF, 19.5 mmol) and **19** (0.500 g, 17.7 mmol) was stirred for 5 h, washed with 20 mL of saturated NaCl, concentrated in vacuo, and chromatographed on silica gel [hexane/ethyl acetate (80:20)] to yield 234 mg of **13a** as a yellowish oil (78%): λ_{max} = 218 nm; IR (neat) 3425, 3078, 2960, 2930, 1675, 1648, 1631, 1451, 1373, 1250, 1188, 1065, 1041, 1010, 930, and 892 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73 (3 H, br s), 1.84 (3 H, br s), 2.80–2.87 (3 H, m), 3.55 (2 H, dd, J = 5.8, 5.5 Hz), 4.75 (1 H, br s), 4.87 (1 H, br s), 5.76 (1 H, br s), 5.96 (1 H, br s); ^{13}C NMR ($CDCl_3$) δ 17.74, 21.04, 38.44, 44.71, 64.00, 112.42, 124.68, 144.50, 144.84, 200.84.

Reaction of 3,5-Dinitrobenzoyl Chloride with Keto Alcohol 13a. To a solution of 3,5-dinitrobenzoyl chloride (225 mg, 0.98 mmol), triethylamine (125 mL, 1.33 mmol), and 2 mL of dry ether was added **13a** (150 mg, 0.89 mmol) dropwise via syringe. The reaction mixture was stirred for 1 h and extracted with 15 mL of hexane/ethyl acetate (80:20) and the organic layer washed with 15 mL of 10% HCl and 15 mL of saturated $NaHCO_3$. The dried ($MgSO_4$) organic layer was concentrated in vacuo to a yellow oil and chromatographed on silica gel [hexane/ethyl acetate (85:15)]. The fractions with R_f = 0.30 [hexane/ethyl acetate (80:20)] were combined and concentrated. Recrystallization from ethanol resulted in 172 mg of **20** as white needles (53%): mp 54–55 °C; IR (Nujol) 1720, 1675, 1629, 1542, 1346, 1290, 1179, 948, 731, and 722 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.81 (3 H, s), 1.84 (3 H, s), 2.85–3.00

Table I

Eu opt., M	nonequivalence	separation, Hz	
		racemic **19**	*A. cana* **19**
1. 2.36	H_3CSiCH_3	2.9 and 4.3 (1:1)	singlets
	$CH_2{=}CCH_3$	7.5 (1:1)	singlet
2. 3.00	H_3CSiCH_3	3.2 and 5.3 (1:1)	singlets
	$CH_2{=}CCH_3$	8.8 (1:1)	singlet
3. 3.64	H_3CSiCH_3	4.4 and 9.6 (1:1)	singlets
	$CH_2{=}CCH_3$	9.6 (1:1)	singlet
	$CH_2{=}CCH_3$	broad 10 (1:1)	singlet

(2 H, M), 3.18–3.27 (1 H, m), 4.38 (1 H, dd, J = 6.5, 11.0 Hz), 4.47 (1 H, dd, J = 6.9, 11.0 Hz), 4.84 (1 H, br s), 4.90 (1 H, br s), 5.81 (1 H, br s), 5.98 (1 H, s), 9.08 (2 H, d, J = 2.1 Hz), 9.19 (1 H, t, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ 17.7, 20.9, 38.5, 41.2, 67.8, 113.2, 122.3, 124.9, 129.3, 133.7, 143.7, 144.5, 148.5, 162.1, 199.2; MS (EI) 362 (1), 195 (16), 150 (13), 122 (15), 75 (12), 69 (100).

Reaction of 3,5-Dinitrobenzoyl Chloride with *A. cana* Fraction 4. To a solution of 3,5-dinitrobenzoyl chloride (283 mg, 1.19 mmol), triethylamine (179 mg, 1.78 mmol), and 2 mL of dry ether was added 200 mg of *A. cana* fraction 4. The mixture was stirred for 1 h and extracted with hexane/ethyl acetate (80:20), and the organic layer was washed with 15 mL of 10% HCl and 15 mL of saturated $NaHCO_3$. The dried ($MgSO_4$) organic layer was concentrated in vacuo to yield a mixture of crystalline products chromatographed on silica gel [hexane/ethyl acetate (85:15)] and yielded 130 mg of colorless crystals (R_f = 0.30): mp 115–117 °C; MS (CI) 265 (5.1), 263 (13.3).

Preparation of (1*R*,3*R*)-Chrysanthemol *tert*-Butyldimethylsilyl Ether (9c). A solution of (1*R*,3*R*)-chrysanthemol (3.500 g, 22.72 mmol) and imidazole (2.318 g, 34.09 mmol) in 10 mL of DMF and TBDMSCl (3.77 g, 24.99 mmol) was stirred for 2 h and quenched with 25 mL of 10% HCl. The dried ($MgSO_4$) organic layer was concentrated in vacuo to yield 5.971 g of **9c** as a colorless oil (90%): IR (neat) 3070, 2970, 2925, 2890, 2856, 1645, 1470, 1460, 1389, 1375, 1358, 1252, 1155, 1105, 1058, 1001, 832, and 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.03 (6 H, s), 0.71–0.78 (1 H, m), 0.88 (9 H, s), 1.02 (3 H, s), 1.10 (3 H, s), 1.01–1.10 (1 H), 1.66 (3 H, s), 1.68 (3 H, s), 3.52 (1 H, dd, J = 10.1, 11.0 Hz), 3.78 (1 H, dd, J = 6.1, 11.0 Hz), 4.87 (1 H, d, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ −4.98, −4.90, 18.36, 18.41, 21.54, 22.21, 22.84, 25.74, 26.07, 28.54, 35.11, 63.76, 123.75, 132.49. Anal. Calcd for $C_{16}H_{32}OSi$: C, 71.57; H, 12.01. Found: C, 71.47; H, 11.97.

Preparation of Diastereomeric Epoxides 23. To a stirred mixture of chrysanthemol *tert*-butyldimethylsilyl ether (**9c**) (2.150 g, 8.05 mmol), 100 mL of CH_2Cl_2, and 100 mL of saturated $NaHCO_3$ at 0 °C was added *m*-CPBA (1.903 g, 8.05 mmol) in 75 mL of CH_2Cl_2 dropwise through an addition funnel. The reaction mixture was stirred for 1 h and quenched with 25 mL of saturated Na_2SO_3. The organic layer was washed with 50 mL of saturated $NaHCO_3$, dried ($MgSO_4$), concentrated in vacuo, and chromatographed on silica gel [hexane/ethyl acetate (90:10)]. The fractions containing the spots with R_f = 0.33 and R_f = 0.42 were combined to yield 1.413 g of diastereomeric epoxides **23** (66%): IR (neat) 2970, 2925, 2850, 1468, 1372, 1250, 1018, 1000, 833, 810, and 770 cm^{-1}. A small amount of each diastereomer was separated by chromatography on silica gel [hexane/ethyl acetate (95:5)].

Diastereomer with lower R_f: ^{1}H NMR ($CDCl_3$) δ 0.03 (6 H, s), 0.35 (1 H, dd, J = 5.1, 8.5 Hz), 0.80–0.87 (1 H, obscured), 0.87 (9 H, s), 1.10 (3 H, s), 1.19 (3 H, s), 1.28 (3 H, s), 1.31 (3 H, s), 2.44 (1 H, d, J = 8.5 Hz), 3.62 (2 H, m); ^{13}C NMR ($CDCl_3$) δ −5.21, −5.15, 18.25, 19.45, 20.58, 21.28, 22.32, 24.71, 25.90, 26.61, 31.79, 57.98, 62.93, 64.71.

Diastereomer with higher R_f: ^{1}H NMR ($CDCl_3$) δ 0.01 (3 H, s), 0.02 (3 H, s), 0.49 (1 H, dd, J = 4.5, 5.0 Hz), 0.86 (9 H, s), 0.95 (1 H, m), 1.08 (3 H, s), 1.10 (3 H, s), 1.27 (3 H, s), 1.28 (3 H, s), 2.62 (1 H, d, J = 4.3 Hz), 3.47 (1 H, dd, J = 8.2, 11.1 Hz), 3.74 (1 H, dd, J = 6.1, 11.1 Hz); ^{13}C NMR ($CDCl_3$) δ −5.26, −5.18, 18.24, 19.03, 19.89, 21.05, 22.32, 24.59, 25.91, 27.04, 30.82, 58.32, 62.73, 63.16. Anal. Calcd for the mixture of diastereomers $C_{16}H_{32}O_2Si$: C, 67.54; H, 11.34. Found: C, 67.38; H, 11.54.

Preparation of Diastereomeric Allylic Alcohols 24. To a stirred solution of diethylamine (142 mg, 1.94 mmol) in 15 mL of anhydrous ether at 0 °C was added *n*-butyllithium (0.816 mL, 2.38 M, 1.94 mmol). To the resulting yellow solution at room temperature was added epoxide **23** (500 mg, 1.77 mmol) in 1 mL of anhydrous ether. The reaction mixture was refluxed overnight and quenched with 10 mL of 10% HCl. The dried ($MgSO_4$) organic layer was concentrated in vacuo to yield a yellow oil and chromatographed on silica gel [hexane/ethyl acetate (90:10)]. The fractions with R_f = 0.46 and R_f = 0.39 [hexane/ethyl acetate (80:20)] were combined and concentrated in vacuo to yield 410 mg (1.44 mmol) of a colorless oil (82%) as a mixture of diastereomers **24** determined by the ^{1}H NMR spectrum: IR (neat) 3400, 3075, 2958, 2930, 2858, 1645, 1462, 1253, 1105, 890, 835, and 772 cm^{-1}. A small amount of each diastereomer was separated by chromatography on silica gel [hexane/ethyl acetate (95:5)].

Diastereomer with lower R_f: ^{1}H NMR ($CDCl_3$) δ 0.06 (3 H, s), 0.66 (1 H, dd, J = 5.6, 9.7 Hz), 0.89–0.91 (1 H, obscured), 0.90 (9 H, s), 1.08 (3 H, s), 1.11 (3 H, s), 1.55 (1 H, br s), 1.79 (3 H, s), 3.47 (1 H, dd, J = 8.3, 10.7 Hz), 3.61 (1 H, d, J = 9.7 Hz), 3.76 (1 H, dd, J = 6.8, 10.7 Hz), 4.82 (1 H, s), 5.00 (1 H, s); ^{13}C NMR ($CDCl_3$) δ −5.23, −5.20, 18.24, 18.41, 21.69, 22.20, 22.45, 25.94, 31.98, 36.26, 63.17, 75.51, 110.12, 147.16.

Diastereomer with higher R_f: ^{1}H NMR ($CDCl_3$) δ 0.01 (6 H, s), 0.61 (1 H, dd, J = 5.3, 9.6 Hz), 0.74 (1 H, m), 0.86 (9 H, s), 1.10 (3 H, s), 1.20 (3 H, s), 1.79 (3 H, s), 3.52 (1 H, dd, J = 7.7 and 10.9 Hz), 3.63 (2 H, m), 4.77 (1 H, s), 4.96 (1 H, s). Anal. Calcd for the mixture of diastereomers $C_{16}H_{32}O_2Si$: C, 67.54; H, 11.34. Found: C, 67.46; H, 11.32.

Preparation of α,β-Unsaturated Ketone 21b. A mixture of allylic alcohols **24** (230 mg, 0.81 mmol) in 15 mL of hexane and 3 g of activated MnO_2 was stirred for 16 h, filtered, and concentrated in vacuo to yield 200 mg of **21b** as an oil (88%): $[\alpha]_D$ = +12.3° (*c* 0.55, $CHCl_3$); λ_{max} = 216 nm; IR (neat) 3090, 2940, 2855, 1660, 1628, 1455, 1333, 1250, 1083, 1002, 930, 851, 830, and 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.02 (3 H, s), 0.03 (3 H, s), 0.86 (9 H, s), 1.02 (3 H, s), 1.25 (3 H, s), 1.81–1.88 (1 H, m), 1.86 (3 H, br s), 2.04 (1 H, d, J = 5.5 Hz), 3.56 (1 H, dd, J = 8.2, 11.2 Hz), 3.78 (1 H, dd, J = 5.9, 11.3 Hz), 5.69 (1 H, br s), 5.87 (1 H, s); ^{13}C NMR ($CDCl_3$) δ −5.23, −5.15, 17.76, 18.21, 20.33, 21.04, 25.87, 30.10, 34.04, 35.99, 62.06, 123.64, 146.30, 199.48. Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 71.57; H, 12.01. Found: C, 71.47; H, 11.97.

Preparative GLC of α,β-Unsaturated Ketone 21b Resulting in the Isolation of Artifact 19. Preparative GLC of **21b** resulted in the isolation of **19**: $[\alpha]_D$ = +6.2° (*c* 0.45, $CHCl_3$. The spectral data were identical with those from synthetic **19**.

Preparation of OTBDMS Derivatives of *A. cana* Fraction 4. To a stirred solution of 159 mg of fraction 4, imidazole (100 mg, 1.51 mmol), and 2 mL of DMF was slowly added TBDMSCl (171 mg, 1.14 mmol). The reaction mixture was stirred for 2 h, quenched with 2 mL of 10% HCl, and extracted [hexane/ethyl acetate (90:10)], and the organic layer was concentrated in vacuo to yield 220 mg of a yellow oil. Preparative TLC of 60 mg of the crude material [hexane/ethyl acetate (85:15)] afforded **21b** and a small amount of the dihydro derivative of **21b**. Preparative GLC gave artifact **19**.

***A. cana* Fraction 4 OTBDMS GLC Derivative 19:** $[\alpha]_D$ = +3.2° (*c* 0.45, $CHCl_3$). The spectral data for *A. cana* fraction 4 TBDMS derivative and synthetic **19** were identical.

Optical Purity Studies on GLC Artifact 19. The optically active shift reagent $(C_{14}H_{14}F_7O_2)_3Eu$ (Aldrich) was added to a 5-mm NMR tube containing a solution of 3 mg of ketone **19** and 0.4 mL of $CDCl_3$. ^{1}H NMR spectra were recorded with each incremental addition of the shift reagent until the peaks were resolved (Table I).

Acknowledgment. This research was supported in part by a grant (DCB-8803825) from the National Science Foundation and by the University of Utah Research Committee.

Registry No. **9a**, 32989-74-5; **9b**, 70144-38-6; **9c**, 133872-74-9; **10a**, 19889-92-0; **10b**, 20384-05-8; **11**, 19889-93-1; **12**, 133872-79-4; **13a**, 133872-80-7; **13b**, 133872-75-0; **14**, 133872-81-8; **15**, 133872-82-9; **16a**, 498-16-8; **16b**, 133872-76-1; **17** (isomer 1), 133872-83-0; **17** (isomer 2), 133872-91-0; **18** (isomer 1), 133872-84-1; **18** (isomer 2), 133872-92-1; **19**, 133886-97-2; **20**, 133872-85-2; **21a**, 133872-86-3; **21b**, 133872-77-2; **22a**, 133872-87-4; **22b**, 133872-78-3; **23** (isomer 1), 133872-88-5; **23** (isomer 2), 133908-55-1; **24** (isomer 1), 133872-89-6; **24** (isomer 2), 133908-54-0; 3,5-dinitrobenzoyl

chloride, 99-33-2; ethyl lavandulate, 133872-90-9; ethyl 3,3-dimethyl acrylate, 638-10-8; prenyl bromide, 870-63-3; (1*R*,3*R*)-chrysanthemic acid, 4638-92-0; (1*R*,3*R*)-ethyl chrysanthemate, 41641-25-2.

Supplementary Material Available: Chemical and spectral characterization data for compounds **9a,b**, **10a,b**, **11**, **16a**, ethyl lavandulate, and ethyl chrysanthemate (3 pages). Ordering information is given on any current masthead page.

Ruthenium-Catalyzed Synthesis of Symmetrical *N,N'*-Dialkylureas Directly from Carbon Dioxide and Amines

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Received November 6, 1990 (Revised Manuscript Received March 15, 1991)

Aliphatic and araliphatic primary amines react with carbon dioxide at 120–140 °C in the presence of ruthenium complexes and terminal alkynes, especially propargyl alcohols, to directly afford N,N'-disubstituted symmetrical ureas. The alkyne ruthenium intermediate acts as a dehydrating reagent. This new and mild method avoids the classical use of carbonyl precursors like phosgene or isocyanates.

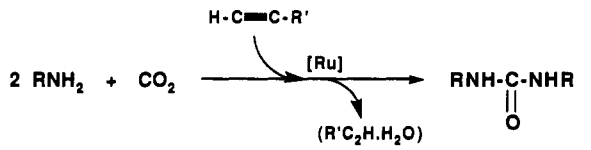
Introduction

Because they often display biological activity, ureas are an important class of organic compounds. The urea functional group is commonly found in natural products. Urea derivatives are widely used as agricultural pesticides, e.g., uron herbicides, or as pharmaceuticals.[1,2] Most syntheses of ureas involve the reaction of an amine either with compounds that incorporate an NCO linkage, like isocyanates,[1,3] formamides,[4] carbamates[1,5] and reactive imidazole ureas,[1,6] or with carbonyl compounds like phosgene,[1] chloroformates,[7] carbonates,[8] or CO itself in the presence of sulfur.[9] The synthesis of ureas by the catalyzed carbonylation of amines with carbon monoxide in the presence of various transition-metal catalysts, e.g., Pd,[10] Mn,[11] Pt,[12] and Cu,[13] has been described. Urea itself and some *N,N'*-dialkylureas can be produced by the reaction of carbon dioxide and ammonia[14] or primary amines[15] at 150–250 °C and pressures of 5–25 MPa. Under milder conditions, ureas can be prepared on a laboratory scale by the reaction of CO_2 and amines in the presence of *N,N'*-dicyclohexylcarbodiimide[16] or *N*-phosphonium salt derivatives.[17] In this case, activated carbamates are intermediates. In the presence of molecular sieve as a dehydrating agent, triphenylstibine oxide (Ph_3SbO) catalyzes the direct conversion of diamines and CO_2 under pressure to cyclic ureas.[18] *N,N,N',N'*-Tetraethylurea has also been obtained from the reaction of carbon dioxide and diethylamine in the presence of Pd(II) complexes, but in poor yield.[19] Apart from these, few reports of the catalyzed synthesis of ureas from CO_2 have appeared.

A more direct synthesis of ureas, and urea itself, from amines and CO_2, would also involve the elimination of water, but under milder conditions. We previously showed that CO_2 and secondary amines can add to terminal alkynes in the presence of ruthenium catalysts to afford carbamates.[20,21]

We now report that, under very similar conditions (e.g., in the presence of a terminal alkyne and a ruthenium complex), CO_2 reacts with primary amines to give ureas in good yield. The reaction is a catalyzed one-step synthesis of symmetrical ureas and represents a new use of carbon dioxide. Preliminary results were reported in a patent.[22]

Scheme I



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