lowed by effective reoxidation leads to imminium cation intermediates and successively the cyanation takes place (Scheme I). Since a trifluoromethyl group generally destabilizes α-cations, generation of such α-cations is quite difficult. Therefore, it is reasonable that the cyanation at the trifluoroethyl group was not observed.

However, at present it is not clear why the regiochemistry of the anodic cyanation is different from that of the anodic methoxylation. The difference in the reaction medium (electrolyte, pH, etc.) would influence on these reactions. The basicity and nucleophilicity of cyanide ions and of methoxide ions also should be considered. Detailed study for the reaction mechanism is now in progress.

Experimental Section

^{1}H NMR spectra were recorded at 60 MHz on a JEOL NMR spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard. ^{19}F NMR spectra were recorded at 60 MHz on a Hitachi R-24F NMR spectrometer using CF_3COOH as external standard. IR spectra were obtained with a Hitachi 295 infrared spectrometer. Mass spectra were obtained with a JEOL JMS-D100 mass spectrometer. High-resolution mass spectra were obtained with a Hitachi M-80B GC-mass spectrometer. Trifluoroethylamines (1-6) were synthetized similarly to the reported procedure.[4]

Electrolysis and Product Analyses. Electrolysis was carried out at a constant current using platinum plates as an anode and a cathode. Electrolytic conditions in each electrolysis are shown in Table I. After electrolysis, the electrolytic solution was concentrated, and the remaining crude liquid was treated with 20 mL of saturated potassium carbonate solution and extracted twice with 30-mL portions of ether. The combined ether layers were dried over anhydrous potassium carbonate, and the solvent was evaporated. The residue was separated and purified by preparative thin-layer chromatography (hexane–AcOEt as mobile phase).

***N*-(Cyanomethyl)-*N*-(2,2,2-trifluoroethyl)aniline (7a)**: ^{1}H NMR δ 3.83 (q, 2 H, CH_2CF_3, J = 9.0 Hz), 4.17 (s, 2 H, CH_2CN), 6.20–7.57 (m, 5 H, C_6H_5); ^{19}F NMR δ −7.50 (t, J = 9.0 Hz); MS m/e 214 (M^+), 145 ($M^+ - CF_3$), 77 (Ph^+); calcd for $C_{10}H_9F_3N_2$ m/e 214.0717, found 214.0735.

2-Cyano-*N*-methyl-*N*-(2,2,2-trifluoroethyl)aniline (8a, Isomer 1): ^{1}H NMR δ 3.13 (s, 3 H, CH_3), 4.03 (q, 2 H, CH_2CF_3, J = 9.0 Hz), 6.23–7.63 (m, 4 H, C_6H_4); ^{19}F NMR δ −9.70 (t, J = 9.0 Hz); MS m/e 214 (M^+), 145 ($M^+ - CF_3$); calcd for $C_{10}H_9F_3N_2$ m/e 214.0717, found 214.0694.

4-Cyano-*N*-methyl-*N*-(2,2,2-trifluoroethyl)aniline (8a, Isomer 2): ^{1}H NMR δ 3.13 (s, 3 H, CH_3), 3.93 (q, 2 H, CH_2CF_3, J = 9.0 Hz), 6.57–7.63 (m, 4 H, C_6H_4); ^{19}F NMR δ −8.15 (t, J = 9.0 Hz); MS m/e 214 (M^+), 145 ($M^+ - CF_3$); calcd for $C_{10}H_9F_3N_2$ m/e 214.0717, found 214.0718.

4,4′-Bis[*N*-methyl-*N*-(2,2,2-trifluoroethyl)amino]biphenyl (9a, Isomer 1): ^{1}H NMR δ 3.63 (s, 6 H, CH_3), 3.80 (q, 4 H, CH_2CF_3, J = 9.5 Hz), 6.60–7.47 (m, 8 H, C_6H_4); ^{19}F NMR δ −7.45 (t, J = 9.5 Hz); MS m/e 376 (M^+), 188 ($M^+/2$); calcd for $C_{18}H_{18}F_6N_2$ m/e 376.1373, found 376.1374.

2,4′-Bis[*N*-methyl-*N*-(2,2,2-trifluoroethyl)amino]biphenyl (9a, Isomer 2): ^{19}F NMR δ −7.60 (t, J = 9.5 Hz), −7.75 (t, J = 9.5 Hz); MS m/e 376 (M^+), 188 ($M^+/2$); calcd for $C_{18}H_{18}F_6N_2$ m/e 376.1373, found 376.1363.

***N*-(1-Cyanoethyl)-*N*-(2,2,2-trifluoroethyl)aniline (7b)**: ^{1}H NMR δ 1.51 (d, 3 H, $CHCH_3$, J = 7.0 Hz), 3.75 (q, 2 H, CH_2CF_3, J = 9.0 Hz), 4.25 (q, 1 H, $CHCH_3$, J = 7.0 Hz), 7.00–7.47 (m, 5 H, C_6H_5); ^{19}F NMR δ −7.70 (t, J = 9.0 Hz); MS m/e 228 (M^+), 213 (M^+ − Me), 159 ($M^+ - CF_3$); calcd for $C_{11}H_{11}F_3N_2$ m/e 228.0874, found 228.0915.

2-Cyano-*N*-ethyl-*N*-(2,2,2-trifluoroethyl)aniline (8b, Isomer 1): ^{1}H NMR δ 1.13 (t, 3 H, CH_2CH_3, J = 7.0 Hz), 3.47 (q, 2 H, CH_2CH_3, J = 7.0 Hz), 3.93 (q, 2 H, CH_2CF_3, J = 9.5 Hz), 6.27–7.70 (m, 4 H, C_6H_4); ^{19}F NMR δ −9.05 (t, J = 9.5 Hz); MS m/e 228 (M^+), 213 (M^+ − Me), 159 ($M^+ - CF_3$), 131 ($M^+ - CF_3 - C_2H_4$), 102 ($C_6H_4CN^+$); calcd for $C_{11}H_{11}F_3N_2$ m/e 228.0874, found 228.0916.

4-Cyano-*N*-ethyl-*N*-(2,2,2-trifluoroethyl)aniline (8b, Isomer 2): ^{1}H NMR δ 1.20 (t, 3 H, CH_2CH_3, J = 7.0 Hz), 3.53 (q, 2 H, CH_2CH_3, J = 7.0 Hz), 3.87 (q, 2 H, CH_2CF_3, J = 9.5 Hz), 6.53–7.57 (m, 4 H, C_6H_4); ^{19}F NMR δ −7.95 (t, J = 9.5 Hz); MS m/e 228 (M^+), 213 (M^+ − Me), 159 ($M^+ - CF_3$), 131 ($M^+ - CF_3 - C_2H_4$), 102 ($C_6H_4CN^+$); calcd for $C_{11}H_{11}F_3N_2$ m/e 228.0874, found 228.0888.

2-Cyano-*N*-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroquinoline (10): ^{1}H NMR δ 2.15 (m, 2 H, CH_2CHCN), 2.97 (m, 2 H, $C_6H_4CH_2$), 3.83 (m, 2 H, CH_2CF_3), 4.35 (m, 1 H, $CHCN$), 6.46–7.17 (m, 4 H, C_6H_4); ^{19}F NMR δ −7.60 (t, J = 9.0 Hz); MS m/e 240 (M^+), 171 ($M^+ - CF_3$), 118 ($M^+ - CF_3 - CH_2CHCN$); calcd for $C_{12}H_{11}F_3N_2$ m/e 240.0874, found 240.0860.

***N*-(1-Cyanobutyl)-*N*-(2,2,2-trifluoroethyl)butylamine (11)**: ^{1}H NMR δ 0.96 (t, 3 H, CH_3), 1.00 (t, 3 H, CH_3), 1.13–1.80 (m, 8 H, $CH_3CH_2CH_2$), 2.73 (t, 2 H, CH_2N), 3.12 (double q, 2 H, CH_2CF_3), 3.60 (t, 1 H, NCHCN); ^{19}F NMR δ −7.33 (t, CF_3, J = 10.0 Hz); MS m/e 236 (M^+), 192 ($M^+ - CH_3CHCH_2$), 167 ($M^+ - CF_3$); calcd for $C_{11}H_{19}F_3N_2$ m/e 236.1499, found 236.1519.

2-Cyano-*N*-(2,2,2-trifluoroethyl)piperidine (12a): ^{1}H NMR δ 1.50–2.07 (m, 6 H), 2.60–2.90 (m, 2 H, NCH_2), 2.97 (double q, 2 H, CH_2CF_3), 3.87 (t, 1 H, NCHCN); ^{19}F NMR δ −6.80 (t, J = 10.0 Hz); MS m/e 192 (M^+), 123 ($M^+ - CF_3$); calcd for $C_8H_{11}F_3N_2$ m/e 192.0874, found 192.0853.

2-Cyano-2,6-dimethyl-*N*-(2,2,2-trifluoroethyl)piperidine (12b): ^{1}H NMR δ 1.19 (d, 3 H, $CHCH_3$, J = 6.0 Hz), 1.50 (s, 3 H, $CCNCH_3$), 1.69 (m, 7 H), 2.67 (m, 1 H, $NCHCH_3$), 3.14 (q, 2 H, CH_2CF_3), J = 9.0 Hz); ^{19}F NMR δ −9.25 (t, J = 9.0 Hz); MS m/e 220 (M^+), 205 ($M^+ - CH_3$), 151 ($M^+ - CF_3$), 122 ($M^+ - CF_3CH_2 - CH_3$); calcd for $C_{10}H_{15}F_3N_2$ m/e 220.1180, found 220.1218.

1-Cyano-*N*-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline (13): ^{1}H NMR δ 2.55–3.17 (m, 4 H), 3.23 (double q, 2 H, CH_2CF_3, J = 9.2 Hz), 4.80 (s, 1 H, NCHCN), 7.10 (br s, 4 H, C_6H_4); ^{19}F NMR δ −7.45 (t, CF_3, J = 9.2 Hz); MS m/e 240 (M^+), 214 (M^+ − CN), 171 ($M^+ - CF_3$), 129 ($M^+ - CH_2NCH_2CF_3$); calcd for $C_{12}H_{11}F_3N_2$ m/e 240.0874, found 240.0853.

α-Cyano-*N*-ethyl-*N*-(2,2,2-trifluoroethyl)benzylamine (14): ^{1}H NMR δ 1.11 (t, 3 H, CH_2CH_3, J = 8.2 Hz), 2.69 (q, 2 H, CH_2CH_3, J = 8.2 Hz), 3.10 (double q, 2 H, CH_2CF_3, J = 9.0 Hz), 5.01 (s, 1 H, NCHCN), 7.14–7.60 (m, 5 H, C_6H_5); ^{19}F NMR δ −7.35 (t, CF_3, J = 9.0 Hz); MS m/e 242 (M^+), 227 ($M^+ - CH_3$), 173 ($M^+ - CF_3$), 116 ($C_6H_5CHCN^+$); calcd for $C_{12}H_{13}F_3N_2$ m/e 242.1030, found 242.1025.

***N*-(1-Cyanoethyl)-*N*-(2,2,2-trifluoroethyl)benzylamine (15)**: ^{1}H NMR δ 1.40 (d, 3 H, $CHCNCH_3$, J = 7.0 Hz), 3.12 (double q, 2 H, CH_2CF_3, J = 9.0 Hz), 3.57 (q, 1 H, NCHCN, J = 7.0 Hz), 3.65 (d, 1 H, $C_6H_5CH_2$, J = 13.0 Hz), 4.00 (d, 1 H, $C_6H_5CH_2$, J = 13.0 Hz), 7.17 (br s, 5 H, C_6H_5); ^{19}F NMR δ −7.32 (t, CF_3, J = 9.0 Hz); MS m/e 242 (M^+), 92 ($C_6H_5CH_3^+$); calcd for $C_{12}H_{13}F_3N_2$ m/e 242.1030, found 242.0997.

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A Convenient Regioselective Synthesis of Substituted Cycloheptenones

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Cycloheptenones are frequently prepared from bicyclo[3.2.0]heptane-1,6-diol monosulfonates by base-induced fragmentation[1-3] of the interannular bond, the position of

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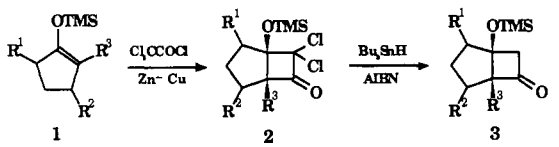
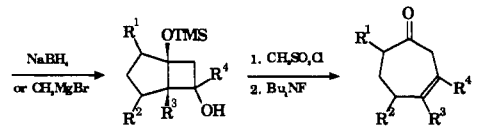
Scheme I



1 2 3

a, $R^1=R^2=R^3=H$
b, $R^1=R^2=H$, $R^3=Me$
c, $R^1=R^3=H$, $R^2=Me$
d, $R^1=Me$, $R^2=R^3=H$
e, $R^1=R^3=H$, R^2=sec-butyl



4 5

a, $R^1=R^2=R^3=R^4=H$
a', $R^1=R^2=R^3=H$, $R^4=Me$
b, $R^1=R^2=H$, $R^3=R^4=Me$
c, $R^1=R^3=H$, $R^2=R^4=Me$
d, $R^2=R^3=H$, $R^1=R^4=Me$
e, $R^1=R^3=R^4=H$, R^2=sec-butyl
e', $R^1=R^3=H$, $R^4=Me$, R^2=sec-butyl

Table I. Synthetic Yields of Substituted Cyclohept-3-enones from Their Respective Silyl Enol Ethers[a]

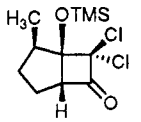
	products (yield, %)[b]			
silyl enol ether	2	3	4	5
1a	**2a** (77)	**3a** (89)	**4a** (98)[d]	**5a** (64)
			4a' (98)	**5a'** (99)
1b	**2b** (85)	**3b** (92)	**4b** (96)	**5b** (99)
1c	**2c** (88)	**3c** (91)	**4c** (95)	**5c** (98)
1d	**2d** (75)[c]	**3d** (90)	**4d** (95)	**5d** (98)
1e	**2e** (79)	**3e** (94)	**4e** (96)[d]	**5e** (59)[e,f]
			4e' (97)	**5e'** (97)[f]

[a] No attempt was made to optimize yields. [b] Yields are isolated ones. [c] Yield of a diastereomeric mixture *exo*-**2d**:*endo*-**2d** = 1.5:1 by gas chromatography. [d] Endo:exo = 3:1. [e] Mixture of cyclohept-3-enone and cyclohept-2-enone (2.5:1). [f] Diastereomeric mixture.

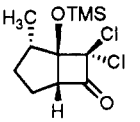
which controls the location of the new double bond. The bicyclic [3.2.0] system is usually synthesized by photochemical [2 + 2] cycloaddition,[4] which gives poor regio- and stereocontrol for intermolecular reactions and thereby limits the scope of this reaction to those intramolecular reactions which are only regioselective.

In this paper we report a new method to prepare substituted cyclohept-3-enones by taking advantage of the regio- and stereoselectivity of thermal [2 + 2] cycloaddition[5] and fluoride-induced fragmentation reactions.[6,7]

The synthetic route to cyclohept-3-enones **5a–e'**, depicted in Scheme I, utilized cyclopentyl silyl enol ethers **1a–e**, prepared by known procedures,[8] as starting material. The thermal [2 + 2] cycloadditions were carried out in diethyl ether at room temperature using dichloroketene generated from trichloroacetyl chloride in the presence of activated zinc, which produced cycloadditions **2a–e** in moderate yields[5] (75–88%) (see Table I). The cycloadditions took place stereoselectively in all cases (except for **1d**) to give 6-keto products.[5a,9] The almost exclusive



exo-**2d**



endo-**2d**

formation of the exo isomer of **2c** (as inferred from our 300-MHz ^{1}H NMR data and gas chromatograms) contrasts the 1.5:1 formation of the *exo*-**2d**:*endo*-**2d** isomers. After studying Dreiding models, we believe that the steric interaction between the carbonyl group of the ketene and the methyl group of the silyl enol ether **1c** might be the source of the stereoselectivity. Twisting the ketene carbonyl group is prohibited by the methyl group in **1c** as the ketene molecule is undergoing bond formation on the same side as the methyl group, thereby giving the exo product exclusively. From Dreiding models it appears that both sides of the cyclopentyl ring in **1d** should be essentially free of steric bias during bond formation. The models indicate that steric interactions between the methyl and silyl ether groups in **1d** might give rise to a small stereoselectivity toward the approaching ketene molecule.

Dichloro ketones **2a–e** were dechlorinated by reaction with tributyltin hydride in the presence of 2,2-azobisisobutyronitrile (AIBN) to give high yields (89–94%) of bicyclic ketones[10] **3a–e**. These ketones[11] were then converted into secondary alcohols **4a** and **4e** and tertiary alcohols **4a'–d** and **4e'** by reaction with sodium borohydride and methylmagnesium bromide, respectively. The purpose for synthesizing both secondary and tertiary alcohols was to compare their reactivity toward fragmentation and to explore the effect of alkylation on the 3-position of cyclohept-3-enones **5a'–d,e'**. The Grignard reaction gave the endo tertiary alcohols, **4a'–d** and **4e'**, exclusively, while the sodium borohydride reduction gave a 3:1 endo:exo mixture of the secondary alcohols **3a** and **3e**. After the secondary alcohols **4a** and **4e** were mesylated in dichloromethane in the presence of triethylamine,[12] the reaction mixture was washed with water to remove the ammonium salt. Due to their instability, the crude mesylates were kept in the same solvent and directly subjected to fragmentation conditions by adding tetrabutylammonium fluoride in THF. Cyclohept-3-enones **5a** and **5e** were obtained in relatively lower yield (59–64%) than those obtained from the tertiary mesylates.

Interestingly, under the fragmentation conditions, 5-*sec*-butylcyclohept-3-enone (**5e**) slowly isomerized into 5-*sec*-butylcyclohept-2-enone, which, once formed, decomposed slowly into unidentified material. In contrast to the secondary alcohols, the tertiary alcohols **4a'–d** and **4e'** underwent fragmentation instantly under the mesylation conditions, providing 3-methylcyclohept-3-enones **5a'–d** and **5e'** in almost quantitative yields.

Isomerization of the unconjugated cyclohept-3-enones **5a'–d** and **5e'** into the conjugated ones was sluggish in basic

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(11) Bicyclic ketone **3a** subjected to fragmentation condition (Bu_4NF/CH_2Cl_2) was converted to cycloheptane-1,3-dione instantly and quantitatively.
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media (Et_3N/CH_2Cl_2 or n-Bu_4NF/CH_2Cl_2), but in acidic media (p-$TsOH/CH_2Cl_2$ or dilute HCl/CH_2Cl_2) the isomerization took place rapidly and quantitatively. Examination of the C-2 proton coupling constants and chemical shifts of the substituted 3-methylcyclohept-3-enones reveals typical diastereotopic behavior for the methylene protons, i.e., the methylene protons of **5a′** (3.19 ppm) and **5b** (3.15 ppm) appear as a singlet, while those of **5c** (3.22, 3.09 ppm, J = 14.5 Hz), **5d** (3.20, 3.08 ppm, J = 14.0 Hz), and **5e′** (3.32, 2.95 ppm, J = 14.8 Hz) appear as a pair of doublets.

In conclusion, a method to prepare regioselectivity substituted cyclohept-3-enones was developed using a combination or regioselective thermal [2 + 2] cycloaddition and fluoride- or chloride-induced fragmentation reaction. Thus, substituted cyclohept-3-enones which might be difficult to prepare otherwise could be obtained conveniently. This methodology could be applied to various natural products containing the cycloheptenone moiety.

Experimental Section

General Procedure. The purity of all title compounds was determined to be greater than 95% by GC, TLC, ^1H NMR spectral analysis, and/or elemental analysis. Melting points are uncorrected. ^1H NMR spectra were recorded at 300 MHz, unless otherwise specified, in $CDCl_3$ solution. Mass spectra were obtained at 70 eV. GC analyses were performed on a 1 m × $^1/_8$ in. column (5% Dexil 300 on Gas Chrom W,100–120 mesh), in the range 60–230 °C (10–20 deg min^{-1}), with N_2 as carrier gas (flow rate 60 mL min^{-1}). Column chromatography was performed with Merck Kieselgel 60 (70–230 mesh ASTM) silica. Tetrahydrofuran (THF) and ether were distilled from sodium benzophenone immediately prior to use. Dichloromethane was distilled from P_2O_5 prior to use. All reactions were carried out under an inert atmosphere of nitrogen or argon and were monitored by thin-layer chromatography with E-Merck 60F-254 precoated silica (0.2 mm) on glass.

Representative Procedure for the Preparation of Cycloheptenones. 7,7-Dichloro-1-(trimethylsiloxy)bicyclo[3.2.0]heptan-6-one (2a). To a slurry of silyl enol ether **1a** (4.26 g, 27.3 mmol) and activated zinc (2.67 g, 40.8 mmol) in anhydrous ether (150 mL) was added freshly distilled trichloroacetyl chloride (4 mL, 35.8 mmol) in anhydrous ether (50 mL) dropwise during a period of 2 h. After stirring for 12 h at room temperature, the reaction mixture was filtered through a Celite 545 column, which was then washed with ether. The ethereal filtrate was washed with saturated $NaHCO_3$ solution twice and dried over anhydrous K_2CO_3. After removal of the solvent under vacuum, the residue was column chromatographed (hexane–ethyl acetate, 30:1) to give **2a** (5.76 g, 79%) as a colorless liquid. ^1H NMR, IR, and mass spectral data are identical with those of a reported sample.[5a]

1-(Trimethylsiloxy)bicyclo[3.2.0]heptan-6-one (3a). To a stirred solution of dichloro ketone **2a** (5.34 g, 20 mmol) in toluene (70 mL) was added tributyltin hydride (12.81 g, 44 mmol) and AIBN (0.1 g) under argon. The resulting mixture was stirred for 1 h at 80 °C and then cooled to room temperature. After removal of the solvent in vacuo, the residue was column chromatographed (hexane–ethyl acetate, 15:1) to give the product (3.52 g, 89%) as a colorless oil: IR (neat) 2934, 1777, 1315, 1249, 1220, 836 cm^{-1}; NMR δ 3.34 (dd, J = 3.4, 8.4 Hz, 1 H), 3.29 (dd, J = 5.3, 17.8 Hz, 1 H), 2.96 (dd, J = 3.6 and 17.8 Hz, 1 H), 2.15 (dd, J = 6.8, 11 Hz, 1 H), 1.97–1.78 (m, 4 H), 1.56 (m, 1 H), 0.16 (s, 9 H); mass spectrum, m/e (relative intensity) 198 (M^+, 4), 183 (28), 170 (base peak), 156 (94), 155 (95), 142 (22), 141 (25), 127 (31), 77 (80), 75 (80); HRMS calcd for $C_{10}H_{18}SiO_2$ 198.1076, obsd 198.1093.

***endo*- and *exo*-1-(Trimethylsiloxy)bicyclo[3.2.0]heptan-6-ol (4a).** To a stirred solution of ketone **3a** (170 mg, 0.86 mmol) in THF–H_2O (9:1, 5 mL) was added sodium borohydride (100 mg, 2.6 mmol) portionwise at 0 °C. When the reaction was complete by TLC analysis, the reaction mixture was poured into diethyl ether (20 mL) and washed with aqueous NH_4Cl solution and water (2 × 10 mL). The organic layer was dried (Na_2SO_4) and evaported in vacuo. Then the residue was column chromatographed (hexane–ethyl acetate, 5:1) to give the alcohol (168 7g, 98%) as a colorless oil, which was found to contain exo and endo isomers in the ratio of 3 to 1. Analytical samples were prepared by column chromatography (hexane–ethyl acetate, 5:1): IR (neat, isomer mixture) 3300, 2948, 1464, 1440–1392 (br), 1308, 1246, 1090, 863 cm^{-1}; NMR exo isomer δ 3.59 (m, 1 H), 2.50 (dd, J = 7.1, 12.7 Hz, 1 H), 2.46 (m, 1 H), 2.17 (dd, J = 5.2, 12.7 Hz, 1 H), 1.84–1.54 (m, 7 H), 0.15 (s, 9 H), endo isomer 4.56 (m, 1 H), 2.70–2.56 (m, 2 H), 1.92–1.59 (m, 7 H), 1.41 (d, J = 4.1 Hz, 1 H), 0.13 (s, 9 H); mass spectrum, m/e (relative intensity) 200 (M^+, 17), 185 (8), 156 (base peak), 143 (39), 131 (67), 75 (72), 73 (76); HRMS calcd for $C_{10}H_{20}SiO_2$ 200.1233, obsd 200.1260.

6-Methyl-1-(trimethylsiloxy)bicyclo[3.2.0]heptan-6-ol (4a′). To a stirred solution of ketone **3a** (198 mg, 1 mmol) in dry THF (10 mL) was added methylmagnesium bromide (1 mL of a 3 M solution in ether, 3 mmol) dropwise over a period of 5 min at −75 °C under argon. Stirring was continued for $^1/_2$ h. The reaction mixture was then allowed to warm to room temperature. After quenching the excess methylmagnesium bromide with water, the resulting mixture was diluted with ether (50 mL) and washed with aqueous NH_4Cl and water; the organic layer was dried ($MgSO_4$). The solvent was removed in vacuo, and the residue was subjected to column chromatography (hexane–ethyl acetate, 5:1) to give the desired alcohol as a colorless oil (210 mg, 98%): IR (neat) 3460, 2950, 1460, 1315, 1304, 1250, 1232, 1200, 1080, 835 cm^{-1}; NMR δ 2.31 (m, 1 H), 2.25 (dd, J = 3.6, 13.1 Hz, 1 H), 1.99 (d, J = 13.1 Hz, 1 H), 1.85–1.60 (m, 6 H), 1.46 (s, 3 H), 1.32 (s, 1 H), 0.13 (s, 9 H); mass spectrum, m/e (relative intensity) (no M^+) 197 (17.9), 196 (18.1), 155 (63.7), 143 (48.1), 141 (8.5), 84 (base peak), 73 (82.1). Anal. Calcd for $C_{11}H_{22}SiO_2$: C, 61.68; H, 10.28. Found: C, 61.23; H, 10.35.[13]

Cyclohept-3-en-1-one (5a). To a stirred solution of endo alcohol **4a** (137 mg, 0.685 mmol), triethylamine (138 mg, 1.37 mmol), and catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (3 mg) in dichloromethane (5 mL) was added methanesulfonyl chloride n173 mg, 1.51 mmol) dropwise at −10 °C. The reaction mixture was stirred for 20 min at −10 °C and then washed with water (5 mL × 2). The organic layer was dried ($MgSO_4$). Without isolation of the mesylate, tetrabutylammonium fluoride in THF (1M solution 1.03 mL, 1.03 mmol) was added at 0 °C. Stirring was continued for 1 h at 0 °C. The reaction mixture was poured into water (5 mL) and extracted with dichloromethane (5 mL). The organic layer was washed with water and dried ($MgSO_4$). Evaporation of the solvent in vacuo resulted in almost pure product (48.2 mg, 64%), the ^1H NMR and IR spectra, of which are identical with the literature values.[14]

3-Methylcyclohept-3-en-1-one (5a′). To a stirred solution of alcohol **4a′** (110 mg, 0.51 mmol) and triethylamine (101 mg, 1.0 mmol) in dichloromethane (5 mL) was added methanesulfonyl chloride (162 mg, 1.12 mmol) dropwise at 0 °C. After the mixture was stirred for 10 min, the solvent was removed in vacuo at ice bath temperature. Then the residue was dissolved in ether (10 mL) and washed with water, 10% $NaHCO_3$ solution, and brine. The organic layer was dried (Na_2SO_4) and evaporated below 0 °C. The residue containing trace of impurities at origin flash chromatographed to give pure **5a′** (62.6 mg, 99%): IR (neat) 2907, 1702 cm^{-1}; NMR δ 5.53 (t, J = 5.1 Hz, 1 H), 3.19 (s, 2 H), 2.55 (t, J = 6.4 Hz, 2 H), 2.25 (m, 2 H), 1.94 (m, 2 H), 1.78 (s, 3 H); mass spectrum, m/e (relative intensity) 124 (M^+, 25.1), 96 (52.4), 81 (77.8); HRMS calcd for $C_8H_{12}O$ 124.0888 obsd 124.0933. The following compounds were synthesized according to their respective methods shown above.

2b: yield 85% (2.38 g); mp 64–65 °C (acetone–H_2O); IR (neat) 2945, 1790, 1439, 1260, 840 cm^{-1}; NMR δ 2.58 (dd, J = 5.5 , 13.5 Hz, 1 H), 2.11 (dd, J = 4.7, 11.4 Hz, 1 H), 1.96 (m, 1 H), 1.78 (m, 1 H), 1.46 (m, 2 H), 1.27 (s, 3 H), 0.21 (s, 9 H); mass spectrum, m/e (relative intensity) (no M^+) 219 (12), 217 (31), 172 (6), 171 (6), 170 (31), 147 (25), 145 (59), 73 (base peak). Anal. Calcd for $C_{11}H_{18}O_2SiCl_2$: C, 46.98; H, 6.41. Found: C, 46.35; H, 6.38.[13]

3b: yield 92% (1.04 g) as a colorless liquid; IR (neat) 2928, 1770, 1461, 1248, 836 cm^{-1}; NMR δ 3.17 (d, J = 18.3 Hz, 1 H), 2.91 (d,

(13) The discrepancies in the microanalytical data are attributed to weight losses during weighing and/or analysis of these volatile, low-melting solids. No improvements were observed in repeated microanalysis.

(14) Parham, W. E.; Parham, F. M.; Dooley, J. F.; Meilahn, M. K. *J. Org. Chem.* **1968**, *33*, 3651.

J = 18.3 Hz, 1 H), 2.16 (dd, J = 5.1, 12.0 Hz, 1 H), 2.00 (d, J = 6.8 Hz, 1 H), 1.91-1.79 (m, 2 H), 1.45 (m, 2 H), 1.10 (s, 3 H), 0.15 (s, 9 H); mass spectrum,m/e (relative intensity) 212 (M^+, 2.0), 197 (18.5), 170 (50.1), 169 (base peak), 155 (21.6), 141 (19), 73 (72.6); HRMS calcd for $C_{11}H_{20}O_2Si$ 212.1233, obsd 212.1238.

4b: yield 96% (310 mg); mp 41-42 °C; IR (KBr) 3328, 2923, 1302, 1245, 834 cm^{-1}; NMR δ 2.14 (d, J = 13.3 Hz, 1 H), 2.11 (1 H), 2.02 (d, J = 13.3 Hz, 1 H), 1.82-1.62 (m, 4 H), 1.39 (m, 2 H), 1.36 (s, 3 H), 0.99 (s, 3 H), 0.15 (s, 9 H); mass spectrum, m/e (relative intensity) (no M^+), 195 (3), 171 (14.5), 170 (80.9), 169 (24.5), 144 (32.7), 143 (base peak), 73 (70.9). Anal. Calcd for $C_{12}H_{24}O_2Si$: C, 63.16; H, 10.53. Found: C, 62.00; H, 10.34.[13]

5b: yield 99% (149 mg) as a colorless liquid;[15] IR (neat) 2898, 1698 cm^{-1}; NMR δ 3.15 (s, 2 H), 2.51 (t, J = 6.6 Hz, 2 H), 2.27 (t, J = 5.8 Hz, 2 H), 1.91 (m, 2 H), 1.75 (s, 3 H), 1.71 (s, 3 H); mass spectrum, m/e (relative intensity) 138 (M^+, 6.8), 137 (13.2), 111 (10.2), 110 (11.1), 109 (40.2), 108 (14.6), 95 (23.4); HRMS calcd for $C_9H_{14}O$ 138.1045, obsd 138.1013.

2c: yield 88% (2.91 g); mp 35-36 °C; IR (neat) 2932, 1798, 1262, 839 cm^{-1}; NMR δ 3.39 (s, 1 H), 2.48 (m, 2 H), 2.29 (m, 1 H), 1.81-1.66 (m, 2 H), 1.08 (d, J = 7.2 Hz, 3 H), 0.21 (s, 9 H); mass spectrum, m/e (relative intensity) (no M^+), 219 (2.8), 218 (2.0), 2.17 (6.9), 216 (3.7), 170 (1.5), 169 (2.6), 168 (1.2), 156 (2.4), 155 (14.9), 154 (14.9), 73 (base peak). Anal. Calcd for $C_{11}H_{18}O_2SiCl_2$: C, 46.98; H, 6.41. Found: C, 46.41; H, 6.35.[13]

3c: yield 91% (1.08 g) as a colorless liquid; IR (neat) 2933, 1778, 1308, 1248, 836 cm^{-1}; NMR δ 3.24 (dd, J = 5.2, 18.1 Hz, 1 H), 3.08 (br s, 1 H), 2.96 (dd, J = 2.9, 18.1 Hz, 1 H), 2.29 (m, 1 H), 2.01-2.16 (m, 2 H), 1.76 (m, 1 H), 1.62 (m, 1 H), 1.03 (d, J = 7.3 Hz, 3 H), 0.17 (s, 9 H); mass spectrum, m/e (relative intensity) 212 (M^+, 5.4), 197 (20.1), 196 (16.8), 195 (24.4), 194 (15.1), 184 (27.4), 183 (17.0), 170 (19.5), 169 (55.1), 168 (39.2), 155 (84), 154 (40.4), 73 (base peak); HRMS calcd for $C_{11}H_{20}O_2Si$ 212.1233, obsd 212.1268.

4c: yield 95% (460 mg); mp 44-45 °C; IR (neat) 3291, 2907, 1446, 1244, 833 cm^{-1}; NMR δ 2.20 (dd, J = 3.5, 13.3 Hz, 1 H), 2.18 (1 H), 2.02 (d, J = 13.3 Hz, 1 H), 1.97 (d, J = 3.3 Hz, 1 H), 1.84 (m, 2 H), 1.69 (dd, J = 4.5, 6 Hz, 1 H), 1.51 (m, 1 H), 1.46 (s, 3 H), 1.26 (br s, 1 H), 1.01 (d, J = 7.3 Hz, 3 H), 0.14 (s, 9 H); mass spectrum, m/e (relative intensity) (no M^+), 170 (37.3), 155 (base peak), 144 (33.6), 143 (62.7), 129 (29), 73 (14.6). Anal. Calcd for $C_{12}H_{24}O_2Si$: C, 63.16; H, 10.53. Found: C, 62.50; H, 10.42.[13]

5c: yield 98% (103 mg) as a colorless liquid; IR (neat) 2897, 1700 cm^{-1}; NMR δ 5.33 (br s, 1 H), 3.22 (d, J = 14.5 Hz, 1 H), 3.09 (d, J = 14.5 Hz, 1 H), 2.60 (m, 1 H), 2.44 (m, 2 H), 1.93-1.70 (m, 2 H), 1.77 (s, 3 H), 1.05 (d, J = 7.0 Hz, 3 H); mass spectrum, m/e (relative intensity) 139 (M^+ + 1, 20) 138 (M^+, 13), 121 (28.5), 109 (10.2), 96 (base peak), 95 (50); HRMS calcd for $C_9H_{14}O$ 138.1045, obsd 138.1030.

2d: as a diastereomeric mixture for 2-methyl; exo:endo = 1.5:1 by gas chromatography; yield 75% (2.11 g) as a colorless oil; IR (neat, mixture) 2926, 1796, 1456, 1248, 854 cm^{-1}; NMR (exo isomer) δ 3.60 (dd, J = 1.9, 7.0 Hz, 1 H), 2.45 (m, 1 H), 2.08 (dd, J = 7.1, 12.0 Hz, 1 H), 1.96-1.83 (m, 2 H), 1.58 (m, 1 H), 1.40 (d, J = 7.2 Hz, 3 H), 0.24 (s, 9 H); (endo isomer) 3.81 (dd, J = 2.7, 9.4 Hz, 1 H, for 5-CH), 1.09 (d, J = 6.7 Hz, 3 H, for 2-CCH_3); mass spectrum, m/e (relative intensity) (no M^+), 219 (1.2), 218 (0.6), 217 (3.7), 170 (5), 169 (5), 155 (2.5), 128 (3.1), 93 (13.8), 73 (base peak).

3d: yield 90% (1.02 g) as a colorless oil; IR (neat, diastereomeric mixture) 2931, 1775, 1455, 1248, 836 cm^{-1}; NMR (exo isomer) δ 3.33 (br s, 1 H), 3.09 (dd, J = 2.2, 18.5 Hz, 1 H), 2.98 (dd, J = 2.9, 18.5 Hz, 1 H), 2.18 (m, 1 H), 1.98-1.81 (m, 3 H), 1.24 (m, 1 H), 1.06 (d, J = 6.2 Hz, 3 H), 0.17 (s, 9 H); (endo isomer) 3.25 (dd, J = 3.4, 18.2 Hz, 1 H for 7-CH), 2.98 (d, J = 18.2 Hz, 1 H for 7-CH), 0.99 (d, J = 7.1 Hz, 3 H), 0.17 (s, 9 H); mass spectrum, m/e (relative intensity) 212 (M^+, 1.3), 197 (6.25), 184 (26.2), 169 (36.2), 155 (20), 142 (15), 127 (10), 73 (base peak); HRMS calcd for $C_{11}H_{20}O_2Si$ 212.1233, obsd 212.1282.

4d: yield 95% (153 mg) as a colorless oil; (spectral data for diastereomeric mixture) IR (neat) 3312, 2925, 1437, 1245, 834 cm^{-1}; NMR 2.32-2.27 (m, 2 H), 2.07-1.53 (m, 6 H), 1.48 (s, 3 H), 1.33-1.25 (m, 1 H), 0.88 (d, J = 6.2 Hz, 1.8 H for exo isomer), 0.86 (d, J = 7 Hz, 1.2 H for endo isomer), 0.15 (s, 9 H); mass spectrum, m/e (relative intensity) 228 (M^+, 12.7), 213 (5), 195 (5), 185 (7), 170 (base peak), 157 (74.5), 144 (60), 129 (41.8), 73 (78.2); HRMS calcd for $C_{12}H_{24}O_2Si$ 228.1539, obsd 228.1522.

5d: yield 98% (70 mg) as a colorless liquid; IR (neat) 2937, 1701 cm^{-1}; NMR δ 5.55 (t, J = 5.5 Hz, 1 H), 3.20 (d, J = 14.0 Hz, 1 H), 3.08 (d, J = 14.0 Hz, 1 H), 2.67 (m, 1 H), 2.23 (m, 2 H), 1.95 (m, 1 H), 1.79 (s, 3 H), 1.62 (m, 1 H), 1.10 (d, J = 6.9 Hz, 3 H); mass spectrum, m/e (relative intensity) 138 (M^+, 50), 111 (7), 110 (55), 109 (6), 95 (41), 68 (base peak); HRMS calcd for $C_9H_{14}O$ 138.1045, obsd 138.1070.

Registry No. **1a**, 19980-43-9; **1b**, 19980-34-8; **1c**, 81834-51-7; **1d**, 19980-32-6; **1e**, 108643-84-1; **2a**, 66324-01-4; **2b**, 125302-40-1; **2c**, 125302-41-2; *exo*-**2d**, 125302-42-3; *endo*-**2d**, 125409-02-1; **2e**, 125302-43-4; **3a**, 125302-44-5; **3b**, 125302-45-6; **3c**, 125302-46-7; *exo*-**3d**, 125302-47-8; *endo*-**3d**, 125410-63-1; *exo*-**3e**, 125302-48-9; *endo*-**3e**, 125409-05-4; **4a'**, 125302-50-3; *endo*-**4a**, 125302-49-0; *exo*-**4a**, 125409-03-2; **4b**, 125302-51-4; **4c**, 125302-52-5; **4d**, 125302-53-6; *endo*-**4e**, 125302-54-7; *exo*-**4e**, 125409-04-3; **4e'**, 125302-59-2; **5a**, 1121-64-8; **5a'**, 14525-96-3; **5b**, 10479-95-5; **5c**, 125302-55-8; **5d**, 125302-56-9; **5e** (regioisomer 1), 125302-57-0; **5e** (regioisomer 2), 71055-00-0; **5e'**, 125302-58-1; Cl_3OCOCl, 76-02-8.

Supplementary Material Available: ^{1}H NMR spectra of **3a**, **4-5a'**, **2-5b-e**, **4-5e'** and analytical and spectral data for **2-5e**, **4e'**, **5e'** (30 pages). Ordering information is given on any current masthead page.

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An Improved Synthesis of the Taxol Side Chain and of RP 56976

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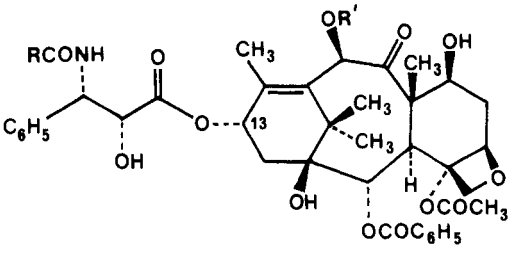
Efforts directed toward the total synthesis of taxol, a highly promising anticancer natural product,[1] continue unabated.[2] In most, if not all, of the numerous approaches recorded to date it would appear that an esterification of the C-13 hydroxyl function of an appropriate taxol precursor with the enantiomerically pure (suitably protected) taxol side chain will ultimately be required to obtain taxol efficiently.[3]



Taxol R = C_6H_5, R' = CH_3CO

RP 56976 R = $(CH_3)_3CO$, R' = H

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