(d), 71.7 (t), 71.3 (t); UV (CH_2Cl_2) λ_{max} (log ϵ) 297 nm (4.34), 245 (sh, 4.24).

Distilbeno 24-Crown-8 (4c): mp 133.5–134.5 °C; m/z 652 (M^+); IR 1620, 1260, 1090, 770, 700 cm^{-1}; ^1H NMR δ 7.00 (s, 20 H), 3.83 (s, 24 H); ^{13}C NMR δ 143.6 (s), 136.5 (s), 131.0 (d), 129.0 (d), 128.6 (d), 72.0 (t), 71.8 (t), 71.3 (t); UV (MeCN) λ_{max} (log ϵ) 297 nm (4.29), 243 (sh, 4.13). Anal. Calcd for $C_{40}H_{44}O_8$: C, 73.60; H, 6.79. Found: C, 73.20; H, 6.80.

Distilbeno 30-Crown-10 (4d): mp 98.0–99.0 °C (hexane); m/z 740 (M^+); IR 1645, 1260, 1150, 1110, 775, 700 cm^{-1}; ^1H NMR δ 7.12 (s, 20 H), 3.83 (m, 16 H), 3.74 (s, 16 H); ^{13}C NMR δ 143.9 (s), 136.3 (s), 131.1 (d), 129.2 (d), 71.9 (t); UV (MeCN) λ_{max} (log ϵ) 298 nm (4.28), 243 (sh, 4.06), 220 (sh, 4.37). Anal. Calcd for $C_{44}H_{52}O_{10}$: C, 71.33; H, 7.08. Found: C, 71.05; H, 7.04.

Triethylene Glycol Dibenzoin Ether (5c): mp 128.5–129.5 °C; m/z 538 (M^+); IR 1690, 1165, 1100, 745, 695 cm^{-1}; ^{13}C NMR δ 137.5 (s), 134.2 (s), 130.3 (d), 129.6 (d), 128.8 (d), 86.5 (d), 71.7 (t), 70.3 (t).

Acknowledgment. This work was supported in part by Grant-in-Aid for Scientific Research No. 59550583 from the Ministry of Education, Science, and Culture of Japan, which is gratefully acknowledged.

Registry No. 1, 119-53-9; **2a**, 6315-52-2; **2b**, 7460-82-4; **2c**, 19249-03-7; **2d**, 37860-51-8; **3a**, 4344-45-0; **3b**, 62698-60-6; **3d**, 82982-14-7; **4b**, 62726-46-9; **4c**, 77325-94-1; **4d**, 98976-66-0; **5c**, 98976-67-1.

A General Synthesis for Symmetrical Highly Branched Perfluoro Ethers: A New Class of Oxygen Carriers[1]

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Most highly branched perfluoro ethers, particularly those sterically crowded around the oxygen, are currently inaccessible synthetically by conventional synthetic techniques used in organofluorine chemistry. Such compounds are of unusual biomedical interest currently because they have been found[1] to be good oxygen carriers and quite surprisingly not to be retained in the liver. Previously linear ethers were thought by biomedical researchers to coordinate in some manner and definitely were found to be retained in the livers of mammals. Direct fluorination technology developed in our laboratories has succeeded with the synthesis of the novel compounds: bis(perfluoroisopropyl) ether, bis(perfluoroisobutyl) ether, bis(perfluoroisopentyl) ether, and bis(perfluoroneopentyl) ether.

Since the original discovery that animals could survive under liquid breathing conditions with oxygenated silicones and especially perfluoro chemicals by L. C. Clark, Jr.,[2] it was thought that ethers, presumably through some base-type interaction physiologically with liver tissue, were essentially retained in the liver in the same manner as perfluorinated amines,[2] making them undesirable for use as oxygen carriers in spite of some other advantages which they exhibit. We have previously theorized and then proven[3] that some types of highly branched fluorocarbons contain holes in their liquid phases which are conducive to higher oxygen solubility. Perfluoro ethers exhibit this property particularly because their bonds are extended by the carbon–oxygen distance.[4] Structures sought in this paper were selected particularly for large oxygen (O_2) holes in the liquid state. The branching, particularly in cases where there was steric crowding around the oxygen, was designed to prevent baselike or any other interaction with mammalian tissue. In addition, we have theorized[5] that the oxygen linkage acts essentially as a flexible hinge in the molecule to permit branched species to be transported across cellular membranes, more rapidly in cases where rigid perfluorocarbons of analogous structures would not bend to facilitate transport.

The direct fluorination technique is now becoming "well established"[6] and is in fact the most generally applicable synthesis of fluorocarbon structures. Here we see an excellent illustration of the advantages of direct fluorination synthetic techniques since the synthesis of some of these materials is impossible by conventional synthetic methods and others are difficult. In fact, none of the compounds in this paper have been reported previously perhaps due to these difficulties. Indeed it has been found[1] that 1-g samples of these ethers are not retained in the liver of mice (as observed by continuous gas chromatographic observation) and are removed from the body within a period of 2–5 days depending on the structure of the compounds.

It should be noted, however, that the first perfluoro ethers were prepared in the 1950s by J. H. Simons using the electrochemical fluorination method.[7] The synthesis of highly branched species not possible by the Simons method for kinetic reasons and often because they are not sufficiently soluble in anhydrous HF appear to be generally accessible through direct fluorination.

Experimental Section

Materials, Analysis, and Physical Measurements. Isopropyl ether was obtained from Aldrich Chemicals. Isobutyl ether was obtained from Tridom-Fluka Chemicals. Isopentyl ether was obtained from Pfaltz & Bauer Chemicals. Neopentyl ether was

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Table I. Fluorination Conditions for Diisopropyl Ether

time, h	He, cm³/min	F_2, cm³/min	zones, °C 1	2	3	4
24	25	0.25	−78	−90	−90	−78
24	25	0.50	−78	−90	−90	−78
24	25	1.0	−78	−78	−90	−78
24	25	1.5	amb	−78	−90	−78
24	25	2.0	amb	−78	−90	−78
24	10	2.0	amb	−78	−90	−78
24	5	2.0	amb	−78	−78	−78
24	0	2.0	amb	amb	−78	−78
24	0	2.0	amb	amb	amb	amb
12	60	0	amb	amb	amb	amb

synthesized by the method of Gash.[8] Fluorine was technical grade and obtained from Air Products and Chemicals, Inc. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Inc., Woodside, NY. Infrared spectra were obtained with a Beckman IR20A spectrometer utilizing a gas cell with KBr windows. ^{19}F NMR spectra were obtained on a Varian EM 390 spectrometer operating at 84.67 MHz. $^{13}C\{^{19}F\}$ NMR spectra were run on a Bruker WH-100 instrument. Mass spectra were obtained with a Bell and Howell Model 21-490 mass spectrometer with the ion source cooled to ambient. Gas chromatography was done on a Bendix 2300 programmable gas chromatograph equipped with a cryogenic controller and thermal conductivity detector. The column used for separation was $^3/_8$ in. × 24 ft packed with 10% fluorosilicone (QF-1-0065) on Chromosorb P (60/80 mesh) with a helium flow of 100 cm³/min. Bis(perfluoroisopropyl) ether was further purified by using a $^1/_4$ in. × 24 ft column packed with 20% Fomblin Y-45 on Chromosorb P (60/80 mesh) with a helium flow of 60 cm³/min. Molecular weight determinations were done by the ideal gas method of expansion of the compound into a calibrated volume. Density measurements were taken by injection of five 10-μL aliquots into a weighed capillary, discarding the high and low values and averaging the three remaining value. The syringe was calibrated with water at 27 °C, and all values are corrected to the density of water at 4 °C. The melting and boiling points were measured in a 6-mm sealed glass tube.

Apparatus. The apparatus used for cryogenic fluorinations has been described previously.[9]

Bis(perfluoroisopropyl) Ether. A 1-cm³ (0.72 g, 7.1 mmol) sample of isopropyl ether was injected into the evaporator of a four-zone cryogenic reactor. The sample was evaporated at 70 °C into the cryogenic reactor, with zones 2 and 3 cooled to −100 °C, utilizing a 100 cm³/min flow of helium. After 4 h zones 1 and 4 were cooled to −78 °C with dry ice and zones 2 and 3 were cooled to −90 °C using a cryogenic delivery system. Fluorination conditions are as listed in Table I.

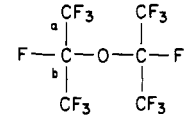
The products were collected in a glass trap maintained at −78 °C with a dry ice/acetone slush. Vacuum line separation into −78 and −131 °C fractions proved the majority of the components to stop at −78 °C with a minor amount passing to the −131 °C trap. The −78 °C fraction contained the desired perfluorinated ether. The weight of this fraction was 1.22 g, corresponding to a 49% yield of products. Final purification was accomplished utilizing gas chromatography.

Bis(perfluoroisopropyl) ether is a clear volatile liquid exhibiting a melting point of −90 °C, a boiling point of 54 °C, and a density of 1.65 cm³ at 27 °C. The vapor pressure above the liquid at 25 °C is 266 mmHg. Its molecular weight determined by the ideal gas method was found to be 355 (cf. 354 for $C_6F_{14}O$). The ^{19}F NMR exhibited a multiplet at −83.3 ppm (J = 4.52 Hz) and a multiplet at −143.2 ppm (signals relative to $CFCl_3$). The integrated intensities were 6:1, respectively. The $^{13}C\{^{19}F\}$ assignments are shown in Chart I.

The infrared spectrum exhibited the expected carbon–fluorine absorptions, the most intense coming at 1275 (vs, br), 1263 (m), 1155 (s) and 727 cm⁻¹ (m, sh). The carbon–oxygen–carbon stretch of the ether linkage gave an absorption at 991 cm⁻¹ (s, sh). The mass spectrum contained a parent minus fluorine peak at m/e 335 as well as peaks corresponding to the following fragments: m/e $C_5F_{11}O$ [(285)⁺], C_4F_9O [(235)⁺], C_3F_7 [(169)⁺], and 69 [$(CF_3)^+$] [base peak]. Elemental analyses was as follows. Anal. Calcd for $C_6F_{14}O$: C, 20.34; F, 75.14. Found: C, F, 79.94. GC retention time at 45 °C was 22 min, 30 s, on Fomblin column. Yield was 25%.

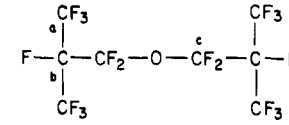
Chart I. $^{13}C\{^{19}F\}$ **Assignments**[a]

bis(perfluoroisopropyl) ether



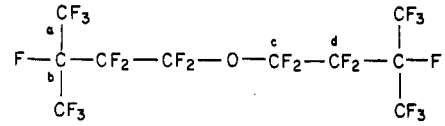
a 118.049
b 102.962

bis(perfluoroisobutyl) ether



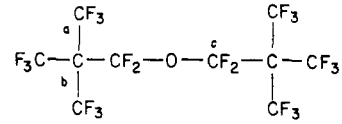
a 118.960
b 88.980
c 117.659

bis(perfluoroisopentyl) ether



a 119.285
b 90.215
c 116.684
d 110.831

bis(perfluoroneopentyl) ether



a 119.805
b 65.112
c 118.895

[a] In ppm relative to external Me_4Si.

Bis(perfluoroisobutyl) Ether. A 1.0-cm³ (0.75 g, 5.7 mmol) sample of isobutyl ether was injected, in 0.2-cm³ increments, into the evaporator of a cryogenic reactor. The sample was evaporated at 125 °C into the cryogenic reactor with zones 2 and 3 at −78 °C, with a helium flow of 100 cm³/min. Four hours after all of the sample had been injected, zones 1–4 were also cooled to −78 °C by using dry ice. After an additional 4 h the fluorination conditions as listed in Table II were commenced. The products were collected in a −78 °C glass trap. The perfluoro product stopped at −78 °C during vacuum line separation with some fragmentation products passing to a −131 °C trap. The weight of the −78 °C fraction was 1.44 g and corresponded to a yield of 55.8%. Final purification of the ether was accomplished by gas chromatography.

Bis(perfluoroisobutyl) ether is a water white liquid with a melting point of −85 °C, a boiling point of 98 °C, and a density of 1.76 cm³ at 27 °C. The vapor pressure above the pure liquid at 27 °C is 40 mmHg. The molecular weight determined by the ideal gas method was found to be 451 (cf. 454 for $C_8F_{18}O$). The ^{19}F NMR consisted of a sextet at −74.0 ppm (J = 5.19 Hz), a multiplet at −77.1 ppm (J = 19 Hz), and a multiplet at −187.6 ppm (signals relative to $CFCl_3$). The integrated intensities were found to be 6:2:1, respectively. The $^{13}C\{^{19}F\}$ assignments are shown in Chart I.

The infrared spectrum consisted of absorptions at 1286 (vs, br), 1172 (s), 1114 (s, sh), and 731 cm⁻¹ (m, sh) corresponding to the carbon–fluorine vibrational modes. The carbon–oxygen–

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Table II. Fluorination Conditions for Diisobutyl Ether and Diisopentyl Ether

time, h	He, cm³/min	F_2, cm³/min	zones, °C			
			1	2	3	4
24	50	0.25	−78	−78	−78	−78
24	50	0.50	−78	−78	−78	−78
24	50	1.0	−78	−78	−78	−78
24	50	2.0	−78	−78	−78	−78
24	50	3.0	amb	−78	−78	−78
24	25	3.0	amb	−78	−78	−78
24	10	3.0	amb	−78	−78	−78
24	0	3.0	amb	−78	−78	−78
24	0	3.0	amb	amb	amb	amb
48	100	0	amb	amb	amb	amb

Table III. Fluorination Conditions for Dineopentyl Ether

time, h	He, cm³/min	F_2, cm³/min	zones, °C			
			1	2	3	4
12	30	0.5	−78	−78	−78	−78
12	30	1.5	−78	−78	−78	−78
12	30	2.5	−78	−78	−78	−78
12	15	2.5	−78	−78	−78	−78
12	5	2.5	amb	−78	−78	−78
12	0	1.0	amb	amb	−78	−78
12	0	2.0	amb	amb	amb	−78
12	0	2.0	amb	amb	amb	amb
24	30	2.0	amb	amb	amb	amb
12	60	0	amb	amb	amb	amb

carbon stretching of the ether linkage was seen at 1001 cm^{-1} (s). The mass spectrum contained its highest m/e value at 435 corresponding to the parent minus fluorine fragment, as well as peaks corresponding to the following fragments: m/e 397 [$(C_8F_{15}O)^+$], 366 [$(C_7F_{14}O)^+$], 219 [$(C_4F_9O)^+$], and 69 [$(CF_3)^+$] [base peak]. Elemental analysis was as follows. Anal. Calcd for $C_8F_{18}O$: C, 21.15; F, 75.33. Found: C, 21.18; F, 75.45. GC retention time at 30 °C was 5 min. The yield was 40%.

Bis(perfluoroisopentyl) Ether. A 1.0-cm³ sample (0.77 g, 4.87 mmol) of isopentyl ether was injected into the cryogenic evaporator in increments of 0.2 cm³. The evaporator was held at a temperature of 150 °C for the duration of the injection period while zones 2 and 3 of the reactor were at −78 °C. Four hours after the injections were completed zones 1 and 4 were cooled to −78 °C with dry ice. The fluorination conditions are listed in Table II.

The products evolving from the reactor were stopped in a glass trap maintained at −78 °C. Vacuum line separation proved the product stopped at −78 °C with a small amount of products passing to a −131 °C trap. The yield in the −78 °C trap was 1.39 g, corresponding to an overall yield of products of 52%. The bis(fluoroisopentyl) ether was further purified by gas chromatography.

Bis(perfluoroisopentyl) ether is a colorless liquid with a melting point of −107 °C, a boiling point of 134 °C, and a density of 1.82 cm³ at 27 °C. The vapor pressure above the liquid at 27 °C is 27 mmHg. The molecular weight determined by the ideal gas method was found to be 555 (cf. 554 for $C_{10}F_{22}O$). The ^{19}F NMR consists of an octet at −74.6 ppm (J = 5.56 Hz), a multiplet at −84.7 ppm, a septet at −120.1 ppm (J = 11.01 Hz), and a multiplet at −187.7 ppm (signals relative to $CFCl_3$). The integrated intensities are 6:2:2:1, respectively. The $^{13}C\{^{19}F\}$ assignments are shown in Chart I.

The most prominent absorptions, due to carbon–fluorine vibrations, in the infrared were 1282 (vs, br), 1209 (s, sh), 1159 (s), and 727 cm^{-1} (m). The absorption due to the ether linkage was found at 985 cm^{-1} (s, sh). The highest m/e in the mass spectrum was at 535 and corresponded to the parent minus fluorine fragment. Other fragments in the mass spectrum were as follows: m/e 497 [$(C_{10}F_{19}O)^+$], 269 [$(C_5F_{11})^+$], 219 [$(C_4F_9)^+$], and 69 [$(CF_3)^+$] [base peak]. Elemental analysis was as follows. Anal. Calcd for $C_{10}F_{22}O$: C, 21.66; F, 75.45. Found: C, 21.44; F, 75.25. GC retention time at 40 °C is 21 min, 15 s. The yield was 41%.

Bis(perfluoroneopentyl) Ether. Neopentyl ether, 1 cm³ (0.77 g, 4.87 mmol), was injected into the evaporator of a cryogenic reactor in 0.2-cm³ increments with the evaporator at 150 °C. Zones 2 and 3 were cooled to −78 °C with dry ice. The ether was injected over a 4-h period with a helium flow of 100 cm³/min. When all of the ether was evaporated, zones 1 and 4 were cooled to −78 °C with dry ice. After an additional 4 h the evaporator was cooled and the fluorination, using the conditions in Table III, was initiated.

The reaction products were collected in a glass trap cooled to −78 °C with dry ice. All of the products stopped at the −78 °C trap on the vacuum line. The products weight was 1.35 g corresponding to >50% yield. Final purification of the ether was accomplished with gas chromatography.

Bis(perfluoroneopentyl) ether is a colorless volatile crystalline solid with a melting point of 68–68.5 °C. It has a vapor pressure at 25 °C of 6 mmHg. The molecular weight determined by the ideal gas method was 552 (cf. 554 for $C_{10}F_{22}O$). The ^{19}F NMR consisted of a pentet at −64.2 ppm (J = 5.92 Hz) and a multiplet at −67.5 ppm (J = 5.92 Hz) (signals relative to $CFCl_3$). The integrated intensities were 4.5:1, respectively. The $^{13}C\{^{19}F\}$ assignments are shown in Chart I.

The most prominent carbon–fluorine vibrations in the infrared were found at 1270 (vs, br), 1220 (s), 1085 (s, sh), and 729 cm^{-1} (m). The absorption associated with the ether linkage was found at 988 cm^{-1} (s). The highest m/e in the mass spectrum was at 535 and corresponded to the parent minus fluorine fragment. Other intense fragments were m/e 497 [$(C_{10}F_{19}O)^+$], 269 [$(C_5F_{11})^+$], 219 [$(C_4F_9)^+$], and 69 [$(CF_3)^+$] [base peak]. Elemental analysis for this compound is as follows: Anal. Calcd for $C_{10}F_{22}O$: C, 21.66; F, 75.45; Found: C, 21.50; F, 75.65. GC retention time at 45 °C is 16 min, 15 s. The yield was 50%.

Results and Discussion

A major contribution has been made in that a new class of oxygen carriers, possibly with unique properties, has been made available. The synthesis by direct fluorination, although not optimized, gives extremely good yields of highly branched perfluorocarbon ethers. Perfluoro ethers are of unusual stability[10] and other applications of these highly branched perfluoro ethers could be easily envisioned. Perfluoro ethers are, for example, lubricants, drilling fluids, electronic solvents, vacuum pump oils, and may serve even as mass markers in mass spectrometers.

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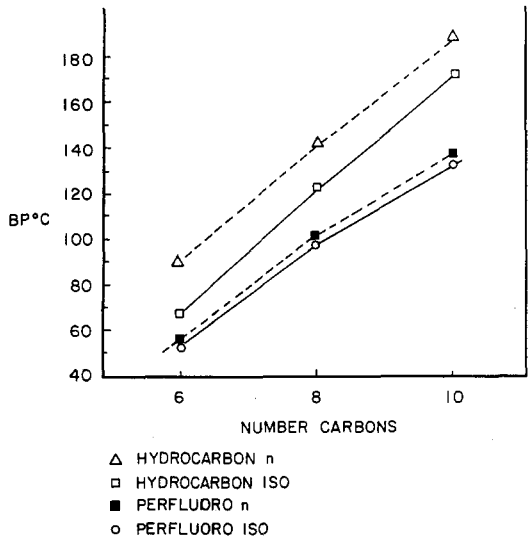

Figure 1.

It is probable that these ethers can not be produced by cobalt trifluoride, silver difluoride, or electrochemical fluorination. Perfluoro ethers are thought to be excellent candidates for emulsification with fluorocarbon surfactants and thus have properties conducive to long emulsion stability so necessary for many oxygen carrier applications.

^{19}F NMR analysis of the perfluoro ethers shows examples of the unusual coupling encountered when dealing with perfluoro systems. Coupling through two and three carbons, as well as through oxygen, is observed. This effect along with the noncoupling between fluorines on vicinal carbons makes characterization by ^{19}F NMR alone challenging, but not impossible.

The mass spectra of the ethers yielded a parent minus fluorine fragment as the highest m/e. This fragment was only seen when the ion source in the spectrometer was cooled to ambient. Characteristic of all the spectra were rearrangements yielding secondary fragments that were not possible by primary cleavage alone.

Highly branched hydrocarbons melt higher and boil at lower temperatures than their linear isomers. With even more highly branched fluorocarbons than the perfluorinated "iso" compounds plotted in Figure 1, this effect is even more pronounced[11] since there is little intermolecular attraction (only van der Waals forces) causing the heat of vaporization to be extremely low.

An interesting effect along these lines is illustrated in Figure 1. It is apparent that the effect is much greater in the hydrocarbon series than that found in the fluorocarbon series. In the hydrocarbons, the H,H, C,H, and C,C interactions are all important, owing to the small size of the hydrogen atom. In fluorocarbons, because the fluorine atom is larger than the hydrogen atom, only the F,F and perhaps the C,F interactions make a substantial contribution to the intermolecular potential within the molecules.[12]

It is obvious that almost any perfluorocarbon ether structure that one could draw could be synthesized by this method. In fact, within a 2-mo period after research is initiated, with any luck whatsoever, experimentalists skilled in these techniques can deliver a 10-g sample for further study.

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Registry No. Isopropyl ether, 108-20-3; bis(perfluoroisopropyl) ether, 83935-39-1; isobutyl ether, 628-55-7; bis(perfluoroisobutyl) ether, 97187-06-9; isopentyl ether, 544-01-4; bis(perfluoroisopentyl) ether, 73309-73-6; neopentyl ether, 28509-24-2; bis(perfluoroneopentyl) ether, 97187-05-8.

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An Approach to the Synthesis of Mevinolin Based on Intramolecular Diels–Alder Cycloaddition

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An approach to the hypocholesterolemic agent mevinolin (**1b**) is presented which utilizes an intramolecular Diels–Alder strategy for construction of the hexahydronaphthalene moiety. Alkylation of diene alcohol 11 with 1-chloro-3-phosphoranylidene-2-propanone gives stabilized phosphorane **12**, which is condensed with acetaldehyde to afford trans enone **7b**. Thermal cyclization of **7b** affords endo (desired) and exo (undesired) adducts **8b** and **13b** in a ratio of 2:3. The influence of dienophile β-methyl group substitution on adduct endo/exo ratio is explored via compounds **7c** (*cis*-methyl), **7a** (unsubstituted), and **7d** (dimethyl), which give endo/exo ratios of 6:1, 6:1, and 1:1 upon thermal cyclization. An alternative highly stereoselective route to **8b** is reported. Alkylation of alcohol 11 with chloroacetic acid affords carboxylic acid **14**, which is converted via imidazolide **15** to *N*-methoxy, *N*-methyl amide **28**. Treatment of **28** with lithium acetylide–ethylenediamine complex gives acetylenic ketone **24**, which is converted to dienone **25** by cyclization in refluxing toluene. Stereoselective axial conjugate addition of a methyl group to **25** is accomplished with methylcopper–boron trifluoride complex, affording key intermediate **8b** in seven steps and 28% overall yield from dihydroorcinol ethyl enol ether.

The discoveries of the potent hypocholesterolemic agents compactin[1,2] (**1a**) and mevinolin[3,4] (**1b**) have led to a great deal of work on the synthesis of these and related compounds.[5–7] As part of our own research in this area, we

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