propylidene group); MS (calcd mass 532) obsd *m/e* 531.00, 516.97, 273.00, 213.00 (100).

Ethyl 2-Deoxy-3,4,6-tri-*O*-acetyl-1-thio-α,β-D-*arabino*-hexopyranoside (8). To a solution of 5 (1.0 g) in acetonitrile (30 mL) were added ethyl mercaptan (1.6 mL), acid resin (0.6 g), and lithium bromide hydrate (1.0 g), and the solution was stirred at room temperature for 18 h. The reaction mixture was worked up as described for 1 and the product was isolated by chromatography on a column of silica gel using ethyl acetate–hexane (1:4, R_f = 0.16 for α and 0.12 for β). The weight of α- and β-anomers were 0.34 and 0.17 g, respectively: mp (α-anomer) 51.5–52.5 °C, (β-anomer) 56–58 °C; $[\alpha]^{20}$D (α-anomer) +183.2 ± 2° (*c* 1.0, $CHCl_3$); $[\alpha]^{20}_D$ (β-anomer) −41.7 ± 2° (*c* 1.02, $CHCl_3$); ^{1}H NMR (α-anomer, $CDCl_3$) δ 5.44 (broad d, *J* = 5.5 Hz, H-1), 5.24 (m, *J* = 4.9, 9.4, 11.8 Hz, H-3), 4.97 (t, *J* = 9.4 Hz, H-4), 4.39 (m, H-5), 4.34 (dd, *J* = 4.6, 11.8 Hz, H-6a), 4.03 (dd, *J* = 2.0, 11.8 Hz, H-6b), 2.62 and 2.53 (m, 2 H, SCH_2), 2.26 (sextet, *J* = 1.3, 5.8, 13.6 Hz, H-2_{eq}), 2.16 (m, *J* = 5.8, 11.7, 13.6 Hz, H-2_{ax}), 2.18, 2.04, and 2.0 (3 s, CH_3COO), 1.28 (t, CH_3CH_2S); ^{1}H NMR (β-anomer, $CDCl_3$) δ 5.00 (m, 2 H, H-3, H-4), 4.64 (dd, *J* = 2.6, 11.5 Hz, H-1), 4.20 (dd, *J* = 5.1, 12.2 Hz, H-6a), 4.09 (dd, *J* = 2.6, 12.2 Hz, H-6b), 3.63 (m, H-5), 2.72 (m, 2 H, SCH_2), 2.37 (m, H-2_{eq}), 2.07, 2.03, and 2.02 (3 s, CH_3COO), 1.84 (broad dd, *J* = 11.3, 13.0 Hz, H-2_{ax}), 1.29 (t, CH_3CH_2S); MS (calcd mass = 334) obsd *m/e* 333.16, 273.17, 213.13.

2,6-Dideoxy-3,4-di-*O*-acetyl-L-*lyxo*-hexopyranose (2-Deoxy-3,4-di-*O*-acetyl-L-fucopyranose, 9). To a solution 3,4-di-*O*-acetyl-L-fucal (5.0 g) and lithium bromide hydrate (5.0 g) in acetonitrile (150 mL) were added Ag 50W-X2 resin (3.0 g) and water (6 mL), and the mixture was stirred at room temperature for 15 min. The product was isolated as described for 1. Purification by chromatography on a column of silica gel using ethyl acetate–hexane (3:8, R_f = 0.10) as eluant gave the title compound (colorless solid, 4.0 g, 73.8% yield); mp 98–99 °C; α:β = 9.4; $[\alpha]^{20}_D$ −57.6 ± 2° (*c*, 1.03, $CHCl_3$), ^{1}H NMR δ 5.45 (d, *J* = 3.2 Hz, H-1α), 5.35 (m, *J* = 3.2, 5.2, 8.0 Hz, H-3α), 5.19 (broad d, *J* = 3.2 Hz, H-4α), 5.10 (broad d, *J* = 3.2 Hz, H-4β), 4.98 (m, H-3β), 4.87 (dd, *J* = 1.6, 8.9 Hz, H-1β), 4.33 (H-5α), 3.73 (m, H-5β), 2.15 and 1.98 (2 s, CH_3COO of α-anomer), 2.17 and 2.00 (acetyl groups of β anomer), 2.04 and 1.86 (m, H-2), 1.20 (d, CH_3 (C6) of β-anomer), 1.13 (d, CH_3 (C6) of α-anomer); MS for anomeric mixture (calcd mass = 232) obsd *m/e* 231.13, 215.12, 155.09 (100).

Methyl 2,6-Dideoxy-3,4-di-*O*-acetyl-α-L-*lyxo*-hexopyranoside (Methyl 2-Deoxy-3,4-di-*O*-acetyl-α-L-fucopyranoside, 10). To a solution 3,4-di-*O*-acetyl-L-fucal (2.0 g) and anhydrous lithium bromide (2.2 g) in acetonitrile (20 mL) were added Ag 50W-X2 resin (2.5 g) and methanol (1 mL), and the reaction mixture was stirred at room temperature for 5 h. The product was isolated as described for 1. Purification by chromatography on a column of silica gel using ethyl acetate–hexane (3:7, R_f = 0.33 for α-anomer, 0.26 for β-anomer) as eluant gave the title compound (colorless solid, 1.6 g): mp 66.4 °C (lit.[29] mp 66.5–67.5 °C). The weight of the β-anomer was 0.33 g (syrup, 83.9% combined yield): $[\alpha]^{20}_D$ (α-anomer) −174.2 ± 2° (*c* 1.00, $CHCl_3$) (lit.[29] −166° (*c* 0.79, $CHCl_3$)]; $[\alpha]^{20}_D$ (β-anomer) −13.6 ± 2° (*c* 1.02, $CHCl_3$); ^{1}H NMR δ 5.24 (m, *J* = 2.9, 4.9, 7.8 Hz, H-3), 5.15 (dd, *J* = 1.2, 2.9 Hz, H-4), 4.83 (broad d, *J* = 3.4 Hz, H-1), 4.03 (m, H-5), 3.31 (s, OCH_3), 2.01 (m, *J* = 3.7, 10.0, 12.7 Hz, H-2_{ax}), 1.82 (m, H-2_{eq}), 2.13 and 1.95 (2 s, CH_3COO), 1.12 (d, *J* = 6.6 Hz, CH_3 (C6)); MS (calcd mass = 246) obsd *m/e* 245.18, 215.17, 155.13 (100).

2,6-Dideoxy-3,4-di-*O*-acetyl-L-*arabino*-hexopyranose (2-Deoxy-3,4-di-*O*-acetyl-L-rhamnopyranose, 11). To a solution 3,4-di-*O*-acetyl-L-rhamnal (5.0 g) and lithium bromide hydrate (5.0 g) in acetonitrile (150 mL) were added AG 50W-X2 resin (3.0 g) and water (6 mL), and the mixture was stirred at room temperature for 15 min. The product was isolated as described for 1. Purification by chromatography on a column of silica gel using ethyl acetate–hexane (3:8, R_f = 0.12) as eluant gave the title compound (pale brown solid, 3.75 g, 69.1% yield): mp 79–80.2 °C; α:β = 2:1; $[\alpha]^{20}_D$ −96.8 ± 2° (*c* 0.96, $CHCl_3$); ^{1}H NMR δ 5.36 (d, *J* = 3.0 Hz, H-1α), 5.33 (m, *J* = 5.1, 9.4, 11.1 Hz, H-3α), 4.98 (m, H-3β), 4.90 (dd, *J* = 1.7, 9.4 Hz, H-1β), 4.75 (t, *J* = 9.4 Hz, H-4), 4.12 (m, H-5α), 3.54 (m, H-5β), 2.39 (m, *J* = 2.0, 5.5, 12.2 Hz, H-$2\beta_{eq}$), 2.26 (m, *J* = 1.5, 5.5, 12.5 Hz, H-$2\alpha_{eq}$), 1.77 (m, *J* = 3.8, 11.1, 12.5 Hz, H-$2\alpha_{ax}$), 1.66 (m, *J* = 9.4, 12.2 Hz, H-$2\beta_{ax}$), 1.23 [d, *J* = 6.6 Hz, CH_3 (C6) of β-anomer], 1.17 [d, *J* = 6.6 Hz, CH_3 (C6) of α-anomer]; MS (calcd mass = 232) obsd *m/e* 231.13, 215.12, 155.09 (100).

5-(Methoxycarbonyl)pentyl 2-Deoxy-3,6-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-*arabino*-hexopyranoside (12). A solution of lactal hexaacetate (18.3 g) in acetonitrile (100 mL) containing anhydrous lithium bromide (9.8 g), 5-(methoxycarbonyl)pentan-1-ol (10 mL), 4-Å molecular sieves (4 g), and the acid resin (10 g) was stirred at room temperature for 16 h. The reaction mixture was worked up as described for 1, and the crude syrup was dissolved in dichloromethane (100 mL) containing pyridine (25 mL) and acetic anhydride (25 mL). After 16 h, the reaction mixture was diluted with dichloromethane and washed with water, ice-cold 1 M hydrochloric acid, and saturated sodium bicarbonate solution. The product was purified by chromatography on a column of silica gel using ethyl acetate–hexane (2:3, R_f = 0.07) as eluant. The weight of the syrupy product was 13.6 g (59.1% yield): $[\alpha]^{20}_D$ +13.0 ± 2° (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.33 (dd, *J* = 1.1, 3.5 Hz, H-4′), 5.27 (m, *J* = 5.1, 8.2, 10.9 Hz, H-3), 5.11 (dd, *J* = 8.0, 10.1 Hz, H-2′), 4.94 (dd, *J* = 3.5, 10.1 Hz, H-3′), 4.82 (broad d, *J* = 2.6 Hz, H-1), 4.54 (d, *J* = 8.2 Hz, H-1′), 4.33 (dd, *J* = 2.4, 12.0 Hz, H-6a), 4.13 (m, H-6′a, H-6′b), 4.04 (dd, *J* = 7.2, 12.0 Hz, H-6b), 3.85 (m, H-5, H-5′), 3.63 (s, $COOCH_3$) 3.63 (dd, *J* = 8.8, 9.2 Hz, H-4), 3.57 and 3.30 (m, OCH_2), 2.30 (t, *J* = 7.5 Hz, CH_2COO), 2.20 (m, H-2_{eq}), 2.04 (m, H-2_{ax}), 1.68–1.54 and 1.35 ($CCH_2CH_2CH_2$ of the aglycon); MS (calcd mass = 704.26) obsd *m/e* 729.22, 705.22, 501.12 (100).

Supplementary Material Available: 500-MHz proton NMR spectra of compounds 1–12 (13 pages). Ordering information is given on any current masthead page.

Synthesis of 2-[(Perfluoroalkyl)phenyl]propionic Acids

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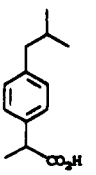
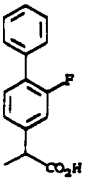
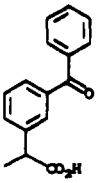
A structural unit common to many useful nonsteroidal antiinflammatory drugs is the 2-phenylpropionic acid moiety, from which the term "profen drugs" is derived. Profen drugs differ in the nature of the substituents on the aromatic ring.[1] Examples include ibuprofen (1), flurbiprofen (2), and ketoprofen (3). No profens have been reported, however, that bear a perfluoroalkyl-substituted phenyl group.



1



2



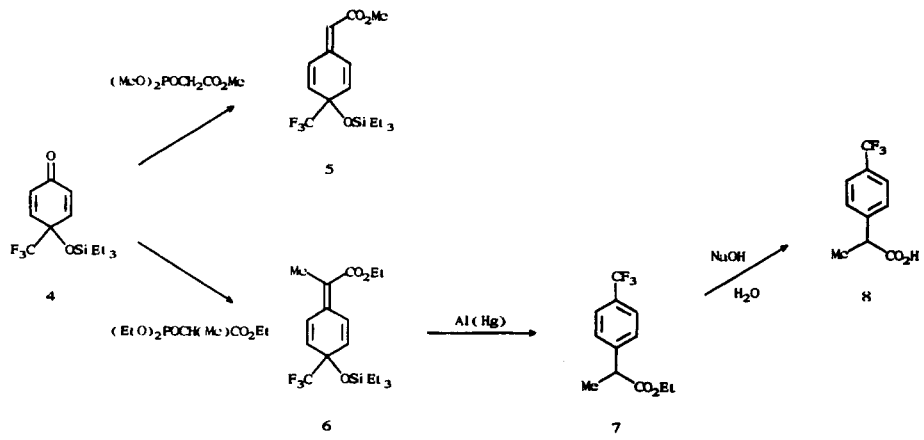
3

Herein is reported a synthetic route to 2-[(perfluoroalkyl)phenyl]propionic acids. The key intermediates are perfluoroalkylated cyclohexadienones **4**, **9a**, and **9b**. We previously reported synthesis of **4** by the novel addition of triethyl(trifluoromethyl)silane to 1,4-benzoquinone.[2] This versatile intermediate undergoes reactions similar to those undergone by quinone monoketals.[3] Fortunately,

(1) Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095.
(2) Stahly, G. P.; Bell, D. R. *J. Org. Chem.* **1989**, *54*, 2873.

0022-3263/91/1956-5472$02.50/0

Scheme I



reactions of 4 leading to arenes occur with retention of the trifluoromethyl group, affording a variety of trifluoromethylated aromatic molecules. For example, reduction and reductive amination of 4 yielded 4-(trifluoromethyl)phenol and 4-(trifluoromethyl)aniline, respectively.[2] We have also found that 4, like the quinone monoketals, reacts with organometallic reagents. Phenyllithium and phenylmagnesium bromide add in 1,2 fashion to the carbonyl group, affording a diene that can be reduced to 4-(trifluoromethyl)biphenyl.[4]

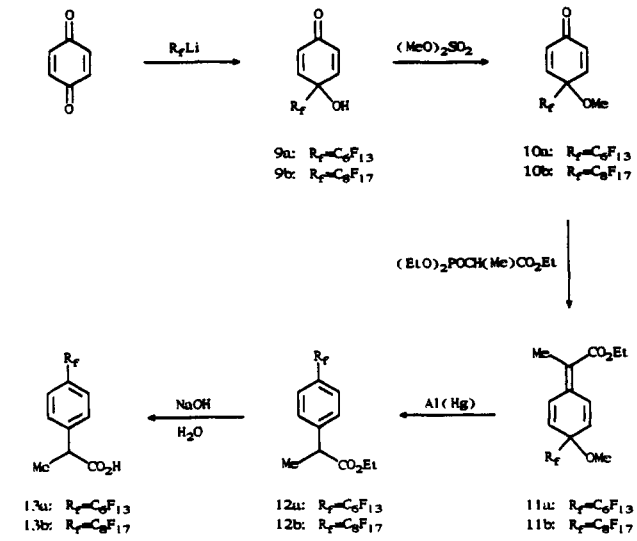
Another reaction reported for quinone monoketals is olefination of the carbonyl group under Peterson or Wittig conditions.[3] Attempts to olefinate 4 using triphenylphosphonium methylide (Wittig reaction)[5] in toluene or DMF were unsuccessful. However, the more reactive Horner–Emmons reagent,[6] methyl 2-(dimethylphosphono)acetate, converted 4 to the triene 5 (Scheme I).

It occurred to us that a properly chosen phosphonate reagent would provide an intermediate, similar to compound 5, that might be reducible to a profen derivative. Even though the success of the Horner–Emmons reaction tends to decrease with increasing steric crowding at the acidic phosphonate carbon atom, 4 did undergo olefination with ethyl 2-(diethylphosphono)propionate to give triene 6 (Scheme I). The yields obtained in this reaction were erratic if glyme was used as solvent, following standard literature conditions, but were more consistent (60–80%) in toluene.

Indeed, dissolving metal reduction of 6 afforded the profen ester 7. Zinc and acid were ineffective for the reduction, but amalgamated aluminum in wet THF worked cleanly and efficiently. Saponification of the ester then gave the desired acid 8.

A similar sequence was used to prepare acids bearing other perfluoroalkyl groups (Scheme II). The required dienone intermediates (**9a** and **9b**) were synthesized by the addition of perfluorohexyl- and perfluorooctyllithium, respectively, to 1,4-benzoquinone.[7] Use of triethyl(trifluoromethyl)silane to make 4 was required because of the instability of trifluoromethyllithium or Grignard reagents. However, other (perfluoroalkyl)lithiums are stable enough to be useful if generated in situ.

Scheme II



It seemed unlikely that olefination reactions could be carried out on the alcohols **9a** and **9b** due to the acidity of the hydroxyl groups. A single attempt using **9a** confirmed this. The necessary protecting group was introduced by methylation with dimethyl sulfate in a two-phase system, affording compounds **10a** and **10b**. These were readily olefinated to give trienes **11a** and **11b**. Dissolving metal reduction of **11a** and **11b** occurred with loss of the methoxy groups to give esters **12a** and **12b**, which were hydrolyzed to the profen acids **13a** and **13b**.

This is a new method for the synthesis of profen derivatives. A primary advantage is that the relationship of the perfluoroalkyl and propionic acid groups (para) is determined by the starting quinone. Thus, isomer separation requirements encountered in typical routes to other profens, which often rely on Friedel–Crafts reactions for ring functionalization,[1] are eliminated. Introduction of the perfluoroalkyl groups is operationally convenient due to the use of perfluoroalkyl iodide or bromide starting materials (triethyl(trifluoromethyl)silane is made from trifluoromethyl bromide[2]) rather than the more difficultly handled fluorinating reagents such as hydrogen fluoride, fluorine, sulfur tetrafluoride, etc. The method appears general with respect to the perfluoroalkyl group. In addition, it is likely that other available cyclohexadienones[8]

(3) Swenton, J. S. *Acc. Chem. Res.* **1983**, *16*, 74.
(4) Stahly, G. P. Unpublished results.
(5) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985; pp 845–854.
(6) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73.
(7) (a) Suzuki, H.; Shiraishi, Y.; Shimokawa, K.; Uno, H. *Chem. Lett.* **1988**, 127. (b) Uno, H.; Shiraishi, Y.; Simokawa, K.; Suzuki, H. *Chem. Lett.* **1987**, 1153.

(8) For example: (a) Evans, D. A.; Hoffman, J. M.; Truesdale, L. K. *J. Am. Chem. Soc.* **1973**, *95*, 5822. (b) Fischer, A.; Henderson, G. N. *Tetrahedron Lett.* **1983**, *24*, 131. (c) Evans, D. A.; Truesdale, L. K. *Tetrahedron Lett.* **1973**, *49*, 4929.

can be converted to profen derivatives by the same sequence of reactions.

Acids 8 and 13a were screened for pharmacological activity.[9] Both exhibited analgesic effects. Compound 8 gave 62% inhibition of writhes in the PQ writhing test and 43% reduction of paw licking time in the formalin AG test at 100 mg/kg. At the same dose level compound 13a gave 55% inhibition in PQ writhing and 89% reduction in formalin AG. Clearly, some profen-like activity is maintained in these derivatives.

Experimental Section

General. NMR spectra were recorded on a GE/NIC NT-360 spectrometer. Proton and carbon chemical shifts are reported in parts per million relative to tetramethylsilane, and fluorine chemical shifts are reported in parts per million relative to fluorotrichloromethane. Attached proton information from APT spectra is reported after the carbon chemical shifts as o (odd number of hydrogens attached to carbon) or e (even number of hydrogens attached to carbon). Infrared spectra were obtained on a Nicolet 20SXB spectrophotometer, and values are reported in reciprocal centimeters. Mass spectra were recorded on a Finnigan 4023 gas chromatograph/mass spectrometer equipped with a 50-m SE-52 fused silica capillary column. Gas chromatography was carried out on a Hewlett-Packard 5890 instrument equipped with a 30 m × 0.53 mm (i.d.) 2.65 μm (film thickness) HP-5 fused silica capillary column. Preparative thin-layer chromatography (PTLC) was carried out on commercially prepared silica gel plates (Analtech), and visualization was by ultraviolet light. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. The preparation of 4-(triethylsiloxy)-4-(trifluoromethyl)-2,5-cyclohexadien-1-one (4) was described previously.[2] Ethyl 2-(diethylphosphono)propionate[10] was synthesized from ethyl 2-bromopropionate and triethyl phosphite.[11]

4-Hydroxy-4-(perfluorohexyl)-2,5-cyclohexadien-1-one (9a). A mixture of 220 mg (2.0 mmol) of 1,4-benzoquinone, 0.48 mL (2.2 mmol) of perfluorohexyl idodide, and 20 mL of dry diethyl ether was placed into a flame-dried flask under a nitrogen atmosphere. The solution was cooled to −78 °C and treated dropwise with 1.46 mL (2.2 mmol) of a 1.5 M solution of methyllithium–lithium bromide complex in diethyl ether. The solution turned blue on addition of the first drop of methyllithium and remained blue thereafter. After the addition, the mixture was stirred cold for 30 min, and 6 mL of 1 N HCl was added. The cold bath was removed, and the blue color was discharged as the solution warmed to room temperature. The resulting solution was poured into 50 mL of 1 N HCl, and the aqueous layer was extracted with two 20-mL portions of diethyl ether. Combination, drying ($MgSO_4$), and concentration of the ether layers afforded a residue that was purified by PTLC (two 2-mm silica gel plates eluted with 1% methanol–99% dichloromethane) to give 412 mg (54% yield) of 4-hydroxy-4-(perfluorohexyl)-2,5-cyclohexadien-1-one (9a) as a beige powder. An analytical sample was obtained by recrystallization from dichloromethane–methanol: mp 104–105 °C; ^1H NMR ($CDCl_3$ + CD_3OD) δ 6.38 (d, 2 H, J = 10 Hz), 6.97 (d, 2 H, J = 10 Hz); ^{19}F NMR ($CDCl_3$) δ −81.28 (t), −119.5 (m), −122.3 (br s), −123.2 (br s), −126.6 (m); IR (KBr) 3231, 1672, 1626, 1404, 1388, 1238, 1206, 871, 806, 738, 698 cm^{-1}; high-resolution mass spectrum calcd for $C_{12}H_5O_2F_{13}$ 428.0081, found 428.0100.

Compound 9b was prepared by a similar procedure.

4-Hydroxy-4-(perfluorooctyl)-2,5-cyclohexadien-1-one (9b): 42% yield; white solid; mp 130–131 °C (dichloromethane–methanol); ^1H NMR ($CDCl_3$ + CD_3OD) δ 6.38 (d, 2 H, J = 10 Hz), 6.97 (d, 2 H, J = 10 Hz); ^{19}F NMR ($CDCl_3$) −81.23 (t), −119.43 (m), −122.01 (m), −123.17 (br s), −126.51 (m); IR (neat) 3220, 2390, 1750, 1620, 1210, 1150 cm^{-1}; high-resolution mass spectrum calcd for $C_{14}H_5O_2F_{17}$ 528.0018, found 527.9968.

4-Methoxy-4-(perfluorohexyl)-2,5-cyclohexadien-1-one (10a). Three mg (0.9 mmol) of tetrabutylammonium hydrogen sulfate and 4 mL of 50% NaOH were added to a solution of 200 mg (0.47 mmol) of 4-hydroxy-4-(perfluorohexyl)-2,5-cyclohexadien-1-one (9a) in 4 mL of toluene. The mixture was stirred for 10 min, treated with 0.060 mL (0.63 mmol) of dimethyl sulfate, stirred vigorously for an additional 2 h, and poured into 100 mL of 1 N HCl. The resulting mixture was acidified with 37% HCl and extracted with three 50-mL portions of diethyl ether. Combination, drying ($MgSO_4$), and concentration of the diethyl ether layers afforded a residue that was purified by PTLC (two 2-mm silica gel plates eluted with dichloromethane) to give 162 mg (78% yield) of 4-methoxy-4-(perfluorohexyl)-2,5-cyclohexadien-1-one (10a) as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 3.31 (s, 3 H), 6.38 (d, 2 H, J = 10 Hz), 6.87 (d, 2 H, J = 10 Hz); ^{19}F NMR ($CDCl_3$) δ −81.32 (t), −117.48 (m), −119.35 (br s), −122.30 (br s), −123.22 (br s), −126.61 (m); IR (neat) 2950, 1692, 1678, 1641, 1392, 1238, 1201, 1146, 850, 720, 705, 696, 669 cm^{-1}; high-resolution mass spectrum calcd for $C_{13}H_7O_2F_{13}$ 442.0238, found 442.0215.

Compound 10b was prepared by a similar procedure.

4-Methoxy-4-(perfluorooctyl)-2,5-cyclohexadien-1-one (10b): 73% yield; white solid; mp 34–36 °C (hexane); ^1H NMR ($CDCl_3$) δ 3.31 (s, 3 H), 6.59 (d, 2 H, J = 10 Hz), 6.86 (d, 2 H, J = 10 Hz); ^{19}F NMR ($CDCl_3$) δ −81.23 (t), −117.23 (br s), −119.10 (br s), −121.79 (m), −123.14 (br s), −126.46 (br s); IR (neat) 2950, 1695, 1643, 1240, 1210, 1150, 860, 710, 560 cm^{-1}; high-resolution mass spectrum calcd for $C_{15}H_7O_2F_{17}$ 542.0174, found 542.0130.

Ethyl 2-[4-(Triethylsiloxy)-4-(trifluoromethyl)-2,5-cyclohexadienylidene]propionate (6). Sixty percent sodium hydride (33 mg, 0.82 mmol) was placed in a flame-dried flask under a nitrogen atmosphere and washed free of mineral oil with three 1-mL portions of petroleum ether. Addition of 1 mL of dry toluene followed by 200 mg of ethyl 2-(diethylphosphono)propionate and stirring of the mixture for 10 min at room temperature resulted in formation of a colorless solution. To this was added 200 mg (0.68 mmol) of 4-(triethylsiloxy)-4-(trifluoromethyl)-2,5-cyclohexadien-1-one (4), and the mixture was allowed to stir for 1 h. It was then poured into 10 mL of 1 N HCl, and the resulting aqueous mixture was extracted with three 5-mL portions of diethyl ether. Combination, drying ($MgSO_4$), and concentration of the organic layers afforded a residue that was purified by PTLC (one 2-mm plate eluted with 25% dichloromethane–75% petroleum ether) to give 160 mg (62% yield) of ethyl 2-(4-(triethylsiloxy)-4-(trifluoromethyl)-2,5-cyclohexadienylidene)propionate (6) as a colorless liquid: ^1H NMR ($CDCl_3$) δ 0.55 (q, 6 H, J = 8 Hz), 0.92 (t, 9 H, J = 8 Hz); 1.34 (t, 3 H, J = 7 Hz), 2.13 (s, 3 H), 4.28 (q, 2 H, J = 7 Hz), 5.95 (d, 1 H, J = 11 Hz), 6.09 (d, 1 H, J = 11 Hz), 6.85 (d, 1 H, J = 11 Hz), 7.32 (d, 1 H, J = 11 Hz); ^{19}F NMR ($CDCl_3$) δ −81.8 (s); IR (neat) 2953, 2909, 2876, 1708, 1456, 1406, 1380, 1365, 1309, 1267, 1235, 1175, 1112, 1077, 998, 868, 801, 745, 701, 611 cm^{-1}; high-resolution mass spectrum calcd for $C_{18}H_{27}F_3O_3Si$ 376.1682, found 376.1674.

The following compounds (11a,b) were prepared by similar procedures.

Ethyl 2-[4-methoxy-4-(perfluorohexyl)-2,5-cyclohexadienylidene]propionate (11a): 85% yield; yellow oil; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H, J = 7 Hz), 2.17 (s, 3 H), 3.15 (s, 3 H), 4.29 (q, 2 H, J = 7 Hz), 5.89 (d, 1 H, J = 10 Hz), 6.03 (d, 1 H, J = 10 Hz), 7.06 (dd, 1 H, J = 10, 2 Hz), 7.47 (dd, 1 H, J = 10, 2 Hz); ^{19}F NMR ($CDCl_3$) δ −81.20 (t), −119.00 (br s), −119.56 (br s), −122.22 (br s), −123.10 (br s), −126.51 (br s); IR (neat) 2880, 1710, 1365, 1240, 1200, 1143, 1070, 1020, 810, 695, 669 cm^{-1}; high-resolution mass spectrum calcd for $C_{17}H_{12}O_3F_{13}$ 511.0579, found 511.0599.

Ethyl 2-[4-methoxy-4-(perfluorooctyl)-2,5-cyclohexadienylidene]propionate (11b): 57% yield; yellow oil; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H, J = 7 Hz), 2.16 (s, 3 H), 3.15 (s, 3 H), 4.29 (q, 2 H, J = 7 Hz), 5.90 (d, 1 H, J = 10 Hz), 6.03 (d, 1 H, J = 10 Hz), 7.05 (dd, 1 H, J = 10, 2 Hz), 7.48 (dd, 1 H, J = 10, 2 Hz); ^{19}F NMR ($CDCl_3$) δ −81.17 (t), −119.10 (br s), −119.50 (br s), −122.12 (m), −123.09 (br s), −126.55 (br s); IR (neat) 2960, 1720, 1430, 1245, 1220, 1155, 815, 660 cm^{-1}; high-resolution mass spectrum calcd for $C_{20}H_{15}O_3F_{17}$ 626.0749, found 626.0753.

Ethyl 2-[4-(Trifluoromethyl)phenyl]propionate (7). Aluminum foil (163 mg, 6.0 mg-atom) was amalgamated by immersion in a solution of 2% mercuric chloride in water for 15 s, washed with absolute ethanol followed by diethyl ether, cut into small pieces, and added to a solution of 228 mg (0.61 mmol) of ethyl

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2-[4-(triethylsiloxy)-4-(trifluoromethyl)-2,5-cyclohexadienylidene]propionate (6) in 10 mL of 10% water–90% tetrahydrofuran. The resulting mixture was heated at 70 °C for 1 h, allowed to cool to room temperature, and filtered. The filter cake was washed with tetrahydrofuran. Concentration of the combined filtrates gave a residue, which was poured into 20 mL of 1 N HCl. The aqueous mixture was extracted with three 10-mL portions of diethyl ether. Combination, drying ($MgSO_4$), and concentration of the organic layers gave a residue, which was purified by PTLC (two 2-mm plates eluted with 50% dichloromethane–50% petroleum ether) to give 97 mg (65% yield) of ethyl 2-[4-(trifluoromethyl)phenyl]propionate (7) as a colorless liquid: ^1H NMR ($CDCl_3$) δ 1.21 (t, 3 H, J = 8 Hz), 1.51 (d, 3 H, J = 7 Hz), 3.78 (q, 1 H, J = 7 Hz), 4.12 (m, 2 H), 7.42 (d, 2 H, J = 8 Hz), 7.59 (d, 2 H, J = 8 Hz); ^{19}F NMR ($CDCl_3$) δ -63.0 (s); high-resolution mass spectrum calcd for $C_{12}H_{13}F_3O_2$ 246.0876, found 246.0873.

The following compounds (12a,b) were prepared by similar procedures.

Ethyl 2-[4-(perfluorohexyl)phenyl]propionate (12a): 91% yield; pale yellow oil; ^1H NMR ($CDCl_3$) δ 1.23 (t, 3 H, J = 7 Hz), 1.53 (d, 3 H, J = 8 Hz), 3.78 (q, 2 H, J = 7 Hz), 4.15 (m, 1 H), 7.45 (d, 2 H, J = 9 Hz), 7.75 (d, 2 H, J = 9 Hz); ^{19}F NMR ($CDCl_3$) δ -80.99 (t), -110.66 (m), -122.00 (br s); -122.25 (br s), -123.30 (br s), -126.48 (m); IR (neat) 2985, 1737, 1617, 1240, 1146, 1019, 837, 807, 745, 695 cm^{-1}; high-resolution mass spectrum calcd for $C_{17}H_{13}O_2F_{13}$ 496.0708, found 496.0713.

Ethyl 2-[4-(perfluorooctyl)phenyl]propionate (12b): 85% yield; pale yellow oil; ^1H ($CDCl_3$) δ 1.22 (t, 3 H, J = 7 Hz), 1.53 (d, 3 H, J = 8 Hz), 3.78 (q, 1 H, J = 7 Hz), 4.15 (m, 2 H), 7.45 (d, 2 H, J = 10 Hz), 7.56 (d, 2 H, J = 10 Hz); ^{19}F NMR ($CDCl_3$) δ -81.33 (t), -111.09 (m), -121.64 (br s), -122.43 (br s), -123.28 (br s), -126.62 (br s); IR (neat) 2985, 2938, 1737, 1616, 1421, 1369, 1298, 1209, 1151, 1026, 705, 656, 561 cm^{-1}; high-resolution mass spectrum calcd for $C_{19}H_{13}O_2F_{17}$ 596.0644, found 596.0610.

2-[4-(Trifluoromethyl)phenyl]propionic Acid (8). A mixture of 1.0 g (4.0 mmol) of ethyl 2-[4-(trifluoromethyl)-phenyl]propionate (7), 5 mL of 1 N sodium hydroxide, and 5 mL of ethanol was heated at reflux for 1 h and poured into 30 mL of 1 N HCl. The resulting aqueous mixture was extracted with three 10-mL portions of dichloromethane. Combination, drying ($MgSO_4$), and concentration of the organic layers afforded 0.86 g (95% yield) of 2-[4-(trifluoromethyl)phenyl]propionic acid (8) as a white solid. An analytical sample was obtained by recrystallization from hexane: mp 56–58 °C; ^1H NMR ($CDCl_3$) δ 1.53 (d, 3 H, J = 9 Hz), 3.81 (q, 1 H, J = 9 Hz), 7.44 (d, 2 H, J = 11 Hz), 7.60 (d, 2 H, J = 11 Hz); ^{13}C NMR ($CDCl_3$) δ 18.0 (o), 45.2 (o), 125.6 (o), 125.6 (o), 128.1 (o), 130.0 (o), 143.5 (e), 179.9 (e); ^{19}F NMR ($CDCl_3$) δ -63.2 (s); IR (KBr) 2963, 1712, 1619, 1419, 1327, 1264, 1232, 1166, 1124, 1072, 1019, 843 cm^{-1}; high-resolution mass spectrum calcd for $C_{10}H_9O_2F_3$ 218.0555, found 218.0556. Anal. Calcd C, 55.06; H, 4.16. Found: C, 55.05; H, 4.16.

The following compounds (13a,b) were prepared by similar procedures.

2-[4-(Perfluorohexyl)phenyl]propionic acid (13a): 95% yield; white solid; mp 61–62 °C (dichloromethane); ^1H NMR ($CDCl_3$) δ 1.55 (d, 3 H, J = 7 Hz), 3.83 (q, 1 H, J = 7 Hz), 7.47 (d, 2 H, J = 8 Hz), 7.56 (d, 2 H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 17.6 (o), 44.7 (o), 126.7 (o), 126.8 (o), 126.9 (o), 127.5 (o), 143.3 (e), 179.1 (e); ^{19}F NMR ($CDCl_3$) δ -81.25 (t), -111.10 (m), -122.00 (br s), -122.30 (br s), -123.20 (br s), -126.50 (br s); IR (neat) 2925, 1710, 1620, 1520, 1460, 1420, 1360, 1290, 1220, 1200, 1140, 795, 565, 536 cm^{-1}; high-resolution mass spectrum calcd for $C_{15}H_9O_2F_{13}$ 468.0395, found 468.0433. Anal. Calcd: C, 38.48; H, 1.94. Found: C, 38.70; H, 1.89.

2-[4-(Perfluorooctyl)phenyl]propionic acid (13b): 94% yield; white solid; mp 89–90 °C (dichloromethane–methanol); ^1H NMR ($CDCl_3$) δ 1.55 (d, 3 H, J = 7 Hz), 3.82 (q, 1 H, J = 7 Hz), 7.47 (d, 2 H, J = 9 Hz), 7.57 (d, 2 H, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 18.1 (o), 45.2 (o), 127.2 (o), 127.3 (o), 127.4 (o), 143.8 (e), 179.3 (e); ^{19}F NMR ($CDCl_3$) δ -81.36 (t), -111.17 (m), -121.56 (br s), -122.51 (m), -123.48 (br s), -126.72 (br s); IR (neat) 2990, 2940, 1690, 1418, 1300, 1225, 1195, 1140, 860, 805, 560 cm^{-1}; high-resolution mass spectrum calcd for $C_{17}H_9O_2F_{17}$ 568.0331, found 568.0331. Anal. Calcd: C, 35.93; H, 1.60. Found: C, 36.32; H, 1.56.

Registry No. 4, 120120-28-7; 6, 134904-84-0; 7, 134904-85-1; 8, 134904-86-2; 9a, 114934-90-6; 9b, 114934-91-7; 10a, 134904-87-3; 10b, 134904-88-4; 11a, 134904-89-5; 11b, 134904-90-8; 12a, 134904-91-9; 12b, 134904-92-0; 13a, 134904-93-1; 13b, 134904-94-2; $C_6F_{13}I$, 355-43-1; $C_8F_{17}I$, 507-63-1; $(EtO)_2POCH(Me)CO_2Et$, 3699-66-9; 1,4-benzoquinone, 106-51-4.

Supplementary Material Available: ^1H NMR data for compounds 6, 7, 9a, 9b, 10a, 10b, 11a, 11b, 12a, and 12b (10 pages). Ordering information is given on any current masthead page.

S–S Bond Formation Reaction Using Bis(1-methyl-1*H*-tetrazol-5-yl) Disulfide

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Bis(1-methyl-1*H*-tetrazol-5-yl) disulfide 1 displays extraordinarily high reactivity to nucleophiles, and its reaction with thiols gives disulfides and 1-methyl-1*H*-tetrazole 5-thiol (NMTT).[1] 1 was also found to be a useful reagent for the geometrical isomerization of *Z* olefins to *E* ones in nonpolar solvents.[2] During the isomerization reaction, 1 is considered to dissociate thermally and generate the tetrazolylthio radical (TetS•), which leads to thermal isomerization in a manner similar to the isomerization by iodine.[3] The disulfide–thiol exchange reaction between 1 and dithiothreitol (DTT) was reported to give cyclic disulfide 3 and NMTT via the hypothetical intermediate 2 by intramolecular second disulfide formation as shown in Scheme I.

Our interest was focused on the formation of the unsymmetrical disulfide bond using 1 because the new S–S bond formation is a very significant class of reactions[4] in the synthesis of biologically active compounds,[5] such as atrial natriuretic peptides (ANP).[6] We tried to isolate acyclic A corresponding to the hypothetical intermediate 2 and examine the character of A. Described herein is the application of 1 to the preparation of versatile monotetrazolyl disulfides A, which were found to be useful for the synthesis of unsymmetrical disulfides B as well as symmetrical ones C possessing groups sensitive to other disulfide-forming reagents, such as iodine (Scheme II).

Preparation of Mixed Disulfides 6. Disulfide 1 was prepared in high yield by two-phase oxidation (CH_2Cl_2–H_2O) with $KHCO_3$–Br_2,[7] because 1 decomposed gradually on dissolution in H_2O. The usual oxidation method using $FeCl_3$ or other reagents in an aqueous solution gave mod-

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