Tetramethyl 1,1,4,4-Cyclohexanetetracarboxylate: Preparation and Conversion to Key Precursors of Fluorinated, Stereochemically Defined Cyclohexanes[1]

Charles R. Davis, Dale C. Swenson, and Donald J. Burton*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242

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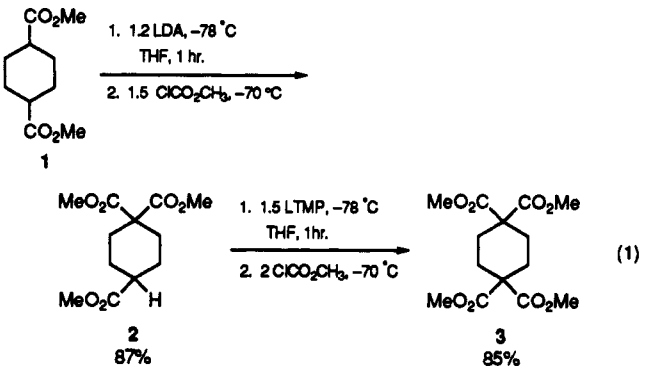
Stereoselective low-temperature diisobutylaluminum hydride (DIBALH) reduction of the title tetraester **3** affords *trans*-1,4-dialdehyde **4a** as the major product. Fluorination of **4a,b**, followed by additional elaboration leads to novel, 1,1,4,4-tetrasubstituted cyclohexanes bearing *trans*-1,4-difluoromethyl and fluoromethyl groups. The effect of ring size and number of ester substituents on the outcome of the reduction has been examined and treatment of dimethyl 1,1-cycloalkyl diesters **7a–c** with excess DIBALH results in reduction of only one ester group. An entry into *trans*-1,4-trifluoromethylated tetrasubstituted cyclohexanes has been gained through stereoselective SF_4 fluorination of 1,1,4,4-cyclohexanetetracarboxylic acid **17**. Stereochemical assignments are supported by X-ray crystallographic data.

Introduction

Cyclohexanes with fluorinated methyl groups in the 1,1,4,4-positions are previously unreported and lack of synthetic methodology for their preparation has hampered investigation of their biological properties. The unique biological properties[2] that result from selective incorporation of fluorinated moieties into an organic molecule are well-known and fluorinated methyl groups have been utilized in anesthetic agents,[3] in bioactive carbohydrates for mechanism probes,[4] in analogs of Vitamin D_3,[5] and as substituents in agrochemicals.[2] We report herein the successful preparation of a series of symmetrical and stereochemically defined 1,1,4,4-tetrasubstituted cyclohexanes containing trifluoromethyl, difluoromethyl, and fluoromethyl groups. This series of target molecules has been augmented by the high-yield synthesis of a number of non-fluorinated and partially-fluorinated *trans* intermediates which should find further application in the construction of other selectively fluorinated systems.

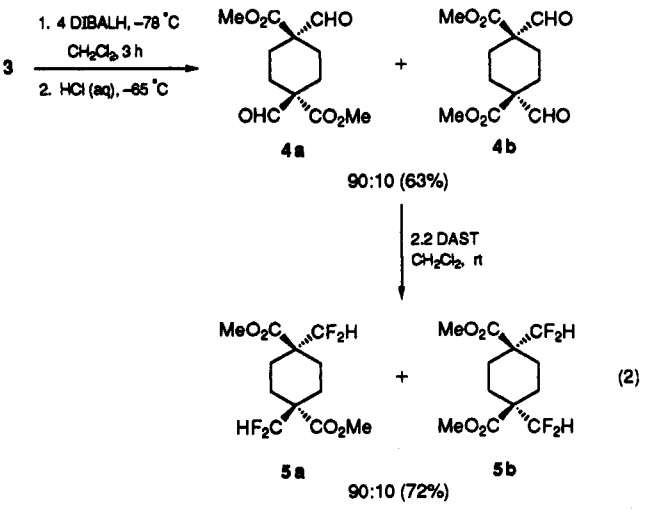
Results and Discussion

Our most straightforward and successful approach has been based on the preparation of non-fluorinated 1,1,4,4-functionalized cyclohexyl precursors followed by known fluorination methods. The unreported tetramethyl 1,1,4,4-cyclohexanetetracarboxylate (**3**) was prepared as outlined *via* consecutive enolate reactions (eq 1). An enolate of the triester, generated by the hindered lithium 2,2,6,6-tetramethylpiperidide (LTMP) base, was quenched with excess CH_3OCOCl to afford tetraester **3**. Only the hindered LTMP facilitated a successful second enolate reaction, and utilization of LDA or $(Me_3Si)_2NLi$ to prepare **3** from **2** resulted only in recovered triester **2**. Presumably, the enolate anion of triester **2** is a poor, hindered nucleophile



which is quenched by HCl formed from faster reaction of the conjugate acid of the amine base with the acyl chloride. The hindered piperidide base apparently reacts more slowly with the acyl chloride and thus allows the enolate to successfully compete for the acyl chloride. Though other tetraesters containing a mixture of Me, Et, and allyl ester groups were prepared, **3** is insoluble in hexane and easily purified by trituration. The symmetry of **3** also simplifies the outcome of the subsequent DIBALH reduction.

In a key transformation, **3** undergoes stereoselective low-temperature reduction with excess DIBALH to afford predominantly *trans*-1,4-dialdehyde **4a** (eq 2). Byprod-



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(3) Larsen, R. E. *Fluorine Chemistry Reviews*; Marcel Dekker Inc.: New York, 1969; Vol. 3, pp 1–44..

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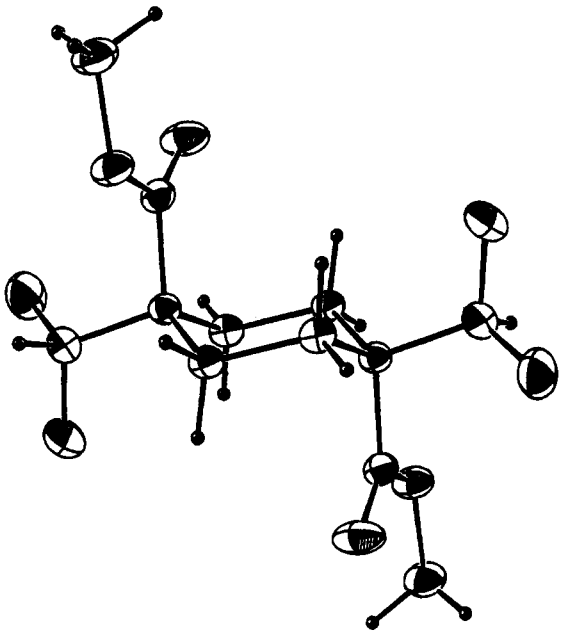
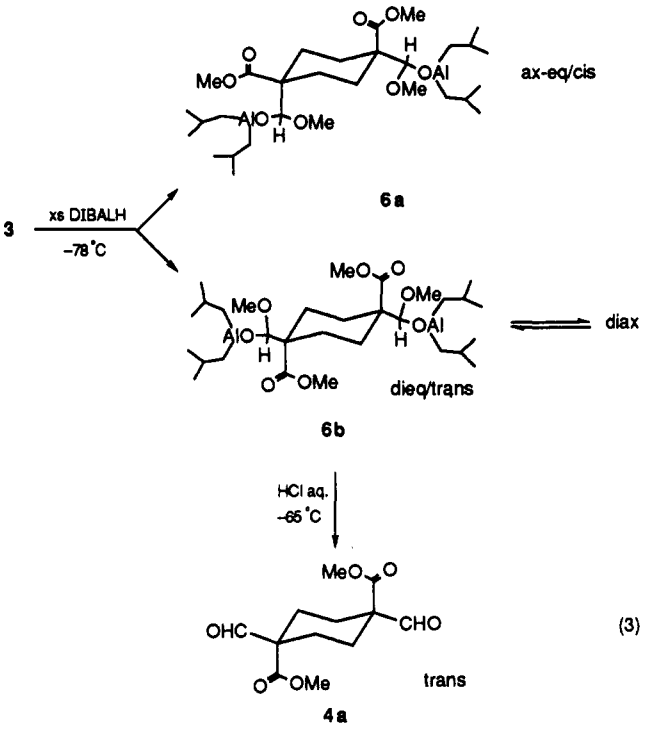


Figure 1. ORTEP diagram of **5a**.

ucts containing more than two aldehyde groups were not detected and it should be noted that excess DIBALH (4.0 equiv) reproducibly converted *two* ester groups to their aldehyde functions. Reductions carried out with 2.5–3.0 equiv of DIBALH often resulted in minor amounts of **3** and the product containing only one reduced ester group, which complicated purification. We were unable to resolve the isomeric mixture of **4a** and **4b**. In addition, these isomers are not readily distinguishable by NMR spectroscopy, and signals (^{1}H, ^{13}C) for the minor isomer appeared only as slightly resolvable shoulders on the signals attributed to the major isomer. (Diethylamido)sulfur trifluoride (DAST) was used to convert **4a** and **4b** to difluoromethylated isomers **5a** and **5b**. DAST treatment of ring substituents has been shown to occur with retention of stereochemistry.[6] Carbon–carbon bond breakage does not occur with simple carbonyl substrates upon treatment with DAST, and rearrangements occur only when substrate structure and solvent polarity favor this.[7] Consequently, an isomeric mixture of **5a,b** reflects the isomeric ratio in the starting dialdehyde. Unlike **4a** and **4b**, difluoromethylated derivatives **5a** and **5b** each give rise to a distinct set of ^{1}H, ^{13}C, and ^{19}F NMR signals. Furthermore, the majority (75%) of *trans*-**5a** was separated (>99% *trans*) from the minor *cis* isomer on the basis of its insolubility in diethyl ether. The corresponding *cis* isomer has been obtained in an enriched but not isomerically pure form (3:2 cis/trans). X-ray analysis of the recrystallized major isomer **5a** has confirmed the *trans* stereochemistry (Figure 1).[8]

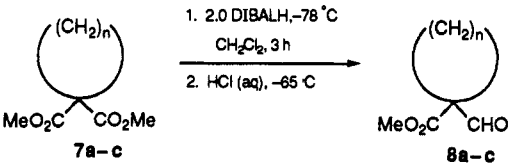
Stereoselectivity in the DIBALH reduction is most likely a result of steric preference for the low-temperature diequatorial bis-alane intermediate **6b**, which should be more sterically relieved than its axial/equatorial counterpart **6a** (eq 3).

The alane substituents presumably act as blocking groups, preventing reduction of the remaining ester groups.



(3)

Intramolecular coordination of the alane group to the remaining ester carbonyl might also enhance this steric effect. Despite the well-known utility of DIBALH in organic synthesis,[9] to our knowledge, this is the first report of its use as a reagent for low temperature monoreduction of cycloalkyl geminal diesters. Similar treatment of 1,1-diester **7a** and two substrates of lower ring size (**7b,c**) resulted only in monoreduction, and the procedure can be considered a useful alternative to known methods for α-formylation of carboxylic esters. Tanimoto and co-



(4)

a, n = 5 76 %
b, n = 4 70 %
c, n = 3 52 %

workers have prepared **8a,b** in high yield by reaction of ketene silyl acetals with ethyl orthoformate followed by hydrolysis.[10] Condensation of carboxylic esters with alkyl formates in the presence of NaH suffers from side reactions.[11] Other methods include Vilsmeier formylation of ketene silyl acetals[12] and hydrolysis of aminocyanomethylated ketene silyl acetals.[13] The latter two methods result in modest yields and one requires the preparation of an additional reagent. Like ketene silyl acetals, geminal diesters are readily accessible; the reduction is convenient, gives good yields, and utilizes the inexpensive, commercially available DIBALH. More importantly, none of the

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(8) Detailed X-ray crystallographic data for **5a**, **14**, and **24** will be published (*Acta Crystallogr.*).

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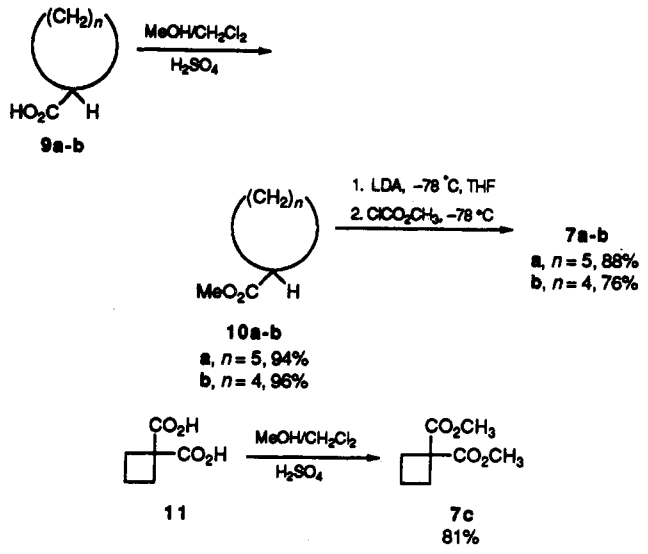
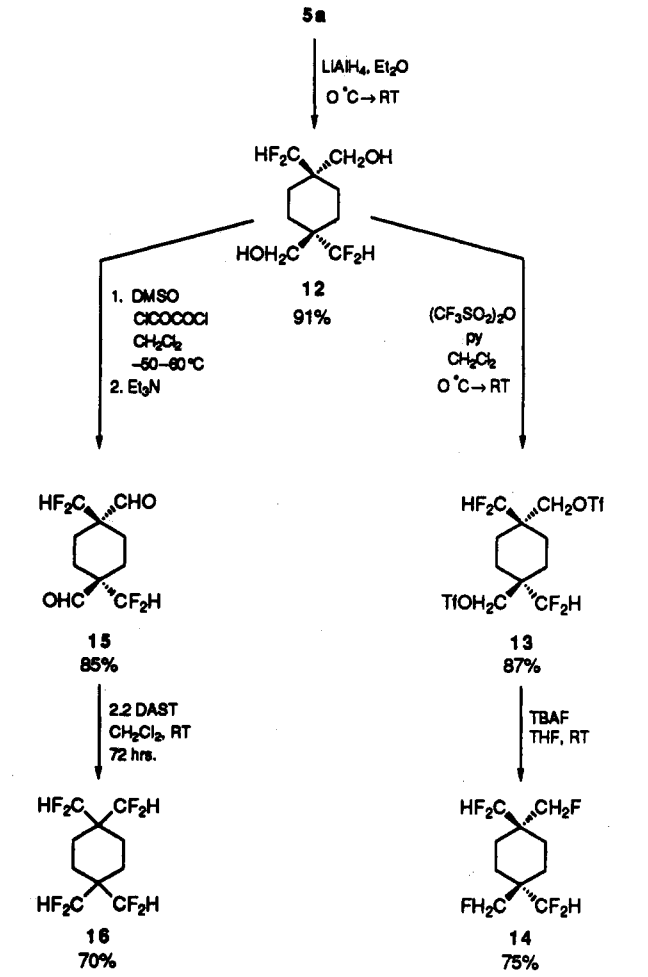
Scheme I



Scheme II



cited methods have been extended to 1,4-stereoselectivity in cyclohexyl substrates.

Preparation of the requisite diesters **7a,b** was adapted from work described by Japanese workers,[14] and simple methanolysis of acids yielded **7c** and **10a,b** (Scheme I). Diesters **7a–c** have been reported by Perkin–Markovnikov reactions using dimethyl malonate and a corresponding

(14) Tsuji, J.; Yamada, T.; Minimi, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.*, **1987**, *52*, 2998.

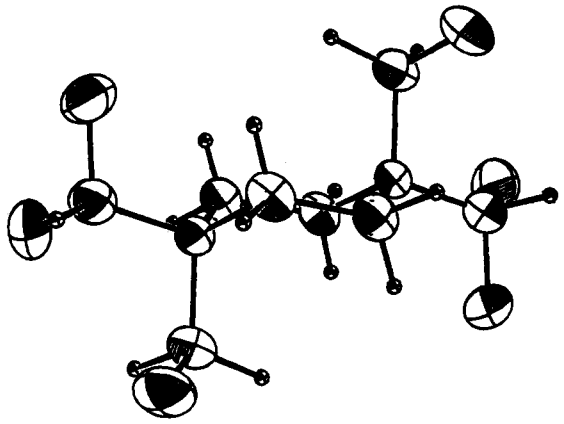


Figure 2. ORTEP diagram of **14**.

dihaloalkane. These reactions have been classically initiated by sodium ethoxide[15] and more recently by electrogenerated superoxide ion.[16] In the latter case the products were not purified; only GC yields were reported and structure identity was established by comparison to authentic samples prepared by the sodium ethoxide method. The method used herein is convenient and produces comparable yields.

The utility of *trans*-dialdehyde **4a** has been demonstrated by its conversion to **5a**, which was subsequently extended to other intermediates having defined stereochemistry. Isomerically pure diester **5a** was refunctionalized as outlined (Scheme II) resulting in a useful preparation of isomerically pure *trans*-fluoromethylated **14** and the symmetrical tetrakis-difluoromethylated derivative **16**. X-ray analysis has confirmed the *trans* stereochemistry of **14** (Figure 2). An attempt to convert **5a** directly to aldehyde **15** at low temperature *via* DIBALH reduction failed and the starting material was recovered. A reduction–Swern oxidation[17] sequence, however, provided **15** in high yield. DAST fluorinations of alcohols and carbonyl groups adjacent to fluorinated groups are sluggish at best, and although the slow conversion of **15** to **16** proceeds to completion, the trifluoromethylated analog **25** failed to react with DAST. The hazards posed by DAST at elevated temperatures limit the ability to force these reactions;[18] furthermore, 1,4-diols lack solubility in solvents amenable with the DAST reagent. We therefore used trifluoromethanesulfonic anhydride to both dissolve and transform[19] diol **12** to its triflate **13**. Cleavage of the triflate with tetrabutylammonium fluoride (TBAF) resulted in the target derivative **14**.

Saponification of **3** yields tetraacid **17** in high yield (Scheme III). This tetraacid has not been previously reported and a useful preparation has been developed. In another key transformation, SF_4 treatment of **17** results in stereoselective *trans*-trifluoromethylation (≥97:3 trans/cis), and the resultant **18** provides an entry into a variety of *trans* intermediates and derivatives containing trifluoromethyl groups. Acyl fluoride products **18** and **19** were not separated but $LiAlH_4$ reduction allowed the separation of **20** from **21** on the basis of solubility (≥95%), and further

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(16) Ojima, F.; Osa, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3187.
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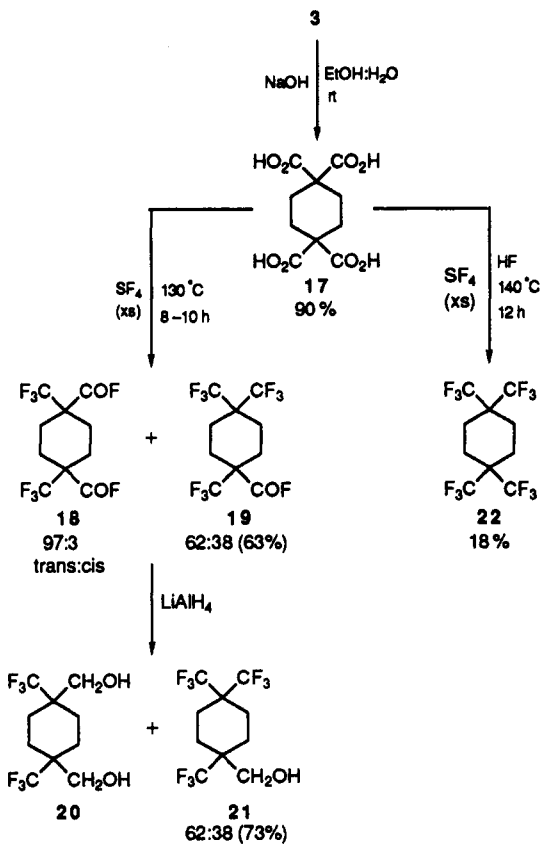
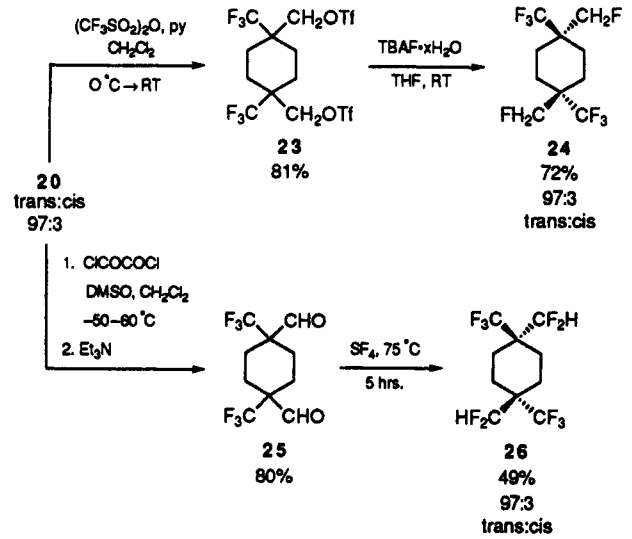
(18) Middleton, W.; Messina, P.; Mange, K. *J. Fluorine Chem.*, **1989**, *42*, 137.
(19) Beard, C. D.; Baum, K.; Grakauskas, V. *J. Org. Chem.* **1973**, *38*, 21, 3673.

Scheme III



Scheme IV



purification was carried out by column chromatography. By analogous procedures, diol **20** was refunctionalized as outlined (Scheme IV), and target derivatives **24** and **26** were isolated in high isomeric purity (>97% trans). X-ray analysis has confirmed the *trans* stereochemistry of **24** (Figure 3).

Geminal dicarboxylic acids have been reported to undergo complete trifluoromethylation in the presence of excess SF_4 only under forcing conditions.[20,21] Utilization of HF in the more difficult fluorinations has been reported[22] and facilitated the preparation of symmetrical, tetrakis-trifluoromethylated **22**, albeit in low yield.

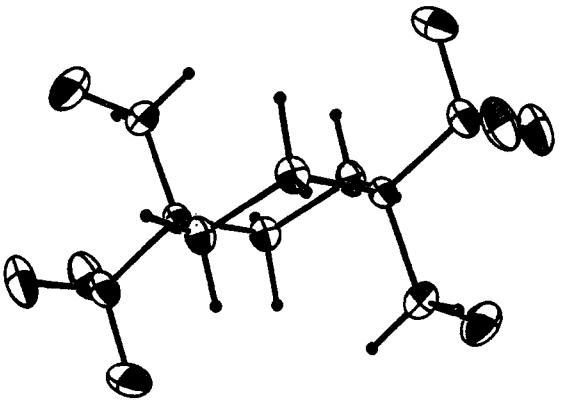


Figure 3. ORTEP diagram of **24**.

Conclusion

Methodology based on fluorination of cyclohexyl precursors has been developed for the preparation of 1,1,4,4-substituted cyclohexanes bearing CF_3, CF_2H, and CH_2F groups, and their biological properties can now be investigated. A *trans*-stereoselective DIBALH reduction and a *trans*-stereoselective SF_4 trifluoromethylation have allowed preparation of the tetrasubstituted cyclohexanes to be carried out with a high degree of stereoselectivity. Treatment of cycloalkyl geminal diesters of lower ring size with excess DIBALH has resulted in reduction of only one ester group and represents a useful alternative to known methods for the preparation of α-formylated cycloalkylcarboxylic esters. The series of flourinated target molecules has been augmented by the high yield synthesis of a number of non-fluorinated and partially-fluorinated *trans* intermediates which should find further application in the construction of other selectively fluorinated bioactive molecules.

Experimental Section

General Procedures. All glassware was oven-dried at 80 °C prior to use. All boiling points are uncorrected. ^{19}F, ^1H, and $\{^1H\}^{13}C$ NMR spectra were recorded on a 300-MHz multinuclear spectrometer. All chemical shifts are reported in parts per million downfield (positive) of the standard. ^{19}F NMR spectra are referenced against internal $CFCl_3$, and ^1H and ^{13}C NMR against internal TMS. Except where noted, NMR spectra were obtained in $CDCl_3$. Except where noted, FTIR were recorded as CCl_4 solutions. All mass spectral analyses were performed at 70 eV in the electron impact mode. GLPC analyses were performed on a 5% OV-101 column with a thermal conductivity detector. Elemental analyses were performed by Schwarzkopf Microanalytical Lab., Inc., Woodside, NY.

Materials. Dimethyl 1,4-cyclohexanedicarboxylate (**1**) (cis/trans mixture), acids **9a,b**, acid **11**, 2,2,6,6-tetramethylpiperidine, tetrabutylammonium fluoride hydrate, methyl chloroformate, diisobutylaluminum hydride (1.0 M CH_2Cl_2 solution), $LiAlH_4$, and oxalyl chloride were obtained from Aldrich Chemical Co. and used without further purification. (Diethylamido)sulfur trifluoride (DAST) was obtained from PCR and sulfur tetrafluoride was obtained from Matheson Gas Products. Trifluoromethanesulfonic anhydride was prepared from CF_3SO_3H according to the literature procedure.[23] *n*-Butyllithium (2.5 M *n*-hexane solution) was obtained from Aldrich, and its concentration was periodically determined by Duhamel's titration procedure (method B).[24]

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(21) Dmowski W.; Kolinski R. *Pol. J. Chem.*, **1978**, *52*, 1, 71–85.
(22) Kunshenko, B. V.; Burmakov, A. I.; Alekseeva, L. A.; Lumanov, V. G.; Yagupol'skii, L. M. *J. Org. Chem. USSR (Engl. Transl.)* **1974**, *10*, 896.
(23) Burdon, J.; Farazmand I.; Stacey, M.; Tatlow, J. C. *J. Chem. Soc.* **1957**, 2574.

Representative Procedure for Preparation of Geminal Esters 2, 3, and 7a,b. Trimethyl 1,1,4-Cyclohexanetricarboxylate (2). A three-necked, 500-mL round-bottomed flask equipped with a magnetic stir bar, low-temperature thermometer, pressure-equalizing addition funnel and N_2 tee, was charged with 250 mL of dry THF and 26.6 g (263 mmol/37 mL) of diisopropylamine. The stirred solution was cooled to approximately −20 °C *via* dry ice/isopropyl alcohol (IPA) bath, and then 263 mmol *n*-BuLi (2.5 M in hexanes, 210 mL) was added dropwise, maintaining the internal temperature at or below 0 °C. The resultant solution was stirred at 0 °C for 10 min and then cooled to −78 °C. A solution of 1,4-dimethylcyclohexanedicarboxylate (1) (45.2 g, 219 mmol) in 50 mL of THF was then slowly added dropwise *via* the addition funnel, maintaining the temperature below −68 °C. The enolate solution was stirred an additional 1 h at −78 °C after which a solution of $ClCO_2Me$ (31.0 g, 329 mmol) in 30 mL of THF was slowly added dropwise, maintaining the temperature below −68 °C. After addition was complete, the solution was allowed to warm to room temperature with continued stirring. For workup, the reaction mixture was transferred to a 2-L separatory funnel, diluted with 350 mL CH_2Cl_2, and washed consecutively with 200 mL of aqueous NH_4Cl and 200 mL of brine. The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude residue was then distilled through a short-path apparatus at reduced pressure. A forerun of $(^iPr)_2NCO_2Me$ amide byproduct was collected at 50–70 °C/1.5 mmHg followed by collection of 49.2 g (87%) of **2**, bp 145 °C (0.25 mmHg). Alternatively, **2** may be purified by column chromatography (hexane/EtAc 80:20, R_f = 0.35): ^1H NMR 1.6–2.4 (m, 9 H), 3.65 (s, 3 H), 3.70 (s, 3 H), 3.75 (s, 3 H); ^{13}C NMR 175.4, 172.4, 171.2, 54.1, 41.4, 30.2, 25.1, 52.7, 52.6, 51.7; GCMS *m/e* 258 (M^+, 0.03), 227 (10.7), 226 (31.2), 199 (7.6), 198 (18.6), 194 (16.2), 166 (57.9), 59 (37.2); IR 1736 (s), 2953 (s), 1453 (m), 1435 (m), 1242 (s), 1171 (s), 805 (s), 774 (s) cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.03. Found: C, 56.04; H, 7.32.

Tetramethyl 1,1,4,4-Cyclohexanetetracarboxylate (3). Similarly, **3** was prepared according to the general procedure using 23.0 g (163.0 mmol) of 2,2,6,6-tetramethylpiperidine in 250 mL of THF, 163 mmol of *n*-BuLi, a solution of **2** (28.0 g, 109 mmol) in 40 mL of THF, and a solution of $ClCO_2Me$ (19 mL, 244 mmol) in 20 mL of THF. After analogous workup, the crude, hexane-insoluble product was triturated with 3 × 50 mL portions of hexane. Drying the solid residue under vacuum yielded 29.6 g (85%) of **3**: mp 145 °C; ^1H NMR 2.1 (s, 2H) 3.7 (s, 3H); ^{13}C NMR 27.7, 53.7, 52.7, 171.5; GCMS, *m/e* 300 (0.2), 285 (6.7), 284 (21.9), 252 (34.3), 196 (20.3), 257 (2.5), 59 (100.0); IR 2953 (w), 1738 (s), 1434 (s), 1249 (s), 1218 (s), 1174 (m), 1080 (s). Anal. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37. Found: C, 53.46; H, 6.36.

Dimethyl 1,1-Cyclohexanedicarboxylate (7a). Similarly, **7a** was prepared according to the general procedure using 19.3 g (136 mmol) of **10a**, 150 mL of THF, 20.6 g $(^iPr)_2NH$ (203 mmol), 205 mmol of *n*-BuLi, and 19.4 g (205 mmol) of $ClCO_2Me$: yield 23.9 g (88%); bp 97 °C (2.5 mmHg); GC > 99%; ^1H NMR 1.5 (m, 6H), 2.0 (m, 4H), 3.7 (s, 6H); ^{13}C NMR 25.3, 22.9, 31.5, 55.1, 52.4, 172.4; GCMS *m/e* 200 (M^+, 0.2), 185 (0.2), 169 (6.5), 81 (100.0), 59 (21.8); IR 2951 (m), 2858 (w), 1735 (s), 1453 (w), 1434 (w), 1243 (s), 1136 (m). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.17; H, 8.13.

Dimethyl 1,1-Cyclopentanedicarboxylate (7b). Similarly, **7b** was prepared according to the general procedure using 5.1 g (40 mmol) of **11b**, 60 mL of THF, 6.1 g of $(^iPr)_2NH$ (60 mmol), 60 mmol of *n*-BuLi, and 5.7 g (60 mmol) of $ClCO_2Me$: yield 5.22 g (76%); bp 102 °C (10 mmHg); GC > 99%; ^1H NMR 1.7 (m, 4H), 2.2 (m, 4H), 3.7 (s, 6H); ^{13}C NMR 25.3, 34.5, 52.4, 60.2, 173.0; GCMS *m/e* 187 (M^+ + 1, 0.1), 155 (15.8), 145 (67.9), 126 (54.2), 113 (41.6), 95 (60.0), 67 (100.0), 59 (39.9); IR 2953 (m), 2928 (w), 2876 (w), 1736 (s), 1434 (w), 1266 (s), 1159 (m); HRMS calcd for $C_8H_{11}O_3^{+\cdot}$ ($M^{+\cdot}$ − OCH_3) 155.0708, obsd 155.0702.

Representative Procedure for Methanolysis of Carboxylic Acids 9a,b and 11. Methyl Cyclohexanecarboxylate (10a). Methanolysis was carried out analogous to a literature procedure described for similar aliphatic acid substrates.[25] A 1-L, three-necked flask equipped with a magnetic stir bar and cold water condenser was charged with 128.5 g (1.0 mol) of cyclohexanecarboxylic acid (**9a**), 96.0 g (3.0 mol) of MeOH, 300 mL of CH_2Cl_2, and 4 mL of concd H_2SO_4. The mixture was stirred and refluxed for 15 h. For workup, the mixture was cooled to room temperature and transferred to a 1-L separatory funnel, washed consecutively with 300-mL portions of water, with aqueous $NaHCO_3$, and again with water. The aqueous layers were combined and extracted with 150 mL of CH_2Cl_2. The organic layers were combined and dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The product residue was distilled through a 10-cm column (186 °C) under N_2: yield 133.4 g (94%); GC > 99%; ^1H NMR 1.2–1.5 (m, 5H), 1.7 (m, 3H), 1.9 (m, 2H), 2.3 (tt, 1H, J = 11.2, 3.7 Hz), 3.65 (s, 3H); ^{13}C NMR 25.6, 25.9, 29.1, 43.2, 51.4, 176.5; GCMS *m/e* 142 (M^+, 9.5), 127 (2.9), 111 (8.8), 112 (8.8), 59; IR 2936 (s), 2857 (m), 1736 (s), 1452 (w), 1248 (m), 1170 (m), 1041 (w).

Methyl Cyclopentanecarboxylate (10b). Similarly, **10b** was prepared according to the general procedure using 5.0 g (44 mmol) of **10a**, 4.2 g of MeOH (130 mmol), 40 mL of CH_2Cl_2, and 1 mL of concd H_2SO_4. Distillation through a 6-cm column yielded 5.37 g (96%) of **10b**: bp 150 °C; GC > 99%; ^1H NMR 1.5–2.0 (m, 8H), 2.7 (pentet, 1H, J = 9.0 Hz), 3.7 (s, 3H); ^{13}C NMR 25.7, 29.9, 43.6, 51.5, 177.2; GCMS *m/e* 128 (M^+, 6.3), 113 (0.5), 97 (15.6), 87 (100.0), 69 (43.2); IR 2952 (s), 2873 (m), 1734 (s), 1436 (w), 1165 (s), 1140 (s).

Dimethyl 1,1-Cyclobutanedicarboxylate (7c). Similarly **7c** was prepared according to the general procedure using 5.0 g of **11** (35 mmol), 6.9 g (210 mmol) of MeOH, 63 mL of CH_2Cl_2, and 1 mL of concd H_2SO_4. Distillation through a 6-cm column yielded 4.86 g (81%) of **7c**: bp 122 °C (55 mmHg); GC > 99%; ^1H NMR 2.0 (pentet, 2H, J = 7.1 Hz), 2.6 (t, 4H, J = 7.1 Hz), 3.8 (s, 6H); ^{13}C NMR 16.2, 28.9, 52.6, 172.3; GCMS *m/e* 173 (M^+ + 1, 0.1), 172 (M^+, 0.1), 141 (27.4), 113 (100.0), 108 (83.7), 81 (41.5), 59 (62.6); IR 3001 (m), 2953 (m), 1732 (s), 1435 (s), 1273 (s), 1200 (m), 1108 (s). Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.78; H, 7.18.

Representative Procedure for DIBALH Reduction of Esters 3 and 7a–c. Preparation of Dimethyl 1,4-Diformyl-1,4-cyclohexanedicarboxylate (4a,b). A 100-mL three-necked flask equipped with a low-temperature thermometer, magnetic stir bar, pressure-equalizing addition funnel, and N_2 tee was charged with 3.16 g (10.0 mmol) **3** and 40 mL of CH_2Cl_2. The solution was cooled to −78 °C *via* dry ice/IPA bath, and 40 mmol DIBALH (40 mL, 1.0 M in CH_2Cl_2) was added dropwise maintaining the temperature below −65 °C. The solution was stirred at −78 °C for an additional 3 h. The mixture was then quenched by slow addition of 8 mL of saturated NH_4Cl followed by slow addition of 10 mL of 4% HCl; each addition was carried out at ≤−65 °C. The mixture was allowed to warm to rt and filtered by water aspiration, and the white solids were rinsed with 150 mL of CH_2Cl_2. The organic filtrate was washed with 50 mL of water, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The residue was further purified by silica gel chromatography (CH_2Cl_2 eluent) to yield 1.65 g (63%) of isomeric **4a,b** as a white, waxy solid: mp 87–88 °C; ^1H NMR 2.0 (m, 4H), 3.8 (s, 3H), 9.6 (s, 1H); ^{13}C NMR 24.4, 198.1, 58.0, 170.8, 52.8; GCMS *m/e* 228 (6.0, M^+ − CO), 227 (0.5, M^+ − CHO), 196 (56.5), 59 (40.7), 168 (79.1), 136 (47.2), 79 (100.0); IR 2955 (w), 1749 (s), 1726 (s), 1453 (m), 1435 (m), 1260 (m), 1225 (s), 1091 (m). Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29. Found: C, 56.59; H, 6.28.

1-Formyl-1-methylcyclohexanecarboxylate (8a). Similarly, **8a** was prepared according to the general procedure using 4.0 g (20 mmol) of **7a**, 50 mL of CH_2Cl_2, and 40 mmol of DIBALH. Purification by silica gel chromatography (CH_2Cl_2 eluent, R_f = 0.35) yielded 2.6 g (76%) of **8a**: GC > 99%; ^1H NMR 1.5 (m, 6H), 1.8–2.0 (m, 4H), 3.8 (s, 3H), 9.5 (s, 1H); ^{13}C NMR 24.9, 22.1, 28.4, 59.0, 52.2 ,171.6, 199.2; GCMS *m/e* 142 (M^+ − CO, 91.1), 141 (10.8), 139 (10.0), 127 (10.95), 113 (46.3), 111 (15.3), 81 (100.0), 67 (60.2); IR 2940 (m), 2858 (w), 1749 (s), 1725 (s), 1434 (w), 1223 (m), 1140 (w), 1082 (w). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.57; H, 8.44.

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(25) Clinton, R. O.; Laskowski, S. C. *J. Am. Chem. Soc.* **1948**, *7*, 3135.

1-Formyl-1-methylcyclopentanecarboxylate (8b). Similarly, **8b** was prepared according to the general procedure using 4.7 g (25.2 mmol) of **7b**, 50 mL of CH_2Cl_2, and 51 mmol of DIBALH. Purification by silica gel chromatography (CH_2Cl_2/pentane 3:2, R_f = 0.25) yielded 2.76 g (70%) of **8b**: GC > 99%; ^{1}H NMR 1.7 (m, 4H), 2.1 (m, 4H), 3.8 (s, 3H), 9.7 (s, 1H); ^{13}C NMR 25.8, 31.6, 64.9, 52.6, 173.3, 197.7; GCMS *m/e* 128 (M^+ - CO, 84.0), 125 (27.8), 115 (21.6), 100 (73.8), 96 (80.3), 95 (30.9), 87 (74.4), 79 (28.7), 67 (100.0), 59 (23.2); 2954 (m), 2874 (w), 1735 (s), 1750 (m), 1434 (w), 1246 (m), 1166 (w). Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.48; H, 7.74.

1-Formyl-1-methylcyclobutanecarboxylate (8c). Similarly, **8c** was prepared according to the general procedure using 4.25 g (25 mmol) of **7c**, 50 mL of CH_2Cl_2, and 50 mmol of DIBALH. Purification by silica gel chromatography (pentane/EtOAc 80:20, R_f = 0.5) yielded 1.8 g (52%) of **8c**. GC > 99%; ^{1}H NMR 1.7 (m, 4H), 2.1 (m, 4H), 3.8 (s, 3H), 9.7 (s, 1H); ^{13}C NMR 25.8, 31.6, 64.9, 52.6, 173.3, 197.7; GCMS *m/e* 128 (M^+ - CO, 84.0), 125 (27.8), 115 (21.6), 100 (73.8), 96 (80.3), 95 (30.9), 87 (74.4), 79 (28.7), 67 (100.0), 59 (23.2); IR 3000 (w), 2954 (m), 2830 (w), 1749 (s), 1722 (s), 1435 (w), 1280 (m), 1220 (m), 1117 (s); HRMS calcd for $C_6H_{10}O_2^{+\cdot}$ ($M^{+\cdot}$ - CO) 114.0680, obsd 114.0668. Anal. Calcd for $C_7H_{10}O_3$: C, 59.15; H, 7.09. Found: C, 58.50; H, 7.10.

Dimethyl 1,4-Bis(difluoromethyl)-1,4-cyclohexanedicarboxylate (5a,b). A three-necked 100-mL flask equipped with a thermometer, N_2 tee, magnetic stir bar, and cold water condenser was charged with 4.7 g (18 mmol) **4a,b** and 60 mL of CH_2Cl_2. The solution was cooled to 0 °C with an ice bath and 5.7 mL of DAST (6.93 g) was added slowly *via* syringe at 0–5 °C. The solution was allowed to warm to rt and stirred an additional 10 h. For workup the mixture was transferred to a separatory funnel, diluted with 100 mL of CH_2Cl_2, and then washed with 50 mL of aqueous $NaHCO_3$ and 50 mL of water. The organic layer was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The residue was further purified by silica gel chromatography (CH_2Cl_2) to yield 3.95 g (72%) of isomeric **5a,b** as a white solid (trans/cis 90:10). The isomeric **5a,b** was swirled in a flask several times with 10–15 mL of Et_2O, each time decanting the ether-soluble *cis* isomer. The procedure was repeated until the *cis* isomer was no longer detected in the solid portion (2.7 g) by ^{19}F NMR analysis. *Trans* isomer **5a**: mp 103–104 °C; ^{1}H NMR 1.6–2.3 (m, 8H), 3.8 (s, 6H), 5.9 (t, 2H, J_{H-F} = 59.0 Hz); ^{19}F NMR -127.7 (d, J_{F-H} = 56.6 Hz); ^{13}C NMR 23.0, 51.2 (t, $^2J_{C-F}$ = 19.2 Hz), 171.1, 52.7 (s), 117.2 (t, J_{C-F} = 248.2 Hz); GCMS *m/e* 269 (M^+ - MeO, 1.0), 260 (M^+ - 2HF, 0.9), 248 (14.9), 59 (100.0), 189 (4.9), 220 (20.1), 161 (36.4); IR 2955 (w), 1751 (s), 1315 (s), 1218 (s), 1149 (s), 1077 (s), 775 (s). Anal. Calcd for $C_{12}H_{16}F_4O_4$: C, 48.00; H, 5.37; F, 25.31. Found: C, 48.22; H, 5.11; F, 24.95. Minor *cis* isomer **5b**: ^{19}F NMR -125.3 (d, J = 56.7 Hz); ^{1}H NMR 1.9 (m, 8H), 3.7 (s, 6H), 5.7 (t, 2H, J = 59.0 Hz).

***trans*-1,4-Bis(difluoromethyl)-1,4-cyclohexanedimethanol (12).** A three-necked 200-mL flask equipped with N_2 tee, magnetic stir bar, cold-water condenser, and pressure-equalizing addition funnel, was charged with 1.0 g (26 mmol) of $LiAlH_4$ and 75 mL of dry diethyl ether. A solution of 2.8 g (9.6 mmol) of isomerically pure **5a** in 50 mL of dry diethyl ether was placed in the addition funnel and cautiously added dropwise to the stirring $LiAlH_4$ solution. The mixture was stirred at rt for an additional 6–8 h and then quenched by cautious addition (over 30 min) of 10 mL of water followed by slow addition of 5–6 mL of 2 M HCl. The mixture was stirred for 10 min and the ether was decanted away from the white solids into a separatory funnel. The solids were thoroughly extracted with diethyl ether (2 × 100 mL) and the combined organic layers washed (2 × 50 mL) with water, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to yield 2.14 g (91%) diol **12** as a white solid which was used without further purification: mp 138–140 °C; ^{1}H NMR (acetone-d_6) 1.55 (m, 8H), 3.7 (d, 4H, J = 5.1 Hz), 4.0 (t, 2H, J = 5.1 Hz), 5.8 (t, 2H, J = 57.3 Hz); ^{19}F NMR (acetone-d_6) -134.4 (d, J_{F-H} = 58.6 Hz); ^{13}C NMR (acetone-d_6) 19.7, 42.57 (t, $^2J_{C-F}$ = 17.0 Hz), 60.9 ($^3J_{C-F}$ = 4.5 Hz), 120.5 (t, J_{C-F} = 243.0 Hz); GCMS *m/e* 226 (M^+ - H_2O), 206 (0.7), 176 (51.5), 157 (14.9), 148 (19.4), 125 (100.0), 97 (24.5); IR (KBr) 3100–3600 (s), 2956 (m), 2889 (w), 1474 (w), 1098 (s), 977 (s), 665 (m); HRMS calcd. for $C_{10}H_{14}F_4O^{+\cdot}$ ($M^{+\cdot}$ - H_2O) 226.0981, obsd 226.0989. Anal. Calcd for $C_{10}H_{16}F_4O_2$: C, 49.18; H, 6.60; F, 31.12. Found: C, 49.67; H, 6.35; F, 30.69.

***trans*-1,4-Bis(difluoromethyl)-1,4-bis[[[(trifluoromethyl)sulfonyl]oxy]methyl]cyclohexane (13).** A three-necked 100-mL flask equipped with a thermometer, N_2 tee, magnetic stir bar, and pressure-equalizing addition funnel was charged with 20 mL of CH_2Cl_2, 1.48 g (6.06 mmol) of **12**, 1.05 g (13.0 mmol) of pyridine, and cooled to 0 °C. Next, 3.77 g (2.25 mL, 13.35 mmol) trifluoromethanesulfonic anhydride was added slowly *via* syringe, maintaining the temperature at ≤25 °C. The mixture was allowed to warm to rt and stirred an additional 2 h. The mixture was then gravity filtered and the residue rinsed with 25 mL of CH_2Cl_2. The organic layer was washed with 40-mL aliquots of cold (0 °C) 1% HCl and water. The CH_2Cl_2 layer was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to yield the solid crude product. The residue was eluted through a column of silica gel (CH_2Cl_2) to remove any triflate salts, and 2.68 g (87%) **13** was isolated as a white solid: mp 110 °C; ^{19}F NMR (acetone-d_6) -74.8 (s, 3F), -130.3 (d, 2F, J_{F-H} = 55.6 Hz); ^{13}C NMR (acetone-d_6) 20.4 (t, $^3J_{C-F}$ = 3.0 Hz), 42.0 (t, $^2J_{C-F}$ = 18.2 Hz), 75.6 (t, $^3J_{C-F}$ = 3.0 Hz), 119.6 (q, J_{C-F} = 318.7 Hz), 119.3 (t, J_{C-F} = 245.7 Hz); ^{1}H NMR (acetone-d_6) 1.9 (m, 8H), 4.9 (s, 4H), 6.1 (t, 2H, J_{H-F} = 55.6 Hz); IR 2972 (w), 1485 (w), 1460 (w), 1399 (m), 1241 (s), 1140 (m), 949 (s), 850 (m). Anal. Calcd for $C_{12}H_{14}F_{10}O_6S_2$: C, 28.35; H, 2.78; F, 37.37. Found: C, 28.42; H, 2.44; F, 37.03.

***trans*-1,4-Bis(difluoromethyl)-1,4-bis(fluoromethyl)cyclohexane (14).** A three-necked 100-mL flask equipped with a thermometer, N_2 tee, magnetic stir bar, and septum port was charged with 3.2 g (12 mmol) of TBAF·$x$$H_2O$, 40 mL of dry THF, and cooled to 0 °C *via* ice bath. To the stirred solution was added dropwise a solution containing 2.57 g (5.05 mmol) of triflate **13** in 15 mL of THF, maintaining the temperature at or below 25 °C. The resultant mixture was stirred at rt for 6–8 h, the THF was removed by rotary evaporation, and the residue was diluted with excess 1:1 Et_2O/pentane and transferred to a separatory funnel. The organics were then washed with 50 mL of ice-cold 1% HCl, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The residue was passed through a column of silica gel (CH_2Cl_2 eluent, monitored by ^{19}F NMR) to yield 0.94 g (75%) of **14** as a white solid: mp 82 °C; ^{1}H NMR 1.6 (s, 8H), 4.5 (d, 4H, J_{H-F} = 47.1 Hz) 5.7 (t, 2H, J_{H-F} = 56.4 Hz); ^{19}F NMR -133.7 (d, 4F, J_{F-H} = 55.0 Hz), -234.9 (t, 2F, J = 47.7 Hz); ^{13}C NMR 19.6 (bs) 42.3 (td, $^2J_{C-F}$ = 17.2, 17.1 Hz), 82.6 (dt, J_{C-F} = 178.2 Hz, $^3J_{C-F}$ = 4.3 Hz), 118.7 (td, J_{C-F} = 245.4 Hz, $^3J_{C-F}$ = 4.5 Hz); GCMS *m/e* 215 (M - CH_2F^+, 0.1), 197 (M^+ - CF_2H, 47.0), 177 (67.7), 157 (15.0), 77 (72.0), 59 (100.0); IR 2977 (m), 2962 (m), 1456 (w), 1373 (w), 1103 (s), 1072 (s). Anal. Calcd for $C_{10}H_{14}F_6$: C, 48.39; H, 5.69; F, 45.92. Found: C, 48.44; H, 5.38; F, 45.71.

***trans*-1,4-Bis(difluoromethyl)-1,4-cyclohexanedicarboxaldehyde (15).** A 250-mL three-necked flask equipped with a low-temperature thermometer, magnetic stir bar, pressure-equalizing addition funnel, and N_2 tee was charged with 75 mL of CH_2Cl_2 and 5.62 g (44.3 mmol) of oxalyl chloride. The solution was cooled to -50 to -60 °C *via* dry ice/IPA bath, and 6.9 g (87 mmol) of dry DMSO in 30 mL of CH_2Cl_2 was added dropwise *via* addition funnel, maintaining the temperature at -50 to -60 °C. The solution was stirred an additional 2–3 min. A solution of 4.50 g (18.4 mmol) of **12**, in 25 mL of CH_2Cl_2 and the minimum amount of DMSO required to dissolve the diol, was then added dropwise at -50 to -60 °C. The mixture was stirred an additional 15–20 min at -50 °C and then quenched by slow addition (7–10 min) of 15 mL of Et_3N. Stirring at low temperature was continued for an additional 5 min, and the solution was then allowed to warm to rt with stirring. For workup, the thick white reaction mixture was transferred to a separatory funnel and diluted with 50 mL CH_2Cl_2 and then washed with 150 mL of water. The aqueous phase was extracted with 100 mL of CH_2Cl_2. The organic layers were combined and washed consecutively with 75-mL volumes of brine, 1% HCl, dilute $NaHCO_3$, and water. After drying ($MgSO_4$) and filtration, the solvent was removed by rotary evaporation and the crude residue was eluted through a column of silica gel (CH_2Cl_2 eluent, monitored by ^{19}F NMR) to yield 3.76 g (85%) **15** as a solid: mp 86–87 °C; ^{1}H NMR 1.5 (m, 4H), 2.2 (m, 4H), 5.6 (t, 2H, J_{H-F} = 55.3 Hz), 9.7 (s, 2H); ^{19}F NMR -126.0 (d, J_{F-H} = 44.5 Hz); ^{13}C NMR 20.5, 52.8 (t, $^2J_{C-F}$ = 19.1 Hz), 118.0 (t, J_{C-F} = 248.4 Hz), 200.8; GCMS *m/e* 222 (1.7), 189 (1.3), 143 (55.2), 120 (55.2), 87 (96.5), 51 (100.0), 59 (95.8), 77 (84.6); IR

2957 (w), 2875 (w), 1735 (s), 1358 (w), 1102 (m), 1077 (s). Anal. Calcd for $C_{10}H_{12}F_4O_2$: C, 50.00; H, 5.04; F, 31.64. Found: C, 50.02; H, 4.81; F, 31.55.

1,1,4,4-Tetrakis(difluoromethyl)cyclohexane (16). A three-necked 200-mL flask equipped with a thermometer, N_2 tee, magnetic stir bar, cold-water condenser, and pressure-equalizing addition funnel was charged with 90 mL of CH_2Cl_2 and 5.10 g (4.2 mL, 31.5 mmol) of DAST. A solution containing 3.43 g (14.3 mmol) of **15** and 15 mL of CH_2Cl_2 was placed in the addition funnel and added in one portion. After addition, the solution was stirred at rt for an additional 72 h or until the ^{19}F NMR spectrum of the reaction mixture simplified to one doublet. For workup the mixture was transferred to a separatory funnel, diluted with 50 mL of CH_2Cl_2 and washed with 50 mL of aqueous $NaHCO_3$ solution and 50 mL of water. The organic layer was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. Short-path distillation of the residue (94–95 °C/1 mmHg) yielded 2.82 g (70%) **16**: mp 36–37 °C; ^1H NMR 1.8 (s, 8H), 5.8 (tt, 4H, J_{H-F} = 56.0 Hz, $^4J_{H-F}$ = 5.6 Hz); ^{19}F NMR −129.2 (d, J_{F-H} = 56.2 Hz); ^{13}C NMR 18.3, 44.0 (pentet, $^2J_{C-F}$ = 17.7 Hz), 117.5 (tt, J_{C-F} = 247.7 Hz, $^3J_{C-F}$ = 6.1 Hz); GCMS *m/e* 264 (M^+ − HF, 3.0), 233 (M^+ − CF_2H, 57.6), 213 (100), 193 (23.9), 173 (24.5), 167 (50.9), 109 (41.5), 51 (65.3); IR 2981 (w), 1490 (w), 1396 (m), 1362 (m), 1120 (s), 1052 (s), 1098 (s). Anal. Calcd for $C_{10}H_{12}F_8$: C, 42.26; H, 4.25; F, 53.48. Found: C, 42.48; H, 4.12; F, 53.17.

1,1,4,4-Cyclohexanetetracarboxylic Acid (17). A 500-mL single-necked flask equipped with a water-cooled condenser and magnetic stir bar was charged with 24.5 g (613 mmol) of NaOH, 95 mL of EtOH, and 215 mL of water. The mixture was stirred until all the NaOH was dissolved. Next, 24.2 g (76.6 mmol) of tetraester **3** was added in one portion. The mixture was stirred at rt for 48 h. For workup, the salt of the acid was quenched by addition (over 4–5 min) of 750 mL of 2 M HCl and the acidified mixture was stirred for an additional 15 min. After transferring to a 2-L separatory funnel, the water-soluble tetraacid product was exhaustively extracted from the aqueous phase with 6 × 500 mL portions of diethyl ether. Each organic fraction was dried over $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation. The residue was further dried for 2–3 h under full vacuum to yield 17.8 g (90%) tetraacid **17** as a white solid: mp 245–246 °C; ^1H NMR (acetone-d_6) 2.1 (s); ^{13}C NMR (acetone-d_6) 29.1, 54.3, 169.2; IR (KBr) 3200–3400 (s), 2961 (m), 1734 (s), 1408 (w), 1285 (s), 1203 (s). Anal. Calcd for $C_{10}H_{12}O_8$: C, 46.16; H, 4.65. Found: C, 46.26; H, 4.66.

1,1,4,4-Tetrakis(trifluoromethyl)cyclohexane (22). A 300-mL Parr Co. Hastelloy C pressure reactor equipped with a 2000 psi rupture disc was charged with 3.12 g of acid **17** (12.0 mmol), sealed, and weighed. The reactor was cooled to −78 °C *via* dry ice/IPA bath and then evacuated. Hydrogen fluoride was then condensed directly into the reactor followed by condensation of 22.0 g (0.2 mol) of SF_4. After condensation, the reactor was warmed to rt, weighed, and slowly heated to 140–150 °C for 12 h. The reactor was cooled to rt and weighed, and the volatiles (HF, SF_4, SOF_2) were vented (fume hood) slowly into a stirred aqueous NaF trap. The crude, brackish reaction mixture was diluted with 200 mL of CH_2Cl_2, transferred to a separatory funnel, and washed with 75 mL of aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The dark residue was eluted through a column of silica gel (pentane eluent, monitored by ^{19}F NMR) to yield 1.6 g (37%) of crude **22** as a solid. The product was free of organic impurities at this point but contained traces of elemental sulfur which were absent after sublimation of the residue. Sublimed yield: 0.77 g (18%); mp 76 °C; ^1H NMR 2.1 (s); ^{19}F NMR −73.1 (s); ^{13}C NMR 20.6, 47.3 (septet, $^2J_{C-F}$ = 25.0 Hz), 125.6 (q, J_{C-F} = 285.5 Hz); IR 2971 (w), 1461 (w), 1369 (m), 1284 (s), 1212 (s), 1031 (m), 944 (m). Anal. Calcd for $C_{10}H_8F_{12}$: C, 33.72; H, 2.26; F, 64.01. Found: C, 33.51; H, 2.27; F, 63.78.

***trans*-1,4-Bis(trifluoromethyl)-1,4-cyclohexanedimethanol (20) and 1,1,4-Tris(trifluoromethyl)-4-cylohexanemethanol (21).** A mixture of acyl fluorides **18** and **19** was prepared according to the procedure described for the preparation of **22** using 13.5 g (51.9 mmol) of **17**, 61 g (560 mmol) of SF_4, and heating at 130 °C for 8–10 h. No HF was used. Analogous workup yielded 10.8 g (63%) of crude **18** and **19** (63:38) for use in the following reduction. An oven-dried, three-necked 250-mL flask equipped with a N_2 tee, magnetic stir bar, cold-water condenser, and pressure-equalizing addition funnel was charged with 2.3 g (60 mmol) of $LiAlH_4$ and 100 mL of dry diethyl ether. A solution containing 9.3 g of **18** and **19** (62:38) in 30 mL of dry diethyl ether was placed in the addition funnel and cautiously added dropwise to the stirring $LiAH_4$ solution. The mixture was stirred at rt for an additional 6–8 h and then quenched by cautious addition (over 30 min) of 5 mL water followed by slow addition of 10 mL of 2 M HCl. The mixture was stirred for 10 min and the ether was decanted away from the white solids into a separatory funnel. The solids were thoroughly extracted with diethyl ether (2 × 100 mL) and the combined organic layers washed (2 × 50 mL) with water, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to yield 7.9 g of a white solid residue containing a 62/38 ratio of **20**/**21**. Separation of the alcohol mixture was accomplished by 2 × 50 mL of a CH_2Cl_2 rinsing which dissolves **21** while **20** remains insoluble. The diol portion contained less than 3% alcohol **21**, and a small amount of *cis* isomer (<3%) was also detected. The fraction containing **21** showed a purity of 95% (^{19}F NMR). Further purification of both fractions by silical gel chromotagraphy (95:5 CH_2Cl_2/MeOH) with monitoring of the column cuts by ^{19}F NMR was undertaken. Alcohol **21** eluted off the column first, and a total of 2.55 alcohol **21** and 3.66 g of diol **20** (72.8% combined yield) were isolated as white solids. (**20**: mp 188–190 °C; ^1H NMR (acetone-d_6) 1.75 (m, 8H), 3.8 (d, 4H, J = 5.7 Hz), 4.1 (t, 2H, J = 5.7 Hz); ^{19}F NMR (acetone-d_6) −75.8 (s); ^{13}C NMR (acetone-d_6) 20.5, 44.4 (q, $^2J_{C-F}$ = 22.0 Hz), 60.2, 130.3 (q, J_{C-F} = 283.4 Hz); GCMS *m/e* 262 (M^+ − H_2O, 0.7), 244 (M^+ − $2H_2O$, 2.6), 230 (49.5), 212 (50.3), 184 (100.0), 143 (94.8), 115 (31.8), 103 (50.8); IR (KBr) 3200–3600 (s), 2954 (w), 1490 (w), 1234 (m), 1165 (s), 1054 (m), 1490 (w). Anal. Calcd for $C_{10}H_{14}F_6O_2$: C, 42.86; H, 5.04; F, 40.68. Found: C, 42.60; H, 4.67; F, 40.33. **21**; mp 49–50 °C; ^1H NMR (acetone-d_6) 1.8–2.1 (m, 8H), 3.8 (d, 2H, J = 5.3 Hz), 4.1 (t, 1H, J = 5.7 Hz); ^{19}F NMR (acetone-d_6) −69.8 (q, 1F, J = 11.5 Hz), −72.3 (q, 1F, J = 11.5 Hz), −75.1 (s, 1F); ^{13}C NMR (acetone-d_6) 20.3 (s), 21.0 (s), 43.6 (q, $^2J_{C-F}$ = 22.0 Hz), 49.0 (septet, $^2J_{C-F}$ = 24.3 Hz), 62.3 (s), 130.1 (q, J_{C-F} = 284.6 Hz), 127.1 (q, J_{C-F} = 284.6 Hz), 126.9 (q, J_{C-F} = 284.6 Hz); IR 3639 (m), 2964 (w), 2987 (w), 1270 (m), 1209 (s), 1046 (m). Anal. Calcd for $C_{10}H_{11}F_9O$: C, 37.75; H, 3.48; F, 53.74. Found: C, 37.92; H, 3.22; F, 53.50.

1,4-Bis(trifluoromethyl)-1,4-cyclohexanedicarboxaldehyde (25). Aldehyde **25** was prepared according to the procedure described for **15** using 40 mL of CH_2Cl_2, 2.81 g of (22.1 mmol) oxalyl chloride, a solution of 3.45 g (44.2 mmol) of dried DMSO in 15 mL of CH_2Cl_2, and a solution of 2.58 g (9.21 mmol) of **20** in 25 mL of CH_2Cl_2 and the minimum amount of DMSO required to dissolve **20**. The reaction mixture was quenched by slow addition (7–10 min) of 7 mL of Et_3N. Analogous workup and purification using silica gel chromatography (CH_2Cl_2, R_f = 0.9) yielded 2.0 g (80%) **25** as a white solid: mp 64 °C; ^1H NMR 1.7 (m, 4H), 2.3 (m, 4H), 9.65 (s, 2H); ^{19}F NMR −73.9 (s); ^{13}C NMR 20.4, 54.4 (q, $^2J_{C-F}$ = 23.2 Hz), 126.3 (q, J_{C-F} = 283.3 Hz), 197.6; GCMS *m/e* 276 (M^+, 1.3), 258 (9.9), 202 (34.7), 179 (38.7), 138 (80.4), 105 (100.0), 77 (85.4); IR 2952 (w), 1742 (s), 1480 (w), 1273 (s), 1183 (s), 1168 (s), 1062 (s). Anal. Calcd for $C_{10}H_{10}F_6O_2$: C, 43.49; H, 3.65; F, 41.27. Found: C, 43.36; H, 3.59; F, 41.01.

***trans*-1,4-Bis(trifluoromethyl)-1,4-bis(difluoromethyl)-cyclohexane (26).** Preparation of **26** was carried out according to the procedure described for **22**, omitting the use of HF, using a 128-mL pressure vessel, 1.84 g (6.66 mmol) of **25**, and 6.0 g (55 mmol) of sulfur tetrafluoride. The reactor was heated at 75 °C for 5 h. Analogous workup and purification by short-path distillation (75 °C/ 30 mmHg) yielded 1.05 g (49.3%) difluoromethylated product **26**, GC 96%. A minor impurity was removed by column chromotagraphy (pentane). Collected fractions were monitored by ^{19}F NMR and the minor impurity eluted off the column first. Product **26** was obtained in high isomeric purity (>97% trans). ^1H NMR 1.98 (s, 4H), 5.9 (t, 1H, J = 54.9 Hz); ^{19}F NMR major isomer (trans) −73.7 (t, 3F, J = 8.5 Hz), −127.2 (dq, 2F, J_{F-H} = 56.4 Hz, J_{F-F} = 9.8 Hz); minor isomer (cis) −75.4 (t, 3F, J = 8.5 Hz), −123.8 (dq, 2F, J_{F-H} = 56.4 Hz, J_{F-F} = 9.8 Hz); ^{13}C NMR 18.3, 45.7 (qt, $^2J_{C-F}$ = 23.4, 19.6 Hz), 115.9 (tq, J_{C-F} = 247.6 Hz, $^3J_{C-F}$ = 2.0 Hz), 127.8 (qt, J_{C-F} = 284.3 Hz, $^3J_{C-F}$ = 4.9 Hz); GCMS *m/e* 300 (M^+ − HF, 4.2), 281 (M^+ − HF_2, 9.2), 249 (M^+ − CF_2H − HF, 100.0), 269 (M^+ − CF_2H, 26.2), 229 (21.7),

209 (30.0); IR 2980 (w), 1272 (m), 1266 (m), 1217 (s), 1181 (s), 1080 (m), 773 (s), 759 (m). Anal. Calcd for $C_{10}H_{10}F_{10}$: C, 37.51; H, 3.15; F, 59.34. Found: C, 37.46; H, 3.12; F, 59.44.

1,4-Bis(trifluoromethyl)-1,4-bis[[[(trifluoromethyl)sulfonyl]oxy]methyl]cyclohexane (23). Triflate **23** was prepared according to the procedure described for **13** using 15 mL of CH_2Cl_2, 0.80 g (2.85 mmol) of **20**, 0.26 g (6.1 mmol) of pyridine, and 1.84 g (6.3 mmol, 1.1 mL) of trifluoromethanesulfonic anhydride. The reaction mixture was stirred at rt for 4–5 h. Analogous workup yielded 1.25 g (80.7%) of solid **23** which was used without further purification: ^{1}H NMR (acetone-d_6) 2.3 (m, 2H), 5.0 (s, 1H); ^{19}F NMR (acetone-d_6) −75.1 (s, 1F), −76.0 (s, 1F); ^{13}C NMR (acetone-d_6) 20.1 (s), 44.1 (q, $^2J_{C-F}$ = 24.4 Hz), 73.9 (s), 128.5 (q, J_{C-F} = 283.1 Hz), 119.5 (q, J_{C-F} = 318.7 Hz).

1,4-Bis(trifluoromethyl)-1,4-bis(fluoromethyl)cyclohexane (24). Preparation of **24** was carried out according to the procedure described for **14** using 1.4 g (5.2 mmol) of TBAF·xH$_2$O in 15 mL of dry THF and a solution of **23** (1.17 g, 2.15 mmol) in 5–10 mL of THF. The reaction was carried out at rt for 2–3 h. After analogous workup, the residue was passed through a column of silica gel (CH_2Cl_2) to yield 0.44 g (72%) of **24** as a crystalline solid: mp 70 °C; ^{1}H NMR 1.7 (s, 2H), 4.5 (d, 1H, J_{H-F} = 47.2 Hz); ^{19}F NMR −231.3 (tq, 1F, J_{F-H} = 47.1 Hz, J_{F-F} = 8.7 Hz), −77.5 (d, 3F, J_{F-F} = 8.2 Hz); ^{13}C NMR 18.4 (bs), 42.1 (qd, $^2J_{C-F}$ = 23.6, 16.8 Hz), 79.2 (d, J_{C-F} = 179.2 Hz), 127.0 (q, J_{C-F} = 283.2 Hz); GCMS m/e 264 (M^+ − HF, 0.9), 245 (6.0), 231 (100.0), 215 (47.7), 195 (68.9), 77 (79.5); IR 2965 (w), 1260 (m), 1247 (m), 1171 (s), 1086 (m), 752 (s). Anal. Calcd for $C_{10}H_{12}F_8$: C, 42.26; H, 4.25; F, 53.48. Found: C, 42.12; H, 4.28; F, 53.27.

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Supplementary Material Available: ^{13}C NMR spectra of compounds **2**, **3**, **4a**, **5a**, **7a–c**, **8a–c**, **10a–b**, **12–17**, **20–26** (45 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.