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Mechanisms for the alkaline hydrolysis of dibromodifluoromethane-alkene adducts to α,β-unsaturated carboxylates

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Dedicated to Professor Paul Tarrant on the occasion of his 85th birthday

Abstract

Alternative mechanisms for the title reactions are probed. The previously-reported pathway involving double dehydrobromination to a difluorodiene is operative in at least one case, but this route is specifically excluded for systems that cannot dehydrobrominate to dienes yet still yield carboxylates upon alkaline hydrolysis. Although S_N2, S_N1, $S_{RN}1$, and monoelimination–addition processes appear formally possible, an S_N2' mechanism is implicated by studies on model compounds. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Dehydrobromination; Hydrolysis; Halomethane

1. Introduction

Bromofluoro and chlorofluoro organics have historically been employed in a variety of industrial applications [1–3], and some of these ubiquitous compounds are significant or persistent environmental hazards [4,5]. A detoxification or remediation strategy based on simple alkaline hydrolysis may exist provided the scope and limitations of the process are understood and predictable. Our interest in the chemistry of dibromodifluoromethane-alkane adducts **1** [6–10] prompted a mechanistic study of their alkaline hydrolysis.

Compounds **1** are generally accessible via radical addition of dibromodifluoromethane to alkenes [11]. Adducts **1** were found to be cleanly converted to α,β-unsaturated carboxylic acids **2** when treated with aqueous hydroxide followed by acidic work-up [6,7]. The generality of this process was shown for a variety of terminal, internal, and cyclic alkenes that were similarly converted to the corresponding halomethane adducts then carboxylic acids [7] (Scheme 1).

Experiments with the cyclohexene adducts **3** and **4** suggest the mechanism shown in Scheme 2 which involves double dehydrobromination to the intermediate difluorodiene **7**. Base-catalyzed conjugate addition of water to **7** produces an unstable difluoroalcohol **8** that spontaneously dehydrofluorinates to acyl fluoride **9** and ultimately **10**. This mechanism was supported by the isolation of intermediates **6**, **7**, and **9** during the reaction. Each of these were subsequently converted quantitatively to **10** under the reaction conditions [6].

Alternatives to the Scheme 2 pathway are implied by the observed conversion of norbornene adducts **11** into **16** [7]. Following a path analogous to Scheme 2, conversion of **11** to carboxylic acid **16** would require the anti-Bredt intermediate **14**. A previous report that 1-norbornene (bicyclo[2,2,1]hept-1-ene) was observed indirectly in a trapping experiment [12] suggests that **14** may be a short-lived intermediate eventhough it cannot be isolated (Scheme 3).

Conversion of **12** to **15** by an S_N2 or S_N1 mechanism on a fluoroalkyl center appears unlikely. Such reactions are generally not observed [13] although formal substitution on fluoroalkyl carbons can arise from other mechanism.[1]

Also conceivable is the S_N2' process on **13** to yield **15**. In that case the observed near-quantitative conversion of

[1] Bromophilic reactions on dibromodifluoromethane or 1,2-dibromo-1,1,2,2-tetrafluoroethane produce carbanions that subsequently eliminate an alpha or beta bromide to produce difluorocarbene or tetrafluoroethene, respectively. Nucleophilic additions to these intermediates yield products that formally appear to result from nucleophilic substitution on a fluoroalkyl carbon. These pathways, however, require geminal or vicinal dibromides, respectively. The 1,3 relationship of the bromines on adducts **1** precludes an analogous route between **11** and **15** [14].

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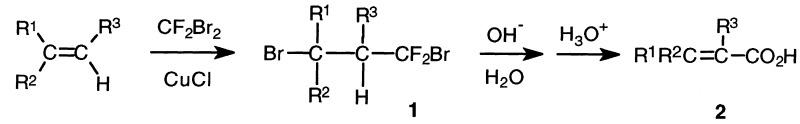
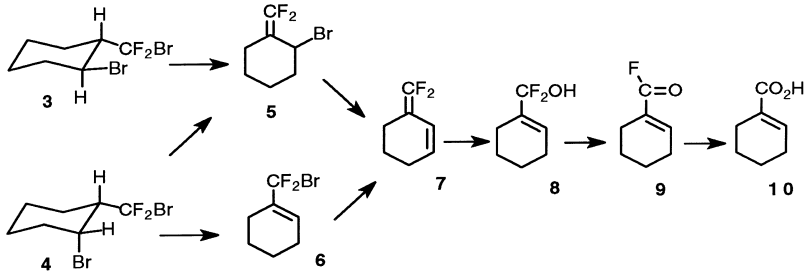
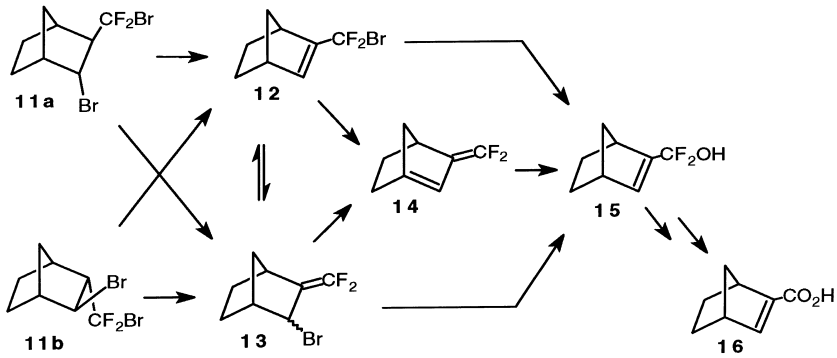


Scheme 1.



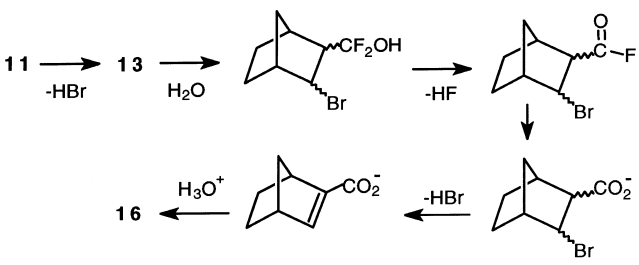
Scheme 2.



Scheme 3.

11 to **16** would require either high regioselectivity for the initial dehydrobromination of **11** to **13** or possibly the isomerization of **12** to **13** under the reaction conditions. Products formally resulting from S_N2' attack on 1-bromo-1,1-difluoro-2-alkenes have recently been reported [15].

A simple monoelimination–addition mechanism is also possible and has been observed in other R_2CHCF_2X systems [16] (Scheme 4). Initial dehydrobromination of **11** to **13** could be followed by hydroxide-catalyzed addition of water to the difluoroalkene to yield a difluoroalcohol that decomposes via an acyl fluoride to a bromocarboxylate that is finally dehydrobrominated to produce **16** upon acidic work-up.[2]



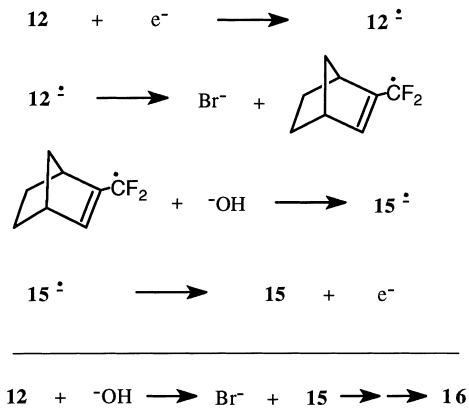
Scheme 4.

A single electron transfer chain process known as $S_{RN}1$ has been observed for some perfluoroalkyl iodides [19,20]. Such a mechanism could conceivably be operative here as shown in Scheme 5.

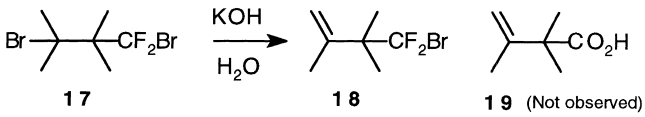
2. Results and discussion

The adduct **17** does not undergo the same alkaline hydrolysis observed for nearly all other halomethane-alkene adducts studied [6,7]. Rather than the completely dehalo-

[2] Initial dehydrofluorination (vs. dehydrobromination) of **11** would give 2-bromo-3-(bromofluoromethylene)bicyclo[2,2,1]heptane which could, in turn, add water yielding an alpha-bromofluoroalcohol, etc. This variation of the monoelimination–addition pathway shown in Scheme 4 has not been rigorously ruled out; however, we note that the greater nucleofugicity of bromide over fluoride favors dehydrobromination. In bimolecular reactions, HBr elimination is generally several orders of magnitude faster than HF elimination (see [17]). For example, at 30°C eliminations of HX from $PhCH_2CH_2X$ in ethoxide/ethanol have relative rates for X = F and Br of 1 and 4300, respectively (see [18]).



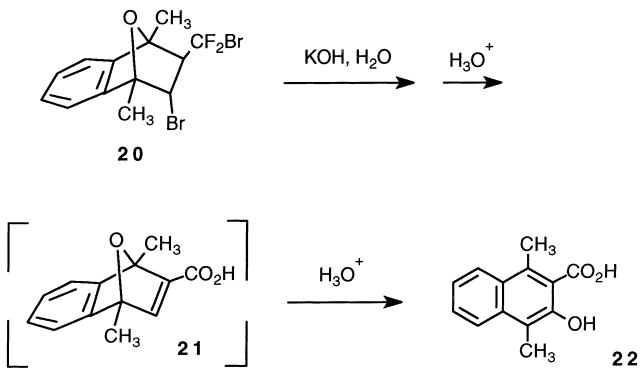
Scheme 5.



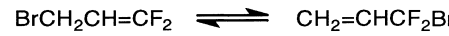
Scheme 6.

genated carboxylic acid **19**, the monodehydrobromination product **18** was observed exclusively (Scheme 6). As expected, this is evidence against a nucleophilic substitution at the trihalomethyl carbon but is consistent with the diene, S_N2', or monoelimination–addition pathways described above each of which require the carbon bearing the trihalomethyl group to be an alkene carbon at some point. This is not possible for molecules such as **17** in which the trihalomethyl group is attached to a quaternary carbon.

We had rejected the diene pathway for the conversion of **11** to **16** based on the predicted instability of bridgehead olefin intermediate **14**. Additional experimental evidence for the existence of a non-diene path was found through compound **20**, which provides a rough structural model for **11**. Model compound **20** undergoes the usual alkaline hydrolysis to **21** (Scheme 7) even though the methyl substituent on bridgehead carbon-1 precludes a diene intermediate analogous to **14**. Although stable in boiling alkali, compounds such as **21** containing the 1,4-dihydro-1,4-dimethyl-1,4-epoxynaphthalene moiety undergo facile acid-catalyzed rearrangement to 1,4-dimethyl-2-naphthols



Scheme 7.



Scheme 8.

[21]. The observation of **22** provides indirect evidence for **21** and further argues against a diene intermediate in the conversion of **11** to **16** thus leaving the S_N2', monoelimination–addition, and $S_{RN}1$ pathways for further consideration.

Monodehydrobromination of **11a** with DBU in ether and refluxing for 24 h yielded *exo*-**13**, *endo*-**13**, and **12**, in a 65:15:20 ratio, respectively. A low temperature reaction yielded the kinetic product *endo*-**13** which was found to equilibrate to the same 65:15:20 mixture at 100°C with a half-life of approximately 5 min. A literature precedent exists for isomerization of the corresponding bromodichloro analogs of **13** between *endo* and *exo* [22] but not to trihalomethyl compounds such as **12**.[3] Allylic shifts of bromine have been observed in similar bromodifluoro systems, and an analogous equilibration of 3-bromo-1,1-difluoropropene and 3-bromo-3,3-difluoropropene has been reported [24] (Scheme 8). This isomerization may be explained as resulting from S_N2' attack of bromide on either isomer. This can be extrapolated to isomers **12** and **13** and may pertain to the possibility of S_N2' attack by hydroxide on **13** to yield **15** and ultimately **16**.

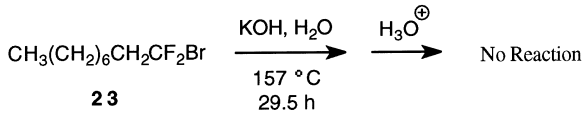
An alkaline hydrolysis experiment was attempted with 1-bromo-1,1-difluorononane **23**. As previously shown, the S_N1 and S_N2 mechanisms are not likely to occur nor could **23** react via an S_N2' mechanism. If **23** underwent alkaline hydrolysis to yield carboxylate, that would be evidence for monoelimination–addition, or $S_{RN}1$ pathway (Scheme 9).

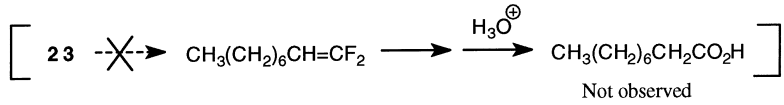
After 29.5 h of heating in 16% aqueous potassium hydroxide, starting material **23** was recovered unchanged. This may be evidence that in order for a bromodifluoromethyl compound to hydrolyze under these conditions, a second bromine must be present in the gamma position. The gamma bromine may increase the acidity of the hydrogen on the beta carbon to allow for beta-gamma dehydrobromination to yield the previously-observed [6,10] monoelimination products such as **6** which subsequently rearrange to 3-bromo-1,1-difluoroalkenes such as **5**.

Difluoromethylene cyclohexane **24** was prepared and used as a model for the proposed intermediate **13** except that, lacking a bromine on carbon-3, it cannot undergo an S_N2' process. Compound **24** also serves to test the "addition" phase of the elimination–addition pathway. After being treated under our standard alkaline hydrolysis conditions, **24** was recovered unchanged and cyclohexane carboxylic acid **25** was not observed (Scheme 10).

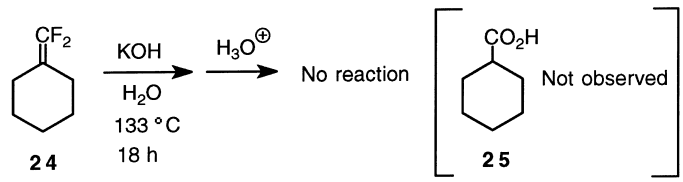
To test the possibility of a single electron transfer, $S_{RN}1$ pathway operating in the conversion of **11a** to **16**, the

[3] The significant amount of trihalomethyl isomer **12** in addition to *exo*- and *endo*-**13** in this equilibrium mixture differs from what was observed for the bromodichloro analogs [22] and may reflect the stabilization reported for *gem*-difluoro substituents on saturated vs. unsaturated carbons [23].

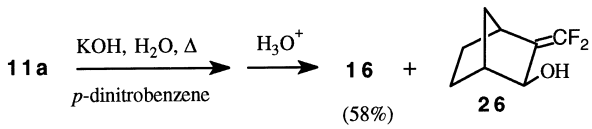




Scheme 9.



Scheme 10.



Scheme 11.

alkaline hydrolysis was carried out both with and without the inhibitor *p*-dinitrobenzene. After 25 h at 136°C, no unreacted starting material or simple monoelimination products were observed in the inhibited reaction. In addition to the expected acid **16**, a significant amount of alcohol side product **26** was detected (Scheme 11). A similar result was obtained in the absence of *p*-dinitrobenzene although the yields of **16** and **26** were slightly higher in that case [7]. This is attributable to the difficulty associated with the work-up of the small scale reaction that contained *p*-dinitrobenzene.

3. Conclusions

These observations support an S_N2' mechanism for the conversion of **11** to **16**. This general pathway is likely operative in the alkaline hydrolysis of other halomethane-alkene adducts although it is not the sole path for all cases since diene **7** was observed for the conversion of **3** and/or **4** to **10** [6]. Although we have not rigorously ruled out allylically-stabilized S_N1, S_N2, or $S_{RN}1$ paths for all cases, our results, and those of others, argue against those mechanisms. The monelimination–addition pathway was discounted by the attempted alkaline hydrolyses of **23** and **24** which were unreactive and were not converted into carboxylates under these conditions. Bromodifluoromethyl groups attached to quaternary carbons are unreactive to alkaline hydrolysis. Nucleophilic substitution by hydroxide does not occur on such systems by any mechanism. Bromodifluoromethyl groups are generally unreactive towards alkaline hydrolysis unless they are activated by adjacent unsaturation.

4. Experimental section

Except where otherwise specified, all reagents were commercial samples obtained from Aldrich Chemical Company and used without purification. Analytical and preparative GC was carried out on a Gow-Mac 69-350 gas chromatograph using 8 ft × 0.25 inch copper columns packed with 10% SE 30 or 10% OV-210 on Chromosorb WHP (He flow = 60 ml/min). All NMR spectra were obtained in $CDCl_3$ solution on Varian Gemini 200 spectrometer operating at 200 MHz for ^1H and 50 MHz for ^{13}C. Infrared spectra were obtained as capillary films of neat liquids unless otherwise noted and were recorded on a Perkin-Elmer 1600 series FTIR spectrophotometer. Elemental analyses were performed by Atllantic Microlab (Norcross, GA) except for those of **12** and **13** which were performed by Robertson Laboratories (Madison, NJ).

*4.1. Preparation of 1,3-dibromo-1,1-difluoro-2,2,3-trimethylbutane (**17**)*

Dibromodifluoromethane was added to 2,3-dimethyl-2-butene according to our adaptation [8] of a literature method [11]. A 20-ml, screw-capped reaction tube equipped with poly(tetrafluoroethylene)-taped threads and a magnetic stir bar was charged with 2,3-dimethyl-2-butene (2.99 g, 35.5 mmol), *t*-butyl alcohol (2.44 g), ethanolamine (1.07 g), copper(I) chloride (0.05 g, 0.5 mmol), and dibromodifluoromethane (15.12 g, 72 mmol). The vessel was tightly capped and the reaction mixture was stirred and heated over an oil bath at 75°C for 16 h during which the mixture changed from clear blue to dark brown. A resinous layer also appeared. The mixture was cooled to ambient temperature and diluted with 10 ml of cyclohexane whereupon it became cloudy. The cyclohexane solution was separated and the residue was extracted twice with 5-ml portions of cyclohexane. The cyclohexane extracts were

combined and filtered through a 20 cc bed of 70–230 mesh silica gel in a 4 cm diameter Büchner funnel equipped with Whatmann No. 1 filter paper yielding a clear, colorless solution which was washed three times with deionized water, dried over anhydrous calcium chloride, filtered, and rotary evaporated which left 0.82 g (7.9%) of **17** that appeared >95% pure by GC and ^{1}H NMR analysis. The product was combined with that from another run at the same scale and vacuum distilled at 77°C (14 Torr). ^{1}H NMR δ 1.97 (t, $J_{FH} = 1.9$ Hz, 6H), 1.52 (s, 6H); ^{13}C NMR δ 129.2 (t, $J_{FC} = 318.2$ Hz, CF_2Br), 72.4, 54.0 (t, $J_{FC} = 16.1$ Hz), 32.7 (t, $J_{FC} = 3.5$ Hz), 24.5. IR: 2997, 2953, 1462, 1389, 1380, 1222, 1102 (st), 897 (st), 879 (st), 546 cm^{-1}. Elemental analysis was not performed due to the observed decomposition of **17** upon standing at room temperature.

4.2. Attempted alkaline hydrolysis of *17*. Preparation of 4-bromo-4,4-difluoro-2,3,3-trimethyl-1-butene (*18*)

A 20-ml, screw-capped reaction tube equipped with poly(tetrafluoroethylene)-taped threads and a magnetic stir bar was charged with 1,3-dibromo-1,1-difluoro-2,2,3-trimethylbutane **17** (0.58 g, 1.97 mmol), potassium hydroxide (0.55 g, 9.8 mmol) and 3 ml of water was stirred and heated over a 181°C oil bath for 6 h. The cooled reaction mixture was extracted twice with 1-ml portions of dichloromethane and the combined organic extracts were dried over anhydrous sodium sulfate and condensed by rotary evaporation to yield 0.35 g of alkene **18**.[4] (83%).^{1}H NMR: δ 5.1 (two partially resolved singlets at 5.06 and 5.08 ppm), 1.9 (s, 3H), 1.35 (s, 6H); ^{13}C NMR: δ 145, 129.2 (t, $J_{FC} = 311$ Hz, CF_2Br), 116, 51.3 (t, $J_{FC} = 19$ Hz, C3), 23, 21; IR: 2992, 2925, 2958, 2855, 1639 (w), 1451, 1384, 1261, 1104, 1020, 884, 808 cm^{-1}.

4.3. Endo-2-bromo-exo-3-(bromodifluoromethyl)-1,4-dimethyl-1,2,3,4-tetrahydro-1,4-epoxynaphthalene (*20*)

Compound **20** was prepared by the addition of dibromodifluoromethane to 1,4-dihydro-1,4-dimethyl-1,4-epoxynaphthalene[5] according to the method described above for the synthesis of **17**. The synthesis of **20** was carried out at 75–85°C for 17 h. Half the starting material (1,4-dihydro-1,4-dimethyl-1,4-epoxynaphthalene) was recovered by vacuum distillation. Compound **20** which was purified by vacuum distillation (110°C, 2 torr) or by preparative TLC using 20 × 20 cm^2, 500 μm silica coated plates and 5:4 CH_2Cl_2:hexane eluent. Yield = 11% based on consumed starting material. ^{1}HNMR: δ 7.28 (mult, 2H), 7.20 (mult, 2H) 4.17 (dd, $J = 4.7$ and 1.3 Hz, 1H), 2.68 (ddd, $J = 19.4$, 6.6, 4.7 Hz, 1H), 1.90 (mult, 3H), 1.85 (s, 3H). ^{13}CNMR: δ 147.1, 144.9, 128.0, 127.0, 122.0, 121.8 (dd, $J_{FC} = 312$ and 307 Hz, CF_2Br), 117.5, 87.1, 86.0, 66.1 (t, $J_{FC} = 21$ Hz, C2), 52.0, 15.4, 15.0. IR: 3086, 2990, 2932, 2865, 1696, 1465, 1389, 1312, 1245, 1091,756, 698 cm^{-1}. Analysis calculated for $C_{13}H_{12}Br_2F_2O$: C, 40.87; H 3.16. Found: C, 41.37; H 3.21.

4.4. Alkaline hydrolysis of *20*. Preparation of 3-hydroxy-1,4-dimethyl-2-naphthalenecarboxylic acid (*22*)

The procedure described for the hydrolysis of **17** to **18** was followed except where noted and using 1.88 g (4.9 mmol) **20** as the starting material. The reaction was run for 9 h at 135°C. After cooling the reaction mixture was diluted with a small amount of water and then extracted four times with 5-ml portions of methylene chloride. The organic portion was set aside and the aqueous phase was acidified with 6 M HCl. A milky white precipitate and an yellow oil is formed at the bottom of flask. The mixture was extracted four times with 5-ml portions of CH_2Cl_2. The combined extracts were washed three times with water, dried over anhydrous sodium sulfate, and rotary evaporated leaving a brown solid which was not soluble in water but did dissolve in 5% aqueous solutions of NaOH or $NaHCO_3$ (effervescence). After dissolving the solid in aqueous $NaHCO_3$ the solution was re-acidified with 6 M HCl and became cloudy. After chilling for several hours a light yellow solid appeared which was identified as **22** (0.28 g, 27% yield). During the m.p. determination the compound decomposed at 183–185°C in an open capillary leaving a dark brown residue. NMR spectra were obtained in acetone-d_6 solution. ^{1}H NMR: δ 8.16 (d with unresolved fine structure, $J = 8.8$ Hz, 1H), 7.96 (d with unresolved fine structure, $J = 8.4$ Hz, 1H) 7.58 (ddd, $J = 8.4$, 6.8, and 1.4 Hz, 1H), 7.41 (ddd, $J = 8.4$, 6.8, and 1.4 Hz, 1H), 2.90 (s, 3H) 2.51 (s, 3H). ^{13}C NMR: δ 173.0, 152.1, 136.5, 136.2, 128.7, 128.4, 126.7, 124.3, 121.0, 115.7, 17.5, 11.0. IR: (KBr pellet) 3324–2605 (br), 1654 (st, sharp), 1512, 1441, 1376, 1294, 180, 1098, 885, 826, 738, 635 cm^{-1}. Analysis calculated for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 71.62; H, 5.59.

4.5. Monodehydrobromination of *11a* with DBU. Preparation and equilibration of *12*, exo-*13*, and endo-*13*

A 100-ml, round-bottomed, three-necked flask was fitted with a reflux condenser, thermometer, and magnetic stirrer.

[4] The ^{1}H NMR chemical shifts we observed do not match a literature report: δ 5.78, 1.05 (s, 3H), 1.956 (s, 6H) but do agree with those of the analogous iodo compound 4,4-difluoro-2,3,3-trimethyl-4-iodo-1-butene [25,26].

[5] The precursor to compound **20** was 1,4-dihydro-1,4-dimethyl-1,4-epoxynaphthalene which was prepared via a Diels–Alder reaction of benzyne and 2,5-dimethylfuran according to a published procedure [27] and has properties consistent with those previously reported [28]. ^{13}CNMR and IR spectral data were not previously reported: ^{13}C NMR: δ 152.1 (C9, C10), 146.2 (C6, C7), 118.0 (C1, C4), 88.0 (C2, C3), 15.0 (CH_3); IR: 3072, 2977, 1453, 1384, 1307, 1236, 1141, 908 (st, sharp), 859, 743 (st,b) 693, 648, 603, 509 cm^{-1}. ^{1}H NMR: δ 7.0 (mult, 4H), 6.7 (s, 2H), 1.84 (s, 6H). The literature value for the 6H singlet is τ 8.66 (δ 1.34) (see [28]).

The system was flushed with dry nitrogen and charged with 2-*exo*-(bromodifluoromethyl)-3-*endo*-bromobicyclo[2,2,1]-heptane, **11a**, (6.08 g, 20.0 mmol), DBU (3.35 g, 22 mmol, 1.1 equiv.), and 30 ml of diethyl ether. The mixture was stirred and refluxed for 24 h. The resulting reaction mixture was diluted with 20 ml of water and the ether layer was separated, washed with 20 ml of 10% aqueous NaCl, dried over anhydrous magnesium sulfate and the ether was removed by rotary evaporation. Vacuum distillation of the residue yielded a colorless oil in 69% based on unrecovered starting material. (b.p. 62–66°C, 5 torr). In the course of isolating the product by distillation, it rearranged to a mixture of isomers. The isomerization, which was found to have a half-life of 5 min at 100°C, led to a 65:15:20 mixture of *exo*-**13**, *endo*-**13**, and **12**, respectively. The kinetic product obtained at low temperatures was *endo*-**13**. The proton on carbon-3 for this compound (bearing a *secondary* carbon bromine bond) appeared at 4.5 ppm as a broad singlet. By ^{13}C NMR, both difluoromethylene carbons appeared as unresolved doublets of doublets near 155 ppm (J_{FC} approximately 300 Hz). In addition, the olefinic carbon appeared as a small triplet ($J = 10$ Hz) at 137 ppm. For the mixture, analysis calculated for $C_8H_9BrF_2$: C, 43.08; H 4.08. Found: C, 43.11; H, 4.17.

4.6. Attempted alkaline hydrolysis of *23*

The procedure described for the conversion of **17** to **18** was followed except where noted. The reaction vessel was charged with 0.50 g (2.1 mmol) of **23** [8], and 0.58 g KOH dissolved in 3 ml of water. The reaction mixture was stirred and heated over a 156°C oil bath for 30 h, cooled to ambient temperature and extracted with three 2-ml portions of methylene chloride. The combined extracts dried over anhydrous sodium sulfate and concentrated by rotary evaporation to yield 0.48 g (83%) of recovered starting material.

4.7. Attempted alkaline hydrolysis of (difluoromethylene)cyclohexane, *24*

The procedure described for the conversion of **17** to **18** was followed except where noted. The reaction tube was charged with 0.59 g (4.5 mmol) of **24**,[6] 1.20 g (21 mmol) KOH and 2.1 g of water. After heating at 133°C for 18 h the mixture was cooled to ambient temperature and worked up to yield 0.32 g (54%) recovered **24**. The aqueous phase was acidified and extracted as usual but no carboxylic acid was isolated or observed.

[6] Compound **24** was prepared in 25% yield from cyclohexanone. ^1H NMR: δ 2.05 (br s, 4H), 1.53 (br s, 6H); ^{13}C NMR: δ 151 (t, $J_{FC} = 280$ Hz, CF_2), 88.1 ($J_{FC} = 18.7$ Hz), 26.5, 26.2, 24.4. IR: 2939, 2859, 1759 ($C=CF_2$), 1453, 1268, 1213, 738 cm^{-1}[29].

4.8. Alkaline hydrolysis of *11a* in the presence of *p*-dinitrobenzene

A 20-ml, screw-cap reaction vessel was charged with 1.09 g (3.59 mmol) of **11a** [7], 1.37 g (>21 mmol) KOH, 7 ml of water, and 0.64 g (3.81 mmol) of *p*-dinitrobenzene. The reaction vessel was heated in an oil bath while stirring for 13 h at 136°C. After cooling, the contents were diluted with 7 ml of water and rinsed into a separatory funnel with 7 ml of methylene chloride. The entire mixture was acidified to pH 2 with 6 M HCl. The organic layer was drawn off and the aqueous phase was extracted with 5 ml of methylene chloride which was combined with the organic phase. The combined organic extracts were washed twice with 10 ml portions of deionized water and then the carboxylic acid **16** was converted to the salt and extracted out of the methylene chloride solution with 15 ml of 5% aqueous sodium bicarbonate. The methylene chloride layer was dried over anhydrous calcium chloride and condensed by rotary evaporation to yield 0.37 g of reddish-brown oil that was identified as crude *exo*-3-(difluoromethylene)bicyclo[2,2,1]heptan-2-ol, **26**. ^1H and ^{13}C NMR analysis showed that the oil did not contain any unreacted **11a** or the monoelimination products **12** or **13**.

The aqueous bicarbonate extract was slowly acidified with 6 M HCl (caution! effervescence) and a small amount of finely divided white precipitate was observed. The mixture was extracted twice with 4-ml portions of methylene chloride. The combined extracts were dried over anhydrous calcium chloride and condensed by rotary evaporation to yield 0.32 g of residue identified as the carboxylic acid **16** contaminated by some *p*-dinitrobenzene that was carried through the work-up. The yield of **16** was 51% by ^1H NMR integration.[7]

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[7] When this reaction is carried out in the absence of *p*-dinitrobenzene the work-up is much simpler and the products can be more easily isolated and characterized [30]. Compound **26**: ^{13}C NMR: δ 153.3 (t, $J_{FC} = 287$ Hz, CF_2), 99 (dd, $J_{FC} = 19.2$ and 17.5 Hz, C3), 74.0 (d, $J_{FC} = 6$ Hz, COH) 44.2, 36.8, 36.0, 28.7, 23.6. ^1H NMR: δ 4.23 (s, 1H, on C2), 2.92 (s, 1H, on C1), 2.33 (s, 1H, on C4), 2.04 (s, 1H, OH), 1.82 (d of mult, $J = 9.6$ Hz, 1H), 1.58 (mult, 2H), 1.26 (mult, 2H), 1.11 (d of mult, $J = 9.6$ Hz, 1H). IR: 3353 (br, OH), 2952, 2866, 1762 (st, $C=CF_2$), 1448, 1248, 1065, 1048, 1018, 811, 774, 744 cm^{-1}. Spectral data for **16** agree with those cited previously [7].

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