Facile Synthesis of Methylenecyclobutyl-Related Compounds via Rearrangement of Methylenecyclopropylcarbinols in the Presence of Multifluorosulfonyl Fluorides and Base

Ming-Hui Qi,[a] Li-Xiong Shao,*[a] Min Shi*[b]

[a] School of Chemistry & Molecular Engineering, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, P. R. of China

[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. of China
Fax +86(21)64166128; E-mail: shaolix@ecust.edu.cn, mshi@mail.sioc.ac.cn

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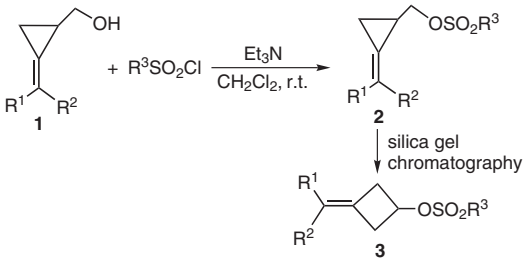
Abstract: Methylenecyclopropylcarbinols treated with multifluorosulfonyl fluorides and triethylamine form the 3-methylenecyclobutyl fluorides and 3-methylenecyclobutyl (2-methylenecyclopropyl)methyl ethers in good to high total yields. A proposed mechanism is based on the obtained results.

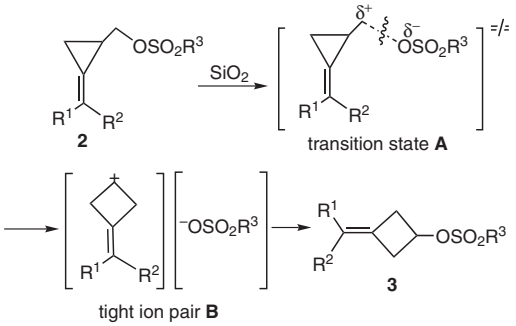
Key words: methylenecyclopropylcarbinols, multifluorosulfonyl fluorides, base, rearrangement, etherification

There has been a mounting interest in the application of methylenecyclopropane (MCP) derivatives in synthetic transformations.[1] Particular attention has been paid to the transition-metal-catalyzed reactions of MCPs with various reactants in organic synthesis over the past decades and some excellent reviews are available.[2] Recent research has resulted in the renaissance of Lewis acid catalyzed chemistry of MCPs, and some novel reaction patterns have been found by us and other groups.[3–6] Previous reports revealed that when 2-(hydroxymethyl)-substituted MCPs (methylenecyclopropylcarbinols) **1**[7] are treated with sulfonation reagents and triethylamine, they give the normal sulfonates **2**, which can be transformed into their isomers, the 3-methylenecyclobutyl analogues **3**, when a silica gel column is used as a workup step (Scheme 1).[8]



Scheme 1 Sulfonation of methylenecyclopropylcarbinols **1** and further rearrangement of the sulfonate

Density functional theory (DFT) studies suggest that silica gel, which serves as both a Lewis acid and a Lewis base, can stabilize the separated charges in the transition state by forming hydrogen bonds. Silica gel significantly accelerates the reaction and acts as an effective catalyst for the transformation. In computational studies, we found that in the rearrangement of the normal sulfonates **2** to their isomers **3**, the carbon skeleton part and the $^{-}OSO_2R^3$ part are a pair of tight ions in the intermediate **B**, while product **3** will be easily formed from attack of the $^{-}OSO_2R^3$ part to the carbon skeleton through tight ion pair **B** (SiO_2, silicic acid, has been omitted in the transition state **A** and intermediate **B** for convenience) (Scheme 2).[8]



Scheme 2 Brief mechanism extracted from the computational studies

In the mechanism, it can be seen that if $^{-}OSO_2R^3$ is a weak nucleophile and/or a good leaving group, the carbon skeletons in the transition state **A** and/or in the intermediate **B** would be attacked by the relatively stronger nucleophiles present in the reaction system. This hypothesis encouraged us to further utilize other sulfonation reagents to examine the reaction pattern of methylenecyclopropylcarbinols **1**. For this purpose, multifluorosulfonyl fluorides **4** were selected as the sulfonation reagent since $R^FSO_2O^-$ (R^F = multifluoro group) is a good leaving group and also a very weak nucleophilic agent.

As a consequence, we found that fluorides **5** and ethers **6**, both of which bearing a 3-methylenecyclobutyl group, were obtained as the products if methylenecyclopropylcarbinols **1** were treated with multifluorosulfonyl fluorides **4** and a base (Scheme 3).

Initial examinations of the reactions of methylenecyclopropylcarbinol **1a** (R^1 = Ph, R^2 = H) with perfluorobu-

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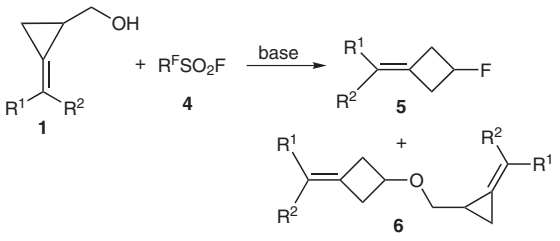
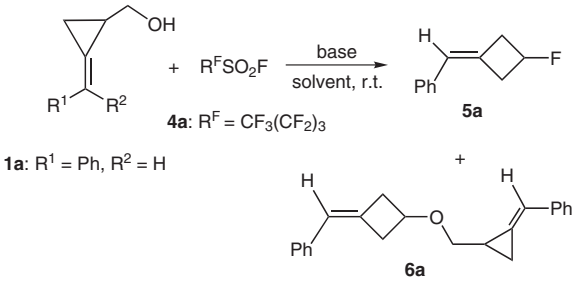


Scheme 3 Reaction of methylenecyclopropylcarbinols **1** in the presence of multifluorosulfonyl fluorides **4** and a base

Table 1 Optimization for the Reaction of Methylenecyclopropylcarbinol **1a** with Fluoride **4a**[a]

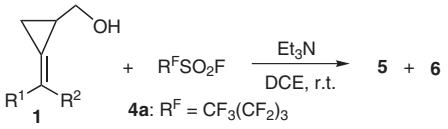


Entry	Base	Solvent	Yield[b] (%)	
			5a	**6a**[c]
1	Et_3N	DCE	57	35
2	DBU	DCE	23	18
3	DABCO	DCE	2	18
4	DMAP	DCE	27	24
5	DIPEA	DCE	22	49
6	Et_2NH	DCE	20	36
7	pyridine	DCE	–	28
8	*i*-Pr_2NH	DCE	47	41
9	Et_3N	Et_2O	27	–
10	Et_3N	benzene	41	–
11	Et_3N	toluene	31	–
12	Et_3N	MeCN	10	–

[a] All reactions were carried out using **1a** (0.3 mmol) and **4a** (0.6 mmol) in the presence of the listed base (0.4 mmol) and solvent (1.0 mL) at r.t. for 24 h.
[b] Isolated yields.
[c] Ratio of *syn*/*anti* = 1:1, as determined by ^{1}H NMR spectroscopy.

tane-1-sulfonyl fluoride (**4a**) were carefully carried out at room temperature. We found that the reactions took place smoothly to give the 3-methylenecyclobutyl fluoride **5a** and the corresponding ether **6a** in moderate to high total yields with various bases and solvents, as shown in Table 1. The combination of triethylamine as the base and 1,2-dichloroethane (DCE) as the solvent is the best choice for this transformation, leading to the formation of products **5a** in 57% yield and **6a** in 35% yield, respectively

Table 2 Reaction of Methylenecyclopropylcarbinols **1** with Fluoride **4a** in the Presence of Triethylamine[a]



Entry	Carbinol **1**	R^1	R^2	Yield[b] (%)	
				5	**6**[c]
1	**1b**	3,4,5-$(MeO)_3C_6H_2$	H	**5b**, 23	**6b**, 30
2	**1c**	4-BrC_6H_4	H	**5c**, 51	**6c**, 29
3	**1d**	4-MeC_6H_4	H	**5d**, 27	**6d**, 47
4	**1e**	4-ClC_6H_4	H	**5e**, 56	**6e**, 31
5	**1f**	2,3-$Cl_2C_6H_3$	H	**5f**, 30	**6f**, 8
6	**1g**	H	Ph	**5a**, 41	**6g**, 24
7	**1h**	H	3-MeC_6H_4	**5h**, 32	**6h**, 38
8	**1i**	4-$MeOC_6H_4$	H	**5i**, 21	**6i**, 28
9	**1j**	4-FC_6H_4	H	**5j**, 9	–
10	**1k**	H	H	**5k**, 7	–

[a] All reactions were carried out using **1** (0.3 mmol) and **4a** (0.6 mmol) in the presence of Et_3N (0.4 mmol) and DCE (1.0 mL) at r.t. for 24 h.
[b] Isolated yields.
[c] Ratio of *syn*/*anti* = 1:1, as determined by ^{1}H NMR spectroscopy.

(Table 1, entry 1). For other bases and solvents screened, the yield(s) of **5a** and/or **6a** varied from low to moderate in all other cases (Table 1, entries 2–12).

To survey the generality of this transformation, a variety of methylenecyclopropylcarbinols **1** was examined with perfluorobutane-1-sulfonyl fluoride (**4a**) under the optimized conditions. For most of the substrates **1** examined, either as the *E*- or *Z*-isomers, the reactions proceeded smoothly to give the corresponding products **5** and/or **6** in moderate to high total yields (Table 2). For substrates **1j** (R^1 = 4-FC_6H_4, R^2 = H) and **1k** (R^1 = R^2 = H), only the corresponding products **5j** and **5k**, respectively, were obtained in very low yields (Table 2, entries 9 and 10). To further determine the structure of products **5**, fluoride **5c** was unambiguously confirmed by an X-ray diffraction analysis (Figure 1).[9] For all products **6**, mixtures of *syn*- and *anti*-isomers were obtained in a ratio of 1:1 (Table 2).

To further examine the generality, we also carried out the transformation of substrates **1** with another multifluorosulfonyl fluoride **4b** under the optimized conditions. Again, all reactions proceeded smoothly to give the corresponding products **5** and **6** in good to high total yields (Table 3).

The reaction of methylenecyclopropylcarbinol **1a** with trifluoromethanesulfonic anhydride was also carried out under the standard conditions. Unfortunately, we found that the reaction system became disordered and no major product could be obtained (Scheme 4).

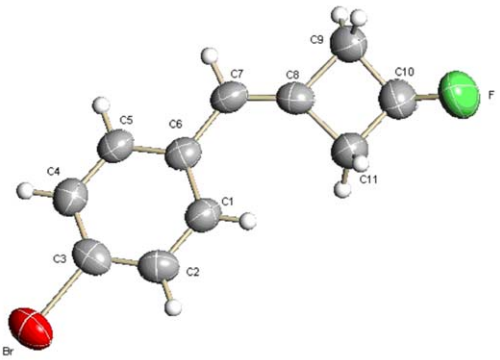
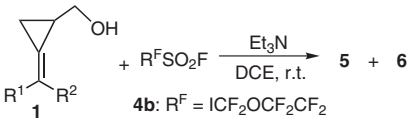


Figure 1 ORTEP drawing of product **5c**

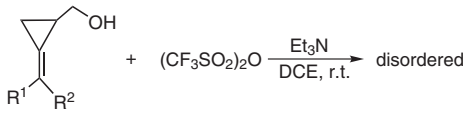
Table 3 Reaction of Methylenecyclopropylcarbinols **1** with Fluoride **4b** in the Presence of Triethylamine[a]



Entry	Carbinol **1** R^1		R^2	Yield[b] (%)	
				5	**6**[c]
1	**1a**	Ph	H	**5a**, 64	**6a**, 27
2	**1c**	4-BrC_6H_4	H	**5c**, 44	**6c**, 26
3	**1d**	4-MeC_6H_4	H	**5d**, 23	**6d**, 42
4	**1e**	4-ClC_6H_4	H	**5e**, 41	**6e**, 36

[a] All reactions were carried out using **1** (0.3 mmol) and **4b** (0.6 mmol) in the presence of Et_3N (0.4 mmol) and DCE (1.0 mL) at r.t. for 24 h.
[b] Isolated yields.
[c] Ratio of *syn*/*anti* = 1:1, as determined by ^1H NMR spectroscopy.

Based on the results obtained above, a plausible mechanism for this transformation of methylenecyclopropylcarbinols **1** is outlined in Scheme 5. Firstly,

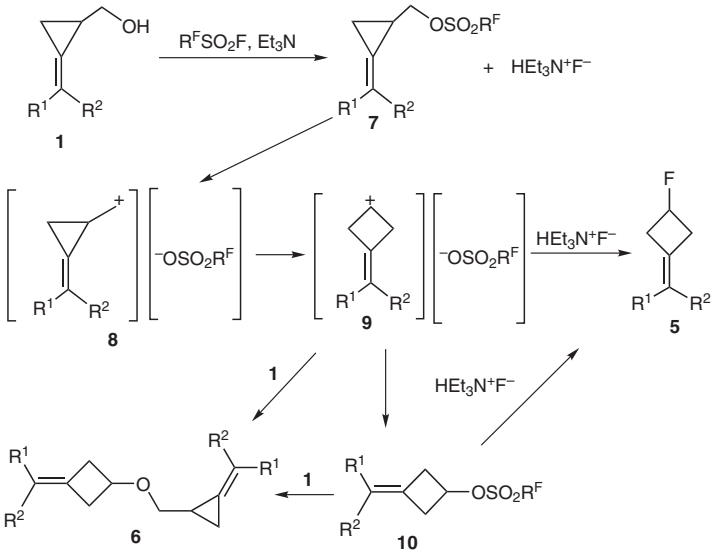


1a: R^1 = Ph, R^2 = H

Scheme 4 Reaction of methylenecyclopropylcarbinol **1a** with $(CF_3SO_2)_2O$ under the standard conditions

methylenecyclopropylcarbinols **1** react with R^FSO_2F in the presence of triethylamine to give the normal sulfonates **7** and triethylamine hydrofluoride ($HEt_3N^+F^-$). The enhanced leaving-group ability of $R^FSO_2O^-$ is well known[10] and the C–O bond will become more polarized according to this property, which will result in a separate ion pair as shown as intermediate **8** (maybe it is more reasonable to show **8** as an intermediate with more polarization in the C–O bond rather than a separated ion pair). Subsequently, the carbon skeleton part in **8**, that is, the methylenecyclopropylmethyl cation, will quickly rearrange to the methylenecyclobutyl cation, as shown as intermediate **9**, which will also be a separated ion pair for the same reason.[10] Nucleophilic attack of **9** by F^- from $HEt_3N^+F^-$ will give product **5**, while nucleophilic attack by substrate **1** will furnish product **6**. At the same time, intermediate **9** can also be shown as the sulfonate **10**, which will also result in products **5** and **6**, if it is attacked by the appropriate nucleophiles (Scheme 5).

In summary, we have found that methylenecyclopropylcarbinols **1** treated with multifluorosulfonyl fluorides **4** can give 3-methylenecyclobutyl fluorides **5** and the corresponding 3-methylenecyclobutyl-related ethers **6** in good to high total yields. A plausible mechanism has been proposed on the basis of the obtained results, which puts its emphasis on the rearrangement of methylenecyclopropylmethyl multifluorosulfonates to methylenecyclobutyl analogues due to the easy leaving-group ability of $R^FSO_2O^-$. Furthermore, the reaction also introduces a new and sim-



Scheme 5 Plausible mechanism for the formation of **5** and **6**

ple one-step synthetic method for 3-methylenecyclobutyl fluorides **5** from methylenecyclopropylcarbinols **1** with easy manipulation and a simple experimental procedure. Efforts are underway in our laboratory to elucidate the mechanistic details and to determine the scope and limitations of the reaction.

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury VX-300 spectrometer for solutions in $CDCl_3$ with tetramethylsilane as an internal standard. IR spectra were measured on a Perkin–Elmer 983 spectrometer. Mass spectra and HRMS were recorded with a HP-5989 instrument, a Finnigan MA$^+$ mass spectrometer and a Micromass GCT mass spectrometer. Satisfactory CHN microanalyses were obtained with a Carlo–Erba 1106 analyzer. Organic solvents were dried by standard methods when necessary. Melting points are uncorrected. All reactions were monitored by TLC using Huanghai GF_{254} silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure.

3-(Arylmethylene)cyclobutyl Fluorides 5 and 3-(Arylmethylene)cyclobutyl [2-(Arylmethylene)cyclopropyl]methyl Ethers 6; General Procedure

Under an argon atmosphere, a methylenecyclopropylcarbinol **1** (0.3 mmol), a multifluorosulfonyl fluoride **4** (0.6 mmol), Et_3N (0.4 mmol) and DCE (1.0 mL) were added successively into a flash-dried Schlenk tube. The reaction mixture was stirred at r.t. and was monitored by TLC. The reaction usually was completed within 24 h. Then, the reaction was quenched with H_2O (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with 1.0 M aq HCl (10 mL) and sat. aq $NaHCO_3$ soln (10 mL), and dried (anhyd $MgSO_4$), then the solution was concentrated under reduced pressure. Pure products were obtained by flash column chromatography (PE–EtOAc, 50:1).

5a

Colorless liquid.

IR (CH_2Cl_2): 2924, 2853, 1789, 1705, 1599, 1496, 1453, 1404, 1353, 1269, 1162, 1023, 742 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.11–3.35 (m, 4 H), 5.17 (d quin, *J* = 56.1, 6.0 Hz, 1 H), 6.29 (t, *J* = 2.4 Hz, 1 H), 7.17–7.23 (m, 3 H, Ar), 7.31–7.34 (m, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.4 (d, J_{CF} = 22.4 Hz), 41.9 (d, J_{CF} = 21.8 Hz), 84.4 (d, J_{CF} = 209.7 Hz), 123.6 (d, J_{CF} = 7.3 Hz), 126.5, 127.1, 128.5, 131.5 (d, J_{CF} = 18.5 Hz), 137.3.

MS: *m*/*z* (%) = 162 (8) [M$^+$], 158 (50), 129 (38), 115 (32), 105 (100).

HRMS: *m*/*z* calcd for $C_{11}H_{11}F$: 162.0845; found: 162.0836.

6a

Colorless liquid.

IR (CH_2Cl_2): 3083, 3060, 3025, 2924, 2855, 1945, 1736, 1685, 1597, 1495, 1450, 1340, 1259, 1184, 1116, 912, 865, 746 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) (*syn*- or *anti*-isomer): δ = 1.25–1.33 (m, 1 H), 1.72 (t, *J* = 8.7 Hz, 1 H), 1.83–1.93 (m, 1 H), 2.90–3.31 (m, 5 H), 3.54 (dd, *J* = 6.3, 10.2 Hz, 1 H), 4.21 (quin, *J* = 6.3 Hz, 1 H), 6.25 (s, 1 H), 6.82 (s, 1 H), 7.14–7.36 (m, 8 H, Ar), 7.53 (d, *J* = 7.8 Hz, 2 H, Ar).

^{1}H NMR (300 MHz, $CDCl_3$) (*anti*- or *syn*-isomer): δ = 1.25–1.33 (m, 1 H), 1.73 (t, *J* = 8.7 Hz, 1 H), 1.83–1.93 (m, 1 H), 2.90–3.31 (m, 5 H), 3.54 (dd, *J* = 6.3, 10.2 Hz, 1 H), 4.21 (quin, *J* = 6.3 Hz, 1 H), 6.25 (s, 1 H), 6.83 (s, 1 H), 7.14–7.36 (m, 8 H, Ar), 7.53 (d, *J* = 7.8 Hz, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$) (*syn*- or *anti*-isomer): δ = 10.1, 13.1, 40.7, 41.1, 70.1, 71.1, 119.1, 122.6, 125.9, 126.1, 126.7, 127.1, 128.4, 128.5, 134.9, 137.6, 137.7.

^{13}C NMR (75 MHz, $CDCl_3$) (*anti*- or *syn*-isomer): δ = 10.1, 13.1, 40.8, 41.2, 70.2, 71.1, 119.1, 122.6, 125.9, 126.1, 126.7, 127.1, 128.4, 128.5, 134.9, 137.6, 137.7.

MS: *m*/*z* (%) = 302 (1) [M$^+$], 143 (62), 128 (100), 115 (35).

HRMS: *m*/*z* calcd for $C_{22}H_{22}O$: 302.1671; found: 302.1674.

5b

Colorless liquid.

IR (CH_2Cl_2): 2960, 2936, 2839, 1750, 1691, 1581, 1507, 1464, 1417, 1350, 1325, 1238, 1184, 1127, 1071, 1008, 931, 879, 826, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.13–3.37 (m, 4 H), 3.85 (s, 3 H, MeO), 3.86 (s, 6 H, 2 × MeO), 5.19 (d quin, *J* = 56.1, 6.0 Hz, 1 H), 6.23 (t, *J* = 2.1 Hz, 1 H), 6.42 (s, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.3 (d, J_{CF} = 22.4 Hz), 41.8 (d, J_{CF} = 22.7 Hz), 56.0, 60.9, 84.3 (d, J_{CF} = 209.9 Hz), 104.1, 123.6 (d, J_{CF} = 7.4 Hz), 130.9 (d, J_{CF} = 18.4 Hz), 133.1, 153.1.

MS: *m*/*z* (%) = 252 (80) [M$^+$], 237 (20), 221 (100), 191 (46).

HRMS: *m*/*z* calcd for $C_{14}H_{17}FO_3$: 252.1162; found: 252.1161.

6b

Colorless liquid.

IR (CH_2Cl_2): 2939, 2839, 1737, 1687, 1584, 1506, 1463, 1417, 1327, 1237, 1185, 1127, 1005 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) (*syn*- or *anti*-isomer): δ = 1.23–1.33 (m, 1 H), 1.72 (t, *J* = 8.7 Hz, 1 H), 1.86–1.94 (m, 1 H), 2.94–3.34 (m, 5 H), 3.52 (dd, *J* = 6.3, 10.2 Hz, 1 H), 3.84 (s, 3 H, MeO), 3.85 (s, 9 H, 3 × MeO), 3.89 (s, 6 H, 2 × MeO), 4.22 (quin, *J* = 6.3 Hz, 1 H), 6.19 (s, 1 H), 6.44 (s, 2 H, Ar), 6.75 (s, 1 H), 6.78 (s, 2 H, Ar).

^{1}H NMR (300 MHz, $CDCl_3$) (*anti*- or *syn*-isomer): δ = 1.23–1.33 (m, 1 H), 1.73 (t, *J* = 8.7 Hz, 1 H), 1.86–1.94 (m, 1 H), 2.94–3.34 (m, 5 H), 3.53 (dd, *J* = 6.3, 10.2 Hz, 1 H), 3.84 (s, 3 H, MeO), 3.85 (s, 9 H, 3 × MeO), 3.89 (s, 6 H, 2 × MeO), 4.22 (quin, *J* = 6.3 Hz, 1 H), 6.19 (s, 1 H), 6.44 (s, 2 H, Ar), 6.76 (s, 1 H), 6.78 (s, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$) (*syn*- or *anti*-isomer): δ = 9.8, 13.1, 40.5, 41.0, 55.9, 56.0, 60.89, 60.91, 70.1, 71.0, 103.6, 104.0, 119.1, 122.6, 125.3, 133.4, 133.5, 134.3, 136.5, 137.3, 153.1, 153.2.

^{13}C NMR (75 MHz, $CDCl_3$) (*anti*- or *syn*-isomer): δ = 9.8, 13.1, 40.6, 41.1, 55.9, 56.0, 60.89, 60.91, 70.1, 71.0, 103.6, 104.0, 119.1, 122.6, 125.3, 133.4, 133.5, 134.3, 136.5, 137.3, 153.1, 153.2.

MS: *m*/*z* (%) = 482 (40) [M$^+$], 233 (66), 232 (42), 202 (100), 189 (32).

HRMS: *m*/*z* calcd for $C_{28}H_{34}O_7$: 482.2305; found: 482.2310.

5c

White solid; mp 55–57 °C.

IR (neat): 2990, 2972, 2954, 2901, 1899, 1756, 1677, 1649, 1487, 1427, 1401, 1358, 1228, 1207, 1173, 1110, 1065, 1019, 1007, 978, 934, 879, 822, 782 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.10–3.32 (m, 4 H), 5.18 (d quin, *J* = 55.8, 6.0 Hz, 1 H), 6.23 (t, *J* = 2.4 Hz, 1 H), 7.04 (d, *J* = 8.4 Hz, 2 H, Ar), 7.42 (d, *J* = 8.4 Hz, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.3 (d, J_{CF} = 22.4 Hz), 41.9 (d, J_{CF} = 22.4 Hz), 84.2 (d, J_{CF} = 209.9 Hz), 120.1, 122.6 (d, J_{CF} = 7.9 Hz), 128.6, 131.5, 132.6 (d, J_{CF} = 17.9 Hz), 136.1.

MS: *m*/*z* (%) = 242 (35), 240 (35) [M$^+$], 196 (29), 194 (29), 161 (90), 146 (31), 141 (63), 115 (100).

Anal. Calcd for $C_{11}H_{10}BrF$: C, 54.80; H, 4.18. Found: C, 54.80; H, 4.15.

6c

White solid; mp 104–106 °C.

IR (CH_2Cl_2): 2922, 2853, 1487, 1400, 1276, 1261, 1184, 1106, 1072, 1007, 875, 820, 764, 750 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) (*syn*- or *anti*-isomer): δ = 1.26–1.31 (m, 1 H), 1.69 (t, *J* = 9.0 Hz, 1 H), 1.82–1.91 (m, 1 H), 2.85–3.31 (m, 5 H), 3.48–3.54 (m, 1 H), 4.20 (quin, *J* = 6.3 Hz, 1 H), 6.18 (s, 1 H), 6.76 (s, 1 H), 7.05 (d, *J* = 8.7 Hz, 2 H, Ar), 7.37–7.46 (m, 6 H, Ar).

^1H NMR (300 MHz, $CDCl_3$) (*anti*- or *syn*-isomer): δ = 1.26–1.31 (m, 1 H), 1.70 (t, *J* = 9.0 Hz, 1 H), 1.82–1.91 (m, 1 H), 2.85–3.31 (m, 5 H), 3.48–3.54 (m, 1 H), 4.20 (quin, *J* = 6.3 Hz, 1 H), 6.18 (s, 1 H), 6.77 (s, 1 H), 7.05 (d, *J* = 8.7 Hz, 2 H, Ar), 7.37–7.46 (m, 6 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$) (*syn*- or *anti*-isomer): δ = 10.0, 13.2, 40.6, 41.1, 70.0, 70.9, 118.2, 119.8, 120.8, 121.7, 126.8, 128.2, 128.6, 131.4, 131.5, 136.0, 136.5.

^{13}C NMR (75 MHz, $CDCl_3$) (*anti*- or *syn*-isomer): δ = 10.0, 13.2, 40.7, 41.2, 70.0, 70.9, 118.2, 119.8, 120.8, 121.7, 126.8, 128.2, 128.6, 131.4, 131.5, 136.0, 136.5.

MS: *m*/*z* (%) = 458 (0.5) [M^+], 143 (11), 142 (100), 141 (36).

Anal. Calcd for $C_{22}H_{20}Br_2O$: C, 57.42; H, 4.38. Found: C, 57.63; H, 4.50.

5d

Colorless liquid.

IR (CH_2Cl_2): 3023, 2967, 2921, 2857, 1896, 1750, 1730, 1700, 1680, 1610, 1514, 1402, 1349, 1179, 1072, 1019, 936, 875, 817, 764, 750 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, Me), 3.10–3.34 (m, 4 H), 5.17 (d quin, *J* = 56.4, 6.0 Hz, 1 H), 6.26 (t, *J* = 2.4 Hz, 1 H), 7.08 (d, *J* = 8.7 Hz, 2 H, Ar), 7.13 (d, *J* = 8.7 Hz, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 41.4 (d, J_{CF} = 22.2 Hz), 41.9 (d, J_{CF} = 22.7 Hz), 84.5 (d, J_{CF} = 209.9 Hz), 123.5 (d, J_{CF} = 7.6 Hz), 127.0, 129.1, 130.3 (d, J_{CF} = 18.2 Hz), 134.5, 136.2.

MS: *m*/*z* (%) = 176 (65) [M^+], 161 (100), 156 (32), 141 (39), 130 (37), 129 (57), 128 (40), 115 (75).

HRMS: *m*/*z* calcd for $C_{12}H_{13}F$: 176.1001; found: 176.1001.

6d

Yellow liquid.

IR ($CDCl_3$): 2962, 2920, 1727, 1512, 1458, 1275, 1261, 1187, 1108, 1031, 967, 871, 815, 750 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) (*syn*- or *anti*-isomer): δ = 1.25–1.34 (m, 1 H), 1.69 (t, *J* = 8.7 Hz, 1 H), 1.82–1.90 (m, 1 H), 2.32 (s, 3 H, Me), 2.34 (s, 3 H, Me), 2.93–3.29 (m, 5 H), 3.54 (dd, *J* = 6.3, 9.9 Hz, 1 H), 4.19 (quin, *J* = 6.3 Hz, 1 H), 6.21 (s, 1 H), 6.78 (s, 1 H), 7.10–7.15 (m, 6 H, Ar), 7.42 (d, *J* = 8.4 Hz, 2 H, Ar).

^1H NMR (300 MHz, $CDCl_3$) (*anti*- or *syn*-isomer): δ = 1.25–1.34 (m, 1 H), 1.70 (t, *J* = 8.7 Hz, 1 H), 1.82–1.90 (m, 1 H), 2.32 (s, 3 H, Me), 2.34 (s, 3 H, Me), 2.93–3.29 (m, 5 H), 3.54 (dd, *J* = 6.3, 9.9 Hz, 1 H), 4.19 (quin, *J* = 6.3 Hz, 1 H), 6.21 (s, 1 H), 6.79 (s, 1 H), 7.10–7.15 (m, 6 H, Ar), 7.42 (d, *J* = 8.4 Hz, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$) (*syn*- or *anti*-isomer): δ = 10.1, 13.1, 21.1, 21.2, 40.6, 41.0, 70.2, 71.1, 119.0, 122.4, 124.7, 126.6, 127.0, 129.1, 129.2, 133.8, 134.89, 134.91, 135.8, 136.8.

^{13}C NMR (75 MHz, $CDCl_3$) (*anti*- or *syn*-isomer): δ = 10.1, 13.1, 21.1, 21.2, 40.7, 41.1, 70.2, 71.2, 119.0, 122.4, 124.7, 126.6, 127.0, 129.1, 129.2, 133.8, 134.89, 134.91, 135.8, 136.8.

MS: *m*/*z* (%) = 330 (0.3) [M^+], 157 (37), 142 (100), 129 (43).

HRMS: *m*/*z* calcd for $C_{24}H_{26}O$: 330.1984; found: 330.1986.

5e

White solid; mp 33–35 °C.

IR ($CDCl_3$): 3029, 2970, 2913, 1902, 1680, 1592, 1492, 1405, 1349, 1226, 1207, 1179, 1091, 1073, 1012, 936, 875, 824 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.11–3.31 (m, 4 H), 5.18 (d quin, *J* = 55.8, 6.0 Hz, 1 H), 6.24 (t, *J* = 2.4 Hz, 1 H), 7.10 (d, *J* = 8.4 Hz, 2 H, Ar), 7.27 (d, *J* = 8.4 Hz, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.3 (d, J_{CF} = 22.4 Hz), 41.9 (d, J_{CF} = 22.3 Hz), 84.3 (d, J_{CF} = 210.1 Hz), 122.6 (d, J_{CF} = 7.4 Hz), 128.3, 128.6, 132.0, 132.4 (d, J_{CF} = 17.8 Hz), 135.7.

MS: *m*/*z* (%) = 196 (36) [M^+], 161 (91), 150 (33), 141 (52), 115 (100).

HRMS: *m*/*z* calcd for $C_{11}H_{10}ClF$: 196.0455; found: 196.0455.

6e

Yellow solid; mp 84–86 °C.

IR ($CDCl_3$): 3032, 2961, 2925, 2854, 1735, 1491, 1403, 1261, 1188, 1090, 1012, 969, 871, 822 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) (*syn*- or *anti*-isomer): δ = 1.28–1.32 (m, 1 H), 1.70 (t, *J* = 9.0 Hz, 1 H), 1.84–1.92 (m, 1 H), 2.87–3.32 (m, 5 H), 3.51 (dd, *J* = 6.3, 10.2 Hz, 1 H), 4.20 (quin, *J* = 6.3 Hz, 1 H), 6.20 (s, 1 H), 6.78 (s, 1 H), 7.12 (d, *J* = 8.1 Hz, 2 H, Ar), 7.25–7.31 (m, 4 H, Ar), 7.45 (d, *J* = 8.1 Hz, 2 H, Ar).

^1H NMR (300 MHz, $CDCl_3$) (*anti*- or *syn*-isomer): δ = 1.28–1.32 (m, 1 H), 1.71 (t, *J* = 9.0 Hz, 1 H), 1.84–1.92 (m, 1 H), 2.87–3.32 (m, 5 H), 3.52 (dd, *J* = 6.3, 10.2 Hz, 1 H), 4.20 (quin, *J* = 6.3 Hz, 1 H), 6.20 (s, 1 H), 6.78 (s, 1 H), 7.12 (d, *J* = 8.1 Hz, 2 H, Ar), 7.25–7.31 (m, 4 H, Ar), 7.45 (d, *J* = 8.1 Hz, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$) (*syn*- or *anti*-isomer): δ = 10.0, 13.2, 40.6, 41.1, 70.1, 70.9, 118.1, 121.6, 126.7, 127.8, 128.2, 128.5, 128.6, 131.7, 132.6, 135.8, 136.11, 136.12.

^{13}C NMR (75 MHz, $CDCl_3$) (*anti*- or *syn*-isomer): δ = 10.0, 13.2, 40.7, 41.2, 70.1, 71.0, 118.1, 121.6, 126.7, 127.8, 128.3, 128.5, 128.6, 131.7, 132.6, 135.8, 136.11, 136.12.

MS: *m*/*z* (%) = 370 (1) [M^+], 177 (23), 142 (100), 141 (56).

HRMS: *m*/*z* calcd for $C_{22}H_{20}Cl_2O$: 370.0891; found: 370.0889.

5f

Colorless liquid.

IR (CH_2Cl_2): 3020, 2971, 2920, 2853, 1680, 1580, 1557, 1450, 1410, 1351, 1275, 1261, 1224, 1183, 1158, 1096, 1074, 1045, 1020, 970, 940, 888, 863, 798, 781, 765, 750 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.17–3.25 (m, 4 H), 5.18 (d quin, *J* = 56.1, 6.0 Hz, 1 H), 6.65 (t, *J* = 2.4 Hz, 1 H), 7.14–7.18 (m, 2 H, Ar), 7.29–7.33 (m, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.2 (d, J_{CF} = 22.7 Hz), 42.0 (d, J_{CF} = 22.4 Hz), 83.9 (d, J_{CF} = 210.5 Hz), 120.3 (d, J_{CF} = 7.3 Hz), 126.1, 126.9, 128.4, 130.9, 133.4, 135.2 (d, J_{CF} = 18.8 Hz), 137.1.

MS: *m*/*z* (%) = 230 (33) [M^+], 197 (25), 195 (72), 184 (26), 175 (40), 160 (24), 151 (28), 149 (100).

HRMS: *m*/*z* calcd for $C_{11}H_9Cl_2F$: 230.0065; found: 230.0065.

6g
Yellow liquid.

IR ($CDCl_3$): 3082, 3059, 3025, 2964, 2905, 1738, 1597, 1494, 1449, 1340, 1188, 1116, 1076, 1008, 912, 865, 768, 744 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) (*syn*- or *anti*-isomer): δ = 1.08–1.12 (m, 1 H), 1.46 (t, *J* = 9.0 Hz, 1 H), 2.08–2.17 (m, 1 H), 2.87–3.25 (m, 5 H), 3.80 (dd, *J* = 6.3, 9.9 Hz, 1 H), 4.16 (quin, *J* = 6.3 Hz, 1 H), 6.23 (s, 1 H), 6.76 (s, 1 H), 7.13–7.35 (m, 8 H, Ar), 7.51 (d, *J* = 7.5 Hz, 2 H, Ar).

^1H NMR (300 MHz, $CDCl_3$) (*anti*- or *syn*-isomer): δ = 1.08–1.12 (m, 1 H), 1.46 (t, *J* = 9.0 Hz, 1 H), 2.08–2.17 (m, 1 H), 2.87–3.25 (m, 5 H), 3.80 (dd, *J* = 6.3, 9.9 Hz, 1 H), 4.16 (quin, *J* = 6.3 Hz, 1 H), 6.24 (s, 1 H), 6.77 (s, 1 H), 7.13–7.35 (m, 8 H, Ar), 7.51 (d, *J* = 7.5 Hz, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$) (*syn*- or *anti*-isomer): δ = 7.2, 16.8, 40.5, 41.0, 70.3, 70.5, 120.1, 122.6, 125.70, 125.72, 126.1, 126.7, 127.0, 128.3, 128.5, 134.9, 137.3, 137.6.

^{13}C NMR (75 MHz, $CDCl_3$) (*anti*- or *syn*-isomer): δ = 7.2, 16.8, 40.7, 41.1, 70.3, 70.5, 120.1, 122.6, 125.70, 125.72, 126.1, 126.7, 127.0, 128.3, 128.5, 134.9, 137.3, 137.6.

MS: *m*/*z* (%) = 302 (0.2) [M^+], 143 (43), 128 (100), 115 (45), 91 (27).

HRMS: *m*/*z* calcd for $C_{22}H_{22}O$: 302.1671; found: 302.1674.

5h
Colorless liquid.

IR (CH_2Cl_2): 2960, 2925, 2855, 1736, 1720, 1604, 1490, 1466, 1459, 1350, 1259, 1179, 1073, 1021, 904, 881, 785 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3 H, Me), 3.12–3.36 (m, 4 H), 5.18 (d quin, *J* = 56.1, 6.0 Hz, 1 H), 6.26 (t, *J* = 2.4 Hz, 1 H), 7.00–7.02 (m, 3 H, Ar), 7.19–7.24 (m, 1 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 41.4 (d, J_{CF} = 22.3 Hz), 41.9 (d, J_{CF} = 22.4 Hz), 84.4 (d, J_{CF} = 209.5 Hz), 123.7 (d, J_{CF} = 7.5 Hz), 124.2, 127.3, 127.9, 128.3, 131.2 (d, J_{CF} = 18.5 Hz), 137.2, 138.0.

MS: *m*/*z* (%) = 176 (75) [M^+], 161 (100), 156 (32), 146 (25), 141 (39), 130 (32), 129 (49), 128 (39), 115 (71).

HRMS: *m*/*z* calcd for $C_{12}H_{13}F$: 176.1001; found: 176.0999.

6h
Yellow liquid.

IR (CH_2Cl_2): 3032, 2921, 2857, 1782, 1736, 1604, 1584, 1489, 1459, 1338, 1261, 1187, 1114, 1039, 905, 785 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) (*syn*- or *anti*-isomer): δ = 1.07–1.11 (m, 1 H), 1.45 (t, *J* = 9.0 Hz, 1 H), 2.08–2.18 (m, 1 H), 2.33 (s, 3 H, Me), 2.36 (s, 3 H, Me), 2.87–3.26 (m, 5 H), 3.79 (dd, *J* = 6.3, 9.9 Hz, 1 H), 4.17 (quin, *J* = 6.3 Hz, 1 H), 6.20 (s, 1 H), 6.73 (s, 1 H), 6.97–7.35 (m, 8 H, Ar).

^1H NMR (300 MHz, $CDCl_3$) (*anti*- or *syn*-isomer): δ = 1.07–1.11 (m, 1 H), 1.46 (t, *J* = 9.0 Hz, 1 H), 2.08–2.18 (m, 1 H), 2.33 (s, 3 H, Me), 2.36 (s, 3 H, Me), 2.87–3.26 (m, 5 H), 3.80 (dd, *J* = 6.3, 9.9 Hz, 1 H), 4.17 (quin, *J* = 6.3 Hz, 1 H), 6.20 (s, 1 H), 6.73 (s, 1 H), 6.97–7.35 (m, 8 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$) (*syn*- or *anti*-isomer): δ = 7.1, 16.8, 21.46, 21.48, 40.6, 41.0, 70.4, 70.6, 120.2, 122.7, 123.8, 124.1, 125.5, 126.9, 127.5, 127.8, 127.9, 128.2, 128.4, 134.7, 137.3, 137.7, 137.9, 138.0.

^{13}C NMR (75 MHz, $CDCl_3$) (*anti*- or *syn*-isomer): δ = 7.1, 16.8, 21.46, 21.48, 40.8, 41.2, 70.4, 70.6, 120.2, 122.7, 123.9, 124.1, 125.5, 126.9, 127.5, 127.8, 127.9, 128.2, 128.4, 134.7, 137.3, 137.7, 137.9, 138.0.

MS: *m*/*z* (%) = 330 (2) [M^+], 157 (47), 142 (100), 129 (30).

HRMS: *m*/*z* calcd for $C_{24}H_{26}O$: 330.1984; found: 330.1985.

5i
Yellow liquid.

IR (CH_2Cl_2): 2963, 2913, 2832, 1608, 1512, 1461, 1347, 1297, 1275, 1257, 1175, 1071, 1035, 828, 764, 750 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.09–3.34 (m, 4 H), 3.80 (s, 3 H, MeO), 5.17 (d quin, *J* = 55.8, 6.3 Hz, 1 H), 6.23 (t, *J* = 2.4 Hz, 1 H), 6.86 (d, *J* = 8.7 Hz, 2 H, Ar), 7.13 (d, *J* = 8.7 Hz, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.2 (d, J_{CF} = 22.1 Hz), 41.8 (d, J_{CF} = 21.8 Hz), 55.3, 84.5 (d, J_{CF} = 209.8 Hz), 113.9, 123.0 (d, J_{CF} = 7.5 Hz), 128.3, 128.8 (d, J_{CF} = 18.5 Hz), 130.2, 158.2.

MS: *m*/*z* (%) = 192 (100) [M^+], 177 (49), 172 (45), 146 (50), 131 (35), 103 (34).

HRMS: *m*/*z* calcd for $C_{12}H_{13}FO$: 192.0950; found: 192.0950.

6i
White solid; mp 73–75 °C.

IR (CH_2Cl_2): 2955, 2932, 2852, 2836, 1729, 1607, 1511, 1463, 1442, 1339, 1293, 1248, 1174, 1107, 1034, 870, 828 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) (*syn*- or *anti*-isomer): δ = 1.25–1.29 (m, 1 H), 1.68 (t, *J* = 8.7 Hz, 1 H), 1.81–1.90 (m, 1 H), 2.84–3.29 (m, 5 H), 3.53 (dd, *J* = 6.3, 10.2 Hz, 1 H), 3.80 (s, 3 H, MeO), 3.81 (s, 3 H, MeO), 4.20 (quin, *J* = 6.3 Hz, 1 H), 6.19 (s, 1 H), 6.76 (s, 1 H), 6.85 (d, *J* = 8.1 Hz, 2 H, Ar), 6.88 (d, *J* = 8.1 Hz, 2 H, Ar), 7.14 (d, *J* = 8.4 Hz, 2 H, Ar), 7.47 (d, *J* = 8.4 Hz, 2 H, Ar).

^1H NMR (300 MHz, $CDCl_3$) (*anti*- or *syn*-isomer): δ = 1.25–1.29 (m, 1 H), 1.69 (t, *J* = 8.7 Hz, 1 H), 1.81–1.90 (m, 1 H), 2.84–3.29 (m, 5 H), 3.54 (dd, *J* = 6.3, 10.2 Hz, 1 H), 3.80 (s, 3 H, MeO), 3.81 (s, 3 H, MeO), 4.20 (quin, *J* = 6.3 Hz, 1 H), 6.19 (s, 1 H), 6.77 (s, 1 H), 6.85 (d, *J* = 8.1 Hz, 2 H, Ar), 6.88 (d, *J* = 8.1 Hz, 2 H, Ar), 7.14 (d, *J* = 8.4 Hz, 2 H, Ar), 7.47 (d, *J* = 8.4 Hz, 2 H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$) (*syn*- or *anti*-isomer): δ = 10.0, 13.2, 40.4, 41.0, 55.2, 55.3, 70.2, 71.2, 113.8, 113.9, 118.5, 121.9, 123.3, 127.8, 128.2, 130.59, 130.62, 132.4, 157.9, 158.8.

^{13}C NMR (75 MHz, $CDCl_3$) (*anti*- or *syn*-isomer): δ = 10.0, 13.2, 40.5, 41.1, 55.2, 55.3, 70.2, 71.2, 113.8, 113.9, 118.5, 121.9, 123.3, 127.8, 128.2, 130.59, 130.62, 132.4, 157.9, 158.8.

MS: *m*/*z* (%) = 362 (12) [M^+], 173 (68), 158 (100).

HRMS: *m*/*z* calcd for $C_{24}H_{26}O_3$: 362.1882; found: 362.1882.

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