JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

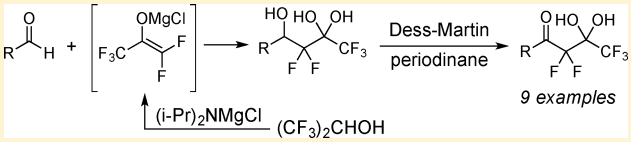
Generation of Magnesium Pentafluoropropen-2-olate from Hexafluoroisopropanol and Synthesis of 2,2,4,4,4-Pentafluoro-3,3-dihydroxyketones

Robert A. Hazlitt, Que-Lynn Tran, Munia F. Sowaileh, and David A. Colby*

Department of BioMolecular Sciences, University of Mississippi, University, Mississippi 38677, United States

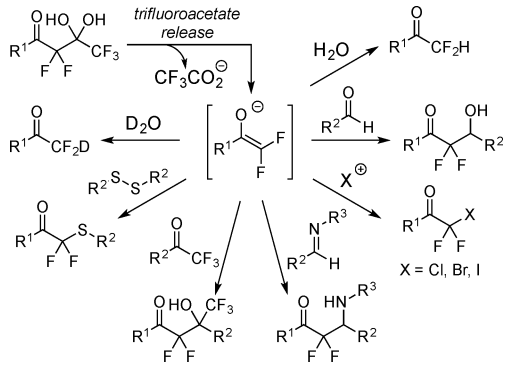
Supporting Information

ABSTRACT: 2,2,4,4,4-Pentafluoro-3,3-dihydroxyketones are valuable precursors to difluoroenolates following fragmentation during the release of trifluoroacetate; however, there are few synthetic strategies to prepare this unique class of compound. We addressed this issue and report a mild, two-step synthesis of 2,2,4,4,4-pentafluoro-3,3-dihydroxyketones from aldehydes. Specifically, aldehydes are treated with pentafluoropropen-2-olate, generated from a new fragmentation of hexafluoroisopropanol with a mixed Mg/Li amide, to give pentafluoroalcohols. A subsequent oxidation with Dess−Martin periodinane provides the targets in good isolated yields.



Incorporation of fluorine into organic molecules is essential in the pharmaceutical, agrochemical, and polymer industries. Major advances in synthetic chemistry have occurred to enable the production of compounds displaying a fluorine atom[1] or a trifluoromethyl group;[2,3] however, methods to assemble difluoromethyl groups are less-developed.[4,5] In 2011, we reported an approach to produce difluoroenolates through the release of trifluoroacetate from highly α-fluorinated gem-diols (Scheme 1).[6] These difluoroenolates participate in aldol reactions, and subsequent investigations demonstrated that these intermediates react with activated imines,[7−9] trifluoromethyl ketones,[10] halogenation reagents,[11] and dithianes.[12] Moreover, the difluoroenolates generated during the release of trifluoroacetate can also be immediately trapped as difluoromethyl ketones[13] or deuterodifluoromethyl ketones[14] with H_2O or D_2O, respectively. Additionally, this method is compatible with catalytic, asymmetric reactions[15] and visible-light photoredox catalysis.[16] Despite the utility of this process and rapid adoption of the method,[17] the requisite highly α-fluorinated gem-diols are not common functional groups in fluorine chemistry and are predominately accessed by only one synthetic strategy.[6]

Scheme 1. Synthetic Reactions of Difluoroenolates Generated by the Release of Trifluoroacetate from Highly α-Fluorinated gem-Diols



Nearly all highly α-fluorinated gem-diols are accessed through methyl ketones by a two-step process of trifluoroacetylation followed by difluorination with Selectfluor (Figure 1A).[6,17] Even though this strategy enables a quick production of substrates for the release of trifluoroacetate, we recently had to develop an alternative method to access a glucose-derived highly α-fluorinated gem-diol from an aldehyde (Figure 1B).[18] Specifically, we exploited an approach from Qian and Nakai in which the treatment of hexafluoroisopropanol with *n*-butyllithium creates a lithium-based pentafluoroenolate that

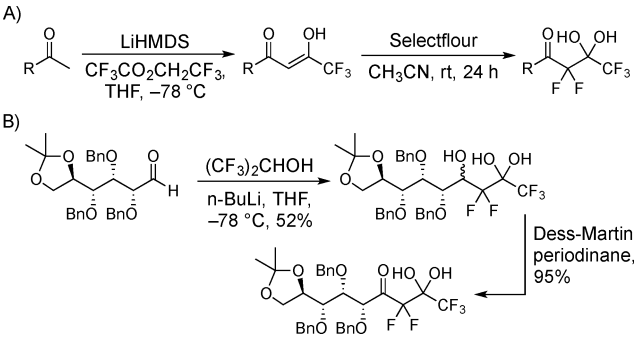


Figure 1. Synthetic approaches to highly α-fluorinated gem-diols: (A) primary synthetic strategy by trifluoroacetylation and subsequent difluorination and (B) addition of lithium pentafluoropropen-2-olate and oxidation.

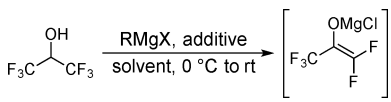
Received: November 30, 2016
Published: January 20, 2017

DOI: 10.1021/acs.joc.6b02863
J. Org. Chem. 2017, 82, 2231−2236

adds smoothly into aldehydes.[19] Next, after the addition of the enolate to the aldehyde, the glucose-derived pentafluorinated product was oxidized with Dess−Martin periodinane to give the targeted gem-diol.[18] In this case, the two-step approach from an aldehyde was quite effective and also provided an opportunity to devise an additional method for the synthesis of highly α-fluorinated gem-diols. Herein, we report that hexafluoroisopropanol can be fragmented with mixed Mg/Li amides of type $R_2NMgCl\cdot LiCl$ and added into aldehydes to produce pentafluorinated products that can be oxidized to the starting materials for the trifluoroacetate-release process. Additionally, we discovered that the difluoroenolates generated from the release of trifluoroacetate can be trapped as difluoroenoxysilanes and concomitantly arylated using palladium catalyst.

The fragmentation of hexafluoroisopropanol requires two equivalents of *n*-butyllithium: one to form the alkoxide, and the second to abstract the methine proton and displace fluoride.[19,20] Even though the fragmentation was also reported to occur with NaH and KH,[19] the latter process is believed to be promoted by the coordination of lithium to fluorine, which assists in the displacement process. All of the subsequent studies have used *n*-buyllithium as a base.[18,20−25] Although *n*-butyllitium is a common laboratory reagent, it is quite flammable, and the potential for hazards are increased when multiple equivalents are required. Another limitation of using organolithium as a base is that very low temperatures are required (i.e., −78 °C). To address the typical limitations of organolithium bases, Knochel and co-workers pioneered the development of mixed Mg/Li amides of type $R_2NMgCl\cdot LiCl$.[26] Accordingly, we aimed to develop a new method to produce magnesium pentafluoropropen-2-olate from hexafluoroisopropanol using magnesium bases (Table 1). Initial efforts with

Table 1. Optimization of the Formation of Magnesium Pentafluoropropen-2-olate from Hexafluoroisopropanol

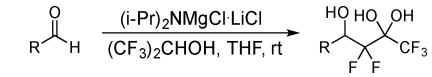


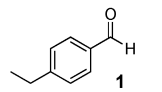
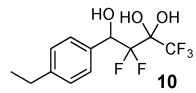
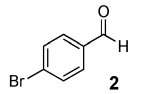
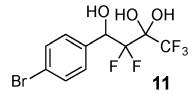
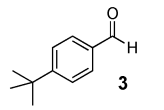
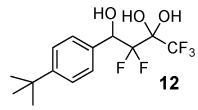
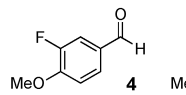
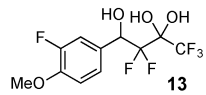
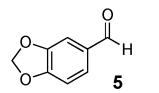
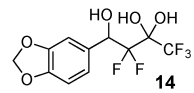
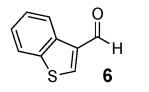
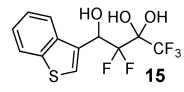
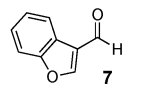
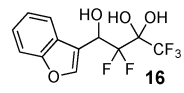
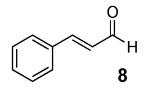
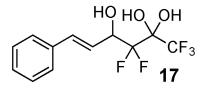
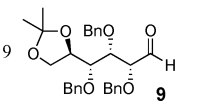
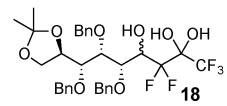
	RMgX	solvent	additive	^{19}F NMR yield (%)
1	MeMgBr	THF		0
2	MeMgBr	THF	LiCl	0
3	*i*-PrMgCl	THF		37
4	*i*-PrMgCl	THF	LiCl	40
5	*i*-PrMgCl	Et_2O		52
6	*i*-PrMgCl	dioxane		18
7	*i*-PrMgCl	THF	LiCl	48
8	$(i\text{-Pr})_2NMgCl$	THF	LiCl	91

methyl magnesium bromide were unproductive, but isopropyl Grignard, with or without added lithium chloride, generated the pentafluoropropen-2-olate in modest yields (i.e., 37−40%) as observed by ^{19}F NMR (entries 1−4). Exchanging the solvent THF with Et_2O or dioxane did not notably increase conversions (entries 5−6); using cesium chloride instead of lithium chloride also did not affect the formation of the pentafluoroenolate (entry 7). Using the mixed Mg/Li amide of type $(i\text{-Pr})_2NMgCl\cdot LiCl$[26] at room temperature proved to be superior and provided the pentafluoropropen-2-olate with 91% conversion (entry 8). The doubling of yield when (i-$Pr)_2NMgCl\cdot LiCl$ was utilized compared to that of i-PrMgCl·LiCl was a substantial improvement (i.e., 40 to 91%).

The next step was to determine if the fluoroenolate generated from $(i\text{-Pr})_2NMgCl\cdot LiCl$ and hexafluoroisopropanol would add to aldehydes. Even though the lithium pentafluoropropen-2-olate reacts well with aldehydes,[18,19,25] the reactivity of the magnesium-counterpart is not characterized in the literature to our knowledge. Benzaldehydes **1**−**5**, heteroaromatic aldehydes **6**−**7**, α,β-unsaturated aldehyde **8**, and aliphatic aldehyde **9** were treated at room temperature with the pentafluoropropen-2-olate generated with $(i\text{-Pr})_2NMgCl\cdot LiCl$ (Table 2). The pentafluoroalcohol **10** was obtained in

Table 2. Addition of Magnesium Pentafluoropropen-2-olate to Aldehydes 1−9



entry	substrate	product	yield[a]
1	 **1**	 **10**	59%
2	 **2**	 **11**	33% (45%)[b]
3	 **3**	 **12**	71% (82%)[b]
4	 **4**	 **13**	77%
5	 **5**	 **14**	68% (78%)[b]
6	 **6**	 **15**	68%
7	 **7**	 **16**	65%
8	 **8**	 **17**	52% (67%)[b]
9	 **9**	 **18**	87%

[a]Isolated yields. [b]Yields determined by ^{19}F NMR.

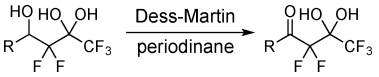
59% isolated yield from addition to 4-ethylbenzaldehyde **1**. In the case of 4-bromobenzaldehyde **2**, the product **11** was isolated in a lower 33% yield, most likely due to debromination of the benzene. All of the other substrates provided the pentafluoroalcohols **12**−**18** in 52−87% isolated yields. Substituted benzene rings, heterocycles, styrene, and alkyl groups are compatible with the magnesium pentafluoropropen-2-olate. Moreover, during the analysis of the ^{19}F NMR spectra following workup, two products were routinely observed: (1) the desired target and (2) the aminal formed by addition of

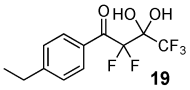
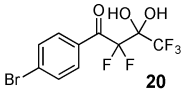
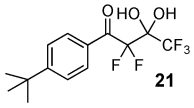
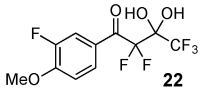
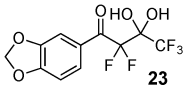
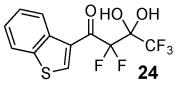
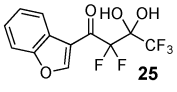
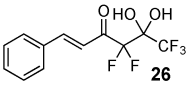
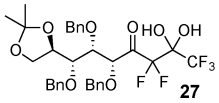
DOI: 10.1021/acs.joc.6b02863
J. Org. Chem. 2017, 82, 2231−2236

diisopropylamine to the gem-diol. The latter was readily cleaved during purification by silica gel flash chromatography. Overall, the conversions with the pentafluoropropen-2-olate generated from $(i\text{-Pr})_2$NMgCl·LiCl were comparable to the intermediate produced with *n*-butyllithium.

With the fluoroalcohols **10**–**18** in hand, oxidations to the fluoroketones[18] were conducted using the oxidant Dess–Martin periodinane (Table 3).[27] Only mild oxidants can be considered for this transformation because the products will easily eliminate trifluoroacetate in the presence of basic conditions.[6] All of the aromatic, heteroaromatic, alkenyl, and alkyl substrates **10**–**18** provided the respective fluoroketones **19**–**27** in good isolated yields of 78–95%. Moreover, some conversions were nearly quantitative, as observed by ^{19}F NMR. In all cases, the byproducts from fragmentation of the compounds **19**–**27** by trifluoroacetate release were not observed. The oxidation of allylic fluoroalcohol **17** provided a lower isolated yield at 41%. Although allylic alcohols are typically good substrates for Dess–Martin periodinane,[27] allylic fluoroalcohols are not oxidized as well with this reagent.[28] In general, the two-step addition/oxidation protocol was successful to produce the pentafluoroketones from readily available aldehydes.

Table 3. Oxidation of Fluoroalcohols 10–18 to 2,2,4,4,4-Pentafluoro-3,3-dihydroxyketones 19–27



entry	substrate	product	yield[a]
1	**10**	 **19**	80%
2	**11**	 **20**	78% (99%)[b]
3	**12**	 **21**	79% (90%)[b]
4	**13**	 **22**	88% (100%)[b]
5	**14**	 **23**	84% (95%)[b]
6	**15**	 **24**	80% (97%)[b]
7	**16**	 **25**	79% (88%)[b]
8	**17**	 **26**	41% (54%)[b]
9	**18**	 **27**	95%[c]

[a]Isolated yields. [b]Yields determined by ^{19}F NMR. [c]Ref 18.

With a new route to starting materials for trifluoroacetate release, additional studies were undertaken to expand the role of the pentafluoroketones as precursors to difluoroenolates. Specifically, difluoroenoxysilanes are valuable fluorinated building blocks,[20] and we aimed to devise a new method to access these key targets. Treatment of the highly α-fluorinated gem-diol **28**[6] with the strong base lithium hexamethyldisilazane, according to the protocol reported by Wolf,[8] promotes the release of trifluoroacetate and unleashes the difluoroenolate, which we immediately trapped with chlorotrimethylsilane (Figure 2). The difluoroenoxysilane **29** was produced in 70% yield by ^{19}F NMR; the isolated yield of **29** was 47%. The next step was to convert the difluoroenoxysilane to a valuable difluoromethyl ketone using the method of Shreeve.[29] Indeed, difluoromethyl ketones are excellent structures in medicinal chemistry due to their propensity to form a stable hydrate.[30,31] Accordingly, gem-diol **30**[13] was treated with LiHMDS and trapped with TMSCl to the difluoroenoxysilane which, in turn, was immediately subjected to palladium-mediated arylation conditions[29] in the presence of bromoanisole, and the difluoromethyl ketone **31** was obtained in a good 78% isolated yield.

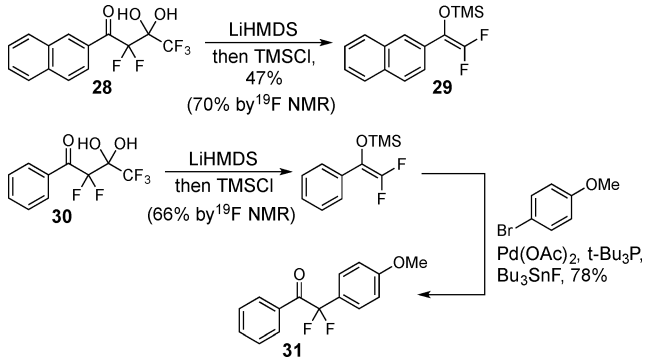


Figure 2. Conversion of fluorinated gem-diols to difluoroenoxysilanes.

In conclusion, this mild, two-step synthesis provides an additional route to 2,2,4,4,4-pentafluoro-3,3-dihydroxyketones from aldehydes. Moreover, this discovery utilizes a mixed Mg/Li amide for the fragmentation of hexafluoroisopropanol and eliminates the requirement of *n*-butyllithium. These advances enabled the expansion of the reactivity of difluoroenolates produced from highly α-fluorinated gem-diols through the release of trifluoroacetate so that difluoroenoxysilanes as well as arylated difluoromethyl ketones can be prepared. This advancement will likely enable new reactivity for fluoroenolates to be characterized.

EXPERIMENTAL SECTION

Representative Reaction Procedure for Preparation of Pentafluorotriols. Hexafluoroisopropanol (58 μL, 0.55 mmol) was added dropwise at rt to a freshly prepared solution of $(i\text{-Pr}_2\text{N})_2$MgCl·LiCl[26] (5 mL, 0.44 M in THF), and the mixture was stirred for 2 h. Then, a solution of 4-ethylbenzaldehyde **1** (113 μL, 0.83 mmol) in THF (1.5 mL) was added over 10 min, and the mixture was stirred for 18 h at rt. The resultant mixture was quenched with saturated aqueous NH_4Cl (2 mL), diluted with H_2O (2 mL), and extracted with Et_2O (3 × 2 mL). The organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. SiO_2 flash chromatography (5/

DOI: 10.1021/acs.joc.6b02863
J. Org. Chem. 2017, 82, 2231–2236

1−3/1 hexanes/EtOAc with 1% AcOH) afforded the product **10** as a colorless oil (97 mg, 59% yield).

1-(4-Ethylphenyl)-2,2,4,4,4-pentafluorobutane-1,3,3-triol 10. See representative reaction procedure. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.46 (d, J = 7.9 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 7.21 (s, 1H), 7.00 (s, 1H), 6.41 (s, 1H), 5.53 (d, J = 22.9 Hz, 1H), 2.69 (q, J = 7.6 Hz, 2H), 1.26 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 145.3, 133.7, 128.9 (2C), 127.9 (2C), 122.7 (q, J_{CF} = 288 Hz, 1C), 116.8 (dd, J_{CF} = 261, 254 Hz, 1C), 93.5 (tq, J_{CF} = 30.5, 27.0 Hz, 1C), 73.0 (dd, J_{CF} = 33.2, 22.2 Hz), 28.7, 15.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ − 81.8 (t, J = 11.8 Hz, 3F), − 118.0 (dq, J = 264, 12.9 Hz, 1F), −131.4 (ddq, J = 264, 22.1, 10.9 Hz, 1F); IR (film) ν_{max} 3351, 2967, 1616, 1202, 1159, 1067 cm^{-1}; HRMS (EI) m/z calcd for $C_{12}H_{11}F_5O_2$ $(M - H_2O)^+$ 282.0679, found 282.0687.

1-(4-Bromophenyl)-2,2,4,4,4-pentafluorobutane-1,3,3-triol 11. See representative reaction procedure. SiO_2 flash chromatography (3/1 hexanes/EtOAc with 0.5% AcOH) afforded the title compound **11** as a colorless solid (64 mg, 33% yield): mp 96−98 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.59 (dt, J = 8.7, 2.1 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 6.90 (br s, 2H), 5.53 (dd, J = 22.1, 2.7 Hz, 1H), 3.12 (br s, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 136.5, 131.9 (2C), 131.3 (2C), 123.2, 123.0 (q, J_{CF} = 287 Hz, 1C), 117.2 (dd, J_{CF} = 259, 253 Hz, 1C), 93.8 (tq, J_{CF} = 30.5, 26.0 Hz, 1C), 72.9 (dd, J_{CF} = 32.9, 22.2 Hz, 1C) ; ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ −81.7 (dd, J = 13.3, 11.0 Hz, 3F), −117.9 (dqd, J = 264, 13.3, 2.5 Hz, 1F), −130.5 (ddq, J = 264, 22.0, 11.0 Hz, 1F); IR (film) ν_{max} 3423, 3213, 1490, 1404, 1286, 1212, 1151, 1064 cm^{-1}; HRMS (EI) m/z calcd for $C_{10}H_6BrF_5O_2$ $(M - H - H_2O)^-$ 331.9477, found 331.9461.

1-(4-(*tert*-Butyl)phenyl)-2,2,4,4,4-pentafluorobutane-1,3,3-triol 12. See representative reaction procedure. SiO_2 flash chromatography (4/1 hexanes/EtOAc with 0.5% AcOH) afforded the title compound **12** as a colorless solid (129 mg, 71% yield): mp 94−96 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.45 (s, 4H), 7.18 (s, 1H), 6.97 (s, 1H), 6.34 (s, 1H), 5.50 (d, J = 23.3 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 152.5, 133.9, 129.1 (2C), 125.7 (2C), 123.1 (q, J_{CF} = 287 Hz, 1C), 117.3 (dd, J_{CF} = 259, 252 Hz, 1C), 94.0 (tq, J_{CF} = 31.3, 27.0 Hz, 1C), 73.4 (dd, J_{CF} = 33.5, 22.2 Hz, 1C), 35.1, 31.6 (3C); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ −81.6 (dd, J = 13.2, 11.2 Hz, 3F), −117.8 (dqd, J = 263, 13.2, 1.5 Hz, 1F), −131.0 (ddq, J = 263, 22.5, 11.2 Hz, 1F); IR (film) ν_{max} 3349, 2966, 1617, 1513, 1205, 1161, 1070 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{16}F_5O_2$ $(M + H - H_2O)^+$ 311.1065, found 311.1080.

2,2,4,4,4-Pentafluoro-1-(3-fluoro-4-methoxyphenyl)butane-1,3,3-triol 13. See representative reaction procedure. SiO_2 flash chromatography (3/1 hexanes/EtOAc with 0.5% AcOH) afforded the title compound **13** as a colorless solid (135 mg, 77% yield): mp 125−126 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.28 (m, 2H), 7.14 (t, J = 8.4 Hz, 1H), 6.92 (br s, 3H), 5.49 (dd, J = 22.3, 2.6 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 152.7 (d, J_{CF} = 243 Hz, 1C), 149.0 (d, J_{CF} = 10.6 Hz, 1C), 129.7 (d, J_{CF} = 5.8 Hz, 1C), 125.6 (d, J_{CF} = 3.2 Hz, 1C), 123.1 (q, J_{CF} = 287 Hz, 1C), 117.2 (dd, J_{CF} = 259, 253 Hz, 1C), 116.6 (d, J_{CF} = 71.4 Hz, 1C), 113.9 (d, J_{CF} = 1.9 Hz, 1C), 93.9 (tq, J_{CF} = 33.0, 27.5 Hz, 1C) 72.7 (dd, J_{CF} = 33.2, 22.0 Hz, 1C), 56.5; ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ −81.6 (d, J = 13.4, 11.0 Hz, 3F), −117.9 (dq, J = 263, 13.3 Hz, 1F), −131.0 (ddq, J = 263, 22.1, 11.1 Hz, 1F), −137.2 (dd, J = 12.4, 8.6 Hz, 1F); IR (film) ν_{max} 3240, 1628, 1519, 1441, 1276, 1203, 1153, 1120, 1107, 1071 cm^{-1}; HRMS (EI) m/z calcd for $C_{11}H_8F_6O_3$ $(M - H - H_2O)^-$ 302.0383, found 302.0356.

1-(Benzo[1,3]dioxol-5-yl)-2,2,4,4,4-pentafluorobutane-1,3,3-triol 14. See representative reaction procedure. SiO_2 flash chromatography (2/1 hexanes/EtOAc with 0.5% AcOH) afforded the title compound **14** as a brown oil (118 mg, 68% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 5.99 (s, 2H), 5.35 (dd, J = 21.9, 1.8 Hz, 1H), 3.79 (br s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 149.0, 148.5, 130.6, 123.2, 123.1 (q, J_{CF} = 287 Hz, 1C), 117.2 (dd, J_{CF} = 259, 252 Hz, 1C), 109.4, 108.5, 102.2, 93.9 (tq, J_{CF} = 30.5, 27.0 Hz, 1C), 73.3 (dd, J_{CF} = 33.3, 22.1 Hz, 1C); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ −81.7, (dd, J = 13.2, 11.2 Hz, 3F), −117.8 (dqd, J = 263, 13.2, 2.4 Hz, 1F), −131.3 (ddq, J = 263, 22.3, 11.1 Hz, 1F); IR (film) ν_{max} 3394, 2920, 1506, 1493, 1447, 1248, 1205, 1161, 1039 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_8F_5O_4$ $(M - H_2O)^+$ 299.0343, found 299.0356.

1-(Benzothiophen-3-yl)-2,2,4,4,4-pentafluorobutane-1,3,3-triol 15. See representative reaction procedure. SiO_2 flash chromatography (5/2 hexanes/EtOAc with 0.5% AcOH) afforded the title compound **15** as a colorless oil (122 mg, 68% yield): ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.09−7.91 (m, 2H), 7.87 (s, 1H), 7.49−7.28 (m, 3H), 7.00 (s, 1H), 6.49 (s, 1H), 6.03 (d, J = 22.9 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 141.1, 139.0, 132.3, 128.3, 125.4, 125.1, 123.8 (t, J_{CF} = 2.2 Hz, 1C), 123.5, 123.1 (q, J_{CF} = 287 Hz, 1C), 117.8 (dd, J_{CF} = 259, 253 Hz, 1C), 94.0 (tq, J_{CF} = 30.8, 28.0 Hz, 1C), 69.2 (dd, J_{CF} = 33.9, 22.5 Hz, 1C); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ −81.6 (dd, J = 13.1, 11.2 Hz, 3F), −118.0 (dq, J = 262, 13.1 Hz, 1F), −129.1 (ddq, J = 262, 22.5, 11.2 Hz, 1F); IR (film) ν_{max} 3368, 1625, 1428, 1204, 1160, 1070 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_9F_5O_3SNa$ $(M + Na)^+$ 351.0090, found 351.0086.

1-(Benzofuran-3-yl)-2,2,4,4,4-pentafluorobutane-1,3,3-triol 16. See representative reaction procedure. SiO_2 flash chromatography (3/1 hexanes/EtOAc with 1.0% AcOH) afforded the title compound **16** as a colorless oil (112 mg, 65% yield): ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.67 (ddd, J = 7.7, 1.2, 0.7 Hz, 1H), 7.54, (dd, J = 8.2, 0.8 Hz, 1H), 7.35 (td, J = 7.8, 1.2 Hz, 1H), 7.27 (td, J = 7.4, 0.9 Hz, 1H), 7.06 (s, 1H), 6.84 (br s, 2H), 5.72 (dd, J = 21.2, 2.6 Hz, 1H), 3.26 (s, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 155.9, 153.4, 128.8, 125.7, 123.9, 123.0 (q, J_{CF} = 287 Hz, 1C), 122.3, 117.4 (dd, J_{CF} = 260, 255 Hz, 1C), 112.0, 107.8, 93.7 (qdd, J_{CF} = 31.2, 29.3, 26.8 Hz, 1C), 68.3 (dd, J_{CF} = 32.7, 22.7 Hz, 1C); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ −81.7 (dd, J = 12.9, 10.9 Hz, 3F), −119.0 (dqd, J = 261, 13.0, 3.0 Hz, 1F), −128.5 (ddq, J = 261, 21.5, 10.8, 1F); IR (film) ν_{max} 3368, 1619, 1454, 1205, 1161, 1073 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_9F_5O_4Na$ $(M + Na)^+$ 335.0319, found 335.0314.

(*E*)-1,1,1,3,3-Pentafluoro-6-phenylhex-5-ene-2,2,4-triol 17. See representative reaction procedure. SiO_2 flash chromatography (3/1 hexanes/EtOAc with 1.0% AcOH) afforded the title compound **17** as a colorless oil (86 mg, 52% yield). All spectral and characterization data matched the reported data.[25]

(5*S*,6*R*,7*R*)-5,6,7-Tris(benzyloxy)-7-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1,1,1,3,3-pentafluoroheptane-2,2,4-triol 18. Hexafluoroisopropanol (8 μL, 0.07 mmol) was added dropwise at rt to a freshly prepared solution of $(i\text{-}Pr_2N)_2MgCl{\cdot}LiCl$[26] (0.63 mL, 0.44 M in THF), and the mixture was stirred for 2 h. Then, a solution of aldehyde **9**[18] (85 mg, 0.17 mmol) in THF (1.5 mL) was added over 10 min, and the mixture was stirred for 18 h at rt. The resultant mixture was quenched with saturated aqueous NH_4Cl (2 mL), diluted with H_2O (2 mL), and extracted with Et_2O (3 × 2 mL). The organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. SiO_2 flash chromatography (5/2 hexanes/EtOAc) afforded the title compound **18** as a colorless oil (d.r. = 2:1, 39 mg, 87% yield). All spectral and characterization data matched the reported data.[18]

Representative Reaction Procedure for Preparation of Pentafluoro-gem-diols. Dess−Martin periodinane (141 mg, 0.333 mmol) was added to a solution of **10** (40 mg, 0.13 mmol) in CH_2Cl_2 (3 mL), and the reaction mixture was stirred for 24 h at rt. Next, the reaction mixture was diluted with CH_2Cl_2 (5 mL), filtered through Celite, and concentrated under reduced pressure. SiO_2 flash chromatography (5/1 hexanes/EtOAc with 1% AcOH) afforded the product **19** as a colorless oil (32 mg, 80% yield).

1-(4-Ethylphenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one 19. See representative reaction procedure. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 3.99 (br s, 2H), 2.74 (q, J = 7.6 Hz, 2H), 1.27 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9 (t, J_{CF} = 28.7 Hz, 1C), 153.1, 130.9 (t, J_{CF} = 3.5 Hz, 2C), 129.5 (t, J_{CF} = 2.3 Hz, 1C), 128.4 (2C), 121.4 (q, J_{CF} = 289 Hz, 1C), 111.7 (t, J_{CF} = 268 Hz, 1C), 92.8 (qt, J_{CF} = 32.5, 26.9 Hz, 1C), 29.2, 14.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −82.0 (t, J = 11.0 Hz, 3F), −112.8 (q, J = 10.5 Hz, 2F); IR (film) ν_{max} 3402, 2972, 1685, 1606, 1205, 1066 cm^{-1}; HRMS (EI) m/z calcd for $C_{12}H_9F_5O_2$ $(M - H_2O)^+$ 280.0523, found 280.0547.

DOI: 10.1021/acs.joc.6b02863
J. Org. Chem. 2017, 82, 2231−2236

1-(4-Bromophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one 20. See representative reaction procedure. SiO_2 flash chromatography (3/1 hexanes/EtOAc) afforded the title compound **20** as a colorless oil (29 mg, 78% yield). All spectral and characterization data matched the reported data.[16]

1-(4-(*tert*-Butyl)phenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one 21. See representative reaction procedure. SiO_2 flash chromatography (3/1 hexanes/EtOAc) afforded the title compound **21** as a colorless solid (54 mg, 79% yield): mp 59−61 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.12 (d, J = 8.8 Hz, 2H), 7.60 (dt, J = 8.9, 2.1 Hz, 2H), 7.47 (br s, 1H), 3.16 (br s, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 188.5 (t, J_{CF} = 26.7 Hz, 1C), 159.0, 131.7, 131.5 (t, J_{CF} = 3.5 Hz, 2C), 126.3 (2C), 123.0 (q, J_{CF} = 288 Hz, 1C), 115.8 (t, J_{CF} = 263 Hz, 1C), 93.3 (qt, J_{CF} = 31.5, 28.0 Hz, 1C), 35.8, 31.2 (3C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.9 (t, J = 11.1 Hz, 3F), −113.1 (q, J = 11.0 Hz, 2F); IR (film) ν_{max} 3420, 2969, 1687, 1604, 1205, 1067 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{15}F_5O_3Na$ $(M + Na)^+$ 349.0839, found 349.0834.

2,2,4,4,4-Pentafluoro-1-(3-fluoro-4-methoxyphenyl)-3,3-dihydroxybutan-1-one 22. See representative reaction procedure. SiO_2 flash chromatography (3/1 hexanes/EtOAc with 1% AcOH) afforded the title compound **22** as a colorless oil (44 mg, 88% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 11.8, 1.9 Hz, 1H), 7.05 (t, J = 8.4 Hz, 1H), 4.89 (br s, 1H), 4.00 (s, 3H), 1.82 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.7 (t, J_{CF} = 29.3 Hz, 1C), 154.3 (d, J_{CF} = 10.7 Hz, 1C), 151.9 (d, J_{CF} = 248 Hz, 1C), 129.2 (q, J_{CF} = 3.9 Hz, 1C), 124.7 (d, J = 5.0 Hz, 1C), 121.1 (q, J_{CF} = 286 Hz, 1C), 118.2 (dt, J_{CF} = 20.0, 3.0 Hz, 1C), 112.7, 111.9 (t, J_{CF} = 267 Hz, 1C), 92.9 (qt, J_{CF} = 32.5, 26.9 Hz, 1C), 56.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −81.9 (t, J = 11.0 Hz, 3F), −113.0 (q, J = 11.0 Hz, 2F), −134.6 (dd, J = 11.8, 8.2 Hz, 1F); IR (film) ν_{max} 3429, 2950, 1684, 1608, 1520, 1442, 1288, 1205, 1108 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_8F_6O_4Na$ $(M + Na)^+$ 341.0224, found 341.0229.

1-(Benzo[1,3]dioxol-5-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one 23. See representative reaction procedure. SiO_2 flash chromatography (3/1 hexanes/EtOAc with 1% AcOH) afforded the title compound **23** as a colorless oil (42 mg, 84% yield). All spectral and characterization data matched the reported data.[6]

1-(Benzothiophen-3-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one 24. See representative reaction procedure. SiO_2 flash chromatography (3/1 hexanes/EtOAc with 1% AcOH) afforded the title compound **24** as a colorless oil (43 mg, 80% yield). All spectral and characterization data matched the reported data.[11]

1-(Benzofuran-3-yl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one 25. See representative reaction procedure. SiO_2 flash chromatography (5/2 hexanes/EtOAc) afforded the title compound **25** as a yellow solid (43 mg, 79% yield): mp 72−74 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.09−8.01 (m, 1H), 7.93 (dd, J = 7.9, 0.6 Hz, 1H), 7.75−7.56 (m, 3H), 7.47−7.36 (m, 1H), 3.21 (br s, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 177.7 (t, J_{CF} = 28.6 Hz, 1C), 156.8, 149.9, 130.7, 127.8, 125.4, 125.3, 123.0 (q, J = 288, 1C), 121.2 (t, J_{CF} = 5.8 Hz, 1C), 115.3 (t, J_{CF} = 262 Hz, 1C), 113.0, 93.2 (qt, J_{CF} = 32.0, 27.8 Hz, 1C); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ −81.6 (t, J = 10.2 Hz, 3F), −116.5 (qd, J = 10.2, 2.0); IR (film) ν_{max} 3406, 1673, 1614, 1546, 1335, 1191, 1127, 1071 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_7F_5O_4Na$ $(M + Na)^+$ 333.0162, found 333.0156.

(*E*)-4,4,6,6,6-Pentafluoro-5,5-dihydroxy-1-phenylhex-1-en-3-one 26. See representative reaction procedure. SiO_2 flash chromatography (3/1 hexanes/EtOAc) afforded the title compound **26** as a colorless oil (20 mg, 41% yield). All spectral and characterization data matched the reported data.[11]

((2,2-Difluoro-1-(naphthalen-2-yl)vinyl)oxy)trimethylsilane 29. A solution of *n*-BuLi (1 mL, 1.8 M in hexanes) was added dropwise to a −78 °C solution of hexamethyldisilazane (3 mL, 0.6 M in THF), and the mixture was stirred for 30 min at −78 °C. Then, a −78 °C solution of **28**[6] (300 mg, 0.94 mmol) in THF (3.6 mL) was added slowly, followed by the rapid addition of TMSCl (59 μL, 0.47 mmol). The mixture was stirred for 20 min at −78 °C, warmed to rt, and then concentrated under reduced pressure. The residue was dissolved in hexanes (20 mL), filtered through Celite, and concentrated under reduced pressure to provide the title compound **29** as a colorless oil (61 mg, 47% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.87−7.80 (m, 3H), 7.63 (dt, J = 8.7, 1.7 Hz, 1H), 7.53−7.46 (m, 2H), 0.23 (d, J = 0.9 Hz, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1 (dd, J_{CF} = 286, 284 Hz, 1C), 133.0, 132.7, 130.1 (dd, J_{CF} = 7.2, 1.5 Hz, 1C), 128.2, 127.9, 127.6, 126.3 (2C), 125.2 (dd, J_{CF} = 6.4, 5.0 Hz, 1C), 123.5 (dd, J_{CF} = 7.9, 2.6 Hz, 1C), 114.2 (dd, J_{CF} = 34.2, 19.4 Hz, 1C), 0.2 (d, J_{CF} = 1.2 Hz, 3C); ^{19}F NMR (376 MHz, $CDCl_3$) δ −99.9 (d, J = 66.7 Hz, 1F), −112.1 (d, J = 66.6 Hz, 1F); IR (film) ν_{max} 3059, 2962, 1719, 1261, 1252, 1151 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{16}F_2OSi$ $(M)^+$ 278.0938, found 278.0931.

2,2-Difluoro-2-(4-methoxyphenyl)-1-phenylethan-1-one 31. A solution of *n*-BuLi (3.1 mL, 1.7 M in hexanes) was added dropwise to a −78 °C solution of hexamethyldisilazane (9 mL, 0.6 M in THF), and the mixture was stirred for 30 min at −78 °C. Then, a solution of **30**[13] (715 mg, 2.65 mmol) in THF (9.8 mL) was added slowly, followed by the rapid addition of TMSCl (504 μL, 3.97 mmol). The mixture was stirred for 10 min at −78 °C, warmed to rt, and concentrated under reduced pressure. The residue was dissolved in hexanes (25 mL), filtered through Celite, and concentrated under reduced pressure. The residue was immediately dissolved in toluene (1.2 mL) under an argon atmosphere, and 4-bromoanisole (99 μL, 0.79 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), and Bu_3SnF (736 mg, 2.38 mmol) were added. Next, a solution of *t*-Bu_3P (79 μL, 1.0 M in toluene) was added dropwise, and the reaction mixture was heated to 85 °C. After 13.5 h, the reaction mixture was cooled to rt, diluted with EtOAc (16 mL), and decanted with additional EtOAc (10 mL). The mixture was treated with saturated aqueous KF (5 mL) and stirred for 1 h at rt. Next, the reaction mixture was filtered through Celite and extracted with EtOAc (3 × 5 mL). The organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. SiO_2 flash chromatography (10/1 hexanes/EtOAc) afforded the title compound **31** as a colorless oil (163 mg, 78%). All spectral and characterization data matched the reported data.[29]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02863.

^{1}H, ^{13}C, and ^{19}F NMR of all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dacolby@olemiss.edu.

ORCID

David A. Colby: 0000-0002-5434-1690

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

These studies were funded by the University of Mississippi and the National Institute of General Medical Sciences (Grant P20GM104932). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the National Institutes of Health (NIH). The Mass Spectrometry and Proteomics Facility of the University of Notre Dame is acknowledged for acquisition of high-resolution mass spectrometry data. The authors also thank Joshua S. Sharp and Sandeep Misra for mass spectrometry support.

■ REFERENCES

(1) Yerien, D. E.; Bonesi, S.; Postigo, A. *Org. Biomol. Chem.* **2016**, *14*, 8398−8427.

(2) Alonso, C.; Martínez de Marigorta, E.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847−1935.

DOI: 10.1021/acs.joc.6b02863
J. Org. Chem. 2017, 82, 2231−2236

(3) Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Acena, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A. *J. Fluorine Chem.* **2014**, *167*, 37−54.
(4) Yang, L.; Chao, L.; Qing-Yun, C. *Curr. Org. Chem.* **2015**, *19*, 1638−1650.
(5) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Acena, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422−518.
(6) Han, C.; Kim, E. H.; Colby, D. A. *J. Am. Chem. Soc.* **2011**, *133*, 5802−5805.
(7) Xie, C.; Wu, L.; Mei, H.; Soloshonok, V. A.; Han, J.; Pan, Y. *Org. Biomol. Chem.* **2014**, *12*, 7836−7843.
(8) Xie, C.; Wu, L.; Zhou, J.; Mei, H.; Soloshonok, V. A.; Han, J.; Pan, Y. *J. Fluorine Chem.* **2015**, *172*, 13−21.
(9) Xie, C.; Wu, L.; Mei, H.; Soloshonok, V. A.; Han, J.; Pan, Y. *Tetrahedron Lett.* **2014**, *55*, 5908−5910.
(10) Zhang, P.; Wolf, C. *J. Org. Chem.* **2012**, *77*, 8840−8844.
(11) John, J. P.; Colby, D. A. *J. Org. Chem.* **2011**, *76*, 9163−9168.
(12) Lin, Y.-M.; Yi, W.-B.; Shen, W.-Z.; Lu, G.-P. *Org. Lett.* **2016**, *18*, 592−595.
(13) Leng, D. J.; Black, C. M.; Pattison, G. *Org. Biomol. Chem.* **2016**, *14*, 1531−1535.
(14) Sowaileh, M. F.; Han, C.; Hazlitt, R. A.; Kim, E. H.; John, J. P.; Colby, D. A. *Tetrahedron Lett.* **2017**, *58*, 396−400.
(15) Zhang, P.; Wolf, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 7869−7873.
(16) Li, W.; Zhu, X.; Mao, H.; Tang, Z.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2014**, *50*, 7521−7523.
(17) Mei, H.; Xie, C.; Aceña, J. L.; Soloshonok, V. A.; Röschenthaler, G.-V.; Han, J. *Eur. J. Org. Chem.* **2015**, *2015*, 6401−6412.
(18) Hazlitt, R. A.; John, J. P.; Tran, Q.-L.; Colby, D. A. *Tetrahedron Lett.* **2016**, *57*, 1906−1908.
(19) Qian, C.-P.; Nakai, T. *Tetrahedron Lett.* **1988**, *29*, 4119−4122.
(20) Decostanzi, M.; Campagne, J. M.; Leclerc, E. *Org. Biomol. Chem.* **2015**, *13*, 7351−7380.
(21) Xu, Y.; Dolbier, W. R.; Rong, X. X. *J. Org. Chem.* **1997**, *62*, 1576−1577.
(22) Narita, T.; Hagiwara, T.; Hamana, H.; Kitamura, K.; Inagaki, Y.; Yoshida, Y. *J. Fluorine Chem.* **1999**, *97*, 263−265.
(23) Narita, T.; Hamana, H.; Takeshita, M.; Nishizawa, K.; Kitamura, K. *J. Fluorine Chem.* **2002**, *117*, 55−61.
(24) Guiot, J.; Ameduri, B.; Boutevin, B.; Lannuzel, T. *Eur. Polym. J.* **2003**, *39*, 887−896.
(25) Jiménez, O.; Bosch, M. P.; Guerrero, A. *J. Org. Chem.* **2005**, *70*, 10883−10885.
(26) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958−2961.
(27) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.
(28) Linderman, R. J.; Jamois, E. A.; Tennyson, S. D. *J. Org. Chem.* **1994**, *59*, 957−962.
(29) Guo, Y.; Shreeve, J. M. *Chem. Commun.* **2007**, 3583−3585.
(30) Fah, C.; Hardegger, L. A.; Baitsch, L.; Schweizer, W. B.; Meyer, S.; Bur, D.; Diederich, F. *Org. Biomol. Chem.* **2009**, *7*, 3947−3957.
(31) Han, C.; Salyer, A. E.; Kim, E. H.; Jiang, X.; Jarrard, R. E.; Powers, M. S.; Kirchhoff, A. M.; Salvador, T. K.; Chester, J. A.; Hockerman, G. H.; Colby, D. A. *J. Med. Chem.* **2013**, *56*, 2456−2465.

DOI: 10.1021/acs.joc.6b02863
J. Org. Chem. 2017, 82, 2231−2236