JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

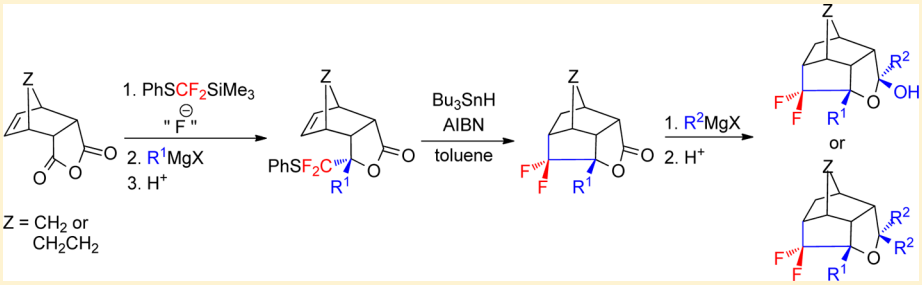
Synthesis of *gem*-Difluoromethylenated Polycyclic Cage Compounds

Chonticha Masusai,[†] Darunee Soorukram,[†] Chutima Kuhakarn,[†] Patoomratana Tuchinda,[†] Chaveng Pakawatchai,[‡] Saowanit Saithong,[‡] Vichai Reutrakul,[†] and Manat Pohmakotr*[,†]

[†]Center of Excellence for Innovation in Chemistry (PERCH-CIC) and Department of Chemistry, Faculty of Science, Mahidol University, Rama VI Road, Bangkok 10400, Thailand

[‡]Center of Excellence for Innovation in Chemistry (PERCH-CIC) and Department of Chemistry, Faculty of Science, Prince of Songkla University, Hat Yai, Songkla 90112, Thailand

Supporting Information



ABSTRACT: The synthesis of *gem*-difluoromethylenated polycyclic cage compounds, utilizing $PhSCF_2SiMe_3$ as a *gem*-difluoromethylene building block, is described. The fluoride-catalyzed nucleophilic addition of $PhSCF_2SiMe_3$ to both maleic anhydride−cyclopentadiene and maleic anhydride−cyclohexadiene adducts was accomplished with high stereoselectivity to provide the corresponding adducts that were treated with Grignard reagents, followed by acid-catalyzed lactonization to afford the corresponding γ-butyrolactones, each as a single isomer. These γ-butyrolactones underwent intramolecular radical cyclization to give the corresponding tetracyclic cage γ-butyrolactones, which were employed as precursors for the synthesis of *gem*-difluoromethylenated tetracyclic cage lactols or tetracyclic cage furans, upon treatment with Grignard reagents.

INTRODUCTION

Over the past decade, organofluorines have gained increasing interest due to their important roles in various fields, which include the pharmaceutical, agrochemical, and materials industries. Because of the special size of the fluorine atom, the high carbon−fluorine bond energy, and the special inductive and resonance effects caused by the fluorine atom, the presence of fluorine atoms in organic molecules was found to be beneficial to the physical and biological properties of fluorine-containing compounds.[1] Consequently, there has been tremendous interests in developing new and efficient methodologies to introduce fluorinated motifs into organic molecules.[2] Among those, convenient methods for the synthesis of *gem*-difluoromethylene-containing analogues of naturally occurring compounds received particular attention.[3] We have recently reported the synthetic utilities of $PhSCF_2SiMe_3$ (**1**)[4] as a useful *gem*-difluoromethylene building block for the syntheses of *gem*-difluoromethylenated 1-azabicyclic compounds,[5,6] spiro-γ-butyrolactones,[7] macrocyclic lactones,[8] and cyclopentanols[9] and as a difluoromethylating agent for the syntheses of difluoromethylketones,[10,11] γ-difluoromethyl-γ-lactams,[12] and bicyclic ketones.[13] The present work focuses on the synthesis of *gem*-difluoromethylenated polycyclic cage compounds, and to the best of our knowledge, the fluorinated cage compounds have rarely been reported in the literature.[14] Carbocyclic and heterocyclic cage compounds (Figure 1) have attracted particular attention from several research groups due to the challenges in their syntheses and for their chemical as well as biological activities.[15,16] Their unique properties and chemical reactivities are associated with the rigid and highly compact structural frameworks. Cage compounds have also been employed as valuable synthetic intermediates in organic synthesis, especially for the synthesis of more complex cage and noncage polycyclic natural products.[16v,z] Therefore, the incorporation of fluorinated motifs into polycyclic cage frameworks is of particular interest, since this class of compounds may be useful for the synthesis of other related highly substituted *gem*-difluoromethylenated polycyclic cage organic compounds and natural products. We report herein a general synthetic entry to *gem*-difluoromethylenated polycyclic cage compounds employing $PhSCF_2SiMe_3$ (**1**) as a useful *gem*-difluoromethylene building block.

RESULTS AND DISCUSSION

Noting our previous success in the fluoride-catalyzed nucleophilic addition of **1** and CF_3SiMe_3 to succinic anhydride,[12,17] we reason that fluoride-catalyzed nucleophilic

Received: October 31, 2014
Published: January 13, 2015

DOI: 10.1021/jo502501v
J. Org. Chem. 2015, 80, 1577−1592

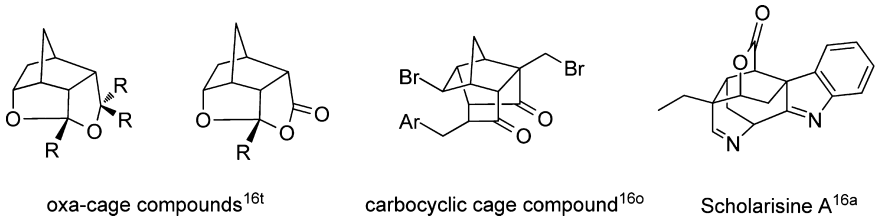
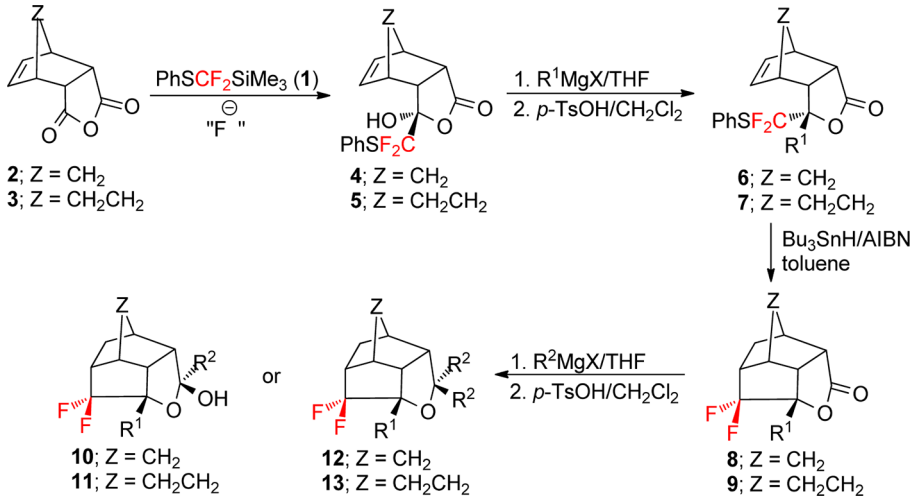


Figure 1. Selected examples of the cage compounds.

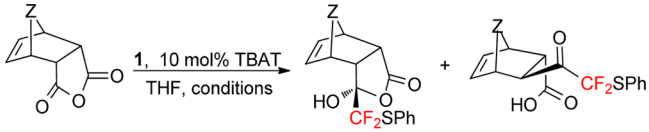
Scheme 1. Synthetic Route to *gem*-Difluoromethylenated Cage Compounds 8−13



addition of **1** to a maleic anhydride−cyclopentadiene adduct **2**[18] and a maleic anhydride−cyclohexadiene adduct **3**[18] should proceed with high stereoselectivity to produce the corresponding adducts **4** and **5** (Scheme 1). Stereoselective addition of Grignard reagents (R^1MgX) to **4** or **5** would provide **6** or **7**, which should serve as key compounds for the synthesis of *gem*-difluoromethylenated cage γ-butyrolactone **8** (6,6-difluorooctahydro-2*H*-3,5-methanopentaleno[1,6-*bc*]furan-2-ones) or **9** (7,7-difluorooctahydro-3,6-methanoindeno[1,7-*bc*]furan-2-(2a^1*H*)-ones) through the readily formed *gem*-difluoromethylene radical upon the reductive cleavage of the PhS−CF_2 bond, followed by intramolecular radical cyclization using Bu_3SnH/AIBN. Finally, the cage γ-butyrolactones **8** and **9** would be transformed to the corresponding polycyclic cage compounds **10** (6,6-difluorooctahydro-2*H*-3,5-methanopentaleno[1,6-*bc*]-furan-2-ols) and **11** (7,7-difluorodecahydro-3,6-methanoindeno[1,7-*bc*]furan-2-ols) as well as **12** (6,6-difluorooctahydro-2*H*-3,5-methanopentaleno[1,6-*bc*]furans) and **13** (7,7-difluorooctahydro-3,6-methanoindeno[1,7-*bc*]furans), respectively, upon treatment with Grignard reagents (R^2MgX).

Fluoride-Catalyzed Nucleophilic Addition of 1 to Anhydrides 2 and 3. Optimization studies on fluoride-catalyzed nucleophilic addition of **1** to a maleic anhydride−cyclopentadiene adduct **2** were conducted (Table 1). Treatment of **1** (2 equiv) with **2** (1 equiv) in THF in the presence of 10 mol% of tetrabutylammonium difluorotriphenylsilicate (TBAT) at −10 °C for 5 h followed by quenching with water provided **4** (83% yield) along with **4A** (9% yield), each as a single isomer (Table 1, entry 1). The relative stereochemistries of **4** and **4A** were determined by X-ray crystallography (see the Supporting Information). Efforts to perform the reaction under other reaction conditions led to inferior results (Table 1). The reaction carried out at −78 °C

Table 1. Fluoride-Catalyzed Nucleophilic Addition of 1 to Anhydrides 2 and 3



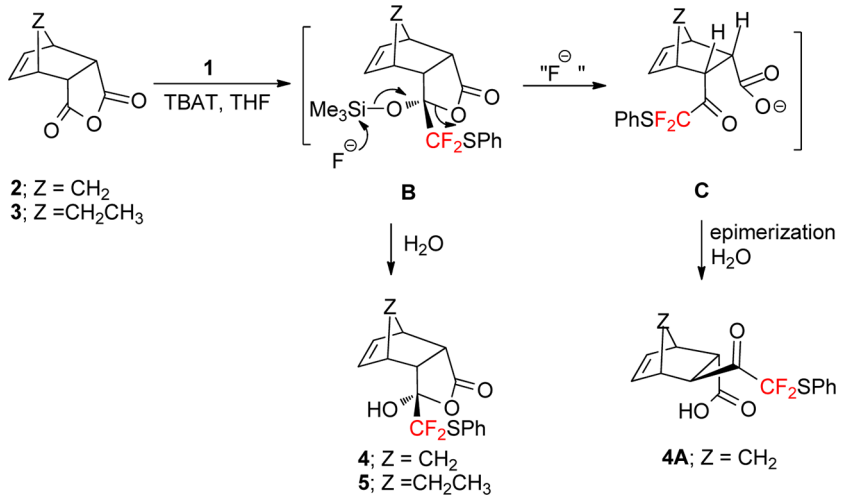
entry	substrate	conditions[a]	**4** or **5** (%)[b,c]	**4A** (%)[b,c]
1	**2**	−10 °C, 5 h	**4** (83)	9
2	**2**	−78 °C, 6 h	**4** (62)	2
3	**2**	0 °C, 3 h	**4** (50)	19
4	**2**	−10 °C to rt, 5 h	**4** (10)	51
5	**2**	−10 °C to rt, 15 h	**4** (13)	55
6	**3**	−10 °C, 5 h	**5** (91)	

[a]Two equivalents of **1** was employed. [b]Isolated yield. [c]A single isomer of the product was obtained.

for 6 h gave lower yields of both **4** (62% yield) and **4A** (2% yield) (Table 1, entry 2). A dramatic decrease in the yields of **4** and a significant quantity of **4A** were observed when the reaction was carried out either at a higher temperature (0 °C to room temperature) or with an extended reaction time (Table 1, entries 3−5). Under the optimized reaction conditions as employed for compound **2** (Table 1, entry 1), compound **3** gave the expected adduct **5** in 91% yield as a single isomer, without the observation of its corresponding competing ring-opened product (Table 1, entry 6). The observed high stereoselectivity for the formation of compounds **4** and **5** could be reasoned by the nucleophile ("$PhSCF_2^-$") preferentially attacking the carbonyl group of the anhydride from the sterically less hindered convex side of **2** or **3**, leading to a

DOI: 10.1021/jo502501v
J. Org. Chem. 2015, 80, 1577−1592

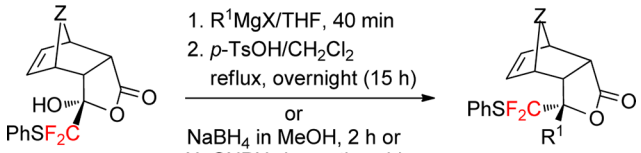
Scheme 2. Proposed Mechanism for the Formation of 4, 5, and 4A



trimethylsilyl ether **B** (Scheme 2). Simple hydrolysis of the trimethylsilyl ether **B** led to adducts **4** and **5**, each as a single isomer. Compound **4A** resulted from a fluoride-catalyzed ring-opening of the intermediate trimethylsilyl ether **B** to yield keto-carboxylate **C** followed by epimerization. The α-proton next to the phenylsulfanyldifluoromethyl carbonyl of the keto-carboxylate **C** should be highly acidic. Thus, under the reaction conditions, **C** underwent epimerization possibly via enolization by the fluoride-catalyzed α-proton abstraction and protonation process to yield the thermodynamically more stable isomer **4A**.

Preparation of *gem*-Difluoromethylenated γ-Butyrolactones 6 and 7. Having the key adducts **4** and **5** in hand, we then carried out the reactions of **4** and **5** with both Grignard reagents and reducing reagents. Initially, treatment of **4** with methylmagnesium chloride (5 equiv) afforded the corresponding γ-butyrolactone **6a** as a single isomer in 89% yield (Table 2, entry 1). The reactions of **4** and **5** with an array of Grignard reagents and reducing reagents, as listed in Table 2, were performed, and the results are also summarized in Table 2. It was found that **4** smoothly reacted with various Grignard reagents to provide the corresponding γ-butyrolactones **6b–g** in moderate to good yields (Table 2, entries 1–7). The reactions of **4** with both $NaBH_4$ and $NaCNBH_3$ afforded **6h** in high yields (Table 2, entries 8 and 9). It should be noted that the reaction of **4** with isopropylmagnesium chloride gave the expected product **6d** along with the reduction product **6h** in 56 and 30% yields, respectively (Table 2, entry 4). Although leading to poor results with isopropylmagnesium chloride, the reactions of **5** with other Grignard reagents provided the corresponding γ-butyrolactones **7a–c** and **7e–g** in high yields (Table 2, entries 10–12 and 14–16). Finally, the reaction of **5** with $NaBH_4$ in MeOH gave **7h** in 83% yield (Table 2, entry 17). It is worth noting that the reaction of **5** with ethylmagnesium chloride yielded the expected product **7b** in 75% yield, together with a separable diastereomeric mixture of **7h** and **7h′** in 7% and 9% yields, respectively (Table 2, entry 11). Compound **7h′** is probably a diastereomer of **7h**, which can be confirmed by NOE experiments (see the Supporting Information). The reaction of **5** with isopropylmagnesium chloride gave the expected product **7d** (21% yield) along with the reduction products **7h** (43% yield) and **7h′** (27% yield) (Table 2, entry 13). A transition state for the stereoselective nucleophilic addition of R^1MgX to **4** or **5** was proposed as shown in Scheme 3.[17] Proton abstraction of **4** or **5**, followed by ring-opening, led to the formation of **D** (Z = CH_2 or CH_2CH_2). Next, **D** was attacked either by R^1MgX or a hydride from the less hindered convex side to yield, after acid-catalyzed lactonization, the product **6** or **7**, each as a single isomer. Although it cannot be established at this stage, the relative stereochemistries of **6** and **7** are believed to possess the *gem*-difluorophenylsulfanylmethyl group ($PhSCF_2$) located on the

Table 2. Preparation of *gem*-Difluoromethylenated γ-Butyrolactones 6 and 7



4; Z = CH_2
5; Z = CH_2CH_2

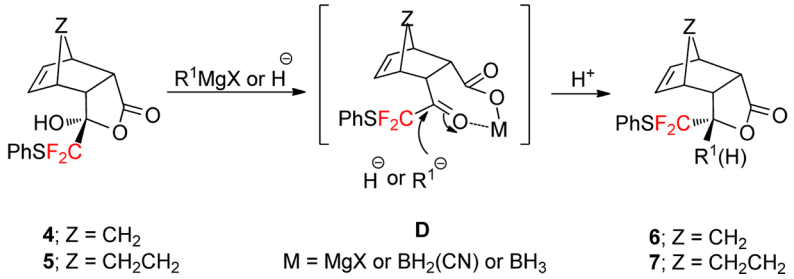
6; Z = CH_2
7; Z = CH_2CH_2

entry	4 or 5	reagent	R^1	product 6 or 7 (% yield)[a,b]
1	4	CH_3MgCl	CH_3	**6a** (89)
2	4	CH_3CH_2MgCl	CH_3CH_2	**6b** (81)
3	4	$CH_3(CH_2)_3MgCl$	$CH_3(CH_2)_3$	**6c** (87)
4	4	$(CH_3)_2CHMgCl$	$(CH_3)_2CH$	**6d** (56), **6h** (30)
5	4	CH_2=$CHMgCl$	CH_2=CH	**6e** (89)
6	4	C_6H_5MgCl	C_6H_5	**6f** (95)
7	4	4-$MeOC_6H_4MgBr$	4-$MeOC_6H_4$	**6g** (69)
8	4	$NaBH_4$	H	**6h** (85)
9	4	$NaCNBH_3$	H	**6h** (90)
10	5	CH_3MgCl	CH_3	**7a** (94)
11	5	CH_3CH_2MgCl	CH_3CH_2	**7b** (75), **7h** (7), **7h′** (9)[c]
12	5	$CH_3(CH_2)_3MgCl$	$CH_3(CH_2)_3$	**7c** (79), **7h′** (3)[c]
13	5	$(CH_3)_2CHMgCl$	$(CH_3)_2CH$	**7d** (21), **7h** (43), **7h′** (27)[c]
14	5	CH_2=$CHMgCl$	CH_2=CH	**7e** (86)
15	5	C_6H_5MgCl	C_6H_5	**7f** (91)
16	5	4-$MeOC_6H_4MgBr$	4-$MeOC_6H_4$	**7g** (61)
17	5	$NaBH_4$	H	**7h** (83)

[a]Isolated yield by preparative thin-layer chromatography (SiO_2). [b]The relative stereochemistry was proposed as shown in Scheme 3. [c]Compound **7h′** is probably a diastereomer of **7h**, which can be confirmed by NOE experiments (see the Supporting Information).

DOI: 10.1021/jo502501v
J. Org. Chem. 2015, 80, 1577–1592

Scheme 3. Proposed Stereoselective Addition of R^1MgX and Hydride to 4 or 5



4; Z = CH_2
5; Z = CH_2CH_2

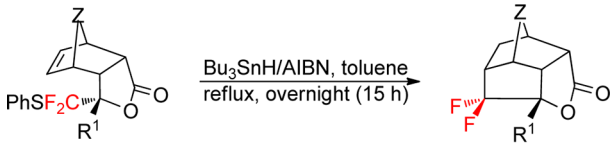
D
M = MgX or $BH_2(CN)$ or BH_3

6; Z = CH_2
7; Z = CH_2CH_2

concave side of the molecules as depicted in Table 2 and Scheme 3. Compounds **6** and **7** whose relative stereochemistries are as shown in Table 2 and Scheme 3 should be capable of undergoing intramolecular radical cyclization upon the reductive cleavage of the phenylsulfanyl group. Thus, the formation of *gem*-difluoromethylenated cage γ-butyrolactones **8** and **9** should confirm the relative stereochemistries of their corresponding starting compounds **6** and **7**, respectively.

Preparation of *gem*-Difluoromethylenated Cage γ-Butyrolactones 8 and 9. Having been successfully prepared, the *gem*-difluoromethylenated γ-butyrolactones **6** and **7** were next subjected to intramolecular radical cyclization mediated by Bu_3SnH/AIBN in refluxing toluene for overnight (15 h) (Table 3).[19] It was found that in all cases the *gem*-difluoromethylenated γ-butyrolactones **6** and **7** readily underwent the reaction to furnish the corresponding *gem*-difluoromethylenated cage compounds **8a–g** and **9a–h** in good to excellent yields (76–99% yields), each as a single isomer. The results are summarized in Table 3. The obtained results fully confirmed the relative stereochemistries of the *gem*-difluoromethylenated γ-butyrolactones **6** and **7** (Table 2 and Scheme 3).

Table 3. Preparation of *gem*-Difluoromethylenated Cage γ-Butyrolactones 8 and 9



6; Z = CH_2
7; Z = CH_2CH_2

8; Z = CH_2
9; Z = CH_2CH_2

entry	6 or 7	R^1	product 8 or 9 (% yield)[a,b]
1	**6a**	CH_3	**8a** (96)
2	**6b**	CH_3CH_2	**8b** (88)
3	**6c**	$CH_3(CH_2)_3$	**8c** (85)
4	**6e**	CH_2=CH	**8d** (87)
5	**6f**	C_6H_5	**8e** (91)
6	**6g**	4-$MeOC_6H_4$	**8f** (76)
7	**6h**	H	**8g** (94)
8	**7a**	CH_3	**9a** (89)
9	**7b**	CH_3CH_2	**9b** (89)
10	**7c**	$CH_3(CH_2)_3$	**9c** (87)
11	**7d**	$(CH_3)_2CH$	**9d** (99)
12	**7e**	CH_2=CH	**9e** (94)
13	**7f**	C_6H_5	**9f** (97)
14	**7g**	4-$MeOC_6H_4$	**9g** (89)
15	**7h**	H	**9h** (87)

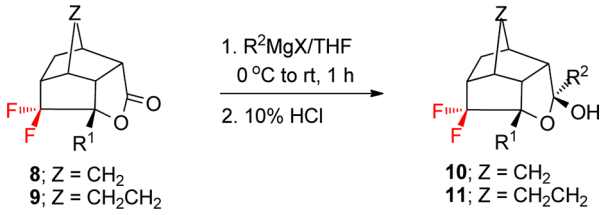
[a]Isolated yield by column chromatography (SiO_2) or preparative thin-layer chromatography (SiO_2). [b]A single isomer of the product was obtained.

Preparation of *gem*-Difluoromethylenated Polycyclic Cage Compounds 10–13. Having established an entry to *gem*-difluoromethylenated cage compounds **8** and **9**, we next demonstrated the synthetic utility of the method for the synthesis of an array of structurally different substituted *gem*-difluoromethylenated cage compounds. Thus, the reactions of **8** and **9** with various Grignard reagents were investigated. Primarily, treatment of **8e** with an excess quantity of methylmagnesium chloride (5 equiv) in THF at 0 °C to room temperature for 1 h followed by an acidic workup (10% HCl) provided the cage lactol **10a**, in a highly stereoselective manner, in 88% yield as a single isomer after chromatography (Table 4, entry 1). Under similar conditions, the reaction of **8f** with methylmagnesium chloride gave a single isomer of the expected cage lactol **10b** in 94% yield (Table 4, entry 2). Similarly, the reactions of **9a**, **9c**, **9f**, **9g**, and **9h** with the Grignard reagents, as indicated in Table 4 (entries 3–11), also proceeded with high stereoselectivity to furnish moderate to good yields (67–91%) of the corresponding cage lactols **11a–i**. The cage lactols **11a**, **11b**, **11c**, **11e**, **11f**, and **11h** were each obtained as a single isomer (Table 4, entries 3, 4, 5, 7, 8, and 10) while cage lactols **11d**, **11g**, and **11i** were obtained as a mixture of isomers (^{19}F NMR analysis) (Table 4, entries 6, 9, and 11). The relative stereochemistry of **11a** was determined by X-ray crystallography (see the Supporting Information). Thus, the relative stereochemistries of **10a,b**, **11b,c**, **11e,f**, **11h**, and the major isomers of **11d**, **11g**, and **11i** were assigned on the same basis of that of **11a**.

It is anticipated that the reaction of *gem*-difluoromethylenated cage γ-butyrolactones **8** and **9** with Grignard reagents, at higher reaction temperature, should provide the *gem*-difluoromethylenated cage furan derivatives **12** and **13**. Thus, compound **8a** was treated with phenylmagnesium chloride, in refluxing THF, for 15 h followed by an acidic workup (10% HCl). Without chromatographic purification, the crude mixture was treated with a catalytic amount of *p*-TsOH in refluxing dichloromethane overnight (15 h) (Scheme 4). As expected, the corresponding *gem*-difluoromethylenated cage furan **12a** was obtained in 59% yield along with keto-alcohol **14a** (6% yield) and an unexpected *gem*-difluoromethylenated cage lactol **16a** (26% yield) (Scheme 4). Under similar reaction conditions, the reaction of *gem*-difluoromethylenated cage lactone **9h** with phenylmagnesium chloride yielded the *gem*-difluoromethylenated cage furan **13a**, keto-alcohol **15a**, and a rearranged product **17a** in 31%, 38%, and 21% yields, respectively. The relative stereochemistries of the keto-alcohols **14a** and **15a** were assigned on the basis of NOESY experiments. The relative stereochemistry of **17a** was confirmed by X-ray crystallography (see the Supporting Information).

DOI: 10.1021/jo502501v
J. Org. Chem. 2015, 80, 1577–1592

Table 4. Preparation of *gem*-Difluoromethylenated Polycyclic Cage Compounds 10 and 11



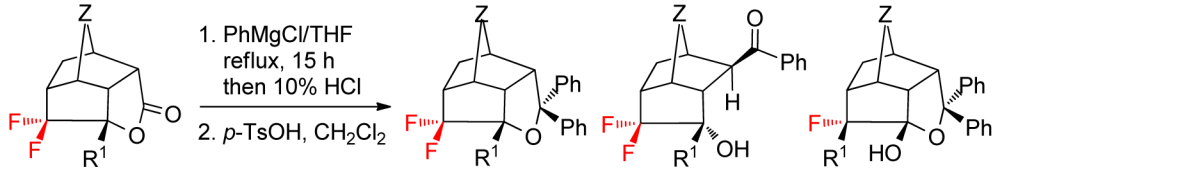
8; Z = CH_2
9; Z = CH_2CH_2

10; Z = CH_2
11; Z = CH_2CH_2

entry	**8** or **9** (R^1)	R^2MgX	R^2	**10** or **11** (% yield)[a]
1	**8e** (C_6H_5)	CH_3MgCl	CH_3	**10a** (88)
2	**8f** (4-$MeOC_6H_4$)	CH_3MgCl	CH_3	**10b** (94)
3	**9a** (CH_3)	C_6H_5MgCl	C_6H_5	**11a** (91)
4	**9a** (CH_3)	2,4-$(MeO)_2C_6H_3MgBr$	2,4-$(MeO)_2C_6H_3$	**11b** (80)
5	**9c** ($CH_3(CH_2)_3$)	C_6H_5MgCl	C_6H_5	**11c** (69)
6	**9f** (C_6H_5)	CH_3MgCl	CH_3	**11d** (77) (97:3)[b]
7	**9f** (C_6H_5)	4-$MeOC_6H_4MgBr$	4-$MeOC_6H_4$	**11e** (75)
8	**9f** (C_6H_5)	2,4-$(MeO)_2C_6H_3MgBr$	2,4-$(MeO)_2C_6H_3$	**11f** (67)
9	**9g** (4-$MeOC_6H_4$)	CH_3CH_2MgCl	CH_3CH_2	**11g** (85) (92:8)[b]
10	**9g** (4-$MeOC_6H_4$)	C_6H_5MgCl	C_6H_5	**11h** (68)
11	**9h** (H)	$CH_3(CH_2)_3MgCl$	$CH_3(CH_2)_3$	**11i** (69) (99:1)[b]

[a]Isolated yield by column or preparative thin-layer chromatography (SiO_2). [b]The diastereomeric ratio was determined by ^{19}F NMR.

Scheme 4. Preparation of *gem*-Difluoromethylenated Polycyclic Cage Compounds 12−17



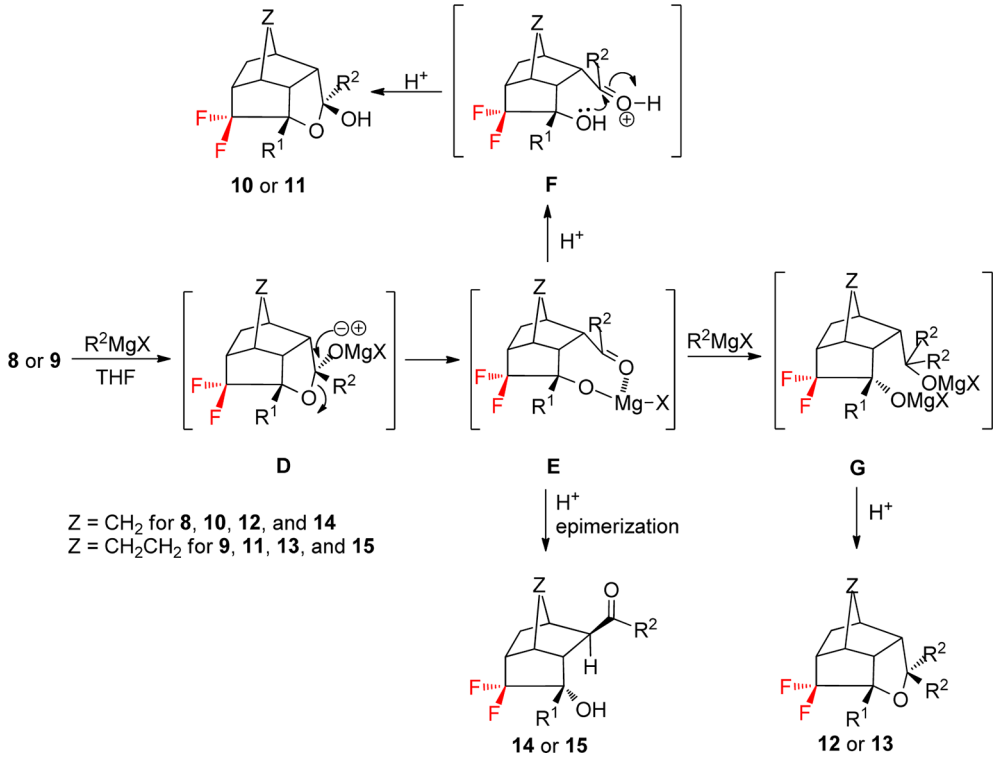
8a; Z = CH_2, R^1 = CH_3
9h; Z = CH_2CH_2, R^1 = H

12a (59%)
13a (31%)

14a (6%)
15a (38%)

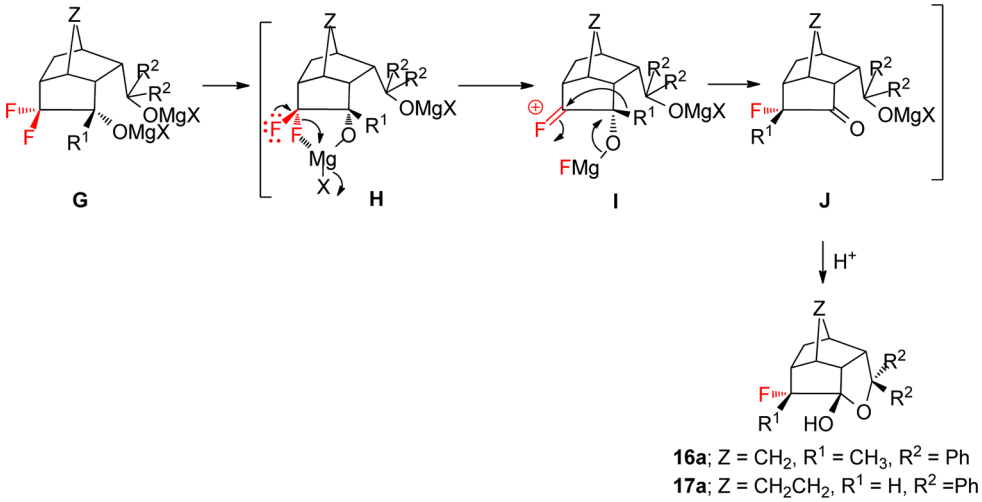
16a (26%) Z = CH_2, R^1 = CH_3
17a (21%) Z = CH_2CH_2, R^1 = H

Scheme 5. Proposed Nucleophilic Addition of R^2MgX to 8 or 9 Leading to Compounds 10−15



DOI: 10.1021/jo502501v
J. Org. Chem. 2015, 80, 1577−1592

Scheme 6. A Plausible Mechanism for the Formation of the Rearranged Products 16a and 17a



Thus, the relative stereochemistry of **16a** was also assigned on the basis of that of **17a**.

The formation and the resulting stereochemical outcome of compounds **10**–**15** can be rationalized by the addition of Grignard reagents to the carbonyl moiety of the *gem*-difluoromethylenated cage lactone **8** or **9** from the less hindered convex side in order to avoid the steric interaction leading to the alkoxide intermediates **D** (Scheme 5). At a low reaction temperature (0 °C, THF), the intermediates **D** underwent ring-opening to give the intermediates **E**, which yielded the *gem*-difluoromethylenated cage lactol **10** or **11** (from the corresponding cage lactone **8** or **9**, respectively), via the intermediates **F**, after acid-catalyzed cyclization. When the reaction was performed at a higher temperature and with a long reaction time (THF, reflux), the intermediates **E** were attacked by the second equivalent of the Grignard reagent leading to intermediates **G**, which upon acid treatment (*p*-TsOH, CH_2Cl_2, reflux), yielded the expected *gem*-difluoromethylenated cage furan **12** or **13**. The unreacted intermediates **E** underwent protonation followed by epimerization of α-carbon next to the carbonyl group to give the corresponding keto-alcohol **14** or **15**.

The formation of the unexpected rearranged products **16a** and **17a** during our investigation (Scheme 4) can be explained, as proposed in Scheme 6. It is possible that the intermediates **H**, derived from **G**, underwent chelation-mediated C–F bond cleavage to furnish fluoronium ion intermediates **I**. A stereoselective 1,2-alkyl (or hydride) migration of **I** gave the rearranged intermediates **J** which afforded the rearranged products **16a** and **17a** after treatment with acid.

CONCLUSIONS

In conclusion, we have demonstrated the synthetic utilities of $PhSCF_2SiMe_3$ (**1**) as a useful *gem*-difluoromethylene building block for the synthesis of *gem*-difluoromethylenated polycyclic cage compounds. The synthesis involved the sequential stereoselective fluoride-catalyzed nucleophilic addition of $PhSCF_2SiMe_3$ to maleic anhydride–cyclopentadiene and –cyclohexadiene adducts, the addition of the Grignard reagents or hydride reagents, and intramolecular radical cyclization. Our developed method may be useful for the synthesis of other related highly substituted polycyclic cage compounds containing a *gem*-difluoromethylene unit. Investigation in this area is now being undertaken.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR spectra were recorded on 400 and 500 MHz spectrometers and are reported in ppm. Proton-decoupled ^{13}C NMR spectra were recorded on 100 and 125 MHz spectrometers and are reported in ppm. ^{19}F NMR spectra were recorded on 376 and 470 MHz spectrometers and are reported in ppm. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl. Dichloromethane (CH_2Cl_2) and toluene were distilled over calcium hydride and were stored over activated molecular sieves (4 Å). All glassware and syringes were oven-dried and kept in a desiccator before use. Preparative thin-layer chromatography plates were performed by using silica gel for preparative layer chromatography. Column chromatography was performed by using silica gel for column chromatography. Other common solvents [CH_2Cl_2, hexanes, ethyl acetate (EtOAc), methanol, and acetone] were distilled before use.

General Procedure for the Synthesis of *gem*-Difluoromethylenated Compounds 4 and 5. To a solution of $PhSCF_2SiMe_3$ (**1**, 2.32 g, 10.0 mmol) and **2** (821 mg, 5.0 mmol) in dry THF (15 mL) was added a solution of 10 mol % of TBAT (540 mg, 1.0 mmol) in dry THF (15 mL) at −10 °C under an argon atmosphere. The reaction mixture was stirred at −10 °C for 5 h and then quenched with water and extracted with EtOAc (3 × 30 mL). The combined organic phase was washed successively with water (30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents, the crude product was purified by column chromatography (SiO_2, 5–30% EtOAc/hexanes) to give a single isomer of **4** (1.34 g, 83%) and a single isomer of **4A** (142 mg, 9%), each as a white solid.

(3R,3aR*,4S*,7R*,7aS*)-3-(Difluoro(phenylthio)methyl)-3-hydroxy-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3H)-one (4).* Less polar; mp 124–125 °C (CH_2Cl_2/hexanes); IR (KBr) 3338br, 3002m, 2970w, 1752br, 1443m, 1385m, 1196m, 1151m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (dt, J = 7.0, 1.6 Hz, 2H), 7.39 (tt, J = 7.4, 1.6 Hz, 1H), 7.32 (tt, J = 7.4, 1.5 Hz, 2H), 6.30 (dd, J = 5.6, 2.9 Hz, 1H), 6.12 (dd, J = 5.6, 2.9 Hz, 1H), 4.01 (s, 1H), 3.40 (dd, J = 9.1, 4.8 Hz, 1H), 3.32 (dd, J = 9.1, 3.9 Hz, 1H), 3.25–3.23 (m, 1H), 3.15 (br.s, 1H), 1.58 (dt, J = 8.8, 1.6 Hz, 1H), 1.42 (d, J = 8.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.9, 136.7, 136.7, 136.6, 133.9, 130.3, 129.2, 129.2, 127.4 (dd, J = 287.8, 287.3 Hz), 124.3, 103.7 (dd, J = 28.5, 28.5 Hz), 52.0, 50.0, 45.7, 45.4, 45.0; ^{19}F NMR (470 MHz, $CDCl_3$): δ −89.8 (d, J = 210.5 Hz, 1F), −89.1 (d, J = 210.5 Hz, 1F); MS: m/z (% relative intensity) 324 (M^+, 3), 258 (3), 165 (45), 160 (100), 149 (7), 110 (31), 99 (17), 77 (22), 67 (85); HRMS (ESI-TOF) calcd for $C_{16}H_{14}F_2O_3SNa$ $[M + Na]^+$ 347.0529, found 347.0528.

DOI: 10.1021/jo502501v
J. Org. Chem. 2015, 80, 1577–1592

(1R,2S*,3S*,4S*)-3-(2,2-Difluoro-2-(phenylthio)acetyl)bicyclo-[2.2.1]hept-5-ene-2-carboxylic acid (**4A**).* More polar; mp 125−126 °C (CH_2Cl_2/hexanes); IR (KBr) 3448−2531br (COOH), 1737s (C═O), 1706s (C═O, acid), 1427m, 1314m, 1227m, 1069m, 1024m, 873s cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, J = 7.2, 2H), 7.46 (tt, J = 7.4, 1.5 Hz, 1H), 7.38 (tt, J = 7.4, 1.5 Hz, 2H), 6.32 (dd, J = 5.6, 3.2 Hz, 1H), 6.20 (dd, J = 5.6, 2.8 Hz, 1H), 3.45 (dd, J = 4.2, 4.2 Hz, 1H), 3.33 (br.s, 1H), 3.22 (d, J = 4.6 Hz, 1H), 3.20 (br.s, 1H), 1.54 (d, J = 9.1 Hz, 1H), 1.44 (dd, J = 9.1, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.1 (dd, J = 28.1, 28.1 Hz), 179.6, 138.3, 137.6, 137.6, 136.8, 131.4, 130.2, 130.2, 125.4, 123.8 (dd, J = 291.9, 288.3 Hz), 49.8, 48.7, 47.9, 47.2, 46.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ −84.4 (d, J = 217.8 Hz, 1F), −83.0 (d, J = 217.8 Hz, 1F); MS: m/z (% relative intensity) 324 (M^+, 8), 258 (12), 165 (42), 159 (61), 137 (48), 109 (35), 99 (48), 77 (68), 67 (100); HRMS (ESI-TOF) calcd for $C_{16}H_{14}F_2O_3SNa$ $[M + Na]^+$ 347.0529, found 347.0527.

(3R,3aR*,4S*,7R*,7aS*)-3-(Difluoro(phenylthio)methyl)-3-hydroxy-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-1(3H)-one (**5**).* Under the same conditions as for **4**, a solution of **3** (713 mg, 4.0 mmol) and **1** (1.86 g, 8.0 mmol) in dry THF 10 mL was treated with a solution of 10 mol % of TBAT (432 mg, 0.8 mmol) in dry THF (10 mL) to provide a single isomer of **5** (1.24 g, 91%) as a white solid. Mp 124−125 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3191br, 2960w, 1788s, 1475w, 1190m, 1145m, 1042m, 970m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.67−7.60 (m, 2H), 7.50−7.37 (m, 3H), 6.40 (dd, J = 7.0, 7.0 Hz, 1H), 6.24 (dd, J = 7.4, 7.4 Hz, 1H), 4.06 (s, 1H), 3.18−3.12 (m, 1H), 3.04 (dd, J = 10.4, 3.3 Hz, 1H), 3.02−2.95 (m, 2H), 1.62−1.50 (m, 2H), 1.45−1.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 136.8, 136.8, 134.3, 131.8, 130.3, 129.2, 129.2, 127.5 (dd, J = 288.2, 287.0 Hz), 124.4, 105.1 (dd, J = 29.0, 29.0 Hz), 47.5, 43.2, 31.7, 29.6, 24.1, 22.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ −90.1 (d, J = 210.9 Hz, 1F), −89.4 (d, J = 210.9 Hz, 1F); MS: m/z (% relative intensity) 338 (M^+, 3), 179 (63), 160 (49), 159 (16), 109 (21), 77 (100); HRMS (ESI-TOF) calcd for $C_{17}H_{16}F_2O_3SNa$ $[M + Na]^+$ 361.0686, found 361.0681.

General Procedure for the Synthesis of *gem*-Difluoromethylenated γ-Butyrolactones 6 and 7. *General Procedure A.* A solution of **4** or **5** (0.5 mmol) in dry THF (15 mL) was treated with a THF solution of alkyl- or arylmagnesium chloride (1.6−3.0 M in THF, 2.5 mmol) at −78 or 0 °C under an argon atmosphere. After stirring at −78 °C for 1 h, or at 0 °C for 40 min, 10% HCl (2 mL) was added at −78 °C or at 0 °C. The aqueous phase was extracted with EtOAc (4 × 10 mL). The combined organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents, the crude product was treated with a catalytic amount of *p*-TsOH in dry CH_2Cl_2 (12 mL) under reflux overnight (15 h). The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents, the crude product was purified by column chromatography (SiO_2) or preparative thin-layer chromatography (SiO_2).

General Procedure B. A solution of alkyl- or aryl bromide (5.0 mmol) in dry THF (3 mL) was added dropwise into a suspension of Mg (turning) (200 mg, 10.0 mmol) in dry THF (2 mL) under an argon atmosphere at room temperature. After stirring at room temperature for 2 h, a solution of freshly prepared Grignard reagent was transferred dropwise to a mixture solution of **4** or **5** (1.0 mmol) in dry THF (3 mL) via a cannula at −78 or 0 °C under an argon atmosphere, and the resulting mixture was stirred for 1 h. The reaction mixture was quenched with 10% HCl (5 mL) at −78 or 0 °C and extracted with EtOAc (4 × 10 mL). The combined organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents, the crude product was treated with a catalytic amount of *p*-TsOH in dry CH_2Cl_2 (20 mL) under reflux overnight (15 h). The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (SiO_2) or preparative thin-layer chromatography (SiO_2).

(3S,3aR*,4S*,7R*,7aS*)-3-(Difluoro(phenylthio)methyl)-3-methyl-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3H)-one (**6a**).* According to the general procedure A, the reaction of **4** (163 mg, 0.5 mmol) with methylmagnesium chloride (3.0 M in THF, 0.83 mL, 2.5 mmol) at 0 °C followed by lactonization gave **6a** (143 mg, 89%) as a white solid after preparative thin-layer chromatography (SiO_2, 30% EtOAc/hexanes). Mp 105−106 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3028w, 2996w, 2948w, 1777s, 1442w, 1385w, 1247w, 1159m, 1095m, 957m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.58−7.56 (m, 2H), 7.41−7.38 (m, 1H), 7.36−7.32 (m, 2H), 6.15 (dd, J = 5.7, 3.0 Hz, 1H), 6.13−6.04 (m, 1H), 3.45 (dd, J = 8.4, 5.2 Hz, 1H), 3.27 (br.s, 1H), 3.18−3.15 (m, 1H), 2.82 (dd, J = 8.5, 3.3 Hz, 1H), 1.62 (dt, J = 8.6, 1.7 Hz, 1H), 1.57 (s, 3H), 1.38 (d, J = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.2, 136.9, 136.9, 135.4 (dd, J = 10.9, 7.4 Hz), 130.2, 129.1, 129.1, 129.1, 128.1 (dd, J = 288.4, 282.8 Hz), 124.9, 85.3 (dd, J = 27.3, 21.6 Hz), 53.6, 50.1, 48.2, 45.8, 43.9, 27.5; ^{19}F NMR (470 MHz, $CDCl_3$): δ −82.0 (dd, J = 204.8, 4.9 Hz, 1F), −79.4 (dd, J = 204.8, 5.2 Hz, 1F); MS: m/z (% relative intensity) 322 (M^+, 30), 257 (34), 159 (100), 110 (26), 77 (28); HRMS (ESI-TOF) calcd for $C_{17}H_{16}F_2O_2SNa$ $[M + Na]^+$ 345.0758, found 345.0737.

(3S,3aR*,4S*,7R*,7aS*)-3-(Difluoro(phenylthio)methyl)-3-methyl-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3H)-one (**6b**).* According to the general procedure A, the reaction of **4** (163 mg, 0.5 mmol) with ethylmagnesium chloride (2.0 M in THF, 1.25 mL, 2.5 mmol) at 0 °C followed by lactonization gave **6b** (136 mg, 81%) as a white solid after preparative thin-layer chromatography (SiO_2, 30% EtOAc/hexanes). Mp 77−78 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2994w, 2948w, 1774s, 1475w, 1244m, 1157m, 980w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.58−7.56 (m, 2H), 7.42−7.38 (m, 1H), 7.36−7.32 (m, 2H), 6.17−6.04 (m, 2H), 3.40 (dd, J = 8.6, 5.2 Hz, 1H), 3.33−3.26 (br, 1H), 3.17−3.10 (br, 1H), 2.85 (dd, J = 8.6, 3.2 Hz, 1H), 2.03−1.87 (m, 2H), 1.63 (d, J = 8.5 Hz, 1H), 1.40 (d, J = 8.5 Hz, 1H), 1.03 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.5, 136.9, 136.0 (dd, J = 7.9, 7.9 Hz), 136.0 (dd, J = 7.9, 7.9 Hz), 134.9, 130.2, 129.1, 129.1, 128.5 (dd, J = 290.0, 284.4 Hz), 125.1, 87.5 (dd, J = 26.1, 19.9 Hz), 53.9, 49.1, 48.1, 46.2, 43.9, 33.1, 8.1; ^{19}F NMR (470 MHz, $CDCl_3$): δ −78.4 (dd, J = 208.0, 4.2 Hz, 1F), −75.6 (dd, J = 208.0, 5.4 Hz, 1F); MS: m/z (% relative intensity) 336 (M^+, 7), 271 (7), 159 (100), 110 (33), 77 (31); HRMS (ESI-TOF) calcd for $C_{18}H_{18}F_2O_2SNa$ $[M + Na]^+$ 359.0893, found 359.0890.

(3S,3aR*,4S*,7R*,7aS*)-3-Butyl-3-(difluoro(phenylthio)methyl)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3H)-one (**6c**).* According to the general procedure A, the reaction of **4** (163 mg, 0.5 mmol) with butylmagnesium chloride (2.0 M in THF, 1.25 mL, 2.5 mmol) at 0 °C followed by lactonization gave **6c** (158 mg, 87%) as a white solid after preparative thin-layer chromatography (SiO_2, 30% EtOAc/hexanes). Mp 87−88 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2962m, 1773s, 1475w, 1442w, 1247w, 1180m, 1130m, 1029m, 963m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.69−7.62 (m, 2H), 7.48 (tt, J = 7.4, 1.7 Hz, 1H), 7.43 (tt, J = 7.3, 1.7 Hz, 2H), 6.23 (dd, J = 5.7, 3.0 Hz, 1H), 6.20−6.14 (m, 1H), 3.49 (dd, J = 8.7, 5.2 Hz, 1H), 3.39 (s, 1H), 3.25−3.20 (m, 1H), 2.95 (dd, J = 8.7, 3.3 Hz, 1H), 2.05−1.91 (m, 2H), 1.71 (dt, J = 8.6, 1.6 Hz, 1H), 1.62−1.51 (m, 1H), 1.48 (d, J = 8.6 Hz, 1H), 1.45−1.35 (m, 3H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.5, 136.8, 136.8, 135.9 (dd, J = 7.9, 7.9 Hz), 134.8, 130.1, 129.0, 129.0, 128.4 (dd, J = 286.2, 284.6 Hz), 125.0, 87.3 (dd, J = 25.8, 20.1 Hz), 53.9, 49.1, 48.4, 46.1, 43.8, 40.0, 25.4, 23.0, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$): δ −78.7 (dd, J = 207.0, 5.5 Hz, 1F), −75.7 (dd, J = 207.0, 5.5 Hz, 1F); MS: m/z (% relative intensity) 365 (M^+ + H, 7), 299 (9), 255 (4), 205 (6), 189 (13), 159 (100), 139 (13), 110 (23), 77 (39); HRMS (ESI-TOF) calcd for $C_{20}H_{22}F_2O_2SNa$ $[M + Na]^+$ 387.1206, found 387.1183.

(3S,3aR*,4S*,7R*,7aS*)-3-(Difluoro(phenylthio)methyl)-3-isopropyl-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3H)-one (**6d**).* According to the general procedure A, the reaction of **4** (118 mg, 0.36 mmol) with isopropylmagnesium chloride (2.0 M in THF, 0.90 mL, 1.8 mmol) at −0 °C followed by lactonization gave **6d** (71 mg, 56%) as a white solid together with the reduction product **6h** (33 mg,

DOI: 10.1021/jo502501v
J. Org. Chem. 2015, 80, 1577−1592

30%) as a colorless viscous oil after preparative thin-layer chromatography (SiO_2, 30% EtOAc/hexanes). **6h**: mp 140−141 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2997m, 1780s, 1475m, 1442m, 1238m, 1178m, 1118m, 1065m, 989m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.57−7.55 (m, 2H), 7.41−7.37 (m, 1H), 7.34−7.31 (m, 2H), 6.12−6.08 (m, 2H), 3.32 (dd, J = 9.1, 5.1 Hz, 1H), 3.18 (br.s, 1H), 3.11 (br.s, 1H), 2.84 (dd, J = 9.1, 3.3 Hz, 1H), 2.34 (sept, J = 6.7 Hz, 1H), 1.61 (d, J = 8.5 Hz, 1 H), 1.39 (d, J = 8.5 Hz, 1H), 1.17 (dd, J = 6.8, 3.6 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.6, 137.1, 137.1, 136.7 (d, J = 12.8 Hz), 134.0 (d, J = 4.3 Hz), 130.1, 129.4 (dd, J = 292.4, 283.1 Hz), 128.9, 128.9, 125.5, 89.7 (dd, J = 29.9, 19.8 Hz), 54.6, 50.2, 46.4, 44.7, 43.9, 36.2, 17.8, 17.5 (d, J = 4.3 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ −72.7 (d, J = 213.9 Hz, 1F), −69.4 (dd, J = 213.9, 10.3 Hz, 1F); MS: m/z (% relative intensity) 351 (M^+ + H, 50), 350 (M^+, 32), 285 (24), 173 (23), 159 (100), 110 (24), 77 (37); HRMS (ESI-TOF) calcd for $C_{19}H_{20}F_2O_2SNa$ $[M + Na]^+$ 373.1050, found 373.1041.

(3S,3aR*,4S*,7R*,7aS*)-3-(Difluoro(phenylthio)methyl)-3-vinyl-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3H)-one (**6e**).* According to the general procedure A, the reaction of **4** (163 mg, 0.5 mmol) with vinylmagnesium chloride (1.6 M in THF, 1.56 mL, 2.5 mmol) at 0 °C followed by lactonization gave **6e** (148 mg, 89%) as a white solid after preparative thin-layer chromatography (SiO_2, 30% EtOAc/hexanes). Mp 127−128 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3029w, 2997w, 1780s, 1475w, 1118m, 1031w, 959w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.56−7.53 (m, 2H), 7.40−7.37 (m, 1H), 7.34−7.31 (m, 2H), 6.16 (dd, J = 5.7, 3.0 Hz, 1H), 6.09−6.05 (m, 1H), 6.01 (dd, J = 17.0, 10.7 Hz, 1H), 5.42 (d, J = 17.0 Hz, 1H), 5.32 (d, J = 10.7 Hz, 1H), 3.26 (dd, J = 8.3, 5.2 Hz, 1H), 3.20 (s, 1H), 3.14−3.12 (m, 1H), 2.87 (dd, J = 8.3, 3.3 Hz, 1H), 1.62 (dt, J = 8.6, 1.6 Hz, 1H), 1.36 (d, J = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.6, 136.8, 136.8, 136.5, 135.7 (d, J = 5.0 Hz), 135.6, 130.1, 129.0, 129.0, 127.3 (dd, J = 290.1, 283.3 Hz), 125.4, 117.3, 86.2 (dd, J = 29.3, 24.6 Hz), 53.6, 48.8, 46.8, 45.6, 43.5; ^{19}F NMR (470 MHz, $CDCl_3$): δ −80.5 (dd, J = 206.6, 1.4 Hz, 1F), −80.0 (dd, J = 206.6, 6.8 Hz, 1F); MS: m/z (% relative intensity) 335 (M^+ + H, 88), 334 (M^+, 65), 268 (24), 225 (14), 174 (12), 159 (100), 109 (14), 77 (24); HRMS (ESI-TOF) calcd for $C_{18}H_{16}F_2O_2SNa$ $[M + Na]^+$ 357.0737, found 357.0730.

(3R,3aR*,4S*,7R*,7aS*)-3-(Difluoro(phenylthio)methyl)-3-phenyl-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3H)-one (**6f**).* According to the general procedure A, the reaction of **4** (163 mg, 0.5 mmol) with phenylmagnesium chloride (2.0 M in THF, 1.25 mL, 2.5 mmol) at 0 °C followed by lactonization gave **6f** (183 mg, 95%) as a white solid after preparative thin-layer chromatography (SiO_2, 30% EtOAc/hexanes). Mp 117−119 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2929w, 1781s, 1442w, 1118m, 1039m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.55−7.52 (m, 2H), 7.42−7.37 (m, 2H), 7.36−7.29 (m, 4H), 7.26−7.23 (m, 2H), 6.18 (dd, J = 5.7, 2.9 Hz, 1H), 6.14−6.10 (m, 1H), 3.35 (s, 1H), 3.29 (dd, J = 8.0, 3.3 Hz, 1H), 3.10−3.05 (m, 2H), 1.62 (dt, J = 8.6, 1.5 Hz, 1H), 1.33 (d, J = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.5, 139.9 (d, J = 3.9 Hz), 136.7, 136.7, 135.9 (d, J = 11.9 Hz), 135.4 (d, J = 3.3 Hz), 129.8, 129.1, 128.8, 128.8, 128.5, 128.5, 128.4 (dd, J = 295.2, 281.4 Hz), 126.3, 126.3, 125.8 (d, J = 3.1 Hz), 87.4 (dd, J = 33.1, 22.1 Hz), 53.6, 52.3, 47.0, 46.2, 43.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ −78.6 (d, J = 208.4 Hz, 1F), −76.9 (dd, J = 208.4, 10.1 Hz, 1F); MS: m/z (% relative intensity) 385 (M^+ + H, 18), 384 (M^+, 12), 318 (4), 275 (21), 225 (14), 159 (100), 77 (20); HRMS (ESI-TOF) calcd for $C_{22}H_{18}F_2O_2SNa$ $[M + Na]^+$ 407.0893, found 407.0877.

(3R,3aR*,4S*,7R*,7aS*)-3-(Difluoro(phenylthio)methyl)-3-(4-methoxyphenyl)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3H)-one (**6g**).* According to the general procedure B, the reaction of **4** (324 mg, 1.0 mmol) with 4-methoxyphenylmagnesium bromide at 0 °C followed by lactonization gave **6g** (286 mg, 69%) as a white solid after preparative thin-layer chromatography (SiO_2, 30% EtOAc/hexanes). Mp 130−132 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3009m, 1780s, 1610s, 1513s, 1442m, 1307m, 1257s, 1182s, 1113s, 1037s, 966m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.46−7.42 (m, 4H), 7.33 (dt, J = 7.4, 1.6 Hz, 1H), 7.28−7.25 (m, 2H), 6.87 (dt, J = 9.0, 2.7 Hz, 2H), 6.18 (dd, J = 5.7, 2.6 Hz, 1 H), 6.13−6.11 (m, 1H), 3.77 (s, 3H), 3.34 (s, 1H), 3.27 (dd, J = 7.7, 3.2 Hz, 1H), 3.10−3.08 (m, 2H), 1.63 (dd, J = 8.6, 1.6 Hz, 1H), 1.34 (d, J = 8.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.6, 160.2, 136.7, 136.7, 135.9 (d, J = 11.8 Hz), 135.4 (d, J = 3.0 Hz), 131.7 (d, J = 3.8 Hz), 129.8, 128.9, 128.9, 128.7 (dd, J = 295.6, 281.0 Hz), 127.8, 127.8, 126.1 (d, J = 3.0 Hz), 113.9, 113.9, 87.2 (dd, J = 33.3, 22.5 Hz), 55.3, 53.7, 52.2, 47.2, 46.2, 43.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ −78.7 (d, J = 207.7 Hz, 1F), −77.1 (dd, J = 207.7, 9.4 Hz, 1F); MS: m/z (% relative intensity) 414 (M^+, 0.7), 305 (0.6), 255 (14), 189 (100), 161 (22), 133 (12), 77 (9); HRMS (ESI-TOF) calcd for $C_{23}H_{20}F_2O_3SNa$ $[M + Na]^+$ 437.0999, found 437.0978.

(3S,3aR*,4S*,7R*,7aS*)-3-(Difluoro(phenylthio)methyl)-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1(3H)-one (**6h**). Method A.* To a solution of **4** (324 mg, 1.0 mmol) in methanol (2 mL) was added $NaBH_4$ (187 mg, 5.0 mmol) at 0 °C. After stirring at 0 °C for 2 h, the reaction mixture was quenched with 10% HCl (1 mL) and then diluted with water (2 mL) and extracted with EtOAc (4 × 5 mL). The combined organic phase was washed successively with water (10 mL) and brine (10 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents, the crude product was treated with *p*-TsOH in CH_2Cl_2 (20 mL) under reflux for overnight (15 h) and then quenched with saturated $NaHCO_3$ and purified by preparative layer chromatography (SiO_2, 30% EtOAc/hexanes) to give **6h** (263 mg, 85%) as a colorless viscous oil.

Method B. To a solution of **4** (163 mg, 0.5 mmol) in acetic acid (3 mL) and a catalytic amount of trifluoroacetic anhydride (TFA) was added $NaCNBH_3$ (330 mg, 1.5 mmol) at 0 °C. After stirring at reflux for overnight (15 h), the reaction was quenched with 10% NaOH, diluted with water (5 mL), and extracted with CH_2Cl_2 (4 × 5 mL). The combined organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by preparative thin-layer chromatography (SiO_2, 30% EtOAc/hexanes) to give **6h** (139 mg, 90%) as colorless viscous oil. IR ($CHCl_3$) 2980w, 1760s, 1411w, 1247w, 1173w, 987m, 934m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.68−7.66 (m, 2H), 7.51−7.48 (m, 1H), 7.45−7.41 (m, 2H), 6.24−6.21 (m, 2H), 4.62 (ddd, J = 15.0, 10.4, 7.5 Hz, 1H), 3.45 (dd, J = 8.7, 5.1 Hz, 1H), 3.33 (br.s, 1H), 3.29−3.28 (m, 1H), 3.12 (ddd, J = 8.7, 7.5, 3.4 Hz, 1H), 1.70 (dt, J = 8.7, 1.7 Hz, 1H), 1.47 (d, J = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.2, 136.5, 136.5, 135.5, 135.3 (dd, J = 6.0, 6.0 Hz), 130.3, 129.3, 129.3, 129.3, 125.9 (dd, J = 286.8, 279.4 Hz), 78.5 (dd, J = 33.0, 23.0 Hz), 53.4, 47.9, 44.9, 44.4, 42.0; ^{19}F NMR (470 MHz, $CDCl_3$): δ −83.5 (dd, J = 213.2, 9.2 Hz, 1F), −80.2 (dd, J = 213.2, 15.0 Hz, 1F); MS: m/z (% relative intensity) 309 (M^+ + H, 4), 308 (M^+, 8), 242 (26), 214 (62), 159 (100), 148 (48), 110 (30), 66 (41); HRMS (ESI-TOF) calcd for $C_{16}H_{14}F_2O_2SNa$ $[M + Na]^+$ 331.0580, found 331.0603.

(3S,4S*,7R*,7aS*)-3-Methyl-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-1(3H)-one (**7a**).* According to the general procedure A, the reaction of **5** (170 mg, 0.5 mmol) with methylmagnesium chloride (3.0 M in THF, 0.83 mL, 2.5 mmol) at 0 °C followed by lactonization gave **7a** (159 mg, 94%) as a white solid after preparative thin-layer chromatography (SiO_2, 20% EtOAc/hexanes). Mp 99−100 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2960w, 2943w, 2873w, 1774s, 1475w, 1442w, 1384w, 1271m, 1143m, 1057m, 962s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.62−7.54 (m, 2H), 7.42−7.38 (m, 1H), 7.36−7.32 (m, 2H), 6.18−6.10 (m, 1H), 6.09−6.06 (m, 1H), 3.10−3.08 (br, 1H), 3.06−3.01 (m, 2H), 2.39 (dd, J = 8.5, 1.4 Hz, 1H), 1.53 (s, 3H), 1.49−1.41 (m, 2H), 1.38−1.28 (m, 1H), 1.27−1.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 136.9, 136.9, 134.0 (dd, J = 4.0, 4.0 Hz), 131.0, 130.2, 129.2, 129.2, 128.5 (dd, J = 289.0, 283.0 Hz), 125.0, 87.0 (dd, J = 28.0, 22.0 Hz), 47.5, 46.5, 30.7, 30.6, 26.4, 26.4, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ −83.3 (d, J = 207.0 Hz, 1F), −79.4 (dd, J = 207.0 Hz, 1F); MS: m/z (% relative intensity) 336 (M^+, 39), 256 (2), 177 (5), 160 (100), 159 (17), 109 (40), 97 (11), 77 (87); HRMS (ESI-TOF) calcd for $C_{18}H_{18}F_2O_2SNa$ $[M + Na]^+$ 359.0893, found 359.0894.

(3S,4S*,7R*,7aS*)-3-Ethyl-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-1(3H)-one (**7b**).* According to the general procedure A, the reaction of **5** (170 mg, 0.5 mmol) with ethylmagnesium chloride

DOI: 10.1021/jo502501v
J. Org. Chem. 2015, 80, 1577−1592

(2.0 M in THF, 1.25 mL, 2.5 mmol) at 0 °C followed by lactonization gave **7b** (132 mg, 75%) as a white solid together with the reduction product **7h** (12 mg, 7%) and **7h′** (15 mg, 9%) after preparative thin-layer chromatography (SiO_2, 20% EtOAc/hexanes × 2). **7b**: mp 107−108 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2948w, 2873w, 1774s, 1474w, 1252w, 1187w, 1143m, 981m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60−7.50 (m, 2H), 7.39−7.36 (m, 1H), 7.34−7.30 (m, 2H), 6.16−6.07 (m, 1H), 6.04 (dd, J = 7.8, 6.6 Hz, 1H), 3.13−3.04 (br, 1H), 3.02−2.96 (m, 1H), 2.95 (dd, J = 9.2, 4.2 Hz, 1H), 2.41 (dd, J = 9.2, 0.9 Hz, 1H), 1.99−1.80 (m, 2H), 1.50−1.38 (m, 2H), 1.35−1.13 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 137.0, 137.0, 134.4 (dd, J = 5.0, 5.0 Hz), 130.4, 130.2, 129.1, 129.1, 128.8 (dd, J = 289.9, 284.9 Hz), 125.1, 89.2 (dd, J = 26.8, 20.2 Hz), 47.5, 45.3, 32.5, 30.7, 30.6, 26.5, 21.9, 8.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ −79.9 (d, J = 210.4 Hz, 1F), −75.1 (d, J = 210.4 Hz, 1F); MS: m/z (% relative intensity) 350 (M^+, 25), 321 (10), 299 (23), 191 (8), 161 (13), 159 (13), 109 (42), 77 (100); HRMS (ESI-TOF) calcd for $C_{19}H_{20}F_2O_2SNa$ $[M + Na]^+$ 373.1050, found 373.1046.

(3R,4S*,7R*,7aS*)-3-(Difluoro(phenylthio)methyl)-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-1(3H)-one (**7h′**).* White solid; mp 93−94 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3029w, 2957m, 2874w, 1784s, 1475m, 1442m, 1245m, 1166m, 1142m, 1063m, 991m, 979m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60−7.50 (m, 2H), 7.41−7.36 (m, 1H), 7.35−7.28 (m, 2H), 6.29−6.25 (m, 1H), 6.16 (dd, J = 7.4, 7.0 Hz, 1H), 4.08 (ddd, J = 11.9, 8.9, 3.2 Hz, 1H), 3.02 (dd, J = 4.5, 1.5 Hz, 1H), 2.82−2.72 (m, 2H), 2.71 (dd, J = 4.5, 1.5 Hz, 1H), 1.56−1.47 (m, 2H), 1.32−1.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 136.6, 136.6, 134.6, 132.3, 130.3, 129.3, 129.3, 127.4 (dd, J = 281.4, 281.4 Hz), 124.9, 83.1 (dd, J = 29.7, 26.8 Hz), 44.8, 39.6, 33.2, 31.8, 23.4, 23.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ −87.3 (dd, J = 215.7, 10.9 Hz, 1F), −85.4 (dd, J = 215.7, 8.5 Hz, 1F); MS: m/z (% relative intensity) 322 (M^+, 73), 242 (2), 213 (2), 163 (53), 159 (15), 133 (7), 109 (20), 77 (100); HRMS (ESI-TOF) calcd for $C_{17}H_{16}F_2O_2SNa$ $[M + Na]^+$ 345.0737, found 345.0749.

(3S,4S*,7R*,7aS*)-3-Butyl-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-1(3H)-one (**7c**).* According to the general procedure A, the reaction of **5** (170 mg, 0.5 mmol) with butylmagnesium chloride (2.0 M in THF, 1.25 mL, 2.5 mmol) at 0 °C followed by lactonization gave **7c** (150 mg, 79%) as a white solid together with **7h′** (5 mg, 3%) after preparative thin-layer chromatography (SiO_2, 20% EtOAc/hexanes). Compound **7c** was recrystallized from CH_2Cl_2/hexane. Mp 70−71 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2961s, 2874m, 1773s, 1474m, 1182m, 1143m, 1025m, 988m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.71−7.60 (m, 2H), 7.52−7.36 (m, 3H), 6.25−6.17 (m, 1H), 6.14 (dd, J = 7.7, 6.5 Hz, 1H), 3.22−3.14 (br, 1H), 3.13−3.08 (br, 1H), 3.06 (dd, J = 9.1, 4.2 Hz, 1H), 2.51 (br.d, J = 8.8 Hz, 1H), 2.00−1.86 (m, 2H), 1.60−1.45 (m, 3H), 1.44−1.22 (m, 5H), 0.97 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 136.9, 136.9, 134.4 (dd, J = 5.0, 5.0 Hz), 130.4, 130.1, 129.1, 129.1, 128.8 (dd, J = 290.6, 284.2 Hz), 125.2, 89.0 (dd, J = 27.0, 20.2 Hz), 47.5, 45.8, 39.4, 30.8, 30.6, 26.5, 25.3, 23.1, 21.9, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ −80.2 (d, J = 209.6 Hz, 1F), −75.4 (d, J = 209.6 Hz, 1F); MS: m/z (% relative intensity) 378 (M^+, 26), 322 (15), 219 (17), 189 (4), 159 (17), 139 (15), 109 (40), 77 (100); HRMS (ESI-TOF) calcd for $C_{21}H_{24}F_2O_2SNa$ $[M + Na]^+$ 401.1363, found 401.1369.

(3S,4S*,7R*,7aS*)-3-Isopropyl-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-1(3H)-one (**7d**).* According to the general procedure A, the reaction of **5** (339 mg, 1.0 mmol) with isopropylmagnesium chloride (2.0 M in THF, 2.50 mL, 5.0 mmol) at −78 °C followed by lactonization gave **7d** (78 mg, 21%) as a white solid together with **7h** (139 mg, 43%) and **7h′** (87 mg, 27%) after preparative thin-layer chromatography (SiO_2, 20% EtOAc/hexanes and then 5% EtOAc/hexanes × 5). **7d**: mp 159−161 °C (CH_2Cl_2/hexane); IR ($CHCl_3$) 2956m, 2873w, 1773s, 1475m, 1254m, 1179m, 1144m, 1034m, 988m, 905m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.60−7.53 (m, 2H), 7.40−7.37 (m, 1H), 7.34−7.30 (m, 2H), 6.09 (dd, J = 15.6, 8.3 Hz, 1H), 6.02 (dd, J = 8.3, 6.5 Hz, 1H), 3.01−2.90 (m, 2H), 2.86 (dd, J = 9.8, 4.1 Hz, 1H), 2.40 (d, J = 9.8 Hz, 1H), 2.34 (sept, J = 6.8 Hz, 1H), 1.49−1.37 (m, 2H), 1.33−1.15 (m, 2H), 1.11 (dd, J = 6.8, 4.4 Hz, 3H), 0.93 (d, J = 6.8, 4.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 137.2, 137.2, 134.9 (d, J = 9.7 Hz), 130.1, 129.5 (d, J = 3.7 Hz), 129.8 (dd, J = 292.5, 283.5 Hz), 129.0, 129.0, 125.5, 91.2 (dd, J = 29.0, 21.0 Hz), 48.8, 42.0, 36.0, 30.4, 26.5, 22.3, 17.7, 17.2, 17.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ −74.2 (d, J = 214.8 Hz, 1F), −70.7 (dd, J = 214.8, 6.9 Hz, 1F); MS: m/z (% relative intensity) 364 (M^+, 14), 321 (22), 313 (54), 255 (9), 205 (8), 159 (25), 109 (51), 77 (100); HRMS (ESI-TOF) calcd for $C_{20}H_{22}F_2O_2SNa$ $[M + Na]^+$ 387.1206, found 387.1205.

(3S,4S*,7R*,7aS*)-3-Vinyl-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-1(3H)-one (**7e**).* According to the general procedure A, the reaction of **5** (170 mg, 0.5 mmol) with vinylmagnesium chloride (1.6 M in THF, 1.56 mL, 2.5 mmol) at 0 °C followed by lactonization gave **7e** (149 mg, 86%) as a white solid after preparative thin-layer chromatography (SiO_2, 20% EtOAc/hexanes). Mp 117−118 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2959w, 2873w, 1781s, 1475w, 1252m, 1185m, 1116m, 1063m, 989m, 907m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45−7.43 (m, 2H), 7.30−7.19 (m, 3H), 6.08−6.01 (m, 1H), 6.00 (dd, J = 13.2, 6.9 Hz, 1H), 5.86 (dd, J = 17.0, 10.7 Hz, 1H), 5.29 (d, J = 17.0 Hz, 1H), 5.20 (d, J = 10.7 Hz, 1H), 2.95−2.84 (m, 2H), 2.77 (dd, J = 8.8, 4.3 Hz, 1H), 2.36 (dd, J = 8.8, 1.3 Hz, 1H), 1.37−1.27 (m, 2H), 1.24−1.15 (m, 1H), 1.12−1.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 136.9, 136.9, 135.9 (d, J = 2.1 Hz), 134.1 (d, J = 6.9 Hz), 131.2, 130.1, 127.6 (dd, J = 292.9, 281.5 Hz), 129.1, 129.1, 125.4, 117.2, 87.7 (dd, J = 30.3, 23.0 Hz), 46.4, 45.1, 30.6, 30.5, 26.5, 21.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ −81.9 (d, J = 208.1 Hz, 1F), −80.5 (d, J = 208.1 Hz, 1F); MS: m/z (% relative intensity) 348 (M^+, 34), 271 (6), 189 (45), 159 (23), 109 (70), 77 (100); HRMS (ESI-TOF) calcd for $C_{19}H_{18}F_2O_2SNa$ $[M + Na]^+$ 371.0893, found 371.0896.

(3R,4S*,7R*,7aS*)-3-Phenyl-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-1(3H)-one (**7f**).* According to the general procedure A, the reaction of **5** (339 mg, 1.0 mmol) with phenylmagnesium chloride (2.0 M in THF, 1.25 mL, 2.5 mmol) at 0 °C followed by lactonization gave **7f** (362 mg, 91%) as a white solid after preparative thin-layer chromatography (SiO_2, 20% EtOAc/hexanes). Mp 132−133 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2959w, 2873w, 1782s, 1474w, 1248w, 1171m, 1116m, 1042m, 1033m, 984m, 904m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.58−7.46 (m, 2H), 7.44−7.39 (m, 2H), 7.38−7.29 (m, 4H), 7.28−7.20 (m, 2H), 6.21 (dd, J = 13.6, 7.0 Hz, 1H), 6.12 (dd, J = 14.5, 7.0 Hz, 1H), 3.24−3.16 (m, 1H), 3.03−2.95 (m, 1H), 2.89 (dd, J = 8.7, 0.8 Hz, 1H), 2.68 (dd, J = 8.7, 4.3 Hz, 1H), 1.51−1.43 (m, 1H), 1.39−1.14 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 139.5 (d, J = 3.5 Hz), 136.9, 136.9, 134.4 (d, J = 7.1 Hz), 131.1, 129.9, 129.2, 128.9, 128.9, 128.7 (dd, J = 292.9, 284.0 Hz), 128.6, 128.6, 126.4, 126.4, 125.9 (d, J = 3.0 Hz), 88.9 (dd, J = 32.0, 22.6 Hz), 50.3, 45.7, 31.1, 30.6, 26.8, 21.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ −80.3 (d, J = 209.6 Hz, 1F), −77.6 (d, J = 209.6 Hz, 1F); MS: m/z (% relative intensity) 398 (M^+, 11), 239 (100), 159 (84), 109 (15), 77 (49); HRMS (ESI-TOF) calcd for $C_{23}H_{20}F_2O_2SNa$ $[M + Na]^+$ 421.1050, found 421.1055.

(3R,4S*,7R*,7aS*)-3-(4-Methoxyphenyl)-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-1(3H)-one (**7g**).* According to the general procedure B, the reaction of **5** (170 mg, 0.5 mmol) with 4-methoxyphenylmagnesium bromide at 0 °C followed by lactonization gave **7g** (131 mg, 61%) as a white solid after preparative thin-layer chromatography (SiO_2, 30% EtOAc/hexanes). Mp 139−140 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2958w, 1781s, 1610m, 1513s, 1258m, 1182m, 1110m, 1036m, 983m, 906m, 810m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44−7.37 (m, 4H), 7.33−7.28 (m, 1H), 7.27−7.20 (m, 2H), 6.88−6.82 (m, 2H), 6.18 (dd, J = 14.2, 7.0 Hz, 1H), 6.09 (dd, J = 14.2, 7.0 Hz, 1H), 3.74 (s, 3H), 3.20−3.12 (br, 1H), 3.01−2.94 (br, 1H), 2.85 (d, J = 8.6 Hz, 1H), 2.68 (dd, J = 8.6, 4.3 Hz, 1H), 1.51−1.42 (m, 1H), 1.38−1.13 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 160.2, 136.8, 136.8, 134.4 (d, J = 6.9 Hz), 131.2 (d, J = 3.6 Hz), 131.1, 129.9, 128.9, 128.9, 128.8 (dd, J = 294.8, 280.5 Hz), 127.8, 127.8, 126.0 (d, J = 3.1 Hz), 113.9, 113.9, 88.8 (dd, J = 32.0, 22.6 Hz), 55.3, 50.1, 45.8, 31.1, 30.6, 28.8, 21.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ −80.5 (d, J = 207.6 Hz, 1F), −77.8 (d, J = 207.6 Hz, 1F); MS: m/z (% relative intensity) 429 (M^+ + H, 0.4), 269 (100), 189

DOI: 10.1021/jo502501v
J. Org. Chem. 2015, 80, 1577−1592

(77), 159 (1), 109 (7), 77 (23); HRMS (ESI-TOF) calcd for $C_{24}H_{22}F_2O_3SNa$ $[M + Na]^+$ 451.1155, found 451.1157.

(3S,4S*,7R*,7aS*)-3-(Difluoro(phenylthio)methyl)-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-1(3H)-one (**7h**).* According to method A for the synthesis of **6h**, a solution of **5** (170 mg, 0.5 mmol) in methanol (1 mL) was treated with $NaBH_4$ (94 mg, 2.5 mmol). The crude product was purified by preparative thin-layer chromatography (SiO_2, 50% CH_2Cl_2/hexanes) to give **7h** (134 mg, 83%) as a white solid. Mp 91−92 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2959w, 2944w, 2874w, 1784s, 1475w, 1342w, 1242w, 1166m, 1145m, 1065w, 1053w, 979m, 968m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66−7.64 (m, 2H), 7.49−7.45 (m, 1H), 7.43−7.39 (m, 2H), 6.30−6.22 (m, 1H), 6.17 (dd, J = 7.4, 7.0, 1H), 4.53 (ddd, J = 15.9, 8.9, 7.7 Hz, 1H), 3.15−3.05 (m, 2H), 2.99 (dd, J = 9.2, 4.2 Hz, 1H), 2.73−2.69 (m, 1H), 1.58−1.47 (m, 2H), 1.46−1.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 136.7, 136.7, 133.9 (dd, J = 3.2, 3.2 Hz), 131.5, 130.4, 129 4, 129.4, 126.2 (dd, J = 285.7, 279.6 Hz), 125.5, 79.8 (dd, J = 33.2, 23.4 Hz), 46.4, 39.7, 30.9, 29.6, 26.0, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ −84.3 (dd, J = 216.0, 6.0 Hz, 1F), −81.6 (dd, J = 216.0, 12.8 Hz, 1F); MS: m/z (% relative intensity) 323 (M^+ + H, 100), 322 (M^+, 29), 243 (1), 159 (9), 133 (2); HRMS (ESI-TOF) calcd for $C_{17}H_{16}F_2O_2SNa$ $[M + Na]^+$ 345.0737, found 345.0730.

Synthesis of *gem*-Difluoromethylenated Polycyclic Cage γ-Butyrolactones 8 and 9. *General Procedure C.* A degassed toluene solution (5 mL) of Bu_3SnH (0.20 mL, 0.75 mmol) and AIBN (7 mg, 1 mol %) was added into a refluxing degassed toluene solution (7 mL) of **6** or **7** (0.5 mmol) under an argon atmosphere. After stirring at reflux for overnight (15 h), the crude product was purified by column chromatography (SiO_2) or preparative thin-layer chromatography (SiO_2).

(6aS)-6,6-Difluoro-6a-methyloctahydro-2H-3,5-methanopentaleno[1,6-bc]furan-2-one (**8a**).* According to the general procedure C, radical cyclization of **6a** (309 mg, 0.96 mmol) gave **8a** (197 mg, 96%) as a white solid after column chromatography (SiO_2, hexanes and then 5% EtOAc/hexanes). Mp 80−82 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2988w, 2971w, 1777s, 1455w, 1344m, 1245s, 1194s, 1089s cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.03 (ddd, J = 10.2, 4.5, 2.2 Hz, 1H), 2.75−2.71 (m, 1H), 2.68−2.60 (m, 2H), 2.53−2.47 (m, 1H), 1.76−1.63 (m, 4H), 1.44 (d, J = 4.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.9, 127.1 (dd, J = 268.5, 245.8 Hz), 89.2 (dd, J = 31.8, 19.4 Hz), 52.4 (d, J = 3.4 Hz), 51.2, 45.0 (dd, J = 25.8, 21.1 Hz), 42.3 (d, J = 5.6 Hz), 41.4, 39.9, 28.2 (d, J = 9.5 Hz), 19.0 (d, J = 6.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ −119.2 (d, J = 240.9 Hz, 1F), −101.0 (d, J = 240.9 Hz, 1F); MS: m/z (% relative intensity) 215 (M^+ + H, 11), 214 (M^+, 4), 196 (6), 170 (38), 149 (91), 147 (16), 121 (17), 97 (22), 91 (100), 77 (42); HRMS (ESI-TOF) calcd for $C_{11}H_{12}F_2O_2Na$ $[M + Na]^+$ 237.0703, found 237.0690.

(6aS)-6a-Ethyl-6,6-difluorooctahydro-2H-3,5-methanopentaleno[1,6-bc]furan-2-one (**8b**).* According to the general procedure C, radical cyclization of **6b** (65 mg, 0.2 mmol) gave **8b** (40 mg, 88%) as a white solid after column chromatography (SiO_2, hexanes and then 5% EtOAc/hexanes). Mp 66−67 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2973m, 2886w, 1769s, 1464w, 1313w, 1291w, 1196m, 1096m, 988m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.00 (ddd, J = 10.2, 4.5, 2.2 Hz, 1H), 2.77−2.74 (m, 1H), 2.67−2.59 (m, 2H), 2.52−2.46 (m, 1H), 1.99−1.87 (m, 1H), 1.75−1.63 (m, 5H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.2, 127.6 (dd, J = 269.1, 246.3 Hz), 91.5 (dd, J = 30.5, 18.4 Hz), 50.9, 50.4 (d, J = 3.5 Hz), 45.4 (dd, J = 25.9, 21.4 Hz), 42.2 (d, J = 5.6 Hz), 41.3, 39.9, 28.1 (d, J = 9.4 Hz), 25.8 (d, J = 5.4 Hz), 7.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ −115.5 (d, J = 242.1 Hz, 1F), −103.3 (dd, J = 242.1, 12.7 Hz, 1F); MS: m/z (% relative intensity) 228 (M^+, 10), 199 (13), 184 (27), 178 (20), 161 (10), 149 (85), 134 (23), 81 (79), 67 (86), 55 (100); HRMS (ESI-TOF) calcd for $C_{12}H_{14}F_2O_2Na$ $[M + Na]^+$ 251.0860, found 251.0839.

(6aS)-6a-Butyl-6,6-difluorooctahydro-2H-3,5-methanopentaleno[1,6-bc]furan-2-one (**8c**).* According to the general procedure C, radical cyclization of **6c** (229 mg, 0.63 mmol) gave **8c** (137 mg, 85%) as a white solid after column chromatography (SiO_2, hexanes and then 5% EtOAc/hexanes). Mp 58−59 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2962s, 2876w, 1769s, 1469w, 1457w, 1346w, 1313w, 1239m, 1196m, 1102m, 1093m, 995w cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.99 (ddd, J = 10.3, 4.5, 2.1 Hz, 1H), 2.77−2.74 (m, 1H), 2.63 (s, 2H), 2.51−2.46 (m, 1H), 1.94−1.82 (m, 1H), 1.74−1.55 (m, 5H), 1.50−1.38 (m, 1H), 1.37−1.21 (m, 3H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.2, 127.6 (dd, J = 269.1, 246.5 Hz), 91.2 (dd, J = 30.4, 18.7 Hz), 50.8, 50.7 (d, J = 3.4 Hz), 45.4 (dd, J = 26.0, 21.2 Hz), 42.2 (d, J = 5.8 Hz), 41.3, 39.9, 32.6 (d, J = 4.6 Hz), 28.1 (d, J = 9.4 Hz), 25.2, 22.9, 13.8; ^{19}F NMR (470 MHz, $CDCl_3$): δ −115.7 (d, J = 241.6 Hz, 1F), −102.9 (dd, J = 241.6, 12.7 Hz, 1F); MS: m/z (% relative intensity) 257 (M^+ + H, 87), 256 (9), 227 (100), 190 (16), 174 (58); HRMS (ESI-TOF) calcd for $C_{14}H_{18}F_2O_2Na$ $[M + Na]^+$ 279.1173, found 279.1164.

(6aS)-6,6-Difluoro-6a-vinyloctahydro-2H-3,5-methanopentaleno[1,6-bc]furan-2-one (**8d**).* According to the general procedure C, radical cyclization of **6e** (67 mg, 0.2 mmol) gave **8d** (39 mg, 87%) as a white solid after column chromatography (SiO_2, hexanes and then 5% EtOAc/hexanes) and preparative thin-layer chromatography, (SiO_2, 20% EtOAc/hexanes). Mp 95−96 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3020m, 2970w, 1774s, 1342m, 1111m, 1008m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.93 (ddd, J = 17.2, 11.0, 3.7 Hz, 1H), 5.49 (d, J = 17.2 Hz, 1H), 5.29 (d, J = 11.0 Hz, 1H), 3.04 (ddd, J = 10.3, 4.4, 1.9 Hz, 1H), 2.93−2.86 (m, 1H), 2.78−2.70 (br, 1H), 2.69−2.63 (br, 1H), 2.60−2.48 (m, 1H), 1.80−1.57 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 131.4 (d, J = 6.0 Hz), 127.4 (dd, J = 271.0, 246.0 Hz), 117.3 (d, J = 2.0 Hz), 89.9 (dd, J = 30.5, 19.5 Hz), 51.6 (d, J = 4.0 Hz), 50.4, 45.2 (dd, J = 25.0, 21.0 Hz), 42.6 (d, J = 6.0 Hz), 41.3, 40.0, 28.1 (d, J = 9.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −117.4 (d, J = 239.1 Hz, 1F), −99.2 (dd, J = 239.1, 11.3 Hz, 1F); MS: m/z (% relative intensity) 227 (M^+ + H, 100), 226 (M^+, 9), 159 (4), 107 (17); HRMS (ESI-TOF) calcd for $C_{12}H_{12}F_2O_2Na$ $[M + Na]^+$ 249.0703, found 249.0708.

(6aR)-6,6-Difluoro-6a-phenyloctahydro-2H-3,5-methanopentaleno[1,6-bc]furan-2-one (**8e**).* According to the general procedure C, radical cyclization of **6f** (196 mg, 0.5 mmol) gave **8e** (129 mg, 91%) as a white solid after column chromatography (SiO_2, hexanes and then 5% EtOAc/hexanes). Mp 156−157 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2959w, 2928m, 1778s, 1283w, 1179m, 1113m, 1004m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38−7.28 (m, 5H), 3.29−3.26 (m, 1H), 3.07 (dd, J = 10.4, 4.6, 1H), 2.90−2.88 (m, 1H), 2.70 (br.s, 1H), 2.67−2.50 (m, 1H), 1.84−1.71 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.4, 135.5, 128.7, 128.1, 128.1, 126.8 (dd, J = 271.3, 246.7 Hz), 126.4, 126.3, 91.4 (dd, J = 31.8, 19.2 Hz), 52.7 (d, J = 3.3 Hz), 50.6, 45.3 (dd, J = 26.3, 20.8 Hz), 43.3 (d, J = 5.4 Hz), 41.5, 40.0, 28.2 (d, J = 9.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ −117.4 (d, J = 239.7 Hz, 1F), −93.6 (dd, J = 239.7, 11.3 Hz, 1F); MS: m/z (% relative intensity) 276 (M^+, 55), 232 (66), 212 (27), 178 (100), 159 (6); HRMS (ESI-TOF) calcd for $C_{16}H_{14}F_2O_2Na$ $[M + Na]^+$ 299.0860, found 299.0836.

(6aR)-6,6-Difluoro-6a-(4-methoxyphenyl)octahydro-2H-3,5-methanopentaleno[1,6-bc]furan-2-one (**8f**).* According to the general procedure C, radical cyclization of **6g** (83 mg, 0.2 mmol) gave **8f** (47 mg, 76%) as a white solid and recovered starting material (14 mg, 17%) after column chromatography (SiO_2, hexanes and then 5% EtOAc/hexanes). Mp 179−180 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2966m, 1778s, 1614m, 1516s, 1465w, 1307m, 1258m, 1235m, 1180s, 1113m, 1069m, 1002m cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 3.74 (s, 3H), 3.26−3.24 (m, 1H), 3.08 (dd, J = 10.4, 4.5 Hz, 1H), 2.87 (br.s, 1H), 2.71 (br.s, 1H), 2.64−2.55 (m, 1H), 1.82−1.68 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.5, 159.9, 127.6, 127.6, 127.5, 126.8 (dd, J = 271.1, 246.0 Hz), 113.6, 113.6, 91.4 (dd, J = 31.8, 19.2 Hz), 55.3, 52.4 (d, J = 3.5 Hz), 50.8, 45.3 (dd, J = 26.3, 20.8 Hz), 43.2 (d, J = 5.3 Hz), 41.4, 40.0, 28.2 (d, J = 9.1 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ −117.8 (d, J = 239.2 Hz, 1F), −93.8 (dd, J = 239.2, 11.3 Hz, 1F); MS: m/z (% relative intensity) 306 (M^+, 31), 262 (21), 208 (65), 207 (100); HRMS (ESI-TOF) calcd for $C_{17}H_{16}F_2O_3Na$ $[M + Na]^+$ 329.0965, found 329.0972.

(6aS)-6,6-Difluorooctahydro-2H-3,5-methanopentaleno[1,6-bc]furan-2-one (**8g**).* According to the general procedure C, radical

DOI: 10.1021/jo502501v
J. Org. Chem. 2015, 80, 1577−1592

cyclization of **6h** (155 mg, 0.5 mmol) gave **8g** (94 mg, 94%) as a white solid after column chromatography (SiO_2, hexanes and then 5% EtOAc/hexanes). Mp 206−208 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2987m, 2970m, 1784s, 1371s, 1317m, 1236m, 1175s, 1059s cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.70−4.65 (m, 1H), 3.31−3.27 (m, 1H), 3.03 (ddd, J = 10.5, 4.4, 2.0 Hz, 1H), 2.77−2.74 (m, 2H), 2.59−2.53 (m, 1H), 1.87−1.80 (m, 3H), 1.72−1.67 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.3, 127.4 (dd, J = 266.6, 241.1 Hz), 81.7 (dd, J = 41.7, 19.1 Hz), 48.9, 45.8 (d, J = 3.0 Hz), 44.1 (dd, J = 24.7, 21.2 Hz), 42.8 (d, J = 5.5 Hz), 41.7, 39.8, 28.0 (d, J = 9.3 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ −116.5 (d, J = 246.5 Hz, 1F), −98.9 (dt, J = 246.5, 11.5 Hz, 1F); MS: m/z (% relative intensity) 201 (M^+ + H, 100), 200 (M^+, 5), 156 (7), 135 (38), 133 (8), 83 (7); HRMS (ESI-TOF) calcd for $C_{10}H_{10}F_2O_2Na$ $[M + Na]^+$ 223.0547, found 223.0563.

(7aS)-7,7-Difluoro-7a-methyloctahydro-3,6-methanoindeno-[1,7-bc]furan-2(2a1H)-one (**9a**).* According to the general procedure C, radical cyclization of **7a** (336 mg, 1.0 mmol) gave **9a** (203 mg, 89%) as a white solid after column chromatography (SiO_2, hexanes and then 5% EtOAc/hexanes) and preparative thin-layer chromatography, (SiO_2, 30% EtOAc/hexanes × 2). Mp 97−99 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2951m, 2874w, 1768s, 1458w, 1237m, 1195m, 1096s, 1085m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.70−2.63 (m, 1H), 2.50−2.43 (m, 1H), 2.33−2.22 (m, 1H), 2.08−2.00 (br, 2H), 1.80−1.65 (m, 2H), 1.64−1.48 (m, 4H), 1.47 (d, J = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.3, 126.7 (dd, J = 269.0, 250.1 Hz), 89.6 (dd, J = 30.3, 18.6 Hz), 47.7, 45.2, 42.5 (dd, J = 24.9, 20.2 Hz), 27.7 (d, J = 5.9 Hz), 26.4, 24.8, 23.1 (dd, J = 7.7, 3.1 Hz), 19.0 (d, J = 7.9 Hz), 16.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ −123.9 (d, J = 236.9 Hz, 1F), −102.1 (dd, J = 236.9, 6.0 Hz, 1F); MS: m/z (% relative intensity) 229 (M^+ + H, 100), 228 (13), 184 (47), 147 (4), 102 (4), 97 (11); HRMS (ESI-TOF) calcd for $C_{12}H_{14}F_2O_2Na$ $[M + Na]^+$ 251.0860, found 251.0857.

(7aS)-7a-Ethyl-7,7-difluorooctahydro-3,6-methanoindeno[1,7-bc]furan-2(2a1H)-one (**9b**).* According to the general procedure C, radical cyclization of **7b** (168 mg, 0.48 mmol) gave **9b** (104 mg, 89%) as a white solid after column chromatography (SiO_2, hexanes and 5% EtOAc/hexanes). Mp 51−52 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2947s, 2873m, 1778s, 1463m, 1222m, 1193m, 1094m, 1039m, 984m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.65 (dt, J = 10.0, 2.2 Hz, 1H), 2.50 (dd, J = 10.0, 3.7 Hz, 1H), 2.32−2.21 (m, 1H), 2.08−2.03 (br, 1H), 2.02−1.90 (m, 2H), 1.80−1.44 (m, 7H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.4, 127.2 (dd, J = 269.8, 250.2 Hz), 92.1 (dd, J = 29.3, 18.0 Hz), 45.6, 45.1, 42.9 (dd, J = 25.1, 20.4 Hz), 27.8 (d, J = 6.0 Hz), 26.5, 25.8 (d, J = 6.5 Hz), 24.8, 23.2 (dd, J = 7.7, 2.9 Hz), 17.0, 7.9 (d, J = 1.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −120.8 (d, J = 238.0 Hz, 1F), −104.4 (dd, J = 238.0, 10.9 Hz, 1F); MS: m/z (% relative intensity) 243 (M^+ + H, 100), 242 (M^+, 79), 214 (17), 135 (27), 111 (10), 109 (59); HRMS (ESI-TOF) calcd for $C_{13}H_{16}F_2O_2Na$ $[M + Na]^+$ 265.1016, found 265.1013.

(7aS)-7a-Butyl-7,7-difluorooctahydro-3,6-methanoindeno[1,7-bc]furan-2(2a1H)-one (**9c**).* According to the general procedure C, radical cyclization of **7c** (238 mg, 0.63 mmol) gave **9c** (148 mg, 87%) as a white solid after column chromatography (SiO_2, hexanes and then 5% EtOAc/hexanes). Mp 54−55 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2958s, 2874m, 1771s, 1471w, 1243m, 1192m, 1095m, 992m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.64 (d, J = 9.9 Hz, 1H), 2.50 (dd, J = 9.9, 4.3 Hz, 1H), 2.32−2.21 (m, 1H), 2.08−1.97 (m, 2H), 1.96−1.85 (m, 1H), 1.80−1.68 (m, 2H), 1.64−1.23 (m, 9H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.4, 127.1 (dd, J = 269.9, 250.2 Hz), 91.8 (dd, J = 29.3, 17.9 Hz), 46.0, 45.0, 42.8 (dd, J = 25.1, 20.3 Hz), 32.6 (d, J = 5.7 Hz), 27.8 (d, J = 6.0 Hz), 26.5, 25.6 (d, J = 1.1 Hz), 24.8, 23.2 (dd, J = 7.7, 2.8 Hz), 22.9, 17.1, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ −120.9 (d, J = 237.1 Hz, 1F), −103.9 (dd, J = 237.1, 12.0 Hz, 1F); MS: m/z (% relative intensity) 270 (M^+, 21), 241 (100), 227 (24), 213 (19), 190 (11), 135 (16); HRMS (ESI-TOF) calcd for $C_{15}H_{20}F_2O_2Na$ $[M + Na]^+$ 293.1329, found 293.1326.

(7aS)-7,7-Difluoro-7a-isopropyloctahydro-3,6-methanoindeno-[1,7-bc]furan-2(2a1H)-one (**9d**).* According to the general procedure C, radical cyclization of **7d** (78 mg, 0.2 mmol) gave **9d** (52 mg, 99%) as a white solid after column chromatography (SiO_2, hexanes and then 5% EtOAc/hexanes). Mp 75−76 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2949m, 1773s, 1471w, 1266w, 1184m, 1095m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.66−2.58 (br, 2H), 2.31−2.21 (m, 1H), 2.09−1.93 (m, 3H), 1.79−1.69 (m, 2H), 1.63−1.45 (m, 4H), 1.08 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 127.8 (dd, J = 271.4, 249.5 Hz), 94.2 (dd, J = 28.3, 17.0 Hz), 45.0, 44.3, 43.0 (dd, J = 25.2, 20.5 Hz), 30.7, 27.8 (d, J = 6.1 Hz), 26.6, 24.8, 23.2 (dd, J = 7.8, 2.7 Hz), 17.4 (d, J = 3.0 Hz), 17.1, 17.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ −118.0 (d, J = 239.3 Hz, 1F), −104.7 (dd, J = 239.3, 12.0 Hz, 1F); MS: m/z (% relative intensity) 256 (M^+, 100), 213 (18), 149 (37); HRMS (ESI-TOF) calcd for $C_{14}H_{18}F_2O_2Na$ $[M + Na]^+$ 279.1173, found 279.1185.

(7aS)-7,7-Difluoro-7a-vinyloctahydro-3,6-methanoindeno[1,7-bc]furan-2(2a1H)-one (**9e**).* According to the general procedure C, radical cyclization of **7e** (349 mg, 1.0 mmol) gave **9e** (227 mg, 94%) as a white solid after column chromatography (SiO_2, hexanes and then 5% EtOAc/hexanes). Mp 105−107 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3028w, 2951m, 2874w, 1778s, 1295w, 1196m, 1180m, 1104m, 999m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.95 (ddd, J = 17.2, 11.0, 3.6 Hz, 1H), 5.49 (d, J = 17.2 Hz, 1H), 5.28 (d, J = 11.0 Hz, 1H), 2.75−2.58 (m, 2H), 2.39−2.26 (m, 1H), 2.19−2.02 (m, 2H), 1.85−1.68 (m, 2H), 1.67−1.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 131.4 (d, J = 7.0 Hz), 127.0 (dd, J = 274.1, 248.1 Hz), 116.5, 90.5 (dd, J = 29.3, 18.8 Hz), 47.1, 44.6, 42.5 (dd, J = 24.8, 20.2 Hz), 28.2 (d, J = 5.6 Hz), 26.6, 24.8, 23.2 (dd, J = 7.5, 2.7 Hz), 17.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ −121.7 (d, J = 238.2 Hz, 1F), −99.7 (dd, J = 238.2, 10.4 Hz, 1F); MS: m/z (% relative intensity) 241 (M^+ + H, 100), 240 (M^+, 53), 196 (9), 169 (13), 159 (11), 115 (64), 109 (45), 105 (16), 77 (46); HRMS (ESI-TOF) calcd for $C_{13}H_{14}F_2O_2Na$ $[M + Na]^+$ 263.0860, found 263.0876.

(7aR)-7,7-Difluoro-7a-phenyloctahydro-3,6-methanoindeno-[1,7-bc]furan-2(2a1H)-one (**9f**).* According to the general procedure C, radical cyclization of **7f** (399 mg, 1.0 mmol) gave **9f** (281 mg, 97%) as a white solid after column chromatography (SiO_2, hexanes and then 5% EtOAc/hexanes). Mp 123−124 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2951m, 2874w, 1777s, 1279w, 1180m, 1060m, 1012m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.27 (m, 5H), 3.08−3.00 (m, 1H), 2.74 (dt, J = 10.1, 2.2 Hz, 1H), 2.47−2.38 (m, 1H), 2.37−2.30 (m, 1H), 2.16−2.10 (br, 1H), 1.90−1.79 (m, 2H), 1.78−1.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 135.8, 128.7, 128.3, 128.3, 126.4 (dd, J = 272.4, 250.4 Hz), 126.0, 126.0, 92.0 (dd, J = 31.2, 18.5 Hz), 47.8 (d, J = 2.2 Hz), 45.0, 42.6 (dd, J = 25.2, 20.2 Hz), 29.5 (d, J = 5.6 Hz), 26.7, 24.8, 23.3 (dd, J = 7.4, 2.6 Hz), 17.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ −122.7 (d, J = 235.5 Hz, 1F), −94.4 (dd, J = 235.5, 11.1 Hz, 1F); MS: m/z (% relative intensity) 291 (M^+ + H, 27), 246 (82), 159 (15), 105 (51), 77 (100); HRMS (ESI-TOF) calcd for $C_{17}H_{16}F_2O_2Na$ $[M + Na]^+$ 313.1016, found 313.1018.

(7aR)-7,7-Difluoro-7a-(4-methoxyphenyl)octahydro-3,6-methanoindeno[1,7-bc]furan-2(2a1H)-one (**9g**).* According to the general procedure C, radical cyclization of **7g** (269 mg, 0.63 mmol) gave **9g** (179 mg, 89%) as a white solid after column chromatography (SiO_2, hexanes and then 5% EtOAc/hexanes). Mp 186−187 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2951w, 2874w, 1777s, 1614w, 1516m, 1256m, 1180s, 1065m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 3.74 (s, 3H), 3.06−2.96 (br, 1H), 2.73 (d, J = 10.0 Hz, 1H), 2.40 (dd, J = 10.7, 10.7 Hz, 1H), 2.34−2.25 (br, 1H), 2.15−2.08 (br, 1H), 1.90−1.77 (m, 2H), 1.76−1.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 159.8, 127.7, 127.3, 127.3, 126.4 (dd, J = 272.3, 249.8 Hz), 113.7, 113.7, 91.9 (dd, J = 31.3, 18.7 Hz), 55.3, 47.6 (d, J = 1.3 Hz), 45.0, 42.5 (dd, J = 25.5, 20.2 Hz), 29.3 (d, J = 5.7 Hz), 26.6, 24.8, 23.3 (dd, J = 7.2, 2.2 Hz), 17.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ −123.0 (d, J = 235.6 Hz, 1F), −94.0 (d, J = 235.6 Hz, 1F); MS: m/z (% relative intensity) 320 (M^+, 68), 276 (100), 189 (6), 135 (24), 77 (18); HRMS (ESI-TOF) calcd for $C_{18}H_{18}F_2O_3Na$ $[M + Na]^+$ 343.1122, found 343.1134.

(7aS)-7,7-Difluorooctahydro-3,6-methanoindeno[1,7-bc]furan-2(2a1H)-one (**9h**).* According to the general procedure C, radical cyclization of **7h** (303 mg, 0.94 mmol) gave **9h** (174 mg, 87%) as a white solid after column chromatography (SiO_2, hexanes and then 5% EtOAc/hexanes). Mp 185−187 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$)

DOI: 10.1021/jo502501v
J. Org. Chem. 2015, 80, 1577−1592

2951m, 2874w, 1774s, 1368m, 1240m, 1169s, 1094s, 1058s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.73 (dd, J = 14.0, 7.3 Hz, 1H), 3.05−2.96 (m, 1H), 2.63 (d, J = 10.1 Hz, 1H), 2.34−2.24 (m, 1H), 2.16−2.07 (br, 2H), 1.89−1.78 (m, 1H), 1.77−1.54 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9, 126.8 (dd, J = 267.2, 245.0 Hz), 82.4 (dd, J = 40.5, 18.6 Hz), 42.9, 41.5 (dd, J = 23.7, 20.4 Hz), 40.7, 28.3 (d, J = 5.6 Hz), 26.5, 25.1, 23.0 (dd, J = 7.6, 3.1 Hz), 17.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ −122.6 (d, J = 242.1 Hz, 1F), −98.6 (dt, J = 242.1, 12.8 Hz, 1F); MS: m/z (% relative intensity) 215 (M^+ + H, 61), 214 (M^+, 40), 135 (21), 133 (13), 109 (60), 91 (100), 83 (18), 77 (71); HRMS (ESI-TOF) calcd for $C_{11}H_{12}F_2O_2Na$ $[M + Na]^+$ 237.0703, found 237.0700.

Synthesis of *gem*-Difluoromethylenated Polycyclic Cage Compounds 10 and 11 from Compounds 8 and 9. *General Procedure D.* A solution of **8** or **9** (0.5 mmol) in dry THF (4 mL) was treated with a THF solution of alkyl- or arylmagnesium chloride (or bromide) (2.5 mmol) at 0 °C under an argon atmosphere. After stirring at 0 °C to room temperature for 1 h, 10% HCl (2 mL) was added to the reaction mixture. The aqueous phase was extracted with EtOAc (4 × 5 mL). The combined organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents, the crude product was purified by column chromatography (SiO_2) or preparative thin-layer chromatography (SiO_2) to give the required products.

(2S,6aR*)-6,6-Difluoro-2-methyl-6a-phenyloctahydro-2H-3,5-methanopentaleno[1,6-bc]furan-2-ol (**10a**).* According to the general procedure D, the reaction of **8e** (56 mg, 0.2 mmol) with methylmagnesium chloride (3.0 M in THF, 0.33 mL, 1.0 mmol) gave **10a** (51 mg, 88%) as a white solid after column chromatography (SiO_2, 20% EtOAc/hexanes) and then preparative thin-layer chromatography (SiO_2, 80% CH_2Cl_2/hexanes × 3). Mp 156−157 °C (CH_2Cl_2/hexanes); IR (KBr) 3393br, 2972m, 1450w, 1380m, 1342m, 1172s, 1093s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43−7.36 (m, 2H), 7.31−7.17 (m, 3H), 3.29 (dd, J = 7.9, 6.4 Hz, 1H), 2.81−2.73 (br, 1H), 2.64−2.58 (m, 1H), 2.51−2.40 (m, 1H), 2.32−2.26 (m, 1H), 2.13−2.05 (m, 1H), 1.83 (s, 1H), 1.64−1.55 (m, 3H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 127.7, 127.7, 127.6, 127.3 (dd, J = 268.8, 244.6 Hz), 126.8, 126.7, 106.3, 91.6 (dd, J = 29.2, 17.8 Hz), 59.1, 55.2 (d, J = 3.7 Hz), 45.7 (dd, J = 25.0, 21.5 Hz), 43.0 (d, J = 6.1 Hz), 41.3, 37.8, 27.4 (d, J = 9.2 Hz), 23.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ −121.2 (d, J = 233.3 Hz, 1F), −99.1 (dd, J = 233.3, 8.6 Hz, 1F); MS: m/z (% relative intensity) 292 (M^+, 2), 277 (19), 275 (36), 273 (11), 254 (14), 178 (100), 177 (57); HRMS (ESI-TOF) calcd for $C_{17}H_{18}F_2O_2Na$ $[M + Na]^+$ 315.1173, found 315.1176.

(2S,6aR*)-6,6-Difluoro-6a-(4-methoxyphenyl)-2-methyloctahydro-2H-3,5-methanopentaleno[1,6-bc]furan-2-ol (**10b**).* According to the general procedure D, the reaction of **8f** (40 mg, 0.13 mmol) with methylmagnesium chloride (3.0 M in THF, 0.22 mL, 0.65 mmol) gave **10b** (39 mg, 94%) as a white solid after column chromatography (SiO_2, 20% EtOAc/hexanes) and then preparative thin-layer chromatography (SiO_2, 80% CH_2Cl_2/hexanes × 3). Mp 153−154 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3589w, 3409br, 2962m, 1612m, 1515s, 1342w, 1250m, 1177m, 1099m, 1035m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.6 Hz, 2H), 3.67 (s, 3H), 3.22−3.14 (m, 1H), 2.70−2.64 (br, 1H), 2.57−2.50 (m, 1H), 2.44−2.33 (m, 1H), 2.25−2.18 (m, 1H), 2.05−1.97 (m, 1H), 1.87 (s, 1H), 1.58−1.48 (m, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 131.8, 127.9, 127.9, 127.3 (dd, J = 268.8, 243.9 Hz), 113.2, 112.9, 106.2, 91.3 (dd, J = 29.2, 17.7 Hz), 59.3, 55.2, 54.9 (d, J = 3.7 Hz), 45.6 (dd, J = 25.0, 21.3 Hz), 42.9 (d, J = 6.0 Hz), 41.2, 37.8, 27.4 (d, J = 9.2 Hz), 23.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ −121.5 (d, J = 233.1 Hz, 1F), −98.9 (dd, J = 233.1, 10.5 Hz, 1F); MS: m/z (% relative intensity) 322 (M^+, 5), 305 (18), 303 (100), 284 (8), 262 (10), 185 (14); HRMS (ESI-TOF) calcd for $C_{18}H_{20}F_2O_3Na$ $[M + Na]^+$ 345.1278, found 345.1279.

(2R,7aS*)-7,7-Difluoro-7a-methyl-2-phenyldecahydro-3,6-methanoindeno[1,7-bc]furan-2-ol (**11a**).* According to the general procedure D, the reaction of **9a** (46 mg, 0.2 mmol) with phenylmagnesium chloride (2.0 M in THF, 0.50 mL, 1.0 mmol) gave **11a** (56 mg, 91%) as a white solid after preparative thin-layer chromatography (SiO_2, 80% CH_2Cl_2/hexanes). Mp 163−164 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3580m, 3384br, 2945s, 2871m, 1449m, 1334m, 1160m, 1094m, 996m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47−7.40 (m, 2H), 7.28−7.17 (m, 3H), 2.84 (d, J = 3.6 Hz, 1H), 2.71−2.65 (m, 1H), 2.44 (d, J = 8.7 Hz, 1H), 2.12−2.03 (m, 1H), 2.01−1.95 (m, 1H), 1.77−1.69 (m, 1H), 1.67−1.48 (m, 2H), 1.47 (d, J = 4.4 Hz, 3H), 1.38−1.16 (m, 2H), 1.13−1.03 (m, 1H), 0.93−0.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.3, 128.2, 128.1, 128.1, 127.5 (dd, J = 266.7, 247.1 Hz), 126.2, 126.2, 109.5, 90.2 (dd, J = 28.7, 17.4 Hz), 54.4, 51.6 (d, J = 2.0 Hz), 42.2 (dd, J = 23.7, 20.5 Hz), 29.0 (d, J = 6.0 Hz), 26.9, 24.2, 22.9 (d, J = 7.0 Hz), 20.9 (d, J = 7.0 Hz), 17.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ −127.3 (d, J = 228.6 Hz, 1F), −107.0 (d, J = 228.6 Hz, 1F); MS: m/z (% relative intensity) 306 (M^+, 0.3), 287 (100), 286 (76), 268 (2), 229 (5), 225 (5), 191 (11), 175 (7); HRMS (ESI-TOF) calcd for $C_{18}H_{20}F_2O_2Na$ $[M + Na]^+$ 329.1329, found 329.1327.

(2R,7aS*)-2-(2,4-Dimethoxyphenyl)-7,7-difluoro-7a-methyldecahydro-3,6-methanoindeno[1,7-bc]furan-2-ol (**11b**).* According to the general procedure D, the reaction of **9a** (46 mg, 0.24 mmol) with 2,4-dimethoxyphenylmagnesium bromide (0.5 M in THF, 2.40 mL, 1.2 mmol) gave **11b** (71 mg, 80%) as a white solid after preparative thin-layer chromatography (SiO_2, 40% CH_2Cl_2/hexanes). Mp 143−144 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3581br, 2941s, 2870w, 1614s, 1588m, 1506s, 1466m, 1456m, 1317m, 1285m, 1160m, 1094m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.57−7.55 (m, 1H), 6.39−6.36 (m, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 3.14 (s, 1H), 2.78−2.72 (m, 1H), 2.70−2.62 (m, 1H), 2.09−2.00 (m, 1H), 1.99−1.93 (m, 1H), 1.71−1.51 (m, 3H), 1.48 (d, J = 4.4 Hz, 3H), 1.42−1.32 (m, 1H), 1.31−1.21 (m, 1H), 1.11−1.01 (m, 1H), 0.99−0.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 156.9, 127.9, 127.6 (dd, J = 266.9, 247.0 Hz), 122.1, 108.2, 103.8, 98.9, 89.3 (dd, J = 28.7, 17.4 Hz), 55.6, 55.3, 53.7, 51.3 (d, J = 2.1 Hz), 42.1 (dd, J = 23.5, 20.5 Hz), 29.0 (d, J = 6.3 Hz), 26.9, 24.7, 22.9 (d, J = 7.0 Hz), 20.7 (d, J = 6.6 Hz), 17.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ −127.4 (d, J = 228.2 Hz, 1F), −107.2 (d, J = 228.2 Hz, 1F); MS: m/z (% relative intensity) 366 (M^+, 0.1), 348 (100), 347 (41), 330 (2), 328 (2), 212 (7), 165 (19); HRMS (ESI-TOF) calcd for $C_{20}H_{24}F_2O_4Na$ $[M + Na]^+$ 389.1540, found 389.1537.

(2R,7aS*)-7a-Butyl-7,7-difluoro-2-phenyldecahydro-3,6-methanoindeno[1,7-bc]furan-2-ol (**11c**).* According to the general procedure D, the reaction of **9c** (124 mg, 0.46 mmol) with phenylmagnesium chloride (2.0 M in THF, 1.15 mL, 2.29 mmol) gave **11c** (110 mg, 69%) as a colorless viscous oil after preparative thin-layer chromatography (SiO_2, 20% EtOAc/hexanes). IR ($CHCl_3$) 3580m, 3384br, 2953s, 2872m, 1449w, 1337m, 1093m, 1058m, 988m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52−7.44 (m, 2H), 7.30−7.14 (m, 3H), 2.68 (s, 1H), 2.67−2.60 (m, 1H), 2.47−2.39 (m, 1H), 2.10−2.00 (m, 1H), 1.99−1.92 (m, 1H), 1.91−1.81 (m, 1H), 1.80−1.67 (m, 2H), 1.66−1.43 (m, 4H), 1.39−1.16 (m, 4H), 1.10−1.01 (m, 1H), 0.96−0.90 (br, 1H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 128.3 (dd, J = 267.8, 248.2 Hz), 128.2, 128.1, 128.1, 126.4, 126.4, 109.5, 92.4 (dd, J = 27.8, 16.6 Hz), 54.0, 51.3 (d, J = 1.6 Hz), 42.8 (dd, J = 24.0, 20.6 Hz), 36.1 (d, J = 4.2 Hz), 29.0 (d, J = 6.3 Hz), 26.9, 26.5, 24.3, 23.4, 22.8 (dd, J = 8.0, 1.4 Hz), 17.8, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ −121.8 (d, J = 228.4 Hz, 1F), −107.4 (d, J = 228.4 Hz, 1F); MS: m/z (% relative intensity) 348 (M^+, 0.5), 331 (100), 330 (73), 329 (7), 312 (3), 310 (3), 291 (6), 271 (0.7), 267 (4), 217 (3), 105 (30); HRMS (ESI-TOF) calcd for $C_{21}H_{26}F_2O_2Na$ $[M + Na]^+$ 371.1799, found 371.1796.

(7aR)-7,7-Difluoro-2-methyl-7a-phenyldecahydro-3,6-methanoindeno[1,7-bc]furan-2-ol (**11d**).* According to the general procedure D, the reaction of **9f** (58 mg, 0.2 mmol) with methylmagnesium chloride (2.0 M in THF, 0.50 mL, 1.0 mmol) gave a 97:3 diastereomeric mixture of **11d** (47 mg, 77%) as a white solid after preparative thin-layer chromatography (SiO_2, 80% CH_2Cl_2/hexanes × 2). Mp 124−125 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3589m, 3431br, 2945s, 2872m, 1497m, 1448m, 1385m, 1333m, 1112m, 1055m, 1009s, 917m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, the minor isomer marked*): δ 7.40−7.34 (m, 2H), 7.35−7.18 (m, 3H), 3.18−3.10 (m, 1H), 2.30−2.20 (m, 3H), 2.04−1.96 (m, 1H), 1.88 (s,

DOI: 10.1021/jo502501v
J. Org. Chem. 2015, 80, 1577−1592

1H), 1.82−1.61 (m, 3H), 1.55−1.40 (m, 3H), 1.47 (s, 3H), 1.18 (s, 3H*). Due to low intensity of ^{1}H NMR signals of **11d**, some peaks of **11d** could not be detected by ^{1}H NMR. ^{13}C NMR (100 MHz, $CDCl_3$, the minor isomer marked*): δ 140.1, 127.8, 127.8, 127.6, 126.7 (dd, J = 269.5, 247.4 Hz), 126.3, 126.3, 108.2*, 108.0, 92.2 (dd, J = 28.7, 17.4 Hz), 52.7, 52.6* (d, J = 2.6 Hz), 52.1 (d, J = 2.7 Hz), 51.0*, 42.4 (dd, J = 23.8, 20.4 Hz), 30.7* (d, J = 6.2 Hz), 30.3 (d, J = 6.1 Hz), 28.5*, 26.7, 26.4*, 24.5* (d, J = 7.4 Hz), 24.1, 23.6, 23.5 (d, J = 7.4 Hz), 22.5*, 18.0*, 17.9. Due to low intensity of ^{13}C NMR signals of **11d**, some peaks of **11d** could not be detected by ^{13}C NMR. ^{19}F NMR (376 MHz, $CDCl_3$, the minor isomer marked*): δ −125.9 (d, J = 228.5 Hz, 1F), −125.2 (d, J = 227.3 Hz, 1F*), −101.9 (dd, J = 228.5, 7.7 Hz, 1F), −100.4 (dd, J = 227.3, 9.9 Hz, 1F*); MS: m/z (% relative intensity) 306 (M^+, 1), 289 (28), 287 (34), 268 (9), 246 (100), 159 (19); HRMS (ESI-TOF) calcd for $C_{18}H_{20}F_2O_2Na$ $[M + Na]^+$ 329.1329, found 329.1327.

(2R,7aR*)-7,7-Difluoro-2-(4-methoxyphenyl)-7a-phenyldecahydro-3,6-methanoindeno[1,7-bc]furan-2-ol (**11e**).* According to the general procedure D, the reaction of **9f** (126 mg, 0.43 mmol) with 4-methoxyphenylmagnesium bromide (0.5 M in THF, 4.30 mL, 2.2 mmol) gave **11e** (129 mg, 75%) as a white solid after preparative thin-layer chromatography (SiO_2, 20% EtOAc/hexanes). Mp 99−101 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3579br, 2942s, 2871m, 1614s, 1514s, 1302m, 1244s, 1172s, 1041m, 1052m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64−7.53 (m, 4H), 7.43−7.30 (m, 3H), 6.97−6.90 (m, 2H), 3.85 (s, 3H), 3.42−3.34 (m, 1H), 2.67−2.60 (m, 1H), 2.57−2.49 (br, 1H), 2.45−2.30 (m, 2H), 2.10−2.00 (m, 1H), 1.91−1.73 (m, 2H), 1.58−1.39 (m, 2H), 1.37−1.27 (m, 1H), 1.22−1.14 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 140.2, 133.4, 127.7, 127.7, 127.6, 127.6, 127.5, 127.0 (dd, J = 269.7, 247.8 Hz), 126.4, 126.4, 113.5, 113.5, 109.4, 92.4 (dd, J = 28.8, 17.3 Hz), 55.3, 54.4, 52.4 (d, J = 2.4 Hz), 42.4 (dd, J = 23.8, 20.3 Hz), 30.6 (d, J = 5.9 Hz), 26.9, 24.3, 23.2 (d, J = 7.2 Hz), 18.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ −125.5 (d, J = 229.4 Hz, 1F), −100.4 (d, J = 229.4 Hz, 1F); MS: m/z (% relative intensity) 381 (M^+ − OH, 69), 380 (100), 360 (30), 159 (4), 136 (11), 135 (79), 105 (10), 77 (22); HRMS (ESI-TOF) calcd for $C_{24}H_{24}F_2O_3Na$ $[M + Na]^+$ 421.1591, found 421.1592.

(2R,7aR*)-2-(2,4-Dimethoxyphenyl)-7,7-difluoro-7a-phenyldecahydro-3,6-methanoindeno[1,7-bc]furan-2-ol (**11f**).* According to the general procedure D, the reaction of **9f** (59 mg, 0.2 mmol) with 2,4-dimethoxyphenylmagnesium bromide (0.5 M in THF, 2.0 mL, 1.0 mmol) gave **11f** (57 mg, 67%) as a white solid after column chromatography (SiO_2, hexanes−80% CH_2Cl_2/hexanes) and then preparative thin-layer chromatography (SiO_2, 10:20:70% EtOAc:CH_2Cl_2:hexanes). Mp 207−208 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3580br, 2941s, 2870m, 1614s, 1588s, 1506s, 1466m, 1317m, 1286m, 1261m, 1155m, 1051m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.5 Hz, 1H), 7.48 (d, J = 7.8 Hz, 2H), 7.32−7.17 (m, 3H), 6.44 (dd, J = 8.5, 2.3 Hz, 1H), 6.39 (d, J = 2.3 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.28−3.21 (m, 1H), 2.85 (s, 1H), 2.83 (s, 1H), 2.33−2.27 (br, 1H), 2.26−2.17 (m, 1H), 1.83−1.75 (m, 1H), 1.74−1.62 (m, 2H), 1.50−1.40 (m, 1H), 1.39−1.29 (m, 1H), 1.21−1.12 (m, 1H), 1.11−1.06 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 157.1, 140.1, 128.0, 127.7, 127.7, 127.5, 127.1 (dd, J = 269.7, 247.7 Hz), 126.4, 126.4, 121.9, 108.1, 104.0, 99.1, 91.6 (dd, J = 28.7, 17.4 Hz), 55.6, 55.4, 53.5, 52.1 (d, J = 2.2 Hz), 42.3 (dd, J = 23.6, 20.5 Hz), 30.7 (d, J = 6.1 Hz), 26.9, 24.6, 23.2 (d, J = 7.2 Hz), 18.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ −125.6 (d, J = 226.4 Hz, 1F), −100.8 (dd, J = 226.4, 9.8 Hz, 1F); MS: m/z (% relative intensity) 428 (M^+, 1), 411 (100), 410 (99), 409 (38), 390 (12), 351 (4), 253 (11), 246 (32), 182 (17), 165 (62), 77 (17); HRMS (ESI-TOF) calcd for $C_{25}H_{26}F_2O_4Na$ $[M + Na]^+$ 451.1697, found 451.1695.

(7aR)-2-Ethyl-7,7-difluoro-7a-(4-methoxyphenyl)decahydro-3,6-methanoindeno[1,7-bc]furan-2-ol (**11g**).* According to the general procedure D, the reaction of **9g** (65 mg, 0.2 mmol) with ethylmagnesium chloride (2.0 M in THF, 0.50 mL, 1.0 mmol) gave a 92:8 diastereomeric mixture of **11g** (55 mg, 85%) as a white solid after preparative thin-layer chromatography (SiO_2, 80% CH_2Cl_2/hexanes × 2). Mp 77−79 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3588br, 3020w, 2943m, 2872w, 1613w, 1514s, 1466w, 1249m, 1178m, 1062m, 947m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, the minor isomer marked*): δ 7.31−7.24 (m, 2H), 6.84−6.76 (m, 2H), 3.73 (s, 3H*), 3.72 (s, 3H), 3.16−3.08 (m, 1H), 2.92−2.86 (m, 1H*), 2.32−2.19 (m, 3H), 2.17−2.12 (m, 1H*), 2.06−1.98 (m, 1H), 1.85−1.61 (m, 6H), 1.60−1.40 (m, 3H), 1.35 (q, J = 7.2 Hz, 2H*), 0.95 (t, J = 7.5 Hz, 3H), 0.77 (t, J = 7.2 Hz, 3H*). Due to low intensity of ^{1}H NMR signals of **11g**, some peaks of **11g** could not be detected by ^{1}H NMR. ^{13}C NMR (100 MHz, $CDCl_3$, the minor isomer marked*): δ 159.0, 132.5, 127.5*, 127.5*, 127.4, 127.4, 126.7 (dd, J = 269.5, 246.7 Hz), 113.2, 113.2, 113.1*, 113.1*, 110.1*, 109.7, 91.6 (dd, J = 28.7, 17.5 Hz), 55.2, 52.1* (d, J = 2.7 Hz), 51.8 (d, J = 2.7 Hz), 51.4, 49.4*, 42.3* (dd, J = 24.1, 20.3 Hz), 42.2 (dd, J = 24.0, 20.4 Hz), 33.3*, 30.5* (d, J = 6.3 Hz), 30.1 (d, J = 6.1 Hz), 29.2, 26.8, 26.5*, 24.6* (d, J = 7.6 Hz), 23.8 (d, J = 7.3 Hz), 23.7, 22.6*, 17.9, 8.2, 7.5*. Due to low intensity of ^{13}C NMR signals of **11g**, some peaks of **11g** could not be detected by ^{13}C NMR. ^{19}F NMR (376 MHz, $CDCl_3$, the minor isomer marked*): δ −126.3 (d, J = 228.0 Hz, 1F), −125.4 (d, J = 226.6 Hz, 1F*), −101.0 (dd, J = 228.0, 7.5 Hz, 1F), −99.2 (dd, J = 226.6, 9.6 Hz, 1F*); MS: m/z (% relative intensity) 350 (M^+, 0.3), 333 (17), 332 (78), 331(100), 301 (70); HRMS (ESI-TOF) calcd for $C_{20}H_{24}F_2O_3Na$ $[M + Na]^+$ 373.1591, found 373.1597.

(2R,7aR*)-7,7-Difluoro-7a-(4-methoxyphenyl)-2-phenyldecahydro-3,6-methanoindeno[1,7-bc]furan-2-ol (**11h**).* According to the general procedure D, the reaction of **9g** (65 mg, 0.2 mmol) with phenylmagnesium chloride (2.0 M in THF, 0.50 mL, 1.0 mmol) gave **11h** (54 mg, 68%) as a white solid after column chromatography (SiO_2, hexanes−80% CH_2Cl_2/hexanes) and then preparative thin-layer chromatography (SiO_2, 80% CH_2Cl_2/hexanes). Mp 207−209 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3420br, 2943m, 2872w, 1612w, 1514s, 1247m, 1178m, 1063m, 997m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62−7.56 (m, 2H), 7.41−7.35 (m, 2H), 7.34−7.23 (m, 3H), 6.85−6.79 (m, 2H), 3.73 (s, 3H), 3.31−3.25 (m, 1H), 2.61−2.55 (m, 1H), 2.28 (s, 1H), 2.30−2.20 (m, 2H), 1.98−1.88 (m, 1H), 1.79−1.62 (m, 2H), 1.47−1.27 (m, 2H), 1.24−1.15 (m, 1H), 1.08−1.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 141.1, 132.3, 128.3, 128.2, 128.2, 127.5, 127.4, 126.9 (dd, J = 269.6, 247.2 Hz), 126.3, 126.3, 113.2, 113.2, 109.3, 92.3 (dd, J = 29.5, 18.2 Hz), 55.2, 54.4, 52.2 (d, J = 2.6 Hz), 42.3 (dd, J = 24.0, 20.4 Hz), 30.5 (d, J = 6.0 Hz), 26.9, 24.2, 23.1 (d, J = 7.3 Hz), 18.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ −126.0 (d, J = 227.2 Hz, 1F), −100.4 (dd, J = 227.2, 9.2 Hz, 1F); MS: m/z (% relative intensity) 398 (M^+, 3), 379 (17), 360 (46), 276 (57), 255 (100), 235 (38), 105 (57), 77 (29); HRMS (ESI-TOF) calcd for $C_{24}H_{24}F_2O_3Na$ $[M + Na]^+$ 421.1591, found 421.1600.

(7aS)-2-Butyl-7,7-difluorodecahydro-3,6-methanoindeno[1,7-bc]furan-2-ol (**11i**).* According to the general procedure D, the reaction of **9h** (43 mg, 0.2 mmol) with butylmagnesium chloride (2.0 M in THF, 0.5 mL, 1.0 mmol) gave a 99:1 diastereomeric mixture of **11i** (38 mg, 69%) as a white solid after column chromatography (SiO_2, hexanes−80% CH_2Cl_2/hexanes). Mp 88−90 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3420br, 2950s, 2872m, 1469w, 1458w, 1369m, 1359m, 1155m, 1094m, 1062s cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 (dd, J = 13.3, 7.0 Hz, 1H), 3.03 (dd, J = 14.1, 7.1 Hz, 1H), 2.15−2.01 (m, 2H), 1.98 (s, 1H), 1.97−1.91 (m, 1H), 1.87−1.78 (m, 1H), 1.76−1.55 (m, 5H), 1.57−1.16 (m, 7H), 0.85 (t, J = 7.1 Hz, 3H). Due to low intensity of ^{1}H NMR signals of **11i**, all peaks of the minor isomer of **11i** could not be detected by ^{1}H NMR. ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.4 (dd, J = 265.9, 242.5 Hz), 110.2, 83.1 (dd, J = 37.1, 17.4 Hz), 49.7, 44.6, 41.1 (dd, J = 22.1, 20.9 Hz), 36.3, 29.0 (d, J = 6.0 Hz), 27.1, 26.1, 23.7, 23.4 (d, J = 6.3 Hz), 23.0, 17.8, 14.0. Due to low intensity of ^{13}C NMR signals of **11i**, all peaks of the minor isomer of **11i** could not be detected by ^{13}C NMR. ^{19}F NMR (376 MHz, $CDCl_3$, the minor isomer marked*): δ −125.3 (d, J = 232.9 Hz, 1F), −123.6 (d, J = 233.7, Hz, 1F*), −104.1 (dt, J = 232.9, 10.5 Hz, 1F), −101.7 (dt, J = 233.7, 13.2 Hz, 1F*); MS: m/z (% relative intensity) 272 (M^+, 2), 253 (100), 240 (11), 234 (7), 141 (12), 107 (31), 102 (28); HRMS (ESI-TOF) calcd for $C_{15}H_{22}F_2O_2Na$ $[M + Na]^+$ 295.1486, found 295.1489.

*Synthesis of gem-Difluoromethylenated Polycyclic Cage Compounds **12a**, **14a**, and **16a** from **8a**.* A solution of **8a** (107 mg, 0.5 mmol) in dry THF (4 mL) was treated with a THF solution of phenylmagnesium chloride (2.0 M in THF, 1.25 mL, 2.5 mmol) at 0

DOI: 10.1021/jo502501v
J. Org. Chem. 2015, 80, 1577−1592

°C. The reaction mixture was then heated at reflux overnight (15 h), cooled to room temperature, and quenched with 10% HCl (2 mL). The aqueous phase was extracted with EtOAc (4 × 5 mL). The combined organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents, the crude product was treated with a catalytic amount of *p*-TsOH in dry CH_2Cl_2 (12 mL) under reflux for overnight (15 h). The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents, the crude product was purified by preparative thin-layer chromatography (SiO_2, 10:20:30% EtOAc:CH_2Cl_2:hexanes and then 80% CH_2Cl_2/hexanes × 3) to give **12a** (105 mg, 59%), **14a** (8 mg, 6%), and **16a** (46 mg, 26%), each as a white solid.

(6aS)-6,6-Difluoro-6a-methyl-2,2-diphenyloctahydro-2H-3,5-methanopentaleno[1,6-bc]furan (**12a**).* Mp 171−172 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2963m, 2878w, 1449m, 1344m, 1163m, 1095s, 1075s, 1015m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45−7.32 (m, 4H), 7.21−7.11 (m, 4H), 7.10−6.99 (m, 2H), 3.67−3.59 (m, 1H), 2.64−2.57 (m, 1H), 2.56−2.50 (m, 1H), 2.29−2.19 (m, 1H), 2.09−2.02 (m, 1H), 1.95−1.87 (m, 1H), 1.60−1.52 (m, 1H), 1.47−1.40 (m, 1H), 1.21−1.11 (m, 1H), 0.99 (d, J = 4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 144.9, 128.4 (dd, J = 266.2, 243.7 Hz), 128.1, 128.1, 127.9, 127.9, 126.8, 126.0, 125.9, 125.9, 125.6, 125.6, 89.1, 88.2 (dd, J = 29.1, 18.2 Hz), 56.5, 55.7 (d, J = 3.8 Hz), 45.2 (dd, J = 24.5, 21.5 Hz), 42.8 (d, J = 6.3 Hz), 40.9, 39.1, 27.3 (d, J = 9.4 Hz), 19.0 (d, J = 5.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −123.1 (d, J = 231.6 Hz, 1F), −103.9 (d, J = 231.6 Hz, 1F); MS: m/z (% relative intensity) 352 (M^+, 16), 275 (100), 206 (22), 77 (13); HRMS (ESI-TOF) calcd for $C_{23}H_{22}F_2ONa$ $[M + Na]^+$ 375.1536, found 375.1541.

((3S,4R*)-2,2-Difluoro-3-hydroxy-3-methyloctahydro-1,5-methanopentalen-4-yl)(phenyl)methanone (**14a**).* Mp 125−126 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3602m, 3415br, 2974m, 1678s, 1598w, 1449m, 1178m, 1081m, 997m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01−7.94 (m, 2H), 7.51−7.45 (m, 1H), 7.43−7.35 (m, 2H), 3.72 (br.s, 1H), 2.79−2.73 (m, 1H), 2.52−2.47 (br, 1H), 2.44 (br.s, 1H), 2.43−2.35 (m, 1H), 2.14 (d, J = 4.7 Hz, 1H), 1.79−1.70 (m, 2H), 1.69−1.60 (m, 1H), 1.34 (d, J = 5.9 Hz, 3H), 1.32−1.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.6, 136.3, 132.9, 129.5 (dd, J = 261.7, 253.7 Hz), 128.7, 128.7, 128.5, 128.5, 79.1 (dd, J = 25.9, 20.4 Hz), 52.6 (d, J = 4.1 Hz), 50.2, 46.4 (dd, J = 28.4, 21.5 Hz), 40.9 (d, J = 5.8 Hz), 40.7, 36.3, 31.7 (dd, J = 7.9, 4.2 Hz), 25.4 (d, J = 12.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −106.6 (d, J = 233.9 Hz, 1F), −96.1 (dd, J = 233.9, 12.0 Hz, 1F); MS: m/z (% relative intensity) 292 (M^+, 31), 275 (7), 105 (100), 77 (67); HRMS (ESI-TOF) calcd for $C_{17}H_{18}F_2O_2Na$ $[M + Na]^+$ 315.1173, found 315.1172.

(6R,6aS*)-6-Fluoro-6-methyl-2,2-diphenyloctahydro-2H-3,5-methanopentaleno[1,6-bc]furan-6a-ol (**16a**).* Mp 175−176 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3583s, 3406br, 2969s, 2877m, 1598w, 1493s, 1449s, 1382s, 1268m, 1144m, 1048m, 939m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53−7.48 (m, 2H), 7.47−7.41 (m, 2H), 7.23−7.15 (m, 4H), 7.12−7.03 (m, 2H), 3.65−3.58 (m, 1H), 2.59−2.51 (m, 1H), 2.44−2.37 (m, 1H), 2.14 (s, 1H), 2.12−2.00 (m, 3H), 1.53−1.44 (m, 1H), 1.43−1.38 (m, 1H), 1.34 (d, J = 23.1 Hz, 3H), 1.11−1.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 144.4, 128.6, 128.6, 128.0, 128.0, 127.1, 126.2, 125.6, 125.6, 125.5, 125.5, 111.9 (d, J = 14.9 Hz), 100.6 (d, J = 195.7 Hz), 90.0, 56.9, 55.7 (d, J = 2.1 Hz), 48.5 (d, J = 20.0 Hz), 42.4 (d, J = 6.0 Hz), 40.7, 38.7, 27.0, 22.0 (d, J = 27.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −163.7 (q, J = 22.9 Hz, 1F, CF); MS: m/z (% relative intensity) 350 (M^+, 12), 331 (5), 273 (69), 202 (23), 191 (62), 179 (15), 167 (100), 105 (18), 77 (21); HRMS (ESI-TOF) calcd for $C_{23}H_{23}FO_2Na$ $[M + Na]^+$ 373.1580, found 373.1586.

Synthesis of *gem*-Difluoromethylenated Polycyclic Cage Compounds 13a, 15a, and 17a from 9h. According to the procedure for the synthesis of **12a**, **14a**, and **16a**, the reaction of **9h** (107 mg, 0.5 mmol) with phenylmagnesium chloride (2.0 M in THF, 1.25 mL, 2.5 mmol) at 0 °C followed by heating at reflux gave **13a** (56 mg, 31%), **15a** (55 mg, 38%), and **17a** (37 mg, 21%), each as a white solid after preparative thin-layer chromatography (SiO_2, 80% CH_2Cl_2/hexanes).

(7aS)-7,7-Difluoro-2,2-diphenyldecahydro-3,6-methanoindeno-[1,7-bc]furan (**13a**).* Mp 183−184 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 2949s, 2871w, 1492w, 1449w, 1368m, 1153m, 1094m, 1068s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51−7.44 (m, 2H), 7.42−7.35 (m, 2H), 7.25−7.15 (m, 4H), 7.14−7.03 (m, 2H), 4.21 (ddd, J = 13.1, 7.2, 1.2 Hz, 1H), 3.04−2.97 (m, 1H), 2.73−2.64 (m, 1H), 2.09−2.00 (m, 1H), 1.97−1.91 (m, 1H), 1.90−1.82 (m, 1H), 1.74−1.47 (m, 3H), 1.40−1.29 (m, 2H), 1.20−1.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 143.4, 128.5, 128.5, 128.1, 128.1, 127.8 (dd, J = 264.3, 241.9 Hz), 127.0, 126.4, 125.6, 125.6, 125.5, 125.5, 92.8, 82.2 (dd, J = 37.5, 17.5 Hz), 50.3, 46.0, 41.3 (dd, J = 21.4, 21.4 Hz), 29.8 (d, J = 6.0 Hz), 27.9, 24.3, 23.8 (d, J = 6.6 Hz), 18.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ −124.7 (d, J = 231.6 Hz, 1F), −104.7 (dt, J = 231.6, 9.7 Hz, 1F); MS: m/z (% relative intensity) 352 (M^+, 13), 351 (14), 275 (100), 182 (4), 181 (12), 77 (18); HRMS (ESI-TOF) calcd for $C_{23}H_{22}F_2ONa$ $[M + Na]^+$ 375.1536, found 375.1524.

((3S,4R*)-2,2-Difluoro-3-hydroxyoctahydro-1H-1,5-methanoinden-4-yl)(phenyl)methanone (**15a**).* Mp 111−112 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3608m, 3447br, 2951s, 2875m, 1678s, 1598m, 1448m, 1346w, 1172m, 1022m, 926m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88−7.80 (m, 2H), 7.48−7.41 (m, 1H), 7.40−7.30 (m, 2H), 4.18 (dd, J = 21.9, 6.6 Hz, 1H), 3.92 (s, 1H), 3.04 (br.s, 1H), 2.90−2.57 (br, 1H), 2.28−2.15 (m, 1H), 1.99−1.88 (m, 2H), 1.82 (br.s, 1H), 1.77−1.65 (m, 1H), 1.60−1.46 (m, 2H), 129−1.16 (m, 1H), 1.15−1.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6, 136.6, 132.9, 128.3 (dd, J = 261.5, 250.2 Hz), 128.6, 128.6, 128.4, 128.4, 75.9 (dd, J = 32.0, 20.0 Hz), 42.7 (dd, J = 27.0, 20.0 Hz), 41.9, 38.9 (d, J = 8.0 Hz), 28.7 (d, J = 6.0 Hz), 27.4, 26.6 (dd, J = 7.0, 7.0 Hz) 21.7, 17.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.6 (d, J = 232.9 Hz, 1F), −90.4 (d, J = 232.9, 14.1 Hz, 1F); MS: m/z (% relative intensity) 292 (M^+, 3), 290 (93), 289 (100), 273 (41), 254 (7), 211 (8), 187 (15), 161 (10), 105 (60); HRMS (ESI-TOF) calcd for $C_{17}H_{18}F_2O_2Na$ $[M + Na]^+$ 315.1173, found 315.1164.

(7R,7aS*)-7-Fluoro-2,2-diphenyldecahydro-3,6-methanoindeno[1,7-bc]furan-7a-ol (**17a**).* Mp 208−209 °C (CH_2Cl_2/hexanes); IR ($CHCl_3$) 3579m, 3363br, 2947s, 2870w, 1493m, 1448m, 1311w, 1070s, 1031m, 991m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.58−7.52 (m, 2H), 7.41−7.33 (m, 2H), 7.28−7.22 (m, 2H), 7.21−7.11 (m, 3H), 7.10−7.03 (m, 1H), 4.62 (dd, J = 53.4, 5.4 Hz, 1H), 3.17 (dd, J = 8.1, 0.9 Hz, 1H), 2.46−2.40 (m, 1H), 2.26 (s, 1H), 2.22−2.15 (m, 1H), 2.09−2.01 (m, 1H), 1.87−1.81 (m, 1H), 1.71−1.55 (m, 2H), 1.54−1.35 (m, 2H), 1.22−1.15 (br, 1H), 1.04−0.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 143.5, 128.7, 128.7, 128.1, 128.1, 127.3, 126.3, 126.1, 126.1, 125.5, 125.5, 111.4 (d, J = 13.4 Hz), 96.8 (d, J = 198.5 Hz), 92.0, 53.8, 50.7, 38.2 (d, J = 17.4 Hz), 28.2, 27.9 (d, J = 8.4 Hz), 24.2, 22.2 (d, J = 3.8 Hz), 18.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ −210.8 (d, J = 50.4 Hz, 1F, CF); MS: m/z (% relative intensity) 350 (M^+, 25), 330 (32), 273 (100), 256 (6), 106 (28), 105 (14), 77 (14); HRMS (ESI-TOF) calcd for $C_{23}H_{23}FO_2Na$ $[M + Na]^+$ 373.1580, found 373.1577.

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic data of all compounds (copies of ^1H, ^{13}C, and ^{19}F NMR), NOE spectra of **7h** and **7h′**, NOESY spectra of **12a**−**15a**, and CIF data for single-crystal X-ray analyses of compounds **4** (CCDC 1029662), **4A** (CCDC 1029663), **11a** (CCDC 1029664), and **17a** (CCDC 1029665). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: (+)-66-2-2015158. Fax: (+)-66-2-6445126. E-mail: manat.poh@mahidol.ac.th.

Notes

The authors declare no competing financial interest.

DOI: 10.1021/jo502501v
J. Org. Chem. 2015, 80, 1577−1592

■ ACKNOWLEDGMENTS

We acknowledge financial support from the Thailand Research Fund (BRG5380019), the Office of the Higher Education Commission and Mahidol University under the National Research Universities Initiative, and the Center of Excellence for Innovation in Chemistry (PERCH-CIC).

■ REFERENCES

(1) (a) Hiyama, T., Ed. *Organofluorine Compounds, Chemistry and Application*; Springer: New York, 2000. (b) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214−231. and references cited. (c) Welch, J. T., Ed. *Selective Fluorination in Organic and Bioorganic Chemistry*; American Chemical Society: Washington, DC, 1991. (d) Fried, J.; Mitra, D. M.; Nagarajan, M.; Mehrotra, M. M. *J. Med. Chem.* **1980**, *23*, 234−237. (e) Nakano, T.; Makino, M.; Morizawa, Y.; Matsumura, Y. *Angew. Chem., Int. Ed.* **1996**, *35*, 1019−1021. (f) Chang, C.-S.; Negishi, M.; Nakano, T.; Morizawa, Y.; Matsumura, Y.; Ichikawa, A. *Prostaglandins* **1997**, *53*, 83−90. (g) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359−4369. (h) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Blackwell: Oxford, 2009. (i) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071−1081. (j) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308−319. (k) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (l) Giornal, F.; Pazenok, S.; Rodefeld, L.; Lui, N.; Vors, J.-P.; Leroux, F. R. *J. Fluorine Chem.* **2013**, *152*, 2−11.

(2) For recent reviews and synthetic methods for syntheses of organofluorines, see: (a) Hafner, A.; Jung, N.; Bräse, S. *Synthesis* **2014**, *46*, 1440−1447. (b) Xu, J.; Liu, X.; Fu, Y. *Tetrahedron Lett.* **2014**, *55*, 585−594. (c) Konno, T. *Synlett* **2014**, *25*, 1350−1370. (d) Ni, C.; Hu, J. *Synthesis* **2014**, *46*, 842−863. (e) Lin, A.; Huehls, C. B.; Yang, J. *Org. Chem. Front.* **2014**, *1*, 434−438. (f) Ma, J.-A.; Li, S. *Org. Chem. Front.* **2014**, *1*, 712−715. (g) Wang, H.; Vicic, D. A. *Synlett* **2013**, *24*, 1887−1898.

(3) For selected recent examples for difluoromethylenation, see: (a) Zemtsov, A. A.; Kondratyev, N. S.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *J. Org. Chem.* **2014**, *79*, 818−822. (b) Zhang, B.; Studer, A. *Org. Lett.* **2014**, *16*, 1216−1219. (c) Salomon, P.; Zard, S. Z. *Org. Lett.* **2014**, *16*, 1482−1485. (d) Min, Q.-Q.; Yin, Z.; Feng, Z.; Guo, W.-H.; Zhang, X. *J. Am. Chem. Soc.* **2014**, *136*, 1230−1233. (e) Munemori, D.; Narita, K.; Nokami, T.; Itoh, T. *Org. Lett.* **2014**, *16*, 2638−2641. (f) Gao, B.; Zhao, Y.; Hu, M.; Ni, C.; Hu, J. *Chem.—Eur. J.* **2014**, *20*, 2750−2754. (g) Prakash, G. K. S.; Krishnamoorthy, S.; Ganesh, S. K.; Kulkarni, A.; Haiges, R.; Olah, G. A. *Org. Lett.* **2014**, *16*, 54−57. (h) Feng, Z.; Min, Q.-Q.; Xiao, Y.-L.; Zhang, B.; Zhang, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 1669−1673. (i) Lee, G. M.; Harrison, D. J.; Korobkov, I.; Baker, R. T. *Chem. Commun.* **2014**, *50*, 1128−1130. (j) Li, W.; Zhu, X.; Mao, H.; Tang, Z.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2014**, *50*, 7521−7523. (k) Ma, G.; Wan, W.; Hu, Q.; Jiang, H.; Wang, J.; Zhu, S.; Hao, J. *Chem. Commun.* **2014**, *50*, 7527−7530. (l) Hu, M.; He, Z.; Gao, B.; Li, L.; Ni, C.; Hu, J. *J. Am. Chem. Soc.* **2013**, *135*, 17302−17305. (m) Prakash, G. K. S.; Ni, C.; Wang, F.; Zhang, Z.; Haiges, R.; Olah, G. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10835−10839. (n) Zhou, Q.; Ruffoni, A.; Gianatassio, R.; Fujiwara, Y.; Sella, E.; Shabat, D.; Barran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3949−3952. (o) Chia, P. W.; Bello, D.; Slawin, A. M. Z.; Ó Hagan, D. *Chem. Commun.* **2013**, *49*, 2189−2191. (p) Thomoson, C. S.; Dolbier, W. R., Jr. *J. Org. Chem.* **2013**, *78*, 8904−8908. (q) Li, L.; Wang, F.; Ni, C.; Hu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12390−12394. (r) Zhao, Y.; Huang, W.; Zheng, J.; Hu, J. *Org. Lett.* **2011**, *13*, 5342−5345. (s) Fourrière, G.; Hijfte, N. V.; Lalot, J.; Dutech, G.; Fragnet, B.; Coadou, G.; Quirion, J.-C.; Leclerc, E. *Tetrahedron* **2010**, *66*, 3963−3972. (t) Yue, X.; Zhang, X.; Qing, F.-L. *Org. Lett.* **2009**, *11*, 73−76. (u) Diab, S. A.; Sene, A.; Pfund, E.; Lequeux, T. *Org. Lett.* **2008**, *10*, 3895−3898. (v) Huguenot, F.; Billac, A.; Brigand, T.; Portella, C. *J. Org. Chem.* **2008**, *73*, 2564−2569. (w) Uneyama, K. *J. Fluorine Chem.* **2008**, *129*, 550−576. (x) Verniest, G.; Surmont, R.; Hende, E. V.; Deweweire, A.; Deroose, F.; Thuring, J. W.; De Kimpe, N. *J. Org. Chem.* **2008**, *73*, 5458−5461. (y) De Kimpe, N.; Van Brabandt, W. *Synlett* **2006**, 2039−2042.

(4) (a) Prakash, G. K. S.; Hu, J.; Olah, G. A. *J. Org. Chem.* **2003**, *68*, 4457−4463. (b) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *J. Fluorine Chem.* **2005**, *126*, 529−534. (c) Mizuta, S.; Shibata, N.; Ogawa, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Chem. Commun.* **2006**, 2575−2577.

(5) Thaharn, W.; Bootwicha, T.; Soorukram, D.; Kuhakarn, C.; Prabpai, S.; Kongsaeree, P.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *J. Org. Chem.* **2012**, *77*, 8465−8479.

(6) Bootwicha, T.; Panichakul, C.; Kuhakarn, C.; Prabpai, S.; Kongsaeree, P.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *J. Org. Chem.* **2009**, *74*, 3798−3805.

(7) Chatupheeraphat, A.; Soorukram, D.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pakawatchai, C.; Saithong, S.; Pohmakotr, M. *Eur. J. Org. Chem.* **2013**, 6844−6858.

(8) Punirun, T.; Peewasan, K.; Kuhakarn, C.; Soorukram, D.; Tuchinda, P.; Reutrakul, V.; Kongsaeree, P.; Prabpai, S.; Pohmakotr, M. *Org. Lett.* **2012**, *14*, 1820−1823.

(9) Peewasan, K.; Kuhakarn, C.; Soorukram, D.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *J. Fluorine Chem.* **2012**, *135*, 367−372.

(10) Pohmakotr, M.; Boonkitpattarakul, K.; Ieawsuwan, W.; Jarussophon, S.; Duangdee, N.; Tuchinda, P.; Reutrakul, V. *Tetrahedron* **2006**, *62*, 5973−5985.

(11) Boonkitpattarakul, K.; Soorukram, D.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *J. Fluorine Chem.* **2011**, *132*, 987−990.

(12) Pharikronburee, V.; Punirun, T.; Soorukram, D.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *Org. Biomol. Chem.* **2013**, *11*, 2022−2033.

(13) Thaharn, W.; Soorukram, D.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 2212−2215.

(14) (a) Struble, M. D.; Strull, J.; Patel, K.; Siegel, M. A.; Lectka, T. *J. Org. Chem.* **2014**, *79*, 1−6. (b) Dolbier, W. R., Jr.; Zhai, Y.-A.; Battiste, M. A.; Ghiviriga, I. *J. Org. Chem.* **2005**, *70*, 10336−10341.

(15) For reviews, see: (a) Eaton, P. E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1421−1436. (b) Griffin, G. W.; Marchand, A. P. *Chem. Rev.* **1989**, *89*, 997−1010. (c) Marchand, A. P. *Chem. Rev.* **1989**, *89*, 1011−1033. (d) Paquette, L. A. *Chem. Rev.* **1989**, *89*, 1051−1065. (e) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432−2506.

(16) For some recent syntheses of polycyclic cage compounds and biological activities of some compounds, see: (a) Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 12964−12967. (b) Tomilov, Y. V.; Platonov, D. N.; Shulishov, E. V.; Okonnishnikova, G. P. *Tetrahedron* **2013**, *69*, 6855−6860. (c) Mott, B. T.; Tripathi, A.; Siegler, M. A.; Moor, C. D.; Sullivan, D. J.; Posner, G. H. *J. Med. Chem.* **2013**, *56*, 2630−2641. (d) Guney, T.; Kraus, G. A. *Org. Lett.* **2013**, *15*, 613−615. (e) Banister, S. D.; Manoli, M.; Doddareddy, M. R.; Hibbs, D. E.; Kassiou, M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6053−6058. (f) Torres, E.; Duque, M. D.; Lopez-Querol, M.; Taylor, M. C.; Naesens, L.; Ma, C.; Pinto, L. H.; Sureda, F. X.; Kelly, J. M.; Vazquez, S. *Bioorg. Med. Chem.* **2012**, *20*, 942−948. (g) Lin, H.-C.; Wu, H.-J. *J. Chin. Chem. Soc. (Weinheim, Ger.)* **2009**, *56*, 1072−1077. (h) Duque, M. D.; Camps, P.; Torres, E.; Valverde, E.; Sureda, F. X.; Lopez-Querol, M.; Camins, A.; Prathalingam, S. R.; Kelly, J. M.; Vazquez, S. *Bioorg. Med. Chem.* **2010**, *18*, 46−57. (i) Gharpure, S. J.; Porwal, S. K. *Tetrahedron Lett.* **2009**, *50*, 7162−7165. (j) Pillekamp, M.; Alachraf, W.; Oppel, I. M.; Dyker, G. *J. Org. Chem.* **2009**, *74*, 8355−8358. (k) Zimmer, R.; Taszarek, M.; Schefzig, L.; Reissig, H.-U. *Synlett* **2008**, 2046−2050. (l) Gharpure, S. J.; Porwal, S. K. *Synlett* **2008**, 242−246. (m) Xu, W.; Dolbier, W. R., Jr.; Salazar, J. *J. Org. Chem.* **2008**, *73*, 3535−3538. (n) James, B.; Viji, S.; Mathew, S.; Nair, M. S.; Lakshmanan, D.; Kumar, R. A. *Tetrahedron Lett.* **2007**, *48*, 6204−6208. (o) James, B.; Suresh, E.; Nair, M. S. *Tetrahedron Lett.* **2007**, *48*, 6059−6063. (p) Ye, Q.; Komarov, I. V.; Kirby, A. J.; Jones, M., Jr. *J. Org. Chem.* **2002**, *67*, 9288−9294. (q) Carreño, M. C.; Luzón, C. G.;

DOI: 10.1021/jo502501v
J. Org. Chem. 2015, 80, 1577−1592

Ribagorda, M. *Chem.—Eur. J.* **2002**, *8*, 208−216. (r) Giomi, D.; Nesi, R.; Turchi, S.; Mura, E. *J. Org. Chem.* **2000**, *65*, 360−364. (s) Wu, H.-J.; Chao, C.-S.; Lin, C.-C. *J. Org. Chem.* **1998**, *63*, 7687−7693. (t) Wu, H.-J.; Tsai, S.-H.; Chern, J.-H.; Lin, H.-C. *J. Org. Chem.* **1997**, *62*, 6367−6373. (u) Wu, H.-J.; Chern, J.-H. *J. Org. Chem.* **1997**, *62*, 3208−3214. (v) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671−719. (w) Lin, R.-L.; Wu, C.-Y.; Chern, J.-H.; Wu, H.-J. *J. Chinese Chem. Soc.* **1996**, *43*, 289−295. (x) Wu, H.-J.; Lin, C.-C. *J. Org. Chem.* **1995**, *60*, 7558−7566. (y) Wu, H.-J.; Huang, F. J.; Lin, C.-C. *J. Chem. Soc., Chem. Commun.* **1991**, 770−771. (z) Marchand, A. P. *Synlett* **1991**, 73−79.

(17) (a) Masusai, C.; Soorukram, D.; Kuhakarn, C.; Tuchinda, P.; Pakawatchai, C.; Saithong, S.; Reutrakul, V.; Pohmakotr, M. *Org. Biomol. Chem.* **2013**, *11*, 6650−6658. (b) Masusai, C.; Soorukram, D.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *J. Fluorine Chem.* **2013**, *154*, 37−42.

(18) Pohmakotr, M.; Thamapipol, S.; Tuchinda, P.; Reutrakul, V. *Tetrahedron* **2007**, *63*, 1806−1820.

(19) For reviews on radical cyclization, see: (a) Zard, S. Z. *Radical Reactions in Organic Synthesis*; Oxford University Press: Oxford, 2003. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996. (c) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1991. (d) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224−2248.

DOI: 10.1021/jo502501v
J. Org. Chem. 2015, 80, 1577−1592