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Highly stereoselective synthesis of 6-perfluoroalkyl-6-fluoroalka-2,3,5-(*Z*)-trienols through carbometallation-elimination of 5-perfluoroalkyl-substituted 4(*E*)-alken-2-ynols with Grignard reagents

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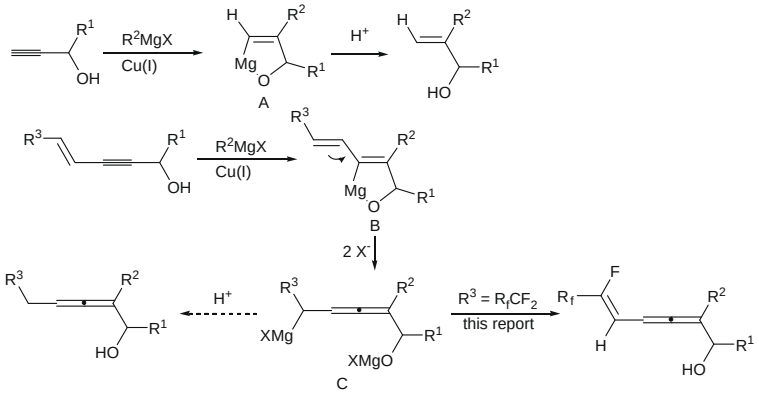
ABSTRACT

A highly regio- and stereoselective sequential carbometallation and *Z*-selective β-elimination reaction of 5-perfluoroalkyl-4(*E*)-en-2-ynols with Grignard reagents in Et_2O has been developed to afford various 6-perfluoroalkyl-6-fluoroalka-2,3,5(*Z*)-trienols in good to excellent yields. Primary or secondary alkyl or aryl Grignard reagents may be used to introduce the R^2 group to the 2-position of the starting materials referring to the hydroxyl group. A mechanism for this transformation has been proposed.

Due to the recent rapid development of many new synthetic methodologies based on allenes, this class of compounds has been becoming a class of popular starting materials in modern synthetic organic chemistry.[1,2] On the other hand, the presence of fluorine atoms in organic compounds may dramatically change their physicochemical properties and biological activities,[3] thus, new methodologies for the synthesis of fluorine-containing allenes[4] will surely be attracting more and more attention. Fluorinated allenes have been prepared by the reaction of fluorine-substituted propargyl bromide with indium,[5] S_N2' type reaction[6] of fluorinated alkynes bearing propargylic leaving groups with AlH_3,[6a] F^-[6b] or Grignard reagent[6c] and the rearrangement reaction of propargyl fluorides.[7] Based on our recent studies on carbometallation of propargylic alcohols,[8] we envisioned that when 4-alken-2-ynols are used, their reactions with Grignard reagents would afford the cyclic metallic intermediate **B**, which may undergo an allylic rearrangement to afford allene-containing magnesium intermediate **C**, which upon hydrolysis, would afford 2,3-allenols. In this Letter, we wish to report our recent observation on the unexpected formation of 6-perfluoroalkyl-6-fluorolka-2,3,5(*Z*)-trienols from the reaction



Scheme 1.

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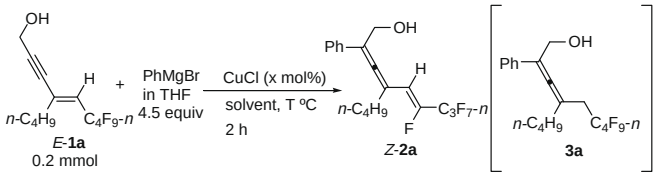
Table 1
Optimization of reaction conditions for the reaction of *E*-**1a** with PhMgBr[a]



Entry	*x*	*T* (°C)	Solvent	Conversion (%)	^{1}H NMR yield of *Z*-**2a** (%)
1	50	−78 °C to rt	Toluene	92	80
2	50	0 °C to rt	Toluene	95	91
3	50	0 °C to rt	THF	18	13
4	50	0 °C to rt	Et_2O	96	92
5	0	0 °C to rt	Et_2O	96	86
6	0	rt	Et_2O	97	85
7[b]	0	rt	Et_2O[c]	99	89
8[d]	0	rt	Et_2O[c]	99	94

[a] PhMgBr (2.0 M in THF, 0.45 mL, 0.9 mmol) reacted with *E*-**1a** (0.2 mmol) in 1 mL of solvent.
[b] 4.5 equiv of PhMgCl (1.73 M in THF) were used.
[c] 0.5 mL of Et_2O was used.
[d] Four equivalents of PhMgCl (1.73 M in THF) were used.

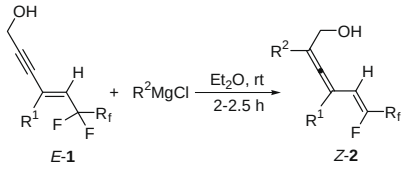
of 5-perfluoroalkyl-substituted 4(*E*)-alken-2-ynols[9] with Grignard reagents (Scheme 1).

At the beginning of our exploration, the reaction of *E*-**1a** with PhMgBr was carried out in toluene and CuCl was used as the catalyst under the conditions we used for the carbometallation of propargylic alcohols (Table 1, entry 1).[8b] Surprisingly, instead of forming the expected 4-butyl-5-perfluorobutyl-2-phenylpenta-2,3-dienol **3a**, a new product, that is, 4-butyl-6,7,7,8,8,9,9,9-octafluoro-2-phenyl-2,3,5(*Z*)-nonatrienol *Z*-**2a**, was formed in 80% ^{1}H NMR yield, which indicated that the **C**-type intermediate (R^3 = *n*-C_4F_9) underwent an extra highly stereoselective defluorometallation[6c,10] to form the fluorinated C=C bond[11] at the 5-position in *Z*-**2a**. The solvent effect was examined by adding the Grignard reagent at 0 °C and then warming up to room temperature (Table 1, entries 2–4): Et_2O gave a result similar to toluene while the reaction in THF afforded *Z*-**2a** in only 13% yield. In addition, this reaction may also proceed in the absence of CuCl with a slightly lower yield (Table 1, entry 5). When PhMgCl was used instead of PhMgBr, the conversion of *E*-**1a** may be improved to 99% for the reaction at room temperature (Table 1, entry 7). Finally, the reaction of *E*-**1a** with 4.0 equiv of PhMgCl at room temperature in ether was defined as the standard conditions. It is worth noting that under the standard procedure the configuration of the carbon–carbon double bond at the 5-position is exclusively *Z* as detected by the analysis of the ^{1}H NMR of the crude reaction mixture. The configuration of the double bond was determined by the ^{19}F{^{1}H}-HOESY NMR spectrum[12] of the compound *Z*-**2a**. With less amount of the Grignard reagent, the reaction is slower.

With the optimized conditions in hand, the scope of this reaction for the synthesis of substituted 6-fluoro-6-perfluoroalkyl-2,3,5(*Z*)-trien-1-ols (*Z*-**2**) was studied. Some of the typical results are summarized in Table 2. Several substituted 5-perfluoroalkylpent-4-en-2-yn-1-ols were successfully applied in this procedure to afford differently substituted 6-perfluoroalkyl-6-fluoro-2,3,5(*Z*)-alkatrienols highly stereoselectively. R^1 can be different alkyl groups, such as *n*-butyl (Table 2, entries 1–7, 13, and 15) or *n*-hexyl group (Table 2, entries 8–12 and 14), or phenyl group (Table 2, entries 16 and 17). R_f group can be *n*-C_3F_7 (Table 2, entries 1–12), *n*-C_5F_{11} (Table 2, entries 13, 14, and 16), or *n*-C_7F_{15} group (Table 2, entries 15 and 17). Phenyl (Table 2, entries 1, 8, and 13–17) or substituted phenyl Grignard reagents with electron-donating group (Table 2, entries 2, 3, 9, and 10) or electron-withdrawing group (Table 2, entries 4 and 11) at the 4-position of the phenyl ring, normal alkyl (Table 2, entries 5, 6, and 12) or secondary alkyl (Table 2, entry 7) magnesium chloride or bromide may all be employed. The reaction with normal alkyl Grignard reagents gave the products in relatively lower yields than aryl magnesium chloride.

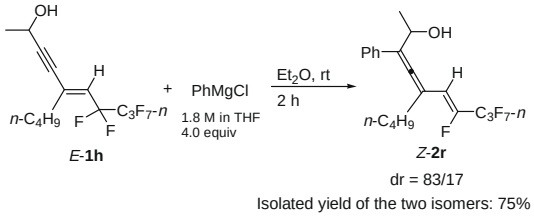
When the substrate is a secondary alcohol, that is, 5-(*n*-butyl)-7,7,8,8,9,9,10,10,10-nonafluoro-5-decen-3-yn-2-ol *E*-**1h**, the reaction afforded the corresponding product *Z*-**2r** with a dr ratio of

Table 2
Highly stereoselective synthesis of fluorine-containing 2,3,5(*Z*)-trienols by carbometallation of 5-perfluoroalkyl-4(*E*)-alken-2-ynols (*E*-**1**) with Grignard reagents



Entry	R^1	R_f	R^2	Yield of *Z*-**2**[a] (%)
1	*n*-C_4H_9	*n*-C_3F_7 (*E*-**1a**)	Ph	95 (*Z*-**2a**)
2	*n*-C_4H_9	*n*-C_3F_7 (*E*-**1a**)	*p*-$CH_3C_6H_4$[b]	87 (*Z*-**2b**)
3	*n*-C_4H_9	*n*-C_3F_7 (*E*-**1a**)	*p*-$CH_3OC_6H_4$[c]	93 (*Z*-**2c**)[e]
4	*n*-C_4H_9	*n*-C_3F_7 (*E*-**1a**)	*p*-FC_6H_4[d]	89 (*Z*-**2d**)[e]
5	*n*-C_4H_9	*n*-C_3F_7 (*E*-**1a**)	*n*-C_4H_9	68 (*Z*-**2e**)
6	*n*-C_4H_9	*n*-C_3F_7 (*E*-**1a**)	*n*-C_5H_{11}	66 (*Z*-**2f**)
7	*n*-C_4H_9	*n*-C_3F_7 (*E*-**1a**)	*i*-Pr	84 (*Z*-**2g**)
8	*n*-C_6H_{13}	*n*-C_3F_7 (*E*-**1b**)	Ph	94 (*Z*-**2h**)
9	*n*-C_6H_{13}	*n*-C_3F_7 (*E*-**1b**)	*p*-$CH_3C_6H_4$[b]	83 (*Z*-**2i**)
10	*n*-C_6H_{13}	*n*-C_3F_7 (*E*-**1b**)	*p*-$CH_3OC_6H_4$[c]	82 (*Z*-**2j**)
11	*n*-C_6H_{13}	*n*-C_3F_7 (*E*-**1b**)	*p*-FC_6H_4[d]	93 (*Z*-**2k**)[e]
12	*n*-C_6H_{13}	*n*-C_3F_7 (*E*-**1b**)	*n*-C_4H_9	73 (*Z*-**2l**)
13	*n*-C_4H_9	*n*-C_5F_{11} (*E*-**1c**)	Ph	91 (*Z*-**2m**)[f]
14	*n*-C_6H_{13}	*n*-C_5F_{11} (*E*-**1d**)	Ph	92 (*Z*-**2n**)
15	*n*-C_4H_9	*n*-C_7F_{15} (*E*-**1e**)	Ph	95 (*Z*-**2o**)[e]
16	Ph	*n*-C_5F_{11} (*E*-**1f**)	Ph[g]	80 (*Z*-**2p**)[e]
17	Ph	*n*-C_7F_{15} (*E*-**1g**)	Ph[g]	83 (*Z*-**2q**)[e]

[a] Isolated yield.
[b] *p*-$CH_3C_6H_4MgBr$ was used.
[c] *p*-$CH_3OC_6H_4MgBr$ was used.
[d] *p*-FC_4H_6MgBr was used.
[e] ⩽4% recovery of the start material.
[f] ⩽5% recovery of the start material.
[g] Three equivalents of PhMgBr were used.

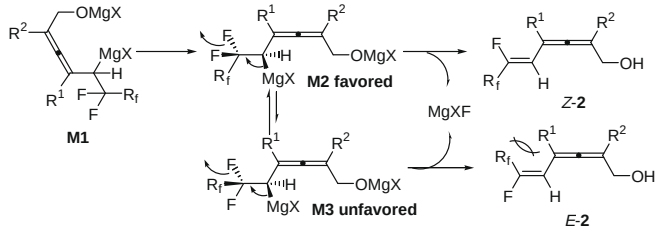


Scheme 2. The carbometallation-elimination reaction of secondary alcohol *E*-**1h** with PhMgCl.

83/17. The two isomers may be easily isolated by flash chromatography on silica gel in 75% and 14% yields, respectively (Scheme 2).

A typical procedure is as follows: Synthesis of 4-(*n*-butyl)-6,7,7,8,8,9,9,9-octafluoro-2-phenylnona-2,3,5(*Z*)-trienol (*Z*-**2a**). To a dry Schlenk tube containing *E*-**1a** (70.0 mg, 0.20 mmol) and 0.5 mL of anhydrous Et_2O was added PhMgCl (1.73 M in THF, 0.48 mL, 0.83 mmol) dropwise by a syringe under a nitrogen atmosphere at room temperature. Then the reaction mixture was stirred at room temperature for 2 h (monitored by TLC). After quenching with an aqueous solution of saturated ammonium chloride (5 mL), the resulting mixture was extracted with diethyl ether (25 mL × 3), washed with brine (10 mL × 2), and dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20/1) afforded *Z*-**2a** (75.5 mg, 95%). According to the ^1H and ^{19}F NMR analysis of the crude reaction mixture before separation, 1.4% of *E*-**1a** was recovered. *Z*-**2a**: oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.30 (m, 4H), 7.30–7.23 (m, 1H), 5.92 (d, J = 34.5 Hz, 1H), 4.60 (s, 2H), 2.39 (t, J = 7.3 Hz, 2H), 1.76 (br s, 1H), 1.58–1.30 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.8–(−81.0) (m, 3F), −118.0–(−118.3) (m, 2F), −126.7–(−127.1) (m, 1F), −127.2–(−127.4) (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4 (d, J = 4.4 Hz), 144.9 (dt, J_1 = 267.8 Hz and J_2 = 28.0 Hz), 133.4, 128.8, 127.7, 126.4, 112.1–111.7 (m), 108.4, 103.5 (d, J = 3.0 Hz), 61.7, 31.7 (d, J = 3.3 Hz), 30.4, 22.2, 13.8; IR (neat) ν (cm^{-1}): 3342, 3064, 3033, 2961, 2933, 2875, 1933, 1681, 1599, 1496, 1454, 1361, 1230, 1187, 1152, 1120, 1056, 1029; MS (EI, 70 eV) *m/z* (%): 414 (M^+, 1.85), 354 (100); Elemental analysis calcd for $C_{19}H_{18}F_8O$: C, 55.08; H, 4.38. Found: C, 54.79; H, 4.26.

A rationale for the *Z*-selectivity is shown in Scheme 3. Due to the stereoelectronic effect,[3b,13] **M2** is more favored than **M3**, subsequent anti-defluorometallation[6c,10a] of **M2** afforded *Z*-**2** highly stereoselectively. In addition, the steric hindrance of the perfluoroalkyl group R_f with the R^1 group in the *E*-**2** may be another reason for the observation of the *Z* stereoselectivity.



Scheme 3. The possible mechanism of the carbometallation-elimination reaction.

In conclusion, a highly regio- and stereoselective synthesis of 6-perfluoroalkyl-6-fluoro-2,3,5(*Z*)-alkatrienols (*Z*-**2**) from differently substituted 5-perfluoroalkylpenta-4(*E*)-en-2-ynols and Grignard reagents has been developed. The R^2 groups from the Grignard reagents have been introduced to the 2-position of the starting materials referring to the hydroxyl group. The *Z*-selectivity may be explained by the stereoelectronic effect and *anti*-nature of the defluorometallation. Due to the importance of the products,[14–18] wide scope, and the ready availability of the starting materials,[9] the method will be useful in organic synthesis. Further studies in this area are being carried out in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.003.

References and notes

1. (a) Patai, S.. In *The Chemistry of Ketenes, Allenes, and Related Compounds*; John Wiley & Sons: New York, 1980; Part 1; (b) Schuster, H. F.; Coppola, G. M. Allenes in Organic Synthesis; John Wiley & Sons: New York, 1984; (c) Landor, S. R.. In *The Chemistry of Allenes*; Academic Press: New York, 1982; Vol. 1–3; (d) Ma, S. Carbopalladation of Allenes. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002; p 1491; (e) Krause, N.; Hashmi, A. S. K.. *Modern Allene Chemistry*. In *Vol. 1–2*; Wiley-VCH: Weinheim, Germany, 2004; (f) Ma, S. Pd-Catalyzed two- or three component cyclization of functionalized allenes. In *Topics in Organometallic Chemistry*; Tsuji, J., Ed.; Springer: Heidelberg, 2005; p 183.
2. For reviews on the chemistry of allenes, see: (a) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207; (b) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067; (c) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590; (d) Lu, X.; Zhang, C.; Xu, Z. *Acc Chem. Res.* **2001**, *34*, 535; (e) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12; (f) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284; (g) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701; (h) Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773; (i) Ma, S. *Chem. Rev.* **2005**, *105*, 2829; (j) Ma, S. *Aldrichimica Acta* **2007**, *40*, 91.
3. For books and reviews, see: (a) Welch, J. T. *Selective Fluorination in Organic and Bioorganic Chemistry*; American Chemical Society: Washington, DC, 1991; (b) Chambers, R. D. *Organofluorine Chemistry: Techniques and Synthons*; Springer: Berlin, Heidelberg, 1997; (c) Kirsch, P. *Modern Fluoroorganic Chemistry*, 1st ed.; WILEY-VCH: Weinheim, 2004; (d) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505; (e) Resnati, G. *Tetrahedron* **1993**, *49*, 9385; (f) Iseki, K. *Tetrahedron* **1998**, *54*, 13887; (g) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119; (h) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214.
4. For the property and reactions of fluorine-containing allenes, see: (a) Dolbier, W. R., Jr.; Burkholder, C. R. *J. Org. Chem.* **1984**, *49*, 2381; (b) Dixon, D. A.; Smart, B. E. *J. Phys. Chem.* **1989**, *93*, 7772; (c) Dolbier, W. R., Jr. *Acc. Chem. Res.* **1991**, *24*, 63; (d) Silvester, M. J. *Aldrichimica. Acta* **1995**, *28*, 45; (e) Bach, A.; Lentz, D.; Luger, P.; Messerschmidt, M.; Olesch, C.; Patzschke, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 296; (f) Lentz, D. *J. Fluorine Chem.* **2004**, *125*, 853.
5. (a) Wang, Z.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 6547; (b) Shen, Q.; Hammond, G. B. *Org. Lett.* **2001**, *3*, 2213; (c) Shen, Q.; Chen, C.-H.; Hammond, G. B. *J. Fluorine Chem.* **2002**, *117*, 131; (d) Lan, Y.; Hammond, G. B. *Org. Lett.* **2002**, *4*, 2437; (e) Shen, Q.; Hammond, G. B. *J. Am. Chem. Soc.* **2002**, *124*, 6534; (f) Xu, B.; Hammond, G. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7404; (g) Xu, B.; Mashuta, M. S.; Hammond, G. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 7265.
6. (a) Dear, R. E. A.; Gilbert, E. E. *J. Org. Chem.* **1968**, *33*, 819; (b) Castelhano, A. L.; Krantz, A. *J. Am. Chem. Soc.* **1987**, *109*, 3491; (c) Mae, M.; Hong, J. A.; Xu, B.; Hammond, G. B. *Org. Lett.* **2006**, *8*, 479.
7. (a) Zapata, A. J.; Gu, Y.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 227; (b) Riyadh, S. M.; Ishii, H.; Fuchigami, T. *Tetrahedron Lett.* **2001**, *42*, 3009; (c) Riyadh, S. M.; Ishii, H.; Fuchigami, T. *Tetrahedron* **2002**, *58*, 5877.
8. (a) Ma, S.; Lu, Z. *Adv. Synth. Catal.* **2006**, *348*, 1894; (b) Lu, Z.; Ma, S. *J. Org. Chem.* **2006**, *71*, 2655.
9. The starting materials were easily prepared by the Sonogashira coupling reaction of perfluoroalkyl substituted vinyl iodide with propargyl alcohol, see: (a) Ma, S.; Ma, Z. *Synlett* **2006**, 1263; (b) Ma, Z.; Ma, S. *Tetrahedron* **2008**, *64*, 6500.
10. (a) Howells, R. D.; Gilman, H. *J. Fluorine Chem.* **1975**, *5*, 99; (b) Battais, A.; Boutevin, B.; Moreau, P. *J. Fluorine Chem.* **1978**, *12*, 481; (c) Yamada, S.; Noma, M.; Konno, T.; Ishihara, T.; Yamanaka, H. *Org. Lett.* **2006**, *8*, 843; (d) Yamada, S.; Noma, M.; Hondo, K.; Konno, T.; Ishihara, T. *J. Org. Chem.* **2008**, *73*, 522.
11. For the recent reports on the synthesis and reactions of fluorinated olefin, see: (a) Suzuta, T.; Abe, T.; Sekiya, A. *J. Fluorine Chem.* **2003**, *119*, 3; Van der (b) Veken, P.; Kertèsz, I.; Senten, K.; Haemers, A.; Augustyns, K. *Tetrahedron Lett.* **2003**, *44*, 6231; (c) Salim, S. S.; Bellingham, R. K.; Satcharoen, V.; Brown, R. C. D. *Org. Lett.* **2003**, *5*, 3403; (d) Wlassics, I.; Barchiesi, E.; Sala, M. *J. Fluorine Chem.* **2003**, *123*, 119; Van der (e) Veken, P.; Senten, K.; Kertèsz, I.; De Meester, I.;

Lambeir, A.-M.; Maes, M.-B.; Scharpé, S.; Haemers, A.; Augustyns, K. *J. Med. Chem.* **2005**, *48*, 1768; (f) De Matteis, V.; van Delft, F. L.; Tiebes, J.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2006**, 1166; (g) Cheng, Z.-L.; Chen, Q.-Y. *J. Fluorine Chem.* **2006**, *127*, 894; (h) Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2007**, *129*, 4536; (i) Francisco, C. G.; González, C. C.; Kennedy, A. R.; Paz, N. R.; Suárez, E. *Chem. Eur. J.* **2008**, *14*, 6704.

12. Neuhaus, D.; Williamson, M. P. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*, 2nd ed.; Wiley-VCH: New York, 2000. See Supplementary data for the spectrum.
13. (a) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*, 1st ed.; University Science Books: Sausalito, CA, 2006; (b) Gorenstein, D. G. *Chem. Rev.* **1987**, *87*, 1047.
14. Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537.
15. Ma, S.; Gao, W. *J. Org. Chem.* **2002**, *67*, 6104.
16. Maynard, D. F.; Okamura, W. H. *J. Org. Chem.* **1995**, *60*, 1763.
17. For the review of the reaction of 2,3-allenols and their derivatives, see: Deng, Y.; Gu, Z.; Ma, S. *Chin. J. Org. Chem.* **2006**, *26*, 1468.
18. For a reference on the synthesis of vinyl allenes, see: Xi, Z.; Zhang, W.; Song, Z.; Zheng, W.; Kong, F.; Takahashi, T. *J. Org. Chem.* **2005**, *70*, 8785.