Stereoselective Synthesis of 2,5-Dihydrofurans by Sequential S_N2' Cleavage of Alkynyloxiranes and Ag^+-Catalyzed Cyclization of the Allenylcarbinol Products

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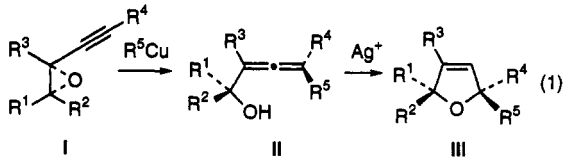
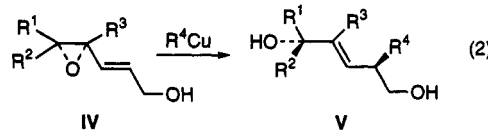
The alkynyloxiranes **5a,b**, **7**, and **18** afford mainly the anti S_N2' products **6a,b**, **8**, and **19a** upon treatment with Me_2CuLi. The derived primary alcohol silyl ethers **9a,b**, **10**, and **19b–d** undergo Ag^+-catalyzed cyclization to the 2,5-dihydrofurans **11a,b**, **12**, and **20b–d**. Diol **26** affords mainly the fused ring 2,5-dihydrofuran **32** under these conditions. The stereochemistry of dihydrofuran **20a** was confirmed by conversion to the known epoxide **21a**.

2,5-Disubstituted tetrahydrofurans are important structural elements of polyether antibiotics[1] and various polyene mycotoxins.[2] An interest in developing general stereocontrolled routes to such compounds prompted our examination of the sequence depicted in eq 1.



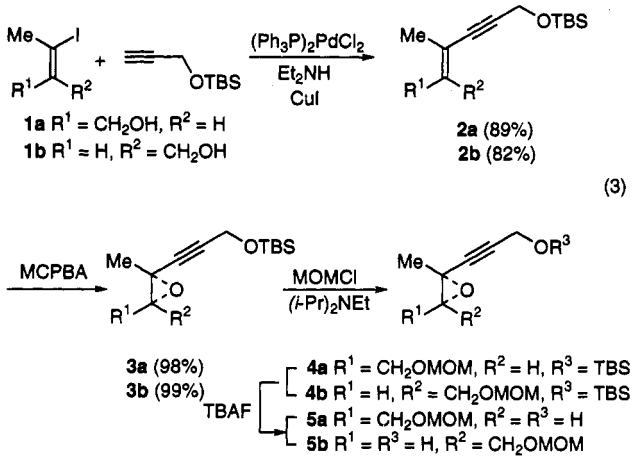
I II III (1)

It is well established that allenylcarbinols (**II**) cyclize to 2,5-dihydrofurans (**III**) with high stereoselectivity.[3] However, the S_N2' displacement of alkynyloxiranes (**I**) can lead to anti or syn products, depending on the copper reagent and, to some extent, the substituents.[4] In our studies on S_N2' displacements of vinyloxiranes by cuprates, we found that an allylic hydroxy grouping greatly assists the anti reaction pathway (eq 2).[5] It was of interest to examine the possibility of such a directing effect for alkynyloxiranes **I** ($R^4 = CH_2OH$) as well.



IV V (2)

Suitable prototype systems were prepared by Sonogashiro coupling[6] of vinylic iodides **1a** and **1b**[7] with the TBS ether of propargyl alcohol (eq 3). Epoxidation of the double bond with *m*-CPBA followed by protection of the

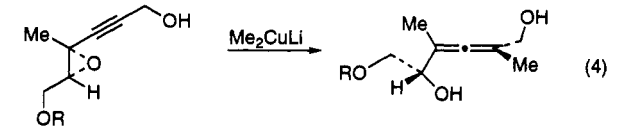


1a $R^1 = CH_2OH$, $R^2 = H$ — **2a** (89%)
1b $R^1 = H$, $R^2 = CH_2OH$ — **2b** (82%) (3)

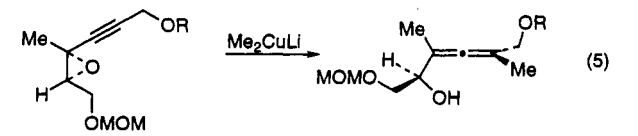
3a (98%) **3b** (99%) TBAF → **4a** $R^1 = CH_2OMOM$, $R^2 = H$, $R^3 = TBS$; **4b** $R^1 = H$, $R^2 = CH_2OMOM$, $R^3 = TBS$; **5a** $R^1 = CH_2OMOM$, $R^2 = R^3 = H$; **5b** $R^1 = R^3 = H$, $R^2 = CH_2OMOM$

epoxy alcohols **3a** and **3b** with MOMCl, and *i*-Pr_2NEt (HB) afforded the ethers **4a** and **4b**. Desilylation with TBAF gave the alcohols of interest, **5a** and **5b**. A third alkynyloxirane system, **7**, was prepared from alcohol **3a** by benzylation (BnBr, NaH) and subsequent TBS cleavage.

Each of the foregoing alcohols **5a**, **7**, and **5b** afforded the S_N2' products, **6a**, **8**, and **6b**, in high yield as 90:10 or better mixtures of diastereoisomers upon treatment with the Gilman methyl cuprate (eqs 4 and 5).[8] In addition,



5a R = MOM — **6a** R = MOM (75%, >90:10)
7 R = Bn — **8** R = Bn (91%, 98:2) (4)



5b R = H — **6b** R = H (71%, 93:7)
4b R = TBS — **9b** R = TBS (80%, 80:20) (5)

up to 15% of protonolysis products (H instead of Me at carbon-5 (compounds **6a**, **6b**, **9b**) or carbon-2 (compounds **8**, **19a**)) were also formed.

•Abstract published in *Advance ACS Abstracts*, November 1, 1993.

(1) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.

(2) Ganguli, M.; Burka, L. T.; Harris, T. M. *J. Org. Chem.* **1984**, *49*, 3762. Sakabe, N.; Goto, T.; Hirata, Y. *Tetrahedron* **1977**, *33*, 3077. Syntheses: Whang, K.; Cooke, R. J.; Okay, G.; Cha, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 8985. Hatakeyama, S.; Sakurai, K.; Numata, H.; Ochi, N.; Takano, S. *J. Am. Chem. Soc.* **1988**, *110*, 5201.

(3) Olsson, L.; Claesson, A. *Synthesis* **1979**, 743. Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 4913.

(4) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron* **1991**, *47*, 1677. Oehlschlager, A. C.; Czyzewska, E. *Tetrahedron Lett.* **1983**, *24*, 5587.

(5) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503. Marshall, J. A.; Blough, B. E. *J. Org. Chem.* **1991**, *56*, 2225.

(6) Sonogashiro, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

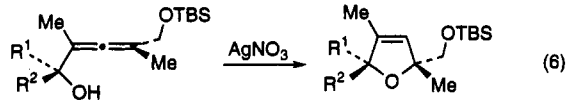
(7) (a) Lautens, M.; Huboux, A. H. *Tetrahedron Lett.* **1990**, *31*, 3105. (b) Cochrane, J. S.; Hanson, J. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, *3*, 361.

0022-3263/93/1958-7180$04.00/0

The TBS ether **4b** gave rise to an 80:20 mixture of diastereomers under these conditions. Thus, the hydroxy substituent clearly improves the diastereoselectivity of the displacement, in keeping with our previous findings.[5]

We also examined other cuprates, MeCu(CN)Li, $Me_2Cu(CN)Li_2$, and $MeMgBr{\cdot}CuBr{\cdot}SMe_2$,[9] with epoxide **5b**. All gave substantially lower yields (30%, 30%, 10%). In the latter case, 50% of the S_N2 product was produced. In view of the high diastereoselectivity of these reactions and literature analogy[4] we assumed that the major products were formed by the anti pathway. This assumption was later confirmed.

Selective silylation of the S_N2' products **6a,b** and **8** followed by treatment of the derived secondary alcohols **9a,b**, and **10** with $AgNO_3$ in aqueous acetone afforded the 2,5-dihydrofurans **11a,b** and **12** in high yield (eq 6). When

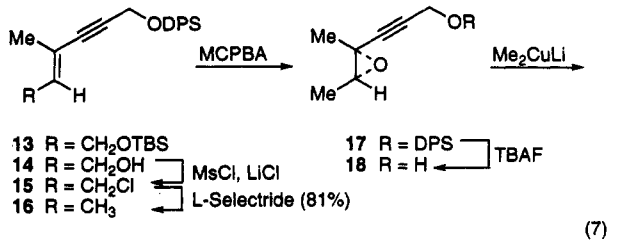


(6)

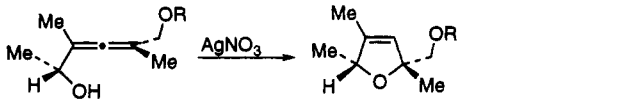
9a $R^1 = CH_2OMOM$, $R^2 = H$ — **11a** (86%)
9b $R^1 = H$, $R^2 = CH_2OMOM$ — **11b** (78%)
10 $R^1 = CH_2OBn$, $R^2 = H$ — **12** (91%)

a mixture of diastereomeric alcohols was used, an identical mixture of dihydrofuran diastereomers was formed in keeping with a highly stereoselective or stereospecific process.

The methyl-substituted alkynyloxirane **18** was prepared from enyne **13**[10] by selective deprotection to alcohol **14** and hydrogenolysis of the derived chloride **15** and then epoxidation with *m*-CPBA and removal of the DPS grouping (eq 7). Cuprate addition proceeded as before to



(7)

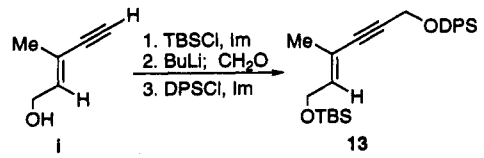


19a R = H (70%, 98:2)
19b R = TBS
19c R = DPS
19d R = TIPS

20a R = H
20b R = TBS (81%)
20c R = DPS (82%)
20d R = TIPS (90%)

yield allenediol **19a** along with the corresponding protonolysis product. Addition of CH_3I to the cuprate reaction effectively suppressed formation of this byproduct (<5%).

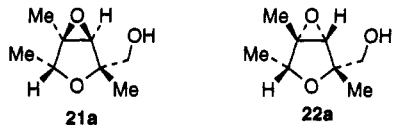
(8) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley Interscience: New York, 1980; pp 100–101.
(9) Lipschutz, B. H.; Sengupta, S. *Org. Reactions* **1992**, *41*, 135.
(10) The following sequence was employed to prepare enyne **13**:



I **13**

Alcohol **I** is available from the Aldrich Chemical Co., Milwaukee, WI.
(11) Klein L. *Tetrahedron Lett.* **1986**, *27*, 4545.

Table I. ^{13}C NMR Data for Epoxides 21a and 22a

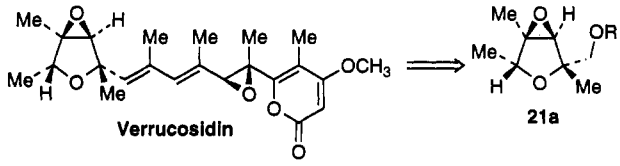


21a[a]	21a[b]	22a[b]
81.80	81.85	79.91
77.29	77.34	73.81
67.88	67.92	66.41
67.46	67.50	66.32
67.30	67.36	64.54
19.83	19.89	18.20
18.54	18.60	14.20
13.84	13.91	13.41

[a] Reference 12, 100 MHz. [b] Present work, 125 MHz.

Selective silylation with TBSCl led to the secondary alcohol **19b** which upon cyclization and desilylation afforded the dihydrofuran **20a**.

Both dihydrofuran **20a** and its diastereomer have been prepared as racemates from 4,5-dimethyl-2-furoic acid by a nonselective route.[11] Upon epoxidation, each affords a mixture of epoxide epimers. One of these (**21a**) was identified through comparison with a degradation product of verrucosidin.[2] Nonracemic epoxy alcohol **21a** has also been synthesized.[12]

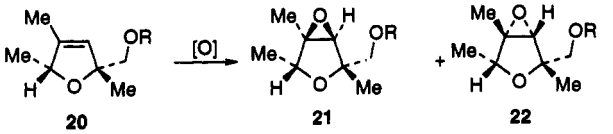


Epoxidation of dihydrofuran alcohol **20a** with *m*-CPBA led to a 10:90 mixture of epoxides **21a** and **22a** in accord with previous findings.[11] A comparison of the ^{13}C-NMR spectral data (Table I) for these isomers with the reported spectrum of authentic **21a** left no doubt as to structure assignment.[12] The reported ^1H-NMR spectrum of **21a** was also in close agreement with that of our material.

As epoxide **21a** represents an attractive precursor to the polyene α-pyrone mycotoxin verrucosidin,[11] it was of interest to improve the ratio of **21a:22a**. According to MM2 calculations,[13] dihydrofurans **20** are essentially planar. Thus, by increasing the bulk of the CH_2OR grouping, it should be possible to favor β-face epoxidation. Accordingly, we prepared a series of ethers, **20b–e**, and examined their epoxidation (Table II). The TBS ether **20b** gave a slightly improved ratio of **21b:22b** (21:79). Both the DPS and TIPS ethers afforded 35:65 mixtures of **21c/d:22c/d**. The use of magnesium monoperoxyphthalic acid (MMPP) for epoxidation[14] gave a nearly 1:1 mixture of epoxides from the TIPS ether **20d**. Surprisingly, the bulky monomethoxytrityl derivative **20e** showed comparable selectivity to the DPS and TIPS ethers. Evidently, the stereochemistry of epoxidations in this system is only

(12) Cha, J. K.; Cooke, R. J. *Tetrahedron Lett.* **1987**, *28*, 5473.
(13) The program Macromodel V3.5 was employed for these calculations. Global minimum multiple conformer searching was achieved with the Monte Carlo subroutine in BATCHMIN through multistep iterations (300–1000) until the minimum energy conformer was found multiple times (10 or more). For a description of the program, see: Mohamad, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W.C. *J. Comput. Chem.* **1990**, *11*, 440. Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379.
(14) Magnesium monoperoxyphthalic acid. Aldrich Chemical Co., Milwaukee, WI.

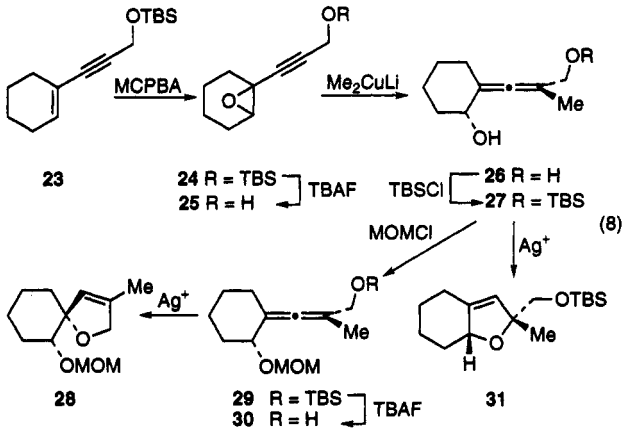
Table II. Epoxidation of Dihydrofurans 20a–e



series	R	[O]	ratio	yield, %
a	H	*m*-CPBA	10:90	98
b	TBS	*m*-CPBA	21:79	72
c	DPS	*m*-CPBA	35:65	97
d	TIPS	*m*-CPBA	35:65	94
d	TIPS	MMPP	46:54	94
e	MMTr	*m*-CPBA	37:63	96

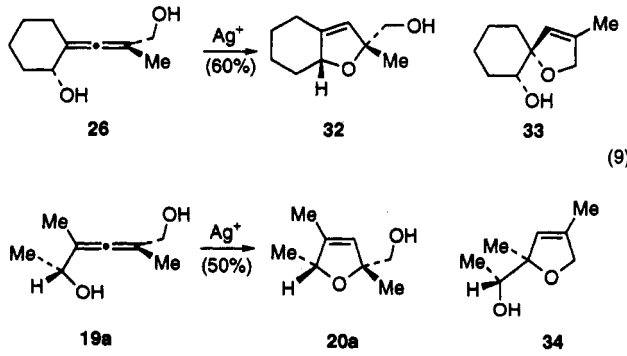
modestly affected by the steric bulk of the ether substituent.

As a final test of the methodology, we examined the conversion of alkynyloxirane **25**[15] to the 2,5-dihydrofurans **28** and **31**. Addition of the Gilman methyl cuprate gave the diol **26** in high yield. Selective silylation and then treatment with $AgNO_3$ led to the fused dihydrofuran **31**. The spiro isomer **28** was obtained by conversion of alcohol **27** to the MOM ether **29** then desilylation and cyclization with $AgNO_3$ (eq 8).



(8)

Interestingly, direct cyclization of diol **26** with $AgNO_3$ afforded only the fused dihydrofuran **32** (eq 9). None of



(9)

the spiro dihydrofuran **33** was detected. Likewise, diol **19a** gave predominantly dihydrofuran **20a** in preference to dihydrofuran **34**. In both cases cyclization of the secondary alcohol is favored, possibly because of preferential complexation of Ag^+ at the less congested end of the allenyl π system.

These findings show that alkynyloxiranes, like their vinyl counterparts, undergo highly anti selective S_N2' displacements with Gilman cuprates. The reaction is assisted by a propargylic hydroxyl substituent. The allenylcarbinol products are readily converted to 2,5-dihydrofurans with complete stereocontrol upon exposure to $AgNO_3$ in aqueous acetone. When a primary propargylic alcohol is employed selective protection allows for the preparation of either 2,5-dihydrofuran regioisomer.

(15) Prepared by Sonogashiro coupling[6] of cyclohexenyl triflate with TBS proparagyl ether.

Experimental Section[16]

(*E*)-6-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-2-hexen-4-yn-1-ol (2a). To a well-stirred solution of iodide **1a**[7] (1.26 g, 6.37 mmol) in Et_2NH (40 mL) were added sequentially $(PPh_3)_2PdCl_2$ (0.224 g, 0.319 mmol), CuI (0.121 g, 0.637 mmol), and TBS-propargyl alcohol (1.63 g, 9.56 mmol). After 20 h, the solution was cooled to 0 °C, quenched with saturated NH_4Cl, layered with Et_2O, and stirred vigorously for 1 h. After addition of EtOAc, the layers were separated, and the organic layer was washed with saturated NH_4Cl, H_2O, and brine and dried over $MgSO_4$. Purification by flash chromatography (silica gel, 50:50 EtOAc/hexane) afforded enyne **2a** (1.37 g, 5.68 mmol, 89%) as a pale yellow liquid: ^{1}H-NMR ($CDCl_3$) δ 5.95 (tq, J = 6.8, 1.5 Hz), 4.41 (s), 4.21 (t, J = 5.9 Hz), 1.80 (td, J = 1.4, 0.70 Hz), 1.28 (t, J = 5.1 Hz), 0.897 (s), 0.112 (s); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 135.5, 120.3, 86.9, 86.0, 59.0, 52.1, 25.8, 18.3, 17.4, -5.1; IR (film) ν 3346 (br), 2213, 1464 cm^{-1}; HRMS (EI) M$^+$ calcd for $C_{13}H_{24}O_2Si$ 240.1546, found 240.1543. Anal. Calcd for $C_{13}H_{24}O_2Si$: C, 64.95; H, 10.06. Found: C, 64.82; H, 10.03.

(*Z*)-6-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-2-hexen-4-yn-1-ol (2b). To a well-stirred solution of iodide **1b**[7] (5.00 g, 25.3 mmol) in Et_2NH (100 mL) was added sequentially $(PPh_3)_2PdCl_2$ (0.886 g, 1.26 mmol), CuI (0.481 g, 2.53 mmol), and TBS-propargyl alcohol (6.45 g, 37.9 mmol). After 12 h, the reaction was quenched and the product isolated as described for **2a**. Purification by distillation (bulb-to-bulb, 110–120 °C, 0.25 Torr) afforded enyne **2b** (5.00 g, 20.8 mmol, 82%) as a pale yellow liquid: ^{1}H-NMR ($CDCl_3$) δ 5.83 (tq, J = 6.8, 1.5 Hz), 4.43 (s), 4.27 (t, J = 6.3 Hz), 1.85 (s), 1.43 (t, J = 5.9 Hz), 0.889 (s), 0.103 (s); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 135.8, 120.2, 92.8, 82.9, 61.1, 52.1, 25.8, 23.0, 18.3, -5.1; HRMS (EI) M - *t*-Bu calcd for $C_9H_{15}O_2Si$ 183.0841, found 183.0840. Anal. Calcd for $C_{13}H_{24}O_2Si$: C, 64.95; H, 10.06. Found: C, 65.13; H, 10.12.

***trans*-6-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-3-methyl-4-hexyn-1-ol (3a).** To a well-stirred solution of enyne **2a** (0.905 g, 3.76 mmol) in CH_2Cl_2 (50 mL), at 0 °C, was added Na_2HPO_4 (1.28 g, 9.03 mmol) and *m*-CPBA (1.30 g, 7.53 mmol). After 10 h, water was added, and the organic layer was washed with saturated $NaHCO_3$, 10% NaOH, and brine and dried over $MgSO_4$ affording epoxide **3a** as a clear, colorless liquid (0.948 g, 3.70 mmol, 98%). A small sample was purified by flash chromatography (silica gel, 50:50 EtOAc/hexane) for further characterization: ^{1}H-NMR ($CDCl_3$) δ 4.30 (s), 3.84 (ddd, J = 12.3, 7.1, 4.5 Hz), 3.69 (ddd, J = 12.3, 6.2, 5.4 Hz), 3.33 (dd, J = 6.2, 4.5 Hz), 1.64 (dd, J = 7.1, 5.4 Hz), 1.52 (s), 0.883 (s), 0.092 (s); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 84.9, 81.4, 64.2, 60.8, 52.0, 51.5, 26.2, 18.9, 18.6, -4.8; IR (film) ν 3422, 1469 cm^{-1}; MS (CI) (M + H)$^+$ 257; (M + NH_4)$^+$ 274; HRMS (EI) M - *t*-Bu calcd for $C_9H_{15}O_3Si$ 199.0790, found 199.0783. Anal. Calcd for $C_{13}H_{24}O_3Si$: C, 60.89; H, 9.43. Found: C, 60.99; H, 9.50.

***cis*-6-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-3-methyl-4-hexyn-1-ol (3b).** To a well-stirred solution of enyne **2b** (2.98 g, 12.4 mmol) in CH_2Cl_2 (50 mL), at 0 °C, was added Na_2HPO_4 (4.22 g, 29.8 mmol) and *m*-CPBA (4.28 g, 24.8 mmol). After 2 h, at 0 °C to rt, water was added, and epoxide **3b** was isolated (as described for **3a**) as a clear, colorless liquid (3.14 g, 12.3 mmol, 99%). A small sample was purified by flash chromatography (silica gel, 50:50 EtOAc/hexane) for further characterization: ^{1}H-NMR ($CDCl_3$) δ 4.29 (s), 3.80 (m), 3.07 (dd, 1H, J = 6.2 Hz), 2.12

(16) For typical experimental protocols and parameters, see: Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 960. We were unable to secure satisfactory C/H analyses for several of the silylated alkynes in this study despite repeated attempts, possibly because of incomplete combustion. These compounds were judged pure by other criteria (^{1}H and ^{13}C NMR, TLC).

(t, 1H, J = 6.3 Hz), 1.53 (s), 0.87 (s), 0.081 (s); MS (CI) $(M + H)^+$ 257; HRMS (EI) M + H calcd for $C_{13}H_{25}O_3Si$ 257.1572, found 257.1571.

***trans*-6-[(*tert*-Butyldimethylsily)oxy]-2,3-epoxy-1-(methoxymethoxy)-3-methyl-4-hexyne (4a).** To a well-stirred solution of alcohol **3a** (0.224 g, 0.874 mmol) in CH_2Cl_2 (30 mL), at 0 °C, was added $(i\text{-Pr})_2NEt$ (0.339 g, 2.62 mmol). After 30 min, MOMCl (0.211g, 2.62 mmol) was added in one portion. After 14 h, at 0 °C to rt, water was added, and the product was isolated by extraction with CH_2Cl_2. Purification by flash chromatography (silica gel, 40:60 EtOAc/hexane) afforded bis ether **4a** (0.214 g, 0.712 mmol, 81%) as a clear liquid: ^{1}H-NMR ($CDCl_3$) δ 4.66 and 4.63 (AB_q, J_{AB} = 6.6 Hz), 4.29 (s), 3.66 (dd, J = 11.6, 5.3 Hz), 3.60 (dd, J = 11.6, 5.7 Hz), 3.34 (t, J = 5.5 Hz), 3.36 (s), 1.50 (s), 0.879 (s), 0.089 (s); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 96.6, 84.5, 80.9, 65.3, 62.1, 55.3, 51.5, 50.4, 25.7, 18.4, 18.2, -5.2; MS (CI) $(M + H)^+$ 301; $(M + NH_4)^+$ 318; HRMS (EI) M - H calcd for $C_{15}H_{27}O_4Si$ 299.1679, found 299.1683. Anal. Calcd for $C_{15}H_{28}O_4Si$: C, 59.96; H, 9.39. Found: C, 60.08; H, 9.34.

***cis*-6-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-1-(methoxymethoxy)-3-methyl-4-hexyne (4b).** The procedure described for **4a** was followed with alcohol **3b** (1.05 g, 4.08 mmol) in CH_2Cl_2 (10 mL). Purification by flash chromatography (silica gel, 30:70 EtOAc/hexane) afforded ether **4b** (1.15 g, 3.83 mmol, 94%) as a faintly yellow liquid: ^{1}H-NMR ($CDCl_3$) δ 4.66 (s), 4.30 (s), 3.82 (dd, 1H, J = 11.5, 4.7 Hz), 3.69 (dd, 1H, J = 11.5, 5.9 Hz), 3.37 (s), 3.09 (dd, 1H, J = 5.9, 4.8 Hz), 1.55 (s), 0.88 (s), 0.091 (s); MS (EI) m/z 269, 255, 239; HRMS (EI) M - OMOM calcd for $C_{13}H_{23}O_2Si$ 239.1467, found 239.1472.

***trans*-2,3-Epoxy-1-(methoxymethoxy)-3-methyl-4-hexyn-6-ol (5a).** To a well-stirred solution of ether **4a** (0.187 g, 0.622 mmol) in CH_2Cl_2 (25 mL), at 0 °C, was added TBAF (0.325g, 1.24 mmol) in one portion. After 19 h, at 0 °C to rt, water was added, and the product was isolated by extraction with CH_2Cl_2. Purification by flash chromatography (silica gel, 50:50 EtOAc/hexane) afforded alcohol **5a** (0.087 g, 0.467 mmol, 75%) as a clear, colorless liquid: ^{1}H-NMR ($CDCl_3$) δ 4.66 and 4.63 (AB_q, J_{AB} = 6.6 Hz), 4.26 (d, J = 6.2 Hz), 3.67 (dd, J = 11.6, 5.4 Hz), 3.61 (dd, J = 11.6, 5.7 Hz), 3.37 (s), 3.36 (t, J = 5.5 Hz), 1.73 (t, J = 6.2 Hz), 1.51 (s); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 96.6, 85.2, 80.7, 65.3, 62.3, 55.4, 50.7, 50.5, 18.4; IR (film) ν 3422, 1256 cm^{-1}; MS (CI) $(M + H)^+$ 187; $(M + NH_4)^+$ 204; HRMS (EI) M - MOM calcd for $C_7H_9O_3$ 141.0552, found 141.0558. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.99; H, 7.58.

***cis*-2,3-Epoxy-1-(methoxymethoxy)-3-methyl-4-hexyn-6-ol (5b).** The procedure described for **5a** was followed with ether **4b** (1.45 g, 4.83 mmol) in THF (35 mL). Purification by flash chromatography (silica gel, 70:30 EtOAc/hexane) gave alcohol **5b** (0.778 g, 4.18 mmol, 87%) as a clear liquid: ^{1}H-NMR ($CDCl_3$) δ 4.70 and 4.65 (AB_q, J_{AB} = 6.6 Hz), 4.24 (s), 3.77 (m), 3.38 (s), 3.09 (t, J = 5.5 Hz), 1.55 (s); MS (CI) $(M + H)^+$ 187; $(M + NH_4)^+$ 204; HRMS (EI) M - OCH_3 calcd for $C_8H_{11}O_3$ 155.0708, found 155.0708. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.90; H, 7.53.

***rel*-(*2S,4S*)-1-(Methoxymethoxy)-3,5-dimethyl-3,4-hexadiene-2,6-diol (6a).** To a well-stirred solution of CuI (0.370 g, 1.94 mmol) in THF (20 mL) under Ar at -25 °C was added CH_3Li (2.80 mL of a 1.4 M solution in Et_2O) dropwise. After 30 min, epoxide **5a** (0.072 g, 0.387 mmol) was added in THF (1 mL). After 12 h, at -23 °C to rt, the reaction was quenched with 1:1 saturated NH_4Cl/3% NH_4OH solution (exothermic) and then layered with Et_2O and the resulting solution stirred for 1 h. The product was isolated by extraction with EtOAc. Purification by flash chromatography (EtOAc) afforded 0.059 g (0.290 mmol, 75%) of a 90:10 mixture of allene **6a** (*anti*:*syn* > 90:10) and the protonolysis product as a clear liquid: ^{1}H-NMR ($CDCl_3$) δ 4.63 and 4.60 (AB_q, J_{AB} = 6.6 Hz), 4.10 (m), 3.93 (m), 3.62 (dd, J = 10.4, 3.7 Hz), 3.56 (dd, J = 10.4, 5.3 Hz), 3.32 (s), 2.90 (m), 1.70 (s), 1.66 (s); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 195.3, 104.2, 103.9, 96.8, 71.4, 70.1, 63.4, 55.4, 15.9, 15.6.

***rel*-(*2R,4S*)-1-(Methoxymethoxy)-3,5-dimethyl-3,4-hexadiene-2,6-diol (6b).** The procedure described for **6a** was employed with epoxide **5b** (0.150 g, 0.806 mmol). Purification by flash chromatography (EtOAc) afforded 0.116 g (0.574 mmol, 71%) of a 90:10 mixture of allene **6b** (*anti*:*syn* > 93:7) and the protonolysis product as a clear liquid: ^{1}H-NMR ($CDCl_3$) δ 4.65 (s), 4.18 (m), 4.00 (m), 3.66 (dd, J = 10.4, 4.1 Hz), 3.54 (dd, J = 10.4, 6.5 Hz), 3.37 (s), 2.85 (d, J = 5.2 Hz), 2.46 (t, J = 5.3 Hz), 1.74 (s), 1.67 (s); MS (CI) $(M + H)^+$ 203; $(M + NH_4)^+$ 220; HRMS (EI) M - OCH_3 calcd for $C_9H_{15}O_3$ 171.1021, found 171.1017. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.19; H, 9.01.

***rel*-(*2S,4S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-(methoxymethoxy)-3,5-dimethyl-3,4-hexadien-2-ol (9a).** To a well-stirred solution of diol **6a** (0.070 g, 0.346 mmol, *anti*:*syn* > 90:10) in CH_2Cl_2 (7 mL) was added Et_3N (0.046 g, 0.450 mmol), DMAP (0.002 g, 0.017 mmol), and TBSCl (0.078 g, 0.519 mmol). After 19 h, additional Et_3N (0.046 g, 0.450 mmol) and TBSCl (0.030 g, 0.199 mmol) were added. After 5 h, water was added, and the product was isolated by extraction with CH_2Cl_2. Purification by flash chromatography (50:50 EtOAc/hexane) afforded ether **9a** (0.099 g, 0.313 mmol, 90%, *anti*:*syn* > 90:10) as a clear liquid: ^{1}H-NMR ($CDCl_3$) δ 4.67 and 4.64 (AB_q, J_{AB} = 6.6 Hz), 4.16 (m), 4.05 (s), 3.68 (dd, J = 10.5, 3.1 Hz), 3.47 (dd, J = 10.5, 7.8 Hz), 3.37 (s), 2.42 (d, J = 4.6 Hz), 1.72 (s), 1.68 (s), 0.88 (s), 0.042 (s); IR (film) ν 3455 (br), 1970, 1464 cm^{-1}.

***rel*-(*2R,4S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-1-(methoxymethoxy)-3,5-dimethyl-3,4-hexadien-2-ol (9b).** To a well-stirred solution of diol **6b** (0.108 g, 0.534 mmol, *anti*:*syn* > 93:7) in CH_2Cl_2 (8 mL) was added imidazole (0.044 g, 0.641 mmol) followed by TBSCl (0.105 g, 0.694 mmol). After 2 h, water was added, and the product was isolated by extraction with CH_2Cl_2. Purification by flash chromatography (50:50 EtOAc/hexane) afforded ether **9b** (0.149 g, 0.471 mmol, 88%, *anti*:*syn* > 93:7) as a clear liquid: ^{1}H-NMR ($CDCl_3$) δ 4.65 (s), 4.15 (m), 4.04 (d, J = 1.7 Hz), 3.65 (dd, J = 10.4, 3.2 Hz), 3.47 (dd, J = 10.4, 7.6 Hz), 3.36 (s), 2.46 (d, J = 4.1 Hz), 1.71 (s), 1.67 (s), 0.865 (s), 0.0324 (s); MS (CI) $(M + H)^+$ 317; $(M + NH_4)^+$ 334; HRMS (EI) M - CH_3 calcd for $C_{15}H_{29}O_4Si$ 301.1835, found 301.1824. Anal. Calcd for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.55; H, 10.14.

***rel*-(*2S,5S*)-2,4-Dimethyl-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-5-[(methoxymethoxy)methyl]-2,5-dihydrofuran (11a).** To a well-stirred solution of allene **9a** (0.042 g, 0.133 mmol, *anti*:*syn* > 90:10) in 1.5 mL of acetone and 1.0 mL of H_2O was added $AgNO_3$ (0.018 g, 0.106 mmol) and $CaCO_3$ (0.011 g, 0.106 mmol) in the dark. After 20 h, water was added, and the product was isolated by extraction with EtOAc. Purification by flash chromatography (silica gel, 50:50 EtOAc/hexane) afforded dihydrofuran **11a** (0.036 g, 0.114 mmol, 86%, *cis*:*trans* > 90:10) as a clear, colorless liquid: ^{1}H-NMR ($CDCl_3$) δ 5.45 (t, J = 1.7 Hz), 4.75 (m), 4.64 and 4.62 (ABq, J_{AB} = 6.5 Hz), 3.63 (dd, J = 10.4, 3.2 Hz), 3.50 (dd, J = 10.4, 6.1 Hz), 3.48 (m), 3.34 (s), 1.69 (t, J = 1.2 Hz), 1.22 (s), 0.855 (s), 0.0005 (s); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 135.2, 128.5, 96.7, 89.9, 86.4, 70.2, 69.9, 55.2, 25.9, 23.2, 18.3, 12.6, -5.39, -5.43; IR (film) ν 1671 cm^{-1}.

***rel*-(*2S,5R*)-2,4-Dimethyl-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-5-[(methoxymethoxy)methyl]-2,5-dihydrofuran (11b).** The procedure described for **11a** was employed with allene **9b** (0.125 g, 0.395 mmol, *anti*:*syn* > 93:7; 12 h). Purification by flash chromatography (silica gel, 20:80 EtOAc/hexane) afforded dihydrofuran **11b** (0.097 g, 0.306 mmol, 78%, *trans*:*cis* = 93:7 by GC) as a clear, colorless liquid: ^{1}H-NMR ($CDCl_3$) δ 5.44 (t, J = 1.7 Hz), 4.72 (m), 4.66 and 4.64 (ABq, J_{AB} = 9.1 Hz), 3.67 (dd, J = 10.7, 3.1 Hz), 3.52 (dd, J = 10.7, 5.2 Hz), 3.48 (m), 3.35 (s), 1.71 (t, J = 1.2 Hz), 1.23 (s), 0.851 (s), 0.0005 (s); MS (CI) $(M + H)^+$ 317; $(M + NH_4)^+$ 334; HRMS (EI) M - OCH_3 calcd for $C_{15}H_{29}O_3Si$ 285.1886, found 285.1887. Anal. Calcd for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.55; H, 10.20.

***rel*-(*3S,5R*)-2,4-Dimethyl-2,3-hexadiene-1,5-diol (19a).** To a well-stirred solution of CuI (2.29g, 12.0 mmol) in THF (40 mL) at -25 °C was added CH_3Li (17.2 mL of a 1.4 M solution in Et_2O). After 30 min, alkynyloxirane **18** (0.760 g, 6.02 mmol) in THF (2.0 mL) was added in one portion. After 10 s, CH_3I (3.42 g, 24.1 mmol) was added followed immediately by quenching with 1:1 3% NH_4OH/saturated NH_4Cl (20 mL, dropwise, exothermic!). The solution was layered with Et_2O (20 mL) and vigorously stirred for 1 h. The product was isolated by extraction with Et_2O. Purification by flash chromatography (silica gel, Et_2O) afforded 0.602 g (4.23 mmol, 70%) of a 93:7 mixture of diol **19a** (*anti*:*syn* > 98:2) and the protonolysis product as a clear, colorless liquid: ^{1}H-NMR ($CDCl_3$) δ 4.16 (q, J = 6.4 Hz), 3.95 and 3.90 (AB_q, J_{AB} = 13.0 Hz), 3.27 (bs), 1.64 (s), 1.63 (s), 1.23 (d, J = 6.4 Hz): ^{13}C-NMR ($CDCl_3$) δ 195.6, 106.3, 101.8, 69.0, 63.8, 21.4, 15.9, 14.3; MS

(CI) $(M + NH_4)^+$ 160; HRMS (EI) M − H_2O calcd for $C_8H_{12}O$ 124.0888, found 124.0887.

***rel*-(3*S*,5*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,4-dimethyl-2,3-hexadien-5-ol (19b).** The procedure described for **9a** was followed with diol **19a** (0.491 g, 2.95 mmol, *anti*:*syn* > 98:2; 15 h). Purification by flash chromatography (silica gel, 20:80 Et_2O/hexane) afforded ether **19b** (0.650 g, 2.53 mmol, 86%) as a clear, colorless liquid: ^{1}H-NMR ($CDCl_3$) δ 4.14 (q, J = 6.4 Hz), 4.05 (s), 1.684 (s), 1.683 (s), 1.25 (d, J = 6.4 Hz), 0.878 (s), 0.045 (s); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 196.1, 105.4, 103.1, 69.2, 65.6, 26.2, 22.4, 18.7, 16.2, 15.4, −4.88, −4.93; MS (CI) $(M + H)^+$, 257; $(M + NH_4)^+$ 274; HRMS (EI) M − H calcd for $C_{14}H_{27}O_2Si$ 255.1780, found 255.1779. Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.01. Found: C, 65.72; H, 11.07.

***rel*-(2*R*,5*R*)-2-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,4,5-trimethyl-2,5-dihydrofuran (20b).** The procedure described for **11a** was followed with allene **19b** (0.217 g, 0.846 mmol, *anti*:*syn* > 98:2). Purification by flash chromatography (silica gel, 20:80 Et_2O/hexane) gave dihydrofuran **20b** (0.176 g, 0.686 mmol, 81%) as a clear, colorless liquid: ^{1}H-NMR ($CDCl_3$) δ 5.33 (t, J = 1.6 Hz), 4.71 (q, J = 6.4 Hz), 3.46 and 3.41 (AB_q, J_{AB} = 9.7 Hz), 1.64 (t, J = 1.3 Hz), 1.22 (d, J = 6.4 Hz), 1.20 (s), 0.868 (s), 0.0171 (s); ^{13}C-NMR ($CDCl_3$) δ 139.7, 126.5, 89.5, 83.6, 71.2, 26.3, 23.6, 21.6, 18.7, 12.6, −4.97, −5.02; MS (CI) $(M + H)^+$, 257; $(M + NH_4)^+$ 274; HRMS (EI) M − H calcd for $C_{14}H_{27}O_2Si$ 255.1780, found 255.1782. Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.01. Found: C, 65.65; H, 10.97.

***rel*-(2*R*,5*R*)-2-(Hydroxymethyl)-2,4,5-trimethyl-2,5-dihydrofuran (20a).** To a solution of ether **20b** (0.645 g, 2.51 mmol) was added TBAF (7.5 mL of a 1.0 M solution in THF). After 2 h, water was added, and the product was isolated by extraction (Et_2O, H_2O, brine, $MgSO_4$). Solvent was removed to afford alcohol **20a**[11] (0.357 g, 2.51 mmol, 100%) as a clear, colorless liquid. A small quantity was purified by flash chromatography (silica gel, 1:1 Et_2O/hexane) for characterization: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.25 (t, J = 1.7 Hz), 4.74 (qq, J = 2.0, 6.4 Hz), 3.45 and 3.41 (AB_q, J_{AB} = 11.4 Hz), 1.80 (bs), 1.67 (dd, J = 1.5, 1.1 Hz), 1.26 (d, J = 6.4 Hz), 1.19 (s): ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 141.0, 125.1, 89.4, 82.9, 68.3, 22.8, 21.0, 12.3 [lit.[11] ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 5.3 (br s), 4.77 (q, J = 7.0 Hz), 3.49 (s), 2.48 (br s), 1.7 (d, J = 1 Hz), 1.29 (d, J = 7 Hz), 1.2 (s)].

***rel*-(2*S*,3*R*,4*S*,5*R*)-2-[[(Triisopropylsilyl)oxy]methyl]-3,4-epoxy-2,4,5-trimethyl-2,3,4,5-tetrahydrofuran (22d).** The procedure described for **3a** was employed with dihydrofuran **20d** (0.158g, 0.529 mmol, 15 h). The product isolated by extraction with CH_2Cl_2 was a 35:65 mixture of epoxides **21d** and **22d** (0.157 g, 0.499 mmol, 94%), purified by flash chromatography (silica gel, 20:80 Et_2O/hexane):

21d: ^{1}H-NMR ($CDCl_3$) δ 4.13 (q, J = 6.8 Hz), 3.61 and 3.60 (AB_q, J_{AB} = 9.9 Hz), 3.55 (s), 1.42 (s), 1.25 (s), 1.20 (d, J = 6.8 Hz), 1.05 (m); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 82.3, 77.7, 69.4, 68.3, 68.0, 20.5, 18.9, 18.37, 18.36, 14.4, 12.3; MS (CI) $(M + H)^+$ 315, $(M + NH_4)^+$ 332; HRMS (EI) M − *i*-Pr calcd for $C_{14}H_{27}O_3Si$ 271.1729, found 271.1726. Anal. Calcd for $C_{17}H_{34}O_3Si$: C, 64.92; H, 10.90. Found: C, 65.03; H, 10.97.

22d: ^{1}H-NMR ($CDCl_3$) δ 3.85 (q, J = 6.2 Hz), 3.75 and 3.46 (AB_q, J_{AB} = 8.8 Hz), 3.37 (s), 1.42 (s), 1.20 (s), 1.16 (d, J = 6.2 Hz), 1.04 (m); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 80.3, 73.8, 66.2, 65.8, 65.5, 18.6, 18.0, 17.9, 14.0, 13.8, 11.9; MS (CI) $(M + H)^+$ 315, $(M + NH_4)^+$ 332; HRMS (EI) M − *i*-Pr calcd for $C_{14}H_{27}O_3Si$ 271.1729, found 271.1732. Anal. Calcd for $C_{17}H_{34}O_3Si$: C, 64.92; H, 10.90. Found: C, 64.89; H, 10.98.

***rel*-(2*S*,3*S*,4*R*,5*R*)-2-(Hydroxymethyl)-3,4-epoxy-2,4,5-trimethyl-2,3,4,5-tetrahydrofuran (21a).** To a well stirred solution of silyl ether **21c** (0.073 g, 0.184 mmol) in CH_2Cl_2 (1.0 mL) was added TBAF (0.096 g, 0.368 mmol). After 20 h, water was added, and the product was isolated by extraction (CH_2Cl_2, H_2O, brine, $MgSO_4$). Purification by flash chromatography (silica gel, 50:50 EtOAc/hexane) afforded alcohol **21a** (0.024 g, 0.152 mmol, 82%) as a clear, colorless liquid: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 4.17 (q, J = 6.8 Hz), 3.53 (bs), 3.40 (s), 1.80 (bs), 1.44 (s), 1.25 (s), 1.22 (d, J = 6.8 Hz); ^{1}H-NMR (C_6D_6, 500 MHz) δ 4.10 (q, J = 6.8 Hz), 3.23 and 3.17 (AB_q, J_{AB} = 10.8 Hz), 3.02 (s), 1.31 (s), 1.03 (s), 0.877 (d, J = 6.8 Hz) [lit.[12] ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.19 (q, J = 6.8 Hz), 3.49 (s), 3.43 (s), 1.46 (s), 1.27 (s), 1.25 (d, J = 6.8 Hz)]; MS (CI) $(M + H)^+$ 159, $(M + NH_4)^+$ 176; HRMS (CI) M + H calcd for $C_8H_{15}O_3$ 159.1021, found, 159.1024.

***rel*-(2*S*,3*R*,4*S*,5*R*)-2-(Hydroxymethyl)-3,4-epoxy-2,4,5-trimethyl-2,3,4,5-tetrahydrofuran (22a).** The procedure described for **21a** was employed with silyl ether **22c** (0.096g, 0.242 mmol, 12 h). Purification by flash chromatography (silica gel, Et_2O) afforded alcohol **22a** (0.030 g, 0.190 mmol, 78%) as a clear, colorless liquid: ^{1}H-NMR ($CDCl_3$) δ 3.87 (q, J = 6.2 Hz), 3.68 and 3.61 (AB_q, J_{AB} = 11.1 Hz), 3.32 (s), 2.26 (bs), 1.42 (s), 1.19 (d, J = 6.2 Hz), 1.13 (s); ^{1}H-NMR (C_6D_6) δ 3.70 and 3.62 (AB_q, J_{AB} = 10.6 Hz), 3.52 (q, J = 6.2 Hz), 2.91 (s), 2.01 (bs), 1.11 (d, J = 6.2 Hz), 0.986 (s), 0.953 (s); MS (CI) $(M + H)^+$ 159, $(M + NH_4)^+$ 176; HRMS (CI) M + H calcd for $C_8H_{15}O_3$ 159.1021, found, 159.1015. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: 60.49; H, 8.87.

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Supplementary Material Available: Experimental procedures for compounds **7–8**, **10**, **12–18**, **19c–d**, **20c–e**, **21–22(a,b,c,e)**, and **23–32** and selected ^{1}H and ^{13}C NMR spectra (46 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.