Pergamon

Tetrahedron 54 (1998) 10779–10788

TETRAHEDRON

Chiral Acyl Radical Equivalents : 5-*exo* Cyclization of Conformationally Constrained 1,3-Dioxolanyl Radicals

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Received 21 April 1998; accepted 25 June 1998

Abstract : Chiral 1,3-dioxolan-2-yl radicals derived from acetals **8** and **9** underwent intramolecular hydrogen abstraction followed by 5-exo-trig cyclization on treatment with tributyltin hydride and AIBN with modest and opposite stereoselectivities. The more highly substituted substrate **13** took part in a similar cascade, triggered by a 5-*exo*-dig cyclization. In this example the more highly substituted nature of the alkene in the stereocontrolled cyclization resulted in essentially complete diastereoselectivity.

The field of asymmetric induction in radical reactions has expanded in an explosive manner over the past ten years. High degrees of stereocontrol have been reached through the use of chiral auxiliaries[1] and thanks to the complexing properties of Lewis acids further progress continues to be made.[2] The enantioselective catalysis of radical reactions has now been reported.[3]

The temporary connection of a chiral diol *via* an acetal function either to the radical acceptor[4] or to the radical donor can result in excellent diastereomeric excess.[5,6]

In a previous study we investigated stereoinduction in 5-*exo* cyclizations in which the auxiliary diol was directly linked to the radical center, that is with the radical localized on the acetal carbon.[5] Simple C_2-symmetric 1,3-dioxanyl radicals were shown to be too flexible to provide high diastereomeric excess, as they preferentially adopt a twist-boat conformation in the transition state for cyclization (Scheme 1).[5,7]

Scheme 1

The six-membered ring must be kept in a chair conformation in order for the two diastereotopic faces of the double bond to be discriminated thanks to shielding by the axial directing group. Sterically constrained 1,3-dioxabicyclo[4.4.0]decan-2-yl radicals - readily available from camphor sulphonic acid - possess the requisite property.

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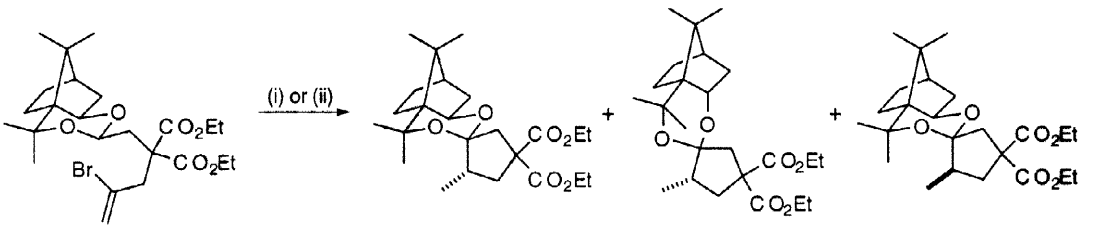
0040-4020/98/$ - see front matter
PII: S0040-4020(98)00633-4

At room temperature, stereoinduction was total (Scheme 2) and the methylcyclopentanone was obtained with 90% enantiomeric excess, after hydrolysis under conditions which minimized the concomitant epimerization.

Scheme 2



(i)	74%	84	:	11	:	5
(ii)	51%	87	:	13	:	0

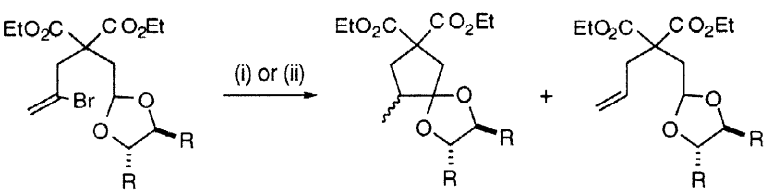
(i) Bu_3SnCl, $NaBH_3CN$, AIBN, tBuOH reflux; (ii) Bu_3SnH, AIBN, PhH, hv, 20°C

However, we noticed that, with this auxiliary, stereoinduction was slightly lowered when the terminal carbon of double bond was substituted.[5]

With simple C_2-symmetric 1,3-dioxolanyl radicals, no selectivity was induced when R = Me,[5,8] and it was necessary to increase the steric bulk of the directing substituents in order to reach an acceptable diastereomeric excess when the cyclization was carried out at room temperature (Scheme 3).

We report in this article, how stereoelectronic considerations led us to design rigid 1,3-dioxabicyclo[4.3.0]nonan-2-yl radicals which provided total stereoinduction with highly substituted double bonds.

Scheme 3

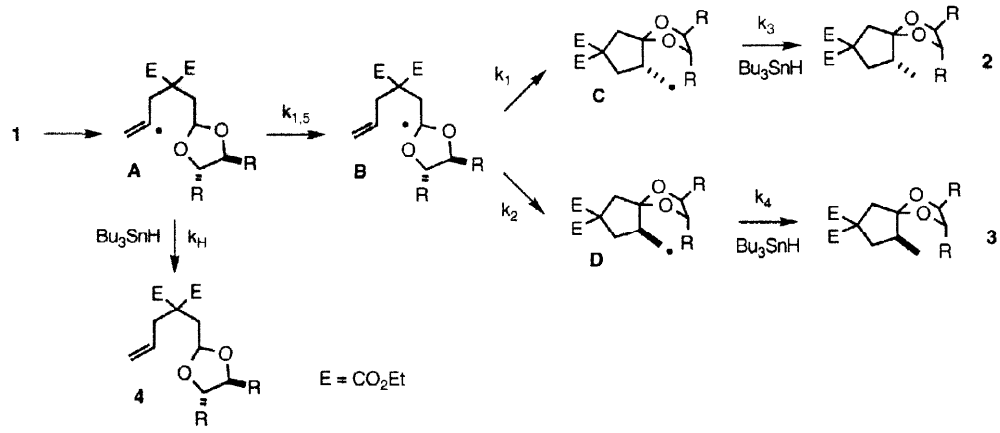


1	2:3	4
a(i) : R=Me	45% (50:50)	not determined
b(i) : R=CH_2OBn	45% (58:42)	
c(i) : R=CMe_2OMe	71% (73:27)	
c(ii) : "	64% (82:18)	

(i) Bu_3SnCl, $NaBH_3CN$, AIBN, tBuOH, 80°C; (ii) Bu_3SnH, AIBN, PhH, hv, 20°C

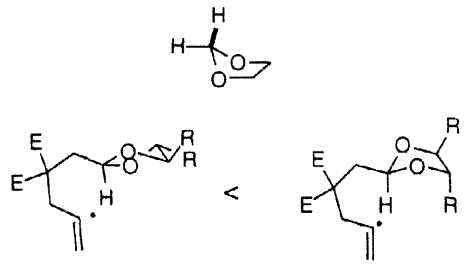
The results reported in Scheme 3 merit closer scrutiny. As shown in Scheme 4, the bimolecular reduction of vinyl radical **A** by tin hydride, leading to **4**, competes with 1,5-hydrogen shift giving radical **B**. The yield of cyclized products is a direct function of this competition: the higher the rate of hydrogen migration, the higher the yield of cyclized products (**2+3**).[9] Thus, it is noteworthy in Scheme 3 that making R bulkier, not only improved the diastereomeric ratio but also increased the overall yield of cyclization products.

Scheme 4



The rate of hydrogen abstraction is controlled by stereoelectronic factors.[10] Though the most favorable geometry in the transition state, a 180° C-H-C angle, cannot be attained in the rearrangement of vinyl radicals, it has been calculated that a bent transition structure is not prohibitive and that distortion costs little energy.[11] At the same time, the p-type lone pairs on oxygens can interact with the σ anti-bonding orbital of the C-H bond, provided that they are synperiplanar. This results in stereoelectronically controlled weakening of the C-H bond adjacent to the oxygen atoms with concomitant acceleration of 1,5-migration. According to Ingold,[10a] if the five-membered dioxolane ring adopts an envelope conformation with C-1 out-of-plane then both oxygens are poised to accelerate the hydrogen atom abstraction.

Figure 1



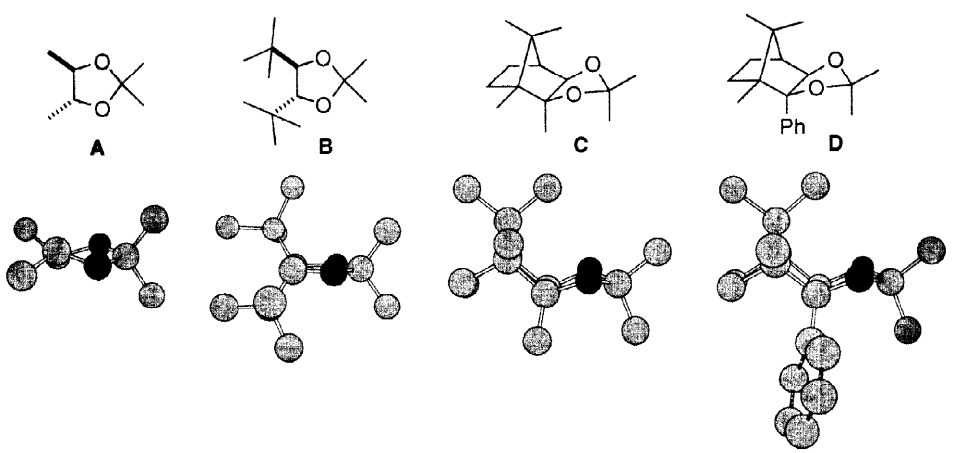
Accordingly, we reasoned that the bulkier R groups in Scheme 3 increased the population of the reactive envelope conformer, as shown in Fig. 1, leading to the higher yields of cyclized product. It is likely that the same stereoelectronic considerations apply to the next step, that is the 5-*exo* cyclization, where optimum σ-p overlap between the incoming C-C bond and the p-type lone pairs should have repercussions on the rate of the reaction. Moreover, since the pseudo-axial substituent in the envelope should not screen the two diastereotopic faces of the double bond in the same manner (Fig. 2), stereoinduction should also be maximized in this conformation.

Figure 2

In our previous publication,[5] we noticed that isopropylidene acetals are good first approximations for the transition states of the cyclizations since a good correlation was found with the experimental selectivities. Molecular mechanics calculations (Chem3D Pro) show that the dioxolane ring adopts a twist conformation when R is a methyl group. Owing to repulsive interactions, as the size of the R groups increases the dioxolane moves progressively to a planar conformation and then to an envelope in rigid systems (Fig. 3). These modifications of conformation are in good agreement with the highest yield and selectivity being reached with substrate **1c** in the first series of dioxolanyl radicals (Scheme 3).

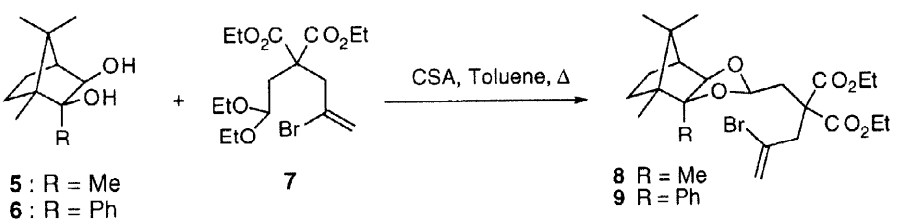
With our opinion bolstered by these calculations (Fig. 3; **C-D**), we have tried, as in the dioxane series, to constrain the dioxolane ring to an envelope conformation. To reach this objective we prepared diols **5** and **6**, both easily available from camphorquinone.[12]

Figure 3



Acetals **8** and **9**, precursors of 1,3-dioxabicyclo[4.3.0]nonan-2-yl radicals, were prepared *via* transacetalization with **7** (Scheme 5). They were subsequently submitted to reduction with tributyltin hydride under the experimental conditions previously employed for the cyclization of 1,3-dioxanyl radicals,[5] with the results outlined in Scheme 6.

Scheme 5

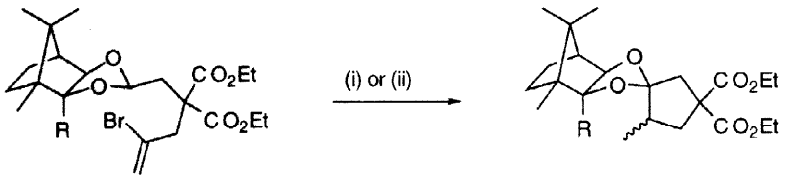


5 : R = Me
6 : R = Ph

7

8 R = Me
9 R = Ph

Scheme 6

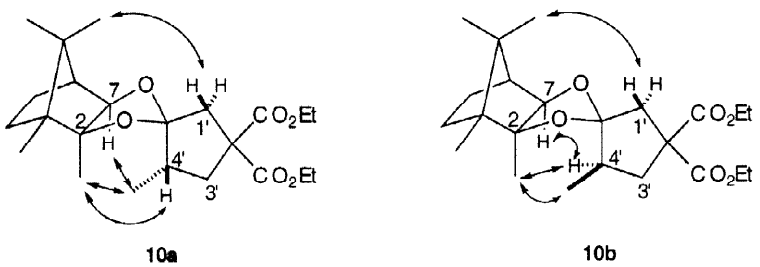


8 R = Me (i)	77%	**10 a,b** (71 : 29)
8 R = Me (ii)	70%	**10 a,b** (78 : 22)
9 R = Ph (i)	67%	**11 a,b** (71 : 29)

(i) Bu_3SnCl, $NaBH_3CN$, AIBN, *t* BuOH reflux; (ii) Bu_3SnH, AIBN, PhH, hv, 20°C

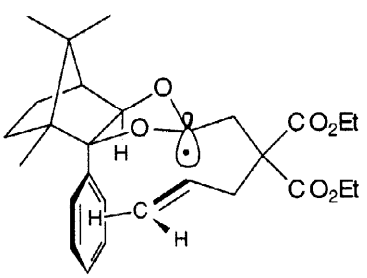
The structures of **10a** and **10b** were assigned from NOESY spectra of pure samples isolated by HPLC. These data are summarized in Figure 4.

Figure 4



Unfortunately, the separation of **11a** and **11b** could not be achieved. However, the ^1H NMR data from the mixture of these isomers gave evidence of an unexpected shielding of the methyl doublet in the major isomer (0.6 ppm in **11a** versus 0.9 ppm in **11b**). This strongly suggests that the methyl protons should suffer anisotropic screening due to the aromatic ring. Therefore, it appears that the phenyl substituted auxiliary induces the opposite stereoselectivity compared to the methyl substituted one. Attractive edge to face interactions[13] between the phenyl ring and the double bond might be responsible for this reversal of face selectivity (Fig. 5).

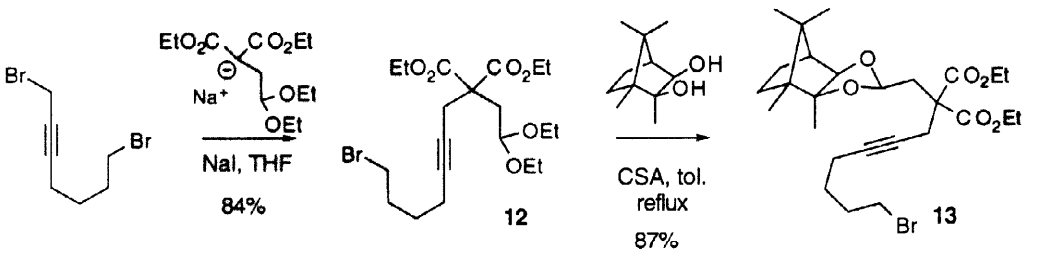
Figure 5



The results in Scheme 6 deserve further comment: as expected, the overall yields were quite good, and even superior to those obtained with **1c** or for the cyclization of 1,3-dioxanyl radicals (Scheme 2). However, there was no significant gain in diastereoselectivity. This might be due to insufficient

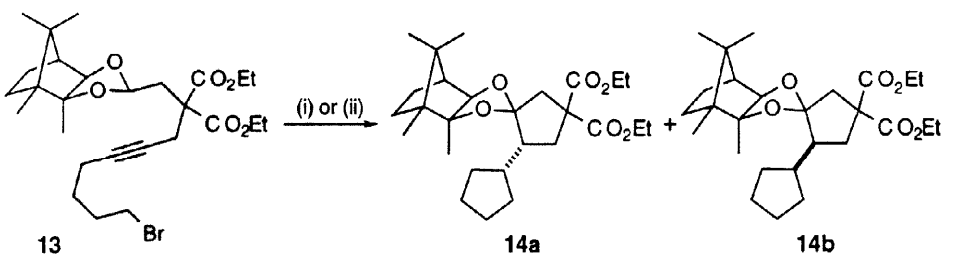
bond and the methyl (or the phenyl group) in the transition state. We reasoned, therefore, that a higher selectivity might be expected using a more hindered trisubstituted double bond, as formed from **13**, as the radical trap. The synthesis of **13** and its cyclization are summarized in schemes 7 and 8.

Scheme 7



Bromoacetal **12**, easily available from 1,7-dibromohept-2-yne, was transformed into **13** under standard transacetalization conditions. The cyclization of **13**, performed at 80 °C and at 20 °C, led to a mixture of isomers **14a** and **14b** in 96:4 and 99:1 ratios, respectively (Scheme 8). At room temperature, due to the increased steric bulk of the double bond, formed through the 5-*exo-dig* cyclization of the primary radical and subsequent 1,5-hydrogen transfer, stereoinduction was nearly complete.

Scheme 8



(i)	72%	96	:	4
(ii)	65%	99	:	1

(i) Bu_3SnCl, $NaBH_3CN$, AIBN, tBuOH reflux; (ii) Bu_3SnH, AIBN, PhH, hv, 20°C

In conclusion, careful consideration of conformational and stereoelectronic effects of 1,3-dioxolan-2-yl radicals has enabled us to design and prepare precursors to constrained 1,3-dioxabicyclo[4.3.0]nonan-2-yl radicals. The cyclization of these radicals in the 5-*exo* manner, onto a trisubstituted alkene took place with essentially complete control of diastereoselectivity. These results nicely complement those obtained earlier with 1,3-dioxabicyclo[4.4.0]decan-2-yl radicals when 100% stereoinduction was achieved for cyclization onto terminal alkenes. Further modification of the auxiliaries, designed to allow hydrolysis under non-epimerizing conditions, is under way.

Experimental Section

General procedures. ^1H NMR spectra were recorded in $CDCl_3$ at 200 or 400 MHz and ^{13}C NMR spectra in $CDCl_3$ at 50.3 MHz as indicated. Chemical shifts (δ) are in ppm downfield from tetramethylsilane and coupling constants (J) are in Hz. All solvents were distilled by standard techniques. LC is column chromatography on silica gel. Semi-preparative HPLC were performed on a

Waters Model 610 apparatus, fitted in series with two columns (25 x 100 mm) Prep Nova-Pak, HR silica 6 µm 60 Å , and coupled to a R 401 refractometer. 2-*exo*-Hydroxy-1-methyl-*exo*-borneol (**5**) and 2-*exo*-Hydroxy-1-phenyl-*exo*-borneol (**6**) were prepared according to known procedures from camphorquinone.[12]

Diethyl 2-(2-Bromoallyl)-2-(1,2,10,10-tetramethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}]dec-4-ylmethyl)malonate (8).

A solution of **7** (316 mg, 0.8 mmol), 2-*exo*-hydroxy-1-methyl-*exo*-borneol **5** (167 mg, 0.88 mmol) and camphorsulfonic acid (0.1 equiv.) in toluene, was heated at reflux for 2 h. After the toluene-ethanol azeotrope had been distilled off, the concentrated solution was neutralized with Et_3N. After concentration *in vacuo*, the residue was purified by LC on silica gel (0 to 5% EtOAc/pentane) which led to **8** (310 mg, 80%).^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.79 (s, 3H), 0.72-0.87 (superimposed m, 1H), 0.88 (s, 3H), 1.11 (s, 3H), 1.15 (s, 3H), 1.23 (t, 6H, *J* = 7.1), 1.13-1.30 (superimposed m, 2H), 1.58-1.77 (m, 1H), 1.86 (d, 1H, *J* = 5.1), 2.48 (m, 2H), 3.22 (s, 2H), 3.47 (s, 1H), 4.17 (q, 4H, *J* = 7.1), 4.71 (t, 1H, *J* = 5.4), 5.58 (d, 1H, *J* = 1.7), 5.75 (broad s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 9.3 (CH_3), 13.7 (2 x CH_3), 18.9 (CH_3), 20.9 (CH_3), 23.1 (CH_2), 23.3 (CH_3), 29.6 (CH_2), 33.5 (CH_2), 43.0 (CH_2), 47.5 (CH), 48.2 (C), 50.5 (C), 54.7 (C), 61.5 (2 x CH_2), 89.1 (CH), 89.7 (C), 98.0 (CH), 122.4 (CH_2), 126.9 (C), 169.8 (C), 169.8 (C). Anal. Calcd for $C_{23}H_{35}O_6Br$: C, 56.68; H, 7.24. Found : C, 56.57; H, 7.22.

Diethyl 2-(2-Bromoallyl)-2-(2-phenyl-1,10,10-trimethyl-3,5-dioxatricyclo[5.2.1.0^{2,6}] dec-4-ylmethyl)malonate (9).

Under the same experimental conditions, transacetalization of **7** (395 mg, 1 mmol) with 2-*exo*-hydroxy-1-phenyl-*exo*-borneol **6** (271 mg, 1.1 mmol) led after purification on silica gel (0 to 3% EtOAc/pentane) to **9** (270 mg, 50%). ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.87 (s, 6H), 0.87-1.3 (superimposed m, 3H), 1.19 (t, 3H, *J* = 7.1), 1.21 (t, 3H, *J* = 7.1), 1.29 (s, 3H), 1.63-1.90 (m, 1H), 2.05 (d, 1H, *J* = 4.9), 2.48 (d, 2H, *J* = 5.1), 3.10 (AB quartet, 2H, J_{AB} = 15.4), 4.33 (t, 1H, *J* = 5.2), 4.36 (broad s, 1H), 4.04-4.37 (m, 4H), 5.44-5.49 (m, 2H), 7.10-7.40 (m, 4H), 7.50-7.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 9.6 (CH_3), 13.6 (2 x CH_3), 21.0 (CH_3), 23.4 (CH_2), 23.7 (CH_3), 29.1 (CH_2), 33.2 (CH_2), 42.4 (CH_2), 47.6 (CH), 50.0 (C), 51.2 (C), 54.6 (C), 61.5 (CH_2), 61.5 (CH_2), 87.0 (CH), 94.4 (C), 98.4 (CH), 122.2 (CH_2), 126.5 (CH), 126.9 (C), 127.2 (2 x CH), 127.9 (CH), 128.4 (CH), 140.1 (C), 169.7 (2 x C). Anal. Calcd for $C_{28}H_{37}O_6Br$: C, 61.20; H, 6.79. Found : C, 61.15; H, 6.87.

General procedures for radical cyclizations.

Method A : In a typical experiment AIBN (7 mg, 0.4 mmol, 0.2 equiv) dissolved in benzene (1 mL) was added by portions over 10 h to a refluxing solution of **8** (97 mg, 0.2 mmol) in degassed *t*-butanol (4 mL), containing Bu_3SnCl (2.7 µL, 0.01 mmol) and $NaBH_3CN$ (25 mg, 0.4 mmol). According to GPC the uncyclized reduction product accounted for less than 5% of the mixture. After solvent evaporation, the residue was dissolved in CH_2Cl_2, the solution was filtered and then submitted to reductive ozonolysis after addition of methanol. Purification by LC (0% to 5% EtOAc/pentane) led to a mixture of **10a** and **10b** (63 mg, 77%). Anal. Calcd for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found : C, 67.61; H, 8.77.

Pure samples of **10a** and **10b** were then isolated by semi-preparative HPLC (2% EtOAc/isooctane; 45 mL/min).

Method B : In a typical experiment a solution of **8** (73 mg, 0.15 mmol), Bu_3SnH (48 µL, 0.18 mmol) and AIBN in benzene (15 mL) was irradiated for 4 h at room temperature. GPC analysis of the crude

mixture indicated a 78:22 ratio of **10a** to **10b**. The two diastereomers were isolated in admixture (43 mg, 70%) after ozonolysis and purification by LC.

Major isomer 10a. ^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.79 (s, 3H), 0.75-0.82 (superimposed m, 1H), 0.84 (s, 3H), 1.00 (d, 3H, *J* = 7), 1.07 (s, 3H), 1.14-1.28 (superimposed m, 2H), 1.19 (t, 3H, *J* = 7.1), 1.22 (t, 3H, *J* = 7.1), 1.30 (s, 3H), 1.61-1.71 (m, 1H), 1.72 (dd, 1H, *J* = 13 and 8.7), 1.88 (d, 1H, *J* = 3.5), 2.29-2.38 (m, 1H), 2.53 (ddd, 1H, *J* = 13, 7.5 and 1.5), 2.68 (d, 1H, *J* = 14.8), 2.73 (broad d, 1H, *J* = 14.8), 3.70 (s, 1H), 4.09-4.24 (m, 4H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 9.0 (CH_3), 13.9 (2 x CH_3), 15.8 (CH_3), 20.3 (CH_3), 22.4 (CH_3), 22.9 (CH_2), 23.7 (CH_3), 29.4 (CH_2), 40.4 (CH_2), 42.0 (CH), 43.9 (CH_2), 47.3 (C), 48.1 (CH), 51.8 (C), 56.8 (C), 61.3 (CH_2), 61.4 (CH_2), 89.4 (CH), 90.0 (C), 117.5 (C), 171.2 (C), 171.5 (C).

Minor isomer 10b. ^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.80 (s, 3H), 0.74-0.81 (superimposed m, 1H), 0.91 (s, 3H), 0.91 (d, 3H, *J* = 7.2), 1.13 (s, 3H), 1.15-1.30 (superimposed m, 2H), 1.21 (t, 3H, *J* = 7.1), 1.21 (t, 3H, *J* = 7.1), 1.27 (s, 3H), 1.62-1.70 (m, 1H), 1.88 (d, 1H, *J* = 3.5), 2.00 (d, 1H, *J* = 13.9), 2.07-2.13 (m, 1H), 2.61 (dd, 1H, *J* = 14.7 and 1.4), 2.65 (dd, 1H, *J* = 13.9 and 7.2), 2.78 (d, 1H, *J* = 14.6), 3.60 (s, 1H), 4.09-4.24 (m, 4H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 9.4 (CH_3), 13.9 (CH_3), 14.0 (CH_3), 17.1 (CH_3), 20.6 (CH_3), 21.2 (CH_3), 23.0 (CH_2), 23.7 (CH_3), 29.9 (CH_2), 38.0 (CH_2), 38.6 (CH_2), 39.1 (CH), 47.7 (C), 48.1 (CH), 51.3 (C), 55.1 (C), 61.4 (CH_2), 61.6 (CH_2), 88.1 (CH), 90.8 (C), 117.6 (C), 171.7 (C), 172.6 (C).

Cyclization of 9.

Under standard conditions at 80 °C, **9** (99 mg, 0.18 mmol) led to a crude reaction mixture containing **11a** and **11b** in a 71:29 ratio, according to GPC, together with less than 5% of the acyclic reduction product. After treatment and subsequent reductive ozonolysis, purification by LC (0 to 3% EtOAc/pentane) led to the isolation of **11a** and **11b** (57 mg, 67%). Anal. Calcd for $C_{28}H_{38}O_6$: C, 73.03; H, 6.13. Found : C, 72.96; H, 6.13.

Major isomer, 11a. ^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.60 (d, 3H, *J* = 7.1), 0.85 (s, 3H), 0.88 (s, 3H), 1.20 (t, 3H, *J* = 7.1), 1.28 (s, 3H), 1.32 (t, 3H, *J* = 7.1), 0.80-1.50 (superimposed m, 5H), 2.10 (d, 1H, *J* = 5.1), 2.32-2.50 (m, 2H), 2.72 (broad d, 1H, *J* = 14.8), 2.80 (d, 1H, *J* = 14.8), 4.09-4.32 (m, 4H), 4.45 (s, 1H), 7.13-7.40 (m, 4H), 7.51-7.58 (m, 1H).

Characteristic signals of the minor isomer :

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 0.80 (s, 3H), 0.81 (s, 3H), 0.98 (d, 3H, *J* = 5.1), 1.09 (s, 3H).

The ^{13}C NMR spectrum of the mixture was too complex to be assigned owing to superimposed signals.

2-Tetrahydropyranyl 2-Propynyl Ether.

A solution of propargyl alcohol (11.8 mL, 0.2 mmol) and dihydropyran (20.1 mL, 0.22 mmol) in dichloromethane (200 mL) was acidified with a catalytic amount of Amberlyst A15. After 2 h at room temperature, the reaction mixture was filtered and the solvent was evaporated. The residue was purified by distillation under reduced pressure (92-95 °C, 45 mm), which led to the title ether (22.4 g, 80%).

7-Bromo-1-(2-tetrahydropyranyloxy)-2-heptyne.

A solution of BuLi in THF (1.4 M, 10.7 mL, 0.015 mol) was added at -80 °C to solution of the above ether (2.103 g, 0.015 mol) in THF (20 mL). After warming up to room temperature, 1,4-dibromobutane (9 mL, 0.075 mol) was added with a catalytic amount of NaI. After 3 days at room temperature, and addition of a drop of water, the solvent was evaporated and the residue was purified by LC (0 to 10% EtOAc/pentane). The title compound was isolated as a colorless oil (3.39 g, 82%). ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.51-1.83 (m, 8H), 1.91-2.06 (m, 2H), 2.28 (tt, 2H, *J* = 7.0 and 2.2), 3.43 (t, 2H, *J* = 6.6), 3.45-3.59 (m, 1H), 3.78-3.91 (m, 1H), 4.24 (AB part of an ABX_2 pattern, 2H, J_{AB} = 15.1), 4.78-4.83 (m, 1H).

1,7-Dibromo-2-heptyne.

Bromotriphenylphosphonium bromide was generated *in situ* by adding, at 0 °C, bromine (1.91 g, 0.012 mol) in dichloromethane (5 mL), to a solution of triphenylphosphine (3.76g, 0.014 mol) in the same solvent (40 mL). The solution was stirred for 20 min at room temperature which led to a white precipitate. The above alkyne (2.71 g, 9.9 mmol) in dichloromethane (30 mL) was then added with a syringe. After 4 h at 0 °C, the solvent was removed and the residue triturated with pentane, filtered and the solution concentrated. Purification by LC (pentane) led to 1,7-dibromo-2-heptyne (1.84 g, 74%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.60-1.75 (m, 2H), 1.90-2.05 (m, 2H), 2.30 (tt, 2H, *J* = 6.8 and 2.3), 3.44 (t, 2H, *J* = 6.7), 3.92 (t, 2H, *J* = 2.3).

Diethyl 2-(7-Bromo-2-heptynyl)-2-(2,2-diethoxyethyl)malonate (12).

A solution of diethyl 2-(2,2-diethoxyethyl) malonate (1.10 g, 4 mmol) in THF (40 mL) was added to a suspension of NaH (0.241 g, 6 mmol) in THF (10 mL). After stirring for 30 min at room temperature, 1,7-dibromo-2-heptyne (1.07 g, 4.2 mmol) in solution in THF (10 mL) was added rapidly. The reaction mixture was stirred for 4 additional hours at room temperature and then diluted with Et_2O (150 mL). The resulting solution was washed with brine (2 x 30 mL), dried over $MgSO_4$ and concentrated. Purification by LC (0 to 5% EtOAc/pentane) led to **12** (1.51 g, 84%). ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.17 (t, 6H, *J* = 7.1), 1.24 (t, 6H, *J* = 7.1), 1.53-1.68 (m, 2H), 1.87-2.02 (m, 2H), 2.18 (tt, 2H, *J* = 6.8 and 2.3), 2.40 (d, 2H, *J* = 5.8), 2.83 (t, 2H, *J* = 2.3), 3.42 (t, 2H, *J* = 6.6), 3.46 (dq, 2H, *J* = 9.3 and 7.1), 3.65 (dq, 2H, *J* = 9.3 and 7.1), 4.17 (q, 2H, *J* = 7.1), 4.18 (q, 2H, *J* = 7.1), 4.55 (t, 1H, *J* = 5.8).

Diethyl 2-(7-Bromo-2-heptynyl)-2-(1,2,10,10-tetramethyl-3,5-dioxatricyclo [5,2,1,0^{2,6}]dec-4-ylmethyl)malonate (13).

Under standard conditions, transacetalization of **12** (404 mg, 0.9 mmol) with 2-*exo*-hydroxy-1-methyl-*exo*-borneol **5** led, after purification on silica gel (3% EtOAc/pentane), to **13** (435 mg, 89%). ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.82 (s, 3H), 0.90 (s, 3H), 0.75-0.93 (m, 1H), 1.16 (s, 3H), 1.18 (s, 3H), 1.24 (t, 6H, *J* = 7.1), 1.15-1.32 (m, 3H), 1.52-1.79 (m, 4H), 1.85-2.00 (m, 3H), 2.51-2.56 (m, 2H), 2.85-2.90 (m, 2H), 3.41 (t, 2H, *J* = 6.6), 3.50 (s, 1H), 4.10-4.26 (m, 4H), 4.73 (t, 1H, *J* = 5.6); ^{13}C NMR ($CDCl_3$, 50.3 MHz) : δ 9.2 (CH_3), 13.8 (2 x CH_3), 17.6 (CH_2), 18.8 (CH_3), 20.7 (CH_3), 23.1 (CH_2), 23.2 (CH_2), 23.3 (CH_3), 26.9 (CH_2), 29.4 (CH_2), 31.3 (CH_2), 33.0 (CH_2), 33.9 (CH_2), 47.5 (CH), 48.0 (C), 50.4 (C), 54.8 (C), 61.3 (2 x CH_2), 75.0 (C), 82.5 (C), 89.0 (CH), 89.6 (C), 97.9 (CH), 169.5 (C), 169.6 (C). Anal. Calcd for $C_{27}H_{41}O_6Br$: C, 59.89; H, 7.63. Found : C, 59.83; H, 7.59.

Cyclization of 13.

Under standard conditions at 80 °C, **13** (162 mg, 0.3 mmol) led to a crude reaction mixture containing **14a** and **14b** in a 96:4 ratio, as determined by GPC. After concentration and subsequent reductive ozonolysis, purification by LC (0 to 3% EtOAc/pentane) led to the isolation of **14a** (100 mg, 72%). Though the minor isomer was lost during chromatographic purification the ^{1}H NMR spectrum of the crude mixture indicated the presence of **14b** together with the product resulting from the reduction of the primary radical. Anal. Calcd for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found : C, 70.06; H, 9.11.

Under standard conditions at 20 °C, **13** (97 mg, 0.18 mmol) was allowed to react with Bu_3SnH (58 µL, 0.216 mmol) in the presence of AIBN (6 mg, 0.036 mmol) in benzene solution (18 mL). This led to a crude reaction mixture containing **14a** and **14b** in a 99:1 ratio, according to GPC. After concentration and subsequent reductive ozonolysis, purification by LC (0 to 3% EtOAc/pentane) led to the isolation of **14a** (54 mg, 65%).

Major isomer 14a. ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.80 (s, 3H), 0.83 (s, 3H), 0.75-0.92 (m, 1H), 1.10 (s, 3H), 1.21 (t, 3H, *J* = 7.1), 1.24 (t, 3H, *J* = 7.1), 1.33 (s, 3H), 1.15-1.98 (m, 14H), 2.28-2.38 (m, 1H), 2.58 (dd, 1H, *J* = 13.4 and 8.1), 2.66 (s, 2H), 3.69 (s, 1H), 4.06-4.22 (m, 4H); ^{13}C

NMR ($CDCl_3$, 50.3 MHz) : δ 9.0 (CH_3), 13.8 (CH_3), 13.9 (CH_3), 20.2 (CH_3), 22.5 (CH_3), 22.9 (CH_2), 23.8 (CH_3), 24.8 (CH_2), 25.3 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 32.4 (CH_2), 33.9 (CH_2), 40.3 (CH), 42.1 (CH_2), 47.3 (C), 48.0 (CH), 50.5 (CH), 51.8 (C), 56.1 (C), 61.2 (CH_2), 61.4 (CH_2), 89.5 (CH), 89.8 (C), 117.9 (C), 171.2 (C), 172.0 (C).

Characteristic signal of the minor isomer 14b :

^1H NMR ($CDCl_3$, 200 MHz) : δ 3.67 (s, 1H).

Characteristic signals of the uncyclized reduction product :

^1H NMR ($CDCl_3$, 200 MHz) : δ 0.89 (t, 3H, J = 7.5), 3.50 (s, 1H).

Acknowledgment. We are thankful to NATO (CRG 961193) and NSF (CHE 9625256) for financial support.

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