Lithium Trimethylalkynylaluminate, A New Chemoselective Alkynylating Agent

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Received January 30, 1996

Lithium trimethylalkynylaluminates, prepared conveniently by reacting trimethylaluminum with lithium alkynide, readily react with aldehydes and ketones to give the corresponding propargyl alcohols in 70-95% yields. The reaction is highly chemoselective; thus many other functional groups such as amides, nitriles, epoxides and halogen compounds are inert under the reaction conditions. The reagents also show an excellent 1,2-regiospecificity in the reactions with cyclic or acyclic α,β-unsaturated carbonyl compounds.

Introduction

Alkynylation has been considered as a useful reaction for extending carbon chain in a molecule in organic synthesis, and it has been traditionally carried out by using alkali metal (Na, Li) alkynides or alkynyl Grignard reagents. Alkali metal alkynides react with aldehydes and ketones at low temperature to give good yields of the corresponding propargyl alcohols.[1] However, they also react with alkyl halides,[2] epoxides,[3] esters,[4] and amides[5] to give moderate yields of the corresponding products. Alkynyl Grignard reagents react similarly.[6,7,8] On the other hand, alkynylalanes have proved to be valuable reagents for coupling tertiary alkyl-alkynyl groups, for opening epoxides and in conjugate addition to α,β-unsaturated carbonyl compounds.[9,10,11]

Recently we reported that sodium diethyldialkynylaluminate (SDAA),[12] readily prepared by treating sodium diethyldihydroaluminate (SDDA) with 2 equiv of terminal acetylenes, is a good reagent for chemoselective alkynylation of carbonyl compounds. However, one disadvantage of the reagent is that only one of the two alkynyl groups is utilized for the alkynylation of carbonyl group. We report here a new chemoselective alkynylating agent, lithium trimethylalkynylalumiate (LTAA).

Results and Discussion

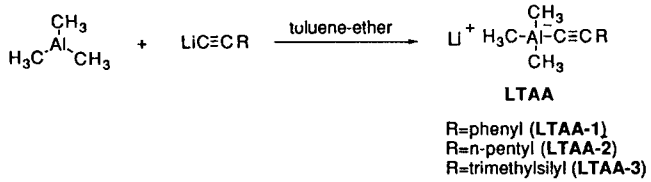
Preparation of Lithium Trimethylalkynylaluminate (LTAA). LTAA can be prepared easily by adding 1 equiv of trimethylaluminum to lithium alkynide at room temperature in toluene-ether (Scheme 1). Ether was added to get a clear solution, since LTAA soution in hydrocarbon solvent such as toluene is sightly turbid. The formation of LTAA was quantitative, as estimated by the reaction of LTAA with excess benzaldehyde.

Reaction of LTAA with Carbonyl Compounds. Reactions of LTAA with representative carbonyl compounds (Scheme 2) have been examined, and the results are summarized in Table 1.

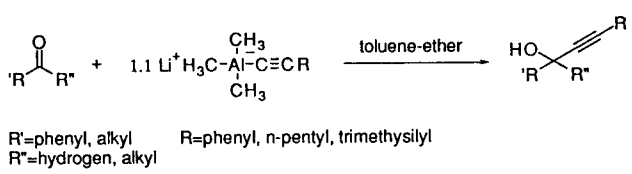
As shown in Table 1, all the aldehydes and ketones examined were readily alkynylated to the corresponding propargyl alcohols in good yields at room temperature. Using phenyl acetylene (LTAA-1), a variety of aldehydes and ketones were readily alkynylated to the corresponding propargyl alcohols in 82%-95% yields. In the case of reagents derived from heptyne (LTAA-2) and trimethylsilylacetylene (LTAA-3), more basic acetylides, proceeded in high yield with benzaldehyde, but the reactions with hexanal, 2-heptanone and cyclohexanone gave somewhat lower yields (70-80%) of the corresponding products, presumably due to the competitive deprotonation of α-hydrogen. Similar results have been reported in the reactions with alkali metal alkynides (60-80%); however, the most reactions must be carried out at low (−30 to −78 °C) temperatures.[1]

LTAA was found to be an excellent 1,2-alkynylating agent of cyclic or acyclic α,β-unsaturated carbonyl compounds. Thus lithium trimethylphenylethynylaluminate (LTAA-1) regioselectively alkynylated 2-cyclohexen-1-one, cinnamaldehyde and benzalacetone to provide the corresponding 1,2-addition products exclusively. The use of sodium acetylide and ethynylmagnesium bromide has also been reported to give mainly 1,2-addition products from conjugated enones; however, the yields were moderate.[13,14] In contrast, alkynylalanes were found to react with enones, which are capable of adopting a cisoid conformation (such as benzalacetone), to provide products arising exclusively from 1,4-addition.[11]

LTAA was found to be highly chemoselective. Thus the reagent did not affect other functional groups such as hali-

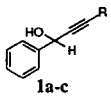
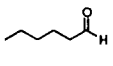
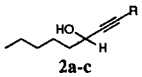
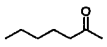
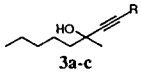
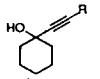
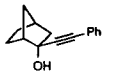
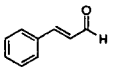
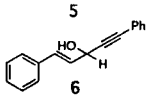
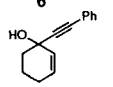
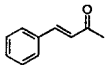
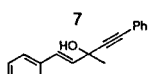


Scheme 1.



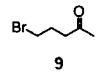
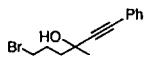
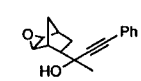
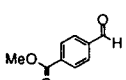
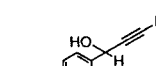
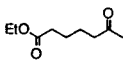
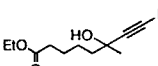
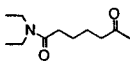
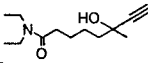
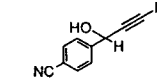
Scheme 2.

Table 1. Reaction of LTAA with Carbonyl Compounds in Toluene-Ether at Room Temperture[a]

Compound	Reagent	Product	Time	Yield (%)[b]
	LTAA-1		1h	95
	LTAA-2		1h	90
	LTAA-3	1a-c	1h	89
	LTAA-1		1h	82
	LTAA-2		1h	70
	LTAA-3	2a-c	1h	75
	LTAA-1		1h	89
	LTAA-2		1h	79
	LTAA-3	3a-c	1h	80
	LTAA-1		1h	90
	LTAA-2		1h	79
	LTAA-3	4a-c	1h	80
	LTAA-1		1h	89
		5		
	LTAA-1		1h	91
		6		
	LTAA-1		1h	84
		7		
	LTAA-1		3h	83
		8		

[a]Reactions were carried out by adding 5 mmol of carbonyl compound to 5.5 mmol of LTAA. [b]Isolated yields.

Table 2. Chemoselective Alkynylation of Carbonyl Compounds with LTAA at 0 ℃ in Toluene-Ether[a], and Comparison with PhC≡CLi and PhC≡CMgBr

Compound	Reagent	Product	Time	Yield (%)[b]
	LTAA-1		12h	82[c]
	PhC≡CLi		1h	10[c](15)[d,e]
9	PhC≡CMgBr	10	1h	70
	LTAA-1		6h	82
	PhC≡CLi		1h	50(59)[d]
11	PhC≡CMgBr	12	1h	28
	LTAA-1		1h	77
	LTAA-2		1h	75
	LTAA-3		1h	65
	PhC≡CLi		1h	50(85)[d]
13	PhC≡CMgBr	14a-c	1h	72
	LTAA-1		4h	86
	PhC≡CLi		1h	60(82)[d]
15	PhC≡CMgBr	16	1h	68
	LTAA-1		6h	87
	PhC≡CLi		1h	80(92)[d]
17	PhC≡CMgBr	18	1h	41
	LTAA-1		1h	88
	LTAA-2		1h	82
	LTAA-3		1h	60
	PhC≡CLi		1h	30(44)[d]
19	PhC≡CMgBr	20a-c	1h	35

[a]Reactions were carried out by adding 5 mmol of carbonyl compound to 5.5 mmol of LTAA. [b]Isolated yields. [c]At −10 ℃. [d]At −50 ℃. [e]2-Methyl-2-phenylethynyltetrahydrofuran was the major product (90% at 0 ℃ and 85% at −50 ℃).

des, epoxide(cyclohexene oxide), esters (ethyl hexanoate and ethyl benzoate), amides (*N,N*-dimethylbenzamide and hexanoyl piperidine) and nitriles (benzonitrile and hexanenitrile) at 0 ℃. We have evaluated the selectivity of LTAA and also compared it with the results obtained by lithium phenylacetylide and phenylethynylmagnesium bromide in the reactions of several functionalized carbonyl compounds. The results are summarized in Table 2. As shown in Table 2, LTAA reacted quite selectively with aldehydes or ketones in the presence of bromide, epoxide, ester, amide and nitrile functionalities. For example, LTAA-1 reacted with 5-bromo-2-pentanone (**9**) to give 5-bromo-2-phenylethynylpentan-2-ol (**10**) in an isolated yield of 82% at −10 ℃, whereas, lithium phenylacetylide gave 2-methyl-2-phenyl-ethynyltetrahydrofuran in 90% yield at 0 ℃ (85% even at −50 ℃) instead of the expected product (**10**). The observed formation of tetrahydrofuran derivative presumably demonstrates that the nucleophilicity of the lithium alkoxide is greater than that of the aluminum alkoxide, both alkoxides are formed from the initial attack by lithium acetylide and LTAA-1. The chemoselectivity of LTAA-1 was also proved in the reaction with 5-acetyl-2,3-epoxybicyclo[2.2.1]heptane (**11**) to give selectively the product with an unaffected epoxide, 1-(2,3-epoxybicyclo[2.2.1]heptan-5-yl)-1-phenylethynyl-ethan-1-ol (**12**) in a good yield (82%) at 0 ℃. In the reactions with 4-carbomethoxybenzaldehyde (**13**) and ethyl 6-oxoheptanoate (**15**), LTAA-1 selectively alkynylated carbonyl groups without attacking the ester function to give the corresponding propargyl alcohols in yields of 77% and 86% respectively. Using LTAA-2, the compound **13** was alkynylated in a similar yield (75%), however a lower yield (65%) was observed in the case of LTAA-3. Both lithium phenylacetylide and phenylethynylmagnesium bromide gave lower yields of the desired product at 0 ℃, but an improved yield was observed when the reaction with the former was carried out at −50 ℃. However, in the reaction with *N,N*-diethyl 6-oxoheptamide (**17**), in contrast to the phenylethynylmagnesium bromide reaction, both LTAA-1 and lithium phenylacetylide gave the alkynylated product **18** in good yields at 0 ℃. Finally, LTAA-1 reacted with 4-cyanobenzaldehyde (**19**) to give the desired product in a yield of 88% at 0 ℃. Reactions using reagent derived from heptyne (LTAA-2) or trimethylsilylacetylene (LTAA-3) gave **19** in yields of 82% and 60% respectvely, however, both lithium phenylacetylide and phenylethynylmagnesium bromide were less effective. It may be too early at this point to attempt to answer why LTAA has such a unique selectivity. However, the followings are believed to be mainly responsible for the unique selectivity of LTAA: The lower reactivity of aluminum-alkynyl bond compared with those of lithium and magnesium, the Lewis base structure of LTAA in contrast to the Lewis acid structure of alkynylalane, and the high affinity

of aluminum to the oxygen atom.

Conclusion

Lithium trimethylalkynylaluminates (LTAA) are good alternative alkynylating agents which exhibits good chemoselectivity in the presence of other functional groups such as halide, epoxide, ester, amide, and nitrile and an excellent regioselectivity in the reactions with α,β-unsaturated carbonyl compounds. The reactivity and selectivity of LTAA are almost similar to those of SDAA, however LTAA must be more ecomomical than SDAA, specially when alkynyl moiety is expensive.

Experimental Section

Preparation of LTAA. The following procedure for the preparation of lithium trimethylphenylethynylaluminate (LTAA-1) is representative. Into a 50 mL flask under nitrogen, 12.4 mL of ether and 0.61 mL (5 mmol) of a 8.2 M *n*-butyl lithium solution in hexane were introduced. The solution was maintained at −20 ℃, and then 0.55 mL (5 mmol) of phenyl acetylene was added with vigorous stirring, followed by 3.94 mL of toluene. The solution was wamed to room temperature and the 2.5 mL of 2 M trimethylaluminum in toluene was added. The formation of LTAA-1 is quantitative. Thus LTAA-1 solution prepared was 0.25 M in alkynide, as estimated by the reaction with excess benzaldehyde.

General Procedure for the Preparation of Propargyl Alcohols. The alkynylation of benzaldehyde is representative. Into a 50 mL flask, was introduced 10 mL of toluene, followed by 22 mL (5.5 mmol) of 0.25 M LTAA-1. The solution was maintained at room temperature, and 10 mL (5 mmol) of 0.5 M solution of benzaldehyde in toluene was added. After 1 h the reaction mixture was hydrolyzed with 50 mL sat. NH_4Cl and product was extracted with 50 mL of ethyl acetate. The ethyl acetate layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude residue was chromatographed on a silica gel column using a hexane : EtOAc : Et_3N (9 : 1 : 0.05) mixture as the eluent to give 0.99 g (95%) of 1-phenylethylnyl-1-phenylmethanol (**1a**). ^1H NMR ($CDCl_3$) δ 2.50 (br s, 1H), 5.71 (s, 1H), 7.33-7.66 (m, 10H); IR (neat) 3356, 3063, 3032, 2876, 2229, 1599, 1491, 1444, 1278, 1031; GCMS m/z (relative intensity) (EI, 70 eV) 208 (M^+ 76), 77 (84), 102 (75), 103 (43), 105 (51), 129 (58), 130 (51). Anal. Calcd for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found: C, 86.30; H, 5.70.

1-(1-Heptynyl)-1-phenylmethanol (1b). Flash chromatography gave 0.90 g of **1b** (89% yield). ^1H NMR ($CDCl_3$) δ 0.90 (m, 3H), 1.40-1.48 (m, 4H), 1.48-1.60 (m, 2H), 2.20-2.30 (m, 3H), 5.50 (s, 1H), 7.28-7.48 (m, 5H); IR (neat) 3375, 3063, 2931, 2860, 2227, 1431; GCMS m/z (relative intensity) (EI, 70 eV) 202 (M^+ 4), 102 (14), 103 (19), 131 (100), 132 (12), 145 (11), 146 (10). Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.09; H, 8.99.

1-(2-Trimethylsilylethynyl)-1-phenylmethanol (1c). Flash chromatography gave 0.91 g of **1c** (89% yield). ^1H NMR ($CDCl_3$) δ 0.20 (s, 9H), 2.50 (br s, 1H), 5.45 (s, 1H), 7.30-7.60 (m, 5H).

1-Phenylethynyl-1-hexanol (2a). Flash chromatography gave 0.91 g of **2a** (90% yield). ^1H NMR ($CDCl_3$) δ 0.97 (t, 3H, J=6.7 Hz), 1.25-1.48 (m, 4H), 1.48-1.65 (m, 2H), 1.77-1.90 (m, 2H), 2.15 (s, 1H), 4.63 (t, 1H, J=7.0 Hz), 7.26-7.47 (m, 5H); IR (neat) 3356, 2931, 2860, 2202, 1668, 1599, 1491, 1442, 1028; GCMS m/z (relative intensity) (EI, 70 eV) 202 (M^+ 3), 103 (15), 129 (14), 131 (100), 132 (11), 145 (11), 146 (10). Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.99; H, 8.85.

1-(1-Heptynyl)-1-hexanol (2b). Flash chromatography gave 0.69 g of **2b** (70% yield). ^1H NMR ($CDCl_3$) δ 0.85-0.95 (m, 6H), 1.20-1.48 (m, 12H), 1.63-1.70 (m, 2H), 1.82 (s, 1H), 2.20 (m, 2H), 4.35 (m, 1H); IR (neat) 3356, 2931, 2860, 2202, 1491, 1379; GCMS m/z (relative intensity) (EI, 70 eV) 79 (15), 81 (38), 83 (18), 91 (15), 95 (13), 107 (14), 125 (100). Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.45; H, 12.23.

1-(2-Trimethylsilylethynyl)-1-hexanol (2c). Flash chromatography gave 0.74 g of **2c** (75% yield). ^1H NMR ($CDCl_3$) δ 0.15 (s, 9H), 0.97 (t, 3H, J=6.7 Hz), 1.25-1.48 (m, 4H), 1.48-1.65 (m, 2H), 1.77-1.90 (m, 2H), 2.15 (s, 1H), 4.63 (t, 1H, J=7.0 Hz).

2-Phenylethynyl-2-heptanol (3a). Flash chromatography gave 0.91 g of **3a** (84% yield). ^1H NMR ($CDCl_3$) δ 0.94 (t, 3H, J=8.4 Hz), 1.20-1.50 (m, 4H), 1.52-1.69 (m, 5H), 1.72-1.82 (m, 2H), 2.13 (s, 1H), 7.30-7.48 (m, 5H); IR (neat) 3373, 2933, 2862, 2343, 1599, 1491, 1460, 1371, 1130; GCMS m/z (relative intensity) (EI, 70 eV) 115 (9), 141 (10), 142 (16), 145 (100), 146 (11), 155 (10). Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.31. Found: C, 83.31; H, 9.23.

2-(1-Heptynyl)-2-heptanol (3b). Flash chromatography gave 0.67 g of **3b** (64% yield). ^1H NMR ($CDCl_3$) δ 0.95 (t, 6H), 1.20-1.80 (m, 18H), 2.20 (t, 2H); IR (neat) 3375, 2933, 2862, 2239, 1455, 1377, 1132; GCMS m/z (relative intensity) (EI, 70 eV) 55 (22), 69 (11), 139 (100). Anal. Calcd for $C_{14}H_{26}O$: C, 79.93; H, 12.46. Found: C, 79.71; H, 12.18.

2-(2-Trimethylsilylethynyl)-2-heptanol (3c). Flash chromatography gave 0.85 g of **3c** (80% yield). ^1H NMR ($CDCl_3$) δ 0.15 (s, 9H), 0.90 (t, 3H, J=6.7 Hz), 1.30 (m, 4H), 1.50 (m, 5H), 1.60 (m, 2H), 2.16 (s, 1H).

1-Phenylethynylcyclohexanol (4a). Flash chromatography (19 : 1 : 0.1 hexane : EtOAc : Et_3N) gave 0.87 g of **4a** (87% yield). ^1H NMR ($CDCl_3$) δ 1.30 (s, 1H), 1.51-1.80 (m, 8H), 1.92-2.19 (m, 2H); IR (neat) 3454, 2935, 2860, 2368, 1373, 1244, 1045; GCMS m/z (relative intensity) (EI, 70 eV) 200 (M^+ 23), 81 (20), 102 (32), 115 (43), 129 (57), 157 (100), 199 (43). Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.90; H, 8.10.

1-(1-Heptynyl)cyclohexanol (4b). Flash chromatography (19 : 1 : 0.1 hexane : EtOAc : Et_3N) gave 0.64 g of **4b** (87% yield). ^1H NMR ($CDCl_3$) δ 0.80-0.90 (t, 3H), 1.20-2.00 (m, 17 H), 2.20-2.30 (t, 2H); IR (neat) 3373, 2933, 2858, 2234, 1448, 1064; GCMS m/z (relative intensity) (EI, 70 eV) 194 (M^+ 4), 55 (100), 67 (40), 95 (39), 123 (20). Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.00; H, 11.71.

1-(2-Trimethylethynyl)cyclohexanol (4c). Flash chromatography gave 0.78 g of **4c** (80% yield). ^1H NMR ($CDCl_3$) δ 0.20 (s, 9H), 1.30 (s, 1H), 1.50-170 (m, 8H), 1.92 (m, 2H).

2-Phenylethynylbicyclo[2.2.1]heptan-2-ol (5). Flash chromatography (9 : 1 : 0.05 hexane : EtOAc : Et_3N) gave 0.90 g of **5** (85% yield). ^1H NMR ($CDCl_3$) δ 1.21-1.47 (m, 4H), 1.53-1.68 (m, 2H), 1.80-2.09 (m, 2H), 2.15-2.31 (m, 2H), 2.48 (s, 1H), 7.20-7.43 (m, 5H); IR (neat) 3385, 2958,

2874, 2361, 1450, 1309, 1167, 1066; GCMS m/z (relative intensity) (EI, 70 eV) 212 (M^+ 23), 67 (45), 102 (49), 115 (60), 129 (63), 144 (47), 155 (43), 165 (52), 166 (67), 211 (100). Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.90; H, 7.55.

1-Phenylethynyl-3-phenyl-2-propen-1-ol (6). Flash chromatography gave 1.08 g of **6** (92% yield). ^1H NMR ($CDCl_3$) δ 2.18 (br s, 1H), 5.30 (d, 1H, J=5.9 Hz), 6.40 (dd, 1H, J=5.9, 15.9 Hz), 6.86 (d, 1H, J=15.9 Hz), 7.21-7.51 (m, 10H); IR (neat) 3317, 3059, 2321, 1620 1599, 1491, 1253; GCMS m/z (relative intensity) (EI, 70 eV) 234 (M^+ 30), 77 (60), 105 (100), 129 (46), 233 (36). Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.12; H, 6.05.

1-Phenylethynyl-2-cyclohexen-1-ol (7). Flash chromatography gave 0.82 g of **7** (83% yield). ^1H NMR ($CDCl_3$) δ 1.78-1.96 (m, 2H), 1.97-2.20 (m, 4H), 2.27 (s, 1H), 5.81-5.93 (m, 2H), 7.26-7.47 (m, 5H); IR (neat) 3375, 3028, 2937, 2361, 1620, 1489, 1442, 1265, 1051; GCMS m/z (relative intensity) (EI, 70 eV) 198 (M^+ 9), 76 (40), 77 (36), 89 (45), 102 (30), 165 (58), 180 (100). Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 40.28; H, 4.39; N, 5.00.

2-Phenylethynyl-4-phenyl-3-buten-2-ol (8). Flash chromatography (19 : 1 : 0.1 hexane : EtOAc : Et_3N) gave 1.03 g of **8** (83% yield). ^1H NMR ($CDCl_3$) δ 1.82 (s, 3H), 2.49 (s, 1H), 6.45 (d, 1H, J=18 Hz), 6.97 (d, 1H, J=18 Hz), 7.26-7.60 (m, 10H); IR (neat) 3394, 3057, 2984, 2345, 1599, 1491, 1266; GCMS m/z (relative intensity) (EI, 70 eV) 248 (M^+ 3), 51 (12), 77 (11), 101 (18), 102 (11), 113 (25), 114 (25), 115 (41), 128 (43), 152 (17), 215 (31), 226 (23), 228 (64), 229 (100), 230 (76). Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.49. Found: C, 87.11; H, 6.53.

5-Bromo-2-pentanone (9). **9** was obtained as a colorless oil in 85% yield by the method of Apsimon and Seguin.[15] ^1H NMR ($CDCl_3$) δ 2.04-2.21 (m, 5H), 2.64 (t, 2H, J=6.2 Hz), 3.40-3.50 (m, 2H); IR (neat) 2964, 1710, 1435, 1367, 1248, 1178; GCMS m/z (relative intensity) (EI, 70 eV) 164 (M^+ 2), 58 (100), 59 (3), 85 (9), 121 (2), 123 (2), 166 (2).

5-Bromo-2-phenylethynylpentan-2-ol (10). Flash chromatography (9 : 1 : 0.05 hexane : EtOAc : Et_3N) gave 1.05 g of **10** (79% yield). ^1H NMR ($CDCl_3$) δ 1.64 (s, 3H), 1.80-2.03 (m, 2H), 2.05-2.30 (m, 3H), 3.49-3.60 (m, 2H), 7.30-7.52 (m, 5H); IR (neat) 3383, 3057, 2978, 2931, 2361, 1599, 1489, 1442, 1371, 1292; GCMS m/z (relative intensity) (EI, 70 eV) 51 (15), 63 (11), 75 (10), 76 (10), 77 (23), 91 (17), 102 (13), 115 (32), 129 (29), 145 (100), 154 (11), 155 (11), 169 (4), 171 (4), 248 (1), 250 (1). Anal. Calcd for $C_{13}H_{15}BrO$: C, 58.44; H, 5.66. Found: C, 58.47; H, 5.63.

5-Acetyl-2,3-epoxybicyclo[2.2.1]heptane (11). Into a stirred solution of *m*-chloroperbenzoic acid (4.49 g, 26 mmol) in chloroform (50 mL) held at 0 ℃ was added acetyl norbonene (3.0 g, 22 mmol) dissolved in chloroform (20 mL) over a 30 min period. The mixture was stirred overnight at room temperature, filtered, washed with 10% sodium hydrogen carbonate solution and dried over anhydrous Na_2SO_4. The solvent was removed by evaporation and the crude residue was chromatographed on a silica gel column using hexane : EtOAc (3 : 1) mixture as the eluent to give 2.17 g (65 %). ^1H NMR ($CDCl_3$) δ 0.76-0.86 (m, 1H), 1.22-1.45 (m, 3H), 2.18 (s, 3H), 2.43-2.53 (m, 2H), 2.73 (s, 1H), 3.15-3.18 (m, 2H); IR (neat) 3026, 2970, 2877, 1700, 1360, 1176, 1018; GCMS m/z (relative intensity) (EI, 70 eV) 152 (M^+ 4) 53 (18), 77 (20), 79 (63), 81 (100), 82 (39), 94 (33).

1-(2,3-Epoxybicyclo[2.2.1]heptan-5-yl)-1-phenylethynylethan-1-ol (12). Flash chromatography (5 : 5 : 0.05 hexane : EtOAc : Et_3N) gave 1.20 g of **12** (95% yield). ^1H NMR ($CDCl_3$) δ 1.20-1.30 (m, 1H), 1.41-1.67 (m, 5H), 1.68-1.8 (m, 2H), 2.30 (s, 1H), 2.46-2.56 (s, 1H), 2.62-2.75 (s, 1H), 3.09-3.23 (m, 2H), 7.28-7.48 (m, 5H); IR (neat) 3376, 3026, 2980, 2867, 2360, 1380, 1156, 1008; GCMS m/z (relative intensity) (EI, 70 eV) 254 (M^+ 1), 81 (21), 102 (13), 116 (16), 129 (18), 145 (100), 146 (16). Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.22; H, 7.15.

4-Carbomethoxybenzaldehyde (13). Prepared by a modification of the published procedure.[16] To a solution of 4-Carboxybenzaldehyde (3.0 g, 20 mmol) and anhydrous K_2CO_3 (4.2 g, 30 mmol) in acetone (200 mL) was added methyl iodide (56.7 g, 400 mmol). After being stirred overnight at 56 ℃, the resultant mixture was then quenched with 10% K_2CO_3 solution 100 mL and extracted with ether. The ether layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude residue was chromatographed on a silica gel column using a hexane : EtOAc (9 : 1) mixture as the eluent to give 2.13 g (65% yield). ^1H NMR ($CDCl_3$) δ 3.96 (s, 3H), 7.96-8.20 (dd, 4H, J=7.2, 8.1 Hz), 10.11 (s, 1H); IR (neat) 3024, 2955, 1724, 1709, 1437, 1284, 1203, 1114; GCMS m/z (relative intensity) (EI, 70 eV) 164 (M^+ 65), 50 (26), 51 (40), 74 (10), 75 (11), 77 (27), 105 (24), 133 (100).

1-Phenylethynyl-(4-carbomethoxy)phenyl-1-methanol (14a). Flash chromatography (9 : 1 : 0.05 hexane : EtOAc : Et_3N) gave 1.17 g of **14** (88% yield). ^1H NMR ($CDCl_3$) δ 2.65-2.75 (s, 1H), 3.95 (s, 3H), 5.75 (s, 1H), 7.30-8.05 (m, 9H); IR (neat) 3350, 3100, 2910, 2250, 1720, 1640, 1500, 1420, 1290, 1200, 1100; GCMS m/z (relative intensity) (EI, 70 eV) 266 (M^+ 13), 51 (53), 77 (74), 102 (100), 129 (59), 133 (43), 207 (61).

1-Heptynyl-(4-carbomethoxy)phenyl-1-methanol (14 b). Flash chromatography gave 0.98 g of **14b** (75% yield). ^1H NMR ($CDCl_3$) δ 0.90 (m, 3H), 1.30 (m, 4H), 1.55 (m, 2H), 2.30 (m, 2H), 2.13 (m, 2H), 3.90 (s, 3H), 5.50 (s, 1H), 7.60-8.05 (m, 4H).

1-(2-Trimethylsilyl)ethynyl-(4-carbomethoxy)phenyl-1-methanol (14c). Flash chromatography gave 0.85 g of **14c** (65% yield). ^1H NMR ($CDCl_3$) δ 0.20 (s, 9H), 2.35 (br s, 1H), 3.95 (s, 3H), 5.50 (s, 1H), 7.60-8.10 (m, 4H).

Ethyl 6-Oxoheptanoate (15). Hydroboration of 1-methylcyclohexene (4.81 g, 50 mmol) in THF with sodium borohydride (1.13 g, 30 mmol) and dimethyl sulfate (3.78 g, 30 mmol), followed by alkaline oxidation, gave trans-2-methylcyclohexanol in 88% yield (crude, after evaporation of the solvent). From the crude alcohol, 6-oxoheptanoic acid was prepared by the method of Schaeffer and Snoddy[17] in 41% yield. **15** was obtained by esterification. ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, J=7.1 Hz), 1.57-1.64 (m, 4H), 2.14 (m, 3H), 2.25-2.34 (m, 2H), 2.42-2.50 (m, 2H), 4.12 (q, 2H, J=7.2 Hz); IR (neat) 2982, 2941, 1734, 1720, 1373, 1182, 1033; GCMS m/z (relative intensity) (EI, 70 eV) 45 (37), 55 (100), 58 (49), 73 (83), 81 (60), 101 (43), 115 (43), 127 (20).

Ethyl 6-hydroxy-6-phenylethynylheptanoate (16). Flash chromatography (5 : 5 : 0.05 hexane : EtOAc : Et_3N)) gave 1.12 g of **16** (82% yield). ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, J=7.1 Hz), 1.60-1.80 (m, 9H), 2.25 (s, 1H), 2.38 (t, 2H,

J=7.4 Hz), 4.15 (q, 2H, J=7.2 Hz), 7.31-7.47 (m, 5H); IR (neat) 3447, 3057, 2980, 2370, 1732, 1599, 1491, 1371, 1246, 1178; GCMS m/z (relative intensity) (EI, 70 eV) 55 (31), 76 (29), 101 (23), 102 (100), 115 (38), 127 (14), 145 (23), 168 (24). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.32; H, 8.11.

***N,N*-Diethyl 6-oxoheptamide (17).** Dicyclohexylcarbodiimide (4.12 g, 20 mmol) was added to a vigorously stirred dry ethyl acetate solution (100 mL) of the 6-oxoheptanoic acid (2.88 g, 20 mmol) and the diethtyl amine (1.46 g, 20 mmol) in dry ethyl acetate (100 mL) under an inert atmosphere at −10 ℃. Stirring was continued for 12 h at room temperature, and the mixture filtered. The filtrate was evaporated *in vacuo* and the crude residue was chromatographed on a silica gel column using a hexane : EtOAc (1 : 2) mixture as the eluent to give 1.60 g of **17** (42% yield). ^{1}H NMR ($CDCl_3$) δ 0.99-1.22 (m, 6H), 1.52-1.62 (m, 4H), 2.10 (s, 3H), 2.20 (t, 2H), 2.40 (t, 2H), 3.18-3.34 (m, 4H); IR (neat) 3323, 2933, 1712, 1641, 1450, 1379, 1257, 1138, 1084; GCMS m/z (relative intensity) (EI, 70 eV) 58 (100), 72 (52), 81 (30), 100 (34), 115 (40), 128 (11), 156 (4).

***N,N*-Diethyl 6-hydroxy-6-phenylethynylheptanamide (18).** Flash chromatography (5 : 5 : 0.05 hexane : EtOAc : Et_3N) gave 1.25 g of **18** (83% yield). ^{1}H NMR ($CDCl_3$) δ 1.05-1.19 (m, 6H), 1.57 (s, 3H), 1.60-1.82 (m, 6H), 2.34 (t, 2H, J=7.6 Hz), 2.51 (s, 1H), 3.22-3.43 (m, 4H), 7.26-7.42 (m, 5H); IR (neat) 3379, 2976, 2935, 1624, 1444, 1381, 1267, 1099; GCMS m/z (relative intensity) (EI, 70 eV) 55 (15), 58 (84), 72 (70), 86 (26), 100 (100), 102 (60), 115 (95), 128 (21). Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.65; H, 9.07; N, 4.78.

1-(4-Cyanophenyl)-1-phenylethylnylmethanol (20). Flash chromatography (8 : 2 : 0.05 hexane : EtOAc : Et_3N) gave 1.07 g of **20** (92% yield). ^{1}H NMR ($CDCl_3$) δ 2.75 (s, 1H), 5.75 (s, 1H), 7.25-7.52 (m, 5H), 7.63-7.76 (m, 4H); IR (neat) 3441, 3059, 2985, 2862, 2362, 2235, 1604, 1489, 1413, 1249, 1051; GCMS m/z (relative intensity) (EI, 70 eV) 233 (M^+ 28), 51 (67), 63 (32), 102 (100), 129 (68), 130 (48), 131 (42), 232 (44). Anal. Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.01. Found: C, 82.35; H, 4.75; N, 6.00.

1-(4-Cyanophenyl)-1-heptynylmethanol (20b). Flash chromatography gave 0.93 g of **20b** (82% yield). ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 3H), 1.30 (m, 4H), 1.50 (m, 2H), 2.25 (m, 2H), 2.68 (br s, 1H), 5.50 (s, 1H), 7.65 (s, 4H).

1-(4-Cyanophenyl)-1-(2-trimethysilylethynyl)methanol (20c). Flash chromatography gave 0.69 g of **20c** (60% yield). ^{1}H NMR ($CDCl_3$) δ 0.20 (s, 9H), 2.70 (br s, 1H), 5.50 (s, 1H), 7.65 (s, 4H).

Aknowledgment. This work was supported by Organic Chemistry Research Center/KOSEF.

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