4.20 (d, 0.2 H, J = 10.0 Hz), 5.30–5.40 (m, 1 H), 5.50–5.60 (m, 1 H); 67.80-MHz ^{13}C NMR ($CDCl_3$) INEPT δ (major) 12.83 (CH_3), 17.97 (CH_3), 28.20 (CH_2), 34.83 (CH_2), 40.01 (CH_2), 42.04 (CH), 42.14 (CH_2), 49.21 (CH), 76.18 (CH_2), 125.54 (CH), 129.74 (CH), 180.78 (C); (minor) 13.00 (CH_3), 17.97 (CH_3), 27.43 (CH_2), 36.83 (CH_2), 41.15 (CH), 43.25 (CH_2), 45.81 (CH_2), 49.36 (CH), 51.05 (C), 78.28 (CH), 127.80 (CH), 180.78 (C); HRMS (m/z) calcd for $C_{13}H_{20}O_2$ M^+ 208.1463, found M^+ 208.1489.

7,8-Dimethyl-8-phenyl-5-(2-propenyl)-3-oxabicyclo-[3.3.0]octan-2-one (20): oil, 0.0184 g (85%) from 0.022 g of **13**; IR ($CHCl_3$) 3025, 2975, 2850, 1760, 1600, 1190, 1020, 920 cm^{-1}; 500-MHz ^1H NMR ($CDCl_3$) δ 0.92 (d, 3 H, J = 6.8 Hz), 1.30 (s, 3 H), 1.74 (t, 1 H, J = 13.1 Hz), 2.13 (dd, 1 H, J = 13.1 and 6.9 Hz), 2.31 (dd, 1 H, J = 13.7 and 7.1 Hz), 2.35 (dd, 1 H, J found M^+ 13.7 and 7.1 Hz), 2.68–2.76 (m, 1 H), 2.98 (s, 1 H), 4.12 (d, 1 H, J = 9.5 Hz), 4.25 (d, 1 H, J = 9.5 Hz), 5.16 (dd, 1 H, J = 13.0 and 1.4 Hz), 5.20 (d, 1 H, J = 8.5 Hz), 5.73–5.81 (m, 1 H), 7.20–7.51 (m, 5 H); 67.8-MHz ^{13}C NMR ($CDCl_3$) INEPT δ 13.50 (CH_3), 16.79 (CH_3), 29.66 (CH_2), 44.75 (CH_2), 45.04 (CH), 48.29 (C), 51.39 (C), 63.42 (CH), 79.28 (CH_2), 120.02 (CH), 126.08 (CH), 126.33 (CH), 128.40 (CH), 132.69 (CH), 146.34 (C), 176.90 (C); HRMS (m/z) calcd for $C_{18}H_{22}O$ M^+ 270.1619, found M^+ 270.1619.

Supplementary Material Available: IR, ^1H NMR, ^{13}C NMR, and high-resolution mass spectral data for compounds **1–4**, **8–12**, **16**, and **17**; NOESY spectrum of **13**; and ^1H NMR and ^{13}C NMR spectra for compounds **1–16** and **18–20** (62 pages). Ordering information is given on any current masthead page.

A Systematic Study of Benzyl Cation Initiated Cyclization Reactions

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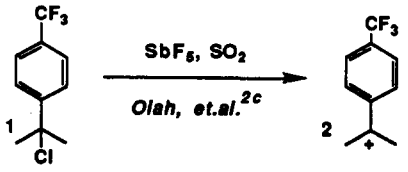
A systematic investigation of benzyl cation initiated cyclization reactions to form six-membered carbocycles is presented. The generation of benzyl cations from benzylic bromides, ethers, and alcohols followed by intramolecular capture provided good yields of cyclized products by use of several different cyclization terminators (e.g., phenyl, alkene, β-keto ester). A study on the effect of changing the electronic nature of substituents para to the benzyl cation showed that even electron-withdrawing substituents such as quaternary ammonium afford high yields of cyclization products. The formation of five- and seven-membered carbocycles was briefly investigated and found to be less general than the formation of the corresponding six-membered carbocycles.

Introduction

The stability of benzyl cations is well-documented and has been the subject of considerable theoretical and experimental study.[1,2] Olah and co-workers have studied these intermediates in super acid media using a variety of spectroscopic techniques and found that even benzyl carbenium ions with electron-withdrawing substituents on the phenyl ring, such as p-trifluoromethyl cation **2**, can be formed (eq 1).[2] The ready availability of benzyl cations has not resulted in their general use as synthesis intermediates, presumably due to the stringent conditions required to generate them.



(1)

The major role of aromatic rings in cyclization has been that of a terminator (internal nucleophile).[3] The use of an aromatic ring to initiate a cyclization has received less attention, but has been utilized in synthesis.[4-8] For ex-

(1) For a review on theoretical and experimental studies on benzyl cations, see: Freedman, H. H. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, 1973; Vol. IV, Chapter 28. Nenitzescu, C. D. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley-Interscience: New York, 1968, Vol. I, Chapter 1. For current examples and leading references, see: (a) Kirmse, W.; Kund, K.; Ritzer, E.; Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **1986**, *108*, 6045. (b) Cella, J. A. *J. Org. Chem.* **1982**, *47*, 2125. (c) Condon, F. E.; West, D. L. *J. Org. Chem.* **1980**, *45*, 2006. (d) Condon, F. E.; Mitchell, G. *Ibid.* **1980**, *45*, 2009. (e) Jost, R.; Sommer, J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 927. (f) Bright, S. T.; Coxon, J. M.; Steel, P. J. *J. Org. Chem.* **1990**, *55*, 1338.

(2) For leading references to work in the area by Olah and co-workers, see: (a) Olah, G. A.; Porter, R. D.; Jeuell, C. L.; White, A. M. *J. Am. Chem. Soc.* **1972**, *94*, 2044. (b) Bollinger, J. M.; Comisarow, M. B.; Cupas, C. A.; Olah, G. A. *J. Am. Chem. Soc.* **1967**, *89*, 5687. (c) Olah, G. A.; Comisarow, M. B.; Kim, C. J. *J. Am. Chem. Soc.* **1969**, *91*, 1458.

(3) Cf. Bartlett, P. A. Olefin Cyclization Processes That Form Carbon-Carbon Bonds. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 341-409.

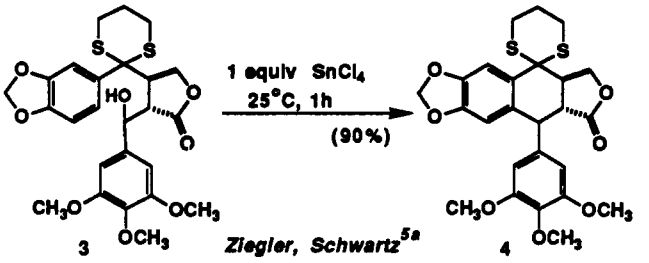
(4) For current examples and leading references for cyclization reactions with the generation of benzyl cations from quinone methide ketals, see: (a) Hart, D. J.; Cain, P. A.; Evans, D. A. *J. Am. Chem. Soc.* **1978**, *100*, 1548. (b) Kametani, T.; Takahashi, K.; Loc, C. V. *Tetrahedron* **1975**, *31*, 235. (c) Pelter, A.; Ward, R. S.; Rao, R. R. *Tetrahedron* **1985**, *41*, 2933. (d) Pelter, A.; Ward, R. S.; Rao, R. R. *Tetrahedron Lett.* **1983**, *24*, 621.

(5) For current examples and leading references for cyclization reactions with the generation of benzyl cations via loss of a benzylic leaving group, see: (a) Ziegler, F. E.; Schwartz, J. A. *J. Org. Chem.* **1978**, *43*, 985. (b) Kuhn, von M.; von Wartburg, A. *Helv. Chim. Acta*, **1967**, *50*, 1546. (c) Brown, E.; Loriot, M.; Robin, J.-P. *Tetrahedron Lett.* **1979**, *20*, 1389. (d) Ganeshpure, P. A.; Stevenson, R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1681. (e) Bradley, J. P.; Jarvis, T. C.; Johnson, C. D.; McDonnell, P. D.; Weatherstone, T. A. P. *Tetrahedron Lett.* **1983**, *24*, 2851. (f) Berney, D.; Schuh, K. *Helv. Chim. Acta* **1980**, *63*, 1785. (g) Nichols, D. E.; Boyles, D. A. *J. Org. Chem.* **1988**, *53*, 5128. (h) Lednicer, D.; Emmert, D. E.; Duncan, G. W.; Lyster, S. C. *J. Med. Chem.* **1967**, *10*, 1051. (i) Lednicer, D.; Emmert, D. E.; Lyster, S. C.; Duncan, G. W. *J. Med. Chem.* **1969**, *12*, 881. (j) Boissin, P.; Dhal, R.; Brown, E. *Tetrahedron Lett.* **1989**, *30*, 4371. (k) Ipaktschi, J.; Lauterbach, G. *Angew. Chem., Intl. Ed. Engl.* **1986**, *25*, 354. (l) Marcuzzi, F.; Melloni, G.; Modena, G. *J. Org. Chem.* **1979**, *44*, 3022. (m) Marcuzzi, F.; Melloni, G. *J. Chem. Res., Synop.* **1979**, 184. (n) Marcuzzi, F.; Melloni, G. *Tetrahedron Lett.* **1975**, *16*, 2771. (o) Mayr, H.; Bäuml, E. *Tetrahedron Lett.* **1984**, *25*, 1127. (p) Mayr, H.; Pock, R. *Chem. Ber.* **1986**, *119*, 2473. (q) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1567. (r) Murphy, W. S.; Wattanasin, S. *Tetrahedron Lett.* **1980**, *21*, 1887. (s) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2920. (t) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 271.

(6) For current examples and leading references for cyclization reactions with the generation of benzyl cations via protonation of a styrene, see: (a) MacMillan, J.; Martin, I. L.; Morris, D. J. *Tetrahedron* **1969**, *25*, 905. (b) Higashimura, T.; Hiza, M. *J. Polym. Sci., Polym. Chem. Ed.* **1981**, *19*, 1957. (c) Bergmann, W.; McAleer, W. J. *J. Am. Chem. Soc.* **1951**, *73*, 4969. (d) Taylor, A. R.; Keen, G. W.; Eisenbraun, E. J. *J. Org. Chem.* **1977**, *42*, 3477. (e) Packer, R. A.; Whitehurst, J. S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 110.

0022-3263/91/1956-2853$02.50/0

ample, Hart, Cain, and Evans used a quinone methide ketal as a precursor to a benzyl cation in the key step of their cherylline synthesis.[4a] With only a few exceptions,[6] the benzyl cations used in intramolecular cyclizations have been limited to those with electron-donating substituents on the aryl ring of the cation. In addition, the cyclization terminator (internal nucleophile) has been limited to an aryl ring with electron-donating substituents ortho and/or para to the site of attack.[6] It is not clear if these stabilizing groups on the cations and activated cyclization terminators are required for successful cyclization reactions. Normally, a cyclization reaction via a benzyl cation is effected by treating a benzylic alcohol with a large excess (5–10 equiv) of a Lewis or protic acid at room temperature or above.[4-8] These harsh conditions drastically decrease the range of functionality that can be tolerated in the cyclization reaction. In spite of this, the Ziegler–Schwartz podophyllotoxin synthesis[5a] points to the potential generality of this methodology in the construction of oxygenated aromatic compounds. These authors found that treatment of benzyl alcohol 3, possessing both a dithioketal and a lactone, with 1 equiv of stannic chloride (25 °C, 1 h) afforded a high yield of the desired cyclization product, 4 (eq 2).[5a] It should be noted that the cyclization terminator was an electron-rich aryl ring and the intermediate benzyl cation was stabilized by a *p*-methoxy group.



3 4 (2)

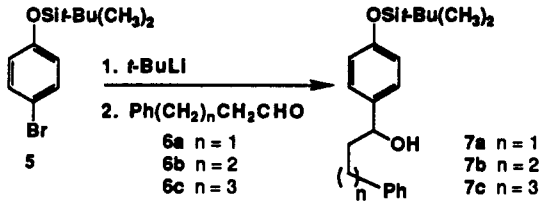
The use of benzyl cations as synthesis intermediates has been limited to isolated applications by many different research groups, and there has been no systematic study of factors affecting their formation and application in cyclization reactions. The systematic study presented here explores the synthetic potential of benzyl cations as cyclization initiators, and the results of the study should be useful in predicting the outcome of similar cyclizations. We present here a study of benzyl cation initiated cyclization reactions that examines the following: (1) the mildest conditions possible to generate a reactive, cationic intermediate, (2) the effect of different leaving groups on the efficiency of the cyclization reaction, (3) the effect of electronically different substituents para to the benzylic cation, (4) the relative efficiencies of forming five-, six-, and seven-membered rings, and (5) the range of cyclization terminators that can serve as efficient traps for the cations.[9]

Design and Synthesis of the Cyclization Substrates

A series of compounds with different leaving groups, terminators, and substituents para to the benzyl cation was constructed. We chose to generate the benzyl cations via elimination of a leaving group attached to the benzylic position, rather than protonation of a styrene or quinone methide ketal, due to the ease of preparation of the cyclization substrates.[4,6] Initial studies[9] showed a phenyl group to be an efficient terminator, and three series of compounds using this terminator were constructed. The first series was designed to systematically examine several readily available leaving groups: bromide, methyl ether, (methoxyethoxy)methyl (MEM) ether, and a free hydroxyl. The MEM ether was examined with the hope that it might function as a bidentate ligand toward Ti(IV) and/or Zn(II) to facilitate the formation of the cationic intermediate under mild conditions.[10,11] A priori, it was not clear if the oxonium ion,[10] benzyl alcohol, or benzyl cation would result from this reaction. In addition, the MEM ether, a common alcohol protecting group introduced by Corey,[11] might be used to mask the alcohol for synthetic transformations and serve as a latent benzyl cation. The second series of compounds was constructed to examine the effect of changing the electronic nature of the para substituent on the aryl ring of the benzyl cation from an electron-donating hydroxyl to an electron-withdrawing quaternary ammonium salt. The third series was designed to examine the formation of five- and six-membered rings keeping other variables constant. Finally, a series of substrates was constructed with a furan, an alkene, and a β-keto ester as the cyclization terminator.

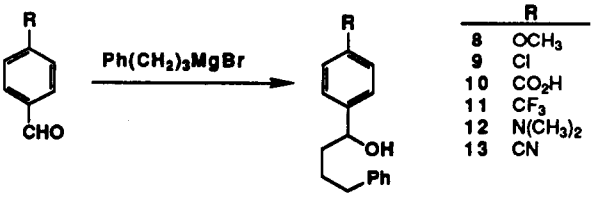
Two general strategies were utilized to construct the substrates: (1) addition of an organometallic reagent, or enolate, to a substituted benzaldehyde derivative and (2) addition of an aryl lithium to an aliphatic aldehyde.

Treatment of aryl bromide 5[12] with *tert*-butyllithium followed by addition of aldehydes 6 afforded benzylic alcohols 7 in high yield (eq 3). Protection of the phenol was necessary since the aryl lithium–lithium phenoxide derived from treatment of 4-bromo-2,6-dimethylphenol with 2 equiv of *tert*-butyllithium (THF, −78 °C) precipitated out of solution; no addition to the aldehyde was observed under these conditions.



(3)

Treatment of commercially available benzaldehyde derivatives with the Grignard reagent derived from 1-bromo-3-phenylpropane afforded substrates 8–13 (eq 4).



(4)

(7) For previous work from our laboratory on the chemistry of benzyl cations and their equivalents, see: (a) Angle, S. R.; Turnbull, K. D. *J. Am. Chem. Soc.* **1989**, *111*, 1136. (b) Angle, S. R.; Louie, M. S.; Mattson, H. L.; Yang, W. *Tetrahedron Lett.* **1989**, *30*, 1193. (c) Angle, S. R.; Louie, M. S. *Tetrahedron Lett.* **1989**, *30*, 5741. (d) Angle, S. R.; Arnaiz, D. O. *J. Org. Chem.* **1990**, *55*, 3708.

(8) For cyclizations employing nonstabilized cations, see: (a) Snider, B. B.; Jackson, A. C. *J. Org. Chem.* **1983**, *48*, 1471. (b) Talley, J. J. *Ibid.* **1985**, *50*, 1695. (c) Jones, D. N.; Peel, M. R. *J. Chem. Soc., Chem. Commun.* **1986**, 216.

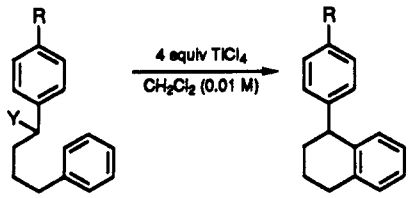
(9) For a preliminary communication of this work, see ref 7c.

(10) (a) Nishiyama, H.; Itoh, K. *J. Org. Chem.* **1982**, *47*, 2496. (b) Overman, L. E.; Castañeda, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303.

(11) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, *17*, 809.

(12) Aryl bromide 5 (bp 120–125 °C, 1 mmHg) was prepared by protection ($Me_2(t\text{-}Bu)SiCl$, imidazole, CH_2Cl_2, 90%) of the commercially available phenol.

Table I. Leaving Group and Para Substituent Study



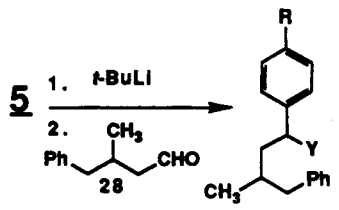
entry	substrate	R[b]	Y[c]	temp (°C)	time (min)	prod	yield[a] (%)
1	15	OH	OMEM	−78	2	44	93
2	16	OH	OCH_3	−78	2	44	96
3	8	OCH_3	OH	−78	2	45	94
4	17	OCH_3	OCH_3	−78	10	45	94
5	18	OCH_3	OMEM	−78	10	45	12
6	19	OCH_3	Br	−78	10	45	90
7	7b	$OSiR_3$	OH	−78	20	46	93
8	20	$OSiR_3$	OCH_3	−78	20	46	96
9	21	$OSiR_3$	OMEM	−78	20	46	18
10	22	$OSiR_3$	Br	−78	20	46	98
11	14	H	OH	−78	5	47	98
12	9	Cl	OH	−78	5	48	91
13	23	OAc	OMEM	23	30	49	89
14	10	CO_2H	OH	23	90	50	95
15	24	CO_2CH_3	OH	23	90	51	96
16	11	CF_3	OH	23	75	52	93
17	12	$N(CH_3)_2$	OH	23	4 h	53	92
18	13	CN	OH	61[d]	16 h	54	90
19	25	$N(CH_3)_3I$	OH	61[d]	65 h	55	70

[a] All yields refer to isolated, purified material. [b] SiR_3 = Si(*t*-Bu)Me_2. [c] OMEM = $OCH_2OCH_2CH_2OCH_3$. [d] $CHCl_3$ was used as the solvent.

The substrates shown (14–27) were prepared in a similar manner or by functionalization of substrates 7–14 (see Experimental Section for details).

	R	Y	n
14	H	OH	2
15	OH	OMEM	2
16	OH	OCH_3	2
17	OCH_3	OCH_3	2
18	OCH_3	OMEM	2
19	OCH_3	Br	2
20	OSi*t*-Bu$(CH_3)_2$	OCH_3	2
21	OSi*t*-Bu$(CH_3)_2$	OMEM	2
22	OSi*t*-Bu$(CH_3)_2$	Br	2
23	$OCOCH_3$	OMEM	2
24	CO_2CH_3	OH	2
25	$N(CH_3)_3I$	OH	2
26	OH	OCH_3	1
27	H	OH	1

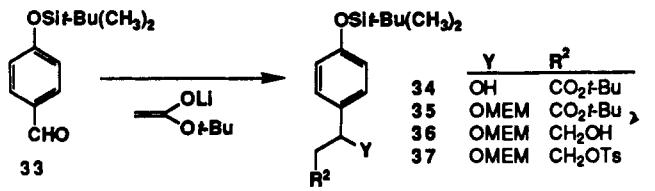
With a desire to probe the 1,3-stereoselectivity of the benzyl cation initiated cyclization reaction, substrates **31** and **32** were prepared from aryl bromide **5** and aldehyde **28** as shown in eq 5.



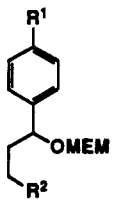
	R	Y
29	OSi*t*-Bu$(CH_3)_2$	OH
30	OSi*t*-Bu$(CH_3)_2$	OMEM
31	OH	OCH_3
32	OH	OMEM

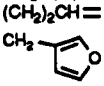
(5)

The final substrates were prepared from readily available tosylate **37**. Treatment of **37** with the Weiler dianion[13] followed by fluoride ion afforded β-keto ester **39**, which was acetylated under standard conditions to afford **40** (eq 6). Methyl ether **41** was obtained from tosylate **37** by deprotection and methylation to afford **38**, followed by condensation with the Weiler dianion. Substrates **42** and **43** were obtained from tosylate **37** by reaction with the requisite Grignard reagent in the presence of the Kochi–Tamura catalyst.[14]



	Y	R^2
34	OH	CO_2t-Bu
35	OMEM	CO_2t-Bu
36	OMEM	CH_2OH
37	OMEM	CH_2OTs



	R^1	R^2
38	OCH_3	CH_2OTs
39	OH	$CH_2C(O)CH_2CO_2CH_3$
40	$OCOCH_3$	$CH_2C(O)CH_2CO_2CH_3$
41	OCH_3	$CH_2C(O)CH_2CO_2CH_3$
42	OH	$(CH_2)_2CH{=}C(CH_3)_2$
43	OH	

(6)

Cyclization Studies

With the desired substrates in hand, the cyclization reactions were examined. Table I presents the results with different leaving groups and substituents para to the benzyl cation. A phenyl terminator was utilized in each case.

Leaving Group. In an attempt to avoid the harsh conditions and long reaction times normally employed for this type of cyclization, a MEM ether was examined as a potential precursor to the benzyl cation. The MEM group might be a less than ideal leaving group, since the formaldehyde liberated upon cleavage of the MEM ether might potentially react with the starting material and/or product. The cyclization of MEM ether **15** under several different conditions is summarized in Table II. Treatment of **15** with $TiCl_4$ (4 equiv, CH_2Cl_2) for 2 min at −78 °C afforded

(13) Weiler, L. *J. Am. Chem. Soc.* **1970**, *92*, 6702.

(14) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303.

Table II. Effect of Acid on 15 to 44 Conversion

acid	equiv	conc[a]	temp (°C)	time (min)	yield[b]
$TiCl_4$	4	0.010	-78	2	93
$TiCl_4$	10	0.010	-78	3	87
$TiCl_4$	4	0.010	-78	4	92
$TiCl_4$	5	0.010	-78	20	70
$ZnCl_2$	10	0.014	23	12 h	56
$BF_3{\cdot}OEt_2$	5	0.073	23	20	0
$BF_3{\cdot}OEt_2$	5	0.075	-78	2 h	0
$BF_3{\cdot}OEt_2$	5	0.071	-39	40	69
CF_3CO_2H	10	0.025	23	70	57

[a] [15] in CH_2Cl_2. [b] GC yield.

cyclization product 44 in 93% yield. Treatment of 15 with $ZnCl_2$ (10 equiv, CH_2Cl_2, heterogeneous) afforded 44 in 56% yield (GC). Other conditions were less successful, affording small amounts (5–50%) of the desired product 44 along with intractable products. Reaction of 15 with $BF_3{\cdot}OEt_2$ (5.0 equiv) afforded no cyclized product after 2 h at -78 °C or 20 min at 23 °C. However, reaction at -39 °C under the same conditions afforded product 44 in 69% yield (GC). Treatment of 15 with trifluoroacetic acid (10 equiv) resulted in the formation of 44 in 57% yield (GC). The importance of secondary reactions with formaldehyde could not be determined at this stage. However, further experiments with $TiCl_4$ showed that the product yield decreased with increasing reaction time. Since the products were stable to $TiCl_4$, the lower yield is indicative of reaction(s) with some external agent, likely formaldehyde.[15] Since the cyclization was rapid at -78 °C, it was impossible to ascertain whether the benzyl alcohol was an intermediate or the cationic intermediate was derived directly from the MEM ether. The acid of choice proved to be $TiCl_4$. Other acids (Table II) afforded cyclization products, but the yields were modest and the reaction conditions had to be carefully optimized. Reactions with $TiCl_4$ were less sensitive to minor changes in conditions. To allow a direct comparison of different cyclization reactions, the following standard conditions were used in every cyclization: 4 equiv $TiCl_4$, 0.01 M in CH_2Cl_2. Temperature and time were the only variables adjusted to drive the reactions to completion.

To test whether the MEM ether was responsible for the relatively mild cyclization conditions, methyl ether 16 was subjected to the standard conditions (2 min at -78 °C) to afford a virtually identical 96% yield of tetrahydronaphthalene 44. Thus, the MEM ether was not unique in its behavior in the cyclization. To probe the intermediacy of the benzyl alcohol in the MEM ether initiated cyclization, the benzylic alcohol/phenol corresponding to 15 and 16 was prepared. Unfortunately, the alcohol was unstable and the cyclization of this substrate could not be examined. Thus, a more complete study of different leaving groups was carried out using protected phenols as the substrates.

Four different leaving groups were examined with phenols protected as the methyl and silyl ethers (Table I, entries 3–10). In these cases, the benzylic alcohol, bromide, and methyl ether all afforded excellent yields of cyclized products. Bromides 19 and 22 were characterized; however, their lability necessitated special handling procedures (see Experimental Section). In contrast to the results with an unprotected phenol/benzylic MEM ether (entry 1, Table I), the systems with a protected phenol/benzylic MEM ether (entries 5 and 9) provided poor yields of cyclized products, undoubtedly due to complications from reaction of the products and/or starting material with the formaldehyde liberated in the MEM ether decomposition.[15] The methyl ether, bromide, and alcohol all afforded excellent yields of cyclized products under identical conditions. The leaving group study has shown that MEM ethers can only be used if a hydroxyl group is para to the benzyl cation. A methyl ether was shown to be a convenient protecting group for the benzylic alcohol and precursor to the cationic intermediate, affording high yields of cyclized products. The choice of which leaving group to use is governed by the synthetic sequence involved and the substitution of the phenol.

Substituents Para to the Benzyl Cation. A series of substrates with substituents para to the cation was studied to probe the electronic effects of the substituents on the efficiency of the cyclization reaction. Substituents with a wide range of Hammett σ values[16] were examined. A benzylic alcohol was utilized as the leaving group in every case, except entry 13, where a MEM ether was employed as the leaving group due to the ease of preparation of the substrate. In all cases, the terminator was kept constant. The electronically neutral case, R = H, (entry 11), afforded a 98% yield of cyclized product under the standard conditions at -78 °C in 5 min. Bright, Coxon, and Steel have recently reported this same conversion using ca. 17 equiv of fluorosulfonic acid at -78 °C for 30 min and obtained an 89% yield of 47.[1f] The inductively withdrawing chloride (entry 12) afforded a 91% yield of cyclized product under identical conditions.

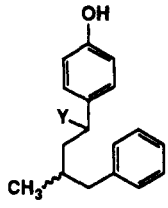
The reaction was severely retarded by electron-withdrawing substituents para to the cationic center. For example, acetylated phenol 23, acid 10, ester 24, and trifluoromethyl substrate 11 (Table I, entries 13–16) all afforded cyclized products with progressively longer reaction times. It is interesting to note that the increase in reaction time parallels the Hammett σ value[16] for each substituent. Acid 10 (entry 14) was only slightly soluble in methylene chloride, but the reaction mixture became homogeneous 10–15 min after the addition of $TiCl_4$; several minutes later, the product began to precipitate from solution. Due to the similar reaction time required for the highly soluble methyl ester 24, we concluded that the low solubility of the acid had no effect on the reaction time. The *p*-dimethylamino substrate 12 (entry 17) required 4 h at 23 °C for complete reaction. The dimethylamino substituent is a powerful electron donor, but upon complexation with $TiCl_4$ it showed reactivity comparable to a *p*-trifluoromethyl group. Entries 18 and 19 (Table I) were included to round out the Hammett σ value[16] range of substituent effects. It was surprising to find even nitrile 13 and quaternary ammonium salt 25 afforded high yields of cyclized products. Both reactions were heterogeneous, and no starting material or product could be observed when the reaction was monitored by ^1H NMR. Presumably, the cyclization occurs through the small amount of material in solution. The lower yield for entry 19 is thought to result from mechanical loss during workup due to the water solubility of the product.

The results summarized in Table I show that a high yield of cyclization products was not unique to benzyl cations with an electron-donating oxygen para to the cationic center. The electronic nature of substituents on the aryl ring of the benzyl cation can be varied over a wide range and even a substrate with a para quaternary ammonium salt (entry 19) underwent cyclization.

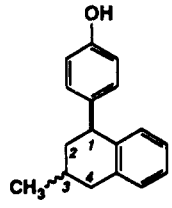
(15) The isolation of 57 (discussed later) shows reaction with formaldehyde is a significant problem.

(16) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A: Structure and Mechanisms*, 3rd ed.; Plenum Press: New York, 1990; pp 196–209.

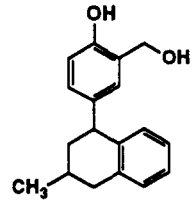
1,3-Stereoselectivity in the Formation of a Six-Membered Ring. The 1,3-stereoselectivity of the cyclization was examined by use of substrates **31** and **32**.



31 R = OCH_3
32 R = OMEM



56a βCH_3
56b αCH_3



57

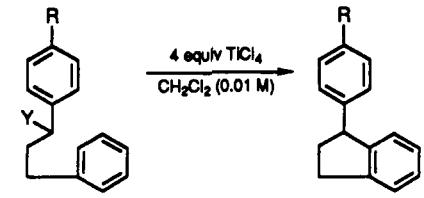
Methyl ether **31**, a 1:1 mixture of diastereomers, afforded cyclized product **56a** and a second product believed to be diastereomer **56b** in 92% yield (3:1 ratio, ^1H NMR). The major diastereomer **56a** was purified to afford a 15:1 mixture (GC) of **56a**/**56b**. The stereochemistry of **56a** was evident from the ^1H NMR spectrum, which showed a resonance for H(1) as a doublet of doublets at δ 4.01 (J = 12.0, 5.5 Hz). This is consistent with the pseudoaxial H(1) hydrogen coupled to the pseudoaxial and pseudoequatorial hydrogens of the adjacent C(2) methylene. The pseudoequatorial orientation of the C(3) methyl was evident from the H(2β)–H(3) coupling constant of 12.3 Hz and the H(4β)–H(3) coupling constant of 11.8 Hz, which show the methine hydrogen at C(3) is in the pseudoaxial orientation (see Experimental Section for a complete NMR assignment). Fractional recrystallization afforded the minor diastereomer **56b** as a 1:2 mixture of isomers **56a**/**56b**. The diastereomeric nature of **56b** was evident from the ^1H NMR spectrum, which was similar to that observed for **56a** except it showed a resonance for H(1) as a 5.5 Hz triplet at δ 4.20.

Cyclization substrate **31** was a 1:1 mixture of diastereomers; the relative stereochemistry of the stereogenic centers bearing the hydroxyl and methyl played no role in the stereoselectivity of the cyclization. The ratio of **56a**/**56b** did not change when the ratio of diastereomers **31** was varied. For example, **31** as a 12:1, 1:1, or a 1:2 mixture of diastereomers afforded identical 3:1 mixtures of **56a**/**56b**.

The cyclization of MEM ether **32** afforded a 52% yield of **56** (4.4:1 mixture of diastereomers, GC) and a 40% yield of hydroxymethyl derivative **57** (4.5:1 mixture of diastereomers, GC). The formation of **57** must occur via a Friedel–Crafts-type reaction between **56** (or **32**) and formaldehyde liberated in the MEM ether decomposition.

Ring Size. The formation of five-membered rings was briefly examined using a phenyl terminator. Formation of five-membered rings via a free benzyl cation using a phenyl ring as a terminator involves a transition state with only two sp^3 carbons in the forming ring. Cyclizations of this type have been reported to be extremely substrate selective, with a majority of the cases attempted affording low yields of the desired products.[17] At low temperatures (−78 to +25 °C; 4 equiv $TiCl_4$), the attempted cyclization of substrates **7a**, **26**, and **27** failed to give any of the desired dihydro-1H-indene products; only starting material and intractable products were obtained. However, at 42 °C good yields of cyclized products were observed (Table III). The higher temperature may be required to overcome the unfavorable interactions present in the transition state leading to the formation of the five-membered ring.

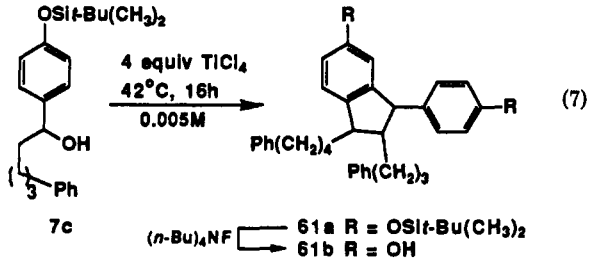
Table III. Formation of Five-Membered Rings



entry	substrate	R[b]	Y	time (min)	prod	yield[a] (%)
1	**26**	OH	OCH_3	10	**58**	75
2	**27**	H	OH	10	**59**	87
3	**7a**	$OSiR_3$	OH	20	**60**	89

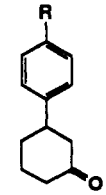
[a] All yields refer to isolated purified material. [b] SiR_3 = Si(*t*-Bu)Me_2.

The formation of a seven-membered ring was examined in a complementary system, **7c**. Under the conditions examined, none of the desired seven-membered ring cyclization product was observed. Under forcing conditions, an 82% yield of dihydro-1H-indene **61a** (3:1 mixture of diastereomers, ^1H NMR) was obtained. Removal of the silyl group afforded phenol **61b** for characterization. The formation of **61a** must result from elimination of the intermediate benzyl cation to a styrene that then acts as a nucleophile toward a second benzyl cation.[1b,7b]



(7)

Other Terminators. Finally, the facility of other terminators in this type of reaction was examined. Terminators containing heteroatom functionality such as a β-keto ester (**39**, **40**, and **41**) or a furan (**43**), where complications due to competitive Lewis acid complexation might be encountered, were of particular interest. Alkene **42** was included to probe the terminator reactivity. These systems all employ a MEM ether as the leaving group (Table IV).[18] β-Keto ester **39** was recovered unchanged upon treatment with $TiCl_4$ from −78 °C to room temperature. This is possibly due to complexation of the β-dicarbonyl functionality with $TiCl_4$. The resulting cationic complex may then resist formation of a second cationic center in the same molecule. Treatment of **39** with trifluoroacetic acid resulted in the formation of the desired cyclohexanone **62** (1:1 mixture of diastereomers, ^1H NMR) in 94% yield (Table IV). Decarbomethoxylation of diastereomers **62** afforded 3-arylcyclohexanone **64** as the sole

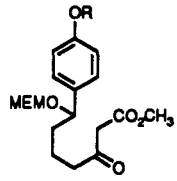
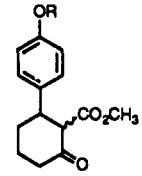
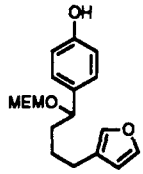
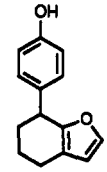
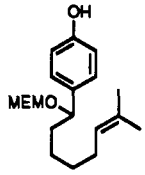
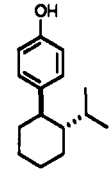


64 R = OH
65 R = OCH_3

(17) (a) Murphy, W. S.; Wattanasin, S. *Chem. Soc. Rev.* **1983**, 213. (b) Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270. (c) van Tamelen, E. E.; Pedlar, A. D.; Li, E.; James, D. R. *J. Am. Soc.* **1977**, *99*, 6778.

(18) These systems were constructed prior to the realization that the formaldehyde from the MEM ether could be troublesome.

Table IV. Terminator Study

substrate			acid[a]	product		yield[b] (%)
39		R = H	A	62		94
41		R = CH_3	A	63		99
40		R = Ac	A			0[c]
43			B	66		76
42			C	67		78 (5:1)[d]

[a] A = 10 equiv of CF_3CO_2H, room temperature, 20–40 min. B = 4 equiv of $TiCl_4$, −78 °C, 3 min. C = 35 equiv of $EtAlCl_2$, −78 °C, 10 min. [b] MEM = $OCH_2OCH_2CH_2OCH_3$. [b] All yields refer to isolated, purified material. [c] See text. [d] Ratio of diastereomers by ^1H NMR.

product, supporting the structure assigned to **62**. Since this substrate behaved differently from the phenyl terminator examined earlier, a brief survey of substituents on the aryl ring of the benzyl cation was undertaken. Methyl ether **41** cyclized at a comparable rate to phenol **39**, affording **63** as a 1:1 mixture of diastereomers (^1H NMR). Decarbomethoxylation of diastereomers **63** afforded **65**, supporting the assigned structure. *O*-Acylphenol **40** failed to cyclize at all under these conditions. Unreacted **40** was recovered after 75 min at room temperature (10 equiv of CF_3CO_2H), and decomposition was observed after 8 days under the same conditions. The cyclization of phenol **39** and methyl ether **41** were followed by ^1H NMR in $CDCl_3$. Treatment of phenol **39** with trifluoroacetic acid resulted in the rapid formation of an intermediate, believed to be a benzylic trifluoroacetate (^1H NMR analysis, <1 min). *O*-Methylphenol **41** also afforded an intermediate believed to be a trifluoroacetate upon treatment with trifluoroacetic acid (^1H NMR analysis, 3 min). The assignment of the intermediate as a trifluoroacetate is based upon the change in chemical shift of the resonance for the benzylic methine hydrogen from δ 4.51 (triplet, J = 8.4 Hz) in **39** to δ 5.83 (triplet, J = 6.9 Hz) in the proposed trifluoroacetate. It is likely that the benzylic trifluoroacetate is the precursor to the benzyl cation; however, the obvious control reaction of subjecting a preformed benzylic trifluoroacetate of known structure to the reaction conditions could not be carried out due to the instability of the compound.

Furan **43** underwent smooth cyclization[19] with use of the standard conditions to afford tetrahydrobenzofuran **66** in 76% yield. The short reaction time was critical to the success of the reaction since the product was not stable under the reaction conditions.

Alkene **42** afforded poor yields of cyclized product(s) under the standard conditions (4 equiv of $TiCl_4$). It was unclear if the initial cyclization to afford a tertiary cation was a problem or the subsequent chemistry of this cation (e.g., intramolecular Friedel–Crafts) was the source of difficulty. Accordingly, ethylaluminum dichloride was employed as the Lewis acid in hope of reducing the intermediate cation.[20] Treatment of **42** with an excess of ethylaluminum dichloride (35 equiv, −78 °C) afforded cyclized product **67** as a 5:1 mixture of diastereomers (^1H NMR). Purification by HPLC afforded the major diastereomer of **67** in 78% yield (>20:1 mixture of diastereomers by ^1H NMR). The ^1H NMR of the major diastereomer of **67** showed a resonance for the benzylic methine hydrogen at δ 2.32 (dt, J = 3.0, 11.0 Hz), indicative of an axial hydrogen coupled to two other axial hydrogens and one equatorial hydrogen. This places the aryl and isopropyl groups in equatorial orientations. The minor diastereomer of **67** showed a resonance in the ^1H NMR for this same hydrogen at δ 2.53 (t, J = 6.7 Hz), indicative of a cis relationship between the aryl and isopropyl groups.

Conclusion

Benzyl cation initiated cyclization reactions have been shown to be high-yield processes. The electronic nature of substituents para to the benzyl cation can be varied over a wide range with little or no effect on the yield of cyclization products. The leaving group can also be varied from a simple methyl ether to a benzyl alcohol or a benzylic bromide without affecting the cyclization reaction. A MEM ether was found to be a viable leaving group only in cases where a hydroxyl substituent was para to the benzyl cation. A major problem with the MEM leaving group was shown to be the reaction of the product and/or starting material with formaldehyde liberated from the MEM group. The nature of the cationic intermediate has not been examined; however, a free cation, unionized polar complex, tight ion pair, or extended ion pair similar to those reported by Jencks[21] for benzylic systems would all give rise to the observed cyclization.

Cyclization terminators of varying structure and reactivity afforded excellent yields of cyclized products. The generality of benzyl cation initiated cyclizations should

(19) For use of furans as cyclization terminators, see: Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572.

(20) Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927.

(21) Aymes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888, 7900.

allow these reactions to become a standard tool for the assembly of aryl substituted carbocycles. Work is currently in progress to exploit this type of cyclization in the synthesis of (+)-pancratistatin.

Experimental Section[22a]

General Information. HPLC was carried out with an RI detector. Capillary GC was carried out with an FID detector on a 25-m HP-101 (methyl silicone) column. The following standard GC parameters were used unless indicated otherwise: flow rate 60 mL/min; injector temperature 200 °C; detector temperature 280 °C; temperature program 40–280 °C at 18 °C/min; initial time 1 min; final time 5 min. Ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Pyridine, CH_2Cl_2, $CHCl_3$, $(i\text{-}Pr)_2NEt$, and Et_2NH were distilled from CaH_2. Solvents for chromatography and recrystallization were distilled prior to use. The molarities indicated for alkyllithiums were established by titration with 2,5-dimethoxybenzyl alcohol.[22b] Melting points are uncorrected. In cases where synthetic intermediates or products were isolated by aqueous workup (aqueous solution, organic solvent), the procedure was to quench the reaction mixture with indicated aqueous solution, dilute with the indicated organic solvent, separate the organic layer, extract the aqueous layer several times with the organic solvent, dry the combined organic extracts over $MgSO_4$, and remove the solvent under reduced pressure (water aspirator) with a Büchi rotary evaporator. The organic solvent/$CuSO_4$ notation indicates the organic layer was washed several times with aqueous $CuSO_4$ solution to remove amine. Unless stated otherwise, all reactions were run under an atmosphere of nitrogen in oven-dried glassware. The pH 6 buffer was prepared by dissolving 23.2 g of KH_2PO_4 and 4.3 g of Na_2HPO_4 (anhydrous) in water and diluting to a volume of 1 L. Bulb to bulb distillations were performed with a Büchi GKR-50 microdistillation apparatus.

1-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-3-phenylpropan-1-ol (7a). *t*-BuLi (6.7 mL, 6.7 mmol, 1.0 M in pentane) was added dropwise to a rapidly stirred solution of bromide **5**[12] (1.93 g, 6.71 mmol) and THF (67 mL) at −78 °C. The rate of addition was adjusted to keep the temperature below −76 °C. After the solution was stirred for 2 h at −78 °C, a solution of hydrocinnamaldehyde[23] (0.901 g, 6.71 mmol) and THF (2 mL) was added dropwise, observing the same temperature control. The solution was allowed to warm to 0 °C and stirred for an additional 30 min. Aqueous workup (pH 6 buffer, ether) afforded 2.35 g of crude product as a clear oil. Flash chromatography (10% ethyl acetate/hexane) afforded 2.21 g (96%) of **7a** as a clear, colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.17 (m, 7 H, Ar*H*), 6.81 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 4.62 (dd, *J* = 7.2, 6.0 Hz, 1 H, CH), 2.77–2.57 (m, 2 H, PhCH_2), 2.18–1.93 (m, 2 H, ArCHCH_2), 1.88 (b s, 1 H, OH), 0.98 (s, 9 H, SiC$(CH_3)_3$), 0.19 (s, 6 H, Si$(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 141.8, 137.3, 128.3, 128.2, 127.0, 125.6, 119.9, 73.3, 40.3, 32.0, 25.6, 18.1, −4.5; IR (neat, cm^{-1}) 3359, 2930, 1608, 840, 808, 781; MS (EI, 70 eV) *m/z* 342 (M^+, 4), 324 (52), 267 (100), 91 (62), 77 (5).

1-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-4-phenylbutan-1-ol (7b). The same procedure as given previously for the preparation of **7a** was carried out with 4-phenylbutanal[24] (**6b**). Bulb to bulb distillation (25 μmHg, oven temperature 150–160 °C) afforded 4.33 g (90%) of **7b** as a white solid: mp 40.5–41.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.13 (m, 7 H, Ar*H*), 6.80 (d, *J* = 7.6 Hz, 2 H, Ar*H*), 4.61 (m, 1 H, CH), 2.62 (t, *J* = 8.6 Hz, 2 H, PhCH_2), 1.86–1.51 (m, 5 H, ArCHCH_2CH_2, O*H*), 0.98 (s, 9 H, SiC$(CH_3)_3$), 0.19 (s, 6 H, Si$(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 142.1, 137.4, 128.2, 128.1, 119.7, 126.9, 125.5, 73.7, 38.3, 35.6, 27.4, 25.6, 18.0, −4.5; IR (CCl_4) cm^{-1} 3353, 2930, 1607, 839, 780; MS (EI, 20 eV) *m/z* 356 (M^+, 8), 247 (38), 237 (100). Anal. Calcd for $C_{22}H_{32}O_2Si$: C, 74.10; H, 9.05. Found: C, 74.33; H, 8.89.

1-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-5-phenylpentan-1-ol (7c). The same procedure as given previously for the preparation of **7a** was carried out with 5-phenylpentanal[25] (**6c**). Flash chromatography (10% ethyl acetate/hexane) afforded 2.73 g (94%) of **7c** as a clear, colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.13 (m, 7 H, Ar*H*), 6.80 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 4.60 (dt, *J* = 6.6, 3.2 Hz, 1 H, CH), 2.60 (t, *J* = 7.7 Hz, 2 H, PhCH_2), 1.90–1.26 (m, 6 H, CH(CH_2)$_3$), 1.76 (d, *J* = 3.3 Hz, 1 H, OH), 1.00 (s, 9 H, SiC$(CH_3)_3$), 0.21 (s, 6 H, Si$(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 142.4, 137.6, 128.2, 128.1, 126.9, 125.5, 119.8, 74.0, 38.7, 35.8, 31.2, 25.6, 25.4, 18.1, −4.5; IR (CCl_4, cm^{-1}) 3617, 2932, 1608, 843; MS (EI, 20 eV) *m/z* 370 (M^+, 27), 237 (100). Anal. Calcd for $C_{23}H_{34}O_2Si$: C, 74.54; H, 9.25. Found: C, 74.67; H, 9.33.

1-(4-Methoxyphenyl)-4-phenylbutan-1-ol (8).[26] Representative Procedure for Grignard Reaction. A solution of *p*-anisaldehyde (2.01 g, 14.8 mmol) and THF (148 mL) was added to a freshly prepared solution of the Grignard reagent derived from 1-bromo-3-phenylpropane (14.4 mL, 17.7 mmol, 1.23 M in THF) at 0 °C. After the solution was stirred for 40 min, aqueous workup (3 N HCl, ice, ether) afforded 3.78 g of crude product as a light yellow solid. Recrystallization (ether/hexane) afforded 3.57 g (94%) of **8** as a white solid: mp 60.0–60.5 °C; lit.[26] oil, bp 195 °C (0.5 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.13 (m, 7 H, Ar*H*), 6.87 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.63 (t, *J* = 5.3 Hz, 1 H, CH), 3.80 (s, 3 H, OCH_3), 2.62 (t, *J* = 7.1 Hz, 2 H, PhCH_2), 1.90–1.57 (m, 5 H, PhCH_2CH_2CH_2, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 142.0, 136.8, 128.1, 127.9, 126.8, 125.4, 113.4, 73.4, 54.8, 38.2, 35.4, 27.3; IR (CCl_4 cm^{-1}) 3617, 3450, 3029 1612, 833; MS (CI, CH_4) *m/z* 257 (MH^+, 6), 256 (M^+, 16), 239 (100), 137 (82), 131 (50), 91 (8). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.57; H, 7.75. Compounds **9–12** were prepared as described previously for compound **8**.

1-(4-Chlorophenyl)-4-phenylbutan-1-ol (9).[27] Recrystallization (ether/hexane) afforded 2.86 g (60%) of **9** as a white solid: mp 41.9–42.0 °C, lit.[27] 43 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.12 (m, 9 H, Ar*H*), 4.66 (b s, 1 H, CH), 2.62 (t, *J* = 7.0 Hz, 2 H, PhCH_2), 1.83–1.55 (m, 5 H, PhCH_2CH_2CH_2, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 142.0, 132.9, 128.4, 128.3, 128.2, 127.2, 125.7, 73.6, 38.4, 35.6, 27.3; IR (CCl_4, cm^{-1}) 3616, 3425, 2941, 831; MS (EI, 20 eV) *m/z* 260 (M^+, 1), 141 (100), 138 (77), 104 (84), 91 (31). Anal. Calcd for $C_{16}H_{17}ClO$: C, 73.70; H, 6.57. Found: C, 73.76; H, 6.64.

4-(1-Hydroxy-4-phenylbutyl)benzoic Acid (10). Recrystallization (methanol) afforded 2.01 g (50%) of **10** as a white solid (2.1 equiv of RMgX was used): mp 137.5–138.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.1 Hz, 2 H, Ar*H*), 7.43 (d, *J* = 8.1 Hz, 2 H, Ar*H*), 7.29–7.14 (m, 5 H, Ph*H*), 4.79 (t, *J* = 5.6 Hz, 1 H, CH), 2.64 (t, *J* = 6.9 Hz, 2 H, PhCH_2), 1.89–1.52 (m, 5 H, PhCH_2CH_2CH_2, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ (C=O not observed) 150.7, 141.9, 130.4, 128.4, 125.9, 125.8, 74.0, 38.6, 35.6, 27.3; IR (KBr, cm^{-1}) 3392 (br, OH), 2937, 1685 (C=O), 867; MS (EI, 20 eV) *m/z* 270 (M^+, 1), 151 (34), 104 (100), 91 (9). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.26; H, 6.75.

4-Phenyl-1-[4-(trifluoromethyl)phenyl]butan-1-ol (11). Recrystallization (ether/hexane) afforded 3.82 g (50%) of **11** as a white solid: mp 45.5–46.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.36 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.50–7.11 (m, 5 H, Ph*H*), 4.66 (b s, 1 H, CH), 2.60 (t, *J* = 6.8 Hz, 2 H, PhCH_2), 2.31 (b s, 1 H, OH), 1.81–1.52 (m, 4 H, PhCH_2CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 141.9, 129.5 (q, *J* = 32.3 Hz, CCF_3), 128.3, 126.0, 125.8, 125.2 (q, *J* = 3.6 Hz, $(CH)_2CCF_3$), 125.1, 124.2 (q, *J* = 272.2 Hz, CF_3), 73.6, 38.5, 35.5, 27.2; IR (CCl_4, cm^{-1}) 3618, 3438, 3029, 2941, 1621, 844; MS (EI, 20 eV) *m/z* 294 (M^+, 1), 175 (21), 104 (100), 91 (6). Anal. Calcd for $C_{17}H_{17}F_3O$: C, 69.38; H, 5.73. Found: C, 69.31; H, 5.70.

(22) (a) Some general experimental protocols have been recently reported: Angle, S. R.; Yang, W. *J. Am. Chem. Soc.* **1990**, *112*, 4524. (b) Alkyllithium titration: Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87.

(23) Purchased from Aldrich Chemical Co., Milwaukee, WI.

(24) Reduction ($LiAlH_4$) of 4-phenylbutanoic acid followed by oxidation under Swern conditions (Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480; ClCOCOCl, DMSO, Et_3N) afforded the known aldehyde **6b**: Julia, M.; Blasioli, C. *Bull. Soc. Chim. Fr.* **1976**, 1941.

(25) By use of the sequence in ref 24, 5-phenylpentanoic afforded the known aldehyde **6c**: Meyers, A. I.; Nazarenko, N. *J. Am. Chem. Soc.* **1972**, *94*, 3243.

(26) Compound **8** was previously reported without spectral data as an oil (Blum, J.; Becker, Y. *J. Chem. Soc., Perkin Trans. 2* **1972**, 982) and has been reported in a patent: *Chem. Abstr.* **1981**, *94*, 174658; Ono, K.; Kawakami, H.; Katsube, J. Eur. Pat. Appl. 17217, 15 Oct 1980.

(27) Compound **9** was previously reported without spectral data by Blum and Becker (see ref 26).

N,N-Dimethyl-4-(1-hydroxy-4-phenylbutyl)benzenamine (12).[28] Recrystallization (ether/hexane) afforded 3.25 g (90%) of **12**[28] as a white solid: mp 70.0–70.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.15 (m, 7 H, Ar*H*), 6.72 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 4.56 (t, *J* = 4.8 Hz, 1 H, CH), 2.92 (s, 6 H, $N(CH_3)_2$), 2.61 (t, *J* = 7.3 Hz, 2 H, $PhCH_2$), 1.90–1.50 (m, 5 H, $PhCH_2CH_2CH_2$, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 142.1, 132.8, 128.1, 127.9, 126.6, 125.3, 112.3, 73.6, 40.3, 38.1, 35.5, 27.4; IR (CCl_4, cm^{-1}) 3617, 3458, 3028, 1616, 819; MS (EI, 20 eV) *m/z* 270 (MH^+, 4), 160 (93), 150 (100), 91 (2). Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61. Found: C, 80.50; H, 8.80.

1-(4-Hydroxyphenyl)-1-[[(methoxyethoxy)methyl]oxy]-4-phenylbutane (15). A rapidly stirred solution of silyl ether **21** (1.89 g, 4.37 mmol) and THF (4.4 mL) was treated with (*n*-Bu)$_4$NF (4.80 mL, 4.8 mmol, 1.0 M in THF) at 23 °C. The resulting solution was stirred for 20 min. Aqueous workup (pH 6 buffer, ether) afforded 1.30 g of crude product as a light yellow solid. Recrystallization (ether/hexane) afforded 1.27 g (92%) of **15** as a white solid: mp 58.0–58.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.09 (m, 7 H, Ar*H*), 6.75 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 5.65 (b s, 1 H, OH), 4.60–4.51 (m, 3 H, OCH_2O, CH), 3.84–3.75 (m, 1 H, OCH_2CH*H*), 3.59–3.45 (m, 3 H, OCH_2CHH), 3.37 (s, 3 H, OCH_3) 2.60 (t, *J* = 7.0 Hz, 2 H, $PhCH_2$), 1.92–1.49 (m, 4 H, $PhCH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 142.1, 132.9, 128.2, 128.1, 125.5, 115.1, 92.5, 77.6, 71.5, 66.7, 58.6, 37.0, 35.5, 27.5; IR (neat, cm^{-1}) 3351, 2839, 1614, 836, 749; MS (CI, NH_3) *m/z* 348 (MNH_4^+, 1), 225 (72), 28 (91), 89 (100); HRMS for $C_{20}H_{26}O_4$ calcd 330.1831, found 330.1823. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.50; H, 7.87.

1-(4-Hydroxyphenyl)-1-methoxy-4-phenylbutane (16). General Procedure for Benzylic Methyl Ether Formation. Trifluoroacetic acid (1.04 mL, 13.5 mmol) was added to a stirred solution of alcohol **7b** (0.400 g, 1.12 mmol) and methanol (11.2 mL) at 23 °C. The resulting solution was stirred for 36 h. Aqueous workup ($NaHCO_3$, ether) afforded 0.285 g of crude product as a yellow solid. Recrystallization (ether/hexane) afforded 0.280 g (97%) of **16** as a white solid: mp 111.0–111.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.12 (m, 7 H, Ar*H*), 6.80 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 4.89 (s, 1 H, OH), 4.03 (t, *J* = 6.0 Hz, 1 H, CH), 3.16 (s, 3 H, CH_3), 2.59 (t, *J* = 6.8 Hz, 2 H, $PhCH_2$), 1.90–1.44 (m, 4 H, $PhCH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 142.3, 133.5, 128.3, 128.2, 128.1, 125.6, 115.3, 83.8, 56.2, 37.3, 35.7, 27.7; IR (CCl_4, cm^{-1}) 3610, 3337, 2935, 1614, 834; MS (EI, 20 eV) *m/z* 256 (M^+, 1), 137 (100), 91 (6); HRMS for $C_{17}H_{20}O_2$ calcd 256.1463, found 256.1478. Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.56; H, 7.95.

1-Methoxy-1-(4-methoxyphenyl)-4-phenylbutane (17). The same procedure as given previously for the preparation of **16** was carried out with **8**. Recrystallization (ether/hexane) afforded 0.501 g (95%) of **17** as a white solid: purity by GC 99.75% (13.24 min, injector temperature 150 °C); mp 40.0–41.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.12 (m, 7 H, Ar*H*), 6.86 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.03 (t, *J* = 6.3 Hz, 1 H, CH), 3.78 (s, 3 H, $ArOCH_3$), 3.15 (s, 3 H, OCH_3), 2.58 (t, *J* = 7.1 Hz, 2 H, $PhCH_2$), 1.89–1.48 (m, 4 H, $PhCH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 142.2, 134.1, 128.2, 128.1, 127.7, 125.5, 113.6, 82.3, 56.1, 54.9, 37.6, 35.7, 27.6; IR (neat, cm^{-1}) 3026, 1611, 832, 746, 734; MS (EI, 20 eV) *m/z* 270 (M^+, 1), 153 (1), 152 (10), 151 (100), 147 (1), 134 (8), 121 (1), 91 (1). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.18; H, 8.25.

1-[[(Methoxyethoxy)methyl]oxy]-1-(4-methoxyphenyl)-4-phenylbutane (18). General Procedure for MEM Protection of an Alcohol. By use of the procedure of Corey et al.,[11] (methoxyethoxy)methyl chloride (0.40 mL, 3.5 mmol) was added to a stirred solution of alcohol **8** (0.301 g, 1.17 mmol), diisopropylethyl amine (0.61 mL, 3.5 mmol), and CH_2Cl_2 (1.5 mL) at 23 °C. The resulting solution was stirred for 3.5 h. Aqueous workup (pH 6 buffer, ether) afforded 0.407 g (99%) of crude **18** as a clear, colorless liquid: purity by GC 97.39% (15.28 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.12 (m, 7 H, Ar*H*), 6.85 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 4.62–4.54 (m, 3 H, OCH_2O, CH), 3.83–3.76 (m, 1 H, $OCHHCH_2O$), 3.79 (s, 3 H, $ArOCH_3$), 3.58–3.44 (m, 3 H, $OCHHCH_2O$), 3.36 (s, 3 H, CH_2OCH_3), 2.61 (t, *J* = 7.2 Hz, 2 H, $PhCH_2$), 1.93–1.52 (m, 4 H, $CHCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 142.1, 133.8, 128.2, 128.1, 128.0, 125.5, 113.5, 92.8, 77.4, 71.6, 66.8, 58.7, 55.0, 37.2, 35.6, 27.5; IR (neat, cm^{-1}) 2935, 1611, 832, 811, 748; MS (DCI, NH_3) *m/z* 362 (MNH_4^+, 20) 239 (100), 91 (11).

1-Bromo-1-(4-methoxyphenyl)-4-phenylbutane (19). By use of a modification of the method of Jung and Hatfield,[29] bromotrimethylsilane (41.6 μL, 0.316 mmol) was added to a rapidly stirred solution of alcohol **8** (67.4 mg, 0.263 mmol) and CH_2Cl_2 (4 mL) at 23 °C. After being stirred for 10 min, the mixture was poured into 5 °C aqueous pH 6 buffer and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). Concentration by sparging with a stream of nitrogen afforded 59.5 mg (>99%) of crude **19** as a clear, colorless oil. Bromide **19** was unstable and used immediately: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.15 (m, 7 H, Ar*H*), 6.86 (d, *J* = 8.7 Hz, 2 H, Ar*H*), 4.98 (t, *J* = 7.6 Hz, 1 H, CH), 3.81 (s, 3 H, OCH_3), 2.66 (t, *J* = 7.6 Hz, 2 H, $PhCH_2$), 2.40–2.12 (m, 2 H, $CHBrCH_2$), 1.90–1.56 (m, 2 H, $PhCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 141.7, 134.3, 128.5, 128.3, 125.9, 114.0, 55.8, 55.3, 39.6, 35.1, 30.0; IR (CCl_4, cm^{-1}) 2935, 1609, 832, 807, 788.

1-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-1-methoxy-4-phenylbutane (20). A solution of phenol **16** (0.148 g, 0.576 mmol), imidazole (47.0 mg, 0.691 mmol), *tert*-butyldimethylsilyl chloride (0.101 g, 0.668 mmol) and CH_2Cl_2 (2 mL) was stirred for 2 h at 23 °C. The resulting suspension was filtered through Celite, and the solids were discarded. Aqueous workup (pH 6 buffer, ether) afforded 0.212 g of crude product. Flash chromatography (5% ethyl acetate/hexane) afforded 0.201 g (94%) of **20** as a clear, colorless liquid: purity by GC 98.95% (15.00 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.09 (m, 7 H, Ar*H*), 6.80 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 4.02 (t, *J* = 6.2 Hz, 1 H, CH), 3.15 (s, 3 H, OCH_3), 2.58 (t, *J* = 7.1 Hz, 2 H, $PhCH_2$), 1.89–1.50 (m, 4 H, $CHCH_2CH_2$), 0.98 (s, 9 H, $SiC(CH_3)_3$), 0.20 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 142.3, 134.8, 128.3, 128.2, 127.7, 125.6, 119.8, 83.5, 56.2, 37.6, 35.8, 27.7, 25.6, 18.1, -4.4; IR (neat, cm^{-1}) 2930, 1608, 840, 781, 748; MS (DCI, NH_3) *m/z* 371 (MH^+, 5), 340 (100), 91 (8).

1-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-1-[[(methoxyethoxy)methyl]oxy]-4-phenylbutane (21). The same procedure as given previously for the preparation of **18** was carried out with **7a**. Crude **21** (1.89 g, 88%) was a clear, colorless liquid: purity by GC 99.76% (17.70 min, injector temperature 150 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.11 (m, 7 H, Ar*H*), 6.77 (d, *J* = 8.4 Hz, 2 H, Ar*H*), 4.62–4.51 (m, 3 H, OCH_2O, CH), 3.81–3.74 (m, 1 H, OCH_2CHHO), 3.56–3.41 (m, 3 H, OCH_2CHHO), 3.35 (s, 3 H, OCH_3), 2.60 (t, *J* = 7.0 Hz, 2 H, $PhCH_2$), 1.91–1.49 (m, 4 H, $PhCH_2CH_2CH_2$), 0.97 (s, 9 H, $SiC(CH_3)_3$), 0.18 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 142.1, 134.5, 128.2, 128.1, 127.9, 125.5, 119.7, 92.8, 77.5, 71.6, 66.8, 58.8, 37.2, 35.6, 27.6, 25.5, 18.0, -4.5; IR (CCl_4, cm^{-1}) 2931, 1608, 842; MS (CI, NH_3) *m/z* 444 (M^+, 7), 339 (68), 325 (40), 91 (29), 89 (100); HRMS for $C_{26}H_{40}H_4Si$ calcd 444.2696, found 444. 2691. Anal. Calcd for $C_{26}H_{40}O_4Si$: C, 70.10; H, 9.05. Found: C, 70.24; H, 9.23.

1-Bromo-1-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-4-phenylbutane (22). The same procedure as given previously for the preparation of **19** was carried out with **7b**. Bromide **22** (70.4 mg, >99%) was unstable and used immediately: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.10 (m, 7 H, Ar*H*), 6.74 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 4.93 (t, *J* = 7.5 Hz, 1 H, CH), 2.60 (t, *J* = 7.6 Hz, 2 H, $PhCH_2$), 2.34–2.05 (m, 2 H, $CHBrCH_2$), 1.85–1.50 (m, 2 H, $PhCH_2CH_2$), 0.95 (s, 9 H, $SiC(CH_3)_3$), 0.17 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 141.7, 134.8, 128.4, 128.3, 125.9, 120.0, 55.8, 39.6, 35.1, 30.0, 25.6, 18.2, -4.4; IR (neat, cm^{-1}) 2931, 1606, 840, 781, 748; MS (DCI, NH_3) *m/z* 419 (M^+, 1), 340 (M-Br, 16), 247 (100), 237 (49), 91 (36).

1-[4-(Acetyloxy)phenyl]-1-[[(methoxyethoxy)methyl]oxy]-4-phenylbutane (23). A rapidly stirred solution of phenol **15** (0.589 g, 1.86 mmol) and pyridine (44 mL) was treated with acetic anhydride (0.52 mL, 5.6 mmol) at 23 °C. After the solution was stirred for 24 h, aqueous workup (pH 6 buffer, ether/$CuSO_4$) afforded 0.655 g of crude product as a light yellow liquid. Flash

(28) Compound **12** was reported in the patent noted in ref 26.

(29) Jung, M. E.; Hatfield, G. L. *Tetrahedron Lett.* **1978**, *19*, 4483.

chromatography (10% ethyl acetate/hexane) afforded 0.603 g (87%) of **23** as a clear, colorless liquid: purity by GC 97.16% (16.10 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.12 (m, 7 H, Ar*H*), 7.03 (d, J = 8.4 Hz, 2 H, Ar*H*), 4.64–4.56 (m, 3 H, OCH_2O, CH), 3.81–3.74 (m, 1 H, OCH_2CHHO), 3.57–3.38 (m, 3 H, OCH_2CHHO), 3.34 (s, 3 H, OCH_3), 2.61 (t, J = 7.2 Hz, 2 H, $PhCH_2$), 2.27 (s, 3 H, $OCCH_3$), 1.90–1.52 (m, 4 H, $PhCH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 149.8, 142.0, 139.6, 128.2, 128.1, 127.7, 125.6, 121.2, 93.2, 77.4, 71.5, 66.9, 58.8, 37.3, 35.5, 27.4, 20.9; IR (neat, cm^{-1}) 2937, 1761, 850; MS (CI, NH_3) m/z 390 (MNH_4^+, 25), 77 (13), 52 (100). Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.95; H, 7.58. Found: C, 71.01; H, 7.70.

1-[4-(Methoxycarbonyl)phenyl]-4-phenylbutan-1-ol (24). A solution of excess diazomethane and ether was added dropwise to a rapidly stirred suspension of acid **10** (0.400 g, 1.48 mmol) and ether (10 mL) until the reaction mixture retained a slightly yellow color. After the solution was stirred for an additional 15 min, glacial acetic acid was added dropwise until the reaction mixture decolorized. Aqueous workup ($NaHCO_3$, ether) afforded 0.424 g of crude product as a light yellow solid. Recrystallization (ether/hexane) afforded 0.410 g (97%) of **24** as a white solid: mp 49.0–49.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8.1 Hz, 2 H, Ar*H*), 7.38 (d, J = 8.1 Hz, 2 H, Ar*H*), 7.28–7.12 (m, 5 H, Ph*H*), 4.74 (t, J = 2.8 Hz, 1 H, CH), 3.90 (s, 3 H, CO_2CH_3), 2.62 (t, J = 6.9 Hz, 2 H, $PhCH_2$), 1.98 (d, J = 3.1 Hz, 1 H, OH), 1.87–1.54 (m, 4 H, $PhCH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 149.9, 141.9, 129.6, 128.9, 128.2, 128.1, 125.6, 73.7, 51.9, 38.4, 35.5, 27.2; IR (CCl_4, cm^{-1}) 3617, 3505, 3029, 2951, 1728, 858; MS (EI, 20 eV) m/z 284 (M^+, 1), 165 (39), 104 (100), 91 (5). Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.95; H, 7.30.

***N*-[4-(1-Hydroxy-4-phenylbutyl)phenyl]-*N*,*N*,*N*-trimethylammonium Iodide (25).** A solution of amine **12** (1.00 g, 3.71 mmol), THF (7 mL), and methyl iodide (1.32 g, 9.28 mmol) was stirred for 14 h with protection from light. The resulting suspension was diluted with ether (10 mL) and filtered, and the filtrate was washed with ether. The solid was dried in vacuo (20 μmHg, 60 °C) with protection from light to afford 1.48 g (97%) of **25** as a white solid: mp 146.5–147.5 °C; ^{1}H NMR (300 MHz; $CDCl_3$:DMSO-d_6 = 6:1) δ 7.90 (d, J = 8.8 Hz, 2 H, Ar*H*), 7.53 (d, J = 8.8 Hz, 2 H, Ar*H*), 7.28–7.15 (m, 5 H, Ar*H*), 5.36 (d, J = 4.6 Hz, 1 H, OH), 4.65 (dd, J = 10.6, 5.8 Hz, 1 H, CH), 3.60 (s, 9 H, $N(CH_3)_3$), 2.58 (dd, J = 7.6, 5.6 Hz, 2 H, $PhCH_2$), 1.69–1.50 (m, 4 H, $PhCH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$:DMSO-d_6 = 6:1) δ 147.4, 144.1, 140.8, 127.0, 126.9, 126.4, 124.3, 118.6, 70.4, 56.2, 37.5, 34.2, 26.0; IR (KBr, cm^{-1}) 3568, 3386, 851, 825; MS (FAB, positive ion, nitrobenzyl alcohol matrix) m/z 284 (M^+, 100), 150 (16), 136 (8). Anal. Calcd for $C_{19}H_{26}INO$: C, 55.48; H, 6.37. Found: C, 55.72; H, 6.51.

1-(4-Hydroxyphenyl)-1-methoxy-3-phenylpropane (26). The same procedure as given previously for the preparation of **16** was carried out with **7a**. Recrystallization (ether/hexane) afforded 0.386 g (90%) of **26** as a white solid: mp 82.0–83.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.13 (m, 7 H, Ar*H*), 6.81 (d, J = 8.4 Hz, 2 H, Ar*H*), 5.78 (b s, 1 H, OH), 4.04 (t, J = 6.7 Hz, 1 H, CH), 3.20 (s, 3 H, OCH_3), 2.72–2.55 (m, 2 H, $PhCH_2$), 2.23–2.11 (m, 1 H, $CHCHH$), 1.99–1.87 (m, 1 H, $CHCHH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 141.6, 133.1, 128.4, 128.2, 125.7, 115.4, 83.0, 56.1, 39.0, 31.9; IR (CCl_4, cm^{-1}) 3610, 3335, 2937, 1614, 834; MS (EI, 20 eV) m/z 242 (M^+, 9), 138 (9), 137 (100). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 78.84; H, 7.51.

(1*R,3*S**)- and (1*R**,3*R**)-1-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-3-methyl-4-phenylbutan-1-ol (29).** The same procedure as given previously for the preparation of **7a** was carried out with 3-methyl-4-phenylbutanal[30] (**28**). Flash chromatography (10% ethyl acetate/hexane) afforded 1.53 g (91%) of **29** as a clear, colorless oil (1:1 mixture of diastereomers, ^{1}H NMR): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.06 (m, 7 H, Ar*H*), 6.80 (m, 2 H, Ar*H*), 4.74–4.66 (m, 1 H, ArC*H*), 2.73–2.63 (m, 1 H, PhC*H*H), 2.44–2.32 (m, 1 H, PhCH*H*), 1.97–1.65 (m, 4 H, $PhCHCH_2CHCH_3$, O*H*), 0.98 (s, 9 H, $SiC(CH_3)_3$), 0.90 (d, J = 5.4 Hz, 3 H, $CHCH_3$), 0.19 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 154.7, 140.9, 140.8, 138.0, 137.4, 129.0, 127.9, 127.1, 126.9, 125.6, 119.8, 72.2, 71.6, 46.0, 45.5, 43.8, 43.3, 31.4, 25.6, 19.9, 19.1, 18.1, –4.5; IR (neat, cm^{-1}) 3359, 2929, 840, 781, 739; MS (EI, 20 eV) m/z 370 (M^+, 7), 261 (100), 91 (5); HRMS for $C_{23}H_{34}O_2Si$ calcd 370.2328, found 370.2342.

(1*R,3*S**)- and (1*R**,3*R**)-1-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-1-[[(methoxyethoxy)methyl]oxy]-3-methyl-4-phenylbutane.** The same procedure as given previously for the preparation of **18** was carried out with **29**. Crude **30** (1.54 g, 92%) was a clear, colorless liquid (1:1 mixture of diastereomers; GC, 17.91 and 18.05 min): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.04 (m, 7 H, Ar*H*), 6.80–6.75 (m, 2 H, Ar*H*), 4.69–4.63 (m, 1 H, ArC*H*), 4.58 (AB q, J = 9.8 Hz, 2 H, OCH_2O), 3.82–3.70 (m, 1 H, $OCHHCH_2O$), 3.56–3.41 (m, 3 H, $OCHHCH_2O$), 3.36 (s, 3 H, OCH_3), 2.74–2.63 (m, 1 H, PhC*H*H), 2.41–2.32 (m, 1 H, PhCH*H*), 1.97–1.41 (m, 3 H, $PhCHCH_2CHCH_3$), 0.98 (s, 9 H, $SiC(CH_3)_3$), 0.88 (m, 3 H, $CHCH_3$), 0.19 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 140.3, 140.3, 134.7, 134.2, 128.6, 127.7, 127.6, 125.2, 119.3, 92.4, 75.6, 75.2, 71.2, 66.5, 66.4, 58.2, 44.8, 44.1, 43.4, 42.8, 31.0, 30.8, 25.2, 19.6, 18.6, 17.6, –4.9; IR (neat, cm^{-1}) 2929, 1607, 840, 807, 781.

(1*R,3*S**)- and (1*R**,3*R**)-1-(4-Hydroxyphenyl)-1-methoxy-3-methyl-4-phenylbutane (31).** The same procedure as given previously for the preparation of **16** was carried out with **29**. Recrystallization (ether/hexane) afforded 0.106 g (97%) of **31** as a white solid (1:1 mixture of diastereomers by ^{1}H NMR): mp 102.5–107.5 °C; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 155.5, 140.9, 140.8, 133.8, 133.1, 129.1, 128.3, 128.1, 128.0, 125.6, 115.3, 115.3, 82.2, 81.8, 56.1, 55.9, 45.2, 44.3, 43.7, 43.6, 31.5, 31.4, 19.8, 19.1; IR (CCl_4, cm^{-1}) 3611, 3335, 2928, 1614, 865, 833. Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.70; H, 7.92.

Fractional recrystallization (ether/hexane) afforded each diastereomer for characterization. The less soluble diastereomer crystallized as a 10:1 mixture of diastereomers (^{1}H NMR): mp 107.0–107.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.07 (m, 7 H, Ar*H*), 6.81 (d, J = 8.5 Hz, 2 H, Ar*H*), 4.94 (s, 1 H, OH), 4.15 (dd, J = 8.6, 5.0 Hz, 1 H, CH), 3.16 (s, 3 H, OCH_3), 2.71 (dd, J = 13.3, 5.2 Hz, 1 H, PhC*H*H), 2.34 (dd, J = 13.3, 8.5 Hz, 1 H, PhCH*H*), 2.00–1.85 (m, 2 H, $ArCHCH_2$), 1.44–1.35 (m, 1 H, $CHCH_3$), 0.85 (d, J = 6.5 Hz, 3 H, $CHCH_3$).

Concentration of the mother liquors afforded the other diastereomer as a 3:1 mixture of diastereomers (^{1}H NMR): white solid, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.10 (m, 7 H, Ar*H*), 6.81 (d, J = 7.6 Hz, 2 H, Ar*H*), 4.96 (s, 1 H, OH), 4.09 (t, J = 6.8 Hz, 1 H, CH), 3.13 (s, 3 H, OCH_3), 2.63 (dd, J = 13.4, 5.5 Hz, 1 H, PhC*H*H), 2.38 (dd, J = 13.2, 7.4, 1 H, PhCH*H*), 1.78–1.59 (m, 2 H, $ArCHCH_2$), 1.44–1.35 (m, 1 H, $CHCH_3$), 0.89 (d, J = 6.1 Hz, 3 H, $CHCH_3$).

(1*R,3*S**)- and (1*R**,3*R**)-1-(4-Hydroxyphenyl)-1-[[(methoxyethoxy)methyl]oxy]-3-methyl-4-phenylbutane (32).** The same procedure as given previously for the preparation of **15** was carried out with **29**. Flash chromatography (10% ethyl acetate/hexane) afforded 0.917 g (97%) of **32** as a white semisolid (1:1 mixture of diastereomers, ^{1}H NMR): mp 101.0–105.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.04 (m, 7 H, Ar*H*), 6.78 and 6.75 (d, J = 6.0 Hz, 2 H, HOAr*H*), 5.06 (b s, 1 H, ArO*H*), 4.69–4.61 (m, 1 H, ArC*H*), 4.56 (AB q, J = 11.1 Hz, 2 H, OCH_2O), 3.84–3.76 (m, 1 H, $OCHHCH_2O$), 3.59–3.43 (m, 3 H, $OCHHCH_2O$), 3.36 (s, 3 H, OCH_3), 2.70 and 2.66 (dd, J = 12.6, 5.1 Hz, 1 H, PhC*H*H), 2.42–2.32 (m, 1 H, PhCH*H*), 1.98–1.88 (m, 2 H, $ArCHCH_2$), 1.46–1.36 (m, 1 H, CH_3CH), 0.88 (d, J = 6.4 Hz, 3 H, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 155.6, 140.4, 140.3, 132.9, 132.2, 128.8, 128.7, 128.1, 127.9, 127.7, 125.3, 115.0, 92.2, 76.0, 75.6, 71.2, 66.6, 66.5, 58.3, 44.7, 43.7, 43.4, 43.0, 31.0, 30.9, 19.4, 18.7; IR (CCl_4, cm^{-1}) 3357, 2927, 1614, 835; MS (CI, NH_3) m/z 344 (M^+, 1), 239 (100), 91 (8); HRMS for $C_{21}H_{28}O_4$ calcd 344.1988, found 344.1992.

One diastereomer was obtained pure by fractional recrystallization (ether/hexane): mp 108.0–109.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.10 (m, 7 H, Ar*H*), 6.78 (d, J = 6.6 Hz, 2 H, HOAr*H*), 4.95 (s, 1 H, ArO*H*), 4.66 (dd, J = 8.8, 4.6 Hz, 1 H, ArC*H*), 4.56 (AB q, J = 10.4 Hz, 2 H, OCH_2O), 3.83–3.76 (m, 1 H, $OCHHCH_2O$), 3.58–3.44 (m, 3 H, $OCHHCH_2O$), 3.36 (s, 3 H, OCH_3), 2.70 (dd, J = 13.4, 5.3 Hz, 1 H, PhC*H*H), 2.37 (dd, J = 13.7, 5.4 Hz, 1 H, PhCH*H*), 1.98–1.88 (m, 1 H, ArCHC*H*H), 1.70

(30) Preparation of aldehyde **28**: hydroboration/oxidation of commercially available 3-methyl-4-phenyl-1-butene afforded the known 3-methyl-4-phenylbutan-1-ol (Powell, K. G.; McQuillin, F. J. *J. Chem. Soc., Chem. Commun.* **1971**, 931), which was oxidized under Swern conditions to afford the known aldehyde (Miravalles, R.; Guillarmod, A. J. *Helv. Chim. Acta* **1966**, *49*, 2313).

(m, 1 H, ArCHCH*H*), 1.46–1.36 (m, 1 H, CH_3CH), 0.88 (d, J = 6.4 Hz, 3 H, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 140.9, 134.1, 129.2, 128.3, 128.1, 125.7, 115.2, 92.8, 75.7, 71.7, 67.0, 58.9, 45.3, 43.8, 31.4, 19.0.

***tert*-Butyl 3-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-3-hydroxypropanoate (34).** *n*-BuLi (95.5 mL, 0.170 mol, 1.78 M in hexane) was added dropwise to a rapidly stirred solution of diethylamine (20.5 mL, 0.198 mol) and THF (113 mL) at −78 °C. After the solution was stirred for 5 min, *tert*-butyl acetate (23.0 mL, 0.170 mol) was added dropwise. The rate of addition was adjusted to keep the temperature below −76 °C. After being stirred an additional 10 min, a solution of 4-[(*tert*-butyldimethylsilyl)oxy]benzaldehyde[31] (**33**; 13.4 g, 0.0566 mol) and THF (20 mL) was added dropwise, observing the same temperature control. After the solution was stirred an additional 1.0 h, aqueous workup (pH 6 buffer, ether) afforded 17.8 g of crude product as a light yellow oil. Flash chromatography (10% ethyl acetate/hexane) afforded 17.2 g (86%) of **34** as a clear, colorless liquid: purity by GC 98.51% (15.16 min); ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 8.4 Hz, 2 H, Ar*H*), 6.81 (d, J = 8.4 Hz, 2 H, Ar*H*), 5.02 (ddd, J = 8.1, 4.2, 4.2 Hz, 1 H, CH), 3.33 (d, J = 3.4 Hz, 1 H, OH), 2.72–2.56 (m, 2 H, CH_2), 1.44 (s, 9 H, $OC(CH_3)_3$), 0.97 (s, 9 H, $SiC(CH_3)_3$), 0.18 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 154.9, 135.7, 126.9, 119.8, 80.9, 70.0, 44.4, 27.9, 25.6, 18.1, −4.5; IR (neat, cm^{-1}) 3442, 2931, 1729, 1714, 1609, 840; MS (EI, 20 eV) m/z 352 (M^+, 19), 295 (100), 237 (74), 235 (57); HRMS for $C_{19}H_{32}O_4Si$ calcd 352.2070, found 352.2071. Anal. Calcd for $C_{19}H_{32}O_4Si$: C, 64.73; H, 9.15. Found: C, 65.04; H, 9.44.

***tert*-Butyl 3-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-3-[[(methoxyethoxy)methyl]oxy]propanoate (35).** The same procedure as given previously for the preparation of **18** was carried out with **34**. Crude **35** (4.71 g, 90%) was a clear, colorless liquid: purity by GC 98.51% (15.16 min); ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, J = 8.4 Hz, 2 H, Ar*H*), 6.78 (d, J = 8.4 Hz, 2 H, Ar*H*), 4.97 (dd, J = 8.9, 3.5 Hz, 1 H, CH), 4.60 (AB q, J = 14.0 Hz, 2 H, OCH_2O), 3.75 (m, 1 H, OCH_2CHHO), 3.52–3.39 (m, 3 H, OCH_2CHHO), 3.36 (s, 3 H, OCH_3), 2.77 (dd, J = 8.9, 6.1 Hz, 1 H, CHCH*H*), 2.52 (dd, J = 9.7, 5.4 Hz, 1 H, CHCH*H*), 1.44 (s, 9 H, $OC(CH_3)_3$), 0.97 (s, 9 H, $SiC(CH_3)_3$), 0.18 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 154.6, 132.7, 127.6, 119.2, 92.2, 79.3, 73.6, 71.0, 66.0, 58.0, 43.4, 27.3, 25.0, 17.5, −5.1; IR (neat, cm^{-1}) 2931, 1733, 1608, 842; MS (CI, NH_3) m/z 458 (MNH_4^+, 23), 335 (100), 295 (83), 89 (89); HRMS for $C_{23}H_{40}O_6Si$ calcd 440.2594; found 440.2604.

3-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-3-[[(methoxyethoxy)methyl]oxy]propan-1-ol (36). A solution of ester **35** (4.30 g, 9.78 mmol) and THF (5 mL) was added dropwise to a rapidly stirred suspension of $LiAlH_4$ (0.408 g, 10.7 mmol) and THF (45 mL) at 0 °C. The resulting suspension was stirred for an additional 30 min. Aqueous workup (saturated aqueous NH_4Cl, ether) afforded 3.32 g (92%) of **36** as a clear, colorless oil: purity by GC >99.99% (14.52 min); ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, J = 8.4 Hz, 2 H, Ar*H*), 6.78 (d, J = 8.4 Hz, 2 H, Ar*H*), 4.84 (dd, J = 9.5, 4.0 Hz, 1 H, CH), 4.58 (AB q, J = 8.9 Hz, 2 H, OCH_2O), 3.93–3.80 (m, 2 H), 3.71–3.59 (m, 1 H), 3.57–3.52 (m, 3 H), 3.40 (s, 3 H, OCH_3), 2.95 (b s, 1 H, OH), 2.04–1.82 (m, 2 H, $CHCH_2$), 0.97 (s, 9 H, $SiC(CH_3)_3$), 0.19 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 Hz, $CDCl_3$) δ 154.7, 134.0, 127.6, 119.5, 92.1, 74.4, 71.4, 66.5, 58.6, 58.4, 40.3, 25.3, 17.7, −4.8; IR (neat, cm^{-1}) 3471, 2931, 1608, 841; MS (CI, NH_3) m/z 388 (MNH_4^+, 2), 370 (M^+, 1), 89 (30), 59 (100); HRMS for $C_{19}H_{34}O_5Si$ calcd 370.2176; found 370.2182.

1-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-1-[[(methoxyethoxy)methyl]oxy]-3-[[(4-methylphenyl)sulfonyl]oxy]propane (37). A rapidly stirred solution of alcohol **36** (3.32 g, 8.97 mmol) and pyridine (72 mL) was cooled to 0 °C and treated with *p*-toluenesulfonyl chloride (8.55 g, 44.8 mmol). The resulting solution was stirred for 15 min at 0 °C, the ice bath was removed, and stirring was continued for an additional 20 min. Aqueous workup (pH 6 buffer, ether/$CuSO_4$) afforded 4.64 g of crude product as a clear oil. Flash chromatography (5% ethyl acetate/hexane) afforded 4.56 g (97%) of **37** as a clear, colorless liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8.2 Hz, 2 H, SO_2ArH), 7.33 (d, J = 8.1 Hz, 2 H, SO_2ArH), 7.05 (d, J = 8.4 Hz, 2 H, Ar*H*), 6.74 (d, J = 8.4 Hz, 2 H, Ar*H*), 4.64 (dd, J = 8.4, 5.2 Hz, 1 H, CH), 4.52 (AB q, J = 12.6 Hz, 2 H, OCH_2O), 4.23–4.17 (m, 1 H, $CHHOSO_2$), 4.01–3.94 (m, 1 H, $CHHOSO_2$), 3.74–3.67 (m, 1 H, $OCHHCH_2O$), 3.52–3.39 (m, 3 H, $OCHHCH_2O$), 3.35 (s, 3 H, OCH_3), 2.44 (s, 3 H, $ArCH_3$), 2.17–1.88 (m, 2 H, $CHCH_2$), 0.96 (s, 9 H, $SiC(CH_3)_3$), 0.17 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 144.2, 132.8, 132.7, 129.4, 127.6, 127.4, 119.6, 92.4, 73.1, 71.2, 67.0, 66.6, 58.4, 36.6, 25.2, 21.1, 17.7, −4.8; IR (neat, cm^{-1}) 2931, 1608, 841; MS (CI, NH_3) m/z 542 (MNH_4^+, 14), 229 (54), 89 (100); HRMS for $C_{26}H_{40}O_7SSi(NH_4^+)$ calcd 542.2608, found 542.2593. Anal. Calcd for $C_{26}H_{40}O_7SSi$: C, 59.51; H, 7.68. Found: C, 59.76; H, 7.91.

1-[[(Methoxyethoxy)methyl]oxy]-1-(4-methoxyphenyl)-3-[[(4-methylphenyl)sulfonyl]oxy]propane (38). The same procedure as given previously for the preparation of **15** was carried out with **37**. Flash chromatography (20% ethyl acetate/hexane) afforded 0.375 g (98%) of 1-(4-hydroxyphenyl)-1-[[(methoxyethoxy)methyl]oxy]-3-[[(4-methylphenyl)sulfonyl]oxy]propane. A solution of the above phenol (0.318 g, 0.775 mmol) and THF (2.0 mL) was added dropwise to a stirred suspension of sodium hydride (22.0 mg, 0.932 mmol) and THF (4.25 mL). Methyl iodide (193 μL, 3.10 mmol) was added, and the resulting solution was stirred for 2.5 h. Aqueous workup (pH 6 buffer, ether) afforded 0.287 g (87%) of **38** as a clear colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.1 Hz, 2 H, SO_2ArH), 7.34 (d, J = 8.0 Hz, 2 H, SO_2ArH), 7.13 (d, J = 8.4 Hz, 2 H, Ar*H*), 6.82 (d, J = 8.4 Hz, 2 H, Ar*H*), 4.66 (dd, J = 8.4, 5.2 Hz, 1 H, CH), 4.53 (AB q, J = 12.6 Hz, 2 H, OCH_2O), 4.26–4.18 (m, 1 H, $CHHOSO_2$), 4.02–3.95 (m, 1 H, $CHHOSO_2$), 3.79 (s, 3 H, $ArOCH_3$), 3.72 (m, 1 H, $OCHHCH_2O$), 3.51–3.42 (m, 3 H, $OCHHCH_2O$), 3.36 (s, 3 H, OCH_3), 2.45 (s, 3 H, $ArCH_3$), 2.18–1.88 (m, 2 H, $CHCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 144.4, 132.6, 132.1, 129.5, 127.7, 127.5, 113.5, 92.4, 73.0, 71.3, 67.1, 66.7, 58.6, 54.8, 36.6, 21.2; IR (CCl_4, cm^{-1}) 2928, 1612, 979, 922, 832, 746.

Methyl 7-(4-Hydroxyphenyl)-7-[[(methoxyethoxy)methyl]oxy]-3-oxoheptanoate (39). By use of the procedure of Weiler,[13] methyl acetoacetate (4.91 mL, 45.5 mmol) was added dropwise to a rapidly stirred suspension of sodium hydride (1.10 g, 46 mmol, 97%) and THF (91 mL) at 0 °C. *n*-BuLi (18.1 mL, 47.9 mmol, 2.65 M in hexane) was then added dropwise. After the mixture was stirred for 10 min, a solution of tosylate **37** (2.39 g, 4.55 mmol) and THF (5 mL) was added. The solution was stirred for 1 h at 0 °C. Aqueous workup (pH 6 buffer, ether) afforded 1.70 g of crude product as an oil. Flash chromatography (15% ethyl acetate/hexane) afforded 1.31 g (62%) of methyl 7-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-7-[[(methoxyethoxy)methyl]oxy]-3-oxoheptanoate. The same procedure as given previously for the preparation of **15** was carried out with the above silyl ether. Flash chromatography (20% ethyl acetate/hexane) afforded 0.728 g (84%) of **39** as a clear, colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 8.4 Hz, 2 H, Ar*H*), 6.76 (d, J = 8.4 Hz, 2 H, Ar*H*), 5.38 (b s, 1 H, OH), 4.57 (AB q, J = 12.9 Hz, 2 H, OCH_2O), 4.51 (t, partially obscured, J = 5.5 Hz, 1 H, CH), 3.83–3.76 (m, 1 H, $OCHHCH_2O$), 3.71 (s, 3 H, CO_2CH_3), 3.58–3.47 (m, 3 H, $OCHHCH_2O$), 3.41 (s, 2 H, $OCCH_2CO$), 3.37 (s, 3 H, OCH_3), 2.54 (t, J = 6.0 Hz, 2 H, CH_2CH_2CO), 1.85–1.70 (m, 4 H, $CHCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 167.6, 155.8, 132.6, 128.1, 115.1, 92.5, 77.2, 71.6, 66.8, 58.7, 52.2, 48.8, 42.6, 36.6, 19.8; IR (neat, cm^{-1}) 3610, 3446, 2953, 1750, 1720, 1654, 1627, 1616, 835; MS (DCI, NH_3) m/z 372 (MNH_4^+, 7), 249 (100), 133 (41), 89 (84); HRMS for $C_{18}H_{26}O_7(NH_4^+)$ calcd 372.2023; found 372.2025.

Methyl 7-[4-(Acetyloxy)phenyl]-7-[[(methoxyethoxy)methyl]oxy]-3-oxoheptanoate (40). The same procedure as given previously for the preparation of **23** was carried out with **39**. Flash chromatography (25% ethyl acetate/hexane) afforded 41.9 mg (74%) of **40** as a clear, colorless liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 8.4 Hz, 2 H, Ar*H*), 7.04 (d, J = 8.4 Hz, 2 H, Ar*H*), 4.65–4.56 (m, 3 H, CH, OCH_2O), 3.83–3.76 (m, 1 H, OCH_2CHHO), 3.72 (s, 3 H, CO_2CH_3), 3.60–3.44 (m, 3 H, OCH_2CHHO), 3.42 (s, 2 H, $OCCH_2CO$), 3.37 (s, 3 H, OCH_3), 2.55 (t, J = 6.8 Hz, 2 H, $CH_2CH_2CH_2CO$), 2.29 (s, 3 H, $ArOCOCH_3$), 1.85–1.56 (m, 4 H, $CHCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 169.3, 167.5, 150.0, 139.3, 127.7, 121.7, 93.2, 77.2, 71.6, 67.0,

(31) Aldehyde **33** (bp 185–187 °C, 1.0 mmHg) was prepared from 4-hydroxybenzaldehyde[23] by silylation as noted in ref 12.

59.0, 52.2, 48.9, 42.5, 36.9, 21.0, 19.7; IR (CCl_4, cm^{-1}) 2928, 1756, 1721, 1629, 850; MS (CI, NH_3) m/z 414 (MNH_4^+, 13), 308 (33), 249 (28), 94 (100); HRMS for $C_{20}H_{28}O_8(NH_4^+)$ calcd 414.2128; found 414.2144.

Methyl 7-[[(methoxyethoxy)methyl]oxy]-7-(4-methoxyphenyl)-3-oxoheptanoate (41). The same procedure as given previously for the preparation of the **39** was carried out with **38**. Flash chromatography (15% ethyl acetate/hexane) afforded 0.118 g (87%) of **41** as a clear, colorless, viscous oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 8.5 Hz, 2 H, Ar*H*), 6.84 (d, J = 8.6 Hz, 2 H, Ar*H*), 4.61–4.51 (m, 3 H, OCH_2O, CH), 3.78 (s, 3 H, $ArOCH_3$), 3.71 (s, 3 H, CO_2CH_3), 3.57–3.46 (m, 4 H, OCH_2CH_2O), 3.41 (s, 2 H, $OCCH_2CO$), 3.37 (s, 3 H, OCH_3), 2.54 (t, J = 6.9 Hz, 2 H, $CH_2CH_2C{=}O$), 1.85–1.51 (m, 4 H, $CHCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 167.4, 158.9, 133.4, 127.8, 113.5, 92.6, 71.5, 66.8, 58.7, 55.0, 52.0, 48.7, 42.4, 36.6, 19.6; IR (neat, cm^{-1}) 2936, 1748, 1717, 1612, 834; MS (CI, NH_3) m/z 386 (MNH_4^+, 100), 280 (75), 263 (50), 94 (88), 78 (42).

8-(4-Hydroxyphenyl)-8-[[(methoxyethoxy)methyl]oxy]-2-methyloct-2-ene (42). A rapidly stirred solution of tosylate **37** (0.950 g, 1.81 mmol), Li_2CuCl_4 (1.80 mL, 0.2 mmol, 0.1 M in THF),[14] and THF (4 mL) was treated with a solution of the Grignard reagent derived from 1-bromo-4-methyl-3-pentene (5.00 mL, 5.44 mmol, 1.09 M in THF) at 0 °C with protection from light. After the solution was stirred for 6 h at 0 °C, aqueous workup (pH 6 buffer, ether) afforded 0.832 g of crude product as a yellow oil. Flash chromatography (5% ethyl acetate/hexane) afforded 0.672 g (85%) of 8-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-8-[[(methoxyethoxy)methyl]oxy]-2-methyloct-2-ene. The same procedure as given previously for the preparation of **15** was carried out with the above silyl ether. Flash chromatography (10% ethyl acetate/hexane) afforded 0.256 g (98%) of **42** as a clear, colorless semisolid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J = 8.3 Hz, 2 H, Ar*H*), 6.76 (d, J = 8.3 Hz, 2 H, Ar*H*), 5.78 (b s, 1 H, OH), 5.07 (t, J = 6.9 Hz, 1 H, $CH{=}C(CH_3)_2$), 4.59–4.48 (m, 3 H, OCH_2O, $ArCH$), 3.89–3.79 (m, 1 H, $OCHHCH_2O$), 3.62–3.51 (m, 3 H, $OCHHCH_2O$), 3.39 (s, 3 H, OCH_3), 1.96–1.76 (m, 4 H, $CH_2CH{=}C$, $ArCHCH_2$), 1.66 (s, 3 H, CH_3CCH_3), 1.56 (s, 3 H, CH_3CCH_3), 1.45–1.16 (m, 4 H, $ArCHCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 133.5, 131.5, 128.3, 124.6, 115.1, 92.6, 77.7, 71.7, 66.8, 58.9, 37.6, 29.6, 27.9, 25.6, 17.6; IR (CCl_4, cm^{-1}) 3611, 3377, 2932, 1614; MS (CI, NH_3) m/z 340 (MNH_4^+, 56), 217 (100); HRMS for $C_{19}H_{30}O_4(NH_4^+)$ calcd 340.2488, found 340.2503.

4-Furan-3-yl-1-(4-hydroxyphenyl)-1-[[(methoxyethoxy)methyl]oxy]butane (43). The same procedure as given previously for the preparation of **42** was carried out with **37** and (furan-3-ylmethyl)magnesium chloride.[32] Flash chromatography (5% ethyl acetate/hexane) afforded 0.820 g (99%) of 1-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-4-furan-3-yl-1-[[(methoxyethoxy)methyl]oxy]butane. The same procedure as given previously for the preparation of **15** was carried out with the above silyl ether. Flash chromatography (20% ethyl acetate/hexane) afforded 0.519 g (91%) of **43** as a clear, colorless, viscous liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 1 H, $RC{=}CHO$), 7.16 (s, 1 H, $RCCH{=}CHO$), 7.11 (d, J = 8.4 Hz, 2 H, Ar*H*), 6.76 (d, J = 8.4 Hz, 2 H, Ar*H*), 6.22 (s, 1 H, $RCCH{=}CHO$), 5.53 (b s, 1 H, OH), 4.60–4.51 (m, 3 H, OCH_2O, $HOArCH$), 3.88–3.78 (m, 1 H, OCH_2CHHO), 3.61–3.50 (m, 3 H, OCH_2CHHO), 3.38 (s, 3 H, OCH_3), 2.41 (t, J = 7.0 Hz, 2 H, $CH(CH_2)_2CH_2$), 1.91–1.39 (m, 4 H, $CHCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 142.4, 138.5, 132.8, 128.1, 124.6, 115.1, 110.7, 92.4, 77.4, 71.5, 66.6, 58.6, 36.9, 26.1, 24.2; IR (neat, cm^{-1}) 3351, 2939, 1614, 836; MS (CI, NH_3) m/z 338 (MNH_4^+, 2), 320 (M^+, 3), 215 (100), 89 (48); HRMS for $C_{18}H_{24}O_5$ calcd 320.1624, found 320.1615. Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.28; H, 7.27.

General Cyclization Procedure. A solution of $TiCl_4$ (4.0 equiv of a 1.0 M solution in CH_2Cl_2) was added to a rapidly stirred solution of cyclization substrate (0.01 M in CH_2Cl_2) at the temperature noted in brackets. The resulting solution was stirred for the time noted in brackets and then poured into saturated aqueous $NaHCO_3$ and stirred for 1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3X). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to afford the crude product.

4-(1,2,3,4-Tetrahydro-1-naphthyl)phenol (44).[33] **From 15.** According to the general cyclization procedure, phenol **15** (30.0 mg, 0.0908 mmol) [-78 °C, 2 min] afforded 22.4 mg of crude product as a clear syrup. Flash chromatography (10% ethyl acetate/hexane) afforded 19.0 mg (93%) of **44** as a white solid, purity by GC 99.78% (13.15 min).

From 16: Phenol **16** (50.0 mg, 0.195 mmol) [-78 °C, 2 min] afforded 42.0 mg (96%) of **44**, purity by GC 99.65%; mp 128.0–129.0 °C (lit.[33] mp 127–128 °C); spectral data are identical with those reported.[33]

1-(4-Methoxyphenyl)-1,2,3,4-tetrahydronaphthalene (45).[34] **From 8.** According to the general cyclization procedure, methyl ether **8** (15.1 mg, 0.0591 mmol) [-78 °C, 2 min] afforded 15.1 mg of crude product as a clear oil. Flash chromatography (5% ethyl acetate/hexane) afforded 13.2 mg (94%) of **45** as a white solid, purity by GC 98.46% (12.80 min).

From 17. Methyl ether **17** (52.0 mg, 0.192 mmol) [-78 °C, 10 min] afforded 43.2 mg (94%) of **45** (94%), purity by GC 98.75%.

From 18. Methyl ether **18** (52.8 mg, 0.153 mmol) [-78 °C, 10 min] afforded 4.5 mg (12%) of **45**, purity by GC 97.56%.

From 19. Methyl ether **19** (67.4 mg, 0.263 mmol) [-78 °C, 10 min] afforded 56.5 mg (90%) of **45**, purity by GC 98.02%; mp 67.0–67.5 °C (lit.[34] mp 66–67 °C); spectra data are identical with those reported.[34]

1-[[(*tert*-Butyldimethylsilyl)oxy]phenyl]-1,2,3,4-tetrahydronaphthalene (46). From 7b. According to the general cyclization procedure, **7b** (85.5 mg, 0.239 mmol) [-78 °C, 20 min] afforded 85.3 g of crude product as a clear liquid. Bulb to bulb distillation (40 μmHg, oven temperature 160–167 °C) afforded 75.9 mg (93%) of **46** as a clear, colorless liquid, purity by GC >99.99% (14.70 min).

From 21. MEM ether **21** (39.5 mg, 0.0913 mmol) [-78 °C, 20 min] afforded (flash chromatography, 5% ethyl acetate/hexane) 5.7 mg (18%) of **46**, purity by GC >99.99%.

From 20. Methyl ether **20** (54.5 mg, 0.147 mmol) [-78 °C, 20 min] afforded 48.0 mg (96%) of **46**, purity by GC 99.79%.

From 22. Bromide **22** (31.5 mg, 0.0951 mmol) [-78 °C, 20 min] afforded 25.0 mg (98%) of **46**, purity by GC >99.99%; ^1H NMR (300 MHz, $CDCl_3$) δ 7.13–7.00 (m, 3 H, Ar*H*), 6.94 (d, J = 8.4 Hz, 2 H, Ar*H*), 6.86 (d, J = 7.5 Hz, 1 H, Ar*H*), 6.75 (d, J = 8.4 Hz, 2 H, Ar*H*), 4.05 (t, J = 6.4 Hz, 1 H, CH), 2.97–2.78 (m, 2 H, $ArCH_2$), 2.19–2.10 (m, 1 H, $CHHCH_2$), 1.94–1.68 (m, 3 H, $CHHCH_2$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.20 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) 153.7, 140.1, 139.7, 137.4, 130.1, 129.6, 128.9, 125.8, 125.5, 119.6, 44.8, 33.3, 29.8, 25.7, 21.0, 18.2, -4.4; IR (neat, cm^{-1}) 2930, 1607, 839, 780, 740; MS (EI, 70 eV) m/z 338 (M^+, 32), 131 (100), 91 (20). Anal. Calcd for $C_{22}H_{30}OSi$: C, 78.05; H, 8.93. Found: C, 78.05; H, 8.88.

1-Phenyl-1,2,3,4-tetrahydronaphthalene (47).[1f] According to the general cyclization procedure, 1,4-diphenyl-1-butanol **14**[1f] (0.100 g, 0.442 mmol) [-78 °C, 5 min] afforded 91.5 mg of crude product as a clear liquid. Bulb to buld distillation (1 mmHg, oven temperature 101 °C) afforded 89.7 mg (98%) of **47** as a clear, colorless liquid: purity by GC 99.08% (11.23 min); spectral data are identical with those reported.[1f]

1-(4-Chlorophenyl)-1,2,3,4-tetrahydronaphthalene (48).[35] According to the general cyclization procedure, chloride **9** (0.125 g, 0.480 mmol) [-78 °C, 5 min] afforded 0.117 g of crude product as a yellow liquid. Flash chromatography (2% ethyl acetate/hexane) afforded 0.106 g (91%) of **48**[35] as a clear, colorless liquid: purity by GC 98.14% (12.54 min); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.00 (m, 7 H, Ar*H*), 6.80 (d, J = 7.7 Hz, 1 H, Ar*H*), 4.09 (t, J = 6.4 Hz, 1 H, $ArCH$), 2.96–2.78 (m, 2 H, $ArCH_2$), 2.20–2.07 (m, 1 H, $CHHCH_2$), 1.92–1.67 (m, 3 H, $CHHCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0, 138.7, 137.5, 131.6, 130.1, 130.0, 129.0, 128.3, 126.1, 125.7, 45.0, 33.2, 29.6, 20.8; IR (neat, cm^{-1}) 3018, 2932, 817,

(32) Tanis, S. P. *Tetrahedron Lett.* **1982**, *23*, 3115.

(33) A known compound: (a) Bencze, W. L.; Kisis, B.; Puckett, R. T.; Finch, N. *Tetrahedron* **1970**, *26*, 5407. (b) Jacques, J.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1956**, 128. (c) Mentzer, C.; Molho, D.; Xuong, D. *Bull. Soc. Chim. Fr.* **1948**, 263. (d) Koenigs, W. *Chem. Ber.* **1891**, *24*, 179.

(34) Davies, D. I.; Waring, C. *J. Chem. Soc.* **1968**, 1865; see also ref 33b–d.

(35) This compound has been reported in a patent: *Chem. Abstr.* **1973**, *78*, 111015. Bencze, W. L.; U.S. Pat. 3714360, 16 Feb 1970.

767, 740; MS (EI, 70 eV) m/z 244 (M^+, 36), 242 (M^+, 100), 179 (82), 178 (55), 91 (34).

1-[4-(Acetyloxy)phenyl]-1,2,3,4-tetrahydronaphthalene (49). According to the general cyclization procedure, (acetyloxy)benzene **23** (0.241 g, 0.648 mmol) [23 °C, 30 min] afforded 0.161 g of crude product as a yellow oil. Flash chromatography (7% ethyl acetate/hexane) afforded 0.153 g (89%) of **49** as a clear, colorless liquid: purity by GC >99.99% (13.60 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14–6.97 (m, 7 H, Ar*H*), 6.85 (d, J = 7.7 Hz, 1 H, Ar*H*), 4.13 (t, J = 6.6 Hz, 1 H, CH), 2.98–2.79 (m, 2 H, ArCH_2), 2.29 (s, 3 H, CH_3), 2.21–2.12 (m, 1 H, C*H*HCH$_2$), 1.94–1.68 (m, 3 H, CH*HCH*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 148.7, 144.8, 138.9, 137.4, 130.0, 129.5, 128.8, 125.9, 125.6, 121.0, 44.9, 33.1, 29.6, 21.0, 20.7; IR (neat, cm^{-1}) 3017, 2857, 1768, 846, 742; MS (EI, 70 eV) m/z 266 (M^+, 21), 224 (40), 130 (100), 91 (14).

4-(1,2,3,4-Tetrahydro-1-naphthyl)benzoic Acid (50). According to the general cyclization procedure, acid **10** (0.537 g, 1.99 mmol) [23 °C, 90 min] afforded 0.520 g of crude product as a light yellow solid. Recrystallization (acetone/hexane) afforded 0.476 g (95%) of **50** as a white solid: purity by GC >99.99% (14.24 min); mp 157.5–158.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 8.2 Hz, 2 H, Ar*H*), 7.21 (d, J = 8.2 Hz, 2 H, Ar*H*), 7.16–7.02 (m, 3 H, Ar*H*), 6.80 (d, J = 7.6 Hz, 1 H, Ar*H*), 4.21 (t, J = 6.4 Hz, 1 H, CH), 2.99–2.79 (m, 2 H, PhCH_2), 2.23–2.15 (m, 1 H, CH_2CHH), 1.94–1.70 (m, 3 H, CH_2CHH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 154.0, 138.3, 137.6, 130.3, 130.0, 129.1, 129.0, 127.1, 126.2, 125.8, 45.7, 33.0, 29.6, 20.8; IR (CCl_4, cm^{-1}) 3541, 2937, 1693, 1610, 854, 810; MS (EI, 20 eV), m/z 252 (M^+, 100), 207 (52), 179 (87), 91 (36). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.79; H, 6.20.

Methyl 4-(1,2,3,4-Tetrahydro-1-naphthyl)benzoate (51). According to the general cyclization procedure, alcohol **24** (0.455 g, 1.60 mmol) [23 °C, 90 min] afforded 0.452 g of crude product as a yellow oil. Flash chromatography (7% ethyl acetate/hexane) afforded 0.409 (96%) of **51** as a white solid: purity by GC 99.37% (14.04 min); mp 42.0–43.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 8.5 Hz, 2 H, Ar*H*), 7.17 (d, J = 8.7 Hz, 2 H, Ar*H*), 7.15–7.00 (m, 3 H, Ar*H*), 6.78 (d, J = 7.7 Hz, 1 H, Ar*H*), 4.18 (t, J = 6.5 Hz, 1 H, CH), 3.90 (s, 3 H, OCH_3), 2.98–2.80 (m, 2 H, ArCH_2), 2.23–2.13 (m, 1 H, C*H*HCH$_2$), 1.93–1.71 (m, 3 H, CH*HCH*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 152.8, 138.3, 137.4, 129.9, 129.5, 129.0, 128.7, 127.8, 126.0, 125.6, 51.8, 45.5, 32.9, 29.5, 20.7; IR (neat, cm^{-1}) 2935, 1720, 1610, 852, 763; MS (EI, 70 eV) m/z 266 (M^+, 100), 207 (63), 179 (79), 91 (57).

1-[4-(Trifluoromethyl)phenyl]-1,2,3,4-tetrahydronaphthalene (52). According to the general cyclization procedure, **11** (50.0 mg, 0.170 mmol) [23 °C, 75 min] afforded 47.5 mg of crude product as a green liquid. Bulb to bulb distillation (35 μmHg, oven temperature 81 °C) afforded 43.5 mg (93%) of **52** as a clear, colorless liquid: purity by GC 99.62% (11.23 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.23 (d, J = 8.5 Hz, 2 H, Ar*H*), 7.15–7.01 (m, 3 H, Ar*H*), 6.78 (d, J = 7.6 Hz, 1 H, Ar*H*), 4.19 (t, J = 6.4 Hz, 1 H, CH), 2.98–2.79 (m, 2 H, ArCH_2), 2.23–2.11 (m, 1 H, C*H*HCH$_2$), 1.92–1.69 (m, 3 H, CH*HCH*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 138.2, 137.6, 130.0, 129.1, 129.0, 128.3 (q, J = 32.2 Hz, CCF_3), 126.3, 125.8, 125.2 (q, J = 3.5 Hz, $(CH)_2CCF_3$), 124.4 (q, J = 271.9 Hz, CF_3), 45.5, 33.1, 29.6, 20.8; IR (neat, cm^{-1}) 2936, 1618, 839, 827, 742; MS (EI, 70 eV) m/z 276 (M^+, 100), 248 (69), 91 (33). Anal. Calcd for $C_{17}H_{15}F_3$: C, 73.90; H, 5.47. Found: C, 74.18; H, 5.32.

***N,N*-Dimethyl-4-(1,2,3,4-tetrahydro-1-naphthyl)benzenamine (53).** According to the general cyclization procedure, amine **12** (1.28 g, 4.75 mmol) [23 °C, 4.0 h] afforded 1.12 g of crude product as a pale yellow liquid. The crude product was dissolved in methanol (5 mL), acidified with dilute HCl (10 mL, 2 N), and washed with ether (2 × 10 mL). The pH of the aqueous phase was then adjusted to 11 with NaOH (6 N). The aqueous phase was extracted with ether (3 × 15 mL), and the combined ether extracts were washed with H_2O (2 × 10 mL) and brine (15 mL), and dried ($MgSO_4$). Concentration afforded 1.10 g (92%) of **53** as a clear, colorless liquid: purity by GC 99.33% (13.88 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11–6.87 (m, 6 H, Ar*H*), 6.68 (d, J = 8.6 Hz, 2 H, Ar*H*), 4.02 (t, J = 6.4 Hz, 1 H, CH), 2.92 (s, 6 H, NCH_3), 2.88–2.69 (m, 2 H, PhCH_2), 2.17–2.07 (m, 1 H, CH_2CHH), 1.94–1.67 (m, 3 H, CH_2CHH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 139.9, 137.1, 135.3, 130.0, 129.1, 128.6, 125.4, 125.3, 112.3, 44.4, 40.4, 33.2, 29.6, 20.9; IR (CCl_4, cm^{-1}) 2935, 1614, 818; MS (EI, 70 eV) m/z 251 (M^+, 100), 222 (40), 91 (9). Anal. Calcd for $C_{18}H_{21}N$: C, 86.01; H, 8.42. Found: C, 86.44; H, 8.41.

4-(1,2,3,4-Tetrahydro-1-naphthyl)benzonitrile (54). According to the general cyclization procedure, 4-[1-(hydroxyphenyl)butyl]benzonitrile[36] (**13**; 0.867 g, 3.44 mmol) [$CHCl_3$ solvent, 61 °C, 16 h] afforded 0.801 g of crude product as a white solid. Recrystallization (ether/hexane) afforded 0.723 g (90%) of **54** as a white solid: purity by GC 99.59% (13.50 min); mp 54.0–54.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 8.2 Hz, 2 H, Ar*H*), 7.19 (d, J = 8.2 Hz, 2 H, Ar*H*), 7.16–7.02 (m, 3 H, Ar*H*), 6.75 (d, J = 7.6 Hz, 1 H, Ar*H*), 4.19 (t, J = 6.1 Hz, 1 H, CH), 2.97–2.79 (m, 2 H, ArCH_2), 2.24–2.14 (m, 1 H, CH_2CHH), 1.90–1.72 (m, 3 H, CH_2CHH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 137.5, 137.4, 132.0, 129.8, 129.5, 129.2, 126.4, 125.8, 118.9, 109.7, 45.6, 32.9, 29.4, 20.5; IR (CCl_4, cm^{-1}) 2937, 2230, 838, 834, 826; MS (EI, 20 eV) m/z 233 (M^+, 100), 205 (70), 104 (25), 91 (15). Anal. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48. Found: C, 87.72; H, 6.52.

***N*-[4-(1,2,3,4-Tetrahydro-1-naphthyl)phenyl]-*N,N,N*-trimethylammonium Iodide (55).** According to the general cyclization procedure, alcohol **25** (45.0 mg, 0.109 mmol) [$CHCl_3$ solvent, 61 °C, 65 h] afforded 32.7 mg of crude product as a brown solid. Recrystallization (CH_2Cl_2/hexane) afforded 30.0 mg (70%) of **55** as a white solid: purity by GC >99.99% (13.77 min); mp 200.0–200.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 9.0 Hz, 2 H, Ar*H*), 7.31 (d, J = 8.9 Hz, 2 H, Ar*H*), 7.15–7.00 (m, 3 H, Ar*H*), 6.73 (d, J = 7.5 Hz, 1 H, Ar*H*), 4.21 (t, J = 6.0 Hz, 1 H, CH), 4.02 (s, 9 H, $N(CH_3)_3$), 2.97–2.79 (m, 2 H, ArCH_2), 2.21–2.12 (m, 1 H, CH_2CHH), 1.86–1.74 (m, 3 H, CH_2CHH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 144.8, 137.3, 130.6, 129.7, 129.0, 126.2, 125.6, 119.7, 57.8, 44.5, 32.7, 29.2, 20.2; IR (KBr, cm^{-1}) 3006, 848, 824; MS (FAB, positive ion; 1:5 dithioerythritol/dithiothreitol matrix) m/z 266 (M^+, 100), 155 (7), 119 (14), 103 (7), 85 (11). Anal. Calcd for $C_{19}H_{24}IN$: C, 58.02; H, 6.15. Found: C, 57.77; H, 5.86.

***trans*- and *cis*-4-(3-Methyl-1,2,3,4-tetrahydro-1-naphthyl)phenol (56a,b) and *trans*- and *cis*-2-(Hydroxymethyl)-4-(3-methyl-1,2,3,4-tetrahydro-1-naphthyl)phenol (57). Preparation from 31.** According to the general cyclization procedure, methyl ether **31** (21.6 mg, 0.0799 mmol) [−78 °C, 2 min] afforded 19.5 mg of crude product as a yellow solid. Flash chromatography (10% ethyl acetate/hexane) afforded 18.7 mg (98%) of **56a,b** as a white solid (3:1 mixture of diastereomers, GC, 7.57 and 7.77 min), GC temperature program 150–280 °C at 16 °C/min.

Preparation from 32. MEM ether **32** (0.163 g, 0.473 mmol) [−78 °C, 2 min] afforded 0.119 g of crude product as a yellow solid. TLC (15% ethyl acetate/hexane) showed the presence of two products: R_f = 0.62 (**56a,b**) and 0.25 (**57**). Flash chromatography (10% ethyl acetate/hexane) afforded 59.1 mg (52%) of **56a,b** (the high R_f material) as a white solid (4.4:1 mixture of diastereomers, GC), purity by GC >99.99% (mp 121.5–132.0 °C) and 50.4 mg (40%) of **57** (the low R_f material) as a white solid (4.5:1 mixture of diastereomers, ^{1}H NMR). Fractional recrystallization (ether/hexane) of the high R_f material (**56a,b**) afforded the major diastereomer **56a** (15:1 mixture of **56a**/**56b**) for characterization: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12–6.91 (m, 6 H, Ar*H*), 6.77 (d, J = 8.4 Hz, 2 H, Ar*H*), 4.59 (s, 1 H, ArO*H*), 4.01 (dd, J = 12.0, 5.5 Hz, 1 H, ArC*H*, H(1)), 2.87 (ddd, J = 16.4, 4.5, 1.9 Hz, 1 H, ArC*H*H, H(4β)), 2.56 (dd, J = 16.2, 11.8 Hz, 1 H, ArCH*H*, H(4α)), 2.12–2.04 (m, 1 H, ArCHC*H*H, H(2β)), 2.03–1.91 (m, 1 H, CH_3CH, H(3)), 1.49 (apparent q, J = 12.3 Hz, 1 H, ArCHCH*H*, H(2α)), 1.07 (d, J = 6.5 Hz, 3 H, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 140.1, 139.6, 137.4, 129.8, 129.4, 128.7, 125.7, 125.6, 115.3, 46.5, 43.3, 39.1, 29.9, 22.3; IR (CCl_4, cm^{-1}) 3613, 2925, 1614, 830; MS (EI, 20 eV) m/z 238 (M^+, 100), 144 (98), 91 (12); HRMS for $C_{17}H_{18}O$ calcd 238.1358, found 238.1365.

The flash chromatography noted previously afforded **57** (50.4 mg, 40%) as a mixture of diastereomers (4.5:1, ^{1}H NMR). Recrystallization (ether/hexane) afforded the major diastereomer enriched to a 7:1 ratio of diastereomers (^{1}H NMR), mp 147.5–148.0 °C. Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (t, J = 4.5 Hz, 1 H, ArC*H*).

(36) Nitrile **13** was prepared according to the procedure of Blum and Becker in ref 26.

Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14–6.96 (m, 4 H, ArH), 6.83 (d, J = 7.9 Hz, 1 H, HOArH), 6.82 (s, 1 H, HOArH), 6.77 (d, J = 7.7 Hz, 1 H, HOArH), 4.82 (d, J = 4.1 Hz, 2 H, $ArCH_2OH$), 3.99 (dd, J = 12.0, 5.5 Hz, 1 H, ArCH), 2.87 (ddd, J = 16.3, 4.5, 1.9 Hz, 1 H, ArCHH), 2.55 (dd, J = 16.3, 11.8 Hz, 1 H, ArCHH), 2.15 (t, J = 4.8 Hz, 1 H, CH_2OH), 2.10–2.02 (m, 1 H, ArCHCHH), 2.00–1.92 (m, 1 H, CH_3CH), 1.48 (apparent q, J = 12.3 Hz, 1 H, ArCHCHH), 1.07 (d, J = 6.5 Hz, 3 H, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 140.0, 138.9, 137.4, 129.8, 129.4, 128.7, 127.9, 125.7, 125.6, 124.6, 116.5, 64.7, 46.5, 43.3, 39.0, 29.9, 22.3; IR (CCl_4, cm^{-1}) 3605, 3444, 2926, 829; MS (EI, 20 eV) m/z 268 (M^+, 94), 143 (100), 129 (45), 91 (27); HRMS for $C_{18}H_{20}O_2$ calcd 268.1463, found 268.1480. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.52. Found: C, 80.33; H, 7.43.

4-(2,3-Dihydro-1*H*-inden-1-yl)phenol (58).[37] According to the general cyclization procedure, alcohol **26** (0.120 g, 0.496 mmol) [42 °C, 20 min] afforded 85.7 mg of crude product as a yellow oil. Flash chromatography (20% ethyl acetate/hexane) afforded 85.7 mg (75%) of **58**[37] as a white glass: purity by GC 97.03% (12.34 min); spectral data are identical with that reported.[37]

1-Phenyl-2,3-dihydro-1*H*-indene (59).[38] According to the general cyclization procedure, 1,3-diphenylpropan-1-ol[39] (**27**; 90.0 mg, 0.424 mmol) [42 °C, 90 min] afforded 81.5 mg of crude product as a clear liquid. Bulb to bulb distillation (35 μmHg, oven temperature 93–95 °C) afforded 71.7 mg (87%) of **59**[38] as a clear, colorless liquid: purity by GC 99.37% (10.40 min).

1-[4-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-2,3-dihydro-1*H*-indene (60). According to the general cyclization procedure, alcohol **7a** (0.502 g, 1.46 mmol) [42 °C, 20 min] afforded 0.503 g of crude product as a yellow liquid. Bulb to bulb distillation (45 μmHg, oven temperature 165 °C) afforded 0.424 g (89%) of **60** as a clear, colorless liquid: purity by GC 96.06% (14.12 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.09 (m, 3 H, ArH), 7.03 (d, J = 8.5 Hz, 2 H, ArH), 6.94 (d, J = 7.2 Hz, 1 H, ArH), 6.76 (d, J = 8.4 Hz, 2 H, ArH), 4.26 (t, J = 8.4 Hz, 1 H, CH), 3.07–2.86 (m, 2 H, $ArCH_2$), 2.65–2.48 (m, 1 H, CHCHH), 2.01 (dddd, J = 12.5, 8.9, 8.9, 8.9 Hz, 1 H, CHCHH), 0.98 (s, 9 H, $SiC(CH_3)_3$), 0.19 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 147.2, 144.2, 137.9, 128.9, 126.4, 126.2, 124.8, 124.2, 119.8, 50.9, 36.6, 31.7, 25.7, 18.2, -4.4; IR (CCl_4, cm^{-1}) 2931, 1608, 842, 825; MS (EI, 20 eV) m/z 324 (M^+, 100), 267 (7), 210 (4); HRMS for $C_{21}H_{28}OSi$ calcd 324.1909, found 324.1903.

6-Hydroxy-3-(4-hydroxyphenyl)-1-(phenylbutyl)-2-(phenylpropyl)-2,3-dihydroindene (61b). A rapidly stirred solution of **7c** (880.8 mg, 2.376 mmol) and CH_2Cl_2 (238 mL) was treated with $TiCl_4$ (9.50 mL, 9.5 mmol, 1.0 M in CH_2Cl_2) added dropwise over 2 min at 42 °C. After the solution was stirred for an additional 45 min, aqueous workup ($NaHCO_3$, CH_2Cl_2, included filtration through Celite) afforded 829.5 mg of crude **61a** as a clear oil. A solution of the crude **61a** and THF (5 mL) was treated with $(n\text{-}Bu)_4NF$ (2.38 mL, 2.4 mmol, 1.0 M in THF) at 23 °C for 15 min. Aqueous workup (pH 6.0 buffer, ether) afforded 750.2 mg of crude product as a viscous clear oil. Flash chromatography (20% acetone/hexane) afforded 463 mg (82%) of **61b** as a white solid as a mixture of diastereomers (3.3:1). Fractional recrystallization (ether/hexane) afforded the major diastereomer: mp 123.5–124.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.00 (m, 11 H, ArH), 6.98 (d, J = 8.4 Hz, 2 H, ArH), 6.74 (d, J = 8.4 Hz, 2 H, ArH), 6.64 (dd, J = 8.2, 2.3 Hz, 1 H, ArH), 6.22 (d, J = 2.1 Hz, 1 H, ArH), 4.68 (s, 1 H, ArOH), 4.50 (s, 1 H, ArOH), 3.78 (d, J = 8.3 Hz, 1 H, ArCHAr), 2.80 (dd, J = 13.2, 5.8 Hz, 1 H, $ArCH(CH_2)_4Ph$), 2.61 (t, J = 7.7 Hz, 2 H, $PhCH_2$), 2.49 (t, J = 5.9 Hz, 2 H, $PhCH_2$), 2.15–2.09 (m, 1 H, ArCHCHCHAr), 1.82–1.35 (m, 10 H, $PhCH_2(CH_2)_3$, $PhCH_2(CH_2)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 153.9, 148.4, 142.6, 142.5, 138.9, 137.7, 129.7, 128.4, 128.3, 128.2, 125.6, 124.2, 115.2, 113.8, 111.6, 56.2, 55.0, 48.3, 36.0, 35.8, 34.0, 33.6, 32.0, 28.9, 26.5; IR (CCl_4, cm^{-1}) 3612, 2928, 1612, 857, 832; MS (FAB, positive ion, thioglycerol matrix) m/z 476 (M^+, 61), 136 (74), 117 (26), 107 (73); HRMS for $C_{34}H_{36}O_2$ calcd 476.2715, found 476.2743. Anal. Calcd for $C_{34}H_{36}O_2$: C, 85.67; H, 7.61. Found: C, 85.40; H, 7.53.

***cis*- and *trans*-3-(4-Hydroxyphenyl)-2-(methoxycarbonyl)cyclohexanone (62).** A rapidly stirred solution of phenol **39** (0.155 g, 0.437 mmol) and $CHCl_3$ (4.4 mL) was treated with trifluoroacetic acid (0.34 mL, 4.4 mmol) at 23 °C. After the solution was stirred for 20 min, aqueous workup ($NaHCO_3$, $CHCl_3$) afforded 0.106 g of crude product. Flash chromatography (15% ethyl acetate/hexane) afforded 0.102 g (94%) of **62** as a clear, colorless liquid (1:1 mixture of diastereomers, ^{1}H NMR): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 and 7.00 (d, J = 8.4 Hz, 2 H, ArH), 6.74 and 6.73 (d, J = 8.3 Hz, 2 H, ArH), 4.76 and 4.60 (s, 1 H, OH), 3.86–3.82 (m, 1 H, ArCH), 3.57 and 3.56 (s, 3 H, OCH_3), 3.36–3.27 (m, 1 H), 2.60–2.33 (m, 3 H), 2.20–1.20 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 173.7, 173.0, 170.1, 154.8, 153.8, 137.8, 133.8, 128.5, 127.9, 115.5, 114.8, 100.0, 64.2, 52.1, 51.4, 46.9, 40.9, 37.3, 33.0, 31.5, 29.0, 25.3, 16.6; IR (CCl_4, cm^{-1}) 3611, 3421, 2950, 1752, 1734, 1717, 1654, 1615, 830; MS (EI, 20 eV) m/z 248 (M^+, 63), 216 (40), 189 (100); HRMS for $C_{14}H_{16}O_4$ calcd 248.1049, found 248.1050.

***cis*- and *trans*-2-(Methoxycarbonyl)-3-(4-methoxyphenyl)cyclohexanone (63).** The same procedure as given previously for the preparation of **62** was carried out with **41** (40 min reaction time). Flash chromatography (10% ethyl acetate/hexane) afforded 67.5 mg (99%) of **63** as a clear, colorless liquid (1:1 mixture of diastereomers, ^{1}H NMR): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16–7.04 (m, 2 H, ArH), 6.85–6.80 (m, 2 H, ArH), 3.87 (m, 1 H, ArCH), 3.78 (s, 3 H, $ArOCH_3$), 3.56 and 3.55 (s, 3 H, CO_2CH_3), 3.42–3.28 (m, 1 H, ArCHCH), 2.59–1.48 (m, 6 H, $ArCHCH_2CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 173.7, 172.9, 169.3, 158.4, 157.6, 138.0, 134.3, 128.4, 127.8, 114.0, 113.3, 99.9, 64.0, 55.1, 51.8, 51.3, 46.8, 41.0, 37.3, 33.0, 31.5, 29.0, 25.3, 16.7; IR (neat, cm^{-1}) 2950, 1747, 1714, 1612, 830; MS (EI, 70 eV) m/z 262 (M^+, 87), 230 (73), 203 (100), 91 (24); HRMS for $C_{15}H_{18}O_4$ calcd 262.1205, found 262.1196.

3-(4-Hydroxyphenyl)cyclohexanone (64). A solution of β-keto ester **62** (45.0 mg, 0.182 mmol), anhydrous lithium bromide (94.6 mg, 1.09 mmol), and dimethyl sulfoxide (8.0 mL) was stirred at 180 °C for 40 min. Aqueous workup (pH 6 buffer, ether) afforded 30.2 mg of crude product as a yellow solid. Recrystallization (ether/hexane) afforded 27.6 mg (80%) of **64** as a white solid: purity by GC >99.99% (11.93 min); mp 118.0–118.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 8.4 Hz, 2 H, ArH), 6.80 (d, J = 8.4 Hz, 2 H, ArH), 5.05 (b s, 1 H, OH), 2.94 (dt, J = 11.4, 4.0 Hz, 1 H, CH), 2.46 (m, 4 H, CH_2COCH_2), 2.09 (m, 2 H, $CHCH_2CH_2$), 1.75 (m, 2 H, $CHCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.4, 154.5, 136.2, 127.6, 115.5, 49.2, 44.0, 41.1, 32.9, 25.4; IR (CCl_4, cm^{-1}) 3611, 3421, 2930, 1715, 1615, 825; MS (EI 20 eV) m/z 190 (M^+, 59), 133 (100), 91 (4); HRMS for $C_{12}H_{14}O_2$ calcd 190.0994, found 190.0992. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.45; H, 7.42.

3-(4-Methoxyphenyl)cyclohexanone (65). The same procedure as given previously for the preparation of **64** was carried out with **63**. Flash chromatography (25% ethyl acetate/hexane) afforded 36.0 mg (98%) of **65** as a clear, colorless liquid: purity by GC >99.99% (11.61 min, injector temp 150 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 8.6 Hz, 2 H, ArH), 6.87 (d, J = 8.6 Hz, 2 H, ArH), 3.80 (s, 3 H, $ArOCH_3$), 2.97 (dddd, J = 11.6, 11.3, 3.8, 3.8 Hz, 1 H, CH), 2.61–2.31 (m, 4 H, $ArCHCH_2COCH_2$), 2.18–2.00 (m, 2 H, $ArCHCH_2CH_2$), 1.88–1.69 (m, 2 H, $ArCHCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.0, 158.2, 136.5, 127.4, 114.0, 55.2, 49.2, 43.9, 41.1, 33.0, 25.4; IR (CCl_4, cm^{-1}) 2938, 1715, 1614, 828; MS (EI, 70 eV) m/z 204 (M^+, 51), 147 (100), 134 (40), 91 (27).

4-(4,5,6,7-Tetrahydrobenzofuranyl)phenol (66). According to the general cyclization procedure, MEM ether **43** (9.4 mg, 0.029 mmol) [-78 °C, 3 min] afforded 9.0 mg of crude product as an orange oil. Flash chromatography (10% ethyl acetate/hexane) afforded 4.8 mg (76%) of **66** as a clear, colorless oil: purity by GC 98.41% (12.15 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (s, 1 H, CH=CHO), 6.96 (d, J = 8.3 Hz, 2 H, HOArH), 6.76 (d, J = 8.3 Hz, 2 H, HOArH), 6.24 (s, 1 H, CH=CHO), 4.66 (s, 1 H, OH), 3.98 (t, J = 5.7 Hz, 1 H, CH), 2.60–2.43 (m, 2 H, $CHCH_2CH_2CH_2$), 2.20–2.12 (m, 1 H, CHCHHCH$_2$), 1.86–1.63 (m, 3 H, CHCHHCH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 151.5,

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140.9, 136.0, 128.9, 118.7, 115.2, 110.2, 39.9, 33.9, 22.3, 21.1; IR (CCl_4, cm^{-1}) 3613, 2937, 1615, 1513, 1438, 1257, 1171, 1104, 892, 828; MS (EI, 70 eV) m/z 214 (M^+, 100), 186 (68), 169 (13), 157 (39), 107 (11), 91 (11), 77 (9); HRMS for $C_{14}H_{14}O_2$ calcd 214.0994, found 214.0992.

***trans*-1-(4-Hydroxyphenyl)-2-isopropylcyclohexane (67).** A rapidly stirred solution of phenol **42** (80.8 mg, 0.248 mmol) and CH_2Cl_2 (25 mL) was cooled to -78 °C, and $EtAlCl_2$ (8.70 mL, 8.7 mmol, 1.0 M in hexane) was added dropwise at a rate to keep the temperature below -76 °C. After the solution was stirred for 10 min, aqueous workup ($NaHCO_3$, ether) afforded 45.5 mg of crude product (5:1 mixture of diastereomers, ^1H NMR). HPLC (8 μm silica gel column, i.d. 1 cm, 15% ethyl acetate/hexane, 0.5 mL/min, retention time 17.25 min) afforded 42.2 mg (78%) of **67** as a white solid, mp 102.0-109.0 °C. The minor diastereomer (^1H NMR (300 MHz, $CDCl_3$) δ 2.53 (t, J = 6.7 Hz, 1 H, ArC*H*)) was not isolated. Major diastereomer (>20:1 mixture of diastereomers, ^1H NMR): purity by GC 99.53% (11.62 min); ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 8.4 Hz, 2 H, Ar*H*), 6.76 (d, J = 8.4 Hz, 2 H, Ar*H*), 4.80 (b s, 1 H, OH), 2.32 (dt, J = 11.2, 3.0 Hz, 1 H, ArC*H*), 1.85-1.01 (m, 10 H, $ArCH(CH_2)_4CHCH(CH_3)_2$), 0.79 (d, J = 6.8 Hz, 3 H, CH_3CHCH_3), 0.67 (d, J = 6.8 Hz, 3 H, CH_3CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 139.1, 128.4, 115.1, 48.1, 47.4, 36.8, 27.5, 27.1, 26.7, 24.8, 21.4, 15.3; IR (CCl_4, cm^{-1}) 3613, 3480, 2929, 1614, 827, 798; MS (EI, 20 eV) m/z 218 (M^+, 82), 133 (100), 107 (84), 91 (5); HRMS for $C_{15}H_{22}O$ calcd 218.1671, found 218.1675.

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Supplementary Material Available: Full spectral data for 1-(4-hydroxyphenyl)-1-[[(methoxyethoxy)methyl]oxy]-3-[[(4-methylphenyl)sulfonyl]oxy]propane, methyl 7-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-7-[[(methoxyethoxy)methyl]oxy]-3-oxoheptanoate, 8-[4-[(*tert*-butyldimethylsilyl)oxy]phenyl]-8-[[(methoxyethoxy)methyl]oxy]-2-methyloct-2-ene, 1-[4-[(*tert*-butyldimethylsilyl]oxy]phenyl]-4-furan-3-yl-1-[[(methoxyethoxy)-methyl]oxy]butane and copies of the ^1H and ^{13}C NMR for compounds lacking combustion data (40 pages). Ordering information is given on any current masthead page.

Homolytic Acylation of Protonated Pyridines and Pyrazines with α-Keto Acids: The Problem of Monoacylation

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The silver-catalyzed decarboxylation of α-keto acids by persulfate leads to acyl radicals, which can effect the selective homolytic acylation of pyridine and pyrazine derivatives. Compared with the previously developed source of acyl radicals by hydrogen abstraction from aldehydes, this procedure is more effective in monoacylation when multiple positions of high nucleophilic reactivity are available in the heterocyclic ring. Although the introduction of an acyl group strongly activates the heterocyclic ring toward further substitution, monoacylation can be achieved by taking advantage of the difference in basicity and lipophilicity between the starting base and the monoacylation products in a two-phase system.

The substitution of protonated heteroaromatic bases by nucleophilic alkyl and carbonyl radicals reflects many aspects of the Friedel-Crafts aromatic substitution, but with opposite reactivity and selectivity.[1] Thus, electron-withdrawing groups activate and alkyl groups deactivate the heterocyclic ring; position 2 of 4-cyanoquinoline is ~130-fold more reactive toward the benzoyl radical than the same position of 4-methylquinoline.[2] Consequently, when multiple positions of high nucleophilic reactivity (e.g., α and γ) are available in the heterocyclic ring, polysubstitution at these positions by acyl radicals occurs easily and it is difficult to arrest the reaction at the monosubstitution stage. Monosubstitution by acyl radicals is, however, of synthetic interest in many compounds that have more than one reactive position in the heterocyclic ring.

Results and Discussion

We have previously reported a method for the acylation of heteroaromatic compounds by using the t-BuOOH/Fe^{2+} redox system in the presence of aldehydes (eq 1).[3] The

$$\text{Het-H} + \text{RCHO} + t\text{-BuOOH} \xrightarrow{Fe^{2+}} \text{Het-COR} + t\text{-BuOH} + H_2O \quad (1)$$

reaction was generally carried out in aqueous acetic acid because of the low water solubility of most aldehydes. We were interested in arresting the reaction at the monosubstitution stage by using a two-phase system, taking advantage of the acid-base equilibria of the heterocyclic compounds[3] and the difference in lipophilicity between the reagents and the reaction products.[4] These attempts failed or gave poor results because the organic solvent usually extracted all of the aldehyde from the aqueous phase, preventing the generation of acyl radicals. Only the lower aliphatic aldehydes, which are slightly water soluble, gave a moderate increase in monoacylation.[5]

We now report a different and quite general source of acyl radicals that allowed us to develop a two-phase system

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