Electroreductive Intramolecular Coupling of Nonconjugated Aromatic Ketones[1]

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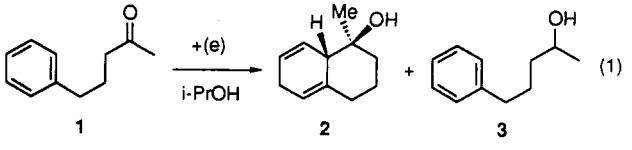
The electroreduction of nonconjugated aromatic ketones gave intramolecularly coupled products. The best result was obtained using an Sn cathode in i-PrOH containing tetraalkylammonium salt as a supporting electrolyte. This reductive cyclization proceeded with remarkable stereoselectivity, and the cis isomer was obtained exclusively. A variety of new bi- and polycyclic compounds were synthesized. The reaction mechanism was studied, and it was suggested that the anion radical generated by one-electron transfer to a carbonyl group attacks an aromatic ring intramolecularly. The choice of counter cation of the anion radical was critical for the reductive cyclization. Other reductive methods employing metal reducing agents were also studied. Reduction with Na in HMPA–THF gave the same cyclized product, though the yield was lower than that with the electroreduction.

Reductive cross-coupling of a carbonyl group with an unsaturated system is a useful and important reaction. In our previous studies, the electroreductive intramolecular coupling of a carbonyl group with a nonactivated carbon–carbon double[2] or triple bond,[3] or a carbon–nitrogen triple bond,[4] and the intermolecular coupling of a carbonyl group with a nonactivated carbon–carbon double bond,[5] or with a carbon–nitrogen double bond[6] have been described.

It has been found in the present study that a novel intramolecular coupling of nonconjugated aromatic ketones is promoted by electroreduction, and cyclized products are obtained stereoselectively. This type of reductive cyclization is hitherto unknown and provides a new synthetic method for bi- and polycyclic compounds. The use of a tetraalkylammonium salt as an electrolyte is essential for this cyclization. The reaction mechanism of this electroreductive cyclization and other reductive methods with metal reducing agents were also studied.

Results and Discussion

A typical reaction is shown in eq 1. The reaction



conditions were surveyed using 5-phenyl-2-pentanone (1), and the results are summarized in Table 1. This intramolecular coupling was highly influenced by the choice of cathode material, solvent, and supporting electrolyte. Tin was the best cathode, while Cu, Ag, Pb, and Zn cathodes gave somewhat poorer results (runs 1–5). Other cathode materials such as Pt, Ni, and Ti gave no reduced product. As a solvent, i-PrOH was the best. t-BuOH resulted in a decrease in the yield of **2** (compare run 1 with run 6), whereas EtOH, DMF, and THF gave rather poor results (runs 7–10). The effect of the cation of the supporting electrolyte was interesting. Tetraalkylammonium salts such as Et_4NOTs and Bu_4NClO_4 gave **2** in 65–70% yields (runs 1, 11, and 12), while no cyclized product was produced when $LiClO_4$ was used as the electrolyte (run 13). Consequently, the best result (**2**: 70%, **3**: 7%) was obtained when the electroreduction was carried out in i-PrOH containing Et_4NOTs using a divided cell equipped with a ceramic diaphragm and an Sn cathode (run 1). The electroreduction could also be carried out without a diaphragm, though the yield of **2** was slightly decreased (**2**: 62%, **3**: 13%).

Table 1. Electroreduction of 5-Phenyl-2-pentanone (1)

run	cathode	solvent	electrolyte	% yield of 2[a]	% yield of 3[a]
1	Sn	i-PrOH	Et_4NOTs	70	7
2	Cu	i-PrOH	Et_4NOTs	54	6
3	Ag	i-PrOH	Et_4NOTs	51	15
4	Pd	i-PrOH	Et_4NOTs	48	13
5	Zn	i-PrOH	Et_4NOTs	40	13
6	Sn	t-BuOH	Et_4NOTs	64	12
7	Sn	EtOH	Et_4NOTs	26	52
8	Sn	DMF	Et_4NOTs	28	26
9	Sn	THF	Bu_4NClO_4	14	28
10	Sn	dioxane/ i-PrOH (1:1)	Et_4NOTs	50	6
11	Sn	i-PrOH	Bu_4NClO_4	68	8
12	Sn	i-PrOH	Bu_4NBr	65	8
13	Sn	i-PrOH	$LiClO_4$	0	60

[a] Isolated yields. Electroreduction of 1 (5 mmol) was carried out in a solvent (40 mL) containing a supporting electrolyte (10 g) using a divided cell.

The cyclized product **2** was a single stereoisomer (>99%) on the basis of ^1H NMR and GLC analyses. The hydroxyl group and the hydrogen on C-10 are located cis to one another in **2**, since the ^{13}C NMR spectrum of the hydrogenated product **4** was the same as reported data[7] (eq 2). Similar *cis*-stereoselectivity has been observed in

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(2) (a) Shono, T.; Mitani, M. *J. Am. Chem. Soc.* **1971**, *93*, 5284. (b) Shono, T.; Nishiguchi, I.; Ohmizu, H.; Mitani, M. *J. Am. Chem. Soc.* **1978**, *100*, 545.

(3) Shono, T.; Nishiguchi, I.; Ohmizu, H. *Chem. Lett.* **1976**, 1233.

(4) (a) Shono, T.; Kise, N. *Tetrahedron Lett.* **1990**, *31*, 1303. (b) Shono, T.; Kise, N.; Fujimoto, T.; Tominaga, N.; Morita, H. *J. Org. Chem.* **1992**, *57*, 7175.

(5) Shono, T.; Kashimura, S.; Mori, Y.; Hayashi, T.; Soejima, T.; Yamaguchi, Y. *J. Org. Chem.* **1989**, *54*, 6001.

(6) Shono, T.; Kise, N.; Fujimoto, T. *Tetrahedron Lett.* **1991**, *32*, 525.

(7) Ayer, W. A.; Browne, L. M.; Fung, S.; Stothers, J. B. S. *Org. Magn. Reson.* **1978**, *11*, 73.

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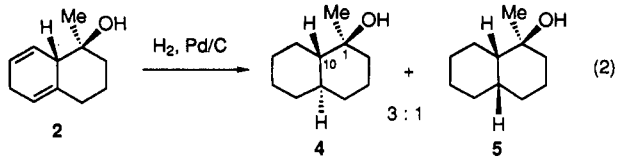
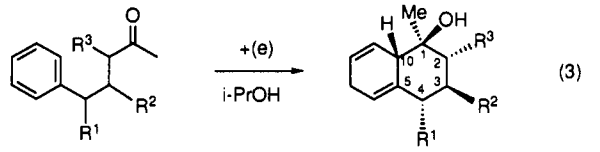
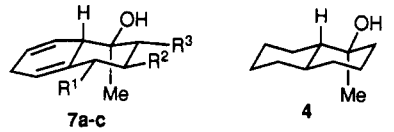


our previously reported electroreductive cyclization of nonconjugated olefinic ketones.[2]

It was found that a methyl group located between the phenyl and carbonyl groups did not inhibit the cyclization and also that the products **7a–c** were formed as a single isomer (eq 3). The stereoconfigurations of **7a–c** were



1 R^1=R^2=R^3=H — **2** 70%
6a R^1=CH_3, R^2,R^3=H — **7a** 60%
6b R^1,R^3=H, R^2=CH_3 — **7b** 68%
6c R^1,R^2=H, R^3=CH_3 — **7c** 60%



studied by analyzing their ^{13}C NMR spectra and those of **2** and **4**[7] (Table 2). The large downfield shifts (8–9 ppm, italicized in Table 2) of the C-3 carbon in **7a**, C-2 and C-4 carbons in **7b**, and C-3 carbon in **7c** show that each methyl group of R^1–R^3 in **7a–c** is located in an equatorial position.[8] The downfield shifts of C-5 carbon in **7a** and C-1 carbon in **7c** are smaller (2–4 ppm), since these carbons are quaternary.[10] The upfield shifts (6–7 ppm) of two methyl groups in **7c** are due to γ-effect between these methyl groups. Consequently, the stereostructures of **7a–c** are assigned as shown in eq 3. These assignments are consistent with the ^1H NMR NOE experiments of **7a** and **7c**.[12]

Other starting materials and products, the latter being obtained under the same reaction condition as run 1 in Table 1, are summarized in Tables 3 and 4. Polycyclic products were obtained by this electroreductive coupling (Table 3). Although the stereoconfigurations of the cyclized products were not determined, their ^1H and ^{13}C NMR spectra showed that each of those shown in Table 3 and many of those in Table 4 was a single stereoisomer.

(8) The changes of ^{13}C NMR chemical shifts induced by substitution of a methyl group on cyclohexane are as follows.[9]

methyl group	C-α	C-β	C-γ	C-δ
equatrial	5.0	9.0	0	-0.2
axial	1.4	5.4	-6.4	0

Positive values donate downfield shifts from cyclohexane (δ 27.1).

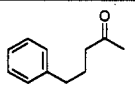
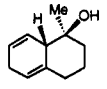
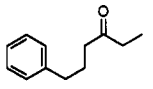
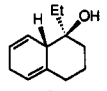
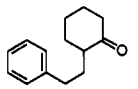
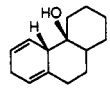
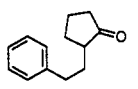
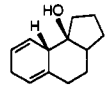
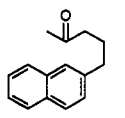
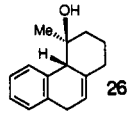
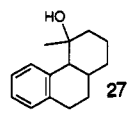
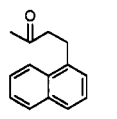
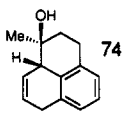
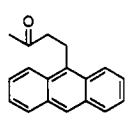
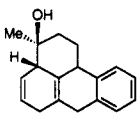
(9) Abraham, R. J.; Loftus, P. *Proton and Carbon-13 NMR Spectroscopy*; Heyden: London, 1978.
(10) Similar result was observed between ^{13}C NMR of 1-methyl-1-cyclohexanol and that of 1,2-dimethyl-1-cyclohexanol.[11]
(11) Grenier-Loustalot, M. F.; Zahidi, A.; Bonastre, J.; Grenier, P. *Bull. Soc. Chim. Fr.* **1979**, I-229.
(12) No NOE enhancement could be observed between H-10 and CH_3-4 in **7a** and between H-10 and CH_3-2 in **7c**.

Table 2. ^{13}C NMR Chemical Shifts of 1, 7a–c, and 4[a]

compound	C-1	C-2	C-3	C-4	C-5	Me
2	74.43	41.98	24.15	34.89	135.96	21.78
7a	74.83	41.61	*33.12*	36.87	139.64	17.46, 21.76
7b	74.34	*50.79*	30.64	*43.68*	135.52	22.21, 22.55
7c	76.75	43.70	*32.39*	34.91	136.11	15.14, 15.79
4[b]	72.71	42.86	23.35	34.59	39.42	21.24

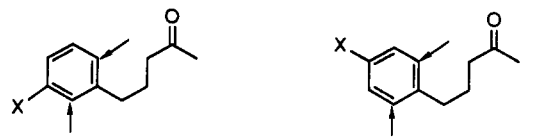
[a] In ppm from internal TMS in $CDCl_3$. [b] Reference 7.

Table 3. Electroreduction of β- or γ-Aryl Ketones

starting material	cyclized product and % yield[a]	% yield of noncyclized alcohol
 1	 70 2	7
 8	 55 9	19
 10	 45 11	37
 12	 30 13	38
 14	 26 15	 27 16
 17	 74 18	
 19	 54[b] 20	

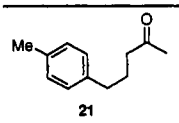
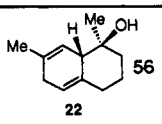
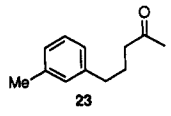
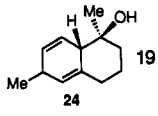
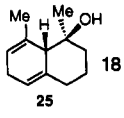
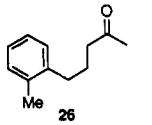
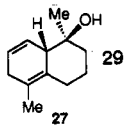
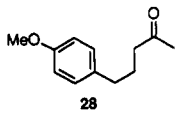
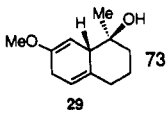
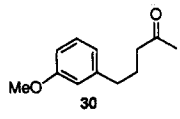
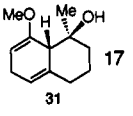
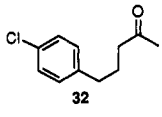
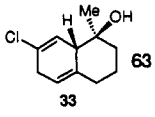
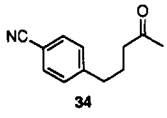
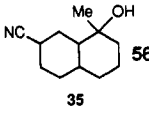
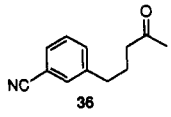
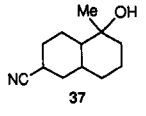
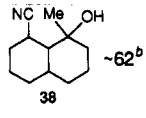
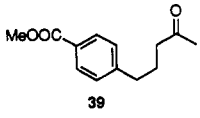
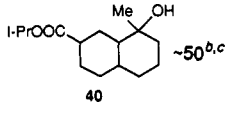
[a] Isolated yields. [b] See ref 13.

It is likely that each cyclized product has the same stereoconfiguration as **2**. As shown in Table 4, a *meta*-substituted electron-donating group (OMe, Me) hindered the cyclization considerably, whereas *para*-substitution and a *meta*-substituted electron-withdrawing group (CN, CO_2Me) did not inhibit it. These results suggest that the active species reacting with the aromatic ring has an anionic character. The meta substituent would show a more remarkable effect on the cyclization than ortho and para substituents, since the intramolecular coupling of *meta*-substituted **1** takes place at the para or ortho position to the meta substituent on the aromatic ring.



This cyclization was limited to six-membered ring formation, and 4-phenyl-2-butanone and 6-phenyl-2-

Table 4. Electroreduction of Ar-Substituted 5-Phenyl-2-pentanone

starting material	cyclized product and % yield[a]		% yield of non-cyclized alcohol
 21	 56 22		12
 23	 19 24	 18 25	36
 26	 29 27		46
 28	 73 29		5
 30	 17 31		36
 32	 63 33		3
 34	 56[b,c] 35		
 36	 37	 ~62[b] 38	
 39	 ~50[b,c] 40		6

[a] Isolated yields. [b] Since cyclized products were obtained as a mixture of several olefinic and saturated compounds, the yield of all cyclized products were determined after hydrogenation (H_2, Pd/C) of the crude products. [c] See ref 14.

hexanone gave noncyclized alcohols under the same reaction conditions. Sterically hindered ketones and aromatic ketones also gave noncyclized products (Scheme 1).

Reduction of 1 Using Nonelectrochemical Methods. Since this type of reductive cyclization is a new reaction, it is instructive to compare the electroreductive methodology with other methods using metal reducing agents (Table 5). The reduction of 1 with Zn, Sn, or Na in i-PrOH gave noncyclized alcohol 3 as the sole product (runs 2–4), and the presence of tetraalkylammonium salts did not affect these reactions. The reduction with Na in wet Et_2O[15] also gave 3 (run 5), and that in liquid NH_3–THF[16] afforded the product 41 in which the aromatic ring of 3 was further reduced (run 6). The reduction with $TiCl_4$–Zn in THF[17] gave 3 and homo-coupled product 42 (run 7). Recently, it is reported that SmI_2 is effective for the intramolecular

Scheme 1

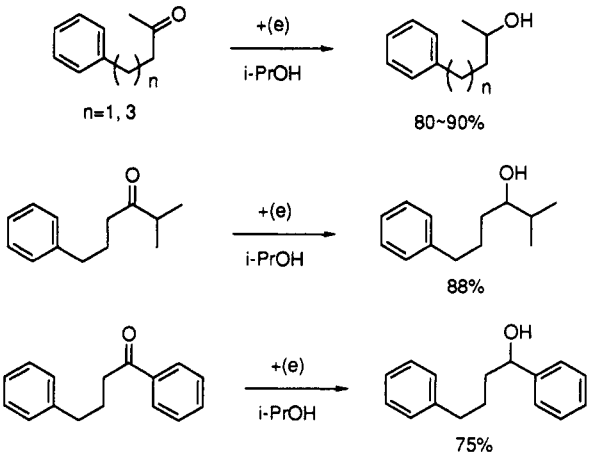
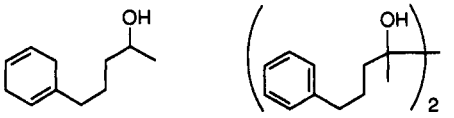


Table 5. Reduction of 5-Phenyl-2-pentanone (1)

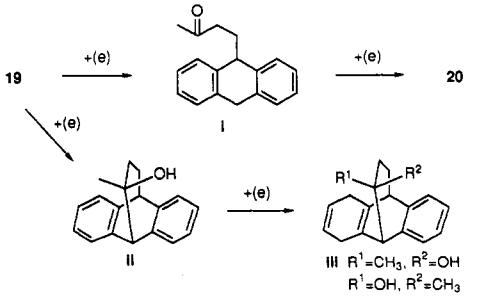
run	reducing agent	condition	yield, %[a] 2	3
1	electroreduction	Et_4NOTs/i-PrOH, 25 °C	70	7
2	Zn	NaOH/i-PrOH, 65 °C	0	84
3	Sn	NaOH/i-PrOH, 65 °C	0	85
4	Na	i-PrOH, 25 °C	0	81
5	Na	wet Et_2O, 25 °C	0	90
6	Na	liquid NH_3/THF, −70 °C	0	0[b]
7	$TiCl_4$–Zn	THF, 65 °C	0	35[c]
8	SmI_2	t-BuOH–HMPA–THF, 0 °C	0	trace[d]
9	Na	HMPA–THF (2:1), 0 °C	42	17

[a] Isolated yields. [b] 41 was obtained in 95% yield. [c] 42 was also obtained in 34% yield. [d] Starting 1 was recovered.

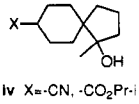

41 42

coupling of ketones with olefins or alkynes,[18] though the reduction of 1 with SmI_2 in t-BuOH–HMPA–THF resulted in no reaction (run 8). On the other hand, the cyclized

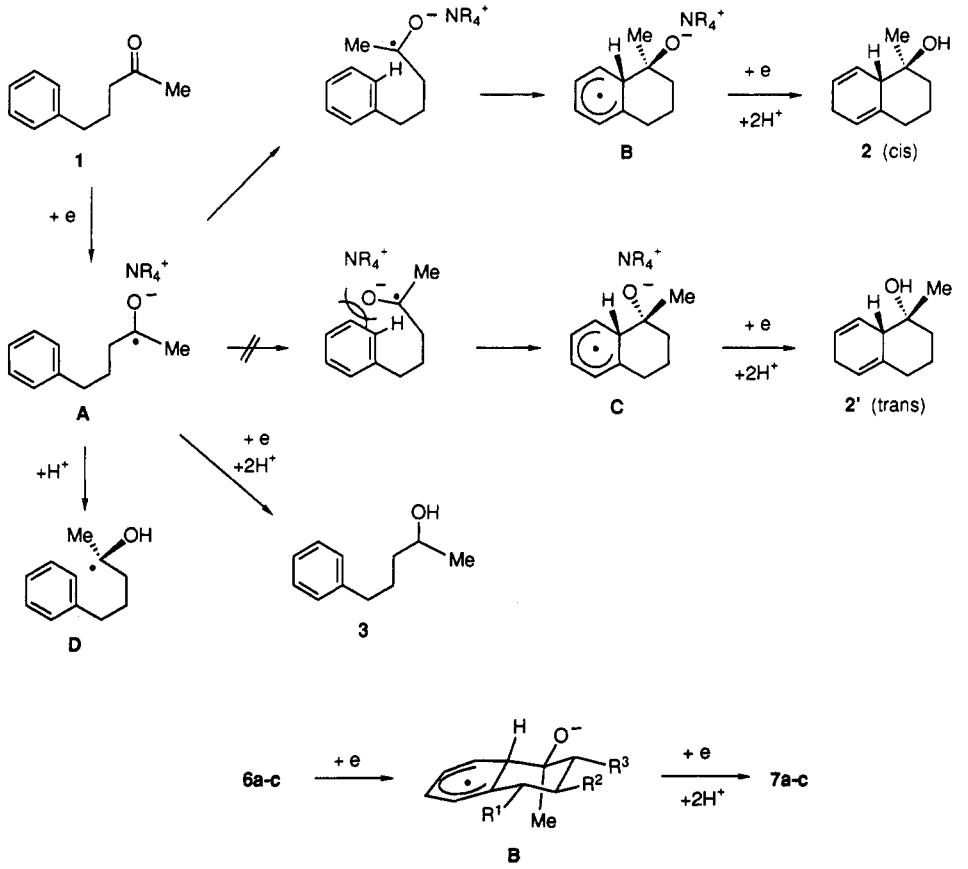
(13) Naphthalene and aliphatic ketones have similar reduction potentials. On the other hand, anthracene is more easily reduced than aliphatic ketones and affords 9,10-dihydroanthracene under the same condition. It therefore seems that the electroreductive reduction of 19 proceeds through the formation of i and its subsequent cyclization. Another structure iii formed through ii is unlikely for the cyclized product instead of 20. Since isolated benzene ring is inert under the present condition, ii cannot be reduced to iii.



(14) The structures iv instead of 35 and 40 are excluded, since no spiro carbon is observed in their ^{13}C NMR spectra.


iv X=-CN, -CO_2Pr-i

Scheme 2

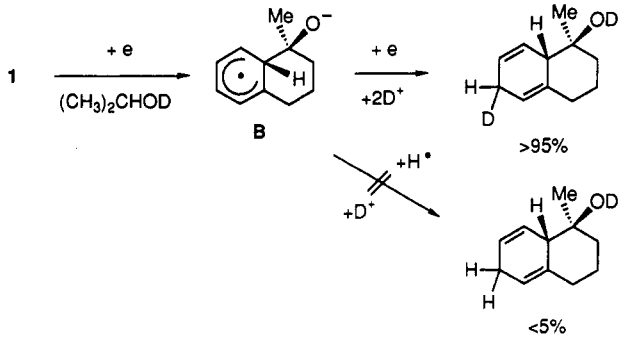


product **2** (42%) was obtained together with **3** (17%) by the reduction with Na in HMPA–THF[16] (run 9).

Reaction Mechanism. Undoubtedly, the electroreductive cyclization of **1** is initiated by the reduction of the carbonyl group, since alkylbenzenes were completely inert under the present reaction conditions whereas ketones were easily reduced to the corresponding alcohols under the same conditions. It is unlikely that anion attacks nonactivated aromatic ring. Therefore, the key intermediate in this reaction is a radical or an anion radical species.

The overall reaction scheme of the electroreductive cyclization of **1** is depicted in Scheme 2. The anion radical **A** generated by one-electron transfer to the carbonyl group of **1** attacks the aromatic ring intramolecularly to give cis intermediate **B** rather than trans **C** due to the electronic repulsion between anionic oxygen atom and π-electrons of phenyl group. Another radical species **D**, which is formed by protonation to anion radical **A**, may be unlikely, since the electroreductive cyclization is strongly affected by the counter cation of supporting electrolyte. In addition, the effect of a substituent on the aromatic ring shows that the active species attacking the aromatic ring has an anionic character as described above. The stereoselectivity observed in this cyclization is much higher (cis/trans > 99) than that reported for the typical radical cyclization (cis/trans ~ 3.8).[19] This extremely high stereoselectivity can be well explained by the strong repulsion between the two negative centers as shown in Scheme 2. The stereoselectivity in the cyclization of **6a–c** is elucidated by assuming the *pseudo*-chair intermediate **B** in which each methyl group of R^1–R^3 is located at an equatorial position.

Scheme 3



The result of the electroreduction of **1** in $(CH_3)_2CHOD$ shows that the product **2** is formed from **B** not through hydrogen abstraction from solvent but further one-electron transfer of **B** and subsequent protonation of the resulting anion (Scheme 3).

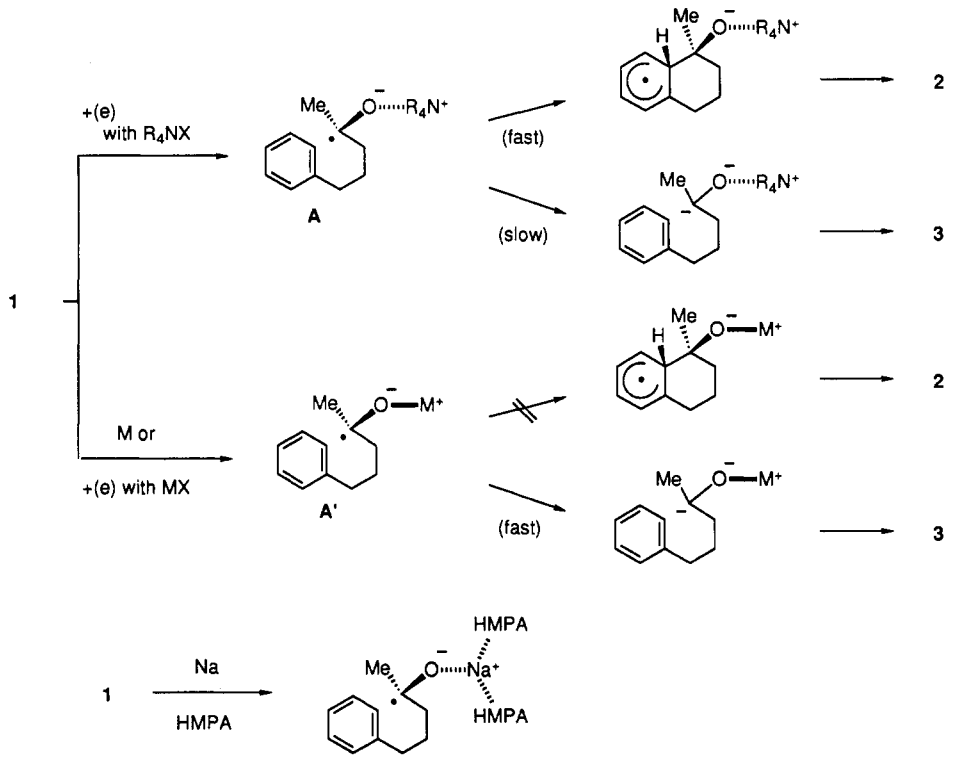
When the aromatic ring is a polynuclear hydrocarbon (**14**, **17**, and **19** in Table 3), the possibility that the reduction of the aromatic ring is the initial step cannot necessarily be excluded.[13]

A critical factor for the present cyclization is that the counter cation of the electrogenerated anion radical **A** is

(15) Eakin, M.; Martin, J.; Parker, W. *Chem. Commun.* **1965**, 206.
(16) House, H. O.; Giese, R. W.; Kronberger, K.; Kaplan, J. P.; Simenone, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 2800.
(17) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041.
(18) (a) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236. (b) Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1989**, *30*, 1063. (c) Shim, S. C.; Hwang, J.-T.; Kang, H.-Y.; Chang, M. H. *Tetrahedron Lett.* **1989**, *31*, 4765.

(19) (a) Beckwith, A. L. J.; Blair, I.; Phillipou, G. *J. Am. Chem. Soc.* **1974**, *96*, 1613. (b) Garst, J. F.; Hines, J. B. *Ibid.* **1984**, *106*, 6443.

Scheme 4



a quaternary ammonium cation (Scheme 4). Since the counter cation of A′ generated by the electroreduction using a metal salt as an electrolyte (Table 1, run 13) or by the reduction with a metal reducing agent (Table 5, runs 2–7) is a metal cation, the covalent nature of the bond between the anion radical and the counter cation is much less in A than in A′. Hence, the further electron transfer to A is slower than the cyclization of A, and the cyclized product **2** is obtained mainly. On the other hand, the electron transfer to A′ is faster than cyclization, and the noncyclized alcohol **3** is formed exclusively. In the reduction with Na–HMPA, the covalent nature between the anion radical and Na cation is decreased by the strong solvation of HMPA to the Na cation and it is therefore possible for the anion radical to attack the aromatic ring intramolecularly. The electroreductive method can easily and effectively achieve the cyclization without using highly toxic HMPA.

Experimental Section

^{1}H NMR spectra were measured on a Varian EM-390 (90 MHz). ^{13}C NMR spectra were measured on a JEOL JNM-GX400 (operating at 100 MHz).

Starting Materials. 5-Phenyl-2-pentanone (**1**)[20] was synthesized in the usual way by alkylation of ethyl acetoacetate with (2-bromoethyl)benzene and subsequent decarbethoxylation,[21] and **6a,b**, **12**, **14**, **17**, **19**, **21**, **23**, **26**, **28**, **30**, and **32** were prepared by the same method. Other nonconjugated aromatic ketones, **8**[22] and **10**,[23] were obtained according to known methods.

6a: bp 88 °C (6 mmHg); IR (neat) 1720, 1604, 1499, 968, 915, 770, 705 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.24 (d, 3 H, J = 7 Hz), 1.46–2.40 (m, 4 H), 1.93 (s, 3 H), 2.44–2.90 (m, 1 H), 6.82–7.39 (br s, 5 H). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.72; H, 9.18.

6b: R_f 0.55 (hexane–AcOEt, 5:1); IR (neat), 1716, 1605, 1585, 1499, 964, 945, 915, 845, 782, 720, 700 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.90 (d, 3 H, J = 6 Hz), 2.01 (s, 3 H), 2.04–2.81 (m, 5 H), 6.80–7.51 (br s, 5 H). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.69; H, 9.10.

6c: R_f 0.6 (hexane–AcOEt, 5:1); IR (neat) 1720, 1608, 1502, 754, 702 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.07 (d, 3 H, J = 5 Hz), 1.30–2.75 (m, 5 H), 2.01 (s, 3 H), 7.06 (s, 5 H). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.65; H, 9.13.

8: bp 85 °C (2 mmHg); IR (neat) 1714, 1603, 1499, 745, 698 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.05 (3 H, J = 7.5 Hz), 1.70–3.00 (m, 8 H), 7.57 (s, 5 H). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.65; H, 9.07.

14: R_f 0.3 (hexane–AcOEt, 5:1); IR (neat) 1712, 1630, 1600, 1508, 896, 854, 820, 748 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.75–2.15 (m, 2 H), 2.02 (s, 3 H), 2.35 (t, 2 H, J = 4.5 Hz), 2.74 (t, 2 H, J = 4.5 Hz), 7.17–7.84 (m, 7 H). Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.80; H, 7.58.

17: bp 128 °C (2 mmHg); IR (neat) 1700, 1600, 1550, 800, 780 cm^{-1}; ^{1}H NMR (CCl_4) δ 2.01 (s, 3 H), 2.55–2.90 (m, 2 H), 3.10–3.45 (m, 2 H), 7.10–8.10 (m, 7 H). Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.76; H, 7.16.

19: mp 87–88 °C; IR (KBr) 1714, 1675, 1626, 1500, 955, 883, 878, 852, 839, 788, 733 cm^{-1}; ^{1}H NMR (CCl_4) δ 2.21 (s, 3 H), 2.79–3.05 (m, 2 H), 3.72–4.05 (m, 2 H), 7.32–7.68 (m, 4 H), 7.90–8.44 (m, 5 H). Anal. Calcd for $C_{12}H_{16}O$: C, 87.06; H, 9.49. Found: C, 87.01; H, 9.50.

21: bp 135 °C (1 mmHg); IR (neat) 1718, 1540, 820 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.60–2.70 (m, 6 H), 1.98 (s, 3 H), 2.26 (s, 3 H), 6.85 (br s, 4 H). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.67; H, 9.11.

23: R_f 0.6 (hexane–AcOEt, 5:1); IR (neat) 1720, 1612, 1509, 1483, 880, 812, 784, 700 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.45–2.46 (m, 4 H), 2.00 (s, 3 H), 2.22 (s, 3 H), 2.25–2.79 (m, 2 H), 6.56–7.18 (m, 4 H). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.76; H, 9.15.

26: R_f 0.5 (hexane–AcOEt, 5:1); IR (neat) 1721, 1512, 1501, 815, 765, 744 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.42–2.58 (m, 4 H), 2.00 (s, 3 H), 2.15 (s, 3 H), 2.43–2.84 (m, 2 H), 6.60–7.18 (m, 4 H). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.69; H, 9.20.

28: R_f 0.4 (hexane–AcOEt, 5:1); IR (neat) 1717, 1614, 1587, 1515, 835, 700 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.55–2.03 (m, 2 H), 1.98 (s, 3 H), 2.27 (t, 2 H, J = 6 Hz), 2.49 (t, 2 H, J = 7 Hz), 3.66 (s,

(20) Ramart-Lucas, M.; Labaune, L. *Ann. Chim.* **1931**, *16*, 295.
(21) Pond, D. M.; Cargill, R. L. *J. Org. Chem.* **1967**, *32*, 4064.
(22) Cason, J.; Kraus, K. W. *J. Org. Chem.* **1961**, *26*, 1768.
(23) Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178.

3 H), 6.57 (d, 2 H, J = 9 Hz), 6.90 (d, 2 H, J = 9 Hz). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.89; H, 8.40.

30: bp 110 °C (0.5 mmHg); IR (neat) 1720, 1607, 1590, 1495, 789, 700 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.65–2.13 (m, 2 H), 2.02 (s, 3 H), 2.33 (t, 2 H, J = 6 Hz), 2.54 (t, 2 H, J = 7 Hz), 3.72 (s, 3 H), 6.39–6.75 (m, 3 H), 6.82–7.13 (m, 1 H). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.92; H, 8.36.

32: R_f 0.6 (hexane–AcOEt, 5:1); IR (near) 1719, 1600, 1500, 830, 795, 660 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.60–2.10 (m, 2 H), 2.02 (s, 3 H), 2.33 (t, 2 H, J = 6 Hz), 2.56 (t, 2 H, J = 7 Hz), 6.98 (d, 2 H, J = 8.5 Hz), 7.17 (d, 2 H, J = 8.5 Hz). Anal. Calcd for $C_{12}H_{15}OCl$: C, 68.41; H, 7.18; Cl, 16.83. Found: C, 68.45; H, 7.24; Cl, 16.67.

Synthesis of 34, 36, and 39. To a solution of LDA (50 mmol) in 60 mL of hexane–THF (1:1) was added a solution of *p*-toluonitrile (40 mmol) in THF (20 mL) at 0 °C. After stirring for 1 h, 1-bromo-3-butanone ethylene ketal[24] (50 mmol) was added, and the mixture was stirred for 3 h at this temperature. After 1 N HCl (100 mL) was added, the reaction mixture was stirred at room temperature overnight. The mixture was extracted with CH_2Cl_2. The product **34** was isolated by column chromatography on silica gel in a 85% yield. The other aromatic ketones **36** (58%) and **39** (23%) were prepared by the same method.

34: R_f 0.55 (hexane–AcOEt, 2:1); IR (neat) 2240, 1719, 1615, 1512, 840 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.67–2.10 (m, 2 H), 2.06 (s, 3 H), 2.36 (t, 2 H, J = 7 Hz), 2.66 (t, 2 H, J = 8 Hz), 7.23 (d, 2 H, J = 8 Hz), 7.53 (d, 2 H, J = 8 Hz). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.85; H, 7.05; N, 7.38.

36: R_f 0.5 (hexane–AcOEt, 2:1); IR (neat) 2235, 1715, 1602, 1586, 1490, 800, 692 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.62–2.11 (m, 2 H), 2.07 (s, 3 H), 2.40 (t, 2 H, J = 6 Hz), 2.66 (t, 2 H, J = 7 Hz), 7.15–7.62 (m, 4 H). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.81; H, 7.07; N, 7.34.

39: bp 150 °C (6 mmHg); IR (neat) 1720, 1715, 1615, 767, 712 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.56–2.10 (m, 2 H), 2.12 (s, 3 H), 2.15–2.90 (m, 4 H), 3.89 (s, 3 H), 7.22 (d, 2 H, J = 8 Hz), 7.97 (d, 2 H, J = 8 Hz). Anal. Calcd for $C_{13}H_{16}O$: C, 70.89; H, 7.32. Found: C, 70.77; H, 7.28.

Typical Procedure for Electroreduction. A solution of Et_4NOTs (10 g) in i-PrOH (40 mL) was put into a divided cell (50-mL beaker) equipped with an Sn cathode (5 × 10 cm^2), a carbon rod anode, and a ceramic diaphragm. To the catholyte was added ketone **1** (5 mmol). Electrolysis was carried out at constant current of 0.2 A until all of the ketone was consumed (4 F/mol). The catholyte was poured into water (200 mL) and extracted with Et_2O. The products **2** and **3** were isolated by column chromatography on silica gel. The noncyclized product **3** was confirmed by the comparison with the sample prepared from **1** by LAH reduction.

2: R_f 0.7 (hexane–AcOEt, 2:1); mp 102–103 °C; UV (hexane) λ_{max} 210 nm (ϵ 2043); IR (KBr) 3350, 1660, 1650, 958, 920, 908, 865, 785, 680 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.99 (s, 3 H), 1.12–2.30 (m, 7 H), 2.52–2.68 (br s, 3 H), 5.32–5.45 (br s, 1 H), 5.61–5.95 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.78 (q), 24.15 (t), 26.76 (t), 34.89 (t), 41.98 (t), 48.88 (d), 74.43 (s), 118.27 (d), 124.07 (d), 125.71 (d), 135.96 (s). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.34; H, 9.83.

7a: R_f 0.5 (hexane–AcOEt, 5:1); mp 79–82 °C; IR (KBr) 3350, 957, 944, 789, 681 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.97 (s, 3H), 1.00 (d, 3 H, J = 5 Hz), 1.32–2.03 (m, 6 H), 2.51–2.70 (m, 3 H), 5.11–5.46 (m, 1 H), 5.65–5.72 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 17.46 (q), 21.76 (q), 26.81 (t), 33.12 (t), 36.87 (d), 41.61 (t), 49.39 (d), 74.83 (s), 115.42 (d), 124.35 (d), 125.77 (d), 139.64 (s). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.84; H, 10.21.

7b: R_f 0.4 (hexane–AcOEt, 5:1); mp 44–46 °C; IR (KBr) 3350, 960, 935, 903, 822, 695 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.92 (d, 3 H, J = 7 Hz), 0.93 (s, 3 H), 0.96–2.28 (m, 6 H), 2.44–2.68 (m, 3 H), 5.22–5.47 (m, 1 H), 5.65–5.87 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 22.21 (q), 22.55 (q), 26.87 (t), 30.64 (d), 43.68 (t), 48.33 (d), 50.79 (t), 74.34 (s), 118.42 (d), 124.07 (d), 125.74 (d), 135.52 (s). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.96; H, 10.24.

7c: R_f 0.6 (hexane–AcOEt, 5:1); IR (neat) 3350, 1650, 958, 919, 783, 678 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.89 (s, 3 H), 0.94 (d, 3 H, J = 6 Hz), 1.04–2.30 (m, 6 H), 2.53–2.76 (br s, 3 H), 5.30–5.48 (m, 1 H), 5.73–5.90 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 15.14 (q), 15.79 (q), 26.80 (t), 32.39 (t), 34.91 (t), 43.70 (d), 49.80 (d), 76.75 (s), 118.05 (d), 124.32 (d), 125.94 (d), 136.11 (s). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.76; H, 10.12.

9: R_f 0.4 (hexane–AcOEt, 5:1); IR (neat) 3400, 986, 966, 912, 880, 870, 860, 820, 784, 680 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.78 (t, 3 H, J = 7.5 Hz), 0.90–2.87 (m, 12 H), 5.27–5.53 (m, 1 H), 5.57–5.92 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 6.43 (q), 23.28 (t), 24.80 (t), 26.60 (t), 34.74 (t), 36.23 (t), 49.62 (d), 75.79 (s), 118.53 (d), 123.92 (d), 125.99 (d), 136.04 (s). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.67; H, 10.15.

11: R_f 0.5 (hexane–AcOEt, 5:1); mp 111–112 °C; UV (hexane) λ_{max} 210 nm (ϵ 3027); IR (KBr) 3350, 988, 960, 893, 823, 773 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.03–2.93 (m, 11 H), 5.51–5.85 (m, 1 H), 5.91–6.30 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.15 (t), 21.44 (t), 26.82 (t), 27.11 (t), 27.25 (t), 28.85 (t), 34.87 (t), 43.63 (d), 49.62 (d), 75.23 (s), 117.82 (d), 123.92 (d), 125.83 (d), 135.99 (s). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.24; H, 9.91.

13: R_f 0.35 (hexane–AcOEt, 5:1); UV (hexane) λ_{max} 211 nm (ϵ 3109); IR (neat) 3350, 966, 948, 900, 860, 780 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.75–2.39 (m, 12 H), 2.43–3.18 (m, 3 H), 5.32–5.60 (m, 1 H), 5.62–5.86 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.19 (t), 26.80 (t), 29.72 (t), 31.30 (t), 31.57 (t), 34.40 (t), 45.78 (d), 48.46 (d), 86.00 (s), 118.19 (d), 124.52 (d), 124.63 (d), 135.84 (s). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.01; H, 9.48.

15: R_f 0.5 (hexane–AcOEt, 4:1); UV (hexane) λ_{max} 273 nm (ϵ 704), 267 (722), 224 (8396), 218 (8043); IR (neat) 3370, 1500, 940, 922, 818, 782, 740 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.82 (s, 3 H), 1.35–2.50 (m, 7 H), 3.18–3.42 (br s, 3 H), 5.50–5.70 (m, 1 H), 6.93–7.57 (m, 4 H). Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.89; H, 8.35.

16: R_f 0.4 (hexane–AcOEt, 4:1); mp 131–132 °C; UV (hexane) λ_{max} 273 nm (ϵ 667), 266 (629), 213 (7315); IR (KBr) 3280, 1588, 1500, 938, 745 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.90 (s, 1 H), 1.15 (s, 3 H), 1.06–2.01 (m, 8 H), 2.21–3.12 (m, 4 H), 6.81–7.10 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 21.24 (q), 23.09 (t), 29.18 (t), 33.98 (t), 35.47 (d), 37.88 (t), 43.16 (d), 48.78 (d), 72.85 (s), 125.48 (d), 125.52 (d), 128.27 (d), 128.90 (d), 135.79 (s), 136.56 (s). Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.16; H, 9.45.

18: R_f 0.6 (hexane–AcOEt, 2:1); mp 104–105 °C; UV (hexane) λ_{max} 264 nm (ϵ 501), 215 (7145); IR (KBr) 3300, 1595, 1470, 975, 920, 765, 700 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.99 (s, 3 H), 1.35 (s, 3 H), 1.70–2.05 (m, 2 H), 2.75–3.45 (m, 5 H), 5.90–6.40 (m, 2 H), 6.99 (br s, 3 H); ^{13}C NMR ($CDCl_3$) δ 21.24 (q), 28.13 (t), 30.63 (t), 38.50 (t), 46.22 (d), 71.95 (s), 125.55 (d), 125.61 (d), 125.81 (d), 125.98 (d), 126.10 (d), 133.21 (s), 134.17 (s), 135.57 (s). Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.67; H, 8.08.

20: mp 141–142 °C; UV (hexane) λ_{max} 273 nm (ϵ 684), 266 (718), 258 (859), 234 (3602), 213 (7490); IR (KBr) 3350, 1500, 992, 940, 852, 843, 784, 763, 759, 680 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.09 (s, 3 H), 1.43–1.64 (br s, 1 H), 1.57–2.38 (m, 4 H), 2.49–2.91 (m, 1 H), 2.64–2.73 (m, 2 H), 3.04–3.45 (m, 1 H), 3.21–3.38 (br s, 2 H), 5.82–6.04 (br s, 2 H), 6.99–7.37 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 21.78 (q), 31.01 (t), 33.88 (t), 34.20 (t), 40.99 (d), 41.82 (t), 49.46 (d), 74.77 (s), 123.28 (s), 124.74 (d), 125.59 (d), 125.89 (d), 126.01 (d), 127.25 (s), 127.59 (d), 127.96 (d), 132.81 (s), 137.82 (s). Anal. Calcd for $C_{18}H_{20}O$: C, 84.99; H, 8.72. Found: C, 85.12; H, 8.55.

22: R_f 0.3 (hexane–AcOEt, 5:1); mp 64–65 °C; IR (KBr) 3300, 947, 930, 878, 820 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.00 (s, 3 H), 1.10–2.83 (m, 10 H), 1.73 (s, 3 H), 5.39–5.64 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.45 (q), 22.95 (q), 24.03 (t), 31.40 (t), 34.38 (t), 41.65 (t), 49.85 (d), 74.89 (s), 118.42 (d), 118.60 (d), 133.05 (s), 135.89 (s). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.79; H, 10.31.

24: R_f 0.35 (hexane–AcOEt, 5:1); IR (neat) 3400, 1618, 968, 924, 891, 861, 842, 818, 786, 717, 700 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.96 (s, 3 H), 1.01 (d, 3 H, J = 5 Hz), 1.28–2.21 (m, 7 H), 2.40–2.96 (m, 2 H), 5.16–5.44 (m, 1 H), 5.49–5.93 (m, 2 H). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.98; H, 10.35.

25: R_f 0.45 (hexane–AcOEt, 5:1); mp 74–76 °C; IR (KBr) 3400, 979, 961, 918, 900, 883, 836, 825, 790, 743 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.00 (s, 3 H), 1.10–2.36 (m, 7 H), 1.89 (s, 3 H), 2.42–2.75 (br s, 3 H), 5.26–5.61 (m, 2 H). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.77; H, 10.23.

27: R_f 0.4 (hexane–AcOEt, 5:1); mp 95–96 °C; IR (KBr) 3350, 971, 936, 897, 860, 801, 791, 684 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.95 (s,

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3 H), 1.11 (s, 1 H), 1.62 (s, 3 H), 1.28–1.99 (m, 6 H), 2.40–2.75 (br s, 3 H), 5.67–5.85 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.18 (q), 21.42 (t), 23.61 (q), 28.63 (t), 32.89 (t), 41.81 (t), 50.07 (d), 74.93 (s), 123.22 (s), 124.57 (d), 125.91 (d), 128.50 (s). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.61; H, 10.30.

29: R_f 0.65 (hexane–AcOEt, 2:1); bp 150 °C (2 mmHg); IR (neat) 3400, 1665, 1622, 1518, 840, 708 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.94 (s, 3 H), 1.03–2.80 (m, 10 H), 3.53 (s, 3 H), 4.47–4.81 (m, 1 H), 5.20–5.45 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.99 (q), 23.86 (t), 28.75 (t), 34.02 (t), 41.40 (t), 49.78 (d), 53.71 (q), 74.77 (s), 90.90 (d), 117.14 (t), 136.10 (s), 154.27 (s). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.18; H, 9.34. Found: C, 74.34; H, 9.41.

31: R_f 0.3 (hexane–AcOEt, 5:1); UV (hexane) λ_{max} 279 nm (ϵ 341), 272 (369), 211 (3217); IR (neat) 3550, 1670, 983, 795 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.96 (s, 3 H), 1.06–2.49 (m, 7 H), 2.58–2.83 (br s, 3 H), 3.60 (s, 3 H), 4.68–4.84 (m, 1 H), 5.29–5.44 (m, 1 H). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.18; H, 9.34. Found: C, 74.39; H, 9.32.

33: R_f 0.4 (hexane–AcOEt, 5:1); mp 68–71 °C; UV (hexane) λ_{max} 210 nm (ϵ 2472); IR (KBr) 3320, 1660, 967, 935, 892, 822 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.02 (s, 3 H), 1.13–2.45 (m, 7 H), 2.55–3.03 (m, 3 H), 5.27–5.46 (m, 1 H), 5.86–6.03 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.75 (q), 23.72 (t), 33.78 (t), 33.87 (t), 41.51 (t), 51.39 (d), 74.54 (s), 117.65 (d), 122.06 (d), 131.08 (s), 135.42 (s). Anal. Calcd for $C_{11}H_{15}OCl$: C, 66.50; H, 7.61; Cl, 17.84. Found: C, 66.34; H, 7.81; Cl, 17.63.

35 (mixture of diastereomers): R_f 0.3–0.4 (hexane–AcOEt, 2:1); IR (neat) 3460, 2252, 922, 798 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.71–2.68 (m, 19 H). Anal. Calcd for $C_{12}H_{19}ON$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.68; H, 10.03; N, 7.06.

37 and 38 (mixture of isomers): R_f 0.45–0.65 (hexane–AcOEt, 1:1); IR (neat) 3450, 2345, 922 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.74–2.73 (m, 19 H). Anal. Calcd for $C_{12}H_{19}ON$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.72; H, 10.08; N, 7.11.

40 (mixture of diastereomers): R_f 0.45–0.6 (hexane–AcOEt, 2:1); IR (neat) 3500, 1730, 1710, 900 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.70–2.58 (m, 25 H), 4.51–5.18 (m, 1 H). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.96; H, 10.14.

Hydrogenation of 2. A solution of **2** (3 mmol) and Pd/C (cat.) in EtOH (10 mL) was stirred at room temperature for 6 h under H_2 (1 atm). After the usual workup, the products **4**[7] (60%) and **5** (20%) were isolated by column chromatography on silica gel.

4: R_f 0.3 (pentane–Et_2O, 4:1); ^{13}C NMR ($CDCl_3$) δ 21.24 (q), 23.35 (t), 25.53 (t), 26.39 (t), 26.66 (t), 34.13 (t), 34.59 (t), 39.42 (d), 42.86 (t), 53.17 (d), 72.71 (s).

5: R_f 0.2 (pentane–Et_2O, 4:1); mp 92–94 °C; IR (KBr) 3340, 945, 900 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.83 (s, 1 H), 1.13 (s, 3 H), 0.98–2.08 (m, 16 H); ^{13}C NMR ($CDCl_3$) δ 20.77 (q), 21.77 (t), 23.40 (t), 24.67 (t), 26.88 (t), 29.08 (d), 31.60 (t), 32.13 (t), 33.97 (t), 47.81 (d), 72.71 (s). Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.45; H, 11.94.

Electroreduction of 1 in $(CH_3)_2CHOD$ was carried out by the same method as described above (1/5 scale). The percentage of monodeuterium incorporation on C-7 in the cyclized product **2** (obtained in a 48% yield) was determined to be >95% by ^{1}H NMR analysis.

Reduction of 1 with Zinc in i-PrOH. A solution of **1** (0.81 g, 5 mmol), zinc powder (1.63 g, 25 mmol), and NaOH (1 g, 25 mmol) in i-PrOH (40 mL) was refluxed for 4 h. After usual workup, **3** was isolated by distillation. The reduction with tin (reflux, 4 h) or Na (25 °C, 6 h) was carried out by the same method.

Reduction of 1 with Na in NH_3–THF. To a solution of **1** (0.16 g, 1 mmol) in liquid NH_3 (10 mL)–THF (2.5 mL)–EtOH (0.4 mL) was added Na (0.23 g) at −70 °C. The mixture was stirred at −70 °C for 1 h and worked up by the usual method.[16] The product **41** was isolated by distillation.

41: bp 105 °C (0.5 mmHg); IR (neat) 3350, 1650, 960 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.11 (d, 3 H, J = 6 Hz), 0.88–2.20 (m, 7 H), 2.25–2.85 (br s, 4 H), 3.38–3.97 (m, 1 H), 5.22–5.46 (m, 1 H), 5.48–5.83 (m, 2 H). Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 73.53; H, 9.86; N, 4.88.