(s), 1280 (s), 1250 (s), 1180 (s), 1145 (s), 1100 (s), 1060 (m), 940 (s), 790 (m) cm^{-1}; NMR (CCl_4) δ 0.97 (d, 6 H, J = 6.5 Hz, 2 × CH_3CH), 1.23–1.90 (m, 6 H, methylenes), 1.90–2.40 (m, 2 H, methynes), 2.20 (s, 6 H, CH_3C= and CH_3C=O); mass spectrum, m/e (%) 224 (M^+, 32), 168 (912), 167 (89), 154 (16), 43 (100); exact mass calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1406.

3-(Methoxycarbonyl)-3′,4-dimethyl-$\Delta^{3,4}$-$\Delta^{2',3'}$-2,5-dioxaspiro[5,4]decane (9a). Diazo ester **3** (1.0 g) and 3-methylcyclohexenone (4.5 g) yielded compound **9a** as a colorless liquid (0.658, 45%): bp 130–132 °C (2.4 torr); IR (neat) 1730 (s, C=O), 1690 (s, C=C), 1460 (s), 1400 (s), 1240 (s), 1140 (s), 990 (m), 910 (m), 785 (m) cm^{-1}; NMR (CCl_4) δ 1.75 (s, 3 H, methyl on C-3′ (of cyclohexyl ring)), 1.88 (m, 4 H, methylenes), 2.00–2.30 (m, 2 H, allylic methylene), 2.22 (s, 3 H, methyl on dioxole ring), 3.70 (s, 3 H, COOMe), 5.50 (q, 1 H, J = 1.3 Hz, vinyl proton); mass spectrum, m/e (%) 224 (M^+, 64), 206 (13), 196 (54), 125 (82), 121 (20), 111 (26), 109 (18), 93 (33), 91 (26), 82 (34), 79 (100), 77 (33), 43 (59); exact mass calcd for $C_{12}H_{16}O_4$ 224.1048, found 224.1055.

3-Acyl-3′,4-dimethyl-$\Delta^{3,4}$-$\Delta^{2',3'}$-2,5-dioxaspiro[5,4]decane (9b). From diazo ketone **5** (1.5 g) and 3-methylcyclohexenone (5.0 g) compound **9b** was obtained as a colorless liquid (0.951 g, 38%): bp 86–88 °C (0.05 torr); IR (neat) 1690 (s, C=O), 1630 (s, C=C), 1450 (s), 1390 (s), 1280 (s), 1170 (s), 1130 (s), 1090 (s), 1040 (m), 980 (m), 935 (s), 735 (s) cm^{-1}1; NMR (CCl_4)δ 1.73 (s, 3 H, methyl on cyclohexyl ring), 1.75–2.00 (m, 4 H, methylenes), 2.10–2.30 (m, 2 H, allylic methylene), 2.12 (s, 3 H, CH_3C=), 2.20 (s, 3 H, CH_3C=O), 5.55 (q, 1 H, J = 1.5 Hz, vinyl proton); mass spectrum, m/e (%) 208 (M^+, 25), 180 (13), 137 (12), 55 (11), 43 (100); exact mass calcd for $C_{12}H_{16}O_3$ 208.1099, found 108.1092.

Acknowledgment. This research was supported in part by a grant of Consejo Nacional de Investigaciones Cientificas y Tecnológicas CONICIT of Venezuela (Grant No. S1-0726). This work is dedicated to Professor Ernest Wenkert to honor his 60th birthday.

Registry No. **6a**, 81099-78-7; **6b**, 96706-06-8; **6c**, 96706-07-9; **6d**, 96706-08-0; **7a**, 96706-09-1; **7b**, 96706-10-4; **7c**, 96706-11-5; **7d**, 96706-12-6; **7e**, 96706-13-7; **7f**, 96706-14-8; **7g**, 96706-15-9; **7h**, 96706-16-0; **7i**, 96706-17-1; **7j**, 96706-18-2; **7k**, 96706-19-3; **7l**, 96706-20-6; **8a**, 96706-21-7; **8b**, 96706-22-8; **8c**, 96706-23-9; **8d**, 96706-24-0; **9a**, 96706-25-1; **9b**, 96706-26-2; $CH_3COC(=N_2)COOCH_3$, 24762-04-7; $CH_3OCOC(=N_2)COCH_3$, 29397-21-5; $(CH_3)_2CHCHO$, 78-84-2; RCHO (R = 2-furoyl), 98-01-1; CH_3CH=CHCHO, 4170-30-3; CH_3COCH_3, 67-64-1; $CH_3COCH(CH_3)_2$, 563-80-4; $CH_3COCH_2CH(CH_3)_2$, 108-10-1; $CH_3CH_2COCH_2CH_3$, 96-22-0; $CH(CH_3)_2COCH(CH_3)_2$, 565-80-0; $(CH_3)_2CHCH_2COCH_2CH(CH_3)_2$, 108-83-8; cyclohexanone, 108-94-1; 2,6-dimethylcyclohexanone, 2816-57-1; 3-methyl-2-cyclohexen-1-one, 1193-18-6.

An Efficient Diastereoselective Synthesis of 6-Hydroxy-4a-phenyl-*cis*-decahydroisoquinolines through *N*-Acyliminium Ion Induced Polyene Cyclization

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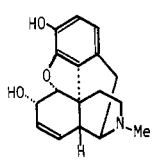
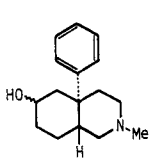
The two kinds of carbamates **13a,b** and **18a,b** were prepared from acids **11** and **17**, respectively, through the Curtius method via the corresponding acid azides. Cyclization of **13a,b** and **18a,b** with paraformaldehyde–formic acid afforded 4a-phenyl-*cis*-decahydroisoquinoline-6-formates **19a,b** with high diastereoselectivity. Reduction of **19a,b** yielded 6-hydroxy-2-methyl-4a-phenyl-*cis*-decahydroisoquinoline (**20a**). The ring juncture of **19** (and **20a**) was determined by conversion of **19b** to *cis*-4a-phenyldecahydroisoquinoline (**25**). The relative configuration of the hydroxyl group at the 6-position of **20a** was determined as cis to the phenyl group by comparison with the alternative isomer **20b** prepared by reduction of **27** derived from **19b**.

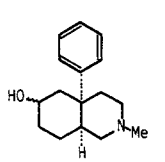
In the search for potent and nonaddictive analgesics, morphine (**1**) has been subjected to many modifications.[1] Many synthetic strategies for morphine-based structural variants have been reported in the last decades,[2-7] and various analogues of morphine have been reported. The investigations on structural variants of the morphine molecule have been an area of considerable interest and are still being actively pursued in the hope of finding significant analgesics with fewer undesirable side effects. Of special interest to us is the development of a facile procedure for the synthesis of 6-hydroxy-4a-phenyldecahydroisoquinolines from readily accessible starting materials, since 6-hydroxy-4a-phenyl-*trans*-decahydroisoquinoline (**2a**) can be considered to be a simpler fragment of morphine as drawn in the structures. We wish to report a general and novel synthesis of 6-hydroxy-4a-phenyl-*cis*-decahydroisoquinolines (**2b**), stereoisomers of **2a**, in this paper.



1



2a



2b

Results and Discussion

The field of biomimetic cationic polyene cyclization reaction has been used for the synthesis of complex multicyclic compounds with excellent sterocontrol.[8,9]

(1) (a) Johnson, M. R.; Milne, G. M. In "Burger's Medicinal Chemistry", 4th ed.; Wolf, M., Ed.; Wiley Interscience: New York, 1981, Part 3, p 699. (b) Palmer, D. C.; Straus, M. J. *Chem. Rev.* **1977**, *77*, 1.
(2) Weller, D. D.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 6650.
(3) Weller, D. D.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1977**, *42*, 1485.
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(6) Ciganek, E. *J. Am. Chem. Soc.* **1981**, *103*, 6261.
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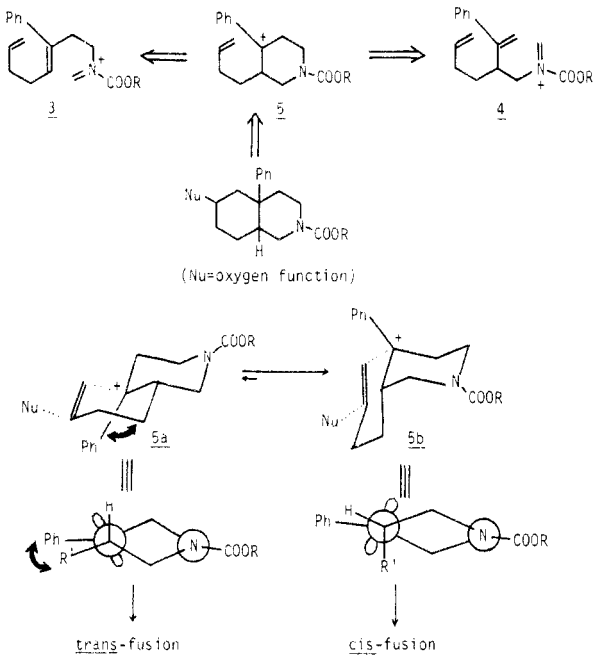
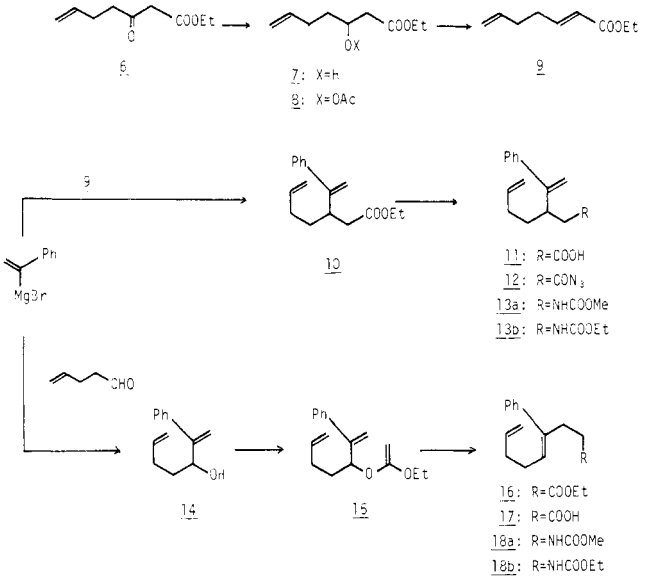
0022-3263/85/1950-3449$01.50/0

Scheme I



Epoxides, allyl alcohols, acetals, or sulfonates have been used as suitable cationic initiators for successful polyene cyclizations. The use of *N*-acyliminium ions as a cationic initiating center for olefin cyclization has been well established.[10] Cationic polyene cyclizations involving *N*-acyliminium ions have been found to achieve remarkable stereocontrolled synthesis of *N*-polycyclic compounds such as 13-azasteroidal compounds[11] and azatricyclic compounds.[12] A diene cyclization using an *N*-(ethoxycarbamoyl)iminium ion intermediate, formed in situ, in a stereocontrolled manner has also been developed into a method of high synthetic potential.[13] As the primary synthetic challenge of the system of 6-hydroxy-4a-phenyldecahydroisoquinoline, a solution of two characteristic problems is required. One is stereocontrolled introduction of oxygen function at the 6-position and another is an easy construction of the 4a-phenyldecahydroisoquinoline skeleton with stereoselectivity without formation of another isomer. Our synthetic strategy directed to 6-hydroxy-4a-phenyl-*cis*-decahydroisoquinoline is based on

Scheme II



an application of polyene cyclization by using *N*-carbamolyiminium ions as cationic initiators for giving the decahydroisoquinoline ring system from **3** and **4** as depicted in Scheme I. Since early investigations, throughout evolution of the polyene cyclization strategy, cyclization of trans double-bond geometry such as **3** into trans ring fusion has been observed.[8,9] However, cyclization of **3** afforded the cis-fused decahydroisoquinoline ring system, which was also obtained from **4**. Of the two benzylic cationic intermediates **5a,b**, **5b** was found to be thermodynamically more favorable than **5a** for the second ring fusion. The results of our studies were described in this paper.

The successful route to the synthesis of carbamates, used for this study, began with readily available α-styrylmagnesium bromide and followed the sequence of steps outlined in Scheme II. Treatment of the acetate **8**, obtained by reduction of **6**[14] followed by acetylation of **7**, with 1,7-diazabicyclo[5.4.0]undec-7-ene yielded the ester **9**. The copper salt (CuI) catalyzed conjugated addition reaction of α-styrylmagnesium bromide to **9** gave a good yield (94%) of the ester **10**. The acid **11**, obtained by hydrolysis of **10**, was successfully converted to the desired carbamates **13a,b** by the Curtius method via the acid azide **12**. The reaction of **12** with methanol gave **13a**, and the use of ethanol instead of methanol yielded **13b**. The key step in a synthesis of another acid **17** leading to the carbamates **18a,b** is the ortho ester Claisen rearrangement reaction[15] of the allyl alcohol **14**. The reaction of α-styrylmagnesium bromide and 4-pentenal afforded **14**. The crucial ortho ester Claisen rearrangement of **15** was carried out by heating **14** with excess triethyl orthoacetate in the presence of a small amount of phenol at 140 °C to yield **16**. Hydrolysis of **16** gave **17** which was converted to the carbamates **18a,b** in the same manner as **11a,b**. Two kinds of carbamates **13a,b** and **18a,b**, thus obtained, were subjected to *N*-alkoxycarbamoyliminium ion formation and subsequent intramolecular cyclization reaction with paraformaldehyde–formic acid.

Treatment of **13a** with paraformaldehyde in formic acid at room temperature afforded the cyclization product **19a**, the spectral data of which were superimposable on those

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(13) Kano, S.; Yokomatsu, T.; Yuasa, Y.; Shibuya, S. *Tetrahedron Lett.* **1983**, *24*, 1813. The method was applied to a synthesis of 4a-[3,4-crowned(15-crown-5)phenyl]isoquinoline, the ring juncture of which should be revised as cis: Kano, S.; Yokomatsu, T.; Nemoto, H.; Shibuya, S. *Tetrahedron Lett.* **1985**, *26*, 1531. The results will be published in detail elsewhere soon.

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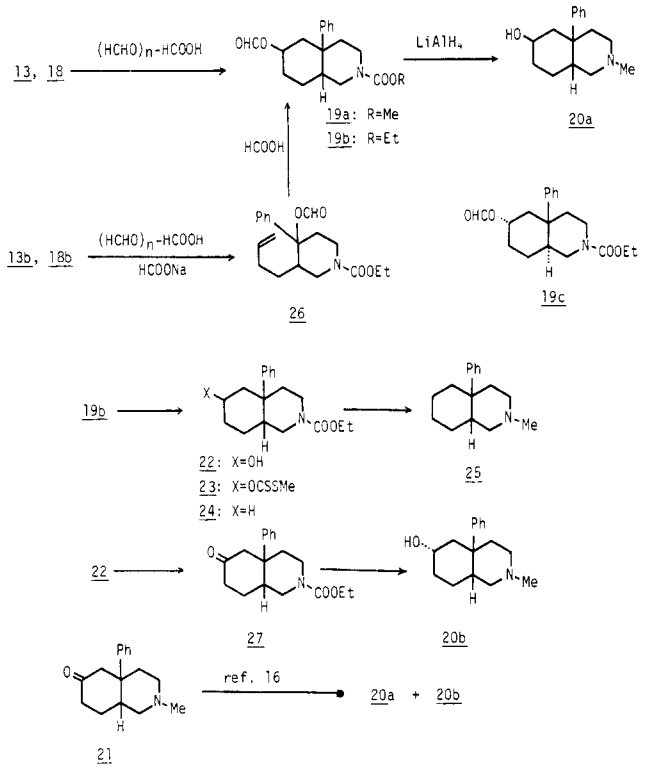
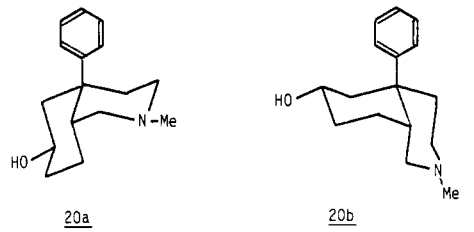
Scheme III



of the cyclization product obtained from **18a** under the same conditions as **13a**. In a similar fashion, **19b** was obtained from **13b** and **18b**. Reduction of **19a** with $LiAlH_4$ in THF gave 6-hydroxy-4a-phenyl-*cis*-decahydroisoquinoline **20a**, mp 69–71 °C (lit.[16] oil), δ 2.09 (NCH_3), which was identical with that obtained from **19b** (Scheme III). Previously, we assigned the ring juncture of the cyclization product to be trans[13] as **19c** based on the comparison with two epimeric isomers of 6-hydroxy-4a-phenyl-*cis*-decahydroisoquinolines, **20a,b**,[16] obtained by reduction of 6-oxo derivative **21**. The spectral data of **20a** derived from **19a,b** were considerably different from those of **20a** (δ 2.3,[16] NCH_3) and **20b** (as a mixture of **20a**, δ 2.31,[16] NCH_3) that appeared in the literature. Based on these facts, we concluded the ring juncture of **19** (and **20a**) to be trans rather than cis. However, the ring juncture of **19** (**20a**) was proved to be cis as follows. Hydrolysis of **19b** (3 N NaOH–EtOH) gave the 6-hydroxy derivative **22**, which was led to the xanthate **23**. Treatment of **23** with tri-*n*-butyltin hydride yielded **24**. Reduction of **24** with $LiAlH_4$ gave *cis*-2-methyl-4a-phenyldecahydroisoquinoline **25** as an oil; this was characterized as the picrate, mp 153–156 °C (lit.[2,16] mp 144–146 °C; the picrate of the trans isomer, mp 218.5–220 °C), and the hydrochloride, mp 219–221 °C (lit. mp 219.5–221 °C,[4] 222–224 °C[16]). Therefore, we wish to revise the ring juncture of the cyclization products obtained from **13** and **18** as cis. Apparently, formation of cis-fused isoquinoline proceeded via the benzylic cationic intermediates **5b**. When the butenyl side chain is confined to the equatorial configuration **5a**, cyclization has no choice but to produce the trans fusion. Because of steric repulsion of the phenyl group on the benzyl cation and butenyl side chain,[17] **5b** should dominate over **5a**, leading to trans fusion. To minimize the dipole–dipole effect, **5a** derived from **3** easily isomerizes to **5b** through ring inversion,[18] as shown in Scheme I. The monocyclic cationic center was trapped as the formate **26** (a 4:1 mixture stereoisomers) by cyclization of **13b** with paraformaldehyde–formic acid in the presence of sodium formate. Cyclization of **18b** under the same conditions also gave **26** in the same ratio of stereoisomers as that obtained from **13b**. Thus, cyclization of **13** and **18** was found to proceed via the common cationic intermediates **5b**.[19] Further cyclization of **26** with formic acid yielded **19b** in nearly quantitative yield. With regard to the configuration of the hydroxy group at the 6 position, important stereochemical information for **19** and **20a** was also deduced from the magnitude of the coupling constants for the 6-carbon–oxygen function, which was clearly visible in the ^1H NMR spectra and was broadened ($W_{1/2}$ = 30 Hz) by the large diaxial proton interaction. This fact indicates that the oxygen function takes the equatorial configuration.[20] Of the two cis-fused equatorial 6-ols **20a,b**[16] the product derived from **19** was



assigned as **20a** by comparison with the alternative isomer **20b** prepared by oxidation of **22** with Jones reagent, followed by reduction of **27** with $LiAlH_4$. In the ^1H NMR spectra of **20a,b**, the NCH_3 signal of **20b** appeared at a lower field (δ 2.29) than that of **20a** because of deshielding effects of both the benzene ring and the C_8–C_{8a} bond, whereas the 6-axial proton signal of **20b** was exhibited in a higher region (δ 3.38–3.81, $W_{1/2}$ = 21 Hz) than that of **20a** owing to the shielding effect of the benzene ring. These facts strongly supported the 4a-phenyl-*cis*-decahydroisoquinoline-6-ol obtained from **19** to be **20a** and the reduction product of **27** to be **20b**.

Thus, the novel diastereoselective synthesis of cis-fused 6-hydroxy-4a-phenyldecahydroisoquinoline was achieved by an application of *N*-acyliminium ion–polyene cyclization.

Experimental Section

Melting points were determined on a Yanagimoto micro hot-stage apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-1 spectrometer, and mass spectra (MS) were determined on a Hitachi RMU-7L instrument. ^1H NMR spectra of a $CDCl_3$ solution with Me_4Si as an internal standard (δ = 0 ppm) were taken on a varian EM 390 spectrometer. All

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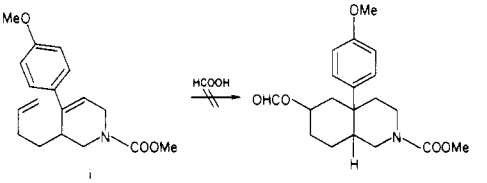
(17) This steric repulsion can be considered as a type of A strain: Johnson, F. *Chem. Rev.* **1969**, *68*, 375.

(18) The ring inversion caused by the similar dipole–dipole effect of A strain was also observed in the substitution reaction of 1-phenylthiocyclohexene derivatives. Trost, B. M.; Lavoice, A. C. *J. Am. Chem. Soc.* **1983**, *105*, 5076.

(19) For the mechanism to yield cis products, the concerted pathway involving deprotonation–protonation–ring closure of **5** should be excluded, since i did not give any cyclization product. Kano, S.; Yokomatsu,



T.; Shibuya, S. unpublished work.

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reactions were run under nitrogen.

Ethyl 2,6-Heptadienoate (9). To a stirred solution of **6** (15 g, 88 mmol) in 2-propanol (150 mL) was added $NaBH_4$ (3.3 g, 0.1 mol) under ice cooling. After the stirring had been continued at the same temperature for 0.5 h, to this mixture was added acetone (30 mL) and then AcOH (20 mL). The solvent was evaporated, and the remaining residue was diluted with water and extracted with $CHCl_3$. The extract was evaporated, and the remaining oil was mixed with Ac_2O (25 mL) and pyridine (25 mL) and was heated at 80 °C for 2 h under stirring. The mixture was made acidic with 10% HCl and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and evaporated. The resulting residue was distilled in vacuo to give **8** (13.1 g, 70 %), bp 95–104 °C (3 torr); this was used for the following reaction without further purification. A mixture of **8** (12.84 g, 60 mmol), DBU (14 g, 0.1 mol), and benzene (50 mL) was heated under reflux for 2 h. The mixture was washed with H_2O, dried (Na_2SO_4), and evaporated to give **9** (6.75 g, 72 %): bp 55–58 °C (3 torr); ^1H NMR ($CDCl_3$) δ 7.02 (1 H, d, t, J = 15 and 7 Hz), 6.08–5.84 (2 H, m), 5.78–5.45 (2 H, m), 4.20 (2 H, q, J = 7 Hz), 1.27 (3 H, t, J = 7 Hz).

Ethyl 3-(α-Styryl)-6-heptenoate (10). To a stirred solution of α-styrylmagnesium bromide (prepared from 6.2 g, 34 mmol, of α-styryl bromide and 1.1 g, 45.4 mmol, of Mg in 60 mL of ether in the presence of 0.5 g, 2.7 mmol, of ethylene bromide) was added CuI (0.5 g, 2.6 mmol) at 0 °C. To this solution was added a solution of **9** (3.5 g, 22.7 mmol) in ether (10 mL) at the same temperature. After the stirring had been continued for 1.5 h, the mixture was quenched with saturated NH_4Cl–28% NH_4OH (1:1) and extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The remaining residue was chromatographed on silica gel (25 g). Elution with benzene gave **10** (5.51 g, 94%); this was used for the following reaction without further purification. ^1H NMR ($CDCl_3$) δ 7.56–7.19 (5 H, m), 6.06–5.56 (1 H, m), 5.28 (1 H, s), 5.09 (1 H, s), 5.16–4.79 (2 H, m), 4.09 (2 H, q, J = 7 Hz), 3.17 (1 H, t, t, J = 6 and 6 Hz), 2.52 (2 H, d, J = 6 Hz), 2.26–1.88 (2 H, m), 1.76–1.42 (2 H, m), 1.20 (3 H, t, J = 7 Hz). MS, m/z 258 (M^+), exact mass, m/z 258.1636 (calcd for $C_{17}H_{22}O_2$, m/z 258.1618).

3-(α-Styryl)-6-heptenoic Acid (11). A stirred solution of **10** (5.0 g, 19.4 mmol) and 10% EtOH–NaOH (50 mL) was heated under reflux for 2 h. The solvent was evaporated, and the remaining residue was diluted with water and washed with ether. The aqueous layer was made acidic with concentrated HCl and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave **11** (3.35 g, 75%) as an oil: ^1H NMR ($CDCl_3$) δ 7.57–7.23 (5 H, m), 6.07–5.54 (1 H, m), 5.29 (1 H, s), 5.11 (1 H, s), 5.20–4.83 (2 H, m), 3.16 (1 H, t, t, J = 6 and 6 Hz), 2.57 (2 H, d, J = 6 Hz), 2.27–1.90 (2 H, m), 1.77–1.43 (2 H, m); IR ($CHCl_3$) 1720 (C=O) cm^{-1}. MS, m/z 230 (M^+), exact mass, m/z 230.1296 (calcd for $C_{15}H_{18}O_2$, m/z 230.1306).

2-Phenylhexa-1,5-dien-3-ol (14). To a stirred solution of α-styrylmagnesium bromide (prepared from 6.2 g, 34 mmol, of α-styryl bromide and 1.1 g, 45.4 mmol, of Mg as above) was added 4-pentenal (3.36 g, 40 mmol) at 0 °C. After the stirring had been continued for 2 h at room temperature, the mixture was decomposed with saturated NH_4Cl and extracted with benzene. The extract was washed with water, dried (Na_2SO_4), and evaporated to give **14**: bp 118–128 °C (2 torr); ^1H NMR ($CDCl_3$) δ 7.41 (5 H, m), 6.13–5.63 (1 H, m), 5.40 (1 H, d, J = 1 Hz), 5.37 (1 H, d, J = 1 Hz), 5.20–4.90 (2 H, m), 4.69 (1 H, t, J = 6 Hz), 2.37–2.18 (2 H, m), 1.93–1.43 (2 H, m). This was used for the following reaction without further purification.

Ethyl 4-Phenylnona-4,8-dienoate (16). A mixture of **14** (7.52 g, 40 mmol), triethyl orthoacetate (22.68 g, 140 mmol), and phenol (0.31 g, 3.4 mmol) was heated under stirring at 140 °C for 6 h. During heating, the volatile products were continuously removed. Removal of excess triethyl orthoacetate in vacuo yielded **16** (9.6 g, 93%) as an oil: by 145–151 °C (2 torr); ^1H NMR ($CDCl_3$) δ 7.49–7.04 (5 H, m), 6.01–5.39 (2 H, m), 5.09–4.79 (2 H, m), 4.07 (2 H, q, J = 7 Hz), 2.82–2.52 (2 H, m), 2.44–2.18 (2 H, m), 2.14–1.92 (4 H, m), 1.21 (3 H, t, J = 7 Hz). MS, m/z 258 (M^+).

4-Phenylnona-4,8-dienoic Acid (17). A mixture of **16** (9 g, 34.9 mmol) and 10% EtOH–NaOH (50 mL) was heated under stirring for 2 h. The solvent was removed, and the remaining residue was diluted with water and washed with ether. The aqeuous layer was made acidic with concentrated HCl and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and evaporated to give **17** (6.82 g, 85%) as an oil: ^1H NMR ($CDCl_3$) δ 7.17–7.07 (5 H, m), 6.00–5.40 (2 H, m), 5.10–4.86 (2 H, m), 2.67 (2 H, broad, t, J = 8 Hz), 2.33 (2 H, m), 1.70 (4 H, m); IR ($CHCl_3$) 2630, 1710 (COOH) cm^{-1}; MS, m/z 230 (M^+), exact mass, m/z 230.1315 (calcd for $C_{15}H_8O_2$, m/z 230.1306).

General Procedure for Preparation of Carbamates 7a,b and 12a,b. To a stirred solution of **11** (or **17**) (565 mg, 2.45 mmol), Et_3N (296 mg, 2.94 mmol), and acetone (2 mL) was added a solution of ClCOOMe (275 mg, 2.94 mmol) in acetone (2 mL) under ice cooling. For a preparation of **13b** and **18b**, ClCOOEt (319 mg, 2.94 mmol) was used instead of ClCOOMe. After the stirring had been continued for 10 min at the same temperature, a solution of NaN_3 (238 mg, 2.94 mmol) in water (1 mL) was added. After the stirring had been continued for 1.5 h at room temperature, the mixture was diluted with water and extracted with toluene. The extract was dried (Na_2SO_4) and evaporated to remove the acetone, and then methanol (1 mL) was added to this solution. For a preparation of **13b** and **18b**, ethanol (1 mL) was used instead of methanol. The mixture was heated for 3 h under reflux and the solvent was evaporated. The resulting residue was chromatographed on silica gel. Elution was hexane–AcOEt (9:1) afforded the corresponding carbamates. **13a**: 88% yield; ^1H NMR ($CDCl_3$) δ 7.40 (5 H, m), 6.07–5.50 (1 H, m), 5.39 (1 H, s), 5.11 (1 H, s), 5.20–4.83 (2 H, m), 4.73 (1 H, broad m, NH), 3.66 (3 H, s), 3.29 (2 H, d, d, J = 6 and 6 Hz), 2.80 (1 H, t, t, J = 6 and 6 Hz), 2.30–2.00 (2 H, m), 1.78–1.43 (2 H, m). MS, m/z 259 (M^+); IR ($CHCl_3$) 3450 (NH), 1720 (C=O), 1640 (C=C) cm^{-1}. **13b**: 82% yield; ^1H NMR ($CDCl_3$) δ 7.32 (5 H, s), 6.07–5.57 (1 H, m), 5.40 (1 H, s), 5.14 (1 H, s), 5.31–4.89 (2 H, m), 4.70 (1 H, broad m, NH), 4.11 (2 H, q, J = 7.5 Hz), 3.28 (2 H, d, d, J = 6 and 6 Hz), 2.81 (1 H, t, t, J = 6 and 6 Hz), 2.30–1.97 (2 H, m), 1.81–1.53 (2 H, m), 1.21 (3 H, t, J = 7.5 Hz); IR ($CHCl_3$) 3445 (NH), 1710 (C=O), 1640 (C=C) cm^{-1}; MS, m/z 273 (M^+), exact mass, m/z 273.1720 (calcd for $C_{17}H_{23}NO_2$, m/z 273.1727). **18a**: 85% yield; ^1H NMR ($CDCl_3$) δ 7.70–7.03 (5 H, m), 6.09–5.38 (2 H, m), 5.17–4.87 (2 H, m), 4.90 (1 H, broad m, NH), 3.66 (3 H, s), 3.16 (2 H, d, t, J = 6 and 6 Hz), 2.54 (2 H, t, J = 6 Hz), 2.20–1.93 (4 H, m); IR ($CHCl_3$) 3450 (NH), 1720 (C=O) cm^{-1}. Electron-impact MS did not give M^+ but CI MS gave MH^+ at m/z 260. **18b**: 68% yield; ^1H NMR ($CDCl_3$) δ 7.51–7.11 (5 H, m), 6.07–5.44 (2 H, m), 5.21–4.87 (2 H, m), 4.67 (1 H, broad m, NH), 4.12 (2 H, q, J = 7 Hz), 3.14 (2 H, d, t, J = 6 and 6 Hz), 2.54 (2 H, t, J = 6 Hz), 2.07 (4 H, m), 1.22 (3 H, t, J = 7 Hz); IR ($CHCl_3$) 3445 (NH), 1725 (C=O) cm^{-1}. EI MS did not give M^+, but CI MS gave NH^+ at m/z 274.

Synthesis of 19a. Method a: A mixture of **13a** (273 mg, 1.05 mmol), paraformaldehyde (45 mg, 1.5 mmol), and formic acid (1 mL) was stirred at room temperature for 1.5 h. The mixture was made basic with saturated $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and evaporated. The resulting residue was chromatographed on silica gel (15 g). Elution with hexane–AcOEt (5:1) gave **19a** (250 mg, 75%) as an oil: ^1H NMR ($CDCl_3$) δ 8.01 (1 H, s), 7.72–7.12 (5 H, m), 5.42–4.92 (1 H, m, $W_{1/2}$ = 30 Hz), 3.72 (3 H, s), 3.02 (1 H, d, d, J = 3 and 12 Hz), 2.78 (1 H, d, with small splitting, J = 12 Hz), 2.59–1.26 (11 H, m); IR ($CHCl_3$) 1690 (C=O) cm^{-1}; MS, m/z 317 (M^+), exact mass, m/z 317.1632 (calcd for $C_{18}H_{23}NO_4$ m/z 317.1625).

Method b: A mixture of **18a** (300 mg, 1.16 mmol), paraformaldehyde (52 mg, 1.73 mmol), and formic acid (1.2 mL) was stirred for 1.5 h and worked up as above to yield **19a** 257 mg, 70%); this was identical with the product obtained from **13a** in all respects.

Synthesis of 19b. Method a: A mixture of **13b** (300 mg, 1.10 mmol), paraformaldehyde (33 mg, 1.1 mmol), and formic acid (1.1 mL) was stirred for 1.5 h and worked up as above to give **19b** (262 mg, 72%); mp 114–116 °C (methanol–ether); ^1H NMR ($CDCl_3$) δ 8.02 (1 H, s), 7.64–7.07 (5 H, m), 5.37–4.91 1 H, m), 4.13 (2 H, q, J = 7.5 Hz), 3.00 (1 H, d, d, J = 3 and 13 Hz), 2.61–2.88 (1 H, m), 1.22 (3 H, t, J = 7.5 Hz); MS, m/z 331 (M^+); IR ($CHCl_3$) 1720, 1680 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{25}O_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 69.00; H, 7.65; N, 4.17.

Method b: A mixture of **18b** (300 mg, 1.1 mmol), paraformaldehyde (33 mg, 1.1 mmol), and formic acid (1.1 mL) was stirred for 1.5 h and worked up as above to give **19b** (236 mg, 65%).

6-Hydroxy-2-methyl-4a-phenyl-*cis*-decahydroisoquinoline (20a). To a stirred solution of $LiAlH_4$ (148 mg, 4 mmol) in THF

(20 mL) was added a solution of **19a** (317 mg, 1 mmol) (or 331 mg, 1 mmol of **19b**) in THF (10 mL) under ice cooling. After the stirring had been continued for 6 h at room temperature, the mixture was decomposed with 20% NaOH. The inorganic precipitate was filtered off, and the filtrate was evaporated to give **20a** (208 mg, 85%): mp 69–71 °C (ether–hexane) (lit.[16] oil); ^{1}H NMR ($CDCl_3$) δ 7.56–7.12 (5 H, m), 4.09–3.72 (1 H, m), 2.08 (3 H, s); IR ($CHCl_3$) 3650, 3590, 1600, 1500, 1470 cm^{-1}; MS, m/z 245 (M^+). Anal. Calcd for $C_{16}H_{23}NO\ H_2O$: C, 72.96; H, 9.57; N, 5.32. Found: C, 72.95; H, 9.41; N, 5.24.

Synthesis of 22. To a sitrred solution of **19b** (800 mg, 2.4 mmol) in EtOH (10 mL) was added 3 N NaOH (1 mL) under ice cooling. The mixture was kept at room temperature under stirring for 0.5 h, poured into saturated Na_2CO_3, and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4), and evaporated to give **22** (690 mg, 95%) as an oil; this was used for the following reaction without purification. MS, m/z 303 (M^+); IR ($CHCl_3$) 3600, 3400 (OH), 1680 (C=O) cm^{-1}.

The Xanthate 23. To a stirred solution of **22** (150 mg, 0.495 mmol) in THF (5 mL) was added NaH (99 mg of 60% mineral oil dipersion, 2.475 mmol) and a pinch of imidazole. After the mixture was warmed at 65 °C for 10 min, carbon disulfide (0.17 mL, 2.97 mmol) was added to the reaction mixture. The mixture was kept at 65 °C under stirring, and idomethane (0.18 mL, 2.97 mmol) was added. After the stirring had been continued at the same temperature for 40 min, the mixture was poured into saturated NaCl and extracted with CH_2Cl_2–ether (1:2). The extract was washed with brine, dried (Na_2SO_4), and evaporated. The resulting residue was chromatographed on silica gel (7 g). Elution with hexane–ether (5:1) gave **23** (118 mg, 60%) as an oil: ^{1}H NMR ($CDCl_3$) (as characteristic signal) δ 7.57–7.07 (5 H, m), 6.00–5.57 (1 H, m), 4.08 (2 H, q, J = 7 Hz), 2.99 (1 H, d, d, J = 14 and 2 Hz), 2.77 (1 H, d with small splitting, J = 14 Hz), 2.42 (3 H, s), 1.22 (3 H, t, J = 7 Hz); IR ($CHCl_3$) 1690 (C=O) cm^{-1}; MS, m/z 393 (M^+, 5%), 348 (50%), 286 (100%).

Synthesis of 24. A mixture of **23** (410 mg, 1.04 mmol), tri-*n*-butyltin hydride (1.95 mL, 2.6 mmol), a pinch of 2,2′-azobis(2-methylpropionitrile), and benzene (26 mL) was heated under reflux for 0.5 h. The solvent was evaporated and the remaining residue was chromatographed on silica gel (15 g). Elution with hexane–ether (5:1) gave **24** (180 mg, 60%) as an oil: ^{1}H NMR ($CDCl_3$) (as characteristic signal) δ 7.50–7.03 (5 H, m), 4.09 (2 H, q, J = 7 Hz), 3.59 (1 H, d, d, J = 13 and 5 Hz), 3.20 (1 H, d, d, J = 13 and 3 Hz), 1.22 (3 H, t, J = 7 Hz); IR ($CHCl_3$) 1680 (C=O) cm^{-1}; MS, m/z 287 (M^+), exact mass, m/z 287.1887 (calcd for $C_{18}H_{25}NO_2$, m/z 287.1884).

***cis*-2-Methyl-4a-phenyldecahydroisoquinoline (25).** To a stirred solution of **24** (182 mg, 0.63 mmol) in THF (6.3 mL) was added $LiAlH_4$ (2.2 mL of 1 M solution in THF) under ice cooling. The mixture was allowed to stand at room temperature for 12 h and then decomposed with 20% NaOH. Inorganic precipitate was filtered off, and the filtrate was evaporated to give **25** (122 mg, 84.5%) as an oil: ^{1}H NMR ($CDCl_3$) (as characteristic signal) δ 7.53–7.00 (5 H, m), 2.22 (3 H, s); MS, m/z 229 (M^+). Picrate mp 153–156 °C (lit.[2,16] 144–146 °C). Anal. Calcd for $C_{22}H_{25}N_4O_7$: C, 57.63; H, 5.72; N, 12.22. Found: C, 57.83; H, 5.81; N, 12.22. Hydrochloride mp 219–221 °C (MeOH–ether) (lit.[4] 219.5–221.5 °C). Anal. Calcd for $C_{16}H_{23}N$ HCl: C, 72.29; H, 9.10; N, 5.27. Found: C, 71.97; H, 8.85; N, 5.18.

Preparation of 26. A mixture of **13b** (273 mg, 1.0 mmol) (or 273 mg, 1.0 mmol of **18b**), paraformaldehyde (30 mg, 1 mmol), and sodium formate (68 mg, 1.0 mmol) and formic acid (1 mL) was stirred for 3 h at room temperature. The mixture was worked up as above to yield **26** (291 mg, 88%): ^{1}H NMR ($CDCl_3$) δ 8.29 (0.2 H, OCHO), 7.98 (0.8 H, OCHO), 5.78–5.24 (1 H, m), 5.04–4.64 (2 H, m); IR ($CHCl_3$) 1730, 1700, 1645 cm^{-1}; MS, m/z 331 (M^+).

Cyclization of 26. A mixture of **26** (248 mg, 0.75 mmol) and formic acid (1 mL) was stirred for 1.5 h at room temperature and worked up as above to give **19b** (236 mg, 95%), which was identical with that obtained from **13b** and **18b**.

Synthesis of 27. To a stirred solution of **2** (200 mg, 0.66 mmol) in acetone (5 mL) was added Jones reagent (1.3 mmol, 1.9 mL of 0.7 M solution prepared from 70 g of CrO_3, 61 mL of concentrated H_2SO_4, and water) under ice cooling. After 10 min, the mixture was diluted with water and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and evaporated to give **27** (167 mg, 85%): mp 99–100 °C; ^{1}H NMR ($CDCl_3$) δ 7.49–7.02 (5 H, m, ArH), 4.09 (2 H, q, J = 7 Hz, OCH_2CH_3), 3.70–3.39 (4 H, m, CH_2NCH_2), 2.60 (2 H, s, 5-H_2), 1.24 (3 H, t, J = 7 Hz, OCH_2CH_3); IR ($CHCl_3$) 1705 (C=O), 1690 (NCO) cm^{-1}; MS, m/z 301 (M^+). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.97; H, 7.73; N, 4.69.

Synthesis of 20b. To a stirred suspension of $LiAlH_4$ (100 mg, 0.4 mmol) in THF (5 mL) was added a solution of **27** (119 mg, 0.4 mmol) in THF (5 mL) under ice cooling. After the sitrring had been continued at room temperature for 12 h, the mixture was worked up as usual to give **20b** as an oil contaminated with a small quantity of **20a** (80 mg, 81%). ^{1}H NMR ($CDCl_3$) δ 7.55–7.05 (5 H, m, ArH), 3.81–3.38 (1 H, m, $W_{1/2}$ = 21 Hz, 6-H), 2.29 (3 H, s, NCH_3); IR ($CHCl_3$) 3640, 3580, 3300, 1600, 1500, 1480, 690 cm^{-1}; MS, m/z 245 (M^+) picrate, mp 104–106 °C (EtOH). Anal. Calcd for $C_{22}H_{26}N_4O_8 \cdot 0.5\ H_2O$): C, 54.65; H, 5.63; N, 11.59. Found: C, 54.50; H, 5.78; N, 10.98.

Registry No. **6**, 17605-06-0; **7**, 97523-07-4; **8**, 97523-08-5; **9**, 97523-09-6; **10**, 97523-10-9; **11**, 97523-11-0; **13a**, 97523-12-1; **13b**, 97523-13-2; **14**, 87046-18-2; **16**, 87046-20-6; **17**, 87046-21-7; **18a**, 97523-14-3; **18b**, 87046-26-2; **19a**, 97523-15-4; **19b**, 97523-16-5; **20a**, 50640-76-1; **20b**, 50640-77-2; **22**, 97523-17-6; **23**, 97523-18-7; **24**, 97523-19-8; **25**, 50640-86-3; *cis*-**26**, 97523-20-1; *trans*-**26**, 97523-22-3; **27**, 97523-21-2; PhC(Br)=CH_2, 98-81-7; CH_2=$CH(CH_2)_2CHO$, 2100-17-6.

Synthesis of $[H^+\subset(1.1.1)]X^-$ Cryptates Assisted by Intramolecular Hydrogen Bonding[1]

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Condensation of [1.1] diazacoronand and diethylene glycol bis(methanesulfonate) as well as with its alkyl-substituted derivatives in the presence of 1 molar equiv of BuLi or KH gives the corresponding $[H^+\subset(1.1.1)]X^-$ cryptates in 31–43% yields. Experimental results indicate that in the intermediate monosubstituted diazacoronand, the NH hydrogen plays a templating role, thus favoring the bicyclic ring closure by intramolecular hydrogen bonding. Similar base-promoted condensations of [2.1] and [2.2] diazacoronands with triethylene glycol bis(methanesulfonates) afford [2.2.1] and [2.2.2] cryptates in 20–35% yields.

Parameters ruling selectivity of complexation of cryptands with metal cations and the stability of the resulting cryptates are well documented.[2] The [1.1.1] cryptand **1** is capable of selectively binding one or two protons inside

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