Table I. Dehalogenation of *vic*-Dihaloalkanes to Alkenes (1 mol) with Sodium Sulfide (2.5 mol) under Phase-Transfer Conditions[a]

substrate	cat., mol	T, °C	time, min (h)	conv,[b] %	yield,[c] %	products	% cis	% trans
meso-1,2-dibromo-1,2-diphenylethane	0.01	25	30[d]	100	97	*trans*-stilbene		100
	0.02	25	15	100		*trans*-stilbene		
	0.05	25	<10	100		*trans*-stilbene		
	0.00	25	(24)	0.00				
	0.01	0	(4)	100		*trans*-stilbene		
d,l-1,2-dibromo-1,2-diphenylethane	0.01	25	95	100	94	stilbene	90.5	9.5
meso-1,2-dichloro-1,2-diphenylethane	0.05	80	(42)	90		α-chloro-*cis*-stilbene		100
methyl *erythro*-2,3-dibromo-3-phenylpropanoate	0.01	25	≤5	100	97	methyl *trans*-cinnamate		100
methyl *threo*-2,3-dibromo-3-phenylpropanoate	0.01	25	10	100	97	methyl cinnamate	50	50
trans-1,2-dibromocyclohexane	0.01	25	(12)	100	90	cyclohexene		
5α,6β-dibromocholestan-3β-ol	0.01	25	40	100	95	5-cholesten-3β-ol		

[a] A toluene solution of substrate and catalyst (20 mL) and an aqueous solution of $Na_2S \cdot 9H_2O$ (24 mL). [b] By GC, NMR, and/or TLC analyses. [c] Isolated pure products. [d] The same reaction time was found by working in the presence of 2,2,6,6-tetramethyl-4-hydroxypiperidinyl *N*-oxide or of *N,N*-diphenylpicrylhydrazyl (0.05 mol), as radical scavengers.

halogenation promoted by iodide ions and Na_2S, the rationale for this behavior should be the same, already discussed[10] in the former case.

Experimental Section

General Methods. GC data were obtained on a Varian 3700 gas chromatograph equipped with a 3% Carbowax 20M on chromosorb W column and were evaluated with a Varian Model 401 data system by the internal standard method. NMR analyses were performed on a Varian EM-390 90-MHz spectrometer in $CDCl_3$ solution with Me_4Si as an internal standard.

Materials and Substrates. Sodium sulfide and toluene were commercial Analar grade products used without further purification. Hexadecyltributylphosphonium bromide was prepared by a standard procedure.[18] All substrates were known products and were prepared according to the literature: *meso*- and *d,l*-1,2-dibromo-1,2-diphenylethane[19] *meso*-1,2-dichloro-1,2-diphenylethane,[20] methyl *erythro*- and *threo*-2,3-dibromo-3-phenylpropanoates,[21] *trans*-1,2-dibromocyclohexane,[22] and 5α,6β-dibromocholestan-3β-ol.[23] The physical properties of the above compounds were in agreement with those reported.

Typical Procedure. Debromination of *meso*-1,2-Dibromo-1,2-diphenylethane. A toluene solution (20 mL) of *meso*-1,2-dibromo-1,2-diphenylethane (6.8 g, 20 mmol) and hexadecyltributylphosphonium bromide (0.1 g, 0.2 mmol), and an aqueous solution (24 mL) of $Na_2S \cdot 9H_2O$ (12 g, 50 mmol) were mixed in a flask and magnetically stirred at 25 °C. The reaction was monitored by TLC (silica gel, light petroleum). After 30 min, conversion was complete. The organic layer was separated and the organic phase extracted with toluene (3 times). The combined organic extracts were filtered from an amount of sulfur, washed with water and dried with Na_2SO_4. Evaporation of the solvent and column chromatography over silica gel (eluent: light petroleum) gave *trans*-stilbene: 3.5 g (97% yield); mp 123-125 °C (lit.[12] mp 124-125 °C); NMR ($CDCl_3$) δ 7.1 (s, 2 H) and 7.2-7.6 (m, 12 H).

Note Added in Proof: After submission of this paper Nakayama et al. reported an analogous system for the reductive debromination of *vic*-dibromides under phase-transfer conditions (Nakayama, J.; Machida, H.; Hoshino, M. *Tetrahedron Lett.* **1983**, *24*, 3001).

Registry No. *meso*-1,2-Dibromo-1,2-diphenylethane, 13440-24-9; *d,l*-1,2-dibromo-1,2-diphenylethane, 13027-48-0; *meso*-1,2-dichoro-1,2-diphenylethane, 15951-99-2; methyl *erythro*-2,3-dibromo-3-phenylpropanoate, 52777-73-8; methyl *threo*-2,3-dibromo-3-phenylpropanoate, 52742-03-7; *trans*-1,2-dibromocyclohexane, 7429-37-0; 5α,6β-dibromocholestan-3β-ol, 1857-80-3; hexadecyltributylphosphonium bromide, 14937-45-2; sodium sulfide, 1313-82-2.

(17) Kornblum, N.; Boyd, D. S.; Pinnick, H. W.; Smith, R. G. *J. Am. Chem. Soc.* **1971**, *93*, 4316.
(18) Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195.
(19) Fieser, L. F. *J. Chem. Educ.* **1954**, 291.
(20) Bergman, E.; Bondi, A. *Chem. Ber.* **1931**, *64*, 1455.
(21) Krimmel, C. P.; Thielu, L. E. "Organic Syntheses"; Wiley: New York, 1963; Vol. IV, p 960.
(22) Snyder, H. R.; Brooks, L. A. "Organic Syntheses"; Wiley: New York, 1943; Vol. II, p 171.
(23) Fieser, L. F. "Organic Syntheses"; Wiley: New York, 1963; Vol. IV, p 195.

A New Method for Cyclopentanone Annelation

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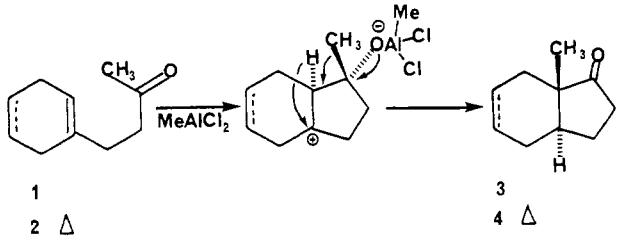
$MeAlCl_2$-initiated cyclization of enone **6d** provides an 85% yield of a 9:1 mixture of trans- and cis-fused hydroazulenones **9** and **10**. Similarly, cyclization of **7d** gives a 31% yield of **11** with an equatorial methyl group, and cyclization of **8d** affords a 46% yield of **12** and a 7% yield of **13**.

Introduction

We have recently published a novel approach to the synthesis of *trans*-hydrindanones.[1] Treatment of γ,δ-unsaturated ketone **1** with 2 equiv of $MeAlCl_2$ in CH_2Cl_2 at 25 °C for 24 h leads to **3** in 30-50% yield. We have subsequently shown that the reaction may be extended to provide an intermediate **4** for steroid syntheses in which the trans-fused CD ring junction has been stereospecifically constructed.[2] Treatment of the readily available dienone

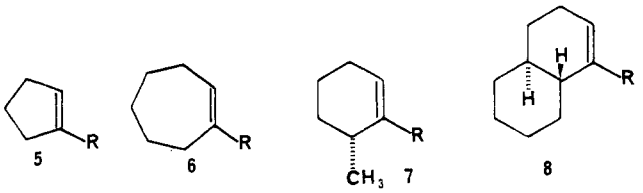
(1) Karras, M.; Snider B. B. *J. Am. Chem. Soc.* **1980**, *102*, 7951.
(2) Snider, B. B.; Kirk, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 2364.

0022-3263/84/1949-0153$01.50/0



2 with 1.1 equiv of $MeAlCl_2$ in CH_2Cl_2 for 2 h at 90 °C gives **4** in 47–53% yield.

We report here studies designed to determine the suitability of this reaction for the synthesis of perhydroazulenones and bicyclo[3.3.0]octanones and the stereochemical effects of substituents on the cycloalkene.[3] Our goal was to develop efficient syntheses of model compounds **5d**, **6d**, **7d**, and **8d** starting from the corresponding



a R=$SiMe_3$
b R=I
c R=$CH_2CH_2C(O)CH_3$
d R=$CH_2CH_2C(=O)CH_3$

readily available cycloalkanones. Butanones **5d** and **6d** were chosen to determine the effect of ring size on the cyclization reaction. Butanones **7d** and **8d** were chosen to examine the influence of substituents on product stereochemistry.

Results and Discussion

Alkenone **5d** is readily available from cyclopentanone by addition of [2-(2,5,5-trimethyl-1,3-dioxan-2-yl)ethyl]magnesium bromide,[4] followed by dehydration of the resulting tertiary alcohol and hydrolysis of the ketal.[5] Although alkenone **6d** is probably available by a similar method, we chose to explore routes based on kinetic enolization that would allow the regiospecific synthesis of the least substituted double bond from unsymmetrical ketones, e.g., 2-methylcycloheptanones, which would be used for pseudoguaianolide syntheses.

Our initial approach to **6d** was based on the conversion of (arylsulfonyl)hydrazones to alkenylcuprate reagents described by Kende.[6] Unfortunately, treatment of cycloheptanone [(2,4,6-triisopropylphenyl)sulfonyl]hydrazone with 2 equiv of *tert*-butyllithium followed by phenylthiocopper and methyl vinyl ketone did not provide any **6d**, although use of 3-penten-2-one did provide the analogous γ,δ-unsaturated ketone in low yield. We therefore turned our attention to related indirect methods.

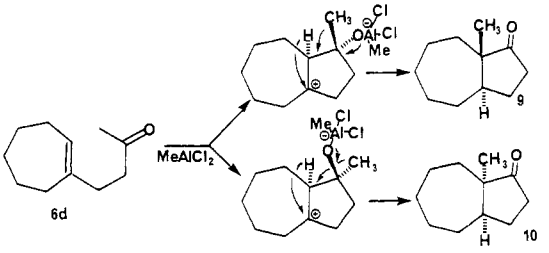
Cycloheptanone tosylhydrazone was converted to the enesilane **6a** by the method of Paquette.[7] Reaction of **6a** with iodine in CH_2Cl_2[8] gave the iodide **6b** in 71% yield. Attempts to prepare cyclohepten-1-yllithium, which could be converted to the cuprate and reacted with methyl vinyl ketone, by transmetalation reactions were discouraging. The reaction of **6b** with Grignard reagents was then examined. Li_2CuCl_4-catalyzed[9] coupling of **6b** with [3,3-(ethylenedioxy)butyl]magnesium bromide[4,5] gave a 60% yield of **6c**. Use of Ni(dppp)Br_2 as a catalyst was also successful.[10] Hydrolysis of **6c** with dilute hydrochloric acid in aqueous THF gave a quantitative yield of **6d**.

Preparation of enesilanes **7a** (75%) and **8a** (66%) proceeded analogously from the tosylhydrazones. These were converted to the iodides **7b** m(70%) and **8b** (65%). Unfortunately, all attempts to couple **7b** or **8b** with [3,3-(ethylenedioxy)butyl]magnesium bromide, by using either the copper or nickel catalysts successfully used with **6b**, failed. The coupling reaction is apparently highly sensitive to steric hindrance.

Heck and co-workers have reported the palladium-catalyzed coupling of isopropenyl bromide with 3-buten-2-ol to give 5-methyl-5-hexen-2-one.[11] We attempted to extend this procedure to cycloalkenyl iodides. Reaction of **7b** with 3-buten-2-ol, palladium acetate, tri-*o*-tolylphosphine, and piperidine at 100 °C for 24 h gave a 24% yield of **7d**. The analogous reaction of **8b** gave a 35% yield of **8d**. While these yields are clearly unsatisfactory, this procedure provided sufficient material to evaluate the cyclization reaction.

Cyclization of 5d, 6d, 7d, and 8d. All cyclizations were carried out with $MeAlCl_2$, a strong Lewis acid with a basic alkyl group, which was the most successful Lewis acid for the cyclization of **1** and **3**. Although $MeAlCl_2$ is more expensive and less readily available then $EtAlCl_2$, studies with **1** and **3** indicated that $MeAlCl_2$ was slightly superior.[1,2] These reactions proceed best when an excess of $MeAlCl_2$ is used. This may result from disproportionation of $MeAlCl_2$ to give Me_2AlCl and the more active catalyst $AlCl_3$. In addition, the ketone is fully complexed in the presence of excess $MeAlCl_2$. If uncomplexed ketone is present, the zwitterionic intermediate can react by intermolecular proton transfer to the basic carbonyl group of uncomplexed ketone in competition with the desired 1,2-hydride shift.

Treatment of **6d** with 0.8 equiv of $MeAlCl_2$ in CH_2Cl_2 for 3 h at 25 °C gave an 85% yield of a 9:1 mixture of **9** and **10**. The structures of **9** and **10** were established by

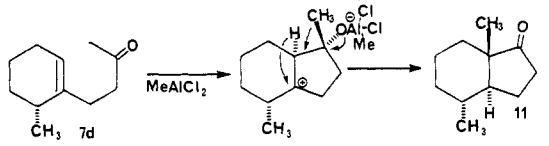


the ^1H NMR chemical shifts of the methyl groups (δ 0.88 and 1.07, respectively), which correspond closely to those of **2** and its cis isomer (δ 0.88 and 1.03, respectively.[12,13]).

(3) While this work was in progress, the synthesis of (±)-androstane-2,17-dione using this procedure was reported: Kametani, T.; Suzuki, Y.; Furuyama, H.; Honda, T. *J. Org. Chem.* **1983**, *48*, 31.
(4) Stowell, J. C.; Keith, D. R.; King, B. T. *Org. Synth.* (*N.Y.*) **1981**, *60*, unchecked procedure No. 2174.
(5) Ponaras, A. A. *Tetrahedron Lett.* **1976**, 3105.
(6) Kende, A. S.; Jungheim, L. N. *Tetrahedron Lett.* **1980**, *21*, 3849.
(7) (a) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, *45*, 3017. (b) Chan, T. H.; Baldassarre, A.; Massuda, D. *Synthesis* **1976**, *801*. (c) Chamberlin, A. R.; Stemke, J. E.; Bond, T. F. *J. Org. Chem.* **1978**, *43*, 147.
(8) Miller, R. B.; Reichenbach, T. *Tetrahedron Lett.* **1974**, 543.
(9) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303.
(10) Kumada, M.; Tamao, K.; Sumitani, K. *Org. Synth.* (*N.Y.*) **1978**, *58*, 127.
(11) Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 3898.
(12) Lansbury, P. T.; Demmin, T. R.; Du Bois, G. E.; Haddon, V. R. *J. Am. Chem. Soc.* **1975**, *97*, 394.

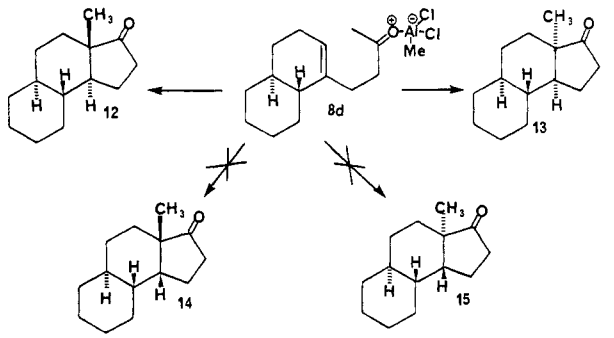
Cyclization of **5d** to a bicyclo[3.3.0]octanone could not be accomplished. Treatment of **5d** with 1.5 equiv of $MeAlCl_2$ in CH_2Cl_2 for 2 days at reflux gave only recovered **5d**. This cyclization is thus very facile for the synthesis of hydroazulenones (0.8 equiv of $MeAlCl_2$, 3 h, 25 °C), acceptable for the synthesis of hydrindanones (**1**, 2 equiv of $MeAlCl_2$, 24 h, 25 °C; **3**, 1.1 equiv of $MeAlCl_2$, 3 h, 90 °C; **7d** and **8d**, 1.5 equiv of $MeAlCl_2$, 40–48 h, 25 °C), and cannot be used for the synthesis of bicyclo[3.3.0] octanones.

Treatment of **7d** with 1.5 equiv of $MeAlCl_2$ in CH_2Cl_2 for 40 h at 25 °C gave a 31% yield of **11**. Although several



minor products were formed, IR spectra of all volatile fractions isolated by preparative GC indicated that **11** was the only cyclopentanone formed. The structure of **11** was established by difference decoupling with irradiation of the methyl doublet, which indicated that the hydrogen α to the methyl group absorbed as a broad doublet of doublets (J = 12, 12 Hz) at δ 1.60 and was therefore axial. Comparison of the ^{13}C NMR spectra of **11** with that of **2** indicated that the methyl group in **11** was equatorial.[14]

Treatment of **8d** with 1.5 equiv of $MeAlCl_2$ in CH_2Cl_2 for 48 h at 25 °C gave a 46% yield of **12**, and a 7% yield of **13**. Side products isolated from this reaction by preparative GC could not be identified but were shown not to be cyclopentanones by IR analysis. The structures of **12**



and **13** were established by comparison of their NMR and mass spectra of those of authentic samples.[12,15] The two other possible isomers **14** and **15** are not known. The ^1H NMR chemical shifts of the methyl groups of **12** (δ 0.88) and **13** (0.97) correspond closely to those reported for the 18-methyl groups of androstan-17-one and 13α-androstan-17-one.[16] By analogy, the chemical shift of the methyl group of **14** should be comparable to that of the 18-methyl group of 14β-androstan-17-one (δ 1.07).[17] This value is markedly different from those observed, which indicates that **14** was not formed. Ketone **15** cannot be rigorously eliminated as a product of the cyclization by this reasoning, since 13α,14β-androstan-17-one is not known. However, it is unlikely to be formed since the middle ring must exist in a high-energy boat conformation.[18]

Mechanism

The observed stereoselectivity of these cyclizations cannot be explained with certainty since the rate-determing step of the reaction is not known. If the initial cyclization is irreversible, this step controls the stereochemistry. If the cyclization is reversible, the stability of the intermediate zwitterions and/or the relative rates of hydride shift control the stereochemistry. The selective formation of trans-fused products may result from preferential formation of the zwitterion with the hydride and methyl group trans, since the oxygen–$MeAlCl_2$ complex is bulkier than the methyl group. The formation of **10** and **13** indicates that the hydride and methyl shifts need not be concerted. Cyclization of **7d** and **8d** occurs as expected on the face of the cyclohexene not bearing a 6-alkyl substituent to give **11**, **12**, and **13**. Interaction of the 3-oxobutyl side chain with axial hydrogens may also play a role in determining facial selectivity.

The failure of **5d** to give the highly strained *trans*-1-methylbicyclo[3.3.0]octan-2-one is not surprising. However, *cis*-1-methylbicyclo[3.3.0]octan-2-one is not strained and could have been formed analogously to **10** and **13**. Its absence implies that the first step is reversible or that the 5-endo-trig geometry leading to the bicyclo[3.3.0]octane zwitterion is so strained that the first step does not occur.

Experimental Section

NMR spectra were taken on Perkin-Elmer R32, Varian EM 390, Bruker WH 90, or a homebuilt 270-MHz spectrometer. IR spectra were recorded on a Perkin-Elmer 683 spectrometer. Mass spectra were recorded on a Hewlett-Packard GC–mass spectrometer. GC analyses were carried out on 10 ft × $^1/_4$ in. 10% Carbowax 20M (A) and 10 ft × $^1/_4$ in. 3% SE-30 (B) on Chromasorb PNAW columns at a flow rate of 50 mL/min. CH_2Cl_2 was dried by distillation from CaH_2. THF was dried by distillation from sodium benzophenone ketyl. $MeAlCl_2$ (21.1%, 1.4 M in hexane) was obtained from Texas Alkyls, Inc. Combustion analyses were performed by Galbraith Laboratories.

4-(Cyclopenten-1-yl)butan-2-one (5d). 2-(2,5,5-Trimethyl-1,3-dioxan-2-yl)ethylmagnesium bromide was prepared from the corresponding bromide[4] and added to cyclopentanone.[5] The resulting alcohol was dehydrated with $POCl_3$ in pyridine[5] and hydrolyzed to give **5d**.[19]

Cycloheptanone (Phenylsulfonyl)hydrazone. Cycloheptanone (3.39 g, 30 mmol) was added to a suspension of (phenylsulfonyl)hydrazide (5.21 g, 30 mmol) in 30 mL of MeOH. Concentrated hydrochloric acid (0.3 mL) was added to give a homogeneous solution. The reaction mixture was cooled overnight at 0 °C, and the precipitated product was separated by filtration to give 5.66 g (71%) of the hydrazone: mp 147–148 °C (lit.[7b] mp 146–147 °C).

2-Methylcyclohexanone tosylhydrazone (3.742 g (70%), mp 126–128 °C) was prepared analogously from 2-methylcyclohexane (2.14 g) and tosylhydrazide (3.55 g) in MeOH (20 mL), except that hydrochloric acid was not added.

***trans*-1-Decalone tosylhydrazone** (0.441 g (69%), mp 153–155 °C) was prepared analogously from *trans*-1-decalone (0.300 g) and tosylhydrazide (0.367 g) in MeOH (3 mL), except that hydrochloric acid was not added.

1-(Trimethylsilyl)cycloheptene (6a, 88% yield) and 1-(trimethylsilyl)-6-methylcyclohexene (7a; 75% yield) were prepared as previously described.[7a]

1-*trans*-1-(Trimethylsilyl)-3,4,4a,5,6,7,8,8a-octahydronaphthalene (8a) was prepared from *trans*-1-decalone tosyl-

(13) These data are inconsistent with those previously reported: Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5311.

(14) The carbon bearing the methyl group (C_8, steroid numbering) is shifted downfield 5.9 ppm. The β carbons C_9 and C_{14} are shifted downfield 9.4 and 6.4 ppm and the γ carbon C_{11} is shifted downfield 0.5 ppm. These values are only consistent with an equatorial methyl group.

(15) The mass spectral data for **25** and **26** reported in the Typical Degradation Procedure section in ref 12 are switched. P. T. Lansbury, private communication, 1983.

(16) Fetizon, M.; Gramain, J.-C. *Bull. Soc. Chim. Fr.* **1966**, 3444.

(17) Nambara, T.; Hosoda, H.; Goya, S. *Chem. Pharm. Bull.* **1968**, *16*, 374.

(18) Johnson, W. S.; Boots, S. G.; Habicht, E. R., Jr. *J. Org. Chem.* **1968**, *33*, 1754.

(19) Cormier, R. A.; Schreiber, W. L.; Agosta, W. C. *J. Am. Chem. Soc.* **1973**, *95*, 4873.

hydrazone (0.683 g) by the procedure of Paquette et al.[7a] Evaporative distillation of the crude product (83 °C, 1.0 torr) gave 0.271 g (66%) of pure **8a**: NMR ($CDCl_3$) δ 5.9–6.1 (br, 1), 2.33–2.00 (m, 2), 2.00–0.8 (m, 12), 0.13 (s, 9); ^{13}C NMR ($CDCl_3$) δ 142.6, 137.0, 45.4, 41.2, 34.5, 33.5, 30.0, 28.0, 27.6, 26.8, 0.0; GC (A, 170 °C) t_R = 6 min.

2-Iodocycloheptene (6b). A solution of alkenylsilane **6a** (252 mg, 1.5 mmol) and iodine (381 mg, 1.5 mmol) in 7.5 mL of CH_2Cl_2 was stirred for 3 h at 25 °C. The reaction was poured into saturated aqueous sodium thiosulfate solution and extracted three times with ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Distillation gave 0.235 g (71%) of pure **6b**: bp 78–81 °C (7 torr) [lit.[20] bp 79–80 °C (7 torr)]; the NMR and IR spectra are identical with those previously reported.[20]

1-Iodo-6-methylcyclohexene (7b, 1.155 g) was prepared analogously from **7a** (1.250 g) in 70% yield: bp 70–72 °C (7 torr) [lit.[21] bp 68–69 °C (7 torr)]; NMR ($CDCl_3$) δ 6.23 (t, 1, J = 3 Hz), 2.33 (br, 1), 2.07–1.8 (m, 2), 1.67–1.33 (m, 4), 1.03 (d, 3, J = 6 Hz).

1-Iodo-3,4,4a,5,6,7,8,8a-octahydronaphthalene (8b, 0.203 g) was prepared analogously from **8a** (0.250 g) in 65% yield: bp 70–80 °C (1 torr); NMR ($CDCl_3$) δ 6.5–6.3 (br, 1) 2.3–0.7 (m, 14). An analytical sample was prepared by preparative GC (B, 170 °C). Anal. Calcd for $C_{10}H_{15}I$: C, 45.82; H, 5.77. Found: C, 46.01; H, 5.84.

1-[3,3-(Ethylenedioxy)butyl]cycloheptene (6c). A solution of [3,3-(ethylenedioxy)butyl]magnesium bromide (7.8 mmol) and **6b** (537 mg, 2.42 mmol) in 7 mL of THF was cooled to 0 °C and treated with 0.14 mL of 0.1 M Li_2CuCl_4 in THF. The reaction was stirred for 8 h at 0 °C and poured into saturated ammonium chloride. The aqueous layer was extracted with two 20-mL portions of pentane. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated. The oily residue was purified by chromatography on silica gel (4:1 hexane–ether) to give 303 mg (60%) of pure **6c**: NMR ($CDCl_3$) δ 5.50 (t, 1, J = 6 Hz), 3.87 (s, 4), 2.23–2.20 (m, 6), 2.20–1.27 (m, 8), 1.23 (s, 3).

4-(Cyclohepten-1-yl)butan-2-one (6d). A solution of **6c** (297 mg, 1.4 mmol) was dissolved in a mixture of 4.9 mL of THF and 2.6 mL of 5% hydrochloric acid. The resulting solution was stirred for 36 h and poured into 5 mL of water. The mixture was extracted with three 20-mL portions of pentane. The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to give 229 mg (98%) of **6d**. The NMR and IR data are identical with those previously reported.[19]

4-(6-Methylcyclohexen-1-yl)butan-2-one (7d). A solution of palladium acetate (21 mg, 0.1 mmol), tri-*o*-tolylphosphine (60 mg, 0.2 mmol), iodoalkene **7b** (289 mg, 1.3 mmol), and 3-buten-2-ol (103 mg, 1.4 mmol) in 0.4 mL of dry piperidine was heated for 24 h at 100 °C under nitrogen.[11] The reaction mixture was diluted with water and extracted three times with ether. The combined organic extracts were washed with water to remove piperidine, dried ($MgSO_4$), and evaporated. Chromatography of the resultant brown oil on silica gel (4:1 hexane–ether) gave 52 mg (24%) of **7d**: NMR ($CDCl_3$) δ 5.43–5.27 (br, 1), 2.6–1.8 (m, 7), 2.13 (s, 3), 1.67–1.4 (m, 4), 1.00 (d, 3, J = 6 Hz); IR (neat) 1715 cm^{-1}.

4-(1-*trans*-3,4,4a,5,6,7,8,8a-Octahydronaphthyl)butan-2-one (8d) was prepared analogously from **8b** (170 mg, 0.65 mmol) except that the reaction was carried out for 48 h at 100 °C. Chromatography of the resultant brown oil on silica gel (4:1 hexane–ether) gave 47 mg (35%) of **8d**: NMR ($CDCl_3$) δ 5.37–5.20 (br, 1) 2.10 (s, 3), 2.5–1.0 (m, 18); IR (neat) 1705 cm^{-1}.

Cyclization of 6d. A solution of **6d** (48 mg, 0.29 mmol) in 5 mL of dry CH_2Cl_2 at 0 °C under nitrogen was treated with $MeAlCl_2$ (0.17 mL of a 1.4 M solution in heptane, 0.24 mmol). The reaction mixture was stirred for 3 h at 25 °C and poured into water. The precipitate was dissolved by addition of 10% hydrochloric acid. The mixture was extracted with three portions of CH_2Cl_2; which were combined, dried ($MgSO_4$), and evaporated to give 51 mg of crude product. Evaporative distillation (50 °C, 0.5 torr) gave 41 mg (85%) of a 9:1 mixture of **9** and **10** as determined by NMR and GC analysis. Pure samples were obtained by preparative GC.

9: NMR ($CDCl_3$) δ 2.5–1.0 (m, 15), 0.88 (s, 3); ^{13}C NMR ($CDCl_3$) δ 223.8, 51.4, 44.8, 36.9, 36.3, 27.6, 26.6, 26.3 (2 carbons), 26.0, 19.9; IR (neat) 2915, 2845, 1730, 1460, 1050 cm^{-1}; GC (A, 170 °C) t_R = 18.5 min. Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found C, 79.70; H, 11.02.

10: NMR ($CDCl_3$) δ 2.4–1.1 (m, 15), 1.07 (s, 3); IR (neat) 2920, 2850, 1730, 1460 cm^{-1}; GC (A, 170 °C) t_R = 16 min.

When 1.5 equiv of $MeAlCl_2$ was used, 10–15% of 4-(1-methylcycloheptyl)butan-2-one was also formed: NMR ($CDCl_3$) δ 2.6–2.2 (m, 2), 2.13 (s, 3), 2.0–1.0 (m, 14), 0.85 (s, 3); IR (neat) 2920, 2850, 1715 cm^{-1}; GC (A, 170 °C) t_R = 14.5 min.

Cyclization of 7d. A solution of **7d** (40 mg, 0.24 mmol) in 5 mL of CH_2Cl_2 at 0 °C under nitrogen was treated with $MeAlCl_2$ (0.26 mL of a 1.4 M solution in heptane, 0.30 mmol). The reaction mixture was stirred for 40 h at 25 °C and worked up as described above to give 35 mg of a brown oil. Evaporative distillation (70–80 °C, 1.5 torr) gave 21 mg (52%) of a mixture of products as determined by GC analysis (B, 150 °C); t_R = 3.6 (7%), 4.0 (13%), 4.5 (8%), 5.9 (6%), 7.6 (**11**, 59%), and 8.9 min (7%). All six fractions were isolated by preparative GC. Only the fraction eluting at 7.6 min shows the presence of a cyclopentanone (1730 cm^{-1}) in the IR spectra. The minor isomers could not be identified. In a similar reaction, a preparative GC of the crude product (35 mg) obtained from 38.8 mg of **7d** gave 11.1 mg (26%) of pure **11**: NMR ($CDCl_3$) δ 2.5–1.0 (m, 12), 0.90 (d, 3, J = 6.3 Hz), 0.88 (s, 3); a difference decoupling spectra with irradiation at δ 0.90 showed a broad dd at δ 1.60 (J = 12, 12 Hz); ^{13}C NMR ($CDCl_3$) δ (steroid numbering) 52.2 (C_{14}), 35.8 (C^*_{16}), 35.6 (C^*_9), 31.8 (C^*_{12}), 31.4 (C^*_8) 22.2 (C_{15}), 21.5 (C_{11}), 19.4 (8-Me), 13.7 (C_{18}), the carbonyl and quaternary carbons were not observed; IR ($CDCl_3$) 2950, 2920, 2860, 1730, 1450, 1400, 1370, 1095, 1050, 1015 cm^{-1}; MS m/e (relative intensity) 166 (M^+, 55), 151 (41), 133 (29), 122 (32), 109 (36), 95 (100), 82 (22), 81 (23), 67 (27), 55 (12), 41 (16). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found C, 79.13; H, 10.80.

Cyclization of 8d. A solution of **8d** (34 mg, 0.16 mmol) in 3 mL of CH_2Cl_2 at 0 °C under nitrogen was treated with $MeAlCl_2$ (0.18 mL of a 1.4 M solution in heptane, 0.25 mmol). The reaction mixture was stirred for 48 h at 25 °C and worked up as described above to give 28 mg (82%) of a brown oil. Evaporation distillation (120 °C, 20 torr) gave 22 mg (64%) of a mixture of products as determined by GC analysis (B, 180 °C): t_R = 7.8 (3%), 9.5 (3%), 11.2 (**13**, 12%), 13.6 (**12**, 72%), and 16.4 min (10%). All fractions were isolated by preparative GC. Only the fractions eluting at 11.2 and 13.6 min show the presence of a cyclopentanone (1730 cm^{-1}) in the IR spectra. The other fractions could not be identified.

13: NMR ($CDCl_3$) δ 0.7–2.5 (m, 19), 0.977 (s, 3); [NMR (lit.[12]) CCl_4 δ 0.93 (s, 3)]. The 18-methyl group of 13α-androstan-17-one absorbs at δ 0.928 in CCl_4 and 0.97 in $CDCl_3$;[16] IR ($CDCl_3$) 2920, 2850, 1735, 1100; MS, m/e (relative intensity) 206 (M^+, 50), 191 (13), 188 (8), 173 (16), 162 (65), 150 (33), 149 (39), 147 (33), 135 (71), 124 (100), 121 (19), 110 (38), 97 (41), 79 (31).

12: NMR ($CDCl_3$) δ 2.5–0.7 (m, 19), 0.88 (s, 3); [NMR (lit.[12]) (CCl_4) δ 0.84 (s, 3)]. The 18-methyl group of androstan-17-one absorbs at δ 0.815 in CCl_4 and 0.865 in $CDCl_3$;[16] IR ($CDCl_3$) 2920, 2860, 1735, 1450 cm^{-1}; MS, m/e (relative intensity) 206 (M^+, 78), 188 (34), 173 (27), 162 (100), 150 (41), 149 (42), 147 (44), 135 (76), 121 (18), 108 (22), 67 (28). These data correspond closely to those previously reported.[12]

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Registry No. **5d**, 42809-28-9; **6a**, 61892-24-8; **6b**, 49565-03-9; **6c**, 87842-55-5; **6d**, 42809-31-4; **7a**, 63031-68-5; **7b**, 40648-10-0; **7d**, 87842-56-6; **8a**, 87842-53-3; **8b**, 87842-54-4; **8d**, 87842-57-7; **9**, 87842-58-8; **10**, 87842-59-9; **11**, 87842-61-3; **12**, 87900-49-0; **13**, 87900-50-3; $MeAlCl_2$, 917-65-7; cyclopentanone, 120-92-3; cyclo-

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heptanone (phenylsulfonyl)hydrazide, 61892-20-4; cycloheptanone, 502-42-1; (phenylsulfonyl)hydrazone, 80-17-1; 2-methylcyclohexanone tosylhydrazone, 52826-41-2; 2-methylcyclohexanone, 583-60-8; tosyl hydrazide, 1576-35-8; *trans*-1-decalone tosylhydrazone, 85319-00-2; *trans*-1-decalone, 21370-71-8; 2-(2,5,5-trimethyl-1,3-dioxan-2-yl)ethyl bromide, 87842-52-2; [3,3-(ethylenedioxy)butyl]magnesium bromide, 78078-49-6; 4-(1-methylcycloheptyl)-2-butanone, 87842-60-2; 3-buten-2-ol, 598-32-3.

Total Synthesis of Racemic Lycoramine

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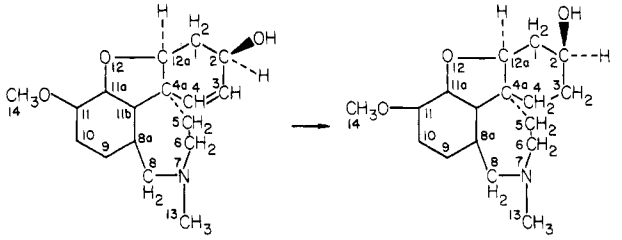
The total synthesis of *d,l*-lycoramine (**2**), an Amaryllidaceae alkaloid, is described. The method utilizes the intermediacy of the biogenetically relevant hydrobenzazepines of type **22**, readily available from cinnamonitrile precursors via a chemospecific cleavage of the more hindered C-6 methoxyl which ensues with concomitant 1,4-addition to the spirocyclic enone system and generates the complete galanthamine-like skeleton. The total synthesis of **2** proceeds in an overall 22% yield from 2,3-dimethoxycinnamonitrile (**3**).

Introduction

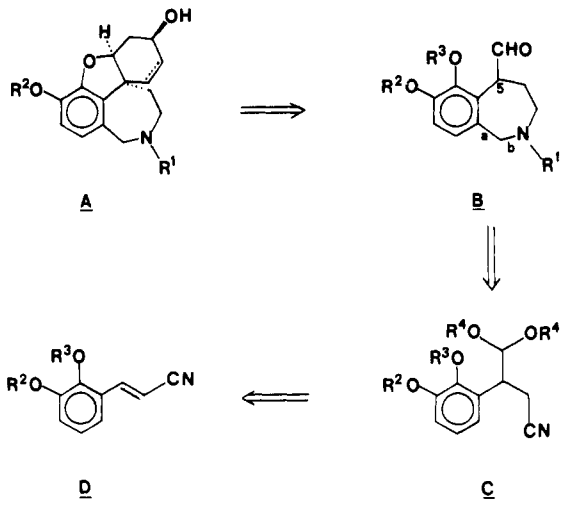
The galanthamine-type alkaloids constitute a group of structurally related bases found in plants from a number of genera within the Amaryllidaceae family.[1] Representative members of this family include galanthamine[2] (**1**) and lycoramine[3] (**2**).



1 **2**

The distinct chemical structure exhibited by these alkaloids, characterized by having a polycyclic system that incorporates a benzylic quaternary carbon atom, and the significant biological activity ascribed[2e,4] to galanthamine (**1**), the parent member of the series, have provided the necessary stimulus for the development of new methodologies and general strategies for the syntheses of these naturally occurring bases.[5] Particularly noteworthy in this respect, is the biomimetic entry to spirocyclic hydrobenzazepines via the intramolecular coupling of phenolic substrates.[2,6]

Scheme I



Close scrutiny of the salient structural features of these alkaloids, such as the presence of a spirocyclic β-oxygenated cyclohexanol system, suggested the utilization of tetrahydrobenzazepine B as a suitable synthetic precursor (Scheme I). Furthermore, if one disconnects bonds a and

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