(2 H, m), 3.61, 3.78, and 3.88 (1 H, three s), 3.4 (3 H, m), 2.8–3.0 (1 H, m), 2.0–2.6 (2 H, series of m), 1.4–2.0 (5 H, series of m), 0.9–1.1 (9 H, m); IR (liquid, CCl_4) 1709, 1636 cm^{-1}; high-resolution mass spectrum, calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1735.

2,10,10-Trimethyl-11-(methoxymethoxy)tricyclo-[6.3.0.0^{1,5}]undecan-6-one (28).[45] Anhydrous ammonia gas (ca. 45 mL) was condensed (dry ice/acetone bath) into a flask containing pieces of sodium metal. The solution was stirred for 15 min and allowed to warm slowly by removing the cooling bath. The dry ammonia liquid was distilled into the reaction flask equipped with a solvent vapor cooling/condensor tower. Approximately 2 cm of lithium wire (ca. 50 mg/cm, 100 mg, 14.4 mmol.), containing 2% sodium, was cut into small pieces and added piecemeal to the stirring liquid cooled at −78 °. The reaction mixture was stirred 30 min whereupon a solution of 0.365 g (1.38 mmol) of enone **27** in 20 mL of ether was added dropwise over 25 min by means of a cannula. Methanol (51 μL, 1.38 mmol) was added and the solution left at the liquid ammonia solution reflux temperature for 5 h. The mixture was recooled to −78 °C, stirred for 1 h, and slowly warmed to room temperature over 7 h. The solution was cooled to 0 °C, 50 mL of saturated ammonium chloride added, and the resulting mixture stirred for 4 h and warmed to room temperature over 4 h. The mixture along with ether and water washes were poured into a separatory funnel containing ca. 100 mL of saturated aqueous ammonium chloride. After mixing, the layers were separated, the aqueous layer was extracted with ether (4 × 100 mL), and the combined ether extracts and organic layer were washed with saturated aqueous sodium chloride (2 × 100 mL) and dried (Na_2SO_4). After solvent removal the crude product was chromatographed eluting with ether a product fraction which was purified by MPLC to give 0.330 g (90%) of ketone **28** as a mixture of diastereomers by using 10% ether in hexane as solvent. For this mixture: IR (liquid, CCl_4) 1730 cm^{-1}; high-resolution mass spectrum, calcd for $C_{16}H_{26}O_3$ 266.1882, found 266.1886. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.01; H, 9.95. By use of MPLC the mixtures of diastereomers of **28** could be partially resolved into three fractions, two of which were pure diastereomers and the third a mixture containing a major component. One medium and two small MPLC columns were placed in series. Samples of the ketone mixture were chromatographed, eluting with 20% ether in hexane to give three main fractions.

The first of these was found by NMR analysis to be the diastereomer depicted as **28C**: **(±)-(1*R**,2*R**,5*S**,8*R**,11*R**)-2,10,10-Trimethyl-11-(methoxymethoxy)tricyclo[6.3.0.0^{1,5}]-undecan-6-one (28C).** NMR (500 MHz, $CDCl_3$) δ 4.66 (1 H, d, J = 6.8 Hz), 4.64 (1 H, d, J = 6.8 Hz), 3.453 (1 H, s), 3.369 (3 H, s), 2.994 (1 H, d, J = 10.0 Hz), 2.466 (1 H, m), 2.376 (1 H, dd, J = 10.2, 19.2 Hz), 2.172 (1 H, ddd, J = 1.8, 3.3, 19.1 Hz), 2.040 (1 H, dd, J = 5.5, 6.5 Hz), 1.90 (1 H, d, J = 10.0 Hz), 1.76 (1 H, d, J = 10.0 Hz), 1.72 (2 H, m, 2 J's observable = 8.9, 13.5 Hz), 1.322 (1 H, dd, J = 5.0, 13.5 Hz), 1.059 (3 H, s), 1.029 (3 H, d, J = 6.9 Hz), 0.95 (1 H, m), and 0.894 (3 H, s).

The second was determined to be diastereomer **28B**: **(±)-(1*R**,2*S**,5*S**,8*R**,11*R**)-2,10,10-Trimethyl-11-(methoxymethoxy)tricyclo[6.3.0.0^{1,5}]undecan-6-one (28B).** NMR (500 MHz, $CDCl_3$) δ 4.62 (1 H, d, J = 6.7 Hz), 4.58 (1 H, d, J = 6.7 Hz), 3.658 (1 H, s), 3.366 (3 H, s), 3.036 (1 H, dd, J = 2.0, 10.0 Hz), 2.501 (1 H, dd, J = 8.9, 19.2 Hz), 2.242 (1 H, dq, J_d = 2.4, J_q = 8.9 Hz), 2.151 (1 H, dt, J_d = 19.2, J_t = 2.0 Hz), 1.95 (1 H, m), 1.7 (4 H, m), 1.39 (1 H, m), 1.313 (1 H, dd, J = 9.4, 13.1 Hz), 1.045 (3 H, s), 1.030 (3 H, d, J = 6.7 Hz), and 0.997 (3 H, s) ppm.

The third fraction was an inseparable mixture whose major component appeared to be diastereomer **28A**: **(±)-(1*R**,2*S**,5*S**,8*R**,11*S**)-2,10,10-Trimethyl-11-(methoxymethoxy)tricyclo[6.3.0.0^{1,5}]undecan-6-one (28A).** NMR (360 and 500 MHz, $CDCl_3$) see text and Table I.

Acknowledgment. We are very grateful to Prof. P. Magnus for providing us with detailed experimental procedures for the synthesis of **23**. We thank the National Institutes of Health (Grant GM26294) and the University of California at Davis NMR Facility for financial support of this research. Purchase of the NT-360 and NM-500 instruments was made possible by instrumentation grants from the National Science Foundation. N.E.S. thanks the Camille and Henry Dreyfus Foundation for a Teacher–Scholar Award.

Registry No. **1**, 93474-41-0; (±)-**2**, 106211-46-5; **3**, 73057-71-3; **4**, 93474-50-1; **5**, 106211-47-6; **6**, 176-10-3; **7**, 93474-47-6; (±)-**8**, 106211-48-7; **8** (alcohol), 106211-49-8; (±)-**10**, 106211-50-1; (±)-**11**, 85431-51-2; (±)-**13**, 106211-51-2; **14**, 93474-40-9; (±)-**15**, 106211-52-3; **16**, 106211-53-4; **22**, 106211-56-7; **23**, 106211-57-8; **23** (ethyl ester), 106211-54-5; **23** (alcohol), 106211-55-6; **24**, 106211-58-9; **25**, 106211-59-0; **26**, 106211-60-3; **27**, 106211-61-4; **28**, 106211-62-5; (±)-**28A**, 106292-64-2; (±)-**28B**, 106292-63-1; (±)-**28C**, 106292-62-0; 2,4,6-$(Me_2CH)_3C_6H_2SO_2NHNH_2$, 39085-59-1; $Br(CH_2)_4Br$, 110-52-1; LiC≡CH, 1111-64-4; $MeCHBr(CH_2)_2CHBrMe$, 24774-58-1; $TMSC{\equiv}CCH_2Br$, 38002-45-8; Me_2CHCO_2Et, 97-62-1; $BrCH_2C{\equiv}CH$, 106-96-7; 2-methyl-cyclopentanone-(±), 32854-37-8; 2-methylcyclopentanone [(2,4,6-triisopropylphenyl)sulfonyl]-hydrazone-(±), 106230-66-4; 1-(3-iodopropyl)cyclopentene, 106211-63-6; γ-butylrolactone, 96-48-0; (3-iodopropylidene)-cyclopentane, 93474-49-8; 1-(*N*,*N*-dicyclohexylamino)-2-methyl-1-propene, 88592-10-3.

1,2-Carbonyl Migrations in Organic Synthesis. An Approach to the Perhydroindanones

Russell C. Klix and Robert D. Bach*

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Received June 2, 1986

The facile Lewis acid catalyzed acyl migration of several bicyclic α,β-epoxy ketones affords a practical route to both *cis*- and *trans*-8-formyl-1-hydrindanones and a variety of related perhydroindanone derivatives. The synthetic utility of 1,2-carbonyl migrations in organic synthesis and some of its limitations are discussed.

One of the challenging problems in steroid synthesis remains the construction of the trans-fused CD ring system that is present in most steroids.[1] A variety of methods have recently been described that address the construction of the basic ring system and the stereochemistry of the ring fusion. For example, Stork and Mook[2] have reported that the preparation of cis-fused 8-methyl-1-hydrindanone can

(1) Blickenstaff, R. T.; Ghosh, A. C.; Wolf, G. C. *Total Synthesis of steroids*; Academic; New York, 1974.

(2) Stork, G.; Mook, R., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3721.

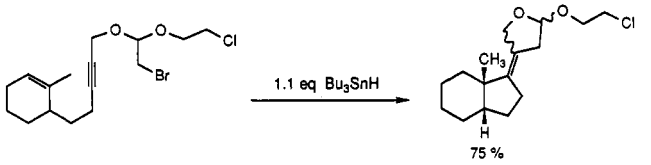
0022-3263/87/1952-0580$01.50/0

Table I. Acyl Migration in β-Epoxide 6

cat. (equiv)[a]	solvent	temp, °C	time	GC yield	isolated yield	ratio of 8/7 + 9[b]	ratio of 9/7
BF_3·Et_2O (0.5)	CH_2Cl_2	25	5 min	73	60	18:82	62:38
BF_3·Et_2O (0.2)	CH_2Cl_2	25	1 h	73	62	24:76	55:45
BF_3·Et_2O (0.2)	CH_2Cl_2	35	30 min	71	60	17:83	68:32
BF_3·Et_2O (0.2)	C_6H_6	80	5 min	53	61	22:78	84:16
$ZnCl_2$ (2.0)	C_6H_6	80	3 h	20	57	85:15	49:51

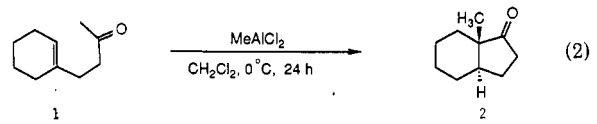
[a] Ratio of catalyst to epoxy ketone. [b] Ratio of 1,2-diketone 8 to 1,3-diketones 7 and 9.

be accomplished by a vinyl radical cyclization. They reported an intramolecular addition of a free radical to a triple bond generating a cis-fused CD ring system (eq 1).

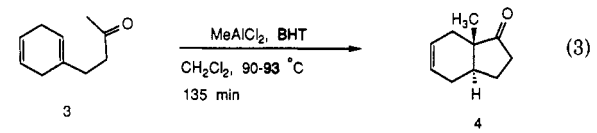


(1)

The structure and stereochemistry of the cyclization was confirmed by ozonolysis to the known *cis*-8-methyl-1-hydrindanone. Snider and Kirk[3] have reported a $MeAlCl_2$-initiated cyclization of methyl ketone **1** that afforded trans-fused hydrindanone **2** in 28% yield (eq 2).

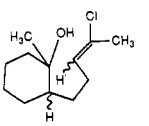


(2)



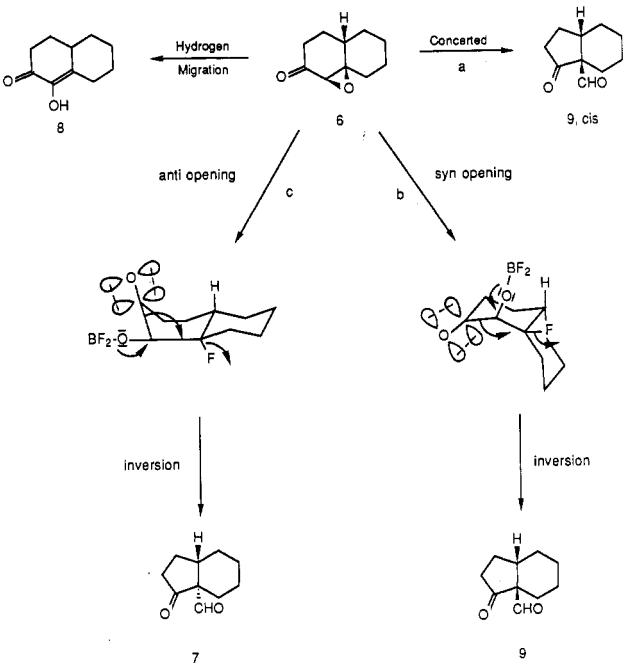
(3)

They also showed that cyclization of diene **3** at 93 °C provided the functionalized trans-fused hydrindanone **4** in 50% yield (eq 3). In an earlier report, Lansbury et al.[4] published a procedure affording a mixture of *cis*- and *trans*-8-methyl-1-hydrindanones (3:1) by utilizing the intramolecular alkylation of carbinol **5**.



We have recently shown[5] that reactions involving a 1,2-carbonyl migration can provide a synthetically useful method for the preparation of 1,3-diketo spiranes. As an extension of this work, we chose to investigate the Lewis acid mediated 1,2-carbonyl rearrangement in 1,2-epoxybicyclo[4.4.0]decan-3-one and its derivatives, since this reaction could potentially afford *trans*-8-formyl-1-hydrindanone upon a concerted ring contraction. We were encouraged in this effort by an earlier detailed study of acid-catalyzed rearrangements of steroidal α,β-epoxy ketones. Collins[6] has shown that treatment of 4α,5-epoxy-5α-cholestan-3-one or its 4β,5β-isomer with 1.1 equiv of boron trifluoride etherate in benzene gave, in each case, a mixture of products arising from hydrogen migration, and carbonyl migration with subsequent deformylation. Although the yields were relatively low, we felt that the synthetic utility of this type of Lewis acid induced ring contraction could be markedly improved by the much milder reaction conditions that we have recently developed.[5] We now report practical syntheses of both *cis*- and *trans*-8-methyl-1-hydrindanone.

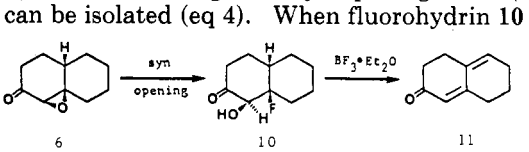
Scheme I



Results and Discussion

The complete stereospecificity of a concerted carbonyl migration[5] can potentially be brought to bear on synthetic problems involving contrathermodynamic products. We initially investigated the Lewis acid mediated 1,2-carbonyl migration in β-1,2-epoxybicyclo[4.4.0]decan-3-one (**6**), since this should give us *trans*-8-formyl-1-hydrindanone (**7**) if the ring contraction followed a concerted pathway with inversion in the usual manner. The aldehyde functionality at C_8 is a versatile group that can be further oxidized, reduced, deformylated, or converted into *trans*-8-methyl-1-hydrindanone (**14**).

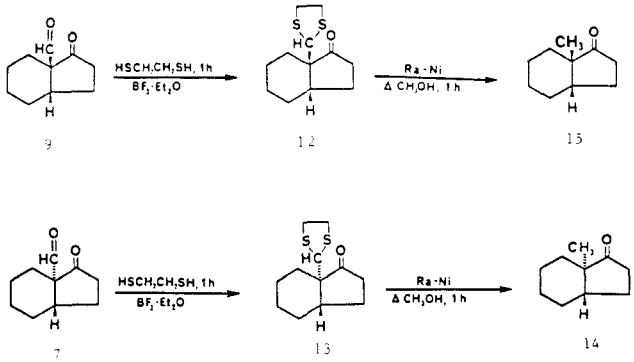
Treatment of α,β-epoxy ketone **6** with 0.2 equiv of boron trifluoride etherate in methylene chloride at 25 °C for 1 h resulted in the formation of three major products and a trace of dienone **11** (eq 4). The desired *trans*-8-formyl-1-hydrindanone (**7**) was produced in moderate yield. All three major compounds were isolated from the reaction mixture (Scheme I); the 1,2-diketone **8** resulting from hydrogen migration and the *cis*- (**9**) and *trans*-8-formyl-1-hydrindanone (**7**) resulting from 1,2-carbonyl migration (Table I). If the reaction is quenched early, the fluorohydrin **10** resulting from syn opening of the β-epoxide can be isolated (eq 4). When fluorohydrin **10** was



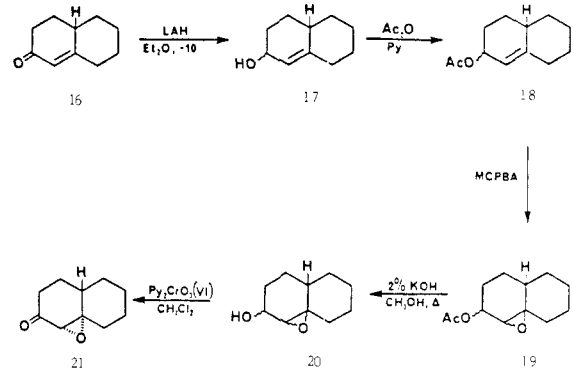
(4)

(3) Snider, B. B.; Kirk, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 2364.
(4) Lansbury, P. T.; Briggs, P. C.; Demmin, T. R.; DuBois, G. E. *J. Am. Chem. Soc.* **1971**, *93*, 1311.
(5) Bach, R. D.; Klix, R. C. *J. Org. Chem.* **1985**, *50*, 5438.
(6) Collins, D. J. *J. Chem. Soc.* **1959**, 3919.

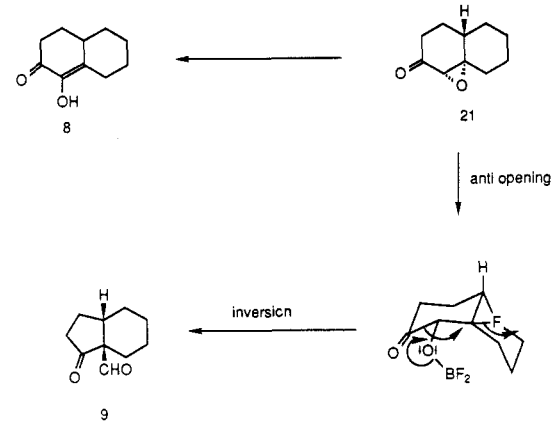
Scheme II



Scheme III



Scheme IV



subjected to 0.2 equiv of boron trifluoride etherate in refluxing methylene chloride for 1 h, the dienone **11** (39%), presumably from elimination of hydrogen fluoride and water, was the major product (eq 4). Since the dienone **11** was only a minor product from the initial rearrangement of **6**, it would appear that formation of the syn fluorohydrin intermediate was not the exclusive pathway in the primary epoxide rearrangement.

If 1,2-carbonyl migration in fluorohydrin **10** occurred with inversion with respect to the carbon bearing the fluorine atom, then one would expect the cis-aldehyde **9** to dominate (Scheme I). The trans aldehyde can be formed by anti opening of the epoxide to form the fluorohydrin followed by carbonyl migration in a two-step double inversion (pathway c) process. If these reactions were totally concerted, then we would have expected all cis-aldehyde **9** with the β-epoxide **6** and all trans-aldehyde **7** with α-epoxide **21**. When nonnucleophilic acids like chlorosulfonic or perchloric acid were used in the reaction with **6**, both the cis and trans aldehydes were formed. Despite the mixture of products, rearrangement of **6** is, however, still synthetically useful because the trans-aldehyde **7** can be readily isolated by column chromatography on a preparative scale (see Experimental Section). As anticipated, the milder reaction conditions and shorter reaction times markedly reduced the amount of deformylation.

The major conclusion to be drawn from this initial investigation is that cyclic α,β-epoxy ketones, where torsional strain can inhibit free carbon–carbon bond rotation attending the carbonyl migration, can afford a mixture of products that may involve fluorohydrin intermediates. This point was recently emphasized by Kunisch et al.,[7] who noted that the Lewis acid catalyzed rearrangement of optically active isophorone oxide was attended by some racemization. Since this reaction proceeded rapidly and in high yield, we initially suggested that the carbonyl migration was concerted.[8] We now suspect that a fluorohydrin is also involved in this simple cyclic α,β-epoxy ketone case and that it can experience racemization under the conditions of the rearrangement.

The stereochemistry of **7** was established by chemical transformation to the known compound *trans*-8-methyl-1-hydrindanone (**14**). The aldehyde group in **7** appeared in the ^{1}H NMR spectrum at 9.61 ppm, which is 0.15 ppm downfield from that in the cis-isomer **15**. Both *cis*- and *trans*-8-formyl-1-hydrindanone were converted to *cis*- (**15**) and *trans*-8-methyl-1-hydrindanone (**14**) as shown in Scheme II. Treatment of the aldehydes with 1,2-ethanedithiol and boron trifluoride etherate affords the cis- and trans-thioacetals **12** and **13** in 70% and 76% yields, respectively. Upon refluxing the thioacetals in methanol with Raney nickel (W-2), we obtained *cis*- (**15**) and *trans*-8-methyl-1-hydrindanone (**14**) in 51% and 65% yield, respectively.

We next decided to investigate the chemistry of the α-epoxide **21** (Scheme III). If concerted 1,2-carbonyl migration occurs, then we would presumably form the trans-product **7**. The α-epoxide can be prepared in a five-step sequence from bicyclo[4.4.0]dec-1-en-3-one (**16**). Since epoxidation of **16** is favored on the β-face, we had to hinder this approach in order to favor epoxidation of the opposite stereoface. Reduction of **16** afforded a diastereomeric mixture of allylic alcohols with the β-alcohol as the major product. Attempts at this point to separate the diastereomers were not made since isolation of the α-epoxide by recrystallization can be easily accomplished at the end of the reaction sequence. Acetylation of the allylic alcohol **17** followed by epoxidation with MCPBA afforded **19** (99%). Treatment of **19** in refluxing methanol with 2% KOH gave the epoxy alcohol **20**, which was then oxidized and purified by recrystallization to remove the small percentage of the β-epoxide. The α-epoxide **21** was isolated in 78% yield. Upon treatment of the α-epoxide **21** with boron trifluoride etherate, we formed *cis*-8-formyl-1-hydrindanone (**9**) and the 1,2-diketone **8** in a ~4:1 ratio (Scheme IV). The stereochemical consequence of the exclusive formation of **9** arising from carbonyl migration must be the result of a double inversion. This behavior, however, was not surprising since examination of molecular models suggests that the carbonyl carbon in **21** cannot attain its proper alignment for neighboring-group participation (NGP) by the carbonyl carbon[7] to migrate over the β-face. To form **9** from a concerted rearrangement, a fluorohydrin would have to have been

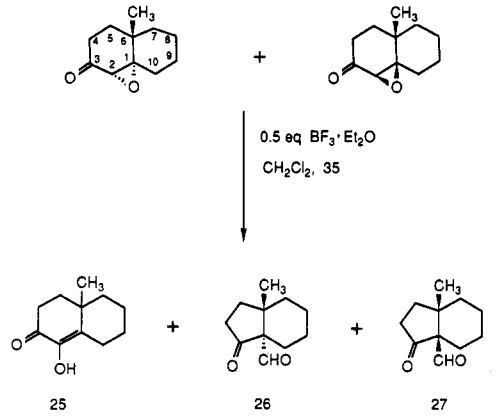
(7) Kunisch, F.; Hobert, K.; Welzel, P. *Tetrahedron Lett.* **1985**, *26*, 6039.
(8) Bach, R. D.; Klix, R. C. *Tetrahedron Lett.* **1985**, *26*, 985.

Table II. Lewis Acid Catalyzed Carbonyl Migration in 1,2-Epoxy-6-methylbicyclo[4.4.0]decan-3-one

cat. (equiv.)[a]	solvent	temp, °C	time	isolated yield	GC yield	ratio of 25/26 + 27[b]	ratio of 26/27
BF_3·Et_2O (0.5)	CH_2Cl_2	35	30 min	60	92	47:53	10:90
BF_3·Et_2O (0.5)	CH_2Cl_2	25	1 h	64	90	38:62	13:87
BF_3·Et_2O (0.2)	CH_2Cl_2	35	1.5 h	73	92	46:54	15:85
BF_3·Et_2O (0.5)	C_6H_6	78	5 min	66	90	51:49	8:92

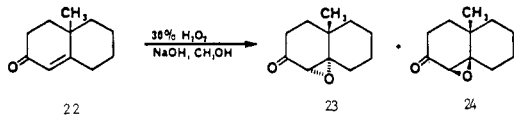
[a] Ratio of catalyst to epoxy ketone. [b] Ratio of 1,2-diketone **25** to 1,3-diketones **26** and **27**.

Scheme V



formed by anti opening of the epoxide. The fluorohydrin can more readily attain the proper geometry to migrate over the "α-face", affording the cis product by concerted acyl migration with attendant loss of the fluoride ion with inversion at the migration terminus. The ratios of **8** to **9** observed with both BF_3·Et_2O catalyst in CH_2Cl_2 at 25 °C for 1 min (23:77) or $CuCl_2$·H_2O in refluxing toluene for 30 min (17:83) were comparable. Therefore, in both the bicyclic systems examined above, geometric constraints appear to preclude a simple concerted acyl migration.

At this point, we decided to investigate the substituent effects on 1,2-carbonyl migrations in several related bicyclic [4.4.0] structures such as the diastereomeric 1,2-epoxy-6-methylbicyclo[4.4.0]decan-3-ones (**23**, **24**). Epoxidation of the α,β-unsaturated ketone **22** with 30% hydrogen peroxide under basic conditions yielded a mixture of the α- and β-epoxides **23** and **24** in a 22:78 ratio (eq 5). No



(5)

attempts were made to separate these diastereomers, and all reactions were run with the above mixture. Treatment of the mixture of epoxides with boron trifluoride etherate under various conditions (Table II) yielded approximately a 1:1 ratio of the 1,2-diketone **25**, resulting from hydrogen migration, and the 1,3-diketone, arising from carbonyl migration. The *trans*-**26** to *cis*-**27** aldehyde ratio was typically about 1:9 (Scheme V). Although no fluorohydrin intermediates were detected in this reaction, by analogy to the examples above, the isolation of mainly the cis-aldehyde **27** probably results from the fluorohydrin. However, a concerted carbonyl migration resulting from the β-epoxide cannot be excluded. Formation of trans-aldehyde **26** (10%) presumably also arises from a fluorohydrin as noted above (Scheme I).

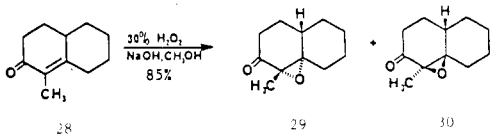
The next compounds that we included in our study were the 1,2-epoxy-2-methylbicyclo[4.4.0]decan-3-ones **29** and **30**, wherein we replaced the hydrogen on the double bond with a methyl group, which in principle has a higher migratory aptitude. Epoxidation of the α,β-unsaturated

Table III. Lewis Acid Catalyzed Carbonyl Migration in 1,2-Epoxy-2-methylbicyclo[4.4.0]decan-3-one

cat. (equiv)[a]	solvent	temp, °C	time	% yield
BF_3·Et_2O (0.5)	C_6H_6	78	1 min	86
BF_3·Et_2O (0.5)	CH_2Cl_2	35	10 min	83
BF_3·Et_2O (0.5)	CH_2Cl_2	25	1 h	78
BF_3·Et_2O (0.5)	C_6H_6	78	10 min	79

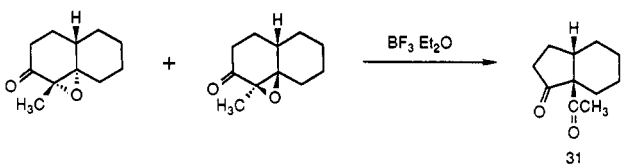
[a] Ratio of catalyst to epoxy ketone.

ketone **28** with 30% hydrogen peroxide under basic conditions yielded a mixture of α- and β-epoxides **29** and **30** in a 12:88 ratio, respectively (eq 6). We did not attempt



(6)

to separate these diastereomers, and all reactions were run with the above mixture. Treatment of the diastereomeric epoxides with boron trifluoride etherate under various conditions (Table III) yielded only *cis*-8-acetyl-1-hydrindanone (**31**, eq 7). Since we apparently formed exclu-



(7)

sively the cis-acetyl group from a mixture of β-epoxide (88%) and α-epoxide (12%), we can rationalize two conceivable routes. One is a concerted 1,2-carbonyl migration, but previous studies in this series suggested the intermediacy of a fluorohydrin. Therefore, if we assume a fluorohydrin intermediate, the fluorine atom must be on the β-face (retention) so that a 1,2-carbonyl migration occurring with inversion would generate the cis stereochemistry at the ring juncture. When the reaction was carried out on a large scale, approximately a 10% mixture of the fluorohydrin and the dienone corresponding to **11** were found, but none of the 1,2-diketone formed by a methyl migration was detected. An overall mechanism similar to the one we suggested previously for the bicyclic epoxides given in Scheme I is proposed.

In summary, we have developed a practical synthesis of both cis- and trans-fused perhydroindanones despite the fact that in some cases the isomeric keto aldehydes must be separated by column chromatography. It is also quite clear that in the β-epoxides derived from the bicyclo-[4.4.0]decanones, the carbonyl carbon experiences considerable difficulty in assuming the proper geometric alignment[8] for a concerted carbonyl migration and a mixture of products is to be expected. The corresponding series of α-epoxides, wherein the carbonyl carbon rotates away from the migration terminus upon oxirane cleavage and carbon–carbon bond rotation, typically involve a

double inversion process with the intermediacy of a fluorohydrin.

Experimental Section

β-1,2-Epoxybicyclo[4.4.0]decan-3-one (6). A solution of 30.0 g (0.2 mol) of a mixture of bicyclo[4.4.0]dec-1-en-3-one (**16**, 84%) and bicyclo[4.4.0]dec-1(6)-en-3-one (16%)[9] and 67.6 mL (0.6 mol) of 30% hydrogen peroxide in 300 mL of methanol was cooled to 0 °C. To this cooled solution was added 16.7 mL (0.1 mol) of 6 N NaOH dropwise over 15 min. The reaction mixture was allowed to come to room temperature and then stirred for 3 h. The reaction mixture was then extracted three times with ethyl ether (100 mL), and the combined organic extracts were washed with 5% sodium bicarbonate and saturated sodium chloride, dried ($MgSO_4$), and concentrated. The residue was distilled to give 17.0 g (67%) of the β-epoxide **6**: bp 67 °C (0.05 mm) (lit.[10] bp 74–76 °C (0.03 mm)); ^{13}C NMR ($CDCl_3$) 206.4, 67.5, 61.3, 35.7, 33.6, 32.9, 31.9, 30.0, 25.8, 25.3, 21.4 ppm; ^1H NMR ($CDCl_3$) δ 1.3–2.4 (m, 13 H), 3.04 (s, 1 H); IR (neat) 2936, 1860, 1710, 1450, 1254, 829 cm^{-1}.

Lewis Acid Catalyzed Rearrangement of β-1,2-Epoxybicyclo[4.4.0]decan-3-one (6). Boron Trifluoride Etherate (0.5 equiv) in Methylene Chloride. To 166 mg (1 mmol) of **6** in 10 mL of dry methylene chloride was added 61.5 μL of boron trifluoride etherate (freshly distilled). The reaction mixture was stirred for 5 min at room temperature and then washed with 5% sodium bicarbonate. The methylene chloride layer was then washed with saturated sodium chloride, dried ($MgSO_4$), and concentrated. The resulting oil was chromatographed on silica gel with hexane and ethyl acetate (9:1) to afford 100 mg (60%) of a mixture of 82% hydrindanones (62% cis (**9**), 38% trans (**7**)) and 18% 2-hydroxybicyclo[4.4.0]dec-1-en-3-one (**8**) (resulting from a 1,2-hydrogen shift). The ratio of products was determined by using NMR spectroscopy on a QE-300 NMR instrument. Physical data for *cis*-**9**: bp 56 °C (0.05 mm); ^{13}C NMR ($CDCl_3$) 214.5, 199.6, 65.6, 36.3, 35.8, 26.0, 24.5, 23.2, 21.8, 21.3 ppm; ^1H NMR ($CDCl_3$) δ 1.3–2.8 (m, 3 H), 9.5 (s, 1 H); IR (neat) 2931, 2858, 2712, 1746, 1711 cm^{-1}. Data for *trans*-**7**: bp 56 °C (0.05 mm); ^{13}C NMR ($CDCl_3$) 212.3, 199.9, 67.5, 47.1, 37.0, 28.3, 26.6, 25.9, 24.3, 22.1 ppm; ^1H NMR ($CDCl_3$) δ 1.2–2.6 (m, 3 H), 9.6 (d, 1 H); IR (neat) 2935, 2861, 2743, 1750, 1707 cm^{-1}. Data for 2-hydroxybicyclo-[4.4.0]dec-1-en-3-one (**8**): mp 87–88 °C (pentane); ^{13}C NMR ($CDCl_3$) 194.3, 141.9, 135.6, 36.5, 34.6, 34.6, 28.7, 26.1, 25.5, 25.1 ppm; ^1H NMR ($CDCl_3$) δ 1.1–2.1 (m, 9 H), 2.3–2.6 (m, 3 H), 3.0–3.2 (d, 1 H), 6.2 (s, 1 H); IR (neat) 3361, 2922, 2856, 1665, 1638, 1386, 1180 cm^{-1}; MS (70 eV) calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0995.

Boron Trifluoride Etherate (0.2 equiv) in Methylene Chloride. To 16.6 g (0.1 mol) of **6** in 1 L of dry methylene chloride was added 2.46 mL of boron trifluoride etherate (freshly distilled). The reaction mixture was stirred for 1 h at room temperature and then quenched with 5% sodium bicarbonate. The methylene chloride layer was washed with saturated sodium chloride, dried ($MgSO_4$), and concentrated. The resulting oil was distilled at 71 °C (0.1 mm) to afford 11.9 g (72%) of a mixture of 76% isomeric hydrindanones (55% cis (**9**), 45% trans (**7**)) and 24% 2-hydroxybicyclo[4.4.0]dec-1-en-3-one (**8**), which were separated on silica gel with hexane and ethyl acetate (9:1).

1-Fluoro-2-hydroxybicyclo[4.4.0]decan-3-one (10). The fluorohydrin **10** was isolated from the above large-scale rearrangement of the β-epoxide **6** with boron trifluoride etherate (~10%): bp 57–58 °C (0.05 mm); mp 92–95 °C (pentane); ^{13}C NMR ($CDCl_3$) 210.3, 75.3, 51.5, 51.2, 37.1, 35.8, 35.5, 34.4, 25.3, 24.3, 20.9 ppm; ^1H NMR ($CDCl_3$) δ 1.1–2.1 (m, 11 H), 2.2–2.3 (m, 1 H), 2.45–2.55 (m, 1 H), 2.75–2.90 (m, 1 H), 3.46 (s, 1 H), 4.1–4.13 (d, 1 H); IR (neat) 3480, 2940, 1716, 1085 cm^{-1}; MS (70 eV) calcd for $C_{10}H_{15}O_2F$ 186.1055, found 186.1050.

Bicyclo[4.4.0]deca-1,6-dien-3-one (11). The dienone **11** was isolated from the above rearrangement of the β-epoxide **6** with boron trifluoride etherate (~10%): ^{13}C NMR ($CDCl_3$) 198.7, 155.5, 131.6, 131.4, 122.8, 37.0, 30.5, 29.1, 25.5, 21.7 ppm: ^1H NMR ($CDCl_3$) δ 1.74–1.83 (m, 2 H), 2.24–2.32 (m, 2 H), 2.40–2.52 (q, 2 H), 2.60–2.68 (t, 2 H), 5.72 (s, 1 H), 6.05–6.12 (m, 1 H); IR (neat) 2940, 1663, 1636, 1590, 1259 cm^{-1}; MS (70 eV) calcd for $C_{10}H_{13}O$ 148.0888, found 148.0886.

Lewis Acid Catalyzed Reaction of 1-Fluoro-2-hydroxybicyclo[4.4.0]decan-3-one (10). Boron Trifluoride Etherate (0.2 equiv) in Refluxing Methylene Chloride. To 47 mg of the fluorohydrin **10** in 2.5 mL of dry methylene chloride was added 6.15 μL of boron trifluoride etherate (freshly distilled). The reaction mixture was stirred for 30 min at 35 °C and then quenched with 5% sodium bicarbonate. The methylene chloride layer was washed with saturated sodium chloride, dried ($MgSO_4$), and concentrated to afford 37 mg (89%) of a product mixture. The mixture contained 4% of *trans*-hydrindanone **7**, 37% of the dienone **11**, and 59% of the unreacted fluorohydrin **10**. The ratios were determined by GC on a 4 ft × $^1/_4$ in. 10% UCW on Chromosorb W column at 180 °C. The stereochemistry of the *trans*-hydrindanone was determined by ^1H NMR (δ 9.6).

3-Hydroxybicyclo[4.4.0]dec-1-ene (17). The α,β-unsaturated ketone **16** (20.0 g, 0.13 mol) in 100 mL of ethyl ether (anhydrous) was added to a stirred solution of 1.7 g (0.044 mol) of lithium aluminum hydride in 500 mL of ethyl ether. After the addition was complete, the reaction mixture was stirred for 30 min at −10 °C. The reaction mixture was hydrolyzed by adding successively 20 mL of water, 20 mL of 15% sodium hydroxide, and another 100 mL of water. The reaction mixture was then filtered, and the ether layer was removed and washed with a saturated sodium chloride solution, dried ($MgSO_4$), and concentrated. The resulting oil was distilled to afford 55.8 g (73%) of **17**, the major product being the β-alcohol (80%): bp 71 °C (0.3 mm); ^{13}C NMR ($CDCl_3$) 143.6, 123.4, 67.0, 37.3, 35.1, 35.0, 31.4, 27.7, 26.7 ppm; ^1H NMR ($CDCl_3$) δ 0.9–2.3 (m, 14 H), 4.3–4.1 (m, 1 H), 5.4 (s, 1 H); IR (neat) 3336, 2925, 2853, 1664, 1448, 1038 cm^{-1}.

3-Acetoxybicyclo[4.4.0]dec-1-ene (18). A solution of 52.0 g (0.34 mol) of a mixture of α- and β-alcohols **17** (1:4), 156 mL (1.65 mol) of freshly distilled acetic anhydride, and 667 mL (0.98 mol) of pyridine was stirred for 12 h. The reaction mixture was poured into cold water and extracted several times with ether. The combined ether layers were washed with saturated sodium chloride, dried ($MgSO_4$), and concentrated. To remove the last traces of pyridine, the resulting oil was chromatographed on silica gel with ether to afford 63.1 g (99%) of **18**: ^{13}C NMR ($CDCl_3$) of β-acetoxy, 170.7, 146.0, 118.7, 69.9, 37.0, 35.2, 34.8, 27.7, 27.1, 27.0, 26.1, 21.2 ppm; ^1H NMR ($CDCl_3$) δ 1.0–2.3 (m, 14 H), 2.1 (s, 3 H), 5.3–5.5 (d, 1 H); IR (neat) 2929, 2856, 1735, 1666, 1241, 1022 cm^{-1}.

1,2-Epoxy-3-acetoxybicyclo[4.4.0]decane (19). To a solution of 60.0 g (0.31 mol) of the allyl acetates **18** in 400 mL of chloroform was added 73.5 g (0.34 mol) of 3-chloroperoxybenzoic acid in 200 mL of chloroform. The reaction mixture was stirred for 12 h, and then an additional 300 mL of chloroform was added. The *m*-chlorobenzoic acid was removed by filtration, and any additional acid was removed by chilling the chloroform and filtering. Removal of the chloroform yielded 65.1 g (100%) of **19**: ^1H NMR ($CDCl_3$) δ 1.2–2.2 (m, 13 H), 2.1 (s, 3 H), 2.9 (d, 1 H), 4.8–5.3 (m, 1 H); IR (neat) 2934, 2860, 1735, 1247 cm^{-1}.

1,2-Epoxybicyclo[4.4.0]decan-3-ol (20). To a solution of 850 mL of 2% KOH in methanol was added 62.0 g (0.30 mol) of **19**. The reaction mixture was refluxed for 15 min, cooled, and then poured into water and extracted with 250 mL of ether (3×). The combined ether extracts were washed with water and saturated sodium chloride, dried ($MgSO_4$), and concentrated to afford 30.8 g (62%) of **20**: ^{13}C NMR ($CDCl_3$) of β-alcohol, 66.5, 64.3, 63.4, 38.2, 33.7, 31.2, 30.7, 25.9, 23.8, 23.0 ppm; ^1H NMR ($CDCl_3$) δ 1.0–2.0 (m, 14 H), 2.9 (d, 1 H), 3.9–4.0 (m, 1 H); IR (neat) 3422, 2933, 2858, 1449, 1017 cm^{-1}.

α-1,2-Epoxybicyclo[4.4.0]decan-3-one (21). To a solution of 92.1 g (0.36 mol) of dipyridine–chromium(VI) oxide in 800 mL of methylene chloride at 25 °C was added 10.0 g (0.06 mol) of **20** in 25 mL of methylene chloride. The reaction mixture was stirred for 1 h and then washed with 10% hydrogen chloride and saturated sodium chloride, dried ($MgSO_4$), and concentrated to afford 9.2 g (93%) of the crude product. Distillation afforded 7.2 g (78%) of **21** with a small amount of the β-epoxide. Recrystallization of the distilled product from pentane yielded the α-epoxide **21** free from the β-epoxide **6**: bp 71 °C (0.3 mm) (lit.[10] bp 51–53 °C (0.2 mm)); mp 52.5–54 °C (pentane); ^{13}C NMR ($CDCl_3$) 206.0, 64.7,

(9) Augustine, R. L.; Caputo, J. A. *Organic Syntheses*; Wiley: New York; Collect. Vol. V, p 869.
(10) DeBoer, A.; Ellwanger, R. E. *J. Org. Chem.* **1974**, *39*, 77.

61.6, 36.4, 35.8, 33.1, 31.1, 25.4, 23.7, 23.4 ppm; ^{1}H NMR ($CDCl_3$) δ 1.25–2.20 (m, 12 H), 2.35–2.50 (dd, 1 H), 2.98 (s, 1 H); IR (melt) 2942, 2860, 1712, 1451, 1260 cm^{-1}.

Lewis Acid Catalyzed Reaction of α-1,2-Epoxybicyclo[4.4.0]decan-3-one (21). To 166 mg (1 mmol) of **21** in 10 mL of dry methylene chloride was added 61.5 μL of boron trifluoride etherate. The reaction mixture was stirred for 1 min at room temperature and then quenched with 5% sodium bicarbonate. The methylene chloride layer was then washed with saturated sodium chloride, dried ($MgSO_4$), and concentrated. The resulting oil was chromtographed on silica gel with hexane and ethyl acetate (9:1) to afford 100 mg (61%) of a mixture of 77% *cis*-hydrindanone **9** and 23% 2-hydroxybicyclo[4.4.0]dec-1-en-3-one (**8**). The ratio of products was determined by using NMR spectroscopy techniques on a QE-300 NMR instrument.

Preparation of the Dithioacetal 13 from *trans*-Hydrindanone 7. Via the above procedure, to a solution of 500 mg (3.0 mmol) of **7** in 5 mL of ethyl ether was added 505 μL (6.0 mmol) of ethanedithiol and 184 μL (1.5 mmol) of boron trifluoride etherate. The resulting oil was chromatographed on silica gel with hexane–ethyl acetate (9:1) to afford 505 mg (70%) of **13**: ^{13}C NMR ($CDCl_3$) 217.8, 52.7, 51.2, 48.8, 39.1, 35.9, 35.0, 25.8, 25.2, 25.0, 21.4 ppm; ^{1}H NMR ($CDCl_3$) δ 1.2–2.6 (m, 11 H), 2.9–3.0 (m, 1 H), 3.1–3.25 (m, 3 H), 4.94 (s, 1 H); IR (neat) 2927, 2865, 1737 cm^{-1}.

Preparation of Dithioacetal 12 from *cis*-Hydrindanone 9. To a solution of 500 mg (3.0 mmol) of **9** in 5 mL of ethyl ether was added dropwise 505 μL (6.0 mmol) of ethanedithiol and 184 μL (1.5 mmol) of boron trifluoride etherate. The reaction mixture was then poured into water and extracted with methylene chloride. The organic layers were combined, washed with 10% sodium hydroxide and saturated sodium chloride, dried ($MgSO_4$), and concentrated. The resulting oil was chromatographed on silica gel with hexane–ethyl acetate (9:1) to afford 555 mg (76%) of **12**: ^{13}C NMR ($CDCl_3$) 218.9, 57.3, 55.5, 40.5, 39.3, 38.7, 36.4, 27.1, 26.8, 23.4, 21.7 ppm; ^{1}H NMR ($CDCl_3$) δ 1.25–1.60 (m, 6 H), 1.7–1.9 (m, 4 H), 1.95–2.05 (m, 1 H), 2.2–2.45 (m, 3 H), 3.1–3.34 (m, 4 H), 4.9 (s, 1 H); IR (neat) 2926, 2858, 1736 cm^{-1}; MS (70 eV) calcd for $C_{12}H_{18}OS_2$ 242.0798, found, 242.0796.

***trans*-8-Methyl-1-hydrindanone (14).** To 353 mg (1.5 mmol) of the dithioacetal **13** in 15 mL of methanol was added 2.5 g of Raney nickel (W-2). The reaction mixture was stirred under a mild reflux for 1 h and then poured into water. The aqueous layer was extracted with methylene chloride, and the combined organic layers were washed with 10% hydrogen chloride, water, and saturated sodium chloride, dried ($MgSO_4$), and concentrated. The resulting oil was purified by gas chromatography using a 6 ft × $^1/_4$ in. aluminum column with 10% Epon 1001 on Chromosorb W NAW at 150 °C, affording 116 mg (51%) of **14**: ^{13}C NMR ($CDCl_3$) 221.4, 47.6, 45.8, 35.4, 32.0, 26.3, 25.6, 24.3, 21.0, 12.7 ppm; ^{1}H NMR ($CDCl_3$) δ 1.0–2.5 (m, 13 H), 0.87 (s, 3 H); IR (neat) 2931, 2859, 1741 cm^{-1}; MS (70 eV) calcd for $C_{10}H_{16}O$ 152.1201, found 152.1203. The trans isomer was uncomtaminated with the cis isomer, as evidenced by the absence of the methyl resonance at δ 1.04.[3,4]

***cis*-8-Methyl-1-hydrindanone (15).** Via the above procedure, to 513 mg (2.2 mmol) of the dithioacetal **12** in 15 mL of methanol was added 3.7 g of Raney nickel (W-2). The resulting oil was purified by gas chromatography, affording 217 mg (65%) of **15**: mp 29–30 °C; ^{13}C NMR ($CDCl_3$) 222.2, 48.1, 42.5, 34.8, 29.4, 26.7, 22.9, 22.3, 22.1, 21.2 ppm; ^{1}H NMR ($CDCl_3$) δ 1.1–2.4 (m, 13 H), 1.04 (s, 3 H); IR (neat) 2929, 2859, 1737 cm^{-1}; MS (70 eV) calcd for $C_{10}H_{16}O$ 152.1201, found 152.1200.

1,2-Epoxy-6-methylbicyclo[4.4.0]decan-3-one (23 and 24). Via a modification of the procedure of Edward and Ferland,[12] 20.0 g (0.12 mol) of 6-methylbicyclo[4.4.0]dec-1-en-3-one[11] and 41 mL (0.36 mol) of 30% hydrogen peroxide in 100 mL of methanol was cooled to 0 °C. To this cooled solution was added 20 mL (0.12 mol) of 6 N NaOH dropwise over 15 min. The reaction mixture was allowed to come to room temperature and then stirred for 3 h. The reaction mixture was then extracted with 100 mL of benzene (3×), and the combined organic extracts were washed with 5% sodium bicarbonate and saturated sodium chloride, dried ($MgSO_4$), and concentrated. The residue was distilled to give 10.1 g (48%) of a mixture of *cis* (**24**) and *trans* (**23**) isomers in a 78:22 ratio: bp 70–74 °C (0.2 mm) (lit.[12] bp 96–98 °C (0.7 mm)); ^{13}C NMR ($CDCl_3$) 207.2 (trans), 206.6 (cis), 69.2, 62.9, 62.3, 37.7, 34.9, 34.3, 34.1, 33.3, 33.1, 31.6, 31.2, 30.3, 29.9, 26.0, 24.0, 22.3, 21.4, 21.2, 20.3 ppm; ^{1}H NMR ($CDCl_3$) 3.07 (s, 1 H, trans), 2.99 (s, 1 H, cis), 2.26–1.02 (m, 12 H), 1.13 (s, 3 H); IR (neat) 1709 cm^{-1}.

Lewis Acid Catalyzed Rearrangement of 1,2-Epoxy-6-methylbicyclo[4.4.0]decan-3-one (23 and 24). Boron Trifluoride (0.5 equiv) in Methylene Chloride. Via the above procedure, to 180 mg (1 mmol) of **23** and **24** in 10 mL of dry methylene chloride at 35 °C was added 61.5 μL of boron trifluoride etherate. The reaction mixture was stirred for 30 min, and after workup, the methylene chloride layer was then extracted with saturated sodium chloride, dried ($MgSO_4$), and concentrated. The resulting oil was chromatographed on a silica gel column with hexane and ethyl acetate (9:1) to afford 165 mg (92%) of a mixture of 53% methylhydrindanones (90% cis (**27**), 10% trans (**26**)) and 47% 2-hydroxy-6-methylbicyclo[4.4.0]decan-3-one (**25**).

Spectral data for the methylhydrindanones **26** and **27**: ^{1}H NMR ($CDCl_3$) δ 9.72 (s, trans, CHO), 9.54 (s, cis, CHO), 5.95 (s, cis OH), 5.94 (s, cis, alkene H); IR (neat) 3436, 1752, 1707, 1671, 1636 cm^{-1}.

Spectral data for 2-hydroxy-6-methylbicyclo[4.4.0]decan-3-one (**25**): ^{13}C NMR ($CDCl_3$) 195.1, 142.5, 139.9, 43.3, 38.5, 35.6, 33.1, 27.3, 24.3, 23.1, 22.6 ppm; ^{1}H NMR ($CDCl_3$) δ 6.11 (s, 1 H), 2.98–1.34 (m, 12 H), 1.22 (s, 3 H); IR (neat) 3402, 1667, 1380 cm^{-1}.

Treatment of **23** and **24** at 25 °C with 0.5 equiv of boron trifluoride etherate for 1 h using the above procedure resulted in recovery of 144 mg (80%) of a mixture of 62% methylhydrindanones (87% cis (**27**), 13% trans (**26**)) and 38% 2-hydroxy-6-methylbicyclo[4.4.0]decan-3-one (**25**).

1,2-Epoxy-2-methylbicyclo[4.4.0]decan-3-one (29 and 30). Via a modification of the procedure of Kretchmer and Frazee,[13] 7.0 g (0.043 mol) of 2-methylbicyclo[4.4.0]dec-1-en-3-one[14] and 14.5 mL (0.128 mol) of 30% hydrogen peroxide in 100 mL of methanol was cooled to 0 °C. To this cooled solution was added 3.6 mL (0.021 mol) of 6 N NaOH dropwise over 15 min. The reaction mixture was allowed to come to room temperature and stirred for 1 h. The reaction mixture was then extracted three times with ethyl ether (100 mL), and the combined organic extracts were washed with 5% sodium bicarbonate and saturated sodium chloride, dried ($MgSO_4$), and concentrated. The residue was distilled to give 6.6 g (85%) of **30** and **29** as a mixture of epimers in an 88:12 ratio of the β- and α-epoxides, respectively, in agreement with the literature:[13] bp 72–73 °C (0.30 mm) (lit.[13] bp 71.5–73.0 °C (0.30 mm)); ^{13}C NMR ($CDCl_3$) of β-epoxide, 206.8, 70.7, 64.0, 37.0, 32.5, 31.0, 30.7, 25.7, 25.6, 21.8, 11.3 ppm; ^{13}C NMR ($CDCl_3$) of α-epoxide, 206.4, 67.5, 63.8, 36.5, 36.3, 31.5, 29.6, 25.0, 23.8, 21.9, 11.1 ppm; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 3 H, β), 1.38 (s, 3 H, α), all other hydrogens fall between 2.1 and 2.5 (m, 26 H); IR (neat) 2935, 2860, 1706, 1449, 833 cm^{-1}.

Lewis Acid Catalyzed Rearrangement of 1,2-Epoxy-2-methylbicyclo[4.4.0]decan-2-one (29 and 30). Boron Trifluoride Etherate (0.5 equiv) in Refluxing Benzene. To 180 mg (1 mmol) of **30** and **29** in 10 mL of dry benzene at 80 °C was added 61.5 μL of boron trifluoride etherate. The reaction mixture was stirred for 1 min and then washed with 5% sodium bicarbonate. The benzene layer was then washed with saturated sodium chloride, dried ($MgSO_4$), and concentrated. The resulting oil was chromatographed on a silica gel column with hexane and ethyl acetate (5:1) to afford 149 mg (83%) of exclusively *cis*-8-acetylhydrindanone (**31**): ^{13}C NMR ($CDCl_3$) 215.3, 205.4, 68.0, 37.2, 36.1, 27.1, 26.5, 26.2, 23.5, 22.7, 21.8 ppm; ^{1}H NMR ($CDCl_3$) δ 1.25–1.45 (m, 4 H), 1.45–1.60 (m, 2 H), 1.65–1.85 (m, 3 H), 1.85–2.00 (m, 2 H), 2.19 (s, 3 H), 2.20–2.47 (m, 2 H), 2.78–2.89 (m, 1 H); IR (neat) 2935, 2860, 1738, 1702, 1450, 1358, 1157 cm^{-1}.

Treatment of 1.8 g (0.01 mol) of a mixture of **29** and **30** using the above conditions yielded after purification 1.32 g (73%) of **31**: MS (70 eV) calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1146.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by

(11) Heathcock, C. H.; Ellis, J. E.; McMurry, J. E.; Coppolino, A. *Tetrahedron Lett.* **1971**, 4995.
(12) Edward, J. T.; Ferland, J. M. *Can. J. Chem.* **1966**, *44*, 1317.
(13) Kretchmer, R. A.; Frazee, W. J. *J. Org. Chem.* **1971**, *36*, 2855.
(14) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

the American Chemical Society, for the support of this research.

Registry No. **6**, 42393-90-8; **7**, 105598-05-8; **8**, 90925-90-9; **9**, 105598-06-9; **10**, 105598-07-0; **11**, 1075-10-1; **12**, 105598-08-1; **13**, 105598-09-2; **14**, 17428-83-0; **15**, 13025-91-7; **16**, 1196-55-0; *cis*-**17**, 30983-79-0; *trans*-**17**, 2763-42-0; *cis*-**18**, 105598-10-5; *trans*-**18**, 105598-04-7; **19**, 105598-11-6; **20**, 105661-54-9; **21**, 105661-55-0; **22**, 826-56-2; **23**, 22241-35-6; **24**, 22241-36-7; **25**, 6432-30-0; **26**, 105598-12-7; **27**, 105598-13-8; **28**, 5164-37-4; **29**, 30538-57-9; **30**, 30538-58-0; **31**, 105661-56-1; $HSCH_2CH_2SH$, 540-63-6; bicyclo[4.4.0]dec-1(6)-en-3-one, 13837-12-2.

Rapid Access to a Series of Highly Functionalized α,β-Unsaturated Cyclopentenones. A Caveat on Aminospirocyclization[1]

P. C. Conrad, P. L. Kwiatkowski, and Philip L. Fuchs*

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

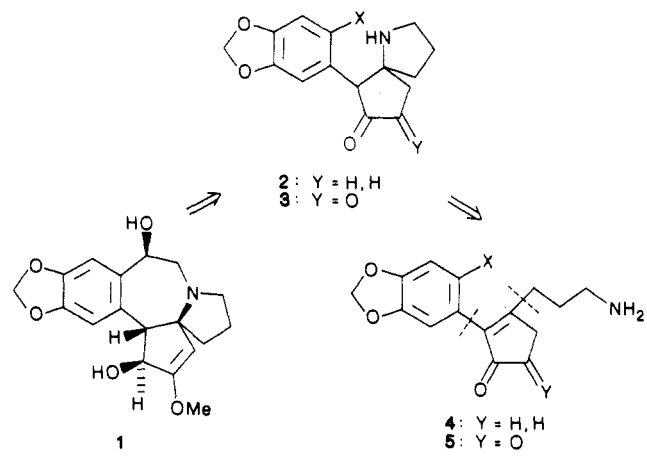
Received June 16, 1986

Conjugate addition of a series of functionalized aryllithium reagents to cyclopentenyl sulfones **9** and **17** results in α-sulfonyl anion intermediates that are further alkylated to afford triply converged adducts **12a–c** and **19**. Refunctionalization of these adducts provides α,β-unsaturated cyclopentenones **4a–c** and **21** in high overall yields. Attempted intramolecular Michael addition of these (γ-aminopropyl)cyclopentenones to produce the spiro [4.4] ring system was unsuccessful.

Several years ago we initiated a program directed toward the total synthesis of 11-hydroxycephalotaxine (**1**),[2] an alkaloid of the pharmacologically important harringtonine family.[3,4] The synthetic strategy adopted was envisaged to involve spirocyclization[5] of amino derivatives **4** and **5** (Scheme I).

Synthesis of the basic cyclopentenone system was smoothly accomplished in greater than 50% overall yield on the basis of our triply convergent (see dashed lines on structures **4** and **5**) cycloalkenone synthesis.[6] Preparation of the requisite aryllithium reagents **8a–c** was accomplished as follows: Treatment of 6-bromopiperonal (**6**) with methylenetriphenylphosphorane under phase-transfer conditions[7] afforded an 86% yield of bromostyrene **7b**. Conversion of **7b** to acetonide **7c**[8] involved catalytic osmylation[9] followed by treatment of the diol with 2,2-dimethoxypropane. Acetal **7a**[8] was synthesized from bromopiperonal (**6**). Reaction of **7a–c** with *tert*-butyllithium[10] afforded **8a–c**[8] in near quantitative yield as assayed by deuterium quenching studies.

Scheme I



Treatment of vinyl sulfone **9**[11] with aryllithium reagents **8a–c** afforded α-sulfonyl anion intermediates **10a–c**, which were subsequently treated with iodide **11** in the same reaction vessel. The resulting intermediates were selectively cleaved at the primary isopropyldimethylsilyl (IPDMS) ether moiety by brief treatment with tetrabutylammonium fluoride (TBAF)[12] to afford adducts **12a–c**[8] in the indicated overall yields. The polarity change resulting from silyl ether cleavage makes purification of the triply converged adducts **12a–c** particularly efficacious since small amounts of residual vinyl sulfone **9**, quenched organometallic, and nonalkylated intermediates **10a–c** are easily removed by simple filtration through silica gel. Adducts **12a–c** were converted to enones **13a–c**[8] by sequential mesylation,[13] azide displacement, *tert*-butyldimethylsilyl ether (TBDMS) cleavage,[14] and Swern oxidation[15] followed by a diazabicycloundecene (DBU) workup to effect β-elimination of the resulting β-sulfonyl ketone intermediates.[6]

(1) Syntheses Via Vinyl Sulfones. 18. Part 17: Palmer, J. T.; Learn, K. S.; Fuchs, P. L. *Synth. Commun.* **1986**, *16*, 1315.
(2) Powell, R. G.; Madrigal, R. V.; Smith, C. R., Jr.; Mikolajczak, K. L. *J. Org. Chem.* **1974**, *39*, 676.
(3) While 11-hydroxycephalotaxine has yet to be synthesized, the parent alkaloid has been prepared by three groups: (a) For a review see: Weinreb, S. M.; Semmelhack, M. F. *Acc. Chem. Res.* **1974**, *8*, 158. (b) Yasuda, S.; Yamada, T.; Hanaoka, M. *Tetrahedron Lett.* **1986**, *27*, 2023.
(4) For a leading reference to clinical antileukemia studies with harringtonine derivatives see: Warrell, R. P., Jr.; Coonley, C. J.; Gee, T. S. *J. Clin. Oncol.* **1985**, *3*, 617. Ohnuma, T.; Holland, J. F. *J. Clin. Oncol.* **1985**, *3*, 604.
(5) The general strategy of aminospirocyclization has been highly successful with enones devoid of α-aryl substituents. See: (a) Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y. *Synthesis* **1975**, 590. (b) Fukuyama, T.; Dunkerton, L. V.; Aratani, M.; Kishi, Y. *J. Org. Chem.* **1975**, *40*, 2011. (c) Bryson, T. A.; Wilson, C. A. *Synth. Commun.* **1976**, *6*, 521. (d) Godleski, S. A.; Heacock, D. J. *J. Org. Chem.* **1982**, *47*, 4820.
(6) Conrad, P. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1978**, *100*, 346.
(7) Tagaki, W.; Inone, I.; Yano, Y.; Okonogi, T. *Tetrahedron Lett.* **1974**, 2587.
(8) The synthesis of intermediates in the **a** and **c** series is highly analogous to that reported in this paper for the **b** compounds. Detailed experimental conditions and spectral data can be found in: Conrad, P. C. Ph.D. Thesis Purdue University, 1980.
(9) Sharpless, K. B.; Akashi, K.; Palermo, R. E. *J. Org. Chem.* **1978**, *43*, 2063.
(10) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210. Newmann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785. Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847.
(11) Barton, D. L.; Conrad, P. C.; Fuchs, P. L. *Tetrahedron Lett.* **1980**, *21*, 1811.
(12) Corey, E. J.; Varma, R. K. *J. Am. Chem. Soc.* **1971**, *93*, 7319.
(13) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.
(14) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(15) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329. Omura, K.; Sharma, A. K.; Swern, D. *Ibid.* **1976**, *41*, 957.

0022-3263/87/1952-0586$01.50/0