mass spectrum, calcd for $C_{22}H_{30}O_4$ m/e 358.215, found m/e 358.215.

11-*cis*,13-*cis*-12-Carboxyretinol (13). To a cold (0 °C) slurry of 228 mg (6.0 mmol) of $LiAlH_4$ in 18 mL of THF was slowly added a solution of 260 mg (0.75 mmol) of methyl 11-*cis*,13-*cis*-12-carboxyretinoate (12) in 2 mL of THF. After being stirred for 0.5 h, the reaction mixture was quenched with a saturated solution of NH_4Cl, diluted with H_2O, and extracted with Et_2O. The organic phase was washed with H_2O and brine and dried (Na_2SO_4). The crude mixture (222 mg) was eluted on a medium-pressure silica gel column (Merck, size B) by using 0.25% MeOH and 33% Et_2O in hexanes to give a retinoid diol (80 mg). Continued elution of the column gave 11-*cis*,13-*cis*-12-carboxyretinol (13): 71 mg (29%); IR (KBr) 1725 cm^{-1}; UV (MeOH) λ_{max} 327 nm (ϵ 26 800); mass spectrum, calcd for $C_{21}H_{30}O_3$ m/e 330.219, found m/e 330.219.

11-*cis*,13-*cis*-12-Carboxyretinol δ-Lactone (4). To a cold (−15 °C) slurry of 118 mg (3.12 mmol) of $LiAlH_4$ in 50 mL of THF was slowly added a solution of 560 mg (1.56 mmol) of methyl 11-*cis*,13-*cis*-12-carboxyretinoate (12) in 10 mL of THF. After being stirred for 5 min, the reaction mixture was quenched with a saturated solution of NH_4Cl, diluted with H_2O, and extracted with Et_2O. The organic phase was washed with H_2O and brine and dried (Na_2SO_4). The crude hydroxy acid 13 (490 mg) was refluxed in 25 mL of cyclohexane by using a Dean–Stark water separator for 6 h, and the solvent was then removed in vacuo. The product was purified by elution on a medium-pressure silica gel column (Merck, size B) by using 40% Et_2O in hexanes to yield 185 mg (38%) of a gum whose spectra showed it to be 11-*cis*,13-*cis*-12-carboxyretinol δ lactone (4): IR (KBr) 1710 cm^{-1}; UV (MeOH) λ_{max} 365 nm (ϵ 20 530); mass spectrum, calcd for $C_{21}H_{28}O_2$ m/e 312.209, found m/e 312.209.

Reaction of 13-*cis*-12-Carboxyretinoic Anhydride (7) with Methanolic Potassium Hydroxide. To a 1-mL Reacti-Vial containing 1 mg (0.003 mmol) of 13-*cis*-12-carboxyretinoic anhydride (7) were added 100 μL of MeOH and 3 μL (0.003 mmol) of KOH/MeOH. The reaction was monitored by HPLC. After 0.5 h, the major product was 13-*cis*-12-carbomethoxyretinoic acid (8), accompanied by trace amounts of methyl 13-*cis*-12-carboxyretinoate (9). Heating of the isolated product mixture for 2 h gave mainly 11-*cis*,13-*cis*-12-carbomethoxyretinoic acid (11) with minor amounts of 8 and 9. The identical mixture was obtained by heating the reaction mixture (without isolation) for 2 h. Identical results were obtained by using NaOH. None of the isomeric methyl 11-*cis*,13-*cis*-12-carboxyretinoic acid (12) was detected in any stage, although it would have been detectable by HPLC had it been present.

HPLC Analysis. The best separations were achieved by using Radial Pak cartridges, although stainless steel columns gave similar results. The half-esters were analyzed by using Radial Pak A with 60% CH_3CN/40% H_2O/0.25% NH_4OAc (2 mL/min) as the eluant; detection was at 350 nm. The lactones were analyzed on Radial Pak B with 2 mL/min of 1:9 Et_2O/hexane; detection was at 350 nm. The retention data are shown in Table III. The solvents were from Burdick and Jackson, and they were degassed prior to use.

Acknowledgment. We are indebted to Ms. Patricia Laidlow for her preparation of pure 13-*cis*-12-carboxyretinol δ-lactone. This work was supported in part by National Cancer Institute Contract No. N01-CP-75932.

Registry No. 1, 83803-32-1; 2, 83803-33-2; 3, 83860-24-6; 4, 83860-25-7; 5, 81176-73-0; 7, 83860-26-8; 8, 83803-34-3; 9, 83803-35-4; 11, 83860-27-9; 12, 83860-28-0; 13, 83803-36-5.

Codeine Analogues. Synthesis of 4a-Aryldecahydroisoquinolines Containing Nitrogen Ring Functionality and of Octahydro-1*H*-indeno[1,2,3-*ef*]isoquinolines. A Total Synthesis of Codeine

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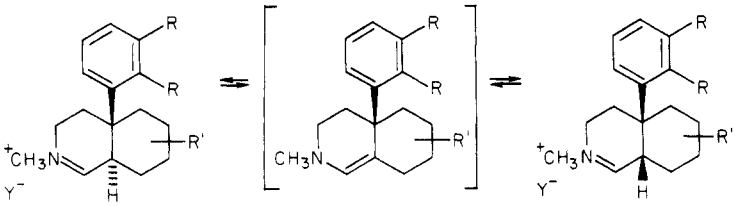
In an extension of earlier work in the benzomorphan series to the C-ring-functionalized 4a-aryldecahydroisoquinolines, the nitrogen ring was activated by partial reduction of an amide to give an enamine, and the enamine and its cis and trans iminium salts were treated with nucleophiles. Introduction of C-1 substituents as prescribed in the benzomorphan series, including the cyano, acetimino, acetyl, and aminomethyl moieties, followed by attempted B-ring closure led instead to ring closure at C-6. Closure of the B ring requires substituents at C-1 to have the β configuration. Preparation of the compounds described above afforded the more stable α isomers, and alternative cyclization at C-6 generally proved more facile than epimerization at C-1. Closure of the B ring was attained via the C-1 β-carboxaldehyde, leading to an intermediate which has been converted to codeine. Thus we report a formal total synthesis of codeine and the first synthesis of 6,6′-bridged 4a-aryldecahydroisoquinolines. The latter compounds, octahydro-1*H*-indeno[1,2,3-*ef*]isoquinolines, represent a novel class of structural analogues of codeine.

Previous reports from this laboratory have described the elaboration of β-aryl α-methylene lactams (1) to C-ring-functionalized 4a-aryldecahydroisoquinolines (4),[1,2] analogues of codeine containing the A, C, and N (nitrogen) rings (Scheme I). Extension of work in the phenyl and *m*-methoxyphenyl series to the 2,3-dimethoxyphenyl series has recently allowed preparation of 5,2′-oxygen-bridged[3] and 6,2′-oxygen-bridged 4a-aryldecahydroisoquinolines,[4] the octahydro-1*H*-benzofuro[3,2-*e*]isoquinolines (3), and the octahydro-1*H*-[1]benzopyrano[4,3,2-*ef*]isoquinolines (5). We now extend to the 4a-aryldecahydroisoquinolines our benzomorphan (2) work[5] involving nitrogen ring

(1) Weller, D. D.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 6650.
(2) Weller, D. D.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1977**, *42*, 1485.
(3) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 5064.
(4) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 1831.
(5) Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 1324.

0022-3263/83/1948-0227$01.50/0

Table I. Iminium Salt Equilibration Studies



trans cis

compd		R	Y	solvent	temp, °C	trans/cis ratio: kinetic	trans/cis ratio: thermodynamic	$t_{1/2}$ (trans)
55[a]		H	AcO	CH_3OH	25			⩽5 min
		H	Cl	CH_3OH	25			2 h
		H	Cl	CH_2Cl_2	25		3/97	48 h
		H	ClO_4	CH_3OH	25		16	16 h
		H	ClO_4	$(C_2H_5)_2O$		⩾95/5		
		H	ClO_4	CH_3CH_2OH			⩽5/95	
35		CH_3O	ClO_4	$CHCl_3$	21		4/96	⩽1 min
		CH_3O	MsO	$CHCl_3$	21		14/86	8.9 min
		CH_3O	MsO	$CHCl_3$	⩽0	90/10	no equilibration	
		CH_3O	TfO	$CHCl_3$	21	83/17	slow equilibration[b,c]	
36		CH_3O	MsO	$CHCl_3$	⩽0	100/0	no equilibration	
		CH_3O	MsO	$CHCl_3$	37		⩽13/87	
56		CH_3O	MsO	$CHCl_3$	20		16/84	⩽5 min
37[a]		CH_3O	ClO_4	CH_3OH	50		5/95	

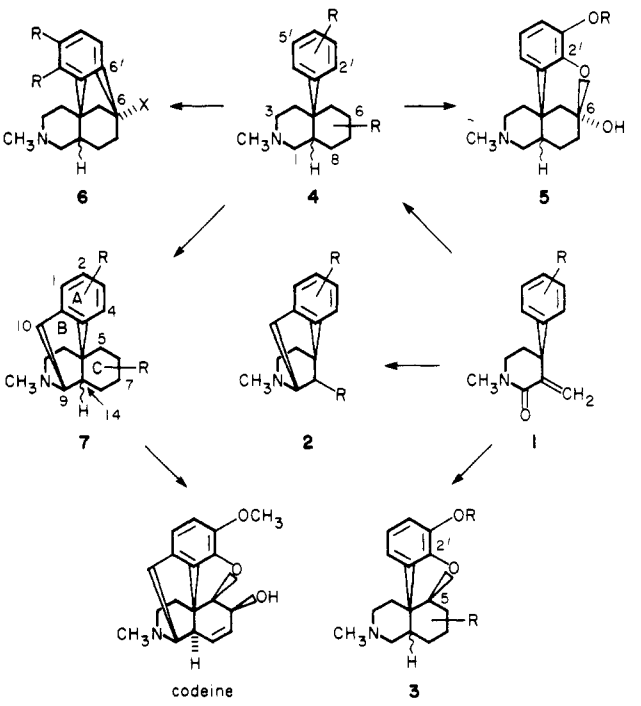
[a] See ref 9. [b] Ratio of 81/19 after 71 h. [c] Accompanied by some decomposition.

functionalization. Direct extrapolation of the benzomorphan work to this series leads exclusively to 6,6′-bridged 4a-aryldecahydroisoquinolines, the octahydro-1*H*-indeno-[1,2,3-*ef*]isoquinolines (**6**, Scheme II), while elaboration via aziridinium ions ultimately allows B-ring closure to the morphinan ring system (**7**, Scheme III).

The total synthesis of dihydrothebainone (**43t**) has elicited considerable interest since the initial reports[6,7] that it could be converted to codeine, and we projected that the methods developed in our benzomorphan work for functionalizing the nitrogen ring and closing the B ring would provide a convenient synthesis of dihydrothebainone when extended to the 4a-(2,3-dimethoxyphenyl)decahydroisoquinolines. Functionalization of the nitrogen ring by our methods requires amide activation, and this can be accomplished in many ways, but clearly the most versatile intermediates are enamines and iminium salts. Initial studies were thus directed to partial reduction and elaboration of the amide functionality with concomitant stereochemical control of the **4a/8a** ring juncture.[8]

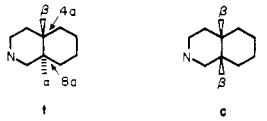
Ring Juncture Stereochemistry. Reduction of amido ketal **46t**[4] with Dibal produces enamine 8 in 90% yield, and the availability of this enamine has allowed a thorough study of its chemistry (Scheme II). It was originally shown

Scheme I



in a related phenyl series[9a] (see Table I) that enamine protonation gives the trans iminium salt as the kinetic product, with the equilibrium product being the cis imi-

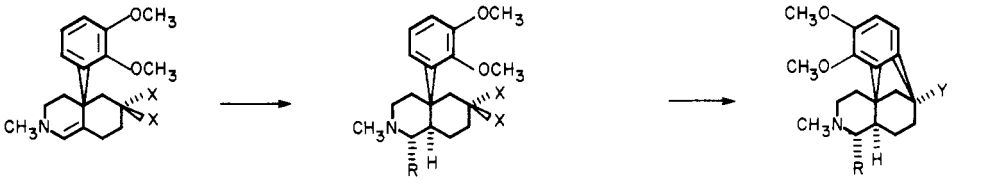
(6) Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1956**, *78*, 1380.
(7) Weller, D. D.; Rapoport, H. *J. Med. Chem.* **1976**, *19*, 1171.
(8) We will refer to the isoquinoline ring juncture in all systems as cis (c) or trans (t) with respect to the **4a/8a** substituents.



t c

(9) (a) Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 5955. (b) Evans, D. A.; Mitch, C. H. *Tetrahedron Lett.* **1982**, *23*, 285.

Scheme II. Preparation of 6,6'-Bridged 4a-Aryldecahydroisoquinolines

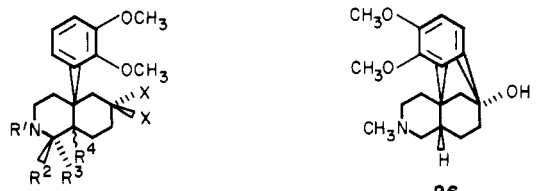


	X,X
8	O,O
9	S,S
10	=CH$_2$

	R	X,X
11	CN	O,O
12	CN	S,S
13	CN	O
14	CHO	O,O
15	CH$_2$NH$_2$	O,O
16	CH$_2$NHAc	O,O

	R	X,X
17	N=CCH$_3$	O,O
18	N=CC$_3$H$_7$	O,O
19	Ac	O
20	Ac	S,S

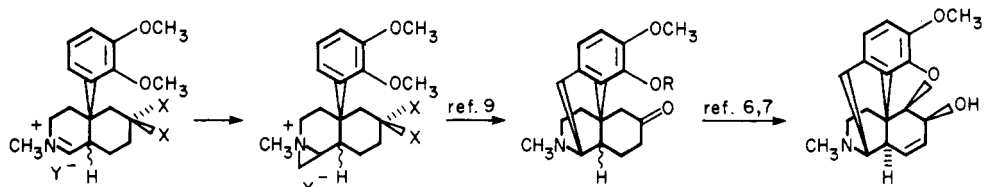
	R	Y
21	Ac	F
22	Ac	OH
23	Ac	OCH$_2$CH$_2$OH
24	H	F
25	H	OH



26

	R'	R^2	R^3	R^4	X,X
27	CH$_3$	(H,CN)		Br	O,O
28	CH$_3$	H	H	H	S,S
29	CN	H	H	H	S,S
30	CH$_3$	(H, CH$_2$Cl)		H	O,O
31	CH$_3$	H	H	H	CH$_2$
32	CH$_3$	Pr	H	H	O,O
33	CH$_3$	H	Ac	H	H,OH
34	CH$_3$	(=O)		H	H,OH

Scheme III. B-Ring Closure and Elaboration to Codeine

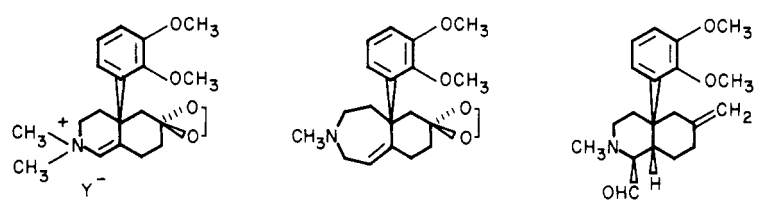


35 X,X = O,O
36 X,X = S,S
37 X,X = CH$_2$

38 X,X = O,O
39 X,X = CH$_2$

42 R = CH$_3$
43 R = H

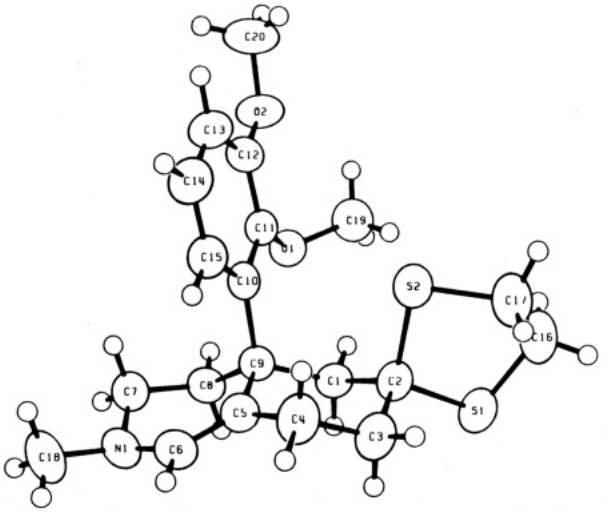
codeine



40 40' 41

nium salt. The rate of equilibration is dependent upon several factors including solvent, counterion, and temperature. Thus dioxolane enamine 8 was treated with perchloric acid, and the iminium salt equilibration was monitored by ^{1}H NMR; equilibration was complete within 1 min at 21 °C. Methanesulfonic acid (MsOH) slowed the equilibration to 8.9 min at 21 °C, and trifluoromethanesulfonic acid (TfOH) essentially stopped the equilibration, producing an 83/17 trans/cis ratio of iminium salts at 21 °C, but some decomposition occurred. Lowering the temperature to 0 °C or below with MsOH finally allowed satisfactory control of the stereochemistry without decomposition, with a kinetic ratio of 90/10 trans/cis.

We also explored the effect of different C-ring substitution patterns including the dithiolane, β-keto ester, and *exo*-methylene moieties (Scheme I); subtle kinetic and thermodynamic differences were observed, with the dithiolane showing the greatest kinetic selectivity (Table I). Origin of this kinetic selectivity lies in hindrance at the β face[8] of the enamine by the aromatic residue, and this



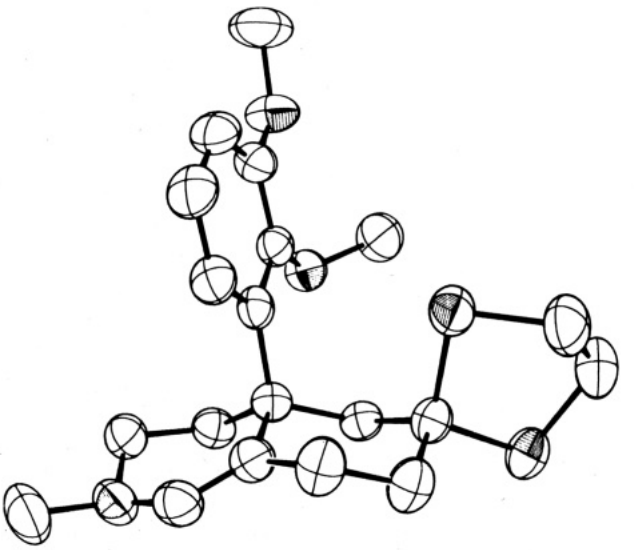
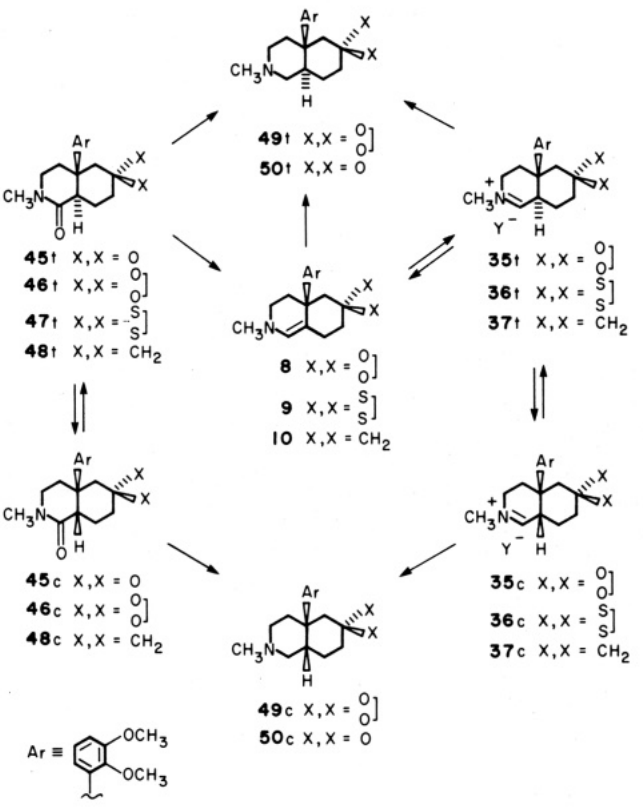


Figure 1. ORTEP drawing of enamine **9** from X-ray study.

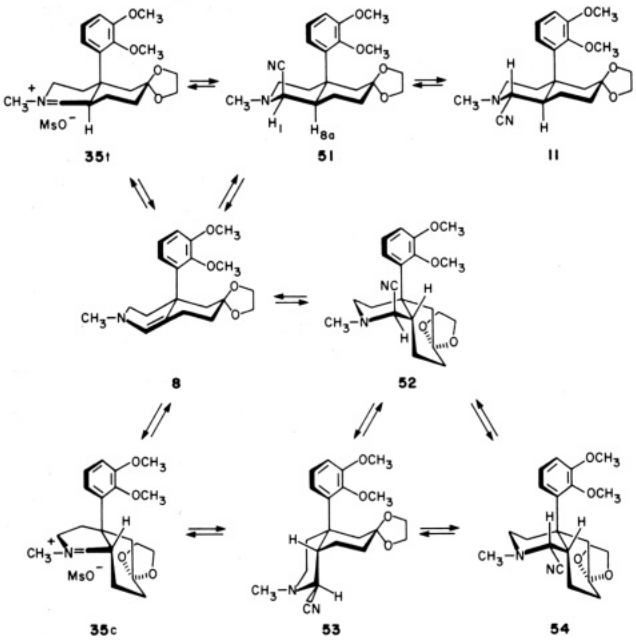
Scheme IV. Stereochemical Correlations



effect has now been visualized by a single-crystal X-ray diffraction study on dithiolane enamine **9**. Figure 1 shows clearly the powerful influence the aromatic residue exerts on the β face of the enamine, thus hindering protonation.

In order to confirm the iminium salt stereochemical assignments, we performed a chemical correlation as depicted in Scheme IV. Reduction of trans amido ketal **46t** with $AlH_3/LiAlH_4$, followed by $NaBH_4$ or H_2, and ketal hydrolysis afforded trans amino ketone **50t**, with analogy to the phenyl[1] and *m*-methoxyphenyl[2] series. The same trans amino ketone was produced by reduction of enamine **8** with $NaBH_4$ or H_2 and by reduction of the presumed trans iminium salt **35t** with $NaBH_4$. Equilibration of trans amido ketal **46t** to cis amido ketal **46c** with KOH/ethanol followed by AlH_3 reduction and ketal hydrolysis afforded cis amino ketone **50c**.[1,2] The same cis amino ketone was

Scheme V. Cyanation of Enamine and Iminium Salts



produced by reduction of the presumed cis iminium salt **35c** with $NaBH_4$. The cis and trans amides and amines also showed the expected GC, HPLC, and mass spectral relationships,[1-4] further enforcing our stereochemical assignments. The IR correlation, however, is not valid in the 2,3-dimethoxyphenyl series, presumably because of interactions between the carbonyl and the *o*-methoxyl.

Nitrogen Ring Functionalization. Having established stereochemical control of the **4a/8a** ring juncture, we focussed on the introduction of a functionalized single carbon unit as directed in the benzomorphan work.[5] Cyanide is the most versatile single carbon unit for this purpose because it can be converted, in principle, into many different functionalities, and cyanation is readily achieved by reactions with enamines and iminium salts.[10] Studies with enamine **8** showed that cyanation with

(10) (a) Rappoport, Z., Ed. "Chemistry of the Cyano Group"; Wiley-Interscience: New York, 1970. (b) Cook, A. G., Ed. "Enamines: Their Synthesis, Structure, and Reactions"; Marcel Dekker: New York, 1969. (c) Bohme, H.; Viehe, H. G., Eds. "Iminium Salts in Organic Chemistry"; Wiley-Interscience: New York, Part 1, 1976; Part 2, 1979. (d) McIntosh, J. M. *Can. J. Chem.* **1980**, *58*, 2604.

aqueous methanolic KCN at pH 12 initially produced a mixture of enamine 8 and two nitriles, A and B; longer reaction times afforded solely nitrile B. Similar reaction at pH 7–8 yielded solely nitrile A, and with time or upon addition of aqueous methanolic NaOH at pH 12 nitrile A was converted to a mixture of enamine 8 and nitrile B. The isolated, recrystallized cyanation product (54%) was predominantly nitrile B.

These data suggest that an axial nitrile is produced first, with epimerization to a more stable equatorial nitrile with time and at high pH. Analysis of the isolated cyanation product by ^{1}H NMR showed an 11-Hz doublet for H-1, indicating a trans-diaxial relationship between H-1 and H-8a and further suggesting **11** and **53** as possible structures for the cyanation product (Scheme V). Axial attack of cyanide followed by the expected protonation from the α face (see Figure 1) would give nitrile **51**. Strong 1,3-diaxial repulsions between the nitrile and the aromatic residue would allow facile epimerization to the equatorial nitrile **11**, whereas the initially formed axial nitrile **52** in the cis case could relieve repulsions by chair–chair interconversion (**52** → **53**), eliminating the driving force for epimerization. On the basis of these arguments we assigned structure **11** to the isolated cyanation product.

We next treated the cis and trans iminium salts **35** with methanolic KCN with the objective of learning more about the **4a/8a** stereochemistry. The trans iminium salt **35t** returned enamine 8 as the major product with a trace of nitrile **11**, whereas the cis iminium salt **35c** gave only nitrile **11** (55%). Similar results were observed when enamine 8 and the iminium salts **35** were treated with HCN, Et_3Al/HCN, and Et_2AlCN.[11]

If our original assignment is correct, then these seemingly contradictory results must be explained. The cis iminium salt **35c** apparently allows rapid proton abstraction, regenerating enamine 8 and allowing HCN addition as described above. Since little nitrile product was found with the trans iminium salt **35t**, then proton abstraction in the reaction medium to give enamine 8 must have occurred only to a minor extent, and direct attack on the β face of the iminium salt must be severely hindered by the aromatic residue. The H-8a proton is apparently protected from abstraction by the iminium salt counterion lying on the α face of the iminium salt, and the enamine is regenerated during isolation.

All attempts to prepare suitable crystals of the nitrile for X-ray analysis were unsuccessful, resulting in mixtures of enamine and nitrile. Because of this problem of enamine/nitrile equilibration, the results from a single-crystal X-ray analysis would have been equivocal even if suitable crystals had been available.

Ring Closure. Closure of the B ring would ultimately allow comparison with materials of known configuration, thus providing independent stereochemical evidence. Even if we were dealing with cis materials, equilibration at the ring juncture would be possible at a later stage, and the relative rarity of *cis*-codeine derivatives[6,12] would make this an attractive route to both cis and trans materials.

B-ring closure attempts began with the treatment of nitrile **11** at 20–25 °C with CF_3CO_2H, anhydrous HF, 15.2 M H_2SO_4/ether, and $AlCl_3$/HCl/*o*-dichlorobenzene. In each case reaction was observed, but none of the desired ring closure took place. Trifluoroacetic acid gave only deketalization and replacement of cyanide with trifluoroacetate. Anhydrous HF afforded material in which the cyano group had been replaced with fluorine and ring closure had occurred at C-6 via protonation of the ketal. Sulfuric acid/ether gave material which had lost the ketal and ring closed at C-6, with the cyano group replaced by NH_2 during an isolation involving ammonia. The aluminum chloride reaction afforded multiple products.

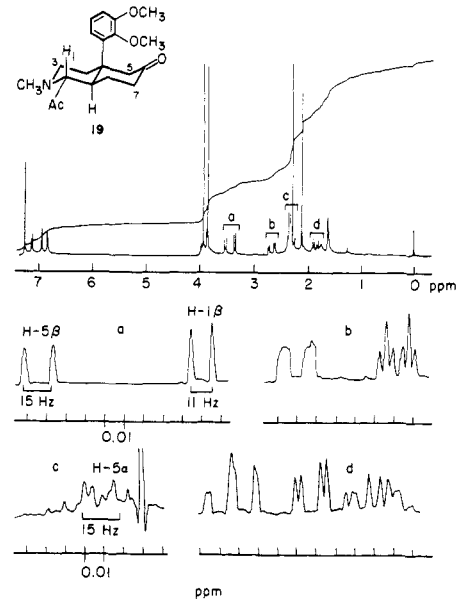


Figure 2. 500-MHz ^{1}H NMR spectrum of diketone **19**.

Similar problems with the instability of α-amino nitriles in simpler analogues[5] had been circumvented by converting the cyano group into a less labile group which still allowed for ring closure, and so the nitrile was converted into a variety of functionalities as outlined below. Reduction of nitrile **11** with $LiAlH_4$ in THF at 20–25 °C gave a 66/34 mixture of diamine **15** and trans amino ketal **49t**. Although **49t** may arise from direct displacement of cyanide by hydride, it may also arise from elimination of HCN followed by reduction of the enamine. Lowering the reaction temperature to −78 °C increased the amount of diamine **15** to 80%.

Reduction with $LiAl(OEt)_2H_2$[13] in THF gave, rather than the desired aldehyde, only deketalized starting material **13** after hydrolysis, and reduction with excess Dibal[14] in THF gave a 70/30 mixture of amino ketal **49t** and a new compound, probably the desired aldehyde **14**, but poor yields hindered progress along this route. Finally, treatment of nitrile **11** with CH_3Li in THF at 0 °C gave quantitative conversion to imine **17** and diketone **19** after hydrolysis. The diketone showed an 11-Hz doublet for H-1, indicating once again a trans-diaxial relationship between H-1 and H-8a (see Figure 2).

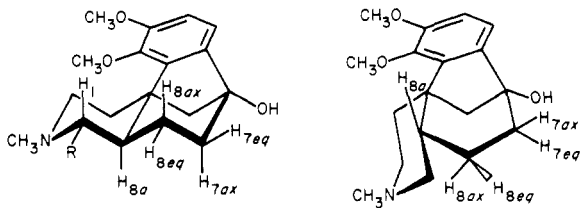
Since diketone **19** was available in high yield, and the corresponding ketone had been ring closed to give an 8-methylenebenzomorphan,[5] it was selected as the prime candidate for ring closure. Trifluoroacetic acid at 20–25 °C returned **19**, but treatment with anhydrous HF gave a 65% yield of a material which ^{1}H NMR clearly showed had undergone ring closure yet still contained the acetyl moiety. Apparently ring closure had preferentially oc-

(11) (a) Nagata, W.; Yoshioka, M. *Org. Synth.* **1972**, *52*, 90, 100. (b) Nagata, W.; Yoshioka, M.; Murakami, M. *Ibid.* **1972**, *52*, 96. (c) Nagata, W.; Yoshioka, M.; Hirai, S. *J. Am. Chem. Soc.* **1972**, *94*, 4635.

(12) Gates, M.; Shepard, M. S. *J. Am. Chem. Soc.* **1962**, *84*, 4125. (b) Kugita, H.; Takeda, M. *Chem. Ind. (London)* **1964**, 2099. (c) *Chem. Pharm. Bull.* **1965**, *13*, 1422. (d) Kugita, H.; Takeda, M.; Inoue, H. *Tetrahedron Lett.* **1967**, 1277. (e) *Tetrahedron* **1969**, *25*, 1851. (f) Takeda, M.; Inoue, H.; Kugita, H. *Ibid.* **1969**, *25*, 1839.

(13) Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc.* **1964**, *86*, 1085.

(14) Zakharkin, L. I.; Korlina, J. M. *Dokl. Akad. Nauk SSSR* **1957**, *116*, 422.



22 R = CH_3CO
25 R = H

26

Figure 3. Perspective representations of tetracyclic alcohols.

curred at C-6, affording the tetracyclic fluoride **21**.

Ring closure with either 15.2 M H_2SO_4/ether or $AlCl_3$/HCl/*o*-dichlorobenzene afforded the tetracyclic alcohol **22** (92%). Similarly, trans amino ketone **50t** underwent facile ring closure with anhydrous HF and 15.2 M H_2SO_4/ether to give the trans tetracyclic fluoride **24** (64%) and alcohol **25** (100%), respectively, and cis amino ketone **50c** cyclized in 15.2 M H_2SO_4/ether to give cis tetracyclic alcohol **26** (53%), thus allowing a comparison of authentic cis and trans tetracycles with presumed trans tetracycle **22**.

The trans tetracycles **24** and **25** show a multiplet (dq, J = 6, 13 Hz) at 0.4 ppm which corresponds to H-8_{ax}, highly shielded by the π cloud of the aromatic ring (see Figure 3). The cis tetracyclic alcohol **26** shows a similar multiplet at δ 1.1 which corresponds to the pseudoaxial H-8, no longer affected by the aromatic ring. Tetracycle **22** showed the multiplet at δ 0.4 along with a 10-Hz doublet for H-1, confirming the assigned stereochemistry both at the ring juncture as trans and at C-1 as α.

On the assumption that formation of the tetracyclic derivatives is not as favorable as formation of the morphinan ring system, protonation of the nitrogen must make it sufficiently difficult to protonate the nearby methyl ketone so that carbocation formation and reaction take place preferentially at C-6 and/or so that it is easier to cyclize at C-6 than to epimerize the C-1 substituent in order to close the B ring. The benzomorphan work[5] showed that B-ring closure was possible despite nitrogen protonation and also that epimerization of the C-1 substituent was possible, but in those molecules no competing cyclization was possible.

Three possibilities remained for achieving the desired B-ring cyclization: (1) protection of the C-6 ketone in some manner which would not allow alternative cyclization; (2) N-demethylation followed by N-acylation to remove charge hindrance; (3) generation of reactive C-1 substituents with an α configuration.

Blocking ring closure at C-6 required some ketone protecting group which would hinder carbocation formation at C-6 under strongly acidic conditions, and the alcohol, ketal, and thioketal were initially selected as reasonable candidates. The system devoid of C-ring functionality was of diminished interest from a pharmacological standpoint. Ring closure of alcohol **33** was not investigated because model studies with amido alcohol **34** showed the secondary alcohol to be extremely labile to carbocation formation. Ring closure of imine ketal **17** in anhydrous HF afforded only tetracycle **23** with no trace of product from the other mode of ring closure. Ketalization of amido ketone **45t** with $HSCH_2CH_2SH/BF_3{\cdot}Et_2O$ followed by reduction, cyanation, CH_3Li addition, and hydrolysis afforded ketone thioketal **20**. Ring closure of **20** was attempted at 20–25 °C in anhydrous HF, 15.2 M H_2SO_4/ether, $MsOH/P_4O_{10}$, and TfOH. Tetracyclic alcohol **22** was obtained with H_2SO_4/ether while anhydrous HF, $MsOH/P_4O_{10}$, and TfOH afforded multiple products. Thus, although the thioketal slowed ring closure at C-6, this was still the preferred site of reaction.

N-Demethylation of morphine alkaloids has been effected with cyanogen bromide,[15] chloroformates,[16] and diethyl azodicarboxylate.[17] Although N-demethylation of both (dimethylamino)acetonitrile and ethyl (dimethylamino)acetate with cyanogen bromide is reported to be facile,[18] treatment of nitrile **11** with 1000 mol % of BrCN in chloroform at 20–25 °C gave adduct **27**. Ketone thioketal **20** was unreactive at 20–25 °C (although amino thioketal **28** was slowly converted to the corresponding N-cyano compound **29**), and raising the reaction temperature to 60 °C gave complete decomposition. Similar results were observed with both methyl and phenyl chloroformate and with diethyl azodicarboxylate.

Next the generation of reactive carbocations from the C-1 substituent was explored. Diamine **15** was first treated with $NaNO_2$/HOAc[19] to generate the diazonium salt, but starting material was returned with several minor components. While isoamyl nitrite in $CHCl_3$/HOAc at 61 °C[20] showed complete consumption of **15**, multiple products resulted with no evidence of ring closure. Diamine **15** was then treated with acetic anhydride in pyridine to give acetamide **16**; treatment with $NaNO_2$/HOAc/Ac_2O at 0 °C gave an unstable intermediate along with N-demethylation. The complete absence of cyclization products from these reactions is perhaps more evidence of the equatorial (α) nature of the C-1 substituents.

Aziridinium salts have previously been used to prepare the morphinan skeleton,[9] but treatment of cis and trans iminium salts **35** with diazomethane to generate the intermediate cis and trans aziridinium salts **38** followed by heating in THF or $CHCl_3$ gave multiple products with no evidence of ring closure. This is in direct contrast to results in simpler systems.[9a] Treatment of the intermediate aziridinium salts with LiCl/CH_3CN[9a] to prepare the *cis*- and *trans*-chloromethyl compounds **30** for further ring closure attempts also resulted in multiple products. In order to confirm our analyses, we prepared dihydrothebainone methyl ether (**42t**) and epidihydrothebainone methyl ether (**42c**) from natural materials; neither was found in the reactions described above after the reaction products were deprotected. Potential byproducts of these latter reactions are the quaternized enamine **40** and the ring-expanded material **40′**.

In order to prepare β substituents at C-1, we first explored displacement of the α-configured cyano group with Grignard reagents;[10d] however, PrMgCl, for example, gave approximately equal amounts of **32** and **18**, resulting from replacement of cyanide and addition to the nitrile, respectively, along with a small amount of enamine **8**. Finally, Me_2SO oxidation of the aziridinium perchlorate **39**[9b] provided the *cis*-β-aldehyde **41** (Scheme III). B-ring closure with $BF_3{\cdot}Et_2O$ followed by removal of the 10-hydroxyl and oxidation of the *exo*-methylene afforded epidihydrothebainone methyl ether (**42c**), whose structure was confirmed by conversion to the natural material **42t**.[9b] Al-

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though the epi ether **42c** was an intermediate in the first total synthesis of codeine,[6] it is more efficient to proceed via the natural ether **42t**.[7] We have found ether cleavage of **42t** with $NaSC_2H_5$ to be specific, affording dihydrothebainone (**43t**) in 100% yield;[21,22] dihydrothebainone has been converted to codeine in 68% yield.[7]

Conclusion

Elaboration of suitably functionalized 4a-aryldecahydroisoquinolines has allowed the preparation of morphinans, and thus a total synthesis of codeine, and additionally has allowed the preparation of *cis*- and *trans*-octahydro-1*H*-indeno[1,2,3-*ef*]isoquinolines. The latter materials are the first 6,6′-bridged 4a-aryldecahydroisoquinolines to be prepared, and represent a novel class of codeine analogues. This work further extends the versatility of β-aryl α-methylene lactams in the preparation of codeine analogues, encompassing the synthesis of the structural classes 1–7 (Scheme I) via one general intermediate.

Experimental Section

General Methods. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Methanol and ethanol were distilled from magnesium. Chloroform was distilled from phosphorus pentoxide. Methanesulfonic acid (MsOH) and trifluoromethanesulfonic acid (TfOH) were distilled neat. Boron trifluoride etherate and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride.

Melting points were measured with Büchi (capillary) and Kofler (microscope slide) apparatuses and are uncorrected. IR spectra were determined in $CHCl_3$ unless otherwise noted. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. ^1H NMR spectra were determined on the following spectrometers: Varian T-60 (60 MHz), Berkeley UCB-250 (250.80 MHz), Nicolet NT-360 (360.06 MHz), Bruker WM-500 (500 MHz). ^{13}C NMR spectra were measured at 25.14 MHz with a Nicolet TT-23 spectrometer and at 63.07 MHz with the UCB-250. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise noted and are expressed in parts per million downfield from Me_4Si; couplings are in hertz. Mass spectra (electron impact, 70 eV) were obtained with AEI MS-12 (low resolution), Finnigan 4000 (GC/mass spectra), and Du Pont CEC 21-110 (high resolution) instruments. Elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California, Berkeley.

Gas chromatography (GC) was done with Varian Aerograph A-90P and Hewlett-Packard 402 gas chromatographs with helium flow rates of 80–100 mL/min. The following 6–8-mm glass columns were used: (A) 1.5 m, 5% SE-30 on 80/100 Chromosorb W; (B) 1.5 m, 3% OV-1 on 80/100 Chromosorb W; (C) 1.8 m, 5% Dexsil 300 on 90/100 Anakrom Q.

High-pressure liquid chromatography (HPLC) was done on an Altex analytical system consisting of two 110A pumps, a 155-10 UV–vis detector, a 420 microprocessor controller/programmer, and an Altex column [3.2 × 250 mm, 5-μm LiChrosorb Si60 normal phase silica gel, flow rate of 1.0 mL/min (one column volume equals 1.5 min), monitoring at 280 nm]. Preparative medium-pressure liquid chromatography (MPLC) was done by using an Altex 110A pump equipped with a preparative liquid head, an Altex 151 UV detector set at 280 nm, and an Altex stainless steel column (10 × 250 mm, 5-μm LiChrosorb Si60 silica gel). Column chromatography (CC) was performed with 63–200-μm silica gel 60 (EM Reagents).

Unless otherwise noted, reactions were conducted under a nitrogen atmosphere with magnetic stirring at room temperature (20–26 °C). Temperatures are reported as internal (iT) and bath (bT). Organic layers were dried over Na_2SO_4 and $MgSO_4$ and evaporated in vacuo with a Berkeley rotary evaporator. Hydrogenations were carried out under 40–50 psi of hydrogen pressure, with shaking, at 20–26 °C in Parr-type systems.

Dihydrothebainone (43t). Dihydrothebainone was prepared as described:[21] HPLC (98.5/1.0/0.5 $CHCl_3/CH_3OH/Et_3N$) t_R = 10.8 min; IR 1703 cm^{-1}; ^1H NMR (250 MHz) δ 6.66 (d, 1 H, J = 8.5), 6.58 (d, 1 H, J = 8.5), 6.17 (br s, 1 H), 4.23 (dd, 1 H, J = 1.5, 13.5), 3.81 (s, 3 H), 2.64 (dd, 1 H, J = 6.0, 18.5), 2.40 (s, 3 H); ^{13}C NMR (25 MHz) δ 210.5, 145.1, 144.9, 130.7, 123.3, 118.3, 109.1, 57.0, 56.1, 50.6, 46.6, 45.1, 42.5, 41.1, 41.0, 38.6, 27.1, 23.8; mass spectrum, m/z (relative intensity) 301 (69), 258 (8), 244 (12), 164 (100), 136 (18), 122 (8).

Dihydrothebainone Methyl Ether (42t).[22] To a 1.36 M solution of NaOEt in ethanol (100 mL, 13.6 mmol, 136 mol %) was added a solution of trimethylanilinium tosylate[23] (4.12 g, 13.3 mmol, 133 mol %) in ethanol (5 mL), and the resulting precipitate was filtered and washed with ethanol (5 mL). The filtrate and washings were combined with dihydrothebainone[21] (3.01 g, 10.0 mmol), the solvent was evaporated, and the residue was heated at 130 °C (bT) for 1.5 h. The resulting solid was dissolved in 2.5 M HOAc(aq) (40 mL), the solution was washed with benzene (3 × 20 mL), the aqueous layer was adjusted to pH 10 and extracted with $CHCl_3$ (3 × 20 mL), and the $CHCl_3$ phases were evaporated to an oil (3.65 g). Dissolving this oil in benzene (60 mL), washing with 1 M NaOH (3 × 10 mL) and saturated NaCl (20 mL), drying, and evaporating gave crude **42t** (2.73 g). Recrystallization afforded pure **42t**: 2.26 g (7.16 mmol, 72%); HPLC (98.5/1.0/0.5 $CHCl_3/CH_3OH/Et_3N$) t_R = 9.3 min; mp 147–148 °C[24] (from 1/5 benzene/hexane); IR 1707 cm^{-1}; ^1H NMR (250 MHz) δ 6.80 (d, 1 H, J = 8.5), 6.75 (d, 1 H, J = 8.5), 4.00 (dd, 1 H, J = 3.0, 12.5), 3.98 (s, 3 H), 3.82 (s, 3 H), 2.43 (s, 3 H); ^{13}C NMR (25 MHz) δ 210.0, 151.5, 149.1, 130.5, 130.4, 122.7, 111.8, 60.2, 57.0, 55.8, 51.3, 46.5, 45.7, 42.5, 41.4, 41.0, 40.0, 26.9, 24.1; mass spectrum, m/z (relative intensity) 315 (51), 164 (100), 136 (21); $[\alpha]^{20}_D$ + 85.6° (c 0.44, $CHCl_3$). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.3; H, 8.0; N, 4.4. Found: C, 72.4; H, 8.0; N, 4.5.

Epidihydrothebainone (43c) was prepared as described:[25] HPLC (98.5/1.0/0.5 $CHCl_3/CH_3OH/Et_3N$) t_R = 2.8 min; mp 116–118 °C (from hexane) (lit.[25] mp 116–118 °C); IR 1694 cm^{-1}; ^1H NMR (250 MHz) δ 6.71 (d, 1 H, J = 8.5), 6.64 (d, 1 H, J = 8.5), 5.94 (s, 1 H), 3.94 (d, 1 H, J = 15.0), 3.85 (s, 3 H), 3.15 (d, 1 H, J = 17.5), 2.96 (br d, 1 H, J = 5.5), 2.77 (dd, 1 H, J = 5.5, 17.5), 2.54 (d, 1 H, J = 15.0), 2.31 (s, 3 H); ^{13}C NMR (25 MHz) δ 212.2, 144.8, 143.8, 131.2, 128.5, 118.5, 109.0, 57.5, 56.2, 50.7, 47.9, 42.6, 41.7, 40.7, 39.8, 29.4, 28.3, 26.5; mass spectrum, m/z (relative intensity) 301 (100), 258 (54), 244 (60), 164 (62), 122 (43).

Epidihydrothebainone Methyl Ether (42c).[24] To a solution of epidihydrothebainone **43c** (810 mg, 2.69 mmol) in THF (40 mL) were added NaH (150 mg, 54.4% oil dispersion, 3.40 mmol, 126 mol %) and Me_2SO_4 (433 mg, 3.43 mmol, 128 mol %), and the suspension was refluxed for 3 h. Second portions of NaH (42 mol %) and Me_2SO_4 (31 mol %) were added, and the suspension was refluxed for 30 min and then poured into 1/1 H_2O/concentrated NH_4OH (100 mL). The mixture was extracted with $CHCl_3$ (2 × 100 mL), and the organic layers were washed with aqueous saturated NaCl (100 mL), dried, and evaporated. Rapid column chromatography (12.5 g silica gel, 97/2/1 $CHCl_3/CH_3OH/Et_3N$) afforded **42c** (525 mg, 1.66 mmol, 62%) as an oil which slowly solidified: HPLC (98.5/1.0/0.5, $CHCl_3/CH_3OH/Et_3N$) t_R = 2.5 min; mp 112–113 °C; IR 1697 cm^{-1}; ^1H NMR (250 MHz) δ 6.82 (d, 1 H, J = 8.5), 6.75 (d, 1 H, J = 8.5), 3.80 (s, 3 H), 3.77 (s, 3 H), 3.71 (d, 1 H, J = 14.5), 3.11 (d, 1 H, J = 18.0), (br d, 1 H, J = 5.5), 2.75 (dd, 1 H, J = 6.0, 18.0), 2.51 (d, 1 H, J = 14.5), 2.27 (s, 3 H); ^{13}C NMR (63 MHz) δ 212.2, 151.0, 147.4, 135.9, 130.5, 122.9, 110.7, 60.2, 57.2, 55.5, 51.3, 47.6, 42.5, 41.3, 40.5, 40.0, 30.8,

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28.0, 26.4; mass spectrum, m/z (relative intensity) 315 (93), 300 (14), 284 (35), 272 (46), 258 (52), 164 (100), 122 (56), 57 (63); $[\alpha]^{20}_D$ +53.2° (c 0.44, $CHCl_3$). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.3; H, 8.0; N, 4.4. Found: C, 71.9; H, 7.8; N, 4.4.

Dihydrothebainone (43t) via Ether Cleavage of 42t.[22] (A) With $NaSC_2H_5$. Sodium hydride (404 mg, 16.8 mmol, 843 mol %) and ethanethiol (620 mg, 10.0 mmol, 500 mol %) were added sequentially to DMF (40 mL) at 25 °C to give a clear solution after initial gas evolution. Ether **42t** (630 mg, 2.0 mmol) was added and the solution was heated for 10 h at 100 °C (bT). The solution was cooled in an ice bath, $CHCl_3$ (40 mL) and H_2O (60 mL) were added, the aqueous phase was washed with $CHCl_3$ (2 × 10 mL), and the combined organic layers were washed with saturated aqueous NaCl (50 mL), dried, and evaporated. The residue was dissolved in benzene (50 mL), and the solution was washed with H_2O (2 × 5 mL) and saturated aqueous NaCl (10 mL), dried, and evaporated to give **43t** (600 mg, 2.0 mmol, 100%), pure by GC, TLC, and ^1H NMR.

(B) With HCl. A solution of ether **42t** (630 mg, 2.0 mmol) in concentrated HCl (15 mL) was heated at 110 °C (bT) with continuous bubbling of gaseous HCl through the solution for 8 h. The acidic solution was cooled in an ice/NaCl bath and adjusted to pH 9 with aqueous 6 M NaOH. The solution was extracted with $CHCl_3$ (3 × 50 mL), and the organic layers were washed with saturated aqueous NaCl (30 mL), dried, and evaporated to give **43t** (515 mg, 1.7 mmol, 86%); ^1H NMR gave evidence for catechol and/or the isomeric phenol. Similar results were observed with HCl and the epi ether **42c**.

***trans*-4a-(2,3-Dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-1-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (46t)** was prepared as described[4] and was identical by GC, ^1H NMR, and IR: ^1H NMR (250 MHz) δ 6.90 (t, 1 H, J = 8), 6.82 (dd, 1 H, J = 2, 8), 6.67 (dd, 1 H, J = 2, 8), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.81 (d, 1 H, J = 6), 3.12 (dd, 1 H, J = 3, 15), 3.02 (q, 1 H, J = 4), 2.76 (s, 3 H), 2.28 (br d, 1 H, J = 12), 2.08 (dq, 1 H, J = 4, 12), 1.58 (dt, 1 H, J = 5, 13), 1.54 (d, 1 H, J = 15).

***trans*-4a-(2,3-Dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (49t)** was prepared as described[4] and was identical by HPLC, ^1H NMR, and IR: ^1H NMR (360 MHz) δ 7.15 (dd, 1 H, J = 1, 8), 6.95 (t, 1 H, J = 8), 6.81 (dd, 1 H, J = 1, 8), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.60 (q, 1 H, J = 7), 3.49 (q, 1 H, J = 7), 3.01 (dd, 1 H, J = 3, 14), 2.82 (t, 1 H, J = 11), 2.74 (dd, 1 H, J = 4, 11), 2.25 (s, 3 H), 1.97 (br dt, 1 H, J = 3, 13), 1.86 (quintet, 1 H, J = 3), 1.83–1.54 (m), 1.40 (d, 1 H, J = 14).

***cis*-4a-(2,3-Dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-1-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (46c)** was prepared as described[4] and was identical by GC, ^1H NMR, and IR: ^1H NMR (250 MHz) δ 6.89 (t, 1 H, J = 8), 6.79 (dd, 1 H, J = 2, 8), 6.68 (dd, 1 H, J = 2, 8), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.04–2.88 (m, 1 H), 2.78 (br d, 1 H, J = 8), 2.66 (s, 3 H), 1.93 (dq, 1 H, J = 4, 13).

4a-(2,3-Dimethoxyphenyl)-2-methyl-6-methylene-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (48). To a solution of amido ketone **45t** (240 mg, 0.76 mmol, 100% trans) in THF (20 mL) was added methylenetriphenylphosphorane (20 mL, 0.29 M suspension in THF, 5.8 mmol, 763 mol %; prepared from methyltriphenylphosphonium iodide and *n*-BuLi) dropwise over 10 min. The mixture was heated at reflux for 72 h, cooled (0 °C), poured into saturated aqueous NH_4Cl (20 mL), and extracted with ether (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried, and evaporated, and the residue was chromatographed (MPLC, EtOAc) to give *exo*-methylene compound **48** (50 mg, 0.16 mmol, 21%; mixture of isomers) as an oil. The remainder of the material (79%) was recovered as partially equilibrated amido ketone **45**. For **48**: HPLC (EtOAc) t_R = 5.4, 6.2 min; IR 2920, 1633 (br) cm^{-1}; ^1H NMR (250 MHz) δ 7.0–6.5 (m, 3 H), 6.58 (br s, 1 H), 6.30 (br s, 3 H), 3.98, 3.95, 3.90, 3.87 (4 s, total 6 H), 3.62 (d, 1 H, J = 15), 2.91, 2.82 (2 s, total 3 H); mass spectrum, m/z 315 (M^+, weak).

4a-(2,3-Dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-2,3,4,4a,5,6,7,8-octahydroisoquinoline (8). A solution of amido ketal **46t**[4] (502 mg, 1.39 mmol) in THF (10 mL) was cooled in an ice bath while Dibal (10 mL, 1.41 M solution in hexane, 14.1 mmol, 1014 mol %) was added over 25 min. Another portion of Dibal (8 mL, 11.3 mmol) was added over 20 min, and the excess hydride was decomposed by dropwise addition of CH_3OH (18 mL). The solution was poured into 1.25 M NaOH (50 mL), the mixture was extracted with ether (3 × 30 mL), and the combined organic extracts were dried and evaporated to yield enamine **8** (432 mg, 1.25 mmol, 90%) as an unstable white solid: ^1H NMR (250 MHz) δ 7.00–6.87 (m, 2 H), 6.81 (dd, 1 H, J = 2, 8), 5.88 (s, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.33 (dd, 1 H, J = 3, 15), 2.55 (s, 3 H), 2.12 (dq, 1 H, J = 3, 14), 1.86 (dt, 1 H, J = 3, 13).

4a-(2,3-Dimethoxyphenyl)-6,6-(ethylenedithio)-2-methyl-2,3,4,4a,5,6,7,8-octahydroisoquinoline (9). Amido thio ketal **47t** (432 mg, 1.10 mmol) in THF (15 mL) was treated with Dibal (20 mL) as described above in the preparation of **8** and isolated as follows. The reaction solution was warmed to 45 °C, and CH_3OH (20 mL) was quickly added. The resulting solid was triturated with benzene (20 mL), the remaining solid and benzene were poured into 1.25 M NaOH (35 mL), the aqueous layer was extracted with ether (2 × 20 mL), and the combined organic layers were dried and evaporated to give enamine **9** (394 mg, 1.04 mmol, 95%) contaminated with 16% of the corresponding amino thioketal **28**: ^1H NMR (60 MHz, benzene-d_6) δ 7.20 (dd, 1 H, J = 2, 8), 6.97 (t, 1 H, J = 8), 6.63 (dd, 1 H, J = 2, 8), 5.74 (m, 1 H), 4.02 (s, 3 H), 3.88 (d, 1 H, J = 5), 3.38 (s, 3 H) 2.70 (t, 4 H), 2.27 (s, 3 H).

4a-(2,3-Dimethoxyphenyl)-2-methyl-6-methylene-2,3,4,4a,5,6,7,8-octahydroisoquinoline (10). Reduction of *exo*-methylene amide **48** as described for the preparation of **8** afforded *exo*-methylene enamine **10** (68%) as an oil; the ^{13}C NMR spectrum was in accord with that reported.[9b] The remainder of the material (32%) in this reaction corresponds to the overreduction product **31**.

***trans*-4a-(2,3-Dimethoxyphenyl)-6,6-(ethylenedithio)-2-methyl-1-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (47t).** To a solution of amido ketone **45t**[4] (1.16 g, 3.65 mmol) in ethanedithiol (3 mL) was added $BF_3{\cdot}Et_2O$ (3 mL). After 16 h the mixture was poured into ice-cold 1.25 M NaOH (60 mL) and extracted with $CHCl_3$ (3 × 20 mL). The organic extracts were dried and evaporated to give a white solid (1.53 g); recrystallization afforded **47t**; 1.16 g (2.95 mmol, 81%); mp 203–204 °C (from benzene/hexane); IR (KBr) 1630 cm^{-1}; ^1H NMR (60 MHz, benzene-d_6) δ 7.13 (dd, 1 H, J = 2, 8), 6.78 (t, 1 H, J = 8), 6.52 (dd, 1 H, J = 2, 8), 3.97 (s, 3 H), 3.61 (dd, 1 H, J = 2, 14), 2.60 (s, 3 H); ^{13}C NMR (25 MHz, 1/1 $CDCl_3$/benzene-d_6) δ 171.3, 164.7, 153.3, 149.2, 132.8, 122.9, 122.6, 112.4, 67.1, 59.8, 55.4, 50.9, 50.4, 47.0, 45.2, 39.8, 37.2, 37.1, 34.0, 23.1; mass spectrum, m/z (relative intensity) 394 (22), 393 (86), 362 (100), 332 (33), 300 (43), 248 (27), 131 (22). Anal. Calcd for $C_{20}H_{27}NO_3S_2$: C, 61.0; H, 6.9; N, 3.6. Found: C, 60.9; H, 6.9; N, 3.5.

***trans*-4a-(2,3-Dimethoxyphenyl)-6-hydroxy-2-methyl-1-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (34).** Amido ketone **45t**[4] (193 mg, 0.61 mmol) was hydrogenated in glacial HOAc (5 mL) over PtO_2 (12 mg) for 18 h. After filtration and evaporation, the residue was dissolved in $CHCl_3$ (25 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL). The organic layer was dried and evaporated to give, after recrystallization, **32** (129 mg, 0.40 mmol, 66%); the alcohol stereochemistry has been assigned based on expected reduction from the less hindered face: HPLC (EtOAc) t_R = 6.9 min; mp 159–161 °C (from benzene/hexane); IR ($CHCl_3$) 3550, 1625 cm^{-1}; ^1H NMR (250 MHz) δ 6.94 (t, 1 H, J = 8), 6.86 (dd, 1 H, J = 2, 8), 6.75 (dd, 1 H, J = 2, 8), 3.96 (br s, 1 H), 3.93 (s, 3 H), 3.88 (s, 3 H), 3.10 (br d, 1 H, J = 16), 2.93 (m, 1 H), 2.67 (s, 3 H), 2.17 (br d, 1 H, J = 14), 2.02 (dq, 1 H, J = 4, 13), 1.86 (br d, 1 H, J = 15), 1.70 (dd, 1 H, J = 4, 13), 1.51 (br d, 1 H, J = 13), 1.40 (dd, 1 H, J = 2, 15); mass spectrum, m/z (relative intensity) 319 (100), 288 (58), 270 (31), 231 (33), 213 (40), 163 (40). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.7; H, 7.9; N, 4.4. Found: C, 67.8; H, 7.8; N, 4.3.

***trans*-4a-(2,3-Dimethoxyphenyl)-2-methyl-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (50t). (A) With $AlH_3/NaBH_4$.** Trans amido ketal **46t** was reduced with AlH_3[26] followed by $NaBH_4$, and the ketal **49t** was hydrolyzed as described,[4] affording amino ketone **50t** in 78% yield.

(B) With AlH_3/H_2. Amido ketal **46t** was reduced with AlH_3[26] followed by hydrogenation over Rh/Al_2O_3, and the ketal **49t** was

(26) Yoon, N. M.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 2927.

hydrolyzed as described[4] to give amino ketone **50t** in 87% yield.

(C) With Dibal/MsOH/$NaBH_4$. To a solution of enamine **8** (19.0 mg, 0.055 mmol; prepared from amido ketal **46t** by Dibal reduction) in CH_3OH (2.9 mL) cooled in an ice/NaCl bath (−15 °C bT) under argon was added MsOH (3.6 μL, 0.055 mmol, 100 mol %). After 30 min, $NaBH_4$ (26 mg, 0.687 mmol, 1250 mol %) was added in one portion, and the bath was allowed to warm. After 11 h, 2 M HCl (15 mL) was added to hydrolyze the ketal, and the solution was taken to pH 11 4 h later with 2 M NaOH and extracted with $CHCl_3$ (2 × 50 mL). The organic layers were dried and evaporated to give amino ketone **50t** (12.6 mg, 0.042 mmol, 76%, 92/8 trans/cis), identical (HPLC, melting point, IR, 250-MHz ^1H NMR) with material prepared by methods A and B: ^1H NMR (250 MHz) δ 7.09 (dd, 1 H, J = 1.2, 8.1), 6.91 (t, 1 H, J = 8.1), 6.81 (dd, 1 H, J = 1.2, 8.1), 3.92 (s, 3 H), 3.83 (s, 3 H), 3.44 (dd, 1 H, J = 1.1, 14.1), 2.27 (s, 3 H).

***cis*-4a-(2,3-Dimethoxyphenyl)-2-methyl-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (50c). (A) With AlH_3.** A solution of cis amido ketal **46c** (53.6 mg, 0.148 mmol) in THF (10 mL) was added dropwise over 1 min to an ice-bath-cooled solution of AlH_3[26] in THF (7 mL, 0.14 M, 0.980 mmol, 662 mol %). After 75 min, 1/1 H_2O/THF (0.1 mL) and 3 M NaOH (0.3 mL) were added. The mixture was extracted with ether (3 × 25 mL), and the ether layers were washed with saturated aqueous NaCl (2 × 15 mL), dried, and evaporated. The residue was dissolved in 3 M H_2SO_4 (65 mL) to hydrolyze the ketal (**49c**), and after 19.5 h the solution was cooled in an ice bath and basified (pH 11) with ice-cold 6 M NaOH. The mixture was then extracted with $CHCl_3$ (3 × 45 mL), and the organic layers were dried and evaporated to give amino ketone **50c**: 40.4 mg (0.133 mmol, 90%, 98/2 cis/trans); an oil; HPLC (98.5/1.0/0.5 $CHCl_3$/CH_3OH/Et_3N) t_R = 3.9 min; IR 2901, 1697, 1584, 1462, 1423, 1266, 1069, 1017, 824 cm^{-1}; ^1H NMR (250 MHz) δ 6.99 (t, 1 H, J = 8.0), 3.91 (s, 3 H), 3.86 (s, 3 H), 3.18–3.05 (m, 1 H), 2.78 (br s, 1 H), 2.28 (s, 3 H); mass spectrum, m/z (relative intensity) 303 (4), 302 (9), 273 (25), 272 (58), 244 (10), 165 (17), 149 (13), 96 (21), 43 (100); calcd for $C_{18}H_{25}NO_3$ m/z 303.1835, found 303.1823.

(B) With Dibal/$HClO_4$/$NaBH_4$. To a solution of cis iminium perchlorate **35c** (27.9 mg, 0.063 mmol; prepared from trans amido ketal **46t** by Dibal reduction and treatment with aqueous 70% $HClO_4$ in CH_3OH) in 2/1 $CHCl_3$/CH_3OH (1.5 mL) cooled in an ice bath was added $NaBH_4$ (30 mg, 0.793 mmol, 1270 mol %) portionwise over 5 min. The bath was removed, and after 15 h the solution was cooled again in an ice bath and acidified to pH 1 with 2 M HCl to hydrolyze the ketal (**49c**). The bath was removed, after 7 h the pH was adjusted to 11 with 2 M NaOH, and the aqueous solution was extracted with ether (2 × 20 mL) and $CHCl_3$ (2 × 20 mL). The combined organic phases were dried and evaporated to give amino ketone **50c** (11.7 mg, 0.039 mmol, 62%), identical (HPLC, 250-MHz ^1H NMR) with the material prepared in A, but with a 84/16 cis/trans ratio.

***trans*-1α-Cyano-4a-(2,3-dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (11). (A) Via Enamine.** A solution of KCN (900 mg, 13.9 mmol, 1112 mol %) in water (7.3 mL) and CH_3OH (33 mL) was acidified to pH 7.9 with glacial HOAc and added to enamine **8** (432 mg, 1.25 mmol). The pH was readjusted to 7.9 with glacial HOAc, and after 3.25 h the mixture was poured into 0.35 M NaOH (200 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried and evaporated to give nitrile **11**: 251 mg (0.68 mmol, 54%); HPLC (50/50 $CHCl_3$/EtOAc, 0.5 mL/min) t_R = 6.2 min; mp 125–126 °C (from benzene/hexane); IR 2245 cm^{-1}; ^1H NMR (360 MHz) δ 6.99–6.90 (m, 2 H), 6.84 (dd, 1 H, J = 2, 8), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.62 (q, 1 H, J = 7), 3.52 (q, 1 H, J = 7), 3.01 (dd, 1 H, J = 3, 15), 2.59 (d, 1 H, J = 11), 2.45 (s, 3 H), 2.36 (dd, 1 H, J = 4, 13), 2.05 (dt, 1 H, J = 3, 12), 1.46 (d, 1 H, J = 15); mass spectrum, m/z (relative intensity) 345 (97, M − HCN), 300 (15), 258 (15), 230 (15), 208 (44), 122 (100). Anal. Calcd for $C_{21}H_{28}N_2O_4$: C, 67.7; H, 7.6; N, 7.5. Found: C, 67.9; H, 7.6; N, 7.3.

(B) Via Iminium Salt. To a solution of enamine **8** (42.3 mg, 0.122 mmol) in CH_3OH (10 mL) was added MsOH (9.7 μL, 0.149 mmol, 122 mol %) to prepare cis iminium mesylate **35c**, and after 24 h a solution of KCN (245 mg, 3.76 mmol, 3080 mol %) in water (1.5 mL) and CH_3OH (10 mL) which had been adjusted to pH 7.8 with glacial HOAc was added. After 3.5 h the reaction mixture was poured into 0.5 M NaOH (50 mL) and extracted with $CHCl_3$ (2 × 50 mL). The $CHCl_3$ extracts were dried and evaporated to give nitrile **11** (25.0 mg, 0.067 mmol, 55%), identical (melting point, IR, 250-MHz ^1H NMR) with the material prepared in A.

***trans*-1α-Cyano-4a-(2,3-dimethoxyphenyl)-6,6-(ethylenedithio)-2-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (12).** The crude thioketal enamine/amine **9**/**28** mixture (718 mg, 1.89 mmol) was treated with KCN (1.23 g, 18.9 mmol, 1000 mol %) in water (10 mL) and CH_3OH (44 mL) at pH 7.7 for 3 h. Isolation as described for the oxygen analogue **11** afforded nitrile **12** (675 mg, 1.76 mmol, 93%) as a foam, contaminated with 24% amino ketal **28**: HPLC (97.5/1.7/0.8 $CHCl_3$/CH_3OH/Et_3N) t_R = 3.6 min; IR 2245 cm^{-1}; ^1H NMR (360 MHz) δ 7.03–6.85 (m, 3 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 3.79 (d, 1 H, J = 11), 3.37 (br d, 1 H, J = 15), 2.72 (br d, 1 H, J = 12), 2.56 (tt, 1 H, J = 3, 12), 2.42 (s, 3 H), 1.84 (t, 1 H, J = 11), 1.55 (dt, 1 H, J = 3, 13). Anal. Calcd for $C_{21}H_{38}N_2O_2S$: C, 62.3; H, 7.0; N, 6.9. Found: C, 62.2; H, 7.0; N, 6.6.

***trans*-1α-(Aminomethyl)-4a-(2,3-dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (15).** To a solution of nitrile **11** (54 mg, 0.145 mmol) in THF (5 mL) cooled in a −78 °C bath was added a solution of $LiAlH_4$ in THF (0.31 mL, 2.34 M, 0.725 mmol, 500 mol %) over 3 min. After 2 h the bath was allowed to warm, and after another 22 h water (10 μL), 0.4 M NaOH (10 μL), and H_2O (20 μL) were added sequentially. Filtration and evaporation afforded diamine **15** (52 mg, 0.139 mmol, 96%), contaminated with amino ketal **49t**, a contaminant in nitrile **11**; ^1H NMR (60 MHz, benzene-d_6) δ 7.28 (br d, 1 H, J = 8), 6.88 (t, 1 H, J = 8), 6.56 (br d, 1 H, J = 8), 3.77 (s, 3 H), 3.40 (s, 3 H), 2.03 (s, 3 H); mass spectrum, m/z (relative intensity) 289 (1, M − ($CHCH(CH_2NH_2)NCH_3$)), 276 (2), 262 (18), 248 (100), 232 (36), 218 (32), 84 (100). Anal. Calcd for $C_{21}H_{30}N_2O_4$: C, 67.3; H, 8.1; N, 7.5. Found: C, 67.4; H, 8.6; N, 6.9.

***trans*-1α-Acetimino-4a-(2,3-dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (17).** To a solution of nitrile **11** (50 mg, 0.134 mmol) in THF (4 mL) cooled in an ice bath was added a solution of CH_3Li in ether (0.166 mL, 1.70 M, 0.282 mmol, 210 mol %) dropwise over 1.25 min. After 25 min CH_3OH (1 mL) was added, and the solution was partitioned between CH_2Cl_2 (15 mL) and H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic extracts were dried and evaporated to give **17**: 51 mg (0.121 mmol, 98%); an oil; ^1H NMR (60 MHz, benzene-d_6) δ 7.50 (br d, 1 H, J = 8), 6.91 (t, 1 H, J = 8), 6.58 (br d, 1 H, J = 8), 3.80 (s, 3 H), 3.37 (s, 3 H), 1.95 (s, 3 H), 1.87 (s, 3 H).

***trans*-1α-Acetyl-4a-(2,3-dimethoxyphenyl)-2-methyl-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (19).** To a solution of nitrile **11** (204 mg, 0.55 mmol) in THF (5 mL) cooled in an ice bath was added a solution of CH_3Li in ether (0.70 mL, 1.65 M, 1.15 mmol, 210 mol %) over 3.5 min. After 25 min the solution was diluted with 0.5 M H_2SO_4 (5 mL). After 18 h the reaction mixture was poured into saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried and evaporated to give diketone **19** (175 mg, 0.51 mmol, 92%) as an oil, containing 9% of amino ketone **50t**, a contaminant derived from the amino ketal **49t** impurity in nitrile **11**: HPLC (97.5/1.7/0.8 $CHCl_3$/CH_3OH/Et_3N) t_R = 3.3 min; IR (neat) 1710 cm^{-1}; ^1H NMR (500 MHz) δ 7.14 (d, 1 H, J = 8), 6.95 (t, 1 H, J = 8), 6.84 (d, 1 H, J = 8), 3.92 (s, 3 H), 3.84 (s, 3 H), 3.47 (d, 1 H, J = 15), 3.34 (d, 1 H, J = 11), 2.71 (ddd, 1 H, J = 1, 3, 13), 2.60 (dt, 1 H, J = 3, 12), 2.33 (d, 1 H, J = 15), 2.28 (s, 3 H), 2.10 (s, 3 H), 1.88 (dt, 1 H, J = 1, 5, 12), 1.82 (dd, 1 H, J = 2, 13.5); mass spectrum, m/z (relative intensity) 345 (3), 302 (100). Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.5; H, 7.9; N, 4.1. Found: C, 69.7; N, 7.8; N, 4.0.

***trans*-1α-Acetyl-4a-(2,3-dimethoxyphenyl)-6,6-(ethylenedithio)-2-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (20).** To a solution of nitrile **12** (350 mg, 0.91 mmol; contaminated with 20% amino ketal **28**) in THF (7 mL) was added a solution of CH_3Li in ether (1.09 mL, 1.67 M, 1.82 mmol, 200 mol %), and the intermediate imine was hydrolyzed by dilution with aqueous 0.5 M H_2SO_4 (7 mL) as described for the preparation of diketone **19**. Isolation afforded **20** (334 mg, 0.79 mmol, 87%), contaminated with 16% amino ketal **28**: HPLC (97.5/1.7/0.8 $CHCl_3$/

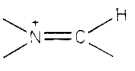
CH_3OH/Et_3N) t_R = 3.6 min; IR (neat) 1700 cm^{-1}; ^1H NMR (360 MHz) δ 7.24 (dd, 1 H, J = 2, 8), 6.99 (t, 1 H, J = 8), 6.88 (dd, 1 H, J = 2, 8), 3.92 (s, 3 H), 3.86 (s, 3 H), 3.36 (dd, 1 H, J = 3, 15), 3.37 (d, 1 H, J = 13), 2.73 (br d, 1 H, J = 13), 2.56 (dt, 1 H, J = 3, 11), 2.21 (s, 3 H), 2.08 (d, 1 H, J = 15), 2.05 (s, 3 H), 1.63 (dt, 1 H, J = 3, 13), 1.34–1.24 (m, 1 H); calcd for $C_{22}H_{30}NO_3S_2$ (M − 1) m/z 420.1669, found 420.1651; calcd for $C_{20}H_{28}NO_2S_2$ (M − acetyl) m/z 378.1563, found 378.1555.

***trans*-4α-Acetyl-9,10-dimethoxy-6aα-fluoro-3-methyl-2,3,4,4a,5,6,6a,10c-octahydro-1*H*-indeno[1,2,3-*ef*]isoquinoline (21).** Diketone **19** (29 mg, 0.084 mmol; contaminated with 17% amino ketone **50t**) was treated with anhydrous HF for 20 h. The HF was evaporated, and the residue was dissolved in CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL). The organic layer was dried and evaporated to give **21** (19 mg, 0.055 mmol, 65%), amino ketone **50t** (21%), and unidentified materials (14%): ^1H NMR (60 MHz, benzene-d_6) δ 7.02 (d, 1 H, J = 8), 6.51 (d, 1 H, J = 8), 3.66 (s, 3 H), 3.33 (s, 3 H), 2.06 (s, 3 H), 1.98 (s, 3 H).

***trans*-9,10-Dimethoxy-6aα-fluoro-3-methyl-2,3,4,4a,5,6,-6a,10c-octahydro-1*H*-indeno[1,2,3-*ef*]isoquinoline (24).** Amino ketone **50t** (34 mg, 0.112 mmol) was treated with anhydrous HF as described for diketone **19**, affording tetracycle **24**: 22 mg (0.072 mmol, 64%); HPLC (97.5/1.7/0.8 $CHCl_3/CH_3OH/Et_3N$) t_R = 6.9 min; mp 84–86 °C (from benzene/hexane); ^1H NMR (360 MHz) δ 6.95 (d, 1 H, J = 8), 6.85 (d, 1 H, J = 8), 3.88 (s, 3 H), 3.81 (s, 3 H), 3.05 (dt, 1 H, J = 4, 11), 2.95–2.87 (m, 1 H), 2.34 (s, 3 H), 1.86 (quintet, 1 H, J = 4), 1.78 (d, 1 H, J = 9), 1.70 (d, 1 H, J = 11), 0.43 (dq, 1 H, J = 6, 13); mass spectrum, m/z (relative intensity) 305 (47), 290 (10), 274 (100). Anal. Calcd for $C_{18}H_{24}NO_2F$: C, 70.8; H, 8.3; N, 4.6. Found: C, 71.0; H, 8.1; N, 4.5.

***trans*-1α-Acetyl-9,10-dimethoxy-6aα-hydroxy-3-methyl-2,3,4,4a,5,6,6a,10c-octahydro-1*H*-indeno[1,2,3-*ef*]isoquinoline (22).** To a solution of diketone **19** (49 mg, 0.142 mmol; contaminated with 9% amino ketone **50t**) in ether (2 mL) cooled in an ice bath was added 15.2 M H_2SO_4 (3 mL) dropwise over 2 min. After 20 h the reaction was poured into 1/1 concentrated NH_4OH/ice (30 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried and evaporated to give tetracycle **22** (45 mg, 0.130 mmol, 92%) as an oil, contaminated with 9% **25**: HPLC (97.5/1.7/0.8 $CHCl_3/CH_3OH/Et_3N$) t_R = 5.2 min; IR (neat) 3190, 1708 cm^{-1}; ^1H NMR (360 MHz) δ 6.94 (d, 1 H, J = 8), 6.85 (d, 1 H, J = 8), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.18 (dt, 1 H, J = 5, 12), 2.94 (ddd, 1 H, J = 2, 6, 11), 2.33 (d, 1 H, J = 10), 2.18 (s, 3 H), 2.13 (s, 3 H), 2.07 (dt, 1 H, J = 4, 16), 1.94 (ddd, 1 H, J = 2, 4, 15), 1.74 (d, 1 H, J = 10), 1.19 (dt, 1 H, J = 4, 14), 0.46 (dq, 1 H, J = 7, 13); mass spectrum, m/z (relative intensity) 330 (8), 302 (100). Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.5; H, 7.9; N, 4.1. Found: C, 69.7; H, 7.8; N, 4.0.

***trans*-4a-(2,3-Dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-3,4,4a,5,6,7,8,8a-octahydroisoquinoline Mesylate (35t).** To a solution of enamine **8** (16.5 mg, 0.048 mmol) in $CHCl_3$ (2.4 mL) cooled in an ice/NaCl bath (−15 °C) was added MsOH (3.5 μL, 0.054 mmol, 113 mol %) to give trans iminium salt **35t** (21.2 mg, 0.048 mmol, 100%, 90/10 trans/cis) upon evaporation. This iminium salt is stable only in solution, and it equilibrates to the cis isomer at temperatures >0 °C. **35t**-OMs: ^1H NMR (250 MHz, −20 °C) δ 9.28 (br s, 1 H, I), 7.0 (br s, 1 H), 6.9 (br s, 1 H), 3.9 (s, 3 H), 3.8 (s, 3 H), 2.8 (s, 6 H).



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The triflate was prepared as above with TfOH instead of MsOH, giving a kinetic ratio of 83/17 trans/cis; the ratio was 81/19 trans/cis after 71 h. Partial decomposition also occurred. **35t**-OTf: ^1H NMR (250 MHz, 20 °C) δ 8.89 (br s, 1 H, I).

The perchlorate was prepared as above with aqueous 70% $HClO_4$ instead of MsOH in $CHCl_3$ and in CH_3OH with identical results; equilibration occurred within 1 min, giving a 4/96 trans/cis ratio. **35t**-ClO_4: ^1H NMR (250 MHz, 20 °C) δ 8.97 (br s, 1 H, I).

***cis*-4a-(2,3-Dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-3,4,4a,5,6,7,8,8a-octahydroisoquinoline Mesylate (35c).** Treatment of enamine **8** as described above with MsOH at 20 °C rather than −15 °C afforded cis iminium salt **35c** (100%, 14/86 trans/cis), stable only in solution. **35c**-OMs: ^1H NMR (250 MHz, 21 °C) δ 9.44 (br s, 1 H, I), 7.02 (t, 1 H, J = 8.6), 6.88 (dd, 1 H, J = 1.2, 8.6), 6.60 (dd, 1 H, J = 1.2, 8.6), 3.86 (s, 3 H), 3.83 (s, 3 H), 2.83 (s, 6 H).

The perchlorate was prepared above in an attempt to prepare the trans material. **35c**-ClO_4: ^1H NMR (250 MHz, 21 °C) δ 9.08 (br s, 1 H, I).

4a-(2,3-Dimethoxyphenyl)-6,6-(ethylenedithio)-2-methyl-3,4,4a,5,6,7,8,8a-octahydroisoquinoline Mesylate (36). Treatment of dithiolane enamine **9** with MsOH as described above in the preparation of **35** afforded trans iminium salt **36t**: ^1H NMR (250 MHz, 12 °C) δ 9.18 (br s, 1 H). Equilibration afforded cis iminium salt **36c**: ^1H NMR (250 MHz, 12 °C) δ 9.37 (br s, 1 H).

***trans*-9,10-Dimethoxy-6aα-hydroxy-3-methyl-2,3,4,4a,5,6,6a,10c-octahydro-1*H*-indeno[1,2,3-*ef*]isoquinoline (25).** Amino ketone **50t** (16.6 mg, 0.055 mmol) was treated for 36 h as described for diketone **19** in the preparation of tetracycle **22**, affording trans tetracyclic alcohol **25**: 16.6 mg (0.055 mmol, 100%); an oil; HPLC (97.5/1.7/0.8 $CHCl_3/CH_3OH/Et_3N$) t_R = 7.1 min; IR 2939, 1464, 1256, 1078, 1060, 1024, 818 cm^{-1}; ^1H NMR (200 MHz) δ 6.93 (d, 1 H, J = 8), 6.82 (d, 1 H, J = 8), 3.86 (s, 3 H), 3.79 (s, 3 H), 3.03 (dt, 1 H, J = 6, 11), 2.92–2.79 (m, 1 H), 2.39 (d, 1 H, J = 10), 2.30 (s, 3 H), 2.14 (dd, 1 H, J = 3, 10), 0.38 (dq, 1 H, J = 6, 13); mass spectrum, m/z (relative intensity) 303 (29), 272 (88), 244 (11), 205 (16), 98 (11), 70 (18), 57 (100); calcd for $C_{18}H_{25}NO_3$ m/z 303.1836, found 303.1834.

***cis*-9,10-Dimethoxy-6aα-hydroxy-3-methyl-2,3,4,4a,5,6,-6a,10c-octahydro-1*H*-indeno[1,2,3-*ef*]isoquinoline (26).** Amino ketone **50c** (35.0 mg, 0.115 mmol) was treated for 15 h as described in the preparation of tetracycle **22**, affording cis tetracyclic alcohol **30c**: 18.7 mg (0.061 mmol, 53%); an oil; HPLC (97.5/1.7/0.8 $CHCl_3/CH_3OH/Et_3N$) t_R = 8.9 min; IR (neat) 3666–2461, 1260, 1031, 812 cm^{-1}; ^1H NMR (250 MHz) δ 6.92 (d, 1 H, J = 8), 6.80 (d, 1 H, J = 8), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.00 (dt, 1 H, J = 4, 13), 2.82 (br d, 1 H, J = 11), 2.67 (dd, 1 H, J = 4, 12), 2.41 (d, 1 H, J = 10), 2.34 (s, 3 H), 2.30 (d, 1 H, J = 13), 1.93 (quintet, 1 H, J = 5–6), 1.78 (dt, 1 H, J = 6, 9), 1.25 (br s, 1 H), 1.11 (octet (?), 1 H, J = 7); mass spectrum, m/z (relative intensity) 303 (24), 272 (24), 83 (10), 57 (100); calcd for $C_{18}H_{25}NO_3$ m/z 303.1836, found 303.1835.

Spectral and Chromatographic Correlations of *trans*-/*cis*-Decahydroisoquinolines. We have previously shown that the trans amino ketones (e.g., **50t**) have longer HPLC retention times and weaker molecular ions in the mass spectrum than the corresponding cis isomers (e.g., **50c**).[3] The trans amido ketals (e.g., **45t**) generally also have shorter GC retention times. The GC retention times which follow are for trans/cis in minutes (for exact conditions consult the respective experimental sections): **45t/45c**, 3.5/4.4;[4] **45t′/45c′** (Ar = *m*-$CH_3OC_6H_4$), 2.6/3.4.[2]

X-ray Crystallographic Analysis.[27-35] Large clear crystals

(27) All calculations were performed on a PDP 11/60 equipped with 128 kilowords of memory, twin RK07 28 MByte disk drives, a Versatec printer/plotter, and a TU10 tape drive by using locally modified Nonius-SDP[3] software operating under RSX-11M.

(28) "Structure Determination Package User's Guide"; Molecular Structure Corp.: College Station, TX, April 1980.

(29) The data reduction formulas are

$$F_o^2 = \frac{\omega}{Lp}(C - 2B) \qquad \sigma_o(F_o^2) = \frac{\omega}{Lp}(C + 4B)^{1/2}$$

$$F_o = (F_o^2)^{1/2} \qquad \sigma_o(F) = \sigma_o(F_o^2)/2F_o$$

where C is the total count in the scan, B the sum of the two background counts, ω the scan speed used in deg/min, and

$$\frac{1}{Lp} = \frac{\sin 2\theta(1 + \cos^2 2\theta_m)}{1 + \cos^2 2\theta_m - \sin^2 2\theta}$$

is the correction for Lorentz and polarization effects for a reflection with a scattering angle of 2θ and radiation monochromatized with a 50% perfect single-crystal monochromator with a scattering angle of $2\theta_m$.

Table II. Crystal and Data Collection Parameters for Compound $C_{20}H_{27}NO_2S_2$

(A) Crystal Parameters at 25 °C[a, b]

a = 16.6245 (21) Å	space group: $P2_1/c$
b = 8.9161 (12) Å	formula weight: 377.57 amu
c = 14.5919 (23) Å	Z = 4
$\alpha = \gamma = 90°$	d (calcd) = 1.273 g cm^{-3}
β = 114.353 (11) Å	μ (calcd) = 2.790
v = 1970.4 (10) Å	size: 0.18 × 0.24 × 0.51 mm

(B) Data Measurement Parameters

diffractometer: Enraf-Nonius CAD-4[33]
radiation: Mo Kα ($\bar{\lambda}$ = 0.710 73 Å)
monochrometer: highly-oriented graphite ($2\theta_m$ = 12.2°); perpendicular mode, assumed 50% perfect
detector: crystal scintillation counter, with PHA
aperture crystal = 173 mm; vertical aperture = 3.0 mm
horizontal aperture = 2.0 + 1.0 tan θ mm (variable)
reflections measured: $+h,+k,\pm l$
2θ range, 3-45°; scan type, θ-2θ
scan speed, 0.67-6.7°/min; scan width, $\Delta\theta$ = 0.70 + 0.347 tan θ
background: measured over an additional 0.25° ($\Delta\theta$) added to each end of the scan
number of reflections collected, 2875; number of unique reflections, 2573
intensity standards: 11.25, 362, 108; measured every 2 h of X-ray exposure time. Over the period of data collection no net decay in intensity was observed
orientation: three reflections were checked after every 500 measurements. Crystal orientation was redetermined if any of the reflections were offset from their predicted positions by more than 0.1°. Reorientation was performed three times during data collection.

[a] Unit cell parameters and their esd's were derived by a least-squares fit to the setting angles of the unresolved Mo K$\bar{\alpha}$ components of 24 reflections with 2θ between 28° and 32°. [b] In this table the esd's of all parameters are given in parentheses, right-justified to the least significant digit(s) given.

of enamine **9** were obtained by evaporation from ethanol. Fragments of one of the large crystals were mounted on glass fibers in air by using cyanoacrylate cement. The crystal used for data collection was an approximately rectangular parallelopiped of dimensions 0.18 × 0.24 × 0.51 mm.

Preliminary precession photographs indicated Laue symmetry $P2/m$ and good crystal quality and yielded preliminary cell dimensions. The crystal was then transferred to the diffractometer and centered in the beam.[33] Our standard peak search and indexing procedures yielded a primitive monoclinic unit cell and a preliminary orientation matrix. Final accurate cell dimensions and an orientation matrix were determined by centering higher-angle reflections well distributed in reciprocal space. The final values for the cell parameters and details of the data collection procedure are given in Table II.

Solution Refinement. The 2875 raw intensity data were reduced to structure factor amplitudes and their esd's by correction for scan speed, background, and Lorentz and polarization effects.[27-29] Analysis of the intensities of several reflections measured at 10° increments of rotation of the crystal around the diffraction vector showed a maximum variation of only 1.5%. No absorption correction was applied to the data. Following rejection of systematic absences ($0k0$, $k \neq 2n$; $h0l$, $l \neq 2n$; $P2_1/C$) and averaging of redundant data, values of the normalized structure factors for the 2573 unique data were calculated.[35]

The structure was solved via MULTAN. All non-hydrogen atoms were located on the E map calculated from the set of phases having the highest combined figure of merit. A difference Fourier map calculated after least-squares refinement of positional and isotropic thermal parameters (R = 11.9%)[30] confirmed that the compound was enamine **9**. Following refinement of the non-hydrogen atoms with anisotropic thermal parameters, a difference Fourier map showed peaks where most hydrogen atoms were expected. Idealized positions (C–H distance 0.95 Å) of all hydrogen atoms were calculated, and their fixed contribution to structure factor calculations was included in the least-squares calculation. Refinement converged following adjustment of some of the hydrogen positions and thermal parameters (B_{iso} = 6.0 Å^2 except for the methyl hydrogens and the methylene hydrogens for C-16 and C-17 which had B_{iso} = 9.0 Å^2). The final residuals[30] for 226 variables refined against the 2036 data for which $F^2 > 3\delta(F^2)$ were R = 3.43%, R_w = 4.60%, and GOF = 2.34. The R value for all 2573 data was 5.12%.

The quantity minimized by the least-squares program was $\sum w(|F_o| - |F_c|)^2$, where w is the weight of a given observation. The p factor[30] used to reduce the weight of intense reflections was set to 0.025 throughout the refinement. The analytical forms for the scattering factor tables for the neutral atoms were used[31] and all non-hydrogen scattering factors were corrected for both the real and imaginary components of anomalous dispersion.[32] Inspection of the residuals ordered in ranges of sin θ/λ, $|F_o|$, and parity and value of the individual indexes showed no unusual features or trends. There was no evidence of secondary extinction in the low-angle, high-intensity data. The largest peak in the final difference Fourier map had an electron density of 0.12 e/Å^3.

Figure 1 shows the ORTEP[3] drawing of enamine **9**. Hydrogen atoms have been given arbitrary small radii for clarity.

Acknowledgment. This research was supported in part by the National Institute on Drug Abuse. The crystal structure analysis was performed by Dr. F. J. Hollander, staff crystallographer at the University of California, Berkeley, X-ray Crystallographic Facility (CHEXRAY), and 360- and 500-MHz ^{1}H NMR spectra were recorded at the University of California, Davis, and Southern California Regional NMR Facilities, respectively.

Registry No. **8**, 83999-50-2; **9**, 83999-51-3; **10**, 83999-52-4; **11**, 83999-56-8; **12**, 83999-57-9; **15**, 83999-58-0; **17**, 83999-59-1; **19**, 83999-60-4; **20**, 83999-61-5; **21**, 83999-62-6; **22**, 83999-64-8; **24**, 83999-63-7; **25**, 83999-75-1; **26**, 84026-54-0; **34**, 83999-54-6; **35c** mesylate, 83999-69-3; **35c** perchlorate, 83999-70-6; **35c** triflate, 83999-71-7; **35t** mesylate, 83999-66-0; **35t** triflate, 83999-67-1; **35t** perchlorate, 83999-72-8; **36c** mesylate, 83999-78-4; **36t** mesylate,

(30) The R, R_w, and GOF values were calculated as follows:

$$R = \frac{\sum||F_o| - |F_c||}{\sum|F_o|}$$

$$R_w = \left(\frac{\sum w(|F_o| - |F_c|)^2}{\sum wF_o^2}\right)^{1/2}$$

$$\text{GOF} = \left(\frac{\sum w(|F_o| - |F_c|)^2}{(n_o - n_v)}\right)^{1/2}$$

where n_o is the number of observations and n_v the number of variable parameters. The weights w were given by

$$w = 4F_o^2/\sigma^2(F_o^2)$$

$$\sigma^2(F_o^2) = \sigma_o^2(F_o^2) + (pF^2)^2$$

where p is the factor used to lower the weight of intense reflections.

(31) Cromer, D. T.; Waber, J. T. "International Tables for X-ray Crystallography; Kynoch Press: Birmingham, England, 1974; Vol. IX, Table 2.2B.

(32) Cromer, D. T., ref 31, Table 2.3.1.

(33) Instrumentation at the University of California Chemistry Department X-ray Crystallographic Facility (CHEXRAY) consists of two Enraf-Nonius CAD-4 diffractometers, one controlled by a DEC 8/a with an RK05 disk and the other controlled by a DEC PDP 8/e with an RL01 disk. Both use Enraf-Nonius software as described in: CAD-4 Operation Manual; Enraf-Nonius: Delft, Nov 1977; updated Jan 1980.

(34) Johnson, C. K. Report ORNL-3794; Oak Ridge National Laboratory: Oak Ridge, TN, 1965.

(35) Wilson, A. J. C. *Nature (London)* **1942**, *150*, 151.

83999-74-0; **42c**, 84026-53-9; **42t**, 74924-35-9; **43c**, 2934-63-6; **43t**, 847-86-9; **46c**, 81012-16-0; **46t**, 81064-05-3; **47t**, 83999-53-5; **48c**, 83999-49-9; **48t**, 83999-76-2; **49t**, 81012-14-8; **50c**, 83999-55-7; **50t**, 81012-15-9; **56c**, 84009-47-2; **56t**, 84009-49-4; codeine, 76-57-3.

Supplementary Material Available: Tables of bond distances, bond angles, thermal parameters, and atom coordinates (6 pages). Ordering information is given on any current masthead page.

Rhodium Carbonyl Catalyzed Carbonylation of Unsaturated Compounds. 2.[1] Synthesis of 5-Alkoxy-2(5*H*)-furanones by the Carbonylation of Acetylenes in Alcohol[2]

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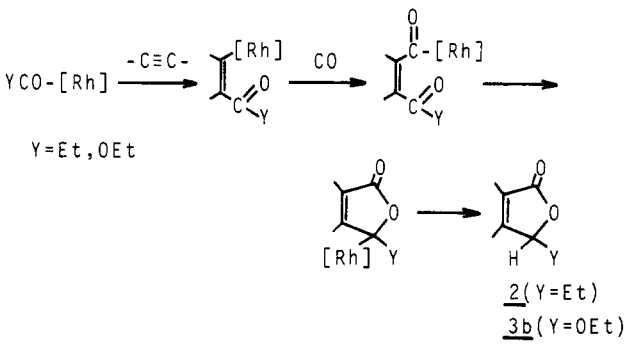
The carbonylation of diphenylacetylene (**1a**) in ethanol in the presence of $Rh_4(CO)_{12}/Na_2CO_3$ as a catalyst gave 5-ethoxy-3,4-diphenyl-2(5*H*)-furanone (**3b**) in a 72% yield, together with 3-(ethoxycarbonyl)-2-phenylindanone (11%) and diethyl 2,3-diphenylsuccinate (4%). The combination of rhodium catalysts with various bases was examined, and the $Rh_4(CO)_{12}$/NaOAc system was found to be the most suitable catalytic system (**3b**, 87% yield). The carbonylation of **1a** in various alcohols such as methanol, 1-propanol, 2-propanol, and 1-octanol gave 5-alkoxy-3,4-diphenyl-2(5*H*)-furanones in good yields. Disubstituted acetylenes such as a 1-phenylpropyne, 2-butyne, and 3-hexyne could be also used to give the corresponding furanones.

The carbonylation of acetylenes with carbon monoxide in the presence of a soluble transition-metal catalyst, particularly of group 8, is a useful synthetic reaction because it yields various valuable products according to the reaction conditions.[3,4] Carbonylation with ring closure presents a convenient route for the one-step synthesis of five- and seven-membered unsaturated lactones.[5,6] In the previous paper we have reported that the rhodium carbonyl catalyzed cross-hydrocarbonylation of acetylenes and ethylene in ethanol yields 5-ethyl-2(5*H*)-furanones (**2**), together with a small amount of 5-ethoxy-2(5*H*)-furanone (**3**).[1] It should be noted that the ethanol, used as the solvent, acts as a hydrogen donor in the formation of **2** and itself constitutes a part of the molecule in the formation of **3**.

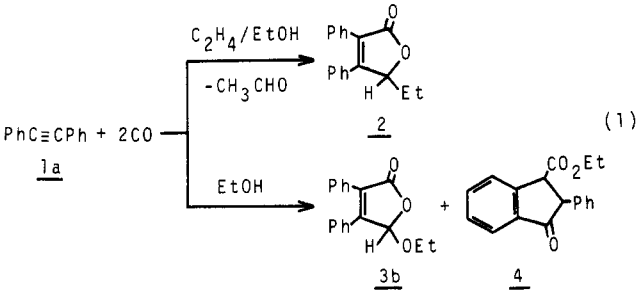
Although the carbonylation of acetylenes in alcohol has been known to give mono- and dicarboxylates such as acrylates, fumarates, maleates, and succinates, no report has appeared on the formation of 5-alkoxy-2(5*H*)-furanone (**3**). Since the furanone **3** is a new type of the carbonylation product from acetylene and is a member of an important class of naturally occuring butenolides,[7] its selective synthesis is desirable. We have found that addition of basic alkali metal salts to $Rh_4(CO)_{12}$ or its precursors improved remarkably the yield of **3**. Full details are described here of this new and facile method for the preparation of 5-alkoxy-2(5*H*)-furanone (**3**) from acetylenes, carbon monoxide, and alcohols.

Scheme I



Results and Discussion

As previously reported,[1] when a mixture of diphenylacetylene (**1a**) and a catalytic amount of $Rh_4(CO)_{12}$ in ethanol was heated at 125 °C under the pressure of C_2H_4 (20 kg/cm²) and CO (30 kg/cm²), 5-ethoxy-3,4-diphenyl-2(5*H*)-furanone (**3b**) and 3-(ethoxycarbonyl)-2-phenylindanone (**4**) were obtained in 4% and 11% yields, respectively, along with 5-ethyl-3,4-diphenyl-2(5*H*)-furanone (**2**, 31%; eq 1). The structure of **3b** was determined on



the basis of its analytical and spectroscopic data. The IR

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(4) Mullen, A. "New Syntheses with Carbon Monoxide"; Falbe, J., Ed.; Springer-Verlag: West Berlin, 1980; p 414.
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