IR (film) 3400 (br), 3100, 3000, 2960, 2940, 2910, 2850, 1620, 1520, 1260, 1180, 1040, 800, 720 cm^{-1}; UV (MeOH) λ_{max} 224 nm (ϵ 15600), 276 (1900), 284 (1600); ^1H NMR (100 MHz, $CDCl_3$) δ 8.1-7.4 (1 H, br s, exchanges with D_2O), 7.13 (2 H, d with further fine splitting, J = 9 Hz), 6.85 (2 H, d with further fine splitting, J = 9 Hz), 6.65 (1 H, dd with further fine splitting, J = 4, 2 Hz), 6.15 (1 H, dd, J = 5, 3 Hz), 5.99 (1 H, br s with fine splitting, $w_{1/2}$ = 8 Hz), 3.92 (2 H, s), 3.78 (3 H, s); mass spectrum, m/e (relative intensity) 187 (M^+, 26), 186 (19), 156 (9), 80 (23), 58 (25), 43 (100).

Acknowledgment. We thank the Ciba-Geigy Corp. (Pharmaceuticals Division), the Charles and Johanna Busch Memorial Fund, the Research Council (Rutgers), and the NIH (Biomedical Sciences Support Grant) for supporting our synthetic programs. We also thank Mr. Peter Bartner, Mrs. Bernice Evans, and Dr. Mohindar Puar, Schering-Plough Corp., for the mass spectra, microanalyses, and NMR spectra.

Registry No. 1, 1003-29-8; 2, 1963-42-4; 3, 33234-48-9; 4, 79499-34-6; 5, 79499-35-7; 6, 79499-36-8; 7, 1072-83-9; 8, 79499-37-9; 9, 79499-38-0; 10, 79499-39-1; 11, 7697-46-3; 12, 79499-40-4; 13, 79499-41-5; 14, 1192-58-1; 15, 79499-42-6; 16, 18159-24-5; 17, 79499-43-7; 18, 79499-44-8; 19, 79499-45-9; o-bromoanisole, 578-57-4; p-bromoanisole, 104-92-7; phenyllithium, 591-51-5; p-bromotoluene, 106-38-7; m-bromoanisole, 2398-37-0; pyrrole, 109-97-7; ethyl benzoate, 93-89-0; α-chlorotoluene, 100-44-7; β-methoxyethoxymethyl chloride, 3970-21-6.

Supplementary Material Available: Experimental details and characterization data for the 2-benzylpyrroles 2-4, 6, 10, 12, 15, 18, and 19 and the 2-acylpyrroles 7, 11, 16, and 17 (12 pages). Ordering information is given on any current masthead page.

Codeine Analogues. Synthesis of Spiro[benzofuran-3(2*H*),4'-piperidines] and Octahydro-1*H*-benzofuro[3,2-*e*]isoquinolines

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Received July 24, 1981

A synthesis of highly functionalized spiro[benzofuran-3(2*H*),4'-piperidines] and octahydro-1*H*-benzofuro-[3,2-*e*]isoquinolines, analogues of codeine containing the benzofuran/piperidine and benzofuran/decahydroisoquinoline ring fragments, has been developed. The process extends to the dimethoxyphenyl series earlier work in the synthesis of 4a-aryldecahydroisoquinolines involving the α-methylene lactam rearrangement and utilizes a novel α-chloro ortho ester Claisen rearrangement to establish the requisite functionality for oxide ring closure. Selective ether cleavage is achieved with methanesulfonic acid/methionine to afford a spiro[chromone-piperidinone], and base-promoted rearrangement then yields the desired spiro[benzofuran-piperidinone]. The C ring is closed by Michael addition of a β-keto ester to the α-methylene lactam moiety, subsequently affording a protected benzofuroisoquinolone. Finally, amide reduction followed by ketone deprotection gives the desired *cis*- and *trans*-benzofuroisoquinolines. The entire synthesis can be performed by starting from o-vanillin with six purifications in 10% overall yield, and the various intermediates additionally provide entries into the synthesis of 4-arylpiperidines, benzomorphans, and 4a-aryldecahydroisoquinolines. Functionality is built in to allow preparation of typical morphine patterns.

The synthesis of novel codeine analogues has been pursued for many years in the hope of finding analgesics with fewer undesirable side effects. One strategy has been to dissect the pentacyclic codeine molecule **1b** into various partial ring structures. For efficiency in designating the various ring combinations and for ease in recognition, we have adopted a nomenclature system in which the hydrophenanthrene rings are indicated as A-C in the usual way, the furan ring is referred to as O (for oxygen ring), and the piperidine ring is referred to as N (for nitrogen ring). Thus codeine (**1b**) contains the ABCNO rings, and partial structures to which considerable synthetic activity has been directed are the bicyclic (AN) arylpiperidines **2**, the tricyclic (ACN) aryldecahydroisoquinolines **3**, and the tricyclic (ABN) benzomorphans **4**. Three classes of analogues which have received meager attention are the ANO spiro[benzofuran-3(2*H*),4'-piperidines] **5**, the ACNO octahydro-1*H*-benzofuro[3,2-*e*]isoquinolines **6**, and the ABNO 3*H*-2a,6-methano-2*H*-furo[4,3,2-*f*,*g*][3]benzazocines **7** (Chart I).

The first synthesis of an ANO system was reported[1] in 1944 and utilized *gem*-dialkylation of arylacetonitriles with bis(2-chloroethyl)methylamine, closing the oxide ring by ether cleavage and nitrile attack to form a lactone. Subsequent workers[2-5] have used the same approach with subtle variations, but none has reported the preparation of ANO compounds containing functionality in the C-2 side chain or the nitrogen ring. Some of these compounds have shown analgesic activity in spite of this lack of functionality.[3-6] The first synthesis of an ACNO system was reported[7] in 1976 and used a heteroatom-directed photoarylation route. Recently an intramolecular Diels-Alder route to this system has appeared.[8] The former method does provide C-ring functionalization, with additional substituents at C-4a and C-12, and the latter

(1) Bergel, F.; Haworth, J. W.; Morrison, A. L.; Rinderknecht, H. *J. Chem. Soc.* **1944**, 261.

(2) Barltrop, J. A. *J. Chem. Soc.* **1946**, 958.

(3) Kagi, H.; Miescher, K. *Helv. Chim. Acta* **1949**, *32*, 2489.

(4) Spielman, M. A. U.S. Patent 2500714, 1950; *Chem. Abstr.* **1950**, *44*, 5922.

(5) (a) Gervais, C.; Anker, D.; Carret, G.; Pacheco, H. *Tetrahedron* **1979**, *35*, 745. (b) Gervais, C.; Anker, D.; Chareire, M.; Pacheco, H. *Bull. Soc. Chim. Fr.* **1979**, II-241. (c) Ong, H. H.; Agnew, M. N. *J. Heterocycl. Chem.* **1981**, *18*, 815.

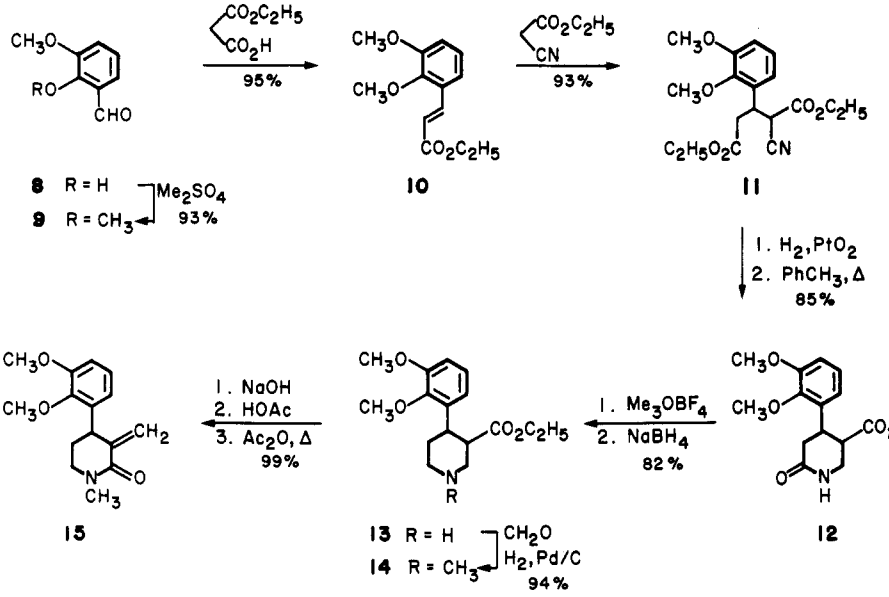
(6) Macdonald, A. D.; Woolfe, G.; Bergel, F.; Morrison, A. L.; Rinderknecht, H. *Br. J. Pharmacol.* **1946**, *1*, 4.

(7) (a) Schultz, A. G.; Lucci, R. D. *J. Chem. Soc., Chem. Commun.* **1976**, 925. (b) Schultz, A. G.; Lucci, R. D.; Fu, W. Y.; Berger, M. H.; Erhardt, J.; Hagmann, W. K. *J. Am. Chem. Soc.* **1978**, *100*, 2150.

(8) (a) Ciganek, E. European Patent 0009780A2, 1980; *Chem. Abstr.* **1980**, *93*, 220720. Various compounds containing C-ring functionality are claimed in this patent, but no characterizations are provided for these compounds. (b) Ciganek, E. *J. Am. Chem. Soc.* **1981**, *103*, 6261.

0022-3263/81/1946-5064$01.25/0

Scheme I. Synthesis of α-Methylene Lactam 15 from o-Vanillin (8)



method may not allow easy C-ring functionalization. Several of these ACNO compounds have shown potent analgesic activity.[8] The only synthesis of an ABNO system was reported in 1963, and a degradative pathway from codeine was used. The analogue prepared showed more than twice the potency of morphine (1a).[9]

Our approach has been to employ the methods we have previously reported for preparing the A, N, and C rings,[10-12] along with an α-chloro ortho ester Claisen rearrangement which provides for oxide ring closure and thus allows preparation of both the ANO and ACNO systems. Potentially, our methods for B ring closure[12] could also be applied to prepare the ABNO and ABCNO systems. This approach provides functionality for subsequent elaboration of the ANO and ACNO systems into typical morphine alkaloid functional patterns.

Results and Discussion

α-Methylene Lactam Preparation. Preparation of (dimethoxyphenyl)-α-methylene lactam 15 follows closely our published syntheses of the phenyl and *m*-methoxyphenyl lactams (Scheme I).[10-12] *o*-Vanillin (8) is methylated with dimethyl sulfate and condensed with ethyl hydrogen malonate to afford the known cinnamate 10.[13] Michael addition of ethyl cyanoacetate to the cinnamate followed by nitrile reduction and thermal cyclization yields amido ester 12. Finally, the amide is reduced by the Borch procedure,[14] secondary amine 13 is methylated, and tertiary amine 14 is converted to α-methylene lactam 15 under standard rearrangement conditions.[15] This preparation formally involves seven steps, but it is possible to use several crude intermediates without reducing the overall yield. Thus α-methylene lactam 15 is prepared from *o*-vanillin in 57% overall yield with purification of only intermediates 13–15 by simple bulb to bulb distillation.

Scheme II. Introduction of Acetic Acid Side Chain

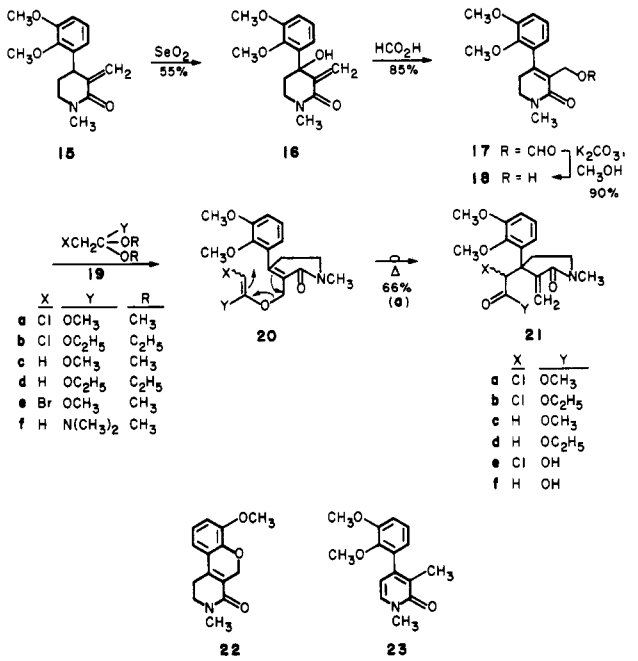


Table I. Ortho Ester Claisen Rearrangement (18 → 21) as a Function of Ortho Ester 19 Structure

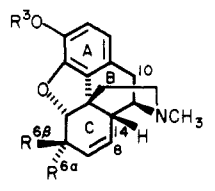
ortho acetate	X	Y	R	product[a]	% yield
19a	Cl	OCH_3	CH_3	ester 21a	66
b	Cl	OC_2H_5	C_2H_5	ester 21b	55
c	H	OCH_3	CH_3	ester 21c	70
d	H	OC_2H_5	C_2H_5	ester 21d	65
e	Br	OCH_3	CH_3	pyridone 23	51
f	H	$N(CH_3)_2$	CH_3	pyridone 23	66

[a] All reactions were performed in diglyme at 180 °C (bath temperature) over 24 h with initial distillative removal of ROH. Excess ortho ester/amide acetal was used (600 mol %) along with pivalic acid as a catalyst (5–10 mol %). Yields refer to products isolated after chromatography.

Acetic Acid Side-Chain Introduction. Functionalization of the piperidone at the 4-position also follows our earlier work (Scheme II).[10,11] Selenium dioxide oxidation

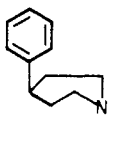
(9) Sargent, L. J.; Ager, J. H. *J. Med. Chem.* **1963**, *6*, 569.
(10) Weller, D. D.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 6650.
(11) Weller, D. D.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1977**, *42*, 1485.
(12) Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 1324.
(13) Horning, E. C.; Koo, J.; Walker, G. N. *J. Am. Chem. Soc.* **1951**, *73*, 5826.
(14) Borch, R. F. *Tetrahedron Lett.* **1968**, 61.
(15) Lee, D. L.; Morrow, C. J.; Rapoport, H. *J. Org. Chem.* **1974**, *39*, 893.

Chart I

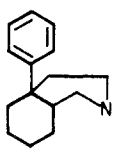


1 ABCNO

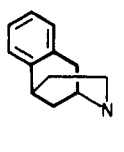
	R^3	$R^{6\beta}$	$R^{6\alpha}$
a morphine	H	H	OH
b codeine	CH_3	H	OH
c codeinone	CH_3	=O	



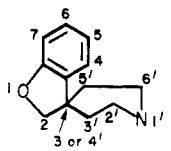
2 AN



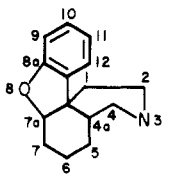
3 ACN



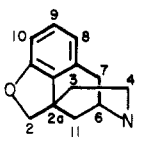
4 ABN



5 ANO



6 ACNO



7 ABNO

affords tertiary alcohol **16**, solvolysis with formic acid yields primary allylic formate **17**, along with tricyclic ether **22**,[16] and hydrolysis gives primary allylic alcohol **18**. The ortho ester Claisen rearrangement is usually performed with unsubstituted ortho esters.[17] In order to introduce simultaneously the functionality necessary for oxide ring closure, we investigated the use of α-halogenated ortho esters in the Claisen rearrangement, and the effect of structural variation on yield and product are summarized in Table I. Trimethyl orthoacetate (**19c**) and triethyl orthoacetate (**19d**) gave the desired esters **21c** and **21d** in 70% and 65% yields, respectively. This Me/Et trend continues with α-chlorinated ortho esters **19a**[18a] and **19b**,[18b] the respective yields being 66% and 55%. Trimethyl bromoorthoacetate (**19e**),[18c] however, did not produce the desired ester, but rather pyridone **23** in 51% yield. We also investigated the use of amide acetal **19f**[18d] as a model for α-halogenated amide acetals since amide acetals have sometimes proved superior to ortho esters;[18d,19] however, amide acetal Claisen rearrangement with **19f** yielded pyridone **23** in 66% yield.

The subtle yield changes induced by methyl vs. ethyl ortho esters and the striking differences observed with unsubstituted and α-chlorinated ortho esters vs. α-brominated ortho esters and amide acetals seem to indicate strict steric requirements for Claisen rearrangement in this system.[20] Variation of solvent and ortho ester stoichiometry had no apparent effect on the rearrangement, but acid was necessary for optimum results. The effect of temperature was not studied in detail, but no appreciable rearrangement is observed below 130 °C. Thus the four steps from lactam **15** to α-chloro ester **21a** proceeded in 44% yield as a single sequence with purification of only the final product.

In order to pursue this Claisen rearrangement study, we prepared a number of ortho esters using the Pinner reaction.[21] While the Pinner reaction works well, it is often a tedious procedure because of the necessity for strictly anhydrous conditions and because of the voluminous intermediate imidates. We have found that trimethyl chloroorthoacetate (**19a**) can be readily prepared by heating commercially available trimethyl orthoacetate (**19c**) in methanol with *N*-chlorosuccinimide and a trace of acid. Analytically pure product is obtained in 32% distilled yield, compared with 36% by the Pinner route, but with considerably less effort.

Ether Cleavage and Oxide Ring Closure. Ether cleavages can be effected with acids and nucleophiles and combinations of the two. Selectivity is achieved by coordination and steric effects. Since our next synthetic objective was specific cleavage of the *o*-methoxyl in α-chloro ester **21a**, the α-methylene lactam **15** was chosen as a model system for evaluation of the different ether cleavage methods. Reaction with 48% HBr below 100 °C resulted in some ether cleavage but incomplete reaction, whereas reaction at 100 °C resulted in cleavage of both ethers and loss of the *exo*-methylene moiety. Boron tribromide cleaved both ethers to give the catechol **25** in 95% yield. Lithium thiomethoxide[22a] caused ether cleavage but also a significant amount of Michael addition to the α-methylene lactam.

Push–pull nucleophile–acid methods were examined next because of the poor results with nucleophiles and acids alone. Treatment of lactam **15** with methanesulfonic acid (MsOH, 2000 mol %) and methionine (MET, 100 mol %)[22b] at 85 °C resulted in selective cleavage of the hindered

(16) Tricyclic ether **22**, byproduct of this solvolysis reaction, accounts for 15% of the product. This class of compounds has bronchodilator activity: Brown, R. E.; Shavel, J. German Offen. 2 411 847, 1974; *Chem. Abstr.* **1975**, *82*, 4302.

(17) When functionalized ortho esters have been used, the functionality has generally been remote from the ortho ester portion of the molecule. Recently[17c] trimethyl methoxyorthoacetate has been used, and 20–55% yields were achieved in the rearrangement. (a) Morimoto, T.; Sekiya, M. *Synthesis* **1981**, 308. (b) Raucher, S.; Macdonald, J. E.; Lawrence, R. F. *J. Am. Chem. Soc.* **1981**, *103*, 2419; *Tetrahedron Lett.* **1980**, 4335. Raucher, S.; Hwang, K.-J.; Macdonald, J. E. *Ibid.* **1979**, 3057. (c) Daub, G. W.; Teramura, D. H.; Bryant, K. E.; Burch, M. T. *J. Org. Chem.* **1981**, *46*, 1485. van Boom, J. H.; Owen, G. R.; Preston, J.; Ravindranathan, T.; Reese, C. B. *J. Chem. Soc. C* **1971**, 3230. (d) Saucy, G.; Cohen, N.; Banner, B. L.; Trullinger, D. P. *J. Org. Chem.* **1980**, *45*, 2080. (e) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *Ibid.* **1980**, *45*, 48. Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (f) Still, W. C.; Schneider, W. C. *Ibid.* **1977**, *99*, 948. (g) Werthemann, L.; Johnson, W. S. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, *67*, 1465.

(18) (a) $ClCH_2C(OMe)_3$: this ortho ester has been claimed as one of three products from the reaction of $FCH{=}CCl_2$ with methanol, but no physical characterization was provided. Delavarenne, S. Y.; Viehe, H. G. *Chem. Ber.* **1970**, *103*, 1198. (b) $ClCH_2(OEt)_3$: McElvain, S. M.; Nelson, J. W. *J. Am. Chem. Soc.* **1942**, *64*, 1825. (c) $BrCH_2C(OMe)_3$: McElvain, S. M.; Anthes, H. I.; Shapiro, S. H. *Ibid.* **1942**, *64*, 2525. (d) $CH_3C(NMe_2)(OMe)_2$: Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425.

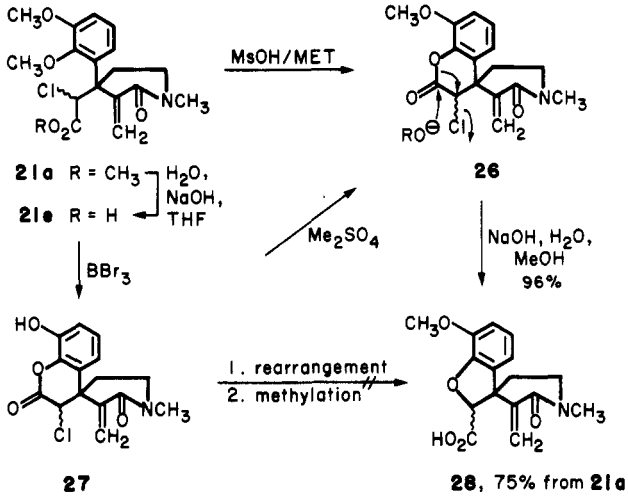
(19) Costin, C. R.; Morrow, C. J.; Rapoport, H. *J. Org. Chem.* **1976**, *41*, 535.

(20) Further evidence for the strict steric requirements in this system comes from Claisen rearrangement of a primary allylic alcohol, **18′**, where the *o*-methoxy group is replaced with a pivaloyloxy substituent. No rearrangement was observed with triethyl chloroorthoacetate (**19b**), whereas we found the rearrangement to proceed in 60% yield with trimethyl chloroorthoacetate (**19a**).

(21) Ortho ester reviews: (a) DeWolfe, R. H. *Synthesis* **1974**, 153. (b) "Carboxylic Ortho Acid Derivatives"; Academic Press: New York, 1970.

(22) (a) LiSMe: Kelley, T. R.; Dali, H. M.; Tsang, W.-G. *Tetrahedron Lett.* **1977**, 3859. (b) $MeSO_3H$/methionine: Irie, H.; Fugii, N.; Ogawa, H.; Yajima, H.; Fujino, M.; Shinagawa, S. *J. Chem. Soc., Chem. Commun.* **1976**, 922. Fujii, N.; Irie, H.; Yajima, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2288. (c) RSH/AlX_3: Node, M.; Nishide, K.; Sai, M.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1981**, *46*, 1991. Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *Ibid.* **1980**, *45*, 4275. Node, M.; Nishide, K.; Sai, M.; Ichikawa, K.; Fuji, K.; Fujita, E. *Chem. Lett.* **1979**, 97. (d) RSH/BF_3-Et_2O: Fujita, E.; Node, M.; Hori, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 611. Node, M.; Hori, H.; Fujita, E. *Ibid.* **1976**, 2237.

Scheme III. Oxide Ring Closure

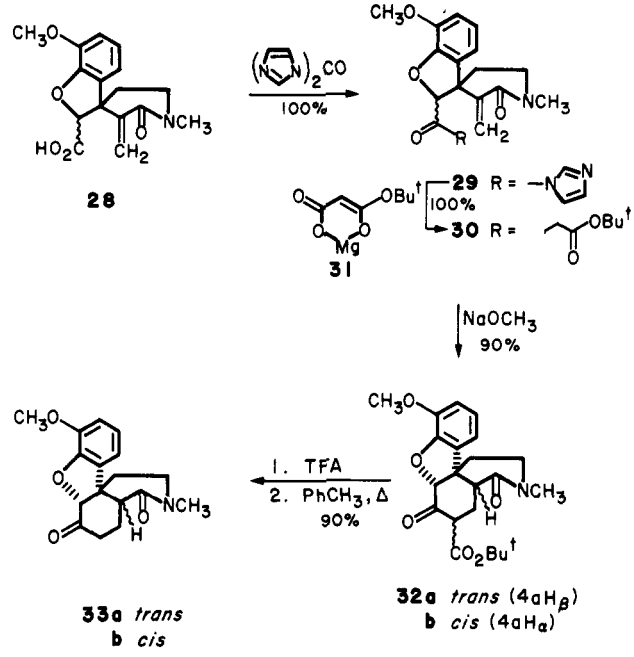


ortho ether, giving the phenol **24** in 95% yield. Cleavage of the hindered ether was expected because adjacent substituents force the ether out of the plane of the ring, rendering the alkyl group more susceptible to nucleophilic attack.[23] Evidence for cleavage of the hindered ether includes disappearance of the downfield methoxy resonance in the ^{13}C NMR spectrum and a measurable nuclear Overhauser enhancement in the aromatic region of the ^1H NMR spectrum upon irradiation of the remaining methoxy resonance. The conditions for maximum yield in this reaction are rigidly defined. Cleavage of both ethers occurred at higher temperatures (>95 °C), with excess methionine (>100 mol %) and with excess acid (>10^4 mol %). Lower temperatures (<75 °C), cosolvents, and smaller amounts of methionine (<100 mol %) led to incomplete reaction. 3-(Dimethylamino)propanethiol[24] was evaluated as a substitute for methionine, in the hope of achieving ether cleavage under milder conditions with the thiol. Cleavage was effected at lower temperatures (45 °C), but the yield was reduced (53%), presumably because of Michael addition of the thiol. Further model ether cleavages were investigated by using acid **21f** as the substrate. Reaction with $EtSH/AlCl_3$[22c] and $HSCH_2CH_2SH/BF_3{\cdot}Et_2O$[22d] produced only polymeric material.

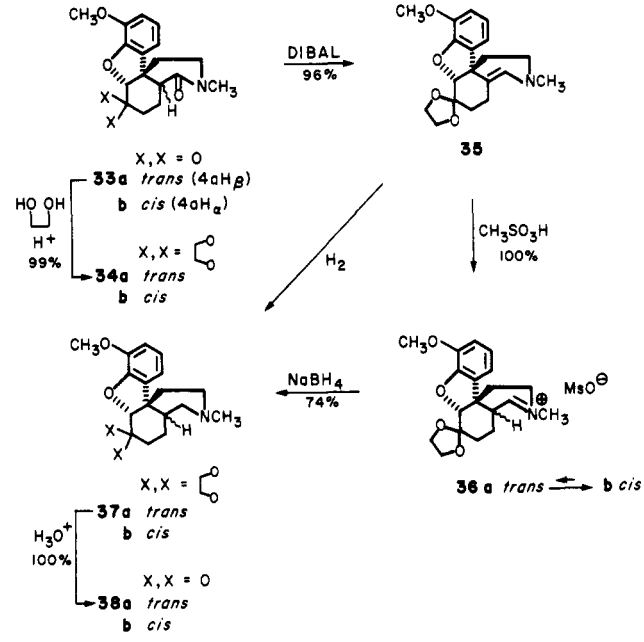
When α-chloro ester **21a** was treated with MsOH/MET, the product was not the desired spiro[benzofuran–piperidinone] **28** but the novel spiro[chromone–piperidone] **26** (Scheme III). Boron tribromide yielded the same lactone after methylation of the presumed intermediate phenolic lactone **27**. Spiro[benzofuran–piperidinone] **28** is then formed by treatment of lactone **26** with alkali.[25]

Maximum yields are obtained when the ether cleavage and rearrangement steps are combined in a sequence, and as in the model system, the conditions are rigidly defined. Reaction temperature and methionine stoichiometry are the most important variables. Poorer results are obtained with 3-(dimethylamino)propanethiol, with added formic acid, and, contrary to early results, with added water. The ester is cleaved more rapidly than the ether; thus with less than 200 mol % of the nucleophile, aqueous hydrolysis of the ester conserves the nucleophile and generates more ether cleavage. Under anhydrous conditions, 200 mol % of the nucleophile suffices to cleave both the ester and the ether.

Scheme IV. Closure of Ring C



Scheme V. Synthesis of Dihydrocodeinone Analogues



With this final two-step sequence proceeding in 75% yield, a functionalized spiro[benzofuran–piperidine] ring system is available in 18% overall yield from *o*-vanillin. Purification can be effected at this point, but for a continuing synthesis it is best deferred to a later stage.

C-Ring Closure. Methods for closing the C ring were developed in our 4a-aryldecahydroisoquinoline syntheses,[10,11] and extrapolation to this oxide ring-closed series has been successful as shown in Scheme IV. Treatment of spiro compound **28** with carbonyldiimidazole followed by treatment of imidazolide **29** with magnesium enolate **31** afforded β-keto ester **30**. Michael addition with NaOMe/MeOH gave isomeric ring-closed β-keto ester **32**, and hydrolysis and decarboxylation yielded benzofuroisoquinoline **33** as a mixture (70/30, presumably trans/cis[10,11]) of epimers at C-4a. This five-step sequence proceeds in 81% overall yield, with final purification of ketone

(23) Ahmad, R.; Saa, J. M.; Cava, M. P. *J. Org. Chem.* **1977**, *42*, 1228.
(24) Andrews, K. J. M.; Bergel, F.; Morrison, A. L. *J. Chem. Soc.* **1953**, 2998.
(25) A related chromone–benzofuran rearrangement has been reported: Newman, M. S.; Dalton, C. K. *J. Org. Chem.* **1965**, *30*, 4126.

Table II. Spectral Correlations for (a) *trans*- and (b) *cis*-Octahydrobenzofuroisoquinolines and Morphinans

compd	IR (carbonyl), cm^{-1}	mass spectrum, *m/z* (relative intensity)[32]
38a	1724	287 (38), 70 (100)
38b	1718	287 (92), 70 (100)
39a[28]	1703	301 (69), 164 (100), 59 (61)
39b[29]	1694	301 (100), 164 (62), 59 (3)
40a[30]	1707	315 (51), 164 (100), 59 (60)
40b[30]	1697	315 (93), 164 (100), 59 (20)
41a[31]	1727	
41b[31]	1725	
42a[10,26]	1712	243 (31), 43 (100)
42b[10,26]	1706	243 (57), 43 (100)
43a[11]	1706	273 (31), 71 (93), 70 (100)
43b[11]	1701	273 (68), 71 (100), 70 (87)

33 by medium-pressure liquid chromatography (MPLC). Thus **33** can be prepared from *o*-vanillin, with five total purifications, in 14% overall yield.

Dihydrocodeinone Analogues. Conversion of keto amide **33** to the corresponding dihydrocodeinone analogues is delineated in Scheme V. The C-7 carbonyl was protected as its ethylenedioxy ketal **34** in order to retain C-ring functionality in subsequent steps. This reaction proceeds rapidly with MsOH as the catalyst and in excellent yield but sluggishly and in poorer yield (40–50%) with *p*-toluenesulfonic acid as the catalyst. Partial reduction of the amide with diisobutylaluminum hydride (DIBAL) afforded enamine **35**. In the 4a-aryldecahydroisoquinoline series, kinetic protonation gives the trans isomer (≥87/13 trans/cis), and equilibration yields the cis isomer (≤5/95 trans/cis).[10,11,26,27,30] Treatment of enamine **35** with MsOH in chloroform at −50 °C produced a 60/40 mixture of iminium salts as analyzed by ^1H NMR. No appreciable equilibration occurs below −20 °C, but at −10 °C the kinetically preferred iminium salt has a half-life of 17.7 min, and above 0 °C the half-life is ≤5 min. The equilibrium ratio is ≤2/98. Analogy with the decahydroisoquinolines suggests that the predominant kinetic product is the trans isomer, but clearly kinetic selectivity is poor (60/40 trans/cis) with the oxide ring closed. The equilibrium product is still predominantly one isomer (<2/98), the cis isomer by similar analogy.[27]

Reduction of cis iminium salt **36b** (<2/98 trans/cis) with $NaBH_4$ at 0 °C yielded a 14/17/69 mixture of enamine **35**/amino ketal **37a**/amino ketal **37b**. Purification by MPLC afforded a 20/80 mixture of amino ketals **37a**/**37b**. Proton abstraction apparently competes with reduction to a minor extent. Catalytic hydrogenation of enamine **35** over Rh/Al_2O_3 produced a 46/29/25 mixture of enamine **35**/amino ketal **37a**/amino ketal **37b**, and purification by MPLC yielded a 54/46 mixture of the amino ketals. The poor selectivity in this system contrasts with the selectivity observed in the decahydroisoquinolines (≥95% selective for both trans and cis).[10,11,26] Deprotection of the ketone by aqueous hydrolysis produced a mixture of amino ketones **38a** and **38b**. The trans/cis ratio is dependent upon the prior reduction, and the isomers are separable by MPLC.

Definitive proof of C-4a/C-12b stereochemistry awaits X-ray analysis, but certain spectral characteristics are consistent with related trans/cis systems (Table II) and thus support our tentative assignments. Also, chromatography of seven different trans/cis isomer pairs with three different HPLC systems has always shown the assigned trans isomer with the longer retention time (see Experimental Section). No unambiguous ^1H NMR or ^{13}C NMR spectral correlation has been found.

The final sequence in this synthesis (**33** → **38**) involves five steps and proceeded in 70% yield with purification of amino ketones **38a** and **38b** by MPLC. These dihydrocodeinone (**1d**) analogues are thus obtained efficiently (10% overall yield) by a route involving six purifications from an inexpensive, readily available starting material (*o*-vanillin). This represents the first documented synthesis of an ACNO ring system, devoid of superfluous substitution, containing functionality in the C ring.[7,8] The ketone at C-7 provides for elaboration into typical morphine alkaloid functional patterns. Some of these benzofuroisoquinoline ring fragment analogues have shown activity both as agonists and antagonists,[8] with the implication that the absence of C-10 from morphine derivatives may allow separation of analgesia from addiction and respiratory depression. Models confirm that the benzofuroisoquinolines very closely mimic the morphine structure, especially when C-ring functionality is present, and further studies are now necessary to examine the potential of these systems.

Summary. A new route to highly functionalized spiro[benzofuran-3(2*H*),4′-piperidines] **5** and octahydro-1*H*-benzofuro[3,2-*e*]isoquinolines **6**, analogues of codeine, has been developed. This method extends our previous work with 4a-aryldecahydroisoquinolines[10,11] and invokes an α-chloro ortho ester Claisen rearrangement, a selective ether cleavage, and a chromone–benzofuran rearrangement. Various intermediates in this work provide entry into the synthesis of arylpiperidines (**13**), benzomorphans (**15**),[12] aryldecahydroisoquinolines (**21**),[10,11] the ANO (**5**) and ACNO (**6**) ring systems, and, potentially, the ABNO (**7**) and ABCNO (**1**) systems. Functionality built into compounds **28**, **32**, **33**, and **38** allows elaboration to typical morphine B- and C-ring patterns, which is in progress.

Experimental Section[33]

General Methods. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Methanol and ethanol were distilled from magnesium. 3-Methyl-3-pentanol was dried over molecular sieves (0.4 nm). Methylene chloride, chloroform, and chloroacetonitrile were distilled from phosphorus pentoxide. Toluene, chlorobenzene, *o*-dichlorobenzene, mesitylene, and 2-methoxyethyl ether (diglyme) were distilled from calcium hydride. Pyridine was distilled from barium oxide. Methanesulfonic acid was distilled under vacuum and contained less than 0.5% methanesulfonic anhydride by ^1H NMR. Boron trifluoride etherate was purified,[34] and Grignard reagents were standardized.[35]

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(27) We have chosen to refer to the stereochemistry in the benzofuroisoquinolines as in the 4a-aryldecahydroisoquinolines. Thus the trans isomers (substituents on C-4a and C-12b trans) correspond to the natural morphine configuration whereas the cis isomers correspond to the 14-*epi*-morphine configuration.

(28) (a) Freund, M.; Speyer, E.; Guttmann, E. *Chem. Ber.* **1920**, *53*, 2250. (b) Skita, A.; Nord, F. F.; Reichert, J.; Stukart, P. *Ibid.* **1921**, *54*, 1560. (c) Schopf, C. *Justus Liebigs Ann. Chem.* **1927**, *452*, 211. (d) Schopf, C.; Hirsch, H. *Ibid.* **1931**, *489*, 224. (e) Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1951**, *34*, 1948.

(29) Rapoport, H.; Lavigne, J. B. *J. Am. Chem. Soc.* **1953**, *75*, 5329.

(30) Moos, W. H.; Rapoport, H., unpublished work.

(31) Gates, M.; Shepard, M. S. *J. Am. Chem. Soc.* **1962**, *84*, 4125.

(32) Mass spectral correlations with stereochemistry in morphine derivatives have been reported before. Mandelbaum, A.; Ginsburg, D. *Tetrahedron Lett.* **1965**, 2479.

(33) For related work in the phenyl and *m*-methoxyphenyl series, see ref 10 and 11 and references cited therein.

(34) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. I, p 70.

Boiling points are uncorrected. Melting points were measured with Buchi (capillary) and Kofler (microscope slide) apparatuses and are uncorrected. IR spectra were determined in $CHCl_3$ unless otherwise noted with Perkin-Elmer 137, 281, 297, 337, and 681 spectrophotometers with polystyrene film for calibration (1601.4-cm^{-1} absorption) and a Nicolet Series 7000 FT spectrometer. UV spectra were determined in $CHCl_3$ with Cary 14 and 219 spectrophotometers. ^1H NMR spectra were determined on the following spectrometers: Varian T-60 (60 MHz); Hitachi Perkin-Elmer R-24B (60 MHz); Varian EM-390 (90 MHz); UCB-180 (a homemade FT instrument operating at 180.09 MHz); UCB-200 (a homemade FT instrument operating at 201.95 MHz); UCB-250 (a homemade FT instrument operating at 250.80 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 (δ) downfield from Me_4Si. ^{15}N NMR spectra (natural abundance) were measured at 18.25 MHz on the UCB-180 with proton decoupling. The spectra were recorded in $CHCl_3$, with $D^{15}NO_3/D_2O$ contained in a concentric inner tube serving for reference and lock, and are expressed in parts per million (δ) relative to CH_3NO_2 (neat) at δ 380.23. Low-resolution mass spectra were obtained with an AEI MS-12 instrument (EI, 70 eV). High-resolution (exact mass) mass spectra were obtained with a Du Pont CEC 21-110 instrument. Elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California.

Gas chromatography (GC) was done with Varian Aerograph A-90P and Hewlett-Packard 402 gas chromatographs with a He flow rate 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, and a 420 microprocessor controller/programmer. The following stainless-steel Altex columns were used: (A) 3.2 × 250 mm, 5-μm LiChrosorb Si60 normal phase (NP) silica gel; (B) 3.2 × 250 mm, 10-μm LiChrosorb C_{18} reverse phase (RP) silica gel. Unless otherwise noted, a flow rate of 1.0 mL/min (one column volume equals 1.5 min) was used, with monitoring at 280 nm. Preparative medium-pressure liquid chromatography (MPLC) was done by using an Altex 110A pump equipped with a preparative liquid head and an Altex 151 UV detector set at 280 nm. The following columns were used: (A) Altex stainless-steel column, 10 × 250 mm, 5-μm LiChrosorb Si60 silica gel (NP); (B) Altex stainless-steel column, 10 × 250 mm, 10-μm Spherisorb ODS silica gel (RP); (C) Ace Michel-Miller glass columns, 25 × 130 or 40 × 240 mm, 40–63-μm silica gel 60 (EM Reagents). Column chromatography (CC) was performed with 63–200-μm silica gel 60 (EM Reagents). Analytical thin-layer chromatography (TLC) was done with aluminum-backed silica plates (E. Merck). Preparative TLC was carried out on 2000-μm-thick silica gel GF (Analtech).

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 evaporated with a Berkeley rotary evaporator by using water aspirator or oil pump reduced pressure, followed by static evaporation with an oil pump. All distillations were bulb to bulb (Kugelrohr-type apparatus) unless otherwise noted. Hydrogenations were carried out under 40–50 psi of hydrogen pressure, with shaking, at 20–26 °C on Parr-type systems. All reactions were monitored and product purity was determined by TLC and HPLC or GC.

2,3-Dimethoxybenzaldehyde (9). A mixture of *o*-vanillin (80.0 g, 0.527 mol), K_2CO_3 (109 g, 0.79 mol, 150 mol %), Me_2SO_4 (133 g, 0.947 mol, 180 mol %), and MeOH (400 mL) was stirred at reflux for 2.5 h. The yellow suspension was cooled to 25 °C, diluted with H_2O (250 mL), and acidified with 2.5 M aqueous H_2SO_4 (125 mL) over 15 min with stirring. After the mixture was stirred an additional 15 min, the white suspension was partitioned between CCl_4 (250 mL) and H_2O (400 mL). The resulting white suspension was extracted with CCl_4 (10 × 75 mL), and the combined organic extracts were washed with H_2O/MeOH (2/1, 225 mL), 0.3 M aqueous NaOH (3 × 300 mL), H_2O (300 mL), and saturated aqueous NaCl (300 mL). The resulting organic layer was dried ($MgSO_4$) and evaporated to yield **9**: 81.4 g (0.49 mol, 93%); mp 50.0–51.5 °C (from hexane) (lit.[36] mp 50–51 °C); IR 1680 cm^{-1}; ^1H NMR (60 MHz) δ 10.5 (s, 1 H), 7.5–7.1 (m, 3 H), 4.0 (s, 3 H), 3.9 (s, 3 H); ^{13}C NMR (25 MHz) δ 189.9, 153.2, 152.8, 130.0, 124.1, 119.2, 118.5, 62.1, 56.1.

(*E*)-Ethyl 3-(2,3-Dimethoxyphenyl)-2-propenoate (10). A solution of aldehyde **9** (328 g, 2.0 mol), ethyl hydrogen malonate (344 g, 2.6 mol, 130 mol %), and piperidine (34 g, 0.4 mol, 20 mol %) in pyridine (1.64 L) was heated at reflux for 7 h. After cooling, the solution was evaporated, the residue was dissolved in $CHCl_3$ (1.8 L), and the $CHCl_3$ solution was washed with 1.5 M aqueous HCl (1.5 L) and saturated aqueous $NaHCO_3$ (1.5 L). The resulting organic layer was dried ($MgSO_4$) and evaporated, and the residue was distilled to afford **10**: 50 g (1.90 mol, 95%); mp 47–48 °C (from ether); bp 125–131 °C (0.03 kPa) [lit.[13] bp 146–147 °C (0.11 kPa)]; IR 2980, 1695, 1635, 1575, 1460, 1260, 1170 cm^{-1}; UV λ_{max} 283 nm (ϵ 3020); ^1H NMR (60 MHz) δ 8.0 (d, 1 H, J = 16 Hz), 7.02 (m, 3 H), 6.50 (d, 1 H, J = 16 Hz), 4.27 (q, 2 H, J = 7 Hz), 3.84 (s, 6 H), 1.30 (t, 3 H, J = 7 Hz); ^{13}C NMR (25 MHz) δ 167.1, 153.3, 148.7, 139.4, 128.7, 124.2, 119.7, 119.5, 114.3, 61.1, 60.4, 55.9, 14.4.

Diethyl 2-Cyano-3-(2,3-dimethoxyphenyl)pentanedioate (11). Sodium (11.0 g, 0.48 mol, 112 mol %) was added to EtOH (703 mL) with mechanical stirring. After 30 min, ethyl cyanoacetate (53.5 g, 0.47 mol, 110 mol %) was added dropwise over 15 min. A solution of cinnamate **10** (101 g, 0.43 mol) in EtOH (156 mL) was then added dropwise over 40 min, and the resulting solution was heated at reflux for 3 h. After cooling, the reaction mixture was treated with glacial HOAc (30 g, 0.51 mol, 119 mol %) and evaporated. The residue was dissolved in $CHCl_3$ (350 mL), the organic layer was washed with saturated $NaHCO_3$ (360 mL), and the aqueous layer was washed with $CHCl_3$ (2 × 270 mL). The combined organic layers were dried ($MgSO_4$) and evaporated, and the residue was distilled, giving **11** (141 g, 0.40 mol, 93%) as a viscous yellow oil (mixture of diastereomers): HPLC ($CHCl_3$, column A) t_R = 4.4 min; mp 50–52 °C (one isomer); bp 164–184 °C (0.03 kPa); IR (neat) 2260, 1735 cm^{-1}; UV λ_{max} 280 nm (ϵ 2690); ^1H NMR (60 MHz) δ 6.98 (m, 3 H), 4.50–3.85 (m, 12 H), 2.95 (m, 2 H), 1.20 (m, 6 H); ^{13}C NMR (25 MHz) δ 170.8, 170.6, 165.2, 152.9, 147.4, 147.2, 132.0, 131.7, 124.1, 119.9, 119.4, 115.8, 115.5, 112.8, 62.8, 62.6, 61.1, 60.6, 59.9, 59.3, 55.8, 42.9, 42.2, 37.5, 36.4, 36.0, 35.0, 14.3, 14.0, 13.8; ^{15}N NMR (2.88 M) δ 254.6; mass spectrum, m/z (relative intensity) 349 (68), 304 (23), 275 (32), 217 (23), 195 (100), 191 (78), 162 (36), 136 (26). Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.9; H, 6.7; N, 4.0. Found: C, 61.8; H, 6.8; N, 4.0.

Ethyl 4-(2,3-Dimethoxyphenyl)-6-piperidinone-3-carboxylate (12). A solution of nitrile **11** (25.0 g, 0.07 mol) in EtOH (92 mL) was mixed with PtO_2 (1.3 g), and saturated ethanolic HCl (40 mL) was added. The mixture was hydrogenated for 6 h, more PtO_2 (0.6 g) was added, and hydrogenation was continued for 12 h. The hydrogenation mixture was filtered with generous EtOH washes, and the filtrate was evaporated. The residue was dissolved in 1 M aqueous H_3PO_4 (150 mL), the solution was washed with benzene (150 mL), and the aqueous layer was basified with excess K_2CO_3 and extracted with $CHCl_3$ (3 × 100 mL). The combined organic extracts were evaporated, the residue was dissolved in toluene (92 mL), and the solution was heated at reflux for 2 h and then evaporated to give a brown oil which was triturated with ether followed by filtration, giving **12** (18.3 g, 0.06 mol, 85%) as a white powder (mixture of diastereomers): HPLC (50/50 $CHCl_3$/EtOAc, column A) t_R = 9.0, 11.3 min; mp 85–87 °C; bp 180–190 °C (0.01 kPa); IR (neat) 3190, 1725, 1665 cm^{-1}; UV λ_{max} 274 nm (ϵ 1610), 278 (1630); ^1H NMR (60 MHz) δ 7.42 (br s, 1 H), 6.92 (m, 3 H), 4.04 (q, 2 H, J = 7 Hz), 3.94 (s, 3 H), 3.92 (s, 3 H), 3.85–2.55 (m, 6 H), 1.12, 1.03 (2 t, total 3 H, J = 7 Hz); ^{13}C NMR (25 MHz, 1/1 $CDCl_3$/acetone-d_6) δ 172.5, 172.0, 171.6, 171.0, 153.5, 153.2, 148.0, 147.8, 136.0, 134.4, 124.5, 124.0, 120.1, 120.0, 112.3, 112.2, 78.8, 77.0, 60.8, 60.6, 56.0, 45.1, 43.8, 42.9, 42.8, 38.1, 36.7, 35.1, 34.1, 30.7, 29.8; ^{15}N NMR (0.16

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M, 0.025 M $Cr(acac)_3$) δ 111.1, 110.5; mass spectrum, *m/z* (relative intensity) 307 (63), 234 (82), 203 (39), 191 (68), 177 (48), 162 (100), 148 (64), 136 (66). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.5; H, 6.9; N, 4.6. Found: C, 62.6; H, 6.8; N, 4.6.

Ethyl 4-(2,3-Dimethoxyphenyl)piperidine-3-carboxylate (13). A solution of lactam **12** (51.5 g, 0.167 mol) in CH_2Cl_2 (550 mL) was treated with Me_3OBF_4[37] (28.9 g, 0.105 mol, 117 mol %). After 24 h the solution was evaporated to a foam, and the foam was dissolved in absolute EtOH (300 mL) and cooled in an ice/NaCl bath. Sodium borohydride (18.5 g, 0.49 mol, 290 mol %) was added in portions in order to maintain a temperature (iT) below 10 °C. The slurry was allowed to warm to 23 °C after the addition had been completed; after 12 h 3 M aqueous H_3PO_4 was added until solution was complete (pH 2–3). The acidic solution was basified with excess K_2CO_3 and extracted with $CHCl_3$ (3 × 500 mL), the combined organic layers were dried and evaporated, and the residue was distilled, affording **13** (40.2 g, 0.137 mol, 82%) as a colorless oil (mixture of diastereomers): HPLC (95/5 MeOH/H_2O, 0.6 mL/min, column B) t_R = 2.7, 3.0 min; bp 110–150 °C (0.04 kPa); IR (neat) 3300, 1725 cm^{-1}; UV λ_{max} 272 nm (ε 1450), 278 (1450); ^1H NMR (60 MHz) δ 6.93 (m, 3 H), 4.02 (q, 2 H, *J* = 7 Hz), 3.98 (s, 6 H), 3.87–2.47 (m, 6 H), 2.42 (br s, 1 H), 2.00–1.30 (m, 2 H), 1.10, 1.03 (2 t, total 3 H, *J* = 7 Hz); ^{13}C NMR (25 MHz) δ 174.2, 173.1, 152.9, 147.2, 137.3, 136.7, 123.9, 123.5, 122.0, 119.6, 119.5, 111.2, 111.1, 110.9, 60.8, 60.0, 59.7, 55.7, 49.3, 48.8, 48.3, 46.7, 46.6, 43.9, 39.0, 37.1, 35.1, 33.8, 26.8, 25.7, 14.3, 14.0; ^{15}N NMR (1.46 M) δ 32.9, 24.1; mass spectrum, *m/z* (relative intensity) 293 (1), 262 (100), 220 (14), 191 (20), 178 (17), 162 (24). Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.5; H, 7.9; N, 4.8. Found: C, 65.3; H, 7.8; N, 4.9.

Ethyl 4-(2,3-Dimethoxyphenyl)-1-methylpiperidine-3-carboxylate (14). A mixture of amine **13** (10.0 g, 0.030 mol), EtOH (91 mL), 37% aqueous CH_2O (10 mL), and 10% Pd/C (1.1 g) was hydrogenated for 24 h. The mixture was filtered with an EtOH rinse, and the filtrate was evaporated to a residue which was mixed with H_2O (130 mL) and extracted with $CHCl_3$ (4 × 50 mL). The combined organic layers were dried and evaporated, and the residue was distilled to give **14** (8.67 g, 0.028 mol, 94%) as a colorless oil (mixture of diastereomers): HPLC (EtOAc, column A) t_R = 18.9, 19.7 min; bp 114–129 °C (0.03 kPa); IR (neat) 1725 cm^{-1}; UV λ_{max} 272 nm (ε 1530), 278 (1530); ^1H NMR (60 MHz) δ 6.87 (m, 3 H), 3.83, 3.78 (2 q, total 2 H, *J* = 7 Hz), 3.82 (s, 6 H), 3.43–1.20 (m, 8 H), 2.33, 2.27 (2 s, total 3 H), 1.00, 0.97 (2 t, total 3 H, *J* = 7 Hz); ^{13}C NMR (25 MHz) δ 173.1, 172.6, 152.8, 152.3, 150.4, 147.2, 137.2, 136.6, 123.9, 123.2, 121.0, 119.5, 110.8, 60.7, 60.5, 59.9, 59.5, 58.7, 58.4, 56.4, 56.1, 55.9, 55.7, 55.5, 47.4, 46.7, 46.2, 44.6, 38.3, 36.4, 33.2, 26.7, 13.9; ^{15}N NMR (0.64 M) δ 35.4, 32.1; mass spectrum, *m/z* (relative intensity) 307 (33), 276 (44), 262 (12), 234 (23), 225 (12), 165 (17). Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.4; H, 8.2; N, 4.6. Found: C, 66.2; H, 8.4; N, 4.7.

4-(2,3-Dimethoxyphenyl)-1-methyl-3-methylene-2-piperidinone (15). A solution of tertiary amine **14** (50.4 g, 0.164 mol), MeOH (300 mL), H_2O (90 mL), and NaOH (14.0 g, 0.35 mol, 213 mol %) was heated at reflux for 8 h. Glacial HOAc (30 mL, 0.52 mol, 320 mol %) was added, and the mixture was evaporated. Acetic anhydride (2 L) was added, the mixture was distilled to near dryness, and the acetic anhydride distillation (2 × 500 mL) was repeated. The dark residue was mixed with H_2O (600 mL), the mixture was basified with K_2CO_3 and extracted with $CHCl_3$ (5 × 300 mL), the combined organic layers were dried and evaporated, and the residue was distilled to give **15**: 42.6 g (0.16 mol, 99%); mp 58–60 °C; HPLC (50/50 $CHCl_3$/EtOAc, column A) t_R = 4.2 min; bp 110–125 °C (0.04 kPa); IR (neat) 1665, 1600 cm^{-1}; UV λ_{max} 270 nm (ε 10500), 278 (8340); ^1H NMR (60 MHz) δ 7.15–6.61 (m, 3 H), 6.37 (t, 1 H, *J* = 2 Hz), 5.00 (t, 1 H, *J* = 2 Hz), 4.22 (m, 1 H), 3.91 (s, 3 H), 3.82 (s, 3 H), 3.36 (m, 2 H), 3.08 (s, 3 H), 2.07 (m, 2 H); ^{13}C NMR (25 MHz) δ 163.9, 152.3, 146.5, 141.4, 135.5, 123.6, 121.7, 119.8, 110.7, 60.3, 55.2, 48.0, 38.7, 34.7, 28.9; ^{15}N NMR (2.33 M) δ 106.1; mass spectrum, *m/z* (relative intensity) 261 (74), 246 (12), 232 (41), 230 (23), 161 (23), 44 (100). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.9; H, 7.3; N, 5.4. Found: C, 68.7; H, 7.2; N, 5.4.

(37) Curphey, T. J. *Org. Synth.* **1971**, *51*, 142.

4-Hydroxy-4-(2,3-dimethoxyphenyl)-1-methyl-3-methylene-2-piperidinone (16). A solution of lactam **15** (25.0 g, 96 mmol) in chlorobenzene (412 mL) was mixed with SeO_2 (7.96 g, 0.072 mol, 75 mol %) and lowered into a 100 °C bath. After 70 min the reaction mixture was evaporated (bT 20–25 °C), and the residue was chromatographed, eluting with EtOAc. Tertiary alcohol **16** (14.7 g, 53 mmol, 55%) was obtained as pale yellow crystals: HPLC (50/50 $CHCl_3$/EtOAc, column A) t_R = 12.3 min; mp 135–136 °C (from CH_2Cl_2/hexane); IR (KBr) 3220, 1640, 1585 cm^{-1}; ^1H NMR (60 MHz) δ 6.89 (m, 3 H), 6.30 (d, 1 H, *J* = 2 Hz), 5.37 (d, 1 H *J* = 2 Hz), 4.19 (br s, 1 H), 3.73 (s, 6 H), 3.7–1.6 (m, 4 H), 2.88 (s, 3 H); mass spectrum, *m/z* (relative intensity) 277 (30), 260 (44), 246 (27), 165 (17), 143 (20), 55 (100). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.9; N, 5.1. Found: C, 64.9; H, 6.9; N, 5.0.

3-[(Formyloxy)methyl]-4-(2,3-Dimethoxyphenyl)-1-methyl-5,6-dihydro-2-pyridinone (17) and 5*H*-7-Methoxy-3-methyl-4-oxo-1,2,3,4-tetrahydro[1]benzopyrano[3,4-*c*]-pyridine (22). Tertiary alcohol **16** (295 mg, 1.06 mmol) was solvolyzed in 97% HCO_2H (10 mL) for 16 h at room temperature, and the solution was evaporated. The residue solidified upon being allowed to stand, and recrystallization (EtOAc) afforded **22** (35 mg) as white needles. Purification of the mother liquors by chromatography ($CHCl_3$) gave additional **22** (33 mg; total 68 mg, 0.28 mmol, 26%): HPLC (50/50 $CHCl_3$/EtOAc, column A) t_R = 3.5 min; mp 190–191 °C (from EtOAc/$CHCl_3$); IR (KBr) 1655, 1620 cm^{-1}; ^1H NMR (250 MHz) δ 6.95–6.82 (m, 3 H), 5.07 (t, 2 H, *J* = 1.8 Hz), 3.89 (s, 3 H), 3.53 (t, 2 H, *J* = 7.2 Hz), 3.04 (s, 3 H), 2.73 (tt, 2 H, *J* = 7.2 Hz, *J'* = 1.8 Hz); ^{13}C NMR (25 MHz) δ 163.7, 148.4, 137.5, 137.3, 122.4, 121.2, 116.3, 114.2, 100.8, 64.2, 56.3, 46.9, 34.3, 23.0; mass spectrum, *m/z* (relative intensity) 245 (100), 216 (77), 201 (25), 187 (43). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.5; H, 6.2; N, 5.7. Found: C, 68.3; H, 6.2; N, 5.9.

The mother liquors also afforded **17** (77 mg, 0.25 mmol, 24%) after chromatography ($CHCl_3$) as a yellow oil which was not stable [rapid purification by preparative TLC (EtOAc) gave **17** in 85% yield on a small scale]: bp 170 °C (0.01 kPa); IR (neat) 1715, 1655, 1620 cm^{-1}; ^1H NMR (60 MHz), δ 8.0 (s, 1 H), 7.12–6.51 (m, 3 H), 4.78 (br s, 2 H), 3.84 (s, 3 H), 3.72 (s, 3 H), 3.50 (t, 2 H, *J* = 7 Hz), 3.04 (s, 3 H), 2.67 (br t, 2 H, *J* = 7 Hz); mass spectrum, *m/z* (relative intensity) 305 (60), 276 (100), 259 (44), 248 (37), 244 (35). Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.9; H, 6.3; N, 4.6. Found: C, 63.2; H, 6.1; N, 5.0.

3-(Hydroxymethyl)-4-(2,3-dimethoxyphenyl)-1-methyl-5,6-dihydro-2-pyridinone (18). Tertiary alcohol **16** (261 mg, 0.94 mmol) was solvolyzed in 97% HCO_2H (10 mL) for 16 h, and the solvent was evaporated. The residue was dissolved in $CHCl_3$ (15 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL), the aqueous layer was extracted with $CHCl_3$ (2 × 15 mL), the combined organic phases were dried and evaporated, the crude product was dissolved in MeOH (10 mL), and K_2CO_3 (41 mg, 0.30 mmol, 32 mol %) was added. After 22 h the mixture was evaporated, and the residue was partitioned between $CHCl_3$ (15 mL) and saturated aqueous NaCl (15 mL). Extracting with $CHCl_3$ (2 × 15 mL), combining the organic extracts, drying, and evaporating (bT <25 °C) yielded a 3/1 mixture of **18**/**22** (225 mg). Purification by chromatography (EtOAc) afforded **18** (81 mg, 0.29 mmol, 31%) as a yellow oil which was not stable [rapid purification by preparative TLC (EtOAc) gave **18** in 90% yield on a small scale]: HPLC (50/50 $CHCl_3$/EtOAc, column A) t_R = 15.6 min; mp 117–118 °C (from CH_2Cl_2/hexane); IR (KBr) 3430, 1650, 1615 cm^{-1}; ^1H NMR (60 MHz) δ 7.3–6.6 (m, 3 H), 4.22 (s, 2 H), 3.90 (s, 3 H), 3.78 (s, 3 H), 3.54 (t, 2 H, *J* = 7 Hz), 3.5 (br s, 1 H), 3.07 (s, 3 H), 2.73 (br t, 2 H, *J* = 7 Hz); mass spectrum, *m/z* (relative intensity) 277 (22), 248 (100), 231 (24), 185 (32). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.9; N, 5.1. Found: C, 64.9; H, 6.6; N, 4.9.

4-[(Methoxycarbonyl)chloromethyl]-4-(2,3-dimethoxyphenyl)-1-methyl-3-methylene-2-piperidinone (21a). Allylic alcohol **18** (1.78 g, 6.40 mmol) was dissolved in diglyme (15 mL), pivalic acid (70 mg, 0.69 mmol, 11 mol %) and trimethyl chloroorthoacetate[18a] (**19a**, 5.64 g, 38.4 mmol, 600 mol, %) were added, and the solution was heated at 165 °C (bT) for 8 h and then at reflux (bT 180–185 °C) for 16 h. Evaporation and purification of the residue by MPLC (EtOAc, column C) afforded **21a** (1.55 g, 4.21 mmol, 66%) as a mixture of diastereomers: HPLC (50/50

$CHCl_3$/EtOAc, column A) t_R = 3.2, 3.8 min; IR 2912, 1718, 1598 cm^{-1}; UV (CCl_4) λ_{max} 281 nm (ϵ 3760); ^1H NMR (60 MHz) δ 7.0–6.5 (m, 3 H), 6.07, 5.90 (2 s, total 1 H, ratio 79/21), 5.33, 5.23 (2 s, total 1 H, ratio 21/79), 3.9 (s, 3 H), 3.83 (s, 3 H), 3.35 (br s, 3 H), 4.0–2.5 (m, 5 H), 2.78 (s, 3 H); ^{13}C NMR (63 MHz) δ 168.4, 164.7, 153.0, 152.6, 149.8, 148.0, 138.8, 135.6, 130.4, 124.8, 124.2, 123.5, 123.1, 122.7, 121.7, 120.6, 114.0, 113.0, 112.9, 112.8, 61.8, 61.4, 61.0, 60.4, 56.8, 55.8, 52.6, 52.0, 49.1, 45.9, 34.9, 34.8, 34.5, 30.9, 30.3, 26.1; mass spectrum, m/z (relative intensity) 367 (2), 340 (9), 332 (8), 325 (9), 272 (13), 261 (43), 260 (100), 244 (16), 229 (17), 215 (23), 189 (15), 174 (17); exact mass calcd for $C_{18}H_{22}{}^{35}ClNO_5$ m/z 367.1186, found m/z 367.1177.

1-Methyl-3-methylene-4-(2,3-dimethoxyphenyl)-4-[(ethoxycarbonyl)chloromethyl]-2-piperidinone (21b). Ester **21b** was prepared as a mixture of diastereomers as described above with the substitution of triethyl chloroorthoacetate[18b] (**19b**) for **19a**. Purification by MPLC (60/40 MeOH/H_2O, column B, 4.2 mL/min) yielded 55% of **21b**: HPLC (EtOAc, column A) t_R = 3.6, 4.2 min; bp 195–210 °C dec (0.01 kPa); IR 1740, 1650, 1610, 1470, 1260, 1010 cm^{-1}; ^1H NMR (60 MHz) δ 7.7–6.6 (m, 3 H), 6.1 (s, 1 H), 5.2 (s, 1 H), 3.9 (s, 3 H), 3.8 (s, 3 H), 4.1–2.6 (m, 5 H), 2.8 (s, 3 H), 1.2 (m, 2 H), 0.87 (t, 3 H, J = 7 Hz); mass spectrum, m/z (relative intensity) 381 (1), 346 (3), 260 (100); exact mass calcd for $C_{19}H_{24}{}^{35}ClNO_5$ m/z 381.1343, found m/z 381.1334.

4-[(Methoxycarbonyl)methyl]-4-(2,3-dimethoxyphenyl)-1-methyl-3-methylene-2-piperidinone (21c). Ester **21c** was prepared as described above with the substitution of trimethyl orthoacetate (**19c**) for **19a**. Purification by chromatography (EtOAc) yielded 70% of **21c**: bp 145–193 °C (0.04 kPa); IR 3017, 1741, 1654, 1601, 1467, 1333, 1262, 1050, 734, 705 cm^{-1}; ^1H NMR (60 MHz) δ 7.1–6.6 (m, 3 H), 6.56 (s, 1 H), 5.56 (s, 1 H), 3.93 (s, 6 H), 3.57 (s, 3 H), 3.25–2.00 (m, 6 H), 2.89 (s, 3 H). This ester was hydrolyzed and fully characterized as the acid **21f** below.

4-[(Ethoxycarbonyl)methyl]-4-(2,3-dimethoxyphenyl)-1-methyl-3-methylene-2-piperidinone (21d). Ester **21d** was prepared as described above with the substitution of triethyl orthoacetate (**19d**) for **19a**. Purification by chromatography (EtOAc) yielded 65% of **21d**, which was characterized as the acid **21f** below.

4-(Carboxychloromethyl)-4-(2,3-dimethoxyphenyl)-1-methyl-3-methylene-2-piperidinone (21e). Ester **21a** (250 mg, 0.68 mmol) was dissolved in 4 M aqueous NaOH (2 mL), MeOH (2 mL), and THF (2 mL). After 6 days the alkaline solution was diluted with H_2O (10 mL) and extracted with $CHCl_3$ (10 mL), the aqueous phase was acidified (pH 1) with 3 M aqueous HCl, and the acidic layer was extracted with $CHCl_3$ (2 × 10 mL). The $CHCl_3$ extract of the alkaline solution was dried and evaporated to give pyridone **23** (98.3 mg, 0.32 mmol, 47%), and the $CHCl_3$ extracts of the acidic solution were combined, dried, and evaporated to give **21e** (127 mg, 0.36 mmol, 53%) as a mixture of diastereomers: IR 2915, 1706, 1578, 1451, 1254 cm^{-1}; ^1H NMR (60 MHz) δ 11.8 (br s, 1 H), 6.9–6.4 (m, 3 H), 6.1 (br s, 1 H), 5.4, 5.3 (2 s, total 1 H), 3.9 (s, 3 H), 3.8 (s, 3 H), 2.8 (s, 3 H), 4.0–1.6 (m, 5 H); mass spectrum, m/z (relative intensity) 355 (3), 353 (8), 317 (16), 303 (4), 288 (4), 273 (26), 260 (100); exact mass calcd for $C_{17}H_{20}{}^{35}ClNO_5$ m/z 353.1030, found m/z 353.1025.

4-(Carboxymethyl)-4-(2,3-dimethoxyphenyl)-1-methyl-3-methylene-2-piperidinone (21f). Acid **21f** was best prepared in two sequences from tertiary alcohol **16**, with purification of ester **21c** by distillation and with hydrolysis and isolation as described above. The overall yield of **21f** from **16** was 28% after recrystallization: HPLC (50/50 MeOH/H_2O, column B) t_R = 6.5 min; mp 194.5–196.5 °C (from $CHCl_3$/hexane); IR (KBr) 1735, 1645, 1585; ^1H NMR (60 MHz) δ 8.0 (br s, 1 H), 6.90 (m, 3 H), 6.59 (s, 1 H), 5.64 (s, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.3–2.3 (m, 4 H), 2.85 (s, 3 H); ^{13}C NMR (25 MHz, 1/1 $CDCl_3/CD_3OD$) δ 172.5, 165.0, 152.5, 147.4, 144.0, 133.9, 122.6, 121.0, 120.6, 112.1, 59.3, 54.9, 45.5, 41.5, 34.0, 31.0; mass spectrum, m/z (relative intensity) 319 (11), 260 (100). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.9; H, 6.6; N, 4.4. Found: C, 63.7; H, 6.7; N, 4.2.

Claisen Rearrangement Sequences. Esters **21a** and **21b** were prepared from α-methylene lactam **15** in 44% and 41% yields, respectively, without intermediate purification.

4-(2,3-Dimethoxyphenyl)-1,3-dimethyl-2-piperidinone (23). Treatment of allylic alcohol **18** as described above with trimethyl bromoorthoacetate[18c] (**19e**) rather than **19a** yielded pyridone **23** in 51% yield as a yellow oil after chromatography (EtOAc) and not the rearranged ester **21** (X = Br, Y = OMe). Similarly, the use of amide acetal[18d] **19f** produced pyridone **23** in 66% yield after purification: HPLC (EtOAc, column A) t_R = 12.1 min; bp 145–165 °C (0.01 kPa); IR 2900, 1630, 1575, 1450, 1250, 1200, 1070, 1015, 1005, 905, 840 cm^{-1}; ^1H NMR (180 MHz) δ 7.2–6.7 (m, 4 H), 6.1 (d, 1 H, J = 7.2 Hz), 3.9 (s, 3 H), 3.65 (s, 3 H), 3.60 (s, 3 H), 2.00 (s, 3 H); ^{13}C NMR (25 MHz) δ 163.1, 152.7, 146.3, 133.5, 127.0, 123.7, 121.1, 112.1, 108.3, 60.4, 55.5, 37.3, 14.1; mass spectrum, m/z (relative intensity) 259 (100), 244 (44), 228 (70), 213 (16), 85 (60), 83 (87). Anal. Calcd for $C_{15}H_{17}NO_3 \cdot 0.5H_2O$: C, 67.2; H, 6.8; N, 5.2. Found: C, 67.3; H, 6.6; N, 5.1.

Trimethyl Chloroorthoacetate (1-Chloro-2,2,2-trimethoxyethane, 19a).[18a] (A) From $ClCH_2CN$. Ortho ester **19a** was prepared by the method of McElvain and Nelson[18b] from chloroacetonitrile, substituting MeOH for EtOH. Fractional distillation afforded **19a** in 36% yield: bp 61–64 °C (2.53 kPa); IR 2925, 2820, 1465, 1430, 1300, 1210, 1160, 1095, 1075, 1015, 945, 875, 740 cm^{-1}; ^1H NMR (60 MHz) δ 3.57 (s, 2 H), 3.28 (s, 9 H); ^{13}C NMR (25 MHz) δ 113.2, 50.1, 41.2. Anal. Calcd for $C_5H_{11}ClO_3$: C, 38.8; H, 7.2; Cl, 22.9. Found: C, 38.9; H, 7.1; Cl, 22.9.

(B) Via Chlorination of Ortho Ester 19c. Trimethyl orthoacetate (**19c**, 35.0 g, 0.29 mol) was combined with MeOH (250 mL), *N*-chlorosuccinimide (47.4 g, 0.35 mol, 122 mol %), and concentrated HCl (0.3 mL) under an argon atmosphere. The solution was heated at 70–80 °C (bT) for 3.5 h, allowed to cool to 25 °C, and then evaporated. The solid residue was triturated with ice-cold CCl_4, the CCl_4 solution was filtered and evaporated, and the resulting liquid was distilled as above to give **19a** (14.2 g, 92 mmol, 32%).

Triethyl Chloroorthoacetate (1-Chloro-2,2,2-triethoxyethane, 19b). Ortho ester **19b** was prepared as described:[18b] bp 70–80 °C (1.5–2.5 kPa) [lit.[18b] bp 68–70 °C (1.33 kPa)]; ^1H NMR (60 MHz) δ 3.60 (s, 2 H), 3.58 (q, 6 H, J = 6 Hz), 1.27 (t, 9 H, J = 6 Hz); ^{13}C NMR (25 MHz) δ 112.7, 58.0, 42.4, 15.1.

4-(2-Hydroxy-3-methoxyphenyl)-1-methyl-3-methylene-2-piperidinone (24). Lactam **15** (81 mg, 0.31 mmol), MsOH (600 mg, 6.24 mmol, 2014 mol %), and *dl*-methionine (47 mg, 0.31 mmol, 100 mol %) were combined, heated at 85 °C (bT) for 9 h, and then cooled in an ice bath. The mixture was partitioned between $CHCl_3$ (10 mL) and 4 M aqueous NaOH (10 mL), the organic layer was washed with 4 M aqueous NaOH (2 × 10 mL), and the combined aqueous layers were acidified (pH 1) with 3 M aqueous H_2SO_4 and extracted with $CHCl_3$ (4 × 10 mL). The combined $CHCl_3$ extracts were dried and evaporated to give **24** (73 mg, 0.29 mmol, 95%) as a yellow oil which solidified on standing: HPLC (50/50 $CHCl_3$/EtOAc, column A) t_R = 4.1 min; mp 126–127 °C (from sublimation); IR 3600, 2940, 1660, 1601, 1475, 1440, 1400, 1355, 1335, 1275, 1230, 1075 cm^{-1}; ^1H NMR (60 MHz) δ 6.9–6.6 (m, 3 H), 6.3 (t, 1 H, J = 2 Hz), 5.05 (t, 1 H, J = 2 Hz), 4.4–4.0 (m, 1 H), 3.9 (s, 3 H), 3.25 (m, 2 H), 3.0 (s, 3 H), 2.4–2.0 (m, 2 H); ^{13}C NMR (25 MHz) δ 163.7, 145.7, 142.4, 139.7, 127.2, 121.6, 119.7, 118.5, 108.3, 55.1, 47.3, 38.1, 34.3, 27.3; mass spectrum, m/z (relative intensity) 247 (54), 230 (8), 218 (5), 204 (13), 83 (6), 44 (100). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.9; N, 5.7. Found: C, 68.4; H, 7.1; N, 5.5.

4-(2,3-Dihyroxyphenyl)-1-methyl-3-methylene-2-piperidinone (25). Lactam **15** (1.00 g, 3.83 mmol) was dissolved in CH_2Cl_2 (65 mL) and added dropwise to a solution of BBr_3 (3.25 g, 13 mmol, 340 mol %) in CH_2Cl_2 (25 mL) cooled in a −78 °C bath. The bath was removed after the addition had been completed, and after 24 h, H_2O (50 mL) was added, the mixture was extracted with ether (2 × 100 mL), and the combined organic layers were dried and evaporated to give **25** (850 mg, 3.64 mmol, 95%) as a white powder: mp 168–170 °C (from $CHCl_3$); IR 3800–3000, 1650, 1600 cm^{-1}; ^1H NMR (60 MHz) δ 6.9–6.2 (m, 5 H), 5.1 (br s, 1 H), 4.2 (m, 1 H), 3.5–3.2 (m, 3 H), 3.0 (s, 3 H), 2.41–1.9 (m, 2 H); mass spectrum, m/z (relative intensity) 233 (100), 216 (7), 205 (6), 190 (15), 176 (13), 161 (9), 147 (15). Anal. Calcd for $C_{13}H_{15}NO_3 \cdot {}^1/_3H_2O$: C, 65.3; H, 6.5; N, 5.9. Found: C, 65.1; H, 6.4; N, 5.8.

Spiro[(4*H*-3-chloro-8-methoxy-2-oxo[1]benzopyran)-4,4′-(1′-methyl-3′-methylene-2′-piperidinone)] (26). Ester **21b**

(492 mg, 1.3 mmol), MsOH (2.50 g, 26.1 mmol, 2000 mol %), *dl*-methionine (192 mg, 1.3 mmol, 100 mol %), and H_2O (250 mg, 13.9 mmol, 1067 mol %) were heated at 95 °C (bT) for 9.5 h. The solution was cooled in an ice bath, mixed with $CHCl_3$ (20 mL) and saturated aqueous $NaHCO_3$ (20 mL), and the organic phase was washed with 2 M aqueous NaOH (20 mL), dried, and evaporated. Preparative TLC (1/1 CH_2Cl_2/EtOAc) of the residue returned starting ester **21a** (170 mg, 0.45 mmol, 35%) and lactone **26** (96 mg, 0.30 mmol, 23%) as an amorphous solid: HPLC (50/50 $CHCl_3$/EtOAc, column A) t_R = 3.6 min; mp 195–197 °C (purified by TLC); bp 185–210 °C dec (0.01 kPa); IR 1780, 1660, 1610, 1276, 1200, 897 cm^{-1}; ^1H NMR (90 MHz) δ 7.4–6.6 (m, 3 H), 6.55 (s, 1 H), 5.05 (s, 1 H), 4.7 (s, 1 H), 3.9 (s, 3 H), 3.6 (s, 1 H), 3.5 (br t, 2 H), 3.05 (s, 3 H), 2.4 (br t, 3 H); mass spectrum, *m/z* (relative intensity) 323 (59), 321 (100), 308 (7), 286 (12), 258 (25), 115 (41); exact mass calcd for $C_{16}H_{16}{}^{35}ClNO_4$ *m/z* 321.0768, found *m/z* 321.0769. Anal. Calcd for $C_{16}H_{16}ClNO_4 \cdot 0.5H_2O$: C, 58.1; H, 5.2; N, 4.2. Found: C, 58.3; H, 5.3; N, 4.0.

Spiro[(4*H*-3-chloro-8-hydroxy-2-oxo[1]benzopyran)-4,4′-(1′-methyl-3′-methylene-2′-piperidinone)] (27). Ester **21b** (123 mg, 0.32 mmol) was dissolved in CH_2Cl_2 (4.5 mL) and added dropwise over 30 min to a solution of BBr_3 (442 mg, 1.76 mmol, 551 mol %) in CH_2Cl_2 (2 mL) cooled in a −78 °C bath. Ten minutes after the addition had been completed, the cooling bath was removed, and after 24 h the reaction mixture was cooled in an ice bath and H_2O (6 mL) added. The mixture was extracted with ether (25 mL) and CH_2Cl_2 (25 mL), and the combined organic phases were dried ($MgSO_4$) and evaporated. Phenolic lactone **27** (98 mg, 0.32 mmol, 100%) was obtained as an unstable yellow powder which turned red when exposed to air: HPLC (60/40 MeOH/H_2O, column B) t_R = 2.4 min; IR (CH_2Cl_2) 3950–2790, 1780, 1730, 1655, 1610, 1460, 1200, 1020 cm^{-1}; ^1H NMR (90 MHz, 1/1 $CDCl_3$/ether) δ 7.1–6.5 (m, 4 H), 5.9 (s, 1 H), 5.0 (s, 1 H), 4.7 (s, 1 H), 4.6 (s, 1 H), 3.1, 3.0 (2 s, total 3 H); mass spectrum, *m/z* (relative intensity) 309 (34), 307 (100), 272 (28), 244 (51), 231 (48). Further characterization of this unstable substance was obtained by methylation of the phenol to provide lactone **26**.

Spiro[(7-Methoxybenzofuran-2-carboxylic acid)-3(2*H*),4′-(1′-methyl-3′-methylene-2′-piperidinone)] (28). (A) From Lactone 26. Lactone **26** (25.5 mg, 0.079 mmol) was dissolved in MeOH (2.1 mL) and added to a solution of KOH (85 mg, 1.30 mmol) in H_2O (2.1 mL). After 48 h the solution was diluted with H_2O (4 mL) and washed with $CHCl_3$ (5 mL). The aqueous layer was acidified (pH 1) with 3 M aqeuous HCl and extracted with $CHCl_3$ (2 × 10 mL). The organic extracts of the acid solution were dried and evaporated to yield **28**: 23.0 mg (0.076 mmol, 96%); HPLC (80/20 H_2O/0.05 M $C_3F_7CO_2NH_4$ in CH_3CN, 2.0 mL/min, column B) t_R = 1.8, 1.9 min; mp 184–186 °C (from 1/1 THF/H_2O); IR 4000–2330, 1750, 1660, 1601, 1500, 1470, 1450, 1415, 1280, 1210, 1070, 1040 cm^{-1}; ^1H NMR (180 MHz) δ 8.8 (br s, 1 H), 7.0–6.4 (m, 3 H), 5.38 (s, 1 H), 5.18 (s, 1 H), 3.90 (s, 3 H), 4.0–2.0 (m, 5 H), 3.1 (s, 3 H); ^{13}C NMR (25 MHz) δ 170.2, 163.8, 146.6, 144.8, 140.5, 132.7, 125.2, 122.6, 115.4, 112.9, 88.5, 56.1, 52.5, 45.6, 35.6, 28.5; mass spectrum, *m/z* (relative intensity) 303 (67), 258 (100), 244 (18), 230 (17). Anal. Calcd for $C_{16}H_{17}NO_5 \cdot {}^1/_3H_2O$: C, 62.1; H, 5.8; N, 4.5. Found: C, 62.0; H, 5.7; N, 4.6.

(B) Via MsOH/MET Sequence. Ester **21a** (520 mg, 1.41 mmol) was dissolved in CH_2Cl_2 (5 mL), and *dl*-methionine (420 mg, 2.81 mmol, 200 mol%) was added followed by MsOH (2.67 g, 27.7 mmol, 1960 mol %). The mixture was lowered into a 95 °C bath and heated for 9 h (the CH_2Cl_2 was rapidly lost from the solution), the solution was cooled in an ice bath, and 2 M aqueous NaOH (32.5 mL) was added followed by MeOH (16 mL). The cooling bath was allowed to warm to 24 °C, and after 12 h the solution was again cooled in an ice bath and acidified (pH 1) with 3 M aqueous HCl. The resulting mixture was extracted with $CHCl_3$ (3 × 50 mL), and the combined organic phases were dried and evaporated to give **28** (320 mg, 1.05 mmol, 75%).

(C) Via BBr_3 Sequence. Phenolic lactone **27** was prepared as described above by starting with ester **21a** (100 mg, 0.27 mmol). The CH_2Cl_2 solution of intermediate lactone **27** was cooled in an ice bath, and 3-methyl-3-pentanol (10 mL), K_2CO_3 (2.05 g, dried at 120 °C for 12 h prior to use), and Me_2SO_4 (1.33 g, 10 mmol) were added sequentially. The mixture was heated at 60 °C (bT) with distillative removal of CH_2Cl_2, after 66 h it was cooled in an ice bath, and MeOH (5 mL), H_2O (5 mL), and 2 M aqueous NaOH (15 mL) were added. The bath was removed, and after 24 h the mixture was acidified (pH 1) with 3 M aqueous HCl and extracted with $CHCl_3$ (2 × 125 mL). The combined organic layers were dried and evaporated to give **28**, 59 mg (0.19 mmol, 72%).

Spiro[[2-[(*tert*-Butoxycarbonyl)acetyl]-7-methoxybenzofuran]-3(2*H*),4′-(1′-methyl-3′-methylene-2′-piperidinone)] (30). Acid **28** (95 mg, 0.31 mmol) was dissolved in CH_2Cl_2 (10 mL), and carbonyl diimidazole (60 mg, 0.37 mmol, 120 mol %) was added. After 20 h the solution was evaporated to give the intermediate imidazolide **29** as a foam. Lithium *tert*-butyl malonate[11] (145 mg, 0.87 mmol, 282 mol %) was mixed wtih THF (1 mL) and cooled in an ice bath, and a solution of isopropylmagnesium bromide in THF (1.1 mL, 0.78 M, 0.86 mmol, 277 mol %) was added dropwise to the malonate slurry over 5 min. The mixture was left for 6 h, heated at reflux for 30 min, and cooled in an ice bath, and the imidazolide solution was added over 5 min. After 21 h the mixture was poured into 1/1 3 M aqueous HCl/saturated aqueous NaCl (10 mL), the resulting solution was washed with ether (3 × 10 mL), and the combined organic layers were diluted with benzene (10 mL) and washed with 1/1 H_2O/saturated aqueous $NaHCO_3$ (10 mL), backwashing the alkaline phase with benzene (2 × 10 mL). Organic layers were combined, dried, and evaporated to give β-keto ester **30** (124 mg, 0.31 mmol, 100%). Purification is possible by MPLC (1/1 $CHCl_3$/EtOAc, column C), but **30** cyclizes to β-keto ester **32** if left in solution. β-Keto ester **30** was isolated as a yellow oil: IR 2905, 1745, 1730, 1665, 1615, 1505, 1385, 1360, 1160, 1045, 1000, 865 cm^{-1}; ^1H NMR (90 MHz) δ 6.9–6.4 (m, 3 H), 6.36 (s, 1 H), 4.81 (s, 1 H), 4.80 (s, 1 H), 3.8–1.7 (m), 3.77 (s, 3 H), 2.94 (s, 3 H), 1.4 (s, 9 H); mass spectrum, *m/z* (relative intensity) 401 (1), 345 (2), 328 (1), 301 (3), 258 (12), 59 (100); exact mass calcd for $C_{22}H_{27}NO_6$ *m/z* 401.1838, found *m/z* 401.1845. Note: since acid **28** generally contains 30–300 mol % bound water, this must be accommodated in the stoichiometry of carbonyldiimidazole and magnesium enolate **31**.

***tert*-Butyl 4,7-Dioxo-9-methoxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline-6-carboxylate (32).** β-Keto ester **30** (124 mg, 0.31 mmol) was dissolved in MeOH (2 mL), and a solution of NaOMe in MeOH (0.5 mL, 0.06 M, 0.03 mmol, 10 mol %) was added. After 12 h saturated NaCl (5 mL) was added, and the resulting solution was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried and evaporated to give **32** (112 mg, 0.28 mmol, 90%) as a 70/30 mixture of diastereomers after purification by MPLC (1/1 $CHCl_3$/EtOAc, column C); one isomer was induced to crystallize: HPLC (40/60 $CHCl_3$/EtOAc, column A) t_R = 2.5, 2.9 min; mp 219–220 °C (from EtOAc, single isomer); IR 3003, 2959, 2899, 1733, 1639, 1493, 1456, 1149, 1060, 910; ^1H NMR (250 MHz) δ 12.21, 12.15 (2 s, total 1 H), 6.95–6.40 (m, 3 H), 4.95, 4.90 (2 s, total 1 H), 3.92, 3.86, (2 s, total 3 H), 3.7–0.8 (m), 3.04, 2.99 (2 s, total 3 H), 1.46, 1.44 (2 s, total 9 H); ^{13}C NMR (25 MHz) δ 171.5, 171.3, 169.1, 164.0, 163.5, 146.0, 132.9, 128.3, 122.2, 121.8, 116.1, 114.6, 113.3, 112.8, 102.7, 101.0, 87.1, 82.6, 82.2, 75.4, 56.1, 48.4, 46.0, 43.7, 42.0, 34.9, 34.4, 34.3, 33.3, 31.7, 28.1, 22.2, 21.3; mass spectrum, *m/z* (relative intensity) 401 (2), 345 (6), 328 (2), 301 (4), 258 (5), 174 (13), 59 (100); exact mass calcd for $C_{22}H_{27}NO_6$ *m/z* 401.1838, found *m/z* 401.1837.

4,7-Dioxo-9-methoxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (33). β-Keto ester **32** (170 mg, 0.42 mmol) was dissolved in CH_2Cl_2 (4 mL) and added dropwise over 60 min to an ice bath cooled solution of trifluoroacetic acid (5.92 g, 52 mmol) in CH_2Cl_2 (10 mL). After 3 h the solution was evaporated, and the residue was dissolved in toluene (10 mL) and heated at reflux for 20 h. The solution was evaporated to give **33** (114 mg, 0.38 mmol, 90%, 70/30 mixture of diastereomers) as a white foam after purification by MPLC (EtOAc, column C): HPLC (60/40 $CHCl_3$/EtOAc, column A) t_R = 9.1, 9.7 min; IR 3000, 1740, 1645, 1495, 1460, 1110, 1060, 910; ^1H NMR (200 MHz) δ 6.96–6.38 (m, 3 H), 4.66, 4.57 (2 s, total 1 H), 3.92, 3.91 (2 s, total 3 H), 3.95–1.35 (m), 3.01 (s, 3 H); ^{13}C NMR (63 MHz) δ 206.7, 206.5, 168.9, 148.3, 146.9, 145.6, 145.0, 132.4, 127.5, 122.9, 122.7, 115.5, 114.3, 113.1, 112.7, 90.2, 89.1, 60.4, 56.1, 52.5, 52.2, 46.6, 45.9, 44.4, 44.2, 39.7, 35.6, 35.1, 34.3, 33.9, 31.6, 23.3, 22.3; mass spectrum, *m/z* (relative intensity) 301 (1), 43 (100); exact mass calcd for $C_{17}H_{19}NO_4$ *m/z* 301.1313, found *m/z* 301.1311.

Benzofuroisoquinoline **33** was prepared from acid **28** in 81% overall yield and from ester **21a** in 61% overall yield without purification of any intermediates.

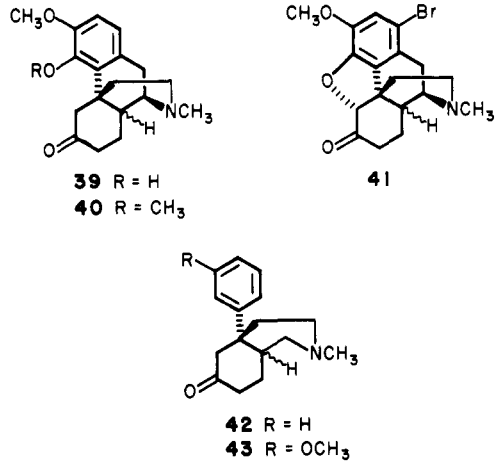
7,7-Ethylenedioxy-9-methoxy-3-methyl-4-oxo-2,3,4,4a,5,6,7,7a-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (34). Amido ketone **33** (51 mg, 0.17 mmol) was dissolved in toluene (30 mL), ethylene glycol (160 mg, 2.6 mmol) and MsOH (8.9 mg, 0.092 mmol, 55 mol %) were added, the solution was heated to reflux, and 20 mL of toluene was distilled. The reaction was diluted with toluene (20 mL) and washed with saturated aqueous K_2CO_3 (50 mL), the aqueous layer was washed with $CHCl_3$ (50 mL), and the combined organic phases were dried and evaporated to give amido ketal **34** (58 mg, 0.17 mmol, 99%, 70/30 mixture of diastereomers) as a colorless oil after purification by MPLC (EtOAc, column C): HPLC (60/40 $CHCl_3$/EtOAc, column A) t_R = 4.1, 6.1 min; IR 2934, 1624, 1486, 1446, 1259, 1172, 1097, 1038, 1011 cm^{-1}; ^1H NMR (250 MHz) δ 6.90–6.75 (m), 6.65–6.60 (dd), 6.45–6.40 (t, plus previous m and dd, total 3 H), 4.32, 4.27 (2 s, total 1 H), 4.15–3.87 (m, 4 H), 3.88 (s, 3 H), 3.04, 3.01 (2 s, total 3 H), 3.65–1.25 (m, total 9 H); mass spectrum, *m/z* (relative intensity) 345 (49), 317 (2), 259 (9), 174 (100). Anal. Calcd for $C_{19}H_{23}NO_5 \cdot H_2O$ C, 62.8; H, 7.0; N, 3.9. Found: C, 63.1; H, 6.7; N, 3.6.

7,7-Ethylenedioxy-9-methoxy-3-methyl-2,3,5,6,7,7a-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (35). Amido ketal **34** (11.0 mg, 0.032 mmol) was dissolved in THF (4 mL) and the mixture cooled in an ice/NaCl bath, DIBAL (0.23 mL, 1.41 M solution in hexane, 0.323 mmol) was added dropwise over 15 min, the cooling bath was removed, and after 7 h excess DIBAL was quenched with MeOH. The resulting mixture was poured into ice-cold 1 M aqueous NaOH (7 mL). Extraction of the mixture with ether (3 × 25 mL) followed by drying ($MgSO_4$) and evaporation afforded enamine **35** (10.0 mg, 0.03 mmol, 96%) as a colorless oil: HPLC (60/40 $CHCl_3$/EtOAc, column A) t_R = 3.3 min; HPLC (98.5/1.0/0.5 $CHCl_3$/MeOH/Et_3N, column A) t_R = 1.7 min; ^1H NMR (250 MHz) δ 6.95–6.55 (m, 3 H), 5.91 (s, 1 H), 4.47 (s, 1 H), 4.30–3.78 (m, 4 H), 3.87 (s, 3 H), 2.62 (s, 3 H), 3.02–1.40 (m, 8 H). Enamine **35** is unstable; it was used directly without further characterization or purification.

7,7-Ethylenedioxy-9-methoxy-3-methyl-1,2,4a,6,7,7a-hexahydro-5*H*-benzofuro[3,2-*e*]isoquinolinium Methanesulfonate (36). Iminium Salt Equilibration Study. Enamine **35** (10.7 mg, 0.032 mmol) was dissolved in $CDCl_3$ (0.5 mL) in a 5-mm NMR tube and cooled to −50 °C, MsOH (3.1 mg, 0.0324 mmol, 100 mol %) was added, and the tube was placed immediately at −50 °C in the NMR probe. The iminium salt protons were observed at δ 9.05 and 8.83 and were assigned to the trans and cis iminium salts **31a** and **31b**, respectively. The initial ratio was ca. 60/40 trans/cis, and no equilibration was observed below −20 °C. Above −20 °C equilibration was rapid, the trans compound having a half-life of 17.7 min at −10 °C. The equilibrium ratio at 20 °C was ≤2/98 trans/cis: ^1H NMR (250 MHz) δ 8.83 (s, 1 H), 6.96–6.76 (m, 3 H), 4.30 (s, 1 H), 4.2–3.8 (m, 4 H), 3.86 (s, 3 H), 3.85–1.55 (m, 9 H), 2.91 (s, 6 H). The iminium salt was always prepared in situ for subsequent reactions.

7,7-Ethylenedioxy-9-methoxy-3-methyl-2,3,4,4a,5,6,7,7a-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (37). (A) Via Reduction of Iminium Salt 36. Amido ketal **34** (29 mg, 0.084 mmol) was dissolved in THF (10 mL) and the mixture cooled in an ice bath, DIBAL (1.1 mL, 1.41 M solution in hexane, 1.55 mmol) was added dropwise over 60 min, the cooling bath was removed, and after 6 h MeOH (1.1 mL) was added. The resulting mixture was poured into ice-cold 1 M aqueous NaOH (10 mL). Extraction with ether (3 × 25 mL) was followed by drying ($MgSO_4$) and evaporation of the combined organic phases. The residue was dissolved in MeOH (5 mL) and the mixture cooled in an ice bath, MsOH (8.9 mg, 0.092 mmol, 110 mol %) was added, and after 5 min the cooling bath was removed. Ten minutes later the solution was again cooled in an ice bath, $NaBH_4$ (40 mg, 1.06 mmol) was added in several portions over 1 min, and after 12 h saturated aqueous NaCl (10 mL) was added to the reaction mixture followed successively by 2 M aqueous HCl (4.5 mL), 3 M aqueous NaOH (10 mL), and H_2O (10 mL). The mixture was extracted with $CHCl_3$ (2 × 50 mL), and the combined organic layers were dried and evaporated to give amino ketal **37** (20.5 mg, 0.062 mmol, 74%, 20/80 trans/cis mixture of diastereomers) as a colorless oil after purification by MPLC (98.5/1.0/0.5 $CHCl_3$/MeOH/Et_3N, column A): HPLC (98.5/1.0/0.5 $CHCl_3$/MeOH/Et_3N, column A) t_R = 2.3, 3.4 min; IR 2850, 1614, 1444, 1382 cm^{-1}; ^1H NMR (250 MHz) δ 7.15–6.75 (m, 3 H), 4.25–3.95 (m, 5–7 H), 3.85 (s, 3 H), 2.90–1.50 (m), 2.42, 2.31 (2 s, total 3 H); mass spectrum, *m/z* (relative intensity) 331 (100), 288 (10), 258 (4), 244 (29), 231 (82), 174 (24), 125 (59); exact mass calcd for $C_{19}H_{25}NO_4$ *m/z* 331.1785, found *m/z* 331.1783.

Chart II



(B) Via Reduction of Enamine 35. Enamine **35** (27.7 mg, 0.084 mmol) was dissolved in MeOH (5 mL), added to a suspension of 5% Rh–Al_2O_3 (8 mg) in MeOH (1 mL), and the mixture was hydrogenated for 13 h and then filtered. The filtrate was shaken with a small amount of K_2CO_3, decanted, and evaporated to give amino ketal **37** (10.6 mg, 0.032 mmol, 38%, 53/47 trans/cis mixture of diastereomers) as a colorless oil after purification by MPLC (98.5/1.0/0.5 $CHCl_3$/MeOH/Et_3N, column A).

9-Methoxy-3-methyl-7-oxo-2,3,4,4a,5,6,7,7a-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (38). A solution of amino ketal **37** (20.5 mg, 0.062 mmol, 20/80 trans/cis) in 3 M aqueous H_2SO_4 (25 mL) was heated (bT 40–50 °C) for 24 h, cooled, washed with benzene (25 mL), and basified with 3 M aqueous NaOH. Extraction of the alkaline solution with $CHCl_3$ (2 × 50 mL) followed by drying and evaporation of the combined $CHCl_3$ layers gave amino ketone **38** (17.7 mg, 0.062 mmol, 100% yield, 20/80 trans/cis) as a colorless oil after purification by MPLC (98.5/1.0/0.5 $CHCl_3$/MeOH/Et_3N, column A): ^1H NMR (250 MHz) δ 7.05–6.75 (m, 3 H), 4.65, 4.50 (2 s, total 1 H), 3.90 (s, 3 H), 3.95–1.50 (m), 2.54, 2.39 (2 s, total 3 H); ^{13}C NMR (63 MHz) δ 207.4, 144.8, 134.1, 122.6, 121.5, 118.1, 114.5, 112.6, 112.2, 91.5, 88.8, 57.4, 56.2, 56.0, 52.6, 51.9, 51.7, 50.2, 46.2, 39.5, 39.4, 36.7, 36.4, 34.6, 29.7, 25.4, 24.3. The ratio of isomers is dependent upon the amino ketal isomer ratio prior to ketal hydrolysis. It is possible to separate the trans from the cis by careful MPLC (same conditions as above).

38a (trans): HPLC (98.5/1.0/0.5 $CHCl_3$/MeOH/Et_3N, column A) t_R = 6.1 min; IR (neat) 2920, 1724, 1615, 1580, 1490, 1275, 1150 cm^{-1}; ^1H NMR (200 MHz) δ 7.10–6.77 (m, 3 H), 4.48 (s, 1 H), 3.90 (s, 3 H), 3.10–1.50 (m), 2.53 (s, 3 H); mass spectrum, *m/z* (relative intensity) 287 (38), 270 (5), 258 (2), 244 (10), 230 (4), 216 (7), 174 (11), 164 (15), 149 (12), 70 (100); exact mass calcd for $C_{17}H_{21}NO_3$ *m/z* 287.1521, found *m/z* 287.1514.

38b (cis): HPLC (98.5/1.0/0.5 $CHCl_3$/MeOH/Et_3N, column A) t_R = 2.9 min; IR (neat) 2930, 1718, 1615, 1595, 1490, 1450, 1360, 1280, 1260 cm^{-1}; ^1H NMR (200 MHz) δ 6.97–6.72 (m, 3 H), 4.63 (s, 1 H), 3.90 (s, 3 H), 2.90–1.75 (m), 2.35 (s, 3 H); mass spectrum, *m/z* (relative intensity) 287 (92), 270 (19), 258 (4), 244 (23), 230 (7), 216 (19), 174 (19), 164 (18), 149 (6), 70 (100); exact mass calcd for $C_{17}H_{21}NO_3$ *m/z* 287.1521, found *m/z* 287.1520.

Amino ketone **38** was prepared directly from keto amide **33** in 70% yield without intermediate purification.

HPLC Retention Times of *trans*-/*cis*-Octahydrobenzofuroisoquinolines. All separations were monitored at 280 nm with a flow rate of 1.0 mL/min by using an Altex stainless-steel column (3.2 × 250 mm) and 5-μm LiChrosorb Si60 normal phase silica gel. Three different solvent systems were used: (D) 2/3

$CHCl_3$/EtOAc; (E) 3/2 $CHCl_3$/EtOAc; (F) 98.5/1.0/0.5 $CHCl_3/CH_3OH/Et_3N$. One column volume equals 1.5 min; data are given in the order trans/cis isomers (see Chart II), solvent system, and retention time in minutes: **32a/32b**, D, 2.9/2.5; **33a/33b**, E, 9.7/9.1; **34a/34b**, E, 6.1/4.1; **35**, E, 3.3; **35**, F, 1.7; **37a/37b**, F, 3.4/2.3; **38a/38b**, F, 6.1/2.9; **39a**[28]/**39b**,[29] F, 10.8/2.8; **40a**[30]/**40b**,[30] F, 9.3/2.5.

Acknowledgment. This research was supported in part by the National Institute on Drug Abuse. The help of Mr. Morgan Conrad in obtaining FT IR spectra and Mr. Rudi Nunlist with the UCB-180 NMR spectometer is gratefully acknowledged.

Registry No. 8, 148-53-8; 9, 86-51-1; 10, 79618-90-9; 11 (isomer 1), 79618-91-0; 11 (isomer 2), 79618-92-1; 12 (isomer 1), 79618-93-2; 12 (isomer 2), 79618-94-3; 13 (isomer 1), 79618-95-4; 13 (isomer 2), 79618-96-5; 14 (isomer 1), 79618-97-6; 14 (isomer 2), 79618-98-7; 15, 79618-99-8; 16, 79619-00-4; 17, 79619-01-5; 18, 79619-02-6; 19a, 74974-54-2; 19b, 51076-95-0; 19c, 1445-45-0; 19d, 78-39-7; 19e, 40070-40-4; 19f, 18871-66-4; 21a (isomer 1), 79619-03-7; 21a (isomer 2), 79619-04-8; 21b (isomer 1), 79619-05-9; 21b (isomer 2), 79619-06-0; 21c, 79619-07-1; 21d, 79619-08-2; 21e (isomer 1), 79619-09-3; 21e (isomer 2), 79619-10-6; 21f, 79619-11-7; 22, 79631-85-9; 23, 79619-12-8; 24, 79619-13-9; 25, 79619-14-0; 26, 79619-15-1; 27, 79619-16-2; 28, 79619-17-3; 29, 79619-18-4; 30, 79619-19-5; 32a, 79619-20-8; 32b, 79646-97-2; 33a, 79619-21-9; 33b, 79646-98-3; 34a, 79619-22-0; 34b, 79646-99-4; 35, 79631-86-0; 36a, 79631-88-2; 36b, 79703-00-7; 37a, 79619-23-1; 37b, 79647-00-0; 38a, 79619-24-2; 38b, 79647-01-1; ethyl hydrogen malonate, 1071-46-1; ethyl cyanoacetate, 105-56-6; lithium *tert*-butyl malonate, 73859-00-4.

Stereochemistry of Transition-Metal-Catalyzed Cross-Coupling Reactions[1]

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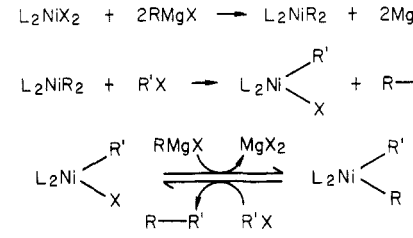
Received July 24, 1981

The stereochemical results of transition-metal-catalyzed cross-coupling of methyllithium with chiral (+)-(*S*)-(4-methylcyclohexylidene)bromomethane (1) are reported. The use of bis(triphenylphosphine) dichlorocobalt(II), iron(III) tris(dibenzoylmethide), and dichloro[1,2-bis(diphenylphosphino)ethane]nickel(II) yielded chiral 1-methyl-4-ethylideneycyclohexane (2) with 89%, 96%, and 96% retention of configuration, respectively. By contrast, the use of silver bromide yielded totally racemic product.

The coupling reaction of organolithium and Grignard reagents with organic halides, by using *stoichiometric* amounts of either Cu(I), Cu(II),[2] Ag(I),[3] or a variety of transition metals,[4] is an attractive means of forming carbon–carbon σ-bonds. The observation by Tamura and Kochi[3] that the coupling reaction can be promoted by using *catalytic* amounts of complexed forms of Ag, copper, and iron indicated this reaction to have potential practicality as a synthetic tool. Almost simultaneously, Kumada[5] and Corriu[6] showed the synthetic applicability by demonstrating that a catalytic amount of a nickel–phosphine complex caused the efficient cross-coupling of Grignard reagents with aryl and vinyl halides. The scope and limitation of this reaction has been reported by Kumada,[7] who also demonstrated that the reaction is stereospecific when isomeric vinyl halides are coupled with phenyl- and methylmagnesium bromide.[8] Moreover, asymmetric inductions have been observed during the reactions of Grignard reagents with organic halides in the presence of a nickel catalyst containing a chiral ligand.[9] The Kumada[7] mechanism for the nickel-catalyzed cross-coupling reaction is shown in Scheme I. Kochi and Morrell[10] have suggested that step 2 in the Kumada mechanism is rate determining and involves an electron transfer from nickel to R'X' to give an intimately associated radical–anion pair. Felkin[11] and Corriu[12] have proposed a mechanism which involves the oxidative addition of Grignard reagents to a Ni(0) intermediate.

Scheme I. Kumada Mechanism for Nickel-Catalyzed Cross-Coupling



The use of ferric chloride for the coupling of Grignard reagents with alkyl halides has been known for some time.[4] Kochi and co-workers[3,13] have carried out a detailed investigation of this reaction. Complexes of β-diketones with Fe(III) were shown to be very effective catalysts for the conversion. Moreover, their use in the coupling of *cis*- and *trans*-vinyl halides with Grignard reagents resulted in coupled products of retained configuration.[13] They have

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