tarimide, [mp 162–164 °C (lit.[45] mp 165–166 °C)] by fusion with urea.

A solution of β-isopropyl-β-methylglutarimide (34 g, 0.2 mol) in ethanol (500 mL) was shaken with hydrogen and Raney nickel catalyst (15 g) at 110 °C with a starting pressure of 1800 psi for 20 h. The resulting solution was filtered and evaporated, leaving a yellow oily residue which solidified on standing. This material was digested with dilute HCl and washed three times with ether. The aqueous acidic solution was neutralized and extracted five times with ether. The ethereal extract was washed once with water, dried ($MgSO_4$), and evaporated to leave a crystalline residue which was recrystallized from a mixture of ethyl acetate and petroleum ether (bp 40–60 °C). (±)-4-Isopropyl-4-methylpiperidin-2-one was obtained as colorless plates: 16.8 g (55%); mp 112.5–113.5. Anal. Calcd for $C_9H_{17}O$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.72; H, 10.87; N, 8.98; O, 10.44.

The ethereal solution of the acid-insoluble material was washed with water and dried ($MgSO_4$). The ether was removed and the residue distilled to give (±)-4-isopropyl-4-methylvalerolactone: 12 g (88%); bp 65 °C (0.10 mm); n^{24}_D 1.4628; IR (neat) ν_{max} 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.35 (t, J = 5.5 Hz, 2 H), 2.34 (d, J = 2.0 Hz, 2 H), 1.76 (t, J = 5.5 Hz, 2 H), 1.42 (q, J = 6.5 Hz, 1 H) 1.01 (s, 3 H), 0.92 (d, J = 6.5 Hz, 6 H). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32; O, 20.48. Found: C, 69.02; H, 10.30; O, 20.11.

(*R*)-(+)-β-Methyladipic Acid. To redistilled pulegone [120 g, 0.79 mol; bp 104–106 °C (14 mm); $[\alpha]^{20}_D$ +24° (neat)] suspended in water (1.2 L) was added potassium permanganate (150 g), and the mixture was shaken for 36 h. The precipitated MnO_2 was removed, and the clear solution was acidified to congo red with concentrated HCl, saturated with salt, and continuously extracted with ether for 12 h to yield a waxy acid: 60 g (50%); mp 75–80 °C. Recrystallization from benzene gave the pure acid: mp 79–81 °C (lit.[36,37] mp 84.5, 78–83 °C); $[\alpha]^{21}_D$ +8.3° (water) [lit. $[\alpha]^{22}_D$ 8.6° (water),[38] +8.42° (water)[37]]. The diethyl ester was prepared by refluxing the acid in an excess of absolute ethanol with a trace of sulfuric acid. The distilled product was obtained: 88% yield; bp 130–135 °C (16–20 mm); n^{14}_D 1.4328 [cf. lit. bp 126.5 °C (10 mm) and n^{18}_D 1.4335,[37] bp 138–144 °C (16–17 mm[39])].

The preparation of (*R*)-(+)-3-methylcyclopentanone was carried out according to the method of Dieckmann.[40] The final product had the following: bp 142–144 °C (732 mm); n^{20}_D 1.4331 (cf. lit.[41] n^{19}_D 1.4340, n^{28}_D 1.4300); $[\alpha]_D^{18}$ +148° (methanol) (lit. $[\alpha]^{20}_D$ +152.8°,[42] $[\alpha]^{12}_D$ +133°[43]); $[\alpha]^{250}$ −2450°, $[\alpha]^{311}$ +4450°, and $[\alpha]^{272}$ −4250° (methanol) (cf. lit.[33] −3062, +4450, −4250, respectively).

(*R*)-(+)-3-Methylcyclopentanone Oxime. To the ketone (5 g, 0.05 mol) in 30% (w/v) aqueous sodium acetate (30 mL) was added hydroxylamine hydrochloride (4 g, 0.058 mol), and the mixture was stirred for 2 h at 50 °C. When the mixture was allowed to stand overnight, colorless needlelike crystals formed. Recrystallization from petroleum ether (bp 60–80 °C) afforded the oxime: 5.1 g (83%); mp 78–79 °C (lit.[43] mp 86 °C).

(*R*)-(+)-5-Methylpiperidin-2-one (24). The oxime (2 g, 0.018 mol) was heated at 150 °C for 15 min with polyphosphoric acid [60 mL, prepared by dissolving phosphorus pentoxide (70 g) in orthophosphoric acid (60 mL)]. On cooling, the mixture was diluted with an equal volume of water and neutralized to pH 6 with 3 M sodium hydroxide.

The solution was then extracted with chloroform (4 × 50 mL). The chloroform extracts were combined, dried ($MgSO_4$), and evaporated to yield a yellowish liquid. The liquid showed an IR spectrum similar to, but not identical with, that of racemic 4-methylpiperidin-2-one. On treatment with dry HCl, a hexane solution of the liquid yielded a colorless white crystalline hydrochloride: 1.8 g (70%); mp 155–160 °C. After recrystallization from ethyl acetate the product melted at 169–171 °C. The ^1H NMR spectrum of the hydrochloride was quite different from that of 4-methylpiperidin-2-one. The free base was regenerated with $NaHCO_3$ and the viscous liquid obtained slowly solidified on cooling at 0 °C: mp 38 °C [lit.[30] mp 40 °C (for (*R*)-(+)-5-methylpiperidin-2-one)]; $[\alpha]^{20}_D$ +89.2° (water) [cf. lit.[30] $[\alpha]^{22}_D$ +82° (ethanol)]. The sample gave only one spot on thin-layer chromatography with a variety of solvents and conditions and only one peak on GLC (SE-30). An IR spectrum of the sample was identical in all respects with that reported[30] for (*R*)-(+)-5-methylpiperidin-2-one. The ^1H NMR spectrum was compatible with this structure and distinctly different from that of a sample of racemic 4-methylpiperidin-2-one prepared by hydrogenation of the glutarimide.

Registry No. (+)-(*R*)-**3**, 5989-27-5; (−)-(*S*)-**3**, 5989-54-8; (+)-(*R*)-**4**, 1195-31-9; (−)-(*S*)-**4**, 499-94-5; **5**, 80845-80-3; **6**, 33669-76-0; (+)-(*R*)-**7**, 80845-81-4; (+)-(*R*)-**7** semicarbazone, 80845-82-5; (+)-(*R*)-**8**, 80845-83-6; (−)-(*S*)-**8**, 80845-84-7; (−)-(*S*)-**9**, 80845-85-8; (−)-(*S*)-**11**, 80845-86-9; (−)-(*S*)-**11**·HCl, 80865-84-5; (+)-(*R*)-**11**, 80845-87-0; (+)-(*R*)-**11**·HCl, 80845-88-1; (+)-**12**, 89-82-7; (−)-(2*R*)-**13**, 5298-65-7; (−)-(2*R*)-**13** semicarbazone, 43060-33-9; (+)-(2*S*)-**14**, 15815-65-3; (+)-(2*S*)-**14** semicarbazone, 80845-89-2; (+)-(2*S*)-**14** bromo ketone, 15815-66-4; (−)-(6*S*)-**15**, 15815-67-5; **16**, 80845-90-5; (+)-(3*R*)-**18**, 80845-91-6; (+)-(3*R*)-**18** methyl ester, 80845-92-7; (+)-(3*R*)-**18** oxime, 80845-93-8; (2*S*)-**19** (isomer I), 80865-85-6; **19** acetate, 80845-94-9; **19** xanthate, 80845-95-0; (+)-(3*R*)-**20**, 80845-96-1; **21**, 80845-97-2; (+)-(4*R*)-**22**, 80845-98-3; (+)-(4*R*)-**22**·HCl, 80845-99-4; (+)-**23** (R = *i*-Pr; R′ = Me), 80846-00-0; (+)-(*R*)-**24**, 1121-71-7; (+)-(*R*)-**24**·HCl, 80846-01-1; (2*S*)-**19** (isomer II), 80846-02-2; *p*-toluenesulfonylhydrazine, 1576-35-8; (+)-4-isopropyl-4-methylpiperidin-2-one, 80876-86-4; β-isopropyl-β-methylglutarimide, 80846-03-3; (+)-(*R*)-β-methylodipic acid, 623-82-5; (+)-(*R*)-diethyl β-methyladipate, 80846-04-4; (+)-(*R*)-3-methylcyclopentanone, 6672-30-6; (+)-(*R*)-3-methylcyclopentanone oxime, 80846-05-5; (*S*)-5-*tert*-butylpiperidin-2-one, 80876-87-5.

(45) G. J. Handley, E. R. Nelson, and T. C. Somers, *Aust. J. Chem.*, **13**, 129 (1960).

Codeine Analogues. Synthesis of 4a-(2,3-Dimethoxyphenyl)decahydroisoquinolines and Octahydro-1*H*-[1]benzopyrano[4,3,2-*ef*]isoquinolines

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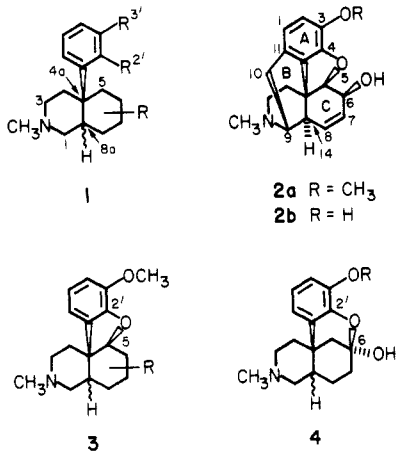
Extension of our methods for the synthesis of phenyl- and (*m*-methoxyphenyl)decahydroisoquinolines to the 2,3-dimethoxyphenyl series is presented. Surprisingly, direct extrapolation of the previous methodology was frequently not possible, as the dimethoxyphenyl system presented unique problems in a number of steps. Detailed studies are reported for selective amide reduction in the presence of an ester, allylic oxidation of α-methylene lactams, and solvolysis of tertiary allylic/benzylic alcohols. Finally, selective ether cleavages in the 4a-aryldecahydroisoquinoline ring system allow elaboration to the new 6,2′-oxygen-bridged 4a-aryldecahydroisoquinolines, the benzopyrano[4,3,2-*ef*]isoquinolines.

The 4a-aryldecahydroisoquinolines 1 (Chart I), representing the A, C, and N (nitrogen) rings of codeine (**2a**), have evoked considerable interest as a class of analgesics.[1] Earlier papers from this laboratory have described the

0022-3263/82/1947-1831$01.25/0

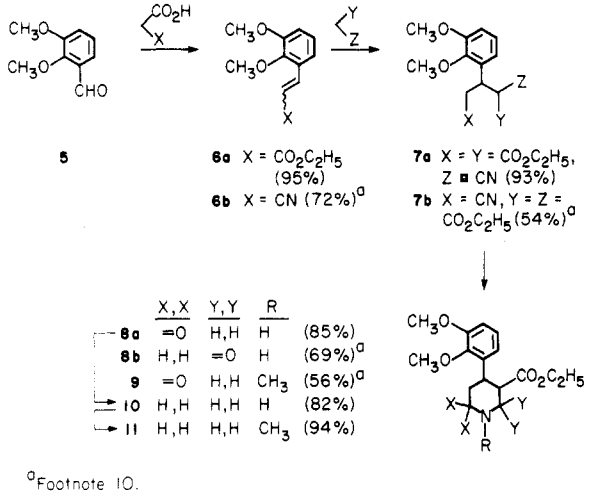
Chart I



preparation of *cis*- and *trans*-4a-phenyl- and -(*m*-methoxyphenyl)decahydroisoquinolines containing functionality in the C ring,[1c,d] and recently we reported preparation of a 5,2′-oxygen-bridged decahydroisoquinoline ring system, the octahydro-1*H*-benzofuro[3,2-*e*]isoquinolines **3**.[2] Herein we describe an extension of our methods to the dimethoxyphenyl series, an extension which has led to the preparation of some derivatives of the new 6,2′-oxygen-bridged decahydroisoquinoline ring system, the octahydro-1*H*-[1]benzopyrano[4,3,2-*ef*]isoquinolines **4**.[3] In morphine numbering, these would represent 4,6-oxygen-bridged systems in contrast to the 4,5-oxygen bridge common in morphinans.

4-Arylnipecotates. Preparation of amino ester **10** by the previous route starting with dimethoxybenzaldehyde **5** required Borch reduction ($R_3OBF_4/NaBH_4$) of δ-amido ester **8a** (Scheme I).[2,4] In contrast with our experience in the *m*-methoxyphenyl series,[1c,d] initial results with this method proved capricious (20–80% yields), prompting a study of alternative methods for selective reduction of amides in the presence of esters. Numerous methods were investigated,[5-9] but none offered improvement.[10] Finally

Scheme I. Preparation of 4-Arylnipecotates



[a] Footnote 10.

Scheme II. Preparation of 4a-(2,3-Dimethoxyphenyl)decahydroisoquinolines

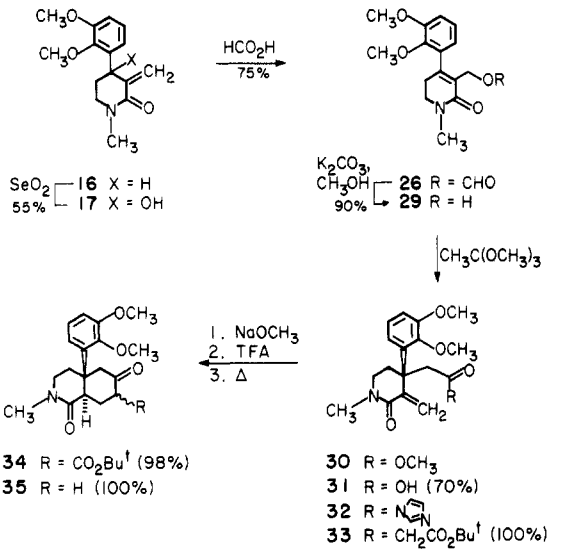
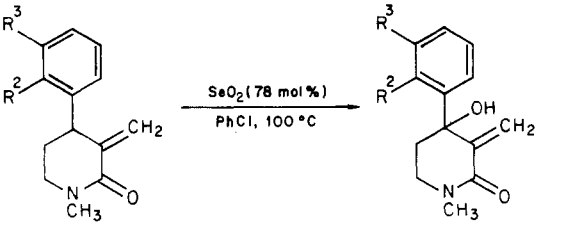


Table I. Effect of Aromatic Substitution on SeO_2 Oxidation[a]



educt	R^3	R^2	product (% yield)[b]
12	H	H	**13** (60)[c]
14	CH_3O	H	**15** (86)[d]
16	CH_3O	CH_3O	**17** (55)[e]
18	CH_3O	HO	*f*
19	HO	HO	*f*
20	CH_3O	AcO	*f*
21	CH_3O	BzO	*f*
22	CH_3O	PvO	**23** (55)
24	$-OCH_2O-$		**25** (40)

[a] Reference 10. [b] Yields refer to isolated products after after chromatography. [c] Reference 1c. [d] Reference 1d. [e] Reference 2. [f] Multiple products.

a boron complex was found to be responsible for the reproducibility problems, presence of the boron complex

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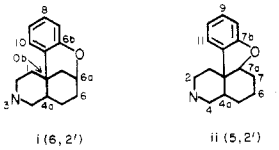
(2) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 5064.

(3) The 6,2′-oxygen-bridged decahydroisoquinolines are a new class of codeine analogues related to the 1*H*-benzofuro[3,2-*e*]isoquinolines which are 5,2′-oxygen-bridged decahydroisoquinolines, ii.[2] The numbering systems given (i (6,2′), 2,3,4,4a,5,6,6a,10c-octahydro-1*H*-[1]benzopyrano-[4,3,2-*ef*]isoquinoline; ii (5,2′), 2,3,4,4a,5,6,7,7a-octahydro-1*H*-benzofuro-[3,2-*e*]isoquinoline) are those for the furo- and pyranoisoquinolines; we denote stereochemistry as cis or trans with respect to the isoquinoline ring juncture.



(4) Borch, R. F. *Tetrahedron Lett.* **1968**, 61.

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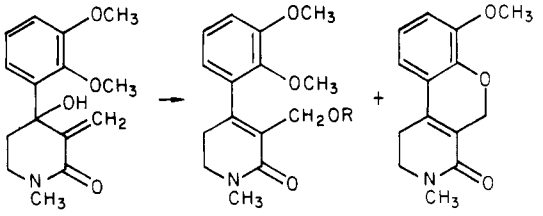
(7) Atta-ur-Rahman; Basha, A.; Waheed, N.; Ahmed, S. *Tetrahedron Lett.* **1976**, 219.

Table II. Preparation of Primary Esters by Solvolytic Rearrangement of Tertiary Alcohols



17 26 27, R = H 28, R = Ac

reaction conditions	time, h	bath temp, °C	ratio of 26/27 [a]
HCO_2H [b]	3–24	25	75/25 [c]
HCO_2H	4	55	75/25
1/1 HCO_2H/HOAc	46	−5	*d*
1/1 HCO_2H/HOAc	72	25	85/15
HOAc	18	80	*d*
HOAc	72	118	70/30
CF_3CO_2H	5.5	25	64/36
1/9 HCO_2H/CH_2Cl_2	48	25	*d*
1/1 HCO_2H/CH_2Cl_2	72	25	75/25
1/9 CF_3CO_2H/CH_2Cl_2	25	25	68/32 [e]
H_2SO_4(concn)/CH_2Cl_2	23	25	*f*
$HClO_4$(aq)/CH_2Cl_2	23	25	*e*
20/4/1 EtOH/H_2O/H_2SO_4(concn)	25	25	*d*
20/4/1 EtOH/H_2O/H_2SO_4(concn)	9	60	*d*
20/4/1 EtOH/H_2O/H_2SO_4(concn)	24	78	*d*
20/4/6 EtOH/H_2O/H_2SO_4(concn)	33	78	10/45/45 (26/27/29)
HCO_2H/NaO_2CH	72	25	78/22 [g]
HOAc/NaOAc	72	118	71/29
1/1 Ac_2O/HOAc; catalytic H_2SO_4(cocn)	4.5	120	*h*

[a] In this table 26 is with R equal to the appropriate residue, e.g., CHO, Ac, $COCF_3$, H. [b] "Standard" reaction conditions. [c] This ratio does not change with prolonged reaction times. [d] No reaction. [e] Compound 27 (50%) accompanied by several minor products. [f] No organic soluble product. [g] 36% unreacted 17. [h] Compound 28.

being clearly demonstrated by flame-ionization analysis (ca. 1.5% boron) and ^{11}B NMR (δ 12.73) spectroscopy. Treatment with anhydrous EtOH/HCl or dilute aqueous H_3PO_4 freed amino ester **10** from the complex and allowed consistently high yields (82%) of distilled product.

Preparation of α-methylene lactam **16** via amino ester **11** has already been described and proceeds in excellent yield (93%).[2] The overall process to lactam **16** requires six steps and three isolations, proceeding in 70% yield from 2,3-dimethoxybenzaldehyde **5**.

4a-Aryldecahydroisoquinolines. Functionalization of the piperidone at C-4 was achieved in the phenyl and *m*-methoxyphenyl series by SeO_2 oxidation (60–90%),[1c,d] but oxidation of dimethoxyphenyl α-methylene lactam **16** with SeO_2 initially produced tertiary alcohol **17** in poor yield (20–45%, Table I). The poor results observed with SeO_2 prompted an extensive search for alternative methods[11–19] to functionalize the piperidinone and thus to prepare acid **31**[10] (Scheme II), but SeO_2 still appeared to be the most promising reagent. Examination of a number of variables in the SeO_2 reaction coupled with a sequential Simplex optimization scheme eventually allowed a large-scale (>5 g) yield of 55% with 78 mol % SeO_2 and 18 mol % H_2O in chlorobenzene at 100 °C.[10,11,20,21]

One more variation was investigated, this being the nature of the aromatic substituents. Thus α-methylene

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(10) Details for this work appear in the supplementary material.

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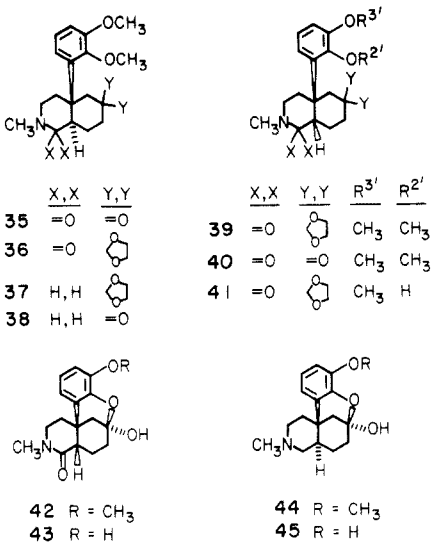
(19) Trost, B. M.; Strege, P. E.; Weber, L.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3407. Trost, B. M.; Weber, L.; Strege, P. E.; Fullerton, T. J.; Dietsche, T. J. *Ibid.* **1978**, *100*, 3416, 3426.

(20) Selenium dioxide (SeO_2) absorbs moisture from the air to give selenous acid (H_2SeO_3), but this reaction is reversible, and even at 20–25 °C selenous acid effloresces to form selenium dioxide. It is practically impossible to remove the last traces of water from selenium dioxide since resublimed material that has been dessicated over phosphorus pentoxide for 1 year still retains 0.045–0.088% water (Waitkins, G. R.; Clark, C, W. *Chem. Rev.* **1945**, *36*, 235). However, it is stated that drying selenium dioxide for 3–4 h at 150 °C in a current of dry air affords material containing no water (Julien, A. P. *J. Am. Chem. Soc.* **1925**, *47*, 1799). Others state that anhydrous selenium dioxide can be prepared (Manchot, W.; Ortner, K. *Z. Anorg. Allg. Chem.* **1922**, *120*, 300. Jannek, J.; Meyer, J. *Ibid.* **1913**, *83*, 51. Meyer, J. *Chem. Ber.* **1922**, *55*, 2082), but their methods are equivocal. Our data suggest that total removal of water is rarely achieved; thus selenium dioxide reactions generally are performed in the presence of moisture (H_2SeO_3 or $SeO_2 \cdot H_2O$).

(21) Optimization methods are gaining popularity in the literature: (a) Long (Long, D. E. *Anal. Chim. Acta* **1969**, *46*, 193) gives an excellent presentation of uncomplicated Simplex methods. (b) Spendley, W.; Hext, G. R.; Himsworth, F. R. *Technometrics* **1962**, *4*, 441. (c) Balasubramanian, S.; Shantarum, R.; Doraiswamy, L. K. *Br. Chem. Eng.* **1967**, *12*, 377. (d) Deming, S. N.; Morgan, S. L. *Anal. Chem.* **1973**, *45*, 278A. (e) Morgan, S. L.; Deming, S. N. *Ibid.* **1974**, *46*, 1170. (f) Darvas, F. *J. Med. Chem.* **1974**, *17*, 799. (g) Dean, W. K.; Heald, K. J.; Deming, S. N. *Science* **1975**, *189*, 805. (h) Lazaro, R.; Bouchet, P.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1977**, 1171. (i) Hendrix, C. D. *CHEMTECH* **1979**, 167. (j) Brookes, A. E.; Leary, J. J.; Golightly, D. W. *Anal. Chem.* **1981**, *53*, 721. (k) Deming, S. N. *Am. Lab. (Fairfield, Conn.)* **1981**, *13*, 42.

Chart II



lactam **16** was converted to phenol **18** and catechol **19** as described[2] and then acylated and alkylated to produce compounds **20–22** and **24**. Oxidation of these substrates allowed a study of steric and electronic effects (Table I). Both the acetyl and the benzoyl substituents were cleaved during the reaction, but the sterically encumbered pivaloyl substituent allowed yields comparable to the dimethoxyphenyl case; thus cleavage of the hindered ether (hence most accessible[22]) followed by further oxidation may fully explain the difficulties encountered in the 2,3-dioxygenated aryl systems.

Solvolysis of tertiary alcohol **17** under a variety of conditions produced mixtures of the desired allylic ester **26** and tricyclic ether **27** (Table II). The tricyclic ether presumably arises via trapping of the intermediate carbonium ion with the ortho ether oxygen, followed by ether cleavage. When the pivaloyl compound **23** was subjected to solvolysis conditions, however, negligible amounts of tricyclic ether **27** were formed. Whether this is a result of steric or electronic factors or both is unknown. Subsequent manipulations did not proceed as efficiently with the pivaloyl group, so the dimethoxyphenyl route was still the preferred pathway. Attempts to cleave the oxygen ring of tricyclic ether **27** (hydrogenolysis; nucleophilic or acidic ether cleavages) and thus convert it to a useful compound were unsuccessful, giving no reaction or cleavage of the methyl ether.[10] Hydrolysis of the solvolysis product **26** was readily accomplished with K_2CO_3/CH_3OH affording allylic alcohol **29** (90%), and ortho ester Claisen rearrangement followed by ester hydrolysis yielded acid **31** (70%) as described.[2]

Elaboration of the C ring (Scheme II) followed closely our published processes,[1c,d,2] proceeding via imidazolide **32** (100%) and β-keto esters **33** (100%) and **34** (98%) to give amido ketone **35** (100%). The acid chloride rather than the imidazolide, lithium *tert*-butylacetate rather than magnesium *tert*-butyl malonate, and Et_3N rather than $NaOCH_3$ all gave inferior yields in this sequence. The conversion of α-methylene lactam **16** to amido ketone **35** can be accomplished in 27% overall yield with purification of only acid **31** by recrystallization and amido ketone **35** by chromatography.

Ketalization of amido ketone **35** (Chart II) afforded quantitative conversion to a product which is solely one isomer, the trans isomer **36** in analogy with previous work.[1c,d] Equilibration to cis amido ketal **39** in refluxing KOH/C_2H_5OH gave a 5/95 mixture of trans/cis amido ketals, confirming the stereochemical assignment, but long reaction times were necessary.[23] The 2′-methoxy group would be expected to cause considerable steric hindrance to protonation cis to the phenyl group, thus leading to exclusive formation of trans product in the ring closure of **33** to **34** and slower trans to cis isomerization. Hydrolysis of **39** afforded cis amido ketone **40**.

Benzopyrano[4,3,2-*ef*]isoquinolines. In order to prepare codeine (**2a**) analogues in the 6,2′-oxygen-bridged decahydroisoquinoline series **4**, we required a selective ether cleavage method. The use of a nucleophilic method such as C_2H_5SK/DMF[24] under anhydrous conditions was expected to allow selective cleavage of the more hindered 2′-methoxy,[21] along with protection of the second ether from cleavage by formation of the 2′-phenoxide.

Treatment of trans amido ketone **35** with anhydrous C_2H_5SK/DMF afforded a new material which had lost one methoxyl by ^1H NMR analysis, and the IR spectrum further indicated that the product was no longer a ketone but rather a hemiketal.[25] The product was homogeneous by HPLC, and since it is structurally impossible to form a 6,3′-oxygen bridge, the ether cleavage was clearly selective. The isoquinoline ring juncture stereochemistry was still in question, however, because the alkaline reaction conditions could presumably cause equilibration; thus further data were necessary before a full structure could be assigned. Treatment of amido ketal **36** with anhydrous C_2H_5SK/DMF yielded a phenol (58%) which gave the same hemiketal prepared above on aqueous hydrolysis (100%). Methylation of this phenol with dimethyl sulfate afforded an 8/92 mixture of trans/cis amido ketals **36/39**, showing that equilibration had indeed occurred during ether cleavage and thus establishing that hemiketal **42** and phenol **41** have predominantly cis stereochemistry.

Since codeine (**2a**) and morphine (**2b**) possess trans ring juncture stereochemistry, another route was necessary in order to avoid equilibration. Previous work in the 4a-aryldecahydroisoquinolines has shown that trans amino ketones can be prepared stereospecifically by reduction of the corresponding trans amido ketals with $AlH_3/NaBH_4$ or AlH_3/H_2 followed by aqueous hydrolysis of the ketal.[1c,d] Trans amino ketone **38** was prepared in this manner from trans amido ketal **36** (95%), thus eliminating the problem of ring juncture equilibration. Treatment of amino ketone **38** with anhydrous C_2H_5SK/DMF as described for amido ketone **35** then gave codeine analogue **44** (60%), while addition of *tert*-butyl alcohol to the reaction mixture yielded a mixture of **44** (43%) and morphine analogue **45** (55%). This represents the first synthesis of 6,2′-oxygen-bridged 4a-aryldecahydroisoquinolines, the octahydro-1*H*-[1]benzopyrano[4,3,2-*e*,*f*]isoquinolines (**4**), a novel class of codeine analogues whose pharmacological properties are currently unknown. In addition to the trans series prepared herein it should be possible to prepare the cis series by using methods already described.[1]

In summary, we have extended methods developed in simpler systems to the preparation of 4a-(2,3-dimethoxyphenyl)decahydroisoquinolines. Although the chemistry is often similar to that of the phenyl and *m*-methoxyphenyl

(22) Ahmad, R.; Saa, J. M.; Cava, M. P. *J. Org. Chem.* **1977**, *42*, 1228.

(23) Equilibration in this series requires 80 h, whereas 8 and 0.5 h are sufficient in the *m*-methoxyphenyl and phenyl series, respectively.

(24) (a) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, 1327. (b) *Aust. J. Chem.* **1972**, *25*, 1719, 1731. (c) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, 4459.

(25) Acetals/ketals have a characteristic IR pattern from 1050 to 1300 cm^{-1}. See: Pasto, D. J.; Johnson, C. R. "Organic Structure Determination"; Prentice-Hall: Engelwood Cliffs, NJ, 1969; pp 378–379.

series, extrapolation of these methods to the dioxygenated series required significant modifications. Finally, preparation of the octahydro-1*H*-[1]benzopyrano[4,3,2-*ef*]isoquinolines 4 is readily achieved in 10% overall yield from 2,3-dimethoxybenzaldehyde (5) with purification of only five intermediates. Elaboration of the 4a-(2,3-dimethoxyphenyl)decahydroisoquinolines described in this report into compounds containing functionality in the nitrogen ring will be described in the future.

Experimental Section

General Methods. Tetrahydrofuran (THF) and 1,2-dimethoxyethane were distilled from sodium/benzophenone. Methanol and ethanol were distilled from magnesium. Acetonitrile was dried over molecular sieves (0.4 nm). Methylene chloride and methylene bromide were distilled from phosphorus pentoxide. Toluene, chlorobenzene, *o*-dichlorobenzene, mesitylene, hexane, *N,N*-dimethylformamide (DMF), ethanethiol, and 2-methoxyethyl ether (diglyme) were distilled from calcium hydride. Pyridine was distilled from barium oxide. Methanesulfonic acid (MsOH) was distilled under vacuum and contained less than 0.5% methanesulfonic anhydride by ^{1}H NMR. Boron trifluoride etherate was purified,[26] and Grignard reagents were standardized.[27]

Boiling points are uncorrected. Melting points were measured with Buchi (capillary) and Kofler (microscope slide) apparatuses and are uncorrected. IR spectra were determined with Perkin-Elmer 137, 281, 297, 337, and 681 spectrophotometers using polystyrene film for calibration (1601.4-cm^{-1} absorption) and with a Nicolet 7000 Series FT-IR spectrometer. UV spectra were determined with Cary 14 and 219 spectrophotometers. ^{1}H 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), Berkeley UCB-180 (180.09 MHz), Berkeley UCB-250 (250.80 MHz). ^{13}C NMR spectra were measured at 25.14 MHz with a Nicolet TT-23 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise noted, and the chemical shifts are expressed in parts per million ppm (δ) downfield from Me_4Si; couplings are expressed in hertz. ^{11}B NMR spectra were measured at 57.78 MHz on the UCB-180 with $CDCl_3$ as the solvent and trimethyl borate (δ 0) as an internal standard. Mass spectra (electron impact, 70 eV) were obtained with AEI MS-12 (low resolution), Finnigan 4000 (GC/MS), and Du Pont CEC 21-110 (exact mass) instruments. Elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California, Berkeley, CA.

Gas chromatography (GC) was done with Varian Aerograph A-90P and Hewlett-Packard 402 gas chromatographs. The following 6–8-mm glass columns were used: (A) 1.5 m, 5% SE-30 on Chromosorb W, 80/100 mesh; (B) 1.5 m, 3% OV-1 on Chromosorb W, 80/100 mesh; (C) 1.8 m, 5% Dexsil 300 on Anakrom Q, 90/100 mesh. Flow rates were typically 80–100 mL/min (helium). 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 stainles-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 × 340 mm, 40–63-μm silica gel 60 (EM Reagents). Column chromatography (CC) and dry column chromatography were 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 $MgSO_4$ and evaporated with a Berkeley rotary evaporator by using water aspirator (13–26 kPa) or oil pump (0.01–0.67 kPa) reduced pressure, followed by static evaporation with an oil pump (0.001 kPa). All distillations were bulb to bulb (Kugelrohr type) unless otherwise noted. Hydrogenations were carried out under 40–50 psi of hydrogen pressure, with shaking, at 20–26 °C on Parr-type systems.

4-[(Methoxycarbonyl)methyl]-4-(2,3-dimethoxyphenyl)-1-methyl-3-methylene-2-piperidinone (30). A suspension of acid **31**[2] (100 mg, 0.31 mmol; resulting from Claisen rearrangement) in DMF (1 mL) was treated with *N,N'*-carbonylbisimidazole (50 mg, 0.33 mmol, 105 mol %), giving immediate dissolution. After 18 h the solution was evaporated, and the residue was partitioned between $CHCl_3$ (10 mL) and 1/1 H_2O/ice (10 mL). The organic phase was dried and evaporated, and the residue was overlaid with MeOH (2 mL) containing a trace of NaOMe. After 21 h the solution was evaporated, the residue was partitioned between H_2O (10 mL) and $CHCl_3$ (10 mL), and the organic phase was washed with H_2O (2 × 10 mL), dried, and evaporated to give ester **30**: 100 mg (0.30 mmol, 96%); bp 145–193 °C (0.04 kPa); IR ($CHCl_3$) 3017, 1741, 1654, 1601, 1467, 1333, 1262, 1050, 734, 705 cm^{-1}; ^{1}H 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). Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.8; H, 6.9; N, 4.2. Found: C, 64.9; H, 6.9; N, 4.5.

Imidazolide of 4-(Carboxymethyl)-4-(2,3-dimethoxyphenyl)-1-methyl-3-methylene-2-piperidinone (32). Claisen acid **31**[2] (504 mg, 1.6 mmol) was suspended in CH_2Cl_2 (10 mL) and *N,N'*-carbonylbisimidazole (291 mg, 1.8 mmol, 114 mol %) was added. After 9.5 h the solution was evaporated to give **32** as a brown, hygroscopic foam. Isolation as described above for the preparation of **30** afforded **32** (98% yield) as a white foam: ^{1}H NMR (60 MHz) δ 8.14 (m, 1 H), 7.47 (m, 1 H), 7.05 (m, 1 H), 6.90 (m, 3 H), 6.60 (s, 1 H), 5.38 (s, 1 H), 3.38 (s, 6 H), 2.85 (s, 3 H), 3.8–2.5 (m).

***tert*-Butyl 4-(2,3-Dimethoxyphenyl)-4-[4-(1-methyl-3-methylene-2-oxopiperidinyl)]-3-oxobutyrate (33).** To a suspension of lithium *tert*-butyl malonate[1c,d] (712 mg, 4.3 mmol, 272 mol %) in THF (8 mL) cooled in an ice bath was added isopropylmagnesium bromide (5.5 mL of a 0.78 M solution in THF, 4.3 mmol, 272 mol %) at 2.3 mL/min. After 4 h the solution was heated at reflux at 45 min and then cooled in an ice bath. To the resulting suspension was added a solution of crude imidazolide **32** (584 mg, 1.6 mmol) in THF (7 mL) at 2.3 mL/min. After 3 days the mixture was added to 1/2 3 M aqueous HCl/saturated aqueous NaCl (30 mL) and extracted with ether (3 × 20 mL). The combined organic phases were evaporated, the residue was dissolved in benzene (25 mL), the benzene layer was washed with 1/1 H_2O/saturated aqueous $NaHCO_3$ (2 × 25 mL), and the combined aqueous phases were washed with benzene (20 mL). The combined benzene phases were dried (Na_2SO_4) and evaporated to give **33** (660 mg, 1.6 mmol, 100%). Column chromatography (95/5 $CHCl_3$/acetone) gave **33** as a white foam: 100%; HPLC (50/50 $CHCl_3$/EtOAc, column A) t_R = 2.5 min; IR (neat) 1730, 1700, 1645, 1605 cm^{-1}; ^{1}H NMR (60 MHz) δ 6.9–6.5 (m, 3 H), 6.43 (br s, 1 H), 5.27 (br s, 1 H), 3.9 (s, 6 H), 3.5–2.0 (m, 11 H), 1.47 (s, 9 H); mass spectrum, *m/z* (relative intensity) 417 (4), 344 (1), 274 (21), 261 (21), 260 (100); exact mass calcd for $C_{23}H_{31}NO_6$ *m/z* 417.2151, found 417.2160.

***tert*-Butyl *trans*-4a-(2,3-Dimethoxyphenyl)-1,6-dioxo-2-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-7-carboxylate (34).** β-Keto ester **33** (660 mg, 1.6 mmol) was dissolved in MeOH (10 mL), and NaOMe (0.150 mL of a 1.0 M solution in MeOH, 0.15 mmol, 10 mol %) was added. After 20 h the solution was added to saturated aqueous NaCl (25 mL), and the mixture was washed with $CHCl_3$ (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), evaporated, and purified by column chromatography (98/2 $CHCl_3$/acetone) to give **34**: 647 mg (1.55 mmol, 98% yield); mp 159–162 °C dec (from PhH/hexane); IR ($CHCl_3$) 1645, 1620 cm^{-1}; ^{1}H NMR (60 MHz) δ 7.0–6.6 (m, 3 H), 3.97 (s, 3 H), 3.87 (s, 3 H), 3.8–1.8 (m), 1.55 (s, 9 H).

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

Anal. Calcd for $C_{23}H_{31}NO_6$: C, 66.2; H, 7.5; N, 3.4. Found: C, 66.2; H, 7.3; N, 3.4.

***trans*-4a-(2,3-Dimethoxyphenyl)-1,6-dioxo-2-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (35).** Trifluoroacetic acid (20.7 g, 182 mmol) was cooled in an ice bath, and β-keto ester **34** (647 mg, 1.55 mmol) was added as a solution in CH_2Cl_2 (14 mL) at 2.3 mL/min. After 35 min the solution was evaporated, and the residue was dissolved in toluene (28 mL). The solution was heated at reflux for 7 min and then evaporated, and the crude product was purified by MPLC ($CHCl_3$, column C) to give **35**: 492 mg (1.55 mmol, 100% yield); tan oil; HPLC ($CHCl_3$, 2 mL/min, column A) t_R = 8.3 min; IR (neat) 1710, 1665 cm^{-1}; ^1H NMR (60 MHz) δ 6.82 (m, 2 H), 6.57 (m, 1 H), 3.90 (s, 3 H), 3.79 (s, 3 H), 2.83 (s, 3 H), 3.6–2.1 (m); ^{13}C NMR δ 209.6, 171.5, 153.9, 148.5, 131.1, 123.1, 120.6, 112.6, 60.4, 55.8, 51.9, 49.7, 47.7, 46.1, 40.4, 36.7, 34.6, 23.2; mass spectrum, *m/z* (relative intensity) 318 (6), 317 (31), 286 (21), 259 (11), 229 (10), 145 (11), 121 (30), 119 (93), 117 (100). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.1; H, 7.3; N, 4.4. Found: C, 67.8; H, 7.3; N, 4.4.

***trans*-4a-(2,3-Dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-1-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (36).** A mixture of amido ketone **35** (100 mg, 0.315 mmol), *p*-toluenesulfonic acid monohydrate (21 mg, 0.11 mmol, 35 mol %), and ethylene glycol (62 mg, 1.0 mmol, 317 mol %) in benzene (25 mL) was heated with distillation of 15 mL of solvent. To the cooled residue were added saturated aqueous K_2CO_3 (10 mL) and benzene (10 mL). The organic layer was washed with saturated aqueous NaCl (5 mL), dried (Na_2SO_4), and evaporated to give **36**: 80 mg (0.22 mmol, 70% yield); no cis ketal **39** was detected by GC; GC (column B, 240 °C) t_R = 3.5 min; mp 164–165 °C (from PhH/hexane); IR (KBr) cm^{-1}; ^1H NMR (60 MHz) δ 6.80 (m, 3 H), 3.90 (s, 3 H), 3.91–3.67 (m, 4 H), 3.5–1.5 (m), 2.70 (s, 3 H); ^{13}C NMR δ 171.6, 153.1, 148.2, 134.2, 122.6, 121.1, 111.6, 108.3, 64.4, 63.8, 60.0, 55.8, 50.7, 47.2, 44.8, 43.1, 37.2, 35.3, 34.1, 21.0; mass spectrum, *m/z* (relative intensity) 361 (9), 360 (40), 330 (15), 262 (47), 111 (19), 99 (100). Anal. Calcd for $C_{20}H_{27}NO_6$: C, 66.5; H, 7.5; N, 3.9. Found: C, 66.5; H, 7.5; N, 3.8.

***cis*-4a-(2,3-Dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-1-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (39).** Trans amido ketal **36** was converted to a 5/95 *trans*-**36**/*cis*-**39** mixture as described with 600 mol % of KOH, and equilibration required 80 h.[1c,d] Isolation afforded **36**/**39** (86% yield) as an oil: GC (column B, 240 °C) t_R 3.5 (**36**), 4.4 (**39**) min; ^1H NMR (60 MHz) δ 6.86 (m, 3 H), 3.96 (m, 4 H), 3.88 (s, 6 H), 3.06–1.64 (m, 11 H), 2.73 (s, 3 H); mass spectrum, *m/z* (relative intensity) 361 (37), 330 (13), 262 (20), 111 (7), 99 (66), 40 (100); exact mass calcd for $C_{20}H_{27}NO_5$ *m/z* 361.1889; found 361.1886.

***cis*-4a-(2,3-Dimethoxyphenyl)-1,6-dioxo-2-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (40).** The mixture of amido ketals **36**/**39** described above was hydrolyzed as described[1c,d] with 1/2 THF/0.5 M aqueous H_2SO_4 for 24 h, giving cis keto amide **40** contaminated with *trans*-**35**: (100% yield); HPLC ($CHCl_3$, 2 mL/min, column A) t_R = 7.2 min; ^1H NMR (60 MHz) δ 7.0 (m, 3 H), 4.0 (s, 3 H), 3.96 (s, 3 H), 3.6–1.5 (m), 2.88 (s, 3 H); mass spectrum, *m/z* (relative intensity) 318 (20), 286 (50), 259 (11), 248 (52), 229 (12), 121 (15), 119 (4), 117 (4); exact mass calcd for $C_{18}H_{23}NO_4$ *m/z* 317.1626, found 317.1625.

***trans*-4a-(2,3-Dimethoxyphenyl)-6,6-(ethylenedioxy)-2-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (37). (A) $AlH_3/NaBH_4$.** A solution of amido ketal **36** (77 mg, 0.21 mmol) in THF (5 mL) was cooled in an ice bath, and AlH_3[28] (1.0 mL, 0.75 M solution in THF, 0.75 mmol, 350 mol %) was added dropwise over 8 min. Dropwise addition of more AlH_3 (0.5 mL) over 4 min was followed by addition of MeOH (1 mL). The resulting solution was poured into 1.25 M aqueous NaOH (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried and evaporated, the enamine/amino ketal residue was dissolved in absolute EtOH (3 mL) and cooled in an ice bath, and $NaBH_4$ (41 mg, 1.07 mmol, 500 mol %) was added. After 18 h the suspension was poured into saturated aqueous $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried and evaporated to give amino ketal **37**: 63 mg (0.181 mmol, 85% yield); mp 128–130 °C (from PhH/hexane); ^1H NMR (60 MHz) δ 7.3–6.8 (m, 3 H), 3.94 (s, 6 H), 3.9–3.4 (m), 3.2–1.2 (m), 2.28 (s, 3 H); mass spectrum, *m/z* (relative intensity) 346 (2), 317 (22), 316 (100), 219 (25), 214 (23). Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.1; H, 8.4; N, 4.0. Found: C, 68.9; H, 8.3; N, 4.0.

(B) AlH_3/H_2, Rh–Al_2O_3. Hydrogenation of the enamine/amino ketal residue above over Rh–Al_2O_3 as described[1c,d] afforded amino ketal **37** (95% yield).

***trans*-4a-(2,3-Dimethoxyphenyl)-2-methyl-6-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (38).** A solution of amino ketal **37** (168 mg, 0.483 mmol) in THF (7 mL) was diluted with 0.5 M aqueous H_2SO_4 (7 mL). After 20 h the solution was poured into saturated aqueous $NaHCO_3$ (60 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried and evaporated to yield amino ketone **38**: 135 mg (0.45 mmol, 92% yield); HPLC (98.5/1.0/0.5 $CHCl_3$/MeOH/Et_3N, column A) t_R = 8.84 min; mp 150–151 °C (from PhH/hexane); IR (KBr) 1690 cm^{-1}; ^1H NMR (60 MHz, benzene-d_6) δ 7.10 (dd, 1 H, *J* = 2, 8), 6.80 (t, 1 H, *J* = 8), 6.52 (dd, 1 H, *J* = 2, 8), 3.9 (s, 3 H), 3.9–3.3 (m), 3.3 (s, 3 H), 2.9–1.2 (m), 2.10 (s, 3 H); mass spectrum, *m/z* (relative intensity) 303 (1), 302 (3), 273 (20), 272 (100), 96 (29). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.3; H, 8.3; N, 4.6. Found: C, 71.4; H, 8.3; N, 4.6.

***cis*-6,6-(Ethylenedioxy)-4a-(2-hydroxy-3-methoxyphenyl)-2-methyl-1-oxo-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline (41).** KH (330 mg of 21.8% oil dispersion, 71.9 mg of KH, 1.79 mmol, 636 mol %) was washed with hexane (4 × 5 mL) under argon, THF (5 mL) was added, and the suspension was cooled to −78 °C (bT). EtSH (0.125 mL, 104 mg, 1.68 mmol) was added, and the mixture was allowed to warm to 20 °C and then heated at 100 °C (bT) with distillative removal of THF. A solution of trans amido ketal **36** (102 mg, 0.28 mmol) in DMF (10 mL) was added, and the brown solution was heated at 100 °C (bT) for 14.5 h. Saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were added, and the organic layer was dried (Na_2SO_4 and evaporated. The residue was purified by preparative TLC ($CHCl_3$/trace glacial HOAc) to give **41**: 56 mg (0.16 mmol, 58% yield); yellow oil; IR (CH_2Cl_2) 3100, 1635 cm^{-1}; UV (absolute EtOH) λ_{max} 277, 282 nm; UV (absolute EtOH/base) λ_{max} 253, 277, 283, 296 nm (returns to original with acid); ^1H NMR (60 MHz) δ 6.67–6.30 (m, 3 H), 3.83 (s, 3 H), 4.0–3.7 (m, 4 H), 2.70 (s, 3 H), 3.0–1.2 (m, 11 H); mass spectrum, *m/z* (relative intensity) 347 (44), 302 (41), 286 (5), 260 (6), 245 (7), 232 (8), 224 (13), 28 (100); exact mass calcd for $C_{19}H_{25}NO_5$ *m/z* 347.1733, found 347.1724.

In a separate experiment the crude phenolic amido ketal reaction mixture was treated with Me_2SO_4 (192 mol %) at 100 °C (bT), resulting in a 6/69/25 mixture of *trans*-**36**/*cis*-**39**/unknown (8/92 trans/cis).

***cis*-6-Hydroxy-7-methoxy-3-methyl-4-oxo-2,3,4,4a,5,6,6a,10c-octahydro-1*H*-[1]benzopyrano[4,3,2-*ef*]isoquinoline (42). (A) Via Phenolic Ketal 41.** Phenol **41** (40 mg, 0.11 mmol) was dissolved in THF (2 mL), and 3 M aqueous H_2SO_4 (2 mL) was added. After 24 h the solution was neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), evaporated, and purified by preparative TLC ($CHCl_3$/trace glacial HOAc) to give **42**: 33 mg (0.11 mmol, 100% yield); tan oil; HPLC (30/70 $CHCl_3$/EtOAc, 1.6 mL/min, column A), t_R = 4.9 min; UV (absolute EtOH) λ_{max} 278, 282 nm; UV (absolute EtOH/base) λ_{max} 278, 284, 300 nm (returns to original with acid); IR (CH_2Cl_2) 3000, 1660, 1240, 1200, 1170, 1140, 1055, 1040 cm^{-1}; ^1H NMR (60 MHz, acetone-d_6) δ 7.1–6.8 (m, 3 H), 3.87 (s, 3 H), 3.03 (s, 3 H), 4.0–1.2 (m, 11 H); mass spectrum, *m/z* (relative intensity) 303 (36), 286 (6), 274 (1), 260 (17), 246 (11), 232 (8), 44 (100); exact mass calcd for $C_{17}H_{21}NO_4$ *m/z* 303.1470, found 303.1463.

(B) Via Amido Ketone 35. KH (1.81 g of 21.8% oil dispersion, 395 mg of KH, 9.84 mmol, 625 mol %) was washed with hexane (4 × 5 mL) under argon, THF (5 mL) was added, and the suspension was cooled in an acetone/CO_2 bath. EtSH (0.700 mL, 587 mg, 9.45 mmol) was added, and the suspension was allowed to warm to 20 °C and then heated to 100 °C (bT) with distillative removal of THF. A solution of amido ketone **35** (500 mg, 1.58 mmol) in DMF (15 mL) was added over 10–15 min, and the suspension was heated at 100 °C (bT) for 3 h. After being allowed to stand for 18 h at 25 °C the mixture was partitioned between CH_2Cl_2 (15 mL) and saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was further washed with CH_2Cl_2 (15 mL), and the combined organic phases were dried (Na_2SO_4) and evaporated.

Purification as described in part A gave hemiketal **42**, 288 mg (0.95 mmol, 60% yield).

***trans*-6-Hydroxy-7-methoxy-3-methyl-2,3,4,4a,5,6,6a,10c-octahydro-1*H*-[1]benzopyrano[4,3,2-*ef*]isoquinoline (44) and *trans*-6,7-Dihydroxy-3-methyl-2,3,4,4a,5,6,6a,10c-octahydro-1*H*-[1]benzopyrano[4,3,2-*ef*]isoquinoline (45).** Potassium *tert*-butoxide (1.5 g, 12.5 mmol) containing residual *tert*-butyl alcohol was added to degassed DMF (30 mL) under argon, and the suspension was degassed with argon for 1 h. EtSH (1.5 mL, 1.26 g, 20.25 mmol) was then added to provide a ca. 0.68 M solution of EtSK in DMF. Amino ketone **38** (60 mg, 0.2 mmol) was added to the EtSK/DMF solution (2.5 mL, 1.7 mmol) and heated at 100 °C (bT) under argon for 8 h. The solution was allowed to cool and after 12 h was evaporated, the residue was dissolved in 0.6 M aqueous NaOH (20 mL), the solution was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic phases were dried and evaporated to an oil which crystallized from PhH to give **44**: 25 mg (0.087 mmol, 43%); mp 125–140 °C; IR ($CHCl_3$) 3330, 3280 cm^{-1}; ^1H NMR (60 MHz) δ 6.90 (m, 3 H), 6.55 (br s), 4.87 (s, 3 H), 2.49 (s, 3 H), 3.5–1.2 (m); mass spectrum, *m/z* (relative intensity) 289 (19), 218 (13), 45 (100). Anal. Calcd for $C_{17}H_{23}NO_3 \cdot 0.15H_2O$: C, 69.9; H, 8.1; N, 4.8. Found: C, 69.9; H, 8.3; N, 4.7.

The aqueous phase was acidified (pH 1), washed with $CHCl_3$ (2 × 10 mL), basified (pH 8.5), and extracted with 3/1 $CHCl_3$/*i*-PrOH (3 × 15 mL). The combined organic extracts were washed with saturated aqueous NaCl (15 mL), dried, and evaporated to yield **45**: 30 mg (0.11 mmol, 55%); yellow oil; ^1H NMR (60 MHz, Me_2SO-d_6) δ 7.18–6.56 (m, 3 H), 3.89 (m, 1 H), 3.80 (br s, 2 H), 2.27 (s, 3 H), 3.1–0.9 (m); mass spectrum, *m/z* (relative intensity) 275 (59), 274 (21), 165 (21), 109 (24), 57 (100); exact mass calcd for $C_{16}H_{21}NO_3$ *m/z* 275.1510, found 275.1520.

Treatment of amino ketone **38** as described above for amido ketone **35** afforded **44** in 60% yield.

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Registry No. **5**, 86-51-1; **6a**, 39059-72-8; **6b**, 81011-95-2; **7a**, 81011-96-3; **7b**, 81011-97-4; **8a**, 81011-98-5; **8b**, 81011-99-6; **9**, 81012-00-2; **10**, 81012-01-3; **11**, 81012-02-4; **12**, 61209-85-6; **13**, 61209-87-8; **14**, 61527-89-7; **15**, 61527-90-0; **16**, 79618-99-8; **17**, 79619-00-4; **18**, 79619-13-9; **19**, 79619-14-0; **20**, 81012-03-5; **21**, 81012-04-6; **22**, 81012-05-7; **23**, 81012-06-8; **24**, 81012-07-9; **25**, 81012-08-0; **26**, 81012-09-1; **27**, 79631-85-9; **29**, 79619-02-6; **30**, 79619-07-1; **31**, 79619-11-7; **32**, 81012-10-4; **33**, 81012-11-5; **34**, 81012-12-6; **35**, 81064-05-3; **36**, 81012-13-7; **37**, 81012-14-8; **38**, 81012-15-9; **39**, 81012-16-0; **40**, 81012-17-1; **41**, 81012-18-2; **42**, 81012-19-3; **44**, 81012-20-6; **45**, 81012-21-7; **46**, 81012-22-8; **47**, 81012-23-9; **48**, 81012-24-0; **49**, 81012-25-1; **50**, 81012-26-2; **51**, 79619-12-8; **52**, 81012-27-3; **53**, 81012-28-4; **54**, 81012-29-5; **55**, 81012-30-8; **56**, 81012-31-9; **57**, 81012-32-0; **58**, 81012-33-1; **59**, 81012-34-2; i, 81012-35-3; ii, 81012-36-4; $EtO_2CCH_2CO_2H$, 1071-46-1; $NCCH_2CO_2H$, 372-09-8.

Supplementary Material Available: Textual and experimental details for the following: (1) selective reduction of amides in the presence of esters; (2) alternative routes to amino ester **11**; (3) alternative methods for allylic oxidation of α-methylene lactams; (4) developmental aspects of the SeO_2 reaction including the effect of solvent, water content, stoichiometry, time, temperature, and aromatic substitution pattern on the yield (15 pages). Ordering information is given on any current masthead page.

Diazoethenes: Their Attempted Synthesis from Aldehydes and Aromatic Ketones by Way of the Horner-Emmons Modification of the Wittig Reaction. A Facile Synthesis of Alkynes[1-3]

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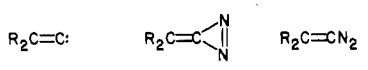
The base-promoted reaction of dimethyl (diazomethyl)phosphonate (**8**) with aldehydes and aryl ketones at low temperatures has been investigated. Alkynes, in modest to excellent yields, are the predominant products of these reactions, a result consistent with the intervention of diazoethenes (**3**). The latter appear to be unstable toward unimolecular decomposition at −78 °C and yield nitrogen and alkylidenecarbenes (**1**).

General interest exists in the physical and chemical properties of the unsaturated carbenes **1**,[4] and these



1 **2** **3**

species, which we shall refer to as alkylidenecarbenes,[5] have therefore been the recent subject of both theoretical[7] and experimental[8] investigations. However, a review of the literature relevent to the chemistry of such species failed

Table I. Theoretical Values of Singlet-Triplet Gap for Vinylidene (1, R = R = H)[a]

method	$\Delta H_{f(T_1)} - \Delta H_{f(S_0)}$, kcal/mol	ref
ab initio (HF)	15.7	7g
SCF (MINDO/2)	20.5	7c
ab initio (HF)	27.2	7f
SCF (MINDO/3)	28.2	this work
ab initio (HF)	31.0	7e
ab initio (SCEP)	32.4	7f
SCF (MNDO)	41.7	this work
ab initio (DEC 1-RSPT-4)	45.2	7g
ab initio (GVB)	45.9	7e
ab initio (MBPT-4)	49.7	7g
ab initio (MBPT-8)	51.1	7g
ab initio (MBPT-[3-3])	51.1	7g
ab initio (MBPT-[1-1])	51.3	7g

[a] Arbitrarily listed according to the increasing magnitude of the gap and not according to the relative sophistication of the theoretical method.

(1) This paper is dedicated to Professor William von E. Doering on the occasion of his 65th birthday.

(2) A preliminary account of portions of this work has been published: Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997.

(3) Taken in part from the dissertation of U.W. submitted in partial fulfillment of requirements for the Ph.D. degree.

(4) Reviews: (a) Hartzler, H. In "Carbenes"; Jones, M., Jr., Moss, R. A., Eds.; Wiley-Interscience: New York, 1975; Vol II. (b) Stang, P. J. *Acc. Chem. Res.* **1978**, *11*, 107. (c) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383. (d) Schaefer, H. F., III. *Acc. Chem. Res.* **1979**, *12*, 288.

(5) This category of carbene has variously been referred to as methylene carbenes[4a] and vinylidenes,[4d] in addition to the term[4b,c] used herein, which is recommended by *Chemical Abstracts*.[6]

(6) Newman, M. S.; Patrick, T. B. *J. Am. Chem. Soc.* **1970**, *92*, 4312.

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