Stereochemistry of Radical Cyclizations to Side-Chain Olefinic Bonds. An Approach to Control of the C-9 Center of Morphine

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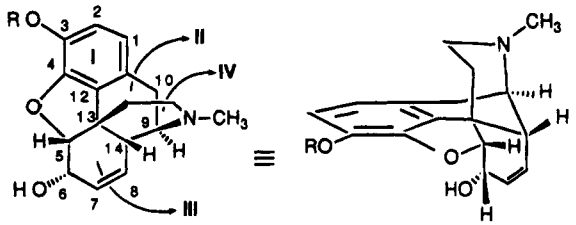
Styrenes of general structure **5** undergo tandem radical cyclization to *cis,cis*-hydrophenanthrofurans **9**, products which contain the carbocyclic skeleton of the morphine alkaloids. Vinylurethane **5E-NHCO$_2$Et** cyclizes to **9α** via the intermediate radical **7E-NHCO$_2$Et** in the chair-chair conformation. Cyclization of **5Z-NHCO$_2$Et** also gives predominantly **9α** instead of the expected **9β**. This anomaly is attributed to the isomerization of **5Z** to **5E** at a rate competitive with that of cyclization.

Introduction

Our strategy for a short and convergent synthesis of the morphine alkaloids **1**[2,3] has, as its key step, a tandem radical cyclization. A study in a model system (Scheme



1a R = H morphine
b R = Me codeine

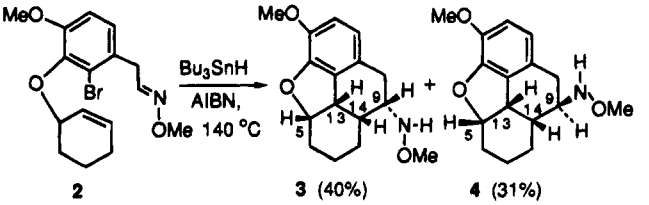
1)[2b] demonstrates the efficiency of this approach for producing the *cis,cis*-hydrophenanthrofuran tetracycle while defining two new chiral centers (labeled C-13 and C-14 in structures **3** and **4**).

This model study also shows that cyclization of substrates which contain the originally conceived functional group array (shown in structure **2**) will afford products in which the third chiral center (corresponding to C-9 of morphine, **1a**) is generated without the desired stereoselectivity. We now wish to report our efforts to design substrates for which conformational constraints in the region of C-9 would impose stereocontrol at this critical center during the second step of the cyclization.

Rationale: Design of Systems with the Potential for Additional Stereocontrol

We postulated that we might gain control at the C-9 chiral center by restricting the flexibility of the side chain which acts as the acceptor in the second radical closure. Consider the radicals involved in the tandem cyclization of substrate **5** (Scheme 2). On the basis of analogy to the cyclization of substrate **2** to tetracycles **3** and **4**, we can predict that phenyl radical **6** will cyclize to tricyclic radical **7** which contains a *cis* ring junction. Also from

Scheme 1. Tandem Cyclization to *cis,cis*-Hydrophenanthrofurans



2 **3** (40%) **4** (31%)

the results of the cyclization of oxime **2**, we can predict that **7cb** and **7cc**, in which the C-14 radical adds to the styrene double bond from the α-face of ring III and the C-14 hydrogen becomes situated on the β-face of the tandem product, will be favored. These two transition states have the same chair conformation for ring III and differ only in the orientation of the side chain which acts as the radical acceptor in the closure of ring II.

Examination of Dreiding models of radical **7** led us to believe that the radical center (C-14) could attain excellent overlap with the styrene π-bond in both available conformations (**7cb** and **7cc**). Also, it appeared that excessive strain would be required for closure to the α-carbon (C-10) and that addition to the styrene double bond might take place at the β-carbon (C-9). This would result in formation of the relatively stable benzylic radical in the desired six-membered ring III (i.e., *cis,cis* tetracyclic radicals **8cb** and/or **8cc** would be produced). If this were the case, then the stereochemistry generated at C-9 in the products **9α** and/or **9β** should be the result of the geometry of the styrene double bond coupled with the conformation of the side chain of radical **7** during closure.

The premise as applied to the morphine case is shown in Scheme 3. If vinylurethane **5E-NHCO$_2$Et** were to undergo tandem cyclization through the chair–boat conformation, the product would be 9β-NHCO$_2$Et, a stereochemical analog of the morphine alkaloids. However, if it were to cyclize via the chair–chair conformation, then the product would be stereoisomer 9α-NHCO$_2$Et. Conversely, were vinylurethane **5Z-NHCO$_2$Et** to undergo cyclization via the chair–boat or chair–chair conformation, the product would be **9α**-NHCO$_2$Et or **9β**-NHCO$_2$Et, respectively.

Preliminary Study: Cyclization of Unsubstituted Styrene 5H

Before testing our stereochemical premise, we wanted to establish that substrates **5** would undergo tandem

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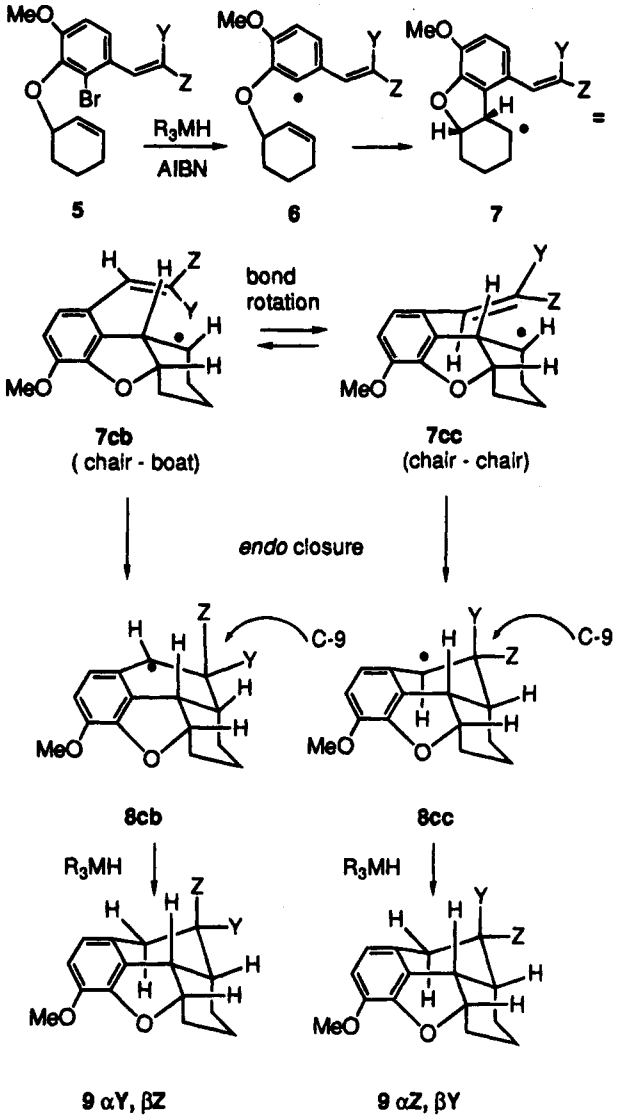
(1) Recipient of an NSF Career Advancement Award, 1992–1993.

(2) (a) Parker, K. A.; Spero, D. M.; Inman, K. C. *Tetrahedron Lett.* **1986**, *27*, 2833. (b) Parker, K. A.; Spero, D. M.; Van Epp, J. *J. Org. Chem.* **1988**, *53*, 4628.

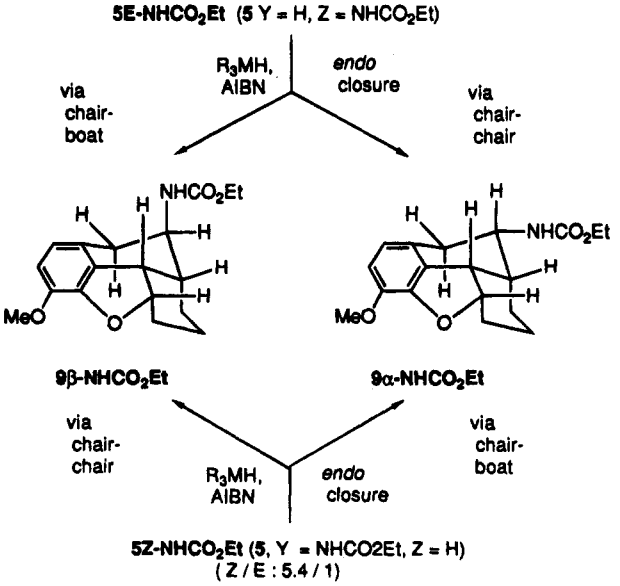
(3) For other recent approaches to the morphine system, including two total syntheses, see: (a) Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028. (b) Ciufolini, M. A.; Rivera-Fortin, M. A.; Byrne, N. E. *Tetrahedron Lett.* **1993**, *34*, 3505. (c) Hudlicky, T.; Boros, C. H.; Boros, E. E. *Synthesis* **1992**, 174. (d) Tius, M. A.; Kerr, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 5959 and references cited therein.

0022-3263/94/1959-3927$04.50/0

Scheme 2. Postulated Endo Cyclization of Intermediate Radical 7

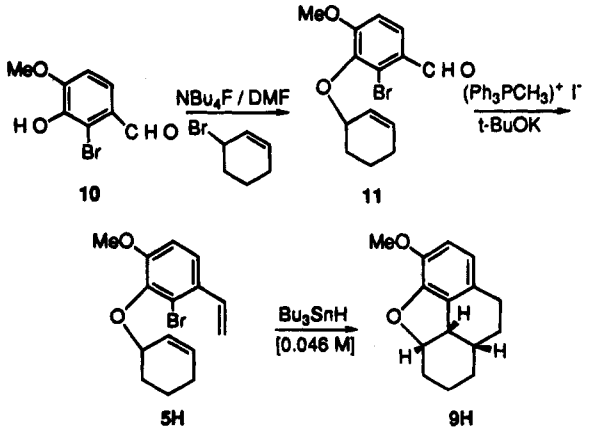


Scheme 3. Postulated Endo Cyclization of Vinylurethanes 5E and 5Z



cyclization to give the desired *cis,cis*-hexahydrophenanthro[4,5-*abc*]furans. This would be the case if, as anticipated, radical **7** would undergo endo ring closure to generate a benzylic radical in a six-membered ring (**8**) rather than exo ring closure to a homobenzylic radical.

Scheme 4. Preparation and Cyclization of a Model Styrene



In order to examine this question, we prepared the simple substrate **5H** (Scheme 4). Alkylation of 2-bromoisovanillin (**10**)[4] with 3-bromocyclohexene according to Clark's protocol (n-Bu_4NF /DMF)[5] gave aryl ether **11** in 85% yield. Conversion of aldehyde **11** to styrene **5H** was accomplished in 75% yield by Wittig olefination.

Treatment of substrate **5H** with tributyltin hydride/AIBN in benzene at 130 °C in a sealed tube afforded 69% of the parent hexahydrophenanthrofuran **9H**. Because this experiment was in agreement with our predictions on the stereochemistry and regiochemistry of ring closure, we were confident that the proposed substrates **5E** and **5Z** would undergo tandem cyclization to the desired tetracyclic ring system. Therefore, we proceeded to the preparation of these materials.

Synthesis of Substituted Styrenes for the Cyclization Studies

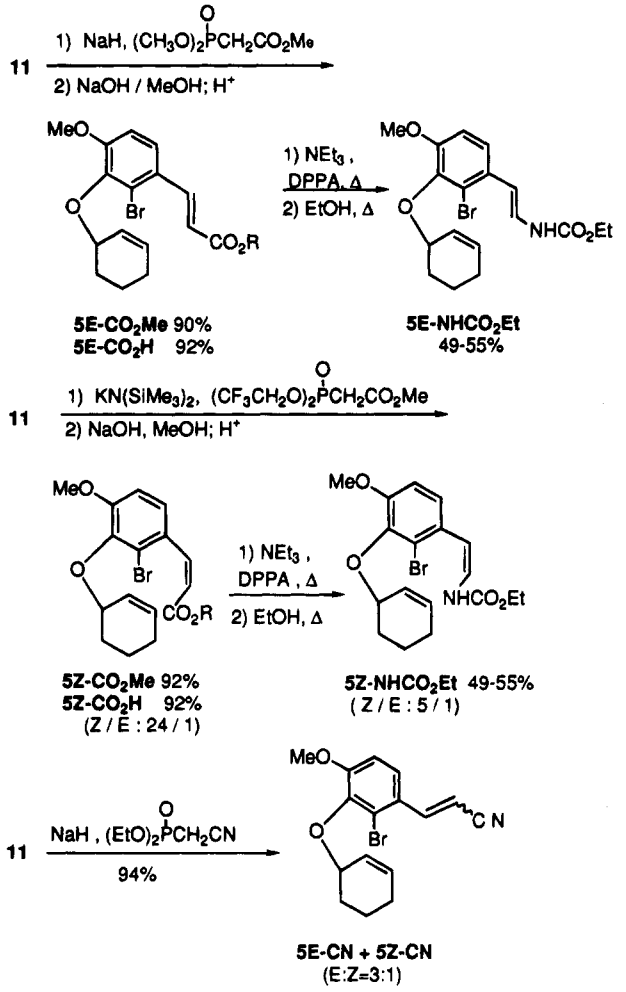
The synthesis of a series of substituted cyclization substrates **5** is outlined in Scheme 5. We envisioned the vinylurethanes **5E-NHCO$_2$Et** and **5Z-NHCO$_2$Et** as the products of the Curtius rearrangement of cinnamic acids **5E-CO$_2$H** and **5Z-CO$_2$H**.

Access to both the (*E*)-cinnamic ester and the (*E*)-vinylurethane was facile. Horner–Emmons olefination of aldehyde **11** with trimethyl phosphonoacetate[6] gave the unsaturated ester **5E-CO$_2$Me** which underwent hydrolysis to the corresponding acid **5E-CO$_2$H**. Treatment of acid **5E-CO$_2$H** with diphenyl phosphorazidate[7] (DPPA) and triethylamine followed by addition of EtOH gave the corresponding vinylurethane **5E-NHCO$_2$Et**.

The (*Z*)-cinnamic ester **5Z-CO$_2$Me** was prepared from aldehyde **11** according to the Still–Gennari protocol.[8] Hydrolysis afforded acid **5Z-CO$_2$H** (*Z*/*E* = 24/1). Treatment of this acid with diphenyl phosphorazidate[7] (DPPA) and triethylamine (as for **5E** above) gave vinylurethanes **5Z-NHCO$_2$Et** and **5E-NHCO$_2$Et** (*Z*/*E* = 5/1). It seems that an isomerization process to the thermodynamically

(4) Brotherton, R. J.; Hazlet, S. E. *J. Org. Chem.* **1962**, *27*, 3253.
(5) (a) Miller, J. M.; So, K. H.; Clark, J. H. *Can. J. Chem.* **1979**, *57*, 1887. (b) Clark, J. H. *Chem. Rev.* **1980**, 429.
(6) (a) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. (b) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 8.
(7) (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203. (b) Yamada, S.; Ninomiya, K.; Shioiri, T. *Tetrahedron Lett.* **1973**, *26*, 2343. (c) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron.* **1974**, *30*, 2151.
(8) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

Scheme 5. Substituted Styrenes for Cyclization Studies



more stable urethane **5E-NHCO$_2$Et** is taking place during the rearrangement of the acid **5Z-CO$_2$H**.

Nitriles **5E-CN** and **5Z-CN** were obtained as a mixture (E/Z = 3/1) upon treatment of aldehyde **11** with diethyl (cyanomethyl)phosphonate.[6,9] The isomers were cleanly separated by chromatography.

Results and Discussion

Each of the six substituted styrenes **5-CO$_2$Me** (**E** and **Z**), **5-NHCO$_2$Et** (**E** and **Z**), **5-CN** (**E** and **Z**) was subjected to radical initiation by tributyltin hydride. In addition, five of these substituted styrenes (**5E-CO$_2$Me**, **5Z-CO$_2$Me**, **5E-NHCO$_2$Et**, **5E-CN**, and **5Z-CN**) were subjected to treatment with tris(trimethylsilyl)silane. In each case, the substrate underwent a tandem cyclization and afforded one or both of the tetracyclic compounds **9α**, **9β** in fair to good yields (eq 1 and Table 1).

Experiments Initiated by Tributyltin Hydride. Tributyltin hydride cyclization of vinylurethane **5E-NHCO$_2$Et** afforded the tetracyclic carbamate **9α**-NHCO$_2$Et as the only product in 29–43% yield. Similarly, ester **5E-CO$_2$Me** reacted with tributyltin hydride to give ester **9α**-CO$_2$Me as the only tetracyclic product in 62% yield. The tricyclic ester **12-CO$_2$Me**, having exclusively *E*-geometry, was also obtained in 6% yield.

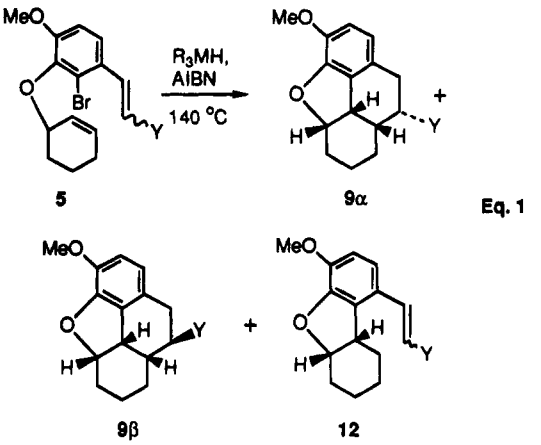
Under similar conditions, unsaturated nitrile **5E-CN**afforded a mixture of epimeric nitriles **9α-CN** and **9β-CN** (α/β = 5/1) in 40% yield with the **9α** isomer predominating. Tricyclic nitrile **12-CN** (E/Z = 3/2) was also isolated in 11% yield.

(9) Jones, G.; Maisey, R. F. *Chem. Commun.* **1968**, 543.

Table 1. Cyclization of Model Styrenes (See eq 1)

entry	substrate	R_3MH	R_3MH (mM)	9α, yield (%)	9β, yield (%)	12 ($E:Z$)[c]
1	5E-CO$_2$Me	Bu$_3$SnH	36	62		6 *E*
		TMS$_3$SiH	14	45		
2	5Z-CO$_2$Me	Bu$_3$SnH	39	42[a]	18[a]	2 (4:3)
		TMS$_3$SiH	54	21[a]	39[a]	
3	5E-NHCO$_2$Et	Bu$_3$SnH	27	29–43		
		TMS$_3$SiH	26	22		
4	5Z-NHCO$_2$Et (84:16 *Z:E*)	Bu$_3$SnH	27	33–43		
5	5E-CN	Bu$_3$SnH	52	33	7	11 (3:2)
		TMS$_3$SiH	30	44		
6	5Z-CN	Bu$_3$SnH	53	18[b]	10[b]	24 (3:1)
		TMS$_3$SiH	41	15	28	

[a] The α,β-mixture was analyzed by NMR integration. [b] Isolated yields. [c] Ratio determined by NMR integration.

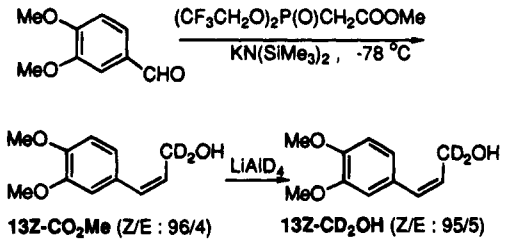


Cyclization of urethane **5Z-NHCO$_2$Et** (containing about 15% of the *E*-isomer) afforded **9α-NHCO$_2$Et** as the only product in 33–43% yield. Under the same reaction conditions, ester **5Z-CO$_2$Me** gave a mixture of **9α-CO$_2$Me** and **9β-CO$_2$Me** (α/β = 2.4/1) in 60% yield. A small amount (2%) of the tricyclic ester **12-CO$_2$Me** (E/Z = 4/3) was also obtained. Cyclization of the **5Z-CN** gave a mixture of **9α-CN** and **9β-CN** (α/β = 1.6/1) in 28% yield and the tricyclic unsaturated nitrile **12-CN** (Z/E = 2.8/1) in 24% yield.

The first and third entries in Table 1 are consistent with a mechanistic picture in which the (*E*)-styrenes react through conformation **7cc** (Y = H) to give the **9α** product. However, the data in entries 2, 4, 5, and 6 do not support either a simple chair–chair or a simple chair–boat model. Furthermore, it seems unlikely that the *E*-isomers would cyclize predominantly through a chair–chair transition state and that the *Z*-isomers would cyclize predominantly through a chair–boat transition state.

The appearance of some 9β product in the cyclization of **5E-CN** (entry 5), the observation that the (*Z*)-styrenes give predominantly the products with the 9α stereochemistry (entries 2, 4, and 6), and the isolation of tricyclic products **12E** as well as products **12Z** in entries 2, 5, and 6 suggest that, under the cyclization conditions, the styrene double bond is isomerized at a rate which is competitive with the rate of the cyclization reaction. Thus, **5Z-CO$_2$Me** is equilibrated to **5E-CO$_2$Me**, **5Z-NHCO$_2$Et** is equilibrated to **5E-NHCO$_2$Et**, and both **5Z-CN** and **5E-CN** are equilibrated to an *E,Z*-mixture. If this is the case, then the product distributions are

Scheme 6. Models for Isomerization Studies



consistent with a chair–chair transition state for both the *E* and the *Z* substrates.

Tris(trimethylsilyl)silane-Mediated Cyclizations. In the cyclizations in which the chain carrier was tris(trimethylsilyl)silane,[10] none of the tricyclic products **12** was observed. Furthermore, **5E-CN** afforded no 9β product. Substrates **5Z-CO$_2$Me** and **5Z-CN**, on the other hand, afforded product mixtures in which the ratio of β- to α-product was larger than the corresponding ratio in the tin hydride experiments.

The absence of tricyclic product **12** in these experiments is consistent with the kinetic studies[11] of Chatgilialoglu and Giese. They have shown that alkyl radicals abstract hydrogen from Bu_3SnH 10 times as rapidly as they abstract hydrogen from TMS_3SiH. Thus, while quenching of monocyclic radical **7** by tributyltin hydride competes somewhat with cyclization to tetracyclic radical **8**, quenching by TMS_3SiH does not compete to a significant extent.

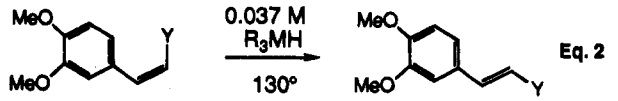
A two-transition-state model (chair–chair for *E*, chair–boat for *Z*) is not sufficient for explaining the different product ratios (α: β) that are obtained with TMS_3SiH and with Bu_3SnH. The exclusive formation of **9α** from **5E-CN** and the predominant formation of **9β** from **5Z-CO$_2$Me** and from **5Z-CN** are consistent with a mechanistic picture in which equilibration of the styrene double bond occurs with both reagents and is slower, relative to bromine atom abstraction (and initiation of cyclization), for TMS_3SiH than for Bu_3SnH.[12]

Equilibration of Styrene Double Bond Geometry by Tributyltin Hydride and Tris(trimethylsilyl)silane. We have now tested the premise that equilibration of styrene double bond geometry is rapid under the cyclization conditions and that tributyltin hydride effects this equilibration more efficiently than does tris(trimethylsilyl)silane. Preparation of the simple (*Z*)-styrenes **13Z-CO$_2$Me** and **13Z-CD$_2$OH** from 3,4-dimethoxybenzaldehyde was straightforward as shown in Scheme 6.[13]

The isomerization of the *Z*-isomer to the *E*-isomer was observed directly by NMR on the reaction mixture (eq 2 and Table 2).[14] For the two cases studied, it is clear that isomerization of the olefin is fast at 130° and also that tributyltin hydride effects isomerization more rapidly than does tris(trimethylsilyl)silane.[15]

Table 2. Isomerization of Model Styrenes (See eq 2)

Y	R_3MH	$\tau_{1/2}$ (min)
CO_2Me	Bu_3SnH	≪5
	$(TMS)_3SiH$	12
CD_2OH	Bu_3SnH	35
	$(TMS)_2SiH$	100



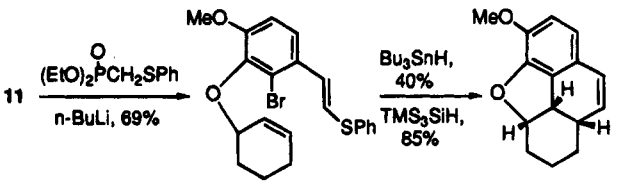
13Z **13E**

Conclusions and Modification of the Strategy

The product distributions obtained when substrates **5** undergo tandem radical cyclization are consistent with the original stereochemical model (Scheme 2) but with the caveat that the styrene double bond in the substrates isomerizes at a rate which is competitive with initiation of the cyclization reaction.

Nevertheless, the studies reported here show that the styrene substrates give the desired hydrophenanthrofuran tetracycle. In the absence of a means of controlling stereochemistry at the C-9 center, we considered systems which would lead to products containing a C-9 which was functionalized but not a stereocenter. For example, thioether **14** (Scheme 7), prepared in one step from aldehyde **11** and diethyl[(phenylthio)methyl]phosphonate,[16] underwent cyclization to the tetracyclic styrene **15** with either tributyltin hydride or with tris(trimethylsilyl) silane.

Scheme 7. Preparation and Cyclization of a Vinyl Sulfide Substrate



14 **15**

The high yield of a single product functionalized at C-9 makes this approach an attractive one for further development in a morphine synthesis.[17]

Experimental Section

Melting points are uncorrected. High-resolution mass spectra were obtained under electron impact (EI), chemical ionization (CI), or fast atom bombardment (FAB) conditions. Thin layer chromatography (TLC) was carried out on silica gel 60F 254 plates. Prep Plate chromatography was performed on precoated silica gel 1000-μm plates. Flash column chromatography was performed with silica gel 60 (230–400 mesh). THF and Et_2O were distilled from sodium benzophenone ketyl. Benzene was distilled from CaH_2.

(10) (a) Kanabus-Kaminska, J. M.; Hawari, J. A.; Griller, D.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **1987**, *109*, 5267. (b) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3641. (c) Giese, B.; Kopping, B.; Chatgilialoglu, C. *Tetrahedron Lett.* **1989**, *30*, 681. (d) Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.* **1991**, *56*, 678. (e) Lesage, M.; Chatgilialoglu, C.; Griller, D. *Tetrahedron Lett.* **1989**, *30*, 2733. (f) Kulicke, K. J.; Giese, B. *Synlett* **1990**, 91. (g) Chatgilialoglu, C.; Giese, B.; Kopping, B. *Tetrahedron Lett.* **1990**, *31*, 6013.

(11) Chatgilialoglu, C.; Dickhaut, J.; Giese, B. *J. Org. Chem.* **1991**, *56*, 6399.

(12) Olefin isomerization with both reagents is now known, the $(TMS)_3SiH$-catalyzed transformation having been reported only recently. See: Ferreri, C.; Ballestri, M.; Chatgilialoglu, C. *Tetrahedron Lett.* **1993**, *34*, 5147.

(13) Attempts to prepare the model **13Z-NHCO$_2$Et** from (*Z*)-cinnamic acid were inexplicably but reproducibly unsuccessful.

(14) Although mixtures of **13E-CN** and **13Z-CN** (9:1 in the commercial material from Aldrich and 5:1 in synthetic material from the Wittig preparation) were available, the ratio of (*E*)- to (*Z*)-nitrile in these samples was close enough to the equilibrium mixture (approximately 4:1) that no attempt to calculate a half-life was made.

(15) Neither **13Z-CO$_2$Me** nor **13Z-CD$_2$OH** isomerized when heated in the absence of a radical initiator.

(16) (a) Green, M. *J. Chem. Soc.* **1963**, 1324. (b) Corey, E. J.; Shulman, J. I. *J. Org. Chem.* **1970**, *35*, 777.

(17) For this successful application, see: Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688.

Benzaldehyde 11. To a solution of n-Bu_4NF (518 mg, 1.98 mmol) and 228 mg (0.99 mmol) of bromoisovanillin **10** in 10 mL of DMF at rt was added 188 μL (1.13 mmol) of 3-bromocyclohexene. The reaction mixture was stirred at rt for 2 h, diluted with water, and extracted with ethyl acetate (3 × 30 mL). The aqueous layer was washed with EtOAc (3 × 30 mL), and the combined organic layer was washed with H_2O (3 × 40 mL), dried over $MgSO_4$, filtered, and concentrated to give an oily residue. The crude product was purified by flash chromatography on silica gel with EtOAc–Hex (1:4) to yield 262 mg (85%) of a yellow oil which solidified, mp 82–83 °C: IR ($CHCl_3$) 3022, 1684, 1569, 1028 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ, 10.27 (s, 1 H), 7.72 (d, 1 H, J = 8.6 Hz), 6.95 (d, 1 H, J = 8.7 Hz), 5.95 (m, 2 H), 4.75 (s, 1 H), 3.93 (s, 3 H), 2.25–1.50 (m, 6 H); 100.6-MHz ^{13}C NMR ($CDCl_3$) δ 191.4, 158.7, 145.0, 132.3, 127.6, 126.7, 125.8, 123.7, 110.8, 76.9, 56.2, 29.1, 25.1, 18.9; HRMS (EI) for $C_{14}H_{15}O_3{}^{79}Br$ (M^+) calcd 310.0204, found 310.0171.

Styrene 5H. To a suspension of 603 mg (1.68 mmol) of methyl triphenylphosponium bromide salt in 10 mL of anhydrous THF at rt was added 188 mg (1.68 mmol) of t-BuOK. The resulting solution was stirred at rt for 15 min and then treated with 200 mg (0.64 mmol) of the aldehyde **11** in THF (1 mL). After the mixture was stirred at rt for 3 h, saturated NH_4Cl was added and the resulting mixture was extracted with Et_2O (3 × 50 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. Purification by flash chromatography over silica gel with EtOAc–Hex (1:15) afforded 149 mg (75%) of a pale yellow oil: IR ($CHCl_3$) 3019, 1650, 1614, 1578 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.50–2.20 (m, 6 H), 3.85 (s, 3 H), 4.73 (t, 1 H, $J \approx 5$ Hz), 5.23 (dd, 1 H, J = 10.9, J = 1.0 Hz), 5.55 (dd, 1 H, J = 17.4, 1.0 Hz), 5.92 (s, 2 H), 6.85 (d, 1 H, $J \approx 8.6$ Hz), 7.03 (dd, 1 H, J = 6.6, 10.8 Hz), 7.25 (d, 1 H, J = 8.5 Hz); 100.6-MHz ^{13}C NMR ($CDCl_3$) δ 153.2, 145.0, 136.1, 131.6, 131.4, 127.3, 121.3, 120.3, 114.8, 111.5, 76.7, 56.2, 29.1, 25.2, 19.1; HRMS (EI) for $C_{15}H_{17}O_2{}^{81}Br$ (M^+) calcd 310.0391 found 310.0364.

General Procedure for the Bu_3SnH or TMS_3SiH Radical Cyclizations. A solution of 1 equiv of the substrate, 1.2–1.5 equiv of tributyltin hydride or TMS_3SiH, and a catalytic amount of AIBN (0.1 equiv) in 3–5 mL of dry benzene was heated in a degased sealed tube at 120–130 °C for 24–48 h. The reaction was monitored by TLC, and after the complete consumption of the starting material the solvent was evaporated and the resulting residue was dissolved in Et_2O. The ethereal solution was washed several times with 10% KF[18] (only when Bu_3SnH was used) and brine, dried over Na_2SO_4, filtered, and concentrated to give the crude product. Purification of the crude product by flash chromatography or preparative TLC over silica gel yielded the desired products.

Hexahydrophenanthrofuran 9H: yellow oil, 69% yield (EtOAc–Hex (1:4)); IR ($CHCl_3$) 3055, 1626, 1601, 1498, 1093, 1011 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 0.90–1.20 (m, 3 H), 1.40–1.68 (m, 2 H), 1.80–2.0 (m, 1 H), 2.20 (m, 1 H), 2.75–2.47 (m, 2 H), 3.38 (t, 1 H, J = 6.5 Hz), 3.85 (s, 3 H), 4.98 (q, 1 H, $J \approx 8$ Hz), 6.60 (d, 1 H, J = 8.1 Hz), 6.72 (d, 1 H, J = 8.3 Hz), 100.6-MHz ^{13}C NMR ($CDCl_3$) δ 145.52, 143.23, 128.0, 126.68, 119.78, 113.17, 86.02, 56.62, 40.83, 31.95, 27.94, 27.64, 24.66, 21.74, 21.26; HRMS (EI) for $C_{15}H_{18}O_2$ (M^+) calcd 230.1306, found 230.1308.

Ester 5E-CO_2Me. To a suspension of 174 mg (7.25 mmol) of NaH in 30 mL of THF at rt was added 0.86 mL (5.31 mmol) of trimethyl phosphonoacetate, and a white slurry was formed. After the mixture was stirred at rt for 20 min, 1.50 g (4.82 mmol) of the aldehyde **11** in THF (3 mL) was added, and the reaction mixture was stirred at rt for 1 h and then refluxed for 1 h. Diethyl ether (100 mL) and water (50 mL) were added to the reaction mixture, and after vigorous shaking the organic phase was separated. The remaining aqueous layer was washed with Et_2O (3 × 30 mL), and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield an oily residue. The crude product was purified by flash chromatography on silica gel with EtOAc–Hex (1:4) to afford 1.59 g (90%) of a white solid, mp 92–93 °C: IR ($CDCl_3$) 3029, 1709, 1625, 1580, 1474, 1428, 1028 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 8.05 (d, 1 H, J = 15.9 Hz), 7.45 (d, 1 H, J = 8.7 Hz), 6.87 (d, 1 H, J = 8.7 Hz), 6.28 (d, 1 H, J = 15.8 Hz), 5.92 (s, 2 H), 4.73 (s, 1 H), 3.88 (s, 3 H), 3.80 (s, 3 H), 2.20–1.52 (m, 6 H); 100.6-MHz ^{13}C NMR ($CDCl_3$) δ 167.1, 155.0, 145.4, 143.7, 131.9, 128.0, 127.0, 122.7, 122.2, 118.5, 111.3, 76.8, 56.1, 51.7, 29.1, 25.2, 19.0; HRMS (EI) for $C_{17}H_{19}O_4{}^{79}Br$ (M^+ − C_6H_8) calcd 285.9840, found 285.9827.

Unsaturated Acid 5E-CO_2H. A solution of 191 mg (0.52 mmol) of the ester **5E-CO_2Me** and 42 mg (1.05 mmol) of NaOH in 10 mL of MeOH was refluxed for 3 h. Diethyl ether (30 mL) and water (10 mL) were added to the reaction mixture, the organic phase was separated, and the aqueous layer was washed with Et_2O (3 × 10 mL). The aqueous phase was acidified in an ice bath with 10% HCl until pH = 1–2, and the resulting mixture was extracted with Et_2O (2 × 40 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield 169 mg (92%) of a white solid: IR ($CDCl_3$) 3470–2400 (br), 1691, 1625, 1575, 1029 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ, 11.8–9.8 (br s, 1 H), 8.20 (d, 1 H, J = 15.8 Hz), 7.40 (d, 1 H, J = 8.6 Hz), 6.90 (d, 1 H, J = 8.9 Hz), 6.30 (d, 1 H, J = 15.9 Hz), 5.93 (s, 2 H), 4.75 (s, 1 H), 3.90 (s, 3 H), 2.20–1.55 (m, 6 H); HRMS (EI) for $C_{16}H_{17}O_4{}^{79}Br$ (M^+ − C_6H_9) calcd 270.9605, found 270.9639.

Vinylurethane 5E-$NHCO_2$Et. A solution of 22 mg (0.062 mmol) of the acid **5E-CO_2H**, 9 μL (0.065 mmol) of NEt_3, and 14 μL (0.065 mmol) of DPPA in 8 mL of benzene was refluxed for 24 h. An excess of anhydrous EtOH was added, and the reaction mixture was refluxed for another 24 h. The solvent was evaporated, and the remaining residue was dissolved in EtOAc. The resulting solution was washed with 5% HCl, H_2O, aq $NaHCO_3$, and aq NaCl, dried over Na_2SO_4, filtered, and concentrated to give an oily residue. The crude product was purified by preparative TLC over silica gel with EtOAc–Hex (1:4) to yield 12 mg (49%) of a white solid, mp 115–118 °C: IR ($CDCl_3$) 3429, 1716, 1648, 1589, 1032 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) δ 7.17 (d, 1 H, J = 8.6 Hz), 7.05 (t, 1 H, J = 14.3, J = 8.8 Hz), 6.82 (d, 1 H, J = 8.7 Hz), 6.62 (d, 1 H, J = 10.4 Hz), 6.28 (d, 1 H, J = 14.5 Hz), 5.92 (s, 2 H), 4.73 (s, 1 H), 4.22 (q, 2 H), 3.83 (s, 3 H), 2.12 (m, 1 H), 1.98 (m, 3 H), 1.78 (m, 1 H), 1.58 (m, 1 H), 1.29 (t, 3 H); HRMS (CI) for $C_{18}H_{22}O_4{}^{79}Br$ (M^+ + H) calcd 396.0809, found 396.0805.

Ester 5Z-CO_2Me. To a stirred solution of 988 mg (2.95 mmol) of the [bis(2,2,2-trifluoroethyl) methoxy]carbonyl methyl phosphonate and 3.54 g (13.4 mmol) of 18-C-6 in 30 mL of anhydrous THF at −78 °C was added 1.78 mL (2.68 mmol) of $KN(SiMe_3)_2$ (1.5 M in THF) under argon. The resulting solution was stirred at −78 °C for 30 min, and then 833 mg (2.68 mmol) of the aldehyde **11** in THF (3 mL) was added dropwise over 10 min. After the solution was stirred at −78 °C for 1 h, saturated NH_4Cl was added, and the resulting mixture was extracted with Et_2O (3 × 50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give an oily residue. The crude product was purified by flash chromatography over silica gel with EtOAc–Hex (14) to yield 906 mg (92%) of the unsaturated ester (Z/E = 24/1) as a yellow oil: IR ($CHCl_3$) 1717, 1631, 1584, 1479, 1029 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.52–2.20 (m, 6 H), 3.67 (s, 3 H), 3.87 (s, 3 H), 4.73 (s, 1 H), 5.92 (s, 2 H), 5.98 (d, 1 H, J = 12.2 Hz), 6.85 (d, 1 H, J = 8.7 Hz), 7.08 (d, 1 H, J = 12.3 Hz), 7.35 (d, 1 H, J = 8.6 Hz); HRMS (EI) for $C_{17}H_{19}O_4{}^{79}Br$ (M^+ − C_6H_8) calcd 285.9840, found 285.9853.

Unsaturated Acid 5Z-CO_2H. A solution of 206 mg (0.56 mmol) of the ester **5Z-CO_2Me** and 45 mg (1.13 mmol) of NaOH in 10 mL of MeOH was refluxed for 3 h. After most of the solvent was evaporated, the remaining residue was dissolved in H_2O and extracted with Et_2O (2 × 25 mL). The ether phase was washed with H_2O (2 × 15 mL), and the combined aqueous phase was acidified with 10% HCl in an ice bath until pH = 1–2. The resulting mixture was extracted with Et_2O (3 × 25 mL), and the combined ethereal layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield 182 mg (92%) of the acid (Z/E = 24/1) as a pale yellow oil which solidified on standing, mp 119–121 °C: IR ($CHCl_3$) 3466–2614 (br), 1692, 1627, 1584, 1476, 1029 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$) δ 1.45–2.15 (m, 6 H), 3.80 (s, 3 H), 4.65 (s, 1 H), 5.85 (s, 2 H), 5.89 (d, 1 H, J = 12.3 Hz), 6.75 (d, 1 H, J = 8.7 Hz),

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7.08 (d, 1 H, J = 12.2 Hz), 7.25 (d, 1 H, J = 8.6 Hz), 9.0–10.4 (br s, 1 H); HRMS (EI) for $C_{16}H_{17}O_4{}^{79}Br$ (M^+) calcd 352.0309, found 352.0275.

Vinylurethane 5Z-NHCO$_2$Et. A solution of 77 mg (0.22 mmol) of the acid **5Z-CO$_2$H**, 30 μL (0.22 mmol) of NEt_3, and 48 μL (0.22 mmol) of DPPA in 10 mL of benzene was refluxed for 24 h. A small excess of anhydrous EtOH was added, and the resulting solution was refluxed for another 24 h. After the solvent was evaporated the remaining residue was dissolved in EtOAc. The resulting solution was washed with 5% HCl, H_2O, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated to give the crude product. Purification by preparative TLC on silica gel with EtOAc–Hex (1:2) gave 48 mg (55%) of the urethane (Z/E = 5.4/1) as a yellow oil: IR ($CDCl_3$) 3428, 1725, 1657, 1589, 1464, 1029 cm^{-1}; 400-MHz ^{1}H NMR (C_6D_6) δ 0.90 (t, 3 H), 1.42 (m, 1 H), 1.72 (m, 2 H), 1.97 (m, 2 H), 2.13 (m, 1 H), 3.23 (s, 3 H), 3.95 (q, 2 H), 4.91 (s, 1 H), 5.65 (d, 1 H, J = 9.4 Hz), 5.78 (m, 1 H), 6.12 (dd, 1 H, J = 10.5, 2.9 Hz), 6.17 (d, 1 H, J = 8.5 Hz), 6.55 (d, 1 H, J = 12.0 Hz), 6.71 (d, 1 H, J = 8.4 Hz), 6.98 (t, 1 H, J = 10.3, 10.0 Hz); HRMS (CI) for $C_{18}H_{22}O_4N{}^{79}Br$ (M^+ + H) calcd 396.0809, found 396.0827.

Cinnamonitrile 5E-CN, 5Z-CN. To a suspension of 12 mg (0.50 mmol) of NaH in 5 mL of THF was added 78 μL (0.48 mmol) of diethyl (cyanomethyl)phosphonate under N_2. The resulting solution was stirred at rt for 1 h, and then 100 mg (0.32 mmol) of the aldehyde **11** in THF (1 mL) was added. The reaction mixture was stirred at rt for 1 h, quenched with water, and then extracted with Et_2O (3 × 30 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give an oily residue. The crude product was purified by flash chromatography over silica gel with EtOAc–Hex (1:3) to yield 100 mg (94%) of the unsaturated nitrile as a separable mixture of isomers (E/Z = 3/1). For the E-isomer: IR (CH_2Cl_2) 3056, 2205, 1610, 1580, 1477, 1031 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$) δ 1.58 (m, 1 H), 1.78 (m, 1 H), 2.20–1.90 (m, 4 H), 3.90 (s, 3 H), 4.75 (s, 1 H), 5.72 (d, 1 H, J = 16.6 Hz), 5.92 (m, 2 H), 6.88 (d, 1 H, J = 8.8 Hz), 7.26 (d, 1 H, J = 8.7 Hz), 7.82 (d, 1 H, J = 16.5 Hz); HRMS (EI) for $C_{16}H_{16}O_2{}^{79}BrN$ (M^+) calcd 333.0363, found 333.0333; 100.6-MHz ^{13}C NMR ($CDCl_3$) δ 155.7, 149.5, 145.6, 132.2, 127.1, 126.7, 122.0, 121.6, 118.1, 111.3, 96.5, 76.8, 56.2, 29.1, 25.1, 18.9. For the Z-isomer: IR (CH_2Cl_2) 3046, 2205, 1610, 1580, 1482, 1031 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$) δ 1.58 (m, 1 H), 1.81 (m, 1 H), 1.90–2.20 (m, 4 H), 3.90 (s, 3 H), 4.75 (s, 1 H), 5.45 (d, 1 H, J = 12.0 Hz), 5.92 (m, 2 H), 6.95 (d, 1 H, J = 8.7 Hz), 7.49 (d, 1 H, J = 12.0 Hz), 7.83 (d, 1 H, J = 8.7 Hz); HRMS (EI) for $C_{16}H_{16}O_2{}^{79}BrN$ (M^+) calcd 333.0363, found 333.0319.

Tetracyclic ester 9α-CO$_2$Me: yellow oil; 62% yield (prep TLC in EtOAc–Hex (1:6)); IR ($CHCl_3$) 3017, 2931, 1726, 1607, 1504, 1094 cm^{-1}; 400-MHz ^{1}H NMR (C_6D_6) δ 6.72 (d, 1 H, J = 8.1 Hz), 6.55 (d, 1 H, J = 8.2 Hz), 4.57 (q, 1 H, J = 7.5 Hz), 3.62 (s, 3 H), 3.35 (s, 3 H), 3.03 (t, 1 H, J = 6.3 Hz), 2.95 (dd, 1 H, J = 17.3, 12.3 Hz), 2.83 (dd, 1 H, J = 17.3, 6.2 Hz), 2.55 (m, 1 H), 2.28 (m, 1 H), 1.62 (m, 1 H), 1.30 (m, 1 H), 1.13 (m, 1 H), 0.95 (m, 1 H), 0.65 (m, 2 H); 100.6-MHz ^{13}C NMR ($CDCl_3$) δ 174.37, 145.43, 143.59, 127.09, 124.83, 119.91, 113.73, 85.76, 56.66, 51.80, 44.47, 41.61, 34.94, 27.57, 23.91, 21.50, 21.21; HRMS (EI) for $C_{17}H_{20}O_4$ (M^+) calcd 288.1361, found 288.1353.

Tetracyclic ester 9β-CO$_2$Me: 250-MHz ^{1}H NMR ($CDCl_3$) δ 6.73 (d, 1 H, J = 8.2 Hz), 6.65 (d, 1 H, J = 8.2 Hz), 5.0 (q, 1 H, J = 7.4 Hz), 3.85 (s, 3 H), 3.65 (s, 3 H), 3.35 (t, 1 H, J = 6.7 Hz), 3.18 (d, 1 H, J = 17.1 Hz), 2.90 (t, 1 H, J ≈ 7 Hz), 2.68 (dd, 2 H, J = 17.1, 6.9 Hz), 1.97 (m, 1 H), 1.60 (m, 1 H), 1.42 (m, 1 H), 1.2–1.8 (m, 3 H).

Tetracyclic nitrile 9α-CN: yellow oil (prep TLC in EtOAc–Hex (1:4)); IR (CH_2Cl_2) 3051, 2235, 2214, 1602, 1497, 1088, 1010 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$) δ 0.90∠1.25 (m, 3 H), 1.72 (m, 1 H), 1.87 (d, 1 H, J = 12.02 Hz), 2.02 (m, 1 H), 2.51 (m, 1 H), 2.85 (dd, 1 H, J = 15.3, 10.7 Hz), 3.10 (m, 2 H), 3.45 (t, 1 H, J = 6.8 Hz), 3.85 (s, 3 H), 5.02 (q, 1 H, J ≈ 8 Hz), 6.65 (d, 1 H, J = 8.2 Hz), 6.75 (d, 1 H, J = 8.3 Hz); 100.6-MHz ^{13}C NMR ($CDCl_3$) δ 145.57, 144.08, 125.73, 122.23, 121.07, 119.68, 113.93, 85.50, 56.57, 40.36, 35.04, 30.42, 27.38, 25.49, 21.48, 20.87; HRMS (EI) for $C_{16}H_{17}O_2N$ (M^+) calcd 255.1259, found 255.1241.

Tetracyclic nitrile 9β-CN: yellow oil (prep TLC in EtOAc–Hex (1:4)); IR (CH_2Cl_2) 3039, 2224, 1606, 1503, 1057 cm^{-1}; 400-MHz ^{1}H NMR ($CDCl_3$) δ 0.95 (m, 1 H), 1.18 (m, 2 H), 1.26 (m, 1 H), 1.65 (m, 1 H), 2.0 (m, 1 H), 2.55 (m, 1 H), 2.90 (dd, 1 H, J = 17.4, 6.65 Hz), 3.02 (d, 1 H, J = 17.6 Hz), 3.10 (m, 1 H), 3.79 (t, 1 H, J = 6.8 Hz), 3.88 (s, 3 H), 5.08 (q, 1 H, J ≈ 8 Hz), 6.65 (d, 1 H, J = 8.3 Hz), 6.75 (d, 1 H, J = 8.2 Hz); 100.6-MHz ^{13}C NMR ($CDCl_3$) δ 145.51, 144.02, 126.04, 121.95, 121.56, 120.04, 114.09, 85.27, 56.64, 37.40, 34.89, 29.95, 27.34, 25.08, 24.61, 21.07; HRMS (EI) for $C_{16}H_{17}O_2N$ (M^+) calcd 255.1259, found 255.1244.

Tetracyclic Urethane 9α-NHCO$_2$Et: yellow oil, 29–43% yield (prep TLC in EtOAc–Hex (1:2)); IR ($CHCl_3$) 3429, 3050, 1710, 1607, 1504, 1058, 1030 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$) δ, 6.72 (d, 1 H, J = 8.2 Hz), 6.60 (d, 1 H, J = 8.2 Hz), 5.0 (q, 1 H, J ≈ 8 Hz), 4.70 (br s, 1 H), 4.15 (q, 3 H), 3.85 (s, 3 H), 3.55 (t, 1 H, J = 6.3 Hz), 3.02 (dd, 1 H, J = 16.4, 6.4 Hz), 2.38 (dd, 2 H, J = 16.5, 11.3 Hz), 1.98 (m, 1 H), 1.63 (m, 1 H), 1.28 (t, 4 H, J ≈ 7.0 Hz), 1.12 (t, 2 H, J ≈ 10 Hz), 0.85 (t, 1 H, J ≈ 11 Hz); 100.6-MHz ^{13}C NMR ($CDCl_3$) δ 156.21, 145.32, 143.68, 127.24, 124.47, 119.66, 113.58, 85.35, 60.88, 56.63, 50.97, 41.23, 36.58, 28.83, 27.92, 21.01, 19.80, 14.62; HRMS (EI) for $C_{18}H_{23}O_4N$ (M^+) calcd 317.1627, found 317.1631.

Vinyl Sulfide 14. To a solution of 252 mg (0.97 mmol) of diethyl [(phenylthio)methyl]phosphonate in 15 mL of THF at 0 °C was added 0.49 mL (0.97 mmol) of n-BuLi (2.0 M in pentane) under argon. The resulting solution was stirred at 0 °C for 30 min, and then 275 mg (0.88 mmol) of the aldehyde **11** in THF (1 mL) was added over 5 min. The reaction mixture was warmed to rt and stirred overnight. Saturated NH_4Cl was added to the reaction mixture and then was extracted with Et_2O (3 × 30 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography over silica gel with EtOAc–Hex (1:6) to yield 254 mg (69%) of the vinyl sulfide as a yellow oil: IR ($CHCl_3$) 3026, 1643, 1585, 1299, 1256, 1032 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$) δ, 1.58 (m, 1 H), 1.81 (m, 1 H), 1.90–2.18 (m, 4 H), 3.83 (s, 3 H), 4.72 (s, 1 H), 5.92 (s, 2 H), 6.70 (d, 1 H, J = 15.3 Hz), 6.82 (d, 1 H, J = 8.7 Hz), 7.05 (d, 1 H, J = 15.3 Hz), 7.18 (d, 1 H, J = 8.6 Hz), 7.25–7.48 (m, 5 H), 100.6-MHz ^{13}C NMR ($CDCl_3$) δ 153.1, 145.2, 135.2, 131.7, 130.7, 130.4, 129.9, 129.1, 127.2, 127.0, 124.3, 121.3, 119.9, 111.5, 76.7, 56.2, 29.1, 25.2, 19.1; HRMS (EI) for $C_{21}H_{21}O_2{}^{79}BrS$ (M^+) calcd 416.0445 found 416.0417.

Tetracyclic Styrene 15: yellow oil, 85% yield (prep TLC in EtOAc–Hex (1:8)); IR ($CHCl_3$) 3055, 1610, 1579, 1502, 1056 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$) δ 0.80–1.15 (m, 2 H), 1.28 (m, 1 H), 1.50–1.70 (m, 2 H), 2.12 (m, 1 H), 2.58 (m, 1 H), 3.60 (t, 1 H, J = 8.3 Hz), 3.88 (s, 3 H), 5.10 (m, 1 H, J ≈ 8 Hz), 5.83 (dd, 1 H, J = 9.6, 5.8 Hz), 6.41 (d, 1 H, J = 9.6 Hz), 6.60 (d, 1 H, J = 8.1 Hz), 6.67 (d, 1 H, J = 8.1 Hz); 100.6-MHz ^{13}C NMR ($CDCl_3$) δ, 144.91, 144.69, 130.89, 125.52, 124.47, 123.71, 116.95, 112.23, 85.93, 56.28, 38.26, 34.15, 29.00, 27.96, 20.18; HRMS (EI) for $C_{15}H_{16}O_2$ (M^+) calcd 228.1150, found 228.1104.

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Supplementary Material Available: Copies of ^{1}H NMR spectra of all new compounds and copies of ^{13}C NMR spectra of **11, 5H, 9H, 5E-CO$_2$Me, 5E-CN, 9α-CO$_2$Me, 9α-NHCO$_2$Et, 9α-CN, 9β-CN, 14**, and **15** (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.