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Inverse Electron Demand Diels–Alder Reactions of 3-Carbomethoxy-2-pyrones. Controlled Introduction of Oxygenated Aromatics: Benzene, Phenol, Catechol, Resorcinol, and Pyrogallol Annulation. Regiospecific Total Synthesis of Sendaverine and a Preparation of 6,7-Benzomorphans

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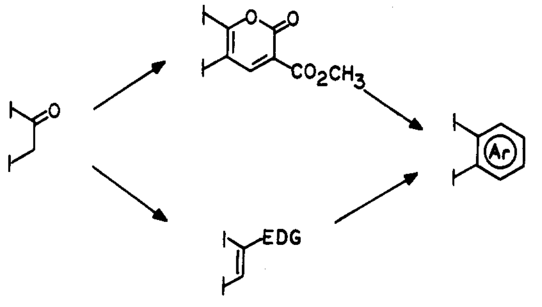
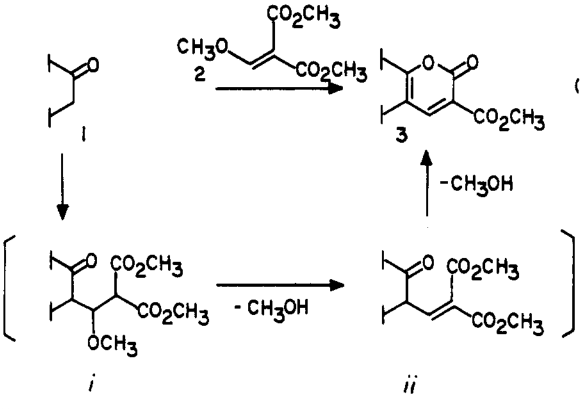
A full investigation of the preparation and Diels–Alder reactions of 3-carbomethoxy-2-pyrones is described. Methods for the preparation of a full range of oxygen-substituted aromatics: benzene, 1-, 2-, or 3-phenol, symmetrical or unsymmetrical *o*-catechol, resorcinol, and pyrogallol annulation from a common 3-carbomethoxy-2-pyrone intermediate are detailed. A regiospecific total synthesis of sendaverine, a 2-benzyltetrahydroisoquinoline possessing a selectively protected, symmetrical *o*-catechol, and a preparation of 6,7-benzomorphans are described.

The ability of α-pyrones to participate in Diels–Alder reactions with electron-deficient dienophiles for the preparation of dienes and aromatics is widely recognized.[2] By contrast, their potential to act as electron-deficient dienes in inverse electron demand Diels–Alder reactions[3] with electron-rich dienophiles is less recognized and has not been widely used.[4] Herein we describe a full investigation[5] of a general process for aryl introduction based on the observations that α-pyrones substituted with additional electron-withdrawing groups may participate in Diels–Alder reactions with electron-rich olefins.[4] The process involves direct conversion of a ketone to a 3-carbomethoxy-2-pyrone, an electron-deficient diene, followed by Diels–Alder reaction with electron-rich dienophiles and complements a related approach which requires conversion of a ketone to an electron-rich olefin and its subsequent Diels–Alder reaction with electron-deficient dienes,[6] eq 1. The results of this investigation suggest considerable potential for these and related inverse electron demand Diels–Alder reactions.



(1)

Preparation of 3-Carbomethoxy-2-pyrones. Four general procedures for the direct conversion of ketones to 3-carbomethoxy-2-pyrones have been employed and each relies on the treatment of ketone enolate, generated with sodium hydride (method A) or lithium diisopropylamide (method B), with dimethyl (methoxymethylene)malonate (2),[7] eq 2. The results are summarized in Table I.



(2)

Treatment of readily enolizable ketones, e.g., **1a** and **1b**, with 2.2 equiv of sodium hydride and **2** in tetrahydrofuran (THF) affords the 3-carbomethoxy-2-pyrones **3** directly in excellent yields (method A). Extension of this method to ketones such as cyclohexanone, **1c–g**, requires the use of

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(1) (a) Searle Scholar Recipient, 1981–1985. Recipient of a Career Development Award, 1983–1988, from the National Cancer Institute of the National Institutes of Health (Grant No. CA 00898). (b) National Institutes of Health Predoctoral Trainee, 1980–1983 (Grant No. GM 07775).

(2) Shusherina, N. P. *Russ. Chem. Rev.* **1974**, *43*, 851. Shusherina, N. P.; Dmitrieva, N. D.; Luk'yanets, E. A.; Levina, R. Y. *Ibid.* **1967**, *36*, 175.

(3) For reviews which discuss the inverse electron demand Diels–Alder reaction, see: (a) Sauer, J.; Sustmann, R., manuscript in preparation. (b) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779. (c) Sauer, J. *Ibid.* **1967**, *6*, 16. Wollweber, H. In "Methoden der Organischen Chemie"; Müller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1970; Vol. V/1c, p 1040. Huisgen, R.; Grashey, R.; Sauer, J. In "The Chemistry of Alkanes", Patai, S., Ed.; Interscience Publishers: London, 1964; p 739.

(4) For prior work on the inverse electron demand Diels–Alder reactions of α-pyrones, see: (a) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988. (b) Ireland, R. E.; McGarvey, G. J.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B.; Thaisrivongs, S. *Ibid.* **1980**, *102*, 6178. (c) Bryson, T. A.; Donelson, D. M. *J. Org. Chem.* **1977**, *42*, 2930. (d) Corey, E. J.; Watt, D. S. *J. Am. Chem. Soc.* **1973**, *95*, 2303. (e) Märkl, G.; Fuchs, R. *Tetrahedron Lett.* **1972**, 4695. (f) Behringer, H.; Heckmaier, P. *Chem. Ber.* **1969**, *102*, 2835. (g) Gingrich, H. L.; Roush, D. M.; Van Saun, W. A. *J. Org. Chem.* **1983**, *48*, 4869.

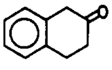
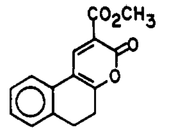
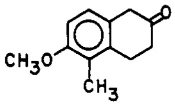
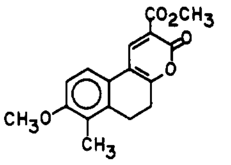
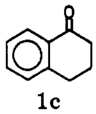
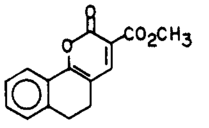
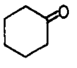
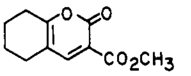
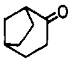
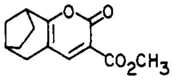
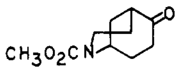
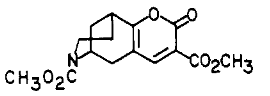
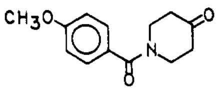
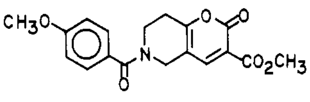
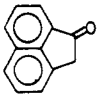
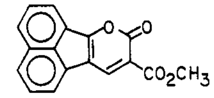
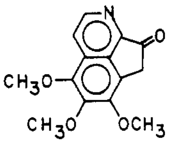
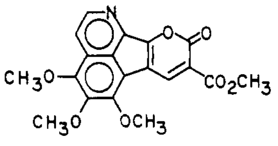
(5) (a) Boger, D. L.; Mullican, M. D. *Tetrahedron Lett.* **1982**, *23*, 4551, 4555. (b) Boger, D. L.; Patel, M.; Mullican, M. D. *Ibid.* **1982**, *23*, 4559. For complementary studies, see: (c) Tius, M. A.; Ali, S. *J. Org. Chem.* **1982**, *47*, 3163. Tius, M. A.; Thurkauf, A.; Truesdell, J. W. *Tetrahedron Lett.* **1982**, *23*, 2823, 2819. (d) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672.

(6) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1983**, *48*, 621. Boger, D. L.; Panek, J. S.; Meier, M. M. *Ibid.* **1982**, *47*, 895. Boger, D. L.; Panek, J. S. *Ibid.* **1981**, *46*, 2179. Boger, D. L.; Schumacher, J.; Mullican, M. D.; Patel, M.; Panek, J. S. *Ibid.* **1982**, *47*, 2673. Neunhoeffer, H.; Bachmann, M. *Chem. Ber.* **1975**, *108*, 3877. Sauer, J.; Mielert, A.; Lang, D.; Peter, D. *Ibid.* **1965**, *98*, 1435. Sauer, J.; Heinrichs, G. *Tetrahedron Lett.* **1966**, 4979.

(7) (a) Technical grade dimethyl (methoxymethylene)malonate is available from Fluka Chemical Corporation and was used after recrystallization (ether, 2×). It may be prepared by the procedure described for diethyl (ethoxymethylene)malonate: Fuson, R. C.; Parham, W. E.; Reed, L. J. *J. Org. Chem.* **1946**, *11*, 194. (b) For related α-pyrone preparations, see: Kraus, G. A.; Pezzanititite, J. O. *J. Org. Chem.* **1979**, *44*, 2480. Lee, K. T.; Whitney, J. G. U.S. Patent 3655694, 1972; *Chem. Abstr.* **1972**, *77*, 5334*m*.

0022-3263/84/1949-4033$01.50/0

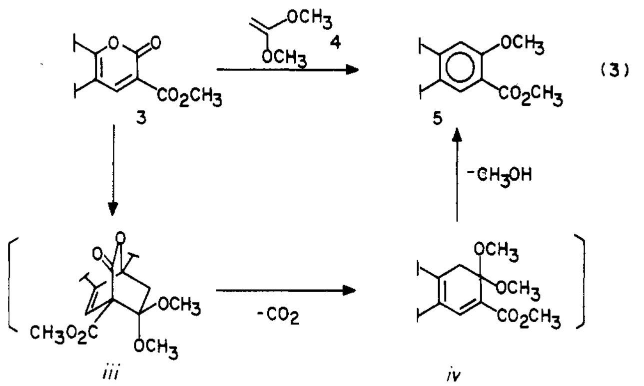
Table I. Preparation of 3-Carbomethoxy-2-pyrones

ketone	method,[a] % yield[b]	3-carbomethoxy-2-pyrone 3[b]
 1a	A, 73-91	 3a
 1b[c]	A, 81	 3b
 1c	B, 90	 3c
 1d	B, 84	 3d
 1e	B, 62	 3e
 1f[d]	B, 56	 3f
 1g	B, 35 C, 59	 3g
 1h	C, 47 D, 96	 3h[e]
 1i[e]	D, 62	 3i[e]

[a] Method A: The enolate of 1 was generated with 2.2 equiv of NaH in THF (0.2 M) at 0 to 25 °C. Method B: The enolate of 1 was generated with 1.2 equiv of LDA in THF (0.2 M) at -78 to -5 °C. Method C: The enolate of 1 was generated with 1.2 equiv of LDA in THF (0.2 M) at -78 to -5 °C, and closure to the α-pyrone was effected with acetic anhydride treatment at 100 to 130 °C. Method D: The enolate of 1 was generated with 2.2 equiv of NaH in THF (0.2 M) at 0 to 25 °C (1h) or 1.1 equiv of LDA in THF (0.2 M) at -78 to -5 °C (1i), and closure to the α-pyrone was effected with catalytic *p*-toluenesulfonic acid treatment in refluxing toluene with distillative removal of methanol, see ref 8a. [b] All yields are based on purified product isolated by column chromatography (SiO_2) or recrystallization. [c] See ref 8b. [d] See ref 5b. [e] See ref 8a.

1.2 equiv of lithium diisopropylamide (LDA) in THF (method B) and the slow step under these conditions is the final closure to the α-pyrone. In instances where the final closure is retarded by factors including ring strain of the α-pyrone, treatment of the initial reaction product, a mixture containing i and ii, with acetic anhydride at elevated temperatures (100–130 °C, method C)[8a] or *p*-toluenesulfonic acid (toluene, 110 °C, azeotropic removal of methanol, method D)[8a] promotes closure to the 3-carbomethoxy-2-pyrone. In each instance, formation of the 3-carbomethoxy-2-pyrone **3** occurs under milder conditions than generally associated with α-pyrone formation[2] and this can be attributed to the presence and position of the carbomethoxy group in **3**.[9]

Diels–Alder Reactions of 3-Carbomethoxy-2-pyrones with 1,1-Dimethoxyethylene: Salicylate Formation. The initial investigation of the ability of 3-carbomethoxy-2-pyrones to participate in Diels–Alder reactions with electron-rich olefins focused on their reaction with 1,1-dimethoxyethyene (**4**) for salicylate formation, eq 3. The results of this survey are summarized in Table II. In each case the Diels–Alder reaction proceeded smoothly under relatively mild conditions (5–10 equiv of **4**, 90–140 °C, toluene) and is accompanied by the loss of carbon dioxide and in situ loss of methanol providing the salicylate **5** directly (59–90%). The reaction proceeds with complete and predictable regiospecificity and the nucleophilic carbon of the dienophile attaches to carbon-6 of the 3-carbomethoxy-2-pyrone.



(3)

Mild Lewis acids are capable of catalyzing this cycloaddition. For instance, treatment of **3d** with **4** (5.0 equiv) in methylene chloride in the presence of 0.1 equiv of nickel(II) acetylacetonate[10a] [Ni(acac)$_2$, 4 days, 25 °C]

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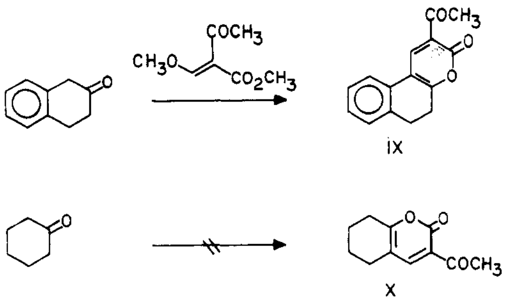
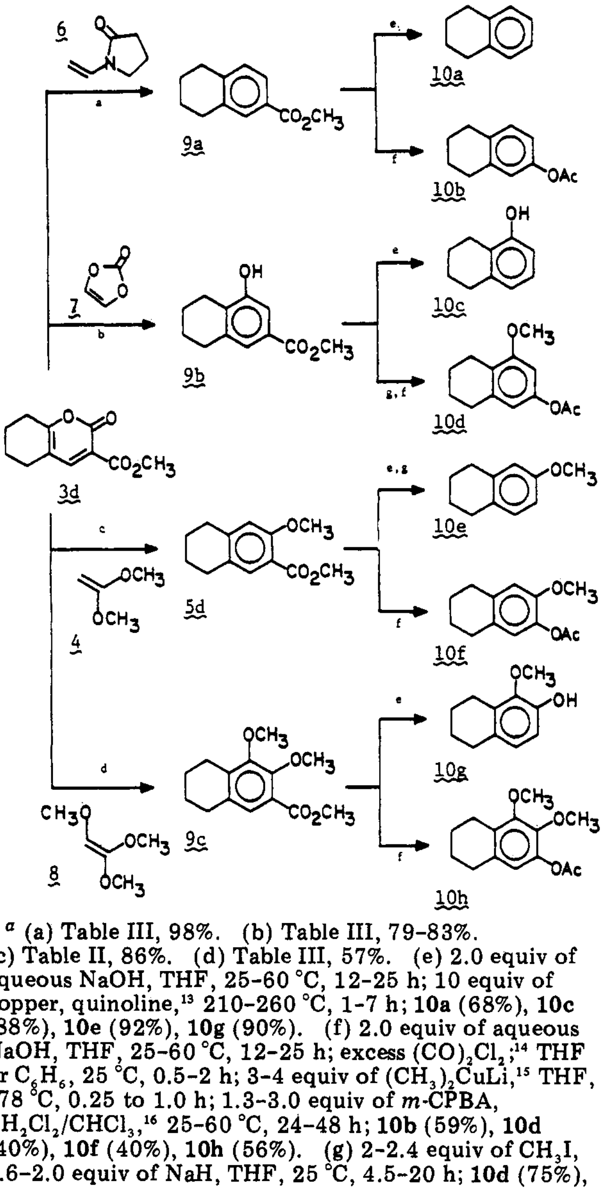
(8) (a) Boger, D. L.; Brotherton, C. E. *J. Org. Chem.*, third paper in a series in this issue. We thank C. Brotherton for development of method C and D for 3-carbomethoxy-2-pyrone formation. (b) Boger, D. L.; Mullican, M. D., *J. Org. Chem.*, second paper in a series in this issue.

(9) In related studies, the 3-acetyl-2-pyrone ix was prepared from β-tetralone and methyl (methoxymethylene)acetoacetate (DBU, 0 °C, 2 h, THF, 71%). Attempts to prepare x in acceptable yields were unsuccessful.



(10) (a) Nickel acetylacetonate is available from Alfa Chemical Company. Copper acetylacetonate, titanyl acetylacetonate, and zinc acetylacetonate were provided by Harshaw Chemical Company. (b) Cupric tetrafluoroborate was dried as described (Corey, E. J.; Koelliker, U.; Neuffer, J. *J. Am. Chem. Soc.* 1971, 93, 1489) and a stock solution in CH_2Cl_2 (6.4 mg/mL) was prepared.

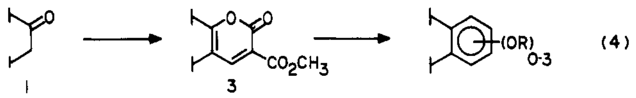
Scheme I[a]

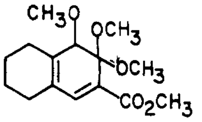


[a] (a) Table III, 98%. (b) Table III, 79–83%. (c) Table II, 86%. (d) Table III, 57%. (e) 2.0 equiv of aqueous NaOH, THF, 25–60 °C, 12–25 h; 10 equiv of copper, quinoline,[13] 210–260 °C, 1–7 h; **10a** (68%), **10c** (88%), **10e** (92%), **10g** (90%). (f) 2.0 equiv of aqueous NaOH, THF, 25–60 °C, 12–25 h; excess $(CO)_2Cl_2$;[14] THF or C_6H_6, 25 °C, 0.5–2 h; 3–4 equiv of $(CH_3)_2CuLi$,[15] THF, −78 °C, 0.25 to 1.0 h; 1.3–3.0 equiv of *m*-CPBA, $CH_2Cl_2/CHCl_3$,[16] 25–60 °C, 24–48 h; **10b** (59%), **10d** (40%), **10f** (40%), **10h** (56%). (g) 2–2.4 equiv of CH_3I, 1.6–2.0 equiv of NaH, THF, 25 °C, 4.5–20 h; **10d** (75%), **10e** (92%).

afforded **5d** in 50% yield. Comparable results were observed with zinc acetylacetonate $[Zn(acac)_2]$[10a], cupric acetylacetonate $[Cu(acac)_2]$,[10a] and titanyl acetylacetonate $[Ti(acac)_2]$[10a] as catalysts whereas cupric tetrafluoroborate $[Cu(BF_4)_2]$[10b] and tris(*p*-bromophenyl)ammonium hexachloroantimonate $[(p\text{-}BrC_6H_4)_3NSb^+Cl_5^-]$[11] promoted only the decomposition of 1,1-dimethoxyethylene with no evidence of Diels–Alder catalysis.

Benzene, 1-, 2- or 3-Phenol, Symmetrical or Unsymmetrical *o*-Catechol, Resorcinol, and Pyrogallol Annulation. The results of a select survey of the inverse electron demand Diels–Alder reactions of **3d**, including the salicylate preparation, designed to allow the utilization of a single intermediate for the introduction of a complete range of oxygenated aromatics, eq 4, are detailed in Scheme I and demonstrate the ability of 3-carbomethoxy-2-pyrones to accommodate a wide range of nucleophilic olefins. The aryl introduction, illustrated with the 3-carbomethoxy-2-pyrone **3d**, relies on the use of one of four electron-rich olefins: *N*-vinyl-2-pyrrolidinone[12a] (**6**), vinylene carbonate[12b] (**7**), 1,1-dimethoxyethylene[12c] (**4**), and 1,1,2-trimethoxyethylene[12d] (**8**), Scheme I. In each case cycloaddition is accompanied by the thermal elimination of carbon dioxide. In the Diels–Alder reactions of **4**, **6**, and **7** with **3d** the aromatized products **9a**, **9b**, and **5d** are the isolated products. Exclusive formation of **9b** can be attributed to the loss of the more acidic proton with elimination of carbon dioxide. In contrast, the principle product of the reaction of **3d** with **8** is **11** containing trace amounts of **9c**. Aromatization of **11**, which is stable to chromatography on silica gel, required removal of excess **8** and acid or base treatment of the product (Table III). The initial Diels–Alder product **11** was isolated in 61% yield without this treatment.





11

The choice of two standard reaction sequences, (1) removal of the carbomethoxy group (NaOH; copper powder, quinoline,[13] Δ) or (2) its conversion to an acetate [NaOH; $(COCl)_2$;[14] $(CH_3)_2CuLi$;[15] *m*-CPBA[16]], completes the preparation of a full range of oxygenated aromatics from a single precursor. In the course of these final conversions it was determined that the copper-promoted decarboxylation in hot quinoline may selectively demethylate methyl ethers ortho to a carboxylate prior or concurrent with decarboxylation. Though the generality of this reaction remains to be determined,[17] this observation in the sequence leading to **10g** and the carbomethoxy to acetate transformation allows the preparation of the selectively protected, symmetrical and unsymmetrical *o*-catechols **10f** and **10g**, the differentially protected resorcinol **10d**, and the selectively protected pyrogallol **10h**. Such differentiation in di- and trioxygenated aromatics is otherwise difficult.

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(11) For examples of triarylamminium salt catalyzed Diels–Alder reactions of electron-rich dienophiles, see: Pabon R. A.; Bellville, D. J.; Bauld, N. L. *J. Am. Chem. Soc.* **1983**, *105*, 5158 and references therein. For a preparation of tris(*p*-bromophenyl)amminium hexachloroantimonate, see: Bell, F. A.; Ledwith, A.; Sherrington, D. C. *J. Chem. Soc. C* **1969**, 2719.

(12) (a) *N*-Vinyl-2-pyrrolidinone (**6**) is available from Aldrich Chemical Company. (b) Vinylene carbonate (**7**) is available from Aldrich Chemical Company. (c) 1,1-Dimethoxyethylene (**4**) is available commercially from Wiley Organics. No attempt was made to minimize the amount of **4** necessary for Diels–Alder reaction with α-pyrones **3**. (d) 1,1,2-Trimethoxyethylene (**8**) was prepared as described: Bakker, C. G.; Scheeren, J. W.; Nivard, R. J. F. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 13. Spinning band distillation required to separate **8** from methyl methoxyacetate and 1,1,1,2-tetramethoxyethylene was found to be unnecessary and material which was 25–35% **8** worked satisfactorily in thermal cycloadditions.

(13) Trost, B. M.; Kinson, P. L. *J. Org. Chem.* **1972**, *37*, 1273. For a review on copper powder, quinoline decarboxylation in the context of the Pschorr synthesis, see: Leake, P. H. *Chem. Rev.* **1956**, *56*, 27.

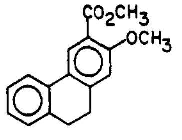
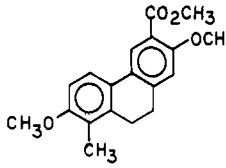
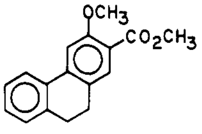
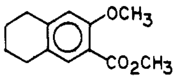
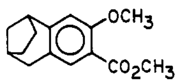
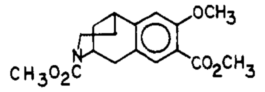
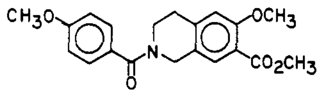
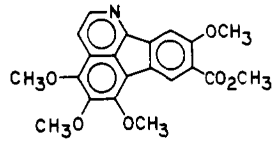
(14) For **10b**, **10d**, and **1g**, catalytic dimethylformamide in THF was used to promote acid chloride formation, see: Burgstahler, A. W.; Weigel, L. O.; Shaefer, C. G. *Synthesis* **1976**, 767. For **10f**, **10h**, and **19**, the preformed potassium salt of the carboxylic acid in benzene was used for the acid chloride formation, see: Miyano, M. *J. Am. Chem. Soc.* **1965**, *87*, 3958.

(15) Prepared immediately before use by addition of 2.0 equiv of MeLi to 1.0 equiv of CuI at 0 °C (5 min), see: Posner, G. H.; Whitten, C. E.; McFarland, P. E. *J. Am. Chem. Soc.* **1972**, *94*, 5106.

(16) Godfrey, I. M.; Sargent, M. V.; Elix, J. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1353. For **10d**, potassium carbonate was added to the reaction mixture.

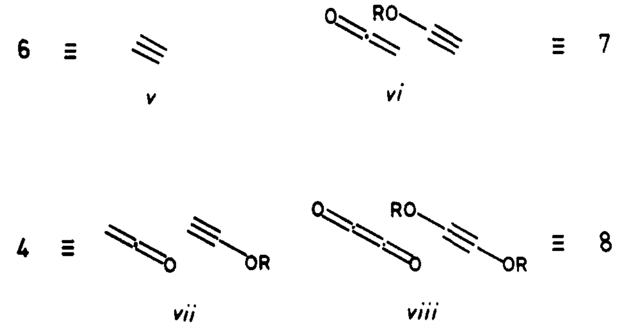
(17) Treatment of *o*-, *m*-, or *p*-anisic acid with 10 equiv of copper powder in quinoline at 220 °C for 1.25 h afforded a mixture of phenol and anisole in all cases. In contrast, the conditions employed in the use of (pentafluorophenyl)copper as catalyst to promote decarboxylation do *not* effect demethylation of aryl methyl ethers ortho to a carboxylate to any significant extent: see ref 8a and references cited therein.

Table II. Diels-Alder Reaction of 3-Carbomethoxy-2-pyrones 3 with 1,1-Dimethoxyethylene 4: Salicylate Formation

3-carbomethoxy-2-pyrone 3	conditions[a] equiv 4, time h (temp, °C)	product	% yield[b]
3a	3.7, 20 (140)	 5a	73
3b	10.0, 21 (140)	 5b[c]	75
3c	10.0, 15 (120)	 5c	78
3d	5.5, 15 (110) 5.0, 96 (25), CH_2Cl_2 catalytic $Ni(acac)_2$	 5d	86 50
3e	6.0, 12 (95)	 5e	90
3f	10.0, 13 (120)	 5f[d]	80
3g	10.0, 24 (120)	 5g	91
3i	8.0, 5 (120)	 5i[e]	83

[a] The reaction was run in a sealed vessel, ref 26, with toluene as solvent (0.6 M), unless otherwise indicated. [b] All yields are based on purified product isolated by column chromatography (SiO_2). [c] See ref 8b. [d] See ref 5b. [e] See ref 8a.

The dienophiles 6, 7, 4, and 8 serve as equivalents of v–viii in their reactions with 3-carbomethoxy-2-pyrones



and the use of 7 vs. 4 serves the purpose of controlling the regiospecificity of addition of the identical equivalents vi vs. vii.

Additional Studies. Other Diels–Alder reactions of 3-carbomethoxy-2-pyrones which have been investigated are summarized in Table III. The electron-rich systems ethyl vinyl ether and 1-(diethylamino)propyne[18a] undergo smooth addition to **3f**, affording **9a** and **12**, respectively. Thus, ethyl vinyl ether serves as an alternative to the use of **6** though the yield of **9a** is diminished. Unactivated acetylenes are capable of addition as evidenced by the Diels–Alder reaction of 2,5-dihydroxy-3-hexyne[18b] with **3d**, Table III, entry 7. In addition, electron-deficient systems represented by dimethyl acetylenedicarboxylate and 3-

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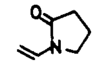
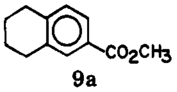
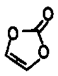
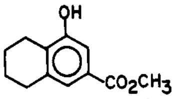
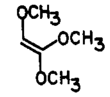
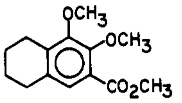
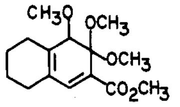
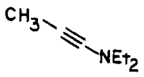
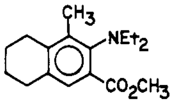
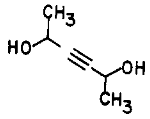
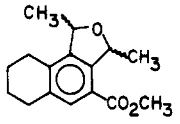
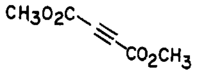
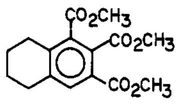
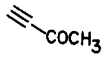
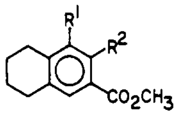
(18) 1-(Diethylamino)propyne is available from Fluka Chemical Corporation. (b) 3-Hexyne-2,5-diol is available from Fluka Chemical Corporation. (c) Dimethyl acetylenedicarboxylate is available from Aldrich Chemical Company. For examples of Diels–Alder reactions of 3- and 5-carbomethoxy-2-pyrones with dimethyl acetylenedicarboxylate, see ref 19. (d) 3-Butyn-2-one is available from Alfa Chemical Company.

Table III. Diels-Alder Reactions of 3-Carbomethoxy-2-pyrone 3d

entry	dienophile (equiv)	conditions[a] temp, °C (time, h)	product(s)	% yield[b]
1	 6 (3.0)	160 (42)	 9a	98
2	 (5.0)	145 (43)[c]	9a	51
3	 7 (5-10.0)	180 (40)	 9b	83
4	 8 (5.0)	150 (78);[d] catalytic CH_3SO_3H or	 9c	57
	8 (10.0)	150 (84);[d] catalytic DBU 150 (12)	9c	51
5	8 (10.0)	120 (59)[c]	 11	61
6	 (2.0)	150 (17)	 12	43
7	 (5.0)	200 (12);[e] CH_2N_2	 13	54
8	 (5.0)	150 (18), 180 (24)	 14	57
9	 (5-10.0)	110 (65)	 15, $R^1 = H; R^2 = COCH_3$ 16, $R^1 = COCH_3; R^2 = H$	21% 15, 4% 16
10		150 (20)		43% 15, 20% 16

[a] The reaction was run in a sealed vessel, ref 26, in mesitylene (0.6 M) unless otherwise indicated. [b] All yields are based on purified product isolated by column chromatography (SiO_2). [c] The reaction was run in a sealed vessel, ref 26, in toluene (0.6 M). [d] The reaction was run neat in a sealed vessel, ref 26. [e] The acid was the immediate product and was converted to the methyl ester by treatment with excess CH_2N_2 in dry Et_2O.

butyn-2-one are capable of Diels-Alder reactions with 3-carbomethoxy-2-pyrones, entries 8-10, Table III. The Diels-Alder reactions between 2π and 4π components of a similar electrophilic nature proceed at retarded rates and with little regioselectivity.[3b,19] Thus, it is not surprising that a mixture of regioisomers **15** and **16** are formed at a slow rate in the reaction of **3d** with 3-butyn-2-one.

Dienophiles which did not undergo a Diels-Alder reaction with 3-carbomethoxy-2-pyrone **3d** include tris[(trimethylsilyl)oxy]ethylene,[20a] 1,1-bis[(trimethylsilyl)oxy]-2-methoxyethylene,[20b] 1,2-dimethoxy-1-[(trimethylsilyl)oxy]ethylene,[20b] 1-bromo-1,2-dimethoxyethylene,[20c] 4,4-dimethoxy-3-buten-2-one,[20d] 4-(dimethylamino)-3-buten-2-one,[20e] and 4-methoxy-3-buten-2-one.[20f]

Regiospecific Total Synthesis of Sendaverine. The *N*-benzyltetrahydroisoquinoline **17** possessing a selectively protected, symmetrical *o*-catechol was isolated from *Corydalis aurea* as alkaloid F-28,[21a] purified,[21b] identified,[21c]

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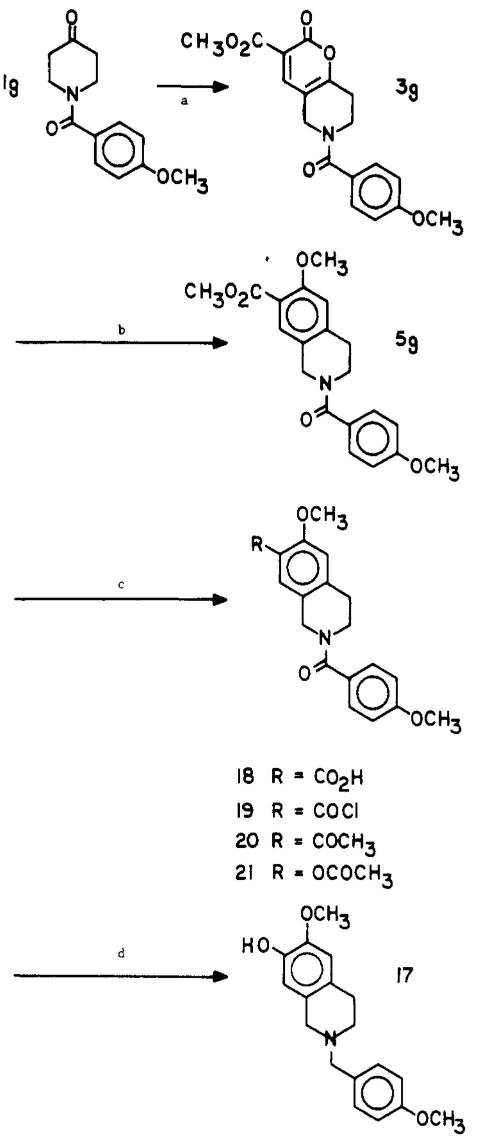
(19) The reactions of 3- and 5-carboalkoxy-2-pyrones with propiolate esters give similar product ratios, see: Reed, J. A.; Schilling, C. L., Jr.; Tarvin, R. F.; Rettig, T. K.; Stille, J. K. *J. Org. Chem.* **1969**, *34*, 2188.

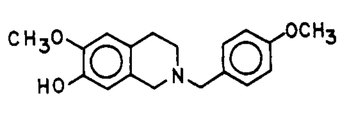
(20) (a) Tris[(trimethylsilyl)oxy]ethylene is available from Fluka Chemical Corporation. (b) Wissner, A. *J. Org. Chem.* **1979**, *44*, 4617. (c) Skold, C. N. *Synth. Commun.* **1976**, *6*, 119. (d) Banville, J.; Brassard, P. *J. Chem. Soc., Perkin Trans. 1*, **1976**, 1852. (e) Benary, E. *Chem. Ber.* **1930**, *63*, 1573. (f) 4-Methoxy-3-buten-2-one is available from Aldrich Chemical Company.

Scheme II[a]

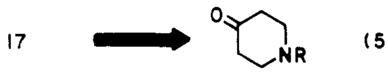


[a] (a) Table I, 59%. (b) Table II, 91%. (c) 2.0 equiv of NaOH, THF:CH_3OH:H_2O, 25 °C, 10 h, 97%; 1.0 equiv of KOH, CH_3OH:H_2O, 25 °C; 7.2 equiv of $(COCl)_2$, C_6H_6, 25 °C, 3 h; 4.0 equiv of Me_2CuLi, THF, -78 °C, 1 h, 76%; 1.8 equiv of *m*-CPBA, CH_2Cl_2, 25 °C, 89 h, 62%. (d) $LiAlH_4$, THF, 0 °C, 1 h, 70%.

and given the name sendaverine.[21b] Recent total syntheses of sendaverine have confirmed the structural identity of 17.[21c,e–g] A simple, regiospecific total synthesis of sendaverine (17) which effectively addresses the preparation of a selectively protected, symmetrical *o*-catechol utilizing an inverse electron demand Diels–Alder reaction of a 3-carbomethoxy-2-pyrone, eq 5, is detailed in Scheme II.

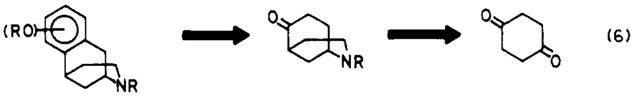


17



Conversion of the readily available ketone **1g** to 3-carbomethoxy-2-pyrone **3g**, Table I, and subsequent treatment with 1,1-dimethoxyethylene (4) afforded the methyl salicylate **5g**, Table II. Ester hydrolysis, acid chloride formation,[14] conversion to the methyl ketone **20**,[15] and Baeyer–Villiger oxidation[16] gave **21**. Lithium aluminum hydride reduction of **21** afforded sendaverine (**17**).[21h]

Preparation of 6,7-Benzomorphans. A simple and direct preparation of a representative series of 6,7-benzomorphans which is based on the utilization of the inverse electron demand Diels–Alder reactions of 3-carbomethoxy-2-pyrones for the controlled and selective introduction of oxygenated aromatics is outlined in eq 6 and is detailed in Scheme III.



The 3-carbomethoxy-2-pyrone **3f**, prepared from ketone **1f** (Table I),[5b] underwent smooth cycloaddition with 1,1-dimethoxyethylene[12c] to give **5f**. Ester hydrolysis and copper-promoted decarboxylation in quinoline[13] provided the phenol-substituted 6,7-benzomorphan **22**. Demethylation of the aryl methyl ether ortho to the carboxylate occurred under the conditions of the reaction.

Similarly, treatment of 3-carbomethoxy-2-pyrone **3f** with 1,1,2-trimethoxyethylene[12d] followed by acid treatment of the crude Diels–Alder adduct afforded **23**. Ester hydrolysis and copper-promoted decarboxylation provided the selectively protected, unsymmetrical *o*-catechol 6,7-benzomorphan **24**. *Selective* demethylation of the aryl methyl ether ortho to the carboxylate occurred prior or concurrent with decarboxylation.

The ease with which a complementary series of 6,7-benzomorphans were prepared from the common intermediate **3f** illustrates the potential utility of this approach. Extensions of this work to accommodate each class of the morphine-related analgesics are in progress.

The ease with which 3-carbomethoxy-2-pyrones may be prepared, the facility with which they participate in inverse electron demand Diels–Alder reactions, and the capability of this approach to accommodate the preparation of selectively protected di- and trioxygenated aromatics indicate that this methodology should prove to be of value in the preparation of natural or synthetic materials in which the concurrent or systematic variation of an aryl oxygenation pattern is required. Additional studies are detailed in the accompanying papers.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-33 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian FT-80A spectrometer. Mass spectra and high-resolution mass spectra were obtained on a Varian CH-5 or Ribermag R10-10 mass spectrometer by Charles Judson. Microanalysis were performed by Tho I. Nguyen on a Hewlett-Packard Model 185B CHN analyzer at the University of Kansas. Medium-pressure liquid chromatography (MPLC) was performed on silica gel 60 (230–400 mesh).[22a]

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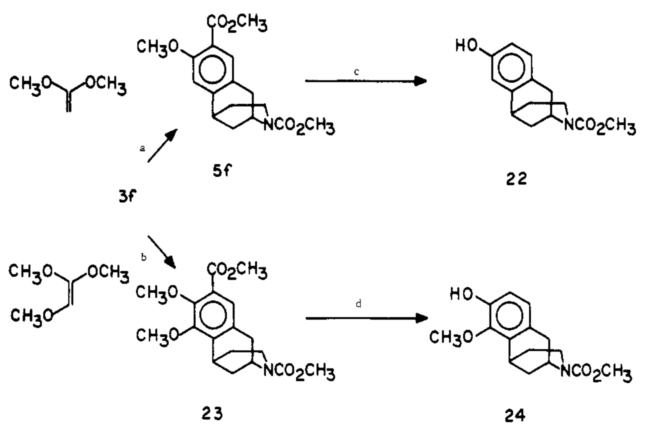
(21) (a) Manske, R. H. F. *Can. J. Res., Sect. B* **1938**, *16*, 81. (b) Kametani, T.; Ohkubo, K.; Noguchi, I. *J. Chem. Soc. C* **1966**, 715. (c) Kametani, T.; Ohkubo, K. *Chem. Pharm. Bull. Jpn.* **1967**, 15, 608. See also: (d) Kametani, T.; Ohkubo, K.; Noguchi, I.; Manske, R. H. F. *Tetrahedron Lett.* **1965**, 3345. Kametani, T.; Ohkubo, K. *Ibid.* **1965**, 4317. Kametani, T.; Ohkubo, K.; Manske, R. H. F. *Ibid.* **1966**, 985. (e) Kametani, T.; Enomoto, Y.; Takahahshi, K.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2836. (f) Mori, M.; Chiba, K.; Kudo, S.; Ikeda, T.; Hashimoto, Y.; Ban, Y. *Heterocycles* **1978**, *9*, 92. (g) Masood, M.; Tiwari, K. P. *Acta Chim. Hung.* **1983**, *113*, 177. (h) The ^1H NMR spectrum of synthetic sendaverine, mp 136–138 °C, was identical with a copy of the ^1H NMR spectrum of authentic sendaverine; mp 139–140 °C, 140–141 °C; provided by Professor T. Kametani. The IR spectrum of synthetic sendaverine was identical with the published[21b] IR spectrum of natural sendaverine.

Scheme III[a]



[a] (a) 10 equiv of 1,1-dimethoxyethylene, toluene, 120 °C, 13.5 h, 80%. (b) ca. 10 equiv of 1,1,2-trimethoxyethylene, neat, 150 °C, 84 h; 0.1 equiv of $MeSO_3H$, benzene, 25 °C, 12 h, 59%. (c) 2 equiv of NaOH, THF-H_2O, 25 °C, 15.5 h; 10 equiv of copper powder, quinoline, 220 °C, 1 h, 97%. (d) 2.0 equiv of NaOH, THF-H_2O, 35 °C, 15.5 h; 10 equiv of copper powder, quinoline, 220 °C, 1 h, 86%.

Preparative centrifugal thin-layer chromatography (PCTLC)[22b] was performed on a Chromatotron Model 7924 (Harrison Research, Palo Alto, CA) on Kieselgel 60 $PF_{254}/CaSO_4 \cdot {}^1/_2H_2O$ (Merck, D-6100 Darmstadt, FRG). Tetrahydrofuran and ether were distilled immediately before use from benzophenone ketyl. Benzene was distilled from benzophenone ketyl. Toluene, mesitylene, and diisopropylamine were distilled from powdered calcium hydride. Methylene chloride was distilled immediately before use from phosphorus pentoxide. Chloroform was stirred over neutral alumina and passed through a plug of neutral alumina. Quinoline was dried over Na_2SO_4 and vacuum distilled from zinc dust. Dimethylformamide (DMF) was vacuum distilled from calcium oxide. Extraction and chromatographic solvents (CH_2Cl_2, EtOAc, ether, and hexane) were distilled before use. All reactions requiring anhydrous conditions were run under positive pressure of argon and reagents were introduced by syringe through a septum unless otherwise indicated. Syringes and reaction flasks were oven-dried. All other reactions were sealed from the atmosphere or run under positive pressure of nitrogen.

Methyl 3-Oxo-5,6-dihydro-3*H*-naphtho[2,1-*b*]pyran-2-carboxylate (3a): Method A. A solution of β-tetralone (**1a**, 1.10 g, 7.56 mmol) in 9.0 mL of dry THF was added dropwise (15 min) to a 0 °C slurry of NaH (670 mg of 60% in oil, 16.75 mmol, 2.20 equiv) in 20 mL of dry THF under argon and stirred for 10 min at 0 °C. Dimethyl (methoxymethylene)malonate (**2**,[7] 1.58 g, 9.07 mmol, 1.20 equiv) in 8.0 mL of dry THF was added slowly (15 min) at 0 °C, and the resulting mixture was stirred at 0 to 25 °C for 3 h. The reaction mixture was poured onto 40 mL of cold 5% aqueous HCl and the aqueous phase was extracted with $CHCl_3$ (7 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography (SiO_2, 2 × 30 cm, 50 to 100% ether–hexane eluant; gradient elution) afforded 1.42 g (1.94 g theoretical, 73%) of **3a**[23a] as a yellow solid. A sample of **3a** crystallized (2×) from EtOAc as fine, yellow needles: mp 129–130 °C; ^1H NMR ($CDCl_3$) δ 8.70 (s, 1 H, vinyl), 7.50–7.05 (m, 4 H, Ar), 3.94 (s, 3 H, CO_2CH_3), 3.00 and 2.94 (two d, J = 7, 7 Hz, 2 H each, benzylic/allylic); IR ($CHCl_3$) ν_{max} 3020, 2970, 1750, 1550, 1260 cm^{-1}; mass spectrum, m/e (relative intensity) 256 (M^+, base), 254 (12), 228 (24), 224 (39), 169 (23), 141 (34), 139 (30), 115 (29); high-resolution mass spectrum, m/e 256.0721 ($C_{15}H_{12}O_4$ requires 256.0735).

Pyrone **3a** was prepared from **1a** in 91% yield on a 34.0 mmol scale.

Methyl 8-Methoxy-7-methyl-3-oxo-5,6-dihydro-3*H*-naphtho[2,1-*b*]pyran-2-carboxylate (3b). Utilizing method A, the sodium enolate of **1b** (1.59 mmol) generated at 0 °C (30 min) and 25 °C (10 min) was treated with **2** (335 mg, 1.92 mmol) at 0 °C. The reaction was stirred for 2.5 h at 0 to 10 °C. Chromatography (SiO_2, 2 × 30 cm, 50 to 100% $CHCl_3$–hexane eluant; gradient elution) afforded 385 mg (477 mg, theoretical, 81%) of **3b** as a yellow solid. A sample of **3b** crystallized (2×) from benzene as fine, yellow needles: mp 186–187 °C; ^1H NMR ($CDCl_3$) δ 8.62 (s, 1 H, vinyl), 7.29 (d, J = 9 Hz, 1 H, C-10 H), 6.78 (d, J = 9 Hz, 1 H, C-9 H), 3.92 and 3.83 (two s, 3 H each, OCH_3/CO_2CH_3), 2.94 and 2.88 (two d, J = 6, 6 Hz, 2 H each, benzylic/allylic CH_2), 2.17 (s, 3 H, $ArCH_3$); IR ($CHCl_3$) ν_{max} 3025, 2970, 1760, 1745, 1550, 1250, 1095 cm^{-1}; mass spectrum, m/e (relative intensity) 300 (M^+, 92), 269 (27), 268 (base), 225 (32), 141 (20), 115 (19), 83 (21); high-resolution mass spectrum, m/e 300.0981 ($C_{17}H_{16}O_5$ requires 300.0997).

Methyl 2-Oxo-5,6-dihydro-2*H*-naphtho[1,2-*b*]pyran-3-carboxylate (3c): Method B. A solution of α-tetralone (**1c**, 440 mg, 3.00 mmol) in 4.0 mL of dry THF was added dropwise (15 min) to a −78 °C solution of freshly generated lithium diisopropylamide[24] (3.60 mmol, 1.20 equiv) in 8.0 mL of dry THF under argon and the resulting mixture was stirred at −78 to −5 °C over 1.75 h. The solution was recooled to −30 °C, **2** (630 mg, 3.62 mmol, 1.21 equiv) in 1.5 mL of THF was added slowly (15 min), and the mixture was stirred at −30 to 25 °C for 5.5 h. The solution was poured onto 20 mL of 5% aqueous HCl and extracted with CH_2Cl_2 (5 × 15 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography (SiO_2, 1.5 × 16 cm, 30 to 100% ether–hexane eluant; gradient elution) afforded 690 mg (768 mg theoretical, 90%) of **3c** as a yellow, crystalline solid. A sample of **3c**[23a] crystallized (2×) from EtOAc as yellow needles: mp 172–173 °C; ^1H NMR ($CDCl_3$) δ 8.16 (s, 1 H, vinyl), 7.91 (m, 1 H, C-10 H), 7.30 (m, 3 H, Ar), 3.89 (s, 3 H, CO_2CH_3), 2.85 (m, 4 H, allylic/benzylic); IR ($CHCl_3$) ν_{max} 3040, 2960, 1760, 1730, 1540, 1250 cm^{-1}; mass spectrum, m/e (relative intensity) 256 (M^+, base), 228 (88), 141 (35), 115 (30); high-resolution mass spectrum, m/e 256.0721 ($C_{15}H_{12}O_4$ requires 256.0735).

Methyl 2-Oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-3-carboxylate (3d). Utilizing method B, a solution of the lithium enolate of cyclohexanone (**1d**, 3.90 mmol) was treated with **2** (810 mg, 4.6 mmol) and stirred at −30 to 25 °C for 2.75 h. Chromatography (SiO_2, 1.5 × 16 cm, 50% ether–hexane eluant) afforded 680 mg (812 mg theoretical, 84%) of **3d** as a white, crystalline solid: mp 107–108 °C (EtOAc–hexane); ^1H NMR ($CDCl_3$) δ 7.99 (s, 1 H, vinyl), 3.86 (s, 3 H, CO_2CH_3), 2.46 (m, 4 H), 1.80 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 166.3 and 163.9 (two s, two CO_2R), 158.0 (s, C-8a), 152.0 (d, C-4), 113.5 and 113.0 (two s, C-3/C-4a), 52.3 (q, OCH_3), 27.9 and 25.2 (two t, C-5/C-8), 21.8 and 21.3 (two t, C-6/C-7); IR ($CHCl_3$) ν_{max} 3040, 2975, 1765, 1745, 1555, 1270, 1220, 1155 cm^{-1}; mass spectrum, m/e (relative intensity) 208 (M^+, 68), 180 (48), 177 (35), 152 (58), 148 (33), 121 (base), 120 (33), 91 (32).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.79; H, 5.94.

3-Carbomethoxy-2-pyrone 3e. Utilizing method B, a solution of the lithium enolate of bicyclo[3.2.1]octan-2-one (**1e**, 2.98 mmol) was treated with **2** (623 mg, 3.6 mmol) at −20 °C and was stirred at −20 to 25 °C for 3 h. Chromatography (SiO_2, 1.5 × 16 cm, 30 to 50% ether–hexane; gradient elution) afforded 430 mg (698 mg theoretical, 62%) of **3e** as a white solid. A sample of **3e** crystallized (2×) from EtOAc–hexane as fine, white needles: mp 81–82 °C; ^1H NMR ($CDCl_3$) δ 8.00 (1 H, s, vinyl), 3.88 (s, 3 H, CO_2CH_3), 2.95–1.45 (m, 10 H); IR ($CHCl_3$) ν_{max} 3050, 2980, 1770, 1745, 1560, 1255, 1235 cm^{-1}; mass spectrum, m/e (relative intensity) 234 (M^+, base), 206 (89), 203 (36), 178 (30), 177 (47), 174 (63), 165 (38), 105 (49), 91 (47), 67 (66); high-resolution mass spectrum, m/e 234.0887 ($C_{13}H_{14}O_4$ requires 234.0891).

3-Carbomethoxy-2-pyrone 3f. Utilizing method B, a solution of the lithium enolate of **1f** (0.91 mmol) generated with lithium diisopropylamide (1.10 equiv) was treated with **2** (200 mg, 1.26

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(22) (a) Meyers, A. I.; Slade, J.; Smith, R. K.; Mihelich, E. D.; Hershenson, F. M.; Liang, C. D. *J. Org. Chem.* **1979**, *44*, 2247. (b) Stahl, E.; Muller, J. *Chromatogr.* **1982**, *15*, 493.

(23) (a) For the ethyl ester of **3c**, see: Ott, E.; Tarbell, D. S. *J. Am. Chem. Soc.* **1952**, *74*, 6266. (b) The ethyl ester has been prepared by a two-step procedure, see: Engel, C. R.; Dionne, G. *Can. J. Chem.* **1978**, *56*, 424.

(24) Prepared immediately before use by addition of 1.0 equiv of *n*-butyllithium to 1.0 equiv of diisopropylamine at −78 °C (5 min) and 0 °C (15 min).

equiv) and stirred at −30 to 25 °C for 4 h. Extractive workup with ethyl acetate and MPLC (SiO_2, 1.5 × 25 cm, 50% EtOAc–hexane eluant) afforded 156 mg (280 mg theoretical, 56%) of **3f** as a colorless oil: ^1H NMR ($CDCl_3$ δ 8.01 (s, 1 H, vinyl), 4.67 (m, 1 H, −NCH−), 4.15–3.25 (m, 1 H, $-NCH_2-$ equat.), 3.90 (s, 3 H, CO_2CH_3), 3.72 (s, 3 H, NCO_2CH_3), 3.05–2.30 (m, 4 H, $-NCH_2-$ axial, allylic −CH− and allylic $-CH_2-$), 2.20–1.60 (m, 4 H, two $-CH_2-$); ^{13}C NMR ($CDCl_3$) δ 166.1 and 163.8 (two s, two CO_2R), 157.9 and 156.0 (two s, $NCO_2CH_3/C{=}CO$), 150.4 (d, $HC{=}C(CO_2R)_2$), 114.9 and 112.3 (two s, $C{=}CH{=}C(CO_2R)_2$), 52.7 and 52.5 (two q, two OCH_3), 44.4 (d, −NCH−), 37.4 (t, $-NCH_2-$), 31.6 (t, allylic CH_2), 31.3 (d, allylic −CH−), 29.5 and 28.0 (two t, two $-CH_2-$); IR ($CHCl_3$) ν_{max} 2960, 1770, 1710, 1695, 1550, 1445, 1220 cm^{-1}; mass spectrum, *m/e* (relative intensity) 307 (M^+, 22), 173 (29), 141 (20), 140 (base), 135 (16), 59 (30); high-resolution mass spectrum, *m/e* 307.1036 ($C_{15}H_{17}NO_6$ requires 307.1056).

Methyl 6-(4-Methoxybenzoyl)-2-oxo-5,6,7,8-tetrahydro-2*H*-pyrano[3,2-*c*]pyridine-3-carboxylate (3g): Method C. A solution of *p*-methoxybenzoyl chloride[25a] (22.0 g, 129 mmol), pyridine (10.2 g, 129 mmol, 1.5 equiv), and the ethylene ketal of 4-piperidone[25b] (12.3 g, 86 mmol) in 260 mL of dry THF was stirred at 25 °C for 1.5 h under nitrogen. The reaction mixture was diluted with 1200 mL of cold ether, washed with 190 mL of cold 5% aqueous HCl, 190 mL of cold water, and 190 mL of saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. The residue was passed through a plug of silica gel (70% EtOAc–hexane eluant) to afford 22.0 g (23.8 g theoretical, 92%) of the ethylene ketal of **1g** as a white, crystalline solid: mp 81.5–82 °C (25% EtOAc–hexane); ^1H NMR ($CDCl_3$) δ 7.39 (d, *J* = 9 Hz, 2 H), 6.90 (d, *J* = 9 Hz, 2 H), 3.98 (s, 3 H, $ArOCH_3$), 3.83 (s, 4 H, $-OCH_2CH_2O-$), 3.69 (m, 4 H, $N(CH_2-)_2$), 1.72 (m, 4 H, $C(CH_2-)_2$); IR ($CHCl_3$) ν_{max} 3000, 2960, 1610, 1430, 1240, 1080, 930, 910, 825 cm^{-1}; mass spectrum, *m/e* (relative intensity) 277 (M^+, 10), 276 (21), 135 (base), 99 (22), 77 (16).

A solution of the ethylene ketal of **1g** (21.0 g, 75.8 mmol) in 110 mL of 10% aqueous H_2SO_4 and 55 mL of THF was stirred at 25 °C for 20 h. The reaction mixture was diluted with 300 mL of water and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with saturated aqueous NaCl (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 5 × 40 cm, 70% EtOAc–hexane) afforded 13.0 g (17.7 g, theoretical, 74%) of **1g** as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.64 (d, *J* = 9 Hz, 2 H), 7.11 (d, *J* = 9 Hz, 2 H), 4.07 (rough t, *J* = 6 Hz, 4 H, $N(CH_2-)_2$), 4.02 (s, 3 H, $ArOCH_3$), 2.67 (rough t, *J* = 6 Hz, 4 H, $N(CH_2CH_2-)_2$); IR (film) ν_{max} 2940, 1710, 1630, 1420, 1240, 1020, 830, 750 cm^{-1}; mass spectrum, *m/e* (relative intensity) 233 (M^+, 11), 232 (10), 135 (base), 77 (18).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.59; H, 6.53; N, 6.10.

Following the procedure for the preparation of **3c**, ketone **1g** (993 mg, 4.00 mmol) in dry THF was added to a −78 °C solution of freshly generated lithium diisopropylamide (1.20 equiv), and the resulting mixture was stirred at −78 °C for 1 h. A solution of **7** (766 mg, 4.40 mmol, 1.20 equiv) in dry THF was added at −78 °C and the solution was stirred at −78 to 25 °C over 3.75 h.[25c] A solution of the crude reaction product in 15 mL of acetic anhydride in the presence of sodium acetate (14.6 mg, 0.18 mmol, 0.04 equiv) was warmed at reflux for 1 h under nitrogen. The reaction mixture was cooled and concentrated in vacuo, and MPLC (SiO_2, 1.5 × 50 cm, 35% CH_2Cl_2–EtOAc eluant) afforded 875 mg of a yellow solid. Trituration of the solid with 10 mL of ether afforded 810 mg (1.37 g theoretical, 59%) of **3g** as a biege solid. A sample of **3g** crystallized (2×) from EtOAc as white prisms: mp 164–166 °C; ^1H NMR ($CDCl_3$) δ 7.97 (s, 1 H, vinylic), 7.42 (d, *J* = 9 Hz, 2 H), 6.93 (d, *J* = 9 Hz, 2 H), 4.48 (br s, 2 H, $NCH_2C{=}C$), 3.88 and 3.84 (two s, 3 H, each, OCH_3/CO_2CH_3; overlapping m, 2 H, NCH_2CH_2), 2.75 (rough t, *J* = 6 Hz, NCH_2CH_2); IR ($CHCl_3$) ν_{max} 3020, 1770, 1750, 1560, 1420, 1245 cm^{-1}; mass spectrum, *m/e* (relative intensity) 343 (M^+, 4), 311 (11), 136 (11), 135 (base), 92 (12), 77 (19).

Anal. Calcd for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99; N, 4.08. Found: C,62.70; H, 5.18; N, 4.28.

3-Carbomethoxy-2-pyrone 3h. Method C. 1h (1.0 mmol) afforded 128 mg (278 mg theoretical, 47%) of **3h** as an orange, crystalline solid: mp 230–231 °C (EtOH); ^1H NMR ($CDCl_3$) δ 8.80 (s, 1 H, vinylic), 8.10–7.45 (m, 6 H, Ar), 3.95 (s, 3 H, CO_2CH_3); IR ($CHCl_3$) ν_{max} 3050, 2980, 1765, 1525, 1260, 1100 cm^{-1}; mass spectrum, *m/e* (relative intensity) 278 (M^+, base), 250 (42), 247 (26), 219 (27), 218 (33), 192 (33), 191 (27), 163 (97), 162 (41); high-resolution mass spectrum, *m/e* 278.0587 ($C_{17}H_{10}O_4$ requires 278.0578).

Methyl 2-Methoxy-9,10-dihydrophenanthrene-3-carboxylate (5a). A solution containing **3a** (1.98 g, 7.7 mmol) and 1,1-dimethoxyethylene (**4**, 2.48 g, 28.2 mmol, 3.67 equiv) in 2.7 mL of dry toluene was warmed at 140 °C (bath temperature) under argon for 20 h in a sealed vessel.[26b] The cooled mixture was concentrated in vacuo and MPLC (SiO_2, 2.5 × 50 cm, 20% ether–hexane eluant) afforded 1.58 g (2.06 g theoretical, 73%) of **5a** as a white solid: mp 83.5–84.5 °C (MeOH–hexane, lit.[27] mp 80–81 °C); ^1H NMR ($CDCl_3$) δ 8.21 (s, 1 H, C-4 H), 7.70 (m, 1 H, C-5 H), 7.23 (m, 3 H, C-6,7,8 H), 6.84 (s, 1 H, C-1 H), 3.93 and 3.91 (two s, 3 H each, OCH_3/CO_2CH_3), 2.87 (s, 4 H, benzylic); IR ($CHCl_3$) ν_{max} 2970, 1735, 1615, 1505, 1405, 1240, 1075 cm^{-1}; mass spectrum, *m/e* (relative intensity) 268 (M^+, base), 237 (45), 235 (22), 197 (22), 178 (20).

Methyl 2,7-Dimethoxy-8-methyl-9,10-dihydrophenanthrene-3-carboxylate (5b). Table II, (835 mg of **3b**, 2.78 mmol).[26b] MPLC (SiO_2, 1.5 × 50 cm, 25% ether–hexane eluant) afforded 652 mg (868 mg theoretical, 75%) of **5b** as a white solid. A sample of **5b** crystallized (2×) from MeOH–hexane as white prisms: mp 128–129 °C; ^1H NMR ($CDCl_3$) δ 8.05 (s, 1 H, C-4 H), 7.54 (d, *J* = 9 Hz, 1 H, C-5 H), 6.78 (s, 1 H, C-1 H), 6.77 (d, *J* = 9 Hz, 1 H, C-6 H), 3.90, 3.89 and 3.84 (three s, 3 H each, two OCH_3 and CO_2CH_3), 2.88 (s, 4 H, benzylic CH_2), 2.21 (s, 3 H, $ArCH_3$); IR ($CHCl_3$) ν_{max} 3040, 2980, 2860, 1725, 1485, 1470, 1440, 1100 cm^{-1}; mass spectrum, *m/e* (relative intensity) 312 (M^+, base), 298 (8), 297 (36), 165 (8); high-resolution mass spectrum, *m/e* 312.1340 ($C_{19}H_{20}O_4$ requires 312.1360).

Methyl 3-Methoxy-9,10-dihydrophenanthrene-2-carboxylate (5c) (Table II, 20.3 mg of **3c**, 0.079 mmol).[26a] Chromatography (SiO_2, 0.6 × 7.0 cm, 20% ether–hexane eluant) afforded 16.5 mg (21.2 mg theoretical, 78%) of **5c** as a white, crystalline solid: mp 50–51 °C (MeOH–H_2O); ^1H NMR ($CDCl_3$) δ 7.70 (m, 2 H), 7.30 (m, 4 H), 3.99 and 3.90 (two s, 3 H each, OCH_3/CO_2CH_3), 2.84 (s, 4 H, benzylic); IR ($CHCl_3$) ν_{max} 2960, 1735, 1620, 1430, 1405, 1250, 900 cm^{-1}; mass spectrum, *m/e* (relative intensity) 268 (M^+, base), 237 (94), 235 (37), 178 (32), 165 (48); high-resolution mass spectrum, *m/e* 268.1098 ($C_{17}H_{16}O_3$ requires 268.1099).

6-Methoxy-7-(methoxycarbonyl)-1,2,3,4-tetrahydronaphthalene (5d) (Table II, 505 mg of **3d**, 2.43 mmol).[26b] Chromatography (SiO_2, 1.5 × 16 cm, 30% ether–hexane eluant) afforded 460 mg (535 mg theoretical, 86%) of **5d** as a white, crystalline solid: mp 98.5–99.5 °C (MeOH–H_2O, lit.[28] mp 99–100 °C); ^1H NMR ($CDCl_3$) δ 7.53 (s, 1 H, C-8 H), 6.65 (s, 1 H, C-5 H), 3.86 (s, 6 H, OCH_3 and CO_2CH_3), 2.75 (m, (MeOH–H_2O, lit.[28] 4 H, CH_2Ar), 1.80 (m, 4 H, CH_2CH_2Ar); IR ($CHCl_3$) ν_{max} 3040, 2970, 1725, 1610, 1280, 1080 cm^{-1}; mass spectrum, *m/e* (relative intensity) 220 (M^+, 75), 189 (base), 187 (69), 161 (51), 91 (35).

Methyl 3-Methoxy-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene-2-carboxylate (5e) (Table II, 20.7 mg of **3e**, 0.088 mmol).[26a] Chromatography (SiO_2, 0.6 × 7.0 cm, 30% ether–hexane eluant) afforded 19.4 mg (21.6 mg theoretical, 90%) of **5e** as a white solid: mp 53–54 °C (MeOH–H_2O, 2×); ^1H NMR ($CDCl_3$) δ 7.48 (s, 1 H, C-1 H), 6.60 (s, 1 H, C-4 H), 3.86 and 3.85

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[25] (a) Prepared by treatment of *p*-anisic acid with oxalyl chloride and catalytic dimethylformamide in benzene, see ref 14. Both *p*-anisic acid and *p*-methoxybenzoyl chloride are available from Aldrich Chemical Company. (b) The ethylene ketal of 4-piperidone (1,4-dioxa-8-azaspiro-[4.5]decane) is available from Aldrich Chemical Company. (c) No 3-carbomethoxy-2-pyrone was detected by ^1H NMR in the crude reaction product. The initial reaction products, i and ii, eq 2, did close to **3g** upon chromatography (SiO_2, 35% yield, 30–40% recovered ii).

[26] (a) The reaction was run in a 1-mL Kontes microflex vial or a 1-dram vial sealed under argon with a screw cap equipped with a Teflon-faced rubber liner. (b) The reaction was run in a 7-mL thick-walled tube internally threaded on one end and sealed under argon with a solid, threaded, Teflon plug. The reaction vessel was fabricated from a chromatography column purchased from Ace Glass Company.

[27] Mosettig, E.; Stuart, A. H. *J. Am. Chem. Soc.* **1939**, *61*, 1.

[28] Arnold, R. T.; Zaugg, H. E.; Sprung, J. *J. Am. Chem. Soc.* **1941**, *63*, 1314.

(two s, 3 H each, OCH_3/CO_2CH_3), 4.12–3.32 (m, 3 H, benzylic), 2.01–1.40 (m, 7 H); IR ($CHCl_3$) ν_{max} 3040, 2980, 1725, 1620, 1275, 1250, 1200, 1080 cm^{-1}; mass spectrum *m/e* (relative intensity) 246 (M^+, 98), 217 (25), 215 (base), 213 (68), 158 (36), 128 (28), 115 (34); high-resolution mass spectrum, *m/e* 246.1238 ($C_{15}H_{18}O_3$ requires 246.1255).

Dimethyl 1,2,3,4,5,6-Hexahydro-8-methoxy-2,6-methano-3-benzazocine-3,9-dicarboxylate (5f) (Table II, 38.5 mg of **3f**, 0.125 mmol).[26a] Chromatography (SiO_2, 0.6 × 7.0 cm, 40 to 60% ether–hexane eluant; gradient elution) afforded 32.0 mg (40.0 mg theoretical, 80%) of **5f** as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.54 (s, 1 H, C-10 H), 6.69 (s, 1 H, C-7 H), 4.65 (m, 1 H, –NCH–), 4.15–3.65 (m, 1 H, $-NCH_2-$ equat.), 3.89 (s, 6 H, CO_2CH_3 and OCH_3), 3.72 (s, 3 H, NCO_2CH_3), 3.23–2.47 (m, 4 H, $-NCH_2-$ axial, CHAr and CH_2Ar), 2.15–1.60 (m, 4 H, two CH_2); IR (film) ν_{max} 2950, 1725, 1690, 1605, 1445, 1400, 1070, 710 cm^{-1}; mass spectrum, *m/e* (relative intensity) 319 (M^+, 13), 217 (30), 185 (base), 88 (33), 59 (20); high-resolution mass spectrum, *m/e* 319.1413 ($C_{17}H_{21}NO_5$ requires 319.1418).

Methyl 6-Methoxy-2-(4-methoxybenzoyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylate (5g) (Table II, 501 mg of **3g**, 1.46 mmol).[26b] MPLC (SiO_2, 1.5 × 50 cm, 60% EtOAc–hexane) afforded 473 mg (519 mg theoretical, 91%) of **5g** as a white, crystalline solid. A sample of **5g** crystallized (2×) from EtOAc as white prisms: mp 126–128 °C; ^1H NMR ($CDCl_3$) δ 7.50 (s, 1 H, C-8 H), 7.40 (d, *J* = 9 Hz, 2 H), 6.90 (d, *J* = 9 Hz, 2 H), 6.72 (s, 1 H, C-5 H), 4.66 (br s, 2 H, NCH_2Ar), 3.85, 3.83 and 3.81 (three s, 3 H each, two OCH_3/CO_2CH_3; overlapping m, 2 H, NCH_2CH_2Ar), 2.90 (rough t, *J* = 6 Hz, 2 H, NCH_2CH_2Ar); IR ($CHCl_3$) ν_{max} 2940, 1730, 1625, 1440, 1250, 1080, 930, 840 cm^{-1}; mass spectrum, *m/e* (relative intensity), 255 (M^+, 29), 205 (22), 135 (base), 92 (10), 77 (26).

Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.48; H, 5.99; N, 4.00.

Methyl 5,6,7,8-Tetrahydronaphthalene-2-carboxylate (9a) (Table III, 1.0 g of **3d**, 4.8 mmol).[26b] Chromatography (SiO_2, 3 × 36 cm, 10 to 20% ether–hexane eluant; gradient elution) afforded 895 mg (913 mg theoretical, 98%) of **9a**[29] as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.73 (m, 2 H, C-1 H and C-3 H), 7.10 (d, *J* = 9 Hz, 1 H, C-4 H), 3.88 (s, 3 H, CO_2CH_3), 2.80 (m, 4 H, CH_2Ar), 1.80 (m, 4 H, CH_2CH_2Ar); IR (film) ν_{max} 2960, 1720, 1615, 1435, 1270, 1095, 750, 720 cm^{-1}.

Methyl 4-Hydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxylate (9b) (Table III, 100 mg of **3d**, 0.48 mmol).[26a] Chromatography (SiO_2, 1 × 13 cm, 30% ether–hexane eluant) afforded 82 mg (99 mg theoretical, 83%) of **9b** as a white, crystalline solid: mp 130–131 °C (benzene–hexane, lit.[30] mp 127.5–128.5 °C); ^1H NMR ($CDCl_3$, *c* = 0.2 M) δ 7.36 (s, 2 H, C-1 H and C-3 H), 5.86 (br s, 1 H, OH), 3.88 (s, 3 H, CO_2CH_3), 2.73 (m, 4 H, CH_2Ar), 1.80 (m, 4 H, CH_2CH_2Ar); IR ($CHCl_3$) ν_{max} 3610, 3440, 1710, 1590, 1440, 1305, 1235, 1035, 1000 cm^{-1}.

Methyl 3,4-Dimethoxy-5,6,7,8-tetrahydronaphthalene-2-carboxylate (9c) (Table III). Pyrone **3d** (459 mg, 2.20 mmol) and 1,1,2-trimethoxyethylene[12d] (4.3 mL, ca. 20 mmol, 5 equiv of 30%) were combined in a 10 mL flask equipped with a condenser and warmed at 150 °C for 78 h under nitrogen. The reaction mixture was cooled to 25 °C and concentrated under high vacuum, and the resulting mixture was dissolved in 3.0 mL of benzene. Methanesulfonic acid (21 mg, 0.22 mmol, 0.10 equiv) was added at 25 °C and the solution was stirred for 5 h at 25 °C under nitrogen. The reaction solution was concentrated to approximately 1.0 mL. Chromatography (SiO_2, 2 × 20 cm, 20% ether–hexane eluant) afforded 315 mg (551 mg theoretical, 57%) of **9c** as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.28 (s, 1 H, Ar) 3.89, 3.87 and 3.84 (three s, 3 H each, two OCH_3, CO_2CH_3), 2.70 (m, 4 H, CH_2Ar), 1.72 (m, 4 H, CH_2CH_2Ar); IR (film) ν_{max} 2940, 1730, 1605, 1320, 1040, 790, 740 cm^{-1}; mass spectrum, *m/e* (relative intensity) 250 (M^+, 34), 219 (24), 217 (38), 203 (21), 103 (22), 91 (16), 55 (21), 41 (base); high-resolution mass spectrum, *m/e* 250.1194 ($C_{14}H_{18}O_4$ requires 250.1204).

1,2,3,4-Tetrahydronaphthalene (10a). A solution of **9a** (895 mg, 4.71 mmol) in 11.0 mL of THF was treated with 14.1 mL of 1.0 N aqueous NaOH (14.1 mmol, 3.0 equiv) and the resulting mixture was warmed at 60 °C for 20 h. The reaction solution was neutralized with aqueous HCl and extracted with ether (4 × 10 mL). The combined extracts were washed with 10 mL of saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo to afford 745 mg (827 mg theoretical, 90%) of the carboxylic acid as a white solid: mp 152–153 °C (hexane, lit.[31] mp 153–156 °C); ^1H NMR ($CDCl_3$) δ 11.70 (br, 1 H, COOH), 7.75 (m, 2 H, C-2 H and C-3 H), 7.18 (d, *J* = 9 Hz, 1 H, C-4 H), 2.86 (m, 4 H, CH_2Ar), 1.86 (m, 4 H, CH_2CH_2Ar); IR ($CHCl_3$) ν_{max} 3600–2400, 2940, 1690, 1610, 1430, 1270 cm^{-1}.

A solution of the carboxylic acid (71 mg, 0.40 mmol) in 1.0 mL of dry quinoline was treated with copper powder[13] (252 mg, 4.00 mmol, 10.0 equiv) and was warmed at 260 °C for 7.5 h.[26a] The mixture was cooled to 25 °C, poured onto 10 mL of 5% aqueous HCl, and extracted with CH_2Cl_2 (7 × 3 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo and chromatography (SiO_2, 1 × 13.5 cm, hexane eluant) afforded 40 mg (53 mg theoretical, 75%) of **10a**[32] as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.03 (s, 4 H, Ar), 2.75 (m, 4 H, CH_2Ar), 1.78 (m, 4 H, CH_2CH_2Ar); IR (film) ν_{max} 3020, 2940, 1490, 1445, 725 cm^{-1}.

6-Acetoxy-1,2,3,4-tetrahydronaphthalene (10b). A solution of the carboxylic acid (202 mg, 1.15 mmol) prepared in the preceding experiment in 4.0 mL of THF under nitrogen was treated with oxalyl chloride (146 mg, 1.15 mmol, 2.00 equiv) and 1 μL of DMF[14] at 25 °C. After CO_2 evolution had ceased (30–60 min) the reaction was concentrated in vacuo to give the crude acid chloride as a yellow oil. A freshly generated solution of Me_2CuLi[15] (3.0 equiv) in 8.0 mL of dry THF at –78 °C was treated with the acid chloride in 1.5 mL of THF, and the resulting mixture was stirred for 15 min –78 °C before the addition of 0.4 mL of MeOH. The cold reaction mixture was poured onto 15 mL of saturated aqueous NH_4Cl and extracted with ether (4 × 4 mL). The combined extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 1 × 13 cm, 10% ether–hexane eluant) afforded 172 mg (200 mg theoretical, 86%) of 6-acetyl-1,2,3,4-tetrahydronaphthalene[33] as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.60 (m, 2 H, C-5 H and C-7 H), 7.07 (d, *J* = 7 Hz, 1 H, C-8 H), 2.80 (m, 4 H, CH_2Ar), 2.55 (s, 3 H, $COCH_3$), 1.80 (m, 4 H, CH_2CH_2Ar); IR (film) ν_{max} 2940, 1680, 1350, 1260, 950, 910, 815, 795 cm^{-1}.

A solution of the methyl ketone (44.1 mg, 0.25 mmol) in 1.2 mL of dry $CHCl_3$ was treated with *m*-CPBA (88 mg of 80–85%) at 25 °C and warmed at reflux for 24 h under argon in the dark. The reaction solution was diluted with 25 mL of ether, washed with 5% aqueous $NaHCO_3$ (2 × 3 mL) and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 1 × 15 cm, 5% ether–hexane eluant) afforded 36.2 mg (47.6 theoretical, 76%; 81% based on recovered starting material) of **10b**[34] as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.05 (d, *J* = 9 Hz, 1 H, C-8 H), 6.73 (m, 2 H, C-5 H and C-7 H), 2.73 (m, 4 H, CH_2Ar), 2.25 (s, 3 H, $OC(O)CH_3$), 1.76 (m, 4 H, CH_2CH_2Ar); IR (film) ν_{max} 2930, 1765, 1490, 1360, 1200, 1175, 1130, cm^{-1}.

5,6,7,8-Tetrahydro-1-naphthalenol (10c). Following the procedure for the preparation of **10a**, **9b** (180 mg, 0.87 mmol) was treated with 0.67 N aqueous NaOH (2.0 equiv) at 40 °C (20 h) and 60 °C (5 h) to afford 169 mg (100%) of the carboxylic acid: mp 195.5–196 °C (dichloroethane, lit.[35] mp 192–194 °C); ^1H NMR (Me_2SO-d_6) δ 12.50 (s, 1 H, COOH), 9.50 (s, 1 H, OH), 7.17 (m, 2 H, C-1 H and C-3 H), 2.60 (m, 4 H, CH_2Ar), 1.70 (m, 4 H, CH_2CH_2Ar); IR (KBr) ν_{max} 3600–2300, 2960, 1690, 1580, 1335, 1315, 1250, 880, 760 cm^{-1}. The carboxylic acid (78 mg, 0.41 mmol) was heated in the presence of copper (260 mg, 4.09 mmol) and quinoline (1.0 mL) for 4 h at 260 °C.[26a] Chromatography (SiO_2, 1 × 13 cm, 15% ether–hexane eluant) afforded 53 mg (60 mg theoretical, 88%) of **10c** as a white, crystalline solid: mp 68–69 °C (hexane, lit.[36] mp 69–71 °C); ^1H NMR ($CDCl_3$) δ 6.99 (dd, *J*

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= 8, 8 Hz, 1 H, C-3 H), 6.80 (d, J = 8 Hz, 1 H, C-4 H), 6.68 (d, J = 8 Hz, 1 H, C-2 H), 4.68 (s, 1 H, OH), 2.68 (m, 4 H, $\mathrm{CH_2Ar}$), 1.85 (m, 4 H, $\mathrm{C}H_2\mathrm{CH_2Ar}$); IR ($\mathrm{CHCl_3}$) ν_{max} 3610, 2940, 1580, 1460, 955, 880 cm^{-1}.

7-Acetoxy-5-methoxy-1,2,3,4-tetrahydronaphthalene (10d). A solution of **9b** (513 mg, 2.48 mmol) in 3.0 mL of dry THF was added dropwise (10 min) to a 0 °C slurry of NaH (160 mg of 60% in oil, 4.00 mmol, 1.60 equiv) in 3.0 mL of dry THF. Following the addition of $\mathrm{CH_3I}$ (827 mg, 5.83 mmol, 2.40 equiv) at 0 °C the resulting mixture was stirred at 25 °C for 4.5 h under argon, treated with 15 mL of cold saturated aqueous $\mathrm{NH_4Cl}$, and extracted with ether (4 × 7 mL). The combined extracts were dried ($\mathrm{Na_2SO_4}$) and concentrated in vacuo. Chromatography ($\mathrm{SiO_2}$, 2 × 20 cm, 10% ether–hexane eluant) afforded 410 mg (546 mg theoretical, 75%) of *O*-methyl **9b** as a colorless oil: ^{1}H NMR ($\mathrm{CDCl_3}$) δ 7.32 (br s, 1 H, C-1 H), 7.20 (br s, 1 H, C-3 H), 3.85 and 3.82 (two s, 3 H each, $\mathrm{OCH_3/CO_2CH_3}$), 2.67 (m, 4 H, $\mathrm{CH_2Ar}$), 1.72 (m, 4 H, $\mathrm{C}H_2\mathrm{CH_2Ar}$); IR (film) ν_{max} 2950, 1725, 1590, 1350, 1290, 1230, 760 cm^{-1}.

Following the procedure for the preparation of **10b**, the methyl ether of **9b** (348 mg, 1.58 mmol) was treated with 5.4 mL of 0.67 N NaOH (2.3 equiv) at 60 °C for 16 h, affording 323 mg (326 mg theoretical, 99%) of the carboxylic acid as a white solid: mp 184–185 °C (benzene–hexane, lit.[37] mp 184–185 °C); ^{1}H NMR ($\mathrm{CDCl_3}$) δ 7.50 (br s, 1 H, C-1 H), 7.35 (br s, 1 H, C-3 H), 3.87 (s, 3 H, $\mathrm{OCH_3}$), 2.78 (m, 4 H, $\mathrm{CH_2C}H_2\mathrm{Ar}$), 1.78 (m, 4 H, $\mathrm{C}H_2\mathrm{CH_2Ar}$); IR ($\mathrm{CHCl_3}$) ν_{max} 3700–2400, 2950, 1690, 1585, 1285, 1095 cm^{-1}. The carboxylic acid (144 mg, 0.70 mmol) was converted to the acid chloride with oxalyl chloride (2.0 equiv) and subsequently treated with $\mathrm{Me_2CuLi}$ (3.0 equiv) at −78 °C for 25 min to afford, after chromatography ($\mathrm{SiO_2}$, 1 × 15 cm, 15% ether–hexane eluant), 121 mg (143 mg theoretical, 85%) of 7-acetyl-5-methoxy-1,2,3,4-tetrahydronaphthalene as a colorless oil: ^{1}H NMR ($\mathrm{CDCl_3}$, c = 0.4 M) δ 7.23 (br s, 2 H, Ar), 3.87 (s, 3 H, $\mathrm{OCH_3}$), 2.71 (m, 4 H, $\mathrm{CH_2Ar}$), 2.55 (s, 3 H, $\mathrm{COCH_3}$), 1.77 (m, 4 H, $\mathrm{C}H_2\mathrm{CH_2Ar}$); IR (film) ν_{max} 2950, 1685, 1580, 1355, 1280, 1095 cm^{-1}; mass spectrum, m/e (relative intensity) 204 ($\mathrm{M^+}$, 37), 189 (base), 161 (42), 91 (31); high-resolution mass spectrum, m/e 204.1127 ($\mathrm{C_{13}H_{16}O_2}$ requires 204.1149).

A solution of the methyl ketone (10.8 mg, 0.053 mmol) in 2.3 mL of dry $\mathrm{CH_2Cl_2}$ was treated with *m*-CPBA (70.8 mg at 80–85%) and anhydrous $\mathrm{K_2CO_3}$ (53.9 mg, 0.39 mmol, 7.4 equiv) and stirred at 40 °C for 41 h in the dark under argon. Filtration and chromatography ($\mathrm{SiO_2}$, 0.6 × 7 cm, 30% $\mathrm{CH_2Cl_2}$–hexane eluant) afforded 5.5 mg (11.7 mg theoretical, 47%; 99% based on recovered starting material) of **10d** as a white, crystalline solid: mp 58–60 °C (pentane); ^{1}H NMR ($\mathrm{CDCl_3}$) δ 6.40 and 6.37 (two s, 1 H each, C-6 H/C-8 H), 3.77 (s, 3 H, $\mathrm{OCH_3}$), 2.65 (m, 4 H, $\mathrm{CH_2Ar}$), 2.26 (s, 3 H, $\mathrm{OC(O)CH_3}$), 1.78 (m, 4 H, $\mathrm{C}H_2\mathrm{CH_2Ar}$); IR ($\mathrm{CHCl_3}$) ν_{max} 2940, 1750, 1600, 1220, 1180, 1130, 1100 cm^{-1}; mass spectrum, m/e (relative intensity) 220 ($\mathrm{M^+}$, 24), 178 (base), 177 (27), 150 (46), 147 (22); high-resolution mass spectrum, m/e 220.1096 ($\mathrm{C_{13}H_{16}O_3}$ requires 220.1099).

6-Methoxy-1,2,3,4-tetrahydronaphthalene (10e). Following the procedure for the preparation of **10a**, salicylate **5d** (537 mg, 2.44 mmol) was converted (2.0 equiv of NaOH) to the carboxylic acid (488 mg, 97%): mp 114–115 °C (EtOAc–hexane, lit.[38] mp 115–116 °C); ^{1}H NMR ($\mathrm{CDCl_3}$) δ 10.53 (br s, 1 H, COOH), 7.79 (s, 1 H, C-1 H), 6.71 (s, 1 H, C-4 H), 4.00 (s, 3 H, $\mathrm{OCH_3}$), 2.69 (m, 4 H, $\mathrm{CH_2Ar}$), 1.77 (m, 4 H, $\mathrm{C}H_2\mathrm{CH_2Ar}$); IR ($\mathrm{CHCl_3}$) ν_{max} 3600–2400, 2970, 1735, 1620, 1425, 1255, 1005, 930, 845 cm^{-1}. The carboxylic acid (52 mg, 0.25 mmol) was warmed in the presence of copper (160 mg, 2.5 mmol) and quinoline (1.0 mL) at 220 °C for 1.5 h.[26a] The crude phenol in 1.0 mL of dry THF was added to a 0 °C slurry of NaH (20 mg at 60% in oil, 0.50 mmol, 2.0 equiv) in 1.0 mL of dry THF followed by addition of $\mathrm{CH_3I}$ (71 mg, 0.50 mmol, 2.0 equiv). The resulting mixture was stirred for 20 h at 25 °C under argon, poured onto 2.0 mL of 5% aqueous HCl, and extracted with ether (4 × 1 mL). The combined extracts were washed with saturated aqueous NaCl, dried ($\mathrm{Na_2SO_4}$), and concentrated in vacuo. Chromatography ($\mathrm{SiO_2}$, 0.6 × 7 cm, 10% ether–hexane eluant) afforded 35 mg (40 mg theoretical, 88%) of **10e**[39] as a colorless oil: ^{1}H NMR ($\mathrm{CDCl_3}$) δ 6.95 (d, J = 9 Hz, 1 H, C-8 H), 6.63 (dd, J = 9, 2 Hz, 1 H, C-7 H), 6.57 (d, J = 2 Hz, 1 H, C-5 H), 3.73 (s, 3 H, $\mathrm{OCH_3}$), 2.71 (m, 4 H, $\mathrm{CH_2Ar}$), 1.73 (m, 4 H, $\mathrm{C}H_2\mathrm{CH_2Ar}$); IR (film) ν_{max} 2930, 1610, 1500, 1200, 1030, 815 cm^{-1}.

7-Acetoxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (10f). A solution of the carboxylic acid (351 mg, 1.70 mmol) prepared in the preceding experiment, in 4.0 mL of THF–$\mathrm{H_2O}$ (4:1), was treated with $\mathrm{K_2CO_3}$ (125 mg, 0.91 mmol, 1.10 equiv) and stirred for 1 h at 25 °C. The reaction mixture was concentrated in vacuo under high vacuum in the presence of $\mathrm{P_2O_5}$. The resulting potassium salt was powdered, suspended in 2.0 mL dry benzene, and treated with oxalyl chloride (760 mg, 6.0 mmol, 7.1 equiv) at 25 °C, and the mixture was stirred at 25 °C for 1.75 h and 10 min at reflux under nitrogen. The reaction mixture was cooled to 25 °C, concentrated in vacuo, dissolved in ether, filtered, and concentrated again, affording 332 mg (382 mg theoretical, 87%) of the crude acid chloride.[14] Following the procedure for the preparation of **10b**, a THF solution of $\mathrm{Me_2CuLi}$ (4.0 equiv) was treated with the acid chloride (70 mg, 0.31 mmol) at −78 °C, and the mixture was stirred for 1 h at −78 °C. Chromatography ($\mathrm{SiO_2}$, 1 × 13 cm, 15% ether–hexane eluant) afforded 49 mg (64 mg theoretical, 76%) of 7-acetyl-6-methoxy-1,2,3,4-tetrahydronaphthalene as a white, crystalline solid: mp 41–42 °C (pentane) (lit.[38] mp 43–44 °C); ^{1}H NMR ($\mathrm{CDCl_3}$) δ 7.46 (s, 1 H, C-8 H), 6.64 (s, 1 H, C-5 H), 3.86 (s, 3 H, $\mathrm{OCH_3}$), 2.75 (m, 4 H, $\mathrm{CH_2Ar}$), 2.58 (s, 3 H, $\mathrm{COCH_3}$), 1.80 (m, 4 H, $\mathrm{C}H_2\mathrm{CH_2Ar}$); IR (film) ν_{max} 2940, 1670, 1610, 1495, 1405, 915, 835, 805, 755 cm^{-1}.

A solution of this ketone (45 mg, 0.21 mmol) in 1.1 mL of dry $\mathrm{CH_2Cl_2}$ was treated with *m*-CPBA (61 mg of 80–85%), and the resulting mixture was stirred at 25 °C for 22 h in the dark under argon. Chromatography ($\mathrm{SiO_2}$, 1 × 11 cm, 15% ether–hexane eluant) afforded 29 mg (49 mg theoretical, 60%; 73% based on recovered starting material) of **10f**[40] as a colorless oil: ^{1}H NMR ($\mathrm{CDCl_3}$) δ 6.70 (s, 1 H, C-8 H), 6.63 (s, 1 H, C-5 H), 3.77 (s, 3 H, $\mathrm{OCH_3}$), 2.68 (m, 4 H, $\mathrm{CH_2Ar}$), 2.28 (s, 3 H, $\mathrm{OC(O)CH_3}$), 1.75 (m, 4 H, $\mathrm{C}H_2\mathrm{CH_2Ar}$); IR (film) ν_{max} 2950, 1770, 1510, 1260, 1210, 1190, 1100 cm^{-1}.

1-Methoxy-5,6,7,8-tetrahydro-2-naphthalenol (10g). Following the procedure for preparation of **10a**, **9c** (67 mg, 0.27 mmol) was converted to 63 mg (99%) of the carboxylic acid: mp 111–112 °C (hexane); ^{1}H NMR ($\mathrm{CDCl_3}$) δ 9.00 (br s, 1 H, COOH), 7.62 (s, 1 H, C-1H), 4.05 and 3.82 (two s, 3 H each, two $\mathrm{OCH_3}$), 2.75 (m, 4 H, $\mathrm{CH_2Ar}$), 1.74 (m, 4 H, $\mathrm{C}H_2\mathrm{CH_2Ar}$); IR ($\mathrm{CHCl_3}$) ν_{max} 3600–2400, 2940, 1740, 1605, 1415, 1220, 1080, 1030, 980 cm^{-1}. The carboxylic acid was warmed in the presence of copper (169 mg, 2.66 mmol) and quinoline (1.0 mL) at 210 °C for 1 h.[26a] Chromatography ($\mathrm{SiO_2}$, 1 × 15 cm, 30% ether–hexane eluant) afforded 43 mg (47 mg theoretical, 91%) of **10g**[41] as a pink solid. A sample of **10g** sublimed (11 μmHg, 33 °C bath temperature) as a white, crystalline solid: mp 51–52 °C; ^{1}H NMR ($\mathrm{CDCl_3}$) δ 6.73 (s, 2 H, C-3 H and C-4 H), 5.49 (br s, 1 H, OH), 3.76 (s, 3 H, $\mathrm{OCH_3}$), 2.71 (m, 4 H, $\mathrm{CH_2Ar}$), 1.75 (m, 4 H, $\mathrm{C}H_2\mathrm{CH_2Ar}$); IR ($\mathrm{CHCl_3}$) ν_{max} 3440, 2940, 1605, 1490, 1290, 1060, 990, 790 cm^{-1}; mass spectrum, m/e (relative intensity) 178 ($\mathrm{M^+}$, base), 163 (27), 150 (41), 147 (35), 135 (47), 91 (34), 77 (34).

Anal. Calcd for $\mathrm{C_{11}H_{14}O_2}$: C, 74.13; H, 7.92. Found: C, 73.80; H, 7.80.

7-Acetoxy-5,6-dimethoxy-1,2,3,4-tetrahydronaphthalene (10h). Following the procedure for the preparation of **10f**, the carboxylic acid (60 mg, 0.25 mmol) prepared in the preceding experiment, was converted to its acid chloride (1.1 equiv of $\mathrm{K_2CO_3}$; 7.0 equiv of oxalyl chloride) and subsequently treated with $\mathrm{Me_2CuLi}$ (3.1 equiv) at −78 °C to give, after chromatography ($\mathrm{SiO_2}$, 1 × 13 cm, 10% ether–hexane eluant), 49 mg (57 mg theoretical, 86%) of 7-acetyl-5,6-dimethoxy-1,2,3,4-tetrahydronaphthalene

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as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.18 (s, 1 H, Ar), 3.89 and 3.83 (two s, 3 H each, OCH_3), 2.72 (m, 4 H, CH_2Ar), 2.61 (s, 3 H, $COCH_3$), 1.75 (m, 4 H, $C\textit{H}_2CH_2Ar$); IR ($CHCl_3$) $\nu_{\max}$ 2940, 1740, 1680, 1595, 1450, 1400, 1320, 1285 cm^{-1}; mass spectrum, *m/e* (relative intensity) 234 (M^+, 51), 220 (12), 219 (73), 91 (26), 77 (27), 43 (base); high-resolution mass spectrum, *m/e* 234.1232 ($C_{14}H_{18}O_3$ requires 234.1255).

The methyl ketone (20 mg, 0.085 mmol) in dry CH_2Cl_2 was treated with *m*-CPBA (26 mg of 80–85%) and the solution was warmed at 40 °C for 84 h under argon in the dark. Chromatography (SiO_2, 1 × 10 cm, ether–hexane eluant) afforded 14 mg (21 mg theoretical, 67%) of **10h** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.53 (s, 1 H, C-8, H), 3.83 and 3.81 (two s, 3 H each, two OCH_3), 2.67 (m, 4 H, CH_2Ar), 2.30 (s, 3 H, $OC(O)CH_3$), 1.73 (m, 4 H, $C\textit{H}_2CH_2Ar$); IR (film) $\nu_{\max}$ 2940, 1770, 1730, 1485, 1200, 1070, 1000 cm^{-1}; mass spectrum, *m/e* (relative intensity) 250 (M^+, 18), 209 (16), 208 (base), 193 (38), 177 (11), 133 (12), 91 (14), 77 (16), 43 (28); high-resolution mass spectrum, *m/e* 250.1192 ($C_{14}H_{18}O_4$ requires 250.1204).

Cycloadduct 11 (Table III, 23.4 mg of **3d**, 0.112 mmol).[26a] Chromatography (SiO_2, 1 × 10 cm, 10 to 30% ether–hexane eluant; gradient elution) afforded 19.4 mg (31.6 mg theoretical, 61%) of **11**: ^{1}H NMR ($CDCl_3$) δ 6.70 (s, 1 H, vinyl), 3.73 (s, 3 H, CO_2CH_3), 3.45, 3.39 and 3.26 (three s, 3 H each, three OCH_3), 2.20 (m, 4 H, allylic), 1.68 (m, 4 H, homoallylic).

Methyl 3-(Diethylamino)-4-methyl-5,6,7,8-tetrahydronaphthalene-2-carboxylate (12) (Table III, 112 mg of **3d**, 0.538 mmol).[26a] Chromatography (SiO_2, 1 × 10 cm, 5% ether–hexane eluant) afforded 65 mg (148 mg theoretical, 44%) of **12** as a colorless oil: bulb-to-bulb distillation 120–130 °C (bath temperature; 0.5 torr); ^{1}H NMR ($CDCl_3$) δ 7.11 (s, 1 H, Ar), 3.84 (s, 3 H, CO_2CH_3), 3.03 (q, *J* = 7 Hz, 4 H, $N(C\textit{H}_2CH_3)_2$), 2.65 (m, 4 H, CH_2Ar), 2.18 (m, 3 H, $ArCH_3$), 1.75 (m, 4 H, $C\textit{H}_2CH_2Ar$), 1.00 (t, *J* = 7 Hz, 6 H, $N(CH_2C\textit{H}_3)_2$); IR (film) $\nu_{\max}$ 2940, 1735, 1600, 1430, 1290, 1190, 1170 cm^{-1}; mass spectrum, *m/e* (relative intensity) 275 (M^+, 28), 260 (base), 214 (68), 72 (39).

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.00; H, 8.90; N, 5.29.

Dihydrofuran 13 (Table III, 50 mg of **3d**, 0.24 mmol).[26a] Chromatography (SiO_2, 1 × 13 cm, 30% ether–hexane eluant) afforded 32 mg (59 mg theoretical, 54%) of the carboxylic acid, which was treated with excess diazomethane[42] in ether at 0 to 25 °C to afford 34 mg (100%) of **13** as a colorless oil: bulb-to-bulb distillation 100–110 °C (bath temperature; 0.05 torr); ^{1}H NMR ($CDCl_3$) δ 7.64 (s, 1 H, Ar), 5.75 and 5.30 (two m, 1 H each, CHOCH), 3.87 (s, 3 H, CO_2CH_3), 2.75 (m, 4 H, CH_2Ar), 1.80 (m, 4 H, $C\textit{H}_2CH_2Ar$), 1.46 (m, 6 H, two $OCHC\textit{H}_3$); IR (film) $\nu_{\max}$ 2940, 1710, 1600, 1430, 1265 cm^{-1}; mass spectrum, *m/e* (relative intensity) 260 (M^+, 11), 246 (19), 245 (base), 213 (22), 128 (11), 115 (11).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.47; H, 7.77.

Trimethyl 5,6,7,8-Tetrahydronaphthalene-1,2,3-tricarboxylate (14) (Table III, 49 mg of **3d**, 0.24 mmol).[26a] Chromatography (SiO_2, 1 × 5 cm, 30% ether–hexane eluant) afforded 41 mg (72 mg theoretical, 57%) of **14** as a colorless oil: bulb-to-bulb distillation 110–115 °C (bath temperature; 0.05 torr); ^{1}H NMR ($CDCl_3$) δ 7.65 (s, 1 H, Ar), 3.86 (s, 9 H, three CO_2CH_3), 2.82 (m, 4 H, CH_2Ar), 1.79 (m, 4 H, $C\textit{H}_2CH_2Ar$); IR (film) $\nu_{\max}$ 2960, 1730, 1435, 995, 900, 715 cm^{-1}.

Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.59; H, 5.95.

Methyl 3-Acetyl-5,6,7,8-tetrahydronaphthalene-2-carboxylate (15) and Methyl 4-Acetyl-5,6,7,8-tetrahydronaphthalene-2-carboxylate (16) (Table III, 28.0 mg of **3d**, 0.134 mmol; 10.0 equiv of dienophile).[26a] Chromatography (SiO_2, 1 × 13 cm, 15 to 30% ether–hexane eluant; gradient elution) afforded 6.2 mg (31.1 mg theoretical, 20%) of **16** as a white, crystalline solid: mp 76–78 °C (ether–pentane); ^{1}H NMR ($CDCl_3$) δ 8.08 (s, 1 H, C-3 H), 7.85 (s, 1 H, C-1 H), 3.91 (m, 3 H, CO_2CH_3), 2.90 (m, 4 H, CH_2Ar), 2.58 (s, 3 H, $COCH_3$), 1.78 (m, 4 H, $C\textit{H}_2CH_2Ar$); IR ($CHCl_3$) $\nu_{\max}$ 2940, 1730, 1690, 1315, 1225 cm^{-1}; mass spectrum, *m/e* (relative intensity) 232 (M^+, 76), 217 (base), 130 (26), 129 (39), 128 (32), 43 (81).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.00; H, 7.09.

Regioisomer **15** was isolated in 43% yield (13.3 mg) as a colorless oil: bulb-to-bulb distillation 130–140 °C (bath temperature; 0.5 torr); ^{1}H NMR ($CDCl_3$) δ 7.53 (s, 1 H, C-1 H), 7.11 (s, 1 H, C-4 H), 3.87 (s, 3 H, CO_2CH_3), 2.80 (m, 4 H, CH_2Ar), 2.49 (s, 3 H, $COCH_3$), 1.81 (m, 4 H, $C\textit{H}_2CH_2Ar$); IR (film) $\nu_{\max}$ 2935, 1720, 1430, 1270 cm^{-1}; mass spectrum, *m/e* (relative intensity) 232 (M^+, 4), 218 (17), 217 (base).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.60; H, 7.00.

7-Acetyl-6-methoxy-2-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (20). A solution of **5g** (410 mg, 1.15 mmol) in 10 mL of THF and 2 mL of MeOH was treated with 2.3 mL of 1.0 N aqueous NaOH (2.3 mmol, 2.0 equiv) at 25 °C (10 h) under nitrogen. The reaction mixture was taken up in 10 mL of water and the aqueous solution was extracted with ether (20 mL), acidified with 2.5 mL of 5% aqueous HCl, and extracted with EtOAc (4 × 15 mL). The combined EtOAc layers were washed with 10 mL of saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo, affording 380 mg (393 mg theoretical, 97%) of the carboxylic acid **18** as a white solid: mp 197–198 °C (EtOH); ^{1}H NMR ($CDCl_3$) 7.87 (br s, 1 H, C-8 H), 7.43 (d, *J* = 9 Hz, 2 H), 6.94 (d, *J* = 9 Hz, 2 H), 6.84 (s, 1 H, C-5 H), 4.73 (s, 2 H, NCH_2Ar), 4.06 and 3.86 (two s, 3 H each, two OCH_3; overlapping m, 2 H, $NC\textit{H}_2CH_2Ar$), 2.98 (rough t, *J* = 6 Hz, 2 H, $NCH_2C\textit{H}_2Ar$); IR (KBr) $\nu_{\max}$ 3600–3400, 3005, 2960, 1710, 1610, 1590, 1430, 1255, 1180 cm^{-1}; mass spectrum, *m/e* (relative intensity) 343 (M^+, 2), 342 (8), 341 (22), 191 (13), 136 (12), 135 (base), 107 (10), 92 (21), 77 (34), 64 (10).

Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 67.00; H, 5.63; N, 4.30.

The carboxylic acid (240 mg, 0.70 mmol) in 50 mL of MeOH was titrated with 1 N aqueous KOH at 25 °C until the solution turned pink to phenophthalein indicator. The solution was concentrated in vacuo and dried under high vacuum in the presence of P_2O_5 to give the potassium salt of **18**. The powdered potassium salt was suspended in 20 mL of dry benzene and treated with oxalyl chloride (320 mg, 2.5 mmol, 7.2 equiv) at 25 °C under nitrogen. After carbon dioxide evolution had ceased (ca. 3 h), the reaction mixture was concentrated in vacuo, filtered through Celite with the aid of ether, and concentrated, affording 277 mg of the crude acid chloride **19**.[14]

A solution of the crude acid chloride (70 mg, 0.18 mmol) in 0.27 mL of dry THF was added to a −78 °C solution of freshly prepared lithium dimethylcuprate[15] (0.70 mmol, 4.0 equiv) in 0.5 mL of dry THF, and the resulting mixture was stirred at −78 °C for 1 h. The reaction solution was quenched with 0.2 mL of MeOH at −78 °C, and poured onto 10 mL of saturated NH_4Cl, and the combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography (SiO_2, 1 × 10 cm, 75% EtOAc–hexane eluant) afforded 45 mg (59 mg theoretical, 76%) of the methyl ketone **20** as a white solid: mp 130–131 °C (EtOAc–hexane, 2×); ^{1}H NMR ($CDCl_3$) δ 7.45 (s, 1 H, C-8 H), 7.38 (d, *J* = 9 Hz, 2 H), 6.89 (d, *J* = 9 Hz, 2 H), 6.70 (s, 1 H, C-5 H), 4.67 (br s, 2 H, NCH_2Ar), 3.90 and 3.84 (two s, 3 H each, two OCH_3; overlapping m, 2 H, $NC\textit{H}_2CH_2Ar$), 2.93 (rough t, 2 H, $NCH_2C\textit{H}_2Ar$), 2.59 (s, 3 H, $COCH_3$); IR ($CHCl_3$) $\nu_{\max}$ 3005, 1670, 1605, 1420, 1250, 1170, 840 cm^{-1}; mass spectrum, *m/e* (relative intensity) 339 (M^+, 28), 204 (12), 189 (20), 136 (base), 77 (30); high-resolution mass spectrum, *m/e* 339.1476 ($C_{20}H_{21}NO_4$ requires 339.1469).

7-Acetoxy-6-methoxy-2-(4-methoxybenzoyl)-1,2,3,4-tetrahydroisoquinoline (21). A solution of methyl ketone **20** (55.1 mg, 0.16 mmol) in 1.0 mL of dry CH_2Cl_2 was treated with *m*-CPBA (42 mg of 80–85%) at 25 °C, and the resulting solution was stirred at 25 °C for 68 h in the dark under argon. Additional *m*-CPBA (20 mg of 80–85%) was added, and the reaction mixture was stirred for 21 h at 25 °C. The mixture was filtered and concentrated in vacuo, and MPLC (SiO_2, 0.9 × 25 cm, 50% EtOAc–hexane eluant) afforded 35.1 mg (56.9 mg theoretical, 62%) of **21** as a white solid: mp 137–138 °C (EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.44 (d, *J* = 9 Hz, 2 H), 6.94 (d, *J* = 9 Hz, 2 H), 6.75 (s, 2 H, C-5 H and C-8 H), 4.68 (br s, 2 H, NCH_2Ar), 3.85 and 3.82 (two s, 3 H each, two $ArOCH_3$; overlapping m, 2 H, $NC\textit{H}_2CH_2Ar$), 2.90

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(42) Arndt, F. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, p 165.

(rough t, 2 H, NCH_2CH_2Ar), 2.30 (s, 3 H, $OC(O)CH_3$); IR ($CHCl_3$) ν_{max} 3040, 1875, 1625, 1520, 1440, 1250, 1105, 1025, 905, 835 cm^{-1}; mass spectrum, *m/e* (relative intensity) 355 (M^+, 26), 313 (13), 163 (17), 135 (base), 92 (14), 77 (30); high-resolution mass spectrum, *m/e* 355.1430 ($C_{20}H_{21}NO_5$ requires 355.1418).

Sendaverine (17). A slurry of lithium aluminum hydride (10.4 mg, 0.27 mmol) in 0.25 mL of dry THF at 0 °C under argon was treated slowly (10 min) with a solution of **21** in 0.9 mL of THF, and the resulting mixture was stirred at 0 °C for 1 h. Sequential addition of 11 μL of water, 44 μL of 5% aqueous NaOH, and 11 μL of water at 0 °C, neutralization with 5% aqueous HCl, filtration through Celite and chromatography (SiO_2, 0.5 × 6 cm, ethyl acetate eluant) afforded 12.0 mg (17.1 mg theoretical, 70%) of pure sendaverine (**17**) as a white, crystalline solid: mp 136–138 °C (lit. mp 139–140 °C[21c] and 140–141 °C;[21b] hexane); ^1H NMR ($CDCl_3$) δ 7.29 (d, J = 9 Hz, 2 H), 6.86 (d, J = 9 Hz, 2 H), 6.55 and 6.53 (two s, 1 H each, C-5 H/C-8 H), 3.82 and 3.80 (two s, 3 H each, two $ArOCH_3$), 3.59 and 3.50 (two s, 2 H each, two NCH_2Ar), 2.72 (m, 4 H, NCH_2CH_2Ar); IR ($CHCl_3$) ν_{max} 3580 (OH), 3025, 2950, 1610, 1510, 1460, 1275, 1250, 1120 cm^{-1}; mass spectrum, *m/e* (relative intensity) 299 (M^+, 26), 298 (25), 178 (22), 150 (42), 121 (base), 91 (14); high-resolution mass spectrum, *m/e* 299.1523 ($C_{18}H_{21}NO_3$ requires 299.1520).

Methyl 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-3-benzazocine-3-carboxylate (22). A solution of **3f** (41.9 mg, 0.13 mmol) in 0.5 mL of THF was treated with 0.4 mL of 0.67 N aqueous NaOH (0.27 mmol, 2.1 equiv), and the resulting mixture was stirred at 25 °C for 15.5 h. The reaction was treated with 0.4 mL of 5% aqueous HCl and extracted with chloroform (8 × 0.8 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give the crude acid (38.2 mg) as a pale yellow gum. A portion of the crude acid (30.8 mg) in 0.35 mL of dry quinoline was treated with copper powder[13] (70 mg, 1.1 mmol, 10.0 equiv), and the mixture was warmed at 220 °C (bath temperature) for 1 h.[26a] The reaction mixture was cooled to 25 °C and poured over 1.5 mL of 10% aqueous HCl, and the aqueous phase was extracted with chloroform (10 × 2 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography (SiO_2, 0.6 × 7.0 cm, 40% ether–hexane eluant) afforded 25.1 mg (25.9 mg theoretical, 97%) of **22** as a white, crystalline solid: mp 157–158 °C (benzene–hexane; 2×); ^1H NMR ($CDCl_3$) δ 6.93 (d, J = 8 Hz, 1 H, C-10 H), 6.63 (d, J = 8 Hz, 1 H, C-9 H), 6.58 (s, 1 H, C-7 H), 5.65 (br s, 1 H, OH), 4.59 (m, 1 H, –NCH–), 4.11–2.45 (several m, 5 H, $-NCH_2-$, –CHAr and $-CH_2Ar$), 3.70 (s, 3 H, NCO_2CH_3), 2.20–1.40 (m, 4 H, two CH_2); IR ($CHCl_3$) ν_{max} 3440, 3040, 2960, 1685, 1455, 1230, 1105, cm^{-1}; EIMS, *m/e* (relative intensity) 247 (M^+, base), 232 (18), 216 (23), 103 (47), 88 (36); high-resolution mass spectrum, *m/e* 247.1193 ($C_{14}H_{17}NO_3$ requires 247.1207).

Dimethyl 7,8-Dimethoxy-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine-3,9-dicarboxylate (23). A solution of pyrone **3f** (34.1 mg, 0.11 mmol) and 1,1,2-trimethoxyethylene[12] (0.44 mL, ca. 1.1 mmol, ca. 10 equiv of 30%) was warmed at 150 °C for 84 h under argon in a sealed vessel.[26a] The reaction mixture was cooled to 25 °C and concentrated under high vacuum. The residue was dissolved in 0.2 mL of dry benzene and treated with methanesulfonic acid (1 μL, 0.015 mmol, 0.14 equiv), and the resulting solution was stirred at 25 °C for 12 h. Centrifugal thin-layer chromatography (SiO_2, 1-mm thickness, 30% ethyl acetate–hexane eluant) afforded 23.0 mg (38.8 mg theoretical, 59%) of **23** as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.23 (s, 1 H, Ar), 4.65 (m, 1 H, –NCH–), 4.15–3.18 (m, 2 H, $-NCH_2-$), 3.90 and 3.88 (two s, 6 H and 3 H, CO_2CH_3/two OCH_3), 3.70 (s, 3 H, NCO_2CH_3), 3.08–2.50 (m, 3 H, CHAr and CH_2Ar), 2.13–1.45 (m, 4 H, two $-CH_2-$); IR (film) ν_{max} 3000, 2950, 1730, 1695, 1450, 1440, 1400, 1340, 1310, 1240, 1090, 1045, 1025, 950, 755, 720 cm^{-1}; EIMS, *m/e* (relative intensity) 349 (M^+, 17), 319 (2), 318 (11), 317 (10), 286 (13), 277 (20), 247 (14), 216 (17), 215 (base), 115 (10), 88 (26), 72 (12), 59(17), 42 (11); high-resolution mass spectrum, *m/e* 349.1529 ($C_{18}H_{23}NO_6$ requires 349.1524).

Methyl 1,2,3,4,5,6-Hexahydro-8-hydroxy-7-methoxy-2,6-methano-3-benzazocine-3-carboxylate (24). A mixture of **23** (22.0 mg, 0.063 mmol), 0.19 mL of 0.67 N aqueous NaOH (0.127 mmol, 2.0 equiv) and 0.25 mL of THF under nitrogen was stirred at 35 °C for 15.5 h. The reaction mixture was poured onto 0.4 mL of 5% aqueous HCl, and the resulting solution was saturated with sodium chloride and extracted with chloroform (8 × 1 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford 34 mg of the crude acid. The crude acid was dissolved in 0.2 mL of dry quinoline and the solution treated with copper powder (39.9 mg, 0.63 mmol, 10.0 equiv) and heated at 220 °C under argon for 1 h.[26a] The cooled reaction mixture was treated with cold, 10% aqueous HCl (2 mL) and the solution saturated with sodium chloride and extracted with chloroform (10 × 1.5 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo, and centrifugal thin-layer chromatography (SiO_2, 1 mm, 50% ether–hexane eluant) afforded 15.0 mg (17.5 mg theoretical, 86%) of **24** as a white, crystalline solid: mp 145–147 °C (benzene–hexane; 2×); ^1H NMR ($CDCl_3$) δ 6.76 (s, 2 H, Ar), 5.48 (br s, 1 H, OH), 4.60 (m, 1 H, –NCH–), 4.10–3.13 (m, 2 H, $-NCH_2-$), 3.82 (s, 3 H, OCH_3), 3.70 (s, 3 H, NCO_2CH_3), 3.03–2.45 (m, 3 H, CHAr and CH_2Ar), 2.15–1.45 (m, 4 H, two $-CH_2-$); IR ($CHCl_3$) ν_{max} 3560, 3360, 3010, 2960, 1675, 1485, 1450, 1275, 1220, 1080, 1030, 970, 800 cm^{-1}; EIMS, *m/e* 277 (M^+, 16), 263 (1), 246 (3), 245 (6), 176(17), 143 (11), 131 (8), 115 (18), 103 (34), 91 (9), 88 (base), 77 (10), 59 (18), 42 (15); high-resolution mass spectrum, *m/e* 277.1302 ($C_{15}H_{19}NO_4$ requires 277.1313).

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Registry No. **1SM**, 4746-97-8; **1a**, 530-93-8; **1b**, 17215-86-0; **1c**, 529-34-0; **1d**, 108-94-1; **1e**, 5019-82-9; **1f**, 85531-89-1; **1g**, 91586-26-4; **1h**, 2235-15-6; **1i**, 91585-98-7; **2SM**, 85531-91-5; **3SM**, 85531-92-6; **3a**, 85531-79-9; **3b**, 85531-85-7; **3c**, 82699-08-9; **3d**, 85531-80-2; **3e**, 85531-87-9; **3f**, 85531-83-5; **3g**, 91586-27-5; **3h**, 91586-28-6; **3i**, 91586-00-4; **4SM**, 85531-93-7; **5SM**, 85531-94-8; **5a**, 85531-84-6; **5b**, 85531-86-8; **5c**, 85531-82-4; **5d**, 78112-34-2; **5d** (acid), 25435-02-3; **5d** (acid chloride), 91586-35-5; **5e**, 85531-88-0; **5f**, 85531-81-3; **5g**, 91586-29-7; **6**, 88-12-0; **6SM**, 85531-95-9; **7**, 872-36-6; 8, 77998-68-6; **9a**, 23194-33-4; **9a** (acid), 1131-63-1; **9a** (acid chloride), 91586-31-1; **9b**, 89228-42-2; **9b** (acid), 91586-32-2; **9b** (methyl ether), 91586-33-3; **9c**, 89228-43-3; **9c** (acid), 91686-30-5; **9c** (acid chloride), 91586-36-6; **10a**, 119-64-2; **10b**, 89228-44-4; **10c**, 529-35-1; **10d**, 89228-45-5; **10e**, 1730-48-9; **10f**, 17212-96-3; **10g**, 89228-46-6; **10h**, 89228-47-7; 11, 91586-30-0; **12**, 91586-39-9; **13**, 91586-40-2; **14**, 91586-41-3; **15**, 91586-42-4; **16**, 91586-43-5; **17**, 5056-80-4; **18**, 91586-45-7; **19**, 91586-46-8; **20**, 91586-44-6; **21**, 91586-47-9; **23**, 91586-48-0; **23** (acid), 91586-38-8; **24**, 91586-49-1; $CH_3CH(OH)C{\equiv}CCH(OH)CH_3$, 3031-66-1; $CH_3O_2CC{\equiv}CCO_2CH_3$, 762-42-5; 7-acetyl-5-methoxy-1,2,3,4-tetrahydronaphthalene, 91586-34-4; 7-acetyl-5,6-dimethoxy-1,2,3,4-tetrahydronaphthalene, 91586-37-7; 7-acetyl-6-methoxy-1,2,3,4-tetrahydronaphthalene, 40420-04-0; 3-butyn-2-one, 1423-60-5; dimethyl (methoxymethylene)malonate, 22398-14-7; ethyl vinyl ether, 109-92-2; 1-(diethylamino)propyne, 4231-35-0; 6-acetyl-1,2,3,4-tetrahydronaphthalene, 774-55-0; *p*-methoxybenzoyl chloride, 100-07-2; 4-piperidone ethylene ketal, 177-11-7; 1,1-dimethoxyethylene, 922-69-0; allylamine, 107-11-9; methyl chloroformate, 79-22-1.

Supplementary Material Available: Complete experimental details for the preparation of ketone **1f** are provided (5 pages). Ordering information is given on any current masthead page.