(sites) of low hydrophobicity that are able to seek out features within the cyclodextrin interior and thus to achieve stabilizing contributions from $\Delta G°_{SS}$, with consequent penetration of the cyclodextrin interior to a depth determined by the particular interactions; this penetration further stabilizes the complex through a $\Delta G°_{MM}$ contribution. According to this viewpoint every inclusion complex is at least partially stabilized by a contribution from the $\Delta G°_{MM}$ term (in solvents that are more polar than the interior of the host).

Acknowledgment. This work was supported by a grant from The Upjohn Company.

Stereospecific Synthesis of Substituted *cis*-Hydrindan-5-ones and Their Regiospecific Enolization and Functionalization: Synthetic Intermediates for Reserpine

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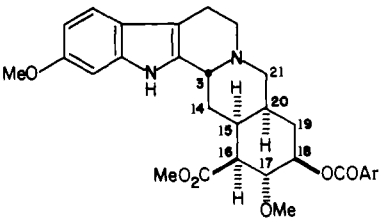
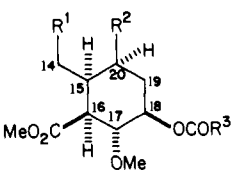
Abstract: An approach to reserpine (**1**) is described which is based on an anionic oxy-Cope rearrangement to establish three of the five contiguous asymmetric centers of the E ring and a regiospecific enol silylation coupled with hydroboration–oxidation to introduce the last two centers. The key intermediate **8b** for the anionic oxy-Cope rearrangement is prepared from the readily available 7,7-dimethoxynorbornenone **6** in 50% overall yield by addition of propargyl alcohol dianion, hydride reduction, and TBS formation. Rearrangement of **8b** followed by hydrogenation affords the desired 4-[(silyloxy)methyl]-1,1-dimethoxytetrahydroindan-6-one **10** in which all the protons were cis in nearly 80% yield. Force-field calculations on the two regioisomeric methyl enol ethers derived from **10** indicate a strong preference (96:4 at 25 °C) for enolization toward the ring juncture. Indeed treatment of **10** under thermodynamic conditions (BMDA, Me_3SiCl) produced a single (>95%) enol ether assigned the desired Δ^{17} (reserpine numbering) structure **11** by a combination of spectroscopic and chemical means. Conversion of **11** into its TBS enol ether **15** followed by hydroboration–oxidation introduced the last two asymmetric centers in an E-ring precursor **5** of reserpine (93% for the last step). Finally the unusual base-catalyzed hydrolysis of the dimethyl ketal which occurs in this process is rationalized by strong intramolecular complexation of a methoxyl group with the boron atom leading to ultimate displacement of this methoxyl group with hydroxide.

Reserpine (**1**), a *Rauwolfia* alkaloid with good antihypertensive properties, has been synthesized several times since Woodward's classical synthesis in the late 1950s.[2] This first synthesis prepared the E-ring derivative **2a** in which the five contiguous asymmetric centers were correctly established and then coupled it to 6-methoxytryptamine to give, after reduction, the lactam **3a** and thence reserpine in several further steps. Pearlman[3] prepared an analogous E-ring intermediate **2b** from a different precursor and then followed the Woodward route to reserpine. In Wender's synthesis,[4] the cyclic amine **4** was prepared by a completely different approach and taken onto reserpine. We have begun an approach to reserpine in which the E-ring target molecule is of lower functionality, namely, the aldehyde tosylate **2c**, which on reaction with 6-methoxytryptamine would give directly the desired immonium salt necessary for cyclization to reserpine.[5] We now report the anionic oxy-Cope rearrangement of the readily available substrate **8b** to produce a *cis*-hydrindenone with three of the five contiguous asymmetric centers established and the regiospecific enolization of a derivative of this hydrindenone which permits the introduction of the final two centers with the correct stereochemistry. In this manner, the hydrindanone **5**, with the correct stereochemistry at the five contiguous asymmetric centers, has been prepared in eight or nine steps in good overall yield (12–14%).

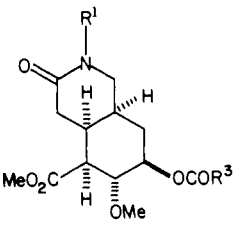
In our earlier work on the rearrangement of substituted allylic alcohols derived from the bicyclic enone **6**, we showed that the stereochemistry of the tertiary hydrogens about the periphery of the cyclohexanone system was all cis due to the geometric demands of the transition state.[6] We reasoned that the use of a simple *trans*-3-alkoxypropenyl-substituted alcohol, e.g., **8b**, would permit the easy preparation of the hydrindenone **9** with the all-cis arrangement of the three contiguous asymmetric centers. This was put into practice as follows: Reaction of the enone **6** (Scheme I) with the dilithium salt of propargyl alcohol dianion gave the endo adduct **7a** in 83% crude yield (62% recrystallized, mp 93–94



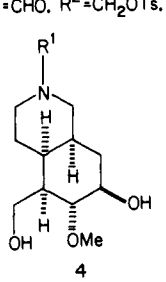
1, Ar = 3,4,5-$(MeO)_3C_6H_2$



2a, R^1=CO_2Me, R^2=CHO, R^3=Me
b, R^1=CO_2Me, R^2=CHO, R^3=Ar
c, R^1=CHO, R^2=CH_2OTs, R^3=Ar



3a, R^3=Me, R^1=6-methoxytrytophyl
b, R^3=Ar, R^1=6-methoxytrytophyl



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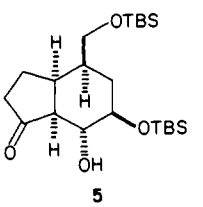

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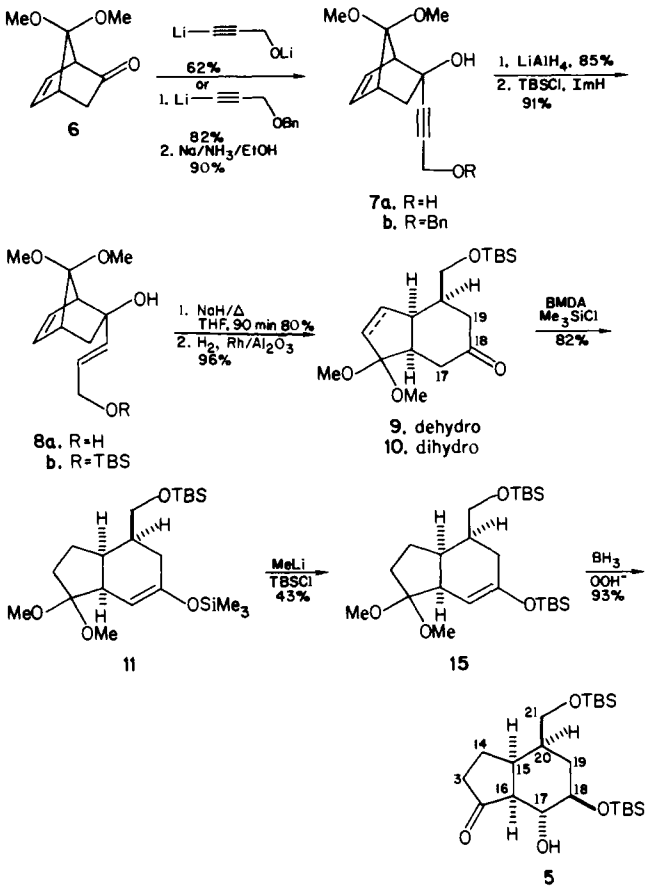
[†] Deceased September 20, 1984.

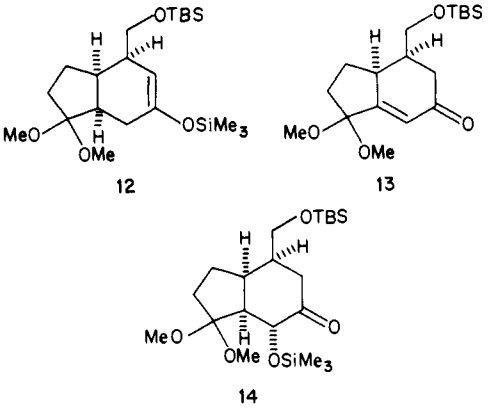
0002-7863/84/1506-7614$01.50/0

Scheme I



°C).[7] This same compound could be prepared in 74% overall yield by a two-step sequence in which the lithium salt of benzyl propargyl ether was added to **6** to give in 82% purified yield the endo adduct **7b**, which could be debenzylated with sodium in liquid ammonia at −78 °C to afford **7a** in 90% yield. Reduction of **7a** with lithium aluminum hydride gave an 85% yield of the pure trans allylic diol **8a**, which could be selectively mono protected as the primary *tert*-butyldimethylsilyl (TBS) ether **8b** in 91% purified yield. The key anionic oxy-Cope rearrangement was effected by refluxing the sodium salt of **8b** (prepared with sodium hydride) in THF for 90 min to give an 80% recrystallized yield of **9** (mp 72–73 °C) as a single pure stereoisomer. This compound must have the three hydrogens (C15, -16, and -20 in reserpine numbering) in the all-cis relationship due to the constraints of the transition state and by analogy to our earlier work in this area.[6] This compound contains the entire carbon skeleton of the desired E-ring precursor **2c** with functionality present to introduce the 17α-methoxyl group and the 18β-[(arylcarbonyl)oxy] function and to eventually cleave the cyclopentane ring to give the desired C14-aldehyde and C16-ester functions.

Catalytic hydrogenation of the allylic ketal double bond of **9** was effected in 96% yield over rhodium on alumina to give **10**. It was now necessary to form the regiospecific enolate of **10** toward the ring juncture in order to introduce the oxygen functionality at C17. There is only one citation in the literature concerning the regioselectivity of enolization of simple perhydroindan-5-ones. Granger et al.[8] report that chlorination of a mixture of *cis*- and *trans*-perhydroindan-5-ones produces the 4-chloro cis isomer and the 6-chloro trans isomer, but no experimental details (including the method of chlorination) are given. Although we expected enolization to occur in the desired direction by analogy to the well-known decalin systems,[9] we carried out force-field calculations of the strain energies in the Δ^{17} and Δ^{18} methyl enol ethers. These revealed an energy difference at 25 °C (assuming $\Delta S = 0$) of 1.9 kcal/mol, implying an equilibrium ratio of 96:4, favoring Δ^{17} enolization.[10] In the event, while treatment of **10** under kinetic conditions conditions (LDA, −78 °C; Me_3SiCl) gave an approximately 1:1 mixture of isomeric enol ethers, use of thermodynamic conditions[11] (BMDA, Me_3SiCl) produced a single silyl enol ether in 82% purified yield. We have assigned structure **11** and not **12** to this compound on the basis of the following data: (1)



Irradiation of the CH_2OTBS multiplet at δ 3.47 and difference spectroscopy permitted assignment of the 20α-H to the signal at δ 2.1, too low a chemical shift for an allylic proton β to an oxygen but reasonable for a homoallylic proton. (2) Irradiation at δ 2.1 collapsed the CH_2OTBS signal to an AB quartet but did not affect the vinyl proton at δ 4.79. (3) Finally, treatment of **11** with 0.5 equiv of palladium acetate and benzoquinone gave an enone **13** in which the CH_2OTBS signal is unchanged. All of this data (along with the ease of hydrolysis of the ketal leading to **5** described below) is consistent with the formation of **11** and not **12**. The ready formation of the regiospecific enol ether from hydrindan-5-ones should be of value in synthetic approaches to other molecules.

Oxidation of **11** with MCPBA[12] gave a quantitative yield of a silyloxy ketone assigned structure **14** on the basis that attack of the electrophile on the olefin would occur from the less hindered convex face of the molecule. We were, however, completely unable to methylate the derived alcohol under any basic conditions, obtaining only products of decomposition (perhaps via oxidation of the enediolate). To avoid problems of this sort, we decided to introduce the 17α-hydroxyl and the 18α-hydrogen in the same step by hydroboration of the TBS enol ether[13] corresponding to **11**, namely, **15**. The resulting hydroxybis(*tert*-butylsilyl) ether could presumably be methylated under basic conditions without

(1) Camille and Henry Dreyfus Teacher-Scholar, 1978–1983. Fellow of the Alfred P. Sloan Foundation, 1979–1981.

(2) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1.

(3) Pearlman, B. A. *J. Am. Chem. Soc.* **1979**, *101*, 6389, 6404.

(4) Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157.

(5) If this immonium salt can be trapped by the C2-position of the indole *under basic conditions*, one would expect antiparallel axial attack on the immonium salt to give the 3β stereochemistry of reserpine rather than the 3-epireserpine. For examples of this principle of antiparallel attack, see: Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032; *J. Chem. Soc., Chem. Commun.* **1982**, 102, 103.

(6) Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 2463; **1978**, *100*, 4309.

(7) Compound **6** is available from hexachlorocyclopentadiene in 5 steps and 50% overall yield. Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1977**, *99*, 5508.

(8) Granger, R.; Nau, P. F. G.; Girard, J. P.; Boussinesq, J. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1966**, *262*, 1598.

(9) For a discussion, see: Akhrem, A. A.; Titov, Y. A. "Total Steroid Synthesis"; Plenum Press: New York, 1970; p 49.

(10) We thank Dr. James Snyder, Merck, Sharp & Dohme Company, Rahway, NJ, for performing these calculations.

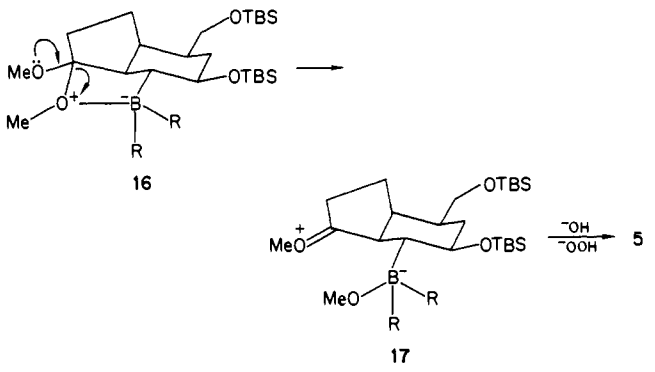
(11) Krafft, M. E.; Holton, R. A. *Tetrahedron Lett.* **1983**, *24*, 1345.

(12) (a) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319. (b) Brook, A. G.; Macrae, D. M. *J. Organomet. Chem.* **1974**, *77*, C19. (c) Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427.

(13) Larson, G. L.; Prieto, J. A. *Tetrahedron* **1983**, *39*, 855.

decomposition, the TBS ethers subsequently hydrolyzed, and the resultant primary, secondary diol differentiated (primary tosylation, secondary acylation). Thus this route looked promising.

Although compound **15** could be prepared in poor yield from **10** directly by the method of Negishi[14] (as a 3:1 mixture of Δ^{17}/Δ^{18} regioisomers), it was more convenient to prepare it in pure form from **11** by trans-silylation process. In this manner **15** was available in an unoptimized purified yield of 43%. Hydroboration of **15** with the borane tetrahydrofuran complex at 25 °C for 24 h followed by oxidation with aqueous basic hydrogen peroxide (0 °C, 0.5 h) afforded a keto alcohol assigned structure **5** in 93% yield. Use of thexylborane furnished this same compound in slightly lower yield. That the ketal of **15** was hydrolyzed during the reaction was evident from the IR spectrum of **5**, which showed a strong absorption at 1740 cm^{-1}. This unusual hydrolysis of a dimethyl ketal under basic conditions is presumably due to the internal dative bond between the *exo*-methoxyl group and the boron at C17 as shown in **16**. This would then allow ejection of the *exo*-methoxyl group by the endo one to generate **17**, which would be trapped by the aqueous hydroxide and converted into **5**.[15]



Compound **5** has the correct stereochemistry at the five contiguous asymmetric centers (C15–C18, C20) for conversion into reserpine.[16] Efforts at the transformation of **5** and other intermediates in this scheme into reserpine are currently under way.

Experimental Section

***endo*-2-(3-Hydroxyprop-1-ynyl)-*exo*-2-hydroxy-7,7-dimethoxybicyclo[2.2.1]hept-5-ene (7a). A.** To a solution of 2.5 mL (43.0 mmol) of propargyl alcohol in 58 mL of THF was added 66.2 mL of *n*-butyllithium solution (1.3 M in hexane, 86.0 mmol) at −78 °C, and the thick white suspension was stirred at −78 °C for 30 min. The norbornenone **6** (3.62 g, 21.5 mmol) in 40 mL of THF was added dropwise, and the reaction mixture was warmed to 25 °C for 12 h. Saturated ammonium chloride solution was added, the phases were separated, and the aqueous phase was extracted well with ether. The combined organic layer was washed with saturated ammonium chloride solution until neutral to litmus, washed with brine, dried over saturated sodium sulfate, and evaporated to give 4.00 g of a crude semisolid. Recrystallization from ether gave 2.98 g (62%) of **7a** as a white solid (mp 93–94 °C).

^1H NMR (200 MHz, $CDCl_3$) δ 6.26–6.31 (1 H, m), 6.16–6.18 (1 H, m), 4.29 (1 H, br s), 4.25 (2 H, br s), 3.32 (3 H, s), 3.21 (3 H, s), 2.98 (1 H, m), 2.89 (1 H, m), 2.00–2.20 (1 H, br s), 1.92–1.97 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 137.18, 131.27, 120.09, 88.06, 81.90, 73.51, 55.61, 52.59, 50.81, 49.64, 45.53, 43.63; IR (neat) 3180–3660, 2700–3100, 2330, 1630, 1440, 1380, 1300, 1280, 1220, 1180, 1120, 1060, 1030, 960, 920, 880, 800, 720 cm^{-1}; MS (70 eV), *m/e* (% intensity) 192 (4.2, M^+ − MeOH), 151 (2.1), 133 (2.4), 127 (5.8), 115 (4.2), 109 (100.0), 103 (4.6), 101 (3.1), 95 (6.8), 91 (10.6), 83 (4.7), 81 (4.8), 77 (12.4), 67 (4.9), 65 (7.0), 59 (7.9), 55 (12.5); high-resolution MS (70 eV), *m/e* 192.0783, calcd for $C_{11}H_{12}O_3$ 192.0787. Anal. ($C_{12}H_{16}O_4$) C, H.

B. To a liquid ammonia (freshly dried by redistillation from sodium, 180 mL) cooled to −78 °C in a three-neck round-bottom flask equipped with a magnetic stirring bar, dry ice condenser, and addition funnel, was added metallic sodium (washed with hexane, 1.214 g, 52.8 mmol) to give the usual blue solution. A solution of the propargylic benzyl ether **7b** (5.526 g, 17.6 mmol) and ethanol (distilled from sodium, 2.05 mL, 1.62 g, 35.2 mmol) in diethyl ether (freshly distilled from sodium, 70 mL) was added dropwise via the addition funnel. After the addition was complete, the addition funnel was washed with 5 mL of diethyl ether, and this wash added to the ammonia solution. After stirring for 5 min, a small amount of isoprene was added dropwise to dispel the blue color. The cooling bath was removed and the ammonia evaporated using water-aspirator vacuum. Water was added to the residue, and the mixture was extracted several times with diethyl ether. The organic layer was separated, washed with brine, and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave 3.561 g (90%) of the crystalline diol **7a** as an essentially pure compound, mp 93–95 °C. ^1H and ^{13}C NMR of this crude material was identical with that of **7a** prepared by method A, as described above.

***endo*-2-(3-(Benzyloxy)prop-1-ynyl)-*exo*-2-hydroxy-7,7-dimethoxybicyclo[2.2.1]hept-5-ene (7b).** *n*-Butyllithium solution (1.6 M in hexane, 1.3 mL, 18.0 mmol) was added dropwise at −78 °C to propargyl benzyl ether (2.51 g, 17.2 mmol) in 25 mL of THF, and the yellow solution was stirred for 30 min. The norbornenone **6** (1.92 g, 11.5 mmol) in 10 mL of THF was added at −78 °C, and the solution was warmed to 25 °C for 5 h. Quenching of the reaction with saturated ammonium chloride solution, extraction with ether, washing of the combined organic phases with brine, drying of it over sodium sulfate, and evaporation of the solvent afforded a crude yellow oil. This was purified by chromatography on activity-2.5 neutral alumina with 50% ether/hexane elution to give 2.96 g (82%) of **7b** as a slightly yellow oil.

^1H NMR (200 MHz, $CDCl_3$) δ 7.31 (5 H, m), 6.28 (1 H, m), 6.15 (1 H, m), 4.54 (2 H, s), 4.22 (1 H, s), 4.10 (2 H, s), 3.32 (3 H, s), 3.21 (3 H, s), 2.99 (1 H, br s), 2.92 (1 H, br s), 1.96–1.99 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 137.59, 137.08, 131.26, 128.35, 128.03, 127.74, 120.07, 89.50, 78.95, 73.45, 71.26, 57.42, 55.64, 52.51, 49.57, 45.51, 43.80; IR (neat) 3430, 2930, 2230, 1440, 1380, 1360, 1290, 1270, 1220, 1185, 1120, 1060, 1000, 910, 730 cm^{-1}; MS (70 eV), *m/e* (% intensity) 314 (M^+, 0.3), 252 (17.6), 237 (6.9), 191 (1.7), 176 (3.5), 133 (3.2), 127 (4.5), 115 (8.1), 109 (100.0), 101 (6.3), 91 (51.7), 77 (10.9); high-resolution MS (70 eV), *m/e* 237.0916, calcd for $C_{16}H_{13}O_2$ 237.0916 ($M^+ - C_6H_5$). Anal. ($C_{19}H_{22}O_4$) C, H.

***endo*-2-((*E*)-3-Hydroxyprop-1-enyl)-*exo*-2-hydroxy-7,7-dimethoxybicyclo[2.2.1]hept-5-ene (8a).** To 134 mL of a 0.33 M solution of lithium aluminum hydride in ether (44.6 mmol) was added 5.0 g (22.3 mmol) of the alcohol **7a** in 100 mL of ether at 0 °C. (Addition of a small amount of THF improved the solubility of the acetylene **7a**.) The white suspension was heated at reflux for 3 h, cooled to 0 °C, quenched with 15% aqueous sodium hydroxide solution (50 mL), and stirred for 3 h. Decantation of the organic layer, washing of it with brine, drying over sodium sulfate, and evaporation gave an oil, which could be purified by silica gel chromatography with 50% ether/hexane elution or by distillation (bp 130–140 °C, 0.09 torr) to give 4.25 g (85%) of **8a** as a colorless oil.

^1H NMR (200 MHz, $CDCl_3$) δ 6.23 (1 H, m), 6.11 (1 H, m), 5.85–5.98 (1 H, dt, J = 15.46, 5.40 Hz), 5.58–5.67 (1 H, dd, J = 15.46, 1.41 Hz), 4.54 (1 H, br s, OH), 4.14 (2 H, m), 3.35 (3 H, s), 3.20 (3 H, s), 2.98 (1 H, m), 2.66 (1 H, m), 1.82–1.90 (1 H, dd, J = 3.63, 12.62 Hz), 1.64 (1 H, d, J = 12.62 Hz), 1.37 (1 H, m, OH); ^{13}C NMR ($CDCl_3$) δ 136.10, 135.42, 131.32, 128.30, 120.75, 78.81, 62.93, 55.79, 52.47, 49.61, 45.74, 40.67; IR (neat) 3050–3650, 2700–3050, 1620, 1570, 1440, 1380, 1280, 1220, 1180, 930–1170, 900, 770, 710 cm^{-1}; MS (16 eV), *m/e* (% intensity) 194 (5.4, M^+ − MeOH), 176 (5.4), 162 (2.8), 147 (1.6), 135 (1.7), 127 (3.9), 117 (5.2), 109 (100.0), 105 (1.6), 91 (5.7), 85 (1.6), 75 (3.0); high-resolution MS (70 eV), *m/e* 127.0764, calcd for $C_7H_{11}O_2$ 127.0759. Anal. ($C_{12}H_{18}O_4$) C, H.

***endo*-2-[(*E*)-3-((*tert*-Butyldimethylsilyl)oxy)prop-1-enyl]-*exo*-2-hydroxy-7,7-dimethoxybicyclo[2.2.1]hept-5-ene (8b).** To a solution of the diol **8a** (2.40 g, 10.63 mmol) in 2.8 mL of dimethylformamide was added *tert*-butyldimethylsilyl chloride (1.92 g, 12.76 mmol) and imidazole (1.81 g, 26.58 mmol), and this mixture was allowed to stir at 25 °C for 36 h. After dilution of it with dichloromethane, washing of the organic layer with water, drying over sodium sulfate, and concentration, there was obtained a crude yellow oil, which was purified by HPLC using 8% ethyl acetate/hexane elution. This gave 3.61 g (91%) of the silyl ether **8b** as an oil.

^1H NMR (200 MHz, $CDCl_3$) δ 6.19 (1 H, m), 6.03 (1 H, m), 5.74–5.86 (1 H, dt, J = 15.35, 4.39 Hz), 5.57 (1 H, d, J = 15.35 Hz),

(14) Negishi, E.; Chatterjee, S. *Tetrahedron Lett.* **1983**, *24*, 1341.

(15) Other nonaqueous methods of oxidation may avoid this ketal hydrolysis. For example, see: Kabalka, G. W.; Hedgecock, H. C., Jr. *J. Org. Chem.* **1975**, *40*, 1776.

(16) That **5** survives the mildly basic conditions without extensive decompositon or destruction (β-elimination, retroaldol condensation, etc.) is promising for its further derivatization. Eventually the ketone will be converted into the kinetic silyl enol ether (LDA, TMSCl) and ozonized to give the required aldehyde ester for reserpine. An approach proposing a similar final step but completely different chemistry in the early stages has been described. Ficini, J.; Guingant, A.; d'Angelo, J.; Stork, G. *Tetrahedron Lett.* **1983**, *24*, 907.

4.51 (1 H, d, J = 1.46 Hz), 4.15–4.18 (2 H, dd, J = 1.95, 4.39 Hz), 3.34 (3 H, s), 3.18 (3 H, s), 2.95 (1 H, m), 2.64 (1 H, m), 1.79–1.87 (1 H, dd, J = 3.91, 12.70 Hz), 1.61 (1 H, d, J = 12.70 Hz), 0.89 (9 H, s), 0.04 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 135.77, 134.17, 131.26, 127.74, 120.61, 78.61, 63.38, 55.78, 52.29, 49.42, 45.59, 40.68, 25.82, 18.26, −5.24; IR (neat) 3500, 2775–3125, 1650, 1585, 1480, 1410, 1310, 1290, 1275, 1250, 1240, 1210, 1140, 1080, 1000, 960, 860, 820, 800, 740, 690 cm^{-1}; MS (70 eV), m/e (% intensity) 308 (M^+ − MeOH, 6.4), 251 (M^+ − MeOH − *t*-Bu, 14.9), 199 (8.2), 191 (5.0), 177 (4.9), 176 (5.0), 163 (5.7), 135 (6.2), 117 (19.7), 110 (8.0), 109 (100.0), 105 (6.1), 95 (7.5), 91 (11.4), 89 (12.5), 75 (57.0), 73 (45.0), 59 (8.2), 55 (5.1); high-resolution MS (70 eV), m/e 251.1100, calcd for $C_{13}H_{19}O_3Si$ 251.1104.

4-([(*tert*-Butyldimethylsilyl)oxy]methyl)-1,1-dimethoxy-3aα,4α,5,7aα-tetrahydro-7*H*-inden-6-one (9). Sodium hydride (50% in oil, 1.1 g, 22.0 mmol) was washed with anhydrous hexane and suspended in 100 mL of THF. The alcohol **8b** (2.5 g, 7.4 mmol) in 50 mL of THF was added dropwise to the suspension at 0 °C. The reaction mixture was heated to reflux for 90 min, cooled to 0 °C, quenched with water, and extracted with ether. The combined organic phases were washed with brine until neutral to litmus, dried over sodium sulfate, and concentrated to give a brown solid. Recrystallization of this solid from hexane or chromatography on activity-3 neutral alumina with 20% ether/hexane gave 2.0 g (80%) of **9** as a white solid (mp 72–73 °C).

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.04 (2 H, br s), 3.53 (2 H, d, J = 6.92 Hz), 3.35 (1 H, m), 3.23 (3 H, s), 3.20 (3 H, s), 2.83 (1 H, m), 1.65–2.65 (5 H, m), 0.89 (9 H, s), 0.05 (6 H, s); IR (neat) 2650–2950, 1705, 1600, 1440, 1390, 1320, 1230, 1170, 1130, 1020, 960, 900, 820, 750 cm^{-1}; MS (70 eV), m/e (% intensity) 340 (M^+, 0.2), 308 (5.2), 251 (26.8), 176 (25.9), 163 (21.0), 161 (6.3), 148 (9.5), 135 (6.5), 133 (7.5), 115 (9.5), 89 (23.7), 75 (100), 73 (37.3), 59 (7.0); high-resolution MS (70 eV), m/e 340.2071, calcd for $C_{18}H_{32}O_4Si$ 340.2070.

4-([(*tert*-Butyldimethylsilyl)oxy]methyl)-1,1-dimethoxy-2,3,3aα,4α,5,7aα-hexahydro-7*H*-inden-6-one (10). A mixture of rhodium on alumina catalyst (0.57 g), hydrindenone **9** (1.60 g, 5.0 mmol), and 250 mL of benzene was hydrogenated at 50 psi for 60 min. Filtration of the mixture through Celite and evaporation of the solvent gave an oil, which was purified by distillation (bp 110–120 °C, 0.06 torr) or by chromatography on activity-3 neutral alumina with 25% ether/hexane to give **10** (1.54 g, 96%) as a clear oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.51 (2 H, m), 3.20 (3 H, s), 3.17 (3 H, s), 2.51 (2 H, m), 2.26 (5 H, m), 1.94 (2 H, m), 1.71 (2 H, m), 0.88 (9 H, s), 0.03 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 211.97, 111.65, 65.46, 49.94, 48.70, 45.53, 40.47, 39.00, 38.73, 36.69, 30.52, 25.88, 19.77, 18.25, −5.44; IR (neat) 2750–3050, 1720, 1470, 1260, 1220, 1100, 910, 850, 780, 735 cm^{-1}; MS (70 eV), m/e (% intensity) 310 (M^+ − MeOH, 19.3), 285 (M^+ − MeOH − *t*-Bu, 4.0), 253 (100.0), 221 (11.3), 211 (17.6), 195 (21.7), 161 (28.5), 157 (47.6), 143 (12.9), 96 (12.9), 89 (35.2), 75 (81.9), 73 (43.7); high-resolution MS (70 eV), m/e 285.1521, calcd for $C_{14}H_{25}O_4Si$ 285.1522. Anal. ($C_{18}H_{34}SiO_4$) C, H.

4-([(*tert*-Butyldimethylsilyl)oxy]methyl)-1,1-dimethoxy-6-[(trimethylsilyl)oxy]-3aα,4α,5,7aα-tetrahydro-1*H*-indane (11). To a solution of 0.17 mL (1.25 mmol) of diisopropylamine in 16 mL of ether was added 0.40 mL of methylmagnesium bromide solution (3 M in ether, 1.22 mmol) at 25 °C. After stirring for 12 h, the ketone **10** (342 mg, 1.00 mmol) in 3 mL of ether was added and stirred for 15 min. The anion was quenched by sequential addition of 0.40 mL (3.00 mmol) of trimethylsilyl chloride, 0.45 mL (3.25 mmol) of triethylamine, and 0.10 mL of hexamethylphosphoramide, and the mixture was stirred at 25 °C for 8 h. Dilution of it with ether, quenching with cold saturated sodium bicarbonate solution, rapid separation of the phases, drying of the organic layer over sodium sulfate, and concentration gave a crude yellow oil. Passage of the crude material through a small amount of silica gel with 10% ethyl acetate/hexane afforded 340 mg (82%) of the silyl enol ether **11** as a light yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.79 (1 H, br s), 3.47 (2 H, m), 3.24 (3 H, s), 3.21 (3 H, s), 1.05–2.75 (9 H, m), 0.89 (9 H, s), 0.19 (9 H, s), 0.03 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 150.87, 111.41, 103.49, 66.08, 50.25, 48.22, 44.08, 38.27, 34.55, 29.99, 28.57, 25.96, 18.95, 18.33, 0.36, −5.35; IR (neat) 2780–3100, 1650, 1450, 1240, 1180, 1100, 1040, 830, 750 cm^{-1}; MS (70 eV), m/e (% intensity) 382 (M^+ − MeOH, 15.5), 325 (M^+ − MeOH − *t*-Bu, 20), 237 (41.7), 235 (19.4), 219 (15.0), 195 (12.1), 179 (16.5), 161 (13.7), 97 (11.3), 89 (17.4), 75 (30.2), 73 (100.0), 59 (10.9); high-resolution MS (70 eV), m/e 382.2349, calcd for $C_{20}H_{38}O_3Si_2$ 382.2359.

4-([(*tert*-Butyldimethylsilyl)oxy]methyl)-1,1-dimethoxy-3aα,4α-dihydro-5*H*-indan-6-one (13). Palladium acetate (32 mg, 0.18 mmol) and benzoquinone (15 mg, 0.18 mmol) were dissolved in acetonitrile, and the silyl enol ether **11** (118 mg, 0.36 mmol) in 0.5 mL of acetonitrile was added dropwise. The brown reaction mixture was stirred at 25 °C for 4 h. Addition of 10% aqueous sodium hydroxide solution to the mixture, extraction of the aqueous phase with ether, washing of the combined organic phases with saturated ammonium chloride solution, drying over sodium sulfate, and concentration afforded 86 mg of an oil. This was purified by chromatography on activity-2.5 neutral alumina with benzene elution to afford 42 mg (34%) of the enone **13** as an oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.03 (1 H, br s), 3.65 (2 H, m), 3.27 (3 H, s), 3.17 (3 H, s), 1.66–2.72 (8 H, m), 0.86 (9 H, s), 0.03 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 198.80, 163.41, 123.17, 106.55, 61.43, 53.40, 49.64, 41.27, 40.88, 40.51, 35.11, 25.87, 23.29, 19.80, −5.58; IR (neat) 2800–3025, 1685, 1460, 1250, 1140, 1100, 900, 840, 780 cm^{-1}; MS (70 eV), m/e (% intensity) 283 (M^+ − *t*-Bu, 60.9), 255 (13.4), 253 (M^+ − isobutylene − OMe, 20.4), 251 (M^+ − *t*-Bu − MeOH, 60.3), 221 (11.5), 195 (38.8), 101 (26), 97 (28.3), 91 (21.1), 89 (78.9), 75 ($OSiMe_2H^+$, 100); high-resolution MS (70 eV), m/e 283.1363, calcd for $C_{14}H_{23}O_4Si$ 283.1365, 251.1087, calcd for $C_{13}H_{19}O_3Si$ 251.1104.

4-([(*tert*-Butyldimethylsilyl)oxy]methyl)-1,1-dimethoxy-7α-[(trimethylsilyl)oxy]-3aα,4α,5,7aα-tetrahydro-7*H*-indan-6-one (14). To a solution of *m*-chloroperoxybenzoic acid (36 mg, 0.21 mmol) in 2.5 mL of dichloromethane at −10 °C was added 72 mg (0.21 mmol) of the silyl enol ether **11** in 1 mL of dichloromethane, and the mixture was stirred for 1 h. The reaction mixture was then diluted with dichloromethane, washed with 20% aqueous sodium bisulfite solution and with saturated sodium bicarbonate solution, dried over sodium sulfate, and concentrated to give 68 mg (95%) of the crude silyloxy ketone **14**. Treatment of this material with 10% aqueous sodium hydroxide or with saturated potassium carbonate solution or chromatography of it on activity-2.5 neutral alumina resulted in decomposition.

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.21 (1 H, d, J = 10.18 Hz), 3.52 (2 H, m), 3.33 (3 H, s), 3.21 (3 H, s), 1.76–2.53 (9 H, m), 0.88 (9 H, s), 0.11 (9 H, s), 0.07 (6 H, s).

4-([(*tert*-Butyldimethylsilyl)oxy]methyl)-6-[(*tert*-butyldimethylsilyl)oxy]-1,1-dimethoxy-3aα,4α,5,7aα-tetrahydro-1*H*-indane (15). A. Potassium hydride (25% solution in oil, 0.28 mL, 1.5 mmol) was washed thoroughly with anhydrous pentane and suspended in 3.1 mL of THF. The ketone **10** (340 mg, 1.0 mmol) in 1 mL of THF was added at 0 °C, and the mixture was warmed to 25 °C for 30 min. The mixture was recooled to 0 °C, triethylborane (1.8 ml, 1 M solution in THF, 1.8 mmol) was added, and stirring was continued for 1 h. Addition of hexamethylphosphoramide (0.15 ml) and *tert*-butyldimethylsilyl chloride (166 mg, 1.1 mmol) in 1 mL of pentane at 0 °C was followed by warming to 25 °C for 12 h. Addition of 1 mL of 3 N aqueous sodium hydroxide solution and 1 mL of 30% hydrogen peroxide solution was followed by stirring at 0 °C for 30 min. Dilution of the reaction mixture with pentane, separation of the layers, washing of the organic phase with brine, drying of it over sodium sulfate, and concentration gave 342 mg of the crude product. Chromatography of the residual material on activity-3 neutral alumina with 15% ether/hexane gave 120 mg (26%) of the enol ether **15** as a 78:22 mixture of Δ^6/Δ^5 regioisomeric olefins.

B. To a solution of the trimethylsilyl enol ether **11** (357 mg, 0.86 mmol) in 1.3 mL of THF was added 0.61 mL of methyllithium solution (1.55 M in ether, 0.95 mmol) at 0 °C. After 30 min at that temperature, hexamethylphosphoramide (0.23 ml) was added, the reaction was cooled to −78 °C, and a solution of *tert*-butyldimethylsilyl chloride (143 mg, 0.95 mmol) in 0.3 mL of pentane was added. After it was warmed to 25 °C and stirred for 12 h, the reaction mixture was diluted with pentane and washed with water until neutral to litmus. The organic phase was dried over sodium sulfate and concentrated to give an oil. Chromatography of this material on activity-2 neutral alumina with 5% ether/hexane gave 164 mg (43%) of the exchanged silyl ether **15** as a clear oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.75 (1 H, br s), 3.44 (2 H, t, J = 6.59 Hz), 3.20 (3 H, s), 3.17 (3 H, s), 2.65 (1 H, m), 2.37 (1 H, m), 1.22–2.01 (7 H, m), 0.89 (9 H, s), 0.85 (9 H, s), 0.11 (6 H, s), 0.09 (6 H, s); ^{13}C NMR ($CDCl_3$) δ 151.05, 111.47, 103.42, 66.09, 50.26, 48.22, 44.17, 38.34, 34.61, 30.03, 28.61, 25.97, 25.77, 18.99, 18.31, 18.05, −4.17, −4.47; IR (neat) 2800–3050, 1680, 1475, 1275, 1210, 1130, 1090, 1070, 1020, 910, 860, 800 cm^{-1}; MS (70 eV), m/e (% intensity) 456 (M^+, 0.2), 424 (M^+ − MeOH, 20.3), 367 (6.9), 279 (15.0), 261 (4.8), 221 (14.6), 147 (8.5), 101 (11.0), 89 (14.5), 75 (24.7), 73 (100.0), 59 (15.8), 41 (13.0); high-resolution MS (70 eV), m/e 424.2824, calcd for $C_{23}H_{44}O_3Si_2$ 424.2829.

4-([(*tert*-Butyldimethylsilyl)oxy]methyl)-6β-[(*tert*-butyldimethylsilyl)oxy]-7α-hydroxy-3aα,4α,5,6,7,7aα-hexahydro-1*H*-indan-1-one (5). A. To 46 mg (0.10 mmol) of the silyl ether **15** in 0.5 mL of THF at 0 °C was added 0.15 mL of borane–tetrahydrofuran complex (1 M solution in THF, 0.15 mmol), and the mixture was stirred at 25 °C for 24 h. Oxidation of the borane by addition of 0.5 mL of 3 N aqueous sodium hydroxide and 0.5 mL of 30% hydrogen peroxide at 0 °C and stirring of the mixture for 30 min was followed by extraction of the mixture several times with ether. The organic phase was washed with brine, dried over sodium sulfate, and concentrated to give 50 mg of an oil. Chro-

matography of this on activity-3 neutral alumina using 20% ether/hexane elution gave 40 mg (93%) of the ketone **5** as a clear oil.

B. To 70 mg (0.15 mmol) of the silyl enol ether **15** in 0.5 mL of THF at 0 °C was added 0.17 mL of thexylborane (0.5 M solution in THF, 0.17 mmol), and the mixture was warmed to 20 °C for 18 h. Addition of 0.2 mL of 3 N aqueous sodium hydroxide solution and 0.2 mL of 30% hydrogen peroxide solution at 0 °C, stirring of the two-phase solution for 30 min, extraction of this mixture with ether, washing of the organic layer with brine, drying of it over sodium sulfate, and concentration gave a crude oil. This was purified by chromatography on activity-3 neutral alumina with 20% ether/hexane to give 50 mg (76%) of the ketone **5** as a clear oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.2-3.7 (5 H, br m), 1.5-2.5 (9 H, br m), 0.90 (9 H, s), 0.89 (9 H, s), 0.10 (6 H, s), 0.07 (6 H, s); IR (neat) 3050-3600, 2750-3000, 1740, 1480, 1260, 1100, 920, 850, 790, 740 cm^{-1}; MS (70 eV), *m/e* (% intensity) 371 (M^+ - *tert*-Bu, 0.7), 353 (M^+ - *t*-Bu - H_2O, 1.9), 271 (3.6), 239 (M^+ - TBSOH - *t*-Bu, 5.3), 223 (M^+ - TBSOH - isobutylene - OH, 7.0), 131 (17.7), 91 (10.2), 89 (17.7), 75 ($OSiMe_2H^+$, 100); high-resolution MS (70 eV), *m/e* 371.2087, calcd for $C_{18}H_{35}O_4Si_2$ 371.2074, 353.1983, calcd for $C_{18}H_{33}O_3Si_2$ 353.1969, 223.1157, calcd for $C_{12}H_{19}O_2Si$ 223.1155.

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Registry No. 1, 50-55-5; **5**, 92420-94-5; **6**, 64145-56-8; **7a**, 92420-95-6; **7b**, 92420-96-7; **8a**, 92420-97-8; **8b**, 92420-98-9; **9**, 92420-99-0; **10**, 92421-00-6; **11**, 92421-01-7; **13**, 92421-02-8; **14**, 92421-03-9; Δ^6-**15**, 92421-04-0; Δ^5-**15**, 92421-05-1; propargyl alcohol, 107-19-7; propargyl benzyl ether, 4039-82-1; trimethylsilyl chloride, 75-77-4; *tert*-butyldimethylsilyl chloride, 18162-48-6.

Communications to the Editor

3-Alkoxy-7-amino-4-chloroisocoumarins: A New Class of Suicide Substrates for Serine Proteases

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Human leukocyte elastase (HLE) is a serine protease involved in a number of disease states including pulmonary emphysema. As such, there is considerable interest in the development of therapeutically useful HLE inhibitors. Previously, a number of heterocyclic structures have been shown to be suicide substrates of serine proteases.[1-3] Here we report that 3-alkoxy-7-amino-4-chloroisocoumarins are suicide substrates of HLE, porcine pancreatic elastase (PPE), and bovine chymotrypsin A_α (ChT).

Incubation of the 7-amino-4-chloroisocoumarins[4] **2** and **6**, the 7-nitro-4-chloroisocoumarins[4] **1** and **5**, 7-amino-3-methoxyisocoumarin[5] **3**, and 4-chloro-3-ethoxyisocoumarin[6] (**4**) with HLE and PPE resulted in a time-dependent loss of enzymatic activity (Table I). ChT was also inactivated by **2** and **6** with $k_{obsd}/[I]$ values of 108 M^{-1} s^{-1} ([I] = 0.1 mM) and 270 M^{-1} s^{-1} ([I] = 0.02 mM), respectively. While >99% inactivation was observed with 7-amino-4-chloroisocoumarins **2** and **6**, a maximum of 70-95% inactivation was observed with **1** and **3-5** under the conditions utilized. Inactivation of PPE (1.7 μM) by the 7-amino-4-chloroisocoumarin **2** (16 μM) in the presence of the reversible competitive inhibitor CF_3CO-Lys-Ala-4-methylanilide[7] (15 μM) resulted in a decrease in the inactivation rate ($k_{obsd}/[I]$ = 76 M^{-1} s^{-1}), indicating that **2** is active-site directed.

Table I. Inactivation of Serine Proteases by Substituted 3-Alkoxyisocoumarins[a]

enzyme		inhibitor concentration, μM	$k_{obsd}/[I]$, M^{-1} s^{-1}	$k_{reactivation}$, s^{-1}
HL elastase	**1**	15	>2600[b]	0.5×10^{-3}
	2	5	10000	0[c]
	3	112	200	
	4	0.6	43000[d]	0.2×10^{-3}[e]
	5	34	>2800[b]	0.33×10^{-3}
	6	4.4	9500	0[c]
PP elastase	**1**	40	>600[b]	0.5×10^{-3}
	2	16	1000	0[c]
	3	91	18	
	4	37	1400	0.16×10^{-3}
	5	30	>1300[b]	1.3×10^{-3}
	6	19	700	0[c]

[a] Unless otherwise noted, enzyme (0.4-2.0 μM) was incubated with inhibitor in 0.25-0.6 mL of 0.1 M Hepes, 0.5 M NaCl, pH 7.5, 8-12% Me_2SO at 25 °C. Aliquots (10-50 μL) were withdrawn at various times and the residual enzymatic activity measured as previously described.[3] The k_{obsd} values were calculated from plots of ln v/v_0 vs. time with $r > 0.99$. [b] Inactivation was extremely rapid and the $k_{obsd}/[I]$ values are based on residual enzymatic activity at 0.25 min. [c] Less than 0.5% activity regained after standing 100 h at 25 °C. Controls retained >90% enzymatic activity over this time period. [d] Inactivation rate measured using the progress curve method[10] with 0.171 mM MeO-Suc-Ala-Ala-Pro-Val-4-nitroanilide and 8 nM HLE. [e] [I] = 0.013 mM.

Loss of the isocoumarin ring chromophore of 7-amino-4-chloro-3-ethoxyisocoumarin (**6**) (0.030 mM, ϵ_{385} = 3330 M^{-1} cm^{-1}; spontaneous hydrolysis, 5.9×10^{-5} s^{-1}) occurred concurrently with inactivation of PPE (6.4 μM, $k_{obsd}/[I]$ = 940 M^{-1} s^{-1}) and ChT (12.6 μM, $k_{obsd}/[I]$ = 200 M^{-1} s^{-1}). A reaction stoichiometry of 1.03 ± 0.07 and 1.31 ± 0.03 equiv of **6** with PPE and ChT, respectively, was calculated from the absorbance change (385 nm). The inactivated enzymes showed no new bands in the UV-visible spectrum before or after dialysis (0.1 M phosphate pH 6.8 buffer, 48 h, 4 °C). The reaction of 4-chloro-3-ethoxyisocoumarin (**4**) (0.066 mM) with ChT (0.050 mM) was monitored by the absorbance decrease at 350 nm (ϵ = 2920 M^{-1} cm^{-1}) and 0.97 equiv of **4** are required for total (>99%) inactivation. PPE (7 μM) hydrolyzed 7-amino-3-methoxyisocoumarin (**3**) (0.054 mM, ϵ_{385} = 4300 M^{-1} cm^{-1}; spontaneous hydrolysis, 3×10^{-5} s^{-1}) with a pre-steady-state rate constant of 0.75×10^{-3} s^{-1} (burst = 0.66 equiv) and a steady-state rate constant of 0.084×10^{-3} s^{-1}.

The reaction of PPE (8.9 μM) with 7-amino-4-chloro-3-methoxyisocoumarin (**2**) (0.031 mM, 0.1 M phosphate buffer,

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(5) 7-Amino-3-methoxyisocoumarin (**3**) was prepared by catalytic hydrogenation of 3-methoxy-7-nitroisocoumarin (500 mg) using Pd-C in MeOH for 45 min at 25 °C: 250 mg from MeOH/isopropyl ether, mp 160-161 °C dec. The 3-methoxy-7-nitroisocoumarin was prepared by treating methyl (4-nitro-2-carboxylphenyl)acetate (2.0 g) with $(CF_3CO)_2O$ (1.4 mL) in CH_2Cl_2 at 25 °C for 16 h: 1.8 g from methylene chloride/petroleum ether, mp 148-150 °C dec. Satisfactory NMR, IR, UV, mass spectra, and elemental analysis were obtained for all compounds.
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