Hydrogen Atom Abstraction Reactions in Organic Synthesis. A Formal Total Synthesis of Racemic Podophyllotoxin

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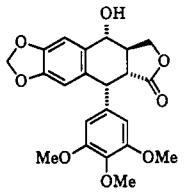
The key step in a synthesis of 1 was a tandem photoenolization/Diels–Alder reaction to produce 11. Hydrolysis of the acetal and ester followed by oxidation afforded 15, an advanced intermediate in the Meyers synthesis of 1.

The class of molecules containing podophyllotoxin (1), picropodophyllin (2), and etoposide, a semisynthetic analogue, have attracted considerable synthetic attention as a consequence of the potent biological activity exhibited by the latter compound. Podophyllotoxin inhibits mitosis



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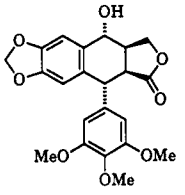

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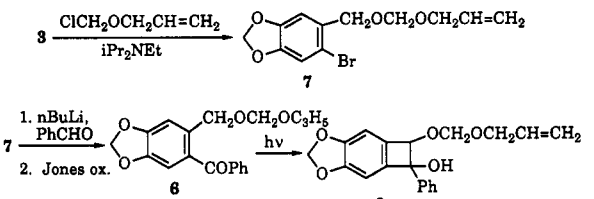
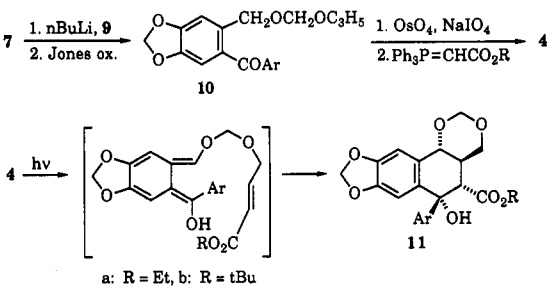
and other microtubule-dependent processes. Both the chemical and the biological properties of 1 have been reviewed.[1] Of significance to synthetic planning is that the trimethoxyphenyl group in 1 is axial and that the trans-fused lactone is prone to epimerization.

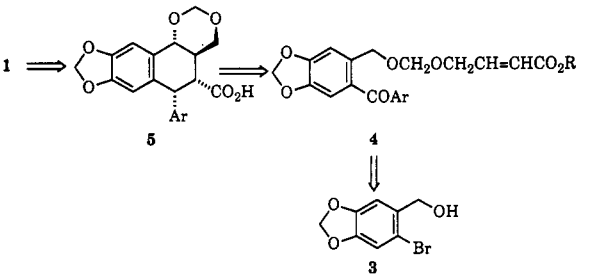
A number of syntheses of 1 or its isomers have been recorded.[2] Many researchers have utilized Friedel–Crafts or cycloaddition strategies. Most closely related to the research described herein are a total synthesis of Durst[3b] and synthetic approaches by Charlton,[4] Jung,[5] and Saa.[2l] Durst's synthesis featured an intramolecular cycloaddition of the carbamate of a benzocyclobutenol to efficiently construct the carbon atom framework. Charlton utilized a photoenolization followed by an intermolecular Diels–Alder reaction as a key step in his route to analogues of 1. Jung envisioned an intramolecular Diels–Alder reaction of an acylated benzocyclobutenol as the key step in his synthetic plan. Unfortunately, his innovative plan was thwarted by the instability of the requisite precursor. Saa recently reported the preparation of simple aryl-substituted benzocyclobutenols from the photolysis of benzophenones. In the context of our research involving intramolecular hydrogen atom abstraction reactions, we explored the strategy depicted below in the retrosynthetic analysis and report herein a formal total synthesis of racemic podophyllotoxin.

Scheme I



Scheme II





a: R = Et, b: R = tBu

The photoenolization reaction depicted above proceeds by the abstraction of a benzylic hydrogen atom by the excited state of the diaryl ketone.[6] The ketone also contains a benzylic ether. Since there was also ample precedent for the photochemically induced fragmentation of a benzylic substituent (particularly if the excited state has π–π^* character), the success of this key step was uncertain.[7] The key step could be readily examined. The model system 6 was constructed from alcohol 3[8] in 20% overall yield by reaction with chloromethyl allyl ether and base (to form acetal 7) followed by synthesis of the benzophenone subunit by metalation, reaction of the resulting aryllithium with benzaldehyde, and Jones oxidation.

(1) Doyle, T. W., In *Etoposide (VP-16) Current Status and New Developments*; Academic Press: New York, 1984.

(2) (a) Gensler, W. J.; Gatsonis, C. D. *J. Org. Chem.* **1966**, *31*, 4004. (b) Kende, A. W.; Liebeskind, L. S.; Mills, J. E.; Rutledge, P. S.; Curran, D. P. *J. Am. Chem. Soc.* **1977**, *99*, 7082. (c) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, *1*, 271. (d) Van der Eycken, J.; De Clercq, P.; Vandewalle, M. *Tetrahedron Lett.* **1985**, *26*, 3871. (e) Vyas, D. M.; Skonezny, P. M.; Jenks, T. A.; Doyle, T. W. *Tetrahedron Lett.* **1986**, *27*, 3099. (f) Macdonald, D. I.; Durst, T. *J. Org. Chem.* **1988**, *53*, 3663. (g) Kaneko, T.; Wong, H.; *Tetrahedron Lett.* **1987**, *28*, 517. (h) Jones, D. W.; Thompson, A. M. *J. Chem. Soc., Chem. Commun.* **1987**, 1797. (i) Andrews, R. C.; Teague, S. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7854. (j) Rajapaska, D.; Rodrigo, R. *J. Am. Chem. Soc.* **1981**, *103*, 6208. (k) Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron Lett.*, **1990**, *31*, 261. (l) Coll, G.; Costa, A.; Deya, P. M.; Saa, J. M. *Tetrahedron Lett.*, **1991**, *32*, 263. (m) Van Speybroeck, R.; Van der Eycken, J.; Vandewalle, M. *Tetrahedron*, **1991**, *47*, 4675.

(3) (a) Glinski, M. B.; Durst, T. *Can. J. Chem.* **1983**, *61*, 573. (b) Macdonald, D. I; Durst, T. *J. Org. Chem.* **1988**, *53*, 3663.

(4) Charlton, J. L.; Plourde, L.; Koh, K.; Secco, A. S. *Can. J. Chem.* **1990**, *68*, 2022.

(5) (a) Jung, M. E.; Lam, P. Y.-S.; Mansuri, M. M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087. (b) Jung, M. E.; Lowen, G. T. *Tetrahedron* **1986**, *27*, 5319.

(6) Arnold, B. J.; Mellows, S. M.; Sammes, P. G.; Wallace, T. W. *J. Chem. Soc., Perkins Trans. 1* **1974**, 401.

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(8) Mann, J.; Piper, S. E.; Yeung, L. K. P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2081.

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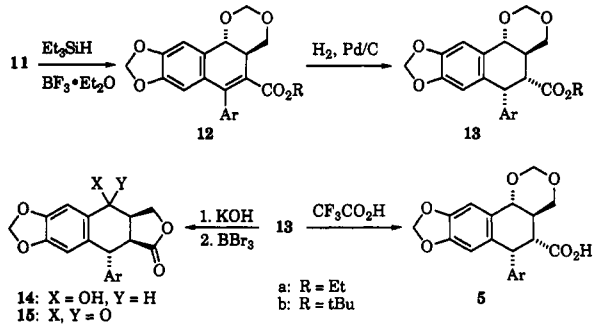
Scheme III



Irradiation of ketone **6** in a Rayonet reactor provided the unstable benzocyclobutenol **8** as a mixture of diastereomers, a clear indication that the photoenolization reaction would predominate over fragmentation. Although the photoenolization reaction was not followed by an intramolecular Diels–Alder reaction, we knew that the likelihood of a tandem photoenolization reaction/Diels–Alder reaction was much better with α,β-unsaturated ester **4**.

Ketone **4** was prepared as shown in Scheme II. The acetal **7** was metalated, and the resulting aryllithium was reacted with 3,4,5-trimethoxybenzaldehyde (**9**). The resulting alcohol was immediately oxidized with Jones reagent to produce ketone **10** in 58% yield from **7**. Oxidation of the allyl group followed by a Wittig reaction on the newly formed aldehyde generated ketone **4a** in 41% yield. Irradiation of **4a** using the conditions described previously afforded hydroxy ester **11a** in 60% yield. We did not isolate any benzocyclobutene-containing products. NMR decoupling experiments indicated that the substituents at C-1, C-2, and C-3 were equatorial. Assuming the currently accepted stereochemical outcome of the photoenolization reaction and assuming a concerted cycloaddition, the tertiary alcohol should be syn to the ester group.

The conversion of **11a** to **1** required removal of the hydroxyl group and the hydrolysis of the ester and acetal groups. We initially studied the reductive cleavage of the tertiary alcohol using Raney nickel. While this reagent had been used by Rodrigo to cleave a closely related ether,[9] when **11a** was subjected to the Rodrigo conditions, it was recovered in high yield. An attempted ionic hydrogenation using triethylsilane and BF_3–Et_2O gave the dihydronaphthalene **12a** in 90% yield. These conditions afforded the best yield of **12a**, in part because the reductive conditions suppressed the undesired oxidation to the naphthalene nucleus. Catalytic hydrogenation of **12a** furnished ester **13a** in 100% yield.

In order to ascertain the facial selectivity of the hydrogenation reaction, we attempted the iridium-based directed hydrogenation procedures developed by Stork,[10] Crabtree,[11] and Schultz;[12] however, **12a** did not react under these conditions. The stereochemistry of **13a**, initially assigned on the basis of NMR analysis, was later supported by an X-ray determination of acid **5**. Interestingly, the catalytic hydrogenation of a related dihydronaphthalene was much less stereoselective.[2k]

Base-mediated hydrolysis of **13a** afforded an acid which was treated with BBr_3 to form lactone **14** in 18% yield from **13a**. The structure of **14** was determined by X-ray spectroscopy. It showed that the product of the two-step sequence was the undesired cis-lactone. Lactone **14** could be converted into keto lactone **15** using the PCC oxidation. Since compound **15** has been converted into **1** by Meyers, the synthesis of **15** thus constitutes a formal total synthesis of **1**. Our 300-MHz NMR spectrum of **15** was identical to that reported by Meyers.[2i]

We suspected that epimerization of the ester moiety had occurred during the hydrolysis of **13a**. Therefore, we prepared *tert*-butyl ester **4b** from **10** in 59% yield. Irradiation of **4b** afforded hydroxy ester **11b** in 51% yield. Using the same conditions that we had employed for the ethyl ester series, we converted **11b** into **13b** in 72% yield. Acid-mediated hydrolysis of **13b** produced acid **5** in 89% yield. The structure of **5** was confirmed by X-ray spectroscopy.

We have demonstrated that a tandem photoenolization/Diels–Alder sequence is capable of rapidly constructing the tetrahydronaphthalene subunit of **1**. The deoxygenation of the resulting tertiary alcohol was accomplished with excellent stereoselectivity. The preparation of **15** constitutes a formal total synthesis of **1**, since Meyers has converted **15** into **1** by an efficient four-step sequence.[2i]

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes/ethyl acetate solvent mixtures for TLC and silica gel flash chromatography (sgc). The purity of all title compounds was determined to be >95% by 300-MHz proton NMR and/or elemental analyses.

5-Bromo-6-(2,4-dioxa-6-heptenyl)-1,3-benzodioxole (7). To alcohol **3**[8] (1.50 g, 6.54 mmol) in 60 mL of CH_2Cl_2 was added diisopropylethylamine (1.12 g, 13.0 mmol) and chloromethyl allyl ether (1.05 g, 9.84 mmol). The mixture was stirred at rt for 10 h. The solution was washed with H_2O and was dried over Na_2SO_4. The solvent was removed in vacuo. The residue was separated by sgc (H:EA = 6:1) to give 0.46 g (71% yield) of **7** as a colorless oil.

Compound **7**: ^1H NMR ($CDCl_3$) δ 6.99 (s, 1 H), 5.95 (s, 1 H), 6.03–5.87 (m, 3 H), 5.35–5.18 (m, 2 H), 4.80 (s, 2 H), 4.58 (s, 2 H), 4.12 (m, 2 H); IR (film) 3080, 1502, 1479 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 147.49, 147.11, 134.09, 130.32, 118.88, 112.38, 108.18, 101.52, 88.89, 80.84, 68.69, 68.01; HRMS m/z for $C_{12}H_{13}BrO_4$ calcd 299.9997, found 299.9993; TLC (Et_2O:H:EtOH = 20:10:1) R_f = 0.74.

5-Benzoyl-6-(2,4-dioxa-6-heptenyl)-1,3-benzodioxole (6). To **7** (0.46 g, 1.53 mmol) in 10 mL of THF under argon at −78 °C was added *n*-BuLi (0.74 mL, 1.84 mmol, 2.50 M in hexane) dropwise with stirring. The solution was warmed to rt for 0.5 h and was cooled to −78 °C. Benzaldehyde (0.24 mL, 2.30 mmol) was added to the solution dropwise at −78 °C. The solution was then stirred at −78 °C for 2 h, quenched at −78 °C by the addition of water, and warmed to rt. The solution was poured into 100 mL of Et_2O. The organic layer was washed with brine, was dried over Na_2SO_4, and was concentrated in vacuo. The residue was separated by sgc (H:EA = 6:1) to give the alcohol (0.20 g, 40% yield) as a colorless liquid.

The above alcohol (72 mg, 0.220 mmol) was dissolved in 10 mL of acetone/ether (v/v = 1/10). Jones reagent (8 N, 0.14 mL, 1.10 mmol) was added dropwise at 0 °C with stirring. The mixture was stirred at 0 °C for 0.5 h and then was washed with brine until the brine washings were clear. The solution was dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was separated by sgc (H:EA = 6:1) to afford 51 mg (71% yield) of compound **6** as a colorless oil.

Compound **6**: ^1H NMR (C_6D_6) δ 8.20 (s, 1 H), 8.17 (d, J = 1.5 Hz, 1 H), 7.57–7.40 (m, 5 H), 6.13 (m, 1 H), 5.68 (s, 2 H), 5.80–5.52 (m, 1 H), 5.40–5.35 (m, 1 H), 5.23 (s, 2 H), 4.91 (s, 2 H), 4.26 (m, 2 H); IR (film) 2980 1659, 1612 cm^{-1}; TLC (H:EA = 6:1); R_f = 0.25.

5-(3,4,5-Trimethoxybenzoyl)-6-(2,4-dioxa-6-heptenyl)-1,3-benzodioxole (10). To **7** (9.76 g, 32.4 mmol) in 150 mL of THF at −78 °C under argon was added *n*-BuLi (16.8 mL, 38.9 mmol,

(9) Rajapaksa, D.; Rodrigo, R. *J. Am. Chem. Soc.* **1981**, *103*, 6208.
(10) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072.
(11) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655.
(12) Schultz, A. G.; McCloskey, P. J. *J. Org. Chem.* **1985**, *50*, 5907.

2.32 M in hexane) dropwise with stirring. The mixture was warmed to 0 °C for 0.5 h and was cooled to −78 °C. Aldehyde **9** (9.54 g, 48.6 mmol) in 30 mL of THF was added to the above solution. The mixture was stirred at −78 °C for 2 h and was warmed to 0 °C. Water was added to quench the reaction. The solution was poured into 300 mL of Et_2O which was washed with brine and was dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was separated by sgc (H:EA = 3:1) to afford 8.45 g of the alcohol.

The above alcohol (8.45 g, 20.2 mmol) was dissolved in 100 mL of acetone. Jones reagent (8 N, 12.6 mL, 101 mmol) was added dropwise with stirring at 0 °C. After 0.5 h, the mixture was poured into 300 mL of Et_2O and was washed with brine until the brine washings were colorless. The solvent was removed in vacuo, and the residue was separated by sgc (H:EA = 4:1) to afford 7.80 g (58% yield) of **10** as a slightly yellow liquid.

Compound **10**: ^1H NMR ($CDCl_3$) δ 7.07 (s, 1 H), 7.02 (s, 2 H), 6.86 (s, 1 H), 6.02 (s, 2 H), 5.82 (m, 1 H), 5.20 (d, J = 15.6 Hz, 1 H), 5.12 (d, J = 10.2 Hz, 1 H), 4.65 (s, 2 H), 4.61 (s, 2 H), 3.98 (d, J = 5.70 Hz, 2 H), 3.91 (s, 3 H), 3.83 (s, 6 H); IR (film) 2941, 2839, 1659 cm^{-1}; HRMS m/z for $C_{22}H_{24}O_8$ calcd 416.147 12, found 416.147 01; TLC (H:EA = 4:1) R_f = 0.20.

Ethyl (*E*)-4-[[[5-(3,4,5-Trimethoxybenzoyl)-1,3-benzodioxol-6-yl]methoxy]methoxy]-2-butenoate (4a). To **10** (0.523 g, 1.26 mmol) in 30 mL of acetone/H_2O (v/v = 1/1) was added $NaIO_4$ (0.593 g, 2.77 mmol) and OsO_4 (6.40 mg, 0.0252 mmol). The mixture was stirred at rt for 16 h and was poured into 100 mL of Et_2O. The organic layer was washed with brine and was dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was not purified but was used directly for next step.

The residue from the above procedure was dissolved in 30 mL of CH_2Cl_2. Ethyl triphenylphosphoranylideneacetate (0.482 g, 1.38 mmol) was added, and the mixture was stirred at rt for 12 h. The solvent was removed, and the residue was purified by sgc (H:EA = 4:1) to give 0.25 g (41% yield) of **4a** as a slightly yellow liquid along with 58 mg of the Z-product (E:Z = 4.3:1).

Compound **4a**: ^1H NMR (C_6D_6) δ 7.22 (s, 2 H), 7.07 (s, 1 H), 6.92 (s, 1 H), 6.90–6.82 (m, 1 H), 6.17–6.10 (m, 1 H), 5.28 (s, 2 H), 4.77 (s, 2 H), 4.40 (s, 2 H), 3.99 (q, J = 7.2 Hz, 2 H), 3.80 (s, 3 H), 3.74 (q, J = 2.1 Hz, 2 H), 3.29 (s, 6 H), 0.95 (t, J = 7.2 Hz, 3 H); IR (film) 2941, 2905, 1718, 1659 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 185.23, 165.96, 152.75, 149.45, 148.52, 143.00, 133.08, 192.72, 191.19, 121.18, 108.30, 107.49, 101.65, 84.48, 87.18, 85.87, 80.80, 80.22, 58.19, 14.11; HRMS m/z for $C_{25}H_{28}O_{10}$ calcd 488.1673, found 488.1683; TLC (Et_2O:H:EtOH = 20:10:1) R_f = 0.55.

Ethyl (4aα,5α,6β,11bα)-4a,5,6,11b-Tetrahydro-6-hydroxy-6-(3,4,5-trimethoxyphenyl)-4*H*-[1,3]benzodioxolo[5,6-*h*]-1,3-benzodioxin-5-carboxylate (11a). Compound **4a** (0.695 g, 1.42 mmol) in 50 mL of benzene was degassed with argon for 10 min and was irradiated in a Pyrex tube in a Rayonet reactor with 350-nm light for 4 h. The solvent was removed in vacuo, and the residue was separated by sgc (H:EA = 4:1) to afford 0.414 g (60% yield) of **11a** as a white solid.

Compound **11a**: ^1H NMR ($CDCl_3$) δ 6.99 (s, 1 H), 6.53 (s, 2 H), 6.36 (s, 1 H), 5.90 (dd, J = 1.2 Hz, 9.6 Hz, 2 H), 5.30 (d, J = 6.0 Hz, 1 H), 4.98 (s, 1 H), 4.97 (d, J = 6.9 Hz, 1 H), 4.56 (d, J = 8.7 Hz, 1 H), 4.02 (q, J = 7.2 Hz, 2 H), 3.84 (s, 3 H), 3.81 (s, 6 H), 3.65 (t, J = 10.5 Hz, 1 H), 2.66 (m, 2 H), 1.05 (t, J = 7.2 Hz, 3 H); IR (film) 3520, 2941, 1730 cm^{-1}; m/z for $C_{25}H_{28}O_{10}$ calcd 488, found 488 CI MS; TLC (Et_2O:H:EtOH = 20:10:1) R_f = 0.38; mp 195–196 °C.

Ethyl (4aα,11bα)-4a,11b-Dihydro-6-(3,4,5-trimethoxyphenyl)-4*H*-[1,3]benzodioxolo[5,6-*h*]-1,3-benzodioxin-5-carboxylate (12a). To **11a** (0.147 g, 0.301 mmol) in 30 mL of CH_2Cl_2 at −78 °C under argon was added Et_3SiH (0.072 mL, 0.451 mmol) in one portion followed by BF_3·OEt_2 (0.041 mL, 0.331 mmol) dropwise. The mixture was stirred at −78 °C and was allowed to warm to rt overnight. Dilute $NaHCO_3$ (15 mL) was added, and the solution was washed with brine and was dried over Na_2SO_4. The solvent was removed in vacuo to give 0.127 g (90% yield) of **12a** as a white solid.

Compound **12a**: ^1H NMR ($CDCl_3$) δ 7.09 (s, 1 H), 6.38 (s, 2 H), 6.36 (s, 1 H), 5.95 (s, 2 H), 5.30 (d, J = 6.3 Hz, 1 H), 4.87 (d, J = 6.3 Hz, 1 H), 4.63 (d, J = 13.8 Hz, 1 H), 4.52 (dd, J = 4.8 Hz, 11.1 Hz, 1 H), 3.92 (q, J = 6.9 Hz, 2 H), 3.88 (s, 3 H), 3.81 (s, 6 H), 3.66 (t, J = 11.1 Hz, 1 H), 3.08 (m, 1 H), 0.90 (t, J = 7.2 Hz, 3 H); IR (film) 2924, 2853, 1703, 1583 cm^{-1}; TLC (Et_2O:H:EtOH = 20:10:1) R_f = 0.50; mp 95–96.5 °C.

Ethyl (4aα,5α,6β,11bα)-4a,5,6,11b-Tetrahydro-6-(3,4,5-trimethoxyphenyl)-4*H*-[1,3]benzodioxolo[5,6-*h*]-1,3-benzodioxin-5-carboxylate (13a). Ester **12a** (0.106 g, 0.226 mmol) in 30 mL of EtOH/THF (v/v = 1/1) was hydrogenated under 1 atm of H_2 with 10% Pd/C (0.030 g) for 5 days. The mixture was purified via sgc using CH_2Cl_2 to afford 0.106 g (100% yield) of **13** as a white solid.

Compound **13a**: ^1H NMR (C_6D_6) δ 7.01 (s, 1 H), 6.35 (s, 1 H), 6.20 (s, 2 H), 5.92 (dd, J = 1.2, 1.2 Hz, 2 H), 5.30 (d, J = 6.0 Hz, 1 H), 4.93 (d, J = 6.0 Hz, 1 H), 4.42–4.33 (m, 3 H), 3.92–3.81 (m, 2 H), 3.80 (s, 3 H), 3.76 (s, 6 H), 3.43 (t, J = 10.5 Hz, 1 H), 2.91 (m, 1 H), 2.57 (m, 1 H), 1.05 (t, J = 7.2 Hz, 3 H); IR (film) 3055, 2930, 2856, 1713 cm^{-1}; MS (CI MS) m/z for $C_{25}H_{28}O_9$ 472; TLC (Et_2O:H:EtOH = 20:10:1) R_f = 0.46; mp 165–166 °C.

(5α,5aα,8aβ,9α)-5,5a,8a,9-Tetrahydro-9-hydroxy-5-(3,4,5-trimethoxyphenyl)furo[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-6(5a*H*)-one (14). Compound **13a** (0.250 g, 0.530 mmol) and 20 mL of 0.1 M NaOH dioxane/H_2O (v/v = 1/1) were heated at reflux for 6 h and cooled to rt. Cold 2 N HCl was added to the solution to adjust the pH to 3.0. The solution was extracted with Et_2O and was dried over Na_2SO_4, and the solvent was removed in vacuo to afford 0.111 g of crude acid which was not purified but was used directly for the next step.

To the crude acid (32 mg, 0.072 mmol) in 15 mL of CH_2Cl_2 was added BBr_3 (0.233 mL of a 1 M solution in CH_2Cl_2, 0.233 mmol) dropwise at −78 °C under argon. The mixture was stirred for 5 h and was quenched with $NaHCO_3$ at −78 °C. The solution was warmed to rt, was poured into 30 mL of CH_2Cl_2, was washed with brine, and was dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was separated by sgc (Et_2O:H:EtOH = 20:10:1) to afford 10.8 mg of **14** as a white solid (18% yield of **14** from **13a**).

Compound **14**: ^1H NMR ($CDCl_3$) δ 7.00 (s, 1 H), 6.60 (s, 1 H), 6.36 (s, 2 H), 5.97 (dd, J = 1.2, 1.2 Hz, 2 H), 4.83 (d, J = 5.1 Hz, 1 H), 4.45 (d, J = 3.0 Hz, 1 H), 4.37 (d, J = 5.4 Hz, 1 H), 4.35 (d, J = 2.1 Hz, 1 H), 3.83 (s, 3 H), 3.79 (s, 6 H), 3.44 (dd, J = 3.6 Hz, 10.8 Hz, 1 H), 3.17 (m, 1 H); IR (CH_2Cl_2) 2940, 1762, 1588 cm^{-1}; HRMS m/z for $C_{22}H_{22}O_8$ calcd 414.131 47, found 414.131 38; TLC (Et_2O:H:EtOH = 20:10:1) R_f = 0.20; mp 184–185.2 °C.

(5α,5aα,8aβ)-5,5a,8a,9-Tetrahydro-5-(3,4,5-trimethoxyphenyl)furo[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxole-6(5a*H*),9(8a*H*)-dione (15). To a suspension of PCC (20 mg, 0.23 mmol) and Celite (10 mg) in 0.5 mL of CH_2Cl_2 at −10 °C was added dropwise a solution of **14** (5.6 mg, 0.14 mmol) in 0.5 mL of CH_2Cl_2. The suspension was allowed to slowly warm to rt over 20 h. The suspension was directly purified by sgc using 20:10:1 Et_2O:H:EtOH to afford 4.0 mg (72% yield) of compound **15** as a white solid.

Compound **15**: NMR ($CDCl_3$) δ 7.50 (s, 1 H), 6.69 (s, 1 H), 6.23 (s, 2 H), 6.05 (d, J = 2.4 Hz, 2 H), 4.77 (d, J = 9.3 Hz, 1 H), 4.69 (s, 1 H), 4.35 (m, 1 H), 3.80 (s, 3 H), 3.75 (s, 6 H), 3.31 (s, 1 H), 3.30 (d, J = 1.5 Hz, 1 H); IR (film) 2916, 1768, 1665, 1478 cm^{-1}; HRMS m/z for $C_{22}H_{20}O_8$ calcd 412.1158, found 412.1160; TLC (Et_2O:H:EtOH 20:10:1) R_f = 0.27; mp 94–95 °C.

***tert*-Butyl (*E*)-4-[[[5-(3,4,5-Trimethoxybenzoyl)-1,3-benzodioxol-6-yl]methoxy]methoxy]-2-butenoate (4b).** To **10** (0.734 g, 1.76 mmol) in 40 mL of acetone/H_2O (v/v = 1/1) was added $NaIO_4$ (0.830 g, 3.88 mmol) and OsO_4 (8.95 mg, 0.0352 mmol). The mixture was stirred at rt for 16 h and then was extracted by Et_2O and was dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was used for next step.

The above residue was dissolved in 25 mL of CH_2Cl_2. *tert*-Butyl triphenylphosphoranylideneacetate (0.73 g, 1.94 mmol) was added, and the mixture was stirred at rt for 12 h. The solvent was removed in vacuo, and the residue was separated by sgc (H:EA = 4:1) to afford 0.540 g (59% yield) of compound **4b** as a slightly yellow oil. It contained approximately 2% of the Z-product.

Compound **4b**: NMR (C_6D_6) δ 7.21 (s, 2 H), 7.05 (s, 1 H), 6.91 (s, 1 H), 6.82 (m, 1 H), 6.10 (m, 1 H), 5.27 (s, 2 H), 4.77 (s, 2 H), 4.39 (s, 2 H), 3.80 (s, 3 H), 3.74 (m, 2 H), 3.28 (s, 6 H), 1.38 (s, 9 H); IR (film) 3057, 2973, 2939, 1711, 1659 cm^{-1}; HRMS: m/z for $C_{27}H_{32}O_{10}$ calcd 516.199 55, found 516.198 96; TLC (Et_2O:H:EtOH = 20:10:1) R_f = 0.67.

***tert*-Butyl (4aα,5α,6β,11bα)-4a,5,6,11b-Tetrahydro-6-hydroxy-6-(3,4,5-trimethoxyphenyl)-4*H*-[1,3]benzodioxolo-**

[5,6-*h*]-1,3-benzodioxin-5-carboxylate (11b). Compound **4b** (1.02 g, 1.98 mmol) in 200 mL of benzene was degassed for 10 min and then was irradiated in a Pyrex tube in a Rayonet reactor with 350-nm light for 9 h. The solvent was removed in vacuo, and the residue was separated by sgc (H:EA = 4:1) to afford 0.520 g (51% yield) of compound **11b** as a white solid.

Compound **11b**: ^{1}H NMR ($CDCl_3$) δ 6.99 (s, 1 H), 6.55 (s, 2 H), 6.38 (s, 1 H), 5.91 (d, J = 1.2 Hz, 1 H), 5.88 (d, J = 1.2 Hz, 1 H), 5.31 (d, J = 6.3 Hz, 1 H), 5.18 (s, 1 H), 4.97 (d, J = 6.3 Hz, 1 H), 4.56 (d, J = 9.0 Hz, 1 H), 4.05 (dd, J = 10.8 Hz, 3.6 Hz, 1 H), 3.84 (s, 3 H), 3.81 (s, 6 H), 3.65 (t, J = 10.2 Hz, 1 H), 2.94–2.82 (m, 2 H), 1.25 (s, 9 H); IR (film) 3385, 1695 cm^{-1}; HRMS m/z for $C_{27}H_{32}O_{10}$ calcd 516.199 55, found 516.199 15; TLC (Et_2O:H:EtOH = 20:10:1) R_f = 0.65; mp 209–210.5 °C. Anal. Calcd: C, 62.78; H, 6.24. Found: C, 63.37; H, 6.61.

***tert*-Butyl (4aα,11bα)-4a,11b-Dihydro-6-(3,4,5-trimethoxyphenyl)-4*H*-[1,3]benzodioxolo[5,6-*h*]-1,3-benzodioxin-5-carboxylate (12b).** To **11b** (0.356 g, 0.688 mmol) in 150 mL of CH_2Cl_2 under argon was added Et_3SiH (0.16 mL, 1.03 mmol) in one portion followed by BF_3·Et_2O (0.093 mL, 0.76 mmol) dropwise at −78 °C. The mixture was then stirred for 1.5 h and was quenched with 20 mL of H_2O at −78 °C. The solution was allowed to slowly warm to rt, was washed with brine, and was dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by sgc (H:EA = 4:1) to afford 0.257 g (75% yield) of **12b** as a white solid.

Compound **12b**: ^{1}H NMR ($CDCl_3$) δ 7.08 (s, 1 H), 6.44 (s, 1 H), 6.33 (d, J = 4.8 Hz, 2 H), 5.95 (s, 2 H), 5.31 (d, J = 6.0 Hz, 1 H), 4.89 (d, J = 6.3 Hz, 1 H), 4.65 (d, J = 13.8 Hz, 1 H), 4.55 (dd, J = 10.8 Hz, 4.8 Hz, 1 H), 3.89 (s, 3 H), 3.80 (s, 6 H), 3.69 (t, J = 10.8 Hz, 1 H), 3.07 (m, 1 H), 1.19 (s, 9 H); IR (film) 2924, 2853, 1699 cm^{-1}; HRMS m/z for $C_{27}H_{30}O_9$ calcd 498.188 98, found 498.187 62; TLC (Et_2O:H:EtOH = 20:10:1) R_f = 0.67; mp 186–187 °C.

***tert*-Butyl (4aα,5α,6β,11bα)-4a,5,6,11b-Tetrahydro-6-(3,4,5-trimethoxyphenyl)-4*H*-[1,3]benzodioxolo[5,6-*h*]-1,3-benzodioxin-5-carboxylate (13b).** Compound **12b** (0.103 g, 0.21 mmol) in 100 mL of EtOH/THF (v/v = 1/1) was hydrogenated at 1 atm of H_2 with 10% Pd/C (0.030 g) for 4 days. The solution was then purified by sgc (CH_2Cl_2) to afford 0.094 g (91% yield) of compound **13b** as a white solid.

Compound **13b**: ^{1}H NMR ($CDCl_3$) δ 6.99 (s, 1 H), 6.34 (s, 1 H), 6.28 (s, 2 H), 5.90 (s, 2 H), 5.31 (d, J = 6.3 Hz, 1 H), 4.94 (d, J = 6.0 Hz, 1 H), 4.41 (dd, J = 3.9, 10.8 Hz, 1 H), 4.33 (s, 1 H), 4.31 (s, 1 H), 3.80 (s, 3 H), 3.77 (s, 6 H), 3.46 (t, J = 10.8 Hz, 1 H), 3.79 (dd, J = 6.9, 12.3 Hz, 1 H), 2.55 (m, 1 H), 1.18 (s, 9 H); IR (film) 2939, 2837, 1695 cm^{-1}; HRMS m/z for $C_{27}H_{32}O_9$ calcd 500.204 63, found 500.204 10; ^{13}C NMR ($CDCl_3$) δ 171.63, 152.34, 147.33, 146.92, 141.00, 136.66, 132.89, 128.61, 108.66, 103.65, 100.34, 93.90, 82.41, 78.95, 76.59, 75.43, 68.56, 60.46, 55.88, 52.59, 36.37, 27.42; TLC (H:EA = 3:1) R_f = 0.45; mp 158.2–159 °C.

(4aα,5α,6β,11bα)-4a,5,6,11b-Tetrahydro-6-(3,4,5-trimethoxyphenyl)-4*H*-[1,3]benzodioxolo[5,6-*h*]-1,3benzodioxin-5-carboxylic Acid (5). To **13b** (93.3 mg, 0.187 mmol) was added 15 mL of 0.5M CF_3COOH in CH_2Cl_2. The mixture was stirred for 30 h, and the solvent was removed in vacuo. The residue was purified by sgc (H:EA = 2:1) to give 73.8 mg (89% yield) of **5** as a white solid.

Compound **5**: ^{1}H NMR ($CDCl_3$) δ 7.01 (s, 1 H), 6.35 (s, 1 H), 6.23 (s, 2 H), 5.92 (dd, J = 1.0, 1.0 Hz, 2 H), 5.29 (d, J = 6.0 Hz, 1 H), 4.93 (d, J = 6.0 Hz, 1 H), 4.44–4.34 (m, 3 H), 3.79 (s, 3 H), 3.72 (s, 6 H), 3.42 (t, J = 10.5 Hz, 1 H), 2.91 (dd, J = 12.3, 6.6 Hz, 1 H), 2.52 (m, 1 H); IR (film) 3395, 2930, 1707 cm^{-1}; HRMS m/z for $C_{23}H_{24}O_9$ calcd 444.142 03, found 444.144 82; TLC (Et_2O:H:EtOH = 20:10:1) R_f = 0.36.

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Registry No. (±)-**1**, 77519-37-0; **3**, 6642-34-8; (*E*)-**4a**, 139896-27-8; (*Z*)-**4a**, 139896-28-9; (*E*)-**4b**, 139896-29-0; **5**, 139896-30-3; **6**, 139896-31-4; **6** alcohol, 139896-32-5; **7**, 139896-33-6; **9**, 86-81-7; **10**, 139896-34-7; **10** alcohol, 139896-35-8; **11a**, 139896-36-9; **11b**, 139896-37-0; **12a**, 139896-38-1; **12b**, 139896-39-2; **13a**, 139896-40-5; **13b**, 139896-41-6; **14**, 77519-38-1; **15**, 64937-82-2; $ClCH_2OCH_2CH{=}CH_2$, 3970-20-5; benzaldehyde, 100-52-7; ethyl triphenylphosphoranylideneacetate, 1099-45-2; *tert*-butyl triphenylphosphoranylideneacetate, 35000-38-5.

Supplementary Material Available: ^{1}H NMR spectra for title compounds and X-ray data for compounds **5** and **14** (28 pages). Ordering information is given on any current masthead page.

Multigram Preparation of 2-Alkylpyrimidines in the Vapor Phase from Carboxylic Acids and 1,3-Diaminopropane over a Dual Catalyst System

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2-Alkylpyrimidines **2** were obtained from cofeeding a carboxylic acid such as pivalic acid (**3a**) or propionic acid (**3b**) and 1,3-diaminopropane (**4**) over first an alumina catalyst at 250–290 °C and second a palladium dehydrogenation catalyst at 300–340 °C to give **2** directly in 56–68% overall yields. On the alumina bed, initial amidation of organic acid occurs to give the monoacyltrimethylenediamine **5**, followed by ring closure to the tetrahydropyrimidine intermediate **6**. An equilibrium between **5**, **6**, and water is established on the alumina bed, with an apparent equilibrium constant of 53 ± 7 mol/Kg at 290 °C. The high temperature of the alumina bed shifts the equilibrium in favor of **6**, which is directly dehydrogenated to **2** over the palladium catalyst. The method avoids the need to isolate and purify solid intermediates. The presence of low levels of sulfur acts as a strong palladium catalyst deactivator. Gradual decline of palladium catalyst activity was observed due to carbon buildup. No decline in alumina catalyst activity was observed. The continuous process allows for the preparation of multigram quantities of **2** with a laboratory-scale reactor.

2-Alkylpyrimidinyl thiophosphates **1** are known as a general class of insecticides.[1] Particularly effective are compounds bearing a bulky group at the 2-position of the pyrimidine ring, such as an isopropyl,[1] *tert*-butyl,[1] or methylcyclopropyl[2] group, as well as fluoroalkyl groups.[3]

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(3) Reifschneider, W.; Larson, L. U.S. Pat. 4558039, 1985; *Chem. Abstr.* 1986, *104*, 125074z.

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