(q, 3 F), −63.5 (q, 3 F)). The ratio evolved with time, and after 2 h no more **4e** was detected on the ^{19}F NMR spectrum. Then, 5% HCl (25 mL) was added. The mixture was extracted with ether (2 × 20 mL). The organic layer was dried ($MgSO_4$). The solvent was evaporated (20 mmHg), and the residue was bulb-to-bulb distilled (15 mmHg) to give an oil which was crystallized from ethanol (95%) affording **5e** as white crystals (3.01 g, 10.64 mmol, 74%): mp 25.4 °C (lit.[9] mp 26.5–27.5 °C); ^1H NMR (200 MHz) 1.24 (t, 3 H, $^3J_{HH}$ = 7.13 Hz), 1.27–1.36 (m, 2 H), 1.43–1.52 (m, 4 H), 2.24 (m, 2 H), 2.59 (m, 2 H), 3.51 (d, 1 H, $^3J_{HH}$ = 11.03 Hz), 3.70 (d × septuplet, 1 H, $^3J_{HH}$ = 11.03 Hz, $^3J_{HF}$ = 7.82 Hz), 4.17 (q, 2 H, $^3J_{HH}$ = 7.13 Hz); ^{19}F NMR −60.3 (q, 3 F, $^3J_{HF}$ = 7.82 Hz), −63.5 (q, 3 F, $^3J_{HF}$ = 7.82 Hz).

Registry No. **1**, 1513-60-6; **4a**, 58064-40-7; **4b**, 143063-57-4; **4c**, 143063-58-5; **4d**, 143063-59-6; **4e**, 143063-60-9; **5e**, 1763-89-9; $CH_2(CO_2Et)_2$, 105-53-3; PhSH, 108-98-5; piperidine, 110-89-4.

Heterocyclic *o*-Quinodimethanes in Synthesis: A Diels–Alder Approach to Xanthene-Derived Heterocycles

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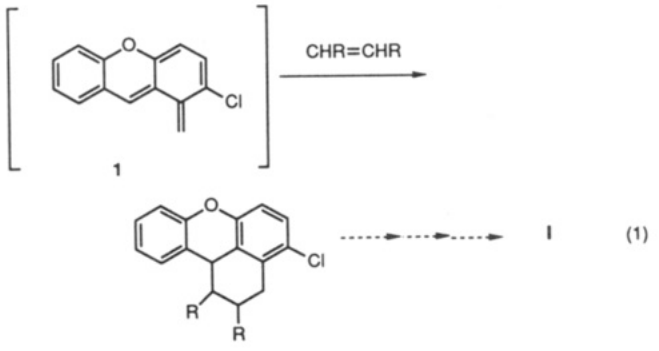
The [4 + 2] cycloaddition strategy has found wide application for six-membered-ring construction in complex systems. Since *o*-quinodimethanes are highly reactive diene components, they have been very effective in this arena for the assembly of polycyclic aromatic compounds.[1] During studies aimed at discovering novel antipsychotic agents,[2] we sought to employ this approach as a general synthetic entry into the ring system exemplified by formula **I**. Thus, *o*-quinodimethane **1** emerged as an attractive intermediate (eq 1). On the basis of literature precedent



for the use of *o*-xylyl dihalides as *o*-quinodimethane precursors,[1] we decided to evaluate the suitability of **2** as a precursor to **1**. Herein, we describe the in situ generation of **1** and trapping experiments with various dienophiles en route to polycyclic molecules.

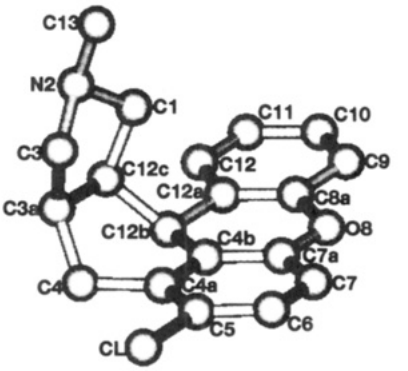


Figure 1. SYBYL drawing of the hydrochloride salt of **14**.

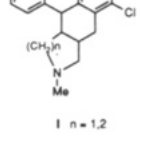
Results and Discussion

Synthesis of **2** is outlined in Scheme I. En route to **2**, a novel approach regiospecifically furnished the previously unreported xanthonecarboxylic acid **3**. Thus, Grignard addition of 2-methoxyphenylmagnesium bromide to 3,6-dichlorophthalic anhydride[3] (**4**) gave keto acid **5**. Demethylation of **5**, followed by cyclization of the resulting phenolic keto acid **6**, according to the conditions of v. dem Knesebeck,[4] furnished xanthone acid **3** in 70% overall yield. Next, we needed to transform the carbonyl and carboxyl functionalities of **3** into benzhydryl and benzyl chlorides, respectively. Since treatment of **3** with BH_3–THF resulted in over-reduction to alcohol **8**,[5] we accessed **7** via $LiAlH_4$ reduction of methyl ester **9**. Treatment of **7** with excess thionyl chloride gave the desired *o*-quinodimethane precursor **2** as a stable, crystalline solid. Scheme II highlights the reactivity of **2** toward various dienophiles.

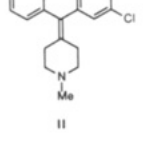
Addition of NaI[6] to a DMF solution of **2** and excess *N*-methylmaleimide at 73 °C gave a major product in 45% yield whose 360-MHz ^1H NMR spectrum was generally consistent with the expected pentacyclic adduct. Definitive proof of structure was obtained through X-ray analysis of **14**, a reduced derivative of **10a** (vide infra, Figure 1). A doublet at 4.33 ppm (J = 5.69 Hz) for H_{12b} and a doublet of doublets at 3.71 ppm (J = 5.66, 9.06 Hz) for H_{12c} led us to assign structure **10a** to the product. This is reflective of Diels–Alder addition in the expected endo mode. An attempt to effect thermal isomerization of **10a** to the exo adduct **10b** (sealed NMR tube, $CDCl_3$, 110 °C) was unsuccessful, while base treatment (DBU) gave a mixture of starting material and aromatized product, **11**.[7] The ap-

(1) For a recent review of *o*-quinodimethanes, see: Charlton, J. L.; Alauddin, M. N. *Tetrahedron* **1987**, *43*, 2873.

(2) For a review of the pharmacology and chemistry of antipsychotic agents see: (a) Kaiser, C.; Setler, P. E. In *Burger's Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; John Wiley & Sons: New York, 1981; Part III, Chapter 56, p 859. Structures embodied by formula **I** were patterned after clopipazan (**II**), a compound which has high affinity for the serotonin (5-HT_2) and dopamine (D_2) receptors; see: (b) Middlemiss, D. N.; Hibert, M.; Fozard, J. R. *Annu. Rep. Med. Chem.* **1986**, *21*, 41.



I n = 1,2



II

(3) Villiger, V. *Chem. Ber.* **1909**, *42*, 3529. For a significant improvement of the preparation of 3,6-dichlorophthalic anhydride, see Experimental Section.

(4) v. dem Knesebeck, A. M.; Ullmann, F. *Chem. Ber.* **1922**, *55*, 306. These authors prepared 2-chloro-7-methylxanthene-1-carboxylic acid by a Friedel–Crafts acylation of *p*-cresol with 3,6-dichlorophthalic anhydride. In this case, regiospecificity clearly is not a problem since the para position is blocked. In our hands, Friedel–Crafts acylation of phenol with **4** gave a separable mixture of (2′-hydroxybenzoyl)- and (4′-hydroxybenzoyl)benzoic acids.

(5) Wechter, W. J. *J. Org. Chem.* **1963**, *28*, 2935. Compound **8** was characterized by NMR only: ^1H NMR (DMSO-d_6) δ 4.43 (s, 2 H), 4.66 (d, 2 H, J = 5.37 Hz), 5.14 (t, 1 H, J = 5.37 Hz), 7.03–7.32 (m, 6 H); mp = 110–111.5 °C (CH_3CN).

(6) Cava, M. P.; Deana, A. A.; Muth, K. *J. Am. Chem. Soc.* **1959**, *81*, 6458.

(7) This reaction was not run with rigorous exclusion of air. Compound **11** was identical by TLC and ^1H NMR to material alternatively produced by DDQ oxidation of **10a** (Experimental Section).

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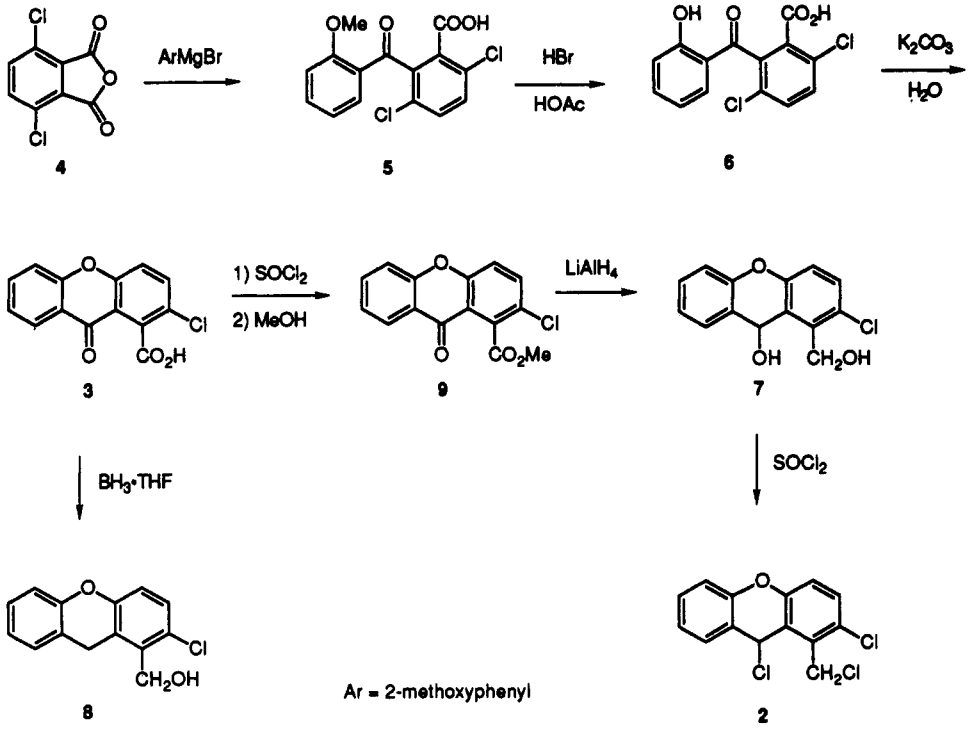
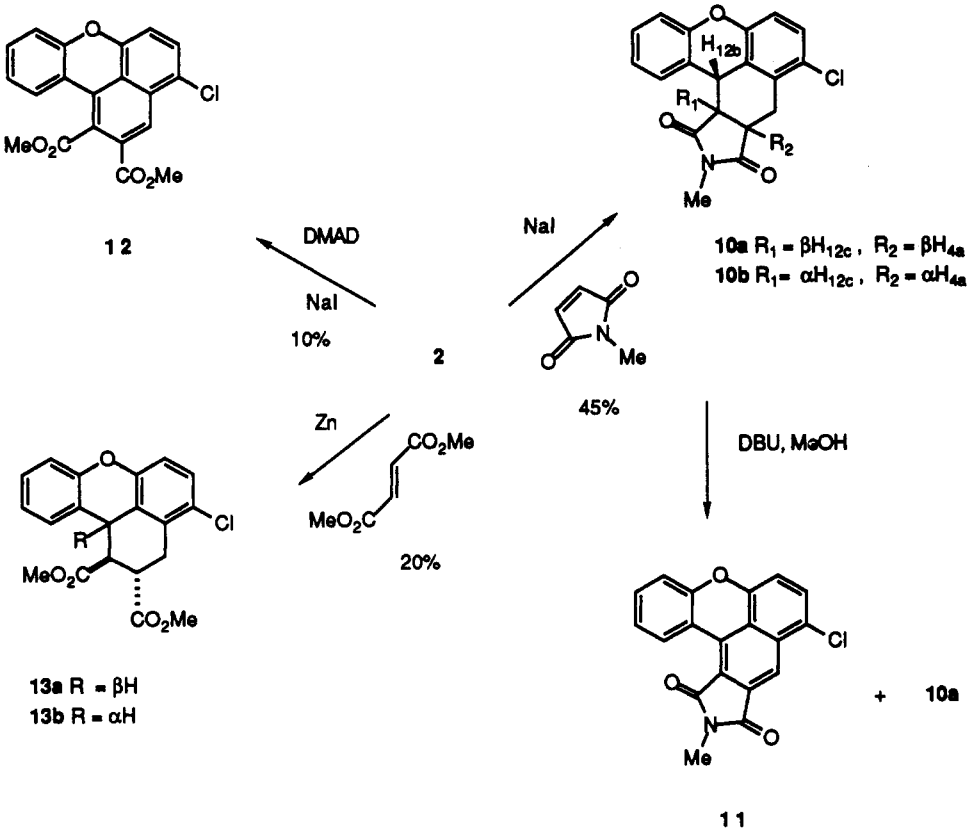
Scheme I



Scheme II



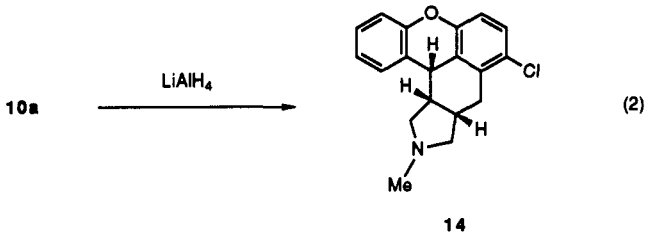
parent thermodynamic stability of **10a** (vs **10b**) is consistent with calculated minimized energies for **10a** and **10b**, which are 3.91 and 7.03 kcal, respectively.[8] Cycloaddition of **2** and dimethyl acetylenedicarboxylate (DMAD) occurred in low yield with concomitant aromatization to give **12**, further underscoring the propensity for the newly formed ring to aromatize. Since the cycloaddition process between **2** and dimethyl fumarate gave complex mixtures using NaI, powdered zinc was used to generate **1**,[9] resulting in a mixture of adducts, **13a** and **13b** (ca. 1.5:1.0). An

(8) Energies were calculated using the MAXIMIN program contained in the SYBYL program package (Tripos Associates, St. Louis, MO).

(9) Boudjouk, P.; Han, B. H. *J. Org. Chem.* **1982**, *47*, 751. The use of ultrasound did not result in a yield enhancement in this case.

attempt to effect cycloaddition between 2 and diethyl azodicarboxylate gave only an intractable, multicomponent mixture.

Further support for the stereochemical course of the cyclization process with *N*-methylmaleimide came from X-ray analysis of isoindole 14, the product of $LiAlH_4$ reduction of **10a** (eq 2). Tetragonal crystals of the hydrochloride salt of 14 (space group $P4_{21c}$–$D4_{2d}$) were solved with a final *R* factor of 0.059. The SYBYL stereodrawing generated from the X-ray coordinates illustrates the syn relationship of the protons on C_{12b}, C_{12c}, and C_{3a} of the hydrochloride salt of 14 (Figure 1). The pyrrolidine ring adopts a standard envelope conformation with a pseudoequatorial *N*-methyl group, the fused cyclohexane ring adopts a boatlike conformation, and the rings of the xanthene tricyclic array are essentially coplanar.[10]



(2)

14

In summary, the novel *o*-quinodimethane 1 was generated via a six-step synthetic sequence starting from 3,6-dichlorophthalic anhydride. Xanthene-derived heterocycles are accessible by a [4 + 2] cycloaddition strategy using intermediate 1.

Experimental Section

General. Proton NMR spectra were recorded on a Bruker AC-300 (300-MHz), AM-360 (360-MHz), or AM-400 (400-MHz) spectrometer with DMSO-d_6 or $CDCl_3$ as solvent and Me_4Si as an internal standard. IR spectra were obtained on a Nicolet 60 SX FT-IR spectrometer with KBr pellets. Mass spectra were taken on a VG Analytical 7070E mass spectrometer. Fast-atom bombardment (FAB) mass spectra were obtained using a thioglycerol matrix. TLC analyses were carried out on 250-μm silica gel plates. Microanalyses were determined by Atlantic Microlab, Inc., Atlanta, GA. X-ray diffraction on 14·HCl was performed by Crystalytics Co., Lincoln, NE.

3,6-Dichlorophthalic Anhydride (4). A stirred mixture of 2.84 kg of H_2SO_4·SO_3 (20–24%), 582.58 g (3.19 mol) of 3-chlorophthalic anhydride,[11] and 3.00 g of pulverized I_2 at 55 °C was treated with chlorine gas at a rapid rate.[3] After an initial exotherm to 62 °C, the chlorination was carried out over 6 h at 60–65 °C. The reaction mixture was poured onto a large excess of ice (22-L vessel) with vigorous mechanical stirring and then allowed to stand at room temperature overnight. The resulting yellow-white solid, consisting mainly of 3,6-dichlorophthalic acid, was collected and washed with 3 N HCl and the filtrate was extracted twice with 2-L portions of diethyl ether. The combined organic extracts were shaken with sufficient 3 N NaOH to convert the mixture of phthalic acids into their corresponding monosodium salts (pH ~1.5–2.0), whereupon a mixture, consisting mainly of 3,4-dichlorophthalic acid monosodium salt[12] (78% by GC), precipitated. The solid was collected, and the filtrate was acidified with excess concentrated HCl to afford an enriched crop of 3,6-dichlorophthalic acid. The initial main crop of crude acid was treated with sufficient 3 N NaOH on a stirring hot plate to obtain a solution of pH ~1.5–2.0. Upon cooling to 30 °C, a white precipitate formed (mainly 3,4-dichlorophthalic acid mono sodium salt, 94% pure) which was collected by filtration.[12] Acidification of the filtrate with excess concentrated HCl gave a second crop of 3,6-dichlorophthalic acid. The 3,6-dichlorophthalic acid crops were combined and heated with 0.75 L of acetic anhydride under reflux for 4 h. Cooling, followed by recrystallization from acetone, furnished 405.7 g (51%, based on 3-chlorophthalic anhydride) of 3,6-dichlorophthalic anhydride; mp 192–194 °C (lit.[4] mp 190–191 °C).

3,6-Dichloro-2-(2-methoxybenzoyl)benzoic Acid (5). A mixture of 17.18 g (0.707 mol) of activated Mg, a crystal of iodine, and 284 mL of anhydrous diethyl ether was heated under reflux until the iodine color was discharged; 139.2 g (0.744 mol) of 2-bromoanisole in 50 mL of diethyl ether was then added at reflux over 30 min. After 20 min of spontaneous reflux, heat was applied and reflux was continued for 2 h. The Grignard reagent was then transferred via cannula under argon pressure into a solution of 146.0 g (0.673 mol) of 3,6-dichlorophthalic anhydride in 2.3 L of tetrahydrofuran with cooling (ice bath) and vigorous mechanical stirring. After standing overnight, the resulting thick precipitate was digested with excess 10% HCl (aq). Evaporation of THF gave a solid which was collected, washed with water, and dissolved in 3 N NaOH. The solution was filtered, and the filtrate was acidified with 12 N HCl. The resulting precipitate was collected, washed with water, and recrystallized from ethanol–ether to yield 163.5 g (75%) of 5: mp 216–218 °C; IR (KBr) 3461, 3257, 1751, 1741 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.33 (s, 3 H), 6.94–7.78 (m, 6 H), 8.46 (br s, 1 H, exchangeable with D_2O). Anal. Calcd for $C_{15}H_{10}Cl_2O_4$: C, 55.41; H, 3.10. Found: C, 55.36; H, 3.11.

3,6-Dichloro-2-(2-hydroxybenzoyl)benzoic Acid (6). A slurry of 157.5 g (0.484 mol) of 5 in 1.4 L of HBr–HOAc (1:1 v/v) was stirred at reflux overnight. The resulting solution was concentrated under reduced pressure, and the solid residue was collected and washed with water. Recrystallization from ether–hexanes afforded 147.5 g (98%) of 6: mp 167–169 °C; IR ($CHCl_3$) 3602, 3490, 1724, 1636 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.59–7.88 (m, 6 H), 8.33 (br s, exchangeable), 9.4 (br s, exchangeable). Anal. Calcd for $C_{14}H_8Cl_2O_4$: C, 54.05; H, 2.59. Found: C, 53.91; H, 2.66.

2-Chloro-9-oxoxanthene-1-carboxylic Acid (3). A suspension of 139.6 g (0.448 mol) of 6 in 1.2 L of 30% K_2CO_3 solution was heated at reflux with stirring for 5.5 h. The reaction was cooled, and the precipitate was collected, dissolved in warm water, and then acidified with 12 N HCl. The resulting solid was collected and recrystallized from methanol to afford 104.6 g (85%) of 7: mp 246–248 °C; IR (KBr) 3430, 1724, 1669 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.48–8.15 (m, 6 H), 13.64 (s, 1 H). Anal. Calcd for $C_{14}H_7ClO_4$: C, 61.22; H, 2.57. Found: C, 61.08; H, 2.74.

Methyl 2-Chloro-9-oxoxanthene-1-carboxylate (9). A slurry of 13.73 g (0.05 mol) of 3 and 100 g of thionyl chloride was refluxed for 4.5 h. Excess $SOCl_2$ was removed under reduced pressure, and the resulting solid was treated with 50 mL of CH_2Cl_2 and excess hexane with ice-bath cooling. The solid was collected, treated with 300 mL of methanol, and then heated on a steam bath for 1.75 h. Acetone was added as needed to maintain a homogeneous solution. Upon cooling, the crude product precipitated. Recrystallization from acetone–methanol furnished 13.27 g (92%) of 9: mp 183–185 °C; ^1H NMR ($CDCl_3$) δ 4.18 (s, 3 H), 7.44–8.32 (m, 6 H); IR ($CHCl_3$) 1740, 1666 cm^{-1}. Anal. Calcd for $C_{15}H_{19}ClO_4$: C, 62.41; H, 3.14. Found: C, 62.50; H, 3.24.

2-Chloro-9-hydroxy-9*H*-xanthene-1-methanol (7). To a suspension of 8.0 g (0.21 mol) of $LiAlH_4$ in 0.64 L of diethyl ether at −78 °C was added 40.0 g (0.14 mol) of 8 in 150 mL of warm THF dropwise with stirring. After 2 h at −78 °C, the reaction was allowed to reach 0 °C gradually and then quenched with hydrated sodium sulfate until H_2 evolution ceased. The mixture was filtered, and the filter cake was washed with THF. The filtrate was concentrated and the residue recrystallized from acetone to give 123.5 g (86%) of 7: mp 154–157 °C; IR (KBr) 3266, 1625 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.77 (dd, 1 H, J = 5.4, 11.8 Hz), 4.96 (dd, 1 H, J = 5.9, 11.8 Hz), 5.19 (t, 1 H, J = 5.7 Hz, exchangeable), 5.90 (d, 1 H, J = 6.9 Hz, exchangeable), 6.06 (d, 1 H, J = 6.9 Hz),

(10) (a) Details for the X-ray analysis of 14·HCl are provided in the supplementary Material. (b) The X-ray analysis of 14·HCl also showed that the nitrogen atom of the five-membered ring is out of plane with respect to the tricyclic aromatic portion of the molecule. This conformational feature may be responsible for the inactivity of 14 in tests predictive of antipsychotic properties. For a discussion of the effect of chemical structure on antipsychotic activity, see ref 1, p 871.

(11) Newman, M. S.; Scheurer, P. G. *J. Am. Chem. Soc.* **1956**, *78*, 5004.

(12) Recrystallization of the combined sodium salt precipitates from warm water gave 69 g of the mono salt of 3,4-dichlorophthalic acid (99.5% by GC, 8.4% yield from 3-chlorophthalic anhydride) as a white solid. Anal. Calcd for $C_8H_3Cl_2NaO_4$: C, 37.39; H, 1.18; Na, 8.94. Found: C, 37.41; H, 1.27; Cl, 27.50; Na, 8.87. Acidification of the mono salt furnished 3,4-dichlorophthalic acid: mp 194–195 °C (lit.[3] mp 195 °C).

7.12–7.59 (m, 6 H). Anal. Calcd for $C_{14}H_{11}ClO_3$: C, 64.01; H, 4.22. Found: C, 64.05; H, 4.36.

2,9-Dichloro-1-(chloromethyl)-9*H*-xanthene (2). To 60 mL of thionyl chloride was added 20 g (76 mmol) of **7** in small portions, with stirring under an argon sweep, taking as much care as possible to avoid contact of **7** with HCl vapors. The mixture was heated at reflux for 2.5 h. Excess thionyl chloride was removed under reduced pressure, and the residue was treated with cold (0 °C) hexane. The resulting solid was collected and recrystallized from methylene chloride to give 17 g (75%) of **11**: mp 145–147 °C; IR (KBr) 3088, 1597, 1456, 1268 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.09 (d, 2 H, J = 1.0 Hz), 6.81 (s, 1 H), 7.6–7.15 (m, 6 H). Anal. Calcd for $C_{14}H_9Cl_3$: C, 56.13; H, 3.03; Cl, 35.50 Found: C, 56.20; H, 3.06; Cl, 35.45.

5-Chloro-3a,4,12b,12c-tetrahydro-2-methyl-1*H*-xantheno-[9,1-*ef*]isoindole-1,3(2*H*)-dione (10a). To a mixture of 2.25 g (15 mmol) of sodium iodide and 1.11 g (10 mmol) of *N*-methylmaleimide in 5 mL of anhydrous DMF at 73 °C under argon was added 1.50 g (5.0 mmol) of **2** in small portions with stirring. After addition, the mixture was diluted with 10 mL of DMF and stirred at 73 °C for 5.5 h. The reaction was poured onto a mixture of ice and sodium bisulfite, and the resulting yellow precipitate was collected and washed thoroughly with water. Recrystallization from acetone–ethyl acetate afforded 0.77 g (45%) of **2**: mp 260–261 °C; IR ($CHCl_3$) 1782, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65 (s, 3 H), 2.71 (dd, 1 H, J = 15.1, 6.8 Hz), 3.48 (ddd, 1 H, J = 6.6, 1.7, 8.8 Hz), 3.71 (dd, 1 H, J = 5.7, 9.1 Hz), 3.90 (dd, 1 H, J = 15.2, 1.4 Hz), 4.33 (d, 1 H, J = 5.7 Hz), 6.80–7.42 (6 H, m). Anal. Calcd for $C_{19}H_{14}ClNO_3$: C, 67.16; H, 4.15; N, 4.12; Cl, 10.43. Found: C, 66.99; H, 4.32; N, 4.19; Cl, 10.24.

5-Chloro-2-methyl-1*H*-xantheno[9,1-*ef*]isoindole-1,3-(2*H*)-dione (11). A solution of **10a** (1.5 g, 4.5 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (3.0 g, 13.5 mmol) in 80 mL of dioxane containing several drops of acetic acid was heated at reflux for 20 h. The reaction was cooled to room temperature, and the resulting precipitate was collected by filtration and washed with methanol to give 1.4 g (91%) of the title compound. An analytical sample was prepared by recrystallization from acetone: mp > 295 °C dec; IR (KBr) 1757, 1703 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.28 (s, 3 H), 7.17–7.32 (overlapping m, 3 H), 7.50–7.53 (m, 1 H), 7.69 (d, 1 H, J = 8.6 Hz), 8.47 (s, 1 H), 9.65 (d, 1 H, J = 9.0 Hz); HRMS calcd for $C_{19}H_{10}NClO_3$ 335.0349, found 335.0328.

Dimethyl 4-Chlorobenzo[*kl*]xanthene-1,2-dicarboxylate (12). To a slurry of NaI (0.45 g, 3.0 mmol), dimethyl acetylenedicarboxylate (0.31 mL, 2.5 mmol), and 5 mL of DMF was added **2** (0.30 mmol, 1 mmol) portionwise and with stirring under argon. After 4.5 h at 70 °C, the reaction was cooled to room temperature and partitioned between ether and water. The aqueous layer was extracted three times with ether, the combined extracts were washed with water, dried (Na_2SO_4), and filtered, and the solvent was removed. The residue was purified by column chromatography (silica gel, 4:1 hexane–ethyl acetate) to afford 37 mg (10%) of the title compound as a bright yellow solid. An analytical sample was obtained by crystallization from ethyl acetate–hexane: mp 195–196 °C; IR (KBr) 3431, 3007, 1725, 1504 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (s, 3 H), 4.00 (s, 3 H), 7.00–7.68 (m, 6 H), 8.68 (s, 1 H); mass spectrum (CI) 369 (MH^+, 35), 338 (100); HRMS calcd for $C_{20}H_{13}ClO_5$ 368.04515, found 368.04391.

Dimethyl 4-Chloro-1(*SR*),2(*SR*),3,11b-tetrahydrobenzo-[*kl*]xanthene-1,2-dicarboxylate (13). To a slurry of 1.4 g (9.9 mmol) of dimethyl fumarate, 0.65 g (9.9 mmol) of zinc powder, and 10 mL of DMF at 50–55 °C was added portionwise and with stirring 1.0 g (3.3 mmol) of **2**. After addition, the mixture was heated at 100–105 °C for 3 h. The dark brown slurry was filtered hot through filter aid, and the filter pad was washed with THF. The filtrate was concentrated, and the residue was purified via flash column chromatography (silica gel, 4:1 hexane–ethyl acetate) to give 245 mg (20%) of a mixture of **13a** and **13b** (1.0:1.5 by 300-MHz ^1H NMR); mp 124–131 °C. Fractional crystallization of the mixture from ethyl acetate gave **13b**: mp 146–148 °C; IR (KBr) 2955, 1727, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.04 (dd, 1 H, J = 3.6, 5.5 Hz), 6.87 (d, 1 H, J = 8.7 Hz), 7.01–7.08 (m, 2 H), 7.19–7.29 (m, 3 H); HRMS calcd for $C_{20}H_{17}ClO_5$ 372.0765, found 372.0748. The mother liquors were concentrated, and the residue was recrystallized from methanol–ether to give **13a**: mp 143–145 °C; IR (KBr) 2953, 1743, 1445 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.04–3.39 (overlapping m, 4 H), 3.75 (s, 3 H), 3.84 (s, 3 H), 4.34 (d, 1 H, J = 10.3 Hz), 6.97 (d, 1 H, J = 8.6 Hz), 7.06–7.26 (m, 5 H); HRMS calcd for $C_{20}H_{17}ClO_5$ 372.0765, found 372.0746.

5-Chloro-2,3,3a,4,12b,12c-hexahydro-2-methyl-1*H*-xantheno[9,1-*ef*]isoindole Hydrochloride (14). To a slurry of 3.00 g (79 mmole) of lithium aluminum hydride in 0.50 L of ether was added 2.97 g (8.74 mmol) of **10a** as a solid. The mixture was stirred at reflux overnight, cooled to 0 °C, and then treated successively with 3.0 mL of water, 3.0 mL of 3 N NaOH (aq), and 12.0 mL of water. After being stirred for 0.5 h, the ether layer was filtered and the filter cake was washed thoroughly with ether. The filtrate was dried over potassium carbonate, filtered, and concentrated. The resulting solid was dissolved in methanol and acidified with etheral HCl. The solvents were partially evaporated on a steam bath and replaced with ethyl acetate. Upon cooling, 1.16 g (43%) of **14** was collected by filtration: mp > 240 °C dec; IR ($CHCl_3$) 3402, 2972, 2346 (br), 1624, 1608, 1577, 1492 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.96 (1 H, q, J = 10.6 Hz), 2.14 (1 H, ddd, J = 10.8, 10.9, 10.8, Hz), 2.53 (d, 3 H, J = 4.8 Hz), 2.58 (1 H, dd, J = 15.6, 6.1 Hz). Anal. Calcd for $C_{19}H_{18}ClNO{\cdot}HCl$: C, 65.53; H, 5.50; Cl, 20.36; N, 3.98. Found: C, 65.45; H, 5.54; Cl, 20.36; N, 4.02.

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Supplementary Material Available: General X-ray data for **14**·HCl, tables of atomic coordinates, bond lengths, thermal parameters, and bond angles for **14**·HCl, numbered ORTEP drawing of **14**·HCl, and NMR spectra of **11–13** (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis and Utility of a DNA Phosphorylating Agent Based on 2-(Triphenylsilyl)ethanol

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Introduction

The enzyme DNA ligase catalyzes the template-driven condensation of the 3′-hydroxyl group of one DNA strand with the 5′-monophosphate group of a second DNA strand. As part of a study of DNA ligase, we required a method for 5′-phosphorylation of an oligonucleotide during phosphoramidite-based, automated DNA synthesis.[1] Furthermore, this phosphorylated oligonucleotide needed to be separable, by reversed-phase HPLC, from the "failure sequences" generated during DNA synthesis. Work with the commercial phosphorylating agent **1** of Urdea[2] showed that, while the phosphorylated DNA could be separated from failure sequences by polyacrylamide gel electrophoresis or ion-exchange chromatography, satisfactory conditions for separation by HPLC could not be established. Uhlmann[3] showed that (*p*-nitrophenyl)ethyl phosphor-

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