H, J = 5 Hz), 7.33 (s, 1 H), 7.5 (d, 1 H, J = 5 Hz), 7.67 (d, 1 H, J = 5 Hz). Anal. Calcd for $C_8H_4Cl_2N_2S$: C, 41.57; H, 1.74; N, 12.12. Found: C, 41.71; H, 1.80; N, 12.08.

4,6-Dichloro-2-methylpyrimidine (**8a**; from **7** and methyllithium): yield 85%; mp 45–46 °C (lit.[19] mp 45–45.5 °C).

4,6-Dichloro-2-phenylpyrimidine (**8c**; from **7** and phenyllithium): yield 68%; mp 95–97 °C (lit.[20] mp 97–98 °C).

4,6-Dichloro-2-(2-thienyl)pyrimidine[21] (**8d**; from **7** and (2-thienyl)lithium): yield 77%; mp 129–130 °C; NMR δ 7.1 (s, 1 H), 7.15 (t, 1 H, J = 4 Hz), 7.5 (d, 1 H, J = 4 Hz), 8.0 (d, 1 H, J = 4 Hz).

5-Bromo-2,4-dichloro-6-(2-thienyl)pyrimidine (10d). A solution of (2-thienyl)lithium (26 mmol) in ether (75 mL) was cooled to −45 °C and treated dropwise with a solution of 5-bromo-2,4-dichloropyrimidine (**9**, 5.7 g, 25 mmol) in ether (10 mL). The mixture was stirred at −40 °C for 1 h, quenched at −20 °C with a mixture of acetic acid (1.5 mL, 26 mmol) and methanol (1.2 mL, 30 mmol), and then treated at −20 °C with a solution of DDQ (5.9 g, 26 mmol). Workup as described above gave 5.81 g of **10d** (75%): mp 123–124 °C; NMR δ 7.13 (t, 1 H, J = 4 Hz), 7.57 (d, 1 H, J = 4 Hz), 8.35 (d, 1 H, J = 4 Hz). Anal. Calcd for $C_8H_3BrCl_2N_2S$: C, 30.99; H, 0.98; N, 9.04. Found: C, 31.08; H, 1.04; N, 8.99.

5-Bromo-2,2′,4′,6-tetrachloro-4,5′-bipyrimidine (10g). (*n*-Butyl)lithium (5 mL, 13 mmol) was added dropwise within 5 min to a solution of 5-bromo-2,4-dichloropyrimidine (**9**, 5.3 g, 26 mmol) in ether (125 mL), maintained at −70 °C and stirred. The mixture, containing a yellow precipitate, was then stirred at −45 °C for 30 min, quenched at −45 °C with a mixture of acetic acid (0.75 mL, 13 mmol) and methanol (0.7 mL, 17 mmol), stirred at −45 °C until the yellow precipitate disappeared (5–10 min), and treated at −45 °C with a solution of DDQ (2.95 g, 13 mmol) in tetrahydrofuran (100 mL). Treatment of the mixture with aqueous sodium hydroxide (3 M, 5 mL, 15 mmol) at 0 °C was followed by workup as described above to give 4.04 g (83%) at **10g**: mp 136–138 °C; NMR δ 8.66 (s, H-5). Anal. Calcd for $C_8HBrCl_4N_4$: C, 25.63; H, 0.27; N, 14.95. Found: C, 25.72; H, 0.35; N, 15.01.

General Procedure for the Preparation of 11, 13a,b, and 14. A solution of 4,6-dichloro-2-(2-thienyl)pyrimidine (**8d**), 2,4-dichloroquinazoline (**12**), or 4-chloro-2-(methylthio)quinazoline (**15**) (25 mmol) in ether (10 mL) was added dropwise to a solution of the respective lithium reagent (26 mmol) in ether (50 mL) at 0 °C. The resultant mixture was stirred at room temperature for 1 h, quenched with water (0.5 mL, 28 mmol), dried over anhydrous sodium sulfate, and decolorized by passing through a short column (10 cm) packed with charcoal or silica gel. Evaporation of the ether was followed by crystallization of the residue from hexanes or hexanes/CH_2Cl_2 (8:2).

6-Chloro-2,4-di(2-thienyl)pyrimidine (**11**; from **8d** and (2-thienyl)lithium): yield 70%; mp 86–88 °C; NMR δ 7.12 (t, 2 H, J = 4 Hz), 7.29 (s, 1 H), 7.50 (m, 2 H), 7.75 (d, 1 H, J = 4 Hz), 8.03 (d, 1 H, J = 4 Hz). Anal. Calcd for $C_{12}H_7ClN_2S_2$: C, 51.70; H, 2.53. Found: C, 51.54; H, 2.58.

2-Chloro-4-phenylquinazoline (**13a**; from **12** and phenyllithium): yield 69%; mp 112–114 °C (lit.[22] mp 114–115 °C.

2-Chloro-4-(2-thienyl)quinazoline (**13b**; from **12** and (2-thienyl)lithium): yield 76%; mp 107–108 °C; NMR δ 7.23 (t, 1 H, J = 4 Hz), 7.67 (m, 2 H), 7.90 (m, 3 H), 8.47 (d, 1 H, J = 8 Hz). Anal. Calcd for $C_{12}H_7ClN_2S$: C, 58.40; H, 2.86; N, 11.35. Found: C, 58.33; H, 2.89; N, 11.28.

2-(Methylthio)-4-(2-thienyl)quinazoline (14). A. From **15** and 2-[(benzylidene)amino]benzonitrile[9] yield 62%; mp 83–84 °C; NMR δ 2.67 (s, 3 H), 7.20 (t, 1 H, J = 4 Hz), 7.57 (m, 2 H), 7.80 (m, 3 H), 8.35 (d, 1 H, J = 8 Hz). Anal. Calcd for $C_{13}H_{10}N_2S_2$: C, 60.43; H, 3.90; N, 10.84. Found: C, 60.54; H, 3.90; N, 10.81.

B. 2-Chloro-4-(2-thienyl)quinazoline (**13b**) was reacted with sodium methyl mercaptide according to a general procedure[23] to give a 75% yield of **14**, identical with the sample obtained in the reaction of **15** with (2-thienyl)lithium, as described above.

2-[(Diphenylmethyl)amino]benzonitrile (19). A. A solution of 2-[(benzylidene)amino]benzonitrile[9] (**18**, 0.75 g, 3.63 mmol) in ether (50 mL) was treated with phenyllithium (4.0 mmol) at 0 °C, and the resultant mixture was stirred at 0 °C for 1.0 h. Quenching with water and the usual workup gave 0.95 g (92%) of **19**: mp 112–114 °C (from hexanes); IR 2220 cm^{-1} (C≡N); NMR δ 5.1 (d 1 H, J = 4 Hz, N–H, exchangeable with D_2O), 5.6 (d, 1 H, J = 4 Hz), 6.5 (d, 1 H, J = 8 Hz), 6.7 (t, 1 H, J = 8 Hz), 7.25 (t, 1 H, J = 8 Hz), 7.33 (m, 10 H), 7.45 (d, 1 H, J = 8 Hz). Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.36; H, 5.75; N, 10.01.

B. Phenyllithium (21 mmol) was added dropwise at 0 °C to a solution of 4-chloroquinazoline (**16**, 3.15 g, 10 mmol) in ether (50 mL). The mixture was stirred at 0 °C for 1 h, then quenched with water, and dried over anhydrous sodium sulfate. Chromatography on silica gel (CH_2Cl_2) afforded **19** (1.54 g, 54%) and **18** (0.1 g, 5%) in order of elution.

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Synthesis of *N,N*-Dimethylnitramine by Nitrodephosphorylation of Hexamethylphosphoramide

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The large-scale synthesis of *N,N*-dimethylnitramine[1,2] poses serious safety problems resulting primarily from the formation of nitrosamine byproduct and the use of potentially explosive mixtures of nitric acid and acetic or trifluoroacetic anhydride.[3,4] In addition, the use of the highly oxidizable amide, dimethylformamide, increases the changes of thermal runaway during the nitration process. In our search for a safe, pilot-plant-scale synthesis of this material (not currently available commercially), we examined the ostensibly exothermic metathesis of a phosphoryl amine with nitric acid—in this case hexamethylphosphoramide (HMPA)—to give dimethylnitramine and phosphoric acid (eq 1). This approach utilizes amides of

$$[(CH_3)_2N]_3P{=}O + 3HONO_2 \rightarrow (HO)_3P{=}O + 3(CH_3)_2NNO_2 \quad (1)$$

phosphoric acid, rather than formic acid, thus circumventing some of the potential oxidative side reactions of *N,N*-dimethylformamide and similar carboxylic acid amides under typical nitration conditions.

This synthesis has proved viable in practice. We isolated a 200% yield of *N,N*-dimethylnitramine and only a small amount (12%) of the carcinogenic *N,N*-dimethylnitrosamine impurity when the reaction was run on roughly a half-mole scale, based on starting HMPA. The reaction was run between 0 and 10 °C; ice-bath cooling was required. The products were isolated by neutralization with

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cooling, followed by chloroform extraction.

Notably, only two of the three dimethylamino ligands underwent nitration to give a 200% yield, rather than all three giving the maximum possible 300% yield of the desired product. Further study will reveal the fate of the currently unaccounted for dimethylamino ligand.

The implications of this observation for explosive technology are significant. A phosphorus-based scaffold might be feasible as an incipient polynitramine framework, with use of variations on the reaction described here. Elaborations of this methodology are being investigated.

Experimental Section

Caution! This procedure produces traces of N,N-dimethylnitrosamine, a known carcinogen.

Hexamethylphosphoramide (50 g, 0.28 mol) was added dropwise to a stirred mass of 600 g (400 mL) of 100% nitric acid in a 1-L flask cooled by an ice bath. The rate of addition was carefully regulated to prevent the reaction mixture from ever heating beyond 10 °C; the addition time was approximately 90 min. After the addition was complete, the reaction mixture was allowed to warm to room temperature over an additional 90 min. Workup was carried out by quenching the reaction mixture into 1 kg of ice, neutralizing with 400 g of NaOH with ice cooling of the diluted mixture, and extracting with 3 × 200 mL of chloroform. Drying, filtering, and concentrating, followed by crystallization from carbon tetrachloride, gave 50 g (200%) of *N,N*-dimethylnitramine, mp 53–55 °C. The mother liquor yielded 3 g (12%) of dimethylnitrosamine, a yellow liquid with nonequivalent methyls in its NMR spectrum. *N,N*-Dimethylnitramine does not pose a significant explosion hazard under normal laboratory conditions. It should be kept from exposure to extreme heat (>150 °C).

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Registry No. $[(CH_3)_2N]_3P{=}O$, 680-31-9; $HONO_2$, 7697-37-2; $(CH_3)_2NNO_2$, 4164-28-7.

Communications

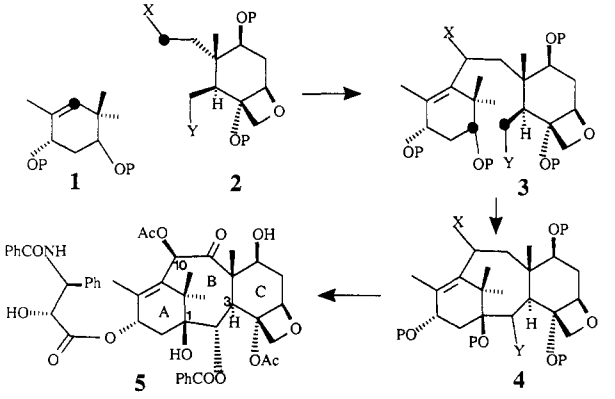
A Convergent Approach to the Taxane Class of Compounds

Summary: A short A + C → AC → ABC route to the taxane class of compounds is described which features a Claisen-rearrangement-mediated stereocontrolled ring closure of the central eight-membered ring in the key AC → ABC step.

Sir: From a synthetic perspective, the taxane diterpenes[2] constitute one of the most demanding classes of compounds as a consequence of both a high level of structural complexity and abundant stereochemical detail. For these reasons, no naturally occurring member of the taxane class of compounds has yielded to total synthesis despite an extraordinary amount of activity in this area[3] and the desire to secure a reliable synthetic source of the highly promising antitumor antileukemic agent taxol **5**[4] and/or its analogues.

Most of the synthetic effort to date has not dealt with stereochemical issues but, instead, has primarily concentrated on elaboration of the taxane carbon framework.[3] We believe that a viable taxane synthesis should accommodate the introduction of most of the stereogenic centers *before* the ring system is assembled. An idealized strategy which conceptualizes this point is depicted in Scheme I. The fully substituted six-membered A and C rings, **1** and **2**, respectively, of taxol are first constructed and then

Scheme I



joined in two separate carbon,carbon bond-forming steps to provide the highly substituted taxane derivative **4**, which requires only modest functional group manipulation to arrive at taxol **5**.[5] The stereocontrolled ring closure of the eight-membered ring, cf. **3** → **4**, represents the most significant challenge in this approach. We describe herein a general solution to this problem which can eventually be incorporated into a more defined plan for the synthesis of taxol similar to that adumbrated in Scheme I.

We have previously demonstrated that our methodology for the preparation of carbocycles, the Claisen rearrangement mediated ring contraction of macrocyclic lactones, is applicable to the preparation of eight-membered rings and, moreover, to strained ring systems.[6] Hence, the

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