JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

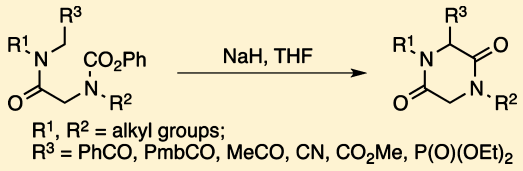
A Dieckmann Cyclization Route to Piperazine-2,5-diones

Claude Larrivée Aboussafy and Derrick L. J. Clive*

Chemistry Department, University of Alberta, Edmonton, Alberta T6G 2G2, Canada

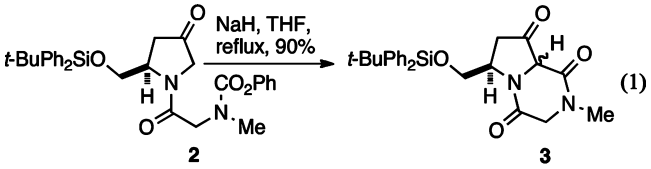
Supporting Information

ABSTRACT: Piperazine-2,5-diones are formed by Dieckmann cyclization (NaH, THF) of substructures of the type CH_2-N(R)C(O)CH_2N-(R′)CO_2Ph in which the terminal methylene (CH_2) that is adjacent to nitrogen closes onto the carbonyl group of the phenyl carbamate unit at the other end of the chain. R and R′ are alkyl groups, and the terminal methylene is activated by a ketone carbonyl, a nitrile, an ester, or a phosphoryl group. The starting materials are assembled by standard acylation and oxidation processes, starting from a β-(alkylamino)alcohol, an (alkylamino)acetonitrile, an (alkylamino) ester, or an (alkylamino)methyl phosphonate.

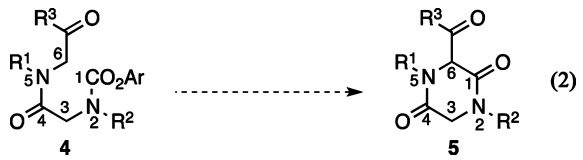


INTRODUCTION

During synthetic studies carried out in this laboratory and directed toward the synthesis of the antitumor antibiotic MPC1001 (**1**), the lactam carbamate **2** was treated with NaH to produce the piperazinedione **3** (eq 1).[1] In this process, the



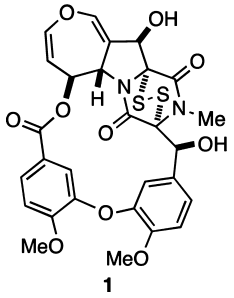
piperazine-2,5-dione substructure of **3** is being constructed by the potentially general sequence **4** → **5** (eq 2), which resembles



the classical Dieckmann cyclization. Surprisingly, the simple disconnection represented by the conversion of **4** into **5** has not been used before, apart from the example of eq 1.[2] In view of the importance of piperazine-2,5-diones,[3] especially for pharmaceutical products,[4] we decided to establish if any special features inherent in structure **2**, especially the restraint of the ketone carbonyl group into a ring, were requirements for effective cyclization, and we now report that the process defined by eq 2 represents a general route to piperazine-2,5-diones. It allows the preparation of such compounds bearing a variety of different substituents.[5]

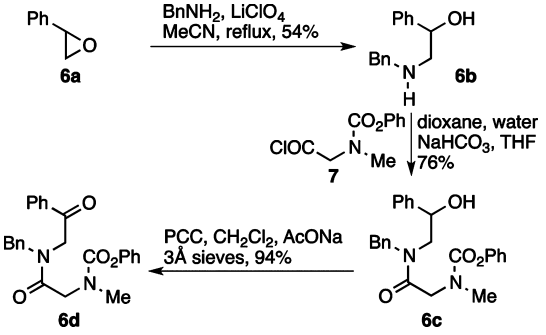
RESULTS AND DISCUSSION

The starting carbamates related to generic structure **4** were easily prepared, often along the lines summarized in Scheme 1 for a particular example, and Table 1 lists the carbamates we



have made in this way or by equally straightforward routes (which are described in the Experimental Section).

Scheme 1. Preparation of Amide Carbamate 6d

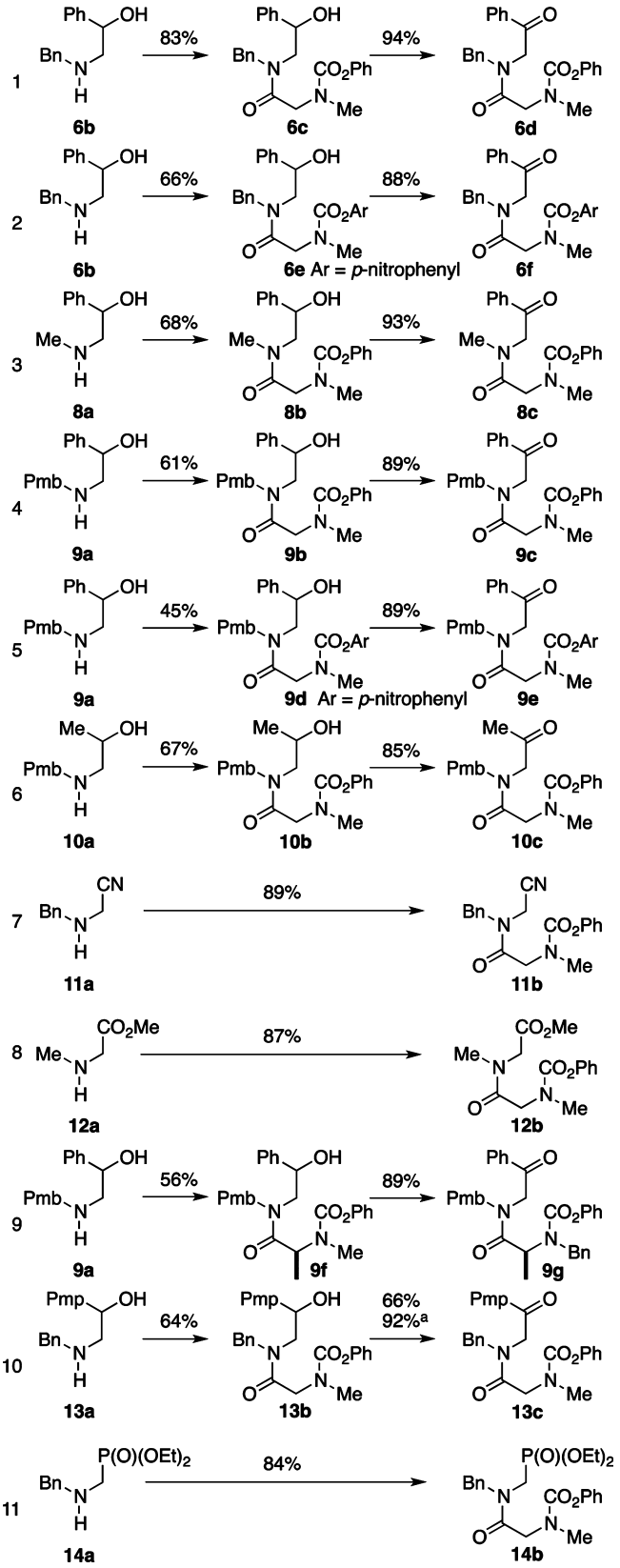


All of the starting amino alcohols (Table 1, first column) are known compounds; those of entries 1−5, 9, and 10 were made by the epoxide route (cf Scheme 1). Although compound **10a** (entry 6) could also be prepared in this way, reductive amination ($NaBH_3CN$) of *p*-methoxybenzaldehyde gave a better yield. The cyano amine **11a** was available in one step from $ClCH_2CN$ and $BnNH_2$, and the amino phosphonate **14a**

Received: April 8, 2012
Published: May 7, 2012

   dx.doi.org/10.1021/jo3007144 | J. Org. Chem. 2012, 77, 5125−5131

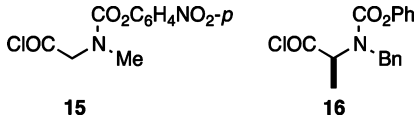
Table 1. Preparation of Substrates for Cyclization



[a]Corrected for recovered **13b**.

was made from $(EtO)_2P(O)H$ and 1,3,5-tribenzyl-1,3,5-triazinane.[6]

Each amino alcohol was acylated on nitrogen using one of the acid chlorides **7**, **15**, or **16**, which were made by *N*-acylation (PhOCOCl, or *p*-$O_2NC_6H_4OCOCl$) of the appropriate amino acid, followed by treatment with $(COCl)_2$. The resulting hydroxy carbamates were then oxidized (cf **6c** → **6d**) with PCC or the Dess–Martin reagent.



When carbamate **6d** was heated with NaH (2.05 equiv) in refluxing THF (0.02 M in **6d**) for 15 min, it was converted into the piperazinedione **6g** in 67% yield (92% after correction for recovered **6d**). These conditions represent the best results from a brief optimization study in which we varied, in an empirical manner, the reaction temperature (room temperature and 70 °C), the concentration of the starting carbamate (0.2 and 0.02 M), the solvent (THF, DMF, DMSO), and the nature of the base (NaH, *t*-BuOK, DBU, LDA, KHMDS, LiHMDS). The related carbamate **6f** gave **6g** in much lower yield under the same conditions. A similar comparison was made between **9c** and **9e**, and once again the phenyl carbamate was far superior. We did not establish the basis of this result, but speculate that the better leaving group facilitates the incursion of intermolecular side reactions. Cyclization of **6d** did not occur with CF_3CO_2H (CH_2Cl_2) or TsOH ($CDCl_3$). In two cases, (Table 2, entries 8 and 11) the cyclization was done in the presence of a small amount of *t*-BuOH (0.2 equiv). With this change, the experiment of entry 8 gave a higher yield, and that of entry 11 proceeded more rapidly. This modification was tried because these two examples were abnormally slow under the usual conditions.

The reaction accommodates different alkyl groups on nitrogen (methyl, benzyl, *p*-methoxybenzyl). As indicated in Table 2, we have also investigated a limited number of activating groups adjacent to the carbon [C(6) in **4**] that must be deprotonated to initiate the ring closure. PhCO and *p*-$MeOC_6H_4CO$ are satisfactory (entries 1–5, 9, 10), as are MeCO (entry 6) and CO_2Me (entry 8). Use of a nitrile for activation is also successful (entry 7), as is a diethoxyphosphoryl group (entry 11).

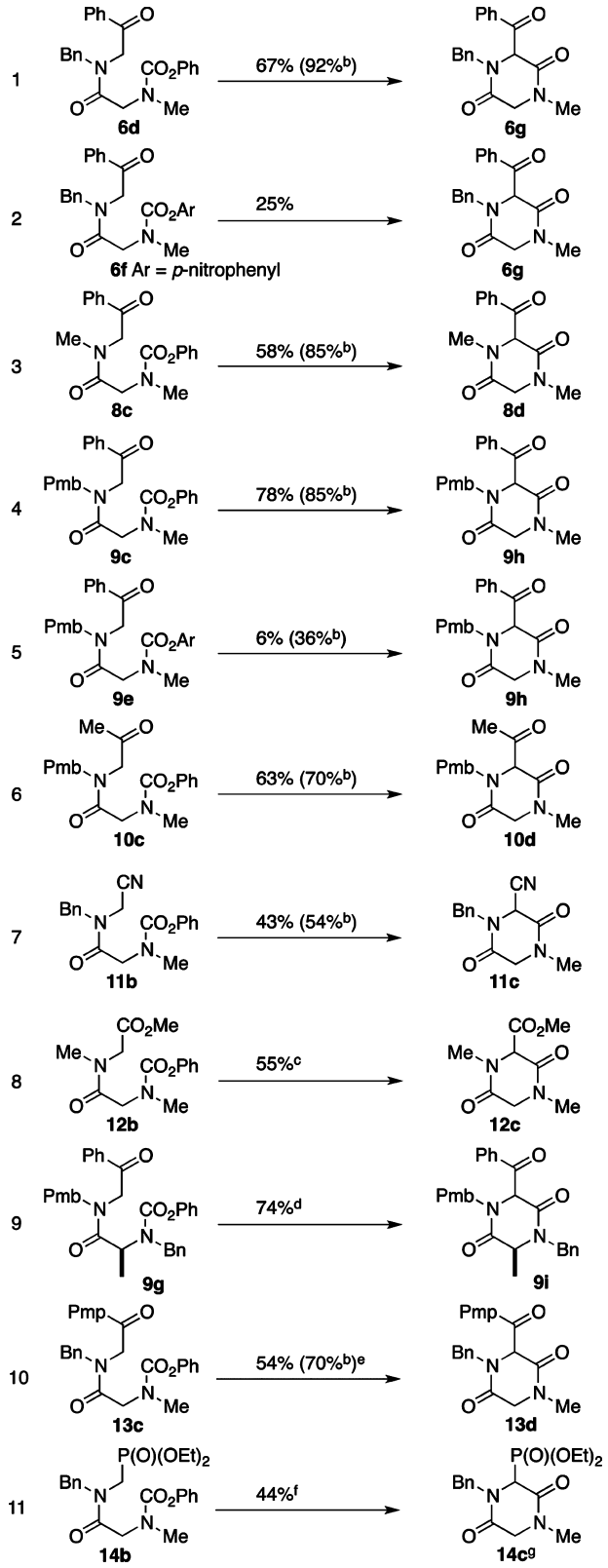
In the case of entry 9, two chromatogaphically inseparable products (ca. 89:11) were formed, and the NMR spectra suggest that they are the expected *cis* and *trans* isomers, although we were unable to identify which was which. We noted that in the ^1H and ^{13}C NMR spectra of the material, the minor signals were very similar to those corresponding to the major isomer but slightly displaced.

The phosphonate **14c** contained a minor byproduct that could not be separated, and when we treated the material with *p*-methoxybenzaldehyde and NaH, the two olefins **14d** (50%) and **14d′** (15%) (Figure 1) were isolated, suggesting that the minor component of the starting phosphonate **14c** was a positional isomer with the phosphoryl group adjacent to the *N*-methyl. Very few phosphonates of piperazine-2,5-diones have been reported.[7] The stereochemistry of **14d** and **14d′** was evident from TROESY (Figure 1) and HMBC NMR experiments, (see the Supporting Information), but we did not establish the origin of the minor phosphonate that gives **14d′**.

In the case of **6d**, a minor byproduct was sometimes obtained. This material had the structure **6h**.[8] When **6d** was

dx.doi.org/10.1021/jo3007144 | J. Org. Chem. 2012, 77, 5125–5131

Table 2. Cyclization to Piperazine-2,5-diones[a]



[a]Unless otherwise indicated, reactions were done using the following conditions: NaH (2.05 equiv), 0.02 M in substrate, THF, 70 °C, 15 min. [b]Corrected for recovered starting material. [c]Reaction time = 24 h, trace *t*-BuOH added. [d]Reaction time = 2.5 h. [e]Reaction time = 30 min. [f]Reaction time = 4.5 h, trace *t*-BuOH added. [g]The material contained a minor byproduct (see text).

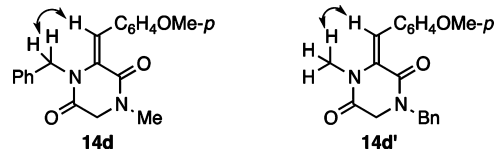
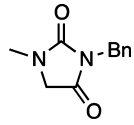


Figure 1. Structures and TROESY correlations for **14d** and **14d′**.

treated with NaH in THF under an atmosphere of O_2, the same imidazolidinedione **6h** was the exclusive product (56% yield), but when **6g** was subjected to the same conditions, we did not detect **6h**.



Piperazinediones **10d**, **11c**, and **12c** are crystalline, and single crystal X-ray analysis served to confirm the structures and indicate the shape of the heterocyclic ring (see the Supporting Information for ORTEP diagrams). Both compounds **10d** and **12c** have a shallow boat conformation with their respective carbonyl substituents (MeCO and CO_2Me) axial, while **11c** has an almost planar heterocyclic ring.

EXPERIMENTAL SECTION

General Procedures. Solvents used for chromatography were distilled before use. Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F−254) were used. Silica gel for flash chromatography was Merck type 60 (230−400 mesh). Dry solvents were prepared under an inert atmosphere and transferred by syringe. Molecular sieves (3 Å) were stored at 150 °C for 5 h and then cooled in a desiccator under N_2 before use. The symbols s, d, t, q used for ^{13}C NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made by APT spectra. Solutions were evaporated under water pump vacuum, and the residue was kept under oil pump vacuum. High resolution mass spectra were obtained with an aoTOF mass analyzer fitted with an electrospray source. NMR spectra of many compounds were run both at room temperature and at a higher temperature (usually at 100 °C) in order to verify the presence of rotamers. Samples for X-ray analysis were crystallized as follows: A portion of the sample was dissolved in the minimum amount of EtOAc at room temperature, and the solution was transferred to a shortened (ca. 4 cm) NMR tube. This was placed inside a sample vial containing hexane, and the vial was closed. After several days, crystals suitable for X-ray analysis had grown.

Phenyl *N*-{[Benzyl(2-hydroxy-2-phenylethyl)carbamoyl]-methyl}-*N*-methylcarbamate (6c). $NaHCO_3$ (185 mg, 2.20 mmol) was added to a stirred and cooled (0 °C) solution of **6b**[9] (200 mg, 0.881 mmol) in dioxane (3 mL) and water (3 mL). Acid chloride **7**[1] (250 mg, 1.10 mmol) in dry THF (1 mL) was added dropwise over 15 min. The cooling bath was left in place, but not recharged, and stirring was continued overnight. The THF and dioxane were evaporated, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 12 cm), using 30−50% EtOAc in hexanes, gave **6c** (306 mg, 83%) as a white foam: FTIR ($CHCl_3$, cast) 3422, 3063, 3030, 2935, 1723, 1650, 1495, 1475, 1453, 1398, 1205 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 2.82−3.02 (four s, 3 H in all), 3.14−3.31 (m, 1 H), 3.43−3.56 (m, 1 H), 4.14−4.24 (m, 1.3 H), 4.40−4.53 (m, 1.7 H), 4.60−4.67 (m, 0.3 H), 4.78−4.87 (m, 1.7 H), 5.50−5.51 (m, 0.3 H), 5.75−5.77 (m, 0.7 H), 7.00−7.40 (m, 15 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 35.7 (q), 35.8 (q), 36.1 (q), 36.2 (q), 48.2 (t), 48.4 (t), 50.4 (t), 50.6 (t), 50.7 (t), 50.8 (t), 53.4 (t), 53.9 (t), 70.3 (d), 70.8 (d), 121.6 (d), 121.7 (d), 124.9−129.2 (numerous d), 137.0 (s), 137.7 (s), 143.1 (s), 143.1

dx.doi.org/10.1021/jo3007144 | J. Org. Chem. 2012, 77, 5125−5131

(s), 143.4 (s), 151.2 (s), 151.3 (s), 151.4 (s), 154.6 (s), 154.9 (s), 168.0 (s), 168.3 (s), 168.5 (s), 168.7 (s); exact mass (electrospray) *m/z* calcd for $C_{25}H_{26}N_2NaO_4$ (M + Na) 441.1785, found, 441.1787.

Phenyl *N*-{[Benzyl(2-oxo-2-phenylethyl)carbamoyl]methyl}-*N*-methylcarbamate (6d). PCC (435 mg, 2.02 mmol) was added to a stirred and cooled (0 °C) mixture of **6c** (282 mg, 0.674 mmol), AcONa (55 mg, 0.674 mmol), and powdered 3 Å molecular sieves (337 mg, 0.5 g/mmol of **6c**) in dry CH_2Cl_2 (10.8 mL). The mixture was stirred at 0 °C for 15 min, the ice bath was removed, and stirring was continued for 30 min. The mixture was filtered through a pad of Celite (3.5 × 3.5 cm), and the pad was rinsed with CH_2Cl_2. Flash chromatography silica gel (6.0 g) was added to the filtrate, and the solvent was evaporated at room temperature. The dry residue was poured onto the top of a chromatography column made up with silica gel (2 × 16 cm) and hexanes. The column was developed using 40–50% EtOAc in hexanes to give **6d** (264 mg, 94%) as a white foam: FTIR ($CHCl_3$, cast) 3063, 3029, 2930, 1724, 1699, 1666, 1472, 1450, 1204 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 2.89–3.03 (m, 3 H), 4.09–4.19 (two s, 1 H), 4.30–4.40 (two s, 1 H), 4.55–4.56 (m, 1 H), 4.66–4.67 (m, 1 H), 4.82–4.86 (m, 1 H), 5.01–5.02 (m, 1 H), 7.02–7.07 (m, 2 H), 7.18–7.39 (m, 8 H), 7.51–7.55 (m, 2 H), 7.62–7.70 (m, 1 H), 7.95–7.98 (m, 2 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 35.5 (q), 35.7 (q), 36.1 (q), 36.2 (q), 50.0 (t), 50.1 (t), 50.3 (t), 50.4 (t), 50.6 (t), 50.8 (t), 53.0 (t), 53.2 (t), 53.3 (t), 121.6 (d), 121.7 (d), 125.0 (d), 125.1 (d), 125.1 (d), 126.8–129.2 (numerous d), 129.1 (d), 129.2 (d), 133.5 (s), 133.8 (s), 134.7 (s), 134.9 (s), 136.9 (s), 137.5 (s), 137.5 (s), 151.2 (s), 151.3 (s), 154.5 (s), 154.6 (s), 154.8 (s), 168.2 (s), 168.6 (s), 168.7 (s), 169.1 (s), 193.9 (s), 194.7 (s); exact mass (electrospray) *m/z* calcd for $C_{25}H_{24}N_2NaO_4$ (M + Na) 439.1628, found, 439.1630.

3-Benzoyl-4-benzyl-1-methylpiperazine-2,5-dione (6g). NaH (60% w/w dispersion in mineral oil, 20 mg, 0.492 mmol) was added in one portion to a stirred solution of **6d** (100 mg, 0.240 mmol) in dry THF (12 mL). The reaction flask was lowered into a preheated oil bath (70 °C), and the mixture was stirred for 15 min. The mixture was cooled (ice bath), and pH 7 buffer was added. The aqueous solution was extracted with EtOAc, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using 20–40% EtOAc in hexanes, gave **6g** [47 mg, 67 or 92% after correction for recovered **6d** (36 mg)] as a white foam: FTIR ($CHCl_3$, cast) 3064, 3029, 3008, 2930, 1678, 1596, 1580, 1496, 1466, 1450, 1227 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.92 (s, 3 H), 3.92 (d, *J* = 17.0 Hz, 1 H), 3.96 (d, *J* = 14.0 Hz, 1 H), 4.36 (d, *J* = 17.0 Hz, 1 H), 5.07 (d, *J* = 14.0 Hz, 1 H), 5.53 (s, 1 H), 7.13–7.17 (m, 3 H), 7.21–7.26 (m, 2 H), 7.43–7.49 (m, 2 H), 7.62 (apparent tt, *J* = 1.5, 7.5 Hz, 1 H), 8.00–8.03 (m, 2 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 34.1 (q), 48.9 (t), 52.6 (t), 65.1 (d), 128.5 (d), 128.9 (d), 129.0 (d), 129.2 (d), 129.9 (d), 134.1 (s), 134.7 (s), 134.7 (d), 160.7 (s), 166.1 (s), 192.6 (s); exact mass (electrospray) *m/z* calcd for $C_{19}H_{18}N_2NaO_3$ (M + Na) 345.1210, found, 345.1209.

3-Benzoyl-4-benzyl-1-methylpiperazine-2,5-dione (6g). NaH (60% w/w dispersion in mineral oil, 5.3 mg, 0.133 mmol) was added in one portion to a stirred solution of **6f** (30 mg, 0.0650 mmol) in dry THF (3.3 mL). The reaction flask was lowered into a preheated oil bath (70 °C), and the mixture was stirred for 30 min. The mixture was cooled (ice bath), and pH 7 buffer was added. The aqueous solution was extracted with EtOAc, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 20–40% EtOAc in hexanes, gave **6g** [5.2 mg, 25 or 33% after correction for recovered **6f** (24.4 mg)] as a white foam.

3-Benzoyl-1,4-dimethylpiperazine-2,5-dione (8d).[10] NaH (60% w/w dispersion in mineral oil, 5 mg, 0.126 mmol) was added in one portion to a stirred solution of **8c** (22 mg, 0.0622 mmol) in dry THF (3.2 mL). The reaction flask was lowered into a preheated oil bath (70 °C), and the mixture was stirred for 15 min. The mixture was cooled (ice bath), and pH 7 buffer was added. The aqueous solution was extracted with EtOAc, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 60–70% EtOAc in hexanes, gave **8d**[10] [8.8 mg, 58 or 85% after correction for recovered **8c** (6.8 mg)] as a white solid: mp 114–115 °C; FTIR ($CHCl_3$, cast) 3064, 2930, 1674 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.88 (s, 3 H), 2.93 (s, 3 H), 3.84 (d, *J* = 17.5 Hz, 1 H), 4.24 (d, *J* = 17.5 Hz, 1 H), 5.61 (s, 1 H), 7.54 (t, *J* = 7.5 Hz, 2 H), 7.66 (apparent tt, *J* = 1.5, 7.5 Hz, 1 H), 8.26–8.28 (m, 2 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 33.1 (q), 34.0 (q), 52.2 (t), 68.6 (d), 128.9 (d), 130.2 (d), 134.0 (s), 134.8 (d), 160.5 (s), 166.2 (s), 191.8 (s); exact mass (electrospray) *m/z* calcd for $C_{13}H_{15}N_2O_3$ (M + H) 247.1077, found, 247.1077.

3-Benzoyl-4-[(4-methoxyphenyl)methyl]-1-methylpiperazine-2,5-dione (9h). NaH (60% w/w dispersion in mineral oil, 6 mg, 0.138 mmol) was added in one portion to a stirred solution of **9c** (30 mg, 0.0671 mmol) in dry THF (3.4 mL). The reaction flask was lowered into a preheated oil bath (70 °C), and the mixture was stirred for 15 min. The mixture was cooled (ice bath), and pH 7 buffer was added. The aqueous solution was extracted with EtOAc, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 40% EtOAc in hexanes, gave **9h** [18.5 mg, 78 or 85% after correction for recovered **9c** (2.4 mg)] as a white foam: FTIR (neat film) 3065, 2934, 2837, 1676, 1513, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.92 (s, 3 H), 3.73 (s, 3 H), 3.91 (d, *J* = 17.5 Hz, 1 H), 4.07 (d, *J* = 14.5 Hz, 1 H), 4.36 (d, *J* = 17.5 Hz, 1 H), 4.88 (d, *J* = 14.5 Hz, 1 H), 5.52 (s, 1 H), 6.71–6.73 (m, part of AA′BB′ spin system, 2 H), 7.03–7.05 (m, part of AA′BB′ spin system, 2 H), 7.45 (t, *J* = 7.5 Hz, 2 H), 7.60 (t, *J* = 7.5 Hz, 1 H), 7.99–8.01 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 33.9 (q), 48.2 (t), 52.5 (t), 55.3 (q), 64.7 (d), 114.3 (d), 126.4 (s), 128.7 (d), 129.8 (d), 130.7 (d), 134.1 (s), 134.5 (d), 159.7 (s), 160.8 (s), 165.9 (s), 192.7 (s); exact mass (electrospray) *m/z* calcd for $C_{20}H_{20}N_2NaO_4$ (M + Na) 375.1315, found, 375.1309.

3-Acetyl-4-[(4-methoxyphenyl)methyl]-1-methylpiperazine-2,5-dione (10d). NaH (60% w/w dispersion in mineral oil, 31 mg, 0.767 mmol) was added in one portion to a stirred solution of **10c** (144 mg, 0.374 mmol) in dry THF (18 mL). The reaction flask was lowered into a preheated oil bath (70 °C), and the mixture was stirred for 15 min. The mixture was cooled (ice bath), and pH 7 buffer was added. The aqueous solution was extracted with EtOAc, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using 40–50% EtOAc in hexanes, gave **10d** [68.4 mg, 63 or 70% after correction for recovered **10c** (14.5 mg)] as pale yellow crystals: mp 112–114 °C; FTIR ($CHCl_3$, cast) 3007, 2935, 2838, 1732, 1674, 1514, 1464, 1248, 1176 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.17 (s, 3 H), 2.93 (s, 3 H), 3.79 (s, 3 H), 3.84 (d, *J* = 17.5 Hz, 1 H), 4.07 (d, *J* = 14.5 Hz, 1 H), 4.12 (d, *J* = 17.5 Hz, 1 H), 4.64 (s, 1 H), 4.85 (d, *J* = 14.5 Hz, 1 H), 6.83–6.85 (m part of AA′BB′ spin system, 2 H), 7.09–7.11 (m part of AA′BB′ spin system, 2 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 28.0 (q), 33.9 (q), 48.1 (t), 52.1 (t), 55.3 (q), 69.5 (d), 114.4 (d), 126.3 (s), 130.6 (d), 159.8 (s), 160.4 (s), 164.8 (s), 200.4 (s); exact mass (electrospray) *m/z* calcd for $C_{15}H_{18}N_2NaO_4$ (M + Na) 313.1159, found, 313.1158. Crystals for X-ray analysis were grown from EtOAc/hexanes, as described in the General Procedures section.

Phenyl *N*-{[Benzyl(cyanoethyl)carbamoyl]methyl}-*N*-methylcarbamate (11b). $NaHCO_3$ (480 mg, 5.73 mmol) was added to a stirred and cooled (0 °C) solution of **11a**[11] (335 mg, 2.29 mmol) in dioxane (7 mL) and water (7 mL). Acid chloride **7**[1] (651 mg, 2.86 mmol) in dry THF (2.5 mL) was added dropwise over 15 min. The cooling bath was left in place, but not recharged, and stirring was continued overnight. The THF and dioxane were evaporated, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 12 cm), using 40–60% EtOAc in hexanes, gave **11b** (689 mg, 89%) as a white foam: FTIR ($CHCl_3$, cast) 3064, 3031, 2941, 1724, 1675, 1496, 1432, 1204 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 2.93–3.08 (two s, 3 H), 4.30–4.48 (m, 3.6 H), 4.59–4.70 (m, 2.4 H), 7.02–7.40 (m, 10 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 34.7 (t), 34.9 (t), 35.3 (t), 35.7 (t), 35.9 (q), 36.2 (q), 50.5 (t), 50.6 (t), 50.8 (t), 116.3 (s), 116.5 (d), 121.6 (d), 121.7 (d), 125.2 (d), 125.2 (d), 126.7 (d), 126.9 (d), 127.5 (d), 127.7 (d), 127.7 (d), 128.4 (d), 128.5 (d), 128.7 (d), 128.8 (d), 129.2 (d), 129.3 (d),

dx.doi.org/10.1021/jo3007144 | J. Org. Chem. 2012, 77, 5125–5131

135.7 (d), 136.2 (d), 151.1 (s), 151.1 (s), 154.4 (s), 154.6 (s), 168.7 (s), 169.2 (s); exact mass (electrospray) m/z calcd for $C_{19}H_{19}KN_3O_3$ (M + K) 376.1058, found, 376.1058.

1-Benzyl-4-methyl-3,6-dioxopiperazine-2-carbonitrile (11c). NaH (60% w/w dispersion in mineral oil, 23 mg, 0.565 mmol) was added in one portion to a stirred solution of **11b** (93 mg, 0.276 mmol) in dry THF (12 mL). The reaction flask was lowered into a preheated oil bath (70 °C), and the mixture was stirred for 15 min. The mixture was cooled (ice bath), and pH 7 buffer was added. The aqueous solution was extracted with EtOAc, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 8 cm), using 40−70% EtOAc in hexanes, gave **11c** [28.8 mg, 43 or 54% after correction for recovered **11b** (19.3 mg)] as pale pink crystals: mp 147−149 °C; FTIR ($CHCl_3$, cast) 3018, 2932, 1689, 1452, 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.04 (s, 3 H), 4.02 (d, J = 18.0 Hz, 1 H), 4.08 (d, J = 14.5 Hz, 1 H), 4.28 (d, J = 18.0 Hz, 1 H), 4.67 (s, 1 H), 5.40 (d, J = 14.5 Hz, 1 H), 7.28−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.3 (q), 48.1 (t), 49.9 (d), 51.5 (t), 113.1 (s), 128.9 (d), 129.1 (d), 129.4 (d), 133.0 (s), 156.9 (s), 162.9 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{13}N_3NaO_2$ (M + Na) 266.0900, found, 266.0899. Crystals for X-ray analysis were grown from EtOAc/hexanes, as described in the General Procedures section.

Methyl 2-{*N*-Methyl-2-[methyl(phenoxycarbonyl)amino]-acetamido}acetate (12b). $NaHCO_3$ (700 mg, 8.37 mmol) was added to a stirred and cooled (0 °C) solution of methyl 2-(methylamino)acetate hydrochloride[12] (260 mg, 1.86 mmol) in dioxane (6 mL) and water (6 mL). Acid chloride **7**[1] (530 mg, 2.33 mmol) in dry THF (2 mL) was added dropwise over 15 min. The cooling bath was left in place, but not recharged, and stirring was continued overnight. The THF and dioxane were evaporated, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 12 cm), using 50−100% EtOAc in hexanes, gave **12b** (477 mg, 87%) as a white foam: FTIR (CH_2Cl_2, cast) 2953, 1726, 1667, 1480, 1397, 1206, 1118 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 2.84−2.87 (m, 2.6 H), 2.99−3.02 (m, 3.4 H), 3.61−3.69 (four s, 3 H), 4.09−4.13 (m, 1.6 H), 4.21−4.25 (m, 1.6 H), 4.35 (s, 0.8 H), 7.01−7.03 (m, 1.15 H), 7.09−7.11 (m, 0.85 H), 7.16−7.23 (m, 1 H), 7.33−7.38 (m, 2 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 34.4 (q), 34.5 (q), 35.0 (q), 35.0 (q), 35.6 (q), 36.0 (q), 49.0 (t), 49.2 (t), 49.7 (t), 50.2 (t), 50.4 (t), 51.7 (q), 52.0 (q), 121.6 (d), 121.8 (d), 125.0 (d), 125.1 (d), 129.1 (d), 129.2 (d), 151.2 (s), 154.5 (s), 154.7 (s), 168.1 (s), 168.4 (s), 168.6 (s), 169.5 (s), 169.7 (s); exact mass (electrospray) m/z calcd for $C_{14}H_{19}N_2O_5$ (M + H) 295.1288, found, 295.1290.

Methyl 1,4-Dimethyl-3,6-dioxopiperazine-2-carboxylate (12c).[13] NaH (60% w/w dispersion in mineral oil, 35 mg, 0.865 mmol) was added in one portion to a stirred solution of **12b** (124 mg, 0.422 mmol) in dry THF (21 mL) containing *t*-BuOH (8.3 μL, 0.0865 mmol). The reaction flask was lowered into a preheated oil bath (70 °C), and the mixture was stirred for 24 h. The mixture was cooled (ice bath), glacial AcOH (50 μL, 0.865 mmol) was added, and the solvent was evaporated. Flash chromatography of the residue over silica gel (2 × 8 cm), using 80−100% EtOAc in hexanes, gave **12c**[13] (47 mg, 55%) as a white solid: mp 121−123 °C; FTIR (CH_2Cl_2, cast) 2952, 1740, 1676, 1485, 1405, 1236 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.94 (s, 3 H), 2.99 (s, 3 H), 3.83 (s, 3 H), 3.84 (d, J = 17.5 Hz, 1 H), 4.17 (d, J = 17.5 Hz, 1 H), 4.58 (s, 1 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 33.0 (q), 34.0 (q), 51.8 (t), 53.7 (q), 66.0 (d), 160.2 (s), 164.7 (s), 167.0 (s); exact mass (electrospray) m/z calcd for $C_8H_{12}N_2NaO_4$ (M + Na) 223.0689, found, 223.0685. Crystals for X-ray analysis were grown from EtOAc/hexanes, as described in the General Procedures section.

3-Benzoyl-1-benzyl-4-[(4-methoxyphenyl)methyl]-6-methylpiperazine-2,5-dione (9i). NaH (60% w/w dispersion in mineral oil, 30 mg, 0.745 mmol) was added in one portion to a stirred solution of **9g** (195 mg, 0.363 mmol) in dry THF (18 mL). The reaction flask was lowered into a preheated oil bath (70 °C), and the mixture was stirred for 2.5 h. The mixture was cooled (ice bath), and pH 7 buffer was added. The aqueous solution was extracted with EtOAc, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 8 cm), using 30−60% EtOAc in hexanes, gave **9i** (69 mg, 74%) as a white foam: $[\alpha]_D^{20}$ −72.02 (c 1.10, CH_2Cl_2); FTIR (neat, film) 3064, 3031, 2997, 2939, 2837, 1692, 1667, 1513, 1450, 1305, 1247, 1172 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.58 (d, J = 7.0 Hz, 3 H), 3.74 (m, 3 H), 3.87 (d, J = 15.0 Hz, 1 H), 3.91 (d, J = 15.0 Hz, 1 H), 4.06 (q, J = 7.0 Hz, 1 H), 5.03 (d, J = 15.0 Hz, 1 H), 5.13 (d, J = 15.0 Hz, 1 H), 5.65 (s, 1 H), 6.72−6.75 (m, part of AA′BB′ spin system, 2 H), 7.00−7.03 (m, part of AA′BB′ spin system, 2 H), 7.18−7.33 (m, 5 H), 7.46 (t, J = 8.0 Hz, 2 H), 7.61 (t, J = 7.5 Hz, 1 H), 8.04−8.06 (m, 2 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 18.5 (q), 47.3 (t), 48.2 (t), 55.3 (q), 55.7 (d), 64.3 (d), 114.2 (d), 114.3 (d), 126.3 (s), 128.1 (d), 128.1 (d), 128.6 (d), 128.7 (d), 128.8 (d), 128.9 (d), 129.9 (d), 130.5 (d), 130.6 (d), 134.3 (s), 134.4 (d), 135.3 (s), 159.6 (s), 160.6 (s), 168.6 (s), 192.6 (s); exact mass (electrospray) m/z calcd for $C_{27}H_{27}N_2O_4$ (M + H) 443.1965, found, 443.1964.

Phenyl *N*-({Benzyl([2-(4-methoxyphenyl)-2-oxoethyl]-carbamoyl}methyl)-*N*-methylcarbamate (13c). Dess−Martin periodinane (397 mg, 0.938 mmol) was added to a stirred solution of **13b** (280 mg, 0.626 mmol), in dry CH_2Cl_2 (13 mL), and stirring was continued for 5 h. Et_2O was added, and the solution was stirred until cloudy. Aqueous NaOH (2 M) was added, and the mixture was stirred until the phases became clear. The aqueous phase was extracted with Et_2O, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 8 cm), using 40−60% EtOAc in hexanes, gave **13c** [183 mg, 66 or 92% after correction for recovered **13b** (79 mg)] as a white foam: FTIR ($CHCl_3$, cast) 3008, 2935, 2838, 1726, 1663, 1514, 1397, 1248, 1205 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 2.88−3.03 (four s, 3 H), 3.82−3.83 (m, 3 H), 4.07−4.39 (four s, 2 H), 4.53−4.65 (two m, 2 H), 4.76−4.95 (m, 2 H), 7.01−7.07 (m, 3.5 H), 7.18−7.39 (m, 9 H), 7.93−7.97 (m, 1.5 H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 36.0 (q), 36.2 (q), 36.6 (q), 36.7 (q), 50.7 (t), 50.8 (t), 51.0 (t), 51.1 (t), 51.2 (t), 53.2 (t), 53.4 (t), 56.0 (q), 56.1 (q), 114.4 (d), 122.1 (d), 122.2 (d), 125.5 (d), 125.6 (d), 125.7 (d), 127.4−130.9 (numerous d and one s), 137.4 (s), 137.4 (s), 138.0 (s), 138.0 (s), 151.7 (s), 151.7 (s), 151.7 (s), 151.8 (s), 155.0 (s), 155.0 (s), 155.1 (s), 155.3 (s), 163.8 (s), 164.1 (s), 168.7 (s), 169.1 (s), 169.1 (s), 169.6 (s), 192.8 (s), 193.4 (s), 193.4 (s); exact mass (electrospray) m/z calcd for $C_{26}H_{26}N_2NaO_5$ (M + Na) 469.1734, found, 469.1727.

4-Benzyl-3-[(4-methoxyphenyl)carbonyl]-1-methylpiperazine-2,5-dione (13d). NaH (60% w/w dispersion in mineral oil, 22 mg, 0.545 mmol) was added in one portion to a stirred solution of **13c** (118 mg, 0.266 mmol) in dry THF (13.3 mL). The reaction flask was lowered into a preheated oil bath (70 °C), and the mixture was stirred for 30 min. The mixture was cooled (ice bath), and pH 7 buffer was added. The aqueous solution was extracted with EtOAc, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using 40−50% EtOAc in hexanes, gave **13d** [50 mg, 54 or 70% after correction for recovered **13c** (27 mg)] as pale yellow crystals: mp 139−140 °C; FTIR ($CHCl_3$, cast) 3333, 3065, 3010, 2936, 2842, 1672, 1598, 1453, 1251, 1170 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.91 (s, 3 H), 3.83−3.93 (m, 5 H), 4.34 (d, J = 17.1 Hz, 1 H), 5.14 (d, J = 14.7 Hz, 1 H), 5.46 (s, 1 H), 6.90−6.93 (m, part of AA′BB′ spin system, 2 H), 7.13−7.16 (m, 2 H), 7.23−7.26 (m, 3 H), 8.00−8.03 (m, part of AA′BB′ spin system, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 33.9 (q), 48.6 (t), 52.4 (t), 64.7 (q), 114.0 (d), 127.0 (d), 128.2 (s), 128.8 (d), 129.0 (d), 132.4 (d), 134.7 (s), 160.9 (s), 164.8 (s), 166.1 (s), 190.4 (s); exact mass (electrospray) m/z calcd for $C_{20}H_{21}N_2O_4$ (M + H) 353.1496, found, 353.1492.

Phenyl *N*-({Benzyl[(diethoxyphosphoryl)methyl]carbamoyl}-methyl)-*N*-methylcarbamate (14b). $NaHCO_3$ (267 mg, 3.18 mmol) was added to a stirred and cooled (0 °C) solution of **14a**[6] (328 mg, 1.27 mmol) in dioxane (4.5 mL) and water (4.5 mL). Acid chloride **7**[1] (363 mg, 1.59 mmol) in dry THF (2 mL) was added dropwise over 15 min. The cooling bath was left in place, but not recharged, and stirring was continued overnight. The THF and

dx.doi.org/10.1021/jo3007144 | J. Org. Chem. 2012, 77, 5125−5131

dioxane were evaporated, and the aqueous solution was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 12 cm), using 70−100% EtOAc in hexanes, gave **14b** (448 mg, 84%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3064, 3031, 2983, 2933, 1730, 1668, 1453, 1395, 1242, 1206, 1050, 1025 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.15−1.25 (m, 6 H), 2.89−3.05 (four s, 3 H), 3.72−3.81 (m, 2 H), 3.98−4.09 (m, 4 H), 4.25−4.54 (four s, 2 H), 4.67−4.73 (m, 2 H), 7.00−7.04 (m, 1.2 H), 7.08−7.13 (m, 0.8 H), 7.18−7.40 (m, 8 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 16.07 (q), 16.14 (q), 16.2 (q), 35.66 (q), 35.73 (q), 36.0 (q), 36.1 (q), 41.0 (t), 42.5 (t), 49.2 (t), 49.5 (t), 49.9 (t), 50.4 (t), 50.5 (t), 50.6 (t), 50.7 (t), 61.7 (t), 61.8 (t), 62.0 (t), 62.1 (t), 121.5 (d), 121.6 (d), 125.0 (d), 125.1 (d), 126.5 (d), 126.7 (d), 127.2 (d), 127.5 (d), 128.4 (d), 128.7 (d), 128.8 (d), 129.1 (d), 129.2 (d), 136.0 (s), 136.6 (s), 151.1 (s), 151.2 (s), 151.3 (s), 154.5 (s), 154.6 (s), 154.8 (s), 167.9 (s), 168.0 (s), 168.3 (s), 168.5 (s); exact mass (electrospray) m/z calcd for $C_{22}H_{29}N_2NaO_6P$ (M + Na) 471.1655, found, 471.1648.

Diethyl (1-Benzyl-4-methyl-3,6-dioxopiperazin-2-yl)-phosphonate (14c). NaH (60% w/w dispersion in mineral oil, 67 mg, 1.67 mmol) was added in one portion to a stirred solution of **14b** (340 mg, 0.812 mmol) and *t*-BuOH (16 μL, 0.166 mmol) in dry THF (40 mL). The reaction flask was lowered into a preheated oil bath (70 °C), and the mixture was stirred for 4.5 h. The mixture was cooled (ice bath), and pH 7 buffer was added. The aqueous solution was extracted with EtOAc, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using 0−6% MeOH in EtOAc, gave **14c** (126 mg, 44%) as a colorless oil: FTIR ($CDCl_3$, cast) 2982, 2934, 1678, 1452, 1254, 1046, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (the spectrum showed the presence of a byproduct, see text) δ 1.28−1.41 (m, 6 H), 2.99 (m, 3 H), 3.84 (dd, J = 1.5, 18.0 Hz, 1 H), 4.07 (d, J = 12 Hz, 1 H), 4.14−4.27 (m, 5 H), 4.43 (dd, J = 5.0, 18.0 Hz, 1 H), 5.58 (d, J = 14.7 Hz, 1 H), 7.21−7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.4 (q), 16.47 (q), 16.49 (q), 16.51 (q) (the last four signals represent coupling of two diastereotopic CH_3 groups to ^{31}P), 34.1 (q), 48.1 (t), 52.4 (t), 57.3 (d), 58.4 (d) (the last two signals represent coupling of the CH signal to ^{31}P), 63.6 (t), 63.7 (t), 64.1 (t), 64.2 (t) (the last four signals represent coupling of two diastereotopic CH_2 groups to ^{31}P), 128.3 (d), 128.5 (d), 129.1 (d), 134.8 (s), 161.3 (s), 164.6 (s); exact mass (electrospray) m/z calcd for $C_{16}H_{23}N_2NaO_5P$ (M + Na) 377.1237, found, 377.1233.

(3*E*)-4-Benzyl-3-[(4-methoxyphenyl)methylidene]-1-methylpiperazine-2,5-dione (14d) and (3*E*)-1-Benzyl-3-[(4-methoxyphenyl)methylidene]-4-methylpiperazine-2,5-dione (14d′). A solution of **14c** (93 mg, 0.262 mmol) and *p*-anisaldehyde (35 μL, 0.289 mmol) in dry THF (9.6 mL) was added to a stirred and cooled (0 °C) mixture of NaH (60% w/w dispersion in mineral oil, 15 mg, 0.385 mmol) in dry THF (5.8 mL). The mixture was stirred for 2 h at 0 °C and then at room temperature for 1 h. Saturated aqueous NH_4Cl (1.7 mL) and water (1.7 mL) were added. The aqueous solution was extracted with EtOAc, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using 30−80% EtOAc in hexanes, gave **14d** (44 mg, 50%) as a colorless oil and **14d′** (13 mg, 15%) as a yellow oil. Compound **14d**: FTIR ($CDCl_3$, cast) 3317, 3063, 3007, 2933, 2837, 1679, 1606, 1512, 1398, 1251 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.05 (s, 3 H), 3.77 (s, 3 H), 4.19 (s, 2 H), 5.06 (s, 2 H), 6.49 (s, 1 H), 6.79−6.80 (m, 2 H), 7.26−7.29 (m, 5 H), 7.32−7.36 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 33.9 (q), 48.1 (t), 52.2 (t), 55.2 (q), 113.2 (d), 124.8 (d), 126.3 (s), 126.8 (d), 127.5 (d), 128.5 (s), 128.9 (d), 131.2 (d), 135.9 (s), 159.4 (s), 160.0 (s), 163.9 (s); exact mass (electrospray) m/z calcd for $C_{20}H_{20}N_2NaO_3$ (M + Na) 359.1366, found, 359.1366. Compound **14d′**: FTIR ($CHCl_3$, cast) 3335, 3007, 2933, 2837, 1680, 1607, 1512, 1252, 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.29 (s, 3 H), 3.83 (s, 3 H), 3.97 (s, 2 H), 4.65 (s, 2 H), 6.49 (s, 1 H), 6.88−6.90 (m, 2 H), 7.26−7.35 (m, 5 H), 7.46−7.48 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.0 (q), 49.4 (t), 49.5 (t), 55.3 (q), 113.4 (d), 123.7 (d), 126.4 (s), 128.1 (d), 128.4 (d), 129.0 (d), 129.6 (s), 131.4 (d), 135.4 (s), 159.5 (s), 159.8 (s), 163.9 (s); exact mass (electrospray) m/z calcd for $C_{20}H_{21}N_2O_3$ (M + H) 337.1547, found, 337.1546.

3-Benzyl-1-methylimidazolidine-2,4-dione (6h).[8] O_2 was bubbled for 4 min into a stirred solution of **6d** (202 mg, 0.485 mmol) in dry THF (24 mL). NaH (60% w/w dispersion in mineral oil, 40 mg, 0.994 mmol) was added in one portion, and the reaction flask was lowered into a preheated oil bath (70 °C). The mixture was stirred for 2.5 h under O_2 (balloon). The mixture was cooled (ice bath), and pH 7 buffer was added. The aqueous solution was extracted with EtOAc, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using 30−60% EtOAc in hexanes, gave **6h** (55 mg, 56%) as a white foam: FTIR ($CHCl_3$, cast) 3033, 2918, 1773, 1712, 1485, 1451, 1411 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.99 (s, 3 H), 3.86 (s, 2 H), 4.65 (s, 2 H), 7.29−7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.7 (q), 42.6 (t), 51.8 (t), 128.0 (d), 128.7 (d), 128.8 (d), 136.1 (s), 156.6 (s), 169.5 (s); exact mass (electrospray) m/z calcd for $C_{11}H_{12}N_2O_2$ (M + H) 205.0972, found, 205.0969.

■ ASSOCIATED CONTENT

Supporting Information

X-ray data (CIF files and ORTEP diagrams) for compounds **10d**, **11c**, and **12c**, experimental procedures, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: derrick.clive@ualberta.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NSERC for financial support. C.L.A. holds a Queen Elizabeth II Graduate Scholarship.

■ REFERENCES

(1) Peng, J.; Clive, D. L. J. *J. Org. Chem.* **2009**, *74*, 513−519.

(2) (a) Rajappa, S.; Natekar, M. V. *Adv. Heterocycl. Chem.* **1993**, *57*, 187−289. (b) Sammes, P. G. *Fortschr. Chem. Org. Naturst.* **1975**, *32*, 51−118. (c) Dinsmore, C. J.; Beshore, D. C. *Tetrahedron* **2002**, *58*, 3297−3312. (d) Martins, M. B.; Carvalho, I. *Tetrahedron* **2007**, *63*, 9923−9932.

(3) E.g. (a) Rameshkumar, N.; Ashokkumar, M.; Subramanian, E. H.; Ilavarasan, R.; Sridhar, S. K. *Eur. J. Med. Chem.* **2003**, *38*, 1001−1114. (b) McCleland, K.; Milne, P. J.; Lucieto, F. R.; Frost, C.; Brauns, S. C.; van De Venter; Du Plessis, J.; Dyason, K. *J. Pharm. Pharmacol.* **2004**, *56*, 1143−1153. (c) Kanoh, K.; Kohno, S.; Asari, T.; Harada, T.; Katada, J.; Muramatsu, M.; Kawashima, H.; Sekiya, H.; Uno, I. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2847−2852.

(4) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Mol. Diversity* **2000**, *5*, 289−304 and references therein. (b) Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem., Int. Ed.* **2012**, *51*, 1114−1122.

(5) Recent examples of other routes to unsymmetrical piperazine-2,5-diones: (a) Tullberg, M.; Grøtli, M.; Luthmn, K. *J. Org. Chem.* **2007**, *72*, 195−199. (b) Davies, S. G.; Garner, A. C.; Ouzman, J. V. A.; Roberts, P. M.; Smith, A. D.; Snow, E. J.; Thomson, J. E.; Tamayo, J. A.; Vickers, R. J. *Org. Biomol. Chem.* **2007**, *5*, 2138−2147. (c) Chai, C. L. L.; Elix, J. A.; Huleatt, P. B. *Tetrahedron* **2005**, *61*, 8722−8739. (d) Long, D. D.; Tennant-Eyles, R. J.; Estevez, J. C.; Wormald, M. R.; Dwek, R. A.; Smith, M. D.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 807−813.

(6) Lewis, R. T.; Motherwell, W. B. *Tetrahedron* **1992**, *48*, 1465−1484.

(7) (a) Overman, L. E.; Rosen, M. D. *Tetrahedron* **2010**, *66*, 6514−6525. (b) Davies, S. G.; Rodríguez-Solla, H.; Tamayo, J. A.; Cowley, A.

R.; Concellón, C.; Garner, A. C.; Parkes, A. L.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 1435−1447. (c) Du, Y.; Wiemer, D. F. *J. Org. Chem.* **2002**, *67*, 5709−5717. (d) Overman, L. E.; Rosen, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4596−4599. (e) Alcaraz, C.; Herrero, A.; Marco, J. L.; Fernández-Alvarez, E.; Bernabé, M. *Tetrahedron Lett.* **1992**, *33*, 5605−5608. (f) Lieberknecht, A.; Griesser, H. *Tetrahedron Lett.* **1987**, *28*, 4425−4278.

(8) Hoffman, R. V.; Reddy, M. M.; Cervantes-Lee, F. *J. Org. Chem.* **2000**, *65*, 2591−2595.

(9) Watson, I. D. G.; Yudin, A. K. *J. Org. Chem.* **2003**, *68*, 5160−5167.

(10) Polaske, N. W.; Dubey, R.; Nichol, G. S.; Olenyuk, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2742−2750. Our ^{1}H NMR spectrum of **8d** differs from the reported data.

(11) Broggini, G.; Garanti, L.; Molteni, G.; Zecchi, G. *Tetrahedron* **1998**, *54*, 14859−14868.

(12) Arshady, R.; Atherton, E.; Clive, D. L. J.; Sheppard, R. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 529−537.

(13) Polaske, N. W.; Nichol, G. S.; Szabó, L. Z.; Olenyuk, B. *Cryst. Growth Des.* **2009**, *9*, 2191−2197.