**Reaction of Methylene Ditosylate and Lithium Chloride.** To a solution of $CH_2(OTs)_2$ (1.07 g, 3.00 mmol) in acetone (4 mL) was added a solution of LiCl (191 mg, 4.50 mmol) in methanol. After the resulting solution had been refluxed 10 h, it was poured into $Et_2O$–water (25 mL each); the organic layer was washed with water (25 mL) and saturated aqueous NaCl (25 mL), dried ($MgSO_4$), and filtered. The filtrate was stripped of solvent to leave 544 mg (98%) of essentially pure $ClCH_2OTs$.

**Bromomethyl Tosylate.** To a solution of $CH_2(OTs)_2$ (1.068 g, 3.00 mmol) in acetone (2.5 mL) was added a solution of LiBr (391 mg, 4.50 mmol) in acetone (1.5 mL). On heating to reflux (2 min), the solution suddenly filled with colorless crystals (LiOTs). Analysis ($^1H$ NMR) indicated ca. 90% conversion to $BrCH_2OTs$. On standing overnight (25 °C), conversion was 100%; no $CH_2(OTs)_2$ or $CH_2Br_2$ was detectable. Addition of $CH_2Cl_2$ to precipitate Li salts, filtration, and removal of solvent left 780 mg (>98%) of pale yellow oil. An analytical sample, mp <20 °C, was obtained by recrystallization from MeOH (0–5 °C) or by distillation (bp 112–114 °C, 0.4 mmHg): $^1H$ NMR $\delta$ 2.46 (s, 3 H), 5.84 (s, 2 H), 7.37 (d, 2 H), and 7.83 (d, 2 H); $^{13}C$ NMR $\delta$ 21.61, 61.27, 128.21, 129.88, 132.75, 145.81. Anal. Calcd for $C_8H_9BrO_3S$: C, 36.24; H, 3.42. Found: C, 37.62; H, 3.38.

**Iodomethyl Tosylate.** To a solution of $CH_2(OTs)_2$ (712 mg, 2.0 mmol) in acetone (4.5 mL) was added a solution of NaI (450 mg, 3.0 mmol) in acetone (1.5 mL). On warming to 50 °C (5 min), the pale yellow solution was filled with colorless, heavy crystals. After being allowed to stand for 0.5 h, the mixture was poured into a mixture of $Et_2O$ and water (30 mL ea), decolorized with a pinch of $NaHSO_3$, washed with water and saturated brine (30 mL ea), and dried in the dark over $MgSO_4$. Filtration and solvent removal left 635 mg (>100%) of pale yellow oil. Analysis ($^1H$ NMR) showed ca. 10% of unreacted $CH_2(OTs)_2$ remaining; Kugelrohr distillation (115–120 °C, 0.2 mmHg) yielded 455 mg (73%) of $ICH_2OTs$ as a nearly colorless oil: $^1H$ NMR $\delta$ 2.46 (s, 3 H), 5.90 (s, 2 H), 7.38 (d, 2 H), and 7.81 (d, 2 H); $^{13}H$ NMR $\delta$ 21.67, 32.51, 128.37, 129.93, 132.13, 145.86. A refrigerated sample appeared unchanged (NMR) after several months. Anal. Calcd for $C_8H_9IO_3S$: C, 30.78; H, 2.91. Found: C, 31.18; H, 2.84.

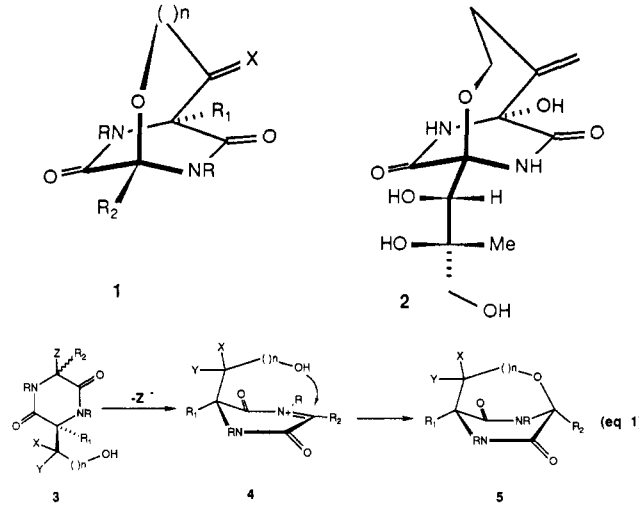
**Acknowledgment.** We thank the Chemistry Department, Syracuse University, and the College of Health Related Professions, SUNY Health Science Center, for financial support.

# *Communications*

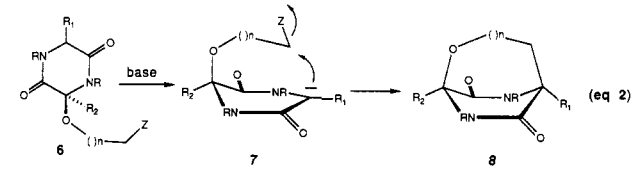
## Versatile New Approach to the Synthesis of Monosubstituted and Bicyclic Piperazine-2,5-diones: Unusual in Situ Generation and Enolate Addition to a Cumulene

*Summary:* Dichloroacetyl chloride condenses with glycinamide **9** to furnish the versatile precursor **10**, which cyclizes to the mono (ether) substituted piperazinediones **11** upon treatment with alkoxides. A new intramolecular enolate C–C bond-forming cyclization from these derivatives furnishes three new bicyclo[*n*.2.2]piperazinediones **14**, **17**, and **18**.

*Sir:* Bicyclo[*n*.2.2]piperazinediones **1** have proven to be valuable, versatile templates from which the total synthesis of bicyclomycin[1] (**2**) and a variety of interesting analogues[2] have been prepared. A primary synthetic difficulty that has been encountered in constructing such systems is the incorporation of the branched $\beta,\gamma$-unsaturated amino acid residue. While this problem has been solved in various ways,[3] the multistep pathways that have been developed to install this functionality preclude convenient access to reasonable quantities of these compounds for further elaboration and study. Additionally, the most successful strategies[1] have employed an intramolecular O–C bond construction to form the bicyclic ring system (eq 1).




Reported herein is an entirely new approach to this class of compounds that features intramolecular C–C bond-forming cyclization reactions (eq 2). Dichloroacetyl




chloride efficiently acylates glycinamide **9** to afford the dichloride **10**[4] (mp 105–106 °C, 88% yield). Condensation of **10** with a variety of alcohols (Table I) in the presence of base furnishes the piperazinediones **11**.[4] This technique gives access to the deceptively simple yet difficult to prepare monoethers of piperazinediones **11**. For example, selective monobromination of various glycine anhydride

(1) (a) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc.* **1984**, *106*, 5748. (b) **1985**, *107*, 3253. (c) Yamaura, M.; Suzuki, T.; Hashimoto, H.; Yoshimura, J.; Shin, C. *Chem. Lett.* **1984**, 1547. (d) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1984**, 2157. (e) Dawson, I. M; Gregory, J. A.; Herbert, R. B.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1986**, 620. (f) Nakatsuka, S.; Yamada, K.; Yoshida, K.; Asano, O.; Murakami, Y.; Goto, T. *Tetrahedron Lett.* **1983**, *24*, 5627.

(2) (a) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Med. Chem.* **1985**, *28*, 733. (b) Sera, A.; Itoh, K.; Yamada, H.; Aoki, R. *Heterocycles* **1984**, *22*, 713. (c) Fukuyama, T.; Robins, B. D.; Sachleben, R. A. *Tetrahedron Lett.* **1981**, *22*, 4155. (d) Nakatsuka, S.; Yoshida, K.; Goto, T. *Ibid.* **1981**, *22*, 4155.

(3) For a review, see: Williams, R. M.; Durham, C. *Chem. Rev.* **1988**, *88*, 511.

(4) All new compounds exhibited satisfactory spectroscopic and analytical data consistent with the assigned structures.

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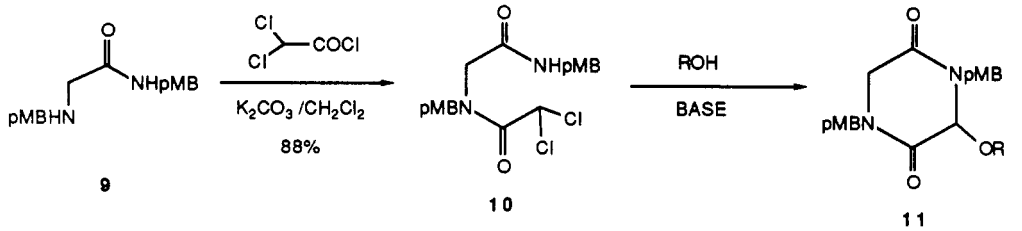
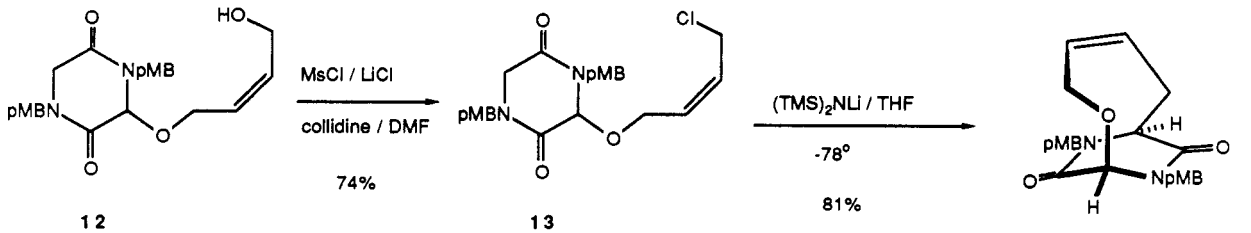
**Scheme I**




9 10 11

pMB = *para*-methoxybenzyl

**Scheme II**




12 13 14

derivatives followed by alcoholysis is plagued by the strong tendency of these substrates to give exclusively 3,6-dibrominated piperazine-2,5-diones.[5] The methodology illustrated in Scheme I obviates the regiochemical and chemoselectivity problems associated with the above oxidative alternatives.[6]

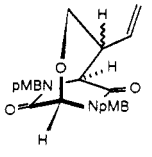
Three new bicyclic piperazinediones have been synthesized as illustrated in Schemes II and III to illustrate the potential of this methodology. Condensation of **10** with (*Z*)-butene-1,4-diol furnished the piperazinedione **12** (oil, 57%, Table I, entry 5), which was converted into the allylic chloride **13** (74%, mp 93–94 °C). Cyclization of **13** was effected by treatment with lithium bis(trimethylsilyl) amide in THF at −78 °C to aford the bicyclo[5.2.2]-piperazinedione **14** (mp 167 °C) in 81% yield. This reaction is also noteworthy in that none of the corresponding isomeric bicyclo[3.2.2] vinyl product resulting from intramolecular $S_N2'$ cyclization was produced.[7] Although a nine-membered-ring product is formed in this reaction, the conformational restraints imposed by the *Z* olefin and rigid piperazinedione provide an excellent geometry for the $S_N2$ transition state leading to **14**. Compound **14** also constitutes the first bicyclo[5.2.2]piperazinedione to have been synthesized.[3]

In an attempt to *directly* introduce the β,γ-unsaturated moiety of bicyclomycin in the cyclization step, alkyne **15** was prepared from the condensation of **10** with 1-[(*tert*-butyldiphenylsilyl)oxy]-2-pentyn-5-ol. Removal of the silyl ether and conversion to the chloride **16** proceeded in 80% overall yield. Treatment of **16** with NaH in hot toluene in the presence of 18-crown-6 effected the formation of two unusual bicyclic products, **17**[8] (23%) and **18**[9] (20%). A slight change in the reaction conditions (KH, THF, 18-crown-6, room temperature) led to formation of **18** as the major product (42%), along with trace amounts (9%) of **17**. Treatment of **16** with $LiN(SiMe_3)_2$ in THF at −78 °C resulted in essentially no reaction and with potassium *tert*-butoxide under the same conditions led to extensive decomposition. The specific choice of base for these re-

(5) For example, attempts to monobrominate *N,N'*-bis(*p*-methoxybenzyl)-2,5-piperazinedione with 0.9 equiv of NBS afforded ~50% of the 3,6-dibromide and ~50% of unbrominated starting material.

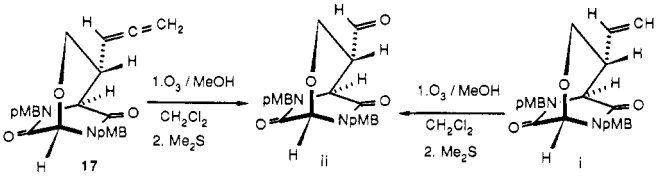
(6) A four-step conversion of sarcosine anhydride to the corresponding monomethoxy derivative has been reported: Williams, R. M. *Tetrahedron Lett.* **1981**, *22*, 2341. However, this method is not general.

(7) Authentic samples of both stereoisomers of the bicyclo[3.2.2] product i were available from longer routes; see: Armstrong, R. W. Ph.D. Thesis, 1984, Colorado State University.

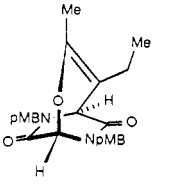



i

(8) The structure and relative stereochemistry of **17** were proven by correlation to the aldehyde ii obtained from ozonolysis of **17** and a known[7] stereoisomer of i. **17**: $^1H$ NMR ($CDCl_3$) (270 MHz) δ 2.8–2.9 (1 H, m), 3.72 (1 H, dd, *J* = 10.4 Hz, *J* = 12.8 Hz), 3.77 (3 H, s), 3.78 (3 H, s), 3.87 (1 H, dd, *J* = 12.8 Hz, *J* = 5.5 Hz), 3.93 (1 H, d, *J* = 0.7 Hz), 4.08 (1 H, d, *J* = 14.7 Hz), 4.24 (1 H, d, *J* = 14.8 Hz), 4.75 (1 H, d, *J* = 14.8 Hz), 4.84 (2 H, d, *J* = 3.9 Hz), 5.03 (1 H, s), 5.08 (1 H, d, *J* = 14.7 Hz), 6.8–6.9 (4 H, m), 7.0–7.15 (4 H, m); $^{13}C$ NMR (67.9 MHz) $CDCl_3$ δ 38.6 (d), 48.0 (t), 49.1 (t), 55.3 (q), 62.9 (d), 67.05 (t), 77.9 (t), 85.9 (d), 88.2 (d), 114.5 (d), 114.6 (d), 127.9 (s), 128.0 (s), 129.5 (d), 129.6 (d), 159.7 (s), 159.9 (s), 163.9 (s), 170.2 (s), 208.2 (s); IR (NaCl, neat) 1940, 1680, 1600, 1500, 1440, 1230 $cm^{-1}$; mass spectrum, *m/e* 434 ($M^+$, 5.4), 418 (0.4), 394 (0.2), 136 (11), 121 (11), 44 (14), 35 (100).




(9) In addition to the spectroscopic and analytical data for **18**, hydrogenation of **18** ($H_2$/$Pd^0$/EtOH) gave a single dihydro derivative (iii) that displayed the expected spectroscopic and analytical properties. **18**: $^1H$ NMR ($CDCl_3$) (270 MHz) δ 1.76 (3 H, s), 3.78 (6 H, s), 4.16 (1 H, d, *J* = 14.7 Hz), 4.27 (1 H, s), 4.56 (2 H, s), 4.78 (1 H, d, *J* = 14.7 Hz), 4.87 (1 H, d, *J* = 11.1 Hz), 4.92 (1 H, d, *J* = 17.1 Hz), 5.25 (1 H, s), 6.32 (1 H, dd, *J* = 17.1 Hz, *J* = 11.1 Hz), 6.8–6.9 (4 H, m), 7.1–7.2 (4 H, m); $^{13}C$ NMR (67.9 MHz) ($CDCl_3$) δ 17.6 (q), 47.9 (t), 55.3 (q + d), 84.7 (d), 110.0 (s), 110.5 (t), 114.5 (d), 127.4 (s), 127.9 (s), 129.5 (d), 129.6 (d), 131.7 (d), 157.6 (s), 159.8 (s), 163.4 (s), 167.9 (s); IR (NaCl, neat) 1692, 1688, 1622, 1610, 1510, 1447, 1240 $cm^{-1}$; mass spectrum, *m/e* 434 ($M^+$, 1.2), 171 (9), 121 (48), 42 (30), 57 (26).




iii

**Scheme III**

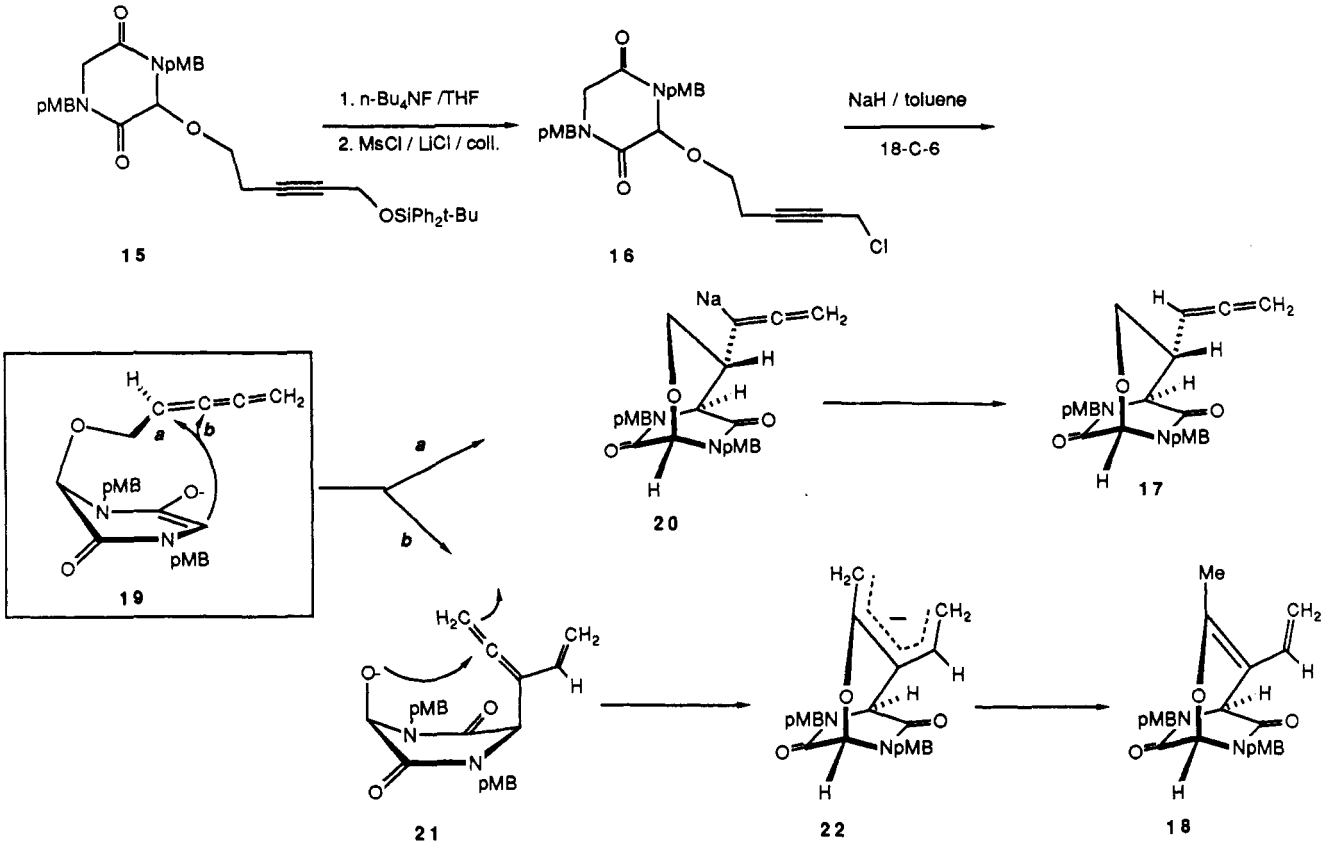



**Table I. Cyclization of 10 → 11**

| ENTRY | SOLVENT / BASE | ALCOHOL (ROH) | YIELD % |
|---|---|---|---|
| 1 | MeOH / NaOMe Δ | MeOH | 60 |
| 2 | EtOH / KOt-Bu Δ | EtOH | 74 |
| 3 | THF / KOt-Bu 0° | HO | 73 |
| 4 | THF / KOt-Bu 25° | HO | 54 |
| 5 | THF / KOt-Bu Δ | HO OH | 57 |
| 6 | THF / KOt-Bu Δ | HO OH | 61 |
| 7 | THF / KOt-Bu Δ | HO OH | 46 |
| 8 | DMF / KOt-Bu 0° | HO H | 67 |
| 9 | THF / NaH 0° | HO OSiR3 | 50 |
| 10 | DMF / KOt-Bu 0° | HO OH | 67 |
| 11 | DMF / KOt-Bu 0° | HO OH | 66 |

actions must be determined empirically and seems intimately related to the reactivity of the electrophilic tether. Under no set of reaction conditions was it possible to detect a product resulting from intramolecular $S_N2'$ cyclization (a bicyclo[4.2.2] *exo*-allene derivative).

A mechanism for the formation of these interesting substances is depicted in Scheme III. Base-induced elimination of HCl from **16** would furnish the cumulene **19**. Subsequent enolate addition via path a furnishes the metalloallene **20**, which protonates to furnish **17**. It is also of interest that the enolate addition to the cumulene appears to proceed stereospecifically since a single diastereomer of **17** was isolated with the relative stereochemistry depicted.[8]

Alternatively, enolate addition via an intramolecular $S_N2'$ (pathway b) reaction furnishes the alkoxy ene–allene **21**, which suffers intramolecular readdition of the alkoxide across the allene moiety resulting in the highly delocalized anion **22**, which protonates to furnish **18**. In spite of the modest yields in the formation of **17** and **18**, these reactions provide the shortest, most direct routes for constructing unsaturated bicyclic piperazinediones. It is expected that the methodology described herein will open numerous new pathways to monosubstituted and new bicyclic piperazinediones that have heretofore been inaccessible or tedious to prepare.

**Acknowledgment.** We thank the National Institutes of Health (AIGM 18957) for support of this research.

**Supplementary Material Available:** Spectroscopic and analytical data for all new compounds (7 pages). Ordering information is given on any current masthead page.

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## Use of Hydrogen Bonds To Control Molecular Aggregation. Extensive, Self-Complementary Arrays of Donors and Acceptors

*Summary:* Strong new hydrogen-bonding motifs can be created by using rigid spacers to link 2-pyridones in series. Asymmetric dipyridones like acetylene **5** have self-complementary arrays of hydrogen-bond donors and acceptors and therefore form strong dimers in $CHCl_3$ ($-\Delta G° > 6.5$

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