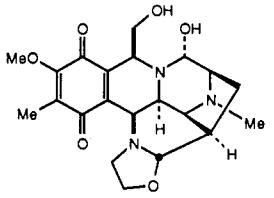
An Asymmetric Approach to Naphthyridinomycin and Quinocarcin via a Remarkably Selective Intramolecular 1,3-Dipolar Cycloaddition Reaction

Summary: A viable strategy for the asymmetric synthesis of the 3,8-diazabicyclo[3.2.1]octane moiety of naphthyridinomycin and quinocarcin based on a *stereospecific* intramolecular 1,3-dipolar cycloaddition reaction is described.

Sir: In connection with the development of an enantioselective synthesis of naphthyridinomycin (**1**) and quinocarcin (**2**),[1-4] we recently reported a strategy for assembly of the 3,8-diazabicyclo[3.2.1]octane moiety of these alkaloids via the cycloaddition of chiral azomethine ylides to a prochiral acrylate dipolarophile (Cf. I → II).[5,6] This



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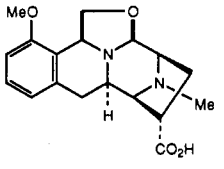

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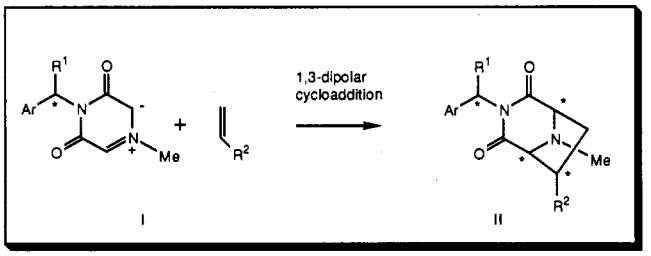
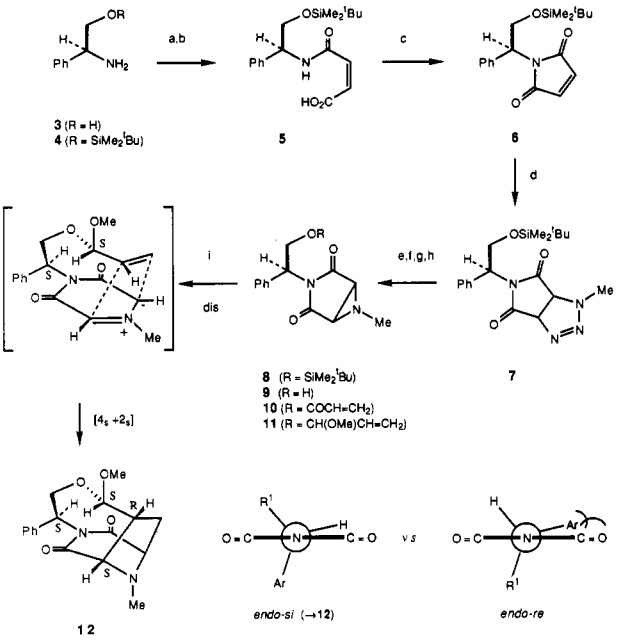


concerted reaction could, in principle, lead to four possible stereoisomeric adducts depending on the addition topology and diastereoselectivity. In fact, it was found that while this intermolecular 1,3-dipolar cycloaddition proceeded with good exo selectivity, the diastereoselectivity (i.e. *re* vs *si* olefin facial preference) associated with the process was nil. Thus it was obvious that a different tactic would be required to achieve the desired diastereofacial selectivity and introduce the endo substituent (R^2 = aminal) needed for the naphthyridinomycin series.

We reasoned that if the dipolarophile were already attached to a glycinol derived azomethine ylide (R^1 = CH_2OR^2), then intramolecular cycloaddition would not only be forced to proceed through an endo transition state but should also exhibit the desired *si* diastereofacial preference as well. The latter prediction was based on our analysis of molecular models, which suggested that steric repulsion between the aromatic ring and one of the imide carbonyls would be minimized in the intramolecular transition state leading to the correct diastereomer (vide infra). We now report a remarkably selective intramolecular 1,3-dipolar cycloaddition[7] that does indeed provide

Scheme I[a]



[a] Reagents: (a) ^{t}BuMe$_2$SiCl, CH_2Cl_2, room temperature 51%; (b) maleic anhydride, Et_2O, 0 °C, 88%; (c) NaOAc/Ac_2O, 120 °C, 33% (d) MeN_3/toluene, room temperature 87%; (e) *hν* (Hg), Pyrex, dioxane, 78%; (f) AcOH–H_2O–THF (3:1:1), 55 °C, 67%; (g) **9** → **10**: H_2C=CHCOCl, Et_3N, CH_2Cl_2, 0 °C, 80%; (h) **9** → **11**: H_2C=C=CHOMe, PPTS, room temperature 63%; (i) **11** → **12**: *hν* (2537 Å), quartz, MeCN (see Table I).

Table I. Intramolecular 1,3-Dipolar Cyclization of 11 to 12[a]

entry	diastereomer ratio *S,S*:*S,R*	total acetal concentration, M	reaction time, h	isolated yield,[b] %
1	(1:1)	0.01	7	35
2	(1:1)	0.001	2	42
3	(4:1)[c]	0.001	2	47
4	(1:7)[c]	0.001	2	trace

[a] Photolyses were performed in quartz vessles at the indicated concentrations in dry, nitrogen-purged acetonitrile using a Rayonet Photochemical Reactor equipped with 2537-Å low-pressure mercury lamps. Reactions were conducted in the presence of either 2 equiv (entry 1) or 10 equiv (entries 2–4) of isoprene to help retard product decomposition (see ref 14). [b] Based on the total amount of 11 consumed, i.e. [(*S,S*)-11 + (*S,R*)-11]. [c] These diasteromerically enriched samples were obtained by normal-phase HPLC on silica gel eluting with hexanes–ethyl acetate.

(1) Naphthyridinomycin: Kluepfel, D.; Baker, H. A.; Piattoni, G.; Sehgal, S. N.; Sidorowicz, A.; Singh, K.; Vezina, C. *J. Antibiot.* **1975**, *28*, 497. Sygusch, J.; Brisse, F.; Hanessian, S.; Kluepfel, D. *Tetrahedron Lett.* **1974**, 4021. Errata: *Ibid.* **1975**, 170. Cyanocyclin: Zmijewski, M. J., Jr.; Goebel, M. *J. Antibiot.* **1982**, *35*, 524. Hayashi, T.; Noto, T.; Nawata, Y.; Okazaki, H.; Sawada, M.; Ando, K. *Ibid.* **1982**, *35*, 771. SF-1739 HP/naphthocyanidine: Itoh, J.; Omoto, S.; Kodama, Y.; Hisamatsu, T.; Niida, T.; Ogawa, Y. *Ibid.* **1982**, *35*, 642.

(2) Quinocarcin: Tomita, F.; Takahashi, K.; Shimizu, K. *J. Antibiot.* **1983**, *36*, 463. Takahashi, K.; Tomita, F. *Ibid.* **1983**, *36*, 468. Hirayama, N.; Shirahata, K. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1705.

(3) Total synthesis of (±)-cyanocyclin A: Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2478. Fukuyama, T.; Li, L.; Laird, A. A.; Frank, R. K. *Ibid.* **1987**, *109*, 1587. Related synthetic work: Parker, K. A.; O'Fee, R. *J. Am. Chem. Soc.* **1983**, *105*, 654. Parker, K. A.; Cohen, I. D.; Babine, R. E. *Tetrahedron Lett.* **1984**, 3543. Danishefsky, S.; O'Neill, B. T.; Springer, J. P. *Ibid.* **1984**, 4203. Danishefsky, S.; O'Neill, B. T.; Taniyama, E.; Vaughan, K. *Ibid.* **1984**, 4199. Evans, D. A.; Biller, S. A. *Ibid.* **1985**, 1911; **1985**, 1907. Fukuyama, T.; Frank, R. K.; Laird, A. A. *Ibid.* **1985**, 2955. Fukuyama, T.; Laird, A. *Ibid.* **1986**, 6173.

(4) Total synthesis of (±)-quinocarcinol: Danishefsky, S.; Harrison, P. J.; Webb II, R. R.; O'Neill, B. T. *J. Am. Chem. Soc.* **1985**, *107*, 1421. Total synthesis of (±)-quinocarcin: Fukuyama, T.; Nunes, J. J. *Ibid.* **1988**, *110*, 5196. Related synthetic work: Williams, R. M.; Ehrlich, P. P.; Zhai, W.; Hendrix, J. *J. Org. Chem.* **1987**, *52*, 2615. Saito, H.; Hirata, T. *Tetrahedron Lett.* **1987**, 4065.

(5) Garner, P.; Sunitha, K.; Shanthilal, P. *Tetrahedron Lett.* **1988**, 3525.

(6) Prior to our initial publication, a related approach to the 3,8-diazabicyclo[3.2.1]octane portion of these targets based on 1,3-dipolar cycloadditions to achiral 2-oxidopyrazinium species had been reported. See: Kiss, M.; Russell-Maynard, J.; Joule, J. A. *Tetrahedron Lett.* **1987**, 2187.

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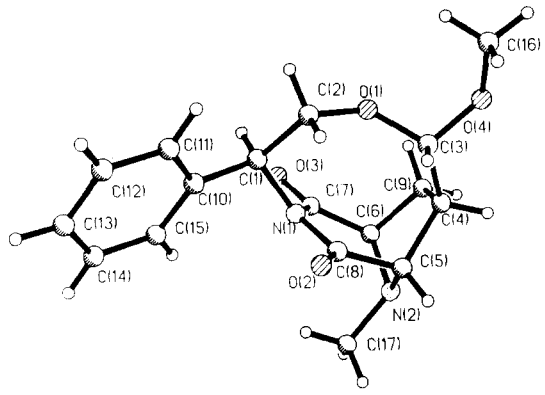

Figure 1. Molecular structure of **12**.

a concise solution to the stereochemical dilemma outlined above setting the stage for an asymmetric synthesis of naphthyridinomycin and quinocarcin from appropriately substituted phenylglycinol derivatives.[8]

Our initial choice of substrate for the proposed intramolecular 1,3-dipolar cycloaddition was the aziridine acrylate **10**, which can be prepared from (*S*)-phenylglycinol following the protocol previously reported for intermolecular substrates[5] except that in this case the alcohol function was protected as a *tert*-butyldimethylsilyl ether (Scheme I).[9] However, photolysis of **10** under our usual conditions failed to give any intramolecular cycloadducts even at high dilution.[10] To circumvent this difficulty, which was reminiscent of a number of unsuccessful intramolecular cycloadditions involving ester linkages,[11] we followed Boeckman's lead and turned to substrate **11** in which the ester was replaced by an acetal moiety. This compound was obtained in 77% yield as a (1:1) mixture of acetal diastereomers by treatment of **9** with methoxyallene in the presence of mild acid.[12] We were gratified to find that photolysis of an acetonitrile solution of **11** at 2537 Å did indeed lead to the isolation of a *single* intramolecular cycloadduct in 35–42% isolated yield after flash chromatography (Table I, entries 1 and 2). The identity of this compound was unambiguously established as **12** by means of X-ray crystallography.[13]

The observed specificity for **12** seems to corroborate our expectation of a preferred transition-state conformation for this intramolecular cycloaddition process that avoids placing the aromatic ring in the imide plane (compare the two Newman projections in Scheme I).[14] It is also worth noting that only the *S,S* acetal diastereomer appears to undergo intramolecular cycloaddition, the *S,R* diastereomer (whose intramolecular *endo-si* mode would lead to an unfavorable dipole–dipole interaction between the methoxy group and an imide carbonyl) being siphoned off during the reaction via polymerization or other nonproductive pathways (compare entries 3 and 4).[15] In any event, the yield of **12** starting from a (1:1) mixture of acetal diastereomers **11** is 70–84% based on the conversion of (*S,S*)-**11** only. The described synthetic sequence provides an efficient *asymmetric* entry to the 3,8-diazabicyclo[3.2.1]octane nucleus of naphthyridinomycin starting from phenylglycinol and would, after subsequent epimerization and oxidation of the acetal-masked formyl group, lead to the corresponding quinocarcin nucleus as well.[16]

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Supplementary Material Available: Tables of data collection details, fractional atomic coordinates, bond distances, bond and torsional angles, anisotropic and isotropic thermal parameters associated with the X-ray structure determination of (±)-**12**, and the crystal structure (11 pages). Ordering information is given on any current masthead page.

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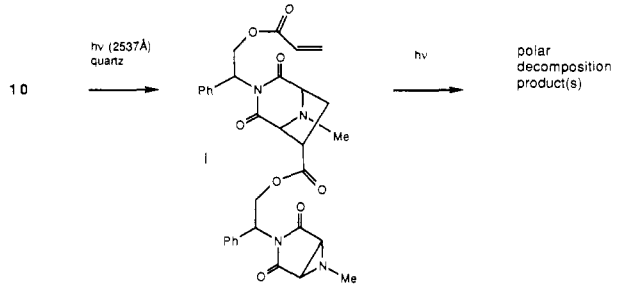
(7) A compilation of known intramolecular azomethine ylide cycloaddition reactions may be found in the following two articles: Pearson, W. H. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: New York, 1988; Vol 1. Stereoselective Synthesis (Part A), p 323. Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol 2, p 277.

(8) Appropriately substituted phenylglycinols can be derived from the corresponding phenylglycines, which are themselves available in high enantiomeric purity via asymmetric Strecker technology. Cf. Kunz, H.; Sager, W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 557 and references cited therein.

(9) Satisfactory IR, NMR, and HRMS or combustion analyses have been obtained for all substances shown.

(10) When this reaction was stopped after only a few minutes of irradiation, the intermolecular cycloadduct i (m/e = 600) could be isolated in 25% yield along with unreacted **10**. Continued photolysis of this material led to the usual polar decomposition product(s).



(11) Parker, K. A.; Adamchuk, M. R. *Tetrahedron Lett.* **1978**, 1689. Boeckman, R. K., Jr.; Demko, D. M. *J. Org. Chem.* **1982**, *47*, 1792. Boeckman, R. K., Jr.; Flann, C. J. *Tetrahedron Lett.* **1983**, 5035. Pirrung, M. C.; Thomson, S. A. *Ibid.* **1986**, 2703.

(12) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 917 and 1179.

(13) Being that enantiomerically pure **12** was found to be noncrystalline, the single-crystal X-ray diffraction experiment was conducted on racemic **12**, mp 120–121 °C, prepared from (±)-phenylglycinol. (±)-**12** crystallizes from hexanes–EtOAc in the orthorhombic space group *Pcab*, with a = 13.912 (4) Å, b = 14.438 (3) Å, c = 15.345 (3) Å, V = 3082.4 (13) Å^3, ρ_{calcd} = 1.363 g/cm^3, Z = 8. Standard direct and difference Fourier methods and least-squares refinement on the basis of 1333 ($F \geq 6\sigma$) reflections led to a final R = 0.0407.

(14) The possibility of some kinetic resolution at the cycloadduct stage cannot yet be rigorously excluded since **12** itself contains potentially photolabile functionality. Even in the presence of isoprene, which is known to quench aliphatic imide triplets (cf. Kanaoka, Y.; Yoshida, K.; Hatanaka, Y. *J. Org. Chem.* **1979**, *44*, 664), we found that product **12** still suffers some nondescript decomposition (though this seems to be concentration dependent). An effort is being made to identify the nature of this decomposition though it is complicated by the absence of distinct and readily isolable products.

(15) The isolated yield of **12** was lower than expected when mixtures enriched in the (*S,S*)-**11** acetal diastereomer were employed (compare entries 2 and 3 in Table I). Product photoinstability (see ref 14) may also be at least partially responsible for this apparent discrepancy. One plausible scenario might involve the (as yet uncharacterized) product(s) derived from (*S,R*)-**11** acting as a photochemical filter and thus slowing down the rate of photochemical decomposition of cycloadduct **12** by effectively competing with it for available photons.

(16) During the preparation of this manuscript a chiral synthesis of the ABE ring system of quinocarcin was reported: Saito, S.; Matsuda, F.; Terashima, S. *Tetrahedron Lett.* **1988**, 6301.

(17) Author to whom inquiries concerning the X-ray structure determination should be addressed.