with highly diastereoselective (1:32) α-face delivery trans to the heterocyclic base; (4) the 5'-hydroxyl group of a nucleoside acts as a β-face directing replacement ligand at boron to effect reversed diastereoselectivity (199:1) by intramolecular hydride delivery; and (5) substitution of sodium borodeuteride gives a reagent with tightly bound isotope that provides 3'-labeled ribonucleosides with virtually complete stereoselectivity. Synthetic details of these ambient or lower temperature procedures, spectroscopic data, and applications of stereodirected reductions with other sites, functional groups, and nucleosides will be reported.

Acknowledgment. We thank the American Cancer Society (CH-405) and Brigham Young University development funds for generous support.

Complex Pyrrolidines via a Tandem Michael Reaction/1,3-Dipolar Cycloaddition Sequence. A Novel Method for the Generation of Unsymmetrical Azomethine Ylides

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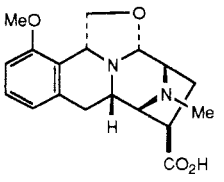
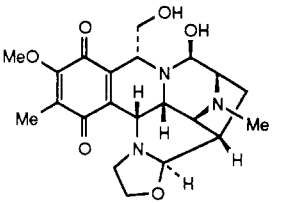
Summary: A novel tandem Michael addition/1,3-dipolar cycloaddition protocol for the assembly of the 3,8-diazabicyclo[3.2.1]octane ring system found in naphthyridinomycin (1) and quinocarcin (2) is described.

We recently presented a synthetic approach to the 3,8-diazabicyclo[3.2.1]octane ring systems of quinocarcin (1) and naphthyridinomycin (2) based on the 1,3-dipolar

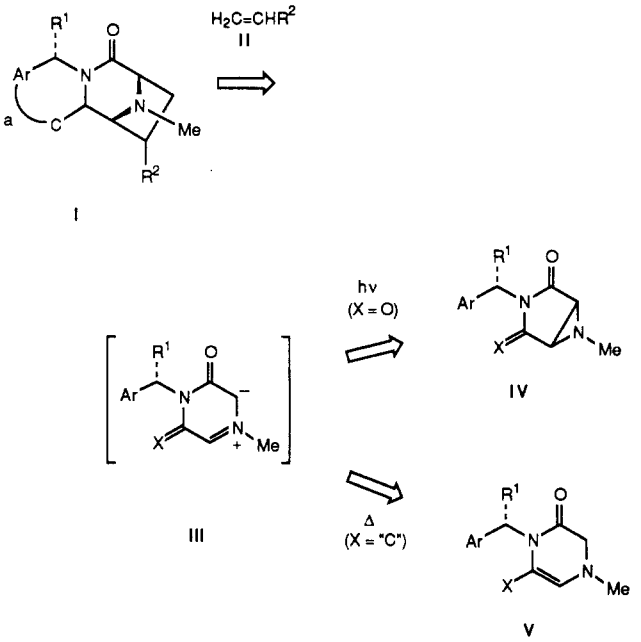


1



2

cycloaddition of symmetrical (but chiral) azomethine ylides III (X = O) available via photochemical opening of aziridines such as IV.[1,2] We envisioned a variation on this strategy that would involve the generation and regioselective trapping of unsymmetrical azomethine ylides III (X = "C") to produce cycloadducts I already differentiated for isoquinoline formation (cf. connection "a").[3] It was anticipated that this net transformation might be accomplished thermally starting from tetrahydropyrazinones V even though this entry to azomethine ylides from enamine-like structures had not been generally exploited.[4] We now report a realization of this goal which takes the form of a novel tandem Michael reaction/1,3-dipolar cycloaddition sequence.[4a,5] Even though this preliminary disclosure will focus on an achiral model substrate (i.e. R^1 = H), the strategy does allow for incorporation of a hydroxymethyl substituent (or some surrogate thereof) at this position as required by the target structures 1 and 2.



I

III

IV

V

Tetrahydropyrazinone 11 was prepared in seven steps from sarcosine (3) as shown in Scheme I. The first three transformations were uneventful and led to the production of the oily amine 6 in 54% overall yield.[6] Alkylation of this substance with bromoacetaldehyde diethyl acetal in hot benzene + triethylamine produced the amino acetal 7 in 87% yield. Treatment of 7 with 6 N HCl resulted in hydrolysis of the acetal and cyclization to the α-amido alcohol 8, mp 104–105 °C, which was isolated in 63% yield. Such harsh conditions were necessitated by the presence of a basic amine group α to the acetal.[7] Amidoalkylation of 8 was achieved by the combined action of (trimethylsilyl)cyanide and boron trifluoride etherate,[8] with the α-amido nitrile 9, mp 85–87 °C, being isolated in 72% yield after flash chromatography along with a minor amount of the isomeric α-amino nitrile 10.[9] These two regioisomers

(1) (a) Garner, P.; Sunitha, K.; Shanthilal, P. *Tetrahedron Lett.* **1988**, 3525. (b) Garner, P.; Sunitha, K.; Ho, W.-B.; Youngs, W. J.; Kennedy, V. O.; Djebli, A. *J. Org. Chem.* **1989**, *54*, 2041. Back references for both targets (and related substances) are cited in these papers.

(2) For a recent and comprehensive review of the known methods for generating azomethine ylides, see: Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* **1989**, *45*, 231.

(3) Joule and his co-workers successfully addressed this same issue via the regioselective cycloaddition of a related 2-oxidopyrazinium species: Kiss, M.; Russell-Maynard, J.; Joule, J. A. *Tetrahedron Lett.* **1987**, 2187.

(4) Cf. (a) Menachery, M. D.; Carroll, P.; Cava, M. P. *Tetrahedron Lett.* **1983**, 167. (b) Tsuge, O.; Kanemasa, S.; Ohe, M.; Yorozu, K.; Takenaka, S.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1987**, 4067. (c) Kanemasa, S.; Tokenaka, S.; Watanabe, H.; Tsuge, O. *J. Org. Chem.* **1989**, *54*, 420.

(5) A conceptually similar tandem conjugate addition/1,3-dipolar cycloaddition process involving nitrones has been observed by Grigg and his co-workers. Cf.: Armstrong, P.; Grigg, R.; Warnock, W. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1325 and references cited therein.

(6) Satisfactory IR, ^{1}H and ^{13}C NMR, and HRMS analyses have been obtained for all substances shown.

(7) Cf. Massa, S.; Mai, A.; Corelli, F. *Tetrahedron Lett.* **1988**, 6471.

(8) Asher, V.; Becu, C.; Anteunis, M. J. O.; Callens, R. *Tetrahedron Lett.* **1981**, 141.

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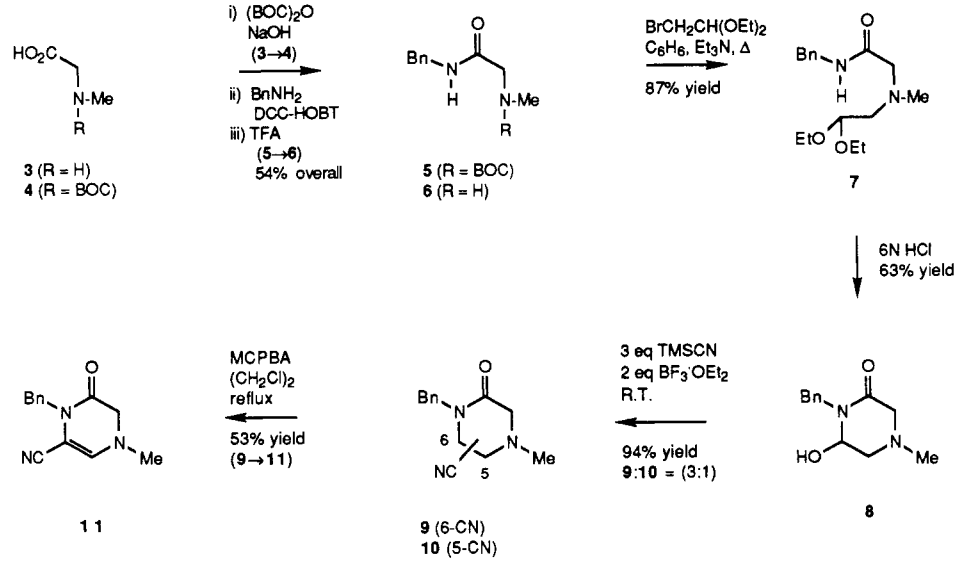
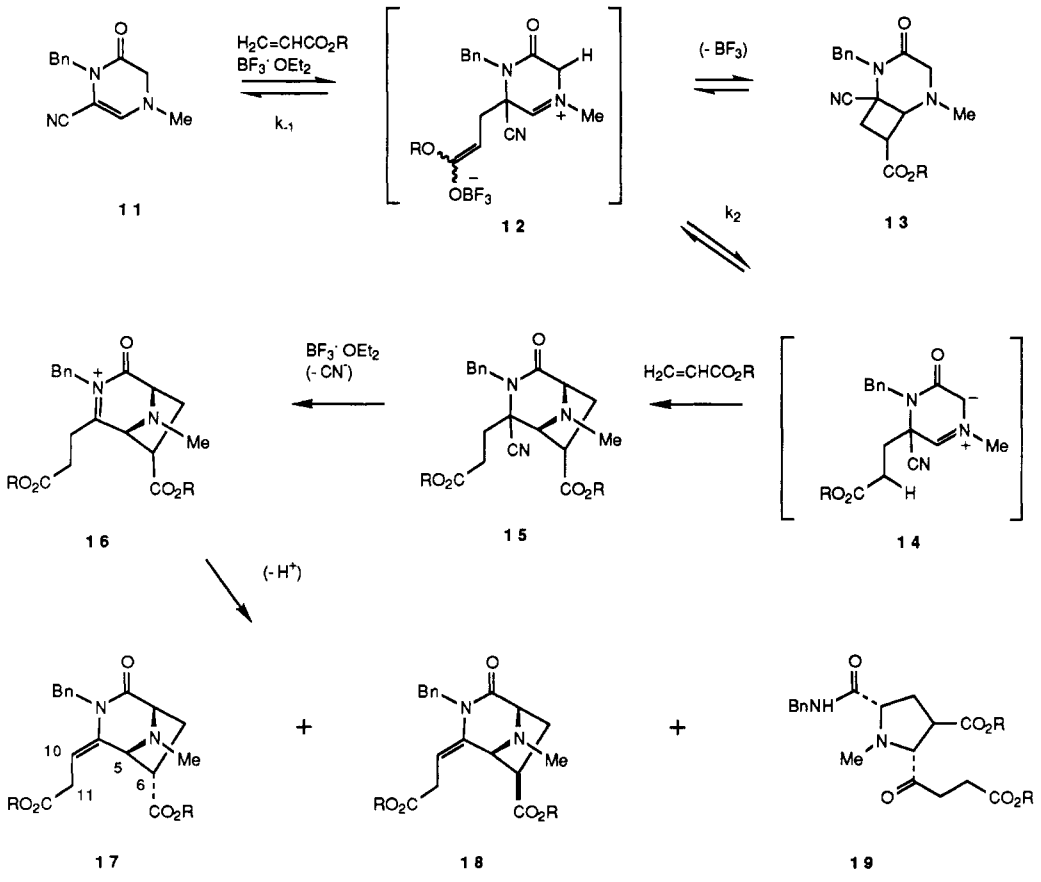
Scheme I



Scheme II[a]



[a] Series **a**, R = Me; series **b**, R = Et; series **c**, R = ^{S}CH(Me)CO_2Et.

were easily distinguished from each other by their unique mass spectral fragmentation patterns, particularly observation of an α,β-cleavage fragment $[M - CN]^+$ for **10** but not **9**. Dehydrogenation of **9** was best accomplished by oxidation with *m*-chloroperbenzoic acid to produce an *N*-oxide that underwent acid-catalyzed dehydration in situ to give the somewhat sensitive tetrahydropyrazinone **11**, mp 102–104 °C, isolated in 53% yield after flash chromatography on basic alumina.[10]

(9) The formation of **10** under these reaction conditions apparently reflects equilibration of the initially formed *N*-acyliminium species to a more stable iminium ion via an intermediate enamine. Support for this explanation comes from the observation that higher reaction temperatures or longer reaction times increases the proportion of **10** in the mixture.

(10) The mechanism of this transformation probably involves dehydration of the protonated amine oxide to give an iminium species which then undergoes a very facile tautomerization to the (neutral) β-cyano enamine **11**. For a related example of MCPBA-mediated iminium ion formation followed by tautomerization to a 3-oxidopyridinium (enamine formation being structurally precluded in this case), see: Tamura, Y.; Saito, T.; Kiyokawa, H.; Chen, L.-C. *Tetrahedron Lett.* **1977**, 4075.

Table I. Tandem Michael/1,3-Dipolar Cycloaddition Sequence[a]

entry	R	% yield 17	18	19	total
1	Me[b]	43	39	–	82
2	Me[c]	34	26	2	62
3	Et[b]	41	26	2	69
4	Et[c]	21	28	7	57
5	^{S}CH(Me)CO_2Et[c]	26[d]	22[d]	9	57

[a] To a 0.09 M solution of **11** in dry CH_3CN was added 3 equiv of BF_3·OEt_2 and either [b] 40 equiv or [c] 10 equiv of acrylate. The mixture was refluxed under N_2 until no starting material remained as judged by TLC. Aqueous (bicarbonate) workup followed by silica gel chromatography afforded **17**, **18**, and **19** in the yields shown. [d] High field ^{1}H NMR analysis indicated a (1:1) mixture of diastereomers.

With compound **11** in hand we began to investigate conditions that might lead to the generation of unsymmetrical azomethine ylides III as discussed above. It was thus found that heating a mixture of **11** and boron trifluoride etherate in the presence of excess methyl acrylate (40 equiv) resulted in the formation of an approximately equimolar mixture of two isomeric substances possessing the diazabicyclo[3.2.1]octane skeleton in 82% combined yield (Table I, entry 1).[11] These products were readily identified as the endo- and exo-cycloadducts **17a** and **18a**, respectively, on the basis of their respective $^3J_{5,6}$ values as noted previously for related systems.[1,3] The *E*-trisubstituted olefin geometry was confirmed (for **17a**) by a series of NOE difference experiments that showed reciprocal enhancements for both H-5 and H-11 as well as H-10 and a benzylic resonance. When the reaction was stopped before **11** had been completely consumed, a cyclobutane **13a** could be isolated and was, in fact, the only product when trimethylsilyl triflate was substituted for BF_3·OEt_2.[12] Subjection of pure **13a** to the original cycloaddition conditions (i.e. excess CH_2=$CHCO_2Me$, BF_3·OEt_2, Δ) also resulted in the production of a 1:1 mixture of adducts **17a** and **18a**, though some transient reversion to **11** could also be detected during this reaction.[13] Similar results were obtained with ethyl acrylate (series b) and ethyl (*S*)-lactylacrylate[14] (series c). During some runs—especially those involving lower acrylate concentrations—small amounts of the (ring-opened) pyrrolidine **19** were isolated as well.

These data are consistent with the sequence shown in Scheme II whereby the β-cyano enamine moiety of **11** undergoes a reversible Michael addition to the BF_3-activated acrylate to give a zwitterionic species **12**, which is in equilibrium with the cyclobutane **13** and the azomethine ylide **14** (or BF_3 complex thereof). The reactive ylide **14** can now be "trapped" by the excess acrylate acting this time as a dipolarophile to give the initial 1,3-dipolar cycloadducts **15**, which eliminate HCN by way of the *N*-acyliminium species **16** to yield the cycloadducts **17** and **18**. The pyrrolidine **19** apparently results from hydrolytic cleavage of **16**. Finally, we speculate that the increased proportion of endo selectivity during these cycloadditions may reflect some sort of BF_3-mediated "chelation" between the azomethine ylide and dipolarophile. This novel tandem Michael addition/1,3-dipolar cycloaddition protocol may prove quite useful for the assembly of complex pyrrolidine structures such as those embodied in targets **1** and **2** since three carbon–carbon bonds are formed in a single synthetic operation.[15] Further studies aimed at delineating the scope of this unique entry to functionalized azomethine ylides (and thus pyrrolidines) from enamine-like structures are currently underway in our laboratory.

Acknowledgment. This investigation was supported by Public Health Service Grant GM 38805 administered by the National Institute of General Medical Sciences. We thank P. Shanthilal and Elise Malecki for their technical contributions to this project.

Supplementary Material Available: Complete characterization data (IR, ^{1}H and ^{13}C NMR, and HRMS) for compounds **17a**, **18a**, **17b**, **18b**, **17c**, and **18c** (4 pages). Ordering information is given on any current masthead page.

(11) Attempted substitution of other Lewis acids (Et_2AlCl, $SnCl_4$, $TiCl_4$, and $TiCl(O^iPr)_3$) for BF_3·OEt_2 gave decidedly inferior results with adducts **17a** and **18a** not even being detected in the crude reaction mixtures.

(12) Cf.: Cook, A. G. In *Enamines: Synthesis, Structure, and Reactions*; Cook, A. G., Ed.; Marcel Dekker: New York, 1969; p 211.

(13) When **13a** was reacted with ethyl acrylate there was obtained **13b**, **17b**, and **18b** (indicating that $k_{-1} > k_2$) along with small amounts of the "mixed" ester adducts corresponding to **17** and **18** that result from addition of ethyl acrylate to dipole **14a**. This seems to rule out the possibility of a Michael–Michael–Michael type of process and is further supported by our failure to observe any intermediate Michael addends.

(14) Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, 3095.

(15) for a recent review of pyrrolidine synthesis via [3 + 2] cycloadditions with a particular emphasis on natural product synthesis, see: Pearson, W. H. In *Studies in Natural Product Chemistry*; Atta-Ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1, Stereoselective Synthesis (Part A), p 323.

Generation of Vinylcarbenes by the Intramolecular Addition of α-Diazo Ketones to Acetylenes

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Summary: Treatment of several α-diazo alkynyl substituted ketones with rhodium(II) carboxylates results in intramolecular addition to the acetylenic π-bond to give a transient cyclopropene which spontaneously rearranges to a vinyl carbene intermediate.

Vinylcarbenes have attracted considerable interest as intermediates in a variety of reactions.[1,2] Methods for generating these species include the pyrolysis[3] or singlet-

† Department of Chemistry, Universita di Catania, Catania, Italy.

(1) For a recent review, see: Steinmetz, M. G.; Srinivasan, R.; Leigh, W. J. *Rev. Chem. Intermed.* **1984**, *5*, 57.

(2) Pincock, J. A.; Boyd, R. J. *Can. J. Chem.* **1977**, *55*, 2482.

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