Use of Silicon-Based Tethers to Control Diastereofacial Selectivity in Azomethine Ylide Cycloadditions[1]

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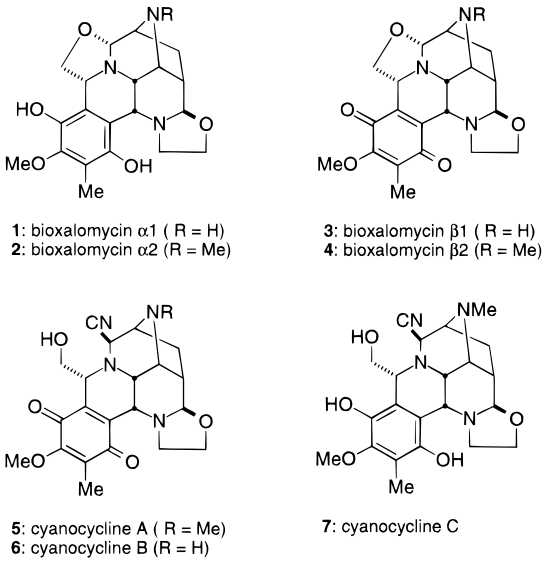
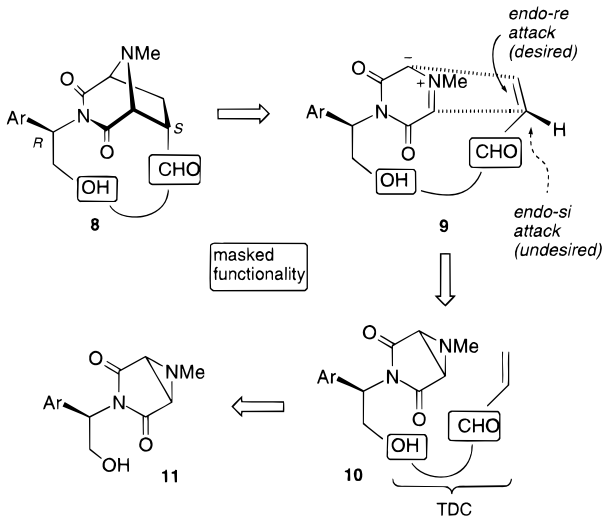
A novel approach to controlling the diastereofacial selectivity of intramolecular dipolar cycloadditions of azomethine ylides (cf. **9** → **8**) by varying the structure a silicon-based tether is described. A correlation is found between the length of the *t*ether *d*ipolarophile *c*onjugate (TDC) and the observed sense of diastereocontrol. Azomethine ylides incorporating longer [$OSiPh_2OCH_2CH_2OCOCH{=}CH_2$], [$OSi(i\text{-}Pr)_2OSi(i\text{-}Pr)_2OCH_2CH{=}CH_2$], and [$OSiPh_2OCH_2CH{=}CH_2$] TDCs favor endo-si attack (**14** → **16**, **19** → **20**, and **21** → **22**) while the shorter TDC [$OSiR_2CH_2CH{=}CH_2$] leads to a reversal in selectivity favoring the endo-re product (**23a**,**b** → **24a**,**b**). Structures of the cycloadducts have been assigned on the basis of selected X-ray diffraction data in combination with chemical/spectral correlation experiments. The work described herein represents a conceptually new approach to stereocontrol and extends the use of silicon-based tethers in asymmetric synthesis.

Introduction

As part of an ongoing project directed toward the asymmetric synthesis of the bioxalomycins **1**−**4**[2] and cyanocyclines **5**−**7**,[3] we required a stereocontrolled route



to a synthetic intermediate corresponding to structure **8**. We envisaged a transform-based strategy which relies on a key aziridine ring-opening/intramolecular 1,3-dipolar cycloaddition to assemble the 3,8-diazabicyclo-[3.2.1]octane nucleus in a single step (cf. **10** → **9** → **8**). Several criteria need to be met if this approach is to be viable: (1) the tether−dipolarophile conjugate (TDC) must be readily prepared and easily attached to an aziridine alcohol **11**, (2) the cycloaddition must lead to



an endo-disposed formyl group (this is geometrically enforced with short tethers), (3) the cycloaddition must proceed via endo-re attack on the prochiral alkene (versus the endo-si alternative), (4) the TDC must be compatible with the photochemical cycloaddition conditions as well as chemically stable to the point of subsequent isoquinoline formation and, finally, (5) the TDC must be easily removed and the released functionality readily processed.[4]

The most "atom-economical" TDC simply involves combining the alcohol and aldehyde functional groups into an acetal linkage. Indeed, we reported[5] that the acetal-conjugated aziridine **12** underwent photoinduced intramolecular cycloaddition to provide the endo-re cy-

† Author to whom inquiries concerning the X-ray structure determination of **24a** should be addressed.

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(1) Preliminary Communication: Garner, P. P.; Cox, P. B.; Klippenstein, S. J.; Youngs, W. J.; McConville, D. B. *J. Org. Chem.* **1994**, *59*, 6510−6511.

(2) Zaccardi, J.; Alluri, M.; Ashcroft, J.; Bernan, V.; Korshalla, J. D.; Morton, G. O.; Siegel, M.; Tsao, R.; Williams, D. R.; Maiese, W.; Ellestad, G. A. *J. Org. Chem.* **1994**, *59*, 4045−4047. This paper suggests that the previously proposed structure for naphthyridinomycin is actually an artifact of the fermentation procedure and that the naturally occurring form of naphthyridinomycin is actually bioxalomycin *β*2. If this is true, then the related SF-1739 may also possess a bis-oxazolidine structure.

(3) Gould, S. J.; He, W.; Cone, M. C. *J. Nat. Prod.* **1993**, *56*, 1239−1245.

(4) For a review of synthetic work on naphthyridinomycin and cyanocycline A, including total syntheses by the Evans and Fukuyama groups, see: Fukuyama, T. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W., Ed.; JAI Press Inc.: Greenwich, CT, 1992; Vol. 2, pp 189−249.

(5) Garner, P.; Sunitha, K.; Ho, W.-B.; Youngs, W. J.; Kennedy, V. O.; Djebli, A. *J. Org. Chem.* **1989**, *54*, 2041−2042.

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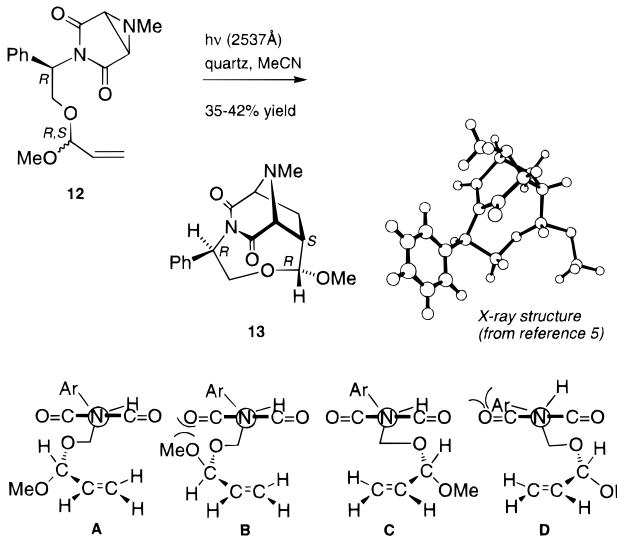
cloadduct **13** exclusively. The stereochemical result (confirmed by X-ray crystallography) was consistent with our qualitative transition state (TS) model for this reaction, which predicted that endo-re cycloaddition would minimize developing steric repulsion (A-strain) by permitting the methine hydrogen to be coplanar with the imide system as in **A**. The alternative endo-si orientation

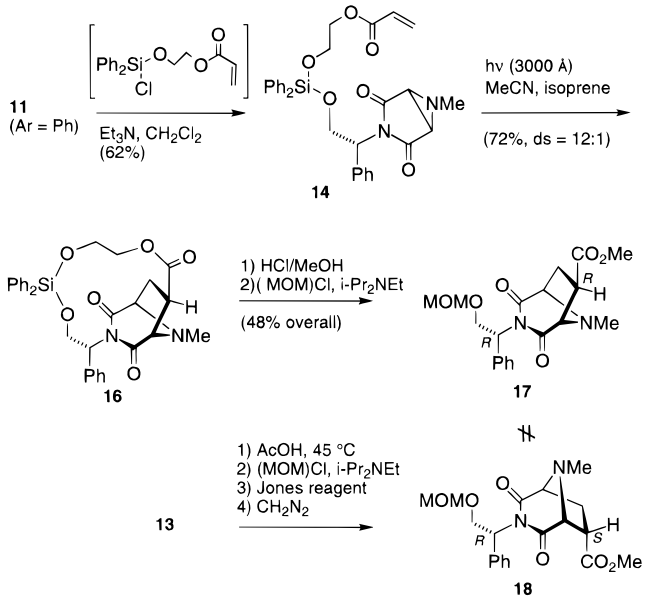


C could be excluded because it entails severe distortion of the tether. This distortion could be alleviated by rotation about the N−C bond to give **D**, but now the aromatic ring is forced to approach the imide plane.

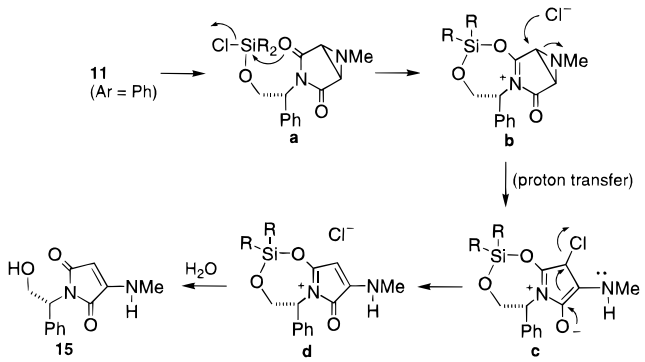
In spite of this promising result, the yield of **13** was unacceptably low for our synthetic plans. Destructive siphoning-off of the (*R*,*S*) acetal appeared to be partly responsible for this since no products derived from this (stereochemically mismatched?) acetal diastereomer could be isolated. Support for this supposition could be gleaned from the X-ray structure of **13**, which indicated that interchange of the acetal H and OMe substituents would bring the latter into close proximity with one of the imide carbonyls (also see **B**). Such an arrangement would be disfavored on both steric and dipolar grounds. The X-ray structure also revealed considerable steric strain in the cycloadduct (which incorporates a trans amide substructure into an eight-membered ring!) as evidenced by the nonplanarity of the imide nitrogen. These considerations led us to hypothesize that a longer, achiral tether might lead to a better result.

Results and Discussion

A silicon-based TDC seemed to fit all the criteria set above. Indeed, several groups have demonstrated the versatility of silicon-based tethers in both intramolecular cycloaddition and radical cyclization reactions.[6] Building on the intramolecular Diels−Alder work of Shea,[6a] we initially considered the use of his "disposable" silicone-based tether (-$OSiPh_2OCH_2CH_2OCO$-) since the ensuing cycloaddition would now involve formation of an unstrained 13-membered ring. Synthesis of the unsymmetrical silicone **14** was conveniently accomplished in one pot by slowly adding 2-hydroxyethyl acrylate + Et_3N to an equimolar quantity of Ph_2SiCl_2 followed by the another 1 equiv of Et_3N and then the aziridine alcohol **11** (Ar = Ph). This general procedure minimized the



formation of symmetrical silicones and was applicable to all unsymmetrical silicone-based TDCs examined (vide infra). Interestingly, the reverse order of addition failed to provide the desired unsymmetrical silicones, but the maleimide **15** could be isolated in ca. 50% yield from the complex reaction mixture. The formation of this compound is consistent with the mechanism presented below and is indicative of the sensitivity of the 3,6-diazabicyclo-[3.1.0]hexane-2,4-dione system.



Photochemically initiated ring-opening/intramolecular 1,3-dipolar cycloaddition was best accomplished using conditions similar to those developed for the acetal-based TDC **12**. Optimal conditions for each TDC studied were determined by systematic variation of the wavelength, concentration, and reaction time. For the case at hand, irradiation of a degassed 0.01 M solution of siloxane **14** in dry acetonitrile containing a few drops of isoprene at 3000 Å resulted in the clean cycloadduct formation. The best conversion was achieved by stopping the photolysis before **14** had been completely consumed because, as we have noted previously,[5] the cycloadducts themselves are somewhat photolytically labile and decompose upon

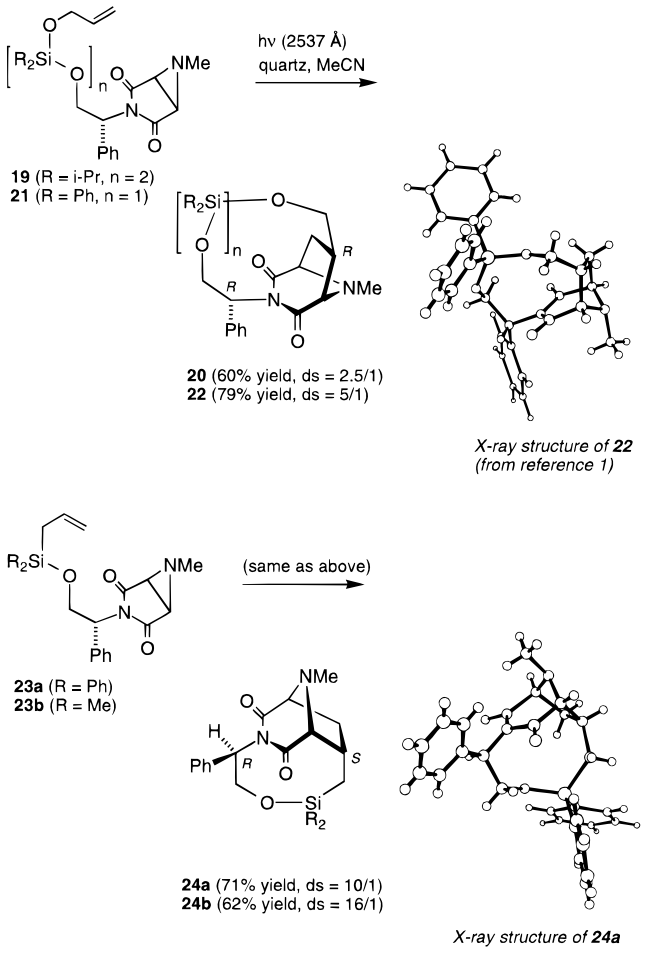
(6) (a) Shea, K. J.; Zandi, K. S.; Staab, A. J.; Carr, R. *Tetrahedron Lett.* **1990**, *31*, 5885−5888. (b) Craig, D.; Reader, J. C. *Ibid.* **1990**, *31*, 6585−6588. (c) Gillard, J. W.; Fortin, R.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstein, M. A.; Glaser, R. *Ibid.* **1991**, *32*, 1145−1148. (d) Shea, K. J.; Staab, A. J.; Zandi, K. S. *Ibid.* **1991**, *32*, 2715−2718. (e) Fleming, S. A.; Ward, S. C. *Ibid.* **1992**, *33*, 1013−1016. (f) Craig, D.; Reader, J. C. *Ibid.* **1992**, *33*, 4073−4076. (g) Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578−7579. (g) Rumbo, A.; Castedo, L.; Mouriño; Mascareñas, J. L. *J. Org. Chem.* **1993**, *58*, 5585−5586. (h) Crimmins, M. T.; Guise, L. E. *Tetrahedron Lett.* **1994**, *35*, 1657−1660. (i) For a recent review of this area, see: Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253−1257.

prolonged exposure to light. In this way, a major cycloadduct was obtained in 45% yield (72% based on recovered **14**). A minor compound, presumed to be the diastereomeric cycloadduct, was visible in the crude ^{1}H NMR spectrum, and the ds was determined to be 12/1 by integration. The observation that lower energy (3000 vs 2537 Å) light can be employed with the TDC **14** is provocative, since it suggests that the acrylate moiety may be acting as an "antenna" chromophore[7] in this photochemical reaction.

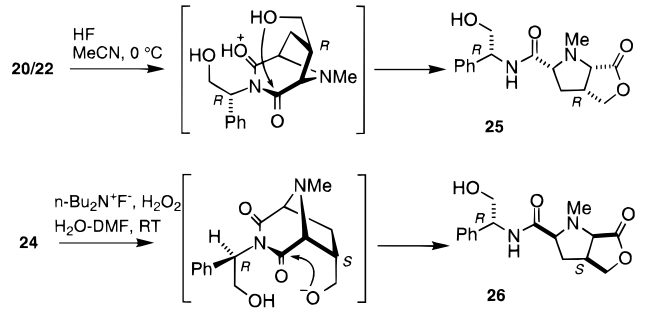
The structure of the major cycloadduct was to be assigned by correlation with compound **18**, which had previously been prepared from **13**, whose structure had been determined unambiguously by X-ray crystallography.[8] In the event, exposure of the major cycloadduct to acidic methanol to remove the silicone tether (with concomitant transesterification) followed by MOM protection of the alcohol produced a compound with the correct molecular formula but whose ^{1}H NMR spectrum did not match that of **18**! These data are consistent with the major cycloadduct of this reaction being the endo-si diastereomer **16** instead of the (expected) endo-re diastereomer. This result was surprising and difficult to reconcile using the simple A-strain-based TS model described previously. The fact that the acrolein acetal TDC **12** (corresponding to an 8-membered ring TS) and the siloxyethyl acrylate TDC **14** (corresponding to a 13-membered ring TS) gave such contrasting stereochemical results suggested that the tether itself might be influencing the diastereofacial selectivity of the cycloaddition.[9]

We therefore assembled readily available silicon-based TDC's corresponding to 12-, 10-, and 9-membered ring TS's to determine experimentally whether there is any correlation between the length and/or structure of the TDC and cycloaddition facial selectivity. The allyldisiloxane[10] and allylsiloxane[6b,c,e,f] TDC's **19** and **21** were synthesized in 28 and 65% yield, respectively, from the aziridine alcohol **11** using the protocol developed for the siloxyethyl acrylate TDC **14** but substituting $(i\text{-}Pr_2SiCl)_2O$ + a catalytic amount of DMAP for Ph_2SiCl_2 in the former case. Although we were unable to produce the unsymmetrical disiloxane **19** in high yield, we believe that this is the first reported use of such disiloxanes, which are commonly used to protect the 5′ and 3′ hydroxyls of ribonucleosides, as a tether for an intramolecular reaction. The allyl silyl ethers[5g] **23a** and **23b** were obtained in 78 and 97% yield, respectively, by treating **11** with either $CH_2{=}CHCH_2SiPh_2Cl$ or $CH_2{=}CHCH_2SiMe_2Cl$ in the presence of Et_3N.

Each of these substrates was subjected to photolysis using the previously described protocol to optimize the reaction conditions for each TDC. Like **14**, both the disiloxane-tethered aziridine **19** and siloxane-tethered aziridine **21** resulted in preferential formation of the (undesired) endo-si diastereomers **20** (ds = 2.5/1) and **22** (ds = 5/1). On the other hand, photolysis of the silyl ether-tethered aziridines **23a** and **23b** at 2537 Å cleanly produced the (desired) endo-re diastereomers **24a** (71% yield, ds = 16/1) and **24b** (62% yield, ds = 10/1).



Stereochemical assignments for cycloadducts **20**, **22**, and **24a/b** are based on chemical correlation experiments tied in with X-ray crystal structures of the endo-si diastereomer **22** (reference 1) and the endo-re diastereomer **24a** (this work).[11] Exposure of the diastereomeric mixtures **20/dia-20** and **22/dia-22** with HF resulted in siloxane cleavage and lactonization to give an inseparable mixture of γ-lactones **25** (major) and **26** (minor), while treatment of the diastereomeric mixtures of **24/dia-24** with $Bu_4N^+F^-$ and H_2O_2 resulted in both silyl ether cleavage and Si−C oxygen insertion and subsequent lactonization to give a mixture of **26** (major) and **25** (minor). These



diastereomeric lactones were readily distinguished from each other by high field ^{1}H NMR spectroscopy (see Experimental Section).

(7) Cf. Agyin, J. K.; Morrison, H.; Siemiarczuk, A. *J. Am. Chem. Soc.* **1995**, *117*, 3875−3876.

(8) Ho, W. B. The Asymmetric Synthesis of (−)-Quinocarcin. Ph.D. Dissertation, Case Western Reserve University, Cleveland, OH 1992.

(9) Support for this hypothesis initially came fron a TS modeling study which indicated a crossover from endo-re to endo-si selectivity as a function of tether structure. See reference 1 for details.

(10) Cf. Markiewicz, W. T.; Padyukova, N. Sh.; Samek, S.; Smrt, J. *Collect. Czech. Chem. Commun.* **1980**, *45*, 1860−1865.

(11) The authors have deposited the atomic coordinates and thermal parameters for compound **24a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Conclusions

The results described herein demonstrate that the diastereofacial selectivity of intramolecular 1,3-dipolar cycloaddition of azomethine ylides corresponding to **9** is under remote, tether-directed stereocontrol. Systems incorporating shorter TDCs (TS ring size ≤ nine atoms) have a greater propensity for the formation of the desired endo-re cycloadduct. Interestingly, the similar results observed for both the diphenyl- and dimethyl-substituted TDCs **23a** and **23b** suggests that tether length (ring size) plays the primary role in determining the mode and level of diastereoselectivity. The ability to control the diastereomer ratios by simply changing the structure of the "temporary" Si-tether represents a conceptually new approach to stereocontrol (compare reference 6d) and further extends the use of silicon-based tethers in asymmetric synthesis.[12]

Experimental Section

All reactions were performed under an inert (N_2 or Ar), moisture-free atmosphere except when working in aqueous media. Solvents/reagents were purified beyond reagent grade as follows: THF was distilled from Na + benzophenone; CH_2Cl_2 and Et_3N were distilled from CaH_2. Photolyses were performed in a Rayonet photochemical reactor (RPR-100) at the indicated wavelength. Silica gel TLC plates were visualized with UV illumination followed by charring with either 5% anisaldehyde in (95:5:1) EtOH−AcOH−H_2SO_4 or 1% phosphomolybdic acid in 95% EtOH. The ^{1}H NMR assignments are based on selective homonuclear decoupling experiments. High resolution mass spectral (HRMS) data are reported in units of *m/e* for M^+ or the highest mass fragment derived from M^+.

Synthesis of Aziridines 14 and 21. A solution of allyl alcohol or 2-hydroxyethyl acrylate (1 equiv) and Et_3N (1 equiv) in freshly distilled CH_2Cl_2 (0.5 M) was added to an ice-cold solution of Ph_2SiCl_2 in CH_2Cl_2 (0.1 M) over a 3 h period by means of a syringe pump. After addition was complete, the reaction solution was allowed to warm to rt and stir overnight. After this time, the solution was recooled to 0 °C and a further 1 equiv of Et_3N added. The reaction was stirred for 5 min at which time the starting aziridine alcohol (1 equiv) was added. After stirring for 1 h, the reaction was judged to be complete by TLC analysis. The reaction mixture was worked up by adding water and back extracting into CH_2Cl_2. The organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed to give the crude product which was purified by flash chromatography over silica gel.

Compound 14: 65% yield; R_f 0.39 in 2:1 hexanes/EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (m, 4 H, Ph), 7.3 (m, 11 H, Ph), 6.31 (dd, 1 H, $J_1 = 17.1$ Hz, $J_2 = 1.5$ Hz, COC*H*CH$_2$), 6.02 (dd, 1 H, $J_1 = 17.1$ Hz, $J_2 = 10.5$ Hz, 1/2 COCHCH_2), 5.72 (dd, 1 H, $J_1 = 10.5$ Hz, $J_2 = 1.5$ Hz, 1/2 COCHCH_2), 5.16 (dd, 1 H, $J_1 = 10.5$ Hz, $J_2 = 5.7$ Hz, PhC*H*), 4.66 (dd, 1 H, $J_1 = J_2 = 10.5$ Hz, 1/2 PhCHCH_2), 4.25 (t, 1 H, $J = 10.5$ Hz, OCH$_2$CH_2O), 4.10 (dd, 1 H, $J_1 = J_2 = 10.5$ Hz, 1/2 PhCHCH_2), 3.92 (m, 2 H, OCH_2CH$_2$O), 2.72 (d, 1 H, $J = 4.5$ Hz, 1/2 N(COC*H*)$_2$), 2.70 (d, 1 H, $J = 4.5$ Hz, 1/2 N(COC*H*)$_2$), 2.39 (s, 3 H, NMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 166.0 (CO), 135.8, 134.8, 131.6, 130.7, 130.4, 128.4, 128.1, 128.0, 127.8 65.2, 61.1, 60.9, 45.0, 41.5; IR ($CHCl_3$) 3060 (m), 2940 (m), 2870 (m), 1780 (w), 1720 (s), 1630, 1610 (w), 1420 (m), 1360 (m), 1120 (s), 960 (m), 690 (m) cm^{-1}; MS (EI) *m/z* 542 (2.6%, $[M]^+$), 514(3%, $[M - CO]^+$), 427 (3.8%, $[M - OCH_2CH_2OCOCHCH_2]^+$), 465 (56%, $[M - Ph]^+$), 297 (100%), 215 (28%), 137 (95%); HRMS *m/z* calcd for $C_{30}H_{30}N_2O_4Si$ $[M]^+$ 542.1873, obsd 542.1904.

(12) The connection between TS ring size and stereocontrol in these intramolecular dipolar cycloaddition reactions is reminiscient of, and possibly related to, Still's seminal work on conformationally mediated stereocontrol in macrocyclic systems. Cf. Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981−3996.

Compound 21: 74% yield: R_f 0.37 in 3:1 hexanes/EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (m, 4 H, Ph), 7.3 (m, 11 H, Ph), 5.91 (m, 1 H, OCH$_2$C*H*CH$_2$), 5.31 (ddd, 1 H, $J_1 = 17.1$ Hz, $J_2 = 3.6$ Hz, $J_3 = 1.2$ Hz, 1/2 OCH$_2$CHCH_2), 5.17 (dd, 1 H, $J_1 = 10.0$ Hz, $J_2 = 6.0$ Hz, PhC*H*), 5.09 (ddd, 1 H, $J_1 = 10.5$ Hz, $J_2 = 3.6$ Hz, $J_3 = 1.3$ Hz, 1/2 OCH$_2$CHCH_2), 4.67 (dd, 1 H, $J_1 = J_2 = 10.0$ Hz, 1/2 PhCHCH_2), 4.26 (m, 2 H, OCH_2CHCH$_2$), 4.17 (dd, 1 H, $J_1 = 10.0$ Hz, $J_2 = 6.0$ Hz, PhCHCH_2O), 2.72 (d, 1 H, $J = 3.9$ Hz, 1/2 N(COC*H*)$_2$), 2.70 (d, 1 H, $J = 3.9$ Hz, 1/2 N(COC*H*)$_2$), 2.40 (s, 3 H, NMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.03 (CO), 136.3, 135.8, 134.8, 132.0, 130.3, 128.4, 127.9, 127.8, 127.7, 114.6, 63.3, 60.9, 56.6, 45.0, 41.5; IR ($CHCl_3$) 3040 (m), 2985 (m), 1710 (s), 1420 (m), 1350 (m), 1120 (s), 885 (m) cm^{-1}; MS (EI) *m/z*, 485 (1.1%, $[M + H]^+$), 484 (3.5%, $[M]^+$), 456 (<1%, $[M - CO]^+$), 428 (31%, $[M - OCH_2CHCH_2 + H]^+$), 427 (13.2%, $[M - OCH_2CHCH_2]^+$), 407 (100%, $[M - Ph]^+$), 359 (9.6%, $[M - N(COCH)_2NMe]^+$), 358 (30.2%), 352 (16%); HRMS *m/z* calcd for $C_{28}H_{28}N_2O_4Si$ $[M]^+$ 484.1818, obsd 484.1825.

Aziridine 19. To an ice-cold solution of (TIPS)-Cl (0.26 mL, 0.83 mmol) and DMAP (5 mg, 0.04 mmol) in freshly distilled CH_2Cl_2 (8.3 mL) was added a solution of allyl alcohol (0.057 mL, 0.83 mmol) and Et_3N (0.12 mL, 0.83 mmol) in CH_2Cl_2 (2.0 mL) over 3 h by means of a syringe pump. After the addition, the reaction mixture was allowed to warm to rt and stir overnight. To this mixture was added Et_3N (0.12 mL, 0.83 mmol) followed by the aziridine alcohol (206 mg, 0.83 mmol) and the resulting solution again allowed to stir overnight. The reaction mixture was poured into H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were dried over Na_2SO_4 and filtered, and the solvent was removed to give the crude product. Purification by flash chromatography over silica gel (eluting with 5:1 hexanes/EtOAc) gave **19** (116 mg, 28% yield) as a colorless oil. R_f 0.5 in 3:1 hexanes/EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2−7.2 (m, 5 H, Ph), 5.9 (m, 1 H, OCH$_2$C*H*=CH$_2$), 5.28 (ddd, 1 H, $J_1 = 17.1$ Hz, $J_2 = 3.9$ Hz, $J_3 = 2.1$ Hz, 1/2 OCH$_2$CH=CH_2), 5.12 (dd, 1 H, $J_1 = 9.6$ Hz, $J_2 = 6.0$ Hz, PhC*H*), 5.06 (ddd, 1 H, $J_1 = 10.5$ Hz, $J_2 = 3.9$ Hz, $J_3 = 1.8$ Hz, 1/2 OCH$_2$CH=CH_2), 4.6 (dd, $J_1 = J_2 = 9.6$ Hz, 1/2 PhCHCH_2), 4.27 (m, 2 H, OCH_2CH=CH$_2$), 4.21 (dd, 1 H, $J_1 = 9.6$ Hz, $J_2 = 6.0$ Hz, 1/2 PhCHCH_2), 2.76 (m, 2 H, N(COC*H*)$_2$, 2.43 (s, 3 H, NMe), 1.0 (m, 28 H, 4 × C$_3H_7$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 137.2, 136.2, 128.5, 128.0, 127.9, 113.8, 63.3, 60.8, 56.9, 45.2, 41.6, 17.2, 16.9, 13.0, 12.9; IR ($CHCl_3$) 3010 (s), 2940 (s), 2860 (s), 1730 (s), 1510 (m), 1180 (br), 1100 (s), 960 (s) cm^{-1}; MS (EI) *m/z*, 503 (100%, $[M - C_3H_7]^+$), 475 (<10%, $[M - SiC_3H_7]^+$), 359 (8%, $[M - {}^iPrSiO_2CH_2CH{=}CH_2]^+$), 383 (35%, [M − 163]; HRMS *m/z* calcd for $C_{25}H_{39}N_2O_5Si_2[M - C_3H_7]^+$ 503.2398, obsd 503.2395.

Synthesis of Aziridines 23a and 23b. The aziridine alcohol (1 equiv) was dissolved in freshly distilled CH_2Cl_2 (0.1 M) and the solution cooled to 0 °C. To this was added Et_3N (1 equiv) followed by the allyl-disubstituted dichlorosilane (1 equiv) and the resulting reaction mixture stirred at 0 °C for 1h. At this time the reaction was judged to be complete by TLC analysis (1:1 hexanes/EtOAc). Workup was performed by quenching the mixture with water and extracting with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed to provide the crude product which was purified by flash chromatography to afford the pure silyl ether.

Aziridine 23a: yield 78%; R_f 0.24 in 3:1 hexanes/EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6−7.3 (m, 15 H, 3 × Ph), 5.81 (m, 1 H, 1/2 SiCH$_2$C*H*CH$_2$) 5.19 (dd, 1 H, $J_1 = 10.2$ Hz, $J_2 = 5.9$ Hz, PhC*H*), 4.92 (m, 2H, SiCH$_2$CHCH_2), 4.66 (dd, 1 H, $J_1 = J_2 = 10.2$Hz, 1/2 PhCHCH_2), 4.14 (dd, 1 H, $J_1 = 10.2$ Hz, $J_2 = 5.9$ Hz, 1/2 PhCHCH_2), 2.71 (ABq, 2 H, $J = 12.0$ Hz, N(COC*H*)$_2$), 2.45 (s, 3 H, NMe), 2.19 (d, 2 H, $J = 7.5$ Hz, SiCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 136.1, 134.9, 134.1, 132.9, 130.1, 128.6, 128.1, 127.9, 115.3, 61.8, 57.0, 45.3, 41.7, 21.7; IR ($CHCl_3$) 3050 (s),1715 (s), 1420 (s), 1360 (m), 1210 (m), 1110 (s), 890 (w) cm^{-1}; MS (EI) *m/z* 468 (5%, $[M]^+$), 427 (100%, $[M - CH_2CH{=}CH_2]^+$), 349 (100%, $[M - (CH_2CH{=}CH_2 + Ph)]^+$); HRMS *m/z* calcd for $C_{28}H_{28}N_2O_5Si$ $[M]^+$ 468.1869, obsd 468.1835.

Aziridine 23b: yield 97%; R_f 0.24 in 3:1 hexanes/EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5 H, Ph), 5.7 (m, 1 H,

1/2 $SiCH_2CHCH_2$) 5.04 (dd, 1 H, J_1 = 9.6 Hz, J_2 = 5.7 Hz, PhC*H*), 4.84−4.42 (m, 2 H, $SiCH_2CHCH_2$), 4.41 (dd, 1 H, J_1 = J_2 = 9.6 Hz, 1/2 $PhCHCH_2$), 3.96 (dd, 1 H, J_1 = 9.6 Hz, J_2 = 5.7 Hz, 1/2 $PhCHCH_2$), 2.71(s, 2 H, $N(COCH)_2$), 2.37 (s, 3 H, NMe), 1.53 (d, 2 H, J = 7.8Hz, $SiCH_2$), 0.02 (s, 6H, $SiMe_2$); ^{13}C NMR (75MHz, $CDCl_3$) δ 172.0 (CO), 133.7, 128.3, 127.9, 127.7 (Ar), 113.5, 60.9, 56.6, 45.1, 41.4, 24.1, −2.8; IR (CH_2Cl_2) 3040 (s), 2980 (s),1720 (s), 1410 (s), 1350 (m), 1180 (m), 1080 (m), 1020 (m), 890 (m); MS (EI) *m/z* 344 (<1%, $[M]^+$), 329 (<1%, $[M - CH_3]^+$), 303 (100%, $[M - C_3H_5]^+$); HRMS *m/z* calcd for $C_{18}H_{24}N_2O_3Si$ $[M]^+$ 344.1556, obsd 344.1506.

General Photolysis Procedure. The starting aziridine was dissolved in spectrophotometric grade MeCN (0.01 M) and transferred to a quartz reaction vessel, and isoprene (2 or 3 drops) was added. The resulting solution was degassed (freeze-thaw method) three times and then irradiated in a Rayonet photochemical reactor (3000 Å for **14**, 2537 Å for **19**, **21**, and **23a**/**b**) until the reaction was judged to be complete by TLC. The solvent was removed to provide the crude product mixture which was purified by flash chromatography over silica gel. Diastereomer ratios were determined from the ^{1}H NMR spectra of unresolved mixtures.

Cycloadduct 16: 46% yield (72% based on recovered SM), ds = 12/1; R_f 0.32 in 2:1 hexanes/EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6−7.1 (m, 15 H, Ph), 5.8 (dd, 1 H, J_1 = 9.6 Hz, J_2 = 6.0 Hz, PhC*H*), 4.88 (dd, 1 H, J_1 = J_2 = 9.6 Hz, 1/2 $PhCHCH_2$), 4.4 (m, 1 H, 1/2 OCH_2CH_2O), 4.11 (m, 3 H, OCH_2CH_2O and 1/2 $PhCHCH_2$), 4.04 (d, 1 H, J = 6.4 Hz, $NCOCHCHCO_2$), 3.92 (m, 1 H, 1/2 OCH_2CH_2), 3.66 (d, 1 H, J = 7.8 Hz, $NCOCHCH_2$), 3.48 (ddd, 1 H, J_1 = 10.8 Hz, J_2 = J_3 = 6.4 Hz, $NCOCHCHCO_2$), 2.52 (m, 1 H, 1/2 $NCOCHCH_2$), 2.4 (m, 1 H, 1/2 $NCOCHCH_2$), 2.32 (s, 3 H, NMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 170.8, 169.4(CO), 136.9, 134.6, 131.7, 130.5, 128.2, 128.1, 127.9, 127.7, 127.5(Ar), 68.9, 66.8, 66.3, 62.4, 61.9, 56.5, 46.1, 35.9, 29.5, 29.4; IR (CH_2Cl_2) 3040 (s), 2975 (s),1735 (s), 1680 (s), 1410 (s), 1340 (m), 1120 (w), 890 (s) cm^{-1}; MS (EI) *m/z*, 542 (26.4%, $[M]^+$), 514 (41.7%, $[M - CO]^+$), 466 (11.8%, $[M - Ph + H]^+$), 465 (100%, $[M - Ph]^+$), 423 (77%), 297 (54.7%), 108 (100%); HRMS *m/z* calcd for $C_{30}H_{30}N_2O_4Si$ $[M]^+$ 542.1873, obsd 542.1873.

Cycloadduct 20: 60% yield, ds = 2.5/1; R_f 0.47 in 3:1 hexanes/EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2 (m, 5 H, Ph), 5.9 (m, 1 H, PhC*H*), 5.07 (dd, J_1 = J_2 =10.2 Hz, 1/2 $PhCHCH_2$), 4.12 (m, 1 H, 1/2 $SiOCH_2$), 3.9 (m, 1 H, 1/2 $SiOCH_2$), 3.79 (d, 1 H, J = 7.5 Hz, $NCOCHCH$), 3.6 (d, 1 H, J = 6.9 Hz, $NCOCHCH_2$), 2.92 (m, 1 H, 1/2 $NCOCHCH_2$), 2.46 (s, 3 H, NMe), 2.02 (dd, J_1 = 13.5 Hz, J_2 = 5.1 Hz, 1/2 $NCOCHCH_2$), 1.0 (m, 27 H, 4 × C_3H_7); IR ($CHCl_3$) 3010 (s), 2950 (s), 2860 (s), 1730 (s), 1680 (s), 1510 (m), 1180 (br), 1100 (s), 960 (s) cm^{-1}; MS (EI) *m/z*, 503 (12.5%, $[M - C_3H_7]^+$), 475 (21.6%, $[M - SiC_3H_7]^+$), 443 (4%), 281 (11.6%, [M − 163]; HRMS *m/z* calcd for $C_{25}H_{39}N_2O_5Si[M - SiC_3H_7]^+$ 475.2628, obsd 475.2627.

Cycloadduct 22: 72% isolated yield (79% based on recovered SM), ds = 5/1; mp 223−224 °C (from hexanes/ EtOAc); R_f 0.47 in 1:1 hexanes/EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66−7.17 (m, 15 H, Ph), 6.13 (dd, 1 H, J_1 = 10.2 Hz, J_2 = 2.7 Hz, PhC*H*), 4.88 (dd, 1 H, J_1 = J_2 = 10.2 Hz, 1/2 $PhCH_2$), 4.28 (dd, 1 H, J_1 = 10.2 Hz, J_2 = 2.7 Hz, 1/2 $PhCH_2$), 3.96 (d, 1 H, J = 11.4 Hz, 1/2 $SiOCH_2$), 3.87 (d, 1 H, J = 4.2 Hz, $NCOCHCHCH_2$), 3.79 (m, 1 H, 1/2 $SiOCH_2$), 3.54 (d, 1 H, J = 6.6 Hz, $NCOCHCH_2$), 2.78 (m, 1 H, $NCOCHCHCH_2$), 2.43 (s, 3 H, NMe), 2.35 (m, 2 H, $NCOCHCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 172.6 (CO), 136.9, 134.8, 134.6, 131.8, 130.9, 130.4, 128.5, 128.3, 128.1, 127.9, 127.7, 127.3 (Ar CH), 68,7, 67.2, 63.1, 60.6, 55.6, 41.7, 35.2, 28.8; IR ($CHCl_3$) 3140 (m), 3060 (m), 2985 (m), 1675 (s), 1420 (m), 1340 (m), 1120 (s), 690 (s) cm^{-1}; MS (EI) *m/z*, 485 (12.1%, $[M + H]^+$), 484 (42.1%, $[M]^+$), 483 (12.7%, $[M - H]^+$) 456 (34.8%, $[M - CO]^+$), 407 (100%, $[M - Ph]^+$), 365 (94.1%), 82 (100%), 77 (8%, $[Ph]^+$); HRMS *m/z* calcd for $C_{28}H_{28}N_2O_4Si$ $[M]^+$ 484.1818, obsd 484.1812.

Cycloadduct 24a: 64% yield (71% with recovered SM), ds = 16/1; mp 199−200 °C (from hexanes/EtOAc); R_f 0.36 in 1:1 hexanes/EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2−7.2 (m, 15 H, Ph), 6.13 (dd, 1 H, J_1 = 11.1 Hz, J_2 = 5.7 Hz, PhC*H*), 4.82 (dd, 1 H, J_1 = J_2 = 11.1 Hz, 1/2 $PhCHCH_2$), 4.25 (dd, 1 H, J_1 = 11.1 Hz, J_2 = 5.2 Hz, 1/2 $PhCHCH_2$), 3.80 (d, 1 H, J = 7.2 Hz, $COCHCH_2$), 3.66 (d, 1 H, J = 6.9 Hz, $COCHCHCH_2$), 3.15 (m, 1 H, $COCHCHCH_2$), 2.58 (s, 3 H, NMe), 2.34 (ddd, 1 H, J_1 = 13.8 Hz, J_2 = 10.8 Hz, J_3 = 7.2 Hz, 1/2 $COCHCH_2$), 1.9 (m, 1 H, $COCHCH_2$), 1.9 (m, 1 H, 1/2 $COCHCHCH_2$), 1.65 (dd, 1 H, J_1 = 16.2 Hz, J_2 = 9.9 Hz, 1/2 $COCHCHCH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 172.2, 136.7, 135.9, 134.9, 134.6, 134.3, 130.2, 129.9, 128.4, 128.1, 127.4, 127.0, 72.5, 66.8, 61.0, 54.4, 36.6, 35.1, 33.2, 13.7; IR ($CHCl_3$) 3020 (s), 1730 (s), 1680 (s), 1420 (s), 1200 (br), 1110 (s), 690 (s) cm^{-1}; MS (EI) *m/z*, 469 (5%, $[M + H]^+$), 468 (20%, $[M]^+$), 427 (8%, $[M - C_3H_5]^+$); HRMS *m/z* calcd for $C_{28}H_{28}N_2O_3Si$ $[M]^+$ 468.1869, obsd 468.1865.

Cycloadduct 24b: yield 49% (62% based on recovered SM), ds = 10/1; mp 129−131 °C (hexanes); R_f 0.24 in 3:1 hexanes/ EtOAc; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5 H, Ph), 5.9 (dd, 1 H, J_1 = 11.1 Hz, J_2 = 5.7 Hz, PhC*H*), 4.60 (dd, 1 H, J_1 = J_2 = 11.1 Hz, 1/2 $PhCHCH_2$), 4.08 (dd, 1 H, J_1 = 11.1 Hz, J_2 = 5.2 Hz, 1/2 $PhCHCH_2$), 3.82 (d, 1 H, J = 7.8 Hz, $COCHCH_2$), 3.47 (d, 1 H, J = 7.2 Hz, $COCHCHCH_2$), 3.0 (m, 1 H, $COCHCHCH_2$), 2.59 (s, 4 H, NMe and 1/2 $COCHCH_2$), 1.88 (dd, 1 H, J_1 = 13.5 Hz, J_2 = 5.4 Hz, 1/2 $COCHCH_2$), 1.15 (m, 1 H, 1/2 $COCHCHCH_2$), 1.86 (m, 1 H, 1/2 $COCHCHCH_2$), 0.86 (dd, 1 H, J_1 = 15.6 Hz, J_2 = 9.9 Hz, 1/2 $COCHCHCH_2$), 0.15 (s, 3 H, Me), 0.06 (s, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 171.9, 136.6, 128.2, 127.1, 126.8, 72.2, 66.6, 60.1, 54.2, 36.4, 35.5, 33.3, 17.3, 1.8, −1.6; IR ($CHCl_3$) 3040 (s), 1710 (s), 1680 (s), 1420 (s), 1110 (s), 630 (s) cm^{-1}; MS (EI) *m/z*, 345 (1.6%, $[M + H]^+$), 344 (4%, $[M]^+$), 343 (8%, $[M - H]^+$), 316 (2.7%, $[M - CO]^+$), 303 (100%, $[M - C_3H_5]^+$), 286 (<1%, $[M - SiMe_2]^+$); HRMS *m/z* calcd for $C_{18}H_{24}N_2O_3Si$ $[M]^+$ 344.1556, obsd 344.1554.

Correlation Experiment for 16. To a solution of **16** (54 mg, 0.1 mmol) in MeOH (1 mL plus a minimum amount of CH_2Cl_2) was added 3 drops of concd HCl. The clear solution was stirred at rt overnight. TLC analysis (20:1 CH_2Cl_2/MeOH) indicated (intermediate) glycolate ester formation so the solution was warmed to 60 °C and stirred for a further 48 h when TLC analysis then revealed that the reaction was essentially complete. The mixture was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc The organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed to give the crude alcohol which was purified by flash chromatography (30:1 CH_2Cl_2/MeOH) to deliver the pure methyl ester alcohol (18 mg, 54% yield) as a viscous oil. A solution of this alcohol (10 mg, 0.03 mmol), diisopropylethylamine (0.05 mL, 0.3 mmol), and methoxymethyl (MOM) chloride (0.007 mL, 0.09 mmol) was stirred at rt overnight. The reaction mixture was partitioned between water and CH_2Cl_2, the combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed to give the crude product. Purification by flash chromatography (20:1 CH_2Cl_2/MeOH) gave the pure MOM ether methyl ester **17** (10 mg, 88%) as a colorless oil. R_f 0.38 in 20:1 CH_2Cl_2/MeOH; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5 H, Ph), 5.85 (dd, 1 H, J_1 = 8.0 Hz, J_2 = 5.5 Hz, PhC*H*), 4.60 (d, 1 H, J = 7.5 Hz, 1/2 OCH_2O), 4.58 (d, 1 H, J = 7.5 Hz, 1/2 OCH_2O), 4.36 (dd, 1 H, J_1 = J_2 = 8.0 Hz, 1/2 OCH_2Ph), 4.16 (dd, 1 H, J_1 = 8.0 Hz, J_2 = 5.5 Hz, OCH_2Ph), 3.92 (d, 1 H, J = 5.5 Hz, $NCOCHCHCO_2Me$), 3.74 (d, 1 H, J = 6.1 Hz, $NCOCHCH_2$), 3.66 (d, 1 H, J = 7.8 Hz, $NCOCHCHCO_2Me$), 3.44 (ddd, 1 H, J_1 = 9.4 Hz, J_2 = 5.5 Hz, J_3 = 4.4 Hz, $CHCO_2Me$), 3.31 (s, 3 H, OMe), 3.28 (s, 3 H, CO_2Me), 2.5 (m, 1 H, 1/2 CH_2CHCO_2Me), 2.46 (s, 3 H, NMe), 2.30 (dd, 1 H, J_1 = 14.0 Hz, J_2 = 5.5 Hz, 1/2 CH_2CHCO_2Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 170.0, 128.4, 128.0, 127.7, 127.5, 96.1, 68.8, 65.9, 65.3, 53.2, 53.1, 45.2, 35.48, 29.9, 29.5; IR ($CHCl_3$) 3010 (s), 1740 (s), 1680 (s), 1410 (s), 1340 (m), 1120 (w), 890 (s) cm^{-1}; MS (EI) *m/z*, 377 (2.6%, $[M + H]^+$), 376 (15.8%, $[M]^+$), 375 (44%, $[M - H]^+$), 317 (26.4%, $[M - CO_2Me]^+$), 315 (15%, $[M - OCH_2OMe]^+$), 273 (100%); HRMS *m/z* calcd for $C_{19}H_{24}N_2O_6$ $[M]^+$ 376.1634, obsd 376.1634.

Cycloadduct 22 → Lactone 25. A 5/1 mixture of silaketal **22** and **dia-22** (40 mg, 0.08 mmol) was dissolved in a cooled solution of HF/CH_3CN (1:9 v/v) and stirred at 0 °C for 10 min when TLC analysis (17:1 $CHCl_3$/MeOH) revealed that the reaction was complete. The mixture was quenched with saturated sodium bicarbonate solution and the resulting suspension extracted with EtOAc. The combined organic

layers were dried over $MgSO_4$ and filtered, and the solvent was removed to give the crude product which was purified by flash chromatography (17:1 $CHCl_3$/MeOH) to give a 5/1 mixture of lactones **25** and **26** (17.6 mg, 70% yield). R_f 0.29 in 17:1 $CHCl_3$/MeOH; ^{1}H NMR (300 MHz, $CDCl_3$, major diastereomer) δ 7.77 (brd, 1 H, J = 9.0 Hz, NH), 7.25 (m, 5 H, Ph), 5.0 (m, 1 H, PhC*H*), 4.34 (dd, 1 H, J_1 = 9.3 Hz, J_2 = 7.8 Hz, 1/2 COOCH_2), 3.94 (dd, 1 H, J_1 = 9.3 Hz, J_2 = 4.8 Hz, 1/2 COOCH_2), 3.81 (m, 2 H, PhCHCH_2), 3.32 (m, 2 H, NCOC*H*-NMeC*H*COO), 3.13 (m, 1 H, COOCH$_2$C*H*), 2.62 (s, 3 H, NMe), 2.58 (m 1 H, 1/2 NCOCHCH_2), 1.70 (ddd, 1 H, J_1 = 13.5 Hz, J_2 = 8.7 Hz, J_3 = 6.6 Hz, 1/2 NCOCHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 172.3, 138.7, 129.0, 128.0, 126.5, 72.0, 71.8, 67.9, 66.6, 55.4, 41.8, 39.0, 35.9; IR ($CHCl_3$) 3350 (br), 3010 (s), 1775 (s), 1665 (s), 1510 (s) cm^{-1}; MS (EI) *m*/*z*, 304 (<10%, $[M]^+$), 286 (19.4%, $[M - H_2O]^+$), 273 (26.4%, $[M - CH_2OH]^+$), 227 (<10%, $[M - Ph]^+$); HRMS *m*/*z* calcd for $C_{16}H_{20}N_2O_4$ $[M]^+$ 304.1423, obsd 304.1434.

Cycloadduct 24a → Lactone 26. A 10/1 mixture of **24a/dia-24a** (37 mg, 0.08 mmol) was dissolved in 0.8 mL of a standard solution of n-$Bu_4N^+F^-$ (0.1 M) + H_2O_2 (2 M) in DMF and stirred at rt for 3 h. A TLC analysis (17:1 $CHCl_3$/MeOH) at this time revealed that all of the starting material had been consumed. The reaction mixture was diluted with water and extracted with EtOAc. The organic extracts were combined, dried over $MgSO_4$ and filtered, and the solvent was removed to give the crude product which was purified by preparative TLC (17:1 $CHCl_3$/MeOH) to deliver a 10/1 mixture of lactones **26** and **25** (10 mg, 42%) as a colorless oil. R_f 0.29 in 17:1 $CHCl_3$/MeOH; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (br d, 1 H, J = 7.2 Hz, NH), 7.25 (m, 5 H, Ph), 5.07 (m, 1 H, PhC*H*), 4.46 (dd, 1 H, J_1 = J_2 = 9.6 Hz, 1/2 COOCH_2), 4.17 (dd, 1 H, J_1 = 9.6 Hz, J_2 = 5.1 Hz, 1/2 COOCH_2), 3.86 (m, 2 H, PhCHCH_2), 3.47 (d, 1 H, J = 8.4 Hz, NCOCHNMeC*H*COO), 3.40 (dd, 1 H, J_1 = J_2 = 7.5 Hz, NCOC*H*NMeCHCOO), 3.22 (m, 1 H, CH_2CHCH_2O), 2.68 (m 1 H, 1/2 NCOCHCH_2), 2.6 (s, 3 H, NMe), 1.70 (ddd, 1 H, J_1 = 13.8 Hz, J_2 = J_3 = 6.6 Hz, 1/2 NCOCHCH_2), 1.61 (br s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 172.6, 138.6, 129.0, 128.0, 126.7, 72.0, 71.7, 68.3, 66.7, 55.5, 42.6, 38.9, 35.7; IR ($CHCl_3$) 3350 (br), 3010 (s), 1775 (s), 1665 (s), 1510 (s) cm^{-1}; MS (EI) *m*/*z*, 304 (<10%, $[M]^+$), 286 (5%, $[M - H_2O]^+$), 273 (15.0%, $[M - CH_2OH]^+$), 227 (<10%, $[M - Ph]^+$); HRMS *m*/*z* calcd for $C_{16}H_{20}N_2O_4$ $[M]^+$ 304.1423, obsd 304.1435.

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Supporting Information Available: ^{1}H NMR spectra for compounds **14**, **16**, **17**, **19**−**22**, **23a**, **24a**, **23b**, **24b**, **25**, and **26** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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