Intramolecular 1,3-Dipolar Cycloaddition of Stabilized Azomethine Ylides to Unactivated Dipolarophiles

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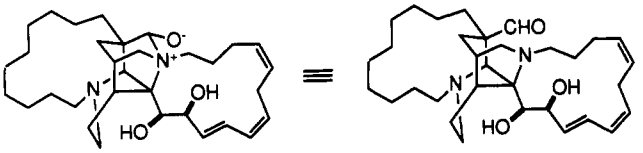
The scope and limitations of the intramolecular 1,3-dipolar cycloaddition of doubly-stabilized azomethine ylides to unactivated olefinic, acetylenic, and aromatic dipolarophiles is reported. The azomethine ylides studied were generated by flash vacuum pyrolysis of their corresponding aziridines and were found to add stereospecifically in good to excellent yields to a variety of unactivated dipolarophiles. Generation of the diazabicyclo[3.3.0]octane (e.g., **15a,b**), diazabicyclo[4.3.0]nonane (e.g., **4**, **13**), and diazabicyclo[5.3.0]decane (e.g., **15c**) ring systems are possible using this technology. In addition, the first examples of cycloaddition of a stabilized azomethine ylide to benzene dipolarophiles are reported. Cycloadditions of this type generate highly functionalized triciclic systems with complete relative stereocontrol at the newly formed stereocenters (e.g., **24–26**). Finally, it has been shown that cycloadducts **31** and **32** are in equilibrium, presumably by way of the intermediate azomethine ylide **33**, under conditions of flash vacuum pyrolysis.

Introduction and Background

As part of a continuing program directed toward the total synthesis of novel alkaloid natural products, we became interested in the bizarre structure of the marine alkaloid sarain-A (**1**).[3] It seemed to us that the unique



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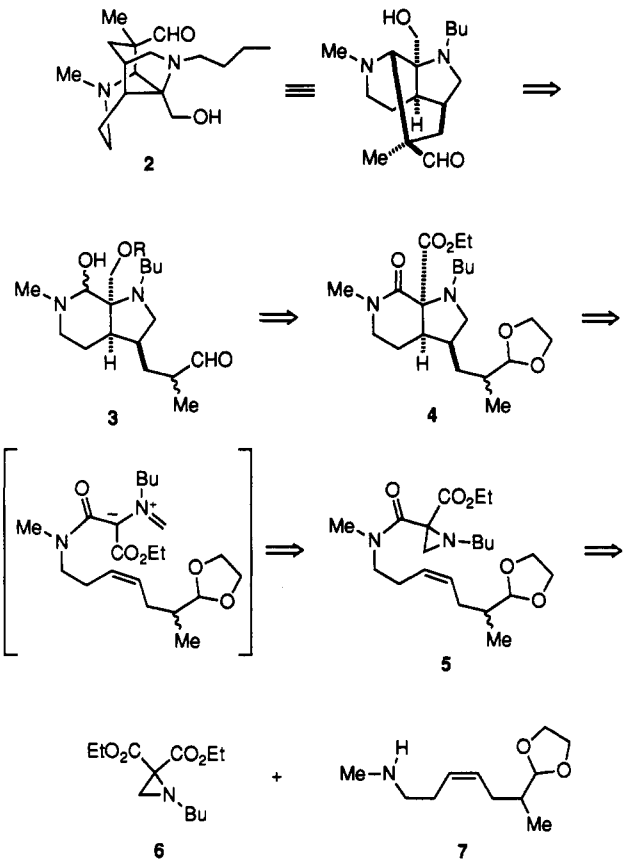
core of the alkaloid might be accessible by a route involving an intramolecular 1,3-dipolar cycloaddition of an azomethine ylide with an unactivated olefin, followed by intramolecular Mannich reaction (Scheme I). Of the methods thus far developed for generation of azomethine ylides, we selected the thermal ring opening of an activated aziridine (**5**, Scheme I). In the course of these studies, Sisko and Weinreb reported the application of essentially the same strategy in a synthetic approach to the sarain-A core.[4]

The 1,3-dipolar cycloaddition of azomethine ylides with various dipolarophiles has been utilized extensively for the generation of novel heterocycles.[5] When an olefin is employed as the dipolarophile, this methodology represents a powerful tool for the construction of substituted pyrrolidines because it creates two new carbon–carbon bonds in a single operation and the reaction often allows for high regio- and stereochemical control of the remote substituents. The intermolecular 1,3-dipolar cycloaddition of azomethine ylides has been extensively studied by Huisgen,[6] Padwa,[7] and numerous others,[8] and generalities

Scheme I



concerning the stereo- and regiochemical outcome of these cycloadditions have emerged, as well as new and useful methods of generating azomethine ylides.[9] In contrast,

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(3) (a) Cimino, G.; Spinella, A.; Trivellone, E. *Tetrahedron Lett.* **1989**, 133. (b) Cimino, G.; Puliti, R.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *Pure. Appl. Chem.* **1989**, *61*, 535. (c) Cimino, G.; Mattia, C. A.; Mazzarella, L.; Puliti, R.; Scognamiglio, G.; Spinella, A.; Trivellone, E. *Tetrahedron* **1989**, *45*, 3863.

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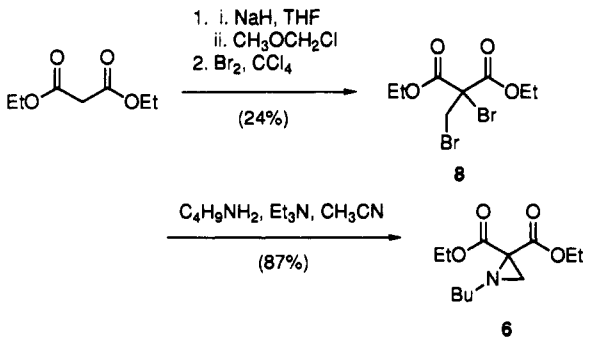
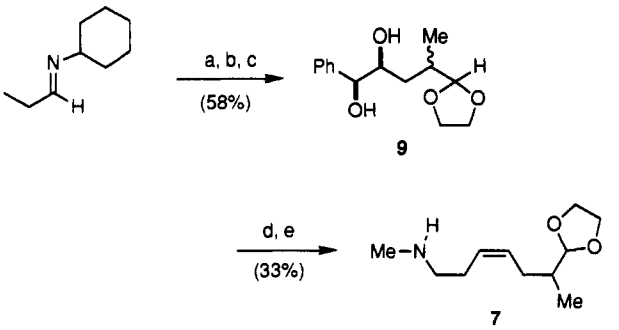
Scheme II



Scheme III



the intramolecular variant of this reaction has received less attention.[10] In addition, the usefulness of this cycloaddition in the synthesis of alkaloid natural products containing the pyrrolidine ring system has not been fully realized, due perhaps to the limited reactivity of olefinic dipolarophiles lacking an electron-withdrawing group.

Although Huisgen[6] and others[8b,f,g] have shown that aziridine rings having two stabilizing groups undergo intermolecular addition with activated dipolarophiles such as maleic anhydride, the addition of azomethine ylides to unactivated olefins often fails. DeShong[10a] has investigated the intramolecular cycloaddition of azomethines containing only one stabilizing group with a number of dipolarophiles and reported that yields with unactivated olefins are modest at best. Therefore we initiated an investigation to (1) determine whether this cycloaddition would prove synthetically viable in our approach to the core of sarain-A and (2) provide a general survey of the intramolecular cyclization of doubly-stabilized azomethine ylides with various unactivated dipolarophiles. In this paper we report the succesful intramolecular 1,3-dipolar cyclization of these doubly-stabilized azomethine ylides with a variety of unactivated dipolarophiles including a novel addition with benzene derivatives. These cycloadditions provide the means for constructing a number of fused bicyclic and tricyclic ring systems of various sizes in a stereocontrolled fashion, and should enhance the value of the 1,3-dipolar cycloaddition of azomethine ylides as a method for synthesizing complex alkaloids containing highly substituted pyrrolidine systems.

Results and Discussion

Initial efforts focused on the synthesis of compound **5** to test the feasibility of our approach to model system **2**. With the goal of a general survey of dipolarophiles in mind, the development of a general method for synthesizing the various aziridines to be studied also played a role in our approach to **5**. The disconnection that seemed most appropriate was across the amide linkage (Scheme I), providing amine **7** and known[11] aziridine diester **6**. This allows for attachment of a variety of dipolarophiles, provided a suitable method for the coupling of the appropriate amines with aziridine **6** could be found.

The synthesis of aziridine **6** was achieved in three steps by modification of the literature synthesis.[11] The sodium enolate of diethyl malonate was generated in THF and then added to an excess of chloromethyl methyl ether to provide monoalkylated product in 40–45% yield, along with 25–35% of bisalkylated material (Scheme II). Although this manner of inverse addition suppressed the overalkylation to some extent, bisalkylated material was always observed. The product ether was fairly unstable and was readily polymerized by trace amounts of acid, but could be purified by fractional distillation at reduced pressure, the pot temperature being kept below 100 °C. The distillate routinely contained 5–10% of bisalkylated material as a contaminant. Treatment of this mixture with bromine in refluxing carbon tetrachloride provided dibromide **8** in 56% yield. This material was transformed into aziridine **6** in 87% yield by treatment with butylamine and excess triethylamine in acetonitrile. Although the yields for the first two steps are low, the sequence was amenable to scale-up and required chromatography only after the last step, and thus multigram quantities of **6** were readily available.

Amine **7** was prepared according to the route shown in Scheme III. Deprotonation of *N*-cyclohexylpropionaldimine[12] with LDA followed by alkylation of the resulting enolate with cinnamyl chloride and hydrolysis of the imine with aqueous oxalic acid provided the desired aldehyde in 81% yield. Treatment of this compound with ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene with azeotropic removal of water provided the corresponding dioxolane acetal in 95% yield. Hydroxylation of the olefin was achieved upon reaction with a catalytic amount of osmium tetraoxide in the presence of *N*-methylmorpholine *N*-oxide and pyridine[13] to provide diol **9** in 75% yield as a mixture of diastereomers. Cleavage of the vicinal diol moiety was achieved upon treatment of **9** with $Pb(OAc)_4$ in benzene,[14] affording the requisite aldehyde in 75% yield. Wittig olefination with 3-(*N*-methylamino)propyltriphenylphosphonium bromide[15] using $NaN(TMS)_2$ as a base at −78 °C in THF then provided amine **7** in 44% yield. Confirmation of the cis geometry of the olefin was provided by ^1H NMR homonuclear decoupling experiments, which revealed the coupling constant between the olefinic protons to be 9.7 Hz, corresponding to that expected for a cis olefin.[16] The

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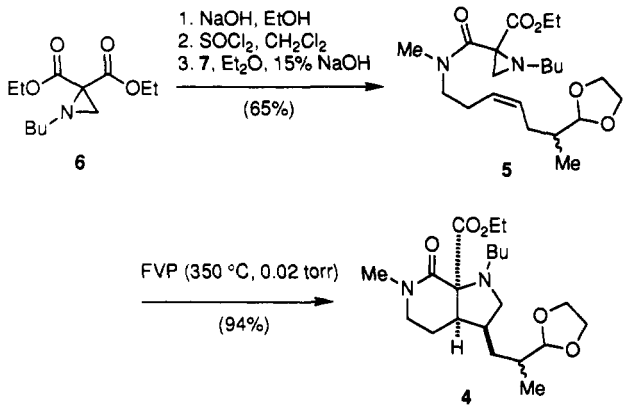
(14) Criegee, R.; Höger, E.; Huber, G.; Kruck, P.; Marktscheffel, F.; Schellenberger, H. *Liebigs Ann. Chem.* **1956**, *599*, 81.

(15) (a) Rooney, C. S.; Rokach, J.; Atkinson, J. G. U. S. Patent 4112112, 1978. (b) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emsweiler, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 217.

Scheme IV

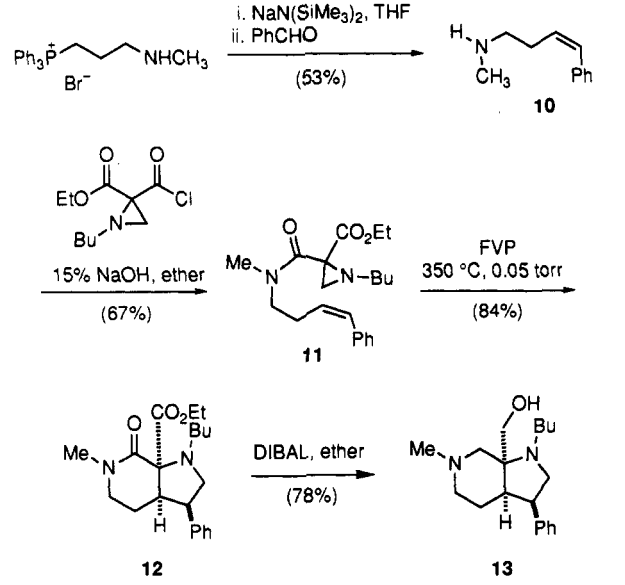


Wittig coupling was extremely sensitive to temperature and choice of base, presumably due to the instability of this particular ylide. Attempted olefination using conditions other that those specified led to no amine **7** or provided material contaminated with trans olefin.

Monosaponification of diester **6** followed by aqueous workup provided low yields of impure carboxylic acid, and attempts to couple the diester and amine **7** directly through the use of the aluminum amide[17] or other methods[18] led to recovery of starting materials or decomposition. Fortunately, reinvestigation of the monosaponification protocol under anhydrous conditions eventually provided a workable solution (Scheme IV). Treatment of diester **6** with a slight excess of NaOH in ethanol at room temperature followed by removal of the solvent provided the crude carboxylate salt. This residue was then dissolved in CH_2Cl_2 and treated with $SOCl_2$ at −78 °C to provide the crude acid chloride, which was unstable at room temperature but could be handled at temperatures below −30 °C without decomposition. Addition of a cold (−78 °C) solution of the crude acid chloride to a rapidly stirring biphasic mixture of 15% aqueous NaOH, ether, and amine **7** effected the Schotten–Baumann[19] coupling, providing amide **5** in 65% yield from aziridine **6**. Amide **5** existed as a mixture of amide rotamers as judged by ^1H and ^{13}C NMR; warming the solution to 80 °C in benzene-d_6 did not alter the spectrum.

With azomethine ylide precursor **5** in hand, we were ready to examine the 1,3-dipolar cycloaddition reaction. Azomethine ylides have been generated from aziridines both thermally and photochemically;[7c,8d,20] however, practical considerations led us to focus on the thermal means of generation. Initial attempts to effect the 1,3-dipolar cycloaddition in refluxing xylene proved fruitless, leading to extensive decomposition. Aware that DeShong[8a] had utilized flash vacuum pyrolysis (FVP) as a means for generating azomethine ylides, we attempted to generate our ylide by this technique. In the event, pyrolysis of a neat sample of aziridine **5** in a quartz tube at 350 °C and 0.02 Torr produced the desired cycloadduct **4** in a remarkable 94% yield as a 1:1 mixture of diastereomers (Scheme V). This reaction proved to be amenable to scale-up, with pyrolysis of multigram quantities of material possible.

Scheme V



Assignment of Ring Fusion Stereochemistry. Before continuing our studies, we needed to assign the relative stereochemistry at the ring fusion in lactam **4**. Inspection of models and previous investigations on similar systems[8a,f,g] indicated that a cis ring fusion should be favored, but we felt more definitive proof was necessary since in theory cycloaddition through an endo transition state can also occur, which provides the undesired isomer having a trans ring fusion.[8a] The noncrystalline nature of lactam **4** and subsequent derivatives forced us to rely on spectroscopy as a means of determining the relative stereochemistry of the ring junction. Since any spectroscopic studies done on **4** or derivatives thereof necessarily involve a mixture of diastereomers, we sought a simpler system for our spectroscopic investigations in which the acetal side chain was replaced with a phenyl substituent, thus affording a single lactam stereoisomer.

The synthesis of this system parallels that of lactam **4** and is shown in Scheme V. Treatment of benzaldehyde with 3-(*N*-methylamino)propyltriphenylphosphonium bromide[15] using $NaN(TMS)_2$ as a base at −78 °C provided the phenyl-substituted secondary amine **10** in 53% yield; again, the cis geometry of the olefin was confirmed by ^1H NMR homonuclear decoupling experiments. Schotten–Baumann coupling of **10** with the acid chloride derived from aziridine **6** (vide supra) gave amide **11** in 66% yield, again as a mixture of rotamers about the amide bond. Flash vacuum pyrolysis of this amide produced cycloadduct **12** in 84% yield as a single stereoisomer. Reduction of both the amide and ester functions was achieved upon addition of excess diisobutylaluminum hydride in ether, affording amino alcohol **13** in 78% yield. Although this material was an oil, MM2 calculations[21] suggested that the methine proton at the ring fusion and the methylene protons of the hydroxymethylene moiety are close enough to exhibit an NOE in the cis isomer, while they are too far apart in the trans isomer for observation of an NOE. The

(16) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 4th ed.; Wiley: New York, 1981. The normal range for J_{ab} in a cis olefin is 6–12 Hz, while that for a corresponding trans olefin is 12–18 Hz.

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(21) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. Since this publication, numerous modifications and additions to the force field parameters have been published. The calculations were done with a SiliconGraphics IRIS-4D using PCMODEL 4.0.

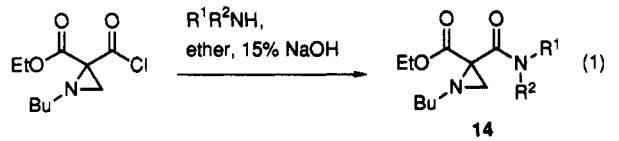
Table I. 1,3-Dipolar Cycloaddition of Unsaturated Aziridines 14a–d

entry	aziridine	yield, %	cycloadduct	yield, %
1	**14a**	54	**15a**	78
2	**14b**	60	**15b**	68
3	**14c**	69	**15c**	78[a]
4	**14d**	75		0[b]

[a] Isomer **17** was also formed, in 4% yield. [b] Only substrate decomposition was observed.

results of a 2D ^{1}H NOESY experiment revealed the presence of an NOE between these protons, indicative of a compound having a cis ring fusion. The cis stereochemistry was later confirmed by X-ray crystallographic analysis of a crystalline lactam in which the phenyl moiety was replaced with an isobutyl group.[22]

Scope of the 1,3-Dipolar Cycloaddition. Parallel with our efforts to construct the core of sarain-A, we continued to investigate this intramolecular cycloaddition. Synthesis of the aziridine precursors (eq 1) was again achieved by



(1)

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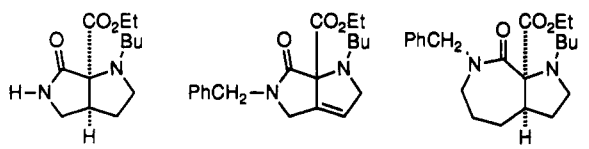
a: R^1 = H, R^2 = $CH_2CH{=}CH_2$
b: R^1 = $PhCH_2$, R^2 = $CH_2C{\equiv}CH$
c: R^1 = $PhCH_2$, R^2 = $CH_2CH_2CH_2CH{=}CH_2$
d: R^1 = $PhCH_2$, R^2 = $CH_2CH_2CH_2CH_2CH{=}CH_2$

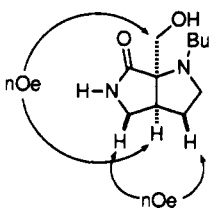
coupling of the requisite amines with the acid chloride of aziridine diester **6**. Although the yields of these coupling reactions are modest (Table I), the conversion to product can be increased by using an excess (1.3–1.5 equiv) of aziridine **6**. Benzyl-substituted secondary amines **14b**, **14c**, and **14d** were prepared by reductive amination of benzaldehyde with the corresponding primary amines.

Pyrolysis of the aziridines was routinely carried out at 300–350 °C and at pressures of 0.07–0.01 Torr. Bicyclic lactams **15a–c** were prepared in this manner.

structure block 1:



15a **15b** **15c**



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Yields for preparation of aziridine amides **14a–d** and for conversion to the corresponding bicyclic lactams are presented in Table I. The results indicate that this method permits facile construction of diazabicyclo[3.3.0]octane, diazabicyclo[4.3.0]nonane, and diazabicyclo[5.3.0]decane ring systems in high yields. Pyrolysis of *N*-allylamide **14a** (entry 1) provides lactam **15a** in 78% yield as a single stereoisomer, and constitutes the only successful 1,3-dipolar cycloaddition of a secondary amide. Attempts to cyclize various other secondary amides led to complete substrate decomposition, with isolation of none of the desired cycloadducts. It is possible that the amide proton quenches the azomethine ylide before cyclization can occur, or there might be a strong conformational bias for the olefinic side chain to lie away from the azomethine ylide in the transition state. On the basis of spectroscopic data and other empirical evidence, we favor the latter hypothesis. The successful cyclization of **15a** reflects the facility with which the diazabicyclo[3.3.0]octane system can be formed. We again confirmed the cis ring fusion stereochemistry of **15a** by ^{1}H NMR spectroscopy. The ethyl ester was chemoselectively reduced to the aldehyde with DIBAL in ether at −78 °C and treatment of this compound with $NaBH_4$ in ethanol provided alcohol **16**. The cis configuration of **16** was established by 2D ^{1}H NMR spectroscopy. Results of a 2D ^{1}H NOESY experiment clearly establish the cis nature of the bicyclic ring; particularly diagnostic were the observed NOE's between the hydroxymethylene protons and the methine proton at the ring fusion (C-7), as well as an NOE between H_b at C-6 and H_b at C-8. The distance between the aforementioned protons is within the limit for observing NOE's only in the case of the cis isomer.

Acetylenes can also function as efficient dipolarphiles in this cycloaddition (entry 2). Pyrolysis of aziridine **14b** affords lactam **15b** in an unoptimized 63%. Given the paucity of examples in which unactivated acetylenes have been used in trapping experiments with azomethine ylides,[9a,23] the success of this reaction demonstrates the viability of unactivated acetylenes as dipolarophiles in the intramolecular 1,3-dipolar cycloaddition with stabilized azomethine ylides.

In addition to the examples discussed above in which the diazabicyclo[4.3.0]nonane skeleton is formed, we have also successfully constructed the diazabicyclo[5.3.0]decane skeleton by this approach. Pyrolysis of aziridine **14c** provides lactam **15c** as a single stereoisomer in 78% yield (entry 3). Although not rigorously proven, the stereochemistry of the ring fusion was assigned as cis on the basis of the assignments of the other cycloadditions. In addition to the desired product, we isolated 4% of compound **17**, in which the azomethine ylide had added to the phenyl ring rather than to the olefin. It is noteworthy that the major cycloaddition product from **14c** has the bicyclo[5.3.0]decane, rather than the alternative bicyclo[5.2.1]decane, skeleton. Cognizant of the fact that 8-membered rings are much more difficult to form than are 5-, 6-, or 7-membered rings,[24] we nevertheless attempted to form the diazabicyclo[6.3.0]undecane skeleton. However, pyrolysis of aziridine **15d** (entry 5) provided none of the desired cycloadduct, instead leading only to substrate decomposition.

The formation of byproduct **17** in the pyrolysis of aziridine **15c** came as a surprise. Although there is a

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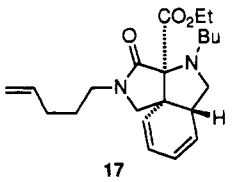

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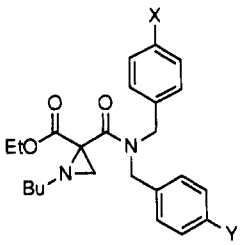
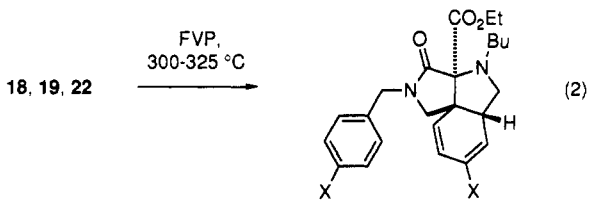
report of intramolecular azomethine ylide addition with a furan,[25] to the best of our knowledge there is no report of a 1,3-dipolar cyclization of an azomethine ylide with a benzene ring. Successful intramolecular cycloaddition of our stabilized azomethine ylide with a benzene ring would generate a fused tricyclic compound containing three contiguous stereocenters (two quaternary) in a stereocontrolled fashion, with functionality in two of the three rings. Thus if we could increase the yield of the cycloaddition, we thought that this novel cyclization might prove to be a useful synthetic tool for the construction of highly functionalized heterocyclic systems. The obvious strategy was to eliminate the possibility of alkene cycloaddition. To this end, a series of dibenzylamides were prepared. Compounds **18–23** were each obtained in the normal manner from the corresponding amines, which were prepared by reductive amination of a benzylamine with a benzaldehyde derivative.



18: X = Y = H
19: X = Y = MeO
20: X = H; Y = MeO
21: X = Y = CN
22: X = Y = CF_3
23: X = H; Y = CF_3

Indeed, flash vacuum pyrolysis of the parent dibenzylamide **18** at 325 °C gave tricyclic lactam **24** in 67% yield (eq 2). The relative configuration of the newly created



(2)

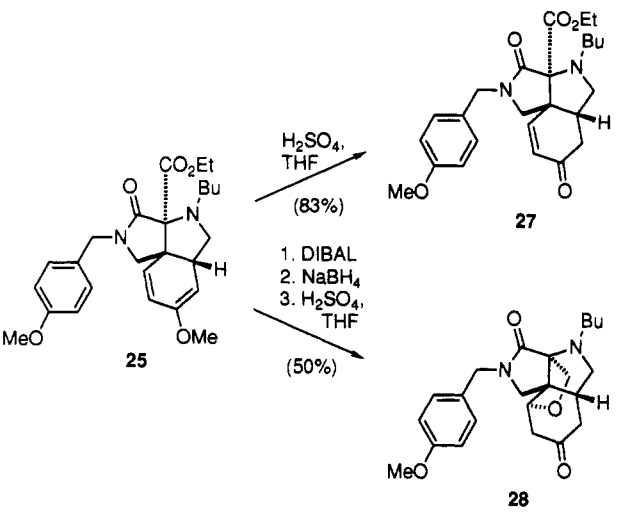
24: X = H (67%)
25: X = MeO (42%)
26: X = CF_3 (68%)

stereocenters was not rigorously proven for this compound, but was assumed to be as shown based on analogy to earlier results. This was later confirmed by chemical transformation of a related system (vide infra).

Similar treatment of bis(*p*-methoxybenzyl)amide **19** at 300 °C provided cycloadduct **25** in 47% yield, along with several other unidentified byproducts in lesser amounts (eq 2). Lactam **25** was prone to decomposition on silica gel and was thermally unstable as well, which may account for the low yield in this reaction. Exposure of **25** to 0.5 M H_2SO_4 in THF resulted in enol ether hydrolysis to

(25) Tsuge, O.; Ueno, K.; Kanemasa, S. *Chem. Lett.* **1984**, 797.

Scheme VI



provide enone **27** in 83% yield (Scheme VI). In addition, two-step chemoselective reduction of the ester moiety in **25** by reduction to the aldehyde with DIBAL at −78 °C, followed by $NaBH_4$-mediated reduction, provided the corresponding alcohol, which when treated with 0.5 M H_2SO_4 in THF and gave tetracyclic ketone **28** in 50% yield. Compound **28** results from hydrolysis of the enol ether followed by intramolecular Michael addition of the hydroxyl group to the resulting enone. Formation of this product serves to confirm the relative configuration of the three ring-fusion stereocenters, since inspection of models indicates that the intramolecular Michael addition is only possible when the configuration of these centers is as depicted.

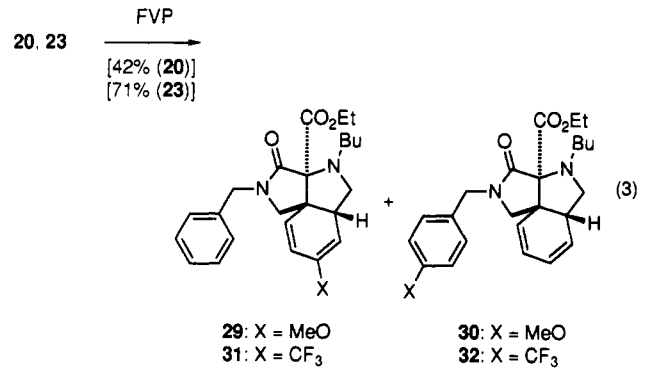
Surprisingly, flash vacuum pyrolysis of bis(*p*-cyanobenzyl)amide **21** failed to provide any of the desired product, leading instead to complete substrate decomposition. Since other investigators have reported successful cycloadditions with nitrile-substituted dipolarophiles,[26] the ineffectiveness of this cyclization was somewhat unexpected. However, pyrolysis of the bis[*p*-(trifluoromethyl)benzyl]amide **22** proved more successful, generating diene **26** in 68% yield and establishing the ability of the azomethine ylide to add to an electron-poor aromatic dipolarophile.

Amides **20** and **23** were prepared to evaluate possible substituent effects on the sensitivity of the 1,3-dipole to electron density in the dipolarophile. Studies on intermolecular azomethine ylide cycloadditions[3] and frontier oribtal energy calculations[27] suggest that these stabilized ylides should be more reactive with electron-rich or electron-poor dipolarophiles than simple unsubstituted dipolarophiles. However, pyrolysis of **24** provided a 1:1 mixture of dienes **29** and **30**, along with trace amounts of unidentified byproducts. The low yield (42%) leaves a large amount of mass unaccounted for, and selective destruction of the more sensitive diene **29** remains a possibility. Pyrolysis of **23** afforded the easily separable isomers **31** and **32** in a ratio of 70:30 and 71% yield.

With **31** and **32** in hand, we were able to ask the question of whether or not the azomethine ylide addition is rever-

(26) Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K. *J. Org. Chem.* **1987**, *52*, 2523.

(27) (a) Houk, K. N.; Smims, J.; Duke, R. E., Jr.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287. (b) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. *J. Am. Chem. Soc.* **1973**, *95*, 7301. (c) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361. (d) Sustmann, R. *Tetrahedron Lett.* **1971**, 2717. (e) Bastide, J.; El Ghandour, N.; Henri-Rousseau, O. *Tetrahedron Lett.* **1972**, 4225.



29: X = MeO
31: X = CF_3

30: X = MeO
32: X = CF_3

sible under the FVP conditions. Indeed, pyrolysis of either pure isomer provided the identical 70:30 mixture of **31** and **32**, proving that cycloadducts **31** and **32** revert to azomethine ylide **33** under conditions of flash vacuum pyrolysis (Scheme VII).

Thus we have demonstrated that the azomethine ylides generated from the thermal ring opening of aziridines stabilized by both an ester and amide group undergo successful 1,3-dipolar cycloaddition to a number of unactivated dipolarophiles to provide fused bicyclic pyrrolidines in good to excellent yields and in a stereocontrolled fashion. In addition, we have discovered that benzene derivatives function as effective dipolarophiles in this cycloaddition, providing novel tricyclic heterocycles containing the substituted pyrrolidine ring system.

Experimental Section

General. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Diethyl ether (ether) and tetrahydrofuran (THF) were distilled from sodium–benzophenone immediately prior to use. Benzene, acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine, and *tert*-butyl alcohol were distilled from CaH_2 prior to use. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with $CDCl_3$ containing tetramethylsilane (TMS, δ 0.00 for ^{1}H) or $CHCl_3$ (δ 7.26 for ^{1}H, 77.06 for ^{13}C) as an internal reference unless otherwise stated. Assignments of individual resonances are supported by DEPT, HETCOR, and/or COSY in many cases. All J values are in hertz. Column chromatography was performed by the method of Still[28] with 32–63 mm silcia gel (Merck) or basic alumina of activity as indicated (Brinkmann). Melting points are uncorrected. Bulb-to-bulb distillations were done with a "coffeepot" Kügelrohr; oven temperatures are uncorrected. All reactions were carried out in oven- or flame-dried glassware under a dry nitrogen or argon atmosphere. Brine refers to a saturated aqueous solution of sodium chloride; Rochelle's salt refers to a saturated aqueous solution of potassium sodium tartrate; NH_4Cl, $NaHCO_3$, and Na_2CO_3 refer to saturated aqueous solutions unless otherwise indicated.

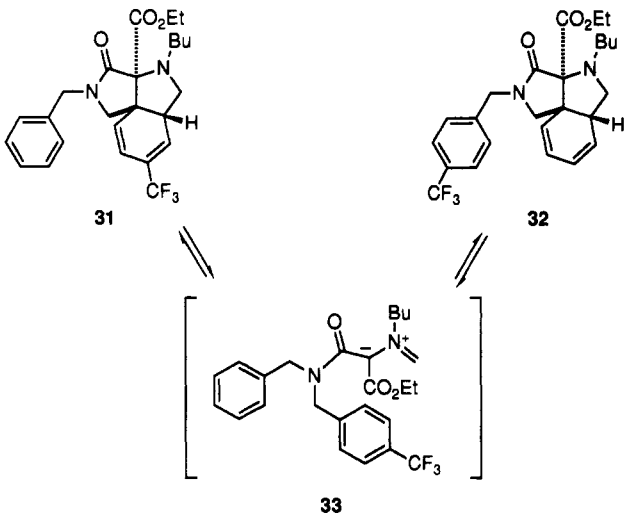
Diethyl Bromo(bromo)malonate (8). A solution of 25.0 g (0.156 mol) of diethyl malonate in 50 mL of THF was added dropwise over 30 min to a stirring suspension of 4.12 g (0.171 mol) of NaH in 250 mL of THF, with gas evolution observed during the addition. The resulting solution was stirred for 30 min after the addition was complete and then was added by cannula over 1 h to a stirring solution of 17.7 mL (0.234 mol) of chloromethyl methyl ether in 100 mL of THF maintained at rt. The resulting milky white solution was stirred for 30 min after addition was complete and then was poured into H_2O (500 mL) and extracted with ether (2 × 500 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated. The resulting yellow oil was purified by fractional distillation through a Vigreux column at 0.12 Torr such that the pot temperature was kept below 100 °C. Isolation of the fraction distilling from 68–75 °C provided 14.28 g (42%) of a clear colorless oil which contained ca. 70% of desired product along with ca. 30% of bisalkylated material. ^{1}H NMR (250 MHz): δ 1.22 (t, 3), 3.30 (s, 3), 3.65 (t, 1), 3.82 (d, 2), 4.18 (q, 2).

A solution of 1.67 mL (32.7 mmol) of dry Br_2 in 10 mL of CCl_4 was added dropwise to a refluxing solution of 6.68 g (32.7 mmol) of the foregoing diethyl (methoxymethyl)malonate in 50 mL of CCl_4. The resulting clear red solution was heated an additional 15 min, during which the red color dissipated somewhat. The reaction mixture was cooled to rt, and the excess Br_2 was destroyed by the addition of saturated aqueous $NaHSO_3$ until the red color disappeared. The resulting mixture was poured into Na_2CO_3 (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated. Purification of the oil by silica gel column chromatography using hexane–EtOAc 25:1 as eluent afforded 6.07 g (56%) of diethyl bromo(bromomethyl)malonate (**8**) as a clear colorless oil. ^{1}H NMR (250 MHz): δ 1.34 (t, 3), 4.05 (s, 2), 4.18 (q, 2).

Diethyl 1-Butylaziridine-2,2-dicarboxylate (6). A solution of 5.11 g (15.4 mmol) of diethyl bromo(bromomethyl)malonate in 60 mL of acetonitrile at rt was treated with 1.67 mL (16.9 mmol) of *n*-butylamine and 4.32 mL (30.8 mmol) of Et_3N, and the resulting solution was stirred at rt for 5 h, during which time a yellow-white precipitate appeared in the flask. The acetonitrile was removed in vacuo, and the residue was dissolved in brine (50 mL) and extracted with ether (3 × 50 mL). The organics were combined, dried over $MgSO_4$, and concentrated. Purification of the yellow oil by silica gel column chromatography using hexane–EtOAc 10:1 as eluent afforded 3.26 g (87%) of **6** as a clear, light yellow oil. ^{1}H NMR (500 MHz): δ 0.88 (t, 3, J = 7.3), 1.21–1.39 (m, 8), 1.55 (m, 2), 2.17 (s, br, 1), 2.36 (m, 2), 2.66 (m, 1), 4.02–4.27 (m, 4). ^{13}C NMR (125 MHz): δ 13.98, 14.07, 20.34, 31.72, 39.27, 46.59, 53.63, 61.76, 61.92, 165.83, 167.95. R_f = 0.15 (hexane–EtOAc 10:1). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 58.67; H, 8.65; N, 5.58.

2-(3,4-Dihydroxy-1-methyl-4-phenylbutyl)-1,3-dioxolane (9). A solution of 20.58 mL (43.21 mmol) of 2.1 M *n*-butyllithium in hexanes was added dropwise over 15 min to a 0 °C solution of 6.34 mL (45.27 mmol) of freshly-distilled diisopropylamine in 150 mL of THF. The resulting LDA was stirred for 15 min, and then a solution of 5.73 g (41.15 mmol) of *N*-cyclohexylpropionaldimine[11] in 15 mL of THF was added dropwise over 5 min. The canary-yellow solution was stirred 15 min and then added by cannula over 45 min to a solution of 6.91 g (45.27 mmol) of cinnamyl chloride in 50 mL of THF maintained at 0 °C. The solution was then warmed to rt for 30 min, 200 mL of 1 M aqueous oxalic acid was added, and the resulting two-phase solution was stirred vigorously overnight. The reaction mixture was poured into H_2O (250 mL) and extracted with ether (2 × 200 mL). The organic layers were washed with $NaHCO_3$ (1 × 100 mL), combined, dried over $MgSO_4$, and concentrated. Purification of the orange oil by silica gel gradient column chromatography using hexane–EtOAc 50:1, 20:1, and 10:1 (one column volume each) afforded 5.77 g (81%) of the aldehyde as a clear, light orange oil. Bp: 110 °C at 1.0 Torr. ^{1}H NMR (500 MHz): δ 1.18 (d, 3, J = 7.0), 2.31

Scheme VII



(28) Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

(m, 1), 2.50 (m, 1), 2.62 (m, 1), 6.16 (m, 1), 6.42 (d, 1, J = 15.7), 7.30 (m, 5), 9.71 (s, 1).

A solution of 5.70 g (32.71 mmol) of the foregoing aldehyde, 2.19 mL (39.25 mmol) of ethylene glycol, and 100 mg of p-toluenesulfonic acid in 70 mL of benzene was heated at reflux for 1 h, with removal of H_2O by a Dean–Stark trap. The solution was cooled to rt, poured into $NaHCO_3$ (100 mL), and extracted with ether (2 × 100 mL). The organic layers were combined, dried over K_2CO_3, and concentrated. Purification by Kügelrohr distillation afforded 6.83 g (95%) of the acetal as a clear, colorless oil. Bp: 120 °C at 0.80 Torr. ^{1}H NMR (400 MHz): δ 1.00 (d, 3, J = 6.9), 1.91 (m, 1), 2.13 (m, 1), 2.48 (m, 1), 3.88 (m, 2), 3.98 (m, 2), 4.78 (d, 1, J = 4.3), 6.26 (m, 1), 6.43 (d, 1, J = 15.8), 7.20–7.38 (m, 5). ^{13}C NMR (100 MHz): δ 13.81, 35.14, 37.32, 65.13, 107.13, 126.01, 126.93, 128.58, 128.77, 131.41, 137.76. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.02; H, 8.31. Found: C, 76.58; H, 8.11.

Pyridine (2.58 mL, 31.92 mmol) and N-methylmorpholine oxide (5.61 g, 41.50 mmol) were added to a solution of 7.00 g (31.92 mmol) of the foregoing olefin in 100 mL of *tert*-butyl alcohol at rt. The solution was stirred for 5 min and ca. 10 mL of a 1% solution of OsO_4 in H_2O was added all at once. The resulting solution was stirred at rt for 4 h and then heated to 55 °C overnight. The solution was cooled to rt, 45 mL of saturated aqueous $NaHSO_3$ was added, and the *tert*-butyl alcohol was removed in vacuo. The residue was poured into brine (150 mL) and extracted with ether (2 × 150 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated. Purification by silica gel column chromatography using 1:1 hexane–EtOAc as eluent afforded 6.07 g (75%) of diol **9** as a clear light yellow oil, isolated as an inseparable 1:1 mixture of diastereomers. Bp: 110 °C at 0.08 Torr. ^{1}H NMR (400 MHz): δ 0.89 (d, 1.5, J = 6.9), 0.93 (d, 1.5, J = 7.0), 1.17 (ddd, 0.5, J = 2.4, 7.5, 14.8), 1.44 (t, 1, J = 6.5), 1.65 (m, 0.5), 1.92–2.06 (m, 1), 2.92 (d, 0.5, J = 3.4), 3.08 (d, 0.5, J = 3.0), 3.27 (d, 0.5, J = 3.7), 3.32 (d, 0.5, J = 4.1), 3.74–3.97 (m, 5), 4.42 (m, 1), 4.65 (t, 1, J = 4.2), 7.27–7.42 (m, 5). ^{13}C NMR (125 MHz): δ 15.07, 15.61, 33.17, 34.29, 34.81, 35.07, 64.80, 64.97, 65.05, 73.54, 74.11, 77.94, 78.44, 107.39, 107.70, 127.00, 127.08, 127.96, 127.98, 128.43, 128.47, 141.27. R_f = 0.22 (hexane–EtOAc 1:1). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.21; H, 8.09.

2-(1-Methyl-6-(*N*-methylamino)hex-3(*Z*)-enyl)-1,3-dioxolane (7). Lead tetraacetate (11.02 g, 24.86 mmol) was added in 1-g portions over 15 min to a stirring solution of 6.00 g (23.68 mmol) of diol **9** in 100 mL of benzene at rt. The reaction mixture was stirred for 45 min after the addition was complete, poured into $NaHCO_3$ (100 mL), and extracted with ether (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated. Purification of the crude material by silica gel column chromatography using 4:1 hexane–EtOAc as eluent afforded 2.55 g (75%) of aldehyde as a clear colorless oil. ^{1}H NMR (400 MHz): δ 1.03 (d, 3, J = 7.0), 2.24 (ddd, 1, J = 2.0, 4.8, 9.6), 2.40 (m, 1), 2.54 (ddd, 1, J = 2.6, 3.9, 7.2), 3.87 (m, 4), 4.75 (d, 1, J = 3.8), 9.71 (t, 1, J = 2.2). ^{13}C NMR (100 MHz): δ 15.20, 32.39, 45.13, 65.04, 65.16, 106.43, 201.77. Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.18; H, 8.43.

A solution of 41.2 mL (41.2 mmol) of 1.0 M $NaN(TMS)_2$ in THF was added dropwise over 15 min to a stirring suspension of 10.2 g (20.60 mmol) of N-methyl-3-aminopropyltriphenylphosphonium bromide (prepared according to the literature procedure[15]) in 300 mL of THF at −78 °C. The resulting orange solution was stirred for 5 min after the addition was complete and a solution of 2.50 g (17.34 mmol) of the foregoing aldehyde in 40 mL of THF was added rapidly, with a concomitant discharge of the orange color. The reaction mixture was warmed to rt, stirred for 30 min, poured into H_2O (300 mL), and extracted with ether (2 × 300 mL). The organic layers were combined, dried over K_2CO_3, and concentrated. Purification of the crude material by silica gel column chromatography using hexane–acetone 1:3 with 4% Et_3N added afforded 1.29 g (38%) of amine **7** as a clear colorless oil. Bp: 75 °C at 0.30 Torr. ^{1}H NMR (400 MHz): δ 0.91 (d, 3, J = 6.9), 1.55 (s, br, 1), 1.76 (m, 1), 1.99 (m, 1), 2.25 (m, 3), 2.42 (s, 3), 2.60 (t, 2, J = 6.9), 3.81–3.97 (m, 4), 4.70 (d, 1, J = 4.3), 5.43 (m, 2). ^{13}C NMR (100 MHz): δ 13.69, 27.74, 29.28, 36.38, 37.36, 51.69, 65.07, 107.19, 128.41, 129.53. Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.19; H, 10.62; N, 7.03. Found: C, 65.80; H, 10.49; N, 6.96.

(*Z*)-*N*-Methyl-4-phenyl-3-butenylamine (10). A solution of 2.62 mL (2.62 mmol) of 1.0 M $NaN(TMS)_2$ in THF was added dropwise over 15 min to a stirring suspension of 650 mg (1.31 mmol) of N-methyl-3-aminopropyltriphenylphosphonium bromide (prepared according to the literature procedure[15]) in 30 mL of THF at −78 °C. The resulting orange solution was stirred for 5 min after the addition was complete and 139 mg (1.31 mmol) of benzaldehyde was added rapidly, with a concomitant discharge of the orange color. The reaction mixture was warmed to rt, stirred 30 min, poured into H_2O (30 mL), and extracted with ether (2 × 30 mL). The organic layers were combined, dried over K_2CO_3, and concentrated. Purification of the crude material by silica gel column chromatography using hexane–acetone 1:2 with 4% Et_3N added afforded 112 mg (53%) of amine **10** as a clear colorless oil, along with 26 mg (12%) of the corresponding (*E*)-isomer, which was discarded. ^{1}H NMR (400 MHz): δ 2.40 (s, 3), 2.54 (m, 2), 2.66 (t, 2, J = 7.7), 5.65 (m, 1), 6.49 (d, 1, J = 11.7), 7.28 (m, 5).

General Procedure for Preparation of Aziridinecarboxamides. A solution of NaOH in absolute ethanol was freshly prepared and titrated prior to use. An aliquot of this solution, corresponding to 1.05 molar equiv, was added to a 0.1 M solution of diester **6** in absolute ethanol at rt and stirred overnight. The solvent was removed in vacuo and the solid residue was dissolved in sufficient CH_2Cl_2 to provide a 0.1 M solution. The solution was cooled to −78 °C and 1.0–1.05 molar equiv of neat $SOCl_2$ was added. The reaction mixture was allowed to slowly warm to −30 °C over a period of 60–90 min and then was recooled to −78 °C and added by cannula to a rapidly stirring two-phase solution of 0.75–1.0 molar equiv of the appropriate amine in a 1:1 mixture of ether–15% aqueous NaOH. The resulting solution was stirred for 30 min at rt, poured into brine, and extracted with ether. The organic layers were combined, dried over K_2CO_3, and concentrated. Purification was achieved by silica gel column chromatography using solvent systems detailed below. Note: The majority of these compounds cannot be purified by distillation due to decomposition.

(*Z*)-1-Butyl-2-(ethoxycarbonyl)-*N*-methyl-*N*-(6-(2′-(1′,3′-dioxolanyl))hept-3-enyl)aziridine-2-carboxamide (5). Purification by silica gel column chromatography using hexane–EtOAc 1:1 as eluent afforded a 66% yield of aziridine **5**. ^{1}H NMR (400 MHz): δ 0.88 (m, 6), 1.19–1.37 (m, 5), 1.52 (m, 2), 1.72 (m, 2), 1.93–2.08 (m, 2), 2.18–2.37 (m, 4), 2.50–2.97 (m, 4), 3.06–3.42 (m, 2), 3.79–3.92 (m, 4), 4.20 (m, 2), 4.66 (m, 1), 5.40 (m, 2). ^{13}C NMR (100 MHz): δ 13.64, 14.00, 14.12, 20.36, 20.96, 24.66, 25.92, 29.22, 29.97, 31.74, 32.00, 32.49, 32.93, 34.61, 35.24, 35.32, 37.01, 37.14, 37.20, 40.24, 41.00, 41.34, 46.28, 47.55, 47.73, 49.18, 49.34, 51.59, 51.75, 54.40, 54.71, 60.29, 61.83, 64.99, 65.01, 106.92, 107.01, 125.77, 126.33 126.86, 127.07, 129.64, 129.94, 130.30, 130.66, 164.87, 166.80, 167.01, 167.10, 168.95. R_f = 0.22 (hexane–EtOAc 1:1). Anal. Calcd for $C_{21}H_{36}N_2O_5$: C, 63.61; H, 9.15; N, 7.05. Found: C, 63.72; H, 9.28; N, 6.65.

(*Z*)-1-Butyl-2-(ethoxycarbonyl)-*N*-methyl-*N*-(4-phenyl-3-butenyl)aziridine-2-carboxamide (11). Purification by silica gel chromatography using hexane–EtOAc 2:1 as eluent afforded a 66% yield of aziridine **11**. ^{1}H NMR (400 MHz): δ 0.88 (m, 3), 1.06–1.77 (m, 9), 2.02–2.38 (m, 2), 2.51–2.86 (m, 2), 2.90–3.00 (3 x s, 3), 3.27–3.65 (m, 2), 4.10–4.26 (m, 2), 5.65 (m, 1), 6.49 (d, 1, J = 11.9), 7.28 (m, 5). ^{13}C NMR (100 MHz): δ 14.01, 14.15, 20.40, 26.14, 27.19, 31.77, 31.94, 32.04, 32.91, 35.34, 35.53, 40.31, 41.03, 41.43, 41.86, 46.29, 47.60, 47.77, 49.60, 51.57, 51.79, 54.48, 54.70, 61.91, 126.74, 126.86, 126.99, 127.70, 128.24, 128.30, 128.41, 128.60, 128.64, 130.72, 131.00, 131.53, 131.67, 137.12, 164.43, 167.01, 168.95. R_f = 0.32 (hexane–EtOAc 1:1). Anal. Calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.81. Found: C, 70.35; H, 8.37; N, 7.75.

1-Butyl-2-(ethoxycarbonyl)-*N*-propenylaziridine-2-carboxamide (14a). Purification by silica gel column chromatography using hexane–EtOAc 4:1 as eluent afforded an 54% yield of aziridine **14a**. Bp: 80 °C at 0.01 Torr. ^{1}H NMR (500 MHz): δ 0.91 (t, 3, J = 7.3), 1.29 (t, 3, J = 7.1), 1.36 (m, 2), 1.53 (m, 2), 2.09 (s, 1), 2.27 (s, 1), 2.36 (m, 1), 2.54 (m, 1), 3.85 (m, 2), 4.26 (dq, 2, J = 7.2, 21.0), 5.14 (m, 2), 5.81 (m, 1), 6.93 (s, br, 1). ^{13}C NMR (125 MHz): δ 13.97, 14.18, 20.38, 31.77, 39.40, 41.21, 47.37, 52.87, 62.04, 116.08, 133.96, 165.98, 167.38. R_f = 0.44 (hexane–EtOAc 1:1). Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.40; H, 8.72; N, 11.01. Found: C, 61.19; H, 8.60; N, 10.96.

1-Butyl-2-(ethoxycarbonyl)-*N*-benzyl-*N*-propynylaziridine-2-carboxamide (14b). Purification by silica gel column chromatography using hexane–EtOAc 4:1 as eluent afforded a

60% yield of aziridine **14b**. ^{1}H NMR (400 MHz): δ 0.87 (m, 3), 1.16–1.77 (m, 9), 2.17 (m, 0.5), 2.35 (m, 1), 2.47 (m, 0.5), 2.60–2.79 (m, 1), 2.96 (m, 0.5), 3.79 (m, 0.5), 4.04 (m, 1), 4.20 (m, 2), 4.59 (m, 1), 4.76–4.91 (m, 1), 7.28 (m, 5). ^{13}C NMR (100 MHz): δ 13.93, 14.00, 14.10, 20.27, 20.38, 31.70, 31.86, 31.92, 33.01, 33.65, 36.14, 36.43, 40.21, 40.70, 41.08, 41.31, 46.09, 47.03, 47.40, 50.14, 50.32, 51.43, 51.77, 54.59, 55.04, 62.16, 62.21, 71.71, 72.80, 73.88, 77.25, 77.85, 78.14, 127.32, 127.52, 127.81, 127.94, 128.16, 128.34, 128.52, 128.61, 128.70, 128.82, 135.50, 135.83, 136.32, 166.67, 166.81, 167.26, 168.57. R_f = 0.27 (hexane–EtOAc 4:1). Anal. Calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18. Found: C, 70.09; H, 7.88; N, 8.11.

1-Butyl-2-(ethoxycarbonyl)-*N*-benzyl-*N*-pent-4-enylaziridine-2-carboxamide (14c). Purification by silica gel column chromatography using hexane–EtOAc 4:1 as eluent afforded a 69% yield of aziridine **14c**: mp 58–60 °C. ^{1}H NMR (400 MHz): δ 0.79–0.94 (m, 3), 1.15–1.81 (m, 9), 2.00 (m, 2), 2.17 (s, 0.5), 2.29 (s, 0.5), 2.31 (s, 0.5), 2.42 (s, 0.5), 2.50–2.85 (m, 3), 3.00–3.20 (m, 4), 4.20 (m, 2), 4.28–4.79 (m, 2), 4.95 (m, 2), 5.73 (m, 1), 7.17–7.32 (m, 5). ^{13}C NMR (100 MHz): δ 13.94, 14.10, 14.17, 20.27, 20.47, 25.54, 26.64, 30.92, 31.02, 31.13, 31.73, 31.85, 32.10, 40.49, 41.16, 41.28, 44.12, 44.76, 46.32, 46.55, 47.52, 51.00, 51.44, 51.65, 54.87, 62.01, 114.82, 115.07, 115.38, 115.74, 127.03, 127.10, 127.49, 127.63, 127.76, 127.94, 128.19, 128.41, 128.51, 128.71, 136.46, 136.86, 137.33, 137.95, 167.23, 167.48. R_f = 0.25 (hexane–EtOAc 4:1). Anal. Calcd for $C_{22}H_{32}N_2O_3$: C, 70.94; H, 8.66; N, 7.52. Found: C, 70.99; H, 9.01; N, 7.26.

1-Butyl-2-(ethoxycarbonyl)-*N*-benzyl-*N*-hex-5-enylaziridine-2-carboxamide (14d). Purification by silica gel column chromatography using hexane–EtOAc 4:1 as eluent afforded a 75% yield of aziridine **14d**: mp 59–60 °C. ^{1}H NMR (400 MHz): δ 0.78–0.93 (m, 3), 1.14–1.42 (m, 7), 1.46–1.75 (m, 4), 2.00 (m, 2), 2.17 (s, 0.5), 2.29 (s, 0.5), 2.31 (s, 0.5), 2.42 (s, 0.5), 2.57–2.83 (m, 2), 3.04–3.38 (m, 2), 4.20 (m, 2), 4.30–4.78 (m, 2), 4.92 (m, 2), 5.71 (m, 1), 7.17–7.35 (m, 5). ^{13}C NMR (100 MHz): δ 13.92, 14.06, 14.32, 20.24, 20.44, 25.74, 25.99, 26.12, 26.28, 26.90, 31.71, 31.83, 32.09, 33.19, 33.40, 40.44, 41.14, 41.20, 44.21, 46.29, 46.74, 47.34, 50.87, 51.41, 51.62, 54.82, 61.96, 114.58, 114.97, 115.41, 127.01, 127.17, 127.46, 127.58, 127.73, 127.96, 128.21, 128.38, 128.48, 128.67, 136.47, 137.25, 137.82, 138.07, 138.52, 145.21, 167.23, 167.39. R_f = 0.50 (hexane–EtOAc 4:1). Anal. Calcd for $C_{23}H_{34}N_2O_3$: C, 71.39; H, 8.86; N, 7.24. Found: C, 71.47; H, 8.98; N, 6.98.

1-Butyl-2-(ethoxycarbonyl)-*N*,*N*-dibenzylaziridine-2-carboxamide (18). Purification by silica gel column chromatography using hexane–EtOAc 6:1 as eluent afforded a 66% yield of aziridine **18**. ^{1}H NMR (400 MHz): δ 0.85 (m, 3), 1.12–1.80 (m, 7), 2.17 (s, 0.2), 2.35 (s, 1), 2.53 (s, 0.8), 2.65 (m, 1.5), 2.95 (m, 0.5), 4.04 (m, 1), 4.23 (m, 2), 4.26 (m, 1), 4.64 (m, 1), 4.90 (m, 1), 7.18–7.36 (m, 10). ^{13}C NMR (100 MHz): δ 13.97, 14.14, 20.28, 31.87, 40.38, 41.36, 46.26, 46.66, 47.21, 49.95, 51.29, 55.21, 62.16, 127.32, 127.74, 128.05, 128.40, 128.44, 128.58, 128.81, 129.04, 135.96, 136.78, 167.18, 167.86. Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.60; N, 7.10. Found: C, 73.31; H, 7.62; N, 6.84.

1-Butyl-2-(ethoxycarbonyl)-*N*,*N*-bis(*p*-methoxybenzyl)aziridine-2-carboxamide (19). Purification by silica gel column chromatography using hexane–EtOAc 2:1 as eluent afforded a 54% yield of aziridine **19**. ^{1}H NMR (400 MHz): δ 0.83 (m, 3), 1.13–1.34 (m, 5.5), 1.48 (m, 1.5), 1.60–1.80 (m, 1), 2.17 (s, 0.3), 2.34 (s, 1), 2.52 (s, 0.7), 2.68 (m, 1.5), 3.80 (s, 3), 3.82 (s, 3), 3.91–4.23 (m, 4), 4.55 (m, 1), 4.82 (m, 1), 6.84 (m, 4), 7.14 (m, 4). ^{13}C NMR (100 MHz): δ 13.99, 14.16, 20.32, 31.92, 41.37, 45.64, 46.29, 49.12, 51.29, 53.09, 55.28, 55.31, 62.09, 113.76, 113.93, 114.16, 127.89, 128.69, 128.95, 129.46, 129.77, 130.36, 158.88, 159.22, 167.26, 167.61. Anal. Calcd for $C_{26}H_{39}N_2O_5$: C, 68.70; H, 7.54; N, 6.16. Found: C, 68.58; H, 7.52; N, 5.87.

1-Butyl-2-(ethoxycarbonyl)-*N*-benzyl-*N*-(*p*-methoxybenzyl)aziridine-2-carboxamide (20). Purification by silica gel column chromatography using hexane–EtOAc 4:1 as eluent gave a 48% yield of aziridine **20**. ^{1}H NMR (400 MHz): δ 0.84 (m, 3), 1.11–1.77 (m, 7.5), 2.17 (m, 0.5), 2.34 (m, 1), 2.53 (m, 1), 2.66 (m, 1.5), 2.90 (m, br, 0.5), 3.28 (s, 3), 3.98 (m, 0.5), 4.21 (m, 2), 4.35 (m, 0.5), 4.60 (m, 1), 4.86 (m, 1), 6.84 (m, 2), 7.08–7.36 (m, 2). ^{13}C NMR (100 MHz): δ 13.98, 14.13, 20.26, 20.31, 31.85, 31.91, 41.30, 41.40, 46.00, 46.28, 49.34, 49.70, 51.27, 55.30, 62.14, 113.78, 113.93, 114.17, 127.25, 127.69, 127.78, 128.01, 128.40, 128.56, 128.75, 129.47, 129.77, 130.39, 136.01, 136.83, 158.91, 159.24, 167.21, 167.70. Anal. Calcd for $C_{25}H_{32}N_2O_4$: C, 70.73; H, 7.60; N, 6.60. Found: C, 70.64; H, 7.75; N, 6.56.

1-Butyl-2-(ethoxycarbonyl)-*N*,*N*-bis(*p*-cyanobenzyl)aziridine-2-carboxamide (21). Purification by silica gel column chromatography using hexane–EtOAc 2:1 as eluent afforded a 53% yield of aziridine **21** as a white solid. Mp: 82–83 °C. ^{1}H NMR (400 MHz): δ 0.76 (t, 3, J = 7.3), 1.15–1.35 (m, 7), 2.37 (s, 1), 2.48 (s, 1), 2.54 (m, 2), 3.87 (d, 1, J = 15.6), 4.24 (m, 2.5), 4.75 (s, 0.5), 4.81 (d, 1, J = 16.3), 5.06 (d, 1, J = 15.6), 7.39 (m, 4), 7.62 (m, 4). ^{13}C NMR (100 MHz): δ 13.82, 14.22, 20.12, 31.65, 41.23, 46.12, 47.01, 50.30, 51.16, 62.40, 64.04, 111.46, 111.95, 118.40, 118.55, 126.95, 128.53, 128.55, 132.21, 132.39, 132.43, 141.13, 141.78, 166.61, 168.31. Anal. Calcd for $C_{26}H_{28}N_4O_3$: C, 70.25; H, 6.35; N, 12.60. Found: C, 70.32; H, 6.22; N, 12.66.

1-Butyl-2-(ethoxycarbonyl)-*N*,*N*-bis[*p*-(trifluoromethyl)benzyl]aziridine-2-carboxamide (22). Purification by silica gel column chromatography using hexane–EtOAc 4:1 as eluent gave a 68% yield of aziridine **22**. Mp: 73–75 °C. ^{1}H NMR (400 MHz): δ 0.78 (t, 3, J = 7.3), 1.14–1.41 (m, 7), 2.39 (d, 1, J = 1.2), 2.52 (d, 1, J = 1.2), 2.60 (m, 2), 3.86 (s, 1), 3.95 (d, 1, J = 15.2), 4.25 (m, 2), 4.79 (d, 1, J = 15.3), 5.06 (d, 1, J = 15.3), 7.41 (m, 4), 7.59 (m, 4). ^{13}C NMR (100 MHz): δ 13.85, 14.20, 20.22, 31.78, 41.36, 46.25, 46.77, 50.07, 51.25, 52.62, 62.37, 77.26, 125.38, 125.42, 125.48, 125.51, 125.55, 125.60, 128.29, 128.33, 128.41, 139.93, 140.63, 166.87, 168.26. R_f = 0.29 (hexane–EtOAc 4:1). Anal. Calcd for $C_{26}H_{28}F_6N_2O_3$: C, 58.89; H, 5.32; N, 5.28. Found: C, 58.85; H, 5.16; N, 5.02.

1-Butyl-2-(ethoxycarbonyl)-*N*-benzyl-*N*-[*p*-(trifluoromethyl)benzyl]aziridine-2-carboxamide (23). Purification by silica gel chromatography using hexane–EtOAc 5:1 and 4:1 (20 fractions each) as eluent gave 69% yield of aziridine **23**: ^{1}H NMR (400 MHz): δ 0.9 (m, 3), 1.4 (m, 7), 2.5 (s, H), 2.7 (m, 2), 3.5 (m, 1), 4.0 (m, 1), 1.4–4.6 (m, 2), 4.8 (m, 2), 4.8 (m, 1), 5.0 (d, 1), 5.2 (d, 1), 7.3–7.7 (m, 9).

General Procedure for the Flash Vacuum Pyrolysis of Aziridine Carboxamides. A 50-cm quartz tube packed with quartz chips was inserted into a Thermolyne tube furnace preheated to the desired temperature. A cold trap leading to the vacuum source was attached to one end of the tube and cooled using liquid N_2. A 5-mL flask containing the neat substrate was attached to the other end of the tube and the system allowed to equilibrate under vacuum. Volatilization of the sample was then achieved by either heating of the flask with a heat gun or sliding of the tube horizontally such that the flask entered the furnace. The product was collected at the other end of the tube. After cooling to rt, the residue was washed from the tube with CH_2Cl_2 and the solvent was removed in vacuo. Purification of the product was achieved by silica gel column chromatography using solvent systems detailed below.

4-Butyl-3-(ethoxycarbonyl)-1-methyl-6-(2′-(1″,3″-dioxolanyl)propyl)-1,4-diazabicyclo[4.3.0]nonan-2-one (4). Pyrolysis was done at 350 °C, 0.02 Torr. Purification by silica gel chromatography using hexane–EtOAc 1:1 as eluent afforded a 94% yield of **4** as a 1:1 mixture of diastereomers. Bp: 155 °C at 0.25 Torr. ^{1}H NMR (500 MHz): δ 0.84 (t, 3, J = 7.2), 0.92 (2 x d, 3, J = 4.3), 1.24 (m, 8), 1.63 (m, 3), 1.88 (m, 1), 2.33 (m, 1), 2.43 (m, 1), 2.88 (m, 3), 2.94 (s, 3), 3.30 (m, 2), 3.41 (m, 1), 3.85 (m, 2), 3.93 (m, 2), 4.18 (m, 2), 4.63 (t, 1, J = 3.3). ^{13}C NMR (125 MHz): δ 13.90, 14.09, 14.34, 20.15, 20.75, 21.38, 30.43, 31.15, 31.91, 43.77, 35.17, 35.47, 35.61, 35.66, 45.89, 46.93, 49.12, 49.18, 49.41, 55.58, 56.10, 60.70, 65.01, 65.06, 65.11, 75.23, 107.41, 107.55, 167.57, 173.72. R_f = 0.25 (hexane–EtOAc 1:1). Anal. Calcd for $C_{21}H_{36}N_2O_5$: C, 63.61; H, 9.15; N, 7.05. Found: C, 63.26; H, 9.32; N, 6.78.

4-Butyl-3-(ethoxycarbonyl)-1-methyl-6-phenyl-1,4-diazabicyclo[4.3.0]nonan-2-one (12). Pyrolysis was done at 350 °C, 0.02 Torr. Purification by silica gel column chromatography using hexane–EtOAc 2:1 as eluent gave lactam **12** in 84% yield as a clear, colorless oil. Bp: 150 °C at 0.05 Torr. ^{1}H NMR (500 MHz): δ 0.89 (t, 3, J = 7.3), 1.30 (t, 3, J = 7.1), 1.32–1.47 (m, 5), 1.76 (ddd, 1, J = 5.0, 11.9, 15.2), 2.76 (m, 1), 2.93 (s, 3), 3.00 (m, 1), 3.10 (m, 1), 3.19 (m, 1), 3.27 (dt, 1, J = 3.7, 8.0), 3.41 (m, 1), 3.56 (m, 2), 4.25 (m, 2), 7.25 (m, 5). ^{13}C NMR (125 MHz): δ 14.14, 14.35, 20.30, 22.67, 31.92, 34.85, 44.17, 48.34, 48.96, 49.43, 54.12, 60.98, 75.09, 126.64, 128.41, 139.30, 167.66, 173.59. R_f = 0.50 (hexane–EtOAc 1:1). Anal. Calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.81.

Found: C, 70.28; H, 8.32; N, 7.85.

4-Butyl-3-(ethoxycarbonyl)-1,4-diazabicyclo[3.3.0]octan-2-one (15a). Pyrolysis was done at 300 °C, 0.02 Torr. Purification by silica gel column chromatography using hexane–EtOAc 1:1 as eluent afforded 78% of lactam **15a** as a single stereoisomer. Bp: 135 °C at 0.30 Torr. Mp: 83–84 °C. ^{1}H NMR (500 MHz): δ 0.91 (t, 3, J = 7.3), 1.28 (t, 3 J = 7.1), 1.35 (m, 2), 1.50 (quintet, 2, J = 7.3), 1.67 (m, 1), 2.23 (m, 1), 2.69 (m, 2), 3.09 (m, 3), 3.19 (ddd, 1, J = 1.2, 3.2, 4.4), 3.63 (t, 1, J = 8.6), 4.19 (m, 1), 4.29 (m, 1), 6.31 (s, br, 1). ^{13}C NMR (125 MHz): δ 14.13, 14.25, 20.51, 31.53, 31.73, 44.90, 46.90, 49.48, 51.00, 61.42, 75.36, 171.34, 173.31. R_f = 0.13 (hexane–EtOAc 1:1). Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.40; H, 8.72; N, 11.01. Found: C, 61.14; H, 8.62; N, 10.96.

1-Benzyl-4-butyl-3-(ethoxycarbonyl)-1,4-diazabicyclo-[3.3.0]oct-6-en-2-one (15b). Pyrolysis was done at 325 °C, 0.02 Torr. Purification by silica gel column chromatography using hexane–EtOAc 1:4 as eluent afforded 64% of lactam **15b** as a single stereoisomer. Bp: 180 °C at 0.08 Torr. ^{1}H NMR (400 MHz): δ 0.93 (t, 3, J = 7.3), 1.20 (t, 3, J = 7.2), 1.38 (m, 2), 1.53 (m, 2), 2.98 (m, 1), 3.13 (m, 1), 3.65 (d, 1, J = 12.1), 3.76 (m, 1), 3.83 (m, 1), 3.92 (m, 1), 4.11 (m, 2), 4.24 (m, 1), 4.89 (d, 1, J = 14.9), 5.91 (s, 1), 7.29 (m, 5). ^{13}C NMR (100 MHz): δ 13.99, 14.26, 20.45, 31.55, 45.49, 46.93, 49.21, 61.27, 61.55, 80.26, 125.59, 127.62, 128.33, 128.61, 135.95, 137.75, 169.26, 170.20. R_f = 0.40 (hexane–EtOAc 2:1). Anal. Calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18. Found: C, 70.20; H, 7.75; N, 7.84.

1-Benzyl-4-butyl-3-(ethoxycarbonyl)-1,4-diazabicyclo-[5.3.0]decan-2-one (15c). Pyrolysis was done at 350 °C, 0.02 Torr. Purification by silica gel column chromatography using hexane–EtOAc 3:1 as eluent afforded 78% of lactam **15c** as a single stereoisomer. Mp: 71–73 °C. ^{1}H NMR (400 MHz): δ 0.91 (t, 3, J = 7.3), 1.28 (t, 3, J = 7.1), 1.35 (m, 4), 1.54 (m, 3), 1.68 (m, 2), 2.02 (m, 2), 2.45 (m, 1), 2.65 (m, 1), 3.06 (m, 2), 3.17 (m, 2), 4.22 (m, 3), 5.06 (d, 1, J = 14.9), 7.21–7.34 (m, 5). ^{13}C NMR (100 MHz): δ 14.20, 14.41, 20.87, 23.73, 28.58, 31.39, 31.80, 42.86, 43.37, 49.21, 49.72, 51.63, 60.94, 77.82, 127.25, 128.15, 128.40, 137.94, 169.69, 171.16. R_f = 0.15 (hexane–EtOAc 4:1). Anal. Calcd for $C_{22}H_{32}N_2O_3$: C, 70.94; H, 8.66; N, 7.52. Found: C, 70.77; H, 8.98; N, 7.27.

1-Benzyl-4-butyl-3-(ethoxycarbonyl)-1,4-diazatricyclo-[3.2.4.0^{3,11}.0^{6,11}]dodeca-7,9-dien-2-one (24). Pyrolysis was done at 325 °C, 0.035 Torr. Purification by silica gel column chromatography using hexane–EtOAc 4:1 as eluent afforded 67% of lactam **24** as a single stereoisomer. ^{1}H NMR (400 MHz): δ 0.91 (t, 3, J = 7.3), 1.25 (t, 3, J = 7.1), 1.33 (m, 2), 1.48 (m, 2), 2.79 (m, 1), 3.02 (m, 4), 3.14 (d, 1, J = 10.0), 3.24 (t, 1, J = 8.4), 4.12–4.28 (m, 2), 4.42 (d, 1, J = 14.7), 4.53 (d, 1, J = 14.7), 5.29 (dd, 1, J = 0.9, 9.7), 5.62 (ddt, 1, J = 0.6, 4.4, 9.7), 5.79 (m, 1), 5.88 (ddd, 1, J = 0.6, 5.6, 9.7), 7.29 (m, 5). ^{13}C NMR (125 MHz): δ 14.16, 14.31, 20.42, 31.68, 43.81, 46.61, 48.98, 50.90, 58.32, 58.95, 60.98, 83.06, 120.69, 123.89, 124.81, 127.24, 127.64, 128.15, 128.68, 136.08, 169.58, 170.44. Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.60; N, 7.10. Found: C, 72.76; H, 7.73; N, 7.00.

1-(*p*-Methoxybenzyl)-4-butyl-3-(ethoxycarbonyl)-8-methoxy-1,4-diazatricyclo[3.2.4.0^{3,11}.0^{6,11}]dodeca-7,9-dien-2-one (25). Pyrolysis was done at 300 °C, 0.02 Torr. Purification by basic alumina column chromatography using hexane–EtOAc 8:1 as eluent afforded 47% of lactam **25** as a single stereoisomer, contaminated by trace byproducts which could not be removed by repeated chromatography. The compound was unstable to silica gel and distillation and thus an analytically pure sample could not be obtained. ^{1}H NMR (400 MHz): δ 0.91 (t, 3, J = 7.2), 1.25 (t, 3, J = 7.2), 1.31–1.51 (m, 4), 2.84 (m, 1), 2.99 (m, 3), 3.06 (s, 2), 3.21 (t, 1, J = 8.0), 3.49 (s, 3), 3.80 (s, 3), 4.20 (m, 2), 4.41 (d, 2, J = 14.5), 4.49 (dd, 1, J = 2.0, 5.0), 5.32 (d, 1, J = 10.1), 5.73 (dd, 1, J = 2.1, 10.1), 6.85 (d, 2, J = 8.7), 7.18 (d, 2, J = 8.7). ^{13}C NMR (100 MHz): δ 14.15, 14.29, 20.40, 31.72, 43.41, 46.01, 48.99, 51.31, 54.17, 55.27, 56.61, 59.93, 61.01, 82.30, 92.42, 114.01, 124.72, 127.26, 128.12, 129.49, 150.83, 159.11, 169.76, 170.72.

1-Benzyl-4-butyl-3-(ethoxycarbonyl)-8-methoxy-1,4-diazatricyclo[3.2.4.0^{3,11}.0^{6,11}]dodeca-7,9-dien-2-one (29) and 1-(*p*-Methoxybenzyl)-4-butyl-3-(ethoxycarbonyl)-1,4-diazatricyclo[3.2.4.0^{3,11}.0^{6,11}]dodeca-7,9-dien-2-one (30). Pyrolysis was done at 300 °C, 0.02 Torr. Purification by basic alumina column chromatography using hexane–EtOAc 4:1 as eluent afforded 42% of lactams **30** and **31**, which were separated by gradient column chromatography on basic alumina using hexane–EtOAc 20:1, 10:1 as eluents (ca. 30 fractions each) to afford 15% of **29** and 13% of **30** along with 6% of a mixture of the two isomers.

Analytical data for **29** follows. ^{1}H NMR (400 MHz): δ 0.91 (t, 3, J = 7.3), 1.25 (t, 3, J = 7.2), 1.28–1.39 (m, 2), 1.47 (m, 2), 1.61 (s, br, 1), 2.87 (m, 1), 2.99 (m, 2), 3.09 (s, 2), 3.24 (t, 1, J = 8.0), 3.50 (s, 3), 4.21 (m, 2), 4.38 (d, 1, J = 14.7), 4.50 (dd, 1, J = 1.8, 4.9), 4.56 (d, 1, J = 14.7), 5.33 (d, 1, J = 10.1), 5.75 (dd, 1, J = 2.2, 10.1), 7.31 (m, 5). ^{13}C NMR (100 MHz): δ 14.18, 14.32, 20.44, 31.75, 43.48, 46.66, 49.02, 51.39, 54.22, 56.79, 59.97, 61.08, 82.26, 92.42, 124.79, 127.25, 127.66, 128.18, 128.52, 128.69, 136.09, 150.88, 169.76, 170.91. R_f = 0.28 (hexane–EtOAc 4:1). Anal. Calcd for $C_{25}H_{32}N_2O_4$: C, 70.73; H, 7.60; N, 6.60. Found: C, 70.51; H 7.45; N, 6.37.

Analytical data for **30** follows. ^{1}H NMR (400 MHz): δ 0.91 (t, 3, J = 7.3), 1.21–1.38 (m, 5), 1.47 (m, 2), 1.64 (s, br, 1), 2.77 (m, 1), 3.05 (m, 3), 3.12 (d, 1, J = 10.0), 3.22 (t, 1, J = 8.3), 3.80 (s, 3), 4.22 (m, 2), 4.37 (d, 1, J = 14.6), 4.45 (d, 1, J = 14.6), 5.28 (d, 1, J = 9.7), 5.62 (ddd, 1, J = 1.0, 4.3, 9.6), 5.79 (m, 1), 5.88 (dd, 1, J = 5.6, 9.2), 6.85 (d, 2, J = 8.7), 7.19 (d, 2, J = 8.7). ^{13}C NMR (100 MHz): δ 14.18, 14.34, 20.44, 31.70, 43.82, 46.04, 49.02, 50.88, 55.31, 58.20, 58.97, 60.98 83.17, 113.81, 114.05, 120.71, 123.88, 124.89, 127.29, 128.17, 128.43, 129.53, 159.14, 169.64, 170.33. R_f = 0.23 (hexane–EtOAc 4:1). Anal. Calcd for $C_{25}H_{32}N_2O_4$: C, 70.73; H, 7.60; N, 6.60. Found: C, 71.11; H, 7.84; N, 6.75.

1-[*p*-(Trifluoromethyl)benzyl]-4-butyl-3-(ethoxycarbonyl)-8-(trifluoromethyl)-1,4-diazatricyclo-[3.2.4.0^{3,11}.0^{6,11}]dodeca-7,9-dien-2-one (26). Pyrolysis was done at 300 °C, 0.02 Torr. Purification by silica gel column chromatography using hexane–EtOAc 4:1 as eluent afforded 68% of lactam **26** as a clear, colorless oil. ^{1}H NMR (400 MHz): δ 0.91 (t, 3, J = 7.3), 1.24 (t, 3, J = 7.2), 1.32 (m, 2), 1.43–1.61 (m, 2), 2.89–3.10 (m, 5), 3.19 (d, 1, J = 10.0), 3.42 (t, 1, J = 8.5), 4.16–4.28 (m, 2), 4.54 (s, 2), 5.57 (d, 1, J = 10.0), 6.00 (dd, 1, J = 1.3, 10.0), 6.17 (m, 1), 7.39 (d, 2, J = 8.0), 7.59 (d, 2, J = 8.0). ^{13}C NMR (100 MHz): δ 14.08, 14.23, 20.32, 31.48, 42.70, 46.22, 48.69, 50.83, 58.42, 58.49, 61.37, 77.26, 82.63, 118.80, 125.81, 127.66, 128.02, 128.07, 128.39, 139.95, 169.09, 170.03. R_f = 0.33 (hexane–EtOAc 4:1). Anal. Calcd for $C_{26}H_{28}F_6N_2O_3$: C, 58.89; H, 5.32; N, 5.28. Found: C, 58.66; H, 5.21; N, 5.07.

1-Benzyl-4-butyl-3-(ethoxycarbonyl)-8-(trifluoromethyl)-1,4-diazatricyclo[3.2.4.0^{3,11}.0^{6,11}]dodeca-7,9-dien-2-one (31) and 1-[*p*-(Trifluoromethyl)benzyl]-4-butyl-3-(ethoxycarbonyl)-1,4-diazatricyclo[3.2.4.0^{3,11}.0^{6,11}]dodeca-7,9-dien-2-one (32). Pyrolysis of 52 mg of aziridine **23** was done at 300 °C, 0.005 Torr. Purification by silica gel column chromatography using hexane–EtOAc 6:1 as eluent afforded 26 mg of **31**, 10 mg of **32**, and 1 mg of a mixture of the two (71% total yield).

Analytical data of **31** follows. ^{1}H NMR (400 MHz): δ 0.9 (t, 3), 1.2 (t, 3), 1.3 (m, 2), 1.5 (m, 2), 2.9–3.1 (m, 5), 3.2 (d, 1), 3.4 (t, 1), 4.1–4.3 (m, 2), 4.5 (s, 2), 5.5 (d, 1), 6.0 (dd, 1), 6.2 (m, 1), 7.2–7.4 (m, 5).

Analytical data for **32** follows. ^{1}H NMR (400 MHz): δ 0.9 (t, 3), 1.2 (t, 3), 1.3 (m, 2), 1.5 (m, 2), 2.8 (m, 1), 3.0–3.1 (m, 4), 3.2 (d, 1), 3.3 (t, 1), 4.1–4.3 (m, 2), 4.5 (dd, 2), 5.3 (d, 1), 5.6 (m, 1), 5.8 (m, 1), 5.9 (m, 1), 7.4 (d, 2), 7.6 (d, 2).

Pyrolytic Equilibration of 31 and 32. Pure samples of the foregoing compounds were subjected to flash vacuum pyrolysis using the general reaction procedure described. In each case the crude product was examined by ^{1}H NMR spectroscopy and found to be a 70:30 mixture of **31** and **32**.

4-Butyl-3-(hydroxymethyl)-1-methyl-6-phenyl-1,4-diazabicyclo[4.3.0]nonane (13). A solution of 150 mg (0.418 mmol) of lactam **12** in 5 mL of ether was cooled to −78 °C and 1.67 mL (2.51 mmol) of a 1.5 M solution of DIBAL in toluene was added over 2 min. The reaction mixture was stirred for 10 min at −78 °C, warmed to rt, and stirred for 60 min. The reaction was quenched by addition of 1.0 mL of H_2O and the resulting mixture was poured into a 1:1 mixture of Rochelle's salt and 15% aqueous NaOH (20 mL) and extracted with EtOAc (2 × 35 mL). The organic layers were combined, dried over K_2CO_3, and concentrated. Purification of the residue by silica gel column chromatography using hexane–acetone 1:2 with 4% Et_3N as eluent afforded 110 mg (78%) of amine **13** as a clear, colorless oil. Bp: 145 °C at 0.05 Torr. ^{1}H NMR (500 MHz): δ 0.92 (t, 3, J = 7.2), 1.24–1.51 (m, 6), 2.06 (m, 1), 2.14 (m, 2), 2.17 (s, 3), 2.38 (q, 1, J = 8.0), 2.57

(m, 1), 2.70 (m, 2), 3.10 (t, 1, J = 9.7), 3.32 (m, 1), 3.37 (m, 1), 3.57 (m, 1), 3.63 (m, 1), 4.16 (s, br, 1), 7.26 (m, 5). ^{13}C NMR (125 MHz): δ 14.10, 20.51, 23.74, 32.19, 42.21, 44.06, 46.38, 48.45, 52.97, 54.17, 57.25, 64.74, 66.10, 68.40, 126.20, 128.09, 128.63, 139.92. R_f = 0.29 (hexane–acetone 2:1, 4% Et_3N). Anal. Calcd for $C_{19}H_{30}H_{30}N_2O$: C, 75.45; H, 10.00; N, 9.26. Found: C, 75.31; H, 9.89; N, 9.30.

***N*-Benzyl-4-pentenamide.** A solution of 1.50 g (15.0 mmol) of 4-pentenoic acid in 30 mL of CH_2Cl_2 was treated with 1.77 g (16.5 mmol) of benzylamine and 4.34 g (16.5 mmol) of 2-(chloromethyl)pyridinium iodide. The resulting solution was cooled to 0 °C, 2.87 mL (16.5 mmol) of diisopropylethylamine (Hünig's Base) was added, and the resulting mixture was warmed to rt and stirred for 46 h. The reaction mixture was poured into $NaHCO_3$ (150 mL) and extracted with ether (2 × 150 mL). The organic layers were combined, dried over K_2CO_3, and concentrated. Purification by silica gel column chromatography using hexane–EtOAc 2:1 as eluent afforded 1.789 g (57%) of the amide as a white solid. Mp: 37–39 °C. ^{1}H NMR (400 MHz): δ 2.29 (m, 2), 2.39 (m, 2), 4.40 (d, 2, J = 5.8), 5.03 (m, 2), 5.81 (ddt, 1, J = 6.5, 10.3, 17.0), 5.98 (s, br, 1), 7.29 (m, 5). ^{13}C NMR (100 MHz): δ 29.61, 35.80, 43.56, 115.61, 127.46, 127.79, 128.66, 137.02, 138.33, 172.15. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.96; H, 7.96; N, 7.25.

***N*-Benzyl-4-pentenylamine.** A solution of 1.00 g (5.28 mmol) of *N*-benzyl-4-pentenamide in 15 mL of THF was cooled to −78 °C, and 16.7 mL (21.1 mmol) of 1.3 M DIBAL in toluene was added dropwise. The resulting solution was warmed to rt and stirred 1 h and then was heated to 50 °C for 90 min. The reaction mixture was cooled to rt and quenched with 5 mL of H_2O, poured into 200 mL of 15% NaOH-Rochelle's salt (1:1), and extracted with ether (2 × 200 mL). The organic layers were combined, dried over K_2CO_3, and concentrated. Purification by Kügelrohr distillation afforded 848 mg (92%) of *N*-benzyl-4-pentenylamine as a clear, colorless oil. Bp: 150 °C at 3.0 Torr. ^{1}H NMR (400 MHz): δ 1.33 (s, br, 1), 1.62 (m, 2), 2.10 (m, 2), 2.65 (t, 2, J = 7.3), 3.79 (s, 2), 4.95 (ddt, 1, J = 1.3, 1.9, 10.2), 5.03 (ddt, 1, J = 1.6, 1.9, 17.1), 5.82 (ddt, 1, J = 6.7, 10.2, 16.9), 7.32 (m, 5). ^{13}C NMR (100 MHz): δ 29.31, 31.58, 48.95, 54.08, 114.63, 126.89, 128.11, 128.40, 138.54, 140.58. R_f = 0.15 (hexane–EtOAc 1:1). Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.68; H, 9.80; N, 7.71.

***N*-Benzyl-5-hexenylamine.** A solution of 44 mg (0.44 mmol) of 5-hexenylamine,[29] 55 mg (0.44 mmol) of benzaldehyde, and 31 mg (0.22 mmol) of K_2CO_3 in 10 mL of benzene containing crushed 4-Å molecular sieves was stirred overnight at rt. The solution was filtered through a plug of Celite using CH_2Cl_2 as eluent, and the filtrate was concentrated in vacuo. The clear, colorless residue was dissolved in absolute ethanol and cooled to 0 °C, and 27 mg (0.736 mmol) of $NaBH_4$ was added all at once. The resulting solution was stirred at rt for 90 min and then was poured into H_2O (20 mL) and extracted with ether (2 × 20 mL). The organic layers were combined, dried over K_2CO_3, and concentrated. Purification by Kügelrohr distillation afforded 60 mg (75%) of *N*-benzyl-5-hexenylamine. Bp: 135 °C at 10 Torr. ^{1}H NMR (400 MHz): δ 1.32 (s, br, 1), 1.43 (m, 2), 1.54 (m, 2), 2.06 (m, 2), 2.63 (t, 2, J = 7.0), 3.79 (s, 2), 4.98 (m, 2), 5.80 (m, 1), 7.32 (m, 5). ^{13}C NMR (100 MHz): δ 26.66, 29.63, 33.68, 49.33, 54.12, 114.49, 126.87, 128.11, 128.39, 138.82, 140.60.

***N*-Benzyl-3-propynylamine.** A solution of 803 mg (14.58 mmol) of propargylamine, 1.55 g (14.58 mmol) of benzaldehyde, and 1.01 g (7.29 mmol) of K_2CO_3 in 40 mL of benzene containing 4-Å molecular sieves was stirred overnight at rt. The solution was filtered through a plug of Celite using CH_2Cl_2 as eluent, and the filtrate was concentrated in vacuo. The clear, colorless residue was dissolved in 100 mL of absolute ethanol and cooled to 0 °C, and 1.1 g (29.00 mmol) of $NaBH_4$ was added all at once. The resulting solution was stirred at rt for 4 h and then was poured into brine (100 mL) and extracted with EtOAc (2 × 150 mL). The organic layers were combined, dried over K_2CO_3, and concentrated. Purification by silica gel column chromatography using hexane–EtOAc 2:1 as eluent afforded 727 mg (34%) of *N*-benzyl-3-propynylamine as a light golden oil. Bp: 150 °C at 15 Torr. ^{1}H NMR (400 MHz): δ 1.59 (s, br, 1), 2.25 (t, 1, J = 2.5), 3.41 (d, 2, J = 2.5), 3.87 (s, 2), 7.33 (m, 5). ^{13}C NMR (100 MHz): δ 37.33, 52.27, 71.56, 82.07, 126.93, 127.17, 128.42, 128.45, 128.51, 139.38.

1-(*p*-Methoxybenzyl)-4-butyl-3-(ethoxycarbonyl)-8-oxo-1,4-diazatricyclo[3.2.4.0^{3,11}.0^{6,11}]dodec-9-en-2-one (27). A solution of 50 mg (0.11 mmol) of diene **25** in 2 mL of THF was treated with 1 mL of 0.5 M H_2SO_4, and the resulting solution was stirred for 1 h at rt. The reaction mixture was then poured into $NaHCO_3$ (20 mL) and extracted with ether (2 × 30 mL). The organic layers were combined, dried over K_2CO_3, and concentrated. Purification by gradient silica gel column chromatography using hexane–EtOAc 2:1 and 1:1 (20 fractions each) as eluents afforded 40 mg (83%) of enone **27** as a clear, colorless oil. ^{1}H NMR (400 MHz): δ 0.91 (t, 3, J = 7.2), 1.25 (t, 3, J = 7.2), 1.31–1.67 (m, 4), 2.43 (dd, 1, J = 5.9, 16.2), 2.52 (m, 1), 2.68 (m, 1), 2.89 (m, 3), 3.07 (m, 1), 3.13 (d, 1, J = 10.6), 3.21 (d, 1, J = 10.6), 3.80 (s, 3), 4.20 (m, 2), 4.46 (s, 2), 5.95 (d, 1, J = 10.2), 6.46 (d, 1, J = 10.2), 6.86 (d, 2, J = 8.7), 7.19 (d, 2, J = 8.7). ^{13}C NMR (100 MHz): δ 14.09, 14.26, 20.17, 31.16, 39.16, 43.59, 46.17, 48.97, 50.61, 54.57, 55.31, 55.97, 61.68, 80.60, 114.24, 127.74, 129.31, 129.52, 147.10, 159.34, 168.66, 169.83, 198.18. R_f = 0.10 (hexane–EtOAc 2:1). Anal. Calcd for $C_{25}H_{32}N_2O_5$: C, 68.16; H, 7.32; N, 6.36. Found: C, 67.71; H, 7.29; N, 6.24.

Tetracyclic Lactam 28. A solution of 60 mg (0.132 mmol) of diene **25** in 2 mL of ether was cooled to −78 °C and treated with 220 mL (0.290 mmol) of a 1.3 M solution of DIBAL in toluene. The resulting solution was stirred for 1 h at −78 °C and then was allowed to slowly warm to −10 °C over 45 min and quenched by addition of 0.5 mL of pH 7 buffer–MeOH (1:1). The reaction mixture was poured into 20 mL of a 1:1 mixture of saturated aqueous Rochelle's salt and 1 M NaOH and extracted with EtOAc (2 × 30 mL). The organic layers were combined, dried over K_2CO_3, and concentrated. The crude material was dissolved in 2 mL of absolute ethanol and was added to a solution of 62 mg (1.65 mmol) of $NaBH_4$ in 2 mL of absolute ethanol at 0 °C. The resulting solution was stirred for 5 min at 0 °C and then warmed to rt and stirred for 30 min. The reaction was quenched by adding 1 mL of H_2O, poured into brine (30 mL), and extracted with EtOAc (3 × 30 mL). The organic layers were combined, dried over K_2CO_3, and concentrated. The resulting crude material was then dissolved in 2 mL of THF and treated with 1 mL of 10% H_2SO_4. The reaction mixture was stirred for 30 min at rt and the poured into $NaHCO_3$ (20 mL) and extracted with EtOAc (2 × 20 mL). The organic layers were combined, dried over K_2CO_3, and concentrated. Purification by silica gel column chromatography using hexane–EtOAc 1:1 as eluent afforded 26 mg (50%) of lactam **28** as a clear, colorless oil which later solidified. Mp: 80–82 °C. ^{1}H NMR (400 MHz): δ 0.91 (t, 3, J = 7.2), 1.24–1.49 (m, 4), 2.17 (dt, 1, J = 4.8, 12.7), 2.32 (m, 2), 2.63 (m, 2), 2.74 (dd, 1, J = 3.0, 18.5), 2.82 (d, 1, J = 9.5), 2.99 (m, 2), 3.15 (dt, 1, J = 7.8, 12.7), 3.23 (d, 1, J = 10.6), 3.65 (d, 1, J = 9.7), 3.79 (s, 3), 3.88 (t, 1, J = 2.8), 4.08 (d, 1, J = 9.7), 4.36 (d, 1, J = 14.5), 4.44 (d, 1, J = 14.5), 6.85 (d, 2, J = 8.7), 7.14 (d, 2, J = 8.7). ^{13}C NMR (100 MHz): δ 14.02, 20.27, 31.28, 39.34, 41.32, 41.41, 45.94, 48.72, 54.07, 55.24, 56.58, 57.11, 76.21, 82.77, 82.93, 114.28, 127.97, 129.37, 159.28, 170.95, 209.35. R_f = 0.15 (hexane–EtOAc 1:1). Anal. Calcd for $C_{23}H_{30}N_2O_4$: C, 69.31; H, 7.59; N, 7.03. Found: C, 69.17; H, 7.59; N, 6.96.

General Procedure for the Synthesis of Secondary Arylamines by Reductive Amination. A 0.10 M solution of 1.0 equiv of the appropriate benzylamine, 1.0 equiv of the requisite aromatic aldehyde, and 0.50 equiv of K_2CO_3 in benzene containing crushed 4-Å molecular sieves was stirred overnight at rt. The solution was filtered through a plug of Celite using CH_2Cl_2 as eluent, and the filtrate was concentrated in vacuo. The clear, colorless residue was dissolved in absolute ethanol to form a solution of ca. 0.10 M and cooled to 0 °C, and 2.0 equiv of $NaBH_4$ was added all at once. The resulting solution was stirred at rt for 90 min, then was poured into H_2O (30 mL) and extracted with ether (2 × 30 mL). The organic layers were combined, dried over K_2CO_3, and concentrated. Purification of the amines was achieved by Kügelrohr distillation or column chromatography as described below.

Bis(*p*-methoxybenzyl)amine. Purification by Kügelrohr distillation afforded 845 mg (90%) of bis(*p*-methoxybenzyl)amine

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as a white solid. ^{1}H NMR (500 MHz): δ 1.55 (s, br, 1), 3.71 (s, 4), 3.80 (s, 6), 6.84 (d, 4, J = 8.7), 7.22 (d, 2, J = 8.7).

Benzyl-*p*-methoxybenzylamine. Purification by Kügelrohr distillation afforded 612 mg (74%) of benzyl-*p*-methoxybenzylamine as a clear, colorless oil. Bp: 130 °C at 0.20 Torr. ^{1}H NMR (250 MHz): δ 1.47 (s, br, 1), 3.75 (s, 2), 3.83 (s, 5), 6.85 (d, 2), 7.20–7.50 (m, 7).

Bis(*p*-cyanobenzyl)amine. Purification by silica gel column chromatography using hexane–EtOAc 1:1 as eluent afforded 250 mg (50%) of bis(*p*-cyanobenzyl)amine as a light yellow solid. Mp: 99–100 °C. ^{1}H NMR (400 MHz): δ 1.70 (s, br, 1), 3.86 (s, 4), 7.46 (d, 4, J = 8.3), 7.61 (d, 4, J = 8.3). ^{13}C NMR (100 MHz): δ 52.69, 110.99, 118.87, 128.62, 132.30, 145.50.

Bis[*p*-(trifluoromethyl)benzyl]amine. Purification by silica gel column chromatography using hexane–EtOAc 5:1 as eluent afforded 92 mg (48%) of bis[*p*-(trifluoromethyl)benzyl]amine as a clear, colorless oil. Bp: 120 °C at 0.10 Torr. ^{1}H NMR (400 MHz): δ 1.66 (s, br, 1), 3.87 (s, 4), 7.47 (d, 4, J = 8.0), 7.59 (d, 4, J = 8.0). ^{13}C NMR (100 MHz): δ 52.65, 123.41, 125.36, 125.40, 125.44, 128.32, 144.19. R_f = 0.50 (hexane–EtOAc 3:1).

Benzyl-*p*-(trifluoromethyl)benzylamine. Purification by silica gel chromatography using hexane–EtOAc 4:1 as eluent afforded 866 mg (81%) of benzyl-*p*-(trifluoromethyl)benzylamine as a clear, colorless oil. ^{1}H NMR (400 MHz): δ 1.7 (s, br, 1), 3.8 (s, 2), 3.9 (s, 2), 7.3–7.7 (m, 9).

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Supplementary Material Available: Complete listings of infrared spectra for most of the compounds reported in this paper, and ^{1}H NMR spectra of compounds **8**, **10** (and its trans isomer), **23**, **25**, **31**, **32**, benzyl-5-pentenylamine, benzyl-2-propynylamine, bis(*p*-methoxybenzyl)amine, benzyl-*p*-methoxybenzylamine, and benzyl-*p*-(trifluoromethyl)benzylamine (16 pages). This material is contained in many 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.

Syntheses and Ion Selectivity of All Conformational Isomers of Tetrakis((ethoxycarbonyl)methoxy)calix[4]arene

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We have found that the conformer distribution in tetra-O-alkylation of 5,11,17,23-tetra-*tert*-butylcalix[4]-arene-25,26,27,28-tetrol by ethyl bromoacetate is remarkably affected by the metal cation present in the base. In general, the cone conformer predominantly results when the base contains template metal cations whereas the partial-cone and 1,3-alternate conformers result when the base contains nontemplate metal cations. In acetone solvent one can realize the change from the 100% cone selectivity to the 100% partial-cone selectivity. By combining the metal template effect with a protection–deprotection method with a benzyl group, we developed synthetic routes to all of the four conformers. Two-phase solvent extraction established that the cone conformer shows Na^+ selectivity whereas the remaining three conformers show K^+ selectivity. ^{1}H NMR studies established that the 1,3-alternate conformer can form both a 1:1 and a 2:1 metal/calixarene complex and the two metal-binding sites display negative allostericity. This paper thus demonstrates that the metal selectivity of ionophoric calix[*n*]aryl esters can be changed not only by the change in the ring size but also by the conformational change.

Introduction

Calixarenes have been used as a useful basic skeleton for the synthesis of lipophilic,[1-3] water-soluble,[4-6] and ionophoric receptors.[7-12] For the molecular design of these functionalized calixarenes, modification of OH groups arranged on the lower rim is most convenient.[13,14] In particular, much attention is being devoted toward the molecular design of calix[4]arene-based ionophores because of their high ion affinity and high ion selectivity; for example, 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis-((ethoxycarbonyl)methoxy)calix[4]arene with a cone conformation (cone-**2a**), readily prepared by the reaction of 5,11,17,23-tetra-*tert*-butylcalix[4]arene-25,26,27,28-tetrol (**1a**) and ethyl bromoacetate in the presence of NaH, shows high Na^+ affinity and high Na^+ selectivity which are comparable with those of cryptand 222.[7-11] Recently, we found that tetra-O-alkylation of **1a** with alkyl bromide (e.g., *n*-PrBr) yields a mixture of conformational isomers, and the conformer distribution is profoundly affected by alkali or alkaline earth metal ions present in the base.[15-17] We

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