3-Methyl-1-phenyl-3(*Z*)-nonene (11f) was prepared as a 9/91 mixture of *E*/*Z* isomers: IR (film) 2930, 1450, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18–7.33 (m, 5 H), 5.18 (t, 1 H, J = 6.8 Hz), 2.67–2.74 (m, 2 H), 2.28–2.37 (m, 2 H), 1.98–2.03 (m, 2 H), 1.89–1.98 (m, 1.8 H), 1.76 (s, 2.7 H), 1.66 (s, 0.3 H), 1.23–1.40 (m, 6 H), 0.88–0.96 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 134.1, 128.4, 128.3, 128.2, 126.3, 125.7, 34.5, 34.0, 31.6, 29.6, 27.8, 23.5, 22.6, 14.1; mass spectrum (EI), m/z 216 ($M^{+\cdot}$), 104, 91, 69, 55; exact mass calcd for $C_{16}H_{24}$ 216.1879, found 216.1880.

1-[(*tert*-Butyldiphenylsilyl)oxy]-6-methyl-6(*E*)-dodecene (11g) was prepared as a 93/7 mixture of *E*/*Z* isomers: IR (film) 2940, 1430, 1110, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.71 (m, 4 H), 7.33–7.43 (m, 6 H), 5.10 (t, 1 H, J = 6.4 Hz), 3.65 (t, 2 H, J = 6.4 Hz), 1.90–1.99 (m, 2 H), 1.65 (s, 0.21 H), 1.55 (s, 2.79 H), 1.19–1.40 (m, 14 H), 1.05 (s, 9 H), 0.88 (t, 3 H, J = 7 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6, 134.9, 134.2, 129.5, 127.5, 124.7, 64.0, 39.7, 32.5, 32.3, 31.6, 29.6, 28.0, 27.9, 27.7, 26.9, 25.4, 22.6, 19.2, 15.9, 14.12, 14.10; mass spectrum (EI), m/z 436 ($M^{+\cdot}$), 379, 335, 269, 199. Anal. Calcd for $C_{29}H_{44}OSi$: C, 79.75; H, 10.16. Found: C, 79.98; H, 10.32.

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Applications of Intramolecular Diels–Alder Reactions to Alkaloid Synthesis. A Formal Total Synthesis of (±)-Dendrobine

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A facile synthesis of the tricyclic enone **3** was completed; since **3** was an intermediate in a previous synthesis of (±)-dendrobine (**1**), this achievement constitutes a formal total synthesis of the racemic title alkaloid. The key strategic element of the approach involved the intramolecular Diels–Alder reaction of the olefinic dienamide **10g**, which was prepared by N-acylation of imine **9g** with acid chloride **8**, to furnish the tricyclic cycloadduct **11g** as the major product. Subsequent elaboration of **11g** into **3** was then consummated by epoxidation, followed by epoxide rearrangement and oxidation of the intermediate allylic alcohol **23**. The synthetic investigations were preceded by a series of model studies that were executed in order to assess the viability and to probe the scope and limitations of the crucial intramolecular [4 + 2] cycloaddition. In these preliminary investigations, we discovered that thermolyses of dienamido olefins **10a–f** afforded mixtures (3.5–14:1) of epimeric cycloadducts **11a–f** and **12a–f**. The steric bulk of the *N*-alkyl substituent on **10a–d** exerted considerable influence upon the energy of activation and the stereochemical course of the respective cycloaddition reactions. A cyclopropyl or isopropyl group positioned at C(8) on the diene moiety of the unsaturated dienamides **10e–g** also facilitated the cyclization and enhanced the endo selectivity of the process.

Introduction

The ornamental orchid "Jinchai Shihu" (*Dendrobium nobile* Lindl.) has been employed in traditional herbal medicine in China as a tonic for the promotion of general health.[2] Although a number of structurally related sesquiterpene alkaloids have been isolated from this plant,[3] the archtypical member of this class and the major alkaloidal constituent is dendrobine (**1**),[4] which itself exhibits antipyretic, hypotensive, and convulsant activity.[5,6] Dendrobine is structurally related to the novel sesquiterpene bislactone picrotoxinin (**2**),[6,7] a potent convulsant and GABA antagonist.[8] Inasmuch as **1** incorporates a total of seven stereogenic centers distributed among a mere 17 skeletal atoms compactly arranged in four rings, it may be argued that dendrobine ranks as one of the most complex molecules of its size. Given its intricate architecture coupled with its biological activity, it is not surprising that dendrobine and its analogues have been subject to a number of biosynthetic[9] and synthetic[10–18] investigations.

(1) Permanent address: Department of Chemistry, Nankai University, Tianjin, People's Republic of China.

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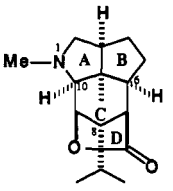
Table I. Cycloadditions of Some Olefinic Dienamides 10

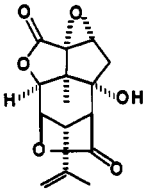
entry	R^1	R^2	temp, °C	time, h	11/12 (% yield)	% 13
a	Me	H	260	10	3.5:1 (15)	51
b	$PhCH_2$	H	240	8	5:1 (65)	7
c	Ph(Me)CH	H	220	4	6:1 (68)	5
d	Ph_2CH	H	170	4	9:1 (70)	a
e	Ph_2CH	c-C_3H_5	155–185	2–16	14–11:1 (84)	a
f	Ph_2CH	i-C_3H_7	165	4	10:1 (57)	a
g	Me	i-C_3H_7	180	10	8:1 (55)	a

[a] Not detected.

The synthetic efforts have culminated in five successful total syntheses of 1[10-14] together with the preparation of the C(8)-epimer of dendrobine.[15] These significant advances not withstanding, we were nevertheless intrigued by the challenge of designing a more concise, stereoselective entry to dendrobine (1).



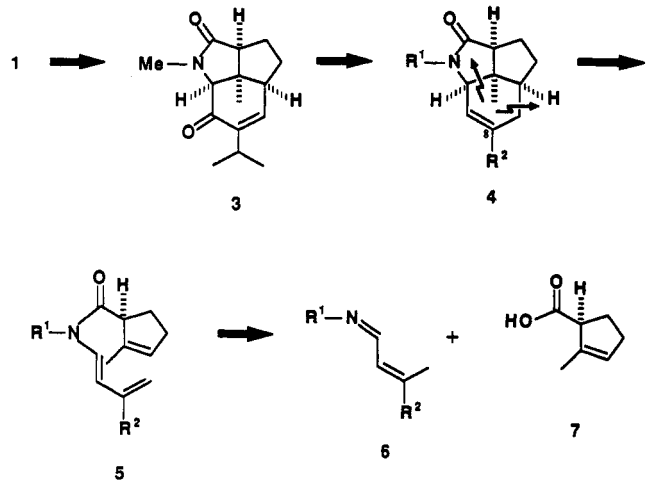
1



2

As part of a program directed toward the invention and development of general strategies for alkaloid synthesis, we have exploited intramolecular Diels–Alder reactions[19] to effect the rapid assemblage of substituted, fused nitrogen heterocycles that constitute principal structural subunits of different classes of alkaloid natural products. These endeavors have culminated in the formulation of efficient routes to a variety of naturally occurring bases.[20] Although the potential of intramolecular [4 + 2] cycloadditions as a key step to fabricate the hydrindane skeletal subunit present in dendrobine (1) has been recognized,[13,15] we were attracted by the prospect of assembling the complete ABC ring system of 1 in a single step by such a process. This strategem offered a potential means of circumventing some of the manipulations and refunctionalizations that were inherent in those previous approaches to 1 that commenced with construction of the *cis*-hydrindan BC ring subunit followed by formation of the A ring. From the retrosynthetic perspective, a variety of two-bond disconnections may be applied to the dendrobine ABC ring substructure, but we were particularly intrigued by the possibility of exploiting the intramolecular Diels–Alder reaction of olefinic dienamides[21,22] as represented by 5 to give the corresponding cycloadducts 4 (Scheme I). Depending upon the precise structure of 4, suitable plans for its elaboration into 1 via the intermediate tricyclic enone 3, which was a key intermediate in Inubushi's[10] total synthesis of dendrobine (1), could be envisioned. The convergency of the approach could be enhanced by maximal incorporation of substitution and functionality prior to the cycloaddition step. We now report those details of our studies in this arena that ultimately led to a concise route to 3 and hence a formal total synthesis of 1.

Scheme I



Results and Discussion

Model Studies and the First Generation Approach. Although the intramolecular [4 + 2] cycloadditions of dienamides had been previously established, there were no examples of cyclizations of dienamides with unactivated, trisubstituted dienophiles of type 5 to give hydroindoles. Consequently, we embarked upon preliminary model studies to assess the feasibility of the pivotal intramolecular Diels–Alder reaction for the construction of the ABC ring subunit present in 1. Toward this end, crotonaldehyde was condensed with a series of primary amines to furnish the intermediate imines **9a–d**. The

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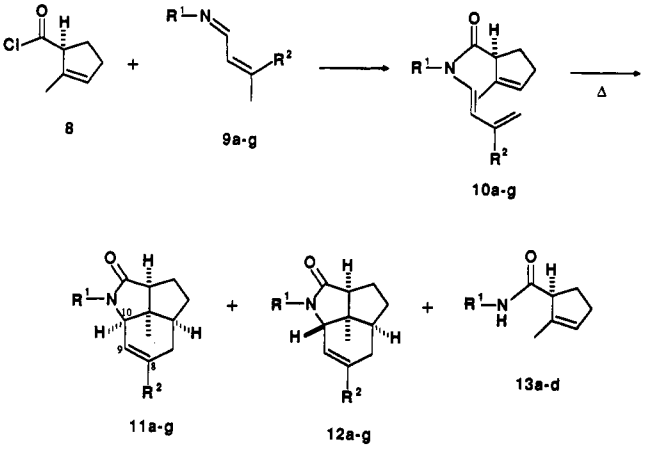
imines **9a–d** thus generated in situ underwent N-acylation[23] with the acid chloride **8**, which was prepared in two steps from methyl 2-methyl-2-cyclopentene-1-carboxylate,[24] to deliver the olefinic dienamides **10a–d**. The thermolyses of **10a–d** were then conducted under a variety of experimental conditions, the best of which are summarized in Table I.[25] Since it was determined by independent experiments that the cycloadducts obtained from these reactions did not interconvert under the conditions of the cyclization, these intramolecular [4 + 2] cycloadditions appear to be kinetically controlled.

The structures of the major cycloadducts **11c** and **11d** were unequivocally established by single-crystal X-ray analysis.[26] The structures of the remaining cycloadducts were then assigned by making comparisons of chemical shifts and coupling patterns for the protons at C(8), C(9) and C(10) (dendrobine numbering) in the ^{1}H NMR spectra. Since the trends in chemical shifts and couplings of the diagnostic protons in **11d** and **12d** are representative of the other cycloadducts, several comments are appropriate. The proton at C(9) (δ 5.52 ppm) is further upfield than the vicinal vinyl proton at C(8) (δ 5.69 ppm) in the α-isomer **11d**, whereas the relative chemical shifts for these two protons in the β-epimer **12d** are reversed (i.e., H-9, δ 5.84 ppm; H-8, δ 5.50 ppm). The protons at C(9) and C(10) appear at higher field in the α-epimer **11d** than the corresponding protons in the β-epimer **12a**, whereas the reverse order obtains for the C(8) proton. Furthermore, the vicinal coupling constant between the proton at C(10) and the olefinic proton at C(9) in **11d** was 5.0 Hz, whereas the corresponding coupling constant in **12d** was 3.0 Hz. Finally, the allylic coupling between the proton at C(10) and C(8) was clearly discernible (J = 2.0 Hz) in the major isomer **11d**, while a smaller allylic coupling between these protons in the minor isomer **12d** resulted merely in broadening the signal for the proton at C(10).

Examination of these results reveals that the size of the alkyl substituent attached to the nitrogen atom linking the dienophile and diene exerts a substantial effect on both the energy of activation and the stereoselectivity of the intramolecular [4 + 2] cycloaddition.[27] As evidenced qualitatively by the required reaction temperatures and times, increasing the steric bulk of the N-alkyl substituent R^1 in **10a–d** resulted in a decrease in the energy of activation for the cyclization. A modest increase in the stereoselectivity of the reaction favoring production of the endo cycloadducts **11a–d** was also observed. This enhanced stereoselectivity might result from the lower reaction temperatures. However, other factors may be involved, since Gschwend observed a similar correlation between E_{act} and the size of an N-alkyl group in a related series of intramolecular Diels–Alder reactions,[27a] but the stereoselectivity in those processes did not vary significantly with size of the N-alkyl substituent. At higher reaction temperatures, fragmentation of the trienes **10a–d** ensued as a major side reaction to give the secondary amides **13a–d**;[21b,c] this elimination reaction reached major proportions in the case of **10a**. This latter observation served notice that efficient access to the fused hydroindoles **4** that lacked the isopropyl substituent at C(8) would require the use of bulky N-alkyl groups in the cyclization step.

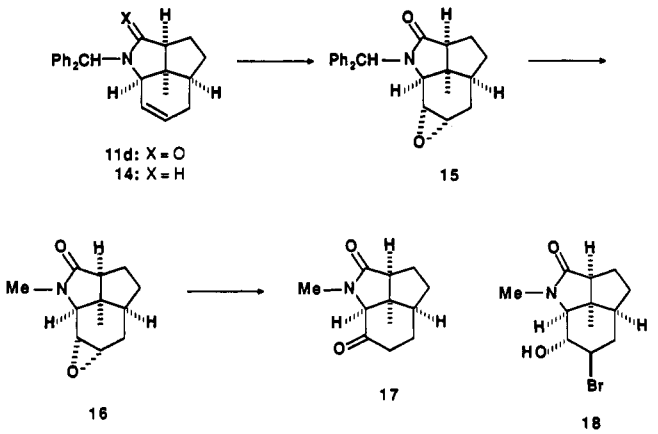
We had thus established the basic viability of intramolecular [4 + 2] cycloadditions of olefinic dienamides to construct the ABC ring subunit of dendrobine (**1**). It now remained to address the varied tasks associated with completing the preparation of **3**. Since the cyclization of **10d** proceeded with a reasonable degree of efficiency and stereoselectivity, the elaboration of **11d** into the tricyclic intermediate **3** emerged as an attractive option. Our initial efforts were directed toward removal of the N-benzhydryl protecting group from **11d** under conditions that would

Scheme II



Series a: R^1 = Me; R^2 = H
b: R^1 = PhCH$_2$; R^2 = H
c: R^1 = Ph(Me)CH; R^2 = H
d: R^1 = Ph$_2$CH; R^2 = H
e: R^1 = Ph$_2$CH; R^2 = c-C$_3$H$_5$
f: R^1 = Ph$_2$CH; R^2 = i-C$_3$H$_7$
g: R^1 = Me; R^2 = i-C$_3$H$_7$

Scheme III



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(24) Methyl 2-methyl-2-cyclopentene-1-carboxylate was prepared in 81% yield by thermal rearrangement of methyl 3-cyclopropylcrotonate at 585 °C in a flow apparatus. We thank Professor Clayton H. Heathcock (University of California, Berkeley) for providing experimental details for effecting this rearrangement. See also: Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1982**, *104*, 7181.

(25) It is interesting to note that when an NMR sample of **10d** was stored at room temperature for a period of approximately six months, a mixture (ca. 25:1) of the cycloadducts **11d** and **12d** was obtained, but the conversion was only about 60%.

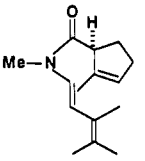
(26) For some of the details of the X-ray analyses of **11c** and **11d**, see: (a) Lynch, V. M.; Li, W.; Martin, S. F. *Acta Crystallogr.* **1988**, *C44*, 187. (b) Lynch, V. M.; Li, W.; Martin, S. F.; Davis, B. E. *Acta Crystallogr.* **1990**, *C46*, 1155. See the supplementary material for complete data from single-crystal X-ray analyses of **11c,d**, **18**, and **23**.

(27) For other examples of the effect of substitution on a nitrogen in the chain linking the diene and dienophile, see: (a) Gschwend, H. W.; Lee, A. O. *J. Org. Chem.* **1973**, *38*, 2169. (b) Guy, A.; Lemaire, M.; Negre, M.; Guette, J. P. *Tetrahedron Lett.* **1985**, *26*, 3575. (c) Parker, K. A.; Adamchuk, M. R. *Ibid.* **1978**, 1689. For related examples of steric effects in all-carbon systems, see: (d) DeClecq, L. A.; Van Royen, L. A.; Mijngheer, R. *Ibid.* **1983**, *24*, 3145. (e) Boeckman, K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033. (f) Sternbach, D. D.; Rossana, D. M.; Onan, K. D. *Tetrahedron Lett.* **1985**, *26*, 591. (g) Jung, M. E.; Gervay, J. *Ibid.* **1988**, *29*, 2429; *J. Am. Chem. Soc.* **1989**, *111*, 5469.

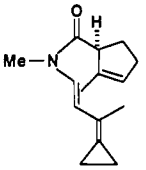
retain the $\Delta^{8,9}$-double bond. While **11d** could be converted into **14** in 95% yield by hydride reduction, all attempts to cleave the *N*-benzhydryl group using alkyl chloroformates[28] were unsuccessful; only starting material was recovered. We then elected to manipulate the C-ring functionality prior to exchanging the *N*-alkyl residue. Implementation of this revised plan commenced with stereoselective epoxidation of **11d** with MCPBA to afford **15** in 95% yield. Although the structural assignment of **15** was initially predicated upon the reasonable premise that the oxygen atom should be delivered to the double bond from the less hindered convex face, this assumption was later unambiguously verified by chemical correlation with **18** (vide infra). Unfortunately, the epoxide moiety in **15** proved resistant to nucleophilic opening at C(8) by isopropyl or isopropenyl magnesium bromide, even in the presence of copper(I) iodide.[29] Similarly, **15** was stable to the action of strong bases such as lithium diethylamide and did not undergo the desired rearrangement to an allylic alcohol.[30] Several preliminary experiments to induce the acid-catalyzed rearrangement (e.g., $MgBr_2 \cdot Et_2O$ and $BF_3 \cdot Et_2O$)[31] of the epoxide function of **15** into a carbonyl group were also unsuccessful.

In some of the preceding experiments, it seemed likely that the *N*-benzhydryl group was interfering with efforts to refunctionalize the epoxide moiety in **15**, and attention was focused on replacing the benzhydryl group with methyl. After some experimentation, we discovered that the *N*-benzhydryl group could be removed directly from the amide **15** by hydrogenolysis (750 psi, 56 °C) in glacial acetic acid using Pearlman's catalyst.[32] N-Methylation of the newly formed secondary amide using *t*-BuOK in glyme gave **16** in 84% overall yield. Treatment of **16** with $MgBr_2 \cdot Et_2O$ did not result in the expected epoxide/carbonyl rearrangement, but rather the bromohydrin **18**, whose structure was established by X-ray analysis, was obtained in 90% yield as the only product. On the other hand, treatment of **16** with either zinc or magnesium triflate[33] delivered the desired ketone **17**. The structure of **17** was assigned based upon its ^1H NMR spectrum, which revealed the disappearance of the signals for the oxirane protons, and a new singlet emerged at 3.46 ppm corresponding to the proton at C(10). The ^{13}C NMR spectrum of **17** displayed the presence of two carbonyl peaks at 210.0 and 177.8 ppm, respectively.

Second Generation Approach. Formal Synthesis of Dendrobine (1). One may envisage a series of manipulations for converting either **17** or **18** into enone **3**, but an excessive number of steps would be required to implement any such plan. In the interest of devising more concise entries to the target alkaloid and its precursors, it occurred to us that incorporation of additional functionality and/or alkyl substituents onto the olefinic dienamide of type **5** might enhance the convergency of the approach and allow more ready access to **3**. Since dendrobine possesses an isopropyl group at C(8), incorporation of an isopropyl group on the dienic partner as in **10g** had obvious appeal. However, we were initially concerned that deprotonation of the *N*-acyl iminium salt formed upon reaction of **9g** with **8** would deliver significant quantities of the isomeric dienamido olefin **19** in addition to the desired **10g**. In order to obviate such a deleterious side reaction, an alternative tactic was devised that entailed use of the cyclopropyl-substituted triene **10e** as the substrate for the intramolecular Diels–Alder reaction. The increased strain associated with formation of a double bond exocyclic to a cyclopropane[34] ring would mitigate strongly against formation of **20**, and there was sufficient precedent for the hydrogenolysis of cyclopropanes to give isopropyl groups.[35]

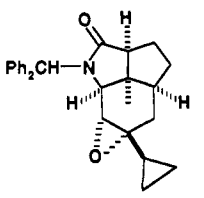


19



20

The requisite triene **10e** was prepared in 71% yield by *N*-acylation of the imine obtained by condensation of benzhydrylamine with 3-cyclopropylcrotonaldehyde.[36] Subsequent thermolysis of **10e** at temperatures ranging from 155 to 185 °C furnished separable mixtures (14–11:1, ca. 80% combined yield) of the two cycloadducts **11e** and **12e**, respectively (Scheme II). None of the undesired fragmentation product **13d** was detected in the reaction mixture. Unfortunately, despite the above noted precedent[35] and considerable experimentation with conditions and catalysts, we were unable to effect selective hydrogenolysis of the cyclopropane ring in **11e** to furnish **11f**. Scission, which was doubtless driven by olefin participation, of the more substituted bond of the cyclopropane ring in **11e** accompanied by double-bond migration and/or reduction was invariably observed to give three or more products as judged from ^1H NMR spectra of the crude reaction mixtures. Attempts to effect hydrogenolysis of the cyclopropane ring of the α-epoxide **21** were equally unavailing.



21

Since we were unable to effect the requisite opening of the cyclopropane ring on **11e** to reveal an isopropyl group, we were compelled to reconsider the option of incorporating the isopropyl substituent on the dienic array. Toward this end, the unsaturated dienamide **10f** was prepared in 71% yield by N-acylation of the imine obtained

(28) For a review of N-demethylations using alkyl chloroformates, see: Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1.

(29) (a) Huynh, C.; Derguini-Boumechal, F.; Listrumelle, G. *Tetrahedron Lett.* **1979**, 1503. (b) Tius, M. A.; Frauq, A. H. *J. Am. Chem. Soc.* **1986**, *108*, 1035.

(30) (a) Cope, A. C.; Martin, M. M.; McKervey, M. A. *Quart. Rev. (London)* **1966**, *20*, 119. (b) Kissel, C. R.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 2060. (c) Sheng, M. N. *Synthesis* **1972**, 194. (d) Gawley, R. E.; Termine, E. J.; Aube, J. *Tetrahedron Lett.* **1980**, *21*, 3115.

(31) House, H. O. *J. Am. Chem. Soc.* **1955**, *77*, 3070, 5083. (b) McCormick, J. P.; Barton, D. L. *J. Org. Chem.* **1980**, *45*, 2566. (c) Sacks, C. E.; Fuchs, P. L. *Synthesis* **1976**, 456.

(32) Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663.

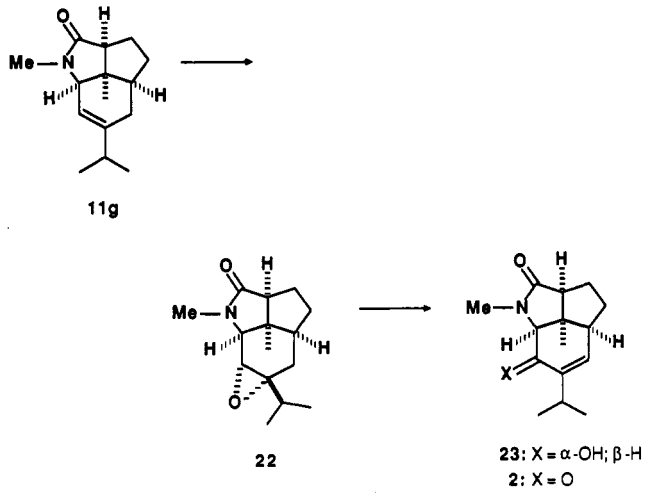
(33) Corey, E. G.; Shimoji, K. *Tetrahedron Lett.* **1983**, *24*, 169.

(34) The strain values of methylenecycopropane and cyclopropane are 41.7 and 28.1 kcal/mol, respectively. See: (a) Schleyer, P. v. R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem. Soc.* **1970**, *92*, 2377. (b) Benson, S. W.; Cruickshank, F. R.; Golden, D. M.; Haugen, G. R.; O'Neal, H. E.; Rodgers, A. S.; Shaw, R.; Walsh, R. *Chem. Rev.* **1969**, *69*, 279 and references cited therein.

(35) (a) Woodworth, C. W.; Buss, V.; Schleyer, P. v. R. *Chem. Commun.* **1968**, 569. (b) Oppolzer, W.; Godel, T. *J. Am. Chem. Soc.* **1978**, *100*, 2583. (c) Zutterman, F.; Krief, A. *J. Org. Chem.* **1983**, *48*, 1135. (d) Vite, G. D.; Spencer, T. A. *J. Org. Chem.* **1988**, *53*, 2560.

(36) Marino, J. P.; Browne, L. J. *J. Org. Chem.* **1976**, *41*, 3629.

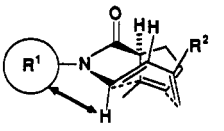
Scheme IV



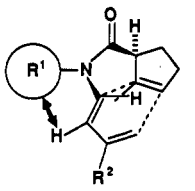
upon condensation of benzhydrylamine with 3-isopropylcrotonaldehyde;[37] none of the isomeric dienamide related to **19** was detected. Subsequent thermolysis of **10f** at 165 °C furnished a separable mixture (10:1) of cycloadducts **11f** and **12f**, respectively (Scheme II). While tactics related to those summarized in Scheme III might be applied to the task of transforming **11f** into **3**, we decided to explore an alternative route that proved more efficacious.

Inasmuch as a cyclopropyl and an isopropyl substituent at C(8) of the trienes **10e** and **10f** decreased the energy of activation for the corresponding intramolecular Diels–Alder reaction, we now seriously entertained the notion that the *N*-methyl dienamide **10g** might cyclize to **11g** without extensive fragmentation. In order to test this hypothesis, **10g** was prepared in 67% overall yield by reaction of **8** with the imine **9g**; once again there was no evidence for the formation of the more highly substituted unsaturated dienamide **19**. Thermolysis of **10g** at 180 °C proceeded cleanly to provide the cycloadducts **11g** and **12g** in a 8:1 ratio. Further elaboration of the major cycloadduct **11g** into the allylic alcohol **23** was accomplished in 76% overall yield by highly stereoselective epoxidation of the double bond followed by rearrangement of the intermediate epoxide using TMSOTf in the presence of 2,6-di-*tert*-butyl-4-methylpyridine[38] (Scheme IV). The structure of **23** was established by single-crystal, X-ray analysis.[26] Oxidation of **23** with pyridinium dichromate[39] then afforded enone **3**, which had spectral characteristics identical with those previously described.[40] Since **3** had been converted in seven steps into (±)-dendrobine (**1**),[10] the present preparation of **3**, which proceeds in 7% overall yield via a longest linear sequence requiring only nine steps from commercially available starting materials, constitutes a concise, formal total synthesis of **1**.

Some Comments on Cyclizations of Olefinic Dienamides 10a–g. The intramolecular Diels–Alder reactions of unsaturated dienamides **10a–g** exhibit some interesting trends in selectivity and reactivity according to the size of the *N*-alkyl group and the nature of the substituent at C(8) of the diene. It appears that the cyclizations of **10a–g** were subject to kinetic control, since the cycloadducts exhibited no tendency to interconvert under the reaction conditions. However, these thermolyses were *not* performed with the intention of providing precise quantitative data, and it is necessary to exercise caution in interpreting the results summarized in Table I. With this caveat in mind, the observed ratios of **11a–g** and **12a–g** correspond to approximate energy differences of 1.3–2.2 kcal/mol between the endo transition state **24**, which yielded **11a–g**, and the exo transition state **25**, which afforded **12a–g**. Inspection of molecular models provides some useful insights with respect to the nature of the interactions that influenced the course of these cyclizations.



24



25

The first tendency that became apparent was that the size of the *N*-alkyl substituent on the olefinic dienamides **10a–g** had a significant effect upon the diastereoselectivity and the rate of the cyclization. As the bulk of the *N*-alkyl group increases, the steric interactions between this residue and the diene moiety are clearly more pronounced in the exo transition state **25** than in the endo transition state **24**; the endo transition state is therefore favored. Larger *N*-alkyl groups also enhance the ground-state population of the cisoid conformational isomer, which is required for cyclization, about the amide N–CO bond. Moreover, bulkyl *N*-alkyl groups will cause buttressing that would presumably compress the dienophilic and dienic moieties more closely together in the ground state, thereby rendering $\Delta S^{\ddagger}$ less negative for the endo and exo transition states.[27a] Relief of steric strain emanating from this buttressing in both endo and exo transition states could contribute to lowering the $\Delta H^{\ddagger}$ for each. Whether the enthalpic or the entropic term was the dominant factor contributing to the lower energies of activation for cyclization of those substrates bearing larger *N*-alkyl substituents must be resolved by more quantitative experiments.

A second trend that is apparent from the cyclizations of **10a–g** is that placement of a branched alkyl residue such as isopropyl or cyclopropyl at C(8) of the dienic array influences the diastereoselectivity and rate of the corresponding intramolecular Diels–Alder reactions. For example, introduction of an isopropyl group onto the dienic moiety at C(8) of **10a** (e.g., **10g**) has approximately the same effect upon enhancing the diastereoselectivity and facilitating the rate of the cycloaddition as replacement of the *N*-methyl substituent of **10a** with a *N*-benzhydryl group (e.g., **10d**). Examination of molecular models of relevant transition states for the cyclizations of **10a** and **10g** reveals the existence of significant steric interactions between the alkyl substituent at C(8) on the diene and the methyl group on the dienophile of **10g** in the exo transition state **25** that are absent in the corresponding endo transition state **24**. This analysis suggests that there should be a greater difference between the relative energies of the exo and endo transition states for **10g** than for **10a**. The cyclization of **10g** should therefore be more endo selective than the cyclization of **10a** as was observed. The presence of a secondary alkyl residue at C(8) will also decrease the energetic differences between the s-cis and s-trans conformations of the diene subunit in the ground states of

(37) (a) Meyers, A. I.; Tomioka, K.; Fleming, M. P. *J. Org. Chem.* **1978**, *43*, 3788. (b) Corey, E. G.; Schmidt, G. *Tetrahedron Lett.* **1980**, *21*, 731.

(38) (a) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899. (b) Murata, S.; Suzuki, M.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 247.

(39) (a) Corey, E. G.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399. (b) Corey, E. G.; Schmidt, G. *Ibid.* **1980**, *21*, 731.

(40) We thank Dr. Takashi Harayama of the Faculty of Pharmaceutical Sciences, Kyoto University, for providing IR and ^{1}H NMR spectra of **3** that had been previously prepared in Professor Inubushi's laboratory.

10e–g relative to the unsubstituted cases **10a–d**, thereby resulting in lower energies of activation for cycloaddition of the former.

Comparison of entries **d–g** in Table I indicates that an alkyl residue on the diene moiety at C(8) does not produce a significant benefit to either reactivity or selectivity if the nitrogen atom already bears a bulky group. Namely, the effects of the *N*-alkyl substituent and the dienic alkyl substituent at C(8) do not appear to be additive. This observation suggests that additional experiments involving more substrates must be undertaken before it is possible to define more specifically the factors involved in determining the rates and distereoselection in the intramolecular Diels–Alder reactions of unsaturated dienamides of the general type **5**. This important issue will be examined in more depth in future investigations, the results of which will be reported independently.

Experimental Section

General. Unless otherwise indicated, all reagents were obtained from commercial suppliers and were used without purification. Tetrahydrofuran (THF), diethyl ether (ether), and dimethoxyethane (DME) were distilled under nitrogen from sodium or potassium/benzophenone ketyl immediately prior to use. Xylenes were distilled under nitrogen from sodium, whereas dichloromethane and methyl iodide were distilled from calcium hydride. All reactions involving air- and/or moisture-sensitive reagents were conducted under an atmosphere of nitrogen, and the glassware was flame-dried under a steam of dry nitrogen prior to use. Reported yields are for isolated and purified compounds determined to be >95% homogeneous by ^{1}H and ^{13}C NMR. Melting points are uncorrected. Preparative high-performance liquid chromatography (HPLC) was performed using Porasil A columns, and flash chromatography was conducted using Brinkmann silica gel G with a 15:1 ratio of silica gel/substrate eluting with mixtures (ratio given) of hexanes/ethyl acetate.

2-Methyl-2-cyclopentene-1-carboxylic Acid (7). A solution of methyl 2-methyl-2-cyclopentene-1-carboxylate[23] (5.00 g, 35.0 mmol) dissolved in a mixture of methanolic KOH (50 mL, 20% in MeOH) and water (15 mL) was heated at reflux for 4 h with stirring. The methanol was removed under reduced pressure, and the mixture was carefully neutralized with external cooling by slow addition of aqueous HCl (4 N). Ether (200 mL) was added, and the layers were separated. The aqueous layer was then extracted with ether (3 × 100 mL), and the combined extracts were washed with water (2 × 50 mL) and brine (2 × 50 mL) and dried ($MgSO_4$). The drying agent was removed by filtration, and the excess solvents were evaporated under reduced pressure; the crude product was purified by flash chromatography (7:1 hexane/ethyl acetate) to give **7** (4.18 g, 93%) as a pale yellow oil. ^{1}H NMR (360 MHz): δ 10.75 (br, 1 H), 5.54 (m, 1 H), 3.35 (br s, 1 H), 2.48–2.17 (comp, 4 H), 1.78 (d, 3 H, J = 1.0 Hz). ^{13}C NMR (90 MHz): 181.7, 137.1, 128.9, 53.7, 31.6, 28.3, 15.1. IR ($CHCl_3$): 2950, 1685 cm^{-1}. Mass spectrum: m/e 126.06832 ($C_7H_{10}O_2$ requires 126.06808), 108, 81 (base), 79, 67, 53, 41, 39.

2-Methyl-2-cyclopentene-1-carboxylic Acid Chloride (8). Oxalyl chloride (2 mL) was added dropwise to a solution of **7** (1.0 g, 8.0 mmol) in benzene (8 mL) at 0 °C. The reaction mixture was then stirred for a 2 h under a slow flow of nitrogen to remove the hydrogen chloride produced during the reaction. The excess benzene was removed under vacuum, and the crude acid chloride thus obtained was used immediately without further purification for the preparation of the dienamides.

General Procedure for the Preparation of Imines 9a–g. A mixture of $MgSO_4$ (2.5 g, 20.0 mmol), primary amine (20.0 mmol or excess $MeNH_2$ for **9a,g**), and unsaturated aldehyde (22.0 mmol) in ether (25 mL) was stirred for 0.5 h at 0 °C and then at room temperature for 1 h. The $MgSO_4$ was removed by vacuum filtration, and the solvent was removed under reduced pressure to give the crude imines **9a–g** as thick oils that were used in the next step without further purification.

2-Butenylidene-((*R*)-(+)-α-methylbenzyl)amine (9c). ^{1}H NMR (360 MHz): δ 7.97 (d, 1 H, J = 8.7 Hz), 7.45–7.25 (comp, 5 H), 6.36 (qdd, 1 H, J = 1.3, 8.7, 15.4 Hz), 6.23 (qd, 1 H, J = 6.6, 15.4 Hz), 4.37 (q, 1 H, J = 6.6 Hz), 1.90 (dd, 3 H, J = 1.3, 6.5 Hz), 1.55 (d, 3 H, J = 6.6 Hz). ^{13}C NMR (90 MHz): δ 161.0, 144.9, 140.2, 132.1, 128.2, 126.5, 126.3, 69.2, 24.4, 18.1. IR ($CHCl_3$): ν 3000, 2960, 2830, 2200, 1700, 1620, 1490, 1450, 1360, 1300, 1180, 1075, 980, 700 cm^{-1}. Mass spectrum: m/e 173.11999 ($C_{12}H_{15}N$ requires 173.12045), 158, 105 (base), 91, 77, 69.

2-Butenylidene(diphenylmethyl)amine (9d). As a single E/E isomer. ^{1}H NMR (360 MHz): δ 8.03 (d, 1 H, J = 8.7 Hz), 7.41–7.23 (comp, 10 H), 6.44 (m, 1 H, J = 0.4, 8.7, 15.5 Hz), 6.27 (m, 1 H, J = 6.6, 15.5 Hz), 5.43 (s, 1 H), 1.92 (dd, 3 H, J = 0.4, 6.6 Hz). ^{13}C NMR (90 MHz): δ 162.6, 143.7, 141.0, 132.1, 128.3, 127.6, 126.8, 77.8, 18.2. IR ($CHCl_3$): ν 2980, 2800, 1640, 1480, 1440, 1155, 1020, 980, 700 cm^{-1}. Mass spectrum: m/e 235.13668 ($C_{17}H_{17}N$ requires 235.13610), 167 (base), 152, 105, 77.

(3-Cyclopropyl-2-butenylidene)(diphenylmethyl)amine (9e). As a mixture (2:1) of E/E and E/Z isomers with respect to the C=N and C=C double bonds. ^{1}H NMR (360 MHz) (major E/E isomer): δ 8.34 (d, 1 H, J = 9.4 Hz), 7.79–7.07 (comp, 10 H), 6.17 (d, 1 H, J = 9.4 Hz), 5.39 (s, 1 H), 1.78 (d, 3 H, J = 1.0 Hz), 1.50 (m, 1 H), 0.78–0.61 (comp, 4 H); (minor E/Z isomer) δ 8.59 (d, 1 H, J = 9.5 Hz), 7.79–7.07 (comp, 10 H), 6.24 (d, 1 H, J = 9.5 Hz), 5.41 (s, 1 H), 1.56 (d, 3 H, J = 0.9 Hz), 1.50 (m, 1 H), 0.78–0.61 (comp, 4 H). IR (CCL_4): ν 3000, 1640, 1490, 1450, 1035, 700 cm^{-1}. Mass spectrum: m/e 275.16810 ($C_{20}H_{21}N$ requires 275.16740), 167 (base), 106, 77.

(3,4-Dimethyl-2-pentenylidene)methylamine (9g). As a mixture (ca. 3:1) of E/E and E/Z isomers. ^{1}H NMR (360 MHz) (E/E isomer): δ 8.21 (dd, 1 H, J = 1.3, 9.3 Hz), 6.00 (d, 1 H, J = 9.3 Hz), 3.57 (s, 3 H), 2.35 (q, 1 H, J = 7.0 Hz), 1.90 (s, 3 H), 1.05 (d, 6 H, J = 7.0 Hz); (E/Z isomer) 8.25 (dd, 1 H, J = 1.2, 9.5 Hz), 5.89 (d, 1 H, J = 9.5 Hz), 3.36 (s, 3 H), 2.31 (q, 1 H, J = 7.0 Hz), 1.05 (d, 6 H, J = 7.0 Hz). Mass spectrum: m/e 125.12079 ($C_8H_{15}N$ requires 125.12045), 110, 95, 82, 79, 69, 55, 42 (base).

General Procedure for the Preparation of the Dienamido Cyclopentenes 10a–g. To a solution of the crude imines **9a–g** prepared above (8.0 mmol) and *N*,*N*-diethylaniline (1.5 g, 10.0 mmol) in toluene (10 mL) was added dropwise the acid chloride **8** (1.16 g, 8.0 mmol) at −78 °C with stirring. The reaction was then gradually warmed to room temperature overnight. Water (10 mL) was added, and the mixture was extracted with (3 × 25 mL). The extracts were combined, washed with water (2 × 15 mL) and brine (2 × 10 mL), and dried ($MgSO_4$). The drying agent was removed by filtration, and the excess solvents were evaporated under reduced pressure to give crude trienamides **10a–g**, which were purified by flash chromatography (hexanes/EtOAc) to give pure **10a–g** (yield given) typically as thick pale yellow oils.

***N*-Benzyl-*N*-1′,3′-butadienyl-2-methyl-2-cyclopentene-1-carboxylic Amide (10b)** (65% yield). ^{1}H NMR (90 MHz): δ 7.60–7.20 (comp, 5 H), 6.65–5.50 (comp, 4 H), 5.20–4.80 (comp, 4 H), 3.90 (br m, 1 H), 2.60–1.55 (comp, 7 H). ^{13}C NMR (20 MHz): δ 173.9, 138.0, 137.0, 134.7, 130.6, 128.7, 128.6, 127.0, 126.7, 125.5, 114.5, 113.6, 113.0, 51.7, 46.8, 31.6, 29.4, 15.5. IR (CCl_4): 2920, 1675, 1635, 1430, 1380, 1190, 1170, 1000, 900, 700 cm^{-1}. Mass spectrum: m/e 267.16274 ($C_{18}H_{21}NO$ requires 267.16230), 187, 159, 144, 91 (base), 81, 65.

***N*-1′,3′-Butadienyl-*N*-((*R*)-(+)-α-methylbenzyl)-2-methyl-2-cyclopentene-1-carboxylic Amide (10c)** (67% yield). ^{1}H NMR (90 MHz): δ 7.35 (s, 5 H), 6.80–4.85 (comp, 7 H), 3.81 (br, 1 H), 2.52–1.50 (comp, 10 H). ^{13}C NMR (20 MHz): δ 174.2, 140.5, 138.2, 134.5, 128.4, 128.0, 126.7, 126.6, 126.4, 126.3, 115.8, 52.1, 51.9, 31.3, 29.2, 16.2, 15.1. IR (CCl_4): ν 2970, 1660, 1640, 1160, 1000, 700 cm^{-1}. Mass spectrum: m/e 281.17839 ($C_{19}H_{23}NO$ requires 281.17795), 173, 134, 119, 105 (base), 81.

***N*-(Diphenylmethyl)-*N*-1′,3′-butadienyl-2-methyl-2-cyclopentene-1-carboxylic Amide (10d)** (45% yield). ^{1}H NMR (360 MHz): δ 7.34–7.22 (comp, 10 H), 6.44–5.80 (comp, 3 H), 5.55 (br, s, 1 H), 5.03–4.89 (comp, 3 H), 2.46 (br, 1 H), 2.33–2.05 (comp, 4 H), 1.69 (s, 3 H). ^{13}C NMR (90 MHz): δ 175.1, 139.0, 138.8, 138.7, 134.2, 129.9, 128.9, 128.5, 128.3, 127.4, 116.4, 62.3, 52.7, 31.8, 29.8, 15.4. IR (CCl_4): ν 2900, 1640, 1160, 910, 700 cm^{-1}. Mass spectrum: m/e 343.19306 ($C_{24}H_{25}NO$ requires 353.19360), 251, 167 (base), 165, 152, 91.

***N*-(Diphenylmethyl)-*N*-(3′-cyclopropyl-1′,3′-butadienyl)-2-methyl-2-cyclopentene-1-carboxylic Amide (10e)** (71% yield). ^{1}H NMR (360 MHz): δ 7.35–7.23 (comp, 10 H), 6.68 (br,

1 H), 5.95 (br, 1 H), 5.54 (br, s, 1 H), 4.81–4.71 (comp, 3 H), 4.00 (br, 1 H), 2.53–2.00 (comp, 4 H), 1.71 (s, 3 H), 1.24 (m, 1 H), 0.55 (m, 2 H), 0.28 (m, 2 H). ^{13}C NMR (90 MHz): δ 175.1, 145.2, 139.2, 139.0, 138.7, 128.8, 128.3, 128.2, 128.1, 127.2, 120.4, 118.9, 113.0, 112.2, 62.1, 52.6, 31.7, 29.7, 15.4, 12.6, 5.0, 4.9. IR (CCl_4): ν 3100, 2900, 1630, 1650, 1400, 1200, 1030, 960, 700 cm^{-1}. Mass spectrum: *m/e* 383.22408 ($C_{27}H_{29}NO$ requires 383.22491), 275, 194, 167 (base), 152, 77.

***N*-(Diphenylmethyl)-*N*-(4′-methyl-3′-methylene-1′-pentenyl)-2-methyl-2-cyclopentene-1-carboxylic Amide (10f)** (42% yield). ^{1}H NMR (360 MHz): δ 7.34–7.15 (comp, 10 H), 6.30 (br, 1 H), 5.70 (br, 1 H), 5.54 (br s, 1 H), 4.80 (d, 2 H, *J* = 15 Hz), 3.95 (m, 1 H), 2.55–2.05 (comp, 5 H), 1.70 (s, 3 H), 0.91 (d, 3 H, *J* = 7.0 Hz), 0.89 (d, 3 H, *J* = 7.0 Hz). ^{13}C NMR (90 MHz): δ 175.3, 150.7, 139.3, 139.1, 138.8, 129.0, 128.9, 128.8, 128.3, 127.2, 126.1, 111.1, 62.1, 52.7, 31.8, 30.4, 29.9, 21.9, 21.8, 15.4. IR (CCl_4): ν 2940, 2920, 1630, 1390, 1230 cm^{-1}. Mass spectrum: *m/e* 385.24191 ($C_{27}H_{31}NO$ requires 385.24056), 342, 218, 182, 167 (base), 152, 81.

***N*-Methyl-*N*-(4′-methyl-3′-methylene-1′-pentenyl)-2-methyl-2-cyclopentene-1-carboxylic Amide (10g)** (67% yield). ^{1}H NMR (300 MHz): δ 7.70 (d, 0.3 H, *J* = 15 Hz), 7.15 (d, 0.7 H, *J* = 14.0 Hz), 5.64 (dd, 1 H, *J* = 14.0, 15.0 Hz), 5.53 (s, 3 H), 4.86 (d, 2 H, *J* = 17.5 Hz), 3.77 (br, 1 H), 3.20 (s, 0.3 Me), 3.13 (s, 0.7 Me), 2.49–1.91 (comp, 5 H), 1.70 (s, 3 H), 1.09 (dd, 6 H, *J* = 6.2, 6.7 Hz). ^{13}C NMR (90 MHz) (major rotamer only): δ 173.7, 151.1, 138.2, 128.5, 127.6, 113.0, 109.3, 51.9, 31.5, 30.2, 30.0, 29.1, 22.2, 22.1, 15.5. IR ($CHCl_3$): ν 2930, 1670, 1630, 1380, 1110 cm^{-1}. Mass spectrum: *m/e* 233.17855 ($C_{15}H_{23}NO$ requires 233.17796), 190, 125, 110, 81 (base).

General Procedure for Thermolysis of the Dienamido Cyclopentenes 10a–g. A 1% degassed solution of the trienamide **10a–g** (1.0 g) dissolved in xylenes (100 mL) was heated in a sealed stainless steel bomb (Paar) fitted with a glass liner in an oil bath at (temperature and time given). After cooling to room temperature, the bomb was opened, and the excess solvents were evaporated under reduced pressure to give a mixture (ratio as determined by ^{1}H NMR and total yield given) of **11a–g** and **12a–g**. The crude product mixture was separated by HPLC using hexanes/ethyl acetate to give **11a–g** and **12a–g** as colorless oils unless otherwise indicated. See Table I for experimental summary.

(1*S,4*R**,8*S**,11*R**)-3,11-Dimethyl-3-azatricyclo[6.2.1.0^{4,11}]undec-5-en-2-one (11a).** ^{1}H NMR (500 MHz): δ 5.90 (m, 1 H), 5.84 (m, 1 H), 3.42 (m, 1 H), 2.84 (s, 3 H), 2.60 (d, 1 H, *J* = 9.7 Hz), 2.22 (qdd, 1 H, *J* = 2.8, 5.7, 17.8 Hz), 2.12 (m, 1 H), 1.96 (m, 1 H), 1.93–1.79 (comp, 2 H), 1.54 (m, 1 H), 1.35 (dq, 1 H, *J* = 6.5, 12.5 Hz), 1.27 (s, 3 H). ^{13}C NMR (125 MHz): δ 176.1, 127.7, 122.0, 62.9, 55.5, 44.4, 42.4, 31.0, 29.2, 27.9, 27.6, 24.4. IR ($CHCl_3$): ν 2920, 1650, 1430, 1390, 1310, 1260, 1110, 1010 cm^{-1}. Mass spectrum: *m/e* 191.13165 ($C_{12}H_{17}NO$ requires 191.13101), 191 (base), 176, 163, 150, 136, 91, 86.

(1*S,4*R**,8*S**,11*R**)-3-Benzyl-11-methyl-3-azatricyclo[6.2.1.0^{4,11}]undec-5-en-2-one (11b).** ^{1}H NMR (500 MHz): δ 7.35–7.23 (comp, 5 H), 5.83 (m, 1 H), 5.76 (m, 1 H), 4.98 (d, 1 H, *J* = 15.0 Hz), 4.07 (d, 1 H, *J* = 15.0 Hz), 3.35 (dd, 1 H, *J* = 2.1, 2.6 Hz), 2.68 (dd, 1 H, *J* = 0.7, 8.9 Hz), 2.15 (tdd, 1 H, *J* = 2.7, 6.1, 17.8 Hz), 2.11–2.00 (comp, 2 H), 1.87 (m, 2 H), 1.58 (dddd, 1 H, *J* = 1.0, 5.0, 6.0, 12 Hz), 1.44 (dq, 1 H, *J* = 6.5, 12.0 Hz), 1.18 (s, 3 H). ^{13}C NMR (125 MHz): δ 176.4, 136.5, 128.6, 127.8, 127.6, 127.3, 122.1, 59.9, 55.7, 44.5, 44.2, 42.4, 31.1, 29.3, 27.9, 18.6. IR (CCl_4): ν 2940, 1680, 1440, 700 cm^{-1}. Mass spectrum: *m/e* 267.16274 ($C_{18}H_{21}NO$ requires 267.16230), 266, 176, 149, 106, 91 (base), 84, 77, 65.

(1*S,4*S**,8*S**,11*R**)-3-Benzyl-11-methyl-3-azatricyclo[6.2.1.0^{4,11}]undec-5-en-2-one (12b).** ^{1}H NMR (500 MHz): δ 7.34–7.24 (comp, 5 H), 5.96 (td, 1 H, *J* = 3.0, 9.5 Hz), 5.65 (ddt, 1 H, *J* = 2.7, 9.3, 3.0 Hz), 4.57 (d, 1 H, *J* = 5.0 Hz), 4.45 (d, 1 H, *J* = 5.0 Hz), 3.74 (m, 1 H), 2.55 (dd, 1 H, *J* = 7.0, 11.0 Hz), 2.48–2.40 (comp, 1 H), 2.27 (m, 1 H), 2.15 (m, 1 H), 1.96 (m, 1 H, 1.86–1.79 (comp, 2 H), 1.62–1.54 (comp, 1 H), 0.90 (s, 3 H). ^{13}C NMR (125 MHz): δ 179.9, 137.4, 128.6, 128.4, 128.0, 127.3, 125.1, 59.9, 54.3, 54.1, 45.5, 40.4, 35.7, 29.7, 25.6, 18.6. IR (CCl_4): ν 2860, 1690, 700 cm^{-1}. Mass spectrum: *m/e* 267.16274 ($C_{18}H_{21}NO$ requires 267.16230), 266, 226, 176, 119, 91 (base), 77, 65.

(1*R*,4*S*,8*R*,11*S*)-11-Methyl-3-[(*R*)-α-phenylethyl]-3-azatricyclo[6.2.1.0^{4,11}]undec-5-en-2-one (11c). The absolute configuration was determined by X-ray analysis[26] on the basis of internal reference with the chiral auxiliary; mp 165–166 °C (from hexane/ethyl acetate, 3:1). ^{1}H NMR (500 MHz): δ 7.26 (m, 4 H), 7.21 (m, 1 H), 5.50 (comp, 2 H), 5.26 (ddd, 1 H, *J* = 1.0, 2.0, 10.0 Hz), 3.69 (dd, 1 H, *J* = 2.0, 5.1 Hz), 2.67 (dd, 1 H, *J* = 1.0, 10.0 Hz), 2.14–1.85, (comp, 5 H), 1.68 (d, 3 H, *J* = 7.3 Hz), 1.58 (ddt, 1 H, *J* = 1.0, 6.0, 12.0 Hz), 1.42 (dq, 1 H, *J* = 6.5, 12.0 Hz), 1.25 (s, 3 H). ^{13}C NMR (125 MHz): δ 177.0, 142.6, 128.4, 127.1, 126.7, 126.5, 124.2, 60.3, 56.0, 49.4, 45.0, 42.6, 31.6, 30.0, 28.4, 24.4, 16.2. IR (CCl_4): ν 2920, 1680, 1420, 700 cm^{-1}. Mass spectrum: *m/e* 281.17731 ($C_{19}H_{23}NO$ requires 281.17795), 266, 190, 174, 120, 105 (base), 91, 79, 77.

(1*S*,4*R*,8*S*,11*R*)-11-Methyl-3-[(*R*)-α-phenylethyl]-3-azatricyclo[6.2.1.0^{4,11}]undec-5-en-2-one (11c′). ^{1}H NMR (500 MHz): δ 7.38–7.26 (comp, 5 H), 5.76 (dddd, 1 H, *J* = 0.7, 2.0, 3.0, 10.0 Hz), 5.60 (ddd, 1 H, *J* = 2.5, 5.0, 10.0 Hz), 5.48 (q, 1 H, *J* = 7.2 Hz), 3.24 (ddd, 1 H, *J* = 0.7, 2.0, 5.0 Hz), 2.62 (dd, 1 H, *J* = 1.5, 10 Hz), 2.10–2.02 (comp, 3 H), 1.89–1.82 (comp, 2 H), 1.61 (d, 3 H, *J* = 7.2 Hz), 1.59 (m, 1 H, *J* = 1.6, 6.2, 6.2, 12.0 Hz), 1.43 (dq, 1 H, *J* = 6.0, 12.0 Hz), 1.11 (s, 3 H). ^{13}C NMR (125 MHz): δ 176.4, 139.0, 128.4, 127.5, 127.3, 127.2, 124.6, 60.3, 55.6, 50.5, 44.7, 42.1, 31.3, 29.5, 28.9, 24.4, 18.2. IR (CCl_4): ν 2920, 1675, 700 cm^{-1}. Mass spectrum: *m/e* 281.17731 ($C_{19}H_{23}NO$ requires 281.17795), 266, 190, 174, 120, 105 (base), 91, 79, 77.

(1*S,4*R**,8*S**,11*R**)-3-(Diphenylmethyl)-11-methyl-3-azatricyclo[6.2.1.0^{4,11}]undec-5-en-2-one (11d).**[26] As a white solid, mp 150–151 °C (from hexane/ethyl acetate, 4:1). ^{1}H NMR (500 MHz): δ 7.39–7.22 (comp, 10 H), 6.32 (s, 1 H), 5.69 (m, 1 H), 5.52 (ddd, 1 H, *J* = 2.0, 5.0, 10.5 Hz), 3.21 (td, 1 H, *J* = 2.0, 5.0 Hz), 2.68 (dd, 1 H, *J* = 1.0, 10.0 Hz), 2.13–2.04 (comp, 3 H), 1.92 (comp, 2 H), 1.65 (m, 2 H), 1.31 (s, 3 H). ^{13}C NMR (125 MHz): δ 176.9, 139.0, 138.2, 129.9, 128.5, 128.0, 127.8, 126.9, 126.1, 124.8, 60.7, 60.4, 55.8, 44.6, 42.3, 31.6, 29.6, 28.1, 24.1. IR (CCl_4): ν 2940, 1680, 1415, 705 cm^{-1}. Mass spectrum: *m/e* 343.19405 ($C_{24}H_{25}NO$ requires 343.19360), 222, 182, 167, 152, 91. Anal. Calcd for ($C_{24}H_{25}NO$): C, 83.93; H, 7.34; N, 4.08. Found: C, 83.65; H, 7.08; N, 3.92.

(1*S,4*S**,8*S**,11*R**)-3-(Diphenylmethyl)-11-methyl-3-azatricyclo[6.2.1.0^{4,11}]undec-5-en-2-one (12d).** As a white solid, mp 143–144 °C (from hexane/ethyl acetate, 4:1). ^{1}H NMR (360 MHz): δ 7.35–7.22 (comp, 10 H), 6.73 (s, 1 H) 5.84 (td, 1 H, *J* = 3.0, 10.0 Hz), 5.50 (tdd, 1 H, *J* = 3.0, 6.0, 10.0 Hz), 3.51 (br d, 1 H, *J* = 3.0 Hz), 2.60 (dd, 1 H, *J* = 7.0, 11.0 Hz), 2.41–1.58 (comp, 6 H), 1.46–1.36 (m, 1 H), 1.11 (s, 3 H). ^{13}C NMR (90 MHz): δ 180.4, 144.3, 138.5, 129.7, 128.5, 128.1, 127.8, 127.2, 127.0, 59.2, 59.0, 53.8, 53.7, 40.9, 35.5, 29.3, 25.5, 19.3. IR (CCl_4): ν 1690, 700 cm^{-1}. Mass spectrum: *m/e* 343.19438 ($C_{24}H_{25}NO$ requires 343.19360), 167 (base), 152, 91.

(1*S,4*R**,8*S**,11*R**)-6-Cyclopropyl-3-(diphenylmethyl)-11-methyl-3-azatricyclo[6.2.1.0^{4,11}]undec-5-en-2-one (11e).** As white solid, mp 119–120 °C (from hexane/ethyl acetate, 3:1). ^{1}H NMR (360 MHz): δ 7.37–7.19 (comp, 10 H), 6.60 (s, 1 H), 5.15 (br s, 1 H), 3.03 (br s, 1 H), 2.66 (dd, 1 H, *J* = 1.5, 9.7 Hz), 2.07–1.45 (comp, 7 H), 1.20 (m, 1 H), 1.11 (s, 3 H), 0.50 (m, 2 H), 0.30–0.18 (m, 2 H). ^{13}C NMR (90 MHz): δ 176.8, 139.4, 138.8, 138.5, 129.8, 128.4, 128.1, 127.9, 127.7, 127.0, 117.0, 61.7, 60.5, 55.8, 45.6, 42.6, 31.7, 29.6, 28.1, 26.7, 17.1, 4.9, 4.3. IR (CCl_4): ν 2920, 2850, 1670, 1450, 1410, 700 cm^{-1}. Mass spectrum: *m/e* 383.22391 ($C_{27}H_{29}NO$ requires 383.22491), 216, 182, 167 (base), 152.

(1*S,4*S**,8*S**,11*R**)-6-Cyclopropyl-3-(diphenylmethyl)-11-methyl-3-azatricyclo[6.2.1.0^{4,11}]undec-5-en-2-one (12e).** As colorless oil. ^{1}H NMR (360 MHz): δ 7.36–7.15 (comp, 10 H), 6.68 (s, 1 H), 5.44 (dd, 1 H, *J* = 3.0, 6.0 Hz), 3.50 (br s, 1 H), 2.57 (dd, 1 H, *J* = 7.4, 10.5 Hz), 2.23–1.13 (comp, 8 H), 1.01 (s, 3 H), 0.49 (m, 2 H), 0.21 (m, 2 H). ^{13}C NMR (90 MHz): δ 180.4, 140.4, 140.2, 138.4, 129.6, 128.3, 128.0, 127.7, 127.6, 127.0, 118.3, 59.3, 59.2, 54.3, 53.7, 40.6, 35.5, 32.0, 25.5, 19.1, 16.3, 4.9, –0.1. IR (CCl_4): ν 2930, 1690, 910, 700 cm^{-1}. Mass spectrum: *m/e* 383.22536 ($C_{27}H_{29}NO$ requires 383.22491), 182, 167 (base), 105, 77.

(1*S,4*R**,8*S**,11*R**)-3-(Diphenylmethyl)-6-isopropyl-11-methyl-3-azatricyclo[6.2.1.0^{4,11}]undec-5-en-2-one (11f).** As colorless thick oil. ^{1}H NMR (360 MHz): δ 7.93–7.15 (comp, 10 H), 6.62 (s, 1 H), 5.20 (br s, 1 H), 3.30 (br s, 1 H), 2.67 (dd, 1 H, *J* = 1.0, 10.0 Hz), 2.12–1.50 (comp, 8 H), 1.12 (s, 3 H), 0.87 (dd, 6 H, *J* = 6.9, 7.1 Hz). ^{13}C NMR (90 MHz): δ 176.7, 143.4, 139.5, 138.5, 129.8, 128.4, 128.1, 127.9, 127.7, 126.9, 116.6, 61.8, 60.6, 55.8,

45.8, 42.6, 35.0, 31.5, 29.5, 28.0, 26.2, 20.7, 20.2. IR ($CHCl_3$): ν 2920, 2830, 1650, 1420 cm^{-1}. Mass spectrum: m/e 385.23940 ($C_{27}H_{31}NO$ requires 385.24056), 342, 218, 182, 167 (base), 152, 105, 91, 77.

(1S*,4R*,8S*,11R*)-3,11-Dimethyl-6-isopropyl-3-azatricyclo[6.2.1.0^{4,11}]undec-5-en-2-one (11g). ^1H NMR (360 MHz): δ 5.46 (br s, 1 H), 3.40 (dd, 1 H, J = 2.5, 5.0 Hz), 2.77 (s, 3 H), 2.53 (br d, 1 H, J = 11.0 Hz), 2.21 (p, 1 H, J = 6.8 Hz), 2.10–1.67 (comp, 5 H), 1.47 (m, 1 H), 1.40–1.17 (comp, 4 H), 0.95 (d, 6 H, J = 6.8 Hz). ^{13}C NMR (90 MHz): δ 176.1, 145.6, 113.8, 64.0, 55.6, 45.7, 43.2, 35.4, 30.9, 29.1, 28.0, 27.7, 26.3, 20.9, 20.7. IR (CCl_4): ν 2950, 1675, 1450, 1390 cm^{-1}. Mass spectrum: m/e 233.17728 ($C_{15}H_{23}NO$ requires 233.17796), 232, 190 (base), 139, 81, 67, 58.

(1S*,4S*,8S*,11R*)-3,11-Dimethyl-6-isopropyl-3-azatricyclo[6.2.1.0^{4,11}]undec-5-en-2-one (12g). ^1H NMR (360 MHz): δ 5.84 (dd, 1 H, J = 2.7, 2.9 Hz), 3.72 (br s, 1 H), 2.86 (s, 3 H), 2.52–1.81 (comp, 8 H), 1.67–1.62 (comp, 4 H), 1.05 (dd, 6 H, J = 0.8, 6.8 Hz). ^{13}C NMR (90 MHz): δ 180.5, 147.1, 116.1, 62.0, 55.4, 54.3, 40.7, 36.2, 34.6, 32.9, 28.3, 26.1, 21.3, 21.2, 18.9. IR (CCl_4): ν 2890, 1690 cm^{-1}. Mass spectrum: m/e 233.17728 ($C_{15}H_{23}NO$ requires 233.17796), 190 (base), 139, 81, 67.

(1S*,4S*,5R*,6S*,8S*,11R*)-3-(Diphenylmethyl)-5,6-epoxy-11-methyl-3-azatricyclo[6.2.1.0^{4,11}]-2-undecanone (15). A solution of MCPBA (80–85% purity, 0.42 g, 1.95 mmol) and **11d** (0.395 g, 1.15 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 4 h, whereupon Et_2O (30 mL) was added. The resulting mixture was washed with 1.5 N NaOH (3 × 3 mL), and the organic layer was washed with water (2 × 5 mL) and brine (2 × 5 mL) and dried ($MgSO_4$). Pure **11d** (0.41 g, 96%) was obtained as a colorless oil after removal of the solvents. The compound slowly solidified upon standing for several days, mp 129.5–130.5 °C. ^1H NMR (360 MHz): δ 7.43–7.21 (comp, 10 H), 6.34 (s, 1 H), 3.48 (d, 1 H, J = 2.3 Hz), 3.00 (m, 1 H), 2.95 (dd, 1 H, J = 2.3, 4.0 Hz), 2.59 (dd, 1 H, J = 6.0, 9.4 Hz), 2.15–1.85 (comp, 6 H), 1.54 (m, 1 H), 1.09 (s, 3 H). ^{13}C NMR (90 MHz): δ 177.6, 139.2, 137.4, 129.6, 128.7, 128.1, 127.7, 127.2, 61.5, 60.6, 55.3, 51.7, 50.9, 43.1, 41.8, 32.2, 30.0, 27.8, 25.6. IR (CCl_4): ν 2920, 1680, 1440, 1390, 1285, 1240, 700 cm^{-1}. Mass spectrum: m/e 359.18763 ($C_{24}H_{25}NO_2$ requires 359.18852), 343, 167 (base), 152. Anal. Calcd for ($C_{24}H_{25}NO_2$): C, 80.19; H, 7.01; N, 3.90. Found: C, 79.94; H, 6.88; N. 3.78.

(1S*,4S*,5R*,6S*,8S*,11R*)-5,6-Epoxy-11-methyl-3-azatricyclo[6.2.1.0^{4,11}]-2-undecanone. A solution of **15** (66 mg, 0.179 mmol) in glacial acetic acid (1.5 mL) containing Pearlman's catalyst (9 mg) was stirred under an atmosphere of hydrogen (750 psi) in a Parr steel reaction vessel at 56 °C for 24 h. The catalyst was removed by filtration, and the acetic acid was removed under high vacuum to give 30 mg (85%) of the intermediate secondary lactam as a white solid (mp 178–179 °C, hexane/ethyl acetate, 1:1). ^1H NMR (360 MHz): δ 7.06 (br, 1 H), 3.78 (d, 1 H, J = 2.5 Hz), 3.26 (br, 1 H), 3.20 (dd, 1 H, J = 2.5, 4.1 Hz), 2.53 (dd, 1 H, J = 5.5, 10.4 Hz), 2.08–1.74 (comp, 6 H), 1.49 (m, 1 H), 1.22 (s, 3 H). ^{13}C NMR (90 MHz): δ 180.1, 57.4, 54.9, 51.5, 50.9, 45.9, 41.6, 32.1, 29.5, 27.1, 25.6. IR (CCl_4): ν 2940, 1640, 740 cm^{-1}. Mass spectrum (CI; CH_4): M + 1 = 194 ($C_{11}H_{15}NO_2$ requires 193).

(1S*,4S*,5R*,6S*,8S*,11R*)-3,11-Dimethyl-5,6-epoxy-3-azatricyclo[6.2.1.0^{4,11}]-2-undecanone (16). To a solution of potassium *tert*-butoxide (45 mg, 0.04 mmol) and the secondary amide obtained in the previous experiment (25 mg, 0.013 mmol) in DME (2 mL) at −78 °C was added methyl iodide (0.5 mL). The reaction mixture was stirred for 2 h at −78 °C and then overnight at room temperature. The excess solvents were evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel using hexanes/ethyl acetate (1:1) as the eluent to give pure **16** (25 mg, 93%) as a colorless oil. ^1H NMR (360 MHz): δ 3.62 (d, 1 H, J = 2.3 Hz), 3.31–3.26 (comp, 2 H), 2.92 (s, 3 H), 2.52 (dd, 1 H, J = 5.1, 10.2 Hz), 1.98–1.72 (comp, 6 H), 1.44 (m, 1 H), 1.21 (s, 3 H). ^{13C} NMR (90 MHz): 177.0, 63.2, 55.2, 51.0, 50.2, 43.6, 41.9, 32.1, 29.3, 28.5, 27.5, 25.8. IR ($CHCl_3$): ν 2920, 2850, 1690, 1400, 1150 cm^{-1}. Mass spectrum: m/e 207.12603 ($C_{12}H_{17}NO_2$ requires 207.12593), 189, 161 (base), 146, 123, 111, 91.

(1S*,4S*,8S*,11R*)-3,11-Dimethyl-3-azatricyclo-[6.2.1.0^{4,11}]undecane-2,5-dione (17). A solution of epoxide **16** (16 mg, 0.077 mmol) and $Zn(OTf)_2$[33] (85 mg, 0.29 mmol) (or magnesium triflate) in CH_2Cl_2 (1.5 mL) was stirred overnight at room temperature. Water (2 mL) was added, and the resulting mixture was extracted with ether (3 × 5 mL). The extracts were combined, washed with 10% Na_2CO_3 (3 mL), water (2 mL), and brine (2 mL), and dried ($MgSO_4$). After removal of the solvents under reduced pressure and purification by HPLC using hexanes/ethyl acetate (1:1), pure ketone **17** (13 mg, yield 81%) was obtained as a colorless oil. ^1H NMR (360 MHz): δ 3.46 (s, 1 H), 2.80 (s, 3 H), 2.60 (dd, 1 H, J = 3.0, 9.0 Hz), 2.52 (td, 1 H, J = 7.0, 15.0 Hz), 2.29 (td, 1 H, J = 7.0, 16.6 Hz), 2.13 (m, 1 H), 2.05–1.84 (comp, 5 H), 1.60 (m, 1 H), 1.32 (s, 3 H). ^{13}C NMR (90 MHz): δ 210.1, 177.8, 73.5, 54.9, 49.6, 45.4, 34.1, 31.0, 29.1, 27.7, 27.2, 24.1. IR (CCl_4): ν 2960, 1700 (br) cm^{-1}. Mass spectrum: m/e 207.12545 ($C_{12}H_{17}NO_2$ requires 207.12593), 179 (base), 124, 110, 81, 70, 57, 42.

(1S*,4S*,5R*,6R*,8S*,11R*)-6-Bromo-3,11-dimethyl-5-hydroxyl-3-azatricyclo[6.2.1.0^{4,11}]-2-undecanone (18).[26] A solution of $MgBr_2{\cdot}Et_2O$ (100 mg, 0.39 mmol) and epoxide **16** (25 mg, 0.12 mmol) in dry ether (1.5 mL) was stirred at room temperature for 30 min. Water (5 mL) was added, and the resulting mixture was extracted with ether (3 × 15 mL). The extracts were combined, washed with brine (2 × 5 mL), and dried ($MgSO_4$). The excess solvent was removed under reduced pressure to give **18** (30 mg, 86%) as a white solid (mp 149–150 °C, from ether). ^1H NMR (500 MHz): δ 4.14 (ddd, 1 H, J = 5.2, 10.0, 12.3 Hz), 3.80 (ddd, 1 H, J = 2.1, 5.5, 10.0 Hz), 3.33 (d, 1 H, J = 5.5 Hz), 2.96 (s, 3 H), 2.76 (d, 1 H, J = 2.1 Hz), 2.56 (ddd, 1 H, J = 5.2, 8.5, 14.0 Hz), 2.49 (dd, 1 H, J = 4.1, 8.4 Hz), 2.02–1.88 (comp, 4 H), 1.84 (ddd, 1 H, J = 7.0, 12.0, 14.0 Hz), 1.38 (m, 1 H), 1.32 (s, 3 H). ^{13}C NMR (125 MHz): δ 175.9, 76.6, 72.0, 56.5, 55.6, 46.9, 44.7, 36.6, 35.5, 31.6, 29.3, 28.8. IR (CCl_4): ν 1680 cm^{-1}. Mass spectrum (CI; CH_4): 290 (M + 1) (base), 288, 208, ($C_{12}H_{18}BrNO_2$ requires 289).

(1S*,4S*,5R*,6S*,8S*,11R*)-3,11-Dimethyl-5,6-epoxy-6-isopropyl-3-azatricyclo[6.2.1.0^{4,11}]-2-undecanone (22). A solution of MCPBA (80–85% purity, 0.50 g, 2.3 mmol) and **11g** (0.31 g, 1.33 mmol) in CH_2Cl_2 (5 mL) was stirred at 0 °C for 2 h, whereupon Et_2O (5 mL) was added. The resulting mixture was washed with 1.5 N NaOH (3 × 3 mL), and the organic layer was washed with water (2 × 5 mL) and brine (2 × 5 mL) and dried ($MgSO_4$). Pure **22** (320 mg, 97%) was obtained as a colorless oil after removal of the solvents. ^1H NMR (360 MHz): δ 3.56 (d, 1 H, J = 2.8 Hz), 3.07 (d, 1 H, J = 2.8 Hz), 2.83 (s, 1 H), 2.45 (dd, 1 H, J = 5.1, 10.2 Hz), 1.99–1.34 (comp, 8 H), 1.13 (s, 3 H), 0.92 (d, 3 H, J = 6.8 Hz), 0.83 (d, 3 H, J = 7.0 Hz). ^{13}C NMR (90 MHz): δ 177.3, 64.0, 63.2, 56.1, 54.7, 44.1, 43.0, 34.0, 31.7, 29.2, 28.4, 27.4, 25.7, 18.1, 17.5. IR ($CHCl_3$): ν 2990, 1665 cm^{-1}. Mass spectrum: m/e 249.17307 ($C_{15}H_{23}NO_2$ requires 249.17288), 234, 221, 206, 190, 178, 148, 136, 123, 111 (base), 86.

(1S*,4S*,5S*,8S*,11R*)-3,11-Dimethyl-5-hydroxy-6-isopropyl-3-azatricyclo[6.2.1.0^{4,11}]undec-6-en-2-one (23).[26] To a stirred mixture of **22** (133 mg, 0.534 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (121 mg, 0.588 mmol) in CH_2CL_2 (2 mL) was added trimethylsilyl triflate[38] (130.5 mg, 0.588 mmol) at −78 °C. After being stirred at −78 °C for 8 h and at room temperature for 2 h, the mixture was poured into 1 N HCl and stirred until complete removal of the trimethylsilyl ether had been achieved according to TLC. The resulting mixture was extracted with ether (3 × 15 mL). The combined extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography using hexanes/ethyl acetate (1:1) to give 103 mg (80%) of **23**, which was recrystallized from ether to give colorless crystals (mp 127–128 °C). ^1H NMR (500 MHz): δ 5.49 (br d, 1 H, J = 1.7 Hz), 4.38 (br, 1 H), 3.58 (d, 1 H, J = 2.8 Hz), 2.76 (s, 3 H), 2.46 (dd, 1 H, J = 5.0, 8.0 Hz), 2.37–2.32 (comp, 2 H), 2.02–1.81 (comp, 3 H), 1.44–1.37 (comp, 5 H), 1.07 (d, 3 H, J = 6.7 Hz), 1.05 (d, 3 H, J = 6.7 Hz). ^{13}C NMR (125 MHz): δ 177.2, 141.9, 128.0, 68.6, 66.0, 55.5, 45.8, 43.2, 34.1, 33.5, 29.7, 28.4, 27.9, 21.8, 21.6. IR ($CHCl_3$): ν 2890, 1665 cm^{-1}. Mass spectrum: m/e 249.17288 ($C_{15}H_{23}NO_2$ requires 249.17303), 124, 111 (base).

(1S*,4S*,8S*,11R*)-3,11-Dimethyl-6-isopropyl-3-azatricyclo[6.2.1.0^{4,11}]undec-6-ene-2,5-dione (3). To a suspension of pyridinium dichromate[39] (37.8 mg, 0.1 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of **23** (12.5 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL), and the mixture was stirred for 5 h at room temperature. Water (2 mL) was added, and the resulting mixture was extracted with ether (3 × 10 mL). The extracts were combined, washed

with brine (2 × 3 mL), and dried ($MgSO_4$). After evaporation of the solvents under reduced pressure, pure **3** was obtained (10 mg, 80%) as a colorless oil by flash chromatography (hexanes/ethyl acetate, 4:1). ^1H NMR (500 MHz): δ 6.55 (dd, 1 H, J = 1.0, 4.7 Hz), 3.54 (s, 1 H), 2.86 (tp, 1 H, J = 1.0, 6.9 Hz), 2.72 (s, 3 H), 2.55 (d, 1 H, J = 7.0 Hz), 2.46 (m, 1 H, J = 4.7, 8.0, 10 Hz), 2.26 (tdd, 1 H, J = 1.4, 6.0, 12.7 Hz), 2.06 (m, 1 H, J = 1.0, 7.0, 8.0, 10.0 Hz), 1.89 (m, 1 H, J = 6.0, 7.0, 12.5, 12.7 Hz), 1.38–1.27 (comp, 4 H), 1.03 (d, 3 H, J = 6.9 Hz), 0.96 (d, 3 H, J = 6.9 Hz). ^{13}C NMR (125 MHz): δ 194.7, 176.8, 143.9, 140.9, 70.4, 55.5, 47.1, 44.7, 33.9, 29.6, 28.7, 27.3, 26.9, 22.0, 21.1. IR (CCl_4): ν 2940, 2860, 1700, 1675, 1465, 1395, 1240 cm^{-1}. Mass spectrum: m/e 247.15723 ($C_{15}H_{21}NO_2$ requires 247.15769), 124, 111 (base).

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Registry No. (±)-**1**, 30646-45-8; (±)-**3**, 40142-12-9; (±)-**7**, 129872-08-8; (±)-**7** methyl ester, 83747-57-3; (±)-**8**, 118495-26-4; **9a**, 129872-10-2; **9a** aldehyde, 123-73-9; **9b**, 129872-11-3; **9c**, 129872-12-4; **9d**, 129872-13-5; (*E,E*)-**9e**, 129872-14-6; (*E,Z*)-**9e**, 129872-15-7; **9e** aldehyde, 59819-88-4; **9f**, 129895-36-9; **9f** aldehyde, 129872-09-9; (*E,E*)-**9g**, 129872-16-8; (*E,Z*)-**9g**, 129872-17-9; (±)-**10a**, 118495-12-8; (±)-**10b**, 118495-13-9; **10c** (isomer 1), 129872-18-0; **10c** (isomer 2), 129872-28-2; (±)-**10d**, 118495-15-1; (±)-**10e**, 129872-19-1; (±)-**10f**, 129872-20-4; (±)-**10g**, 118495-24-2; (±)-**11a**, 118495-16-2; (±)-**11b**, 118495-17-3; **11c**, 112899-11-3; **11c'**, 129940-03-0; (±)-**11d**, 118495-18-4; (±)-**11e**, 129872-21-5; (±)-**11f**, 129872-22-6; (±)-**11g**, 118495-25-3; (±)-**12a**, 118574-41-7; (±)-**12b**, 118574-42-8; **12c**, 118574-40-6; (±)-**12d**, 118574-43-9; (±)-**12e**, 129940-01-8; (±)-**12f**, 129940-02-9; (±)-**12g**, 118574-44-0; (±)-**13a**, 118495-19-5; (±)-**13b**, 118495-20-8; **13c**, 118495-21-9; (±)-**15**, 129872-23-7; (±)-**16**, 129872-25-9; (±)-**16** (*N*-demethyl derivative), 129872-24-8; (±)-**17**, 129872-26-0; (±)-**18**, 129872-27-1; (±)-**22**, 118495-27-5; (±)-**23**, 118574-45-1; $MeNH_2$, 74-89-5; $PhCH_2NH_2$, 100-46-9; (*R*)-Ph(Me)CHNH$_2$, 3886-69-9; Ph_2CHNH_2, 91-00-9.

Supplementary Material Available: A summary of X-ray crystallographic data and ORTEP plots are provided for compounds **11c,d**, **18**, and **23** (45 pages). Ordering information is given on any current masthead page.

Stereochemical Control in the Ester Enolate Claisen Rearrangement. 1. Stereoselectivity in Silyl Ketene Acetal Formation[1]

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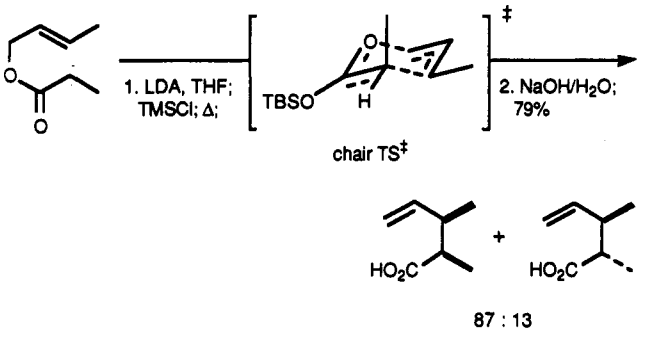
Methods for the stereoselective deprotonation and silylation of esters were systematically investigated. A kinetically controlled enolization in combination with a kinetic resolution process accounts for the selective formation of (*E*)- and (*Z*)-silyl ketene acetals in THF and THF/dipolar solvent systems with bases such as LDA, LHMDS, and KHMDS. A thermodynamic equilibration mechanism seems to be of minor significance with ester enolates. Improved reaction conditions were exemplified in a highly stereoselective Claisen rearrangement in THF/45% DMPU.

Introduction

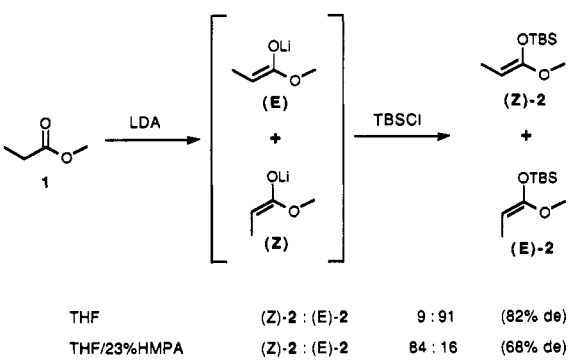
Since its introduction in 1972,[2] the silyl ketene acetal variant of the Claisen rearrangement has become increasingly popular in organic synthesis.[3] A wide field of applications includes the preparation of polyether antibiotics,[4] sesquiterpenes,[5] iridoids,[6] tetronates,[7] marine natural products,[8] amino acids,[9] *C*-glycosides,[10] large carbocycles,[11] and monochiral stannanes and silanes.[12]

Several factors contribute to the versatility of the ester

Scheme I



Scheme II



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