mL of water. The resulting white solid was collected by filtration and was dried under reduced pressure (4 mmHg), producing 11.5 mg (74%) of the bromohydrin 17: ^{1}H NMR (360 MHz, acetone-d_6) δ 3.06 (dd, 2 H, $J_{15,16}$ = 5.5, 5.5 Hz, 15-H), 4.31 (br dd, 1 H, $J_{3,4}$ = 8.6, $J_{2,3}$ = 2.9 Hz, 3-H), 4.72 (br s, 1 H, OH), 4.78 (dd, 1 H, $J_{2,1}$ = 3.1, $J_{2,3}$ = 2.9 Hz, 2-H), 4.90 (m, 1 H, 4-H), 4.95 (br s, 1 H, OH), 5.43 (br s, 1 H, OH), 5.78 (br d, 1 H, $J_{1,2}$ = 3.1, 1-H), 7.71 (d, 1 H, $J_{12,11}$ = 8.8 Hz, 12-H), 7.98 (d, 1 H, $J_{7,6}$ = 8.6 Hz, 7-H), 8.18 (d, 1 H, $J_{6,7}$ = 8.6 Hz, 6-H), 8.30 (d, 1 H, $J_{11,12}$ = 8.8 Hz, 11-H) [note that 16-H's are obscured by the water peak at δ 2.80]; MS (CI, NH_3) m/z 382 and 380 ($[M + NH_4]^+$, 13), 365 and 363 ($[M + H]^+$, 24), 300 (48), 285 (70), 267 (95), 249 (100), 233 (19); HRMS (CI, NH_3) calcd for $C_{17}H_{15}O_4{}^{79}BrH$ ($[M + H]^+$) m/z 363.0232, found m/z 363.0210.

***syn*-1,2-Epoxy-1,2,3,4,15,16-hexahydro-*trans*-3,4-dihydroxycyclopenta[*a*]phenanthren-17-one (4a).** A 5-mL, round-bottomed flask equipped for magnetic stirring was charged with 9.8 mg (0.027 mmol) of bromohydrin 17 and 1 mL of dry THF. To this solution was added, under nitrogen, 7.5 mL (0.033 mmol) of 4.37 M sodium methoxide in methanol at rt, which resulted in the immediate formation of light brown precipitates. The resulting mixture was stirred at rt for 1 h and was poured into a separatory funnel containing 25 mL of ethyl acetate. This mixture was washed with water (2 × 10 mL) and then with brine (20 mL) and was dried (Na_2SO_4). Filtration and concentration in vacuo by rotary evaporation afforded 6.1 mg (80%) of *syn*-diol epoxide **4a** as a pale yellow solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.80 (br dd, 2 H, $J_{16,15}$ = 5.3, 4.9 Hz, 16-H), 3.45 (br dd, 2 H, $J_{15,16}$ = 5.3, 4.9 Hz, 15-H), 3.73 (br d, 1 H, $J_{2,1}$ = 4.1 Hz, 2-H), 3.78 (ddd, 1 H, $J_{3,4}$ = 6.9 Hz, $J_{3,OH}$ = 5.1 Hz, $J_{3,2}$ = 1.6 Hz, 3-H), 4.67 (d, 1 H, $J_{1,2}$ = 4.1 Hz, 1-H), 4.71 (dd, 1 H, $J_{4,3}$ = 6.9 Hz, $J_{4,OH}$ = 6.8 Hz, 4-H), 5.36 (d, 1 H, $J_{OH,4}$ = 6.8 Hz, 4-OH), 5.72 (d, 1 H, $J_{OH,3}$ = 5.1 Hz, 3-OH), 7.73 (d, 1 H, $J_{12,11}$ = 8.8 Hz, 12-H), 7.84 (d, 1 H, $J_{7,6}$ = 8.5 Hz, 7-H), 8.22 (d, 1 H, $J_{6,7}$ = 8.5 Hz, 6-H), 8.35 (d, 1 H, $J_{11,12}$ = 8.8 Hz, 11-H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 24.12 (16-C), 35.85 (15-C), 46.66 (2-C), 58.35 (1-C), 70.02 (3-C), 71.75 (4-C), 119.68, 123.51, 125.47, 126.99, 128.67, 129.54, 133.94, 135.38, 141.02, 156.78, 205.75 (17-C); MS (EI, 70 eV) m/z 282 (M^+, 58), 264 ($M^+ - H_2O$, 100), 236 ($M^+ - H_2O - CO$, 72), 235 ($M^+ - H_2O - CO - H$, 72), 223 (21), 207 (29), 194 (31), 189 (23), 178 (20), 165 (52), 152 (37), 97 (23), 95 (20), 80 (23), 71 (27), 69 (29), 57 (43) 43 (45); HRMS (EI, 70 eV) calcd for $C_{17}H_{14}O_4$ m/z 282.0892, found m/z 282.0909.

Acknowledgment. We are grateful for financial support for this work provided by the National Institutes of Health (Grant No. CA 25185).

Note Added in Proof. Since submission of the manuscript in August, 1991, a paper describing the synthesis of **3** appeared. See: Young, R. J.; Cortez, C.; Luna, E.; Lee, H.; Harvey, R. G. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 23.

Registry No. **3**, 143290-36-2; **4a**, 143216-77-7; **5**, 2811-50-9; **6a**, 71996-27-5; **6b**, 10481-34-2; **7**, 17521-83-4; **8**, 143216-78-8; **9**, 21070-86-0; **10**, 792-07-4; **11**, 98656-35-0; **12**, 24684-50-2; **13**, 143216-79-9; **14**, 143216-80-2; **15a**, 143216-81-3; **15b**, 143216-82-4; **16**, 143216-83-5; **17**, 143216-84-6; TBDMSOTf, 69739-34-0; vinylmagnesium bromide, 1826-67-1; 6-methoxy-1-tetralone, 1078-19-9.

Supplementary Material Available: ^{1}H NMR spectra of **3**, **4a**, **14**, **16**, and **17** and ^{13}C NMR spectra of **3**, **4a**, **14**, and **16** (9 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.

Diels-Alder Reactions of Dihydropyridinones: Synthetic Entry to the Manzamine A Tricyclic Core†

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For the construction of the tricyclic core of manzamine A (1), the Diels-Alder reactions of some dihydropyridinones were surveyed. The N-protecting group of the dihydropyridinone played an important role in achieving a successful Diels-Alder reaction. In view of its electron-withdrawing character as well as its thermal stability, the *p*-toluenesulfonyl protecting group was found to be best in our synthesis. An effective method for the preparation of 3-alkyldihydropyridinones via the Michael addition to dehydroalanine derivatives has also been devised. By the utilization of a high-pressure Diels-Alder reaction of the *N*-tosyl-3-alkyldihydropyridinone (**17**) with the Danishefsky diene, a facile construction of the central pyrroloisoquinoline skeleton (**21**) was successfully achieved.

Introduction

The manzamine family of marine alkaloids (manzamine A-F) was isolated from several Okinawan marine sponges by Higa,[1] and later Nakamura[2] also isolated the same compounds as keramamines. The first isolated congener, manzamine A[1a] (keramamine A[2], **1**), has been the subject of recent synthetic investigations owing to its unique molecular structure and remarkable biological properties including antitumor[1] and antibacterial activity,[2] while the simplest manzamine, manzamine C,[1b] and related analogues have already been synthesized in this laboratory.[3] Quite recently, the new and biogenetically related alkaloid

† This paper is dedicated to the late Professor Emeritus Shigehiko Sugasawa, Univeristy of Tokyo.

‡ Faculty of Pharmaceutical Sciences.

§ The Chemical Analysis Center.

⊥ The Institute of Physical and Chemical Research.

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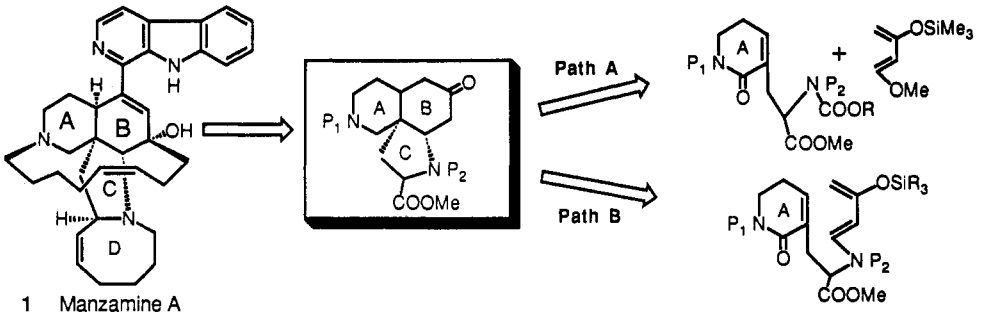
0022-3263/92/1957-5741$03.00/0

Scheme I



1 Manzamine A

ircinals have been isolated by Kobayashi.[4] A plausible biosynthetic pathway has also been presented recently by Baldwin,[5] which may stimulate synthetic studies along these lines.

For the challenging construction of the central azacyclic core of **1**, several groups have independently reported their own synthetic endeavours during the past few years, which include various approaches[6] based on the Diels–Alder reaction and one approach through a radical pathway.[7] Described herein are the full details of our own strategy to the key pyrroloisoquinoline intermediate for **1**, which utilizes a Diels–Alder reaction of 3-alkyl-5,6-dihydro-2-pyridinones under suitably optimized conditions.[8]

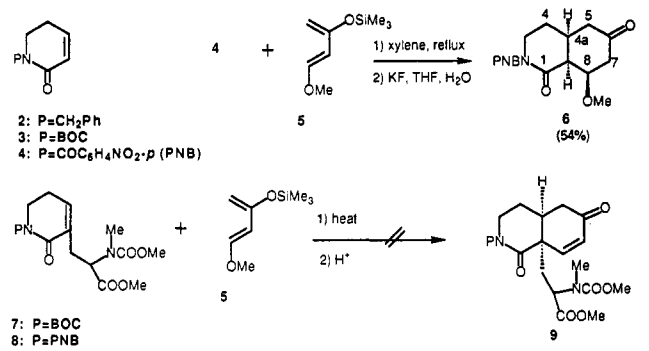
Results and Discussion

Synthetic Strategies. To ensure the cis relationship of the central AB ring system of this unique structure, we have been interested in the Diels–Alder reaction of 3-substituted dihydropyridinones either in an intermolecular manner (path A) or an intramolecular fashion (path B) as shown in Scheme I. Our explorations to elaborate a suitable dienophile partner have now begun along the line of path A. The challenging feature of this approach is to overcome the relative unreactivity of the dienophile 3-alkyldihydropyridinone. We have thus carefully surveyed both the effect of substituents on the dienophile's reactivity, especially the protecting groups, and various conditions for an effective Diels–Alder reaction.

Diels–Alder Reaction of 3-Alkyldihydropyridinones. At the outset of our synthesis, simple dihydropyridinones with different N-protecting groups were prepared to test their suitability as promising dienophiles. The required dihydropyridinones such as **2**, **3**, and **4** were prepared in a straightforward manner from the readily available 2-piperidone through N-protection, sulfenylation and subsequent oxidative elimination.[9]

Initial attempts at Diels–Alder reaction with *N*-benzyldihydropyridinone (**2**) and the highly reactive Danishefsky diene (**5**)[10] failed to afford the expected adducts under either thermal or Lewis acid conditions. Even

Scheme II



2: P=CH_2Ph
3: P=BOC
4: P=$COC_6H_4NO_2$-*p* (PNB)

5

6 (54%)

7: P=BOC
8: P=PNB

9

in the case of *N*-*tert*-butoxycarbonyl (Boc) derivative **3**, only a messy mixture was obtained upon heating with **5**, presumably because of the thermal instability of the substrate. After these unsuccessful trials, we were delighted to find that the *N*-*p*-nitrobenzoyl (PNB) derivative **4** reacted with the diene **5** to furnish the desired adduct after refluxing in xylene for 20 h. Treatment of the crude adduct with KF in aqueous THF afforded the perhydroisoquinolinone **6** in 54% yield from **4** (Scheme II). These results indicated that the electron-withdrawing character of the N-protecting group was essential for successful cycloaddition. A simple molecular orbital (MO) calculation then revealed that the LUMO of the reactive *N*-PNB derivative **4** is much lower than that of the *N*-benzyl derivative **2**.[11]

On the basis of the results obtained above, we have focused our attention on the Diels–Alder reaction of 3-alkyl-substituted dihydropyridinones with the aim of constructing the ABC tricyclic core of **1**. Thus, the Diels–Alder reactions of the two dienophiles (**7** and **8**) were examined to obtain a hydroisoquinoline derivative such as **9**. To our disappointment, however, deprotection of the *N*-Boc group occurred when **7** was heated with **5** in xylene, while a messy mixture was obtained upon attempted cycloaddition of the more reactive dienophile **8** (Scheme II).

After these unsuccessful experiments, we have chosen the *N*-*p*-toluenesulfonyl (Ts) group as a promising *N*-protecting group. In an initial model study, the simple *N*-Ts-dihydropyridinone **10** was treated with excess diene **5**, in *p*-cymene at reflux for 5 h, to furnish after treatment with camphorsulfonic acid (CSA), the desired hydroisoquinoline **11** in a moderate yield. The cis ring fusion in **11** was unequivocally established based on an NOE experiment. An enhancement of the signal corresponding to the angular H (4a-H) was observed upon irradiation of the angular methyl group.

With these initial results in hand, the Diels–Alder reactions of the two *N*-Ts-dihydropyridinones (**16** and **17**)

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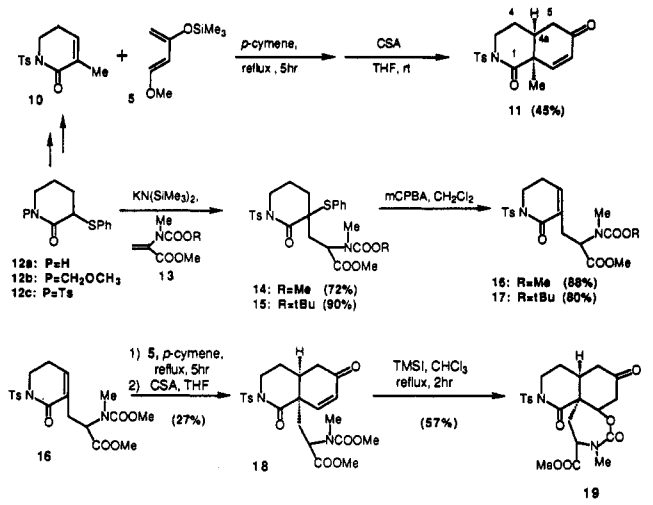
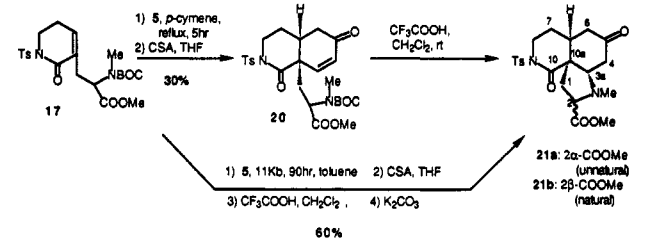
(11) Details of these MO calculation will be reported elsewhere in due course.

Scheme III



Scheme IV



were then examined. These dienophiles (**16** and **17**) were prepared from *N*-tosyl-3-(phenylthio)-2-piperidone (**12c**) through the efficient sequence shown in Scheme III. The key feature of this route is an effective Michael addition reaction of **12c** with the dehydroalanine derivatives **13**.[12] Due to the sluggishness of the *N*-Boc acrylate **13** (R = *t*-Bu) toward Michael reaction, a combined use of KN(TMS)$_2$ and 18-crown-6 in THF was developed to promote effective Michael addition. Under these optimized conditions, the Michael reaction proceeded reproducibly in ~90% yield.

The reaction of *N*-tosyl (Ts) derivative **16** with excess diene **5** (*p*-cymene, reflux 5 h) afforded, after acid treatment, the desired enone **18** as a diastereomeric mixture in 27% yield, along with recovered **16** (54%). In an attempt to improve the yield by carrying out this reaction under the influence of various Lewis acids, as well as ultrasound sonication, unsatisfactory results were obtained, presumably due to the acid lability of the diene **5**.

We next examined the deprotection of the carbamate group (NCOOMe) in **18** by trimethylsilyl iodide (TMSI).[13] The reaction of **18** with excess TMSI in $CHCl_3$ at reflux gave the unexpected cyclic carbamate **19** in 57% yield instead of the desired pyrroloisoquinoline. We next turned our attention to the N_b-Boc derivative **17** because cleavage of the *N*-Boc group could be achieved much more easily than cleavage of the *N*-COOMe group. Thus, the same Diels–Alder reaction with the N_b-Boc derivative **17** was carried out as above to give the corresponding enone **20** as a diastereomeric mixture in a slightly better yield (30%), but the purification of the product proved to be quite difficult. However, brief treatment of crude **20** with CF_3COOH in CH_2Cl_2 at room temperature, followed by quenching with aqueous K_2CO_3, furnished the desired

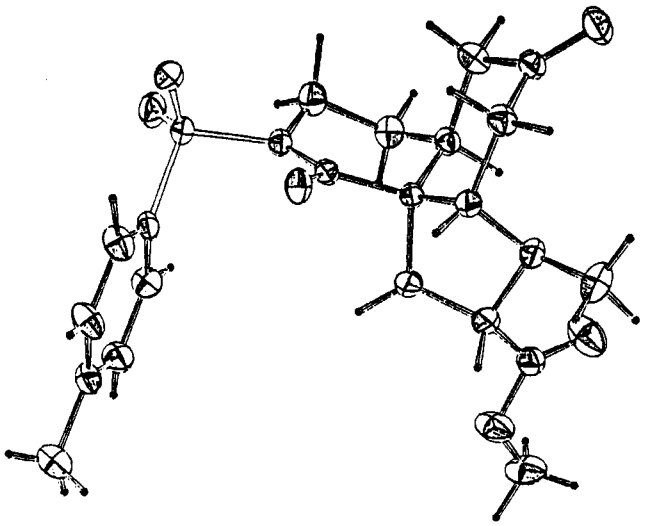
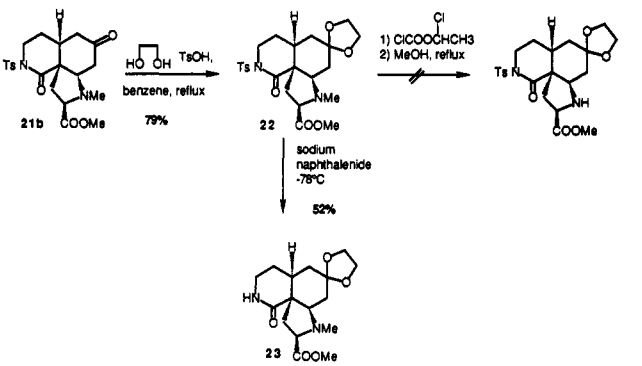


Figure 1. ORTEP drawing of **21a**.

Scheme V



tricyclic pyrroloisoquinoline (**21a** and **21b**) in moderate yield, as a diastereomeric mixture (Scheme IV).

High-Pressure Diels–Alder Reaction. To overcome the sluggishness of the dienophile **17** toward the fairly unstable diene **5**, we attempted a high-pressure Diels–Alder reaction.[14] Encouraged by the success of the reaction of **17** with excess **5** in toluene at 10 kbar for 20 h at ambient temperature, which afforded **20** (20%) and recovered **17** (40%), we conducted the same reaction at 11 kbar for 90 h. After evaporation of the excess reagents, the residue was treated with CSA in THF to give the enone **20** as a major product, along with a small amount of **17**. Crude **20** was then directly treated with CF_3COOH to furnish **21** (**21a**:**21b** = 1:1), after treatment with base, in 60% overall yield from **17**. The structures of **21a** and **21b** were fully characterized by spectroscopic means, including H–H COSY, NOESY, and NOEDS experiments. In addition, confirmation of the structure of **21a** was made by a single-crystal X-ray diffraction analysis (Figure 1).

Further Transformations. A preliminary exploration of N-deprotection of **21b** was undertaken to provide a more advanced intermediate. Thus, **21b** was converted to the ketal **22** in the usual manner (79%). Attempted N-demethylation of **22** by ClCOO(Cl)CHCH$_3$[15] or other chloroformate reagents was completely unsuccessful, presumably because of the low basicity and steric hindrance of this amine. On the other hand, the Ts group of **22** was easily removed by treatment with sodium naphthalenide

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at low temperature, to afford **23** (Scheme V). This facile N-detosylation may allow us to prepare the 13-membered ring from **23**. Further progress along these lines, as well as investigation of the intramolecular Diels–Alder reaction (path B), will be reported in due course.

Experimental Section

General. Melting points are uncorrected. Unless otherwise noted, IR spectra was measured as a KBr disk, and ^1H and ^{13}C NMR spectra was measured as a solution in $CDCl_3$.

***N*-(*p*-Nitrobenzoyl)-5,6-dihydro-2(1*H*)-pyridinone (4).** To a cooled (0 °C) and stirred mixture of the 3-(phenylthio)piperidone **12a** (prepared as below, 2.80 g, 13.5 mmol) in CH_2Cl_2 (100 mL) and saturated $NaHCO_3$(aq) (20 mL) was added *m*-CPBA (3.20 g, 80%, 1 equiv) portionwise. The resulting mixture was then kept stirring until TLC indicated almost no starting material (1 h) remained. The mixture was extracted with CH_2Cl_2 (~200 mL) and washed well with saturated $NaHCO_3$(aq) (30 mL × 2). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue (3.00 g) thus obtained was taken into benzene (50 mL) and heated under reflux for 1 h. The yellow mixture was concentrated to give an oily residue, which was purified by SiO_2 column (80 g, AcOEt/*n*-hexane = 1/1) to afford nearly pure 5,6-dihydro-2(1*H*)-pyridinone (1.17 g). To a cooled (−78 °C) and stirred solution of this *N*-H-dihydropyridinone (0.95 g, 9.8 mmol) in THF (25 mL) was added *n*-BuLi (1.49 M in hexane, 6.6 mL, 1 equiv), and the resulting mixture was kept stirring at this temperature for 10 min. A THF (10 mL) solution of *p*-nitrobenzoyl chloride (1.82 g, 1 equiv) was slowly added at −78 °C, and the mixture was warmed to rt over 30 min. After being stirred at rt for 30 min, the mixture was diluted with CH_2Cl_2 (150 mL)–H_2O (20 mL) and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the dried solvent gave a residue (1.80 g), which was purified by SiO_2 column (100 g, AcOEt/*n*-hexane = 1/2), to afford the *N*-(*p*-nitrobenzoyl)-5,6-dihydro-2(1*H*)-pyridinone (**4**, 1.10 g, 41% from **12a**) as a pale yellow solid. **4**: mp 121–123 °C (AcOEt/*n*-hexane); IR 1700, 1680, 1520, 1380, 1350, 1305 cm^{-1}; ^1H NMR (270 MHz) δ 2.64 (2 H, m, 5-CH_2), 4.05 (2 H, t, J = 6.6 Hz, 6-CH_2), 5.98 (1 H, dt, J = 9.1, 1.9 Hz, olefinic), 7.04 (1 H, dt, J = 9.9, 4.4 Hz, olefinic), 7.65 (2 H, d, J = 8.8 Hz, aromatic) 8.25 (2 H, d, J = 8.8 Hz, aromatic); LREIMS m/z 246 (M^+, 16). Anal. Calcd for $C_{12}H_{10}N_2O_4$: C, 58.54; H, 4.09; N, 11.38; Found: C, 58.45; H, 4.14; N, 11.32.

***rac*-(4a*S**,8*R**,8a*S**)-8-Methoxy-2-(*p*-nitrobenzoyl)-*cis*-1,2,3,4,4a,5,6,7,8,8a-decahydro-1,6-dioxoisoquinoline (6).** A mixture of the *N*-PNB dienophile (**4**, 715 mg, 2.90 mmol) and Danishefsky diene (**5**, 1.0 g, ~2 equiv) in degassed dry xylene (10 mL) was refluxed for 20 h under Ar. After being cooled to rt, the mixture was concentrated under reduced pressure to afford a crude residue, which was taken into THF (20 mL) and H_2O (10 mL) and treated with KF (0.6 g) at rt for 0.5 h. The mixture was diluted with CH_2Cl_2 (100 mL) and extracted. The organic layer was separated, washed with brine, and dried over Na_2SO_4. Evaporation of the dried solvent gave a residue (1.0 g), which was purified by SiO_2 column (100 g, AcOEt/*n*-hexane = 3/1) to afford the dioxoisoquinoline **6** (540 mg, 54%) as a yellow powder. **6**: mp 170–171.5 °C (AcOEt/*n*-hexane); IR (neat) 2950, 1700, 1690, 1680, 1520, 1380 cm^{-1}; LREIMS m/z 346 (M^+, 16), 150 (100); ^1H NMR (500 MHz) δ 1.91 (1 H, m, 4-H), 2.31 (1 H, m, 4-H), 2.50 (1 H, dd, J = 15.4, 3.3 Hz, 7-H), 2.54 (1 H, m, 5-H), 2.67 (1 H, dd, J = 14.5, 7.2 Hz, 5-H), 2.71 (1 H, m, 4a-H), 2.94 (1 H, dd, J = 15.3, 2.7 Hz, 7-H), 3.01 (1 H, dd, J = 7.1, 3.8 Hz, 8a-H), 3.41 (3 H, s, OMe), 3.72 (1 H, dt like, 3-H), 4.00 (1 H, dt, J = 13.2, 4.4 Hz, 3-H), 4.32 (1 H, m, 8-H), 7.71 (2 H, d, J = 8.5 Hz, aromatic), 8.24 (2 H, d, J = 8.3 Hz, aromatic), the stereochemistry of the 8-OMe group was determined by NOE experiments; i.e., no NOE was observed between 8-OMe and angular 8a-H, while a clear NOE was observed between 8-OMe and 7β-H; ^{13}C NMR (100 MHz) δ 27.32, 33.83, 42.21, 44.03, 44.96, 47.40, 56.84, 81.53, 123.43, 128.38, 142.15, 149.0, 172.61, 173.08, 206.90. Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.95; H, 5.24; N, 8.09. Found: C, 58.94; H, 5.23, N, 7.94.

***N*-(*p*-Toluenesulfonyl)-3-methyl-5,6-dihydro-2(1*H*)-pyridinone (10).** To a cooled (−60 °C) and stirred solution of the (phenylthio)piperidone **12c** (prepared as below, 365 mg, 1 mmol) in THF (10 mL) was added $KN(TMS)_2$ (0.5 M solution in toluene, 2.0 mL, 1 mmol) and the solution kept stirring at this temp for 15 min. To this lactam enolate was added CH_3I (0.2 mL) at this temperature, and the mixture was then gradually warmed to rt. The resulting yellow mixture was then diluted with H_2O–AcOEt and extracted with AcOEt (~100 mL). The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue (390 mg), which was treated with *m*-CPBA (218 mg, 80%) in CH_2Cl_2 (20 mL) at rt for 1 h. The mixture was diluted with saturated $NaHCO_3$(aq)–AcOEt and extracted with AcOEt (100 mL). The organic layer was washed with saturated $NaHCO_3$(aq) (10 mL) and brine (10 mL). Evaporation of the dried ($MgSO_4$) extracts gave a residue (350 mg), which was then taken into toluene (10 mL) and heated under reflux for 1 h. After the solvent was removed under reduced pressure, the crude product was purified by SiO_2 column (AcOEt/*n*-hexane = 1/2) to afford the pure 3-methyldihydropyridinone **10** (165 mg, 62%) as a white solid. **10**: IR 2950, 1670, 1650, 1600, 1170, 810 cm^{-1}; ^1H NMR (270 MHz) δ 1.79 (3 H, s, Me), 2.42 (3 H, s, Me), 2.50 (2 H, m, 5-CH_2), 4.05 (2 H, t, J = 6.6 Hz, 6-H), 6.54 (1 H, t like, olefinic), 7.32 (2 H, d, J = 8.2 Hz, aromatic), 7.92 (2 H, d, J = 8.2 Hz, aromatic); ^{13}C NMR (125.6 MHz) δ 16.40, 22.42, 25.09, 44.37, 128.47, 129.35, 131.51, 136.14, 138.97, 144.53, 164.41; LRFABMS m/z 266 (MH^+, 100); HRFABMS m/z calcd for $C_{13}H_{16}NO_3S$ (MH^+) 266.0851, found 266.0847.

8a-Methyl-2-(*p*-toluenesulfonyl)-*cis*-1,2,3,4,4a,5,6,8a-octahydro-1,6-dioxoisoquinoline (11). A mixture of the 3-methyldihydropyridinone **10** (195 mg, 0.73 mmol) and the diene **5** (2.6 mmol) in *p*-cymene (5 mL, distilled and degassed) was heated at gentle reflux for 3 h. TLC indicated some starting material remained at this stage, and a further amount of the diene **5** (0.3 mL) was added. Reflux was resumed for 2 h more. After the mixture was cooled to rt, most of the solvent was removed by evaporator to afford a residue, which was then taken into THF (10 mL) and treated with CSA (50 mg) under ice cooling for 1 h. The mixture was diluted with AcOEt–saturated $NaHCO_3$(aq) and extracted with AcOEt (~100 mL). The organic layer was separated and washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by SiO_2 column (50 g, AcOEt/*n*-hexane = 1/2) to afford the recovered dienophile **10** (30 mg, 15%) and the desired perhydroisoquinoline **11** (99 mg, 45%) as a white solid. **11**: mp 175–178 °C (AcOEt/*n*-hexane); IR 1680, 1350, 1165, 1090 cm^{-1}; ^1H NMR (500 MHz) δ 1.48 (3 H, s, Me), 1.90 (1 H, m, 4-H), 2.05 (1 H, m, 4-H), 2.37 (2 H, m, 4a, 5-H), 2.44 (3 H, s, Me), 2.66 (1 H, dd like, 5-H), 3.87 (1 H, m, 3-H), 4.05 (1 H, m, 3-H), 5.93 (1 H, d, J = 10.1 Hz, olefinic), 6.68 (1 H, dd, J = 10.1, 0.6 Hz, olefinic), 7.23 (2 H, d, J = 8.0 Hz, aromatic), 7.88 (2 H, d, J = 8.0 Hz, aromatic); ^{13}C NMR (125.65 MHz) δ 21.66, 24.93, 25.85, 38.63, 39.50, 45.29, 47.47, 128.15, 128.54, 129.45, 135.42, 145.10, 151.35, 172.72, 196.11; LREIMS m/z 333 (M^+, 10.5), 135 (100); HREIMS m/z calcd for $C_{17}H_{19}NO_4S$ (M^+) 333.1032, found 333.1029.

3-(Phenylthio)-2-piperidone (12a). A mixture of *N*-(methoxymethyl)-3-(phenylthio)-2-piperidone (**12b**, 3.69 g, 15 mmol, prepared from commercial 2-piperidone through N-methoxymethylation and sulfenylation by the method of Zoretic[9]) in EtOH (100 mL) and concd HCl (20 mL) was heated under reflux for 6 h. After being cooled to rt, the mixture was concentrated to evaporate most of EtOH. The concentrated mixture was then extracted with CH_2Cl_2 (200 mL) and washed with saturated $NaHCO_3$(aq) (30 mL × 2) and brine (30 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to afford a crude residue (2.50 g). Recrystallization of this material from AcOEt/*n*-hexane gave 3-(phenylthio)-2-piperidone (**12a**) as colorless crystals (2.37 g, 78%). **12a**: mp 110–111 °C (AcOEt/*n*-hexane); IR 3200, 2950, 1660 cm^{-1}; ^1H NMR (500 MHz) δ 1.70 (1 H, m, 5-H), 1.91–2.16 (3 H, m, 4, 5-H), 3.32 (2 H, m, 6-H), 3.82 (1 H, t like, 3-H), 6.15 (1 H, s, NH), 7.30–7.55 (5 H, m, aromatic); LREIMS m/z 207 (M^+, 66). Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.76; Found: C, 63.66; H, 6.31; N, 6.70.

***N*-(*p*-Toluenesulfonyl)-3-(phenylthio)-2-piperidone (12c).** To a cooled (−60 °C) and stirred mixture of *N*-tosyl-2-piperidone (3.50 g, 13.8 mmol) and diphenyl disulfide (3.40 g, 15.6 mmol) in dry THF (150 mL) was added $KN(TMS)_2$ (0.5 M solution in toluene, 55 mL, 27.5 mmol) dropwise by syringe. The resulting

mixture was then kept stirring at −60 °C for 0.5 h. After TLC analysis, the mixture was quenched by the addition of satured NH_4Cl(aq) (20 mL) and further with ether–AcOEt (1/1, ~100 mL). The organic layer was separated, and aqueous layer was extracted with AcOEt (~100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by SiO_2 column (300 g, AcOEt/*n*-hexane = 1/1) to afford the pure 3-(phenylthio)-2-piperidone (**12c**, 3.50 g, 70%) as a white solid. **12c**: mp 105 °C (MeOH); IR 2950, 1695, 1350, 1280, 1170 cm^{-1}; ^1H NMR (270 MHz) δ 1.90 (2 H, m, 5-CH_2), 2.10 (2 H, m, 4-CH_2), 2.44 (3 H, s, Me), 3.70 (1 H, t, J = 6.0 Hz, 6-H), 3.90 (2 H, m, 3, 6-H), 7.19–7.32 (7 H, m, aromatic), 7.91 (2 H, d, J = 8.25 Hz, aromatic); LRFABMS m/z 362 (MH^+, 100). Anal. Calcd for $C_{18}H_{19}NO_3S_2$: C, 59.75; H, 5.26; N, 3.87; Found: C, 59.91; H, 5.33; N, 3.66.

***N*-(Methoxycarbonyl)-*N*-methyldehydroalanine Methyl Ester (13, R = Me).** *N*-(Methoxycarbonyl)dehydroalanine methyl ester was prepared according to the method reported[12a] as follows.

To a cooled (0 °C) and stirred solution of *N*-(methoxycarbonyl)-DL-serine methyl ester (8.0 g, 45 mmol) in CH_2Cl_2 (60 mL) was added triethylamine (TEA, 13 mL) and MsCl (7 mL, 2.0 equiv), and the mixture was stirred at this temperature for 0.5 h. After TLC analysis, a further amount of TEA (15 mL) was added, and the mixture was stirred at rt for 1 h. The mixture was diluted with Et_2O (200 mL) and saturated $NaHCO_3$(aq) to obtain a clear organic layer. The organic layer was separated and washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by SiO_2 column (115 g, AcOEt/*n*-hexane = 1/1) to afford the *N*-(methoxycarbonyl)-dehydroalanine methyl ester (6.80 g, 96%).

To a stirred solution of the above prepared dehydroalanine methyl ester (4.0 g, 25 mmol) and Ag_2O (24 g, 100 mmol, 4 equiv) in DMF (160 mL) was added MeI (13 mL) at rt, and the mixture was warmed to 50–60 °C for 1 h. After TLC analysis, the mixture was diluted with CH_2Cl_2 (200 mL), and solid mass was filtered to obtain a clear yellow organic layer. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by SiO_2 column (50 g, AcOEt/*n*-hexane = 1/1) to afford the *N*-methyl-*N*-(methoxycarbonyl)dehydroalanine methyl ester (**13**, R = Me, 3.4 g, 80%) as a faint yellow oil. **13** (R = Me): IR (neat) 2950, 1720, 1630 cm^{-1}; ^1H NMR (500 MHz) δ 3.15 (3 H, s, NMe), 3.40 (3 H, s, OMe), 3.55 (3 H, s, OMe), 5.25 (1 H, s, vinyl), 6.00 (1 H, s, vinyl); ^{13}C NMR (125.65 MHz) δ 36.99, 52.39, 53.07, 118.76, 140.74, 155.56, 164.65; LRFABMS m/z 174 (MH^+, 100); HRFABMS m/z calcd for $C_{17}H_{12}O_4N$ (MH^+) 174.0766, found 174.0770.

***N*-(*tert*-Butoxycarbonyl)-*N*-methyldehydroalanine Methyl Ester (13, R = *t*-Bu).** *N*-(*tert*-Butoxycarbonyl)-dehydroalanine methyl ester was easily prepared from *N*-(*tert*-butoxycarbonyl)-DL-serine methyl ester via elimination of its mesylate.[12a] To a stirred solution of this dehydroalanine methyl ester (7.0 g, 34.8 mmol) and Ag_2O (9.0 g, 100 mmol, 4 equiv) in DMF (70 mL) was added MeI (16 mL) at rt, and the mixture was kept stirring overnight. After TLC analysis, the mixture was diluted with Et_2O (200 mL), and the solid mass was filtered to obtain a clear yellow organic layer. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by SiO_2 column (300 g, AcOEt/*n*-hexane = 1/4) to afford the *N*-methyl-*N*-(*tert*-butoxycarbonyl)dehydroalanine methyl ester (**13**, R = t-Bu, 6.10 g, 81.5%) as a faint yellow oil. **13** (R = t-Bu): 2980, 1730, 1710, 1630 cm^{-1}; ^1H NMR (500 MHz) δ 1.43 (9 H, s, *t*-Bu), 3.13 (3 H, s, NMe), 3.79 (3 H, s, OMe), 5.33 (1 H, s, vinyl), 5.80 (1 H, s, vinyl); ^{13}C NMR (125.65 MHz) δ 28.07, 36.61, 52.14, 81.08, 115.31, 141.52, 153.88, 165.33; LRFABMS m/z 216 (MH^+, 50), 160 (100); HRFABMS m/z calcd for $C_{10}H_{18}O_4N$ (MH^+) 216.1236, found 216.1242.

3-[2-(Methoxycarbonyl)-2-[*N*-(methoxycarbonyl)-*N*-methylamino]ethyl]-2-(*p*-toluenesulfonyl)-5,6-dihydro-2-(1*H*)-pyridinone (16). To a cooled (−60 °C) and stirred solution of the (phenylthio)piperidone **12c** (1.73 g, 4.79 mmol) in THF (50 mL) was added $KN(TMS)_2$ (1.73 g, solid, 1.75 mmol) in one portion, and stirring was continued at this temperature until a clear yellow solution was formed. To this solution was added dropwise a THF (10 mL) solution of the *N*-methyl-*N*-(methoxycarbonyl)dehydroalanine methyl ester (**13**, R = Me, 900 mg, 5.2 mmol). The resulting mixture was gradually warmed to −30 to −20 °C over 1 h, and at this temperature a further amount of $KN(TMS)_2$ (150 mg, 0.75 mmol) was delivered to ensure the reaction. After being stirred for an additional 1 h, the mixture was quenched by the addition of saturated NH_4Cl(aq) (10 mL) and warmed to rt. The mixture was then diluted with AcOEt (~150 mL), and the organic layer was separated. After being washed with brine (10 mL × 2), the organic layer was dried and concentrated. The residue thus obtained was purified by SiO_2 column (100 g, AcOEt/*n*-hexane = 1/1) to afford the Michael adduct **14** (1.84 g, 71.9%) as a yellow oil. **14**: IR (neat) 2950, 1740, 1695sh, 1440, 1330, 1160 cm^{-1}; ^1H NMR (270 MHz) δ as a mixture of diastereomers, 1.80 (2 H, m), 2.30 (1 H, m), 2.45 and 2.47 (3 H, s, Me), 2.69 and 2.71 (3 H, s, Me), 3.50–3.70 (2 H, m, aromatic), 7.89–7.95 (2 H, m, aromatic); LREIMS m/z 534 (M^+, 10), 503 (15).

The adduct obtained (**14**, 800 mg, 1.49 mmol) was then taken into CH_2Cl_2 (30 mL) and saturated $NaHCO_3$(aq) (10 mL), and the whole was cooled to 0 °C. To this mixture was added a CH_2Cl_2 (20 mL) solution of *m*-CPBA (500 mg, 80%, 2.3 mmol) slowly by pipette, and the resulting mixture was kept stirring under cooling for 0.5 h. The mixture was diluted with AcOEt (200 mL)–saturated $NaHCO_3$(aq) (10 mL), and the organic layer was separated. The organic layer was further washed with brine (20 mL) and dried over $MgSO_4$. Evaporation of the solvent gave a residue (800 mg), which was purified by SiO_2 column (50 g, ether) to afford the dienophile **16** (556 mg, 88.0%). **16**: IR (neat) 2950, 1740, 1680, 1595, 1450 cm^{-1}; ^1H NMR (270 MHz) δ as a mixture of rotamers 2.43 (3 H, s, Me), 2.50 (2 H, m, CH_2), 2.66 and 2.99 (3 H, each s, Me), 2.90 (2 H, m, CH_2), 3.64, 3.66 and 3.67 (6 H, each s, OMe), 3.90 (1 H, m, CHNTs), 4.10 (1 H, m, CHNTs), 4.60 and 4.69 (1 H, m, CHCOOMe), 6.53 and 6.61 (1 H, t like, olefinic), 7.32 (2 H, d, J = 7.6 Hz, aromatic), 7.91 (2 H, m, aromatic); LREIMS m/z 424 (M^+, 2), 393 (25); HREIMS m/z calcd for $C_{19}H_{24}N_2O_7S$ (M^+) 424.1298, found 424.1299.

8a-[2-(Methoxycarbonyl)-2-[*N*-(methoxycarbonyl)-*N*-methylamino]ethyl]-2-(*p*-toluenesulfonyl)-*cis*-1,2,3,4,4a,5,6,8a-octahydro-1,6-dioxoisoquinoline (18). A mixture of the dihydropyridinone (**16**, 390 mg, 0.91 mmol) and the diene (**5**, 1.0 mL) in *p*-cymene (4 mL, distilled and degassed) was heated at 220–250 °C (bath temp) for 3 h under Ar. After TLC analysis, a further amount of the diene (**5**, 0.5 mL) was added to ensure completion of the reaction, heating was resumed under reflux for 2 h, and the resulting orange mixture was cooled to rt. Most of the solvent and reagent were removed by evaporator (70–80 °C, bath temperature) and finally vacuum pump to afford a residue, which was taken into THF (20 mL) and treated with CSA (20 mg) at rt for 2 h. To ensure completion of the reaction, a further amount of CSA (20 mg) was added and stirring was continued for 1 h. The resulting dark mixture was diluted with AcOEt (100 mL)–saturated NH_4Cl(aq) (20 mL) and extracted with AcOEt. The organic layer was separated and neutralized with saturated $NaHCO_3$(aq) (20 mL × 2) and washed with brine. After evaporation of the dried ($MgSO_4$) solvent, the residue was purified by SiO_2 column (50 g, AcOEt/*n*-hexane = 1/2) to afford the desirable perhydroisoquinoline (**18**, 120 mg, 26.8%) along with the recovered starting material (**16**, 210 mg, 53.8%) as a yellow oil. **18**: IR (neat) 2950, 1740, 1685, 1600, 1360, 1300, 1170, 1090 cm^{-1}; ^1H NMR (270 MHz) δ as a mixture of diastereoisomers 1.88 (1 H, m, 4-H), 2.30 (2 H, m, CH_2), 2.43 (3 H, s, Me), 2.62 (3 H, s, NMe), 2.75 (2 H, m, CH_2), 3.70 (3 H, m, CH_2, CH), 3.72 (3 H, s, OMe), 3.78 (3 H, s, OMe), 4.10 (2 H, m, CH_2NTs), 5.22 (1 H, dd like, CHCOOMe), 5.91 (1 H, d, J = 10.2 Hz, olefinic), 6.46 (1 H, dd, J = 10.2, 2.0 Hz, olefinic), 7.31 (2 H, d, J = 8.2 Hz, aromatic), 7.84 (2 H, d, J = 8.2 Hz, aromatic); LRFABMS m/z 439 (MH^+, 93); HRFABMS m/z calcd for $C_{23}H_{29}N_2O_8S$ (MH^+) 493.1637, found 493.1639.

Tricyclic Carbamate 19 via the Reaction of 18 with TMSI. To a stirred solution of the enone (**18**, 120 mg, 0.24 mmol) in $CHCl_3$ (distilled, 5 mL) was added TMSI (0.2 mL) at rt, and the resulting mixture was heated under reflux for 2 h. After TLC analysis, the mixture was diluted with CH_2Cl_2 (50 mL) and saturated $NaHCO_3$(aq) (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic layers were washed with brine (10 mL × 2) and dried over K_2CO_3–$MgSO_4$. Evaporation of the solvent gave a

residue, which was purified by SiO_2 column (30 g, ether) to afford, from the less polar fraction, the recovered starting material (18, 20 mg, 16.6%) and, from the more polar fraction, the tricyclic carbamate (19, 60 mg, 57.5%) as a yellow amorphous solid. 19: IR 2950, 1740, 1695, 1480, 1355, 1170 cm^{-1}; ^1H NMR (500 MHz) δ 1.80 (2 H, m, CH_2), 1.90–2.50 (2 H, m, CH_2), 2.20 (2 H, m, CHCO, CH), 2.43 (3 H, s, Me), 2.54 (3 H, s, Me), 2.60 (2 H, m, CH_2CO), 2.95 (1 H, m), 3.65 (2 H, m, CH_2NTs), 3.73 (s, 3 H, OMe), 4.17 (1 H, m, CHCOOMe), 5.05 (1 H, t, J = 8.0 Hz, 7a-H), 7.31 (2 H, d, J = 8.5 Hz, aromatic), 7.83 (2 H, d, J = 8.5 Hz, aromatic); ^{13}C NMR (125.65 MHz) δ 21.60, 26.37, 30.91, 33.77, 35.53, 37.14, 42.52, 45.14, 45.37, 52.60, 53.27, 55.32, 128.34, 129.27, 136.19, 144.65, 158.25, 171.12, 172.67, 208.66; LREIMS m/z 479 (M^+, 0.5), 435 (13.8), 346 (18.0), 321 (100); HREIMS m/z calcd for $C_{22}H_{27}N_2O_9S$ (M^+) 479.1489, found 479.1489. (The presence of the other isomer was not clearly detected and the stereochemistry of C-7a could not be assigned.)

3-[2-(Methoxycarbonyl)-2-[*N*-(*tert*-butoxycarbonyl)-*N*-methylamino]ethyl]-2-(*p*-toluenesulfonyl)-5,6-dihydro-2-(1*H*)-pyridinone (17). To a cooled (−25 °C) and stirred solution of the 3-(phenylthio)piperidone 12c (4.32 g, 12.0 mmol) and 18-crown-6 (0.7 g) in dry THF (100 mL) was added $KN(TMS)_2$ (0.5 M solution in toluene, 12.5 mL, 6 mmol, 0.5 equiv) by syringe, and the mixture was kept stirring for 5 min. To this mixture was then added the amidoacrylate 13 (R = *t*-Bu, 2.56 g, 12.2 mmol), and stirring was continued for 1 h at this temperature. After being checked by TLC, the mixture was diluted with saturated NH_4Cl(aq) (30 mL) at this temperature and extracted with AcOEt (~200 mL). The organic layer was separated, washed with brine, and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by SiO_2 column (120 g, AcOEt/*n*-hexane = 1/4) to afford the Michael adduct (15, 6.25 g, 90.5%) as a colorless amorphous solid. 15: IR 2980, 1730, 1700, 1685, 1595, 1470, 1440, 1160, 1080 cm^{-1}; ^1H NMR (500 MHz) δ as a mixture of diastereomers 1.40–1.50 (~8.5 H, m), 1.60 (2.5 H, m), 1.90–2.00 (3.5 H, m), 2.24–2.47 (6 H, Me × 2), 2.65 (2 H, m), 3.58–4.38 (1 H, m), 7.30–7.90 (9 H, m, aromatic); LRFABMS m/z 577 (MH^+, 17), 521 (5.8), 477 (100); HRFABMS m/z calcd for $C_{28}H_{37}O_7N_2S_2$ (MH^+) 577.2042, found 577.2035.

To a suspension of the above Michael adduct (15, 1.18 g, 2.04 mmol) in CH_2Cl_2 (50 mL) and saturated $NaHCO_3$(aq) (20 mL) was added slowly a CH_2Cl_2 (50 mL) solution of *m*-CPBA (600 mg, 2.7 mmol) over 1 h with ice cooling (0 °C). After TLC analysis, the mixture was diluted with AcOEt (~150 mL)–saturated $NaHCO_3$(aq) (20 mL), and the organic layer was separated. The organic extracts were washed with brine and dried over $MgSO_4$. Concentration of the solvent gave a residue, which was purified by SiO_2 column (50 g, AcOEt/*n*-hexane = 1/2) to afford the dienophile 17 (778.6 mg, 80%) as a colorless amorphous solid. 17: IR 2950, 1730, 1700, 1680, 1585, 1380, 1360, 1080 cm^{-1}; ^1H NMR (500 MHz) δ as a mixture of rotamers 1.36 (4.5 H, s, *t*-Bu), 1.41 (4.5 H, s, *t*-Bu), 2.42 (3 H, s, Me), 2.50 (2 H, m, CH_2), 2.59 (1.5 H, s, Me), 2.63 (1.5 H, s, Me), 2.80 (2 H, m, CH_2), 3.66 (1.5 H, s, OMe), 3.67 (1.5 H, s, OMe), 4.00 (2 H, m, CH_2NTs), 4.40 (0.5 H, m, CHCOOMe), 4.53 (0.5 H, m, CHCOOMe), 6.56 (0.5 H, t like, olefinic), 6.61 (0.5 H, t like, olefinic), 7.31 (2 H, d, J = 8.25 Hz, aromatic), 7.91 (2 H, J = 8.25 Hz, aromatic); LRFABMS m/z 467 (MH^+, 4.5), 411 (19.8), 367 (100); HRFABMS m/z calcd for $C_{22}H_{31}O_7N_2S$ (MH^+) 467.1852, found 467.1856.

***rac*-Methyl (2*R**,3a*S**,6a*S**,10a*S**)-3-Methyl-5,10-dioxo-9-(*p*-toluenesulfonyl)-1,2,3,3a,4,5,6,6a,7,8,9,10-dodecahydropyrrolo[2,3-*i*]isoquinoline-2-carboxylate (21b) and Its 2-Epimer 21a. 1. Diels–Alder Reaction of 17 under Usual Thermal Conditions.** A mixture of the dihydropyridinone (17, 122 mg, 0.26 mmol) and the diene (5, 0.4 mL) in *p*-cymene (3 mL, distilled and degassed) was heated at 200–220 °C (bath temperature) for 3 h under Ar, after which the resulting orange mixture was cooled to rt. Most of the solvent and excess 5 were removed by evaporator (70~80 °C, bath temp) and finally vacuum pump to afford a residue, which was taken into THF (10 mL) and treated with CSA (50 mg) at rt for 2 h. The resulting dark mixture was diluted with AcOEt (100 mL)–saturated NH_4Cl(aq) (10 mL) and extracted with AcOEt. The organic layer was separated and neutralized with saturated $NaHCO_3$(aq) (10 mL × 2) and washed with brine. After evaporation of the dried ($MgSO_4$) solvent, the residue was purified by SiO_2 column (20 g, AcOEt/*n*-hexane = 1/2) to afford the perhydroisoquinoline 20 (54 mg, 30%) along with the recovered starting material 17 (38 mg, 31%). 20: IR (neat) 2960, 1740, 1680, 1360, 1360, 1165, 1090 cm^{-1}; ^1H NMR (270 MHz) δ as a mixture of diasteromers and rotamers 1.25 (9 H, s, *t*-Bu), 2.43 (3 H, s, Me), 2.58 (3 H, s, NMe) 3.76 (3 H, s, OMe), 4.12–4.15 (2 H, m), 5.15 (1 H, dd like) 5.89 (1 H, d, J = 10.1 Hz, olefinic), 6.41 (1 H, dd like, olefinic), 7.30 (2 H, d, J = 7.9 Hz, aromatic), 7.84 (2 H, d, J = 7.9 Hz, aromatic); LREIMS m/z 535 (M^+, 0.2), 434 (1.9), 375 (37.5), 279 (100).

2. High-Pressure Diels–Alder Reaction of 17. A mixture of the dienophile 17 (350 mg, 0.75 mmol) and the diene 5 (1 mL) in a 5-mL Teflon tube, which was filled with toluene, was subjected to high-pressure conditions (11 kbar) for 90 h at ambient temperature. After the pressure was released, the reaction mixture was transferred to a 50-mL round-bottomed flask to remove most of the solvent and reagent by evaporator (70–80 °C, bath temperature) and finally by vacuum pump. The residue obtained was taken into THF (25 mL) and treated with CSA (220 mg) at rt for 1 h. The mixture was diluted with saturated $NaHCO_3$(aq)–AcOEt and extracted with AcOEt (~100 mL). The organic layer was separated and then successively washed with saturated $NaHCO_3$(aq) and brine. After the organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure to afford a residue, which was purified by SiO_2 short column (50 g, AcOEt/*n*-hexane = 1/1) to afford crude enone 20 (548 mg).

To a stirred solution of the crude enone (526 mg) in CH_2Cl_2 (20 mL) was added trifluoroacetic acid (2.5 mL) at rt, and the mixture was stirred at rt for 3 h to remove the *N*-Boc group. After TLC analysis, the mixture was quenched with saturated $NaHCO_3$(aq) (10 mL) and then with K_2CO_3 to basify the mixture. The resulting suspension was kept stirring for 3 h, and no further change was observed on TLC. The mixture was diluted with CH_2Cl_2 (200 mL) and extracted with CH_2Cl_2. The organic layer was separated and washed with brine (20 mL) and dried over $MgSO_4$. Evaporation of the solvent gave a residue (414 mg), which was repeatedly purified by SiO_2 column (AcOEt/*n*-hexane = 2/1) to afford the tricyclic pyrroloisoquinoline 21 (195 mg total, 60% from 17, 62 mg of pure 21a, 62 mg of pure 21b, and 50 mg of mixture). 21a: mp 212–214 °C (CH_2Cl_2–Et_2O); IR 1740, 1720, 1685, 1345, 1270, 1165 cm^{-1}; ^1H NMR (500 MHz) δ 1.81 (1 H, m, 7-H), 2.12 (2 H, m, 6, 4-H), 2.22 (2 H, m, 4, 7-H), 2.29 (3 H, s, NMe), 2.35 (2 H, m, 4a, 1-H), 2.40 (1 H, m, 1-H), 2.44 (3 H, s, Me), 2.59 (1 H, m, 6-), 3.18 (1 H, dd, J = 9.2, 6.6 Hz, 3a-H), 3.32 (1 H, t, J = 4.3 Hz, 2-H), 3.70 (3 H, s, OMe), 3.89 (1 H, m, 8-H), 4.09 (1 H, m, 8-H), 7.33 (2 H, d, J = 8.5 Hz, aromatic), 7.88 (2 H, d, J = 8.5 Hz, aromatic); ^{13}C NMR (125.6 MHz) δ 21.69, 24.53, 33.41, 36.67, 39.21, 39.49, 41.63, 42.67, 51.57, 52.53, 62.70, 65.88, 128.59, 129.49, 135.62, 145.08, 172.15, 172.96, 208.52; LREIMS m/z 434 (M^+, 4.5), 375 (19.5), 279 (100); HREIMS m/z calcd for $C_{21}H_{26}N_2O_6S$ (M^+) 434.1505, found 434.1504. Anal. Calcd for $C_{21}H_{26}N_2O_6S$: C, 58.04; H, 6.04; N, 6.45; Found: C, 57.80; H, 5.99; N, 6.34.

Crystal data for 21a ($C_{21}H_{26}N_2O_6S$; MW = 434): orthorhombic, space group $P2_1/c$, a = 13.569 (17) Å, b = 12.391 (13) Å, c = 12.726 (20) Å; β = 104.72 (9)°; cell volume 2046.7 Å^3, Z = 4; D_{calcd} = 1.410 g cm^{-3}. Lattice constants and intensity data were measured using graphite-monochromated Cu Kα (λ = 1.5417 Å) radiation on a Rigaku AFC-5 diffractometer. A total of 3240 unique reflections with $F(o) > 3\sigma F(o)$ were obtained using $\omega \leq 30° \leq \omega - 2\theta$ scanning method with a 2θ scan speed of 4° min^{-1} to $3° < 2\theta < 120°$. The structure was solved by the UNICS-III system MULTAN 80 (Library of Computer Center of Tokyo University, Sakurai, T.; Kobayashi, K. *Rep. Inst. Phys. and Chem. Res.* **1979**, *55*, 69) based on direct methods and refined to a final R value of 0.0525.

21b: mp 185–187 °C (CH_2Cl_2–Et_2O); IR 1735, 1710, 1675, 1345, 1190, 1160 cm^{-1}; ^1H NMR (500 MHz) δ 1.82 (1 H, m, 7-H), 2.17 (2 H, m, 4, 6-H), 2.22 (4 H, m, 1, 4, 6a, 7-H), 2.30 (3 H, s, NMe), 2.35 (1 H, m, 1-H), 2.40 (1 H, m, 6-H), 2.44 (3 H, s, Me) 3.66 (3 H, s, OMe), 3.78 (1 H, dd, J = 8.4, 5.6 Hz, 3a-H), 3.89 (1 H, m, 8-H), 3.99 (1 H, t, J = 3.5 Hz, 2-H), 4.09 (1 H, m, 8-H), 7.32 (2 H, d, J = 8.5 Hz, aromatic), 7.90 (2 H, d, J = 8.5 Hz, aromatic); ^{13}C NMR (125.6 MHz) δ 21.71, 24.68, 36.06, 38.76, 39.74, 39.92, 41.24, 43.07, 52.17, 52.23, 65.98, 68.46, 128.50, 129.53, 135.58, 144.17, 172.74, 173.16, 207.78; LREIMS m/z 434 (M^+, 18.0), 375 (14.5), 279 (100); HREIMS m/z calcd for $C_{21}H_{26}N_2O_6S$ (M^+) 434.1505,

found 434.1542. Anal. Calcd for $C_{21}H_{26}N_2O_6S$: C, 58.04; H, 6.04; N, 6.45. Found: C, 58.16; H, 6.00; N, 6.37.

***rac*-Methyl (2*R**,3a*S**,6a*S**,10a*S**)-3-Methyl-5,10-dioxo-9-(*p*-toluenesulfonyl)-1,2,3,3a,4,5,6,6a,7,8,9,10-dodecahydropyrrolo[2,3-*i*]isoquinoline-2-carboxylate 5-Ethylene Ketal (22).** A mixture of the ketone **21b** (653 mg, 1.5 mmol), ethylene glycol (620 mg, 10 mmol), and $TsOH·H_2O$ (65 mg) in dry benzene (25 mL) was heated under reflux for 13 h with continuous removal of water. The mixture was quenched by the addition of saturated $NaHCO_3$(aq) (10 mL) and extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4, followed by evaporation of the solvent to give a crude residue (720 mg). Crystallization of this material from AcOEt/*n*-hexane (1.5/1) afforded almost pure ketal **22** (418 mg). The mother liquor was concentrated and purified by SiO_2 column (5.0 g, AcOEt/*n*-hexane = 1/5) to afford a further amount of the desired ketal **22** (150 mg, total yield 568 mg, 79%). **22**: mp 171.5–172.5 °C (CH_2Cl_2–AcOEt); IR 2950, 1730, 1680, 1600, 1350, 1160 cm^{-1}; ^1H NMR (500 MHz) δ 1.35 (1 H, t, J = 13.4 Hz, 6a-H), 1.42 (1 H, dd, J = 15.4, 4.6 Hz, 4-H), 1.61 (1 H, dt, J = 13.4, 3.3 Hz, 6-H), 1.75 (1 H, m, 7-H), 1.85 (1 H, dt, J = 15.4, 3.3 Hz, 4-H), 2.02 (1 H, dd, J = 13.4, 4.3 Hz, 1-H), 2.24–2.34 (3 H, m, 1, 6, 7-H), 2.38 (3 H, s, NMe), 2.44 (3 H, s, Me) ,3.64 (3 H, s, OMe), 3.75 (1 H, td, J = 12.2, 5.1 Hz, 8-H), 3.84–3.98 (6 H, m, OCH_2CH_2O, 3a, 2-H), 4.12 (1 H, m, 8-H), 7.30 (2 H, d, J = (8.3 Hz, aromatic), 7.87 (2 H, d, J = 8.3 Hz, aromatic); LRFABMS m/z 479 (MH^+, 100); HRFABMS m/z calcd for $C_{23}H_{31}O_7N_2S$ (MH^+) 479.1852, found 479.1857. Anal. Calcd for $C_{23}H_{30}O_7N_2S$: C, 57.53; H, 6.32; N, 5.85; Found: C, 57.62; H, 6.26; N, 5.69.

***rac*-Methyl (2*R**,3a*S**,6a*S**,10a*S**)-3-Methyl-5,10-dioxo-1,2,3,3a,4,5,6,6a,7,8,9,10-dodecahydropyrrolo[2,3-*i*]isoquinoline-2-carboxylate 5-Ethylene Ketal (23).** Sodium naphthalenide was prepared by stirring a mixture of sodium metal (209 mg, 9 mmol) and naphthalene (1.53 g, 12 mmol) in dry DME (20 mL) under Ar at rt for 2 h. To a cooled (−78 °C) and stirred solution of the *N*-Ts ketal (**22**, 400 mg, 0.83 mmol) in DME (20 mL) was added dropwise the above-prepared sodium naphthalenide solution by cannula until a blue color persisted (6 mL). After TLC analysis, the mixture was quenched by the addition of saturated NH_4Cl(aq) to obtain a neutral aqueous layer, which was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvents gave a residue (540 mg), which was purified by SiO_2 column (5.4 g, AcOEt) to afford the pure NH compound **23** (140 mg, 52%) as a white solid. **23**: mp 196.5–197 °C (CH_2Cl_2–AcOEt); IR 3300, 2950, 1730, 1650 cm^{-1}; ^1H NMR (500 MHz) δ 1.58–1.97 (4 H, m, 1, 6, 6a-H), 2.03 (1 H, d, J = 12.0 Hz, 1-H), 2.15 (2 H, m, 4, 7-H), 2.29 (2 H, m, 4, 6-H), 2.45 (3 H, s, NMe), 3.28 (1 H, m, 8-H), 3.41 (1 H, m, 8-H), 3.67 (3 H, s, OMe), 3.72–4.00 (6 H, m, OCH_2CH_2O, 2, 3a-H), 5.76 (1 H, brs, NH); LREIMS m/z 324 (M^+), 265 (100). Anal. Calcd for $C_{16}H_{24}N_2O_5$: C, 59.24; H, 7.46; N, 8.64. Found: C, 59.49; H, 7.49; N, 8.56.

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Registry No. **1**, 104196-68-1; **4**, 132143-27-2; **4** (R = H), 6052-73-9; **5**, 54125-02-9; (±)-**6**, 132143-30-7; **10**, 130291-45-1; (±)-**11**, 143076-11-3; (±)-**12a**, 143076-12-4; (±)-**12c**, 143076-20-4; **13** (R = Me), 130291-56-4; **13** (R = Bu-*t*), 56776-34-2; (±)-**14** (isomer 1), 143076-13-5; (±)-**14** (isomer 2), 143076-22-6; (±)-**15** (isomer 1), 143076-14-6; (±)-**15** (isomer 2), 143076-24-8; (±)-**16**, 143076-15-7; (±)-**17**, 143076-16-8; (±)-**18** (isomer 1), 143104-23-8; (±)-**18** (isomer 2), 143076-23-7; **19**, 130291-53-1; (±)-**20** (isomer 1), 143076-17-9; (±)-**20** (isomer 2), 143076-25-9; (±)-**21a**, 143167-08-2; (±)-**21b**, 143167-09-3; (±)-**22**, 143076-18-0; (±)-**23**, 143076-19-1; CH_2=C(COOMe)NHCOOMe, 76637-56-4; CH_2=C(COOMe)NHCOOBu-*t*, 55477-80-0; Ph_2S_2, 882-33-7; *N*-(methoxycarbonyl)-DL-serine methyl ester, 143076-21-5; *N*-tosyl-2-piperidone, 23438-61-1.

Supplementary Material Available: High-resolution ^1H NMR spectra of compounds **10**, **11**, **13**, and **16–21** and ^{13}C NMR spectra of **11**, **13**, **19**, and **21** (17 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.

Tandem Cyclization–Cycloaddition Reaction of Rhodium Carbenoids. Studies Dealing with Intramolecular Cycloadditions

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A series of 5-alkenyl-1-diazo-2,5-pentanediones, when treated with a catalytic quantity of rhodium(II) acetate, were found to give cycloadducts derived from the intramolecular trapping of a carbonyl ylide intermediate. Tethers of three or four methylenes readily enter into intramolecular cycloaddition, while longer and shorter tethers were reluctant to do so. Alkenes attached to the formally cationic terminus of the carbonyl ylide readily undergo internal cycloaddition if the tether allows for a relatively strain-free transition state. The internal cycloaddition reaction does not occur when the olefinic side chain is attached by means of an ester functionality. Bimolecular trapping experiments established that carbonyl ylide formation occurred, but the dipole does not undergo intramolecular cycloaddition. The inability of these α-diazo keto esters to undergo internal cycloaddition is related to conformational factors. The equilibrium between the two possible conformations of the dipole lies predominantly on the side of the *Z*-isomer. In this orientation, intramolecular dipolar cycloaddition cannot occur, and instead the dipole collapses by means of a proton transfer to give an enol ether.

A major challenge in organic synthesis today is to devise reactions that can form several carbon–carbon bonds in one operation leading to the construction of polycyclic structures with proper regio- and stereochemical control. The predictability and selectivity with which intramolecular 4 + 2-cycloaddition reactions occur has led to their widespread use in organic synthesis. Intramolecular Diels–Alder cycloadditions have been particularly useful in natural product synthesis since this reaction results in the formation of an extra ring and exhibits increased re-

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