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Synthesis of the Chiral (8*S*)-7-Aza-1,3(*E*),9-decatriene System from Natural α-Amino Acids and Its Intramolecular Diels–Alder Reaction Directed toward Chiral *trans*-Hydroisoquinolones

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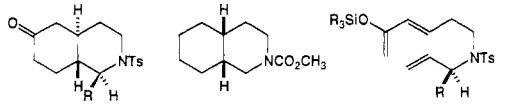
L-Alanine and L-valine were converted into optically active 7-aza-1,3(*E*),9-decatrienes containing a (*tert*-butyldimethylsilyl)oxy group at C(2) and a methyl or isopropyl group at C(8). Intramolecular thermal [4 + 2] cycloaddition reactions of these trienes gave optically active *trans*-nonahydro-6(2*H*)-isoquinolones. The relatively bulky isopropyl group at C(8) increased the trans selectivity in the ring closure. These results are in contrast with literature reports on ring closure of analogous aza trienes that lack the (*tert*-butyldimethylsilyl)oxy group at C(2), which give predominantly cis-fused rings.

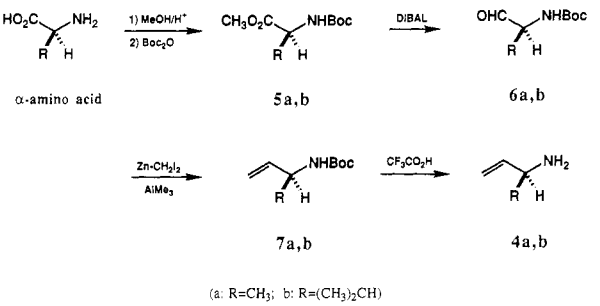
Trans-fused hydroisoquinoline frameworks are frequently encountered in bioactive alkaloids such as yohimbine, levonantradol, and modified dopamine agonists.[1] We have been interested in the synthesis of the trans-fused hydroisoquinolone skeleton **1** by intramolecular [4 + 2] cycloaddition of substituted azatrienes.[2] Oppolzer,[3] Martin,[4] and others[5] have used the intramolecular Diels–Alder reaction of amino or amido trienes to gain access to cis-fused hydroisoquinoline derivatives such as **2**, which are also building blocks for the total synthesis of alkaloids with such a structural array.[4]



1 **2** **3**

Although most reports on the intramolecular thermal [4 + 2] cycloaddition reaction of aza trienes indicate a cis addition, both cis and trans ring junctions can result depending on the choice of diene geometry and stereoelectronic effects.[2-5] A practical trans-selective cycloaddition has not previously been achieved. We wished to examine whether modification of the diene structure and introduction of a chiral center at C(8) in **3** could affect the stereochemical outcome of its intramolecular [4 + 2] cycloaddition reaction. In particular, we hoped to establish whether the alkyl substituent at C(8) of **3** can cause the preferential formation of a *trans*-isoquinolone rather than the cis isomer.

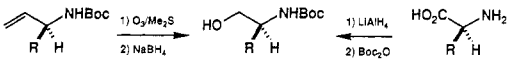
Scheme I



α-amino acid **5a,b** **6a,b** **7a,b** **4a,b**

(a: R=CH_3; b: R=$(CH_3)_2CH$)

Scheme II



7 **8** L-α-amino acid

Results and Discussion

Synthesis of Substrates. We have reported on the synthesis of the chiral allylamines **4** without any detectable reacemization (Scheme I).[6] The N-protected amino ester **5** is reduced to aldehyde **6** followed by olefination of the carbonyl group. It was necessary to olefinate **6** without racemization of the chiral center. However, owing to the basicity of traditional olefinating reagents, such as the Wittig reagent, amino aldehyde **6** enolizes with such reagents and racemizes in such an olefination.[7] Luly et

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(5) (a) Cox, M. T. J. *J. Chem. Soc., Chem. Commun.* **1975**, *903*. (b) Cannon, J. G.; Lee, T.; Hsu, F. L.; Long, J. P.; Flynn, J. R. *J. Med. Chem.* **1980**, *23*, 502. (c) Ciganek, E. *J. Am. Chem. Soc.* **1981**, *103*, 6261. (d) Wattanasin, S.; Kasawala, F. G.; Boeckmann, R. K., Jr. *J. Org. Chem.* **1985**, *50*, 3810. (e) Martin, S. F.; Grzejszczak, S.; Ruger, H.; Williamson, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 4072.

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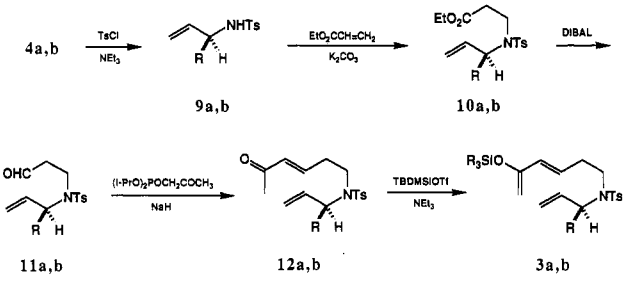
0022-3263/89/1954-4114$01.50/0

Scheme III

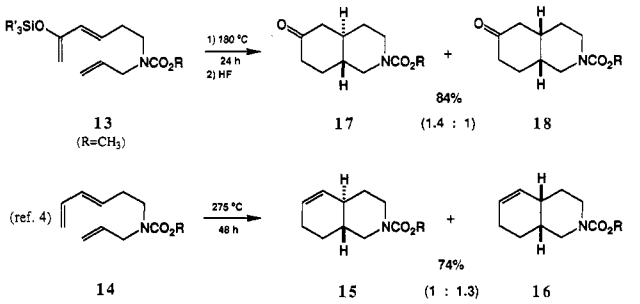


al.[8] reported the one-pot two-stage transformation of N-protected amino esters to nonracemized allylamines at −78 °C by reduction and Wittig condensation. However, use of their procedure on **5** afforded the allylamines **7** with very low optical purity. Application of the Peterson reaction[9] to **6**, using (trimethylsilyl)methyl Grignard reagent, did not bring about the desired β-elimination but rather 1,3-silyl migration,[10] giving a mixture of products. We finally found that the Nozaki–Ohshima reagent,[11] generated in situ from a combination of zinc, trimethylaluminum, and diiodomethane, converted **6** into **7** without racemization (Scheme I).[6]

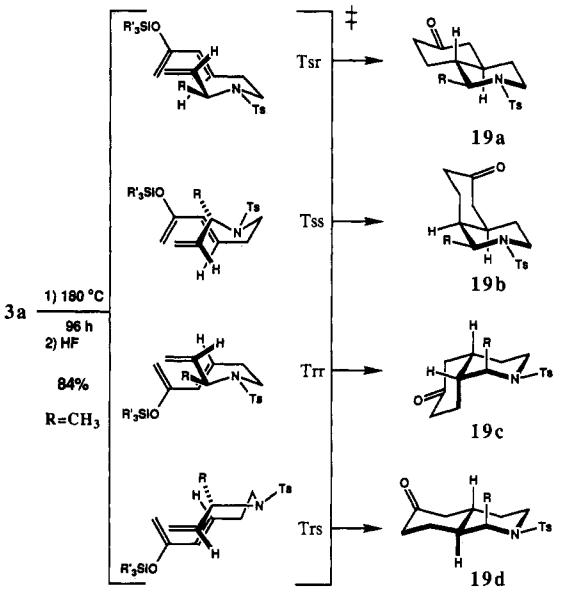
The optical purity of **7** obtained by this method was shown to be >99% by ozonolysis and ensuing reduction with $NaBH_4$, and comparison of the $[\alpha]_D$ value of amino alcohol **8** with that of an authentic sample derived from an L-α-amino acid (Scheme II).

The synthetic route to **3** from the optically pure allylamines **4** is outlined in Scheme III. Deprotection of the *N*-Boc group of **7a** with trifluoroacetic acid in dichloromethane afforded quantitatively the corresponding ammonium salt, which was directly converted into *p*-toluenesulfonamide **9a**. Michael addition of **9a** to a slight excess of ethyl acrylate led to the amino ester **10a** (83% from **7a**). N-Alkylation of **9a** with ethyl 3-bromopropanoate also provided **10a** but in somewhat lower yield (74%). The ester group of **10a** was reduced with diisobutylaluminum hydride[12] to the corresponding aldehyde **11a** (90%), which was condensed with the sodium salt of diisopropylphosphonoacetone in THF, giving rise to azadecadienone **12a** in 87% yield. The enone moiety of **12a** was shown to be >98% *E* by ^1H NMR analysis. Finally, the enone was converted into the enol silyl ether **3a** in 93% yield by treatment with *tert*-butyldimethylsilyl triflate and triethylamine in ether.[13] The spectral data for **3a** (^1H, ^{13}C, H COSY, and C–H COSY) were in accord with the indicated structure. The L-valine analogue, (**3b**, R = *i*-C_3H_7) was prepared in the same way in a similar yield.

Scheme IV



Scheme V



(**19a** : **19b** : **19c** : **19d** = 3 : 2 : 1 : 2.2)

To test the effect of a silyloxy group at C(2) on the steric course of the intramolecular [4 + 2] cycloaddition, aza triene **13** was prepared through essentially the same route as that for **3** (Scheme III). However, the N-protective CO_2CH_3 group was introduced after the Michael addition of allylamine to ethyl acrylate.[14] The stereochemistry of the diene moiety was verified to be >98% *E* by ^1H NMR spectroscopy.

Intramolecular Diels–Alder Reactions. The 7-aza triene **14**, which lacks the (*tert*-butyldimethylsilyl)oxy (TBDMSO) group at C(2), has been reported to give *trans*- and *cis*-octahydroisoquinolines **15** and **16** in the ratio 1:1.3 (Scheme IV).[4] Accordingly, the stereochemical outcome of the intramolecular [4 + 2] cycloaddition reaction of **13** should indicate whether or not the TBDMSO group can enhance trans selectivity.

A sealed ampule containing a degassed solution of **13** in toluene was heated at 180 °C for 24 h, and the products were purified by short-path column chromatography on silica gel. Treatment of the products with HF in CH_3CN gave the *trans*- and *cis*-hydroisoquinolones **17** and **18** (84%) in the ratio 1.4:1 (Scheme IV).

Although it was not possible to determine the relative stereochemistry of **17** and **18** by ^1H NMR spectroscopy, an X-ray crystallographic analysis of **18** confirmed that it

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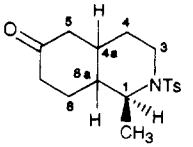
Table I. Principal NMR Data for the Cycloadducts 19a–d[a]



product	CH_3		H(8a)		H(4a)	
	^{13}C δ, ppm	orient.[b]	$J_{H(1)-H(8a)}$, Hz	orient.[b]	$J_{H(8a)-H(4a)}$, Hz	orient.[b]
19a	18.5	e	8.4	a	8.8	a
19b	19.2	e	3.6	e	3.8	a
19c	15.7	a	1.1	e	3.8	a
19d	11.0	a	2.0	a	10	a

[a] Taken on a Varian VXR-500 instrument: 500 MHz for proton and 126 MHz for carbon-13. [b] For the nitrogen-containing six-membered ring: a = axial and e = equatorial.

is the cis isomer. Thus the isomeric ratio obtained in the cycloaddition of **14**[4] was reversed, indicating that the TBDSMO group at C(2) of **13** provides some enhancement of the trans ring-forming pathway. However, because of the high cyclization temperature (275 °C) used for **14**, its intramolecular Diels–Alder reaction may be thermodynamically controlled; consequently, an evaluation of the TBDSMO effect simply on the basis of the isomer ratio seems meaningless. In fact, **13** decomposed at 275 °C, so we could not determine whether or not its cycloaddition is kinetically controlled under the given reaction conditions. In a practical sense, however, the silyloxy diene moiety highly enhances the reactivity of **13** in its intramolecular Diels–Alder reaction: **13** required 24 h at 180 °C for the completion of the cycloaddition while **14** is reported to require 48 h at 275 °C.[4]

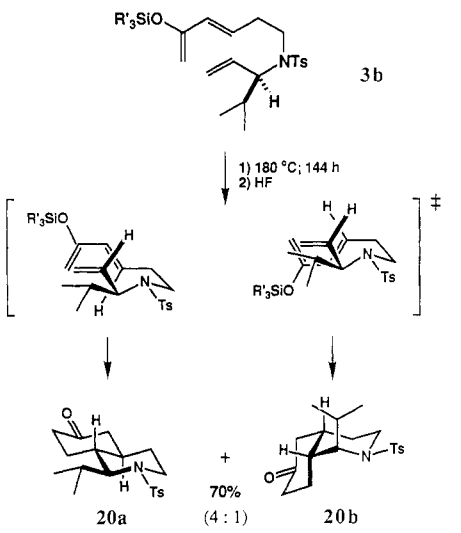
We turned our attention to the effect of the C(8) alkyl group of **3** on the diastereoselectivity of its cycloaddition. The Diels–Alder reaction of **3a** was executed in the same way as that for **13** to give the four isomeric cycloadducts **19a–d** in the ratio 3:2:1:2.2 (HPLC analysis, Scheme V). The isomers were roughly separated by column chromatography on silica gel and purified by preparative HPLC.

The structures of these isomers were unambiguously determined by ^1H (500 MHz) and ^{13}C (126 MHz) NMR analysis, including two-dimensional experiments such as homonuclear chemical shift correlation, heteronuclear chemical shift correlation, *J*-resolved correlation, nuclear Overhauser correlation, and homodecoupling if necessary. The significant data are summarized in Table I.

Four possible transition state structures leading to the cycloadducts **19a–d** are designated T_{rr}, T_{rs}, T_{sr}, and T_{ss}, where the subscripts denote the *re* or *si* face of the diene (first) and the dienophile (second) moieties in **3a** (Scheme V). Each transition state may involve two possible conformations, i.e., chair or boat, with respect to the nitrogen-containing six-membered structure developing in the transition state.[15] Since a study of models suggested that all the boat conformations would suffer from larger nonbonded repulsions than the corresponding chain structures, the transition-state structures were assumed to be the four chairs (Scheme V).

Destabilization arising from 1,3-diaxial or gauche interactions should obviously be minimized in the T_{sr} transition state because it has no 1,3-diaxial interaction, while the others have at least one such destabilizing factor. However, such destabilization was not reflected in the isomer ratio: the chiral methyl did not improve the desired trans selectivity, and the ratio (**19a** + **19d**):(**19b** + **19c**) was 1.5:1, which is almost the same as that for **13**. However,

Scheme VI



the trans/cis ratio of **19a**:**19c**, 3:1, seemed to shed light on a molecular design that could lead to the desired trans cycloadduct more selectively. We expected that changing the alkyl group from methyl to isopropyl (**3b**) would cause the cycloaddition to proceed predominantly through the T_{sr} transition state because destabilization due to the more bulky alkyl group would be increased substantially in the other transition-state structures.

We carried out the intramolecular Diels–Alder reaction of **3b** in the same way as for **3a** and obtained only the cycloadducts **20a** and **20b** in a ratio of 4:1, with no products stemming from the T_{ss} and T_{rs} transition states being detected (Scheme VI). Carbon-13 NMR chemical shifts for the isopropyl group[16] indicated that it is equatorial in the major isomer **20a** and axial in the minor isomer **20b**. In addition, ^1H NMR analysis, including two-dimensional experiments, led us to assign **20a** as trans and **20b** as cis. It is thus evident that increasing the bulk of the alkyl group at C(8) of the 7-aza triene substantially enhances the trans selectivity of its intramolecular ring closure.

Experimental Section

Melting points were determined on a Yamato capillary melting point apparatus and are uncorrected. IR spectra were obtained with a Hitachi 215 grating infrared spectrometer, only the major absorptions being cited. The ^1H NMR spectra, 60, 100, 300, and 500 MHz, were recorded on JEOL PMX-60-SI, JEOL FX-100, Varian VXR-300, and Varian VXR-500 instruments, respectively. The ^{13}C NMR experiments at 25, 75, and 126 MHz were carried

(15) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187.

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out on JEOL FX-100, Varian VXR-300, and Varian VXR-500, machines, respectively. Unless otherwise indicated, deuteriochloroform containing tetramethylsilane (TMS:1%) or without TMS was used for the JEOL instruments or the Varian machines, respectively, where the chemical shifts are given in δ units relative to internal TMS for the former or relative to internal $CHCl_3$ for the latter. Optical rotations were taken on a JASCO DIP-4 digital polarimeter. High resolution mass spectra were obtained on a JEOL JMS-DX303 instrument operated in the chemical ionization (CI) mode. X-ray reflection data were collected on a Rigaku AFC-5 four-circle diffractometer at 20 °C. Preparative HPLC was performed on a Shimazu SPD-6A pump employing a Develosil 30-3 column. Analytical TLC was executed on precoated Merck silica gel 60 F254. All solvents were reagent grade unless otherwise noted. THF and ether were distilled from sodium benzophenone ketyl prior to use. Toluene was distilled from sodium. Benzene and triethylamine were distilled from calcium hydride. Acetonitrile and dichloromethane were distilled from phosphorus pentoxide prior to use. Ethanol and methanol were distilled from magnesium. Column chromatography was performed on Mercks silica gel 60-7743. All reactions were executed under an atmosphere of dry nitrogen or argon, employing flame-dried glassware.

***tert*-Butyl (1*S*)-*N*-(1-Formylethyl)carbamate (6a).** To a stirred solution of **5a** (2.52 g, 13.0 mmol) in toluene (30 mL) was added DIBAL (1 M in hexane, 26.6 mL, 26.6 mmol) dropwise at −78 °C during 15 min. After stirring for 1.5 h, the reaction was quenched with AcOH (17 mL, 5 M in benzene) at −78 °C and then warmed to room temperature. The mixture was poured into 10% aqueous tartaric acid (50 mL) and extracted with hexane–EtOAc (1:1) (20 mL × 3). The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (SiO_2, hexane–AcOEt (3:1)) to give **6a** (1.65 g, 74%) as colorless crystals: mp 89–90 °C; $[\alpha]^{26}_D$ +29.8° (*c* 0.73, $CHCl_3$); ^1H NMR (60 MHz) δ 1.34 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.45 (s, 9 H, $C(CH_3)_3$), 4.18 (m, 1 H, NCH), 5.25 (b, 1 H, NH), 9.54 (s, 1 H, CHO); IR ($CHCl_3$) 3450, 2983, 1709, 1495, 1367, 1233 cm^{-1}. This aldehyde was used in the next reaction without purification.

***tert*-Butyl (1*S*)-*N*-(1-formyl-2-methylpropyl)carbamate (6b):** mp 43.8–44.6 °C; $[\alpha]^{24}_D$ +103° (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 3430, 2980, 1710, 1495, 1370, 1160 cm^{-1}; ^1H NMR (60 MHz) δ 0.95 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.06 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.44 (s, 9 H, $C(CH_3)_3$), 1.88–2.45 (m, 1 H, CCHC), 4.36–3.96 (m, 1 H, NCH), 4.80–5.35 (b s, 1 H, NH), 9.55 (b s, 1 H, CHO).

***tert*-Butyl (1*S*)-*N*-(1-Methyl-2-propenyl)carbamate (7a).** To a stirred solution of zinc powder (6.6 g, 101 mmol) and diiodomethane (0.90 g, 33.6 mmol) in THF (55 mL) was added $AlMe_3$ (1 M in hexane, 6.7 mL, 6.7 mmol) at 25 °C. The resulting mixture was stirred until the exothermic reaction had subsided (15 min). To this was added dropwise a solution of **6a** (2.00 g, 11.2 mmol) in THF (20 mL) at −30 °C. The resulting mixture was stirred at −30 to −20 °C for 5 h, diluted with ether (60 mL), and poured into 0.5 N aqueous HCl, and the product was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was subjected to column chromatography (SiO_2) to give **7a** as a semisolid (0.94 g, 48%): $[\alpha]^{25}_D$ −6.33° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3500, 2980, 1700, 1490, 1360, 1160 cm^{-1}; ^1H NMR (60 MHz) δ 1.21 (d, *J* = 7.5 Hz, 3 H, CH_3), 1.45 (s, 9 H, $C(CH_3)_3$), 3.97–4.68 (m, 1 H, NCH), 4.75 (b s, 1 H, NH), 4.90–5.44 (m, 2 H, CH_2=C), 5.55–6.02 (m, 1 H, CH=C); ^{13}C NMR (25 MHz) δ 20.7 (q), 28.4 (q), 48.2 (d), 79.2 (s), 113.5 (t), 140.2 (d), 154.9 (s); exact mass calcd for $C_9H_{18}NO_2$ 172.1338 (M^+ + H), found 172.1326.

***tert*-Butyl (1*S*)-*N*-(2-Hydroxy-1-methylethyl)carbamate (8a).** Into a solution of **7a** (120 mg, 0.68 mmol) in MeOH (5 mL) and CH_2Cl_2 (10 mL) was introduced ozone at −78 °C until the solution became faintly blue. Excess ozone was evaporated by bubbling the mixture with a stream of nitrogen at −78 °C, and then dimethyl sulfide (1 mL) was added to the mixture, the whole being stirred overnight at room temperature. After removal of the solvent, the residue was dissolved in EtOH (2 mL), and then $NaBH_4$ (20.2 mg, 0.53 mmol) was added to the solution, the mixture being stirred at 0 °C for 2 h. The reaction was quenched with water and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a semisolid, which was purified by medium-pressure liquid chromatography (Develosil 60 prepacked column, hexane–AcOEt (2:1)), giving **8a** (50.8 mg, 41%) as colorless crystals: mp 58.8–59.8 °C; $[\alpha]^{26}_D$ −9.8° (*c* 1.31, $CHCl_3$); IR (CCl_4) 3455, 2990, 1705, 1500, 1365, 1170 cm^{-1}; ^1H NMR (60 MHz) δ 1.21 (d, *J* = 7.6 Hz, 3 H, CH_3), 1.48 (s, 9 H, $C(CH_3)_3$), 3.24–4.05 (b m, 4 H, OH, OCH_2, NCH), 4.70–5.14 (b s, 1 H, NH).

***tert*-Butyl (1*S*)-*N*-(1-isopropyl-2-propenyl)carbamate (8b):** $[\alpha]^{24}_D$ +25° (*c* 1.60, $CHCl_3$); IR ($CHCl_3$) 3550, 2990, 1705, 1495, 1160 cm^{-1}; ^1H NMR (60 MHz) δ 0.92 (d, *J* = 6.3 Hz, 6 H, $C(CH_3)_2$), 1.47 (s, 9 H, $C(CH_3)_3$), 1.53–1.94 (m, 1 H, CCHC), 4.32–4.84 (b, 2 H, NH, NCH), 4.93–5.35 (m, 2 H, CH_2=C), 5.50–6.08 (m, 1 H, CH=C); ^{13}C (25 MHz) δ 18.0 (q), 18.7 (q), 28.4 (q), 32.2 (d), 58.2 (d), 79.0 (s), 115.0 (t), 137.4 (d), 155.6 (s); exact mass calcd for $C_{11}H_{22}NO_2$ 200.1651 (M^+ + H), found 200.1641.

(1*S*)-*N*-(1-Methyl-2-propenyl)-*p*-toluenesulfonamide (9a). A solution of **7a** (874 mg, 4.96 mmol) in CH_2Cl_2 (4 mL) was stirred with CF_3CO_2H (2 mL) at room temperature for 30 min. After the volatile material was removed in vacuo, the residue was dissolved in CH_2Cl_2 (10 mL), and to this was added Et_3N (1.6 mL, 11.5 mmol) and a solution of *p*-toluenesulfonyl chloride (1.00 g, 5.26 mmol) in CH_2Cl_2 (5 mL) at room temperature, the reaction being continued for 12 h, followed by an addition of water. The mixture was extracted with CH_2Cl_2 (15 mL × 3), washed with brine, dried (Na_2SO_4), and concentrated to give **9a** (1.06 g, 93%) as colorless crystals after purification by column chromatography (SiO_2, hexane–EtOAc (3:1)): mp 59.8–61.6 °C; $[\alpha]^{23}_D$ −6.39° (*c* 2.69, $CHCl_3$); IR ($CHCl_3$) 3380, 3260, 3030, 1600, 1330, 1155, 1095 cm^{-1}; ^1H NMR (60 MHz) δ 1.18 (d, *J* = 6.0 Hz, 3 H, CH_3), 2.43 (s, 3 H, $ArCH_3$), 3.67–4.33 (m, 1 H, NCH), 5.00 (b, 1 H, NH), 4.73–5.27 (m, 2 H, CH_2=C), 5.35–6.08 (m, 1 H, CH=C), 7.27 (d, *J* = 8.0 Hz, 2 H, ArH), 7.78 (d, *J* = 8.0 Hz, 2 H, ArH); exact mass calcd for $C_{11}H_{16}NO_2S$ 226.0902 (M^+ + H), found 226.0900.

(1*S*)-*N*-(1-Isopropyl-2-propenyl)-*p*-toluenesulfonamide (9b): mp 74.0–75.5 °C; $[\alpha]^{24}_D$ +18.5° (*c* 1.73, $CHCl_3$); IR ($CHCl_3$) 3390, 3275, 3020, 2960, 1405, 1330, 1160, 1090 cm^{-1}; ^1H NMR (60 MHz) δ 0.86 (d, *J* = 6.3 Hz, 6 H, $C(CH_3)_2$), 1.48–2.00 (m, 1 H, CCHC), 2.43 (s, 3 H, $ArCH_3$), 3.40–3.83 (m, 1 H, NCH), 4.72–5.93 (m, 4 H, CH=CH_2, NH), 7.27 (d, *J* = 8.1 Hz, 2 H, ArH), 7.80 (d, *J* = 8.1 Hz, 2 H, ArH); ^{13}C NMR (25 MHz) δ 18.2 (q), 21.4 (q), 32.7 (d), 61.9 (d), 116.5 (t), 127.2 (d), 129.4 (d), 135.7 (d), 138.2 (s), 142.9 (s); exact mass calcd for $C_{13}H_{20}NO_2S$ 254.1215 (M^+ + H), found 254.1209.

Ethyl 3-[*N*-(*p*-Tolylsulfonyl)-*N*-[(1′*S*)-1′-methyl-2′-propenyl]amino]propanoate (10a). To a stirred solution of **9a** (737 mg, 3.15 mmol) in CH_3CN (9 mL) was added K_2CO_3 (656 mg, 4.74 mmol) and ethyl acrylate (0.41 mL, 3.78 mmol) at room temperature, and the mixture was stirred under reflux for 12 h. The reaction mixture was cooled to room temperature and ether was added to it, the resulting suspension being filtered through a Celite pad. Removal of the solvent in vacuo left behind an oil, which, on column chromatography (SiO_2, hexane–AcOEt (2:1)), afforded **10a** (964 mg, 83%) as an oil: $[\alpha]^{26}_D$ −55.0° (*c* 1.35, $CHCl_3$); IR (film) 2980, 1725, 1590, 1335, 1150 cm^{-1}; ^1H NMR (60 MHz) δ 1.15 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.25 (t, *J* = 7.0 Hz, 3 H, CH_3), 2.40 (s, 3 H, $ArCH_3$), 2.53–2.93 (m, 2 H, CH_2COO), 3.17–3.55 (m, 2 H, NCH_2), 4.10 (q, *J* = 7.0 Hz, 2 H, OCH_2), 4.35–4.73 (m, 1 H, NCH), 4.75–5.23 (m, 2 H, CH_2=C), 5.34–5.96 (ddd, *J* = 18, 8.1, 4.4 Hz, 1 H, C=CH), 7.26 (d, *J* = 8.2 Hz, 2 H, ArH), 7.78 (d, *J* = 8.2 Hz, 2 H, ArH); ^{13}C NMR (25 MHz) δ 14.2 (q), 17.0 (q), 21.5 (q), 36.5 (t), 39.3 (t), 54.6 (d), 60.5 (t), 117.0 (s), 127.1 (d), 130.0 (d), 137.5 (t), 143.3 (s), 171.4 (s); exact mass calcd for $C_{16}H_{24}NO_4S$ 326.1426 (M^+ + H), found 326.1412.

Ethyl 3-[*N*-(*p*-tolylsulfonyl)-*N*-[(1′*S*)-1′-isopropyl-2′-propenyl]amino]propanoate (10b): $[\alpha]^{25}_D$ −15.5° (*c* 1.62, $CHCl_3$); IR (film) 3025, 2995, 1720, 1590, 1335, 1155 cm^{-1}; ^1H NMR (60 MHz) δ 0.82 (d, *J* = 7.2 Hz, 6 H, $C(CH_3)_2$), 1.23 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.45–2.05 (m, 1 H, $C(CH_3)_3$), 2.42 (s, 3 H, $ArCH_3$), 2.53–2.92 (m, 2 H, CH_2COO), 3.21–4.01 (m, 1 H, C=CH), 7.26 (d, *J* = 8.1 Hz, 2 H, ArH), 7.78 (d, *J* = 8.1 Hz, 2 H, ArH); ^{13}C NMR (25 MHz) δ 14.2 (q), 20.2 (q), 21.5 (q), 30.1 (d), 35.7 (t), 40.2 (t), 60.6 (t), 67.9 (d), 119.4 (t), 127.5 (d), 129.4 (d), 134.3 (d), 137.5 (s), 143.1 (s), 171.5 (s); exact mass calcd for $C_{18}H_{28}NO_4S$ 354.1739 (M^+ + H), found 354.1742.

***N*-(2-Formylethyl)-*N*-[(1′*S*)-1′-isopropyl-2′-propenyl]-*p*-toluenesulfonamide (11a).** To a stirred solution of **10a** (736

mg, 2.23 mmol) in toluene (6 mL) was added dropwise DIBAL (1 M in hexane, 2.5 mL, 2.5 mmol) at −78 °C, the mixture being stirred at that temperature for 2 h. To this was added EtOH (0.4 mL), and the mixture was stirred at −78 to 0 °C for 20 min, being poured into 10% aqueous tartaric acid solution (20 mL) under vigorous stirring. The mixture was extracted with AcOEt (10 mL × 3), and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give **11a** (575 mg, 90%) as an oil after purification by short-path column chromatography (SiO_2): $[\alpha]^{26}_D$ −56.5° (*c* 1.72, $CHCl_3$); IR (film) 2975, 1720, 1595, 1335, 1150 cm^{-1}; ^1H NMR (60 MHz) δ 1.16 (d, *J* = 7.0 Hz, 3 H, CH_3), 2.41 (s, 3 H, $ArCH_3$), 2.70–3.08 (m, 2 H, CH_2O), 3.21–3.54 (m, 2 H, NCH_2), 4.22–4.81 (m, 1 H, NCH), 4.81–5.32 (m, 2 H, CH_2=C), 5.32–5.95 (ddd, *J* = 18, 8.2, 4.4 Hz, 1 H, C=CH), 7.25 (d, *J* = 8.2 Hz, 2 H, ArH), 7.77 (d, *J* = 8.2 Hz, 2 H, ArH), 9.70 (b s, 1 H, CHO); ^{13}C NMR (25 MHz) δ 16.9 (q), 21.5 (q), 36.9 (t), 46.2 (q), 54.6 (d), 117.1 (t), 127.1 (d), 129.8 (d), 137.3 (s), 137.5 (d), 143.4 (s), 200.3 (s); exact mass calcd for $C_{14}H_{20}NO_3S$ 282.1164 (M^+ + H), found 282.1176.

***N*-(2-Formylethyl)-*N*-[(1′*S*)-1′-isopropyl-2′-propenyl]-*p*-toluenesulfonamide (11b)**: $[\alpha]^{26}_D$ −17.7° (*c* 1.96, $CHCl_3$); IR ($CHCl_3$) 3025. 2975, 1725, 1600, 1335, 1160 cm^{-1}; ^1H NMR (60 MHz) δ 0.85 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.98 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.20–2.10 (m, 1 H, CH), 2.39 (s, 3 H, $ArCH_3$), 2.72–3.15 (m, 2 H, CH_2CO), 3.21–3.58 (m, 2 H, CH_2N), 3.84 (dd, *J* = 10, 8.0 Hz, 1 H, NCH), 4.73–5.22 (m, 2 H, CH_2=C), 5.28–5.92 (m, 1 H, C=CH), 7.25 (d, *J* = 8.2 Hz, 2 H, ArH), 7.70 (d, *J* = 8.2 Hz, 2 H, ArH), 9.74 (b s, 1 H, CHO); ^{13}C NMR (25 MHz) δ 20.2 (q), 21.5 (q), 30.1 (d), 37.8 (t), 45.5 (t), 67.9 (d), 119.5 (t), 127.5 (d), 129.5 (d), 134.3 (d), 137.4 (s), 143.3 (s), 200.3 (s); exact mass calcd for $C_{16}H_{24}NO_3S$ 310.1477 (M^+ + H), found 310.1470.

***N*-[5-Oxo-3(*E*)-hexenyl]-*N*-[(1′*S*)-1′-methyl-2′-propenyl]-*p*-toluenesulfonamide (12a).** To a stirred suspension of NaH (60 wt % in oil, 74.8 mg, 1.87 mmol) in THF (5 mL) was added slowly diisopropyl (2-oxopropyl)phosphonate (456 mg, 2.05 mmol) at room temperature, the mixture being stirred until it became homogeneous. To the solution was added a solution of the aldehyde **11a** (530 mg, 1.85 mmol) in THF (3 mL) at 0 °C under stirring. The reaction was continued for 1.5 h and then quenched with water. The mixture was extracted with hexane–EtOAc (1:1) (10 mL × 3) and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give **12a** (525 mg, 87%) as an oil after purification by short-path column chromatography (SiO_2): $[\alpha]^{25}_D$ −61.0° (*c* 2.15, $CHCl_3$); IR (film) 2975, 1695, 1670, 1595, 1335, 1150 cm^{-1}; ^1H NMR (300 MHz) δ 1.17 (d, *J* = 6.8 Hz, 3 H, CH_3), 2.22 (s, 3 H, CH_3COC), 2.40 (s, 3 H, $ArCH_3$), 2.54 (m, 2 H, CH_2C=C), 3.05–3.23 (m, 2 H, CH_2CN), 4.50 (m, 1 H, CHN), 5.01–5.15 (m, 2 H, CH_2=C), 5.58 (ddd, *J* = 17, 10, 4.5 Hz, C=CHCN), 6.04 (dt, *J* = 16, 1.5 Hz, 1 H, C=CHCO), 6.72 (dt, *J* = 17, 7.8 Hz, 1 H, CH=CCO), 7.27 (d, *J* = 7.7 Hz, 2 H, ArH), 7.68 (d, *J* = 7.7 Hz, 2 H, ArH); ^{13}C NMR (75 MHz) δ 17.1 (q), 21.6 (q), 26.9 (q), 34.6 (t), 42.4 (t), 54.5 (d), 116.9 (t), 127.0 (d), 129.6 (d), 132.5 (d), 137.5 (d), 137.6 (s), 143.2 (d), 144.0 (s), 198.2 (s); exact mass calcd for $C_{17}H_{24}NO_3S$ 322.1477 (M^+ + H), found 322.1440.

***N*-[5-Oxo-3(*E*)-hexenyl]-*N*-[(1′*S*)-1′-isopropyl-2′-propenyl]-*p*-toluenesulfonamide (12b)**: $[\alpha]^{25}_D$ −19.7° (*c* 1.40, $CHCl_3$); IR (film) 2970, 1695, 1675, 1630, 1165 cm^{-1}; ^1H NMR (500 MHz) δ 0.79 (d, *J* = 7.2 Hz, 3 H, CH_3), 0.91 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.65–1.74 (m, 1 H, CCHC), 2.14 (s, 3 H, CH_3CO), 2.32 (s, 3 H, $ArCH_3$), 2.40–2.65 (m, 2 H, CH_2C=C), 3.04–3.15 (m, 2 H, NCH_2), 3.76 (dd, *J* = 9.6, 8.0 Hz, 1 H, NCH), 4.87 (d, *J* = 14 Hz, 1 H, *H*HC=C), 4.98 (d, *J* = 8.6 Hz, 1 H, H*H*C=C), 5.43–5.51 (m, 1 H, C=CHCN), 5.97 (d, *J* = 14 Hz, 1 H, C=CHCO), 6.61 (dt, *J* = 14, 6.3 Hz, 1 H, CH=CCO), 7.18 (d, *J* = 7.5 Hz, ArH), 7.60 (d, *J* = 7.5 Hz, 2 H, ArH); ^{13}C NMR (126 MHz) δ 20.25 (q), 20.28 (q), 21.5 (q), 26.9 (q), 30.3 (d), 33.8 (t), 43.4 (t), 67.8 (t), 119.5 (t), 127.4 (d), 132.6 (d), 134.4 (d), 137.7 (d), 143.2 (d), 144.0 (s), 198.3 (s); exact mass calcd for $C_{19}H_{28}NO_3S$ 350.1790 (M^+ + H), found 350.1782.

***N*-[5-[(*tert*-Butyldimethylsilyl)oxy]-3(*E*),5-hexadienyl]-*N*-[(1′*S*)-1′-methyl-2′-propenyl]-*p*-toluenesulfonamide (3a).** To a stirred solution of **12a** (522 mg, 1.60 mmol) in ether (10 mL) containing Et_3N (0.78 mL, 4.80 mmol) was added TBDMSOTf (740 mg, 2.80 mmol) at 0 °C, the mixture being stirred at that temperature for 1.5 h. The mixture was filtered through a Celite pad to remove the ammonium triflate, and the filtrate was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to furnish **3a** (656 mg, 93%) as an oil after purification by column chromatography (SiO_2, hexane–EtOAc (10:1) containing 5% Et_3N): $[\alpha]^{26}_D$ −45.1° (*c* 1.50, $CHCl_3$); IR (film) 2950, 2925, 2650, 1595, 1320, 1150, 1015 cm^{-1}; ^1H NMR (500 MHz) δ 0.15 (s, 6 H, $Si(CH_3)_2$), 0.94 (s, 9 H, $SiC(CH_3)_3$), 1.18 (d, *J* = 6.8 Hz, 3 H, CH_3), 2.40 (s, 3 H, $ArCH_3$), 2.33–2.41 (m, 1 H, *H*HCC=C), 2.41–2.50 (m, 1 H, H*H*CC=C), 3.04 (dd, *J* = 16, 10, 5.7 Hz, 1 H, *H*HCN), 3.12 (ddd, *J* = 16, 10, 5.7 H, 1 H, H*H*CN), 4.21 (s, 1 H, *H*HC=COSi), 4.23 (s, 1 H, H*H*C=COSi), 4.48 (m, 1 H, NCHC=C), 5.04 (dm, *J* = 17 Hz, 1H, *H*HC=C), 5.08 (dm, *J* = 11 Hz, 1 H, H*H*C=C), 5.62 (ddd, *J* = 17, 11, 4.7 Hz, 1 H, C=CHCN), 5.83–5.86 (m, 2 H, CH=CHCOSi), 7.24 (d, *J* = 7.7 Hz, 2 H, ArH), 7.70 (d, *J* = 7.7 Hz, 2 H, ArH); ^{13}C NMR (126 MHz) δ −4.7 (q), 17.3 (q), 18.3 (s), 21.5 (q), 25.8 (q), 34.3 (t), 43.5 (t), 54.6 (d), 94.5 (t), 116.6 (t), 127.1 (d), 127.2 (d), 129.6 (d), 130.0 (d), 138.1 (s), 143.0 (s), 154.7 (s). The diene was too unstable for either elemental analysis or exact mass determination.

***N*-[5-[(*tert*-Butyldimethylsilyl)oxy]-3(*E*),5-hexadienyl]-*N*-[(1′*S*)-1′-isopropyl-2′-propenyl]-*p*-toluenesulfonamide (3b)**: $[\alpha]^{23}_D$ −7.93° (*c* 2.17, $CHCl_3$); IR (film) 2955, 2930, 2805, 1595, 1465, 1325, 1160, 1020 cm^{-1}; ^1H NMR (60 MHz) δ 0.16 (s, 6 H, $Si(CH_3)_2$), 0.97 (s 9 H, $SiC(CH_3)_3$), 0.82–1.10 (m, 6 H, $C(CH_3)_2$), 1.43–2.10 (m, 1 H, CCHC), 2.36–2.71 (m, 2 H, CH_2C=C), 2.42 (s, 3 H, $ArCH_3$), 2.98–3.40 (m, 2 H, NCH_2), 3.88 (dd, *J* = 5.0, 4.1 Hz, 1 H, NCHC=C), 4.25 (s, 2 H, CH_2=COSi), 4.88–5.24 (m, 2 H, CH_2=C), 5.35–5.95 (m, 3 H, C=CH, CH=CHCO), 7.37 (d, *J* = 4.5 Hz, 2 H, ArH), 7.76 (d, *J* = 4.5 Hz, 2 H, ArH); ^{13}C NMR (126 MHz) δ −4.6 (q), 18.3 (s), 20.30 (q), 20.31 (q), 21.5 (q), 25.8 (q), 30.3 (d), 33.6 (t), 44.5 (t), 67.8 (d), 94.7 (t), 119.1 (t), 127.1 (d), 127.4 (d), 129.3 (d), 130.1 (d), 134.7 (d), 138.1 (s), 142.8 (s), 154.7 (s). The diene was too unstable for either elemental analysis or exact mass determination.

Methyl *N*-[5-[(*tert*-butyldimethylsilyl)oxy]-3(*E*),5-hexadienyl]-*N*-allylcarbamate (13): IR (film) 2950, 2850, 1710, 1665, 1465, 1405, 1320, 1250 cm^{-1}; ^1H NMR (60 MHz) δ 0.18 (s, 6 H, $Si(CH_3)_2$), 0.99 (s, 9 H, $SiC(CH_3)_3$), 2.13–2.56 (m, 2 H, CH_2C=CCO), 3.34 (m, 2 H, NCH_2), 3.71 (s, 3 H, OCH_3), 3.88 (d, *J* = 5.7 Hz, 2 H, C=CCH_2N), 4.25 (s, 2 H, CH_2=COSi), 4.93–5.36 (m, 2 H, CH_2=C), 5.52–5.80 (m, 1 H, C=CH), 5.95 (m, 2 H, CH=CHCO); ^{13}C NMR (126 MHz) δ −4.6 (q), 18.3 (s), 25.8 (q), 31.1 (t), 49.9 (t), 52.5 (q), 94.3 (t), 116.6 (t), 127.6 (d), 130.1 (d), 132.8 (s), 134.0 (d), 155.0 (s), 156.7 (s); exact mass calcd for $C_{17}H_{32}NO_3Si$ 326.2151 (M^+ + H), found 326.2168.

Physical properties for the intermediates involved in the synthetic route leading to **13** as follows. **Methyl *N*-allyl-*N*-(2-formylethyl)carbamate**: IR (film) 3095, 2955, 2840, 1700, 1645, 1480, 1440, 1410, 1250 cm^{-1}; ^1H NMR (60 MHz) δ 2.70 (m, 2 H, CH_2CO), 3.53 (t, *J* = 6.1 Hz, 2 H, CH_2N), 3.67 (s, 3 H, OCH_3), 3.86 (d, *J* = 5.8 Hz, 2 H, CH_2C=C), 4.90–5.36 (m, 2 H, CH_2=C), 5.47–6.13 (m, 1 H, C=CH), 9.72 (t, *J* = 1.1 Hz, 1 H, CHO); ^{13}C NMR (25 MHz) δ 33.6 (t), 39.4 (q), 50.5 (t), 52.9 (t), 118.4 (t), 134.5 (d), 157.5 (s), 201.8 (d); exact mass calcd for $C_8H_{14}NO_3$ 172.0974 (M^+ + H), found 172.0978.

Methyl *N*-allyl-*N*-[5-oxo-3(*E*)-hexenyl]carbamate: IR (film) 2960, 1710, 1680, 1645, 1635, 1480, 1405, 1255 cm^{-1}; ^1H NMR (60 MHz) δ 2.25 (s, 3 H, CH_3CO), 2.42 (t, *J* = 8.0 Hz, 2 H, CH_2C=C), 2.53 (t, *J* = 8.0 Hz, 2 H, NCH_2), 3.72 (s, 3 H, OCH_3), 3.89 (d, *J* = 5.8 Hz, 2 H, C=CCH_2N), 4.93–5.38 (m, 2 H, CH_2=C), 5.51–6.08 (m, 1 H, C=CHCN), 5.90–6.29 (m, 1 H, C=CHCO), 6.80 (dt, *J* = 16, 7.0 Hz, 1 H, CH=CCO); ^{13}C NMR (126 MHz) δ 26.9 (q), 31.5 (t), 45.3 (t), 49.9 (t), 52.7 (t), 117.0 (t), 132.7 (d), 133.7 (d), 144.4 (d), 156.6 (s), 198.6 (s); exact mass calcd for $C_{11}H_{18}NO_3$ 212.1287 (M^+ + H), found 212.1283.

(1*S*)-1,3,4,4a,5,7,8,8a-Octahydro-1-methyl-2-(*p*-tolylsulfonyl)-6(2*H*)-isoquinolone (19). A degassed solution of **3a** (330 mg, 0.75 mmol) in toluene (10 mL), prepared by repeating the sequence freezing (liquid N_2), evacuation (0.001 mmHg), warming up, and freezing again, three times, was sealed in an ampoule, and the ampoule was heated at 180 °C for 96 h. The ampoule was opened and the contents were concentrated under reduced pressure, followed by short-path column chromatography (SiO_2, hexane–AcOEt (8:1) containing 1% Et_3N), affording the primary cycloadducts (323 mg, 98%): IR (film) 2925, 2850, 1720, 1670, 1595, 1330, 1150 cm^{-1}; ^1H NMR (60 MHz) δ 0.10 (s, 6 H),

0.91 (s, 9 H), 1.80–2.30 (m, 11 H), 2.38 (s, 3 H), 2.56–4.88 (m, 4 H), 7.20 (d, 2 H), 7.63 (d, 2 H); exact mass calcd for $C_{23}H_{38}NO_3SSi$ 436.2342 ($M^+ + H$), found 436.2340.

The product was dissolved in CH_3CN (5 mL), and to this was added a solution of HF in CH_3CN (1 M, 0.8 mL, 0.8 mmol) at 0 °C, the resulting solution being stirred at room temperature for 2 h, followed by dilution (water). The mixture was extracted with CH_2Cl_2 (15 mL × 3), and the combined CH_2Cl_2 solutions were washed with brine, dried over Na_2SO_4, and concentrated in vacuo, followed by short-path chromatography (SiO_2, hexane–AcOEt (1:1)) to give a mixture of **19a–d** (206 mg, 84%): IR ($CHCl_3$) 3050, 2945, 2880, 1710, 1340, 1261 cm^{-1}; exact mass calcd for $C_{17}H_{24}NO_3S$ 322.1477 ($M^+ + H$), found 322.1478. This mixture was subjected to a medium-pressure liquid chromatography (Develosil 60 prepacked column) eluted initially with hexane–AcOEt (3:1) to effect the isolation of **19d** (the least polar) and **19a** without any mutual overlap, followed by a elution with a more polar system (1:1) to afford a mixture of remaining isomers. This mixture was separated by HPLC (Develosil 30-3 prepacked column) eluted with hexane–AcOEt–CH_3CN (8:2:1) to give **19c** and **19b** (the most polar) without any mutual overlap. The physical properties of these products are as follows.

(1*S*,4*R*,8*R*)-*trans*-1,3,4,4a,5,7,8,8a-Octahydro-1-methyl-2-(*p*-tolylsulfonyl)-6(2*H*)-isoquinolone (19a): mp 74.3–77.5 °C; $[\alpha]^{23}_D$ +28.8° (*c* 2.02, $CHCl_3$); ^1H NMR (500 MHz) δ 1.44–1.17 (m, 3 H, C(4)H, C(4a)H, and C(8)H), 1.30 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.56 (qd, *J* = 8.8, 2.3 Hz, 1 H, C(8a)H), 1.80 (m, 1 H, C(4)H), 2.05 (dd, *J* = 14, 12 Hz, 1 H, C(5)H), 2.08–2.18 (m, 1 H, C(8)H), 2.25–2.40 (m, 3 H, C(5)H, $C(7)H_2$), 2.42 (s, 3 H, $ArCH_3$), 3.16 (qd, *J* = 6.7, 8.8 Hz, 1 H, C(1)H), 3.30 (dt, *J* = 7.8, 6.5 Hz, 1 H, C(3)H, 3.71 (m, 1 H, C(3)H), 7.28 (d, *J* = 7.5 Hz, 2 H, ArH), 7.68 (d, *J* = 7.5 Hz, 2 H, Arh); ^{13}C NMR (126 MHz) δ 18.5 (q), 21.5 (q), 30.2 (t), 31.6 (t), 38.5 (d), 40.6 (d), 42.9 (t), 44.3 (d), 47.5 (t), 57.8 (d), 126.6 (d), 129.4 (d), 138.4 (s), 142.9 (s), 209.2 (s).

(1*S*,4*R*,8*S*)-*cis*-1,3,4,4a,5,7,8,8a-Octahydro-1-methyl-2-(*p*-tolylsulfonyl)-6(2*H*)-isoquinolone (19b): $[\alpha]^{24}_D$ +15.8° (*c* 0.58, $CHCl_3$); ^1H NMR (500 MHz) δ 1.24 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.55–1.58 (m, 1 H, C(4)H), 1.58–1.70 (m, 1 H, C(4)H), 1.89–1.95 (m, 1 H, C(8a)H), 1.97–2.04 (m, 2 H, $C(8)H_2$), 2.10–2.17 (m, 1 H, C(4a)H), 2.19 (dt, *J* = 14, 2.7 Hz, 1 H, C(5)H, 2.29 (ddd, *J* = 14, 12, 7.5 Hz, 1 H, C(7)H), 2.40 (s, 3 H, $ArCH_3$), 2.53 (dd, *J* = 14, 5.9 Hz, 1 H, C(5)H), 2.68 (td, *J* = 12, 3.1 Hz, 1 H, C(3)H), 3.10 (qd, *J* = 12, 3.1 Hz, 1 H, C(1)H), 4.05 (dt, *J* = 12, 4.1 Hz, 1 H, C(3)H), 7.26 (d, *J* = 7.5 Hz, 2 H, ArH), 7.64 (d, *J* = 7.5 Hz, 2 H, ArH); ^{13}C NMR (126 MHz) δ 19.2, 21.0, 21.5, 27.0, 38.4, 39.8, 41.2, 46.3, 48.3, 57.6, 127.1, 129.6, 136.9, 143.1, 210.7.

(1*S*,4*S*,8*R*)-*cis*-1,3,4,4a,5,7,8,8a-Octahydro-1-methyl-2-(*p*-tolylsulfonyl)-6(2*H*)-isoquinolone (19c): $[\alpha]^{23}_D$ +18.4° (*c* 0.41, $CHCl_3$); ^1H (500 MHz) δ 1.11 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.28 (m, 1 H, C(8)H), 1.38–1.43 (m, 1 H, C(4)H), 1.48 (qd, *J* = 13, 5.2 Hz, 1 H, C(4)H), 1.77–1.84 (m, 1 H, C(4a)H), 1.91 (dt, *J* = 13, 3.8 Hz, 1 H, C(8a)H), 2.07 (qd, *J* = 14, 5.9 Hz, 1 H, C(8)H), 2.16 (dt, *J* = 14, 2.0 Hz, 1 H, C(7)H), 2.27–2.37 (m, 2 H, $C(5)H_2$), 2.40 (s, 3 H, $ArCH_3$), 2.51 (dd, *J* = 15, 6.2 Hz, 1 H, C(7)H), 2.90 (dd, *J* = 13, 3.3 Hz, 1 H, C(3)H), 3.66 (ddd, *J* = 12, 4.9, 1.5 Hz, 1 H, C(3)H, 4.08 (q, *J* = 7.0 Hz, 1 H, C(1)H), 7.27 (d, *J* = 7.5 Hz, 2 H, ArH), 7.75 (d, *J* = 7.5 Hz, 2 H, ArH); ^{13}C NMR (126 MHz) δ 15.6, 21.5, 26.2, 26.5, 31.5, 39.6, 39.7, 40.4, 46.5, 52.8, 126.9, 129.6, 137.9, 143.1, 210.6.

(1*S*,4*S*,8*S*)-*trans*-1,3,4,4a,5,7,8,8a-Octahydro-1-methyl-2-(*p*-tolylsulfonyl)-6(2*H*)-isoquinolone (19d): mp 119.7–121.2 °C; $[\alpha]^{24}_D$ +40.8° (*c* 1.01, $CHCl_3$); ^1H NMR (500 MHz) δ 0.91 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.23–1.49 (m, 2 H, C(4)H and C(8)H), 1.63 (m, 1 H, C(4)H), 1.72–1.88 (m, 3 H, C(4a)H, C(8)H, and C(8a)H), 1.99 (dd, *J* = 14, 13 Hz, 1 H, C(5)H), 2.27–2.45 (m, 2 H, C(5)H and C(7)H), 2.43 (s, 3 H, $ArCH_3$), 2.94 (td, *J* = 13, 3.5 Hz, 1 H, C(3)H), 3.77 (m, 1 H, C(3)H), 4.23 (qd, *J* = 7.0, 3.4 Hz, 1 H, C(1)H), 7.30 (d, *J* = 7.3 Hz, 2 H, ArH), 7.69 (d, *J* = 7.5 Hz, 2 H, ArH); ^{13}C NMR (126 MHz) δ 10.9 (q), 21.4 (q), 29.0 (t), 33.2 (t), 34.4 (d), 38.9 (t), 41.0 (t), 43.3 (d), 47.6 (t), 51.5 (d), 126.8 (d), 129.6 (d), 138.0 (s), 143.0 (s), 209.4 (s).

***trans*- and *cis*-1,3,4,4a,5,7,8,8a-Octahydro-2-(methoxycarbonyl)-6(2*H*)-isoquinolone (17 and 18).** The Diels–Alder reaction of **13** was performed at 180 °C for 24 h in the same way as that described for **3a** to give a mixture of **17** and **18** in 84% yield: IR ($CHCl_3$) 2990, 1750, 1725, 1350, 1260 cm^{-1}; exact mass calcd for $C_{11}H_{18}NO_3$ 212.1287 $M^+ + H$), found 212.1283. Separation of **17** and **18** was achieved by medium-pressure liquid chromatography (Develosil 60 prepacked column) eluted with hexane–AcOEt (3:1).

17: ^1H NMR (500 MHz, 55 °C) δ 1.28–1.42 (m, 2 H, C(4)H and C(8)H, 1.46–1.59 (m, 2 H, C(4a)H and C(8a)H), 1.65 (ddd, *J* = 17, 6.0, 3.1 Hz, 1 H, C(4)H), 1.97 (m, 1 H, C(8)H), 2.08 (ddd, *J* = 13, 12, 1.0 Hz, 1 H, C(5)H), 2.31–2.49 (m, 4 H, $C(7)H_2$, C(1)H, and C(5)H), 2.72 (td, *J* = 13, 2.4 Hz, 1 H, C(3)H), 3.71 (s, 3 H, OCH_3), 4.21 (b d, *J* = 12 Hz, 2 H, C(1)H and C(3)H); ^{13}C NMR (126 MHz) δ 29.6 (t), 32.9 (t), 40.3 (t), 40.8 (d), 41.8 (d), 43.9 (t), 47.6 (t), 49.2 (t), 52.6 (q), 155.9 (s), 209.3 (s).

18: mp 78.0–79.5 °C; ^1H NMR (500 MHz, 55 °C) δ 1.47 (m, 2 H, $C(4)H_2$), 1.81–1.90 (m, 1 H, C(8)H), 1.92–2.01 (m, 1 H, C(8)H), 2.14 (m, 1 H, C(8a)H), 2.23–2.30 (m, 1 H, C(4a)H), 2.26–2.40 (m, 2 H, $C(7)H_2$), 2.50–2.56 (m, 2 H, $C(5)H_2$), 2.92 (ddd, *J* = 14, 7.5, 6.5 Hz, 1 H, C(3)H), 3.14 (dd, *J* = 14, 3.4 Hz, 1 H, C(1)H), 3.68 (s, 3 H, OCH_3), 3.90–4.03 (m, 2 H, C(1)H and C(3)H); ^{13}C NMR (126 MHz) δ 25.5 (t), 27.1 (t), 34.7 (d), 37.1 (d), 39.7 (t), 43.3 (t), 45.8 (t), 47.4 (t), 52.6 (q), 156.3 (s), 210.1 (s).

X-ray Structure Determination of 18 ($C_{11}H_{17}NO_3$), m_r = 211.26. Crystals of **18**, grown by slow evaporation of the solvents from its hexane–AcOEt solution, are colorless plates (approximate dimensions: 0.15 × 0.50 × 0.20 mm) with developed faces {100} elongated along the *b* axis. The space group was shown to be $P2_1/c$ from the systematic absences noted as *h*0*l* for *l* odd, 0*k*0 for *k* odd. Lattice parameters were determined with 20 reflections in the range $20 < 2\theta < 27°$ by the least-squares method: a = 17.767 (3) Å, b = 5.3051 (8) Å, c = 11.794 (2) Å, β = 99.85 (1)°, V = 1095.3 (3) Å^3; Z = 4; D_x = 1.281 mg m^{-3}; μ(Cu Kα) = 0.72 mm^{-1}. Intensities were measured up to $\sin\theta/\lambda$ 0.5753 Å^{-1} by using $\omega - 2\theta$ scan technique where scan speed was 4° min^{-1} in ω and scan range was 1.2° + 0.15° tan θ in 2θ. The radiation was Ni-filtered Cu Kα (λ = 1.5418 Å) at 40 kV and 200 mA (rotating anode). Background was measured for 4 s on either side of the peak. Three standard reflections were monitored periodically during the data collection for every 57 reflections with a fluctuation within 1.4% in F. In reducing the data Lorentz and polarization corrections were applied, but no absorption correction was used. All 1763 unique reflections, ranging over h = 20 to 20, k = 0 to 6, l = 0 to 13, were used for refinement; 1644 reflections larger than 1.0 $\sigma(F_o)$. The structure was solved by MULTAN78 and refined (anisotropically for non-H atoms) by block-diagonal least squares: the quantity minimized was $\sum w(|F_o| - |F_c|)^2$ where w refers to weights, $1.0/[\sigma(F_o)^2 - 0.0526|F_o| + 0.0037|F_o|^2]$ for $|F_o| > 0$ and 2.631 for $|R_o| = 0$. H-atom positions were determined from difference Fourier map and refined isotropically by least squares. Extinction correction was performed for the strongest reflections [$I_{corr} = I_o(1 + (1.6 \times 10^{-6})I_c)$]. The final values of R and R_w were 0.048 and 0.060, respectively, for 1681 nonzero reflections (S = 2.22). In the last cycle of least-squares refinement (Δ/σ)max was 0.2 for non-H atoms and 0.7 for H atoms. In a final difference Fourier map maximum and minimum $\Delta\rho$ were 0.18 and −0.14 e Å^{-3}, respectively. Atomic scattering factors were taken from *International Tables for X-Ray Crystallography*.[17] Computations were carried out at the Crystallographic Research Center, Institute for Protein Research, Osaka University, and at the Okayama University Computer Center: Programs; MULTAN78,[18] HBLS-V and DAPH,[19] MOLCON,[20] and ORTEP.[21]

The two six-membered rings take chair conformations for **18**. The two rings are joined through the bond C(4a)-C(8a) with the tortion angles C(1)–C(8a)–C(4a)–C(5) 178.3(2)° and C(8)–C-

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(8a)-C(4a)-C(4) 71.4(2)°. The atoms C(1), C(3), N(2), C(9), O(12), and O(10) lie in a plane with a maximum deviation of 0.022 (2) Å at N(2): C(11) deviates only by 0.063 (3) Å from the plane. The N(2)-C(9) length (1.343 (3) Å) is close to a typical C-N bond length found in peptides.

(1*S*,4*R*,8*R*)-*trans*- and (1*S*,4*S*,8*R*)-*cis*-1,3,4,4a,5,7,8,8a-Octahydro-1-isopropyl-2-(*p*-tolylsulfonyl)-6(2*H*)-isoquinolone (20a and 20b). The Diels-Alder reaction of **3b** was performed in the same way as that described for **3a** to give a mixture of **20a** and **20b** in 70% yield: IR ($CHCl_3$) 3005, 2960, 1710, 1325, 1145 cm^{-1}; exact mass calcd for $C_{19}H_{28}NO_3S$ 350.1790 (M^+ + H), found 350.1784. Separation of **20a** and **20b** was achieved by medium-pressure liquid chromatography (Develosil 60 prepacked column, hexane-AcOEt (3:1)).

20a: mp 121.1-127.0 °C; $[\alpha]^{24}_D$ +18.1° (*c* 0.93, $CHCl_3$); ^1H NMR (500 MHz) δ 0.88 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.01 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.02-1.07 (d, *J* = 6.7 Hz, 1 H, C(4a)H), 1.12-1.21 (m, 1 H, C(4)H), 1.31-1.39 (m, 1 H, C(8a)H), 1.47 (m, 1 H, C(8)H), 1.67-1.75 (m, 1 H, C(4)H), 1.80 (m, 1 H, C(9)H), 1.93 (dd, *J* = 13, 13 Hz, 1 H, C(5)H), 1.98-2.03 (m, 1 H, C(8)H), 2.16-2.29 (m, 2 H, C(5)H and C(7)H), 2.31-2.36 (m, 1 H, C(7)H), 2.41 (s, 3 H, $ArCH_3$), 3.17 (ddd, *J* = 14, 9.1, 4.7 Hz, 1 H, C(3)H), 3.33 (dd, *J* = 8.8, 4.9 Hz, 1 H, C(1)H), 3.64-3.72 (m, 1 H, C(3)H), 7.22 (d, *J* = 7.2 Hz, 2 H, ArH), 7.68 (d, *J* = 7.2 Hz, 2 H, ArH); ^{13}C NMR (126 MHz) δ 19.8 (q), 20.2 (q), 21.5 (q), 28.4 (t), 33.0 (y), 33.6 (t), 35.6 (d), 38.4 (t), 41.0 (t), 43.3 (d), 47.4 (t), 63.9 (d), 127.0 (d), 129.6, 138.1 (s), 143.2 (s), 209.2 (s).

20b: $[\alpha]^{23}_D$ +13.0° (*c* 0.20, $CHCl_3$); ^1H NMR (500 MHz) δ 0.86 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.03 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.24-1.30 (m, 1 H, C(4)H), 1.36 (qd, *J* = 13, 4.8 Hz, 1 H, C(4)H), 1.69-1.76 (m, 1 H, C(8)H), 1.85 (qd, *J* = 13, 4.8 Hz, 1 H, C(8)H), 2.03-2.14 (m, 2 H, C(5)H and C(9)H), 2.20-2.29 (m, 2 H, C(7)H and C(8a)H), 2.30-2.42 (m, 2 H, C(7)H and C(4a)H), 2.41 (s, 3 H, $ArCH_3$), 2.50 (m, 1 H, C(5)H), 2.86 (ddd, *J* = 14, 13, 3.2 Hz, 1 H, C(3)H), 3.56 (d, *J* = 11, 1 H, C(1)H), 3.68 (m, 1 H, C(3)H), 7.24 (d, *J* = 7.5 Hz, 2 H, ArH), 7.68 (d, *J* = 7.5 Hz, 2 H, ArH); ^{13}C NMR (126 MHz) δ 20.5 (q), 20.8 (q), 21.5 (q), 25.5 (t), 27.0 (t), 27.1 (d), 32.2 (d), 35.1 (d), 40.7 (t), 46.8 (t), 64.3 (t), 127.0 (d), 129.5 (d), 138.6 (s), 142.9 (s), 210.6 (s).

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Supplementary Material Available: Tables of atomic coordintes and equivalent isotropic thermal parameters, bond lengths and interbond angles, torsion angles, anisotropic thermal parameters of the non-H atoms, H-atom coordinates and isotropic thermal parameters, and bond lengths and interbond angles involving H-atoms and ORTEP view and stereoview (8 pages); listing of observed and calculated structure factor amplitudes (8 pages). Ordering information is given on any current masthead page.

The Facility of Formation of a Δ^6 Bond in Dihydromorphinone and Related Opiates

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Treatment of naltrexone, dihydromorphinone, or related opiates that contain a 6-keto group with acetic anhydride or *tert*-butyldimethylsilyl chloride under mild conditions afforded enol derivatives having a Δ^6 bond. Naltrexone also was found to undergo the Robinson annelation reaction with methyl vinyl ketone with facility and in high yield to give the β-hydroxy ketone **3**, whose stereochemistry was determined by means of 2D NMR spectroscopy. Upon acid treatment, **3** was dehydrated to the α,β-unsaturated ketone **4**. Acid-catalyzed equilibration of **4** afforded the unconjugated olefin **5**. These studies suggest that the Δ^6 bond is more stable than one that is exocyclic to ring C of the opiate because it permits ring flattening which may partially relieve torsional ring strain. The Δ^6 bond also may relieve an eclipsing interaction between a C-6 exocyclic substituent and the vicinal furan oxygen.

A number of studies on opiates that contain a C-6 carbonyl function have suggested that they can more readily be converted to enols or enolic derivatives than conventional ketones. For example, it has been reported that dihydromorphinone and related ketones are relatively resistant to addition by Grignard reagents and can form tertiary alcohols only with organolithium compounds.[1] Also, these opiates react more readily than normal ketones with hydrazine or with *N*-aminosuccinimide to afford pyrroles.[2] This reactivity profile and the fact that crystallographic studies[3,4] have shown ring C to be in a flatt-

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