C, 55.00; H, 6.29; N, 5.83. Found: C, 54.74; H, 6.46; N, 5.55.

6,6′-Bis(3-methoxypropen-2-yl)-2,2′-bipyridine (12). To a MeOH solution (10 mL) of **11a** (400 mg, 0.877 mmol), NaOMe (477 mg, 8.77 mmol) was added. The solution was stirred for 2 h at 25 °C followed by the addition of aqueous HCHO (5 mL, 37% w/v). After being stirred for an additional 48 h at 60 °C, the solution was cooled, MeOH evaporated, and the residue extracted with CH_2Cl_2, followed by an aqueous wash of the organic layer and drying over anhydrous $MgSO_4$. The solvent was evaporated and the residue concentrated in vacuo followed by chromatography (ThLC) on Al_2O_3 eluting with C_6H_6/EtOAc (1:1) to afford (41%) **12**, as white microcrystals: ^1H NMR δ 3.46 (s, CH_3, 6 H), 4.58 (dd, H_x, J_{xb} = 1.4 Hz, J_{xa} = 0.9 Hz, 2 H), 5.60 (dt, H_b, $J_{bx} = J_{xb}$, J_{ba} = 1.5 Hz, 2 H), 6.11 (dt, H_a, $J_{ax} = J_{xa}$, $J_{ab} = J_{ba}$, 2 H), 7.53 (dd, 5-py H, J = 7.8, 1.3 Hz, 2 H), 7.78 (t, 4-py H, J = 7.8 Hz, 2 H), 8.37 (dd, 3-py H, J = 7.8, 1.3 Hz, 2 H); IR (KBr) 1550, 1430, 1085 cm^{-1}; MS, m/e 296 (M^+, 8), 281 (100), 249 (43), 219 (24). Due to the unstable character of this molecule, satisfactory elemental analysis was not possible.

2,9-Bis(3-methoxypropen-2-yl)-1,10-phenanthroline (13). The general procedure was the same as described above for **12**. **13** was recrystallized from petroleum ether as white needles (60%): mp 168–170 °C dec; ^1H NMR δ 3.56 (s, CH_3, 6 H), 4.86 (dd, H_x, J_{xb} = 1.4 Hz, J_{xa} = 0.9 Hz, 2 H), 5.80 (dt, H_b, $J_{bx} = J_{xb}$, J_{ba} = 1.4 Hz, 2 H), 6.30 (dt, H_a, $J_{ax} = J_{xa}$, $J_{ab} = J_{ba}$, 2 H), 7.72 (s, 5,6-phen H, 2 H), 7.92 (d, 3,8-phen H, J = 8.5 Hz, 2 H), 8.19 (d, 4,7-phen H, J = 8.5 Hz, 2 H); ^{13}C NMR δ 58.24 (OCH_3), 72.77 (CH_2), 116.91 (=CH_2), 119.68 (C3), 125.90 (C5), 127.80 (C4a), 136.16 (C4), 144.57 (=CR_2), 145.20 (C10b), 156.03 (C2), IR (CsI) 2900, 1660, 1570, 1470, 1350, 1090, 900 cm^{-1}; MS, m/e 520 (M^+, 10), 305 (100), 275 (41), 273 (32), 205 (34). Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.66; H, 6.02; N, 8.55.

General Procedure for Preparation of 14 and 15. To a dry THF solution (30 mL) of **11a** (500 mg, 109 mmol) was added *sec*-BuLi (2.41 mL, 1 M, 2.41 mmol) over a 10-min period under nitrogen atmosphere at −78 °C. The reaction was stirred for 2 h followed by the introduction of formaldehyde gas. After complete disappearance of the red coloration, the mixture was warmed to 25 °C and stirred for an additional 24 h. After concentration in vacuo, the residue was dissolved in CH_2Cl_2, washed with aqueous Na_2CO_3, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude residue was chromatographed (column) on silica gel eluting with CH_2Cl_2/MeOH/$CHCl_3$ (2:1:1), affording two components **14** (first fraction) and **15** (second fraction).

6-Vinyl-6′-(3-hydroxypropen-2-yl)-2,2′-bipyridine (14) was recrystallized from C_6H_{12}, as white crystals (15%): mp 94–95 °C; ^1H NMR δ 4.25 (s, OH, 1 H), 4.67 (m, CH_2, 2 H), 5.52 (dd, H_a, J_{ax} = 10.3 Hz, J_{ab} = 1.9 Hz, 1 H), 5.56 (d, H_b, J = 0.8 Hz, 1 H), 5.87 (d, H_a, J = 0.8 Hz, 1 H), 6.34 (dd, H_b, J_{bx} = 17.4 Hz, $J_{ba} = J_{ab}$, 1 H), 6.92 (dd, H_x, $J_{xb} = J_{bx}$, J_{xa} = 10.3 Hz, 1 H), 7.34 (dd, 5-py H, J = 7.7, 1.3 Hz, 1 H), 7.63 (dd, 5′-py H, J = 7.8, 1.3 Hz, 1 H), 7.77 (t, 4-py H, J = 7.8 Hz, 1 H), 7.84 (t, 4′-py H, J = 7.8 Hz, 1 H), 8.17 (dd, 3′-py H, J = 7.8, 1.3 Hz, 1 H), 8.44 (dd, 3-py H, J = 7.8, 1.3 Hz, 1 H) [see Figure 1]; IR (KBr) 3300 (OH), 1550, 1430 cm^{-1}; MS, m/e 238 (M^+, 87), 237 (100), 210 (26), 209 (99), 208 (72), 207 (66), 185 (57). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.63, H, 5.88; N, 11.76. Found: C, 75.40; H, 5.67; N, 11.50.

6,6′-Bis(3-hydroxypropen-2-yl)-2,2′-bipyridine (15) was recrystallized from C_6H_{12}, as white plates (35%): mp 157–160 °C dec; ^1H NMR δ 4.12 (s, OH, 2 H), 4.68 (m, CH_2, 4 H), 5.58 (d, H_b, J = 0.7 Hz, 2 H), 5.89 (d, H_a, J = 0.7 Hz, 2 H), 7.65 (dd, 5-py H, J = 7.8, 1.5 Hz, 2 H), 7.85 (t, 4-py H, J = 7.8 Hz, 2 H), 8.23 (dd, 3-py H, J = 7.8, 1.5 Hz, 2 H); IR (KBr) 3300 (OH), 1550, 1425, 1025 cm^{-1}; MS, m/e 268 (M^+, 96), 267 (100), 249 (33), 239 (62), 238 (92), 237 (46), 219 (43). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97; N, 10.45. Found: C, 71.24; H, 5.70; N, 10.15.

Acknowledgment. We thank the National Science Foundation and the Louisiana State University Center for Energy Studies for partial support of this work.

Stereocontrolled Synthesis of Cis-Fused Hydroisoquinolines by an Intramolecular Diels–Alder Reaction of (*Z*)-Dienes[1]

S. Wattanasin* and F. G. Kathawala

Sandoz Research Institute, E. Hanover, New Jersey 07936

R. K. Boeckman, Jr.

Department of Chemistry, University of Rochester, Rochester, New York 14627

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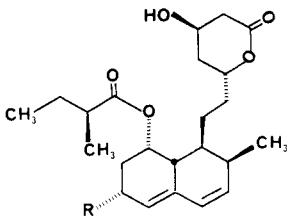
An efficient stereocontrolled synthesis of highly functionalized cis-fused octahydroisoquinolines via an intramolecular Diels–Alder reaction of (*Z*)-dienes is described.

Numerous investigations[2] regarding the use of the intramolecular Diels–Alder reaction as a strategy for stereoselective synthesis of a variety of complex structures have been reported. However, a general method for construction of a substituted cis-fused hydroisoquinoline skeleton with complete stereocontrol via intramolecular cycloaddition has not been published.[3]

In connection with our program concerning structural modifications[4] of the naturally occurring fungal metabolites compactin[5] (**1**, R = H) and mevinolin[6] (**1**, R = CH_3), which



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possess interesting hypocholesterolemic activities,[7] we became interested in the synthesis of an aza analogue **2**

* Address correspondence to this author at Sandoz, where this work was carried out.

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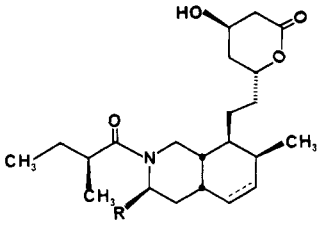
as a potential target molecule for investigation of its biological properties.

Central to our synthetic plan is the use of an intramolecular Diels–Alder reaction to assemble the highly substituted cis-fused hydroisoquinoline **3** a key intermediate



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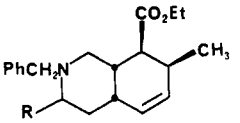


3 (a) R = H

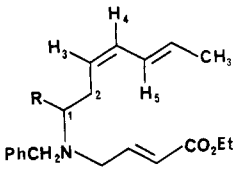
(b) R = β-CH_3

(c) R = α-CH_3

which contains all the required stereochemical features of the bicyclic moiety of **2**.

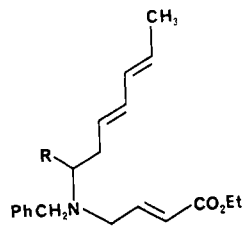
We were particularly interested in the possibility of using a (*Z*)-diene as a stereocontrol element in an intramolecular Diels–Alder reaction which might provide an easy entry into functionalized cis-fused hydroisoquinolines. Unlike an (*E*)-diene, which has two easily accessible transition states,[8] a (*Z*)-diene, because of its geometry, can only attain a single transition state in the intramolecular Diels–Alder reaction.[9] It is possible, however, that the strategy of using the (*Z*)-diene for total stereocontrol could be limited[10] through deleterious side reactions such as 1,5 hydrogen migrations giving isomeric dienes before the desired cycloaddition occurred, as observed by Borch[10a] and, very recently, by Martin.[3f] In addition, the only two examples[9c,e] of the successful intramolecular cycloaddition of (*Z*)-dienes with the connecting chain containing a nitrogen were examples of systems that possessed *highly* activated dienophile groups and gave 5,6-bicyclic compounds as products.

We herein report the successful use of a (*Z*)-diene unit as the control element in the triene **4** to permit the completely stereospecific construction of the highly functionalized cis-fused hydroisoquinoline **3**. Results of the comparative cyclization of the corresponding (*E*)-diene **5** and effects of a methyl group in the connecting chain are discussed.



4

(a) R = H; (b) R = CH_3



5

Synthesis of Dienes 4a and 4b

The desired (*Z*)-dienes **4a** and **4b** were prepared by pathways A and B, respectively.

The known alcohol **6** was prepared by a modification of a published procedure.[11] Silylation of the alcohol **6** with *tert*-butyldiphenylsilyl chloride (imidazole, DMF, room temperature, 48 h) gave **7** (95%). Stereospecific partial reduction via the method of Zweifel[12] afforded the (*Z*)-diene **8** contaminated by 10% of the starting material **7**. This mixture, however, was uncontaminated by any trace of the isomeric (*E*)-olefin.[13] Subsequent desilylation[14]

(1) Presented at the 188th National Meeting of the American Chemical Society, Philadelphia, PA, 1984; Abstract ORG-10.

(2) For reviews of intramolecular Diels–Alder reactions, see: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10; *Synthesis* **1978**, 793; *Heterocycles* **1980**, *14*, 1615; (b) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63; (c) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183.

(3) Simple hydroisoquinolines have been prepared by intramolecular Diels-Alder reactions. See: (a) Oppolzer, W.; Keller, K. *J. Am. Chem. Soc.* **1971**, *93*, 3836. (b) Cox, M. T. *J. Chem. Soc., Chem. Commun.* **1975**, 193. (c) Cannon, J. G.; Lee, T.; Hsu, F.-L; Long, J. P.; Flynn, J. R. *J. Med. Chem.* **1980**, 23, 502. (d) Oppolzer, W.; Francotte, E.; Battig, K. *Helv. Chim. Acta.* **1981**, *64*, 478. (e) Ciganek, E. *J. Am. Chem. Soc.* **1981**, *103*, 6261. (f) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *48*, 5170.

(4) Computer modeling experiments of the natural products as well as their derivations were carried out in association with Prof. G. Marshall at Tripos Associates, St. Louis, MO.

(5) Isolation: Brown, A. G.; Smale, T. C.; King, J. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans 1* **1976**, 1165. Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346. Total Synthesis: Wang, N. Y.; Hsu, C. T.; Sih, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 6358. Hirama, M.; Uei, M. *Ibid.* **1982**, *104*, 4251. Grieco, P. A.; Zelle, R. E.; Lis, R.; Finn, J. *Ibid.* **1983**, *105*, 1403. Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* **1983**, *24*, 3687.

(6) Isolation: Alberts, A. W.; Chen, J.; Kuraon, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M; Joshua, H.; Harria, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer, *J. Proc. Natl. Acad. Sci. USA* **1980**, *77*, 3957. Endo, A. *J. Antibiot.* **1979**, *32*, 852. Total Synthesis: Hirama, M.; Iwashita, M. *Tetrahedron Lett.* **1983**, *24*, 1811.

(7) Mabuchi, H.; Haba, T.; Tatami, R.; Miyamoto, S.; Sakai, Y.; Wakasugi, T.; Watanabe, A.; Koizumi, J.; Takeda, R. N. *Engl. J. Med.* **1981**, 305, 478. Tobert, J. A.; Hitzenberger, G.; Kukovetz, W. R.; Holmes, I. B.; Jones K. H. *Atherosclerosis* **1982**, *41*, 61.

(8) There have been a large number of examples utilizing intramolecular Diels-Alder reaction of (*E*)-dienes. However, in many of these cases a mixture of products resulting from both endo and exo transition states was obtained. See: (a) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200. (b) Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180. (c) Takebayashi, T.; Iwasawa, N.; Mukaiyama, T.; Hata, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1669. (d) Ref 3f.

(9) Successful intramolecular Diels–Alder reactions of (*Z*)-dienes include: (a) House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061. (b) Oppolzer, W.; Fehr, C.; Warneke, *J. Helv. Chim. Acta* **1977**, *60*, 48; (c) Pyne, S. G.; Hensel, M. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1982**, *104*, 5719. (d) Boeckman, R. K.; Alessi, T. R. *Ibid.* **1982**, *104*, 3216. (e) Yoshida, M.; Nakai, H.; Ohno, M. *Ibid.* **1984**, *106*, 1133.

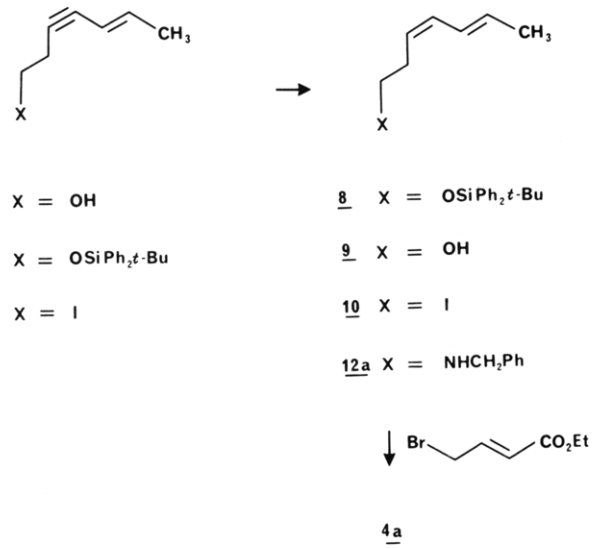
(10) Unsuccessful intramolecular Diels–Alder reaction of (*Z*)-dienes include: (a) Borch, R. F.; Evans, A. J.; Wade, J. J. *J. Am. Chem. Soc.* **1977**, *99*, 1612; (b) Ref 3f.

(11) Crombie, L.; Krasinski, A. H. A.; Manzoor-i-Khuda, M. *J. Chem. Soc.* **1963**, 4970.

(12) Zweifel, G.; Polston, N. L. *J. Am. Chem. Soc.* **1970**, *92*, 4068.

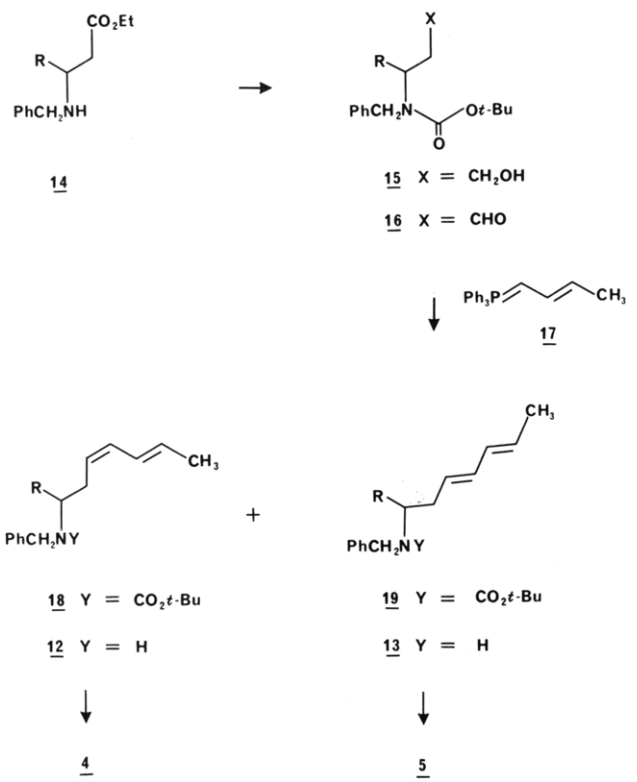
(13) Attempts to effect a stereospecific partial reduction of **6** and **7** under catalytic hydrogenation conditions were unsuccessful.

Pathway A



4a

Pathway B (a) R = H; (b) R = CH_3



14

15 X = CH_2OH

16 X = CHO

17

18 Y = CO_2t-Bu

12 Y = H

19 Y = CO_2t-Bu

13 Y = H

4 5

(n-Bu_4NF, THF, room temperature) of this mixture gave a 9:1 mixture of the (Z)-diene alcohol **9** and the alcohol **6**. Iodination of this mixture of **9** and **6** via reaction with I_2, triphenylphosphine, and imidazole in toluene at room temperature yielded a 9:1 mixture of iodides 10 and **11**. This mixture as well as the previous mixture realized at the stage of the alcohols **9** and **6** proved to be inseparable by chromatography. Fortunately, upon N-benzylation of a mixture of **10** and **11** with benzylamine and triethylamine in DMF,[15] the desired (Z)-diene amine **12a** was obtained in pure form (38% from **7**) after a routine chromatographic separation.

(14) Hanessian, S.; Lavalle, P. *Can. J. Chem.* **1977**, 55, 562.

(15) We thank Prof. S. F. Martin (University of Texas, Austin) for experimental details of a similar N-benzylation reaction in DMSO.

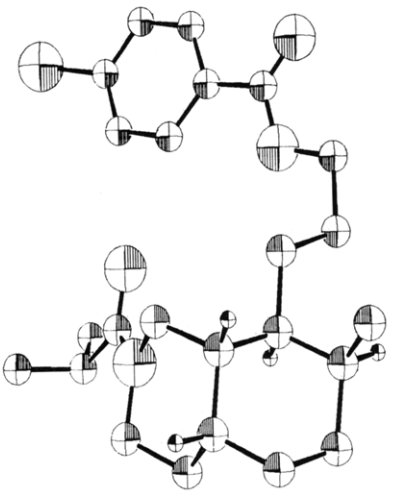
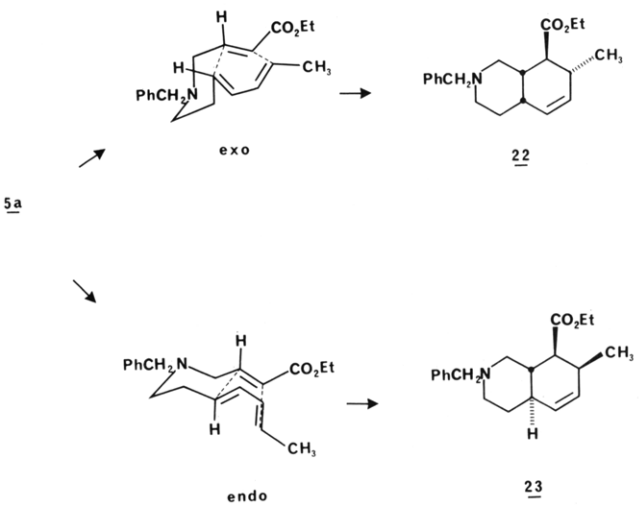


Figure 1. Molecular conformation, derived from X-ray structure analysis of **20**.

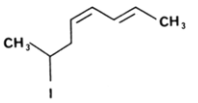
Scheme I



Treatment of the (Z)-diene amine **12a** with excess *trans*-ethyl 4-bromocrotonate and diisopropylethylamine in DMF at room temperature for 24 h afforded the (Z)-diene **4a** in 77% yield.[16]

Lithium aluminum hydride reduction of the known amino ester **14b**[17] and protection of the N-benzyl group with the t-BOC group gave **15b**, which upon oxidation (PCC, CH_2Cl_2) of **15b** yielded the aldehyde **16b** (81% overall yield). Wittig reaction (−78 °C, 15 min) of **16b** with the ylide **17** in HMPA–THF (1:2) afforded a 4:1 mixture of the desired (Z)-diene **18b** and the isomeric (E)-diene **19b** in 90% yield.[18] Deprotection[19] (Me_3SiI, CH_2Cl_2) of this mixture of **18b** and **19b** gave an identical mixture of the amines **12b** and **13b** in 95% yield. Separation of these amines as well as of the previous dienes was not feasible.

(16) Pathway A did not lend itself to the preparation of methyl (Z)-diene **4b** due to the unsuccessful N-benzylation of iodide i to give **12b**.



i

(17) Biggs, D. F.; Coutts, R. T.; Selly, M. L.; Towill, G. A. *J. Pharm. Sci.* **1972**, *61*, 1739.

(18) Attempts to effect a more favorable Z/E ratio under a variety of reaction conditions have thus far produced no improvement.

(19) Lott, R. S.; Chauhan, U. S.; Stammer, C. H. *J. Chem. Soc., Chem. Commun.* **1979**, 495.

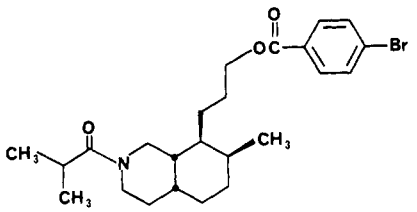
However, treatment of this inseparable 4:1 mixture of **12b** and **13b** with 1 equiv of *trans*-ethyl 4-bromocrotonate in triethylamine (1 equiv) in DMF at room temperature for 48 h afforded the desired (*Z*)-aza triene **4b** in 30% yield after purification, contaminated by only a trace of the isomeric (*E*)-aza triene **5b** as judged by NMR analysis.[20]

Use of the analogous reaction sequence in pathway B to synthesize the (*Z*)-triene **4a** provided an inseparable mixture of amines **12a** and **13a**.[21] Treatment of this mixture with *trans*-ethyl 4-bromocrotonate as described above gave a 1:1 mixture of **4a** and **5a** which could not be separated by chromatography.[22]

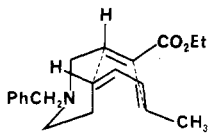
Intramolecular Diels–Alder Reaction of Dienes

Heating a solution of the (*Z*)-diene **4a** in xylene at 160 °C (sealed tube) for 48 h afforded cleanly a single cycloadduct, the *cis*-hydroisoquinoline **3a**, in 71% yield. No evidence of the formation of any isomeric cycloadducts was observed.

The stereochemistry of **3a** was established to be that depicted by a combination of difference decoupling and difference nuclear Overhauser effect (NOE) measurements. These experiments revealed the position[23] of the axial angular proton (H_{8a}) adjacent to the carboethoxy group, which had the expected small (6 Hz) coupling with the *cis* ring-junction proton (H_{4a}). Furthermore, upon irradiation of the secondary methyl group (C_7-CH_3), this same proton (as well as the H_7 and the vinylic protons) showed the expected NOE enhancement. These data define the cis relationship of the methyl group and ring junction proton as well as the cis ring-junction stereochemistry. The structure of **3a** was further confirmed by x-ray structure analysis[24] of its derivative **20**[24,25] (Figure 1).



20

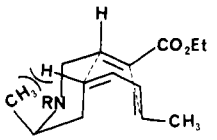


21

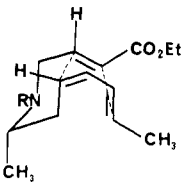
This finding demonstrates that cyclization of (*Z*)-diene **4a** has occurred with complete stereoselectivity through the expected single endo transition state **21** and 1,5 sigmatropic hydrogen shifts which would result in the loss of the geometric integrity of the diene apparently do not present a limitation in this less activated system.[9c,e]

For comparison, an inseparable 1:1 mixture of the (*Z*)-diene **4a** and (*E*)-diene **5a** was heated under the same conditions to produce a mixture of **3a** (35%), **22** (15%), and **23** (16%).[26] The structural assignments of **22** and **23** were fully supported by the infrared, ^1H NMR, and ^{13}C NMR spectra. These results demonstrate that the corresponding (*E*)-diene **5a** does not undergo intramolecular Diels–Alder reaction with a significant degre of stereocontrol. The (*E*)-azadiene **5a** cyclized via the two easily accessible exo and endo transition states which are of comparable energy to afford a 1:1 ratio of **22** and **23** (Scheme I).

Cyclization of the methyl (*Z*)-diene **4b** occurred (xylene, 160 °C) to produce a mixture of **3b** (15%) and its epimer



3b T.S.



3c T.S.

3c (44%), the stereochemistry being different only at the methyl group adjacent to the nitrogen. The spectral data (^1H, ^{13}C NMR, and MS) of these two cycloadducts supported their assigned structures. Examination of models of the two possible endo transition states leading to **3b** and **3c** revealed that an eclipsing 1,3-interaction develops between the axial methyl group and the angular hydrogen in transition state **3b**, whereas this type of interaction is absent altogether in transition state **3c** in which the methyl occupied an "equatorial-like" environment. This interaction very well may account for the favored formation of the equatorial methyl-*cis*-hydroisoquinoline **3c** realized in the cyclization of **4b**.

While this route does not provide an easy access to the cis-fused hydroisoquinoline having a β-methyl group at C-3, it provides a very convenient access to the corresponding α-methyl compound, since refluxing **4b** in *o*-dichlorobenzene N_2, 18 h) produced **3c** as the major stereoisomer (>5:1) in 62% yield.

Our findings substantially extend the scope and synthetic utility of (*Z*)-diene cycloadditions and serve to demonstrate the utility of the intramolecular Diels–Alder reaction of (*Z*)-dienes bearing a nitrogen in the connecting chain as a viable method for the stereospecific construction of functionalized cis-fused hydroisoquinolines.

Experimental Section

General Methods. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an Analect Instruments FX-200 FTIR spectrometer for thin films unless otherwise noted. Proton and carbon NMR spectra were obtained on either a JEOL FX 90Q or a JEOL FX 200 instrument. The spectra were measured in deuteriochloroform solution, unless otherwise stated, relative to tetramethylsilane (δ 0.00). Each signal is described in terms of chemical shift in parts per million from tetramethylsilane, multiplicity, coupling constant (Hz), and intensity in that order with the use of the following abbreviations:

(20) In contrast, the use of an excess of the bromocrotonate (2–3 equiv) gave a mixture (4:1) of **12b** and **13b** in higher yields (60–70%).

(21) In this case, Wittig reaction of **16a** with ylide **17** under the same conditions as described for **16b** afforded a 1:1 mixture of **18a** and **19a**.

(22) Establishment of the stereochemistry of (*Z*)-dienes **4a** and **4b** was readily accomplished by ^1H NMR by using difference decoupling and difference NOE techniques. These measurements showed the expected coupling constants (10 Hz) of H_3 and H_4 in **4a** and **4b**. In addition, H_5 and the methylene proton on C-2 showed the expected NOE enhancement.

(23) Atoms have been numbered according to the isoquinoline numbering system.

(24) Compound **20** was prepared from **3a** by the following unambiguous sequence of reactions: (i) $LiAlH_4$, (ii) H_2/Pd–C, (iii) isobutyryl chloride/Et_3N, (iv) I_2/Ph_3P/imidazole, (v) potassium dimethyl malonate/PhH/HMPA, (vi) aqueous NaOH; dilute HCl/PhH/heat ($-CO_2$); HCl/CH_3OH; (vii) $LiBH_4$/THF; *p*-bromobenzoyl chloride.

(25) Details will be reported in due course.

(26) The product ratio was further confirmed by GC analysis of the crude mixture.

s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were recorded on LKB-9000 GC–MS or VG 7070E mass spectrometer. Exact-mass determinations were obtained on the VG 7070E instrument. Microanalyses were performed by W. Bonkoski, Physical Chemistry Department, Sandoz, Inc.

All reactions were run under nitrogen. All organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated on a Buchi Rotavapor. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl. Hexamethylphosphoramide (HMPA), methylene chloride, triethylamine, and dimethylformamide (DMF) were distilled from calcium hydride.

All other solvents were reagent grade and used as received. Thin-layer chromatography (TLC) was performed on 0.25-mm E. Merck precoated silica gel plates (60F-254). Preparative thick-layer chromatography (preparative TLC) was performed on 1 mm × 20 cm × 20 cm Analtech precoated silica gel plate (silica gel GF). Silica gel 60 (230–400 mesh) supplied by Merck was used for column chromatography.

1-((*tert*-Butyldiphenylsilyl)oxy)hept-5-en-3-yne (7). To a solution of alcohol **6** (760 mg, 0.0069 mol) in DMF (7 ml) was added imidazole (939 mg, 0.0138 mol) and *tert*-butylchlorodiphenylsilane (1.8 mL, 0.007 mol). The mixture was stirred at room temperature for 24 h and poured into water (50 mL). The mixture was extracted with petroleum ether (bp 30–60 °C). The combined extracts were washed with water and brine and dried, and the solvent was removed to obtain 2.3 g of an oil. Purification by column chromatography on silica gel (ether–petroleum ether, 1:20) gave **7** as a colorless oil (2.24 g, 93%): IR 3050, 2960, 2859, 1474, 1429, 1058, 917, 823, 736, 689 cm^{-1}; ^1H NMR δ 1.0 (s, 9 H), 1.71 (dd, J = 8.5 and 2.5 Hz, 3 H), 2.55 (t, J = 8.5 Hz, 2 H), 3.75 (t, J = 8.5 Hz, 2 H), 5.45 (dd, J = 20 and 2.5 Hz, 1 H), 6.05 (m, 1 H), 7.40 (m, 6 H), 7.20 (m, 4 H); mass spectrum, m/e 291 (M^+ – *t*-Bu). Anal. Calcd for $C_{23}H_{28}OSi$: C, 79.36; H, 8.10. Found: C, 79.80; H, 8.49.

(*Z*,*E*)-*N*-Benzyl-3,5-heptadien-1-amine (12a). To a solution of ether **7** (2 g, 0.00574 mole in THF (10 mL) was added at −5 → 0 °C a solution of disiamylborane (0.0069 mol) in THF. The reaction mixture was stirred at 0 °C (ice-water bath) for 2 h, then diluted with glacial acetic acid (3 mL), and maintained at 55–60 °C for 5 h. The reaction mixture was then cooled and made basic by 50% aqueous NaOH solution, and 30% hydrogen peroxide (3 mL) was added. After the reaction mixture was stirred at room temperature for 30 min, sodium chloride was added, and the mixture was extracted with ether. The extracts were washed with water, dried, and concentrated to give a clear oil (1.94 g) of **8**, contaminated by 10% of the starting material (**7**) as judged from NMR analysis. This mixture proved to be inseparable by chromatography and was used directly in the next step.

To the above product (350 mg) in dry THF (6 mL) was added tetrabutylammonium fluoride (1 M, 4 mL, 0.004 mol) and glacial acetic acid (0.23 mL, 0.004 mol). After 24 h at room temperature, water was added and the mixture was extracted with ether. The crude product was purified by preparative TLC (ether–petroleum ether, 1:1) to afford a 9:1 mixture of **9** and **6** as a colorless oil (93 mg).

A mixture of the above alcohol (90 mg), triphenylphosphine (252 mg, 0.964 mmol), imidazole (66 mg, 0.964 mmol), and iodine (245 mg, 0.964 mmol) in toluene (3 mL) was stirred at room temperature for 3 h. The reaction was diluted with ether and filtered through a short pad of silica gel 60 (230–400 mesh). Evaporation furnished a 9:1 mixture of **10** and **11** as a pale yellow oil (170 mg) which was used without further purification.

To a solution of the above iodide (126 mg) in DMF (1.5 mL) was added triethylamine (0.08 mL, 0.5675 mmole and benzylamine (0.63 mL, 0.5675 mmol). After 2 days at room temperature, the mixture was diluted with water and extracted with ether. The extracts were washed with water and brine and dried. Purification of the crude product by preparative TLC (methanol–ethyl acetate, 1:9; containing a few drops of ammonium hydroxide) gave 60 mg (about 38% from **7**) of the (*Z*)-diene amine **12a** in pure form as judged by NMR analysis: ^1H NMR δ 1.75 (d, J = 8.5 Hz, 3 H), 2.15 (br s, 1 H), 2.40 (m, 2 H), 2.70 (m, 2 H), 3.80 (s, 2 H), 5.25 (q, J = 10 Hz, 1 H), 5.70 (m, 1 H), 6.00 (t, J = 10 Hz, 1 H), 6.35 (t, J = 14 Hz, 1 H), 7.20–7.70 (m, 5 H); ^{13}C NMR δ 18.22, 28.08, 48.77, 53.65, 126.19, 127.11, 128.30, 128.46, 130.03, 130.63, 139.62; mass spectrum, m/e 201 (M^+). **12a** was also obtained as its hydriodide salt. Anal. Calcd for $C_{14}H_{20}NI$: C, 51.02; H, 6.07; N, 4.25. Found: C, 51.00; H, 5.72; N, 4.09.

Ethyl 4-[1-*N*-Benzyl-(*Z*,*E*)-3,5-heptadienyl]-2-butenoate (4a). To a solution of **12a** (40 mg, 0.199 mmol) and diisopropylethylamine (0.06 mL, 0.298 mmol) in DMF (2 mL) at room temperature was added *trans*-ethyl 4-bromocrotonate (57 mg, 0.298 mmol). After 24 h, the reaction mixture was poured into water and extracted with ether. The crude product was purified by preparative TLC (chloroform) to give (*Z*)-triene **4a** (48 mg, 77%) as an oil: IR 2980, 2800, 1710, 1650, 1450, 1380, 1270, 1020, 740, 700 cm^{-1}; ^1H NMR δ 1.28 (t, J = 8.5 Hz, 3 H), 1.75 (d, J = 8.5 Hz, 3 H), 2.30 (t, J = 8.5 Hz, 1 H), 2.50 (t, J = 8.5 Hz, 1 H), 3.25 (dd, J = 8.5 and 2.5 Hz, 2 H), 3.60 (s, 2 H), 4.20 (q, J = 8.5 Hz, 2 H), 5.25 (q, J = 10 Hz, 1 H), 5.65 (m, 1 H), 6.00 (m, 2 H), 6.25 (br t, 1 H), 7.0 (m, 1 H), 7.30 (m, 5 H); ^{13}C NMR δ 14.26, 18.25, 25.67, 53.69, 54.62, 58.44, 60.28, 122.75, 126.59, 126.84, 127.81, 128.27, 128.73, 129.64, 129.68, 146.42; mass spectrum, m/e 313 (m^+). Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.56; H, 8.81; N, 4.46. Found: C, 76.15; H, 9.27; N, 4.48.

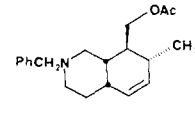
Ethyl *cis*-1,2,3,4,4aβ,7,8,8aβ-Octahydro-2-benzyl-7β-methyl-8-isoquinolinecarboxylate (3a). A deoxygenated solution of (*Z*)-triene **4a** (20 mg) and bis(3-*tert*-butyl-4-hydroxy-5-methylphenyl)sulfide (2 mg) in xylene (6 mL) was heated at 160–165 °C in a thick-walled glass tube for 48 h. The tube was cooled and opened, and the solvent was removed by distillation. TLC and ^1H NMR analysis of the crude product showed that the derived Diels-Alder adduct was exclusively formed. Purification by preparative TLC (ether–petroleum ether, 2:3) afforded cis-fused hydroisoquinoline **3a** as a pale yellow oil (14.3 mg, 71%): IR 3021, 2975, 2936, 2803, 2761, 1728, 1456, 1374, 1300, 1250 cm^{-1}; ^1H NMR δ 0.90 (d, J = 8.5 Hz, CH_3), 1.20 (t, J = 8.5 Hz, ester CH_3), 1.55 (m, 1 H, H_4), 1.65 (m, 1 H, H_4), 2.10 (m, 4 H, H_{8a}, H_{4a}, H_1, H_3), 2.55 (m, 1 H, H_7), 2.75 (m, 1 H), H_3), 2.92 (d, J = 12 Hz, H_1), 3.20 (dd, J_{H8-H8a} = 11 Hz, J_{H7-H8} = 6 Hz, H_8), 3.27 (d, J = 14 Hz, 1 H, CHPh), 4.00 (q, J = 8.5 Hz, ester CH_2), 5.60 (m, 2 H, H_5, H_6), 7.30 (m, 5 H, aryl); ^{13}C NMR δ 14.16, 17.60, 32.41, 35.31, 40.79, 47.56, 53.76, 57.14, 59.86, 63.22, 126.84, 127.95, 128.89, 128.27, 129.14, 129.52, 131.28, 138.49, 173.32; exact mass calcd for $C_{20}H_{27}NO_2$, 313.204; found, 313.204.

Ethyl *cis*-1,2,3,4,4aβ,7,8,8aβ-Octahydro-2-benzyl-7α-methyl-7-isoquinolinecarboxylate (22) and Ethyl *trans*-1,2,3,4,4aα,7,8,8aβ-Octahydro-2-benzyl-7β-methyl-8-isoquinolinecarboxylate (23). Treatment of a 1:1 mixture of **4a** and **5a** (250 mg) in a similar manner to that described for the preparation of **3a** afforded **22** (39.2 mg, 15.6%, highest R_f), **3a** (87 mg, 35%, identical in all respects, TLC and NMR, with the previously obtained sample), and **23** (40 mg, 16%, lowest R_f) after separation by column chromatography on silica gel (hexane–isopropylalcohol, 95:5).

22: ^1H NMR δ 1.0 (d, J = 8.5 Hz, 3 H), 1.21 (t, J = 8.5 Hz, 3 H), 1.3–1.8 (m, 2 H), 1.9 (dt, 1 H), 2.05 (m, 2 H), 2.45 (m, 2 H), 2.65 (t, J = 14 Hz, 2 H), 2.85 (dd, J = 2 and 14 Hz, 1 H), 3.40 (q, J = 16 Hz, 2 H), 3.90 (m, 1 H), 4.15 (m, 1 H), 5.60 (d, J = 14 Hz, 1 H), 5.65 (m, 1 H), 7.30 (m, 5 H); ^{13}C NMR δ 14.40, 20.21, 30.20, 34.92, 35.42, 36.79, 47.27, 54.25, 56.50, 59.92, 126.81, 128.01, 128.74, 129.14; exact mass calcd for $C_{20}H_{27}NO_2$, 313.204; found, 313.205.[27]

23: ^1H NMR δ 0.92 (d, J = 8.5 Hz, 3 H_3), 1.15 (t, J = 8.5 Hz, 3 H), 1.40 (qd, $J_{\alpha H3-\beta H4}$ = 13 Hz, $J_{\beta H4-H4a}$ = 13 Hz, J_{H4-H4} = 13 Hz, $J_{\beta H3-\beta H4}$ = Hz, βH_4), 1.70 (m, 3 H), αH_1, H_4, H_{4a}), 1.8 (qd, $J_{H4a-H8a}$ = 11 Hz, $J_{\alpha H1-H8a}$ = 11 Hz, J_{8-8a} = 11 Hz, $J_{\beta H1-H8a}$ = 3 Hz, H_{8a}), 2.0 (td, $J_{\alpha H3-\beta H4}$ = 13 Hz, J_{H3-H3} = 13 Hz, $J_{\alpha H3-\alpha H4}$ = 4Hz, $_{\alpha}H_3$), 2.55–2.60 (br m, 2 H, H_7, H_8), 2.95 (dm, J = 11 Hz,

(27) Further confirmation of the structure assignment to **22** was obtained from NMR measurements carried out on compound ii which was



ii

prepared from **22** by reduction (LiAlH4, THF, 3 °C) and esterification (acetyl chloride triethylamine, CH_2Cl_2).[25]

βH_3), 3.22 (br d, J = 11 Hz, βH_1), 3.55 (q, J = 13 Hz, 2 H), 4.1 (q, J = 8.5 Hz, 2 H), 5.45 (br d, J_{H4a-H5} = 10 Hz, H_5), 5.60 (dm, J = 10 Hz, H_6), 7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.19, 17.55, 31.80, 32.44, 35.33, 40.82, 47.59, 53.75, 57.17, 59.86, 63.24, 126.84, 128.09, 129.14, 129.56, 131.28, 138.52, 173.32; exact mass calcd for $C_{20}H_{27}NO_2$, 313.204; found, 313.203.

***tert*-Butyl *N*-Benzyl-*N*-(1-methyl-3-oxopropyl)carbamate (16b).** A solution of ester **14b**[17] (7 g, 0.0316 mol) in ether (30 mL) was added dropwise to a suspension of lithium aluminum hydride (1.2 g, 0.0316 mol) in ether (30 mL). After 30 min, the reaction was quenched by addition of methanol (150 mL) and filtered through a short pad of neutral alumina. The filtrate was concentrated and the residue was redissolved in ether. Filtration and evaporation afforded a clear colorless oil of crude alcohol (5.5 g, 98%) which was used without further purification.

To a solution of the above alcohol (5.5 g, 0.0307 mol) and triethylmaine (6 ml, 0.0431 mol) in methylene chloride (50 mL) at 0 °C was added dropwise a solution of di-*tert*-butyl dicarbonate (7 g, 0.0321 mol) in methylene chloride (50 mL). After 1 h at 0 °C, the reaction mixture was stirred at room temperature overnight. Ethyl acetate (150 mL) and water (100 mL) were added, and the layers were separated. The aqueous phase was extracted once more with ethyl acetate, and the extracts were washed with cold 3 N HCl, water, saturated aqueous sodium bicarbonate, and brine and dried. The crude product was purified by column chromatography on silica gel. Elution with ethyl acetate–petroleum ether (1:1) afforded **15b** (7.9 g, 92%) as a colorless oil: IR 3420, 2950, 1686, 1410, 1366, 1250, 1160, 880, 750, 700 cm^{-1}; ^1H NMR δ 1.10 (d, J = 8.5 Hz, 3 H), 1.35 (s, 9 H), 1.60 (br t, 2 H), 3.50 (br s, 3 H), 4.30 (q, J = 20 Hz, 2 H), 4.50 (br s, 1 H), 7.30 (m, 5 H); mass spectrum, m/e 223 (M^+ – t-Bu).

To a solution of alcohol **15b** (7.8 g, 0.028 mol) in methylene chloride (70 mL) at 5 °C was added portionwise pyridinium chlorochromate (15.06 g, 0.070 mol). After 2 h at room temperature, the reaction mixture was diluted with ether and filtered through a short pad of silica gel (30 g). Concentration and purification of the crude product by column chromatography on silica gel (ether–petroleum ether, 1:1) gave a colorless oil of aldehyde **16b** (6.9 g, 90%): IR 3018, 2981, 2936, 2732, 1720, 1681, 1461, 1406, 1361, 1245, 1166, 1124, 1074 cm^{-1}; ^1H NMR δ 1.15 (d, J = 8.5 Hz, 3 H), 1.5 (br s, 9 H), 2.52 (m, 1 H), 2.72 (m, 1 H), 4.40 (br s, 3 H), 7.30 (m, 5 H), 9.51 (br s, 1 H); ^{13}C NMR δ 19.15, 27.41, 28.41, 47.88, 48.67, 49.43, 127.04, 128.44, 200.45. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.13; H, 8.23; N, 4.92.

Ethyl 4-[1-*N*-Benzyl-1-methyl-(*Z*,*E*)-3,5-heptadienyl]-2-butenoate (4b). To a stirred suspension of crotylphosphonium bromide (12.7 g, 0.032 mol) in THF (100 mL) at 0 °C was added dropwise *n*-BuLi (1.6 M, 22 mL, 0.035 mol). After being stirred at 0 °C for 30 min, the resulting dark orange mixture was cooled to −78 °C and HMPA (60 mL) was added dropwise. Aldehyde **16b** (7.4 g, 0.0266 mol) in THF (20 mL) was then added rapidly to the above solution at −78 °C. After 15 min, the reaction mixture was poured into water and extracted with ether. The combined extracts were washed with water and brine and dried. Purification of the crude product by column chromatography on silica gel (ether–petroleum ether, 1:5) gave an inseparable mixture of **18b** and **19b** as a colorless oil (9.0 g, 90%, **18b**:**19b** = 4:1): IR 2978, 2930, 1681, 1451, 1406, 1366, 1342, 1239, 1166 cm^{-1}; ^1H NMR δ 1.10 (t, 3 H), 1.25 (t, 3 H), 1.35 (br s, 9 H),0 (q, J = 10 Hz, a vinylic proton of **18b**), 5.40 (m, the corresponding vinylic proton of **19b**), 5.70 (m, 1 H), 5.95 (t, J = 14 Hz, 1 H), 6.21 (t, J = 14 Hz, 1 H), 7.30 (m, 5 H); mass spectrum, m/e 258 (M^+ – t-Bu). The ratio of **18b** and **19b** (4:1) was determined by integration of the ^1H NMR (200 MHz) spectrum; the mixture was not separable and was used as such.

To a solution of a 4:1 mixture of **18b** and **19b** (1.5 g, 0.0047 mol) in methylene chloride (8 mL) at room temperature was added trimethylsilyl iodide (0.7 mL, 0.005 mol) dropwise. After the mixture was stirred for 20 min, methanol (0.4 mL) was added, and stirring was continued for 5 min. Concentration and purification of the crude product by column chromatography on silica gel (methanol–ethyl acetate, 1:9) afforded an inseparable mixture of **12b** and **13b** (0.91 g, 90%). NMR analysis indicated a 4:1 ratio of **12b** and **13b**: ^1H NMR δ (2xd, J = 8.5 Hz, 3 H), 1.75 (t, 3 H), 2.50 (m, 2 H), 3.0 (m, 1 H), 3.40 (br s, 1 H), 4.0 (q, J = 17 Hz, 2 H), 5.20 (q, J = 10 Hz, a vinylic proton of **12b**), 5.40 (m, the corresponding vinylic proton of **12b**), 5.71 (m, 1 H), 6.11 (m, 1 H), 6.73 (m, 1 H), 7.45 (m, 5 H).

To a solution of a 4:1 mixture of **12b** and **13b** (765 mg, 3.55 mmol) and triethylamine (0.45 mL) in DMF (15 mL) at room temperature was added *trans*-ethyl 3-bromocrotonate (687 mg, 3.55 mmol). After 48 h at room temperature, water was added and the reaction mixture was extracted with ether. The extracts were dried and concentrated, and the crude product was purified by column chromatography on silica gel. Elution with ether–petroleum ether (3:7) afforded (*Z*)-triene **4b** (330 mg, 30%) as a pale yellow oil: ^1H NMR δ 1.0 (d, J = 8.5 Hz, 3 H), 1.25 (t, J = 8.5 Hz, 3 H), 1.75 (d, J = 8.5 Hz, 3 H), 2.15 (m, 1 H), 2.40 (m, 1 H), 2.85 (q, J = 8.5 Hz, 1 H), 3.22 (m, 2 H), 3.60 (q, J = 17 Hz, 2 H), 4.15 (q, Hz, 1 H, 5.65 (m, 1 H, 6.00 (m, 2 H), 6.28 (t, J = 14 Hz, 1 H), 6.90 (m, 1 H), 7.30 (m, 5 H); ^{13}C NMR δ 14.26, 14.53, 18.28, 31.68, 50.68, 53.76, 54.81, 60.21, 122.00, 126.84, 126.96, 128.22, 128.52, 129.49, 140.07, 147.93; mass spectrum, m/e 327 (M^+); exact mass calcd for $C_{21}H_{29}NO_2$, 327.219; found, 327.216.

Ethyl *cis*-1,2,3,4,4aβ,7,8,8aβ-Octahydro-2-benzyl-3β,7β-dimethyl-8-isoquinolinecarboxylate (3b) and Ethyl *cis*-1,2,3,4,4aβ,7,8,8aβ-Octahydro-2-benzyl-3α,7β-dimethyl-8-isoquinolinecarboxylate (3c). In a similar manner to that described for the preparation of **3a**, (*Z*)-diene **4b** (500 mg) gave **3b** (78 mg, 15%, lower R_f) and **3c** (220 mg, 44%, higher R_f) after separation by column chromatography on silica gel (ether–petroleum ether, 1:4). ^1H NMR analysis of the crude mixture showed that less than 5% of other isomeric adducts were formed.

3b: ^1H NMR δ 0.90 (d_1, J = 8.5 Hz, C_7-CH_3), 1.05 (d, J = 8.5 Hz, C_3-CH_3), 1.15 (t, J = 8.5 Hz, 3 H), 1.55 (tt, $J_{\alpha H4-\beta H4}$ = 14 Hz, $J_{H3-\alpha H4}$ = 6 Hz, $J_{\alpha H4-H4a}$ = 14 Hz, $J_{\alpha H-\beta H4}$ = 14 Hz, $J_{H3-\beta H4}$ = 6 Hz, βH_4), 2.05 (m, H_{8a}), 2.30 (dd, $J_{\alpha H1-\beta H1}$ = 14 Hz, $J_{\alpha H1-H8a}$ = 6 Hz, αH_1), 2.40 (br t, H_{4a}, H_7), 2.30 (dd, $J_{\alpha H1-\beta H1}$ = 14 Hz, $J_{\beta H1-H8a}$ = 5 Hz, βH_1), 2.72 (q, J = 6 Hz, H_3), 2.95 (br t, J_{H7-H8} = 5 Hz, J_{H8-H8a} = 8.5 Hz, H_8), 3.30 (d, J = 14 Hz, NC*HPh*), 3.65 (d, J = 14 Hz, NC*HPh*), 3.95 (m, 2 H), 5.5 (m, 2 H, H_5 and H_6), 7.30 (m, 5 H); ^{13}C NMR δ 24.56, 27.23, 30.42, 37.78, 39.71, 42.46, 45.62, 47.66, 58.82, 60.89, 61.86, 62.50, 118.10, 118.32, 119.11, 119.39, 119.54, 120.00, 120.08, 121.24, 121.68, 129.90, 157.66; exact mass calcd for $C_{21}H_{29}NO_2$, 327.219; found, 327.221.[28]

3c: ^1H NMR ($CDCl_3$) δ 0.80 (d, J = 8.5 Hz, C_7-CH_3), 1.1 (t, J = 8.5 Hz, 3 H), 1.15 (d, J = 8.5 Hz, C_3CH_3), 1.25 (q, $J_{H3-H\alpha H4}$ = 14 Hz, $J_{\alpha H4-H4}$ = 14 Hz, $J_{\alpha H4-H4a}$ = 14 Hz, 1 H, αH_4, 1.65 (td, $J_{\alpha H4-\beta H}$ = 14 Hz, $J_{H3-\beta H4}$ = 5 Hz, $J_{\beta H4-H4a}$ = 5 Hz, βH_4), 2.15 (m, 3 H, H_3, αH_1, H_{8a}), 2.65 (m, H_7), 2.82 (d, J = 17 Hz, 1 H, NC*HPh*), 3.02 (br d, J = 14 Hz, βH_1), 3.20 (dd, J_{H7-H8} = 14 Hz, J_{H8-H8a} = 6 Hz, H_8), 3.80 (m, 2 H), 4.10 (d, J = 17 Hz, 1 H, NC*HPh*), 5.60 (m, 2 H, H_5 Hz), 7.30 (m, 5 H); ^{13}C NMR δ 14.07, 17.26, 21.18, 29.95, 32.24, 35.55, 39.34, 41.80, 55.20, 57.68, 57.88, 59.60, 129.38, 127.91, 128.64, 130.15, 130.66, 140.54, 173.86; exact mass calcd for $C_{21}H_{29}NO_2$, 327.219; found, 327.216. The multiplicites of H_1, H_5, H_6, H_7, H_8 and H_{8a} signals of this compound are very similar to those of **3a**.

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(28) The stereochemistry of the C_3-methyl group of **3b** and **3c** was further supported by the nature of the diastereotopic protons on the *N*-benzyl group. See: Lyle, R. E.; Thomas, J. J. *Tetrahedron Lett.* **1969**, 897.