raphy (elution with EtOAc/hexane, 2:1) to give 82 mg of (3*R**)-5-(hydroxymethyl)-3-methyl-1-cyclopentadecanol (**36**) (87%) as a colorless liquid: IR 3400 (br) cm^{-1}; FDMS *m/e* 270 (M^+, 100), 252 (11).

A mixture of **36** (60 mg, 0.22 mmol) and pyridinium chlorochromate (142 mg, 0.66 mmol) in CH_2Cl_2 (5 mL) was stirred at 25 °C for 15 h and filtrated on Celite. The filtrate was subjected to the usual workup to leave a residue, which was purified by a short flash column eluted with ether to afford 53 mg of **37** (90% yield) as a colorless liquid: R_f 0.39 in EtOAc/hexane (1:5); IR 2940, 2720, 1730, 1710, 1470, 1440, 1365, 1240, 1190, 1125 cm^{-1}; ^1H NMR δ 0.95 (d, 0.75 H, J = 6.6 Hz), 0.96 (d, 2.25 H, J = 6.6 Hz), 1.29 (br, 23 H), 2.10–2.70 (m, 4 H), 2.90 (m, 1 H), 9.74 (d, 0.25 H, J = 2 Hz), 9.75 (d, 0.75 H, J = 2.2 Hz); FDMS *m/e* 266 (M^+, 100), 265 (6), 238 (19), 125 (10), 110 (4); HRMS for $C_{17}H_{30}O_2$ (M^+) calcd *m/z* 266.4228, found 266.4231.

(*R*)-3-Methyl-1-cyclopentadecanone (38). A mixture of **37** (20 mg, 0.075 mmol) and $RhCl(PPh_3)_3$ (75 mg, 0.11 mmol) in benzene (3 mL) was refluxed for 8 h. After cooling, EtOH (2 mL) was added. The mixture was diluted with brine (5 mL) and extracted with EtOAc (30 mL) followed by usual workup. The resulting crude product was purified by preparative chromatography developed with EtOAc/hexane (1:2) to afford 7.2 mg of **38** (40%) as a colorless liquid: $[\alpha]^{25}_D$ −11.4° (*c* = 0.70, MeOH); IR 2950, 1718, 1460, 1430, 1380, 1320, 1280 cm^{-1}; ^1H NMR δ 0.94 (d, 3 H, J = 6.1 Hz, 1.15–1.80 (m, 23 H), 1.80–2.45 (m, 4 H); MS *m/e* 238 (M^+, 10), 223 (3), 195 (23), 164 (4); HRMS for $C_{16}H_{30}O$ (M^+) calcd *m/z* 238.4136, found 238.4149.

Registry No. 1, 124355-45-9; **2**, 124355-46-0; **3**, 124355-44-8; **4**, 116487-76-4; **5**, 116487-77-5; **6**, 116487-78-6; **7**, 124355-47-1; **8**, 124355-49-3; **9**, 124355-51-7; **10** (isomer 1), 124355-48-2; **10** (isomer 2), 124379-61-9; **11** (isomer 1), 124355-50-6; **11** (isomer 2), 124439-17-4; **12** (isomer 1), 124355-52-8; **12** (isomer 2), 124439-97-0; **13**, 124355-53-9; **14**, 124355-55-1; **15** (isomer 1), 124355-54-0; **15** (isomer 2), 124355-67-5; **16** (isomer 1), 124355-56-2; **16** (isomer 2), 124439-18-5; **17**, 124355-57-3; **18**, 124355-58-4; **19**, 124355-59-5; **20**, 124379-60-8; **21**, 124355-60-8; **22**, 124355-61-9; **23**, 124439-14-1; **24**, 124439-15-2; **25**, 124439-16-3; **26**, 124355-62-0; **27**, 124355-63-1; **28**, 124355-64-2; **29**, 119725-14-3; **30**, 119708-20-2; **31**, 830-13-7; **32**, 75232-70-1; **33**, 119708-21-3; **34**, 119708-22-4; **35**, 124355-65-3; **36**, 124355-66-4; **37**, 119708-23-5; **38**, 10403-00-6; ethyl 4-bromobutyrate, 2969-81-5; cyclododecanone, 830-13-7; ethyl cyanoformate, 623-49-4.

Supplementary Material Available: Characterization for compounds not described above (4 pages). Ordering information is given on any current masthead page.

A Stereocontrolled Organopalladium Route to 2,5-Disubstituted Pyrrolidine Derivatives. Application to the Synthesis of a Venom Alkaloid of the Ant Species *Monomorium latinode*

Jan-E. Bäckvall,* Hans E. Schink, and Z. Dolor Renko

Department of Organic Chemistry, University of Uppsala, Box 531, 751 21 Uppsala, Sweden

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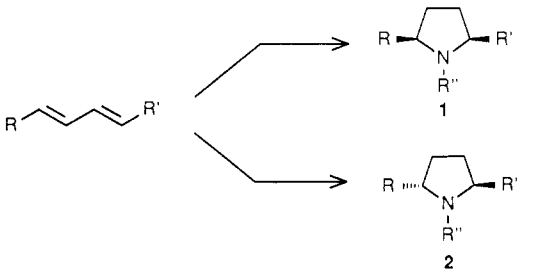
A general method for the preparation of cis- and trans-2,5-disubstituted pyrrolidines from conjugated dienes has been developed. The approach involves a stereocontrolled syn- or anti-1,4-addition of an amino and an oxygen function to the diene via palladium catalysis. Subsequent stereospecific cyclization produces the pure cis- and trans-2,5-disubstituted pyrrolidines, respectively. The method was applied to the synthesis of an ant venom alkaloid from the species *Monomorium latinode*.

Pyrrolidines that are stereospecifically substituted in the 2- and 5-positions have attracted interest for two reasons: (i) there are many natural products with this structure;[1-3] (ii) 2,5-disubstituted pyrrolidines have found use as chiral auxiliaries.[4,5]

A number of stereoselective methods for the synthesis of pyrrolidines have been reported during the last decade.[2,4-8] Although there are many procedures for the preparation of *cis*- and *trans*-2,5-dialkylpyrrolidines, both isomers are not usually available via the same approach. We have recently developed methodology for the functionalization of conjugated dienes, that offers a dual control of the 1,4-relative stereochemistry.[9,10] This is based on

Scheme I



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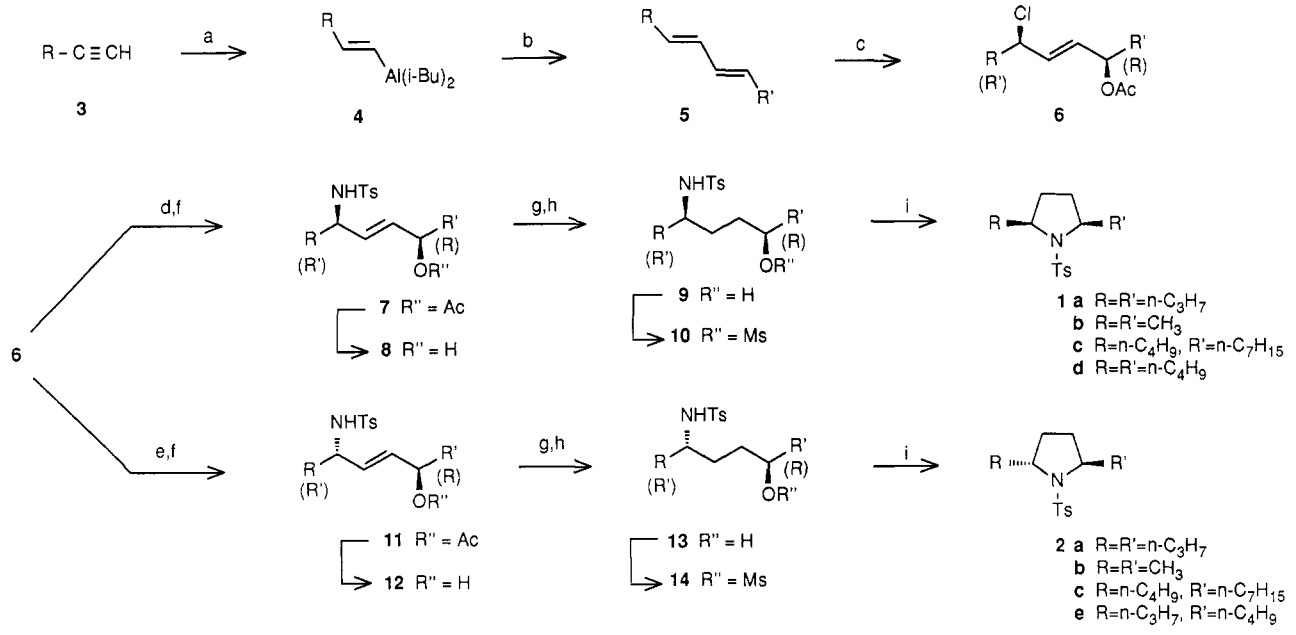
Scheme II[a]



[a] (a) $(i\text{-Bu})_2AlH$, hexane; (b) for R = R', CuCl, THF; for R ≠ R'; (*E*)-R'CH=CHI, $PdCl_2(PPh_3)_2$ (5%), THF–hexane; (c) $Pd(OAc)_2$ (7.5%), LiCl, LiOAc, benzoquinone, HOAc–pentane; (d) NaNHTs, $Pd(PPh_3)_4$ (5%), CH_3CN; (e) NaNHTs, Cs_2CO_3, DMF; (f) NaOH, MeOH–H_2O; (g) H_2/PtO_2, MeOH; (h) MsCl, Et_3N, THF; (i) K_2CO_3, MeOH.

the palladium-catalyzed chloroacetoxylation approach. By using this methodology it should thus be possible to introduce a nitrogen into an acyclic diene, so that both the cis- and trans-2,5-disubstituted pyrrolidines **1** and **2** are obtained (Scheme I). In this paper we describe a general synthesis of derivatives **1** and **2** and apply it to the preparation of an ant venom alkaloid.

Results and Discussion

The synthesis of the 2,5-dialkylpyrrolidines is summarized in Scheme II. Hydroalumination of the appropriate acetylene **3** produced vinylalane **4**, which on subsequent palladium-catalyzed coupling with the appropriate (*E*)-vinyl iodide afforded the (*E*,*E*)-diene **5**.[11] Alternatively, when R = R' the vinylalane **4** was treated with CuCl to give the symmetric coupling product **5**,[12] again with exclusive *E*,*E* stereochemistry. Palladium-catalyzed chloroacetoxylation of **5** was highly 1,4-syn selective (>96%) producing the *R**,*R** isomer **6**. When R ≠ R' a mixture of two regioisomers was formed, where the chloro group is close to either the R or the R' group. The chloride in these chloroacetates can be substituted by nucleophiles with either retention (Pd(0)-catalysis) or with inversion (S_N2) without affecting the acetate or the geometry of the double bond.[9a]

Palladium-catalyzed substitution of the chloro group in **6** utilizing sodium *p*-toluenesulfonamide (NaNHTs) proceeded smoothly to give **7** in 85–90% yield. Hydrolysis of **7** followed by hydrogenation (PtO_2) of the double bond afforded sulfonamido alcohol **9** in good yield and of *R**,*R** configuration. In the hydrogenation of the double bond in **8**, and also in **12** (vide infra), it is necessary to maintain a hydrogen pressure of at least 5 atm in order to avoid isomerization at C–O or C–N. The alcohol **9** was transformed to the mesylate **10**, which was cyclized in nearly quantitative yield to the *cis*-2,5-dialkylpyrrolidine **1** (>98% cis). The overall yield for the transformation of **6a** to **1a** was 72%.

The corresponding *trans*-pyrrolidine was obtained via S_N2-substitution of the chloride in **6** by sodium *p*-toluenesulfonamide. This reaction was rather sluggish in acetonitrile or dimethyl sulfoxide (DMSO) but worked satisfactorily in *N*,*N*-dimethylformamide (DMF) under certain conditions. Thus, reaction of **6** with NaNHTs in DMF at 60 °C in the presence of a crown ether or Cs_2CO_3 afforded the substitution product **11** in 52–62% isolated yield.[13] The corresponding reaction without added crown ether or Cs_2CO_3 gave only 20–25% isolated yield of **11**. Subsequent hydrolysis and hydrogenation afforded **13**, which was transformed to its mesylate and cyclized to give **2** (>95% trans). The overall yield for the transformation of **6a** to **2a** was 50%.

Since the S_N2 substitution with NaNHTs gave a lower yield than the corresponding palladium-catalyzed substitution, an alternative route to the *R**,*S** isomer **11** from the *E*,*Z*-diene via the *R**,*S** chloroacetate was considered. The *R**,*S** isomer **11** would then be available from the corresponding *R**,*S** chloroacetate via a palladium-catalyzed substitution of the chloro group by the sulfonamido group with retention of configuration. Reaction of the *R**,*S** chloroacetate from (*E*,*Z*)-2,4-hexadiene with NaNHTs in CH_3CN in the presence of $Pd(PPh_3)_4$ resulted in a smooth reaction, and the sulfonamido acetate **11b** was isolated in 70% yield. Using the reagents given in Scheme II, **11b** was transformed to **2b** in an overall yield of 79%.

To demonstrate the utility of this general 2,5-dialkylpyrrolidine synthesis we have applied it to the synthesis of the ant venom alkaloid **15c** (Scheme III). Compound **15c** is the major component of the venom extract of the ant species *Monomorium latinode*. The requisite diene **5c** was readily prepared from nonyne and hexyne (Scheme

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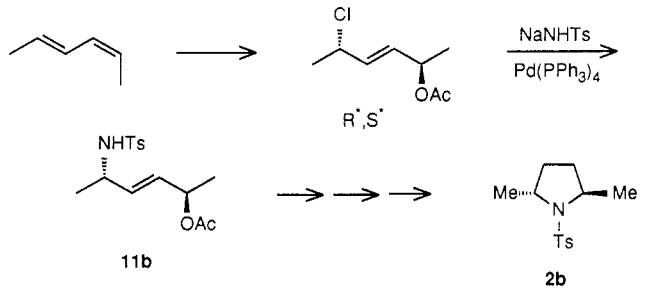
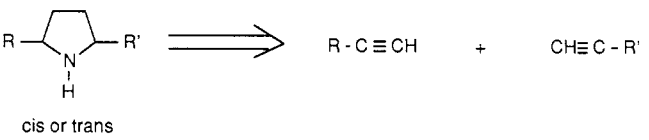


III). Application of the sequence shown in Scheme II on **5c** afforded **2c**, which was transformed to the target **15c** by removal of the tosyl group. The stereoisomer **16c** was also prepared in the same manner, via **1c**. Compounds **15c** and **16c** were identified by comparison with spectral data given in the literature for authentic *trans*- and *cis*-5-butyl-2-heptylpyrrolidine.[7]

The present general method for the preparation of *cis*- and *trans*-2,5-dialkylpyrrolidines utilizes acetylenes as starting materials. The procedure should thus allow for



cis or trans

specific deuterium labeling in the 3- and 4-position by exchanging the terminal hydrogens for deuterium in the starting acetylenes or reducing the double bond in the sulfonamido alcohol **8** or **12** with deuterium (transformation g, Scheme II). It may also be noted that the transformation of the aforementioned double bond to a protected diol prior to cyclization would lead to pyrrolidines related to the natural product codonopsinine.[2a]

Conclusion

The synthetic route to 2,5-disubstituted pyrrolidines presented allows a full control of the stereochemistry at the 2- and 5-positions. The building blocks required for the synthesis are readily available, and the convenience and generality of the method should make it a useful complement to other stereospecific pyrrolidine syntheses.

Experimental Section

General Comments. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. For N-(*p*-tolylsulfonyl)pyrrolidines, trans/cis ratios were determined from their ^1H NMR spectra by comparing the integrals of the peaks at δ 3.8 and 3.6. IR spectra were obtained as thin films. Only the strongest and structurally most important peaks are listed. GC–MS were recorded by electron ionization at 70 eV. Melting points are uncorrected. Slow additions of dienes were performed by using a Sage Instruments Model 355 syringe pump. Commercially available chemicals were used without further purification, while solvents for reactions and flash chromatography were dried and/or distilled using standard procedures. The sodium salt of tosylamide (NaHNTs),[14] tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$),[9] (*E*)-(*R**,*R**)-5-chloro-3-hexen-2-yl acetate (**6b**),[9] (*E*)-(*R**,*S**)-5-chloro-3-hexen-2-yl acetate,[9] and (*E*,*E*)-5,7-dodecadiene (**5d**)[12] were prepared according to literature procedures. For flash chromatography,[15] Merck silica gel 60 (230–400 mesh) was used.

(*E*,*E*)-4,6-Decadiene (5a) was prepared via hydroalumination of 1-pentyne and subsequent CuCl-promoted coupling according to Zweifel.[12] Starting with 0.20 mol of 1-pentyne, the desired diene was obtained in 60% yield. ^1H NMR: δ 6.00 (m, 2 H, olefinic), 5.56 (m, 2 H, olefinic), 2.03 (q, J = 7 Hz, 4 H, CH=CHCH_2), 1.40 (sextet, J = 7 Hz, 4 H, CH_2CH$_3$), 0.90 (t, J = 7.3 Hz, 6 H, CH_3). ^{13}C NMR: δ 132.2, 130.5, 34.7, 22.6, 13.7. MS: m/z (relative intensity) 138 (M^+, 21), 109 (18), 95 (18), 81 (24), 67 (100).

(*E*,*E*)-5,7-Pentadecadiene (5c). Using the procedure described by Negishi,[11] **5c** was prepared in 65% yield from (*E*)-1-iodo-1-hexene and 1-nonyne via reaction with catalytic amounts of $PdCl_2(PPh_3)_2$. ^1H NMR: δ 6.00 (m, 2 H, olefinic), 5.56 (m, 2 H, olefinic), 2.03 (m, 4 H, CH=CHCH_2), 1.31 (m, 14 H, CH_2), 0.89 (m, two triplets overlapping, 6 H, CH_3). ^{13}C NMR: δ 132.44, 132.36, 130.32, 130.27, 32.6, 32.3, 31.8, 31.6, 29.4, 29.2 (2 C), 22.7, 14.1, 13.9. MS: m/z (relative intensity) 208 (M^+, 30), 123 (12), 109 (15), 95 (30), 81 (68), 67 (100).

(*E*,*E*)-4,6-Undecadiene (5e) was prepared by the same method as **5c** from (*E*)-1-iodo-1-hexene (10 mmol) and 1-pentyne (70% yield). ^1H NMR: δ 6.00 (m, 2 H, olefinic), 5.56 (m, 2 H, olefinic), 2.04 (m, 4 H, CH=CHCH_2), 1.33 (m, 6 H, CH_2), 0.89 (m, two triplets overlapping, 6 H, CH_3). ^{13}C NMR: δ 132.4, 132.1, 130.5, 130.3, 34.7, 32.3, 31.4, 22.6, 22.2, 13.9, 13.7. MS: m/z (relative intensity) 152 (M^+, 21), 123 (11), 109 (23), 95 (47), 81 (75), 67 (100).

General Procedures. The procedures below are for convenience described for R = R′ = propyl (Scheme II). They were applied to substrates with other R and R′ groups and the yields are still practically the same; room temperature = 20–23 °C.

(*E*)-(*R,*R**)-7-Chloro-5-decen-4-yl Acetate (6a).** (*E*,*E*)-4,6-Decadiene **5a** (3.46 g, 25 mmol) was diluted in pentane to a volume of 10 mL and added, at room temperature, over a period of 20 h, to a stirred (400 rpm) solution of LiCl (2.12 g, 50 mmol), LiOAc·$2H_2O$ (5.10 g, 50 mmol), *p*-benzoquinone (5.40 g, 50 mmol), and $Pd(OAc)_2$ (422 mg, 1.88 mmol) in 100 mL of glacial acetic acid and 60 mL of pentane. After complete addition, the mixture was stirred for an additional 28 h. The reaction was quenched by addition of brine (75 mL) and the precipitates were removed by filtration. After another 10 min of stirring, the phases were separated and the aqueous phase was extracted with pentane/ether (3 × 75 mL, 90/10). The combined organic extracts were washed with water (2 × 25 mL), saturated aqueous Na_2CO_3 (3 × 75 mL), and 2 M NaOH (3 × 75 mL). The combined alkaline aqueous phases were back-extracted with pentane/ether (2 × 50 mL, 90/10). Finally, the combined organic phases were washed with brine (2 × 50 mL) and dried $MgSO_4$. After concentration and flash chromatography (pentane/ether, 95/5), 3.55 g (61%) of the chloroacetate **6a** was obtained, as a yellow oil. ^1H NMR: δ 5.73 (dd, J = 15.5, 7.3 Hz, 1 H, CH=C*H*CHCl), 5.66 (dd, J = 15.5, 5.6 Hz, 1 H, CH=C*H*CHOAc), 5.25 (dt, J = 5.6, 6.5 Hz, 1 H, C*H*OAc), 4.34 (dt, J = 7.3, 6.8 Hz, 1 H, C*H*Cl), 2.05 (s, 3 H, OAc), 1.85–1.25 (m, 8 H, CH_2), 0.91 (m, two triplets overlapping, J = 7.3 Hz, 6 H, CH_3). ^{13}C NMR: δ 170.1, 132.8, 130.5, 73.1, 61.8, 40.5, 36.4, 21.3, 19.8, 18.4, 13.9, 13.6. IR: 2958, 2928, 1740, 1237 cm^{-1}.

Anal. Calcd for $C_{12}H_{21}ClO_2$: C, 61.9; H, 9.10. Found: C, 62.1; H, 8.95.

Using the same procedure chloroacetates **6c**, **6d**, and **6e** were prepared from dienes **5c**, **5d**, and **5e**, respectively. Compounds **6c**, **6d**, and **6e** have very similar spectral properties to those of **6a**.

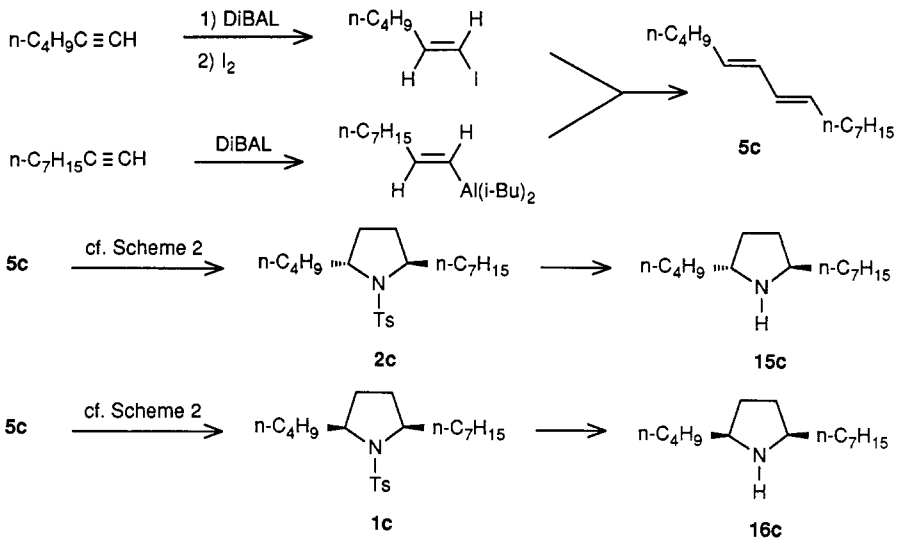
(*E*)-(*R,*R**)-7-(*p*-Toluenesulfonamido)-5-decen-4-yl Acetate (7a).** To a stirred suspension of chloroacetate **6a** (698 mg, 3.0 mmol) and $Pd(PPh_3)_4$ (173 mg, 0.15 mmol) in acetonitrile (10 mL) under argon was added solid NaHNTs (1.16 g, 6.0 mmol). After stirring for 3 h at room temperature, the reaction mixture was poured into hexane/ethyl acetate (65 mL, 80/20), and the resulting organic phase was washed with brine, containing 2% NaOH (3 × 25 mL). The aqueous phase was back-extracted with hexane/ethyl acetate (2 × 25 mL, 80/20). The combined organic phases were washed with saturated aqueous NH_4Cl (2 × 20 mL) and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue, a brown oil, was purifed by flash chromatography (hexane/ethyl acetate, 80/20). The product **7a** was obtained as a thick, pale brown oil (980 mg, 89%). This compound has the same spectroscopic data as its isomer **11a** described below.

Using the same procedure compounds **7b**, **7c**, and **7d** were prepared from the corresponding chloroacetates. Compound **7b** has the same spectroscopic data as **11b** described below. Compounds **7c** and **7d** have very similar spectral properties to those of **7a**.

(*E*)-(*R,*S**)-7-(*p*-Toluenesulfonamido)-5-decen-4-yl**

(14) Bottino, F.; Di Grazia, M.; Finocchiaro, P.; Fronczek, F.; Mamo, A.; Pappalarado, S. *J. Org. Chem.* **1988**, *53*, 3521.
(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Scheme III



Acetate (11a). To a stirred solution of chloroacetate **6a** (1.20 g, 5.16 mmol) in dimethylformamide (20 mL) were added solid NaHNTs (1.99 g, 10.3 mmol) and solid Cs_2CO_3 (1.58 g, 5.16 mmol). The resulting deep red suspension was stirred at 50 °C for 48 h. After workup, using the same procedure as described for compound **7a**, 1.18 g (62%) of the amidoacetate **11a** was isolated as a pale brown solid, mp (recryst, ethyl acetate/hexane) 64–66 °C. ^{1}H NMR: δ 7.84 (d, J = 8.2 Hz, 2 H, aromatic), 7.28 (d, J = 8.2 Hz, 2 H, aromatic), 5.35 (m, 2 H, olefinic), 5.05 (dt, J = 7 Hz, 5 Hz, 1 H, C*H*OAc), 4.80 (d, J = 8 Hz, 1 H, N*H*Ts), 3.75 (ddt, J = 7–8 Hz, 1 H, C*H*NHTs), 2.41 (s, 3 H, ArCH_3), 1.98 (s, 3 H, OAc), 1.50–1.10 (m, 8 H, CH_2), 0.83 (m, two triplets overlapping, J = 7 Hz, 6 H, CH_3). ^{13}C NMR: δ 170.1, 143.1, 138.3, 132.2, 130.2, 129.5, 127.1, 73.4, 55.2, 37.9, 36.3, 21.5, 21.1, 18.5, 18.2, 13.8, 13.6. IR: 3277, 2958, 2873, 1734, 1240, 1161 cm^{-1}.

Anal. Calcd for $C_{19}H_{29}NO_4S$: C, 62.1; H, 7.95. Found: C, 62.1; H, 7.81.

Using the same procedure compounds **11b**, **11c**, and **11e** were prepared from **6b**, **6c**, and **6e**, respectively. Spectral data for **11b** are given below. Compound **11c** and **11e** have very similar spectral properties to those of **11a**.

(*E*)-(*R,*S**)-5-(*p*-Toluenesulfonamido)-3-hexen-2-yl Acetate (11b).** **11b** was prepared from (*E*)-(*R**,*S**)-5-chloro-3-hexen-2-yl acetate[9a] using the same method as described for **7a**. The desired product was obtained as a colorless oil in 70% yield. ^{1}H NMR: δ 7.75 (d, J = 8.7 Hz, 2 H, aromatic), 7.29 (d, J = 8.7 Hz, 2 H, aromatic), 5.44 (m, 2 H, olefinic), 5.18 (m, 1 H, C*H*OAc), 4.54 (d, J = 7.5 Hz, 1 H, N*H*Ts), 3.92 (m, 1 H, C*H*NHTs), 2.42 (s, 3 H, ArCH_3), 2.00 (s, 3 H, OAc), 1.18 (d, J = 6.5 Hz, 3 H, CH_3), 1.15 (d, J = 6.5 Hz, 3 H, CH_3). ^{13}C NMR: δ 169.9, 142.9, 138.0, 132.3, 130.0, 129.3, 127.0, 69.7, 50.6, 21.5, 21.2, 21.0, 19.7.

Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.85; H, 6.80. Found: C, 57.79; H, 6.69.

(*E*)-(*R,*S**)-4-(*p*-Toluenesulfonamido)-5-decen-7-ol (12a).** The amidoacetate **11a** (1.10 g, 3.0 mmol) was dissolved in methanol (15 mL), and aqueous NaOH (6 M, 10 mL) was added. The solution was refluxed for 45 min. After cooling, the mixture was concentrated in vacuo. The residue was diluted with water (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (25 mL) and dried over $MgSO_4$. Concentration in vacuo yielded 937 mg (95%) of the alcohol **12a** as a thick colorless oil, which solidified on standing, mp 92–93 °C. ^{1}H NMR: δ 7.84 (d, J = 8.2 Hz, 2 H, aromatic), 7.28 (d, J = 8.2 Hz, 2 H aromatic), 5.32 (m, 2 H, olefinic), 4.67 (d, J = 8 Hz, 1 H, N*H*Ts), 3.87 (m, unresolved, 1 H, C*H*OH), 3.75 (ddt, J = 7–8 Hz, 1 H, C*H*NHTs), 2.41 (s, 3 H, ArCH_3), 1.50–1.10 (m, 9 H, CH_2 overlapping O*H*), 0.85 (m, two triplets overlapping, J = 7 Hz, 6 H, CH_3). ^{13}C NMR: δ 143.3, 138.3, 134.8, 130.5, 129.5, 127.3, 71.8, 55.3, 38.9, 38.0, 21.5, 18.6, 14.0, 13.6. IR: 3500, 3276, 2958, 2872, 1322, 1159 cm^{-1}.

(*E*)-(*R,*S**)-2-(*p*-Toluenesulfonamido)-3-hexen-5-ol (12b).** **12b** was prepared from compound **11b** using the method described for **12a**. ^{1}H NMR: δ 7.77 (d, J = 8 Hz, 2 H, aromatic), 7.29 (d, J = 8 Hz, aromatic), 5.45 (m, 2 H, olefinic), 5.36 (d, J = 8 Hz, 1 H, N*H*Ts), 4.12 (m, 1 H, C*H*OH), 3.85 (m, 1 H, C*H*NTs), 2.41 (s, 3 H, ArCH_3), 1.62 (broad s, 1 H, O*H*), 1.15 (d, J = 6.5 Hz, 3 H, CH_3), 1.11 (d, J = 6.5 Hz, 3 H, CH_3). ^{13}C NMR: δ 143.3, 138.0, 135.0, 130.5, 129.6, 127.2, 67.7, 50.8, 23.0, 21.8, 21.5.

Using the procedure described for **12a** amido alcohols, **8a**, **8b**, **8c**, **8d**, **12c**, and **12e** were obtained in 95–100% yield from their corresponding amidoacetates. Compounds **8a** and **8b** have the same spectral data as their isomers **12a** and **12b**, respectively. Compounds **8c**, **8d**, **12c**, and **12e** have very similar properties to those of **12a**.

(*R,*S**)-4-(*p*-Toluenesulfonamido)decan-7-ol (13a).** The amido alcohol **12a** (651 g, 2.0 mmol) was dissolved in methanol (10 mL) and placed, together with PtO_2 (23 mg, 0.10 mmol), in the reaction vessel. Hydrogen pressure (5 atm) was applied, and the mixture was shaken at room temperature for 3 h. Filtration through Celite filter aid and concentration in vacuo afforded 652 mg (99.5%) of **13a** as a white solid. Mp: 86–87 °C. ^{1}H NMR: δ 7.86 (d, J = 8.2 Hz, 2 H, aromatic), 7.29 (d, J = 8.2 Hz, 2 H, aromatic), 5.06 (d, J = 8.5 Hz, 1 H, *H*NTs), 3.45 (m, unresolved, 1 H, C*H*OH), 3.22 (m, 1 H, C*H*NTs), 2.41 (s, 3 H, ArCH_3), 1.79 (broad s, 1 H, O*H*), 1.62–1.05 (m, 12 H, CH_2), 0.88 (t, J = 7.3 Hz, 3 H, CH_3), 0.75 (t, J = 7.1 Hz, 3 H, CH_3). ^{13}C NMR: δ 143.0, 138.4, 129.5, 127.0, 71.5, 53.8, 39.7, 37.3, 32.6, 31.1, 21.4, 18.7, 18.5, 14.0, 13.7. IR: 3498, 3282, 2957, 2871, 1322, 1158 cm^{-1}.

Anal. Calcd for $C_{17}H_{29}NO_3S$: C, 62.3; H, 8.92. Found: C, 62.1; H, 8.76.

(*R,*S**)-2-(*p*-Toluenesulfonamido)hexan-5-ol (13b).** **13b** was prepared from compound **12b** by using the same method as described for **13a**. ^{1}H NMR: δ 7.77 (d, J = 8.5 Hz, 2 H, aromatic), 7.30 (d, J = 8.5 Hz, 2 H, aromatic), 4.75 (d, J = 8 Hz, 1 H, N*H*Ts), 3.71 (m, 1 H, C*H*OH), 3.31 (m, 1 H, C*H*NHTs), 2.43 (s, 3 H, ArCH_3), 1.50–1.35 (m, 4 H, CH_2), 1.10 (d, J = 6 Hz, 3 H, CH_3), 1.03 (d, J = 6 Hz, 3 H, CH_3). ^{13}C NMR: δ 143.0, 138.2, 129.5, 126.9, 67.6, 49.9, 34.6, 33.3, 23.3, 21.4.

Using the same hydrogenation procedure as described for **13a** compounds **9a**, **9b**, **9c**, **9d**, **13c**, and **13d** were obtained in almost quantitative yield. The spectral data for **9a** and **9b** are the same as those of their isomers **13a** and **13b**, respectively. Compounds **9c**, **9d**, **13c**, and **13d** have very similar spectral data as those of **13a**.

(*R,*S**)-4-(Mesyloxy)-7-(*p*-toluenesulfonamido)decane (14a).** To a stirred solution of **13a** (652 mg, 1.99 mmol) and triethylamine (243 mg, 2.4 mmol) in tetrahydrofuran (5 mL), cooled on an ice bath, was added neat methanesulfonyl chloride (275 mg, 2.4 mmol). The reaction was stirred at 0 °C for 1.5 h, the ice bath was removed, and the reaction was stirred for another hour at room temperature. Ice-cold water (2 mL) was added, and the phases were separated. The aqueous phase was extracted with

hexane/EtOAc (3 × 5 mL, 60/40). The combined organic phases were washed with brine (5 mL) and dried over $MgSO_4$. The crude product, obtained after concentration in vacuo, was purified by flash chromatography (hexane/EtOAc, 70/30). The mesylate **14a** was obtained as a white solid (726 mg, 90%). Mp: 105–106 °C. ^{1}H NMR: δ 7.75 (d, J = 8 Hz, 2 H, aromatic), 7.30 (d, J = 8 Hz, aromatic), 4.62 (broad m, 2 H, C*H*OMs overlapping N*H*Ts), 3.20 (m, 1 H, C*H*NHTs), 2.98 (s, 3 H, mesyl), 2.41 (s, 3 H, ArCH_3), 1.75–1.05 (m, 12 H, CH_2), 0.91 (t, J = 7.3 Hz, 3 H, CH_3), 0.75 (t, J = 7.1 Hz, 3 H, CH_3). ^{13}C NMR: δ 143.2, 138.2, 129.6, 126.9, 83.5, 53.8, 38.6, 37.3, 36.5, 30.3, 30.2, 21.5, 18.5, 18.2, 13.8, 13.7. IR: 3302, 2960, 2873, 1330, 1171, 906 cm^{-1}.

(*R,*S**)-2-(Mesyloxy)-5-(*p*-toluenesulfonamido)hexane (14b).** **14b** was prepared from amido alcohol **13b** using the same procedure as described for **14a**. ^{1}H NMR: δ 7.77 (d, J = 8.5 Hz, 2 H, aromatic), 7.31 (d, J = 8.5 Hz, 2 H, aromatic), 4.76 (m, 1 H, C*H*OMs), 4.63 (d, J = 8 Hz, 1 H, N*H*Ts), 3.31 (m, 1 H, C*H*NTs), 3.00 (s, 3 H, mesyl), 2.41 (s, 3 H, ArCH_3), 1.68–1.50 (m, 4 H, CH_2), 1.36 (d, J = 6 Hz, 3 H, CH_3), 1.00 (d, J = 6 Hz, 3 H, CH_3). ^{13}C NMR: δ 143.3, 138.0, 129.6, 126.9, 79.4, 49.2, 38.5, 32.6, 32.4, 21.4 (2 C), 21.1.

Using the same procedure as described for **14a** the mesylates **10a**, **10b**, **10c**, **10d**, **14c**, and **14d** were prepared from the corresponding amido alcohols in 90–95% yield. The spectral data for **10a** and **10b** are the same as those of their isomers **14a** and **14b**, respectively. Compounds **10c**, **10d**, **14c**, and **14d** have very similar spectral data to those of **14a**.

***cis*- and *trans*-2,5-Dialkylpyrrolidines.** The stereochemistry of these compounds are readily assigned by ^{1}H NMR analysis. Thus $(\delta_{CH-N})_{trans} > (\delta_{CH-N})_{cis}$ with a difference of approximately 0.2–0.3 ppm. Several of the compounds were identified with spectral data given in the literature.

***trans*-*N*-(*p*-Tolylsulfonyl)-2,5-dipropylpyrrolidine (2a).** To a stirred solution of the mesylate **14a** (608 mg, 1.50 mmol) in methanol (10 mL) was added solid potassium carbonate (726 mg, 5.25 mmol). The mixture was stirred for 3 h at room temperature. After concentration in vacuo, water (5 mL) was added followed by extraction with hexane/EtOAc (4 × 10 mL, 70/30). The combined organic extracts were washed with brine and dried over $MgSO_4$. Concentration in vacuo afforded 440 mg (95%) of the pyrrolidine as a white solid (>95% trans). Mp: 60–61 °C. ^{1}H NMR: δ 7.72 (d, J = 8 Hz, 2 H, aromatic), 7.27 (d, J = 8 Hz, 2 H, aromatic), 3.82 (m, 2 H, C*H*Pr), 2.41 (s, 3 H, ArCH_3), 1.90 (broad m, 4 H, diastereotopic methylene protons, two from chain and two from ring), 1.64 (m, 2 H, diastereotopic methylene protons from ring, small coupling to methine protons), 1.21 (m, 6 H, sum of remaining methylene protons), 0.85 (t, J = 7 Hz, 6 H, CH_3). ^{13}C NMR: δ 142.5, 139.9, 129.3, 126.8, 60.6, 35.9, 27.9, 21.4, 19.6, 13.9. IR: 2960, 2872, 1496, 1457, 1156, 666 cm^{-1}.

Anal. Calcd for $C_{17}H_{27}NO_2S$: C, 66.0; H, 8.79. Found: C, 65.9; H, 8.67.

***trans*-*N*-(*p*-Tolylsulfonyl)-2,5-dimethylpyrrolidine (2b)** was prepared from mesylate **14b** using the same procedure as described for **2a**. Yield: 97% (>95% trans). ^{1}H NMR: δ 7.75 (d, J = 8.5 Hz, 2 H, aromatic), 7.26 (d, J = 8.5 Hz, 2 H, aromatic), 4.02 (m, 2 H, C*H*CH$_3$), 2.41 (m, 3 H, ArCH_3), 1.52 (m, 4 H, methylene protons), 1.20 (d, J = 6 Hz, 6 H, CH_3). ^{13}C NMR: δ 142.4, 139.6, 129.2, 126.7, 56.0, 31.0, 21.1.

***trans*-*N*-(*p*-Tolylsulfonyl)-2-heptyl-5-butylpyrrolidine (2c)** was prepared from mesylate **14c** using the same procedure as described for **2a**. Yield: 91% (>95% trans). Thick colorless oil. ^{1}H NMR: δ 7.72 (d, J = 8, Hz, 2 H, aromatic), 7.27 (d, J = 8 Hz, 2 H, aromatic), 3.81 (m, unresolved, 2 H, methine), 2.41 (s, 3 H, ArCH_3), 1.90 (broad m, 4 H, diastereotopic methylene protons, two from ring, two from chains), 1.64 (m, 2 H, methylene protons from ring), 1.40–1.05 (m, 16 H, sum of remaining methylene protons), 0.89 (m, 6 H, CH_3). ^{13}C NMR: δ 142.4, 140.0, 129.3, 126.9, 60.8 (2 C), 33.8, 33.6, 31.8, 29.4, 29.2, 28.6, 28.0 (2 C), 26.4, 22.62, 22.57, 21.4, 14.1, 14.0.

Anal. Calcd for $C_{22}H_{37}NO_2S$: C, 69.61; H, 9.82. Found: C, 69.54; H, 9.73.

***trans*-*N*-(*p*-Tolylsulfonyl)-2-butyl-5-propylpyrrolidine (2e)** was prepared from mesylate **14c** using the same procedure as described for **2a**. Yield: 89% (>95% trans). Mp: 49–51 °C. ^{1}H NMR: δ 7.71 (d, J = 8 Hz, 2 H, aromatic), 7.27 (d, J = 8 Hz, 2 H, aromatic), 3.79 (m, unresolved, 2 H, methine), 2.40 (s, 3 H, ArCH_3), 1.91 (broad m, 4 H, diastereotopic methylene protons, two from ring, two from chains), 1.64 (m, 2 H, diastereotopic methylene protons from ring), 1.20 (broad m, 8 H, sum of remaining methylene protons), 0.83 (m, two triplets overlapping, 6 H, CH_3). ^{13}C NMR: δ 142.4, 139.9, 129.3, 126.8, 60.7, 60.6, 36.0, 33.4, 28.5, 27.9 (2 C), 22.5, 21.4, 19.6, 14.0, 13.9.

Anal. Calcd for $C_{18}H_{29}NO_2S$: C, 66.8; H, 9.04. Found: C, 66.75; H, 8.95.

***cis*-*N*-(*p*-Tolylsulfonyl)-2,5-dipropylpyrrolidine (1a)** was prepared from mesylate **10a** using the same procedure as described for its trans isomer **2a**. Yield: 90% (>98% cis). Mp: 72–73 °C. ^{1}H NMR: δ 7.72 (d, J = 8.3 Hz, 2 H, aromatic), 7.28 (d, J = 8.3 Hz, 2 H, aromatic), 3.57 (unresolved m, 2 H, C*H*Pr), 2.41 (s, 3 H, ArCH_3), 1.81 (m, 2 H, diastereotopic methylene protons from propyl chains), 1.55–1.15 (m, 10 H, remaining methylene protons), 0.94 (t, J = 7 Hz, 6 H, CH_3). ^{13}C NMR: δ 143.0, 135.3, 129.5, 127.5, 61.5, 39.4, 29.6, 21.5, 19.5, 14.0. IR: identical with the spectrum from its trans isomer.

Anal. Calcd from $C_{17}H_{27}NO_2S$: C, 66.0; H, 8.79. Found: C, 65.8; H, 8.67.

***cis*-*N*-(*p*-Tolylsulfonyl)-2,5-dimethylpyrrolidine (1b)** was prepared from mesylate **10b** using the same procedure as described for **2a**. Yield: 99% (>95% cis). This compound was previously reported by Barluenga et al.[8c] Our spectral data are in accord with those reported. ^{1}H NMR: δ 7.75 (d, J = 8.5 Hz, 2 H, aromatic), 7.31 (d, J = 8.5 Hz, 2 H, aromatic), 3.67 (m, 2 H, C*H*CH$_3$), 2.43 (s, 3 H, ArCH_3), 1.54 (m, 4 H, CH_2), 1.35 (d, J = 6 Hz, 6 H, CH_3). ^{13}C NMR: δ 143.0, 135.2, 129.5, 127.4, 57.5, 32.0, 23.7, 21.5.

***cis*-*N*-(*p*-Tolylsulfonyl)-2-heptyl-5-butylpyrrolidine (1c)** was prepared from mesylate **10c** using the same procedure as described for **2a**. Yield: 94% (>98% cis). Thick colorless oil. ^{1}H NMR: δ 7.72 (d, J = 8 Hz, 2 H, aromatic), 7.28 (d, J = 8 Hz, 2 H, aromatic), 3.54 (m, unresolved, 2 H, methine), 2.41 (s, 3 H, ArCH_3), 1.84 (m, unresolved, 2 H, methylene protons from chains), 1.52–1.15 (m, 18 H, sum of remaining methylene protons), 0.89 (q, two triplets overlapping, 6 H, CH_3). ^{13}C NMR: δ 143.0, 135.4, 129.5, 127.5, 61.67, 61.63, 37.2, 36.9, 31.8, 29.6 (2 C), 29.5, 29.3, 28.5, 26.3, 22.6 (2 C), 21.5, 14.1 (2 C).

Anal. Calcd for $C_{22}H_{37}NO_2S$: C, 69.61; H, 9.82. Found: C, 69.42; H, 9.74.

***cis*-*N*-(*p*-Tolylsulfonyl)-2,5-dibutylpyrrolidine (1d)** was prepared from mesylate **10d** using the same procedure as described for **2a**. Yield: 89% (>98% cis). Mp: 68–70 °C. ^{1}H NMR: δ 7.71 (d, J = 8 Hz, 2 H, aromatic), 7.27 (d, J = 8 Hz, 2 H, aromatic), 3.55 (m, unresolved, 2 H, C*H*Bu), 2.41 (s, 3 H, ArCH_3), 1.85 (m, 2 H, methylene protons from chains), 1.60–1.20 (m, 14 H, sum of remaining methylene protons), 0.91 (t, J = 7 Hz, 6 H, CH_3). ^{13}C NMR: δ 143.0, 135.4, 129.5, 127.5, 61.7, 37.0, 29.7, 28.5, 22.6, 21.5, 14.1.

Anal. Calcd for $C_{19}H_{31}NO_2S$: C, 67.6; H, 9.26. Found: C, 67.70; H, 9.09.

***trans*-2,5-Dipropylpyrrolidine (15a).** The *p*-toluenesulfonyl group was removed from **2a** according to the method described by Rapoport[7a] using sodium in liquid ammonia. The crude product was purified by flash chromatography (hexane/ethyl acetate, 60/40, followed by ethyl acetate/triethylamine, 90/10). The pyrrolidine was obtained as an oil in 80% yield. ^{1}H NMR: δ 3.11 (m, unresolved, 2 H, CHPr), 1.92 (broad m, 2 H, methylene protons from ring), 1.54–1.20 (m, 11 H, sum of remaining methylene protons), 0.91 (t, J = 7 Hz, 6 H, CH_3). ^{13}C NMR: δ 57.7, 39.5, 32.5, 20.5, 14.3. MS: m/z (relative intensity) 155 (M$^+$, 0.60), 154 (M − H, 1.5), 112 (M − C_3H_7, 100), 69 (M − $2C_3H_7$, 19).

***trans*-2-Heptyl-5-butylpyrrolidine (15c)** was prepared from tosylate **2c**, using the procedure described for **15a**. The spectral characteristics were identical with those of a known sample of **15c**.[7a] ^{1}H NMR: δ 3.10 (unresolved m, 2 H, methine), 1.93 (broad m, 3 H), 1.58–1.12 (m, 20 H), 0.89 (q, two triplets overlapping, 6 H, CH_3). ^{13}C NMR: δ 58.02, 58.00, 37.2, 36.9, 32.5 (2 C), 31.8, 29.8, 29.5, 29.3, 27.3, 22.8, 22.6, 14.1 (2 C). MS: m/z (relative intensity) 168 (M − C_4H_9, 58), 126 (M − C_7H_{15}, 100).

***cis*-2,5-Dipropylpyrrolidine (16a)** was prepared from tosylate **1a** using the method described for **15a**. ^{1}H NMR: δ 2.93 (m, unresolved, 2 H, C*H*Pr), 1.82 (m, 2 H, methylene protons from ring), 1.55–1.20 (m, 11 H), 0.89 (t, J = 7 Hz, 3 H, CH_3). ^{13}C NMR:

δ 59.1, 39.0, 31.3, 20.6, 14.3. MS: *m/z* (relative intensity) 155 (M^+, 0.79), 154 (M – H, 1.9), 112 (M – C_3H_7, 100), 69 (M – $2C_3H_7$, 20).

***cis*-2-Heptyl-5-butylpyrrolidine (16c)** was prepared from tosylate **1c**, using the method described for **15a**. The spectral characteristics were identical with those of a known sample of **16c**.[7a] ^{1}H NMR: δ 2.93 (m, unresolved, 2 H, methine), 1.82 (m, 2 H, methylene protons from ring), 1.65–1.15 (m, 21 H), 0.88 (q, two triplets overlapping, 6 H, CH_3). ^{13}C NMR: δ 59.41, 59.39, 36.7, 36.4, 31.8, 31.3 (two carbons), 29.8, 29.7, 29.3, 27.5, 22.9, 22.7, 14.1 (2 C). MS: *m/z* (relative intensity) 224 (M – H, 1), 168 (M – C_4H_9, 60), 126 (M – C_7H_{15}, 100).

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Registry No. **1a**, 123994-00-3; **1b**, 81330-01-0; (±)-**1c**, 123994-01-4; **1d**, 123994-02-5; (±)-**2a**, 123993-96-4; (±)-**2b**, 123993-97-5; (±)-**2c**, 123993-98-6; (±)-**2e**, 123993-99-7; **3** (R = *n*-C_3H_7), 627-19-0; **3** (R = *n*-C_7H_{15}), 3452-09-3; **5a**, 53721-79-2; **5c**, 123993-59-9; **5d**, 30651-68-4; **5e**, 123993-60-2; (±)-**6a**, 123993-61-3; (±)-**6b**, 124095-79-0; (±)-**6c**, 123993-62-4; (±)-**6c** (R = *n*-C_7H_{15}, R′ = *n*-C_4H_9), 123994-05-8; (±)-**6d**, 123993-63-5; (±)-**6e**, 123993-64-6; (±)-**6e** (R = *n*-C_4H_9, R′ = *n*-C_3H_7), 123994-06-9; (±)-**7a**, 123993-65-7; (±)-**7b**, 123993-66-8; (±)-**7c**, 123993-67-9; (±)-**7c** regioisomer, 124561-41-7; (±)-**7d**, 123993-68-0; (±)-**8a**, 124020-50-4; (±)-**8b**, 123993-77-1; (±)-**8c**, 123993-78-2; (±)-**8c** regioisomer, 124561-42-8; (±)-**8d**, 123993-79-3; (±)-**9a**, 123993-84-0; (±)-**9b**, 123993-85-1; (±)-**9c**, 123993-86-2; (±)-**9c** regioisomer, 124561-43-9; (±)-**9d**, 123993-87-3; (±)-**10a**, 123993-92-0; (±)-**10b**, 123993-93-1; (±)-**10c**, 123993-94-2; (±)-**10c** regioisomer, 124561-44-0; (±)-**10d**, 123993-95-3; (±)-**11a**, 123993-69-1; (±)-**11b**, 123993-70-4; (±)-**11c**, 123993-71-5; (±)-**11c** regioisomer, 124561-45-1; (±)-**11e**, 123993-72-6; (±)-**11e** regioisomer, 124581-01-7; (±)-**12a**, 123993-73-7; (±)-**12b**, 123993-74-8; (±)-**12c**, 123993-75-9; (±)-**12c** regioisomer, 124561-46-2; (±)-**12e**, 123993-76-0; (±)-**12e** regioisomer, 124561-47-3; (±)-**13a**, 123993-80-6; (±)-**13b**, 123993-81-7; (±)-**13c**, 123993-82-8; (±)-**13c** regioisomer, 124561-48-4; (±)-**13e**, 123993-83-9; (±)-**13e** regioisomer, 124561-49-5; (±)-**14a**, 123993-88-4; (±)-**14b**, 123993-89-5; (±)-**14c**, 123993-90-8; (±)-**14c** regioisomer, 124561-50-8; (±)-**14e**, 123993-91-9; (±)-**14e** regioisomer, 124561-51-9; (±)-**15a**, 123994-03-6; (±)-**15c**, 116558-84-0; **16a**, 123994-04-7; (±)-**16c**, 116558-83-9; (*E*)-*n*-C_4H_9CH=CHI, 16644-98-7; NaNHTs, 18522-92-4; (*E*)-(*R**,*S**)-(±)-$CH_3CHClCH$=CHCHCOAc)CH_3, 124095-80-3.

New Routes to Functionalized Benzazepine Substructures: A Novel Transformation of an α-Diketone Thioamide Induced by Trimethyl Phosphite

Francis G. Fang, Martin E. Maier,[1] and Samuel J. Danishefsky*

Department of Chemistry, Yale University, New Haven, Connecticut 06511

Gayle Schulte

Chemical Instrumentation Center, Yale University, New Haven, Connecticut 06511

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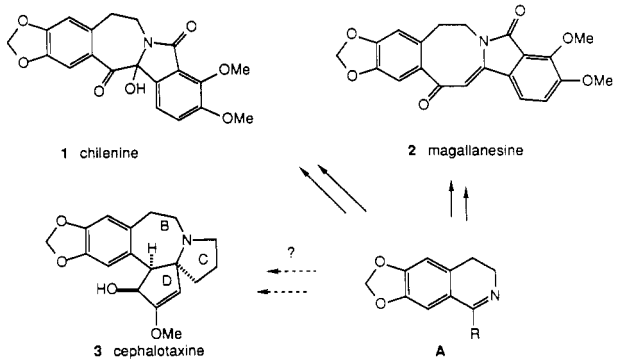
General protocols for the transformation of substituted dihydroisoquinolines into functionalized benzazepine products are described. An important element involves initial hydrolytic succinoylation of a dihydroisoquinoline to afford a ring-opened intermediate. Subsequent closure to the homologous benzazepine ring is accomplished by condensation of several carbenoid-type equivalents with monothioimide and thioamide carbonyl groups. Application of this methodology to a formal synthesis of cephalotaxine (**3**) is described.

Introduction

Recently, we have described novel protocols for the transformation of readily available dihydroisoquinolines (cf. A) to isoindolobenzazepine and isoindolobenzazocine ring systems in the context of the total syntheses of chilenine (**1**) and magallanesine (**2**).[2,3] In an effort to expand the scope of these methods to include pyrrolobenzazepine structures relevant to a total synthesis of cephalotaxine (**3**),[4,5] we undertook an investigation into the hydrolytic succinoylation and subsequent reductive ring closure of several substituted dihydroisoquinolines (cf. eq i).



The successful implementation of this process for the case R = H would constitute a formal synthesis of **3**.[6] A potentially more useful application of this strategy would be one in which the three-carbon chain necessary for construction of the D ring of **3** was incorporated into the

(1) Present address: Falkultät für Chemie, Universitat Konstanz, Postfach 5560 D-7750, Konstanz 1, Konstanz, West Germany.

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