mmol) of tris(*p*-methoxyphenyl)phosphine (**5b**) was obtained 0.180 g (29%) of ^{15}N-labeled *N*-phenyl-*P,P,P*-tris(*p*-methoxyphenyl)-phospha-λ^5-azene (**4b**) after recrystallizing from methanol. From 0.547 g (1.80 mmol) of tris(*p*-methylphenyl)phosphine (**5c**) was obtained 0.380 g (53%) of ^{15}N-labeled *N*-phenyl-*P,P,P*-tris(*p*-methylphenyl)phospha-λ^5-azene (**4c**). From 0.526 g (2.00 mmol) of triphenylphosphine (**5d**) was obtained 0.202 g (29%) of ^{15}N-labeled *N*-phenyl-*P,P,P*-triphenylphospha-λ^5-azene (**4d**). From 0.316 g (1.00 mmol) of tris(*p*-fluorophenyl)phosphine (**5e**) was obtained 0.154 g (38%) of ^{15}N-labeled *N*-phenyl-*P,P,P*-tris(*p*-fluorophenyl)phospha-λ^5-azene (**4e**). From 0.604 g (1.80 mmol) of tris(*p*-chlorophenyl)phosphine (**5f**) was obtained 0.393 g (51%) of ^{15}N-labeled *N*-phenyl-*P,P,P*-tris(*p*-chlorophenyl)phospha-λ^5-azene (**4f**). From 0.700 g (1.50 mmol) of tris[*p*-(trifluoromethyl)phenyl]phosphine (**5g**) was obtained 0.205 g (24.5%) of ^{15}N-labeled *N*-phenyl-*P,P,P*-tris[*p*-(trifluoromethyl)phenyl]-phospha-λ^5-azene (**4g**) after recrystallizing from cyclohexane. From 0.500 g (1.05 mmol) of tris[*p*-(methoxycarbonyl)phenyl]-phosphine (**5h**) was obtained 0.126 g (23%) of ^{15}N-labeled *N*-phenyl-*P,P,P*-tris[*p*-(methoxycarbonyl)phenyl]phospha-λ^5-azene (**4h**) after recrystallizing from isopropyl alcohol. From 0.460 g (1.36 mmol) of tris(*p*-cyanophenyl)phosphine (**5i**) was obtained 0.152 g (26%) of ^{15}N-labeled *N*-phenyl-*P,P,P*-tris(*p*-cyanophenyl)phospha-λ^5-azene (**4i**) after recrystallizing from ethyl ether.

Acknowledgment. We thank the Robert A. Welch Foundation of Houston, TX for financial support. The purchase of the CHN analyzer at UTA through a grant from the Defense Advanced Research Projects Agency monitored by the Office of Naval Research is gratefully acknowledged.

Stereocontrolled Epoxidations of Cycloheptene Derivatives in the Palladium-Catalyzed Route to Tropane Alkaloids. Total Syntheses of Scopine and Pseudoscopine

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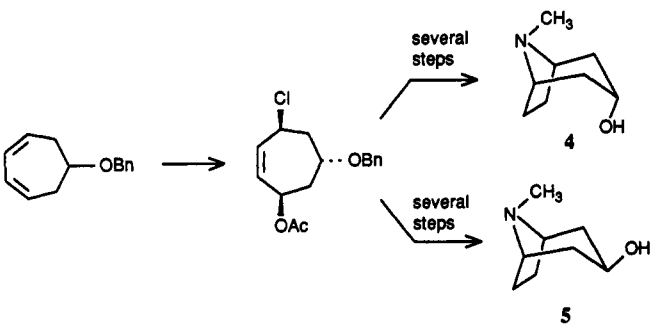
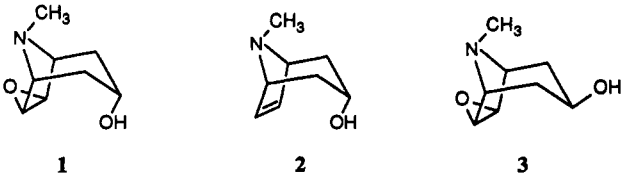
Received October 2, 1990

Stereoselective total syntheses of the tropane alkaloids scopine (1) and pseudoscopine (3) have been developed via the chloroacetoxylation approach. Palladium-catalyzed 1,4-chloroacetoxylation of diene **6** afforded the key intermediate **7**. Subsequent substitution of the allylic chloride by $TsNH^-$ with either retention (Pd(0) catalysis) or inversion (S_N2) of configuration gave **10** and **16**, respectively. The epoxy oxygen was introduced syn to the nitrogen function prior to cyclization by utilizing the syn-directive effect of the allylic sulfonamido group in the epoxidation. Cyclization of the epoxides **12** and **21**, followed by replacement of the tosyl group by a methyl group and subsequent debenzylation, afforded the title compounds 1 and 3, respectively.

Tropane alkaloids show an interesting and diverse pharmacological activity and they are still used in medicine, which makes them an important class of natural products.[1,2] Ever since Willstätter[2] and Robinson[3] published their classical tropinone syntheses, organic chemists have put much effort in to developing general methods to prepare the 8-azabicyclo[3.2.1]octane ring system, i.e. the tropane skeleton.[4] An important member of these alkaloids is scopine (1) with a unique epoxy bridge between C-6 and C-7. Although the Robinson method has wide generality for the preparation of many tropane alkaloids,[5] it cannot be used to synthesize scopine since it fails when epoxysuccinaldehyde is employed.[6] Instead, scopine has been prepared by epoxidation of 6,7-dehydrotropine (2), a reaction that takes 7 days without complete conversion.[7] Pseudoscopine (3), an isomer of scopine, is not as well studied since it is not a naturally occurring compound and synthetic approaches toward 3 are rare in the chemical literature.[8]

Scheme I





(1) (a) Fodor, G. *The Alkaloids*; Academic Press: New York, 1960; Vol. 6, p 145. (b) Fodor, G. *Prog. Phytochem.* **1968**, *1*, 491. (c) Fodor, G. *The Alkaloids*; Academic Press: New York, 1971; Vol. 13, Chapter 8. (d) Fodor, G.; Dharanipragada, R. *Nat. Prod. Rep.* **1986**, *3*, 181.

(2) Holmes, H. L. *The Alkaloids*; Academic Press: New York, 1950; Vol. 1, Chapter 6.

(3) Robinson, R. J. *J. Chem. Soc.* **1917**, *111*, 762.

(4) For recent approaches to tropane alkaloids, see: (a) Davies, H. M. L.; Young, W. B.; Smith, H. D. *Tetrahedron Lett.* **1989**, *30*, 4653. (b) Bathgate, A.; Malpass, J. R. *Ibid.* **1987**, *28*, 5937. (c) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Org. Chem.* **1985**, *55*, 1818. (d) Petersen, J. S.; Toteberg-Kaulen, S.; Rapoport, H. *Ibid.* **1984**, *49*, 2948. (e) Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Wong, S. C.; Ali, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2435. (f) Hayakawa, Y.; Baba, Y.; Makino, S.; Noyori, R. *Ibid.* **1978**, *100*, 1786.

(5) Examples of tropane alkaloids prepared by the Robinson approach: (a) Teloidinone: Schöpf, C.; Arnold, W. *Justus Liebigs Ann. Chem.* **1947**, *109*, 558. (b) Valerinone: Stoll, A.; Becker, B.; Jucker, E. *Helv. Chim. Acta* **1952**, *35*, 1263. (c) 6-Alkoxytropinones: Stoll, A.; Jucker, E.; Lindemann, A. *Ibid.* **1954**, *37*, 495; **1954**, *37*, 649.

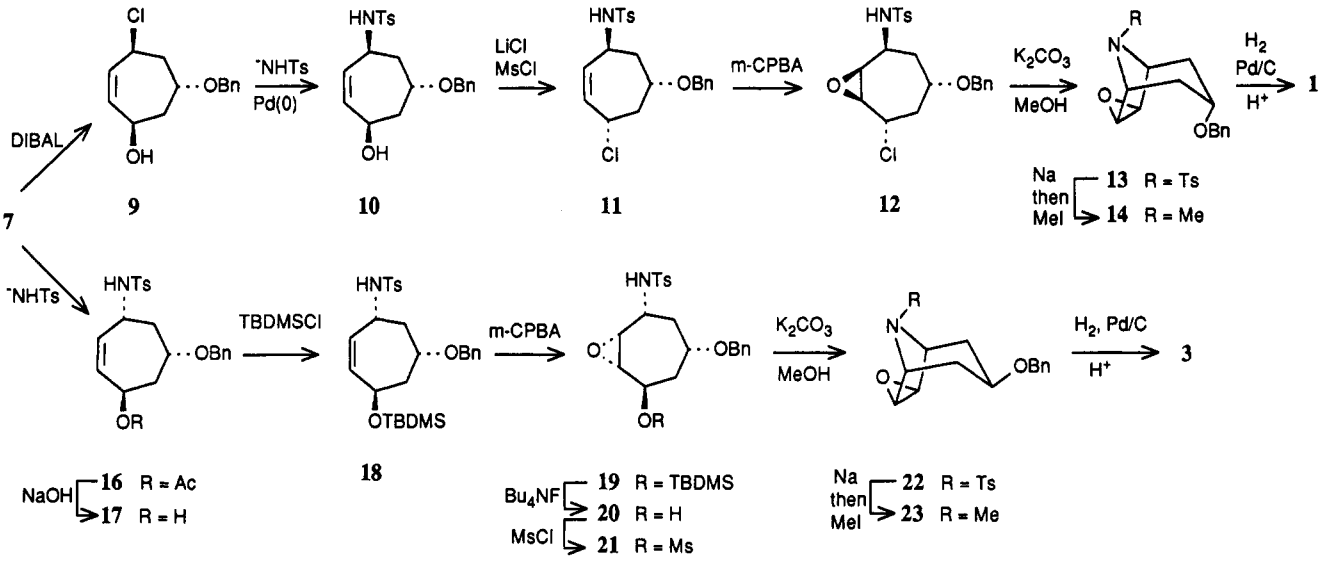
(6) Schöpf, C.; Schmetterling, A. *Angew. Chem.* **1952**, *64*, 591.

(7) Dobo, P.; Fodor, G.; Janzso, G.; Koczor, I.; Toth, J.; Vincze, I. *J. Chem. Soc.* **1959**, 3461.

(8) (a) Heusner, A.; Zelle, K. *Chem. Ber.* **1958**, *91*, 2399. (b) Polonovski, M.; Polonovski, M. *Bull. Chem. Soc. Fr.* **1928**, *43*, 79.

0022-3263/91/1956-2769$02.50/0

Scheme II (Bn = Benzyl, Ts = *p*-Toluenesulfonyl, TBDMS = *tert*-Butyldimethylsilyl, Ms = Methanesulfonyl)

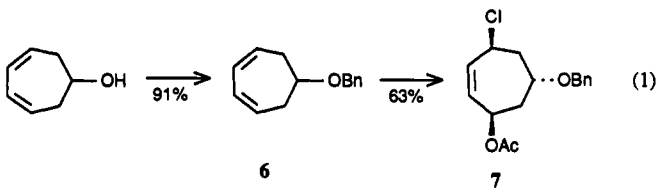


In 1987 we described[9] the preparation of simple tropane alkaloids via the palladium-catalyzed 1,4-acetoxychlorination[10] of cycloheptadienes (Scheme I). The nitrogen was introduced stereoselectively using *p*-toluenesulfonamide as nucleophile,[11] replacing chlorine either with retention (Pd catalysis) or with inversion (S_N2). Subsequent transformation of respective products afforded tropine (**4**) and pseudotropine (**5**).

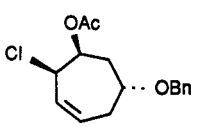
It is known that an allylic *p*-toluenesulfonamide (HNTs) group has a syn directive effect on the epoxidation of cyclic olefins by *m*-chloroperbenzoic acid (*m*-CPBA).[12] We therefore found it of interest to investigate whether a stereoselective epoxidation step could be incorporated into our reaction sequence prior to cyclization. Success in controlling the stereochemical outcome of the epoxidation would make both scopine and pseudoscopine accessible by our approach to tropane alkaloids.

Results and Discussion

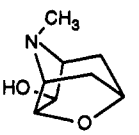
The preparation of the intermediate **7** and its further elaboration to scopine (**1**) and pseudoscopine (**3**) are outlined in eq 1 and Scheme II. The readily accessible



3,5-cycloheptadienol was protected as its benzyl ether **6**. To avoid formation of side products in the benzylation of the alcohol it was necessary to perform the reaction under the specific conditions described in the Experimental Section. The palladium-catalyzed 1,4-acetoxychlorination of **6** was highly diastereoselective and afforded chloroacetate **7** in 63% yield with the relative stereochemistry at the three asymmetric carbons as indicated (eq 1). The reaction was not completely regioselective, and the 1,2-isomer **8** was present in small amounts (7:8 = 10:1) in the crude product.[13]



8



15

A. Synthesis of Scopine. To reach the 3α-hydroxyl isomers of the tropane alkaloids (e.g. scopine), the nitrogen function has to be introduced trans to the benzyloxy group. Previously this was done by a palladium-catalyzed substitution of the chlorine in chloroacetate **7**, a reaction that occurs with retention.[9] However, since this reaction showed poor reproducability (yields sometimes dropped to 30–40%, and diamidation was a competing side reaction) we developed an alternative procedure. The chloroacetate **7** was transformed into chloro alcohol **9** (diisobutylaluminum hydride, 0 °C), which on subsequent reaction with NaNHTs in the presence of a catalytic amount of $Pd(PPh_3)_4$ in acetonitrile afforded amido alcohol **10** in an overall yield of 63%.

The trans 1,4-relationship required for the cyclization was created by inverting the stereochemistry at C-4. Replacement of an allylic hydroxyl group by a chloride with inversion in cyclic systems, using triphenylphosphine and *N*-chlorosuccinimide, has previously been described.[14,15] This method, when applied to **10**, gave a 66:34 mixture (86% total yield) of 1,4- and 1,2-isomers. Other reagents[16] were also tried but they afforded low yields of the desired product. An acceptable yield of **11** (76%, 9:1 mixture of **11** and its epimeric chloride) was finally obtained by em-

(9) Bäckvall, J. E.; Renko, Z. D.; Byström, S. E. *Tetrahedron Lett.* **1987**, *28*, 4199.
(10) Bäckvall, J. E.; Nyström, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676.
(11) For other examples of the use of *p*-toluenesulfonamide as nucleophile displacing allylic chlorides and acetates, see: (a) Byström, S. E.; Aslanian, R.; Bäckvall, J. E. *Tetrahedron Lett.* **1985**, *26*, 1749. (b) Bäckvall, J. E.; Schink, H. E.; Renko, Z. D. *J. Org. Chem.* **1990**, *55*, 826.
(12) Bäckvall, J. E.; Oshima, K.; Palermo, R. E.; Sharpless, K. B. *Ibid.* **1979**, *44*, 1953.
(13) (a) The ^1H NMR spectrum of **8** resembles that of *cis*-1-acetoxy-2-chloro-3-cycloheptene described by Bäckvall et al.[13b] (b) Bäckvall, J. E.; Granberg, K. L.; Hopkins, R. B. *Acta Chem. Scand.* **1990**, *44*, 492. Distinguishable peaks in the ^1H NMR of **8** in a mixture with **7**: δ 5.42 (ddd, J = 10, 4, 2 Hz, 1 H, C*H*OAc), 5.01 (ddd, J = 11, 3, 2 Hz, 1 H, CH_3Cl), 3.82 (m, 1 H, C*H*OBn).
(14) Oppolzer, W.; Gaudin, J. M.; Birkinshaw, T. N. *Tetrahedron Lett.* **1988**, *29*, 4705.
(15) Bäckvall, J. E.; Granberg, K. L.; Heumann, A. *Isr. J. Chem.* In press.
(16) (a) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, *13*, 4339. (b) Mitsunobu, O. *Synthesis* **1981**, 1.

ploying a slight modification of the method of Collington and Meyers.[17]

Epoxidation of 11 using *m*-CPBA in CH_2Cl_2 at 20 °C occurred with the desired stereochemistry (>98% syn) to give 12. The subsequent cyclization of 12 to 13, in methanol with potassium carbonate as base, was very efficient, and the overall yield from 11 to 13 was 87%. The *N*-methyl analogue was obtained from 13 in a one-pot sequence. Thus, removal of the *p*-toluenesulfonyl group with sodium naphthalide[18] in THF at −78 °C, followed by addition of methyl iodide, afforded scopine benzyl ether (14) in 88% yield. To the best of our knowledge, this method for N-alkylation has not been used[19] and it is superior to the procedure previously employed involving deprotection followed by reductive alkylation with formaldehyde and $NaBH_4$.[9,20]

Removal of the O-protecting group[21] using palladium on carbon (Pd/C) or Pearlman's catalyst ($Pd(OH)_2/C$) in methanol at hydrogen pressures from 1 to 6 atm resulted only in recovered starting material. Other methods such as sodium in liquid ammonia or Pd/C in acetic acid under 5 atm of hydrogen were too harsh, resulting in formation of scopoline (15). On the other hand, we observed that debenzylation of the *N*-tosyl derivative 13 occurred cleanly to give *N*-tosylscopine.[22] It therefore occurred to us that the hydrochloride of 14 would work better than the free amine. Indeed, hydrogenolysis of 14 in ethanol containing aqueous hydrochloric acid in the presence of Pd/C proceeded smoothly to give scopine (1) and scopoline (15) as their hydrochloride, in a ratio of 85:15. Pure scopine was obtained by a subsequent chromatographic purification.

B. Synthesis of Pseudoscopine. In pseudoscopine (3) the 3-hydroxy group and nitrogen are cis to one another. This stereochemistry was obtained by reaction of 7 with NaNHTs in DMSO at 80 °C, which afforded 16 in 77% yield. We were then required to introduce the epoxy group syn to the nitrogen. Peracid epoxidation (*m*-CPBA) of amidoacetate 16 was nonselective, forming equal amounts of syn and anti epoxides (with respect to HNTs). To favor syn epoxidation the steric bulk on the anti face of the ring was increased by transforming the acetate 16 to *tert*-butyldimethylsilyl ether 18.[23] In this manner it was possible to promote formation of the desired syn isomer 19, and epoxidation of 18 occurred with a syn/anti selectivity of 87:13.

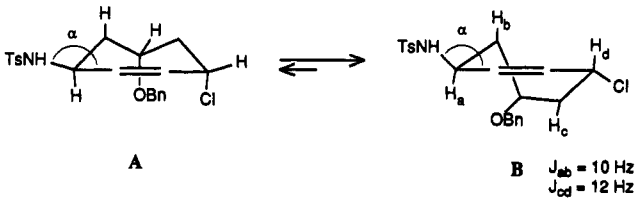
The silyl group was removed by tetrabutylammonium fluoride in THF, and the overall yield for the four steps from 16 to 20 was 60%. Mesylation of 20 and subsequent cyclization of 21 by use of potassium carbonate in methanol afforded 22. For the conversion of 22 into pseudoscopine, the same reactions as described for the synthesis of scopine (1) were used. Removal of the tosyl group (Na, naphthalene) and quenching with methyl iodide afforded pseudoscopine benzyl ether (23) in 60% yield.

It was also necessary in this case to protonate the amine in order to bring about debenzylation. However, the intramolecular reaction with opening of the epoxide cannot occur in the pseudoscopine system. Thus, stirring 23 in methanol in the presence of Pd/C and methanesulfonic acid under 1 atm of hydrogen for 4 h afforded pseudoscopine (3) quantitatively.

C. Directive Effect in the Epoxidation of 1,4-Disubstituted 2-Cycloheptenes. A number of studies have been concerned with the influence of allylic substituents on the stereochemistry of peracid epoxidations of olefins.[12,24] In most cases, however, only cyclohexene derivatives have been investigated, and relatively few studies have been done on other cyclic systems.[24c,25] Stereochemical studies on peracid epoxidation of olefins with substituents in both allylic positions are also rare.[23b,26] Although the main purpose of the present work has not been to investigate directive effects in peracid epoxidations, we have made some interesting observations worth discussing.

It is known that allylic sulfonamido[12] and hydroxyl functions[24a] have a strong syn-directive effect in cyclohexene systems. The sulfonamido alcohol 10 therefore appeared to be a very promising substrate for a stereocontrolled epoxidation of the double bond. Surprisingly, epoxidation of 10 with *m*-CPBA in CH_2Cl_2 at room temperature occurred with poor stereoselectivity. The ratio between the anticipated syn epoxide and the undesired anti epoxide was only 2:1. For comparison, the acetate of 10 was subjected to the same conditions and in this case the syn selectivity was higher (>90%). The lower stereoselectivity in the former case might be due to hydrogen bonding between the sulfonamido and the hydroxyl groups, forcing both allylic substituents into pseudoaxial positions and thus hindering syn epoxidation.[24b]

The very high syn selectivity (>98%) in the epoxidation of 11 is remarkable. From the ^1H NMR spectrum it is evident that the twisted form (B) predominates over the chair form (A) in solution. There are several explanations as to why epoxidation from the upper side of B would be favored. The main reason is probably that the angle (α) between the C–N bond and the plane of the π-system is small enough in B to give a favorable directive effect of the TsNH group. In addition, epoxidation from the underside would be hindered by the benzyloxy substituent.



A B J_{ab} = 10 Hz J_{cd} = 12 Hz

Epoxidation of 16 afforded, as mentioned earlier, a 1:1 mixture of syn (to sulfonamide) and anti epoxides. The pivaloate of 17 upon treatment with *m*-CPBA also gave a 1:1 syn/anti mixture of epoxides. This shows that peracid epoxidation is less sensitive to steric hindrance by ester groups than by a silyl group. Assuming that the esters are in pseudoequatorial positions these results are in accordance with those of Whitham.[24b] Since the di-

(17) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.
(18) (a) Battisti, A.; Bank, S.; Closson, W. D.; Gortler, L. B.; Sungchul, J.; Wriede, P. J. *J. Am. Chem. Soc.* **1967**, *89*, 5311. (b) Closson, W. D.; Sungchul, J.; Schulenberg, S. *J. Am. Chem. Soc.* **1970**, *92*, 650.
(19) For a related reaction, see: Adams, C. E.; Walker, F. J.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 420.
(20) Sondegam, B. L.; Hemo, J. H.; Charles, G. *Tetrahedron Lett.* **1973**, *14*, 261.
(21) Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1981.
(22) Compound 13 was easily debenzylated in methanol with Pd/C at 5 atm of hydrogen pressure, to afford *N*-(*p*-toluenesulfonyl)scopine in 92% yield.
(23) (a) Chavdarian, C. G.; Heathcock, C. H. *Synth. Commun.* **1976**, *6*, 277. (b) Sabol, J. S.; Cregge, R. J. *Tetrahedron Lett.* **1989**, *30*, 3377.
(24) (a) Henbest, A.; Wilson, R. A. *J. Chem. Soc.* **1957**, 1958. (b) Chamberlain, P.; Roberts, M. C.; Whitham, G. H. *J. Chem. Soc. B* **1970**, 1374. (c) Berti, G. *Topics in Stereochemistry*; Wiley: New York, 1973; Vol. 7. (d) Chautempts, P.; Pierre, J. L. *Tetrahedron* **1973**, *32*, 549. (e) Kočovsky, P.; Stary, I. *J. Org. Chem.* **1990**, *55*, 3236.
(25) (a) Cope, A. C.; Keough, A. H.; Peterson, P. E.; Simmons, H. E., Jr.; Wood, G. W. *J. Am. Chem. Soc.* **1957**, *79*, 3900. (b) Cope, A. C.; Heeren, J. K.; Seeman, V. *J. Org. Chem.* **1963**, *28*, 516. (c) Hardinger, S. A.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 2739.
(26) (a) Nakajima, M.; Hasegawa, A.; Kurihara, N. *Chem. Ber.* **1962**, *95*, 2708. (b) Hasegawa, A.; Sable, H. Z. *J. Org. Chem.* **1966**, *31* 4154.

rective effect of the sulfonamide is not strong enough to give better selectivity, a possible directive effect of the carbonyl cannot be ruled out, although such effects are normally small, unless the carbonyl is part of a carbamate.[24e] The dramatic improvement on changing the acyloxy group for a silyloxy group (18) therefore seems to arise mainly from steric effects. Even the latter case was not completely syn-stereoselective (syn:anti = 87:13) showing that conformational effects make it difficult to predict the stereoselectivity of peracid epoxidation in these systems.

Experimental Section

General Comments. ^1H and ^{13}C NMR spectra were recorded at 300 and 75.4 MHz, respectively, with $CDCl_3$ as solvent. Mass spectra were obtained using electron ionization at 70 eV. Infrared spectra were recorded for thin films. Melting points were measured in open capillary tubes and are uncorrected. Elemental analyses were performed by Analytische Laboratorien, Engelskirchen, Germany, and Mikrokemi AB, Uppsala, Sweden. High-pressure liquid chromatography (HPLC) analyses were performed on a Waters Radial-PAK silica column (10 μ, 0.8 x 10 cm) using hexane and ethyl acetate (EtOAc) as mobile phase. Thin-layer chromatography (TLC) was run on Merck precoated silica gel 60-F 254 plates. Commercially available chemicals were used as delivered. *m*-Chloroperbenzoic acid (*m*-CPBA) used was of technical grade (80–90%) and supplied by Aldrich. Standard procedures were used for drying and purification of solvents. 3,5-Cycloheptadienol,[27] *p*-toluenesulfonamide monosodium salt[28] (NaHNTs), and tetrakis(triphenylphosphine)palladium[10] ($(Pd(PPh_3)_4$) were prepared according to known procedures. "Collected on silica" means that silica gel was added to the solution of crude product after removal of the drying agent. The slurry obtained was stripped to dryness in vacuo, and the dry powder was applied to a silica column and chromatographed as usual.[29] Merck silica gel 60 (230–400 mesh) was used for flash chromatography. All reactions were performed under inert atmosphere (nitrogen or argon) at room temperature (i.e. 20–23 °C) unless otherwise stated.

6-(Benzyloxy)-1,3-cycloheptadiene (6). A modification of a previously reported procedure[30] was used. 3,5-Cycloheptadienol (3.03 g, 27.5 mmol) in THF (20 mL) was added to a stirred solution of NaH (80% in white oil, 859 mg, 28.6 mmol) and benzyl bromide (10.34 g, 60.5 mmol) in THF (80 mL). The mixture was then heated at 50 °C for 15 h. The NaBr precipitate formed was removed by filtration, and the resulting solution was diluted with ether (50 mL). The organic layer was washed with H_2O (250 mL), and the aqueous phase was extracted with ether (70 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and purified by flash chromatography (hexane/EtOAc, 95/5), to afford 5.01 g (91%) of **6** as a colorless oil containing 4% of dibenzyl ether formed as a byproduct. ^1H NMR: δ 7.4–7.2 (m, 5 H, PhH), 5.8–5.7 (m, 4 H, olefin), 4.56 (s, 2 H, benzylic), 3.8 (m, 1 H, C*H*OBn), 2.7–2.5 (m, 4 H, CH_2). ^{13}C NMR: δ 138.7, 128.3, 128.0, 127.5, 126.3, 77.3, 72.1, 70.6, 36.8. IR: 3025, 2900, 2880, 1495, 1400, 1330, 1090, 1070, 1030, 750, 700, 685 cm^{-1}.

1β-Acetoxy-4β-chloro-6α-(benzyloxy)-2-cycloheptene (7). To a stirred solution of LiCl (2.12 g, 50.0 mmol), $LiOAc{\cdot}2H_2O$ (5.10 g, 50.0 mmol), *p*-benzoquinone (8.11 g, 75.0 mmol), and $Pd(OAc)_2$ (281 mg, 1.25 mmol) in glacial acetic acid (85 mL) was added a solution of **6** (85% pure, 5.0 g, 21.3 mmol) in glacial acetic acid (15 mL). The reaction mixture was stirred in a stoppered flask and quenched after 36 h by addition of brine (75 mL) and pentane/ether (90/10, 100 mL). After 10 min of additional stirring the mixture was filtered and the filtrate was washed with pentane/ether (90/10, 50 mL). The phases were separated, and the aqueous phase was extracted with pentane/ether (90/10, 4 x 50 mL). The combined organic phases were washed with water (2 x 50 mL), 10% aqueous Na_2CO_3 (3 x 50 mL), and 2 M aqueous NaOH (2 x 50 mL). The combined alkaline phases were back-extracted with pentane/ether (90/10, 50 mL), and the combined organic extracts were washed with brine (50 mL). The solution was dried ($MgSO_4$) and concentrated in vacuo to afford 5.88 g of crude product containing **7** and 1,2-isomer **8**[13] in a ratio of 10:1. Purification of the crude oil by flash chromatography (hexane/EtOAc, 90/10) afforded 3.96 g (63%) of chloroacetate **7** as a pale yellow oil. ^1H NMR: δ 7.32 (m, 5 H, aromatic), 5.87 (m, J = 11, 3 Hz, 1 H =C*H*CHCl), 5.70 (m, 2 H, =C*H*CHOAc overlapping C*H*OAc), 4.92 (m, J = 9, 3, 3 Hz, 1 H, CHCl), 4.60 (q, 2 H, benzylic), 3.96 (m, J = 6, 6, 5, 4 Hz, 1 H, C*H*OBn), 2.35 (ddd, J = 14, 6, 3 Hz, 1 H, eq CH_2CHCl), 2.25 (ddd, J = 14, 9, 4 Hz, 1 H, ax CH_2CHCl), 2.21 (m, J = 14 Hz, 1 H, eq CH_2CHOAc), 2.07 (s, 3 H, OAc), 2.03 (ddd, J = 14, 10, 5 Hz, 1 H, ax CH_2CHOAc). ^{13}C NMR: δ 170.1, 138.2, 134.1, 133.2, 128.4, 127.62, 127.58, 72.40, 70.34, 68.46, 53.92, 41.06, 36.56, 21.21; IR: 3064, 3032, 2936, 2865, 1738, 1454, 1441, 1371, 1240, 1076, 1028, 739, 697 cm^{-1}. MS: m/z (relative intensity) 294 (M^+, <0.5), 259 (M – Cl, 5), 235 (M – OAc, 1), 200 (1), 199 (6), 143 (13), 128 (21), 107 (30), 93 (20), 92 (26), 91 (100).

Anal. Calcd for $C_{16}H_{19}ClO_2$: C, 65.2; H, 6.50. Found: C, 65.1; H, 6.63.

1β-Hydroxy-4β-chloro-6α-(benzyloxy)-2-cycloheptene (9). To an ice-cooled stirred solution of **7** (3.00 g, 10.18 mmol) in THF (60 mL) was added dropwise diisobutylaluminum hydride (1 M in hexane, 50 mL, 50 mmol). After complete addition (15 min) the mixture was stirred at 2 °C for another 45 min. The cold mixture was then slowly poured into a slurry of ice (200 g) and 2 M aqueous HCl (250 mL). Ether (150 mL) was added, the phases were separated, and the aqueous phase was extracted with ether (3 x 100 mL). The combined ethereal phases were washed with 2 M aqueous HCl (2 x 50 mL). After back-extraction of the acidic aqueous phase with ether (50 mL), the combined organic phases were washed with brine (2 x 50 mL) and dried ($MgSO_4$). Concentration in vacuo gave 2.60 g (96%) of **9** as a colorless oil. The crude material was of 95% purity (HPLC analysis) and was used without further purification. Material of higher purity was obtained by flash chromatography, hexane/EtOAc (80/20). ^1H NMR: δ 7.35 (m, 5 H, aromatic), 5.82 (m, 2 H, olefinic), 4.85 (m, 1 H, CHCl), 4.71 (dd, J = 10, 3 Hz, 1 H, C*H*OH), 4.58 (d, 2 H, benzylic), 3.98 (dddd, J = 6, 5, 4.5, 3.5 Hz, 1 H, C*H*OBn), 2.28 (m, 2 H, CH_2CHCl), 2.14 (dddd, J = 14, 4.5, 3, 1 Hz, 1 H, eq CH_2CHOH), 2.05 (ddd, J = 14, 10, 3.5 Hz, 1 H, ax CH_2OH), 1.69 (br s, 1 H, OH). ^{13}C NMR: δ 138.2 (two carbons), 131.7, 128.4, 127.7, 127.5, 72.95, 70.52, 65.62, 54.13, 40.68, 40.51. IR: 3362, 3030, 2929, 2864, 1496, 1454, 1344, 1216, 1073, 1028, 736, 696 cm^{-1}. MS: m/z (relative intensity) 252 (M^+, <0.1), 234 (M – H_2O, 0.11), 217 (M – Cl, 1.2), 161 (M – benzyl, 2), 92 (21), 91 (100).

Anal. Calcd for $C_{14}H_{17}ClO_2$: C, 66.5; H, 6.78. Found: C, 66.9; H, 6.90.

1β-(*p*-Toluenesulfonamido)-4β-hydroxy-6α-(benzyloxy)-2-cycloheptene (10). To a stirred suspension of $Pd(PPh_3)_4$ (578 mg, 0.50 mmol) and NaHNTs (2.70 g, 14 mmol) in CH_3CN (70 mL) was added **9** (2.59 g, 9.74 mmol) dissolved in CH_3CN (10 mL). The reaction mixture was stirred for 4 h and quenched by bubbling air through the mixture for 5 min. EtOAc (50 mL) was added together with silica gel (25 g), and the solvents were removed in vacuo. Flash chromatography hexane/EtOAc (50/50) afforded 2.50 g (66%) of **10** as a pale yellow solid. Mp: 142–143 °C (recrystallized from EtOAc/ligroin). ^1H NMR: δ 7.74 (d, J = 8 Hz, 2 H, aromatic), 7.27 (m, 7 H, aromatic), 5.62 (dddd, J = 12, 4, 2, 1 Hz, 1 H, =C*H*CHOH), 5.51 (dddd, J = 12, 4.5, 2, 1 Hz, 1 H, =C*H*CHNHTs), 5.10 (d, J = 8 Hz, 1 H, *H*NTs), 4.57 (unresolved m, 1 H, C*H*OH), 4.40 (q, 2 H, benzylic), 4.25 (unresolved m, 1 H, C*H*NHTs), 3.83 (m, $w/2$ = 11 Hz, 1 H, C*H*OBn), 2.38 (s, 3 H, ArCH_3), 1.98 (m, 2 H, CH_2), 1.82 (m, 3 H, CH_2 and OH). ^{13}C NMR: δ 143.3, 138.4, 137.5, 137.4, 132.8, 129.7, 128.3, 127.5, 127.4, 127.1, 72.52, 70.04, 65.50, 48.25, 40.38, 38.22, 21.48. IR: 3475 (broad), 3273 (broad), 3029, 2922, 2862, 1454, 1325, 1156, 1093, 1049 cm^{-1}. MS: m/z (relative intensity) 387 (M^+, 0.1), 232 (M – HNTs, 15), 155 (17), 108 (18), 91 (100).

Anal. Calcd for $C_{21}H_{25}NO_4S$: C, 65.1; H, 6.50. Found: C, 65.1; H, 6.45.

1β-(*p*-Toluenesulfonamido)-4α-chloro-6α-(benzyloxy)-2-cycloheptene (11). LiCl (170 mg, 4.0 mmol) and **10** (775 mg, 2.0 mmol) were dissolved in DMF (3 mL) and 2,4,6-trimethyl-

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pyridine (2 mL). This solution was cooled in an ice bath, and the slurry formed was treated with methanesulfonyl chloride (232 μL, 3.0 mmol). The yellow slurry was stirred overnight while the mixture was allowed to reach ambient temperature. The reaction mixture was treated with water (15 mL) and extracted with ether (3 × 30 mL). The organic extract was washed with 10% aqueous $Cu(NO_3)_2$ (3 × 30 mL). The light blue aqueous phase was back-extracted with ether (2 × 30 mL), and before drying ($MgSO_4$) the combined organic phases were washed with brine (50 mL). The crude product was collected on silica and purified by flash chromatography (hexane/EtOAc, 80/20) to yield 620 mg (76%) of a white solid which contained 11 and the epimeric chloride in a 9:1 ratio (HPLC analysis). This mixture could be used in the next reaction step since the corresponding epoxidation products were separable by flash chromatography. Mp: 119 °C (recrystallized from EtOAc and hexane). ^{1}H NMR: δ 7.75 (d, J = 8 Hz, 2 H, aromatic), 7.30 (m, 7 H, aromatic), 5.78 (m, $J_{olefinic}$ = 12 Hz, 1 H, =C*H*CHCl), 5.50 (m, $J_{olefinic}$ = 12 Hz, 1 H, C*H*CHNHTs), 4.83 (d, J = 8 Hz, 1 H, *H*NTs), 4.49 (m, J = 12, 3, 3, 2.5, 2 Hz, 1 H, CHCl), 4.38 (q, 2 H, benzylic), 4.24 (m, J = 10, 8, 3, 3, 3, 2 Hz, 1 H, C*H*NHTs), 3.71 (dddd, J = 10, 6, 4, 4 Hz, 1 H, C*H*OBn), 2.55 (m, J_{gem} = 13 Hz, 1 H, eq CH_2CHCl), 2.38 (s, 3 H, ArCH_3), 2.12 (ddd, J = 13, 12, 10 Hz, 1 H, ax CH_2CHCl), 2.08 (m, J_{gem} = 14 Hz, 1 H, eq CH_2CHNTs), 1.88 (ddd, J = 14, 10, 4 Hz, 1 H, ax CH_2CHNHTs). ^{13}C NMR: δ 143.6, 138.1, 137.3, 135.1, 133.6, 129.8, 128.4, 127.6, 127.5, 127.2, 71.88, 70.18, 53.95, 48.39, 42.84, 39.21, 21.52. IR: 3274, 3030, 2945, 2868, 1598, 1496, 1453, 1328, 1158, 1094, 753, 689 cm^{-1}. MS: m/z (relative intensity) 405 (M$^+$, <1), 314 (M = 91, 2), 250 (M − 155, 5), 172 (11), 155 (16), 108 (8), 106 (4), 92 (12), 91 (100).

Anal. Calcd for $C_{21}H_{24}ClNO_3S$: C, 62.1; H, 5.96. Found: C, 62.0; H, 5.94.

1β-(*p*-Toluenesulfonamido)-2β,3β-epoxy-4α-chloro-6α-(benzyloxy)cycloheptene (12). To a stirred solution of 11 (90% pure, 619 mg, 1.37 mmol of 11) in CH_2Cl_2 (12 mL) was added solid *m*-CPBA (329 mg). After 24 h another portion of *m*-CPBA (329 mg) was added. The reaction mixture was then stirred until full conversion had taken place (as indicated by TLC, hexane/EtOAc, 70/30), usually after a further 24 h. Filtration of the reaction mixture and removal of the solvent in vacuo gave a residue which was dissolved in ether (20 mL). The etheral solution was washed with cold 10% aqueous Na_2SO_3 (3 × 5 mL), 10% aqueous Na_2CO_3 (3 × 5 mL), and brine (5 mL) and dried ($MgSO_4$). The crude product was collected on silica and chromatographed with hexane/EtOAc (80/20 and 70/30) to afford 12 (497 mg, 86%) as a white solid, mp 127 °C (recrystallized from EtOAc/hexane). In a separate run recrystallized 11 (272 mg, 0.67 mmol) afforded 12 in 92% yield. ^{1}H NMR: δ 7.75 (d, J = 8 Hz, 2 H, aromatic), 7.30 (m, 7 H, aromatic), 4.83 (d, J = 6 Hz, 1 H, *H*NTs), 4.39 (q, 2 H, benzylic), 4.15 (ddd, J = 7, 5, 5 Hz, 1 H, CHCl), 4.00 (dddd, J = 9, 6, 3.5, 2 Hz, 1 H, C*H*NHTs), 3.73 (dddd, J = 7, 7, 6, 3 Hz, 1 H, C*H*OBn), 3.38 (dd, J = 5, 4.5 Hz, 1 H, proton on C3), 3.21 (ddd, J = 4.5, 3.5, 1 Hz, 1 H, proton on C2), 2.39 (s, 3 H, ArCH_3), 2.21 (two overlapping doublets, 2 H, CH_2CHCl), 2.07 (ddd, J = 14, 9, 3 Hz, 1 H, ax CH_2CHNHTs), 1.66 (dddd, J = 14, 7, 2, 1 Hz, 1 H, eq CH_2CHNHTs). ^{13}C NMR: δ 143.8, 138.2, 136.4, 129.9, 128.3, 127.5, 127.3, 127.2, 72.00, 70.49, 60.51, 57.86, 54.02, 47.13, 39.24, 34.00, 21.53. IR: 3276, 3030, 2933, 2867, 1453, 1161, 1095, 1074, 736, 666, 550 cm^{-1}. MS: m/z (relative intensity) 421 (M$^+$, <1), 266 (3), 160 (5), 155 (18), 109 (6), 92 (11), 91 (100).

Anal. Calcd for $C_{21}H_{24}ClNO_4S$: C, 59.8; H, 5.73. Found: C, 59.7; H, 5.61.

3α-(Benzyloxy)-6β,7β-epoxy-8-(*p*-toluenesulfonyl)-1β-azabicyclo[3.2.1]octane (13). Solid K_2CO_3 (645 mg, 4.67 mmol) was added to a stirred solution of 12 (197 mg, 0.47 mmol) in methanol (14 mL). The suspension was stirred in a stoppered flask for 56 h. The progress of the reaction was monitored by TLC. The solvent was removed in vacuo, and the residue was dissolved in water and EtOAc. The phases were separated, and the aqueous phase was extracted twice with EtOAc. The combined organic extracts were washed with brine and dried ($MgSO_4$). After concentration in vacuo 13 (purity 95%, HPLC analysis) was obtained as a white solid (180 mg, 95%). MP: 134 °C (recrystallized from EtOAc/hexane). ^{1}H NMR: δ 7.62 (d, J = 8 Hz, 2 H, aromatic), 7.27 (m, 7 H, aromatic), 4.44 (s, 2 H, benzylic), 4.21 (dd, J = 3.5, 2 Hz, 2 H, CHN), 3.70 (tt, J = 5, 1 Hz, 1 H, C*H*OBn), 3.42 (s, 2 H, CHO), 2.40 (s, 3 H, ArCH_3), 2.16 (ddd, J = 15, 5, 3.5 Hz, 2 H, CH_2), 1.93 (ddd, J = 15, 2, 1 Hz, 2 H, CH_2). ^{13}C NMR: δ 142.7, 138.4, 138.2, 129.2, 128.4, 127.5, 127.08, 127.05, 70.59, 70.50, 55.49, 53.36, 32.35, 21.53. IR: 3031, 2925, 2862, 1338, 1285, 1205, 1161, 1070, 734, 670 cm^{-1}. MS: m/z (relative intensity) 385 (M$^+$, <0.5), 294 (M − 91, 16), 230 (12), 155 (9), 122 (7), 91 (100), 65 (14).

Anal. Calcd for $C_{21}H_{23}NO_4S$: C, 65.4; H, 6.01. Found: C, 65.3; H, 5.93.

Scopine Benzyl Ether (14). Freshly cut pieces of sodium (57 mg, 2.47 mmol) were added to a stirred solution of naphthalene (318 mg, 2.47 mmol) in THF (7.5 mL). After 1 h the resultant dark solution was cooled to −78 °C, and 13 (159 mg, 0.412 mmol) in THF (2.5 mL) was added over 5 min. The reaction was quenched after stirring for 30 min at −78 °C by the dropwise addition of MeI (180 μL, 2.9 mmol). The cooling bath was removed, and the pale yellow solution was allowed to reach room temperature. Water (3 mL) was added, and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. Flash chromatography of the crude product (hexane/EtOAc (70/30) and EtOAc/triethylamine (95/5)) afforded 89 mg (88%) of 14 as an almost colorless oil. ^{1}H NMR: δ 7.30 (m, 5 H, aromatic), 4.45 (s, 2 H, benzylic), 3.68 (br s, 2 H, CHO), 3.60 (tt, 5, 1.5 Hz, 1 H, C*H*OBn), 3.19 (dd, J = 4, 2 Hz, 2 H, CHN), 2.52 (s, 3 H, CH_3), 2.03 (ddd, J = 15, 5, 4 Hz, 2 H, CH_2), 1.76 (ddd, J = 15, 2, 1.5 Hz, 2 H, CH_2). ^{13}C NMR: δ 138.9, 128.3, 127.3, 127.0, 70.63, 70.23, 58.39, 57.03, 42.07, 30.78; IR: 3030, 2933, 1330, 1204, 1091, 1074, 1027, 856, 736 cm^{-1}. MS (via GC): m/z (relative intensity) 245 (M$^+$, 3), 155 (9), 154 (M − benzyl, 100), 138 (9), 110 (11), 97 (10), 96 (25), 91 (56).

Scopine Hydrochloride (1·HCl). A freshly prepared solution of 14 (25 mg, 0.10 mmol) in absolute ethanol (925 μL) and aqueous 2 M HCl (0.15 mmol, 75 μL) was added to 10% Pd/C (16 mg). A hydrogen pressure of 5 atm was applied, and the mixture was shaken for 12 h, uing a Parr Series 390 hydrogenation apparatus. The catalyst was removed by filtration through Celite and rinsed with small portions of absolute ethanol. Removal of the solvent in vacuo gave 20 mg of a white solid that contained scopine[HCl] and scopoline[HCl] in a ratio of 85:15, determined by ^{1}H NMR in D_2O. The spectrum of the major component was identical to the ^{1}H NMR spectrum of a commercial sample of scopine[HCl] (Sigma NO. S-0382).

Scopine (1). Scopine[HCl] (80 mg, containing 30% scopoline[HCl]) was dissolved in 10% aqueous K_2CO_3 (2 mL), extracted with $CHCl_3$ (5 × 5 mL), and dried ($MgSO_4$). The oily residue obtained after concentration in vacuo was purified by flash chromatography (EtOAc/triethylamine (95/5 and 80/20)) to give 39 mg of scopine as a pale yellow solid. ^{1}H NMR: δ 3.85 (tt, J = 5, 1 Hz, 1 H, C*H*OBn), 3.64 (s, 2 H, CHO), 3.17 (br d, J = 4Hz, 2 H, CHN), 2.51 (s, 3 H, NCH_3), 2.08 (ddd, J = 15, 5, 4 Hz, CH_2), 1.97–1.72 (1 H, OH), 1.76 (ddd, J = 15, 2, 1 Hz, 2 H, CH_2). ^{13}C NMR: δ 63.13, 58.20, 56.74, 41.71, 33.81. MS: m/z (relative intensity) 155 (M$^+$, 43), 138 (10), 126 (10), 112 (34), 110 (31), 94 (40), 82 (37), 68 (23), 57 (53), 42 (100).

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.9; H, 8.44. Found: C, 62.04; H, 8.38.

1β-Acetoxy-4α-(*p*-toluenesulfonamido)-6α-(benzyloxy)-2-cycloheptene (16). To a stirred solution of NaNHTs (990 mg, 5.12 mmol) in dry DMSO (15 mL) was added 7 (1.02 g, 3.46 mmol). The reaction mixture was heated at 80 °C for 3 h. After cooling the mixture was diluted with 75 mL of hexane/EtOAc (70/30) and washed with brine containing 2% NaOH (3 × 50 mL) and NH_4Cl (75 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was flash chromatographed (hexane/EtOAc, 70/30) which afforded 1.17 g (79%) of 16 as white crystals. Mp: 98 °C. ^{1}H NMR: δ 7.69 (d, 2 H, aromatic), 7.31 (m, 7 H, aromatic), 5.61 (m, 3 H, olefin and C*H*OAc), 4.67 (d, J = 9 Hz, 1 H, N*H*Ts), 4.55 (d, J = 12 Hz, 2 H, benzylic), 4.12 (m, 1 H, C*H*NTs), 3.88 (m, 1 H, C*H*OBn), 2.41 (s, 3 H, CH_3Ar), 2.22 (dd, J = 12, 3 Hz, 1 H, CH_2), 2.03 (s, 3 H, OAc), 1.93 (m, 3 H, CH_2). ^{13}C NMR: δ 170.1, 143.2, 138.2, 137.7, 133.9, 132.0, 129.6, 128.5, 127.8, 127.6, 126.9, 76.6, 73.2, 68.3, 50.0, 38.0, 36.0, 21.5, 21.2; IR: 3268, 3032, 2928, 2875, 1735, 1598, 1496, 1453, 1372, 914, 815, 792, 698 cm^{-1}.

1β-Hydroxy-4α-(*p*-toluenesulfonamido)-6α-(benzyloxy)-2-cycloheptene (17). NaOH (0.5 mL, 2 M) was added to a

solution of **16** (200 mg, 0.47 mmol) in MeOH (2 mL). The mixture was refluxed for 4 h, and the MeOH was removed in vacuo. Water (5 mL) was added and the pH was adjusted to 5 with 2 M aqueous HCl. The aqueous phase was extracted with EtOAc (3 × 10 mL), dried ($MgSO_4$), and concentrated. The residue was flash chromatographed (hexane/EtOAc, 70/30) to give 152 mg (84%) of **17** as white crystals. Mp: 87 °C. ^1H NMR: δ 7.71 (d, J = 8 Hz, 2 H, aromatic), 7.4–7.2 (m, 7 H, aromatic), 5.72 (dd, J = 12, 2 Hz, 1 H, olefin), 5.52 (m, 2 H, NHTs, olefin), 4.68 (dd, J = 10, 2 Hz, 1 H, C*H*OH), 4.52 (2, d, J = 11 Hz, 2 H, benzylic), 4.01 (m, 1 H, C*H*NTs), 3.86 (dd, J = 4, 3 Hz, 1 H, C*H*OBn), 2.43 (s, 3 H, CH_3Ar), 2.17 (ddd, J = 14, 10, 4, 1 H, CH_2), 2.0–1.8 (m, 3 H, CH_2). ^{13}C NMR: δ 138.3, 137.9, 130.8, 129.7, 128.5, 127.9, 127.5, 127.0, 77.4, 76.6, 73.8, 70.9, 65.5, 50.1, 39.9, 38.0, 21.5. IR: 3279, 3063, 3030, 2925, 2869, 2366, 2344, 2251, 1598, 1496, 1452, 1327, 1159, 1093, 1053, 911, 846, 815, 734, 698, 666 cm^{-1}. MS: m/z (relative intensity): 388 (M^+, <0.5), 263 (1), 232 (3), 172 (4), 155 (11), 110 (25), 91 (100), 81 (13), 65 (15).

1β-((*tert*-Butyldimethylsilyl)oxy)-4α-(*p*-toluenesulfonamido)-6α-(benzyloxy)-2-cycloheptene (18). The alcohol **17** (992 mg, 2.56 mmol) was dissolved in dry DMF (4 mL), and the solution was cooled to 0 °C. Imidazole (284 mg, 4.17 mmol) and *tert*-butyldimethylsilyl chloride (496 mg, 3.29 mmol) were added, and the mixture was stirred for 4 h. The mixture was partitioned between ether and brine. The etheral phase was collected, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the residue (hexane/EtOAc, 80/20) afforded 1.21 g (94%) of **18** as a colorless oil. ^1H NMR: δ 7.7 (d, J = 8 Hz, 2 H, aromatic), 7.3 (m, 7 H, aromatic), 5.68 (dd, J = 12, 5 Hz, 1 H, olefin), 5.45 (dd, J = 12, 5 Hz, 1 H, olefin), 5.39 (d, J = 8 Hz, 1 H, N*H*Ts), 4.51 (2 d, J = 11 Hz, 2 H, benzylic), 4.41 (m, 1 H, C*H*OSi), 4.01 (m, 1 H, C*H*NTs), 3.86 (m, 1 H, C*H*OBn), 2.4 (s, 3 H, CH_3Ar), 2.0–1.74 (m, 4 H, CH_2), 0.88 (m, 9 H, ^{t}Bu-Si), 0.05 (s, 6 H, CH_3). ^{13}C NMR: δ 143.6, 139.0, 131.3, 130.0, 128.8, 128.1, 127.8, 127.4, 74.3, 71.1, 66.2, 50.5, 40.5, 38.8, 26.2, 26.1, 21.9. IR: 3278, 3030, 2953, 2928, 2884, 2856, 1598, 1471, 1360, 1330, 1305, 1254, 1161, 1093, 1066, 837, 815, 777, 734 cm^{-1}.

Anal. Calcd for $C_{27}H_{39}NO_4SSi$: C, 64.63; H, 7.83. Found: C, 64.47; H, 7.64.

1β-((*tert*-Butyldimethylsilyl)oxy)-4α-(*p*-toluenesulfonamido)-2α,3α-epoxy-6α-(benzyloxy)cycloheptane (19). *m*-CPBA (128 mg) was added to a solution of **18** (285 mg, 0.57 mmol) in $CHCl_3$ (1.5 mL) at 0 °C. The reaction was stirred for 1 h at 0 °C, for 2 h at 20 °C, and left in the refrigerator overnight. After filtration, the mixture was washed with Na_2SO_3 (5 mL, 10%), $NaHCO_3$ (5 mL, 5%), H_2O (5 mL), and brine (5 mL). The aqueous phase was extracted with $CHCl_3$ (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to afford 281 mg (96%) of crystalline **19**. The ratio of desired and undesired isomers was 87/13, and no starting material could be detected by HPLC. Separation of the isomers at this stage was not necessary since that was achieved at the cyclization step. ^1H NMR: δ 7.7 (d, J = 8 Hz, 2 H, aromatic), 7.4–7.2 (m, 7 H, aromatic), 4.78 (d, J = 9 Hz, 1 H, N*H*Ts), 4.26 (m, 1 H, CHOSi), 4.18 (d, J = 9 Hz, 2 H, benzylic), 3.72 (dt, J = 9, 4 Hz, 1 H C*H*NHTs), 3.3 (m, 1 H, C*H*OBn), 2.93 (m, 2 H, epoxide), 2.3 (s, 3 H, CH_3Ar), 1.8 (m, 1 H, CH_2), 1.6 (m, 3 H, CH_2), 0.76 (s, 9 H, ^{t}Bu-Si), –0.8 (s, 6 H, CH_3Si). ^{13}C NMR: δ 143.6, 137.9, 129.9, 128.4, 127.7, 127.5, 127.1, 71.4, 70.5, 67.4, 59.4, 57.7, 50.3, 38.3, 36.1, 25.8, 25.7, 21.5, 18.4, 18.0; IR: 3276, 2954, 2929, 2884, 2857, 2361, 1454, 1333, 1305, 1257, 1163, 1092, 1071, 1037, 911, 837, 815, 778, 734, 698, 666, 649 cm^{-1}.

1β-Hydroxy-4α-(*p*-toluenesulfonamido)-2α,3α-epoxy-6α-(benzyloxy)cycloheptane (20). Bu_4NF (3.28 mL, 1M THF, 3.28 mmol) was added to a stirred solution of **19** (680 mg, 1.31 mmol) in THF (10 mL). The mixture was stirred for 20 h and was then partitioned between ether and brine. After drying ($MgSO_4$) and concentration of the organic layer the residue was purified by flash chromatography (hexane/EtOAc, 70/30) to afford 506 mg (95%) of **20** (contaminated with ~10% of the 2β,3β-epoxide[31]) as white crystals. MP: 145 °C. ^1H NMR: δ 7.78 (d, J = 8 Hz, 2 H, aromatic), 7.4–7.18 (m, 7 H, aromatic), 4.99 (d, J = 8 Hz, 1 H, N*H*Ts), 4.43 (dd, J = 7, 5 Hz, 1 H, C*H*OH), 4.33 (s, 2 H, benzylic), 3.89 (dt, J = 9, 2 Hz, 1 H, C*H*NTs), 3.47 (dd, J = 8, 2 Hz, 1 H, C*H*OBn), 3.06–3.14 (m, 2 H, epoxide), 2.42 (s, 3 H, CH_3Ar), 2.01 (m, 1 H, CH_2), 1.89–1.6 (dd, J = 8, 2 Hz, 3 H, CH_2). ^{13}C NMR: δ 151.5, 143.6, 129.9, 128.4, 127.7, 127.5, 127.2, 127.0, 71.5, 70.6, 66.6, 58.9, 58.3, 50.3, 38.4, 35.7, 21.5; IR: 3278, 2928, 1598, 1496, 1452, 1328, 1160, 1092, 1065, 912, 734, 698, 666 cm^{-1}.

Anal. Calcd for $C_{21}H_{25}NO_5S$: C, 62.51; H, 6.25. Found: C, 62.61; H, 6.09.

1β-(Mesyloxy)-4α-(*p*-toluenesulfonamido)-2α,3α-epoxy-6α-(benzyloxy)cycloheptane (21). Methanesulfonyl chloride (101 μL, 1.30 mmol) was added to a stirred solution of Et_3N (170 μL, 1.22 mmol) and **20** (350 mg, 0.87 mmol) in THF over a 10-min period. After the mixture was stirred for 2 h ice/H_2O (10 mL) was added, and the mixture was extracted with hexane/EtOAc (3 × 25 mL, 60/40). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was used in the next step without further purification.

3α-(Benzyloxy)-6α,7αepoxy-8-(*p*-toluenesulfonamido)-1α-azabicyclo[3.2.1]octane (22). The crude mesylate **21** was dissolved in MeOH, and K_2CO_3 (126 mg, 1.27 mmol) was added. The reaction mixture was stirred for 120 h and was then concentrated in vacuo. After dilution with brine, the aqueous phase was partitioned between EtOAc and brine. Drying of the organic extract ($MgSO_4$) and purification by flash chromatography (hexane/EtOAc, 70/30) gave 271 mg (81%, based on **20**) of **22** as white crystals. ^1H NMR: δ 7.64 (d, J = 8 Hz, 2 H, aromatic), 7.31 (m, 7 H, aromatic), 4.47 (s, 2 H, benzylic), 4.33 (t, J = 3 Hz, 2 H, CHN), 3.88 (m, J = 10, 3, 6 Hz, 1 H, C*H*OBn), 3.32 (s, 2 H, epoxide), 2.4 (s, 3 H, CH_3Ar), 2.18 (ddd, J = 13, 10, 3 Hz, 2 H, CH_2), 1.85 (dt, J = 13, 3 Hz, 2 H, CH_2). ^{13}C NMR: δ 142.8, 138.7, 138.0, 129.3, 128.5, 127.8, 127.5, 126.9, 70.4, 70.0, 55.7, 51.7, 33.4, 21.5. IR: 3030, 2927, 1734, 1296, 1338, 1162, 1098, 1064, 1032, 672, 608 cm^{-1}.

Anal. Calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.01. Found: C, 65.26; H, 5.88.

Pseudoscopine Benzyl Ether (23). Sodium (50 mg, 2.17 mmol) and naphthalene (280 mg, 2.19 mmol) were stirred in dimethoxyethane (DME) (6 mL) for 1 h, and the blue solution was then cooled to –78 °C. Compound **22** (140 mg, 0.36 mmol) in DME (5 mL) was added and the mixture was stirred for 40 min at –78 °C. After quenching with MeI (200 μL 3.2 mmol), the solution was stirred at –78 °C for 15 min and then another 40 min at ambient temperature. Water (2 mL) was added, and the mixture was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (hexane/EtOAc, 70/30, EtOAc/NEt_3, 95/5) to give 272 mg (60%) of **23** as a yellow oil. ^1H NMR: δ 7.22 (m, Ph, 5 H), 4.42 (s, 2 H, benzylic), 3.75 (m, 1 H, C*H*OBn), 3.38 (s, 2 H, epoxide), 3.25 (t, 2 H, CHN), 2.45 (s, 3 H, CH_3), 1.87 (m, 2 H, CH_2), 1.71 (m, 2 H, CH_2). ^{13}C NMR: δ 143.0, 128.4, 127.5, 127.7, 70.6, 70.0, 55.0, 53.1, 53.0, 33.0. MS: m/z (relative intensity): 245 (M^+, 2), 139 (88), 138 (23), 110 (39), 97 (21), 96 (47), 91 (100), 57 (21), 42 (51).

Pseudoscopine (3). $MeSO_3H$ (22 μL, 0.34 mmol) was added to a stirred mixture of **23** (23.9 mg, 0.097 mmol) and 10% Pd/C (35 mg) in MeOH (1.5 mL). Hydrogen pressure (1 atm) was applied, and the stirring was continued for 4 h. The mixture was filtered through Celite and concentrated in vacuo, and the residue was diluted with 50% aqueous K_2CO_3 (10 mL). The aqueous phase was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were dried and concentrated in vacuo to afford a quantitative yield of pseudoscopine. Mp: 121–122 °C (lit. mp 122–123 °C,[8a] 125–126 °C[8b]). ^1H NMR: δ 4.03 (tt, 1 H, J = 9.5, 6.5 Hz, C*H*OH), 3.49 (s, 2 H, epoxide), 3.27 (dd, J = 4, 2.5 Hz, 2 H, CHN), 2.53 (s 3 H, CH_3), 1.86 (ddd, J = 13.5, 6.5, 2.5 Hz, 2 H, eq CH_2), 1.70 (ddd overlapping br s, J = 13.5, 9.5, 4 Hz, 3 H, ax CH_2 and OH). ^{13}C NMR: δ 63.6, 58.4, 55.4, 35.7, 33.7. IR: 3350, 2920, 1440, 1340, 1260, 1070, 1040, 860, 840 cm^{-1}. MS: m/z (relative intensity) 155 (M^+, 69), 112 (65), 110 (54), 94 (33), 86 (47), 84 (68), 82 (35), 57 (51), 42 (100), 29 (30).

Acknowledgment. Financial support from the Swedish Board of Technical Development and the Swedish Natural Science Research Council is gratefully acknowledged.

(31) Epoxide protons from the isomeric 2β,3β-epoxide are distinguishable in the ^1H NMR spectrum at δ 3.32–3.16.