2.15-4.0 (5 H, m); m/z 371 (M^+, 6), 356 (18), 340 (2.6), 327 (4.6), 43 (100). Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.85; H, 6.93; N, 3.52.

***cis*-1,2,7,9,10-Pentamethoxyaporphine (21).** The noraporphine **20** (255 mg, 0.69 mmol) was dissolved in acetonitrile (10 mL) containing water (2.5 mL). Sodium cyanoborohydride (178 mg), followed by 37% aqueous formaldehyde solution (0.55 mL), was added to this magnetically stirred solution. After 2 h the mixture was diluted with water and extracted with methylene chloride (4 × 30 mL). After treatment with decolorizing carbon, the organic solution was filtered through filter-aid to give a light yellow solution. After removal of the solvent, the residue was crystallized from ether, containing a small amount of methanol, to yield the aporphine **21** (175 mg, 66%): mp 186-191 °C; ν_{max} 1605, 1520 and 1115 cm^{-1}; λ_{max} 218 (ϵ 40 500), 236 (sh) (24 000), 285 (16 000), and 298 nm (15 000); λ_{min} 255 nm (ϵ 4000); ^1H NMR δ 8.15 (1 H, s), 6.78 (1 H, s), 6.55 (1 H, s), 4.30 (1 H, d, J = 3 Hz), 3.95 (3 H, s), 3.91 (3 H, s), 3.86 (3 H, s), 3.68 (3 H, s), 3.18 (3 H, s, $CHOCH_3$), 2.85-3.45 (2 H, m), 2.3-2.75 (2 H, m), 2.57 (3 H, s, NCH_3); m/z 385 (M^+, 21), 383 (26), 370 (100, $M^+ - CH_3$), 368 (78, $M^+ - CH_3 - H_2$). Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.48; H, 7.06; N, 3.95.

Synthesis and Conformational Analysis of Two Chiral (Nonracemic) 4-Substituted Quinolizidines

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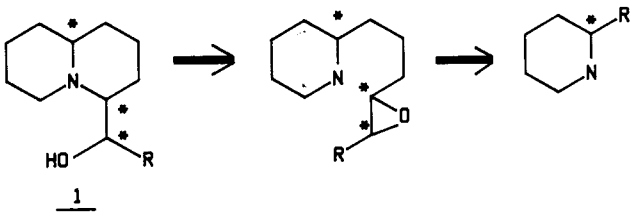
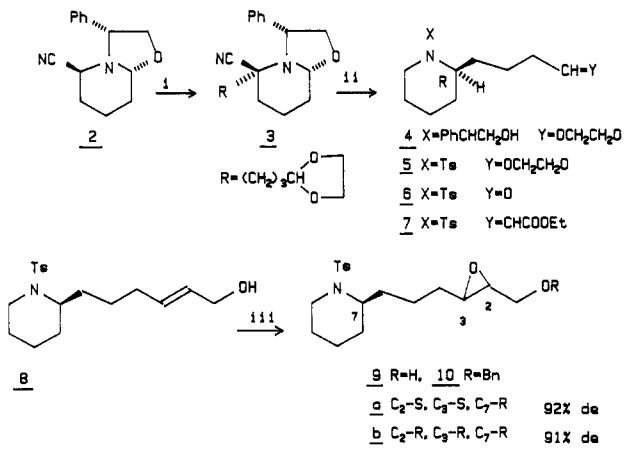
The synthesis of (4*R*,10*R*,11*R*)- and (4*S*,10*R*,11*S*)-4-(1,2-dihydroxyethyl)quinolizidine (**13a** and **13b**) in enantiomerically pure form has been carried out. The chiral centers were established by formation of a chiral 2-substituted piperidine and cyclization of optically active epoxides. The solution conformations of these molecules have been determined by 300-MHz proton NMR measurements.

Chiral β-amino alcohols are interesting molecules from several points of view. Many exhibit potent biological activity (e.g., ephedrine, quinine). Their use as chiral directing agents in organic synthesis has been widely exploited.[1] More importantly from a synthetic organic viewpoint, they appear to possess the capability of functioning as catalysts in a number of situations. For example, derivatives in which the nitrogen has been quaternized are useful phase-transfer catalysts, capable of inducing asymmetry.[2] The hydroxy group appears to be obligatory for significant chirality transfer in these reactions.[3] Also, chiral amino alcohols (frequently obtained from amino acids) have been used successfully as chiral catalysts in a number of reactions.[4] Some time ago, we set out to examine the effect of small stereochemical differences on such chirality transfers. To achieve this, we required a set of stereoisomers in which the spatial arrangement of the heteroatoms was well defined and easily determined. To simplify the synthetic plan, it was necessary that such molecules be derived by small changes, late in a general synthetic route. The choice of the target molecules was influenced strongly by our previous experience[5] with the

Scheme I



Scheme II[a]



[a] (i) LDA/THF/-78 °C, 4-iodobutanal ethylene ketal (84%); (ii) $NaBH_4$/EtOH (82%); H_2/Pd/C; TsCl/Et_3N/CH_2Cl_2; H_3O^+ (74%); $(EtO)_2P(O)CH_2COOEt$/BuLi (92%); Dibal (88%); (iii) Ti(O-iPr)$_4$/DET/BuOOH.

(1) For some recent examples, see: Meyers, A. I.; Lefker, B. A. *J. Org. Chem.* **1986**, *51*, 1541. Meyers, A. I.; Wanner, K. T. *Tetrahedron Lett.* **1985**, *26*, 2047. Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776. Kelly, J. W.; Eskew, N. L.; Evans, S. A. *J. Org. Chem.* **1986**, *51*, 95. Brown, H. C.; Prasad, J. V. N. V. *J. Org. Chem.* **1986**, *51*, 4526. Stetin, C.; deJeso, B.; Pommier, J. C. *J. Org. Chem.* **1985**, *50*, 3863.

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(3) See, for example: Balcells, J.; Colonna, S.; Fornasier, R. *Synthesis* **1976**, 266. Wynberg, H.; Greijanus, B. *J. Chem. Soc., Chem. Commun.* **1978**, 427. Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.

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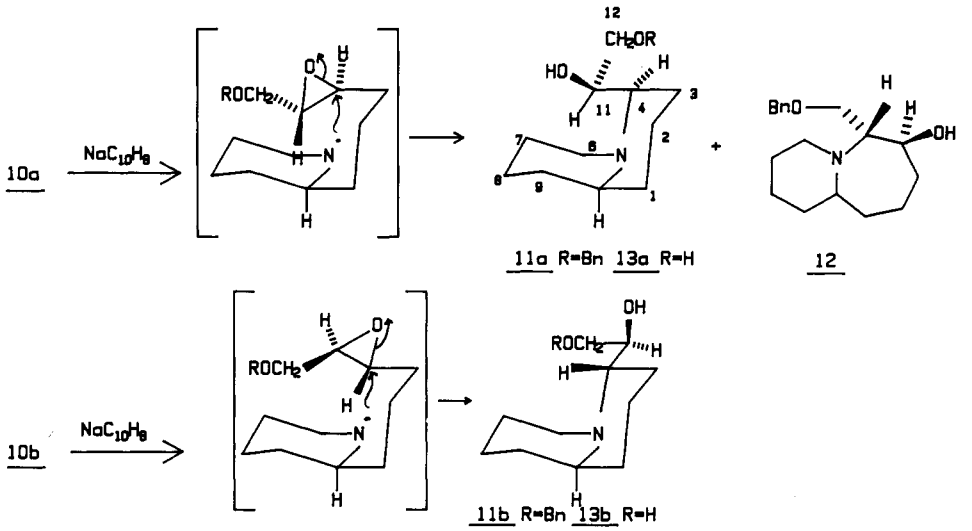
Scheme III



quinolizidine ring system. The well-defined proton NMR of these systems promised the ability to determine their conformational properties, which is obligatory for a rational interpretation of chirality transfer.

In this paper, we describe the synthesis of two diastereomers of molecules of type **1**, each in enantiomerically pure form. Subsequent papers will describe the application of these materials as catalysts in a number of reactions.

The target molecules possess three chiral centers. It was envisaged that two of these could be established by ring opening of an epoxide (Scheme I). The ability to obtain two stereochemically opposite epoxides from the same precursor by using the Sharpless procedure[6] was particularly attractive. Thus the stereochemical problem devolved to a synthesis of a chiral α-substituted piperidine, a problem that has nicely been solved by the methodology developed by Husson.[7]

Alkylation of the chiral oxazolidine **2** derived from glutaraldehyde and (*R*)-phenylglycinol with 4-iodobutanal ethylene acetal gave **3** (Scheme II). It is interesting to note that alkylation of **2** with ethyl 4-iodobutyrate or ethyl 6-iodohexanoate could not be achieved. Reductive cleavage (excess $NaBH_4$, then H_2, Pd/C) followed immediately by tosylation of the nitrogen atom gave **5** (X = Ts). In analogy with Husson's work, the single chiral center in **5** is assigned the *R* configuration. Hydrolysis of the unseparated mixture of **5** and the tosylate of 2-phenylethanol followed by chromatographic purification produced aldehyde **6** in 74% overall yield from **4**. The diastereomeric purity of **4** and thus the enantiomeric purity of **5** and **6** was established by proton and carbon NMR experiments. Chain homologation using the Horner–Emmons modification of the Wittig reaction[8] provided the conjugated ester **7**. The double-bond configuration in **7** is expected[8] to be *E*, and this was supported by proton and carbon NMR spectra, which showed no indication of any other stereoisomers. Reduction of **7** with Dibal gave alcohol **8**, the common intermediate in the synthesis of the two stereoisomers. The overall yield of **8** from **2** was 41%.

Translation of the *E* configuration of **8** into tetrahedral asymmetry was achieved by Sharpless epoxidation[6] with (+)-DET or with (−)-DET. These reactions gave two diastereomeric, physically different epoxy alcohols. After purification, **9a** was an oil whereas **9b** was a crystalline solid. When the rule[6] developed for prediction of the stereochemistry of the products is used, **9a** can be assigned the 2*S*,3*S*,7*R* configuration and **9b** the 2*R*,3*R*,7*R* configuration. The two diastereomers exhibited identical R_f values, and their ^1H NMR spectra were indistinguishable. The ^{13}C NMR spectra showed small signals for one carbon (C10) which correlated with the major C10 absorption in the other diastereomer, but the de calculation made on this basis deviated very significantly from that made on the basis of the ^1H NMR and results obtained from the MPTA ester. The ^{19}F NMR of the (+)-MPTA derivatives[9] showed signals that were overlapping, but on the basis of their ^1H NMR spectra, and using the absorptions for the C1 protons, diastereomeric excesses for **9a** and **9b** of approximately 92% and 91% could be determined. Some signal overlap still exists in these spectra, and the de's quoted above represent worst-case scenarios, especially since the consistency of the enantiomeric purity of commercial MPTA has been questioned.[6b] Benzylation of the alcohols provided **10a** and **10b** respectively, which again show essentially identical R_f and ^1H NMR spectra. The ^{13}C NMR of **10a** and **10b** were similar in form to those described above for the epoxy alcohols **9a** and **9b**.

Cyclization of the epoxides **10** to quinolizidines was effected by treatment with 2 equiv of sodium naphthalenide in DME at −60 °C[10] (Scheme III). At this point in the synthesis, a distinct difference between the stereoisomers was observed. Epoxide **10b** afforded a single crystalline amino alcohol (**11b**) in 70% yield, whereas **10a** gave two isomeric products plus traces of other compounds. The major product (35%) is assigned structure **11a** on the basis of its spectroscopic properties as detailed below. The structure of the other isomer (4%) remains in doubt at this time although **12** cannot be ruled out. The chromatographic mobilities of **11a** and **11b** are quite different, and it was possible to obtain these materials without cross contamination, thus ensuring that pure enantiomers of **11a** and **11b** were in hand.

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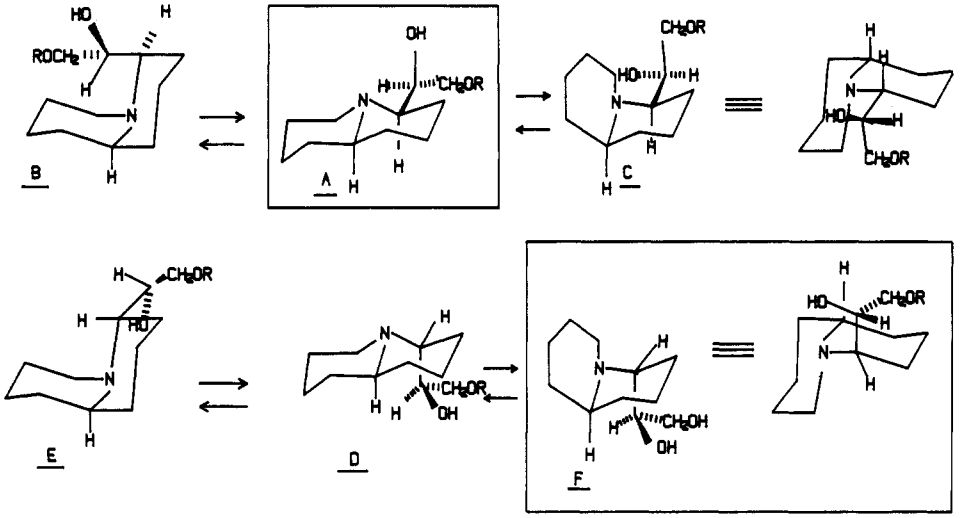
Scheme IV[a]



[a] R = CH_2Ph.

Table I. Observed and Expected Chemical Shifts for Conformations of 11a and 11b

	dihedral angle of proton with nitrogen lone pair				δ for C4, C6e, C6a, C10	
conformation	C4	C6e	C6a	C10	expected	observed
11a						
A	180	60	180	180	2, 3, 2, 2	2.12, 3.30, 1.79, 1.97
B	60	60	60	60	3, 3, 3, 3	
C	60	60	180	60	3, 3, 2, 3	
11b						
D	60	60	180	180	3, 3, 2, 2	
E	180	60	60	60	2, 3, 3, 3	
F	60	60	180	60	3, 3, 2, 3	2.80, 3.05, 2.55, 2.91

The proton NMR spectra of **11a** and **11b** were very informative. The formation of the six-membered ring was indicated by NMR decoupling experiments since, in each case, the AB quartet due to the C12 protons was coupled to only one other proton whose chemical shift (δ 4.45 for **11a** and 4.21 for **11b**) was indicative of an oxygenated carbon. This proton was further coupled to only one other proton (δ 2.14 in **11a** and 2.78 in **11b**). The alternative ring closure to the seven-membered ring would produce **12**, whose coupling pattern would be quite different. DEPT editing of the ^{13}C NMR spectra allowed identification of the methine resonances, and subsequent single frequency proton decoupled carbon spectra and C–H correlated 2D spectra provided unambiguous identification of the C10 proton, which was necessary for the conformational analysis of these systems (vide infra).

The differences in cyclization efficiency of **10a** and **10b** can be nicely rationalized on the basis of steric effects (Scheme III). Assuming that epoxide opening occurs with inversion of configuration and axially with respect to the nitrogen-containing ring,[11] it can be seen that, in an all-chair transition state, the epoxide and its associated benzyloxy group must lie directly over the piperidine ring in **10a** whereas, in **10b**, it is rotated away from the ring. When the same assumptions are used, the configuration of **11a** can be designated (using the quinolizidine numbering system) as 4*R*,10*R*,11*R* and that of **11b** must be 4*S*,10*R*,11*S*. (Note that the priorities of the substituents on C11 change during the cyclization, leading to a reversal of its stereochemical descriptor.) Catalytic hydrogenolysis of **11a** and **11b** gave **13a** (27% from **8**, 11.1% from **2**) and **13b** respectively (50% from **8**, 21% from **2**).

In order to meaningfully interpret stereochemical data from reactions using **11a,b** or **13a,b** as catalysts, their preferred solution conformations must be known. The possibility of N-inversion is a complicating factor which allows conversion of a cis-fused quinolizidine system into a trans-fused one.

For the (+)-DET-derived product **11a**, the 4*R*,10*R*,11*R* configuration can be accommodated by three possible all-chair conformations A, B, and C, Scheme IV. Conformer A represents the C4-equatorial substituent in a trans-fused quinolizidine system. N-inversion of A can produce the two cis-fused conformations B and C in which the C4 substituent is axially or equatorially disposed respectively. Conformers A and C permit intramolecular hydrogen bonding whereas B does not. Similarly, the (−)-DET-derived product **11b** (4*S*,10*R*,11*S*) can exist in the three all-chair conformations D, E, and F (Scheme IV), of which only E does not permit intramolecular hydrogen bonding. Such hydrogen bonding is expected to be an important factor in determining the preferred conformations of quinolizidines. For example, the solution conformation of lupinine, a C1-hydroxymethyl-substituted quinolizidine, is known to be the axially substituted, trans-fused form.[12] Only in this conformation can intramolecular hydrogen bonding occur.

Our conclusions regarding the preferred conformations of **11a** and **11b** rest primarily on their ^1H NMR spectra. The ^1H and ^{13}C NMR spectra of variously substituted

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quinolizidines have been the subject of many investigations,[13] and conformational effects, particularly in the proton spectra, seem well defined. The results can be summarized as follows: protons immediately adjacent to nitrogen show characteristic chemical shifts which depend on the dihedral angle between the proton and the nitrogen lone pair of electrons. An antiperiplanar arrangement causes a significant upfield shift (typical value = 2 ppm) relative to protons that have dihedral angles of 60° or 120° (typical value = 3 ppm) ($\Delta\delta$ = 0.8–1 ppm). The dihedral angles of the protons on the three conformations of each of **11a** and **11b** are shown in Table I along with the expected and observed chemical shifts. The specific protons were identified by the decoupling experiments previously described. As can be seen, the data support the presence of conformer A for **11a** and conformer F for **11b** as the predominant forms.

As the foregoing outlines, we now have in hand two stereoisomers of a nonracemic quinolizidine system whose functionality makes them potentially useful for catalytic purposes. Such application of these materials will be the subject of a future communication.

Experimental Section

Unless otherwise noted, infrared spectra were run as neat liquids and only the four most intense peaks are reported. The NMR spectra were run at 300 MHz for ^{1}H, 75 MHz for ^{13}C, and 188 MHz for ^{19}F in $CDCl_3$ solution. Values in brackets are for the minor diastereomer. Where DEPT editing of the carbon spectra was done, the multiplicities that would have been seen in the off-resonance spectra are indicated. The ^{19}F NMR shifts were measured relative to internal trifluoroacetic acid. Optical rotations were measured at 24 °C in $CHCl_3$ solution with c = 1.0 unless otherwise noted. Gas chromatographic analyses were performed by using a 1.5 ft × $^1/_8$ in. column packed with 5% OV-101 on Chromosorb W or an 8 ft × $^1/_4$ in. column packed with 20% SE-30 on Chromosorb W. Mass spectra were run in the electron-impact (EI), field-ionization (FI), and fast-atom-bombardment (FAB) modes. Solvents were removed under reduced pressure, and the drying agent used was anhydrous magnesium sulfate. THF and dimethoxyethane (DME) were dried over potassium and benzophenone, ethanol was distilled from magnesium ethoxide, and methylene chloride was distilled from P_4O_{10} and stored over activated molecular sieves. *tert*-Butyl hydroperoxide in toluene was prepared as described,[6c] and titanium isopropoxide was distilled and stored under nitrogen. (*R*)-(+)-α-(Trifluoromethyl)phenylacetic acid was used as received from the Aldrich Chemical Co. Column chromatography utilized silica gel 60. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

Alkylation of Oxazolidine 2. A solution of LDA [prepared from 9.83 mL (65.9 mmol) of diisopropylamine and 26.4 mL (65.9 mmol) of 2.5 M BuLi in hexane] in 60 mL of THF was cooled to −78 °C under nitrogen. To this was added a solution of 7.15 g (31.4 mmol) of **2**[7] in 30 mL of THF over 15 min. After the mixture was stirred at −78 °C for 45 min, a solution of 10.58 g (43.9 mmol) of the ethylene ketal of 4-iodobutanal[14] in 15 mL of the same solvent was added over 40 min. The solution was stirred at −78 °C for 2.5 h and then quenched by addition of 100 mL of phosphate buffer (pH 6.2, 0.5 M). The organic layer was separated and the aqueous layer extracted with 5 × 50 mL of methylene chloride. The combined organic layers were dried and concentrated to give a yellow oil. Chromatography (1:1 hexane/ether) produced **3** as a pale yellow oil (9.06 g, 84%), which slowly crystallized on standing. Recrystallization from ether/petroleum ether gave white crystals: mp 68–69 °C; $[\alpha]_D$ −119.3° (c 1.01); IR (neat) 2955, 2875, 2216, 1139, 1109 cm^{-1}; ^{1}H NMR δ 7.35 (m, 5 H), 4.59 (t, 1 H, J = 4.5 Hz), 4.24 (t, 1 H, J = 8.5 Hz), 4.16 (dd, 1 H, J = 9.2, 2.3 Hz), 4.01 (dd, 1 H, J = 9.2, 4.6 Hz), 3.73–3.90 (m, 5 H), 2.2–1.0 (m, 12 H); ^{13}C NMR δ 144.1 (s), 128.7 (d), 127.6 (d), 127.3 (d), 119.0 (s), 103.9 (d), 92.3 (d), 74.9 (t), 64.9 (t), 62.4 (t), 39.3 (t), 34.3 (t), 33.3 (t), 29.6 (t), 20.2 (t), 18.3 (t); MS(FI), m/z 342.

Anal. Calcd for $C_{20}H_{26}N_2O_3$: C, 70.14; H, 7.65; N, 8.18. Found: C, 70.58; H, 7.70; N, 8.18.

Decyanation of Nitrile 3. To a suspension of 21 g (0.555 mol) of sodium borohydride in 500 mL of freshly distilled ethanol was added 18.1 g (0.053 mol) of **3** in 75 mL of ethanol, dropwise with stirring over 45 min and under nitrogen. The solution was refluxed for 4 h and cooled and enough water added to dissolve the precipitate (ca. 300 mL). The solution was mixed with brine, extracted with methylene chloride, dried, and evaporated to give a pale yellow oil. Chromatography with 20:1 CH_2Cl_2/MeOH gave 13.84 g (82%) of **4**: $[\alpha]_D$ −30°; IR (neat) 3392, 2940, 1142, 1129, 703 cm^{-1}; ^{1}H NMR δ 7.40 (m, 5 H), 4.83 (t, 3 H, J = 4.5 Hz), 4.05–3.65 (m, 7 H), 2.90 (m, 1 H), 2.65 (m, 2 H), 1.98–1.3 (m, 12 H); ^{13}C NMR δ 140.5, 128.6, 128.3, 127.5, 104.4, 67.4, 64.8, 62.0, 57.6, 43.1, 34.0, 27.9, 26.2, 25.6, 21.5, 19.6; MS(FI), m/z 319.

(*R*)-4-(*N*-Tosylpiperidin-2-yl)butanal (6). A flame-dried flask containing 80 mL of dry MeOH, 4.6 g (0.0144 mol) of **4**, and 1.0 g of 10% Pd on carbon was stirred overnight under a hydrogen atmosphere. The solution was filtered through Celite and evaporated, giving an oily solid (4.6 g, 99%), which comprised **5** (X = H) and 2-phenylethanol. These could be separated by chromatography (10:1 EtOAc/MeOH). Direct tosylation was carried out by adding 6.84 g (35.9 mmol) of tosyl chloride to a stirred solution of the mixture (4.43 g) in 80 mL of methylene chloride and 5 mL of triethylamine at 0 °C under nitrogen. After being stirred for 3 h at this temperature, the solution was allowed to warm to ambient temperature for 0.5 h, at which point 40 mL of water was added. The solution was stirred a further 5 min, the layers were separated, and the organic layer was washed successively with dilute acid, dilute base, water, and brine. Evaporation of the dried solution afforded a yellow oil, which contained **5** and the tosylate of 2-phenylethanol.

To the crude mixture were added 30 mL of THF, 10 mL of ether, and 50 mL of 1 N HCl with stirring. After 5 h at room temperature, the solution was made basic with saturated $NaHCO_3$, the layers were separated, and the organic layer was dried and concentrated to give a yellow oil. Flash chromatography with 5:1 hexane/EtOAc gave 3.2 g (73% from **3**) of **6**: $[\alpha]_D$ +13.85° (c 0.26); IR (neat) 2941, 1725, 1335, 1155 cm^{-1}; ^{1}H NMR δ 9.74 (t, 1 H, J = 1.8 Hz), 7.50 (AB q, 4 H, J = 8.4 Hz), 4.05 (m, 1 H), 3.76 (dd, 1 H, J = 3.6, 14.3 Hz), 2.99 (ddd, 1 H, J = 3.0, 12.6, 14.4 Hz), 2.49 (s, 3 H), 2.40 (t, 2 H, J = 7.1 Hz), 1.8–1.1 (m, 10 H); ^{13}C NMR δ 142.9, 139.0, 129.7, 127.1, 60.3, 52.6, 40.7, 33.9, 29.0, 27.5, 24.4, 21.9, 18.5; MS(FI), m/z 309.

(*S*)-Ethyl 6-(*N*-Tosylpiperidin-2-yl)hex-2-enoate (7). To a solution of 10.94 mL (0.273 mol) of BuLi [2.5 M in hexane] in 75 mL of THF at 0 °C was added 5.56 g (24.8 mmol) of triethyl phosphonoacetate[15] under nitrogen. After the mixture was stirred for 30 min at 0 °C, a solution of 5.12 g (16.6 mmol) of **6** in 75 mL of THF was added dropwise over 1 h at 0 °C. After the mixture was stirred for 2.5 h, 10 mL of water and 40 mL of brine were added and the organic layer was separated, washed with brine, dried, and evaporated to give a yellow oil. Chromatography with 5:1 petroleum ether/EtOAc gave 5.8 g (92%) of **7** as a colorless oil $[\alpha]_D$ +28° (c 0.9); IR (neat) 2940, 1718, 1652, 1154, 1336 cm^{-1}; ^{1}H NMR δ 7.51 (AB q, 4 H, J = 8.3 Hz), 6.93 (dt, 1 H, J = 15.7, 6.9 Hz), 5.81 (dt, 1 H, J = 15.6, 1.5 Hz), 4.20 (q, 2 H, J = 7.1 Hz), 4.04 (m, 1 H), 3.78 (dd, 1 H, J = 12.9, 3.7 Hz), 2.98 (ddd, 1 H, J = 2.5, 13.7, 13.8 Hz), 2.40 (s, 3 H), 2.20 (m, 2 H), 1.8–1.0 (m, 10 H), 1.25 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 165.6, 147.6, 141.8, 137.9, 128.6, 125.9, 120.6, 59.1, 51.6, 39.5, 30.7, 28.0, 26.5, 23.8, 23.3, 20.4, 17.4, 13.2; MS(FI), m/z 379.

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Anal. Calcd for $C_{20}H_{29}NO_4S$: C, 63.29; H, 7.69; N, 3.69. Found: C, 63.18; H, 7.41; N, 3.91.

(*S*)-6-(*N*-Tosylpiperidin-2-yl)hex-2-en-1-ol (8). To a solution of 5.8 g (15.3 mmol) of **7** in 150 mL of ether at 0 °C was added 30.6 mL of Dibal (1.5 M in toluene) with stirring over 5 min. The mixture was stirred at 0 °C for 1.5 h and then allowed to warm to room temperature for 45 min. The solution was cooled to 0 °C, and 90 mL of 2 N HCl was added, followed by enough 6 N HCl to dissolve all the solids. The organic layer was separated, washed with saturated $NaHCO_3$ solution, dried, and concentrated to give an oil, which was purified by chromatography with 2:1 petroleum ether/EtOAc. Compound **8** (4.5 g, 88%) was obtained as a colorless oil: $[\alpha]_D$ +31.5° (*c* 0.46); IR (neat) 3470, 1600, 1335, 1153 cm^{-1}; ^1H NMR δ 7.50 (AB q, 4 H, J = 8.2 Hz), 5.65 (m, 2 H), 4.09 (d, 2 H, J = 3.6 Hz), 4.03 (m, 1 H), 3.75 (dd, 1 H, J = 14.3, 2.5 Hz), 2.98 (ddd, 1 H, J = 2.3, 11.5, 16.2 Hz), 2.45 (s, 3 H), 2.05 (s, 2 H), 1.65 (s, 2 H), 1.51–1.20 (m, 8 H); ^{13}C NMR δ 141.7, 138.0, 128.6, 128.4, 125.9, 62.7, 51.7, 40.0, 30.8, 27.8, 26.3, 24.8, 23.3, 20.4, 17.4; MS(+FAB), *m/z* 336, 320, 238, 155, 91.

Anal. Calcd for $C_{18}H_{27}NO_3S$: C, 64.06; H, 8.06; N, 4.15. Found: C, 63.71; H, 8.63; N, 3.95.

(2*S*,3*S*,7*R*)-2,3-Epoxy-6-(*N*-tosylpiperidin-2-yl)hexanol (9a). To 180 mL of dry methylene chloride containing 4 g of 3A crushed activated molecular sieves was added 1.33 mL (4.45 mmol) of distilled titanium isopropoxide, and the stirred mixture was cooled to −23 °C under nitrogen. Distilled (+)-DET (1.11 g, 5.39 mmol) in 3 mL of methylene chloride was added, followed by 5.00 g (14.8 mmol) of **8** in 25 mL of the same solvent. After the mixture was stirred for 30 min at −23 °C, 6.1 mL (34.1 mmol) of *tert*-butyl hydroperoxide (TBHP) [5.6 M in toluene] was added over 10 min. The reaction was quenched after 6 h by the addition of 10 mL of saturated aqueous Na_2SO_4 solution and allowed to warm to ambient temperature. After filtration through Celite, the layers were separated and the organic layer was combined with a fraction obtained by extraction of the Celite with boiling EtOAc. The combined organic layers were dried and concentrated to yield 7.23 g of a pale yellow oil containing **9a**, (+)-DET, and excess TBHP. Column chromatography using 7:5 petroleum ether/EtOAc gave 4.55 g of a colorless oil. Analysis of the ^1H NMR spectrum of the (+)-MPTA ester indicated a de of 92%. The diastereomers could not be separated by chromatography: $[\alpha]_D$ +18.3° (*c* 1.2); IR (neat) 3430, 2938, 1330, 1153 cm^{-1}; ^1H NMR δ 7.50 (AB q, 4 H, J = 8.4 Hz), 4.03 (m, 1 H), 3.89 (ddd, 1 H, J = 2.4, 3.0, 2.6 Hz), 3.75 (dd, 1 H, J = 14.0, 1.3 Hz), 3.62 (m, 1 H), 3.07–2.87 (m, 3 H), 2.40 (s, 3 H), 1.98 (m, 1 H), 1.81–1.10 (m, 12 H); ^{13}C NMR δ 142.8, 138.9, 129.6, 126.9, 61.7, 55.8, 52.8 [52.5], 40.6, 31.6, 29.3, 27.4, 24.2, 22.9, 21.4, 18.4.

(2*R*,3*R*,7*R*)-2,3-Epoxy-6-(*N*-tosylpiperidin-2-yl)hexanol (9b). To a stirred mixture of 50 mL of methylene chloride, 0.55 mL (1.8 mmol) of $Ti(^iPrO)_4$, and 300 mg of powdered activated 3A molecular sieves was added 0.44 g (2.13 mmol) of (−)-DET in 3 mL of methylene chloride at −35 °C under nitrogen. Alcohol **8** (1.1 g, 3.3 mmol) in 10 mL of methylene chloride was added, and the solution was aged for 20 min at −35 °C. TBHP (1.35 mL of a 5.6 M solution in toluene, 7.6 mmol) was added over 5 min. After the mixture was stirred for 6 h at −35 °C, 6 mL of ether was added followed by 2 mL of saturated Na_2SO_4 solution. The mixture was stirred for 1.5 h at room temperature and filtered through Celite, and the Celite was washed with ether. The orange Celite pad was extracted with boiling EtOAc, and the combined organic solutions were concentrated to afford the crude product, contaminated with (−)-DET and excess TBHP. This was chromatographed by using 7:5 petroleum ether/EtOAc to give 0.92 g (80%) of a white solid, which was recrystallized from petroleum ether/EtOAc to give **9b**: mp 88–89 °C; $[\alpha]_D$ +54.19° (*c* 0.62); IR ($CHCl_3$) 3506, 2934, 1323, 1152 cm^{-1}; ^1H NMR δ 7.48 (AB q, 4 H, J = 10 Hz), 4.04 (m, 1 H), 3.89 (ddd, 1 H, J = 1.9, 5.6, 11.3 Hz), 3.76 (dd, 1 H, J = 3.5, 14.2 Hz), 3.64 (m, 1 H), 3.07–2.89 (m, 3 H), 2.45 (s, 3 H), 1.8–1.1 (m, 12 H); ^{13}C NMR δ 142.8 (s), 138.9 (s), 129.6 (d), 126.9 (d), 61.8 (t), 58.3 (d), 55.8 (d), [52.8] 52.5 (d), 40.6 (t), 31.1 (t), 29.2 (t), 27.4 (t), 24.2 (t), 22.7 (t), 21.5 (q), 18.4 (t).

Anal. Calcd for $C_{18}H_{27}NO_4S$: C, 61.16; H, 7.69; N, 3.96. Found: C, 61.40; H, 7.77; N, 3.87.

Benzylation of 9a to 10a. To a stirred suspension of 0.103 g (4.3 mmol) of oil-free sodium hydride in 45 mL of THF was added 1.155 g (3.3 mmol) of **9a** in 20 mL of THF under nitrogen. After the mixture was stirred for 15 min at room temperature, 0.735 g (4.3 mmol) of benzyl bromide was added and the mixture was stirred for a further 20 h at ambient temperature. Careful addition of 15 mL of water followed by phase separation, drying of the organic material, and concentration produced a crude yellow oil, which was chromatographed by using 2:1 petroleum ether/EtOAc to give **10a** as a colorless oil (1.295 g, 89%): $[\alpha]_D$ +17.2° (*c* 0.36); IR (neat) 2938, 1490, 1332, 1154 cm^{-1}; ^1H NMR δ 7.50 (AB q, 4 H, J = 8.6 Hz), 7.35 (m, 5 H), 4.57 (AB q, 2 H, J = 11.9 Hz), 4.04 (m, 1 H), 3.80–3.68 (dd, 2 H, J = 3.3, 11.3 Hz, partially overlapping a dd, J = 3.4 Hz), 3.46 (dd, 1 H, J = 11.3, 5.7 Hz), 3.05–2.86 (m, 3 H), 2.80 (m, 1 H), 2.40 (s, 3 H), 1.7–1.05 (m, 12 H); ^{13}C NMR δ 142.8 (s), 139.0 (s), 138.0 (s), 129.7 (d), 128.5 (d), 127.8 (d), 127.0 (d), 73.3 (t), 70.5 (t), 56.9 (d), 56.0 (d), 52.9 (d), 40.7 (t), 31.5 (t), 29.4 (t), 27.5 (t), 24.3 (q), 23.1 (t), 21.5 (t), 18.5 (t).

Benzylation of 9b to 10b. In the same manner as described above for **9a**, alcohol **9b** was converted into benzyl ether **10b** (92%): $[\alpha]_D$ +42.58° (*c* 0.62); IR (neat) 2938, 1332, 1154, 1094 cm^{-1}; ^1H NMR δ 7.50 (AB q, 4 H, J = 8.7 Hz), 7.30 (m, 5 H), 4.58 (AB q, 2 H, J = 11.9 Hz), 4.01 (m, 1 H), 3.80–3.67 (dd, 2 H, J = 3.3, 11.4 Hz, partially overlapping a dd, J = 3.5 Hz), 3.46 (dd, 1 H, J = 5.7, 11.4 Hz), 3.05–2.90 (m, 3 H), 2.79 (m, 1 H), 2.40 (s, 3 H), 1.8–1.0 (m, 12 H); ^{13}C NMR δ 142.9 (s), 139.1 (s), 138.1 (s), 129.7 (d), 128.5 (d), 127.6 (d), 127.0 (d), 73.4 (t), 70.5 (t), 56.9 (d), 56.1 (d), 52.7 (d), 40.7 (t), 31.3 (t), 29.3 (t), 27.6 (t), 24.4 (q), 22.9 (t), 21.6 (t), 18.5 (t).

(4*R*,10*R*,11*R*)-4-[1-Hydroxy-2-(benzyloxy)ethyl]quinolizidine (11a). To 1.7 g (3.84 mmol) of **10a** in 50 mL of DME was added a sodium naphthalenide solution [0.982 g (7.69 mmol) of naphthalene and 0.177 g (7.68 mmol) of sodium in 125 mL of DME which was stirred for 1 h after the solution turned green] over 15 min at −60 °C under nitrogen. After 1 h of stirring at −60 °C, 2 mL of water was added. The organic layer was then washed with brine, dried, and concentrated. The resulting oily solid contained naphthalene, which was removed by chromatography through a plug of silica gel with petroleum ether as eluant. The concentrated methanol extracts of the chromatography were separated on preparative TLC with 9:0.3:0.15 $CHCl_3/MeOH/NH_4OH$. The major product **11a** was isolated as a colorless oil (0.41 g, 35%) and the minor product (**12**?) as a pale yellow oil (47 mg, 4%). The spectroscopic data for **11a** follows: $[\alpha]_D$ +27.31° (*c* 0.52); IR (neat) 3428, 2929, 2796, 1099 cm^{-1}; ^1H NMR δ 7.30 (m, 5 H), 4.56 (AB q, 2 H, J = 12 Hz), 4.23 (m, 1 H), 3.54 (dd, 1 H, J = 7.3, 9.6 Hz), 3.41 (dd, 2 H, J = 4.5, 9.5 Hz), 3.31 (br d, 1 H, J = 11.3 Hz), 2.12 (m, 1 H), 1.97 (m, 1 H), 1.79 (ddd, 1 H, J = 11.9, 11.6, 2.3 Hz), 1.7–1.1 (m, 12 H); ^{13}C NMR δ 138.3 (s), 128.4 (d), 127.6 (d), 127.7 (d), 73.5 (t), 72.3 (t), 67.8 (d), 63.1 (d), 62.7 (d), 50.9 (t), 34.4 (t), 33.3 (t), 26.6 (t), 24.7 (t), 24.3 (t), 23.3 (t); MS(FI), *m/z* 289.

Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.83. Found: C, 74.89; H, 9.07; N, 4.45.

(4*S*,10*R*,11*S*)-4-[1-Hydroxy-2-(benzyloxy)ethyl]quinolizidine (11b). In the same manner as described above for **11a**, **11b** was obtained (70%) from **10b** as white crystals, mp 74–75 °C (from petroleum ether) (TLC solvent 9:1.0:0.4 $CHCl_3/MeOH/NH_4OH$): $[\alpha]_D$ +8.13° (*c* 0.8); IR (KBr) 3190, 2932, 2849, 1126 cm^{-1}; ^1H NMR δ 7.34 (m, 5 H), 4.57 (AB q, 2 H, J = 12.1 Hz), 4.24 (m, 1 H), 3.50 (d of AB q, 2 H, J = 9.3, 9.6 Hz), 3.05 (m, 1 H), 2.92 (m, 1 H), 2.79 (m, 1 H), 2.56 (m, 1 H), 1.8–1.3 (m, 12 H); ^{13}C NMR δ 138.0 (s), 128.4 (d), 127.7 (d), 73.4 (t), 72.3 (t), 67.1 (d), 56.9 (d), 56.3 (d), 49.4 (t), 29.1 (t), 27.6 (t), 23.4 (t), 22.7 (t), 21.8 (t), 19.3 (t); MS(FI), *m/z* 289.

Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.83. Found: C, 74.66; H, 9.31; N, 4.68.

(4*R*,10*R*,11*R*)-4-(1,2-Dihydroxyethyl)quinolizidine (13a). To a solution of 5 mL of glacial acetic acid containing 0.105 g (0.363 mmol) of **11a** was added 35 mg of 10% Pd on carbon, and this mixture was stirred under a hydrogen atmosphere for 24 h. The mixture was filtered through Celite and concentrated, the residue taken up in ether, and the ether solution washed with 3 × 5 mL of saturated aqueous $NaHCO_3$. The combined aqueous layers were then concentrated to dryness, taken up in 20 mL of ether, combined with the ether from the washing, dried, and evaporated to afford **13a** as a colorless oil (71 mg, 98%), which was pure

according to TLC analysis (9:0.4:0.8 $CHCl_3$/MeOH/NH_4OH): $[\alpha]_D$ +10.0° (c 0.26); IR (neat) 3380, 2929, 2856, 1100 cm^{-1}; ^1H NMR δ 4.21 (br s, 2 H), 4.07 (m, 1 H), 3.63 (dd, 1 H, J = 7.7, 11.2 Hz), 3.41 (dd, 2 H, J = 3.7, 11.1 Hz), 3.34 (br d, 1 H, J = 11.3), 2.09 (m, 1 H), 1.97 (m, 1 H), 1.80 (m, 1 H), 1.7–1.1 (m, 12 H); ^{13}C NMR δ 69.6 (d), 64.7 (t), 64.3 (d), 63.2 (d), 51.0 (t), 33.8 (t), 32.8 (t), 26.1 (t), 24.5 (t), 24.3 (t), 23.3 (t); MS(FI), m/z 199.

(4*S*,10*R*,11*S*)-4-(1,2-Dihydroxyethyl)quinolizidine (13b). In a manner similar to that described above for the preparation of **13a**, **13b** was obtained as a colorless oil (97%), which was pure according to TLC analysis: $[\alpha]_D$ −2.29° (c 0.7); IR (neat) 3360, 2932, 2861, 1033 cm^{-1}; ^1H NMR δ 4.09 (m, 1 H), 3.78 (dd, 1 H, J = 4.9, 10.7 Hz), 3.57 (dd, 1 H, J = 8.6, 10.7 Hz), 3.13 (br s, 2 H), 2.73 (br d, 1 H, J = 4.1 Hz), 2.58 (br d, 1 H, J = 11.5 Hz), 1.9–1.3 (m, 12 H); ^{13}C NMR δ 68.2 (t), 65.4 (d), 65.0 (d), 52.9 (d), 48.4 (t), 29.7 (t), 25.3 (t), 24.0 (t), 20.5 (t), 20.4 (t), 19.6 (t); MS(FI), m/z 199.

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A Novel Darzens-Type Condensation Using α-Chloro Ketimines

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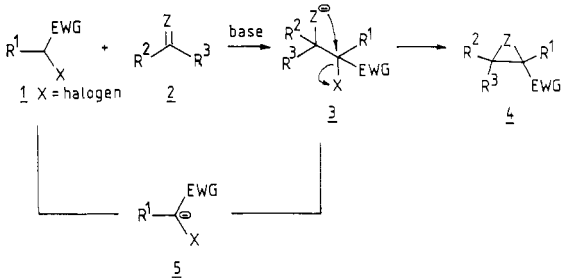
3-Chloro-1-azaallylic anions, generated by deprotonation of α-chloro ketimines with lithium diisopropylamide, reacted with ketones and aldehydes to produce 2-imidoyloxiranes (α,β-epoxy ketimines). This novel aza-Darzens-type condensation allows α-chloro ketones to condense with carbonyl compounds via protection as α-chloro ketimines. The aza-Darzens-type reaction with benzophenones as carbonyl substrate proceeded via a Favorskii-like rearrangement of an intermediate α,β-epoxy ketimine, the intermediate cyclopropylideneamine being trapped in an intramolecular way. Subsequent ring opening of the bicyclic intermediate adduct according to a so-called abnormal opening furnished rearranged 3-butenamide derivatives.

The Darzens reaction is a well-known classical reaction that enables the construction of highly functionalized oxiranes. In the most classical way,[1,2] it concerns the base-induced condensation of α-halogenated carboxylic esters **1** (EWG = COOR′) or α-halogenated nitriles **1** (EWG = CN) with carbonyl substrates **2** (Z = O) to afford α,β-epoxy esters **4** (Z = O, EWG = COOR′)[1] or 2-cyano-oxiranes **4** (Z = O, EWG = CN),[3,4] respectively (Scheme I). This reaction has been extended to various related substrates **1** such as α-halogenated sulfoxides **1** (EWG = S(O)R′),[5–10] α-halogenated sulfones (EWG = SO_2R'),[11] α-halogenated sulfoximines **1** (EWG = S(O)(=NR′)R″),[12,13] α-halogenated carboxylic amides **1** (EWG = $CONH_2$), etc. However, acyl-substituted compounds **1** (EWG = COR′), i.e. α-halogenated ketones (X = halogen), have not been condensed in Darzens-type reactions except when no α′-hydrogen atoms are present in the α-halo ketone or when special, less common substrates were used.[14] Examples of the Darzens-type reaction in the field of α-halo ketones include condensations of aromatic α-halo ketones[15] (mostly phenacyl halides)[16,17] or involve reactions of certain α-halo ketones leading to low yields of the desired acyl-substituted oxiranes.[1] A peculiar case entails an intramolecular version of the Darzens-type reaction of an aromatic α-bromo ketone.[18] The reason for the insuitability of α-halo ketones to act as substrates in Darzens-type reactions originates from their pronounced reactivity in basic medium, leading to preferred competing reactions such as the Favorskii

Scheme I



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