From Quinidine to New Enantiopure Materials—Tricyclic Allylic *N,O*-Acetals and a Stereospecific, One-Pot Conversion of 1,2-Secondary,Tertiary Diols into Spiroepoxides

Cornelius von Riesen, Peter G. Jones and H. M. R. Hoffmann*

Abstract: Hydrobromination of quinidine (**1**) with fuming HBr furnished diastereomeric secondary bromides **2a** and **2b** in 82% yield. After acetylation the resulting bromides **2a**–Ac and **2b**–Ac could be separated and converted stereospecifically into ethylidene rubanes (*Z*)-**4** and (*E*)-**4**, respectively. *cis*-Dihydroxylation of (*Z*)-olefin **4** with OsO_4 was shown to be feasible by two catalytic variants, giving the two diastereomeric diols **5a** and **5b**, separable by chromatography. A simple one-pot procedure was developed for converting the sterically hindered 1,2-secondary, tertiary diols stereospecifically into spiroepoxides (**5a** → **6a**-Ac; **5b** → **6b**-Ac). Our procedure involves overall inversion of configuration. The procedure complements the Kolb–Sharpless route to epoxides from 1,2-disecondary diols with overall retention of configuration. The other two diastereomeric spiroepoxides **6c** and **6d** were prepared in one pot under different conditions (chloramine T, then alkali). Two unprecedented tricyclic allylic *N,O*-acetals (*Z*)-**7** and (*E*)-**7** were also obtained. The structure of spiroepoxide **6c** (as a CH_2Cl_2 monosolvate) and of tricyclic olefinic *N,O*-acetal (*E*)-**7** was corroborated by X-ray crystallography.

Keywords
chemoselectivity · cinchona alkaloids · clathrates · osmium tetroxide · spiro compounds

Introduction

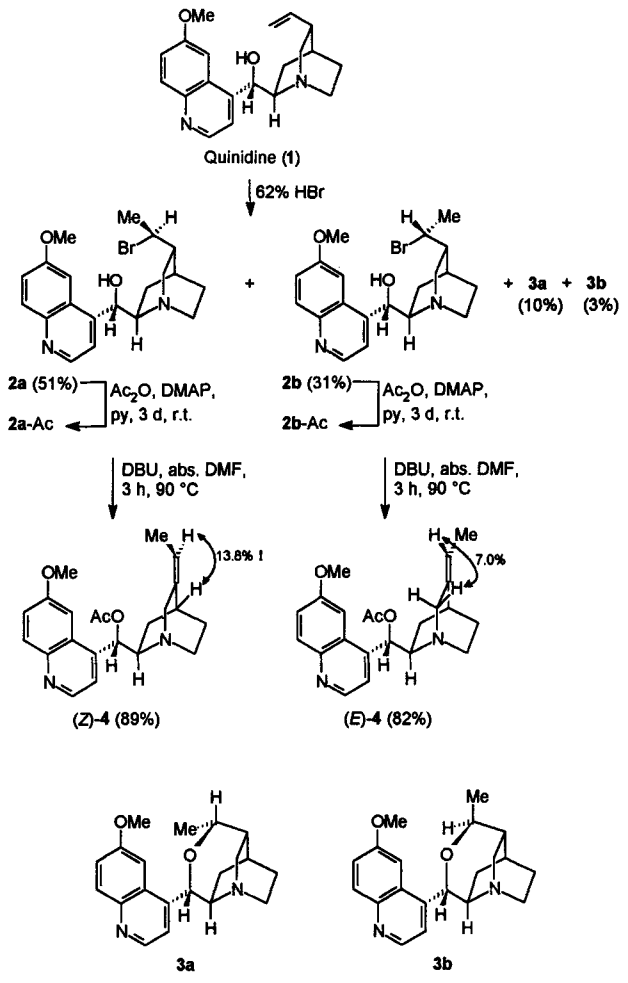
Cinchona alkaloids are produced on a large scale worldwide (300–500 tons per annum) by extraction from the bark of various *cinchona* species, now widely cultivated commercially.[1] Quinidine sulfate is currently available at around 130 dollars per kilogram. About 60% of the alkaloid goes into the production of pharmaceuticals. The bulk of the remaining 40% is used in the food industry as the bitter principle of soft drinks such as bitter lemon and also tonic water (the bitter taste of which can be partially disguised by gin!). A quinine-containing extract from the powdered bark of the *cinchona* tree has served for the treatment of malaria since at least the 17th century.[2] Quinidine is an antimalarial, which is still in use against chloroquin-resistant infections, and and also a cardiac depressant[3] (antiarrhythmic). Derivatives of cinchona alkaloids (cinchonicine and quinicine) have been used as chiral auxiliaries for the first separation of diastereomeric salts by Pasteur.[4] Quinicine ("quinotoxine") is a key intermediate and *relais* of the first total synthesis of quinine and quinidine by Woodward and Doering.[5] The cinchona alkaloids also serve as highly versatile auxiliaries in asymmetric synthesis, including enantioselective Diels–Alder reactions,[6] [2+2] cycloadditions,[7] dehydrohalogenations,[8] hydrocyanation,[9] SmI_2-mediated reductions,[10] Michael additions[11] and in the Sharpless AD reaction.[12] Metabolites of quinidine have been investigated from the point of view of medicinal activity and are used in the clinic. A *Chemical Abstracts* search for the period 1987–1991 indicates some 2145 publications, which have appeared in a diverse range of journals, especially those of applied medicine and pharmacology.[13]

[*] Prof. H. M. R. Hoffmann, Dr. C. von Riesen[+]
Department of Organic Chemistry, University of Hannover
Schneiderberg 1B, D-30167 Hannover (Germany)
Fax: Int. code +(511)762-3011
Prof. P. G. Jones
Department of Inorganic and Analytical Chemistry
Hagenring 30, D-38106 Braunschweig (Germany)
[+] New address: Quinine Factory Buchler GmbH
Harxbütteler Str. 3, D-38110 Braunschweig (Germany)

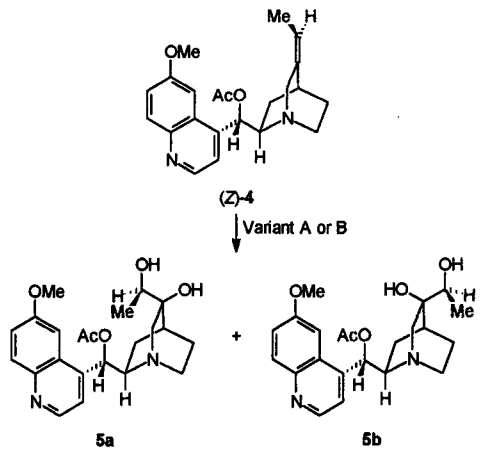
Results and Discussion

Isomerization of Quinidine to Trisubstituted Olefins (*Z*)-4 and (*E*)-4: Metabolism of quinidine proceeds at several sites and may involve oxygenation of the vinyl side chain. With a view to preparing new metabolites and enantiopure materials we have optimized a simple functionalization and degradation procedure of the vinyl group. Hydrobromination of **1** with 48% HBr[14] did not go to completion, undoubtedly owing to competing protonation of basic sites within the molecule. However, in fuming 62% HBr (ca. 6 equiv) the quinidine dissolved completely to give a clear, homogeneous solution and afforded the desired diastereoisomeric secondary bromides **2a** and **2b**, and seven-membered cyclic ethers **3a** and **3b** as by-products (Scheme 1).[15] Separation of polar amino alcohols **2a** and **2b** was not straightforward. After a standard conversion into the acetylated derivatives **2a**–Ac and **2b**–Ac, a simple column chromatographic separation was possible (MTB ether/methanol). Elimination of HBr from the single diastereomers was stereospecific (i.e., antiperiplanar). Thus, bromide **2a**–Ac furnished olefin (*Z*)-**4**, whereas diastereomeric **2b**–Ac furnished olefin (*E*)-**4**. From a preparative standpoint, protection

  0947-6539/96/0206-0673 $ 15.00+.25/0



Scheme 1. Stereospecific elimination from **2a** and **2b** to give (*E*)- and (*Z*)-trisubstituted rubane olefins (*E*)-**4** and (*Z*)-**4** (the numbering of the quinidine skeleton follows convention; cf. X-ray crystal structures in Figs. 1 and 2).



Scheme 2. Synthesis of diastereomeric diols **5a** and **5b** by *cis*-dihydroxylation of (*Z*)-configurated ethylidene rubane in the presence of catalytic OsO_4. Variant A: OsO_4, NMO, DABCO, THF/H_2O, RT, 7 d. Variant B: $K_3[Fe(CN)_6]$, OsO_4, K_2CO_3, *t*BuOH/H_2O, RT, 3 h.

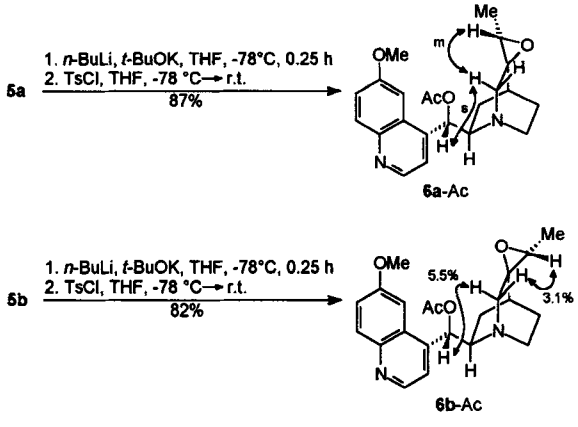
Table 1. Dihydroxylation of (*Z*)-4 (see Scheme 2).

	OsO_4	Time	Yield [%]	**5a**:**5b**
variant A	0.01 equiv	7 d	84	1.2:1
variant B	0.01 equiv	3 h	94	2.4:1

of the weakly acidic OH group by acetylation improved the yield of the base-mediated elimination decisively.

Previously, the mixture of olefins (*E*)-**4** and (*Z*)-**4** was dihydroxylated with almost stoichiometric quantities of OsO_4.[14] However, because of the toxicity and expense of OsO_4, it is mandatory that the dihydroxylation be carried out by a catalytic variant. Under normal conditions OsO_4 is coordinated to the bridgehead nitrogen and thus inactivated. Using DABCO (1,4-diazabicyclo[2.2.2]octane) as a coordination ligand for OsO_4 and also diastereomerically pure (*Z*)-configurated ethylidene rubane (*Z*)-**4**, we were able to prepare the diols **5a** and **5b** with *catalytic* amounts of OsO_4 under *homogeneous* conditions (variant A). A two-phase system (variant B) was modelled on the protocol of Sharpless,[12] however without the dihydroquinine- or dihydroquinidine-derived chiral ligand. Under two-phase conditions, attack of the sterically more accessible face of the π bond dominated by a factor of 2.4:1 (Table 1). Thus, the dihydroxylation is substrate-controlled (s.c.) and *syn* (see Scheme 7 below).

The transformation of diol **5a** as well as diol **5b** into spiroepoxides **6a**–Ac and **6b**–Ac, respectively, was accomplished by a stereoselective and also chemoselective tosylation–cyclization procedure. Under standard conditions (TsCl, NEt_3 or pyridine) no reaction of the diols was observed. Deprotonation with *n*-butyllithium and addition of tosyl chloride was also unsatisfactory, giving only some spiroepoxide and recovered diol. Treatment of the diol with 2 equivalents of *n*-butyllithium and 2 equivalents of potassium *t*-butoxide in THF at −78 °C, followed by addition of tosyl chloride in THF at −78 °C, made an immediate difference. The reaction mixture was allowed to slowly reach RT and provided the desired spiroepoxides **6a**–Ac and **6b**–Ac in a clean, stereospecific reaction (Scheme 3). The (*Z*)-configurated methyl group of the starting olefin (*Z*)-**4** (which points towards the reader) points away from the reader in the final spiroepoxides **6a** and **6b**. Inversion of configuration at the secondary carbon was put beyond doubt by NOE.

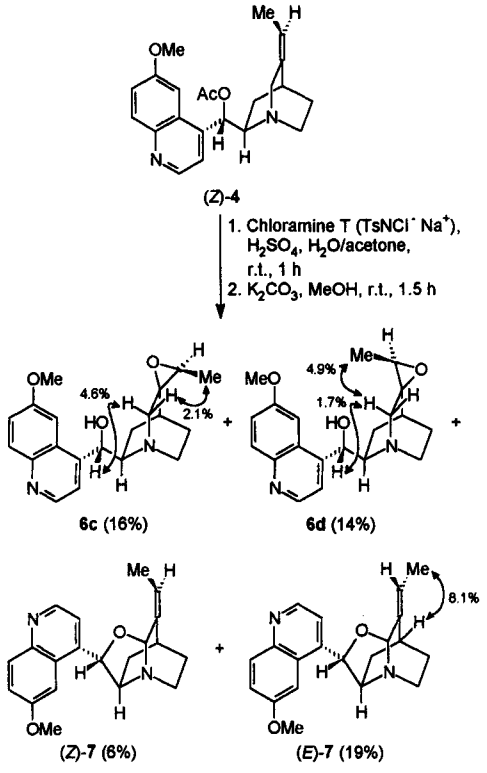


Scheme 3. Stereospecific conversion of diols **5a** and **5b** into spiroepoxides **6a**–Ac and **6b**–Ac, respectively.

Spiroepoxides **6a** and **6b** are readily and individually available. In order to prepare the two "missing" stereoisomeric spiroepoxides **6c** and **6d** from the same (*Z*)-olefinic precursor (*Z*)-**4**, the mechanism of epoxidation was changed. In fact, treatment of (*Z*)-**4** with chloramine T ($TsNCl^-Na^+$) in water/acetone and sulfuric acid (1 equiv of acid per chloramine T)

0947-6539/96/0206-0674 $ 15.00+.25/0 Chem. Eur. J. 1996, 2, No. 6

followed by addition of K_2CO_3 provided not only the desired spiroepoxides **6c** and **6d**, but also the new oxazatricyclic olefins (*Z*)-**7** and (*E*)-**7** in a simple, one-pot procedure (Scheme 4). The allylic *N,O*-acetals are stabilized on stereoelectronic grounds: The newly formed C–O bond and the lone pair of the bridgehead nitrogen atom are nearly orthogonal. C–O bond cleavage with formation of an iminium ion is forbidden by the Bredt rule.



Scheme 4. One-pot preparation of the two "missing" stereoisomeric spiroepoxides **6c** and **6d** from olefin (*Z*)-**4**, and formation of unprecedented tricyclic allylic *N,O*-acetals (*Z*)-**7** and (*E*)-**7**.

C,H analyses for spiroepoxide **6c** obtained from CH_2Cl_2 were completely wrong (calcd. C 70.55, H 7.11, N 8.23; found C 58.33, H 6.04, N 6.64), although spectroscopic data (^1H, ^{13}C, HH COSY, NOE and HRMS) were in complete agreement with the assigned structure. Slow evaporation of a dichloromethane solution of **6c** at room temperature provided single crystals suitable for X-ray crystallography (Fig. 1, top). We were surprised to find that volatile CH_2Cl_2 (b.p. 40.8 °C) was stoichiometrically encapsulated in the crystal and only slowly lost to the atmosphere (only with a resulting collapse of the crystal lattice). Figure 1 (bottom) shows a packing diagram. Apart from a conventional intermolecular hydrogen bond between the C(9)OH proton and the bridgehead nitrogen atom (O···N 283 pm), there is also an interaction of a methylene proton from CH_2Cl_2 with the spiroepoxide oxygen (C···O 321 pm). The microanalytical data obtained (see above) agree well with the formulation of spiroepoxide **6c** as a host–guest, CH_2Cl_2 clathrate[16] (calcd. C 59.42, H 6.18, N 6.60; found C 58.33, H 6.04, N 6.64).

The X-ray crystal structure of unsaturated oxazatricycle (*E*)-**7** (Fig. 2) was in full agreement with the spectroscopic findings. In the mass spectrum the molecular peak ($M^+ = 322$) was also the most intense peak, pointing to a compact cagelike structure, and in accord with a stereoelectronic stabilization of the *N,O*-acetal group (see above).

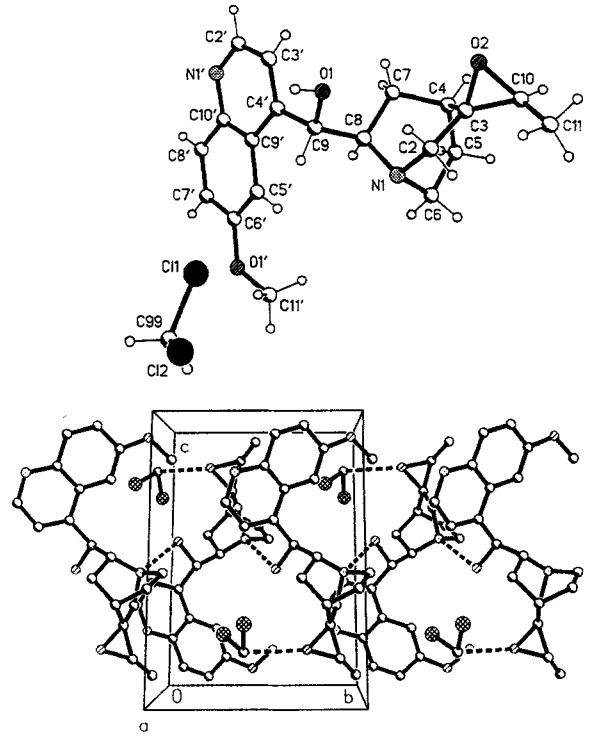


Fig. 1. Top: Crystal structure of **6c**·CH_2Cl_2. Bottom: packing diagram (blue: nitrogen; green: chlorine; red: oxygen).

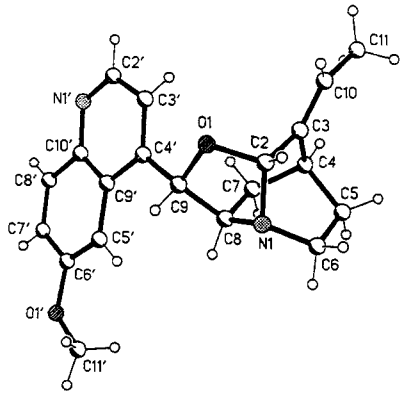
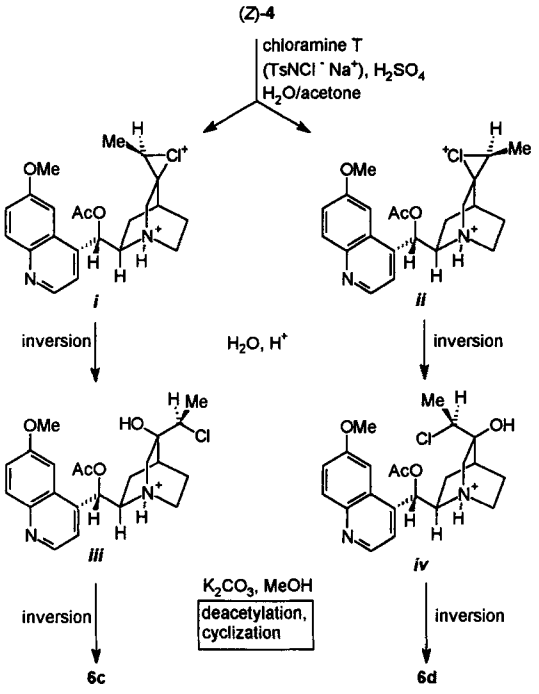


Fig. 2. Crystal structure of (*E*)-**7**.

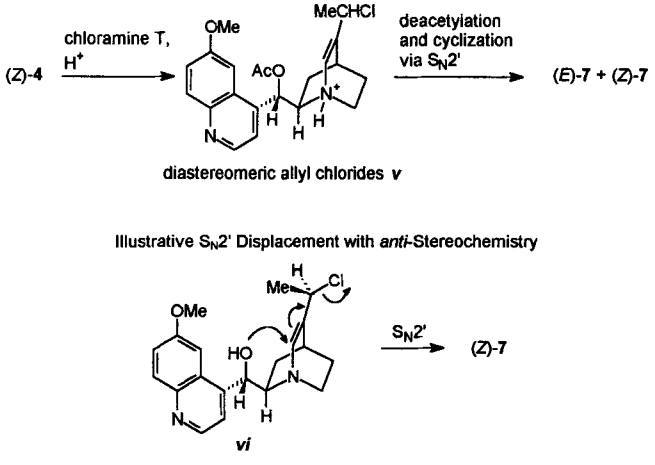
Mechanistic Considerations: In acidic solution the bridgehead nitrogen of amino olefin (*Z*)-**4** is protonated (Scheme 5). Chloramine T functions as a source of solvated chlorine cations Cl^+_{solv}, which attack the olefinic double bond from either face with generation of cyclic chloronium ion **i** and **ii**. Nucleophilic attack by water is assumed to proceed with inversion of configuration and to generate the pair of diastereomeric chlorohydrins **iii** and **iv**, respectively. Finally, addition of alkali promotes cyclization to spiroepoxides **6c** and **6d**, similarly to the final step of the monotosylation–cyclization sequence (cf. Scheme 7).

Note that the transformation of amino olefin (*Z*)-**4** into epoxides **6c** and **6d** involves two *anti*-oriented steps. Thus, the (*Z*)-configurated methyl group in diastereomerically pure starting material (*Z*)-**4** retains its configuration in the resulting spiroepoxides **6c,d** (Scheme 5). An open, tertiary carbenium ion (instead of the chlorine bridged cation) is unlikely as an intermediate, since in this case spiroepoxide formation would not be stereoselective.



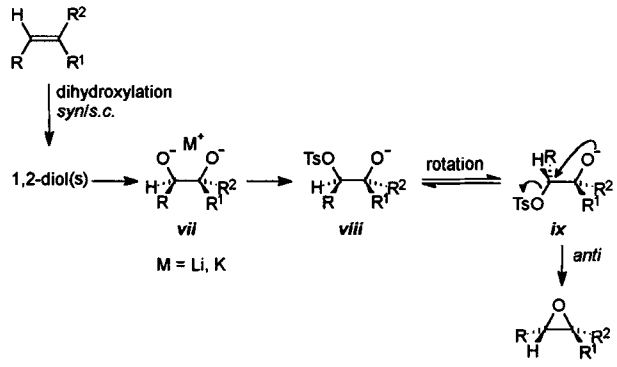
Scheme 5. Possible intermediates in the transformation from diastereomerically pure amino olefin (*Z*)-**4** to spiroepoxides **6c** and **6d**.

The tricyclic *N,O*-acetals (*E*)-**7** and (*Z*)-**7** arise from an allyl chloride[17] *v* by an S_N2' displacement with 1,3-chirality transfer. Whereas the olefin configuration of the starting material (*Z*)-**4** is lost in the product [(*Z*)-**7**/(*E*)-**7** ca. 1:3], the configuration of the new chiral centre at C(2) is necessarily fixed, since it is generated by an intramolecular S_N2' reaction.



Scheme 6. Loss of olefin configuration in amino olefin (*Z*)-**4** en route to allylic *N,O*-acetals (*E*)-**7** and (*Z*)-**7**.

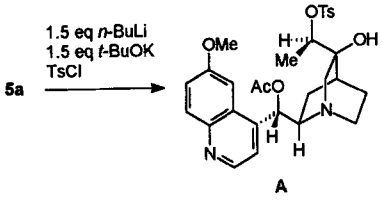
The stereospecific tosyl chloride–base mediated 1,2-diol → epoxide conversion is thought to involve a disciplined functionalization/nucleophilic displacement sequence. Deprotonation of the hindered tertiary hydroxy group requires strong base. For simplicity, the reaction is formulated without the counterions Li^+ and K^+ (Scheme 7). Double deprotonation of the diol with the super base is assumed to generate a metal-bridged oxygen dianion **vii** or its monoanion equivalent. Chemoselective monotosylation at the sterically more accessible secondary site[18] (**vii** → **viii**), rotation about the carbon–carbon bond



Scheme 7. Stereospecific tosyl chloride–base mediated 1,2-diol → epoxide conversion.

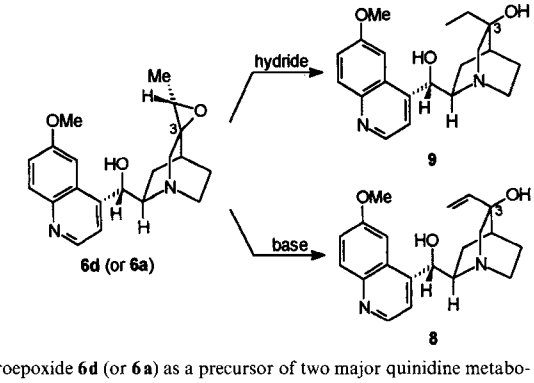
(**viii**⇌**ix**) and intramolecular nucleophilic displacement complete the sequence, with inversion of configuration at the secondary and retention at the tertiary carbon centre. Competing elimination from the secondary tosylate **vii** was not observed at the temperature range studied (−78 °C → RT). In fact, secondary tosylate **A** was isolated as a by-product when less than 2 equivalents of *n*BuLi/*t*BuOK were employed (Scheme 8).

Due to the change in mechanism, our method complements the literature procedure[19] with respect to 1) structural pattern of the diol and 2) overall steric course of the reaction. In fact, the Kolb–Sharpless[19] reaction proceeds with 1,2-disecondary and 1,2-primary, secondary diols, but is unsatisfactory for crowded diols derived from trisubstituted double bonds. The literature reaction entails a double inversion, that is, overall retention of configuration (rather than inversion) and proceeds under electrophilic conditions via a cyclic acetoxonium (3-dioxolan-2-ylium) cation.[19]



Scheme 8. Secondary monotosylate **A** isolated as a by-product in the preparation of spiroepoxide **6a**–Ac with less than 2 equiv of BuLi/*t*BuOK.

Spiroepoxides **6a** and **6d** have the correct absolute configuration at carbon C(3) to serve as possible precursors of two major quinidine metabolites (Scheme 9). A base-mediated opening of **6d** (and **6a**) would provide allylic alcohol **8**. Nucleophilic epoxide opening of **6d** (and **6a**) by hydride ion at the more accessible secondary carbon would furnish tertiary alcohol **9** with the correct absolute configuration at C(3).



Scheme 9. Spiroepoxide **6d** (or **6a**) as a precursor of two major quinidine metabolites: allylic alcohol **8** and tertiary alcohol **9**.

0947-6539/96/0206-0676 $ 15.00+.25/0 Chem. Eur. J. 1996, 2, No. 6

Conclusions

Synthetic transformations of polyfunctional molecules may often appear to be tedious and low-tech. However, putting a sequence of steps together requires planning and offers the challenge of achieving control, namely, chemo-, regio- and stereocontrol. For example, the basic sites of the alkaloid blunt the reactivity of added electrophiles. Simple practical considerations are also often forgotten, such as solubility and chromatographic behaviour of intermediates, which in the present case was adjusted by protecting groups. The various transformations described are reliable and capable of being scaled up. A variety of further Cinchona derivatives can be expected in the near future.

Experimental Procedure

General Remarks: The numbering of the quinidine skeleton follows the cinchonane/rubane convention for cinchona alkaloids. Melting points: Büchi apparatus, not corrected. Infrared spectra: Perkin–Elmer 1710 spectrometer. ^{1}H NMR spectra: Bruker WH 90, WP 200 SY or AM 300 spectrometer. Chemical shifts are reported in δ values relative to tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra: Bruker WP 200 SY or a Bruker AM 300. Chemical shifts are reported in δ values relative to TMS. APT (attached proton test): spin echo-based selection of multiplicities of ^{13}C signals; quaternary C and CH_2 carbon atoms give positive signals (+), while CH and CH_3 give negative signals (−). Low- and high-resolution electron-impact mass spectra: Finnigan MAT 312 spectrometer with an ionization potential of 70 eV at room temperature, unless otherwise stated. Microanalyses were performed in the Department of Organic Chemistry of the University of Hannover. Preparative column chromatography was performed on J. T. Baker silica gel (particle size 30–60 μm). Analytical TLC was carried out on aluminium-backed 0.2 mm silica gel 60 F_{254} plates (E. Merck). E (ethyl ether). MTBE (methyl t-butyl ether).

(8*R*,9*S*,10*S*)-10-Bromo-10,11-dihydro-6′-methoxycinchonan-9-ol (2a), (8*R*,9*S*,10*R*)-10-Bromo-10,11-dihydro-6′-methoxycinchonan-9-ol (2b), (8*R*,9*S*,10*R*)-10,11-Dihydro-9,10-epoxy-6′-methoxycinchonane (3a) and (8*R*,9*S*,10*S*)-10,11-Dihydro-9,10-epoxy-6′-methoxycinchonane (3b): To an aqueous solution of HBr (≈50 mL, 62%) was added quinidine (20 g, 61.7 mmol) at 0 °C. After removal of the ice bath the mixture was stirred for 3 d at RT, then diluted with H_2O (50 mL) and made alkaline with aqueous KOH (25%) (perfusor, 30 mL h^{-1}). The aqueous layer was extracted with $CHCl_3$ and the organic phase dried ($MgSO_4$). Chromatography (silica gel, MTBE/MeOH) afforded **2a** and **2b** (1.6:1, isolated yield). The seven-membered cyclic ethers **3a** and **3b** (5:1, ^{1}H NMR) were also separated.

Data of **2a**: Yield: 12.7 g (51%), m.p. 100 °C (decomp.). $[\alpha]_D^{20} = +223.8$ ($c = 1.12$ in $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1031, 1053, 1112, 1225, 1244, 1326, 1381, 1429, 1455, 1471, 1510, 1591, 1621, 2869, 2941, 3401 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.996 (m, 1H), 1.8 (m, 2H), 2.2 (m, 3H), 3.05–3.53 (m, 4H; H-2, H-6), 3.76 (s, 3H; H-11′), 4.33 (m, 1H; H-8), 4.56 (m, 1H; H-10), 6.38 (s, 1H; H-9), 6.97 (d, J = 2 Hz, 1H; H-5′), 7.15 (dd J = 2, 9 Hz, 1H; H-7′), 7.66 (d, J = 4 Hz, 1H; H-3′), 7.78 (d, J = 9 Hz, 1H, H-8′), 8.63 (d, J = 4 Hz, 1H, H-2′). ^{13}C NMR (50 MHz, APT, $CDCl_3/CF_3CO_2H$): δ = 18.09 (+, C-7, C-5), 24.62, 24.96 (−, C-11, C-4), 44.02 (−, C-3), 49.32, 50.88 (+, C-2, C-6), 53.43 (−, C-10), 55.91 (−, C-11′), 59.48 (−, C-8), 68.26 (−, C-9), 100.26 (−, C-5′), 118.30 (−, C-3′), 122.29 (−, C-7′), 125.85 (+, C-9′), 130.84 (−, C-8′), 143.41, 146.41 (+, C-4′, C-10′), 146.83 (−, C-2′), 158.30 (+, C-6′). MS-MAT (260 °C): m/z (%): 406 (13) [M^+], 404 (13), 326 (22), 325 (56), 324 (18), 202 (14), 189 (13), 173 (13), 172 (22), 160 (13), 159 (14), 137 (100), 122 (38), 94 (34), 84 (55). HRMS calcd. for $C_{20}H_{25}N_2O_2Br$: 406.1079, found 406.1095. $C_{20}H_{25}N_2O_2Br$: calcd C 59.39, H 6.23, N 6.93; found C 58.40, H 6.11, N 6.86.

Data for **2b**: Yield: 7.7 g (31%), m.p. 100 °C (decomp.). $[\alpha]_D^{20} = +118.3$ ($c = 0.545$ in $CHCl_3$). IR (KBr): 1030, 1110, 1229, 1243, 1433, 1455, 1472, 1510, 1592, 1622, 2872, 2943, 3403 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3/CF_3CO_2H$): δ = 0.998 (m, 1H), 1.80 (m, 1H), 2.04 (m, 1H), 2.27 (m, 1H), 2.55 (m, 1H; H-4), 3.06–3.44 (m, 4H; H-2, H-6), 3.75 (s, 3H; H-11′), 4.16 (m, 1H; H-8), 4.47 (m, 1H; H-10), 6.37 (s, 1H; H-9), 6.92 (d, J = 2 Hz, 1H, H-5′), 7.12 (dd, J = 2, 9 Hz, 1H; H-7′), 7.67 (d, J = 4 Hz, 1H; H-3′), 7.77 (d, J = 9 Hz, 1H; H-8′), 8.57 (d, J = 4 Hz, 1H; H-2′). ^{13}C NMR (50 MHz, APT, $CDCl_3/CF_3CO_2H$): δ = 17.31, 23.44 (+, C-7, C-5), 23.72, 25.62 (−, C-11, C-4), 42.52 (−, C-3), 47.53, 49.21 (+, C-2, C-6), 50.21 (−, C-10), 55.98 (−, C-11′), 59.80 (−, C-8), 66.21 (−, C-9), 99.44 (−, C-5′), 118.45 (−, C-3′), 123.53 (−, C-7′), 125.35 (+, C-9′), 129.41 (−, C-8′), 141.01, 146.53 (+, C-4′, C-10′), 145.20 (−, C-2′), 158.72 (+, C-11′). MS-MAT (250 °C): m/z (%): 406 (7) [M^+], 404 (7), 326 (3), 325 (5), 324 (7), 278 (3), 277 (4), 211 (3), 173 (3), 172 (4), 137 (100), 122 (25), 108 (12), 94 (27).

Data for **3a**: Yield: 1.9 g (10%). IR ($CHCl_3$): $\tilde{\nu}$ = 1028, 1100, 1132, 1168, 1192, 1232, 1508, 1592, 2496, 2524, 2896, 2944, 3072, 3668 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.47 (d, J = 6 Hz, 3H; H-11), 1.52–1.90 (m, 4H), 2.39 (m, 2H), 2.83 (m, 1H), 3.2 (m, 2H), 3.47 (d, J = 9 Hz, 1H), 3.76 (m, 1H), 4.05 (s, 3H; H-11′), 4.25 (dq, J = 1, 6 Hz, 1H; H-10), 5.95 (s, 1H; H-9), 7.32 (d, J = 2 Hz, 1H, H-5′), 7.37 (dd, J = 2, 9 Hz, 1H; H-7′), 7.62 (d, J = 4 Hz, 1H; H-3′), 8.02 (d, J = 9 Hz, 1H; H-8′), 8.72 (d, J = 4 Hz, 1H; H-2′). NOE: H-10 with H-9 (0.5), H-11 (5.81), 2.83 (H-3) (3.9), 3.76 (H-2$_{endo}$) (2.8); H-9 with H-10 (3.3), 3.76 (H-2$_{endo}$) (8.3), 3.47 (H-8) (3.7); H-11 with H-10 (3.80), 2.39 (H-7) (2.90). ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ = 20.23, 22.03, 37.49 (−, C-11, C-3, C-4), 20.89, 23.49 (+, C-7, C-5), 46.38, 50.34 (+, C-2, C-6), 56.15 (−, C-11′), 62.04 (−, C-8), 70.80 (−, C-10), 78.37 (−, C-9), 101.11 (−, C-5′), 117.84 (−, C-3′), 121.30 (−, C-7′), 125.26 (+, C-9′), 131.25 (−, C-8′), 143.31, 143.77 (+, C-4′, C-10′), 146.90 (−, C-2′), 158.11 (+, C-11′). MS-MAT (270 °C):): m/z (%): 324 (100) [M^+], 309 (25), 295 (34), 281 (15), 265 (12), 252 (11), 241 (16), 226 (12), 215 (11), 210 (13), 187 (21), 159 (17), 138 (57), 122 (34), 111 (42), 95 (30). HRMS calcd. for $C_{20}H_{24}N_2O_2$: 324.1838, found 324.1835.

Data for **3b**: Yield: 0.48 g (2%). ^{1}H NMR (200 MHz, $CDCl_3$), characteristic signals from mixed spectrum: δ = 1.37 (d, J = 6 Hz, 3H; H-11), 4.08 (s, 3H; H-11′), 4.76 (q, J = 6 Hz, 1H; H-10), 6.29 (s, 1H; H-9).

(8*R*,9*S*,10*S*)-9-Acetoxy-10-bromo-10,11-dihydro-6′-methoxycinchonane (2a–Ac): To a mixture of **2a** (4.2 g, 10.3 mmol) and DMAP (125 mg, 1.03 mmol) were added acetic anhydride (10 mL) and pyridine (1.7 mL, 2.1 mmol) at 0 °C. The mixture was stirred for 3 d at RT. After removal of the solvent the residue was dissolved in $CHCl_3$ and extracted with sat. aq. $NaHCO_3$. The organic layer was dried ($MgSO_4$), evaporated and chromatographed (MTBE/MeOH) to yield **2a–Ac**, 4.35 g (94%), m.p. 139 °C. $[\alpha]_D^{20} = +84.3$ (c = 1.105 in $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1028, 1082, 1229, 1370, 1434, 1476, 1510, 1594, 1622, 1714, 1754, 2508, 2950 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30–1.88 (m, 5H; H-5, H-7, H-3), 1.95 (m, H-4), 1.79 (d, J = 6 Hz, 3H; H-11), 2.18 (s, 3H; H-13), 2.70 (m, 2H; H-6), 2.95 ("d", J = 9 Hz, 2H; H-2), 3.27 (m, 1H; H-8), 3.98 (s, 3H; H-11′), 4.40 (m, 1H, H-10), 6.57 (d, J = 6 Hz, 1H; H-9), 7.35 (m, 3H; H-3′, H-5′, H-7′), 8.02 (d, J = 9 Hz, 1H; H-8′), 8.74 (d, J = 4 Hz, 1H; H-2′). ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ = 21.13 (−, C-13), 22.57, 26.65 (+, C-7, C-5), 25.23, 25.47 (−, C-11, C-4), 45.01 (−, C-3), 49.72, 51.57 (+, C-2, C-6), 55.60 (−, C-11′), 58.88 (−, C-8), 73.38 (−, C-9), 100.88 (−, C-5′), 118.06 (−, C-3′), 122.08 (−, C-7′), 126.90 (+, C-9′), 131.72 (−, C-8′), 143.73, 144.57 (+, C-4′, C-10′), 147.32 (−, C-2′), 157.95 (+, C-6′), 169.88 (+, C-12). MS-MAT (110 °C): m/z (%): 448/446 (4) [M^+ + 1], 389 (3), 367 (100), 325 (6), 306 (23), 295 (5), 243 (6), 188 (11), 172 (9), 136 (13). HRMS calcd for $C_{22}H_{27}N_2O_3$: 367.2022, found 367.2031. $C_{22}H_{27}N_2O_2Br$: calcd C 59.18, H 6.10, N 6.28; found C 59.02, H 6.08, N 6.30.

(8*R*,9*S*,10*R*)-9-Acetoxy-10-bromo-10,11-dihydro-6′-methoxycinchonane (2b–Ac): Compound **2b** (3.4 g, 8.35 mmol) was allowed to react as described for **2a–Ac** to give **2b–Ac**, 3.45 g (92%), m.p. 152 °C. $[\alpha]_D^{20} = +42.0$ (c = 0.50 in $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1030, 1087, 1234, 1304, 1374, 1453, 1475, 1509, 1593, 1622, 1746, 2873, 2943 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.42–1.83 (m, 5H; H-5, H-7, H-3), 1.75 (d, J = 6 Hz, 3H; H-11), 2.13 (s, 3H; H-13), 2.32 (m, 1H; H-4), 2.71 (m, 3H), 2.95 (m, 1H), 3.27 (m, 1H; H-8), 3.95 (s, 3H; H-11′), 4.31 (m, 1H; H-10), 6.48 (d, J = 6 Hz, 1H; H-9), 7.32 (d, J = 4 Hz, 1H; H-3′), 7.36 (d, J = 2 Hz, 1H; H-5′), 7.38 (dd, J = 2, 9 Hz, 1H; H-7′), 8.03 (d, J = 9 Hz, 1H; H-8′), 8.76 (d, J = 4 Hz, 1H; H-2′). ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ = 21.04 (−, C-13), 22.60, 26.55 (+, C-5, C-7), 24.05, 26.52 (−, C-11, C-4), 45.00 (−, C-3), 48.71, 49.48 (+, C-2, C-6), 52.91 (−, C-10), 55.49 (−, C-11′), 58.51 (−, C-8), 73.48 (−, C-9), 101.29 (−, C-5′), 118.47 (−, C-3′), 121.71 (−, C-7′), 126.79 (+, C-9′), 131.81 (−, C-8′), 143.34, 144.65 (+, C-4′, C-10′), 147.37 (−, C-2′), 157.85 (+, C-6′), 169.75 (+, C-12). MS-MAT (110 °C): m/z (%): 448 (9)/ 446 (11) [M^+], 403 (3), 396 (4), 387 (5), 367 (100), 351 (4), 324 (14), 306 (77), 295 (10), 264 (11), 243 (16), 202 (15), 188 (20), 172 (22), 136 (30). HRMS calcd for $C_{22}H_{27}N_2O_3Br$: 446.1205, found 446.1199. $C_{22}H_{27}N_2O_3Br$: C 59.18, H 6.10, N 6.28; found C 59.34 H, 6.08, N 6.48.

(8*R*,9*S*)-9-Acetoxy-(*Z*)-3-ethylidene-6′-methoxyrubane [(*Z*)-4]. To a solution of **2a–Ac** (5 g, 11.2 mmol) in anhydrous DMF (15 mL) was added DBU (2.0 mL, 13.4 mmol) dropwise at 100 °C under N_2, and the mixture was stirred for 3 h. The solvent was removed (Kugelrohr apparatus), and the residue dissolved in $CHCl_3$. After extraction with H_2O the organic layer was dried ($MgSO_4$), evaporated and purified by chromatography through a very short column (MTBE/MeOH) to yield (*Z*)-**4**, 3.64 g (89%), m.p. 118 °C. $[\alpha]_D^{20} = +31.7$ (c = 1.06 in $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1027, 1085, 1231, 1372, 1434, 1474, 1510, 1593, 1622, 1745, 2861, 2936 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (d, J = 6 Hz, 3H; H-11), 1.58 (m, 2H; H-5), 1.77 (m, 2H; H-7), 2.05 (s, 3H; H-13), 2.35 (m, 1H; H-4), 2.62–2.83 (m, 2H; H-6), 3.22 (d, J = 18 Hz, 1H; H-2$_{exo}$), 3.42 (m, 1H; H-8), 3.67 (d, J = 18 Hz, 1H; H-2$_{endo}$), 3.93 (s, 3H; H-11′), 5.20 (m, 1H; H-10), 6.47 (d, J = 7 Hz, 1H; H-9), 7.32 (d, J = 4 Hz, 1H; H-3′), 7.33 (dd, J = 2, 9 Hz, 1H; H-7′), 7.43 (d, J = 2 Hz, 1H; H-5′), 7.98 (d, J = 9 Hz, 1H; H-8′), 8.71 (d, J = 4 Hz, 1H; H-2′). NOE: H-4 with H-10 (13.77), H-5 (5.67), H-7 (6.55). ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 12.21 (1°, C-11), 20.86 (1°, C-13), 27.09, 30.29 (2°, C-7, C-5), 32.99 (3°, C-4), 49.02 (2°, C-2), 50.83 (2°, C-6), 55.48 (1°, C-11′), 58.83 (3°, C-8), 73.83 (3°, C-9), 101.31 (3°, C-5′), 113.40 (3°, C-10), 118.64 (3°, C-3′), 121.70 (3°, C-7′), 126.83 (4°, C-9′), 131.68 (3°,

C-8'), 141.38, 143.59, 144.64 (4°, C-4', C-10', C-3), 147.31 (3°, C-2'), 157.80 (4°, C-6'), 169.83 (4°, C-12). MS-MAT (120 °C): *m/z* (%): 366 (98) [M^+], 351 (23), 323 (16), 306 (99), 291 (16), 277 (12), 231 (33), 211 (14), 201 (21), 189 (58), 188 (67), 172 (19), 154 (9), 136 (100). HRMS calcd for $C_{22}H_{26}N_2O_3$: 366.1943, found 366.1943. $C_{22}H_{26}N_2O_3$: C, 72.09, H 7.16, N 7.65; found C 72.00, H 7.14, N 7.74.

(8*R*,9*S*)-9-Acetoxy-(*E*)-3-ethylidene-6'-methoxyrubane [(*E*)-4]: Compound **2b**–Ac (2.5 g, 5.6 mmol) was allowed to react as described for (*Z*)-**4** to give (*E*)-**4**, 1.68 g (82%), m.p. 82 °C. $[\alpha]_D^{20} = +20.9$ (*c* = 1.00 in $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 1028, 1084, 1240, 1372, 1432, 1472, 1503, 1592, 1620, 1740, 2864, 2952 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.62 (d, *J* = 6 Hz, 3H; H-11), 1.50–1.93 (m, 4H; H-5, H-7), 2.12 (s, 3H; H-13), 2.63–2.93 (m, 3H; H-4, H-6), 3.18 (d, *J* = 18 Hz, 1H; $H\text{-}2_{exo}$), 3.44 (m, 1H; H-8), 3.73 (d, *J* = 18 Hz, 1H; $H\text{-}2_{endo}$), 3.98 (s, 3H; H-11'), 5.18 (m, 1H; H-10), 6.52 (d, *J* = 7 Hz, 1H; H-9), 7.36 (d, *J* = 4 Hz, 1H; H-3'), 7.38 (dd, *J* = 2, 9 Hz, 1H; H-7'), 7.47 (d, *J* = 2 Hz, 1H; H-5'), 8.03 (d, *J* = 9 Hz, 1H; H-8'), 8.77 (d, *J* = 4 Hz, 1H; H-2'). NOE: H-2$_{exo}$ with H-10 (1.2), H-2$_{endo}$ (7.0). ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ = 12.63 (–, C-11), 20.91 (–, C-13), 25.83 (–, C-4), 26.38, 29.19 (+, C-7, C-5), 50.50, 51.53 (+, C-2, C-6), 55.55 (–, C-11'), 58.99 (–, C-8), 73.53 (–, C-9), 101.47 (–, C-5'), 113.13 (–, C-10), 118.80 (–, C-3'), 121.79 (–, C-7'), 127.08 (+, C-9'), 131.72 (–, C-8'), 140.23, 143.83, 144.73 (+, C-4', C-10', C-3), 147.38 (–, C-2'), 157.91 (+, C-6'), 169.85 (+, C-12). MS-MAT: *m/z* (%): 366 (100) [M^+], 351 (35), 338 (2), 323 (12), 306 (15), 277 (9), 258 (6), 243 (4), 231 (22), 189 (2). HRMS calcd for $C_{22}H_{26}N_2O_3$: 366.1943, found 366.1925.

(3*S*,8*R*,9*S*,10*R*)-9-Acetoxy-10,11-dihydro-3,10-dihydroxy-6'-methoxycinchonane (5a) and **(3*R*,8*R*,9*S*,10*S*)-9-Acetoxy-10,11-dihydro-3,10-dihydroxy-6'-methoxycinchonane (5b)**: **Variant A:** OsO_4 (1.0 mL, 0.1 mmol, 0.1 M solution in *t*BuOH) was added to a solution of (*Z*)-**4** (3.8 g, 10.4 mmol), DABCO (3.5 g, 31 mmol) and an aqueous solution of NMO (4-methylmorpholine *N*-oxide) (6.1 mL, 31 mmol, 60%) in THF/H_2O (4:1, 100 mL). After having been stirred for 7 d at RT, the mixture was diluted with $CHCl_3$ and extracted with sat. aq. $NaHSO_3$/NaCl (1:1). The organic layer was dried ($MgSO_4$), the solvent evaporated and the crude product purified by column chromatography (MTBE/MeOH, 15:1, increasing polarity during separation) to afford **5a** (1.92 g, 46%), followed by **5b** (1.57 g, 38%), (**5a**:**5b** = 1.2:1, isolated yield).

Variant B: To a two-phase sytem of K_2CO_3 (0.47 g, 3.35 mmol), $K_3[Fe(CN_6)]$ (1.12 g, 3.35 mmol) and (*Z*)-**4** (438 mg, 1.2 mmol) in *t*BuOH/H_2O (1:1) (10 mL) was added OsO_4 (0.12 mL, 0.012 mmol, 0.1 M solution in *t*BuOH). The mixture was stirred for 3 h at RT and then worked up as described for variant A to give **5a**/**5b** (2.4:1, ^1H NMR), 450 mg, 94%.

Data of **5a**: m.p. 130 °C (decomp.). $[\alpha]_D^{20} = +74.7$ (*c* = 0.57 in MeOH). IR (KBr): $\tilde{\nu}$ = 1231, 1308, 1370, 1435, 1475, 1511, 1593, 1623, 1750, 2937, 3419 cm^{-1}. ^1H NMR (200 MHz, CD_3OD): δ = 1.23 (d, *J* = 6 Hz, 3H; H-11), 1.40 (m, 2H), 1.90–2.38 (m, 3H), 2.19 (s, 3H; H-13), 2.55 (d, *J* = 15 Hz, 1H; $H\text{-}2_{exo}$), 2.89 (m, 2H; H-6), 3.14 (d, *J* = 15 Hz, 1H; $H\text{-}2_{endo}$), 3.27 (m, 1H; H-8), 4.00 (s, 3H; H-11'), 4.22 (q, *J* = 6 Hz, 1H; H-10), 6.59 (d, *J* = 4 Hz, 1H; H-9), 7.45 (m, 3H; H-3', H-7', H-5'), 7.98 (d, *J* = 9 Hz, 1H; H-8'), 8.68 (d, *J* = 4 Hz, 1H; H-2'). ^{13}C NMR (50 MHz, CD_3OD): δ = 16.33 (–, C-11), 20.98 (–, C-13), 21.42, 24.57 (+, C-7, C-5), 29.63 (–, C-4), 50.53, 55.89 (+, C-2, C-6), 56.39 (–, C-11'), 58.40 (–, C-8), 68.92 (–, C-10), 73.91 (+, C-3), 74.81 (–, C-9), 102.13 (–, C-5'), 119.23 (–, C-3'), 123.68 (–, C-7'), 127.82 (+, C-9'), 131.52 (–, C-8'), 144.87, 145.50 (+, C-4', C-10'), 147.99 (–, C-2'), 159.80 (+, C-6'), 171.10 (+, C-12). MS-MAT (230 °C): *m/z* (%): 400 (22) [M^+], 383 (13), 355 (14), 341 (18), 313 (15), 296 (13), 267 (27), 253 (16), 231 (30), 189 (54), 188 (58), 170 (100), 152 (83). HRMS calcd for $C_{22}H_{28}N_2O_5$: 400.1998, found 400.1994.

Data for **5b**: m.p. 68 °C. $[\alpha]_D^{20} = +7.0$ (*c* = 1.00 in MeOH). IR (KBr): $\tilde{\nu}$ = 1231, 1372, 1435, 1475, 1511, 1593, 1623, 1747, 2936, 3442 cm^{-1}. ^1H NMR (200 MHz, CD_3OD): δ = 1.15 (d, *J* = 6 Hz, 3H; H-11), 1.50–1.93 (m, 3H), 2.21 (m, 1H), 2.36 (m, 1H), 2.13 (s, 3H; H-11'), 2.48 (d, *J* = 15 Hz, 1H; $H\text{-}2_{exo}$), 2.58–2.88 (m, 2H; H-6), 3.02 (d, *J* = 15 Hz, 1H; $H\text{-}2_{endo}$), 3.54 (m, 1H; H-8), 3.79 (q, *J* = 6 Hz, 1H; H-10), 4.01 (s, 3H; H-11'), 6.76 (d, *J* = 7 Hz, 1H; H-9), 7.46 (dd, *J* = 2, 9 Hz, 1H; H-7'), 7.57 (d, *J* = 4 Hz, 1H; H-3'), 7.70 (d, *J* = 2 Hz, 1H; H-5'), 7.98 (d, *J* = 9 Hz, 1H; H-8'), 8.68 (d, *J* = 4 Hz, 1H; H-2'). ^{13}C NMR (50 MHz, CD_3OD): δ = 16.18 (–, C-11), 20.86 (–, C-13), 22.07, 24.76 (+, C-7, C-5), 30.37 (–, C-4), 50.51, 55.45 (+, C-2, C-6), 56.34 (–, C-11'), 59.92 (–, C-8), 70.56 (–, C-10), 73.41 (+, C-3), 73.89 (–, C-9), 102.77 (–, C-5'), 120.52 (–, C-3'), 123.58 (–, C-7'), 128.36 (+, C-9'), 131.43 (–, C-8'), 145.01, 145.59 (+, C-4', C-10'), 148.11 (–, C-2'), 159.55 (+, C-6'), 171.49 (+, C-12). MS-MAT (170 °C): *m/z* (%) = 400 (38) [M^+], 385 (7), 355 (13), 341 (22), 322 (10), 312 (15), 296 (11), 267 (29), 253 (11), 231 (20), 188 (33), 189 (35), 170 (100), 153 (24).

(3*S*,8*R*,9*S*,10*S*)-9-Acetoxy-10,11-dihydro-3,10-epoxy-6'-methoxycinchonane (6a–Ac): To a solution of **5a** (340 mg, 0.85 mmol) and *t*BuOK (191 mg, 1.7 mmol) in anhydrous THF (20 mL) was added *n*BuLi (1.1 mL, 1.7 mmol, 1.6 M solution in hexane) at –78 °C. After 15 min tosyl chloride (324 mg, 1.7 mmol) in anhydrous THF (2 mL) was added, the mixture was allowed to reach RT slowly and then quenched with H_2O. The aqueous layer was extracted with $CHCl_3$, and the organic layer was dried ($MgSO_4$). After removal of the solvent the crude product was purified by column chromatography (MTBE/MeOH) to afford **6a**–Ac, 283 mg (87%), m.p. 55 °C. $[\alpha]_D^{20} = -10.8$ (*c* = 0.895 in $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 1228, 1508, 1744, 1592, 1620, 2872, 2960, 3000 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 5 Hz, 3H; H-11), 1.52 (m, 1H; H-5), 1.72 (m, 1H; H-4), 1.76–1.89 (m, 3H; H-5, H-7), 2.10 (s, 3H; H-13), 2.59 (d, *J* = 15 Hz, 1H; $H\text{-}2_{exo}$), 2.78–2.93 (m, 2H; H-6), 2.98 (q, *J* = 5 Hz, 1H; H-10), 3.34 (m, 1H; H-8), 3.35 (d, *J* = 15 Hz, 1H; $H\text{-}2_{endo}$), 3.92 (s, 3H; H-11'), 6.48 (d, *J* = 6 Hz, 1H; H-9), 7.31–7.40 (m, 2H; H-5', H-7'), 7.60 (d, *J* = 4 Hz, 1H; H-3'), 8.03 (d, *J* = 9 Hz, 1H; H-8'), 8.75 (d, *J* = 4 Hz, 1H; H-2'). NOE: H-9 with H-2$_{endo}$ (s); H-10 with H-2$_{endo}$ (m); H-2$_{endo}$ with H-10 (w), H-2$_{exo}$ (s), H-9 (s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.87 (–, C-11), 21.07 (–, C-13), 21.47 (+, C-7), 25.45 (–, C-4), 26.90 (+, C-5), 50.23 (+, C-2), 52.52 (+, C-6), 55.66 (–, C-11'), 57.81, 59.12 (–, C-8, C-10), 63.25 (+, C-3), 73.59 (–, C-9), 101.37 (–, C-5'), 118.54 (–, C-3'), 121.88 (–, C-7'), 126.85 (+, C-9'), 131.79 (–, C-8'), 143.28, 144.66 (+, C-4', C-10'), 147.32 (–, C-2'), 158.07 (+, C-6'), 169.82 (+, C-12). MS-MAT: *m/z* (%): 382 (51) [M^+], 367 (23), 339 (6), 322 (30), 323 (31), 307 (24), 295 (12), 265 (20). HRMS calcd for $C_{22}H_{26}N_2O_4$: 382.1893, found 382.1889.

(3*S*,8*R*,9*S*,10*R*)-9-Acetoxy-10,11-dihydro-3-hydroxy-6'-methoxy-10-tosyloxycinchonane (A): This by-product was obtained when **5a** was treated with 1.5 equiv *n*BuLi and 1.5 equiv *t*BuOK according the procedure desribed above, m.p. 130 °C (decomp.). $[\alpha]_D^{20} = +50.7$ (*c* = 1.03 in $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1033, 1061, 1084, 1177, 1190, 1244, 1308, 1367, 1510, 1622, 1728, 2941 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 6 Hz, 3H; H-11), 1.80–2.00 (m, 5H; H-5, H-7, H-4), 2.10 (s, 3H; H-13), 2.28 (s, 3H; H-7''), 2.57 (d, *J* = 15 Hz, 1H; $H\text{-}2_{exo}$), 2.80 (m, 2H; H-6), 3.08 (d, *J* = 15 Hz, 1H; $H\text{-}2_{endo}$), 3.10 (m; 1H; H-8), 3.96 (s, 3H; H-11'), 5.32 (q, *J* = 6 Hz, 1H; H-10), 7.01 (d, *J* = 8 Hz, 2H; H-3'', H-5''), 7.12 (m, 2H; H-5', H-3'), 7.36 (dd, *J* = 9, 2 Hz, 1H; H-7'), 7.52 (d, *J* = 8 Hz, 2H; H-2'', H-6''), 7.97 (d, *J* = 9 Hz, 1H; H-8'), 8.51 (d, *J* = 4 Hz, H-2'). MS-MAT (170 °C): *m/z* (%): 554 (6) [M^+], 496 (7), 495 (13), 494 (32), 479 (5), 382 (20), 339 (12), 321 (66), 307 (21), 279 (11), 265 (100), 251 (15), 225 (13), 188 (14), 172 (19), 152 (71).

(3*R*,8*R*,9*S*,10*R*)-9-Acetoxy-10,11-dihydro-3,10-epoxy-6'-methoxycinchonane (6b–Ac): Compound **5b** (163 mg, 0.32 mmol) was allowed to react as described for **6a**–Ac to give **6b**–Ac, 128 mg (82%), m.p. 52 °C. $[\alpha]_D^{20} = +7.8$ (c = 0.60, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1229, 1510, 1595, 1622, 1745, 2871, 2952 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 5 Hz, 3H; H-11), 1.60–1.82 (m, 3H), 2.12 (m, 1H), 1.67 (brs, 1H; H-4), 2.18 (s, 3H; H-13), 2.63–2.93 (m, 2H; H-6), 2.68 (d, *J* = 15 Hz, 1H; $H\text{-}2_{exo}$), 2.98 (q, *J* = 5 Hz, 1H; H-10), 3.13 (d, *J* = 15 Hz, 1H; $H\text{-}2_{endo}$), 3.37 (m, 1H; H-8), 3.96 (s, 3H; H-11'), 6.58 (d, *J* = 6 Hz, 1H; H-9), 7.38 (m, 3H; H-5', H-7', H-3'), 8.03 (d, *J* = 9 Hz, 1H; H-8'), 8.75 (d, *J* = 4 Hz, 1H; H-2'). NOE: H-9 with H-2$_{endo}$ (5.48); H-10 with H-2$_{exo}$ (3.12). ^{13}C NMR (50 MHz, $CHCl_3$): δ = 13.84 (–, C-11), 21.07 (–, C13), 23.69, 24.85 (+, C-7, C-5), 26.29 (–, C-4), 50.15, 52.29 (+, C-2, C-6), 55.68 (–, C-11'), 58.79 (–, C-8), 60.67 (–, C-10), 63.07 (+, C-3), 73.59 (–, C-9), 101.37 (–, C-5'), 118.46 (–, C-3'), 121.95 (–, C-7'), 126.87 (+, C-9'), 131.74 (–, C-8'), 143.74, 144.65 (+, C-4', C-10'), 147.42 (–, C-2'), 157.96 (+, C-6'), 169.93 (+, C-12). MS-MAT (130 °C): *m/z* (%): 382 (44) [M^+], 367 (10), 339 (5), 323 (13), 306 (5), 265 (7), 189 (12), 188 (15), 172 (11), 152 (100). HRMS calcd for $C_{22}H_{26}N_2O_4$: 382.1893, found 382.1900.

(2*R*,8*R*,9*S*)-2,9-Epoxy-(*E*)-3-ethylidene-6'-methoxyrubane [(*E*)-7)], (2*R*,8*R*,9*S*)-2,9-Epoxy-(*Z*)-3-ethylidene-6'-methoxyrubane [(*Z*)-7], (3*S*,8*R*,9*S*,10*R*)-10,11-Dihydro-3,10-epoxy-6'-methoxycinchonan-9-ol (6d) and **(3*R*,8*R*,9*S*,10*S*)-10,11-Dihydro-3,10-epoxy-6'-methoxy-cinchonan-9-ol (6c)**: To a solution of (*Z*)-**4** (15.87 g, 43.4 mmol) and chloramine T trihydrate (12.21 g, 43.4 mmol) in acetone/H_2O (1:1) (200 mL) was added conc. H_2SO_4 (2.31 mL, 43.4 mmol). The mixture was stirred for 1 h at RT, then diluted with MeOH (300 mL) and saturated with K_2CO_3. The mixture was stirred vigorously for 1.5 h. After removal of methanol and acetone the aqueous layer was extracted with $CHCl_3$. The combined organic layer was dried ($MgSO_4$), the solvent removed and the crude product purified by chromatography (MTBE/MeOH, 20:1, increasing polarity during separation). First (*E*/*Z*)-**7** (2.3:1, ^1H NMR) (3.51 g, 25%) was eluted. Crystallization (E) afforded (*E*)-**7** as platelets. Then **6d** (2.04 g, 14%) and the most polar compound **6c** (2.34 g, 16%) were eluted. Compound **6c** was also purified by crystallization (CH_2Cl_2) to give colourless needles.

Data for (*E*)-**7**: m.p. 165 °C. $[\alpha]_D^{20} = +402.6$ (*c* = 1.03 in CH_2Cl_2). IR ($CHCl_3$): $\tilde{\nu}$ = 1088, 1228, 1508, 1620, 2872, 2940 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 (m, 1H; H-7), 1.31 (m, 1H; H-7), 1.62 (m 2H; H-5), 1.75 (d, *J* = 7.5 Hz, 3H; H-11), 2.64 (m, 1H; H-4), 3.07 (m, 1H; $H\text{-}6_{eq}$), 3.28 (m, 1H; $H\text{-}6_{axial}$), 3.97 (s, 3H; H-11'), 4.07 (m, 1H; H-8), 5.17 (s, 1H; H-2), 5.74 (q, *J* = 7.5 Hz, 1H; H-10), 5.83 (d, *J* = 4 Hz, 1H; H-9), 7.17 (d, *J* = 2 Hz, 1H; H-5'), 7.42 (dd, *J* = 2, 9 Hz, 1H; H-7'), 7.57 (d, *J* = 4 Hz, 1H; H-3'), 8.08 (d, *J* = 9 Hz, 1H; H-8'), 8.82 (d, *J* = 4 Hz, 1H; H-2'). NOE: H-11 with H-4 (8.08). ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 13.02 (1°, C-11), 22.57 (4°, C-4), 25.65 (2°, C-7), 29.47 (2°, C-5), 38.41 (2°, C-6), 55.50 (1°, C-11'), 56.10 (3°, C-8), 79.22 (3°, C-9), 91.45 (3°, C-2), 100.81 (3°, C-5'), 120.02 (3°, C-3'), 120.85 (3°, C-10), 121.28 (3°, C-7'), 126.31 (4°, C-9'), 131.69 (3°, C-8'), 142.53, 142.69, 143.87 (4°, C-3, C-4', C-10'), 147.74 (3°, C-2'), 157.65 (4°, C-6'). MS-MAT (110 °C): *m/z* (%): 322 (100) [M^+], 307 (23), 293 (19), 279 (13), 264 (72), 251 (47), 237 (27), 212 (44), 198 (25), 183 (48), 167 (26), 136 (21). FAB-MS: *m/z* (%): 323 (100), 154 (38), 136 (31). HRMS calcd for $C_{20}H_{22}N_2O_2$: 322.1681, found 322.1686. $C_{20}H_{22}N_2O_2$: C 74.50 H, 6.88, N 8.69; found C 74.54, H 6.88, N 8.61.

0947-6539/96/0206-0678 $ 15.00+.25/0 Chem. Eur. J. 1996, 2, No. 6

Data for (*Z*)-**7**: ^{1}H NMR (200 MHz, $CDCl_3$), characteristic signals: δ = 1.90 (d, J = 7.5 Hz, 3H; H-11), 5.51 (s,1H; H-2), 5.52 (dq, J = 7.5, 1 Hz, 1H; H-10), 5.82 (d, J = 4 Hz, 1H; H-9).

Data for **6d**: m.p. 49 °C. $[\alpha]_D^{20}$ = +174.0 (c = 1.065 in MeOH). IR ($CHCl_3$): $\tilde{\nu}$ = 1240, 1508, 1592, 1620, 2872, 2960, 3400 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25 (d, J = 5 Hz, 3H; H-11), 1.36–1.50, 1.80–2.22 (m, 4H; H-5, H-7), 1.42 (m, 1H; H-4), 2.63 (d, J = 15 Hz, 1H; H-2$_{exo}$), 2.91–3.13 (m, 3H; H-8, H-6), 3.02 (q, J = 5 Hz, 1H; H-10), 3.6 (brs, 1H; OH), 3.86 (d, J = 15 Hz, 1H; H-2$_{endo}$), 3.90 (s, 3H; H-11′), 5.62 (d, J = 4 Hz, 1H; H-9), 7.13 (d, J = 2 Hz, 1H; H-5′), 7.32 (dd, J = 2, 9 Hz, 1H; H-7′), 7.51 (d, J = 4 Hz, 1H; H-3′), 7.98 (d, J = 9 Hz, 1H; H-8′), 8.63 (d, J = 4 Hz, 1H; H-2′). NOE: H-9 with H-2$_{endo}$ (1.67), H-5′ (12.05), H-3′ (1.99); H-2$_{endo}$ with H-11 (4.88), H-2$_{exo}$ (17.60), H-9 (1.29). ^{13}C NMR (50 MHz, APT, CD_3OD): δ = 14.74 (–, C-11), 21.72 (+, C-7), 23.91 (+, C-5), 32.54 (–, C-4), 50.53 (+, C-2), 51.34 (+, C-6), 56.47 (–, C-11′), 59.49, 60.45 (–, C-8, C-10), 63.80 (+, C-3), 71.15 (–, C-9), 102.13 (–, C-5′), 119.80 (–, C-3′), 123.38 (–, C-7′), 127.72 (+, C-9′), 131.38 (–, C-8′), 144.58, 149.82 (+, C-4′, C-10′), 148.08 (–, C-2′), 159.68 (+, C-6′). MS-MAT (170 °C): m/z (%): 340 (35) [M^+], 325 (18), 311 (5), 189 (30), 172 (24), 152 (100), 138 (19). HRMS calcd for $C_{20}H_{24}N_2O_3$: 340.1787, found 340.1796. $C_{20}H_{24}N_2O_3$: C 70.55, H 7.11, N 8.23; found C 69.20, H 7.10, N 8.26.

Data for **6c**: m.p. 119 °C. $[\alpha]_D^{20}$ = +114.0 (c = 0.82 in MeOH). IR (KBr): $\tilde{\nu}$ = 1227, 1242, 1509, 1591, 1622, 2870, 2939, 3408 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (d, J = 5 Hz, 3H; H-11), 1.44 (m, 2H; H-7, H-4), 1.63 (m, 2H; H-5), 2.31 (m, 1H; H-7), 2.64–2.89 (m, 2H; H-6), 2.78 (d, J = 15 Hz, 1H; H-2$_{exo}$), 3.00 (q, J = 5 Hz, 1H; H-10), 3.22 (m, 1H; H-8), 3.42 (d, J = 15 Hz, 1H; H-2$_{endo}$), 3.89 (s, 3H; H-11′), 5.64 (d, J = 4.5 Hz, 1H; H-9), 7.28–7.37 (m, 2H; H-5′, H-7′), 7.53 (d, J = 4 Hz, 1H; H-3′), 7.98 (d, J = 9 Hz, 1H; H-8′), 8.68 (d, J = 4 Hz, 1H; H-2′). NOE: H-11 with H-2$_{exo}$ (2.05), H-10 (4.83); H-10 with H-11 (8.70), H-4 (5.31); H-2$_{endo}$ with H-2$_{exo}$ (7.80), H-9 (3.50); H-9 with H-2$_{endo}$ (4.60), H-5′, H-7′ (21.74), H-3′ (4.13). ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 13.94 (1°, C-11), 22.06 (2°, C-7), 23.59 (2°, C-5), 31.46 (4°, C-4), 48.31 (2°, C-2), 50.09 (2°, C-6), 55.39 (3°, C-11′), 59.00 (3°, C-8), 59.12 (3°, C-10), 62.96 (4°, C-3), 70.96 (3°, C-9), 100.96 (3°, C-5′), 118.56 (3°, C-3′), 121.71 (3°, C-7′), 126.43 (4°, C-9′), 130.52 (3°, C-8′), 143.43, 148.08 (4°, C-4′, C-10′), 146.92 (3°, C-2′), 157.76 (4°, C-6′). MS-MAT (150 °C): m/z (%): 340 (37) [M^+], 324 (18), 189 (26), 172 (18), 152 (100), 138 (23). HRMS calcd for $C_{20}H_{24}N_2O_3$: 340.1787, found 340.1786. $C_{21}H_{26}N_2O_3Cl_2$: C 59.42, H 6.18, N 6.60; found C 58.33, H 6.04, N 6.64.

Crystallographic Measurements: **6c**·CH_2Cl_2: $C_{21}H_{26}Cl_2N_2O_3$, M_r = 425.34, monoclinic, $P2_1$, a = 992.50(8), b = 882.26(10), c = 1249.55(12) pm, β = 105.332(6)°, Z = 2, λ(Mo$_{K\alpha}$) = 71.073 pm, T = –100 °C. Data collection: colourless prism 0.8 × 0.5 × 0.3 mm, Siemens P4 diffractometer, 3027 reflections (2903 unique) to 2θ = 55°. Structure refinement: on F^2 using SHELXL-93 (G. M. Sheldrick, University of Göttingen). H atoms as rigid methyl groups or riding. A weak confirmation of the absolute configuration was provided by the x method (H. D. Flack, *Acta Crystallogr.* **1983**, *A39*, 876–881); x refined to 0.1(2). Final $wR(F^2)$ = 0.198, conventional $R(F)$ = 0.062, for 256 parameters and 246 restraints; S = 1.00, max. $\Delta\rho$ = 1211 e nm^{-3} (in solvent region).

(*E*)-**7**: $C_{20}H_{22}N_2O_2$, M_r = 322.40, orthorhombic, $P2_12_12_1$, a = 778.10(8), b = 1263.1(2), c = 1683.8(2) pm, Z = 4, T = –100 °C. Data collection: colourless prism 0.9 × 0.45 × 0.4 mm, 4187 reflections, 3790 unique, otherwise as above. Structure refinement: As for **6c**, but absolute configuration was assumed. Final $wR(F^2)$ 0.091, conventional $R(F)$ = 0.040, for 220 unrestrained parameters; S = 0.95, max. $\Delta\rho$ = 163 e nm^{-3}.

Further details of the crystal structure investigations may be obtained from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen (Germany) on quoting the depository numbers CSD-404174 and CSD-404175.

Acknowledgments: We thank Ulrike Eggert and Dr. Jens Bartling for exploratory work and the Fonds der Chemischen Industrie for financial support.

Received: September 1, 1995 [F202]

[1] D. C. McHale, *The Biologist* **1986**, *33*, 45.
[2] M. R. Uskokovic, G. Grethe, *The Alkaloids*, Academic Press, New York, **1973**, *Vol. 14*, 181; R. Verpoorte, J. Schripsema, T. van der Leer, *The Alkaloids*, Academic Press, New York, **1988**, *Vol. 34*, 331.
[3] A. D. Malcolm, G. K. David, *Acta Leidensia* **1987**, *55*, 87.
[4] L. Pasteur, *C. R. Acad. Sci.* **1853**, *37*, 110.
[5] R. B. Woodward, W. von E. Doering, *J. Am. Chem. Soc.* **1945**, *67*, 860.
[6] O. Raint, H. B. Kagan, *Tetrahedron Lett.* **1989**, *30*, 7403.
[7] a) H. Wynberg, E. G. J. Staring, *J. Am. Chem. Soc.* **1982**, *104*, 166. b) H. Wynberg, E. G. J. Staring, *J. Org. Chem.* **1985**, *50*, 1977. c) E. G. J. Staring, H. Wynberg, H. Mooriag, *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 374. d) H. Wynberg, *Top. Stereochem.*, Wiley's, New York, **1986**, *16*, 87–129.
[8] H. U. Basler, S. K. Boyer, U. Pittelkow, *Tetrahedron: Asymmetry* **1991**, *2*, 721.
[9] S. Kobayashi, Y. Tsuchiya, T. Mukaiyama, *Chem. Lett.* **1991**, 541.
[10] S. Takeuchi, Y. Ohgo, *Chem. Lett.* **1988**, 403.
[11] A. Sera, K. Takagi, H. Katayama, H. Yamada, K. Matsumoto, *J. Org. Chem.* **1988**, *53*, 1157.
[12] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.
[13] a) F. Follath, U. Ganzinger, E. Schuetz, *Clin. Pharmacokinet.* **1983**, *8*, 63. b) D. E. Drayer, C. E. Cook, M. M. Reidenberg, *Clin. Res.* **1976**, *24*, 623 A. c) D. E. Drayer, D. T. Lowenthal, K. M. Restivo, A. Schwartz, C. E. Cook, M. M. Reidenberg, *Clin. Pharmacol. Ther.* **1978**, *24*, 31. d) H. L. Conn, Jr., R. J. Luchi, *Am. J. Med.* **1964**, *37*, 685. e) D. H. Huffman, C. E. Hignite, C. Tschanz, *Clin. Res.* **1977**, *25*, 553 A. f) N. H. G. Holford, P. E. Coates, T. W. Guentert, S. Riegelmann, L. B. Sheiner, *Br. J. Clin. Pharmacol.* **1981**, *11*, 187. g) C. T. Ueda, J. G. Nickols, *J. Pharm. Sci.* **1980**, *69*, 1400. h) P. U. Nwangwu, T. L. Holcslaw, H. Rosenberg, L. D. Small, S. J. Stohs, *J. Pharm. Pharmacol.* **1979**, *31*, 488.
[14] a) F. I. Carroll, P. Abraham, K. Gaetano, S. W. Mascarella, R. A. Wohl, J. Lind, K. Petzoldt, *J. Chem. Soc. Perkin Trans I* **1991**, 3017. b) T. A. Henry, W. Solomon, E. M. Gibbs, *J. Chem. Soc.* **1935**, 966.
[15] Cf. Z. Dega-Szafran, W. Mitura, *Bull. Acad. Polon. Sci. Ser. Sci. Chim.* **1965**, *13*, 591; J. Suszko, J. Thiel, *Rocz. Chem. Ann. Soc. Chim. Polon.* **1974**, *48*, 1281. The NMR data given by these authors are subject to an offset error (ca. 0.8 ppm).
[16] D. Worsch, F. Vögtle, *Top. Curr. Chem.* **1987**, *140*, 23–41.
[17] Functionalization of the olefin (*Z*)-**4** with migration of the double bond is expected to provide two diastereomeric allylic chlorides **v**. The S_N2' reaction is usually not diastereoselective and proceeds with both *syn* and *anti* orientation of nucleophile and leaving group. See G. Stork, A. F. Kreft, *J. Am. Chem. Soc.* **1977**, *99*, 3850; G. Stork, A. R. Schoofs, *ibid.* **1979**, *101*, 5081; R. M. Magid, *Tetrahedron* **1980**, *36*, 1901–1930.
[18] H. M. R. Hoffmann, *J. Chem. Soc.* **1965**, 6748.
[19] H. C. Kolb, K. B. Sharpless, *Tetrahedron* **1992**, *48*, 10515.

  0947-6539/96/0206-0679 $ 15.00+.25/0