An Enantioselective Entry to Substituted 6-Membered Nitrogen Heterocycles from Chiral Pyridinium Salts via Selective Epoxidation of Tetrahydropyridine Intermediates

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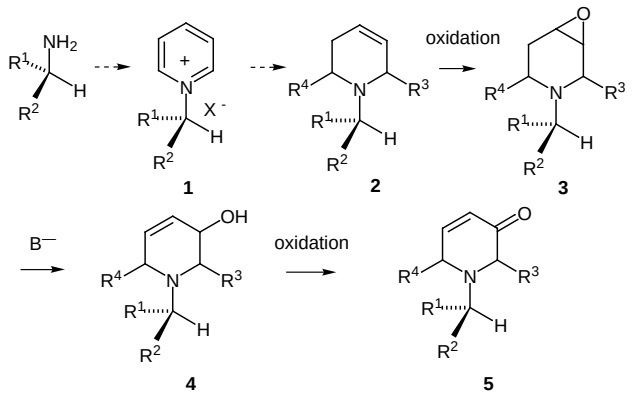
Received 3 August 2000

Abstract: Epoxidation reactions of chiral 2- and 2,6-substituted 1,2,5,6-tetrahydropyridines **6**, **11**, **12** and **21** proceed with good to high stereoselectivity and excellent yields using pertrifluoroacetic acid as reagent. Epoxides such as **15**, **16** and **19** are unstable but they can be deprotonated by LDA to give allylic alcohols such as **28**, **30** or **32**. These alcohols turned out to be potentially useful synthons, whose further oxidation or conversion to enones (**29**, **31**) allows, in principle, introduction of a number of substituents on the piperidine ring. In particular, this is exemplified by a five-steps synthesis, from chiral tetrahydropyridine **6**, of tetrasubstituted piperidine **7** in 26% overall yield.

Key words: alkaloids, chiral auxiliaries, enones, epoxidations, protonations

The control of the enantioselective synthesis of substituted six-membered nitrogen heterocycles has been the subject of much attention due to the importance of this motif in the field of alkaloid synthesis and medicinal chemistry.[1] We have recently introduced[2] a new general approach to these intermediates, which starts from chiral pyridinium salts **1** (Scheme 1), readily obtained using the Zincke procedure. This methodology proceeds via highly reactive dihydropyridine species.

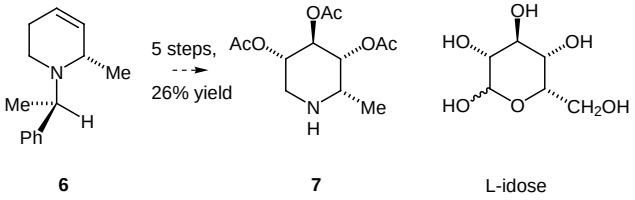


Scheme 1

Reactions of salts **1** with Grignard reagents offer in particular a very short entry to 2-alkyl or 2,6-dialkyl substituted tetrahydropyridines **2**.[3] The presence of a double bond in these heterocycles is of particular interest since it can be potentially used for introduction of further functionalities, thus allowing an enantioselective access to a number of highly substituted piperidines.

In this paper, we now report such an extension of our strategy, which consists of controlled oxidation reactions of these tetrahydropyridines **2** to give epoxides **3** with good to high diastereoselectivity. These epoxides are rather unstable but can be easily converted to useful synthons such as allylic alcohols **4** or enones **5** with complete regioselectivity.

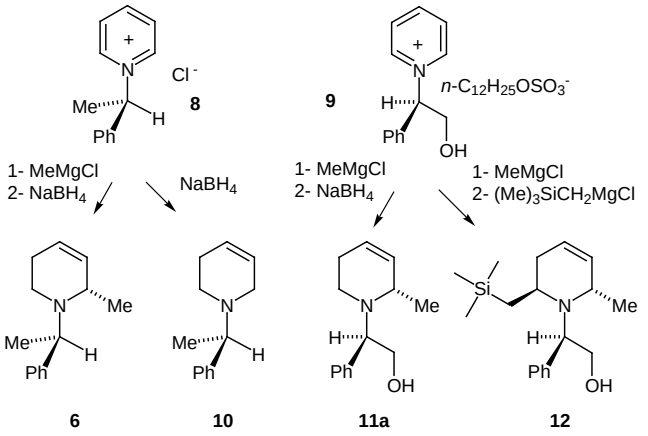
As an example of the application, we also present a short enantioselective synthesis, starting from tetrahydropyridine **6** (Scheme 2), of the highly substituted piperidine **7**, a derivative, which can be considered as an azasugar equivalent of L-idose.[4]



Scheme 2

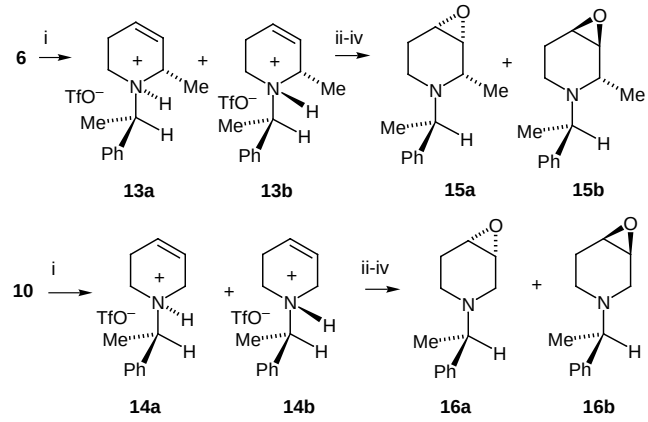
For epoxidation studies, we first prepared, from salts **8** and **9** (Scheme 3), a set of chiral tetrahydropyridines (**6**, **10**, **11a** and **12**) according to our reported procedure.[3a]

After preliminary experiments, pertrifluoroacetic acid was selected as the most convenient epoxidizing agent.[5] Using this procedure, it is necessary to work both on tetrahydropyridine salts as starting materials and to treat the crude reaction mixture with sodium sulfite in order to avoid formation of undesirable *N*-oxides. We first studied reactions of tetrahydropyridines **6** and **10** under these conditions. Interestingly, the temporary nitrogen protection of these derivatives by prior addition of an acid resulted in the formation of two diastereoisomeric ammonium salts (**13a**, **b** for **6** and **14a**, **b** for **10**, Scheme 4). The diastereoisomeric ratio of these salts was easily evaluated by ^{1}H NMR spectroscopy in $CDCl_3$. Thus tetrahydropyridine **6** gave salts **13a** and **13b** in a 80:20 ratio while tetrahydropyridine **10** gave salts **14a** and **14b** with no selectivity



Scheme 3

(50:50 ratio). Epoxidation of the mixture of salts **13** and **14** gave couples of epoxides **15a**/**15b** and **16a**/**16b** in 83:17 and 52:48 ratios, respectively, as measured by GC and GC-MS analysis. Thus, in both cases, the diastereoisomeric ratio of obtained epoxides was found to be practically identical to the diastereoisomeric ratio of ammonium salts.

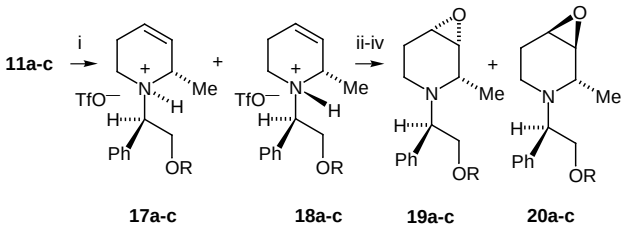


Reagents and conditions: (i) CF_3CO_2H, CH_2Cl_2; (ii) CF_3CO_3H, CH_2Cl_2, 0 °C, 10 min; (iii) Na_2SO_3; (iv) $NaHCO_3$; **15a**/**15b** = 80/20; **16a**/**16b** ≈ 50/50

Scheme 4

The yield of the epoxide mixture was practically quantitative, but separation of each isomer turned to be very difficult due to the instability of these products, which gave mainly isomeric diols after chromatography over silica gel or alumina. Nevertheless, it was possible to isolate a pure sample of epoxide **15a** by chromatography over alumina, albeit in low yield. The relative stereochemistry of this last compound was deduced from X-ray analysis of a further derivative (vide infra) and this allowed unambiguous stereochemical assignments for isomeric epoxides **15a** and **15b**. However, the structures of isomers **16a** and **16b** could not be distinguished.

We next studied, as a second model, epoxidation of tetrahydropyridine **11a** possessing a phenylethanol side chain and its corresponding acetate derivative **11b** or methyl ether **11c** (Scheme 5). The results are summarized in the table in Scheme 5. Yields of unstable diastereoisomeric epoxide mixtures are again practically quantitative. Albeit less evident than for the epoxidation of tetrahydropyridines **6** and **10**, the diastereomeric excess observed for protonated species **17a−c** and **18 a−c** (60−70%) roughly corresponded to that of the formed epoxides **19a−c** and **20a−c** (40−60%). The stereochemistry of the major isomers **19** was again deduced from X-ray analysis of a derivative of **19c** (vide infra).



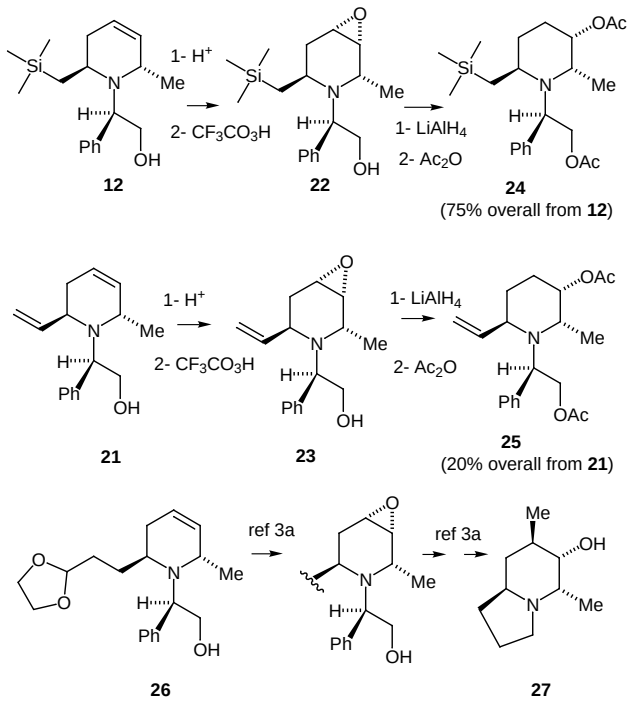
R	salts (% ratio); de	epoxides (%ratio); de
H	**17a** (84), **18a** (16); 68%	**19a** (71), **20a** (29); 42%
$COCH_3$	**17b** (80), **18b** (20); 60%	**19b** (70), **20b** (30); 40%
CH_3	**17c** (85), **18c** (15); 70%	**19c** (80), **20c** (20); 60%

Reagents and conditions: (i) CF_3CO_2H, CH_2Cl_2; (ii) CF_3CO_3H, CH_2Cl_2, 0 °C, 1.5 h; (iii) Na_2SO_3; (iv) $NaHCO_3$

Scheme 5

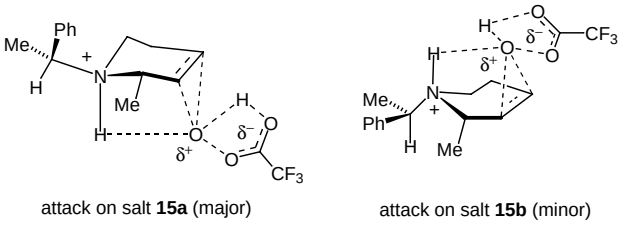
Protonation and epoxidation of tetrahydropyridines **12** and **21** (Scheme 6) afforded practically in each case only one ammonium salt and a single epoxide **22** or **23**, respectively (checked by GC and GC-MS, which showed only traces of minor epoxides). These epoxides were not isolated but reduced and acetylated to give acetates **24** (75% yield from **12**) or **25** (20% yield from **21**). The lower yield observed for the latter derivative **25** is attributed to a competing oxidation of the exocyclic double bond. These results must be completed by our recent report[3a] on the completely selective oxidation of tetrahydropyridine **26**, which gave, using this procedure, a three steps access to indolizidine **27**. Thus, this remarkable epoxidation selectivity observed for 2,6-*trans* dialkyl substituted series appears as a quite general phenomenon. It is also closely similar to the excellent selectivity also observed for the epoxidation of a related quinolizidine.[5,6]

The relationship between the observed diastereomeric excess of ammonium salts and epoxides is likely to be interpreted as a directing effect of the ammonium proton, which also activates the peracid. Such a mechanism is depicted in Scheme 7 for the epoxidation of salts **15**. Albeit this interpretation has to be taken with care, it is however



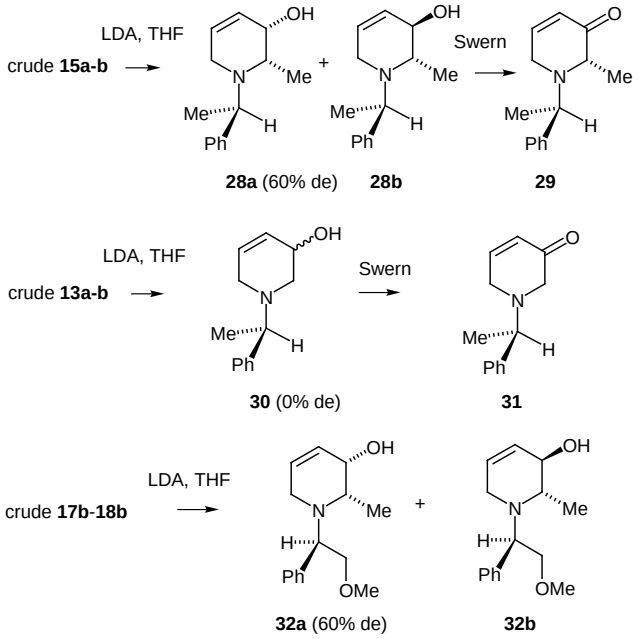
Scheme 6

in good agreement with the recent observation of such directing effects during the epoxidation of allylic alkenylammonium salts.[7,8] As a consequence, it is reasonable to deduce the absolute stereochemistry of the main ammonium salt, formed by treatment of the tetrahydropyridines with acids, from the stereochemistry of the main obtained epoxide. Such an assumption was used for stereochemical assignments of salts **13a** and **17a**–**c**.



Scheme 7

As we already noticed, all epoxides obtained from our tetrahydropyridines were too unstable to be isolated (ring opening to give diols). Accordingly, we used the crude mixture of these derivatives for further transformations. In particular, it was found that treatment with LDA gave potentially useful new allylic alcohols in good yields (Scheme 8). Thus, under these conditions a crude mixture of epoxides **15a**, **b** gave derivatives **28a** and **28b**, respectively, which were separated over alumina. Major alcohol **28a** was thus obtained as a crystalline product in 52% overall yield from tetrahydropyridine **6**. Swern oxidation of the crude mixture of alcohols **28a**, **b** gave a single enone **29** in quantitative yield. The same sequence applied to epoxides **13a**, **b** afforded a 50:50 mixture of inseparable alcohols **30**, which, after oxidation gave a single new chiral enone **31**. Methoxy derivative **32a** was obtained as crystals (47% yield) suitable for an X-ray analysis.[9] The structure of this product is represented in Figure 1. This result allowed us to determine the relative stereochemistry of the major epoxides obtained in these series (see Scheme 5). In addition, the coupling constant of H-2 and H-3 ($J_{H2\text{-}H3}$ deduced from ^{1}H NMR spectra, see experimental) is between 4.2 Hz and 5.3 Hz for major allylic alcohols.



Scheme 8

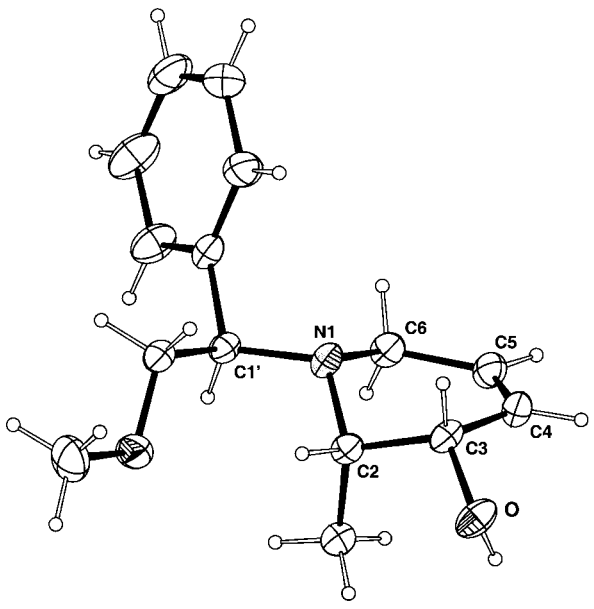
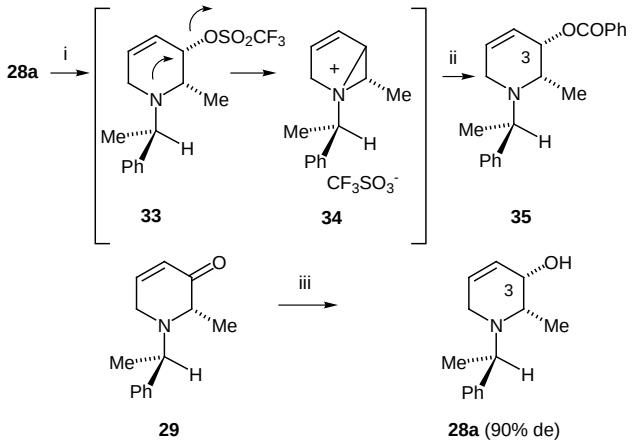


Figure 1 X-Ray structure of derivative **32a**

We also briefly investigated the conditions in which inversion of configuration of alcohol at position 3 could be accomplished, using derivative **28a** as a model (Scheme 9). In our hands, this transformation turned to be unsuccessful. For example, reaction with triflic anhydride in the presence of 2,6-di-*tert*-butyl pyridine[10] in CH_2Cl_2, followed by addition of one equivalent of sodium benzoate, resulted in formation of benzoic ester **35** with complete retention of configuration at C-3. Ester saponification of **35** gave back only alcohol **28a**. This result is likely to be interpreted as a double inversion process involving intermediate formation of triflate **33** and aziridinium **34**.[11] Reduction of enone **29** was also unsuccessful, giving again alcohol **28a** with an excellent selectivity.

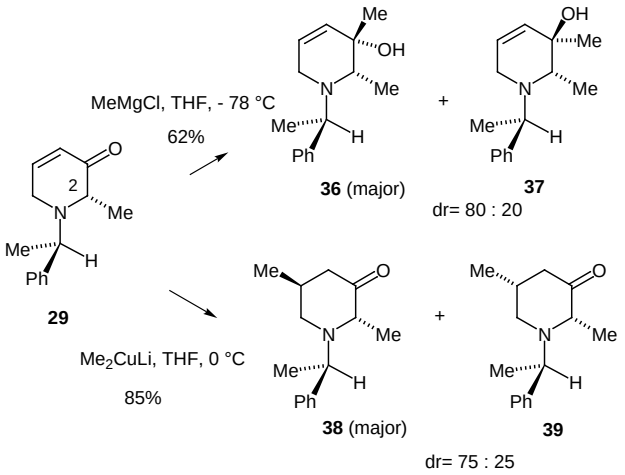


Reagents and conditions: (i) Triflic anhydride, 2,6-di-*tert*-butyl pyridine, $CHCl_3$; (ii) $PhCO_2Na$; (iii) $LiAlH_4$, THF or $NaBH_4$, MeOH

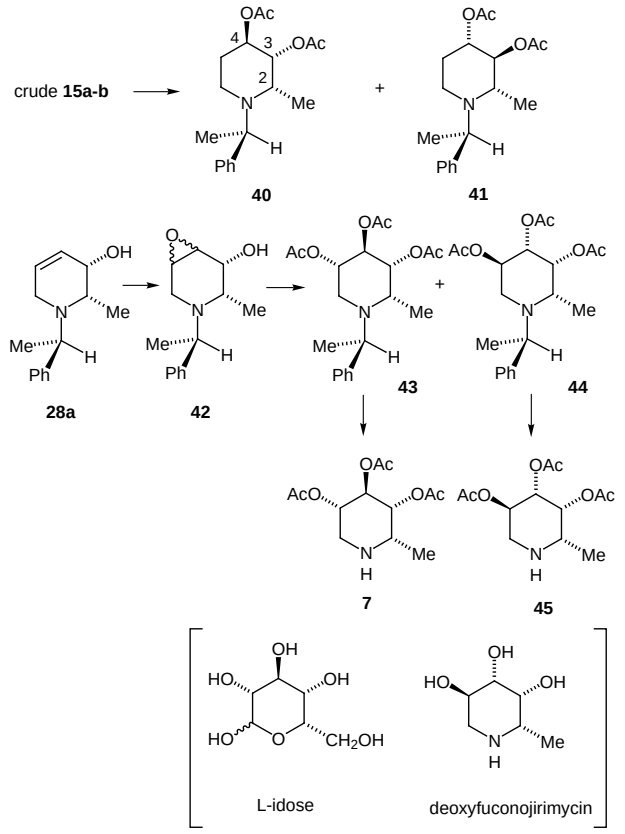
Scheme 9

Enones such as **29** are potentially useful synthons for introduction of substituents on the ring by formation of new carbon-carbon bonds. Albeit we did not study this aspect in details, some preliminary results are summarized in Scheme 10. As expected, reaction of enone **29** with methylmagnesium chloride gave two alkylated alcohols **36** and **37**, while the corresponding organocopper reagent gave two ketones **38** and **39**. The regioselectivity is excellent and the diastereomeric excess is appreciable (60% and 50%, respectively). Attribution of reaction stereochemistry is only tentative in this case. We assumed that the preferred attack of the organometallic reagent proceeded on the face opposite to that of the methyl group in position 2 by analogy with the hydride reduction of ketone **29** (see Scheme 9).

We finally turned our attention toward the synthesis of polyhydroxylated piperidines (Scheme 11). Ring opening of a crude mixture of epoxides **15a**, **b** in refluxing acetic acid, followed by acetylation, gave a mixture of two *trans*-diacetates **40** and **41** in 67% yield and a 60:40 ratio. Stereochemistry of these products was assigned on the basis of ^{1}H NMR coupling constants observed for protons 2,



Scheme 10



Scheme 11

3 and 4 ($J_{H2\text{-}H3}$ = 4.8 Hz and $J_{H3\text{-}H4}$ = 10.0 Hz for **40**; $J_{H2\text{-}H3}$ = 8.5 Hz and $J_{H3\text{-}H4}$ = 8.7 Hz for **41**).

Trifluoroperacetic acid epoxidation of allylic alcohol **28a** gave a mixture of diasteoisomeric epoxides **42** in a 68:32 ratio (undetermined stereochemistry). Treatment of these epoxides with acetic acid followed by acetylation gave two triacetates **43** and **44** in approximately the same ratio. These derivatives were separated by chromatography and

recovered in 59% and 29% yield, respectively, from **28a**. The stereochemistry of triacetate **43** was deduced from an X-ray analysis, which is depicted in Figure 2.[12]

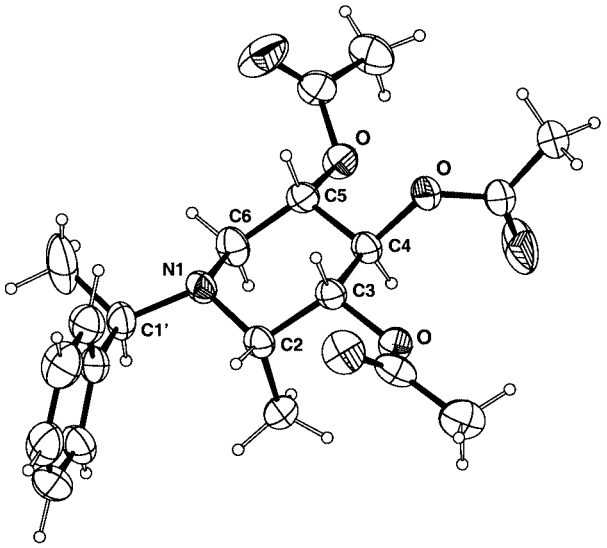


Figure 2 X-ray structure of derivative **43**

This X-ray analysis allowed us to secure stereochemical assignments for epoxide **15a** (see Scheme 4). It also allowed us to attribute the structure **44** to the minor triacetate, since the ring opening of the epoxides **42** normally proceeds in a *trans* manner. Finally, catalytic hydrogenation of **43** and **44** afforded piperidine **7**, which can be considered as an azasugar equivalent of L-idose, and piperidine **45**, respectively, an acetate protected derivative of the glucosidase inhibitor deoxyfuconojirimycin.

We hope that the reported results will be useful in understanding the stereochemical aspects concerning the epoxidation of *N*-alkyl substituted tetrahydropyridines. These new results also extend the synthetic possibilities offered by our methodological approach, starting from new chiral pyridinium salts. If the observed selectivities are not always perfect, this is compensated by very short syntheses of rather complex products, starting from easily available intermediates and using simple procedures.

Experiments involving organometallics were carried out in dried glassware under a positive pressure of dry N_2. THF and Et_2O were distilled from sodium benzophenone ketyl. Methyl magnesium chloride, vinyl magnesium chloride and methyllithium were purchased from Aldrich. Column chromatography: silica gel 60, 0.070−0.200 (SDS) or aluminiumoxide 90, 0.063−0.200 (Merck). NMR spectra were recorded on a Bruker AC-200, AC-AC-250 or AC-300. Mass spectra were recorded on a AEI MS-50 (EI) or AEI MS-9 (CI) spectrometer. Optical rotations were measured on a Perkin−Elmer 14 at 20 °C.

(1*R*,1*R*,2*S*,6*S*)-(+)-2-Methyl-3-(1-phenylethyl)-7-oxa-3-azabicyclo[4.1.0]heptane (15a)

Trifluoroacetic anhydride (1.2 mL, 8.6 mmol) was added dropwise, at 0 °C, to a stirred solution of 50% hydrogen peroxide (0.25 mL, 4.3 mmol) in CH_2Cl_2 (20 mL). After further stirring for 1.5 h at 0 °C, was added a mixture of salts **13a** and **13b** (dr = 80:20)**,** obtained from tetrahydropyridine **6** (361 mg, 1.8 mmol) and trifluoroacetic acid (0.34 mL, 4.5 mmol) in dry CH_2Cl_2 (3 mL). The ice bath was removed and the reaction mixture was stirred for 10 min. Sat. Na_2SO_3 was then added and the organic layer separated, washed with $NaHCO_3$ and H_2O, dried (Na_2SO_4), and concentrated in vacuo to provide a mixture of isomeric epoxides **15a** and **15b** (370 mg, 95% yield, dr = 83:17) as a colorless oil. Due to their instability (ring opening giving diols) the mixture of epoxides was used without further purification. A small sample of each isomer can be isolated by chromatography over alumina albeit in low yield.

Major Isomer 15a

$[\alpha]_D$ +40° (*c* 1.33, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.30 (m, 5H, ArH), 3.84 (q, 1H, *J* = 6.7 Hz), 3.27 (m, 1H), 3.04 (m, 2H), 2.62 (ddd, 1H, *J* = 12.5, 7.7, 4.9 Hz), 2.24 (ddd, 1H, *J* = 12.5, 5.2, 5.2 Hz), 1.90 (m, 2H), 1.34 (d, 3H, *J* = 6.7 Hz), 1.20 (d, 3H, *J* = 6.2 Hz).

^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 143.2, 128.2, 127.6, 126.9, 57.5, 56.2, 52.3, 49.6, 37.4, 25.2, 21.6, 12.8.

MS (EI): *m/z* = 217 (M^+, 15), 202 (75), 105 (100).

HRMS (EI): *m/z* calcd for $C_{14}H_{19}NO$ (M^+): 217.1467. Found: 217.1477.

Minor Isomer 15b

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.27 (m, 5H), 4.04 (q, 1H, *J* = 7.0 Hz), 3.21 (m, 1H), 2.97 (q, 1H, *J* = 6.8 Hz), 2.88 (d, 1H, *J* = 4.2 Hz), 2.62 (m, 1H), 2.21 (m, 1H), 1.80−2.08 (m, 2H), 1.40 (d, 3H, *J* = 7.0 Hz), 1.30 (d, 3H, *J* = 6.8 Hz).

^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 141.0, 128.0, 127.5, 126.9, 57.8, 56.7, 51.1, 50.2, 37.1, 25.7, 20.0, 17.2.

MS (EI): *m/z* = 217 (M^+, 15), 202 (90), 105 (100).

(1*R*,2*S*,2*R*,6*S*)-2-(2-Methyl-7-oxa-3-azabicyclo[4.1.0]hept-3-yl)-2-phenylethanol (19a)

Trifluoroacetic anhydride (2.17 mL, 15 mmol) was added dropwise to a solution of 50% hydrogen peroxide (0.44 mL, 7.5 mmol) in CH_2Cl_2 (25 mL) at 0 °C. After stirring at 0 °C for 1.5 h, a solution of tetrahydropyridine **11a** (332 mg, 1.53 mmol) and trifluoroacetic acid (0.29 mL, 3.82 mmol) in dry CH_2Cl_2 (3 mL) was added dropwise. The ice bath was removed and the mixture was stirred for 0.5 h. The reaction mixture was then extracted as for epoxides **15a**, **b** to give isomeric epoxides **19a** and **20a** (340 mg, 95% yield, dr = 71:29) as a colorless oil.

MS (CI): m/z = 234 $[M+H]^+$ (100), 216 $[MH-H_2O]^+$ (18).

HRMS (CI): *m/z* calcd for $C_{14}H_{20}NO_2$ (MH^+): 234.1494. Found: 234.1491.

NMR data for each epoxide can be deduced from the NMR spectra of the crude mixture.

Major Epoxide 19a

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.22−7.38 (m, 5H), 3.71−3.83 (m, 3H), 3.43 (m, 1H), 3.27 (m, 1H), 3.13 (t, 1H, *J* = 4.5 Hz), 2.68 (ddd, 1H, *J* = 13.5, 11.5, 3.9 Hz), 2.48 (m, 1H), 1.93 (tdd, 1H, *J* = 14.7, 5.3, 2 Hz), 1.79 (m, 1H), 1.14 (d, 3H, *J* = 6.7 Hz).

^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 141.0, 128.6, 128.3, 127.6, 66.1, 63.3, 54.9, 52.0, 48.0, 36.9, 23.8, 12.6.

Minor Epoxide 20a

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.22−7.38 (m, 5H), 3.96 (dd, 1H, *J* = 6.9, 5.4 Hz), 3.78 (m, 2H), 3.43 (m, 1H), 3.30 (m, 1H), 2.93 (br

d, 1H, *J* = 4.1 Hz), 2.60 (m, 2H), 1.98 (m, 1H), 1.78 (m, 1H), 1.18 (d, 3H, *J* = 6.8 Hz).

^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 140.5, 128.3, 128.2, 127.3, 66.2, 62.4, 55.9, 51.0, 50.8 (2C), 36.6, 23.8, 15.0 (2C).

(1*R*,1*R*,2*S*,6*S*)-3-(2-Acetoxy-1-phenylethyl)-2-methyl-7-oxa-3-azabicyclo[4.1.0]heptane (19b)

Use of the above epoxidation procedure (preparation of epoxides **19a**, **20a**) starting from tetrahydropyridine **11b** gave a mixture of isomeric epoxides **19b** and **20b** (80 mg, 95% yield, dr = 71:29) as a colorless oil:

MS (EI): *m/z* = 202 ($M^+-C_3H_5O_2$, 100).

MS (CI): *m/z* = 276 $[M+H]^+$ (100), 260 $[MH-CH_4]^+$ (10), 216 $[MH-C_2H_4O_2]^+$ (30), 94 (60).

HRMS (CI): Calcd for $C_{16}H_{22}NO_3$ (MH^+): 276.1600. Found: 276.1603.

NMR data for each epoxide can be deduced from the NMR spectra of the crude mixture.

Major Epoxide 19b

IR (neat): ν = 2978, 2939, 2844, 1740, 1678, 1492, 1451, 1425, 1382, 1234, 1042 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.20−7.40 (m, 5H), 4.42 (dd, 1H, *J* = 11.2, 5.1 Hz), 4.20 (dd, 1H, *J* = 11.2, 6.4 Hz), 3.93 (dd, 1H, *J* = 6.4, 5.1 Hz), 3.32 (m, 2H), 3.14 (t, 1H, *J* = 4.4 Hz), 2.62 (ddd, 1H, *J* = 14.5, 10.8, 3.8 Hz), 2.40 (m, 1H), 2.00 (m, 1H), 1.97 (s, 3H), 1.75 (m, 1H), 1.20 (d, 3H, *J* = 6.7 Hz).

^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 170.8, 141.0, 128.5, 128.2, 127.6, 65.7, 62.4, 54.9, 52.1, 49.4, 37.3, 23.4, 20.9, 12.6 (2C).

Minor Epoxide 20b

IR (neat): ν = 2978, 2939, 2844, 1740, 1678, 1492, 1451, 1425, 1382, 1234, 1042 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.20−7.40 (m, 5H), 4.51 (dd, 1H, *J* = 11.5, 5.9 Hz), 4.38 (dd, 1H, *J* = 11.5, 6.4 Hz), 4.21 (dd, 1H, *J* = 6.4, 5.9 Hz), 3.46 (q, 1H, *J* = 6.8 Hz), 3.27 (m, 1H), 2.95 (d, 1H, *J* = 4.1 Hz), 2.55 (ddd, 1H, *J* = 12.3, 8.4, 4.1 Hz), 2.38 (dt, 1H, *J* = 12.3, 5.3 Hz), 2.02 (m, 1H), 2.02 (s, 3H), 1.72 (m, 1H), 1.29 (d, 3H, *J* = 6.8 Hz).

^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 171.0, 140.6, 128.3, 127.9, 127.2, 63.6, 60.4, 56.4, 51.2, 50.5 (2C), 37.2, 25.0, 21.2, 17.6.

MS (EI): *m/z* = 202 ($M^+-C_3H_5O_2$, 100).

(1*R*,1*R*,2*S*,6*S*)-3-(2-Methoxy-1-phenylethyl)-2-methyl-7-oxa-3-azabicyclo[4.1.0]heptane (19c)

Use of the above epoxidation procedure (preparation of epoxides **19a**, **20a**) starting from tetrahydropyridine **11c** (231 mg, 1 mmol) gave a mixture of isomeric epoxides **19c** and **20c** (240 mg, 97% yield, dr = 80:20) as a colorless oil:

MS (EI): *m/z* = 202 ($M^+-C_2H_5O$, 100).

MS (CI): *m/z* = 248 $[M+H]^+$ (100), 216 $[MH-CH_3OH]^+$ (12).

HRMS (CI): Calcd for $C_{15}H_{22}NO_2$ (MH^+): 248.1650. Found: 248.1638.

NMR data for each epoxide can be deduced from the NMR spectra of the crude mixture.

Major Isomer 19c

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20−7.40 (m, 5H), 3.84 (t, 1H, *J* = 5.0 Hz), 3.62 (dd, 1H, *J* = 10.0, 5.0 Hz), 3.57 (dd, 1H, *J* = 10.0, 5.0 Hz), 3.31 (m, 2H), 3.25 (s, 3H), 3.11 (t, 1H, *J* = 4.4 Hz), 2.61 (ddd, 1H, *J* = 13.4, 10.9, 3.7 Hz), 2.43 (m, 1H), 1.98 (m, 1H), 1.70 (m, 1H), 1.15 (d, 3H, *J* = 6.7 Hz).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 142.3, 128.3, 128.1, 127.2, 75.3, 63.6, 59.1, 54.9, 52.2, 49.3, 37.2, 23.2, 12.9.

Minor Isomer 20c

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20−7.40 (m, 5H), 4.09 (dd, 1H, *J* = 6.3, 5.2 Hz), 3.75 (dd, 1H, *J* = 9.8, 5.2 Hz), 3.68 (dd, 1H, *J* = 9.8, 6.3 Hz), 3.45 (q, 1H, *J* = 7.0 Hz), 3.34 (s, 3H), 3.31 (m, 1H), 2.94 (d, 1H, *J* = 4.2 Hz), 2.53 (ddd, 1H, *J* = 12.2, 8.7, 4 Hz), 2.36 (dt, 1H, *J* = 12.2, 5.2 Hz), 1.92 (m, 1H), 1.72 (m, 1H), 1.28 (d, 3H, *J* = 7 Hz).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 141.7, 128.1, 127.9, 126.8, 72.5, 61.3, 58.9, 56.6, 51.2, 50.3 (2C), 37.2, 25.2, 17.9 (2C).

(1*R*,2*R*,5*S*,6*S*)-5-Acetoxy-6-methyl-2-trimethylsilanylmethyl-1-(1-phenyl-2-ethanolacetate)-piperidine (24)

Trifluoroacetic anhydride (0.48 mL, 3.4 mmol) was added dropwise to a solution of 50% hydrogen peroxide (0.1 mL, 1.7 mmol) in CH_2Cl_2 (6 mL) at 0 °C. After stirring at 0 °C for 1.5 h, a solution of tetrahydropyridine **12** (102 mg, 0.34 mmol), trifluoroacetic acid (0.06 mL, 0.84 mmol), in CH_2Cl_2 (3 mL) was added dropwise. The ice bath was removed and the mixture was stirred for 1.8 h. The reaction was then extracted as for epoxides **15a**, **b** to give practically pure epoxide **22** in nearly quantitative yield. This unstable crude epoxide was dissolved in THF, an excess of $LiAlH_4$ was added, and the resulting mixture refluxed for 3 h. After cooling, an excess of EtOAc was carefully added, followed by MeOH. Filtration over Celite using MeOH as eluent gave a crude alcohol, which, after removal of solvent under reduced pressure, was treated overnight with Ac_2O (0.5 mL) and pyridine (1 mL). After evaporation, the residue was chromatographed over alumina using a mixture of EtOAc/heptane. Piperidine **24** (103 mg, 0.25 mmol, 75% yield) was isolated as a colorless oil:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20−7.35 (m, 5H), 4.55 (t, 1H, *J* = 7.2 Hz), 4.40 (m, 3H), 3.15 (m, 2H), 1.96 (s, 3H), 1.90 (s, 3H), 1.45−1.70 (m, 3H), 1.15 (m, 1H), 1.02 (d, 3H, *J* = 6.7 Hz), 0.90 (dd, 1H, *J* = 13.8, 3.4 Hz), 0.80 (dd, 1H, *J* = 13.8, 11.3 Hz), 0.00 (s, 9H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 171.0, 170.4, 140.9, 128.3, 128.1, 127.0, 72.4, 63.6, 56.7, 49.1, 48.5, 31.7, 25.0, 21.4, 20.8, 12.2, −0.37.

MS (CI): *m/z* = 406 $[M+H]^+$ (58), 346 $[M-OAc]^+$ (100).

HRMS (CI): *m/z* calcd for $C_{22}H_{36}NO_4Si$ (MH^+): 406.2414. Found: 406.2389.

(1*R*,2*R*,5*S*,6*S*)-5-Acetoxy-6-methyl-2-vinyl-1-(1-phenyl-2-ethanol-acetate)-piperidine (25)

Tetrahydropyridine **21** (170 mg, 0.7 mmol) was treated using the same procedure as for preparation of piperidine **24**, to give piperidine **25** (48 mg, 0.14 mmol, 20% yield) as a colorless oil.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.25−7.45 (m, 5H), 5.88 (ddd, 1H, *J* = 20.0, 10.0, 2.75 Hz), 5.25 (dt, 1H, *J* = 20.0, 2.0 Hz), 5.12 (dd, 1H, *J* = 10.0 Hz, 2.0 Hz), 4.45−4.55 (m, 4H), 3.55 (dt, 1H, *J* = 8.75, 2.75 Hz), 3.10 (dq, 1H, *J* = 6.5, 4.5 Hz), 2.00 (s, 3H), 1.98 (s, 3H), 1.60−1.75 (m, 4H), 1.08 (d, 3H, *J* = 6.7 Hz).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 140.6, 128.4, 127.2, 116.5, 72.9, 62.7, 59.7, 56.0, 49.2, 31.7, 24.3, 21.0 (2C), 11.2.

MS (EI): *m/z* = 345 (M^+, 2) 272 (100).

(1*R*,2*S*,3*S*)-(+)-2-Methyl-1-(1-phenylethyl)-1,2,3,6-tetrahydropyridin-3-ol (28a)

To a solution of diisopropylamine (1.48 mL, 10.58 mmol) in dry THF (5 mL) at 0 °C under Ar was added *n*-BuLi (1.6 M in hexane,

6.6 mL, 10.58 mmol) and the resulting mixture was stirred for 15 min at 0 °C. To the above solution was then introduced slowly a mixture of epoxides **15a** and **15b** (919 mg, 4.23 mmol) in dry THF (6 mL) and the ice bath was removed. After 1.5 h of stirring, the reaction was quenched with sat. NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by chromatography over alumina with heptane/EtOAc (94:6 to 86:14) to give major alcohol **28a** (472 mg, 52% yield) as a white solid and alcohol **28b** (80 mg, 9% yield) as a yellow oil.

Major Isomer 28a

White crystals of **28a** were obtained from dry Et_2O/heptane: mp 102 °C; $[\alpha]_D$ +94° (*c* 1.06, $CHCl_3$).

IR ($CDCl_3$): ν = 3606, 2983, 2938, 2790, 1457, 1375 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.20−7.40 (m, 5H), 5.79 (dddd, 1H, *J* = 10, 4.1, 2.1, 2.1 Hz), 5.60 (dm, 1H, *J* = 10.0 Hz), 4.31 (m, 1H), 3.75 (q, 1H, *J* = 6.6 Hz), 3.35 (dm, 1H, *J* = 17.3 Hz), 2.97 (qd, 1H, *J* = 6.6, 5.3 Hz), 2.94 (dm, 1H, *J* = 17.3 Hz), 1.86 (m), 1.35 (d, 3H; *J* = 6.6 Hz), 0.84 (d, 3H, *J* = 6.6 Hz).

^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 145.3, 128.6, 128.0, 127.3, 127.1 (3C), 68.6, 60.4, 52.7, 44.7, 21.9, 4.4.

MS (EI): *m/z* = 217 (M^+, 8), 148 (30), 105 (100), 44 (90).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.37; H, 8.81; N, 6.45. Found: C, 77.34; H, 8.66; N, 6.49.

Minor Isomer 28b

$[\alpha]_D$ −17° (*c* 1.39, $CHCl_3$).

IR (neat): ν = 3677, 2975, 2940, 1445, 1395, 1368 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.28 (m, 5H), 5.87 (m, 2H), 3.62 (q, 1H, *J* = 6.6 Hz), 3.52 (m, 1H), 3.48 (dd, 1H, *J* = 17.0, 2.3 Hz), 2.93 (d, 1H, *J* = 17.0 Hz), 2.83 (dq, 1H, *J* = 6.7, 2 Hz), 2.54 (br d, 1H, *J* = 10.6 Hz), 1.36 (d, 3H, *J* = 6.6 Hz), 0.74 (d, 3H, *J* = 6.7 Hz).

^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 145.0 (C arom.), 129.1, 128.6, 127.2, 126.0, 68.8, 60.9, 54.4, 44.9, 21.9, 7.0.

MS (EI): *m/z* = 217 (M^+, 25), 148 (42), 105 (100), 44 (22).

HRMS (EI): *m/z* calcd for $C_{14}H_{19}NO$ (M^+): 217.1467. Found: 217.1456.

(1*R*,2*S*)-(+)-2-Methyl-1-(1-phenylethyl)-1,6-dihydro-2*H*-pyridin-3-one (29)

To a solution of oxalyl chloride (0.135 mL, 1.58 mmol) in dry CH_2Cl_2 (2.4 mL) was added dropwise at −78 °C a solution of DMSO (0.246 mL, 3.47 mmol) in dry CH_2Cl_2 (3 mL) and the mixture was stirred at this temperature for 10 min. To the above solution was added dropwise a mixture of allylic alcohols **28a** and **28b** (172 mg, 0.79 mmol) in dry CH_2Cl_2 (1.5 mL) and the mixture was stirred at −78 °C for 15 min. Et_3N (0.75 mL, 10.4 mmol) was then added and the solution allowed to warm to r.t. Distilled H_2O (8 mL) was added and the reaction stirred for 10 min. CH_2Cl_2 was added and the organic layer washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo to give pure ketone **29** (166.6 mg, 98% yield). White crystals of **29** were obtained from dry pentane: mp 61 °C; $[\alpha]_D$ +138° (*c* 1.37, $CHCl_3$).

IR ($CDCl_3$): ν = 1669 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 5H), 6.98 (ddd, 1H, *J* = 10.0, 4.9, 2 Hz), 6.04 (ddd, 1H, *J* = 10.0, 2.1, 2.1 Hz), 3.82 (q, 1H, *J* = 6.6 Hz), 3.65 (ddd, 1H, *J* = 19.9, 4.9, 1.6 Hz), 3.41 (ddd, 1H, *J* = 19.9, 2.4, 2.4 Hz), 3.38 (q, 1H, *J* = 7.0 Hz), 1.39 (d, 3H, *J* = 6.6 Hz), 1.06 (d, 3H, *J* = 7.0 Hz).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 199.7, 147.7, 143.9, 128.7, 127.4, 127.2, 126.3, 60.0, 59.7, 44.4, 21.7, 9.2.

MS (EI): *m/z* = 215 (M^+, 10), 148 (13), 105 (100).

MS (CI): *m/z* = 216 (MH^+).

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.95; H, 7.84; N, 6.49.

(1*R*)-1-(1-Phenylethyl)-1,6-dihydro-2*H*-pyridin-3-one (31)

Obtained from a mixture epoxides **13a**, **b** using the above procedure:

$[\alpha]_D$ 0° (*c* 0.90, $CHCl_3$).

IR (neat): ν = 1689 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 5H), 7.01 (ddd, 1H, *J* = 9.9, 3.8, 3.5 Hz), 6.10 (ddd, 1H, *J* = 9.9, 2.0, 2.0 Hz), 3.59 (q, 1H, *J* = 6.7 Hz), 3.25 (m, 2H), 3.17 (m, 2H), 1.42 (d, 3H, *J* = 6.7 Hz).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 196.3, 149.1, 142.0, 128.5, 127.6, 127.4, 63.8, 58.7, 49.6, 19.1.

MS (EI): *m/z* = 201 (M^+, 52), 186 (50), 134 (18), 105 (100), 68 (44).

HRMS (EI): *m/z* calcd for $C_{13}H_{15}NO$ (M^+): 201.1153. Found: 201.1161.

(1*R*,2*S*,3*S*)-(+)-1-(2-Methoxy-1-phenylethyl)-2-methyl-1,2,3,6-tetrahydropyridin-3-ol (32a)

The mixture of epoxides **17b** and **18b** (189 mg, 0.76 mmol) was subjected to the same procedure as for the synthesis of allylic alcohol **28a** and **28b**. The residue was purified by chromatography over alumina with heptane/EtOAc (94:6 to 86:14) to give major alcohol **32a** (89 mg, 47% yield) as a white solid, and minor alcohol **32b** (16 mg, 8.5% yield) as a yellow oil.

Major Isomer 32a

White crystals of **32a** were obtained from dry Et_2O/heptane: mp 82 °C; $[\alpha]_D$ +42° (*c* 1.95, $CHCl_3$).

IR ($CDCl_3$): ν = 3594, 2990, 2927, 2882, 1452, 1381 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.20−7.40 (m, 5H), 5.09−5.23 (m, 2H), 4.21 (m, 1H), 4.00 (dd, 1H, *J* = 6.0, 5.6 Hz), 3.78 (dd, 1H, *J* = 9.9, 6.0 Hz), 3.67 (dd, 1H, *J* = 9.9, 5.6 Hz), 3.39 (qd, 1H, *J* = 6.5, 4.2 Hz), 3.33 (s, 3H), 2.78−2.94 (m, 2H), 1.90 (m, 1H), 1.13 (d, 3H, *J* = 6.5 Hz).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 141.4, 128.4, 128.1, 128.0, 127.2 (3C), 73.7, 69.0, 62.7, 59.1, 54.4, 46.0, 9.4.

MS (CI): *m/z* = 248 $[M+H]^+$ (100), 230 $[MH-H_2O]^+$ (60), 216 $[MH-CH_3OH]^+$ (15).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.75; H, 8.62; N, 5.66.

Minor Isomer 32b

Mp 74 °C; $[\alpha]_D$ −63° (*c* 0.88, $CHCl_3$).

IR (neat): ν = 3675, 2991, 2932, 2876, 1450, 1401, 1372 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.20−7.36 (m, 5H), 5.85 (m, 1H), 5.68 (ddd, 1H, *J* = 9.8, 4.1, 2.2 Hz), 3.73 (m, 3H), 3.52 (dd, 1H, *J* = 12.9, 6.9 Hz), 3.47 (qd, 1H, *J* = 6.6, 2.3 Hz), 3.29 (s, 3H), 2.83 (ddd, 1H, *J* = 18, 4.1, 2.1 Hz), 2.73 (m, 1H), 0.95 (d, 3H, *J* = 6.6 Hz).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 141.6, 129.2, 128.6, 128.0, 127.6, 125.8 (3C), 76.0, 68.8, 65.9, 59.0, 55.6, 46.0, 8.4.

MS (CI): *m/z* = 248 $[M+H]^+$ (100), 230 $[MH-H_2O]^+$ (7), 216 $[MH-CH_3OH]^+$ (10).

HRMS (CI): *m/z* calcd for $C_{15}H_{22}NO_2$ (MH^+): 248.1651. Found: 248.1660.

(1*R*,2*S*,3*S*)-(+)-2,3-Dimethyl-1-(1-phenylethyl)-1,2,3,6-tetrahydropyridin-3-ol (36)

Ketone **29** (151 mg, 0.70 mmol) was dissolved in dry THF (4 mL) and the solution was cooled to −78 °C under Ar. To the above solution was then introduced dropwise a 2 M commercial solution of methylmagnesium chloride (1.2 mL, 2.1 mmol). The reaction was stirred for 20 min at −78 °C, warmed to r.t. and stirred at this temperature for 1.5 h. The reaction was quenched with sat. NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give a mixture of allylic alcohols **36** and **37** in a 79:21 ratio. The residue was purified by chromatography over alumina with heptane/EtOAc (100:0 to 90:10) to furnish major alcohol **36** (73 mg, 45% yield) and minor alcohol **37** (14 mg, 8.5% yield) as yellow oils.

Major Isomer 36

$[\alpha]_D$ +53° (*c* 0.48, $CHCl_3$).

IR (neat) ν = 3606, 2976, 2936, 1454, 1373 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.28 (m, 5H), 5.67 (ddd, 1H, *J* = 10.0, 4.0, 2.2 Hz), 5.51 (dm, 1H, *J* = 10.0 Hz), 3.69 (q, 1H, *J* = 6.6 Hz), 3.34 (ddd, 1H, *J* = 17.2, 4.0, 2.0 Hz), 2.89 (ddd, 1H, *J* = 17.2, 2.3, 2.3 Hz), 2.63 (qd, 1H, *J* = 6.5, 0.9 Hz), 1,50 (br m, 1H), 1.33 (d, 3H, *J* = 6.6 Hz), 1.31 (s, 3H), 0.84 (d, 3H, *J* = 6.5 Hz).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 143.9, 131.8, 128.4, 127.6, 127.0, 125.3, 71.9, 60.6, 57.8, 44.8, 28.3, 22.0, 4.9.

MS (EI): *m/z* = 231 (M^+, 19), 148 (100), 105 (100), 84 (80).

HRMS (EI): *m/z* calcd for $C_{15}H_{21}NO$ (M^+): 231.1623. Found: 231.1621.

Minor Isomer 37

$[\alpha]_D$ +9° (*c* 2.97, $CHCl_3$).

IR (neat) ν = 3675, 2982, 2939, 1645, 1454, 1376 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.28 (m, 5H), 5.73 (ddd, 1H, *J* = 9.7, 4.2, 1.8 Hz), 5.63 (dm, 1H, *J* = 9.7 Hz), 3.62 (q, 1H, *J* = 6.5 Hz), 3.48 (ddd, 1H, *J* = 17.5, 4.2, 1.9 Hz), 3.41 (br m, 1H), 2.87 (dm, 1H, *J* = 17.5 Hz), 2.57 (q, 1H, *J* = 6.7 Hz), 1.37 (d, 3H, *J* = 6.5 Hz), 1.01 (s, 3H), 0.75 (d, 3H, *J* = 6.7 Hz).

^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 144.8, 131.4, 128.7, 127.3, 126.7, 69.9, 60.9, 58.7, 44.8, 23.2, 22.1, 5.5.

MS (EI): *m/z* = 232 (MH^+, 45), 231 (M^+, 40), 148 (65), 105 (100).

HRMS (EI): *m/z* calcd for $C_{15}H_{21}NO$ (M^+): 231.1623. Found: 231.1620.

(1*R*,2*S*,3*R*,4*R*)-(−)-3,4-Diacetoxy-2-methyl-1-(1-phenylethyl)-piperidine (40)

The mixture of epoxides **15a** and **15b** (236 mg, 1.08 mmol) was dissolved in HOAc (4 mL) and this solution was refluxed for 0.5 h. After removal of solvent under reduced pressure, the residue was dissolved in anhyd pyridine (5 mL) and Ac_2O (1 mL, 10.8 mmol). After stirring overnight at r.t., the reaction mixture was diluted with Et_2O and washed four times with H_2O. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give a mixture of diacetates **40** and **41** in a 60:40 ratio (GC analysis). The residue was purified by chromatography over alumina using heptane/EtOAc (100:0 to 92:8) to furnish diacetate **40** (133 mg, 40% yield) and diacetate **41** (89 mg, 26% yield).

Major Isomer 40 (colourless oil)

$[\alpha]_D$ −5° (*c* 0.30, $CHCl_3$).

IR (neat) ν = 2975, 2819, 2257, 1740, 1492, 1454, 1371, 1251, 1232, 1053 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.27 (m, 5H), 5.00 (m, 1H), 4.96 (dd, 1H, *J* = 10.0, 4.8 Hz), 3.73 (q, 1H, *J* = 6.5 Hz), 3.21 (dq, 1H, *J* = 6.9, 4.8 Hz), 2.88 (ddd, 1H, *J* = 12.5, 5.3, 2.7 Hz), 2.60 (ddd, 1H, *J* = 12.5, 12.5, 2.9 Hz), 2.03 (m, 1H), 2.02 (s, 3H), 1.95 (s, 3H), 1.71 (dddd, 1H, *J* = 12.5, 12.5, 10.5, 5.2 Hz), 1.32 (d, 3H, *J* = 6.5 Hz), 0.93 (d, 3H, *J* = 6.9 Hz).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 170.1, 170.8, 145.3, 128.5, 127.0, 126.9, 73.3, 69.8, 59.6, 52.5, 39.5, 29.8, 22.6, 21.2, 21.1, 5.9.

MS (CI): *m/z* = 320 (MH^+).

MS (EI): *m/z* = 319 (M^+, 22), 304 (100), 260 (59), 105 (100).

HRMS (EI): *m/z* calcd for $C_{18}H_{25}NO_4$ (M^+): 319.1784. Found: 319.1789.

Minor Isomer 41 (colourless oil)

$[\alpha]_D$ +93° (*c* 0.81, $CHCl_3$).

IR (neat): ν = 2982, 2838, 2811, 1744, 1495, 1452, 1368, 1251, 1232, 1049 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.28 (m, 5H), 4.74 (dd, 1H, *J* = 8.7, 8.5 Hz), 4.58 (ddd, 1H, *J* = 10.7, 8.7, 4.8 Hz), 4.24 (q, 1H, *J* = 7.0 Hz), 3.00 (ddd, 1H, *J* = 11.7, 3.9, 3.9 Hz), 2.35 (dq, 1H, *J* = 8.5, 6.1 Hz), 2.02 (s, 3H), 2.01 (m, 1H), 2.00 (m, 1H), 1.99 (s, 3H), 1.63 (m, 1H), 1.45 (d, 3H, *J* = 7.0 Hz), 1.20 (d, 3H, *J* = 6.10 Hz).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 170.5, 170.3, 139.8, 128.0, 128.0, 127.1, 75.9, 73.0, 56.7, 55.9, 42.5, 29.3, 21.1, 21.0, 19.4, 15.6.

MS (CI): m/z = 320 (MH^+).

MS (EI): m/z = 319 (M^+, 15), 304 (67), 260 (24), 105 (100).

HRMS: (EI): *m/z* calcd for $C_{18}H_{25}NO_4$ (M^+): 319.1784. Found: 319.1774.

Mixture of Epoxides 42

Trifluoroacetic anhydride (1 mL, 7 mmol) was added dropwise to a solution of 50% hydrogen peroxide (0.12 mL, 2.09 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After 1.5 h at 0 °C under stirring was added a solution of allylic alcohol **28a** (90.4 mg, 0.416 mmol) and trifluoroacetic acid (0.1 mL, 1.25 mmol) in CH_2Cl_2 (2 mL). The ice bath was removed and the reaction mixture was stirred for 0.5 h. Treatment under the conditions used for preparation of epoxides **15a** and **15b** gave a mixture of diastereoisomeric epoxides **42** (94.5 mg, 97% yield, 68:32 ratio) as a colorless oil.

MS (EI): m/z = 233 (M^+, 25), 232 (26), 218 (39), 105 (100).

HRMS (EI): Calcd for $C_{14}H_{19}NO_2$ (M^+): 233.1415. Found: 233.1398.

The two epoxides can be distinguished by NMR.

Major Isomer

^1H NMR (250 MHz, $CDCl_3$): δ = 7.20−7.40 (m, 5H), 3.91 (q, 1H, *J* = 6.9 Hz), 3.82 (m, 1H), 3.30 (dd, 1H, *J* = 3.9, 3.3 Hz), 3.17 (br d, 1H, *J* = 3.9 Hz), 3.06 (d, 1H, *J* = 13.7 Hz), 2.91 (dd, 1H, *J* = 13.7, 3.3 Hz), 2.81 (qd, 1H, *J* = 6.7, 3.6 Hz), 1.70 (m, 1H), 1.37 (d, 3H, *J* = 6.9 Hz), 1.03 (d, 3H, *J* = 6.7 Hz).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 143.4, 128.5, 127.5, 127.1, 69.1, 57.8, 54.3, 54.2 (2C), 51.7, 43.3, 20.5, 10.3.

MS (EI): *m/z* = 233 (M^+, 25), 232 (26), 218 (39), 105 (100).

HRMS (EI): *m/z* calcd for $C_{14}H_{19}NO_2$ (M^+): 233.1415. Found: 233.1398.

Minor Isomer

^1H NMR (250 MHz, $CDCl_3$): δ = 7.20−7.40 (m, 5H), 3.89 (m, 1H), 3.74 (q, 1H, *J* = 6.7 Hz), 3.46 (ddd, 1H, *J* = 4.2, 4.2, 1.2 Hz), 3.36

(dd, 1H, *J* = 4.2, 2.9 Hz), 3.04 (d, 1H, *J* = 13.6 Hz), 2.97 (br d, 1H, *J* = 13.6 Hz), 2.76 (qd, 1H, *J* = 6.7, 5.6 Hz), 2.00 (m, 1H), 1.34 (d, 3H, *J* = 6.7 Hz), 1.00 (d, 3H, *J* = 6.7 Hz).

^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 144.2, 128.6, 127.5, 127.2, 68.9, 59.3, 54.7, 53.7 (2C), 51.9, 42.7, 21.6, 7.5.

(1*R*,2*S*,3*R*,4*R*,5*S*)-(+)-3,4,5-Triacetoxy-2-methyl-1-(1-phenylethyl)-piperidine (43)

The mixture of epoxides **42** (94.4 mg, 0.405 mmol) was dissolved in HOAc (4 mL) and the solution was stirred overnight at r.t. and then refluxed for 1 h. After evaporation of the solvent to dryness, the residue was dissolved in anhyd pyridine (5 mL) and Ac_2O (1 mL, 10.8 mmol) was added. This solution was left overnight at r.t. and then diluted with CH_2Cl_2. The organic phase was washed with H_2O and evaporated at reduced pressure to afford a mixture of isomers **43** and **44** in a 68:32 ratio. Chromatography over alumina (heptane/EtOAc, 95:5 to 91:9) gave the major isomer **43** (89 mg, 59% yield) as a white solid and the minor isomer **44** (45 mg, 29% yield) as a colorless oil. White crystals of **43** were obtained from dry Et_2O/heptane.

Isomer 43

Mp: 130−132 °C; $[\alpha]_D$ +1° (*c* 1.63, $CHCl_3$).

IR (neat): ν = 2979, 1745, 1455, 1437, 1372, 1252, 1229 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19−7.36 (m, 5H), 5.25 (dd, 1H, *J* = 10.2, 9.9 Hz), 5.02 (ddd, 1H, *J* = 10.5, 9.9, 5.9 Hz), 4.94 (dd, 1H, *J* = 10.2, 5.5 Hz), 3.76 (q, 1H, *J* = 6.5 Hz), 3.24 (qd, 1H, *J* = 6.8, 5.5 Hz), 3.21 (dd, 1H, *J* = 11.7, 5.9 Hz), 2.54 (dd, 1H, *J* = 11.7, 10.5 Hz), 2.03 (s, 3H), 2.02 (s, 3H), 1.95 (s, 3H), 1.33 (d, 3H, *J* = 6.5 Hz), 0.97 (d, 3H, *J* = 6.8 Hz).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ =170.5, 170.2, 169.8, 144.7, 128.6, 127.2, 126.8, 71.9, 71.3, 71.0, 59.7, 51.7, 43.4, 22.4, 20.9, 20.9, 5.7.

MS (EI): *m/z* = 377 (M^+, 2.5), 362 (19), 317 (14), 105 (100), 43 (74).

MS (CI): *m/z* = 378 (MH^+).

HRMS (CI): *m/z* calcd for $C_{20}H_{28}NO_6$ (MH^+): 378.1916. Found: 378.1933.

Isomer 44

$[\alpha]_D$ −27.5° (*c* 3.09, $CHCl_3$).

IR (neat): ν = 2979, 1745, 1455, 1437, 1372, 1252, 1229 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20−7.38 (m, 5H), 5.21 (dd, 1H, *J* = 3.5, 2.3 Hz), 5.12 (ddd, 1H, *J* = 9.5, 9.5, 4.5 Hz), 4.75 (dd, 1H, *J* = 9.5, 3.5 Hz), 4.13 (q, 1H, *J* = 7.0 Hz), 3.28 (dd, 1H, *J* = 11.3, 4.5 Hz), 2.62 (dq, 1H, *J* = 6.4, 2.3 Hz), 2.14 (s, 3H), 2.04 (s, 3H), 1.97 (dd, 1H *J* = 11.3, 9.5 Hz), 1.97 (s, 3H), 1.46 (d, 3H, *J* = 7.0 Hz), 1.19 (d, 3H, *J* = 6.4 Hz).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 171.0, 170.4, 170.2, 139.8, 128.2, 127.8, 127.2, 72.5, 72.2, 69.0, 55.9, 54.7, 47.2, 21.1, 20.9, 20.8, 19.1, 15.3.

MS (EI): *m/z* = 377 (M^+, 3.5), 362 (23), 317 (11), 105 (100), 43 (72).

MS (CI): *m/z* = 378 (MH^+).

HRMS (CI): *m/z* calcd for $C_{20}H_{28}NO_6$ (MH^+): 378.1916. Found: 378.1920.

(2*S*,3*R*,4*R*,5*S*)-(+)-3,4,5-Triacetoxy-2-methylpiperidine (7)

Triacetate derivative **43** (27 mg, 0.072 mmol) was dissolved in a mixture of EtOH (1.5 mL), EtOAc (1.5 mL) and 20% aqueous HCl (1 mL). The resulting homogeneous solution was hydrogenated in a Parr apparatus at 4.5 psi, in the presence of a catalytic amount of 10% palladium on charcoal, during 14 h. After filtration over Celite and removal of solvent under reduced pressure, the residue was washed with pentane and filtered over silica gel. Removal of solvent under reduced pressure afforded piperidine hydrochloride **7**·HCl (20.1 mg, 90%) as a light yellow oil.

Free Base 7

$[\alpha]_D$ +10° (*c* 0.91, $CHCl_3$).

IR (neat): ν = 2976, 2932, 2257, 1741, 1371, 1253, 1232 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.13 (dd, 1H, *J* = 5.9, 5.4 Hz), 4.76 (dd, 1H, *J* = 5.9, 3.5 Hz), 4.69 (ddd, 1H, *J* = 5.4, 5.4, 3.8 Hz), 3.26 (qd, 1H, *J* = 6.9, 3.5 Hz), 3.11 (dd, 1H, *J* = 14.3, 3.8 Hz), 2.97 (dd, 1H, *J* = 14.3, 5.4 Hz), 2.10 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 1.12 (d, 3H, *J* = 6.9 Hz).

^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 170.0, 169.9, 169.4, 70.9, 68.8, 68.4, 49.2, 44.0, 21.1, 20.9, 20.9, 15.5.

MS (CI): m/z = 274 (MH^+).

HRMS (CI): *m/z* calcd for $C_{12}H_{20}NO_6$ (MH^+): 274.1290. Found: 274.1308.

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(8) The rather significant difference in this relationship observed for epoxidation of tetrahydropyridines **11** can be tentatively attributed to a competing (but small) directing effect of the phenylethanol side chain oxygen function.

(9) Crystal data of **32a**: Colorless crystal (0.15 x 0.35 x 0.45 mm) recrystallized from Et_2O/heptane mixture. $C_{15}H_{21}NO_2$, MW = 247.33. Orthorhombic system, space group $P2_12_12_1$, Z = 4, a = 5.297 (2), b = 9.563 (3), c = 27.540 (10) Å, V = 1395 Å^3, d_C = 1.178 g cm^{-3}, F(000) = 536, λ (Mo Kα) = 0.7107 Å; μ = 0.077 mm^{-1}; 2640 data measured on a Philips PW1100 diffractometer of which 1468 unique (Rint = 0.030) and 1114 observed with I ≥ 2.0 σ(I). Structure solved with *SHELX76* and refined with *SHELXL93*. Hydrogen atoms riding. Refinement converged to R(Fo) = 0.0376 for the observed Fo and wR(Fo^2) = 0.1158 for all the 1468 data with goodness-of-fit S = 1.065. Residual electron density between −0.12 and 0.13 eÅ^{-3}. All crystallographic results have been

deposited at the Cambridge Crystallographic Data Centre, U.K., as Supplementary Material (CIF file). (Sheldrick, G. M. (1986), *SHELXS86*, Program for the Solution of Crystal Structures, University of Göttingen, Germany; Sheldrick, G. M. (1993), *SHELXL93*, Program for the Refinement of Crystal Structures, University of Göttingen, Germany (Program for the Solution of Crystal Structures, University of Göttingen, Germany; Sheldrick, G. M. (1993), *SHELXL93*, Program for the Refinement of Crystal Structures, University of Göttingen, Germany).

(10) Used of this highly hindered, non nucleophilic base is rendered necessary since pyridine itself reacted with the intermediate triflate **33** or aziridinium **34** to give a pyridinium salt.

(11) Deduced from a ^{1}H NMR spectroscopy study of the reaction in $CDCl_3$ (apparition of a downfield proton at 5.8 ppm, tentatively H_3, $J_{H2\text{-}H3}$ = 2 Hz).

(12) Crystal data of **43**: Small colorless needle (0.07 x 0.20 x 0.26 mm) recrystallized from an Et_2O/heptane mixture. $C_{20}H_{27}NO_6$, MW = 377.43. Orthorhombic system, space group $P2_12_12_1$, Z = 4, a = 7.209 (5), b = 11.513 (7), c = 25.893 (12) Å, V = 2149 Å^3, d_C = 1.167 g cm^{-3}, F(000) = 808, λ (Cu Kα) = 1.5418 Å; μ = 0.71 mm^{-1}; 2908 data measured on a Nonius CAD-4 diffractometer of which 2163 unique (Rint = 0.075) and 1485 observed with I ≥ 2.0 σ(I). Structure solved with *SHELX76* and refined with *SHELXL93*. Hydrogen atoms riding. Refinement converged to R(Fo) = 0.0783 for the observed Fo and wR(Fo^2) = 0.2654 for all the 2163 data with goodness-of-fit S = 1.030. Residual electron density between −0.28 and 0.39 eÅ^{-3}. All crystallographic results have been deposited at the Cambridge Crystallographic Data Centre, U.K., as Supplementary Material (CIF file). (Sheldrick, G. M. (1986), *SHELXS86*, Program for the Refinement of Crystal Structures, University of Göttingen, Germany; Sheldrick, G. M. (1993), *SHELXL93*, Program for the Refinement of Crystal Structures, University of Göttingen, Germany).

Article Identifier:
1437-210X,E;2000,0,14,2117,2126,ftx,en;C03200SS.pdf