CHIRAL 1,2-DIHYDROPYRIDINES AND 2,5-DIHYDROPYRIDINIUM SALT EQUIVALENTS. SYNTHESIS OF (+)-ANATABINE AND A CHIRAL BENZOMORPHANE§

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Abstract - Sodium borohydride reduction of readily available chiral pyridinium salts (**2a-b**) in alkaline medium led to 1,2-dihydropyridines (**3a-b**) which spontaneously cyclized to give 2,5-dihydropyridinium salt equivalents (**4a-b**). Use of these intermediates for a short synthesis of the tobacco alkaloid (+)-anatabine and of the benzomorphane derivative ((+)-**14**) is reported.

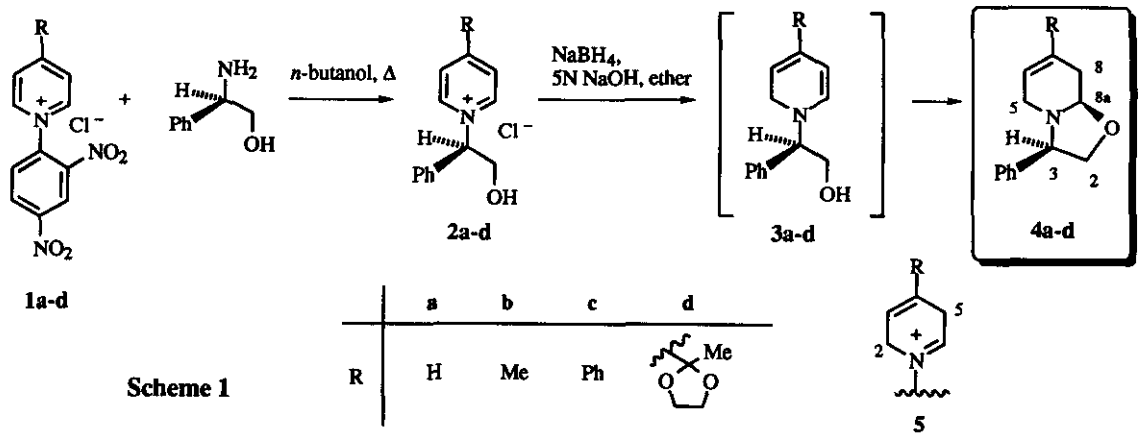
Alkaloids containing six-membered nitrogen heterocycles are abundant in nature and many of them exhibit interesting biological activities. Accordingly, the search for practical and general approaches allowing regio- and stereocontrolled synthesis of highly functionalized derivatives of these heterocycles has gained continued attention. Among others, a set of powerful strategies makes use of the versatile synthetic potential of dihydropyridine intermediates as an effective method for their construction.[1] In earlier studies, we demonstrated that a variety of chiral dihydropyridine intermediates (or dihydropyridinium salt equivalents) can be successfully used for asymmetric syntheses of such heterocycles.[2] Our entry into this field was greatly facilitated by the finding that the Zincke's synthesis of pyridinium salts could be easily extended to asymmetric series using various chiral primary amines[3] as starting material.

In this paper we report details of the sequence[4] depicted in Scheme 1 by way of its application to a synthesis of (+)-anatabine and of a chiral benzomorphane derivative according to Scheme 2 and Scheme 3, respectively.

Treatment of Zincke's salt (**1a**)[5] (Scheme 1) with 1.1 equivalent of (*R*)-(–)-phenylglycinol in refluxing *n*-butanol overnight gave, after simple extraction, pure salt (**2a**) in nearly 90% yield. Since (*R*)-(–)-phenylglycinol is now made available by a very convenient procedure,[6] chiral pyridinium salt (**2a**) could be routinely prepared in our laboratory in 100 g scale. Synthesis of 4-substituted salts (**2c-d**) met with no special difficulties by using this procedure. Zincke's salt (**1b**) proved to be sensitive to bases and was prepared in refluxing methanol, while the dioxolane protection was needed for the preparation of salt (**1d**) since 4-acetylpyridine was not nucleophilic enough to react with 1-chloro-2,4-dinitrobenzene.

§Dedicated to Prof. Arnold Brossi on the occasion of his 70th anniversary.

Reduction of salts (**2a-d**) with $NaBH_4$ was performed in a two-phase 5N NaOH-ether mixture. This strongly alkaline medium was necessary to prevent reduction to tetrahydropyridines which is normally obtained by using $NaBH_4$ in methanol.[1a] In addition, ether as solvent helped the reaction by extracting non polar dihydropyridine intermediates as soon as they were formed. Intermediate dihydropyridines (**3a-d**) could not be characterized, even by nmr studies of the crude reaction mixture, and we only isolated oxazolidines (**4a-d**). In the case of salt (**2a**), we observed the formation of the corresponding 1,4-dihydropyridine as a by-product to the extent of 15%. This last compound, which did not cyclize spontaneously, was shown to be very unstable[2c,2e] and could thus be eliminated from 1,2-dihydropyridine (**3a**) in the crude reaction mixture by filtration over alumina. This allowed us to isolate pure **4a** which was obtained in 70% yield from the salt (**2a**). In the case of salts (**2c-d**), substitution at position 4 prevented the formation of 1,4-dihydro isomers which were not detected.

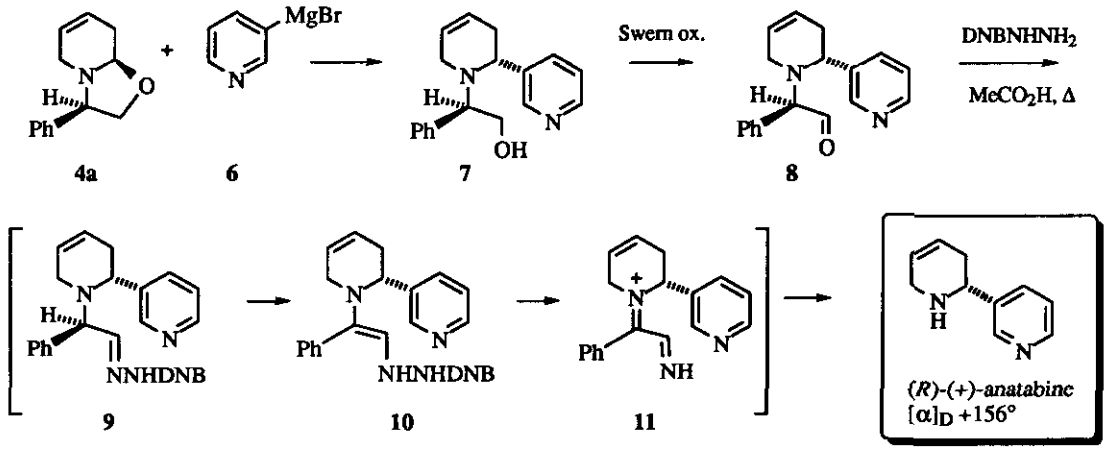


Scheme 1

Oxazolidines (**4a-d**) which are formed *via* 2,5-dihydropyridinium salt intermediates (**5**) may be considered as chiral masked forms of these presumably very unstable species. Previous work in this field showed that salts such as (**5**) could also be trapped by cyanide ion giving (racemic) intermediates of interest in alkaloid synthesis.[7] In the absence of any nucleophile such as cyanide or an internal alkoxide (as in the present case), to trap salt (**5**) from the corresponding 1,2-dihydropyridine, a rapid dimerisation process can occur between this electrophilic salt (**5**) and the nonprotonated nucleophilic dihydropyridine. Very likely, this can explain the behaviour of simple 1,2-dihydropyridines which were reported to dimerise spontaneously in air.[8]

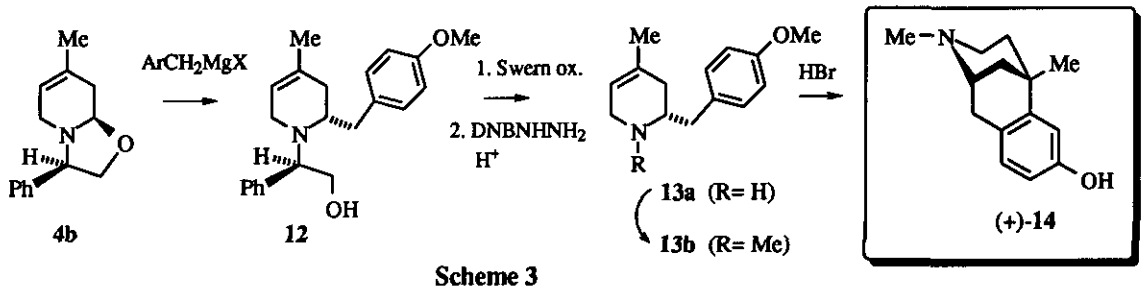
Use of the intermediate (**4a**) in a synthesis of (+)-anatabine, a minor tobacco alkaloid, is summarized in Scheme 2. Noteworthy is the fact that the biosynthesis of this naturally occurring compound implies presumably an enzymatically controlled condensation of 1,2-dihydropyridine with 2,5-dihydropyridine,[9] both derived from nicotinic acid. Treatment of oxazolidine (**4a**) with Grignard reagent (**6**), obtained from the corresponding lithium salt by exchange with $MgBr_2$, afforded adduct (**7**) together with its diastereoisomer in a 9 to 1 proportion (80% d.e. as estimated by ^1H-nmr spectroscopy). Pure **7** was isolated in 32% yield after chromatography over alumina. In the final step for obtaining anatabine, removal of the phenylethanol auxiliary by hydrogenolysis could not be used since the intracyclic double bond is susceptible to hydrogenation under such conditions. Oxidative conditions for this removal were therefore explored. Swern oxidation gave the unstable aldehyde (**8**),

which was immediately treated with 3 equivalents of 2,4-dinitrophenylhydrazine (DNBNHNH$_2$) in a refluxing mixture of *n*-propanol and acetic acid. This procedure, which was adapted from an old protocol used for the deamination of 2-aminosugars[10] gave, presumably *via* intermediates (**9**) and (**10**), the ozazone derivative (**11**) which was hydrolyzed under the reaction conditions. (*R*)-(+)-Anatabine was thus obtained in a 55% overall yield from (**7**). (*R*)-(+)-Anatabine is the enantiomer of the natural product, but, since (*S*)-(+)-phenylglycinol is also readily available, (*S*)-(–)-anatabine should as well be accessible by our method. The optical purity of the synthetic compound was estimated near 95% by comparison of the optical rotations ([α]$_D$ +156° for the synthetic, and [α]$_D$ –178° for the natural enantiomer[11]) and other data obtained in the same series.[4]



Scheme 2

A second application, also demonstrating the synthetic interest of intermediates (**4**), is presented (Scheme 3). Treatment of oxazolidine (**4b**) with *p*-methoxybenzylmagnesium chloride gave adduct (**12**). Albeit the diastereoselectivity was low (25%), adduct (**12**) could be obtained in a reasonable yield of 47% after chromatography on silica gel. Removal of the phenylethanol chain was achieved by our two-step procedure (Swern oxidation, treatment with dinitrophenylhydrazine in acidic medium), affording tetrahydropyridine (**13a**) in 66% yield. Reductive methylation led to **13b** .



Scheme 3

Finally, Grewe's cyclization proceeded in a 46% yield to give benzomorphan derivative ((+)-**14**) possessing analgesic activity. The optical rotation of ((+)-**14**) ($[\alpha]_D$ = +71°)was in agreement with literature data[12] ($[\alpha]_D$ = +75°) and an e.e. of *ca.* 90% was obtained by our procedure. This last result completed our recent work on the asymmetric synthesis of benzomorphan and morphinan drugs.[2d]

ACKNOWLEDGEMENT

We thank Mr.Gérard Henry for efficient technical assistance.

EXPERIMENTAL

1-(2,4-Dinitrophenyl)-4-methylpyridinium chloride (1b). To a solution of 4-picoline (19.5 g, 210 mmol) in MeOH (400 ml), 1-chloro-2,4-dinitrobenzene (40 g, 197.5 mmol) was added and the resulting solution was refluxed during 24 h. After evaporation of solvent, the crude residue was filtered over silica gel with CH_2Cl_2-MeOH (from 95/5 to 60/40 ratio) to give salt (**1b**) (49.6 g, 85%) as a black powder. ^{1}H-Nmr (CD_3OD) δ: 2.87 (3H, *s*), 8.20 (2H, d, J = 7 Hz), 8.31 (1H, d, J = 8.5 Hz), 8.88 (1H, dd, J = 8.5 Hz, J = 2.5 Hz), 9.14 (2H, d, J = 7 Hz), 9.24 (1H, d, J = 2.5 Hz). ^{13}C-Nmr (CD_3OD) δ: 23.0, 123.2, 129.9 (2C), 131.3, 133.0, 139.9, 144.6, 145.9 (2C), 150.8, 165.4. Ms (FAB) *m/z* (relative intensity) 260 (M^+; 100), 94 (10).

1-(2,4-Dinitrophenyl)-4-phenylpyridinium chloride (1c). To a solution of 4-phenylpyridine (2.4 g, 15.5 mmol) in MeOH (50 ml), 1-chloro-2,4-dinitrobenzene (3.13 g, 15.5 mmol) was added and the resulting solution was refluxed during 48 h. Removal of the solvent, precipitation in acetone and filtration gave salt (**1c**) as a pale yellow powder (4.3 g, 78%). ^{1}H-Nmr (CD_3OD) δ: 7.69 (3H, m), 8.16 (2H, dd, J = 8 Hz, J = 2 Hz), 8.32 (1H, d, J = 8 Hz), 8.67 (2H, d, J = 7 Hz), 8,90 (1H, dd, J = 8 Hz, J = 3 Hz), 9.24 (2H, d, J = 7 Hz), 9.26 (1H, d, J = 3 Hz). ^{13}C-Nmr (CD_3OD) δ: 123.2, 125.8 (2C), 129.7 (2C), 131.2 (3C), 132,9, 134.4, 134.6, 139.9, 144.7, 146.8 (2C), 151.0, 160.6. Ms (FAB) *m/z* (relative intensity) 322 (M^+; 100), 156 (46).

1-(2,4-Dinitrophenyl)-4-(2-methyl-1,3-dioxolan-2-yl)pyridinium chloride (1d). To a solution of 3-(2-methyl-1,3-dioxolan-2-yl)pyridine (5.3 g, 32.1 mmol) in acetone (350 ml), 1-chloro-2,4-dinitrobenzene (6.5 g, 32.1 mmol) was added and the mixture was refluxed during 48 h. The precipitate formed was filtered to give salt(**1c**)(8.25 g, 70%) as a brown powder. ^{1}H-Nmr (CD_3OD) δ: 1.80 (3H, s), 3.95 (2H, m), 4.22 (m, 2H), 8.33 (1H, d, J = 8.5 Hz), 8.40 (2H, d, J = 7 Hz), 8.90 (1H, dd, J = 8.5 Hz, J = 2 Hz), 9.27 (1H, d, J = 2 Hz), 9.31 (2H, d, J = 7 Hz). ^{13}C-Nmr (CD_3OD) δ: 26.6, 66.5 (2C), 108.0, 122.9, 125.9 (2C), 131.0, 132.6, 139.6, 144.1, 147.3 (2C), 150.8, 186.8. Ms (FAB) *m/z* (relative intensity) 332 (M^+; 100), 166 (35).

(–)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]pyridinium chloride (2a). (*R*)-(–)-Phenylglycinol (48 g, 0.35 mol) was added to a solution of Zincke's salt (**1a**)[5] (89.9 g, 0.32 mol) in *n*-butanol (1 l) at 20°C . The resulting deep red solution was then refluxed during 20 h. Removal of solvent under reduced pressure left a residue which was treated with 0.5 l of H_2O. The precipitate (2,4-dinitrophenylamine) was eliminated by filtration and the operation was repeated twice. The combined aqueous phase was basified with concentrated ammonia (5 ml) and washed twice with AcOEt (200 ml) in order to remove the remaining 2,4-dinitrophenylamine and the excess of (*R*)-(–)-phenylglycinol. Evaporation of water gave salt (**2a**) (69.9 g, 88% yield from **1a**) as a pale orange gum; $[\alpha]_D$ = –29° (c = 1.5, EtOH). ^{1}H-Nmr (CD_3OD) δ: 4.38 (1H, dd, J = 12.5 Hz, J = 4.2 Hz), 4.63 (1H, dd, J = 12.5 Hz, J = 9 Hz), 4.95 (br s, OH), 6.27 (1H, dd, J = 9 Hz, J = 4.2 Hz), 7.40-7.66 (5H, m), 8.17 (2H, dd, J

= 7.5 Hz, J = 6.5 Hz), 8.65 (1H, t, J = 7.5 Hz), 9.23 (2H, d, J = 6.5 Hz). ^{13}C-Nmr (CD_3OD) δ: 63.2, 77.2, 129.4 (4 C), 130.1, 131.1 (2C), 135.1, 145.3 (2 C), 147.5. Ms (FAB) *m/z* (relative intensity) 200 (M^+; 100).

(–)-4-Methyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]pyridinium chloride (2b). Treatment of salt (**1b**) (7 g, 23.7 mmol) with (*R*)-(–)-phenylglycinol (3.9g, 28.5 mmol) under the conditions used for the preparation of salt (**2a**) gave salt (**2b**) (3.75 g, 63% yield from **1b**); $[\alpha]_D$ = –42° (c = 2.4, EtOH). ^{1}H-Nmr (CD_3OD) δ: 2.71 (3H, s), 4.34 (1H, dd, J = 14.5 Hz, J = 4 Hz), 4.51 (1H, dd, J = 14.5 Hz, J = 8.5 Hz), 6.02 (1H, dd, J = 8.5 Hz, J = 4 Hz), 7.50 (5H, m), 7.94 (2H, d, J = 7 Hz), 8.91 (2H, d, J = 7 Hz). ^{13}C-Nmr (CD_3OD) δ: 22.1, 63.2, 76.4, 129.2 (2C), 129.8 (2C), 130.5 (2C), 130.0, 135.9, 144.2 (2C), 161.8. Ms (FAB) *m/z* (relative intensity) 214 (M^+;100), 94 (10).

(–)-4-Phenyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]pyridinium chloride (2c). Treatment of salt (**1c**) (5 g, 14 mmol) with (*R*)-(–)-phenylglycinol (2.3 g, 16.8 mmol) under the conditions used for the preparation of salt (**2a**) gave salt (**2c**) (3.44 g, 79% from **1c**); $[\alpha]_D$ = –41° (c = 2.4, EtOH). ^{1}H-Nmr (CD_3OD) δ: 4.38 (1H, dd, J = 13 Hz, J = 3 Hz), 4.58 (1H, dd, J = 13 Hz, J = 9 Hz), 6.14 (1H, dd, J = 9 Hz, J = 3 Hz), 7.46-7.65 (8H, m), 7.92 (2H, m), 8.34 (2H, d, J = 8 Hz), 9.11 (2H, d, J = 8 Hz). ^{13}C-Nmr (CD_3OD) δ: 63.2, 76.4, 125.8 (2C), 129.1 (2C), 129.3 (2C), 130.6 (2C), 130.8 (2C), 131.1, 133.4, 134.6, 135.2, 145.1 (2C), 157.7. Ms (FAB) *m/z* (relative intensity) 276 (M^+;100), 156 (65), 121 (18), 103 (17).

(–)-4-(2-Methyl-1,3-dioxolan-2-yl)-1-[(1*R*)-2-hydroxy-1-phenylethyl]pyridinium chloride (2d). Treatment of salt (**1d**) (3 g, 8.16 mmol) with (*R*)-(–)-phenylglycinol (1.34 g, 9.8 mmol) under the conditions used for the preparation of salt (**2a**) gave salt (**2d**) (2.49 g, 95% yield from **1d**); $[\alpha]_D$ = –6° (c = 2.3, EtOH). ^{1}H-Nmr (CD_3OD) δ: 1.63 (3H, s), 3.36 (2H, m), 4.14 (2H, m), 4.36 (1H, dd, J = 12 Hz, J = 4 Hz), 4.53 (1H, dd, J = 12 Hz, J = 8 Hz), 6.12 (1H, dd, J = 8 Hz, J = 4 Hz), 7.46-7.62 (5H, m), 8.14 (2H, d, J = 6 Hz), 9.08 (2H, d, J = 6 Hz). ^{13}C-Nmr (CD_3OD) δ: 26.6, 63.0, 66.2 (2C), 76.7, 107.6, 125.8 (2C), 129.3 (2C), 130.4 (2C), 130.9, 134.6, 145.5 (2C), 163.6. Ms (FAB) *m/z* (relative intensity) 286 (M^+;100), 166 (28).

(3*R*, 8a*R*)-(–)-3-Phenyl-3,5,8,8a-tetrahydro-2*H*-oxazolo[3,2-*a*]pyridine (4a). Pyridinium salt (**2a**) (10 g, 42.5 mmol) in H_2O (50 ml) was added dropwise to a two-phase solution of $NaBH_4$ (5 g, 132 mmol) in aqueous 5N NaOH (100 ml) and ether (400 ml) under vigorous stirring. After 1 h the organic phase was decanted and rapidly filtered over alumina (60 g). Removal of solvent gave the unstable oxazolidine (**4a**) (5.97 g, 70%) as a pale yellow oil which was used without further purification or stored at –20°C; $[\alpha]_D$ = –154° (c = 3.4, $CHCl_3$). ^{1}H-Nmr ($CDCl_3$) δ: 2.30 (1H,m), 2.50 (1H, m), 2.80 (1H, m), 3.30 (1H, m), 3.60 (1H, dd, J = 8 Hz, J = 8 Hz), 3.75 (1H, dd, J = 8 Hz, J = 8 Hz), 4.05 (1H, dd, J = 9 Hz, J = 4 Hz), 4.25 (1H, dd, J = 8 Hz, J = 8 Hz), 5.70 (2H, m), 7.35 (5H,m). ^{13}C-Nmr ($CDCl_3$) δ: 32.3, 49.5, 67.8, 73.4, 91.3, 123.2, 125.3, 127.9 (2C), 128.7 (2C), 137.8, 138.6. HRms (EI): calcd for $C_{13}H_{15}NO$ 201.1154, found *m/z* 201.1163.

(3*R*, 8a*R*)-(–)-7-Methyl-3-phenyl-3,5,8,8a-tetrahydro-2*H*-oxazolo[3,2-*a*]pyridine (4b). Pyridinium salt (**2b**) (2 g, 8 mmol) was reduced using the same procedure as for the reduction of salt (**2a**) to give oxazolidine (**4b**) as a pale yellow oil (1.43 g, 83%) which was stored at –20°C; $[\alpha]_D$ = –104° (c = 1.6, $CHCl_3$). ^{1}H-Nmr ($CDCl_3$) δ: 1.75 (3H, s), 2.33 (2H, m), 2.72 (1H, m), 3.24 (1H, m), 3.60 (1H, dd, J = 8 Hz, J = 8 Hz), 3.77 (1H, dd, J = 8 Hz, J = 8 Hz), 4.06 (1H, dd, J = 6 Hz, J = 6 Hz), 4.27 (1H, dd, J = 8 Hz, J = 8 Hz), 5.27 (1H, m), 7.20-7.50 (5H, m). ^{13}C-Nmr ($CDCl_3$) δ: 23.1, 36.9, 48.8, 67.7, 73.7, 91.8, 127.8, 128.6 (5C), 132.4, 139.2. HRms (EI): calcd for $C_{14}H_{17}NO$ 215.1310, found *m/z* 215.1305.

(3*R*, 8a*R*)-(–)-3,7-Diphenyl-3,5,8,8a-tetrahydro-2*H*-oxazolo[3,2-*a*]pyridine (4c). Pyridinium salt (**2c**) (0.43 g, 1.23 mmol) was reduced according to the procedure used for the reduction of salt (**2a**) to give oxazolidine (**4c**) as a pale yellow oil (0.25 g, 71%) which was stored at –20°C. ^{1}H-Nmr ($CDCl_3$) δ: 2.73-3.03 (3H, m), 3.51 (1H,m), 3.71 (1H, dd, J = 8 Hz, J = 8 Hz), 3.83 (1H, dd, J = 8 Hz, J = 8 Hz), 4.21 (1H, dd, J = 8 Hz, J = 4 Hz), 4.32 (1H, dd, J = 8 Hz, J = 8 Hz), 6.07 (1H, m), 7.22-7.52 (10 H, m). ^{13}C-Nmr ($CDCl_3$) δ: 34.3, 49.3, 67.7, 73.9, 92.0, 121.9, 125.4-128.0 (10C), 133.9, 139.6, 141.6 (2C). Ms (CI): *m/z* (relative intensity) 278 (MH^+; 100).

(3*R*, 8a*R*)-(–)-7-(2-Methyl-1,3-dioxolan-2-yl)-3-phenyl-3,5,8,8a-tetrahydro-2*H*-oxazolo-[3,2-*a*]pyridine (4d). Pyridinium salt (**2d**) (280 mg, 0.87 mmol) was reduced using the same procedure as for the reduction of salt (**2a**) to give oxazolidine (**4c**) as a pale yellow oil (189 mg, 76%) which was stored at –20°C. ^{1}H-Nmr ($CDCl_3$) δ: 1.50 (3H, s), 2.29 (1H, m), 2.55 (1H, m), 2.79 (1H, m), 3.37 (1H, m), 3.61 (1H, dd, J = 8 Hz, J = 8 Hz), 3.72-4.01 (5H, m), 4.05 (1H, dd, J = 8 Hz, J = 4 Hz), 4.27 (1H, dd, J = 8 Hz, J = 8 Hz), 5.87 (1H, m), 7.26-7.48 (5H, m). ^{13}C-Nmr ($CDCl_3$) δ: 23.3, 30.7, 48.0, 63.6, 63.0, 67.0, 73.2, 91.4, 107.9, 119.6, 127.3 (2C), 127.7 (3C), 135.2, 138.2. Ms (EI): *m/z* (relative intensity) 287 ($M^{+\cdot}$; 48), 87 (100).

(2*R*)-(–)-2-(Pyridin-3-yl)-1-[(1*R*)-2-hydroxy-1-phenylethyl]-1,2,3,6-tetrahydropyridine (7). To a solution of oxazolidine (**4a**) (1.67 g, 8.3 mmol) in dry ether (20 ml), was added Grignard reagent (**6**) prepared[13] from 3-bromopyridine (2.4 ml, 24.9 mmol) in ether (30 ml). The resulting solution was stirred for 24 h at ambient temperature. The organic phase was washed with a saturated solution of ammonium chloride. Evaporation of solvent left a gum which was chromatographed over alumina (70 g) with AcOEt/heptane (20:80) as eluant. The major isomer (**7**) (740 mg, 32%) was isolated as an oil; $[\alpha]_D$ = –21° (c = 1.5, $CHCl_3$). ^{1}H-Nmr ($CDCl_3$) δ: 2.22 (1H, m), 2.42 (1H, br s, O*H*), 2.62 (1H, m), 3.03 (1H, m), 3.31 (1H, m), 3.85 (1H, dd, J = 2 Hz, J = 2 Hz), 3.96 (2H), 4.14 (1H, m), 5,75-5.89 (2H, m), 7.2 (1*H*, m), 7.41 (5*H*, m), 7.67 (1*H*, m), 8.48 (1H, m), 8.6 (1H, s). ^{13}C-Nmr ($CDCl_3$) δ: 29.2, 43.8, 56.2, 62.7, 65.8, 123.4, 124.2, 125.9, 127.8, 128.3, 128.6, 128.7, 135.8, 137.7, 139.6, 148.5, 149.8 (2C). Ms (EI): *m/z* (relative intensity) 280 ($M^{+\cdot}$; 1), 249 (100), 144 (77), 104 (100). A small amount of the minor **(2*S*)-isomer** was also isolated and characterized. $[\alpha]_D$= –103° (c= 0.75, $CHCl_3$). ^{1}H-Nmr ($CDCl_3$) δ: 2.05 (1H, m), 2.35 (3H, m), 3.15 (1H, m), 3.35 (1H, m), 3.65 (1H, dd, J = 10 Hz, J = 4 Hz), 3.75 (1H, dd, J = 5 Hz, J = 4 Hz), 3.90 (1H, dd, J = 10 Hz, J = 5 Hz), 4.05 (1H, dd, J = 9 Hz, J = 9 Hz), 5.80 (2H, sharp m), 7.10 (1H, m), 7.35 (5H, m), 7.85 (1H, m), 8.57 (2H, m).

(*R*)-(+)-Anatabine. To a cooled (–78° C) solution of oxalyl chloride (0.23 ml, 2.6 mmol)) in dry CH_2Cl_2 (5 ml) was added DMSO (0.28 ml, 3.88 mmol) in dry CH_2Cl_2 (5 ml) at –78° C. After 0.75 h at –78° C adduct (**7**) (180 mg, 0.64 mmol) was added and the resulting solution stirred at –78° C during 3 h and then treated with triethylamine (0.72 ml, 5.17 mmol). After 10 min at ambient temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with H_2O. Evaporation of organic phase left the crude unstable aldehyde (**8**) (176 mg) which was dissolved in *n*-propanol (3 ml) and acetic acid (5 ml) and refluxed overnight in the presence of 2,4-dinitrophenylhydrazine (376 mg, 1.9 mmol). After evaporation of solvents, the residue was dissolved in MeOH and filtered. The filtrate was concentrated and dissolved in aqeous 1N HCl. The aqueous phase was washed with ether and then made alkaline with 1N NaOH. The base was extracted 3 times with CH_2Cl_2. Bulb-to-bulb distillation finally gave pure (*R*)-(+)-anatabine (60 mg, 58% yield from **7**) as a colourless oil; $[\alpha]_D$ = +156° (c =

1.6, $CHCl_3$), lit.,[11] $[\alpha]_D = -178°$ for natural enantiomer. ^1H and ^{13}C-Nmr spectra were in full agreement with the corresponding literature data.[9]

(2*R*)-(–)-2-(*p*-Methoxyphenylmethyl)-4-methyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-1,2,3,6-tetrahydropyridine (12). To a solution of oxazolidine (**4b**) (800 mg, 3.72 mmol) in THF (10 ml) was added at 20° C an excess of *p*-methoxyphenylmethylmagnesium chloride (*ca.* 10 mmol) in THF (15 ml). After 4 h at ambient temperature, the reaction mixture was diluted with ether and washed with saturated NH_4Cl. Removal of solvent left an oil which was chromatographed over silica gel with heptane/AcOEt (20:80) as eluant to give major adduct (**12**) (590 mg, 47%) as a colourless oil; $[\alpha]_D = -88°$ (c= 1.4, $CHCl_3$). ^1H-Nmr ($CDCl_3$) δ: 1.56-1.73 (4H, m), 2.13 (1H, m), 2.46 (1H, dd, J = 13 Hz, J = 10 Hz), 2.73 (1H, dd, J = 13 Hz, J = 4 Hz), 3.13 (2H, br s), 3.30 (1H, m), 3.73-3.93 (6H, m), 5.36 (1H, m), 6.83 (2H, d, J = 8 Hz), 7.00 (2H, d, J = 8 Hz), 7.20-7.43 (5H, m). ^{13}C-Nmr ($CDCl_3$) δ: 23.4, 32.4, 32.5, 43.9, 55.3, 56.9, 62.8, 66.1, 113.9 (2C), 116.7, 127.8, 128.5-130.1 (6C), 130.8, 132.6, 140.0, 158.1. Ms (CI): *m/z* (relative intensity) 338 (MH^+; 100). The minor **(2*S*)-isomer** was isolated in 32% yield (402 mg); $[\alpha]_D = +15°$ (c= 1.6, $CHCl_3$). ^1H-Nmr ($CDCl_3$). δ: 1.56-1.73 (4H, m), 2.07 (1H, m), 2.41 (1H, dd, J = 13 Hz, J = 10 Hz), 2.76 (1H, dd, J = 13 Hz, 4 Hz), 3.00 (1H, m), 3.32 (2H, m), 3.69-3.93 (6H, m), 5.45 (1H, br s), 6.74 (4H, s), 7.39 (5H, m). ^{13}C-Nmr ($CDCl_3$) δ: 23.3, 30.9, 32.4, 45.3, 54.9, 55.22, 63.6, 67.4, 113.8 (2C), 118.7, 127.9, 128.6-130.0 (6C), 131.1, 132.4, 140.45, 157.9. Ms (CI): *m/z* (relative intensity) 338 (MH^+; 100).

(2*R*)-(–)-2-(*p*-Methoxyphenylmethyl)-1-methyl-1,2,3,6-tetrahydropyridine (13b). Swern oxidation [*vide supra* preparation of (+)-anatabine] of adduct (**12**) (540 mg, 6.4 mmol) gave the corresponding crude aldehyde which was dissolved in *n*-propanol (10 ml) and acetic acid (10ml). 2,4-Dinitrophenylhydrazine (10% H_2O, 1.2 g, 4.84 mmol) was added and the resulting solution was refluxed during 36 h. After removal of solvents, the crude residue was acidified with MeOH-HCl and chromatographed over silica gel with CH_2Cl_2/MeOH (99:1) as eluant to give (**13a**).HCl (269 mg, 66% yield from **12**). Ms (EI): *m/z* (relative intensity) 217 ($M^{+\cdot}$; 6), 216 (14), 121 (38), 96 (100). The corresponding base (**13a**) (164 mg, 0.75 mmol) was dissolved in acetonitrile (13 ml) and stirred for 15 min with formaldehyde (37% in H_2O, 0.4 ml, 5 mmol) and $NaBH_3CN$ (100 mg, 1.6 mmol). The solution was then neutralised by the addition of a few drops of acetic acid and left for 45 mn after which the solvent was evaporated and the product extracted with CH_2Cl_2 and 2N KOH. Evaporation of the organic phase followed by bulb-to-bulb distillation gave the pure amine (**13b**) (141 mg, 80 % yield from **13a**); $[\alpha]_D = +20°$ (c= 1.1, $CHCl_3$). ^1H-Nmr ($CDCl_3$) δ: 1.63 (s, 3H), 1.82 (2H, m), 2.37 (1H, dd, J = 13 Hz, J = 11 Hz), 2.44 (3H, s), 2.75 (1H, m), 3.03 (1H, dd, J = 13 Hz, J = 4 Hz), 3.12 (2H, m), 3.80 (3H, s), 5.37 (1H, m), 6.83 (2H, d, J = 8 Hz), 7.08 (2H, d, J = 8 Hz). ^{13}C-Nmr ($CDCl_3$) δ: 23.1, 33.7, 35.2, 41.4, 53.0, 55.3, 60.3, 113.9 (2C), 118.6, 130.3 (2C), 131.7, 132.1, 158.0.

(1*S*, 5*S*)-(+)-2,5-Dimethyl-2'-hydroxy-6,7-benzomorphane (14). Tetrahydropyridine (**13b**) (140 mg, 0.61 mmol) was dissolved in 48% HBr (1.5 ml) and heated at 140° C under stirring during 36 h. The reaction mixture was made alkaline by careful addition of 32% NH_4OH at 0° C and the base extracted with CH_2Cl_2. Chromatography over silica gel with CH_2Cl_2/MeOH (93:7) as eluant gave pure benzomorphane derivative ((+)-**14**) as a pale yellow solid (63 mg, 46%); $[\alpha]_D = +71°$ (c= 0.9, EtOH), lit.,[12] $[\alpha]_D = +75°$(EtOH).

REFERENCES

1- a) U. Eisner and J. Kuthan, *Chem. Rev.*, 1972, **72**, 1; b) D. M. Stout and A. I. Meyers, *Chem. Rev.*, 1982, **82**, 223; c) M.-L. Bennasar, R. Lavilla, M. Alvarez, and J. Bosch, *Heterocycles*, 1988, **27**, 789; d) D. L. Comins and S. O'Connor, *Adv. Heterocycl. Chem.*, 1988, **44**, 199.

2- a) M. Mehmandoust, C. Marazano, R. Singh, B. Gillet, M. Cesario, J.-L. Fourrey, and B. C. Das, *Tetrahedron Lett.*, 1988, **29**, 4423; b) C. Marazano, S. Yannic, Y. Genisson, M. Mehmandoust, and B. C. Das, *Tetrahedron Lett.*, 1990, **31**, 1995; c) D. Gnecco, C. Marazano, and B. C. Das, *J. Chem. Soc., Chem. Commun.*,1991, 625; d) Y. Genisson, C. Marazano, and B. C. Das, *J. Org. Chem.*, 1993, **58**, 2052. e) Y.-S. Wong, C. Marazano, D. Gnecco, and B. C. Das, *Tetrahedron Lett.*, 1994, **35**, 707.

3- Y. Genisson, C. Marazano, M. Mehmandoust, D. Gnecco, and B. C. Das, *Synlett*, 1992, 431.

4- For a preliminary report of this work see: M. Mehmandoust, C. Marazano, and B. C. Das, *J. Chem. Soc., Chem. Commun.*,1989, 1185.

5- F. N. Stepanov, N. A. Aldanova, A. G. Yurchenko, and N. L. Dovgan, *Metody Polucheniya Khim. Reakttivov i Preparatov, Gos. Kom. Sov. Min. SSSR po Khim*, 1962, **4-5**, 86-92 (*Chem. Abstr.*, 1964, **60**, 15800e).

6- A. Abiko and S. Masamune, *Tetrahedron Lett.*, 1992, **33**, 5517.

7- M. Fry and J. A. Beisler, *J. Org. Chem.*, 1970, **35**, 2809; J. Bosch, M. Rubiralta, and J. Bolos, *Tetrahedron*, 1987, **43**, 391, and references cited therein.

8- A. Casini, B. Di Rienzo, F. Micheletti Moracci, S. Tortorella, F. Liberatore, and A. Arnone, *Tetrahedron Lett.*, 1978, 2139.

9- E. Leete and M. E. Mueller, *J. Am. Chem. Soc.*, 1982, **104**, 6440.

10- J. E. Hodge, Advances in Carbohydrate Chem., 1955, **10**, 169, and references cited therein.

11- E. Späth and F. Kesztler, Ber., 1937, **70**, 239 and 704.

12- J. H. Ager, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, 1969, **12**, 288.

13- L. D. Cama, K. J. Wildonger, R. Guthikonda, R. W. Ratcliffe, and B. G. Christensen, *Tetrahedron*, 1983, **39**, 2531.

Received, 11th April, 1994