DIASTEREOSELECTIVE REDUCTION OF DERIVATIVES OF 3,4-DIHYDRO-1-METHYLIDENE-2-TARTAROYLISOQUINOLINE

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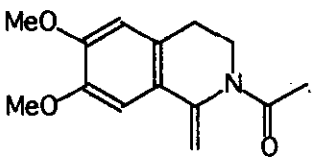
Abstract–Various enamides were prepared from 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline by reaction with (*R, R*)-tartaric acid derivatives. The enamides were reduced with hydrogen over a platinum catalyst to afford diastereomeric mixtures enriched in the (1*R*)-isomer. The diastereoselectivity of the reduction step was assessed by conversion of the mixtures into *N*-acetylsalsolidine and measurement of its specific rotation. The enamide (**5c**), in which the hydroxyl groups of the 2-tartaroyl group are unprotected, cyclizes to an aminal (**9**) in the presence of acids. The reduction of **5c** with sodium borohydride in acidic media afforded a diastereomeric mixture enriched in the (1*S*)-isomer.

The catalytic reduction of linear enamides using homogeneous catalysts of high enantiomeric purity was reported some years ago by Kagan and coworkers.[1—3] In their first two reports, they demonstrated that α-*N*-acylaminoacrylic acids were converted into the corresponding saturated α-*N*-acylamino acids in high optical yield. Also, it was shown[3] that simple enamides would undergo asymmetric hydrogenation and that imines would undergo asymmetric hydrosilylation. Somewhat later Achiwa[4] showed that the enamide, 2-acetyl-1,2,3,4-

tetrahydro-6,7-dimethoxy-1-methylideneisoquinoline (**1**), may be reduced catalytically to 2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline (*N*-acetylsalsolidine) (**2**) using a variety of rhodium complexes. Optical yields varied with the catalyst and with the reaction conditions but did not exceed 45%. Recently, Noyori *et al.*,[5] using the same enamide (**1**) and a chiral ruthenium complex, reported that (*S*)-salsolidine was obtained, after deacetylation of the product (**2**), in 96% enantiomeric excess(ee). Noyori *et al.*[5] have applied the same approach equally successfully to related enamides of the isoquinoline series. Here we report the catalytic reduction, using heterogeneous catalysis, of enamides derived from the hydrochloride of 3,4-dihydro-1-methylisoquinoline (**3**)[6] and various derivatives of tartaric acid.



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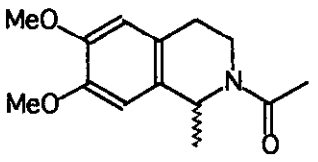

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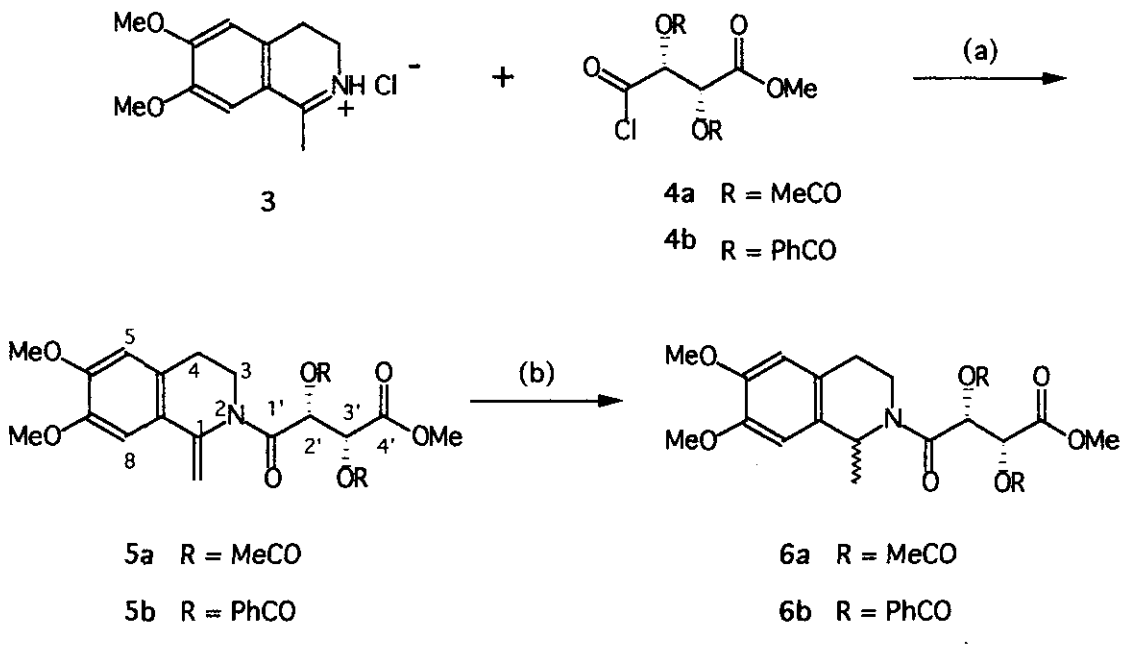
The enamides examined in this study were prepared from **3**[6] and an acyl halide derived from a suitably protected (*R,R*)-tartaric acid. Iminium salt (**3**) was treated with acid chloride (**4a**)[7] or (**4b**)[7,8] in the presence of triethylamine to afford the enamide (**5a**) or (**5b**), respectively (Scheme 1). Hydrogenation of **5a** or **5b** over Adams catalyst afforded unresolvable mixtures of diastereomers (**6a**) or (**6b**), respectively.

In order to assess the diastereoselectivity of the reduction, the amide group of **6a** was removed by treatment with a solution of potassium hydroxide and hydrazine hydrate in refluxing ethylene glycol for 15 min under an atmosphere of nitrogen. The hydrazinolysis product, salsolidine, was acetylated with acetic anhydride in the presence of aqueous sodium hydroxide. *N*-Acetylsalsolidine (**2**) was obtained in 68% yield, based on **5a**. The ee values for **2**, listed in Table 1, are based on comparison of the specific rotation of **2** isolated from the various reactions with the value determined for pure (*R*)-(−)-*N*-acetylsalsolidine[(*R*)-(-)-**2**, $[\alpha]_D^{25}$ -172.8° (*c* 1.83, $CHCl_3$).[9] The latter was prepared by resolution of (±)-salsolidine according to established procedures,[10, 11] followed by *N*-acetylation.

The value of % ee determined from rotation values can often be misleading. Accordingly, a second method was developed to check the values obtained from the rotation data. Compound (**5a**) was converted into the dihydroxy

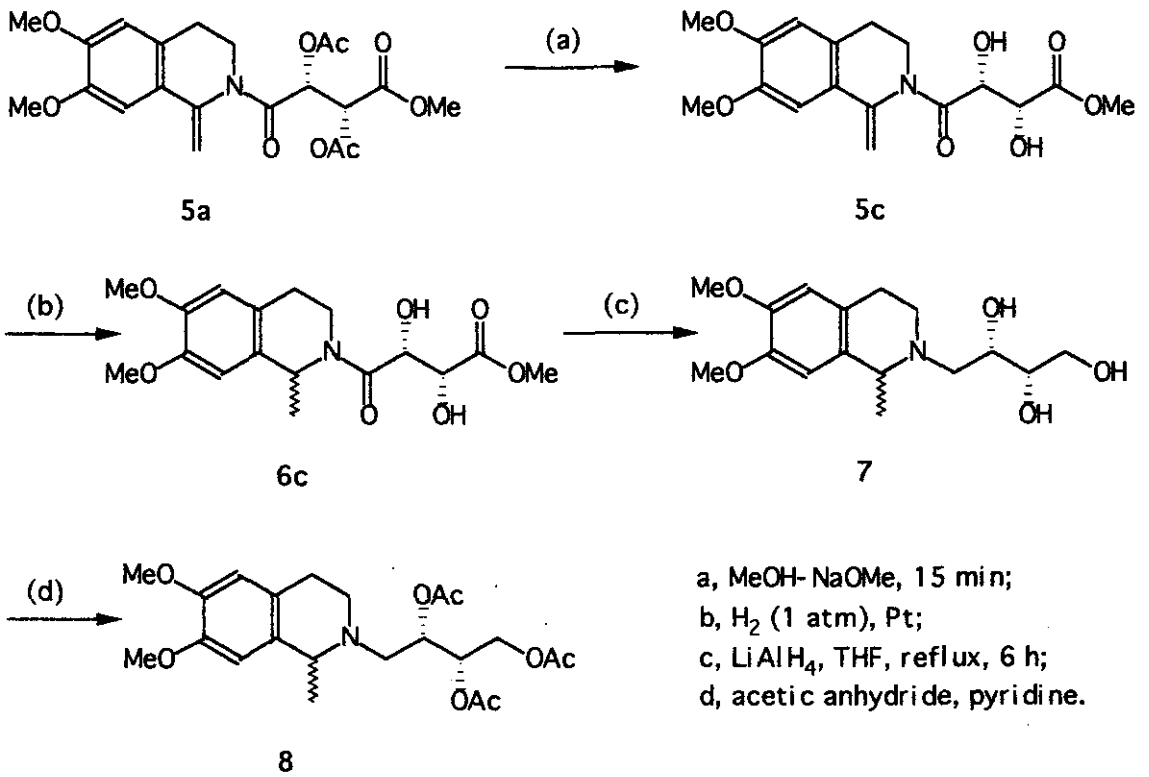
compound (**5c**), by transesterification in MeOH-NaOMe, which was then hydrogenated to the salsolidine derivative (**6c**). Reduction of **6c** with lithium aluminum hydride afforded the amine (**7**). We were unable to separate **6c** or **7** into their respective diastereomeric components even after extensive trials on hlpc. Acetylation of **7** with acetic anhydride/pyridine yielded the triacetate (**8**) (Scheme 2). This mixture of diastereomers was cleanly resolved by hplc on a silica column. Integration of the two peaks indicated a de of 31.6% in the reduction step.



Scheme 1

A sample of **6c** from the same batch used to prepare triacetate (**8**) was hydrolyzed and converted into **2** by the protocol described above. The product (**2**) had $[\alpha]_D^{20}$ - 55.7°(*c* 1.51, $CHCl_3$), from which it was calculated that the ee was 32.3%. (The % ee of **2** is a measure of the diastereoselectivity in the reduction step.) This value compares favorably with the value obtained by hplc resolution of the diastereomeric mixture (**8**). Therefore, it

appears that the % ee can be calculated in this system from measurements of rotation of samples of **2** prepared from the various reduction products.



Scheme 2

Three enamides (**5a, 5b** and **5c**) were reduced and the products hydrolyzed, and converted into **2** according to the protocol already described. The results, including the optical rotation and % ee recorded in Table 1, reveal that solvent and temperature affect the stereoselectivity of the reaction. Higher optical yields are obtained when the temperature is lowered, (e.g., see the cases of the diacetate (**5a**) in methanol at ambient temperature and at -78° C, and of the dibenzoate (**5b**) and the dihydroxy compound (**5c**) in THF at ambient temperature and at -78° C). For reductions performed in *tert*-butyl alcohol the optical yields are fairly uniform for **5a, 5b** and **5c**. However, in THF and methanol the optical yields vary over a wide range from compound to compound and

seemingly bear little relationship between solvent polarity and structure.

Table 1. The specific rotation and % ee of *N*-acetylsalsolidine(**2**) prepared from various enamides by the sequence, catalytic hydrogenation over Pt, hydrazinolysis, and *N*-acetylation

Hydrogenation conditions	Enamide		
	5a	**5b**	**5c**
THF, room temperature	-17.9(10.4)*	-52.4(30.3)	-48.2(27.9)
THF, -8° C	—	-64.8(37.5)	—
THF, -78° C	—	-75.4(43.7)	-62.9(36.4)
MeOH, room temperature	-54.9(31.8)	-28.5(16.5)	-36.2(21.0)
MeOH, -78° C	-67.4(39.0)	—	—
tert-BuOH, 26° C	-58.1(33.7)	-49.8(28.8)	-60.7(35.2)

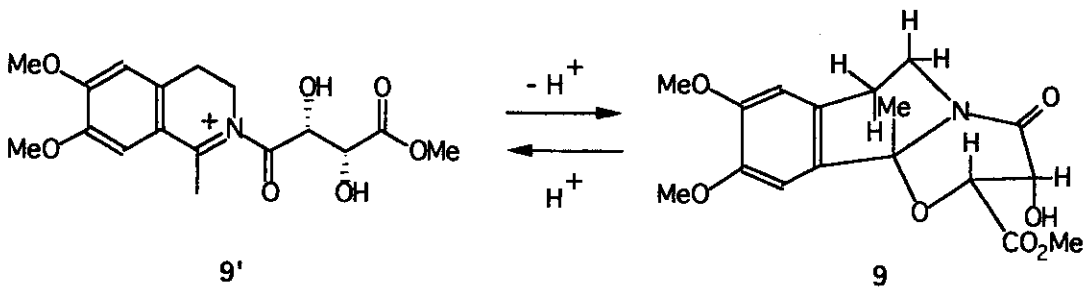
* The figures in brackets are the % ee values calculated from rotation data.

Reduction with hydrogen over PtO_2 leads, in all the systems examined, to the stereoselective formation of the (1*R*)-isomer. However, when the dihydroxy compound (**5c**) was reduced under acidic conditions with $NaBH_4$ the (1*S*)-isomer was formed stereoselectively but in low ee (12%); the isolated yield of **2** was 58%. A possible explanation of this behaviour comes from the observation that compound (**5c**) cyclizes to the aminal (**9**) in acidic chloroform, and **9** may be the species undergoing reduction.

Compound (**9**) was isolated as an unstable oil; its structure was deduced from an examination of its ^1H nmr spectrum and from differential nOe measurements. Apparently, the methylidene group in **5c** had been transformed into a *C*-methyl group in **9** through interaction of the methylidene with an hydroxyl group of the side chain, probably through the intervention of the acyl iminium salt (**9'**). Differential nOe measurements on **9** showed that (a) irradiation of the *C*-Me signal at δ 1.76 enhanced the signals at δ 4.82 (H-3'), δ 6.83 (H-8) and δ 3.30 ($H\text{-}3_{ax}$), (b) irradiation at δ 3.30 ($H\text{-}3_{ax}$) affected the signals at δ 4.41 ($H\text{-}3_{eq}$) and δ 2.65 ($H\text{-}4_{eq}$), (c) irradiation at δ 2.65 ($H\text{-}4_{eq}$) increased the intensity of the signals at δ 3.00 ($H\text{-}4_{ax}$) and 6.54 (H-5), and (d)

irradiation at δ 4.82 (H-3′) enhanced the signal at 4.50 (H-2′). These data support the structure proposed for **9**.

If the aminal is present in acidic ethanol in equilibrium with **9′**, the aminal would be expected to undergo reduction from the face opposite to the *C*-methyl group to afford the (*S*)-isomer. Also, the axial OH group at C-2′ in **9** might complex with the sodium borohydride and promote formation of the (*S*)-isomer at C-1, by facilitating the delivery of hydride to the lower face of the molecule.



9′ **9**

These results show that compound (**5c**) may be reduced to diastereomeric mixtures enriched in either the (1*S*)- or the (1*R*)-isomer depending on the reducing agent employed. Other derivatives of **5c** are under examination in the hope that greater stereoselectivity in the reduction step may be achieved.

EXPERIMENTAL

General Methods. The ^{1}H nmr spectra were recorded on a Bruker AM-500 spectrometer at 500 MHz, or a Varian EM–390 spectrometer at 90 MHz; $CDCl_3$ was the solvent and tetramethylsilane (TMS) was used as the internal standard, unless otherwise stated. Chemical shifts are reported in ppm (δ) downfield from the signal of TMS. The symbols, s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broadened), are used to report the multiplicity and shape of signals. Nuclear Overhauser enhancement (nOe) difference spectra were obtained by subtraction of the off-resonance control FID from the on-resonance FID. The signal of interest was saturated selectively for 5.0 s and the decoupler was gated off during acquisition. This saturation period also served as the relaxation delay. Either 8 or 16 scans were acquired for each irradiation with the cycle of irradiations repeated 4—10 times. Free induction decays were processed using exponential multiplication (line broadening: 4—5 Hz) before Fourier transformation. Samples were not degassed. EI mass spectra were recorded on a VG Micromass 7070F mass spectrometer at an ionizing voltage of 70 eV or on a VG Analytical ZAB-E mass spectometer, and CI spectra were recorded using NH_3 at ~ 1 Torr (1 Torr = 133.3 Pa) as reagent

gas; data are given as *m/z* (% relative intensity). The exact masses were determined under EI conditions; the high-resolution measurements were performed by peak matching using perfluorokerosene as a reference standard and at a resolution of ~ 4000.

Melting points were determined using a Gallenkamp apparatus and are uncorrected. Optical rotations were measured using a Perkin–Elmer 247 MC polarimeter in a 1-ml microcell that is 1 dm in length. Flash chromatography was performed on Kieselgel 60 (230—400 mesh). The homogeneity of the products was established on the basis of chromatographic and spectroscopic (^{1}H nmr and mass spectral) examination.

Preparation of enamide **5a**

A solution of **3**[6] (5.0 g, 0.021 mol) in dry dioxane (200 ml) containing triethylamine (5.9 ml, 0.042 mol) was treated dropwise with stirring with a solution of **4**[7] (5.49 g, 0.021 mol) in dioxane (50 ml) over a period of 10 min. The resulting mixture was stirred an additional 3 h at the same temperature, the precipitate of triethylamine hydrochloride was removed by filtration, and the precipitate was washed with dioxane (50 ml). The combined filtrates were evaporated and the residue taken up in benzene (75 ml). The benzene solution was washed twice with 1% hydrochloric acid (100 ml), once with an aqueous solution of sodium chloride and finally with a saturated solution of sodium bicarbonate (50 ml). The solution was dried over sodium sulfate and evaporated to afford **5a** [single spot on tlc, silica, chloroform–methanol (98:2, v/v)] as a brownish oil (7.03 g, 78%). An analytical sample was prepared by column chromatography on silica (230–400 mesh) using chloroform–methanol (99:1, v/v) as eluent. Compound (**5a**) was obtained as a yellow oil, $[\alpha]_D^{23}$ – 16.6° (*c* 0.63, $CHCl_3$); ^{1}H nmr (90 MHz, $CDCl_3$, δ): 1.95, 2.05 (3 H each, 2 x s, 2 x CH_3CO_2), 2.75-2.95 (2 H, m, C-4 H's), 3.40-3.58 (1 H, m, H-3_{ax}), 3.65 (3 H, s, CO_2CH_3), 3.85, 3.88 (3 H each, 2 x s, 2 x OCH_3), 4.27-4.53 (1 H, m, H-3_{eq}), 5.33 (I H, br s, $w_{1/2}$ = 3.0 Hz, methylidene proton), 5.43 (1 H, d, J=4.5 Hz, H-3′), 5.65 (1 H, br s, $w_{1/2}$ = 3 Hz, methylidene proton), 6.33 (1 H, d, J=4.5 Hz, H-2′), 6.60, 7.15 (1 H each, 2 x s, C-5 and C-8); ms (EI): 435 (8), 392 (19), 376 (4), 318 (7), 247 (13), 205 (100), 190 (39); ms(CI, NH_3): 436 $(M+H)^+$ (100), 392 (10), 298 (7), 206 (96). Mol. wt., calcd for $C_{21}H_{25}NO_8$: 435.1529; found: 435.1539.

Preparation of enamide **5b**

2,3-Di-*O*-benzoyltartaric acid anhydride[8] was converted into (2*R*,3*R*)-dibenzoyloxy-3 methoxycarbonylpropanoyl

chloride (**4b**) in a yield of 63% by the procedure described for the preparation of the diacetoxy analog (**4a**).[7] Treatment of **4b** (6.47 g, 16.6 mmol) with **3** (4.0 g, 16.6 mmol), according to the method described previously for the preparation of **5a**, afforded **5b** (7.05 g, 76%) as colorless crystals from methanol, mp 108-111°C (decomp.), $[\alpha]_D^{25}$ - 2.65° (*c* 2.04, $CHCl_3$); ^{1}H nmr (90 MHz, $CDCl_3$, δ): 2.57-2.75 (2 H, m, H-4_{ax}, H-4_{eq}), 3.32-3.59 (1 H, m, H-3_{ax}), 3.68, 3.76, 3.80 (3 H each, 3 x s, 2 x OCH_3 and CO_2CH_3), 4.18-4.53 (1 H, m, H-3_{eq}), 5.42 (1 H, br s, $w_{1/2}$ = 3 Hz, methylidene proton), 5.61 (1 H, br s, $w_{1/2}$ = 3 Hz, methylidene proton), 5.83 (1 H, d, J=6.0 Hz, H-3′), 6.26, 6.93 (1 H each, 2 x s, H-5 and H-8), 6.68 (1 H, d, J=6.0 Hz, H-2′), 7.30-8.05 (10 H, m, aromatic protons); ms(EI): 559 (M^+) (10), 454 (28), 206 (30); ms (CI, NH_3): 560 (M+H) (65), 454 (10), 354 (18), 318 (30), 264 (10), 206 (100). Mol. wt., calcd for $C_{31}H_{29}NO_9$: 559.1842; found: 559.1842.

Hydrolysis of **5a** to diol **5c**

A solution of **5a** (935 mg, 2.15 mmol) in methanol (50 ml) containing sodium methoxide (945 mg, 17.5 mmol) was stirred at room temperature for 15 min. Acetic acid (0.1 ml) was added and the solution was taken to dryness. A solution of saturated sodium bicarbonate was added to the residue and the resulting mixture was extracted with $CHCl_3$ (3 x 20 ml). The combined extract was washed, dried over sodium sulfate, and evaporated to afford a residue which crystallized from methanol. Compound (**5c**) (754 mg, 88%) was obtained as colorless needles, mp 139-141°C, $[\alpha]_D^{23}$ + 60.6° (*c* 1.21, $CHCl_3$); ^{1}H nmr (90 MHz, $CDCl_3$, D_20, δ): 2.57-3.52 (3 H, m, C-4 protons and H-3_{ax}), 3.80 (3 H, s, CO_2CH_3), 3.88, 3.93 (3 H each, 2 x s, 2 x OCH_3), 4.20 (1 H, d, J=3.0 Hz, H-3'), 4.63-4.85 (1 H, m, H-3_{eq}), 5.18 (1 H, br s, $w_{1/2}$ = 3 Hz, methylidene proton), 5.23 (1 H, d, J=3.0 Hz, H-2′), 5.65 (1 H, br s, $w_{1/2}$ = 3 Hz, methylidene proton), 6.60, 7.10 (1 H, d, 2 x s, H-5 and H-8); ms(EI): 351 (M^+) (12), 336 (51), 292 (7), 262 (7), 248 (12), 206 (100), 190 (20); ms(CI, NH_3): 352 $(M+H)^+$ (100), 336 (7), 246 (4), 206 (21), 192 (7). Mol. wt., calcd for $C_{17}H_{21}NO_7$: 351.1318; found: 351.1317.

General procedure for reduction of enamides. Reduction of **5c** to **6c**

Compound (**5c**)(150 mg, 0.43 mmol) in methanol (30 ml) was treated with hydrogen over Adams catalyst (15 mg) at room temperature and atmospheric pressure for 3 h. The catalyst was removed by filtration and the filtrate evaporated. The residue was chromatographed on silica (230–400 mesh) using chloroform–methanol (20:1, v/v) as eluent. Compound (**6c**) was obtained as a colorless oil (132 mg, 87%), $[\alpha]_D^{25}$ - 35.7° (*c* 1.97, $CHCl_3$); ^{1}H nmr (90 MHz, $CDCl_3$, D_20, δ): 1.45 (~ 2 H, d, J=7.5 Hz, CHC*H*$_3$), 1.57 (~ 1 H, d, J=7.5 Hz, CHC*H*$_3$),

2.72-3.07 (2 H, m, H-4_{ax} and H-4_{eq}), 3.33-3.68 (1 H, m, H-3_{ax}), 3.87 (9 H, br s, 2 x OCH_3, and CO_2CH_3), 4.27-4.50 (2 H, m, H-3_{eq} and H-3′), 4.80 (1 H, d, J=3.0 Hz, H-2′), 5.46 (1 H, q, J=7.5 Hz, H-1), 6.63 (2 H, br s, H-5 and H-8); ms(EI): 353 (M^+) (20), 338 (25), 264 (50), 206 (35), 192 (100); ms(CI, NH_3): 354 $(M+H)^+$ (100), 264 (15), 206 (18). Mol. wt., calcd for $C_{17}H_{23}NO_7$: 353.1475; found: 353.1481.

General procedure for hydrolysis of the amide group and conversion of the hydrolysis product into (*R*)-**2**.

Conversion of **6c** into *(R)-(-)-2*

A mixture of **6c** (125 mg, 0.35 mmol), potassium hydroxide (120 mg, 12.14 mmol), and hydrazine hydrate (0.2 ml, 98%, 4.1 mmol) in ethylene glycol (15 ml) was heated at reflux temperature in a nitrogen atmosphere for 15 min. A saturated aqueous solution of sodium chloride (50 ml) was added to the cooled reaction mixture which was then extracted with chloroform (4 x 15 ml). The extract was washed with water and added to a solution of sodium hydroxide (20%). The two-phase system was treated with acetic anhydride (2.0 ml, 21.2 mmol) and vigorously stirred for 20 min. The phases were separated and the chloroform phase was washed, dried over sodium sulfate, and evaporated. The residue was chromatographed on a silica column (230–400 mesh) using chloroform–methanol (98:2, v/v) as eluent. Compound (**2**) was isolated as a colorless oil (68 mg, 77%),$[\alpha]_D^{25}$ - 36.2 (*c* 1.49, $CHCl_3$); ^{1}H nmr (90 MHz, $CDCl_3$, δ): 1.40 (~ 1.8 H, d, J=7.5 Hz, CH*CH*$_3$), 1.50 (~ 1.2 H, s, CH*CH*$_3$), 2.15 (~ 1.8 H, s, $COCH_3$), 2.18 (~ 1.2 H, s, $COCH_3$), 2.45-2.92 (2 H, m, H-4_{ax} and H-4_{eq}), 3.42-3.76 (2 H, m, H-3_{ax} and H-3_{eq}), 3.83 (6 H, br s, 2 x OCH_3), 4.86 (~ 0.4 H, br q, J=7.5 Hz, C*H*CH_3) and 5.33 (~ 0.6 H, br q, J=7.5 Hz, C*H*CH_3), 6.60 (2 H, br s, H-5 and H-8).

Conversion of **6c** into *N - 2′,3′,4′ -trihydroxybutyl- 1,2,3,4 - tetrahydro- 6,7 -dimethoxy -1 methylisoquinoline* (**7**) and its triacetate (**8**)

Compound (**6c**) (285 mg, 0.81 mmol) in boiling THF was treated with lithium aluminum hydride (400 mg, 10.5 mmol) over a period of 6 h. The excess of hydride was decomposed with a saturated aqueous solution of sodium sulfate, the inorganic precipitates were removed by filtration and the solid residue was washed four times with hot THF. The combined organic filtrate was evaporated to afford compound (**7**) (172 mg, 70%) as a yellow oil which darkened quickly on exposure to air. The product (**7**) was treated directly with acetic anhydride (1 ml, 10.6 mmol) in dry pyridine (10 ml, 0.11 mol) to afford **8** after the standard processing as an oil (198 mg, 82%), $[\alpha]_D^{20}$ - 27.4° (*c* 2.23, $CHCl_3$); ^{1}H nmr (90 MHz, $CDCl_3$, δ): 1.31 (3 H, d, J = 6.6 Hz, CH_3 at C-1), 2.05, 2.07, 2.11

(3 H each, 3 s, CH_3CO_2), 2.46 - 3.20 (7 H, br m, 2 H-1', 2 H-3, 2 H-4, H-1), 3.83 (6 H, br s, 2 x OCH_3), 4.02 (1 H, dd, J_1 = 11.7 Hz, J_2 = 6.6 Hz, H-4'), 4.28 (1 H, dd, J_1 = 11.7 Hz, J_2 = 4.7 Hz, H-4'), 5.22 (1 H, m, H-2'), 5.42 (1 H, m, H-3'), 6.54 (2 H, br s, H-5 and H-8). An analytical sample was prepared by chromatography on silica (230–400 mesh) using $CHCl_3$–MeOH (98:2, v/v) as eluent. Anal. Calcd for $C_{22}H_{31}NO_8$: C, 60.40, H, 7.14, N, 3.20. Found: C, 60.28, H, 6.95, N, 2.87.

Resolution of the diastereomeric mixture was effected on a silica column (analytical, SI 60) using dichloromethane–methanol (99.25 : 0.75, v/v) at a flow rate of 1.9 ml/min and a chart speed of 5 mm/min. The diastereomeric composition was obtained by integration of the peak areas. The % de (31.6%) was calculated according to the equation, % ee = $\frac{x-y}{x+y}$ x 100.

A portion of compound (**6c**), prepared from the same hydrogenation of **5c** as that used in the preparation of **8**, was converted into **2** by the procedure previously described but using THF as the solvent in the hydrogenation reaction. Compound (**2**), isolated in this experiment, had $[\alpha]_D^{20}$-55.6° (*c* 1.51, $CHCl_3$), % ee = 32.2% based on the revised value of $[\alpha]_D^{20}$-172.8° (*c* 1.83, $CHCl_3$) obtained by resolution of (±)-salsolidine with L-(+)-tartaric acid followed by *N*-acetylation.

Reduction of **5c** with sodium borohydride in acidic medium

Acetyl chloride (3 ml, 42 mmol) was added with stirring at 20°C to absolute ethanol (150 ml) and after 10 min the mixture was cooled to -5°C (ice–salt bath). The cooled solution was treated all at once with compound (**5c**) (340 mg, 0.97 mmol) and stirred for 2 h at -5°C. To this solution sodium borohydride (0.5 g, 13.2 mmol) in absolute ethanol (20 ml) was added dropwise over a period of 15 min and stirring was continued for a further 15 min. At this point, a solution of sodium bicarbonate (4 g) in water (50 ml) was added and volatile solvents were then removed under vacuum. The remaining aqueous solution was extracted with chloroform (3 x 25 ml), the extract was evaporated to dryness, and the residue was treated successively with hydrazine–potassium hydroxide and acetic anhydride in the manner described for the preparation of (-)-**2** from **6c**. Column chromatography on silica using chloroform–methanol (98:2, v/v) afforded (+)-**2** as a colorless oil (139 mg, 58%); $[\alpha]_D^{25}$+ 20.45° (*c* 1.39, $CHCl_3$).

Conversion of compound (**5c**) into the aminal (**9**)

Compound (**5c**) (150 mg, 0.43 mmol) was added to a mixture of chloroform (25 ml) containing concentrated hydrochloric acid (2 drops) and anhydrous magnesium sulfate (1.0 g, 8.33 mmol) and the mixture was stirred for 30 min. The inorganic material was removed by filtration, the solvent was evaporated and the residue was chromatographed on silica (230–400 mesh) using chloroform–methanol (97:3, v/v) as eluent. Compound (**9**) (127 mg, 85%) was recovered as an unstable colorless oil, $[\alpha]_D^{25}$ - 62.0° (*c* 2.05, $CHCl_3$); ^1H nmr (500 MHz, $CDCl_3$, δ): 1.75 (3 H, s, C-CH_3), 2.20 (1 H, br s, OH), 2.62-2.67 (1 H, m, H-4_{eq}), 2.98-3.05 (1 H, m, H-4_{ax}), 3.27-3.33 (1 H, m, H-3_{ax}), 3.79, 3.85, 3.90 (3 H each, 3 x s, CO_2CH_3, and 2 x OCH_3), 4.33-4.37 (1 H, m, H-3_{eq}), 4.49 (1 H, s H-2′), 4.82 (1 H, s, H-3′), 6.54 (1 H, s, H-5), 6.83 (1 H, s, H-8); ms(EI): 351 (M^+) (25), 336 (100), 248 (33), 206 (20), 190 (15); ms(CI, NH_3): 352 $(M+H)^+$ (30), 336 (100), 206 (15). Mol. wt., calcd for $C_{17}H_{21}NO_7$: 351.1318; found: 351.1324.

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