SHORT PAPER

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Total synthesis of bernumicine and bernumidine, two alkaloids from *Berberis nummularia*†

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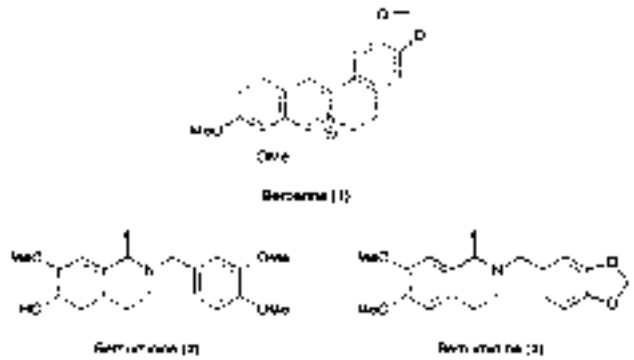
Bernumicine and bernumidine are two alkaloids extracted from *Berberis nummularia*. Their total synthesis has been completed and it has been shown that the configuration of the stereogenic carbon of both is (*R*).

Keywords: *Berberis nummularia*, bernumicine, berhumidine, alkaloids

Plants of the genus *Berberis* have been used in traditional medicine for centuries in various part of the world. This is the case for the common barberry (*Berberis vulgaris*) whose bark is known to give a tonic, purgative and antiseptic extract. The chief constituent of barberry barks is berberine **(1)** (Scheme 1).[1] This compound has many interesting biological properties, including activity against bacteria, fungi and viruses. Berberine is also present in the roots of *B. aquifolium* and *B. arista* as well as in many other plants.



Scheme 1

In 1993, Karimov and Shakirov reported the results of their investigations on *B. nummularia*, a plant growing in the Fergana province of Uzbekistan.[2] Not surprisingly, berberine and some other previously known alkaloids were identified in the ethanol extract of young shoots. More interestingly, two new alkaloids were found in the chloroform extract of the leaves. The structures of these new optically active amines were deduced from NMR, UV, IR and MS studies. They were named bernumicine **(2)** and bernumidine **(3).** In this paper, we report the first total synthesis of these two alkaloids.

Bernumicine can be regarded as a derivative of salsoline **(4)** (Scheme 2). Racemic O-benzyl-salsoline **(5)** was prepared earlier by a Bischler-Napieralski / reduction procedure,[3] but we preferred a Pictet-Spengler strategy, using the conditions described by Venkov.[4] The rather unstable amine **(5)** was stabilized as its benzyl carbamate **(6),** which upon treatment with acetaldehyde diethyl acetal[4] gave the tetrahydroisoquinoline. Both protecting groups were then hydrogenolysed[5] to give racemic salsoline **(4).** The overall yield of **(4)** from **(5)** was 86%. Coupling of the benzylic moiety with salsoline was achieved *via* the tosylate. It appeared more efficient to prepare

Scheme 2

the tosylate of **(7)** in THF and react it *in situ* with salsoline **(4)** to give racemic bernumicine **(2)** in 76% yield (65% from **(5)).**

In order to obtain non-racemic bernumicine, we resolved *rac*-**(4)**.[6] This was done by treatment with (L)-(+)-tartaric acid. The (*R*)-(+)-salsoline – (L)-(+)–tartaric acid salt precipitates in water, whereas the (*S*)-(-)-salsoline salt is soluble.[6,7] (*R*)-(+)-**(4)** was treated with the tosylate of **(7)** to give (*R*)-bernumicine. HPLC experiments run on *rac*-**(2)** and (R)-**(2)** showed that the isolated (R)-bernumicine **(2)** was enantiopure. The absolute configuration of this enantiopure bernumicine was confirmed by X-ray crystallography. Figure 1 presents the structure that we obtained from single crystals of non-racemic bernumicine - (L)-tartaric acid salt. This salts precipitates as a dihydrate.

In a similar way, the racemic salsolidine **(11)**[6–8] (Scheme 2) was obtained from amine **(9)** and coupled with the tosylate of **(8)** gave racemic bernumidine **(3).** In order to obtain non-racemic **(3),** we resolved Salsolidine **(11)** with D-(-)-tartaric acid.[8] The (*R*)-(+)-Salsolidine-D-(-)-tartaric acid precipitates first. Two recrystallizations led to a sample of (*R*)–(+)-**(11)** of limited optical purity: $[\alpha]_D$ 44 (c=2.0; EtOH, lit.[9] $[\alpha]_D$ 62.8 (c=0.1, EtOH). From this sample, we obtained (*R*)-(+)-**(3)** for which the measured $[\alpha]_D$ was +18 (c=0.05, $CHC1_3$), while e.e. was 70% by HPLC. The $[\alpha]_D$ reported[2] for natural bernumidine is +21 (c 0.01, $CHCl_3$).

Experimental

Preparation of 2-(3-benzyloxy-4-methoxy-phenyl)-ethylamine **(5)**: A mixture of the commercially available 4-benzyloxy-3-methoxy-benzaldehyde (9.69g, 40mmol), ammonium acetate (3.55g,

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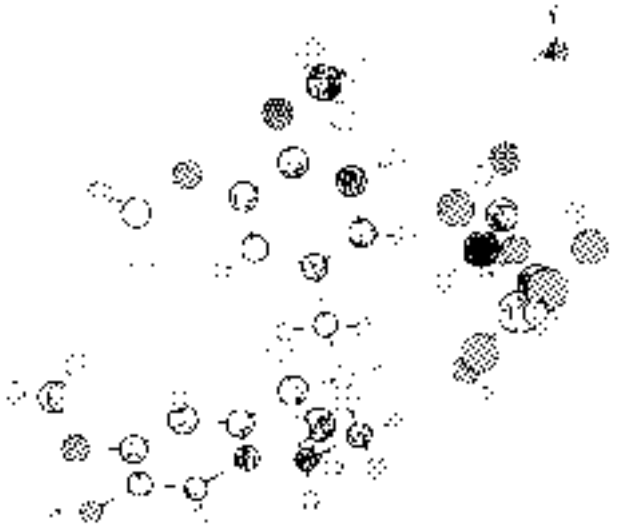

Fig. 1 X-ray structure of the (*R*)-bernumicine (L)-tartrate

1.15equiv), and nitromethane (87ml, 40eq) was brought to reflux.[10] The reaction was monitored by TLC (silica gel, CH_2Cl_2) and stopped as soon as possible to avoid Michael addition of nitromethane to the product. The excess of nitromethane was removed by evaporation, the crude material taken up in CH_2Cl_2 (200ml) and washed with water (2 × 100ml). After drying over $MgSO_4$, concentration, and recrystallization in ethanol, 11.4g (quantitative) of yellow solid 3-benzyloxy-4-methoxy-β-nitrostyrene were obtained. M.p. 129–131°C. ^{1}H NMR ($CDCl_3$, 250MHz) 3.93 (s, 3H), 5.17 (s, 2H), 6.92 (d, *J* 8.7Hz, 1H), 7.02 (d, *J* 1.6Hz, 1H), 7.16(dd, *J* 8.7Hz, 1.6Hz, 1H), 7.3–7.5 (m, 6H), 7.89 (d, *J* 13.5Hz, 1H). ^{13}C NMR ($CDCl_3$, 62.5MHz) 56.01, 71.05, 111.63, 112.97, 122.55, 124.85, 127.22, 127.58, 128.61, 134.98, 136.20, 139.23, 148.45, 153.36.

In a two-necked, 500 ml flask fitted with a reflux condenser and under argon atmosphere, a suspension of lithium aluminium hydride (2.67g, 70mmol) in 50ml THF was brought to reflux. A solution of 10.0g (35.1 mmol) of the nitroalkene in 150ml THF was added dropwise over 2 h, with reflux. After 30 min, the flask was cooled to 0°C and water (22ml) was added very carefully. After 5 min stirring, the slurry was filtered over celite. The solid phase was repeatedly washed with THF. The organic phases were dried over Na_2SO_4 and concentrated to yield 7.05g (78%) of 2-(3-benzyloxy-4-methoxy-phenyl)-ethylamine[11] **(5),** m.p. 161–162°C.^{1}H NMR ($CDCl_3$, 250MHZ): 1.4 bs, 2H), 2.54 (t, *J* 6.7Hz, 2H), 2.78 (t, *J* 6.7Hz, 2H), 3.78 (s, 3H), 5.06 (s, 2H), 6.74 (s, 1H), 6.75 (d, *J* 7.9Hz, 1H), 6.79 (d, *J* 7.9Hz, 1H), 7.2–7.4 (m, 5H). ^{13}C NMR ($CDCl_3$, 62.5MHz): 38.79, 43.01, 55.60, 70.51, 111.55, 114.60, 120.97, 126.91, 127.35, 128.02, 131.79, 136.72, 147.48, 147.70. The material is air- and light-sensitive and was rapidly protected as carbamate **(6):**

Potassium carbonate (4.5g, 33mmol) was added to a suspension of **(5)** (5.66g, 22 mMol) in 20 ml water 4.5g. After cooling to 0°C, 4.88g (28.6mmol) of benzyl chloroformate was added with vigourous stirring. After 90 min at 20°C, the carbamate **(6)** precipitated. Water (40 ml) and CH_2Cl_2 (40ml) were added, the aqueous phase was extracted with 4 × 50ml CH_2Cl_2, the combined organic phases dried over $MgSO_4$ and concentrated, yielding 6.96 g (22mmol) of carbamate **(6)**[11] as a white solid, m.p. 84–85°C, ^{1}H NMR ($CDCl_3$, 20MHz) 2.69 (t, *J* 6.8Hz, 2H), 3.37 (t, *J* 6.8Hz, 2H), 3.84 (s, 3H), 4.80 (t, *J* 6.8Hz, 1H), 5.1 (bs, 4H), 6.7–7.0 (m, 3H), 7.2–7.5 (m, 10H); ^{13}C NMR ($CDCl_3$, 50MHz): 35.27, 42.06, 55.88, 66.32, 70.95, 12.13, 114.95, 121.21, 121.29, 127.60, 127.70, 127.95, 128.24, 131.09, 136.49, 136.95, 148.10, 148.36, 156.10.

Benzyl (6-benzyloxy-7-methoxy-1-methyl-3,4-dihydro-1H-isoquinoline-)2-carboxylate:[12] in a 25ml round-bottomed flask fitted with a reflux condenser and a magnetic stirrer, were introduced 5.3g (16.8mmol) of carbamate **(6)**, 3.20g (1.6 eq.) of 1,1-diethoxyethane and 0.25g of *p*-toluenesulfonic acid in 8ml CH_2Cl_2. The reaction mixture was refluxed overnight, then another portion of 0.25g *p*-toluenesulfonic acid was added, and relux continued for 8 h. The crude material was then concentrated *in vacuo*,then taken up in 70ml CH_2Cl_2, and washed with 20ml of 1M HCl, then 20ml of a 10% $NaHCO_3$ solution. After drying over $MgSO_4$ and concentration, the white solid (5.7g, quantitative yield) was recrystallized in ether, m.p. 106–108°C. ^{1}H NMR ($CDCl_3$, 20MHz) 1.45 (d, *J* 5.6Hz, 3H), 2.64 (d, *J* 15.1Hz, 1H), 2.75–3.0 (m, 1H), 3.15–3.4 (m, 1H), 3.85 (s, 6H), 4.13 and 4.25 (two b.d., *J* 8.7Hz,1H), 5.1–5.3 (m, 1H), 5.17 (s, 2H), 6.59 (s, 2H), 7.3–7.5 (m, 5H). ^{13}C NMR ($CDCl_3$, 50MHz) 21.60, 22.10, 28.20, 28.37, 37.24, 37.62, 49.94, 55.70, 55.82, 66.80, 109.44, 111.10, 125.40, 125.74, 127.79, 128.29, 129.73, 130.29, 136.67, 147.37, 154.69, 154.91 (two isomers due to carbamate function).

Rac-salsoline **(4):** 5.0g (12.0 mmol) of this carbamate were dissolved in 60ml of a 4.4% solution of formic acid in methanol.[5] 2.5g of palladium (10% on carbon) were added, and the reaction vessel was purged with hydrogen at atmospheric pressure. After 30h at room temperature, the reaction mixture was filtered, the catalyst was washed with 100ml CH_2Cl_2, dried over $MgSO_4$ and concentrated to yield 2.31g (quantitative) of *rac*-**(4)** as a white solid, m.p. 220–221°C. ^{1}H NMR ($CDCl_3$, 300MHz) 1.50 (d, *J* 6.5Hz, 3H), 2.69 (dt, *J* 16.5, 6.0 Hz, 1H), 2.82 (ddd, *J* 16.5, 5.49, 5.7 Hz, 1H), 3.04 (ddd, 12.5, 5.7, 5.0 Hz, 1H), 3.27 (ddd, *J* 12.5, 5.0, 5.5 Hz, 1H), 3.7–3.9 (m, 2H), 3.82 (s, 3H), 4.10 (q, *J* 6.5 Hz,1H), 6.6 (s, 1H), 6.61 (s, 1H). ^{13}C NMR ($(CD_3)_2CO$, 75MHz) 19.15, 24.33, 38.30, 49.88, 55.83, 109.99, 115.01, 123.84, 124.42, 145.96, 146.68. Calcd. For $C_{11}H_{15}O_2N$ 68.37, 1.82, 7.28; fnd. 68.22, 7.72, 7.26.

Rac-salsoline **(11):** prepared identically from commercially available 2-(3′,4′-dimethoxy)-ethylamine in quantative yield. Benzyl 2-(3′,4′-dimethoxy-phenyl)-ethylaminocarboxylate: m.p. 73–77°C. ^{1}H NMR ($CDCl_3$, 200MHz) 2.75 (t, *J* 6.5Hz, 2H), 3.45 (q, *J* 6.5 Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 4.75 (t, *J* 6.5 Hz, 1H), 5.09 (s, 2H), 6.6-6.85 (m, 3H), 7.2–7.5 (m, 5H). ^{13}C NMR ($CDCl_3$, 75MHz) 35.50, 42.21, 55.67, 55.76, 66.35, 111.26, 111.79, 120.54, 128.02, 128.41, 131.08, 136.46, 147.52, 148.85, 156.19.

Benzyl (6,7-dimethoxy-1-methyl-3,4-dihydro-1H-isoquinolein-)2-carboxylate **(10):** m.p. 106–108°C. ^{1}H NMR ($CDCl_3$, 250MHz) 1.45 (d, *J* 5.5 Hz, 3H), 2.64 (d, *J* 15.1 Hz, 1H), 2.75–3.0 (m, 1H), 3.15–3.4 (m, 1H), 3.85 (s, 6H), 4.13 (d, *J* 8.7 Hz, 0.5H, carbamate isomers), 4.27 (d, *J* 8.7 Hz, 0.5H), 5.1–5.3 (m, 1H), 5.17 (s, 2H), 6.59 (s, 2H), 7.3–7.5 (m, 5H). ^{13}C NMR (($CDCl_3$, 62.5MHz) 21.60, 22.10, 28.20, 28.37, 37.24, 37.62, 49.94, 55.70, 55.82, 66.80, 109.44, 111.10, 125.40, 125.74, 127.79, 128.29, 129.73, 130.29, 136.67, 147.37, 154.69, 154.91.

Rac-salsolidine **(11)**: M.p. 99–102°C. ^{1}H NMR ($CDCl_3$, 200MHz) 1.65 (d, *J* 6.2 Hz, 3H), 2.9–3.3 (m, 2H), 3.1–3.55 (m, 2H), 3.78 (s, 6H), 4.50(q, *J* 6.2 Hz,1H), 6.51 (s, 1H), 6.53 (s, 1H), 10.0 (s, 1H). ^{13}C NMR ($CDCl_3$, 62.5MHz) 21.08, 25.11, 38.78, 51.52, 55.81, 55.99, 108.68, 111.32, 123.24, 125.01, 148.26, 148.65. CHN: Calcd. For $C_{12}H_{17}O_2N$ 69.54, 8.27, 6.75; fnd. 69.39, 8.22, 6.58.

Resolution of salsoline **(4)**:[6] A mixture of 8.0g (41.4mmol) of *rac*-salsoline **(4)** and L-(+)-tartaric acid (6.21g, 1.0 eq.) was dissolved in 80ml of hot water. The precipitate was filtered and recrystallized 4 times in hot water until the optical rotation of the (L)-tartrate remained constant ($[\alpha]_D$ = +25(c=0.5 in EtOH)). The crystals (5.28g) were dissolved in 30ml of hot water and 33% ammonia was added until the solution was basic. (R)-(+)-Salsoline crystallized as white needles (3.64g, 18.8mMol). $[\alpha]_D$ = +72 (c=0.1 in EtOH).

Resolution of salsolidine **(11)**:[8] a mixture of 2.00g (9.65mmol) of *rac*-salsolidine **(11)** and D-(-)-tartaric acid (1.45g, 1 eq.) was dissolved in 10ml of hot water. A precipitate falled out on cooling, was recrystallized once in hot water. The solid was taken up in 5ml of a saturated Na_2CO_3 solution, and extracted in ether (4 × 5ml). 460mg of (+)-salsolidine **(11),** $[\alpha]_D$ = +44 (c=2 in EtOH).

Bernumicine **(2):** In a round-bottomed flask under argon atmosphere was placed a 0.5 molar solution of 3,4-dimethoxy-benzyl alcool in dry THF. After addition of a small crystal of 1,1–*o*-phenantroline, a solution of *n*-butyllithium in hexane was added dropwise at room temperature, until a persistent violine coloration appeared. After 5 min stirring, 1.1eq of *p*-toluenesulfonyl chloride was added. After 15 min, LiCl precipitated. A mixture of salsoline **(4)** (1.0eq.) and diisopropylethylamine (1.1eq.) in dry CH_2Cl_2 was added, and the mixture was kept at room temperature for several days. The reaction mixture was partioned between ether and water, the aqueous phase extracted with ether, the organic phases were dried over $MgSO_4$, concentrated, and purified by chromatography on silicagel (pentane/ethyl acetate 2/1).

225 mg of *rac*-bernumicine **(2)** were obtained from 165mg of *rac*-**(4)** after 15 days (76% yield), m.p. 159-160°C. ^{1}H NMR ($CDCl_3$, 300MHz) 1.35 (d, *J* 6.5 Hz, 3H), 2.55 (dt, *J* 15.6, 4.5 Hz,1H), 2.71 (ddd, *J* 12.1, 5.3, 4.5 Hz,1H), 2.80 (ddd, *J* 15.6, 9.1, 5.3 Hz,1H), 3.05 (ddd, *J* 12.1, 9.1, 4.5 Hz,1H), 3.64 (d, *J* 13.3Hz,1H), 3.73 (d, *J* 13.3Hz,1H), 3.79 (q, *J* 6.5 Hz,1H), 3.83 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 5.45 (bs, 1H), 6.51 (s, 1H), 6.63 (s, 1H), 6.80 (d, *J* 8.3 Hz,1H), 6.88 (dd, *J* 8.3, 0.5 Hz, 1H), 7.00 (d, *J* 0.5 Hz,1H). ^{13}C NMR ($CDCl_3$,

75MHz): 20.03, 26.34, 43.58, 55.68, 55.94, 56.00, 57.69, 109.67, 110.94, 111.87, 114.27, 120.71, 126.98, 131.67, 132.26, 143.84, 144.94, 148.04, 145.05. CHN: Calcd. for $C_{20}H_{25}O_4N$ 69.94, 7.34, 4.08; fnd. 69.68, 7.19, 4.10.

967mg of (*R*)-**(4)** yielded after 8 days 979mg (40%) of (*R*)-**(2),** $[\alpha]_D$ = +45.5 (c=0.02, $CHCl_3$). Enantiomeric purity was checked by HPLC: Daicel CHIRALPAK AD column, 250mm. Elution cyclohexane/isopropanol, 1ml/min, linear gradient from 80% cyclohexane to 60% after 20 min. room temperature 5.61 min (*(S)*-bernumicine), 6.56mn (*(R)*-bernumicine). The optically active sample was >99% e.e. Addition of 1 eq. of) (L)-tartaric acid followed by recrystallization in EtOH-H_2O, produced white crystals. The absolute configuration of **(2)** was ascertained by X-ray diffraction analysis.

Crystal data: for $C_{24}H_{35}NO_{12}$ or $(C_{20}H_{26}NO_4)^+.(C_4H_5O_6)^-.2H_2O$, M_F = 529.54, F(000) = 1128, orthorhombic, space group $P2_12_12_1$ (N° 19), *a* = 7.615(2) Å, *b* = 13.664(3) Å, *c* = 25.150(9) Å, *V*= 2671(1) $Å^3$, $d_{calc.}$ = 1.344 g/cm^3, *Z* = 4, μ(MoKα) = 1.08 cm^{-1}. radiation MoKα (0.7107 Å), diffractometer Enraf Nonius CAD-4, temperature 20°C, crystal size 0.39 x 0.36 x 0.35 mm, scan Mode ω-2θ,θ range 2-30°C, no of unique data 2795 [$I > 1.5\sigma(I)$], R^a 0.052, $R_W{}^b$ 0.054, GOF 1.98. The crystal structure was solved using direct methods, SIR92.[13] Hydrogen atoms were located by difference-Fourier syntheses, but not refined. All the calculations, from the data reduction to the final refinements and geometry calculations were performed using the teXsan software.[14] The data have been deposited at the Cambridge Structural Database and registered under the reference CCDC 143668.

Bernumidine **(3):** samples of *(R,S)*- and *(R)*-bernumidine **(3)** were prepared from 200mg of *(R,S)*- and *(R)*-**(11)** and piperonyl alcohol following the preceding protocol. Yields were 38 to 46% after 8 days. ^{1}H NMR ($CDCl_3$, 200MHz): 1.35 (d, *J* 6.5, 3H), 2.57 (dt, *J* 15.5, 4.0 Hz,1H), 2.68 (ddd, *J* 12.1, 4.5, 4.0 Hz, 1H), 2.81 (ddd, *J* 15.5, 9.0, 4.5 Hz,1H), 3.04 (ddd, *J* 12.1, 9.0, 4.0 Hz,1H), 3.59 (d, *J* 13.3 Hz,1H), 3.70 (d, *J* 13.3 Hz, 1H), 3.77(q, *J* 7.0 Hz,1H), 3.81 (s, 3H), 3.83 (s, 3H), 5.91 (s, 2H), 6.52 (s, 1H), 6.56 (s, 1H), 6.73 (d, *J* 7.5 Hz,1H), 6.80 (dd, *J* 7.5, 1 Hz, 1H), 6.93 (D, *J* 1Hz, 1H). ^{13}C NMR ($CDCl_3$, 50MHz): 19.80, 26.73, 43.71, 55.71, 55.88, 56.00, 57.82, 100.81, 107.83, 109.16, 110.58, 111.60, 121.68, 126.17, 132.19, 133.45, 146.48, 147.33, 147.42, 147.72. CHN (*rac* sample): Calcd.for $C_{20}H_{23}O_4N$ 70.36, 6.79, 4.10; fnd. 70.16, 6.79, 4.00.

$[\alpha]_D$ = +18 (c=0.05, $CHCl_3$) for the sample prepared from *(R)*-**(11).** HPLC: Daicel CHIRALPAK AD column, 250mm. Elution cyclohexane/isopropanol, 1ml.min, linear gradient from 80% cyclohexane to 60% after 20min. Room temperature 4.70 mn (*(S)*- bernumidine), 6.22 min (*(R)*- bernumidine). The optically active *(R)*-**(11)** was 70% e.e.

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