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ENANTIOSELECTIVE SYNTHESIS OF THE TETRAHYDROBENZYL-ISOQUINOLINE ALKALOID (-)-NORARMEPAVINE USING POLYMER SUPPORTED REAGENTS

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Abstract – We describe, in full, the enantioselective synthesis of the tetrahydrobenzylisoquinoline alkaloid (-)-norarmepavine (**1**) in 77% e.e. This compound was prepared using solid-supported reagents and scavengers in multi-step sequences of reactions to give materials that required no conventional purification at the individual steps.

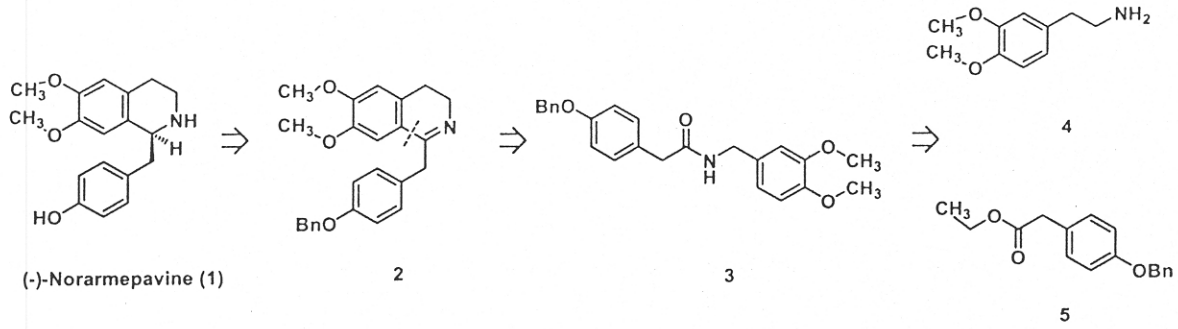
The utilization of solid-supported reagents in chemical synthesis has been shown to markedly improve productivity in many critical aspects of the generation of new chemical entities and complex target molecules.[1] The potential to configure the reactions in both a serial and convergent fashion offers many distinct advantages compared to solid-phase on-bead synthesis. In addition, the simple removal of spent reagents through filtration enables reactions to be driven to completion through the addition of excess reagents and for lower yielding reactions to be worked up using scavenger resins. We have previously reported on the use of these concepts in the sequential multi-step synthesis of various natural products using solid-supported reagents and scavengers to effect all the individual steps.[2] As a consequence, no chromatographic purification procedures were necessary and all steps proceeded with minimum optimization. In order to extend these methods to the asymmetric synthesis of natural compounds we have investigated in this work the preparation of the tetrahydrobenzylsoquinoline alkaloid (-)-norarmepavine (**1**).[3]

Norarmepavine was isolated in 1963 from the American lotus, *Nelumbo lutea* (Nymphaeaceae).[4] This alkaloid has been tested for biological activity in three pharmacological screening procedures.[4,5] In mice it produces mydriasis, bradypnea and a decrease in spontaneous motor activity after oral doses of 200 mg/Kg.

At a dose of 100 mg/Kg only slight mydriasis in one out of two animals was observed whereas intraperytoneally, a dose of 50 mg/Kg caused writhing in the animal, however this effect is probably related to the low pH necessary to solubilize the compound. At a dose of 50 mg/Kg orally compound (**1**) exerted only a weak analgesic action in rats and failed to produce anti-pyresis or disminish edema in the Randall and Selitto anti-inflammatory test. In ether-chloralose anaesthetized cats (-)-norarmepavine produced transient depressor effects after being dosed at 10 mg/Kg intravenously but failed to alter the responses to standard agents affecting the autonomic nervous system.

To the best of our knowledge, the work below constitutes the first enantioselective total syntheses of this natural product using a sequence of polymer-supported reagents and only the second total synthesis of this alkaloid.[6]

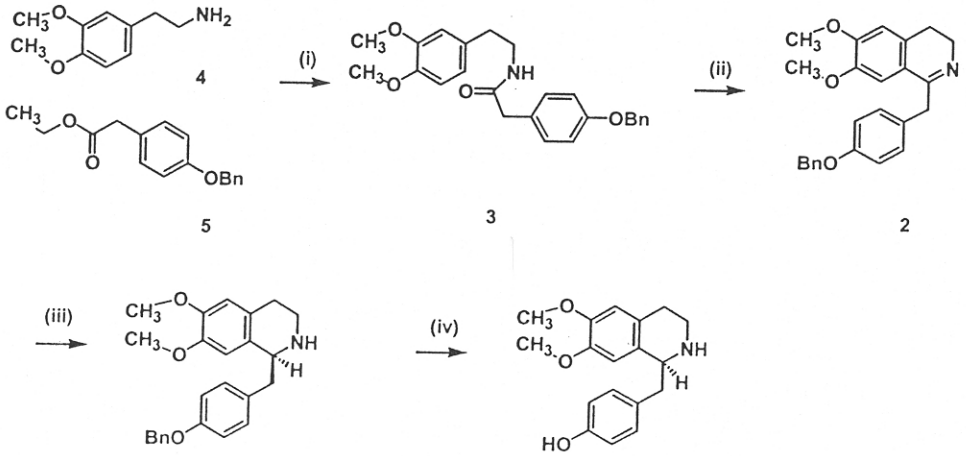
Retrosynthetic analysis of (-)-norarmepavine (**1**) suggests the amine (**4**) and the ethyl ester (**5**) as suitable starting materials (Scheme 1). The desired core structure (**2**) could be formed via a Bischler-Napieralski cyclisation of **3** and the required stereochemistry would be obtained via enantioselective reduction of the imine (**2**).



Scheme 1

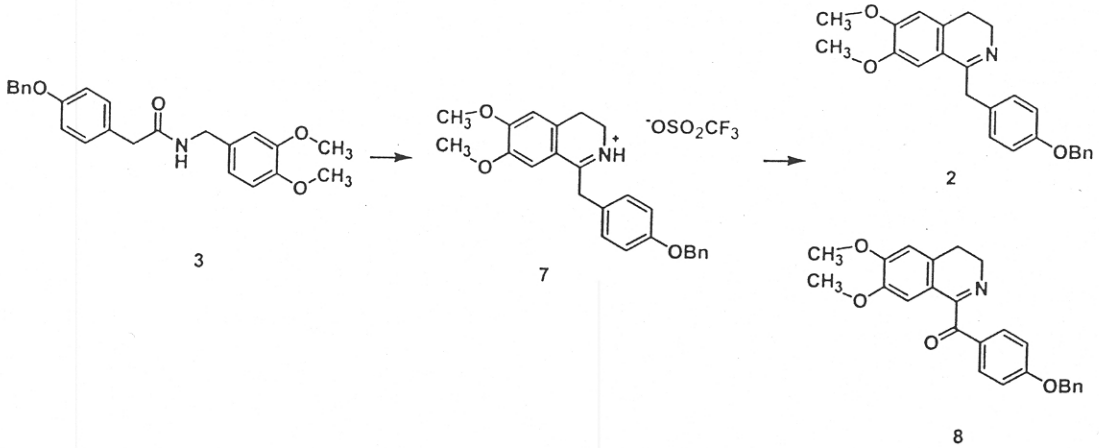
The synthesis begins with commercially available 2-(3,4-dimethoxyphenyl)ethylamine (**4**) and ethyl 4-benzyloxyphenylacetate (**5**). Microwave irradiation (MW) under solvent-free conditions of a mixture of these components led to the amide (**3**) in better than 90 % yield (see Scheme 2).[7] The amide formed was pure enough to take through the next reaction without further purification. The route to the isoquinoline nucleus involved the Bischler-Napierlaski reaction of the amide (**3**). Initial experiments to catalyse this reaction using trifluoromethanesulfonic anhydride (Tf_2O)[8] and polymer-supported 4-dimethylaminopyridine (●-DMAP) in CH_2Cl_2 followed by treatment with polymer-supported *N*-(2-aminoethyl)aminomethyl polystyrene (●-NH_2), in order to destroy the excess of Tf_2O, led to the iminium triflate (**7**) (see Scheme 3). Treatment *in situ* of the salt with polymer-supported 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (●-BEMP) generated the

free base (**2**).[9] In order to guarantee the success of this reaction, it is very important that the order and timing of the addition of the reagents is strictly followed (see Table 1). The best yields were obtained with the slow addition of a solution of Tf_2O in CH_2Cl_2 over 6 h to a mixture of the amide and ●-DMAP at 0°C (Entry 5 in Table 1). If the addition of reagents is done faster the proportion of unreacted starting material increases dramatically.



(i) MW, 100°C 30 sec, 200°C 30 min, remove solvent 200°C 30 min 90%. (ii)(a) ●-DMAP, Tf_2O, DCM, 0°C; (b) ●-NH_2 ; (c) ●-BEMP 67% (5:1) (imine (**2**) : amide (**3**)). (iii) (a) starting material added to the reducing agent dropwise over 15 min, (**10b**) in DCM at -35°C and slowly warmed until -10°C for 1 h and then at 0°C for 4 h, evaporation of solvent (b) Amberlyst 15 (●-SO_3H), CH_3OH (catch) 45 min then filtrated and release with NH_3/CH_3OH overnight. 82% e.e.=78% (Mosher ester), $[\alpha]_D^{20}$ -12.4° (*c*=0.805, $CHCl_3$). (iv) H_2, $Pd(OH)_2/C$, CH_3OH, rt, overnight, 90%. e.e.=77% (Pirkle reagent)[13], $[\alpha]_D^{20}$ -9.5° (*c*=0.825, $CHCl_3$)[4,6, and 14]

Scheme 2



Scheme 3

Entry	Procedure	●-DMAP	Tf_2O	●-NH_2[a]	●-BEMP[b]	Results (imine (2)/amide (3))[c]
1	A	5 eq	2.7 eq dropwise	6 eq	4 eq	(1.5:1)
2	A	5 eq	5.3 eq dropwise	10 eq	4 eq	(2.5:1)
3	A	5 eq	5.0 eq dropwise	10 eq	4 eq	[d]
4	A	3 eq	5.0 eq 2h30min	10 eq	12 eq	(4:1)
5	A	3 eq	5.0 eq 6h	10 eq	10 eq	**(5:1)**[e]
6	B	5 eq	3.0 eq dropwise	6 eq	4 eq	(1:2)

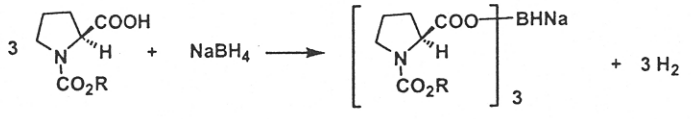
Procedure A: A solution of Tf_2O in DCM is added to astirred mixture of the amide (**3**) and ●-DMAP at 0°C. In Entries 1 and 2 after the addition of Tf_2O the mixture was left at 0°C 1 h and at rt 30 min. In Entries 3 and 5 the mixture is left at 0°C for 30 and 15 min after the addition of Tf_2O and in Entry 4 the PS-NH_2 is added directly as a single batch after the addition of the Tf_2O.

Procedure B: A solution of Tf_2O in DCM is added over a suspension of ●-DMAP in DCM followed by a solution of the amide (**3**) in DCM. The reaction mixture is left at rt for 32 h and then ●-NH_2 is added.

a In Entries 1,2,3,4,and 5 the reaction is left 16 h at rt after the addition of ●-NH_2. In Entry 6 the time is 4 h, **b** In Entries 1, 2, 3, 4, 5, and, 6 the reaction is left at rt for: 3, 3, 17, 19, 5, and 1 h after the addition of ●-BEMP, **c** Ratio (**2**)/(**3**)obtained from the ^{1}H-NMR spectrometry, **d** When ●-BEMP is added before ●-NH_2, the reaction is gave addition impurities, **e** In this case yield crude = 90%, LCMS 67% of (**2**), 13% of (**3**), 5% oxidation product (**8**).

Table 1

The asymmetric reduction of the prochiral imine (**2**)[10] was carried out using chiral sodium acyloxyborohydrides. A number of trial reactions were conducted using the borohydrides (**10a**) and (**10b**) (see Scheme 4).[11] While the use of tris[(*S*)-*N*-benzyloxycarbonylproline]hydroborate (**10a**), gave the corresponding amine (**6**) in a 63% enantiomeric excess, the use of tris[(*S*)-*N*-isobutyloxycarbonylproline]-hydroborate (**10b**) yielded the amine (**6**) in a 78% enantiomeric excess. In both cases the enantiomeric excess was determined by conversion to the corresponding Mosher ester.[12] The best results were obtained when the imine (**2**) was added to the reducing agent dropwise over 15 min using CH_2Cl_2 as a solvent at -35°C. The mixture was slowly warmed to -10°C for 1 h and then maintained at 0°C for 4 h. Following a catch and release protocol with ●-SO_3H and ammonia 2M in methanol the product was obtained in a 82% isolated yield and 78% enantiomeric excess, determined by ^{1}H- NMR spectral analysis of the Mosher ester. The absolute stereochemistry was assumed to be (*S*) in agreement of the work done by Yamada and Atarashi.[11b,c and d]



9 a R= Bn
9 b R=$CH_2CH(CH_3)_2$

10 a R= Bn
10 b R=$CH_2CH(CH_3)_2$

Scheme 4

Finally, hydrogenation of the benzyl protecting group using palladium hydroxide on carbon in methanol lead to (-)-norarmepavine (**1**) in 90% yield. The enantiomeric excess of synthetic **1** was determined as 77% using ^{1}H NMR spectroscopy in the presence of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol, chiral shift reagent.[13] All of the spectroscopic data for the synthetic material were identical in all respects with those of the naturally occurring compound.[4,6,14] The specific rotation of synthetic **1** $[\alpha]_D^{20}$ -9.5° (*c*=0.825, $CHCl_3$) was in reasonable agreement with the literature[4,6] value $[\alpha]_D^{25}$ –23.0° (*c*=1.33, $CHCl_3$) and supported the assignment of the absolute stereochemistry as (*S*).

EXPERIMENTAL

^{1}H-NMR spectra were recorded on a Bruker DPX-400 spectrometer and are reported as follows: chemical shift, ^{1}H (ppm), (number of protons, multiplicity, coupling constant, J in Hertz). Spectra were recorded in $CDCl_3$ unless otherwise stated. ^{13}C-NMR and DEPT ^{13}C-NMR spectra were recorded on a Bruker DPX-400 spectrometer and are recorded as follows: chemical shift, δ_C (ppm), (assignment). Spectra were recorded in $CDCl_3$ unless otherwise stated. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were reported neat (film) on a Perkin Elmer Spectrum One FTIR spectrophotometer. MS spectra were obtained on a Kratos MS890MS spectrometer at the Department of Chemistry, University of Cambridge. Microwave experiments were performed on a Smith Synthesizer manufactured by Personal Chemistry, Upsala Sweden. All reactions were carried out under an argon atmosphere with dry solvents unless otherwise stated. THF was distilled from sodium benzophenone ketyl; dichloromethane (DCM) from CaH_2. All other reagents and solvents were used as supplied.

Preparation of 2-(4-benzyloxyphenyl)-N-[2-(3,4-dimethoxyphenyl)ethyl]acetamide (3). A mixture of 2-(3,4-dimethoxyphenyl)ethylamine (**4**) (2.5 g, 14 mmol) and ethyl-2-(4-(benzyloxyphenyl) acetate (**5**) (3.78 g, 14 mmol) was subjected to microwave irradiation at 100 °C for 30 sec then at 200 °C for 30 min. The ethanol formed was removed under vacuum and the remaining residues subjected to microwave irradiation at 200 °C for a further 30 min, yielding a yellow/orange solid. This was recrystallised in CH_3OH to give a white crystalline solid (5.06 g, 90%): mp 115-116 °C (lit.,[15] mp 116 °C and 114-115 °C); IR ν_{max} 3321, 1639, 1541, 1511, 1236, 1143, 1022 cm^{-1}; HR-MS found 428.1846, calcd 428.1838 for $C_{25}H_{27}NO_4Na^+$; ^{1}H-NMR ($CDCl_3$) δ = 7.45-7.31 (5H, m), 7.08 (2H, d, J = 8.55 Hz), 6.91 (2H, d, J = 8.55 Hz), 6.72 (1H, d, J = 8.13 Hz), 6.62 (1H, d, J = 1.90 Hz), 6.56 (1H, dd, J = 8.13 and 1.90 Hz), 5.44 (1H, br s), 5.05 (2H, s), 3.44 (2H, dd, J = 12.70 and 6.70 Hz), 2.67 (2H, t, J = 6.93 Hz); ^{13}C-NMR δ = 35.06 (CH_2), 40.72 (CH_2), 42.95 (CH_2), 55.84 (CH_3), 55.94 (CH_3), 70.05 (CH_2), 111.40 (CH), 111.86 (CH), 115.32 (2xCH), 120.62 (CH), 127.04 (C) 127.41 (2xCH), 128.02 (CH), 128.60 (2xCH), 130.52 (2xCH), 131.14 (C), 136.86 (C), 147.69 (C), 149.07 (C), 158.06 (C), 171.27 (C).

Preaparation of 1-(4-benzyloxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (2) via Bischler-Napieralski cyclization. A solution of Tf_2O (0.55 mL, 3.36 mmol) in DCM (3 mL) was added over a period of 6 h to a cooled (ice-water bath) solution of the amide (**3**) (272 mg, 0.67 mmol) and ●-DMAP (672 mg, 2.01 mmol) (Fluka Cat. N° 39410) in DCM (15 mL). 10 min after the addition ●-NH_2 (2.5 g, 6.72 mmol) (Nova Biochem Cat. N° 01-64-0178 A26718) was added and the mixture shaken at rt for 16 h. ●-BEMP (Aldrich Cat. No 53,649-0) was added and the mixture shaken for an additional 5 h. The reaction mixture was filtered, the resins washed with DCM, and the filtrate evaporated under reduced pressure to give the title compound (**2**) as a pale brown solid mp 108.5-109.8 °C (aqueous EtOH) (lit.,[15b, 16] mp 101 °C) (67% pure by LCMS plus 13% of starting material (**3**) and 5% of the oxidation product (**8**)): IR ν_{max} 1605, 1570, 1510, 1248, 1211, 1143, 1018 cm^{-1}; HR-MS found 410.1732, calcd 410.1717 for $C_{25}H_{25}NO_3Na^+$; ^{1}H-NMR ($CDCl_3$) δ = 7.41-7.29 (5H, m), 7.22 (2H, d, J = 8.50 Hz), 6.89 (2H, d, J = 8.50 Hz), 6.97 (1H, s), 6.65 (1H, s), 5.02 (2H, s), 3.99 (2H, s), 3.88 (3H, s), 3.73 (3H, s), 3.73 (2H, t, J = 7.52 Hz), 2.65 (2H, t, J = 7.70 Hz); ^{13}C-NMR δ = 25.77 (CH_2), 45.53 (CH_2), 47.07 (CH_2), 55.89 (CH_3), 56.00 (CH_3), 69.98 (CH_2), 109.76 (CH), 110.27 (CH), 115.03 (2xCH), 121.54 (C), 127.41 (2xCH), 127.86 (CH), 128.50 (2xCH), 129.52 (2xCH), 130.35 (C), 131.84 (C), 137.05 (C), 147.25 (C), 150.73 (C), 157.43 (C), 165.66 (C).

Preparation of 1-(4-benzyloxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6).

Preparation of the reducing agent (**10a**): A solution of (*S*)-*N*-benzyloxycabonylproline (**9a**) (400 mg, 1.61 mmol) in THF (1.0 mL) was added dropwise for 1 h to a stirred suspension of $NaBH_4$ (20.3 mg, 0.54 mmol) in THF (1.0 mL) at 0°C (ice-water bath). After vigorous hydrogen evolution ceased, the mixture was stirred at rt for 6 h and then concentrated under reduced pressure.

Preparation of the reducing agent (**10b**): A solution of isobutyl chloroformate (4.4 mL, 34.04 mmol) in acetone (52 mL) was added dropwise to a mixture of L-proline (4.0 g, 34.74 mmol) and sodium bicarbonate (10.5 g, 125.0 mmol) in water (52 mL). The solution was stirred at rt overnight. After removal of the acetone, the aqueous solution was washed with ethyl acetate and acified to *p*H 2 with concentrated hydrochloric acid, the temperature was maintained below 20°C. The organic phase was separated and washed with brine and dried over anhydrous magnesium sulphate. The solvent was removed to give (S)-*N*-isobutyloxycarbonylproline (**9b**) as colorless oil. The spectroscopy data were in agreement with those reported in the literature.[11d]

A solution of the (*S*)-*N*-isobutyloxycarbonylproline (**9b**) (501.6 mg, 2.33 mmol) in THF (1.68 mL) was added dropwise over 10 min to a stirred suspension of $NaBH_4$ (29.1 mg, 0.77 mmol) in THF (1.68 mL) at

0°C (ice-water bath). After vigorous hydrogen evolution ceased, the mixture was stirred at rt overnight and then concentrated under reduced pressure.

To a cooled (-35°C) solution of **10b** (526.7 mg, 0.78 mmol) in DCM (3 mL) was added a solution of **2** (86 mg, 0.22 mmol) in DCM (3 mL) dropwise over 15 min. The mixture was allowed to warm to –10 °C over 1 h and then kept at 0°C for 4 h. The solvent was removed under vacuum and the residue dissolved in CH_3OH (11 mL). After cooling to 0°C ●-SO_3H (1 g, 2.22 mmol) (Fluka Cat. N° 06423) was added and the mixture shaken at rt for 45 min. The beads were filtered off and washed with DCM and CH_3OH. A solution of ammonia in methanol (2M, 3.0 mL) at 0 °C was added and the mixture left shaking at rt overnight. The reaction mixture was filtered, the resins washed with DCM, and the filtrate evaporated under reduced pressure to give the title compound (**6**) as a pale yellow amorphous solid (71.1 mg, 82%): e.e.= 78% (determined by conversion to the corresponding Mosher ester). $[\alpha]_D^{20}$ -12.4° (*c*=0.805, $CHCl_3$). IR ν_{max} 1609, 1582, 1508, 1258, 1220, 1111, 1019 cm^{-1}, HR-MS found 412.1889, calcd 412.1886 for $C_{25}H_{27}NO_3Na^+$; ^{1}H-NMR ($CDCl_3$) δ = 7.44-7.30 (5H, m), 7.17 (2H, d, J = 8.48 Hz), 6.95 (2H, d, J = 8.48 Hz), 6.62 (1H, s), 6.59 (1H,s), 5.05 (2H, s), 4.13-4.09 (1H, m), 3.85 (3H, s), 3.80 (3H, s), 3.23-3.12 (2H, m), 2.94-2.85 (2H, m), 2.80-2.66 (2H, m); ^{13}C-NMR δ =29.31 (CH_2), 40.55 (CH_2), 41.68 (CH_2), 55.73 (CH_3), 55.86 (CH_3), 56.78 (CH), 69.95 (CH_2), 109.46 (CH), 111.78 (CH), 114.92 (2xCH), 127.17 (C), 127.33 (2xCH), 127.82 (CH), 128.46 (2xCH), 130.26 (2xCH), 130.34 (C), 131.18 (C), 137.02 (C), 146.92 (C), 147.39 (C), 157.42 (C).

Preparation of (-)-norarmepavine (1). To a solution of **6** (60 mg, 0.155 mmol) in CH_3OH (2.6 mL) was added $Pd(OH)_2$-C (20%; 12 mg). The reaction mixture was stirred at rt under hydrogen for 22 h. The reaction mixture was filtered through cotton and then through celite and washed with CH_3OH and DCM to give a pale yellow amorphous solid (41.5 mg, 90%) which required no further purification. e.e.= 77% (determined by chiral shift ^{1}H NMR (600 MHz) spectroscopy using (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol. $[\alpha]_D^{20}$ -9.5° (*c*=0.825, $CHCl_3$). IR ν_{max} 1611, 1513, 1257, 1223, 1111 cm^{-1}; HR-MS found 300.1599, calcd 300.1601 for $C_{18}H_{22}NO_3$; ^{1}H-NMR ($CDCl_3$) δ = 7.03 (2H, d, J = 8.35 Hz), 6.65 (2H, d, J = 8.35 Hz), 6.58 (1H, s), 6.57 (1H, s), 4.20-4.17 (1H, m), 3.84 (3H, s, MeO), 3.79 (3H, s, MeO), 3.27-3.19 (1H, m), 3.11 (1H, dd, J = 4.73 and 13.94 Hz), 2.79-2.76 (2H, m); ^{13}C ($CDCl_3$) δ = 28.33 (CH_2), 39.84 (CH_2), 41.17 (CH_2), 55.20 (CH_3), 55.94 (CH_3), 56.46 (CH), 109.59 (CH), 111.68 (CH), 115.91 (2xCH), 126.32 (C), 128.53 (C), 128.68 (C), 130.35 (2xCH), 147.24 (C), 147.77 (C), 155.75 (C).

ACKNOWLEDGEMENTS

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7. The best results are obtained when the mixture is first heated at 200 °C for 30 min followed by removal under vacuum of the ethanol liberated and heating again at 200 °C for another 30 min. In doing so, one avoids the cleavage of the amide to the starting materials which takes place over prolonged heating at high temperature in the presence of ethanol.
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9. The spectroscopic data where in agreement to those obtained for the same compound obtained through a Bischler-Napieralski cyclization but using $POCl_3$ in reflux toluene (for experimental conditions see ref. 8 and references therein).
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