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An Enantiospecific Synthesis of Solenopsin A

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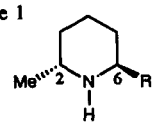
Abstract: Enantiomerically pure solenopsin A (1) was prepared in 11 steps from L-aspartic acid (3) in an overall yield of 17%. 6R-(N-tosylamino)heptadecan-2-one (8), prepared from 3, underwent cyclization on acid catalysis to N-tosylamino-2,3-dehydro-2-methyl-6R-undecylpiperidine (9), which on reduction and deprotection gave 1.

The solenopsins A and B (**1** and **2**) are constituents of the venom of the fire ant, *Solenopsis invicta* (= S. *saevissima*), the habitat of which is the south-east part of the United States of America (Scheme 1).[1] Both molecules are biologically active in having hemolytic, insecticidal and antibiotic properties.[2] Despite the apparent simplicity of their structures, the synthesis of the enantiomerically pure isomers is not trivial.[3,4] The essential problem lies in the creation of the *trans* configuration for the 2,6-dialkyl substituents. So far four solutions have been reported. The first entails the transfer of chirality on successive alkylations of 2-cyano-6-oxazolopiperidine.[5] The second involves the diastereoselective reduction of a bornyl β-keto ester to a chiral secondary alcohol which by conversion to its azide and subsequent internal dipolar addition controls the construction of the 2-methylpiperidine ring.[6] The third depends essentially on the cyclization of 6R-aminoheptadecan-2-one to the related 1,2-dehydropiperidine which is then selectively reduced.[7] The fourth solution exploits the innate chirality of 5-methyl L-glutamate which on elaboration provides an analogous amino-ketone which undergoes stereocontrolled cyclization.[8,9] We now describe a practical enantiospecific synthesis of **1** that embodies the chief features of the last two approaches, but which takes advantage of our procedure for preparing enantiomerically pure β-amino acids from aspartic acid.[10]

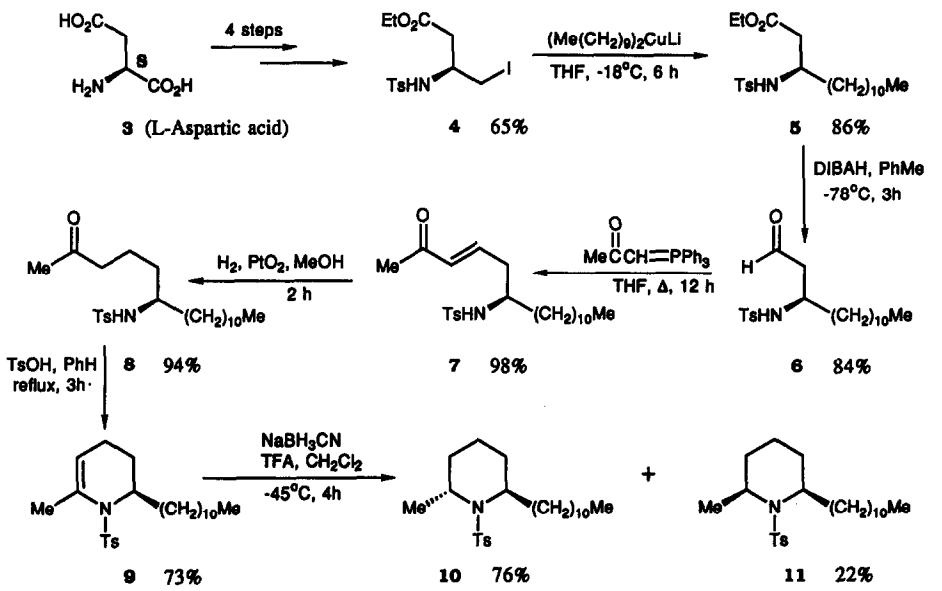
Scheme 1



1 R = $(CH_2)_{10}Me$
2 R = $(CH_2)_{12}Me$

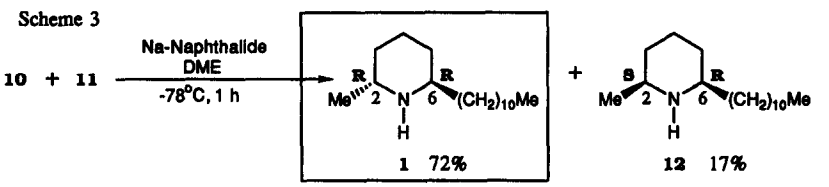
L-Aspartic acid (**3**) was first transformed in 4 steps into the key intermediate,[10] the N-protected iodohomoserine ester **4** (Scheme 2). Next, treatment of **4** with lithium didecylcuprate in THF gave the undecyl-β-amino ester **5** in 86% yield. Reduction of the ester group with diisobutylaluminum hydride (DIBAH) furnished the corresponding aldehyde **6** in similar yield. Wittig reaction with acetylmethylidenetriphenylphosphorane gave exclusively the α,β-unsaturated ketone **7**, which was hydrogenated over Adams catalyst to the methyl ketone **8**. Both **7** and **8** were formed in essentially quantitative yield.[11] Cyclization was achieved by catalysis with *p*-toluenesulfonic acid. The resulting dehydropiperidine **9**, obtained in 73% yield,[11] was then submitted to sodium cyanoborohydride in the presence of trifluoroacetic acid (TFA) in CH_2Cl_2. Reduction afforded the *trans* and *cis* piperidines **10** and **11** as an inseparable mixture in a ratio of 7:2 in 98% yield.[12] The identity of each isomer was confirmed by the independent preparation of the *cis* isomer **11** by the catalytic hydrogenation of **9**.[13]

Scheme 2



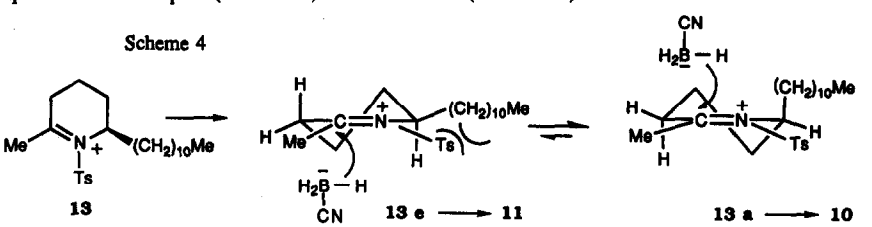
Finally, deprotection of the isomers was effected with sodium naphthalide in dimethoxyethane (DME) (Scheme 3). Purification of the resulting oil by column chromatography over alkaline Al_2O_3 delivered pure solenopsin A (**1**) of the 2R,6R configuration in 72% yield.[14] The synthetic solenopsin A possesses spectral data identical to those of the natural material and displays commensurate optical activity.[15]

Scheme 3



The reduction of **9** proceeded with significant stereocontrol (*trans:cis* ratio = 7:2). Nevertheless, comparison with similar reductions of the N-*t*-butoxycarbonyl,[4k] and N-benzyl[4i] analogues of **9** (*trans:cis* ratio = 9:1) suggests that the N-tosyl group in the iminium cation **13** derived from **9** is not so susceptible to $A^{1,2}$ strain.[16] In other words, the preference for the axial half-chair conformation and its attack by hydride (**13a** → **10**) over its equatorial counterpart (**13e** → **11**) is less marked (Scheme 4).

Scheme 4



The advantages of the present synthesis are its operational simplicity and conciseness. The same procedure should also be applicable for preparing 2,5-dialkylpyrrolidines of natural occurrence. Such studies are under way and the results will be reported in due course.

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11. Compounds **5-9** were obtained in a pure state by column chromatography over silica gel (eluent: hexane: EtOAc). All are oils, except **8** which is crystalline (m.p. 65-66°C, from hexane). Optical rotations ($[\alpha]_D^{20}$) were determined in $CHCl_3$ and had the following values: **5**, +14.2° (c 1.4); **6**, +13.1° (c 1.3); **7**, +36.1° (c 1.1); **8**, +9.2° (c 1.1); **9**, -178.4° (c 1.5). ^{1}H-NMR (200 MHz, $CDCl_3$): **5**, 0.86 (t, J = 6.7 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H), 1.10-1.60 (m, 20H), 2.37 (dd, J = 2.0, 5.2 Hz, 2H), 2.40 (s, 3H), 3.40 (m, 1H), 4.05 (qd, J = 7.1, 1.2 Hz, 2H), 5.26 (d, J = 9.0 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.5 Hz, 2H); **6**, 0.87 (t, J = 6.8 Hz, 3H), 1.05-1.51 (m, 20H), 2.41 (s, 3H), 2.59 (t, J = 1.2 Hz, 1H), 2.62 (t, J = 0.4 Hz, 1H), 3.49-3.61 (m, 1H), 4.86-4.93 (t, br, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.73 (d, J =

8.2 Hz, 2H), 9.62 (t, J = 1.2 Hz, 1H); **7**, 0.86 (t, J = 6.8 Hz, 3H), 1.07-1.50 (m, 20H), 2.16 (s, 3H), 2.33 (dd, J = 7.3, 13.0 Hz, 2H), 2.40 (s, 3H), 3.23-3.38 (m, 1H), 4.58 (d, J = 8.2 Hz, 1H), 5.96 (d, J = 15.8 Hz, 1H), 6.60 (dt, J = 15.8, 7.3 Hz, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H); **8**, 0.88 (t, J = 6.7 Hz, 3H), 1.05-1.41 (m, 24H), 2.09 (s, 3H), 2.33 (t, J = 6.9 Hz, 2H), 2.42 (s, 3H), 3.15-3.22 (m, 1H), 4.40 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H); **9**, 0.88 (t, J = 6.7 Hz, 3H), 1.26 (s, br, 20H), 1.05-1.90 (m, 4H), 2.12 (s, br, 3H), 2.40 (s, 3H), 4.04-4.18 (m, 1H), 4.99-5.06 (m, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.1 Hz, 2H).

12. Reduction of **9** with $NaCNBH_3$/TFA at -45°C gave the *trans* and *cis* N-tosyl piperidines **10** and **11**. The crude oil was purified over silica gel (eluent, hexane: EtOAc 4:1). The isomer ratio was estimated from the intensity of the C2-H and Me signals. ^{1}H-NMR (400 MHz, $CDCl_3$) 0.88 (t, J = 6.8 Hz, 3H), 1.23 (d, J = 6.9 Hz, 0.78 x 3H, *trans* isomer), 1.25 (m, br, 18H), 1.30 (d, J = 6.9 Hz, 0.22 x 3H, *cis* isomer), 1.35-1.82 (m, 8H), 2.40 (s, 3H), 3.56-3.67 (m, 0.78H, *trans* isomer), 3.93-4.01 (m, 0.22H, *cis* isomer), 4.10-4.20 (m, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H).

13. A pure sample of the *cis* isomer (**11**) was obtained by hydrogenation of **9** over 10% Pd/C in MeOH. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.89 (t, J = 6.8 Hz, 3H), 1.20-1.41 (m, 20H), 1.30 (d, J = 6.9 Hz, 3H), 1.46-1.80 (m, 6H), 2.41 (s, 3H), 3.92-3.99 (m, 1H), 4.10-4.18 (m, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H).

14. Good separation was obtained by using basic aluminum oxide, Fluka, type 5016, and eluting with Et_2O and then Et_2O containing 1% *i*-$PrNH_2$. The *cis* isomer (**12**), isosolenopsin A, was also obtained as an oil (17% yield): HCl salt $[\alpha]_D^{22}$ = -10.6° (c = 0.33, $CHCl_3$); IR 2927, 2854, 1602, 1461, 1377, 1261, 1097, 1016, 937, 875, 804; ^{1}H-NMR (200 MHz, $CDCl_3$): 0.86 (t, J = 6.8 Hz, 3H), 1.06 (d, J = 6.2 Hz, 3H), 1.24 (s, br, 18H), 1.30-1.98 (m, 9H), 2.41-2.52 (m, 1H), 2.53-2.70 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): 14.06, 22.63, 22.90, 24.76, 25.93, 29.29, 29.55, 29,58, 29.61, 29.77, 31.86, 32.02, 34.22, 37.24, 52.47, 57.11.

15. Pure solenopsin A (**1**) was isolated as an oil in 72% yield: $[\alpha]_D^{20}$ = -1.30° (c = 1.3, MeOH), lit.[7] $[\alpha]_D^{23}$ = -2.2° (c = 0.8, MeOH); HCl salt m.p. 147-150°C, lit.[5] 146°C; HCl salt $[\alpha]_D^{20}$ = -7.7° (c = 0.51, $CHCl_3$), lit.[7] $[\alpha]_D^{23}$ = -7.6° (c = 0.7, $CHCl_3$); free base, ^{1}H-NMR (400 MHz, $CDCl_3$): 0.88 (t, J = 6.8 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H), 1.26 (s, br, 18H), 1.38-1.70 (m, 9H), 2.83-2.90 (m, 1H), 3.12-3.20 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): 14.08, 19.58, 21.24, 22.66, 26.46, 29.33, 29.62, 29.64, 29.78, 30.82, 31.90, 33.01, 34.10, 45.82, 50.82; MS 252 (42), 238 (100), 224 (11), 210 (22), 184 (38), 98 (99); Anal. calcd for HCl salt, $C_{17}H_{36}ClN$: C, 70.43; H, 12.52; N, 4.83; found C, 70.24; H, 12.40; N, 4.72;

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