Tetrahedron: *Asymmetry* 20 (2009) 1160–1163

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

A simple and efficient enantioselective route to 2,6-disubstituted piperidines: synthesis of (2*R*,6*S*)-isosolenopsin A and (2*S*,6*R*)-isosolenopsin

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ARTICLE INFO

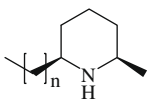
Article history:
Received 26 February 2009
Accepted 27 March 2009
Available online 22 April 2009

ABSTRACT

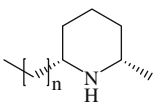
The enantioselective synthesis of 2,6-*cis*-disubstituted piperidine alkaloids, (2*R*,6*S*)-isosolenopsin A **2** and (2*S*,6*R*)-isosolenopsin **5** from fire ant venom is described. Starting from the dodecanal and decanal, the synthesis presents two key steps. The first step involves Keck allylation to afford the chiral homoallylalcohol with the required stereochemistry and the second key step consists of Grubbs olefin cross metathesis. The synthesis was achieved in five steps with 44% overall yield.

1. Introduction

Piperidine-containing alkaloids are widespread in Nature and possess a broad spectrum of interesting biological activities. Among the numerous naturally occurring piperidines, *cis* and *trans* 2,6-disubstituted piperidine scaffolds constitute an important class of alkaloids.[1] This 2,6-disubstituted pattern is found in many animal alkaloids[2] and representative members of this family are depicted in Figure 1. Particularly, 2,6-*cis*-disubstituted piperidines (isosolenopsins) attract considerable attention due to their broad range of biological activities.[3] Isosolenopsin A **2** and isosolenopsin **5** are perhaps the best example of these interesting compounds that have been isolated from the venom of fire ants of the genus *Solenopsis*.[4] These compounds exhibit cytotoxic, haemolytic, necrotic, antibacterial, insecticidal, antifungal and anti-HIV properties.[5] In addition, these compounds were also found to block neuromuscular transmissions, while isosolenopsin A at low concentrations reduces mitochondrial respiration and uncouples oxidative phosphorylation through the inhibition of Na^+ and K^+ATPases.[5,6]



n = 8, (2*R*,6*S*)-Isosolenopsin **1**
n = 10, (2*R*,6*S*)-Isosolenopsin A **2**
n = 12, (2*R*,6*S*)-Isosolenopsin B **3**
n = 14, (2*R*,6*S*)-Isosolenopsin C **4**



n = 8, (2*S*,6*R*)-Isosolenopsin **5**
n = 10, (2*S*,6*R*)-Isosolenopsin A **6**
n = 12, (2*S*,6*R*)-Isosolenopsin B **7**
n = 14, (2*S*,6*R*)-Isosolenopsin C **8**

Figure 1. Representative examples of isosolenopsins.

Owing to the challenges posed by the substitution pattern and also due to the remarkable biological properties, the synthesis of these compounds has attracted much attention. As a consequence, a number of total syntheses of these compounds in racemic and optically active forms have been established.[7] However, many of the reported methods either make use of chiral building blocks or require longer reaction sequences; often accompanied with low yields. The lack of efficient synthesis as well as our own interest in the synthesis of enantiopure bioactives[8] prompted us to investigate the total synthesis of isosolenopsin A. Herein, we report a short stereoselective synthesis of isosolenopsin and isosolenopsin A based upon the Keck allylation as the key asymmetry inducing reaction.

2. Results and discussion

During the course of our synthetic studies on bioactives, we found that Keck allylation of aldehyde derivatives using (*S*)-BINOL and (*R*)-BINOL proceeded smoothly to provide homoallylic alcohols with the desired enantioselectivity. Thus, our retrosynthetic strategy (Scheme 1) relies on the Keck allylation approach starting from the dodecanal and a well-known Grubbs cross metathesis. As shown in Scheme 1, disconnection of **2** revealed a key fragment **13**, which could be subjected to reductive amination and diastereoselective cyclization to realize the target molecule. The key fragment **13** was obtained by cross metathesis of chiral homoallyl tosyl ester **11** and methyl vinyl ketone followed by the azidation. Compound **10** could be made from aldehyde (dodecanal) via Keck allylation.

Our synthesis (Scheme 2) started with dodecanal **9**, which was subjected to Keck allylation with allyltributyltin in the presence of (*S*)-BINOL and $Ti(O^iPr)_4$ to produce homoallylalcohol **10** in 84%

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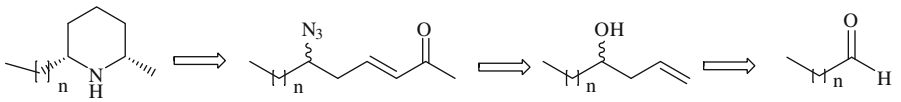
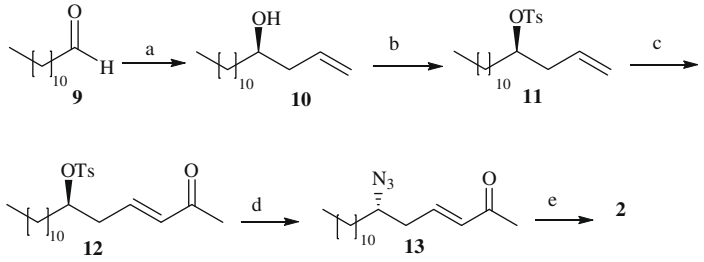
0957-4166/$ - see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2009.03.030

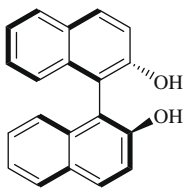


Scheme 1. Retrosynthetic analysis of isosolenopsins.

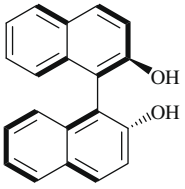


Scheme 2. Reagents and conditions: (a) **I**, allyltributyl tin, $Ti(O^iPr)_4$, DCM, −20 °C; (b) TsCl, 1:1 pyridine, DCM; (c) Grubb's second generation catalyst (5 mol %), DCM, 40 °C, 6 h; (d) NaN_3, DMF, 70 °C, 6 h; (e) (i) Pd/C (10%), H_2 (balloon); (ii) ethanolic·HCl.

yield. The enantiomeric purity of **10** was found to be 92% ee by chiral HPLC.[9] Protection of 2° hydroxyl group as a tosyl ester (OTs)[10] followed by a cross metathesis reaction with methyl vinyl ketone using Grubb's second generation catalyst (5 mol %) in DCM at 40 °C afforded α,β-unsaturated ketone **12**[11] in good yield. The stereochemistry of the double bond of compound **12** was confirmed as *E* by the large coupling constant (J = 16 Hz) from the ^{1}H NMR spectrum. The treatment of α,β-unsaturated ketone **12** with NaN_3 in DMF at 70 °C afforded azido compound **13**[10] in excellent yield (80%). Finally, one-pot reductive amination followed by diastereoselective cyclization[11] using Pd/C (10%) afforded (2*R*,6*S*)-isosolenopsin A **2** in good yield, which was isolated and characterized as its hydrochloride.



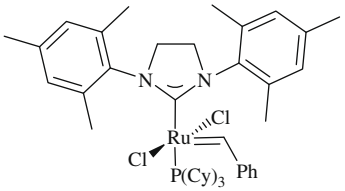
I-(*S*)-BINOL



II-(*R*)-BINOL

2.1. Synthesis of (2*S*,6*R*)-isosolenospsin

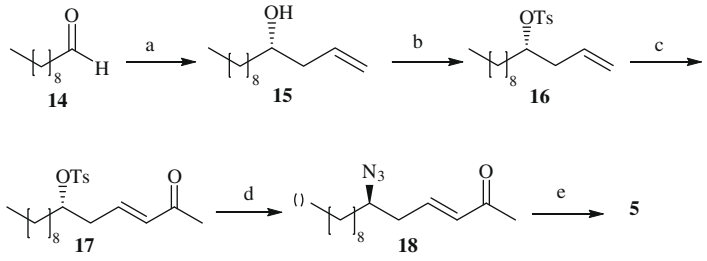
Decanal **14** was subjected to Keck allylation using (*R*)-BINOL and Ti $(O^iPr)_4$ to give the homoallyl alcohol **15** with virtually complete inversion of the configuration and gave the desired homoallylic alcohol. The free hydroxyl group was then transformed into the tosylate **16** in 98% yield. Treatment of this tosylate with methyl vinyl ketone in the presence of Grubb's second generation catalyst (5 mol %) at 40 °C temperature yielded α,β-unsaturated ketone **17**, whose stereochemistry was deduced as *E* from its ^{1}H NMR spectrum. Reaction of **17** with sodium azide in DMF afforded **18**, which finally on reductive amination followed by diastereoselective cyclization using Pd/C (10%) afforded (2*S*,6*R*)-isosolenopsin (see Scheme 3).



Grubb's catalyst

3. Conclusion

In conclusion, the present report describes short and efficient total syntheses of isosolenopsin and isosolenospsin A with high enantioselectivity. Important features of this approach include (a) Keck allylation to establish the required stereocenter and (b) Grubbs cross metathesis strategy for the construction of the key fragment. This method allows access to both enantiomers of isosolenopsin and isosolenopsin A depending on whether (*R*) or (*S*)-BINOL was used as a catalyst. Thus, this flexible, efficient and



Scheme 3. Reagents and conditions: (a) **II**, allyltributyl tin, $Ti(O^iPr)_4$, DCM, −20 °C; (b) TsCl, 1:1 pyridine, DCM; (c) Grubb's second generation catalyst (5 mol %), DCM, 40 °C, 6 h; (d) NaN_3, DMF, 70 °C, 6 h; (e) (i) Pd/C (10%), H_2 (balloon); (ii) ethanolic·HCl.

high yielding protocol developed in the present study paves the way for the construction of related isosolenopsin derivatives for further biological studies.

4. Experimental

4.1. General information

All commercially available reagents were used without further purification unless otherwise stated. The solvents used were all of AR grade and were distilled under a positive pressure of dry nitrogen atmosphere where necessary. All reactions were performed in pre-dried apparatus under an atmosphere of nitrogen unless otherwise stated. The progress of the reactions was monitored by analytical thin layer chromatography (TLC) performed on Merck Silica Gel 60F_{254} plates. Visualization was performed using 5% H_2SO_4 solution followed by heating. Column chromatography was carried out using silica gel 60–120 mesh (Qingdao Marine Chemical, China). High-resolution mass spectra were obtained on LC-MSD-Trap-SL instrument. NMR spectra were recorded on Bruker 300 MHz spectrometers, with tetramethylsilane as an internal standard, using $CDCl_3$. The chemical shifts are expressed as δ values in parts per million (ppm) and the coupling constants (J) are given in hertz (Hz). Yields that were of purified compounds were not optimized. Optical rotations were measured with JASCO DIP 300 digital polarimeter at 25 °C.

4.1.1. (*R*)-Pentadec-1-en-4-ol 10

A mixture of (*S*)-BINOL (0.5 mmol, 0.143 g), 1.0 M $Tl(O^iPr)_4$ in DCM (0.5 mmol, 0.1 equiv) and over dried 4-Å molecular sieves (2 g) in DCM (10 mL) was refluxed for 1 h. The red brown mixture was cooled to room temperature and aldehyde **9** (5 mmol, 0.920 g) was added. After being stirred for 10 min the contents were cooled to −78 °C and allyltributyl tin (5.5 mmol, 1.76 mL) was added. The reaction mixture was stirred for 10 min and then placed in a −20 °C freezer for 70 h. Saturated $NaHCO_3$ 1.5 mL was then added and contents were stirred for 1 h, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel using hexane/EtOAc (9:1) as eluent to give **10** (0.947 g, 84%) as a colourless oil.

TLC: R_f = 0.55 (hexane/EtOAc, 90:10); $[\alpha]_D^{25} = +4.5$ (c 1.0, $CHCl_3$); IR (KBr): 3343, 2924, 2855, 1460 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.75–5.92 (m, 1H), 5.07–5.20 (m, 2H), 3.57–3.70 (m, 1H), 2.07–2.36 (m, 2H), 1.16–1.53 (m, 20H), 0.88 (t, 3H, J = 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.88, 117.96, 70.65, 41.87, 36.76, 31.87, 29.61, 29.57, 29.31, 25.62, 22.64, 14.07. HRESIMS m/z $[M]^+$ found 226.2254; calculated 226.2297 for $C_{15}H_{30}O$.

4.1.2. (*R*)-Pentadec-1-en-4-yl 4-methylbenzenesulfonate 11

To a stirred solution of homoallyl alcohol **10** (0.904 g, 4 mmol) in dry DCM (8 mL) at 0 °C temperature, were added pyridine (8 mL) and tosyl chloride (0.915 g, 4.8 mmol) under a nitrogen atmosphere. Resultant mixture was allowed to stir at room temperature for overnight. The reaction mixture was then quenched with saturated $CuSO_4$ solution and extracted with DCM. The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated to yield the tosylate **11** (1.48 g) as a pale yellow liquid in 98% yield. TLC: R_f = 0.68 (hexane/EtOAc, 90:10); $[\alpha]_D^{25} = +9.6$ (c 1.00, $CHCl_3$); IR (KBr): 2925, 2855, 1361, 1178, 903, 665 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, 2H, J = 8.3 Hz), 7.32 (d, 2H, J = 8.1 Hz), 5.55–5.72 (m, 1H), 4.97–5.08 (m, 2H), 4.50–4.61 (m, 1H), 2.44 (s, 3H), 2.36 (t, 2H, J = 6.8 Hz), 1.04–1.38 (m, 20H), 0.88 (t, 3H, J = 6.2 Hz). ^{13}C NMR(75 MHz, $CDCl_3$): δ 144.35, 134.46, 132.25, 129.58, 127.71, 118.52, 83.03, 38.71, 33.56, 31.85, 29.56, 29.42, 29.31, 29.12, 24.61, 22.63, 21.55, 14.06. HRESIMS m/z $[M]^+$ found380.2432; calculated 380.2385 for $C_{22}H_{36}O_3S$.

4.1.3. (*R*,*E*)-2-Oxoheptadec-3-en-6-yl 4-methylbenzenesulfonate 12

In a two-necked flask equipped with nitrogen inlet, a magnetic stirring bar and a rubber septum was placed Grubb's second generation catalyst (0.123 g, 5 mol %). A solution of tosylate **11** (1.140 g, 3 mmol) and methyl vinyl ketone (1.050 g, 15 mmol) in CH_2Cl_2 (20 mL) was introduced at 40 °C temperature and the resultant pink solution was stirred for 6 h. When TLC analysis indicated complete consumption of **11, t**he reaction mixture was exposed to air and concentrated to give the crude product, which was purified by flash column chromatography on silica gel using hexane/EtOAc (8:2) as eluent to give α,β-unsaturated ketone **12** (1.063 g, 84%) as a pale yellow liquid. TLC: R_f = 0.58 (hexane/EtOAc, 80:20); $[\alpha]_D^{25} = +9.0$ (c 0.25, $CHCl_3$); IR (KBr): 2925, 2855, 1677, 1458, 1360, 1178, 900, 667 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, 2H, J = 8.3 Hz), 7.34 (d, 2H, J = 8.1 Hz), 6.54–6.68 (m, 1H), 6.02 (d, 1H, J = 16.0 Hz), 4.57–4.68 (m, 1H), 2.48–2.64 (m, 2H), 2.45 (s, 3H), 2.20 (s, 3H), 1.05–1.37 (m, 20H), 0.88 (t, 3H, J = 6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.30, 144.78, 141.24, 134.23, 129.78, 127.71, 81.62, 37.37, 34.22, 31.88, 29.58, 29.49, 29.32, 29.07, 26.83, 24.74, 22.66, 21.61, 14.10. HRESIMS m/z $[M+1]^+$ found 423.2554; calculated 423.2569 for $C_{24}H_{38}O_4S$.

4.1.4. (*S*,*E*)-6-Azidoheptadec-3-en-2-one 13

To a stirred solution of α,β-unsaturated ketone **12** (0.844 g, 2 mmol) in dry DMF (10 mL) at 70 °C temperature under nitrogen atmosphere was added sodium azide (1.300 g, 20 mmol). The reaction mixture was then allowed to stir at 70 °C for 6 h and subsequently extracted with ethyl acetate after being quenched with water. The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated to get the crude product, which was purified by flash column chromatography on silica gel using hexane/EtOAc (8:2) as eluent to give azide **13** (0.468 g) as a pale yellow liquid in 80% yield. TLC: R_f = 0.70 (hexane/EtOAc, 80:20); $[\alpha]_D^{25} = -2.6$ (c 1.00, $CHCl_3$); IR (KBr): 2924, 2855, 2101, 1679, 1459, 1254, 982 cm^{-1}. ^1H NMR(300 MHz, $CDCl_3$): δ 6.70–6.83 (m, 1H), 6.16 (d, 1H, J = 16.0 Hz), 3.38–3.50 (m, 1H), 2.35–2.53 (m, 2H), 2.28 (s, 3H), 1.10–1.40 (m, 20H), 0.88 (t, 3H, J = 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.09, 142.72, 133.73, 61.57, 37.32, 34.20, 31.88, 29.69, 29.59, 29.51, 29.45, 29.31, 27.05, 25.99, 22.67, 14.11. HRESIMS m/z $[M+1]^+$ found 294.250; calculated 294.2545 for $C_{17}H_{32}N_3O$.

4.1.5. (2*R*,6*S*)-2-Methyl-6-undecylpiperidine 2 (isosolenopsin A·HCl)

To a solution of **13** (0.293 g, 1 mmol) in ethyl acetate (10 mL) was added 10% palladium on carbon, and hydrogenated under 1 atm pressure of hydrogen at rt for 12 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated. After addition of a few drops of ethanolic-HCl, white solid was formed. To the resultant white solid was added ether, the insoluble part was separated and recrystallized from CH_2Cl_2–ether to give (2*R*,6*S*)-isosolenopsin A hydrochloride **2**·HCl as colourless crystals in 80% yield. $[\alpha]_D^{25} = +7.6$ (c 1.00, $CHCl_3$); Data were in full agreement with those reported in the literature.[7a]

4.1.6. (*S*)-Tridec-1-en-4-ol 15

A mixture of (*R*)-BINOL (0.5 mmol, 0.143 g), 1.0 M TlP in DCM (0.5 mmol, 0.1 equiv) and over dried 4-Å molecular sieves (2 g) in DCM (10 mL) was heated at reflux for 1 h. The red brown mixture was cooled to room temperature and aldehyde **14** (5 mmol, 0.780 g) was added. After being stirred for 10 min the contents were cooled to −78 °C and allyltributyl tin (5.5 mmol, 1.76 mL)

was added. The reaction was stirred for 10 min and then placed in a −20 °C freezer for 70 h. Saturated $NaHCO_3$ 1.5 mL was then added and contents were stirred for 1 h, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel using hexane/EtOAc (9:1) as eluent to give **15** (0.811 g, 82%) as a colourless oil. TLC: R_f = 0.54 (hexane/EtOAc, 90:10); $[\alpha]_D^{25} = -7.5$ (*c* 1.00, $CHCl_3$); IR (KBr): 3311, 2925, 2855, 1461 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.74–5.90 (m, 1H), 5.18–5.08 (m, 2H), 3.57–3.67 (m, 1H), 2.07–2.35 (m, 2H), 1.22–1.50 (m, 16H), 0.91 (t, 3H, *J* = 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.88, 117.88, 70.62, 41.87, 36.75, 31.84, 29.60, 29.57, 29.54, 29.27, 25.62, 22.62, 14.05. HRESIMS *m/z* $[M]^+$ found 198.1962; calculated 198.1984 for $C_{13}H_{26}O$.

4.1.7. (*S*)-Tridec-1-en-4-yl 4-methylbenzenesulfonate 16

To a stirred solution of homoallyl alcohol **15** (0.792 g, 4 mmol) in dry DCM (8 mL) at 0 °C temperature, were added pyridine (8 mL) and tosyl chloride (0.915 g, 4.8 mmol) under a nitrogen atmosphere. The resultant mixture was allowed to stir at room temperature for overnight. The reaction mixture was then quenched with saturated $CuSO_4$ solution and extracted with DCM. The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated to yield the tosylate **16** (1.38 g) as a pale yellow liquid in 98% yield; TLC: R_f = 0.65 (hexane/EtOAc, 90:10); $[\alpha]_D^{25} = -13.5$ (*c* 1.00, $CHCl_3$); IR (KBr): 3076, 2926, 2857, 1598, 1457, 1360, 1179, 904, 665 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, 2H, *J* = 8.1 Hz), 7.33 (d, 2H, *J* = 8.1 Hz), 5.55–5.72 (m, 1H), 5.08–5.97 (m, 2H), 4.50–4.61 (m, 1H), 2.44 (s, 3H), 2.35 (t, 2H, *J* = 6.0 Hz), 1.49–1.63 (m, 2H), 1.05–1.63 (m, 16H), 0.88 (t, 3H, *J* = 6.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.34, 134.39, 132.20, 129.5, 127.66, 118.47, 82.97, 38.66, 33.51, 31.77, 29.32, 29.28, 29.17, 29.06, 24.56, 22.57, 21.49, 14.01. HRESIMS *m/z* $[M]^+$ found 352.2018; calculated 352.2072 for $C_{20}H_{32}O_3S$.

4.1.8. (*S,E*)-2-Oxopentadec-3-en-6-yl 4-methylbenzenesulfonate 17

In a two-necked flask equipped with nitrogen inlet, a magnetic stirring bar and a rubber septum was placed Grubbs second generation catalyst (0.123 g, 5 mol %). A solution of tosylate **16** (1.056 g, 3 mmol) and methyl vinyl ketone (1.050 g, 15 mmol) in CH_2Cl_2 (20 mL) was introduced at 40 °C temperature and the resultant pink solution was stirred for 6 h. When TLC analysis indicated complete consumption of **16,** the reaction mixture was exposed to air and concentrated to give the crude product, which was purified by flash column chromatography on silica gel using hexane/EtOAc (8:2) as eluent to give α,β-unsaturated ketone **17** (0.991 g, 84%) as a pale yellow liquid; TLC: R_f = 0.60 (hexane/EtOAc, 80:20); $[\alpha]_D^{25} = -22.9$ (*c* 0.75, $CHCl_3$); IR (KBr): 2925, 2855, 1677, 1458, 1359, 1177, 899, 667 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, 2H, *J* = 8.3 Hz), 7.34 (d, 2H, *J* = 8.3 Hz), 6.02 (d, 1H, *J* = 15.8 Hz), 5.97–6.07 (m, 2H), 4.57–4.68 (m, 1H), 2.48–2.63 (m, 2H), 2.45 (s, 3H), 2.20 (s, 3H), 1.45–1.70 (m, 2H), 1.06–1.37 (m, 16H), 0.88 (t, 3H, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.92, 144.72, 141.20, 134.15, 129.71, 127.62, 81.57, 37.27, 34.12, 31.74, 29.28, 29.23, 29.14, 28.96, 26.73, 24.63, 22.55, 21.51, 14.01. HRESIMS *m/z* $[M]^+$ found 394.2199; calculated394.2178 for $C_{22}H_{34}O_4S$.

4.1.9. (*R,E*)-6-Azidopentadec-3-en-2-one 18

To a stirred solution of α,β-unsaturated ketone **17** (0.788 g, 2 mmol) in dry DMF (10 mL) at 70 °C temperature under nitrogen atmosphere was added sodium azide (1.300 g, 20 mmol). After stirring for 6 h at 70 °C the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was purified by flash column chromatography on silica gel using hexane/EtOAc (8:2) as eluent to give azide **18** (0.424 g) as a pale yellow liquid in 80% yield; TLC: R_f = 0.72 (hexane/EtOAc, 80:20); $[\alpha]_D^{25} = -3.6$ (*c* 1.00, $CHCl_3$); IR (KBr): 2926, 2857, 2102, 1678, 1459, 1255, 981 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.70–6.84 (m, 1H), 6.16 (d, 1H, *J* = 15.8 Hz), 3.38–3.51 (m, 1H), 2.35–2.54 (m, 2H), 2.28 (s, 3H), 1.19–1.64 (m, 18H), 0.88 (t, 3H, *J* = 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.01, 142.69, 133.64, 61.48, 37.23, 34.11, 31.76, 29.37, 29.20, 29.17, 26.94, 25.90, 22.57, 14.01. HRESIMS *m/z* $[M]^+$ found 265.2183; calculated 265.2154 for $C_{15}H_{27}N_3O$.

4.2. (2*S*,6*R*)-2-Methyl-6-nonylpiperidine 5 (isosolenopsin·HCl)

To a solution of **18** (0.265 g) in ethyl acetate (10 mL) was added 10% palladium on carbon, and hydrogenated under 1 atm pressure of hydrogen at room temperature for 12 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated. After addition of a few drops of ethanolic-HCl, a white solid was formed. To the resultant white solid was added ether, the insoluble part was separated and recrystallized from CH_2Cl_2–ether to give (2*S*,6*R*)-isosolenopsin hydrochloride **5**·HCl as colourless crystals in 80% yield; $[\alpha]_D^{25} = -10.1$ (*c* 1.00, $CHCl_3$); data were in full agreement with those reported in the literature.[7g]

Acknowledgements

The authors thank Dr. J.S. Yadav, Director IICT for this constant encouragement. RSCK thanks CSIR, New Delhi for financial support.

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