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Stereocontrolled synthesis of piperidine alkaloids, (−)-241D and (−)-isosolenopsin

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ABSTRACT

Highly diastereocontrolled synthesis of alkaloids, (−)-241D and (−)-isosolenopsin was achieved in 7.7% and 5.3% yields, respectively, using a Barbier-type allylation of a chiral imine and D-proline catalyzed aldol addition reaction of a β-amino aldehyde with acetone as the key steps. The synthesis involves a nine-step sequence using (*S*)-valinate imine in a Barbier-type allylation for the first time.

2,6-*cis*-Disubstituted piperidines and 2,6-*cis*-disubstituted 4-piperidinols possess biological as well as pharmaceutical importance.[1] (−)-241D (**1a**), a *cis, cis*-2-nonyl-6-methyl-4-hydroxypiperidine is isolated from the skin of poison dart Dendrobate frog. Racemic piperidine,[2] (±)-241D has been found to block the action of acetylcholine by a noncompetitive blockade of nicotinic receptor channels.[2c] Similarly, 2-methyl 6-alkylated *cis*-piperidines, isosolenopsins,[3] extracted from fire ant's venom of the genus '*Solenopsis*', were found to be responsible for various hemolytic, necrotoxic, phytotoxic, antibiotic, insecticidal, antifungal, and anti-HIV properties.[3c,3d] Isosolenopsin A (**2b**) was found to block neuromuscular transmissions while isosolenopsin **2d**, at low concentrations, reduced mitochondrial respiration through the inhibition of Na^+ and K^+ ATPases.[3c,3d] These interesting biological properties and availability of minute quantities from natural sources inspired chemists to explore new and efficient approaches for the synthesis of **1a** and **2a** (Fig. 1).

Various synthetic efforts have been reported[4] for asymmetric synthesis of 2,6-*cis*-disubstituted piperidine skeleton in enantiopure form. Although, these synthetic approaches offer certain advantages, they have a few drawbacks, such as longer synthetic operations and expensive chiral reagents or starting materials. Thus more efficient strategies are welcome.

Herein, we wish to report a new strategy for a stereoselective asymmetric synthesis of 2,6-*cis*-disubstituted piperidines (Scheme 1), using a Barbier-type allylation[5] of a chiral imine and an organo-catalyzed aldol reaction[6] as key steps. The synthetic utility of this approach has been fully exploited in enantioselective syntheses of alkaloids (−)-241D and (−)-isosolenopsin as their hydrochloride salt forms, based on asymmetric syntheses of δ-amino β-hydroxy ketone **4a** and δ-amino α,β-unsaturated ketone **4b**, respectively, as depicted in Schemes 2 and 3.

Our synthetic strategy starts from commercially available materials decanal (**8**) and methyl (*S*)-valinate hydrochloride salt. In the first step decanal (**8**) was treated with methyl (*S*)-valinate hydrochloride in the presence of triethylamine and anhydrous Na_2SO_4

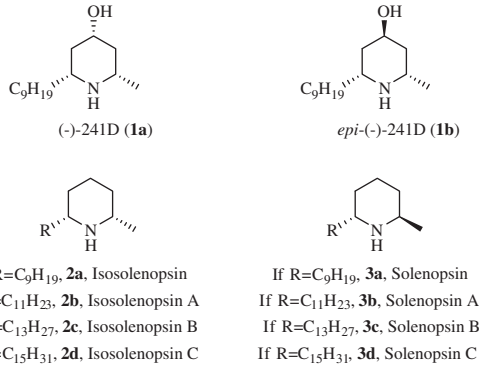

Figure 1. Structures of the alkaloids 241D and isosolenopsins.

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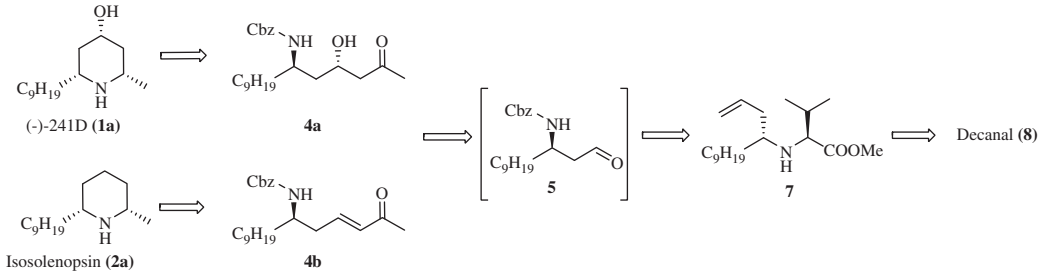
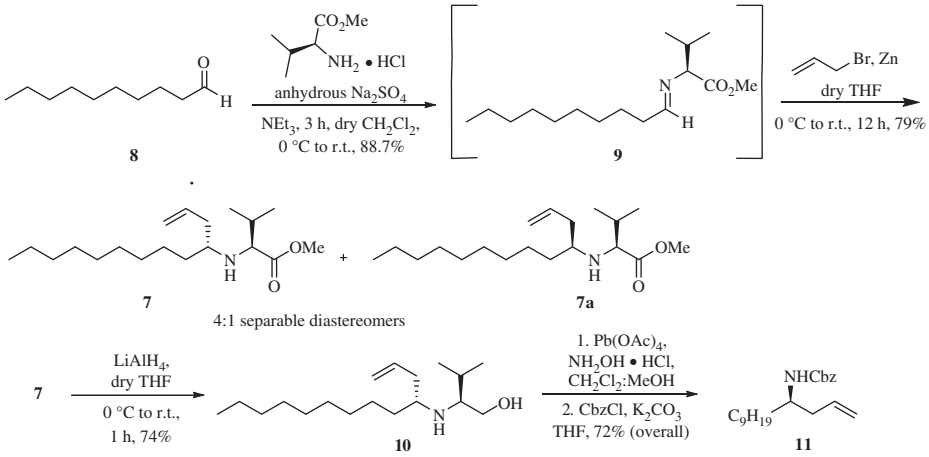
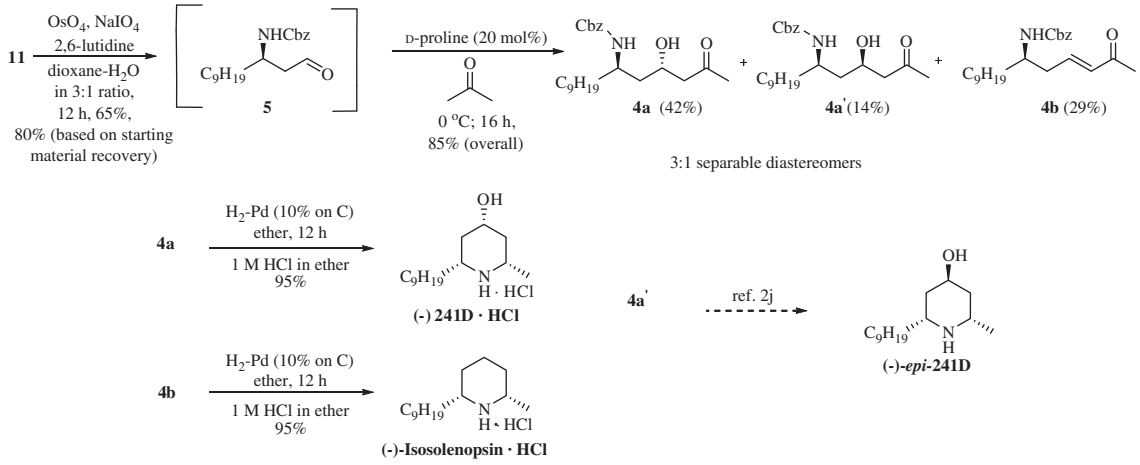


Scheme 1. Retrosynthesis of (−)-241D and (−)-isosolenopsin.



Scheme 2. Synthesis of Cbz-homoallyl amine.



Scheme 3. Syntheses of (−)-241D·HCl and (−)-isosolenopsin·HCl and a formal synthesis of (−)-*epi*-241D.

to generate the corresponding (*S*)-valinate imine **9**. This unstable imine **9**, was immediately subjected to Barbier-type allylation,[5] that is, allyl bromide in the presence of activated zinc dust, to stereoselectively furnish a separable mixture of α-amino esters **7** and **7a** in a 4:1 ratio. The ester functionality of the major isomer **7** was reduced to the corresponding primary alcohol **10** in 74% yield using $LiAlH_4$. 1,2-Amino alcohol **10**, was treated with $Pb(OAc)_4$ and $H_2NOH{\cdot}HCl$, which removed the isopentyl alcohol moiety,[5a] to obtain the free amine, which was subsequently protected as its Cbz derivative **11** in 72% yield with an enantioselectivity of 83% using Cbz-Cl/K_2CO_3 (Scheme 2).[7] Thus, the desired amino group was introduced by using a stereoselective addition to the (*S*)-valinate imine **9**. To the best of our knowledge, this is the first application of this novel methodology in a total synthesis of natural product alkaloid.

Homoallyl amine **11** was subjected to a one-pot oxidative cleavage, using OsO_4-$NaIO_4$ in the presence of 2,6-lutidine, to afford β-amino aldehyde **5** in 65% yield.[8] This β-amino aldehyde **5**, underwent an organo-catalyzed aldol reaction with acetone in the presence of D-proline (20 mol %) to furnish a column chromatographically separable diastereomeric pair of 1,3-amino alcohols **4a** (42%) and **4a′** (14%) in 3:1 ratio along with α,β-unsaturated ketone **4b** (29%) (Scheme 3). The α,β-unsaturated ketone **4b** was found to be the *E* stereoisomer, by ^1H NMR spectroscopy. Hydrogenation (10% Pd/C) of compound **4a** under an H_2 atmosphere removed the Cbz protecting group to give free amine, which underwent a smooth

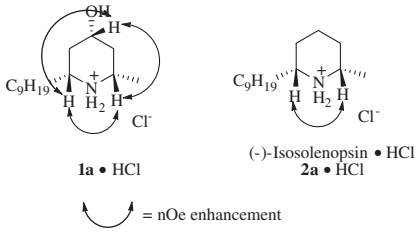


Figure 2. nOe enhancements of (−)-241D·HCl and (−)-isosolenopsin·HCl.

intramolecular cyclization,[2j] followed by reduction of the imine which accomplished (−)-241D (**1a)** in its crude form. This was further treated with 1 N HCl diluted in ether to furnish, (−)-241D as its hydrochloride salt. Similarly, compound **4b** was subjected to hydrogenation conditions, followed by acid treatment to furnish (−)-isosolenopsin·HCl (**2a·HCl).** Compound **4a**′ could be transformed into (−)-*epi*-241D (**1b**) by a known procedure.[2j,2k]

The optical rotations observed for (−)-241D·HCl and (−)-isosolenopsin·HCl were (−)-241D·HCl ($[\alpha]_D^{20}$ −15.1, *c* 0.26 MeOH), [literature value[2c] for (+)-241D·HCl is $[\alpha]_D^{20}$ +15.8, *c* 1.30 EtOH]) and for (−)-isosolenopsin·HCl ($[\alpha]_{D^{21}}$ −11.1, *c* 0.7 $CHCl_3$), [literature value,[3h] $[\alpha]_D^{20}$ −12.5, *c* 0.2 $CHCl_3$]). The stereochemistry of these piperidines, (−)-241D·HCl and (−)-isosolenopsin·HCl was exclusively 2,6-*cis*-*cis*-piperidin-4-ol and 2,6-*cis*-piperidine, respectively, which was further confirmed from nOe studies performed on the alkaloids (Fig. 2). It is noteworthy that the present synthetic route involves only nine-steps[9] to prepare both the alkaloids (−)-241D·HCl and (−)-isosolenopsin·HCl in 7.7% and 5.3% yields, respectively, and accompanies a formal synthesis of (−)-*epi*-241D in enantiopure manner starting from a common β-amino aldehyde **5** with nine-steps which makes this procedure amenable for scale-up.

In conclusion, we have described a new strategy for enantioselective syntheses of the alkaloids (−)-241D·HCl and (−)-isosolenopsin·HCl and a formal synthesis of (−)-*epi*-241D using a Barbier-type allylation of a novel chiral imine and an organo-catalyzed aldol reaction using D-proline. Further, applications of this methodology to the synthesis of enantiopure *cis*-piperidine rings are currently being pursued in our laboratory.

Acknowledgments

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7. (a) The enantiomeric excess of the compound **11** was determined from the following chiral HPLC method. The ee was determined as 83%; HPLC chiral peak OJ-H (46 × 25 cm), flow rate 1.0 mL/min (2% 2-propanol in hexane), retention time 5.29 (91.64%), 6.56 (8.3%). (b) The lower enantioselectivity is may be due to retroallylation-allylation of the intermediate aluminium salt formed during the $LiAlH_4$ reduction of **7**.
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9. *Spectral data for representative compounds:*
*Methyl (S)-3-methyl-2-((R)-tridec-1-en-4-ylamino)butanoate (**7**):* $[\alpha]_D^{20}$ −11 (*c* 1.5, $CHCl_3$); IR (KBr): υ_{max} 3328, 2925, 2855, 1733, 1464, 1376, 1255, 1162, 914, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.80–5.59 (m, 1H), 5.18–4.92 (m, 2H), 4.10–3.91 (m, 1H), 3.68 (s, 3H), 2.95 (dd, *J* = 22.3, 6.2 Hz, 1H), 2.76 (dd, *J* = 8.7, 4.7 Hz, 1H), 2.43–2.12 (m, 2H), 2.12–1.90 (m, 1H), 1.90–1.70 (m, 1H), 1.68–1.44 (m, 2H), 1.43–1.15 (m, 19H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR NMR ($CDCl_3$, 75 MHz): δ 176.2, 136.1, 116.9, 64.0, 62.4, 51.0, 40.6, 31.9, 31.8, 30.3, 29.9, 29.6, 29.3, 27.9, 27.6, 22.7, 19.4, 18.9, 14.1; ESI-MS: *m*/*z* 312.5 $(M+H)^+$.
*(S)-3-Methyl-2-((R)-tridec-1-en-4-ylamino)butan-1-ol (**10**):* $[\alpha]_D^{20}$ −8 (*c* 0.08, $CHCl_3$); IR (KBr): υ_{max} 2957, 2917, 2873, 1640, 1466, 1219, 914, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ5.87–5.68 (m, 1H), 5.13–4.98 (m, 2H), 3.49 (dd, *J* = 10.6, 4.5 Hz, 1H), 3.27 (dd, *J* = 10.6, 6.0 Hz, 1H), 2.70–2.57 (dt, *J* = 11.3, 6.0 Hz, 1H), 2.51–2.41 (ddd, *J* = 6.0, 3.8, 2.3 Hz, 1H), 2.26 (br. S, 1H), 2.14 (t, *J* = 5.3 Hz, 2H), 1.79 (m, 1H), 1.46–1.18 (m, 17H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.89 (distorted t, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.5, 117.1, 61.4, 60.5, 54.7, 44.2, 38.9, 34.4, 31.9, 29.9, 29.8, 29.5, 29.3, 25.9, 22.6, 19.7, 18.1, 14,1; ESI-MS: *m*/*z* 284.0 $(M+H)^+$.
*Benzyl N-((R)-tridec-1-en-4-yl)carbamate (**11**):* $[\alpha]_D^{20}$ +11 (*c* 0.5, $CHCl_3$); IR (KBr): υ_{max} 3329, 3072, 3035, 2927, 2856, 1700, 1534, 1460, 1253, 1060, 913, 735, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.43–7.27 (m, 5H), 5.93–5.67 (m, 1H), 5.19–4.96 (m, 4H), 4.56 (d, *J* = 8.2 Hz, 1H), 3.70 (m, 1H), 2.40–1.92 (m, 2H), 1.54–1.14 (m, 16 H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR NMR: ($CDCl_3$, 75 MHz): δ 155.9, 136.6, 134.2, 128.4, 127.9, 117.9, 117.7, 66.4, 50.6, 39.4, 34.6, 31.8, 29.8, 29.5, 29.3, 25.8, 22.6, 14.1.; ESI-MS: *m*/*z* 354.3 $(M+Na)^+$.
*Benzyl N-((R)-1-oxododecan-3-yl)carbamate (**5**):* IR (KBr): υ_{max} 3325, 2925, 2855, 1710, 1518, 1458, 1221, 1063, 773, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 9.71 (s, 1H), 7.37–7.21 (m, 5H), 5.13–4.95 (m, 3H), 4.09–3.89 (m, 1H), 2.69–2.44 (m, 2H), 1.63–1.40 (m, 2H), 1.40–1.13 (m, 14H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR NMR ($CDCl_3$, 75 MHz): δ 200.9, 155.9, 136.5, 136.3, 128.5, 128.1, 128.0, 66.7, 48.7, 47.1, 34.8, 31.8, 29.6, 29.4, 29.2, 26.1, 26.0, 22.6, 14.0; ESI-MS: *m*/*z* 356.2 $(M+Na)^+$.
*Benzyl N-((4S,6R)-4-hydroxy-2-oxopentadecan-6-yl)carbamate (**4a**):* $[\alpha]_D^{20}$ +2.8 (*c* 0.75, $CHCl_3$); IR (KBr): υ_{max} 3332, 2924, 2853, 1709, 1460, 1250, 773, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.22 (m, 5H), 5.17–5.00 (m, 3H), 4.83 (d, *J* = 8.9 Hz, 1H), 4.12–3.97 (m, 1H), 3.93–3.63 (m, 2H), 2.62 (dd, *J* = 16.6, 4.3 Hz, 1H), 2.41 (dd, *J* = 16.6, 4.3 Hz, 1H), 2.16 (s, 3H), 1.64–1.08 (m, 16H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR NMR ($CDCl_3$, 75 MHz): δ 208.7, 157.2, 129.7, 128.5, 128.2, 128.0, 114.3, 66.9, 64.4, 50.2, 48.4, 42.8, 35.3, 31.8, 31.0, 29.7, 29.5, 29.4, 29.3, 26.1, 22.7, 14.1.; ESI-MS: *m*/*z* 414.3 $(M+Na)^+$; HRMS: Calcd for $C_{23}H_{37}NNaO_4$ $(M+Na)^+$: 414.2615, found: 414.2630.
*Benzyl N-((4R,6R)-4-hydroxy-2-oxopentadecan-6-yl)carbamate (**4a**′):* $[\alpha]_D^{20}$: −7.6 (*c* 0.3, $CHCl_3$); IR (neat): υ_{max} 3345, 2924, 2853, 1458, 1220, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38–7.24 (m, 5H), 5.12–4.98 (m, 2H), 4.72 (d, *J* = 8.3 Hz, 1H), 4.12–3.98 (dt, *J* = 9.1, 6.8, 2.3 Hz, 1H), 3.72–3.58 (dt, *J* = 13.6, 7.6, 6.8 Hz,

1H), 2.75 (d, J = 17.4 Hz, 1H), 2.47 (dd, J = 9.3, 9.1 Hz, 1H), 2.14 (s, 3H), 1.57 (t, J = 6.8 Hz, 2H), 1.53–1.38 (m, 2H), 1.37–1.14 (m, 13H), 0.89 (t, J = 7.6 Hz, 3H).; ^{13}C NMR NMR ($CDCl_3$, 75 MHz): δ 209.9, 156.3, 129.8, 128.4, 128.0, 127.9, 66.6, 65.6, 49.6, 49.1, 41.9, 35.9, 31.8, 30.6, 29.6, 29.5, 29.4, 29.2, 25.7, 22.6, 14.1.; ESI-MS: m/z 414.6 $(M+Na)^+$. HRMS: Calcd for $C_{23}H_{38}NO_4$ $(M+H)^+$: 392.2715, found 392.2812.

Benzyl N-((R,E)-2-oxopentadec-3-en-6-yl)carbamate (**4b**): $[\alpha]_D^{20}$ +17.5 (c 0.4, $CHCl_3$); IR (KBr): $\upsilon_{max,}$ 3328, 2927, 2856, 1699, 1678, 1534, 1458, 1361, 1253, 1057, 979, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz); δ 7.38–7.17 (m, 5H), 6.76–6.58 (m, 1H), 6.02 (d, J = 15.9 Hz, 1H), 5.04 (dd, J = 12.3, 12.1 Hz, 2H), 4.58 (d, J = 8.5 Hz, 1H), 3.84–3.67 (br.s, 1H), 2.54–2.35 (m, 1H), 2.35–2.22 (m, 1H), 2.16 (s, 3H), 1.68–1.15 (m, 16H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR NMR ($CDCl_3$, 75 MHz): δ 198.3, 162.1, 155.9, 143.7, 136.4, 133.6, 128.5, 128.1, 128.0, 66.7, 50.5, 38.6, 34.9, 31.8, 29.7, 29.5, 29.2, 26.9, 25.9, 22.7, 14.1.; ESI-MS: m/z 396 $(M+Na)^+$. HRMS: Calcd for $C_{23}H_{36}NO_3$ $(M+H)^+$: 374.2690. Found: 374.2699.

(−)-241D Hydrochloride or (−)-1a·HCl: $[\alpha]_D^{20}$ −15.1 (c 0.26, MeOH) [lit.[2c] $[\alpha]_D^{20}$ +15.8 (c 1.30, MeOH) for it's enantiomer[2c]].; IR (KBr): υ_{max} 3318, 2927, 2856, 1714, 1527, 1458, 1355, 1251, 1220, 772 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz): δ 3.82–3.62 (m, 1H), 3.28–3.13 (m, 2H), 3.13–2.97 (m, 1H), 2.21–1.98 (m, 2H), 1.73–1.56 (m, 1H), 1.56–1.40 (m, 1H), 1.40–1.08 (m, 19H), 0.80 (t, J = 6.9 Hz, 3H);. ^{13}C NMR NMR (CD_3OD, 75 MHz): δ 69.0, 59.3, 55.4, 43.1, 41.0, 36.9, 35.5, 33.0, 32.9, 32.8, 28.7, 26.2, 21.6, 16.9.; ESI-MS: m/z 242.1 $(M+H)^+$; HRMS: Calcd for $C_{15}H_{32}NO$ $(M+H)^+$: 242.2478, found: 242.2499.

(−)-Isosolenopsin hydrochloride or (−)-2a·HCl: mp = 175 °C; $[\alpha]_D^{21}$ −11.1 (c 0.7, $CHCl_3$) [lit.[3h] −12.5 (c 0.2, $CHCl_3$)]; IR (KBr): υ_{max} 3312, 2924, 2853, 1683, 1622, 1464, 1364, 1125, 1038, 723 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.21–3.01 (m, 1H), 2.92 (t, J = 9.8 Hz, 1H), 2.17–1.86 (m, 3H), 1.86–1.68 (m, 2H), 1.68–1.40 (m, 4H), 1.3–1.13 (m, 17H), 0.87 (t, J = 6.7 Hz, 3H).; ^{13}C NMR NMR ($CDCl_3$, 75 MHz): δ 58.0, 54.0, 33.4, 31.9, 30.5, 29.7, 29.5, 29.4, 29.3, 27.6, 25.3, 22.9, 22.7, 19.2, 14.0; ESI-MS: m/z 226 $(M+H)^+$; HRMS: Calcd for $C_{15}H_{32}N$ $(M+H)^+$: 226.2529. Found: 226.2561.