



# Enantioselective syntheses of both enantiomers of *cis*-pyrrolidine 225H

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## ABSTRACT

The efficient and expeditious syntheses of both enantiomers of the amphibian alkaloid *cis*-225H have been achieved. Utilizing a common *cis*-2,5-disubstituted pyrrolidine building block derived from (+)-2-tropinone, the enantioselective syntheses have established the absolute configuration of these alkaloids as (+)-(2*R*,5*S*) and (–)-(5*S*,2*R*).

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## 1. Introduction

Alkaloids isolated from amphibian skin extracts are represented by over 20 structural classes with over 800 unique compounds identified as of 2005.<sup>1</sup> The amphibian alkaloids have provided valuable leads toward the development of new therapeutic agents and have been attractive targets for synthesis.<sup>2</sup> The unsymmetrical 2,5-disubstituted pyrrolidine alkaloids (**1**) are a unique class of alkaloids in that these simple monocyclic amines have been isolated from two very distinct sources.<sup>1</sup> Initially, the 2,5-disubstituted pyrrolidine alkaloids were isolated from the venom of several ant species and thought to serve as a chemical defense mechanism against predators.<sup>3</sup> More recently, the 2,5-disubstituted pyrrolidine alkaloids have been found in the skin extracts of various neotropical amphibian species.<sup>4</sup> With few exceptions, the 2,5-disubstituted pyrrolidine alkaloids are rare in amphibian species and when present are only obtained in trace amounts. However, the 2,5-disubstituted pyrrolidine alkaloid 197B (**2**) was found to be the major alkaloid in the skin extracts of one population of Columbian frog (*Dendrobates histrionicus*).<sup>4</sup> The source of these anuran alkaloids has been presumed to be dietary<sup>3d</sup>, although feeding studies have shown that pyrrolidine alkaloids are not readily accumulated in amphibian skin.<sup>5</sup> This suggests that a rather remarkable ecological and perhaps evolutionary relationship exists between ant and frog species living in neotropical environments (Fig. 1).

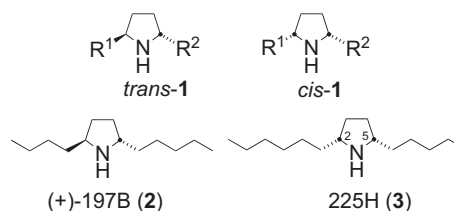


Figure 1. Pyrrolidine Alkaloids.

Among, the 2,5-disubstituted pyrrolidine alkaloids that have been isolated, the *trans*-isomers (e.g., **2**) have been shown to be exclusively found in ant extracts<sup>3</sup> and predominate over the *cis*-isomers in anuran extracts.<sup>1,4</sup> As such the *trans*-2,5-disubstituted pyrrolidine alkaloids have been the subject of numerous studies, ranging from the development of synthetic methods<sup>6</sup> and total synthesis<sup>7</sup> to pharmacological evaluation.<sup>2</sup> However, due to the paucity of the *cis*-isomers (e.g., 225H, **3**), these alkaloids have not been fully characterized and the absolute configurations of these molecules are unknown.<sup>1</sup> In addition, these alkaloids have not received much attention from the synthetic community.<sup>8</sup> As part of program aimed at CNS drug discovery based upon novel molecular scaffolds it was of interest to develop an enantioselective synthetic approach that would allow for the unequivocal determination of the absolute configuration of both enantiomers of the 2,5-disubstituted pyrrolidine alkaloid *cis*-225H **3** and *ent*-**3**. Herein we describe the synthesis of both enantiomers of *cis*-225H from a common intermediate.

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## 2. Results and discussion

Previous work in our laboratory has shown that the pyrrolidine derivative **4**, was a useful chiral building block for the construction of amphibian alkaloid skeletons containing a *cis*-pyrrolidine subunit.<sup>9</sup> The orthogonal reactivity of the side chain functional groups and the nitrogen atom protecting group of **4** offered easy access to more complicated ring systems. In addition, we had shown previously that the *S*-configuration at C5 of **4** was inert to a wide variety of functional group transformations and could be exploited without worry of epimerization. Readily prepared from (+)-(1*R*)-2-tropinone (**5**)<sup>10</sup>, the versatility of **4** for enantioselective synthesis seemed well suited for the preparation of both enantiomers of *cis*-225H (**3** and *ent*-**3**, Fig. 2).

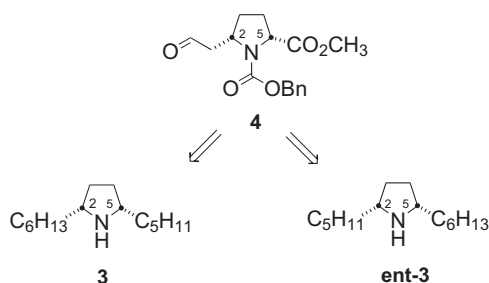
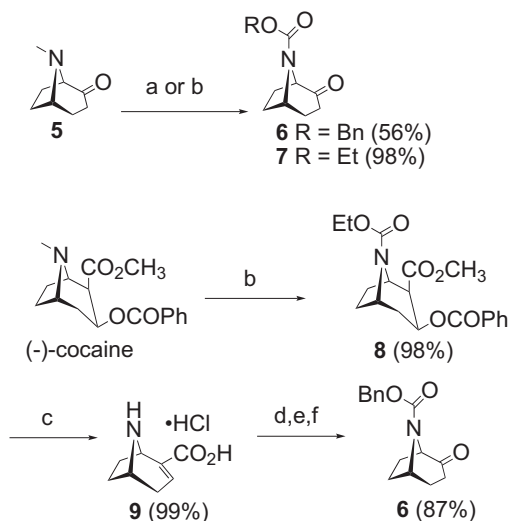


Figure 2. Retrosynthetic approach.

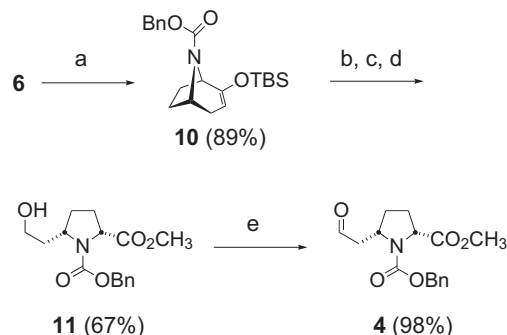
Starting from (+)-2-tropinone (**5**) it was our intent to prepare **4** by direct demethylation/acylation with benzyl chloroformate (CbzCl) followed by subsequent conversion into the *cis*-pyrrolidine derivative. The (+)-tropinone **5** was readily obtained from (–)-cocaine<sup>10</sup> or via resolution of (±)-2-tropinone with L-tartaric acid.<sup>11</sup> As we had previously shown, the direct demethylation/acylation of **5** only gave a modest yield (56%) of the desired Cbz-2-tropinone **6**.<sup>9</sup> This was disappointing since the corresponding ethyl carbamate **7**, could be obtained in 98% yield employing ethyl chloroformate under similar conditions (Scheme 1). Although **7** was a viable starting point, the ethyl carbamate would not provide the overall efficiency that was desired, due to deprotection chemistry that would be required late in the synthetic sequence.



Scheme 1. Reagents and conditions: (a) CbzCl, K<sub>2</sub>CO<sub>3</sub>, toluene, reflux. (b) EtOCOCl, K<sub>2</sub>CO<sub>3</sub>, toluene, reflux. (c) 12 N HCl, reflux. (d) DMAP, (PhO)<sub>2</sub>PON<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>. (e) 1 N HCl, reflux. (f) CbzCl, Na<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>OH/H<sub>2</sub>O.

Since the demethylation step was clearly problematic with CbzCl, we elected to explore an alternative route to **6**. We envisaged that a separate demethylation step prior to introduction of the Cbz-group would give higher overall yields of **6**. In the revised synthetic route (Scheme 1), demethylation was attempted first. Treatment of confiscated grade cocaine<sup>12</sup> with ethyl chloroformate provided **8** in 98% yield. Subsequent hydrolysis and concomitant dehydration of **8** in concentrated HCl at reflux for 12 h afforded noranhydroecognine·HCl (**9**) in quantitative yield. The carboxylic acid moiety of **9** was then reacted with diphenylphosphoryl azide catalyzed by 4-dimethylaminopyridine in dichloromethane giving the intermediate acyl azide, which then underwent a Curtius rearrangement in 1 N HCl at reflux. The crude mixture was treated with CbzCl to furnish **6** in 84% overall yield. The yield of this one-pot three-step heterogeneous reaction was closely related to the dryness of the intermediate **9**. Thoroughly drying the acid **9** and grinding it into a fine powder was found to greatly facilitate the formation of the acyl azide and as a result led to a higher overall yield of the Cbz-2-tropinone **6**.

With **6** in hand, our attention was focused on the preparation of pyrrolidine **4**. The tropinone **6** was treated with a THF solution of NaH followed by the addition of TBSCl to furnish silyl enol ether **10** in 89% yield. Compared with the methyl enol ether employed in earlier studies,<sup>9</sup> the silyl enol ether was more stable toward chromatography and was readily purified prior to the ozonolysis step. Ozone was slowly bubbled through a solution of enol ether **10** in dichloromethane/methanol (9:1) at –78 °C. Treatment of the intermediate ozonide with sodium borohydride followed by addition of diazomethane (from Diazald®) furnished the pyrrolidine **11**, in 67% yield over the three steps. Subsequent Swern oxidation of **11** provided the *cis*-pyrrolidine **4** in 98% yield (Scheme 2).

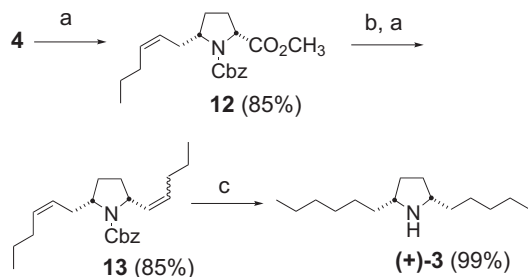


Scheme 2. Reagents and conditions: (a) TBSCl, NaH, THF, 0 °C. (b) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH, –78 °C. (c) NaBH<sub>4</sub>, 0 °C. (d) CH<sub>2</sub>N<sub>2</sub>, Et<sub>2</sub>O, 0 °C. (e) (COCl)<sub>2</sub>, DMSO, CH<sub>2</sub>Cl<sub>2</sub>, –78 °C, then Et<sub>3</sub>N.

The conversion of the intermediate ozonide to the alcohol derivative **11** and subsequent oxidation to **4** was preferable to the direct conversion of **10** into the aldehyde moiety (e.g., using dimethylsulfide or triphenylphosphine to reduce the ozonide). This indirect method gave more reliable yields and furnished **4** with fewer byproducts and impurities. This revised synthetic route gave the pyrrolidine building block **4** in a 49% overall yield from (–)-cocaine and was a significant improvement over our previous method.<sup>9</sup>

The pyrrolidine **4** existed as a mixture (3:1) of conformational isomers due to hindered rotation about the N–Cbz bond (rotamers). Since the presence of rotamers significantly complicated the NMR spectrum it was practical to advance subsequent intermediates to a point where the conformational isomers did not contribute to the complexity of the molecule before a meaningful structural characterization was made.

The construction of the C2 and C5 alkyl appendages of 225H was envisaged to employ an iterative process of olefination. Subsequent hydrogenation would then provide the saturated side chains as well simultaneously remove the Cbz-protecting group to give pyrrolidine alkaloid 225H. As illustrated in Scheme 3, treatment of the **4** with the Wittig ylide generated from a solution of *n*-butyl-triphenylphosphonium bromide and KH in THF at 0 °C afforded the *Z*-olefin **12** in 85% isolated yield. The carboxyl moiety of **12** was then reduced with diisobutylaluminum hydride (DIBALH) in toluene at –78 °C, and concomitant Wittig olefination furnished the diene **13** as an unresolvable mixture of geometrical isomers in 85% yield for the two-step process.



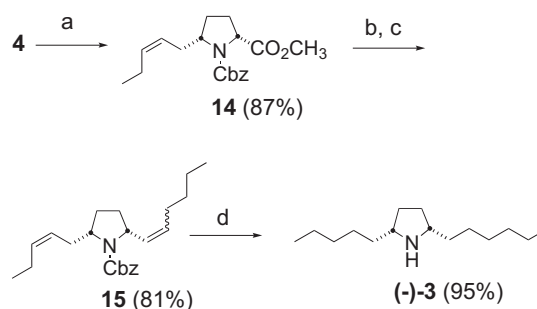
**Scheme 3.** Reagents and conditions: (a)  $\text{Ph}_3\text{P}(\text{CH}_2)_3\text{CH}_3\text{Br}$ , KH, THF, 0 °C. (b) DIBALH,  $\text{CH}_2\text{Cl}_2$ , –78 °C. (c)  $\text{H}_2$  (1 atm), 10% Pd/C,  $\text{CH}_3\text{OH}$ .

Conceivably, these steps could have resulted in some epimerization of the stereocenter at C2 due to the potentially labile nature of the intermediate aldehyde moiety toward the basic reaction conditions of either the reduction or the Wittig reaction. However, minor epimerization was of little concern at this point since we envisaged that any 2,5-*trans*-pyrrolidines formed as byproducts could be quite easily separated from the *cis*-isomer by chromatography after the final steps of the synthesis. The mixture of conformational and geometrical isomers of diene **13** was exposed to a hydrogen atmosphere (1 atm) in the presence of 10% palladium on activated carbon. Simultaneous hydrogenation of the two alkene moieties and hydrogenolysis of the Cbz-group afforded the pyrrolidine 225H (**3**) in quantitative yield. From these results it could be then established that **3** was the dextrorotatory isomer, (+)-*cis*-225H  $\{[\alpha]_D^{25} +21.9\}$  ( $c$  1.0,  $\text{CH}_3\text{OH}$ ) and thus had the absolute configuration of 2*R*, 5*S*.

While it was clear from the NMR spectra of **3** that no *trans*-isomers were present, attempts to confirm the enantiomeric purity using the NMR chiral shift reagent 1,1'-binaphthyl-2,2'-diylphosphoric acid were inconclusive.<sup>13,14</sup> Since the specific rotation data for the naturally occurring *cis*-pyrrolidine 225H has not been previously reported we decided to synthesize the other enantiomer *ent*-**3** for comparison. It was envisaged that the synthesis of the levorotatory isomer would not only validate the enantioselectivity of the approach it would also demonstrate the versatility of the pyrrolidine building block **4**.

Because of the asymmetry of the side chains of **4**, we had to slightly modify our approach for construction of the C2 and C5 appendages of *ent*-**3** (Scheme 4). Treatment of **4**, with the Wittig ylide generated from *n*-propyltriphenylphosphonium bromide in a THF solution of KH provided the *Z*-alkene **14** in 89% yield. Homologation of the ester moiety of **14** was achieved in similar fashion to that described previously for **3**. Reduction of the carboxylate with DIBALH to the corresponding aldehyde and concomitant Wittig olefination with the ylide generated from *n*-pentyltriphenylphosphonium bromide furnished **15** as an unresolvable mixture of geometrical and conformational isomers in 81% yield for the two-steps. Hydrogenation of the mixture then conveniently furnished the *ent*-**3** in 95% yield. It was determined that *ent*-**3** was the

levorotatory enantiomer  $\{[\alpha]_D^{25} -20.6\}$  ( $c$  0.5,  $\text{CH}_3\text{OH}$ ) and established the absolute configuration of *ent*-**3** as 2*S*, 5*R*.



**Scheme 4.** Reagents and conditions: (a)  $\text{Ph}_3\text{P}(\text{CH}_2)_2\text{CH}_3\text{Br}$ , KH, THF, 0 °C. (b) DIBALH,  $\text{CH}_2\text{Cl}_2$ , –78 °C. (c)  $\text{Ph}_3\text{P}(\text{CH}_2)_4\text{CH}_3\text{Br}$ , KH, THF, 0 °C. (d)  $\text{H}_2$  (1 atm), 10% Pd/C,  $\text{CH}_3\text{OH}$ .

Since both pyrrolidines **3** and *ent*-**3** were clearly *cis*-isomers and based upon the similar but opposite optical rotations, it was clear that the syntheses proceeded with a similar degree of enantioselectivity. Because it was unlikely that epimerization of either stereocenter would lead to a *cis*-isomer over the more stable *trans*-isomers, we were comfortable with the assignments of the absolute configurations of the (+)-(*2R*, 5*S*) 225H and (–)-(*2S*, 5*R*) 225H.

### 3. Conclusion

In summary, the efficient and expeditious syntheses of both enantiomers of the amphibian alkaloid *cis*-pyrrolidine 225H exploits the inherent stereochemistry of a (1*R*)-tropane ring system of (–)-cocaine for the construction of the core *cis*-2,5-disubstituted pyrrolidine. Utilizing the intermediate **4** as a common building block, the enantioselective syntheses of both of the (+)-*cis*-225H (72% yield) and (–)-*cis*-225H (67% yield) were achieved. This has served to establish the absolute configurations of both the dextrorotatory and the levorotatory isomers of *cis*-225H.

## 4. Experimental section

### 4.1. General methods

All chemicals were purchased from Aldrich Chemical Company and used as received unless otherwise noted. Anhydrous dichloromethane was purchased from Mallinckrodt Baker, Inc. Chromatography refers to flash chromatography on silica gel (Sorbtech, Inc.: 40–62 Å, 230–400 mesh). Proton and carbon NMR were recorded on a Varian-400 MHz nuclear magnetic resonance spectrometer at ambient temperature in  $\text{CDCl}_3$  from Cambridge Isotope Laboratories, Inc.  $^1\text{H}$  NMR chemical shifts are reported as  $\delta$  values (ppm) relative to tetramethylsilane.  $^{13}\text{C}$  NMR chemical shifts are reported as  $\delta$  values (ppm) relative to chloroform-*d* (77.0 ppm). Optical rotations were measured on Autopol III polarimeter at the sodium D line (2 mL sample cell). Melting points (mp) were measured with an Electrothermal R Mel-Temp apparatus and are uncorrected.

**4.1.1. (1*R*,5*S*)-8-Ethoxycarbonyl-8-azabicyclo[3.2.1]octan-2-one (**7**).** To a solution of **5**<sup>10</sup> (0.64 g, 4.6 mmol) and  $\text{K}_2\text{CO}_3$  (380 mg, 2.3 mmol) in toluene (8 mL) was added ethyl chloroformate (2.2 mL, 23 mmol). The reaction mixture was heated to reflux for 24 h. The solvent was removed under vacuum and the resulting residue was dissolved in water (9 mL). The aqueous layer was extracted with dichloromethane (3×10 mL). The organic layers were combined and dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed under reduced pressure and the residue was purified by

chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/hexane, 3:7) to yield **7** (0.89 g, 98%) as a pale yellow oil.  $[\alpha]_D^{20}$  –15.4 (c 0.4, CH<sub>3</sub>OH). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.47 (s, 1H), 4.40 (s, 1H), 4.10–4.14 (m, 2H), 2.35–2.45 (m, 2H), 2.17–2.22 (m, 3H), 1.78–1.84 (m, 3H), 1.23 (t, *J* 6.8 Hz, 3H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  14.6, 30.6 (2), 32.5 (2), 52.8, 61.5, 64.1, 154.3, 205.7. Anal. Calcd for C<sub>10</sub>H<sub>15</sub>NO<sub>3</sub>: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.90; H, 7.67; N, 7.10.

**4.1.2. (1R,2R,3S,5S)-3-(Benzoyloxy)-2-methoxycarbonyl-8-ethoxycarbonyl-8-azabicyclo[3.2.1]octane (8).** Confiscated (–)-cocaine hydrochloride (20 g) was dissolved in water (50 mL). The aqueous solution was washed with ether to remove any trace organic impurities. A saturated solution of Na<sub>2</sub>CO<sub>3</sub> was added until the solution was at pH 10. The resultant slurry was extracted with dichloromethane (100 mL). The aqueous portion was discarded. The organic solution was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo to furnish (–)-cocaine (18.1 g, 100%).

(–)-Cocaine (9.76 g, 32.1 mmol) and NaHCO<sub>3</sub> (4.05 g, 48.3 mmol) were added to anhydrous toluene (100 mL). To the suspension was added ethyl chloroformate (17.5 g, 15.3 mL, 161 mmol). The reaction mixture was heated to reflux for 12 h, then another portion of ethyl chloroformate (10.5 g, 9.18 mL, 96.5 mmol) was added. Stirring and heating were continued for an additional 12 h. Toluene was removed under reduced pressure and the residue was portioned between ethyl acetate (100 mL) and water (100 mL). The aqueous layer was separated and extracted with ethyl acetate (2×100 mL). The combined organic portions were washed with saturated Na<sub>2</sub>CO<sub>3</sub> solution (100 mL), brine (100 mL), dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was purified by chromatography (SiO<sub>2</sub>, EtOAc/hexanes, 1:2) affording **8** (11.4 g, 98%) as a slightly yellow oil. *R*<sub>f</sub> = 0.34 (EtOAc/hexanes, 1:2).  $[\alpha]_D^{25}$  –30.4 (c 1.0, CH<sub>3</sub>OH). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.98–7.90 (m, 2H), 7.59–7.51 (m, 1H), 7.42–7.37 (m, 2H), 5.50–5.41 (m, 1H), 4.76–4.41 (m, 2H), 4.20–4.00 (m, 2H), 3.63 (s, 3H), 3.09 (br s, 1H), 2.61–2.56 (m, 1H), 2.18–1.72 (m, 5H), 1.30–1.19 (m, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  170.4, 166.0, 153.9, 133.3, 129.7, 128.5, 66.7, 61.2, 61.1, 54.9, 54.6, 52.6, 52.4, 52.0, 51.6, 49.4, 48.9, 33.7, 33.3, 28.9, 28.2, 27.9, 27.3, 14.8. Anal. Calcd for C<sub>19</sub>H<sub>23</sub>NO<sub>6</sub>: C, 63.15; H, 6.41; N, 3.88. Found: C, 63.22; H, 6.49; N, 3.91.

**4.1.3. Noranhydroecognine HCl (9).** The carbamate **8** (10.1 g, 28.5 mmol) was added to concentrated hydrochloric acid (12 N, 100 mL). The mixture was heated to reflux for 6 h. After cooling to room temperature, the aqueous solution was extracted with ethyl ether (2×50 mL) and the organic extracts were discarded. The aqueous portion was concentrated under reduced pressure at elevated temperature. The remaining water was removed by suspension of the slurry in toluene followed by azeotropic distillation under reduced pressure. The resultant solid was dried in a vacuum oven (80 °C, 30 mmHg.) for 12 h. The solid was ground into a fine powder and heated under vacuum for an additional 12 h. This afforded **9** (5.41 g, 99%) as a white powder. Mp 260–262 °C (dec). Anal. Calcd for C<sub>8</sub>H<sub>12</sub>ClNO<sub>2</sub>: C, 50.67; H, 6.38; N, 7.39. Found: C, 50.38; H, 6.39; N, 7.27.

**4.1.4. (1R,5S)-8-Benzoyloxycarbonyl-8-azabicyclo[3.2.1]octan-2-one (6).** The finely powdered **9** (3.22 g, 17.0 mmol) and sodium carbonate (4.50 g, 42.5 mmol) were suspended in anhydrous dichloromethane (100 mL) followed by the addition of 4-dimethylaminopyridine (104 mg, 0.84 mmol). The suspension was purged with N<sub>2</sub>, sealed, and stirred for 15 min before diphenylphosphoryl azide (5.71 g, 4.48 mL, 20.7 mmol) was added dropwise. The stirring was continued for 48 h at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in water (40 mL). The mixture was cooled to 0 °C, hydrochloric acid (1 N, 120 mL) was added slowly and carefully

with the evolution of gas. The aqueous solution was then heated in a preheated oil bath (120 °C) for 40 min until the carbon dioxide and nitrogen gas evolution ceased. The aqueous solution was concentrated under reduced pressure and the residue was basified (pH 9.5–10) by the addition of a saturated solution of Na<sub>2</sub>CO<sub>3</sub>. The aqueous solution was then extracted with dichloromethane (2×50 mL). The combined organic portions were washed with brine (50 mL), dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The residue without further purification was dissolved in the mixture of methanol (108 mL) and water (12 mL) and cooled to 0 °C. Solid sodium bicarbonate (4.6 g) was added portionwise followed by the addition of benzyl chloroformate (2.4 mL). The reaction mixture was allowed to warm to room temperature and stirred for 5 h. The solvent was removed under reduced pressure and the aqueous solution was diluted with water (50 mL) and extracted with dichloromethane (2×50 mL). The combined organic fractions were washed by brine, dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was purified by chromatography (SiO<sub>2</sub>, EtOAc/hexanes, 1:2) to afford **6** (3.84 g, 87%) as a clear oil.  $[\alpha]_D^{25}$  –5.9 (c 1.0, CH<sub>3</sub>OH). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.39–7.27 (m, 5H), 5.19–5.07 (m, 2H), 4.54–4.44 (m, 2H), 2.48–2.42 (m, 2H), 2.38–2.32 (m, 2H), 2.25–2.18 (m, 2H), 1.86–1.77 (m, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  205.5, 154.0, 136.5, 128.6, 128.2, 128.0, 67.2, 64.3, 53.0, 32.6, 30.6, 28.0, 27.2. Anal. Calcd for C<sub>15</sub>H<sub>17</sub>NO<sub>3</sub>: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.65; H, 6.65; N, 5.29.

**4.1.5. (1R,5S)-8-Benzoyloxycarbonyl 2-(tert-butyl-dimethylsilyloxy)-8-azabicyclo[3.2.1]oct-2-ene (10).** Sodium hydride (60 mg, 2.5 mmol) was suspended in anhydrous THF (4 mL) under nitrogen atmosphere at 0 °C. A solution of ketone **9** (130 mg, 0.50 mmol) in dry THF (2 mL) was added dropwise and stirred for 2 h. Then *tert*-butyl(chloro)dimethylsilane (1.0 M in THF, 1 mL) was added dropwise and stirred overnight at room temperature. The mixture was cooled to 0 °C, the reaction was quenched by a slow addition of water (10 mL) and diluted with ethyl ether (20 mL). The organic fraction was separated and the aqueous portion was extracted with ethyl ether (2×20 mL). Combined organic portions were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography (SiO<sub>2</sub>, EtOAc/hexanes, 5:95) to afford **10** (166 mg, 89% yield) as a colorless oil.  $[\alpha]_D^{25}$  –43.5 (c 1.2, CH<sub>3</sub>OH). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.28–7.35 (m, 5H), 5.09–5.19 (m, 2H), 4.11–4.49 (m, 2.5H<sub>rotamers</sub>), 2.61–2.79 (m, 0.5H<sub>rotamers</sub>), 1.94–2.18 (m, 3H), 1.74 (dd, *J* 16.4, 4.6 Hz, 1H), 1.58–1.67 (m, 2H), 0.90 (s, 9H), 0.14 (m, 6H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  154.8, 154.4, 137.1, 128.6, 128.1, 128.0, 97.3, 66.8, 57.7, 52.5, 34.4, 33.7, 32.4, 31.4, 30.2, 29.4, 25.8, 18.2, –4.5, –4.1. Anal. Calcd for C<sub>21</sub>H<sub>31</sub>NO<sub>3</sub>Si: C, 67.52; H, 8.36; N, 3.79. Found: C, 67.73; H, 8.58; N, 3.79.

**4.1.6. (2R,5S)-1-Benzoyloxycarbonyl-2-methoxycarbonyl-5-(2-hydroxyethyl)pyrrolidine (11).** Silyl ether **10** (781 mg, 2.1 mmol, 1.0 equiv) was dissolved in a solution of dichloromethane (50 mL) and methanol (5 mL). At –78 °C, O<sub>3</sub> was bubbled into the solution until a light blue color was observed and persisted. A stream of nitrogen was bubbled through the solution for 10 min. At –78 °C, NaBH<sub>4</sub> (250 mg) was added by one portion. After 30 min, another portion of NaBH<sub>4</sub> (300 mg) was added and the reaction was warmed to room temperature. The solvent was removed under reduced pressure. The residue was triturated with 2 N HCl (25 mL) to pH 1. The aqueous solution was extracted with dichloromethane (3×20 mL). The combined organic portions were dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure to afford a light yellow oil. The oil was dissolved in ethyl ether (20 mL) and diazomethane was freshly prepared from *p*-toluenesulfonylmethyl nitrosamide (Diazald) and bubbled through the solution at 0 °C. When a yellow color persisted, diazomethane stream was

removed and nitrogen was bubbled through the solution for 5 min. The mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. The residue was purified by chromatography (SiO<sub>2</sub>, hexanes/EtOAc, 4:6) affording ester **11** (430 mg, 67% yield, three steps) as a colorless oil.  $[\alpha]_D^{25} +52$  (c 0.6, CH<sub>3</sub>OH). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.28–7.37 (m, 5H), 5.03–5.22 (m, 2H), 4.37 (t, *J* 8.3 Hz, 1H), 3.93 (dd, *J* 9.8, 4.6 Hz, 1H), 3.64–3.82 (m, 3H), 3.60 (s, 3H), 2.30–2.37 (m, 1H), 1.95–2.11 (m, 2H), 1.61–1.82 (m, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  173.6, 156.1, 136.4, 128.7, 128.3, 127.9, 67.8, 59.9, 59.1, 55.8, 52.4, 37.8, 30.9, 29.2. Anal. Calcd for C<sub>16</sub>H<sub>21</sub>NO<sub>5</sub>: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.28; H, 7.00; N, 4.49.

**4.1.7. (2R,5S)-1-Benzylloxycarbonyl-2-methoxycarbonyl-5-(2-oxoethyl)pyrrolidine (4).** To a solution of oxalyl chloride (150 mg, 0.1 mL, 1.18 mmol) in dichloromethane (30 mL) at –78 °C was added dimethyl sulfoxide (184 mg, 0.17 mL, 2.25 mmol) dropwise. The mixture was stirred at –78 °C for 10 min before a solution of the alcohol **11** (300 mg, 0.98 mmol) in dichloromethane (2 mL) was added slowly. The mixture was stirred for 15 min, then triethylamine (541 mg, 0.75 mL, 5.35 mmol) was added and the mixture was warmed to room temperature. Water (30 mL) was added and the organic layer was separated and the aqueous layer was extracted with dichloromethane (2×30 mL). The combined organic portions were washed by brine, dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by chromatography (SiO<sub>2</sub>, EtOAc/hexanes, 1:1) to afford **4** (294 mg, 98%) as a clear oil.  $[\alpha]_D^{25} +23.6$  (c 1.0, CH<sub>3</sub>OH). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.81 (s, 0.6H<sub>rotamers</sub>), 9.71 (s, 0.4H<sub>rotamers</sub>), 7.35–7.27 (m, 5H), 5.19–5.03 (m, 2H), 4.50–4.32 (m, 2H), 3.74 (s, 1.2H<sub>rotamers</sub>), 3.61 (s, 1.8H<sub>rotamers</sub>), 3.24 (dd, *J* 20.1, 3.7 Hz, 0.6H<sub>rotamers</sub>), 3.05 (dd, *J* 20.1, 3.7 Hz, 0.4H<sub>rotamers</sub>), 2.72–2.62 (m, 1H), 2.27–2.16 (m, 2H), 2.03–1.94 (m, 1H), 1.75–1.66 (m, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  200.9, 200.7, 173.2, 173.0, 154.3, 153.9, 136.3, 136.1, 128.5, 128.4, 128.2, 128.1, 128.0, 127.6, 67.3, 67.0, 59.9, 59.5, 54.0, 53.2, 52.3, 52.1, 48.9, 48.2, 31.0, 30.2, 28.9, 28.0, 22.2. Anal. Calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>5</sub>: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.51; H, 6.53; N, 4.49.

**4.1.8. (2R,5S,Z)-1-Benzylloxycarbonyl 2-methoxycarbonyl-5-(hex-2-enyl)-pyrrolidine (12).** Potassium hydride (40% in mineral oil) was washed with anhydrous hexanes and dried by a stream of argon. Potassium hydride (47.3 mg, 1.18 mmol) and Ph<sub>3</sub>P(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>Br (628 mg, 1.57 mmol) were suspended in of anhydrous THF (10 mL). The reaction mixture was stirred under the atmosphere of nitrogen at room temperature for 30 min and then cooled to 0 °C. A solution of aldehyde **4** (120 mg, 0.39 mmol) in THF (1 mL) was added dropwise. Upon completion of the addition, the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of saturated solution of ammonium chloride (1 mL). The mixture was then partitioned between ethyl acetate (20 mL) and water (20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×20 mL). The combined organic portions were washed with brine, dried on anhydrous MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by chromatography (SiO<sub>2</sub>, EtOAc/hexanes, 1:4) affording the *Z*-alkene **12** (115 mg, 85%). *R*<sub>f</sub>=0.44 (EtOAc/hexanes, 1:4).  $[\alpha]_D^{25} +15.6$  (c 1.0, CH<sub>3</sub>OH). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.39–7.22 (m, 5H), 5.53–5.44 (m, 2H), 5.43–5.29 (m, 2H), 4.41–4.30 (m, 1H), 4.00–3.83 (m, 1H), 3.77 (s, 1.4H), 3.61 (s, 1.6H), 2.84–2.62 (m, 1H), 2.31–2.13 (m, 2H), 2.10–1.87 (m, 4H), 1.84–1.70 (m, 1H), 1.42–1.34 (m, 2H), 0.93 (t, *J* 0.7 Hz, 1.6H<sub>rotamers</sub>), 0.84 (t, *J* 0.7 Hz, 1.4H<sub>rotamers</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  173.5, 173.3, 154.9, 154.1, 136.6, 136.5, 132.4, 132.2, 128.4, 128.3, 128.0, 127.8, 127.6, 125.6, 125.3, 67.2, 66.8, 60.2, 59.8, 59.2, 58.6, 52.1, 52.0, 32.0, 31.2, 29.4, 29.3, 29.0, 28.7, 28.0, 22.7, 22.6, 13.7, 13.6. Anal. Calcd for C<sub>20</sub>H<sub>27</sub>NO<sub>4</sub>: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.34; H, 8.01; N, 4.21.

**4.1.9. (2S,5R)-1-Benzylloxycarbonyl 2-(hex-2-enyl)-5-(1-pentenyl)-pyrrolidine (13).** Methyl ester **12** (142 mg, 0.41 mmol) was dissolved in anhydrous dichloromethane (15 mL) and cooled to –78 °C. Diisobutylaluminum hydride (1 M in toluene, 0.50 mL) was added dropwise over 30 min. After completion of the addition, the reaction mixture was stirred at –78 °C for 2 h until the starting material was no longer observed by TLC. The reaction was quenched by the addition of methanol (0.5 mL) and warmed to room temperature. The mixture was poured into ice-cold hydrochloric acid (1 N, 2 mL). The aqueous layer was extracted with dichloromethane (2×20 mL). The combined organic portions were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The aldehyde was typically carried on to the next step without further purification.

Potassium hydride (40% in mineral oil) was washed by anhydrous hexanes and dried by a stream of argon. Potassium hydride (50 mg, 1.3 mmol) and Ph<sub>3</sub>P(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>Br (663 mg, 1.7 mmol) were suspended in 10 mL of anhydrous THF. The reaction was stirred under the atmosphere of nitrogen at room temperature for 30 min and then cooled to 0 °C. A solution of the aldehyde (131 mg, 0.42 mmol) in THF (1 mL) was added dropwise. Upon completion of the addition the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of saturated solution of ammonium chloride (1 mL). The reaction was then partitioned between ethyl acetate (20 mL) and water (20 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2×20 mL). Combined organic fractions were washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by chromatography (SiO<sub>2</sub>, EtOAc/hexanes, 1:11) to afford **13** (116 mg, 85% two steps). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.40–7.23 (m, 5H), 5.55–5.30 (m, 4H), 5.12 (s, 2H), 4.61–4.57 (m, 1H), 3.95–3.85 (m, 1H), 2.62–2.51 (m, 2H), 2.20–1.80 (m, 6H), 1.80–1.60 (m, 4H), 1.51–1.18 (m, 4H), 1.00–0.85 (m, 4H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  155.5, 137.1, 133.2, 130.5, 130.1, 128.4, 128.1, 128.0, 125.9, 67.7, 59.0, 56.2, 32.9, 31.7, 30.0, 22.8, 14.3. Anal. Calcd for C<sub>23</sub>H<sub>33</sub>NO<sub>2</sub>: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.66; H, 9.49; N, 4.08.

**4.1.10. (+)-cis-225H (3).** A solution of diene **13** (45 mg, 0.13 mmol) 10% palladium on activated carbon (10 mg) in methanol (10 mL) was stirred under a hydrogen atmosphere (1 atm) overnight. The solution was filtered through a pad of Celite and washed with ethyl acetate (20 mL) and the filtrate was concentrated in vacuo. The residue was purified by chromatography (SiO<sub>2</sub>, CH<sub>3</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>, 1:10) to provide (+)-cis-225H **3** (32 mg, 99%) as a light yellow oil.  $[\alpha]_D^{25} +21.9$  (c 1.0, CH<sub>3</sub>OH). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.98–2.88 (m, 2H), 1.87–1.79 (m, 2H), 1.54–1.21 (m, 22H), 0.92–0.84 (m, 5H). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  59.6, 37.0, 36.9, 32.3, 32.0, 31.5, 29.7, 27.7, 27.4, 22.8, 22.8, 14.3, 14.3. Anal. Calcd for C<sub>15</sub>H<sub>31</sub>N: C, 79.92; H, 13.86; N, 6.21. Found: C, 79.68; H, 13.97; N, 6.18.

**4.1.11. (2R,5S,Z)-1-Benzylloxycarbonyl-2-methoxy-carbonyl-5-(pent-2-enyl)pyrrolidine (14).** Potassium hydride (40% in mineral oil) was washed with anhydrous hexanes and dried by a stream of argon. Potassium hydride (60 mg, 1.5 mmol) and Ph<sub>3</sub>P(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>Br (770 mg, 2.0 mmol) were suspended in anhydrous THF (10 mL). The reaction was stirred under an atmosphere of nitrogen at room temperature for 30 min and then cooled to 0 °C. A solution of aldehyde **4** (153 mg, 0.50 mmol) in of THF (1 mL) was added dropwise. Upon completion of the addition the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (1 mL). The reaction was then partitioned between ethyl acetate (20 mL) and water (20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×20 mL). The combined organic layers were washed with brine,



dried over anhydrous  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The residue was purified by chromatography ( $\text{SiO}_2$ , EtOAc/hexanes, 1:4) to furnish the Z-alkene **14** (146 mg, 87%).  $R_f=0.4$  (EtOAc/hexanes=1:4).  $[\alpha]_D^{25} +13.0$  (c 1.0,  $\text{CH}_3\text{OH}$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39–7.22 (m, 5H), 5.55–5.44 (m, 2H), 5.33–5.27 (m, 2H), 4.41–4.30 (m, 1H), 4.00–3.83 (m, 1H), 3.77 (s, 1.4H), 3.61 (s, 1.6H), 2.84–2.62 (m, 1H), 2.31–2.13 (m, 2H), 2.13–1.87 (m, 4H), 1.78–1.70 (m, 1H), 2.32–2.14 (m, 2H), 1.23 (t,  $J$  0.6 Hz, 1.6H<sub>rotamers</sub>), 1.19 (t,  $J$  0.6 Hz, 1.4H<sub>rotamers</sub>).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  173.5, 173.3, 154.9, 154.1, 136.6, 136.5, 132.4, 132.2, 128.4, 128.3, 128.0, 127.8, 127.6, 125.6, 125.3, 67.2, 66.8, 60.2, 59.8, 59.2, 58.6, 52.1, 52.0, 32.0, 31.2, 29.4, 28.7, 28.0, 20.7, 20.6, 13.9, 13.7. Anal. Calcd for  $\text{C}_{19}\text{H}_{25}\text{NO}_4$ : C, 68.86; H, 7.60; N, 4.23. Found: C, 69.04; H, 7.44; N, 4.21.

**4.1.12. (2R,5S)-1-Benzoyloxycarbonyl 2-(hex-1-enyl)-5-(pent-2-enyl) pyrrolidine (15).** The ester **14** (86 mg, 0.26 mmol) was taken up in 15 mL of anhydrous dichloromethane and cooled to  $-78^\circ\text{C}$  in a dry ice/acetone bath. At  $-78^\circ\text{C}$ , diisobutylaluminum hydride (1 M in toluene, 0.276 mL) was added dropwise over 30 min. After completion of the addition, the reaction mixture was stirred at  $-78^\circ\text{C}$  for 2 h. The reaction was quenched by the addition of methanol (0.5 mL) and warmed to room temperature. The mixture was poured into ice-cold hydrochloric acid (1 N, 2 mL). The aqueous layer was extracted with dichloromethane (2×20 mL). The combined organic portions were washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The aldehyde was typically carried on to the next step.

Potassium hydride (40% in mineral oil) was washed with anhydrous hexanes and dried by a stream of argon. Potassium hydride (28.8 mg, 0.72 mmol) and  $\text{Ph}_3\text{P}(\text{CH}_2)_4\text{CH}_3\text{Br}$  (409 mg, 0.96 mmol) were suspended in 10 mL of anhydrous THF. The reaction was stirred under the atmosphere of nitrogen at room temperature for 30 min and then cooled to  $0^\circ\text{C}$ . A solution of aldehyde (72 mg, 0.24 mmol) in THF (1 mL) was added dropwise. Upon completion of the addition the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of saturated solution of ammonium chloride (1 mL). The reaction was then partitioned between ethyl acetate (20 mL) and water (20 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2×20 mL). Combined organic fractions were washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The residue was purified by column chromatography ( $\text{SiO}_2$ , EtOAc/hexanes, 1:11) to afford the diene **15** (75 mg, 81% two steps).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40–7.23 (m, 5H), 5.65–5.40 (m, 4H), 5.17 (s, 1H), 5.12 (s, 1H), 4.61–4.57 (m, 1H), 3.79–3.85 (m, 1H), 2.62–2.51 (m, 2H), 2.20–1.80 (m, 4H), 1.77–1.62 (m, 4H), 1.51–1.11 (m, 4H), 1.11–0.83 (m, 6H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  155.5, 137.1, 133.2, 130.5, 130.1, 128.4, 128.1, 128.0, 125.9, 67.7, 59.0, 56.2, 32.9, 31.7, 30.0, 22.8, 14.3. Anal. Calcd for  $\text{C}_{23}\text{H}_{33}\text{NO}_2$ : C, 77.70; H, 9.36; N, 3.94. Found: C, 77.66; H, 9.49; N, 4.08.

**4.1.13. (–)-cis-225H (ent-3).** A solution of diene **15** (57 mg, 0.080 mmol) 10% palladium on activated carbon (10 mg) in methanol (10 mL) was stirred under a hydrogen atmosphere (1 atm) overnight. The solution was filtered through a pad of Celite and washed with ethyl acetate (20 mL) and concentrated in vacuo. The residue was purified by chromatography ( $\text{SiO}_2$ ,  $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ , 1:10) to provide (–)-cis-pyrrolidine 225H (17 mg, 95%) as a light yellow oil.  $[\alpha]_D^{25} -20.6$  (c 0.5,  $\text{CH}_3\text{OH}$ ).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

$\delta$  2.96–2.88 (m, 2H), 1.80–1.70 (m, 2H) 1.59–1.21 (m, 22H), 0.95–0.85 (m, 5H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  58.9, 37.0, 36.9, 32.3, 32.0, 31.5, 29.7, 27.7, 27.4, 22.8, 22.8, 14.3, 14.2. Anal. Calcd for  $\text{C}_{15}\text{H}_{31}\text{N}$ : C, 79.92; H, 13.86; N, 6.21. Found: C, 79.84; H, 14.20; N, 6.05.

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## Supplementary data

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