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Enantiodivergency and Enantioconvergency in the Synthesis of the Dendrobate Alkaloid 241D

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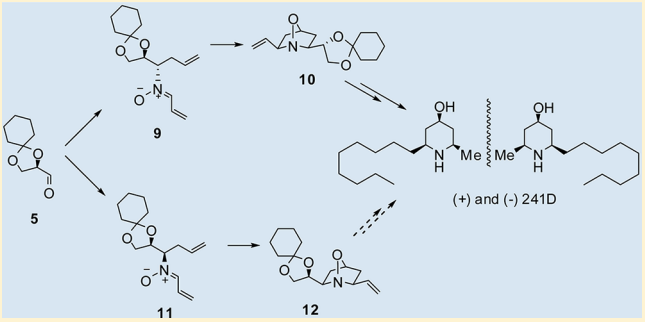
Supporting Information

ABSTRACT: A diastereodivergent preparation of two *N*-alkenylnitrones (**9** and **11**) from easily available (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde (**5**) led to an enantiodivergent synthesis of both enantiomers of the dendrobate alkaloid 241D in a sequential two-directional approach involving intramolecular nitrone cycloaddition as the key step. Either of these two nitrones could, in principle, be utilized for the preparation of the title compounds in an enantioconvergent fashion as well. The methodology was extended to prepare an analogue (**33**) of (−)-241D.



INTRODUCTION

Piperidines having diverse substitution patterns are found in natural as well as synthetic compounds of biological importance.[1,2] This heterocyclic system has remained a privileged target in drug development studies since nearly 12000 piperidine derivatives have been involved in clinical or preclinical studies.[1g] This, in turn, has led to the development of many attractive synthetic methodologies for the access of individual targets. A recent report[3] describes the synthesis of library of such types of compounds.

A subclass of *cis*-2,6-disubstituted[4] and *all-cis*-2,4,6-trisubstituted piperidines[5] are ubiquitous in the plant and animal kingdom, many of which display interesting biological properties. For example, the dendrobate alkaloid 241 D (**1**, Figure 1)[6] and the parent 4-oxo derivative were found[7] to be potent inhibitors of histrionicotoxin binding to the nicotinic receptor as well as the noncompetitive blocker of acetylcholine to nicotinic receptor channel complex. Because of their low natural abundance, several syntheses[8] of this alkaloid have been developed. However, development of a common route to both enantiomers as well as structural variations thereof from a single source and involving a common set of reactions could be an advantage in terms of diversity and possible application in medicinal chemistry. Herein, we report a synthesis of both enantiomers of the alkaloid 241 D which aims to fulfill some of the stated objectives.

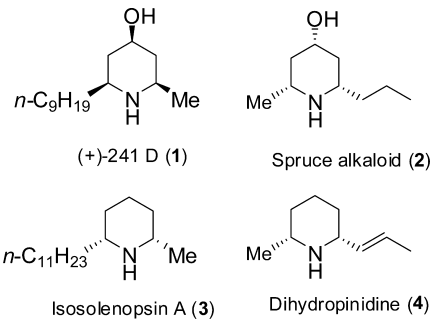
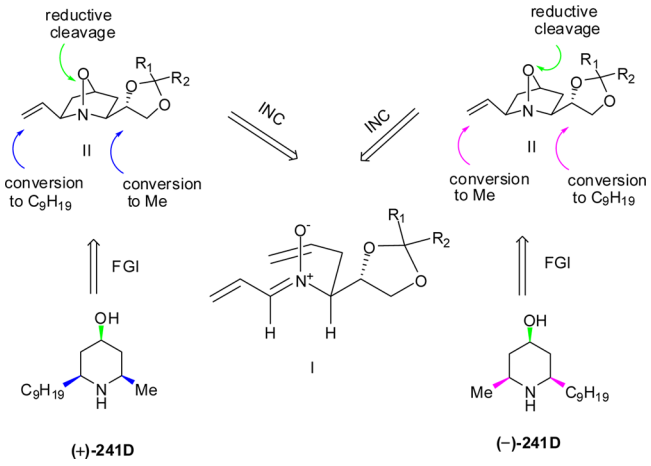


Figure 1. Selected piperidine natural products having a *cis*-2,6-disubstitution pattern.

Our retrosynthetic analysis (Scheme 1) of the alkaloid 241D (**1**) hinged on the belief that intramolecular nitrone cycloaddition[9,10] (INC) of the nitrone **I** would selectively lead to the bicyclic cycloadduct **II** in a fashion similar to our earlier

Scheme 1. Retrosynthetic Analysis of Both Enantiomers of 241D in a Divergent Way from One of the Optically Pure Oxazabicycle II



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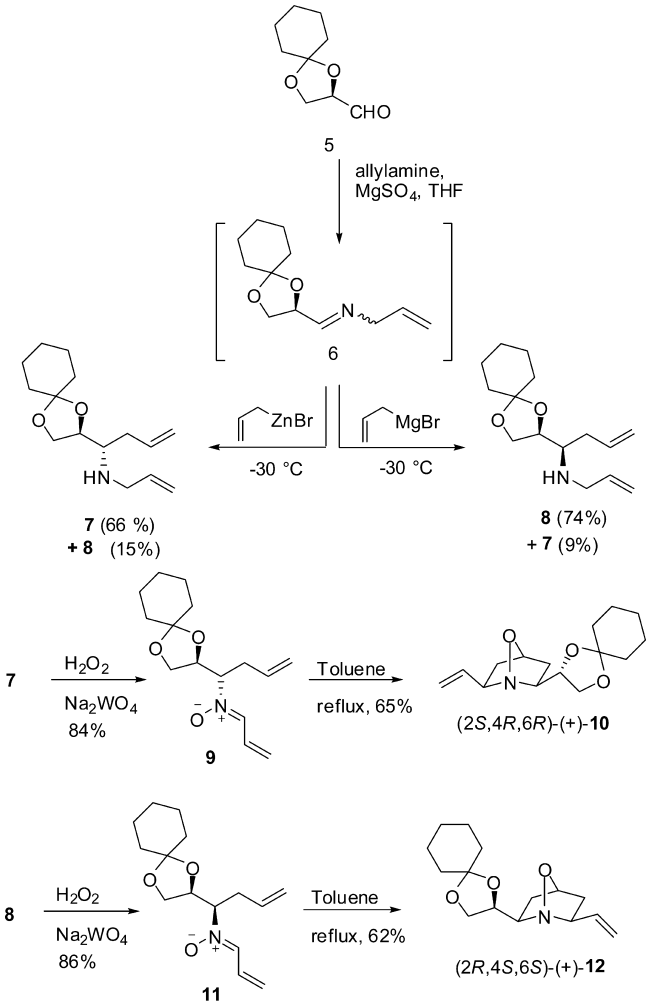
observation[11] with related system. Structure **II** would then be differentially manipulated to install the nine carbon alkyl chain as well as the methyl group in a sequential two-directional approach (following the pink or the blue arrow) to obtain both enantiomers of the targeted alkaloid.

RESULTS AND DISCUSSION

Our synthesis started from the preparation of the diastereomerically pure homoallylic amines **7** and **8** (Scheme 2) from

Scheme 2. Preparation and Cycloaddition of the Nitrones 9 and 11



the *N*-allylimine **6** with some modification of our reported procedure.[12] Thus, the *anti*-amine **7** was obtained in a yield of 66% and with a diastereomeric excess of 51%. Similarly, the *syn*-homoallylic amine **8** was obtained in 74% yield with a de of 65%.

Intramolecular cycloaddition of *N*-alkenylnitrones having appropriate substitution at the azo-methine carbon has been elegantly utilized[13] over several occasions for the stereoselective preparation of heterocycles including piperidine derivatives. However, to the best of our knowledge, intramolecular cycloaddition of *N*-alkenylnitrone having an ethenyl substitution at the α-carbon[14] has been little exploited. This led us to study the preparation and cycloaddition of the nitrones **9** and **11**. To this end, oxidation of **7** was carried out using the sodium tungstate–H_2O_2 protocol[15] to obtain the nitrone **9** in high yield as a single isomer (Scheme 2) assigned as the thermodynamically more stable *Z*-isomer. This assignment was further supported by the NOE correlation between the designated protons H_a (δ 7.09, d, J = 9.6 Hz) and H_b (δ 3.65, ddd, J = 10.8, 8.0, 3.6 Hz) in **9**. Similarly, oxidation of the *syn*-amine **8** also produced the *Z*-nitrone **11**. Both nitrones **9** and **11** proved to be unstable for storage over longer periods of time but could be adequately characterized. Cycloaddition of the nitrone **9** proceeded smoothly in refluxing toluene to provide the cycloadduct **10** as the only isolable product in moderate yield.

The *all-cis* stereochemistry of the cycloadduct was secured from NOESY studies, which established correlations between the protons as designated in **10**. Similarly, the nitrone **11** delivered stereoselectively the azabicyclic product **12** whose stereochemistry was also found to be *all-cis* from NOESY studies (Figure 2).

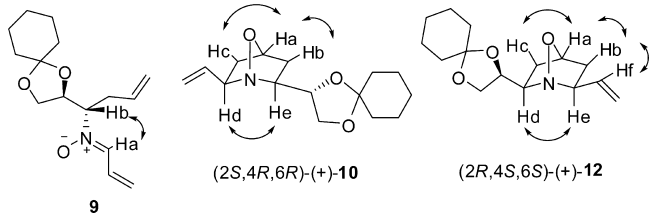


Figure 2. NOESY studies for the *Z*-nitrone **9** and *all-cis*- stereochemistry of cycloadducts **10** and **12**.

Having access to the desired cycloadducts **10** and **12**, we focused on their conversion to the alkaloid 241D along the projected pathway. Thus, the vinyl substituent in compound **10** was nonstereoselectively (ca. 1:1) osmylated, and the resulting diol **13** (Scheme 3) led, on periodate cleavage, to the aldehyde **14**. The formyl group in the latter was synthetically manipulated to a methyl group through a three-step sequence, e.g., reduction to a hydroxymethyl **15**, mesylation of the primary alcohol, and reductive removal of the mesylate **16** leading to compound **17** in an overall yield of 65%. Similarly, the dioxolane moiety in compound **17** was transformed into a nonyl chain through another three-step sequence viz. acid-mediated deprotection to the diol **18**, its subsequent oxidative cleavage to a formyl group in readiness for an *in situ* Wittig olefination with a eight-carbon phosphonium salt leading to the *cis*-olefin **19**, and saturation of the double bond in the latter. Further reductive cleavage of the N–O bond in **20** then provided (−)-241D as evident from comparison of optical rotation data. Hence, the absolute configuration of the cycloadduct **10** was established to be 2*S*,4*R*,6*R*.

We reasoned that a reversal in the synthetic manipulation, i.e., conversion of the formyl group to a nonyl chain, and transformation of the dioxolane moiety to a methyl group would lead to the (+)-enantiomer of the natural product since the pseudosymmetry will be maintained. Thus, the formyl group in **14** on Wittig olefination led to **22** (Scheme 4). Subsequent hydrogenation followed by deketalization gave the diol **24**. The latter was converted into a methyl group, as in **27**, through the intermediates **25** and **26** over a four-step sequence detailed above for the conversion **13** → **17**. Subsequent reduction of the N–O bond in **27** resulted in the formation of (+)-241D, as expected. The entire synthesis proceeded in a linear sequence of 12 steps from the starting aldehyde **5** for the

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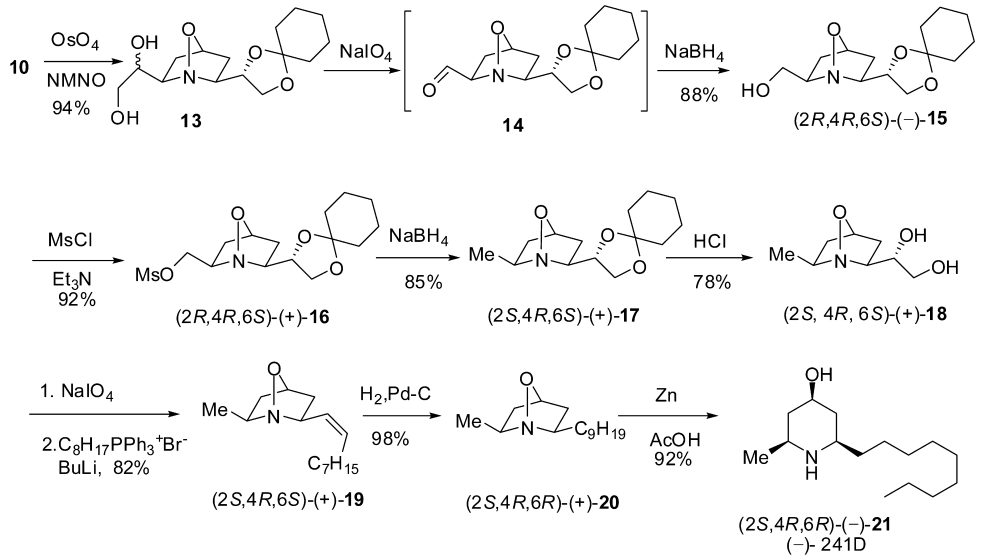
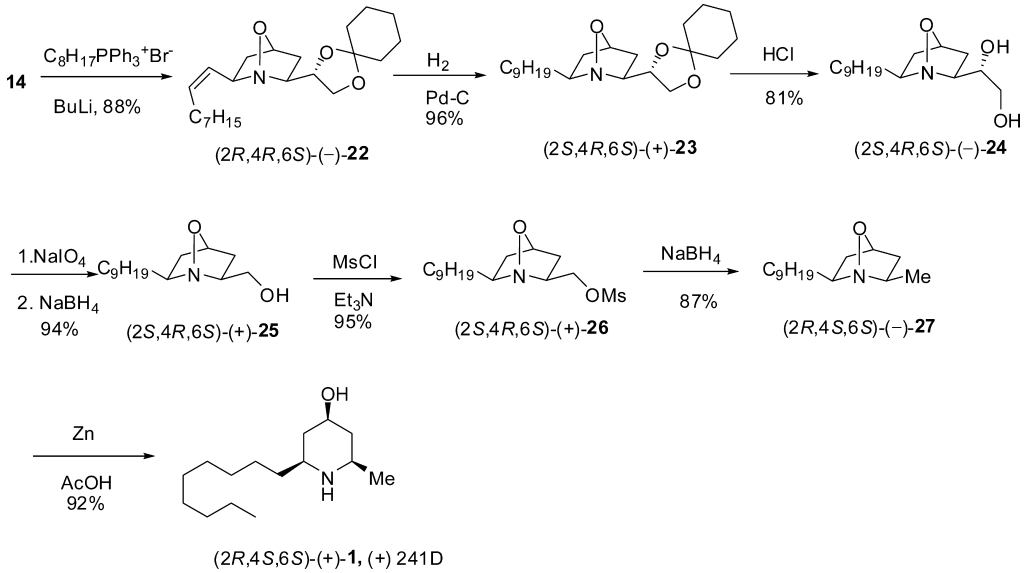
Scheme 3. Total Synthesis of Dendrobate Alkaloid (−)-241D



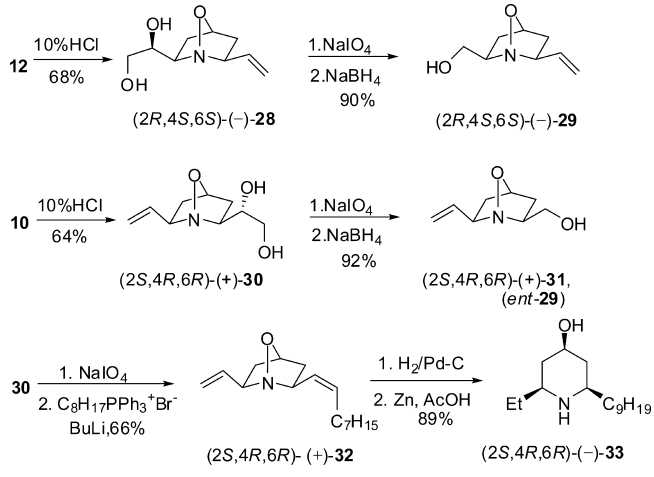
Scheme 4. Total Synthesis of Dendrobate Alkaloid (+)-241D



(−)-241D, and in equal number of steps for the (+)-isomer, the overall yields being 16% for **1** and 13% for *ent*-**1**.

We realized that the stereodefined cycloadduct **12**, obtained from the *syn*-nitrone **11**, could similarly be utilized in a two-directional way to (+)- and (−)- 241D. A simple demonstration of this possibility was then undertaken. Thus, deprotection of the dioxolane moiety in compound **12** using HCl leading to **28** (Scheme 5) followed by its conversion to the primary alcohol **29** through a combination of periodate cleavage and hydride reduction proceeded smoothly. The cycloadduct **10** was similarly subjected to acid mediated deprotection leading to the diol **30** on which the chemistry was repeated to obtain the primary alcohol **31**. Compounds **29** and **31** thus obtained were found to be enantiomeric. Compound **30** was also transformed into **33**, a simple analogue of (−)-241D, using the sequence outlined in Scheme 5.

Scheme 5. Synthesis of an Analogue of (−)-241D



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CONCLUSION

In conclusion, we have demonstrated synthesis of both enantiomers of the dendrobate alkaloid 241D starting from (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde[16] involving intramolecular cycloaddition of a diastereomerically pure nitrone having an ethenyl substituent at the α-carbon. A second diastereomeric nitrone obtained from the same source has been shown to have potential to deliver both enantiomers of the target alkaloid. The process appears to be adaptable for the synthesis of related structures since either of the two pendant functionalities, i.e., the vinyl substituent and the dioxolane moiety, in each of the azabicycles **10** and **12** may be converted, in principle, to related compounds (e.g., **33**), possibly in both enantiomeric forms if the two-directional approach is combined. Use of easily available starting material, commonly used reagents, simple reaction conditions, good overall yields, and excellent stereocontrol are some of the advantages offered by the developed process. It may thus complement to the existing literature and find application.

EXPERIMENTAL SECTION

General Methods. Column chromatography was performed on silica gel, Merck grade 230−400 mesh and neutral alumina. Reactions were monitored by thin-layer chromatography. TLC plates were visualized with UV, in an iodine chamber, or with vaniline solution, unless noted otherwise. Melting points were recorded in open capillaries and are uncorrected. IR spectra were recorded using KBr disks, chloroform solution, or neat. Chemical shifts (δ) are given from TMS (0 ppm) as internal standard for ^{1}H NMR and $^{13}CDCl_3$ (77.0 ppm) for ^{13}C NMR. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, ddd = doublet of double doublet, dt = doublet of triplet, br = broad, etc. HRMS data were obtained from a paid source from IACS or IICB, Kolkata.

Dichloromethane and dimethyl sulfoxide were distilled over calcium hydride under an inert atmosphere. THF, toluene, benzene, and ether were freshly distilled under argon from a purple solution of sodium benzophenone ketyl. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification.

*N-Allyl-1-(S)-((S)-1,4-dioxaspiro[4.5]decan-2-yl)but-3-en-1-amine (**7**).* A stirred solution of the aldehyde **5** (3.05 g, 17.7 mmol) in dry THF (40 mL) was cooled to 5 °C, and anhydrous $MgSO_4$ (8.5 g, 70.6 mmol) was added under argon atmosphere. After the solution was stirred for 10 min, a solution of allylamine (1.15 g, 1.5 mL, 19.4 mmol) in THF (6 mL) was added dropwise over 10 min. The reaction was then allowed to come to room temperature and stirred for 14 h. It was filtered, and the filtrate was then concentrated in vacuo and diluted with dry tetrahydrofuran (25 mL). The solution was cooled to −30 °C, and then a solution of allylzinc bromide [prepared in situ by treating allyl bromide (2.5 mL) with Zn dust (2.0 g) in dry THF (20 mL) under sonication] was added dropwise over 30 min under argon. It was stirred at this temperature for 8 h and then quenched with aq NH_4Cl solution (10 mL) before being extracted with ethyl acetate (2 × 100 mL). The combined organic extract was washed with water (1 × 50 mL) and brine solution (1 × 50 mL), dried over $MgSO_4$, and then filtered. The filtrate was concentrated in vacuo to leave a crude product which was purified by flash chromatography over silica gel using 5% ethyl acetate in hexane to give in the order **7** (2.9 g, 66%) followed by **8** (0.67 g, 15%) as oils. Data for **7**: $[\alpha]_D$ +15.9 (*c* 0.44, $CHCl_3$); IR ($CHCl_3$) 3333, 3076, 2976, 2935, 1641, 1449, 1164, 1103 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.87−5.79 (m, 2 H), 5.16 (dd, *J* = 1.6, 9.6 Hz, 2 H), 5.13−5.06 (m, 2 H), 4.04−3.99 (m, 2 H), 3.89−3.84 (m, 1 H), 3.23 (dd, *J* = 1.2, 6.0 Hz, 1 H), 3.19 (dd, *J* = 1.2, 6.0 Hz, 1 H), 2.77 (q, *J* = 5.6 Hz, 1 H), 2.31−2.26 (m, 2 H), 1.62−1.39 (m, 11 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 137.1 (d), 134.9 (d), 117.8 (t), 115.7 (t), 109.3 (s), 77.3 (d), 66.3 (t), 58.1 (d), 50.4 (t), 36.3 (t), 35.2 (t), 34.8(t), 25.2 (t), 24.0 (t), 23.8 (t); HRMS (QTOF ES+) found *m*/*z* 252.1968 (M + 1)$^+$, $C_{15}H_{26}NO_2$ requires 252.1964. Compound **8**: $[\alpha]_D$ −7.37 (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) 3431, 3075, 2936, 1668, 1449, 1101 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.88−5.76 (m, 2 H), 5.18 (dd, *J* = 1.6, 16.8 Hz, 2 H), 5.14−5.07 (m, 2 H), 4.07 (q, *J* = 6.4 Hz, 1 H), 3.99 (dd, *J* = 6.4, 7.6 Hz, 1 H), 3.70 (t, *J* = 7.2 Hz, 1 H), 3.38 (dd, *J* = 1.2, 6.0 Hz, 1 H), 3.33 (dd, *J* = 6.0, 19.6 Hz, 1 H), 2.70 (dd, *J* = 6.4, 12.0 Hz, 1 H), 2.29−2.23 (m, 1 H), 2.12−2.03 (m, 1 H), 1.75 (brs, 1 H,), 1.61−1.23 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 136.6 (d), 134.5 (d), 117.0 (t), 115.3 (t), 109.0 (s), 77.4 (d), 65.9 (t), 58.2 (d), 49.7 (t), 35.8 (t), 34.7 (t), 34.4 (t), 24.7 (t), 23.5 (t), 23.3 (t); MS (QTOF ES+) found *m*/*z* 274 (M + Na)$^+$, $C_{15}H_{25}NNaO_2$ requires 274.

*(Z)-N-Allylidene-1-(S)-((S)-1,4-dioxaspiro[4.5]decan-2-yl)but-3-en-1-amine Oxide (**9**).* To a stirred solution of the amine **7** (2.04g, 7.97 mmol) in acetone + water (9:1, 25 mL) was slowly added $Na_2WO_4{\cdot}7H_2O$ (126 mg, 4 mol %) followed by H_2O_2 (30%, 3.30 mL, 31.9 mmol) over 10 min, and the resulting mixture was stirred for 20 h by which time the reaction was complete. The acetone was then evaporated in vacuo, and the residue was extracted with ethyl acetate (2 × 50 mL). The combined organic extract was washed successively with water (1 × 50 mL) and brine solution (1 × 50 mL) and then dried over $MgSO_4$. It was filtered, and the filtrate was concentrated to leave a pale yellow crude product which was purified by chromatography over neutral alumina using 10% ethyl acetate in hexane to give the nitrone **9** (1.77 g, 84%) as a viscous liquid: $[\alpha]_D$ +16.5 (*c* 0.49, $CHCl_3$); IR ($CHCl_3$) 2937, 2863, 1449, 1144, 1164, 1104, 927 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.09 (d, *J* = 9.6 Hz, 1 H), 6.97 (ddd, *J* = 9.6, 10.4, 18.8 Hz, 1 H), 5.79−5.68 (m, 2 H), 5.58 (d, *J* = 10.4 Hz, 1 H), 5.17 (d, *J* = 17.2 Hz, 1 H), 5.10 (d, *J* = 10.4 Hz, 1 H), 4.48−4.43 (m, 1 H), 4.05 (dd, *J* = 6.0, 9.2 Hz, 1 H), 3.89 (dd, *J* = 4.8, 9.2 Hz, 1 H), 3.65 (ddd, *J* = 3.6, 8.0, 10.8 Hz, 1 H), 2.83−2.75 (m, 1 H), 2.60 (ddd, *J* = 3.2, 6.8, 14.4 Hz, 1 H), 1.65−1.58 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 137.6, 133.1, 126.3, 124.2, 118.6, 110.4, 77.4 (overlapped with $CDCl_3$), 75.5, 66.0, 36.7, 34.6, 33.5, 25.1, 24.0, 23.7; HRMS (QTOF ES+) found *m*/*z* 288.1544 (M + Na)$^+$, $C_{15}H_{23}NNaO_3$ requires 288.1576.

*(2S,4R,6R)-2-((S)-1,4-Dioxaspiro[4.5]decan-2-yl)-6-vinyl-7-oxa-1-azabicyclo[2.2.1]heptane (**10**).* In a one-necked, 250 mL, round-bottomed flask equipped with a magnetic stirring bar was placed nitrone **9** (1.02 g, 3.77 mmol) in dry and degassed toluene (120 mL), and the solution was was heated to 115 °C under argon for 22 h. It was then concentrated in vacuo, and the pale yellow residue was purified by flash chromatography over silica gel using 5% ethyl acetate in hexane to give the cycloadduct **10** as a colorless oil (650 mg, 65%): $[\alpha]_D$ + 16.28 (*c* 0.74, $CHCl_3$); IR ($CHCl_3$) 2938, 2863, 1449, 1282, 1163, 1101, 1036, 927, 759 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.83−5.74 (m, 1 H,), 5.12−5.01 (m, 2 H), 4.91 (t, *J* = 4.8 Hz, 1 H), 4.14 (dd, *J* = 6.0, 8.8 Hz, 1 H), 3.99 (dd, *J* = 4.4, 8.8 Hz, 1 H), 3.87 (quin, *J* = 4.8,Hz, 1 H), 3.38−3.33 (m, 1 H,), 2.85 (dt, *J* = 4.4, 8.4 Hz, 1 H), 1.94 (ddd, *J* = 4.4, 7.2, 12.0 Hz, 1 H), 1.84 (dd, *J* = 8.0, 10.6 Hz, 1 H), 1.74 (dd, *J* = 8.0, 12.4 Hz, 2 H), 1.60−1.35 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 139.9 (d), 114.6 (t), 109.5 (s), 79.4 (d), 78.1 (d), 69.8 (d), 69.3 (d), 68.5 (t), 39.8 (t), 37.1 (t), 36.9 (t), 34.8 (t), 25.1 (t), 24.1 (t), 23.8 (t); HRMS(QTOF ES+) found *m*/*z* 288.1573 (M + Na)$^+$, $C_{15}H_{23}NNaO_3$ requires 288.1576.

*N-Allyl-1-(S)-((S)-1,4-dioxaspiro[4.5]decan-2-yl)but-3-en-1-amine (**8**).* The imine **6** was prepared as before starting from aldehyde **5** (3.05 g, 17.7 mmol) in dry THF (40 mL), allylamine (1.15 g, 19.4 mmol), and anhydrous $MgSO_4$ (8.5 g, 70.6 mmol). The reaction mixture was cooled to −30 °C, and then allylmagnesium bromide (1 M, 18 mL, 18 mmol) was added dropwise to it over 30 min under argon. It was stirred at this temperature for 12 h and then quenched with aq NH_4Cl solution (10 mL). It was extracted with ethyl acetate (2 × 100 mL), and the combined organic extract was washed with water (1 × 50 mL) and brine solution (1 × 50 mL) and dried over $MgSO_4$. It was then filtered, and the filtrate was concentrated in vacuo. The product was purified by flash chromatography over silica gel using 5% ethyl acetate in hexane to give in the order **7** (0.40 g, 9%) followed by **8** (3.28 g, 74%) as oils.

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*(Z)-N-Allylidene-1-(R)-((S)-1,4-dioxaspiro[4.5]decan-2-yl)but-3-en-1-amine Oxide (**11**).* Nitrone **11** was prepared following the procedure described for **9**: yield 86%. $[\alpha]_D$ +3.9 (*c* 1.16, $CHCl_3$); IR ($CHCl_3$) 2936, 2859, 1448, 1163, 1142, 1097, 926 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.08 (d, *J* = 9.2 Hz, 1 H), 7.04−6.98 (m, 1 H), 5.74−5.67 (m, 2 H), 5.58 (d, *J* = 9.2 Hz, 1 H), 5.16 (d, *J* = 13.0 Hz, 1 H), 5.10 (d, *J* = 10.0 Hz, 1 H), 4.49 (q, *J* = 6.8 Hz, 1 H), 4.10 (dd, *J* = 6.4, 8.4 Hz, 1 H), 3.85 (dd, *J* = 6.0, 8.4 Hz, 1 H), 3.67 (ddd, *J* = 3.2, 8.0, 10.8 Hz, 1 H), 2.78 (ddd, *J* = 7.2, 10.8, 14.8 Hz, 1 H), 2.16 (ddd, *J* = 3.2, 6.8, 14.0 Hz, 1 H), 1.61−1.37 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 137.4, 132.5, 126.6, 123.9, 118.9, 110.2, 77.6, 74.8, 65.8, 36.7 (t), 34.6 (t), 32.3 (t), 25.0 (t), 23.9 (t), 23.6 (t); HRMS (QTOF ES+) found *m*/*z* 288.1554 $(M + Na)^+$, $C_{15}H_{23}NNaO_3$ requires 288.1576.

*(2R,4S,6S)-2-((S)-1,4-Dioxaspiro[4.5]decan-2-yl)-6-vinyl-7-oxa-1-azabicyclo[2.2.1]heptane (**12**).* Compound **12** was prepared following the procedure described for **10**: yield 62%; $[\alpha]_D$ = +5.5 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 2936, 2860, 1448, 1284, 1163, 1103, 1036, 927, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 5.87 (ddd, *J* = 7.6, 10.0, 17.2 Hz, 1 H), 5.10 (d, *J* = 18.0 Hz, 1 H), 5.05 (d, *J* = 11.6 Hz, 1 H), 4.86 (t, *J* = 4.4 Hz, 1 H), 4.22 (q, *J* = 6.8 Hz, 1 H), 3.97 (dd, *J* = 6.8, 8.4 Hz, 1 H), 3.71−3.68 (m, 1 H), 3.40 (dd, *J* = 7.2, 11.6 Hz, 1 H), 3.08 (dd, *J* = 7.2, 12.4 Hz, 1 H), 1.84 (dd, *J* = 8.0, 11.6 Hz, 1 H), 1.76−1.72 (m, 1 H), 1.68−1.4 (m, 12 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 140.1 (d), 114.6 (t), 109.9 (s), 78.7(d), 76.8 (d), 69.7 (d), 69.3 (d), 65.3 (t), 39.7 (t), 36.4 (t), 34.9 (t), 34.6 (t), 25.2 (t), 24.0 (t), 23.7 (t); HRMS (QTOF ES+) found *m*/*z* 288.1578 $(M + Na)^+$, $C_{15}H_{23}NNaO_3$ requires 288.1576.

*1-((2R,4R,6S)-6-((S)-1,4-dioxaspiro[4.5]decan-2-yl)-7-oxa-1-azabicyclo[2.2.1]hept-2-yl)ethane-1,2-diol (**13**).* In a one-necked, round-bottomed flask, equipped with a magnetic stirring bar, olefin **10** (502 mg, 1.88 mmol) was taken in acetone/water (3:1) (25 mL) at room temperature, then solid NMO (265 mg, 2.28 mmol) was added at once, and 1% OsO_4 solution (by weight in water, 1.8 mL) was added dropwise over 5 min and stirred for 3 h. It was quenched by addition of granular sodium bisulfite (50 mg) and stirred for another 15 min. The reaction mixture was then filtered, and the filtrate was concentrated in vacuo before being extracted with ethyl acetate (2 × 30 mL). The combined organic part was washed with water (2 × 30 mL) and brine solution (1 × 30 mL) and then dried over $MgSO_4$. It was then filtered, and the filtrate was concentrated under reduced pressure to leave a crude diol, which was purified over silica gel using 70% ethyl acetate−hexane to give viscous liquid **13** (530 mg, 94%) as a diastereomeric mixture (∼1:1 from ^1H NMR): IR ($CHCl_3$) 3391, 2935, 2861, 1449, 1384, 1283, 1163, 1103, 1039, 927, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.92−4.90 (m, 1 H), 4.12−4.08 (m, 2 H), 3.95−3.82 (m, 2 H), 3.74−3.67 (m, 1 H), 3.58−3.54 (m, 1 H), 3.46−3.45 (m, 1 H), 3.35−3.34 (brm, 1 H), 2.94−2.81 (m, 2 H), 1.95−1.93 (m, 2 H), 1.78−1.69 (m, 2 H), 1.61−1.32 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 109.7, 79.9, 79.6, 77.8, 77.78, 73.5, 69.9, 69.7, 69.2, 68.8, 68.0, 64.5, 62.2, 36.8, 36.77, 36.7, 35.6, 35.4, 34.8, 25.1, 24.0, 23.7; HRMS (QTOF ES+) found *m*/*z* 322.1628 $(M + Na)^+$, $C_{15}H_{25}NNaO_5$ requires 322.1630.

*((2R,4R,6S)-6-((S)-1,4-Dioxaspiro[4.5]decan-2-yl)-7-oxa-1-azabicyclo[2.2.1]hept-2-yl)methanol (**15**).* In a one-necked, round-bottomed flask, equipped with a magnetic stirring bar, diol **13** (198 mg, 0.67 mmol) was placed in acetonitrile/water (3:1) (6 mL) at 5−10 °C, then $NaIO_4$ (285 mg, 1.34 mmol) was added over 5 min and stirred for 30 min. The solution was filtered, and the filtrate was washed with dichloromethane (20 mL). The combined organic solution was washed with water (1 × 10 mL) and brine solution (1 × 10 mL) and then dried over $MgSO_4$. The solution was filtered again, and the filtrate was concentrated in vacuo. The crude aldehyde **14** was taken in a 10 mL round-bottomed flask and dissolved in dry methanol (3 mL) under nitrogen atmosphere. It was cooled to 10 °C, and then $NaBH_4$ (30 mg, 0.8 mmol) was added portionwise. After 30 min, methanol was evaporated, and the residue was extracted with ethyl acetate (2 × 10 mL). The combined organic extract was washed with water (5 mL) and brine solution (5 mL) and dried over $MgSO_4$. It was then filtered, and the filtrate was concentrated in vacuo. The crude product was purified over silica gel using 50% ethyl acetate−hexane solution to give the product **15** as a viscous liquid 165 mg (92% over two steps): $[\alpha]_D$ −5.0 (*c* 0.75, $CHCl_3$); IR ($CHCl_3$) 3348, 2948, 2921.4, 2862, 1336, 1287, 1160, 1111, 1065, 1038, 929 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.87 (t, *J* = 4.8 Hz, 1 H), 4.15 (dd, *J* = 6.0, 8.4 Hz, 1 H), 3.96 (dd, *J* = 4.4, 8.8 Hz, 1 H), 3.92−3.87 (m, 1 H), 3.41−3.29 (m, 2 H), 3.02 (sep, *J* = 4.4 Hz, 1 H), 2.85 (dt, *J* = 4.4, 8.4 Hz, 1 H), 2.54−2.52 (brd, 1 H), 1.99−1.93 (m, 1 H), 1.79−1.74 (m, 1 H), 1.65 (dd, *J* = 8.0, 12.0 Hz, 1 H), 1.61−1.51 (m, 8 H), 1.48−1.39 (m, 2 H), 1.35−1.33 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 109.6, 79.2, 77.9, 69.6, 68.9, 68.2, 64.7, 37.0, 36.9, 35.0, 34.8, 25.1, 24.0, 23.8; HRMS (QTOF ES+) found *m*/*z* 292.1522 $(M + Na)^+$, $C_{14}H_{23}NNaO_4$ requires 292.1525.

*((2R,4R,6S)-6-((S)-1,4-Dioxaspiro[4.5]decan-2-yl)-7-oxa-1-azabicyclo[2.2.1]hept-2-yl)methyl Methanesulfonate (**16**).* In a one-necked, round-bottomed flask, equipped with a magnetic stirring bar, alcohol **15** (198 mg, 0.74 mmol) was placed in dry dichloromethane (6 mL) at 0 °C under argon atmosphere. Then triethylamine (0.2 mL, 1.5 mmol) was added dropwise with stirring. After 5 min, a solution of methanesulfonyl chloride (120 μL, 1.49 mmol) in dry dichloromethane (1 mL) was added dropwise over 5 min, and stirring was continued for another 2 h. The reaction mixture was diluted with dichloromethane (20 mL), and the organic part was washed successively with HCl (1 N, 10 mL) solution, water (10 mL), and brine solution (10 mL) and dried over anhydrous $MgSO_4$. The mixture was then filtered, and the filtrate was concentrated under reduced pressure to leave the crude product which was purified by flash chromatography over silica gel using 45% ethyl acetate in hexane solution to give a colorless oil (237 mg, 92%): $[\alpha]_D$ +3.1 (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 2937, 2861, 1449, 1356, 1173, 1100, 964, 829, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.91 (t, *J* = 4.8 Hz, 1 H), 4.17−4.11 (m, 2 H), 3.97 (dd, *J* = 4.4, 8.4 Hz, 1 H), 3.95−3.90 (m, 2 H), 3.25−3.21 (m, 1 H), 3.08 (s, 3 H), 2.89−2.85 (m, 1 H), 2.20−1.97 (m, 1 H), 1.78 (ddd, *J* = 3.2, 8.0, 12.0 Hz, 2 H), 1.64−1.51 (m, 10 H), 1.41−1.32 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 109.7, 79.1, 77.9, 70.6, 69.5, 68.1, 65.8, 37.6, 36.9, 36.8, 35.7, 34.8, 25.1, 24.0, 23.8; HRMS (QTOF ES+) found *m*/*z* 370.1305 $(M + Na)^+$, $C_{15}H_{25}NNaO_6S$ requires 370.1300.

*(2S,4R,6S)-2-Methyl-6-((S)-1,4-dioxaspiro[4.5]decan-2-yl)-7-oxa-1-azabicyclo[2.2.1]heptanes (**17**).* In a 25 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and argon balloon was placed the mesylate **16** (250 mg, 0.72 mmol) in anhydrous DMSO (6 mL) at room temperature, then $NaBH_4$ (108 mg, 2.88 mmol) was added portionwise, and the resulting solution was heated to 135 °C and stirred over 18 h. The reaction mixture was then allowed to come to room temperature, and water (10 mL) was added before the mixture was stirred for another 10 min. It was then extracted with diethyl ether (2 × 20 mL), and the combined organic part was washed sequentially with water (2 × 10 mL) and brine solution (10 mL) and dried over anhydrous $MgSO_4$. It was then filtered, and the filtrate was concentrated to leave a pale yellow crude product which was purified by flash chromatography using 5% ethyl acetate−hexane to give **17** as a colorless oil (155 mg, 85%): $[\alpha]_D$ +18.2 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 2936, 2863, 1448, 1365, 1282, 1163, 1100, 1039, 927 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.84 (t, *J* = 4.8 Hz, 1 H), 4.13 (dd, *J* = 6.0, 8.4 Hz, 1 H), 3.95 (dd, *J* = 4.4, 8.8 Hz, 1 H), 3.85 (quin, *J* = 5.6 Hz, 1 H), 2.98−2.88 (m, 1 H), 2.76 (sext, *J* = 4.4 Hz, 1 H), 1.90−1.74 (m, 1 H), 1.73 (dd, *J* = 7.6, 11.2 Hz, 1 H), 1.66 (dd, *J* = 7.6, 12.0 Hz, 1 H), 1.58−1.22 (m, 11 H), 1.11 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 109.4 (s), 79.6 (d), 78.2 (d), 69.9 (d), 68.5 (t), 62.8 (d), 41.0 (t), 37.0 (t), 36.6 (t), 34.8 (t), 25.2 (t), 24.1 (t), 23.8 (t), 22.6 (q); HRMS (QTOF ES+) found *m*/*z* 276.1573 $(M + Na)^+$, $C_{14}H_{23}NNaO_3$ requires 276.1576.

*(S)-1-((2S,4R,6S)-6-Methyl-7-oxa-1-azabicyclo[2.2.1]hept-2-yl)-ethane-1,2-diol (**18**). General Procedure for the Acidic Deprotection of Cyclohexylidene Acetal.* A solution of the acetal **17** (202 mg, 0.79 mmol) in THF (4 mL) was cooled to 0 °C, and then HCl (10%, 3 mL) was added dropwise with stirring. The resulting mixture was stirred for 18 h before being diluted with water (4 mL) and neutralized with $NaHCO_3$. It was then extracted with chloroform (2 × 10 mL),

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and the combined organic extract was washed successively with water (2 × 5 mL) and brine solution (1 × 5 mL) and dried over $MgSO_4$. It was then filtered, and the filtrate was concentrated in vacuo to leave a crude viscous liquid which was purified by flash chromatography over silica gel using 80% ethyl acetate in hexane to provide **18** (105 mg, 78%) as a colorless viscous oil: $[\alpha]_D$ +3.14 (*c* 0.67, MeOH); IR ($CHCl_3$) 3436, 2980, 1638, 1453, 1295, 1050, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ = 4.86 (t, *J* = 4.5 Hz, 1 H), 3.70−3.68 (m, 2 H), 3.64 (dd, *J* = 4.5, 10.0 Hz, 1 H), 3.00−2.92 (m, 2 H), 2.88 (brs, 2 H), 1.92−1.89 (m, 1 H), 1.77 (dd, *J* = 7.5, 11.0 Hz, 1 H), 1.65 (dd, *J* = 8.0, 11.5 Hz, 1 H), 1.48−1.45 (m, 1 H), 1.13 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 79.5, 73.4, 69.6, 64.7, 63.2, 40.9, 35.0, 22.5; HRMS (QTOF ES+) found *m*/*z* 196.0953 $(M + Na)^+$, $C_8H_{15}NNaO_3$ requires 196.0950.

*(2S,4R,6S)-2-Methyl-6-((Z)-non-1-enyl)-7-oxa-1-azabicyclo[2.2.1]-heptane (**19**). General Procedure for Wittig Olefination.* In a one-necked, round-bottomed flask, equipped with a magnetic stirring bar, diol **11** (104 mg, 0.58 mmol) was placed in a mixture of acetonitrile + water (4:1, 5 mL) at 0−5 °C and then $NaIO_4$ (185 mg, 0.87 mmol) was added portionwise over 2 min with stirring. The reaction mixture was filtered after 20 min, and the filter cake was washed with dichloromethane (15 mL). The combined filtrate was washed with water (1 × 10 mL) and brine solution (1 × 10 mL) and then dried ($MgSO_4$). It was filtered, and the filtrate was concentrated in vacuo to leave the crude aldehyde as a pale yellow liquid which was used as such in the next step.

In a 25 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, a rubber septum, and argon balloon was placed *n*-octyl(triphenyl)phosphonium bromide (375 mg, 0.85 mmol) in dry THF (10 mL) at −78 °C. *n*-BuLi (2 M in hexane, 425 μL, 0.85 mmol) was then added dropwise over 5 min, and the resulting solution was allowed to warm to 0 °C over 5−10 min when the solution turned deep orange-red. It was cooled back to −78 °C, and then a solution of the crude aldehyde (80 mg, 0.57 mmol) in THF (5 mL) was added dropwise over 5 min with stirring at the same temperature. After 30 min, the solution was allowed to come to room temperature and stirred for another 6 h. The reaction mixture was then quenched with aq NH_4Cl solution (3 mL) and extracted with ethyl acetate (2 × 25 mL). The combined organic extract was washed successively with water (1 × 25 mL) and brine solution (1 × 25 mL) and then dried over $MgSO_4$. It was then filtered, and the filtrate was concentrated under reduced pressure to leave the crude product which was purified by flash chromatography over silica gel using a mixture of ethyl acetate−hexane (1:20) to give the olefin **19** (112 mg, 82% over two steps) as a colorless oil: $[\alpha]_D$ +10.0 (*c* 0.42, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ = 5.44 (dd, *J* = 8.8, 10.0 Hz, 1 H), 5.36 (dt, *J* = 7.2, 9.2 Hz, 1 H), 4.85 (t, *J* = 4.8 Hz, 1 H), 3.60 (td, *J* = 8.0, 12.8 Hz, 1 H), 3.03−2.96 (m, 1 H), 2.08−1.97 (m, 2 H), 1.82 (dd, *J* = 8.0, 11.6 Hz, 1 H), 1.74 (dd, *J* = 8.0, 11.6 Hz, 1 H), 1.57−1.53 (m, 1 H), 1.47−1.41 (m, 1 H), 1.39−1.27 (m, 10 H), 1.16 (d, *J* = 6.8 Hz, 3 H), 0.88 (t, *J* = 3.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 132.7 (d), 129.2 (d), 79.1 (d), 63.8 (d), 62.5 (d), 41.0 (t), 40.8 (t), 31.8 (t), 29.5 (t), 29.23 (t), 29.18 (t), 27.7 (t), 22.8 (q), 22.7 (t), 14.1 (q); HRMS (QTOF ES+) found *m*/*z* 238.2188 $(M + 1)^+$, $C_{15}H_{28}NO$ requires 238.2171.

*(2S,4R,6R)-2-Methyl-6-nonyl-7-oxa-1-azabicyclo[2.2.1]heptane (**20**).* In a one-necked, round-bottomed flask equipped with a stirring bar, fitted with a hydrogen balloon, olefin **19** (60 mg, 0.25 mmol) was placed in MeOH (2 mL), and Pd−C (10%) (6 mg) was added. The heterogeneous mixture was then vigorously stirred under hydrogen atmosphere for 2 h. It was then filtered through Celite, the filter cake was washed with methanol (10 mL), and the combined filtrate was concentrated in vacuo to leave a crude product which on purification by column chromatography over silica gel using 5% ethyl acetate in hexane gave **20** in quantitative yield: $[\alpha]_D$ + 6.1 (*c* 0.31, $CHCl_3$); IR ($CHCl_3$) 2927, 2855, 1730, 1463, 1286, 1132, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.80 (t, *J* = 5.2 Hz, 1 H), 2.91 (ddd, *J* = 4.0, 7.2, 11.6 Hz, 1 H), 2.70 (ddd, *J* = 4.4, 7.2, 11.6 Hz, 1 H), 1.71 (dd, *J* = 8.2, 11.2 Hz, 1 H), 1.65 (dd, *J* = 7.6, 11.6 Hz, 1 H), 1.48−1.40 (m, 2 H), 1.27 (m, 16 H), 1.16 (d, *J* = 6.8 Hz, 3 H), 0.90 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 79.2 (d), 67.4 (d), 62.6 (d), 40.7 (t), 39.1 (t), 36.9 (t), 31.9 (t), 29.63 (t, two signals), 29.60 (t), 29.32 (t), 26.6 (t), 22.8 (q), 22.7 (t), 14.1 (q); HRMS (QTOF ES+) found *m*/*z* 240.2344 $(M + 1)^+$, $C_{15}H_{30}NO$ requires 240.2327.

*(2S,4R,6R)-2-Methyl-6-nonylpiperidin-4-ol (**21**) ((−)-241D).* A solution of **20** (20 mg, 0.08 mmol) in acetic acid/water (v/v, 70:30, 500 μL) was treated with zinc powder (52 mg, 0.8 mmol) at room temperature for 15 min by which time starting material was not detected by TLC. Water (1 mL) was then added, and the mixture was filtered. The filter cake was washed with water (5 mL) and the combined aqueous solution was neutralized with solid $NaHCO_3$. It was then repeatedly extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phase was washed with H_2O (1 × 5 mL) and brine solution (1 × 5 mL) and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give a yellow solid which was purified by chromatography over neutral alumina using ethyl acetate−hexane mixture (20:1) to give a colorless solid (18 mg, 91%). Recrystallization from ethyl acetate furnished (−)-241D as colorless needles: mp 106−107 °C (lit.[8d] 107 °C); $[\alpha]_D$ −4.5 (*c* 0.76, $CHCl_3$), −5.9 (*c* 0.75, MeOH) [lit.[8d] −6.5 (*c* 1.32, MeOH)]; IR ($CHCl_3$) 3272, 3189, 2922, 2851, 1469, 1385, 1321, 1112, 1034, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.67 (dddd, *J* = 4.4, 4.4, 11.2, 11.2 Hz, 1 H), 2.68 (dqd, *J* = 2.0, 6.0, 10.4 Hz, 1 H), 2.61−2.56 (m, 2 H), 2.06−1.98 (m, 1 H), 1.48−1.34 (m, 2 H), 1.26 (m, 16 H), 1.16 (d, *J* = 6.4 Hz, 3 H), 1.05−0.92 (m, 2 H), 0.89 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 69.0 (d), 54.9 (d), 50.2 (d), 43.5 (t), 41.2 (t), 36.4 (t), 31.9 (t), 29.71 (t), 29.70 (t, overlapped), 29.58 (t), 29.34 (t), 26.0 (t), 22.7 (t), 22.1 (q), 14.1 (q); HRMS (QTOF ES+) found *m*/*z* 242.2483 $(M + 1)^+$, $C_{15}H_{32}NO$ requires 242.2484.

*(2R,4R,6S)-2-((Z)-Non-1-enyl)-6-((S)-1,4-dioxaspiro[4.5]decan-2-yl)-7-oxa-1-azabicyclo[2.2.1]heptanes (**22**).* The olefin **22** was prepared from the starting aldehyde **14** in a manner similar to that described for **19**: yield 88%; $[\alpha]_D$ −0.2 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 2930, 2855, 1639, 1449, 1281, 1217, 1163, 1101, 1037, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 5.43−5.35 (m, 2 H), 4.91 (t, *J* = 4.8 Hz, 1 H), 4.15 (dd, *J* = 6.0, 8.8 Hz, 1 H), 3.96 (dd, *J* = 4.4, 8.4 Hz, 1 H), 3.89−3.84 (m, 1 H), 3.64−3.59 (m, 1 H), 2.85 (dt, *J* = 4.4, 8.8 Hz, 1 H), 2.06−1.99 (m, 1 H), 1.88 (dd, *J* = 8.0, 11.2 Hz, 1 H), 1.73 (dd, *J* = 7.6, 12.0 Hz, 1 H), 1.59−1.53 (m, 11 H), 1.13−1.25 (m, 12 H), 0.89 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 132.3 (d), 130.0 (d), 109.5 (s), 79.3 (d), 78.1 (d), 70.0 (d), 68.6 (t), 64.1 (d), 41.3 (t), 37.0 (t), 36.9 (t), 34.7 (t), 31.8 (t), 29.7 (t), 29.5 (t), 29.2 (t), 27.8 (t), 25.2 (t), 24.1 (t), 23.8 (t), 22.7 (t), 14.1 (q); HRMS (QTOF ES+) found *m*/*z* 386.2677 $(M + Na)^+$, $C_{22}H_{37}NNaO_3$ requires 386.2671.

*(2S,4R,6S)-2-Nonyl-6-((S)-1,4-dioxaspiro[4.5]decan-2-yl)-7-oxa-1-azabicyclo[2.2.1]heptane (**23**).* Compound **23** was prepared following the procedure described for **20**: yield 96%; $[\alpha]_D$ +1.74 (*c* 0.57, $CHCl_3$); IR ($CHCl_3$) 2929, 2855, 1638, 1463.6, 1449, 1282, 1163, 1102, 1040, 908 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.83 (t, *J* = 4.8 Hz, 1 H), 1.14 (dd, *J* = 6.0, 7.6 Hz, 1 H), 3.97 (dd, *J* = 4.4, 8.8 Hz, 1 H), 3.86 (ddd, *J* = 4.4, 6.0, 10.0 Hz, 1 H), 2.77−2.71 (m, 2 H), 1.89 (ddd, *J* = 4.4, 7.2, 11.6 Hz, 1 H), 1.72−1.66 (m, 2 H), 1.60−1.42 (m, 11 H), 1.31−1.20 (m, 16 H), 0.88 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 109.9, 79.8, 78.7, 70.6, 68.9, 68.3, 40.2, 37.9, 37.5, 37.2, 35.2, 32.4, 30.1, 29.8, 27.3, 25.6, 24.6, 24.3, 23.2, 22.8, 14.6; HRMS (QTOF ES+) found *m*/*z* 388.2829 $(M + Na)^+$, $C_{22}H_{39}NNaO_3$ requires 388.2828.

*(S)-1-((2S,4R,6S)-6-Nonyl-7-oxa-1-azabicyclo[2.2.1]hept-2-yl)-ethane-1,2-diol (**24**).* Compound **24** was prepared following the procedure described for **18**: yield 81%; $[\alpha]_D$ −12.9 (*c* 0.57, $CHCl_3$); IR (neat) 3401, 3344, 2953, 2918, 2850, 1451, 1097, 1135, 1054, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.85 (t, *J* = 4.8 Hz, 1 H), 3.71 (d, *J* = 4.8 Hz, 2 H), 3.62−3.61 (m, 1 H), 2.93−2.88 (m,1 H), 2.77−2.71 (m, 1 H), 2.42 (brs, 1 H), 1.92−1.87 (m, 1 H), 1.73 (dd, *J* = 7.6, 11.6 Hz, 1 H), 1.66 (dd, *J* = 8.0, 11.6 Hz, 1 H), 1.52−1.41 (m, 2 H), 1.26 (m, 16 H), 0.88 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 79.1, 73.3, 69.9, 68.0, 64.9, 39.5, 36.6, 35.3, 31.9, 29.6 (two

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signals), 29.5, 29.3, 26.7, 22.7, 14.1; HRMS (QTOF ES+) found m/z 308.2196 $(M + Na)^+$, $C_{16}H_{31}NNaO_3$ requires 308.2202.

*((2S,4R,6S)-6-Nonyl-7-oxa-1-azabicyclo[2.2.1]hept-2-yl)methanol (**25**).* Compound **25** was prepared following the procedure described for **15**: yield 94%; $[\alpha]_D$ +7.1 (c 0.64, $CHCl_3$). IR ($CHCl_3$) 3371, 2923, 2853, 1465.6, 1291, 1050, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.79 (t, J = 4.8 Hz, 1 H), 3.42−3.36 (m, 2 H), 2.96 (sep, J = 4.0 Hz, 1 H), 2.77−2.73 (m, 1 H), 2.58 (brs, 1 H), 1.72 (dd, J = 8.0, 11.6 Hz, 1 H), 1.58 (dd, J = 8.0, 11.6 Hz, 2 H), 1.49 (ddd, J = 3.2, 4.8, 7.6 Hz, 1 H), 1.38 (ddd, J = 2.8, 4.4, 7.2 Hz, 2 H), 1.31−1.26 (m, 14 H), 0.88 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 78.7, 68.7, 67.4, 65.0, 39.6, 36.7, 34.7, 31.9, 29.6, 29.5, 29.3, 26.7, 22.7, 14.1; HRMS (QTOF ES+) found m/z 278.2096 $(M + Na)^+$, $C_{15}H_{29}NNaO_2$ requires 278.2096.

*((2S,4R,6S)-6-Nonyl-7-oxa-1-azabicyclo[2.2.1]hept-2-yl)methyl Methanesulfonate (**26**).* Compound **26** was prepared following the procedure described for **16**: yield 95%; $[\alpha]_D$ +0.9 (c 0.64, $CHCl_3$); IR ($CHCl_3$) 2919, 2850, 1467, 1449, 1336, 1167, 985, 977, 955 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.82 (t, J = 4.8 Hz, 1 H), 4.16 (dd, J = 8.8, 10.4 Hz, 1 H), 3.92 (dd, J = 4.8, 6.4 Hz, 1 H), 3.21−3.14 (m, 1 H), 3.09 (s, 3 H), 2.78−2.74 (m, 1 H), 1.75−1.67 (m, 2 H), 1.61−1.43 (m, 4 H), 1.26 (brm, 14 H), 0.88(t, J = 4.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 78.6, 71.2, 67.3, 65.7, 39.4, 37.6, 36.7, 35.4, 31.9, 29.6, 29.57, 29.50, 29.3, 26.6, 22.7, 14.1; HRMS (QTOF ES+) found m/z 334.2048 $(M + 1)^+$, $C_{16}H_{32}NO_4S$ requires 334.2052.

*(2R,4S,6S)-2-Methyl-6-nonyl-7-oxa-1-azabicyclo[2.2.1]heptanes (**27**).* Compound **27** was prepared following the procedure described for **17**, yield 87%. Compound **27** is proved to enantiomeric with the compound **20** from the physical and optical measurement data: $[\alpha]_D$ −7.2 (c 0.79, $CHCl_3$); IR ($CHCl_3$) 2927, 2855, 1730, 1463, 1286, 1132, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 4.78 (t, J = 4.8 Hz, 1 H), 2.91−2.86 (m, 1 H), 2.71−2.65 (m, 1 H), 1.71−1.57 (m, 4 H) 1.44−1.40 (m, 2 H), 1.26 (brm, 14 H, 7 $-CH_2$ in nonyl), 1.14 (d, J = 6.4 Hz, 3 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 79.2 (d), 67.4 (d), 62.6 (d), 40.7 (t), 39.1 (t), 36.9 (t), 31.9 (t), 29.6 (t), 29.58 (t, two signals), 29.3 (t), 26.4 (t), 22.8 (q), 22.7 (t), 14.0 (q); HRMS (TOF ES+) found m/z 240.2323 $(M + 1)^+$, $C_{15}H_{30}NO$ requires 240.2327.

*(2R,4S,6S)-2-Methyl-6-nonylpiperidin-4-ol (**1**) ((+)-241D).* This compound was prepared in the manner identical to that described for its (−)-enantiomer: yield 92%; mp 106 °C (lit.[8e] mp 108 °C); $[\alpha]_D$ + 5.56 (c 0.31, MeOH) [lit.[8h] +5.9 (c 0.65, MeOH)] [lit.[8e] +6.5 (c 1.2, MeOH)]; IR ($CHCl_3$) 3271, 3189, 2921, 2851, 1469.5, 1384, 1321, 1112, 1035, 772 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.63 (dddd, J = 4.4, 4.4, 11.2, 11.2 Hz, 1 H), 2.67 (dqd, J = 2.4, 6.4, 11.2 Hz, 1 H), 2.52 (ddd, J = 4.0, 6.0, 10.4 Hz, 1 H), 1.99−1.90 (m, 2 H), 1.61 (brs, 1 H), 1.42−1.36 (m, 2 H), 1.25 (m, 15 H), 1.11 (d, J = 6.0 Hz, 3 H), 1.02−0.95 (m, 2 H), 0.87 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 69.3 (d), 54.8 (d), 50.1 (d), 43.9 (t), 41.7 (t), 36.8 (t), 31.9 (t), 29.74 (t), 29.70 (t), 29.6 (t), 29.31 (t), 26.0 (t), 22.7 (t), 22.5 (q), 14.1 (q); MS (QTOF MS ES+) found m/z 241 (M^+), $C_{15}H_{31}NO$ requires 241.

*(S)-1-((2R,4S,6S)-6-Vinyl-7-oxa-1-azabicyclo[2.2.1]hept-2-yl)-ethane-1,2-diol (**28**).* Compound **28** was prepared following the procedure described for **18**: yield 68%; $[\alpha]_D$ − 4.3 (c 0.44, MeOH); IR ($CHCl_3$) 3391, 2983, 2953, 1644, 1463, 1289, 1102, 1045, 879, 838 cm^{-1} ; ^1H NMR ($CDCl_3$, 400 MHz) δ = 5.82 (ddd, J = 7.2, 10.4, 17.6 Hz, 1 H), 5.16−5.07 (m, 2 H), 4.94 (t, J = 4.8 Hz, 1 H), 3.79−3.76 (m, 1 H), 3.51−3.38 (m, 4 H), 3.04−3.02 (m, 1 H), 2.31−2.28 (m, 1 H), 1.89 (dd, J = 8.0, 11.6 Hz, 1 H), 1.79−1.60 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 139.6, 114.8, 79.6, 73.4, 69.1, 68.5, 62.2, 39.6, 35.4; HRMS (QTOF ES+) found m/z 186.1126 $(M + 1)^+$, $C_9H_{16}NO_3$ requires 186.1130.

*((2R,4S,6S)-6-Vinyl-7-oxa-1-azabicyclo[2.2.1]hept-2-yl)methanol (**29**).* Compound **29** was prepared following the procedure described for **15**: yield 90% (two steps); $[\alpha]_D$ −20.3 (c 0.40, $CHCl_3$); IR ($CHCl_3$) 3415, 2925, 2854, 1649, 1290, 1165, 1041, 938 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 5.85 (ddd, J = 7.6, 10.4, 17.6 Hz, 1 H), 5.16−5.06 (m, 2 H), 4.87 (t, J = 4.8 Hz, 1 H), 3.45−3.37 (m, 3 H), 3.06 (sep, J = 4.4 Hz, 1 H), 2.57 (brs, 1 H), 1.87 (dd, J = 8.0, 11.6 Hz, 1 H), 1.79−1.73 (m, 1 H), 1.69−1.61 (m, 1 H), 1.48−1.40 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 139.8, 114.7, 78.8, 68.9, 68.6, 65.0, 39.8, 34.9; HRMS (QTOF ES+) found m/z 156.1019 $(M + 1)^+$, $C_8H_{14}NO_2$ requires 156.1025.

*(S)-1-((2S,4R,6R)-6-Vinyl-7-oxa-1-azabicyclo[2.2.1]hept-2-yl)-ethane-1,2-diol (**30**).* Compound **30** was prepared following the procedure described for **18**: yield 64%; $[\alpha]_D$ +4.8 (c 1.16, MeOH); IR ($CHCl_3$) 3391, 2983, 2954, 1643, 1463, 1289, 1100, 1044, 879, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 5.84−5.75 (m, 1 H), 5.15−5.05 (m, 2 H), 4.92 (t, J = 4.8 Hz, 1 H), 3.72−3.66 (m, 3 H), 3.41−3.30 (m, 1 H), 3.03−2.99 (m, 1 H), 2.72−2.65 (brs, 2 H, 2 × OH), 1.98−1.92 (m, 1 H), 1.88 (dd, J = 8.0, 11.6 Hz, 1 H), 1.77−1.74 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 139.7, 114.8, 79.2, 73.5, 69.4, 69.1, 64.5, 39.6, 35.4; HRMS (QTOF ES+) found m/z 208.0950 $(M + Na)^+$, $C_9H_{15}NNaO_3$ requires 208.0950.

*((2S,4R,6R)-6-vinyl-7-oxa-1-azabicyclo[2.2.1]hept-2-yl)methanol (**31**).* Compound **31** was prepared following the procedure described for **15**, yield 92% (two steps). Compound **31** is seen to be enantiomeric with compound **29** from the physical and optical measurement data: $[\alpha]_D$ +22.2 (c 0.40, $CHCl_3$); IR ($CHCl_3$) 3414, 2925, 2853, 1648, 1289, 1165, 1041, 937 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 5.84 (ddd, J = 7.6, 10.4, 17.6 Hz, 1 H), 5.16−5.07 (m, 2 H), 4.87 (t, J = 4.8 Hz, 1 H), 3.44−3.34 (m, 3 H), 3.09−3.02 (m, 1 H), 2.50 (dd, J = 3.6, 9.2 Hz, 1 H), 1.87 (dd, J = 8.0, 11.6 Hz, 1 H), 1.77−1.74 (m, 1 H), 1.67−1.62 (m, 1 H), 1.45−1.42 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 139.8, 114.7, 78.8, 68.9, 68.6, 64.9, 39.8, 34.9; HRMS (QTOF ES+) found m/z 178.0843 $(M + Na)^+$, $C_8H_{13}NNaO_2$ requires 178.0844.

*(2S,4R,6R)-2-((Z)-Non-1-enyl)-6-vinyl-7-oxa-1-azabicyclo[2.2.1]-heptane (**32**).* Compound **32** was prepared from **30** in a manner similar to that described for **19**: yield 66%; $[\alpha]_D$ +25.5 (c 1.45, $CHCl_3$); IR ($CHCl_3$) 2955, 2926, 2855, 1644, 1462, 1283, 916, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 5.86 (ddd, J = 7.2, 10.0, 17.2 Hz, 1 H), 5.49 (dd, J = 7.8, 10.8 Hz, 1 H), 5.38 (dt, J = 7.2, 10.8 Hz, 1 H), 5.13 (d, J = 17.6 Hz, 1 H), 5.06 (d, J = 10.4 Hz, 1 H), 4.92 (t, J = 4.8 Hz, 1 H), 3.70 (dt, J = 4.4, 8.0 Hz, 1 H), 3.46−3.41 (m, 1 H), 2.08−1.99 (m, 2 H), 1.89 (dd, J = 8.0, 11.6 Hz, 1 H), 1.85 (dd, J = 8.0, 11.6 Hz, 1 H), 1.77−1.71 (m, 1 H), 1.63−1.61 (m, 1 H, buried with H_2O peak), 1.38−1.29 (m, 10 H), 0.90 (t, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 140.3 (d), 132.6 (d), 129.3 (d), 114.4 (t), 78.9 (d), 69.1 (d), 63.8 (d), 41.3 (t), 39.7 (t), 31.8 (t), 29.4 (t), 29.2 (t), 29.1 (t), 27.8 (t), 22.7 (t), 14.1 (q); HRMS (TOF ES+) found m/z 250.2166 $(M + 1)^+$, $C_{16}H_{28}NO$ requires 250.2171.

*(2S,4R,6R)-2-Ethyl-6-nonylpiperidin-4-ol (**33**).* In a one-necked, round-bottomed flask equipped with a stirring bar, fitted with a hydrogen balloon, olefin **32** (60 mg, 0.24 mmol) was placed in MeOH (3 mL), and Pd−C (10%) (6 mg) was added. The heterogeneous mixture was then vigorously stirred under hydrogen atmosphere for 2 h. It was then filtered through Celite, the filter cake was washed with methanol (10 mL), and the combined filtrate was concentrated in vacuo to leave a crude product which was dissolved in a mixture of glacial acetic acid and water (4:1, v/v, 1 mL) and stirred vigorously in the presence of activated zinc dust (125 mg, excess) for 15 min. Water (3 mL) was then added, and the mixture was filtered. The filter cake was washed with water (5 mL), and the combined aqueous solution was neutralized with solid $NaHCO_3$. It was then repeatedly extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phase was washed with H_2O (1 × 10 mL) and brine solution (1 × 10 mL) and dried over $MgSO_4$. It was filtered, and the filtrate was concentrated under reduced pressure to give a colorless solid which was purified by chromatography over neutral alumina using ethyl acetate−hexane mixture (20:1) to give a colorless solid (54 mg, 89%): $[\alpha]_D$ − 2.2 (c 0.99, MeOH); ^1H NMR ($CDCl_3$, 400 MHz) δ = 3.68−3.62 (m, 1 H), 2.55−2.43 (m, 2 H), 2.03−2.00 (m, 2 H), 1.64 (brs, 2 H), 1.48−1.44 (m, 4 H), 1.27 (brm, 14 H), 1.06−0.98 (m, 2 H), 0.94 (t, J = 7.6 Hz, 3 H), 0.89 (t, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 69.4 (d), 56.4 (d), 54.8 (d), 42.1 (t), 41.6 (t), 36.8 (t), 31.9 (t), 29.7 (t), 29.6 (t), 29.5 (t), 29.3 (t), 26.0 (t), 22.7 (t), 14.1 (q), 10.5 (q); HRMS (QTOF ES+) found m/z 256.2634 $(M + 1)^+$, $C_{16}H_{34}NO$ requires 256.2640.

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■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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