

A Novel Route to Chiral *trans*-6-Alkyl-2-hydroxymethyl-1,2,5,6-tetrahydropyridines by Allylation of Chiral Imines and Ring-Closing Metathesis – Total Synthesis of (–)-3-*epi*-Deoxoprosopinine

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A novel route to enantiomerically pure *trans*-6-alkyl-2-hydroxymethyl-1,2,5,6-tetrahydropyridines is reported in five steps from Garner's aldehyde with overall yields higher than 35 %. This strategy is based on the allylation of chiral imino alcohols formed in situ followed by a ring-closing metathesis.

This new method was used for the first total synthesis of (–)-3-*epi*-deoxoprosopinine.

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Introduction

The therapeutic potential of piperidines has been the subject of intensive research and various synthetic strategies have been reported^[1]. Consequently, synthesis of this class of heterocycles is still undergoing considerable improvement and innovation. For example, the efficient chiral synthesis of 2,6-disubstituted piperidines has been developed in recent years.^[2] On the other hand, the chiral synthesis of the corresponding tetrahydropyridines has attracted much less attention^[3] although its unit occurs in many natural biologically active compounds.^[4] In addition, the double bond offers an easy access to highly substituted piperidines. In fact, this lack of interest is due, in part at least, to the difficulty of controlling regio- and stereochemistry with the double bond in the right position. Our interest in this field has been focused on the synthesis of *trans*-2,6-disubstituted-1,2,5,6-tetrahydropyridines. Indeed, in connection with our program directed toward the synthesis of piperidine alkaloids with biological activity^[5], we wish here to describe a flexible and efficient asymmetric route to the *trans*-2,6-disubstituted-1,2,5,6-tetrahydropyridines. The basic strategy we used involved two key reactions including a diastereoselective allylation of chiral imines and a ring-closing metathesis (RCM) (Figure 1).

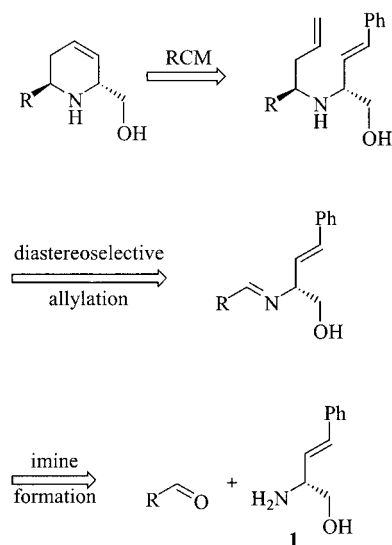


Figure 1. Retrosynthetic analysis

To demonstrate the efficacy of this new methodology, the first total synthesis of (–)-3-*epi*-deoxoprosopinine (**2**) is also described in this report (Figure 2).

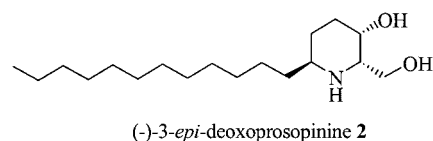


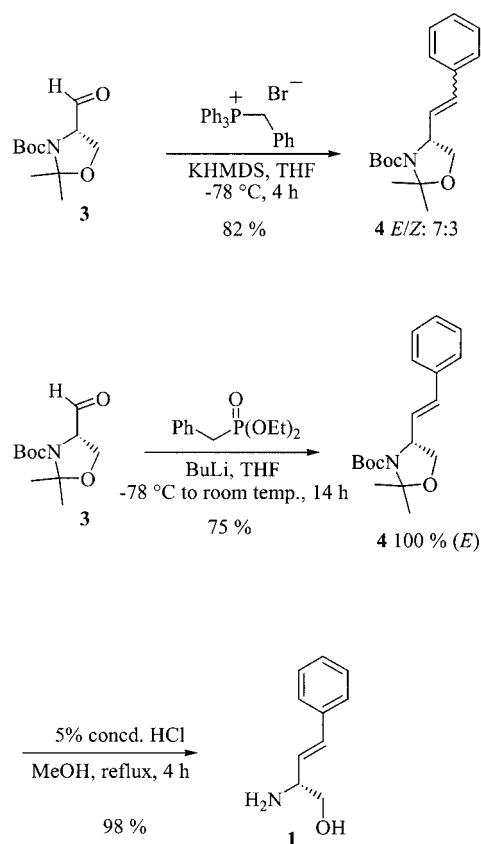
Figure 2. Structure of (–)-3-*epi*-deoxoprosopinine (**2**)

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Results and Discussion

The first aim of our strategy concerned the synthesis of the chiral amino alcohol **1** (Scheme 1). In our previous studies,^[6] we showed that a Wittig olefination on Garner's aldehyde **3** with benzylidene ylide afforded the corresponding styryl derivative **4** as a *E/Z* (7:3) mixture of isomers in good yield (85 %). Although the stereochemistry induced by the double bond was destroyed in the RCM step, (*E*)-**4** and (*Z*)-**4** isomers had to be separated by column chromatography for easier purification, NMR analysis and *dr* measurement in the next steps, particularly for the allylation step (vide infra). Thus, we were pleased to find that the Horner–Wadworth–Emmons olefination of **3** using the semi-stabilized diethyl benzylphosphonate proceeded stereospecifically to give (*E*)-**4** as the sole isolable product in 75 % yield. Moreover, this procedure is more convenient for the preparation of (*E*)-**4** on a large scale (> 25 mmol).



Scheme 1

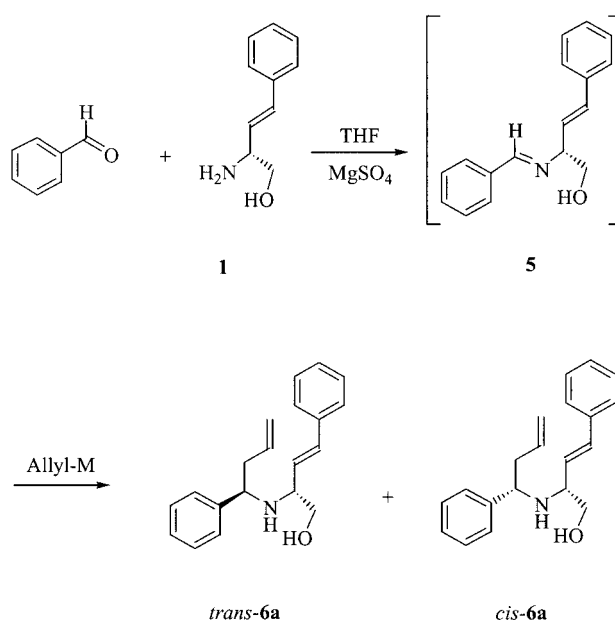
The protecting groups were removed from the amine and hydroxy functions of intermediate **4** by treatment with concentrated HCl in methanol to give the corresponding amino alcohol **1** in nearly quantitative yield (98 %). In spite of its extensive degradation in air at room temperature, **1** can be stored at –20 °C for one year, at least, without detectable degradation. It should be noted that the opposite enantiomers of (*E*)-**1** could be obtained by starting from the (*R*)-Garner's aldehyde **3**. This could be useful for the synthesis

of natural products in all enantiomeric forms and demonstrates the versatility of this strategy. We chose to introduce a styryl group in the requisite imine for the following reasons:

(1) The styryl group is a good substrate for the RCM reaction.^[7]

(2) The phenyl group represents a sufficiently bulky substituent to induce a good diastereoselectivity in the allylation step.

The next step involved the formation of an imine by condensation of (*E*)-**4** with an aldehyde, followed by allylation of the C=N double bond formed. The diastereoselective addition of organometallic reagents to imines has been widely described,^[8] but principally for chiral imino alcohols derived from valinol or phenylglycinol. In order to investigate this crucial step, we decided to prepare in situ the imine derived from the chiral amino alcohol **1** with benzaldehyde used as the model substrate. The imine was first prepared in THF by condensation of (*E*)-**4** with benzaldehyde in the presence of an excess of MgSO₄ during 12 h stirring (Scheme 2). After filtration of the magnesium salts, the resulting solution of the imine **5** was treated with various allylmagnesiums. The results are summarized in Table 1. No reaction was observed with allylzinc bromide and allylcuprate, while allylzinc bromide catalyzed with cerium chloride heptahydrate^[9] gave disappointingly low yields (< 10 %). In the case of allylcerium chloride,^[10] prepared in situ by stirring allylmagnesium bromide with cerium chloride, the desired diethylenic amines were isolated in a mixture of *trans*-**6a**/*cis*-**6a** (85:15) with a satisfactory yield (60–70 %). However, 10–15 % of the starting materials was also recovered. Finally, we found that allylmagnesium bromide gave better results by a careful control of the reaction temperature. Indeed, after 12 h stirring at –78 °C the reaction was not total. After several attempts, we found that the optimum



Scheme 2

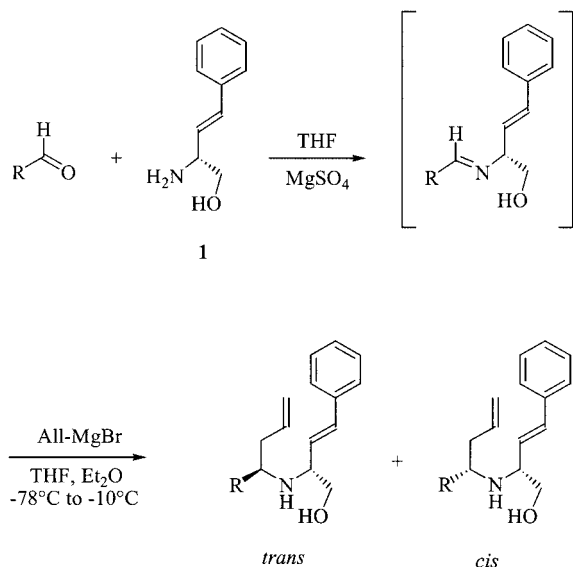
Table 1. Diastereoselective allylation with various allylmagnesiums

Entry	Organometallic (equiv.)	Solvent	Yield	<i>trans</i> - 6a : <i>cis</i> - 6a
1	All-ZnBr (3)	THF	No reaction	—
2	(All) ₂ CuMgBr (3)	Et ₂ O/THF	No reaction	—
3	All-ZnBr, CeCl ₃ ·7H ₂ O (3)	THF	< 10 % ^[a]	n.d.
4	All-CeCl ₂ (3)	Et ₂ O/THF	60–70 % ^[b]	85:15 ^[c]
5	All-MgBr (3)	Et ₂ O/THF	85 % ^[b]	86:14 ^[c]

^[a] Yield estimated by ¹H NMR spectroscopy. ^[b] Yield of isolated product. ^[c] Ratios of diastereoisomers measured by ¹H NMR spectroscopy.

diastereoselectivities and yields were obtained when the reaction mixture was stirred for 1 h at –78 °C and then carefully warmed up to –10 °C over a period of 5 h.

To establish the scope and limitations of this methodology, various chiral imino alcohols were prepared from aromatic to hindered aldehydes and were treated as described previously with allylmagnesium bromide (Scheme 3, Table 2).



Scheme 3

Table 2. Diastereoselective synthesis of chiral amino alcohols

Entry	R	<i>trans</i> : <i>cis</i> ^[a]	Product	Yield (%), <i>trans</i> : <i>cis</i> ^[b]
1	Ph	86:14	6a	73:12
2	PhCH ₂ CH ₂	89:11	6b	62:8
3	C ₆ H ₁₃	90:10	6c	62:8
4	cyclohexyl	90:10	6d	66:7
5	isopropyl	90:10	6e	68:8
6	C ₁₂ H ₂₅	87:13	6f	56:n.d.

^[a] Ratios of diastereoisomers measured by ¹H NMR spectroscopy.

^[b] Yield of isolated product.

In all cases, the *trans* adduct was preferentially formed with good diastereoselectivity and correct yield. The good stereocontrol observed in this reaction can be rationalized in terms of a chelation-controlled model^[11] (Figure 3). One magnesium cation would be coordinated by a hydroxy group and the lone pair electrons of the imino nitrogen. The attack of the magnesium reagent occurs from the less hindered face (*Re* face) of the chelate to give the *trans* adduct as the main product.

The remaining task for the synthesis of the desired tetrahydropyridine was the RCM reaction. In recent years, RCM has emerged as a powerful method for C–C bond formation.^[12] Its efficiency has been proven in the synthesis of numerous natural products. However, it is well known that RCM is ineffective with free amine owing to chelations with ruthenium.^[13] To save one step of protection, we attempted to carry out RCM in acidic media to form an ammonium

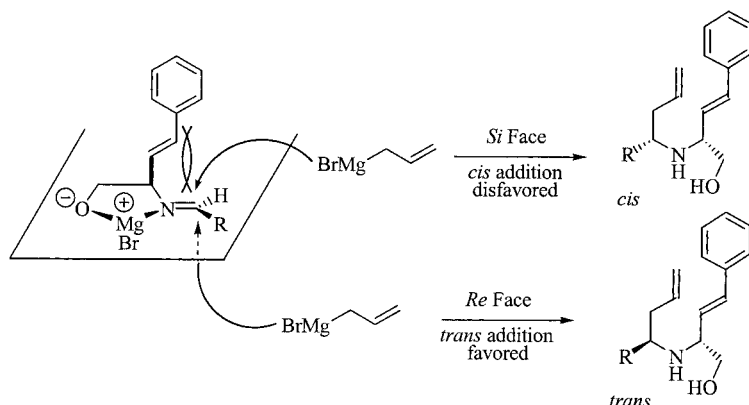
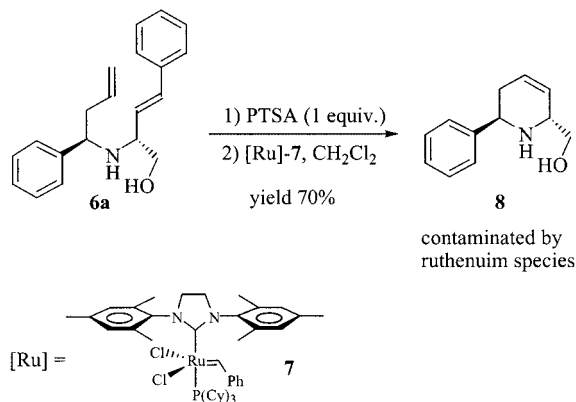


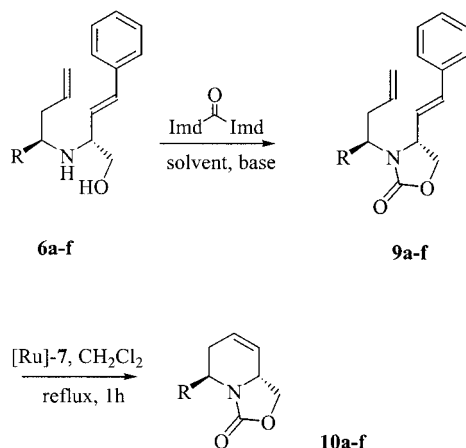
Figure 3. Stereoselectivity of the diastereoselective addition of allylmagnesium bromide over imino alcohols

derivative without complexation ability^[14] (Scheme 4). In these conditions, diethylenic amino alcohol **6a** exposed to second-generation Grubbs' catalyst **7** gave the expected tetrahydropyridine **8** in good yield (70 %). However, in spite of several successive chromatographic runs on silica gel, the dark brown color of the RCM products indicated a contamination by residual ruthenium species.



Scheme 4

To avoid this problem, we focused our effort on protecting amine and hydroxy functions as oxazolidinones by treatment of *trans*-diethylenic amino alcohols with carbonyldiimidazole in the presence of Et₃N^[15] (Scheme 5, Table 3). However, in the case of more hindered amines **6d**



Scheme 5

Table 3. Formation of the oxazolidinones and RCM reaction

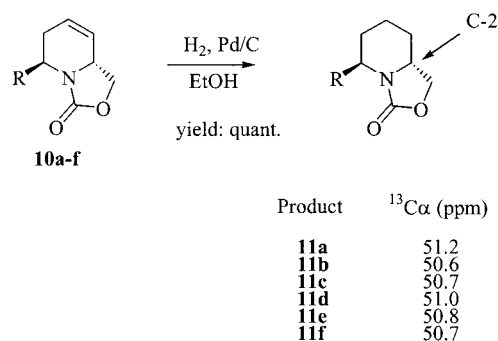
Entry	Substrate	Base/Solvent Yield (%)	Product	RCM Yield (%) ^[a]	Product
1	6a	Et ₃ N/CH ₂ Cl ₂ (89)	9a	88	10a
2	6b	Et ₃ N/CH ₂ Cl ₂ (97)	9b	92	10b
3	6c	Et ₃ N/CH ₂ Cl ₂ (81)	9c	89	10c
4	6d	DBU/THF (80)	9d	99	10d
5	6e	DBU/THF (93)	9e	98	10e
6	6f	Et ₃ N/CH ₂ Cl ₂ (91)	9f	99	10f

^[a] Yield of isolated product.

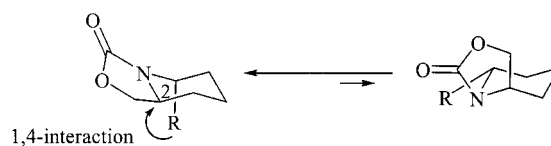
and **6e**, only the *O*-carbonylimidazole derivatives were isolated. We envisaged that this difficulty could be overcome by the use of a stronger base such as DBU to raise the amine nucleophilicity. This alternative, indeed, led to the formation of the required oxazolidinones **9d** and **9e** in excellent yield.

Having obtained the diethylenic substrate, we considered the RCM step. Treatment of **9a–f** with the second-generation Grubbs' catalyst **7** in refluxing dichloromethane afforded the expected tetrahydropyridines **10a–f** in nearly quantitative yields.

To confirm the relative stereochemistry of our tetrahydropyridines **10a–f**, we analyzed the displacement by the chemical shift of C-2 in ¹³C NMR on the hydrogenated derivatives (Scheme 6). Indeed, the C-2 chemical shift of the *trans* isomer was generally at 51 ppm whereas the *cis* isomer appeared 7 ppm downfield ($\delta = 58$ ppm).^[16] This difference can be attributed to the gauche 1–4 interaction (also called the γ -effect) between R and C-2, which is only possible in the *trans* isomer (Figure 4).^[17] In the case of our compounds, the ¹³C NMR spectroscopic data of C-2, in the range 50.6 to 51.2 ppm, were in total accordance with the data expected for *trans* isomers.



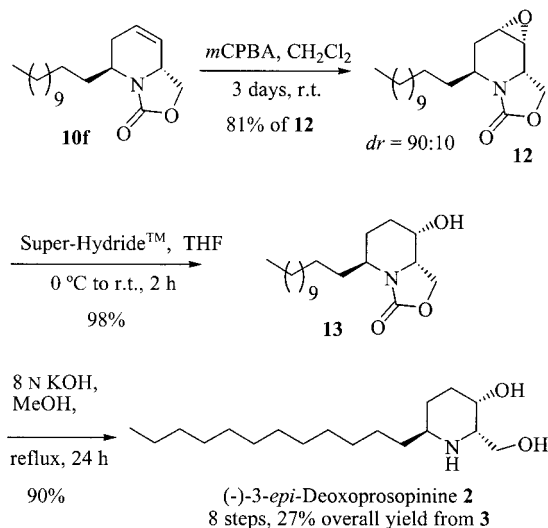
Scheme 6

Figure 4. Conformation of the *trans*-oxazolidinones

In addition the spectroscopic data (IR, ¹H, ¹³C) of **8** matched those reported in the literature.^[18] The X-ray crystal structure of the **11f** derivative confirmed also a *trans* relative stereochemistry (vide infra).

We demonstrated the synthetic usefulness of this new methodology through the first total synthesis of (–)-3-*epi*-deoxoprosopinine (**2**) (Scheme 7). Hydroxylated piperidines are naturally occurring compounds that exhibit a wide range of biological activities.^[19] Among these, *Prosopis* alkaloids possess interesting properties, including analgesic, anesthetic and antibiotic activity.^[20] While natural products have been the subject of considerable attention, to the best

of our knowledge only a few analogues have been reported in the literature. From our point of view, it could be interesting to investigate the biological properties of some analogues. In this context, by application of our novel methodology, we concentrated on the preparation of (–)-3-*epi*-deoxoprosopinine (**2**).



Scheme 7

Starting from **10f** as described previously, epoxidation of the double bond with *m*CPBA gave the *endo* epoxide **12** as the major isomer ($dr = 90:10$), which is easily separated from the *exo* minor isomer by flash chromatography. It should be noted that the use of dimethyldioxirane, generated from oxone® and acetone^[21], gave essentially the same ratio. To provide the hydroxy function in the C-3 position, the epoxide **12** was opened by Super Hydride® in quantitative yield. To confirm the *endo* selectivity of the epoxidation step, an X-ray crystal structure of **13** was determined. As shown in Figure 5, a *cis* relation was observed between C-2 C-3 substituents. In addition, the *trans* relation between C-2 C-6 confirms the relative stereochemistry envisaged in the allylation step (vide supra).

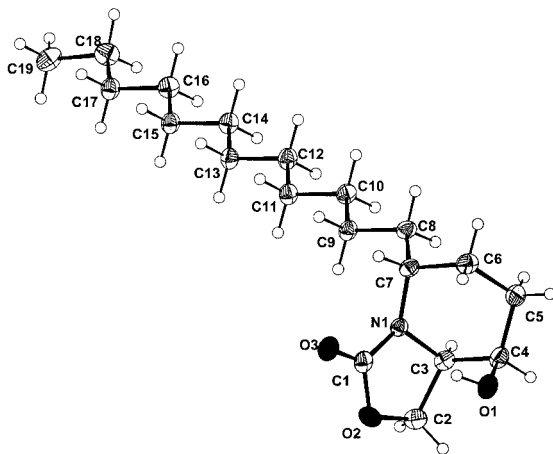


Figure 5. Molecular diagram of **13**. Atoms of the asymmetric unit are depicted as ellipsoids at the 50 % probability level

The final step comprises the deprotection of amine and primary hydroxy functions by hydrolysis of the oxazolidinone. This conversion was achieved in nearly quantitative yield using hard basic conditions and reflux in methanol. In this way, (–)-3-*epi*-deoxoprosopinine (**2**) was obtained in 27 % overall yield and eight steps from the commercially available Garner's aldehyde **3**.

Conclusion

A novel and general synthesis of *trans*-2,6-disubstituted tetrahydropyridines in five steps with overall yields up to 37 % was introduced. Highlights of these synthetic ventures include a diastereoselective allylation of chiral imines and an RCM. Furthermore, we demonstrated the versatility of this strategy by the ease with which the chiral amino alcohol **1** was obtained in its (*R*) or (*S*) form. Its synthetic usefulness was illustrated by the short and efficient total synthesis of the (–)-3-*epi*-deoxoprosopinine (**2**) in eight steps and 38 % overall yield. Further application of this procedure to other polyhydroxylated alkaloids is currently under investigation.

Experimental Section

General Methods: ¹H NMR and ¹³C NMR spectra were recorded at 200 and 50 MHz using residual CDCl₃ ($\delta = 7.26$ ppm) and CDCl₃ ($\delta = 77.16$ ppm) as internal standards, respectively. Flash column chromatography was performed on Merck silica gel (60 Å, 230–400 mesh). HMRS were recorded at the “Service Commun d’Analyse Spectroscopique d’Anger” or at the “Centre Régional Universitaire de Spectroscopie de Rouen”. Grubbs’ catalyst was purchased from Strem. All reactions were performed under N₂ in a flame-dried flask using anhydrous solvents. Grignard reagents were titrated by Watson and Eastham’s method.^[22]

(4*R*,1′*E*)-3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4-styryloxazolidine (4**):** A solution of the phosphonate (6.95 g, 30.48 mmol) in THF (100 mL) was treated with BuLi (15.24 mL, 1.6 M in hexane, 24.38 mmol), at -78°C . The resulting mixture was stirred at -78°C for 30 min and then a solution of aldehyde **3** (3.49 g, 15.24 mmol) in THF (35 mL) was slowly added over 30 min. After addition, the mixture was stirred at -78°C for 2 h and at room temperature for 12 h. The mixture was quenched with water and diluted with Et₂O. The aqueous phase was extracted with Et₂O (3 ×). The combined organic extracts were washed with brine (1 ×), dried with anhydrous MgSO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography (5 % EtOAc/petroleum ether) and crystallization from petroleum ether gave (*E*)-**4** (3.46 g, 75 %) as colorless crystals. $[\alpha]_D^{20} = -83.0$ ($c = 0.976$, CHCl₃) [ref.:^[23] $[\alpha]_D^{20} = -88.7$ ($c = 1$, CHCl₃)]. M.p. 85°C (ref.:^[23] m.p. 81°C). IR (KBr): $\tilde{\nu} = 1700, 2977 \text{ cm}^{-1}$. ¹H NMR: $\delta = 1.46$ (s, 9 H), 1.57 (s, 3 H), 1.68 (s, 3 H), 3.85 (dd, $J = 2.3$, $J = 8.8$ Hz, 1 H), 4.13 (dd, $J = 6.1$, $J = 8.8$ Hz, 1 H), 4.66 (m, 1 H), 6.17 (dd, $J = 7.6$, $J = 15.1$ Hz, 1 H), 6.52 (d, $J = 15.1$ Hz, 1 H), 7.24–7.41 (m, 5 H) ppm. ¹³C NMR: $\delta = 23.9, 26.8, 28.6, 59.6, 68.4, 79.9, 94.4, 126.5, 127.7, 128.7, 131.8, 136.8, 152.1$ ppm. HRMS (EI) calcd. for C₁₈H₂₅NO₃ [M^+] 303.1834, found 303.1834.

(2R,3E)-2-Amino-4-phenylbut-3-en-1-ol (1): A solution of **4** (5.2 g, 17.16 mmol) in MeOH (55 mL) was treated with concentrated HCl (2.7 mL, 5 % v/v). After stirring at reflux for 4 h, the volatiles were evaporated under reduced pressure. The residue was taken up with CH₂Cl₂ and H₂O and the resulting mixture was basified with solid NaOH. The aqueous layer was extracted with CH₂Cl₂ (5 ×) and the combined extracts were dried with anhydrous MgSO₄. Removal of the solvent left an oil which was precipitated in CH₂Cl₂/petroleum ether to give **1** (2.77 g, 98 %) as a white solid. Owing to its rapid degradation in air, **1** was used in the next step without further purification. $[\alpha]_D^{20} = -21$ ($c = 0.162$, CHCl₃). M.p. 98 °C. IR (KBr): $\tilde{\nu} = 1591, 2902, 3060, 3282, 3342$ cm⁻¹. ¹H NMR: $\delta = 1.99\text{--}2.06$ (m, 3 H), 3.42–3.50 (m, 1 H), 3.65–3.71 (m, 2 H), 6.17 (dd, $J = 6.4, J = 16$ Hz, 1 H), 6.57 (d, $J = 16$ Hz, 1 H), 7.20–7.40 (m, 5 H) ppm. ¹³C NMR: $\delta = 55.5, 66.7, 126.5, 127.8, 128.7, 130.8, 131.0, 136.8$ ppm. HRMS (ESI) calcd. for C₁₀H₁₄NO [M + H⁺] 164.1075, found 164.1076. C₁₀H₁₃NO: calcd. C 73.59, H 8.03, N 8.58; found C 73.64, H 7.95, N 8.49.

Synthesis of Diethylenic Amino Alcohols. General Procedure: The appropriate aldehyde (1.84 mmol) and MgSO₄ were added to a solution of amino alcohol **1** (300 mg, 1.84 mmol) in THF (4 mL). The mixture was stirred overnight and filtered. The resulting mixture was slowly added over 30 min to a solution of allylmagnesium bromide (1 M in Et₂O, 5.52 mmol) in THF (5 mL) cooled to –78 °C. After the addition, the mixture was stirred at –78 °C for 1 h and slowly warmed up to –10 °C over 5 h. Then, the reaction mixture was hydrolyzed with saturated aqueous NH₄Cl. The aqueous phase was extracted with Et₂O (4 ×). The combined organic extracts were washed with brine (1 ×), dried with anhydrous MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography affording the corresponding diethylenic amino alcohols.

(2R,1'R)-4-Phenyl-2-(1-phenylbut-3-enylamino)but-3-en-1-ol (trans-6a): Purification by flash chromatography (30 % EtOAc/petroleum ether) gave **trans-6a** (394 mg, 73 %) as a yellow oil. $[\alpha]_D^{20} = -90.8$ ($c = 1.166$, CHCl₃). M.p. 62 °C. IR (KBr): $\tilde{\nu} = 1599, 1639, 2925, 3061, 3323$ cm⁻¹. ¹H NMR: $\delta = 2.14$ (br. s, 2 H), 2.45–2.53 (m, 2 H), 3.39–3.49 (m, 2 H), 3.65–3.75 (m, 1 H), 3.82 (t, $J = 6.7$ Hz, 1 H), 5.02–5.12 (m, 2 H), 5.60–5.81 (m, 1 H), 5.99 (dd, $J = 7.3, J = 16$ Hz, 1 H), 6.45 (d, $J = 16$ Hz, 1 H), 7.24–7.33 (m, 10 H) ppm. ¹³C NMR: $\delta = 42.1, 59.9, 60.0, 64.2, 117.7, 126.5, 127.3, 127.8, 128.6, 129.5, 132.1, 135.1, 136.8, 144.0$ ppm. HRMS (EI) calcd. for C₁₉H₂₀N (M – CH₂OH⁺) 262.1596, found 262.1593.

(2R,1'S)-4-Phenyl-2-(1-phenylbut-3-enylamino)but-3-en-1-ol (cis-6a): Purification by flash chromatography (30 % EtOAc/petroleum ether) gave **cis-6a** (65 mg, 12 %) as a yellow oil. $[\alpha]_D^{20} = -228.2$ ($c = 0.953$, CHCl₃). M.p. 102 °C. IR (KBr): $\tilde{\nu} = 1600, 1642, 2911, 3031, 3198$ cm⁻¹. ¹H NMR: $\delta = 2.30$ (br. s, 2 H), 2.36–2.53 (m, 2 H), 3.11–3.21 (m, 1 H), 3.38–3.62 (m, 2 H), 3.87 (dd, $J = 5.8, J = 7.9$ Hz, 1 H), 5.10–5.20 (m, 2 H), 5.64–5.85 (m, 1 H), 5.96 (dd, $J = 8.4, J = 16$ Hz, 1 H), 6.40 (d, $J = 16$ Hz, 1 H), 7.27–7.44 (m, 10 H) ppm. ¹³C NMR: $\delta = 43.7, 58.8, 59.2, 65.4, 118.1, 126.5, 127.4, 127.5, 127.9, 128.6, 128.7, 128.7, 133.1, 135.4, 136.7, 143.6$ ppm.

(2R,1'S)-4-Phenyl-2-(1-phenylethylbut-3-enylamino)but-3-en-1-ol (trans-6b): Purification by flash chromatography (30 % EtOAc/petroleum ether) gave **trans-6b** (366 mg, 62 %) as a pale-yellow oil. $[\alpha]_D^{20} = -84.7$ ($c = 1.255$, CHCl₃). IR (KBr): $\tilde{\nu} = 1601, 1638, 2924, 3061, 3315$ cm⁻¹. ¹H NMR: $\delta = 1.62\text{--}1.91$ (m, 2 H), 2.09 (s br, 2 H), 2.27 (t, $J = 6.1$ Hz, 2 H), 2.57–2.85 (m, 3 H), 3.39–3.53 (m, 2 H), 3.59–3.72 (m, 1 H), 5.09–5.17 (m, 2 H), 5.74–5.91 (m, 1 H),

6.00 (dd, $J = 7.8, J = 16.0$ Hz, 1 H), 6.54 (d, $J = 16.0$ Hz, 1 H), 7.14–7.40 (m, 10 H) ppm. ¹³C NMR: $\delta = 32.4, 36.6, 38.2, 53.5, 60.0, 65.3, 117.7, 125.9, 126.5, 127.8, 128.5, 128.7, 129.5, 132.6, 135.0, 136.7, 142.1$ ppm. HRMS (FAB) calcd. for C₂₂H₂₈NO [M + H⁺] 322.2171, found 322.2172.

(2R,1'R)-4-Phenyl-2-(1-phenylethylbut-3-enylamino)but-3-en-1-ol (cis-6b): Purification by flash chromatography (30 % EtOAc/petroleum ether) gave **cis-6b** (47 mg, 8 %) as a pale-yellow oil. $[\alpha]_D^{20} = -95.0$ ($c = 0.370$, CHCl₃). IR (KBr): $\tilde{\nu} = 1601, 1638, 2924, 3061, 3315$ cm⁻¹. ¹H NMR: $\delta = 1.68\text{--}1.86$ (m, 2 H), 2.10–2.20 (m, 1 H), 2.35–2.43 (m, 1 H), 2.58–2.80 (m, 3 H), 3.33–3.42 (m, 2 H), 3.59–3.67 (m, 1 H), 5.11–5.15 (m, 2 H), 5.71–5.79 (m, 1 H), 5.93 (dd, $J = 6.6, J = 15.9$ Hz, 1 H), 6.38 (d, $J = 15.9$ Hz, 1 H), 7.15–7.35 (m, 10 H) ppm. ¹³C NMR: $\delta = 31.7, 36.0, 39.3, 52.9, 59.8, 64.9, 118.2, 126.0, 126.5, 127.9, 128.5, 128.7, 129.1, 132.6, 135.5, 136.7, 142.4$ ppm.

(2R,1'S)-2-(1-Hexylbut-3-enylamino)-4-phenylbut-3-en-1-ol (trans-6c): Purification by flash chromatography (40 % EtOAc/petroleum ether) gave **trans-6c** (343 mg, 62 %) as a colorless oil. $[\alpha]_D^{20} = -97.0$ ($c = 1.014$, CHCl₃). IR (KBr): $\tilde{\nu} = 1639, 2927, 3078, 3317$ cm⁻¹. ¹H NMR: $\delta = 0.85$ (t, $J = 7.0$ Hz, 3 H), 1.25–1.42 (m, 10 H), 2.19 (t, $J = 6.3$ Hz, 2 H), 2.66–2.77 (m, 1 H), 3.35–3.50 (m, 2 H), 3.59–3.71 (m, 1 H), 5.06–5.13 (m, 2 H), 5.72–5.89 (m, 1 H), 6.00 (dd, $J = 7.8, J = 15.9$ Hz, 1 H), 6.54 (d, $J = 15.9$ Hz, 1 H), 7.21–7.41 (m, 5 H) ppm. ¹³C NMR: $\delta = 14.2, 22.7, 26.0, 29.5, 32.0, 35.0, 38.5, 54.0, 59.9, 65.2, 117.3, 126.5, 127.8, 128.7, 129.7, 132.3, 135.5, 136.8$ ppm. HRMS (EI) calcd. for C₂₀H₂₉NO [M⁺] 299.2249, found 299.2247.

(2R,1'R)-2-(1-Hexylbut-3-enylamino)-4-phenylbut-3-en-1-ol (cis-6c): Purification by flash chromatography (40 % EtOAc/petroleum ether) gave **cis-6c** (44 mg, 8 %) as a colorless oil. $[\alpha]_D^{20} = -68$ ($c = 0.233$, CHCl₃). IR (KBr): $\tilde{\nu} = 1639, 2927, 3078, 3317$ cm⁻¹. ¹H NMR: $\delta = 0.84\text{--}0.90$ (m, 3 H), 1.11–1.50 (m, 10 H), 2.05–2.37 (m, 2 H), 2.74–2.77 (m, 1 H), 3.41–3.49 (m, 2 H), 3.67–3.69 (m, 1 H), 5.11–5.15 (m, 2 H), 5.71–5.78 (m, 1 H), 6.00 (dd, $J = 7.6, J = 16$ Hz, 1 H), 6.54 (d, $J = 16$ Hz, 1 H), 7.25–7.39 (m, 5 H) ppm. ¹³C NMR: $\delta = 14.3, 22.8, 25.4, 29.7, 32.0, 33.9, 39.1, 53.7, 59.9, 64.7, 118.4, 125.1, 126.6, 128.0, 128.8, 132.9, 135.5, 136.4$ ppm.

(2R,1'R)-2-(1-Cyclohexylbut-3-enylamino)-4-phenylbut-3-en-1-ol (trans-6d): Purification by flash chromatography (30 % EtOAc/petroleum ether) gave **trans-6d** (363 mg, 66 %) as a yellow oil. $[\alpha]_D^{20} = -106.2$ ($c = 1.068$, CHCl₃). IR (KBr): $\tilde{\nu} = 1638, 2924, 3076, 3334$ cm⁻¹. ¹H NMR: $\delta = 0.89\text{--}1.26$ (m, 5 H), 1.37–1.48 (m, 1 H), 1.64–1.79 (m, 5 H), 2.01 (s, 2 H), 2.09–2.33 (m, 2 H), 2.51 (app. q, $J = 5.5$ Hz, 1 H), 3.36–3.49 (m, 2 H), 3.58–3.70 (m, 1 H), 5.06–5.14 (m, 2 H), 5.74–5.91 (m, 1 H), 6.00 (dd, $J = 7.5, J = 15.9$ Hz, 1 H), 6.54 (d, $J = 15.9$ Hz, 1 H), 7.24–7.41 (m, 5 H) ppm. ¹³C NMR: $\delta = 26.7, 26.8, 29.1, 29.5, 35.9, 41.2, 59.0, 60.3, 65.2, 117.0, 126.5, 127.8, 128.7, 129.9, 132.4, 136.4, 136.9$ ppm. HRMS (EI) calcd. for C₂₀H₂₉NO [M⁺] 299.2249, found 299.2247.

(2R,1'S)-2-(1-Cyclohexylbut-3-enylamino)-4-phenylbut-3-en-1-ol (cis-6d): Purification by flash chromatography (30 % EtOAc/petroleum ether) gave **cis-6d** (38 mg, 7 %) as a yellow oil. $[\alpha]_D^{20} = -60.2$ ($c = 0.772$, CHCl₃). IR (KBr): $\tilde{\nu} = 1639, 2924, 3076, 3386$ cm⁻¹. ¹H NMR: $\delta = 1.00\text{--}1.37$ (m, 5 H), 1.41–1.51 (m, 1 H), 1.63–1.79 (m, 5 H), 1.93–2.07 (m, 1 H), 2.25–2.33 (m, 3 H), 2.51 (dt, $J = 3.8, J = 8.8$ Hz, 1 H), 3.31–3.44 (m, 2 H), 3.57–3.70 (m, 1 H), 5.06–5.14 (m, 2 H), 5.62–5.83 (m, 1 H), 5.95 (dd, $J = 7.6, J = 15.9$ Hz, 1 H), 6.51 (d, $J = 15.9$ Hz, 1 H), 7.28–7.36 (m, 5 H) ppm.

^{13}C NMR: δ = 26.8, 26.9, 27.0, 28.3, 29.7, 36.0, 41.0, 58.4, 60.4, 64.9, 117.7, 126.4, 127.8, 128.7, 129.5, 132.2, 136.7, 136.8 ppm.

(2*R*,1'*R*)-2-(1-Isopropylbut-3-enylamino)-4-phenylbut-3-en-1-ol (trans-6e): Purification by flash chromatography (30 % EtOAc/petroleum ether) gave **trans-6e** (324 mg, 68 %) as a yellow oil. $[\alpha]_{\text{D}}^{20}$ = -133.8 (c = 1.11, CHCl_3). IR (KBr): $\tilde{\nu}$ = 1599, 1639, 2958, 3077, 3333 cm^{-1} . ^1H NMR: δ = 0.92 (d, J = 6.9 Hz, 6 H), 1.71–1.87 (m, 1 H), 2.05–2.31 (m, 4 H), 2.52 (dt, J = 5.3, J = 6.1 Hz, 1 H), 3.37–3.49 (m, 2 H), 3.60–3.71 (m, 1 H), 5.06–5.17 (m, 2 H), 5.74–5.92 (m, 1 H), 6.01 (dd, J = 7.8, J = 16.0 Hz, 1 H), 6.55 (d, J = 16.0 Hz, 1 H), 7.24–7.41 (m, 5 H) ppm. ^{13}C NMR: δ = 18.4, 18.9, 30.8, 35.9, 59.6, 60.3, 65.2, 117.0, 126.4, 127.7, 128.7, 129.8, 132.4, 136.3, 136.8 ppm. HRMS (CI/ NH_3) calcd. for $\text{C}_{17}\text{H}_{26}\text{NO}$ [$\text{M} + \text{H}^+$] 260.2014, found 260.2003.

(2*R*,1'*S*)-2-(1-Isopropylbut-3-enylamino)-4-phenylbut-3-en-1-ol (cis-6e): Purification by flash chromatography (30 % EtOAc/petroleum ether) gave **cis-6e** (38 mg, 8 %) as a yellow oil. $[\alpha]_{\text{D}}^{20}$ = -36.2 (c = 0.55, CHCl_3). IR (KBr): $\tilde{\nu}$ = 1599, 1639, 2958, 3077, 3333 cm^{-1} . ^1H NMR: δ = 0.92 (d, J = 6.9 Hz, 6 H), 1.76–2.33 (m, 5 H), 2.54 (dt, J = 3.8, J = 9.3 Hz, 1 H), 3.29–3.43 (m, 2 H), 3.58–3.66 (m, 1 H), 5.06–5.14 (m, 2 H), 5.61–5.79 (m, 1 H), 5.93 (dd, J = 7.6, J = 15.9 Hz, 1 H), 6.50 (d, J = 15.9 Hz, 1 H), 7.24–7.39 (m, 5 H) ppm. ^{13}C NMR: δ = 17.2, 19.0, 30.0, 35.1, 58.6, 60.3, 64.9, 117.8, 126.4, 127.8, 128.7, 129.5, 132.2, 136.7 ppm.

(2*R*,1'*S*)-2-(1-Dodecylbut-3-enylamino)-4-phenylbut-3-en-1-ol (trans-6f): Purification by flash chromatography (30 % EtOAc/petroleum ether) gave **trans-6f** (397 mg, 56 %) as a pale-yellow oil. $[\alpha]_{\text{D}}^{20}$ = -58.0 (c = 0.933, CHCl_3). IR (KBr): $\tilde{\nu}$ = 1600, 1639, 1653, 2924, 3079, 3320 cm^{-1} . ^1H NMR: δ = 0.88 (t, J = 6.7 Hz, 3 H), 1.24 (br. s, 22 H), 1.97 (br. s, 2 H), 2.20 (app. t, J = 6.4 Hz, 2 H), 2.66–2.78 (m, 1 H), 3.35–3.50 (m, 2 H), 3.59–3.71 (m, 1 H), 5.06–5.13 (m, 2 H), 5.71–5.89 (m, 1 H), 6.00 (dd, J = 7.8, J = 15.9 Hz, 1 H), 6.04 (d, J = 15.9 Hz, 1 H), 7.24–7.41 (m, 5 H) ppm. ^{13}C NMR: δ = 14.3, 22.8, 26.1, 29.5, 29.8, 32.1, 34.9, 38.4, 54.0, 60.0, 65.2, 117.4, 126.5, 127.8, 128.7, 129.4, 132.5, 135.4, 136.7 ppm. HRMS (CI/ NH_3) calcd. for $\text{C}_{26}\text{H}_{44}\text{NO}$ [$\text{M} + \text{H}^+$] 386.3423, found 386.3442. The **cis-6f** diastereoisomer was obtained only in impure form and was not further characterized.

Synthesis of Cyclic Carbamates. General Procedure with Et_3N : Et_3N (175 μL , 1.26 mmol) and carbonyldiimidazole (292 mg, 1.80 mmol) were added to a solution of the appropriate diethylenic amino alcohols (1.20 mmol) in CH_2Cl_2 (7 mL). The mixture was stirred overnight and then diluted with CH_2Cl_2 (10 mL) and washed with 0.5 N aqueous HCl solution (2 $\times$). The combined aqueous phases were extracted with CH_2Cl_2 (3 $\times$). The combined organic extracts were dried with anhydrous MgSO_4 and concentrated under reduced pressure. Purification by flash chromatography gave the corresponding cyclic carbamates.

(4*R*,1'*R*)-3-(1-Phenylbut-3-enyl)-4-styryloxazolidin-2-one (9a): Purification by flash chromatography (15 % EtOAc/petroleum ether) gave **9a** (341 mg, 89 %) as a white solid. $[\alpha]_{\text{D}}^{20}$ = -148.8 (c = 1.06, CHCl_3). M.p. 88 $^{\circ}\text{C}$. IR (KBr): $\tilde{\nu}$ = 1642, 1654, 1747, 2979, 3062 cm^{-1} . ^1H NMR: δ = 2.70–2.83 (m, 1 H), 2.89–3.05 (m, 1 H), 3.95 (app. t, J = 7.9 Hz, 1 H), 4.11 (app. q, J = 7.9 Hz, 1 H), 4.32 (app. t, J = 7.9 Hz, 1 H), 5.12–5.24 (m, 3 H), 5.79–5.99 (m, 1 H), 6.12 (dd, J = 8.7, J = 15.7 Hz, 1 H), 6.41 (d, J = 15.7 Hz, 1 H), 7.39–7.41 (m, 10 H) ppm. ^{13}C NMR: δ = 36.2, 57.5, 58.1, 67.0, 117.9, 126.7, 126.9, 128.1, 128.3, 128.5, 128.7, 128.9, 134.5, 134.8, 135.4, 137.9, 158.2 ppm. HRMS (EI) calcd. for $\text{C}_{13}\text{H}_{13}\text{NO}_2$ [M^+] 215.0946, found 215.0946. $\text{C}_{21}\text{H}_{21}\text{NO}_2$: calcd. C 78.97, H 6.63, N 4.39; found C 78.84, H 6.51, N 4.63.

(4*R*,1'*S*)-3-(1-Phenylethylbut-3-enyl)-4-styryloxazolidin-2-one (9b): Purification by flash chromatography (15 % EtOAc/petroleum ether) gave **9b** (337 mg, 81 %) as a colorless oil. $[\alpha]_{\text{D}}^{20}$ = -118.1 (c = 1.475, CHCl_3). IR (KBr): $\tilde{\nu}$ = 1641, 1655, 1747, 2924, 3061 cm^{-1} . ^1H NMR: δ = 1.83–2.00 (m, 1 H), 2.06–2.36 (m, 2 H), 2.46–2.57 (m, 1 H), 2.62–2.77 (m, 2 H), 3.63–3.78 (m, 1 H), 3.91–4.04 (m, 1 H), 4.31–4.45 (m, 2 H), 5.05–5.13 (m, 2 H), 5.70–5.91 (m, 1 H), 6.06 (dd, J = 6.9, J = 15.9 Hz, 1 H), 6.57 (d, J = 15.9 Hz, 1 H), 7.17–7.38 (m, 10 H) ppm. ^{13}C NMR: δ = 33.3, 38.3, 54.4, 59.1, 67.4, 118.0, 126.2, 126.8, 128.5, 128.6, 128.9, 129.0, 135.0, 135.3, 135.4, 141.4, 157.8 ppm. HRMS (EI) calcd. for $\text{C}_{23}\text{H}_{25}\text{NO}_2$ [M^+] 347.1885, found 347.1888.

(4*R*,1'*S*)-3-(1-Hexylbut-3-enyl)-4-styryloxazolidin-2-one (9c): Purification by flash chromatography (15 % EtOAc/petroleum ether) gave **9c** (381 mg, 97 %) as a colorless oil. $[\alpha]_{\text{D}}^{20}$ = -119.1 (c = 1.006, CHCl_3). IR (KBr): $\tilde{\nu}$ = 1641, 1654, 1747, 2928, 3028 cm^{-1} . ^1H NMR: δ = 0.84–0.91 (m, 3 H), 1.26–1.30 (m, 8 H), 1.50–1.60 (m, 1 H), 1.69–1.84 (m, 1 H), 2.19–2.33 (m, 1 H), 2.42–2.57 (m, 1 H), 3.59–3.74 (m, 1 H), 3.92–4.05 (m, 1 H), 4.36–4.49 (m, 2 H), 5.04–5.13 (m, 2 H), 5.72–5.89 (m, 1 H), 6.09 (dd, J = 8.7, J = 15.7 Hz, 1 H), 6.60 (d, J = 15.7 Hz, 1 H), 7.27–7.40 (m, 5 H) ppm. ^{13}C NMR: δ = 14.2, 22.7, 26.7, 29.1, 31.7, 31.9, 38.5, 54.5, 58.9, 67.3, 117.6, 126.8, 127.2, 128.7, 129.0, 134.7, 135.5, 135.6, 157.9 ppm. HRMS (EI) calcd. for $\text{C}_{21}\text{H}_{29}\text{NO}_2$ [M^+] 327.2198, found 327.2195.

(4*R*,1'*S*)-3-(1-Dodecylbut-3-enyl)-4-styryloxazolidin-2-one (9f): Purification by flash chromatography (10 % EtOAc/petroleum ether) gave **9f** (449 mg, 91 %) as a colorless oil. $[\alpha]_{\text{D}}^{20}$ = -41.3 (c = 1.067, CHCl_3). IR (KBr): $\tilde{\nu}$ = 1641, 1662, 1750, 2926, 3027 cm^{-1} . ^1H NMR: δ = 0.88 (t, J = 6.7 Hz, 3 H), 1.25 (br. s, 20 H), 1.48–1.86 (m, 2 H), 2.18–2.31 (m, 1 H), 2.41–2.56 (m, 1 H), 3.58–3.73 (m, 1 H), 3.92–4.04 (m, 1 H), 4.35–4.49 (m, 2 H), 5.03–5.12 (m, 2 H), 5.64–5.91 (m, 1 H), 6.08 (dd, J = 8.7, J = 15.9 Hz, 1 H), 6.59 (d, J = 15.9 Hz, 1 H), 7.32–7.39 (m, 5 H) ppm. ^{13}C NMR: δ = 14.3, 22.8, 26.8, 29.5, 29.7, 29.8, 31.7, 32.1, 38.5, 54.6, 58.9, 67.3, 117.6, 126.8, 127.2, 128.8, 129.0, 134.7, 135.5, 135.6, 157.9 ppm. HRMS (EI) calcd. for $\text{C}_{27}\text{H}_{41}\text{NO}_2$ [M^+] 411.3137, found 411.3135.

Synthesis of Cyclic Carbamates. General Procedure with DBU: DBU (536 μL , 3.60 mmol) and carbonyldiimidazole (486 mg, 3.0 mmol) were added to a solution of the appropriate diethylenic amino alcohols (1.20 mmol) in THF (7 mL). The mixture was stirred for 60 h and then filtered. Removal of the solvent left a residue, which was purified by flash chromatography affording the corresponding cyclic carbamates.

(4*R*,1'*R*)-3-(1-Cyclohexylbut-3-enyl)-4-styryloxazolidin-2-one (9d): Purification by flash chromatography (10 % EtOAc/petroleum ether) gave **9d** (312 mg, 80 %) as a colorless oil. $[\alpha]_{\text{D}}^{20}$ = -108.5 (c = 1.310, CHCl_3). IR (KBr): $\tilde{\nu}$ = 1641, 1654, 1735, 2927, 3062 cm^{-1} . ^1H NMR: δ = 0.82–0.94 (m, 2 H), 1.02–1.35 (m, 3 H), 1.63–1.81 (m, 6 H), 2.41–2.49 (m, 2 H), 3.24–3.36 (m, 1 H), 3.90–4.02 (m, 1 H), 4.34–4.47 (m, 2 H), 5.06–5.15 (m, 2 H), 5.74–5.94 (m, 1 H), 6.10 (dd, J = 8.5, J = 15.9 Hz, 1 H), 6.57 (d, J = 15.9 Hz, 1 H), 7.31–7.37 (m, 5 H) ppm. ^{13}C NMR: δ = 26.0, 26.3, 30.6, 30.7, 34.8, 38.9, 59.4, 59.9, 67.3, 117.6, 126.8, 127.0, 128.7, 128.9, 134.9, 135.5, 136.1, 158.1 ppm. HRMS (EI) calcd. for $\text{C}_{14}\text{H}_{19}\text{NO}_2$ [M^+], found.

(4*R*,1'*R*)-3-(1-Isopropylbut-3-enyl)-4-styryloxazolidin-2-one (9e): Purification by flash chromatography (15 % EtOAc/petroleum ether) gave **9e** (318 mg, 93 %) as a colorless oil. $[\alpha]_{\text{D}}^{20}$ = -117.4 (c = 0.680, CHCl_3). IR (KBr): $\tilde{\nu}$ = 1641, 1656, 1747, 2963, 3028

cm⁻¹. ¹H NMR: δ = 0.96 (d, J = 6.7 Hz, 3 H), 0.98 (d, J = 6.7 Hz, 3 H), 2.04–2.18 (m, 1 H), 2.43–2.51 (m, 2 H), 3.26 (dt, J = 10, J = 6.1 Hz, 1 H), 3.92–4.05 (m, 1 H), 4.37–4.51 (m, 2 H), 5.07–5.16 (m, 2 H), 5.76–5.96 (m, 1 H), 6.12 (ddd, J = 1.2, J = 7.6, J = 15.7 Hz, 1 H), 6.59 (d, J = 15.7 Hz, 1 H), 7.31–7.42 (m, 5 H) ppm. ¹³C NMR: δ = 20.4, 20.7, 30.0, 35.4, 59.8, 60.7, 67.3, 117.6, 126.8, 127.0, 128.7, 129.0, 134.9, 135.5, 136.0, 158.1 ppm. HRMS (EI) calcd. for C₁₈H₂₃NO₂ [M⁺] 285.1729, found 285.1730.

RCM. General Procedure: [Ru]-7 (43 mg, 0.05 mmol) was added at room temperature to a solution of cyclic carbamates **9a–f** (1.0 mmol) in CH₂Cl₂ (200 mL). After stirring at reflux for 1 h the solution was cooled to room temperature and DMSO (177 μ L, 2.5 mmol) was added. The solution was stirred overnight, concentrated under reduced pressure and purified by flash chromatography to give the tetrahydropyridines **10a–f**.

(5*R*,8*aR*)-5-Phenyl-4,5,6,8*a*-tetrahydroxazolidino[3,4-*a*]pyridin-3-one (10a): Purification by flash chromatography (30 % EtOAc/petroleum ether) gave **10a** (189 mg, 88 %) as colorless crystals. [α]_D²⁰ = +36.3 (c = 1.076, CHCl₃). M.p. 90 °C. IR (KBr): $\tilde{\nu}$ = 1646, 1747, 2923 cm⁻¹. ¹H NMR: δ = 2.54–2.68 (dm, J = 18.3 Hz, 1 H), 2.73–2.90 (dm, J = 18.3 Hz, 1 H), 3.96–4.07 (m, 2 H), 4.38–4.50 (m, 1 H), 5.24 (app. d, J = 7.0 Hz, 1 H), 5.64–5.71 (dm, J = 11.6 Hz, 1 H), 6.03–6.13 (m, 1 H), 7.27–7.41 (m, 5 H) ppm. ¹³C NMR: δ = 26.4, 49.6, 50.5, 68.0, 125.8, 126.8, 127.3, 127.9, 128.8, 138.9, 157.6 ppm. HRMS (EI) calcd. for C₁₃H₁₇NO₂ [M⁺] 215.0946, found 215.0946. C₁₃H₁₃NO₂: calcd. C 72.54, H 6.09, N 6.51; found C 72.50, H 6.31, N 6.43.

(5*R*,8*aR*)-5-Phenylethyl-4,5,6,8*a*-tetrahydroxazolidino[3,4-*a*]pyridin-3-one (10b): Purification by flash chromatography (30 % EtOAc/petroleum ether) gave **10b** (224 mg, 92 %) as a colorless oil. [α]_D²⁰ = +2.4 (c = 0.970, CHCl₃). IR (KBr): $\tilde{\nu}$ = 1648, 1749, 2923, 3028 cm⁻¹. ¹H NMR: δ = 1.69–2.08 (m, 3 H), 2.49–2.68 (m, 1 H), 2.72 (t, J = 7.5 Hz, 3 H), 3.99 (dd, J = 6.1, J = 7.9 Hz, 1 H), 4.06–4.18 (m, 1 H), 4.18–4.30 (m, 1 H), 4.47 (app. t, J = 8.1 Hz, 1 H), 5.63 (dm, J = 10.4 Hz, 1 H), 5.84–5.92 (m, 1 H), 7.20–7.35 (m, 5 H) ppm. ¹³C NMR: δ = 28.3, 32.8, 33.6, 48.0, 49.4, 68.0, 124.7, 126.1, 126.5, 128.5, 128.6, 141.6, 157.9 ppm. HRMS (EI) calcd. for C₁₅H₁₇NO₂ [M⁺] 243.1259, found 243.1264 ppm. HRMS (EI) calcd. for C₁₀H₁₇NO₂ [M⁺] 183.1259, found 183.1258.

(5*R*,8*aR*)-5-Hexyl-4,5,6,8*a*-tetrahydroxazolidino[3,4-*a*]pyridin-3-one (10c): Purification by flash chromatography (15 % EtOAc/petroleum ether) gave **10c** (207 mg, 89 %) as a colorless oil. [α]_D²⁰ = –30.8 (c = 0.684, CHCl₃). IR (KBr): $\tilde{\nu}$ = 1648, 1750, 2927, 3034 cm⁻¹. ¹H NMR: δ = 0.83–0.91 (m, 3 H), 1.26–1.68 (m, 10 H), 1.84–1.96 (m, 1 H), 2.43–2.60 (m, 1 H), 3.95 (dd, J = 6.1, J = 7.8 Hz, 1 H), 3.94–4.06 (m, 1 H), 4.24–4.33 (m, 1 H), 4.47 (dd, J = 7.9, J = 8.7 Hz, 2 H), 5.60 (dm, J = 10.2 Hz, 1 H), 5.79–5.89 (m, 1 H) ppm. ¹³C NMR: δ = 14.2, 22.7, 26.3, 28.2, 29.1, 31.6, 31.8, 48.0, 49.4, 68.0, 124.7, 126.6, 158.0 ppm. HRMS (EI) calcd. for C₁₃H₂₁NO₂ [M⁺] 223.1572, found 223.1583.

(5*R*,8*aR*)-5-Cyclohexyl-4,5,6,8*a*-tetrahydroxazolidino[3,4-*a*]pyridin-3-one (10d): Purification by flash chromatography (20 % EtOAc/petroleum ether) gave **10d** (219 mg, 99 %) as a colorless solid. [α]_D²⁰ = –26.9 (c = 0.975, CHCl₃). M.p. 120 °C. IR (KBr): $\tilde{\nu}$ = 1652, 1747, 2925 cm⁻¹. ¹H NMR: δ = 0.82–1.77 (m, 11 H), 2.18 (dm, J = 18.1 Hz, 1 H), 2.37 (dm, J = 18.1 Hz, 1 H), 3.66 (dd, J = 6.7, J = 10.2 Hz, 1 H), 3.92 (app. t, J = 7.5 Hz, 1 H), 4.26–4.31 (m, 1 H), 4.47 (app. t, J = 8.4 Hz, 1 H), 5.62 (dm, J = 10.2 Hz, 1 H), 5.78–5.88 (m, 1 H) ppm. ¹³C NMR: δ = 25.0, 26.0, 26.0, 26.4, 30.0, 30.7, 37.6, 50.0, 53.1, 68.1, 124.7, 126.6, 158.0 ppm.

(5*R*,8*aR*)-5-Isopropyl-4,5,6,8*a*-tetrahydroxazolidino[3,4-*a*]pyridin-3-one (10e): Purification by flash chromatography (20 % EtOAc/petroleum ether) gave **10e** (177 mg, 98 %) as a colorless oil. [α]_D²⁰ = –69.9 (c = 0.783, CHCl₃). IR (KBr): $\tilde{\nu}$ = 1653, 1750, 2963 cm⁻¹. ¹H NMR: δ = 0.94 (d, J = 6.7 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3 H), 1.70–1.88 (m, 1 H), 2.15 (dm, J = 18.1 Hz, 1 H), 2.40 (dm, J = 18.1 Hz, 1 H), 3.56 (dd, J = 6.9, J = 10.4 Hz, 1 H), 3.91 (dd, J = 6.9, J = 7.9 Hz, 1 H), 4.22–4.33 (m, 1 H), 4.47 (app. t, J = 8.7 Hz, 1 H), 5.61 (dm, J = 10.4 Hz, 1 H), 5.77–5.87 (m, 1 H) ppm. ¹³C NMR: δ = 19.8, 20.2, 25.5, 28.5, 49.9, 54.4, 68.1, 124.7, 126.4, 158.0 ppm. HRMS (EI) calcd. for C₁₀H₁₅NO₂ [M⁺] 181.1102, found 181.1105.

(5*R*,8*aR*)-5-Dodecyl-4,5,6,8*a*-tetrahydroxazolidino[3,4-*a*]pyridin-3-one (10f): Purification by flash chromatography (20 % EtOAc/petroleum ether) gave **10f** (304 mg, 99 %) as a colorless solid. [α]_D²⁰ = –20.7 (c = 1.030, CHCl₃). M.p. 30 °C. IR (KBr): $\tilde{\nu}$ = 1653, 1751, 2924 cm⁻¹. ¹H NMR: δ = 0.88 (t, J = 6.2 Hz, 3 H), 1.25–1.33 (m, 20 H), 1.38–1.46 (m, 1 H), 1.58–1.66 (m, 1 H), 1.91 (dm, J = 18.0 Hz, 1 H), 2.52 (dm, J = 18 Hz, 1 H), 3.96 (dd, J = 6.3, J = 7.9 Hz, 2 H), 4.00–4.06 (m, 1 H), 4.25–4.31 (m, 1 H), 4.48 (app. t, J = 8.2 Hz, 1 H), 5.61 (dm, J = 10.2 Hz, 1 H), 5.81–5.89 (m, 1 H) ppm. ¹³C NMR: δ = 14.2, 22.8, 26.3, 28.2, 29.4, 29.7, 29.8, 31.6, 32.0, 48.1, 49.5, 68.0, 124.7, 126.6, 158.0 ppm.

Hydrogenation of Tetrahydropyridines 10a–f. General Procedure: Pd/C (50.5 mg, 0.05 mmol) was added to a solution of tetrahydropyridines **26–31** (0.5 mmol) in EtOH (7 mL). The mixture was stirred under H₂ for 4 h. The catalyst was removed by filtration to give piperidines **11a–f**.

5(5*R*,8*aR*)-5-Phenyloxazolidino[3,4-*a*]piperidin-3-one (11a): (108 mg, quant.) was isolated as a colorless oil. [α]_D²⁰ = +73.1 (c = 1.380, CHCl₃). IR (KBr): $\tilde{\nu}$ = 1747, 2938 cm⁻¹. ¹H NMR: δ = 1.40–1.54 (m, 2 H), 1.72–1.82 (m, 2 H), 1.91–2.00 (m, 1 H), 2.32–2.40 (m, 1 H), 3.74–3.88 (m, 1 H), 3.97 (dd, J = 5.8, J = 8.5 Hz, 1 H), 4.48 (app. t, J = 8.4 Hz, 1 H), 5.21 (app. d, J = 5.5 Hz, 1 H), 7.23–7.42 (m, 5 H) ppm. ¹³C NMR: δ = 18.4, 27.5, 30.9, 51.2, 51.8, 68.5, 126.5, 127.1, 128.8, 138.7, 157.7 ppm. HRMS (EI) calcd. for C₁₃H₁₅NO₂ [M⁺] 217.1103, found 217.1098.

(5*R*,8*aR*)-5-Phenylethyloxazolidino[3,4-*a*]piperidin-3-one (11b): (122 mg, quant.) was isolated as a colorless oil. [α]_D²⁰ = +60.9 (c = 0.660, CHCl₃). IR (KBr): $\tilde{\nu}$ = 1748, 2938 cm⁻¹. ¹H NMR: δ = 1.26–1.43 (m, 1 H), 1.54–1.83 (m, 6 H), 1.96–2.15 (m, 1 H), 2.55–2.80 (m, 2 H), 3.61–3.75 (m, 1 H), 3.86 (dd, J = 5.3, J = 8.4 Hz, 1 H), 4.00–4.09 (1H), 4.28 (app. t, J = 8.4 Hz, 1 H) ppm. ¹³C NMR: δ = 18.3, 28.0, 31.0, 32.1, 32.9, 49.8, 50.6, 68.3, 126.0, 128.4, 128.5, 141.8, 157.2 ppm. HRMS (EI) calcd. for C₁₅H₁₉NO₂ [M⁺] 245.1416, found 245.1416.

(5*R*,8*aR*)-5-Hexyloxazolidino[3,4-*a*]piperidin-3-one (11c): (112 mg, quant.) was isolated as a colorless oil. [α]_D²⁰ = +18.0 (c = 1.340, CHCl₃). IR (KBr): $\tilde{\nu}$ = 1752, 2928 cm⁻¹. ¹H NMR: δ = 0.83–0.89 (m, 3 H), 1.26–1.33 (m, 10 H), 1.40–1.47 (m, 1 H), 1.57–1.70 (m, 4 H), 1.77–1.81 (m, 1 H), 3.67–3.81 (m, 1 H), 3.86–3.95 (m, 1 H), 3.86 (dd, J = 5.8, J = 8.1 Hz, 1 H), 4.37 (app. t, J = 7.9 Hz, 1 H) ppm. ¹³C NMR: δ = 14.2, 18.2, 22.7, 26.4, 27.6, 29.2, 30.1, 31.1, 31.9, 49.8, 50.7, 68.3, 157.2 ppm. HRMS (EI) calcd. for C₁₃H₂₃NO₂ [M⁺] 225.1724, found 225.1735.

(5*R*,8*aR*)-5-Cyclohexyloxazolidino[3,4-*a*]piperidin-3-one (11d): (108 mg, quant.) was isolated as colorless crystals. [α]_D²⁰ = +19.6 (c = 0.680, CHCl₃). M.p. 68 °C. IR (KBr): $\tilde{\nu}$ = 1759, 2932 cm⁻¹. ¹H NMR: δ = 0.82–1.88 (m, 17 H), 3.51–3.59 (m, 1 H),

3.64–3.78 (m, 1 H), 3.87 (dd, $J = 5.3$, $J = 8.4$ Hz, 1 H), 4.38 (app. t, $J = 8.2$ Hz, 1 H) ppm. ^{13}C NMR: $\delta = 18.4$, 24.9, 26.1, 26.1, 26.2, 29.6, 30.3, 31.3, 36.0, 51.0, 54.9, 68.3, 157.5 ppm.

(5*R*,8*aR*)-5-Isopropylloxazolidino[3,4-*a*]piperidin-3-one (11e): (91 mg, quant.) was isolated as a colorless oil. $[\alpha]_{\text{D}}^{20} = +10.8$ ($c = 0.757$, CHCl_3). IR (KBr): $\tilde{\nu} = 1743$, 2960 cm^{-1} . ^1H NMR: $\delta = 0.89$ (d, $J = 6.6$ Hz, 3 H), 0.91 (d, $J = 6.6$ Hz, 3 H), 1.26–2.02 (m, 7 H), 3.43 (dd, $J = 3.8$, $J = 10.7$ Hz, 1 H), 3.65–3.77 (m, 1 H), 3.85 (dd, $J = 5.2$, $J = 8.4$ Hz, 1 H), 4.36 (app. t, $J = 8.4$ Hz, 1 H) ppm. ^{13}C NMR: $\delta = 18.2$, 19.7, 19.9, 25.3, 26.8, 31.1, 50.8, 56.2, 68.2, 157.4 ppm. HRMS (EI) calcd. for $\text{C}_{10}\text{H}_{17}\text{NO}_2$ [M^+] 183.1259, found 183.1258.

(5*R*,8*aR*)-5-Dodecylloxazolidino[3,4-*a*]piperidin-3-one (11f): (154 mg, quant.) was isolated as colorless crystals. $[\alpha]_{\text{D}}^{20} = +13.1$ ($c = 0.673$, CHCl_3). M.p. 54 °C. IR (KBr): $\tilde{\nu} = 1744$, 2919 cm^{-1} . ^1H NMR δ 0.87 (t, $J = 6.4$ Hz, 3 H), 1.24–1.33 (m, 21 H), 1.41–1.45 (m, 1 H), 1.60–1.70 (m, 5 H), 1.76–1.80 (m, 1 H), 3.73–3.78 (m, 1 H), 3.86 (dd, $J = 5.6$, $J = 8.4$ Hz, 1 H), 3.90–3.94 (m, 1 H), 4.37 (t, $J = 8.4$ Hz, 1 H) ppm. ^{13}C NMR: $\delta = 14.2$, 18.2, 22.8, 26.4, 27.6, 29.5, 29.6, 29.8, 30.2, 31.1, 32.0, 49.8, 50.7, 68.4 ppm.

(5*R*,7*S*,8*R*,8*aR*)-5-Dodecyl-7,8-epoxyoxazolidino[3,4-*a*]piperidine-3-one (12): *m*CPBA (1.93 g, 7.82 mmol) was added to a solution of the tetrahydropyridine **10f** (0.60 g, 1.95 mmol) in CH_2Cl_2 (25 mL) cooled to 0 °C. The solution was stirred for 72 h at room temperature and then hydrolyzed with satd. aqueous NaHCO_3 /10 % aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (1:1) solution. The aqueous phase was extracted with CH_2Cl_2 (3 $\times$), washed with brine, dried with anhydrous MgSO_4 filtered and concentrated in vacuo. Purification by flash chromatography (30 % EtOAc/petroleum ether) gave **12** (0.51 g, 81 %) as colorless crystals which could be recrystallized from pentane. $[\alpha]_{\text{D}}^{20} = +13.5$ ($c = 1.513$, CHCl_3). M.p. 55 °C. IR (KBr): $\tilde{\nu} = 1751$, 2924 cm^{-1} . ^1H NMR: $\delta = 0.87$ (t, $J = 6.1$ Hz, 3 H), 1.24 (br. s, 20 H), 1.39–1.63 (m, 2 H), 1.72 (dd, $J = 6.3$, $J = 15.6$ Hz, 1 H), 2.25 (dd, $J = 7.8$, $J = 15.6$ Hz, 1 H), 3.10 (m, 1 H), 3.31 (app. t, $J = 4.7$ Hz, 1 H), 3.71–3.83 (m, 1 H), 4.10–4.16 (m, 1 H), 4.30 (dd, $J = 5.3$, $J = 8.5$ Hz, 1 H), 4.48 (t, $J = 8.5$ Hz, 1 H) ppm. ^{13}C NMR: $\delta = 14.2$, 22.8, 25.7, 26.1, 29.3, 29.5, 29.7, 29.7, 32.0, 33.0, 45.5, 49.0, 50.0, 50.2, 65.2, 157.6 ppm. $\text{C}_{19}\text{H}_{33}\text{NO}_3$: calcd. C 70.55, H 10.28, N 4.33; found C 70.40, H 10.32, N 4.41.

The *exo* diastereoisomer was obtained only in impure form and was not further characterized.

(5*R*,8*S*,8*aR*)-5-Dodecyl-8-hydroxyoxazolidino[3,4-*a*]piperidine-3-one (13): Super-Hydride® (1 M in THF, 1.86 mL, 1.86 mmol) was added to a solution of the epoxide **12** (200 mg, 0.62 mmol) in THF (9 mL) at 0 °C. The resulting mixture was stirred at room temperature for 2 h, then hydrolyzed with 1 N HCl. The aqueous phase was extracted with Et_2O (3 $\times$). The combined organic extracts were washed with brine, dried with anhydrous MgSO_4 and filtered. Removal of solvent left a solid that was precipitated in pentane to give **13** (197 mg, 98 %) as a white solid. The residue was used without further purification. $[\alpha]_{\text{D}}^{20} = +26.3$ ($c = 0.820$, CHCl_3). M.p. 113 °C. IR (KBr): $\tilde{\nu} = 1715$, 2920, 3397 cm^{-1} . ^1H NMR δ 0.87 (t, $J = 5.5$ Hz, 3 H), 1.25 (br. s, 20 H), 1.40–1.43 (m, 2 H), 1.63–1.65 (m, 1 H), 1.76–1.83 (m, 2 H), 2.02–2.10 (m, 1 H), 3.76 (br. s, 1 H), 3.79–3.82 (m, 1 H), 3.92–3.99 (m, 1 H), 4.30 (t, $J = 8.8$ Hz, 1 H), 4.38 (dd, $J = 5.6$, $J = 8.8$ Hz, 1 H) ppm. ^{13}C NMR: $\delta = 14.3$, 20.7, 22.8, 25.7, 26.5, 29.5, 29.6, 29.7, 29.8, 29.9, 32.1, 49.2, 54.1, 63.9, 64.5, 157.9 ppm. $\text{C}_{19}\text{H}_{35}\text{NO}_3$: calcd. C 70.11, H 10.84, N 4.30; found C 70.06, H 10.96, N 4.37.

(–)-3-*epi*-Deoxoprosopine (2): A solution of the oxazolidinone **13** (150 mg, 0.46 mmol) in MeOH (7.5 mL) and 8 N NaOH (3 mL) was heated at 100 °C for 18 h. The mixture was extracted with CH_2Cl_2 (3 $\times$), washed with brine, dried with anhydrous MgSO_4 and concentrated under reduced pressure. The residue was crystallized from acetone / pentane to give pure (–)-3-*epi*-deoxoprosopine (124 mg, 90 %) as a colorless solid. $[\alpha]_{\text{D}}^{20} = -3.4$ ($c = 1.957$, CHCl_3). M.p. 64 °C. IR (KBr): $\tilde{\nu} = 2925$, 3335 cm^{-1} . ^1H NMR: $\delta = 0.87$ (t, $J = 6.8$ Hz, 3 H), 1.25 (br. s, 21 H), 1.40 (m, 1 H), 1.50 (m, 1 H), 1.64–1.66 (m, 1 H), 1.75–1.80 (m, 1 H), 1.90–1.94 (m, 1 H), 2.86–2.88 (m, 1 H), 3.10 (m, 1 H), 3.17 (br. s, 3 H), 3.72 (dd, $J = 7.6$, $J = 11$ Hz, 1 H), 3.84 (dd, $J = 5.2$, $J = 11$ Hz, 1 H), 3.92–3.94 (m, 1 H) ppm. ^{13}C NMR: $\delta = 4.2$, 22.8, 26.3, 26.7, 27.7, 29.5, 29.8, 32.1, 32.7, 50.6, 55.6, 61.4, 67.8 ppm.

X-ray Crystallographic Study: Data were collected on an Enraf–Nonius Kappa CCD diffractometer at 123 K using graphite-monochromated Mo- K_α radiation ($\lambda = 0.71073$ Å, and ω scans). The structure was solved by direct methods using the program SHELXS-97^[24] and refined by full-matrix least-squares refinement on F^2 using the program SHELXL-97.^[25] Non-hydrogen atoms were refined anisotropically. The hydrogen atoms, all visible from the difference Fourier map, were placed in geometrically calculated positions and included in the final refinement using the “riding” model with isotropic temperature factors fixed at 1.2-times that of the parent atom.

Crystal Data for 13: $\text{C}_{19}\text{H}_{35}\text{NO}_3$, $M_r = 325.48$, monoclinic, space group $P2_1$, $a = 6.4649(11)$, $b = 8.6141(12)$, $c = 17.005(2)$ Å, $\beta = 100.092(7)^\circ$, $V = 932.4(2)$ Å³, $Z = 2$, $D_{\text{calcd.}} = 1.159$ g·cm^{–3}, $\mu(\text{Mo-}K_\alpha) = 0.077$ mm^{–1}. Of 12671 reflections measured, 3790 were unique ($R_{\text{int}} = 0.036$), with 2058 having $I = 2\sigma(I)$, R indices [$I = 2\sigma(I)$] $R_1 = 0.0680$, $wR_2 = 0.1528$, GoF on $F^2 = 1.032$ for 209 refined parameters and 1 restraint.

CCDC-213577 (**13**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

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