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N-Tritylprolinal: An Efficient Building Block for the Stereoselective Synthesis of Proline-Derived Amino Alcohols

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N-Tritylprolinal (prepared in four steps from L-proline) shows a very high Felkin diastereoselectivity in its reaction with various nucleophiles, leading to a straightforward and highly stereoselective access to *syn*-proline-derived amino alcohols.

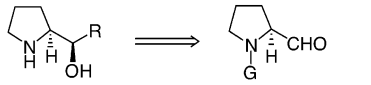
Introduction

1,2-Amino alcohols constitute a large class of structures which have been widely used in organic synthesis and catalysis. Among these, prolinol derivatives **1** have received considerable interest due to their efficiency as ligands in organometallic chemistry[1] as well as structural targets in several biologically interesting molecules such as dolastatine,[2] detoxins,[3] and serine protease inhibitors.[4] These prolinol derivatives are generally prepared by nucleophilic addition to N-protected prolinals such as **2a**−**d** bearing a benzyl or a carbalkoxy protecting group on the nitrogen atom (Scheme 1).

However, the addition of organometallic nucleophiles on the aldehyde **2a** usually shows[5] a low diastereoselectivity. The same behavior is observed with aldehydes **2b**,[3,4,6] **2c**,[3,7] and **2d**.[8] However, good stereoselectivities can be achieved by means of double diastereoselection.[9] The syn adduct **3** (Scheme 2) is obtained generally as the major diastereomer, but some examples are reported where the anti adduct **4** is mainly obtained.

We report here our results concerning the synthesis of enantiomerically pure *N*-tritylprolinal **2e**[10] and its reactions with various nucleophiles.

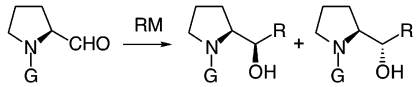
SCHEME 1



1

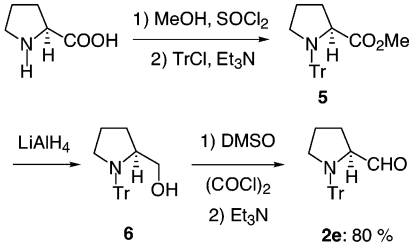
2a: G = Bn
2b: G = Boc
2c: G = Cbz
2d: G = CO_2Me
2e: G = Trityl (Tr)

SCHEME 2



2a-d **3** **4**

SCHEME 3



Results

The aldehyde **2e** was prepared on a large scale and in a good overall yield (80%) starting from L-proline following the four-step sequence depicted in the Scheme 3. All attempts to reduce directly the ester **5** into **2e** (DIBAL-H in various solvents) were unsuccessful.

Aldehyde **2e** was obtained as an amorphous powder. Its enantiomeric purity was ascertained by its reaction with the two enantiomerically pure diamines **7a** and **7b** (Scheme 4).[11] The two corresponding aminals **8a** and **8b** were obtained as a single product (based on ^{1}H NMR), showing that the enantiomeric purity of the aldehyde **2e** is >95% ee. This enantiomeric purity is remarkably stable in time, as no racemization was detected after 15 days at room temperature.[12]

Having in hand an efficient synthesis of aldehyde **2e**, we turned then to its reactions with organometallic nucleophiles. Our results are reported in Table 1.

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(1) See, for example: Soai K.; Ookawa, A.; Ogawa, K.; Kaba, T. *J. Chem. Soc., Chem. Commun.* **1987**, 467−468. Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 769−573. Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824.

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SCHEME 4

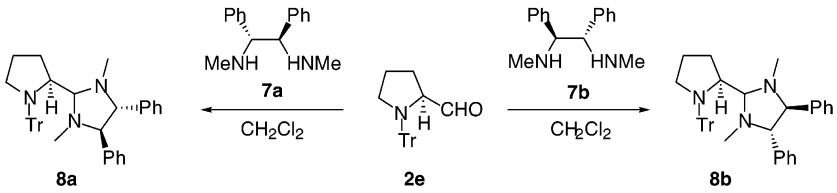
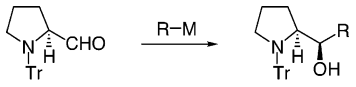


TABLE 1. Reaction of *N*-Tritylprolinal 2e with Various Nucleophiles



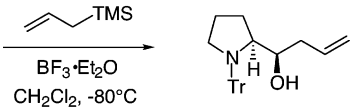
2e **9a-g**

entry	R-M	solvent	*T* (°C)	product	yield[a] (%)	dr[b]
1	*n*-BuLi	Et_2O	−80	**9a**	65	93/7
2	*n*-BuLi	THF	−80	**9a**	n.d.[c]	86/14
3	*n*-BuLi	THF	−30	**9a**	n.d.[c]	70/30
4	*n*-BuMgBr	Et_2O	−80	**9a**	78	>98/2
5	MeMgCl	Et_2O	−80	**9b**	90	>98/2
6	*i*PrMgBr	Et_2O	−80	**9c**	76	>98/2
7	vinylMgCl	Et_2O	−80	**9d**	94	>98/2
8	TMS−CC−Li	Et_2O	−80	**9e**	88	>98/2
9	PhMgBr	Et_2O	−80	**9f**	90	>98/2
10	PhMgCl	Et_2O/THF[d]	−80	**9f**	88	>98/2
11	AllylMgBr	Et_2O	−80	**9g**	85[e]	63/37
12	AllylMgBr	THF	−80	**9g**	92[e]	50/50

[a] Isolated yield in the major product after flash chromatography. [b] Diastereomeric ratio measured by ^{1}H NMR on the crude material. [c] Not determined. [d] Et_2O/THF 10/1. [e] Isolated yield in the diastereomer mixture.

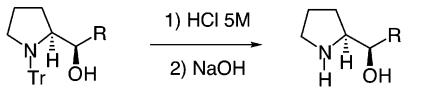
As can be seen in Table 1, the diastereoselectivity is excellent in most cases when the reaction is conducted in ether at low temperature. Only one diastereomer could be detected by ^{1}H NMR, except in the case of of *n*-BuLi (entry 1), where the diastereoselectivity is slightly lower, and in the case of allylMgBr which showed a low stereoselectivity (entry 11). The reasons for this drop in diastereoselectivity are still unclear, but this problem could be overcome by using the Sakurai reaction,[13] as depicted in Scheme 5. The compound **9g** was obtained as only one diastereomer.

SCHEME 5



9g, 63 %, d.r. > 98 / 2

SCHEME 6



9b: R = Me
9c: R = *i*Pr
9f: R = Ph
9g: R = Allyl

10: R = Me, 66%
11: R = *i*Pr, 82%
12: R = Ph, 86%
13: R = Allyl, 81%

One of the main interests of this methodology is the ease in removing the trityl protecting group. In our case, a simple treatment with aqueous HCl (6 N) gave, after neutralization, the corresponding amino alcohols **10**−**13** (Scheme 6) in good yields without any detectable dehydration product. Physical data (mp, $[\alpha]^{24}_D$, and ^{1}H NMR) for compound **10** were found to be identical to those reported in the litterature,[14] thus confirming the relative and absolute configurations in **9b**. ^{1}H NMR data for compound **12** were found also to be identical to literature data.[8c]

The relative configurations were ascertained for compounds **9a**, **9f**, and **9g** as described in Scheme 7. Com-

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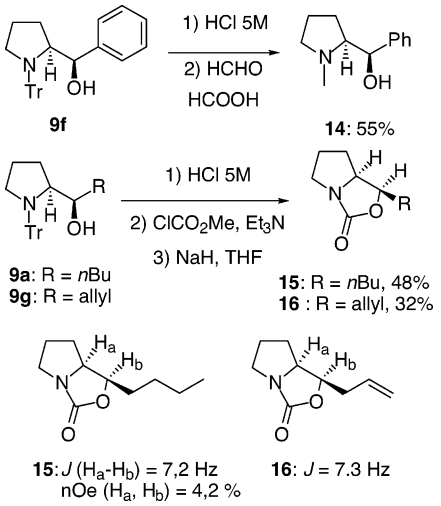
(11) Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 2677−2680.

(12) *N*-Tritylamino aldehydes have been reported to be of high configurational stability: Dellaria, J. F., Jr.; Maki, R. J.; Stein, H. H.; Cohen, J.; Whittern, D.; Marsh, K.; Hoffman, D. J.; Plattner, J. J.; Perun, T. J. *J. Med. Chem.* **1990**, *33*, 534−542. Thaisrivongs, S.; Pals, D. T.; Kroll, L. T.; Turner, S. R.; Han, F.-S. *J. Med. Chem.* **1987**, *30*, 976−982.

SCHEME 7

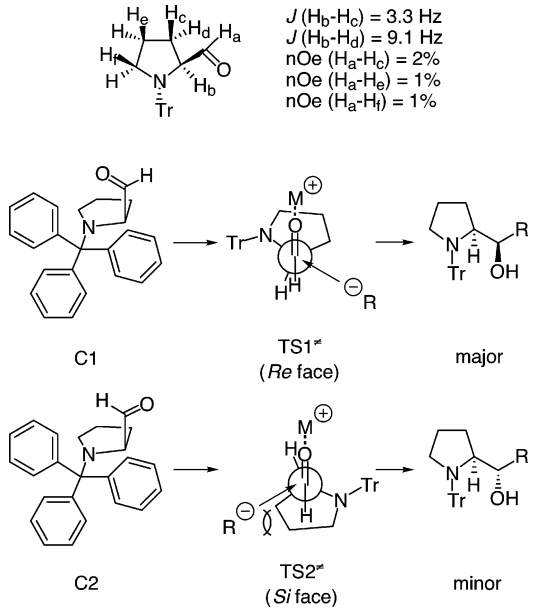


pound **9f** gave the amino alcohol **14** in 55% overall yield upon detritylation and *N*-methylation. Comparison of its spectral data ($[\alpha]^{24}_D$ and ^{1}H NMR) with those reported in the literature[15] confirmed the relative and absolute configurations (ee > 98%) of **9f**. Compounds **9a** and **9g** were transformed into the corresponding oxazolidinones **15** and **16** by detritylation, reaction with methylchloroformate, and ring closure. NMR experiments (coupling constants measurements and NOE effects) showed unambiguously the cis relationship between the two vicinal protons and then the relative configurations of the starting materials.

Discussion

It has been shown recently[16] that in the reduction of aminoketones the presence of a trityl group on nitrogen atom prevents any chelation due to important steric crowd. However, in the case of *N*-tritylaziridinyl aldehydes, an organometallic chelation to nitrogen bearing a sterically hindered trityl group has been reported.[17] In our case, the fact that the reaction of **2e** with allylsilane in the presence of $BF_3{\cdot}Et_2O$ (monodentate Lewis acid) shows the same stereoselectivity as the reactions with lithium or Grignard reagents provides a good indication of a general nonchelate transition state. Examination of the ^{1}H NMR spectrum for the aldehyde **2e** shows nontypical coupling constants between the proton H_b (α to the carbonyl moiety) and the two vicinal protons H_c and H_d (Scheme 7); the *pseudo*axial position of the carbonyl group was evidenced by NOE effects between H_a and H_c, H_e and H_f. This *pseudo*axial position was

SCHEME 8



confirmed by PM3 calculations[18] which show also that the trityl group adopts a position trans to the carbonyl moiety (Scheme 8).

In such a conformation, two possible reactive conformers can be involved. The first one (C1 in the Scheme 8) presents the carbonyl group lying over the five-membered ring. In such a conformation, the *Si* face is masked by the trityl group, and a nucleophilic attack (TS1‡ in Scheme 8) on the *Re* face gives the observed major product. This transition state is slightly different from a Felkin−Anh classical transition state (the dihedral angle of carbonyl and amino groups is not ca. 90°), but resembles merely to the transition states proposed in the reductions of α-*N*-tritylamino ketones.[16] The other possible conformation with the *pseudo*axial carbonyl moiety lying out of the five-membered ring (C2 in Scheme 8) leads to an attack of the organometallic species hindered by the five-membered ring. The transition state (TS2‡ in Scheme 8) obtained from this conformer is then higher in energy and the corresponding product is not or little observed.

In conclusion, we have disclosed a high stereoselective synthesis of substituted prolinols by using the (2*S*)-*N*-tritylprolinal. This aldehyde has been prepared from L-proline in three steps with a 80% overall yield. It shows a remarkable stability toward epimerization as well as an efficient stereocontrol in its reactions with various organometallic species. Further advances in this field as well as applications in organic synthesis will be reported in due course.

Experimental Section

(2*S*)-1-Triphenylmethyl-2-pyrrolidinecarboxylic Acid Methyl Ester 5. To a solution of l-proline (11.51 g, 100 mmol) in methanol (100 mL) was added thionyl chloride (23.80 g, 14.50 mL, 200 mmol) at −10 °C. After addition, the reaction mixture was allowed to warm to room temperature. After 18 h stirring, the solvent and other volatile compounds were

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(15) Compound **14** and its OH-epimer are reported; see ref 8a.

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(18) PM3 calculations were conducted using CS ChemBats3D Pro v5.0 (CambridgeSoft Corp.).

removed in vacuo. The resulting intermediate was dissolved in $CHCl_3$ (120 mL), and Et_3N (41.85 mL, 300 mmol) was added, followed by trityl chloride (27.92 g, 100 mmol) in $CHCl_3$ (50 mL). The reaction mixture was stirred for 18 h at room temperature and hydrolyzed with a 2:1 mixture of saturated aqueous NH_4Cl solution and NH_3 (28% in water). After the layers were separated, the aqueous one was extracted twice with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Recrystallization from Et_2O afforded the title compound (33.46 g, 90%) as a white solid. Mp: 119−120 °C. $[\alpha]^{20}_D = -42.0$ ($c = 2.70$, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3040, 2930, 2850, 2240, 1950, 1890, 1810, 1710, 1585, 1480, 1440, 1270, 1150, 900, 695. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.89−1.08 (m, 2H), 1.48−1.66 (m, 2H), 2.86 (dt, $^2J = 11.2$ Hz, $^3J = 7.1$ Hz, 1H), 3.43 (ddd, $^2J = 11.2$ Hz, $^3J = 8.1$, 5.1 Hz, 1H), 3.69 (s, 3H), 3.92 (dd, $^3J = 8.6$, 2.0 Hz, 1H), 7.16 (t, $^3J = 7.4$ Hz, 3H), 7.26 (t, $^3J = 7.6$ Hz, 6H), 7.59 (d, $^3J = 6.8$ Hz, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 24.4, 31.3, 44.0, 51.7, 62.8, 77.5, 126.2, 127.7, 129.3, 144.76, 177.3. Anal. Calcd for $C_{25}H_{25}NO_2$ (MW 371.47): C, 80.83; H, 6.78; N, 3.77. Found: C, 80.49; H, 6.78; N, 3.59.

(2*S*)-1-Triphenylmethyl-2-pyrrolidinemethanol 6. Ester **5** (14.84 g, 40 mmol) dissolved in dry THF (50 mL) was added dropwise under an argon atmosphere to a suspension of $LiAlH_4$ (1.21 g, 32 mmol) in dry THF (30 mL) at room temperature. The reaction course was monitored by TLC, and once all the starting material was consumed (2 h at room temperature), the mixture was quenched dropwise under vigorous stirring with an aqueous solution of sodium potassium tartrate (50 mL, 1 M). Et_2O (50 mL) was added, the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over anhydrous $MgSO_4$. Removal of solvents in vacuo yielded the title compound as a white foam (13.39 g, 97%) which was used without further purification. For analytical purposes, **6** was purified by flash column chromatography on silica gel (cyclohexane/EtOAc/Et_3N, 9/1/0.2). Mp: 55−56 °C. $[\alpha]^{20}_D = +44.0$ ($c = 2.20$, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3400, 3060, 2960, 2870, 1950, 1820, 1590, 1490, 1450, 1020, 900, 700. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.54−0.65 (m, 1H), 0.92−1.93 (m, 1H), 1.37−1.47 (m, 2H), 2.36 (bs, 1H), 3.00 (ddd, $^2J = 12.5$ Hz, $^3J = 4.1$, 8.4 Hz, 1H), 3.17−3.24 (m, 1H), 3.47−3.52 (m, 1H), 3.56 (dd, $^2J = 10.0$ Hz, $^3J = 7.3$ Hz, 1H), 3.66 (dd, $^2J = 9.9$ Hz, $^3J = 3.8$ Hz, 1H), 7.19 (t, $^3J = 7.6$ Hz, 3H), 7.27 (t, $^3J = 7.6$ Hz, 6H), 7.62 (d, $^3J = 7.6$ Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.2, 29.2, 51.0, 61.3, 65.9, 77.7, 126.3, 127.7, 129.7, 145.2. HRMS: calcd for $C_{24}H_{26}NO$ (MH^+) 344.2014, found 344.2018.

(2*S*)-1-Triphenylmethyl-2-pyrrolidinemethanal 2e. To a solution of $(COCl)_2$ (3.5 mL, 40 mmol) in dry CH_2Cl_2 (35 mL) under argon was added dropwise at −80 °C a solution of DMSO (5.7 mL, 80 mmol) in CH_2Cl_2 (15 mL). After 10 min, the alcohol **6** (13.39 g, 38.9 mmol) dissolved in CH_2Cl_2 (35 mL) was added dropwise at −80 °C. After 1.5 h stirring at this temperature, Et_3N (22.5 mL, 160 mmol) was added. After 1.5 h stirring at −80 °C, the reaction was hydrolyzed with a 2:1 mixture of a saturated aqueous NH_4Cl solution and NH_3 (28% in water). The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over anhydrous $MgSO_4$ and the volatile compounds removed in vacuo. The solid obtained was dissolved in THF and filtered, and the solvent removed under reduced pressure to give, after recrystallization from ether, the title compound (12.59 g, 92%) as a white solid. Mp: 140−141 °C dec. $[\alpha]^{20}_D = -15.2$ ($c = 2.54$, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3060, 2960, 2860, 2800, 2700, 1960, 1900, 1815, 1715, 1595, 1490, 1450, 900, 705. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.76−0.86 (m, 1H), 1.14 (ddd, $^2J = 16.8$ Hz, $^3J = 12.7$, 8.7 Hz, 1H), 1.39−1.49 (m, 1H), 1.62 (ddd, $^2J = 16.8$ Hz, $^3J = 8.2$, 4.1 Hz, 1H), 2.94 (ddd, $^2J = 11.7$ Hz, $^3J = 7.1$, 4.1 Hz, 1H), 3.31 (dt, $^2J = 11.7$ Hz, $^3J = 7.1$ Hz, 1H), 3.79 (dt, $^3J = 9.1$, 3.3 Hz, 1H), 7.20 (t, $^3J = 7.4$ Hz, 3H), 7.30 (t, $^3J = 7.6$ Hz, 6H), 7.59 (d, $^3J = 7.6$ Hz, 6H), 9.88 (d, $^3J = 2.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.4, 28.1, 50.7, 68.5, 77.0, 126.5, 127.8, 129.5, 144.5, 204.4. Anal. Calcd for $C_{24}H_{23}NO$ (MW 341.45): C, 84.42; H, 6.79; N, 4.10. Found: C, 84.41; H, 6.87; N, 4.12.

(2*S*,4′*R*,5′*R*)-2-(1,3-Dimethyl-4,5-diphenylimidazolidin-2-yl)-*N*-tritylpyrrolidine 8a. The aldehyde **2e** (50 mg, 0.146 mmol) was kept reacting with the (*R*,*R*)-*N*,*N*′-dimethyl-1,2-diphenylethylenediamine **7a** (35 mg, 0.146 mmol) in CH_2Cl_2 (3 mL) in the presence of 4 Å molecular sieves. After 20 h of stirring at room temperature, the reaction mixture was filtered and the solvent evaporated under reduced pressure to afford quantitatively the aminal **8a** as a white solid. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.23−0.34 (m, 1H), 1.06−1.20 (m, 1H), 1.47−1.69 (m, 1H), 1.75−1.85 (m, 1H), 1.88 (s, 3H), 2.85 (s, 3H), 3.10 (t, $J = 9.7$ Hz, 1H), 3.35−3.43 (m, 1H), 3.58 (d, $^3J = 8.6$ Hz, 1H), 3.76 (d, $^3J = 8.3$ Hz, 1H), 3.85 (d, $^3J = 8.3$ Hz, 1H), 4.62 (bs, 1H), 7.03−7.33 (m, 19H), 7.62 (d, $^3J = 7.6$ Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.7, 27.8, 33.2, 42.3, 51.9, 65.3, 75.7, 78.9, 79.5, 86.9, 126.2, 127.2, 127.5, 127.7, 127.7, 128.1, 128.2, 128.6, 128.0, 140.0, 140.2, 145.8.

(2*S*,4′*S*,5′*S*)-2-(1,3-Dimethyl-4,5-diphenylimidazolidin-2-yl)-*N*-tritylpyrrolidine 8b. The aminal **8b** was prepared quantitatively by the same procedure described for **8a** using (*S*,*S*)-*N*,*N*′-dimethyl-1,2-diphenylethylenediamine **7b** as a white solid. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.26−0.39 (m, 1H), 1.06−1.21 (m, 1H), 1.42−1.54 (m, 1H), 1.93 (s, 3H), 1.89−2.04 (m, 1H), 2.46 (s, 3H), 3.00 (t, $J = 9.7$ Hz, 1H), 3.16−3.39 (m, 1H), 3.70 (d, $^3J = 9.6$ Hz, 1H), 3.68−3.75 (m, 1H), 3.90 (d, $^3J = 1.5$ Hz, 1H), 4.15 (d, $^3J = 9.4$ Hz, 1H), 7.10−7.36 (m, 19H), 7.61 (d, $^3J = 7.6$ Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.6, 27.0, 38.6, 40.0, 51.5, 64.0, 73.0, 75.2, 78.6, 93.0, 126.1, 127.3, 127.5, 127.6, 128.0, 128.1, 128.3, 130.0, 130.4, 136.8, 140.3, 145.8.

General Procedure for Compounds 9a−f. To the aldehyde **2e** (0.341 g, 1 mmol) in dry Et_2O (10 mL) under argon was added the organometallic solution (2 mmol) at −80 °C. The reaction was followed by TLC. After 5 h of stirring, the reaction was hydrolyzed at −80 °C with a 2:1 mixture of a saturated aqueous NH_4Cl solution and NH_3 (28% in water). The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over anhydrous $MgSO_4$ and the solvents removed in vacuo. The resulting solid was purified by flash column chromatography on silica gel (cyclohexane/EtOAc/Et_3N, 9/1/0.2) to afford compounds **9a**−**f**.

(α*R*,2*S*)-α-(1-Butyl)-1-triphenylmethyl-2-pyrrolidinemethanol 9a. Prepared from *n*-BuMgCl (2 mmol, 1.35 mL, 1.48M in ether) in 78% yield (0.307 g). Mp: 86−87 °C. $[\alpha]^{20}_D = -7.8$ ($c = 2.08$, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3420, 3050, 3000, 2930, 2860, 1950, 1815, 1710, 1590, 1485, 1445, 1075, 1030, 1000, 900, 705. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.16 (dquin, $^2J = 11.9$ Hz, $^3J = 8.6$ Hz, 1H), 1.08−1.41 (m, 8H), 1.62 (ddt, $^2J = 12.5$ Hz, $^3J = 8.6$, 5.9 Hz, 1H), 0.83 (t, $^3J = 6.9$ Hz, 3H,), 2.87 (bs, 1H), 3.02 (ddd, $^2J = 11.7$ Hz, $^3J = 8.1$, 3.3 Hz, 1H), 3.16 (ddd, $^2J = 11.9$ Hz, $^3J = 7.0$, 9.4 Hz, 1H), 3.38 (ddd, $^3J = 8.6$, 5.6, 3.1 Hz, 1H), 3.92−3.88 (m, 1H), 7.18 (t, $^3J = 7.4$ Hz, 3H), 7.26 (t, $^3J = 7.6$ Hz, 6H), 7.55 (d, $^3J = 7.1$ Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 22.7, 25.1, 25.2, 28.5, 33.0, 53.3, 64.2, 74.3, 78.2, 126.3, 127.6, 130.0, 144.8. Anal. Calcd for $C_{28}H_{33}NO$ (MW 399.57): C, 84.17; H, 8.32; N, 3.51. Found: C, 84.14; H, 8.42; N, 3.51.

(α*R*,2*S*)-α-Methyl-1-triphenylmethyl-2-pyrrolidinemethanol 9b. Prepared from CH_3MgCl (2 mmol, 0.66 mL, 3.0 M in THF) in 90% yield (0.323 g). Mp: 52−53 °C. $[\alpha]^{20}_D = +24.4$ ($c = 2.25$, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3400, 3060, 2960, 2860, 1590, 1490, 1445, 900, 700. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.11 (dquin, $^2J = 11.8$ Hz, $^3J = 8.9$ Hz, 1H), 1.08 (ddt, $^2J = 12.9$ Hz, $^3J = 8.6$, 4.2 Hz, 1H), 1.20−1.28 (m, 1H), 1.60 (ddt, $^2J = 12.7$ Hz, $^3J = 8.6$, 5.8 Hz, 1H), 0.91 (d, $^3J = 6.4$ Hz, 3H), 2.90 (bs, 1H), 2.99 (ddd, $^2J = 12.0$ Hz, $^3J = 8.4$, 3.1 Hz, 1H), 3.13 (ddd, $^2J = 11.9$ Hz, $^3J = 9.4$, 6.9 Hz, 1H), 3.30 (ddd, $^3J = 8.9$, 6.1, 3.0 Hz, 1H), 4.06 (dq, $^3J = 3.1$, 6.4 Hz, 1H), 7.13 (t, $^3J = 6.6$ Hz, 3H), 7.22 (t, $^3J = 7.6$ Hz, 6H), 7.52 (d, $^3J = 8.1$ Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.8, 24.9, 25.0, 53.2, 65.1,

69.8, 78.2, 126.3, 127.6, 129.9, 144.8. Anal. Calcd for $C_{25}H_{27}NO$ (MW 357.49): C, 83.99; H, 7.61; N, 3.92. Found: C, 83.90; H, 7.78; N, 3.79.

(α*R*,2*S*)-α-(1-Methylethyl)-1-triphenylmethyl-2-pyrrolidinemethanol 9c. Prepared from *i*-PrMgCl (2 mmol, 1.29 mL, 1.55 M in ether) in 76% yield (0.292 g). Mp: 124−125 °C. $[\alpha]^{20}_D = -1.7$ ($c = 2.06$, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3400, 3060, 2960, 2860, 1950, 1590, 1490, 1470, 1445, 1000, 900, 710. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.18 (sext, $J = 9.2$ Hz, 1H), 1.16−1.32 (m, 2H), 1.43−1.52 (m, 1H), 1.59−1.68 (m, 1H), 0.57 (d, $^3J = 6.6$ Hz, 3H), 0.97 (d, $^3J = 6.6$ Hz, 3H), 3.00−3.06 (bs, 1H), 3.03 (ddd, $^2J = 11.9$ Hz, $^3J = 7.4$, 2.6 Hz, 1H), 3.17 (ddd, $^2J = 12.0$ Hz, $^3J = 9.7$, 6.6 Hz, 1H), 3.45 (dd, $^3J = 9.4$, 2.8 Hz, 1H), 3.58 (ddd, $^3J = 8.6$, 5.8, 2.8 Hz, 1H), 7.18 (t, $^3J = 7.4$ Hz, 3H), 7.26 (t, $^3J = 7.6$ Hz, 6H), 7.55 (d, $^3J = 7.1$ Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.5, 20.5, 25.0, 25.1, 31.0, 53.4, 62.6, 78.3, 80.3, 126.3, 127.6, 130.0, 144.7. Anal. Calcd for $C_{27}H_{31}NO$ (MW 385.54): C, 84.11; H, 8.10; N, 3.63. Found: C, 84.22; H, 8.15; N, 3.49.

(α*R*,2*S*)-α-Ethenyl-1-triphenylmethyl-2-pyrrolidinemethanol 9d. Prepared from vinylMgCl (2 mmol, 1.19 mL, 1.8 M in THF) in 94% yield (0.348 g). Mp: 50−51 °C. $[\alpha]^{20}_D = -20.5$ ($c = 2.09$, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3400, 3040, 2960, 2860, 1950, 1590, 1490, 1445, 1000, 925, 900, 710. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.19 (dquin, $^2J = 11.8$ Hz, $^3J = 8.9$ Hz, 1H), 1.06−1.14 (m, 1H), 1.25−1.33 (m, 1H), 1.55−1.64 (m, 1H), 3.03 (ddd, $^2J = 11.7$ Hz, $^3J = 7.9$, 3.6 Hz, 1H), 3.20 (ddd, $^2J = 12.2$ Hz, $^3J = 9.3$, 7.0 Hz, 1H), 3.16 (bs, 1H), 3.50 (ddd, $^3J = 8.9$, 5.6, 3.4 Hz, 1H), 4.44−4.47 (m, 1H), 5.06 (dt, $^2J = {}^4J = 1.5$, 2.0 Hz, $^3J = 10.7$ Hz, 1H), 5.18 (dt, $^2J = {}^4J = 1.5$, 2.0 Hz, $^3J = 17.3$ Hz, 1H), 5.65 (ddd, $^3J = 17.3$, 10.7, 5.1 Hz, 1H), 7.19 (t, $^3J = 7.1$ Hz, 3H), 7.27 (t, $^3J = 7.6$ Hz, 6H), 7.57 (d, $^3J = 7.1$ Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.9, 26.2, 53.2, 64.2, 75.1, 78.3, 114.7, 126.4, 127.7, 130.0, 138.2, 144.7. Anal. Calcd for $C_{26}H_{27}NO$ (MW 369.50): C, 84.51; H, 7.37; N, 3.79. Found: C, 84.51; H, 7.38; N, 3.56.

(α*R*,2*S*)-α-(2-Trimethylsilylethynyl)-1-triphenylmethyl-2-pyrrolidinemethanol 9e. Prepared from aldehyde **5e** (1,-02 g, 3 mmol) in ether (30 mL) and lithium trimethylsilylacetylide (9 mmol, 0.58 M in THF) in 88% yield (1.165 g). Lithium trimethylsilylacetylide was obtained from trimethylsilylacetylene (1.12 g, 11.4 mmol) in THF (12 mL) and *n*-BuLi (9 mmol, 3.6 mL of a 2.5 M solution in hexane). Mp: 70−71 °C. $[\alpha]^{20}_D = -69.5$ ($c = 2.05$, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3400, 3060, 2950, 2160, 1945, 1590, 1485, 1440, 1245, 1000, 900, 845, 705. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.15 (s, 9H), 0.20−0.31 (m, 1H), 1.31−1.42 (m, 2H), 1.90−1.99 (m, 1H), 3.05 (ddd, $^2J = 11.8$ Hz, $^3J = 8.3$, 3.4 Hz, 1H), 3.24 (ddd, $^2J = 11.8$ Hz, $^3J = 9.0$, 6.7 Hz, 1H), 3.38 (bs, 1H), 3.64 (ddd, $^3J = 8.4$, 4.6, 4.1 Hz, 1H), 4.61 (d, $^3J = 4.1$ Hz, 1H), 7.19 (t, $^3J = 7.1$ Hz, 3H), 7.28 (t, $^3J = 7.9$ Hz, 6H), 7.54 (d, $^3J = 8.1$ Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −0.0, 24.8, 28.1, 53.4, 64.0, 66.1, 78.2, 91.1, 105.3, 126.5, 127.8, 129.8, 144.5. Anal. Calcd for $C_{29}H_{33}NOSi$ (MW 439.66): C, 79.22; H, 7.57; N, 3.19. Found: C, 79.03; H, 7.74; N, 3.18.

(α*R*,2*S*)-α-Phenyl-1-triphenylmethyl-2-pyrrolidinemethanol 9f. Prepared from C_6H_5MgBr (2 mmol, 1.21 mL, 1.65 M in ether) in 90% yield (0.378 g). Mp: 71−72 °C. $[\alpha]^{20}_D = -77.8$ ($c = 2.29$, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3400, 3060, 2940, 2860, 1945, 1810, 1590, 1480, 1440, 1315, 1170, 1080, 1000, 900, 700. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.26 (dquin, $^2J = 11.7$ Hz, $^3J = 8.6$ Hz, 1H), 0.084 (ddt, $^2J = 13.2$ Hz, $^3J = 8.6$, 4.6 Hz, 1H), 1.32−1.40 (m, 1H), 1.49 (ddt, $^2J = 12.7$ Hz, $^3J = 8.1$, 5.1 Hz, 1H), 3.09 (ddd, $^2J = 11.7$ Hz, $^3J = 8.1$, 3.6 Hz, 1H), 3.34 (ddd, $^2J = 12.2$ Hz, $^3J = 8.9$, 6.9 Hz, 1H), 3.34 (bs, 1H), 3.78 (ddd, $^3J = 8.7$, 5.1, 3.6 Hz, 1H), 5.17 (d, $^3J = 3.6$ Hz, 1H), 7.14 (d, $^3J = 7.1$ Hz, 2H), 7.18−7.34 (m, 12H), 7.65 (d, $^3J = 7.6$ Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.9, 25.8, 53.4, 66.1, 75.7, 78.3, 125.5, 128.1, 126.5, 126.6, 127.7, 130.0, 142.3, 144.7. Anal. Calcd for $C_{30}H_{29}NO$ (MW 419.56): C, 85.88; H, 6.97; N, 3.34. Found: C, 85.70; H, 7.09; N, 3.18.

(α*R*,2*S*)-α-(2-Propenyl)-1-triphenylmethyl-2-pyrrolidinemethanol 9g. To the aldehyde (0.511 g, 1.5 mmol) in dry CH_2Cl_2 (15 mL) under argon was added allyltrimethylsilane (3 mmol, 0.48 mL) followed by $BF_3{\cdot}Et_2O$ (1.5 mmol, 0.19 mL) at −80 °C. The reaction was followed by TLC. After 5 h of stirring at the same temperature, the reaction was hydrolyzed with a 2:1 mixture of a saturated aqueous NH_4Cl solution and NH_3 (28% in water). The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over anhydrous $MgSO_4$ and the solvents removed in vacuo. The solid obtained was purified by flash column chromatography on silica gel (cyclohexane/EtOAc/Et_3N, 9/1/0.2) to afford the title product (0.364 g, 63%) as white solid. Mp: 40−41 °C. $[\alpha]^{20}_D = -7.8$ ($c = 1.50$, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3400, 3040, 2930, 2860, 1940, 1810, 1710, 1630, 1590, 1480, 1440, 1200, 1000, 900, 710. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.15 (dquin, $^2J = 11.7$ Hz, $^3J = 8.8$ Hz, 1H), 1.09 (ddt, $^2J = 12.9$ Hz, $^3J = 8.6$, 4.2 Hz, 1H), 1.21−1.30 (m, 1H), 1.59 (ddt, $^2J = 12.2$ Hz, $^3J = 8.6$, 5.6 Hz, 1H), 1.89 (ddd, $^2J = 12.7$ Hz, $^3J = 6.6$, 5.6 Hz, 1H), 2.10 (ddd, $^2J = 12.7$ Hz, $^3J = 8.2$, 7.1 Hz, 1H), 2.78 (bs, 1H), 2.98 (ddd, $^2J = 12.2$ Hz, $^3J = 7.9$, 2.8 Hz, 1H), 3.15 (ddd, $^2J = 12.2$ Hz, $^3J = 9.7$, 7.1 Hz, 1H), 3.38 (ddd, $^3J = 8.4$, 5.6, 2.8 Hz, 1H), 3.98 (ddd, $^3J = 8.3$, 5.5, 2.9 Hz, 1H), 4.93 (d, $^3J = 12.2$ Hz, 1H), 4.94 (d, $^3J = 15.2$ Hz, 1H), 5.56−5.66 (m, 1H), 7.13 (t, $^3J = 7.4$ Hz, 3H), 7.22 (t, $^3J = 7.1$ Hz, 6H), 7.51 (d, $^3J = 7.6$ Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.0, 25.2, 38.2, 53.1, 63.8, 73.8, 78.2, 116.7, 126.3, 127.6, 129.9, 135.4, 144.8. Anal. Calcd for $C_{27}H_{29}NO$ (MW 383.53): C, 84.55; H, 7.62; N, 3.65. Found: C, 84.26; H, 7.62; N, 3.37.

(α*R*,2*S*)-α-Methyl-2-pyrrolidinemethanol 10. To **9b** (0.388 g, 1.085 mmol) in Et_2O (5 mL) was added HCl (5 N aqueous solution, 5 mL). After 3 h of vigorous stirring, the two phases were separated, and the aqueous phase washed three times with Et_2O (3 × 5 mL). The aqueous phase was cooled and made alkaline with concentrated aqueous NaOH followed by the extraction with chloroform (5 × 5 mL). The extract was dried (Na_2SO_4) and evaporated in vacuo to afford the title compound (0.082 g, 66%). Mp: 83−85 °C. $[\alpha]^{20}_D = -36.6$ ($c = 1.07$, MeOH) (lit.[14a] $[\alpha]^{20}_D = -36.4$ ($c = 1.0$, MeOH)). IR ($CHCl_3$) cm^{-1}: 3269, 2971, 2875, 1621, 1539, 1412, 1379, 1217, 769, 751, 665. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.13 (d, $^3J = 6.3$ Hz, 3 H), 1.55−1.80 (m, 4 H), 2.48 (bs, 2 H), 2.86−2.99 (m, 2 H), 3.06 (dt, $^3J = 7.5$ Hz, d, $^3J = 3.6$ Hz, 1 H), 3.75 (dq, $^3J = 6.3$, 3.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.4, 24.2, 25.9, 47.0, 63.5, 68.1.

(α*R*,2*S*)-α-(1-Methylethyl)-2-pyrrolidinemethanol 11. To **9c** (0.107 g, 0.278 mmol) in Et_2O (4 mL) was added HCl (5 N aqueous solution, 4 mL). After 3 h of vigorous stirring, the two phases were separated, and the aqueous layer washed three times with Et_2O (3 × 5 mL). The aqueous phase was cooled and made alkaline with concentrated aqueous NaOH followed by extraction with chloroform (5 × 5 mL). The extract was dried (Na_2SO_4) and evaporated in vacuo to afford the title compound (0.033 g, 82%). Mp: 65−67 °C. $[\alpha]^{20}_D = -39.2$ ($c = 0.82$, MeOH). IR ($CHCl_3$) cm^{-1}: 3282, 2958, 2872, 1621, 1539, 1470, 1417, 1385, 1365, 1336, 1216, 1066, 1001, 912, 752, 664. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.86 (d, $^3J = 6.6$ Hz, 3 H), 1.01 (d, $^3J = 6.6$ Hz, 3 H), 1.55−1.80 (m, 5 H), 2.75−2.92 (m, 3 H), 2.95−3.02 (m, 1 H), 3.18−3.27 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.8, 19.9, 23.7, 25.9, 31.58, 46.60, 60.33, 77.06. HRMS: calcd for $C_8H_{18}NO$ (MH^+) 144.1388, found 144.1391.

(α*R*,2*S*)-α-Phenyl-2-pyrrolidinemethanol 12. To **9f** (1.85 g, 4.4 mmol) in Et_2O (10 mL) was added HCl (5 N aqueous solution, 10 mL). After 3 h of vigorous stirring, the two phases were separated, and the aqueous layer was washed three times with Et_2O (3 × 5 mL). The aqueous phase was cooled and made alkaline with concentrated aqueous NaOH followed by extraction with $CHCl_3$ (3 × 10 mL). The extract was dried (Na_2SO_4), and the solvents were evaporated under vacuum to afford the title compound (0.673 g, 86%). ^1H NMR ($CDCl_3$, 400 MHz): δ 1.40−1.50 (m, 1H), 1.58−1.77 (m, 3H), 2.80 (bs, 2H), 2.86−2.93 (m, 1H), 2.97−3.03 (m, 1H), 3.34−3.41 (m, 1H), 4.70 (d,

^3J = 4.3 Hz, 1H), 7.24 (t, ^3J = 6.8 Hz, 1H), 7.33 (t, ^3J = 7.1, 7.8 Hz, 2H), 7.38 (d, ^3J = 7.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.10, 25.61, 46.94, 64.04, 74.29, 125.99, 128.32, 127.24, 142.43.

(α*R*,2*S*)-α-(2-Propenyl)-2-pyrrolidinemethanol 13. To **9g** (0.437 g, 1.139 mmol) in Et_2O (10 mL) was added HCl (5 N aqueous solution, 10 mL). After 3 h of vigorous stirring, the two phases were separated, and the aqueous layer was washed three times with Et_2O (3 × 5 mL). The aqueous phase was cooled and made alkaline with concentrated aqueous NaOH followed by the extraction with chloroform (4 × 5 mL). The extract was dried (Na_2SO_4) and evaporated in vacuo to afford the amino alcohol (0.130 g, 81%). Mp: 81−83 °C. $[\alpha]^{20}_D = -18.0$ (*c* = 0.80, MeOH). IR ($CHCl_3$) cm^{-1}: 3269, 3076, 2970, 2875, 1640, 1540, 1413, 1366, 1339, 1212, 915, 771, 751, 665. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.62 (m, 4 H), 2.18−2.28 (m, 2 H), 2.38 (bs, 2 H), 2.88−3.02 (m, 2 H), 3.18−3.19 (m, 1 H), 3.63−3.70 (m, 1 H), 5.06−5.17 (m, 2 H), 5.80−5.92 (m, 1 H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.5, 25.9, 38.8, 46.9, 62.0, 71.6, 117.4, 135.2. HRMS: calcd for $C_8H_{16}NO$ (MH^+) 142.1232, found 142.1230.

(α*R*,2*S*)-1-Methyl-α-phenyl-2-pyrrolidinemethanol 14. The amino alcohol **12** (0.673 g, 3.8 mmol) was dissolved in water (2 mL), and formic acid (98%, 1 mL) and formaldehyde (37% aqueous solution, 1.5 mL) were added. The reaction mixture was stirred for 10 h at refluxing temperature and then cooled and made alkaline with concentrated aqueous NaOH, followed by extraction with CH_2Cl_2. The extract was dried (Na_2SO_4) and the solvent evaporated under vacuum. The residue was filtered over silica gel (AcOEt) to afford the title compound (0.460 g, 63%) as slightly yellow oil. $[\alpha]^{20}_D = -60.7$ (*c* = 0.72, $CHCl_3$) (lit.[8a] $[\alpha]^{20}_D = -59.0$ (*c* = 0.73, $CHCl_3$)). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.21−1.33 (m, 1H), 1.56−1.77 (m, 3H), 2.34 (dt, *J* = 9.3, 7.6 Hz, 1H), 2.46 (s, 3H), 2.52 (ddd, ^3J = 9.2, 6.6, 3.0 Hz, 1H), 3.11−3.17 (m, 1H), 3.54 (bs, 1H), 4.87 (d, ^3J = 3.0 Hz, 1H), 7.23 (t, ^3J = 7.1 Hz, 1H), 7.33 (t, ^3J = 7.8, 7.3 Hz, 2H), 7.38 (d, ^3J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.0, 23.9, 40.1, 57.7, 69.8, 71.0, 125.6, 128.2, 126.8, 141.8.

(1*R*,7*S*)-Tetrahydro-1-butyl-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one 15. To **9a** (136 mg, 0.34 mmol) in Et_2O (5 mL) was added HCl (5 N aqueous solution, 3 mL). After 5 h of vigorous stirring, the two phases were separated and the aqueous one washed three times with Et_2O (3 × 3 mL). The aqueous phase was cooled and made alkaline with concentrated aqueous NaOH followed by extracting the amino alcohol with $CHCl_3$ (3 × 5 mL). The extract was dried (Na_2SO_4) and the solvent evaporated under vacuum. The obtained crude amino alcohol was dissolved in anhydrous CH_2Cl_2 (5 mL). Et_3N (0.15 mL, 0.94 mmol) and methyl chloroformate (32 μL, 0.41 mmol) were added. After 20 h of stirring at room temperature, NaH (16 mg, 0.68 mmol) was added, and the reaction mixture was allowed to stir for an additional 20 h before being quenched with aqueous $NaHCO_3$. The two phases were separated, the organic phase was dried (Na_2SO_4), and the solvents were evaporated in vacuo. Purification by flash chromatography over silica gel with AcOEt−cyclohexane (1:2) gave 19 mg (30% yield) of the title compound. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, ^3J = 7.1 Hz, 3H), 1.30−1.66 (m, 6H), 1.69−1.93 (m, 3H), 2.01−2.12 (m, 1H), 3.17 (ddd, ^2J = 11.4 Hz, ^3J = 9.8, 3.5 Hz, 1H), 3.64 (dt, ^2J = 11.4 Hz, ^3J = 8.1, 8.4 Hz, 1H), 3.78 (ddd, ^3J = 10.9, 7.1, 5.4 Hz, 1H), 4.62 (dt, ^3J = 7.8, 5.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.0, 22.6, 25.0, 25.2, 28.2, 30.3, 45.9, 63.5, 75.5, 162.0.

(1*R*,7*S*)-Tetrahydro-1-(2-propenyl)-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one 16. To **9g** (0.364 g, 0.949 mmol) in Et_2O (10 mL) was added HCl (5 N aqueous solution, 10 mL). After 3 h of vigorous stirring, the two phases were separated, and the aqueous phase was washed three times with Et_2O (3 × 3 mL). The aqueous phase was cooled and made alkaline with concentrated aqueous NaOH followed by extracting the amino alcohol with $CHCl_3$ (3 × 5 mL). The extract was dried (Na_2SO_4) and the solventd evaporated under vacuum. The obtained crude amino alcohol was dissolved in anhydrous CH_2Cl_2 (8 mL). Et_3N (0.61 mL, 3,75 mmol) and methyl chloroformate (76 μL, 1 mmol) were added. After 20 h of stirring at room temperature, NaH (72 mg, 3 mmol) was added, and the reaction mixture was allowed to stir for an additional 20 h before being quenched with aqueous $NaHCO_3$. The two phases were separated, the organic phase was dried (Na_2SO_4), and the solvents were evaporated under vacuum. Purification by flash chromatography over silica gel with AcOEt−cyclohexane (1:2) gave 52 mg (32% yield) of the title compound. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.42−1.53 (m, 1H), 1.72−1.78 (m, 1H), 1.80−1.90 (m, 1H), 2.01−2.09 (m, 1H), 2.34−2.38 (m, 1H), 2.52−2.60 (m, 1H), 3.11−3.18 (m, 1H), 3.57−3.64 (m, 1H), 3.75−3.81 (m, 1H), 4.68 (q, ^3J = 7.3 Hz, 1H), 5.11−5.19 (m, 2H), 5.72−5.83 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.0, 25.2, 34.9, 45.7, 63.2, 75.4, 118.7, 132.3, 161.6.

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Supporting Information Available: Spectral data for **2e**, **5**, **6**, **8a**,**b**, **9a**−**g**, and **10**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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