Photoinduced Electron Transfer (PET) Promoted Oxidative Activation of 1-(*N*-Benzyl-*N*-methylglycyl)-(*S*)-prolinol: Development of Novel Strategies Towards Enantioselective Syntheses of α-Amino Acids, Their *N*-Methyl Derivatives and α-Hydroxy Acids Employing (*S*)-Prolinol as a Recyclable Chiral Auxiliary

Ganash Pandey,*[a] Parthasarathi Das,[a] and P. Yella Reddy[a]

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PET activation of 1-(*N*-benzyl-*N*-methylglycyl)-(*S*)-prolinol (**1**) in dry acetonitrile, utilizing 1,4-dicyanonaphthalene (DCN) as a light-harvesting electron-acceptor and methyl viologen (MV^{++}) as an electron-transfer mediator, leads to the formation of 3-[benzyl(methyl)amino]perhydropyrrolo-[2,1-*c*][1,4]oxazin-4-one (**3**). When this photolysis is carried out in aqueous acetonitrile, exclusively 3-hydroxy-perhydropyrrolo[2,1-*c*][1,4]oxazin-4-one (**4**) is produced. The formation of **3** can be rationalized in terms of intramolecular cyclization of the in situ generated iminium cation intermediate (**2**) by the OH moiety of (*S*)-prolinol, while **4** is generated by hydrolysis of **2** followed by acetalization. Nucleophilic alkylation of **3** and **4**, using Grignard reagents and allyltrimethylsilane/TiCl4, provides **12a–d** & **15** and **17a–c** & **21**, respectively, in a highly stereoselective manner. Hydrolysis of the resultant amides (**12**, **15**, **17**, and **21**) provides α-amino acid derivatives (**14**) and α-hydroxy acids, respectively, in optically active form, along with the recovered (*S*)-prolinol chiral auxiliary in its recyclable form.

Introduction

The generation of radical ions, critical intermediates in the development of a modern concept of organic reactivity,[1–2] by PET processes has acquired prominence in the past decade[3–4] as photoexcitation readily induces well-defined redox potential differences between interacting substrates – a prerequisite for electron transfer. Significant progress has been made in understanding the reactivity profiles of these high-energy odd-electron species,[5] which have facilitated the application of PET reactions in driving energetically uphill processes in chemical synthesis.[6–8] The product formation from PET reactions is dependent, among many other parameters, on the redox potentials of the donor–acceptor (D–A) pairs and the solvent polarity[9–11] and therefore, a change in any one of these parameters has a significant influence on the reaction dynamics of the radical ions. For example, *tert*-amine radical cations, generated by PET processes from amine–arene pairs, are known to undergo H^+ transfer from the α-C–H bond to the geminate ion radical within the solvent cage, resulting in an amine–arene adduct through coupling of the resultant radical species.[12] However, we[13] as well as others[14] have reported that PET reactions between a *tert*-amine and certain potent electron acceptors in polar solvents lead to a sequential two-electron oxidation [electron-proton-electron (E-P-E) sequence] of the amine, leading to iminium cation intermediates. Based on these premises, we have developed a photosystem utilizing 1,4-dicyanonaphthalene (DCN) as a light-harvesting electron-acceptor and methyl viologen dication (MV^{++}) as an electron-transfer mediator, as shown in Figure 1, for the in situ generation of iminium cation intermediates from *tert*-amines for synthetic purposes.[6,7,13]

Since the orientation of deprotonation of an amine radical cation, the precursor for the generation of an iminium cation by the above route, depends upon the kinetic acidity,

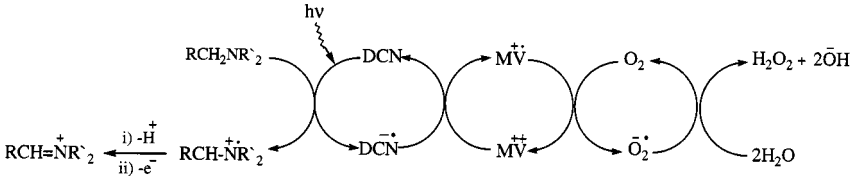

Figure 1. A photosystem to effect sequential two-electron oxidation of amines

this being subject to the steric arrangement of the α-C–H bond of the amine,[15] the generation of iminium cations from unsymmetrically substituted *tert*-amines has been shown to be highly regioselective.[16] The application of this concept has also been demonstrated in the synthesis of cyc-

[a] Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411008, India
Fax: (internat.) + 91-20/589-3153
E-mail: pandey@ems.ncl.res.in

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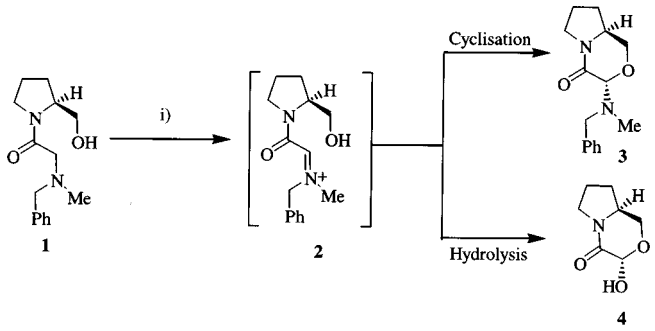
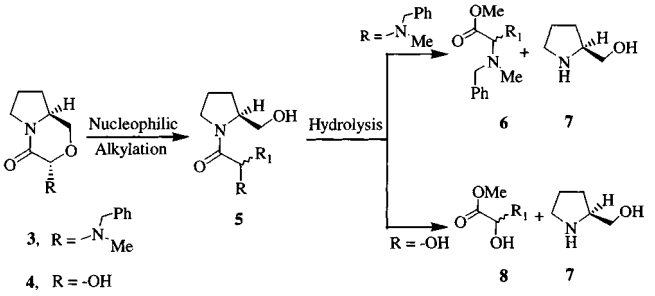
lic amino ethers by intramolecular trapping of in situ generated iminium cations by a tethered hydroxy group. This has proved to be an excellent route for the alkylation of cyclic amines at their α-positions.[16] As part of our ongoing research efforts in this area, we envisaged the synthesis of **3** and **4** as predesigned substrates that would allow the preparation of α-amino acids and their *N*-methyl derivatives, and of α-hydroxy carboxylic acids, respectively, by PET activation of **1** as shown in Scheme 1.



Scheme 1. PET activation of 1-(*N*-benzyl-*N*-methylglycyl)-(*S*)-prolinol (**1**): i) hν, DCN/MV^{++}, CH_3CN

The design of compounds **3** and **4** was conceived by considering their unique structural features: a reactive α-amino ether and hemiacetal functionality, highly suitable for stereoselective nucleophilic alkylation reactions; ease of hydrolysis of the resultant amides to procure the corresponding α-amino acids, their *N*-methyl derivatives, and α-hydroxy carboxylic acids, respectively, and the recovery of the (*S*)-prolinol chiral auxiliary in its recyclable form. (Scheme 2). We are pleased to disclose the findings of our studies in this article.[17]

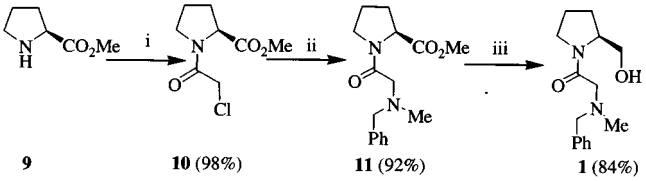


Scheme 2. Proposed setereoselective alkylations of substrates **3** and **4**

Results and Discussion

Synthesis and Utilization of 3-[Benzyl(methyl)amino]-perhydropyrrolo[2,1-*c*][1,4]oxazin-4-one (3)

Although there are some very good methodologies[18−20] for the synthesis of α-amino acids through the alkylation of several glycine-derived chiral templates, the problems associated with cleavage of the auxiliary ring system and the recovery of chiral information, as well as the difficulty in extending these strategies to the synthesis of *N*-methylated[21] α-amino acids show that there is scope for further development in this area. In this context, we set out to explore the route shown in Scheme 2 using **3** as a new glycine-derived template for the synthesis of α-amino acids and their *N*-methyl derivatives. The synthesis of the predesigned substrate **3** was envisaged as being possible by PET activation of **1**, easily available in 84% yield by amination of **10**, which, in turn, could be obtained by reaction of (*S*)-proline ester **9** with chloroacetyl chloride using benzyl(methyl)amine in the presence K_2CO_3 as a base in acetonitrile, followed by reduction of **11** with $NaBH_4$ (Scheme 3).



Scheme 3. Synthesis of 1-(*N*-benzyl-*N*-methylglycyl)-(*S*)-prolinol (**1**): i) $ClCH_2COCl$, $NaHCO_3/H_2O$, 2 h; ii) $PhCH_2(Me)NH$, K_2CO_3/CH_3CN, 6 h; iii) $NaBH_4$, EtOH, 12 h

The PET cyclization of **1** involved irradiation of a mixture of **1** (2.0 g, 7.69 mmol), DCN (0.32 g, 1.79 mmol), and MV^{++} (0.08 g, 0.311 mmol) in CH_3CN using Pyrex-filtered light (> 280 nm) emanating from a 450-W Hanovia medium-pressure mercury lamp at ambient temperature, without removing dissolved air present in the solution. The progress of the reaction was monitored by TLC as well as by HPLC. After 8 h of irradiation, the concentration of **1** was considerably diminished, and photolysis was discontinued. Removal of the solvent under reduced pressure followed by chromatographic purification of the crude mixture gave **3** (73% yield) as a diastereomeric mixture (*dr* = 13.3:1) along with a minor amount of **4** (3−5%). The diastereomeric ratio of **3** was measured by HPLC analysis. DCN was recovered quantitatively (ca. 97%), but our efforts to obtain pure diastereomers were, however, unsuccessful.

The formation of **3** (*de* = 93%) may be rationalized in terms of regioselective in situ generation of iminium cation **2** by selective deprotonation of the acidic methylene group of the glycine moiety, followed by further one-electron transfer to the regenerated DCN according to the cycle shown in Figure 1. The stereochemistry of **3** was determined by comparing the chemical shift values for the 3-H signals, which appeared relatively upfield at δ = 4.75 in the major isomer, as opposed to δ = 4.85 in the minor isomer.[22] This assignment was further corroborated by the absence of any NOE between 3-H and 8a-H. The preference for the formation of the major diastereomer **3** (*de* = 93%) in the cyclization of **2** may be explained by assuming back side attack of the OH moiety of prolinol on the iminium cation, leading to a preferred energy-minimized transition state structure (**A**), with the amine functionality remaining in an equatorial position (**C**) so as to produce the energetically favourable *trans*-bicyclic system, as shown in Figure 2.

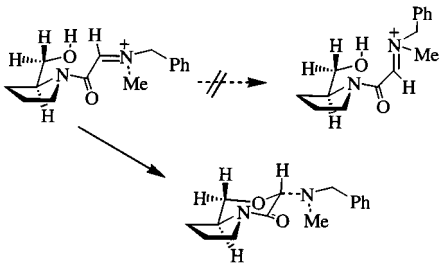
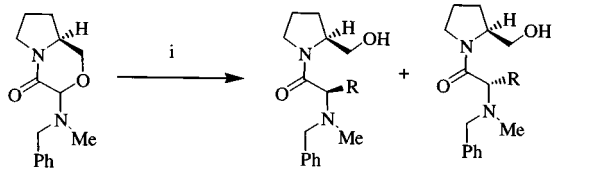


Figure 2. Transition-state model to explain the stereoselectivity during the PET cyclisation of **1**

Nucleophilic ring-opening of **3** (Scheme 4) was initially carried out by the addition of a separately prepared Grignard reagent[23] (4 equiv.) to a stirred solution of **3** in dry diethyl ether at −50°C and stirring for a further 4 h at this temperature. After allowing the reaction mixture to warm to room temp., it was quenched by the addition of saturated NH_4Cl solution. Purification of the crude mixture by column chromatography gave the corresponding amides **12a−d** and **13a−d** in a combined yield of 70−75%. The diastereomeric ratios of **12a−d/13a−d** are indicated in Scheme 4. These ratios were determined by comparing the relative integrals of the *N*-methyl peaks in the ^{1}H-NMR spectra and were further confirmed by analyzing the products by HPLC. The products were also characterized by their IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectral data.

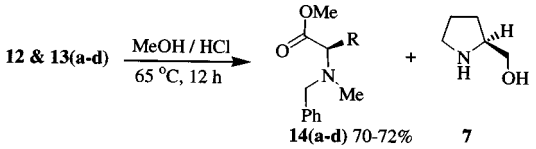


		12	**13**	Yield (%) (isolated)
a	R = CH_2Ph	5.3	1	76
b	R = Me	3.6	1	72
c	R = Ph	2.8	1	70
d	R = $CH(Me)_2$	2.2	1	68

Scheme 4. Stereoselective alkylation of **3** using Grignard reagents: i) RMgX ether, −50°C

Due to the close similarity of the R_f values of **12a−d** and **13a−d**, we did not succeed in isolating them in pure form by column chromatography. Thus, the diastereomeric mixtures of **12a−d** and **13a−d** were hydrolyzed directly by heating in dry methanolic HCl for 12 h in a sealed tube. Standard workup of basification and purification gave the corresponding α-amino acid esters in yields of 70−72%. (*S*)-Prolinol, the chiral auxiliary, was recovered in 96% yield (Scheme 5).

Since determination of the enantiomeric excesses (*ee* values) of the α-amino acid esters **14a−d** by HPLC using a chiral column proved difficult, their optical purities and absolute configurations were assessed by comparing the

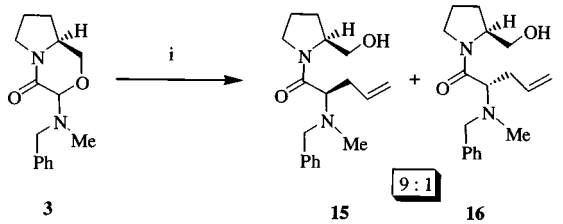


		$[\alpha]_D^{25}$	Optical Purity (%)
a.	R = CH_2Ph	-51.2 (c=1, $CHCl_3$)	70
b.	R = Me	-59.3 (c=1, $CHCl_3$)	60
c.	R = Ph	+ 5.8 (c=1, $CHCl_3$)	49
d.	R = $CH(Me)_2$	-26.1 (c=1.2, $CHCl_3$)	38

Scheme 5. Hydrolysis of substrates **12** and **13**

measured optical rotations with those of authentic samples independently prepared from the commercially available α-amino acids. Debenzylation, achieved by hydrogenation in the presence of 10% Pd on charcoal, gave the corresponding *N*-methyl α-amino acid esters. The free amino acids could also be obtained from **14** by *N*-demethylation of the corresponding debenzylated products according to known procedures.[24]

In order to explore an alternative approach to alkylation, Lewis acid mediated allylation[25−26] of **3** was also carried out. Addition of allyltrimethylsilane (2.8 mmol) followed by $TiCl_4$ (2.88 mmol) to a stirred solution of **3** (1.93 mmol) in dry dichloromethane at −78°C gave **15** and **16** in a 9:1 ratio in a combined yield of 90% (Scheme 6). Again, chromatography did not permit separation of the diastereomers. The absolute stereochemistry of the allylated product **15**, was determined by transforming it into the corresponding amino acid ester **24**, obtained by hydrolysis and subsequent catalytic hydrogenation of the resulting hydrolysed product **23**, and finally comparing its optical rotation value $[\alpha]_D$ with that of an authentic sample prepared independently from commercially available (*S*)-norvaline.



Scheme 6. $TiCl_4$-mediated allylation of **3**: i) $TiCl_4$, allyltrimethylsilane, dichloromethane, −78 °C, 4 h

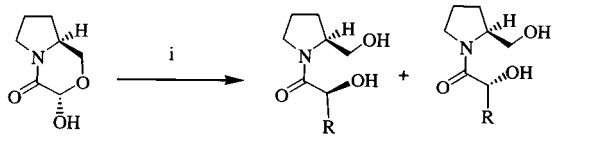
Synthesis and Utilization of 3-Hydroxyperhydropyrrolo[2,1-*c*][1,4]oxazin-4-one (4)

Enantiomerically pure α-hydroxy carboxylic acids are synthetically as well as biologically important substrates.[27] Therefore, syntheses of α-hydroxy carboxylic acids in optically pure form have attracted considerable interest. Gen-

erally, these compounds are prepared by diastereoselective reduction of chiral α-keto esters and amides.[28][29] Alternative approaches involving asymmetric oxygenation of chiral imide enolates, as reported by Evans et al.,[30] and alkylation of the chiral *N*-(benzyloxyacetyl)-*trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine have also been reported.[31]

The possibility of producing **4** in good yield through PET activation of **1** in aqueous CH_3CN (Scheme 2) and the presence of its hemiacetal functionality led us to envisage utilization of this molecule for the enantioselective synthesis of α-hydroxy carboxylic acids through nucleophilic alkylation followed by hydrolytic recovery of the (*S*)-prolinol chiral auxiliary. To this end, PET activation of **1** in CH_3CN/H_2O (3:1), according to a similar photoirradiation protocol as described for the synthesis of **3**, gave **4** in 92% yield. The diastereomeric ratio of **4** (17:3) was ascertained by comparing the integrals of the 3-H signals in the ^{1}H-NMR spectrum [δ = 5.30 (major), 5.25 (minor)]. Our various efforts to obtain pure diastereomers were, however, unsuccessful. Therefore, we decided to proceed to the next step using **4** directly as a diastereomeric mixture, with the hope that diastereomers could be resolved after the alkylation step.

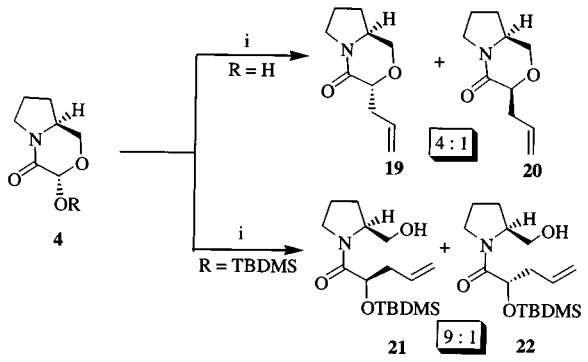
In order to transform **4** into a molecule from which the corresponding α-hydroxy carboxylic acids could easily be obtained, we considered nucleophilic alkylation of the cyclic hemiacetal functionality by means of a Grignard reaction. Cyclic acetals, particularly lactols, have frequently been utilized in C−C bond-forming reactions with Grignard reagents,[32] which offer a high degree of stereocontrol. We first alkylated **4** by treating a stirred solution in dry THF at −40°C with 4 equiv. of a separately prepared Grignard reagent and allowing the mixture to warm to room temp. over a period of 6 h. Standard workup and purification gave the products **17a−c** and **18a−c** in a combined yield of 50−60%. Details of the product yields, together with their diastereomeric ratios (*dr*) as estimated by HPLC (R = Ph) or by ^{1}H-NMR (R = Me, allyl), are given in Scheme 7.



		17	18	Yield (%) (isolated)
a	R = Ph	4	1	50
b	R = Me	5.66	1	60
c	R = Allyl	4.55	1	60

Scheme 7. Stereoselective alkylation of **4** using Grignard reagents: i) RMgX, THF, −40°C, room temperature, 6 h

In each case, the major diastereomers could easily be isolated in pure form by careful column chromatography on silica gel (60−120 mesh), eluting with mixtures of petroleum ether and ethyl acetate. The absolute stereochemistry at the new chiral centre of **17a−c** was established by comparing the optical rotation values $[\alpha]_D$ of the corresponding α-hydroxy carboxylic acids, obtained after catalytic hydrogenation followed by hydrolysis, with the known values of the commercially available α-hydroxy acids. The catalytic hydrogenation, using 10% Pd/C as Exemplified in the Experimental Section, of **17c** gave **25**. As an alternative strategy,[33] we also alkylated **4** (R = H) by adding allyltrimethylsilane in the presence of $TiCl_4$ in dry dichloromethane, which gave a separable 4:1 mixture of **19** and **20**. The formation of **19** and **20** can be rationalized in terms of nucleophilic addition of allyltrimethylsilane to the oxocarbenium species generated by $TiCl_4$-mediated elimination of the hydroxyl moiety of **4**. Therefore, in order to obtain a ring-opened intermediate identical to that obtained following a Grignard reaction (Scheme 8), we decided to protect the OH group of **4** as OTBDMS. Similar strategies have also been reported by others[34] in the context of allylation reactions of lactols. Allylation of **4** (R = TBDMS) in a similar manner as described above gave corresponding mixtures of **21** and **22** (9:1) along with minor amounts of **19−20** (< 8%). After TBDMS deprotection, the major diastereomer **21** was isolated in pure form by careful column chromatography. The (*S*) configuration at the new chiral centre in **21** was ascertained by comparing the $[\alpha]_D$ value of the 2-hydroxypentanoic acid, obtained by deprotection of the TBDMS group from **21** and **22** to give separable **26** (major diastereomer) followed by catalytic hydrogenation and hydrolysis of the hydrogenated product **27**, with that of the authentic material.



Scheme 8. $TiCl_4$-mediated allylation of **4**: i) $TiCl_4$, allyltrimethylsilane, dichloromethane, −78°C, 4 h

Conclusion

We have developed a new glycine-derived chiral template, based on the recyclable chiral (*S*)-prolinol chiral auxiliary, that allows the synthesis of α-amino acids, their *N*-methyl derivatives, and α-hydroxy acids with good optical purities. Both enantiomers of chiral 2-hydroxypentanoic acid and their related derivatives can be prepared from **4**, simply by changing the nature of the alkylation reaction.

Experimental Section

Solvents and anhydrous liquid reagents were dried according to established procedures. All reported yields refer to the isolated material and were not optimized. Temperatures above and below ambient temperature refer to bath temperatures unless otherwise stated. − The equipment used for photolysis consisted of a 450-W Hanovia medium-pressure mercury lamp and a Pyrex-filtered immersion well and reaction vessels. − Analytical TLC was performed using precoated silica gel plates (0.25 mm). − Column chromatography was performed on silica gel using standard chromatographic techniques. − HPLC was performed on a reversed-phase Nucleosil® C_{18} column using water and acetonitrile as eluents. − Mass spectra (*m*/*z*, relative intensity) were recorded in electronic impact mode at a voltage of 70 eV.

Synthesis of 1-(Chloroacetyl)-(*S*)-proline Methyl Ester (10): To a stirred solution of Methyl (*S*)-prolinoate (10.0 g, 77.52 mmol) in 150 mL of ice-cold water was added $NaHCO_3$ (13.02 g, 155.04 mmol). After dissolution of the $NaHCO_3$, chloroacetyl chloride (13.14 g, 116.28 mmol) was added dropwise over a period of 15 min and stirring was continued for a further 1 h at 0 °C. The reaction mixture was then neutralized with 10% HCl solution and extracted with chloroform. The combined organic extracts were dried with anhydrous sodium sulfate and concentrated under reduced pressure to give **10** in 98% yield. − IR (neat): $\tilde{\nu}$ = 2950, 1735, 1645 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.10−2.40 (m, 4 H), 3.60−3.70 (m, 2 H), 3.75 (s, 3 H), 4.10 (s, 2 H), 4.55−4.60 (m, 1 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 24.8, 29.2, 42.5, 47.7, 52.5, 59.3, 165.5, 172.1. − MS; *m*/*z* (rel. intensity): 205 [M^+] (4), 146 (51), 70 (100).

Synthesis of 1-(*N*-Benzyl-*N*-methylglycyl)-(*S*)-proline Methyl Ester (11): A solution of **10** (9.5 g, 46.19 mmol) in dry acetonitrile (100 mL) was placed in a 250-mL two-necked round-bottomed flask equipped with a magnetic stirring bar and fitted with an argon gas balloon. Anhydrous K_2CO_3 (7.65 g, 55.43 mmol) was then added to the flask under stirring. After 10 min, benzyl(methyl)-amine (6.70 g, 55.42 mmol) was added dropwise over a period of 10 min and stirring was continued at room temperature. The progress of the reaction was monitored by TLC. After completion (6 h), the reaction mixture was filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography eluting with acetone/petroleum ether (1:4) to give 12.6 g of **11** (94% yield) as a viscous liquid. − IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 1730, 1640, 1495 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.90−2.35 (m, 4 H), 2.40 (s, 3 H), 3.15 (dd, 2 H, *J* = 9.8, 5.2 Hz), 3.55−3.65 (m, 4 H), 3.75 (s, 3 H), 4.55−4.65 (m, 1 H), 7.30−7.35 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 25.0, 28.9, 42.4, 46.8, 52.0, 58.78, 60.0, 61.7, 127.1, 128.2, 129.2, 138.5, 169.2, 172.7. − MS; *m*/*z* (rel. intensity): 290 [M^+] (3), 134 [$PhCH_2N(Me)CH_2]^+$ (94), 120 [$PhCH_2NMe]^+$ (33), 91 [$PhCH_2]^+$ (100).

Synthesis of 1-(*N*-Benzyl-*N*-methylglycyl)-(*S*)-prolinol (1): An ethanolic solution (120 mL) of **11** (11.2 g, 38.62 mmol) was placed in a 250-mL round-bottomed flask equipped with a magnetic stirring bar. Sodium tetrahydroborate (2.19 g, 57.93 mmol) was added portionwise under stirring. On completion of the addition, the reaction mixture was stirred at room temp. for 12 h. It was then concentrated and the residue was washed with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate and the combined extracts were washed with brine. The combined organic phases were then concentrated under reduced pressure and the crude residue was purified by column chromatography eluting with acetone/petroleum ether (2:3) to give 8.45 g (84%) of **1** as a viscous liquid. − IR ($CHCl_3$): $\tilde{\nu}$ = 3400, 1634, 1495 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.45−1.55 (m, 1 H), 1.80−2.10 (m, 3 H), 2.40 (s, 3 H), 3.15 (s, 2 H), 3.30−3.35 (m, 2 H), 3.60−3.70 (m, 4 H), 4.15−4.20 (m, 1 H), 7.25−7.30 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 24.1, 27.5, 42.4, 47.2, 60.0, 60.7, 61.6, 65.8, 126.9, 127.0, 128.9, 138.0, 170.8. − MS; *m*/*z* (rel. intensity): 262 [M^+] (3), 134 [$PhCH_2N(Me)CH_2]^+$ (100), 120 [$PhCH_2NMe]^+$ (41), 91 [$PhCH_2]^+$ (79).

PET Activation of 1-(*N*-Benzyl-*N*-methylglycyl)-(*S*)-prolinol. − Synthesis of 3-[Benzyl(methyl)amino]perhydropyrrolo[2,1-*c*][1,4]-oxazin-4-one (3): A solution of **1** (2.0 g, 7.63 mmol), DCN (0.32 g, 1.79 mmol), and MV^{++} (0.08 g, 0.311 mmol) in acetonitrile (1.8 L) was irradiated using a 450-W Hanovia medium-pressure mercury vapor lamp housed in a Pyrex-jacketed immersion well for 8 h. During the course of the irradiation, the color of the solution turned first to blue, then darkened, but ultimately turned to pale-yellow. Progress of the reaction was monitored by TLC (acetone/petroleum ether, 3:7) and HPLC. After 74% conversion of the starting material, irradiation was discontinued. The solvent was removed under reduced pressure and the residual crude photolysate was purified by column chromatography eluting with acetone/petroleum ether to give first DCN in 98% yield (0.31 g). Further elution with the same solvent system gave 1.6 g (73%) of **3** as a mixture of two diastereomers (*de* = 93%). − IR ($CHCl_3$): $\tilde{\nu}$ = 3010, 1640, 1450 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.45−2.30 (m, 4 H), 2.40 (s, 3 H), 3.30 (dd, 1 H, *J* = 10.8 Hz, *J* = 5.8 Hz), 3.65−3.80 (m, 5 H), 4.15 (dd, 1 H, *J* = 9.8 Hz, *J* = 5.2 Hz), 4.75 (s, 1 H), 7.30−7.35 (m, 5 H); discernible signals for the other diastereomer: δ = 2.45 (s, 3 H), 4.85 (s, 1 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 22.8, 29.0, 37.2, 45.4, 57.0, 57.6 (57.2), 67.4, 91.2 (88.1), 127.2, 128.3, 129.2, 138.8, 165.9. − MS; *m*/*z* (rel. intensity): 260 [M^+] (not visible) 135 [$PhCH_2N(Me)CH_3$] (100), 120 [$PhCH_2NMe]^+$ (40), 91 [$PhCH_2]^+$ (57).

General Procedure for the Alkylation of 3 Using Grignard Reagents: This is exemplified by the synthesis of 1-(*N*-benzyl-*N*-methylphenylalanyl)-(*S*)-prolinol (**12a** and **13a**). A 50-mL two-necked round-bottomed flask, equipped with a magnetic stirring bar and an argon gas balloon, was charged with a solution of **3** (0.51 g, 1.96 mmol) in dry diethyl ether (20 mL) and then cooled to −50 °C. Benzylmagnesium bromide, freshly prepared from magnesium (0.19 g, 7.84 mmol) and benzyl bromide (1.34 g, 7.84 mmol) in diethyl ether (10 mL), was added slowly to the cooled, stirred solution, and stirring was continued for 4 h at −50 °C. After allowing the mixture to warm to room temperature and stirring for an additional 2 h, the reaction was quenched by the addition of saturated ammonium chloride solution. The aqueous layer was extracted with diethyl ether, and the combined extracts were washed with brine and dried with anhydrous sodium sulfate. Concentration under reduced pressure followed by purification of the residue by column chromatography on silica eluting with acetone/petroleum ether (1:4) gave 0.52 g of **12a** and **13a** (5.3:1) in a combined yield of 76% as a viscous liquid. The diastereomeric ratio was determined by measuring the relative integrals of the *N*-methyl group signals in the ^1H-NMR spectrum and was further corroborated by HPLC analysis using a C_{18} column and aqueous acetonitrile as eluent. − IR ($CHCl_3$): $\tilde{\nu}$ = 3450, 1638, 1460 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.40−2.10 (m, 4 H), 2.45 (s, 3 H, major), 2.42 (s, 3 H, minor), 2.60−2.75 (m, 1 H), 3.00 (dd, 1 H, *J* = 12.8 Hz, *J* = 5.8 Hz), 3.30−3.60 (m, 4 H), 3.70 (dd, 1 H, *J* = 12.8 Hz, *J* = 5.8 Hz), 3.80 (s, 2 H), 4.10−4.20 (m, 1 H), 7.30−7.35 (m, 10 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 24.4, 28.3, 32.8, 38.9 (38.7), 47.3, 58.4 (58.2), 61.3, 66.6, 66.9, 126.4, 127.2, 128.4, 128.5, 128.9, 129.5, 138.0, 139.4, 172.6. − MS; *m*/*z* (rel. intensity): 352 [M^+] (1), 261 [$M^+ - 91$] (11), 224 [$PhCH_2N(Me)CHCH_2Ph]^+$

(96), 91 [$PhCH_2$]$^+$ (100). − Similar procedures were adopted with other Grignard reagents, furnishing the products detailed below.

1-(*N*-Benzyl-*N*-methylalanyl)-(*S*)-prolinol (12b & 13b): Yield 72%; *dr* = 3.6:1. − IR ($CHCl_3$): $\tilde{\nu}$ = 3450, 1635, 1450 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.25 (d, 3 H, *J* = 6.2 Hz), 1.50−1.55 (m, 1 H), 1.60−2.10 (m, 4 H), 2.25 (s, 3 H, major), 2.30 (s, 3 H, minor), 3.30−3.35 (m, 1 H), 3.55−3.70 (m, 4 H), 4.05−4.15 (m, 1 H), 4.20−4.25 (m, 1 H), 7.30−7.35 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 8.9 (9.8), 24.2, 27.5, 37.3 (37.7), 47.4, 57.4 (57.1), 59.7, 60.5 (60.1), 65.9, 126.7, 127.9, 128.6, 138.9, 173.5. − MS; *m*/*z* (rel. intensity): 276 [M^+] (1), 192 (46), 148 [$PhCH_2N(Me)CHMe]^+$ (32), 91 [$PhCH_2]^+$ (100).

1-(*N*-Benzyl-*N*-methylphenylglycyl)-(*S*)-prolinol (12c & 13c): Yield 70%; *dr* = 2.8:1. − IR ($CHCl_3$): $\tilde{\nu}$ = 3400, 1637, 1495 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.5−1.60 (m, 1 H), 1.65−2.00 (m, 4 H), 2.40 (s, 3 H), 3.30−3.35 (m, 1 H), 3.60−3.85 (m, 4 H), 4.20−4.30 (m, 1 H), 4.55 (s, 1 H), 7.30−7.35 (m, 10 H); discernible signal for the other diastereomer: δ = 2.35 (s, 3 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 24.6, 28.1, 39.4, 47.6, 58.5, 61.7, 67.7, 69.8 (69.2), 127.2, 128.2, 128.4, 128.8, 129.1, 129.4, 129.6, 139.4, 139.7, 173.4. − MS; *m*/*z* (rel. intensity): 224 (75), 210 [$PhCH_2N(Me)CHPh]^+$ (82), 118 (18), 91 [$PhCH_2]^+$ (100).

1-(*N*-Benzyl-*N*-methylvalinyl)-(*S*)-prolinol (12d & 13d): Yield 68%; *dr* = 2.2:1. − IR ($CHCl_3$): $\tilde{\nu}$ = 3400, 1635, 1452 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.97 (d, 3 H, *J* = 6.8 Hz), 1.12 (d, 3 H, *J* = 7.2 Hz), 1.55−1.60 (m, 1 H), 1.85−1.95 (m, 3 H), 2.25−2.30 (m, 1 H), 2.35 (s, 3 H), 3.17 (t, 1 H, *J* = 9.2 Hz), 3.50−3.80 (m, 5 H), 3.97 (d, 1 H, *J* = 5.8 Hz), 4.35−4.45 (m, 1 H), 7.30−7.35 (m, 5 H); discernible signals for the other diastereomer: δ = 0.87 (d, 3 H, *J* = 6.8 Hz), 2.30 (s, 3 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 19.6, 19.9, 24.5, 28.2, 28.6 (27.8), 38.5 (38.2), 47.9, 57.8, 60.7, 67.3, 70.1, 126.7, 128.1, 129.2, 140.0, 173.8. − MS; *m*/*z* (rel. intensity): 261 [M^+ − *i*Pr] (12), 176 [$PhCH_2N(Me)CHCHMe_2]^+$ (100), 91 [$PhCH_2]^+$ (81).

Synthesis of 1-(*N*-Benzyl-*N*-methylallylglycyl)-(*S*)-prolinol (15 & 16): A 50-mL two-necked round-bottomed flask, equipped with a magnetic stirring bar and an argon gas balloon, was charged with a solution of **3** (0.50 g, 1.91 mmol) in dry CH_2Cl_2 (20 mL) and then cooled to −78°C. Allyltrimethylsilane (0.33 g, 2.88 mmol) followed by $TiCl_4$ (0.54 g, 2.85 mmol) was then slowly added to the stirred solution. After stirring for 4 h at −78°C, the reaction mixture was allowed to warm to room temperature and then quenched by the addition of saturated ammonium chloride solution. After basification with aqueous $NaHCO_3$, the mixture was extracted with CH_2Cl_2 and the combined extracts were washed with brine and dried with anhydrous sodium sulfate. Concentration under reduced pressure followed by column chromatography of the residue on silica gel eluting with acetone/petroleum ether (1:4) gave 0.52 g (90%) of **15** and **16** (9:1) as a clear liquid. − IR ($CHCl_3$): $\tilde{\nu}$ = 3460, 1637, 1454 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.45−2.10 (m, 4 H), 2.30 (s, 3 H, major), 2.28 (s, 3 H, minor), 2.40−2.50 (m, 1 H), 2.65−2.75 (m, 1 H), 3.20−3.70 (m, 7 H), 4.20−4.30 (m, 1 H), 4.95−5.20 (m, 2 H), 5.65−5.75 (m, 1 H), 7.30−7.35 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 24.5, 28.2, 29.0 (29.8), 38.4 (38.6), 47.9, 58.0, 61.1, 64.9, 67.3, 117.2, 127.2, 128.4, 128.0, 135.1, 139.3, 172.0. − MS; *m*/*z* (rel. intensity): 302 [M^+] (4), 261 [M^+ − allyl] (10), 174 [$PhCH_2N(Me)CHCHMe_2]^+$ (100), 91 [$PhCH_2]^+$ (60).

General Method for the Hydrolysis of 12a−d & 13a−d and 15 & 16: This is exemplified by the hydrolysis of 1-(*N*-benzyl-*N*-methylphenylalanyl)-(*S*)-prolinol (**12a** & **13a**). A mixture of compounds **12a** and **13a** (0.50 g, 1.42 mmol) was dissolved in 15 mL of dry 6 N methanolic HCl and the solution was transferred to a narrow-necked test tube. The tube was sealed and heated to 65°C for 12 h in an oil bath. The sealed tube was then cooled to room temperature and opened by scissoring the tip. The methanolic HCl was evaporated to dryness and the resulting viscous residue was basified with saturated sodium bicarbonate solution (to pH = 8). The aqueous layer was extracted with diethyl ether and the combined extracts were dried with anhydrous sodium sulfate. Concentration followed by purification of the crude residue by chromatography on a silica gel column eluting with ethyl acetate/petroleum ether (1:12) gave methyl (*S*)-*N*-benzyl-*N*-methylphenylalaninoate (**14a**) (0.28 g, 72%) as a clear liquid. Further elution with $CHCl_3$/MeOH gave (*S*)-prolinol (0.14 g, 96%) as a viscous liquid. **14a**: $[\alpha]_{D(obsd)}^{25}$ = −51.2 (*c* = 1, $CHCl_3$); $[\alpha]_{D(authentic)}^{25}$ = −73.6 (*c* = 1.4, $CHCl_3$). − IR (neat): $\tilde{\nu}$ = 3010, 1745, 1454 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.40 (s, 3 H), 3.10 (dd, 1 H, *J* = 7.2 Hz, *J* = 7.0 Hz), 3.25 (dd, 1 H, *J* = 7.2 Hz, *J* = 7.0 Hz), 3.65 (dd, 1 H, *J* = 7.2 Hz, *J* = 4.8 Hz), 3.70 (d, 1 H, *J* = 14.6 Hz), 3.75 (s, 3 H), 3.87 (d, 1 H, *J* = 14.6 Hz), 7.30−7.35 (m, 10 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 36.0, 38.0, 51.1, 59.0, 67.4, 126.4, 127.1, 128.3, 128.4, 128.8, 129.4, 138.6, 139.4, 173.6. − MS; *m*/*z* (rel. intensity): 283 [M^+] (2), 224 [$PhCH_2N(Me)CHCH_2Ph]^+$ (42), 192 [M^+ − benzyl] (53), 91 [$PhCH_2]^+$ (100). − Similar procedures were adopted to obtain other amino acid esters. The physical data of the respective products are as follows.

(*S*)-*N*-Benzyl-*N*-methylalanine Methyl Ester (14b): Yield 70%. − $[\alpha]_{D(obsd)}^{25}$ = −59.3 (*c* = 1, $CHCl_3$); $[\alpha]_{D(authentic)}^{25}$ = −99.1 (*c* = 1.2, $CHCl_3$). − IR (neat): $\tilde{\nu}$ = 3000, 1740, 1456 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.37 (d, 3 H, *J* = 7.3 Hz), 2.35 (s, 3 H), 3.50 (q, 1 H, *J* = 7.3 Hz), 3.70 (d, 1 H, *J* = 13.4 Hz), 3.75 (s, 3 H), 3.80 (d, 1 H, *J* = 13.4 Hz), 7.25−7.35 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 14.9, 37.8, 51.0, 58.3, 60.6, 126.0, 128.2, 128.7, 139.4, 173.6. − MS; *m*/*z* (rel. intensity): 207 [M^+] (2), 192 [M^+ − methyl] (12), 176 [$PhCH_2N(Me)CHMe]^+$ (21), 91 [$PhCH_2]^+$ (100).

(*S*)-*N*-Benzyl-*N*-methylphenylglycine Methyl Ester (14c): Yield 70%. − $[\alpha]_{D(obsd)}^{25}$ = +5.8 (*c* = 1, $CHCl_3$); $[\alpha]_{D(authentic)}^{25}$ = +11.9 (*c* = 1.2, $CHCl_3$). − IR (neat): $\tilde{\nu}$ = 3020, 1745 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.30 (s, 3 H), 3.57 (d, 1 H, *J* = 13.8 Hz), 3.67 (d, 1 H, *J* = 13.8 Hz), 3.75 (s, 3 H) 4.40 (s, 1 H), 7.25−7.45 (m, 10 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 39.0, 51.5, 58.6, 72.0, 127.0, 128.1, 128.2, 128.5, 128.8, 136.7, 139.0, 172.2. − MS; *m*/*z* (rel. intensity): 224 (10), 210 [$PhCH_2N(Me)CHPh]^+$ (60), 91 [$PhCH_2]^+$ (100).

(*S*)-*N*-Benzyl-*N*-methylvaline Methyl Ester (14d): Yield 70%. − $[\alpha]_{D(obsd)}^{25}$ = −26.1 (*c* = 1.2, $CHCl_3$); $[\alpha]_{D(authentic)}^{25}$ = −68.1 (*c* = 1.3, $CHCl_3$). − IR (neat): $\tilde{\nu}$ = 3010, 1745 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.90 (d, 3 H, *J* = 7.6 Hz), 1.12 (d, 3 H, *J* = 7.6 Hz), 2.15 (m, 1 H), 2.30 (s, 3 H), 2.92 (d, 1 H, *J* = 15.2 Hz), 3.55 (d, 1 H, *J* = 16.2 Hz), 3.75 (s, 3 H), 3.80 (d, 1 H, *J* = 16.2 Hz), 7.30−7.35 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 19.5, 20.0, 27.5, 37.8, 50.5, 58.8, 73.1, 127.0, 128.3, 128.6, 139.7, 172.2. − MS; *m*/*z* (rel. intensity): 192 [M^+ − *i*Pr] (15), 176 [$PhCH_2N(Me)CHCHMe_2]^+$ (58), 91 [$PhCH_2]^+$ (100).

(*S*)-*N*-Benzyl-*N*-methylallylglycine Methyl Ester (23): Yield 76%. − IR (neat): $\tilde{\nu}$ = 3020, 1745, 1640 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.30 (s, 3 H), 2.50−2.55 (m, 2 H), 3.45 (t, 1 H, *J* = 6.6 Hz), 3.62 (d, 1 H, *J* = 14.6 Hz), 3.75 (s, 3 H), 3.82 (d, 1 H, *J* = 14.6 Hz), 5.15−5.20 (m, 2 H), 5.85−5.90 (m, 1 H), 7.30−7.35 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 34.2, 38.0, 51.0, 58.6, 65.8, 117.0, 127.1, 128.3, 128.8, 135.0, 139.5, 172.5. − MS; *m*/*z* (rel. intensity): 233 [M^+] (1), 192 [M^+ − allyl] (49), 174 [$PhCH_2N(Me)CHCH_2CH{=}CH_2]^+$ (43), 91 [$PhCH_2]^+$ (100).

Synthesis of (*S*)-*N*-Benzyl-*N*-methylnorvaline Methyl Ester (24): A solution of **23** (0.23 g, 0.98 mmol) in ethanol (25 mL) was placed in a 50-mL round-bottomed flask equipped with a magnetic stirring bar. To the stirred solution, 10% palladium on activated charcoal was added and the flask was saturated with hydrogen at atmospheric pressure. After stirring for 12 h at room temperature, the mixture was filtered through Celite, the filtrate was concentrated, and the residue was purified by column chromatography on silica eluting with ethyl acetate/petroleum ether (1:12) to give (*S*)-(−)-*N*-benzyl-*N*-methylnorvaline methyl ester **24** (0.20 g, 90%) as a viscous liquid. − $[\alpha]_{D(obsd)}^{25}$ = −62.2 (*c* = 1, $CHCl_3$); $[\alpha]_{D(authentic)}^{25}$ = −76.4 (*c* = 1.2, $CHCl_3$). − IR (neat): $\tilde{\nu}$ = 3000, 1740 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.90 (t, 3 H, *J* = 6.2 Hz), 1.40−1.50 (m, 2 H), 1.70−1.85 (m, 2 H), 2.30 (s, 3 H), 3.32 (t, 1 H, *J* = 7.2 Hz), 3.57 (d, 1 H, *J* = 16.2 Hz), 3.75 (s, 3 H), 3.82 (d, 1 H, *J* = 16.2 Hz), 7.30−7.35 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 14.0, 19.7, 32.0, 37.9, 51.0, 58.8, 65.6, 127.1, 128.4, 128.9, 139.9, 173.4. − MS; *m*/*z* (rel. intensity): 235 [M^+] (2), 176 [$PhCH_2N(Me)CHCH_2CH_2CH_3]^+$ (92), 91 [$PhCH_2]^+$ (100).

Synthesis of 3-Hydroxyperhydropyrrolo[2,1-*c*][1,4]oxazin-4-one (4): A solution of **1** (2.0 g, 7.63 mmol), DCN (0.32 g, 1.79 mmol), and MV^{++} (0.080 g, 0.311 mmol) in 1.8 L acetonitrile/water (3:2) was irradiated for 10 h using an identical setup as described above for the synthesis of **3**. After most of the starting material had been consumed, irradiation was discontinued. The solvent was removed under reduced pressure and purification of the crude photolysate by column chromatography eluting with acetone/petroleum ether gave 1.10 g (92%) of **4** (m.p. 154−156°C) as a mixture of two diastereomers (*dr* = 6.6:1). DCN was recovered in 98% yield. − IR ($CHCl_3$): $\tilde{\nu}$ = 3380, 1637 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.35−1.60 (m, 1 H), 1.70−2.20 (m, 3 H), 3.45−4.00 (m, 5 H), 5.10 (br. s, 1 H), 5.25 (s, 1 H, minor), 5.30 (s, 1 H, major). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 22.2, 28.5, 44.6, 57.6, 62.0, 88.8 (89.5), 166.3. − MS; *m*/*z* (rel. intensity): 157 [M^+] (2), 129 (18), 98 (25), 70 (100).

Alkylation of 4 Using Grignard Reagents: Reactions were carried out according to the General Procedure as described for the alkylation of **3**, to furnish the following products.

(2*S*)-2-(Hydroxymethyl)-1-[(2*R*)-2-hydroxy-2-phenylacetyl]pyrrolidine (17a): Yield: 50%. − IR ($CHCl_3$): $\tilde{\nu}$ = 3381, 1630, 1452 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.40−1.60 (m, 1 H), 1.75−1.85 (m, 2 H), 1.90−2.10 (m, 1 H), 2.90 (dt, 1 H, *J* = 9.6, 6.4 Hz), 3.50−3.65 (m, 3 H), 4.10−4.15 (m, 1 H), 4.65 (d, 1 H, *J* = 5.4 Hz), 5.10 (d, 1 H, *J* = 5.4 Hz), 7.30−7.35 (m, 5 H). − ^{13}C NMR ($CDCl_3$, 75.3 MHz): δ = 24.2, 27.4, 47.0, 61.6, 65.5, 72.7, 128.5, 128.9, 138.8, 172.8. − MS; *m*/*z* (rel. intensity): 142 [M^+ − Ph] (13), 70 (100).

(2*S*)-2-(Hydroxymethyl)-1-[(2*R*)-2-hydroxypropanoyl]pyrrolidine (17b): Yield 60%. − IR ($CHCl_3$): $\tilde{\nu}$ = 3376, 1635 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.35 (d, 3 H, *J* = 6.2 Hz), 1.45−2.15 (m, 4 H), 3.50−3.75 (m, 4 H), 4.10−4.15 (m, 1 H), 4.35 (q, 1 H, *J* = 6.2 Hz). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 20.7, 24.4, 28.1, 47.1, 61.6, 65.7, 65.8, 175.3. − MS; *m*/*z* (rel. intensity): 142 [M^+ − Me] (13), 70 (100).

(2*S*)-1-[(2*R*)-2-Allyl-2-hydroxyacetyl]-2-(hydroxymethyl)-pyrrolidine (17c): Yield 60%. − IR ($CHCl_3$): $\tilde{\nu}$ = 3360, 1640 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.40−2.00 (m, 4 H), 2.45−2.55 (m, 2 H), 3.30 (m, 1 H), 3.55−3.80 (m, 3 H), 4.15−4.25 (m, 2 H), 4.95−5.10 (m, 2 H), 5.85−5.95 (m, 1 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 24.3, 28.4, 39.8, 47.3, 61.5, 65.9, 69.2, 117.8, 132.4, 173.5. − MS; *m*/*z* (rel. intensity): 199 [M^+] (1), 84 (46), 70 (100).

Synthesis of (2*S*)-(2-Hydroxymethyl)-1-[(2*R*)-2-hydroxypentanoyl]pyrrolidine (25): A solution of **17c** (0.36 g, 1.80 mmol) in ethanol (15 mL) was placed in a 25-mL round-bottomed flask equipped with a magnetic stirring bar. To the stirred solution, palladium on activated charcoal (10% Pd) was added and the flask was saturated with hydrogen at atmospheric pressure. After stirring for 12 h at room temperature, the mixture was filtered through Celite, and the filtrate was concentrated to yield **25** in 98% yield. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.90 (t, 3 H, *J* = 6.6 Hz), 1.45−1.70 (m, 4 H), 1.85−2.10 (m, 4 H), 3.30 (m, 1 H), 3.60−3.85 (m, 3 H), 4.10−4.30 (m, 2 H).

General Procedure for the Hydrolysis of 17a and **25:** This is exemplified by the hydrolysis of (*S*)-2-(hydroxymethyl)-1-[(2*R*)-2-hydroxy-2-phenylacetyl]pyrrolidine (**17a**). Amide **17a** (0.42 g, 1.78 mmol) was suspended in 1 M H_2SO_4 (15 mL) and the mixture was heated at 60−80°C for 0.5−1 h to ensure complete hydrolysis. After cooling to ambient temperature, the solution was neutralized by the addition of saturated $NaHCO_3$ solution. The resulting mixture was cooled, acidified with conc. HCl, and extracted with ethyl acetate. The combined extracts were dried with Na_2SO_4 and concentrated to give (*R*)-mandelic acid (0.24 g, 88%). The purity of the product was checked by ^1H NMR and by optical rotation measurements; $[\alpha]_{D(obsd)}^{25}$ = −150.4 (*c* = 1.6, H_2O); $[\alpha]_{D(lit)}^{25}$ = −155.0 (*c* = 2.5, H_2O).

(2*R*)-2-Hydroxypentanoic Acid: Yield: 82%. − $[\alpha]_{D(obsd)}^{25}$ = +3.1 (*c* = 2.26, H_2O); $[\alpha]_{D(lit)}^{25}$ = +3.2 (*c* = 2, H_2O).[35]

Hydrolysis of (2*S*)-2-(Hydroxymethyl)-1-[(2*R*)-2-hydroxypropanoyl]-pyrrolidine (17b): (*S*)-2-(Hydroxymethyl)-1-[(2*R*)-2-hydroxypropanoyl]pyrrolidine (**17b**) (0.35 g, 2.02 mmol) was hydrolyzed by refluxing in dry methanol (12 mL) containing conc. H_2SO_4 (0.5 mL) for 2 h to furnish (*R*)-methyl lactate (0.16 g) in 78% yield. − $[\alpha]_{D(obsd)}^{20}$ = +7.18 (neat); $[\alpha]_{D(lit)}^{20}$ = +7.46 (neat).[36]

Synthesis of 3-Allylperhydropyrrolo[2,1-*c*][1,4]oxazin-4-one (19): According to the same reaction procedure as described above for the synthesis of **15** and **16**, the synthesis of 3-allylperhydropyrrolo[2,1-*c*][1,4]oxazin-4-one was carried out. Purification by column chromatography on silica eluting with ethyl acetate/petroleum ether (2:3) gave diastereomerically pure **19** in 96% yield as a clear liquid. − IR (neat): $\tilde{\nu}$ = 2945, 1635, 1340 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.30−1.45 (m, 2 H), 1.75−2.00 (m, 2 H), 2.10−2.20 (m, 1 H), 2.50−2.60 (m, 1 H), 2.70−2.80 (m, 1 H), 3.30−3.75 (m, 3 H), 4.20−4.30 (m, 2 H), 5.10−5.25 (m, 2 H), 5.85−5.95 (m, 1 H). − ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ = 22.5, 29.0, 36.9, 45.0, 57.6, 68.0, 76.5, 117.5, 134.2, 168.2. − MS; *m*/*z* (rel. intensity): 196 [M^+ − 1] (<1), 151 (15), 112 (100), 84 (50), 70 (46).

Protection of 4 as *tert*-Butyldimethylsilyl Ether: A 100-mL two-necked round-bottomed flask equipped with a reflux condenser, a magnetic stirring bar, and an argon gas balloon was charged with a solution/suspension of **4** (1.2 g, 7.64 mmol) in dry dichloromethane (60 mL). To the stirred solution, imidazole (0.78 g, 11.46 mmol) was added. After complete dissolution of **4** and the imidazole, TBDMSCl (1.44 g, 9.55 mmol) was added and the reaction mixture was refluxed. The progress of the reaction was monitored by TLC. After completion (4 h), the mixture was washed with water. The organic layer was extracted with CH_2Cl_2 and the combined organic layers were dried with anhydrous sodium sulfate. After concentration under reduced pressure, the crude residue was purified by column chromatography on silica gel eluting with ethyl acetate/petroleum ether (1:8) to afford TBDMS-protected **4** (1.86 g) in 96% yield (1.94 g, *dr* = 85:15). − ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.45 (s, 6 H), 0.90 (s, 9 H), 1.40−2.10 (m, 4 H), 3.45−4.00 (m, 4 H), 4.15 (dd, 1 H, *J* = 12.2 Hz, *J* = 5.8 Hz), 5.10 (s, 1 H, major), 5.15 (s, 1 H, minor).

Synthesis of (2*S*)-1-[(2*S*)-2-Allyl-2-hydroxyacetyl]-2-(hydroxymethyl)pyrrolidine (26): According to the same procedure as described above for the synthesis of **19**, **21** and **22** were prepared. The crude mixture of **21** and **22** thus obtained was subjected to TBDMS deprotection by treating with tetrabutylammonium fluoride solution. Purification of the deprotected product by column chromatography on silica eluting with acetone/petroleum ether (2:3) gave diastereomerically pure **26** in 92% yield. − IR ($CHCl_3$): $\tilde{\nu}$ = 3382, 1668, 1638 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.45−2.20 (m, 4 H), 2.30−2.60 (m, 2 H), 3.30−3.50 (m, 1 H), 3.55−3.85 (m, 3 H), 4.20 (dq, 1 H, *J* = 7.2 Hz, *J* = 4.8 Hz), 4.37 (dd, 1 H, *J* = 9.6 Hz, *J* = 5.2 Hz), 5.05−5.25 (m, 2 H), 5.85 (m, 1 H). − ^{13}C NMR ($CDCl_3$, 75.3 MHz): δ = 24.5, 27.5, 39.0, 47.3, 61.3, 66.0, 69.0, 118.0, 132.7, 174.0. − MS; *m*/*z* (rel. intensity): 199 [M^+] (3), 182 (31), 152 (15), 128 (14), 85 (53), 70 (100).

Synthesis of (2*S*)-2-(Hydroxymethyl)-1-[(2*S*)-2-hydroxypentanoyl]pyrrolidine (27): According to the same hydrogenation procedure as described above for the synthesis of **25**, the allyl group of **26** was reduced to furnish (2*S*)-2-(hydroxymethyl)-1-[(2*S*)-2-hydroxypentanoyl]pyrrolidine (**27**) in 94% yield. − IR ($CHCl_3$): $\tilde{\nu}$ = 3400, 1666 cm^{-1}. − ^1H NMR (200 MHz): δ = 0.95 (t, 3 H, *J* = 6.6 Hz), 1.45−1.80 (m, 3 H), 1.80−2.25 (m, 5 H), 3.25 (ddd, 1 H, *J* = 7.8, 5.2, 3.8 Hz), 3.55−3.75 (m, 3 H), 4.10−4.35 (m, 2 H). − MS; *m*/*z* (rel. intensity): 202 [M^+ + 1] (1) 170 (86), 141 (33), 128 (21), 70 (100).

Synthesis of (2*S*)-2-Hydroxypentanoic Acid: (2*S*)-2-Hydroxypentanoic acid was synthesized in 80% yield from (2*S*)-2-(hydroxymethyl)-1-[(2*S*)-2-hydroxypentanoyl]pyrrolidine (**27**) according to the same hydrolysis procedure as described for **17a**. The purity of the acid was verified by measuring its optical rotation; $[\alpha]_{D(obsd)}^{25}$ = −2.5 (*c* = 1.8, H_2O); $[\alpha]_{D(lit)}^{25}$ = −2.7 (*c* = 2.2, H_2O).[35]

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