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New fast and practical method for the enantioselective synthesis of α-vinyl, α-alkyl quaternary α-amino acids

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Abstract—We describe a fast and practical enantioselective synthesis of (*S*)-*N*-Cbz-α-vinyl, phenylalanine, suitable for the preparation of different *N*-Cbz-α-vinyl aminoacids of both configurations. The new protocol exploits a Wittig reaction on highly enantiomeric enriched *N*-Cbz-α-formyl-α-alkyl amino esters, readily accessible from L-serine through a stereoselective alkylation of Seebach's oxazolidine, carried out with a significant improvement of the previously reported method. The synthetic scheme is suitable for gram scale preparation of the desired product with a 94% ee.

1. Introduction

In recent years, the importance of α,α-disubstituted α-amino acids has grown exponentially, in parallel with the quest for valuable tools to design and prepare short peptidic chains endowed with particular conformational properties.[1]

A particularly interesting class is represented by quaternary α-amino acids bearing β-γ unsaturation. Natural amino acids modified by the introduction of a vinyl moiety at the α position cannot only induce remarkable conformational changes if introduced in peptides,[2,3] but also possess important biological features. As a consequence of the concurrent presence of a natural side-chain and a vinyl moiety, they can act as enzymatic inhibitors[4] and, when incorporated in a peptide, increase the resistance to proteolysis, eventually enhancing the bioavailability of the molecule.[3,5]

Furthermore, the impressive application range of olefin metathesis and ring closing metathesis reactions has aroused new interest in the synthesis of olefinic α-amino acids as functional building blocks for the synthesis of conformationally constrained peptidomimetics[6] and the covalent capture of self-assembled peptides.[7] However, almost all reported examples make use of allyl or homoallyl glycine derivatives, probably due to the ease of synthesis and the reduced steric hindrance near the reactive olefinic centers when the double C–C bond is used for further functionalizations. Therefore, a practical method for the enantioselective synthesis of α-vinyl-α-aminoacids would expand the scope and applications of the olefin metathesis reaction of peptides.

Our particular interest in quaternary vinyl-glycines was dictated by the need for a practical and scaleable method for the enantioselective preparation of *N*-Cbz vinyl Phe that we exploited as a building block for the construction of proline-based bicyclic lactams through a peptide coupling and an RCM reaction sequence.[8]

Although a fairly good number of enantioselective syntheses of β,γ-unsaturated amino acids without an additional substituent at the α-position have been reported, less literature precedents are found for the asymmetric synthesis of quaternary vinyl-glycines.

Approaches to this class of compounds can be classified according to the following general strategies: (a) alkylation of amino acid derivatives by two-carbon alkyl halides functionalized with a group susceptible to an elimination reaction;[9] (b) deconjugative α-alkylation of dehydro amino acid derivatives or 3-vinyl-4-imidazolidinones;[10] (c) phenylselenylation of vinylglycine derivatives followed by alkylation and elimination;[11] (d) Wittig methylenation of

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protected α-alkyl serinal derivatives or masked α-formyl glycine equivalents;[12] (e) aldol reactions of a quaternary lithiated bis-lactim ether with aldehydes followed by dehydration;[13] (f) Pd(II)-mediated sigmatropic rearrangement of allylic *N*-*p*-methoxyphenyl trifluoroacetimidates.[14]

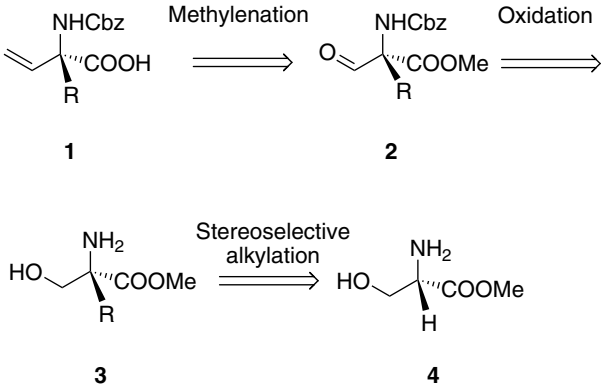
Each of the previous methods suffers from one or more limitations due to a lengthy or laborious synthetic scheme, use of toxic reagents, lack of generality, or overall low yields.

2. Results and discussion

Although our primary aim was the synthesis of vinyl phenylalanine, we set up a synthetic scheme that could allow the preparation of homologated β,γ-unsaturated derivatives and the introduction of various alkyl groups on the α-carbon starting from a common intermediate. The most straightforward solution to the former issue could be a Wittig olefination of a formyl group whereas a stereoselective alkylation reaction could serve for the installation of the quaternary stereocenter.

A retrosynthetic scheme was then devised whereby the final quaternary vinyl amino acids could be derived by methylenation of enantioenriched *N*-Cbz-α-alkyl serinal derivatives, easily obtainable by oxidation of the primary alcohol of the corresponding serine derivatives (Scheme 1).

One of the most reliable methods for the preparation of such compounds through a highly stereoselective alkylation reaction relies on the use of an enolate derived from *N*-formyl-2-*t*-butyl-4-carbomethoxy oxazolidine **5** (Scheme 2), pioneered by Seebach two decades ago.[15,16] The major advantages of this protocol lie in the high stereoinduction values and the commercial availability of chiral precursors in both enantiomeric forms. On the other hand, the use of carcinogenic HMPA as an additive and alkylation yields not higher than 68% are strong limitations. Moreover, the yield of the benzylation reaction, which was of particular interest for our purposes, was reported to be at the lowest end of the range. Initial benzylation experiments were performed following the experimental procedure reported by Seebach with the only modification being the use of DMPU in place of HMPA (Scheme 2).



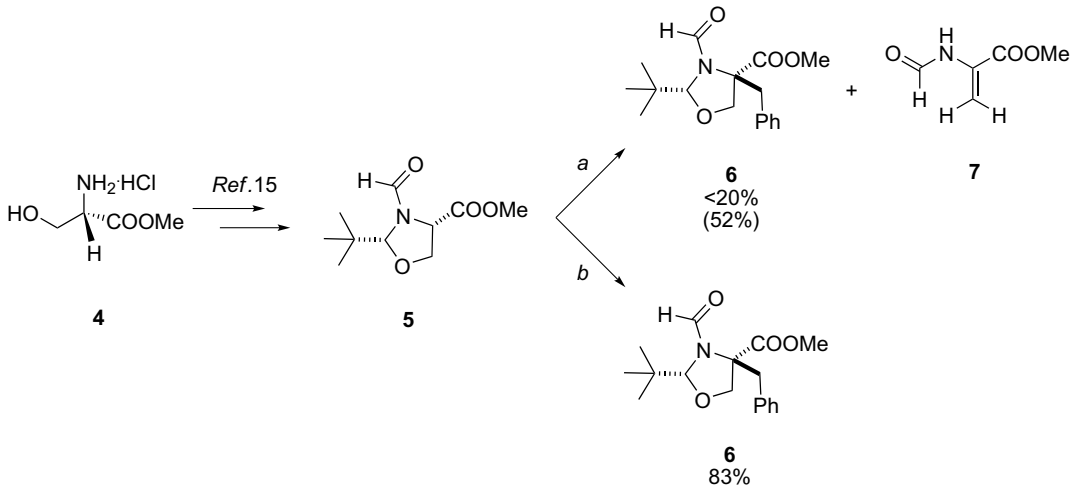
Scheme 1.

The results were disappointing, as yields not higher than 20% were attained. Modification of the experimental conditions such as an increase in the amount of benzyl bromide and/or base (LDA), variation of the final concentration of **5**, THF/hexane ratio, and reaction time and temperature were of no avail, the best yield being only 39% versus 52% in the original procedure. As already noticed by Seebach, the low yields of alkylated product are mainly due to a concurrent elimination reaction of the enolate leading to the deprotected α,β-unsaturated ester **7**.

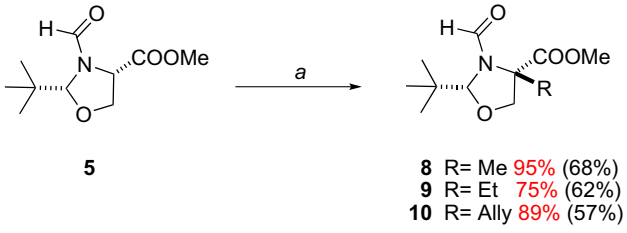
We reasoned that the only way to reduce the relative amount of elimination product was to enhance the rate of the alkylation step. The use of Na^+ or K^+ counterions of the enolate should promote the formation of less tight ion-pairs, making the enolate more reactive toward electrophiles. Moreover, we observed that at −78 °C the formation of the enolate requires only seconds to be complete while the elimination reaction is much slower. We also verified that at −78 °C sodium hexamethyldisilazide is compatible with the presence of benzyl bromide. Taken together, these observations led to the idea of forming the enolate at −78 °C in the presence of excess benzyl bromide. A similar procedure has been already adopted for the preparation of enolsilane derivatives under kinetic control.[17] Much to our delight, such a modified procedure, involving a slow, dropwise addition at −78 °C of NaHMDS (1.5 equiv) to a mixture of the oxazolidine **5** in 6:1:1 THF/hexane/DMPU and 4 equiv of benzyl bromide, led to a dramatic increase in the yield (83%). To test the generality of this new protocol, the same alkylation reaction was carried out with different alkyl halides (methyl iodide, ethyl iodide, allyl bromide). The yields were always higher than 75% (see Scheme 3) exceeding by 10–30% those previously reported for the same substrates.

A further modification of the original protocol involved the following simultaneous deprotection of the formamido, methyl ester, and hemiaminal groups. To retain the ester functionality, which is required for the next step, we found that treatment of the oxazolidine **6** with a saturated HCl methanol solution selectively removed the formamido group. Evaporation of the solvent followed by treatment with aqueous 3 M HCl in THF led to benzyl serine methyl ester **3** in almost quantitative yield.[18] It is interesting to note that the deformylated oxazolidine intermediate **11** was shown to be a mixture of two diastereoisomers, epimeric at the hemiaminal center. This can be explained by the equilibration of the free oxazolidine with the acyclic iminium and/or oxocarbenium ions (**12** and **13**), as depicted in Scheme 4.

The protection of the amine group in compound **3** as a Cbz derivative turned out to be less trivial than expected. Standard reaction conditions led to poor yields of the desired compound, and to variable amounts of the N,O-diprotected derivative as well as the ozazolidinone derived by intramolecular attack of the hydroxyl group onto the carbonyl carbon of the benzyl carbamate. The formation of an oxazolidinone may be favored by the Thorpe–Ingold effect exerted by the geminal benzyl and carboxymethyl groups. After many trials we found that an almost quantitative



Scheme 2. Reagents and conditions: (a) LDA, BnBr, DMPU, THF/hexane 10:1, −78 °C to rt in 12 h; (b) NaHMDS, BnBr, DMPU, THF/hexane 6:1, −78 °C, 90′.

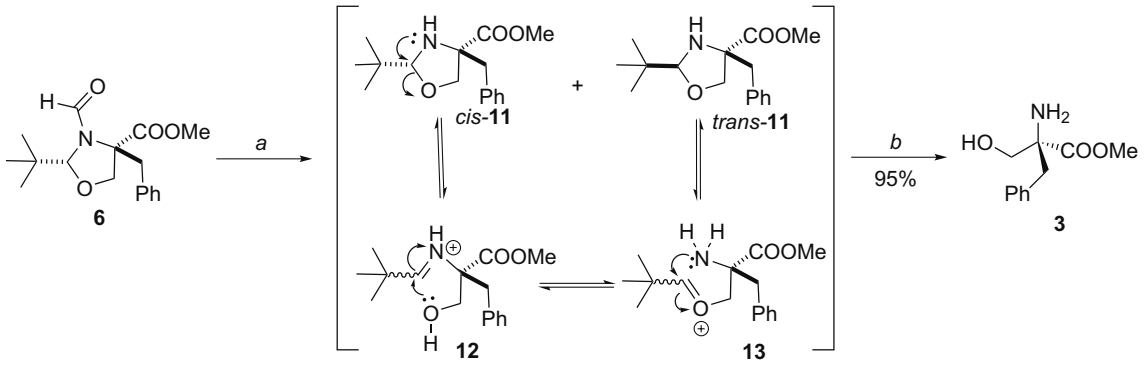


Scheme 3. Reagents and conditions: (a) NaHMDS, DMPU, THF/hexane 6:1, −78 °C. For **8**: CH_3I; for **9**: EtI; for **10**: AllylBr. The yields in brackets were previously reported.[15]

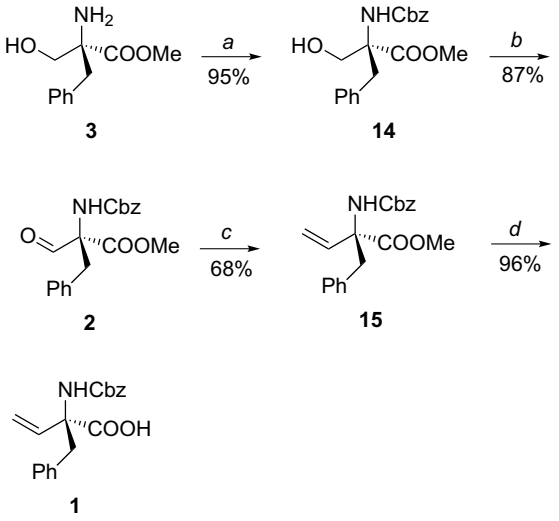
yield of **14** could be obtained by inverse addition of the amino alcohol **3** to a THF solution of 1.4 equiv of dibenzyldicarbonate with no added base at 0 °C. Under these conditions the reaction is complete in less than a minute (Scheme 5).

The following oxidation of the primary alcohol was initially performed under Swern conditions,[19] furnishing the desired benzyl serinal derivative **2** in very good yields (92%). Comparable results (93%) were also obtained by the use of a more practical oxidizing agent such as PCC[20] in the presence of molecular sieves, thus avoiding the use of low temperature regimes. Crude **2** was routinely used in the ensuing methylenation reaction. We were aware that any methylenation procedure involving as a first step the addition of a carbon nucleophile onto the aldehyde would have inevitably produced a β-alkoxy ester, prone to undergo a facile retro-Claisen reaction to give the ester enolate of *N*-Cbz phenylalanine **18**. Standard Wittig conditions using THF as a solvent led to the formation of the retro-Claisen compound **19** (Scheme 6) as the major or unique reaction product, in spite of a large variation of experimental conditions involving the base, temperature, and addition order of reagents. These negative results prompted us to screen other olefination conditions.

We first considered the Takai–Nozaki olefination,[21] treating **2** with the organo zinc reagent CH_2I_2–Zn–Me_3Al in anhydrous THF, but the results obtained were minimal and unsatisfactory, even performing the addition of the aldehyde at lower temperature (−78 °C instead of 0 °C). Switching to CH_2Br_2–Zn–$TiCl_4$[22] did not lead to any improvement. We also tried samarium iodide–CH_2I_2[23] and dimethyl-1-diazo-oxopropylphosphonate[24] as methylenation agents, but, once again, we obtained only the side product **18**.



Scheme 4. Reagents: (a) HCl–MeOH; (b) 3 M aq HCl/THF.



Scheme 5. Reagents and conditions: (a) Cbz_2O, THF, 0 °C; (b) PCC, 4 Å MS, CH_2Cl_2; (c) Ph_3PCH_3Br, KHMDS, toluene, −78 °C to rt; (d) $LiOH{\cdot}H_2O$, H_2O/THF/MeOH.

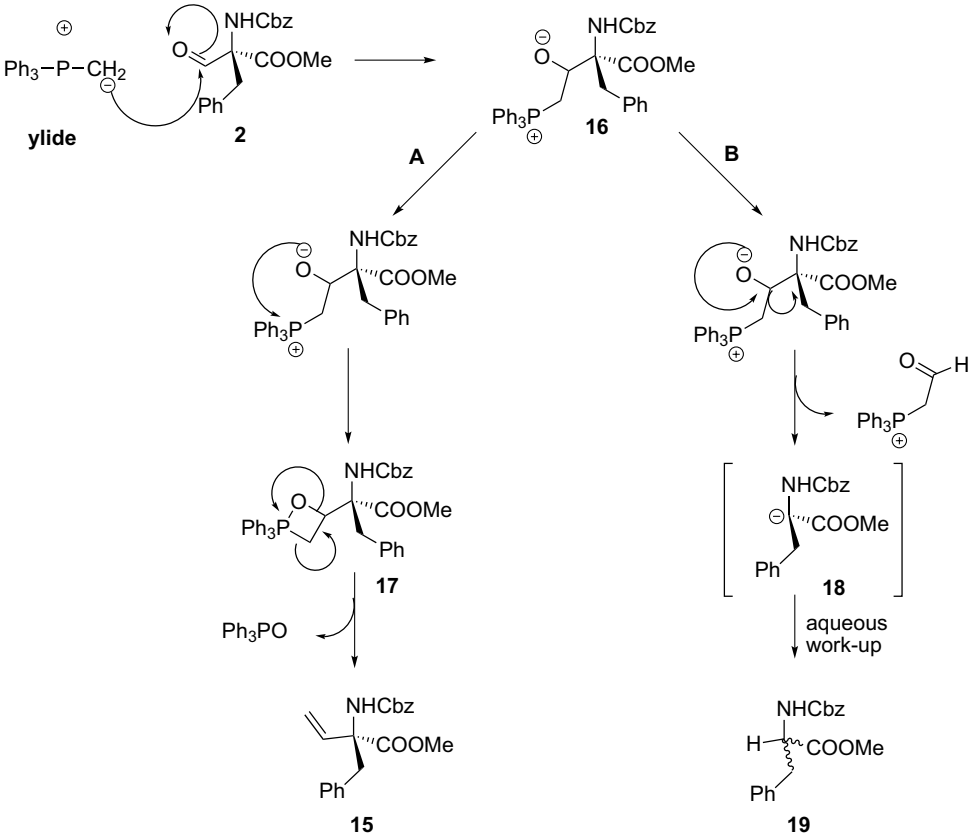
After establishing the ineffectiveness of alternative routes, we re-examined the Wittig reaction. We reasoned that the preponderant formation of the retro-Claisen product would be reduced if the stability of the intermediate phosphorane would be reduced by avoiding complexation with Li ions acting as Lewis acids (Scheme 6).[25]

Switching from THF to a less polar solvent such as toluene, salt free conditions were shown to be really effective, affording the desired vinyl derivative **15** in a satisfactory 68% yield over two steps under carefully controlled temperature conditions (see Section 4). Methyl ester saponification with LiOH afforded the desired *N*-Cbz-α-vinyl phenyl alanine in almost quantitative yield. The synthesis of the target compound was thus accomplished in an overall 35% yield from serine methyl ester (corresponding to a 86% average yield for each of the seven steps), significantly higher than the ones provided by all the other previously reported methods.

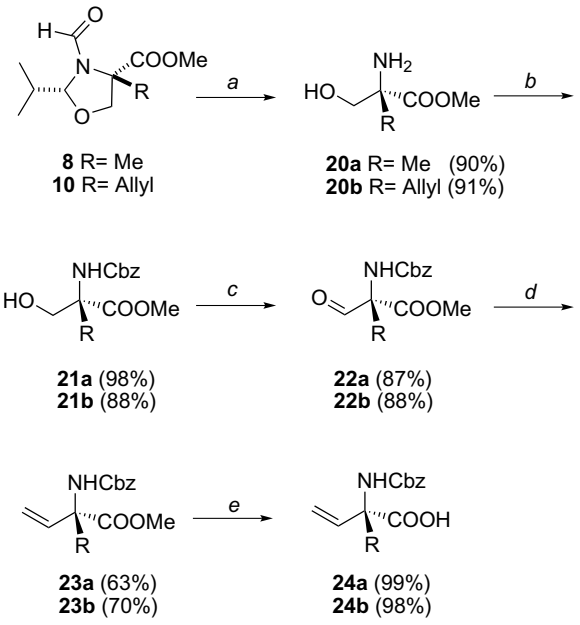
The whole synthetic scheme was then repeated using the methyl and allyl derivatives **8** and **9**, leading, respectively, to *N*-Cbz-α-vinyl alanine **24a** and *N*-Cbz-α-vinyl α-allyl glycine **24b** in comparable yields (Scheme 7).

The enantiomeric excess of the final *N*-Cbz-α-vinyl phenyl alanine was measured by ^1H NMR analysis of the corresponding Mosher's esters (Scheme 8).[26]

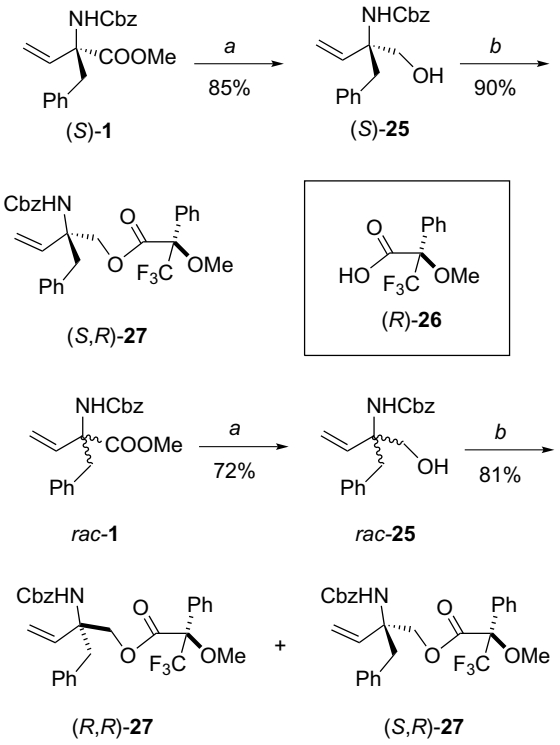
Reduction of the carboxylic acid methyl ester of (*S*)-**1** with $LiAlH_4$ gave the expected primary alcohol (*S*)-**25**, that was eventually converted into the corresponding ester (*S*,*R*)-**27** by reaction with the Mosher acid (*R*)-(+)-**26** in the presence of DCC. The same sequence was previously performed on *rac*-**1**,[8] obtaining an equimolar mixture of the two Mosher's esters (referred to as *rac*-**27** in Section 4) to test



Scheme 6. Proposed mechanistic explanation for the formation of compound **19** during the Wittig reaction.



Scheme 7. Reagents and conditions: (a) (i) HCl–MeOH; (ii) 3 N aq HCl/THF; (b) Cbz_2O, THF, 0 °C; (c) PCC, 4 Å MS, CH_2Cl_2; (d) Ph_3PCH_3Br, KHMDS, toluene, −78 °C to rt; (e) $LiOH{\cdot}H_2O$, H_2O/THF/MeOH.



Scheme 8. Reagents and conditions: (a) $LiAH_4$, THF, 0 °C to rt; (b) (*R*)-**26**, DCC, CH_2Cl_2.

the viability of the method. Baseline separation of signals was observed only in spectra of Mosher esters in DMSO-d_6 solution. Relative integration of the doublets at 4.41. and 4.49 [for (*S*,*R*)-**27**] and 4.31 and 4.61 [for (*R*,*R*)-**27**], assigned to the diastereotopic methylene protons linked to the ester oxygen, gave an enantiomeric excess >94% (Fig. 1).

3. Conclusions

In conclusion, we have described a fast and practical enantioselective synthesis of (*S*)-*N*-Cbz-α-vinyl phenylalanine, suitable for the preparation of different (*S*)-*N*-Cbz-α-vinyl

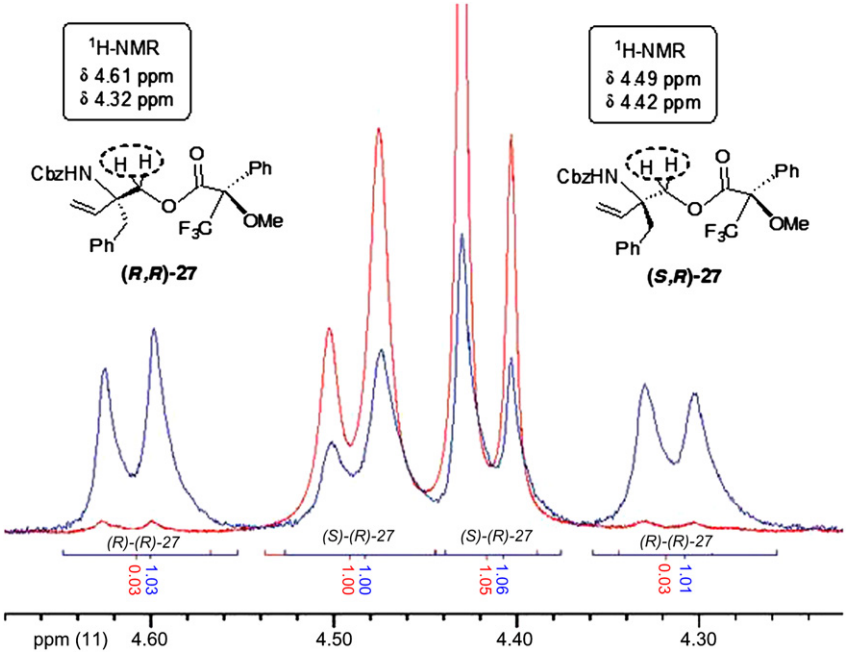


Figure 1. In blue: DMSO-d_6 ^{1}H NMR of the equimolar mixture of Mosher's esters **27**; in red: DMSO-d_6 ^{1}H NMR of the enantioenriched Mosher's ester (*S*,*R*)-**27**.

α-alkyl amino acids and their enantiomers as well. The new protocol exploits a Wittig reaction on highly enantioenriched *N*-Cbz, α-formyl, and α-alkyl amino esters, readily accessible from L-serine through a stereoselective alkylation of Seebach's oxazolidine **5**, performed with a significant improvement of the previously reported method. The new protocol (1) affords final products with good overall yields (>43% from Seebach's oxazolidine **5**); (2) can provide easy access to both enantiomers of the target compounds with a very good enantiomeric excess (>94%); (3) is very practical, with a limited number of steps and simple experimental procedures; (4) can be easily applied also to a multi-gram scale synthesis: in our laboratory we routinely processed 8–10 g batches.

4. Experimental

4.1. General

THF and toluene were distilled from sodium/benzophenone ketyl and CH_2Cl_2 from CaH_2. TLC was performed on Kieselgel 60 F254 (Merck) glass Plate with detection by UV light, iodine, or a solution of 4,4-methylenebis-*N*,*N*-dimethylaniline, ninidrine, KI in an aqueous ethanolic solution of AcOH. Flash chromatography was performed on Merck Kieselgel 60 (230–400 mesh). Melting points were determined on a Kofler apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 343 polarimeter. The ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with Bruker Avance 400 instruments. In the peak listing of ^{13}C spectra abbreviations s and t refer to zero and two protons attached to the carbons, as determined by DEPT experiments. Infrared spectra were recorded on a Perkin–Elmer FTIR 1600 series spectrometer. Mass spectra were recorded on a Finnigan LCQ-DECA mass spectrometer. Elemental analyses were performed on a Carlo Erba Elemental Analyzer Mod. 1106.

4.2. General procedure for the alkylation of oxazolidine 5

To a 0.2 M solution of **5**[15] (1 equiv) in freshly distilled THF stirred in a nitrogen atmosphere were added in sequence DMPU (1:6 of the THF volume), the alkyl halide (4 equiv), and hexane (1:6 of the THF volume). The resulting solution was then cooled to −78 °C and NaHMDS (1.2 equiv of a 1.0 M solution in THF) was added dropwise (very slowly); the reaction mixture turned to pale yellow. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl; the reaction mixture was then allowed to warm to rt, diluted with water, and extracted three times with AcOEt; the combined organic phases were dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The resulting crude was purified by flash chromatography.

4.3. (2*R*,4*S*)-Methyl 4-benzyl-2-*tert*-butyl-3-formyloxazolidine-4-carboxylate 6

The reaction was performed on 8 g (37.2 mmol) of **5**, using freshly distilled benzyl bromide (22 mL, 148.8 mmol) as electrophile, and quenched after 70 min. The crude was then purified by flash chromatography on silica gel (elution with hexanes/AcOEt 7:3), affording 9.4 g of the title compound (83%) as colorless crystals, mp = 129–130 °C (Et_2O/pentane) $[\alpha]_D = +32.6$ (*c* 1.2, $CHCl_3$, 23 °C). IR (Nujol) 2960, 1740, 1670, 1434, 1400, 1376, 1364, 1347, 1129, 1062, 1032, 980, 964, 885 cm^{-1}. ^{1}H NMR (DMSO-d_6, 120 °C): δ 0.90 (s, 9H), 3.40 (d, $J = 13.7$ Hz, 1H), 3.47 (d, $J = 13.7$ Hz, 1H), 3.73 (s, 3H), 4.08 (d, $J = 9.1$ Hz, 1H), 4.25 (d, $J = 9.1$ Hz, 1H), 4.63–4.93 (br s, 1H), 7.14–7.21 (m, 2H), 7.23–7.33 (m, 3H), 8.53 (s, 1H). ^{13}C NMR ($CDCl_3$, DMSO-d_6, 120 °C): δ 26.6, 38.0 (s), 53.1, 69.3 (s), 73.4 (t), 97.7, 127.9, 129.1, 130.9, 135.8 (s), 162.0, 171.7 (s). The benzylic methylene signal is obscured by the solvent. DEPT spectrum recorded in $CDCl_3$ revealed methylene carbon at 44.6 ppm; MS (ESI) *m*/*z*: 306.2 $[M+H]^+$, 328.1 $[M+Na]^+$. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.93; H, 7.53; N, 4.54.

4.4. (2*R*,4*S*)-Methyl 2-*tert*-butyl-3-formyl-4-methyloxazolidine-4-carboxylate 8

The reaction was performed on 1 g (4.65 mmol) of **5**, using methyl iodide (4.34 mL, 69.75 mmol) as electrophile and quenched after 40 min. The crude was then purified by flash chromatography on silica gel (elution with hexanes/AcOEt = 6:4), affording 1.1 g of the title compound (95%) as a colorless oil. $[\alpha]_D = -32.6$ (*c* 0.9, $CDCl_3$, 23 °C). IR (neat) 2975, 2920, 2880, 1745, 1676, 1405, 1385, 1370, 1350, 1303, 1146, 1121, 1080, 968 cm^{-1}. ^{1}H NMR (DMSO-d_6, 120 °C): δ 0.95 (s, 9H), 1.65 (s, 3H), 3.72 (s, 3H), 3.75 (d, $J = 8.8$ Hz, 1H), 4.40 (d, $J = 8.7$ Hz, 1H), 5.10 (s, 1H), 8.40 (s, 1H). ^{13}C NMR (DMSO-d_6, 120 °C): δ 22.6, 26.5, 37.8 (s), 53.1, 65.6 (s), 76.1 (t), 97.1, 161.9, 172.6 (s). MS (ESI) *m*/*z*: 230.2 $[M+H]^+$, 252.1 [M+Na] Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.52; H, 8.22; N, 6.01.

4.5. (2*R*,4*S*)-Methyl 2-*tert*-butyl-4-ethyl-3-formyloxazolidine-4-carboxylate 9

The reaction was performed on 1 g (4.65 mmol) of **5**, using ethyl iodide (5.6 mL, 69.7 mmol) as electrophile and quenched after 60 min. The crude was then purified by flash chromatography on silica gel (elution with hexanes/AcOEt = 6:4), affording 848 mg of the title compound (75%) as a colorless oil. $[\alpha]_D = -29.1$ (*c* 0.7, $CHCl_3$, 23 °C). IR (neat): 2980, 2920, 2890, 1745, 1676, 1482, 1462, 1440, 1404, 1358, 1335, 1268, 1230, 1216, 1090, 1072, 1039, 970, 890 cm^{-1}. ^{1}H NMR ($CDCl_3$, 7:3 mixture of rotamers): δ 0.88 (t, $J = 7.4$ Hz, 0.9 H), 0.90 (s, 6 H), 0.94 (t, $J = 7.4$ Hz, 2.1H), 1.01 (s, 3H), 1.90 (dq, $J_1 = 7.4$ Hz, $J_2 = 14.7$ Hz, 0.7H), 2.07 (dq, $J_1 = 7.4$ Hz, $J_2 = 14.7$ Hz, 0.3H), 2.19 (dq, $J_1 = 7.4$ Hz, $J_2 = 14.7$ Hz, 0.7 H), 2.51 (dq, $J_1 = 7.4$ Hz, $J_2 = 14.7$ Hz, 0.3H), 3.75 (s, 0.9H), 3.78 (d, $J = 8.9$ Hz, 0.9H), 3.94 (d, $J = 8.9$ Hz, 2.1H), 4.29 (d, $J = 8.9$ Hz, 0.9H), 4.62 (d, $J = 8.9$ Hz, 2.1H), 4.90 (s, 0.3H), 5.32 (s, 0.7H), 8.42 (s, 0.3H), 8.46 (s, 0.7H) ^{13}C NMR ($CDCl_3$, mixture of rotamers): δ 8.0, 8.5, 25.6 (t), 25.9, 26.3, 31.5 (t), 37.9 (s), 38.8 (s), 53.0, 53.3, 68.8 (s), 69.2 (s), 73.5 (t), 74.8 (t), 97.4, 98.5, 160.0,

163.0, 172.5 (s). MS (ESI) *m/z*: 244.2 $[M+H]^+$, 266.1 $[M+Na]^+$. Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.30; H, 8.81; N, 5.79.

4.6. (2*R*,4*S*)-Methyl 4-allyl-2-*tert*-butyl-3-formyloxazolidine-4-carboxylate 10

The reaction was performed on 1g (4.65 mmol) of **5**, using freshly distilled allyl bromide (6.0 mL, 69.7 mmol) as electrophile, and quenched after 65 min. The crude was then purified by flash chromatography on silica gel (elution with hexanes/AcOEt = 7:3), affording 1.059 g of the title compound (89%) as a colorless oil. $[\alpha]_D = -8.6$ (*c* 0.8, $CHCl_3$, 23 °C). IR (neat) 2960, 2910, 2875, 1740, 1670, 1434, 1477, 1436, 1399, 1376, 1365, 1350, 1319, 1296, 1126, 1097, 990, 930, 886 cm^{-1}. ^1H NMR (DMSO-d_6, 120 °C): δ 0.94 (s, 9H), 2.83–2.95 (m, 2H), 3.73 (s, 3H), 3.99 (d, $J = 9.0$ Hz, 1H), 4.37 (d, $J = 9.0$ Hz, 0.5H), 5.07 (s, 1H), 5.13–5.23 (m, 2H), 5.73 (tdd, $J = 7.1$, 10.2, 17.3 Hz, 1H), 8.44 (s, 1H). ^{13}C NMR ($CDCl_3$, mixture of rotamers): δ 25.9, 26.4, 36.8 (t), 37.9 (s), 38.8 (s), 42.9 (t), 53.2, 53.4, 67.7 (s), 68.5 (s), 73.5 (t), 74.5 (t), 97.4, 98.7, 120.7 (t), 121.9 (t), 129.8, 131.9, 160.1, 162.9, 171.4 (s), 172.0 (s). MS (ESI) *m/z*: 256.1 $[M+H]^+$, 278.2 $[M+Na]^+$. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.32; H, 8.35; N, 5.69.

4.7. General procedure for the hydrolysis of 4-alkyl-oxazolidines

A solution of the suitable 4-alkyl oxazolidine (1.0 mmol) in saturated HCl methanol was stirred at 0 °C for 5 min and then at rt for 6 h (or until complete consumption of the starting material, as seen by TLC). The solvent was evaporated under reduced pressure and the residue taken up in THF (2.7 mL) and 3 M HCl aqueous solution (1 mL), and the whole stirred overnight at rt. Then the reaction mixture was basified with solid Na_2CO_3, diluted with AcOEt, and extracted three times. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness under reduced pressure, affording the desired alkyl serine derivative.

4.8. (2*S*)-Methyl 2-amino-2-(hydroxymethyl)-3-phenyl-propanoate 3

The reaction was performed on 4 g (13.11 mmol) of **6** as described in the general procedures, affording 2.6 g of the title compound (95%), as a white solid, which can be crystallized from AcOEt/Et_2O, affording white needles, mp = 91–93 °C (AcOEt/Et_2O). TLC R_f 0.28 (AcOEt/MeOH 98:2). $[\alpha]_D = +5.4$ (*c* 1.2, $CDCl_3$, 23 °C). IR (Nujol): 2923.1, 2360.4, 2340.6, 1734.2, 1558.4 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.46 (br s, 3H, exchanges with D_2O); 2.83 (d, $J = 13.4$ Hz, 1H); 3.12 (d, $J = 13.4$ Hz, 1H); 3.63 (d, $J = 10.8$ Hz, 1H); 3.75 (s, 3H); 3.89 (d, $J = 10.8$ Hz, 1H); 7.12–7.15 (m, 2H); 7.25–7.34 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 42.2 (t), 52.8, 64.1 (s), 68.2 (t), 127.6, 129.0, 130.2, 135.6 (s), 175.5 (s). MS (ESI) *m/z*: 210.1 $[M+H]^+$, 232.1 $[M+Na]^+$. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.15; H, 7.35; N, 6.55.

4.9. (2*S*)-Methyl 2-amino-3-hydroxy-2-methylpropanoate 20a

The reaction was performed on 800 mg (3.49 mmol) of **8** as described in the general procedures, affording 418 mg of the title compound (90%) as a colorless oil. TLC R_f 0.32 AcOEt/MeOH 95:5. $[\alpha]_D = -17.2$ (*c* 1.2, $CHCl_3$, 23 °C). IR (neat) 3369.7, 2924.6, 2854.4, 1732.3, 1261.8, 1156.2 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.15 (s, 3H); 3.20–3.96 (b, exchanges with D_2O, 2H); 3.32 (d, $J = 10.5$ Hz, 1H); 3.53 (d, $J = 10.5$ Hz, 1H); 3.63 (s, 3H); 4.96–5.28 (b, exchanges with D_2O, 1H). ^{13}C NMR ($CDCl_3$): δ 21.3, 54.1, 60.8 (s), 70.1 (t), 178.5 (s). MS (ESI) *m/z*: 134.0 $[M+H]^+$, 156.1 $[M+Na]^+$. Anal. Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.33; N, 10.52. Found: C, 45.23; H, 8.25; N, 10.57.

4.10. (2*S*)-Methyl 2-amino-2-(hydroxymethyl)pent-4-enoate 20b

The reaction was performed on 510 mg (2 mmol) of **10** as described in the general procedures, affording 289 mg (91%) of the title compound as yellow oil. TLC R_f 0.38 AcOEt/MeOH 98:2. $[\alpha]_D = +2.3$ (*c* 1.7, $CHCl_3$, 23 °C). IR (neat) 3418.6, 2363.5, 1728.8, 1643.7, 1441.0, 1228.6, 1060.3 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.24 (dd, $J_1 = 8.4$ Hz, $J_2 = 13.6$ Hz, 1H), 2.47 (dd, $J_1 = 13.6$ Hz, $J_2 = 6.5$ Hz, 1H), 2.63 (br s, 3H, exchange with D_2O), 3.50 (d, $J = 10.8$ Hz, 1H), 3.64 (s, 3H), 3.79 (d, $J = 10.8$ Hz, 1H), 5.08–5.20 (m, 2H), 5.57–5.71 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 40.7(t), 52.9, 62.8 (s), 68.2 (t), 120.4 (t), 132.0, 176.1 (s). MS (ESI) *m/z* 160.0 $[M+H]^+$, 182.1 $[M+Na]^+$. Anal. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.89; H, 8.37; N, 8.80.

4.11. General procedure for the selective N-protection of the α-alkyl-serines

The suitable alkyl serine derivative (1 mmol) was added to an ice-chilled solution of dibenzyldicarbonate (1.4 mmol) in anhydrous THF (3.8 mL). The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ and the reaction mixture extracted with AcOEt three times. The combined organic layers were dried on Na_2SO_4 and evaporated to dryness under reduced pressure at rt.

4.12. (*S*)-Methyl 2-benzyl-2-(benzyloxycarbonylamino)-3-hydroxypropanoate 14

The reaction was performed by adding 1.0 g (5 mol) of solid **3** to the ice-chilled solution of dibenzyldicarbonate and quenched after 15 min. The aqueous work-up and purification by flash chromatography (elution with hexanes/AcOEt 4:3), afforded 1.63 g of the title compound (95%) as a colorless oil. TLC R_f 0.37 (Ex/AcOEt 6:4). $[\alpha]_D = -70.0$ (*c* 1.9, $CHCl_3$, 23 °C). IR (neat): 3419.9; 3031.8; 2953.2; 1733.6; 1699.6 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.90–3.16 (b, 1H exchanges with D_2O); 3.10 (d, $J = 13.6$ Hz, 1H); 3.39 (d, $J = 13.6$ Hz, 1H); 3.80 (s, 3H); 3.97 (d, $J = 11.0$ Hz, 1H), 4.33 (d, $J = 11.1$ Hz, 1H), 5.07 (d, $J = 12.2$ Hz, 1H); 5.22 (d, $J = 12.2$ Hz, 1H); 5.64 (s, 1H); 6.94–7.04 (m, 2H); 7.17–7.27 (m, 3H); 7.33–7.46 (m,

5H). ^{13}C NMR ($CDCl_3$): δ 52.9 (t), 68.0, 82.0, 80.6 (t), 82.0 (t), 142.4, 143.4, 143.5, 143.7 (2 peaks), 144.9, 150.0 (s), 151.4 (s), 170.5 (s), 187.3 (s). MS (ESI): 344.3 $[M+H]^+$, 366.2 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.59; H, 6.21; N, 4.22.

4.13. (*S*)-Methyl 2-(benzyloxycarbonylamino)-3-hydroxy-2-methylpropanoate 21a

The reaction was performed by adding 418 mg (3.14 mmol) of **20a** dissolved in 3.5 mL of distilled THF to the ice-chilled solution of dibenzyldicarbonate and quenched after 15 min. The aqueous work-up and purification by flash chromatography (gradient elution hexanes/AcOEt, from 8:2 to 6:4) afforded 822 mg of the title compound (98%) as a white solid, mp 61–62 °C (AcOEt). TLC R_f 0.33 (Ex/AcOEt 6:4). $[\alpha]_D = +3.9$ (*c* 1.7, $CDCl_3$, 23 °C) {lit.[27] $[\alpha]_D = +5.4$ (*c* 0.50, $CHCl_3$, 27 °C)}. IR (Nujol) 3378.1, 1744.8, 1686.4, 1545.0, 1280.3, 1228.1, 1073.3 cm^{-1}. ^{1}H NMR (DMSO-d_6, 120 °C): δ 1.43 (s, 3H); 3.60 (d, $J = 10.8$ Hz, 1H); 3.62 (s, 3H); 3.65 (d, $J = 10.8$ Hz, 1H); 4.37–4.70 (b, exchanges with D_2O, 1H); 5.05 (s, 2H); 6.57–6.71 (b, exchanges with D_2O, 1H); 7.28–7.40 (m, 5H).^{13}C NMR ($CDCl_3$): δ 21.5, 53.3, 61.8 (s), 66.9 (t), 67.3 (t), 128.5, 128.7, 129.0, 136.5 (s), 156.0 (s), 174.0 (s). MS (ESI) *m*/*z*: 268.2 $[M+H]^+$, 290.1 $[M+Na]^+$. Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.49; H, 6.37; N, 5.44.

4.14. (*S*)-Methyl 2-(benzyloxycarbonylamino)-2-(hydroxymethyl)pent-4-enoate 21b

The reaction was performed by adding 300 mg (1.88 mol) of **20b** dissolved in 3 mL of distilled THF to the ice-chilled solution of dibenzyldicarbonate and quenched after 15 min. The aqueous work-up and purification by flash chromatography (gradient elution hexanes/AcOEt, from 7:3 to 1:1) afforded 486 mg of the title compound (88%) as a colorless oil. TLC R_f 0.32 Ex/AcOEt 55:45. $[\alpha]_D = -2.1$ (*c* 0.5, $CHCl_3$, 23 °C). IR (neat) 3414.0, 3070.4, 2954.0, 2363.8, 1721.0, 1690.2, 1643.2, 1506.6, 1445.4, 1329.1, 1234.2, 1056.6, 923.7, 827.7, 741.8, 698.7 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.59–2.74 (m, 2H), 3.64 (s, 3H), 3.72 (AB system, $J = 12.1$ Hz, 2H; after D_2O exchange: δ 3.69 (d, $J = 11.0$ Hz, 1H); 3.73 (d, $J = 11.0$, 1H)); 4.42–4.59 (br s, 1H, exchanges with D_2O), 5.00–5.10 (m, 4H) 5.66–5.79 (m, 1H); 6.49 (s, 1H, exchanges with D_2O); 7.26–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 37.4 (t), 53.31, 65.4 (s), 65.7 (t), 67.3 (t), 120.5 (t), 128.4, 128.6, 128.9, 131.5, 136.5 (s), 155.7 (s), 172.8 (s). MS (ESI) *m*/*z*: 294.2 $[M+H]^+$, 317.3 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61,42; H, 6,53; N, 4,78. Found: C, 61.45; H, 6.56; N, 4.79.

4.15. General procedure for the oxidation of the α-alkyl-serines

Activated 4 Å molecular sieves (threefolds the weight of the starting material) and PCC (1.5 mmol) were added in sequence to a solution of the suitable *N*-Cbz-α-alkyl serine derivative (1 mmol) in dry CH_2Cl_2 (5 mL). The resulting brownish suspension was vigorously stirred for 2 h, and then more PCC (0.5 mmol) and MS (1:6 of the initial amount used) were added. After 1 h and 30 min, the reaction mixture was filtered through a pad of Celite® and silica, washing carefully first with anhydrous Et_2O (4 × 5 mL) and then with CH_2Cl_2, until a clear and colorless filtrate was obtained. Evaporation of the solvent under reduced pressure at rt afforded a crude that was used in the next step without any further purification.

4.16. (*S*)-Methyl 2-benzyl-2-(benzyloxycarbonylamino)-3-oxopropanoate 2

The reaction was performed on 1 g of **14** (2.91 mmol), following the general procedure for the oxidation, and afforded a pale yellow oil that was used in the next step without any further purification. A sample from the reaction mixture (300 mg) was purified by flash chromatography (elution with hexanes/AcOEt 77:23) for sake of characterization, affording 261 mg of the title compound (87%) as a colorless oil. TLC R_f 0.37 (hexanes/AcOEt 77:23). $[\alpha]_D = -16.1$ (*c* 0.9, $CDCl_3$, 23 °C). IR (neat) 3408.4, 2954.6, 1726.3, 1687.2, 1496.4, 1272.7, 1213.4, 1075.7, 1042.4 cm^1. ^{1}H NMR ($CDCl_3$): δ 3,53 (d, $J = 14.0$ Hz, 1H); 3.61 (d, $J = 14.0$ Hz, 1H); 3.81 (s, 3H); 5.16 (d, $J = 12.2$ Hz, 1H); 5.21 (d, $J = 12.2$ Hz, 1H); 5.84 (s, 1H), 6.93–7.00 (m, 2H); 7.20–7.27 (m, 3H); 7.33–7.45 (m, 5H); 9.63 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 37.2 (t), 53.5, 67.2 (t), 71.8 (s), 126.3, 127.4, 128.2, 128.5 (2 peaks), 129.7, 133.7 (s), 135.8 (s), 154.9 (s), 167.0 (s), 192.6. MS (ESI) *m*/*z*: 342.2 $[M+H]^+$, 364.1 $[M+Na]^+$. Anal Calcd for $C_{19}H_{19}NO_5$ C, 66.85; H, 5.61; N, 4.10. Found: C, 66.99; H, 5.64; N, 4.05.

4.17. (*S*)-Methyl 2-(benzyloxycarbonylamino)-2-methyl-3-oxopropanoate 22a

The reaction was performed on 712 mg of **21a** (2.66 mmol), following the general procedures for the oxidation and afforded a pale yellow oil that was used in the next step without any further purification. A sample from the reaction mixture (200 mg) was purified by flash chromatography (elution with hexanes/AcOEt 7:3) for sake of characterization, affording 174 mg of the title compound (87%) as a colorless oil. TLC R_f 0.27 (Ex/AcOEt 7:3). $[\alpha]_D = -19.2$ (*c* 1.0, $CDCl_3$, 23 °C). IR (neat) 3405.1, 3067.3, 3024.7, 2925.0, 1746.8, 1689.2, 1545.7, 1279.8, 1229.3, 1071.3 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.70 (s, 3H); 3.81 (s, 3H); 5.13 (s, 2H); 6.00 (br s, 1H); 7.37 (br s, 5H); 9.54 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 19.5, 54.0, 67.4 (s), 67.7 (t), 128.6, 128.8, 129.0, 136.3 (s), 155.5 (s), 169.3 (s), 193.8. MS (ESI) *m*/*z*: 266.1 $[M+H]^+$, 288.0 $[M+Na]^+$. Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.89; H, 5.61; N, 5.36.

4.18. (*S*)-Methyl 2-(benzyloxycarbonylamino)-2-formylpent-4-enoate 22b

The reaction was performed on 440 mg of **21b** (1.5 mmol), following the general procedures for the oxidation, and afforded a pale yellow oil that was used in the next step without any further purification. A sample from the reaction mixture (150 mg) was purified by flash chromatogra-

phy (elution with hexanes/AcOEt 65:35) for sake of characterization, affording 132 mg of the title compound (88%) as a colorless oil. TLC R_f 0.32 Ex/AcOEt 65:35. $[\alpha]_D = -17.8$ (c 0.5, $CHCl_3$, 23 °C). IR (neat) 3401.4, 3070.2, 3032.6, 2955.4, 1727.8, 1688.6, 1505.3, 1444.3, 1376.7, 1230.3, 1041.6, 928.6, 841.1, 744.5, 698.9 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.65–2.79 (m, 2H); 3.71 (s, 3H); 5.08 (s, 2H); 5.09–5.16 (m, 2H); 5.72 (tdd, $J = 7.2$, 10.2, 17.4 Hz, 1H); 7.29–7.40 (m, 5H); 7.39–7.47 (br s, exchanges with D_2O); 9.68 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 36.7 (t), 53.9, 67.7 (t), 70.5 (s), 121.5 (t), 128.5, 128.8, 129.0, 130.3, 136.0 (s), 168.0 (s), 173.8 (s), 193.6. MS (ESI) m/z: 292.2 [M+H]+, 314.1 [M+Na]+. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.93; H, 5.94; N, 4.75.

4.19. General procedure for the methylenation of *N*-carbobenzyloxy-α-formyl-α-alkyl-glycines

The phosphonium salt Ph_3PCH_3Br (2 mmol), dried overnight at 110 °C, was quickly transferred to a flame-dried flask and purged with nitrogen; anhydrous distilled toluene (3.7 mL) was added. The resulting suspension was magnetically stirred and treated with KHMDS (1.9 mmol, 3.8 mL of a 0.5 M solution in toluene), affording a brilliant yellow suspension. After 90 min, the reaction mixture was cooled to −78 °C and a solution of the suitable crude aldehyde (1 mmol) in anhydrous distilled toluene (2.5 mL) was added dropwise. After 45 min the temperature was slowly warmed to −60 °C; after 10 min, the reaction mixture was slowly warmed to −40 °C, and finally, after 30 min, stirred at rt. After 1 h at room temperature, the reaction mixture was cooled to −20 °C and quenched with 3 N HCl (5.5 mL) and saturated NH_4Cl (5.5 mL) aqueous solutions. The reaction mixture was diluted with AcOEt, the organic layer separated, and the aqueous one extracted twice with the same solvent. The combined organic solvents were dried over Na_2SO_4 and evaporated to dryness under reduced pressure, affording a crude, which was purified by flash chromatography, affording the desired vinyl derivative.

4.20. (*S*)-Methyl 2-benzyl-2-(benzyloxycarbonylamino)but-3-enoate 15

The reaction was performed on 700 mg of **2** (2.0 mmol), following the general procedures for the methylenation. The crude was purified by flash chromatography (gradient elution hexanes/AcOEt, from 95:5 to 8:2), affording 472 mg of the title compound (68%) as a colorless oil. TLC R_f 0.43 (hexanes/AcOEt 82:18). $[\alpha]_D = -37.6$ (c 1.1, $CDCl_3$, 23 °C). IR (neat): 3420.1; 3031.6; 2951.6; 1733.8; 1684.1; 1506.5 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.33 (d, $J = 13.4$ Hz, 1H); 3.65 (d, $J = 13.5$ Hz, 1H); 3.79 (s, 3H); 5.09 (d, $J = 12.3$ Hz, 1H); 5.22 (d, $J = 12.3$ Hz, 1H); 5.30 (d, $J = 17.5$ Hz, 1H); 5.36 (d, $J = 10.5$ Hz, 1H); 5.70 (br s, 1H); 6.09 (dd, $J = 10.6$ Hz, $J_2 = 17.3$ Hz, 1H); 6.95–7.03 (m, 2H); 7.15–7.26 (m, 3H); 7.32–7.46 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 40.3 (t), 52.8, 65.1 (s), 66.5 (t), 116.1 (t), 126.9, 128.1, 128.2 (2 peaks), 128.4, 129.9, 135.4 (s), 136.5, 154.3 (s), 171.7 (s). MS (ESI) m/z: 340.0 $[M+H]^+$, 362.1 $[M+Na]^+$. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13; O, 18.86. Found: C, 70.89; H, 6.17; N, 4.20.

4.21. (*S*)-Methyl 2-(benzyloxycarbonylamino)-2-methylbut-3-enoate 23a

The reaction was performed on 180 mg of **22a** (0.67 mmol), following the general procedures for the methylenation. The crude was purified by flash chromatography (eluting with hexanes/AcOEt 8:2), affording 112 mg of the title compound (63%), as a colorless oil. TLC R_f 0.30 Ex/AcOEt 8:2. $[\alpha]_D = +3.5$ (c 1.7, $CDCl_3$, 23 °C). IR (neat) 3347.3; 2951.9; 1735.3; 1719.0; 1518.1; 1454.8; 1275.0; 1123.9 cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.52 (s, 3H); 3.63 (s, 3H); 5.05 (s, 2H); 5.15 (d, $J = 10.7$ Hz, 1H); 5.23 (d, $J = 17.3$ Hz, 1H); 6.16 (dd, $J_1 = 10.7$ Hz, $J_2 = 17.4$ Hz, 1H); 7.10–7.25 (br s, 1H, exchanges with D_2O); 7.27–7.43 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 23.5, 53.9, 61.0 (s), 67. 1 (t), 116.0 (t), 128.5, 128.6, 128.9, 136.7 (s), 138.1, 155.1 (s), 173.4 (s). MS (ESI) m/z: 264.1 $[M+H]^+$, 286.0 $[M+Na]^+$. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.78; H, 6.62; N, 5.35.

4.22. (*S*)-Methyl 2-(benzyloxycarbonylamino)-2-vinylpent-4-enoate 23b

The reaction was performed on 175 mg of **22b** (0.60 mol), following the general procedures for the methylenation. The crude was purified by flash chromatography (eluting with hexanes/AcOEt 8:2), affording 122 mg of the title compound (70%), as a colorless oil. TLC R_f 0.33 hexanes/AcOEt 8:2. $[\alpha]_D = -17.6$ (c 0.8, $CHCl_3$, 23 °C). IR (neat) 3357.5, 3072.0, 3031.5, 3952.5, 2363.7, 1729.1, 1642.4, 1500.6, 1443.7, 1229.4, 1078.7, 926.1, 820.9, 778.1, 741.7, 698.2 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.65–2.79 (m, 2H); 3.64 (s, 3H); 5.02–5.09 (m, 4H); 5.07 (tdd, $J_1 = 7.9$, $J_2 = 13.1$, $J_3 = 17.5$, 1H); 5.19 (d, $J = 10.8$ Hz, 1H); 5.23 (d, $J = 17.6$ Hz, 1H); 6.10 (dd, $J_1 = 10.8$, $J_2 = 17.5$, 1H); 6.92–7.06 (br s, 1H, exchanges with D_2O); 7.27–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 40.2 (t), 53.4, 64.2 (s), 67.0 (t), 116.1 (t), 120.3 (t), 128.5 (2), 128.9, 132.0, 136.6, 136.8 (s), 154.7 (s), 172.5 (s). MS (ESI) m/z: 290.1 $[M+H]^+$, 312.0. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.59; H, 6.67; N, 4.97.

4.23. General procedure for the saponification of *N*-Cbz-α-vinyl-α-alkyl-glycine methyl esters

$LiOH \cdot H_2O$ (2 mmol) in 2.5 mL of H_2O and distilled THF (5 mL) were added to a stirred solution of the suitable *N*-Cbz-α-alkyl-α-vinyl-glycine derivative (1 mmol) in MeOH (1 mL). After 8 h the solvents were evaporated under reduced pressure, the resulting residue taken up with H_2O and acidified with 12 N HCl, then extracted three times with AcOEt.

The combined organic solvents were dried over Na_2SO_4 and evaporated to dryness under reduced pressure, affording the desired free carboxylic acid.

4.24. (*S*)-2-Benzyl-2-(benzyloxycarbonylamino)but-3-enoic acid 1

The reaction was performed on 295 mg of **15** (0.87 mmol) according to the general procedure for the saponification, and afforded 271 mg of the title compound (96%) as a colorless oil. TLC R_f 0.42 (EtOAc/MeOH 99:1). $[\alpha]_D = -30.9$ (*c* 1.0, $CDCl_3$, 23 °C). IR (neat) 3400.2, 3033.7, 1709.8, 1688.7, 1495.3, 1446.7 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.39 (d, $J = 13.4$ Hz, 1H), 3.60 (d, $J = 13.4$ Hz, 1H), 5.11 (d, $J = 12.2$ Hz, 1H), 5.21 (d, $J = 12.2$ Hz, 1H), 5.34 (d, $J = 17.3$ Hz, 1H), 5.37 (d, $J = 10.6$ Hz, 1H), 5.48–6.80 (br s, 1H, exchanges with D_2O), 5.63 (s, 1H), 6.11 (dd $J_1 = 10.6$ Hz, $J_2 = 17.3$ Hz, 1H), 7.04–7.11 (m, 2H), 7.16–7.26 (m, 3H), 7.35–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 40.8 (t), 65.4 (s), 67.3 (t), 116.8 (t), 127.5, 128.2, 128.7 (2 peaks), 129.0, 130.5, 135.6 (s), 136.6, 136.7 (s), 155.1 (s), 176.3 (s). MS (ESI) *m*/*z*: 326.2 $[M+H]^+$, 348.1 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.27; H, 5.92; N, 4.53.

4.25. (*S*)-2-(Benzyloxycarbonylamino)-2-methylbut-3-enoic acid 24a

The reaction was performed on 190 mg of **22a** (0.72 mmol) according to the general procedure for the saponification, and afforded 177 mg of the title compound (99%) as a colorless oil. TLC R_f 0.43 AcOEt/MeOH 98:2. $[\alpha]_D = +7.2$ (*c* 1.0, $CDCl_3$, 23 °C). IR (neat): 3431.3, 3050.2, 2543.4, 1686.1, 1450.9, 1208.7 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.71 (s, 3H), 5.14 (s, 2H), 5.31 (d, $J = 10.5$ Hz, 1H), 5.36 (d, $J = 17.5$ Hz, 1H), 5.60 (s, 1H), 5.67–6.40 (br s, 1H, exchanges with D_2O), 6.10 (dd, $J_1 = 10.5$ Hz, $J_2 = 17.5$ Hz, 1H), 7.37 (m, 5H) ^{13}C NMR ($CDCl_3$): δ 23.6 (q), 60.7, 60.8 (s), 67.4 (t), 116.4 (t), 128.5 (d), 128.6 (d), 128,8 (s), 128.9 (d), 137.5 (d), 147.9 (s), 77.1 (s). MS (ESI) *m*/*z*: 250.1 $[M+H]^+$, 272.0 $[M+Na]^+$. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.67; H, 6.09; N, 5.63.

4.26. (*S*)-2-(Benzyloxycarbonylamino)-2-vinylpent-4-enoic acid 24b

The reaction was performed on 100 mg of **22b** (0.346 mmol) according to the general procedure for the saponification, and afforded 93 mg of the title compound (98%) as a colorless oil.

TLC R_f 0.38 AcOEt/MeOH 98:2. $[\alpha]_D = -7.5$ (*c* 0.4, $CHCl_3$, 23 °C). IR (neat) 3427.9, 3081.8, 2363.5, 1713.4, 1502.8, 1415.8, 1232.7, 1083.4, 992.8, 926.5, 743.5, 696.1 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.68–2.88 (m, 1H), 2.93–3.08 (m, 1H), 5.08–5.22 (m, 4H), 5.28–5.38 (app. d, 2H), 5.61–5.79 (m, 2H), 6.10 (dd, $J_1 = 10.5$, $J_2 = 17.3$ Hz, 1H), 7.29–7.43 (m, 5H), 11.30–12.50 (br s, 1H, exchanges with D_2O) ^{13}C NMR ($CDCl_3$): δ 40.3(t), 60.9 (s), 67.4 (t), 116.6 (t), 120.7 (t), 128.5, 128.6, 128.9, 131.7, 136.3, 136.6 (s), 155.1(s), 176.4 (s). MS (ESI) *m*/*z*: 276.2 $[M+H]^+$, 298.1 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.64; H, 6.31; N, 4.99.

4.27. (2*S*) and (2*S* and 2*R*)-benzyl 2-benzyl-1-hydroxybut-3-en-2-ylcarbamate [(*S*)-25 and *rac*-25]

$LiAlH_4$ (177 mg, 4.65 mmol) was transferred in a flame dried flask, and was dissolved in anhydrous THF (3 mL), in a nitrogen atmosphere. The resulting solution was ice-chilled and (*S*)-**1** (220 mg, 0.67 mmol) in 3 mL di THF was added dropwise. When the addition was over, the reaction mixture was stirred at rt for 2 h. The reaction was quenched by the addition of Et_2O, AcOEt, and H_2O, the two layers were separated and the organic one was filtered on Celite®. The solvent was evaporated under reduced pressure and the resulting crude purified by flash chromatography (elution with hexanes/AcOEt 7:3), affording 176 mg of (*S*)-**25** (85%). The same procedure, applied on *rac*-**1** (120 mg, 0.37 mmol), afforded after chromatographic purification 83 mg of *rac*-**25** (72%).

(*S*)-**25**: colorless oil. $[\alpha]_D = +27.3$ (*c* 1.0, $CDCl_3$, 23 °C). ^1H NMR ($CDCl_3$): δ 3.06 (AB system, $J = 14.4$ Hz, 2H), 3.74 (d, $J = 12.1$ Hz, 1H), 3.78 (d, $J = 12.1$ Hz, 1H) 4.72 (s, 1H, exchanges with D_2O), 4.93 (br s, 1H, exchanges with D_2O), 5.06 (d, $J = 17.4$ Hz, 1H), 5.12 (d, $J = 12.5$ Hz, 1H), 5.15 (d, $J = 12.5$ Hz, 1H), 5.26 (d, $J = 10.8$ Hz, 1H), 5.88 (dd, $J_1 = 10.8$, $J_2 = 17.4$ Hz, 1H) 7.08–7.18 (m, 2H), 7.20–7.29 (m, 3H), 7.31–7.47 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 41.6 (t), 65.8 (s), 67.3 (t), 67.8 (t), 115.9 (t), 127.3, 127.9, 128.7, 129.0, 131.1, 136.0 (s), 136.7 (s), 139.5, 156.6 (s). MS (ESI) *m*/*z*: 312.2 $[M+H]^+$, 334.1 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.16; H, 6.64; N, 4.42.

4.28. (3*R*)-[(2′*S*) and (2′*S* and 2′*R*)-2′-benzyl-2′-(benzyloxycarbonylamino)but-3′-enyl]3,3,3-trifluoro-2-methoxy-2-phenylpropanoate [(*S*,*R*)-27 and (*S* and *R*)-(*R*)-27]

Mosher's acid (*R*)-(+)-**26**, (49.45 mg, 0.211 mmol) and DCC (43.53 mg, 0.211 mmol) were added to a solution of (*S*)-**25** (55 mg, 0.176 mmol) in 5ml of CH_2Cl_2. The whole was stirred at rt in a nitrogen atmosphere until complete disappearance of the starting material (monitored by TLC, eluting with hexanes/AcOEt 9:1). Then the reaction mixture was filtered, and the solvent evaporated under reduced pressure; the resulting crude was purified by flash chromatography, eluting with hexanes/AcOEt 7:3, affording 81 mg of (*S*,*R*)-**27** as a colorless oil (90%). The same procedure, applied to *rac*-**25** (55 mg, 0.176 mmol), afforded after chromatographic purification 73 mg of *rac*-**27** as a colorless oil (81%).

(*S*,*R*)-**27**: $[\alpha]_D = +7.2$ (*c* 1.0, $CDCl_3$, 23 °C). ^1H NMR (DMSO-d_6): δ 2.98 (d, $J = 13.4$ Hz, 1H), 3.04 (d, $J = 13.4$ Hz, 1H), 3.45 (s, 3H), 4.42 (d, $J = 10.9$, 1H), 4.49 (d, $J = 10.9$ Hz, 1H), 4.98–5.18 (m, 4H), 5.75 (dd, $J_1 = 11.2$, $J_2 = 17.6$ Hz, 1H), 6.95–7.05 (m, 2H), 7.18–7.27 (m, 3H), 7.30–7.47 (m, 9H), 7.51–7.58 (m, 2H). MS (ESI) *m*/*z* 528.2 $[M+H]^+$. Anal. Calcd for $C_{29}H_{28}F_3NO_5$: C, 66.03; H, 5.35; N, 2.66. Found: C, 66.22; H, 5.37; N, 2.43.

rac-**27**: ^1H NMR (DMSO-d_6): δ 2.91–3.07 (m, 2H); 3.45 (s, 3H); 4.32 (d, $J = 11.1$ Hz, 0.5H); 4.42 (d, $J = 10.9$ Hz,

0.5H); 4.49 (d, $J = 10.8$ Hz, 0.5H); 4.61 (d, $J = 11.1$ Hz, 0.5H); 4.98–5.18 (m, 4H); 5.71 (dd, $J_1 = 11.1$ Hz, $J_2 = 17.6$ Hz, 0.5H); 5.75 (dd, $J_1 = 11.2$ Hz, $J_2 = 17.6$ Hz, 0.5H); 6.86–6.96 (m, 2H); 7.13–7.22 (m, 3H); 7.26 (br s, 0.5H); 7.29–7.41 (m, 5.5H); 7.44–7.53 (m, 5H).

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