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Amino−Zinc−Enolate Carbometalation Reactions: Application to Ring Closure of Terminally Substituted Olefin for the Asymmetric Synthesis of *cis*- and *trans*-3-Prolinoleucine

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Received October 8, 2002

The amino−zinc−enolate cyclization reaction is a straightforward route for the synthesis of 3-substituted prolines. As classical intramolecular carbometalation reactions, the applicability of the addition of zinc to a double bond was limited to a substrate in which the terminal alkene carbon was unsubstituted. Being interested in the synthesis of *cis*- and *trans*-3-prolinoleucine derivatives for our structure−activity relation (SAR) studies, we focused our effort on the preparation of these compounds by amino−zinc−enolate cyclization of terminally substituted double bonds. Herein we report that the attachment of an activating group such as cyclopropyl to the terminal olefin carbon allows the amino−zinc−enolate cyclization of a terminally substituted alkene. The reaction is stereospecific, leading to a *trans*-3-substituted proline derivative, whereas a cis stereochemistry was observed with the amino−zinc−enolate cyclization of terminally nonsubstituted olefins. Absolute configurations obtained for the 3-prolinoleucine were established by X-ray analysis, NMR, and optical activity comparison of the cis and trans derivatives obtained by an unambiguous pathway.

Introduction

The anionic cyclization of olefinic alkylmetals provides a regiospecific and highly stereoselective route to functionalized carbocycles.[1] The reactivity of the organometallic species, concerning the nature of both metals (lithium, magnesium, aluminum, ...) and olefin (terminally substituted or unsubstituted, activated or unactivated), is well documented.[2] Recently, the carbocyclization of stabilized carbanion has been studied.[3] In this last example, the difficulty for the reaction to occur may be due to an endothermic process (involving the conversion of a stabilized enolate anion to an unstabilized sp^3 or sp^2 carbanion) associated with the nature of the alkene or alkyne (substituted or unsubstituted). Among these reactions, the amino−zinc−enolate cyclization, which we reported,[4] allows the synthesis of *cis*-3-substituted prolines. These molecules are chimeras combining the amino acid side chain functionality with proline conformational rigidity.[5] They are used as probes in structure−activity relationship (SAR) studies of biologically active peptides (such as tachykinins,[6] bradykinins,[7] opioid peptides,[8] cholecystokinin,[9] angiotensin I,I[10] and PLG[11]) and have served in the development of enzyme inhibitors.[12] Furthermore, functionalized pyrrolidine rings derived from proline have also been viewed as constrained non-peptide β-turn mimetics,[13] as peptidomimetics with improved

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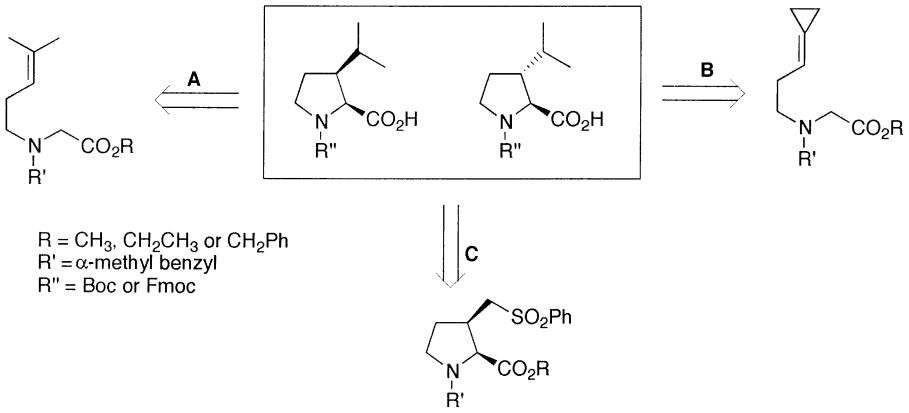
10.1021/jo026535n CCC: $25.00
Published on Web 02/13/2003

SCHEME 1



bioactivity and metabolic stability,[8−10] and as scaffold to build up low molecular weight primary screening libraries.[14] Several approaches have been developed for the synthesis of 3-substituted prolines involving inter- or intramolecular cyclization, or functionalization of a proline derivative.[15−55] Some of them provide access to enantiopure 3-prolinoamino acids in quantities suitable for peptide synthesis. However, the functionalization is often limited to side chains that do not really mimic the side chain of natural amino acids. In the course of our peptide SAR studies using 3-substituted prolines, we were interested in the preparation of (2*S*,3*S*) and (2*S*,3*R*)-prolinoleucines. Three pathways (namely A, B, and C) have been explored for the synthesis of these probes (Scheme 1). Pathways A and B are based on the amino−zinc−enolate cyclization of α,*β*,*β*-trisubstituted hindered olefins, involving the conversion of a secondary stabilized carbanion to a tertiary unstabilized organometallic species. Pathway C is based on the dialkylation of a chiral sulfone, which we described recently.[4e] Here, we report our results with a complete study of the stereochemistry of these 3-prolinoleucines.

Results and Discussion

Pathway A. It is well-known that the common organometallic (Li, Mg) reagents decrease in stability in the order Me > primary alkyl > secondary alkyl > tertiary alkyl[56] and that the isomerization of linear to cyclic organometallic species implies a thermodynamically favored process.[1] Thus, the synthesis of prolinoleucine via amino−zinc−enolate cyclization of α,*β*,*β*-trisubstituted olefins seems not to be thermodynamically favored. However, while the simple amino−lithium−enolate carbocyclization of α-substituted olefin was not observed, the transmetalation of the lithium enolate by zinc salts

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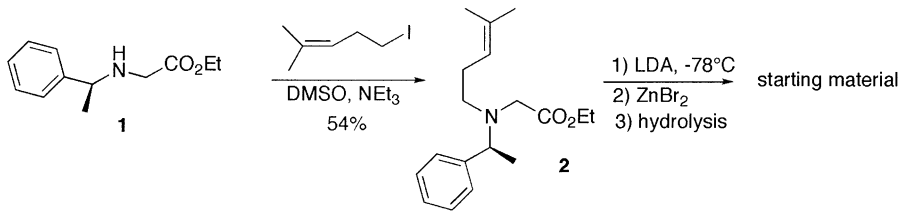
SCHEME 2



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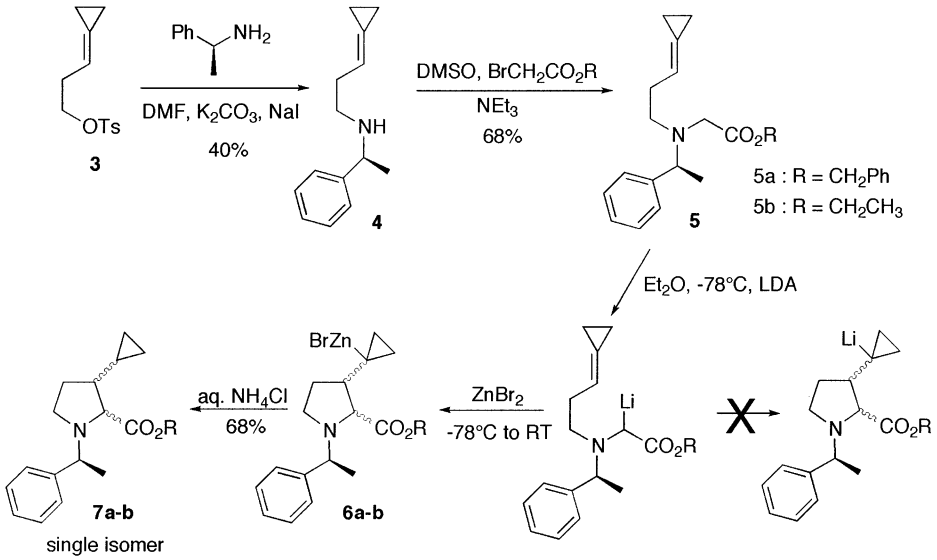

resulted in a nearly quantitative cyclization.[4a] The particular reactivity of zinc−enolate led us to explore the scope of the amino−zinc−enolate carbometalation.

The starting material was prepared by *N*-alkylation of *N*-(*S*)-α-methylbenzylglycine ethyl ester[57] **1** with 5-iodo-2-methyl-2-pentene[58] in dry DMSO with a moderate yield (Scheme 2). All attempts for cyclization of olefin **2** (Et_2O or THF, −78 °C, LDA, $ZnBr_2$, room temperature to reflux) failed and the starting material was recovered after hydrolysis of the reaction mixture. These results can be explained by an endothermic process involving the conversion of a secondary stabilized enolate anion to a tertiary unstabilized, hindered, sp^3 carbanion.

These findings led us to explore the activation of the substituted olefin toward nucleophilic attack via pathway B.

Pathway B. Some studies have been reported on the attachment of moderately activating groups to olefins for carbocyclization[59] and it has been shown that the cyclopropyl moiety in contrast with the isopropyl moiety exhibits a higher reactivity in 1,3-dipolar cycloadditions when linked to double bonds.[60] This group was suitable as it has the required structure for the prolinoleucine and the starting materials were obtained as described in Scheme 3. Alkylation of (*S*)-α-methylbenzylamine with 1-tosyloxy-3-cyclopropylidene propane[61] **3** in DMF followed by a subsequent alkylation with bromoacetate esters (benzyl or ethyl) led to compound **5**.

Compound **5** was metalated with LDA in Et_2O at −78 °C (Scheme 3) and no cyclization of the corresponding lithium−enolate was observed since hydrolysis of the reaction mixture produced the starting olefin. However, the addition of 3 equiv of $ZnBr_2$ at −78 °C resulted in a regio- and diastereoselective cyclization reaction, leading after hydrolysis to compound **7**, as a single diastereoisomer with a 68% yield. The cyclopropyl ring opening (which should allow the conversion of a tertiary, hindered, unstabilized, organometallic species to a primary one) is not observed. The simple relief of strain around the link between the π-system and the cyclopropyl group provides a potent thermodynamic force associated with this amino−zinc−enolate cyclization process. The higher reactivity of the cyclopropylethylene derivative **5** compared to the 1,1-dialkylethylene derivative **2** may simply reflect a decrease in angle strain of the cyclopropylidene system along the reaction coordinate.

The unexpected relative trans stereochemistry of the oily compound **7** was first established by using standard ^1H, ^{13}C, and COSY NMR techniques and by differential nuclear Overhauser effects on the fully deprotected proline derivative **8**, obtained by hydrogenolysis over palladium charcoal (Scheme 4). Indeed, if poor information was given by $^3J(\alpha-\beta)$ (6.4 Hz), no NOE effect was observed between Hα and Hβ, whereas a strong NOE effect was observed between Hα and Hϵ. The relative trans stereochemistry was also supported by epimerisa-

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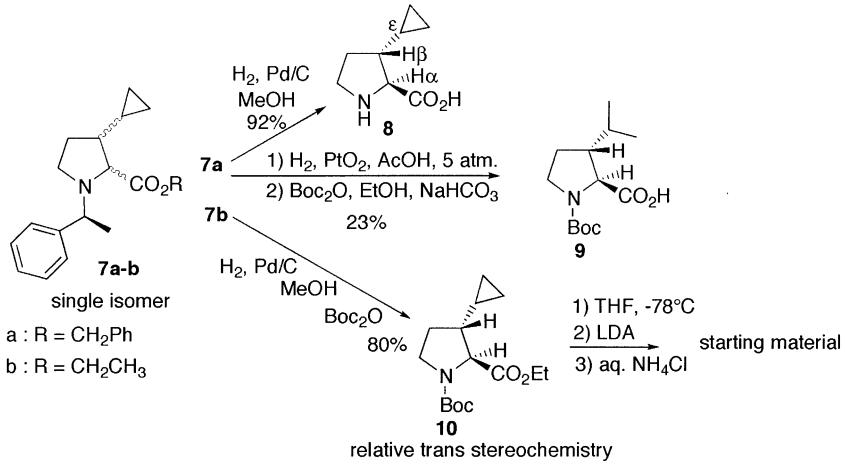
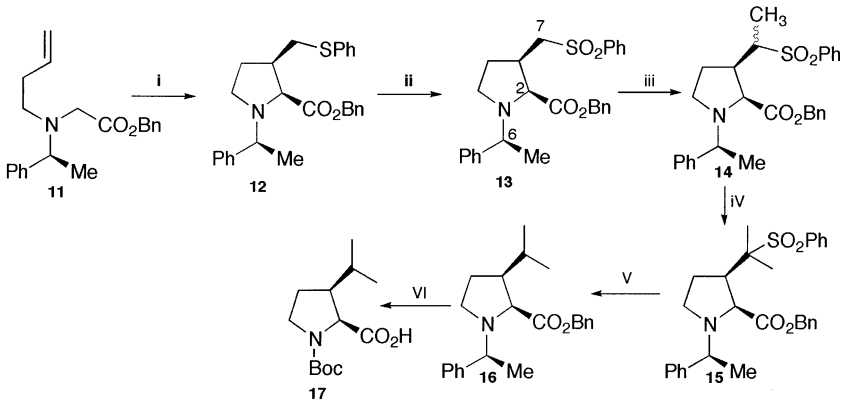
SCHEME 4



SCHEME 5[a]



[a] Reagents and conditions: (i) THF, −78 °C, LDA, $ZnBr_2$, −78 °C to rt, then CuCN/2LiCl, $PhSSO_2Ph$, 74%. (ii) CH_2Cl_2, THF (4 equiv), mCpBA (2 equiv), 80%. (iii) THF/DMPU (3/1), −78 °C, LDA, CH_3I, 93%. (iv) THF/DMPU (3/1), −78 °C, LDEA, CH_3I, 68%. (v) MeOH, Na/Hg (4 equiv), KH_2PO_4 (3 equiv), 82%. (vi) H_2/PdC, MeOH, Boc_2O, 91%.

tion assays of compound **10** obtained from **7b** after removal of the chiral auxiliary over palladium charcoal in the presence of Boc_2O. Considering that the cis derivative should epimerise toward the more stable trans isomer in the presence of a base, **10** was treated with LDA and the reaction mixture was quenched by a saturated NH_4Cl solution at room temperature. In these conditions, the derivative **10** was recovered unchanged confirming the supposed trans configuration.

Despite several attempts, crystallization of compound **7** failed and even though the reaction led to one stereoisomer with a trans relative stereochemistry, we have not been successful in the determination of the absolute configurations of the newly created chiral centers.

Pathway C. To determine the absolute configurations of the chiral centers created during the cyclization process, we focused our effort on the synthesis of *cis*- and *trans*-prolinoleucines via an unambiguous pathway based on dialkylation of a chiral sulfone[62] obtained through the amino−zinc−enolate cyclization of α-substituted olefin (Scheme 5). The thioether **12** was obtained in a "one-pot" procedure starting from olefin **11**,[4c] which was subjected to amino−zinc−enolate cyclization. The cyclic organozinc compound was then reacted with $PhSSO_2Ph$[63] after a new transmetalation step with the THF-soluble CuCN salts,[64] leading to compound **12** as a single isomer. The thioether **12** was then oxidized to the sulfone **13** by mCpBA (2 equiv) in the presence of TFA (4 equiv) to avoid *N*-oxidation. This general precursor has the (2*S*,3*R*) configuration as previously demonstrated by hydrolysis of the zinc derivative.[4a] Compound **13** presents three potentially acidic centers (Scheme 5), namely hydrogens 2, 6, and 7. Deuterium incorporation experiments have shown that at −78 °C, the most acidic center was in position 7, the steric hindrance of the chiral auxiliary on the nitrogen preventing abstraction of the proton 2, α to the ester function. After deprotonation with LDA at −78 °C, the sulfone **13** was cleanly monoalkylated in position 7 with methyliodide, creating a new chiral center with poor diastereoselectivity (65/35), leading to derivative **14**.

The second alkylation, which could only be achieved by changing LDA with LDEA, a less hindered base, led cleanly to the crystalline derivative **15** when the temperature was kept strictly at −78 °C. Otherwise, a mixture of diastereoisomers was obtained when the temperature was brought to room temperature before the addition of the electrophile. The structure and absolute

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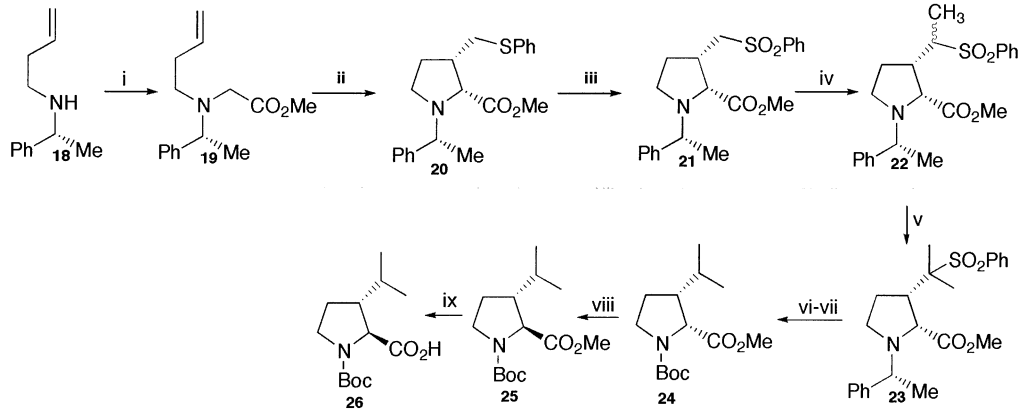
SCHEME 6[a]



[a] Reagents and conditions: (i) THF/DMPU (1/1), $BrCH_2CO_2CH_3$, K_2CO_3, 92%. (ii) THF, −78 °C, LDA, $ZnBr_2$, −78 °C ro rt, then CuCN/2LiCl, $PhSSO_2Ph$, 74%. (iii) CH_2Cl_2, THF (4 equiv), mCpBA (2 equiv), 80%. (iv) THF/DMPU (3/1), −78 °C, LDA, CH_3I, (93%). (v) THF/DMPU (3/1), −78 °C, LDIEA, CH_3I, (66%). (vi) MeOH, Na/Hg (4 equiv), KH_2PO_4 (3 equiv). (vii) H_2/PdC/MeOH, Boc_2O (63%, two steps). (viii) THF, LDA −78 °C to rt, aq NH_4Cl, (95%). (ix) LiOH/H_2O/MeOH (96%).

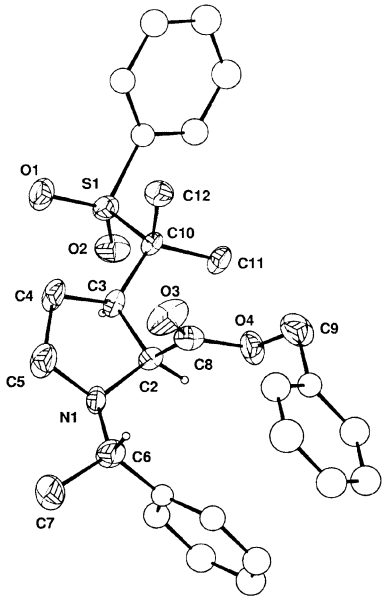


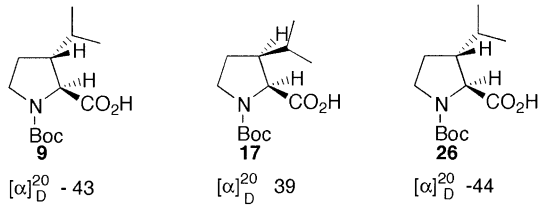
FIGURE 1. Cameron view of compound **15**. X-ray crystal data for **15**: $C_{29}H_{33}N_1O_4S_1$; $M = 491.6$; orthorhombic space group $P2_12_12_1$; $a = 7.197(4)$ Å, $b = 14.153(1)$ Å, $c = 25.985(3)$ Å; $V = 2647(1)$ Å^3; $Z = 4$; $T = 295$ K; $\mu = 0.15$ mm^{-1}; Enraf-Nonius Mach-3 diffractometer, radiation Mo K_α (0.71069 Å), reflections total 3656 ($1 < \theta < 25°$); reflections observed 1423 ($>3\sigma(I)$); parameters refined 193; refinement on F (CRYSTALS), $R = 0.0639$, $R_w = 0.0805$, GOF = 1.15; $\Delta\rho_{min} = -0.31$ e/Å^3, $\Delta\rho_{max} = +0.38$ e/Å^3.

configuration of the sulfone **15** chiral centers were established by X-ray analysis (Figure 1).

The derivative **17**, which was suitable for peptide synthesis, was obtained after a desulfonylation step by Na/Hg amalgam, followed by catalytic hydrogenolysis over palladium charcoal in the presence of Boc_2O.

The trans isomer, with (2*S*,3*R*) absolute configuration was obtained as described by the Scheme 6, starting from the previously described (*R*)-but-3-enyl-(1-phenyl-ethyl)-amine **18**, which was alkylated with methylbromoacetate in a mixture of THF/DMPU (1/1) yielding **19** (92%). After the same reaction sequence described in Scheme 5, the cis isomer **23** was isolated. Epimerisation of the α-center

SCHEME 7



was performed with compound **24** obtained after desulfonylation and subsequent catalytic hydrogenation over palladium charcoal in the presence of Boc_2O. Deprotonation of the α-center with LDA at −78 °C, followed by quenching of the reaction mixture at room temperature with aqueous NH_4Cl resulted in a quantitative epimerisation of the α-center leading to the trans derivative **25**. After saponification, the Boc-protected (2*S*,3*R*)-*trans*-prolinoleucine **26** was obtained and was suitable for peptide synthesis.

Having established unambiguously by X-ray analysis the absolute configuration of the prolinoleucine obtained by pathway C, we were able to deduce the absolute configuration of prolinoleucine **7** obtained by amino−zinc−enolate cyclization of the α,*β*,*β*-trisubstituted olefin. The cyclopropyl ring opening by catalytic hydrogenation over PtO_2[65] followed by Boc protection led to compound **9** (Scheme 4). The simple comparison of NMR spectra and optical activity of compound **9** with those of compounds **17** and **26** allowed us to conclude (Scheme 7) a trans relative stereochemistry for compound **9** with 2*S*,3*R* absolute configuration, *S*-methylbenzyl inducing the *S*-configuration of the α-center.

A cis stereochemistry was observed for the product obtained by amino−zinc−enolate cyclization of the α-substituted olefin[4a] (Scheme 8). This stereochemistry was explained by a chairlike transition state where zinc interacts with nitrogen, the double bond, and the enolate oxygen.[4a] A similar transition state leading to the cis-isomer (Scheme 8) shows a strong steric hindrance

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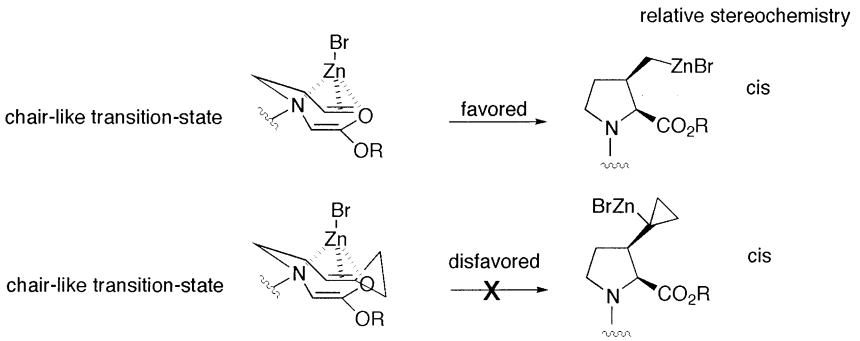
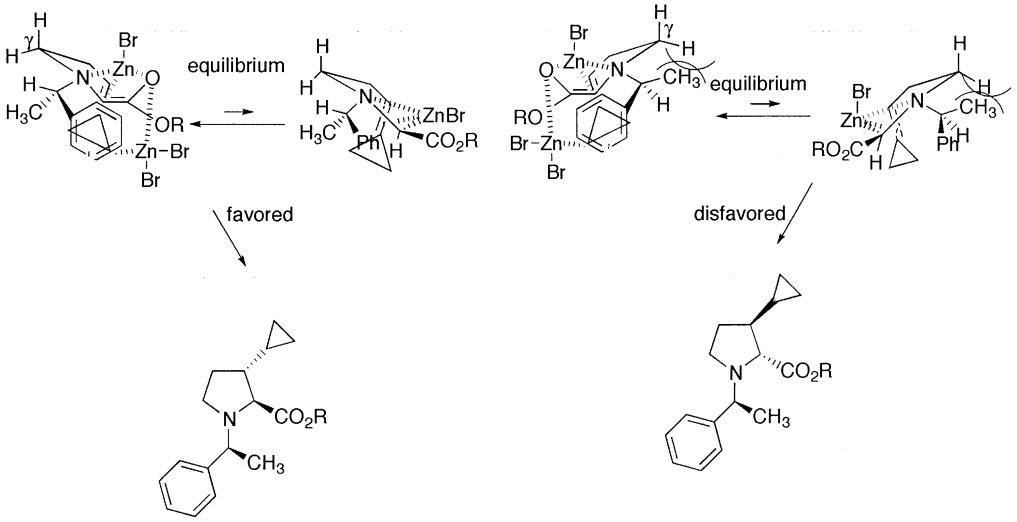
SCHEME 8



SCHEME 9



between the enolate moiety and the cyclopropyl group. If a product-like transition state is considered, a prevalent interaction appears between the ester function and the cyclopropylmetal group formed after cyclization. Thus, in that case the more stable trans diastereoisomer should be the major product.

If the structure of the amino−zinc−enolate likens to the Reformatzky reagent, which exists as an equilibrium between the *O*- and *C*-metalated species,[66] this equilibrium, as shown by Van Koten,[67] is completely displaced toward the *O*-metalated species when zinc is bounded to α-amino nitrogen, the amino−zinc−enolate adopting in that case a *Z* configuration. Moreover, a further study realized by Lorthiois et al. on this reaction has shown that asymmetric induction was governed by a π-chelation between the aromatic ring of the chiral auxiliary and the amino−zinc−enolate.[68] Therefore, the following transition states are postulated during the amino−zinc−enolate cyclization process of the α,β,β-trisubstituted olefin to explain the observed stereochemistry (Scheme 9):

A product-like transition state involving a perpendicular approach of the enolate moiety and the cyclopropylidene explains the relative trans stereochemistry obtained for the cyclic compound. In this transition state, the chiral inductor adopts a position in which the methyl group bound to the chiral center has a lowered steric hindrance with both hydrogens in position γ when one face of the cyclopropylidene is concerned rather than the other one, *S*-(α)-methylbenzyl group leading to the *S* configuration in position 2.

Conclusion

The amino−zinc−enolate cyclization is a straightforward route for the short-step asymmetric syntheses of 3-substituted prolines. It has been applied for the preparation of cis and trans prolinoleucine. The relative stereochemistry obtained for the cyclic compound is governed by the nature of the alkenes. A cis stereochemistry is obtained for the α-substituted olefin whereas a trans stereochemistry is observed for the olefin activated by a hindered cyclopropyl group. The absolute configuration of the chiral centers created after cyclization has been determined by comparison of the NMR spectra and optical activity with *cis*- and *trans*-prolinoleucine obtained via an unambiguous pathway. We are currently working on peptides incorporating these probes for conformational studies.

Experimental Section

General Considerations. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone and kept over 4 Å molecular sieves. Dimethyl sulfoxide

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(DMSO), triethylamine (NEt_3), and dichloromethane (CH_2Cl_2) were distilled from CaH_2. MeOH was distilled from Mg. Dry dimethylformamide (DMF) and other reagents were commercially available. Zinc bromide ($ZnBr_2$) was dried by fusion under flame and nitrogen; the fused salts were allowed to solidify under nitrogen and then dissolved in dry diethyl ether (1 or 1.3 M). Lithium chloride (LiCl) was dried with a heat gun under reduced pressure. After cooling under nitrogen, CuCN was added, followed by dry THF (1 M), the mixture was then stirred until complete dissolution (1 h). Lithium diethylamide (LDEA, 1 M) was prepared prior to use as follows: BuLi (1 equiv) was added to freshly distilled diethylamine (1 equiv) in dry THF at −78 °C under argon. The temperature was brought to 0 °C and the base was stored at this temperature. Anhydrous reactions were performed under an argon atmosphere; glasswares were flame-dried prior to use under a stream of nitrogen. Usual workup means that the organic layer was washed twice with aqueous saturated NH_4Cl (NH_4Cl/NH_4OH (1 M), 2/1 until complete decoloration for the cyclization-transmetalation by copper salts reactions, followed by brine), dried over $MgSO_4$, and evaporated in vacuo.

(*S*)-(1-Phenyl-ethylamino)-ethyl acetate ester 1: Freshly distilled ethylbromoacetate (33.2 mL, 0.3 mol) was added dropwise at 0 °C to a solution of L-(−)-α-methylbenzylamine (38.6 mL, 0.3 mol) in dry DMSO (100 mL) under argon. After 5 min of stirring at rt dry NEt_3 (41.6 mL, 0.3 mol) was added. The solution was stirred for 10 min and ethyl acetate was added. After the usual workup and concentration, the residual pale yellow liquid was distilled under reduced pressure yielding a colorless liquid (54.8 g, 88%): ^{1}H NMR (200 MHz; $CDCl_3$) δ 7.3−7.28 (m, 5H), 4.12 (q, 2H, J = 7.3 Hz), 3.75 (q, 1H, J = 6.5 Hz), 3.23 (AB system, 2H, ^2J = 3 Hz), 1.36 (d, 3H, J = 6.5 Hz), 1.21 (tr, 3H, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 144.8, 128.6, 127.3, 126.9, 60.8, 57.8, 57.8, 49, 41.1, 24.4, 14.3. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.56; H, 8.21; N, 6.76. Found: C, 69.31; H, 8.37; N, 6.71.

(*S*)-[Pent-3-enyl-4-methyl-(1-phenyl-ethyl)-amino]-ethyl acetate ester 2: 5-Iodo-2-methyl-2-pentene[19] (5.46 g, 26 mmol) and NEt_3 (3.61 mL, 26 mmol) were added to a stirred solution of (*S*)-α-methylbenzylglycine ethyl ester **1** (4.14 g, 10 mmol) in dry DMSO (12 mL) under argon and heated at 50 °C for 48 h. The mixture was cooled and diluted with CH_2Cl_2. The organic layer was washed twice with aqueous saturated NH_4Cl. The aqueous layers were extracted once with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated to afford 9 g of a brown oil that was purified by flash chromatography yielding 3.1 g (53.6%) of a pale yellow liquid: $[\alpha]\ ^{20}_D$ −38 (*c* 1, $CHCl_3$). R_f (cyclohexane/ethyl acetate, 9/1, UV/PMA) 0.62. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4−7.2 (m, 5H), 5.06 (m, 1H), 4.17 (q, 2H, J = 7 Hz), 4.08 (q, 1H, J = 6.7 Hz), 3.41(AB system, 2H, ^2J = 17 Hz), 2.6 (m, 2H), 2.12 (m, 2H), 1.69 (s, 3H), 1.58 (s, 3H), 1.34 (d, 3H, J = 6.7 Hz), 1.28 (tr, 3H, J = 7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.3, 144.8, 132.6, 128.2, 127.6, 126.9, 122, 60.5, 60.2, 51.6, 51.2, 26.8, 25.7, 19.5, 17.7, 14.3. Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.74; H, 9.34; N, 4.84. Found: C, 74.82; H, 9.28; N, 4.79.

(*S*)-3-Cyclopropylidenepropane-(1-phenyl-ethyl)-amine 4: A mixture of (*S*)-α-methylbenzylamine (3.06 mL, 23.8 mmol), NaI (7.2 g, 47.61 mmol), K_2CO_3 (6.6 g, 47.61 mmol), and 1-tosyloxy-3-cyclopropylidenepropane[22] (4 g, 15.87 mmol) in DMF (30 mL) was heated to 100 °C overnight, and then cooled to rt. The mixture was diluted with Et_2O and water was added. The organic layer was washed once with brine, dried over $MgSO_4$, and concentrated. A pale yellow oil was obtained (1.3 g, 40%) after distillation (120 °C, 0.1 mbar) followed by chromatography (CH_2Cl_2/EtOH, 99/1): $[\alpha]\ ^{20}_D$ −34 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 5.73 (m, 1H), 3.80 (q, 1H, J = 6.5 Hz), 2.62 (m, 2H), 2.38 (m, 2H), 1.37 (d, 3H, J = 6.5 Hz), 1.05 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 128.5, 126.6, 126.7, 123.1, 116, 58.3, 47.3, 32.5, 24.4, 2.5, 2.

(*S*)-[3-Cyclopropylidenepropane-(1-phenyl-ethyl)-amino]-benzyl acetate ester 5a: Benzylbromoacetate (2.05 mL, 31 mmol) and dry NEt_3 (3.5 mL, 25 mmol) were added to a solution of (*S*)-3-cyclopropylidenepropane-(1-phenyl-ethyl)-amine **4** (2.5 g, 12.4 mmol) in dry DMSO (15 mL). The reaction mixture was stirred overnight at rt. Et_2O and water were added. The organic layer was decanted and washed once with brine, dried over $MgSO_4$, and concentrated to form a yellow oil. After purification by flash chromatography (cyclohexane/ethyl acetate, 99/1), a pale yellow oil (2.8 g, 68%) was obtained. $[\alpha]\ ^{20}_D$ −30 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 10H), 5.7 (m, 1H), 5.15 (s, 2H), 4.1 (q, 1H, J = 6.6 Hz), 3.54 (d, AB system, 1H, ^2J = 17.3 Hz), 3.4 (d, AB system, ^2J = 17.3 Hz), 2.76 (m, 2H), 2.35 (m, 2H), 1.38 (d, 3H, J = 6.6 Hz), 1.02 (m, 2H), 0.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 144.7, 136.1, 130, 128.6, 128.3, 127.6, 127, 116.1, 66.1, 60.5, 51.7, 51, 30.5, 19.5, 2.5, 1.8. Anal. Calcd for $C_{23}H_{27}NO_2$: C, 79.08; H, 7.78; N, 4.01. Found: C, 79.21; H, 8.33; N, 4.10.

(*S*)-[3-Cyclopropylidenepropane-(1-phenyl-ethyl)-amino]-ethyl acetate ester 5b: Same protocol as for **5a**: from (*S*)-3-cyclopropylidenepropane-(1-phenyl-ethyl)-amine **4** (600 mg, 2.98 mmol), dry DMSO (5 mL), ethylbromoacetate (700 μL, 6 mmol), and dry NEt_3 (840 μL, 6 mmol). After purification by flash chromatography (cyclohexane/ethyl acetate, 99/1), a pale yellow oil (2.8 g, 68%) was obtained. $[\alpha]^{20}_D$ −29 (*c* 1, $CHCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3 (m, 5H), 5.73 (m, 1H), 4.15 (q, 2H, J = 7.2 Hz), 4.08 (q, 1H, J = 6.7 Hz), 3.47 (d, AB system, 2H, ^2J = 17.3 Hz), 3.32 (d, AB system, 2H, ^2J = 17.3 Hz), 2.74 (m, 2H), 2.34 (m, 2H), 1.37 (d, 3H, J = 6.7 Hz), 1.27 (tr, 3H, J = 7.2 Hz), 1.02 (m, 2H), 0.97 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 144.8, 128.3, 127.7, 126.9, 116.1, 110.7, 60.5, 60.3, 51.6, 51, 30.4, 19.5, 14.4, 2.5, 1.8. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.26; H, 8.71; N, 4.87. Found: C, 75.95; H, 9.07; N, 4.98.

3-Cyclopropyl-1-(1-phenyl-ethyl)-pyrrolidine-2-carboxylic-acid-benzyl ester 7a: LDA (2.2 mL, 4.4 mmol) was added at −78 °C to a solution of amine **5a** (1.4 g, 4 mmol) in dry diethyl ether (8 mL) under argon. $ZnBr_2$ (1 M, 12 mL) was then added at the same temperature. The reaction mixture was stirred as the temperature was brought to rt. Et_2O was added. A pale yellow oil (950 mg, 68%) was obtained after the usual workup and purification by flash chromatography (cyclohexane/ethyl acetate, 97/3): $[\alpha]\ ^{20}_D$ −60.5 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 5H), 7.29 (m, 5H), 5.14 (s, 2H), 3.74 (q, 1H, J = 7 Hz), 3.25 (d, 1H, J = 5 Hz), 3 (m, 1H), 2.7 (m, 1H), 2.06 (m, 1H), 1.6 (m, 2H), 1.36 (d, 3H, J = 7 Hz), 0.78 (m, 1H), 0.41 (m, 2H), 0.05 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 144.2, 136.4, 128.8, 128.6, 127.9, 127.4, 70, 66.5, 62.3, 50.3, 50.1, 30.3, 22.9, 16.1, 4.5, 3.9. Anal. Calcd for $C_{23}H_{27}NO_2$: C, 79.08; H, 7.78; N, 4.01. Found: C, 79.42; H, 8.11; N, 3.96.

3-Cyclopropyl-1-(1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid ethyl ester 7b: Same protocol as for **7a:** LDA (650 μL, 1.3 mmol), amine **5b** (290 mg, 1 mmol), diethyl ether (2 mL), and $ZnBr_2$ (1 M, 3 mL). A pale yellow oil (200 mg, 70%) was obtained after the usual workup and purification by flash chromatography (cyclohexane/ethyl acetate, 97/3): $[\alpha]\ ^{20}_D$ −66.5 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 5H), 4.17 (q, 2H, J = 7.1 Hz), 3.74 (q, 1H, J = 6. 8 Hz), 3.17 (d, 1H, J = 5.5 Hz), 2.98 (m, 1H), 2.65 (m, 1H), 2.05 (m, 1H), 1.6 (m, 2H), 1.38 (d, 3H, 5.5 Hz), 1.27 (tr, 3H, J = 7.1 Hz), 0.8 (m, 1H), 0.45 (m, 2H), 0.1 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 144.1, 128.5, 128, 127.3, 70.3, 62.5, 60.7, 50.3, 50, 30.2, 22.6, 16, 14.6, 4.4, 3.7. Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.27; H, 8.71; N, 4.87. Found: C, 75.77; H, 9.01; N, 4.85.

3-Cyclopropyl-pyrrolidine-2-carboxylic acid 8: A solution of compound **7a** (350 mg, 1 mmol) and Pd/C (150 mg) in MeOH (2 mL) was stirred for 2 h under hydrogen. After filtration on a Celite pad, which was washed with EtOH, the solvent was concentrated leaving a white powder that was washed with CH_2Cl_2 (143 mg, 92%): mp >264°C; $[\alpha]\ ^{20}_D$ 4 (*c* 1, H_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (d, 1H, ^{3}J = 8 Hz),

3.28 (m, 1H), 2.02 (m, 1H), 1.76 (m, 1H), 1.66 (m, 1H), 0.75 (m, 1H), 0.42 (m, 2H), 0.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.3, 66.3, 48.4, 45.3, 29.9, 13.7, 3.99, 2.92. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.93; H, 8.38; N, 9.03. Found: C, 61.88; H, 8.50; N, 9.15.

(2*S*,3*R*)-3-Isopropyl-1-(*tert*-butyloxycarbonyl)-pyrrolidine-2-carboxylic acid 9: Compound **7a** (350 mg, 1 mmol) was dissolved in 4 mL of MeOH/CH_3COOH (1/3). PtO_2 (100 mg) was added and the reaction mixture was stirred for 5 days under hydrogen at a pressure of 5 bar, at rt. After concentration, the crude material was dissolved in MeOH and the pH was adjusted to 9 with $NaHCO_3$. Boc_2O was added and the reaction mixture was stirred at room temperature for 3 h. After filtration over a Celite pad and concentration, the crude material was purified by flash chromatography (CH_2Cl_2/MeOH, 9/1). A white powder (60 mg, 23%) was obtained after crystallization. $[\alpha]^{20}_D$ −43 (*c* 1, $CHCl_3$); mp 88−90 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.8 (broad peak, 1H), 4.1 and 3.95 (2d, 1H, Boc cis−trans isomerization, ^3J = 7.5 Hz), 3.55 (m, 1H), 3.4 (m, 1H), 2.17 (m, 1H), 1.95 (m, 1H), 1.70 (m, 2H), 1.46 and 1.42 (2s, 9H, Boc cis−tans isomerization), 0.99 (d, 3H, ^3J = 7.5 Hz), 0.95 (d, 3H, ^3J = 7.5 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 179.8, 177.6, 155.33, 153.86, 80.6, 80.4, 62.6, 51.4, 49.5, 46.3, 45.9, 30.3, 28.4, 28.3, 27.6, 26.9, 21.1, 19.5, 19.3. Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.71; H, 9.12; N, 5.32.

***N*-Boc-3-isopropyl-pyrrolidine-2-carboxylic acid ethyl ester 10:** A solution of amine **7b** (275 mg, 1 mmol) and Pd/C (80 mg) in MeOH (3 mL) was stirred under H_2 atmosphere. After filtration over a Celite pad, which was washed with EtOH, the solvent was concentrated, giving an oil. After the addition of dry EtOH (5 mL), $NaHCO_3$ (92.5 mg, 1.1 mmol), and Boc_2O (337 mg, 1.5 mmol) the reaction mixture was stirred overnight. Filtration over a Celite pad and purification by flash chromatography (cyclohexane/ethyl acetate, 9/1) afforded a colorless oil (213 mg, 80%): $[\alpha]^{20}_D$ −33 (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.20−4.04 (q, 2H), 4.05−4.03−3.94−3.92 (2d, 1H, Boc cis−trans isomerization), 3.65−3.34 (m, 2H), 2.01−1.88 (m, 1H), 1.72−1.45 (m, 2H), 1.39−1.34 (2s, 9H), 1.24−1.15 (2tr, 3H), 0.82−0.67 (m, 1H), 0.50−0.41 (m, 2H), 0.17−0.06 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 174, 79.8, 65−64.55, 60.6, 50−48.9, 45.8−45.6, 30.4−29.8, 28.4−28.3, 14.2−14.1, 4.18, 3.49.

(*S*)-[But-3-enyl-(1-phenyl-ethyl)-amino]-acetic acid benzyl ester 11: To a solution of (*S*)-but-3-enyl-(1-phenyl-ethyl)-amine (12.75 g, 72.7 mmol)[4c] in a dry THF/DMPU mixture (150 mL, 1/1) was slowly added benzylbromoacetate (12.02 mL, 72.7 mmol). The mixture was stirred for 30 min and dry Na_2CO_3 (7.72 g, 72.7 mmol) was added. The reaction mixture was stirred for 4 h at rt and then diluted with Et_2O. The organic layer was filtered through a Celite pad (which was washed with Et_2O) and washed with water (2×) and brine. The combined aqueous layers were extracted once with Et_2O. The combined organic layers were dried over $MgSO_4$, and concentrated yielding 21.3 g (90%) of a pale yellow oil after purification by flash chromatography (cyclohexane/ethyl acetate: 97/3). $[\alpha]^{20}_D$ −28 (*c* 1, $CHCl_3$). ^{1}H NMR (250 MHz; $CDCl_3$) δ 7.35 (m, 10H), 5.75 (m, 1H), 5.14 (s, 2H), 4.98 (m, 2H), 4.07 (q, 1H, J = 6.7 Hz), 3.52 (d, 1H, AB system, J_{AB}= 17.3 Hz), 3.36 (d, 1H, AB system, J_{AB}= 17.3 Hz), 2.71 (m, 2H), 2.22 (m, 2H), 1.36 (d, 3H, J = 6.7 Hz). ^{13}C NMR (50 MHz; $CDCl_3$) δ 172.1, 144.6, 136.7, 135.9 128.6, 128.3, 127.6, 127, 115.6, 66.1, 60.4, 51.5, 50.8, 32.5, 19.4. Anal. Calcd for $C_{21}H_{25}NO_2$: C, 78.01; H, 7.73; N, 4.33. Found: C, 77.86; H, 7.87; N, 4.34.

(2*S*,3*S*)-3-Phenylsulfanylmethyl-1-(1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid benzyl ester 12: LDA (25 mL, 50 mmol) was added at −78 °C to a solution of amine **11** (16.15 g, 50 mmol) in dry THF (100 mL) under argon. $ZnBr_2$ (1 M in Et_2O, 125 mL) was then added and the reaction mixture was stirred as the temperature was brought to rt (4 h). CuCN/2LiCl (1 M in THF, 50 mL) was then added at 0 °C followed by $PhSSO_2Ph$ (12.5 g, 50 mmol). After 2 h of stirring at rt, the reaction mixture was quenched by an aqueous saturated solution of NH_4Cl. Et_2O was added. A pale yellow glue (15.9 g, 74%) was obtained after the usual workup and purification by flash chromatography (cyclohexane/ethyl acetate, 92/8): $[\alpha]^{20}_D$ −25 (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (m, 15H), 5.13 (s, 2H), 3.74 (q, 1H, J = 6.6 Hz), 3.67 (s, 3H), 3.51 (d, 1H J^3= 7.2 Hz), 3.15 (m, 1H), 3 (m, 2H), 2.65 (m, 2H), 2.2 (m, 1H), 1.8 (m, 1H), 1.37 (d, 3H, J = 6.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172, 144.2, 139.5, 135.5, 133.9, 129.4, 128.9, 128.6, 128.5, 128, 127.3, 66.2, 65.3, 61.8, 57.5, 49.6, 35.9, 29.7, 22.9. Anal. Calcd for $C_{27}H_{29}NO_4S$: C, 75.17; H, 6.73; N, 3.25. Found: C, 75.06; H, 6.84; N, 3.38.

(2*S*,3*S*)-3-Phenylsulfonylmethyl-1-(1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid benzyl ester 13: mCpBA (12.6 g, 54.8 mmol) was added portionwise to a cold solution (0 °C) of **12** (11.8 g, 27.4 mmol) in CH_2Cl_2 (140 mL) and TFA (8.5 mL, 109 mmol). After the mixture was stirred for 1 h, the organic layer was washed with 10% $Na_2S_2O_3$ (1×), 10% $NaHCO_3$ (3×), and brine (1×), dried over $MgSO_4$, concentrated, and purified by flash chromatography (cyclohexane/ethyl acetate, 7/3), yielding 10.1 g (80%) of a colorless glue. $[\alpha]^{20}_D$ −44.8 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, 2H, J = 7.5 Hz), 7.6 (m, 1H), 7.53 (m, 2H), 7.28 (m, 8H), 7.13 (m, 2H), 5.04 (d, 2H, AB system, J = 4.3 Hz), 3.67 (q, 1H, J = 6.5 Hz), 3.42 (d, 1H J =7 Hz), 3.14 (m, 1H), 3.06 (m, 2H), 2.79 (m, 2H), 2.2 (m, 1H), 1.8 (m, 1H), 1.32 (d, 3H, J = 6.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 144.5, 139.7, 135.8, 134.1, 129.7, 129.2, 128.9, 128.7, 127.6, 111, 66.5, 66.1, 61.3, 57.8, 49.9, 36.2, 30.5, 30, 27.3, 23.2. Anal. Calcd for $C_{27}H_{29}NO_4S$: C, 69.97; H, 6.26; N, 3.02. Found: C, 69.90; H, 6.28; N, 3.09.

(2*S*,3*S*)-3-(1-Methyl-1-phenylsulfonylmethyl)-1-(1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid benzyl ester 14 (as a mixture of two diastereoisomers): LDA (5.5 mL, 11 mmol) was added to a dry THF/DMPU (40 mL, 3/1) solution of sulfone **13** (4.63 g, 10 mmol) at −78 °C under argon. After a few seconds of stirring, CH_3I (2.52 mL, 40 mmol) was added. The reaction mixture was stirred for 30 min and brought to room temperature. Et_2O was added. A pale yellow oil was obtained after the usual workup and concentration. The crude materials were purified by flash chromatography (cyclohexane/ethyl acetate, 8/2), yielding 4.4 g (93.6%) of a colorless glue as a mixture of two diastereoisomers (65/35). ^{1}H NMR (400 MHz, $CDCl_3$) (major diastereoisomer) δ 7.7−7.2 (m, 15H), 5.14 (AB systems, 2H, J_{AB1} = 11.2 Hz), 3.75 (d, 1H, J = 7.3 Hz), 3.74, (q, 1H, J = 6.7 Hz), 3.39 (m, 1H), 2.9 (m, 2H), 2.7 (m, 1H), 1.35 (d, 3H, J = 6.7 Hz), 1.11 (d, 3H, J = 7 Hz). ^{1}H NMR (400 MHz, CDCl3) (minor diastereoisomer)δ 7.7−7.2 (m, 15H), 4.98 (AB system, 2H, J_{AB1} = 8 Hz), 3.58 (q, 1H, J = 6.5 Hz), 3.46 (d, 1H, J = 6.5 Hz), 3.24 (m, 1H), 3.07 (m, 1H), 2.8 (m, 1H), 2.58 (m, 1H), 2.4 (m, 1H), 1.9 (m, 1H). Anal. Calcd for $C_{28}H_{31}NO_4S$: C, 70.44; H, 6.49; N, 2.93. Found: C, 70.30; H, 6.75; N, 2.99.

(2*S*,3*S*)-3-(1,1-Dimethyl-1-phenylsulfonylmethyl)-1-(1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid benzyl ester 15: LDEA (1 M, 16.8 mL) was added to a dry THF/DMPU (3/1, 40 mL) solution of sulfone **14** (4 g, 8.38 mmol) at −78 °C under argon. After a few seconds of stirring, CH_3I (2.1 mL, 33.5 mmol) was added at this temperature. The reaction mixture was stirred for 1 h and brought to room temperature. Et_2O was added. A pale yellow oil was obtained after the usual workup and concentration. After two crystallizations (Et_2O/pentane first, then slow evaporation of $CHCl_3$), colorless needles (2.8 g, 68%) were obtained. $[\alpha]^{20}_D$ −21 (*c* 1, $CHCl_3$); mp 146−148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, 2H, J = 7.3 Hz), 7.65 (m, 1H), 7.55 (m, 2H), 7.3 (m, 5H), 7.11 (m, 2H), 5.05 (d, AB system, 1H, J = 12 Hz)), 4.99 (d, AB system, 1H, J = 12 Hz), 3.53 (q, 1H, J = 6.5 Hz), 3.43 (d, 1H, J = 6.2 Hz), 3.3 (m, 1H), 3.15 (m, 1H), 2.95 (m, 1H), 2.25 (m, 2H), 1.31 (d, 3H, J = 6.5 Hz), 1.20 (, s, 3H), 1.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 145, 135, 134, 129.3, 129.2, 128.9, 128.7, 127.4, 66.4, 64.7, 64.5, 60.8, 49.6, 46, 25.4, 23.9, 22.1, 17.7. Anal. Calcd for $C_{29}H_{33}NO_4S$: C, 70.87; H, 6.72; N, 2.85.

Found: C, 70.72; H, 6.88; N, 2.84. X-ray crystal data: $C_{29}H_{33}NO_4S$; $M = 491.6$; orthorhombic space group $P2_12_12_1$; $a = 7.197(4)$ Å, $b = 14.153(1)$ Å, $c = 25.985(3)$ Å; $V = 2647(1)$ Å^3; $Z = 4$; $T = 295$ K; $\mu = 0.15$ mm^{-1}; Enraf-Nonius Mach-3 diffractometer, radiation Mo $K\alpha$ (0.71069 Å), reflections total 3656 ($1 < \theta < 25°$); reflections observed 1423 ($>3\sigma(I)$); parameters refined 193; refinement on F (CRYSTALS), $R = 0.0639$, $R_w = 0.0805$, GOF = 1.15; $\Delta\rho_{min} = -0.31$ e/Å^3, $\Delta\rho_{max} = +0.38$ e/Å^3.

(2*S*,3*S*)-3-Isopropyl-1-(1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid benzyl ester 16: KH_2PO_4 (760.2 mg, 5.58 mmol) and freshly prepared 3% Na/Hg amalgam (4.86 g, 7.40 mmol) were added portionwise to dry solution of sulfone **15** (908.9 g, 1.85 mmol) in freshly distilled MeOH (20 mL). The mixture was vigorously stirred for 1 h at room temperature. After filtration over a Celite pad, the crude material was concentrated and purified by flash chromatography (cyclohexane/ethyl acetate, 98/2) leaving an oil (287 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (m, 10H), 5.07 (d, AB system, 1H, $J = 12.2$ Hz), 5.01 (d, AB system, 1H, $J = 12.2$ Hz), 3.66 (q, 1H, $J = 6.5$ Hz), 3.48 (d, 1H, $J = 6.7$ Hz), 3.18 (m, 1H), 3.09 (m, 1H), 2.02 (m, 2H), 1.81 (m, 1H), 1.33 (d, 3H, $J = 6.5$ Hz), 1.26 (m, 1H), 0.85 (d, 3H, $J = 6.5$ Hz), 0.82 (d, 3H, $J = 6.5$ Hz), 3.54 (s, 3H), 3.53 (q, 1H, $J = 7.5$ Hz), 3.4 (d, 1H, $J = 5$ Hz), 3.3 (m, 1H), 3.1 (m, 1H), 2.9 (m, 1H), 2.25 (m, 2H), 1.3 (d, 3H, $J = 7.5$ Hz), 1.22 (s, 3H), 1.18 (s, 3H). Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.63; H, 8.26; N, 3.98. Found: C, 78.68; H, 8.25; N, 3.88.

(2*S*,3*S*)-3-isopropyl-1-(*tert*-butyloxycarbonyl)-pyrrolidine-2-carboxylic acid 17: A mixture of Amine **16** (250 mg, 0.71 mmol), 10% Pd/C (100 mg), and Boc_2O (156 mg, 0.71 mmol) in MeOH (5 mL) was stirred overnight at room temperature under hydrogen. After filtration over a Celite pad and concentration, the crude material was purified by flash chromatography (CH_2Cl_2/MeOH, 95/5), leaving an oil (168 mg, 91%). $[\alpha]^{20}{}_D$ 39 (c 1, $CHCl_3$); mp 86−88 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.2 (broad peak, 1H), 4.41−4.29 (2d, 1H, Boc cis−trans isomerization, $J = 7.5$ Hz), 3.7 (m, 1H), 3.27 (m, 1H), 2 (m, 2H), 3.28 (m, 1H), 1.45−1.42 (2s, 9H, Boc cis−trans isomerization), 1.07 (d, 3H, $J = 5$ Hz), 0.94 (d, 3H, $J = 5$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178, 80, 62, 51.3, 50.4, 45.7, 29, 28.3, 28.1, 27.5, 22.1, 21.4. Anal. Calcd for $C_{13}H_{24}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.62; H, 9.19; N, 5.36.

(*R*)-[But-3-enyl-(1-phenyl-ethyl)-amino]-acetic acid methyl ester 19: Methylbromoacetate (6.34 mL, 65 mmol) was slowly added to a stirred solution of (*R*)-but-3-enyl-(1-phenyl-ethyl)-amine (11.37 g, 65 mmol)[4c] in a dry THF/DMPU mixture (80 mL, 1/1) at 0 °C under argon. Dry K_2CO_3 (9.08 g, 65 mmol) was added and the mixture was stirred for 6 h at rt. Et_2O (200 mL) was added and the organic layer was filtered through a Celite pad (which was washed with Et_2O). The organic layer was washed with water (2×) and brine. The combined aqueous layers were extracted once with Et_2O. The combined organic layers were dried over $MgSO_4$, and concentrated yielding 14.7 g (91.5%) of a pale yellow oil after purification by flash chromatography (cyclohexane/ethyl acetate, 98/2). $[\alpha]\ ^{20}{}_D$ 32 (c 1, $CHCl_3$). ^{1}H NMR (250 MHz; $CDCl_3$) δ 7.38−7.21 (m, 5H), 5.8−5.69 (m, 1H), 5.04−4.93 (m, 2H), 4.05−4.02 (q, 1H, $J = 6.7$ Hz), 3.66 (s, 3H), 3.45 (d, AB, J_{AB}=17.2 Hz, 1H), 3.29 (d, AB, $J_{AB} = 17.2$ Hz, 1H), 2.71−2.65 (m, 2H), 2.23−2.17 (m, 2H), 1.35 (d, 3H, $J = 6.7$ Hz). ^{13}C NMR (62.5 MHz; $CDCl_3$) δ 172.5, 144.5, 136.7, 128.2, 127.5, 126.9, 115.5, 60.4, 51.3, 50.7, 32.3, 19.4. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.75; H, 8.71; N, 5.64.

(2*R*,3*R*)-3-Phenylsulfanylmethyl-1-(1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid methyl ester 20: Same protocol as for compound **12:** LDA (28.35 mL, 56.7 mmol), amine **19** (14 g, 56.7 mmol), THF (110 mL), $ZnBr_2$ (1 M in Et_2O, 142 mL), CuCN/2LiCl (1M in THF, 57 mL), and $PhSSO_2$-Ph (14.2 g, 56.7 mmol). After the usual workup and purification by flash chromatography (cyclohexane/ethyl acetate, 92/8), a pale yellow glue (15 g, 74%) was obtained: $[\alpha]^{20}{}_D$ 24 (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.18 (m, 10H), 3.74−3.72 (q, 1H, $J = 8$ Hz), 3.67 (s, 3H), 3.49 (d, 1H, $J^3 = 8$ Hz), 3.09−3.06 (m, 1H), 3.04−3.02 (m, 1H), 3−2.99 (m, 1H), 2.74−2.71 (m, 1H), 2.60−2.58 (m, 1H), 2.18−2.15 (m, 1H), 1.83−1.80 (m, 1H), 1.39 (d, 3H, $J = 8$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.1, 143.8, 135.8, 129.5, 128.8, 128.2, 127.3, 127, 126.1, 66, 62.5, 61.4, 51, 49.6, 41.3, 35.2, 29.6, 22.4. Anal. Calcd for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94. Found: C, 70.76; H, 7.16; N, 3.89.

(2*R*,3*R*)-3-Phenylsulfonylmethyl-1-(1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid methyl ester 21: Same protocol as for compound **13:** mCpBA (7.3 g, 32 mmol), **20** (6.2 g, 16 mmol), CH_2Cl_2 (100 mL), and TFA (5 mL, 64 mmol). Workup and purification by flash chromatography (cyclohexane/ethyl acetate, 7/3) yielded 9.8 g (80%) of a colorless glue. $[\alpha]^{20}{}_D$ 40 (c 1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.87−7.84 (m, 2H), 7.57−7.54 (m, 3H), 7.26−7.22 (m, 5H), 3.7 (q, 1H, $J = 7.5$ Hz), 3.58 (s, 3H), 3.4 (d, 1H, $J = 7.5$ Hz), 3.25−3.20 (m, 1H), 3.09−2.09 (m, 3H), 2.8−2.7 (m, 1H), 2.2−2.1 (m, 1H), 1.85−1.75 (m, 1H), 1.32 (d, 3H, $J = 7.5$ Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172, 143, 133.8, 129.3, 128.3, 128, 127.2, 65.6, 61.1, 57.5, 51.2, 49.5, 41.3, 35.7, 29.6, 22.6. Anal. Calcd for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.61. Found: C, 64.97; H, 6.59; N, 3.48.

(2*R*,3*R*)-3-(1-Methyl-1-phenylsulfonylmethyl)-1-(1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid methyl ester 22 (as a mixture of two diastereoisomers): Same protocol as for compound **14**: LDA (16 mL, 28 mmol), THF/DMPU (70 mL, 3/1), sulfone **21** (10.83 g, 28 mmol), and CH_3I (7.05 mL, 112 mmol). After workup, the crude materials were purified by flash chromatography (cyclohexane/ethyl acetate, 7/3), yielding 10.5 g (93%) of a colorless glue as a mixture of two diastereoisomers (65/35). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87−7.81 (m, 2H), 7.63−7.5 (m, 3H), 7.29−7.25 (m, 5H), 3.76 (2q, 1H), 3.65 (s, 3H, 65%), 3.57 (s, 3H, 35%), 3.45 (2d, 1H), 3.25−3.20 (m, 1H), 3.09−2.09 (m, 3H), 2.8−2.7 (m, 1H), 2.2−2.1 (m, 1H), 1.85−1.75 (m, 1H), 1.69−1.65 (2 broad d, 6H), 1.11 (d, 3H, $J = 6.5$ Hz, 65%), 1.07 (d, 3H, $J = 6.7$ Hz, 35%). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172, 143, 133.8, 129.3, 128.3, 128, 127.2, 65.6, 61.1, 57.5, 51.2, 49.5, 41.3, 35.7, 29.6, 22.6. Anal. Calcd for $C_{22}H_{24}NO_4S$: C, 65.09; H, 6.50; N, 3.61. Found: C, 64.97; H, 6.59; N, 3.48.

(2*R*,3*R*)-3-(1,1-Dimethyl-1-phenylsulfonylmethyl)-1-(1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid methyl ester 23: Same protocol as for compound **16**: LDEA (1 M, 50 mL), THF/DMPU (3/1, 100 mL), sulfone **22** (10 g, 10 mmol), and CH_3I (6.3 mL, 100 mmol). After the usual workup, the leaving pale yellow oil was crystallized twice (Et_2O/pentane) and white crystals (6.8 g, 66%) were obtained. $[\alpha]^{20}{}_D$ 11 (c 1, $CHCl_3$); mp 96−98 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.84−7.80 (m, 2H), 7.7−7.5 (m, 3H), 7.20−7.20 (m, 5H), 3.54 (s, 3H), 3.53 (q, 1H, $J = 7.5$ Hz), 3.4 (d, 1H, $J = 5$ Hz), 3.3 (m, 1H), 3.1 (m, 1H), 2.9 (m, 1H), 2.25 (m, 2H), 1.3 (d, 3H, $J = 7.5$ Hz), 1.22 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173, 145, 135.4, 133.6, 130.6, 128.8, 128.3, 127.2, 127, 64.3, 63.9, 60.6, 50.7, 49.2, 45.6, 23.4, 21.5, 17.6. Anal. Calcd for $C_{23}H_{29}NO_4S$: C, 66.48; H, 7.08; N, 3.37. Found: C, 66.63; H, 7.16; N, 3.30.

(2*R*,3*R*)-3-Isopropyl-1-(*tert*-butyloxycarbonyl)-pyrrolidine-2-carboxylic acid methyl ester 24: KH_2PO_4 (6.22 g, 45,3 mmol) and freshly prepared 3% Na/Hg amalgam (39.67 g, 60.4 mmol) were added portionwise to a dry solution of sulfone **23** (6.28 g, 15.1 mmol) in freshly distilled MeOH (70 mL). The mixture was vigorously stirred for 1 h at room temperature. After filtration over a Celite pad, the crude material was concentrated. Et_2O was added and the organic layer was washed twice with 10% Na_2CO_3 and brine, dried over $MgSO_4$, and concentrated to an oil. A mixture of this oil (1.87 g, 6.8 mmol), 10% Pd/C (500 mg), and Boc_2O (1.63 g, 7.5 mmol) in MeOH was stirred overnight at room temperature under hydrogen. After filtration over a Celite pad and concentration, the crude material was purified by flash chromatography (pentane/ethyl acetate, 95/5), leaving an oil (1.6 g,

87%). [α] $^{20}_{D}$ −38 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.64−4.55 (2d, 1H, Boc cis−trans isomerization, *J* = 7.75 Hz), 3.97−3.96 (2s, 3H, Boc cis−trans isomerization), 3.92 (m, 1H), 3.53 (m, 1H), 2.23 (m, 2H), 2.02 (m, 1H), 1.72−1.66 (2s, 9H, Boc cis−trans isomerization), 1.30 (d, 3H, *J* = 6.5 Hz), 1.16 (d, 3H, 6.5H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.6, 79.8, 62.3, 61.6, 51.6, 51.4, 50.6, 46.2, 45.9, 29.3, 29.1, 28.4, 28.3, 27.6, 22.1, 21.5. Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.96; H, 9.29; N, 5.16. Found: C, 61.80; H, 9.43; N, 5.09.

(2*S*,3*R*)-3-Isopropyl-1-(*tert*-butyloxycarbonyl)-pyrrolidine-2-carboxylic acid methyl ester 25: LDA (2.52 mL, 5.05 mmol) was added to compound **24** (1.35 g, 5 mmol) in dry THF at −78 °C under argon. The temperature was brought to rt and the reaction mixture was quenched by saturated aqueous NH_4Cl. Et_2O was added and the organic layer was washed with brine and dried over $MgSO_4$, leaving an oil (1.28 g, 95%) after concentration and purification by flash chromatography (pentane/ethyl acetate, 95/5). [α] $^{20}_{D}$ −27 (*c* 1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.64−4.55 (2d, 1H, Boc cis−trans isomerization, *J* = 7.75 Hz), 3.97−3.96 (2s, 3H, Boc cis−trans isomerization), 3.92 (m, 1H), 3.53 (m, 1H), 2.23 (m, 2H), 2.02 (m, 1H), 1.72−1.66 (2s, 9H, Boc cis−trans isomerization), 1.30 (d, 3H, *J* = 6.5 Hz), 1.16 (d, 3H, 6.5H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.6, 79.8, 62.3, 61.6, 51.6, 51.4, 50.6, 46.2, 45.9, 29.3, 29.1, 28.4, 28.3, 27.6, 22.1, 21.5. Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.96; H, 9.29; N, 5.16. Found: C, 61.80; H, 9.43; N, 5.09.

(2*S*,3*R*)-3-Isopropyl-1-(*tert*-butyloxycarbonyl)-pyrrolidine-2-carboxylic acid 26: A solution of compound **25** (1.03 g, 4 mmol) and LiOH (95.6 mg, 4 mmol) in CH_3CN/H_2O (6 mL, 1/1) was stirred for 5 h at rt. After concentration to 3 mL, water was added. The aqueous phase was extracted twice with ethyl acetate. The pH was adjusted to 2 by slow addition at 0 °C of HCl (3 M). The aqueous phase was extracted twice again with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated, giving an oil, which was crystallized with ether/pentane yielding white pellets (988 mg, 96%). [α] $^{20}_{D}$ −44 (*c* 1, $CHCl_3$); mp 88−90 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.1−3.95 (2d, 1H, Boc cis−trans isomerization, *J* = 7.5 Hz), 3.55 (m, 1H), 3.4 (m, 1H), 2.17 (m, 1H), 2.02 (m, 1H), 1.70 (m, 1H), 1.46−1.42 (2s, 9H, Boc cis−trans isomerization), 0.99 (d, 3H, *J* = 7.5 Hz), 0.93 (d, 3H, 7.5 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 179.8, 177.6, 155.3, 153.9, 80.6, 80.4, 62.6, 54.4, 49.5, 46.3, 45.9, 30.3, 28.4, 28.3, 27.6, 26.9, 21.1, 19.5, 19.3 Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.62; H, 9.02; N, 5.30.

JO026535N