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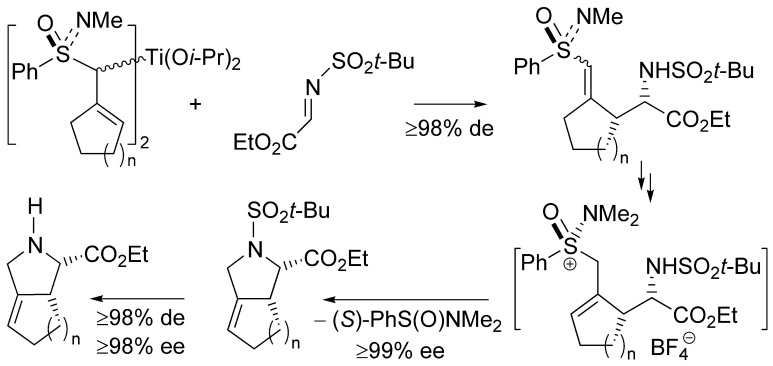

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Asymmetric Synthesis of Unsaturated, Fused Bicyclic Proline Analogues through Amino Alkylation of Cyclic Bis(allylsulfoximine)titanium Complexes and Migratory Cyclization of δ-Amino Alkenyl Aminosulfoxonium Salts

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Abstract: Described is an asymmetric synthesis of new $\Delta^{3a,4}$-unsaturated, fused bicyclic proline analogues from cyclic bis(allylsulfoximine)titanium complexes and *N*-*tert*-butylsulfonyl imino ethyl ester. Treatment of the enantiomerically pure five-, six-, seven-, and eight-membered cyclic bis(allylsulfoximine)titanium complexes with the imino ester gave mixtures of the corresponding (*E*,syn)- and (*Z*,syn)-configured, δ-sulfoximine substituted, cyclic γ,δ-unsaturated α-amino acid esters with high regio- and diastereoselectivities in good yields. Activation of the *N*-methyl sulfoximine group of these amino acid derivatives through methylation with Me_3OBF_4 afforded in nearly quantitative yields the corresponding (dimethylamino)-sulfoxonium salts. A novel migratory cyclization of these salts with DBU gave via an isomerization to the corresponding allylic (dimethylamino)sulfoxonium salts and an intramolecular substitution of the (dimethylamino)sulfoxonium group the enantio- and diastereomerically pure, bicyclic, *N*-*tert*-butylsulfonyl protected proline analogues having a six- and eight-membered unsaturated carbocyclic ring. Cyclization of the alkenyl (dimethylamino)sulfoxonium salts was independent of the configuration of the double bond. *N*,*N*-Dimethylphenylsulfinamide of ≥99% ee was obtained in good yield as a further reaction product. Conversion of the sulfinamide to *N*,*S*-dimethyl-*S*-phenylsulfoximine of ≥99% ee, the starting material for the synthesis of the allylic sulfoximines, had been accomplished previously. Finally, cleavage of the *tert*-butylsulfonyl protecting group with anhydrous acid furnished the fused bicyclic proline analogue containing an unsaturated six-membered ring in high yield.

Introduction

The synthesis and application of fused bicyclic α-amino acids have received much attention in recent years.[1−3] Many of these amino acids display interesting pharmacological activities,[1e,2] and they have served as building blocks for the synthesis of conformationally constrained peptides.[3] Frequently, such peptidomimetics show besides interesting structures improved pharmacological activities and metabolic stabilities. Particularly interesting are bicyclic proline analogues[4] which have not only been studied as angiotensin,[5] bradykinin,[5] thyroliberin,[6] and glutamic acid[7] analogues, but also served as building blocks for the synthesis of peptidomimetics.[3,4] Proline confers conformational restrictions into peptides, which can induce the formation of β-turns and its replacement with analogues can provide additional information about receptor recognition and affinity. Besides these applications, proline and its derivatives

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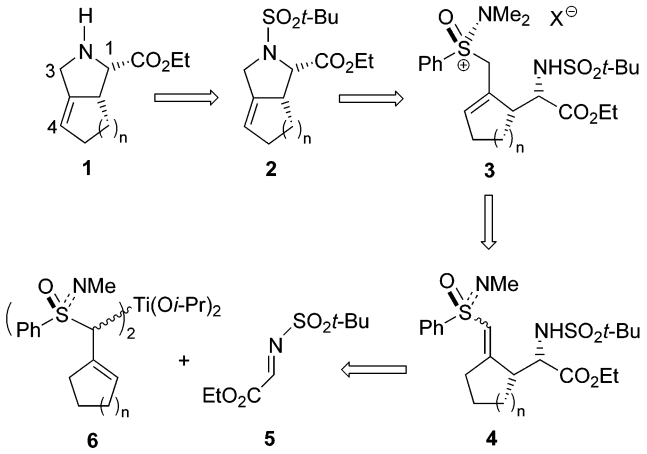
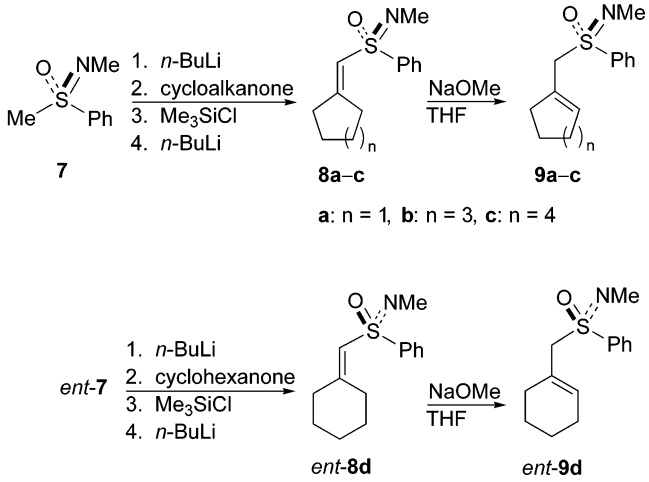
Scheme 1. Retrosynthetic Analysis of Unsaturated Bicyclic Proline Analogues



Scheme 2. Synthesis of Cyclic Allylic Sulfoximines



have gained considerable importance in asymmetric synthesis.[8,9] All of these factors have contributed to the ever-growing interest in the asymmetric synthesis of mono- and bicyclic proline analogues.[4,10] We have been interested in the asymmetric synthesis of the fused bicyclic proline analogues **1** having a $\Delta^{3a,4}$-unsaturated carbocyclic ring of different size and an allylic amine moiety (Scheme 1). Proline analogues of this type were not known up to now.[11] The only exemption being a derivative of **1** containing a five-membered carbocyclic ring ($n = 1$), which was obtained from an β,γ-unsaturated α-amino acid by using the Pauson−Khand cycloaddition method.[4k] Because of the double bond, proline anlogues **1** should allow the stereoselective synthesis of various derivatives which are not or only difficult accessible thus far. In addition, access to 1-substituted and 1,3- or 1,4-disubstiuted derivatives can perhaps be provided through application of deprotonation methodologies[12] to suitable N-protected derivatives of **1** (vide infra). Hence, proline analogues **1** could not only serve as starting material for the synthesis of new biologically active amino acids and peptidomimetics but may perhaps also contribute to the development of improved catalysts and auxiliaries.

We had recently observed that treatment of the six-membered cyclic bis(allylsulfoximine)titanium complex *ent*-**6** ($n = 2$) with the *N*-*tert*-butylsulfonyl imino ester **5** gave with high regio- and diastereoselectivity the sulfoximine substituted, γ,δ-unsaturated amino acid derivative *ent*-**4** ($n = 2$) as a mixture of *E*- and *Z*-isomers.[13] On the premise of a successful extension of this amino alkylation to other cyclic bis(allylsulfoximine)titanium complexes **6** ($n = 1, 3, 4$) as well, an asymmetric synthesis of **1** from the monocyclic amino acids **4** was invisioned which would involve an isomerization of the latter to the allylic (dimethylamino)sulfoxonium salts **3** following methylation of the sulfoximine group and a subsequent intramolecular substitution of the (dimethylamino)sulfoxonium group. Selection of imino ester **5**, whose synthesis we have described recently,[13] should allow a facile deprotection of the intermediate N-sulfonyl protected amino acid **2** with formation of **1**.[13,14] Although nothing was known about allylic (dimethylamino)sulfoxonium salts of type **3** at the outset of our investigations, observations made[15] during a study of the elimination of acyclic 1-alkenyl (dimethylamino)sulfoxonium salts[16] hinted that such a migratory cyclization of the *N*-methyl derivative of **4** might perhaps be feasible. Further support for the feasibility of a cyclization of **3** came from the demonstrated nucleofugacity of the (dimethylamino)sulfoxonium group in aziridine synthesis.[17]

Results and Discussion

Synthesis of Cyclic Allylic Sulfoximines. The known cyclic allylic sulfoximines **9a**, **9b**, and *ent*-**9d**[18] were prepared from the sulfoximines **7** and *ent*-**7** (≥ 99% ee),[19−21] respectively and the corresponding cycloalkanones in yields of 58−74% by using an improved procedure described recently,[22] which does not require the isolation of any intermediate including the 1-alkenyl sulfoximines **8a**, **8b**, and *ent*-**8d** (Scheme 2).

Similarly, the new eight-membered cyclic sulfoximine **9c**[23] was obtained from **7** and cyclooctanone without isolation of **8c**

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Scheme 3. Amino Alkylation of Cyclic Bis(allylsulfoximine)-titanium Complexes

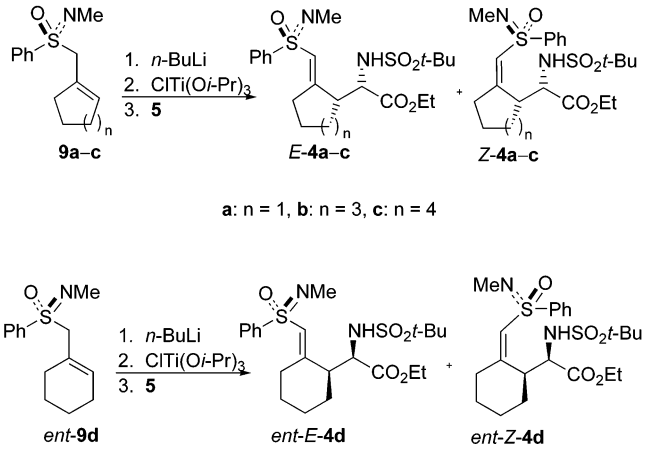

Table 1. Amino Alkylation of Cyclic Bis(allylsulfoximine)titanium Complexes **6** With Imino Ester **5**.

allylic sulfoximine	amino acid derivative	*E*:*Z*[a]	E yield (%)	E de[a](%)	Z yield (%)	Z de[a](%)
6a	*E*-**4a**/*Z*-**4a**	1.3−1.4:1	43	≥98	25	≥98
ent-**6d**	*ent*-*E*-**4d**/*ent*-*Z*-**4d**	4.6−5.3:1	56	≥98	13	≥98
6b	*E*-**4b**/*Z*-**4b**	1:2.7−2.8	25	≥98	72	≥98
6c	*E*-**4c**/*Z*-**4c**	1:11−13	7	≥98	78	≥98

[a] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

in 79% overall yield, based on **7**. The *S*-phenyl derivatives **9a**−**c** and *ent*-**9d** were selected for the synthesis of **1** because of the extreme ease of the attainment of **7** and *ent*-**7** in enantiomerically pure form.[21]

Amino Alkylation of Cyclic Bis(allylsulfoximine)titanium Complexes. We were pleased to see that the successive treatment of the allylic sulfoximines **9a**−**c** with *n*-BuLi, 2.1 equiv of ClTi(O*i*-Pr)$_3$ and imino ester **5**[13] gave mixtures of the *E*- and *Z*-configured α-amino acid derivatives *E*-**4a**−**c** and *Z*-**4a**−**c**, respectively, in good yields (Scheme 3, Table 1). Similarly, a mixture of *ent*-*E*-**4d** and *ent*-*Z*-**4d** was prepared as described previously from the allylic sulfoximine *ent*-**9d** and **5**.[13] Crystallization and chromatography of the mixtures of the *E*- and *Z*-diastereomers allowed for the isolation of the pure amino acid derivatives. The diastereoselectivities of the formation of both the *Z*- and *E*-isomers were in all cases high (≥98% de) as indicated by NMR spectroscopy of the crude reaction mixtures and independent of the ring size of the allylic sulfoximine. Interestingly, the *E*/Z ratios changed from 1.3 to 1.4:1 for the five-membered cyclic 1-alkenyl sulfoximine **4a** to 1:11−13 for the eight-membered cyclic 1-alkenyl sulfoximine **4c**. Assignment of the configurations of the double bond of the isomers was made by NOE experiments, which revealed for the *E*-isomers strong NOE effects between the olefinic proton and the allylic proton at the stereogenic center whereas for the *Z*-isomers strong NOE effects between the olefinic proton and an allylic proton of the methylene group were observed.

The absolute configuration of *ent*-*E*-**4d** had already been established by X-ray crystal structure analysis.[13] A X-ray crystal structure analysis of *Z*-**4c** showed it to have the absolute configuration depicted in Figure 1. Thus, both compounds have the same relative configurations at the S-atom, Cα-atom and Cβ-atom. In addition, chemical correlation showed that isomers *ent*-*E*-**4d** and *ent*-*Z*-**4d** both have the same configuration at the

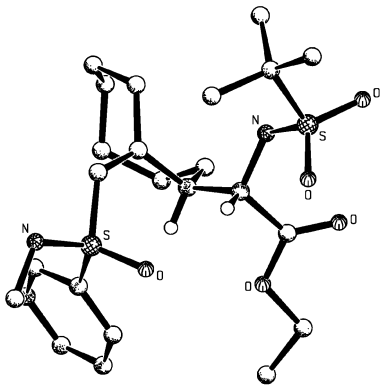

Figure 1. Structure of *Z*-**4c** in the crystal.

Cα-atom and Cβ-atom (vide infra). Thus, it is proposed that α-amino acid derivatives *E*-**4a**−**c** and *Z*-**4a**−**c** all have the same configuration at the Cα-atom and Cβ-atom.

Stereochemical Consideration of the Amino Alkylation. On the basis of the synthesis, structure, dynamics, and reactivity of acyclic bis(allylsulfoximine))titanium complexes[22] and the similar stereochemical course of the reaction of both the acyclic[13] and the cyclic titanium complexes with **5**, the following is proposed for the conversion of **9a**−**c** into *E*-**4a**−**c** and *Z*-**4a**−**c** and of *ent*-**9d** into *ent*-*E*-**4d** and *ent*-*Z*-**4d**. First, titanation of the lithio derivative of **9** with ClTi(O*i*-Pr)$_3$ leads to a mixture of the diastereomeric complexes (*R*,*R*)-**6** and (*S*,*S*)-**6** and equimolar amounts of Ti(O*i*-Pr)$_4$ (Scheme 4). Second, these complexes are configurationally labile in regard to the Cα-atoms and their reaction with **5** is slower than their equilibration, a situation which can be described by the Curtin−Hammett principle.[24] Third, transfer of the allylic moieties of **6** to **5** occurs stepwise with the intermediate formation of the mixed mono-(allylsulfoximine)titanium complexes *R*,*E*-**10** and *R*,*Z*-**10**, which are also configurationally labile in regard to the Cα-atom and are thus in equilibrium with their stereoisomers *S*,*E*-**10** and *S*,*Z*-**10**, respectively. Fourth, asymmetric induction in the stereoselective generation of the Cα-atom and Cβ-atom of *E*/*Z*-**4** is provided by the sulfoximine group and not by the Cα-atom because of the configurational lability of the latter.

To rationalize the *E*/*Z*-stereoselectivities of the reaction of **6** with **5** in dependence of the ring size, the two Si,Re chairlike six-membered cyclic transition state models **TS-1** and **TS-2** are proposed for the transfer of the first allylic moiety. Similar transition state models have been put forward previously to rationalize the stereochemistry of the reaction of similar acyclic bis(allylsulfoximine)titanium complexes with **5**.[13] In **TS-1** and **TS-2** the imino ester and the sulfoximine group are coordinated through their N-atoms to the Ti-atom, and the *tert*-butylsulfonyl and the ester group both occupy pseudoaxial positions. The major and decisive differences between the Si,Re transition state models **TS-1** and **TS-2** and the analogous Re,Si transition state models **TS-3** and **TS-4**, which would lead to the formation of the diastereomers of *E*/*Z*-**4** having the opposite configurations at both stereogenic C-atoms, are the positions of the *S*-phenyl groups. In **TS-1** and **TS-2** the phenyl groups are placed in sterically less encumbered positions than in **TS-3** and **TS-4** thus making the former transitions states lower in energy. In

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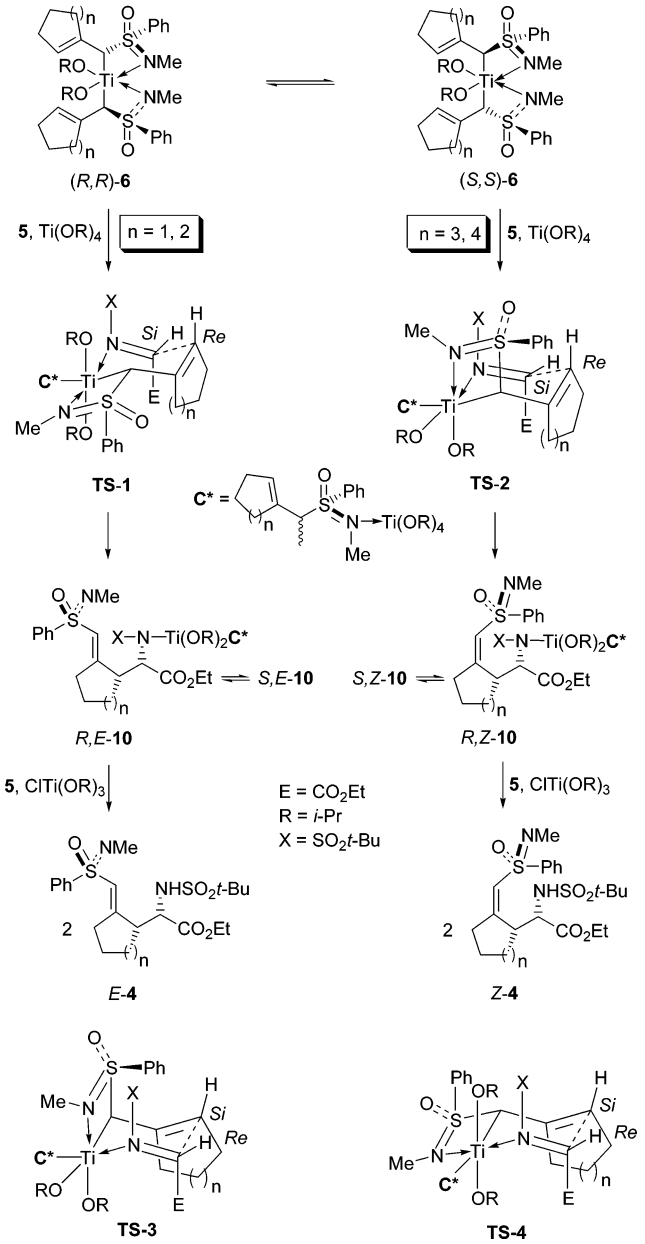
Scheme 4. Stereochemical Rationalization of the Amino Alkylation



comparing **TS-1** and **TS-2**, the major difference between both is the position of the sulfoximine group, being pseudoequatorial in the first and pseudoaxial in the second. The sulfoximine group is expected to cause in **TS-1** a destabilizing 1,2-interaction with the methylene groups of the unsaturated ring and in **TS-2** a destabilizing 1,3-interaction with the *tert*-butylsulfonyl group. It is proposed that in the case of small rings ($n = 1, 2$) the 1,2-interaction is less destabilizing than the 1,3-interaction, while in the case of larger rings ($n = 3, 4$) it is vice versa. Hence, in the reaction of **5** with **6**, $n = 1$ and 2, the (*R*,*R*)-configured complex is more reactive giving via **TS-1** preferentially *E*-**4**, whereas with **6**, $n = 3$ and 4, it is the (*S*,*S*)-configured complex which has the higher reactivity yielding via **TS-2** preferentially *Z*-**4**. Similar transition state models (not depicted in Scheme 4) and arguments can be applied to the reaction of the mono-(allylsulfoximine)titanium complexes *E*-**10** and *Z*-**10** with **5**.

We had previously observed that the reaction of acyclic complexes of type **6** with **5** requires for the first step to occur an activation of the bis(allyl)titanium complex by $Ti(O\textit{i}\text{-}Pr)_4$ and for the second step that of the mono(allyl)titanium complex by $ClTi(O\textit{i}\text{-}Pr)_3$.[13] We have proposed that the role played by these Lewis acids may be that of a coordination to the N-atom of the sulfoximine group[25] of the mono- and bis(allyl)titanium complexes, thereby creating a free coordination site at the Ti-atoms for the coordination of **5**.[13] Because we assumed that the cyclic complexes **6** and **10** would require a similar activation by the Lewis acids, 2 equiv of $ClTi(O\textit{i}\text{-}Pr)_3$ were used from the start in the synthesis of **4**.

Migratory Cyclization of 4-(Dimethylamino) 1-Alkenyl Sulfoxonium Salts. Treatment of the 1-alkenyl sulfoximines *ent*-*E*-**4d**, *ent*-*Z*-**4d**, and *Z*-**4c** with Me_3OBF_4[16] in CH_2Cl_2 at ambient temperature for 1.5 h afforded the 1-alkenyl (dimethylamino)sulfoxonium salts *ent*-*E*-**11a**, *ent*-*Z*-**11a**, and *Z*-**11b**, respectively, in essentially quantitative yields (Scheme 5). The methylation reagent has to be free of HBF_4 because of an otherwise occurring protonation of the starting sulfoximine, which prevents its complete conversion. As hoped for, treatment of the *E*-configured sulfoxonium salt *ent*-*E*-**11a** with 1.1 equiv of DBU at ambient temperature gave the protected bicyclic α-amino acid *ent*-**2a** in 80% yield (Table 2). The relative configuration of *ent*-**2a** was determined through a combination of ^{1}H NMR spectroscopy and NOE experiments which revealed a strong NOE effect between 1-H and 7a-H and between 7a-H and 6-H_{axial} (Figure 2). According to the magnitudes of the vicinal coupling constants and the NOE's the cyclohexene ring of *ent*-**2a** adopts a half-chair conformation and the sulfonyl group a N−S conformation where the *tert*-butyl group is placed in the anti position to the ester group. Because of the formation of mixtures of *E*- and *Z*-isomers in the reaction of the titanium complexes **6a**−**c** and *ent*-**6d** with **5**, it was of particular importance to see whether the *Z*-isomer *ent*-*Z*-**4d** could also be converted to *ent*-**2a**. To this end the Z-configured salt *ent*-*Z*-**11a** was treated with DBU under the same conditions, which also furnished *ent*-**2a** in 76% yield.

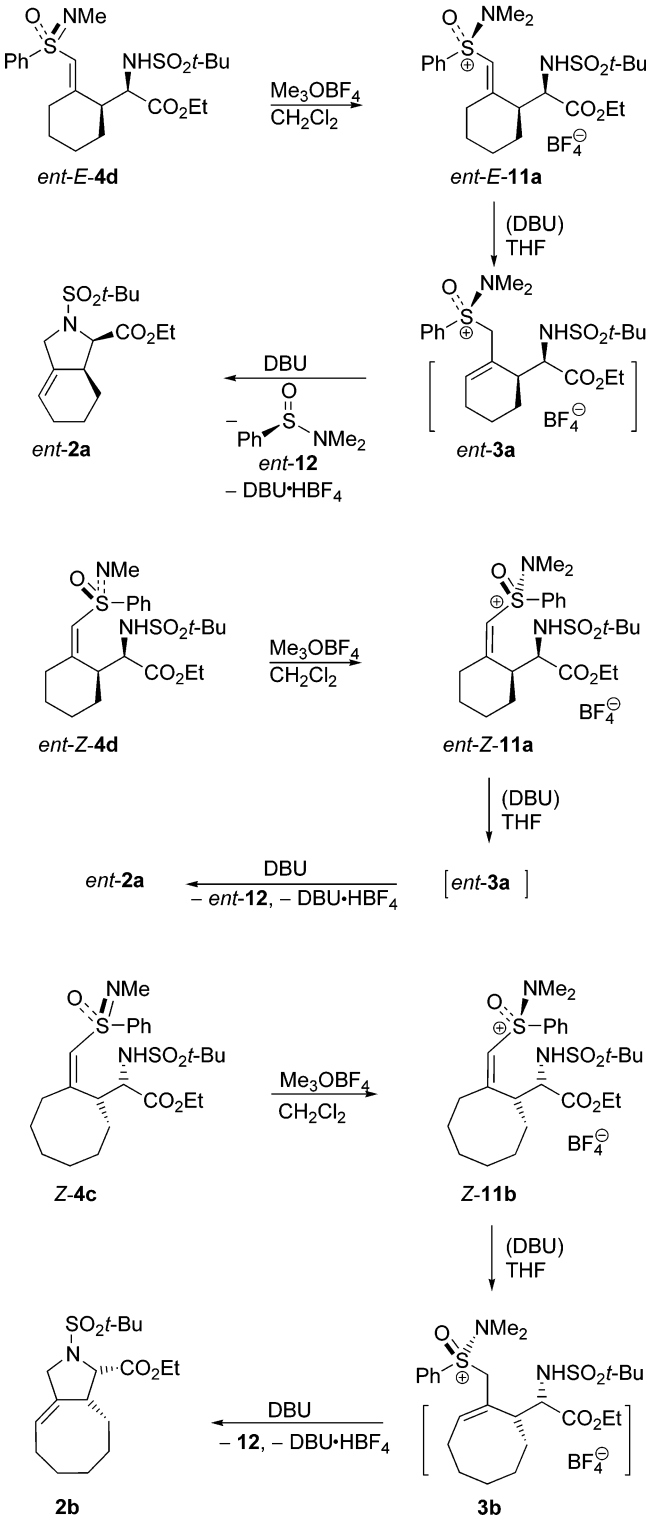
The formation of *ent*-**2a** from both the *Z*-isomer *ent*-*Z*-**4d** and the *E*-isomer *ent*-*E*-**4d** also proves that both have the same configuration at the Cα-atom and Cβ-atom. Finally, the cyclization of the eight-membered cyclic sulfoxonium salt *Z*-**11b** was studied. Gratifyingly, treatment of *Z*-**11b** with DBU afforded the bicyclic amino acid **2b** in 81% yield. The bicyclic amino acids were obtained as single diastereomers. No epimerization at the C1-atom with formation of the more stable trans isomers had taken place during treatment with the base. Cyclization of salt *ent*-*E*-**11a** could also be achieved upon treatment with 1.1 equiv of freshly prepared LiN(H)*t*-Bu first at −78 °C and then at ambient temperature, which gave *ent*-**2a** in 77% yield.

In the cyclizations described above, the sulfinamides **12** and *ent*-**12**,[16] respectively, were isolated in 74−76% yield as a further reaction product. GC analysis showed them to be of ≥99% ee. We had already shown that treatment of **12** with MeMgCl in THF at −78 °C afforded (*S*)-methyl phenylsulfoxide of ≥99% ee in 93% yield.[23] This sulfoxide can easily be converted to sulfoximine **7** of ≥99% ee.[19,20,26]

It is assumed that the DBU induced formation of *ent*-**2a** and **2b** starts with a regioselective isomerization of the 1-alkenyl

(25) For reviews on sulfoximines, see: (a) Pyne, S. G. *Sulfur Reports* **1999**, *21*, 281. (b) Reggelin, M.; Zur, C. *Synthesis* **2000**, *1*, 1.
(26) Bach, T.; Körber, C. *Eur. J. Org. Chem.* **1999**, 1033.

Scheme 5. Cyclization of 4-Amino 1-Alkenyl Sulfoximines



(dimethylamino)sulfoxonim salts *ent*-*E*-**11a**, *ent*-*Z*-**11a** and *Z*-**11b**, respectively, leading to the novel allylic (dimethylamino)sulfoxonium salts *ent*-**3a** and **3b**, respectively. Isomerization of the sulfoximines *ent*-**8d** and **8c** to the allylic sulfoximines *ent*-**9d** and **9c**, respectively, already is a facile process (cf. Scheme 2) and that of the sulfoxonium salts *ent*-*E*-**11a**, *ent*-*Z*-**11a**, and *Z*-**11b** should be even more facile because of the much stronger acidifying effect of the (dimethylamino)sulfoxonium group.[27a,b] For example, while sulfoximine **7** has an estimated

Table 2. Synthesis of Unsaturated Bicyclic Proline Analogues.

sulfoxonium salt	proline analog	yield (%)	de[a] (%)	sulfinamide	yield (%)	ee (%)
ent-*E*-**11a**	*ent*-**2a**	80	≥98	*ent*-**12**	76	[b]
ent-*Z*-**11a**	*ent*-**2a**	76	≥98	*ent*-**12**	[b]	[b]
Z-**11b**	**2b**	81	≥98	**12**	74	≥99

[a] Determined by ^{1}H NMR spectroscopy of the reaction mixture. [b]Not determined.

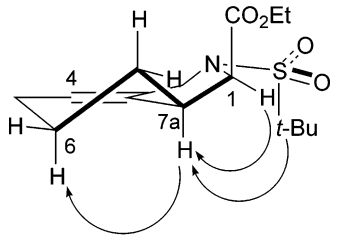


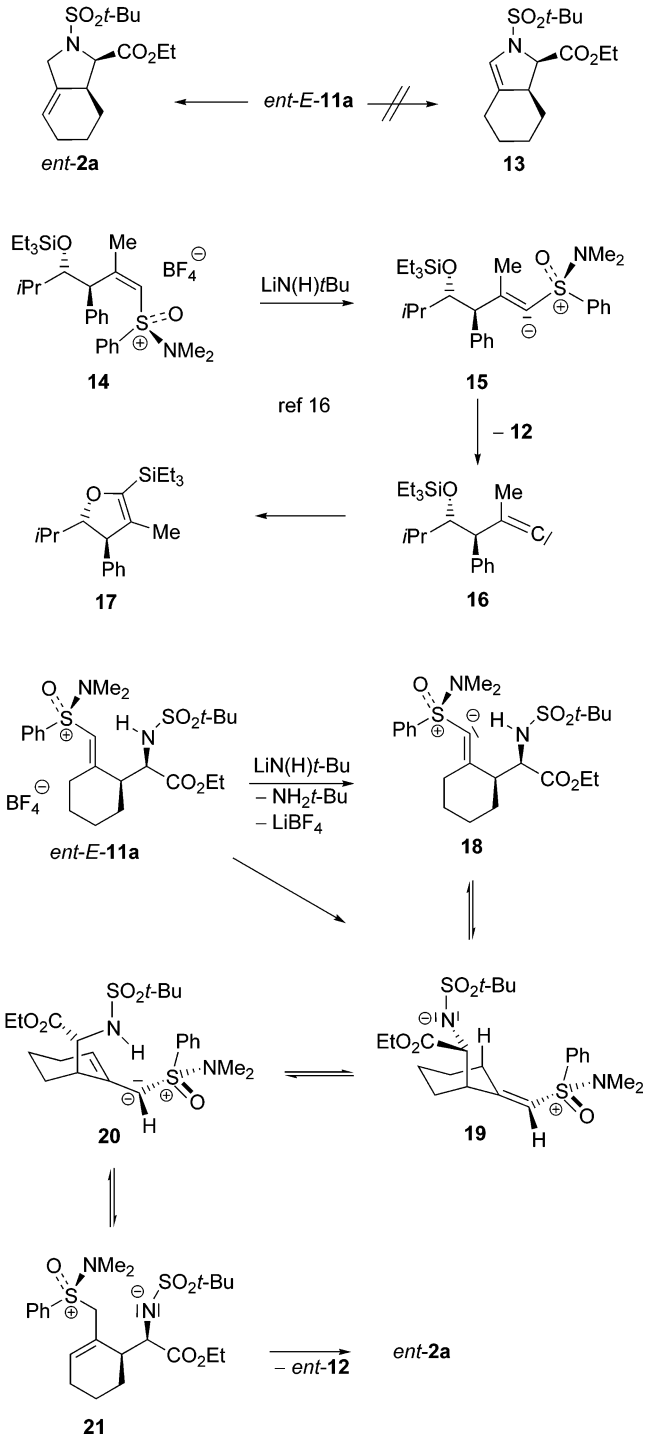
Figure 2. NOE's of *ent*-**2a**.

pK_a of 33, that of the corresponding (dimethylamino)sulfoxonium salt is 14.4,[27a] and the acidity of the allylic sulfoxonium salts *ent*-**3a** and **3b** are expected to be even higher because of the additional double bond. As the final step of the cyclization, we propose an intramolecular substitution of the allylic sulfoxonium group of *ent*-**3a** and **3b** following deprotonation with DBU at the N-atom. The nucleofugacity of the (dimethylamino)-sulfoxonium group attached to an alkyl group toward N-nucleophiles has already been demonstrated in the synthesis of aziridines from 1-alkenyl (dimethylamino)sulfoxonium salts and primary amines[17] and the (dimethylamino)sulfoxonium group located in an allylic position should have even a higher reactivity.[28]

Somewhat surprising was the formation of *ent*-**2a** in the reaction of salt *ent*-*E*-**11a** with 1.1 equiv of the strong base LiN(H)*t*-Bu. On the basis of the reaction of the δ-silyloxy alkenyl sulfoxonium salt **14** with LiN(H)*t*-Bu, formation of the isomer **13** would have been expected (Scheme 6). Salt **14** reacts with the lithium amide under deprotonation at the α-position to give the ylide **15** which suffers an elimination of sulfinamide **12** with formation of the alkylidene carbene **16**.[16] The later undergoes cyclization and 1,2-silyl migration to give the 2,3-dihydrofuran derivative **17**. The lack of an analogous formation of **13** from salt *ent*-*E*-**11a** via alkylidene carbene formation and cyclization of the latter may perhaps be due to the unique properties of the sulfonamide group of *ent*-*E*-**11a**. It is not only acidic but also positioned in close spatial proximity to both the olefinic and the two allylic H-atoms of *ent*-*E*-**11a**. The six-membered ring of sulfoximine *ent*-*E*-**4d**, the starting material for the synthesis of salt *ent*-*E*-**11a**, adopts in the crystal and in solution a conformation in which the allylic substituent is placed in a pseudoaxial position.[13] Thus, it is assumed that salt *ent*-*E*-**11a** adopts preferentially a similar conformation in solution. Deprotonation of salt *ent*-*E*-**11a** with LiN(H)*t*-Bu can take place either at the N-atom or at the double bond. Deprotonation of *ent*-*E*-**11a** at the double bond would give ylide **18**,[16] which could suffer an intramolecular proton transfer from the N-atom to the C-atom

(27) (a) Bordwell, F. G.; Branca, J. C.; Johnson, C. R.; Vanier, N. R. *J. Org. Chem.* **1980**, *45*, 3884. (b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (c) Kravtsov, D. N.; Peregudov, A. S.; Petrov, E. S.; Terekhova, M. I.; Shatenstein, A. I. *Bull. Acad. Sci. USSR* **1981**, *30*, 993.
(28) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*: *Reactions, Mechanisms, and Structure*; Wiley: New York, 2001.

Scheme 6. Reaction of 1-Alkenyl Aminosulfoxonium Salts With LiN(H)*t*-Bu



with formation of the betaine **19**. A subsequent second intramolecular proton transfer in **19** from the allylic position to the N-atom would yield the allylic ylide **20** which then could undergo a third proton transfer from the N-atom to the C-atom with formation of the betaine **21**. Finally, betaine **21** should cyclize with formation of *ent*-**2a** and *ent*-**12**. The alternative deprotonation of salt *ent-E*-**11a** at the N-atom would directly give betaine **19**.

Although the pK_a-values of 2-alkenyl and 1-alkenyl (dimethylamino)sulfoxonium salts have not been determined yet, estimations[27b] based on the acidity of alkyl (dimethylamino)-

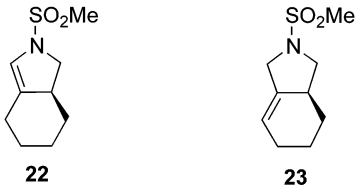
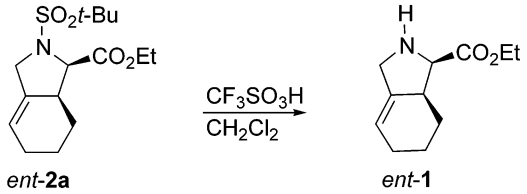


Figure 3. Calculation of model compounds.

Scheme 7. Deprotection of *ent*-**2a**



sulfoxonium salts suggest pK_a-values of the former two sulfoxonium salts in the range of 10−20. Because, for example, *N*-methyl-phenylsulfonamide has a pK_a-value of 17.5[27c] the crucial proton-transfer reactions depicted in Scheme 6 would be conceivable. Thus, it is proposed that the isomerization of the double bond of salt *ent-E*-**11a** through an intramolecular 1,3-H-shift mediated by the sulfonamido group is faster than the α-elimination.

To exclude the notion that the alkylidene carbene pathway is in fact operating in the reaction of salt *ent-E*-**11a** with LiN(H)*t*-Bu and that **13** escapes isolation only because of a base-catalyzed isomerzation to *ent*-**2a** orienting calculations for the model compounds **22** and **23** have been carried out at both the B3LYP/6-31+G* and the MP2/6-31+G* level. These calculations revealed that the enamine **22** is about 2.5−3.1 kcal/mol more stable than the allylic amine **23** (Figure 3).[29] Thus, a primary formation of **13** in the reaction of *ent-E*-**11a** with the base and its subsequent isomerization to *ent*-**2a** with *t*BuNH$_2$ can be ruled out with a high probability.

Deprotection of *N-tert*-Butylsulfonyl Amino Acid. The *N-tert*-butylsulfonyl imino ester **5**[13] was selected for the synthesis of the amino acid derivatives **1** and not the corresponding *N*-tolylsulfonyl derivative[30] because of the much easier deprotection of *N-tert*-butylsulfonylamines[14] as compared to *N*-tolylsulfonylamines.[14,31] This feature of the *tert*-butylsulfonyl group had already been successfully exploited in the deprotection of acyclic *N-tert*-butylsulfonyl amino acids of type **4**.[13] As anticipated treatment of the amino acid derivative *ent*-**2a** with 3.3 equiv of CF_3SO_3H in CH_2Cl_2 (0.1 M) at −30 °C for 45 min led to its ready deprotection and afforded the α-amino acid ester *ent*-**1** in 83% yield (Scheme 7).

Conclusion

We have described a highly selective asymmetric synthesis of new unsaturated fused bicyclic proline analogues, the key steps of which are a highly regio- and diastereoselective amino alkylation of cyclic bis(allylsulfoximine)titanium complexes with *tert*-butylsulfonyl imino ester and a novel migratory cyclization of δ-amino alkenyl sulfoxonium salts. Fortunately, the cyclization is independent of the configuration of the exocyclic double

(29) A detailed computational study is currently carried out in our laboratories and a full account of the research will be published elsewhere.
(30) Tschaen, D. H.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058.
(31) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991.

bond. Although the synthesis has been completed only for the six- and eight-membered fused proline analogues, we are confident that the five- and the seven-membered analogues can also be obtained. The allylic (dimethylamino)sulfoxonium group seems to be endowed with a high nucleofugacity. The nucleofuge, the (dimethylamino)sulfoxonium group, can be isolated as *N*,*N*-dimethylphenylsulfinamide of ≥ 99% ee and converted in two steps to the sulfoximine used as the starting material for the synthesis of the cyclic allylic sulfoximines. The value of the *N*-*tert*-butylsulfonyl imino ester is again demonstrated by the ready cleavage of the *N*-*tert*-butylsulfonyl protected bicyclic amino acid to give the parent amino acid derivative.

Experimental Section

General. The allylic sulfoximines **9a**−**d** of ≥99% ee were synthesized from sulfoximines **7** and *ent*-**7**, respectively,[18,23] by using the procedure described previously.[22] Sulfoximines **7** and *ent*-**7**,[19−21] imino ester **5**,[13] the amino acid derivatives *ent*-*E*-**4d** and *ent*-*Z*-**4d**,[13] and ClTi(O*i*-Pr)$_3$[32] of ≥96% purity (^{1}H NMR) were prepared according to the literature. All reactions were carried out in absolute solvents under an argon atmosphere with syringe and Schlenk techniques in oven-dried glassware. THF and Et_2O were distilled under argon from lead/sodium/benzophenone, and CH_2Cl_2 was distilled from CaH_2. Me_3OBF_4, which was prepared according to the literature,[33] was thoroughly washed with several portions of absolute CH_2Cl_2 and absolute Et_2O in order to remove HBF_4, dried by passing a stream of argon through the filter cake, and stored at 2 °C under argon. Reagents were obtained from commercial sources and used without further purification unless otherwise stated. Column chromatography: silica gel 60, 0.063−0.200 mm. HPLC was performed with LiChrosorb Si 60, 250 × 25 mm, 7 μm. Melting points are uncorrected. Optical rotations were measured at approximately 22 °C. Specific rotations are in grad·mL/dm·g, and *c* is in g/100 mL. ^{1}H NMR spectra were recorded at 300, 400, and 500 MHz. Chemical shifts (δ) in ^{1}H NMR and ^{13}C NMR spectra are reported in ppm relative to Me_4Si (δ 0.00 ppm). ^{13}C NMR spectra were recorded at 75, 100, and 125 MHz. Peaks in the ^{13}C NMR spectra are denoted as "u" for carbons with zero or two attached protons or "d" for carbons with one or three attached protons, as determined from APT puls sequence. Assignments in the ^{1}H NMR spectra were made by GMQCOSY, GNOE, or GTOCSY experiments, and those in the ^{13}C NMR spectra were made by DEPT, HETCOR, or GHSQC experiments. IR spectra: only peaks of ν > 1000 cm^{-1} are listed, s = strong, m = medium, and w = weak. MS: EI, 70 eV; CI, 100 eV, only peaks of *m*/*z* > 80 and an intensity >10%, except decisive ones, are listed. Elemental analyses were carried out in the Microanalytical Laboratory of the Institut für Organische Chemie, RWTH Aachen.

X-ray Analyses. The crystal structure was solved using direct methods as implemented in the XTAL3.7 package of crystallographic routines.[34,35] The crystal of *Z*-**4d** contained severely disordered solvent molecules. The disorder could not be resolved. Therefore carbon atoms have been assigned to each of the five highest electron density peaks from the solvent molecules. The absolute configuration of *Z*-**4d** as depicted in Figure 1 was determined by the method of Flack.[36] The molecular structure was visualized with the program SCHAKAL.[37]

General Procedure for the Synthesis of Sulfoximine Substituted α-Amino Acid Derivatives *E*-4a−c and *Z*-4a−c (*GP1*). *n*-BuLi (1.37 mL of 1.6 M solution in *n*-hexane, 2.2 mmol) was added dropwise to a solution of the allylic sulfoximine (2.0 mmol) in THF (20 mL) at −78 °C. After the mixture had been stirred at −78 °C for 30 min, neat ClTi(O*i*-Pr)$_3$ (4.0 mmol) was added dropwise, and stirring at this temperature was continued for 30 min. The cooling bath was removed and the mixture was allowed to stir for 15 min at ambient temperature for homologization. After cooling the mixture to −78 °C, the imino ester (2.2 mmol) was added dropwise and the mixture was stirred for 5 h. Then the mixture was allowed to warm to ambient temperature within 16 h. Saturated aqueous $(NH_4)_2CO_3$ (150 mL) was added, and the mixture was stirred at ambient temperature for 30 min. Then the mixture was extracted with EtOAc (150 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The remaining yellow oil was dissolved in CH_2Cl_2 and *n*-pentane was added until the solution became slightly turbid. The solution was kept overnight at 2 °C to give the major diastereomer of the amino acid derivative of ≥98% de (^{1}H NMR) as fine white crystals. Preparative HPLC (EtOAc/*n*-hexane, 4:1) of the mother liquor afforded the minor diastereomer as a colorless solid of ≥98% de (^{1}H NMR).

General Procedure for the Synthesis of the Aminosulfoxonium Salts *ent*-*E*-11a, *ent*-*Z*-11a and *Z*-11b (*GP2*). The sulfoximine (1 mmol) and Me_3OBF_4 (1.1 mmol) were placed at ambient temperature in a Schlenk flask, which was then consecutively evacuated and refilled with dry argon three times. Then CH_2Cl_2 (30 mL) was added and the mixture was stirred at ambient temperature for 90 min. Subsequently water (20 mL) was added and stirring at ambient temperature was continued for 10 min. The mixture was extracted with CH_2Cl_2 and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to give the salt admixed with approximately 5% (^{1}H NMR) of the starting material. The salt was used without further purification for the cyclization step.

General Procedure for the Synthesis of the Bicyclic Proline Analogues *ent*-2a and 2b (*GP3*). To a solution of the freshly prepared (dimethylamino)sulfoxonium salt (1.0 mmol) in THF (20 mL) was added DBU (165 μL, 1.1 mmol) dropwise at ambient temperature. After the mixture had been stirred at ambient temperature for 8 h, saturated aqueous NH_4Cl (30 mL) was added and stirring was continued for 5 min. Then the mixture was extracted with CH_2Cl_2 and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The remaining yellow oil was purified by flash chromatography (Et_2O/*n*-hexane, 1:1) to afford the protected α-amino acid and the sulfinamide.

(−)-(*E*,*S*$_S$,2*S*,3*R*)- and (−)-(*Z*,*S*$_S$,2*S*,3*R*)-(2-(*N*-Methyl-*S*-phenylsulfonimidoyl-methylene)-cyclopentyl)-(2-methylpropane-2-sulfonylamino)-Acetic Acid Ethyl Ester (*E*-4a and *Z*-4a). Following *GP1*, the reaction of sulfoximine **9a** (1.02 g, 4.3 mmol) with the imino ester **5** (1.05 g, 4.8 mmol) gave a mixture of the crude alkenyl sulfoximines *E*-**4a** and *Z*-**4a** in a ratio of 1.3−1.4:1 in approximately 95% chemical yield (^{1}H NMR). Recrystallization from CH_2Cl_2/*n*-pentane afforded *E*-**4a** (851 mg, 43%) of ≥98% de as colorless crystals. Preparative HPLC (EtOAc/*n*-hexane, 4:1) of the mother liquor provided *Z*-**4a** (492 mg, 25%) of ≥98% de as a colorless solid.

E-**4a**. mp 130 °C; $[\alpha]_D$ −48.2 (*c* 0.33, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.2 Hz, 3H), 1.29 (s, 9H), 1.54−1.86 (m, 4H), 2.04−2.18 (m, 1H), 2.67 (s, 3H), 2.97−3.05 (m, 1H), 3.06−3.16 (m, 1H), 4.00 (dq, *J* = 7.2, *J* = 10.7 Hz, 1H), 4.12−4.23 (m, 2H), 4.62 (d, *J* = 9.9 Hz, 1H), 6.47 (s, 1H), 7.49−7.59 (m, 3H), 7.91−7.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.06 (d), 23.87 (u), 24.09 (d), 26.85 (u), 29.22 (d), 30.34 (u), 50.20 (d), 57.80 (d), 60.26 (u), 61.91 (u), 125.35 (d), 128.82 (d), 129.01 (d), 132.17 (d), 139.38 (u), 159.45 (u), 171.10 (u); IR (KBr) ν 3447 (w), 3116 (m), 2995 (m), 2943 (m), 2880 (s), 2802 (m), 2771 (w), 1733 (s), 1615 (w), 1471 (s), 1448 (m), 1368 (w), 1315 (s), 1244 (s), 1229 (s), 1126 (s), 1097 (s), 1069 (s), 1021 (s) cm^{-1}; MS (EI) *m*/*z* 456 (M^+, 26), 256 (26), 235 (21), 234 (16), 203 (30), 187 (38), 186 (99), 182 (15), 180 (30), 165 (12), 157 (12), 156 (45), 155 (19), 125 (57), 110 (17), 109 (22), 108 (55), 107

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(33) (a) Meerwein, H. *Org. Synth.* **1966**, *46*, 120. (b) Curphey, T. J. *Org. Synth.* **1971**, *51*, 142.
(34) XTAL 3.7 System, Hall, S. R.; du Boulay, D. J.; Olthof-Hazekamp, R., Eds.; Universities of Western Australia and Maryland, Lamb: Perth, 2000.
(35) CCDC 208638 contains the supplementary crystallographic data for this paper.
(36) Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876.
(37) Keller, E. SCHAKAL 92; Universität Freiburg, Germany, 1992.

(17), 106 (17), 102 (56), 81 (11), 80 (16); Anal. Calcd for $C_{21}H_{32}N_2O_5S_2$: C, 55.24; H, 7.06; N, 6.13. Found: C, 54.91; H, 6.95; N, 6.10.

Z-**4a**. mp 52 °C; $[\alpha]_D$ −150.2 (*c* 0.37, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H), 1.32 (s, 9H), 1.39−1.49 (m, 1H), 1.55−1.67 (m, 1H), 1.70−1.84 (m, 2H), 2.22−2.34 (m, 1H), 2.53−2.66 (m, 4H), 3.65 (m, 1H), 4.22 (m, 2H), 4.74 (dd, J = 4.4, J = 9.9 Hz, 1H), 5.36 (d, J = 9.9 Hz, 1H), 6.26 (s, 1H), 7.42−7.54 (m, 3H), 7.83−7.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.54 (d), 22.36 (u), 24.63 (d), 28.03 (u), 29.53 (d), 36.13 (u), 44.46 (d), 60.43 (d), 60.68 (u), 62.25 (u), 124.76 (d), 128.91 (d), 129.38 (d), 132.68 (d), 140.43 (u), 161.83 (u), 171.46 (u); IR (KBr) ν 3289 (w), 3061 (w), 2976 (s), 2936 (m), 2874 (m), 2803 (w), 1737 (s), 1631 (m), 1478 (m), 1446 (m), 1368 (m), 1309 (s), 1239 (s), 1148 (s), 1129 (s), 1106 (s), 1081 (m), 1024 (m) cm^{-1}; MS (EI) *m*/*z* 456 (M^+, 5), 383 (11), 336 (17), 335 (83), 320 (12), 235 (18), 181 (15), 180 (100), 156 (25), 155 (13), 152 (11), 125 (38), 109 (13), 108 (37), 107 (12), 106 (18), 102 (11); Anal. Calcd for $C_{21}H_{32}N_2O_5S_2$: C, 55.24; H, 7.06; N, 6.13. Found: C, 55.24; H, 7.29; N, 6.10.

(−)-(*Z*,*S*$_S$,2*S*,3*R*)- and (−)-(*E*,*S*$_S$,2*S*,3*R*)-(2-(*N*-Methyl-*S*-phenylsulfonimidoyl-methylene)-cycloheptyl)-(2-methylpropane-2-sulfonylamino)-Acetic Acid Ethyl Ester (*Z*-4b and *E*-4b). Following *GP1*, the reaction of sulfoximine **9b** (960 mg, 3.6 mmol) with the imino ester **5** (887 mg, 4.0 mmol) gave a crude mixture of the alkenyl sulfoximines *Z*-**4b** and *E*-**4b** in a ratio of 2.7−2.8:1 in approximately 98% chemical yield (^{1}H NMR). Recrystallization from CH_2Cl_2/*n*-pentane afforded *Z*-**4b** (1.279 g, 72%) of ≥ 98% de as colorless crystals. Preparative HPLC (EtOAc/*n*-hexane, 4:1) of the mother liquor provided *E*-**4b** (446 mg, 25%) of ≥98% de as a colorless solid.

Z-**4b**. mp 135 °C; $[\alpha]_D$ −159.0 (*c* 1.01, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.25−0.40 (m, 1H), 1.00−1.70 (m, 6H), 1.36 (t, J = 7.1 Hz, 3H), 1.37 (s, 9H), 1.91−2.02 (m, 1H), 2.24−2.38 (m, 2H), 2.64 (s, 3H), 3.71−3.79 (m, 1H), 4.19−4.35 (m, 2H), 4.59 (dd, J = 4.3, J = 9.5 Hz, 1H), 5.45 (d, J = 9.6 Hz, 1H), 6.50 (s, 1H), 7.51−7.62 (m, 3H), 7.92−7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.22 (d), 24.22 (d), 25.04 (u), 26.93 (u), 29.11 (d), 30.21 (u), 31.97 (u), 35.38 (u), 42.85 (d), 60.42 (u), 61.19 (d), 61.89 (u), 128.80 (d), 128.94 (d), 131.03 (d), 132.34 (d), 140.12 (u), 161.18 (u), 170.82 (u); IR (KBr) ν 3125 (w), 3062 (m), 2978 (m), 2923 (s), 2872 (m), 2799 (w), 1738 (s), 1610 (w), 1470 (m), 1447 (m), 1396 (w), 1369 (w), 1342 (m), 1313 (s), 1235 (s), 1207 (s), 1153 (s), 1130 (s), 1114 (s), 1098 (s), 1080 (m), 1016 (m) cm^{-1}; MS (EI) *m*/*z* 484 (M^+, 3), 363 (12), 209 (17), 208 (100), 180 (19), 156 (12), 136 (24), 125 (15); Anal. Calcd for $C_{23}H_{36}N_2O_5S_2$: C, 57.00; H, 7.49; N, 5.78. Found: C, 56.81, H, 7.61, N, 5.65.

E-**4b**. mp 141 °C; $[\alpha]_D$ −115.3 (*c* 1.29, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J = 7.2 Hz, 3H), 1.16−1.31 (m, 11H), 1.46−1.70 (m, 2H), 1.72−2.08 (m, 5H), 2.61−2.73 (m, 4H), 3.18−3.26 (m, 1H), 3.66−3.78 (m, 1H), 3.85−3.98 (m, 2H), 4.79 (d, J = 10.4 Hz, 1H), 6.28 (s, 1H), 7.50−7.62 (m, 3H), 7.87−7.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.00 (d), 24.00 (d), 25.26 (u), 27.92 (u), 28.39 (u), 29.17 (d), 30.07 (u), 30.17 (u), 52.00 (d), 59.98 (u), 61.38 (u), 61.80 (d), 128.62 (d), 129.07 (d), 132.30 (u), 159.89 (u), 170.33 (u); IR (KBr) ν 3490 (w),3055 (m), 2990 (m), 2953 (m), 2930 (s), 2901 (m), 2857 (m), 2799 (w), 1755 (s), 1620 (m), 1582 (w), 1447 (s), 1384 (w), 1367 (m), 1321 (s), 1243 (s), 1217 (m), 1189 (m), 1153 (s), 1124 (s), 1109 (s), 1085 (m), 1023 (m) cm^{-1}; MS (EI) *m*/*z* 485 ($[M+1]^+$, 37), 411 (11), 333 (15), 332 (40), 285 (34), 284 (100), 262 (14), 232 (11), 231 (59), 215 (21), 214 (79), 213 (21), 210 (18), 209 (15), 208 (77), 184 (50), 183 (100), 182 (21), 181 (47), 180 (12), 156 (23), 141 (18), 136 (36), 135 (13), 134 (39), 125 (62), 117 (11), 109 (15), 107 (24), 106 (14), 105 (11), 102 (47), 93 (11), 91 (20), 80 (14); Anal. Calcd for $C_{23}H_{36}N_2O_5S_2$: C, 57.00; H, 7.49; N, 5.78. Found: C, 56.79; H, 7.76; N, 5.66.

(−)-(*Z*,*S*$_S$,2*S*,3*R*)- and (−)-(*E*,*S*$_S$,2*S*,3*R*)-(2-(*N*-Methyl-*S*-phenylsulfonimidoyl-methylene)-cyclooctyl)-(2-methylpropane-2-sulfonylamino)-Acetic Acid Ethyl Ester (*Z*-4c and *E*-4c). Following *GP1*, the reaction of sulfoximine **9c** (1.278 g, 4.6 mmol) with the imino ester **5** (1.120 g, 5.1 mmol) gave a mixture of the crude alkenyl sulfoximines *Z*-**4c** and *E*-**4c** in a ratio of 11−13:1 in approximately 95% chemical yield (^{1}H NMR). Recrystallization from CH_2Cl_2/*n*-pentane afforded *Z*-**4c** (1.797 g, 78%) of ≥ 98% de as colorless crystals. Preparative HPLC (EtOAc/*n*-hexane, 4:1) of the mother liquor provided *E*-**4c** (163 mg, 7%) of ≥ 98% de as a colorless oil.

Z-**4c**. mp 157 °C; $[\alpha]_D$ −121.0 (*c* 0.85, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.45−0.60 (m, 2H), 1.14−1.47 (m, 4H), 1.02−1.13, (m, 1H), 1.38 (s, 9H), 1.38 (t, J = 7.1 Hz, 3H), 1.49−1.59 (m, 1H), 1.72−1.87 (m, 1H), 1.87−1.98 (m, 1H), 2.23−2.35 (m, 1H), 2.36−2.46 (m, 1H), 2.63 (s, 3H), 3.54−3.63 (m, 1H), 4.21−4.31 (dq, J = 7.1, J = 10.7 Hz, 1H), 4.31−4.42 (dq, J = 7.2, J = 11.0 Hz, 1H), 4.48 (dd, J = 4.7, J = 9.6 Hz, 1H), 5.25 (d, J = 9.6 Hz, 1H), 6.43 (s, 1H), 7.50−7.62 (m, 3H), 7.90−7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.60 (d), 23.64 (u), 24.54 (d), 24.82 (u), 27.68 (u), 25.23 (u), 29.39 (d), 33.36 (u), 34.06 (u), 43.39 (d), 60.84 (u), 62.27 (u), 62.58 (d), 129.32 (d), 129.49 (d), 130.05 (d), 132.74 (d), 140.20 (u), 162.79 (u), 171.24 (u); IR (KBr) ν 3676 (w), 3655 (w), 3593 (w), 3447 (w), 3306 (w), 3062 (w), 2928 (s), 2869 (s), 2800 (m), 1735 (s), 1604 (m), 1448 (s), 1385 (m), 1369 (m), 1317 (s), 1228 (s), 1129 (s), 1080 (s), 1025 (m) cm^{-1}; MS (EI) *m*/*z* 498 (M^+, 2), 377 (11), 223 (24), 222 (100), 194 (17), 156 (21), 150 (24), 125 (22), 102 (10); Anal. Calcd for $C_{24}H_{38}N_2O_5S_2$: C, 57.80; H, 7.68; N, 5.62. Found: C, 57.82; H, 7.99; N, 5.36.

E-**4c**. $[\alpha]_D$ −70.3 (*c* 0.19, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74−0.89 (m, 2H), 0.92−1.05 (m, 1H), 1.08−1.57 (m, 3H), 1.14 (t, J = 7.1 Hz, 3H), 1.22 (s, 9H), 1.57−1.71 (m, 2H), 1.74−1.91 (m, 2H), 2.17−2.28 (m, 1H), 2.34−2.44 (m, 1H), 2.59−2.70 (m, 1H), 2.60 (s, 3H), 3.77−3.93 (m, 3H), 4.33 (d, J = 10.4 Hz, 1H), 6.24 (m, 1H), 7.44−7.54 (m, 3H), 7.82−7.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.42 (d), 24.47 (d), 25.59 (u), 26.36 (u), 26.46 (u), 28.24 (u), 29.01 (u), 29.19 (u), 29.60 (d), 52.07 (d), 60.49 (u), 62.00 (u), 62.25 (d), 129.14 (d), 129.50 (d), 129.22 (d), 132.73 (d), 140.44 (u), 160.62 (u), 170.94 (u); IR (KBr) ν 3274 (m), 3061 (m), 2932 (s), 2871 (s), 2802 (w), 1738 (s), 1604 (w), 1446 (s), 1396 (w), 1372 (m), 1313 (s), 1242 (s), 1182 (s), 1131 (s), 1080 (s), 1046 (m), 1024 (m) cm^{-1}; MS (EI) *m*/*z* 498 (M^+, 9), 425 (11), 362 (15), 299 (13), 298 (51), 250 (10), 249 (45), 228 (19), 222 (34), 201 (14), 198 (19), 197 (91), 195 (13), 170 (15), 169 (43), 155 (34), 148 (12), 141 (10), 125 (54), 109 (16), 107 (10), 102 (11); Anal. Calcd for $C_{24}H_{38}N_2O_5S_2$: C, 57.80; H, 7.68; N, 5.62. Found: C, 57.86; H, 7.46; N, 5.40.

(*R*$_S$)-*N*,*N*-Dimethylamino-*S*-((*E*,2*R*,3*S*)-2-(ethoxycarbonyl-(2-methylpropane-2-sulfonyl-amino)-methyl)-cyclohexylidenemethyl)-phenylsulfoxonium-tetrafluoroborate (*ent*-*E*-11a). Following *GP2*, the reaction of sulfoximine *ent*-*E*-**4d** (311 mg, 0.66 mmol) with Me_3OBF_4 (108 mg, 0.73 mmol) afforded a mixture (384 mg) of salt *ent*-*E*-**11a** and sulfoximine *ent*-*E*-**4d** in a ratio of 94:6 (^{1}H NMR) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, J = 7.1 Hz, 3H), 1.34 (s, 9H), 1.53−1.91 (m, 4H), 1.96−2.08 (m, 1H), 2.28−2.45 (m, 2H), 2.95−3.04 (m, 1H), 3.11 (s, 6H), 3.34−3.43 (m, 1H), 3.59 (dq, J = 7.1 Hz, J = 10.7 Hz, 1H), 3.73 (dq, J = 7.2, J = 10.7 Hz, 1H), 4.30 (t br, J = 10.4 Hz, 1H), 5.12 (d br, J = 10.17 Hz, 1H), 6.96 (s br, 1H), 7.79−7.87 (m, 2H), 7.92−7.98 (m, 1H), 8.11−8.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.15 (d), 20.56 (u), 24.39 (d), 27.26 (u), 28.52 (u), 29.41 (u), 37.87 (d), 49.89 (d), 57.74 (d), 60.54 (u), 61.96 (u), 114.00 (d), 129.13 (d), 130.75 (u), 131.45 (d), 137.32 (d), 170.10 (u), 176.67 (u).

(*R*$_S$)-*N*,*N*-Dimethylamino-*S*-((*Z*,2*R*,3*S*)-2-(ethoxycarbonyl-(2-methylpropane-2-sulfonyl-amino)-methyl)-cyclohexylidenemethyl)-phenylsulfoxonium-tetrafluoroborate (*ent*-*Z*-11a). Following *GP2*, the reaction of sulfoximine *ent*-*Z*-**4d** (380 mg, 0.81 mmol) with Me_3OBF_4 (133 mg, 0.89 mmol) afforded a mixture (468 mg) of salt *ent*-*Z*-**11a** and sulfoximine *ent*-*Z*-**4d** in a ratio of 93:7 (^{1}H NMR) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85−0.98 (m, 1H), 1.29−1.48 (m,

2H), 1.36 (t, J = 7.1 Hz, 3 H), 1.41 (s, 9H), 1.67−1.85 (m, 1 H), 1.94−2.05 (m, 1H), 2.11−2.22 (m, 1H), 2.60−2.78 (m, 2H), 3.08 (s, 6H), 3.49−3.57 (m, 1H), 4.20−4.32 (m, 2H), 4.40 (t, J = 10.4 Hz, 1H), 5.36 (d, J = 10.2 Hz, 1H), 7.22 (s, 1H), 7.80−7.88 (m, 2H), 7.90−7.96 (m, 1H), 8.18−8.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.05 (d), 19.27 (u), 24.04 (d), 28.62 (u), 29.03 (u), 35.05 (u), 37.42 (d), 41.60 (d), 57.10 (d), 60.30 (u), 62.12 (u), 115.02 (d), 128.74 (d), 130.76 (u), 131.26 (d), 136.84 (d), 169.76 (u), 176.83 (u).

(S_S)-*N*,*N*-Dimethylamino-*S*-((*Z*,1*R*,2*S*)-2-(ethoxycarbonyl-(2-methyl-propane-2-sulfonyl-amino)-methyl)-cyclooctylidenemethyl)-phenyl-sulfoxonium-tetrafluoroborate (*Z*-11b). Following *GP2*, the reaction of sulfoximine *Z*-**4c** (530 mg, 1.06 mmol) with Me_3OBF_4 (173 mg, 1.17 mmol) afforded a mixture (645 mg) of salt *Z*-**11b** and sulfoximine *Z*-**4c** in a ratio of 96:4 (^{1}H NMR) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72−0.86 (m, 1H), 0.98−1.13 (m, 1H), 1.13−1.26 (m, 1H), 1.27−1.58 (m, 5H), 1.39 (m, 12H), 1.85−2.10 (m, 2H), 2.46−2.58 (m, 1H), 2.78−2.88 (m, 1H), 3.16 (s, 6H), 3.55−3.65 (m, 1H), 4.26−4.41 (m, 3H), 5.06 (d, J = 10.2 Hz, 1H), 7.19 (s, 1H), 7.82−7.89 (m, 2H), 7.91−7.99 (m, 1H), 8.23−8.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.17 (d), 22.97 (u), 24.09 (u), 24.58 (u), 27.62 (u), 33.61 (u), 35.05 (u), 24.09 (d), 37.39 (d), 44.58 (d), 60.70 (u), 62.51 (u), 62.61 (d), 117.15 (d), 128.78 (d), 131.26 (d), 130.16 (u), 136.85 (d), 169.64 (u), 181.99 (u).

(−)-(1*R*,9*S*)-2-(2-Methyl-propane-2-sulfonyl)-2,3,5,6,7,7a-hexahydro-1*H*-isoindole-1-carboxylic Acid Ethyl Ester (*ent*-2a). From *ent*-*E*-**11a** and DBU: Following *GP3*, the reaction of sulfoximine *ent*-*E*-**11a** (384 mg, 0.66 mmol) with DBU (109 μL, 0.73 mmol) yielded the protected α-amino acid *ent*-**2a** (168 mg, 80%) as a slowly crystallizing white solid and sulfinamide *ent*-**12** (85 mg, 76%) as a colorless oil of ≥99% ee. From *ent*-*Z*-**11a** and DBU: Following *GP3*, the reaction of sulfoximine *ent*-*Z*-**11a** (468 mg, 0.81 mmol) with DBU (134 μL, 0.89 mmol) provided *ent*-**2a** (195 mg, 76%). From *ent*-*E*-**11a** and LiN(H)-*t*-Bu: To a solution of freshly distilled *t*$BuNH_2$ (from CaH_2) (52 μL, 0.48 mmol) in THF (5 mL) was added at −78 °C *n*-BuLi (300 μL, 0.48 mmol of a 1.6 M in *n*-hexane) dropwise. Then the solution was allowed to warm to room temperature and stirring was continued for 10 min. The solution of LiN(H)*t*-Bu was added dropwise at −78 °C to a solution of *ent*-*E*-**11a** (253 mg, 0.44 mmol) in THF (20 mL). After the mixture had been stirred at −78 °C for 1 h, it was warmed to room temperature and stirring was continued for 10 h. Then saturated aqueous NH_4Cl (30 mL) was added and the mixture was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (Et_2O/*n*-hexane, 1:1) afforded *ent*-**2a** (107 mg, 77%). *ent*-**2a**. mp 64 °C; $[\alpha]_{365}$ −21.5 (*c* 1.11, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85−0.97 (dq, J = 13.3, J = 2.7 Hz, 1H, 7-H_{ax}), 1.27 (t, J = 7.1 Hz, 3H, Et), 1.38 (s, 9H, *t*-Bu), 1.42−1.55 (m, 1H, 6-H_{ax}), 1.81−1.91 (m, 1H, 6-H_{eq}), 1.94−2.14 (m, 3H, 5-H, 7-H_{eq}), 2.91 (s br, 1H, 7a−H), 4.10−4.24 (m, 3H, Et, 3-H), 4.26−4.37 (d br, J = 12.6 Hz, 1H, 3-H), 4.58 (d br, J = 8.5 Hz, 1H, 1-H), 5.62 (s br, 1H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.26 (d), 21.55 (u), 24.03 (u), 24.22 (d), 24.45 (u), 43.14 (d), 52.99 (u), 60.70 (u), 61.30 (u), 65.55 (d), 119.69 (d), 135.89 (u), 170.99 (u); IR ($CHCl_3$) ν 2981 (m), 2938 (s), 2876 (m), 1742 (s), 1480 (m), 1457 (m), 1395 (w), 1376 (w), 1321 (s), 1231 (w), 1193 (s), 1130 (s), 1054 (s), 1023 (m) cm^{-1}; MS (CI, isobutane) *m*/*z* 316 ([M+H]$^+$, 100), 196 (34); Anal. Calcd for $C_{15}H_{25}NO_4S$: C, 57.12; H, 7.99; N, 4.44. Found: C, 57.00; H, 8.11; N, 4.40.

(−)-(1*S*,11*R*)-2-(2-Methyl-propane-2-sulfonyl)-2,3,5,6,7,8,9,9a-octahydro-1*H*-cyclo-octa[*c*]pyrrole-1-carboxylic Acid Ethyl Ester (2b). Following *GP3*, the reaction of sulfoximine *Z*-**11b** (645 mg, 1.06 mmol) with DBU (175 μL, 1.17 mmol) yielded the protected α-amino acid **2b** (297 mg, 81%) as a slowly crystallizing white solid and sulfinamide **12** (134 mg, 74%) as a colorless oil. mp 67 °C; $[\alpha]_{365}$ −60.3 (*c* 0.39, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3H, Et), 1.39 (s, 9H, *t*-Bu), 1.40−1.51 (m, 4H), 1.53−1.75 (m, 4H), 2.06−2.26 (m, 2H, 5-H), 3.26 (m br, 1H, 9a−H), 4.11 (d br, J = 12.9 Hz, 1H, 3-H), 4.14−4.24 (m, 3H, Et, 3-H), 4.70 (d br, J = 8.5 Hz, 1H, 1-H), 5.50−5.58 (m, 1H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.22 (d), 24.32 (d), 24.92 (u), 25.10 (u), 28.23 (u), 29.47 (u), 25.64 (u), 43.13 (d), 54.46 (u), 60.75 (u), 61.27 (u), 65.53 (d), 120.84 (d), 139.03 (u), 170.80 (u); IR (capillary) ν 2979 (s), 2928 (s), 2858 (s), 1743 (s), 1458 (s), 1394 (m), 1373 (m), 1320 (s), 1189 (s), 1153 (s), 1127 (s), 1051 (s) cm^{-1}; MS (CI, isobutane) *m*/*z* 344 ([M+H]$^+$, 83), 224 (100); Anal. Calcd for $C_{17}H_{29}NO_4S$: C, 59.44; H, 8.51; N, 4.08. Found: C, 59.47; H, 8.33; N, 3.93.

(−)-(1*R*,9*S*)-2,3,5,6,7,7a-Hexahydro-1*H*-isoindole-1-carboxylic Acid Ethyl Ester (*ent*-1). To a solution of *ent*-**2a** (196 mg, 0.62 mmol) in CH_2Cl_2 (27 mL) was added CF_3SO_3H (20.5 mL of 0.1 M in CH_2Cl_2) at −30 °C. After the mixture had been stirred for 45 min at −30 °C, saturated aqueous $NaHCO_3$ (60 mL) was added. The mixture was extracted with CH_2Cl_2 (100 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification of the remaining brown oil by flash chromatography (EtOH/*n*-hexane, 2:1) gave the α-amino acid ester *ent*-**1** (101 mg, 83%) as a light yellow oil. $[\alpha]_{436}$ −49.6 (*c* 0.38, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (dq, J = 13.4, J = 2.7 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.42−1.56 (m, 1H), 1.78−1.91 (m, 1H), 1.91−2.13 (m, 3H), 2.49 (s br, 1H), 2.79 (s br, 1H), 3.56 (d br, J = 13.7 Hz, 1H), 3.75 (d br, J = 13.7 Hz, 1H), 3.96 (d, J = 8.8 Hz, 1H), 4.08−4.24 (m, 2H), 5.53 (s br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.34 (d), 22.13 (u), 24.62 (u), 24.72 (u), 42.48 (d), 50.02 (u), 60.36 (u), 63.22 (d), 117.67 (d), 139.39 (u), 174.04 (u); IR (capillary) ν 3363 (w), 2933 (s), 2859 (s), 1733 (s), 1447 (m), 1370 (w), 1336 (w), 1185 (s), 1102 (m), 1024 (w), 819 (w), 794 (w) cm^{-1}; MS (EI) *m*/*z* 195 (M$^+$, 10), 123 (10), 122 (100), 94 (30); HRMS calcd for $C_{11}H_{17}NO_2$ 195.125929, found 195.125959.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of *ent*-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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