Enantioselective Organocatalytic Thiol Addition to α,β-Unsaturated α-Amino Acid Derivatives

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Abstract: A new class of Michael acceptors based on α,β-unsaturated amino acids has been prepared and applied in asymmetric organocatalysis. With the use of thiourea derivatives of cinchona alkaloid-derived catalysts, efficient addition of thiols to the dehydroamino acids occurred with formation of β-thiol functionalized α-amino acids in high yields, moderate diastereoselectivities and ee values up to 95%.

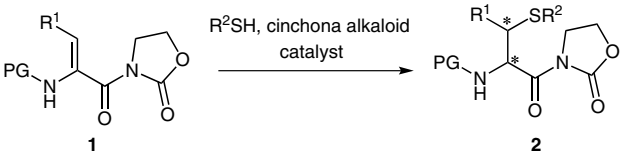
Key words: organocatalysis, cinchona alkaloids, amino acids, thiols, conjugate addition

Bifunctional organocatalysis is a widely applied method for the preparation of enantiomerically enriched organic compounds.[1] Succeeding the pioneering work by the Wynberg[2] group on the cinchona alkaloids as bifunctional catalysts, numerous studies have been reported concerning the design of new and efficient organocatalysts for enantioselective organic reactions.[3] Particular attention has been paid to the conjugate addition[4] of various carbon- and heteroatom-based nucleophiles to different classes of electron-poor alkenes, such as nitroalkenes, conjugated enones, α,β-unsaturated esters and derivatives with an oxazolidinone moiety,[5] 2-pyrrolidinone,[6] pyrrole,[7] or a benzamide[8] function.

Thiols are known to be well suited as nucleophiles for enantioselective organocatalytic conjugate additions usually referred to as sulfa-Michael additions.[9,10] In most of the reported studies of organocatalytic sulfa-Michael reactions aromatic thiols were employed as nucleophiles.[9a] In a recent study Deng and co-workers[5] described the enantioselective formation of β-thiol esters by addition of aliphatic thiols to α,β-unsaturated N-acylated oxazolidin-2-ones catalyzed by a C6′-thiourea-substituted cinchona alkaloid derivative. More recently, Connon and co-workers reported that a C5′ urea substituted cinchona alkaloid derivative efficiently catalyzes the sulfa-Michael reaction between aliphatic thiols and nitro alkenes with the formation of the products in excellent enantioselectivity.[9a] Lately, Wang and co-workers[9b] reported an enantioselective synthesis of *cis*-β-thio-α-amino acids by a 1,4-addition/ring-opening cascade reaction with aromatic thiols as nucleophiles and catalyzed by the chiral thiourea-tertiary amine catalyst developed by Takemoto.[6,8]

Inspired by the work of Deng and co-workers on asymmetric synthesis of β-thiol esters,[5] we envisioned that thiol addition to N-acylated oxazolidin-2-one derivatives of α,β-unsaturated amino acids could serve as a general method for the preparation of β-thiol amino acids.

Even though β-thiol functionalized amino acids are of significant interest in peptidomimetics, limited attention has been given to asymmetric synthesis of these compounds. The reported methods include conjugate addition of thiols to α,β-unsaturated amino acids leading to racemates[11] and mesylation of the hydroxyl group of threonine or analogues followed by nucleophilic substitution by a thiol.[12] The latter method leads to formation of enantiomerically pure unnatural amino acids but is limited to species with a hydroxyl group at the β-position. In order to extend the possibilities for asymmetric synthesis of β-thiol functionalized amino acids, we decided to prepare a novel series of α,β-unsaturated N-acetylated oxazolidin-2-ones bearing a protected amine group at the α-position. With the use of cinchona alkaloid derivatives as catalysts, we anticipated that thiol addition to α,β-unsaturated N-acetylated oxazolidin-2-ones (see Scheme 1) could provide enantiomerically enriched compounds that could be easily converted into β-thiol amino acids.



Scheme 1 Thiol addition to dehydroamino acid derivatives; PG = protective group

Initially, we prepared **1** with an acetyl group at the enamine nitrogen atom by the Erlenmeyer–Plöchl azlactone synthesis[13] followed by ring opening with oxazolidinone. Subsequently, this substrate was reacted with thiophenol in the presence of a C6′ thiourea cinchona alkaloid derivative described previously.[14] However, no product of thiol addition could be observed, indicating a low reactivity of

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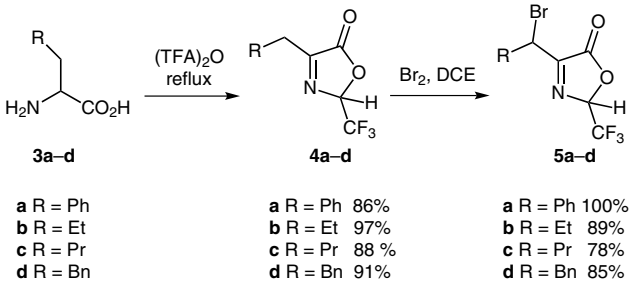
the β-carbon atom in the substrate, possibly as a result of the pronounced enamine character at this position. In order to increase the susceptibility of the β-carbon atom for nucleophilic attack, we decided to introduce a trifluoroacetyl group as the protective group at the enamine nitrogen atom in **1**.

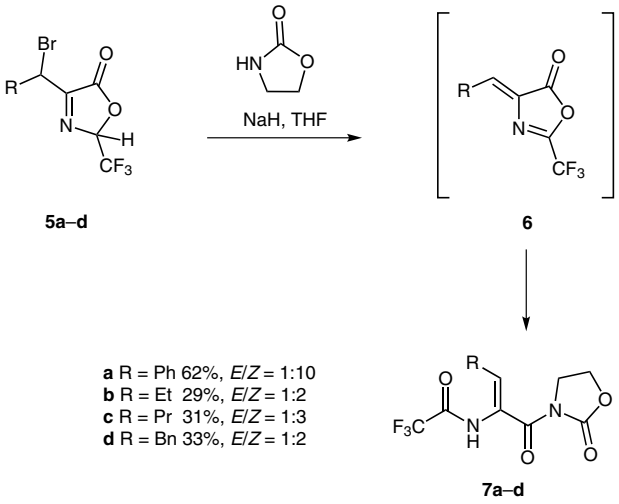
The Erlenmeyer–Plöchl azlactone synthesis of azlactones with trifluoroacetic acid anhydride (TFAA) is known, however, to lead to unstable products.[15] Our attempts to prepare the trifluoromethyl-substituted azlactones by this strategy also failed to give isolable products as required for the reaction with oxazolidinone under basic conditions. We decided, therefore, to prepare the desired α,β-unsaturated N-trifluoacetylated oxazolidin-2-ones by treatment of amino acids **3a**–**d** with TFAA thus leading to the stable pseudoazlactones **4a**–**d** in high yields (Scheme 2).[16,17] Bromination in 1,2-dichloroethane (DCE) resulted in the formation of **5a**–**d** in good to excellent yields. In agreement with the literature, small amounts of dibrominated compounds were formed in the reaction of pseudoazlactones derived from norleucine and norvaline.[18]



Scheme 2 Synthesis of brominated pseudoazlactones **5a**–**d**

Treatment of brominated pseudoazlactones **5a**–**d** with two equivalents of aniline were reported previously to result in elimination of HBr with formation of azlactones in situ prior to ring opening to afford dehydroamino acid anilides.[17] Thus, we decided to treat **5a**–**d** with 2.2 equivalents of the sodium salt of oxazolidinone in THF. This resulted in the formation of dehydroamino acids **7a**–**d** in poor to reasonable yields and with a preference for the *Z*-isomer (Scheme 3).[19] The *E*-and *Z*-isomers were subsequently separated by recrystallization from a mixture of petroleum ether and ethyl acetate or by column chromatography.

Subsequently, optimal conditions for asymmetric thiol addition were established by reacting the pure *Z*-isomer of substrate **7a** with thiophenol in a series of solvents and in the presence of one of the three thiourea derivatives of quinidine shown in Table 1.[5,14,20] The reaction proceeded efficiently to give full conversion after 12 hours in CH_2Cl_2 and in the presence of 10 mol% of the C6′ thiourea derivative **A** (Table 1, entry 1). The product of the 1,4-addition of thiophenol was formed with moderate diastereoselectivity and with good enantioselectivity for the major diastereoisomer (79%). The higher reactivity of **7a** compared to the related N-acetyl protected species (see above) is in



Scheme 3 Preparation of the dehydroamino acid derivatives with trifluoroacetyl-substituted azlactones formed in situ

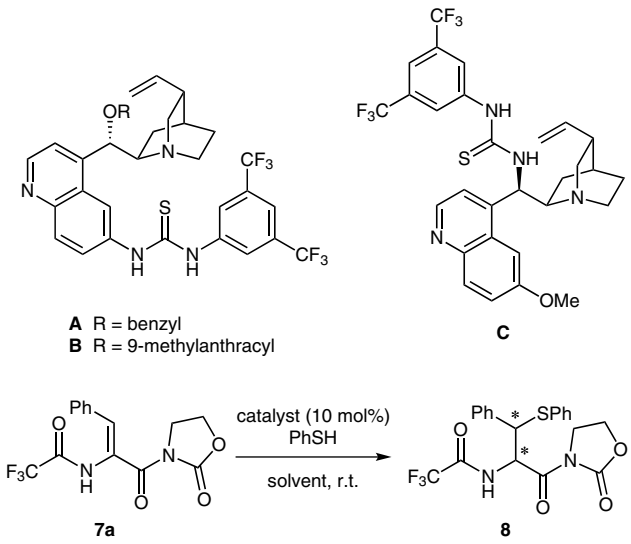
keeping with a decrease in electron density at the β-position upon introduction of a trifluoroacetyl group at the enamine nitrogen atom as revealed also by the fact that the ^{13}C NMR chemical shift of this carbon atom is 132.19 ppm for **7a** but only 112.47 ppm if an acetyl group is present.

With $CHCl_3$ as the solvent, full conversion was also observed after 12 hours. The diastereoselectivity was almost the same as in CH_2Cl_2 but the enantioselectivity was low for both diastereoisomers (entry 2). A reasonable enantioselectivity was observed in THF, even though the conversion was not more than 70% (entry 3). A further increase in enantioselectivity was seen in toluene, but again the conversion was low after 12 hours (entry 4). Addition of 2.0 equivalents of thiophenol instead of 1.2 equivalents gave full conversion after 12 hours. However, a significant decrease in the enantioselectivity was observed.

Replacing the benzyl group in catalyst **A** with a 9-methyl anthracyl moiety led to the formation of the sterically more congested catalyst **B** (Table 1).[5] With this catalyst and CH_2Cl_2 as the solvent the major diastereomer was obtained with an ee of 90% and the minor diastereomer in 75% ee (entry 6). The enantioselectivity was moderate for both diastereoisomers in $CHCl_3$ (entry 7) and high in toluene, even though the conversion was only 60% after 12 hours with 1.2 equivalents of thiophenol (entry 8). As observed with catalyst **A**, addition of 2.0 equivalents of thiophenol resulted in full conversion after 12 hours with formation of the diastereoisomers in poor enantioselectivity (entry 9). The diastereoisomeric ratio was changed by the use of catalyst **C** (entries 10–12). However, full conversion was not observed and the enantioselectivity was low for both diastereomers with this catalyst. In conclusion, the best results were obtained in CH_2Cl_2 with **B** as the catalyst (entry 6).[21]

Having identified the optimal conditions, the catalytic reactions between the substrates **7a**–**d** and a series of thiols were examined (Table 2). With ethanethiol, 2-propene-1-thiol, α-toluenethiol and substituted analogues thereof,

Table 1 Optimization of the Conjugate Addition of Thiols[a]



Entry	Cat.	Solvent	PhSH (equiv)	Conv. (%)[b]	dr	ee (%)[c]
1	**A**	CH_2Cl_2	1.2	100	75:25	79/57
2	**A**	$CHCl_3$	1.2	100	80:20	47/36
3[d]	**A**	THF	1.2	70	75:25	60/45
4[d]	**A**	toluene	1.2	50	75:25	85/63
5	**A**	toluene	2.0	100	75:25	2/46
6	**B**	CH_2Cl_2	1.2	100	75:25	90/75
7	**B**	$CHCl_3$	1.2	100	75:25	80/60
8[d]	**B**	toluene	1.2	60	67:33	90/74
9	**B**	toluene	2.0	100	75:25	42/57
10[d]	**C**	CH_2Cl_2	1.2	75	83:17	28/45
11[d]	**C**	$CHCl_3$	1.2	75	85:15	28/–18
12[d]	**C**	toluene	1.2	57	91:9	57/30

[a] Standard reaction conditions: 0.2 M substrate, room temperature, reaction time 12 h.
[b] Conversion as determined by ^{1}H NMR spectroscopic analysis.
[c] The ee was determined by chiral HPLC (AD column) analysis.
[d] No improvement of the conversion was observed with a reaction time of 24 h.

3.0 equivalents were added. This resulted in a decrease in the reaction time without a dramatic change in the enantioselectivity (Table 2).

The reaction of the *Z*-isomer of the phenyl-substituted substrate **7a** with ethanethiol was slow and gave the diastereoisomers in almost equal amounts (entry 1). High enantioselectivity was observed for the major diastereoisomer while only a moderate ee was obtained for the minor isomer. A lower enantioselectivity was seen with allylthiol as the nucleophile (entry 2); that is, the ee of the major diastereoisomer was 86% but only 25% for the minor isomer. Benzylthiol reacted with **7a** within four hours with a slight preference for one diastereoisomer (entry 3). The major diastereomer was formed with high enantioselectivity (94% ee), while the ee for the minor isomer (47%) was significantly lower also compared with the results for thiophenol as the nucleophile (Table 1, entry 6). The diastereoselectivity was 2:1 with 4-methoxybenzylthiol and an excellent enantioselectivity was obtained for the major isomer (entry 4).[21,22]

The reaction of the *Z*-isomer of the ethyl-substituted substrate **7b** with thiophenol gave the products in good diastereoselectivity, and the enantioselectivity was also relatively high for the major isomer (entry 6). With the less reactive thiols, 2-propene-1-thiol, α-toluenethiol, and 4-methoxy-α-toluenethiol, an inversion with respect to the diastereoselectivity was observed (entries 5, 7 and 8). In these reactions, the highest ee values were observed for the minor diastereoisomer with only a slight change in enantioselectivity as compared with the phenyl-substituted substrate **7a**. In the reactions of the *Z*-isomer of the *n*-propyl-substituted substrate **7c** (entries 9 and 10) the ee values did not exceed 80%, indicating that 1,4-addition is sterically influenced by the size of the alkyl group at the β-position. With the pure *E*-form of **7c**, we obtained low ee values for both diastereoisomers (57% for the major diastereomer and 24% for the minor species), and the ee of the major isomer was only slightly higher (63%; entries 9b and 9c) with the *E*/*Z*-mixture.

With the *Z*-form of substrate **7d** (entry 11), a relatively low yield (75%) was obtained as a result of an isomerization of the double bond into conjugation with the phenyl group. For this substrate, the ee values were moderate to low for both diastereoisomers.

In order to determine the absolute configuration at the α- and β-carbon atoms in the major product of the 1,4-addition of 4-methoxybenzylthiol to **7a**, an X-ray crystal structure analysis[23] was performed of the major isomer obtained by crystallization of **12** from hexane–EtOAc (Figure 1). The *R*-configuration was assigned to the β-carbon and the *S*-configuration to the α-carbon of the amino acid derivative. Thus, the addition of thiophenol to the

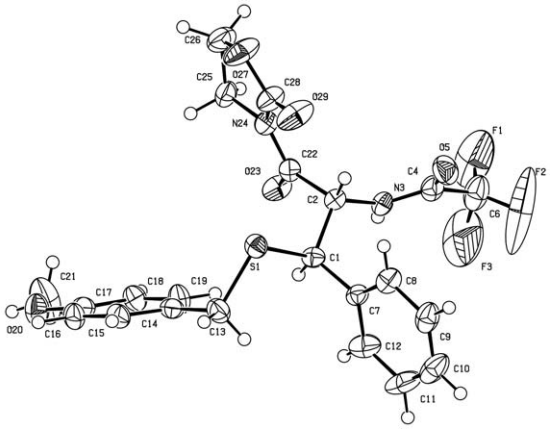
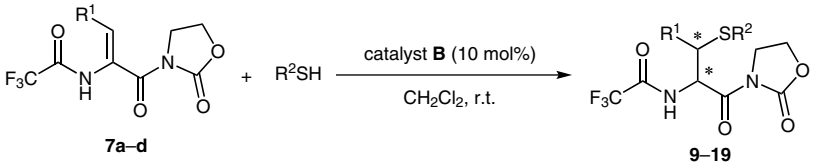


Figure 1 X-ray crystal structure of the major enantiomer of **12**

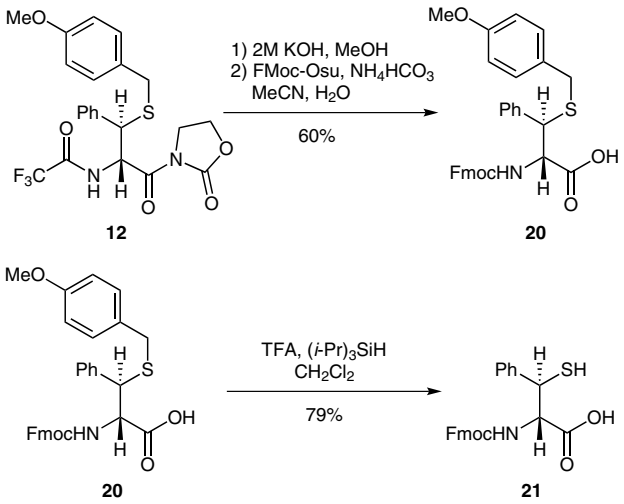
Table 2 Scope of the Thiol Addition to Dehydroamino Acid Derivatives[a]



Entry	7[b]	R^1	R^2	Equiv of thiol	Time (h)	Product	Yield (%)[c]	dr	ee (%)[d]
1	**7a**	Ph	Et	3.0	16	**9**	96	55:45	94/52
2	**7a**	Ph	allyl	3.0	8	**10**	97	52:48	86/25
3	**7a**	Ph	Bn	3.0	4	**11**	93	52:48	94/47
4	**7a**	Ph	4-$MeOC_6H_4CH_2$	3.0	6	**12**	99	67:33	95/46
5	**7b**	Et	allyl	3.0	16	**13**	94	42:58	80/57
6	**7b**	Et	Ph	1.2	8	**14**	92	83:17	87/51
7	**7b**	Et	Bn	3.0	16	**15**	95	48:52	90/71
8	**7b**	Et	4-$MeOC_6H_4CH_2$	3.0	16	**16**	91	48:52	80/58
9a	(*Z*)-**7c**	*n*-Pr	Ph	1.2	16	**17**	91	80:20	80/65
9b	(*E*)-**7c**	*n*-Pr	Ph	1.2	16	**17**	92	70:30	57/24
9c	(*E*,*Z*)-**7c**[e]	*n*-Pr	Ph	1.2	16	**17**	93	67:33	63/28
10	**7c**	*n*-Pr	Bn	3.0	16	**18**	95	45:55	72/44
11	**7d**	Bn	Ph	1.2	8	**19**	75	71:29	77/58

[a] Standard conditions: 0.2 M substrate, r.t.
[b] Experiments were performed with the Z-isomer of the substrates unless otherwise stated.
[c] The combined yield of both diastereoisomers.
[d] The ee values were determined by chiral HPLC analysis (AD or ADH column).
[e] The composition of the mixture was 30% *E*- and 70% *Z*-isomer.

phenyl-substituted substrate **7a** catalyzed by **B** leads mainly to the *anti*-diastereoisomer of the product.



Scheme 4 Formation of enantiopure β-phenyl-substituted cysteine protected with a Fmoc group at the amine moiety [FMoc-OSu: *N*-(9-fluorenylmethoxycarbonyloxy)succinimide]

To examine the applicability of the products for solid-phase Fmoc-chemistry, a one-pot procedure was developed to remove the trifluoroacetyl and the oxazolidinone groups, followed by protection of the primary amine function with an Fmoc-group (Scheme 4). This resulted in 60% yield of the corresponding Fmoc-protected amino acid **20**.[24] Furthermore, the 4-methoxybenzyl group could be easily removed with TFA and triisopropylsilane in CH_2Cl_2. This resulted in formation of the Fmoc-protected phenyl-substituted cysteine **21** in 79% yield.[25]

In conclusion, we have prepared a new class of substrates for asymmetric organocatalyzed sulfa-Michael additions. With the new substrates we were able to perform a cinchona alkaloid-catalyzed sulfa-Michael reaction with aromatic as well as aliphatic thiols with good yields, modest to excellent enantioselectivities, and low to moderate diastereoselectivities. The final products can be converted into β-thiol-substituted amino acids for application in the synthesis of peptidomimetics.

Acknowledgment

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(19) **Synthesis of 7:** Oxazolidinone (5.0 g, 57.4 mmol, 2.3 equiv) was dissolved in anhydrous THF (250 mL), and NaH (1.3 g, 55 mmol, 2.2 equiv) was added in portions. The resulting mixture was stirred for 30 min, then a solution of **5a** (8.0 g, 25 mmol, 1 equiv) in anhydrous THF (50 mL) was added dropwise and stirring was continued for 30 min. Saturated NH_4Cl was added and the resulting mixture was extracted three times with EtOAc. The organic layers were combined, washed with brine and dried with $MgSO_4$. The product was purified by column chromatography (PE–EtOAc, 2:1) yielding a 1:10 mixture of *E*/*Z*-isomers **7a** (5.3 g, 15.5 mmol, 62%). The *Z*-isomer was obtained by recrystallization (EtOAc–PE).
Compound (*Z*)-7: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64 (s, 1 H), 7.47–7.40 (m, 5 H), 6.94 (s, 1 H), 4.44 (t, *J* = 7.6 Hz, 2 H), 4.05 (t, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5, 155.5 (q, *J* = 38.0 Hz), 152.9, 132.2, 131.6, 128.8, 129.4, 129.0, 125.6, 115.4 (q, *J* = 286.0 Hz), 63.0, 42.9.
Compound (*E*)-7: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 7.49–7.42 (m, 5 H), 6.65 (s, 1 H), 4.43 (t, *J* = 8.0 Hz, 2 H), 4.07 (t, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 155.7 (q, *J* = 38.0 Hz), 151.9, 132.0, 130.1, 129.7, 129.5, 129.1, 125.9, 115.4 (q, *J* = 286.0, 62.5, 42.0 Hz); IR (neat): 3253, 1617, 1717, 1685, 1529, 1388, 1209, 1184, 1155 cm^{-1}; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd. for $C_{14}H_{12}F_3N_2O_4$: 329.0749; found: 329.0746.

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(21) In addition to the *cinchona* derivatives, we performed a series of experiments with the thiourea catalyst developed by Takamoto.[6,8] With this organocatalyst, the reaction between thiophenol and (*Z*)-**7a** yielded the products in a diastereomeric ratio of 95:5 in CH_2Cl_2 but both isomers were formed in an unsatisfactory ee (i.e., 70% ee for the major diastereomer and 36% for the minor isomer). With 4-methoxybenzylthiol as the nucleophile, the reaction with the (*Z*)-**7a** catalyzed by the Takamoto thiourea led to the formation of products in a diastereomer ratio of 63:37 and in poor enantioselectivity (25% ee for the major isomer and 24% for the minor isomer).

(22) **Synthesis of 12:** Compound **7a** (885 mg, 2.69 mmol) and catalyst **B** (207 mg, 0.27 mmol) were dissolved in CH_2Cl_2 (13 mL). 4-methoxybenzylthiol (1.12 mL, 8.07 mmol) was added and the resulting mixture was stirred overnight. The product was concentrated and purified by column chromatography (PE–EtOAc, 2:1), yielding a 33:67 mixture of *syn*/*anti*-isomers of a slowly solidifying oil (1.24 g, 2.58 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.41–7.32 (m, 3 H), 7.28–7.26 (m, 1 H), 7.16 (dd, *J* = 6.4, 2 Hz, 1.33 H), 7.10 (dd, *J* = 6.4, 2 Hz, 0.67 H), 7.00 (d, *J* = 9.6 Hz, 1 H), 6.87 (dd, *J* = 6.4, 2 Hz, 0.67 H), 6.84 (dd, *J* = 6.4, 2 Hz, 1.33 H), 6.33 (t, *J* = 7.6 Hz, 0.67 H), 6.02 (dd, *J* = 8.4, 5.2 Hz, 0.33 H), 4.46 (t, *J* = 8 Hz, 1.33 H), 4.36 (m, 0.33 H), 4.29 (d, *J* = 5.2 Hz, 0.33 H), 4.23 (d, *J* = 7.6 Hz, 0.67 H), 4.15 (m, 0.67 H), 4.06 (m, 0.67 H), 3.98–3.92 (m, 1.33 H), 3.83 (s, 1 H), 3.83 (s, 2 H), 3.73 (d, *J* = 12.8 Hz, 0.67 H), 3.65–3.60 (m, 0.67 H), 3.34 (d, *J* = 13.6 Hz, 0.33 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 168.2, 158.9, 158.8, 156.6 (q, *J* = 38 Hz), 156.5 (q, *J* = 38 Hz), 152.9, 152.5, 136.8, 136.3, 130.2, 130.1, 129.3, 129.1, 128.9, 128.7, 128.7, 128.6, 128.5, 128.4, 128.3, 121.6, 115.5 (q, *J* = 286 Hz), 113.9, 62.6, 62.4, 56.4, 55.3, 54.1, 50.7, 49.4, 42.6, 42.5, 35.4, 34.6; IR (neat): 3319, 1779, 1728, 1698, 1537, 1214, 1173, 702 cm^{-1}; HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{22}F_3N_2O_5S$: 483.1202; found: 483.1207; HPLC [Daicel Chiralcel AD; *i*-PrOH–heptane, 15:85 (0–40 min) then 30:70 (40–120 min); 1.0 mL/min; λ = 220nm]: t_R (major diastereoisomer) = 21.5 (minor), 110.8 (major) min; t_R (minor diastereoisomer) = 14.9 (minor), 21.5 (major) min. Recrystallization of the crude product (EtOAc–PE) gave the minor *syn*-isomer as a racemate (120 mg, 0.25 mmol, 9%). The mother liquor was concentrated and further recrystallized (EtOAc–PE) to give the *anti*-isomer as a pure enantiomer (503 mg, 1.04 mmol, 39%). Mp 142–144 °C; $[\alpha]_D$ –203.4 (*c* = 0.42, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 3 H), 7.28 (m, 2 H),

7.16 (d, J = 8.4 Hz, 1 H), 6.98 (d, J = 8.8 Hz, 1 H), 6.83 (d, J = 8.8 Hz, 1 H), 6.32 (t, J = 8.4 Hz, 1 H), 4.48 (t, J = 8.0 Hz, 2 H), 4.23 (d, J = 7.2 Hz, 1 H), 4.07–4.01 (m, 1 H), 3.99–3.94 (m, 1 H), 3.81 (s, 3 H), 3.74 (d, J = 8.8 Hz, 1 H), 3.63 (d, J = 8.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 158.8, 156.5 (q, J = 38 Hz), 152.8, 136.8, 136.3, 130.2, 129.3, 128.7, 128.6, 128.4, 115.5 (q, J = 286 Hz), 113.9, 62.4, 55.2, 54.1, 50.7, 42.5, 35.4.

(23) (a) **Crystal Structure Data for Compound 12:** M_w = 482.27; colorless platelet; 0.27 × 0.22 × 0.06 mm; orthorhombic; $P2_12_12_1$; a = 10.0062(7) Å, b = 11.8687(4) Å, c = 18.6029(12) Å; V = 2209.3(2) Å^3; Z = 4; D = 1.451 g·cm^{-3}; μ = 0.209 mm^{-1}. 66682 reflections were measured with a Nonius KappaCCD diffractometer (Mo radiation, graphite monochromator, λ = 0.71073 Å) up to a resolution of $\sin\theta/\lambda$ = 0.65 Å^{-1} at 208 K. 5067 reflections were unique (R_{int} = 0.0423) of which 4371 were observed with $I_o \geq 2\sigma(I_o)$. The structure was solved by direct methods with the PATTY option of the DIRDIF program system[23b,c] and refined against F^2 using SHELXL.[23d] All non-hydrogen atoms were refined with anisotropic temperature factors. The hydrogen atoms were placed at calculated positions and refined isotropically in riding mode. The three fluorine atoms could not be refined adequately because of rotational disorder. The absolute structure was determined based on the anomalous dispersion of 2199 Friedel pairs, Flack parameter = 0.00(12), the Hooft parameter y = 0.014(16). R_1 = 0.0685 [$I \geq 2\sigma(I)$]; R_1 = 0.0806 [all reflections]; S = 1.537. Residual electron density between 1.334 and –0.562 e·Å^{-3}. The data were deposited with the Cambridge Crystallographic Data Centre (CCDC 882528). More detailed information can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. (b) Beurskens, P. T.; Beurskens, G.; Bosman, W. P.; de Gelder, R.; García-Granda, S.; Gould, R. O.; Israël, R.; Smits, J. M. M. *DIRDIF-96*; Crystallography Laboratory: University of Nijmegen (The Netherlands), **1996**. (c) Beurskens, P. T.; Beurskens, G.; Strumpel, M.; Nordman, C. E. In *Patterson and Pattersons*; Glusker, J. P.; Patterson, B. K.; Rossi, M., Eds.; Clarendon Press: Oxford, **1987**, 356–367. (d) Sheldrick, G. M. *SHELXL-97*; University of Göttingen: Germany, **1997**.

(24) **Experimental procedure for the conversion of 12 into the β-phenyl-substituted cysteine 20:** Enantiomerically pure compound **12** (200 mg, 0.41 mmol) was dissolved in a 1:2 mixture of 2 M KOH and MeOH (12 mL total volume) and stirred overnight. The resulting mixture was neutralized with 2 M HCl and the methanol was removed by evaporation. Ammonium bicarbonate (328 mg, 4.15 mmol) and a solution of Fmoc-OSu (138 mg, 0.41 mmol) in MeCN (4 mL) was added and the resulting mixture was stirred for 4 h. The mixture was acidified with 2 M HCl until pH 2. The mixture was extracted three times with EtOAc and the organic layers were combined, washed with brine and dried with $MgSO_4$. The solvents were evaporated and the product was purified by column chromatography (PE–EtOAc–AcOH, 3:2:0.1) yielding **20** (134 mg, 0.25 mmol, 60%) as a white solid. Mp 60–62 °C; $[\alpha]_D$ –72.1 (c = 0.37, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, J = 4.4 Hz, 2 H), 7.58 (t, J = 8.0 Hz, 2 H), 7.49–7.31 (m, 9 H), 7.18 (d, J = 5.5 Hz, 2 H), 6.82 (d, J = 8.4 Hz, 2 H), 5.27 (d, J = 9.2 Hz, 1 H), 4.94 (m, 1 H), 4.44 (d, J = 6.8 Hz, 1 H), 4.35 (t, J = 7.2 Hz, 1 H), 4.26 (m, 2 H), 3.79 (s, 3 H), 3.68 (d, J = 13.2 Hz, 1 H), 3.56 (d, J = 13.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 158.6, 143.7, 141.2, 136.4, 132.5, 130.5, 130.1, 129.7, 129.0, 128.7, 128.6, 128.2, 127.7, 127.1, 125.2, 125.1, 124.9, 119.9, 113.9, 67.4, 57.4, 55.2, 50.5, 47.0, 35.2; IR (neat): 3063, 3032, 2953, 1710, 1511, 1478, 1247, 1214, 1175, 701 cm^{-1}; HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{32}H_{30}NO_5S$: 540.1839; found: 540.1877.

(25) Although the ee values of **20** and **21** could not be readily measured by using HPLC techniques, the absence of any epimerization according to ^{1}H HMR spectroscopic analysis is a strong indication that these compounds are enantiopure.

