Chiral Recognition of Amino Acid Derivatives: An NMR Investigation of the Selector and the Diastereomeric Complexes

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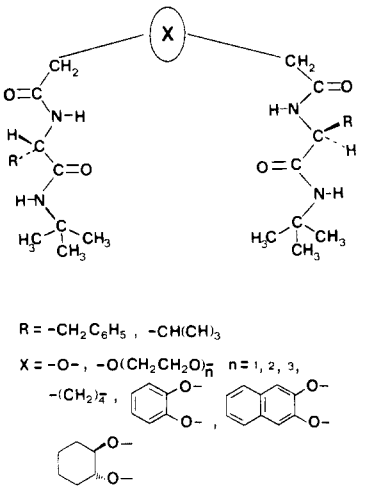
A tetraamidic selector containing two chiral synthons ((*S*)-phenylalanine) spaced by a 3,6,9-oxadecanoyl bridge (Phe-3-*O*-TA) (**1**) was used as stationary phase in capillary GC to perform chiral resolution of *N*-TFA-amino esters. In this paper we report an investigation on the mechanism of chiral recognition by NMR spectroscopy (1D and 2D, COSY, NOESY, and *J*-resolved experiments and ^{13}C relaxation times). First the conformation of the selector in $CDCl_3$ and CD_3OD was studied to evaluate the structural features that might justify the enantiomeric discrimination ability. Then the self-associations of the selector and of the enantiomers (*S*)- and (*R*)-methyl (**2a**, **2b**) and (*S*)- and (*R*)-*n*-butyl *N*-TFA-phenylalaninate (**3a**, **3b**) were investigated at variable temperature and concentration in $CDCl_3$. Finally, titration experiments were carried out to detect the sites of the binding interactions between the selector and the enantiomers. A simple recognition mode is proposed to account for both the enantioselectivity of the phase and the elution order of the enantiomers observed in GC ($t'_R < t'_S$). This is the first spectroscopic study on the mechanism of chiral recognition in GC concerning the real phase and not a model system.

Chiral recognition of amino acids experienced important advances by the introduction of high performance gas[1] and liquid chromatography,[2] which allowed one to approach the problem of racemization in natural and synthetic systems. Furthermore, these methods are helpful in investigating the phenomenon of chiral recognition since, by amplifying the stereoselective effects, they contribute to the understanding of the enantiospecific interactions that occur between a "selector" and the enantiomers.

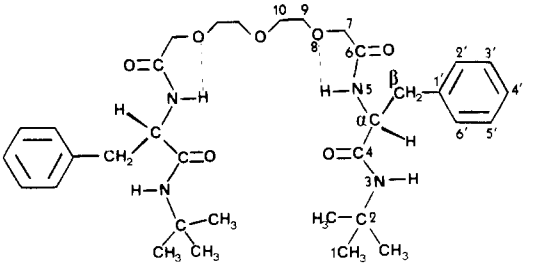
Several models have been proposed for the mechanism of chiral recognition, such as the "three-point rule"[3] or the intercalation theory,[4] mostly inferred from chromatographic or crystallographic data. Thermodynamic studies[5] and theoretical calculations[6] have been performed to account for the enantioselectivity of Chirasil-Val[7] in GC, and spectroscopic investigations of small bimolecular systems have been reported by Pirkle[8] as a model for his popular and versatile HPLC column.

As a result of a systematic approach to the mechanism of chiral recognition, we reported the enantiomeric separation of alkyl esters of (*R,S*)-*N*-TFA-amino acids with optically active tetraamidic phases by capillary GC.[9] Structures featuring C_2 symmetry and containing two chiral synthons ((*S*)-phenylalanine or (*S*)-valine) spatially arranged at various distances one from each other by alkanoyl, dioxaaryl, and oligooxaalkanoyl spacers and derivatized at the terminal sites as *tert*-butylamides (Chart I) were designed in order to study the cooperativity of both arms in the complexation process.

Chart I



The best results were achieved with the chiral stationary phase containing three ethereal oxygens in the bridge (Phe-3-*O*-TA (**1**)), whereas with an equivalent alkanoyl chain no enantiomeric separation was obtained.[9]



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In this paper we report an ^1H and ^{13}C NMR investigation on the mechanism of chiral recognition. The conformation of the selector (**1**) in $CDCl_3$ and CD_3OD was studied by 1D and 2D experiments (COSY, NOESY, *J*-resolved) and by ^{13}C longitudinal relaxation time measurements, in order to establish if a preferential preorganization of the system is required for the enantioselective

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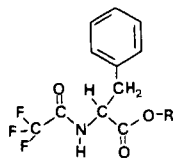
Table I. ^{1}H NMR Chemical Shifts (ppm) and Coupling Constants (hertz) of Phe-3-*O*-TA in $CDCl_3$ and in CD_3OD (0.1 M) at 500 MHz[a]

proton	$CDCl_3$[b]	CD_3OD[b]
H 1	1.18 (s)	1.12 (s)
H β	2.96 (m, ^2J = 13.6, ^3J = 8.6)	2.82 (m, ^2J = 13.6, ^3J = 7.65)
H β	3.07 (m, ^2J = 13.6, ^3J = 6.5)	2.90 (m, ^2J = 13.6, ^3J = 7.15)
H 9,10	3.66–3.69 (s)	3.49–3.57 (s)
H 7	3.97 (d, ^2J = 15.7)	3.81 (d, ^2J = 15.5)
H 7	4.01 (d, ^2J = 15.7)	3.89 (d, ^2J = 15.5)
H α	4.59 (m, ^3J = 7.9, 6.5, 8.6)	4.50 (m, ^3J = 7.15, 7.65)
H 3	5.60 (s, br)	
H Ar	7.21–7.30 (m)	7.07–7.16 (m)
H 5	7.48 (d, ^3J = 7.9)	7.79 (s)

[a] Chemical shifts and coupling constants were determined by *J*-resolved experiments. [b] In parentheses the apparent multiplicity and coupling constants are reported.

process. We have also separately investigated the self-association of the selector (1) and of the enantiomers, (*S*)- and (*R*)-methyl (**2a**, **2b**) and (*S*)- and (*R*)-*n*-butyl TFA-phenylalaninate (**3a**, **3b**) at variable temperature and concentration in $CDCl_3$, which can compete with the chiral recognition.



2: R = CH_3
3: R = C_4H_9

Finally, titration experiments at room and low temperature were carried out in order to detect the binding interactions between the selector and the enantiomers and to evaluate the formation of the diastereomeric complexes.

It is noteworthy that, since Phe-3-*O*-TA is effective in GC as an OV-101 dispersion, the present study represents the first effort to relate gas chromatographic properties to direct spectroscopic observations concerning the real phase and not a model system.

Results and Discussion

Conformation of the Selector Phe-3-*O*-TA (1) in $CDCl_3$ and CD_3OD. ^{1}H and ^{13}C NMR spectra of the selector (1) were recorded in $CDCl_3$ and CD_3OD (0.1 M). ^{1}H chemical shifts and the relative assignments are reported in Table I. ^{13}C chemical shifts are reported in the Experimental Section. In $CDCl_3$ the amide proton H5 was assigned to the resonance at 7.48 ppm on the basis of a COSY experiment showing cross peaks connecting the resonance at 4.59 ppm (α-proton) with those at 7.48 and 2.96–3.07 ppm (β-protons). The resonance peak at 5.60 ppm was assigned to the H3 amide proton on account of its chemical shift and as it did not show any connectivity in the COSY spectrum. Moreover, a NOESY experiment shows cross peaks between the amide proton H5 and the β-protons and between the amide proton H3 and the methyl protons H1, suggesting that these nuclei are closer than 2 Å. The broad peak at about 4 ppm, assigned to the methylene protons H7, can be shown to be formed by two doublets by a 2D *J*-resolved experiment (results not shown), thus indicating a nonequivalence due to ring formation via hydrogen bonding probably between the amide proton H5 and the ethereal oxygen O8. Solvent- and temperature-dependence experiments on the parent

Table II. ^{13}C NMR Longitudinal Relaxation Times T_1 (s) for Phe-3-*O*-TA in $CDCl_3$ and in CD_3OD

carbon	T_1 ($CDCl_3$)	T_1 (CD_3OD)	carbon	T_1 ($CDCl_3$)	T_1 (CD_3OD)
C 6	4.80	4.96	C 9	0.48	0.55
C 4	4.80	4.96	C 10	0.48	0.54
C 1′	2.90	3.09	C α	0.58	0.67
C 3′, 5′	0.82	1.01	C β	0.39	0.43
C 2′, 6′	0.80	0.99	C 2	7.90	29.00
C 4′	0.57	0.64	C 1	0.71	0.83
C 7	0.48	0.65			

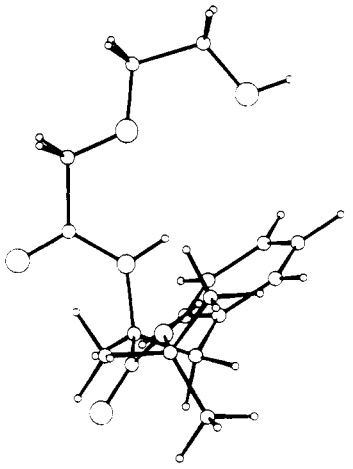


Figure 1. Minimum energy conformation for one arm of Phe-3-*O*-TA, as calculated by the AMPAC program.

dicarboxylic acid Phe-3-*O* had previously led to the same conclusion.[10]

At this concentration (0.1 M) it appears that the aromatic rings are not completely free to rotate, as indicated by the value of the ratio of the relaxation times[11] $T_{1o,m}/T_{1p}$ = 1.4, as well as by the relatively short T_1's for both the aromatic carbon C1' (2.9 s) and the quaternary carbon C2 (7.9 s) (Table II). T_1's for the carbonyl carbons are 4.8 s, thus confirming the intramolecular H-bonding, which could lock the molecule in a tight conformation.

In CD_3OD the amide proton H3 undergoes fast exchange with the solvent, whereas the amide proton H5 exchanges more slowly (24 h). Accordingly, in a NOESY experiment, only the cross peak between the amide proton H5 and the β-protons is present. The methylene protons H7, instead, give two well-resolved doublets with a coupling constant very similar to that in $CDCl_3$ (15.5 Hz). It also appears that in CD_3OD the terminal part of the molecule is more flexible, as indicated by the higher rotational freedom experienced both by the aromatic rings, testified by the increased $T_{1o,m}/T_{1p}$ ratio (1.6), and the *tert*-butyl groups, as suggested by the T_1 of the quaternary carbon C2, which rises to 29 s.

The values of the ^3J coupling constants ($^3J_{NH-CH_\alpha}$ = 7.87 Hz; $^3J_{CH_\alpha-CH_\beta}$ = 8.6 and 6.5 Hz) allow one to estimate the relative torsion angles: ϕ = 152.9°, χ = 36.8° and 142.3°.[12] On these bases, and assuming a trans(*Z*) conformation for the amide groups, we have calculated the most probable conformation for one chain of the selector using the AMPAC program based on the MNDO method.[13] As it is shown

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(13) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899. The AMPAC program is available at the NMR and Data Processing Laboratory, Syracuse University, Syracuse, NY.

Table III. Temperature Dependence ($-\Delta\delta/T \times 10^3$) of the Amide Protons of the Selector (1) and of Methyl (2) and *n*-Butyl *N*-TFA-phenylalaninate (3) in Pure and Mixed Solution in $CDCl_3$ at c = 0.1 M[a]

solution	selector H3	selector H5	enantiomer He
1[b]	4.6	3.5	
2[b]			3.2
3[b]			3.7
1 + 3a[c]	6.2	4.4	11.9
1 + 3b[c]	5.4	3.4	8.9

[a] Concentrations in the mixtures are referred to 1. [b] Temperture range: 243–297 K. [c] Temperature range: 230–292 K, molar ratio 1:1.7.

Table IV. Concentration Dependence of the Chemical Shifts of the Amide Protons of 1 and of Methyl (2) and *n*-Butyl *N*-TFA-phenylalaninate (3)

signal	$\Delta\delta/\Delta c$[a] (ppm/mol × L^{-1})
H5 (1)[b]	0.1233
H3 (1)[b]	1.8746
He (2)[c]	0.4589
He (3)[c]	0.3908

[a] Data points have been processed with a linear regression; correlation coefficients are always greater than 0.997. [b] Concentration range: 0.018–0.36 M. [c] Concentration range: 0.050–0.5 M.

in Figure 1 both N–H's are pointing inward, suggesting, therefore, that the molecule adopts most likely an α-helix arrangement, as suggested also in the case of Chirasil-Val.[5,6] At elevated temperatures (such as that used in GC), the open-chain conformation should be increasingly favored due to its lower entropy of conformation.[14]

Self-Association of the Selector and of the Enantiomers. In order to study the extent of self-association of the phase Phe-3-*O*-TA in an apolar solvent, we performed variable-temperature experiments in $CDCl_3$ at a concentration of 0.1 M in the range 294–243 K. By lowering the temperature, the amide protons H3 and H5 undergo a downfield shift of 0.237 ppm and 0.197 ppm, respectively. The relative temperature coefficients ($-\Delta\delta/T = 4.592 \times 10^{-3}$ ppm/K for H3 and 3.532×10^{-3} ppm/K for H5) (Table III) confirm[15] that the terminal amide H3 is more exposed to intermolecular interactions, whereas the other one is less affected, being already involved in intramolecular hydrogen bonding with the ethereal oxygen.

A similar conclusion is reached by dilution experiments performed in the concentration range between 0.018 and 0.36 M. The increase of the phase concentration induces a pronounced downfield shift of 0.652 ppm for the H3, whereas the H5 is shifted only of 0.043 ppm (Table IV).

In an apolar environment, therefore, we can conclude that the selector is intermolecularly associated mainly through the terminal amide groups, maintaining, however, a certain geometry of the bridge through intramolecular hydrogen bonds.

In agreement with the literature,[16] the enantiomers methyl (*S*)- (**2a**) and (*R*)-(**2b**) and *n*-butyl (*S*)- and (*R*)-phenylalaninate (**3a** and **3b**) also experience a certain degree of self-association as evidenced by variable-temperature and dilution experiments in $CDCl_3$ (Tables III and IV). In fact, by lowering the temperature from T = 297 K to 243 K the $-\Delta\delta/T$ coefficients for the amide protons of **2** and **3** are 3.2×10^{-3} and 3.7×10^{-3}, respectively. Moreover, upon increasing the concentration from 0.05 to 0.4 M, the amide protons of both amino esters experience downfield shifts of 0.16 and 0.14 ppm, respectively (Table IV).

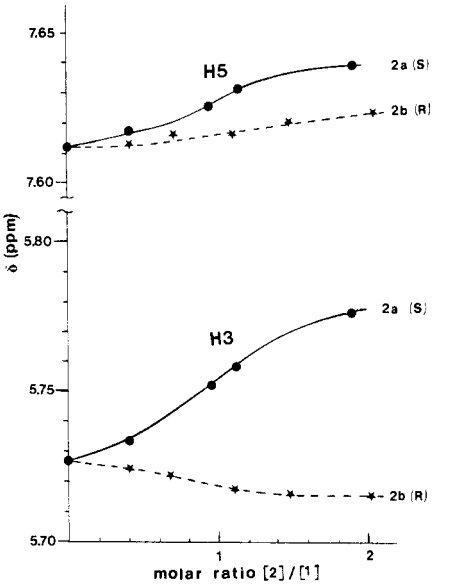

Figure 2. Chemical shift variation of the amide protons H5 and H3 of Phe-3-*O*-TA (1) by additional increase of methyl (*S*)- and (*R*)-TFA-phenylalaninate (**2a**, **2b**) in $CDCl_3$, c = 0.1 M, T = 263 K.

Table V. Chemical Shift Differences ($\Delta\delta = \delta_{complex} - \delta_{free}$)[a] (ppm) for the Protons of 1 in the Presence of 2a, 2b, and 3a, 3b (0.1 M in $CDCl_3$) at 263 K (molar ratio 1:1)

signal	1 + 2a	1 + 2b	1 + 3a	1 + 3b
H 3	0.024	0.011	0.038	0.006
H α	0.004	−0.005	0.008	0.003
H 5	0.014	0.005	0.021	0.014
H 7	−0.003	−0.004	0	0
H 9-10	0	−0.005	0	0

[a] At the present operating conditions, difference in chemical shifts of 0.003 ppm or less are within the experimental error. Shifts for protons not mentioned in the table fall into this range.

Table VI. Chemical Shifts (ppm) of the Amide Proton of the Derivatives 2a, 2b, and 3a, 3b Free and in the Presence of 1, T = 240 K

deriv	δ_{free}	$\delta_{complex}$	$\Delta\delta$
2a	6.981	7.520	0.539
2b	6.986	7.485	0.499
3a	7.003	7.546	0.543
3b	7.003	7.478	0.475

Enantiomeric Recognition. Titration experiments were performed by adding to the selector (1) (0.1 M in $CDCl_3$) increasing amounts of each enantiomer **2a**, **2b**, **3a**, and **3b** at room temperature. Evident changes in local magnetic environments are observed, especially for the amide protons of **1**, H3 and H5, indicative of binding interactions with the enantiomers. The results of titration experiments of the selector with **2a** and **2b** are reported in Figure 2. In the presence of **2a** (molar ratio **2**/1 = 1:1) both H3 and H5 protons of the selector experience a downfield shift (0.026 and 0.048 ppm, respectively), whereas in the presence of **2b** they undergo a very weak shift (0.009 and −0.013 ppm, respectively). Analogous results were obtained upon titration with **3a** (0.033 and 0.060 ppm) and **3b** (0.018 and 0.005 ppm). At lower temperature (263 K) the magnitude of the shift is considerably enhanced (Table V).

Variable-temperature experiments carried out with 1 (0.1 M in $CDCl_3$) in the presence of the *S* enantiomer **3a** con-

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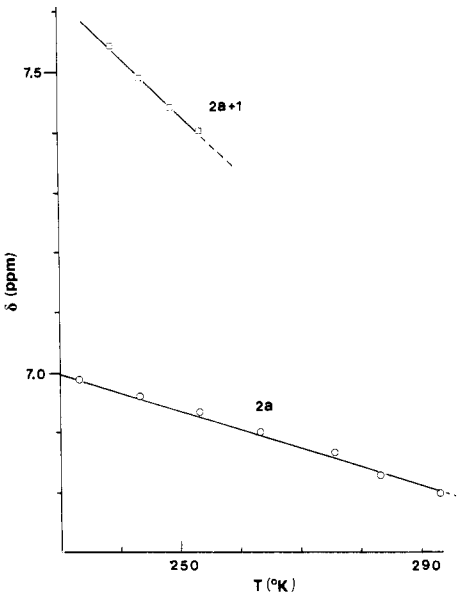

Figure 3. Temperature dependence of the chemical shift of the amide-proton and methyl (*S*)-TFA-phenylalaninate (**2a**) in the presence (□) and in the absence (○) of Phe-3-*O*-TA.

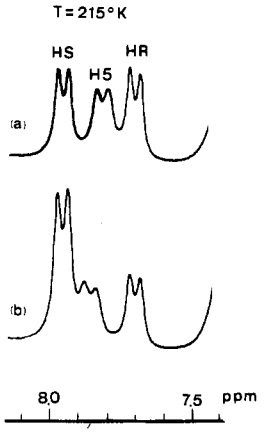

Figure 4. Splitting of the NMR signal of the amide proton of methyl (*S*)- and (*R*)-TFA-phenylalaninate (**2a, 2b**) in the presence of the selector in $CDCl_3$ at 215 K: (a) selector + racemic mixture of **2a** and **2b**; (b) signal identification by addition of excess **2a** to the solution a.

firm that both the amide protons of the selector participate to the binding process and that the amide proton H3 is more affected by the guest. In contrast, the *R* enantiomer **3b** produces a very weak perturbation, if any, at the amide protons of the selector (Table III).

Even more evident changes in the ^1H NMR spectrum of the enantiomers are observed upon addition of the selector, suggesting that the formation of the mixed diastereomeric complex *S* enantiomer **1** successfully competes with self-association (Figure 3). Moreover, the amide proton HS of the *S* enantiomers undergoes a more extensive shift than the HR of the *R* enantiomers, suggesting a stronger interaction with the selector (Table VI).

Finally, by adding to the selector equimolar amounts of racemic methyl (*R,S*)-*N*-TFA-phenylalaninate at 215 K, the He protons are split into two well-spaced (0.21 ppm) sets of doublets (Figure 4a). The doublet at lower field is assigned to the *S* enantiomer by further addition of an excess of that enantiomer (Figure 4b). In the absence of the selector the resonances of the amide protons for the racemic methyl phenylalaninate are not split at room temperature, while at 215 K they are not visible, being completely overlapped by the aromatic protons. Thus, at

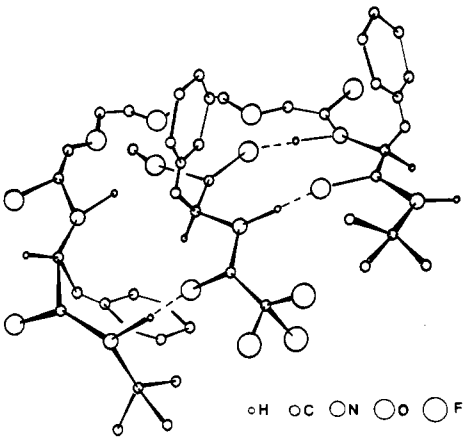

Figure 5. Diastereomeric complex of the selector and methyl (*S*)-TFA-phenylalaninate proposed as a model for the enantiomeric interaction.

low temperature, the selector behaves as a very good "chiral shift reagent".

At the moment, it is not possible to distinguish whether a 1:1 mixed diastereomeric complex has been formed rather than an intercalation or supramolecular-type aggregate. Actually, in the titration experiments of **1** with **2a** and **3a**, a continuous downfield shift is observed up to a molar ratio **2a**:**1** = 2, with a decrease of slope after the 1:1 ratio, suggesting either a weak 1:1 or a stepwise complexation, as if binding to the first chain of the selector would induce a reorientation of the second chain, thus fostering further binding, as in an allosteric process.

The structural details of the diastereomeric complexes must wait for intermolecular NOE experiments and for the comparison with the other differently spaced selectors, which are in progress. However, in light of the present data, it is possible to propose a tentative model for the diastereomeric complexes that can account for the enantiomeric discrimination (Figure 5).

The *S* enantiomer with the same configuration as the selector can better fit into the cleft formed by the two chains of **1**, establishing binding interactions with the two amidic protons and with the carbonyl group and preserving the original helical arrangement of the selector. In contrast, the enantiomer with the opposite configuration would lead to severe overcrowding, giving rise to a weaker complexation and, hence, to a shorter retention time.

Conclusions

The enantiomeric separation of methyl and *n*-butyl (*R,S*)-*N*-TFA-phenylalaninate on the chiral phase Phe-3-*O*-TA may be substantiated by direct spectroscopic evidence of conformational modifications upon complexation. Although the nature of the chiral recognition might differ in the NMR spectra and the chromatographic systems owing to the use of the apolar solvent and especially to the different temperature conditions, the results here reported are in remarkable agreement with the chromatographic retention parameters (the elution order observed being always $t'_R < t'_S$).

Experimental Section

All reagents were of reagent grade and the solvent used in spectroscopic studies were of spectrophotometric quality. ^1H NMR experiments were performed at 200 or 500 MHz. ^{13}C NMR spectra were obtained both with broad-band and off-resonance proton decoupling. Calculations of minimum conformational energy were performed with the AMPAC[13] program.

Optical and chemical purity of the enantiomers **2a**, **2b** and **3a**, **3b** were checked by using a Dani 8500 gas chromatograph with

a capillary column containing the phase Phe-3-*O*-TA dispersed in OV-101.

Polarimetric measurements were performed with an Autopol III (Rudolph Research) automatic polarimeter, using a 10-cm path cell. Melting points were obtained on an Electrotermal melting point apparatus and are uncorrected.

Preparation of the Chiral Stationary Phase Phe-3-*O*-TA (1). The chiral stationary phase Phe-3-*O*-TA was prepared as described in the literature,[9] optically and chemically pure. ^{1}H chemical shifts in $CDCl_3$ and in CD_3OD are reported in Table I. ^{13}C NMR ($CDCl_3$): δ 28.47 (C_1), 38.8 (C_β), 51.19 (C_2), 54.6 (C_α), 70.44 (C_7), 70.55 (C_9), 71.02 (C_{10}), 126.74 ($C_{4'}$), 128.47 ($C_{2'}$, $C_{6'}$), 129.36 ($C_{3'}$, $C_{5'}$), 137.02 ($C_{1'}$), 169.34 (C_4), 169.50 (C_6) ppm. ^{13}C NMR (CD_3OD): δ 28.77 (q, J = 124.91 Hz, C_1), 39.79 (t, J = 130.59 Hz, C_β), 52.07 (s, C_2), 55.59 (d, J = 141.94 Hz, C_α), 71.08 (t, J = 141.94 Hz, C_{10}), 71.48 (t, J = 141.94 Hz, C_9), 71.98 (t, J = 141.94 Hz, C_7), 127.82 ($C_{4'}$), 129.36 ($C_{2'}$, $C_{6'}$), 130.62 ($C_{3'}$, $C_{5'}$), 138.07 ($C_{1'}$), 171.99 (C_4), 171.98 (C_6) ppm.

Preparation of (*S*)-(−)- and (*R*)-(+)-Methyl *N*-(Trifluoroacetyl)phenylalaninate (2a, 2b) and (*S*)-(−)- and (*R*)-(+)-*n*-Butyl *N*-(Trifluoroacetyl)phenylalaninate (3a, 3b). (*R*)- and (*S*)-*N*-(trifluoroacetyl)phenylalanine, prepared as described in the literature,[17] were esterified by addition of methyl or *n*-butyl iodide to a suspension of equimolar amounts of the free acid and $NaHCO_3$ in DMF.[18] The mixture was stirred at room temperature for 24 h; then water was added to remove DMF. The products were isolated by extraction with ethyl acetate, dried over Na_2SO_4, and concentrated by evaporation under reduced pressure. Last traces of DMF were eliminated by percolation on a silica gel column, using hexane as eluent. The products were purified on preparative TLC (Merck silica gel), using a mixture of hexane and ethyl acetate (85:15) as the mobile phase.

Optical purity, checked by GC using Phe-3-*O*-TA, was 100% in all cases.

2a: mp 53–54°C; $[\alpha]^{25}_D$ = −9.9 (c = 1, EtOH 95%) (lit.[19] −7.2, c = 1, EtOH). **2b**: mp 52–53 °C; $[\alpha]^{25}_D$ = +10.7° (c = 1, EtOH 95%). ^{1}H NMR ($CDCl_3$, c = 0.1 M): δ 3.19 (d, J = 6 Hz, 1 H), 3.20 (d, J = 6 Hz, 1 H), 3.78 (s, 3 H), 4.88 (m, 1 H), 6.77 (d, 1 H), 7.04–7.08 (m, 2 H), 7.25–7.35 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ 37.44, 52.74, 53.67, 116 (q, J_{C-F} = 280 Hz), 127.68, 128.91, 129.25, 134.74, 156.5 (q, J_{C-F} = 32 Hz), 170.44 ppm. IR (KBr): 3270, 3100, 2950, 1750, 1700, 1580, 1555, 1440, 1330, 1280, 1180 cm^{-1}. Anal. Calcd for $C_{12}H_{12}NO_3F_3$: C, 52.36; H, 4.39; N, 5.09. Found: C, 52.34; H, 4.48; N, 4.88. **3a**: mp 42–43 °C (lit.[20] mp 35.5–36.5 °C); $[\alpha]^{25}_D$ = −19.38 (c = 1, EtOH 95%). **3b**: mp 41–42 °C; $[\alpha]^{25}_D$ = +19.68 (c = 1, EtOH 95%). ^{1}H NMR ($CDCl_3$, c = 0.1 M): δ 0.93 (t, J = 7 Hz, 3 H), 1.35 (m, J = 7 Hz, 2 H), 1.62 (m, J = 6.5 Hz, 2 H), 3.17–3.22 (m, 2 H), 4.16 (t, J = 6 Hz, 2 H), 4.85 (m, 1 H), 6.79 (d, 1 H), 7.06–7.09 (m, 2 H), 7.25–7.33 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ 13.67, 19.1, 30.43, 37.39, 53.69, 66.12, 115.84 (q, J_{C-F} = 280 Hz), 127.57, 128.86, 129.27, 134.88, 156.67 (q, J_{C-F} = 38 Hz), 170.21 ppm. IR (KBr): 3300, 2940, 1750, 1710, 1560, 1460–1450, 1080 cm^{-1}. Anal. Calcd for $C_{15}H_{18}NO_3F_3$: C, 56.78; H, 5.72; N, 4.41. Found: C, 56.46; H, 5.85; N, 4.15.

^{1}H NMR Studies and Titration and Variable-Temperature Experiments. Samples for ^{1}H NMR studies were prepared by using $CDCl_3$ or CD_3OD with tetramethylsilane as internal standard. Titration experiments were performed by adding directly in a 5-mm tube increasing amounts of a 1 M solution of the amino acid derivative to a 0.1 M solution of 1 and stirring with a Maxy Mixer apparatus. Molar ratios were checked by integration of the α-protons of the selector and of the amino acid derivative. In the variable-temperature experiments care was taken to allow equilibrium of sample temperature before acquiring the FID. Variable-concentration experiments were performed by using samples made by dilution of the same standard solution (0.3 M for the selector and 1 M for the amino acid derivative).

^{13}C NMR T_1 Measurements. Relaxation times were measured by the inversion–recovery method.

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Registry No. 1, 104608-19-7; **2a**, 23635-30-5; **2b**, 65638-78-0; **3a**, 52574-47-7; **3b**, 73366-06-0; methyl, 74-88-4; *n*-butyl iodide, 542-69-8.

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A Short, Oxetane-Based Synthesis of (±)-Sarracenin

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(±)-Sarracenin (1) was synthesized in nine steps and six pots from the simple precursors acetaldehyde and cyclopentadiene. Paterno–Büchi photocycloaddition of this pair yielded two diastereomeric oxetanes (**3x**, **3n**). The major, exo isomer underwent highly regioselective acid-catalyzed methanolysis at the methyl-bearing oxetane center to give a 3-cyclopentenol derivative (**8**). Attachment of a methyl 2-(2-phenylethenyl)ethanoate moiety, a 3-oxopropanoate equivalent, with inversion of the toluenesulfonate **9** derived from **8** gave a diene (**11**) containing all of the necessary carbon atoms. Following decarbomethoxylation, both olefins were simultaneously ozonized to an in situ equivalent of a trialdehyde (**2**) which has played a role in previous synthetic studies and biosynthetic postulates in this area. Spontaneous dehydration of **2** produced (±)-sarracenin in 18% overall yield from the tosylate **9**, the first purified intermediate in the sequence.

(−)-Sarracenin (1) is a tricyclic secoiridoid (i.e., lacks the cyclopentane ring found in iridoids) first isolated from the roots and leaves of *Sarracenia flava* (golden trumpet). Its structure was described in 1976 by Miles, Atwood, and Bryson.[2] In the same paper it was proposed that sarracenin is a likely component of a biosynthetic manifold connecting it and other secoiridoids (secologanin and morronoside) with certain indole alkaloids via the intermediacy of the trialdehyde equivalent **2** and the latter's

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