Preparation and Properties of Enantiomerically Pure 
N\textsuperscript{a}-Tritylamo Acid Fluorides

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Cyanuric fluoride-mediated fluorination of chiral N\textsuperscript{a}-tritylamo acids leads to the corresponding acyl fluorides which are powerful acylating agents for peptide synthesis. The acyl fluorides react with NaBH\textsubscript{4}, the stabilized phosphorane Ph\textsubscript{3}P\textsuperscript{+} C(Me)CO\textsubscript{2}Me and Ruppert’s reagent providing access to enantiomerically pure tritylamo alcohols, aikenes and trifluoromethyl ketones, respectively.

The search for the most efficient amino acid activated derivatives for use in peptide synthesis, especially of peptides incorporating difficult sequences, has recently resulted in the development of a new family of coupling intermediates, namely the amino acid fluorides. These are N\textsuperscript{a}-protected with the most widely used protecting groups in modern peptide synthesis, tert-butoxycarbonyl (Boc), benzzyloxy carbonyl (Cbz) and 9-fluorenylmethoxycarbonyl (Fmoc)\textsuperscript{1} or even with bis(Boc),\textsuperscript{2} or other N,N-bis(alkoxy carbonyl) groups.\textsuperscript{3} Particularly useful acylating agents appear to be the Fmoc amino acid fluorides (Fmoc-\text{AA-F}) which have been successfully applied to the synthesis of the naturally occurring antibiotic peptide peptabois.\textsuperscript{4} The latter contain high proportions of sterically hindered \(
\alpha\)-amino acids in their backbones and \(\alpha\)-amino alcohols at the C-terminus. These agents are usually prepared from the corresponding N-protected amino acids by the action of cyanuric fluoride (CNF) in the presence of pyridine.\textsuperscript{5}

Prompted by these results we decided to investigate the possibility of applying this methodology to activate N\textsuperscript{a}-tritylamo acids\textsuperscript{6} towards coupling with amino components. It is well-established that the former can be used successfully in peptide synthesis as their corresponding esters with 1-hydroxynbenzotriazole (Trt-AA-OBt).\textsuperscript{7} We now wish to report our preliminary results on the preparation of the isoleuble N\textsuperscript{a}-tritylamo acid fluorides and their reactions with a variety of nucleophiles.

Treatment of the N\textsuperscript{a}-tritylamo acid (1) in anhydrous dichloromethane (DCM) with two mole equivalents of CNF at \(-10^\circ\text{C}\) for 1 h gave acyl fluoride 3 in 55–75% yield after work-up including flash column chromatography (Scheme 1). Triphenylmethanol (TrtOH) was obtained as a by-product, mainly formed through hydrolysis of 3 on the column followed by HF-induced Trt–N splitting. This is also presumed to be the reason for the moderate yields (55–75%) of the isolated products thus obtained.

The fluorides 3, thus obtained, had IR carbonyl band frequencies at 1834–1842 cm\textsuperscript{-1} and, with the exception of the fluoride of N-tritylprolglutamic acid (Trt-Glp-F), were very soluble in diethyl ether (DEE); the more lipophilic fluorides 3c–e were even soluble in hexane. The fluorides were crystalline except for Trt-\text{Val-F} and Trt-Leu-F. In order to determine whether their formation or coupling with amino components is accompanied by racemization, we applied the reaction conditions used to effect similar couplings with the esters Trt-AA-OBt,\textsuperscript{7} to the enantiomerlic fluorides 3a and 3b using, as the coupling reagent, TsOH \cdot H-Ala-NHMe.\textsuperscript{9} In the case of fluorides, couplings were clean and complete within 10 min at 0 °C and the expected epimeric dipeptides, 5a and 5b (Scheme 2) respectively, were obtained in 85–88% yields. HPLC examination showed both formation of fluorides and their subsequent coupling to be devoid of any detectable racemization. The limits of the coupling ability of these reagents were determined by coupling the sterically demanding components Trt-Ile-F and TsOH \cdot H-Val-OBlz. The coupling was clean although it required 6 h at room temperature for completion. The expected dipeptide 5c was obtained in 80% yield. However, the very hindered TrtNH\textsubscript{2} failed to react with,
Amino Acid Fluorides

Scheme 1. The conversion of N\textsuperscript{α}-trityl amino acids (1) into the corresponding fluorides (3) using cyanuric fluoride.

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\begin{align*}
&\text{(1) H-AA-X/TEA} \\
&\text{(DMF)}
\end{align*}
\]

order to verify this finding, each of the fluorides 3a and 3b was treated with a 40% aqueous solution of MeNH\textsubscript{2} in a way identical with that described for the aminolysis of the benzo(triazolyl) esters.\textsuperscript{8} Aminolysis was complete within 5 min at 0°C, although detectable amounts of Trt-Phe-OH could also be observed by TLC on comparison with an authentic sample. Thus, some hydrolysis of 3 occurs, but the product of hydrolysis can be readily removed from the amides by washing with 1 M aqueous NaOH. The amides 6 (Scheme 2), 78–80% yields, were detritylated with T\textsubscript{5}OH-H\textsubscript{2}O\textsuperscript{0} and coupled\textsuperscript{7} to Trt-Ala-O\textsubscript{OBt} giving, exceptionally, the corresponding dipeptides 7 in 88–90% yields. Examination of these compounds by HPLC showed that aminolysis of the fluorides is not accompanied by detectable racemisation.

Taking into consideration the ability of the trityl group to confer excellent configurational stability to chiral α-amino acid derivatives when used for N\textsuperscript{α}-protection,\textsuperscript{10} we investigated the reactions of fluorides 3 with other nucleophiles. When the fluoride 3g was subjected to NaBH\textsubscript{4} reduction\textsuperscript{11} in diglyme at 0°C, the equivalent alcohol 12 (Scheme 3) was formed within 10 min as the sole product in 85% yield. Alcohol 12 is a potential intermediate for the synthesis of a variety of chiral γ-aminobutyric acid derivatives.\textsuperscript{12}

The reaction with two carbon nucleophiles was also investigated. Reaction with the stable phosphonate Ph\textsubscript{3}P-C(Me)CO\textsubscript{2}Me\textsuperscript{10} converted 3a into ester 8 with an isolated yield of 42%. The reaction between 3a and Et\textsubscript{3}SiCF\textsubscript{3},\textsuperscript{13} in the presence of a catalytic quantity of tetrabutylammonium fluoride (TBAF) hydrate at 0°C, led to the formation of the silyl ether 9a as the main product. When the same reaction was repeated with Ruppert’s reagent, Me\textsubscript{3}SiCF\textsubscript{3},\textsuperscript{14} we obtained the analogous silyl ether 9b. Sequential treatment with excess TBAF led to two new products identified as the trifluoromethyl ketone 10, and possibly the alke 11. On the other hand, treatment of isolated 9b with TBAF hydrate at 0°C produced within 5 min the trifluoromethyl ketone 10, which was isolated in 87% yield. It should be

\[
\begin{align*}
&\text{(3) R=H, R\textsubscript{2}=CH\textsubscript{2}Ph} \\
&\text{(7a) R=H, R\textsubscript{2}=CH\textsubscript{2}Ph} \\
&\text{(7b) R=CH\textsubscript{2}Ph, R\textsubscript{2}=H}
\end{align*}
\]

Scheme 2. Exemplification of the conversion of the N\textsuperscript{α}-trityl amino acid fluorides (3) into dipeptides 5 and 7.

e.g., 3a, a result consistent with the reported failure to prepare Boc-Gin(Trt)-OBzl from Boc-Glu(F)-OBzl.\textsuperscript{1}

We have recently shown that the ester Trt-Glp-OBt is valuable for incorporating the Glp moiety into peptide chains as it allowed efficient synthesis of the hormone TRH and derivatives.\textsuperscript{9} During the course of those studies, it was observed that coupling of Trt-Glp-OBt with 2HCl-H-His-OMe produced, as the sole product, the dipeptide Trt-Glp-His-OMe and this was attributed to the low solubility of the amino component in the coupling medium. When, however, the same experiment was repeated under otherwise identical reaction conditions but using as acylation reagent, Trt-Glp-F (3g), the disappearance of 3g was complete (TLC) within 30 min at room temperature and the sole product of the reaction was now the expected dipeptide 5d, as shown by comparison with an authentic sample. Thus, 3g appears to be very suitable for incorporating Glp into peptide chains. During the preparation of the fluorides 3, it became apparent that these compounds are less stable to hydrolysis than the corresponding benzo(triazolyl) esters. In
noted that direct formation of 10 from fluoride 3a could not be realized even using an equimolar quantity of Ruppert’s reagent: only trace amounts of 10 could be detected on TLC together with starting material and trimethylsilyl ether 9b. A number of synthetic methods have been developed for trifluoromethyl ketones, as these compounds are known to act as serine protease inhibitors.

Since work-up destroyed part of the fluorides 3, their preparation in the solid phase was attempted. o-Chlorotriyl chloride resin [PTrt(Cl)-Cl] was used to anchor the amino acid, e.g., t-Phe, onto the solid support. Thus, treatment of t-Phe with trimethylsilyl chloride followed by PTrt(Cl)-Cl in the presence of TEA, following the preparation of the corresponding PTrt-t-Phe-OH, led to the preparation of the polymeric derivative PTrt(Cl)-t-Phe-OH (13). Treatment of this with CNF in DCM as solvent and TEA as the base for 2 h at −10 °C, gave the corresponding fluoride 14 (Scheme 4) in 98% yield. Excess reagents and by-products of the reaction were simply removed by washing the resin with dry DCM. Coupling of H-Ala-NHMe with 14, followed by detritylation with a 20% solution of TFA in DCM and detritylation with TrtCl in the presence of TEA led to the preparation of the dipeptide 5a in 93% total yield. A sample of this peptide was examined by HPLC and, like the one obtained by the solution method, found to be free of the epimeric dipeptide 5b.

In conclusion, N⁴-tritylamino acid fluorides (3) have been obtained in moderate yields through CNF-mediated fluorination of N⁴-tritylamino acids. The moderate yields usually obtained, can be overcome by use of polymeric N⁴-tritylamino acids, which avoids aqueous work-up and/or FCC necessary for their purification. They have been shown to be powerful acylating agents of amino components and thus are valuable intermediates in peptide synthesis, in particular in assembling difficult sequences. Moreover, they enter readily into a variety of reactions with other nucleophiles and therefore are interesting intermediates in asymmetric synthesis using peptidogenic amino acids as starting materials. Preparation of a larger variety of analogues of 3 is now in progress as are further studies of their reactions with the above and other nucleophiles, aimed at the preparation of chiral amino acid derivatives for use in peptide synthesis.

**Experimental**

**General.** The N⁴-tritylamino acids 1 used in the present work were obtained from the corresponding i- or o-amino acids through O-silylation followed by N-tritylation and O-Si bond splitting with MeOH. Polymeric N⁴-(o-chloro)tritylphenylalanine was obtained from the PTrt(Cl)-Cl resin and t-Phe according to a published procedure and found to have 0.89 mmol AA g⁻¹ resin substitution. The PTrt(Cl)-Cl resin was purchased from CBL Patras, Greece and had 1.1 mmol equiv. Cl⁻ g⁻¹ resin substitution. The Trt-Glp-OH was obtained through DCC-mediated cyclization of N⁴-tritylglutamic acid.

Capillary melting points were taken on a Büchi SMP-20 apparatus and are uncorrected. Optical rotations were determined with a Carl-Zeiss precision polarimeter. IR spectra were recorded as KBr pellets or with neat oily samples on a Perkin-Elmer 16PC FT-IR spectrophotometer. ¹H NMR spectra were obtained at 200.132 and 400.13 MHz and ¹³C NMR at 50.32 and 100.62 MHz on Bruker AC 200F and AM 400WB MHz spectrometers, respectively. CDCl₃ and tetramethylsilane (TMS) were used as the solvent and the internal standard, respectively. Electron impact (EI) spectra were obtained on a Fisons VG 7070E mass spectrometer at an electron bombardment energy of 70 eV, using the direct inlet probe at a temperature of 250 °C. LSI spectra were obtained on a Fisons VG-ZAB-T four-sector instrument. The compounds were ionized by liquid secondary ion (LSI) ionization in the positive ion mode using a caesium ion gun operated with an accelerating voltage of 30 kV.
m-Nitrobenzyl alcohol was used as the matrix solution, unless otherwise stated, and it was carefully mixed with 1 μl of sample solution in CHCl₃ on the tip of the probe prior to analysis. Ions were subjected to an accelerating voltage of 8 kV and detected using a photomultiplier detector. Data were acquired and processed using OPUS V3.1X software. FCC was performed on Merck silica gel 60 (230–400 mesh) and TLC on Merck silica gel F₅₄₄ films (0.2 mm) precoated on aluminium foil. The solvent systems used were: (A) PhMe-EtOAc (8:2), (B) hexane-acetone (95:5), (C) hexane-PhMe (8:2), (D) Hexane-PhMe (1:1), (E) CHCl₃-MeOH–H₂O (93:7:0.6), and (F) CHCl₃-MeOH (95:5). Spots were visualized with UV light at 254 nm, ninhydrin and the charring agent (NH₄)₂SO₄-conc. H₂SO₄–H₂O (20 g: 4 ml: 100 ml). All solvents used were dried according to standard procedures prior to use.

HPLC was performed on a system consisting of an LKB pump, a UV–VIS detector LDC 1204A with an 8 μl flow cell and a 50 μl loop injector. HPLC analysis of freshly prepared solutions of dipptides 5 and 7 in the eluent was performed under the following experimental conditions. The analytical column used was a Supelcosil LC-18, 5 μm particle size, 250 × 4.6 mm i.d., purchased from Supelco, equipped with an RP-18 guard column, 4 × 4.6 mm i.d., purchased from Brownlee Labs. The eluted peaks were recorded at 254 nm. Elution was carried out at 1 ml min⁻¹ with 50% (v/v) aqueous acetonitrile which was continuously degassed using a 0.2 μm membrane filter (BAS vacuum degasser LC-26). The capacity factor k'=(tₑ–t₀)/t₀ was used to define the relative position (retention time) of the eluted compound (tₑ) to the first eluted non-retarded peak (t₀).

All new compounds gave satisfactory microanalytical data to within ±0.3 of the calculated values.

**Preparation of N⁴-tritylaminodiacid fluorides (3).** To a cold (−10 °C) solution of 6 mmol of Trt-AA-OH (1) and dry Py (42 mmol, 3.4 ml) in DCM (8 ml), a solution of CNF (12 mmol, 1 ml) in DCM (4 ml) was added dropwise over a period of 15 min and the resulting reaction mixture was further stirred at that temperature for 45 min. Glacial AcOH (30 mmol, 1.71 ml) was added, and the reaction mixture stirred for 15 min, then diluted with DCM (30 ml) and washed once with ice-cold 5% NaHCO₃ aqueous solution and twice with ice-cold water. The organic phase was dried (Na₂SO₄) and evaporated under reduced pressure to leave a yellowish residue. Alternatively, the reaction mixture was triturated with DEE (60 ml) and the resulting yellowish precipitate filtered off and washed with DEE. The combined filtrates were then concentrated under reduced pressure to leave crude product. The residue thus obtained was subjected to FCC using 10 g silica gel per 1 g of Trt-AA-OH and toluene as the eluent. The ninhydrin-positive fractions were pooled and evaporated under reduced pressure to leave the pure product as a thick oil which can be used as such in further reactions. However, addition of hexane or DEE (in the case of 1g) caused crystallization of the compound in most cases. Yields of reactions are not optimized and refer to the crystalline product, where applicable. Optical rotation values were obtained for 1% solutions in CHCl₃ and TLC was performed using the solvent system A for development.

When shorter reaction times were used for preparation of Trt-Phe-F (3a) and Trt-Pro-F (3f), weak peaks at masses higher than the expected molecular ions were observed in the EI-MS. Thus in the former case, in addition to the molecular ion at m/z 409, a minor peak at m/z 603 might be explained as arising from the MH ion of 4a (Scheme 1), whereas in the latter case, two minor peaks observed at m/z 472 and 549 might be rationalised as arising from the M ion of 2 [R¹, R²=(CH₃)₂], and the M−3H ion of 4 [R¹, R²=(CH₃)₂], respectively. In the same MS, the base peak was at m/z 241 (Trt−2 H).
NMR: δ 7.52 – 7.08 (15 H, m, ArH), 3.392 (1 H, dd, J 4.80 and 11.12 Hz, CH2), 2.514 (1 H, d, J 11.12 Hz, NH), 2.206 (1 H, m, CHMe2), 1.059 (3 H, d, J 6.84 Hz, Me) and 1.002 (3 H, dd, J 1.24 and 7.00 Hz, Me). 13C NMR: δ 163.885 (d, J 383.34 Hz, COF), 145.42 (ipso-ArC), 128.59, 128.10 and 126.10 (all other ArC), 71.030 (PhC), 60.567 (dd, J 13.88 and 45.18 Hz, CH), 33.321 (d, J 10.36 Hz, CHMe2), 19.142 (CH3) and 17.668 (CH3).

(1)-Tri-Leu-F (3e): yield: 75%, oil, [α]D25 = +59.1°, Rf 0.87. Anal. C24H38F2NO: C, H, N, IR: 1834 cm⁻¹. EI-MS (m/z): 359 (M – H2O), 328 (M – ArC), 241 (Tri – H2), 165 (Tri – PhH). 1H NMR: δ 7.52 – 7.19 (15 H, m, ArH), 3.394 (1 H, dd, J 4.81 and 11.15 Hz, CH2), 2.516 (1 H, d, J 11.14 Hz, NH), 2.213 (1 H, m, CHMe2), 1.32 – 1.26 (1 H, m, CH2), 1.057 (3 H, d, J 6.83 Hz, Me), 0.999 (3 H, dd, J 1.85 and 7.02 Hz, Me) and 0.882 (1 H, m, CH2). 13C NMR: δ 163.772 (d, J 384.14 Hz, COF), 145.289 (ipso-ArC), 128.251, 127.408 and 126.459 (all other ArC), 70.899 (PhC), 60.429 (d, J 45.24 Hz, CH3), 33.200 (CHMe2), 34.163 (CH2) and 19.025 (CH3) and 17.543 (CH3).

(1)-Tri-Pro-F (3f): yield: 60%, m.p. 165 – 168 C, [α]D25 – 31.6°, Rf 0.74. Anal. C25H36F3NO: C, H, N, IR: 1842 cm⁻¹. EI-MS (m/z): 359 (M), 282 (M – Ph), 241 (Tri – H2), 165 (Tri – PhH). 1H NMR: δ 7.57 – 7.18 (15 H, m, ArH), 4.080 (1 H, dd, J 2.28 and 9.32 Hz, CH3), 3.406 (1 H, dd, J 5.50, 8.04 and 11.57 Hz, NCH3), 2.913 (1 H, dt, J 6.93 and 11.57 Hz, NCH3), 1.704 – 1.514 (2 H, m, CH2), 1.100 (1 H, dq, J 9.13 and 12.72 Hz, CHCH2) and 1.007 – 0.921 (1 H, m, CHCH3). 13C NMR: δ 165.554 (d, J 375.99 Hz, COF), 144.088 (ipso-ArC), 130.483, 128.053 and 126.340 (all other ArC), 76.530 (PhC), 61.775 (dd, J 3.48 and 59.54 Hz, CH3), 49.540 (NCH3), 30.440 (d, J 2.06 Hz, CHCH2) and 29.905 (NCH2CH2).

(1)-Tri-Glp-F (3g): yield: 55%, m.p. 156 – 162°C, [α]D25 – 23.0°, Rf 0.31. Anal. C26H38F3NO3: C, H, N, IR: 1840, 1712, 1692 cm⁻¹. EI-MS (m/z): 373 (M), 299 (M – CH2 – CHCOF), 243 (Trt), 165 (Tri – PhH). 1H NMR: δ 7.35 – 7.22 (15 H, m, ArH), 4.353 (1 H, d, J 9.21 Hz, CH3), 2.885 – 2.120 (4 H, m, CH2CH2). 13C NMR: δ 174.872 (d, J 2.26 Hz, CON), 162.752 (d, J 373.27 Hz, COF), 141.772 (ipso-ArC), 129.988, 127.687 and 127.443 (all other ArC), 75.106 (PhC), 60.581 (d, J 65.32 Hz, CH3), 30.725 (COCH2) and 24.655 (d, J 2.11 Hz, CH2CH2).

Preparation of PTrt(Cl)(l)-Ph-Phe-F (14). To a cold (−10°C) suspension of PTrt(Cl)(l)-Ph-Phe-OH (3.45 g, 3.07 mmol AA) and dry TEA (9.21 mmol, 1.28 ml) in DCM (20 ml), a solution of CNF (9.21 mmol, 0.77 ml) in DCM (5 ml) was added dropwise over a period of 20 min and the resulting reaction mixture further stirred at that temperature for 2 h. The resulting resin was then filtered off and washed three times with dry DCM and twice with DEE and dried overnight at 50°C under high vacuum to give 3.457 g (98%) of resin. IR: 1834 cm⁻¹.

Procedure for coupling of fluorides 3 with x-amino esters and amides. Preparation of dipeptides 5. A suspension of the amino component H-AAA-X (1 mmol), as its salt with hydrogen chloride or p-toluensulfonic acid, in DMF (1 ml) was cooled to 0°C and treated with dry TEA (0.35 ml, 2.5 mmol). To the resulting reaction mixture the fluoride 3 (0.95 mmol) was added and stirring was continued at the same temperature for 10 min, when reaction was found to be complete (disappearance of 3 by TLC). In the case of dipeptide 5d the reaction was complete within 30 min at room temperature whereas in the case of dipeptide 5e, 6 h at room temperature were required for completion of the reaction. Work-up of all couplings involved dilution with EtOAc and sequential washings with 5% aqueous citric acid, H2O, 5% aqueous NaHCO3 and H2O. The organic phases were dried (Na2SO4) and evaporated to leave crystalline residues which, upon addition of DDE and filtration, gave pure products. HPLC analysis of dipeptides 5a and 5b was performed prior to the addition of DDE and showed them to be free of the alternative diastereomer.


Tri-(l)-Glp-(l)-His-OMe (5d): yield: 57%. Dipeptide 5d had physical properties identical with those reported in Ref. 10 for the same compound.

Preparation of dipeptide 5a from PTrt(Cl)(l)-Phe-F (14). To an ice-cold solution of TsOH·H-Ala-NHMe (1.1 mmol, 0.30 g) in DMF (3 ml), was added TEA (2 mmol, 0.28 ml) followed by the polymeric fluoride 14 (0.5 g, 0.44 mmol AA). The resulting reaction mixture was stirred at the same temperature for 30 min and then for 1 h at room temperature. The resulting resin was filtered and washed as follows: 2 x DMF, 2 x MeOH, 1 x DMF, 1 x MeOH and 1 x DEE and then dried as for resin 14 to give 0.523 g (98%) of product (IR: 1660 cm⁻¹). This product resin was then treated with 10 ml of a 20% TFA solution in DCM for 30 min at 0°C, and for 15 min at room temperature and finally filtered off. The resin was washed several times with DCM and the combined filtrates were concentrated under reduced pressure. To an ice-cold solution of the resulting
oil residue in CHCl₃ (2 ml) was then added TrtCl (0.6 mmo1, 0.17 g) followed by the dropwise addition of TEA (3 mmol, 0.45 ml). Stirring at the same temperature for 15 min and then at room temperature for 2 h led to complete trietylation. The solvent was removed under reduced pressure and the residue was worked-up as for dipeptides 5. FCC of the crude product to remove ninyhydrin-inactive by-products, using solvent system F as the eluent, gave 0.2 g (93%) of pure 5a. HPLC analysis of a sample of this dipeptide 5a (κ' 7.175) showed it to be free of 5b.

Amidation of fluorides 3 with concentrated aqueous amines. Preparation of amides 6 and dipeptides 7. To an ice-cold solution of fluoride 3a (2.7 mmol) in DMF (3 ml), was added TEA (0.6 ml, 4 mmol) followed by 40% aqueous MeNH₂ (0.3 ml). Stirring was continued at the same temperature for 5 min, when reaction was found to be complete (disappearance of 3 by TLC). Work-up of reaction mixtures was similar to that described for the preparation of dipeptides 5, except that 1 M NaOH was used instead of 5% aqueous NaHCO₃ in order to effect the removal of some Trt-AA-ÖH formed from hydrolysis of 3. The thus obtained pure amides 6 were detritylated according to Ref. 8 and coupled to Trt-Ala-ÖBt according to Ref. 7 to give excellent yields of the dipeptides 7. These couplings required overnight reaction at room temperature for completion. HPLC analysis of dipeptides 7a and 7b showed them to be free of the alternative diastereomer in each case.

It should be noted that during the course of the present work Trt-Ala-ÖBt was obtained for the first time in crystalline form from EtOAc. It was of the active amide form and had m.p. 158–161 °C, [α]D₂⁰ +83.3° (c 1, CHCl₃) and IR: 1736 cm⁻¹.


Trt-(L)-Ala-(L)-Phe-NHMe (7a): yield: 90%, m.p. 194–197 °C, [α]D₂⁰ −64.4° (c 1, CHCl₃), Rf (E) 0.46, κ 7.71. Anal. C₂₅H₃₉N₂O₂: C, H, N: IR: 3360, 3328, 3230, 1650, 1626 cm⁻¹. LSI-MS (m/z): 492 (MH⁺), 414 (MH⁺ – PhMe), 286 [MH⁺ – (HCO-Phe-NHMe)²⁻], 243 (Trt).


Procedure for the Wittig olefination of fluorides 3 with the stabilized phosphorane Ph₃P=C(Me)CO₂Me. A solution of 3a (1 mmol, 0.41 g) and the phosphorane (1.5 mmol, 0.52 g) in acetonitrile (1 ml) was brought to reflux and kept at that temperature for 10 h. Then the solvent was evaporated off under reduced pressure and the residue was subjected to FCC using as eluent initially solvent system D, then PhMe–hexane (8:2) and finally PhMe to give 0.2 g of product 8, in the form of an inseparable mixture of double bond isomers, as an oil. Alkene 8 had physical data as follows: Rf (D) 0.25. IR: 3472 and 1738 cm⁻¹. LSI-MS (m/z, matrix: thioglycerol): 422 [MH⁻–(CH₂O·CO)], 344 (422–PhH), 243 (Trt). ¹H NMR: δ 7.40–7.14 (20 H, m, ArH), 3.559 (1 H, m, CH), 3.0371 (3 H, s, OMe) and 2.991–2.636 (5 H, m, CH₂ and C=CH₂). ¹³C NMR: δ 173.77 (δ, d, J 22.14 Hz, –CF), 172.67 (CO), 137.22 (d, J 63.39 Hz, –C), 145.68 and 136.90 (iso-ArC), 129.81–126.31 (all other ArC), 70.99 (Ph₃C), 58.08 (d, J 62.07 Hz, CH), 51.226 (OCH₂), 42.394 (CH₃) and 41.695 (CH₂).

Procedure for the reaction of fluorides 3 with Ruppert’s reagent. Preparation of silyl ethers 9 and trifluoromethyl ketone 10. To an ice-cold solution of 3a (2 mmol, 0.82 g) and R₂SiCF₃ (5 mmol) in THF (3 ml) was added a catalytic quantity of TBAF hydrate. After 30 min at 0 °C, the reaction mixture was diluted with DEE and washed sequentially as for dipeptides 5 to give 0.8 g of crude product which was purified by FCC using PhMe as the eluent. The purified product 9a, which was obtained in 50% yield, solidified in the freezer and had m.p. 71–74 °C, [α]D₂⁰ +37.8° (c 1, CHCl₃), Rf (B) 0.56. Anal. C₁₉H₁₃F₆O₇Si: C, H, N: IR: similar to 9b. EI-MS (m/z): 573 (M – CHF₂), 546 (573 – Et), 496 (573 – Ph), 482 (573 – PhCH₂), 368 (482 – CH₂SiEt₂), 330 (368 – F₂), 1H NMR: δ 6.70–6.90 (20 H, m, ArH), 2.882 (2 H, d, J 5.97 Hz, CH₃), 1.840 (1 H, td, J 5.97 and 0.82 Hz, CH), 1.526 (2 H, br s, NH), 0.599 (9 H, t, J 7.61 Hz, SiCH₂CH₂) and 0.260 (6 H, q, J 7.61 Hz, SiCH₃CH₂). ¹³C NMR: δ 145.123 and 138.174 (ipsos-ArC), 129.6–126.1 (all other ArC and two CF₃ quaternaries), 73.478 (Ph₃C), 46.142 (CH₂CH₂) and 35.203 (CH₂CH₂).

In a separate identical experiment using Me₃SiCF₃ as the reagent, 9b was formed as the main product with Rf (B) 0.49. When the starting material had disappeared (TLC), excess TBAF hydrate was added at room temperature and the resulting reaction mixture was diluted with DEE and washed twice with brine. Drying (Na₂SO₄) and evaporation of the organic layer left a dark brown oily residue which was subjected to FCC using solvent system C to give 0.2 g of each of two pure products as oils with Rf 0.31 and 0.29 for the same solvent system (C), and 0.38 and 0.35 for system B, respectively. The same reaction mixture was obtained (TLC) when 9a was treated with excess TBAF hydrate at room temperature. LSI-MS, IR and ¹H NMR examination of these products showed them to be the ketone 10 and the alkenes 11, respectively. Alkene 11 had IR: 3346 (NH), 1664 (C=O), 1186 and 1126 (CF₃) cm⁻¹. ¹H NMR: δ 7.40–6.90 (20 H, m, ArH), 5.409 (1 H, br, NH), 3.362 and 3.106 (2 H, two d, J 13.63 Hz, CH₂), LSI-MS (m/z, matrix: thioglycerol): 460 (MH⁺–CH₂F₂), 382 (MH⁺–CH₂F₂–PhH), 349 (TrtNHCH₂Ph), 243 (Trt).
Preparation of trifluoromethyl ketone 10 from trimethylsilyl ether 9b. To an ice-cold solution of 3a (2 mmol, 0.82 g) and Me₂SiCF₃ (5 mmol) in THF (3 ml) was added a catalytic quantity of TBAF hydrate. After 1 h at 0 °C, the reaction mixture was concentrated under reduced pressure to give a residue which upon FCC using solvent system C as the eluent gave 0.59 g (48%) of pure 9b as an oil which crystallized in the freezer. The product had m.p. 91–94 °C, [α]D₂⁰ +49.2° (c 1, CHCl₃), Rf (B) 0.49. Anal. C₃₃H₂₁₅F₂₁NO₅: C, H, NIR: 1190 and 1138 (CF₃), 884, 860 and 840 (O·SiMe₃) cm⁻¹.

To an ice-cold solution of 9b (0.66 mmol, 0.4 g) in THF (3 ml) was added TBAF hydrate (0.66 mmol, 0.17 g) in one portion. After 5 min at the same temperature the reaction mixture was diluted with DEE, washed twice with H₂O, dried and evaporated to give 0.26 g (87%) of pure ketone 10, as an oil which crystallized upon trituration with hexane. Ketone 10 had m.p. 184–187 °C, [α]D₂⁰ +110.3° (c 1, CHCl₃), Rf (B) 0.40. Anal. C₃₂H₂₄F₂₃NO: C, H, N IR: 3320 (NH), 1756 (C=O), 1200 and 1146 (CF₃) cm⁻¹. ¹H NMR: δ 7.40–6.90 (20 H, m, ArH), 4.154 (1 H, dd, J 6.51 and 4.96, CH), 3.146 (1 H, dd, J 13.63 and 4.96 Hz, PhCH), 2.625 (11 H, dd, J 13.63 and 6.51 Hz, PhCH'), 2.53 (1 H, br. NH). LSI-MS (m/z, matrix: thioglycolier): 460 (MH), 382 (MH–PhH), 362 (MH–HOCOF₃), 243 (Trt).

Procedure for the reduction of fluorides 3 with NaBH₄. Preparation of alcohol 12. To an ice-cold solution of fluoride 3g (2 mmol, 0.75 g) in diglyme (12 ml) was added NaBH₄ (6 mmol, 0.23 g) and the reaction mixture was stirred at 0 °C for 10 min when the clean reaction was found to be complete (TLC). The reaction mixture was then carefully diluted with 30 ml of a 5% aqueous citric acid solution and extracted twice with EtOAc. The combined organic layers were washed with H₂O, 5% aqueous NaHCO₃ solution and H₂O, dried (Na₂SO₄) and evaporated to leave a residue which upon addition of DEE and refrigeration afforded 0.61 g (85%) yield of crystalline product. Alcohol 12 had m.p. 176–178 °C, [α]D₂⁰ –74.4° (c 1, CHCl₃), Rf (EtOAc) 0.37. Anal. C₂₄H₂₁₂NO₂: C, H, N IR: 3298 and 1656 cm⁻¹. LSI-MS (m/z): 715 (2M+H), 358 (MH), 357 (M), 243 (Trt).

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