Heteroatom Chemistry
Volume 4, Number 2/3, 1993

α-Trifluoromethyl Substituted α-Aminoacids and α-Hydroxyacids with Organometallic Moieties in the Side Chain [1,2]

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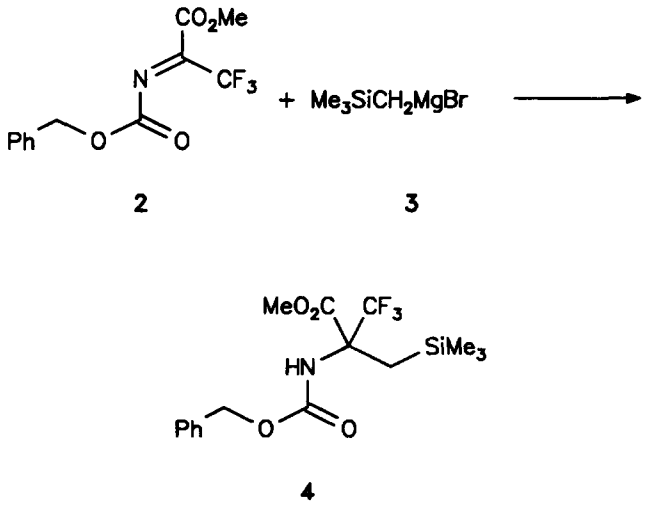
Received 25 September 1992

ABSTRACT

Several strategies for the synthesis of α-trifluoromethyl substituted α-aminoacids and α-hydroxyacids with organometallic moieties in the side chain are described. The preparative potential of organometallic substituents (organosilicon, organotin, and organocobalt moieties) offers a convenient methodology for the synthesis of highly functionalized α-aminoacid and α-hydroxyacid derivatives.

α-Trifluoromethyl substituted α-aminoacids play an important role as suicide inhibitors of pyridoxal phosphate dependent enzymes [3,4]. Furthermore, the trifluoromethyl substituent exerts a considerable effect on the conformational flexibility [5] and the chemical or metabolic stability of peptides [6] formed with these aminoacids. The lipophilicity of the trifluoromethyl group renders these aminoacids efficient carriers of polar groups through membranes.

Recent studies on the introduction of organometallic moieties into estradiol derivatives revealed that, in certain cases, the binding affinity to the receptor is retained [7]. Organometallic moieties as sidechains of aminoacids (e.g., ferrocenyl aminoacids) have already been described [8]. Besides potential therapeutic effects, certain organometallic moieties in the side chain of aminoacids are highly appreciated as building blocks for the synthesis of more complex aminoacids.



SCHEME 1

RESULTS AND DISCUSSION

Silicon in the Side Chain

The methyl 2-trifluoromethyl-3-trimethylsilylalaninate **4** is prepared in high yield *via* amidoalkylation of the Grignard compound **3** with acylimines **2** of methyl 3,3,3-trifluoropyruvate **1** [9].

Similarly, a preparative route to trifluoromethyl substituted α-aminoacids and α-hydroxyacids with trimethylsilylethynyl side chains proceeds *via* amidoalkylation [10] or hydroxyalkyl-

Dedicated to Prof. James Cullen Martin on the occasion of his sixty-fifth birthday.

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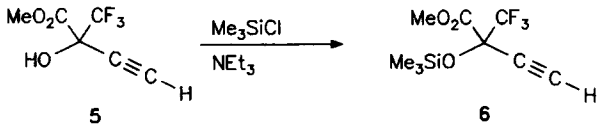
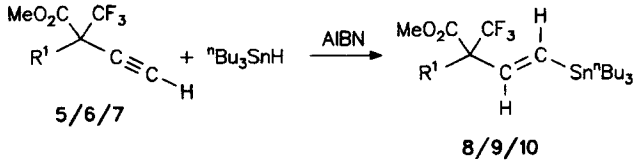
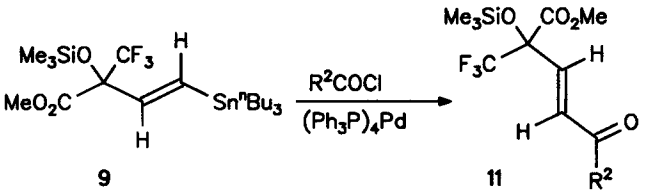
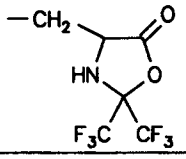




	R^1
5/8	OH
6/9	$OSiMe_3$
7/10	$NHCO_2CH_2Ph$

SCHEME 2



	11a	11b	11c
R^2	–Me		

SCHEME 3

ation [11] of trimethylsilylethynylmagnesium bromide with **2** or **1**.

Tin in the Side Chain

Amidoalkylation or hydroxyalkylation of metallated terminal alkynes with the acylimines **2** or with 3,3,3-trifluoropyruvates **1** provides a general route to α-trifluoromethyl substituted α-aminoacids [10] or α-hydroxyacids [11] with triple bonds in the side chain. Hydrostannation [12] of the alkynes **5**, **6**, or **7** with tri-(*n*-butyl)stannane in the presence of azobisisobutyronitrile (AIBN) gives the (E)-vinylstannanes **8**, **9**, or **10**.

The values of both coupling constants $^2J(^1H^{119/117}Sn)$ and $^3J(^1H^{119/117}Sn)$ in these compounds as measured in the ^1H NMR spectra are in the range from 53 to 62 Hz, providing no information about the regiochemistry. The coupling constant $^3J(^1H^1H)$ of the olefinic protons is about 19 Hz, a typical value for a vicinal coupling in a trans-substituted olefin. This proves the regiochemistry of the hydrostannation and establishes the (E)-configuration of the vinylstannane. The protons at C-4 of the vinylstannanes are shielded compared to the protons at C-3. The variation of the shift value of the latter proton in the three compounds also parallels the changes in structure.

The palladium catalyzed cross-coupling of organotin compounds with organic electrophiles is a mild, high-yielding method for the formation of carbon–carbon bonds [12]. The presence of many additional functional groups is tolerated. Application of this methodology, for example, to the tin compound **9** yields α-trifluoromethyl substituted hydroxyacids **11** with a vinyl ketone sidechain and additional functionality (e.g., **11c**). Tetrakis-(triphenylphosphine)palladium is used successfully as catalyst. The (E)-configuration of the olefin is retained, as judged by the value of the vicinal coupling constant.

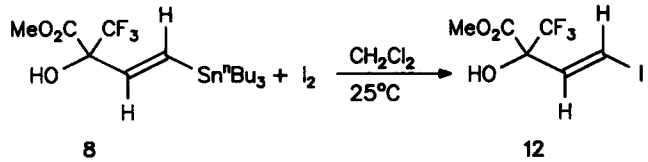
Iododestannation [13] of **8** gives the corresponding hydroxyacid **12** with a vinyl iodide side chain. Again, the (E)-configuration is retained.

Cobalt in the Side Chain

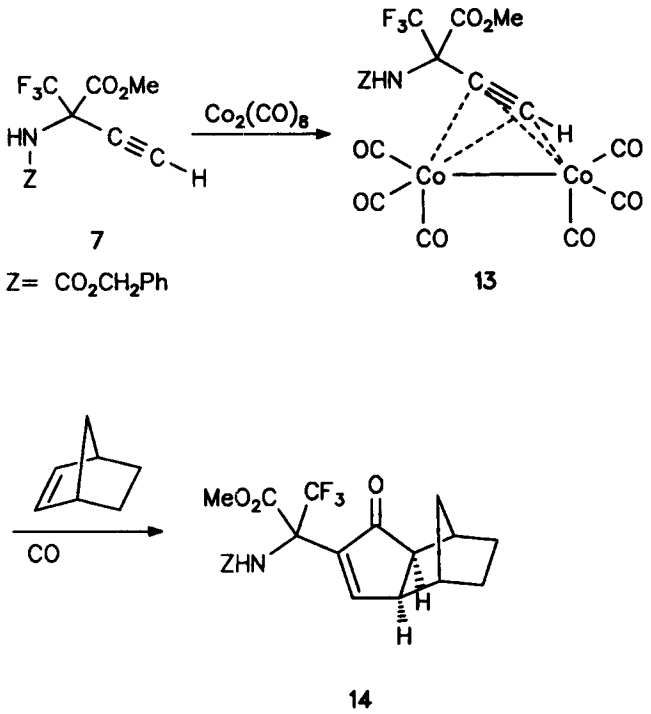
The alkyne side chain of the aminoacid derivative **7** reacts with dicobalt octacarbonyl to give 3,4-η^2-[methyl 2-(benzyloxycarbonylamino)-2-trifluoromethylbut-3-ynoate]-hexacarbonyldicobalt **13**.

Cobalt carbonyl complexes of this type are well-known as important building blocks for the regio- and stereoselective synthesis of cyclopentenones. Application of the Pauson-Khand protocol [14] to the stable racemic cobalt complex **13** (reaction with olefins, e.g., norbornene) gives exclusively a diastereoisomeric mixture of a cyclopentenone substituted α-trifluoromethyl aminoacid derivative **14** in good yields. In general, terminal alkynes give 2-substituted cyclopentenones.

The presence of the vinyl ketone moiety is proven by the ^{13}C NMR absorptions at δ = 208.6/208.1, 137.2/137.9, and 166.9/166.5, respectively.



SCHEME 4



SCHEME 5

The complete assignment of the hydrogen and carbon atoms can be done *via* COSY and C,H-correlation experiments. The exo-orientation of the cyclopentenone ring toward the norbornane substructure in **14** is proven by a NOESY experiment.

EXPERIMENTAL

For chromatography, silica gel 60 (63–200 μm, Merck) or neutral alumina (63–200 μm, Merck) was used, and, for flash chromatography, silica gel 60 (30–63 μm, Riedel-de Haën) was used. Chloroform, hexanes, and ethyl acetate were distilled over calcium chloride; ether, tetrahydrofuran, hexanes, benzene, and toluene were dried over sodium or sodium benzophenone ketyl under nitrogen.

For distillations, a "Spaltrohr" column (Fischer, Bonn) or a "Kugelrohr" oven (Büchi GKR-50) was used.

Melting points (not corrected) were determined using a Tottoli apparatus (BÜCHI SMP-20); elemental microanalyses were carried out with a Heraeus CHN-Elemental Analyzer. The IR spectra were recorded using Perkin-Elmer 157 G or 257 spectrophotometers; ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded with a BRUKER AM 360 spectrometer at 360, 90, and 339 MHz, respectively. ^{19}F NMR spectra were also obtained using a JEOL FX 90 Q spectrometer (84 MHz) and BRUKER AC 250 (235 MHz). As reference standards, TMS was used for ^{1}H and ^{13}C NMR spectra (internal) and trifluoroacetic acid for ^{19}F NMR spectra (external). The ^{13}C NMR spectra were recorded with ^{1}H decoupling. Signals downfield to the reference standards have positive shift values quoted in parts per million; coupling constants are quoted in hertz. Mass spectra were recorded with electron impact ionization (EI, 70 eV) with a Varian MAT CH5 instrument.

Methyl N-Benzyloxycarbonyl-2-trifluoromethyl-3-trimethylsilylalaninate **4**

A solution of the acyl imine **2** (10 mmol, 2.89 g) in abs ether (50 mL) was added at −70°C to a 1 M solution of trimethylsilylmethylmagnesium chloride in ether (10 mmol, 10 mL) under a nitrogen atmosphere. The reaction mixture was allowed to warm slowly to room temperature and mixed with ice water (100 mL). pH 1 was adjusted with 1N HCl. The layers were separated and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layer was dried over magnesium sulfate, filtered, and evaporated. The residue was distilled *in vacuo* using a Kugelrohr apparatus to give 3.66 g of *methyl N-benzyloxycarbonyl-2-trifluoromethyl-3-trimethylsilylalaninate* **4** (97%) as a colorless oil. $C_{16}H_{22}F_3NO_4Si$ [377.44]. Calcd: C, 50.92 H, 5.88 N, 3.71. Found: C, 51.52 H, 6.02 N, 3.79. IR (film): ν = 3410; 1745; 1510 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = −0.20 (s, 9H, $Si(CH_3)_3$); 1.24 (d, 1H, $^{2}J(^{1}H^{1}H)$ = 15.0, *H*C-3); 2.12 (d, 1H, $^{2}J(^{1}H^{1}H)$ = 15.0, *H*C-3); 3.53 (s, 3H, CO_2CH_3); 5.04 (s, 2H, $C_6H_5CH_2O$); 5.82 (s, br, 1H, N*H*), 7.34 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$): δ = −1.3 ($Si(CH_3)_3$); 17.4 (*C*-3); 53.6 (CO_2CH_3); 64.5 (q, $^{2}J(^{13}C^{19}F)$ = 29.0, *C*-2); 67.1 ($C_6H_5CH_2O$); 124.5 (q, $^{1}J(^{13}C^{19}F)$ = 288.0, CF_3); 153.9 (OCONH); 168.1 (*C*-1); 128.3, 128.4, 128.6 (CH_{ar}); 136.0 (C_{ar}). ^{19}F NMR ($CDCl_3$): δ = 4.0 (s). MS: *m/e* = 377 $[M]^+$; 362 $[M - CH_3]^+$; 318 $[362 - CO_2]^+$; 91 $[C_7H_7]^+$; 73 $[Si(CH_3)_3]^+$.

Methyl 2-Trifluoromethyl-2-trimethylsilyloxybut-3-ynoate **6**

A solution of triethylamine (20 mmol, 2.03 g) in abs ether (20 mL) was added to a solution of methyl 2-hydroxy-2-trifluoromethylbut-3-ynoate **5** [11] (10 mmol, 1.82 g) and trimethylchlorosilane (20 mmol, 2.20 g) in abs ether (50 mL) at 0°C with stirring. Stirring was continued at room temperature for 24 hours. Then the reaction mixture was hydrolyzed with ice water and extracted with ether (3 × 50 mL). The combined organic layers were dried over magnesium sulfate and evaporated *in vacuo*. The residue was distilled using a Spaltrohr column to give 2.01 g of *methyl 2-trifluoromethyl-2-trimethylsilyloxybut-3-ynoate* **6** (79%). Mp: 40°C; bp: 130°C/10 mbar. $C_9H_{13}F_3O_3Si$ [254.28]. Calcd: C, 42.51 H, 5.15. Found: C, 42.34 H, 5.23. IR (film): ν = 3265; 2130; 1760 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ =

0.20 (s, 9H, $Si(CH_3)_3$); 2.74 (s, 1H, *HC*-4); 3.79 (s, 3H, CO_2CH_3). ^{13}C NMR ($CDCl_3$): δ = −0.9 ($Si(CH_3)_3$); 52.1 (CO_2CH_3); 71.3 (q, $^2J(^{13}C^{19}F)$ = 33.8, *C*-2); 74.3 (broad, *C*-3); 76.1 (*C*-4); 120.0 (q, $^1J(^{13}C^{19}F)$ = 286.3, CF_3); 163.7 (*C*-1). ^{19}F NMR ($CDCl_3$): δ = −0.2 (s). MS: *m/e* = 239 $[M - CH_3]^+$; 211 $[239 - CO]^+$; 195 $[M - CO_2CH_3]^+$; 89 $[(CH_3)_3SiO]^+$; 73 $[(CH_3)_3Si]^+$.

Methyl (E)-2-Hydroxy-4-tri-n-butylstannyl-2-trifluoromethylbut-3-enoate **8**

Tri-*n*-butylstannane (5 mmol, 1.45 g) was added to a mixture of methyl 2-hydroxy-2-trifluoromethylbut-3-ynoate **5** [11] (5 mmol, 0.91 g) and azobisisobutyronitrile (AIBN) (0.5 mmol, 0.08 g). The mixture was heated to 60°C for 3 hours; the reaction progress was monitored by ^{19}F NMR. Chromatography (eluent chloroform/hexanes 1:5) gave 1.3 g *methyl (E)-2-hydroxy-4-tri-n-butylstannyl-2-trifluoromethylbut-3-enoate* **8** (55%) as a colorless oil. $C_{18}H_{33}F_3O_3Sn$ [473.14]. Calcd: C, 45.69; H, 7.03. Found: C, 46.05; H, 6.55. IR (film): ν = 3500; 1740; 1600 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.86–0.96 (m, 15H, $Sn(CH_2CH_2CH_2CH_3)_3$. $Sn(CH_2CH_2CH_2CH_3)_3$); 1.32 (m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$); 1.49 (m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$); 3.91 (s, 3H, CO_2CH_3); 3.94 (s, 1H, O*H*); 6.14 (d, $^3J(^1H^1H)$ = 19.0, satellites $^2J(^1H^{119/117}Sn)$ = 57.2, 1H, *H*C-4); 6.91 (d, $^3J(^1H^1H)$ = 19.0, satellites $^3J(^1H^{119/117}Sn$ = 61.3/59.9, *H*C-3). ^{13}C NMR ($CDCl_3$): δ = 9.7 (satellites $^1J(^{13}C^{119/117}Sn)$ = 349.6/333.0, $Sn(CH_2CH_2CH_2CH_3)_3$); 13.7 ($Sn(CH_2CH_2CH_2CH_3)_3$); 27.2 (satellites $^2J(^{13}C^{119/117}Sn)$ = 51.7, $Sn(CH_2CH_2CH_2CH_3)_3$); 29.0 (satellites $^3J(^{13}C^{119/117}Sn)$ = 20.7, $Sn(CH_2CH_2CH_2CH_3)_3$); 54.4 (CO_2CH_3); 78.2 (q, $^2J(^{13}C^{19}F)$ = 29.6, *C*-2); 122.8 (q, $^1J(^{13}C^{19}F)$ = 286.3, CF_3); 135.8 (satellites $^2J(^{13}C^{119/117}Sn)$ = 17.8/14.6, *C*-3); 136.5 (satellites $^1J(^{13}C^{119/117}Sn)$ = 329.8/313.6, *C*-4); 169.5 (*C*-1). ^{19}F NMR ($CDCl_3$): δ = 0.8 (s). MS: *m/e* = 418/416/414 $[M - C_4H_8]^+$; 361/359/357 [418/416/414 − $C_4H_9]^+$; 305/303/301 [361/359/357 − $C_4H_8]^+$; 177/175/173 $[SnC_4H_9]^+$.

Methyl (E)-4-Tri-n-butylstannyl-2-trifluoromethyl-2-trimethylsilyloxybut-3-enoate **9**

Tri-*n*-butylstannane (20 mmol, 5.82 g) was added to a mixture of methyl 2-trifluoromethyl-2-trimethylsilyloxybut-3-ynoate **6** (20 mmol, 5.09 g) and azobisisobutyronitrile (AIBN) (2.0 mmol, 0.33 g). The mixture was heated to 60°C for 3 hours; the reaction progress was monitored by ^{19}F NMR. Chromatography (eluent chloroform/hexanes 1:5) and subsequent distillation using a Spaltrohr column gave 1.3 g of *methyl (E)-2-hydroxy-4-tri-n-butylstannyl-2-trifluoromethyl-2-trimethylsilyloxybut-3-enoate* **9** (66%) as a colorless oil. Bp: 120°C/0.5 mbar. $C_{21}H_{41}F_3O_3SiSn$ [545.33]. Calcd: C, 46.25 H, 7.58. Found: C, 46.24; H, 7.62. IR (film): ν = 1760; 1465; 1440 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.20 (s, 9H, $Si(CH_3)_3$); 0.89 (t, $^3J(^1H^1H)$ = 7.2, 9H, $Sn(CH_2CH_2CH_2CH_3)_3$; 0.93 (m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$); 1.30 (m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$); 1.49 (m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$); 3.83 (s, 3H, CO_2CH_3); 6.15 (d, $^3J(^1H^1H)$ = 19.0, satellites, $^2J(^1H^{119/117}Sn)$ = 56.8, 1H, *H*C-4); 6.69 (d, $^3J(^1H^1H)$ = 19.0, satellites $^3J(^1H^{119/117}Sn)$ = 61.8, 1H, *H*C-3). ^{13}C NMR ($CDCl_3$): δ = 1.7 ($Si(CH_3)_3$); 9.7 (satellites $^1J(^{13}C^{119/117}Sn)$ = 348.7/332.8, $Sn(CH_2CH_2CH_2CH_3)_3$); 13.6 ($Sn(CH_2CH_2CH_2CH_3)_3$); 27.1 (satellites $^2J(^{13}C^{119/117}Sn)$ = 53.4, $Sn(CH_2CH_2CH_2CH_3)_3$); 29.0 (satellites $^3J(^{13}C^{119/117}Sn)$ = 21.2, $Sn(CH_2CH_2CH_2CH_3)_3$); 52.9 (CO_2CH_3); 81.8 (q, $^2J(^{13}C^{19}F)$ = 29.2, *C*-2); 122.8 (q, $^1J(^{13}C^{19}F)$ = 287.0, CF_3); 136.0 (satellites $^1J(^{13}C^{119/117}Sn)$ = 333.0, *C*-4); 138.6 (satellites $^2J(^{13}C^{119/117}Sn)$ = 6.9, *C*-3); 168.4 (*C*-1). ^{19}F NMR ($CDCl_3$): δ = 0.4 (s). MS: *m/e* = 489/487/485 $[M - C_4H_9]^+$; 433/431/429 [489/487/485 − $C_4H_8]^+$; 177/175/173 [Sn-$C_4H_9]^+$; 73 $[Si(CH_3)_3]^+$.

Methyl (E)-2-Benzyloxycarbonylamino-4-tri-n-butylstannyl-2-trifluoromethylbut-3-enoate **10**

Tri-*n*-butylstannane (10 mmol, 2.91 g) was added to a solution of methyl 2-benzyloxycarbonylamino-2-trifluoromethylbut-3-ynoate **7** [9] (10 mmol, 3.15 g) and azobisisobutyronitrile (AIBN) (1.0 mmol, 0.16 g) in abs benzene (10 mL). The mixture was heated to 60°C for 3 hours: the reaction progress was monitored by ^{19}F NMR. Flash chromatography (eluent ethyl acetate/hexanes 1:50) gave 2.84 g *methyl (E)-2-benzyloxycarbonylamino-4-tri-n-butylstannyl-2-trifluoromethylbut-3-enoate* **8** (47%) as a colorless oil. $C_{26}H_{40}F_3NO_4Sn$ [606.29]. Calcd: C, 51.51; H, 6.65; N, 2.31. Found: C, 50.98; H, 6.98; N, 2.15. IR (film): ν = 3320; 1750–1720; 1500 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.88 (t, $^3J(^1H^1H)$ = 7.3, 9H, $Sn(CH_2CH_2CH_2CH_3)_3$); 0.94 (t, $^3J(^1H^1H)$ = 7.8, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$); 1.29 (m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$); 1.47 (m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$); 3.77 (s, broad, CO_2CH_3); 5.11 (s, 2H, $C_6H_5CH_2O$); 5.46 (s, broad, 1H, N*H*); 6.14 (d, $^3J(^1H^1H)$ = 19.2, satellites $^2J(^1H^{119/117}Sn)$ = 55.6, 1H, *H*C-4); 6.64 (d, $^3J(^1H^1H)$ = 19.2, satellites $^2J(^1H^{119/117}Sn)$ = 52.8, 1H, *H*C-3); 7.35 (m, 5H, H_{ar}). ^{13}C NMR ($CDCl_3$, assignment supported by DEPT-135): δ = 9.8 (satellites $^1J(^{13}C^{119/117}Sn)$ = 349.7/334.3, $Sn(CH_2CH_2CH_2CH_3)_3$); 13.7 ($Sn(CH_2CH_2CH_2CH_3)_3$); 27.2 (satellites $^2J(^{13}C^{119/117}Sn)$ = 54.6, $Sn(CH_2CH_2CH_2CH_3)_3$); 28.9 (satellites $^3J(^{13}C^{119/117}Sn)$ = 21.4, $Sn(CH_2CH_2CH_2CH_3)_3$); 53.3 (CO_2CH_3); 67.2 (q, $^2J(^{13}C^{19}F)$ = 27.4, *C*-2); 67.6 ($C_6H_5CH_2O$); 123.4 (q, $^1J(^{13}C^{19}F)$ = 286.2, CF_3); 135.2 (broad, *C*-3); 136.8 (satellites $^1J(^{13}C^{119/117}Sn)$ = 315.9, *C*-4); 154.3 (OCONH); 165.6 (*C*-1); 128.4, 128.5, 128.6, 135.8 (C_{ar}). ^{19}F NMR ($CDCl_3$): δ = 3.6 (s). MS: *m/e* = 550/548/546 $[M - C_4H_9]^+$; 442/440/438 [550/548/546 − $C_6H_5CH_2OH]^+$; 386/384/382 [442/440/438 − $C_4H_8]^+$; 330/328/326 [386/384/382 − $C_4H_8]^+$; 108

$[C_6H_5CH_2OH]^+$; 107 $[C_6H_5CH_2O]^+$; 91 $[C_7H_7]^+$; 79 $[C_6H_7]^+$; 77 $[C_6H_5]^+$; 59 $[CO_2CH_3]^+$.

Palladium Catalyzed Cross-Coupling of Methyl (E)-4-Tri-n-butylstannyl-2-trifluoromethyl-2-trimethylsilyloxybut-3-enoate **9** *with Acid Chlorides—General Procedure*

A solution of the vinyl stannane **9** (5 mmol, 2.73 g), tetrakis(triphenylphosphine)palladium (2.5 μmol, 3 mg), and an acid chloride (5 mmol) in abs tetrahydrofuran (10 mL) was refluxed for 6–8 hours. The reaction progress was monitored by ^{19}F NMR. After cooling and evaporation of the solvent, water (5 mL) was added and the mixture was extracted with ether (3 × 20 mL). A saturated solution (10 mL) of potassium fluoride in ethanol was added to the combined organic layers to precipitate tri-*n*-butyltin fluoride. After filtration, the mother liquor was evaporated *in vacuo* and the residue was distilled using a Spaltrohr column. Alternatively, the crude reaction mixture was evaporated and filtered through silica gel (eluent ethyl acetate/hexanes 1:50), and the eluate was purified by flash chromatography (eluent ethyl acetate/hexanes 1:10) or distillation with a Spaltrohr column.

Methyl 2-Trifluoromethyl-2-trimethylsilyloxy-5-oxohex-3-enoate **11a**

Yield: 1.01 g (68%). Bp: 150°C/25 mbar. $C_{11}H_{17}F_3O_4Si$ [298.34]. Calcd: C, 44.29; H, 5.74. Found: C, 44.16; H, 6.01. IR (film): ν = 1765; 1710; 1690; 1640 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.23 (s, 9H, $Si(CH_3)_3$); 2.33 (s, 3H, *H*C-6); 3.88 (s, 3H, CO_2CH_3); 6.52 (d, $^3J(^1H^1H)$ = 15.6, *H*C-3); 6.90 (d, $^3J(^1H^1H)$ = 15.6, *H*C-4). ^{13}C NMR ($CDCl_3$): δ = 1.6 ($Si(CH_3)_3$); 27.9 (*C*-6); 53.8 (CO_2CH_3); 80.3 (q, $^2J(^{13}C^{19}F)$ = 30.5, *C*-2); 122.2 (q, $^1J(^{13}C^{19}F)$ = 287.9, CF_3); 133.8 (*C*-3); 138.3 (*C*-4); 167.1 (*C*-1); 196.9 (*C*-5). ^{19}F NMR ($CDCl_3$): δ = 2.0 (s). MS: *m/e* = 298 $[M]^+$; 283 $[M - CH_3]^+$; 255 $[283 - CO]^+$; 239 $[M - CO_2CH_3]^+$; 89 $[(CH_3)_3SiO]^+$; 73 $[(CH_3)_3Si]^+$; 59 $[CO_2CH_3]^+$.

Methyl 5-Cyclopropyl-2-trifluoromethyl-2-trimethylsilyloxy-5-oxopent-3-enoate **11b**

Yield: 1.23 g (76%). Bp: 153°C/16 mbar. $C_{13}H_{19}F_3O_4Si$ [324.37]. Calcd: C, 48.13; H, 5.90. Found: C, 47.76, H, 6.43. IR (film): ν = 1765; 1690; 1675; 1640 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.24 (s, 9H, $Si(CH_3)_3$); 1.00 (m, 2H, cyclopropyl); 1.14 (m, 2H, cyclopropyl); 2.16 (m, 1H, cyclopropyl); 3.87 (s, 3H, CO_2CH_3); 6.67 (d, 1H, $^3J(^1H^1H)$ = 15.5, *H*C-3); 6.95 (d, $^3J(^1H^1H)$ = 15.5, *H*C-4). ^{13}C NMR (assignment supported by DEPT-135): δ = 1.62 ($Si(CH_3)_3$); 12.0 (cyclopropyl CH_2); 12.1 (cyclopropyl CH_2); 20.0 (cyclopropyl *C*H); 53.8 (CO_2CH_3); 80.3 (q, $^2J(^{13}C^{19}F)$ = 30.5, *C*-2); 122.6 (q, $^1J(^{13}C^{19}F)$ = 287.8, CF_3); 133.0 (*C*-3); 136.9 (*C*-4); 167.1 (*C*-1); 199.1 (*C*-5). ^{19}F NMR ($CDCl_3$): δ = 1.4 (s). MS: *m/e* = 309 $[M]^+$; 269 $[M - C_3H_4]^+$; 265 $[M - CO_2CH_3]^+$; 89 $[(CH_3)_3SiO]^+$; 73 $[(CH_3)_3Si]^+$; 69 $[CF_3/C_3H_5CO]^+$.

Methyl 6-[2',2'-Bis(trifluoromethyl)-5'-oxo-1',3'-oxazolidin-4'-Yl]-2-trifluoromethyl-2-trimethylsilyloxy-5-oxohex-3-enoate **11c**

Diastereoisomeric mixture; yield: 1.17 g (45%). $C_{16}H_{18}F_9NO_6Si$ [519.39]. Calcd: C, 37.00; H, 3.49; N, 2.70. Found: C, 37.97; H, 3.70; N, 2.64. IR ($CHCl_3$): ν = 3410; 1835; 1760; 1710; 1690; 1645 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.23 (s, 9H, $Si(CH_3)_3$); 2.97 (dd, $^2J(^1H^1H)$ = 18.3, $^3J(^1H^1H)$ = 10.1, 1H, *H*C-6; D1); 2.98 (dd, 1H, $^2J(^1H^1H)$ = 18.3, $^3J(^1H^1H)$ = 10.1, 1H, *H*C-6, D2); 3.32 (dd, $^2J(^1H^1H)$ = 18.3, $^3J(^1H^1H)$ = 2.2, 1H, *H*C-6, D2); 3.33 (dd, $^2J(^1H^1H)$ = 18.3, $^3J(^1H^1H)$ = 2.2, 1H, *H*C-6, D1); 3.67 (d, $^3J(^1H^1H)$ = 6.9, 1H, N*H*, D2); 3.68 (d, $^3J(^1H^1H)$ = 6.2, 1H, N*H*, D1); 3.88 (s, 3H, CO_2CH_3); 4.43 (2x ddd, $^3J(^1H^1H)$ = 10.1, $^3J(^1H^1H)$ = 6.9, $^3J(^1H^1H)$ = 2.2, D1; $^3J(^1H^1H)$ = 10.1, $^3J(^1H^1H)$ = 6.2, $^3J(^1H^1H)$ = 2.2, D2, 1H, *H*C-4'); 6.58 (d, $^3J(^1H^1H)$ = 15.7, 1H, *H*C-3); 7.00 (d, $^3J(^1H^1H)$ = 15.7, 1H, *H*C-4). ^{13}C NMR ($CDCl_3$): δ = 1.6 ($Si(CH_3)_3$); 44.5 (*C*-6); 50.5 (*C*-4'); 54.0 (CO_2CH_3); 80.2 (q, $^2J(^{13}C^{19}F)$ = 30.6, *C*-2); 87.8 (q, $^2J(^{13}C^{19}F)$ = 33.6, *C*-2', D1); 88.6 (q, $^2J(^{13}C^{19}F)$ = 33.6, *C*-2', D2); 120.8 (q, $^1J(^{13}C^{19}F)$ = 285.5, CF_3); 121.3 (q, $^1J(^{13}C^{19}F)$ = 288.6, CF_3); 122.4 (q, $^1J(^{13}C^{19}F$ = 288.1, CF_3); 131.6 (*C*-3); 140.2 (*C*-4); 166.6 (*C*-1); 170.5 (*C*-5); 195.3 (*C*-5). ^{19}F NMR ($CDCl_3$): δ = −3.35 (q, $^4J(^{19}F^{19}F)$ = 8.6, CF_3C-2', D1) and −3.34 (q, $^4J(^{19}F^{19}F)$ = 8.6, CF_3C-2', D2), total 3F; −2.13 (q, $^4J(^{19}F^{19}F)$ = 8.6, CF_3C-2', 3F); 1.71 (s, 3F, CF_3 C-2). MS: *m/e* = 519 $[M]^+$; 504 $[M - CH_3]^+$; 460 $[M - CO_2CH_3]^+$; 429 $[M - (CH_3)_3SiOH]^+$; 283 $[(CH_3)_3SiO(CF_3)C(CO_2CH_3)CH{=}CHCO]^+$; 255 $[283 - CO)]^+$; 89 $[(CH_3)_3SiO]^+$; 73 $[(CH_3)_3Si]^+$; 59 $[CO_2CH_3]^+$.

Methyl (E)-2-Hydroxy-4-iodo-2-trifluoromethylbut-3-enoate **12**

A solution of iodine (5 mmol, 1.27 g) in abs dichloromethane (20 mL) was added dropwise at room temperature to a vigorously stirred solution of the vinyl stannane **8** (5 mmol, 2.37 g) in abs dichloromethane (10 mL). The mixture was evaporated *in vacuo*, and the residue was purified by flash chromatography (eluent ethyl acetate/hexanes 1:5) and subsequent distillation in a Kugelrohr oven to give 0.67 g (43%) of methyl (E)-2-hydroxy-4-iodo-2-trifluoromethylbut-3-enoate **12**. Bp: 130°C/15 mbar. $C_6H_6F_3O_3I$ [310.01]. Calcd: C, 23.25; H, 1.95. Found: C, 23.62; H, 2.03. IR (film): ν = 3490; 1750; 1620 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.89 (s, 3H, CO_2CH_3); 4.02 (s, 1H, O*H*); 6.75 (d, $^3J(^1H^1H)$ = 14.7, *H*C-3); 7.08 (d, $^3J(^1H^1H)$ = 14.7, *H*C-4). ^{13}C NMR ($CDCl_3$): δ = 54.7 (CO_2CH_3); 78.7 (q, $^2J(^{13}C^{19}F)$ = 30.8, *C*-2); 85.1 (*C*-4); 121.6 (q, $^1J(^{13}C^{19}F)$ = 286.5, CF_3); 134.8 (q, $^3J(^{13}C^{19}F)$ = 1.0, *C*-3); 167.7 (*C*-1). ^{19}F NMR

($CDCl_3$): δ = −0.6 (s). MS: *m/e* = 310 $[M]^+$; 251 $[M - CO_2CH_3]^+$; 183 $[M - I]^+$; 181 $[M - HCF_3]^+$; 127 $[I]^+$.

3,4-η²-[Methyl 2-(Benzyloxycarbonylamino)-2-trifluoromethylbut-3-ynoate]-Hexacarbonyldicobalt **13**

Methyl 2-benzyloxycarbonylamino-2-trifluoromethylbut-3-ynoate **7** (10 mmol, 3.15 g) was added to a solution of octacarbonyldicobalt (10 mmol, 3.42 g) in hexanes (40 mL). The mixture was stirred under a nitrogen atmosphere at room temperature for 5 hours. The solvent was evaporated *in vacuo* after the evolution of carbon monoxide had ceased, and the residue was purified chromatographically on neutral alumina (gradient elution from hexanes to chloroform) to give the cobalt complex **13** as a red oil. $C_{20}H_{12}F_3NO_{10}Co_2$ [601.18]. IR (film): ν = 2130; 2100; 2085; 2065; 2060; 2040; 2035; 1760–1740; 1500 cm^{-1}. ^{13}C NMR ($CDCl_3$): δ = 53.4 (CO_2CH_3); 66.6 (q, $^2J(^{13}C^{19}F)$ = 32, *C*-2); 67.8 ($C_6H_5CH_2O$); 85.1 (*C*-3); 123.2 (q, $^1J(^{13}C^{19}F)$ = 285, CF_3); 153.8 (OCONH); 165.3 (*C*-1); 198.0 (*C*O); 128–129 (CH_{ar}, not resolved); 135.6 (C_{ar}). *C*-4 is hidden below the $CDCl_3$ signal. ^{19}F NMR (toluene): δ = 4.3 (s, broad). MS: *m/e* = 545 $[M - 2\ CO]^+$; 489 $[545 - 2\ CO]^+$; 461 $[489 - CO]^+$; 433 $[461 - CO]^+$; 91 $[C_6H_5CH_2]^+$.

Methyl N-Benzyloxycarbonyl-3,3,3-trifluoro-2-(exo-3'-oxotricyclo[5.2.1.0$^{2',6'}$]dec-4'-en-4'-Yl)-alaninate **14**

The crude product **13** was dissolved in abs toluene (50 mL); norbornene (20 mmol, 1.88 g) was added, and the mixture was heated to 100°C (ext. temperature) under a carbon monoxide atmosphere. The reaction progress was monitored by ^{19}F NMR. The solvent was evaporated *in vacuo*, and the residue was chromatographed on flash silica gel (eluent ethyl acetate/hexanes 1:5) to give 2.36 g (54%) of *methyl N-benzyloxy-carbonyl-3,3,3-trifluoro-2-(exo-3'-oxotricyclo[5.2.1.0$^{2',6'}$]dec-4'-en-4'-yl)-alaninate* **14** as a diasteroisomeric mixture. $C_{22}H_{22}F_3NO_5$ [437.42]. Calcd: C, 60.41; H, 5.07; N, 3.20. Found: C, 60.03; H, 5.23; N, 3.31. IR (film): ν = 3390; 3340; 1760–1700; 1510; 1460 cm^{-1}. ^1H NMR ($CDCl_3$, assignment based on DQF-COSY): δ = 0.95–1.07 (m, 2H, *H*C-10'); 1.24–1.36 (m, 2H, *H*C-8', *H*C-9'); 1.53–1.73 (m, 2H, *H*C-8', *H*C-9'); 2.26–2.28 (m, 2H, *H*C-2', *H*C-7'); 2.38–2.42 (m, 1H, *H*C-1'); 2.70–2.72 (m, 1H, *H*C-6'); 3.78 (s, broad, 3H, CO_2CH_3); 5.00–5.12 (m, 2H, $C_6H_5CH_2O$); 7.30–7.35 (m, 5H, H_{ar}); 7.60 (m, 2H, N*H*, *H*C-5'). ^{13}C NMR ($CDCl_3$, assignment based on CH-correlation and DEPT-135): δ = 28.2/28.4 (*C*-9'); 29.1 (*C*-8'); 31.2 (*C*-10'); 38.0/38.3 (*C*-7'); 39.5 (*C*-1'); 48.6/48.7 (*C*-6'); 53.9/54.2 (*C*-2'); 63.7/64.0 (q/q, $^2J(^{13}C^{19}F)$ = 30.1/30.1, *C*-2); 67.2 ($C_6H_5CH_2O$); 123.4/123.3 (q, $^1J(^{13}C^{19}F)$ = 287.9/287.9, CF_3); 137.2/137.9 (*C*-4'); 153.9/154.0 (OCONH); 165.4 (*C*-1); 165.5/166.9 (*C*-5'); 208.1/208.6 (*C*-3'); 128.0, 128.1, 128.2, 128.2, 128.5, 128.5, 135.8, 135.9 (C_{ar}). ^{19}F NMR ($CDCl_3$): δ = 4.7 (s). MS: *m/e* = 437 $[M]^+$; 330 $[M-C_6H_5CH_2O]^+$; 302 $[330\text{-}CO]^+$; 84 $[C_6H_{12}]^+$.

ACKNOWLEDGMENTS

We thank Volkswagen-Stiftung, Hannover, and HOECHST AG, Frankfurt, Main, for generous financial support.

REFERENCES

[1] Synthesis of α-Trifluoromethyl Substituted Amino Acids, Part 16, Part 15: K. Burger, K. Mütze, W. Hollweck, B. Koksch, P. Kuhl, H.-D. Jakubke, J. Riede, A. Schier, *J. Prakt. Chem./Chem.-Ztg.*, in press.
[2] (a) N. Sewald: Ph.D. Thesis, TU München, 1991; (b) K. Gaa: Ph.D. Thesis, TU München, 1990.
[3] C. Walsh, *Tetrahedron, 38*, 1982, 871.
[4] J. T. Welch, *Tetrahedron, 43*, 1987, 3123.
[5] K. Burger, C. Schierlinger, *Tetrahedron Lett., 33*, 1992, 193.
[6] J. K. Coward, J. J. McGuire, J. Galivan: The Influence of Fluoro Substituents on the Reactivity of Carboxylic Acids, Amides, and Peptides in Enzyme-Catalyzed Reactions, in J. T. Welch (ed): *Selective Fluorination in Organic and Bioorganic Chemistry*, ACS Symposium Series 456, Washington, ch. 14 (1991).
[7] H. El Amouri, A. Vessières, D. Vichard, S. Top, M. Gruselle, G. Jaouen, *J. Med. Chem., 35*, 1992, 3130.
[8] K. Schlögl, *Monatsh. Chem., 88*, 1957, 601.
[9] K. Burger, E. Höß, K. Gaa, N. Sewald, C. Schierlinger, *Z. Naturforsch. B: Chem. Sci, 46*, 1991, 361.
[10] K. Burger, N. Sewald, *Synthesis*, 1990, 115.
[11] N. Sewald, K. Burger, *Z. Naturforsch. B: Chem. Sci., 45*, 1990, 871.
[12] J. K. Stille, *Angew. Chem., 98*, 1986, 504: *Angew. Chem. Int. Ed. Engl., 25*, 1986, 508 and literature cited therein.
[13] (a) D. Seyferth, *J. Am. Chem. Soc., 79*, 1957, 2133; (b) S. D. Rosenberg, A. J. Gibbons, H. E. Ramsden, *J. Am. Chem. Soc., 79*, 1957, 2137.
[14] P. L. Pauson, *Tetrahedron, 41*, 1985, 5855.