ELSEVIER

Journal of Fluorine Chemistry 74 (1995) 107–112

JOURNAL OF FLUORINE CHEMISTRY

Implementation of the Dakin–West reaction for the preparation of an α-amino-pentafluoroethyl ketone

Timothy T. Curran

Marion Merrell Dow Research Institute, 2110 E. Galbraith Road, Cincinnati, OH 45215, USA

Received 4 October 1994; accepted 29 December 1994

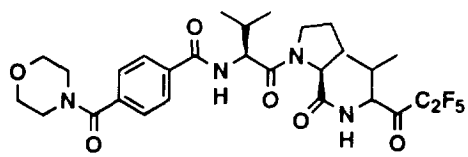
Abstract

We have successfully implemented the Dakin–West reaction to prepare 4-(carbamoyl- or benzoylamino)-5-methyl-1,1,1,2,2-pentafluorohexan-3-one (**3**, **7a** and **7b**). We also isolated and characterized the impurities obtained from this Dakin–West reaction. Although we were successful in the literature-described conversion of **3** to **4**, we have been unsuccessful at benzamide cleavage of **7a** or **7b** under a variety of conditions, presumably owing to the presence of an electrophilic pentafluoroethyl ketone moiety. We illustrated that 5-pentafluoroethyl oxazole **15** can be derived from *N*-benzoyl-pentafluoroethyl ketone **7a** and that oxazole **15** is also resistant to ring opening.

Keywords: Dakin–West reaction; amino-pentafluoroethyl ketone

1. Introduction

MDL 101146 (**1**)



MDL 101146 (**1**) — pentafluoroethyl ketone

is a tripeptidyl pentafluoroethyl ketone and a potent inhibitor of human neutrophil elastase [1]. A particular challenge involved with the large-scale preparation of MDL 101146 is the synthesis of a suitably *N*-protected 4-amino-1,1,1,2,2-pentafluoro-5-methylhexan-3-one, the right-hand piece of **1**. Amine HCl **4** has previously been prepared in two steps from 2-(*t*-butoxycarbonyl)amino-3-methyl-*N*-methoxy-*N*-methylbutanamide **2** as follows: (a) CF_3CF_2Li addition in Et_2O at −70 °C and 0.1 M, and (b) treatment with HCl/EtOAc, Scheme 1 [2]. To avoid the dilute, low-temperature pentafluoroethylation step for scale-up, we were interested in considering alternative methods to prepare amine HCl **4** or a functional equivalent of **4**.

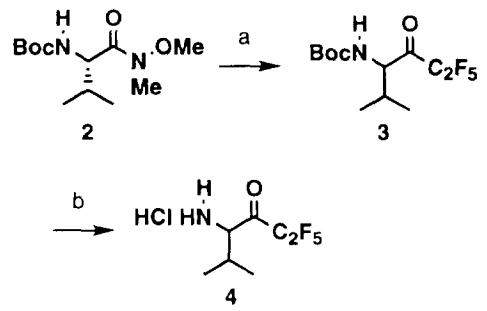
In the literature, the method of choice for the preparation of higher-order α-amino-perfluoroalkyl ketones is the low-temperature addition of R_fLi to esters or activated esters [3]. Other published methods for the preparation of perfluorinated ketones are the Henry reaction [4] followed by nitro reduction and oxidation, the condensation of a R_fZnX [5] or R_fMgX [6] with an aldehyde followed by oxidation, or the condensation of carboxylate dianions with trifluoroacetaldehyde hemiacetal followed by rearrangement and oxidation [7].

The Dakin–West reaction has been successfully implemented for the preparation of perfluoromethyl ketones [8], but to our knowledge has not been fully exploited for the preparation of higher-order perfluoroalkyl ketones. It was our intent to utilize the Dakin–West reaction to prepare amine HCl **4**, a precursor, or a functional equivalent.

2. Results and discussion

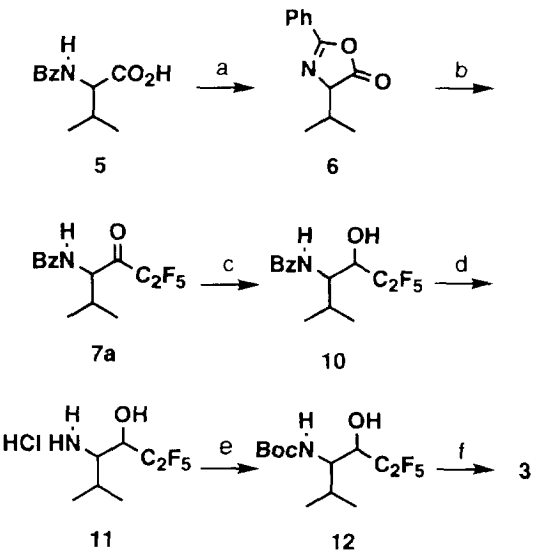
Reaction of commercially available *N*-benzoyl valine (**5**) with Ac_2O at 90–95 °C provided azalactone **6** [9] in quantitative yield as a white solid, Scheme 2. The azalactone **6** was used crude in the subsequent reaction. Azalactone **6** was treated with $(CF_3CF_2CO)_2O$ followed by the dropwise addition of Et_3N (exothermic). The resulting orange solution was warmed at 50–55 °C for 10–12 h, then 4-(dimethylamino)pyridine (DMAP) was added, and heating continued for an additional 10–12 h. The reaction mixture was then allowed to cool to RT. Selective decarboxylation [10] was promoted by treating the reaction mixture with a solution of $(CO_2H)_2$ in tetrahydrofuran (THF) which provided pentafluoroethyl ketone **7a** in 63% overall yield.

SSDI 0022-1139(95)03251-7



a) CF_3CF_2I (3 eq), MeLi•LiBr (3 eq), Et_2O, -70 °C; 64%. b) EtOAc, HCl, 0 °C to RT; quant.

Scheme 1



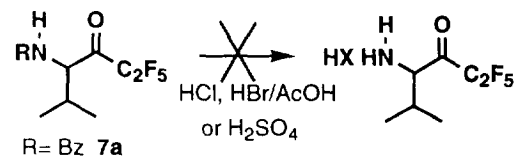
a) Ac_2O, 90-95 °C, 45 min b) 1) $(CF_3CF_2CO)_2O$ (2.5 eq), Et_3N (2.5 eq), 50-55 °C, 10-12 h 2) DMAP (0.4 eq), 50-55 °C, 10-12 h 3) $(CO_2H)_2$ (3.4 eq), THF, RT, 12 h; 63 %, 4-steps c) $NaBH_4$ (0.9 eq), EtOH, 0 °C, 45 min d) HCl (conc.), reflux, 17 h; 82 %, 2-steps e) NaOH (1.2 eq), *t*-BuOH, H_2O, Boc_2O (1 eq), 0 °C to RT, 14 h; 95 % f) 1) $(COCl)_2$ (10 eq), DMSO,CH_2Cl_2, -40 °C 2) Et_3N (20 eq), -40 °C to RT, 5 h; 93 %

Scheme 2.

A major by-product formed during the course of the reaction was determined to be enamindione **8** [11], Fig. 1. This enamindione is an oil and is easily separated from the desired pentafluoroethyl ketone **7a**; nevertheless, it was desirable to try to avoid its formation. Substituting Hünig's base ($EtNi\text{-}Pr_2$) for Et_3N gave two additional impurities; enamindione **9a** and enaminone **9b** as an inseparable 1:2 mixture, Fig. 1. Substituting pyridine for Et_3N gave a 40% yield of the desired **7a**.

Reduction of pentafluoroethyl ketone **7a** with $NaBH_4$ provided crude alcohol **10** in quantitative yield. Benzamide hydrolysis of alcohol **10** with refluxing HCl provided amine HCl **11** in 82% yield. *t*-Butyl carbamate protection under standard conditions [12], di-*t*-butyl pyrocarbonate (Boc_2O), *t*-BuOH and aqueous NaOH, provided *N*-Boc amino alcohol **12** in 95% yield. Swern oxidation [13] of alcohol **12** provided pentafluoroethyl ketone **3** in 93% yield. The conversion of pentafluoroethyl ketone **3** into HCl salt **4** was conducted as previously described [2]. Alternative methods investigated for the conversion of **12** to **3** which provided little or no desired product were tetra-*n*-propylammonium perruthenate (TPAP) [14], PtO_2/O_2 in aqueous dioxane [15], or $Al(Oi\text{-}Pr)_3$ in acetone/PhMe [16]. Additionally, attempts to directly oxidize amine HCl **11** using PtO_2/O_2 in H_2O gave no desired product; starting **11** was isolated quantitatively.

In an attempt to avoid the reduction, deprotection, protection and oxidation steps (conversion of **7a** to **3**), we attempted benzamide cleavage of pentafluoroethyl ketone **7a**. Reaction of **7a** with conc. HCl [17], HBr/HOAc [18] or H_2SO_4 at 0 °C, RT or 55–60 °C failed to provide the desired amine salt, Eq. (1).



R= Bz **7a**
R= *p*-MeO Bz **7b**

In an attempt to facilitate benzamide cleavage under acidic conditions, a more electron-rich amide, (*p*-methoxybenzamidyl) pentafluoroethyl ketone **7b**, Fig. 1, was prepared in a manner similar to **7a**. Subjecting **7b** to the above-mentioned benzamide hydrolysing conditions offered no advantage. Alternatively, attempts to "activate" the amide toward hydrolysis by synthesis of the acetimidate [19], *N*-Boc amide [20] or Vilsmeier activation and reduction [21] failed to provide the desired products, Scheme 3. Starting materials were recovered in all cases; in addition, under the Vilsmeier conditions, monohydro- and dihydro-products **13** and **14** were obtained.

We next attempted to protect the ketone as its ketal under acidic or basic conditions. Reaction of **7a** with catalytic *p*-toluenesulfonic acid (*p*-TsOH) in ethylene glycol with removal of H_2O afforded incomplete conversion to oxazole

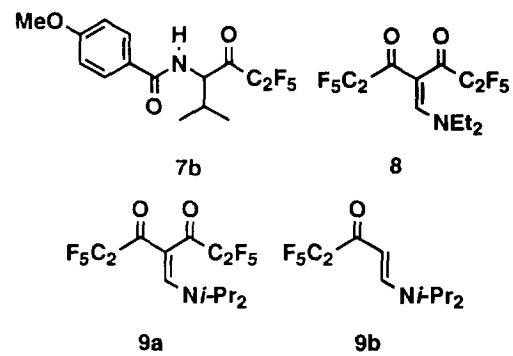
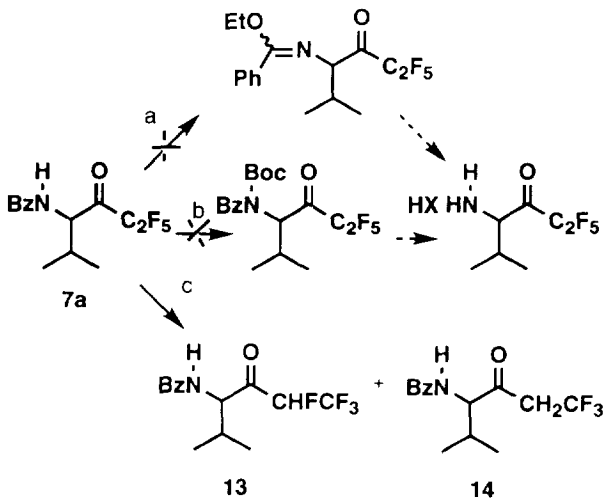


Fig. 1.



a) Et_3OBF_4, CH_2Cl_2, reflux b) Boc_2O (1.2 eq), DMAP (0.4 eq), CH_3CN, RT 24 h c) 1) $POCl_3$ (2 eq), hexane, 65 °C, 50 min 2) Zn (5 eq), EtOH, 65 °C, 1 h

Scheme 3

15, Scheme 4. Other ketalizing conditions which proved to be less successful were $(MeO)_3CH$, $BF_3 \cdot OEt_2$ in MeOH or CH_2Cl_2 [22], and K_2CO_3 with Me_2SO_4 [23]. Both reactions provided more than 90% recovered **7a**. Although a meager 49% yield of the oxazole **15** was obtained, we thought that we could improve this yield by merely driving the equilibrium. Therefore, we investigated the use the oxazole **15** as a masked α-amino-ketone. Treatment of the oxazole **15** with trifluoroacetic acid (TFA)/H_2O [24] or methanolic HCl [25], or reaction of oxazole **15** with benzyl chloroformate followed by treatment with $NaBH_4$ [26], failed to provide the desired products **16** or **17**, Scheme 4.

3. Conclusion

The Dakin–West reaction has been used to prepare 4-(*t*-butyloxycarbonylamino)-5-methyl-1,1,1,2,2-pentafluoro-hexan-3-one (**3**) in six steps and 51% overall yield from *N*-benzoyl valine. It was also shown that 4-(benzoylamino)-5-methyl-1,1,1,2,2-pentafluoro-hexan-3-one (**7a**) can be an intermediate for the preparation of 2-phenyl-4-isopropyl-5-pentafluoroethyloxazole (**15**).

4. Experimental details

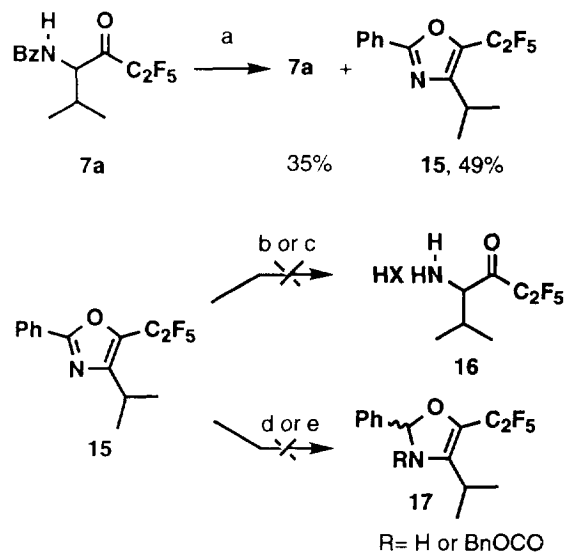
4.1. General

Melting points were obtained on a Thomas Hoover melting-point apparatus and are uncorrected. IR spectra were recorded on a Mattson Galaxy Series 5000 FTIR. NMR spectra were recorded on a Varian XL-300 or Gemini 300 at 300 MHz (^1H), and chemical shifts are recorded in ppm relative to TMS (internal standard), or at 282 MHz (^{19}F) relative to $CFCl_3$ (external standard). Mass spectra were obtained on a Finnigan MAT4600 spectrometer.

4.2. (4R*)-4-(Benzoyl)amino-5-methyl-1,1,1,2,2-pentafluorohexan-3-one (7a)

A solution of *N*-benzoyl valine (**5**, 20.17 g, 92.4 mmol) in Ac_2O (141 ml) was warmed to 90–95 °C (oil bath temperature) for 50 min. The resulting reaction mixture was allowed to cool and evaporated in vacuo (RT to 55 °C, 15 mmHg). Azeotropic removal of trace amounts of AcOH and Ac_2O by addition of hexane and Et_2O (2×20 ml each), followed by evaporation (RT, 15 mmHg) gave azalactone **6** as a white solid, 18.5 g, 99% crude. This was used 'as is' in the next step. ^1H NMR ($CDCl_3$): 8.0 (d, 2H, J=7 Hz), 7.6 (m, 1H), 7.5 (m, 2H), 4.3 (d, 1H, J=4.4 Hz), 2.4 (m, 1H), 1.15 (d, 3H, J=6.8 Hz), 1.0 (d, 3H, J=6.9 Hz). IR (KBr): ν_{max} 2967, 1822, 1655, 1452, 1339, 1325, 1298, 1043, 1020 cm^{-1}. CIMS (CH_4): *m/e* (% relative intensity) 204 ($M+H^+$, 100).

The crude azalactone **6** was treated with $(CF_3CF_2CO)_2O$ (45 ml, 228 mmol, 2.5 eq.), placed in an ice bath, and Et_3N (31 ml, 222 mmol, 2.5 eq.) was added dropwise over 13 min. The resulting reaction mixture was removed from the ice bath and allowed to warm to RT (3 min) then further heated at 50 to 55 °C (oil bath temperature) for 11.5 h. The reaction mixture was allowed to cool, then excess pentafluoropropionic acid and anhydride were evaporated in vacuo (RT, 0.4 mmHg, 2.5 h). The resulting reaction mixture was treated with 4-(dimethylamino)pyridine (DMAP) (3.6 g, 0.4 eq.) and heated at 50 to 55 °C (oil bath temperature) for 11 h.



a) $(CH_2OH)_2$, PhMe, *p*-TsOH (cat), reflux
b) TFA/H_2O, RT c) MeOH/HCl, 50 °C
d) AcOH then $NaBH_4$, RT to 55 °C
e) BnOCOCl, 0 °C then $NaBH_4$

Scheme 4.

The resulting reaction mixture was allowed to cool and was treated with a solution of $(CO_2H)_2$ (114 ml, 1 g/4 ml THF, anhydrous) and stirred for 16 h at RT. The reaction was then diluted with EtOAc (300 ml) and 1/2 saturated $NaHCO_3$ (300 ml).

Phases were separated, and the aqueous phase was extracted with EtOAc (1 × 300 ml). The organic phases were combined and washed sequentially with 1/2 saturated $NaHCO_3$ (300 ml), 5% HCl (300 ml), and then brine (300 ml). The organic phase was then dried ($MgSO_4$), filtered, and the filtrate evaporated in vacuo (RT, 15 mmHg) to provide a reddish solid. Pentane was added (250 ml) and the mixture stirred in an ice bath for 1 h and then filtered. The resulting solid was recrystallized two times from hexane (250 ml) to provide the desired compound **7a** as a slightly yellow solid, 18.4 g, 63% yield: m.p. 92–94 °C. ^{1}H NMR ($CDCl_3$): 7.8 (d, 2H, J = 6.9 Hz), 7.6 (m, 1H), 7.47 (m, 2H), 6.5 (d, 1H, J = 8.1 Hz), 5.4 (m, 1H), 2.45 (m, 1H), 1.1 (d, 3H, J = 6.7 Hz), 0.94 (d, 3H, J = 7.0 Hz); ^{19}F NMR ($CDCl_3$): −82.0 (s), −121.0 (d, J = 296 Hz), −125.7 (d, J = 296). IR (KBr): ν_{max} 3270, 2974, 1753, 1649, 1532, 1491, 1473, 1373, 1331, 1211, 1163, 1149, 1085 cm^{-1}. CIMS (CH_4): m/e (% relative intensity) 324 ($M+H^+$, 100). Anal. Found: C, 51.97; H, 4.22; N, 4.32. $C_{14}H_{14}NO_2F_5$. Calc.: C, 52.02; H, 4.37; N, 4.33.

4.3. 4-(p-Methoxybenzoyl)amino-5-methyl-1,1,1,2,2-pentafluorohexan-3-one (7b)

Compound **7b** was prepared from *N*-(*p*-methoxybenzoyl)valine in a manner analogous to **7a**. From 1.28 g (5.09 mmol) of *N*-(*p*-methoxybenzoyl)valine, 640 mg, 36% of **7b** was obtained. R_f = 0.45, 20% EtOAc/hexane; ^{1}H NMR ($CDCl_3$): 7.8 (d, 2H, J = 9.0 Hz), 7.0 (d, 2H, J = 9.0 Hz), 6.4 (m, 1H), 5.4 (ddd, 1H, J = 1.3, 4.1, 8.6 Hz), 3.9 (s, 3H), 2.4 (m, 1H), 1.1 (d, 3H, J = 6.8 Hz), 0.94 (d, 3H, J = 7.0 Hz). ^{19}F NMR ($CDCl_3$): −82.0 (s), −121.1 (d, J = 296 Hz), −122.8 (d, J = 296 Hz). IR (KBr): ν_{max} 3435, 3275, 2978, 1749, 1643, 1610, 1579, 1529, 1508, 1479, 1446, 1388, 1371, 1329, 1309, 1261, 1211, 1182 cm^{-1}. CIMS (CH_4): m/e (% relative intensity) 354 ($M+H^+$, 100).

4.4. 4-(Diethylamino)methylene-1,1,1,2,2,6,6,7,7,7-decafluoroheptan-3,5-dione (8)

By-product **8** was isolated by chromatography on SiO_2 from the mother liquors of **7a**. R_f = 0.2, 20% EtOAc/hexane. ^{1}H NMR ($CDCl_3$): 7.7 (s, 1H), 3.6 (q, 2H, J = 7.2 Hz), 3.2 (q, 2H, J = 7.2 Hz), 1.4 (t, 3H, J = 7.2 Hz), 1.2 (t, 3H, J = 7.2 Hz). ^{19}F NMR ($CDCl_3$): −81.6 (s), −117.1 (s). IR (neat): ν_{max} 2992, 1689, 1647, 1595, 1471, 1454, 1381, 1356, 1323, 1219, 1194, 1155 cm^{-1}. CIMS (CH_4): m/e (% relative intensity) 392 ($M+H^+$, 100)

4.5. 4-(Diisopropylamino)methylene-1,1,1,2,2,6,6,7,7,7-decafluoroheptan-3,5-dione (9a) and (E)-5-(diisopropyl)amino-1,1,1,2,2-pentafluoropent-4-en-3-one (9b)

By-products **9a** and **9b** were isolated by chromatography on SiO_2 from the mother liquors of **7a** when EtN*i*-Pr_2 was used as base in place of Et_3N in the Dakin–West reaction. A 1:2 mixture of **9a**:**9b** respectively was isolated as an inseparable red oil.

For **9a**: ^{1}H NMR ($CDCl_3$): 7.7 (s, 1H), 3.85 (m, 1H), 3.6 (m, 1H), 1.4 (m, 6H), 1.3 (m, 6H). ^{19}F NMR ($CDCl_3$): −81.7 (s), −117.5 (s). CIMS (CH_4): m/e (% relative intensity) 420 ($M+H^+$, 100).

For **9b**: ^{1}H NMR ($CDCl_3$): 8.0 (d, 1H, J = 12.2 Hz), 5.5 (dd, 1H, J = 1.4, 12.2 Hz), 4.0 (m, 1H), 3.7 (m, 1H), 1.3 (d, 6H, J = 6.8 Hz), 1.28 (d, 6H, J = 6.8 Hz). ^{19}F NMR ($CDCl_3$): −83.0 (s), −123.8 (s). CIMS (CH_4): m/e (% relative intensity) 274 ($M+H^+$, 100).

4.6. (3R*,4R*)- and (3R*,4S*)-4-Amino-5-methyl-1,1,1,2,2-pentafluorohexan-3-ol hydrochloride (11)

A solution of ketone **7a** (18.34 g, 56.78 mmol) in EtOH (absol., 270 ml) was cooled to 0 °C, treated with $NaBH_4$ (2.30 g, 0.86 eq.) in one portion, and stirred for 45 min. The resulting reaction mixture was poured into saturated NH_4Cl (400 ml) and diluted with EtOAc (400 ml). Phases were separated and the aqueous phase extracted with EtOAc (400 ml). The organic phases were combined and washed with brine (2 × 400 ml), dried ($MgSO_4$), filtered, and the filtrate evaporated in vacuo (35 °C, 15 mmHg) to provide an orange oil. The oil was dissolved in 50 ml of 33% EtOAc/hexane and filtered through 20 g of SiO_2 (1 cm × 6.5 cm). The SiO_2 pad was washed with 33% EtOAc/hexane (500 ml) and the filtrate evaporated in vacuo (35 °C, 15 mmHg; RT, 0.4 mmHg) to give **10** as an orange oil, 20 g, which was used in the next step. R_f = 0.18, 20% EtOAc/hexane. ^{1}H NMR ($CDCl_3$): 7.76 (d, 2H, J = 8.2 Hz), 7.6 (m, 1H), 7.5 (m, 2H), 6.3 (d, 1H, J = 8.3 Hz), 5.3 (d, 1H, J = 8.2 Hz), 4.4 (m, 1H), 4.3 (m, 1H), 2.2 (m, 1H), 1.1 (d, 6H, J = 6.7 Hz). ^{19}F NMR ($CDCl_3$): −83.6 (s), −122.5 (d, J = 276 Hz), −131.1 (dd, J = 22, 276 Hz). IR ($CHCl_3$): ν_{max} 3308, 2968, 1647, 1604, 1579, 1524, 1489, 1467, 1373, 1315, 1213, 1196, 1130, 1097, 1011 cm^{-1}. CIMS (CH_4): m/e (% relative intensity) 326 ($M+H^+$, 100).

The crude alcohol **10** was treated with HCl (conc., 240 ml) and warmed at reflux for 14 h. An additional portion of HCl (conc., 50 ml) was added and reflux continued for 3 h. The resulting reaction mixture was allowed to cool, then was evaporated to dryness in vacuo (55 °C, 15 mmHg). The resulting solid was dissolved in H_2O (200 ml) then washed with Et_2O (2 × 200 ml). The aqueous phase was evaporated to dryness in vacuo (55 °C, 15 mmHg; RT, 0.4 mmHg) to provide **11** as a white solid, 11.9 g, 82% yield (two steps): m.p. 171–175 °C. ^{1}H NMR (D_2O): 4.4 (ddd, 1H, J = 2.3, 6.3, 23.1 Hz), 3.4 (app t, 1H, J = 5.9 Hz), 2.2 (m, 1H), 0.95

(d, 3H, J=7.0 Hz), 0.9 (d, 3H, J=6.8 Hz). ^{19}F NMR (D_2O): −83.0 (s), −119.7 (d, J=278 Hz), −131.6 (dd, J=23.1, 278 Hz). IR (KBr): ν_{max} 3246, 3219, 3040, 2980, 2931, 1497, 1223, 1190, 1143, 1101, 1074 cm^{-1}. CIMS (CH_4): m/e (% relative intensity) 222 ($M+H^+$, 100). Anal. Found: C, 32.32; H, 5.06; N, 5.36. $C_7H_{13}NOF_5Cl$. Calc.: C, 32.63; H, 5.09; N, 5.44.

4.7. (3R,4R*)- and (3R*,4S*)-4-(t-Butoxycarbonyl)-amino-5-methyl-1,1,1,2,2-pentafluoro-hexan-3-ol (**12**)*

A solution of NaOH (817 mg, 20.4 mmol) in H_2O (17.6 ml) was cooled in an ice bath, and the amine hydrochloride (**11**, 4.13 g, 16.1 mmol) was added in one portion followed by the addition of t-BuOH (14 ml). The slurry was treated with Boc_2O (3.51 g, 16.1 mmol, 1 eq.) in one portion and stirred for 20 h while gradually warming to RT. The resulting reaction mixture was diluted with H_2O (100 ml) and Et_2O (100 ml). Phases were separated, and the aqueous phase was extracted with Et_2O (1×100 ml). The organic phases were combined, dried ($MgSO_4$), filtered, and the filtrate concentrated in vacuo (RT, 15 mmHg). Purification via SiO_2 plug filtration (SiO_2 100 g, 3.5 cm×9.5 cm; hexane (400 ml); then 1 l of 10% EtOAc/hexane); R_f=0.17 in 20% EtOAc/hexane) provided the desired *N*-Boc alcohol **12**, 4.92 g, 95% yield, as a colorless oil which solidified on standing. ^{1}H NMR ($CDCl_3$): 5.1 (m, 1H), 4.2 (m, 1H), 3.3 (m, 1H), 2.3 (m, 1H), 1.45 (s, 9H), 1.0. (app t, 6H, J=7 Hz). ^{19}F NMR ($CDCl_3$): −83.6 (s), −122.9 (d, J=277 Hz), −131.3 (dd, J=277 Hz). IR (neat) ν_{max} 3360, 2974, 2935, 1647, 1508, 1475, 1458, 1393, 1368, 1304, 1248, 1213, 1173, 1095, 1055 cm^{-1}. CIMS (CH_4): m/e (% relative intensity) 322 ($M+H^+$, 4), 266 ($M+H^+-C_4H_8$, 100).

4.8. (4R)-4-(t-Butoxycarbonyl)amino-5-methyl-1,1,1,2,2-pentafluoro-hexan-3-one (**3**)*

A solution of alcohol **12** (4.228 g, 13.17 mmol) in CH_2Cl_2 (73 ml) and dimethyl sulfoxide (DMSO, 12.8 ml) was cooled to −43 °C and treated dropwise with $(COCl)_2$ (11.9 ml, 136 mmol, 10 eq.; 50 min, −43 to −35 °C). The resulting reaction mixture was stirred at −40 °C for 2.5 h then treated dropwise with Et_3N (39 ml, 280 mmol; 2 h, −40 to −28 °C). The cold bath was removed and the resulting reaction mixture (thick slurry) was allowed to warm to RT while stirring overnight. The reaction mixture was poured into 1 M HCl saturated with NaCl (100 ml) and diluted with EtOAc (100 ml).

Phases were separated and the aqueous phase extracted with EtOAc (100 ml). The organic phases were combined and washed sequentially with 0.5 M HCl 1/2 saturated with brine (1×100 ml) then 1/2 saturated brine (1×100 ml), dried ($MgSO_4$), filtered, and filtrate evaporated in vacuo (RT, 15 mmHg). Analysis of the resulting crude yellow oil by GC showed no alcohol present and 92% total area of desired ketone. Purification by SiO_2 filtration (100 g SiO_2 (3.5 cm×9.5 cm), hexane (400 ml), then 800 ml of 5% EtOAc/hexane) provided **3** as a white solid, 3.937 g, 93% yield. R_f=0.77 in 20% EtOAc/hexane: m.p. 69–70 °C. ^{1}H NMR ($CDCl_3$): 5.0 (m, 1H), 4.8 (m, 1H), 2.3 (m, 1H), 1.44 (s, 9H), 1.1 (d, 3H, J=6.8 Hz), 0.84 (d, 3H, J=6.9 Hz). ^{19}F NMR ($CDCl_3$): −82.1 (s), −121.4 (d, J=297 Hz), −122.8 (d, J=297 Hz). IR ($CHCl_3$): ν_{max} 3443, 2976, 1753, 1716, 1500, 1369, 1234, 1197, 1163 cm^{-1}. UV (MeOH): λ_{max} 225 nm (ϵ=754). CIMS (CH_4): m/e (% relative intensity) 320 ($M+H^+$, 100). Anal. Found: C, 45.28; H, 5.71; N, 4.26. $C_{12}H_{18}NO_3F_5$. Calc.: C, 45.14; H, 5.68; N, 4.39.

4.9. (2R,4R*)- and (2R*, 4S*)-4-(Benzoyl)amino-5-methyl-1,1,1,2,-tetrafluorohexan-3-one (**13**) and (4R*)-4-(benzoyl)amino-5-methyl-1,1,1-trifluorohexan-3-one (**14**)*

A solution of ketone **7a** (441 mg, 1.37 mmol) in hexane (1 ml) and $POCl_3$ (0.26 ml) was heated at 65 °C for 50 min. The reaction mixture was cooled to 0 °C, then activated Zn dust (440 mg) and EtOH (1 ml) were added. The reaction was then warmed to 65 °C for 1 h. The reaction mixture was allowed to cool, filtered, and filtrate evaporated in vacuo. The crude oil was treated with H_2O (1 ml) and EtOAc (20 ml). Phases were separated and the organic phase was dried ($MgSO_4$), filtered, and filtrate evaporated in vacuo. Purification of the crude oil by chromatography provided 67 mg of **7a** (15%), 60 mg of **13** (14%) and 64 mg of **14** (16%) along with mixtures of **13** and **14** (68 mg).

For **13**: R_f=0.45, 20% EtOAc/hexane. ^{1}H NMR ($CDCl_3$): 7.8 (m, 2H), 7.5 (m, 1H), 7.46 (m, 2H), 6.6 (d, 1H, J=7.1 Hz), 5.3 (m, 1H), 5.2 (m, 1H), 2.4 (m, 1H), 1.1 (dd, 3H, J=4.3, 6.7 Hz), 0.94 (dd, 3H, J=2.3, 6.9 Hz). ^{19}F NMR ($CDCl_3$): −74.5 and −74.8 (dd, J=7.2, 11.3 Hz), −207.3 and −207.5 (d appt, J=11.3, 46.5 Hz). IR (KBr): ν_{max} 3293, 1746, 1647, 1630, 1530, 1489, 1356, 1263, 1202, 1140 cm^{-1}. CIMS (CH_4): m/e (% relative intensity) 306 ($M+H^+$, 100).

For **14**: R_f=0.30, 20% EtOAc/hexane. ^{1}H NMR ($CDCl_3$): 7.8 (m, 2H), 7.5 (m, 1H), 7.46 (m, 2H), 6.7 (m, 1H), 4.8 (dd, 1H, J=5.0, 8.2 Hz), 3.46 (dq, 2H, J=62.8, 19.9 Hz), 2.3 (m, 1H), 1.1 (d, 3H, J=6.8 Hz), 0.94 (d, 3H, J=6.9 Hz); ^{19}F NMR ($CDCl_3$): −62.8 (t, J=10 Hz). IR (KBr): ν_{max} 3264, 1734, 1638, 1528, 1489, 1412, 1375, 1331, 1273, 1142, 1109, 1076 cm^{-1}. CIMS (CH_4): m/e (% relative intensity) 288 ($M+H^+$, 100).

*4.10. 2-Phenyl-4-isopropyl-5-pentafluoroethyl-oxazole (**15**)*

A solution of ketone **7a** (500 mg, 1.55 mmol) in ethylene glycol (0.12 ml) and PhMe (7 ml) was treated with p-TsOH (cat), and warmed at reflux for 5 h with removal of H_2O via a Dean–Stark trap. The reaction mixture was allowed to cool, diluted with Et_2O (20 ml) and the organic phase washed with saturated aqueous $NaHCO_3$ (2×25 ml), dried ($MgSO_4$), filtered, and filtrate evaporated in vacuo. Purification via flash

chromatography on SiO_2 (10% EtOAc/hexane) provided 232 mg of **15** (49%) along with 175 mg of recovered **7a** (35%).

For **15**: m.p. 44–47 °C; $R_f = 0.82$, 10% EtOAc/hexane. ^1H NMR ($CDCl_3$): 8.1 (m, 2H), 7.5 (m, 3H), 3.2 (m, 1H), 1.3 (d, 6H, $J = 6.9$ Hz). ^{19}F NMR ($CDCl_3$): −85.1 (s), −114.7 (s). IR (KBr): ν_{max} 2976, 1557, 1487, 1450, 1373, 1348, 1331, 1215, 1150, 1130, 1103, 1070 cm^{-1}. CIMS (CH_4): *m/e* (% relative intensity) 306 ($M+H^+$, 100).

Acknowledgements

The author wishes to thank F.M. Laskovics, M. Kolb, J. Burkhart and N. Peet for their suggestions and encouragement throughout the conduct of this work. The author thanks members in Analytical and Structural Services (D. Friedrich and D. Robke) for acquiring some spectral data and for their aid in spectral assignment.

References

[1] N. Peet et al., European Patent Application, OPI 0 529 568.
[2] M.R. Angelastro, J.P. Burkhart, P. Bey and N.P. Peet, *Tetrahedron Lett., 33* (1992) 3265.
[3] (a) P.G. Gassman and N.J. O'Reilly, *Tetrahedron Lett., 26* (1985) 5243; (b) P.G. Gassman and N.J. O'Reilly, *J. Org. Chem., 52* (1987) 2481; (c) H. Uno, Y. Shiraishi, K. Simodawa and H. Suzuki, *Chem. Lett.* (1987) 1153; (d) H. Uno, Y. Shiraishi and H. Suzuki, *Bull. Chem. Soc. Jpn., 62* (1989) 2636.
[4] B. Imperiali and R.H. Abeles, *Tetrahedron Lett., 27* (1986) 135.
[5] P.D. Edwards, *Tetrahedron Lett., 33* (1992) 4279.
[6] (a) E.T. McBee, C.W. Roberts and A.F. Meiners, *J. Am. Chem. Soc., 79* (1957) 335; (b) D.D. Denson, C.F. Smith and C. Tamborski, *J. Fluorine Chem., 3* (1973/74) 247.
[7] D.V. Patel, K. Rielly-Gauvin and D.E. Ryono, *Tetrahedron Lett., 29* (1988) 4665.
[8] (a) M. Kolb, J. Barth and B. Neises, *Tetrahedron Lett., 27* (1986) 1579; (b) M.Kolb and B. Neises, *Tetrahedron Lett., 27* (1986) 4437.
[9] H.E. Carter, *Org. Reactions, 3* (1946) 198.
[10] W. Steglich and G. Hofle, *Chem. Ber., 102* (1969) 883.
[11] S.L. Schreiber, *Tetrahedron Lett., 21* (1980) 1027.
[12] O. Keller, W.E. Keller and G. van Look, *Organic Syntheses, 63* (1984) 160.
[13] A.J. Mancuso, S.-L. Huang and D. Swern, *J. Org. Chem., 43* (1978) 2489.
[14] W.P. Griffith and S.V. Ley, *Aldrichimica Acta, 23* (1990) 13.
[15] R.C. Rommele and H. Rapoport, *J. Org. Chem., 54* (1989) 1866.
[16] C. Djerassi, *Org. Reactions, 6* (1951) 207.
[17] E.S. Stratford and R.W. Curley, *J. Med. Chem., 26* (1983) 1463.
[18] R.F.C. Brown and I.D. Rae, *Aust. J. Chem., 17* (1964) 447.
[19] A. Ewenson, R. Laufer, M. Chorev, Z. Selinger and C. Gilon, *J. Med. Chem., 31* (1988) 416.
[20] L. Grehn, K. Gunnarsson and U. Ragnarsson, *J. Chem. Soc., Chem. Commun.* (1985) 1317.
[21] A. Basha and A. Rahman, *Experimentia, 33* (1977) 101.
[22] F.A.J. Meskens, *Synthesis* (1981) 501.
[23] H.E. Simmons and D.W. Wiley, *J. Am. Chem. Soc., 82* (1960) 2288.
[24] R.C. Andrews, S.J. Teague and A.I. Meyers, *J. Am. Chem. Soc., 110* (1988) 7854.
[25] M. Suzuki, T. Iwasaki, M. Miyoshi, K. Okamura and K. Matsumoto, *J. Org. Chem., 38* (1973) 3571.
[26] D. Comins and M.A. Weglarg, *J. Org. Chem., 53* (1988) 4437.