Pergamon

Tetrahedron Vol. 50, No. 8, pp. 2459-2468, 1994

0040-4020/94 $6.00+0.00

0040-4020(93)E0225-5

Synthesis of Pentacyclic Retinoids

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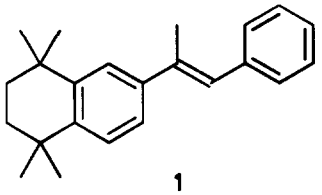
Abstract: Two pentacyclic analogues of the retinoid temarotene (**1**) have been prepared. We describe the first palladium-catalyzed coupling of a stannylated pyridine with an aromatic triflate and a novel way for the preparation of the benzo-[c]-1,8-naphthyridine skeleton.

INTRODUCTION

We have already reported the synthesis of tetrahydroanthracene-analogues[1] of the retinoid temarotene (**1**) (see scheme 1), which has been used successfully in the chemoprevention of cancer.[2] The fact that conformational restriction in retinoid structure often results in an increase of potency is well documented.[3] Thus we aimed at the synthesis of rigid pentacyclic analogues of retinoids with a tetrahydroanthracene structure which were unknown then.



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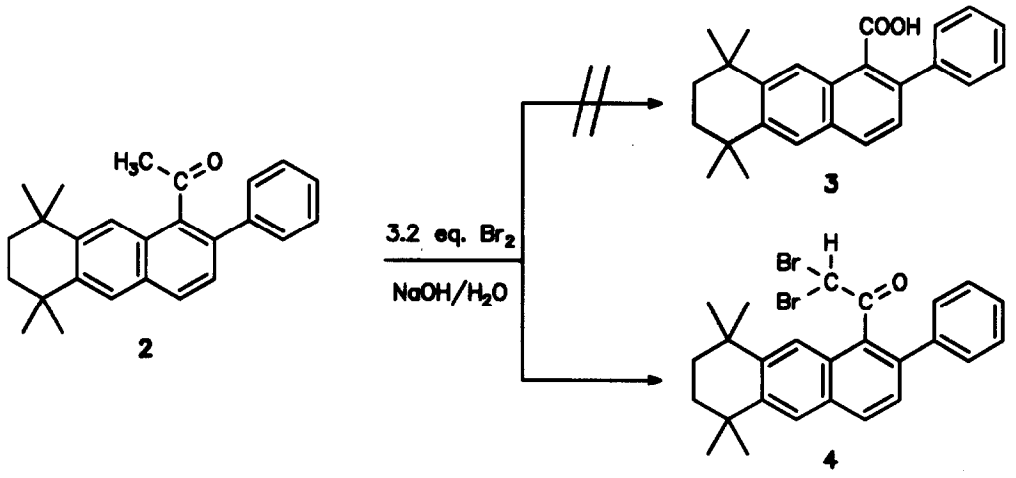
Scheme 1

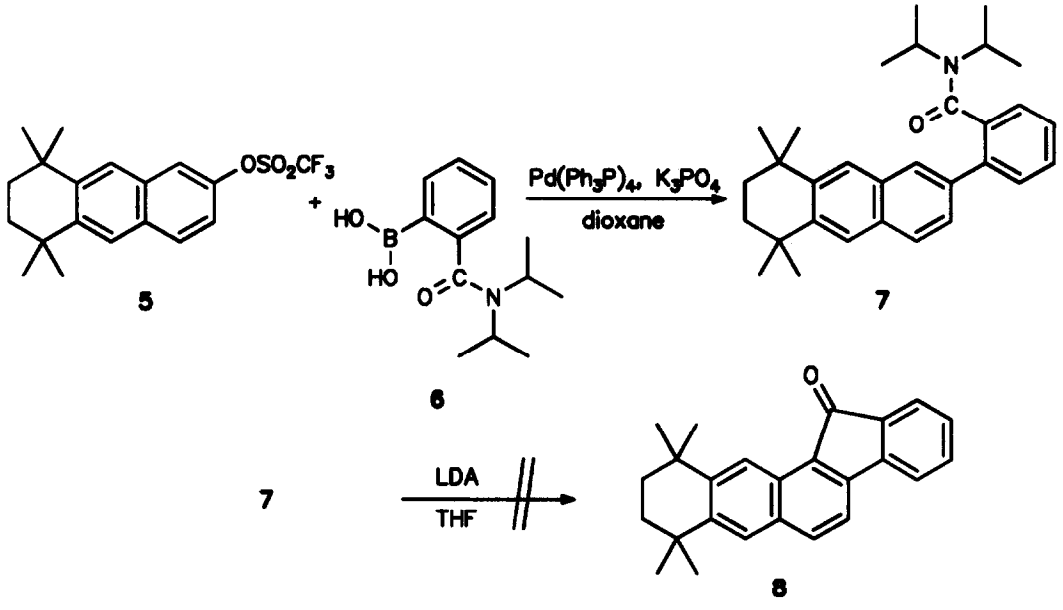
RESULTS AND DISCUSSION

The synthesis of the fluorenone **8** was first tried by haloform reaction of the ketone **2** to the corresponding anthracenecarboxylic acid **3**, which we wanted to cyclize in acidic medium. But reaction with three equivalents of bromine in aqueous sodium hydroxide solution[4] only resulted in the formation of the dibromoketone **4** (see scheme 2). The possibility of uncomplete haloform reactions due to steric hindrance is known in the literature.[5] Other attempts to oxidize **2** with sodium hypochlorite[6] or pentacyanonitrosylferrate(II)[7] also failed.



Scheme 2

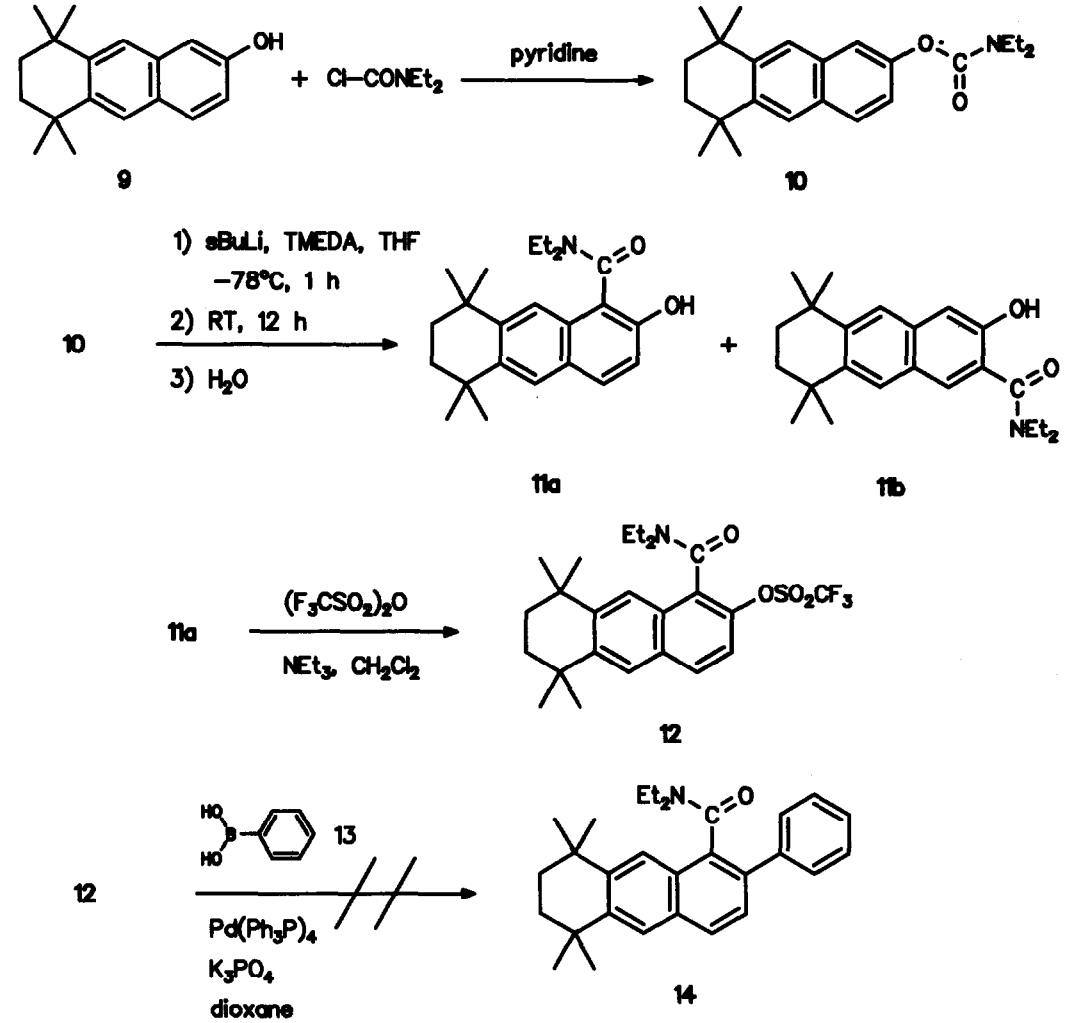
So we tried a cyclization reaction via a remote-metallation reaction.[8] After treatment of the biaryl-carboxamide **7** (synthesized from the triflate[1b] **5** and the boronic acid[9] **6** under Suzuki conditions[10] with lithium diisopropylamide (LDA) the starting material, however, has been recovered completely (see scheme 3).



Scheme 3

We then tried to synthesize the analogous biaryl **14** to cyclize it with LDA to compound **8**. The anthracenol[1a] **9** is converted[11] into the carbamate **10** which in turn is subjected to ortho-metalation followed by an anionic Friesrearrangement[12] yielding the isomeric ortho-hydroxy-carboxamides **11a** and **11b**. Compound **11a** could be transformed[13] to the corresponding triflate **12**, but coupling[10] with benzene boronic acid (**13**) to the biaryl **14** failed and the anthracenol **9** was isolated as single product (see scheme 4). This could result from

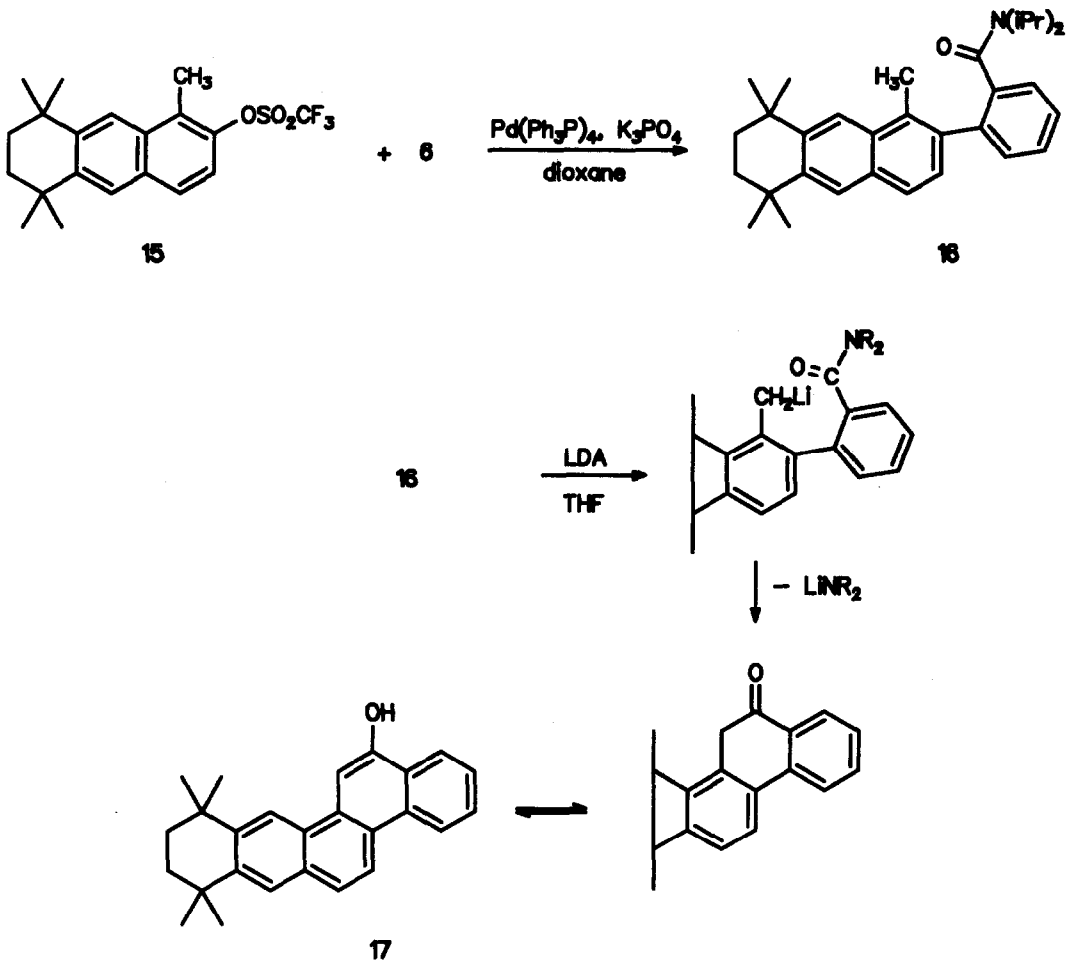
a low hydrolytic stability of the phenylogous carbamic acid-triflic acid anhydride under the basic coupling conditions. After this we concentrated on the synthesis of other pentacyclic structures.



Scheme 4

The synthesis of the phenanthrol **17** was easily accomplished using a method described by Snieckus.[14] The triflate[1b] **15** was coupled[10] with the boronic acid[9] **6** to the biaryl **16**, which was subjected to a remote metallation yielding a tolyl anion. This anion reacts with intramolecular substitution of the amide and tautomerization to the desired compound **17** (see scheme 5).

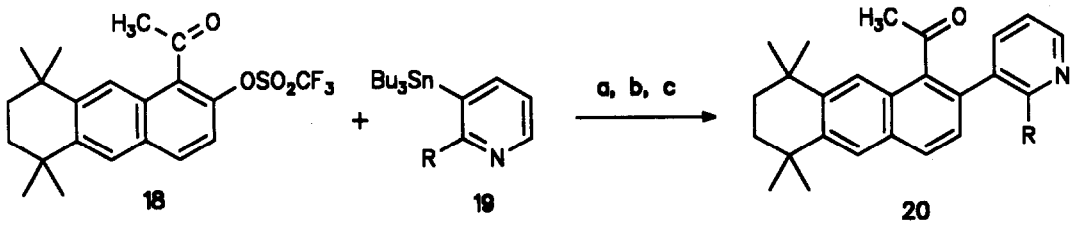
Finally we achieved the synthesis of the naphthyridine **21**. In analogy to syntheses of phenanthridine by Snieckus et al. [15] and benzo[c]1,8-naphthyridines by Gronowitz et al. [16] we wanted to couple the ortho-acetyltriflate[1c] **18** with the stannane **19a** and then cyclize the resulting biaryl **20a**. The stannane **19a** has been prepared using a method of Turner applied to the synthesis of substituted aminopyridines.[17]



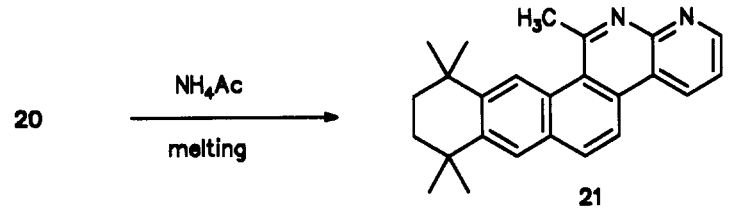
Scheme 5

In the reaction between **18** and **19a** using $Pd(Ph_3P)_4$ as catalyst,[18] however, no coupling took place. To avoid the steric hindrance of the pivaloylamino group, we used the stannylated 2-fluoropyridine **19b** which was synthesized via ortho-metalation of 2-fluoropyridine following a method of Queguiner et al.[19] The surprising formation of a coumaranone instead of the desired coupling product **20b** in the coupling reaction of **18** and **19b** using $Pd(Ph_3P)_2(OAc)_2$ as catalyst[20] has been desribed elsewhere.[1c] We succeeded finally applying a catalytic system, which has been used in the coupling of arylstannanes with vinylic triflates by Farina,[21] consisting of trisdibenzylideneacetonedipalladium(0) ($Pd_2(dba)_3$) and triphenylarsane ($AsPh_3$). The formation of the biaryl **20b** is to our knowledge the first coupling of an aromatic triflate with a stannylated pyridine. **20b** could be cyclized successfully using a melting of ammonium acetate as an equivalent of ammonia (see scheme 6). Our synthesis of **21** represents a novel convergent way for the synthesis of the benzo[c]1,8-naphthyridine skeleton.

In conclusion the triflates **15** and **18**, which have been used successfully for the synthesis of aryltetrahydroanthracene retinoids and are all derived from 2-methoxynaphthalene,[1] are also suitable precursors for the synthesis of their pentacyclic congeners.



	R	cat.	yield 20 (%)
a	–NH–CO–^{t}Bu	$Pd(Ph_3P)_4$	0
b	–F	$Pd(Ph_3P)_2(OAc)_2$	0
c	–F	$Pd_2(dba)_3/AsPh_3$	48



Scheme 6

EXPERIMENTAL

General

Merck silica gel 60 was used for Flashchromatography (FSC). Melting points were determined on a Leitz HM-Lux and are uncorrected. NMR spectra were recorded with a Jeol JNM-GX 400 (400 MHz) using tetramethylsilane as internal standard. The IR spectra were measured with a Hitachi 270-30. Mass spectra were recorded with a Vacuum Generators VG 7070 H using electron impact ionisization (70 eV). A Labormatic/Wösthoff CH-Analyzer and a Hewlett-Packard CHN-Autoanalyzer 185 (only for N) were used for elementary analysis.

2,2-Dibromo-1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-phenyl-1-anthracenyl)-ethanone (**4**). Bromine (0.15 mL, 450 mg, 2.82 mmol) was added to 5% aqueos sodium hydroxide (5 mL). A solution of 1-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-phenyl-1-anthracenyl)-ethanone[1c] (**2**) (315 mg, 0.88 mmol) in dioxane (5 mL) was added dropwise and the mixture was stirred at 50° C for 2 h. A solution of 5% aqueos sodium bisulfite (5 mL) was added and the mixture was acidified with conc. HCl. A white precipitate separated, was washed with n-hexane and gave pure **4** (260 mg, 57%) as a colourless powder, m. p. 158° C. $C_{26}H_{26}Br_2O$ (514.34) calcd. C 60.71, H 5.11; found C 60.54, H 5.10. MS: m/z (%)= 516 (3, M^+, ^{81}Br), 514 (6, M^+, ^{79}Br), 354 (26), 342 (30), 341 (100). IR (KBr): ν = 2950, 2925, 1710, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm)= 7.93-7.91 (m, 2 H, aromat. H), 7.82 (s, 1 H, 5'-H od 10'-H), 7.52-7.40 (m, 6 H, aromat. H), 5.63 (s, 1 H, $CHBr_2$), 1.78 (s, 4 H, CH_2), 1.41 u. 1.40 (2 s, 6 H each, CH_3). ^{13}C-NMR ($CDCl_3$): δ (ppm)= 191.62 (CO), 147.28 u. 145.96 (C-4'a u. C-10'a), 140.14 (C-1"), 137.36 (C-2'), 131.25 (aromat. C-H), 131.02 (-C-COCHBr$_2$), 129.97 (C-2" and C-6" or C-3" and C-5"), 129.70 and 129.64 (C-5'a and C-9'a), 129.38 (C-2" and C-6" or C-3" and C-5"), 129.06, 126.40, 125.26

and 123.44 (aromat. C-H), 45.42 ($CHBr_2$), 35.32 (C-1' or C-4'), 35.28 and 35.23 (CH_2), 34.89 (C-1' or C-4'), 32.72 and 32.65 (CH_3)

2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-anthracenyl)-benzoic acid diisopropylamide (**7**). Potassium triphosphate trihydrate (2.0 g, 7.5 mmol) was added to a solution of trifluoromethanesulfonic acid-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-anthracenyl)-ester[1a] (**5**) (580 mg, 1.5 mmol), 2-(dihydroxyboryl)-benzoic acid (**6**) (423 mg, 1.8 mmol) and $Pd(Ph_3P)_4$ (87 mg, 0.08 mmol) in dioxane (10 mL). The mixture was refluxed under N_2 for 6 h and filtrated over silica gel with ethyl acetate. Removal of the solvent in vacuo and FSC (dichloromethane/ethyl acetate, 10:1) gave a colourless oil, which was treated with n-hexane resulting in the precipitation of **7** (400 mg, 60%) as a colourless powder, m. p. 73° C. $C_{31}H_{39}NO$ (441.71) calcd. C 84.29, H 8.92, N 3.17; found C 84.32, H 8.69, N 3.30. MS: m/z (%)= 441 (100, M^+), 440 (40), 342 (66), 341 (56), 271 (49). IR (KBr): ν = 2960, 2940, 2860, 1630, 1460, 1440, 1370, 1340, 960 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm)= 7.92 and 7.88 (2 s, 1 H each, aromat. H), 7.84 (d, 1 H, 9'-H, ^{3}J= 9 Hz), 7.77 (s, 1 H, aromat. H), 7.55-7.40 (m, 4 H, aromat. H), 7.28-7.26 (m, 1 H, aromat. H), 3.43-3.39 and 3.30-3.22 (2 m, 1 H each, N-CH), 1.72 (s, 4 H, CH_2), 1.41 (d, 3 H, N-CH-$\underline{CH_3}$, J= 7 Hz), 1.36 (s, 3 H, 4'-CH_3), 1.35 (s, 6 H, 1'-CH_3), 1.32 (s, 3 H, 4'-CH_3), 1.15, 0.86 and 0.23 (3 d, 3 H each, N-CH-$\underline{CH_3}$, all J= 7 Hz). ^{13}C-NMR ($CDCl_3$): δ (ppm)= 170.59 (CO), 144.63 and 144.53 (C-4'a and C-10'a), 138.07, 137.82, 136.01, 131.51 and 130.97 (quatern. aromat. C-atoms), 129.49, 128.47, 127.59, 127.35, 127.18, 126.74, 126.29, 125.59 and 124.37 (aromat. C-H), 50.57 and 45.53 (N-CH), 35.09 and 35.04 (CH_2), 34.58 and 34.55 (C-1' and C-4'), 32.63, 32.55, 32.40 and 32.36 (1'-CH_3 and 4'-CH_3), 20.84, 20.72, 19.61 and 19.58 (N-CH-$\underline{CH_3}$).

N,N-Diethylcarbamic acid-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-anthracenyl)-ester (**10**). A solution of 5,6,7,8-tetrahydro-5,5,8,8-tetramethylanthracene-2-ol[1a] (**9**) (1.02 g, 4 mmol) and N,N-diethylcarbamic acid chloride (0.57 mL, 610 mg, 4.5 mmol) in pyridine (30 mL) was refluxed under N_2 for 12 h. The mixture was hydrolyzed with water (50 mL) and extracted with Et_2O (50 mL). Removal of the solvent in vacuo, FSC (dichloromethane) and treatment of the resulting oil with methanol gave **10** (510 mg, 39%) as colourless crystals, m. p. 70° C. $C_{23}H_{31}NO_2$ (353.55) calcd. C 78.13, H 8.86, N 3.96; found C 78.12, H 8.59, N 4.30. MS: m/z (%)= 353 (41, M^+), 100 (100). IR (KBr): ν = 2950, 2920, 2850, 1725, 1715, 1460, 1410, 1375, 1260, 1210 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm)= 7.75 and 7.71 (2 s, 1 H each, 9'-H and 10'-H), 7.70 (d, 1 H, 4'-H, ^{3}J= 9 Hz), 7.47 (d, 1 H, 1'-H, ^{4}J= 2 Hz), 7.15 (dd, 1 H, 3'-H, ^{3}J= 9 Hz, ^{4}J= 2 Hz), 3.52-3.40 (m, 4 H, N-CH_2), 1.78 (s, 4 H, CH_2), 1.38 and 1.37 (2 s, 6 H each, 5'-CH_3 and 8'-CH_3), 1.30-1.18 (m, 6 H, N-CH_2-$\underline{CH_3}$). ^{13}C-NMR ($CDCl_3$): δ (ppm)= 154.49 (CO), 148.61, 144.72 and 143.64 (C-8'a, C-10'a and $\underline{C}$-OCONEt$_2$), 132.09 and 129.62 (C-4'a and C-9'a), 128.28 (C-4'), 124.68 and 120.83 (C-9' and C-10'), 117.49 (C-3'), 42.18 and 41.86 (N-CH_2), 35.06 and 35.02 (CH_2), 34.53 and 34.47 (C-5' and C-8'), 32.48 (5'-CH_3 and 8'-CH_3), 14.26 and 13.43 (N-CH_2-$\underline{CH_3}$).

Lithiation of N,N-Diethylcarbamic acid-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-anthracenyl)-ester (**10**). To a solution of N,N-diethylcarbamic acid-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-anthracenyl)-ester (**10**) (1.01 g, 2.86 mmol) and dry TMEDA (0.53 ml, 416 mg, 3.58 mmol) in dry THF (20 mL) was added under N_2 sec.-Butyllithium (1.3M solution in cyclohexane/n-Hexane 92:8, 2.8 ml, 3.58 mmol) at -78°C. After stirring at -78°C for 1 h and at room temperature for 12 h the mixture was hydrolyzed with saturated aqueous NH_4Cl-solution (20 mL) and the mixture was extracted with Et_2O (50 ml). Removal of the solvent in vacuo and FSC (dichloromethane/ethyl acetate, 3:1) gave 5,6,7,8-tetrahydro-3-hydroxy-5,5,8,8-tetramethylanthracene-2-carboxylic acid diethylamide (**11a**) as second and 5,6,7,8-tetrahydro-2-hydroxy-5,5,8,8-tetramethylanthracene-1-carboxylic acid diethylamide (**11b**) as third fraction.

a) *5,6,7,8-Tetrahydro-3-hydroxy-5,5,8,8-tetramethylanthracene-2-carboxylic acid diethylamide* **(11a)**. Colourless crystals (340 mg, 34%), m. p. 203° C (n-hexane). $C_{23}H_{31}NO_2$ (353.55) calcd. C 78.13, H 8.86, N 3.96; found C 77.60, H 8.61, N 4.13. MS: m/z (%)= 353 (41, M^+), 100 (100). IR (KBr): ν = 2950, 2890, 1580, 1230, cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm)= 8.89 (s, 1 H, -OH), 7.73, 7.67 and 7.66 (3 s, 1 H each, 1-H, 9-H and 10-H), 7.23 (s, 1 H, 4-H), 3.58 (q, 4 H, N-CH_2, J= 7 Hz), 1.76 (s, 4 H, CH_2), 1.381 and 1.377 (2 s, 6 H each, 5-CH_3 and 8-CH_3), 1.30 (t, 6 H, N-CH_2-$\underline{C}H_3$, J= 7 Hz). ^{13}C-NMR ($CDCl_3$): δ (ppm)= 171.20 (CO), 153.35 (C-OH), 146.71 and 142.40 (C-8a and C-10a), 133.94 (C-4a), 127.01 (C-1), 125.65 (C-9a), 125.41 and 123.43 (C-9 and C-10), 120.87 ($\underline{C}$-CONEt$_2$), 110.92 (C-4), 42.07 (b, N-CH_2), 35.02 (CH_2), 34.72 and 34.40 (C-5 and C-8), 35.51 and 32.44 (5-CH_3 and 8-CH_3), 13.53 (N-CH_2-$\underline{C}H_3$).

b) *5,6,7,8-Tetrahydro-2-hydroxy-5,5,8,8-tetramethylanthracene-1-carboxylic acid diethylamide* **(11b)**. Colourless crystals (430 mg, 43%), m. p. 245°C (chloroform/acetone). $C_{23}H_{31}NO_2$ (353.55) calcd. C 78.13, H 8.86, N 3.96; found C 77.83, H 8.60, N 4.01. MS: m/z (%)= 353 (53, M^+), 280 (38), 265 (86), 72 (100). IR (KBr): ν = 3350, 3000, 2970, 1620, 1510, 1480, 1460, 1350, 1290, 1270 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 35°C): δ (ppm)= 7.92 (s, 1 H, OH), 7.63 and 7.52 (2 s, 1 H each , 9-H and 10-H), 7.48 (d, 1 H, 4-H, J= 9 Hz), 6.93 (d, 1 H, 3-H, J= 9 Hz), 3.63 (bs, 2 H, N-CH_2), 3.32-3.25 (m, 2 H, N-CH_2), 1.75 (s, 4 H, CH_2), 1.37 and 1.33 (2 s, 6 H each, 5-CH_3 and 8-CH_3), 1.18 (bs, 6 H, N-CH_2-$\underline{C}H_3$). ^{13}C-NMR ($CDCl_3$, 35°C): δ (ppm)= 169.73 (CO), 152.28 (C-OH), 145.60 and 141.72 (C-8a and C-10a), 130.10 (C-4), 128.83 and 127.01 (C-4a and C-9a), 125.32 and 120.40 (C-9 and C-10), 118.30 (C-7), 114.81 ($\underline{C}$-CONEt$_2$), 41.30 (b, N-CH_2), 35.18 and 35.14 (CH_2), 34.74 and 34.30 (C-5 and C-8), 35.21 and 32.48 (5-CH_3 and 8-CH_3), 13.71 (N-CH_2-$\underline{C}H_3$).

Trifluoromethanesulfonic acid[1-(N,N-diethylcarbamoyl)-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-anthracenyl]ester(**12**). Trifluoromethanesulfonic acid anhydride (0.25 ml, 413 mg, 1.46 mmol) was added under N_2 to a solution of 5,6,7,8-tetrahydro-2-hydroxy-5,5,8,8-tetramethylanthracene-1-carboxylic acid diethylamide (**11b**) (430 mg, 1.22 mmol), dry NEt_3 (0.20 ml, 148 mg, 1.46 mmol) and a few crystals of 4-pyrrolidinyl-pyridine in dry dichloromethane (30 mL). After stirring at room temperature for 3 h and at 35° C for 1 h the mixture was filtrated over silica gel with dichloromethane. After removal of the solvent in vacuo treatment of the resulting oil with n-hexane gave **12** (380 mg, 64%) as colourless crystals, m. p. 97 °C. $C_{24}H_{30}F_3NO_4S$ (485.63) calcd. C 59.35, H 6.24, N 2.89; found C 59.50, H 6.22, N 2.88. MS: m/z (%)= 485 (66, M^+), 352 (55), 281 (100), 242 (63), 72 (84), 69 (60). IR (KBr): ν = 2950, 2925, 1625, 1480, 1455, 1440, 1420, 1270, 1240, 1210, 1200 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm)= 7.82 (s, 1 H, 9'-H or 10'-H), 7.81 (d, 1 H, 4'-H, J= 9 Hz), 7.70 (s, 1 H, 9'-H or 10'-H), 7.32 (d, 1 H, 3'-H, J= 9 Hz), 3.79-3.68 (m, 2 H, N-CH_2), 3.16 (q, 2 H, N-CH_2, J= 7 Hz), 1.77 (s, 4 H, CH_2), 1.41 (t, 3 H, N-CH_2-$\underline{C}H_3$, J= 7 Hz), 1.40, 1.37, 1.35 and 1.34 (4 s, 3 H each, 5'-CH_3 and 8'-CH_3), 1.02 (t, 3 H, N-CH_2-$\underline{C}H_3$, J= 7 Hz). ^{13}C-NMR ($CDCl_3$): δ (ppm)= 164.45 (CO), 147.12, 146.39 and 141.83 (C-8'a, C-10'a and $\underline{C}$-OSO_2CF_3), 130.75 (quatern. aromat. C-atom), 130.11 (C-4'), 128.58 and 126.59 (quatern. aromat. C-atoms), 125.50 and 122.63 (C-9' and C-10'), 118.51 (CF_3, $^1J_{C\text{-}F}$= 320 Hz), 118.03 (C-3'), 43.20 and 39.03 (N-CH_2), 34.92 (C-5' or C-8'), 34.80 (CH_2), 34.69 (C-5' or C-8'), 32.59, 32.43, 32.38 and 32.31 (5'-CH_3 and 8'-CH_3), 13.96 and 12.78 (N-CH_2-$\underline{C}H_3$).

2-(5,6,7,8-Tetrahydro-1,5,5,8,8-pentamethyl-2-anthracenyl)-benzoic acid diisopropylamide (**16**). Potassium triphosphate trihydrate (1.33 g, 5 mmol) was added under N_2 to a solution of trifluoromethanesulfonic acid-(5,6,7,8-tetrahydro-1,5,5,8,8-pentamethyl-2-anthracenyl)-ester[1b] (**15**) (400 mg, 1 mmol), 2-(dihydroxyboryl)-benzoic acid (**6**) (294 mg, 1.25 mmol) and $Pd(Ph_3P)_4$ (58 mg, 0.05 mmol) in dioxane (7 mL). The mixtured was refluxed for 6 h and filtrated over silica gel with ethyl acetate. Removal of

the solvent in vacuo and FSC (dichloromethane/ethyl acetate, 10:1) gave an oil which was treated with n-hexane and gave **(16)** (320 mg, 70%) as colourless crystals, m. p. 54° C. $C_{32}H_{41}NO$ (455.74) calcd. C 84.33, H 9.09, N 3.07; found C 84.20, H 9.07, N 3.41. MS: m/z (%)= 455 (41, M^+), 355 (43), 354 (100). IR (KBr): ν = 2950, 2930, 1625, 1445, 1430, 1370, 1330 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm)= 8.29 (bs, 1 H, aromat. H), 7.87-7.83 (m, 1 H, aromat. H), 7.62-7.56 (m, 1 H, aromat. H), 7.49-7.41 (m, 2 H, aromat. H), 7.37-7.26 (m, 2 H, aromat. H), 3.47-3.40 and 3.21-3.17 (2 m, 1 H each, N-CH), 1.75 (s, 4 H, CH_2), 1.44-1.24 (m, 18 H, CH_3), 0.95-0.81 (m, 6 H, N-CH-$\underline{CH_3}$).

8,9,10,11-Tetrahydrobenzo-8,8,11,11-tetramethyl-[k]-chrysene-14-ol **(17)**. n-Butyllithium (1.6M solution in hexane, 0.41 ml, 0.66 mmol) was added under nitrogen to a solution of dry diisopropylamine (0.08 ml, 56 mg, 0.55 mmol) in dry THF (10 mL) at 0°C. After stirring at 0° C for 15 min a solution of 2-(5,6,7,8-tetrahydro-1,5,5,8,8-pentamethyl-2-anthracenyl)-benzoic acid diisopropylamide **(16)** (100 mg, 0.22 mmol) in dry THF (5 mL) was added dropwise. After stirring at 0° C for 15 min and at room temperature for 1 h the mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with Et_2O (30 mL). After removal of the solvent in vacuo the residue was separated via FSC (dichlormethane/n-hexane, 3:1). The first fraction contained the product, which was washed with cold n-hexane and gave **16** as colourless crystals (50 mg, 64%) which soon turned yellow, m. p. 174° C. $C_{26}H_{26}O$ calcd. 354.1986; found 354.1984 (HR-MS). MS: m/z (%)= 354 (100, M^+), 339 (61). IR (KBr): ν = 3520, 2950, 2930, 1595, 1460, 750 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm)= 8.72 (dd, 1 H, 1-H or 4-H, ^{3}J= 8 Hz, ^{4}J= 1 Hz), 8.53 (s, 1 H, 7-H, 12-H or 13-H), 8.50 (d, 1 H, 6-H, ^{3}J= 9 Hz), 8.35 (dd, 1 H, 1-H or 4-H, ^{3}J= 8 Hz, ^{4}J= 1 Hz), 8.00 and 7.87 (2 s, 1 H each, 7-H, 12-H or 13-H), 7.76 (d, 1 H, 5-H, ^{3}J= 9 Hz), 7.71-7.69 and 7.66-7.62 (2 m, 1 H each, 2-H and 3-H), 5.76 (s, 1 H, OH), 1.82 (s, 4 H, CH_2), 1.50 and 1.44 (2 s, 6 H each, CH_3). ^{13}C-NMR ($CDCl_3$): δ (ppm)= 150.09 (C-OH), 144.63 and 144.24 (C-7a and C-11a), 131.96, 130.75, 128.73 and 127.74 (quatern. aromat. C-atoms), 127.13, 125.79 and 125.76 (aromat. C-H), 124.62 (quatern. aromat. C-atom), 124.51 (aromat. C-H), 123.27 (C-14a), 123.22, 122.10, 120.43 and 120.31 (aromat. C-H), 102.53 (C-13), 35.28 and 35.11 (CH_2), 34.93 and 34.52 (C-8 and C-11), 32.75 and 32.44 (CH_3).

2,2-Dimethylpropane-N-(3-tributylstannyl-2-pyridyl)-amide **(19a)**. n-Butyllithium (1.6M solution, 6.25 ml, 10 mmol) was added dropwise under nitrogen to a solution of 2,2-dimethylpropane-N-2-pyridylamide[17] (712 mg, 4 mmol) in dry THF (30 mL). After stirring at 0° C for 4 h the mixture was cooled to -78°C and a solution of tributyltin chloride (2.72 ml, 3.26 g, 10 mmol) in dry THF (5 mL) was added dropwise. After stirring at -78° C for 15 min and at room temperature for 30 min the mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with Et_2O (30 mL). After removal of the solvent in vacuo the resulting oil was separated via FSC (n-hexane/ethyl acetate, 3:2). The first fraction gave **19a** (1.2 g, 64%) as a colourlesss oil. $C_{22}H_{40}N_2OSn$ (467.33) calcd. C 56.64, H 8.65, N 6.00; found C 56.79, H 8.57, N 5.70. MS: m/z (%)= 415 (10), 413 (13), 412 (20), 411 (100), 410 (27), 409 (32), 408 (10), 407 (14). IR (neat): ν = 3320, 2940, 2900, 2860, 1675, 1570, 1560, 1500, 1460, 1430 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ (ppm)= 8.24 (dd, 1 H, 6'-H, ^{3}J= 5 Hz, ^{4}J= 2 Hz), 7.98 (s, 1 H, NH), 7.82 (dd, 1 H, 4'-H, ^{3}J= 7 Hz, ^{4}J= 2 Hz), 7.02 (dd, 1 H, 5'-H, ^{3}J= 7 Hz, ^{3}J= 5 Hz), 1.57-1.45 (m, 6 H, CH_2), 1.37-1.28 (m, 6 H, CH_2), 1.32 (s, 9 H, $C(CH_3)_3$), 1.05-1.01 (m, 6 H, CH_2), 0.92-0.85 (m, 9 H, Sn-$(CH_2)_3$-$\underline{CH_3}$). ^{13}C-NMR ($CDCl_3$): δ (ppm)= 177.83 (CO), 156.22 ($\underline{C}$-NH-CO'Bu), 147.67 and 147.53 (C-4' and C-6'), 121.61 (C-$SnBu_3$), 120.75 (C-5'), 39.62 (CO-$\underline{C}(CH_3)_3$), 29.44 (Sn-CH_2-$\underline{CH_2}$), 27.84 (CO-C($\underline{CH_3}$)$_3$), 27.80 (Sn-$(CH_2)_2$-$\underline{CH_2}$), 14.03 (Sn-$(CH_2)_3$-$\underline{CH_3}$), 12.29 (Sn-$\underline{CH_2}$).

3-Tributylstannyl-2-fluoropyridine **(19b)**. LDA (2M solution in heptane/THF/ethylbenzene, 5 mL, 10

mmol) was added slowly under nitrogen to a solution of 2-fluoropyridine (940 mg, 10 mmol) in dry THF (10 ml). After stirring at -78° C for 3 h a solution of tributyltin chloride (3.25 ml, 3.91 g, 12 mmol) in dry THF (30 mL) was added dropwise. After stirring at -78° C for 15 min and at room temperature for 3 h the mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl (20 mL) and extracted with Et_2O (30 mL). After removal of the solvent in vacuo the resulting oil was separated via FSC (dichloromethane/n-hexane, 2:1). The first fraction gave **19b** (2.86 g, 74%) as a yellow oil. $C_{17}H_{30}FNSn$ (386.17) calcd. C 52.87, H 7.85, N 3.63; found C 52.92, H 7.82, N 3.62. MS): m/z (%)= 387 (3, M^+, ^{120}Sn), 330 (66), 274 (100), 272 (76), 216 (76). IR (neat): ν = 2950, 2910, 2840, 1570, 1410, 1385, 1230, 1220, 1060, 790 cm^{-1}. ^1H-NMR ($CDCl_3$): δ (ppm)= 8.16 (dd, 1 H, 6-H, ^3J= 5 Hz, ^4J= 2 Hz), 7.91-7.75 (m, 1 H, 5-H), 7.19-7.04 (m, 1 H, 4-H), 1.73-1.14 (m, 18 H, CH_2), 0.95-0.61 (m, 9 H, CH_3). ^{13}C-NMR ($CDCl_3$): δ (ppm)= 169.95 (d, C-F, $^1J_{C,F}$= 229 Hz), 149.13 (d, C-6, $^3J_{C,F}$= 14 Hz), 147.88 (d, C-4, $^3J_{C,F}$= 14 Hz), 121.61 (d, C-$SnBu_3$, $^2J_{C,F}$= 62 Hz), 121.41 (C-5), 28.85 (Sn-CH_2-$\underline{CH_2}$), 27.18 (Sn-$(CH_2)_2$-$\underline{CH_2}$), 13.56 (-CH_3), 9.84 (Sn-$\underline{CH_2}$).

1-[2-(2-Fluoro-3-pyridyl)-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-1-anthracenyl]-ethanone (**20**). A solution of trifluoromethanesulfonic acid-(1-acetyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-anthracenyl)-ester[1c] (**18**) (860 mg, 2 mmol), lithium chloride (146 mg, 6 mmol), tris-(dibenzylidenacetone)-dipalladium(0) (92 mg, 0.1 mmol) and triphenylarsane (122 mg, 0.4 mmol) in dry NMP (10 mL) was stirred under nitrogen for 5 min. Then 3-tributylstannyl-2-fluoropyridine (**19b**) (926 mg, 2.4 mmol) was added. After stirring for 2 h at 100° C 10% aqueos sodium hydroxide (50 mL) was added and the mixture was extracted with dichlormethane (50 mL). The organic phase was filtrated over silica gel with ethyl acetate. After removal of the solvent in vacuo the residue was separated via FSC (dichloromethane, then dichloromethane/ethyl acetate, 10:1). The main fraction gave **20b** (360 mg, 48%) as colourless crystals, m. p. 159° C (n-hexane). $C_{25}H_{26}FNO$ (375.52) calcd. C 79.96, H 6.99, N 3.73; found C 79.63, H 6.97, N 3.88. MS: m/z (%)= 375 (69, M^+), 360 (100), 318 (35). IR (KBr): ν = 2950, 1695, 1425, 1215, 800 cm^{-1}. ^1H-NMR ($CDCl_3$): δ (ppm)= 8.27-8.25 (m, 1 H, 6"-H), 7.86 (s, 1 H, 9'-H or 10'-H), 7.85 (d, 1 H, 4'-H, ^3J= 9 Hz), 7.77-7.73 (m, 1 H, 4"-H or 5"-H), 7.74 (s, 1 H, 9'-H or 10'-H), 7.34 (dd, 1 H, 3'-H, ^3J= 9 Hz, J= 2 Hz), 7.29-7.25 (m, 1 H, 4"-H or 5"-H), 2.30 (s, 3 H, $COCH_3$), 1.81 (s, 4 H, CH_2), 1.41 and 1.37 (2 s, 6 H each, 5'-CH_3 and 8'-CH_3). ^{13}C-NMR ($CDCl_3$): δ (ppm)= 206.44 (CO), 160.25 (d, C-F, $^1J_{C,F}$= 240 Hz), 147.36 (d, C-6", $^3J_{C,F}$= 14 Hz), 146.37 and 145.89 (C-8'a and C-10'a), 142.79 (d, C-4", $^3J_{C,F}$= 4 Hz), 138.96 and 131.56 (C-4'a and C-9'a), 128.61 (C-4'), 127.15 (<u>C</u>-$COCH_3$), 126.78 (d, C-2', $^3J_{C,F}$= 5 Hz), 126.31 (d, C-5", $^5J_{C,F}$<1 Hz), 125.53 (C-9' or C-10'), 122.59 (d, C-3", $^2J_{C,F}$= 30 Hz), 122.03 (C-9' or C-10'), 121.53 (d, C-3', $^5J_{C,F}$= 5 Hz), 34.97 and 34.89 (CH_2), 34.64 (C-5' and C-8'), 32.59 (CO-$\underline{CH_3}$), 32.46 and 32.40 (5'-CH_3 and 8'-CH_3).

8,9,10,11-Tetrahydro-8,8,11,11,15-pentamethylanthraceno[1,2-c]1,8-naphthyridine (**21**). 1-[2-(2-Fluoro-3-pyridyl)-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-1-anthracenyl)-ethanone (**20**) (360 mg, 0.96 mmol) was added portionwise to molten (130° C) ammonium acetate (20 g). The mixture was stirred at 160° C for 30 min and then poured into water (100 mL). 10% Aqueous sodium hydroxide (40 mL) was added and the mixture was extracted with ethyl acetate (100 mL). Silica gel (0.5 g) was added to the organic phase and the solvent was removed in vacuo. The mixture was given on a silica gel column and after FSC (ethyl acetate) the third fraction gave **21** (270 mg, 79%) as colourless crystals, m. p. 186° C (n-hexane/acetone). $C_{25}H_{26}N_2$ calcd. 354.2096; found 354.2092 (HR-MS). MS: m/z (%)= 354 (71, M^+), 340 (38), 339 (100). IR (KBr): ν (cm^{-1})= 2950, 2930, 1645, 1605. ^1H-NMR ($CDCl_3$): δ (ppm)= 9.09 (dd, 1 H, 2-H, ^3J= 4 Hz, ^4J= 2 Hz), 8.95 (s, 1 H, 7-H or 12-H), 8.92 (dd, 1 H, 4-H, ^3J= 8 Hz, ^4J= 2 Hz), 8.44 and 8.11 (2 d, 1 H each, 5-H and 6-H, ^3J= 9 Hz), 7.96 (s, 1 H, 7-H

or 12-H), 7.57 (dd, 1 H, 3-H, ^3J= 8 Hz, ^3J= 4 Hz), 3.54 (s, 3 H, 13-CH_3), 1.86-1.84 (m, 4 H, CH_2), 1.50 and 1.46 (2 s, 6 H each, 8-CH_3 and 11-CH_3). ^{13}C-NMR ($CDCl_3$): δ (ppm)= 161.28 (C-13), 152.67 (C-14a), 151.81 (C-2), 145.67 and 145.18 (C-7a and C-11a), 133.88 (quatern. aromat. C-atom), 132.33 and 131.82 (aromat. C-H), 128.54 (quatern. aromat. C-atom), 126.29 and 125.22 (aromat. C-H), 123.23 (quatern. aromat. C-atom), 121.46 and 118.81 (C-3 and C-5), 117.97 (C-4a), 35.20 (C-8 or C-11), 35.02 and 34.94 (CH_2), 34.48 (C-8 or C-11), 32.69 and 32.26 (8-CH_3 and 11-CH_3), 31.88 (13-CH_3), the signal of one quaternary carbon atom is hidden.

ACKNOWLEDGEMENTS

We thank the *Wella AG*, Darmstadt, and the *Fonds der Chemischen Industrie* for financial support.

REFERENCES

1. (a) Hanefeld, W.; Jung M. *Liebigs Ann. Chem.* in press.
   (b) idem *ibid.* in press.
   (c) idem *Pharmazie* in press.
2. (a) Bollag, W.; Ott, F. *Eur. J. Cancer Clin. Oncol.* **1987**, *23*, 131-135.
   (b) Lasnitzki, I.; Bollag, W. *Eur. J. Cancer Clin. Oncol.* **1987**, *23*, 861-865; Chem. Abstr. **1989**, *110*, 165710j.
3. Dawson, M. I.; Hobbs, P. D.; Derdzinski, K. A.; Chao, W.-R.; Frenking, G.; Loew, G. H.; Jetten, A. M.; Napoli, J. L.; Williams, J. B.; Sani, B. P.; Wille Jr., J. J.; Schiff, L. J. *J. Med. Chem.* **1989**, *32*, 1504-1517.
4. Johnson, W. S.; Gutsche, C. D.; Offenhauer, R. D. *J. Am. Chem. Soc.* **1946**, *68*, 1648-1650.
5. Bull, B. A.; Fuson, R. C. *J. Am. Chem. Soc.* **1934**, *56*, 736-738.
6. Mowry, D.; Ringwald, E. C. *J. Am. Chem. Soc.* **1950**, *72*, 2037-2038.
7. Katho, A.; Beck, M. T. *Synlett* **1992**, 165-166.
8. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933.
9. Sharp, M. J.; Cheng, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5093-5096.
10. Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221-223.
11. Hoppe, D.; Brönneke, A. *Synthesis* **1982**, 1045-1048.
12. Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935-1940.
13. Huth, A.; Beetz, I.; Schumann, I. *Tetrahedron* **1989**, *45*, 6679-6682.
14. Fu, J.-M.; Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5459-5462.
15. Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5463-5466.
16. Gronowitz, S.; Hoernfeldt, A. B.; Yang, Y. H. *Chem. Scr.* **1986**, *26*, 311-314.
17. Turner, J. A. *J. Org. Chem.* **1983**, 48, 3401-3408.
18. Tamayo, N.; Echavarren, A. M.; Paredes, M. C.; Farina, F.; Noheda, P. *Tetrahedron Lett.* **1990**, *31*, 5189-5192.
19. Marsais, F.; Pineau, P.; Nivolliers, F.; Mallet, M.; Turck, A.; Godard, A.; Queguiner, G. *J. Org. Chem.* **1992**, *57*, 565-573.
20. Robl, J. A. *Tetrahedron Lett.* **1990**, *31*, 3421-3424.
21. Farina, V.; Roth, G. P. *Tetrahedron Lett.* **1991**, *32*, 4243-4246.

(*Received in Germany* 2 *November* 1993; *accepted* 7 *December* 1993)