Pergamon

Tetrahedron 57 (2001) 4867–4871

TETRAHEDRON

Total synthesis of phorbazole C

Alexander Radspieler and Jürgen Liebscher*

Institut für Chemie, Humboldt-Universität zu Berlin, Hessische Strasse 1-2, D-10115 Berlin, Germany

Dedicated to Professor Dr Siegfried Hünig on the occasion of his 80th birthday

Received 15 February 2001; revised 12 April 2001; accepted 13 April 2001

Abstract—The first total synthesis of the marine natural product phorbazole C **1** occurring in the sea sponge *Phorbas aff. clathrata* is reported. In the key steps of the convergent approach the 3,4-dichloro-5-ethoxycarbonyl-pyrrole-2-carboxylic acid (**4**) forms an amide **9** with protected 4-(2-amino-1-hydroxyethyl)phenol **3** and the central oxazole is established by cyclodehydration of the acylaminoketone **2**.

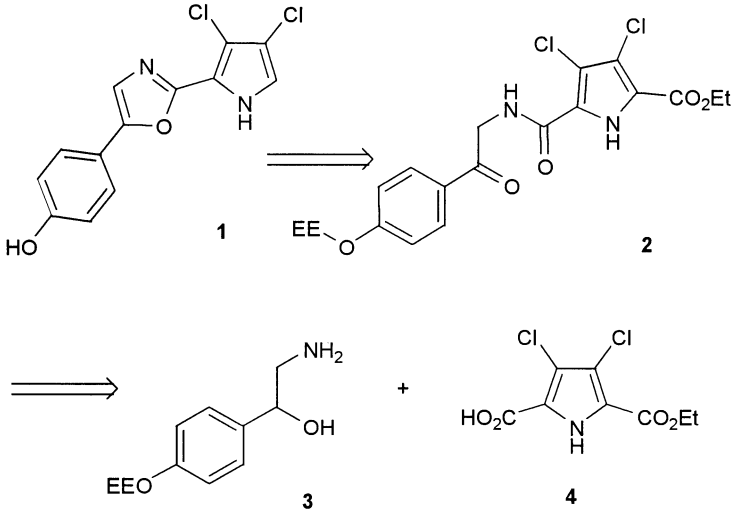
1. Introduction

Phorbazole C **1** belongs to a family of four compounds first isolated by Kashman et al.[1] from the sea sponge *Phorbas aff. clathrata* collected at Sodwana Bay, South Africa in 1994. These compounds have in common a unique structure of a pyrrole-, an oxazole- and a phenol ring, but differ in number and positions of chloro atoms. Little is known about the physiological properties of phorbazoles. For further examinations, it would be necessary to find easy access to these materials. To the best of our knowledge a total synthesis of phorbazole C is not known so far. A synthetic study reported an approach to the backbone-structure, i.e. crucial substituents were missing in the product.[2] Recently, we succeeded in the synthesis of an isomer of phorbazole A.[3] We report here the first total synthesis of phorbazole C **1**.

2. Results and discussion

The structure was approached in a convergent retrosynthetic manner according to Scheme 1 with formation of an amide **2** starting from the aminoethanol **3** and the dichloropyrrolecarboxylic acid **4** and formation of the oxazole ring by cyclodehydration of the acylaminoketone **2** as key steps.

4-Hydroxybenzaldehyde (**5**) was protected as ethoxyethylacetal **6** according to a literature procedure[4] followed by

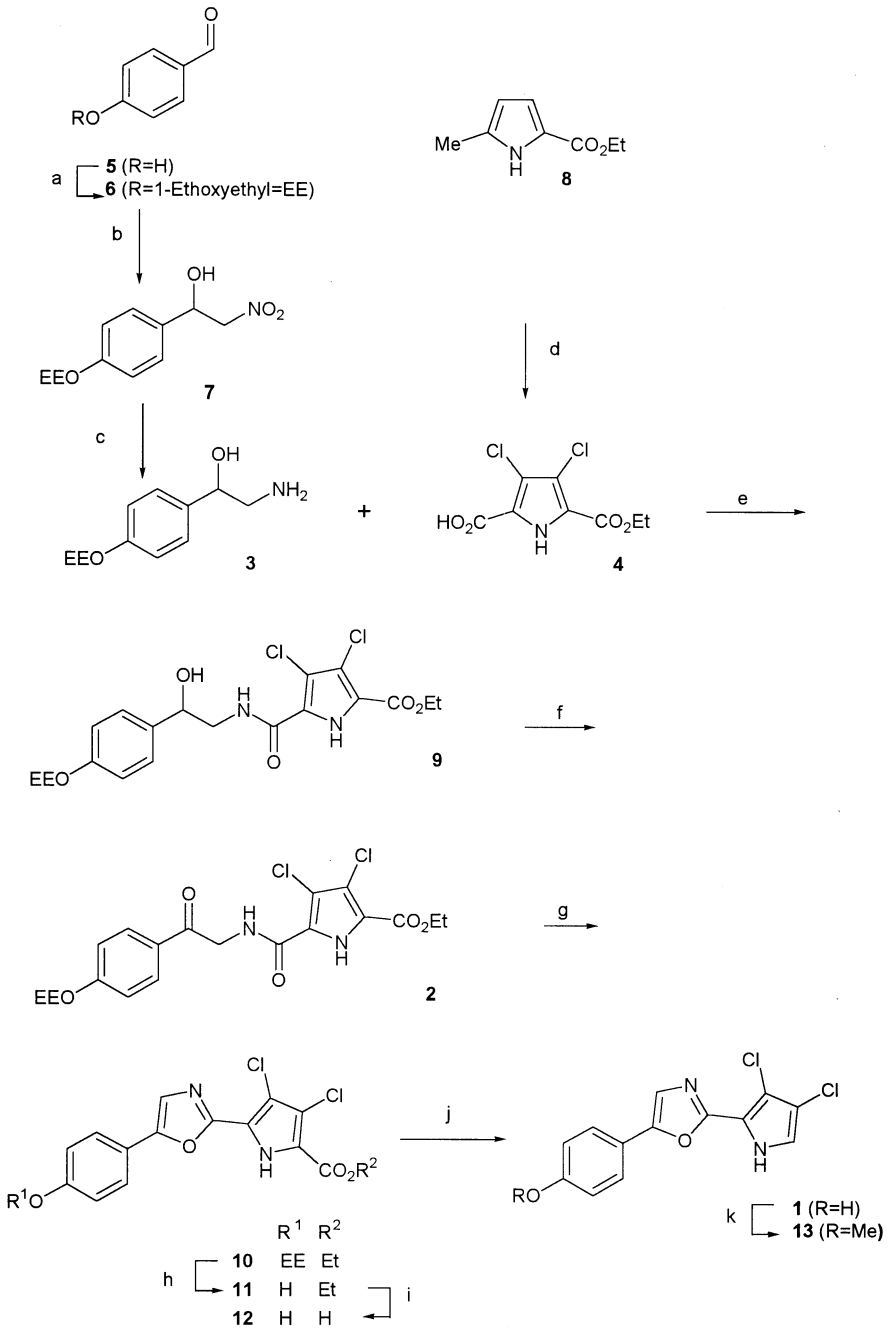


Scheme 1. Retrosynthetic analysis of phorbazole C (**1**).

Keywords: total synthesis; phorbazole C; natural product; oxazole.

* Corresponding author. Tel.: +49-30-2093-9039; fax: +49-30-2093-8907; e-mail: liebscher@chemie.hu-berlin.de

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00425-2



Scheme 2. (a) EtO–$CHCH_2$, MOM-Cl [cat], Et_2O, 78%; (b) $MeNO_2$, NEt_3, DMSO, rt, 84%; (c) H_2, 20 bar, Pd/C, NEt_3HCl, EtOH, rt, 88%; (d) 1. SO_2Cl_2, Et_2O, reflux; 2. H_2O, dioxane, 90°C, 47%; (e) DCC, HOBt, EtN^iPr_2, CH_2Cl_2, rt., 65%; (f) DMP, CH_2Cl_2, rt, 98%; (g) PPh_3, C_2Cl_6, NEt_3, CH_2Cl_2, rt, 87%; (h) HCl (1 M), EtOH, THF, rt, 77%; (i) NaOH (2 M), EtOH, reflux, 84%; (j) $H_2NC_2H_4OH$, 170°C, 85%; (k) MeI, K_2CO_3.

homologation using a Henry reaction with nitromethane and triethylamine in DMSO (Scheme 2). The resulting nitroaldol **7** was catalytically hydrogenated to the aminoethanol **3** under mild conditions (20 bar, room temperature) in the presence of triethylamine hydrochloride as weak proton source. The pyrrolecarboxylic acid **4** was accessible from known ethyl 5-methylpyrrole-2-carboxylate [5] (**8**) by oxidative chlorination with sulfuryl chloride. The crude product was hydrolysed in a dioxan solution at 90°C. The amide formation of the resulting pyrrolecarboxylic acid **4** with the aminoethanol **3** was achieved with DCC as coupling reagent in the presence of HOBt and ethyldiisopropylamine in dichloromethane in 65% yield. Other commonly used reagents ($SOCl_2$, BuOCOCl, BOP-Cl) failed to effect this transformation or provided considerably lower yields (EDC, DPPA, TBTU, HATU). The acylaminoalcohol **9** could be oxidised to the ketone **2** in excellent yields by Dess–Martin periodinane (DMP).[6] Cyclodehydration of the acylaminoketone **2** to the oxazole **10** was successful using a modified Wipf protocol (triphenylphosphine, perchloroethane, triethylamine).[7,8] The yield could even be slightly increased by the use of polymer bound triphenylphosphine (87% versus 81%). Classical reagents for oxazole syntheses by cyclodehydration[9] such as $SOCl_2$, $POCl_3$ or Ac_2O did not afford formation of the oxazole ring but resulted in deprotection of the phenolic hydroxy group of **2** instead. The oxazole **10**

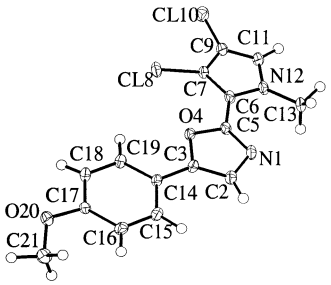


Figure 1. A molecule of O-methylated phorbazole C **13** in the crystal.[11]

was deprotected by treatment with diluted hydrochloric acid[10] and the ester moiety of resulting ethyl hydroxyphenyloxazolylpyrrolecarboxylate **11** was saponified with diluted NaOH. Final decarboxylation of the resulting pyrrole-2-carboxylic acid **12** was achieved by heating in 1,2-aminoethanol at 170°C, while reflux with sodium hydroxide in ethanol or glycol was not forcing enough for this transformation.

High yields were obtained in all steps. Thus the total yield of the transformation of 4-hydroxybenzaldehyde **5** into phorbazole C **1** via 9 steps was 18%. The material **1** obtained in this synthetic pathway showed spectroscopic data identical with those of natural phorbazole C.[1] The structure was further verified by X-ray analysis of the O-methyl derivative **13** (Fig. 1).[11]

3. Experimental

3.1. General

Reagents and materials were obtained from commercial suppliers and were used without further purification unless otherwise mentioned. Flash chromatography, silica gel 60 (0.040–0.063 mm), Merck; TLC, silica gel 60 F_{254} with fluorescent indicator, Merck, aluminium plates, melting points (uncorrected), Boetius heating block; ^1H and ^{13}C NMR, DPX 300 (Bruker) and AC 300 (Bruker); δ in ppm; J in [Hz]; HRMS MAT 711 (Varian) bei 70 eV. X-Ray crystal analysis STOE Ipds diffractometer.

3.2. Syntheses

3.2.1. 4-(1-Ethoxyethoxy)benzaldehyde (6). To a suspension of 4-hydroxybenzaldehyde (12.21 g, 0.10 mol) and ethoxyethene (8.65 g, 0.12 mol) in Et_2O (50 mL) a catalytic amount of chloromethoxymethane (0.1 mL) was added. After 48 h of reflux the clear solution was cooled to room temperature and was washed with 1 M aqueous NaOH (2×50 mL). The aqueous phase was extracted with Et_2O (2×50 mL). The combined organic phases were washed with brine (30 mL) and dried ($MgSO_4$), concentrated and distilled under vacuum (bp 91–96°C, 2×10^{-2} mbar) affording 15.21 g (78%) of product **6** as colorless oil. R_f=0.32 (hexane/EtOAc=8:2); ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (t, 3H, J=7.1 Hz, CH_3CH$_2$O), 1.47 (d, 3H, J=5.3 Hz, CH_3CHO$_2$), 3.47 (dq, 1H, J=9.3, 7.1 Hz, CH$_3$CHH'O), 3.68 (dq, 1H, J=9.3, 7.1 Hz, CH$_3$CHH'O), 5.45 (q, 1H, J=5.3 Hz, CH$_3$CHO$_2$), 7.02 (d, 2H, J=8.7 Hz, O^{ph}C^{ph}CH), 7.75 (d, 2H, J=8.7 Hz, O^{ph}C^{ph}CH^{ph}CH), 9.81 (s, 1H, HC=O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.1 (*C*H$_3$CH$_2$O), 19.9 (*C*H$_3$CHO$_2$), 61.1 (CH$_3$*C*H$_2$O), 99.1 (CH$_3$*C*HO$_2$), 116.8 (O^{ph}C^{ph}*C*H), 130.4 (^{ph}*C*CH=O), 131.8 (O^{ph}C^{ph}CH^{ph}*C*H), 162.1 (O^{ph}C), 190.8 (H*C*=O).

3.2.2. 1-[4-(1-Ethoxyethoxy)phenyl]-2-nitro-1-ethanol (7). To a solution of **6** (3.88 g, 0.02 mol) and nitromethane (3.2 mL, 0.06 mmol) in dry DMSO (15 mL) NEt_3 (2.79 mL, 0.02 mol) was added. After standing at room temperature for 14 h, the mixture was poured into a saturated aqueous NH_4Cl solution. The pH was brought to 7 by adding 0.1 M hydrochloric acid and the mixture was extracted with Et_2O (2×150 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated with a rotatory evaporator. Column chromatography with hexane/EtOAc (9:1) afforded starting material (349 mg, 9%). Further eluation with hexane/EtOAc (8:2) gave 4.29 g (84%) of product **7** as colorless oil. R_f=0.25 (hexane/EtOAc=7:3); ^1H NMR, $CDCl_3$) δ 1.18 (t, 3H, J=7.1 Hz, CH_3CH$_2$O), 1.48 (d, 3H, J=5.3 Hz, CH_3CHO$_2$), 2.93 (brs, 1H, OH), 3.54 (dq, 1H, J=9.3, 7.1 Hz, CH$_3$CHH$'$O), 3.75 (dq, 1H, J=9.3, 7.1 Hz, CH$_3$CHH'O), 4.46 (dd, 1H, J=13.6, 3.2 Hz, CHH$'$NO$_2$), 4.58 (dd, 1H, J=13.5, 9.5 Hz, CHH'NO$_2$), 5.35–5.42 (m, 2H, CHOH, CH$_3$CHO$_2$), 7.00 (d, 2H, J=8.7 Hz, O^{ph}C^{ph}CH), 7.29 (d, 2H, J=8.6 Hz, O^{ph}C^{ph}CH^{ph}CH); ^{13}C NMR $CDCl_3$): δ 15 (*C*H$_3$CH$_2$O), 20.5 (*C*H$_3$CHO$_2$), 61.7 (CH$_3$*C*H$_2$O), 71.0 (HOCH), 81.6 (NO$_2$CH$_2$), 99.8 (CH$_3$*C*HO$_2$), 118.1 (O^{ph}C^{ph}*C*H), 127.7 (O^{ph}C^{ph}CH^{ph}*C*H), 131.7 (^{ph}*C*CHOH), 157.8 (O^{ph}C).

3.2.3. 2-Amino-1-[4-(1-ethoxyethoxy)phenyl]-ethanol (3). A mixture of **7** (5.10 g, 0.02 mol), triethylammonium chloride (2.75 g, 0.02 mmol), 10% Pd/C (200 mg), EtOH (70 mL) and water (7 mL) was hydrogenated in an autoclave (coated with glass) at 20 bar under stirring for 5 h. Eventually more hydrogen gas must be provided if the pressure drops too much. The reaction mixture was filtered and the residue was washed with EtOH (30 mL). The combined filtrate was diluted with saturated aqueous K_2CO_3 (100 mL). The volume of the mixture was reduced to its half by a rotatory evaporator. After extraction with EtOAc (3× 70 mL) and drying ($MgSO_4$) the solvent was removed under vacuum and the residue was purified by column chromatography CH_2Cl_2/MeOH/NEt_3 (9:1:0.5) affording **3** (3.965 g, 88%) as pale yellow oil. R_f=0.25 (CH_2Cl_2/MeOH/NEt_3=9:1:0.5); ^1H NMR, $CDCl_3$): δ 1.19 (t, 3H, J=7.1 Hz, CH_3CH$_2$O), 1.47 (d, 3H, J=5.3 Hz, CH_3CHO$_2$), 2.74 (dd, 1H, J=12.8, 7.6 Hz, CHH$'$NH$_2$), 2.82 (dd, 1H, J=12.8, 4.2 Hz, CHH'NH$_2$), 3.03 (br s, 3H, OH, NH$_2$), 3.54 (dq, 1H, J=9.3, 7.1 Hz, CH$_3$CHH$'$O), 3.77 (dq, 1H, J=9.3, 7.1 Hz, CH$_3$CHH'O), 4.54 (dd, 1H, J=7.6, 4.2 Hz, CHOH), 5.35 (q, 1H, J=5.3 Hz, CH$_3$CHO$_2$), 6.95 (d, 2H, J=8.6 Hz, O^{ph}C^{ph}CH), 7.22 (d, 2H, J=8.6 Hz, O^{ph}C^{ph}CH^{ph}CH); ^{13}C NMR, $CDCl_3$): δ 15 (*C*H$_3$CH$_2$O), 20.2 (*C*H$_3$CHO$_2$), 49.2 (NH$_2$CH$_2$), 61.3 (CH$_3$*C*H$_2$O), 73.7 (HOCH), 99.6 (CH$_3$*C*HO$_2$), 117.2 (O^{ph}C^{ph}*C*H), 127.0 (O^{ph}C^{ph}CH^{ph}*C*H), 136.2 (^{ph}*C*CHOH), 156.2 (O^{ph}C).

3.2.4. Ethyl 5-methyl-1*H*-pyrrole-2-carboxylate (8). A solution of $NaNO_2$ (82.80 g, 1.20 mol) in water (125 mL) was slowly added to a solution of ethyl acetoacetate

(130.14 g, 1.00 mol) in acetic acid (350 mL) under stirring and ice cooling while the temperature was maintained below 10°C. After 12 h stirring at room temperature, 4,4-dimethoxy-2-butanone (132.3 g, 1.0 mol) was added. Zinc dust (142.6 g, 2.2 mol) was added under vigorous stirring as fast as foaming allowed. The mixture was heated to 120°C for 10 min. After the mixture had cooled down below 50°C it was poured into ice water (1 L). The mixture was stirred at 0°C for 1 h. The precipitating orange solid was filtered off, washed thoroughly with ice water and dried in a desiccator ($CaCl_2$). It was purified by distillation via a short air condenser under high vacuum (bp 110–120°C, 0.7×10^{-1} mbar) and recrystallized from hexane affording 33.7 g (22%) of colorless crystals. Mp=98–100°C, R_f=0.67 (hexane/EtOAc=9:1); ^{1}H NMR (DMSO-d_6): δ 1.23 (t, 3H, J=7.1 Hz, CH_3CH$_2$O), 2.18 (s, 3H, CH$_3^{py}$C), 4.16 (q, 2H, J=7.1 Hz, CH$_3$CH_2O), 5.83 (m, 1H, H^{py}C), 6.63 (m, 1H, H^{py}C), 11.53 (br s, 1H, NH); ^{13}C NMR DMSO-d_6): δ 12.7 (CH_3^{py}C), 14.5 (CH_3CH$_2$O), 59.2 (CH$_3$CH_2O), 108.3 (H^{py}C), 115.7 (H^{py}C), 120.6 (^{py}CC=O), 134.3 (^{py}CCH$_3$), 160.4 (C=O).

3.2.5. 3,4-Dichloro-5-ethoxycarbonylpyrrol-2-carboxylic acid (4). SO_2Cl_2 (40.55 g, 0.30 mol) was added dropwise to a solution of **8** (7.66 g, 0.05 mol) in dry Et_2O (250 mL) under stirring and ice cooling. After stirring at room temperature for 3 h volatile components were removed under vacuum and the remainder was dissolved in dioxane (130 mL) and water (20 mL). The mixture was heated to 90–95°C for 2 h and was concentrated to dryness under vacuum. The remainder was recrystallized from acetic acid affording 5.92 g (47%) of slightly yellow crystals. Mp=180°C (decomp.); ^{1}H NMR (DMSO-d_6): δ 1.30 (t, 3H, J=7.1 Hz, CH_3CH$_2$O), 4.27 (q, 2H, J=7.1 Hz, CH$_3$CH_2O), 13.11 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 14.1 (CH_3CH$_2$O), 61.0 (CH$_3$CH_2O), 116.4 (^{py}CCl), 117.2 (^{py}CCl), 120.6 (^{py}CCO$_2$), 122.0 (^{py}CCO$_2$), 158.3 (^{py}CCO$_2$), 159.7 (^{py}CCO$_2$).

3.2.6. Ethyl 3,4-dichloro-5-[({2-[4-(1-ethoxyethoxy)phenyl]-2-hydroxyethyl}amino)carbonyl]-1*H*-pyrrole-2-carboxylate (9). To a solution of **4** (1240 g, 5.50 mmol) in dry CH_2Cl_2 (30 mL) 1-hydroxybenzotriazole (HOBt) (768 mg, 5.50 mmol), ethyldiisopropyamine (646 mg, 5.50 mmol) and **3** (1260 mg, 5.00 mmol) were added. The mixture was stirred until it gave a clear solution. After the addition of DCC (1035 mg, 5.50 mmol) the mixture was stirred at room temperature for 4 h. After cooling to 0°C *N*,*N*′-dicyclohexylurea was filtered off and the filtrate was diluted with CH_2Cl_2 (30 mL), washed twice with saturated aqueous NH_4Cl, twice with half-concentrated aqueous K_2CO_3 and with phosphate buffer pH=7. After drying ($MgSO_4$) the solvent was removed under vacuum and the remainder was purified by column chromatography with $CHCl_3$/MeOH (98:2) affording 1493 mg (65%) of the product **9** as colorless solid. R_f=0.30 (CH_2Cl_2/acetone=9:1); ^{1}H NMR, $CDCl_3$): δ 1.12 (t, 3H, J=7.1 Hz, CH_3CH$_2$OCHO), 1.30 (t, 3H, J=7.1 Hz, CH_3CH$_2$OC=O), 1.41 (d, 3H, J=5.3 Hz, CH_3CHO$_2$), 3.40–3.48 (m, 2H, CHH′NH, CH$_3$CHH′OCHO), 3.68 (dq, 1H, J=9.3, 7.1 Hz, CH$_3$CHH'OCHO), 3.81 (m, 1H, CHH'NH), 3.97 (br s, 1H, OH), 4.29 (q, 2H, J=7.1 Hz, CH$_3$CH_2OC=O), 4.80 (m, 1H, CHOH), 5.29 (q, 1H, J=5.3 Hz, CH$_3$CHO$_2$), 6.90 (d, 2H, J=8.6 Hz, O^{ph}C^{ph}CH), 7.23 (d, 2H, J=8.6 Hz, O^{ph}C^{ph}CH^{ph}CH), 7.27 (br s, 1H, NHC=O), 10.62 (br s, 1H, ^{py}NH); ^{13}C NMR, $CDCl_3$): δ 14.2 (CH_3CH$_2$O), 15.1 (CH_3CH$_2$O), 20.2 (CH_3CHO$_2$), 47.0 (NHCH$_2$), 61.3 (CH$_3$CH_2O), 61.5 (CH$_3$CH_2O), 72.1 (HOCH), 99.5 (CH$_3$CHO$_2$), 112.8 (^{py}CCl), 117.4 (O^{ph}C^{ph}CH), 117.7 (^{py}CCl), 119.8 (^{py}CC=O), 123.4 (^{py}CC=O), 127.1 (O^{ph}C^{ph}CH^{ph}CH), 134.9 (^{ph}CCHOH), 156.7 (O^{ph}C), 158.5 (^{py}CC=O), 158.9 (^{py}CC=O).

3.2.7. Ethyl 3,4-dichloro-5-[({2-[4-(1-ethoxyethoxy)phenyl]-2-oxoethyl}amino)carbonyl]-1*H*-pyrrole-2-carboxylate (2). Dess–Martin periodinane[6] (509 mg, 1.11 mmol) was added to a solution of **9** (459 mg, 1.00 mmol) in dry CH_2Cl_2 (15 mL). The mixture was stirred at room temperature until the reactant disappeared (~45 min). The mixture was quenched by adding a solution of 8 g $Na_2S_2O_3$ in saturated aqueous $NaHCO_3$ (30 mL) and intensive stirring for 5 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated under vacuum. The remaining solid was recrystallized from EtOH affording **3** (420 mg, 98%) as colorless crystals. Mp 199–200°C, R_f=0.6 (CH_2Cl_2/acetone=9:1); ^{1}H NMR (DMSO-d_6): δ 1.09 (t, 3H, J=7.1 Hz, CH_3CH$_2$OCHO), 1.31 (t, 3H, J=7.1 Hz, CH_3CH$_2$OC=O), 1.43 (d, 3H, J=5.1 Hz, CH_3CHO$_2$), 3.49 (dq, 1H, J=9.3, 7.1 Hz, CH$_3$CHH′OCHO), 3.66 (dq, 1 H, J=9.4, 7.1 Hz, CH$_3$CHH'OCHO), 4.32 (q, 2H, J=7.1 Hz, CH$_3$CH_2OC=O), 4.79 (d, 1H, J=5.2 Hz, CHH'NH), 5.65 (q, 1H, J=5.1 Hz, CH$_3$CHO$_2$), 7.13 (d, 2H, J=8.7 Hz, O^{ph}C^{ph}CH), 7.99 (d, 2H, J=8.7 Hz, O^{ph}C^{ph}CH^{ph}CH), 8.54 (t, 1H, J=5.2 Hz, NHC=O), 12.97 (br s, 1H, ^{py}NH); ^{13}C NMR (DMSO-d_6): δ 14.2 (CH_3CH$_2$O), 15.2 (CH_3CH$_2$O), 20.1 (CH_3CHO$_2$), 46.0 (NHCH$_2$), 61.0 (CH$_3$CH_2O), 61.2 (CH$_3$CH_2O), 98.8 (CH$_3$CHO$_2$), 113.9 (^{py}CCl), 116.3 (^{py}CCl), 116.4 (O^{ph}C^{ph}CH), 119.2 (^{py}CC=O), 124.4 (^{py}CC=O), 128.3 (^{ph}CC=O), 130.3 (O^{ph}C^{ph}CH^{ph}CH), 157.9 (O^{ph}C), 158.5 (^{py}CC=O), 161.2 (^{py}CC=O), 193.1 (O=CCH$_2$). Anal. calcd for $C_{20}H_{24}Cl_2N_2O_6$ (457.31): C, 52.53; H, 4.85; N, 6.13; Cl, 15.51. Found: C, 52.20; H, 4.83; N, 6.12; Cl, 15.65.

3.2.8. Ethyl 3,4-dichloro-5-{5-[4-(1-ethoxyethoxy)phenyl]-1,3-oxazol-2-yl}-1*H*-pyrrole-2-carboxylate (10). To a solution of triphenylphosphine (787 mg, 3.00 mmol) in dry CH_2Cl_2 (15 mL), hexachloroethane (592 mg, 2.50 mmol), triethylamine (607 mg, 6.00 mmol) and a solution of **2** (457 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) were added. After stirring at room temperature, the clear solution was washed with saturated aqueous NH_4Cl (10 mL), saturated aqueous $NaHCO_3$ (10 mL) and with water (10 mL). After drying ($MgSO_4$), removing the solvent under vacuum and column chromatography hexane/EtOAc (6:4) **10** (356 mg, 81%) was obtained as colorless solid. Mp 199–200°C, R_f=0.2 (hexane/EtOAc=6:4); ^{1}H NMR (DMSO-d_6): δ 1.10 (t, 3H, J=7.0 Hz, CH_3CH$_2$OCHO), 1.33 (t, 3H, J=7.1 Hz, CH_3CH$_2$OC=O), 1.42 (d, 3H, J=5.1 Hz, CH_3CHO$_2$), 3.50 (dq, 1H, J=9.4, 7.0 Hz, CH$_3$CHH′OCHO), 3.67 (dq, 1H, J=9.4, 7.0 Hz, CH$_3$CHH'OCHO), 4.34 (q, 2H, J=7.1 Hz, CH$_3$CH_2OC=O), 5.55 (q, 1H, J=5.1 Hz, CH$_3$CHO$_2$), 7.12 (d, 2H, J=8.8 Hz, O^{ph}C^{ph}CH), 7.75 (s, 1H, ^{ox}CH), 7.83 (d, 2H, J=8.7 Hz, O^{ph}C^{ph}CH^{ph}CH), 13.51 (br s, 1H, ^{py}NH); ^{13}C NMR (DMSO-d_6): δ 14.2 (CH_3CH$_2$O),

15.2 (CH_3CH_2O), 20.2 (CH_3CHO_2), 61.0 (CH_3CH_2O), 61.1 (CH_3CH_2O), 98.9 (CH_3CHO_2), 112.3 (^{py}CCl), 117.1 (^{py}CCl), 117.4 ($O^{ph}C^{ph}CH$), 119.7, 119.8, 120.6 (^{py}CC=O, $^{py}C^{ox}$C, $^{ph}C^{ox}$C), 122.6 (^{ox}CH), 126.1 ($O^{ph}C^{ph}CH^{ph}CH$), 150.7, 151.4 (O^{ox}C,O^{ox}CN), 157.3 (O^{ph}C), 158.6 (^{py}CC=O).

3.2.9. Ethyl 3,4-dichloro-5-[5-(4-hydroxyphenyl)-1,3-oxazol-2-yl]-1*H*-pyrrole-2-carboxylate (11). 1 M hydrochloric acid (1 mL) was added to a solution of **10** (439 mg, 1.00 mmol) in THF (7 mL). The solution was stirred at room temperature until all **10** disappeared (~5 h, TLC). The solution was diluted with brine (10 mL), neutralized with $NaHCO_3$ and extracted with EtOAc (3×15 mL). The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated under vacuum. After column chromatography hexane/EtOAc (1:1) **11** (282 mg, 77%) was obtained as colorless solid. Mp 227–229°C; R_f:0.19 (hexane/EtOAc=1:1); ^{1}H NMR (DMSO-d_6): δ 1.33 (t, 3H, J=7.1 Hz, CH_3CH_2OC=O), 4.34 (q, 2H, J=7.1 Hz, CH_3CH_2OC=O), 6.87 (d, 2H, J=8.8 Hz, $O^{ph}C^{ph}CH$), 7.66 (s, 1H, ^{ox}CH), 7.72 (d, 2H, J=8.8 Hz, $O^{ph}C^{ph}CH^{ph}CH$), 9.87 (s, 1H, HO^{ph}C), 13.47 (br s, 1H, ^{py}NH); ^{13}C NMR (DMSO-d_6): δ 14.3 (CH_3CH_2O), 61.0 (CH_3CH_2O), 112.2 (^{py}CCl), 115.9 ($O^{ph}C^{ph}CH$), 117.0 (^{py}CCl), 118.3, 119.6, 119.8 (^{py}CC=O, $^{py}C^{ox}$C, $^{ph}C^{ox}$C), 121.7 (^{ox}CH), 126.2 ($O^{ph}C^{ph}CH^{ph}CH$), 151.0, 151.3 ($O^{ox}C$ ^{ox}CH, O^{ox}CN), 158.3 (O^{ph}C), 158.7 (^{py}CC=O).

3.2.10. 3,4-Dichloro-5-[5-(4-hydroxyphenyl)-1,3-oxazol-2-yl]-1*H*-pyrrole-2-carboxylic acid (12). 11 (352 mg, 1.00 mmol) was dissolved in a mixture of EtOH (8 mL) and 2N NaOH (2 mL). After refluxing for 2 h (TLC), the solution was concentrated under vacuum and carefully neutralized with 0.5 M hydrochloric acid. After dilution with saturated aqueous NH_4Cl (50 mL) the mixture was extracted with THF (5×15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under vacuum affording **12** (295 mg, 87%) as colorless solid which was further used without prior purification. Mp 180°C (decomp.); R_f: 0.15 (CH_2Cl_2/EtOH=7:3); ^{1}H NMR (DMSO-d_6): δ 6.87 (d, 2H, J=8.7 Hz, $O^{ph}C^{ph}CH$), 7.62 (s, 1H, ^{ox}CH), 7.72 (d, 2H, J=8.7 Hz, $O^{ph}C^{ph}CH^{ph}CH$); ^{13}C NMR (DMSO-d_6): δ 112.0 (^{py}CCl), 115.9 ($O^{ph}C^{ph}CH$), 116.7 (^{py}CCl), 118.3, 119.2, 120.6 (^{py}CC=O, $^{py}C^{ox}$C, $^{ph}C^{ox}$C), 121.6 (^{ox}CH), 126.2 ($O^{ph}C^{ph}CH^{ph}CH$), 151.1 ($O^{ox}C$ ^{ox}CH), 158.3 (O^{ox}CN), 160.0 (O^{ph}C), 172.1 (^{py}CC=O).

3.2.11. Phorbazole C; 2-(3,4-dichloro-1*H*-pyrrol-2-yl)-5-(4-hydroxyphenyl)-1,3-oxazole (1). An air free solution of **12** (339 mg, 1.00 mmol) in 2-aminoethanol (6 mL) was heated under argon for 40 min. After the mixture had cooled down to 50°C it was poured into saturated aqueous NH_4Cl (60 mL). The mixture was brought to pH 4–5 with 1 M hydrochloric acid and was extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. After column chromatography (hexane/EtOAc=6:4) phorbazole C was obtained as colorless solid (248 mg, 84%). All analytical data correspond to those reported in the literature.[1] Mp 238–239° (ref. mp 240°C); R_f: 0.28 (hexane/EtOAc=6:4). ^{1}H NMR (DMSO-d_6): δ 6.87 (d, 2H, J=8.7 Hz, $O^{ph}C^{ph}CH$), 7.27 (d, 1H, J=3.2 Hz, $^{py}NH^{py}CH$), 7.56 (s, 1H, ^{ox}CH), 7.61 (d, 2H, J=8.7 Hz, $O^{ph}C^{ph}CH^{ph}CH$), 9.83 (br s, 1H, HO^{ph}C), 12.51 (br s, 1H, ^{py}NH); ^{13}C NMR (DMSO-d_6): δ 110.0 ($^{py}C Cl^{py}CCl^{py}CH$), 111.1 ($^{py}CCl^{py}CCl^{py}CH$), 116.0 ($O^{ph}C^{ph}CH$), 116.3 ($^{py}C^{ox}$C), 118.5 ($^{ph}C^{ox}$C), 119.1 (^{py}CH), 121.1 (^{ox}CH), 125.7 ($O^{ph}C^{ph}CH^{ph}CH$), 150.2 ($O^{ox}C^{ph}$C), 152.4 (O^{ox}CN), 158.0 (O^{ph}C). HRMS (EI) calcd for $C_{13}H_8Cl_2N_2O_2$ 293.99628, found 293.9963.

3.2.12. 2-(3,4-Dichloro-1*H*-pyrrol-2-yl)-5-(4-methoxyphenyl)-1,3-oxazole (13). Crystals of the derivative **13** suitable for X-ray crystal analysis (crystal system: triclinic, space group P-1, unit cell dimensions: a=7.8283(14) Å, α=77.90(3)°, b=8.1721(16) Å, β=82.16(2), c=12.336(3) Å, (γ=67.376(13)°, volume 710.9(3) Å^3, Z=2, calculated density: 1.510 mg/m^3, crystal size: 0.92×0.85×0.20 mm) were obtained from a solution of **1** (10 mg), MeI (100 mg) and K_2CO_3 (100 mg) in acetone (1 mL) after 20 min of stirring at room temperature. The following parameters were used for C-ray crystal analysis: Temperature: 180(2) K; wavelength: 0.71073 Å; theta range for data collection: 1.69–25.08°; limiting indices: $-9\le h\le 9$, $-9\le k\le 9$, $-14\le l\le 14$; reflections collected/unique 3835/2529 [R(int)=0.0510]; completeness to θ=25.08 100.0%; max. and min. transmission: 0.9134 and 0.6762; refinement method: Full-matrix least-squares on F^2; data/restraints/parameters: 2529/0/239; goodness-of-fit on F^2: 0.986; Final R indices [$I>2\sigma(I)$], $R1$=0.0485, $\omega R2$=0.1245; R indices (all data): $R1$=0.0934, $\omega R2$=0.1596; extinction coefficient: 0.002(3); largest diff. peak and hole 0.373 and −0.318e Å^{-3}.

Acknowledgements

We gratefully acknowledge financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Dr Burkhard Ziemer, Institut für Chemie, Humboldt-Universität Berlin for the X-ray crystal analysis.

References

1. Rudi, A.; Stein, Z.; Green, S.; Goldberg, I.; Kashman, Y.; Benayahu, Y.; Schleyer, M. *Tetrahedron Lett.* **1994**, *35*, 2589–2592.
2. Loughlin, W. A.; Muderawan, I. W.; McCleary, M. A.; Volter, K. E.; King, M. D. *Aust. J. Chem.* **1999**, *52*, 231–234.
3. Radspieler, A.; Liebscher, J. *Synthesis* **2001** in press.
4. Hünig, S.; Schweeberg, H.; Schwarz, H. *Liebigs Ann.* **1954**, *587*, 132–145.
5. Motekaitis, R. J.; Heinert, D. H.; Martell, A. E. *J. Org. Chem.* **1970**, *35*, 2504–2511.
6. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
7. Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 3604–3606.
8. Appel, R. *Angew. Chem.* **1975**, *87*, 863–871; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801–812.
9. Robinson, R. *J. Chem. Soc.* **1909**, *95*, 2167–2174.
10. Tius, M. A.; Faug, A. H. *J. Am. Chem. Soc.* **1986**, *108*, 1035–1039.
11. Full details have been deposited at the Cambridge Crystallographic Data Centre, reference number CCDC 156638. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.