# First Total Synthesis of *N*-(3-Guanidinopropyl)-2-(4-hydroxyphenyl)-2-oxoacetamide

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The first total synthesis of the $\alpha$-oxo amide-based natural product, *N*-(3-guanidinopropyl)-2-(4-hydroxyphenyl)-2-oxoacetamide (**3**), isolated from aqueous extracts of hydroid *Campanularia* sp., has been achieved. The $\alpha$-oxo amide **12**, prepared *via* the oxidative amidation of 1-[4-(benzyloxy)phenyl]-2,2-dibromoethanone (**9a**) with 4-{[(*tert*-butyl)(dimethyl)silyl]oxy}butan-1-amine (**10a**), has been used as the key intermediate in the total synthesis of **3** as HBr salt. On the way, an expeditious total synthesis of polyandrocarpamide C (**2c**), isolated from marine ascidian *Polyandrocarpa* sp., was carried out in four steps.

**Introduction.** – The $\alpha$-oxo amides are an intriguing class of reactive functionalities, found in a number of natural products and pharmaceuticals [1]. Coscinamides **1a**–**1c** [2] and polyandrocarpamides **2a**–**2c** [3] *etc.* posses a indol-3-yl oxo amide framework in their structures. The polyandrocarpamides **2a**–**2c** were isolated by *Lindquist* and *Fenical* from marine ascidian *Polyandrocarpa* sp. [3]. Recently, *Houssen* and *Jaspars* isolated *N*-(3-guanidinopropyl)-2-(4-hydroxyphenyl)-2-oxoacetamide (**3**), an oxo amide-based natural product, from aqueous extracts of marine invertebrates *Campanularia* sp. [4]. Despite its structural resemblance to histone deacetylase (HDAC) inhibitors such as suberoylanilide hydroxamic acid (SAHA; **4**) and trichostatin A (TSA; **5**), **3** did not inhibit the growth of ARP-1 cells, presumably indicating its diminished activity towards HDACs [5] (*Fig.*).

**Results and Discussion.** – As a part of our ongoing work on total syntheses of biologically relevant natural products and their congeners [6], herein we report the first total synthesis of *N*-(3-guanidinopropyl)-2-(4-hydroxyphenyl)-2-oxoacetamide (**3**) and also the total synthesis of polyandrocarpamide C (**2c**).

The retrosynthetic strategy for the synthesis of **3**, involving oxidative amidation methodology as the key step, is outlined in *Scheme 1*. Deprotection of the OH group as well as the amino groups in **6** with suitable reagents would yield the natural product **3**. The hydroxy protected natural oxo amide **6** in turn could be generated by *Mitsunobu* reaction of an appropriately protected guanidine building block **7** with *N*-hydroxyalkyl

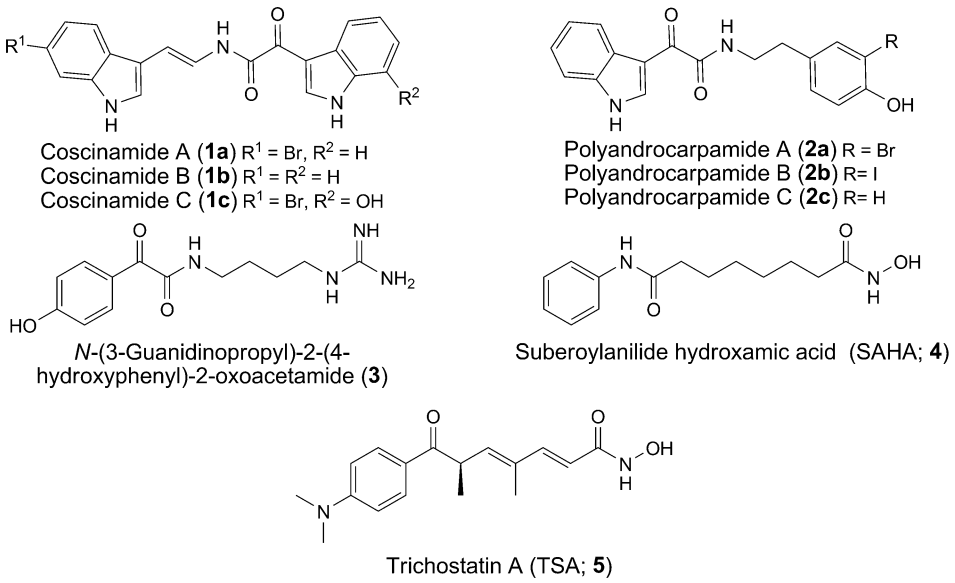
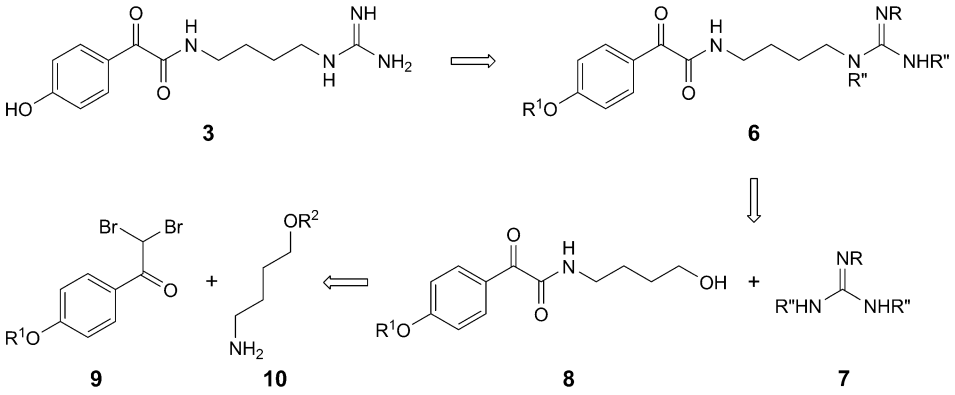



Figure. *Natural products containing α-oxo moieties* **1**–**3**, *and HDAC inhibitors* **4** *and* **5**

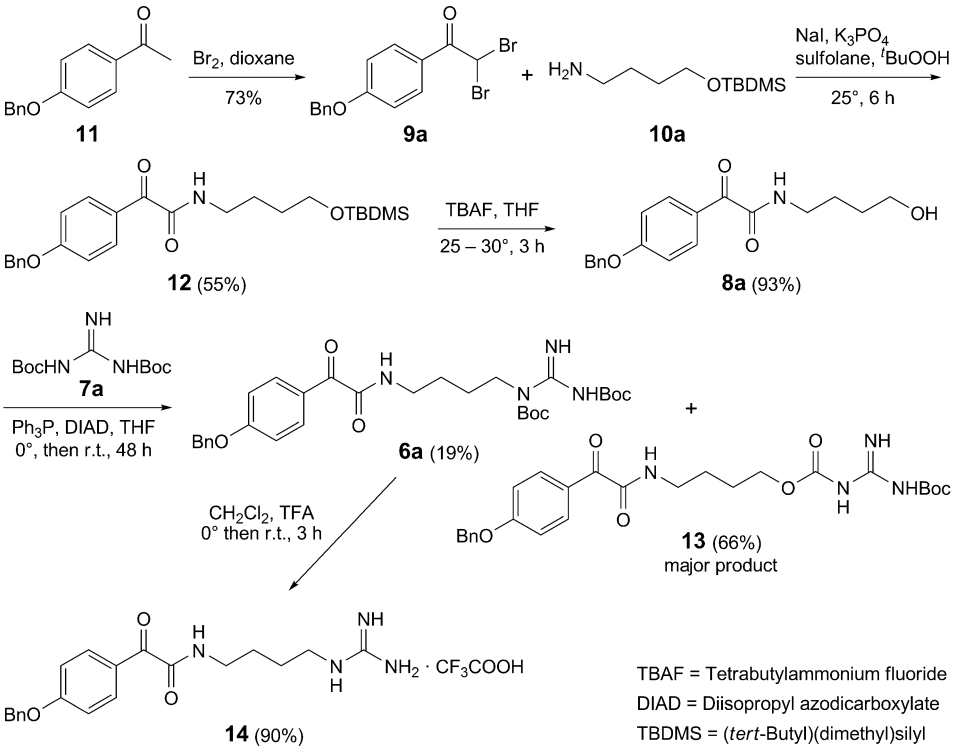
Scheme 1. *Retrosynthetic Scheme for the Synthesis of* **3**




α-oxo amide **8**. The latter could be prepared by oxidative amidation of 2,2-dibromoethanone **9** with hydroxy-protected 4-aminobutan-1-ol (**10**).

The total synthesis of **3** was initiated with the synthesis of 1-[4-(benzyloxy)phenyl]-2,2-dibromoethanone (**9a**; *Scheme 2*), which was prepared from 1-[4-(benzyloxy)phenyl]ethanone (**11**) by bromination with $Br_2$ in dioxane in 73% yield [7]. The oxidative coupling of **9a** with TBDMS-protected 4-aminobutan-1-ol **10a** was carried out as described in [8], and the α-oxo amide **12** was isolated in 55% yield. The removal of the TBDMS groups in **12** was achieved by treatment with 1.0M solution of $Bu_4NF$ in THF [9], and the free alcohol **8a** was then isolated as pale-yellow solid in 93% yield. The

Scheme 2. *Synthesis of* **14**, *the* O-*Benzyl Trifluoroacetic Acid Salt of* **3**

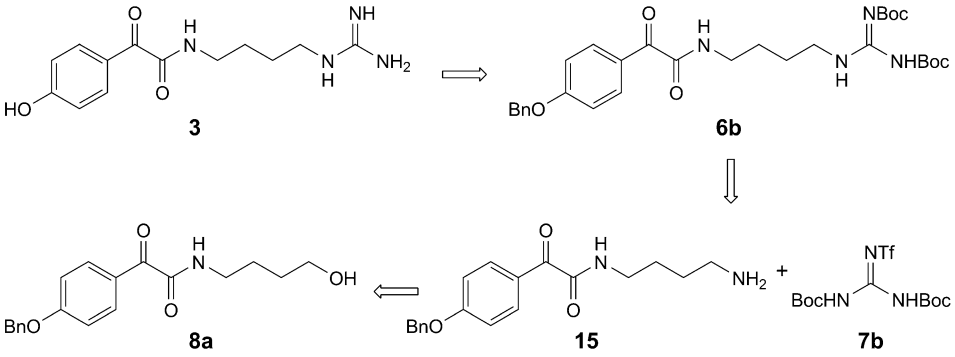



*Mitsunobu* reaction [10] of *N*,*N*′-di-Boc-guanidine **7a** [11] and **8a** was then attempted. Initially, the reaction was performed with diisopropyl azodicarboxylate (DIAD) and $Ph_3P$. However, the required guanidino-substituted $\alpha$-oxo amide **6a** was obtained only in 19% yield, whereas the major product formed in the reaction was identified as **13**, a transesterification product [12]. Our attempts to improve the yield of the *Mitsunobu* reaction of **8a** and **7a** under various conditions utilizing different activating agents/bases and solvent combinations were unsuccessful, and these reactions always gave **6a** in low yields (less than 20%). The removal of the *N*,*N*′-di-Boc group [13] in **6a** with $CF_3COOH$ (TFA) in $CH_2Cl_2$ yielded the *O*-Bn derivative of the natural product **3** as TFA salt, *i.e.*, **14**, in 90% yield.

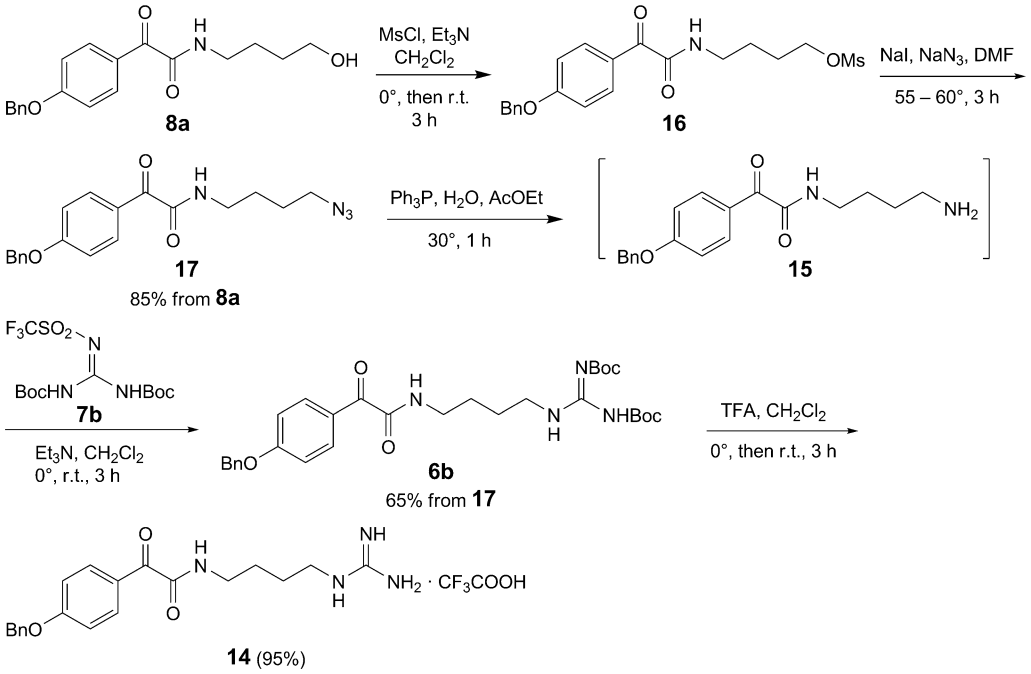
Though the synthesis of *O*-Bn derivative **14** of the natural product **3** was achieved *via* oxidative amidation-*Mitsunobu* reaction strategy, we have attempted to develop an alternative approach to address the low overall yield in the synthesis, especially in the *Mitsunobu* reaction. Our solution was to introduce the guanidine unit in **3** *via* displacement of the aminotriflate group in *N*,*N*′-di-Boc-*N*″-triflylguanidine (**7b**; triflyl (Tf), trifluoromethanesulfonyl) with the pre-constructed primary amino functionality in $\alpha$-oxo amide **15** (*Scheme 3*).

Thus, we started the total synthesis of **3** with **8a** as the key intermediate (*Scheme 4*). The mesyl (Ms; methanesulfonyl) protection of the primary OH group in **8a** was

Scheme 3. *Modified Retrosynthetic Scheme for the Synthesis of* **3**




Scheme 4. *Synthesis of* **14** via N,N'-*Di-Boc*-N"-*triflylguanidine*

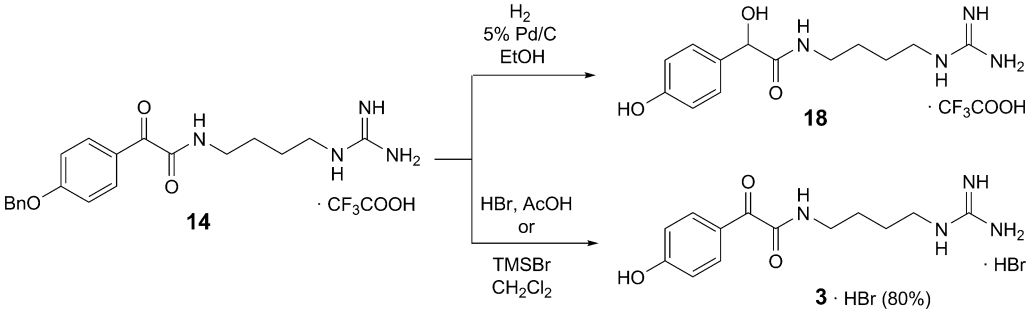



carried out with $Et_3N/CH_2Cl_2/MsCl$ [14], and the product **16** was used *in situ* for the azidation. Thus, removal of the Ms group in **16** with $NaN_3$ [15] gave the azido derivative **17**, which, *via Staudinger* reduction, yielded the free amine **15** [16]. As the latter underwent multiple reactions and decomposition during its isolation, especially while concentrating the reaction mixture, our attempts to isolate the free amine in very pure form were not successful. Hence, *in situ* guanidination of **15** was attempted with *N*,*N*′-di-Boc-*N*″-triflylguanidine (**7b**). Thus, **15** in $CH_2Cl_2$ was reacted directly with **7b** and the di-Boc guanidino $\alpha$-oxo amide **6b** was isolated in 65% overall yield over two steps

starting from **17**. The removal of the Boc groups in **6b** was carried out with TFA in $CH_2Cl_2$ at room temperature, and the free guanidino product was isolated as TFA salt **14** in 95% yield as white crystalline solid.

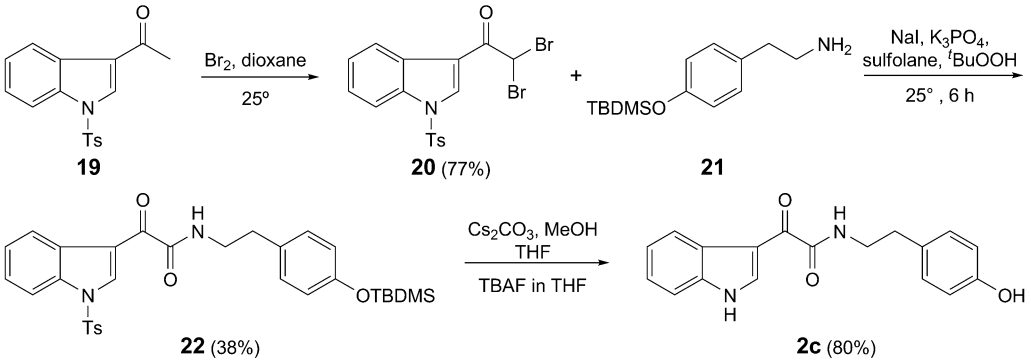
Thus, after the successful introduction of the guanidino moiety in very high yields, our attempts were directed towards the removal of the *O*-Bn group in **14** (*Scheme 5*). This was initially attempted with Pd/C-mediated hydrogenolysis; however, the major product formed in this was identified as over-hydrogenated product **18**. Our attempts to prepare **3** under different hydrogenation reaction conditions (such as lower temperature, different $H_2$ pressures, and various grades of Pd/C, and % loading of Pd/C, *etc.*) were not successful. However, when the reaction was carried out with HBr/AcOH at 0°, the debenzylation proceeded smoothly and **3** was isolated in 80% yield as HBr salt. The deprotection of **14** went equally well with $TMSBr/CH_2Cl_2$, and **3** · HBr was isolated in comparable yields. By this alternate approach, the total synthesis of **3** · HBr was achieved in an overall yield of 15.67% over a seven-step process.

Scheme 5. *Removal of the* O-*Benzyl Group*




In the literature, a synthesis of polyandrocarpamide C (**2c**) has been reported using (indol-3-yl)-2-oxoacetate or (2-indol-3-yl)-2-oxochloride as starting materials [17]. Herein, we report the total synthesis of **2c** *via* oxidative amidation as key step of the synthesis (Scheme *6*). The 3-acetyl-1-tosyl-1*H*-indole (**19**) was subjected to dibromi-

Scheme 6. *Synthesis of Polyandrocarpamide C* (**2c**)



nation with $Br_2$ in dioxane to give **20** in 77% yield. The oxidative amidation of **20** with 2-(4-[(*tert*-butyl)(dimethyl)silyl]oxy}phenyl)ethanamine (**21**) was carried out as under standard reaction conditions to yield the $\alpha$-oxo amide **22**. Detosylation and desilylation of **22** yielded **2c** in overall 23.4% yield starting from **19**.

**Conclusions.** – We achieved the first total synthesis of the natural product *N*-(3-guanidinopropyl)-2-(4-hydroxyphenyl)-2-oxoacetamide (**3**) as HBr salt in high yield. The synthesis of polyandrocarpamide C (**2c**) was also carried out as a part of this study. In the total synthesis of these two $\alpha$-oxo amide-based natural products, oxidative amidation has been employed as the key step of the process. The total syntheses of these natural products were realized under mild reaction conditions and starting from easily accessible starting materials. The synthesis of more natural products utilizing oxidative amidation–*Mitsunobu* reaction is under progress, and will be reported in due course.

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## Experimental Part

*General.* All reactions were carried out in oven-dried glassware under $N_2$, with magnetic stirring, and the reactions were monitored by TLC, using *Merck* aluminum-backed plates pre-coated with silica gel ($SiO_2$; 0.25 mm, *60 $F_{254}$*). The TLC plates were visualized under UV light (254 nm) or developed using a soln. of $KMnO_4$. Purifications were performed by column chromatography (CC) with $SiO_2$ (60–120 mesh) purchased from *SRL* and eluted with hexanes/AcOEt.

M.p.: *Electrothermal* melting point apparatus; uncorrected. IR Spectra: a *PerkinElmer 1650 Fourier Transform* spectrometer. NMR Spectra: in $CDCl_3$, $CD_3OD$, or ($D_6$)DMSO (all with $Me_4Si$ as internal standard) on *Varian Gemini* 200-MHz *Fourier* transform (FT) and 400-MHz FT spectrometers, chemical shifts in ppm; and coupling constants ($J$) in Hz. MS: *HP-5989A quadrupole* mass spectrometer; in *m*/*z*.

*2-[4-(Benzyloxy)phenyl]*-N-*(4-{[(*tert*-butyl)(dimethyl)silyl]oxy}butyl)-2-oxoacetamide* (**12**). To a stirred pre-cooled (20–25°) mixture of *2,2-dibromo-1-[(4-benzyloxy)]phenylethanone* (**9a**; 10.0 g, 0.026 mol), NaI (7.81 g, 0.052 mol), sulfolane (=2,3,4,5-tetrahydrothiophene 1,1-dioxide; 50.0 ml), and $K_3PO_4$ (13.81 g, 0.065 mol, powdered) were added, followed by *4-[(*tert*-(butyl)(dimethyl)silyloxy)]butan-1-amine* (**10a**; 6.35 g, 0.031 mol) under $N_2$. The mixture was stirred for *ca.* 1.5–2 h at r.t. A soln. of $^t$BuOOH (*ca.* 5.5M in decane, 5.9 ml, 0.033 mol) was added to the mixture within 10 min, and stirring was continued for another 5–6 h at r.t. The mixture was diluted with $H_2O$ (200 ml) and extracted with AcOEt (3 × 50 ml). The combined AcOEt extracts were washed with 10% aq. $NaHSO_3$ soln. (2 × 50 ml), dil. HCl (5%; 75 ml), and 10% NaCl soln. (100 ml). The org. layer was dried ($Na_2SO_4$) and concentrated under reduced pressure. The residue was purified by CC ($SiO_2$ (60–120 mesh); using AcOEt/hexanes) 20:80 to afford **12** (6.31g, 55%). Pale-yellow solid. M.p. 91–92°. IR (KBr): 3300, 3072, 2929, 1643, 1604, 1568, 1541, 1471, 1382, 1317, 1264, 1225, 1169, 1100. $^1$H-NMR (400 MHz, $CDCl_3$): 0.05 (*s*, 6 H); 0.88 (*s*, 9 H); 1.59–1.69 (*m*, 4 H); 3.40 (*q*, $J$ = 6.6, 2 H); 3.60 (*t*, $J$ = 6.4, 2 H); 5.10 (*s*, 2 H); 7.00 (*d*, $J$ = 9.2, 2 H); 7.20 (br. *s*, NH); 7.44–7.34 (*m*, 5 arom. H); 8.41 (*d*, $J$ = 8.8, 2 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 5.3; 18.2; 25.8; 29.9; 30.1; 39.0; 62.5; 70.0; 114.5; 126.5; 127.3; 128.1; 128.6; 133.8; 135.9; 162.2; 163.6; 185.8. ESI-MS: 442 ([$M$ + H]$^+$).

*2-[4-(Benzyloxy)phenyl]*-N-*(4-hydroxybutyl)-2-oxoacetamide* (**8a**). To a soln. of **12** (6.3 g, 0.0142 mol) in THF (33 ml) was added $Bu_4NF$ soln. (1M in THF, 15.7 ml, 0.0156 mol) at 5–10°. The mixture was stirred for 2 h (monitored by TLC). After disappearance of **12** (TLC); the mixture was diluted with $H_2O$ and extracted with $^t$BuOMe (65 ml). The org. layer was washed with 10% NaCl soln.

(35 ml) and concentrated under vacuum. The residue was purified by flash CC ($SiO_2$; AcOEt/hexanes 30:70) to give **8a** (4.36 g, 93%). Pale-yellow solid. M.p. 97–100°. IR (KBr): 3102, 1670, 1636, 1603, 1573, 1510, 1455, 1426, 1386, 1317, 1264, 1176, 1117. $^1$H-NMR (400 MHz, $CDCl_3$): 1.61–1.75 (*m*, 4 H); 3.40 (*q*, *J* = 6.8, 2 H); 3.71 (*t*, *J* = 6.0, 2 H); 5.15 (*s*, 2 H); 7.00–7.04 (*m*, 2 H); 7.34 (*s*, NH); 7.42–7.39 (*m*, 5 arom. H); 8.38–8.42 (*m*, 2 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 25.8; 29.7; 39.1; 62.2; 70.1; 114.6; 126.4; 127.4; 128.2; 128.6; 133.8; 135.8; 162.4; 163.7; 185.8. ESI-MS: 328.2 ($[M+H]^+$), 350.1 ($[M+Na]^+$).

*4-({2-[4-(Benzyloxy)phenyl]-2-oxoacetyl}amino)butyl Methanesulfonate* (**16**). Under $N_2$, to a soln. of **8a** (3.5 g, 0.010 mol) in $CH_2Cl_2$ (35 ml) was added $Et_3N$ (2.16 g, 0.0214 mol), and the mixture was cooled to 0–5°. MsCl (1.53 g, 0.0133 mol) in $CH_2Cl_2$ (30 ml) was added to the mixture slowly over a period of 30 min at 0–5°, and stirring was continued for 4 h at r.t. (monitored by TLC). The mixture was then diluted with $H_2O$. The $CH_2Cl_2$ layer was separated and washed with 10% aq. $NaHSO_3$ soln., followed by 10% aq. NaCl soln. The $CH_2Cl_2$ layer was dried ($Na_2SO_4$) and concentrated under vacuum to give **16**, which was used as such for the next step of the reaction. An anal. pure sample of **16** was obtained by purification of the crude product by CC ($SiO_2$; AcOEt/hexanes 25:75). Off-white solid. IR (KBr): 3098, 2943, 1670, 1638, 1603, 1572, 1509, 1459, 1353, 1265, 1168. $^1$H-NMR (400 MHz, $CDCl_3$): 1.73–1.86 (*m*, 4 H); 2.99 (*s*, 3 H); 3.40 (*q*, *J* = 6.8, 2 H); 4.24 (*t*, *J* = 6.2, 2 H); 5.10 (*s*, 2 H); 7.20 (*s*, NH); 7.44–7.33 (*m*, 5 arom. H); 8.39–8.43 (*m*, 2 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 25.5; 26.4; 37.3; 38.5; 69.1; 70.1; 114.6; 126.4; 127.4; 128.2; 128.6; 133.8; 135.8; 162.3; 163.8; 185.4. ESI-MS: 406.2 ($[M+H]^+$).

N-*(4-Azidobutyl)-2-[4-(benzyloxy)phenyl]-2-oxoacetamide* (**17**). To a soln. of crude **16** in DMF (20 ml), $NaN_3$ (1.04 g, 0.0160 mol) was added at r.t., and the mixture was heated at 60° for 1 h (monitored on TLC). After completion of the reaction, the mixture was diluted with $H_2O$ (80 ml) and extracted with AcOEt (2 × 30 ml). The AcOEt layer was washed with 10% aq. NaCl soln. (2 × 25 ml) and concentrated under vacuum. The crude product was purified by CC ($SiO_2$; AcOEt/hexanes 25:75) to give **17** (3.25 g, 85% over two steps). Light-cream solid. M.p. 83–85°. IR (KBr): 2343, 2093, 1670, 1637, 1604, 1573, 1510, 1454, 1427, 1351, 1316, 1265. $^1$H-NMR (400 MHz, $CDCl_3$): 1.63–1.73 (*m*, 4 H); 3.30 (*t*, *J* = 6.4, 2 H); 3.39–3.44 (*m*, 2 H); 5.12 (*s*, 2 H); 7.01–7.04 (*m*, 2 H); 7.23 (*s*, NH); 7.44–7.39 (*m*, 5 arom. H); 8.39–8.43 (*m*, 2 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 26.2; 26.5; 38.6; 50.9; 70.1; 114.6; 126.4; 127.4; 128.2; 128.6; 133.8; 135.9; 162.3; 163.8; 185.5. ESI-MS: 353.20 ($[M+H]^+$).

*Di(*tert*-butyl) [{[4-({2-[4-(benzyloxy)phenyl]-2-oxoacetyl}amino)butyl]amino}methylylidene]bis-carbamate* (**6b**). To a soln. of **17** (2.8 g, 0.0079 mol) in AcOEt (14 ml) were added $H_2O$ (1.4 ml) and $Ph_3P$ (5.21 g, 0.0198 mol), and the mixture was stirred for 1 h at 30°. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was dil. with $H_2O$ (20 ml). The layers were separated, and the AcOEt layer was washed with 10% citric acid soln. The combined aq. layer was basified with dilute aq. NaOH soln. and extracted with $CH_2Cl_2$ (2 × 20 ml). The $CH_2Cl_2$ layer was washed with brine (30 ml) and dried ($Na_2SO_4$). The dry $CH_2Cl_2$ layer was cooled, and $Et_3N$ (1.6 g, 0.0158 mol) was added, followed by addition of **7b** (3.71 g, 0.00945 mol) at 0–5°. The reaction was completed in *ca.* 2.5 h (monitored by TLC). The mixture was diluted with $H_2O$, and $CH_2Cl_2$ layer was washed with 10% NaCl soln. The $CH_2Cl_2$ layer was dried ($Na_2SO_4$) and concentrated under vacuum. The residue was purified by CC ($SiO_2$; AcOEt/hexanes 20:80) to afford **6b** (2.93 g, 65%, over two steps). White solid. M.p. 99–101°. IR (KBr): 2347, 1726, 1644, 1604, 1572, 1455, 1422, 1368, 1326, 141261, 1227, 1168, 1135. $^1$H-NMR (400 MHz, $CDCl_3$): 1.49 (*s*, 18 H); 1.61–1.66 (*m*, 4 H); 3.42–3.47 (*m*, 4 H); 5.15 (*s*, 2 H); 7.00 (*d*, *J* = 9.2, 2 H); 7.30 (*s*, 1 H, NH); 7.43–7.37 (*m*, 5 arom. H); 8.35 (*s*, 1 H, NH); 8.40 (*d*, *J* = 8.8, 2 H); 11.49 (*s*, 1 H, NH). $^{13}$C-NMR (100 MHz,$CDCl_3$): 26.5; 26.7; 28.0; 28.2; 38.8; 40.2; 70.1; 79.2; 83.0; 114.2; 126.5; 127.4; 128.2; 128.6; 133.8; 135.9; 153.2; 156.1; 162.3; 163.4; 163.7; 185.58. ESI-MS: 569.40 ($[M+H]^+$).

tert-*Butyl [4-({2-[4-(Benzyloxy)phenyl]-2-oxoacetyl}amino)butyl][*N-*(*tert*-butoxycarbonyl)carbamimidoyl]carbamate* (**6a**). To a soln. **8a** (0.60 g, 0.0018 mol), $Ph_3P$ (0.94 g, 0.0036 mol), and N,N′-*di-Boc-guanidine* (**7a**; 1.4 g, 0.0054 mol) in dry THF (0.98 ml) was added dropwise a soln. of DIAD in THF (0.74 g, 0.0036 mol) at −5° under $N_2$. The mixture was stirred for 1.5–2 h at −5° to 0°, warmed to r.t., and stirred at r.t. for *ca.* 48 h. The mixture was concentrated under reduced pressure, and the residue was purified by CC ($SiO_2$ (60–120 mesh) hexanes/AcOEt 3:1) to furnish two products: **6a**. and **13**. *Data of* **6a** Yield: 0.2 g (19%). White solid. M.p. 118°. $^1$H-NMR (400 MHz, $CDCl_3$): 1.49 (*s*, 9 H); 1.51 (*s*, 9 H); 1.72–1.60 (*m*, 4 H); 3.91 (*t*, *J* = 7.2, 4 H); 5.15 (*s*, 2 H); 7.02 (*d*, *J* = 9.2, 2 H); 7.44–7.32 (*m*, 5 arom. H);

7.68 (*t*, *J* = 6, 1 H, NH); 8.36 (*d*, *J* = 8.8, 2 H); 9.20 (*s*, 1 H, NH); 9.37 (*s*, 1 H, NH). ESI-MS: 569.4 ([*M* + H]$^+$).

Data of **13** Yield: 0.63 g (66%). White solid. M.p. 142°. $^1$H-NMR (400 MHz, $CDCl_3$): 1.49 (*s*, 9 H); 1.73 (*m*, 4 H); 3.42 (*q*, *J* = 6.4, 2 H); 4.12 (*t*, *J* = 5.6, 2 H); 7.02 (*d*, *J* = 8.8, 2 H); 5.15 (*s*, 2 H); 7.22 (*s*, 1 H, NH); 7.26–7.43 (*m*, 5 arom. H); 8.41 (*d*, *J* = 8.8, 2 H). ESI-MS: 513.2 ([*M* + H]$^+$).

*2-[4-(Benzyloxy)phenyl]*-N-*(4-guanidinobutyl)-2-oxoacetamide Trifluoroacetate Salt* (= *2-[4-(Benzyloxy)phenyl]*-N-*(4-carbamimidamidobutyl)-2-oxoacetamide Trifluoroacetate*; **14**). Under $N_2$, 2.2 g of **6b** were added to a soln. of TFA in $CH_2Cl_2$ (1:1 mixture; 11 ml) at 0°, and the mixture was stirred for *ca.* 3 h at r.t. The reaction was completed in 2 h (TLC). The mixture was concentrated under vacuum, and the residue was co-distilled twice with $^t$BuOMe to remove traces of TFA. The residue was stirred with $^t$BuOMe, and the white precipitate so formed was filtered and dried under vacuum. Yield of **14**: 1.78 g (95%).

The synthesis of **14** was also achieved from **6a** under identical reaction conditions in 90% yield. M.p. 115–117°. IR (KBr) 3368, 1704, 1667, 1645, 1604, 1574, 1547, 1509, 1473, 1455, 1427, 1381, 1316, 1250, 1231, 1268, 1203. $^1$H-NMR (400 MHz, $CD_3OD$) : 1.66 (*t*, *J* = 3.2, 4 H); 3.22 (*t*, *J* = 6.6, 2 H); 5.20 (*s*, 2 H); 3.38 (*t*, *J* = 6.2, 2 H); 7.12 (*d*, *J* = 8.8, 2 H); 7.45–7.30 (*m*, 5 arom. H); 8.09–8.12 (*m*, 2 H). $^{13}$C-NMR (100 MHz, $CD_3OD$): 27.1; 27.3; 39.4; 42.0; 71.2; 115.9; 127.4; 128.6; 129.1; 129.5; 133.8; 137.7; 158.6; 165.3; 167.1; 189.2. ESI-MS: 369.20 ([*M* + H]$^+$).

N-*(4-Guanidinobutyl)-2-hydroxy-2-(4-hydroxyphenyl)acetamide* (= N-*(4-Carbamimidamidobutyl)-2-hydroxy-2-(4-hydroxyphenyl)acetamide*; **18**). $H_2$ Gas was bubbled through a suspension of **14** (0.5 g, 0.0013) in EtOH (7.5 ml) and 5% Pd/C (50% wet) at 0–5°. After disappearance of starting material in *ca.* 7 h, the reaction mass was filtered, and filtrate was concentrated under vacuum to give **18** (0.48 g, 95%). Pale-yellow oil. $^1$H-NMR (400 MHz, $CDCl_3$): 1.40–1.42 (*m*, 4 H); 3.03–3.08 (*m*, 5 H); 4.04 (*s*, $NH_2$); 4.76 (*d*, *J* = 4.4, OH); 5.94 (*d*, *J* = 4.4, 1 H); 6.70 (*d*, *J* = 8.4, 2 H); 7.16 (*d*, *J* = 8.4, 2 H); 7.56 (*s*, 1 H, NH); 7.96 (*t*, *J* = 5.6, 1 H, NH); 9.34 (*s*, 1 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 27.4; 28.0; 39.8; 42.4; 75.1; 116.7; 129.7; 133.0; 158.9; 156.0; 176.5. ESI-MS: 281.3 ([*M* + H]$^+$).

N-*(4-Guanidinobutyl)-2-(4-hydroxyphenyl)-2-oxoacetamide Hydrobromide* (= N-*{4-[(Aminoiminomethyl)amino]butyl}-4-hydroxy-2-oxobenzeneacetamide Hydrobromide* (1:1); **3** · HBr). TFA Salt of guanidine derivative, **14** (1.5 g, 0.0031 mol), was added to a soln. of 33% HBr in AcOH (10 ml) at 0–5°. The mixture was stirred for 2.5 h. The progress of the reaction was monitored by TLC, and after completion, the mixture was concentrated under vacuum. The residue was diluted with AcOEt (20 ml) and $H_2O$ (15 ml). The aq. layer was washed with $Et_2O$ (15 ml), and aq. layer containing product was concentrated under vacuum completely. The residue was dissolved in MeOH (3 ml), and the product was precipitated after addition of 15 ml of $Et_2O$. The light-brown product was dried under vacuum at 50° to furnish **3** (0.90 g, 80%). M.p. 154–156°. IR (KBr): 1664, 1644, 1612, 1594, 1528, 1474, 1437, 1372, 1337, 1310, 1282, 1257. $^1$H-NMR (400 MHz, $CD_3OD$): 1.63–1.67 (*m*, 4 H); 3.22 (*t*, *J* = 6.8, 2 H); 3.37 (*t*, *J* = 6.2, 2 H); 6.84–6.88 (*m*, 2 H); 8.00–8.04 (*m*, 2 H). $^{13}$C-NMR (100 MHz, $CD_3OD$): 27.1; 27.4; 39.4; 42.0; 116.5; 126.0; 134.1; 158.4; 165.0; 167.5; 189.2. ESI-MS: 279.15 ([*M* + H]$^+$). HR-MS: 279.1471 ([*M* + H]$^+$, $C_{13}H_{19}N_4O_3^+$; calc. 279.1457).

*2,2-Dibromo-1-{1-[(4-methylphenyl)sulfonyl]-1*H-*indol-3-yl}ethanone* (**20**). To a pre-cooled dioxane (100 ml) in a round-bottom flask was added $Br_2$ (9.8 g, 0.0612 mol) under $N_2$ at 20°. To the yellow suspension thus obtained was added *3-acetyl*-N-*[(4-methylphenyl)sulfonyl)]-1*H-*indole* (**19**; 8.0 g, 0.025 mol) in 1–2 min and stirred for 2–3 h. After complete disappearance of starting material (TLC), the mixture was poured into a mixture of ice and sat. aq. $NaHCO_3$ soln. and stirred for 1–2 h. The product was filtered and further purified by flash CC ($SiO_2$; AcOEt/hexanes 20:80) to give **20** (18 g, 77%). Light-pink solid. M.p. 162–165°. IR (KBr): 3128, 3015, 1656, 1531, 1383. 1173. $^1$H-NMR (400 MHz, $CDCl_3$): 2.37 (*s*, 3 H); 6.43 (*s*, 1 H); 7.20–7.51 (*m*, 4 H); 7.82–8.01 (*m*, 3 H); 8.28–8.35 (*m*, 1 H); 8.60 (*s*, 1 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 21.6; 40.0; 113.1; 113.5; 123.0; 125.2; 126.2; 127.2; 127.8; 130.3; 133.2; 134.0; 134.5; 134.6; 146.2; 182.1. ESI-MS: 493.9 ([(*M* + 2) + Na]$^+$).

N-*[2-(4-{[(*tert*-Butyl)(dimethyl)silyl]oxy}phenyl)ethyl]-2-{1-[(4-methylphenyl)sulfonyl]-1*H-*indol-3-yl}-2-oxoacetamide* (**22**). To a cooled suspesion of *2-{4-[(*tert*-butyl)(dimethyl)silyloxy]phenyl}ethanamine* (**21**; 4.12 g, 0.0163 mol), $K_3PO_4$ (9.44 g, 0.0445 mol) and sulfolane (= 2,3,4,5-tetrahydrothiophene 1,1-dioxide; 35.0 ml) was added **20** (7.0 g, 0.0148 mol), and the mixture was stirred for 1–2 h under $N_2$ at

r.t. $^t$BuOOH soln. (5M in decane, 3.6 ml, 0.017 mol) was added and the mixture was stirred for 6–8 h. The mixture was diluted with $H_2O$ (200 ml) and extracted with AcOEt (2 × 50 ml). The combined AcOEt layer was washed with 10% aq. $NaHSO_3$ soln., 10% aq. citric acid soln. (100 ml), and 10% aq. NaCl soln. (100 ml). The org. layer was dried ($Na_2SO_4$) and concentrated under reduced pressure. The residue was purified by flash CC ($SiO_2$; AcOEt/hexanes 20:80) to give **22** (3.25 g, 38%). Off-white solid. M.p. 136–138.5°. IR (KBr): 1690, 1645, 1608, 1509, 1477, 1443, 1377, 1290, 1251, 1190, 1176, 1132. $^1$H-NMR (400 MHz, $CDCl_3$): 0.19 (*s*, 6 H); 0.97 (*s*, 9 H); 2.36 (*s*, 3 H); 2.85 (*t*, *J* = 7.2, 2 H); 3.60 (*q*, *J* = 7.2, 2 H); 6.83 (*d*, *J* = 8.4, 2 H); 7.12 (*d*, *J* = 8.4, 2 H); 7.27–7.42 (*m*, 4 H); 7.87 (*d*, *J* = 4.4, 2 H); 7.98 (*dd*, *J* = 1.8, 6.8, 1 H); 8.32 (*dd*, *J* = 1.4, 6.4, 1 H); 9.42 (*s*, 1 H). $^{13}$C-NMR (100 MHz, $CDCl_3$): 4.4; 18.1; 21.2; 25.4; 34.6; 40.1; 113.9; 115.2; 120.7; 122.6; 125.4; 125.7; 127.7; 128.5; 129.4; 130.1; 130.5; 134.4; 134.5; 138.6; 145.5; 154.3; 161.5; 181.4. ESI-MS: 577.2 ($[M+H]^+$).

N-*[2-(4-Hydroxyphenyl)ethyl]-2-(1*H*-indol-3-yl)-2-oxoacetamide* (**2c**). To a soln. of **22** (1.2 g, 0.0021 mol) in MeOH (24 ml) was added anh. $CsCO_3$ (0.85 g, 0.0063 mol), and the mixture was stirred at r.t. for 2–3 h. After disappearance of the starting material (TLC), the mixture was cooled, acidified to neutral pH with AcOH, and concentrated under vacuum. The white residue thus obtained was suspended in a mixture $H_2O$/hexane, and the product was filtered after stirring. The product was further purified by dissolving in MeOH, precipitating with $H_2O$, and was dried at 50° under vacuum to give **2c** (0.51 g, 80%). $^1$H-NMR (400 MHz, $CDCl_3$): 2.83 (*t*, *J* = 7.2, 2 H); 3.56–3.61 (*m*, 2 H); 6.78–6.81 (*m*, 2 H); 7.14 (*d*, *J* = 7.4, 2 H); 7.28–7.31 (*m*, 2 H); 7.45–7.49 (*m*, 1 H); 7.82 (*s*, 1 H); 8.32–7.35 (*m*, 1 H); 8.88 (*s*, 1 H). $^{13}$C-NMR (100 MHz, $CD_3OD$): 36.7; 42.2; 113.2; 114.1; 116.4; 123.0; 123.9; 124.9; 128.0; 130.9; 131.1; 138.0; 139.6; 157.1; 165.7; 183.0. ESI-MS: 309.10 ($[M+H]^+$). HR-MS: 307.1073 ($[M-H]^+$, $C_{18}H_{15}N_2O_3^+$; calc. 307.1083).

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