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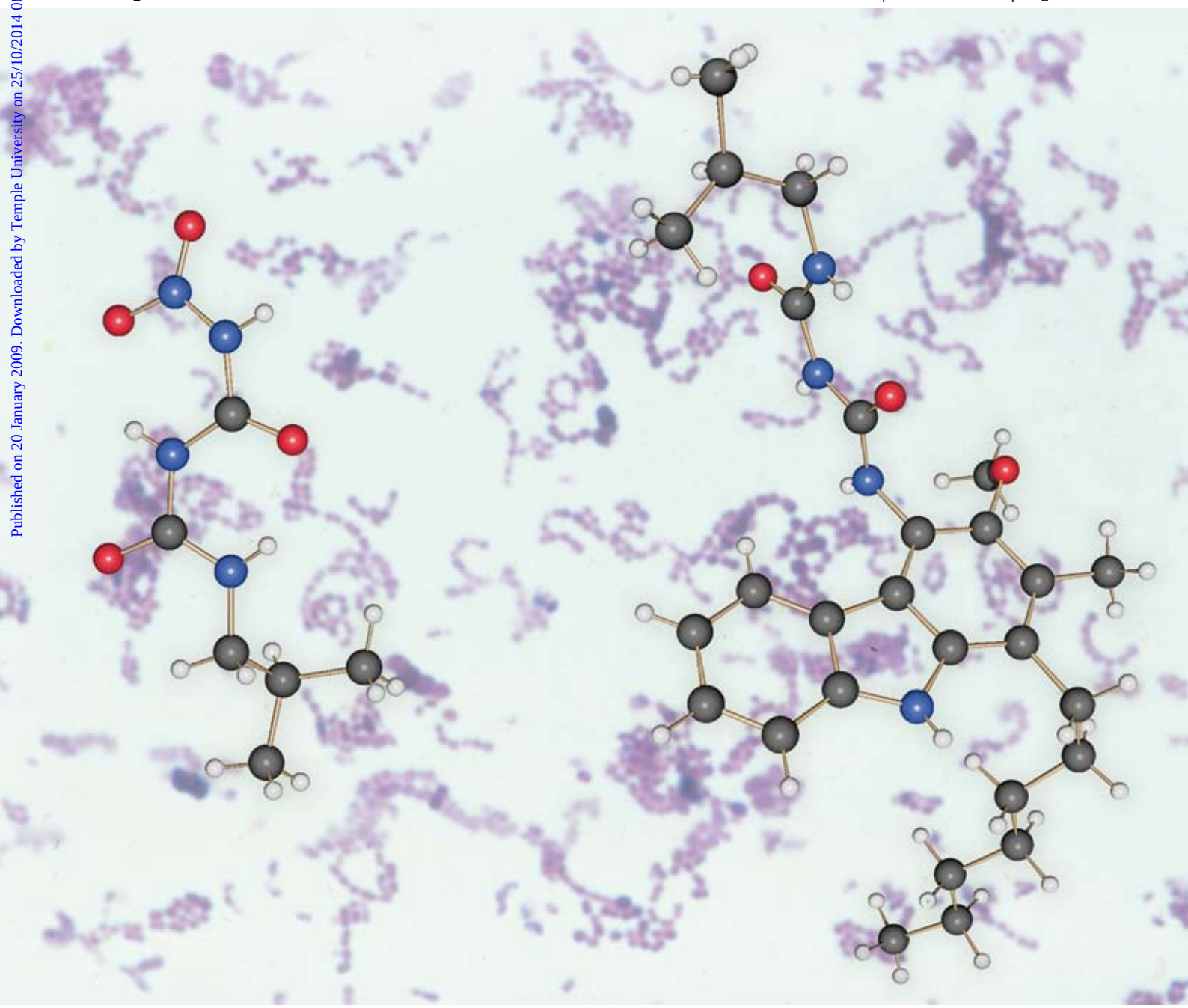

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First total synthesis of the whole series of the antiostatins A and B†

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The first synthesis of the whole antiostatin family is described by using an iron-mediated carbazole synthesis, regioselective nitration at C-4 and establishing 5-isobutyl-1-nitrobiuret as a reagent for introduction of the antiostatin B side chain at C-4.

Currently, carbazoles are of high interest due to their pharmacological potential.[1] In 1990, Seto *et al.* at the University of Tokyo isolated the antiostatins A_1 to A_4 and B_2 to B_5 from *Streptomyces cyaneus* 2007-SV_1 (Fig. 1).[2] They exhibit a strong inhibitory activity against free radical induced lipid peroxidation. The antiostatins are structurally unique because of their nitrogen substituent at C-4, which is part of an isobutylbiuret side chain for the antiostatins B. So far, no synthesis has been reported for any member of this family of carbazoles, despite synthetic efforts by several groups in the field.[3,4] In the present paper, we describe the first total synthesis of all antiostatins.

Our strategy is based on the iron-mediated carbazole synthesis.[5] We decided to introduce the nitrogen substituent at C-4 after completion of the carbazole ring system. Thus, a monocyclic precursor was designed which is easily exploitable for access to all different antiostatins by introduction of the different alkyl side chains at C-1 using a Sonogashira–Hagihara coupling (Scheme 1).

Nitration of 2,6-dimethoxytoluene (**3**) followed by regioselective ether cleavage of **4** afforded the nitrophenol **5** (Scheme 1). Conversion to the aryl triflate **6** paved the way for introduction of different alkyl chains at C-1 of the carbazole nucleus.[6] Except for **7b** and **7f**, all required alkynes are commercially available. 6-Methylhept-1-yne (**7f**) was prepared in two steps from 1-bromo-4-methylpentane.[7] For the stereogenic centre in the side chain of antiostatin A_2 (**1b**), we assumed an *S* configuration in analogy to other chiral carbazole alkaloids: carbazoquinocin A and D,[8,9] and carbazomadurin B.[10,11] Thus, (*S*)-3-methylpent-1-yne (**7b**) has been prepared in three steps from commercial (*S*)-2-methylbutan-1-ol by oxidation with the Dess–Martin reagent[12] and subsequent Corey–Fuchs homologation to the terminal alkyne.[13]‡ Sonogashira–Hagihara coupling[14] of aryl triflate **6** with the alkynes **7** led to the alkynylarenes **8**, which on catalytic hydrogenation provided the arylamines **9** (Table 1).

Electrophilic substitution of the arylamines **9** by reaction with the iron complex salt **10** afforded the iron complexes **11**

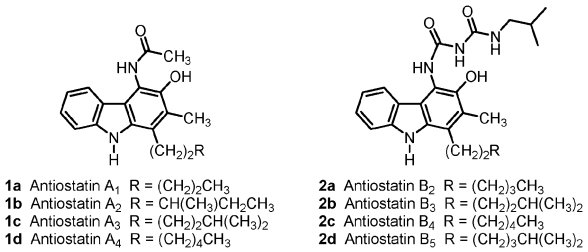
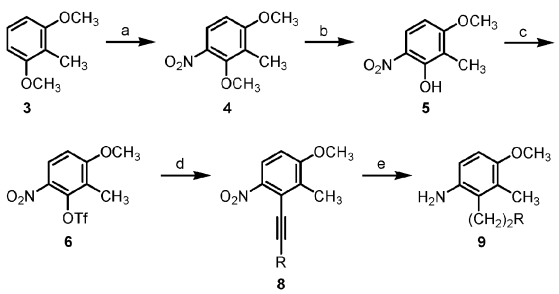


Fig. 1 Antiostatins A_1–A_4 and B_2–B_5.



Scheme 1 Synthesis of the arylamines **9**. *Reagents and conditions*: (a) claycop, Ac_2O, Et_2O, rt, 1 h, 94%; (b) $AlCl_3$, CH_2Cl_2, rt, 21 h, 96%; (c) Tf_2O, Et_3N, CH_2Cl_2, −20 °C, 97%; (d) cat. $Pd(PPh_3)_2Cl_2$, cat. CuI, H– ≡ –R (**7a–f**), Bu_4NI, CH_3CN–Et_3N (5 : 1), reflux, 3–5 h; (e) 1–5 bar H_2, 10% Pd/C, CH_3OH–CH_2Cl_2 (or EtOAc), rt, 3–5 d; yields for **8** and **9**: Table 1.

(Scheme 2, Table 1). Oxidative cyclization of **11** using an excess of ferricenium hexafluorophosphate in the presence of sodium carbonate led to the carbazoles **12**.[15] Direct nitration at C-4 of the unprotected carbazoles **12** was limited. Thus, nitration of **12d** (NO_2BF_4 in THF at −50 to −20 °C, 64%) afforded regioselectively **22d**, an intermediate for antiostatin B_4 (**2c**) (see Scheme 5). However, after transformation to the corresponding *tert*-butyl carbamates **13**, nitration with claycop provided the 4-nitrocarbazoles **14** in excellent yields. Catalytic hydrogenation of **14a–d** led to the 9-Boc-4-aminocarbazoles **15a–d**, the precursors for the antiostatin A series.

For the synthesis of the antiostatins A, the carbazoles **15a–d** were acetylated at the amino group to afford the acetamides **16a–d** (Scheme 3). Conversion to **17a–d** by thermal removal of the Boc group[16] and subsequent cleavage of the methyl ether provided the antiostatins A_1 to A_4 (**1a–d**). The spectroscopic data and melting points of the antiostatins A_1 to A_4 (**1a–d**) were in good agreement with those reported for the natural products by Seto *et al.*[2]§ The ^1H NMR spectrum of our synthetic antiostatin A_2 ((*S*)-**1b**), with $[\alpha]_D^{20}$ = +5.0

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† Electronic supplementary information (ESI) available: Copies of the ^1H and ^{13}C NMR spectra of all antiostatins. CCDC numbers 708519–708521. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b821039j

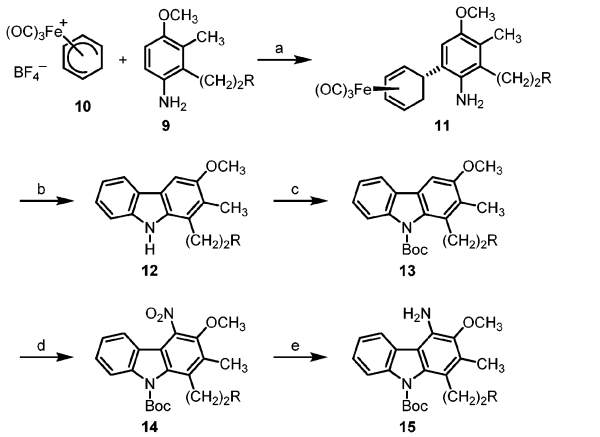
(c 0.5, $CHCl_3$), was identical to the spectrum obtained from an authentic sample of the natural product (see ESI†), kindly provided by Prof. Seto and Dr Shin-ya. Due to the small amount available of the natural product (0.4 mg), the absolute configuration of natural antiostatin A_2 could not be determined yet.

We have developed an efficient reagent for introduction of the antiostatin B side chain at C-4. Nitration of biuret (**18**) using the classical procedure reported by Thiele and Uhlfelder in 1898 led to 1-nitrobiuret (**19**) (Scheme 4).[17] Alkylation with isobutylamine by adaptation of literature procedures gave 1-isobutylbiuret (**20**).[18] A further nitration finally provided 5-isobutyl-1-nitrobiuret (**21**), which has been structurally confirmed by X-ray analysis (Fig. 2).¶

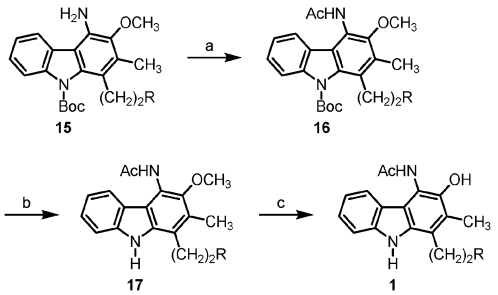
For an access to antiostatin B series, the unprotected 4-aminocarbazoles were required. Removal of the Boc protecting group from the 9-Boc-4-nitrocarbazoles **14c–f** provided the unprotected 4-nitrocarbazoles **22c–f** (Scheme 5). This three-step route to the 4-nitrocarbazoles **22** proceeds in much better overall yield compared to the direct nitration of the carbazoles **12** (*cf.* above). Catalytic hydrogenation of the 4-nitrocarbazoles **22c–f** led to the 4-aminocarbazoles **23c–f**, which have been structurally confirmed by an X-ray analysis of **23d** (Fig. 3).¶ Slow addition of a solution of 5-isobutyl-1-nitrobiuret (**21**) in acetonitrile to a solution of the aminocarbazoles **23c–f** in acetonitrile at reflux afforded the 5-isobutyl-1-(carbazol-4-yl)biurets **24c–f**. The structural assignments have been unequivocally confirmed by an X-ray crystal structure determination of *O*-methylantiostatin B_4 (**24d**) (Fig. 4).¶ Finally, cleavage of the ether provided the antiostatins B_2 to B_5 (**2a–d**). The spectroscopic data of the antiostatins B_2 to B_5 (**2a–d**) were in full agreement with those reported for the natural products.[2]§

In conclusion, we have developed a highly efficient synthesis of the whole series of the antiostatins A and B. Due to the flexibility of our modular approach, we can introduce all the different alkyl chains at C-1 *via* a palladium(0)-catalysed coupling and, at the stage of an advanced precursor, focus either on the antiostatins A or B. For the antiostatins B, 5-isobutyl-1-nitrobiuret has been devised as reagent for elaboration of the isobutylbiuret side chain at C-4 by reaction with the corresponding aminocarbazole.

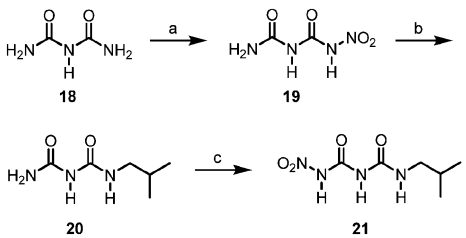
We are grateful to Prof. H. Seto and Dr K. Shin-ya for providing us the files of the original ^1H NMR spectra of antiostatin A_1 and B_4, and for sending us the sample of natural antiostatin A_2. We thank the BASF, Ludwigshafen, for a gift of pentacarbonyliron.



Scheme 2 Synthesis of the 9-Boc-4-aminocarbazoles **15**. *Reagents and conditions*: (a) CH_3CN, 82 °C, 1–2 h; (b) Cp_2FePF_6, Na_2CO_3, CH_2Cl_2, rt, 3–5 d; (c) Boc_2O, DMAP, CH_3CN, rt, 20–24 h; (d) claycop, Ac_2O, Et_2O, rt, 4.5–20 h; (e) 5 bar H_2, 30% Pd/C, CH_3OH–CH_2Cl_2, rt, 3–7 d; yields: Table 1.



Scheme 3 Synthesis of the antiostatins A_1–A_4 (**1a–d**). *Reagents and conditions*: (a) AcCl, Et_3N, THF, 0 °C to reflux, 13–24 h, 81–97%; (b) 180 °C, 45 min, 100%; (c) BBr_3, CH_2Cl_2, −78 to −20 °C, 6–24 h, 65–94%.



Scheme 4 Synthesis of 5-isobutyl-1-nitrobiuret (**21**). *Reagents and conditions*: (a) conc. H_2SO_4, conc. HNO_3, 0 °C to rt, 2 h, 51%; (b) *i*-$BuNH_2$, EtOH, rt, 2 h, then 150 °C until melt, 99%; (c) conc. H_2SO_4, conc. HNO_3, 0 °C, 2 h, 24% (after recrystallization from EtOH).

Table 1 Transformation of the aryl triflate **6** into the 9-Boc-4-nitrocarbazoles **14** and the 9-Boc-4-aminocarbazoles **15** *via* the iron-mediated synthesis[a]

7	R	**8**, yield (%)	**9**, yield (%)	**11**, yield (%)	**12**, yield (%)	**13**, yield (%)	**14**, yield (%)	**15**, yield (%)
7a	$(CH_2)_2CH_3$	100	100	100	63	93	81	100
7b	(*S*)-$CH(CH_3)CH_2CH_3$	90	88	95	93	100	81	100
7c	$(CH_2)_2CH(CH_3)_2$	98	95	89	93	98	83	99
7d	$(CH_2)_4CH_3$	100	100	100	96	100	91	92
7e	$(CH_2)_3CH_3$	82	96	96	81	100	90	—
7f	$(CH_2)_3CH(CH_3)_2$	85	84	100	91	100	81	—

[a] The 9-Boc-4-aminocarbazoles **15a–d** have been applied as synthetic precursors for the antiostatins A_1 to A_4 (**1a–d**) (Scheme 3). The 9-Boc-4-nitrocarbazoles **14c–f** have been applied as synthetic precursors for the antiostatins B_2 to B_5 (**2a–d**) (Scheme 5).

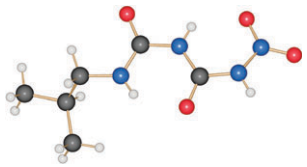
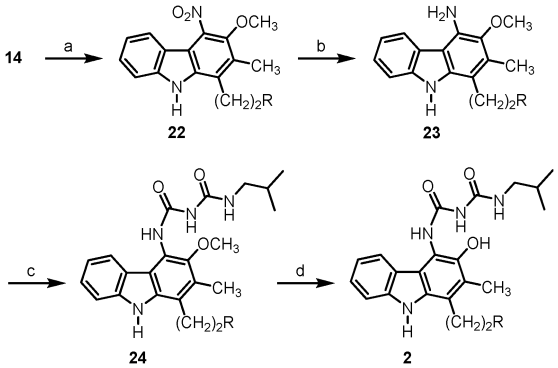


Fig. 2 X-Ray structure of 5-isobutyl-1-nitrobiuret (**21**).



Scheme 5 Synthesis of the antiostatins B_2–B_5 (**2a–d**). *Reagents and conditions*: (a) 180 °C, 45 min, 100%; (b) 5 bar H_2, 30% Pd/C, EtOAc, rt, 3–5 d, 82–100%; (c) **21**, CH_3CN, reflux, 4.5–5 h, 83–91%; (d) BBr_3, CH_2Cl_2, −78 to 0 °C, 2–3.5 h, 74–94%.

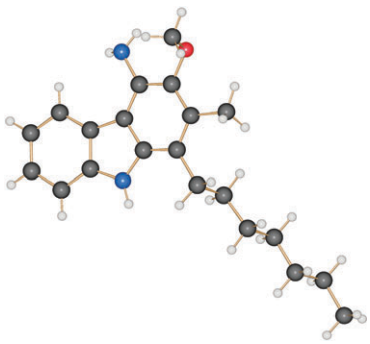


Fig. 3 X-Ray structure of the 4-aminocarbazole **23d**.

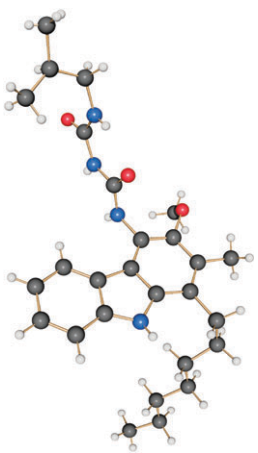


Fig. 4 X-Ray structure of *O*-methylantiostatin B_4 (**24d**).

Notes and references

‡ Synthesis of (*S*)-3-methylpent-1-yne (**7b**): 1. (*S*)-2-methylbutan-1-ol, Dess–Martin periodinane,[12] CH_2Cl_2, rt, 50 min, 83% (*S*)-2-methylbutanal; 2. Corey–Fuchs procedure:[13] (a) CBr_4, Zn, PPh_3, CH_2Cl_2, rt, 14 h, 77%; (b) BuLi, THF, −78 °C, 1 h, then rt, 2.5 h, 50%.

§ Selected data. Antiostatin A_1 (**1a**): yellow solid, mp 190–192 °C; ^{1}H NMR (500 MHz, acetone-d_6): δ = 0.92 (t, J = 7.2 Hz, 3 H), 1.37–1.42 (m, 2 H), 1.43–1.51 (m, 2 H), 1.65–1.71 (m, 2 H), 2.41 (s, 3 H), 2.50 (s, 3 H), 3.00 (m, 2 H), 7.12 (t, J = 7.9 Hz, 1 H), 7.33 (t, J = 7.9 Hz, 1 H), 7.46 (d, J = 7.9 Hz, 1 H), 8.08 (s) and 8.10 (s, Σ 1 H), 8.16 (d, J = 7.9 Hz, 1 H), 9.72 (br s, 1 H), 10.21 (br s, 1 H). Antiostatin A_2 ((*S*)-**1b**): mp 185 °C. Antiostatin A_3 (**1c**): mp 191–192 °C. Antiostatin A_4 (**1d**): mp 180–183 °C. Antiostatin B_2 (**2a**): mp 119–120 °C. Antiostatin B_3 (**2b**): mp 119–120 °C. Antiostatin B_4 (**2c**): Yellow solid, mp 117–120 °C; ^{1}H NMR (500 MHz, acetone-d_6): δ = 0.91 (t, J = 6.9 Hz, 3 H), 1.02 (d, J = 6.7 Hz, 6 H), 1.28–1.43 (m, 6 H), 1.48–1.54 (m, 2 H), 1.66–1.72 (m, 2 H), 1.90–1.95 (m, 1 H), 2.43 (s, 3 H), 3.02 (m, 2 H), 3.23 (t, J = 6.2 Hz, 2 H), 6.90 (br s, 1 H), 7.13 (t, J = 8.0 Hz, 1 H), 7.33–7.37 (m, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 8.27 (br s, 1 H), 8.44 (br d, J = 7.5 Hz, 1 H), 8.91 (br s, 1 H), 10.23 (br s, 1 H), 10.94 (br s, 1 H); ^{13}C NMR and DEPT (125 MHz, acetone-d_6): δ = 12.78 (CH_3), 14.33 (CH_3), 20.21 (2 CH_3), 23.29 (CH_2), 29.17 (CH_2), 29.51 (CH), 30.05 (CH_2), 30.47 (CH_2), 30.57 (CH_2), 32.64 (CH_2), 47.58 (CH_2), 111.45 (CH), 114.90 (C), 116.67 (C), 119.11 (CH), 121.99 (CH), 122.81 (C), 122.92 (C), 125.44 (CH), 125.52 (C), 134.71 (C), 140.84 (C), 142.99 (C), 154.73 (C═O), 155.99 (C═O). Antiostatin B_5 (**2d**): mp 92 °C.

¶ Crystal data for **21**: $C_6H_{12}N_4O_4$, M_r = 204.20 g mol^{-1}, orthorhombic, *Pbca*, λ = 0.71073 Å, a = 10.571(1), b = 6.448(1), c = 28.570(3) Å, V = 1947.4(4) Å^3, Z = 8, ρ_{calcd} = 1.393 g cm^{-3}, μ = 0.117 mm^{-1}, T = 198(2) K, θ range = 3.44–25.00°, reflections collected: 13855, independent: 1543 (R_{int} = 0.0342), R_1 = 0.0386, wR_2 = 0.0919 [$I > 2\sigma(I)$]. Crystal data for **23d**: $C_{21}H_{28}N_2O$, M_r = 324.45 g mol^{-1}, monoclinic, $P2_1/c$, λ = 0.71073 Å, a = 15.921(3), b = 4.739(1), c = 26.736(5) Å, β = 113.91(3)°, V = 1844.1(6) Å^3, Z = 4, ρ_{calcd} = 1.169 g cm^{-3}, μ = 0.072 mm^{-1}, T = 198(2) K, θ range = 3.05–26.00°, reflections collected: 27 882, independent: 3615 (R_{int} = 0.0538), R_1 = 0.0528, wR_2 = 0.1061 [$I > 2I(I)$]. Crystal data for **24d**: $C_{27}H_{38}N_4O_3$, M_r = 466.61 g mol^{-1}, hexagonal, $R\bar{3}$, λ = 0.71073 Å, a = 27.586(4), c = 19.842(4) Å, V = 13077(4) Å^3, Z = 18, ρ_{calcd} = 1.067 g cm^{-3}, μ = 0.070 mm^{-1}, T = 198(2) K, θ range = 3.05–25.40°, reflections collected: 53 022, independent: 5332 (R_{int} = 0.0424), R_1 = 0.0704, wR_2 = 0.2044 [$I > 2I(I)$]. The structures were solved by direct methods and refined by full-matrix least-squares on F^2.

1 For some recent reviews, see: (*a*) H.-J. Knölker and K. R. Reddy, *Chem. Rev*., 2002, **102**, 4303; (*b*) H.-J. Knölker, *Top. Curr. Chem*., 2005, **244**, 115; (*c*) H.-J. Knölker and K. R. Reddy, in *The Alkaloids*, ed. G. A. Cordell, Academic Press, Amsterdam, 2008, vol. 65, p. 1; (*d*) H.-J. Knölker, *Chem. Lett*., 2009, **38**(1), 8.
2 C.-J. Mo, K. Shin-ya, K. Furihata, K. Furihata, A. Shimazu, Y. Hayakawa and H. Seto, *J. Antibiot*., 1990, **43**, 1337.
3 T. Choshi, H. Fujimoto, E. Sugino and S. Hibino, *Heterocycles*, 1996, **43**, 1847.
4 (*a*) G. W. Gribble *et al*., *Curr. Org. Chem*., 2005, **9**, 1493; (*b*) G. W. Gribble, *Invited Lecture 12, 23rd European Colloquium on Heterocyclic Chemistry*, Antwerp, Belgium, September 9–13, 2008.
5 H.-J. Knölker, *Chem. Soc. Rev*., 1999, **28**, 151.
6 H.-J. Knölker, W. Fröhner and R. Heinrich, *Synlett*, 2004, 2705.
7 N. M. Carballeira, D. Sanabria, N. L. Ayala and C. Cruz, *Tetrahedron Lett*., 2004, **45**, 3761.
8 K. Tanaka, K. Shin-ya, K. Furihata and H. Seto, *J. Antibiot*., 1995, **48**, 326.
9 K. Shin and K. Ogasawara, *Synlett*, 1996, 922.
10 N. Kotada, K. Shin-ya, K. Furihata, Y. Hayakawa and H. Seto, *J. Antibiot*., 1997, **50**, 770.
11 J. Knöll and H.-J. Knölker, *Synlett*, 2006, 651.
12 D. B. Dess and J. C. Martin, *J. Org. Chem*., 1983, **48**, 4155.
13 (*a*) E. J. Corey and P. L. Fuchs, *Tetrahedron Lett*., 1972, 3769; (*b*) L. F. Tietze, R. R. Singidi, K. M. Gericke, H. Böckemeier and H. Laatsch, *Eur. J. Org. Chem*., 2007, 5875.
14 (*a*) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett*., 1975, **16**, 4467; (*b*) R. Chinchilla and C. Nájera, *Chem. Rev*., 2007, **107**, 874.
15 H.-J. Knölker and T. Hopfmann, *Tetrahedron*, 2002, **58**, 8937.
16 V. H. Rawal and M. P. Cava, *Tetrahedron Lett*., 1985, **26**, 6141.
17 J. Thiele and E. Uhlfelder, *Justus Liebigs Ann. Chem*., 1898, **303**, 93.
18 (*a*) T. L. Davis and K. C. Blanchard, *J. Am. Chem. Soc*., 1929, **51**, 1801; (*b*) T. L. Davis and N. Constan, *J. Am. Chem. Soc*., 1936, **58**, 1800; (*c*) W. K. Detweiler and E. D. Amstutz, *J. Am. Chem. Soc*., 1951, **73**, 5451; (*d*) D. A. Dunnigan and W. J. Close, *J. Am. Chem. Soc*., 1953, **75**, 3615; (*e*) M. J. Plater, J. P. Sinclair, S. Aiken, T. Gelbrich and M. B. Hursthouse, *Tetrahedron*, 2004, **60**, 6385.