Total Synthesis of Quinoxapeptin A – C: Establishment of Absolute Stereochemistry**

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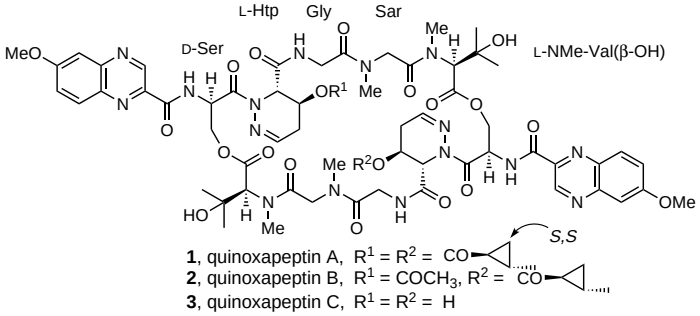
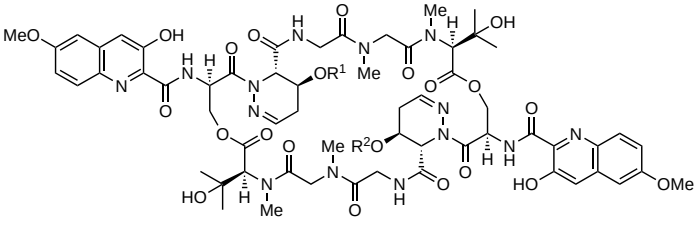
Quinoxapeptin A and B (**1** and **2**) are novel chromodepsipeptides isolated from a norcardioform actinomycete of indeterminant morphology obtained from a bark disc of *Betula papyrifera* found at the Denali National Park in Alaska.[1] Having been isolated at Merck in the course of screening microbial extracts for HIV-1 reverse transcriptase (RT) inhibitors, they were shown to be potent inhibitors of both HIV-1 and HIV-2 RT. Importantly, they were found to be equally active against two single mutants as well as a double mutant of HIV-1 RT responsible for the emerging clinical resistance to recently introduced RT inhibitors.[2] Structural



1, quinoxapeptin A, $R^1 = R^2 =$ CO
2, quinoxapeptin B, $R^1 = COCH_3$, $R^2 =$ CO
3, quinoxapeptin C, $R^1 = R^2 = H$

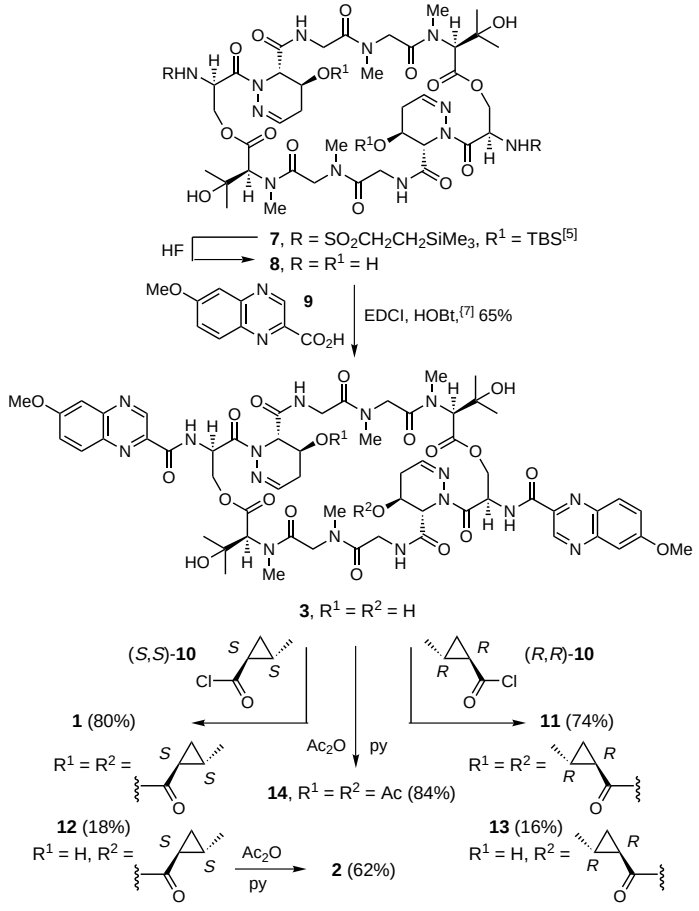


4, luzopeptin A, $R^1 = R^2 = COCH_3$
5, luzopeptin B, $R^1 = H$, $R^2 = COCH_3$
6, luzopeptin C, $R^1 = R^2 = H$

studies on the quinoxapeptins disclosed to date have established the two-dimensional structures of **1** and **2**, but not the relative or absolute stereochemistries. Their close structural relationship with luzopeptin A – C (**4** – **6**),[3] whose structures were established by X-ray crystallography by Clardy and Arnold[4] and confirmed by total synthesis,[5] suggest that they possess the same absolute stereochemistry within the symmetrical decadepsipeptide. However, the absolute stereochemistry of the unusual L-(4*S*)-hydroxy-2,3,4,5-tetrahydropyridazine-3-carboxylic acid (L-Htp)[6] subunit acyl substituent, 2-methylcyclopropane carboxylic acid, was unknown.

Herein, we disclose the first total syntheses of quinoxapeptin A and B (**1** and **2**) and their synthetic precursor **3**, named quinoxapeptin C in analogy with the luzopeptins, which confirm the cyclic decadepsipeptide structure and stereochemistry and which establish the 1*S*,2*S* absolute configuration for the L-Htp acyl cyclopropane substituents. In anticipation that the luzopeptins and quinoxapeptins possess the identical cyclic decadepsipeptide and differ only in the structure of the chromophore and L-Htp acyl substituent, key elements of the approach included the penultimate introduction of the chromophore and a final L-Htp alcohol acylation permitting the divergent synthesis of the luzopeptins[5] and quinoxapeptins from a common advanced intermediate.

Simultaneous SES[7] and TBS[7] deprotection of the cyclic decadepsipeptide **7**[5] disclosed in our recent luzopeptin A – C total syntheses by treatment with HF (neat, 2 – 3 mL, 100 μL anisole/5 – 10 mg, 0 °C, 1.5 h) provided **8** which was immediately coupled with 6-methoxyquinoxaline-2-carboxylic acid[8] (**9**, 4 equiv EDCI,[7] 5 equiv HOBt,[7] DMF, 0 – 25 °C, 6 h, 65 % overall) to provide quinoxapeptin C (**3**, Scheme 1). Quinoxapeptin C (**3**) was acylated with both (*S*,*S*)-**10**[9] and (*R*,*R*)-**10**[9] to provide quinoxapeptin A (**1**) and its unnatural cyclopropane diastereomer **11**, respectively. The spectroscopic and physical properties of natural[2] and synthetic **1** possessing the



Scheme 1.

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[**] This work was supported by the National Institutes of Health (CA41101), The Skaggs Institute for Chemical Biology, a NIH postdoctoral fellowship (GM1876, M.W.L.), and a sabbatical leave from Shionogi & Co. Ltd. (M.K.). We wish to thank Dr. G. M. Salituro (Merck) for supplying copies of the ^{1}H NMR and ^{13}C NMR spectra for natural **1** and **2**.

  1433-7851/99/3816-2424 $ 17.50+.50/0

(1*S*,2*S*)-2-methylcyclopropane carboxylic acid substituent were identical and distinguishable from the unnatural diastereomer **11** derivatized with (*R*,*R*)-**10** (Table 1). The ^{1}H NMR distinctions between **1** and **11** were subtle and center solely on the chemical shifts of the cyclopropane ($\delta =$ 0.94/0.62 versus 0.87/0.72) and Gly α-protons ($\delta = 4.02$ versus 3.98); the chemical shifts of the cyclopropane protons are dependably more diagnostic (Table 1). The rigid conformation of the decadepsipeptide places the L-Htp acyl substituent directly above the Gly α-center perturbing the chemical shifts of two of the cyclopropane protons and one of the two Gly α-protons. In these studies, variable amounts of the monoacylated products **12** and **13** were isolated and characterized, and **12**, bearing the (*S*,*S*)-2-methylcyclopropane carboxylic acid substituent, was acylated with Ac_2O (Ac_2O/pyridine(py) 1:1, 25 °C, 17 h, 62 %) to provide material identical with quinoxapeptin B (**2**).[2] The bis-acetate **14**, which may likely constitute an as yet unidentified naturally occurring member of the quinoxapeptins, was also prepared by reaction of **3** with acetic anhydride (Ac_2O/py 1:1, 25 °C, 15 h, 84 %) and provided a direct comparison to luzopeptin A (**1**) differing only in the structure of the chromophore.[10, 11]

The initial biological comparisons with the synthetic samples are summarized in Table 2. The quinoxapeptin derivative **11**

Table 1. Characterization data for **1**–**3** and **11**–**14**.

1: White solid; $R_f = 0.45$ (alumina, 4 % EtOH/CH_2Cl_2); $[\alpha]_D^{20} = +11$ ($c =$ 0.095, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 9.60$ (s, 2H), 9.00 (d, 2H, $J = 6.3$ Hz), 8.95 (d, 2H, $J = 6.7$ Hz), 7.80 (d, 2H, $J = 10.0$ Hz), 7.44 (m, 4H), 6.97 (d, 2H, $J = 3.7$ Hz), 5.81 (m, 2H), 5.69 (m, 2H), 5.61 (d, 2H, $J =$ 16.6 Hz), 5.52 (dd, 2H, $J = 1.1$, 11.0 Hz), 5.46 (m, 2H), 5.22 (s, 2H), 4.44 (dd, 2H, $J = 5.9$, 17.7 Hz), 4.42 (d, 2H, $J = 11.0$ Hz), 4.02 (d, 2H, $J =$ 16.2 Hz), 4.00 (s, 6H), 3.52 (d, 2H, $J = 16.2$ Hz), 3.25 (s, 6H), 2.94 (s, 6H), 2.59 (dd, 2H, $J = 4.1$, 18.8 Hz), 2.21 (br. d, 2H, $J = 18.8$ Hz), 1.34–1.29 (m, 4H), 1.27 (s, 6H), 1.09 (d, 6H, $J = 5.5$ Hz), 1.03 (s, 6H), 0.94 (m, 2H), 0.62 (ddd, 2H, $J = 3.7$, 7.2, 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 173.1$, 170.7, 169.1, 169.0, 168.0, 167.1, 163.1, 162.2, 145.9, 143.9, 141.2, 141.0, 136.5, 130.4, 124.6, 106.7, 72.2, 63.7, 61.4, 60.7, 57.0, 56.0, 52.3, 49.0, 42.0, 34.8, 32.5, 29.7, 28.8, 26.2, 25.5, 21.2, 17.7, 17.5; IR (film): $\tilde{\nu}_{max} = 3385$, 3316, 2927, 2851, 1730, 1674, 1644, 1513, 1489, 1417, 1293, 1220, 1161, 1022, 840 cm^{-1}; MALDI FT-MS (2,5-dihydroxybenzoic acid (DHB)): *m*/*z*: 1499.5844 ([*M*+Na$^+$], $C_{68}H_{84}N_{16}O_{22}$ requires 1499.5920)

2: White solid; $R_f = 0.53$ (alumina, 4 % EtOH/CH_2Cl_2); $[\alpha]_D^{20} = +36$ ($c =$ 0.014, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta = 9.60$ (two s, 2H), 9.00 (d, 1H, $J = 6.1$ Hz), 8.97 (d, 1H, $J = 6.1$ Hz), 8.96 (d, 1H, $J = 5.2$ Hz), 8.88 (d, 1H, $J = 6.2$ Hz), 7.81 (d, 1H, $J = 7.9$ Hz), 7.80 (d, 1H, $J = 7.9$ Hz), 7.45 (s, 1H), 7.44 (m, 1H), 6.99 (d, 1H, $J = 3.5$ Hz), 6.97 (d, 1H, $J = 4.0$ Hz), 5.81 (m, 2H), 5.75 (m, 1H), 5.71 (m, 1H), 5.63 (d, 1H, $J = 16.6$ Hz), 5.62 (d, 1H, $J = 16.6$ Hz), 5.53 (d, 2H, $J = 11.4$ Hz), 5.51 (s, 1H), 5.43 (br. s, 1H), 5.23 (s, 1H), 5.17 (s, 1H), 4.50 (dd, 1H, $J = 6.2$, 17.9 Hz), 4.45–4.39 (m, 3H), 4.01 (two d, 2H, $J = 16.7$, 16.7 Hz), 3.53 (d, 2H, $J = 16.7$ Hz), 3.27 (s, 3H), 3.26 (s, 3H), 3.23 (br. s, 1H), 3.19 (br. s, 1H), 2.95 (s, 6H), 2.67–2.61 (m, 2H), 2.24–2.18 (m, 2H), 2.04 (s, 3H), 1.36–1.31 (m, 2H), 1.10 (d, 3H, $J =$ 5.7 Hz), 1.04 (s, 3H), 1.03 (s, 3H), 0.96 (m, 1H), 0.65 (m, 1H); IR (film): $\tilde{\nu}_{max} = 3384$, 3317, 2924, 2850, 1733, 1683, 1635, 1506, 1418, 1290, 1221, 1162, 1020, 834 cm^{-1}; MALDI FT-MS (DHB): *m*/*z*: 1459.5559 ([*M*+Na$^+$], $C_{65}H_{80}N_{16}O_{22}$ requires 1459.5531)

3: White solid; $R_f = 0.45$ (SiO_2, 8 % CH_3OH/CH_2Cl_2); $[\alpha]_D^{20} = -66$ ($c = 0.18$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 9.59$ (s, 2H), 9.11 (d, 2H, $J =$ 5.9 Hz), 8.85 (d, 2H, $J = 5.2$ Hz), 7.86 (d, 2H, $J = 10.0$ Hz), 7.45 (m, 4H), 7.04 (br. s, 2H), 5.79 (m, 2H), 5.66 (s, 2H), 5.44 (d, 2H, $J = 16.2$ Hz), 5.23 (d, 2H, $J = 11.0$ Hz), 5.17 (s, 2H), 4.63 (dd, 2H, $J = 3.3$, 11.1 Hz), 4.43 (dd, 2H, $J = 5.6$, 18.4 Hz), 4.25 (s, 2H), 4.09 (d, 2H, $J = 18.4$ Hz), 4.00 (s, 6H), 3.71 (d, 2H, $J = 16.7$ Hz), 3.20 (s, 6H), 3.11 (br. s, 2H), 2.92 (s, 6H), 2.45 (dd, 2H, $J = 3.0$, 17.3 Hz), 2.34 (m, 2H), 1.34 (s, 6H), 1.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 169.7$, 169.5, 169.3, 169.2, 168.0, 163.1, 162.2, 145.9, 143.9, 142.6, 141.0, 136.5, 130.5, 124.5, 106.7, 72.1, 65.1, 61.7, 61.0, 58.6, 56.0, 52.5, 49.7, 42.3, 35.0, 33.2, 29.6, 28.9, 28.2, 25.6; IR (film): $\tilde{\nu}_{max} = 3375$, 2929, 1725, 1688, 1661, 1621, 1511, 1487, 1416, 1296, 1008, 891 cm^{-1}; MALDI FT-MS (DHB): *m*/*z*: 1335.5053 ([*M*+Na$^+$], $C_{58}H_{72}N_{16}O_{20}$ requires 1335.5006)

11: White solid; $R_f = 0.5$ (alumina, 4 % CH_3OH/CH_2Cl_2); $[\alpha]_D^{22} = +54$ ($c =$ 0.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 9.59$ (s, 2H), 8.97 (d, 2H, $J = 6.2$ Hz), 8.86 (d, 2H, $J = 5.8$ Hz), 7.80 (d, 2H, $J = 10.0$ Hz), 7.44–7.42 (m, 4H), 6.99 (br. d, 2H), 5.82 (d, 2H, $J = 6.2$ Hz), 5.68 (br. s, 2H), 5.62 (d, 2H, $J = 16.4$ Hz), 5.54 (d, 2H, $J = 11.3$ Hz), 5.45 (br. s, 2H), 5.21 (s, 2H), 4.42 (dd, 2H, $J = 17.8$, 6.2 Hz), 4.40 (d, 2H, $J = 8.6$ Hz), 4.00 (s, 6H), 3.98 (d, 2H, $J = 11.6$ Hz), 3.51 (d, 2H, $J = 16.8$ Hz), 3.27 (s, 6H), 2.95 (s, 6H), 2.59 (dd, 2H, $J = 18.5$, 3.8 Hz), 2.23 (br. d, 2H, $J = 18.5$ Hz), 1.37–1.31 (m, 4H), 1.29 (s, 6H), 1.08 (d, 6H, $J = 5.8$ Hz), 1.04 (s, 6H), 0.87 (m, 2H), 0.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 173.2$, 170.7, 169.1, 169.0, 168.0, 167.3, 163.1, 162.2, 145.9, 143.9, 141.2, 141.0, 136.5, 130.4, 124.6, 106.7, 72.2, 63.7, 61.6, 60.7, 57.0, 56.0, 52.3, 48.8, 42.0, 34.8, 32.5, 28.9, 26.1, 25.5, 21.0, 17.9, 17.5; IR (film): $\tilde{\nu}_{max} = 3317$, 2922, 2852, 1727, 1674, 1638, 1489, 1418, 1291, 1221, 1165, 1021, 839 cm^{-1}; MALDI FT-MS (DHB): *m*/*z*: 1499.5884 ([*M*+Na$^+$], $C_{68}H_{84}N_{16}O_{22}$ requires 1499.5844)

12: White solid; $R_f = 0.53$ (alumina, 4 % EtOH/CH_2Cl_2); $[\alpha]_D^{25} = -94$ ($c =$ 0.015, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 9.59$ (s, 2H), 9.14 (d, 1H, $J = 6.3$ Hz), 9.03 (d, 1H, $J = 7.0$ Hz), 8.96 (d, 1H, $J = 6.1$ Hz), 8.77 (br. d, 1H, $J = 3.3$ Hz), 7.86 (d, 1H, $J = 9.9$ Hz), 7.80 (d, 1H, $J = 9.8$ Hz), 7.44 (m, 4H), 7.01 (m, 2H), 5.82–5.73 (m, 2H), 5.61 (d, 1H, $J = 16.7$ Hz), 5.48 (dd, 1H, $J = 1.3$, 11.6 Hz), 5.42 (d, 1H $J = 16.8$ Hz), 5.32 (br. s, 1H), 5.29-5.27 (m, 3H), 5.23 (s, 1H), 5.18 (s, 1H), 4.62 (m, 1H), 4.61 (dd, 1H, $J = 4.8$, 11.3 Hz), 4.46 (dd, 1H, $J = 2.8$, 11.0 Hz), 4.33 (dd, 1H, $J = 5.5$, 18.2 Hz), 4.08 (br. d, 1H, $J = 18.1$ Hz), 4.00 (d, 1H, $J = 18.1$ Hz), 4.00 (s, 6H), 3.68 (d, 1H, $J =$ 16.6 Hz), 3.56 (d, 1H, $J = 16.6$ Hz), 3.24 (s, 3H), 3.20 (br. s, 1H), 3.20 (s, 3H), 3.16 (br. s, 1H), 2.94 (s, 3H), 2.92 (s, 3H), 2.64 (dd, 1H, $J = 4.4$, 17.8 Hz), 2.44 (dd, 1H, $J = 3.5$, 17.8 Hz), 2.32–2.25 (m, 2H), 1.34 (m, 4H), 1.31 (s, 3H), 1.29 (s, 3H), 1.10 (d, 3H, $J = 5.4$ Hz), 1.04 (br. s, 6H), 0.98 (ddd, 1H, $J = 4.2$, 4.2, 8.5 Hz), 0.66 (ddd, 1H, $J = 3.7$, 3.7, 10.8 Hz); IR (film): $\tilde{\nu}_{max} = 3395$, 3318, 2922, 2850, 1732, 1667, 1640, 1489, 1417, 1292, 1221, 1159, 1021, 838 cm^{-1}; MALDI FT-MS (DHB): *m*/*z*: 1417.5461 ([*M*+Na$^+$], $C_{63}H_{78}N_{16}O_{21}$ requires 1417.5425)

13: White solid; $R_f = 0.4$ (alumina, 4 % CH_3OH/CH_2Cl_2); $[\alpha]_D^{22} = +96$ ($c =$ 0.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 9.59$ (s, 2H), 9.13 (d, 1H, $J = 6.2$ Hz), 8.96 (d, 1H, $J = 9.3$ Hz), 8.94 (d, 1H, $J = 6.5$ Hz), 8.74 (br. d, 1H), 7.86 (d, 1H, $J = 10.0$ Hz), 7.80 (d, 1H, $J = 9.9$ Hz), 7.49–7.42 (m, 4H), 7.06–6.97 (m, 2H), 5.85–5.76 (m, 2H), 5.74 (br. s, 1H), 5.62 (d, 1H, $J =$ 16.8 Hz), 5.50 (d, 1H, $J = 10.0$ Hz), 5.43 (d, 1H, $J = 16.5$ Hz), 5.34 (br. s, 2H), 5.28 (d, 1H, $J = 9.3$ Hz), 5.23 (s, 1H), 5.18 (s, 1H), 4.66–4.57 (m, 2H), 4.47–4.41 (m, 2H), 4.34 (dd, 1H, $J = 18.2$, 5.1 Hz), 4.05 (d, 1H, $J =$ 19.2 Hz), 4.00 (s, 6H), 4.00 (d, 1H, $J = 18.2$ Hz), 3.68 (d, 1H, $J = 16.4$ Hz), 3.55 (d, 1H, $J = 16.8$ Hz), 3.26 (s, 3H), 3.20 (s, 3H), 2.95 (s, 3H), 2.92 (s, 3H), 2.64 (dd, 1H, $J = 18.8$, 3.8 Hz), 2.45 (br. d, 1H, $J = 18.2$ Hz), 2.37–2.24 (m, 2H), 1.42–1.34 (m, 2H), 1.31 (s, 3H), 1.30 (s, 3H), 1.10 (d, 3H, $J =$ 6.2 Hz), 1.05 (s, 3H), 1.04 (s, 3H), 0.91–0.84 (m, 1H), 0.77–0.70 (m, 1H); IR (film): $\tilde{\nu}_{max} = 3351$, 2921, 2851, 1732, 1682, 1668, 1652, 1634, 1505, 1488, 1418, 1292, 1261, 1221, 1159, 1100, 1021, 800 cm^{-1}; MALDI FT-MS (DHB): *m*/*z*: 1417.5431 ([*M*+Na$^+$], $C_{63}H_{78}N_{16}O_{21}$ requires 1417.5425)

14: White solid; $[\alpha]_D^{20} = -39$ ($c = 0.075$, CH_2Cl_2); ^{1}H NMR ($CHCl_3$, 500 MHz): $\delta = 9.59$ (s, 2H), 8.97 (d, 2H, $J = 6.3$ Hz), 8.89 (d, 2H, $J =$ 5.9 Hz), 7.79 (d, 2H, $J = 10.0$ Hz), 7.44 (m, 4H), 6.98 (d, 2H, $J = 3.3$ Hz), 5.81 (d, 2H, $J = 5.9$ Hz), 5.78 (br. s, 2H), 5.63 (d, 2H, $J = 16.5$ Hz), 5.53 (d, 2H, $J = 10.7$ Hz), 5.48 (s, 2H), 5.18 (s, 2H), 4.49 (dd, 2H, $J = 6.3$, 18.4 Hz), 4.40 (dd, 2H, $J = 2.6$, 11.4 Hz), 4.00 (s, 6H), 3.99 (d, 2H, $J = 17.6$ Hz), 3.53 (d, 2H, $J = 16.5$ Hz), 3.27 (s, 6H), 3.19 (br. s, 2H), 2.95 (s, 6H), 2.68 (dd, 2H, $J = 3.9$, 18.6 Hz), 2.20 (d, 2H, $J = 18.8$ Hz), 2.05 (s, 6H), 1.30 (s, 6H), 1.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 170.5$, 169.9, 169.2, 169.1, 167.8, 167.6, 163.1, 162.2, 145.9, 143.9, 141.1, 141.0, 136.5, 130.4, 124.6, 106.7, 72.2, 63.8, 61.0, 60.8, 57.0, 56.0, 52.3, 48.9, 42.0, 34.9, 32.6, 28.9, 26.2, 25.5, 20.8; IR (film): $\tilde{\nu}_{max} = 3297$, 2917, 2847, 1731, 1667, 1634, 1519, 1488, 1416, 1296, 1244, 1019, 899 cm^{-1}; MALDI FT-MS (DHB): *m*/*z*: 1419.5268 ([*M*+Na$^+$], $C_{62}H_{76}N_{16}O_{22}$ requires 1419.5218)

  1433-7851/99/3816-2425 $ 17.50+.50/0

Table 2. Biological activity (IC_{50}) for HIV-1 RT inhibition, L1210 and HCT116 cytotoxic activity.

Compound	HIV-1 RT[a] [μM]	L1210[b] [nM]	HCT116[c] [nM]
1	0.6	0.3	1
2	0.9	2	7
3	0.3	> 100	> 100
4	6	0.008	0.3
5	3	30	30
6	0.4	> 100	> 100
11	0.7	2	6
13	0.9	> 100	> 100
14	0.8	7	n.d.[d]
Sandramycin	2	0.001	0.007

[a] HIV-1 reverse transcriptase inhibition. [b] L1210 mouse leukemia cytotoxic assay. [c] Human colon carcinoma assay. [d] n.d. = not determined.

possessing the unnatural (*R,R*)-2-methylcyclopropane carboxylic acid substituent proved to be only slightly less potent than natural quinoxapeptin A (**1**) in both the HIV-1 RT and cytotoxic assays. In addition, the quinoxapeptins displayed activity trends analogous to those observed with the luzopeptins with the important exception that the RT inhibition was more potent and the cytotoxic activity less potent enhancing the selective RT inhibition observed with the quinoxapeptins. The comparison of the quinoxapeptin derivative **14** with luzopeptin A (**4**) is instructive in this regard, where **14** was nearly 10-fold more potent against HIV-1 RT and 1000 times less potent in the L1210 cytotoxic assay. The HIV-1 RT inhibition follows the trend of quinoxapeptin C > A analogous to the luzopeptin C > B > A potency with the L-Htp free alcohols being the most active agents in each series. A reverse potency order was observed in the cycotoxic assays with quinoxapeptin A ≫ C and luzopeptin A > B ≫ C with the L-Htp free alcohols being inactive. Thus, the synthetic precursor **3** (quinoxapeptin C), which has not yet been disclosed as a natural product, exhibits the most potent HIV-1 RT inhibition in the series and lacks a dose-limiting in vitro cytotoxic activity making it the most attractive member of the series examined to date.

Received: March 12, 1999 [Z13157IE]
German version: *Angew. Chem.* **1999**, *111*, 2533 – 2536

Keywords: antitumor agents · natural products · peptides · structure-activity relationships · total synthesis

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Rhodium(I)-Catalyzed [2+2+2] Cycloadditions with N-Functionalized 1-Alkynylamides: A Conceptually New Strategy for the Regiospecific Synthesis of Substituted Indolines**

Bernhard Witulski* and Thomas Stengel

Stereoselective syntheses of multifunctionalized indoles and indolines (2,3-dihydroindoles) are a continuous challenge because of the enormous relevance of this class of compounds in the fields of natural products, pharmaceuticals, and drug-related targets.[1] Substructures of highly functionalized indoles are found in numerous natural products and pharmaceutically active compounds, for instance in the ergot alkaloids,[2] the telocidines,[3] the diazonamides[4] as well as in *N*-methylwelwitindolinone C,[5] an indolinone alkaloid that

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[**] This work was supported by the Deutsche Forschungsgemeinschaft (Wi 1696/1 – 1 und 1 – 2). We thank Prof. Dr. M. Regitz for his generous support.

  1433-7851/99/3816-2426 $ 17.50+.50/0