# Synthesis of Kuehneromycin B and Panudial from Kuehneromycin A

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*Received 3 September 2003*

Dedicated to Prof. Dr. W. Steglich on the occasion of his 70th birthday.

**Abstract:** Syntheses of kuehneromycin B and panudial are presented starting from kuehneromycin A using a thermal decarboxylation under pH control.

**Key words:** total synthesis, terpenoids, natural products, hydrolysis, decarboxylation

Kuehneromycin B (**1**) (Figure 1), recently described by Anke and Steglich,[2] is a minor component found in *Kuehneromyces sp. 8758*. Kuehneromycin B inhibits reverse transcriptase of HIV and other retroviruses. Biosynthetically, kuehneromycin B is the decarboxylation product of kuehneromycin A (**2**), which is a major component, found in the same mushroom.[2,3]

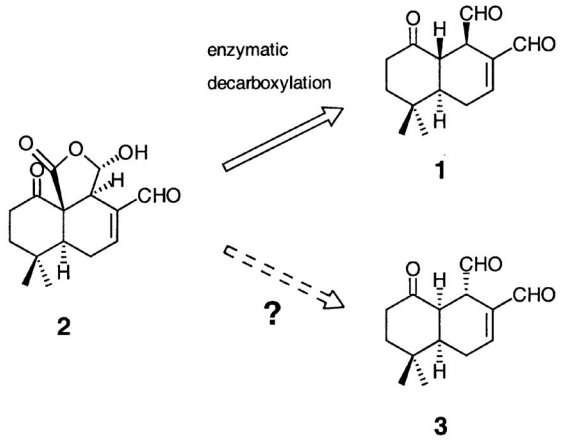


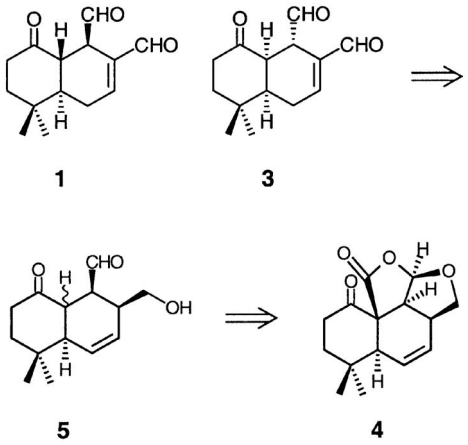

**Figure 1** Relationship between kuehneromycin B (**1**), kuehneromycin A (**2**) and panudial (**3**).

Panudial (**3**) (Figure 1), a stereoisomer of kuehneromycin B is found in *Panus* species (strain 9096) and inhibits platelet aggregation.[4] Whereas the biosynthetic precursor of panudial is unknown, Steglich et al. demonstrated the interconversion of kuehneromycin B into panudial and vice versa on treatment with DBU.[2]

Here, we wish to report our studies on the decarboxylation of kuehneromycin A (**2**) leading to kuehneromycin B (**1**) and panudial (**3**).

**SYNTHESIS** 2004, No. 5, pp 0665–0667
Advanced online publication: 10.02.2004
DOI: 10.1055/s-2004-815966; Art ID: T09503SS


Our first plan was to start from an intermediate **4** of our synthesis of anhydromarasmone.[5] Decarboxylation under mild basic conditions (dilute NaOH solution) should lead to **5**, which upon oxidation should give a mixture of **1** and **3** (Scheme 1).



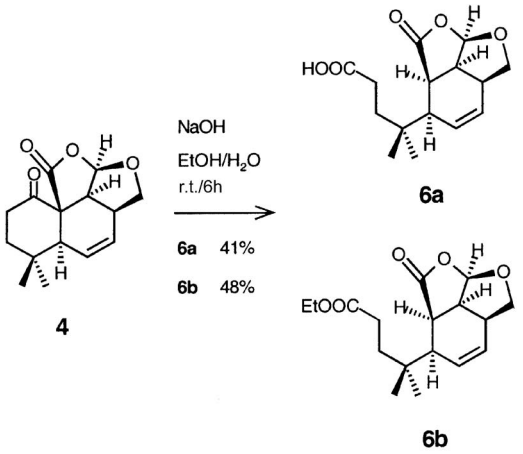

**Scheme 1** First synthetic approach to kuehneromycin B and panudial.

Consumption of the starting material occurred smoothly at 25 °C within 6 hours and two new compounds appeared, as reaction monitoring revealed. Unfortunately, during this reaction, the expected acyl-O-cleavage[6] with concomitant decarboxylation did not occur. Instead, we found alkyl-O-cleavage[7] exclusively, leading to the diastereomerically pure[8] carboxylic acid **6a** and the corresponding ethyl ester **6b** (Scheme 2).

Since strong bases usually give alkyl-O-cleavage, in the next experiment we used $NaHCO_3$ as base and DMSO as solvent to inhibit ester formation. Unfortunately, under these conditions, **4** also gave alkyl-O-cleavage leading only to **6a**.

Therefore, we switched to kuehneromycin A (**2**) as the starting material and studied direct decarboxylation reactions under neutral conditions according to Figure 1.

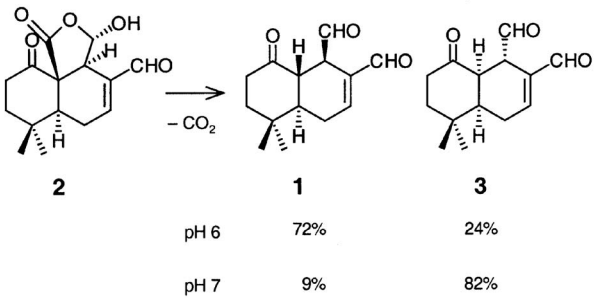
Heating a small sample of kuehneromycin A in $D_2O$–acetone-$d_6$ to 120 °C for 10 minutes gave a mixture of kuehneromycin B and panudial (approximately 1:1 as seen from $^1H$ NMR). For preparative purposes, we switched to pH 7 buffer together with acetone as co-solvent to have a defined reaction medium. Under these conditions, after 10 minutes at 120 °C we found a mixture of panudial (**3**) and




**Scheme 2** Attempted decarboxylation under basic conditions leading to alkyl-O-cleavage.

kuehneromycin B (**1**) (selectivity 9:1) (Scheme 3). The two compounds could be readily separated via flash chromatography on reversed phase silica gel using MeOH–water (9:1) as eluent.

In addition to this experiment, we further explored the pH influence of the reaction medium on decarboxylation. With pH 6 buffer–acetone as reaction medium after 10 minutes at 120 °C we obtained kuehneromycin B (**1**) as main product with minor amounts of panudial (**3**) (Scheme 3).




**Scheme 3** Decarboxylation of kuehneromycin A (**2**) at different pH.

In all decarboxylation reactions the $^1$H NMR spectra showed two additional diastereomers of **3** and **1** (together less than 5%).

Whereas $^1$H and $^{13}$C NMR spectra of the synthetic compounds were identical to those obtained from natural sources, we experienced some inconsistencies regarding the specific rotations.

To reveal the reason for these inconsistencies we recorded CD spectra of our synthetic compounds and compared the data obtained with those published by Steglich et al.[2] (Figure 2).

The CD spectra of isolated and synthetic kuehneromycin B and panudial are identical.[9] Therefore absolute configurations of kuehneromycin B and panudial are as depicted in Figure 1 and both compounds are stereochemically related to kuehneromycin A.

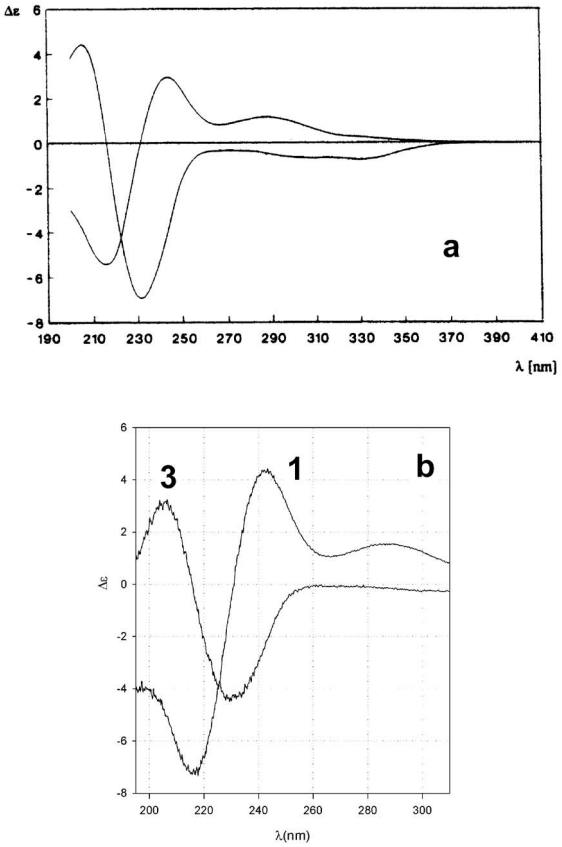



**Figure 2** a) CD spectra from lit.[2] reproduced with kind permission of *Zeitschrift für Naturforschung*; b) CD spectra of synthetic kuehneromycin B (**1**) and panudial (**3**). For details see the experimental part.

Kuehneromycin A[3] (**2**) and tetracycle[5] (**4**) were synthesized as described previously. All reactions were run without inert gas in closed vials. Organic solvents were distilled prior to use. Reactions were monitored on TLC plates (silica gel glass plates Si60 $F_{254}$ and RP18 $F_{254s}$, Merck, Darmstadt). NMR spectra were recorded on Bruker AV 360, AV 500 and AM 600 spectrometers. Mass spectra were obtained in EI mode on a Finnigan MAT 8200. Optical rotations were recorded on a Perkin Elmer Polarimeter MC 241. CD spectra were obtained on a Jasco-J 715 spectropolarimeter with PTC 343 peltier unit at 20 °C.

**Lactones 6a and 6b; General Procedure**

Tetracycle **4** (19 mg, 72.5 μmol) was dissolved in EtOH (0.6 mL). Aqueous 1 N NaOH (80 μl, 80 mol, 1.1 equiv) was added and the reaction mixture was stirred at r.t. for 6 h (reaction was monitored by TLC on silica gel plates with $Et_2O$–pentane, 3:1). The reaction was quenched with a mixture of cold 1 N HCl and sat. aq $NH_4Cl$ (10 mL, 1:1). Extraction with $Et_2O$ (5 × 10 mL) followed by drying with $MgSO_4$, filtration and evaporation of the solvent gave the crude products, which were purified by preparative TLC (silica gel, $Et_2O$–pentane, 3:1).

**6a**

Yield: 8.4 mg (41%); $[\alpha]_D^{20}$ –54 (*c* = 0.04, $CDCl_3$).

$^1$H NMR (360 MHz, $CDCl_3$): δ = 6.01 (d, *J* = 4.5 Hz, 1 H, H11), 5,98 (dt, *J* = 10.2, 2.7 Hz, 1 H, H6), 5.71 (dt, *J* = 10.2, 2.7 Hz, 1 H,

H7), 4.35 (t, *J* = 8.9 Hz, 1 H, H12), 3.66 (t, *J* = 8.9 Hz, 1 H, H12), 3.29–3.18 (m, 2 H, H9, H10), 2.83 (dddd, *J* = 19.3, 10.4, 8.9 Hz, 2.7 Hz, 1 H, H8), 2.37 (dd, *J* = 8.4, 8.2 Hz, 2 H, H3), 2.30 (m, 1 H, H5), 1.92–1.83 (m, 1 H, H2), 1.79–1.70 (m, 1 H, H2), 1.12 (s, 6 H, H13, H14).

$^{13}$C NMR (90.56 MHz): δ = 178.8 (C1), 173.2 (C15), 128.9 (C6), 127.5 (C7), 105.6 (C11), 73.0 (C12), 45.6 (C9), 44.0 (C5), 41.0 (C10), 36.0 (C2), 34.3 (C4), 34.2 (C8), 29.3 (C3), 25.2 (C13), 24.4 (C14).

MS (EI, 80 °C): *m*/*z* (%) = 281 (6) $[M+H]^+$, 280 (1) $[M^+]$, 263 (10) $[M – OH]^+$, 262 (33) $[M – H_2O]^+$, 218 (8), 188 (42), 166 (95), 115 (100), 97 (99), 69 (84).

**6b**

Yield: 10.7 mg (48%); $[\alpha]_D^{20}$ +6 (*c* = 0.11, $CDCl_3$).

$^1$H NMR (360 MHz, $CDCl_3$): δ = 6.01 (d, *J* = 4.5 Hz, 1 H, H11), 5,98 (dt, *J* = 10.2, 2.7 Hz, 1 H, H6), 5.70 (dt, *J* = 10.2, 2.8 Hz, 1 H, H7), 4.35 (t, *J* = 9.0 Hz, 1 H, H12), 4.12 (q, *J* = 7.1 Hz, 2 H, H1′), 3.66 (t, *J* = 8.9 Hz, 1 H, H12), 3.28–3.17 (m, 2 H, H9, H10), 2.82 (dddd, *J* = 19.5, 9.1, 6.1, 2.7 Hz, 1 H, H8), 2.34–2.27 (m, 3 H, H3, H5), 1.88–1.79 (m, 1 H, H2), 1.77–1.68 (m, 1 H, H2), 1.26 (t, *J* = 7.2 Hz, 3 H, H2′), 1.11 (s, 6 H, H13, H14).

$^{13}$C NMR (90.56 MHz): δ = 174.1 (C1), 173.2 (C15), 129.1 (C6), 127.4 (C7), 105.6 (C11), 73.0 (C12), 60.4 (C1′), 45.6 (C9), 43.9 (C5), 41.0 (C10), 36.4 (C2), 34.2 (C4), 34.1 (C8), 29.7 (C3), 25.2 (C13), 24.4 (C14), 14.2 (C2′).

MS (EI, 80 °C): *m*/*z* (%) = 308 (2) $[M^+]$, 281 (79) $[M – C_2H_3]^+$, 263 (14) $[M – C_2H_5O]^+$, 262 (24), 232 (8), 188 (22), 166 (14), 143 (100), 97 (75), 69 (69).

**Kuehneromycin B (1); Typical Procedure**

Kuehneromycin A (**2**) (12.3 mg, 44 mol) was dissolved in acetone (0.6 mL). A pH 6 buffer ($Na_2HPO_4$–$KH_2PO_4$–$H_2O$, 4 mL)[10] was added and the mixture was heated in a closed vial at 120 °C for 10 min. After cooling to r.t., the reaction mixture was extracted with $CHCl_3$ (5 × 5 mL). The combined extracts were washed with brine, dried with $MgSO_4$, filtered and evaporated to dryness in vacuo. The crude product was purified by preparative TLC (RP18 silica gel, MeOH–$H_2O$, 70:30); yield: 7.5 mg (72%).

$^1$H NMR (600 MHz, $CDCl_3$): δ = 10.33 (d, *J* = 1.9 Hz, 1 H, H11), 9.35 (s, 1 H, H12), 6.99 (dt, *J* = 6.1, 2.2 Hz, 1 H, H7), 3.82 (ddddd, *J* = 10.0, 3.9, 2.2, 2.0, 1.6 Hz, 1 H, H9), 2.87 (ddd, *J* = 12.8, 10.0, 1.2 Hz, 1 H, H10), 2.52 (ddd, *J* = 14.7, 8.0, 6.1 Hz, 1 H, H2β), 2.50 (ddd, *J* = 18.9, 6.1, 5.8 Hz, 1 H, H6α), 2.40 (ddd, *J* = 15.0, 4.2, 2.5 Hz, 1 H, H2α), 2.34 (dddd, *J* = 19.4, 11.4, 3.6, 2.5 Hz, 1 H, H6β), 1.80 (ddd, *J* = 13.7, 6.0, 2.5, 1 H, H3β), 1.65 (td, *J* = 12.7, 4.8 Hz, 1 H, H5), 1.63 (ddd, *J* = 13.6, 6.0, 4.8 Hz, 1 H, H3α), 1.15 (s, 3 H, H14), 1.06 (s, 3 H, H13).

$^{13}$C NMR (90.56 MHz): δ = 208.9 (C1), 202.1 (C11), 192.3 (C12), 151.3 (C7), 140.7 (C8), 49.9 (C10), 46.3 (C9), 45.9 (C5), 40.8 (C3), 37.6 (C2), 32.8 (C4), 28.9 (C13), 27.9 (C6), 19.1 (C14).

MS (EI, 80 °C): *m*/*z* (%) = 234 (6) $[M^+]$, 206 (100) $[M – CO]^+$, 188 (5), 173 (10), 150 (22), 132 (81), 108 (24), 107 (34).

HRMS: *m*/*z* $[M – CO]^+$ calcd for $C_{13}H_{18}O_2$: 206.1307; found: 206.1308.

CD: (*c* = 0.5 mg/mL, $CH_3CN$, 20 °C) $\lambda_{max}$ (Δε) = 216 (–7.2), 231 (0.0), 243 (4.3), 266 (1.1), 288 (1.8) nm.

**Panudial (3); Typical Procedure**

Kuehneromycin A (**2**) (15.9 mg, 57 mol) was dissolved in acetone (0.7 mL). A pH 7 buffer ($Na_2HPO_4$–$KH_2PO_4$–$H_2O$, 4.6 mL)[10] was added and the mixture was heated in a closed vial at 120 °C for 10 min. After cooling to r.t., the reaction mixture was extracted with $CHCl_3$ (5 × 10 mL). The combined extracts were washed with brine, dried with $MgSO_4$, filtrated and evaporated to dryness in vacuo. The crude product was purified by preparative TLC (RP18 silica gel, MeOH–$H_2O$, 70:30); yield: 11.0 mg (82%).

$^1$H NMR (360 MHz, $CDCl_3$): δ = 9.62 (s, 1 H, H11), 9.55 (s, 1 H, H12), 6.94 (m, 1 H, H7), 4.11 (m, 1 H, H9), 3.68 (d, *J* = 4.8 Hz, 1 H, H10), 2.54 (td, *J* = 14.1, 7.0 Hz, 1 H, H2β), 2.50 (dt, *J* = 19.7, 5.0 Hz, 1 H, H6α), 2.28 (ddd, *J* = 14.5, 5.2, 2.0 Hz, 1 H, H2α), 2.01 (ddt, *J* = 19.7, 11.8, 2.5 Hz, 1 H, H6β), 1.91 (dd, *J* = 5.0, 2.1 Hz, 1 H, H5), 1.90 (td, *J* = 14.1, 5.0 Hz, 1 H, H3α), 1.69 (ddt, *J* = 14.2, 7.2, 2.0 Hz, 1 H, H3β), 1.42 (s, 3 H, H14), 1.01 (s, 3 H, H13).

$^{13}$C NMR (90.56 MHz): δ = 209.0 (C1), 199.2 (C11), 192.5 (C12), 151.5 (C7), 135.3 (C8), 44.7 (C9), 43.7 (C5), 42.6 (C10), 37.7 (C2), 35.2 (C3), 33.0 (C4), 27.7 (C13), 26.4 (C14), 26.1 (C6).

MS (EI, 80 °C): *m*/*z* = 234 (2) $[M]^+$, 206 (100) $[M – CO]^+$, 188 (12), 173 (10), 150 (24), 132 (81), 108 (20), 107 (56), 91 (28).

HRMS: *m*/*z* $[M – CO]^+$ calcd for $C_{13}H_{18}O_2$: 206.1307; found: 206.1305.

CD: (*c* = 0.4 mg/mL, $CH_3CN$, 20 °C) $\lambda_{max}$ (Δε) = 206 (3.3), 216 (0.0), 229 (–4.3), 263 (–0.04), 310 (–0.3) nm.

## Acknowledgment

This work was generously supported by the Deutsche Forschungsgemeinschaft. We thank Prof. Dr. W. Steglich, Ludwig-Maximilians-Universität München, for copies of the NMR spectra of the natural samples and for helpful discussions. We thank Thusnelda Stromer, TU München, for CD spectra of our synthesized samples and Dr. Haijun Jiao, Universität Rostock, for performing the DFT calculations.

## References

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(8) Under the assumption of thermodynamic control DFT calculations (B3LYP/6-31G*) led to ΔΔG(**6a**/10-*epi*-**6a**) of ca. 8 kcal/mol. Thus, the equilibrium constant is ca. $10^6$ in favor of **6a**.
(9) Unfortunately, the compounds have been mislabeled in the CD spectra shown in Figure 2a. In the text of ref.[2] the data of the CD spectra have been listed correctly.
(10) *CRC Handbook of Chemistry and Physics*, 82nd ed.; Chapman & Hall/CRC: New York, **2001**.