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Total Synthesis of Antibiotic Karnamicin B_1

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Abstract: The novel antifungal karnamicin B_1 (**1**), 5-hydroxy-3,4-dimethoxy-2-{2-(4-oxopentyl)-4-thiazolyl}pyridine-6-carboxamide was first synthesized *via* the formation of partially methylated trihydroxy pyridine by ring-transformation from the corresponding furan derivative and subsequent regioselective introduction of 2,6-substituents using Meisenheimer-type reaction. © 1997 Elsevier Science Ltd.

Karnamicins,[1] a complex of antifungal antibiotics with a novel chemotype, was isolated in 1989 from the cultured broth of *Saccharothrix aerocolonigenes* No.806-4. The complex resulted in the isolation of four type components, karnamicin A, B, C and D, which have similar biological and chemical properties. These antibiotics exhibited a wide spectrum of antifungal and antibacterial activities against gram-positive bacteria. Karnamicins have a unique skeleton composed of fully substituted hydroxypyridine and thiazole moieties. We describe here the first total synthesis of antibiotic karnamicin B_1 (**1**) (Fig. 1), by the synthesis of the hydroxypyridine ring system from the corresponding furan derivatives by ring transformation, and then construction of the thiazole moiety, as shown in Scheme 1.

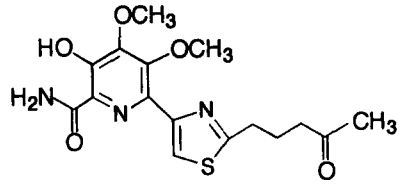

Fig. 1 Karnamicin B1 (1)

At first, treatment of methyl 3,4-dimethoxyfuran-2-carboxylate (**2**)[2] with saturated aqueous ammonia

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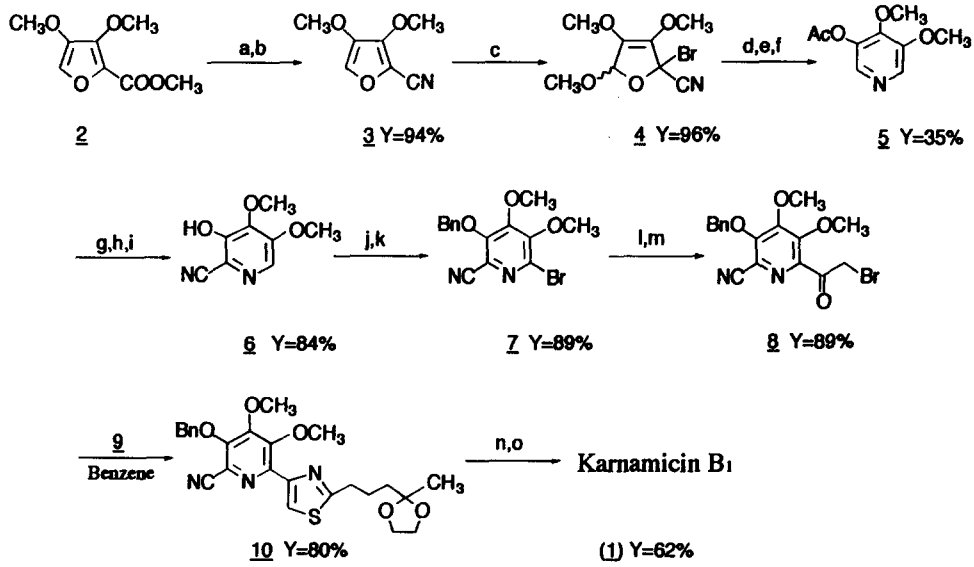
in the presence of ammonium chloride, and then triphenyl phosphine-CCl_4,[3] gave the corresponding cyanide (**3**). The reaction of **3** with brominein methanol gave a 1,4-adduct, bromo-methoxyfuran derivative (**4**) in high yield, instead of normal dimethoxyfuran derivative.[4] This compound was successfully converted to the desired hydroxypyridine derivative (**5**) in three steps: i) reduction of the cyano group with $LiAlH_4$, ii) ring transformation with 0.05*N*-HCl, iii) protection of the hydroxyl group with Ac_2O. For the introduction of the amide group into **5**, cyanation with a Meisenheimer-type reaction was tried.[5] Oxidation of **5** with *m*-chloroperbenzoic acid (*m*-CPBA), and treatment with dimethyl sulfate followed by potassium cyanide in aqueous solution, gave regioselectively the corresponding 2-cyanide (**6**). The structure of **6** was proved by X-ray analysis (Fig. 2). The successive bromination of **6** with benzyltrimethylammonium tribromide (Me_3NBnBr_3)[6] gave the 6-bromo derivative (**7**). Subsequently, a coupling reaction of **7** with tributyl(1-ethoxyvinyl)tin in the presence of $Pd(PPh_3)_4$ catalyst gave the corresponding 2-(1-ethoxyvinyl) derivative, which was easily converted into bromo acetyl derivative (**8**) by treatment with *N*-bromosuccinimide (NBS).[7]

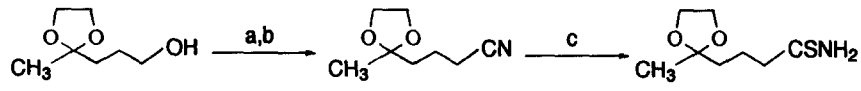
Scheme 1. Synthesis of Karnamicin B_1.



Reagents: a) NH_3aq.-NH_4Cl, b) PPh_3-CCl_4/THF, c) MeOH-Br_2/Et_2O, d) $LiAlH_4$/THF, e) 0.05*N*-HCl, f) Ac_2O-Et_3N/CH_2Cl_2, g) *m*-CPBA/CH_2Cl_2, h) Me_2SO_4, i) KCN/H_2O, j) Me_3NBnBr_3/MeOH-CH_2Cl_2, k) BnBr-K_2CO_3/DMF, l) CH_2=C(OEt)$SnBu_3$-$Pd(PPh_3)_4$/THF, m) NBS-H_2O/DMSO, n) K_2CO_3/*t*-BuOH, o) TMSI/CH_2Cl_2.

On the other hand, the hydroxyl group of 4,4-ethylenedioxypentanol (**11**)[8] was converted into thioamide (**9**) *via* the corresponding cyanide (**12**), as shown in Scheme 2.

Scheme 2. Synthesis of Thioamide component (9).



11 12 Y=70% 9 Y=66%

Reagents: a) TsCl-Py/CH_2Cl_2, b) KCN/18-Crown-6-ether/CH_3CN, c) H_2S/Py-Et_3N

Condensation of **8** with **9** gave the karnamicin derivative (**10**). Finally, the cyano group of **10** was converted to the amide group by using potassium hydroxide in a *t*-butyl alcohol solution,[9] and then, deprotection of the hydroxyl and keto groups with trimethylsilyl iodide (TMSI)[10] gave 5-hydroxy-3,4-dimethoxy-2-{2-(4-oxopentyl)-4-thiazolyl}pyridine-6-carboxamide (**1**); karnamicin B_1.[11] The spectral data of synthetic karnamicin was in good accordance with those reported for the natural product.

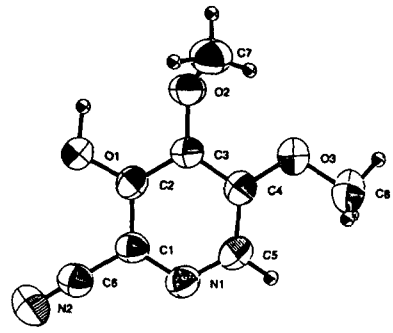


Fig. 2. ORTEP drawing of the molecular structure of 2-cyanide (6).

In summary, we report that the first total synthesis of antibiotic karnamicin B_1 could be accomplished by the construction of the hydroxypyridine ring system *via* the ring transformation of the corresponding furan derivatives, and then regioselective formation of the thiazolyl moiety. By only changing the thioamide component, the synthesis of all other karnamicins would be achieved *via* the same pathway.

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11. All new products in this study gave satisfactory analytical results, and data are as follows. **2**; mp. 45.2-45.4°C; MS(EI): *m/z* 186 $(M)^+$; ^{1}H-NMR ($CDCl_3$): δ 3.78(s, 3H, ester-CH_3), 3.87(s, 3H, OCH_3), 4.07(s, 3H, OCH_3), 7.09(s, 1H, furan-5). **3**; mp. 53.0-54.0°C; ^{1}H-NMR ($CDCl_3$): δ 3.79(s, 3H, OCH_3), 4.12(s, 3H, OCH_3), 7.07(s, 1H, furan-5). **4**; mp. 115.0-116.0°C; MS(EI): *m/z* 264 $(M)^+$; ^{1}H-NMR ($CDCl_3$): δ 3.37(s, 3H, OCH_3), 3.41(s, 3H, OCH_3), 4.15(s, 3H, OCH_3) 6.17(s, 1H, furan-5). **5**; syrup; MS(EI): *m/z* 197 $(M)^+$; ^{1}H-NMR ($CDCl_3$): δ 2.36(s, 3H, acetyl), 3.96(s, 3H, OCH_3), 3.98(s, 3H, OCH_3), 8.01 and 8.17(each s, 1H, Py-2,6). **6**; mp. 180-184°C; MS(EI): *m/z* 180 $(M)^+$; ^{1}H-NMR (acetone-d_6): δ 3.96(s, 3H, OCH_3), 4.07(s, 3H, OCH_3), 8.08(s, 1H, Py-6). **7**; mp. 71.0-71.5°C; ^{1}H-NMR ($CDCl_3$): δ 4.04(s, 3H, OCH_3), 4.12(s, 3H, OCH_3), 5.32(s, 2H, CH_2-Bn), 7.42(s, 5H, Ph). **8**; mp. 92.0-92.5°C; ^{1}H-NMR ($CDCl_3$): δ 3.99(s, 3H, OCH_3), 4.05(s, 3H, OCH_3), 4.63(s, 2H, CH_2Br), 5.39(s, 2H, CH_2-Bn), 7.40(s, 5H, Ph). **11**; syrup; MS(EI): *m/z* 145 $(M-1)^+$; ^{1}H-NMR ($CDCl_3$): δ 1.31(s, 3H, CH_3), 1.68(m, 2H, CH_2), 1.75(m, 2H, CH_2), 2.72(br-s, 1H, OH), 3.64(t, 2H, *J*=7.6Hz, CH_2), 3.95(m, 4H, OCH_2x2). **12**; syrup; MS(EI): *m/z* 154 $(M-1)^+$; ^{1}H-NMR ($CDCl_3$): δ 1.33(s, 3H, CH_3), 1.79(m, 4H, CH_2x2), 2.41(m, 2H, CH_2), 3.94(m, 4H, OCH_2x2), **9**; syrup; MS(EI): *m/z* 189 $(M)^+$; ^{1}H-NMR ($CDCl_3$): δ 1.31(s, 3H, CH_3), 1.74(t, 2H, *J*=8.4Hz, CH_2), 1.91(m, 2H, CH_2), 2.73(t, 2H, *J*=8.4Hz, CH_2), 3.94(m, 4H, OCH_2x2), 7.17(br-s, 1H, NH), 7.52(br-s, 1H, NH). **10**; syrup; MS(EI): *m/z* 480 $(M-1)^+$; ^{1}H-NMR ($CDCl_3$): δ 1.34(s, 3H, CH_3), 1.78(m, 2H, CH_2), 1.92(m, 2H, CH_2), 3.12(m, 2H, CH_2), 3.91(s, 3H, OCH_3), 3.95(m, 4H, OCH_2x2), 4.07(s, 3H, OCH_3), 5.30(s, 2H, CH_2-Bn), 7.40(s, 5H, Ph), 7.87 (s, 1H, Th-5). **1**; mp. 150-153°C (151-153°C[1]); MS(EI): *m/z* 364 $(M-1)^+$; ^{1}H-NMR ($CDCl_3$): δ 2.12(m, 2H, CH_2), 2.16(s, 3H, $COCH_3$), 2.59(t, 2H, *J*=7.2Hz, CH_2), 3.11(t, 2H, *J*=7.2Hz, CH_2), 3.96(s, 3H, OCH_3), 4.12(s, 3H, OCH_3), 5.82(br-s, 1H, NH), 7.83(s, 1H, Th-5), 8.54(s, 1H, NH), 12.47(s, 1H, OH).

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