Tetrahedron Letters, Vol.31, No.38, pp 5495-5498, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

# ENANTIOSELECTIVE TOTAL SYNTHESIS OF MEDERMYCIN (LACTOQUINOMYCIN)

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Summary: Medermycin has been first synthesized from D-rhamnose derivatives and comfirmed to be identical with lactoquinomycin.

In the last several years, more than ten pyranonaphthoquinone (isochromanequinone) antibiotics[1,2] have been isolated as microbial metabolites; kalafungin (**1**), nanaomycin D (2:enantiomer of **1**), medermycin (**3**), lactoquinomycin (**3**) and mederrhodin A(6-hydroxymedermycin)[2] serve as representative examples. Generally, they show a variety of biological activities and bear a structure of kalafungin (**1**) or nanaomycin D (**2**) as a major constituent.

Medermycin was isolated in 1976 from *Streptomyces* sp.[3] and the structure was assigned to be **3**[2,4]. However, in 1985, Tanaka et al.[5] reported the isolation and structure **3** of lactoquinomycin and suggested that medermycin could be an isomer of lactoquinomycin on the basis of their different physico-chemical properties and biological activities, although both natural products were not directly compared with each other.

Thus it would be necessary to be particularly rigorous in defining the structures of synthetic intermediates. The structure **3** is a C-glycoside of kalafungin (**1**). Since we have already achieved the enantiodivergent total synthesis of kalafungin (**1**) and its enantiomer, nanaomycin D (**2**) from an enone (L-isomer of **4**), the strategy can be extended to the total synthesis of **3** to confirm the structure. Hererin we describe the first total synthesis and structural identification of medermycin and lactoquinomycin (**3**).

Our strategy for reducing the problem to manageable proportions envisioned a late introduction of the dimethylamino group. The starting materials were compounds **4**[1,6], **5** and **6**. The acetal **5**[7] was prepared from 4-bromo-3-hydroxybenzaldehyde[8] in two steps (90%) ; i) $Me_2SO_4/K_2CO_3/Me_2CO$; ii) $CH(OMe)_3$/ IR120B/ MeOH). The lactone **6**[7] (mp 103°C, $[\alpha]_D$ +34°) was derived from D-rhamnal through a three-step sequence (63%); i) BnBr/NaH/DMF; ii) NBS[9]/$H_2O$/MeCN; iii) PCC/MS-3A/$CH_2Cl_2$). Coupling of **6** with the lithiated **5** (BuLi/THF, -78°C, 1h) followed by oxidation of the acetal ($H_2NSO_3H/NaClO_2$/aq. $Me_2CO$, 12h) gave a single carboxylic acid **7**[7], the α-anomeric hydroxyl structure of which was presumed from the anomeric effect[11] (but not characterized) and suggested by the NMR study of the β-C-glycoside **8**. Reduction of **7** with $Et_3SiH$[12] ($CF_3COOH/CH_2Cl_2$) afforded the 1'-deoxy compound, which was treated with 1,1'-bis(benzotriazolyl)-oxalate[13] (Py/MeCN) to give the active ester followed by addition of $Et_2NH$ to yield the diethylamide. After debromination ($Bu_3SnH$, AIBN/PhMe, 80°C, 1h), the β-C-glycoside **8** was obtained in 54% overall yield from **6** (oil, $[\alpha]_D$ +28° (c 0.76)). The NMR analysis indicated the structure **8** to be the β-glycoside. Though other β-C-glycosylations[10] were widely investigated by a variety of conditions on several stages, the better results were not realized. Near quantitative conversion of **8** to **9**[7][90%, oil, $[\alpha]_D$ +81° (c 0.45, MeOH)] resulted from de-O-benzylation ($H_2$/Pd(OH)$_2$-C/MeOH) and methoxymethylation (MM-Cl/i-$Pr_2NEt/CHCl_3$, 40°C, 1h).

Regioselective formylation[1] of **9** at C-2 (t-BuLi/TMEDA/DMF/THF, -78°→rt, 1.5h) gave the benzaldehyde derivative (70%), which was hydrolyzed (aq. HCl/dioxane, 75°C, 1h) to the hemiacetal **10** and treated with thiophenol (TsOH, 130°C, 1h) to give a mixture (86%) of **11a**[7] [Rf 0.56 (EtOAc-hexane 10/1), mp 75°C, $[\alpha]_D$ -235°] and **11b**[7] [Rf 0.44, mp 68°C, $[\alpha]_D$ +118°]. Oxidation of the mixture **11** (mCPBA/$CH_2Cl_2$) to give the sulfone, followed by O-protection (1,1-dimethoxycyclohexane/CSA/DMF, 40°C, 25mmHg, 1.5h) produced a mixture of **12a**[7] [Rf 0.32 (PhH-EtOAc 15/1), mp 187°C, $[\alpha]_D$ +255°] and **12b**[7] [Rf 0.25, mp 165°C, $[\alpha]_D$ -136°].

Now, further conversion of **12** into **14** can be accomplished according to our previous synthesis[1]. The mixture of **12** was coupled with the enone **4** (BuLi/t-BuOH/THF, -78°→rt, 1h) to give the hydroquinone, which was O-methylated ($Me_2SO_4/K_2CO_3/Me_2CO$, 70°C, 12h) and successively reduced by $NaBH_4$ (MeOH, 0°C, 5min) to give stereoselectively the 4α-alcohol **13**[7] (50%, mp 85°C, $[\alpha]_D$ +34°). Acid hydrolysis (aq. HCl/AcOH, 80°C, 2h) afforded the corresponding hemiacetal, which was subjected to a Wittig reaction ($Ph_3P$=CHCOOEt/PhMe, 105°C, 12h) to give a mixture of lactone **14** and the ester **15** through Michael cyclization of a Wittig product with or without lactonization[1]. Their less hindered 3'-hydroxyl groups were selectively O-silylated (TBDMS-Cl/Imd/DMF) to afford exclusively a mixture of **16** and **17**, which was readily separated by silica gel column chromatography (hexane-EtOAc 5/2); **16**[7] [28% from **13**; Rf 0.44 (PhH-EtOAc 5/1), mp 115°C, $[\alpha]_D$ +90°]; **17** [24% from **13**; Rf 0.69, yellow foam, mp 79°C, $[\alpha]_D$ -40°]. Their structures were confirmed by the NMR analyses, which showed the presence of 4'-hydroxyl groups[7]. The undesired **17** could be recycled (TsOH/PhMe, 70°C, 2days) to a mixture of **14** and **15** through retro-Michael and Michael cyclizations at C-3. Methoxymethylation (MM-Cl/i-$Pr_2NEt$) and de-O-silylation ($Bu_4NF$/THF) of **16** generated the 3'-alcohol, which was oxidized (PCC/MS-3A/$CH_2Cl_2$) to the ketone **18**[7] [85%; mp 119°C, $[\alpha]_D$ +245°]. The setting for installation of the amino group was now at hand. Reaction with $NH_2OH$•HCl (Py, 15min) afforded the oxime, which was reduced (3.5atm $H_2$/Raney Ni/EtOH) to yield the desired **19**[7] [62%; Rf 0.46 ($CHCl_3$-MeOH 10/1), mp 118°C, $[\alpha]_D$ +92°] and the undesired epimer **19'**[7] [24%; Rf 0.57, $[\alpha]_D$ +127°]. N-Dimethylation of **19** (37% aq. HCHO/$NaBH_3CN$/AcOH/MeCN) followed by oxidative demethylation (CAN/$H_2O$/MeCN, 15min) gave the labile quinone **20**[7] [79%; $[\alpha]_D$ +51° (c 0.26, MeOH)]. Deprotection with $AlCl_3$ ($CH_2Cl_2$, 1.5h) completed the synthesis of **3**. After quenching with $KH_2PO_4$-$Na_2HPO_4$ buffer (pH 7.1), EtOAc extraction and purification on CM-Toyopearl 650M with MeOH afforded, after recrystallization from BuOH, dark orange rods of **3**[7] [80%, mp ~155°C (decomp)[5], $[\alpha]_D$ +265° (c 0.14, MeOH)[5]]. The monohydrochloride[7] was obtained by exposure to aq. HCl-MeOH; yellow solid, mp ~190°C (decomp)[3], $[\alpha]_D$ +183° (c 0.09, MeOH)[3].The physico-chemical and spectral data[7] of **3** and its hydrochloride were completely identical with those of authentic samples[14] of medermycin and lactoquinomycin and their hydrochlorides under the same conditions, although medermycin and lactoquinomycin were first reported as the hydrochroride and free base, respectively. Thus the synthesis confirmed the structural identification of both antibiotics.

Acknowledgement: We are grateful to the Institute of Microbial Chemistry for the generous support of our program. Financial support by the Ministry of Education, Science and Culture (Grant-in-Aid Scientific Research) is gratefully acknowledged. We also thank Messrs. Y. Tatsuzawa & H. Kobayashi for their technical assistances.

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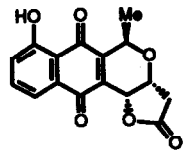
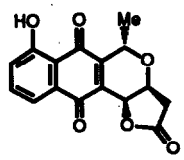


Kalafungin (1)



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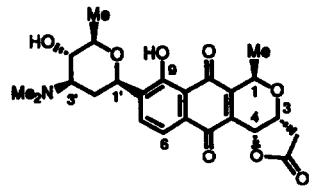
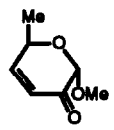


Lactoquinomycin, Medermycin (3)



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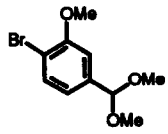

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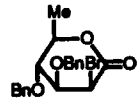

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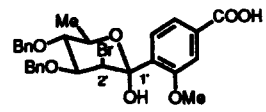

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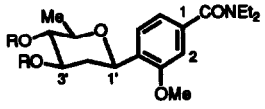
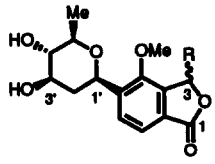
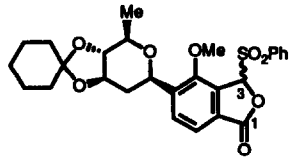


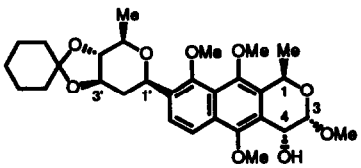
8: R=Bn
9: R=MM



10: R=OH
11a, b: R=SPh



12a, b



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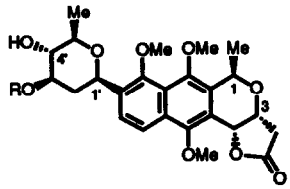
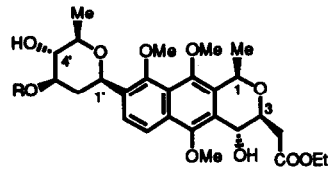
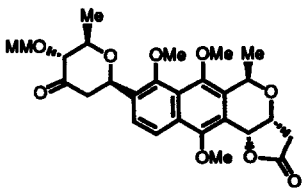


14: R=H
16: R=TBDMS



15: R=H
17: R=TBDMS



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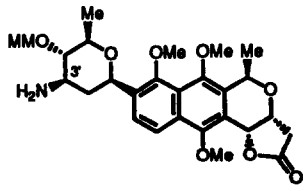

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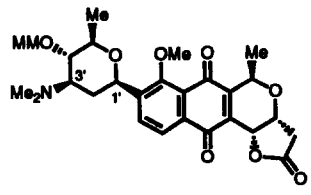

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7) All reactions were carried out at room temperature, unless otherwise stated. All compounds were purified by recrystallization or silica gel column chromatography, and were fully characterized by spectroscopic means and elemental analyses. Optical rotations were measured in $CHCl_3$ at *c* 0.5 (23°C). Rf-values were measured on silica gel Merck TLC60F-254. NMR (270, 400 or 500MHz: δ, ppm from TMS, and J in Hz) spectra were in $CDCl_3$ solution. Significant $^1$H-NMR spectral data are the following. **5**: 3.32 (s, OMeX2), 3.92 (s, OMe). **6**: 1.41 (d, J=6, Me-5), 4.87 (d, J=3, H-2). **7**: 1.45 (d, J=6, Me-5'), 3.94 (s, OMe), 4.88 (d, J=4, H-2'). **8**: 1.49 (dt, J=13, 11.6 & 11.6, H-2'ax), 2.42 (ddd, J=13, 4.8 & 2.0, H-2'eq), 4.76 (dd, J=11.6 & 2.0, H-1'). **9**: 3.37 & 3.45 (each s, OMe of MM), 4.80 (dd, J=11.6 & 2.0, H-1'). **11a**: 4.11 (s, OMe), 4.87 (dd, J=11.6 & 1.7, H-1'), 6.77 (s, H-3). **11b**: 4.13 (s, OMe), 4.90 (dd, J=11.4 & 1.8, H-1'), 6.76 (s, H-3). **12a**: 4.22 (s, OMe), 4.97 (dd, J=10.8 & 2.1, H-1'), 6.43 (s, H-3). **12b**: 4.18 (s, OMe), 4.93 (dd, J=10.8 & 2.3, H-1'), 6.42 (s, H-3). **13**: 1.41 (d, J=6, Me-5'), 1.66 (d, J=7, Me-1), 3.32 (d, J=4, OH-4), 4.94 (d, J=3, H-3), 5.04 (dd, J=12 & 3, H-1'), 5.42 (q, J=7, H-1). **16**: 2.34 (d, J=2, OH-4'), 3.25 (dt, J=9, 9 & 2, H-4'), 4.76 (dd, J=5, 3 & 0, H-3), 5.57 (d, J=3, H-4). **17**: 1.31 (t, J=7, Me of Et), 2.33(d, J=2, OH-4'), 3.24 (J=8.2, 8.2 & 2, H-4'), 4.79 (s, OH-4), 4.84 (d, J=9, H-4). **18**: 2.74 (dd, J=13.6 & 11.6, H-2'ax), 2.86 (dd, J=13.6 & 3.0, H-2'eq), 4.11 (d, J=10, H-4'). **19**: 1.60 (ddd, 13, 11.6 & 11.2, H-2'ax), 2.22 (ddd, J=13, 5 & 2, H-2'eq), 3.09 (ddd, J=11.6, 8.8 & 5, H-3'). **19'**: 1.91 (ddd, 14, 11 & 4, H-2'ax), 2.02 (dt-like, J=14, 4 & 4, H-2'eq), 3.65 (q-like, J=4, 4 & 4, H-3'). **20**: 2.29 (s, $NMe_2$), 3.46 (s, OMe of MM), 3.89 (s, OMe-9). **3**: 1.29 (ddd, 12.4, 12.2 & 11.8, H-2'ax), 2.25 (ddd, J=12.2, 3.8 & 2, H-2'eq), 2.31 (s, $NMe_2$), 3.18 (t-like, J=8.8 & 8.8, H-4'), 4.88 (dd, J=11.8 & 2, H-1'), 5.08 (q, J=7, H-1), 12.50 (s, OH-9). **3•HCl**: 2.83 (s, NMe2), 4.90 (dull d, J=10.6 & 1, H-1'), 5.08 (q, J=7, H-1), 5.26 (d, J=3, H-4), 12.26 (s, OH-9).

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14) We thank Profs. Ōmura[2)] and Tanaka[5)] for their generous gifts of natural medermycin and lactoquinomycin, respectively.

(Received in Japan 21 June 1990)