ENANTIODIVERGENT TOTAL SYNTHESES OF (−)-NANAOMYCIN D AND ITS ENANTIOMER, (+)-KALAFUNGIN

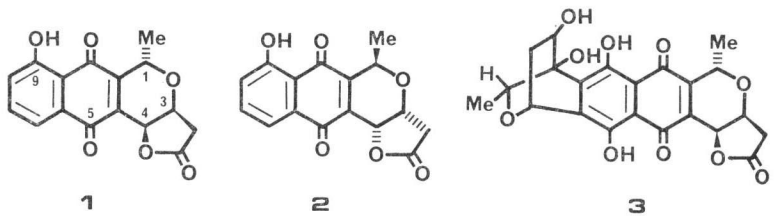
Sir:

Nanaomycin D (**1**)[1], kalafungin [**2**: (+)-nanaomycin D][2], nanaomycin A[3] and granaticin (**3**)[4] are members of a growing family of pyranonaphthoquinone (benzoisochromanquinone) antibiotics (Chart 1), which have been shown to possess significant antimicrobial activities and potential antitumor activities[5]. Remarkably, nanaomycin D (**1**) is the enantiomer of kalafungin (**2**). Because of their biological properties and unique structures, immense synthetic studies have been accomplished with various strategies; however, stereospecific syntheses of these optically active antibiotics have not been reported to date[6~8].

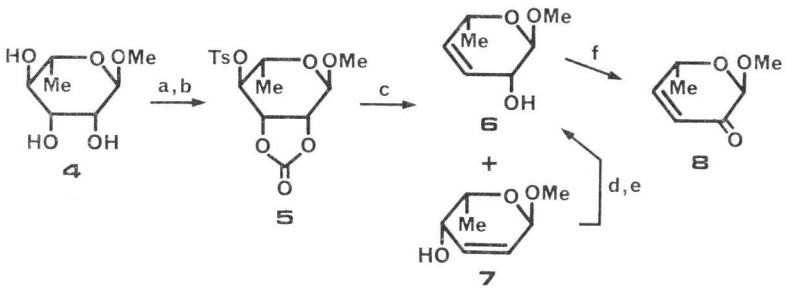
Herein we report the first, enantiospecific total syntheses of (−)-nanaomycin D (**1**) and its enantiomer, (+)-kalafungin (**2**) from a common optically active intermediate **13** by the "enantiodivergent" strategy[6], which is promising for application to the syntheses of both optical antipodes of other members of this important class of antibiotics.

Methyl α-L-rhamnoside (**4**) was converted into the tosylated cyclic carbonate **5** [80%; mp 99.5~101°C, $[\alpha]_D^{24}$ +23° (*c* 1.0, $CHCl_3$)], successively by reaction with trichloromethyl chloroformate and tosyl chloride in pyridine (Scheme 1). Treatment of **5** with Zn powder and NaI in refluxing aqueous MeCN gave[10,11], presumably through the corresponding 3,4-epoxide with removal of the carbonate protecting group, a mixture of the desired unsaturated alcohol **6** [60%; bp_7 90°C, $[\alpha]_D^{24}$ −206° (*c* 1.0, $CHCl_3$)] and its migrated alcohol **7** [28%; bp_3 75°C, mp 45~47°C, $[\alpha]_D^{24}$ +123° (*c* 1.0, $CHCl_3$)]. Oxidation of **6** with pyridinium chlorochromate led exclusively to the stable α,β-unsaturated ketone, methyl 3,4,6-trideoxy-α-L-*glycero*-hex-3-enopyranosid-2-ulose [**8**: 86%; bp_5 74°C, $[\alpha]_D^{24}$ −58° (*c* 1.0, $CHCl_3$)]. The migrated alcohol **7** was efficiently recycled to a 4:1 mixture of **6** and the C-2 epimeric alcohol in 85% yield by mesylation followed by exposure to K_2CO_3 in aqueous THF to result in S_N2' type solvolysis. The mixture thus obtained could be similarly converted into the ketone **8** (85%). The structure of **7** was clarified by ^1H NMR study ($CDCl_3$: $J_{1,2ax}$=4 Hz, $J_{1,2eq}$=2 Hz, $J_{3ax,4}$=2.5 Hz, $J_{3eq,4}$=2.5 Hz and $J_{4,5}$=1.5 Hz) of the corresponding benzoylated dihydro compound which was formed by

Chart 1.



Scheme 1.



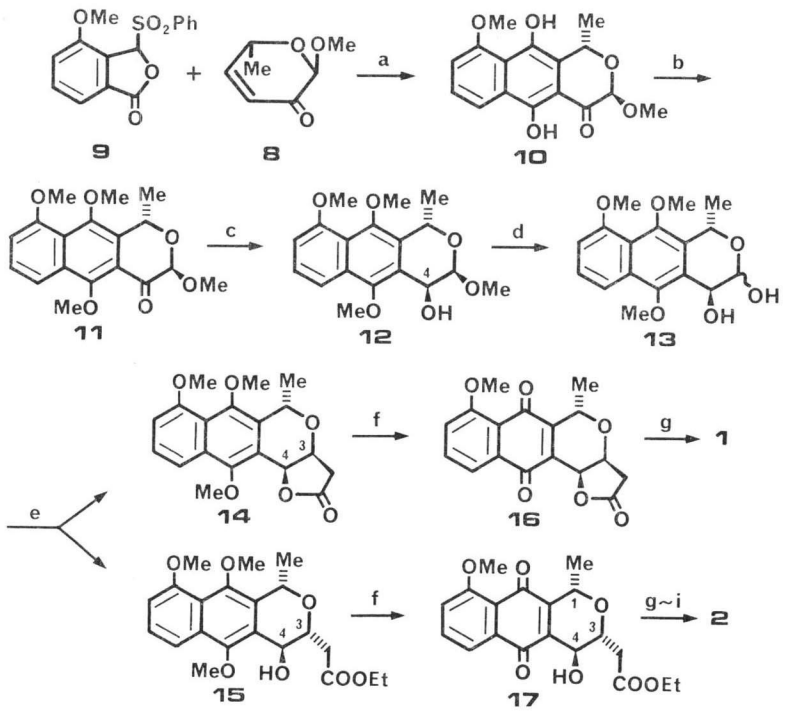
(a) $Cl_3COCOCl$, pyridine, room temp, 1 hour; (b) tosyl chloride, pyridine, 60°C, 36 hours; (c) NaI, Zn, 95% MeCN, 75°C, 36 hours; (d) mesyl chloride, pyridine, room temp, 0.5 hour; (e) K_2CO_3, aq THF, 50°C, 9 hours; (f) pyridinium chlorochromate, Molecular Sieves 3A, CH_2Cl_2, 5°C, 0.5 hour.

benzoylation of **7** (BzCl, Et_3N, CH_2Cl_2) followed by hydrogenation (Pd black, H_2, MeOH).

4-Methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone (**9**) was synthesized according to HAUSER's conditions[12]: mp 191°C.

As shown in Scheme 2, condensation[12] of **8** with the lithium *tert*-butoxide generated anion of **9** gave the hydroquinone **10** [80%; mp 125°C, $[\alpha]_D^{24}$ −304° (*c* 1.0, $CHCl_3$)], which was treated with Me_2SO_4 to produce the methylated compound **11** ($[\alpha]_D^{24}$ −154° (*c* 1.0, $CHCl_3$)) quantitatively. Stereoselective reduction of **11** was realized in the desired sense by hydride delivery by $NaBH_4$ with a *syn* stereodirecting influence of the pyrano oxygen atom[13], giving exclusively the alcohol **12** [90%; mp 176~177.5°C, $[\alpha]_D^{24}$ −97° (*c* 1.0, $CHCl_3$)]. The *S*-configuration at C-4 was confirmed by the ^1H NMR spectra of the following derivatives **14** and **15**, and successful transformation into **1**. Acid hydrolysis of **12** to **13** took place quantitatively without epimerization at C-1 and C-4. The anomeric mixture **13** was submitted to WITTIG reaction with ethoxycarbonylmethylenephosphorane to give two products **14** [53%, mp 232~234°C, $[\alpha]_D^{24}$ −279° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.58 (1H, d, H-4, $J_{3,4}$=3.0 Hz)] and **15** [41%; oil, $[\alpha]_D^{24}$ −25° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.86 (1H, d, H-4, $J_{3,4}$=9.5 Hz)] as expected[14,15]. The lactone **14** results from intramolecular MICHAEL cyclization of the intermediary α,β-unsaturated ester and concomitant lactonization of the resultant 3,4-*cis* product, and the other 3,4-*trans* ethyl ester **15** from only MICHAEL cyclization. The lactone **14** was treated with ceric ammonium nitrate[8] in MeCN to give the quinone **16** as orange needles [92%; mp 214~216°C (dec), $[\alpha]_D^{24}$ −65° (*c* 0.5, $CHCl_3$)], which was de-*O*-methylated by $AlCl_3$[8] to yield nanaomycin D [**1**: 95%; red rods, mp 171~173°C, $[\alpha]_D^{24}$ −163° (*c* 0.44, $CHCl_3$)] identical in all respects including antibacterial activity with an authentic sample of the natural antibiotic[1], thereby confirming the absolute structure.

Scheme 2.



(a) BuLi, *t*-BuOH, THF, −78°C→room temp, 3 hours; (b) Me_2SO_4, K_2CO_3, Me_2CO, 40°C, 24 hours; (c) $NaBH_4$, MeOH, room temp, 5 minutes; (d) 0.5 N HCl, AcOH, 75°C, 2 hours; (e) Ph_3P=CHCOOEt, PhMe, 105°C, 30 hours; (f) $(NH_4)_2Ce(NO_3)_6$, aq MeCN, room temp, 15 minutes; (g) $AlCl_3$, CH_2Cl_2, room temp, 0.5 hour; (h) H_2SO_4, PhH, room temp, 20 minutes; (i) PhMe, 105°C, 7 hours.

On the other hand, the ester **15** was converted by the similar oxidative demethylation into the corresponding quinone **17** [88%; orange oil, $[\alpha]_D^{24}$ −269° (*c* 0.5, $CHCl_3$)]. Treatment with $AlCl_3$ furnished the de-*O*-methylated product, the C-1 and C-4 positions of which were favorably epimerized with lactonization by H_2SO_4 in benzene followed by refluxing in toluene to complete the lactonization, affording kalafungin [**2**: 90%; red rods, mp 171~173°C, $[\alpha]_D^{24}$ +160° (*c* 0.30, $CHCl_3$)] identical with the natural antibiotic[2]. The desired epimerization was caused by keto-enol tautomerism with the quinone portion[6], and stereospecifically controlled by the stereochemistry of the C-3 position.

Thus, (−)-nanaomycin D (**1**) and (+)-kalafungin [**2**: (+)-nanaomycin D] have been synthesized from methyl α-L-rhamnoside (**4**) in overall yields of 18% and 13%, respectively (31% yield in total) in multi-gram quantities.

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