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Enantioselective Total Synthesis of the Antifungal Dilactone, UK-2A: The Determination of the Relative and Absolute Configurations.

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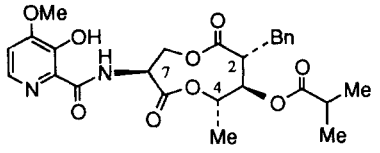
Abstract

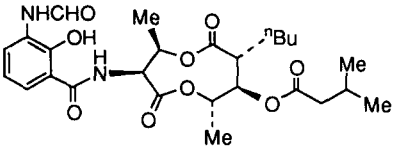
The synthesis of the antifungal dilactone, UK-2A, is described. In addition to providing a workable synthetic route to this potent antifungal antibiotic, this has allowed us to determine the assignment of the relative and absolute configurations in the nine-membered ring.

Keywords: Antifungals; Asymmetric synthesis; Medium-ring heterocycles; Mitsunobu reactions.

UK-2A is a nine-membered dilactone which has recently been isolated along with the structurally similar congeners, UK-2B, 2C and 2D, from the mycelial cake of *Streptomyces* sp. 517-02 by Taniguchi *et al.*[1-3]. The plane structure of UK-2A has been elucidated by detailed ^{1}H- and ^{13}C-NMR analyses and chemical degradation studies, and the relative configuration of the three consecutive chiral centers from C_2 to C_4 in UK-2A was determined as (2*R*, 3*R*, 4*S*) or its antipode from the degradation products[2]. However, the relative configuration at the C_7 position and the absolute configuration of UK-2A still remain to be determined.[2]



UK-2A



Antimycin A_3

Although the structure of UK-2A is seemingly similar to the well-known antimycins[4,5], the benzyl group at the C_2 position in UK-2A has never existed in known antimycins[6] and one methyl group is lacking at the C_8 position. Furthermore, UK-2A has a 3-hydroxy-4-methoxypicolinyl group which had never been found in naturally occurring products, while the antimycins instead have the 3-formamidosalicylyl group which is believed essential to

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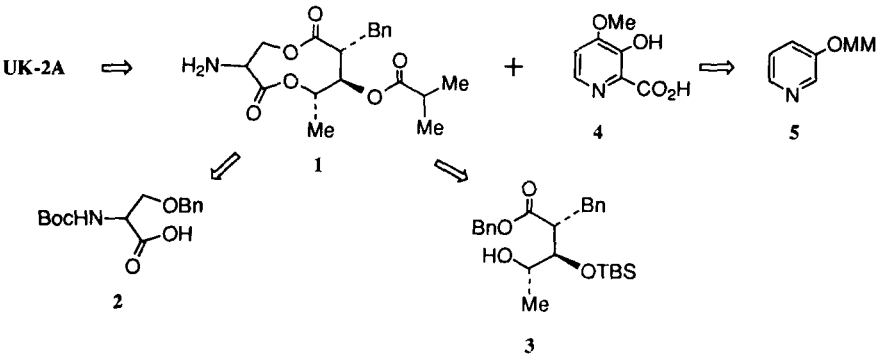
blocking the electron flow in the mitochondrial respiratory chain between cytochromes b and c_1[7-11]. Another and the most strikingly difference between them is their biological activities. UK-2A has strongly inhibited the growth of various kinds of yeasts and filamentous fungi, but the cytotoxic activity against several kinds of mammalian cells was very weak, while the antimycins have inhibited mammalian cells as strongly as fungi[1]. Based on these results, we have considered UK-2A as an attractive target for asymmetric synthesis, and at the same time as a potential antifungal agent. In this communication, we wish to describe the first total synthesis of UK-2A in an optically pure form.

As the relative configurations of the three consecutive chiral centers from C_2 to C_4 in UK-2A was determined as (2*R*, 3*R*, 4*S*) or its antipode[2], we decided to synthesize the two diastereomers, (2*R*, 3*R*, 4*S*, 7*S*)-UK-2A and (2*R*, 3*R*, 4*S*, 7*R*)-UK-2A. Our synthetic strategy is illustrated in Scheme 1, where the key intermediates were the nine-membered dilactone **1** and 3-hydroxy-4-methoxypicolinic acid (**4**). The nine-membered dilactone **1** was prepared from the L- or D-serine derivative **2** and optically active 4-hydroxypentanoic acid derivative **3** which should be obtained using a well-established asymmetric reaction because of the undetermined stereochemistry of the target. As the raw material of 3-hydroxy-4-methoxypicolinic acid (**4**), we have selected 3-(methoxymethoxy)pyridine (**5**)[12]. First, we will describe the synthesis of (2*R*, 3*R*, 4*S*, 7*S*)-UK-2A.

Scheme 1

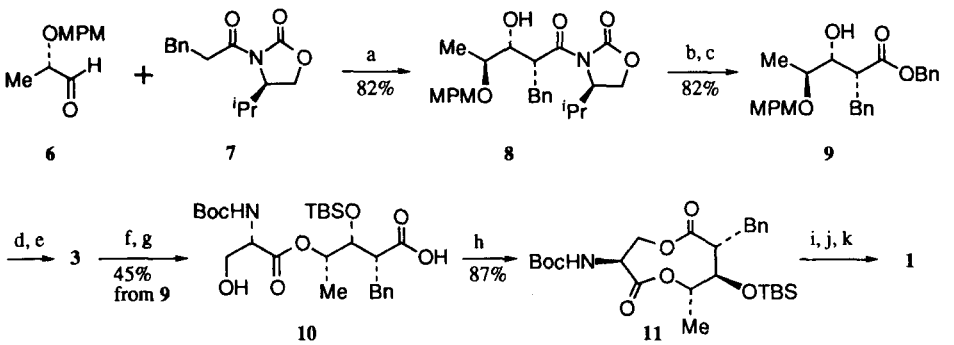


The synthesis of the nine-membered dilactone **1** was achieved through the asymmetric Evans aldol reaction[13] between aldehyde **6**, prepared in two steps from ethyl (*S*)-(-)-lactate by *p*-methoxybenzylation[14] and the DIBAL reduction (67%), and *N*-hydrocinnamoyloxazolidinone **7**, prepared from hydrocinnamoyl chloride and (*R*)-4-isopropyloxazolidinone (78%) (Scheme 2). The aldol reaction occurred with high diastereoselectivity (>98% de) to provide after column chromatography alcohol **8** {$[\alpha]^{25}_D$ +19.7 (*c* 1.00, $CHCl_3$)} as a single diastereomer in 82% yield. In order to prepare the cyclization precursor **10**, the chiral auxiliary was first removed with $LiOH/H_2O_2$[15] and the following benzyl esterification gave rise to **9** {$[\alpha]^{25}_D$ +48.7 (*c* 1.01, $CHCl_3$)} in 82% yield. Protection of the hydroxy group and cleavage of the MPM group to give alcohol **3** was carried out without incident. The ester formation with suitably protected L-serine **2** followed by the debenzylation (H_2/10% $Pd(OH)_2$-C) afforded the seco acid **10** (45% in 4 steps). Initial attempts to perform a lactonization of seco acid **10** using both Yamaguchi's method and modified Yamaguchi's method[16,17] were unsatisfactory.[1] Therefore, the

1. Complex mixture of products were obtained presumably due to the strong basicity of DMAP.

alternative standard, the intramolecular Mitsunobu reaction[18] was conducted by the treatment of **10** with diisopropyl azodicarboxylate (DIAD) and Ph_3P. The desired lactonization cleanly occurred and afforded dilactone **11** {$[\alpha]^{25}_D$ +70.7 (*c* 1.01, $CHCl_3$)} in 87% yield.[2] Further elaboration to one of the key intermediates **1** required little effort, and consequently we have obtained **1** on a multi-gram scale.

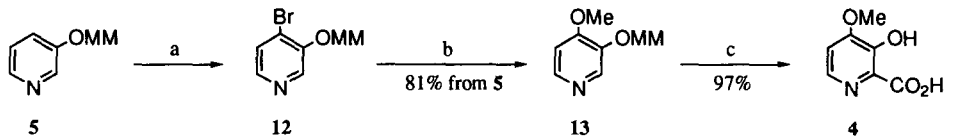
Scheme 2



Reagents: a) Bu_2BOTf, Et_3N; b) LiOH, H_2O_2; c) BnOH, DIAD, Ph_3P; d) TBSCl, ImH; e) DDQ, H_2O; f) **2**, EDCI, DMAP; g) H_2, 10%$Pd(OH)_2$-C; h) DIAD, Ph_3P; i) HF-Py-Py; j) *i*-PrCOCl, Py; k) TFA then $NaHCO_3$.

The synthesis of 3-hydroxy-4-methoxypicolinic acid (**4**) started from 3-(methoxymethoxy)pyridine (**5**)[3] which was used as a precursor of the 4-bromo-3-(methoxymethoxy)-pyridine (**12**) (Scheme 3).[4] After replacing the bromine with a methoxy group, relithiation was carried out with *t*-butyllithium in THF at -78°C and CO_2 quenching furnished a carboxyl group at the C_2 position (>98% regioselectivity). Simple acidic work-up gave 3-hydroxy-4-methoxypicolinic acid (**4**) in 97% yield.

Scheme 3



Reagents: a) *t*-BuLi, $BrCF_2CF_2Br$, Et_2O, -78°C; b) NaOMe, MeOH; c) *t*-BuLi, CO_2, THF, -78°C, then aq.HCl.

The final stage, the coupling of dilactone **1** with 3-hydroxy-4-methoxypicolinic acid (**4**), was successfully achieved in the presence of EDCI/HOBt which completed synthesis of (2*R*, 3*R*, 4*S*, 7*S*)-UK-2A. The spectral properties of (2*R*, 3*R*, 4*S*, 7*S*)-UK-2A including

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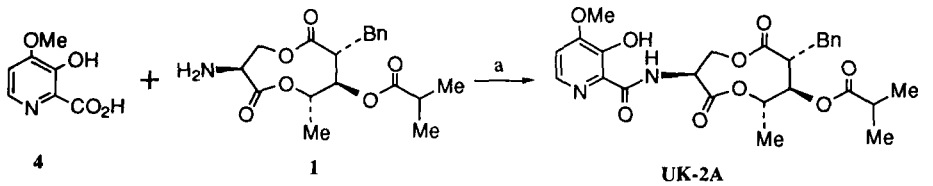
2. The yield of lactonization was greatly improved if compared to the case of the antimycin A_3 syntheses. It was presumably due to the lack of the C_8 methyl group. See: a) Kinoshita, M.; Wada, M.; Aburagi, S.; Umezawa, S. *J. Antibiot.* **1971**, *24*, 724. b) Kinoshita, M.; Aburagi, S.; Wada, M.; Umezawa, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1279. c) Aburagi, S.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 198. d) Wasserman, H. H.; Gambale, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 1423.
3. This compound was synthesized from commercial 3-hydroxypyridine when reacted with $MeOCH_2Cl$ and ^tBuOK in THF-DMF at 0°C; the yield of distilled 3-(methoxymethoxy)pyridine (**5**) was 71%.
4. Lithiation of 3-(methoxymethoxy)pyridine (**5**) was performed according to Ronald's procedure[12].

specific rotation {$[\alpha]^{23}_D$ +89.3 (*c* 1.01, $CHCl_3$); lit. $[\alpha]^{23}_D$ +89.11 (*c* 0.8, $CHCl_3$)} were identical with those in the literature[2]. On the other hand, (2*R*, 3*R*, 4*S*, 7*R*)-UK-2A was also synthesized in the same manner with (2*R*, 3*R*, 4*S*, 7*S*)-UK-2A, but ^1H- and ^{13}C-NMR spectra of it was clearly different from those of natural UK-2A.[5] Therefore, the relative and absolute configurations in the dilactone of UK-2A was unequivocally determined as (2*R*, 3*R*, 4*S*, 7*S*) and, at the same time, we achieved the first total synthesis of UK-2A in an optically pure form.

Scheme 4



Reagents: a) EDCI, HOBt, NMM, 25°C: 41% from **11**.

In summary, we have developed a synthetic route to the naturally occurring form of UK-2A. Our route is highly stereoselective and applicable to the synthesis of their stereoisomers and analogs. In addition to the completion of the total synthesis, this has allowed us to determine the assignment of the relative and absolute configurations in the nine-membered ring of UK-2A.

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5. The details will be reported later in a full account.