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Formal total synthesis of (−)-anisomycin based on the stereoselective nucleophilic substitution along with aryl migration

Machiko Ono,* Keiko Suzuki and Hiroyuki Akita *

School of Pharmaceutical Sciences, Toho University, 2-2-1, Miyama, Funabashi, Chiba 274-8510, Japan

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Abstract

The stereoselective conversion of (4*R*)-5-hydroxy-4-(4′-methoxyphenyl)-2(*E*)-pentenoate **5** into the (4*S*)-4-hydroxy-5-(4′-methoxyphenyl)-2(*E*)-pentenoate **6** using an $AgNO_3$/MS 4Å/$MeNO_2$ system was accomplished along with complete inversion at the C_4-position, and the synthesis of the intermediate (4*S*)-**7** for the chiral synthesis of (−)-anisomycin **8** from (4*S*)-**6** based on osmium tetroxide-catalyzed stereoselective dihydroxylation was achieved.

We previously reported that silica gel promotes the γ-lactonization and the concomitant 1,2-aryl migration of 4-aryl-5-tosyloxy pentanoate **1** to give γ-lactone **2** along with complete inversion in high yield (Scheme 1).[1] In the case of this reaction, an intramolecular attack of the ester carbonyl group to the σ-bridged phenonium ion **A** proceeded selectively at the C_4-position to provide γ-lactone. If the 4-aryl-5-tosyloxy-2(*E*)-pentenoate **3** is subjected to solvolysis in the presence of a nucleophile, 1,2-aryl migration followed by the intermolecular nucleophilic substitution along with inversion at the C_4-position should occur to afford the 5-aryl-4-substituted-2(*E*)-pentenoate derivatives **4**. However, this type of reaction has not been reported so far. In this paper, we wish to report the stereoselective conversion of (4*R*)-5-hydroxy-4-(4′-methoxyphenyl)-2(*E*)-pentenoate **5** into the (4*S*)-4-hydroxy-5-(4′-methoxyphenyl)-2(*E*)-pentenoate **6** and its application to the formal total synthesis of (−)-anisomycin **8** via synthetic intermediate (4*S*)-**7** (Scheme 2).

The antibiotic (−)-anisomycin **8**, isolated from the fermentation broth of *Streptomyces* sp., was reported to possess the 2*R*,3*S*,4*S* absolute configuration.[2] (−)-Anisomycin **8** exhibits strong and selective activity against pathogenic protozoa and fungi and has clinically been used with success in the treatment of vaginitis due to *Trichomonas vaginilis* and of amoebic dysentery.[2]

At first, 1,2-aryl migration along with the intermolecular nucleophilic substitution at the C_4-position using (±)-**5** was examined. The substrate (±)-**5**[3] was treated with Ts_2O to give the corresponding tosylate (±)-**9** (96% yield) which was subjected to solvolysis in water-saturated $MeNO_2$ to provide the desired

* Corresponding authors. Fax: +81-474-76-6195; e-mail: akita@phar.toho-u.ac.jp

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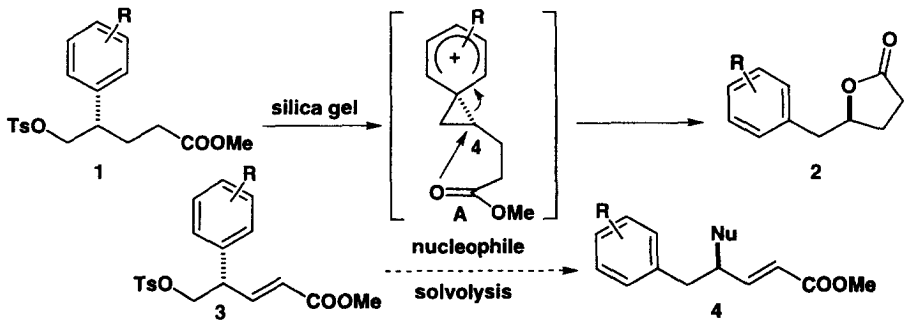
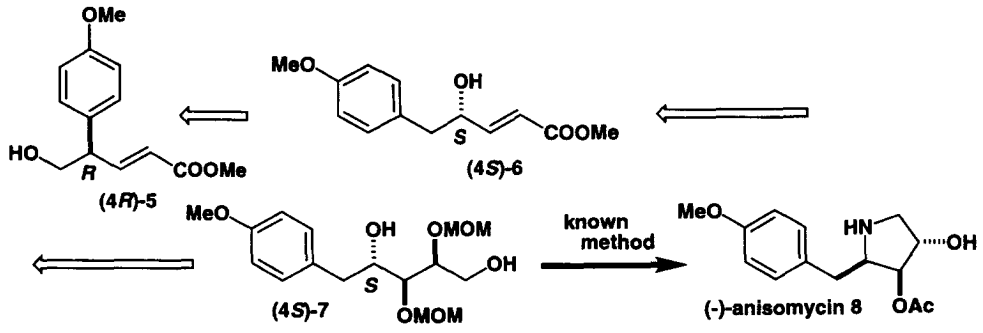
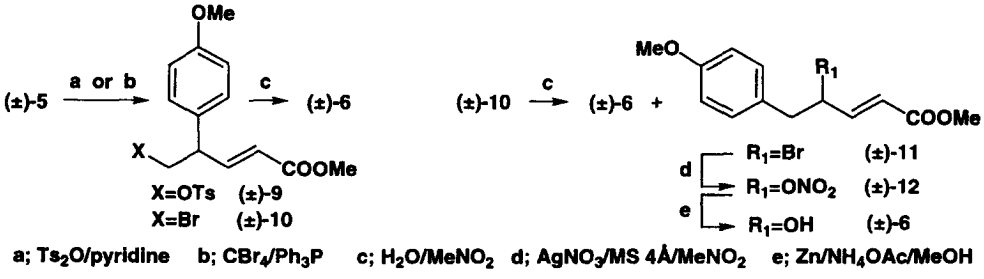


Scheme 1.



Scheme 2.

compound (±)-**6**[4] (51% yield) together with the starting compound (±)-**9** (34% recovery) (Scheme 3). The structure of (±)-**6** was determined by NMR analysis and finally confirmed by conversion of (4*S*)-**6** into the synthetic intermediate (4*S*)-**7** for (−)-anisomycin **8**. In the case of this reaction, the reaction rate was found to be sluggish at 90°C for 2 days. Then, the leaving group in the substrate was exchanged to a bromo group. Bromination of (±)-**5** gave the corresponding bromide (±)-**10**[5] (92% yield) which was subjected to solvolysis in the same manner as in the case of (±)-**9** to afford (±)-**6** (6% yield) and an inseparable mixture ((±)-**10**:(±)-**11**=1.5:1; 76% yield) of the starting (±)-**10** and an aryl migration product (±)-**11**. This mixture was treated with $AgNO_3$ in the presence of molecular sieves (MS 4 Å) at room temperature for 1 day to furnish the nitrate (±)-**12** in 83% yield. This result focuses on the direct formation of (±)-**12** from (±)-**10**.

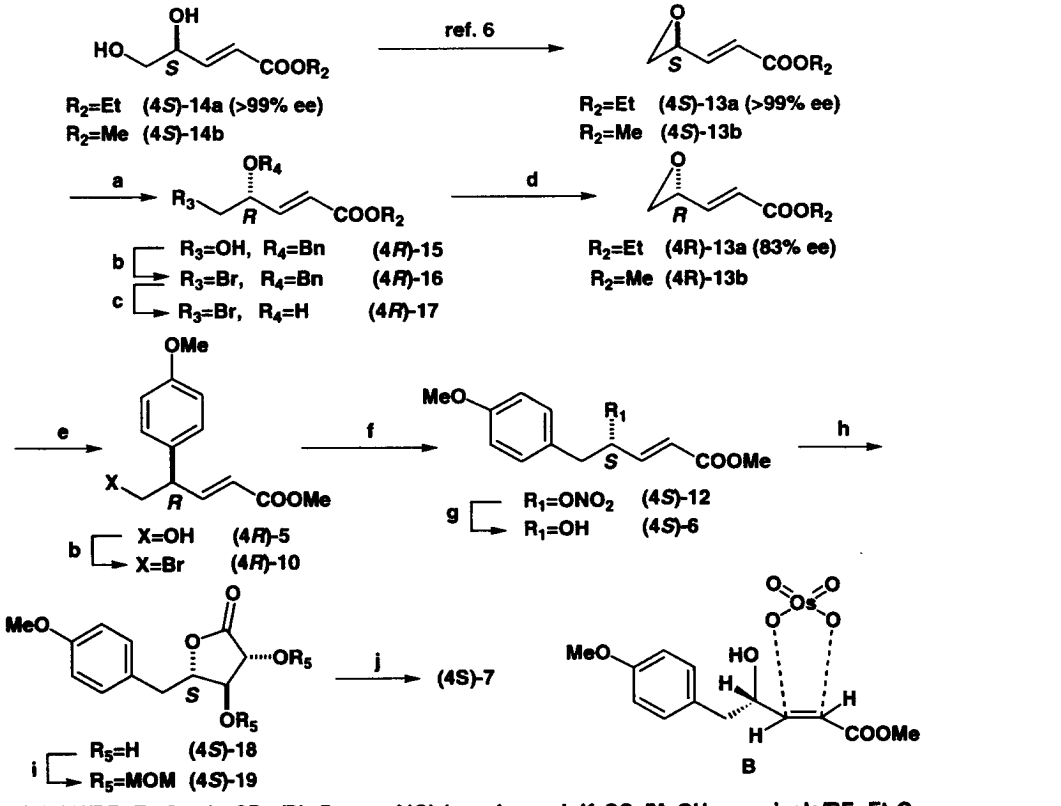


Scheme 3.

The reaction of (±)-**10** and $AgNO_3$, MS 4 Å in $MeNO_2$ at room temperature for 4 h yielded (±)-**12** (91% yield) which was treated with Zn and NH_4OAc in MeOH to give the desired (±)-**6** in 88% yield. When the substrates possessing a methoxyl group at least at the *ortho* and/or *para* positions of phenyl group are applied, this type of reaction should occur because electrophilicity of the presumed phenonium ion is adequately high. This presumption should be supported by the fact that tosylate **1** possessing a

methoxyl group at least at the 2′, 4′ and 6′ positions of the phenyl ring afforded γ-lactone **2** in good yield.[1] From a preliminary experiment of this reaction, $MeNO_2$ was regarded as the best reaction solvent and the presence of Ag^+ was essential. The oxygen nucleophiles such as hydroxyl, trifluoroacetoxyl and nitrate groups were considered to be active ones, while nitrogen nucleophiles such as azide ion, primary or secondary amines and phthalimide, and AgCN were inactive to afford the starting (±)-**10**.

In order to clarify the stereochemical course of this reaction, the synthesis of (4*R*)-**5** from (4*R*)-4,5-epoxy-2(*E*)-pentenoate **13b** is required because the reaction of (±)-**13b** and anisole in the presence of $BF_3 \cdot Et_2O$ was reported to afford (±)-**5** as a main product (Scheme 4).[3] Conversion of (4*S*)-**14a** into the enantiomerically pure (4*S*)-**13a** was achieved,[6] while the enantiomeric purity of (4*R*)-**13a** derived from (4*S*)-**14a** is reported to decrease down to 83% ee.[6] In order to overcome the latter disadvantage, the requisite (4*R*)-**13b** was obtained from (4*S*)-**13b** ($[\alpha]_D$ +22.3 (c=0.51, $CHCl_3$) corresponding to 92% ee) which was prepared from (4*S*)-**14b** by modification of the reported procedure.[6] The reaction of (4*S*)-**13b** with benzyl alcohol in the presence of $BF_3 \cdot Et_2O$ gave (4*R*)-**15** ($[\alpha]_D$ −57.0 (c=0.52, $CHCl_3$) corresponding to 92% ee) in 55% yield. Bromination of (4*R*)-**15** provided (4*R*)-**16** ($[\alpha]_D$ −40.2 (c=0.52, $CHCl_3$) corresponding to 92% ee; 95% yield)) followed by deprotection of the benzyl group using $AlCl_3$/*m*-xylene system[7] afforded bromohydrin (4*R*)-**17** ($[\alpha]_D$ −2.50 (c=0.52, $CHCl_3$) in 87% yield). An alkaline treatment of (4*R*)-**17** yielded the desired (4*R*)-**13b** ($[\alpha]_D$ −29.1 (c=0.51, $CHCl_3$) corresponding to 93% ee) in 85% yield. The reaction of (4*R*)-**13b** and anisole in the presence of $BF_3 \cdot Et_2O$ gave (4*R*)-**5** ($[\alpha]_D$ +2.00 (c=0.51, $CHCl_3$) corresponding to 93% ee; 51% yield) which was



Scheme 4.

converted into the bromide (4*R*)-**10** ([α]$_D$ +3.00 (c=0.5, $CHCl_3$) in 92% yield). Treatment of (4*R*)-**10** with $AgNO_3$ and MS 4 Å in $MeNO_2$ furnished the nitrate (4*S*)-**12** ([α]$_D$ +15.9 (c=0.51, $CHCl_3$); 91% yield) which was converted to the desired (4*S*)-**6** ([α]$_D$ +1.00 (c=0.5, $CHCl_3$) corresponding to 93% ee) in 87% yield in the same way as in the case of (±)-**12**. Osmium tetroxide-catalyzed dihydroxylation followed by treatment with *N*-methylmorpholine *N*-oxide gave the 3,4-*anti*-γ-lactone (4*S*)-**18** ([α]$_D$ −72.2 (c=0.41, MeOH) corresponding to 93% ee; 78% yield) and the 3,4-*syn*-diastereomer ([α]$_D$ −86.0 (c=0.11, MeOH); 2% yield). This high diastereoselectivity (3,4-*anti*:3,4-*syn* =39:1) was understood by the reported explanation.[8] A transition state **B** in which the carbon–oxygen bond is near the plane of the conjugated double bond is compatible with the observed stereochemical course of the dihydroxylation reaction. Presumably, this conformation results from a favorable interaction between the *p*-orbital of the double bond and an unshared pair on the γ-oxygen. Consequently, osmium tetroxide attacks from the less stereochemically hindered β-side. Recrystallization of the 93% ee of (4*S*)-**18** afforded the enantiomerically pure (4*S*)-**18**. Treatment of (4*S*)-**18** with chloromethyl methyl ether (MOM–Cl) furnished the di-MOM ether (4*S*)-**19** ([α]$_D$ −19.7 (c=0.49, $CHCl_3$); 55% yield) and the mono-MOM ether (29% yield). Reduction of (4*S*)-**19** with Dibal-H gave the (4*S*)-diol **7** ([α]$_D$ −39.3 (c=0.51, MeOH)) in 72% yield, whose spectral data were identical with those ([α]$_D$ −22.7 (c=16.21, MeOH) and ^{1}H NMR) of the reported (4*S*)-**7**.[9] The synthesis of (−)-anisomycin **8** from (4*S*)-**7** is readily achieved.[9]

From these experiments, conversion of the bromide (4*R*)-**10** into the nitrate (4*S*)-**12** from a stereochemical point of view was found to occur along with complete inversion at the C_4-position. In conclusion, the stereoselective conversion of (4*R*)-5-hydroxy-4-(4′-methoxyphenyl)-2(*E*)-pentenoate **5** into the (4*S*)-4-hydroxy-5-(4′-methoxyphenyl)-2(*E*)-pentenoate **6** using $AgNO_3$/MS 4 Å/$MeNO_2$ system was accomplished along with complete inversion at the C_4-position, and the synthesis of the intermediate (4*S*)-**7** for the chiral synthesis of (−)-anisomycin **8** from (4*S*)-**6** based on osmium tetroxide-catalyzed stereoselective dihydroxylation was achieved.

A detailed mechanism via phenonium ion and the scope and limitation of this type of reaction are being undertaken.

Acknowledgements

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