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An Aldol-Based Approach to the Synthesis of the Antibiotic Anisomycin

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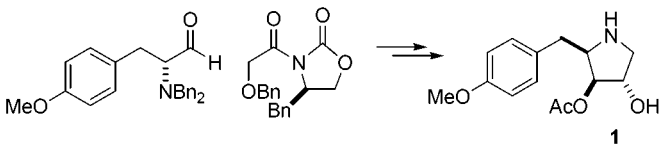
ABSTRACT



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A new approach to the synthesis of the antibiotic anisomycin is reported that relies upon a key aldol disconnection. The glycolate aldol coupling proceeds in 75% yield and with >95% diastereoselectivity, which allows the 13-step synthesis to proceed in 35% overall yield.

Anisomycin **1** was first isolated from the fermentation broths of *Streptomyces griseolus* and *Streptomyces roseochromogenes* by Sobin and Tanner in 1954.[1] Renewed interest in this antibiotic[2] has arisen from reports of high antitumor activity in vitro, with IC_{50} values in the nanomolar range,[3] and recent studies that have shown that anisomycin may be used in a synergistic fashion with a cyclin-dependent protein kinase inhibitor to kill carcinoma cells.[4] Anisomycin has found widespread use as a tool in molecular biology, where it has been shown to inhibit protein synthesis[5] and to activate JNK and p38 kinases.[6]

Anisomycin has attracted much synthetic interest over the past 30 years, with over 20 syntheses of the antibiotic or its biosynthetic precursor deacetylanisomycin being reported in the literature.[7] However, many of these syntheses have suffered from a series of protection and deprotection steps in the later stages, and the need for an efficient synthesis still remains.

We were attracted to the synthesis of anisomycin **1** following our successful synthesis of the iminosugar DAB-1[8] utilizing a highly diastereoselective *syn* glycolate aldol reaction with a serine-derived α-dibenzylamino aldehyde.[9] We envisaged that a similar approach (Figure 1), using a

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(4) (a) Van der Bosch, J.; Rueller, S.; Schlaak, M. German Patent DE 19,744,676, 1999; *Chem. Abstr.* **1999**, *130*, 291581. (b) Rueller, S.; Stahl, C.; Kohler, G.; Eickhoff, B.; Breder, J.; Schlaak, M.; van der Bosch, J. *Clin. Cancer Res.* **1999**, *5*, 2714.
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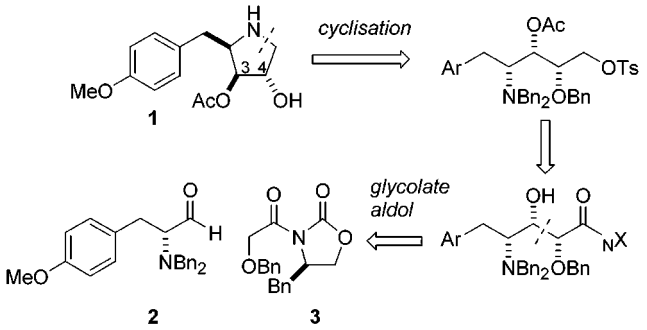
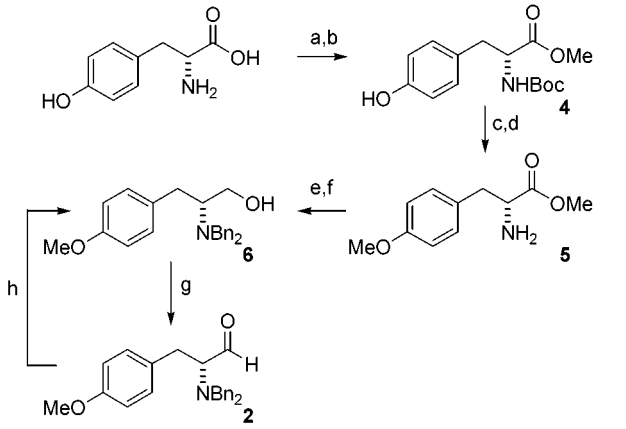


Figure 1. Retrosynthetic analysis of anisomycin (**1**).

tyrosine derived aldehyde **2** and the glycolate derivative of Evans oxazolidinone **3**, would allow a highly efficient synthesis of anisomycin.

D-Tyrosine was readily converted to its methyl ester hydrochloride salt, using in situ generation of the required acid (Scheme 1). Direct benzylation of the amino functionality was found to be impossible in the presence of the phenol; however, the amino functionality could be selectively protected to give the Boc-protected methyl ester **4** in excellent yield. The free phenol was then alkylated with methyl iodide in the presence of potassium carbonate,[10] and treatment with trifluoroacetic acid gave the primary amine **5**. Subsequent *N*,*N*-dibenzylation (BnBr, K_2CO_3) and reduction of the ester with lithium borohydride also proceeded in excellent yield to give the key precursor, amino alcohol **6**.

Scheme 1. Synthesis of Tyrosine-Derived Aldehyde **2**[a]



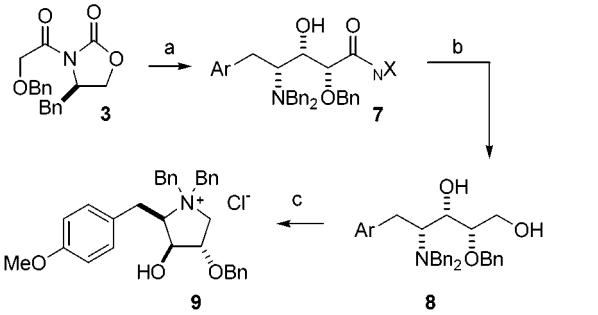
[a] Conditions: (a) AcCl, MeOH (100%); (b) Boc_2O, $NaHCO_3$, EtOH (99%); (c) MeI, K_2CO_3, DMF (97%); (d) TFA, CH_2Cl_2 (100%); (e) BnBr, K_2CO_3, MeCN (95%); (f) $LiBH_4$, MeOH (87%); (g) Swern (100%); (h) DIBAL-H, toluene (90%).

The desired tyrosine-derived aldehyde **2** was obtained via Swern oxidation. We and others[9] have found this two-step reduction/oxidation protocol to be the most efficient for the generation of aldehydes of this type.

The optical purity of alcohol **6** was confirmed by chiral HPLC using a Chiracel OD-H column (solvent; 10% propan-2-ol in hexane). Reassuringly, when compared with traces for the racemic alcohol, this showed that there was no appreciable racemization of alcohol **6** (material >98% ee). Alcohol **6** was found to be a convenient point in the synthesis to store gram quantities of material as a result of its observed stability. Samples of aldehyde **2** (synthesized and isolated using standard Swern procedures) were treated with DIBAL-H to regenerate alcohol **6**. Again the alcohol was confirmed by chiral HPLC to be >98% ee, suggesting that minimal racemization had occurred during the oxidation of **6** to **2**. Thus aldehyde **2** could be produced with high optical purity in seven steps and 80% overall yield from D-tyrosine.

The *syn* glycolate aldol reaction employed in the synthesis of DAB-1[8] was found to be the result of "matched" stereoselectivity of the two components. On the basis of this precedent, it was anticipated that formation of the C(3)−C(4) stereochemistry observed in **1** would require a "mismatched" aldol reaction. In this reaction the stereochemical induction from the oxazolidinone component would be required to outweigh that imposed by the α-chiral aldehyde.[11] The glycolate derivative of Evans oxazolidinone **3** was prepared as described in the literature from benzyloxyacetyl chloride and (4*R*)-benzyloxazolidin-2-one.[12] Formation of the *Z*-boron enolate (Bu_2BOTf, Et_3N, CH_2Cl_2) and reaction with aldehyde **2** gave the desired *syn* aldol adduct **7** in good yield (75%) and as the major diastereomer (>95% de, Scheme 2).[13]

Scheme 2. Glycolate Aldol Coupling[a]



[a] Conditions: (a) (i) Et_3N, Bu_2BOTf, CH_2Cl_2; (ii) **2** (75%); (b) $LiBH_4$, MeOH (80%); (c) (i) TsCl, DMAP, CH_2Cl_2; (ii) Dowex Cl^- (85%).

Aldol adduct **7** was readily reduced to the diol **8** using $LiBH_4$.[14] Selective tosylation of the primary alcohol in the presence of TsCl/DMAP resulted in the formation of the

(9) For a recent review on the role of α-dibenzylamino aldehydes in synthesis, see: Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121.

(10) The use of K_2CO_3 was shown to be of crucial importance in maintaining the stereochemical integrity of the α-amino ester.

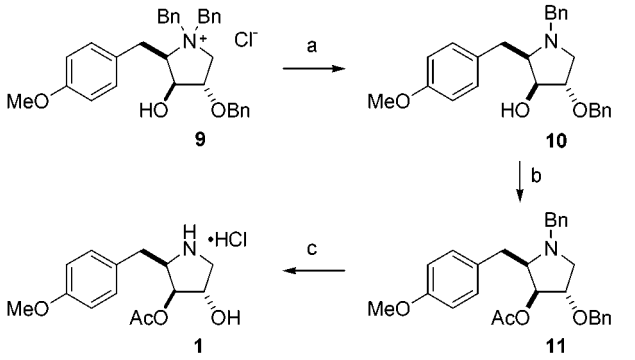
(11) A full analysis of the results of this and other related glycolate aldol reactions will be reported in a separate communication.

(12) Fuhry, M. A. M.; Holmes, A. B.; Marshall, D. R. *J. Chem Soc., Perkin Trans. 1* **1993**, 2743.

pyrrolidinium tosylate salt,[15] with no evidence of ditosylated material being formed. Conversion to the chloride salt **9** was achieved using Dowex resin treated with 1% HCl. Counterion exchange was confirmed by the absence of the diagnostic tosylate peaks [observed at $\delta = 2.29$ (s), 7.83 (d, J 8.2 Hz) and 7.10 (d, J 8.2 Hz)] in the ^{1}H NMR spectrum.

Completion of the synthesis of anisomycin **1** was achieved most efficiently via partial deprotection of the quaternary salt (Scheme 3). When the salt **9** was subjected to hydrogenation under basic conditions for 10 min or less, the benzyl-protected pyrrolidine **10** could be isolated in high yield (94%). Acetylation of this benzylated material was found to be more efficient than direct acylation of the chloride salt. This is presumed to be due to the increased solubility of the substrate, which also greatly enhances the ease of isolation of the product material. Final debenzylation was found to require "fresh" palladium hydroxide for complete deprotection to take place. Difficulties associated with partial salt formation during Celite filtration of the deprotected pyrrolidine were obviated by using acidic conditions provided by the addition of 2 equiv of a 1 M solution of HCl in ether to the reaction mixture to generate the pyrrolidine hydrochloride salt. This allowed analytically pure anisomycin **1** to be isolated as its hydrochloride salt in quantitative yield.

Scheme 3. Synthesis of Anisomycin (**1**)[a]



[a] Conditions: (a) Pd/C (cat.), K_2CO_3, H_2, MeOH, 10 min (94%); (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (92%); (c) $Pd(OH)_2$ (cat.), H_2, HCl, MeOH (100%).

In summary, an extremely rapid synthesis of anisomycin **1** has been achieved in 13 steps with a 35% overall yield. The synthesis relies upon a key glycolate aldol coupling, which has been shown to proceed in high yield and with excellent diastereoselectivity. Of note, this synthesis does not require extensive protecting group swaps in the final steps. Rather, the synthesis relies upon a stepwise deprotection of the benzyl protecting groups that were introduced at an early stage in the synthesis. The efficiency of the synthesis of the differentially protected aldehyde **2** (prepared in 80% overall yield from D-tyrosine) will allow future access to a wide range of analogues using this synthetic route.

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Supporting Information Available: Experimental procedures for the synthesis of compounds **7**−**10** and spectral data for compounds **11** and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) A synthetic route involving selective mono-*N*-debenzylation of the aldol adduct **7**, cyclization to a protected pyrrolidin-2-one, and then reduction to the protected pyrrolidine **10** was not pursued, as in practice it was found to be most convenient to carry out the aldol coupling and reduction to alcohol **8** without purification of the intermediate aldol adduct **7**.

(14) The Evans oxazolidinone was also recovered in reasonable yield (60%).

(15) Similar mesylate-induced cyclizations have been observed in the synthesis of *N*-(3-pyrrolodinylmethyl)benzamides: Thomas, C.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 841.