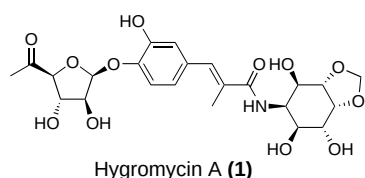


An Asymmetric Synthesis of C-2-*epi*-Hygromycin A**

Barry M. Trost,* Olivier Dirat, Joseph Dudash, Jr., and Erik J. Hembre

Hygromycin A (**1**) is a fermentation-derived natural product first isolated from *Streptomyces hygroscopicus* in 1953.^[1] The mode of action of hygromycin A is peptidyltransferase inhibition and the compound shares the same binding site on the ribosome as chloramphenicol.^[2] Inhibition through **1** occurs specifically by interfering with peptide bond forma-

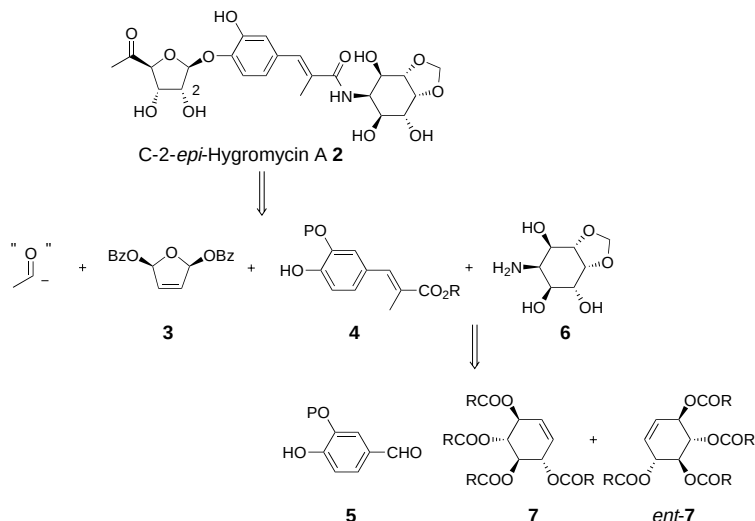


tion, in a way similar to that by chloramphenicol, and is evident by the fact that **1** inhibits the effects of chloramphenicol. It has been reported that **1** has a relative broad spectrum of activity against Gram-positive and Gram-negative bacteria.^[1a,b] Recently, **1** has attracted renewed interest due to the discovery of its hemagglutination inactivation activity^[3] as well as its high antitreponemal activity,^[4] especially as an effective agent for the control of swine dysentery, a mucohemorrhagic disease of economic importance to swine producers. Furthermore the antibiotic also demonstrates efficacy in the treatment of an induced dysentery infection model of swine at a level of 5–20 g ton⁻¹ feed.^[1b]

In spite of the unique structure and interesting biological activity of **1**, only a few reports have appeared on the synthesis of the structural components of **1**,^[5] and only one report of its total synthesis has been described.^[5a] The stereocontrolled synthesis of the β -*cis* glycosidic link between the sugar residue and the central cinnamate unit has not yet been achieved with an anomeric ratio of greater than 2:1. As part of our efforts towards the total synthesis of nucleosides and related structures, we undertook an investigation of the applicability of palladium-catalyzed asymmetric allylic alkylations (AAA)^[6] directed towards a synthesis of hygromycin and analogues. Herein, we report a simple, totally noncarbohy-

drate-based synthetic strategy that culminated in the synthesis of C-2-*epi*-hygromycin A (**2**) which derives from two different mechanisms for the enantiodiscrimination that derives from the AAA reaction.

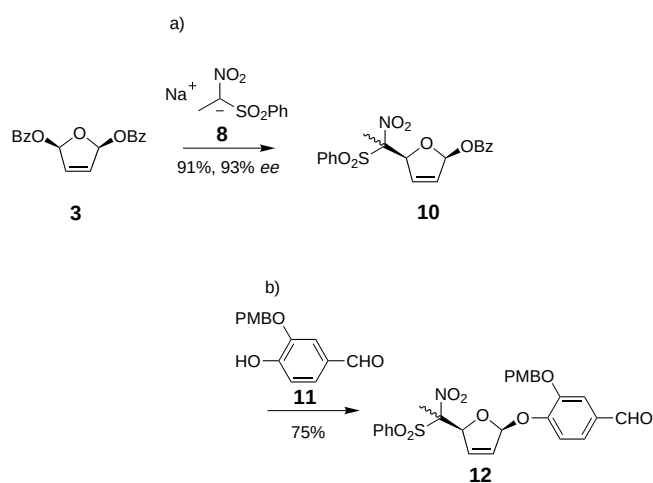
Scheme 1 illustrates the retrosynthetic analysis of **2** in which the furanoside part comes from two AAAs on the bisbenzoate **3**,^[7] one involving an acetyl nucleophile equivalent,



Scheme 1. Retrosynthesis of **2**.

the other involving a phenol, either **4** or **5**, as nucleophile.^[8] Additionally, the aminocyclitol **6** derives from deracemization of the racemic conduritol B tetraester **7**. Its synthesis, which required eight steps from racemic conduritol tetraester **7/ent-7**, employed a *meso*-type of π -allylpalladium intermediate to achieve the enantiodiscrimination and has been recorded elsewhere.^[9]

As an acetyl equivalent, we chose to use the sodium salt of 1-phenylsulfonylethyl-1-nitroethane **8** (Scheme 2) for its soft nucleophilicity and its lack of acidic protons after alkylation.^[10] The insolubility of this salt led us to use phase-transfer



Scheme 2. Stereoselective synthesis of the β -*cis* glycosidic link. a) 4% **9**, 1% [η^3 -C₃H₅PdCl]₂, 10% (*n*-C₆H₁₃)₄NBr, CH₂Cl₂, H₂O, RT; b) 6% *ent*-**9**, 2% [Pd₂(dba)₃] · CHCl₃, (C₂H₅)₃N, THF, 50 °C. dba = *trans,trans*-dibenzylideneacetone.

[*] Prof. B. M. Trost, Dr. O. Dirat, Dr. J. Dudash, Jr., Dr. E. J. Hembre
Department of Chemistry
Stanford University
Stanford, CA 94305-5080 (USA)
Fax: (+1) 650-725-0002
E-mail: bmtrost@stanford.edu

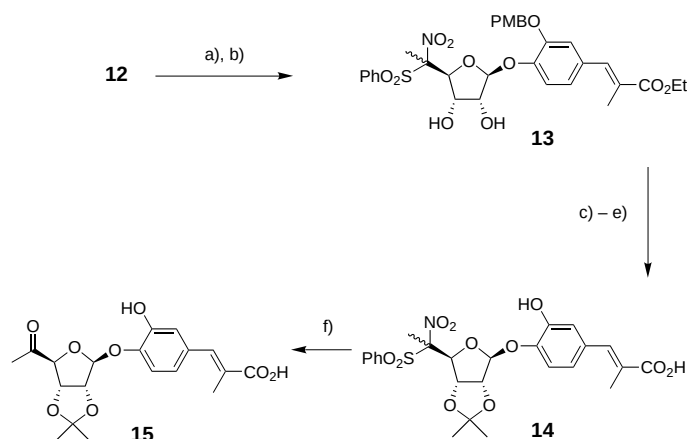
[**] We thank the National Science Foundation and the National Institute of Health, General Medical Sciences, for their generous support of our programs. O.D. thanks the Association pour la Recherche contre le Cancer (ARC) for a postdoctoral fellowship. Mass spectra were kindly provided by the Mass Spectrometry Facility, University of San Francisco, supported by the NIH Division of Research Resources.

Supporting information (Experimental and Spectroscopic data of all new compounds) for this article is available on the WWW under <http://www.angewandte.com> or from the author.

conditions, and we were delighted to find that using 4% of ligand **9** with 1% [η^3 -C₃H₅PdCl]₂ and 10% (*n*C₆H₁₃)₄NBr in a 0.2 M mixture of dichloromethane and water afforded the monobenzoate **10**^[11] in 91% yield and 93% *ee*, with respect to the dihydrofuran ring. While inconsequential in the current application, the issue of the diastereoselectivity, with respect to the side chain, in this reaction is interesting. The ratio of diastereoisomers is, on average, 5:1 by ¹H NMR analysis; however, different ratios are observed for each ring enantiomer, as determined by chiral HPLC (4.5:1 for the major ring enantiomer and 8:1 for the minor ring enantiomer). This observation shows not only that the ligand is imparting chirality on the nucleophile, but it exhibits a matched–mismatched behavior.^[12]

The second allylic alkylation reaction does not require the use of a chiral ligand; however, on some occasions, the higher reactivity of the chiral ligands in promoting these alkylations has made them the preferred ligands. Such proved to be the case here. Using *ent*-**9** as ligand and phenol **11** as nucleophile, a low conversion was obtained at room temperature using common concentrations (0.1 M), but an increase of the temperature (50 °C) and concentration (0.5 M) gave our optimized yield of 75%. The palladium source proved to be significant, as switching [Pd₂(dba)₃]·CHCl₃ to [η^3 -C₃H₅PdCl]₂ dropped the yield from 75% to 45%. Direct use of phenol **4** proceeded well but ultimately proved to be unsuccessful because of the wrong chemoselectivity in the subsequent attempts to perform oxidations; that is, the cinnamate-type double bond oxidized faster than the olefin of the dihydrofuran.

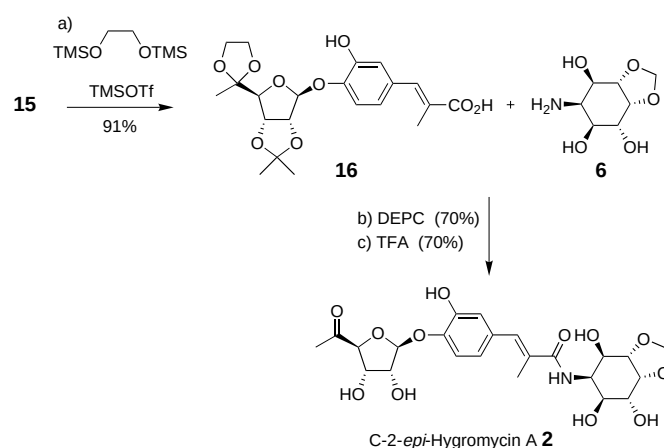
Considerable experimentation revealed the ordering of steps to be highly crucial for the synthesis of the furanose part of C-2-*epi*-hygromycin A. The sequence commenced with a diastereoselective dihydroxylation^[13, 14] of **12** followed by a stereoselective Wittig reaction to form **13** (Scheme 3).



Scheme 3. Synthesis of the furanose part. a) OsO₄, NMO, CH₂Cl₂, RT 98% yield; b) Ph₃P=C(Me)CO₂Et, CH₂Cl₂, 45 °C, 99% yield; c) *p*-TsOH, CH₃OH, THF, 50 °C, 100% yield; d) (CH₃)₂C(OCH₃)₂, *p*-TsOH, CH₂Cl₂, RT, 95% yield; e) LiOH, CH₃OH, H₂O, THF, 50 °C, 100% yield; f) THF, RT. NMO = 4-methylmorpholine-*N*-oxide, PMB = *p*-methoxybenzyl.

The PMB protecting group was surprisingly labile under mild acidic conditions, and was efficiently removed by a stoichiometric amount of *p*-toluenesulfonic acid in methanol. The diol was then protected and the ester saponified, leading to **14** in very high yield. The nitrosulfone **14** was then converted into the methyl ketone **15** by using buffered TiCl₃ in water in 80% yield.^[15] Thus, the furanoside unit **15** can be synthesized in eight steps and 50% overall yield from the bis-benzoate **3** with total stereocontrol of the β -*cis* glycosidic link.

All attempts to achieve the coupling of the aminocyclitol (**6**) with **14** followed by the transformation of the nitrosulfone into the methyl ketone failed. The coupling of **15** with the aminocyclitol (**6**) using DEPC in DMF^[16] with different bases, or with no base at all, resulted in amide bond formation, but with complete epimerization at C-4.^[17] A solution to this epimerization problem was found by protecting the ketone. While all the acid-catalyzed methods failed to protect **15**, we were able to achieve this protection using Noyori's conditions in 91% yield (Scheme 4).^[18] The coupling reaction of **16** could now be achieved without epimerization at C-4. A final concomitant deprotection of the ketone and the diol



Scheme 4. Completion of the synthesis. a) CH₂Cl₂, 0 °C; b) (C₂H₅)₃N, DMF, 0 °C; c) H₂O, RT. DEPC = diethylcyanophosphate; TFA = trifluoroacetic acid.

under acidic conditions completed the enantioselective synthesis of C-2-*epi*-hygromycin A **2**.

This synthetic route provides ready access to hygromycin analogues. It develops a new synthon for an acetyl anion equivalent for π -allylpalladium chemistry. Most importantly, it demonstrates the power of asymmetric allylic alkylations (AAAs) for creating effective strategies to complex targets. Desymmetrization of *meso*-diol intermediates provides asymmetric access to the furanose unit and discrimination of enantiotopic termini of a *meso*-type π -allyl intermediate provides asymmetric access to the aminocyclitol moiety. Furthermore, the increased kinetics associated with the chiral ligands are also beneficial for nonenantioselective allylic alkylations. Significantly, this method provides complete diastereoselectivity in the glycosylation step. The shortness of the longest linear sequence (11 steps) and the modular nature make this route a reasonable strategy for access and study of analogues. The shortness of this route derives in part

from the fact that, not employing carbohydrate building blocks at all, minimal use of protecting groups is needed.

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Supramolecular Hydrogen-Bonded Oligo(*p*-phenylene vinylene) Polymers**

Abdelkrim El-ghayoury, Albertus P. H. J. Schenning, Paul A. van Hal, Jeroen K. J. van Duren, René A. J. Janssen,* and E. W. Meijer*

In plastic electronics, π -conjugated oligomers and polymers are applied as advanced materials in a manifold of electro-optical devices such as light-emitting diodes (LEDs),^[1] field-effect transistors (FETs),^[2] and important for the present study, solar cells.^[3] Oligomers possess, due to their well-defined chemical structure, specific electronic and optical properties.^[4] However, the material properties of oligomers are generally secondary to those of their polymeric analogues, since entanglements of macromolecular chains, which are responsible for the typical polymer properties, are lacking. An attractive approach would be to combine the well-defined character of π -conjugated oligomers with the processability of polymers.

Recently, we reported on supramolecular polymers based on the dimerization of strong quadruple hydrogen-bonding self-complementary 2-ureido-4[1*H*]pyrimidinone units ($K_{\text{dim}} = 6 \times 10^7 \text{ M}^{-1}$ in chloroform),^[5] which exhibit real macroscopic polymeric properties such as an increase of viscosity.^[6] Improvement of material properties of low molecular weight telechelic polymers was therefore realized.^[7] These recent developments pave the way to combine the finest properties of conjugated oligomers and polymers by incorporating well-defined π -conjugated moieties in these hydrogen-bonded polymeric assemblies. Furthermore, it provides easy access to multifunctional copolymers by simply mixing the different components containing the quadruple hydrogen-bonded units. A few examples of the combination of π -conjugated oligomers with hydrogen-bonding motifs have been reported. Self-assembled fibers of mono- and bithiophene urea compounds have been described which show efficient charge transport.^[8] More recently, mono- and bifunctional oligo(*p*-vinylene phenylene)s, (OPV)s, functionalized with ureido-s-triazine have been reported that form stacks in dodecane.^[9] In a previous paper we disclosed monofunctionalized ureido-pyrimidinone with OPVs (MOPVUP) and hydrogen-bonded π -conjugated dimers were obtained.^[10]

[*] Prof. Dr. E. W. Meijer, Prof. Dr. R. A. J. Janssen, Dr. A. El-ghayoury, Dr. A. P. H. J. Schenning, P. A. van Hal, J. K. J. van Duren
Laboratory of Macromolecular and Organic Chemistry
Eindhoven University of Technology
P.O. Box 513, 5600 MB Eindhoven (The Netherlands)
Fax: (+31)40-2451036
E-mail: E.W.Meijer@tue.nl
R.A.J.Janssen@tue.nl

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