Application of the AAA Reaction to the Synthesis of the Furanoside of *C*-2-*epi*-Hygromycin A: A Total Synthesis of *C*-2-*epi*-Hygromycin A

Barry M. Trost,* Joseph Dudash, Jr., and Olivier Dirat[a]

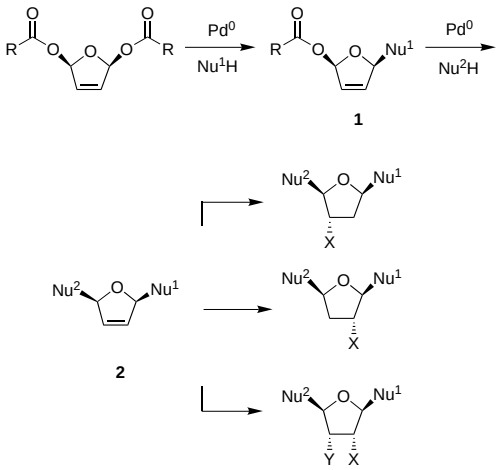
Abstract: A strategy for stereocontrolled syntheses of furanoside type of natural products is developed for a glycosyl aryl ether. This strategy resolves the issue of low diastereoselectivity typical of normal glycosidation methods for furanosides. All the stereochemistry ultimately derives from a desymmetrization of a 2,5-diacyloxy-2,5-dihydrofuran using Pd catalyzed asymmetric allylic alkylation which sets both the absolute stereochemistry and 1,4-relative stereochemistry. Diastereocontrolled elaboration of the 3,4-double bond then completes the synthesis. A new conjunctive reagent, 1-nitro-1-phenylsulfonyl-ethane, is developed to serve as an acyl anion equivalent. The utility of a phenol as a nucleophile in the Pd catalyzed glycosylation is demonstrated. From this strategy emerged a short, practical synthesis of *C*-2-*epi*-hygromycin A.

Keywords: asymmetric catalysis · asymmetric synthesis · hygromycin A · palladium · total synthesis

Introduction

Furanosides, such as nucleosides and ribose analogues, represent an important class of carbohydrate derivatives for which stereoselective syntheses at the anomeric center have been challenging. While synthesis of the constitutionally isomeric pyranosides is aided by the anomeric effect, the α:β anomer ratio in furanosides is often dictated by steric effects, giving rise to a mixture of products. One approach to these compounds has been the Koenigs–Knorr glycosylation,[1] which utilizes a neighboring group effect to direct the stereoselectivity at the anomeric center. With the advent of *C*-2 deoxy nucleoside analogues as anti-HIV agents, this glycosylation method became less general. Stereoselective syntheses have been reported[2] for deoxy-ribose derivatives, which rely on cyclization techniques, but these are less convergent than the glycosylation approach. Thus, a general method for the synthesis of furanosides that exhibits the stereoselectivity of non-glycosylation methods, but provides the flexibility and convergency of glycosylation method would complement nicely existing technologies.

Scheme 1 outlines the strategy under development in our laboratories. *cis*-2,5-Diacyloxy-2,5-dihydrofuran, readily available by the direct oxidation of furan, undergoes regio-, diastereo-, and enantioselective substitution to provide either enantiomer of the mono- (i.e., **1**) or di- (i.e., **2**) substituted



Scheme 1. A strategy to furanosides.

systems. The diastereoselectivity is fully controlled by the metal catalyst so that no ambiguity exists. The variability of the two nucleophiles then defines what types of furanosides can be accessed. The olefin becomes a useful functional group to allow introduction of simply hydrogen (X = Y = H) or various substituents. The regio- and diastereoselectivity of introduction of such substituents will then be dictated by the 2,5-substituents. This stategy minimizes the presence of interfering functional groups and thereby also minimizes the use of protecting groups. Since the absolute configuration is controlled by the desymmetrisation of the *meso*-diester, either enantiomer of the product is equally easily accessible.

Previous work in these laboratories developed a method for the synthesis of nucleosides[3a] by our asymmetric allylic

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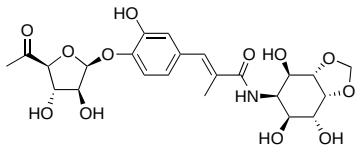
  0947-6539/02/0801-0259 $ 17.50+.50/0

alkylation (AAA) reaction.[3b] This desymmetrization of dihydrofuran derivatives was extended from N-glycoside synthesis to C-glycosides in the total synthesis of showdomycin.[4] In this paper, we report the full details of the development of this methodology to include O-glycosides, represented by the synthesis of the furanoside moiety of the *C*-2 epimer of hygromycin A.[5]

Hygromycin A (**3**) is a fermentation-derived natural product first isolated from *Streptomyces hygrospicus* in 1953.[6] The mode of action of hygromycin A is peptidyltransferase inhibition and the compound shares the same binding site on the ribosome as chloramphenicol.[7] It has been shown that



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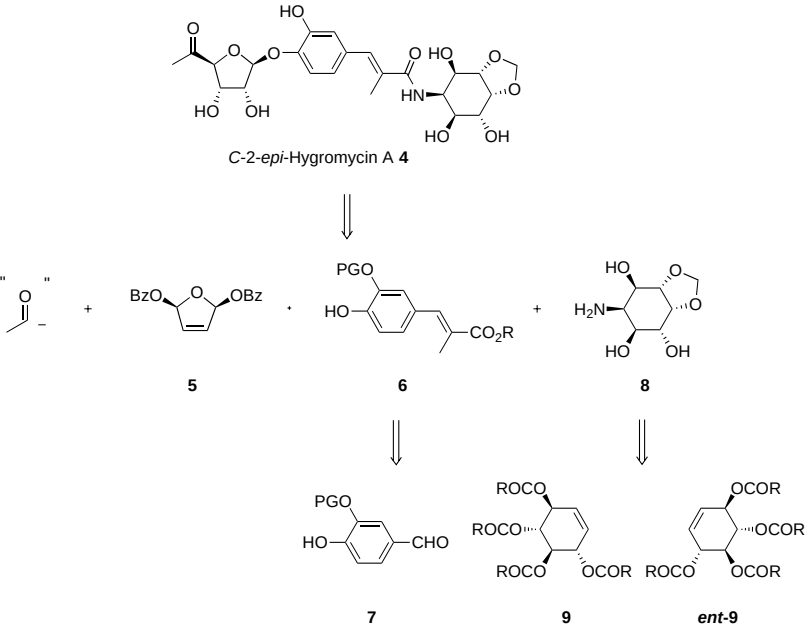
inhibition occurs specifically by interfering with peptide bond formation, resembling chloramphenicol, and is closely related as **3** inhibits the effects of the latter. It has been reported that **3** has a relative broad spectrum of activity against Gram-positive and Gram-negative bacteria.[6a,b] Recently, **3** has attracted renewed interest due to the discovery of its hemaglutination inactivation activity[8] as well as its high antitreponemal activity,[9] 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 per ton feed.[6b]

In spite of the unique structure and interesting biological activity of **3**, only a few reports have appeared on the synthesis of the structural components of **3**,[10] and only one report of its total synthesis has been described.[10a] 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.

Scheme 2 illustrates the retrosynthetic analysis whereby the furanoside part comes from two AAA's on the bis-benzoate **5**,[11] one involving an acetyl nucleophile equivalent, the other involving a phenol, either **6** or **7**, as nucleophile. Additionally, the aminocyclitol **8** derives from deracemization of the racemic conduritol B tetraester **9**. Its synthesis, which required eight steps from racemic conduritol tetraester **9**/***ent*-9**, employed a *meso*-type of π-allylpalladium intermediate as the enantiodiscriminating mechanism and has been reported elsewhere.[12]

Results and Discussion

In theory, either the acetyl equivalent or the phenol could be used as the nucleophile in the initial desymmetrization step. Our attempts at using phenols in the enantiodiscriminating reaction led to mixtures of mono- and bis-alkylated products. We attributed the increase in the disfavored second ionization to the slow decomplexation of palladium from the mono-alkylated product, which is electronically similar to the starting material. Thus, we turned to the carbon nucleophile for the asymmetric induction step. As an acetyl equivalent, we chose to use 1-nitro-1-phenylsulfonylethane for its soft nucleophilicity and its lack of acidic protons after alkylation.[13] Generation of the anion of this nitrosulfone and subsequent reaction proved difficult with a variety of bases, including triethylamine, DBU, sodium hydride, cesium carbonate, and *n*-butyllithium, due to the lack of solubility of the anion in organic media. This insolubility led us to use phase transfer conditions, and we were delighted to find that using the sodium salt **10**, 4 mol% of ligand **11** with 1 mol% $[\eta^3\text{-}C_3H_5PdCl]_2$ and 10 mol% $(n\text{-}C_6H_{13})_4NBr$ in a 0.2 M mixture of dichloromethane and water afforded the monobenzoate **12**[14] in 91% yield and with 93% *ee* (Scheme 3). It should be noted that the ratio of ligand to palladium was crucial for high enantioselectivity, as 3 mol% ligand resulted in *ee's* on the order of 40–70%. While inconsequential in the current application, the issue of the diastereoselectivity in this reaction is interesting. The ratio of diastereoisomers is, on average, 5:1 by ^{1}H NMR analysis; however, different ratios are observed for each enantiomer, as determined by chiral HPLC [4.5:1 for the major enantiomer and 8:1 for the minor

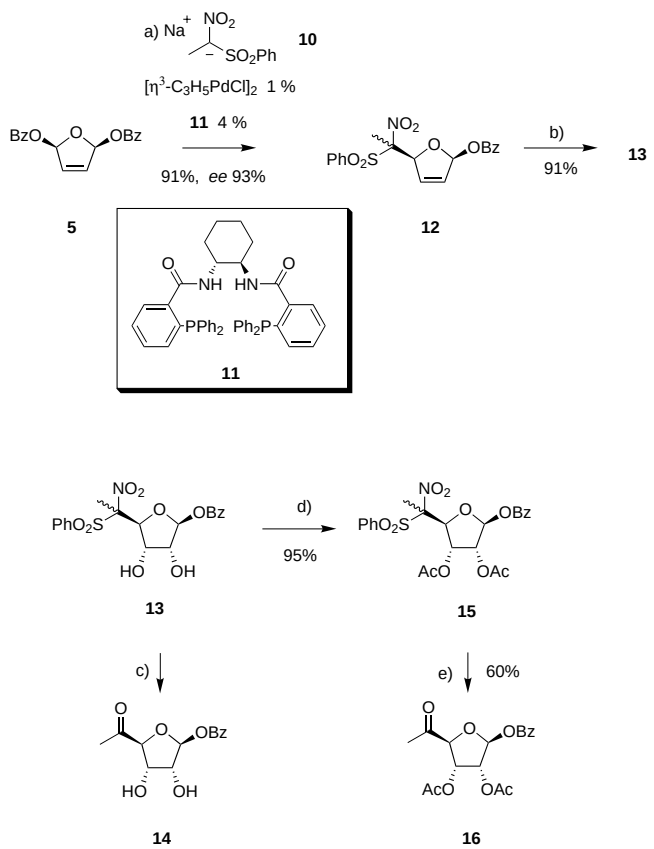


Scheme 2. Retrosynthesis of *C*-2-*epi*-hygromycin A.

0947-6539/02/0801-0260 $ 17.50+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 1

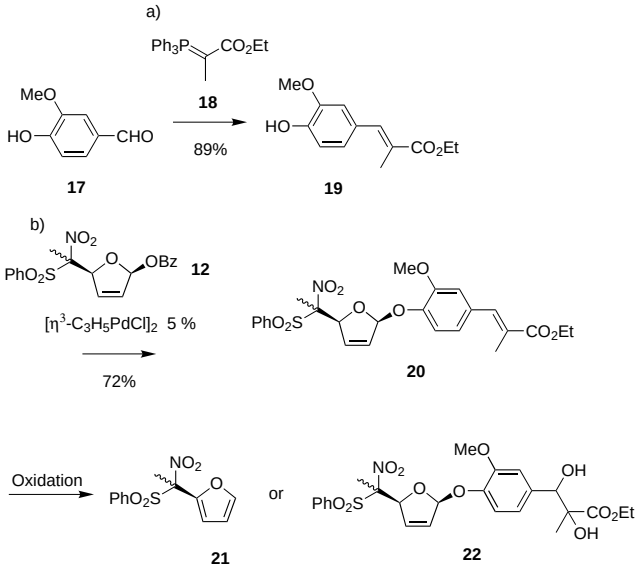
enantiomer]. This observation shows not only that the ligand is imparting chirality in the nucleophile, but it exhibits a matched–mismatched behavior.[15]

In an effort to ascertain the ability to convert the nitrosulfone to the ketone, model studies were conducted for the reduction. The mono-alkylated product was stereoselectively dihydroxylated[16, 17] with OsO_4/NMO to give the diol **13** in 91% yield. This compound was treated with a 13% $TiCl_3$ in 20% HCl solution[18] to give a 2:1 mixture of the desired ketone **14** and starting material. Since reaction of the diol substrate could not be pushed to 100% conversion, the diol was acetylated to give **15** in 95% yield. While reaction of this compound with $TiCl_3$ was unsuccessful, irradiation in the presence *N*-benzyl nicotinamide in benzene with a 150 W tungsten lamp[19] for 48 hours gave the ketone **16** in 60% yield (Scheme 3).



Scheme 3. 1-Nitro-1-phenylsulfonyl-ethane as an acyl anion equivalent in palladium catalyzed AAA reaction: a) 10% *n*Hex_4NBr, CH_2Cl_2, H_2O, RT. b) OsO_4, NMO, CH_2Cl_2, H_2O, RT. c) $TiCl_3$, aq HCl, THF, H_2O, RT. d) Ac_2O, Py, RT. e) BNAH, *hν*, C_6H_6, RT.

Confident that the nitrosulfone functionality would serve as a suitable acetyl synthon, the second alkylation reaction was examined. The ability of phenols to function as leaving groups in Pd catalyzed allylic alkylations[20] raises the question of their suitability in the current case, especially since the phenol should bear a strong electron withdrawing group to make it a better leaving group and poorer nucleophile. A protected version of the central phenol moiety of hygromycin A was prepared by Wittig reaction of vanillin (**17**) and ethyl 2-(phosphoranylidene)propionate (**18**). Subjecting this phenol **19** to the palladium reaction conditions with the mono-alkylated allylic benzoate **12** gave the desired cinnamate derivative **20** in 72% yield (Scheme 4). The reaction required triisopropyl phosphite as the ligand and was complete in one hour.



Scheme 4. Palladium catalyzed glycosidation with elaborated phenol. a) CH_2Cl_2, RT. b) 15% $(iC_3H_7O)_3P$, Cs_2CO_3, THF, RT.

The next task was oxidation of the dihydrofuran. A variety of epoxidation conditions resulted in elimination of the cinnamate moiety to give the furan **21**. Dihydroxylation with OsO_4 gave the unanticipated result of reaction at the styryl olefin to give diol **22**. With this result in hand, it was decided to introduce a simpler phenol in the second alkylation, thus eliminating the issues of chemoselective oxidation.

With vanillin as the nucleophile in the second alkylation, the desired product **23** was obtained in 82% yield. Again, the olefin of the dihydrofuran proved resistant to epoxidation, using a variety of conditions, including peracids, dioxiranes, and transition metal catalyzed methods. Formation of the halohydrin (*N*-bromosuccinimide, H_2O, DMSO) was also examined but met with no success. Attempted hydroboration of the olefin led to decomposition. Thus, we were forced to return to *cis*-dihydroxylation of the olefin as our only means of functionalizing the olefin. The diol **24** was produced in 87% yield by the OsO_4/NMO protocol. Several strategies were unsuccesfully explored to convert the *cis*-diol to the naturally-occurring *trans*-diol. Since the major objective was the development of the general strategy controlling the *cis*-2,5 stereochemistry, attention focused on completing a synthesis of *C*-2-*epi*-hygromycin A.

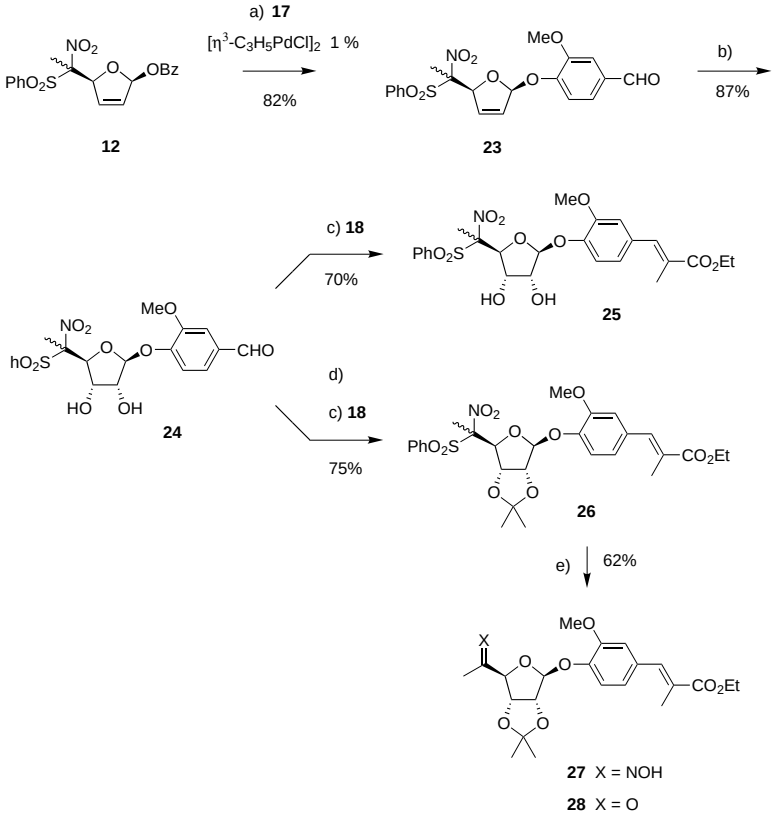
Homologation of aldehyde **24** to the cinnamate **25** occurred uneventfully by Wittig reaction in 70% yield. Application of methods used in the model studies to convert the nitrosulfone to the ketone mainly resulted in decomposition, due to sensitivity of the anomeric center. Buffering the reaction media for both the $TiCl_3$ and *N*-benzyl nicotinamide (BNAH) protocols with Et_3N did not prevent the decomposition.

However, upon a report in the literature of conversion of an α-nitro-2-thiopyridyl moiety to a ketone in an acid sensitive system,[21] the titanium (Scheme 5) reduction was revisited. Protection of the diol **24** as the acetonide followed by homologation gave the enoate **26** in 75% yield. This nitrosulfone was successfully reduced using a 20% solution of commercially available solid $TiCl_3$ in water with ammonium acetate buffer to afford a 2:1 mixture of the oxime **27** and ketone **28** in 62% yield. The oxime could be resubjected to the conditions to provide the ketone in 80% yield. All that remained was deprotection of the methyl ether and hydrolysis of the ester. Procedures for demethylation proved too harsh, as decomposition resulted under a variety of conditions.

Difficulty in removing the methyl ether of vanillin led to a second-generation synthesis, where the phenol nucleophile is introduced as its benzyl ether derivative. Palladium-catalyzed alkylation gave the desired product **29** in 76% yield (Scheme 6). The diol **30** was obtained in 83% yield after reaction with OsO_4, followed by Wittig reaction to give the enoate **31** in 72% yield. Protection of the diol as the acetonide followed by saponification of the ester gave the carboxylic acid **32** in 60% yield for the two steps. The nitrosulfone was reduced to the ketone **33** in 74% yield without observation of the intermediate oxime. Unfortunately, the benzyl protecting group could not be removed without concomitant reduction of the olefin under a variety of conditions. Thus, a third-generation synthesis was developed utilizing a *p*-methoxybenzyl (PMB) protecting group (Scheme 6) which ultimately led to total synthesis of *C*-2-*epi*-hygromycin A. While the previous alkylation reactions with phenols proceeded quite well with the achiral triisopropyl phosphite, the reaction proved to be more capricious with the PMB-protected phenol. Although the second allylic alkylation reaction does not require the use of a chiral ligand, on some occasions, the higher reactivity of the chiral ligands in promoting these alkylations has made them into the preferred ligands. Such proved to be the case here. Using *ent*-**11** as ligand and phenol **34** as nucleophile, a low conversion was obtained at room temperature using common concentrations (0.1M), but an increase of the temperature (50°C) and concentration (0.5M) gave aldehyde **35** in an optimized yield of 75%. The palladium source proved to be significant, as switching from $[Pd_2dba_3]\cdot CHCl_3$ to $[\eta^3\text{-}C_3H_5PdCl]_2$ dropped the yield from 75 to 45%.

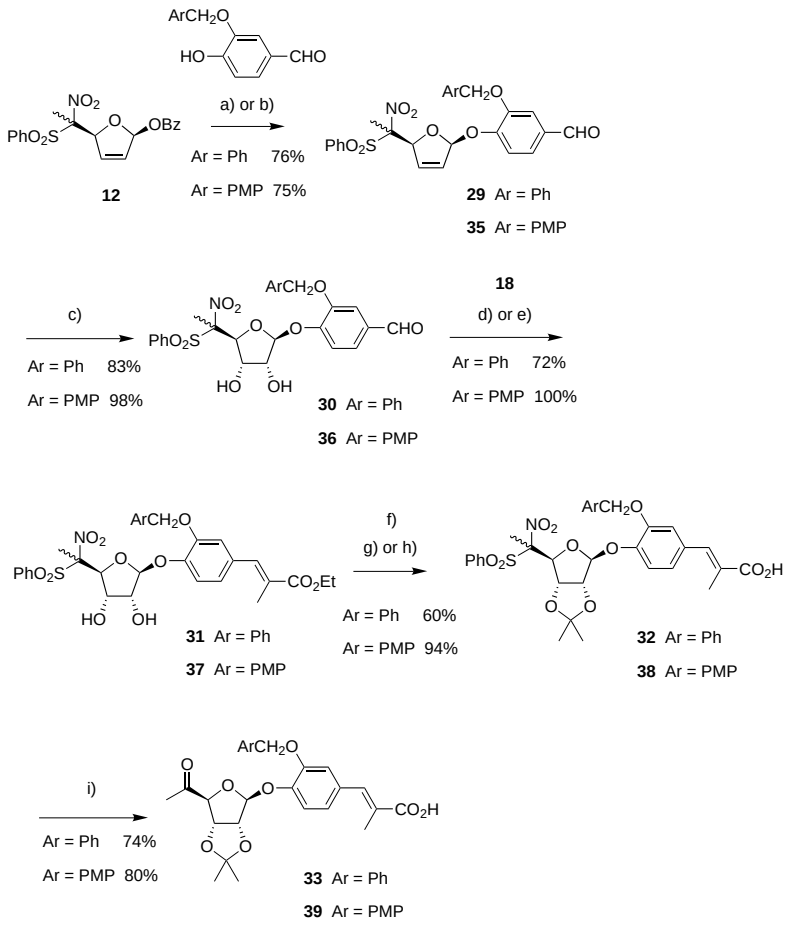
Our initial sequence for completion of the synthesis commenced with a diastereoselective dihydroxylation of **35** followed by a stereoselective Wittig reaction to form **37** in 98% yield. The PMB protecting group was surprisingly labile under mildly acidic conditions, but the diol could be protected as the acetonide with the PMB group intact in 94% yield after careful optimization of the reaction concentration (0.1M).[22] Following ester saponification in very high yield, the nitrosulfone **38** was converted into the methyl ketone **39** by using buffered $TiCl_3$ in water in 80% yield. The furanoside unit **39** was synthesized in seven steps and 50% overall yield from the bis-benzoate **5** with total stereocontrol of the β-*cis* glycosidic link.

Unfortunately, coupling of the PMB-protected **39** with the aminocyclitol **8** using diethylcyanophosphonate (DEPC) in DMF with different bases or with no base at all[23] led to epimerization at *C*-4.[24] An obvious alternative was to couple the aminocyclitol **8** with the nitrosulfone **38** followed by the unmasking of the ketone. The coupling step worked well, but the transformation of the nitrosulfone into the methyl ketone failed. Another approach to preventing *C*-4 epimerization would be to protect the ketone as its corresponding ketal before coupling with the aminocyclitol. While formation of the ketal under acid catalyzed conditions were unsuccessful, the reaction was accomplished readily using Noyori's conditions.[25] Another issue was the PMB deprotection. While acid catalyzed deprotection of the PMB at the nitrosulfone stage were high yielding, only complex mixtures were obtained when attempted at the ketone stage. Thus, the steps were re-ordered. Deprotection of the PMB group with *p*-TsOH followed by formation of acetonide **40** was carried out (Scheme 7) in near quantitative

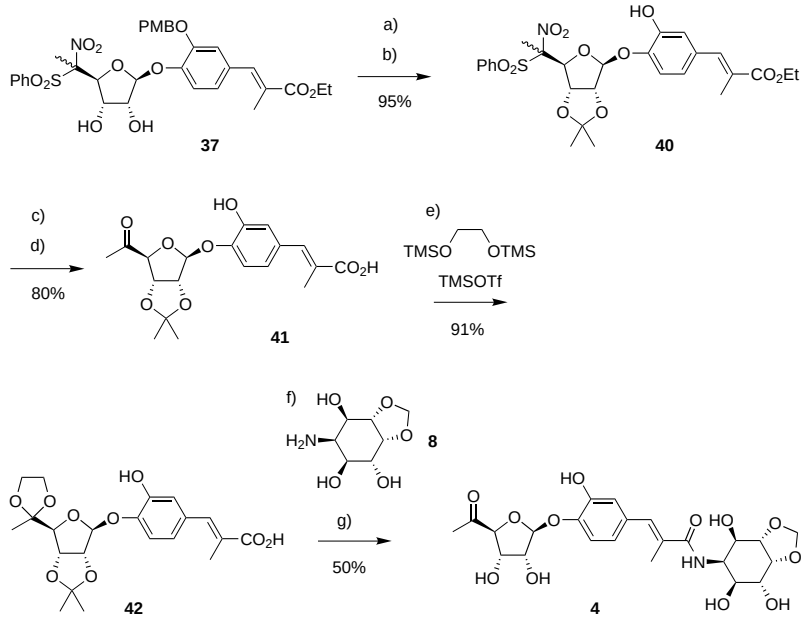


Scheme 5. Initial study using vanillin: a) 7% ($iC_3H_7O)_3P$, Cs_2CO_3, THF, RT. b) OsO_4, NMO, CH_2Cl_2, H_2O, RT. c) CH_2Cl_2, RT. d) 2,2-DMP, *p*-TsOH, acetone, RT. e) $TiCl_3$, NH_4OAc buffer, THF, H_2O, RT.

0947-6539/02/0801-0262 $ 17.50+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 1



Scheme 6. Synthesis of furanoside: a) For Ar = Ph, 1% $[\eta^3\text{-}C_3H_5\text{-}PdCl]_2$, 14% $(iC_3H_7O)_3P$, Cs_2CO_3, THF, RT. b) For Ar = PMP, 2% $[Pd_2dba_3]\cdot CHCl_3$, 8% *ent*-**11**, $(C_2H_5)_3N$, THF, 50 °C. c) OsO_4, NMO, CH_2Cl_2, H_2O, RT. d) For Ar = Ph, CH_2Cl_2, RT. e) For Ar = PMP, CH_2Cl_2, 50 °C. f) 2,2-DMP, *p*-TsOH, acetone, RT. g) For Ar = Ph, NaOH, H_2O, CH_3OH, 50 °C. h) For Ar = PMP, LiOH, H_2O, CH_3OH, THF, 40 °C. i) $TiCl_3$, NH_4OAc, H_2O, THF, RT.



Scheme 7. Completion of the synthesis: a) *p*-TsOH, CH_3OH, THF, 50 °C. b) 2,2-DMP, *p*-TsOH, CH_2Cl_2, RT. c) LiOH, H_2O, CH_3OH, THF, 40 °C. d) $TiCl_3$, NH_4OAc, H_2O, THF, RT. e) CH_2Cl_2, 0 °C. f) DECP, $(C_2H_5)_3N$, DMF, 0 °C. g) TFA, H_2O, RT.

yield (95% for two steps). Saponification of the ester and reduction of the nitrosulfone to the ketone gave the desired acid **41**, which was protected as its ethylene ketal **42** using Noyori's conditions in 73% yield (three steps). The synthesis of the furanoside unit **42** was synthesized in nine steps and 46% overall yield from the bis-benzoate **5**. The coupling reaction could now be achieved without epimerization at *C*-4. A final concomitant deprotection of the ketone and the diol under acidic conditions completed the enantioselective synthesis of *C*-2-*epi*-hygromycin A **4**.

Conclusion

The AAA reaction methodology has been successfully applied to the synthesis of an analogue of the hygromycin furanoside moiety. This endeavor extends this strategy from N- and C-glycosides to O-glycosides, allowing for the further application to a variety of carbohydrate derivatives. More importantly, the stereoselective creation of the anomeric center does not rely on either the neighboring group or anomeric effect, thus creating a new paradigm for glycosylation reactions and hopefully expanding the synthetic technologies available for sugar chemistry.

Experimental Section

General methods: see ref. [12].

Benzoic (2*S*,5*S*)-5-(1-benzenesulfonyl-1-nitroethyl)-2,5-dihydrofuran-2-yl ester (12): A solution of *cis*-2,5-dibenzoxy-2,5-dihydrofuran (**5**; 2 g, 6.41 mmol), π-allylpalladium chloride dimer (23 mg, 0.064 mmol, 1 mol%) and (*R*,*R*)-**11** (178 mg, 0.26 mmol, 4 mol%) in dichloromethane (30 mL) were added to a sonicated, degassed solution of 1-nitro-1-phenylsulfonylethane sodium salt **10**[26] (1.922 g, 8.11 mmol) and tetra-*n*-hexylammonium bromide (0.28 g, 0.64 mmol) in water (30 mL). The reaction was vigorously stirred at room temperature for 16 h. The phases were separated, the organic layer dried over magnesium sulfate, filtrated and evaporated in vacuo.

The nitrosulfone **12** (2.354 g, 5.84 mmol) was isolated pure as a white gummy solid after column chromatography (petroleum ether/ethyl acetate 7:3) with 91 % yield as a 5:1 mixture of diastereoisomers (by ^{1}H NMR) with 93 % *ee* (by chiral HPLC). Data for **12**: $R_f = 0.3$ (heptane/diethyl ether 1:1), 0.52 (heptane/diethyl ether 1:3); $[\alpha]_D^{20} = +94.6$ ($c = 4.57$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3096$, 3067, 2978, 2871, 1731, 1556, 1449, 1336, 1261, 1157, 946 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.99 - 7.84$ (m, 4H), 7.65 – 7.51 (m, 4H), 7.46 – 7.39 (m, 2H), 7.13 (d, $J = 1.2$ Hz, 1H), 6.19 (ddd, $J = 6.0$, 2.1, 1.3 Hz, 1H), 6.06 (dt, $J = 6.1$, 1.6 Hz, 1H), 5.66 (d, $J = 1.9$ Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.9$, 135.5, 133.6, 131.3, 130.7, 130.3, 130.0, 129.7, 129.6, 129.1, 128.5, 106.6, 102.5, 85.9, 14.2; elemental analysis calcd (%) for $C_{19}H_{17}NO_7S$: C 56.57, H 4.25, N 3.47; found: C 56.71, H 4.54, N 3.49; HPLC Chiracel OD column; $\lambda = 230$ nm, 10 % isopropanol in heptane; 1 mL min^{-1}; t_R: 13.6 and 15.2 min (*S* enantiomer); 18.2 and 22.6 min (*R* enantiomer).

(2*S*,3*R*,4*S*,5*S*)-5-(1-Benzenesulfonyl-1-nitroethyl)-2-benzoyloxy-3,4-dihydroxy-tetrahydrofuran (13): *N*-Methylmorpholine-*N*-oxide (66 mg, 0.56 mmol, 1.5 equiv) followed by osmium tetroxide (4 % solution in water, 0.05 mL, 0.02 mmol, 5 mol %) was added to a solution of dihydrofuran **12** (150 mg, 0.37 mmol, 1 equiv) in methylene chloride (3.7 mL) at room temperature. The reaction was stirred for 16 h, then concentrated in vacuo and chromatographed on silica gel (50 % ethyl acetate/pentane) to give diol **13** as a white solid (146 mg, 91 %). M.p. 168 – 170 °C; $[\alpha]_D^{20} = -2.2$ ($c = 1.04$, CH_3OH); IR (neat): $\tilde{\nu} = 3488$, 3252, 1730, 1558, 1449, 1386, 1315, 1268, 1155, 1125, 1049, 980 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD): $\delta = 8.02 - 7.94$ (m, 4H), 7.77 – 7.71 (m, 1H), 7.63 – 7.58 (m, 3H), 7.50 – 7.45 (m, 2H), 6.23 (s, 1H), 4.75 (d, $J = 8.0$ Hz, 1H), 4.40 (dd, $J = 8.0$, 4.4 Hz, 1H), 4.10 (d, $J = 4.4$ Hz, 1H), 3.31 (d, $J = 11.7$ Hz, 2H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 168.5$, 136.4, 135.1, 132.8, 132.7, 130.8, 130.3, 129.9, 129.8, 108.0, 101.9, 83.6, 75.2, 72.2, 13.6; elemental analysis calcd (%) for $C_{19}H_{19}NO_9S$: C 52.17, H 4.38, N 3.20; found: C 51.95, H 4.49, N 2.95.

(2*S*,3*R*,4*S*,5*S*)-5-Acetyl-2-benzoyloxy-3,4-dihydroxy-tetrahydrofuran (14): A solution (3.7 mL, 13 equiv) of titanium trichloride (Aldrich, 10 wt. % solution in 20 – 30 wt. % hydrochloric acid) was added to a solution of nitrosulfone **13** (80 mg, 0.18 mmol, 1 equiv) in THF (2.8 mL) at room temperature. The reaction was stirred for 4.5 h, then diluted with ethyl acetate and water, the aqueous layer was washed twice with methylene chloride, the organic layers were washed with brine, dried ($MgSO_4$), and evaporated in vacuo. After column chromatography on silica gel (50 % ethyl acetate/pentane), the ketone **14** (32 mg, 67 %) was obtained as a white solid. M.p. 103 – 105 °C; $[\alpha]_D^{20} = -50.7$ ($c = 3.11$, CH_2Cl_2); IR (neat): $\tilde{\nu} =$ 3403, 2925, 1724, 1269, 1130, 1057, 934 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.95$ (d, $J = 7.8$ Hz, 2H), 7.62 – 7.56 (m, 1H), 7.47 – 7.42 (m, 2H), 6.43 (s, 1H), 4.61 (dd, $J = 6.5$, 4.7 Hz, 1H), 4.44 (d, $J = 6.6$ Hz, 1H), 4.32 (d, $J =$ 4.7 Hz, 1H), 4.03 (br s, 2H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 209.3, 165.2, 133.8, 129.8, 129.1, 128.7, 101.6, 87.8, 74.6, 72.5, 26.3; HRMS: calcd for $C_{11}H_{11}O_5$: 223.0606; found: 223.0604 $[M - C_2H_3O]^+$.

(2*S*,3*R*,4*S*,5*S*)-3,4-Diacetoxy-5-(1-benzenesulfonyl-1-nitroethyl)-2-benzoyloxy-tetrahydrofuran (15): Pyridine (0.5 mL, 6.3 mmol, 18.9 equiv) followed by acetic anhydride (547 mg, 6.3 mmol, 18.9 equiv) was added to the diol **13** (146 mg, 0.33 mmol, 1 equiv) at room temperature. The reaction was stirred for 16 h at room temperature. Methanol (2 mL) was added at room temperature to quench excess acetic anhydride, and the mixture was concentrated in vacuo. The residue was azeotroped twice with toluene to remove excess pyridine. The residue was purified by chromatography on silica gel (35 % ethyl acetate/pentane) to yield diacetate **15** (162 mg, 95 %) as a clear oil. $[\alpha]_D^{20} = -12.6$ ($c = 2.09$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3068$, 1758, 1739, 1559, 1450, 1368, 1316, 1233, 1054 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.97 - 7.91$ (m, 4H), 7.71 – 7.67 (m, 1H), 7.61 – 7.51 (m, 3H), 7.47 – 7.41 (m, 2H), 6.42 (s, 1H), 5.75 (dd, $J = 8.2$, 4.7 Hz, 1H), 5.47 (d, $J = 4.7$ Hz, 1H), 5.12 (d, $J = 8.2$ Hz, 1H), 2.14 (s, 3H), 1.99 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.3$, 163.8, 135.4, 134.1, 133.6, 131.2, 130.6, 129.8, 129.2, 128.6, 105.3, 98.0, 80.5, 73.5, 68.9, 20.3, 19.9, 14.5; HRMS: calcd for $C_{16}H_{18}NO_9S$: 400.0702; found: 400.0708 $[M - C_7H_5O_2]^+$.

(2*S*,3*R*,4*S*,5*S*)-3,4-Diacetoxy-5-acetyl-2-benzoyloxy-tetrahydrofuran (16): A solution of diol **14** (29 mg, 0.11 mmol, 1 equiv), acetic anhydride (173 mg, 1.74 mmol, 16 equiv), and pyridine (0.16 mL, 1.98 mmol, 18 equiv) was stirred for 16 h at room temperature. Methanol (2 mL) was added to quench excess reagent, then the reaction was diluted with ethyl acetate. The organic layer was washed with 1N sodium hydrogen sulfate, the aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. Diacetate **16** was obtained as a clear oil (32 mg, 84 %).

Alternate procedure from **15**: *N*-Benzyl nicotinamide (32 mg, 0.3 mmol) was added to a solution of **15** (24 mg, 0.05 mmol) in benzene (3 mL) at room temperature. The mixture was stirred and irradiated with a 150 W tungsten lamp for 24 h, at which time an additional amount of *N*-benzyl nicotinamide (32 mg, 0.3 mmol). After a total reaction time of 48 h, the mixture was diluted by diethyl ether and the organic layer was washed by a 1M solution of HCl and water. The organic layer was dried over magnesium sulfate, filtrated and evaporated in vacuo. Compound **16** (10 mg, 0.027 mmol) was isolated pure was a clear oil after purification on silica gel (ethyle acetate/pentane 2:5) with 60 % yield. $[\alpha]_D^{20} = -54.2$ ($c = 2.96$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 2926$, 1734, 1727, 1366, 1236, 1056, 1024, 713 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.97$ (d, $J = 7.1$ Hz, 2H), 7.63 – 7.58 (m, 1H), 7.49 – 7.44 (m, 2H), 6.49 (s, 1H), 5.68 (appt, $J = 6.3$, 5.2 Hz, 1H), 5.50 (d, $J = 4.9$ Hz, 1H), 4.56 (d, $J = 6.6$ Hz, 1H), 2.21 (s, 3H), 2.16 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 205.9$, 169.7, 169.5, 164.6, 134.1, 130.0, 128.8, 128.6, 99.3, 85.1, 74.2, 71.2, 26.2, 20.4, 20.3; HRMS: calcd for $C_{15}H_{15}O_7$: 307.0817; found: 307.0812 $[M - C_2H_3O]^+$.

3-(4-Hydroxy-3-methoxyphenyl)-2-methylacrylic ethyl ester (19): A solution of vanillin (3.6 g, 23.66 mmol, 1 equiv) and ethyl 2-(triphenylphosphoranylidene)propionate (9.3 g, 25.92 mmol, 1.1 equiv) in methylene chloride (47 mL) was stirred at room temperature for 6 h. The solvent was evaporated in vacuo and the residue chromatographed on silica gel (15 % ethyl acetate/pentane) to give enoate **19** as a clear oil (5 g, 89 %). IR (neat): $\tilde{\nu} = 3409$, 2963, 2938, 1700, 1605, 1518, 1450, 1284, 1162 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.61$ (s, 1H), 7.00 – 6.91 (m, 3H), 6.00 (s, 1H), 4.25 (q, $J = 7.1$ Hz, 2H), 3.87 (s, 3H), 2.13 (s, 3H), 1.33 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.1$, 146.4, 146.1, 138.8, 128.3, 126.3, 123.7, 114.4, 112.4, 60.7, 55.8, 14.2, 13.9; elemental analysis calcd (%) for $C_{13}H_{16}O_4$: C 66.07, H 6.83; found: C 65.99, H 6.84.

(2*S*,5*S*)-3-{4-[5-(1-Benzenesulfonyl-1-nitroethyl)-2,5-dihydrofuran-2-yloxy]-3-methoxy-phenyl}-2-methylacrylic ethyl ester (20): A solution of the dihydrofuran **12** (200 mg, 0.5 mmol, 1 equiv), π-allypalladium chloride dimer (4.6 mg, 0.013 mmol, 5 mol %) and triisopropyl phosphite (0.04 mL, 0.175 mmol, 15 mol %) in THF (2.25 mL) was added to a suspension of cesium carbonate (228.0 mg, 0.7 mmol, 1.4 equiv) and phenol **19** (142 mg, 0.6 mmol, 1.2 equiv) in THF (2.25 mL). The reaction was stirred for 1.5 h at room temperature, then quenched with 1N sodium hydrogen sulfate. The mixture was diluted with diethyl ether, the layers were separated, the organic layer was washed with brine, filtered through silica gel, and concentrated in vacuo. After column chromatography on silica gel (30 % ethyl acetate/pentane) **20** was obtained as a yellow oil (179 mg, 72 %), as well as the starting furan (47 mg, 24 % yield; 96 % yield based on recovered starting material). $[\alpha]_D^{20} = -65.1$ ($c = 1.48$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 2978$, 2871, 1704, 1556, 1512, 1449, 1335, 1272, 1158, 1070, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.96$ (d, $J = 8.0$ Hz, 2H), 7.68 – 7.49 (m, 4H), 7.20 (d, $J = 8.3$ Hz, 1H), 7.00 (d, $J = 8.5$ Hz, 1H), 6.92 (s, 1H), 6.31 (s, 1H), 6.27 (d, $J = 5.5$ Hz, 1H), 5.90 (d, $J = 6.0$ Hz, 1H), 5.69 (s, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 3.81 (s, 3H), 2.14 (s, 3H), 1.84 (s, 3H), 1.34 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.8$, 149.9, 146.2, 138.2, 135.2, 131.8, 131.2, 130.9, 130.7, 129.6, 129.1, 127.9, 122.8, 118.5, 113.7, 109.4, 106.8, 85.4, 60.8, 60.7, 55.8, 14.2, 13.4; HRMS: calcd for $C_{25}H_{27}NO_9S$: 518.1952; found: 518.1948 $[M]^+$.

2-(1-Benzenesulfonyl-1-nitroethyl)furan (21): An aqueous solution (0.7 mL) of titanium trichloride (Aldrich, 102 mg, 0.65 mmol, 13 equiv) and ammonium acetate (306 mg, 2.1 mmol, 78 equiv) buffer was added to a solution of nitrosulfone **12** (20 mg, 0.05 mmol, 1 equiv) in THF (0.7 mL) at room temperature. The reaction was stirred for 4.5 h, then diluted with ethyl acetate and water, the aqueous layer was washed twice with methylene chloride, the organic layers were washed with brine, dried ($MgSO_4$), and evaporated in vacuo. The furan **21** was obtained as a white solid (10 mg, 71 %). M.p. 76 – 78 °C; IR (neat): $\tilde{\nu} = 3142$, 2876, 1582, 1560, 1448, 1332, 1314, 1154, 1072, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.71 – 7.66 (m, 3H), 7.52 – 7.46 (m, 3H), 6.65 (d, $J = 3.5$ Hz, 1H), 6.42 (dd, $J = 3.5$, 1.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 145.1$, 142.6, 135.2, 133.9, 131.1, 130.0, 129.6, 128.8, 115.3, 111.7, 103.5, 17.8; HRMS: calcd for $C_{12}H_{11}NO_5S$: 281.0357: found 281.0348 $[M]^+$.

(2*S*,5*S*)-3-{4-[5-(1-Benzenesulfonyl-1-nitroethyl)-2,5-dihydrofuran-2-yloxy]-3-methoxyphenyl}-2,3-dihydroxy-2-methylpropionic ethyl ester (22): *N*-

0947-6539/02/0801-0264 $ 17.50+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 1

Methylmorpholine-*N*-oxide (38 mg, 0.32 mmol, 1.2 equiv) followed by osmium tetroxide (4% solution in water, 0.007 mL, 0.014 mmol, 5 mol%) was added to a solution of the dihydrofuran diene **20** (140 mg, 0.27 mmol, 1 equiv) in methylene chloride (2.7 mL), at room temperature. The reaction was stirred for 16 h, then concentrated in vacuo and chromatographed on silica gel (50% ethyl acetate/pentane) to produce diol **22** as a brown oil (48 mg, 30%). $[\alpha]_D^{20} = -35.0$ ($c = 3.87$, CH_2Cl_2); IR (neat): $\tilde{\nu} =$ 3506, 2925, 1730, 1510, 1315, 1265, 1157, 1096, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.98-7.94$ (m, 2H), 7.69–7.67 (m, 1H), 7.56–7.50 (m, 2H), 7.13 (dd, $J = 8.2$, 4.8 Hz, 1H), 7.00 (s, 1H), 6.92 (d, $J = 8.2$ Hz, 1H), 6.27 (m, 2H), 5.88 (d, $J = 6.0$ Hz, 1H), 5.65 (m, 1H), 4.80 (s, 1H), 4.32 (q, $J = 7.1$ Hz, 2H), 3.80 (s, 3H), 1.86 (s, 3H), 1.34 (t, $J = 7.1$ Hz, 3H), 1.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 176.0$, 150.0, 135.2, 134.8, 133.7, 131.2, 131.0, 129.4, 129.1, 120.7, 118.6, 111.8, 109.8, 106.8, 85.3, 77.6, 77.2, 62.4, 55.8, 29.6, 22.3, 14.0, 13.3.

(2*S*,5*S*)-4-[5-(1-Benzenesulfonyl-1-nitroethyl)-2,5-dihydrofuran-2-yloxy]-3-methoxybenzaldehyde (23): A pre-stirred solution of dihydrofuran **12** (700 mg, 1.74 mmol, 1 equiv), π-allylpalladium chloride dimer (6.2 mg, 0.017 mmol, 1 mol%) and triisopropyl phosphite (0.06 mL, 0.244 mmol, 7 mol%) in THF (8.7 mL) was added to a suspension of cesium carbonate (1.2 g, 3.83 mmol, 2.2 equiv) and vanillin (528 mg, 3.47 mmol, 2 equiv) in THF (5 mL). The reaction was stirred for 3 h, then diluted with water and diethyl ether, the organic layer was filtered through silica gel and evaporated in vacuo. Column chromatography on silica gel (30% ethyl acetate/pentane) produced **23** as a clear oil (618 mg, 82%). $[\alpha]_D^{20} = -89.6$ ($c = 1.1$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3006$, 2837, 1717, 1686, 1555, 1449, 1333, 1266, 1157, 1070, 988, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 9.88$ (s, 1H), 7.9 (d, $J = 7.3$ Hz, 2H), 7.70–7.33 (m, 6H), 6.40 (s, 1H), 6.28 (d, $J =$ 6.0 Hz, 1H), 5.95 (d, $J = 6.0$ Hz, 1H), 5.75 (s, 1H), 3.85 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 191.1$, 151.3, 135.3, 132.1, 131.1, 130.6, 130.4, 130.1, 129.5, 129.1, 125.9, 117.0, 110.1, 108.5, 106.5, 85.6, 55.9, 13.4; elemental analysis calcd (%) for $C_{20}H_{19}NO_8S$: C 55.42, H 4.42, N 3.23; found: C 55.58, H 4.56, N 3.01.

(2*S*,3*R*,4*S*,5*S*)-4-[5-(1-Benzenesulfonyl-1-nitroethyl)-3,4-dihydroxy-tetrahydrofuran-2-yloxy]-3-methoxybenzaldehyde (24): *N*-Methylmorpholine-*N*-oxide (177 mg, 1.43 mmol, 1.5 equiv) followed by osmium tetroxide (4% solution in water, 0.33 mL, 0.05 mmol, 5 mol%) was added to a solution of dihydrofuran **23** (399 mg, 0.98 mmol, 1 equiv) in methylene chloride (9.6 mL) at room temperature. The reaction was stirred for 16 h, then concentrated in vacuo and chromatographed on silica gel (75% ethyl acetate/pentane) to give diol **24** as a tan solid (387 mg, 87%). M.p. 163–165 °C; $[\alpha]_D^{20} = -66.8$ ($c = 0.94$, CH_3OH); IR (neat): $\tilde{\nu} = 3356$, 2924, 1679, 1589, 1558, 1507, 1331, 1267, 1156, 1002, 941 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 9.85$ (s, 1H), 7.95 (d, $J = 7.3$ Hz, 2H), 7.77–7.71 (m, 1H), 7.63–7.55 (m, 2H), 7.38–7.32 (m, 2H), 7.07 (d, $J = 8.2$ Hz, 1H), 5.69 (s, 1H), 4.85 (d, $J = 7.3$ Hz, 1H), 4.80–4.76 (m, 1H), 4.43 (d, $J = 4.4$ Hz, 1H), 3.86 (s, 3H), 3.12 (brs, 2H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 193.2$, 152.0, 151.4, 136.5, 136.2, 133.1, 132.6, 130.3, 126.9, 116.2, 111.7, 108.2, 106.3, 83.5, 75.7, 72.3, 56.5, 13.2; elemental analysis calcd (%) for $C_{20}H_{21}NO_{10}S$: C 51.38, H 4.53, N 2.99; found: C 51.16, H 4.70, N 2.76.

(2*S*,3*R*,4*S*,5*S*)-3-{4-[5-(1-Benzenesulfonyl-1-nitroethyl)-3,4-dihydroxytetrahydrofuran-2-yloxy]-3-methoxyphenyl}-2-methylacrylic ethyl ester (25): A solution of aldehyde **24** (218 mg, 0.47 mmol, 1 equiv) and ethyl 2-(triphenylphosphoranylidene)propionate (255 mg, 0.71 mmol, 1.5 equiv) in methylene chloride (5 mL) was stirred at room temperature for 16 h. The solvent was evaporated in vacuo and the residue chromatographed on silica gel (75% ethyl acetate/pentane) to give enoate **25** as a white solid (160 mg, 70%). M.p. 67–69 °C; $[\alpha]_D^{20} = -66.3$ ($c = 1.01$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3473$, 2981, 1700, 1560, 1512, 1448, 1332, 1245, 1156, 1008, 939, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.97$ (d, $J = 7.3$ Hz, 2H), 7.77–7.70 (m, 1H), 7.63–7.54 (m, 3H), 6.97–6.88 (m, 3H), 5.59 (s, 1H), 4.82 (d, $J = 7.4$ Hz, 1H), 4.70 (dd, $J = 7.4$, 4.6 Hz, 1H), 4.38 (d, $J = 4.6$ Hz, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 3.80 (s, 3H), 3.15 (brs, 2H), 2.12 (s, 3H), 1.83 (s, 3H), 1.35 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.9$, 149.1, 145.5, 138.3, 138.2, 135.2, 134.0, 131.3, 131.1, 129.1, 122.8, 116.1, 113.8, 106.7, 105.5, 82.7, 74.7, 71.1, 60.9, 55.8, 14.1, 13.9, 13.6; elemental analysis calcd (%) for $C_{25}H_{29}NO_{11}S$: C 54.43, H 5.30, N 2.54; found: C 54.60, H 5.50, N 2.30.

(2*S*,3*R*,4*S*,5*S*)-3-{4-[6-(1-Benzenesulfonyl-1-nitroethyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yloxy]-3-methoxyphenyl}-2-methylacrylic ethyl ester (26): 2,2-Dimethoxypropane (0.2 mL, 1.7 mmol, 3 equiv) followed by *p*-toluenesulfonic acid (21 mg, 0.12 mmol, 20 mol%) was added to a solution of diol **24** (217 mg, 0.46 mmol, 1 equiv) in acetone (5 mL) at room temperature. The reaction was stirred for 6.5 h at room temperature, then diluted with ethyl acetate, and quenched with saturated sodium bicarbonate. The organic layer was washed with saturated sodium bicarbonate, dried ($MgSO_4$), and evaporated in vacuo. After purification on silica gel (60% ethyl acetate/pentane), an acetonide was obtained as a white solid (150 mg, 75%). A solution of the latter (74 mg, 0.15 mmol, 1 equiv) and ethyl 2-(triphenylphosphoranylidene)propionate (89 mg, 0.25 mmol, 1.7 equiv) in methylene chloride (1.2 mL) was stirred at room temperature for 16 h. The solvent was evaporated in vacuo and the residue chromatographed on silica gel (60% ethyl acetate/pentane) to give enoate **26** (88 mg) as a clear oil in quantitative yield. $[\alpha]_D^{20} = -64.4$ ($c = 3.43$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 2985$, 1702, 1559, 1512, 1448, 1336, 1243, 1157, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.92$ (d, $J = 7.5$ Hz, 2H), 7.73 (t, $J = 7.7$ Hz, 1H), 7.59–7.54 (m, 3H), 7.04–6.88 (m, 3H), 5.73 (s, 1H), 5.14 (d, $J = 5.8$ Hz, 1H), 5.05 (s, 1H), 4.90 (d, $J = 5.8$ Hz, 1H), 4.24 (q, $J = 6.9$ Hz, 2H), 3.81 (s, 3H), 2.12 (s, 3H), 1.87 (s, 3H), 1.49 (s, 3H), 1.44–1.27 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.9$, 149.7, 145.6, 138.2, 135.5, 133.5, 131.6, 131.4, 131.3, 129.3, 127.8, 122.8, 115.4, 114.0, 113.5, 108.2, 106.7, 88.7, 85.3, 81.1, 77.2, 60.8, 55.9, 25.5, 24.7, 15.0, 14.2, 14.0; elemental analysis calcd (%) for $C_{28}H_{33}NO_{11}S$: C 56.84, H 5.62, N 2.37; found: C 56.58, H 5.61, N 2.18.

(2*S*,3*R*,4*R*,5*S*)-3-{4-[6-(1-Hydroxyiminoethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yloxy]-3-methoxyphenyl}-2-methylacrylic ethyl ester (27): A freshly prepared 20% by weight solution of titanium trichloride (Aldrich, 350 mg, 2.3 mmol, 13 equiv) in water (2.8 mL) buffered with ammonium acetate (1.05g, 13.6 mmol, 48 equiv) was added to a solution of nitrosulfone **26** (100 mg, 0.17 mmol, 1 equiv) in THF (2.8 mL) at room temperature. The reaction was stirred for 6 h, then diluted with methylene chloride and water. The aqueous layer was washed with methylene chloride. The organic layers were combined, dried ($MgSO_4$), and evaporated in vacuo. After column chromatography on silica gel (40% ethyl acetate/pentane), both the oxime **27** (30 mg, 42%) and the ketone **28** were isolated (13 mg, 20%). Data for **27**: $[\alpha]_D^{20} = -169.1$ ($c = 0.86$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3428$, 2984, 1703, 1512, 1450, 1371, 1243, 1108, 1025, 993 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.61$ (s, 1H), 7.09 (d, $J = 8.4$ Hz, 1H), 6.99–6.92 (m, 2H), 5.84 (s, 1H), 5.46 (d, $J = 5.8$ Hz, 1H), 4.96 (d, $J =$ 5.8 Hz, 1H), 4.74 (s, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 3.82 (s, 3H), 2.12 (s, 3H), 1.72 (s, 3H), 1.53 (s, 3H), 1.36–1.31 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.9$, 156.6, 149.6, 145.7, 138.4, 130.6, 127.4, 122.9, 116.2, 114.1, 112.7, 106.7, 87.5, 85.5, 80.4, 60.8, 56.0, 26.4, 24.9, 14.2, 14.0, 11.3; elemental analysis calcd (%) for $C_{22}H_{29}NO_8+\frac{1}{2}H_2O$: C 59.47, H 6.80, N 3.16; found: C 59.30, H 6.61, N 3.05.

Data for **28**: $[\alpha]_D^{20} = -127.3$ ($c = 1.53$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 2983$, 1704, 1513, 1464, 1373, 1242, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.61$ (s, 1H), 7.16 (d, $J = 8.4$ Hz, 1H), 7.02–6.92 (m, 2H), 5.87 (s, 1H), 5.36 (d, $J =$ 5.8 Hz, 1H), 4.86 (d, $J = 5.8$ Hz, 1H), 4.54 (s, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 3.80 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H), 1.52 (s, 3H), 1.36–1.32 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 206.9$, 168.9, 149.3, 145.5, 138.2, 130.9, 127.7, 122.8, 115.3, 114.0, 112.8, 106.6, 91.3, 84.6, 80.6, 60.8, 55.9, 26.4, 26.2, 24.7, 14.2, 14.0; elemental analysis calcd (%) for $C_{22}H_{28}O_8$: C 62.85, H 6.71; found: C 63.00, H 6.84.

(2*S*,5*S*)-4-[5-(1-Benzenesulfonyl-1-nitroethyl)-2,5-dihydrofuran-2-yloxy]-3-benzyloxybenzaldehyde (29): A pre-stirred solution of dihydrofuran **12** (527 mg, 1.31 mmol, 1 equiv), π-allylpalladium chloride dimer (4.8 mg, 0.013 mmol, 1 mol%), and triisopropylphosphite (0.04 mL, 0.18 mmol, 14 mol%) in THF (3.5 mL) at room temperature was added to a suspension of cesium carbonate (847 mg, 2.6 mmol, 2 equiv) and 3-benzyloxy-4-hydroxybenzaldehyde (564 mg, 2.4 mmol, 1.8 equiv) in THF (3.5 mL). The reaction was stirred for 4 h, then diluted with ethyl acetate. The organic layer was washed with water, the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. After column chromatography on silica gel (40% ethyl acetate/petroleum ether) followed by crystallization of the oil from methylene chloride/pentane, dihydrofuran **29** was obtained as a white solid (518 mg, 76%). M.p. 53–55 °C; $[\alpha]_D^{20} = -50.1$ ($c = 1.09$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3065$, 2869, 1690, 1588, 1555, 1505, 1333, 1285, 1159, 986 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 9.87$ (s, 1H), 7.91 (d, $J = 7.2$ Hz, 2H), 7.74–7.26 (m, 11H), 6.42 (s, 1H), 6.19 (d, $J = 6.0$ Hz, 1H), 5.92 (d, $J = 6.0$ Hz, 1H), 5.74 (s, 1H), 5.09 (s, 2H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 190.9$, 151.6, 149.6, 136.1, 135.7, 135.2, 133.6, 132.0, 131.0, 130.8, 130.6, 130.3, 129.8,

129.4, 129.0, 128.5, 128.1, 127.3, 125.9, 117.4, 112.5, 108.3, 106.5, 85.6, 70.7, 13.4; elemental analysis calcd (%) for $C_{26}H_{23}NO_8S$: C 61.29, H 4.55, N 2.75; found: C 61.09, H 4.77, N 2.53.

(2*S*,3*R*,4*S*,5*S*)-4-[5-(1-Benzenesulfonyl-1-nitroethyl)-3,4-dihydroxy-tetrahydrofuran-2-yloxy]-3-benzyloxybenzaldehyde (30): *N*-Methylmorpholine-*N*-oxide (127 mg, 1.1 mmol, 1.5 equiv) followed by osmium tetroxide (4% solution in water, 0.4 mL, 5 mol%) was added to a solution of dihydrofuran **29** (373 mg, 0.72 mmol, 1 equiv) in methylene chloride (7.2 mL) at room temperature. The reaction was stirred at room temperature for 19 h. The solvent was evaporated in vacuo and the residue purified. After column chromatography on silica gel (60% ethyl acetate/petroleum ether), diol **30** (330 mg, 83%) was obtained as a white solid. M.p. 65–66 °C; $[\alpha]_D^{20} = -39.6$ ($c = 1.07$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3475, 2956, 1686, 1587, 1559, 1507, 1435, 1332, 1266, 1155, 1000\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 9.81$ (s, 1H), 7.93 (d, $J = 7.4$ Hz, 2H), 7.86–7.29 (m, 10H), 7.07 (d, $J = 8.2$ Hz, 1H), 5.67 (s, 1H), 5.09 (s, 2H), 4.84 (d, $J = 7.4$ Hz, 1H), 4.59 (dd, $J = 7.4$, 4.4 Hz, 1H), 4.31 (d, $J = 4.4$ Hz, 1H), 3.46 (br s, 2H), 1.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 191.2, 151.0, 149.2, 136.2, 135.9, 135.4, 133.8, 131.7, 131.3, 130.9, 129.4, 129.2, 128.8, 128.3, 127.5, 126.5, 126.3, 115.6, 112.4, 106.5, 104.9, 83.1, 74.8, 71.2, 70.9; 14.1$; elemental analysis calcd (%) for $C_{26}H_{25}NO_{10}S+H_2O$: C 56.52, H 4.74, N 2.53; found: C 56.52, H 4.40, N 2.33.

(2*S*,3*R*,4*S*,5*S*)-3-{4-[5-(1-Benzenesulfonyl-1-nitroethyl)-3,4-dihydroxytetrahydrofuran-2-yloxy]-3-benzyloxyphenyl}-2-methylacrylic ethyl ester (31): A solution of aldehyde **30** (329 mg, 0.61 mmol, 1 equiv) and ethyl 2-(triphenylphosphoranylidene)propionate (355 mg, 0.97 mmol, 1.6 equiv) in methylene chloride (6 mL) was stirred at room temperature for 16 h. The solvent was evaporated in vacuo and the residue chromatographed on silica gel (60% ethyl acetate/pentane) to give enoate **31** (273 mg, 72%) as a white solid. M.p. 60–62 °C; $[\alpha]_D^{20} = -54.9$ ($c = 1.09$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3456, 2980, 1699, 1559, 1510, 1332, 1245, 1008\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.97$ (d, $J = 7.2$ Hz, 2H), 7.78–7.71 (m, 1H), 7.63–7.52 (m, 3H), 7.39–7.31 (m, 5H), 6.98–6.90 (m, 3H), 5.58 (s, 1H), 5.07 (s, 2H), 4.78 (d, $J = 7.2$ Hz, 1H), 4.70 (dd, $J = 11.4$, 6.6 Hz, 1H), 4.31 (d, $J = 11.5$ Hz, 1H), 4.25 (q, $J = 7.1$ Hz, 2H), 2.68 (m, 2H), 2.01 (s, 3H), 1.86 (s, 3H), 1.34 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.0, 148.1, 146.1, 145.8, 138.2, 136.8, 135.6, 135.2, 133.9, 131.2, 130.9, 129.2, 129.1, 128.6, 128.1, 127.5, 127.3, 123.6, 116.3, 106.7, 105.5, 82.5, 74.6, 71.1, 60.9, 14.1, 13.8, 13.5$; elemental analysis calcd (%) for $C_{31}H_{33}NO_{11}S$: C 59.32, H 5.29, N 2.23; found: C 59.43, H 5.30, N 2.06.

(2*S*,3*R*,4*S*,5*S*)-3-{4-[6-(1-Benzenesulfonyl-1-nitroethyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yloxy]-3-benzyloxy-phenyl}-2-methylacrylic acid (32): 2,2-Dimethoxypropane (0.14 mL, 1.15 mmol, 3 equiv) followed by *p*-toluenesulfonic acid (7.3 mg, 0.038 mmol, 10 mol%)was added to a solution of diol **31** (240 mg, 0.38 mmol, 1 equiv) in acetone (3.8 mL) at room temperature. The reaction was stirred for 6 h at room temperature, then diluted with ethyl acetate and quenched with saturated sodium bicarbonate solution. The organic layer was washed with saturated sodium bicarbonate solution, dried ($MgSO_4$), and evaporated in vacuo. After column chromatography on silica gel (50% ethyl acetate/petroleum ether), the acetonide (261 mg) was produced as a clear oil.

To a solution of the latter (261 mg, 0.37 mmol, 1 equiv) in methanol (4 mL) was added NaOH solution (1N in water, 2.35 mL, 6 equiv). The reaction was heated at 50 °C for 16 h. The reaction was neutralized with acetic acid (0.13 mL) and concentrated. The residue was diluted with ethyl acetate and the organic layer was extracted with saturated sodium bicarbonate solution. The aqueous layer was acidified with 2N hydrochloric acid, the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. After column chromatography on silica gel, carboxylic acid **32** (123 mg, 60%) was produced as a white solid. M.p. 97–99 °C; $[\alpha]_D^{20} = -54.4$ ($c = 0.71$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3065, 2989, 1681, 1559, 1510, 1335, 1256, 1157\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ = 7.92 (d, $J = 7.5$ Hz, 2H), 7.71 (d, $J = 12.0$ Hz, 2H), 7.59–7.54 (m, 2H), 7.44–7.31 (m, 5H), 7.08–6.89 (m, 3H), 5.77 (s, 1H), 5.16 (d, $J = 6.1$ Hz, 1H), 5.11–5.06 (m, 3H), 4.88 (d, $J = 6.0$ Hz, 1H), 2.02 (s, 3H), 1.87 (s, 3H), 1.49 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.2, 148.6, 146.6, 140.5, 136.8, 135.5, 133.5, 131.6, 131.2, 130.9, 129.2, 129.1, 128.7, 128.6, 128.0, 127.3, 123.9, 116.7, 113.4, 108.4, 106.7, 88.8, 85.4, 81.0, 71.1, 26.4, 24.7, 16.2, 13.5$; HRMS: calcd for $C_{32}H_{33}NO_{11}S$: 639.1774; found: 639.1763 $[M]^+$.

(2*S*,3*R*,4*S*,5*S*)-3-{4-[6-Acetyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yloxy]-3-benzyloxyphenyl}-2-methylacrylic acid (33): An aqueous solution (4 mL) of titanium trichloride (Aldrich, 386 mg, 2.5 mmol, 13 equiv) and ammonium acetate (1.2 g, 15.1 mmol, 78 equiv) buffer was added to a solution of nitrosulfone **32** (123 mg, 0.19 mmol, 1 equiv) in THF (4 mL) at room temperature. The reaction was stirred for 4.5 h, then diluted with ethyl acetate and water. The aqueous layer was washed twice with methylene chloride, the organic layers were washed with brine, dried ($MgSO_4$), and evaporated in vacuo. After column chromatography on silica gel (50% ethyl acetate/pentane), the ketone **33** (65 mg, 74%) was obtained as a white solid. M.p. 143–144 °C; $[\alpha]_D^{20} = -125.7$ ($c = 1.08$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 2987, 2634, 1715, 1681, 1510, 1420, 1255, 1100, 993\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.68$ (s, 1H), 7.37 (s, 5H), 7.18 (d, $J = 8.3$ Hz, 1H), 7.05–6.97 (m, 2H), 5.89 (s, 1H), 5.36 (d, $J = 5.7$ Hz, 1H), 5.07 (s, 2H), 4.82 (d, $J = 6.0$ Hz, 1H), 4.56 (s, 1H), 2.03 (s, 6H), 1.52 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 206.8, 173.9, 148.2, 146.6, 140.5, 136.7, 130.3, 128.7, 128.1, 127.3, 123.9, 116.7, 115.3, 112.9, 106.7, 91.3, 84.6, 80.5, 71.2, 26.4, 26.2, 24.8, 13.6$; elemental analysis calcd (%) for $C_{26}H_{28}O_8+\frac{1}{2}H_2O$: C 65.39, H 6.12; found: C 65.03, H 6.04.

4-[(2*S*,5*S*)-5-(1-Benzenesulfonyl-1-nitroethyl)-2,5-dihydrofuran-2-yloxy]-3-(4-methoxybenzyloxy)-benzaldehyde (35): Triethylamine (2.71 mL, 19.5 mmol) was added to a solution of **12** (5.24 g, 13 mmol), **34**[27] (5.03 g, 19.5 mmol), $[Pd_2dba_3]\cdot CHCl_3$ (270 mg, 0.26 mmol, 2 mol%) and (*S*,*S*)-**11** (721 mg, 1.04 mmol, 8 mol%) in dry degassed THF (26 mL, 0.5M). After 1.5 h at 50 °C, the mixture was cooled to room temperature and ethyl acetate and water were added. The organic layer was washed with brine, dried over magnesium sulfate, filtrated and evaporated in vacuo. Compound **35** (5.23 g, 9.70 mmol) was isolated pure as a white solid after column chromatography (petroleum ether/ethyl acetate 8:2 then 6:4) with 75% yield. $R_f = 0.3$ (heptane/diethyl ether 1:3), 0.75 (diethyl ether); m.p. 63–65 °C; $[\alpha]_D^{23} = -40.3$ ($c = 1.00$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 2831, 1723, 1673, 1650, 1584, 1515, 1441, 1387, 1253, 1156, 1004\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 9.89$ (s, 1H), 7.95 (d, $J = 6.9$ Hz, 2H), 7.50–7.25 (m, 8H), 6.91 (d, $J = 8.4$ Hz, 2H), 6.41 (s, 1H), 6.21 (d, $J = 6.0$ Hz, 1H), 5.95 (d, $J = 6.0$ Hz, 1H), 5.73 (s, 1H), 5.04 (s, 2H), 3.82 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 190.9, 159.5, 151.6, 149.6, 135.6, 135.2, 133.5, 132.1, 130.8, 130.6, 130.4, 129.8, 129.4, 129.1, 129.0, 128.1, 126.0, 117.6, 113.9, 112.5, 106.5, 85.6, 70.6, 55.2, 13.6$; elemental analysis calcd (%) for $C_{27}H_{25}NO_9S$: C 60.11, H 4.63; found: C 60.00, H 4.92.

4-[(2*S*,3*R*,4*S*,5*S*)-5-(1-Benzenesulfonyl-1-nitroethyl)-3,4-dihydroxytetrahydrofuran-2-yloxy]-3-(4-methoxybenzyloxy)-benzaldehyde (36): *N*-Methylmorpholine-*N*-oxide (5.3 g, 45.3 mmol) then osmium tetroxide (4% solution in water) (5.5 mL, 0.86 mmol, 5 mol%) was added to a solution of **35** (9.37 g, 17.3 mmol) in dichloromethane (190 mL) at room temperature. The reaction was stirred overnight, then evaporated in vacuo. The diol **36** (9.6 g, 16.8 mmol) was isolated pure as a white solid after column chromatography (petroleum ether/ethyl acetate 4:6) with 98% yield. $R_f = 0.32$ (diethyl ether); m.p. 77–79 °C; $[\alpha]_D^{20} = -48.5$ ($c = 0.24$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3425, 2935, 1686, 1587, 1559, 1332, 1252, 1156, 1070, 1002\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 9.84$ (s, 1H), 7.97 (d, $J = 8.1$ Hz, 2H), 7.74–7.32 (m, 7H), 7.09 (d, $J = 8.4$ Hz, 1H), 6.93 (d, $J = 8.7$ Hz, 2H), 5.65 (s, 1H), 5.04 (s, 2H), 4.83 (d, $J = 7.5$ Hz, 1H), 4.69 (dd, $J = 7.4$, 4.8 Hz, 1H), 4.35 (d, $J = 4.2$ Hz, 1H), 3.81 (s, 3H), 3.42 (br s, 2H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 190.9, 159.6, 150.8, 149.1, 135.3, 133.3, 131.6, 131.1, 130.8, 129.4, 129.3, 129.2, 128.0, 126.2, 115.5, 115.0, 114.0, 112.4, 106.4, 104.8, 83.1, 74.8, 70.8, 60.5, 55.3, 14.3$; elemental analysis calcd (%) for $C_{27}H_{27}NO_{11}S$: C 56.54, H 4.74; found: C 56.45, H 4.60.

(*E*)-3{4-[(2*S*,3*R*,4*S*,5*S*)-5-(1-Benzenesulfonyl-1-nitroethyl)-3,4-dihydroxy-tetrahydrofuran-2-yloxy]-3-(4-methoxybenzyloxy)-phenyl}-2-methylacrylic ethyl ester (37): Ethyl 2-(triphenylphosphoranylidene)propionate (7.9 g, 21.6 mmol) and the mixture was stirred at 45 °C for one hour was added to a solution of **36** (9.5 g, 16.6 mmol) in dichloromethane (83 mL, 0.2M). It was then evaporated in vacuo, and **37** (10.9 g, 16.6 mmol) was isolated pure as a white solid after column chromatography (petroleum ether/ethyl acetate 1:1) with a quantitative yield. $R_f = 0.42$ (diethyl ether); M.p. 73–75 °C; $[\alpha]_D^{20} = -44.9$ ($c = 0.40$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3386, 2931, 1702, 1609, 1560, 1514, 1331, 1244, 1157, 1006\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.98 (d, $J = 7.2$ Hz, 2H), 7.78–7.71 (m, 1H), 7.59–7.54 (m, 3H), 7.32 (d, $J =$ 7.2 Hz, 2H), 6.96–6.89 (m, 5H), 5.55 (s, 1H), 4.98 (s, 2H), 4.78 (d, $J =$ 7.2 Hz, 1H), 4.61 (br s, 1H), 4.29 (m, 3H), 4.27 (q, $J = 7.2$, 2H), 3.81 (s, 3H), 2.93 (br s, 2H), 2.05 (s, 3H), 1.83 (s, 3H), 1.34 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR

0947-6539/02/0801-0266 $ 17.50+.50/0 *Chem. Eur. J.* **2002**, *8*, No. 1

(75 MHz, $CDCl_3$): $\delta = 168.7, 159.5, 148.3, 146.0, 138.0, 135.2, 133.8, 131.2, 130.8, 129.4, 129.1, 128.5, 127.7, 123.5, 116.8, 116.4, 114.0, 106.6, 105.7, 82.9, 74.8, 71.0, 70.9, 60.9, 60.4, 55.3, 26.3, 21.0, 14.3, 14.1, 14.0$; elemental analysis calcd (%) for $C_{32}H_{35}NO_{12}$: C 58.44, H 5.36; found: C 58.62, H 5.45.

(*E*)-3-[4-[(3a*R*,4*S*,6*S*,6a*R*)-6-(1-Benzenesulfonyl-1-nitroethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yloxy]-3-(4-methoxybenzyloxy)-phenyl]-2-methylacrylic acid (38): *p*-Toluenesulfonic acid (1.45 mg, 7.6 μmol, 10 mol%) was added to a solution of **37** (50 mg, 76 μmol) and distilled 2,2-dimethoxypropane (93 μL, 0.76 mmol) in acetone (0.76 mL, 0.1M), and the mixture was stirred at room temperature for 4 h. Ethyl acetate was then added and the organic phase was washed with a saturated solution of $NaHCO_3$ and brine, dried over magnesium sulfate, filtrated and evaporated in vacuo. The acetonide (50 mg, 72 μmol) was isolated pure as a white solid after column chromatography (petroleum ether/ethyl acetate 8:2) with 94% yield. Data for the acetonide: $R_f = 0.44$ (heptane/diethyl ether 1:3); m.p. 48 °C; $[\alpha]_D^{24} = -53.0$ ($c = 1.00$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 2985, 2958, 2874, 1732, 1703, 1613, 1600, 1558, 1515, 1450, 1336, 1071\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.90$ (dd, $J = 1.0, 8.3$ Hz, 2H), 7.71 (tt, $J = 1.2, 7.3$ Hz, 1H), 7.55 (m, 3H), 7.32 (d, $J = 8.8$ Hz, 2H), 7.00 (d, $J = 8.8$ Hz, 1H), 6.93 (m, 2H), 6.88 (d, $J = 8.8$ Hz, 2H), 5.72 (s, 1H), 5.11 (dd, $J = 1.7, 5.9$ Hz, 1H), 5.03 (m, 3H), 4.83 (d, $J = 6.1$ Hz, 1H), 4.23 (q, $J = 7.1$ Hz, 2H), 3.79 (s, 3H), 2.01 (s, 3H), 1.85 (s, 3H), 1.46 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 3H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 168.7, 159.4, 148.5, 146.1, 138.0, 135.4, 133.4, 131.5, 131.2, 131.1, 129.2, 129.0, 128.7, 127.6, 123.3, 116.6, 116.4, 113.9, 113.2, 108.3, 106.6, 88.7, 85.3, 81.0, 70.9, 60.9, 55.3, 26.5, 24.8, 16.2, 14.3, 14.0$; elemental analysis calcd (%) for $C_{35}H_{39}O_{12}NS$: C 60.25, H 5.63, N 2.01, S 4.60; found: C 60.40, H 5.75, N 1.96, S 4.66.

To a solution of the latter (147 mg, 0.21 mmol) in methanol (3 mL) and THF (3 mL), was added a solution of LiOH (0.378 g, 8.86 mmol) in water (3 mL), and the mixture was stirred at 40 °C for one hour. After cooling to room temperature, the solution was acidified by a 5% solution of $NaHSO_3$ and extracted by ethyl acetate. The organic phase was washed brine, dried over magnesium sulfate, filtrated and evaporated in vacuo to afford **38** (141 mg, 0.21 mmol) as a white solid with a quantitative yield. $R_f = 0.25$ (heptane/diethyl ether 1:3), 0.58 (diethyl ether); m.p. 108–110 °C; $[\alpha]_D^{23} = -60.2$ ($c = 1.00$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3415, 2936, 1702, 1561, 1512, 1444, 1248, 1158, 1108\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.90$ (dd, $J = 1.2, 8.5$ Hz, 2H), 7.71 (tt, $J = 1.2, 7.6$ Hz, 1H), 7.56 (m, 3H), 7.32 (d, $J = 8.5$ Hz, 2H), 7.02 (d, $J = 8.8$ Hz, 1H), 6.96 (m, 2H), 6.88 (d, $J = 8.8$ Hz, 2H), 5.73 (s, 1H), 5.13 (dd, $J = 1.7, 5.9$ Hz, 1H), 5.04 (d, $J = 1.7$ Hz, 1H), 4.98 (s, 2H), 4.84 (d, $J = 6.1$ Hz, 1H), 3.79 (s, 3H), 2.04 (s, 3H), 1.84 (s, 3H), 1.47 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.9, 159.4, 148.5, 146.5, 140.4, 135.4, 133.4, 131.5, 131.1, 130.7, 129.2, 129.0, 128.7, 123.7, 116.6, 116.5, 113.9, 113.3, 108.2, 106.6, 88.7, 85.3, 80.9, 70.9, 55.3, 26.5, 24.8, 16.2, 13.7$; LRMS (EI): calcd for $C_{33}H_{35}O_{12}NS$: 669.71; found: 669.18.

(*E*)-3-[4-((3a*R*,4*S*,6*S*,6a*R*)-6-Acetyl-2,2-dimethyl-tetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yloxy)-3-(4-methoxybenzyloxy)-phenyl]-2-methylacrylic acid (39): A solution of ammonium acetate (1.27 g, 16.4 mmol) and titanium(III) chloride (0.422 g, 2.73 mmol) in water (4.2 mL) was added to a solution of **38** (141 mg, 0.21 mmol) in THF (4.2 mL), at room temperature and the mixture was stirred overnight. Ethyl acetate was added and the organic layer was washed by a 1M solution of sodium potassium tartrate, the aqueous phase back extracted and the combined organic phases washed with brine, dried over magnesium sulfate, filtrated and evaporated in vacuo. Compound **39** (83 mg, 0.17 mmol) was isolated pure as a white foam after column chromatography (petroleum ether/ethyl acetate 1:3) with 80% yield. $R_f = 0.35$ (heptane/diethyl ether 1:3), 0.71 (diethyl ether); $[\alpha]_D^{23} = -101.7$ ($c = 1.00$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 2937, 2634, 1717, 1681, 1613, 1515, 1419, 1374, 1250\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.68$ (s, 1H), 7.28 (d, $J = 8.8$ Hz, 2H), 7.14 (d, $J = 8.6$ Hz, 1H), 7.03 (m, 2H), 6.88 (d, $J = 8.8$ Hz, 2H), 5.86 (s, 1H), 5.34 (d, $J = 5.9$ Hz, 1H), 4.98 (s, 2H), 4.80 (d, $J = 6.1$ Hz, 1H), 4.53 (s, 1H), 3.79 (s, 3H), 2.05 (d, $J = 1.2$ Hz, 3H), 2.01 (s, 3H), 1.51 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 206.7, 173.9, 159.4, 148.1, 146.4, 140.4, 130.1, 129.0, 128.6, 126.2, 123.8, 116.7, 115.1, 113.9, 112.8, 106.5, 91.2, 84.5, 80.5, 70.9, 55.2, 26.5, 26.3, 24.8, 13.7$; elemental analysis calcd (%) for $C_{27}H_{30}O_9$: C 65.05, H 6.07; found: C 65.16, H 6.07.

(*E*)-3{-4-[(3a*R*,4*S*,6*S*,6a*R*)-6-(1-Benzenesulfonyl-1-nitroethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yloxy]-3-hydroxyphenyl}-2-methylacrylic ethyl ester (40): *p*-Toluenesulfonic acid (3.35 g, 17.5 mmol) was added to a solution of **37** (9.6 g, 14.6 mmol) in a 1:1 mixture of THF and methanol (500 mL, 0.03M), and the mixture was stirred at 50 °C for 8 h. The mixture was then evaporated in vacuo. The crude was purified on a plug of silica gel (petroleum ether/diethyl ether 1:1 then 100% ethyl acetate). The corresponding triol (7.84 g, 14.6 mmol) was obtained pure as a white foam with a quantitative yield. $R_f = 0.23$ (diethyl ether). The latter (7.84 g, 14.6 mmol) was then dissolved in dichloromethane (150 mL, 0.1M), 2,2-dimethoxypropane (18 mL, 146 mmol) and *p*-toluenesulfonic acid (0.28 g, 1.46 mmol) were added. After 5 min, ethyl acetate was added and the organic phase was washed with a saturated solution of $NaHCO_3$ and brine, dried over magnesium sulfate, filtrated and evaporated in vacuo. Compound **40** (7.96 g, 13.8 mmol) was isolated pure as a white solid after column chromatography (petroleum ether/diethyl ether 1:1) with 95% yield. $R_f = 0.76$ (diethyl ether); $[\alpha]_D^{23} = -69.8$ ($c = 1.00$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3486, 2988, 1701, 1613, 1557, 1250, 1158\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.88$ (dd, $J = 1.2, 8.6$ Hz, 2H), 7.74 (tt, $J = 1.2, 7.6$ Hz, 1H), 7.58 (m, 2H), 7.52 (s, 1H), 7.00 (d, $J = 2.2$ Hz, 1H), 6.95 (d, $J = 8.5$ Hz, 1H), 6.84 (dd, $J = 8.5, 2.2$ Hz, 1H), 5.70 (s, 1H), 5.48 (dd, $J = 1.5, 6.1$ Hz, 1H), 5.45 (s, 1H), 5.04 (d, $J = 1.2$ Hz, 1H), 4.86 (d, $J = 6.1$ Hz, 1H), 4.22 (q, $J = 7.1$ Hz, 2H), 2.07 (d, $J = 1.5$ Hz, 3H), 1.80 (s, 3H), 1.51 (s, 3H), 1.31 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 168.7, 145.6, 143.1, 137.9, 135.7, 133.1, 131.5, 131.4, 131.0, 129.4, 129.0, 127.8, 122.5, 117.0, 113.9, 113.4, 108.0, 106.4, 89.3, 85.5, 81.0, 60.8, 26.4, 24.7, 17.7, 14.3, 14.0$; elemental analysis calcd (%) for $C_{27}H_{31}O_{11}NS$: C 56.15, H 5.41, N 2.42, S 5.55; found: C 56.30, H 5.56, N 2.29.

(*E*)-3-{4-[(3a*R*,4*S*,6*S*,6a*R*)-6-Acetyl-2,2-dimethyltetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yloxy]-3-(hydroxy)-phenyl}-2-methylacrylic acid (41): LiOH (5.8 g, 138 mmol) was added to a solution of **40** (7.96 g, 13.8 mmol) in a 1:1:1 mixture of methanol, THF, and water (150 mL), and the mixture was stirred at 40 °C for 4 h. After cooling to room temperature, the solution was acidified by a 5% solution of $NaHSO_3$ and extracted by ethyl acetate. The organic phase was washed brine, dried over magnesium sulfate, filtrated and evaporated in vacuo to afford the acid (7.6 g, 13.8 mmol) as a white foam with a quantitative yield. $R_f = 0.53$ (diethyl ether); $[\alpha]_D^{23} = -66.3$ ($c = 1.00$, CH_2Cl_2); IR (neat): $\tilde{\nu} = 3486, 2991, 2646, 1682, 1557, 1264, 1156\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.88$ (dd, $J = 1.2, 8.6$ Hz, 2H), 7.75 (tt, $J = 1.2, 7.6$ Hz, 1H), 7.65 (s, 1H), 7.58 (t, $J = 8.1$ Hz, 2H), 7.03 (d, $J = 1.7$ Hz, 1H), 6.97 (d, $J = 8.5$ Hz, 1H), 6.88 (dd, $J = 2.0, 8.8$ Hz, 1H), 5.72 (s, 1H), 5.50 (dd, $J = 1.5, 6.1$ Hz, 1H), 5.05 (d, $J = 1.2$ Hz, 1H), 4.87 (d, $J = 6.1$ Hz, 1H), 2.09 (s, 3H), 1.80 (s, 3H), 1.51 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.8, 145.6, 143.5, 140.2, 135.8, 133.1, 131.0, 130.9, 129.4, 126.6, 122.9, 117.2, 113.9, 113.4, 108.0, 106.4, 89.3, 85.4, 81.0, 60.4, 26.4, 24.7, 17.7, 14.2, 13.7$; elemental analysis calcd (%) for $C_{25}H_{27}O_{11}NS$: C 54.64, H 4.95, N 2.55; found: C 54.80, H 5.02, N 2.36.

To a solution of the latter (284 mg, 0.517 mmol) in THF (9 mL), was added at room temperature a solution of ammonium acetate (3.12 g, 40 mmol) and titanium(III) chloride (1.03 g, 6.7 mmol) [**Note**: this reagent should be handled and kept in a dry box] in water (4.2 mL) and the mixture was stirred 3 h. Ethyl acetate was added and the organic layer was washed by a 1M solution of sodium potassium tartrate, the aqueous phase back extracted and the combined organic phases washed with brine, dried over magnesium sulfate, filtrated and evaporated in vacuo. Compound **41** (156 mg, 0.414 mmol) was isolated pure as a white foam after column chromatography (petroleum ether/ethyl acetate 1:1 then 1:3) with 80% yield. $R_f = 0.59$ (diethyl ether); $[\alpha]_D^{23} = -137.4$ ($c = 1.00$, MeOH); IR (neat): $\tilde{\nu} = 3330, 2932, 2644, 1712, 1682, 1510, 1263, 1101\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.69$ (s, 1H), 7.11 (d, $J = 8.3$ Hz, 1H), 7.06 (d, $J = 2.0$ Hz, 1H), 6.92 (dd, $J = 8.5, 2.0$ Hz, 1H), 5.76 (s, 1H), 5.24 (dd, $J = 5.9, 1.0$ Hz, 1H), 4.86 (d, $J = 5.9$ Hz, 1H), 4.71 (s, 1H), 2.11 (d, $J = 1.0$ Hz, 3H), 2.10 (s, 3H), 1.51 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 206.6, 173.8, 146.9, 144.0, 140.3, 131.8, 126.8, 122.7, 117.6, 116.3, 113.4, 108.8, 91.5, 84.9, 80.3, 26.4, 26.3, 24.9, 13.8$; elemental analysis calcd (%) for $C_{19}H_{22}O_8$: C 60.31, H 5.86; found: C 60.51, H 6.08.

(*E*)-3-{4-[(3a*R*,4*S*,6*S*,6a*R*)-2,2-Dimethyl-6-(2-methyl-[1,3]dioxolan-2-yl)-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yloxy]-3-(hydroxy)-phenyl}-2-methylacrylic acid (42): Freshly distilled 1,2-bis-trimethylsilyloxyethane (0.97 mL, 4 mmol) and trimethylsilyl trifluoromethanesulfonate (30 μL, 0.13 mmol) were added to a solution of **41** (0.5 g, 1.32 mmol) in dichloromethane (13 mL), at 0 °C. The mixture was stirred at 0 °C for 6 h. Pyridine (3 mL) and ethyl acetate were then added. The organic phase was washed with a saturated solution of $NaHCO_3$ and brine, dried over magnesium sulfate, filtrated and evaporated in vacuo. Compound **42** (0.505 g, 1.20 mmol) was isolated pure as a white foam after column chromatography (petroleum ether/ethyl acetate 1:1) with 91% yield. $R_f = 0.55$ (diethyl ether); $[\alpha]_D^{23} =$

-92.2 ($c = 1.00$, MeOH); IR (neat): $\tilde{\nu} = 3400$, 2986, 1882, 1614, 1505, 1250, 1100 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.65$ (s, 1H), 7.03 (d, $J = 8.1$ Hz, 1H), 7.02 (s, 1H), 6.90 (d, $J = 8.1$ Hz, 1H), 5.88 (s, 1H), 4.84 (s, 2H), 4.33 (s, 1H), 4.09 (m, 2H), 4.03 (m, 2H), 2.10 (s, 3H), 1.50 (s, 3H), 1.35 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 177.6$, 147.7, 143.5, 139.8, 131.5, 127.1, 122.5, 117.3, 116.4, 112.8, 108.5, 91.5, 85.4, 80.3, 65.4, 64.5, 26.5, 25.0, 20.7, 13.9; elemental analysis calcd (%) for $C_{21}H_{26}O_9$: C 59.71, H 6.20; found: C 59.92, H 6.42; HRMS: calcd for $C_{21}H_{26}O_9$: 422.1577; found: 422.1568 $[M]^+$.

***C*-2-*epi*-Hygromycin A (4)**: Diethylcyanophosphonate (30 μL, 150 μmol) and triethylamine (28 μL, 200 μmol) were added to a solution of **42** (50 mg, 118 μmol) and **6** (30 mg, 150 μmol) in DMF (2 mL) at 0 °C. After 3 h at this temperature, ethyle acetate was added and the organic phase was washed by brine, dried over magnesium sulfate, filtrated and evaporated in vacuo. The amide (49 mg, 83 μmol) was isolated pure after three purifications on silica gel (preparative TLC) (ethyl acetate/methanol 85:15) with 70% yield. $R_f = 0.25$ (ethyl acetate/methanol 85:15); $[\alpha]_D^{23} = -44.1$ ($c = 1.00$, MeOH); IR (neat): $\tilde{\nu} = 3420$, 1610, 1510 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): $\delta =$ 7.23 (s, 1H), 7.11 (d, $J = 8.3$ Hz, 1H), 6.92 (d, $J = 2.0$ Hz, 1H), 6.86 (dd, $J =$ 2.0, 8.3 Hz, 1H), 5.81 (s, 1H), 5.23 (s, 1H), 4.93 (d, $J = 6.1$ Hz, 1H), 4.89 (dd, $J = 1.7$, 6.1 Hz, 1H), 4.79 (s, 1H), 4.50 (dd, $J = 2.7$, 6.1 Hz, 1H), 4.23 (d, $J =$ 1.7 Hz, 1H), 4.20 (m, 3H), 3.92 (m, 5H), 3.80 (dd, $J = 2.7$, 2.7 Hz, 1H), 2.11 (d, $J = 1.3$ Hz, 3H), 1.49 (s, 3H), 1.35 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 172.8$, 148.3, 145.3, 134.9, 132.3, 132.0, 122.6, 117.9, 116.8, 113.8, 109.9, 109.3, 96.1, 92.9, 87.0, 82.1, 78.1, 72.5, 71.6, 71.2, 66.7, 65.9, 50.3, 49.8, 27.1, 25.2, 23.0, 14.7; LRMS (ESI): calcd for $C_{28}H_{36}NO_{13}$: 594.22; found: 594.20 $[M - H]^-$.

To a solution of the latter (70 mg, 117 μmol) in water (0.5 mL), was added at room temperature trifluoroacetic acid (0.6 mL). After 1 h, benzene was added and the mixture was evaporated in vacuo. This operation was repeated three times. **4** (42 mg, 82 μmol) was isolated pure after purification on sephadex LH-20 (7 g) (methanol/ethyl acetate 1:3) followed by sephadex G-10 (7 g) (water) with 70% yield. $R_f = 0.10$ (ethyl acetate/methanol 85:15); $[\alpha]_D^{22} = -60.4$ ($c = 1.00$, MeOH); IR (KBr): $\tilde{\nu} = 3420$, 1710, 1610, 1510 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): $\delta = 7.25$ (s, 1H), 7.14 (d, $J = 8.3$ Hz, 1H), 6.93 (d, $J = 2.0$ Hz, 1H), 6.87 (dd, $J = 2.0$, 8.5 Hz, 1H), 5.56 (s, 1H), 5.22 (s, 1H), 4.78 (s, 1H), 4.50 (m, 2H), 4.43 (d, $J = 7.3$ Hz, 1H), 4.26 (d, $J = 4.4$ Hz, 1H), 4.21(dd, $J = 3.2$, 6.6 Hz, 1H), 4.17 (m, 2H), 3.96 (dd, $J = 6.7$, 6.7 Hz, 1H), 3.80 (dd, $J = 2.8$, 2.8 Hz, 1H), 2.14 (s, 3H), 2.12 (d, $J = 1.5$ Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 210.7$, 172.6, 148.5, 145.7, 134.9, 132.9, 132.2, 122.6, 118.3, 118.2, 108.9, 96.2, 88.6, 78.2, 76.3, 74.2, 72.5, 71.5, 71.2, 64.3, 50.3, 26.2, 14.6; elemental analysis calcd (%) for $C_{23}H_{29}NO_{12}$: C 54.01, H 5.71, N 2.74; found: C 54.22, H 5.56, N 2.63; LRMS (ESI): calcd for $C_{23}H_{28}NO_{12}$: 510.16; found: 510.54 $[M - H]^-$.

Acknowledgements

We thank the National Science Fondation and the National Institutes of Health for their generous support of our programs. O.D. was supported by a fellowship from Association pour la Recherche contre le Cancer (ARC). Mass spectra were provided by the Mass Spectroscopy Facility at the University of California-San Francisco supported by the NIH Division of Research Resources.

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Received: September 3, 2001 [F3528]

  0947-6539/02/0801-0268 $ 17.50+.50/0