ORGANIC LETTERS

2000
Vol. 2, No. 6
791−794

A de Novo Synthesis of 2,6-Dideoxy-*C*-aryl Glycosides Based on Ring Closing Metathesis and Diastereoselective Epoxide Cleavage/ Anomerization Reactions

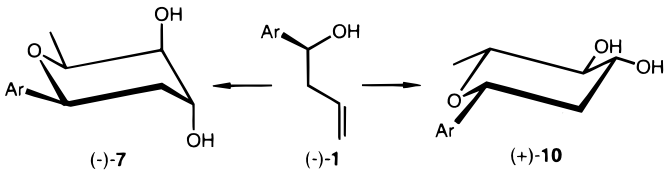
Bernd Schmidt

Universität Dortmund, Fachbereich Chemie, Organische Chemie I, Otto-Hahn-Strasse 6, D-44227 Dortmund, Germany

bschmidt@citrin.chemie.uni-dortmund.de

Received January 7, 2000

ABSTRACT



This paper describes a synthesis of enantiomerically pure 2,6-dideoxy-*C*-aryl glycosides, starting from non-carbohydrate precursors. The synthesis starts from homoallylic alcohols (obtained in enantiomerically pure form by enzymatic resolution), which are elaborated to dihydropyrans using ring closing metathesis as the key step. Epoxidation and epoxide cleavage complete the synthesis. The stereochemical outcome of the sequence depends on the conditions of the epoxide cleavage reaction.

Tetracyclins, anthracyclins, and angucyclins are classes of important antibiotics, which are biosynthetically formed via a polyketide pathway.[1−3] Several antibiotics of these classes have a *C*-glycoside substructure with a partially deoxygenated carbohydrate directly linked to the aromatic system. Therefore, these compounds are often referred to as *C*-aryl glycosides,[4] although this is not a homogeneous group of natural products if the biosynthesis is taken into account. Examples are the gilvocarcins,[5−7] ravidomycin,[8,9] the chrysomycins,[10] the vineomycins,[11] aquayamycin,[12] medermycin,[13] and the pluramycins.[14,15] In the case of the pluramycins NMR spectroscopic evidence for the participation of the *C*-glycosidic moiety in binding to specific DNA sequences was presented.[16] Quite recently the mechanism of the *C*-glycosyl transfer was investigated for an angucycline-type antibiotic.[17]

Several synthetic studies toward *C*-aryl glycosides have been conducted, and there are excellent reviews available on the synthesis of these compounds[18] and on the synthesis

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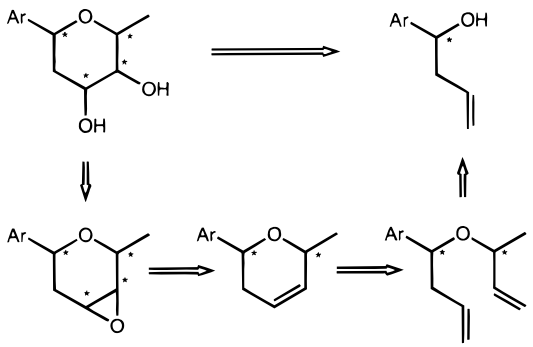
10.1021/ol005522y CCC: $19.00
Published on Web 03/01/2000

of *C*-glycosides in general.[19,20] Formation of the *C*-glycosidic bond by glycosylation of aromatic systems is the most common route to *C*-aryl glycosides. Recent examples for this strategy have been published by the groups of Schmidt,[21] Suzuki,[22] Satoh,[23] and Toshima.[24] Examples for de novo syntheses are the selenium-mediated cyclization of alkenols[25] and the [4 + 2] cycloaddition of aromatic aldehydes and dienes.[26]

The 2,6-dideoxy substitution pattern is very common for *C*-aryl glycosides. If synthesis is accomplished by formation of the *C*-glycosidic C−C bond, either one is limited to the absolute and relative configurations and deoxygenation patterns available from naturally occurring carbohydrates such as olivose or laborious manipulations are necessary to synthesize non-natural analogues from naturally occurring carbohydrates.

In this communication we present a flexible de novo approach to *C*-aryl glycosides with a 2,6-deoxygenation pattern based on ring closing olefin metathesis[27,28] as the C−C bond forming key step (Scheme 1).[29,30] Homoallylic

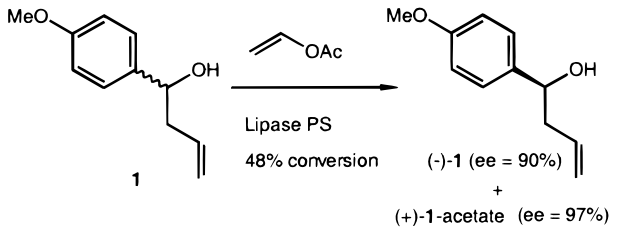
Scheme 1. Retrosynthetic Approach to the 2,6-Dideoxy-*C*-aryl Glycosides



alcohols are used as a starting material, because these are accessible in enantiomerically pure form via several different methods.

Enzymatic resolution of racemic homoallylic alcohol **1** is a convenient method to obtain both enantiomers.[31] Best results were obtained with an immobilized Lipase PS (Amano, from *Pseudomonas cepacia*). Assignment of absolute configuration was achieved by comparing the optical rotation with the literature value.[32] Determination of ee was achieved by NMR shift measurements (500 MHz, C_6D_6) using the Eu(hfc)$_3$ reagent (Scheme 2).

Scheme 2. Enzymatic Resolution of Homoallylic Alcohol **1**



With both enantiomers in hand, the diastereomeric dihydropyrans *cis*- and *trans*-**5** were synthesized in enantiomerically pure form as described in Scheme 3 (synthesis shown starting from (−)-(*S*)-**1**). Alkylation of (−)-**1** with *dl*-ethyl-2-bromopropionate yields an easily separable mixture of diastereomeric esters (−)-**2a** and (−)-**2b**. NMR shift measurements (500 MHz, C_6D_6, Eu(hfc)$_3$) indicate that no racemization occurs during this reaction, as the ee observed for (−)-**2a**,**b** is identical with the one observed for the starting material (−)-**1**.

Reduction of diastereomeric esters **2a**,**b** to the aldehydes **3a**,**b** and subsequent Wittig olefination to the metathesis precursors **4a**,**b** work without isomerization, as from both reactions diastereomerically pure compounds were obtained. Finally, ring closing metathesis[33] of the allylic−homoallylic ethers **4a** and **4b** yields dihydropyrans **5a** and **5b**, respectively.[34] Elucidation of relative configuration was achieved by NOESY experiments.

The final steps in the synthesis of a *C*-aryl glycoside involve epoxidation and epoxide cleavage. For conformationally rigid epoxides regioselectivity of nucleophilic attack is ruled by the preferred formation of the *trans*-diaxial cleavage products ("Fürst-Plattner rule").[35] We have recently studied the regio- and stereochemical outcome of dihydro-

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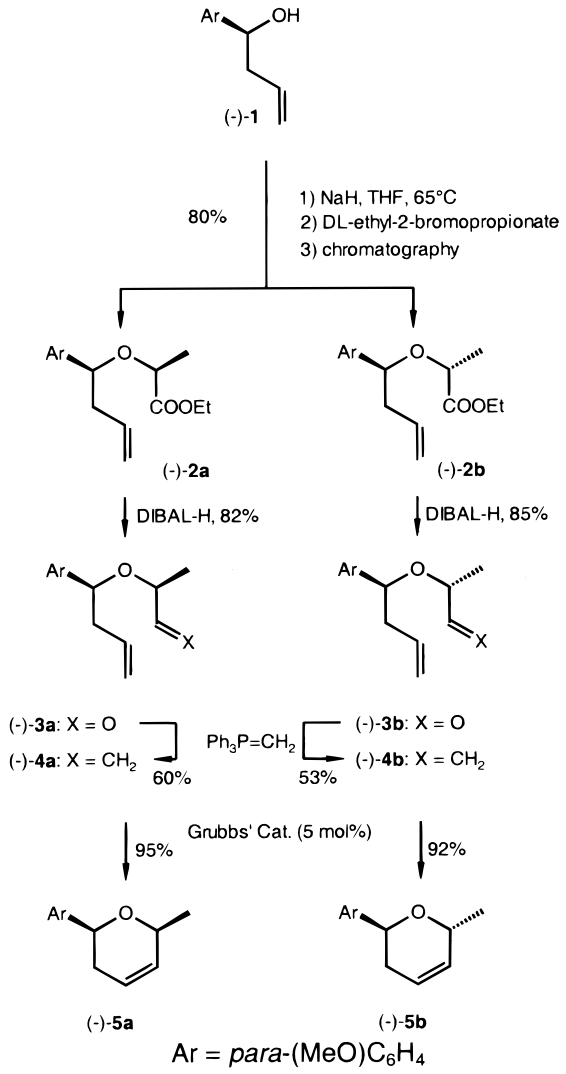
Scheme 3. Synthesis of Dihydropyrans *cis*-**5a** and *trans*-**5a** ((−)-Enantiomer Shown)



pyran oxide cleavage reactions[36] and found that an aromatic substituent will provide sufficient rigidity to ensure clean *trans*-diaxial cleavage, regardless of the relative configuration of the starting dihydropyran oxide. Thus, if the dihydropyran oxide is cleaved with an O-nucleophile, there is no need to control the diastereoselectivity of the epoxidation step. Upon treatment of **5a** with MCPBA a 1:1 mixture of dihydropyran oxides *trans*- and *cis*-**6a** results, which are easily separated by chromatography. Treatment of both diastereomers of **6a** (separately or as a mixture) with water in the presence of sulfuric acid or CAN gives one single diastereomer of **7**, a *C*-aryl glycoside with the non-natural *trans*-diaxial arrangement of the hydroxy groups (Scheme 4).

C-Aryl glycosides with equatorially configured substituents become accessible via this synthesis by combination of a Lewis acid mediated epoxide opening reaction with a Lewis acid mediated anomerization (Scheme 5). Epoxidation of **5b** leads to a separable mixture of diastereomers of dihydropyran

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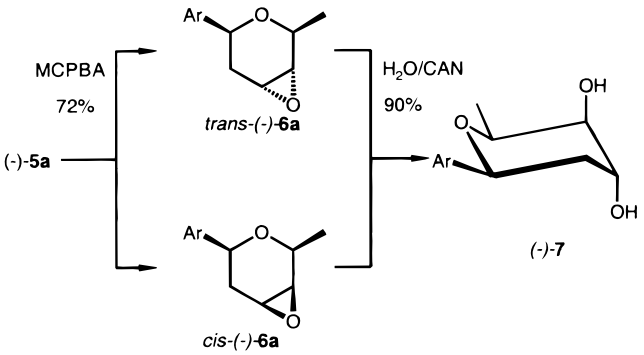
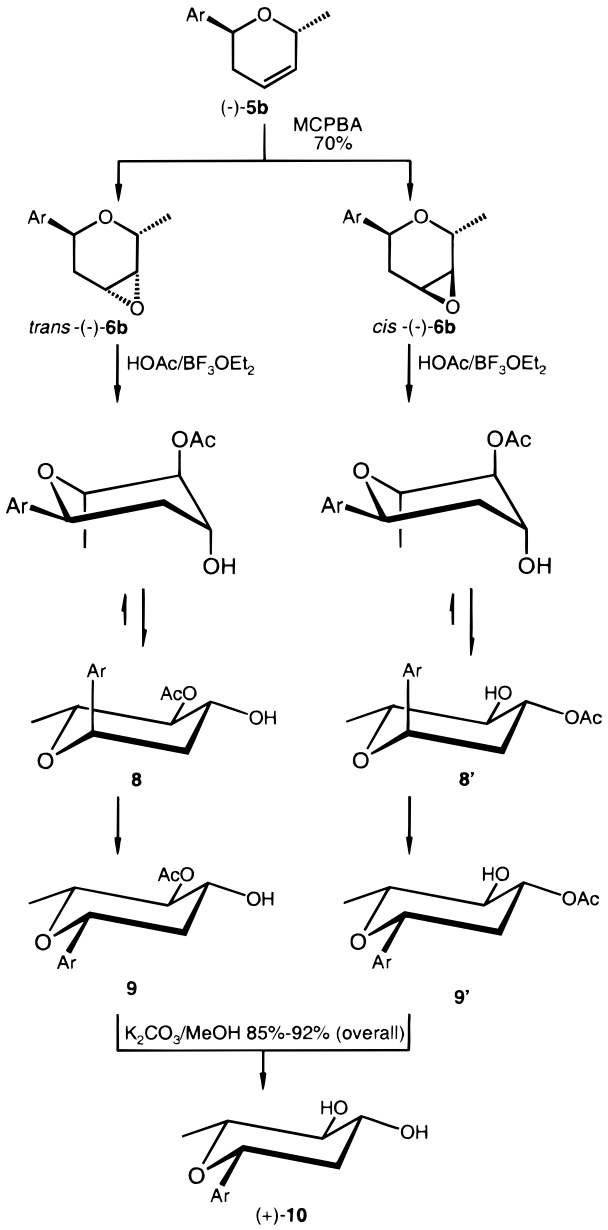
Scheme 4. Synthesis of a Non-Natural *C*-Aryl Glycoside ((−)-Enantiomer Shown)

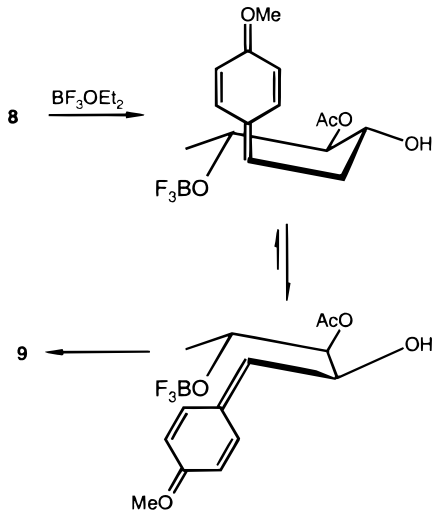


Scheme 5. Synthesis of a *C*-Aryl Glycoside with Natural Absolute and Relative Configuration ((+)-Enantiomer Shown)



oxides *trans*-**6b** and *cis*-**6b**. Attack of acetic acid in the presence of BF_3OEt_2 leads, in the first instance, to regioisomeric *C*-glycosides **8** and **8′**, which may well exist as an equilibrium of conformers, with the aryl substituent in either the equatorial or the axial position. Unfavorable 1,3-diaxial interactions provide a strong driving force for an anomerization to the thermodynamic products. This anomerization proceeds via a mechanism first discussed by Suzuki et al. in the course of their studies toward hafnium-mediated *C*-glycosylation.[37] The Lewis acid weakens the C1−O bond by attack at the tetrahydropyran oxygen, leading to an open-chain intermediate, which may undergo isomerization and recyclization to the all-equatorial regioisomers **9** and **9′** (Scheme 6).

Scheme 6. Mechanism of the Anomerization Step



The fact that a positively charged aromatic substituent is involved in the rearrangement may suggest that in addition to the steric interactions mentioned above a reverse anomeric effect is working here. However, from our experimental findings it cannot be judged if such an effect contributes to the driving force for the rearrangement or if this rearrangement is solely caused by steric effects (i.e., minimization of unfavorable 1,3-*trans*-diaxial interactions).[38] Deprotection of **9** and **9′** (separately or as a mixture of regioisomers) gives the same *C*-aryl glycoside **10** with the all-equatorial arrangement of substituents. Thus, from (*S*)-(−)-**1** (1*R*,3*R*,4*S*,5*R*)-(+)-**10**[39] results, which has the absolute configuration of the naturally occurring *C*-aryl glycosides, such as the vineomycins or aquayamcycin.

In summary, this contribution presents a de novo approach to *C*-aryl glycosides, exemplified for the 2,6-dideoxy substitution pattern. Naturally occurring as well as non-natural configurations become accessible via the same methodology from starting materials that are conveniently prepared in enantiomerically pure form. Further synthetic studies toward the synthesis of other *C*-aryl glycosides using this method are currently underway.

Acknowledgment. I thank the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft, and Prof. Dr. P. Eilbracht for generous support.

OL005522Y

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(39) Selected physical data for (−)-**7**: $[\alpha]_D = -11$ (*c* 1.40, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, $J = 8.8$ Hz, 2H), 6.84 (d, $J = 8.8$ Hz, 2H), 4.71 (dd, $J = 12.0$, 1.8 Hz, 1H), 4.12 (q, $J = 6.5$ Hz, 1H), 4.03 (m, 1H), 3.75 (s, 3H), 3.28 (m, 1H), 2.01 (ddd, $J = 14.3$, 12.0, 2.0 Hz, 1H), 1.71 (dm, $J = 14.3$ Hz, 1H), 1.24 (d, $J = 6.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 134.1, 127.3, 113.7, 73.9, 70.9, 70.4, 68.0, 55.2, 34.8, 17.0. Selected physical data for (+)-**10**: $[\alpha]_D = +13$ (*c* 1.40, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD) δ 7.31 (d, $J = 8.8$ Hz, 2H), 6.91 (d, $J = 8.8$ Hz, 2H), 4.46 (dd, $J = 11.8$, 2.0 Hz, 1H), 3.80 (s, 3H), 3.69 (ddd, $J = 11.3$, 9.0, 5.0 Hz, 1H), 3.43 (dq, $J = 9.0$, 6.3 Hz, 1H), 3.05 (dd, $J = 9.0$, 9.0 Hz, 1H), 2.16 (ddd, $J = 12.8$, 5.0, 2.0 Hz, 1H), 1.69 (ddd, $J = 12.8$, 11.8, 11.3 Hz, 1H), 1.35 (d, $J = 6.3$ Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 160.6, 135.1, 128.4, 114.6, 78.8, 78.4, 77.5, 73.8, 55.7, 42.7, 18.5.