

Elaboration of D-(–)-Ribose into a Tricyclic, Natural Product-like Scaffold

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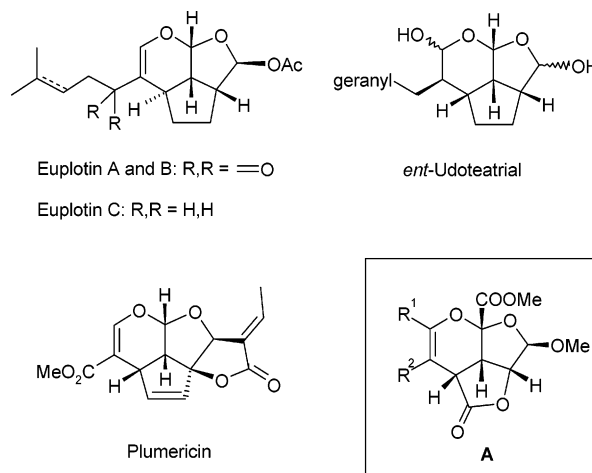
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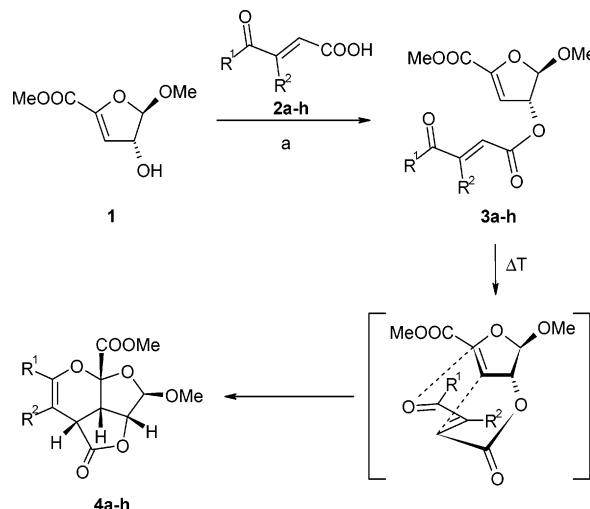
Abstract: The construction of natural product-like, tricyclic compounds is reported. Starting from a D-(–)-ribose-derived dihydrofuran, the tricyclic scaffold is prepared via an intramolecular hetero-Diels–Alder reaction. The reaction proceeds with very high diastereoselectivity through an *endo* transition state, as established on the basis of X-ray structural analysis of the products. Further modification and derivatization of the obtained products is described.

Natural products have had a large impact on drug discovery. Many natural products, or derivatives thereof, are used in modern medicine. Furthermore, the large structural diversity of natural compounds has always served medicinal scientists as a source of inspiration in the search for new molecular entities with pharmacological activity.¹ The synthesis of natural product analogues, therefore, represents a key challenge for medicinal chemists.^{2–4} In addition, combinatorial methods are increasingly applied for the generation of derivatives of natural products and natural product-like scaffolds.^{5–7} During our work aimed at the synthesis of natural product-like scaffolds, we became attracted to a group of compounds belonging to the *iridoid* family (see Scheme 1). These tricyclic compounds, which have a common perhydrofurofuran core,^{8,9} possess a variety of interesting biological activities. The synthetic scaffold **A** shows a high degree of structural similarity to these compounds. This scaffold, in turn, should be accessible through an intramolecular hetero-Diels–Alder reaction of a simple, D-(–)-ribose-derived precursor. The hetero-Diels–Alder reaction is one of the most important reactions for the construction of heterocyclic six-membered rings.^{10–14} Its

SCHEME 1. Structural Similarity of a D-(–)-Ribose Derived Tricyclic Scaffold (**A**) to Selected Natural Compounds (euplotins,¹⁵ *ent*-udoteatrial,¹⁶ and plumericin¹⁷)



SCHEME 2. Synthetic Approach to a Tricyclic Scaffold through Hetero-Diels–Alder Reaction of D-(–)-ribose Derived Precursors^a



^a Reagents and conditions: (a) Et₃N, pivaloyl chloride, DMAP, 2 h, 0 °C.

concerted character allows the selective formation of up to three stereogenic centers in a single reaction step. Therefore, we investigated the usefulness of the intramolecular hetero-Diels–Alder reaction for the construction of the synthetic scaffold **A**. Here, we report the synthesis and further derivatization of this scaffold.

The precursors for the hetero-Diels–Alder reaction were readily prepared according to literature procedures. Following the method by Schmidt et al.,¹⁸ the dihydrofuranoside **1** was obtained in five steps from D-(–)-ribose

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TABLE 1. Hetero-Diels–Alder Reactions of D-(–)-Ribose Derived Acylacrylate Ester^a

1 $\xrightarrow{2a-h}$ 3a-h $\xrightarrow{\text{conditions}}$ 4a-h

	R1	R2	3a–h yield (%) ^a	4a–h yield (%)	conditions
a	methyl	H	61	53	<i>o</i> -xylene, reflux, 16 h
b	phenyl	H	69	73	<i>o</i> -xylene, reflux, 5 h
c	4-bromophenyl	H	67	45	<i>o</i> -xylene, reflux, 18 h
d	3-nitrophenyl	H	63	(96) ^c	toluene, reflux, 20 h
e	4-nitrophenyl	H	78	(99) ^c	<i>o</i> -xylene, reflux, 3 h
f	methyl	benzyl	75	24	toluene, 170 °C, ^d 3 h
g	methyl	pentyl	60	30	toluene, 170 °C, ^d 5 h
h	methyl	acetyl	<i>b</i>	51	1,2-dichloroethane, rt, 20 h

^a Reaction conditions: see Scheme 2. ^b Intermediate was not isolated; cyclization takes place spontaneously. ^c Crude material was directly used in the next step (see Scheme 3). ^d The reaction was carried out in a sealed, Teflon-coated steel autoclave.

with an overall yield of 35%. The acrylic acids **2a–h** were also prepared according to literature procedures.^{19,20} The esterification of alcohol **1** (Scheme 2 and Table 1) with the different acids was best carried out via the mixed anhydrides obtained with pivaloyl chloride. Isolated yields of the esters **3a–g** varied between 60% and 80%. These esters were subsequently treated in high-boiling aromatic hydrocarbons or, alternatively, in a sealed steel autoclave at 170 °C with toluene as the solvent. Ester **3h** behaved exceptionally in this reaction. Isolation of this compound was not possible, since cyclization took place under the conditions of esterification, i.e., at room temperature in 1,2-dichloroethane. This observation of a faster reaction is in good agreement with the expected influence of an electron-withdrawing substituent at the diene moiety in this inverse electron-demand hetero-Diels–Alder reaction.²¹ Table 1 shows the tricyclic derivatives **4a–h** formed in the cyclization reaction. Yields were in the range of 50–70%, except for the two derivatives **4f** and **4g**, which were isolated in low yields, due to partial decomposition at 170 °C. The two compounds **4d** and **4e** were not purified but were directly used for further modifications (see below).

The stereochemical outcome of the hetero-Diels–Alder reaction was, of course, of particular interest. On the basis of the ¹H NMR spectra of the crude materials only a single diastereomer was formed in all reactions. Structural analysis (¹H NMR nuclear Overhauser experiments) as well as X-ray structures of compounds **4a,b,g** revealed that the hetero-Diels–Alder reaction must follow the pathway shown in Scheme 2. Only if the two substituents R¹ and R² are arranged *endo* to the sugar are the respective diastereomers formed. The reaction proceeds, thus, with *endo* selectivity as commonly observed in inverse electron-demand hetero-Diels–Alder reactions.^{12,14}

In a recent report, Aungst and Funk²² reported on the total synthesis of (±)-euplotin A using a hetero-Diels–Alder reaction as a key step in the synthesis. The stereochemical outcome, however, was different from the one observed here. The difference is most likely a result of the altered substitution pattern of the dihydrofurane, leading to changed steric and electronic parameters in the transition state. On the other hand, Kim and co-workers described an analogous stereochemical course in an *intermolecular* Diels–Alder reaction between cyclopentadiene and a cyclic, sugar-derived dienophile.²³ Furthermore, we observed the same course in the *intramolecular* hetero-Diels–Alder reaction of acyclic allylic alcohols of acylacrylates.²⁴

The obtained tricyclic compounds **4d** and **4e**, containing 3- and 4-nitrophenyl groups in position R¹, were further derivatized as shown in Schemes 3 and 4. Catalytic hydrogenation with palladium on charcoal under a hydrogen atmosphere led to the reduction of the nitro group as well as the double bond (Scheme 3). Although the corresponding products **5a** and **5b** could be isolated and purified, we observed some instability during the purification process. It turned out to be advantageous to directly use the crude material in the subsequent acylation reaction with the different electrophiles. In this way, considerably higher yields of the products **6** and **7** were obtained. The overall yields over three steps varied between 30% and 50% (Scheme 3).

In general, the 3-acylamino derivatives (**6a–e**) were obtained in higher yields than the corresponding 4-acylamino compounds (**7a–e**). Somewhat unexpectedly, the stereochemistry of the hydrogenation reaction (**4** → **5**) did not proceed with complete selectivity. Compounds **5a** and **5b** were obtained with selectivities of 93:7 and 84:16, respectively. After acylation in the subsequent step,

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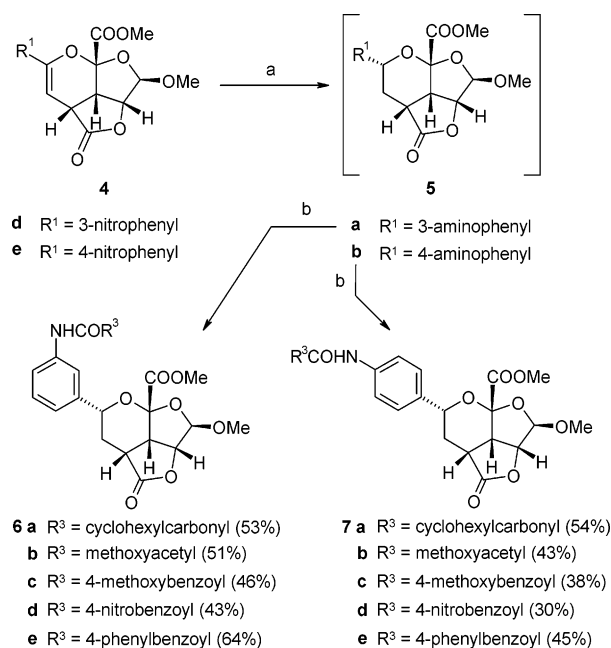
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SCHEME 3. Reduction of Tricyclic Products 4d,e and Further Derivatization of the Obtained Aromatic Amines 5a,b with Various Acyl Chlorides^{a,b}

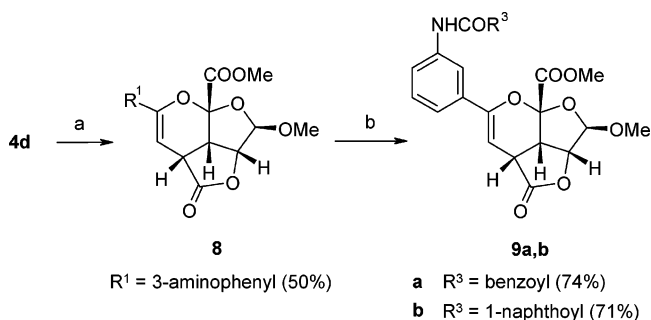


^a Reagents and conditions: (a) Pd/C (10%), MeOH. (b) $R^3\text{COCl}$, DMAP, pyridine. ^b Yields given for products **6** and **7** are over three steps starting from esters **3d** and **e**, respectively.

however, the major isomers were isolated after column chromatography in pure form. The spacial orientation of the aminophenyl substituents shown for compounds **6** and **7** was confirmed by ^1H NMR spectroscopic methods.

To increase the diversity of potential new types of structures, we also tried to preserve the enol double bond present in compounds **4**, i.e., to selectively reduce the nitro to the amino group in the presence of the enol ether. This worked best by using ammonium formate as the hydrogen source in the catalytic reduction. Scheme 4 shows the conversion of compound **4d** to the corresponding aminophenyl derivative **8**, in which the enol ether still exists. Due to partial reduction of the enol double bond, the yield is modest. Nevertheless, the compound was obtained and could readily be further reacted with

SCHEME 4. Selective Reduction of the Nitro Group in 4d Followed by Acylation of the Resulting Aniline^a



^a Reagents and conditions: (a) Pd/C (10%), HCOONH_4 , MeOH. (b) $R^3\text{COCl}$, DMAP, pyridine.

benzoyl and 1-naphthoyl chloride to give the corresponding compounds **9a** and **9b**.

In summary, the tricyclic scaffold **A** is accessible via an intramolecular hetero-Diels–Alder reaction of D-(–)-ribose-derived esters of different acylacrylic acids. The cyclization reaction proceeds in a highly stereoselective manner. The tricyclic intermediates can be further modified and derivatized with various reagents. The natural product-like compounds are being tested for their biological activities in cellular assays.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>. Crystallographic data (excluding structure factors) for **4a**, **4b**, and **4g** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications numbers CCDC 248308, CCDC 248309, and CCDC 248310, respectively.

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