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SYNTHESIS OF 3-AMINO SUGARS OF THE DAUNOSAMINE TYPE THROUGH hetero-DIELS-ALDER REACTION OF ENAMINONES**

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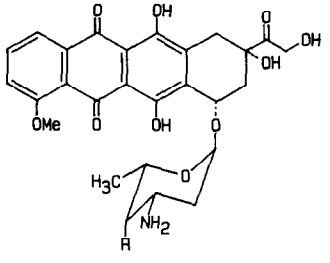
Summary: The thermally induced hetero-Diels-Alder reaction of vinyl ethers **2a-d** and N-acylenaminones **3a-h** leads to the diastereomeric adducts **4a-h** and **5a-h** in 75 - 98 % yield providing cis-compounds **4a-h** as the main products. Isomerisation of **4a-f** with Lewis acids gives the thermodynamically more stable **5a-f**. Transformation of **4** and **5** by hydrogenation leads to 3-amino sugar glycosides.

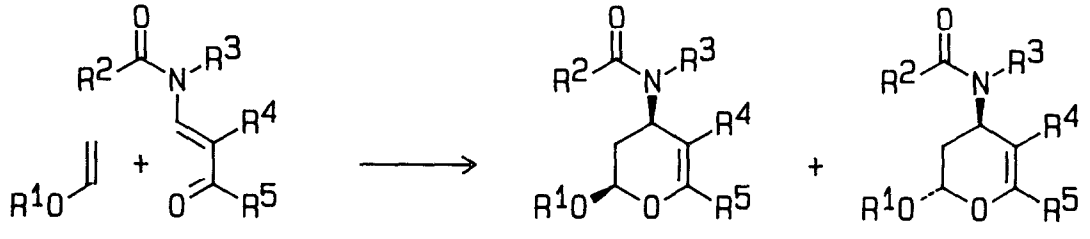
Variation of the sugar moiety in anthracycline antibiotics, which are of great value in the treatment of cancer, can improve their efficiency and decrease their toxicity[1]. Thus, doxorubicin **1a** shows high cardiotoxicity whereas the 4'-deoxy-compound **1b** is nearly free of this side effect; in addition **1b** displays a higher activity against colon cancer[1a]. Since several methods exist for the formation of the glycosidic bond[2], general routes to a wide variety of 3-amino sugars are wanted[3]. Recently we have shown that the hetero-Diels-Alder reaction of tricarbonyl-compounds and enol ethers gives access to hydroxy-dihydropyranyl-ethers[4], in addition by employing O-acyl compounds of chiral acids asymmetric induction can be obtained[5]. Furthermore the use of N-acyl enaminecarbaldehydes allows the synthesis of branched 3-amino sugars[6].



1a: R=OH; **1b**: R=H

In this paper we describe a highly flexible and effective route to racemic 3-amino sugars of the daunosamine type based on a non-induced hetero-Diels-Alder reaction of vinyl ethers **2** and N-acylenaminones **3**. The asymmetric induction, which can be achieved by employing chiral amines, chiral acyl-moieties or chiral alcohols will be described later.

The hetero-Diels-Alder reaction of **2a-d** and **3a-h** was accomplished by heating a mixture of the educts in toluene at 120 - 140°C in the presence of small amounts of hydroquinone. The diasteromeric cycloadducts **4a-h** and **5a-h**, which can be separated by chromatography (e.g. **4f/5f**, silica gel, chloroform/hexane 10:1) were obtained in 76 - 98 % yield (Table 1). In all transformations the cis-isomers **4a-h**, which may be formed in a kinetically controlled reaction via an endo-E-syn-transition state, were the main products; however, treatment of **4a-f** with Lewis acids causes isomerisation to the thermodynamically more stable trans-products **5a-f**; thus stirring a solution of the primarily obtained mixture of **4f/5f** in dichloromethane with 1 mol equivalent borontrifluoride etherate (20°C, 1 h) affords **5f** in 85% yield after crystallisation and repeated isomerisation of the mother liquor.



2 3 4 5

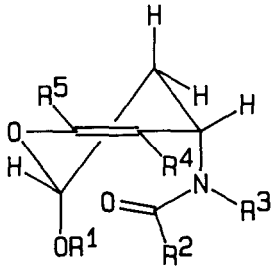
	R^1	R^2	R^3	R^4	R^5
a	Et	Ph	H	H	CO_2CH_3
b	Et	CO_2CH_3	H	H	CO_2CH_3
c	Et	CH_3	Bzl	H	CO_2CH_3
d	$C(CH_3)_3$	- C_6H_4- CO -		H	CO_2CH_3
e	Et	- C_6H_4- CO -		H	CO_2CH_3
f	Et	- C_6H_4- CO -		H	CCl_3
g	Et	Ph	H	SPh	CH_3
h	Et	CH_3	Bzl	SPh	CH_3

Table 1. Cycloaddition of **2a-d** and **3a-h**

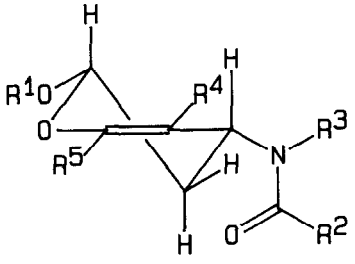
products	reaction conditions °C/h	yield %	ratio of isomers	m.p. °C
4/5 a	135/12	98	1.3:1[a]	109/150
b	140/60	78	1.3:1[a]	101/93
c	135/48	76	3.4:1[b]	-/-
d	110/48	90	2.9:1[b]	178/141
e	120/12	95	5.0:1[a]	121/139
f	120/16	94	1.5:1[a]	134/142
g	125/170	93	2.1:1[b]	82/137
h	134/130	89	3.2:1[b]	-/134

[a] taken from ^1H NMR data of crude products; [b] after isolation

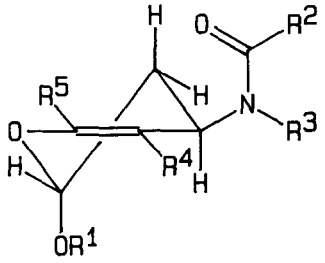
The different stability of **4** and **5** can be explained by comparing their preferred conformations. Thus **4a**, **4b** and **4g** exist predominately in conformation **K4I** with an unfavourable pseudo axial orientation of the amide-moiety; **4c**, **4d** and **4f** prefer conformation **K4II** which implies a less stable equatorial orientation of the OR-function due to the anomeric effect. The trans-diastereomers **5a-f** can exist in conformation **K5I** with the most stable orientation of all substituents. Only for the thio compounds, mixtures of conformers are found. It is possible to distinguish the different conformations by comparing the coupling constants $J_{2,3}$. In **K4II** a big and a small coupling constant (**4f** : 8.5/2 Hz) and in **K4I** and **K5I** two small coupling constants are found for 2-H (**4a**:2.2/2.2 Hz; **5f**: 2.7/2.7 Hz).



K4I

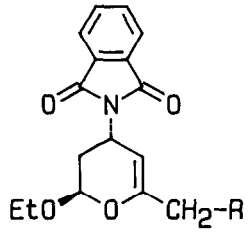


K4II

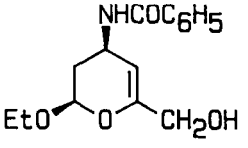


K5I

The cycloadducts **4** and **5** can easily be transformed into 3-amino sugar derivatives in different ways. Thus treatment of **5f** with 2 mol of tri-n-butyltin hydride gives the monochloro derivative **6a** (toluene, 90°C, 2 h, 56 %, m.p. 141°C), with 4 mol of the hydride **6b** is obtained (toluene, 100°C, 2 h, 45 % m.p. 120°C). Reduction of **4a** with lithium borohydride yields the alcohol 7. Finally the catalytic hydrogenation of **5g** with Raney nickel leads to (±)-methyl N-benzoyl-4-deoxy-ristosaminide **8** [8] in 65 % yield (MeOH, 60°C, 15 min, m.p. 116°C).



6a: R=Cl; 6b: R=H



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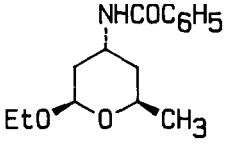

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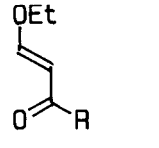

9a: R=CO_2CH_3
9b: R=CCl_3

The N-acyl enaminones **3a-e** and **3f** which were used in the cycloadditions can be obtained by treatment of the enol ethers **9a** [9] resp. **9b** [10] with ammonia or primary amines followed by acylation with acylchlorides (e.g. 1. Bzl-NH_2, THF, 20°C, 1 h; 2. CH_3COCl, Et_3N/DMAP, 50°C, 1 h; yield 70 - 95%). The synthesis of the thiocompounds **3g** and **3h** was achieved via a formylation of phenylthioacetone [11], treatment with ammonia or amines and N-acylation (yield: 70 - 90 %).

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** Intra- and Intermolecular hetero-Diels-Alder reaction: Part 13. Part 12: [6]

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7 ^{1}H NMR (200 MHz, $CDCl_3$): **4f**: δ= 7.80 (m, 4H, aromatic H), 5.74 (dd, J = 1.0, 3.0 Hz; 5-H), 5.24 (dd, J = 2.0, 8.5 Hz; 1 H, 2-H), 5.20 (ddd, J = 3.0, 7.0, 9.5 Hz; 1 H, 4-H), 4.10 (dq, J = 7.0, 9.6 Hz, 1 H, OCH_2CH_3), 3.75 (dq, J = 7.0, 9.6 Hz, 1 H, OCH_2CH_3), 2.62 (ddd, J = 8.5, 9.5, 13.0 Hz; 1 H, 3-H_{ax}), 2.18 (dddd, J = 1.0, 2.0, 7.0, 13.0 Hz; 1 H, 3-H_{eq}), 1.26 (t, J = 7.0 Hz, 3 H, OCH_2CH_3). - **5f**: δ= 7.80 (m, 4 H, aromatic-H), 5.74 (dd, J = 1.4, 2.5 Hz; 1 H, 5-H), 5.52 (t, J = 2.7 Hz; 1 H, 2-H), 5.34 (ddd, J = 2.5, 6.6, 11.0 Hz; 1 H, 4-H), 4.10 (dq, J = 7.0, 9.5 Hz; 1 H, OCH_2CH_3), 3.74 (dq, J = 7.0, 9.5 Hz; 1 H, OCH_2CH_3), 2.30 (ddd, J = 2.8, 11.0, 13.0 Hz; 1 H, 3-H_{ax}), 2.10 (dddd, J = 1.4, 2.6, 6.6, 13.0 Hz; 1 H, 3-H_{eq}), 1.26 (t, J = 7.0 Hz, 1 H, OCH_2CH_3).

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9a was synthesized according to the excellent procedure of Effenberger [10]: Cl-CO-CO_2Me, CH_2=CH-OEt, 0°C, 12 h, 67 % yield; the ethyl ester was obtained in 91 % yield.

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