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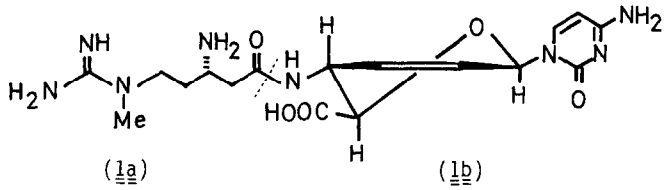
SYNTHESIS OF A URACININE DERIVATIVE via HETERO DIELS-ALDER REACTION [1)]

Richard R. Schmidt* and Adalbert Wagner
Fakultät Chemie, Universität Konstanz
D-7750 KONSTANZ, Germany

Abstract: *The regiospecificity of the O-acylated 1-hydroxy-4-amino butadiene derivative 8 in Diels-Alder reactions with unsymmetrical dienophiles was reversed with the O-silylated butadiene derivative 9. This enabled a short synthesis of the racemic uracinine derivative 4 to be carried out.*

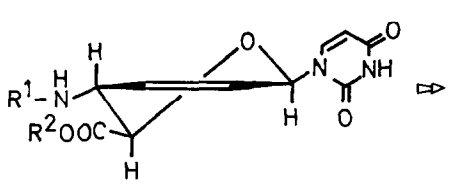
Blasticidin S (1) is a nucleoside antibiotic produced by *Streptomyces griseochromogenes* with excellent fungicidal properties in rice plants [2)]; in addition antiviral and antitumor activity has been reported [3)]. Cleavage of 1 led to blastidic acid (1a), cytosinine (1b), and uracinine (2), respectively [4)]. In the synthesis of 1b reported by KONDO, NAKAI, and GOTO [2)] tri-O-acetyl-galactal is transformed in many steps into the uracinine intermediate 3.

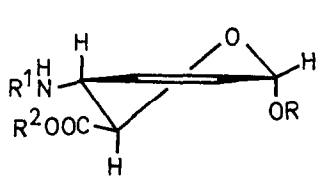
Scheme 1

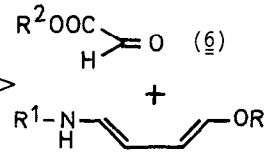


(1a) (1b)

(1): Blasticidin S







(2): $R^1 = R^2 = H$: Uracinine

(3): $R^1 = COCH_3$; $R^2 = CH_3$

(4): $R^1 = COOEt$; $R^2 = CH_3$

(5) (6) (7)

Our investigations into the synthesis of carbohydrates and related natural products via hetero Diels-Alder reactions [1] lead to a short route for the synthesis of 1b and 2, respectively: Disconnection of the glycosidic bond gives pseudoglycal uronate 5; its retrosynthetic Diels-Alder reaction yields glyoxylate 6 and a 4-amino-1-hydroxy-butadiene derivative 7. The uracinine derivative 4 was obtained as outlined in this retrosynthetic scheme.

The 1-benzoyloxy-4-ethoxycarbonylamino-butadiene 8 was successfully applied in HOMO-diene-LUMO-dienophile controlled Diels-Alder reactions [5]. However, with unsymmetrical CC-dienophiles and with heterodienophiles the only regioisomer obtained was that predicted on the basis of HOMO of 8 having a higher coefficient at C-1 than at C-4 (see 8A) leading with 6 to the wrong regioisomers [5,6]. A reversal of the regiochemistry could be obtained by decreasing the electron release of the 4-amino group or by increasing the electron donating ability of the 1-hydroxy group. Because an overall lower reactivity in Diels-Alder reactions was expected with the first structural variation, the second possibility was investigated by preparation of an O-silylated analogue.

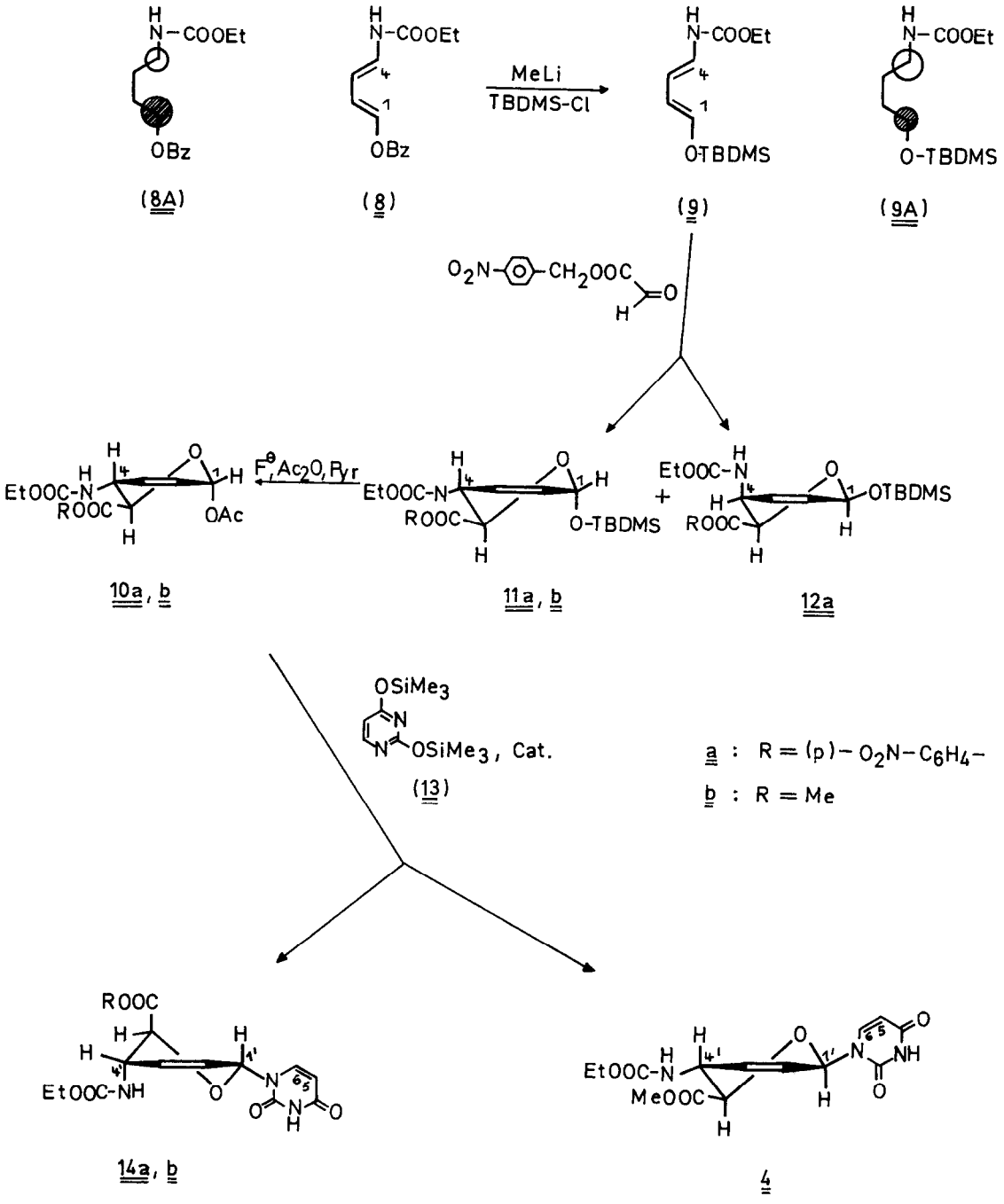
The benzoyl group of 8 was cleaved with methyllithium (THF, $0^{o}C$) and the O-lithiated intermediate silylated with tert.-butyl-dimethylsilylchloride (TBDMS-Cl) to give butadiene derivative 9 (crude 96 %, oil). Hetero Diels-Alder reaction with p-nitrobenzyl glyoxylate (C_6H_6, reflux, 40 h) yielded regiospecifically the expected 4-amino-4-deoxy-pseudoglycaluronate derivatives 11a and 12a (~1:1, 38 %; separation with petroleumether/ethylacetate = 7:3 on silica gel). Therefore the relative electron density in the HOMO at C-1 and C-4 of 9 is as suggested in 9A.

Because 1-O-acylpseudoglycals are excellent glycosylating agents [7] 11a was simultaneously desilylated and acylated using a combination of tetrabutylammonium fluoride, acetic anhydride/pyridine giving the α-anomer 10a (43 %, oil). However, N-glycosylation of 2.4-bis-(trimethylsilyloxy)-pyrimidine (13) with 10a using antimony pentachloride as catalyst (CH_2Cl_2, $25^{o}C$, 30 min) yielded exclusively the N-α-glycoside 14a (44 %, mp. 135-136°C) [8].

Earlier observations on the stereoelectronic influence of groups attached to the 6-position on the anomer ratio indicated that ß-glycoside formation may be favoured for methyl esters [9]. Therefore 11a was transesterified with sodium methoxide/methanol giving the corresponding methyl ester 11b (70 %, oil), which was activated by desilylation and acetylation (→ 10b, 52 %, oil). By glycosidation of 13 (AcOEt, r.t., $SbCl_5$, 40 min) the α- and ß-anomers 14b and 4 were obtained (~1:2, 68 %; 14b: oil, 4: mp. 139-140°C).

The structures of compounds 10a,b, 11a,b, 12a, 14a,b, and 4 were assigned by ^{1}H-NMR-data [10]. Because of the anomeric and/or allylic effect [11] compounds 10a,b, 11a,b and 12a prefer the $^{o}H_5$-conformation and 14a,b the $^{5}H_o$-conformation (see Scheme 2). However, the operation of these effects in 4 would force all substituents into sterically unfavoured axial positions. This may be the reason for the preference of the $^{o}H_5$-conformation in 4 [12].

Scheme 2 [a]



[a] The compounds are racemates; only one enantiomer is depicted.

1) De novo-Synthesis of Carbohydrates and Related Natural Products, Part 12 - This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.- Part 11, see ref. 5.

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8) Modification of the reaction conditions led to other byproducts but no β-anomer was formed.

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10) The isolated products gave satisfactory analytical and spectral data. ^{1}H-NMR-data ($CDCl_3$, TMS int.): 10a: δ 6.41 (m,1H,1-H); 6.02 (ddd,1H,3-H; $J_{2,3}$ = 10.0 Hz; $J_{1,3}$ = $J_{3,4}$ = 1.0 Hz); 5.88 (ddd,1H,2-H; $J_{1,2}$ = $J_{2,4}$ = 2.4 Hz, $J_{2,3}$ = 10.0 Hz); 4.58 (br.dd, 1H,4-H; $J_{4,5}$ = 9.2 Hz, $J_{4,NH}$ = 9.5 Hz); 4.36 (d,1H,5-H). 10b: δ 6.41 (br.s, 1H,1-H); 6.02 (dd,1H,3-H; $J_{2,3}$ = 10.0 Hz); 5.86 (ddd,1H,2-H; $J_{1,2}$ = $J_{2,4}$ = 2.5 Hz); 4.53 (br.dd,1H,4-H; $J_{4,5}$ = $J_{4,NH}$ = 9.2 Hz); 4.30 (d,1H,5-H). 11a: δ 5.84 (ddd,1H,3-H; $J_{2,3}$ = 10.0 Hz, $J_{1,3}$ = $J_{3,4}$ = 1.7 Hz); 5.78 (dd, 1H,2-H; $J_{1,2}$ = 1.7 Hz); 5.45 (d,1H,1-H); 4.56 (br.dd,1H,4-H; $J_{4,5}$ = $J_{4,NH}$ = 9.5 Hz); 4.37 (d,1H,5-H). 11b: δ 5.80 (dd,1H,3-H; $J_{2,3}$ = 10.0 Hz; $J_{3,4}$ = 1.2 Hz); 5.76 (d,1H,2-H); 5.46 (br.s,1H,1-H); 4.50 (br.dd,1H,4-H; $J_{4,5}$ = $J_{4,NH}$ = 9.2 Hz); 4.28 (d,1H,5-H). 12a: δ 5.99 (ddd,1H,3-H; $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 4.9 Hz, $J_{1,3}$ = 1.2 Hz); 5.83 (d,1H,2H); 5.41 (br.s, 1H,1-H); 4.53 (m,1H,4-H); 4.48 (d,1H,5-H; $J_{4,5}$ = 3.1 Hz). 14a: δ 7.48 (d,1H,6-H; $J_{5,6}$ = 8.6 Hz); 6.53 (br.s,1H,1'-H); 6.26 (ddd,1H,3'-H; $J_{2',3'}$ = 10.0 Hz, $J_{3',4'}$ = 4.7 Hz; $J_{1',3'}$ = 1.8 Hz); 5.85 (ddd,1H,2'-H; $J_{1',2'}$ = $J_{2',4'}$ = 1.7 Hz); 5.76 (d,1H,5-H); 4.66 (d,1H,5'-H; $J_{4',5'}$ = 4.3 Hz); 4.45 (m,1H,4'-H). 14b: δ 7.46 (d,1H,6-H; $J_{5,6}$ = 8.3 Hz); 6.45 (br.s, 1H,1'-H); 6.19 (ddd,1H,3'-H; $J_{2',3'}$ = 10.0 Hz, $J_{3',4'}$ = 4.6 Hz, $J_{1',2'}$ = 1.8 Hz); 5.76 (dd,1H,2'-H, $J_{1',2'}$ = 0.8 Hz); 5.68 (d,1H,5-H); 4.51 (d,1H,5'-H; $J_{4',5'}$ = 4.2 Hz); 4.52 (mc,1H,4'-H). 4: δ 7.45 (d,1H,6-H; $J_{5,6}$ = 8.2 Hz); 6.50 (s,1H,1'-H); 6.17 (d,1H,3'-H; $J_{2,3}$ = 10.0 Hz); 5.80 (d,1H,2'-H); 5.77 (d,1H,5-H); 4.60 (mc,1H,4'-H); 4.33 (d,1H,5'-H; $J_{4',5'}$ = 9.2 Hz).

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12) The ^{1}H-NMR data of the pseudoglycal moiety of 3 [2] and 4 show only slight chemical shift differences.

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