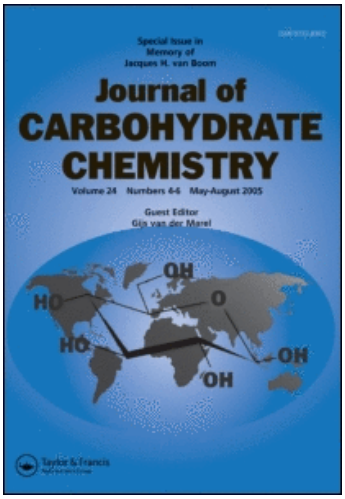

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Wojciech Karpiesiuk; Anna Banaszek

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COMMUNICATION

FIRST, HIGHLY STEREOSELECTIVE SYNTHESIS OF NEOTREHALOSAMINES

Wojciech Karpiesiuk and Anna Banaszek

Institute of Organic Chemistry, Polish Academy of Sciences
01-224 Warsaw, Poland

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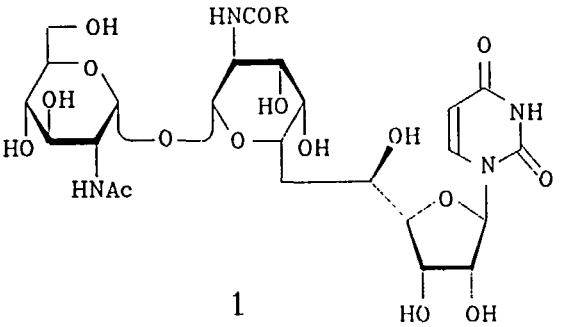
Among the known non-symmetrical naturally occurring aminotrehaloses possessing antimicrobial activity, the stereoselective synthesis of α,α-linked D-glucosaminyl-D-glucoside as well as of D-glucosaminyl-D-mannoside has been reported.[1] In contrast, the synthesis of the α,β-isomer composed of two 2-amino sugar units occurring in tunicamycin antibiotics 1 has not been studied to the same extent and is not readily obtainable in pure form.



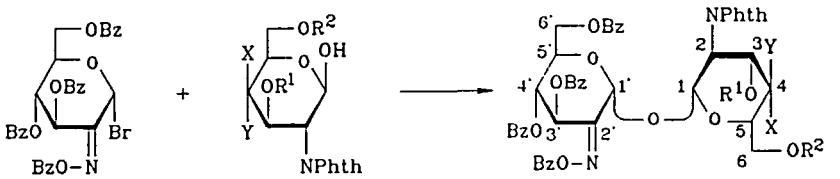
1

Recently syntheses of tunicamycins have been reported[2] but the nonselective construction of the neotrehalosamine part led to the desired α,β-glycosyl glycoside in an only low yield. Therefore, a more efficient synthetic method endowed with the potential for the synthesis of tunicamycin and its analogues is required.

We now wish to report a highly efficient stereoselective approach to α,β-trehalosamine-type disaccharides composed of two different 2-amino sugars. We envisioned that Lichtenthaler's et al.[3] methodology devised to synthesize oligosaccharides with an α-D-glucosamine unit from 3,4,6-tri-*O*-benzoyl-2-(benzoyloxoimino)-2-deoxy-α-D-glucopyranosyl bromide (2) would provide a useful strategy for the construction of non-symmetrical neotrehalosamines. We anticipated that the crucial creation of an α,β 1→1 glycosidic linkage would be achieved, due to stereochemical control exerted by the nonparticipating C-2 oxoimino group of bromide 2, leading to a 1,2-*cis* α-glycoside from one side, as well as by steric hindrance of the C-2 phthalimido group of the glycosylic acceptor 3 - 5,[4] furnishing a β-*trans* glycosidic linkage from the other side. As a result, kinetically controlled α,β-trehalose would be formed as the main product.

Our basic strategy is outlined in Scheme 1.

SCHEME 1



2 3, 4, 5 6, 7, 8 (main product: α,β)

3 → 6 X = H, Y = OAc, R^1 = R^2 = Ac

4 → 7 X = OAc, Y = H, R^1 = R^2 = Ac

5 → 8 X = OBn, Y = H, R^1 = Bn, R^2 = Ac

TABLE 1

Glycosylation conditions:

A: dioxane, TMU*, $AgSO_3CF_3$, r.t.
B: dioxane, DTBMP**, $AgSO_3CF_3$, r.t.
C: CH_2Cl_2, DTBMP, $AgSO_3CF_3$, -78 °C
D: CH_2Cl_2, *sym*-collidine, $AgSO_3CF_3$, -78 °C

* TMU = 1,1,3,3-tetramethylurea

** DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine

PRODUCT[a]	REACTION CONDITIONS	TIME (h)	YIELD (%) of α,β-TREHALOSE	RATIO α,β:OTHERS[b]
6[c]	A	48	12	4:1
	B	3	20	1:2
	D	1.5	80	>50:1
7[d]	B	3	34	4:5
	D	1	78	>50:1
8[e]	B	4	36	3:4
	C	2	51	5:1
	D	1.5	74	>50:1

a. Elemental analysis and NMR data for all new compounds were all in agreement with the postulated structure.
b. "Others" denote: β,β-isomer (main), and α,α and β,α (traces).
c. Amorphous powder, $[\alpha]_D^{20}$ +45.5° (*c* 3.1, $CHCl_3$).
d. Amorphous powder, $[\alpha]_D^{20}$ +27.3° (*c* 1.2, $CHCl_3$).
e. Mp 98-100 °C, $[\alpha]_D^{20}$ +78.1° (*c* 1.5, $CHCl_3$).

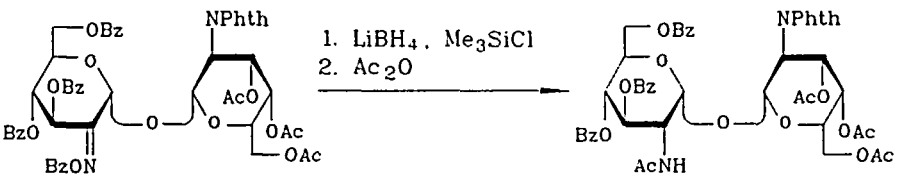
In order to find the optimal conditions for the condensation many experiments were carried out until we found that the use of silver triflate as a catalyst in the presence of *sym*-collidine in dichloromethane at -78 °C, provided under kinetic control the most

satisfactory results, giving the desired α,β-trehaloses 6 - 8 almost stereospecifically.[5] The results are summarized in Table 1.[6]

Compounds 6 - 8 are in fact the precursors of the desired neotrehalosamines; for their conversion to neotrehalosamines of type 9 the stereoselective, reductive amination of 3,4,6-tri-*O*-benzoyl-2-(benzoyloxoimino)-2-deoxy-α-D-glucopyranosyl residue is necessary, thus affording α-D-glucosamine unit. In principle, such amination has been successful[3] using diborane as the reducing agent. Nevertheless, alternative methods that allow selective reduction of oxoiminoester group would be of value.

While exploring different reducing agents, we have found that a $LiBH_4$-Me_3SiCl-THF mixture, first applied for the reduction of the carbonyl, nitro and cyano functions,[7] is the reducing species of choice for compounds 6 - 8. Stereoselective reduction of the imino group, with concomitant loss of the benzoyloxy group gives, after acetylation an N-acetyl-glucosaminyl unit (Scheme 2).

SCHEME 2



7 9

In a typical procedure Me_3SiCl (10 mmoles) was added dropwise to a solution of $LiBH_4$ (5 mmoles) in THF (5 mL) at -20 °C under argon. After ~ 1 h a solution of trehalose 7 (1 mmol) was slowly added at -20 °C, whereupon the reaction mixture was allowed to reach room temperature and kept there overnight. The reaction mixture was cooled, treated with methanol, and then concentrated under vacuo. The residue was acetylated with acetic anhydride to afford, after purification by chromatography (toluene-methanol

9:1) pure 9 in 60% yield: $[\alpha]_D^{18}$ +25.2° (c 0.5, $CHCl_3$); ^1H NMR (Bruker, 500 MHz, $CDCl_3$) δ 1.85, 2.05, 2.09, 2.17 (4s, 4 x 3H, NAc and 3 x OAc), 4.07 (m, 1H, H-5), 4.18-4.23 (m, 2H, H-6a and H-2'), 4.25-4.31 (m, 2H, H-6b and H-6a'), 4.39 (1H, H-6b'), 4.54-4.61 (m, 2H, H-2 and H-5'), 5.24 (d, 1H, H-1'), 5.50 (dd, 1H, H-4), 5.52-5.58 (m, 2H, H-3' and H-4'), 5.72 (d, 1H, H-1), 5.76 (dd, 1H, H-3), 6.54 (d, 1H, NH), 7.3-8.1 (m, 19H, arom.); $J_{1,2}$ = 8.5, $J_{2,3}$ = 11.4, $J_{3,4}$ = 3.4, $J_{4,5}$ = 0.8, $J_{1',2'}$ = 3.9, $J_{2',NH}$ = 9.5 Hz

ACKNOWLEDGMENT

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4. It is interesting to note that the reaction of 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-α-D-glucopyranosyl bromide with $Et_4N^+Cl^-$ led to a quantitative yield of the β-chloride, whereas the reaction of the β-bromide proceeded with 50% retention of the configuration; see R. U. Lemieux, T. Takeda and B. Y. Chung, in *Synthetic Methods for Carbohydrate Ed. by H. S. El Khadem, ACS Symposium Series*, 39, 90 (1976).

5. The α-configuration of 2-oxoimino-glucopyranosyl unit of products 6 - 8 was evidenced by the chemical shift values of H-1' (δ ~ 6.4) and C-1' (δ ~ 93) compared to that described for analogous α-glycosides[3] and distinct from their β-counterparts (δ ~ 5.9); see also K. Bock, C. Pedersen, and H. Pedersen, *Adv. Carbohydr. Chem. Biochem.*, **42**, 193 (1984). The β-configuration of 2-phthalimido-D-galactosaminyl as well as the D-glucosaminyl residue was confirmed from the coupling constants $J_{1,2}$ ~ 8.6 Hz.

6. A general procedure follows.- To a mixture of alcohol (**2**, **3** or **4**) (1 mmol), silver triflate (2.5 mmol) and *sym*-collidine (1.05 mmol) in dichloromethane (5 mL) containing molecular sieves 3A (~ 100 mg), a solution of bromide **2** (1.3 mmol) in dichloromethane (2 mL) was added dropwise at -78 °C under argon. After stirring for the required time (1-2 h), the reaction mixture was diluted with dichloromethane, filtered through celite and the filtrate was successively washed with an aq. solution of $Na_2S_2O_3$, water, 0.1 N HCl, sat. $NaHCO_3$ and water. Evaporation of solvent left a syrup which was passed through a silica gel column, with toluene-ethyl acetate (8:1) as eluent.

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