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SIMPLE SYNTHESIS OF *O,N*-PROTECTED TUNICAMINE - THE UNDECOSE PART OF TUNICAMYCINS

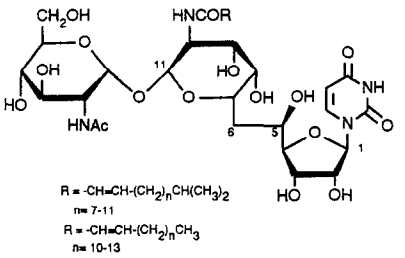
Wojciech Karpiesiuk and Anna Banaszek*

Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, Kasprzaka 44, POLAND

Abstract: The title compound **9** was synthesized by Wittig reaction of phosphonium salt **6** with aldehyde **7** to afford *Z*-olefin **8**, with subsequent following hydration *via* a hydroboration-oxidation process.

Tunicamycins have attracted the interest of many research groups on account of their major role in inhibition of the biosynthesis of glycoproteins[1]. This property of tunicamycins may be related to their inhibitory effect on several enzymes, involved in glycosylation processes[2]. The antimicrobial activities of tunicamycins are believed to be associated with their ability to inhibit abnormal processing glycosylation[3]. Nevertheless, further studies of the biological activities of tunicamycins are indispensable. In this connection synthetic products of high purity are best suited whereas the natural tunicamycins owing to the diversity of their *N*-acyl residues, are difficult to be obtained in a homogeneous state. On the other hand, tunicamycin is an interesting target due to its undecose structure, as it is a *C*-disaccharide composed of D-galactosamine and D-ribose, joined through their terminal carbons. Surprisingly, only few papers on the synthesis of the tunicamycin system have been published[4-7].

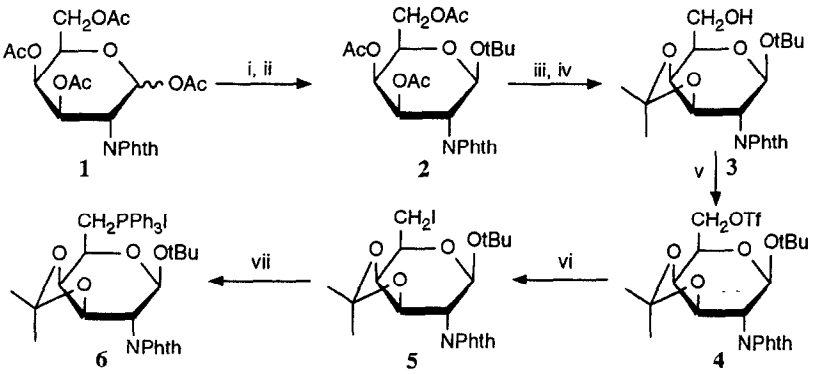
The tunicamycins



Seeking a simple and convenient procedure for the synthesis of the undecose structure we turned attention to the Wittig reaction which allows for coupling the terminal monosaccharide iodophosphonium ylide with the terminal sugar aldehyde[8]. However, it has been reported by Secrist[9] that the 6-phosphonium iodide of *O,N*-protected D-galactosamine failed to react with the aldehyde derived from β-D-ribofuranoside. Despite the reported results, we decided to examine this reaction, modifying the Secrist procedure. From this

standpoint well-selected protection of the functional groups of the Wittig partners was of importance. Thus, considering in advance the extension of tunicamine synthesis to that of tunicamycin, the amino group was blocked with the phthaloyl residue, owing to its stereodirecting role in stereoselective preparation of neotrehalosdiamines[10].

SCHEME I



i. HBr, AcOH; ii ^{t}BuOH, $AgSO_3CF_3$, s-collidine, CH_2Cl_2, -20°C; iii. MeONa, MeOH, 10 min; iv. acetone, $CuSO_4$, CSA; v. Tf_2O, pyridine, CH_2Cl_2; vi. nBu_4NI, DMF; vii. Ph_3P, sulfolane.

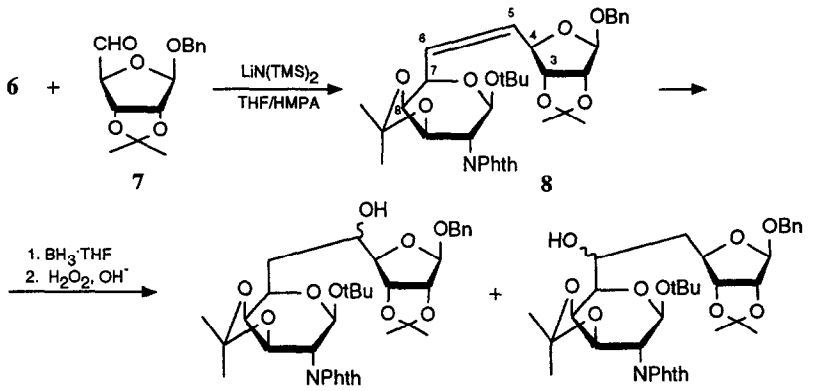
As outlined in Scheme I, the ^{t}butyl glycoside **2** was obtained in 85% yield as the only isolated product. Usual deacetylation, followed by the protection of 3,4-hydroxy groups with the isopropyl moiety, led to **3** (57%) accompanied by its 4,6-di-*O*-isopropylidene derivative easily convertable (on treatment with catalytic amount of camphosulfonic acid in acetone) to **3**. Attempts at direct iodination[11] of **3** to **5** either failed or gave the iodide **5** in a low yield. Therefore, the 6-OH group in **3** was first converted to the *O*-triflic derivative **4** (92% yield) which reacted with *n*-Bu_4NI in DMF to afford **5** (82%). Treatment of iodide **5** with PPh_3 in sulfolane at 110°C yielded the phosphonium iodide **6** (92%).

In keeping with earlier observations on relative sensitivity of the phthalimido group towards bases, the generation of the ylide from **6** required a milder base than BuLi used by Secrist[8,9]. Thus, the reaction was conducted by dropwise addition of HMDSLi (1 M solution in hexane) to a mixture of the phosphonium iodide **6** and aldehyde **7** in HMPA-THF solvents, at -70°C (Scheme II). Our procedure for deprotonation of **6** allowed for keeping the *N*-phthaloyl group intact, and for avoiding the well-known[12] competing, facile β-elimination process, thus giving the desired undecose derivative **8** in high yield (76%); no other reaction products were discernible.

The configuration of the chiral centers C-5 (D-*galacto*) and C-4 (D-*ribo*) of the parent monosaccharides **6** and **7**, respectively, was preserved in product **8**, as indicated by its ^{1}H NMR data ($J_{3,4}$ < 0.5 Hz; $J_{7,8}$ 2.3 Hz). The *Z*-configuration of the C-5–C-6 olefinic linkage was confirmed by coupling constants $J_{5,6}$ 11.2 Hz,

this being in full agreement with that reported by Secrist for an analogous undecose[8].

SCHEME II



9 (5 R)
10 (5 S)

11 (6 S)
12 (6 R)

To obtain the title tunicamine, introduction of a hydroxy group of *R* configuration at the C-5 position was required. For this purpose hydration based on the hydroboration-oxidation reaction was adopted (Scheme II). Unfortunately, olefin **8** lacks evident intra- or intermolecular stereodirecting factors[13]. Therefore, the structure of the hydroxylated products could hardly be predicted. To the best of our knowledge, the hydroboration-oxidation reaction has never been applied for any analogous olefin. Thus, in a typical experiment a solution of **8** in THF was treated with BH_3·THF at 0°C for 1 h. Standard oxidation (H_2O_2 - NaOH aq.) afforded alcohols **9-12** as a 61 : 10 : 21 : 8 (**9** : **10** : **11** : **12**) mixture of diastereoisomers, with evident predominance of the desired product **9** (5*R*). All stereoisomers, converted to their *O*-acetyl derivatives, were separated by chromatography. Their structure was deduced from the ^{1}H NMR data[14], being for **9** identical with those reported[5], and for **10-12** - comparable to those of analogous compounds[15,16]. Additionally, the structure of **9** was assigned by X-ray studies[17].

The stereochemical outcome of the hydration of **8** is very intriguing with regard to diastereofacial selection. Preferential formation of the diastereoisomers **9** and **11**, may be explained by Kishi model[18] invoking intermolecular hydroboration caused by steric hindrance for the attack on the opposite side of the olefinic linkage which should then lead to **10** and **12**. On the other hand, the highly favoured formation of the desired 5-OH regioisomer **9** (tunicamine) may result from intramolecular, oxygen-direct hydroboration of the furanose ring[13].

Thus, we are able to synthesize the tunicamine derivative **9** from readily available substrates on a large scale and in a high yield. Together with our earlier study on stereoselective synthesis of neotrehalosdiamines[10] and modeling synthesis of deaminotunicaminyluracil[15], the present findings offers a new and convenient route

to the tunicamycin system and its modified analogues.

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14. Characteristic ^{1}H NMR (500 MHz, $CDCl_3$) data of **9-12**: **9** (as 5-OAc derivative): δ 1.87 (ddd, 1 H, H-6a); 2.45 (ddd, 1 H, H-6b); 3.86 (dt, 1 H, H-7); 4.03 (dd, 1 H, H-4); 5.36 (ddd, 1 H, H-5); $J_{4,5}$ 6.1, $J_{5,6a}$ 10.0, $J_{5,6b}$ 2.0, $J_{6a,6b}$ 15.2, $J_{6a,7}$ 2.1, $J_{6b,7}$ 10.4 Hz; **10** (as 5-OAc derivative): δ 2.11-2.19 (m, 1 H, H-6a); 2.28 (ddd, 1 H, H-6b); 3.97 (dt, 1 H, H-7); 4.34 (dd, 1 H, H-4); $J_{4,5}$ 6.3, $J_{5,6b}$ 4.7, $J_{6a,6b}$ 14.2, $J_{6a,7}$ 7.3, $J_{6b,7}$ 7.1 Hz; **11** (as 5-OAc derivative): δ 2.00-2.05 (m, 1 H, H-5a); 2.11-2.16 (m, 1 H, H-5b); 3.97 (dd, 1 H, H-7); 4.33 (t, 1 H, H-4); 5.49 (ddd, 1 H, H-6); $J_{4,5a}$=$J_{4,5b}$ 7.5; $J_{5a,6}$ 4.8, $J_{5b,6}$ 8.0, $J_{6,7}$ 6.8 Hz; **12**: δ 1.79 (ddd, 1 H, H-5a); 2.21 (ddd, 1 H, H-5b); 3.71 (dd, 1 H, H-7); 4.30 (m, 1 H, H-6); 4.55 (dd, 1 H, H-4); $J_{4,5a}$ 5.4, $J_{4,5b}$ 9.6, $J_{5a,5b}$ 14.4, $J_{5a,6}$ 9.4, $J_{5b,6}$ 2.5, $J_{6,7}$ 8.3 Hz. All these data closely correspond to those of their anologues having 1,2;3,4-di-*O*-isopropylidene-galactose moiety instead of *N*-phthaloyl-galactopyranoside[15]. The structure of those two products (*i.e.* the counterparts of **9** and **12**) has been additionally established by X-ray studies[16].
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