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The Wittig reaction with 2-deoxysugars: the role of triphenyl and trialkyltin halides

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Abstract—The application of the Wittig reaction to prepare chain-extended polyols starting from protected 2-deoxysugars has been investigated. The standard conditions cause alcohol elimination from the deoxysugar, leading to a diene. Triphenyl and tributyltin halides have been found to prevent alcohol elimination, so that the expected alkene is produced.

The importance of the Wittig reaction in organic synthesis can hardly be overestimated. Its use in the synthesis of naturally occurring molecules and as a general method for the preparation of alkenes has made it one of the cornerstones of synthetic chemistry. Over the years, the original Wittig reaction has evolved to include many variations that constitute some of the most powerful processes for the construction of carbon–carbon bond frameworks.[1] Wittig and related reagents have also been used with sugar derivatives, with which they have been successful in producing chain-extended sugars and related compounds. Having a carbonyl function, even though hidden in the cyclic form, ketoses and aldoses are cheap and commercially available substrates for the Wittig reaction, allowing to obtain the chain extension of an enantiomerically pure polyfunctionalized compound.[2] No applications of the Wittig reaction using 2-deoxysugars as substrates have been reported until a Schimdt's paper in 1995.[3] In this work, the classic Wittig reaction was applied to tri-*O*-benzyl-2-deoxygalactose to obtain the proper alkene in good yield, in order to synthesize natural phytosphingosine.

Carrying out a synthetic project[4] directed toward the preparation of 2-deoxy analogs of agelasphin,[5] a biologically active glycosphingolipid isolated from marine sponges, we needed to use the Wittig reaction, the key step for the preparation of the desired phytosphingosine, starting from 6-*O*-TIPS-3,4-di-*O*-benzyl-2-deoxygalactose **1a**. This compound is usually prepared in our laboratory using a recently reported procedure:[6] 6-*O*-TIPS-3,4-di-*O*-benzylgalactal is treated first with *N*-iodosuccinimide (NIS) in CH_3CN–H_2O and then with $Na_2S_2O_4$ to remove the iodine atom. According to the literature,[3] the protected 2-deoxysugar **1a** was then allowed to react with the ylide obtained from *n*-dodecyltriphenylphosphonium bromide and *n*-BuLi. However, in spite of our many attempts in different experimental conditions, the diene **3a**[7] was exclusively obtained, deriving from benzylic alcohol elimination in the open-ring sugar followed by Wittig reaction of the resulting enone. It is to be noted that the same diene has been reported as the only product of the Wittig reaction with 2-deoxysugars when *t*-BuOK, instead of *n*-BuLi, is used to generate the ylide.[3]

Surprisingly, when a different batch of 2-deoxysugar, prepared using Ph_3SnH instead of $Na_2S_2O_4$ for the removal of the iodine atom, was used, the target alkene **2a**[8] was obtained in 78% yield. It seemed clear that the different outcome was due to some product present in one of the two batches of 2-deoxysugar, which we were not able to remove during the purification. We carefully examined the batch prepared with $Na_2S_2O_4$, and found no impurity. As for the batch prepared with Ph_3SnH, an obvious possibility was that an impurity deriving from this latter compound could be present in the sample. To check this possibility we recorded a ^{119}Sn NMR spectrum. It showed peaks at δ −45.9, −114.4, and −144.5, confirming the presence of tin-containing impurities in the sample. A preparative HPLC separation of this sample allowed us to isolate a compound, whose MS spectrum displayed a peak at m/z 401, corresponding to $[^{120}SnPh_2I]^+$, in agreement[9] with the impurity being Ph_3SnI. At this point, we prepared an authentic sample of Ph_3SnI from commercially avail-

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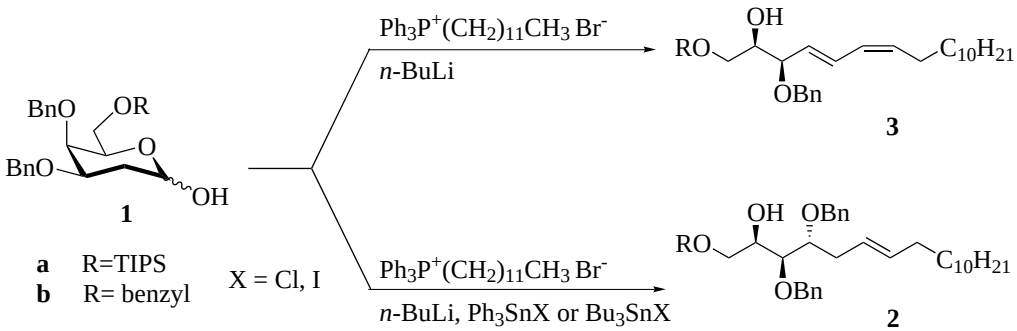
able Ph_3SnCl and NaI, as reported.[9] The ^1H and ^{119}Sn (δ −114.4) NMR spectra of this synthetic compound results were identical to those of the impurity present in our sample.



To prove that the isolated impurity was actually responsible for the different outcome of the reaction, we performed the Wittig reaction using a mixture of compound **1a** synthesized with $NIS/Na_2S_2O_4$ and 0.2 equivalents of Ph_3SnI. The reaction gave the alkene **2a** in good yield (Table 1, entry 2), while only trace amounts of the diene **3a** were obtained. In order to make sure that the method of preparation of the 2-deoxysugar had no influence on the reaction, we also used a 2-deoxysugar prepared in another way, namely 3,4,6-tri-*O*-benzyl-2-deoxygalactose **1a** obtained by treatment of 3,4,6-tri-*O*-benzylgalactal with aqueous H_2SO_4.[3] Also with this substrate, the Wittig reaction performed without Ph_3SnI gave only the diene **3b**, while the alkene **2b** was obtained in the presence of 0.2 equivalents of Ph_3SnI (Table 1, entry 4).

Because Ph_3SnI is not commercially available, it was interesting to find out if the cheap and readily available Ph_3SnCl, Bu_3SnI, and Bu_3SnCl were also effective. As shown in Table 1, all these compounds can drive the reaction toward the expected alkene. The reactions were performed with 0.5 equivalents of tin halides, because the yield of the reaction performed using 0.2 equivalents of Ph_3SnCl was unsatisfactory. In addition, we found that larger amounts (1 equivalent) of Ph_3SnCl do not affect the yield.

A typical experimental procedure, as applied to 3,4,6-tri-*O*-benzyl-2-deoxygalactose **1b**, is as follows. Commercially available Ph_3SnCl (0.5 mmol, 193 mg) was dissolved in 10 ml of dry CH_2Cl_2 and added to compound **1b** (416 mg, 1 mmol), prepared from 3,4,6-tri-*O*-acetyl-D-galactal according to the reported procedure.[6] Then, the ylide was prepared from 4 mmol of *n*-BuLi (2.5 ml of a 1.6 M solution in *n*-hexane) and 5 mmol (2.56 g) of *n*-dodecyltriphenylphosphonium bromide in 8 ml of dry toluene (an excess of ylide was always used, because the presence of the acidic hydroxyl proton in the 2-deoxysugar). The 2-deoxysugar, dissolved in CH_2Cl_2, was then added dropwise to the Wittig reagent and allowed to react at room temperature for 2 h. The reaction mixture was then diluted with 400 ml of CH_2Cl_2 and washed with water (three times, 400 ml each), followed by brine (400 ml). The organic layer was purified by column chromatography (*n*-hexane/EtOAc, 8:2) to give 480 mg of (2*R*,3*S*,4*R*)-1,3,4-tri-*O*-benzyloctadec-6-ene-1,2,3,4-tetrol **2b** (80% yield) as a mixture of *E*/*Z* stereoisomers, identified by comparison of its ^1H and ^{13}C spectra with those reported.[3]

In conclusion, the Wittig reaction can be used to extend the chain of protected 2-deoxysugars, leading to diastereomerically and enantiomerically pure tetrols or triols, depending on the reaction conditions. If catalytic amounts of triphenyl or tributyltin halides are added to the reaction mixture, the expected alkene is obtained in good yield, otherwise alcohol elimination occurs and a diene is the only product. Both products are useful substrates in the synthesis of glycosphingolipids as precursors of phytosphingosine and sphingosine, respectively. The mechanism by which triphenyl or tributyltin halides can affect the outcome of the reaction is still unknown, and it will be object of further studies in our laboratory.

Table 1. Effect of trialkyl or triaryltin halides on Wittig reaction of 3,4,6-tri-*O*-benzyl-2-deoxygalactose

Entry	Substrate (equiv.)	Trialkyl or triaryltin halide (equiv.)	*n*-BuLi (equiv.)	n-$C_{12}H_{25}PPh_3Br$ (equiv.)	**2b**, Yield (%)	**3b**, Yield (%)
1	**1a**, 1.0	–	4.0	5.0	–	60
2	**1a**, 1.0	Ph_3SnI, 0.2	4.0	5.0	78	–
3	**1b**, 1.0[a]	–	4.0	5.0	–	70
4	**1b**, 1.0[a]	Ph_3SnI, 0.2	4.0	5.0	81	–
5	**1b**, 1.0	Ph_3SnCl, 0.2	4.0	5.0	40	12
6	**1b**, 1.0	Ph_3SnCl, 0.5	4.0	5.0	80	–
7	**1b**, 1.0	Ph_3SnCl, 1.0	4.0	5.0	83	–
8	**1b**, 1.0	Bu_3SnCl, 0.5	4.0	5.0	85	–
9	**1b**, 1.0	Bu_3SnI, 0.5	4.0	5.0	68	–

[a] Prepared with aqueous H_2SO_4.

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7. (2*R*,3*R*,4*E*,6*Z*)-3-*O*-Benzyl-1-*O*-TIPS-4,6-octadecadiene-1,2,3-triol **3a**: $[\alpha]_D^{25}$ −6.1 ($CHCl_3$, $c=3.9$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30–7.22 (5H, m, aromatic protons), 6.49 (1H, dd $J=15.1$ and 11.1 Hz, H-5), 5.93 (1H, t, $J=11.1$ Hz, H-6), 5.57 (1H, dd, $J=15.1$, 7.7 Hz, H-4), 5.41 (1H, m, H-7), 4.55 (1H, $J=11.8$ Hz, benzylic proton), 4.32 (1H, $J=11.8$ Hz, benzylic proton), 3.95 (1H, t, $J=7.7$ Hz, H-3), 3.65 (1H, dd, $J=9.9$ and 4.7 Hz, H-1a), 3.62 (1H, dd, $J=9.9$ and 4.1 Hz, H-1b), 3.59 (1H, m, H-2), 2.61 (1H, m, OH-2), 2.11 (2H, q, $J=14.7$, 7.3 Hz, H_2-8), 1.25 (alkyl chain CH_2 protons), 1.10 (3H, m, TIPS methine protons), 1.08 (TIPS methyl protons), 0.88 (3H, t, $J=7.0$ Hz, H_3-18); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.4 (CH, C-7), 129.5 (CH, C-5), 129.0 (CH, C-4), 128.5–127.7 (CH, aromatic carbons), 127.0 (CH, C-6), 79.4 (CH, C-3), 73.7 (CH, C-2), 69.7 (CH_2, benzylic methylene group), 63.2 (CH_2, C-1), 29.7–29.2 (alkyl chains CH_2 groups), 27.3 (CH_2, C-8), 18.0 (CH_3, TIPS methyl groups), 14.1 (CH_3, C-18), 11.8 (CH, TIPS methine groups); HRFABMS (triethanolamine, negative ion mode): m/z 543.4201 ($C_{34}H_{59}O_3Si$, calcd 543.4233).
8. (2*R*,3*S*,4*R*)-3,4-Di-*O*-benzyl-1-*O*-TIPS-octadec-6-ene-1,2,3,4-tetrol (approx. 3:1 *Z*/*E* mixture) **2a**: $[\alpha]_D^{25}$ −3.7 ($CHCl_3$, $c=0.9$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 35–7.28 (10H, m, aromatic protons), 5.56–5.38 (2H, m, H-6 and H-7), 4.70 (1H, d, $J=11.8$ Hz, benzylic proton), 4.61 (2H, s, benzylic protons), 4.60 (1H, d, $J=11.8$ Hz, benzylic protons), 3.97 (1H, m, H-2), 3.79–3.70 (4H, m, H_2-1, H-2, and H-4), 3.11 (1H, br. s, 2-OH), 2.51–2.37 (2H, m, H_2-5), 2.03–1.96 (2H, m, H_2-8), 1.25 (alkyl chain CH_2 protons), 1.08 (TIPS methine protons), 1.05 (TIPS methyl protons), 0.88 (3H, t, $J=7.0$ Hz, H_3-18); ^{13}C NMR (125 MHz, $CDCl_3$): δ 132.2 (CH, C-7), 128.7–127.6 (CH, aromatic carbons), 124.4 (CH, C-6), 80.1 (CH, C-3), 78.1 (CH, C-4), 73.7 (CH_2, benzylic methylene group), 72.5 (CH_2, benzylic methylene group), 71.3 (CH, C-2), 63.8 (CH_2, C-1), 34.2 (CH_2, C-5, *E* isomer), 32.7 (CH_2, C-8, *E* isomer), 29.7–29.2 (CH_2, alkyl chains CH_2 groups), 29.0 (CH_2, C-5, *Z* isomer), 27.6 (CH_2, C-8, *Z* isomer), 18.0 (CH_3, TIPS methyl groups), 14.1 (CH_3, C-18), 11.8 (CH, TIPS methine groups); HRFABMS (triethanolamine, negative ion mode): m/z 652.4792 ($C_{41}H_{67}O_4Si$, calcd 652.4809).
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