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THE STILL-WITTIG REARRANGEMENT IN THE PREPARATION OF A SYNTHETICALLY USEFUL 4C-HYDROXYMETHYL-HEX-2-ENO-PYRANOSIDE

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ABSTRACT: The Still-Wittig rearrangement of the stannyl-ether **9** is successfully carried out under optimal reaction conditions to give the 4C-hydroxymethy-hex-2-enopyranoside **10** in good yields (70–74%).

Unsaturated sugars typified by the 1,2-dideoxy-hex-1-enopyranosides and the 2,3-dideoxy-hex-2-enopyranosides undergo a wide variety of chemical reactions[1] and consequently, they are commonly employed in organic synthesis.[2] The reactions that are commonly carried out on these unsaturated sugars are the Claisen rearrangement and its modified versions.[3] These reactions are especially useful for the introduction of functionalized two-carbon units into the molecule and are effective for stereospecific preparation of C-branched unsaturated sugars. However, the use of the corresponding [2,3]-Wittig rearrangement[4] for the placement of functionalized one-carbon units, such as the hydroxymethyl group, into the unsaturated sugar moiety has been limited only to the reaction **1** → **2** + **3**.

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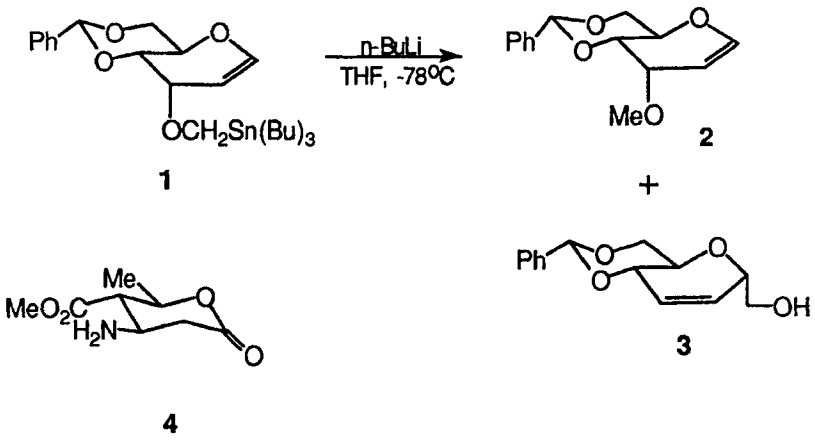
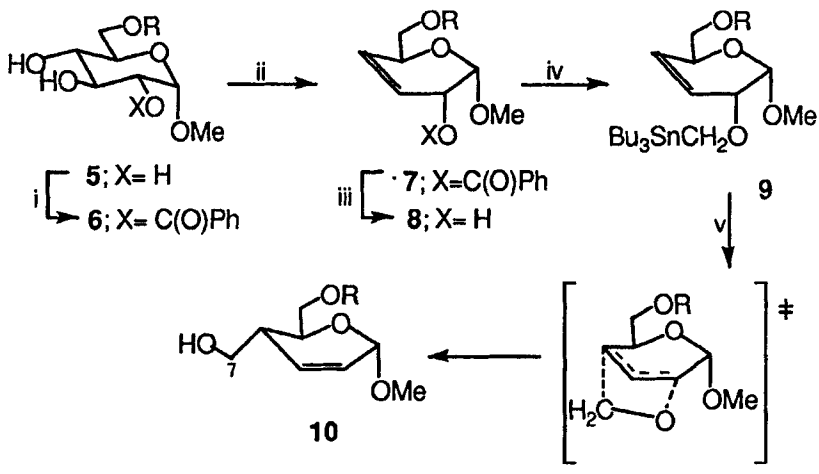
Tulshian and Fraser-Reid reported[3b] that the Still-Wittig[4] rearrangement of the stannyl-ether **1** proceeded to give only a very low yield (25%) of the desired C-glycoside **3**; the majority of the product was the methyl ether **2** (75%) resulting from proton abstraction by the incipient carbanion.



1 **2** **3** **4**

We have been interested in the preparation of the 4C-hydroxymethyl-hex-2-enopyranoside **10** from the stanny-ether **9**, which is readily obtained from methyl α-D-glucoside. The application of the Still-Wittig rearrangement reaction to 3,4-dideoxy-hex-3-enopyranosides have not been reported. We report, here, that the Still-Wittig rearrangement protocol is sucessfully employed for the conversion, **9→10**. Compound **10** is a useful chiral intermediate that is rich in functional groups; for example, it already possesses two of the three stereogenic centers present in **4** and can be readily converted to **4**. Compound **4** is the key intermediate[5] used for the synthesis of the medicinally important antibiotic, thienamycin.



a, R=t-BuPh$_2$Si. i) (n-Bu)$_2$SnO, MeOH; PhC(O)Cl, Et$_3$N, 1,4-dioxane. ii) Ph$_3$P, CHI$_3$, imidazole, PhMe. iii) NaOMe, MeOH-CH$_2$Cl$_2$. iv) KH, THF; (n-Bu)$_3$SnCH$_2$I, Bu$_4$NI, THF. v) n-BuLi, THF, -84°C; NH$_4$Cl.

Scheme I[a]

The synthesis of the Still-Wittig precursor **9** is shown in Scheme I. Selective benzoylation of the known triol **5**[6] using the procedure of Munavu and Szmant[7] provided an excellent yield (92%) of the 2-O-benzoate **6**. Subsequent treatment of **6** with iodoform-triphenylphosphine[8] gave the unsaturated benzoate **7** in high yield (94%). It is noteworthy that 6-O-desilylation did not occur, suggesting that the reductive-elimination reaction conditions used here are mild.[9]

Removal of the benzoyl group in **7** using NaOMe in dry MeOH proceeded uneventfully to yield the allylic alcohol **8**[3a] ($[\alpha]_D^{23.5}$ -7.09; c 1.07, $CHCl_3$) in 99% yield. Treatment of **8** with KH in dry THF generated the corresponding alkoxide

which was alkylated with n-Bu_3SnCH_2I,[10] in the presence of a catalytic amount of Bu_4NI, to give the stannyl-ether **9** in 93% yield.

Compound **9** was readily characterised by NMR; in the ^1H NMR, the stannylmethylene protons appear as a pair of AB doublets (J= 10.0 Hz), one centered at δ 3.76 and the other at δ 3.82, and in its ^{13}C NMR, the C-6 and the stannylmethylene carbon resonated at δ 59.91 and δ 75.77, respectively.

Having the stannyl-ether **9** in hand, the key rearrangement reaction was examined. Treatment of a 0.05M solution of compound **9** in dry THF with 1.5 equivalent of n-BuLi at -78°C for 2h and, followed by NH_4Cl quench, afforded a 55–60% yield of the homoallylic alcohol **10**. The methyl ether arising from protonation of the carbanion intermediate was not detected. Further experiments (varying reaction time, reaction temperature, and the amount of n-BuLi) were conducted in order to optimize the yield of **10**. When the reaction was conducted at -40°C (1.5 eq. n-BuLi) for 30 min and then quenched, the yield of **10** was 58%. Conducting the reaction at -78°C (3h), but employing 10 equivalent of n-BuLi[11] resulted in a lower yield of **10** (33–55%). The optimal yield of **10** (70–74%) was obtained when the rearrangement was carried out at -84°C and using 1.5 equivalent of n-BuLi. It was also noted that for larger scale reactions (≈ 0.8–1.0 g) a lower yield (50–63%) of **10** was obtained.

The salient features of the ^1H NMR of **10** are the multiplet at δ 3.48–3.70 attributed to the C-7 methylene protons and a broad hump ranging from δ 2.60–2.96 due to the hydroxyl group. In its ^{13}C NMR the C-6 signal resonated at δ 63.43 and the C-7 signal was observed at δ 66.19.

In summary, we have shown that the Still-Wittig rearrangement of compound **9** is sucessfully effected at -84°C using 1.5 eq. of n-BuLi and at a reaction scale of ≈0.50–0.60 g of **9**. This procedure is suited for the preparation of the synthetically useful compound **10**. Also, it is found that the iodoform-triphenylphosphine method is a mild method for effecting reductive-elimination in the presence of a 6-O-(tert-butyldiphenylsilyl) group.

Experimental.

For general procedures, see reference 12. Optical rotations were measured using an Optical Activity AA-5 polarimeter at the sodium-D line (589.6 nm). Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl, dichloromethane and toluene were dried by distillation from calcium hydride, and methanol was dried by distillation from magnesium methoxide.

Methyl 2-O-benzoyl-6-O-(tert-butyldiphenylsilyl)-α-D-glucopyranoside (6).

Dibutyltin oxide (11.9g, 47.9 mmol) was added to the triol[6] **5** (20.6 g, 47.6 mmol) in dry methanol (190 mL) and the resulting milky mixture was refluxed until it became homogenous and clear. After an additional 30 min., the mixture was evaporated to give a thick oil, which was dried under high vacuum overnight. The 2,3-O-dibutylstannylene, obtained as a white foam, was dissolved in dry 1,4-dioxane (324 mL) and dry triethylamine (7.3 mL, 52.4 mmol) was added. Then benzoyl chloride (6.3 mL, 54.3 mmol) was added dropwise at R.T. and, after a brief period, some inorganic salts were precipitated. After 15 h, the salts were filtered off, the residue washed with 1,4-dioxane (20 mL) and the combined filtrates were concentrated. The resulting syrup was chromatographed (EtOAc-

petroleum ether, 1:2) to provide 23.7 g (93%) of **6**. $[\alpha]_D^{23.5}$ + 58.5° (c. 1.20, $CHCl_3$). IR υ_{max}(CH_2Cl_2, film): 3430, 1720, 1600, 1580, 1500 cm^{-1}. ^1H NMR, δ: 1.12 (s, 9H, t-Bu), 2.90-3.30 (br hump, 2H, OH), 3.33 9s, 3H, OMe), 3.71 (dd, 2H, H-6, J= 5.1, 1.5 Hz), 3.91 (m, 2H, H-4, H-5), 4.06-4.19 (m, 1H, H-3), 4.91 (dd, 1H, H-2, J= 9.6, 3.6 Hz), 4.98 (d, 1H, H-1, J= 3.6 Hz), 7.35-7.60 (m, 10H, Ph-H), 7.65-7.75 (m, 3H, Ph-H), 8.13 (d, 2H, Ph-H, J= 7.6 Hz). ^{13}C NMR, δ: 19.14, 26.74, 55.02, 64.32(-), 70.38, 71.70, 72.36, 73.78, 96.93, 127.70, 128.32, 129.51, 129.78, 129.85, 132.97, 133.23, 135.57, 166.39. Anal. Calcd for $C_{30}H_{30}O_7Si$: C, 67.12; H, 6.76. Found: C, 66.91; H, 6.76.

Methyl 2-O-benzoyl-6-O-(tert-butyldiphenylsilyl)-3,4-dideoxy-α-D-hex-3-enopyranoside (7).

Ph_3P (3.03 g, 11.6 mmol), imidazole (0.393 g, 5.774 mmol) and recrystallized iodoform (2.27 g, 5.77 mmol) were added to a solution of the diol **6** (1.52 g, 2.83 mmol) in dry toluene (80 mL). The reaction mixture was refluxed for 40 min., cooled to R.T. and then transferred to a separatory funnel. The remaining brown gummy residue was washed several times with ethyl acetate (15 mL). The combined organic phases were washed with satd. $NaHCO_3$ (2 x 50 mL), dried, filtered and concentrated. The residue was chromatographed (Et_2O-petroleum ether, 1:8) to yield **7** as a colorless oil (1.34 g, 94%). $[\alpha]_D^{23.5}$ –34.3° (c 1.24, $CHCl_3$). IR υ_{max}(film): 1720, 1613, 1600, 1581, 1500 cm^{-1}. ^1H NMR, δ: 1.10 (s, 9H, t-Bu), 3.46 (s, 3H, OMe), 3.78 (dd, 1H, H-6, J= 10.0, 6.0 Hz), 3.83 (dd, 1H, H-6', J= 10.0, 5.5 Hz), 4.23-4.35 (m, 1H, H-5), 5.22 (d, 1H, H-1, J= 4.5 Hz), 5.49-5.59 (m, 1H, H-2), 5.83 (br d, 1H, H-3, J= 10.5 Hz), 6.06 ("dt", 1H, H-4, J=

10.5, 1.9, 1.9 Hz), 7.30-7.65 (m, 10H, Ph-H), 7.62-7.75 (m, 3H, Ph-H), 8.10 (d, 2H, Ph-H, J= 7.6 Hz). ^{13}C NMR, δ: 19.34, 26.90, 53.47, 56.00, 65.97, 67.39, 69.07, 96.05, 122.95, 127.77, 128.41, 129.82, 129.90, 133.21, 133.47, 135.67, 135.71, 166.14. Anal. Calcd for $C_{30}H_{34}O_5Si.¼H_2O$: C, 71.05; H, 6.86. Found: C, 70.92; H, 6.88.

Methyl 6-O-(tert-butyldiphenylsilyl)-2-O(tributylstannylmethyl)-3,4-dideoxy-α-D-erythro-hex-3-enopyranoside (9).

KH (35% dispersion in mineral oil, 0.208 g, 5.19 mmol) was washed with dry THF (2x 4 mL), under N_2 and then dry THF (40 mL) was added. The suspension was cooled to 0°C and a solution of **8** (1.01 g, 2.54 mmol) in dry THF (5 mL) was added, via cannula, to the suspension. After addition was complete, the ice bath was removed and the mixture warmed slowly to R.T. During this time there was vigorous evolution of H_2 gas. The mixture was recooled to 0°C after 1 h, Bu_4NI (0.982 g, 2.66 mmol) was added and a solution of Bu_3SnCH_2I (1.49 g, 3.44 mmol) in dry THF (5 mL) was slowly added via cannula. Then the mixture was warmed slowly to R.T. , stirred at R.T. for 1 h and t-BuOH (1 mL) was added. MeOH (4 mL), satd. NH_4Cl solution (8 mL) and water (5 mL) were added, successively, followed by EtOAc (15 mL). The aqueous layer was removed and the organic phase was washed with brine (2x 25 mL), dried, filtered and concentrated. Chromatographic separation of the residue (ether-petroleum ether, 1:16) provided 1.69 g (95%) of the stannyl ether **9** as a colorless oil. $[\alpha]_D^{23.5}$ -16.7° (c, 1.20, $CHCl_3$). IR υ_{max}(neat): 1600, 1590, 1550, 1500 cm^{-1}. ^1H NMR, δ: 0.66-0.96 (m, 15H, 3[$SnCH_2$], 3Me), 1.03 (s, 9H, t-Bu), 1.14-1.68 (m, 12H, 3[$(CH_2)_2$], 3.44

(s, 3H, OMe), 3.62 (dd, 1H, H-6, J= 10.0, 6.0 Hz), 3.72 (dd, 1H, H-6', J= 10.0, 5.0 Hz), 3.76 (d, 1H, OCHSn, J= 10.0 Hz), 3.82 (d, 1H, OCHSn, J= 10.0 Hz), 4.10-4.20 (m, 1H, H-2), 4.98 (d, 1H, H-1, J= 4.0 Hz), 5.66-5.86 (m, 2H, H-3, H-4), 7.26-7.50 (m, 6H, Ph-H), 7.57-7.78 (m, 4H, Ph-H). ^{13}C NMR, δ: 9.02, 13.73, 19.27, 27.30, 29.11, 29.31, 55.80, 59.91, 66.17, 69.36, 75.77, 96.83, 124.91, 127.42, 127.64, 129.65, 133.54, 135.60, 135.66. Anal. Calcd for $C_{36}H_{58}O_4SiSn$: C, 61.61; H, 8.34. Found: C, 61.53; H, 8.52.

Methyl6-O-(tert-butyldiphenylsilyl)-4-C-(hydroxymethyl)-2,3,4-trideoxy-α-D-erythro-hex-2-enopyranoside (10).

A solution of compound **9** (0.550 g, 0.790 mmol) in dry THF (15 mL) was cooled to -84°C (CO_2 slurry in acetone), under argon, and followed by dropwise addition of n-BuLi (0.90 mL, 1.19 mmol, 1.32M in hexane). After 3 h, the reaction was judged complete by t.l.c. and satd. NH_4Cl (3 mL) was added to the mixture. The reaction mixture was allowed to warm slowly to R.T., and EtOAc (10 mL) followed by brine (10 mL) were added. The aqueous layer was removed and reextracted with more EtOAc (3 x 15 mL). The combined organic layers were dried, filtered and evaporated *in vacuo* to give the crude product **6**. Purification by chromatography (EtOAc-petroleum ether, 1:4) gave pure **10** (0.239 g, 74%). $[\alpha]_D^{23.5}$ +31.5° (c 1.11, $CHCl_3$). IR υ_{max}(film, CH_2Cl_2): 3575–3275, 1600, 1589, 1500 cm^{-1}. ^1H NMR, δ: 1.04 (s, 9H, t-Bu), 2.36-2.58 (m, 1H, H-4), 2.60-2.96 (br hump, 1H, OH), 3.32 (s, 3H, OMe), 3.48-3.70 (m, 2H, H-7), 3.70-4.00 (m, 3H, H-5, H-6), 4.83 (d, 1H, H-1, J= 2.0 Hz), 5.84 (br s, 2H, H-2,H-3), 7.31-7.60

(m, 6H, Ph-H), 7.68-7.88 (m, 4H, Ph-H). ^{13}C NMR, δ: 19.23, 26.84, 40.58, 55.12, 63.43(-), 66.19(-), 70.40, 95.08, 126.40, 127.83, 129.90, 130.90, 133.04, 135.68. Anal. Calcd for $C_{24}H_{32}O_4Si$: C, 69.85; H, 7.82. Found: C, 70.14; H, 7.84.

Compound **10** was also characterised as its 7-O-acetate: $[\alpha]_D^{23.5}$ +39.7 (c 0.817, $CHCl_3$). IR υ_{max}(CH_2Cl_2, film): 1743, 1600, 1589, 1500 cm^{-1}. ^1H NMR, δ: 1.10 (s, 9H, t-Bu), 1.96 (s, 3H, C(O)Me), 2.50-2.62 (m, 1H, H-4), 3.45 (s, 3H, OMe), 3.75-3.92 (m, 3H, H-5, H-6), 3.90 (dd, 1H, H-7, J= 10.2, 6.2 Hz), 4.05 (dd, 1H, H-7', J=10.2, 5.7 Hz), 4.88 ("t", 1H, H-1, J=2.0 Hz), 5.81 (dd, 1H, H-2, J= 10.3, 2.0 Hz), 5.89 (br d, 1H, H-3, J= 10.3 Hz), 7.30-7.50 (m, 6H, Ph-H), 7.57-7.77 (m, 4H, Ph-H). ^{13}C NMR, δ: 19.24, 20.77, 26.78, 35.72, 55.23, 64.29(-), 65.10(-), 69.71, 95.00, 126.52, 127.64, 127.69, 129.69, 133.36, 133.50, 135.61, 135.72, 171.07. Anal. Calcd for $C_{25}H_{30}O_5Si$: C, 68.69; H, 7.54. Found: C, 68.74; H, 7.67.

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