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DI-TERT-BUTYLMETHYLSILYL (DTBMS) TRIFLUOROMETHANESULFONATE. PREPARATION AND SYNTHETIC APPLICATIONS OF DTBMS ESTERS AND ENOL ETHERS

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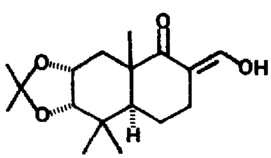
Summary: DTBMS triflate, readily available from dichloromethylsilane, provides carboxylic esters which resist reduction by hydridoaluminate or acid catalyzed hydrolysis, and vinylogous esters (enol ethers of hydroxymethylene ketones) which resist 1,4-addition of methyllithium.

A proclivity toward 1,4-addition of methyllithium to the trimethylsilyl (TMS) ether **3a** interfered with the 1,2-addition which we required for preparing unsaturated aldehyde **2** from α-hydroxymethylene ketone **1**.[1] The problem was solved by blocking 1,4-addition with bulky substituents on silicon. Thus, the proportion of 1,2-adduct **4** versus 1,4-adduct **5** improved slightly with the t-butyldimethylsilyl (TBDMS) ether **3b** and dramatically with the di-t-butylmethylsilyl (DTBMS) ether **3c** (table 1). The aldehyde **2** was obtained in 90% yield overall from **1** by silyla-



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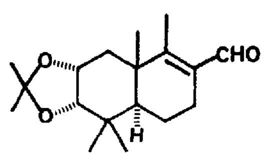

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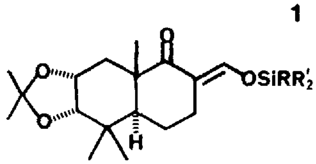

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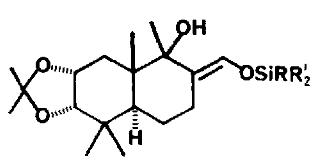

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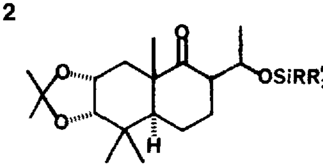

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Table 1. Reaction of Methyllithium with Keto Enol Ethers **3**.

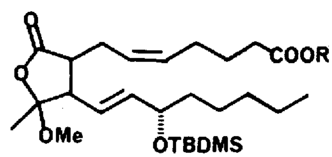
Entry	Silyl Ether 3			Yield (%)	
	R	R'		1,2-Adduct **4**	1,4-Adduct **5**
a	Me	Me	(TMS)	59	39
b	t-Bu	Me	(TBDMS)	70	25
c	Me	t-Bu	(DTBMS)	90	10

tion with DTBMS triflate (vide infra), reaction of the silyl ether **3c** with methyllithium, and treatment of the 1,2-adduct **4c** with pyridinium p-toluenesulfonate in acetone solution.[2]

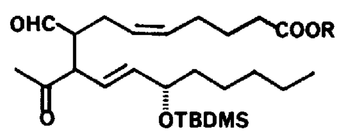
DTBMS ethers were prepared previously by the reaction of alcohols with DTBMS perchlorate.[3] The new reagent, di-tert-butyldimethylsilyl trifluoromethanesulfonate (DTBMS triflate), is readily available (82% yield) from di-tert-butylmethylsilane[3] which is prepared from inexpensive dichloromethylsilane[4] and tert-butyllithium:

Di-tert-butylmethylsilyl Trifluoromethanesulfonate. Trifluoromethanesulfonic acid (2.10 mL, 1.10 equiv, 23.7 mmol) was added dropwise to di-tert-butylmethylsilane[3] (3.41 g, 21.5 mmol) with stirring at 4°C (ice bath) under an atmosphere of dry nitrogen. After complete addition, the solution was warmed to room temperature and stirred for 16 hr during which time hydrogen evolution occurred. The resulting clear yellow liquid was distilled through a Vigreux column (200 mm) topped with a short path condenser. **DTBMS triflate** (6.27 g, 95.0% yield) is a colorless oil (bp 63-65°C/15 mm Hg) which fumes on exposure to air. ^1H NMR ($CDCl_3$, 60 MHz) δ 1.12 (s, 18H), 0.50(s, 3H). M^+ calcd for $C_{10}H_{21}F_3O_3SSi$: 306.0933. Found: 306.0921.

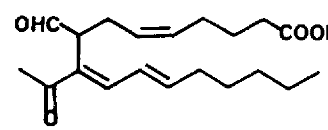
Our previous synthesis of anhydro levuglandin D_2 (**8**)[5] involved hydride reduction of a lactone in the presence of a sterically hindered tert-butyl ester to achieve the selective conversion of **6a** into **7a**. However, difficulty was encountered in converting the tert-butyl



6a, R = *t*-Bu
6b, R = DTBMS



7a, R = *t*-Bu
7b, R = DTBMS

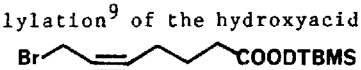


8

ester into a carboxylic acid. Thus, treatment of **7a** with formic acid delivered **8** in only 12-21% yield. We now find that lithium tert-butyldiisobutyl hydridoaluminate[6] selectively reduces DTBMS ester **6b** to **7b**. Moreover, treatment of **7b** with aqueous HF in THF affords **8** in 43-63% yield. Conversion of DTBMS esters to carboxylic acids can also be achieved by treatment with Bu_4NF in wet THF. Under these conditions, both silyl protecting groups are removed from **6b** delivering the corresponding hydroxycarboxylic acid in 73% yield.

Other interesting transformations involving DTBMS esters were encountered during the synthesis of **6b**. Initially the DTBMS hydroxyester **9c** was prepared from the acid **9a**[7] by removal of the THP group (72%)[8] followed by selective silylation[9] of the hydroxyacid **9b**. However,

9a, R = THP, R' = H
9b, R = R' = H
9c, R = H, R' = DTBMS
9d, R = THP, R' = DTBMS



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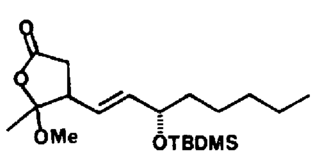
11a, X = OH
11b, X = Br



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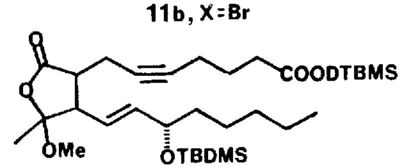

13

these steps can be reversed. Silylation of **9a** affords **9d** (92%)[10], and the THP protecting group was removed selectively in the presence of a DTBMS ester with pyridinium p-toluenesulfonate in warm ethanol[11] to deliver **9c** (78%).[12] Catalytic partial hydrogenation[13] of **9c** provides **11a** (94%). The bromides **10** (91%) and **11b** (98%) were prepared form **9c** and **11a** respectively by reaction with methanesulfonyl chloride and LiBr.[14] Reaction of these bromides with the lithium enolate[15] of lactone **12**[5] provided **13** and **6b** respectively.

TBDMS ethers of α-hydroxymethylene ketones are labile compounds prone to hydrolysis.[1] TBDMS esters are similarly labile. In contrast, DTBMS enol ethers and carboxylic esters are stable derivatives which should find important applications in organic synthesis.

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(1) Tius, M. A. J. Org. Chem. **1982**, 47, 3163.

(2) (a) **1,2-Adduct 4c.** A solution of hydroxymethylene ketone **1** (65 mg, 0.16 mmol), triethylamine (60 μL, 0.4 mmol), and DTBMS-OTf (90 mg, 0.3 mmol) in ether (1 mL) was stirred 30 min at 20°C, then cooled to -78°C. Methyllithium (1 mL, 1.5 mmol, 1.5 M in ether) was added and after 15 min, the mixture was poured into saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with ether (2 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography on a column (20 x 150 mm) of silica gel (tlc Rf 0.29 in 15% ethyl acetate in hexanes) afforded 1,2-adduct **4c** (62 mg, 84% yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.83 (s, 3H), 0.91 (s, 3H), 0.97 (s, 9H), 0.98 (s, 9H), 1.08 (s, 3H), 1.31 (s, 3H), 1.35 (s, 3H), 1.48 (s, 3H), 1.40-1.70 (7H), 2.87-3.00 (H), 3.68 (d, H, J=4.23 Hz), 4.16 (dt, H, J=4.30 Hz), 3.65 (d, H, J=1.68 Hz). M^+ calcd for $C_{27}H_{50}O_4Si$: 466.3478. Found: 466.3462. (b) **DTBMS Enol Ether 3c.** Intermediate **3c** in the synthesis of **4c** can be isolated by flash chromatography (tlc Rf 0.38 in 15% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.18 (3H, s), 0.95 (3H, s), 0.97 (9H, s), 1.11 (3H, s), 1.31 (3H, s), 1.44 (3H, s), 1.57 (2H, s), 1.63-1.80 (2H), 2.18 (H, dd, J=5.86, 13.18 Hz), 2.10-2.22 (H), 2.75 (H, dd, J=5.86, 10.61 Hz), 3.70 (H, d, J=4.62 Hz), 4.25 (H, ddd, J=1.53, 6.22, 10.84 Hz), 7.41 (H, br s); M^+ calcd for $C_{26}H_{46}O_4Si$: 450.3165. Found: 450.3154.

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(8) **7-Hydroxy-5-heptynoic Acid (9b).** 7-Tetrahydropyranyloxy-5-heptynoic acid[6] (**9a**, 1.13 g, 5 mmol) in dilute aqueous sulfuric acid (2% V/V, 5 mL) and tetrahydrofuran (5 mL) was stirred 3 days at room temperature. Tetrahydrofuran was removed by rotary evaporation, the aqueous residue basified to pH 12 with sodium hydroxide (15% W/V), and washed with diethyl ether (2 x 10 mL). The combined ether washings were extracted with dilute sodium

hydroxide (2% W/V, 10 mL) and discarded. The aqueous extracts were combined, acidified to pH 2 with dilute aqueous hydrochloric acid (10% W/V), and extracted with diethyl ether (4 x 25 mL). The extracts were rinsed with saturated aqueous sodium chloride (20 mL), combined, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to a colorless oil. This oil was purified by flash chromatography on a column (40 mm x 150 mm) of silica gel with ethyl acetate/hexanes (50% V/V) containing acetic acid (1% V/V), as eluting solvent. TLC analysis of the eluate fractions in the same solvent, developing with a vanillin indicator shows that the dark red staining THP-ether **9a** (Rf = 0.34, 417 mg, 37% recovery) elutes before the blue green staining hydroxy acid **9b** (Rf = 0.17). The hydroxy acid **9b** (323 mg, 72% yield) is a colorless viscous oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.44(br s, 2H), 4.25(t, 2H, J = 2.1 Hz), 2.50(t, 2H, J = 7.3 Hz), 2.33(tt, 2H, J = 6.8, 2.1 Hz), 1.87(quin, 2H, J = 7.0 Hz). M^+ calcd for $C_7H_{10}O_3$: 142.0632. Found: 142.0651.

(9) **Di-t-butylmethylsilyl 7-Hydroxy-5-heptynoate (9c).** 7-Hydroxy-5-heptynoic acid (**9b**, 750 mg, 5.28 mmol) in anhydrous tetrahydrofuran (5.3 mL) was stirred rapidly under nitrogen and treated dropwise at room temperature with dry triethylamine (2.05 mL, 7.5 mmol) and then di-tert-butylmethylsilyl trifluoromethanesulfonate (1.66 g, 1.02 equiv, 5.4 mmol). After 15 min, the clear solution was concentrated *in vacuo* and the oily residue purified by flash chromatography on a column (40 mm x 140 mm) of silica gel with 20% ethyl acetate in hexanes as eluting solvent. The silyl ester **9c** is a colorless oil (690 mg, 44% yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.22(t, 2H, J = 2.0 Hz), 2.44(t, 2H, J = 7.4 Hz), 2.27(tt, 2H, J = 6.9, 2.1 Hz), 1.79(quin, 2H, J = 7.1 Hz), 1.67(br s, H), 0.99(s, 18H), 0.29(s, 3H). M^+ calcd for $C_{16}H_{30}O_3Si$: 298.1964. Found: 298.1963.

(10) **Di-tert-butylmethylsilyl 7-Tetrahydropyranyloxy-5-heptynoate (9d).** 7-Tetrahydropyranyloxy-5-heptynoic acid (**9a**, 1.6 g, 7.1 mmol) in anhydrous tetrahyrofuran (15 mL) was treated with dry triethylamine (1.7 mL, 1.1 equiv, 7.8 mmol) and di-tert-butylmethylsilyl trifluoromethanesulfonate (2.18 g, 1.0 equiv, 7.1 mmol) as for **9c** above to afford **9d** as a colorless oil (2.5 g, 92% yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.77(t, H, J = 3.1 Hz), 4.24(dt, H, J = 13.0, 2.1 Hz), 4.19(dt, H, J = 13.0, 1.9 Hz), 3.78(m, H), 3.53(m, H), 2.44(t, 2H, J = 7.3 Hz), 2.28(tt, 2H, J = 7.2, 2.0 Hz), 1.79(quin, 2H, J = 7.1 Hz), 1.57 (br m, 6H), 0.99(s, 18H), 0.29(s, 3H). M^+ calcd for $C_{21}H_{38}O_4Si$: 382.2539. Found: 382.2534.

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(12) A solution of the tetrahydropyranyl ether **9d** (2.48g, 6.48 mmol) in absolute ethanol (52 mL) containing pyridinium p-toluenesulfonate[11] (162 mg, 0.644 mmol) was heated at 55-60°C for 1.5 hr under dry nitrogen. Ethanol was then removed by rotary evaporation. The residual liquid was purified by flash chromatography through a column of silica gel (55 mm x 160 mm) eluting with 20% ethyl acetate in hexanes to afford hydroxy DTBMS ester **9c** (1.51 g, 78%) identical with that described above.[9]

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