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A STREAMLINED SYNTHESIS OF TBDMS PROTECTED C1 SUBSTITUTED SORBIC ALCOHOL DERIVATIVES FROM SORBALDEHYDE

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Abstract

By combining the Grignard reaction with Corey's silyl ether protection protocol we developed a streamlined synthesis that produces tert-butyldimethylsilyl ether (TBDMS) protected sorbic alcohol derivatives with aromatic and aliphatic C1 substituents from sorbaldehyde in good yields. This methodology avoids time consuming purification of the products by flash column chromatography (FCC) and can be conducted by undergraduate researchers. Consistent product purity of this methodology is demonstrated by kinetic experiments. Additionally, this study illustrates an example where synthetic modifications allow overcoming characteristic challenges of conducting research in organic synthesis at the undergraduate level.

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Introduction

It remains challenging to stay productive in undergraduate chemistry research at a primarily undergraduate institution. The main difficulties lie in the high turnover and in the busy schedules of committed undergraduate students. This is especially true when conducting chemical research in a synthesis based field. Driving synthetic research projects to completion requires generally a substantial time investment of students because of the involved synthetic steps. For example, one synthetic organic chemistry experiment entails the following components: 1) reaction design and setup (1-2 h); 2) reaction time (2-24 h or longer); 3) workup procedure that includes often liquid-liquid extractions, washes, drying steps, filtrations, and rotary evaporations (2-3 h); 4) purification by flash column chromatography (FCC) on silica (2-5 h depending on reaction scale); and 5) product characterization (NMR, IR, MS, etc.). All activities, with the exception of the reaction time and product characterization (at least in some cases), require hands-on experimental work by undergraduate researchers with an adequate skill level. To further complicate the situation the stability of synthetic products dictates the time flexibility that researchers have at their disposal to complete (or postpone) each component of a reaction. The synthesis of labile products often requires the sequential completion of all activities in one day, but stable compounds allow for more flexibility with reaction time, workup, and FCC purification without affecting the outcome of the experiment significantly. We report herein an example where procedural changes that simplified and circumvented aspects of established synthetic methods were needed to conduct research in organic synthesis at the undergraduate level. Specifically, our changes utilized reactions where the reaction time is flexible, incorporated the conversion of a labile product to a stabilized version, and avoided time consuming FCC purifications. These modifications allowed undergraduate researchers to balance their curriculum schedules with their research efforts.

(2*E*,4*E*)-2,4-hexadien-1-ol, often called by its trivial names sorbic or sorbyl alcohol, consists of a six carbon atom chain that is equipped with a hydroxyl group on carbon 1 and two *E* (*trans*) double bonds beginning at carbons 2 and 4 (**Figure 1, top**). It is the alcohol of sorbic acid, which was discovered and named by A. W. Hofmann in 1859.[1] Sorbic acid is well known for its use in the food industry.[2] Sorbic alcohol itself is listed as a flavoring agent and fragrance,[3] but it is also used as a base chemical in organic synthesis. The synthetic versatility of sorbic alcohol derivatives is rooted in their structure that combines the reactivity of an allylic alcohol with that of a conjugated diene[4] and is supported by the common appearance of the 2,4-hexadienyl group in natural compounds (**Figure 1, bottom**).[5]

The synthetic community has also given considerable attention to C1 monosubstituted sorbic alcohol derivatives (**C1-SAD**s) and illustrated their importance in organic chemistry. For example, they were used directly in enzymatic[6] and organocatalyzed processes,[7] served as a mechanistic model to study the Claisen rearrangement,[8] or became crucial building blocks in methodology development[9] and natural product synthesis.[10,11,12] An important part in controlling the reactivity of **C1-SAD**s during synthesis was their conversion to silyl ether protected variants.[13,14,15] One of

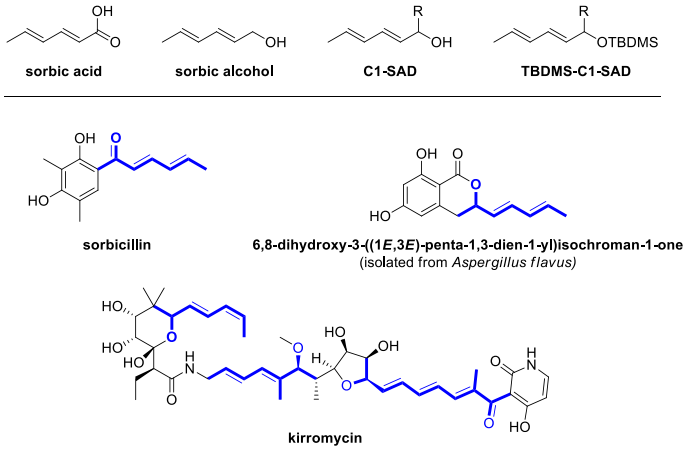


Figure 1. (top) structures of sorbic acid, sorbic alcohol, C1-SAD, and TBDMS-C1-SAD; (bottom) small selection of natural products exhibiting C1-SAD substructures.

the most commonly used silyl ether protecting group for alcohols is the *tert*-butyldimethylsilyl group (TBDMS), which was introduced by Corey in 1972.[16] This alcohol protection could readily be introduced and removed (with tetrabutylammonium fluoride)[17] and tolerated most common organic reaction conditions, which explained its rising popularity in organic synthesis. Therefore, we developed a straightforward two-step synthesis of TBDMS protected **C1-SAD**s (**TBDMS-C1-SAD**s) from sorbaldehyde.

Experimental Methods

General Information. Commercially available chemicals, reagents and solvents, such as n-hexane, hexanes, methanol (MeOH), dichloromethane (DCM), and ethyl acetate (EtOAc) were used as commercially obtained were purchased from Sigma-Aldrich, Fisher Scientific, VWR, and Acros Organics and used without further purification, unless otherwise stated. Anhydrous tetrahydrofuran (THF) and anhydrous DCM were purchased from EMD Millipore Corporation in DriSolv containers and used without further purification. Reactions were monitored by gas chromatography-mass spectrometry (GCMS) and thin layer chromatography (TLC). TLC was performed using Sorbtech polyester backed Silica G TLC plates (thickness: 200 µm, dimensions: 2.5 x 7.5 cm or (4 x 8 cm). TLC plates contained a UV254 visualizing agent and potassium permanganate ($KMnO_4$) stain was used with heat as a developing agent. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker Avance III 400 instrument equipped with a BBO 400 MHz S1 5mm probe (with Z gradient). NMR spectra are referenced using residual undeuterated solvent peaks ($CHCl_3$ at 7.26 ppm ^{1}H NMR, 77 ppm ^{13}C NMR). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad. Silica plugs and flash column chromatography (FCC) were performed using Sigma-Aldrich or Mallinckrodt Chemicals silica gel 60 with a particle size of 40–63 µm and air to produce pressure. Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet iS5 equipped with an iD1 Transmission chamber or on a Thermo Scientific Nicolet 6700 FT-IR. The following abbreviations were used to explain intensities: s = strong, m = medium, w = weak, br = broad. GCMS data were recorded on an Agilent Technologies 6890N Network GC System equipped with Supelco SLB ® -5ms Capillary GC Column (L × I.D. 30 m × 0.25 mm, d f 0.25 µm), an Agilent Technologies 5973 inert Mass Selective Detector and an Agilent Technologies 7683B Series Injector.

Safety Precautions: *Grignard and organolithium reagents used in the experiments below are pyrophoric. Their improper use could lead to laboratory fires, severe burnings and death. These chemicals should only be handled by appropriately trained researchers who are under professional supervision. Recommended safety protocols should be followed.*[18]

General Method: *tert-butyldimethyl[(3E,5E)-hepta-3,5-dien-2-yloxy]silane* ***(TBDMS-Me-SAD).*** To a solution of sorbaldehyde (0.52 g, 5.41 mmol) in THF (20 mL) was added a solution of methylmagnesium chloride (3 M, 2.16 mL, 6.49 mmol, 1.2 eq.) over 10 minutes at room temperature under inert atmosphere (Ar). The reaction mixture was stirred for 2 hours, quenched with distilled water (10 mL), acidified with 1.0 M HCl solution (10 mL), and extracted with ethyl acetate (3x 15 mL). The combined organic layers were washed with brine (10 mL), saturated $NaHCO_{3(aq)}$ (10mL), dried over $MgSO_4$, gravity filtered, and evaporated producing the crude alcohol as a yellow oil. Once the crude alcohol was dissolved in dichloromethane (50 mL) under ambient conditions, imidazole (1.84 g, 27.05 mmol, 5 eq) and *tert*-butyldimethylchlorosilane (0.98 g, 6.49 mmol, 1.2 eq.) were added and the solution was stirred for 24 hours. After the addition of distilled water (15 mL), the reaction mixture was extracted with dichloromethane (3x 15 mL) and the combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and evaporated. The residue was dissolved in methanol and hexane (15 mL each), extracted with hexane (6x 10 mL), evaporated, filtered through a silica plug (23 g of silica) with a hexane:ethyl acetate mixture (9:1, 150 mL), and concentrated. A diastereoisomeric mixture of **TBDMS-Me-SAD** (*3E,5E* : *3Z,5E* = 85:15) was obtained as a colorless oil (0.94 g, 77% yield, racemate). This reaction was performed three times and a % yield ranging from 70% to 77% was obtained. The diastereoisomeric ratio of the product mixture was dictated by the diastereomeric purity of the starting sorbaldehyde. **^{1}HNMR** ($CDCl_3$, δ ppm): 5.90-6.18 (m, 2H); 5.59 (dd, 1H, *J* =14.2, 6.6Hz); 5.50 (dd, 1H, *J* = 14.5, 5.8 Hz); 4.26 (p, 1H, *J* = 6.2 Hz); 1.70 (d, 3H, *J* = 6.8 Hz); 1.16 (d, 3H, *J* = 6.3 Hz); 0.84 (s, 9H); 0.00 (s, 3H); -0.01 (s, 3H). **^{13}CNMR** ($CDCl_3$, δ ppm): 135.5, 131.1, 128.8, 128.4, 69.1, 25.9, 24.6, 18.3, 18.1, -4.6, -4.8. **IR** (NaCl, ν in cm^{-1}): 2957 (s), 2929 (s), 2885.79 (s), 2857 (s), 1472 (m), 1463 (m), 1256 (s), 1049 (s), 835 (s), 776 (m). **MS** (EI) m/z (Fragment): 226.2 [M^+], 211.2 [M-CH_3^+], 169.1 [M-tBu^+], 95.1 [M-$SiMe_2tBu^+$]. **TLC**: R_f = 0.78 (9:1 hexane:EtOAc), 0.71 (95:5 hexane:EtOAc), 0.49 (99:1 hexane:EtOAc).

tert-Butyldimethyl[(4E,6E)-octa-4,6-dien-3-yloxy]silane ***(TBDMS-Et-SAD).*** Prepared according to the **General Method** on a 4.95 mmol scale using 3 M ethylmagnesium bromide in Et_2O. A diastereoisomeric mixture of **TBDMS-Et-SAD** (*4E,6E* : *4Z,6E* = 85:15) was obtained as a colorless oil (1.09 g, 92% yield). This reaction was performed three times and a % yield ranging from 83% to 92% was obtained. **^{1}HNMR** ($CDCl_3$, δ ppm): 5.94-6.19 (m, 2H); 5.63 (dd, 1H, *J* = 14.4, 7.2 Hz); 5.42-5.50 (m, 1H); 4.00 (q, 1H, *J* = 6.4 Hz); 1.73 (d, 3H, *J* = 6.4 Hz); 1.43-1.51 (m, 2H); 0.87 (s, 9H); 0.83-0.84 (m, 3H); 0.02 (s, 3H); 0.00 (s, 3H). **^{13}CNMR** ($CDCl_3$, δ ppm): 134.2, 131.2, 129.5, 128.6382, 74.6, 31.3, 25.9, 18.3, 18.1, 9.7, -4.3, -4.8. **IR** (NaCl, ν in cm^{-1}): 3019 (m), 2957 (s), 2930 (s), 2885 (s), 2857 (s), 1472 (m), 1255 (s),1255 (s), 1106 (s). **MS** (EI) m/z (Fragment): 240.2 [M^+], 211.1 [M-Et^+], 183.1 [M-tBu^+], 109.1 [M-$SiMe_2tBu^+$]. **TLC**: R_f = 0.76 (9:1 hexane:EtOAc), 0.74 (95:5 hexane:EtOAc), 0.58 (99:1 hexane:EtOAc).

tert-Butyldimethyl{[(4E,6E)-2-methylocta-4,6-dien-3-yl]oxy}silane **(*TBDMS-iPr-SAD*).** Prepared according to the **General Method** on a 4.8 mmol scale (2 M isopropylmagnesium chloride in THF). A diastereoisomeric mixture of **TBDMS-*i*Pr-SAD** (*4E,6E* : *4Z,6E* = 85:15) was obtained as a colorless oil (0.89 g, 80% yield). This reaction was performed two times and a % yield ranging from 77% to 80% was obtained. **^{1}HNMR** ($CDCl_3$, δ ppm): 6.04-6.01 (m, 2H); 5.63 (dd, 1H, *J* =14.4, 5.8 Hz); 5.47 (dd, 1H, *J* = 14.5, 6.3 Hz); 3.80(t, 1H, *J* = 6.4 Hz); 1.73 (d, 3H, *J* = 6.0 Hz); 1.63 (septd, 1H, *J* = 6.8, 1.2 Hz); 0.88 (s, 9H); 0.84-0.87 (m, 6H); 0.01 (s, 3H), -0.02 (s, 3H). **^{13}CNMR** ($CDCl_3$, δ ppm): 132.8, 131.2, 130.5, 128.5, 78.4, 35.0, 25.9, 18.32, 18.26, 18.1, 18.0, -4.1, -4.9. **IR** (NaCl, ν in cm^{-1}): 3019 (m), 2959 (s), 1471 (s), 1255 (s),

1071 (m), 836 (m), 779 (m). **MS** (EI) m/z (Fragment): 254.2 [M^+], 211.1 [M-Ipr$^+$], 197.1 [M-tBu$^+$], 123.1 [M-SiMe$_2$tBu$^+$]. **TLC**: R_f = 0.79 (9:1 hexane:EtOAc), 0.76 (95:5 hexane:EtOAc), 0.56 (99:1 hexane:EtOAc).

tert-butyl[(6E,8E)-deca-6,8-dien-5-yloxy]dimethylsilane ***(TBDMS-nBu-SAD).*** Prepared according to the **General Method** on a 12.36 mmol scale (1.6 M n-butyllithium in hexane). A diastereoisomeric mixture of **TBDMS-*n*Bu-SAD** (*6E,8E* : *6Z,8E* = 85:15) was obtained as a colorless oil (2.58 g, 79% yield). This reaction was performed two times and a % yield ranging from 70% to 79% was obtained. **^{1}HNMR** ($CDCl_3$, δ ppm): 6.08-5.97 (m, 2H); 5.64 (dd, 1H, *J* = 14.4, 7.2 Hz); 5.49 (dd, 1H, *J* = 14.4, 6.7 Hz); 4.07 (q, 1H, *J* = 6.4 Hz); 1.72 (d, 3H, *J* = 6.7 Hz); 1.48-1.44 (br m, 2H); 1.28-1.26 (br m, 7H); 0.87 (s, 9H); 0.02 (s, 3H); 0.00 (s, 3H). **^{13}CNMR** ($CDCl_3$, δ ppm): 134.6, 131.2, 129.3, 128.6, 73.4, 38.2, 27.5, 25.9, 22.7, 18.2, 18.1, 14.1, -4.3, -4.8. **IR** (NaCl, ν in cm^{-1}): 3019 (m), 2957 (s), 2930 (s), 2857 (s), 1472 (m), 1388 (s), 1255 (s), 836 (s). **MS** (EI) m/z (Fragment): 268.2 [M^+], 211.2 [M-tBu$^+$], 135.1 [M-SiMe$_2$tBu$^+$]. **TLC**: R_f = 0.80 (9:1 hexane:EtOAc), 0.73 (95:5 hexane:EtOAc), 0.51 (99:1 hexane:EtOAc).

tert-Butyldimethyl{[(2E,4E)-1-phenylhexa-2,4-dien-1-yl]oxy} silane ***(TBDMS-Ph-SAD)***. Prepared according to the **General Method** on a 10.1 mmol scale (1.0 M phenylmagnesium bromide in THF). Acidified with 10 mL of saturated $NH_4Cl_{(aq)}$ solution instead of 1.0 M HCl. A diastereoisomeric mixture of **TBDMS-Ph-SAD** (*2E,4E* : *2Z,4E* = 85:15) was obtained as a colorless oil (2.72 g, 93% yield). This reaction was performed two times and a % yield ranging from 77% to 93% was obtained. **^{1}HNMR** ($CDCl_3$, δ ppm): 7.33-7.28 (br m, 5H); 6.19 (dd, 1H, *J* = 14.8, 10.4 Hz); 6.01 (td, 1H, *J* = 14.8, 1.6 Hz); 5.71 (dd, 1H, *J* = 14.8, 6.8 Hz); 5.62 (dd, 1H, *J* = 14.8, 6.4 Hz); 5.19 (d, 1H, *J* = 6.4 Hz); 1.74 (dd, 3H, *J* = 6.4, 1.2 Hz); 0.91 (s, 9H); 0.06 (s, 3H); 0.00 (s, 3H). **^{13}CNMR** ($CDCl_3$, δ ppm): 136.5, 134.2, 131.0, 129.5, 129.3, 128.2, 126.9, 125.9, 75.4, 25.9, 18.4, 18.1, -4.5, -4.8. **IR** (NaCl, ν in cm^{-1}): 3063 (w), 3022 (w), 2956 (m), 2929 (m), 2885 (w), 2857 (m), 1492 (w), 1472 (w). **MS** (EI) m/z (Fragment): 288.1 [M^+], 273.1 [M-CH_3^+], 231.1 [M-tBu$^+$], 157.1 [M-SiMe$_2$tBu$^+$]. **TLC**: R_f = 0.72 (9:1 hexane: EtOAc), 0.67 (95:5 hexane: EtOAc), 0.57 (99:1 hexane: EtOAc).

tert-Butyldimethyl{[(2E,4E)-1-(4-methylphenyl)hexa-2,4-dien-1-yl]oxy}silane ***(TBDMS-p-Tol-SAD).*** Prepared according to the **General Method** on a 12.20 mmol scale (1.0 M 4-methylphenylmagnesium bromide in THF). Acidified with 10 mL of saturated $NH_4Cl_{(aq)}$ solution instead of 1.0 M HCl. A diastereoisomeric mixture of **TBDMS-p-Tol-SAD** (*2E,4E* : *2Z,4E* = 85:15) was obtained as a colorless oil (2.289 g, 74% yield). **^{1}HNMR** ($CDCl_3$, δ ppm): 7.22 (d, 2H, *J* = 8.0 Hz); 7.12 (d, 2H, *J* = 8.0 Hz); 6.18 (dd, 1H, *J* = 14.8, 10.4 Hz); 6.01 (td, 1H, *J* = 15.2, 1.6 Hz); 5.70 (dd, 1H, *J* = 14.8, 6.8 Hz); 5.62 (dd, 1H, *J* = 14.8, 6.4 Hz); 5.17 (d, 1H, *J* = 6.4 Hz); 2.33 (s, 3H); 1.75 (dd, 3H, *J* = 6.4, 1.2 Hz); 0.94 (s, 9H); 0.06 (s, 3H); 0.00 (s, 3H). **^{13}CNMR** ($CDCl_3$, δ ppm): 141.3, 136.8, 134.4, 131.0, 129.3, 129.1, 128.9, 125.9, 75.2, 25.9, 21.1, 18.4, 18.1, -4.5, -4.7. **IR** (NaCl, ν in cm^{-1}): 3020 (m), 29956 (s), 2928 (s), 2885 (s), 2856 (s), 1512 (m). **MS** (EI) m/z (Fragment): 302.2 [M^+], 287.2 [M-CH_3^+], 245.1 [M-tBu$^+$], 171.1 [M-SiMe$_2$tBu$^+$]. **TLC**: R_f = 0.72 (9:1 hexane: EtOAc), 0.64 (95:5 hexane: EtOAc), 0.46 (99:1 hexane: EtOAc).

tert-Butyldimethyl{[(2E,4E)-1-(4-phenoxyphenyl)hexa-2,4-dien-1-yl]oxy}silane ***(TBDMS-p-OPh-Ph-SAD).*** Prepared according to the **General Method** on 9.62 mmol scale (0.5M phenoxyphenylmagnesium bromide in THF). Acidified with 10 mL of saturated $NH_4Cl_{(aq)}$ solution instead of 1.0 M HCl. A diasterosiomeric mixture of **TBDMS-p-OPh-Ph-SAD** (*2E,4E* : *2Z,4E* = 85:15) was obtained as a colorless oil (2.84g, 78% yield). **^{1}HNMR** ($CDCl_3$, δ ppm): 7.23-7.33 (m, 4H); 7.05-7.07 (m, 1H); 6.95-7.01 (m, 4H); 6.18 (dd, 1H, *J* = 15.2, 10.4 Hz); 6.02 (td, 1H, *J* = 14.8, 1.6 Hz); 5.71 (dd, 1H, *J* = 14.8, 6.4 Hz); 5.61 (dd, 1H, *J* = 15.2, 6.8 Hz); 5.17 (d, 1H, *J* = 6.4 Hz); 1.74 (dd, 3H, *J* = 6.8, 1.2 Hz); 0.90 (s, 9H); 0.06 (s, 3H); 0.00 (s, 3H). **^{13}CNMR** ($CDCl_3$, δ ppm): 136.1, 134.1, 130.9, 129.7, 129.3, 127.3, 127.3, 123.2, 123.1, 118.9, 118.7, 118.7, 74.9, 25.9, 18.4, 18.2, -4.4, -4.7. **IR** (NaCl, ν in cm^{-1}): 3020 (w), 2955 (m), 2928 (m), 2856 (m), 1590 (m), 1503 (s), 1239 (s). **MS** (EI) m/z (Fragment): 380.2 [M^+], 365.2 [M-CH_3^+], 323.1 [M-tBu$^+$], 249.1 [M-SiMe$_2$tBu$^+$]. **TLC**: R_f = 0.68 (9:1 hexane: EtOAc), 0.64 (95:5 hexane: EtOAc), 0.33 (99:1 hexane: EtOAc).

tert-Butyl({[(2E,4E)-1-(4-fluorophenyl)hexa-2,4-dien-1-yl]oxy}) dimethylsilane ***(TBDMS-p-F-Ph-SAD).*** Prepared according to the **General Method** on a 5.75 mmol scale (1.0 M 4-fluorophenylmagnesium bromide in THF). Acidified with 10 mL of saturated $NH_4Cl_{(aq)}$ solution instead of 1.0 M HCl. A diastereoisomeric mixture **TBDMS-p-F-Ph-SAD** (*2E,4E* : *2Z,4E* = 85:15) was obtained as a colorless oil (1.68 g, 80% yield). **^{1}HNMR** ($CDCl_3$, δ ppm): **^{1}HNMR** ($CDCl_3$, δ ppm): 7.30-7.26 (m, 2H); 7.01-6.96 (m, 2H); 6.17 (dd, 1H, *J* = 15.2, 10.4 Hz); 6.01 (td, 1H, *J* = 15.2, 1.6 Hz); 5.71 (dd, 1H, *J* = 14.8, 6.8 Hz); 5.57 (dd, 1H, *J* = 14.8, 6.4 Hz); 5.17 (d, 1H, *J* = 6.4 Hz); 1.75 (dd, 3H, *J* = 6.8, 1.2 Hz); 0.91 (s, 9H); 0.06 (s, 3H); 0.00 (s, 3H). **^{13}CNMR** ($CDCl_3$, δ ppm): 161.9 (d, *J* = 245 Hz), 140.0 (d, *J* = 2.7 Hz), 133.9, 130.8, 129.8, 129.5, 127.5 (d, *J* = 8.0 Hz), 114.9 (d, *J* = 21.2 Hz), 74.7, 25.9, 18.3, 18.1, -4.5, -4.8. **IR** (NaCl, ν in cm^{-1}): 3020 (s), 2956 (s), 2929 (s), 2885 (s), 2857 (s), 1605 (s), 1507 (s), 1154 (m). **MS** (EI) m/z (Fragment): 306.3 [M^+], 291.1 [M-CH_3^+], 249.1 [M-tBu$^+$], 175.1 [M-SiMe$_2$tBu$^+$]. **TLC**: R_f = 0.70 (9:1 hexane: EtOAc), 0.66 (95:5 hexane: EtOAc), 0.52 (99:1 hexane: EtOAc).

tert-Butyl({[(2E,4E)-1-(4-chlorophenyl)hexa-2,4-dien-1-yl]oxy}) dimethylsilane ***(TBDMS-p-Cl-Ph-SAD).*** Prepared according to the **General Method** on a 5.20 mmol scale (1.0 M 4-chlorophenylmagnesium bromide in THF). Acidified with 10 mL of saturated $NH_4Cl_{(aq)}$ solution instead of 1.0 M HCl. A diastereoisomeric mixture of **TBDMS-p-Cl-Ph-SAD** (*2E,4E* : *2Z,4E* = 85:15) was obtained as a colorless oil (1.35 g, 80% yield). **^{1}HNMR** ($CDCl_3$, δ ppm): 7.27 (d, 2H, *J* = 4.8 Hz); 7.26 (d, 2H, *J* =2.4 Hz); 6.17 (dd, 1H, *J* = 15.2, 10.4 Hz); 6.00 (td, 1H, *J* = 12.4, 1.6 Hz); 5.72 (dd, 1H, *J* = 15.2, 6.8 Hz); 5.57 (dd, 1H, *J* = 15.2, 6.4 Hz); 5.15 (d, 1H, *J* = 6.4 Hz); 1.75 (d, 3H, *J* = 6.8 Hz); 0.90 (s, 9H); 0.06 (s, 3H); 0.00 (s, 3H). **^{13}CNMR** ($CDCl_3$, δ ppm): 142.8, 133.6, 132.4, 130.8, 130.0, 129.7, 128.3, 127.3, 74.8, 25.9, 18.3, 18.1, -4.5, -4.8. **IR** (NaCl, ν in cm^{-1}): 3020 (m), 2956 (s), 2885 (s), 2857 (s), 1489 (s), 1472 (s), 1463 (s), 837 (m). **MS** (EI) m/z (Fragment): 322.1 [M^+], 307.1 [M-CH_3^+], 265.1 [M-tBu$^+$], 191.0 [M-SiMe$_2$tBu$^+$]. **TLC**: R_f = 0.74 (9:1 hexane: EtOAc), 0.65 (95:5 hexane: EtOAc), 0.54 (99:1 hexane: EtOAc).

tert-Butyldimethyl{[(4E,6E)-1-phenylocta-4,6-dien-1-yn-3-yl]oxy}silane **(*TBDMS-PhC≡C-SAD*).** Into a stirring solution of THF (20 mL) and phenylacetylene (1.42 mL, 11.7 mmol, 1.3 eq) at –78°C, n-butyllithium (1.6 M in hexane, 7.5 mL, 10.8 mmol, 1.2 eq) was added dropwise over 10 minutes. The reaction mixture was warmed to 0°C with an ice bath and stirred for 30 minutes at this temperature. After cooling to –78°C a solution of sorbic aldehyde (966.7 mg, 10.0mmol) in THF (20 mL) was added dropwise and the reaction mixture was warmed to room temperature over 1 h. After stirring at r.t. for an additional 3 h the reaction was quenched with distilled water (10 mL), acidified with a saturated solution of NH_4Cl (10 mL), and extracted with ethyl acetate (3x 15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, gravity filtered, and evaporated, producing the crude alcohol as a yellow oil. Once the crude alcohol was dissolved in dichloromethane (100 mL), imidazole (3.00 g, 56 mmol, 5eq) and *tert*- butyldimethylchlorosilane (1.68 g, 13.35 mmol, 1.2 eq.) were added and the solution was stirred for 24 hours. After the addition of distilled water (15 mL), the reaction mixture was extracted with dichloromethane (3x 15 mL) and the combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and evaporated. The crude material was purified by FCC on silica (9:1 hexanes/ethyl acetate). A diastereoisomeric mixture of **TBDMS-PhC≡C-SAD** (*2E,4E* : *2Z,4E* = 85:15) was obtained as a colorless oil (1.74 g, 56% yield). The diastereoisomeric ratio of the product mixture was primarily dictated by the purity of the starting sorbaldehyde as it was not significantly altered by the reaction sequence. **^{1}HNMR** ($CDCl_3$, δ ppm): 7.47-7.44 (m, 2H); 7.33-7.32 (m, 3H); 6.38 (dd, 1H, *J* = 15.2, 10.4 Hz); 6.12 (td, 1H, *J* = 10.4, 1.2 Hz); 5.79 (dd, 1H, *J* = 14.8, 6.4 Hz); 5.72 (dd, 1H, *J* = 15.2, 6.0 Hz); 5.18 (d, 1H, *J* = 5.6 Hz); 1.80 (dd, 3H, *J* = 6.8, 1.2 Hz); 0.97 (s, 9H); 0.21 (s, 3H); 0.20 (s, 3H). **^{13}CNMR** ($CDCl_3$, δ ppm): 136.1, 131.6, 130.8, 130.7, 130.5, 129.8, 128.2, 122.9, 89.1, 85.2, 63.8, 25.9, 18.4, 18.2, -4.4, -4.6. **IR** (NaCl, ν in cm^{-1}): 3022 (w), 2929 (s), 2885 (s), 2856 (s), 1253 (s). **MS** (EI) m/z (Fragment): 312.2 [M^+], 297.2 [M-CH_3^+], 255.1 [M-tBu^+], 181.1 [M-$SiMe_2tBu^+$]. **TLC**: R_f = 0.70 (9:1 hexane: EtOAc), 0.63 (95:5 hexane: EtOAc), 0.33 (99:1 hexane: EtOAc).

Reaction Kinetics: The following stock solutions were prepared in 10 mL Schlenk tubes: Two 0.1 M solutions in EtOAc of separately obtained **TBDMS-Me-SAD** batches; a 2.0 M solution of maleic anhydride (MA) in EtOAc, and a 0.1 M solution of hexamethylbenzene (HMB) in EtOAc. Appropriately sized Hamilton syringes were used to transfer volumes accurately. Reactions were prepared in GC vials by adding stock solutions / additional solvent in the following order: 1) 200 µL of the respective **TBDMS-Me-SAD** stock solution, 2) 200 µL of EtOAc, 3) 100 µL of HMB, and 4) 500 µL of MA resulting in a total reaction volume of 1.0 mL. These Diels-Alder reactions were monitored by GC-MS in equally spaced time intervals. Product peaks had retention times between 9-11 minutes and were identified by exhibiting the following MS pattern: MS (EI) m/z (Fragment): 324.0 [M^+], 309.1 [M-CH_3^+], 267.1 [M-tBu^+]. The internal standard HMB was used to calculate the concentration of products at any given time. Calculated concentrations were plotted over time and graphs shown in Figure 2 were obtained.

Results and Discussion

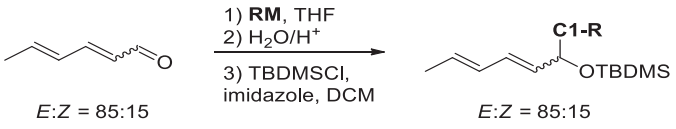
C1-SADs were generally synthesized from sorbaldehyde via a nucleophilic addition reaction using Grignard[19,20] or organolithium[21] reagents. However, their synthesis and especially their storability was problematic in our initial work. During freezer storage (–20 °C) our FCC purified **C1-SAD** samples underwent undesired side reactions that led, depending on the C1 substituent, to significant decomposition. Compounds featuring a vinylic C1 substituent lasted only hours, while aromatic **C1-SAD**s decomposed within days. Only aliphatic derivatives could be used in further research, but still showed decomposition impurities within months. It should be noted that **C1-SAD** samples were spectroscopically (^{1}H NMR) pure after FCC and could have been used in subsequent reactions on the same day. The conversion of **C1-SAD**s to **TBDMS-C1-SAD**s employing Corey's silyl ether protection protocol[16] proved beneficial for us, as it led to reduced reactivity, significantly enhanced freezer storability (years), and allowed the undergraduate researchers flexibility with their reaction schedule.

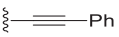
Because FCC purification of both **C1-SAD**s and **TBDMS-C1-SAD**s slowed our research productivity and increased our solvent costs immensely, we looked into procedural modifications that allowed us a more efficient synthetic pathway without significantly compromising the purity of our products. Completion of the Grignard reaction required an acidic aqueous workup, liquid-liquid extractions, drying over $MgSO_4$, gravity filtration, and rotary evaporation. In most of our cases quenching of excess Grignard reagent in the aqueous workup step was expected to produce volatile compounds that were removed during rotary evaporation. As a result ^{1}H-NMR analysis of the crude alcohol indicated >95% purity, which was consistent with literature reports: Grignard reactions involving sorbaldehyde produced typically high yields after FCC purification (72 to 99%).[22] Assuming quantitative conversion (based on an absent aldehyde peak in the ^{1}H-NMR) we exposed crude **C1-SAD** samples without further FCC purification to a variation of Corey's TBDMS protection protocol that used low boiling dichloromethane[23] (DCM) instead of dimethylformamide (DMF) as a solvent under ambient conditions. The reaction time of this step was flexible and could range from 24 h to 96 h without affecting the overall yield. After the addition of water, DCM extraction, drying over $MgSO_4$, gravity filtration, and evaporation ^{1}H-NMR analysis of the crude **TBDMS-C1-SAD** samples indicated the presence of imidazole and TBDMSCl, which were both used in excess. Dissolving the residue in methanol and extracting six times with hexane proved successful in removing most impurities. The concentrated sample was filtered through a silica plug using a hexane : EtOAc eluent mixture (9:1, 95:5, or 99:1). **TBDMS-C1-SAD**s obtained via this methodology indicated similar purity as comparable FCC purified samples (^{1}H-NMR). This modified reaction sequence proved efficient for the synthesis of aliphatic and aromatic **TBDMS-C1-SAD**s (**Table 1**).

Aliphatic **TBDMS-C1-SAD**s were obtained in good yields (77 % to 83 %) with this new procedure (entries 1-4). Both Grignard and Li-reagents were used successfully as nucleophiles and gave similar yields (compare entry 4 with entries 1-3), unless they were sterically too demanding (see *t*BuMgCl, entry 5). Aromatic **TBDMS-C1-SAD**s were also produced in good yields (74% to 93%, entries 6-10) and appeared not to depend on the

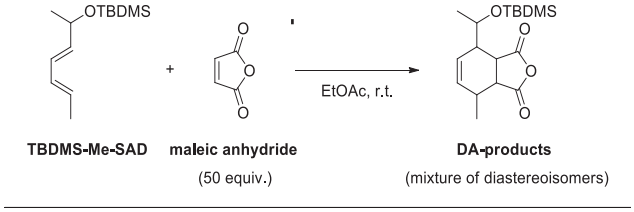
electronic character of the aromatic nucleophile. But our streamlined synthesis showed limitations when **TBDMS-PhC≡C-SAD** was produced (entry 11). Purification by FCC on silica could not be circumvented in this case because the *in situ* generated Li-phenylacetylide (PhC≡CLi) nucleophile was employed. The acidic aqueous workup of the reaction mixture following the nucleophilic addition to sorbaldehyde produced the high boiling byproduct phenylacetylene (b.p. 142 °C to 144 °C), which could not be removed by rotary evaporation. This was confirmed by IR analysis of the initially isolated **TBDMS-PhC≡C-SAD** sample, which showed the presence of the alkynic C–H bond at 3300 cm^{-1} (pointing to the presence of phenyl acetylene as this bond is absent in our expected product). After FCC on silica the purified **TBDMS-PhC≡C-SAD** did not display this characteristic IR peak anymore.

Table 1. Synthesis of TBDMS-C1-SADs.



Entry	RM	C1-R	Isolated Yield (%)
1	MeMgCl	Me	77
2	EtMgBr	Et	83
3	*i*PrMgCl	*i*Pr	80
4	*n*BuLi	*n*Bu	79
5	*t*BuMgCl	*t*Bu	not detected
6	PhMgBr	Ph	93
7	*p*-tolylMgBr	*p*-tolyl	74
8	*p*-OPh-PhMgBr	*p*-OPh-Ph	78
9	*p*-F-PhMgBr	*p*-F-Ph	80
10	*p*-Cl-PhMgBr	*p*-Cl-Ph	80
11	PhC≡CLi[b]		56[a]

[a]generated in situ from PhC≡CH and n-BuLi. [b]isolated by FCC on silica.



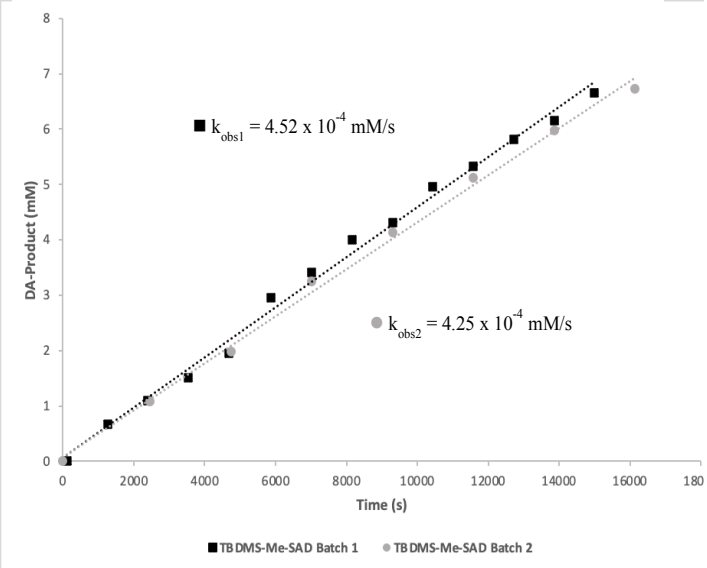


Figure 2. (top) illustration of the Diels-Alder reaction of TBDMS-Me-SAD with maleic anhydride in EtOAc at room temperature; (bottom) graph illustrating the formation of Diels-Alder products (exo plus endo) over time for each reaction with a different TBDMS-Me-SAD batch.

Purity consistency of this modified synthetic pathway was tested by comparing Diels-Alder reaction rates of two separately synthesized **TBDMS-Me-SAD** batches, which were converted with excess maleic anhydride (50 equiv.) in EtOAc under pseudo-first order reaction conditions (**Figure 2, top**). GC-MS monitoring of these reactions in the presence of hexamethylbenzene as an internal standard displayed the expected linear relationship for the formation of Diels-Alder products (*exo* and *endo* combined) over time and similar rate constants k_{obs1} = 4.52 x 10^{-4} mM/s (■) and k_{obs2} = 4.25 x 10^{-4} mM/s (●) for each reaction (**Figure 2, bottom**). These results suggested that our streamlined synthetic pathway produced **TBDMS-Me-SAD** samples with consistent purity.

We envision that the straightforward synthesis of **TBDMS-C1-SAD**s presented herein will give us access to a variety of analogues in the near future. The simplicity of this reaction sequence combined with its time flexibility renders this process ideal for undergraduate research. For example, one or two Grignard reactions could be setup by a trained student in 1 h using premade Grignard solutions. Each reaction would run for 2 h, which allows for time management (i.e. setting up the reactions before class). Both reactions could be worked up (acidification, extraction, washes, drying, filtration, evaporation) in 2 h (1 h per reaction), which would allow for the immediate protection of the concentrated **C1-SAD** samples using our protocol. The reaction time of these TBDMS protections is tolerant (ranging from 24 h to 96 h), which equips the student with the needed flexibility to complete the remaining work up and purification steps (2-3 h for both reactions) at a later time. This flexible synthesis schedule suits undergraduate researchers very well and will increase our efficiency in obtaining **TBDMS-C1-SAD**s.

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