organics

MDPI

Article

Esterifications with 2-(Trimethylsilyl)ethyl 2,2,2-Trichloroacetimidate

Wenhong Lin, Shea T. Meyer, Shawn Dormann and John D. Chisholm *

1-014 Center for Science and Technology, Department of Chemistry, Syracuse University, Syracuse, NY 13244, USA; wlin11@syr.edu (W.L.); smeyer@syr.edu (S.T.M.); sdormann@syr.edu (S.D.)
* Correspondence: jdchisho@syr.edu; Tel.: +1-315-443-6894

Abstract: 2-(Trimethylsilyl)ethyl 2,2,2-trichloroacetimidate is readily synthesized from 2-trimethylsilylethanol in high yield. This imidate is an effective reagent for the formation of 2-trimethylsilylethyl esters without the need for an exogenous promoter or catalyst, as the carboxylic acid substrate is acidic enough to promote ester formation without an additive. A deuterium labeling study indicated that a β-silyl carbocation intermediate is involved in the transformation.

Keywords: esters; β-silyl carbocations; trichloroacetimidates; protecting groups; C-O bond formation

Citation: Lin, W.; Meyer, S.T.; Dormann, S.; Chisholm, J.D. Esterifications with 2-(Trimethylsilyl)ethyl 2,2,2-Trichloroacetimidate. *Organics* **2021**, *2*, 17–25. https://doi.org/10.3390/org2010002

Academic Editor: Wim Dehaen
Received: 17 January 2021
Accepted: 1 February 2021
Published: 4 February 2021

1. Introduction

Esters are ubiquitous protecting groups for organic molecules with a carboxylic acid functionality. Demand for specialized esters that can be cleaved under mild conditions in complex molecules has led to the development of a number of creative solutions [1,2]. The trimethylsilylethyl (TMSE) ester [3,4] has become popular in this context, as the ester can be easily cleaved (with acid, [5] base [6] or fluoride [7–9]) without disturbing most other benzyl or alkyl esters. TMSE esters may also be transformed to other esters or lactones by capturing the carboxylate resulting from treatment with fluoride with an electrophile [10,11]. Similar chemistry can be employed to decarboxylate TMSE-protected β-keto esters, facilitating the enantioselective formation of all carbon quaternary centers [12]. Despite its synthetic utility, the most common methods of forming TMSE esters directly from a carboxylic acid remain dependent on carbodiimide based reagents [3,13–17], Mukaiyama's reagent [18–20], or utilize Mitsunobu conditions [21–25]. While effective, these transformations are often plagued by issues with the separation of side products and also create significant waste streams.

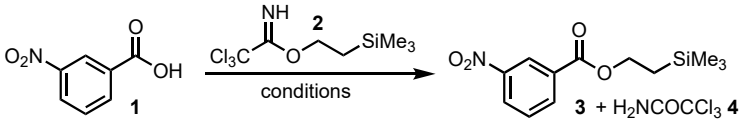
Recently, we have been involved in a number of studies evaluating the promoter free reactivity of trichloroacetimidate electrophiles with nitrogen [26,27], sulfur [28], and oxygen [29] nucleophiles. Carboxylic acids have been noted to be alkylated under promoter-free conditions via symbiotic activation by trichloroacetimidates that are precursors to stabilized carbocations, including the 2-phenylisopropyl [30,31], 4-methoxybenzyl [32], diphenylmethyl [33], and *tert*-butyl imidates [34]. Given that trichloroacetimidates are simple to prepare from inexpensive starting materials and that the esterifications often proceed under mild conditions without the need for an exogenous promoter or catalyst, the formation of TMSE esters using this chemistry was investigated. Use of the previously unknown trimethylsilylethyl trichloroacetimidate **2**, which may be a precursor to a β-silyl stabilized carbocation that can be trapped with an carboxylic acid, would provide a mild method for installing a TMSE ester with trichloroacetamide **4** as the sole by product, which is easily removed by washing with aqueous sodium hydroxide.

2. Results and Discussion

Initially, the preparation of trimethylsilylethyl 2,2,2-trichloroactimidate **2** was investigated. Imidate **2** was readily formed in 97% yield by reaction of commercially available 2-trimethylsilylethanol with trichloroacetonitrile using DBU as a catalyst following the

conditions developed by Schmidt and co-workers [35]. With the imidate (**2**) in hand, the esterification reaction was explored (Table 1) using 3-nitrobenzoic acid **1** as a test substrate. Use of TMSOTf led to the destruction of the imidate without formation of any ester product. Switching to the Brønsted acids CSA and PPTS did provide some ester product when catalytic amounts of the acids were used; however, the yields were low (entries 4 and 6). These poor yields were attributed to decomposition of the imidate in the presence of the strong acid catalysts. Esterification under promoter free conditions [32–34] was then explored by heating carboxylic acid **1** and imidate **2** in refluxing toluene for 24 h (entry 7). These conditions gave complete conversion to the TMSE ester, but the ester product was difficult to separate from the excess imidate. Allowing the reaction mixture to cool to rt and treating the mixture with 1% TFA/H_2O resulted in the hydrolysis of the excess imidate and led to the isolation of an 81% yield of the desired ester **3**. As we had previously shown that these conditions were optimal for esterifications with other imidates [34], no further optimization was performed.

Table 1. Esterification of 3-nitrobenzoic acid **1** with trimethylsilylethyl (TMSE) imidate **2**.

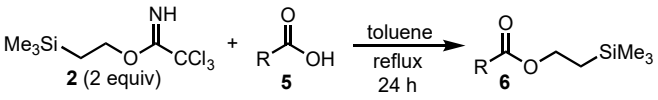


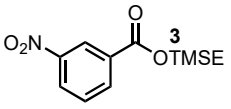
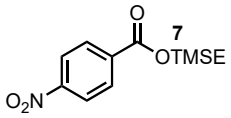
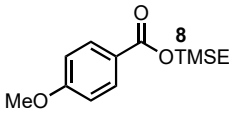
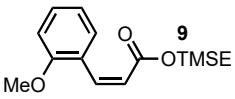
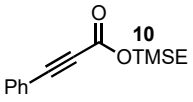
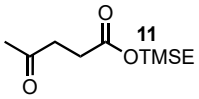
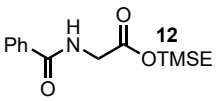
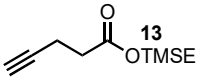
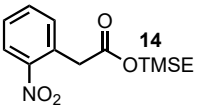
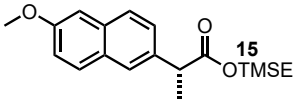
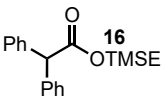
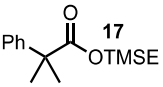
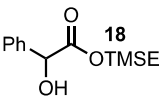
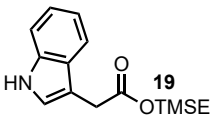
Entry	Equiv 2	Promoter (Equiv.)	Solvent	*t* (h)	*T*	Yield [a]
1	1.2	TMSOTf (1.0)	DCM	1	rt	0 [b]
2	1.2	TMSOTf (0.2)	DCM	1	rt	0 [b]
3	1.2	CSA (1.0)	DCM	1	rt	0 [b]
4	1.2	CSA (0.2)	DCM	1	rt	22
5	1.2	PPTS (1.0)	DCM	1	rt	0 [b]
6	1.2	PPTS (0.2)	DCM	1	rt	17
7	2.0	none	toluene	24	reflux	81 [c]

[a] isolated yields. [b] imidate was consumed, but the starting acid remained. [c] crude reaction was subjected to 1% aq. TFA to remove excess imidate.

The scope of the esterification reaction was then explored (Table 2). Benzoic acids bearing electron-withdrawing groups generally produced higher yields than benzoic acids with electron-donating groups due to the acid being both a substrate and a proton source, which can activate the imidate. The lower yield observed with compound **7** was attributed to the sensitivity of this substrate, which has been shown to decompose when exposed to mild acid like silica gel or wet $CDCl_3$ [36]. Esters conjugated with alkenes (like **9**) and alkynes (like **10**) were also successfully formed under these reaction conditions. No isomerization of the *Z* alkene in ester **9** was observed in the crude ^{1}H NMR or the purified product. Alkyl substituted esters were also good substrates for the esterification reaction (Table 2, entries 6–12). The lower yield in the case of alkynyl ester **13** was due to difficulties in handling this volatile product. No racemization was observed in the formation of the naproxen ester **15**, demonstrating that the conditions are compatible with nearby chiral centers. The presence of alcohol in the carboxylic acid substrate was detrimental to the esterification process; however, as some of the alcohol was converted to the OTMS ether by the excess imidate. Clean conversion to the TMSE ester was accomplished by using one equiv of imidate **2**, but the yield of ester was lower when compared to other acids. In the case of ester **19,** the yield was low and the ester appeared to be undergoing decomposition. This may have been due to side reactions between the indole and the imidate, as indoles are known to be alkylated with imidate electrophiles [37–42], although these reactions usually require a Lewis acid promoter. Lowering the reaction temperature to 100 °C and increasing the reaction time to 29 h improved the yield to 78% in this case.

Table 2. Esterifications with Imidate **2**.



Entry	Product	Yield
1		81
2		56
3		66
4		58
5		56
6		90
7		65
8		44 [a]
9		75
10		76
11		63
12		57
13		45 [b]
14		38 (78 [c])

[a] Product was volatile. [b] Only 1 equiv of imidate was used.[c] Performed at 100 °C.

In earlier cases of thermal esterifications with trichloroacetimidates, evidence suggested that carbocation intermediates were involved [34]. For the esterification with 2-(trimethylsilyl)ethyl 2,2,2-trichloroacetimidate **2,** this implicates the proposed mechanism shown in Figure 1. Proton transfer from the acid **5** to the imidate **2** forms the protonated imidate **20**, which then dissociates trichloroacetamide **4** leading to the formation of the β-silyl carbocation **21**. β-Silyl carbocations like **21** are known to be unusually stable due to hyperconjugation from the nearby silicon-carbon bond [43]. Based on experimental and computational evidence, the structure of this cation is best represented by the bridged silyl cation **22** rather than the primary carbocation structure represented by **21** [43,44]. Addition of the carboxylate to the cation **22** then provides the observed ester product.

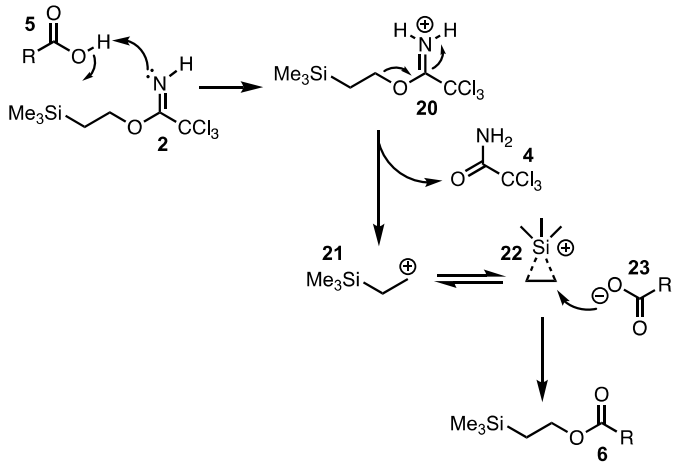
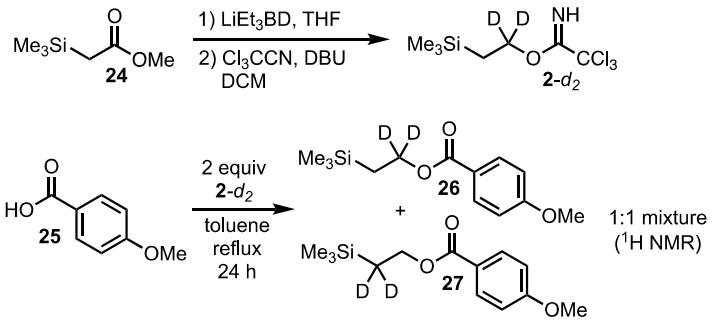


Figure 1. Proposed mechanism of the esterification.

While the ability of the trimethylsilyl group to stabilize a β-carbocation is well known, an S_N2 mechanism where the carboxylate directly displaced the acetamide from the protonated imidate **20** could not be ruled out. To gain further insight into the reaction mechanism, a deuterated version of imidate **2** was synthesized (Scheme 1). This involved the reduction of methyl trimethylsilylacetate **24** with lithium triethylborodeuteride to provide the deuterated alcohol. This alcohol was then converted to the corresponding deuterated imidate **2**-d_2, which was utilized in an esterification with 4-methoxybenzoic acid **25**. This esterification resulted in the formation of two deuterated esters (**26** and **27**) in equal amounts, implying that the bridged β-silyl cation **22** was indeed an intermediate in the esterification reaction.



Scheme 1. Deuterium labeling implicates a bridged carbocation intermediate.

Attempts were also made to form trimethylsilylethyl ethers with alcohols (4-nitrobenzyl alcohol and diphenylmethanol were utilized) and phenols (4-nitrophenol and 4-chlorophenol were used) under similar conditions (toluene, reflux). These experiments showed no formation of the TMSE ether, and the starting materials were recovered. Evidently, phenols and alcohols are not acidic enough to promote etherification through activation of the imidate. Employing Lewis or Brønsted acids to catalyze or promote the formation of TMSE ethers

(TMSOTf and CSA were used) led to decomposition of the imidate and only trace amounts of the desired TMSE ether, so these attempts were abandoned.

3. Conclusions

In summary, 2-(trimethylsilyl)ethyl 2,2,2-trichloroacetimidate was prepared from the corresponding alcohol. This reagent provides a new method for the formation of the valuable TMSE esters by simply heating the unprotected carboxylic acid with the imidate. These thermal reactions proceed under near neutral conditions and create significantly less waste than other transformations that depend on carbodiimide- and diazodicarboxylate-based reagents. A mechanistic study implies that the esterifications proceed through a carbocation manifold.

4. Materials and Methods

All anhydrous reactions were run under a positive pressure of argon. DCM was dried by passage through an alumina column. 1,2-Dichloroethane (DCE) was freshly distilled from calcium hydride before use. Silica gel column chromatography was performed using 60 Å silica gel (230−400 mesh). Melting points are uncorrected. Copies of NMR (^{1}H and ^{13}C) spectra and chiral HPLC traces for ester 15 are available in the associated Supplementary Materials.

4.1. Synthesis of Imidates

2-(Trimethylsilyl)ethyl 2,2,2-trichloroacetimidate (2). 2-(Trimethylsilyl)ethanol (10.2 mmol, 1.46 mL) and trichloroacetonitrile (10 mmol, 1.00 mL) were dissolved in dichloromethane (20 mL) in a flame-dried round bottom flask under argon. With a gas tight syringe, 1,8-diazabicyclo[5.4.0]undec-7-ene (1.05 mmol, 157 µL) was gradually added into the reaction mixture at room temperature. The reaction was stirred vigorously for an hour. The resulted reaction mixture was then concentrated in vacuo. The residue was purified with a silica gel plug (85% hexanes/10% EA/5% Et_3N) to give imidate **2** as a clear oil (2.55 g, 97%). TLC R_f = 0.59 (10% EA/90% hexanes); IR (ATR) 3346, 2954, 2897, 1660, 1249, 835, 821 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (bs, 1H), 4.40 (t, *J* = 8.4 Hz, 2H), 1.17 (t, *J* = 8.4 Hz, 2H), 0.09 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 163.0, 91.7, 68.1, 17.0, −1.4. HRMS (ESI): *m/z* Calcd for $C_7H_{14}Cl_3NOSiNa$ (M + Na^+): 283.9802. Found: 283.9802.

2-(Trimethylsilyl)(1,1-d_2)ethyl 2,2,2-trichloroacetimidate (2-d_2). Synthesized using the same procedure as **2** using the known 2-(trimethylsilyl)(*1,1-d_2*)ethanol (2-(trimethylsilyl)(*1,1-d_2*)ethanol was prepared as previously reported [45]). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (bs, 1H), 1.15 (s, 2H), 0.09 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 163.0, 91.7, 67.4 (t, *J* = 22.6 Hz), 16.7, −1.4.

4.2. Esterification Reactions

General Procedure for Esterification with 2-(Trimethylsilyl)ethyl 2,2,2-trichloroacetimidate. Trichloroacetimidate **2** (260 mg, 1.0 mmol, 2.0 equiv) was added via a syringe to a stirred solution of the specified acid (0.5 mmol, 1.0 equiv.) in anhydrous toluene (2 mL, 0.25 M) at room temperature. The reaction mixture was warmed to a gentle reflux. After 18–24 h, the reaction mixture was allowed to cool to room temperature and concentrated in vacuo. In cases where the excess imidate was difficult to separate from the TMSE ester product (as in esters **3**, **8**, and **10**), the crude residue was dissolved in ethyl acetate and stirred with 1% aq. TFA until consumption of excess imidate **2** was observed by TLC. The organic layer was then washed with 2 M aq. NaOH (2×), which removes the trichloroacetamide by-product) and brine, dried with Na_2SO_4, filtered, and concentrated. The residue was then purified by silica gel chromatography to provide the ester product.

2-(Trimethylsilyl)ethyl 3-nitrobenzoate (3). TLC R_f = 0.35 (10% EA/90% hexanes); IR (ATR) 3088, 2956, 2899, 1722, 1533, 1350, 1259, 861, 838 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.87 (t, *J* = 1.8 Hz, 1H), 8.42 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 8.37 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 4.49 (t, *J* = 8.5 Hz, 2H), 1.18 (t, *J* = 8.6 Hz, 2H), 0.11 (9H, s); ^{13}C{^{1}H} NMR

($CDCl_3$, 100 MHz) δ 164.6, 148.3, 135.2, 132.5, 129.5, 127.2, 124.5, 64.3, 17.5, −1.5; HRMS (ESI): *m/z* Calcd for $C_{12}H_{17}NO_4SiNa$ ($M + Na^+$): 290.0819. Found: 290.0817.

2-(Trimethylsilyl)ethyl 4-nitrobenzoate (7). TLC R_f = 0.294 (5% EA/95% hexanes); IR (ATR) 3122, 2953, 2896, 1708, 1522, 1348, 1249, 859, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.30 (d, *J* = 9.0 Hz, 2H), 8.22 (d, *J* = 9.0 Hz, 2H), 4.48 (t, *J* = 8.5 Hz, 2H), 1.17 (t, *J* = 8.5 Hz, 2H), 0.10 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 164.8, 136.1, 130.6, 123.5, 115.8, 64.4, 17.4, −1.5. This compound has been previously reported [46].

2-(Trimethylsilyl)ethyl 4-methoxybenzoate (8). TLC R_f = 0.54 (10% EA/90% hexanes); IR (ATR) 2952, 2897, 1707, 1274, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 4.40 (t, *J* = 8.4 Hz, 2H), 3.87 (s, 3H), 1.13 (t, *J* = 8.3 Hz, 2H), 0.08 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 166.5, 163.2, 131.5, 123.2, 113.5, 62.9, 55.4, 17.4, −1.4. Anal. Calcd for $C_{13}H_{20}O_3Si$: C, 61.87; H, 7.99. Found: C, 61.47; H, 7.79. HRMS (ESI) *m/z* Calcd for $C_{13}H_{20}O_3SiNa$ ($M + Na^+$): 275.1073. Found: 275.1071.

2-(Trimethylsilyl)ethyl (2Z)-3-(2-methoxyphenyl)prop-2-enoate (9). TLC R_f = 0.31 (5% EA/95% hexanes); IR (ATR) 3040, 2951, 2895, 1717, 1249, 859, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.58 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.30–7.34 (m, 1H), 7.17 (d, *J* = 12.4 Hz, 1H), 6.93 (td, *J* = 11.3, 0.5 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 5.97 (d, *J* = 12.4 Hz, 1H), 4.19 (t, *J* = 8.5 Hz, 2H), 3.85 (s, 3H), 0.92 (t, *J* = 8.5 Hz, 2H), 0.02 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.5, 157.1, 138.9, 130.8, 130.3, 124.1, 120.1, 119.9, 110.2, 62.3, 55.4, 17.1, −1.6. Anal. Calcd for $C_{14}H_{22}O_3Si$: C, 64.71; H, 7.96. Found: C, 64.74; H, 7.76.

2-(Trimethylsilyl)ethyl 3-phenylprop-2-ynoate (10). TLC R_f = 0.33 (5% EA/95% hexanes); IR (ATR) 2952, 2897, 2217, 1704, 1282, 858, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.58–7.60 (m, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 2H), 4.34 (t, *J* = 8.6 Hz, 2H), 1.11 (t, *J* = 8.6 Hz, 2H), 0.09 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.3, 133.0, 130.5, 128.5, 119.7, 85.8, 81.0, 64.5, 17.3, −1.5. Anal. Calcd for $C_{14}H_{18}O_2Si$: C, 68.25; H, 7.36. Found: C, 67.98; H, 7.60.

2-(Trimethylsilyl)ethyl 4-oxopentanoate (11). TLC R_f = 0.47 (20% EA/80% hexanes); IR (ATR) 2955, 1717 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.11–4.15 (m, 2H), 2.71 (t, *J* = 6.3 Hz, 2H), 2.51 (t, *J* = 6.3 Hz, 2H), 2.15 (s, 3H), 0.93–0.97 (m, 2H) 0.00 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 208.3, 174.4, 64.4, 39.5, 31.4, 29.7, 18.7, 0.00. HRMS (ESI) *m/z* Calcd for $C_{10}H_{20}O_3SiNa$ ($M + Na^+$): 239.1073. Found: 239.1072.

(Trimethylsilyl)ethyl benzoylaminoethanoate (12). TLC R_f = 0.58 (20% EA/80% hexanes); IR (ATR) 3319, 2951, 2897, 1734, 1646, 1536,1249, 1194, 1176, 859 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80–7.84 (m, 2H), 7.43–7.55 (m, 3H), 6.65 (bs, 1H), 4.28–4.34 (m, 2H), 4.23 (d, *J* = 4.7 Hz, 2H), 1.02–1.08 (m, 2H), 0.06 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.6, 168.9, 135.3, 133.2, 130.1, 128.6, 65.1, 43.5, 18.9, 0.0. HRMS (ESI) *m/z* Calcd for $C_{14}H_{21}NO_3SiNa$ ($M + Na^+$): 302.1182. Found: 302.1178.

2-(Trimethylsilyl)ethyl pent-4-ynoate (13). TLC R_f = 0.45 (10% EA/90% hexanes); IR (ATR) 3309, 2953, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.16–4.20 (m, 2H), 2.45–2.54 (m, 4H), 1.96 (m, 1H), 0.96–1.00 (m, 2H), 0.02 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.4, 84.1, 70.5, 64.4, 35.0, 18.8, 15.8, 0.0. HRMS (ESI) *m/z* Calcd for $C_{10}H_{18}O_2SiNa$ ($M + Na^+$): 221.0968. Found: 221.0968.

2-(Trimethylsilyl)ethyl 2-nitrobenzoate (14). TLC R_f = 0.21 (10% EA/90% hexanes); IR (ATR) 2953, 2897, 1732, 1525, 1380, 1249, 859, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, *J* = 8.1 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 4.21 (m, 2H), 4.02 (s, 2H), 1.00 (m, 2H), 0.02 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz) δ 170.0, 148.9, 133.5, 133.3, 129.9, 128.5, 125.3, 63.6, 40.0, 12.2, −1.6. Anal. Calcd for $C_{13}H_{19}NO_4Si$: C, 55.49; H, 6.81; N, 4.98. Found: C, 55.11; H, 6.44; N, 4.90.

2-(Trimethylsilyl)ethyl (2R)-2-(6-methoxynaphthalen-2-yl)propanoate (15). TLC R_f = 0.65 (20% EA/80% hexanes); IR (ATR) 2950, 1722, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.67–7.77 (m, 3H), 7.42 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.12–7.16 (m, 2H), 4.11–4.23 (m, 2H), 3.91 (s, 3H), 3.84 (q, *J* = 7.2 Hz, 1H), 1.58 (d, *J* = 7.2 Hz, 3H), 0.92–0.97 (m, 2H) 0.00 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.3, 159.1, 137.4, 135.2, 130.8, 130.5, 128.6, 127.8, 127.5, 120.4,

107.1, 64.6, 56.9, 47.2, 20.1, 18.8, 0.0. Anal. Calcd for $C_{19}H_{26}O_3Si$: C, 69.05; H, 7.93. Found: C, 69.30; H, 7.76. The enantiopurity was determined by chiral HPLC (AD-H column), n-hexane: *i*-PrOH = 99:1, 1 mL/min; t_1 = 7.5; t_2 = 8.6 min.

2-(Trimethylsilyl)ethyl 2,2-diphenylacetate (16). TLC R_f = 0.59 (10% EA/90% hexanes); IR (ATR) 2952, 2895, 1730, 1496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22–7.34 (m, 10H), 4.99 (s, 1H), 4.22–4.28 (m, 2H), 0.97–1.02 (m, 2H), 0.00 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.4, 140.3, 130.2, 130.1, 128.7, 65.1, 58.8, 18.8, 0.0. Anal. Calcd for $C_{19}H_{24}O_2Si$: C, 73.03; H, 7.74. Found: C, 73.37; H, 8.10.

2-(Trimethylsilyl)ethyl 2-methyl-2-phenylpropanoate (17). TLC R_f = 0.37 (5% MTBE/95% hexanes); IR (ATR) 3060, 2952, 2896, 1724, 1250, 858, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31–7.37 (m, 4H), 7.21–7.26 (m, 1H), 4.16 (t, *J* = 8.5 Hz, 2H), 1.58 (s, 6H), 0.92 (t, *J* = 8.5 Hz, 2H), −0.02 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.9, 144.9, 128.3, 126.6, 125.7, 63.1, 46.5, 26.5, 17.1, -1.6. Anal. Calcd for $C_{15}H_{24}O_2Si$: C, 68.13; H, 9.15. Found: C, 67.78; H, 9.22.

2-(Trimethylsilyl)ethyl 2-hydroxy-2-phenylacetate (18). TLC R_f = 0.18 (10% EA/90% hexanes); IR (ATR) 3457, 3064, 3032, 2953, 2897, 1728, 1250, 859, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31–7.44 (m, 5H), 5.14 (s, 1H), 4.17–4.35 (m, 2H), 3.50 (bs, 1H), 0.97 (t, *J* = 8.6 Hz, 2H), 0.00 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.8, 138.5, 128.5, 128.4, 126.6, 73.0, 64.7, 17.2, −1.6. HRMS (ESI) *m/z* Calcd for $C_{13}H_{20}O_3SiNa$ ($M + Na^+$): 275.1073. Found: 275.1071.

2-(Trimethylsilyl)ethyl 2-(1H-indol-3-yl)acetate (19). TLC R_f = 0.63 (20% EA/80% hexanes); IR (ATR) 3350, 1715, 1662, 1462, 1309, 1248 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (bs, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 8.2, 1H), 7.11–7.22 (m, 3H), 4.18–4.24 (m, 2H), 3.76 (s, 2H), 0.98–1.03 (m, 2H), 0.03 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.8, 137.6, 128.8, 124.6, 123.6, 121.1, 120.4, 112.7, 110.1, 64.6, 33.1, 18.8, 0.0. Anal. Calcd for $C_{15}H_{21}NO_2Si$: C, 65.41; H, 7.69; N, 5.09. Found: C, 65.02; H, 8.04; N, 5.15.

2-(Trimethylsilyl)(1,1-d_2)ethyl 4-methoxybenzoate (26) and 2-(Trimethylsilyl)(2,2-d_2)ethyl 4-methoxybenzoate (27). TLC R_f = 0.54 (10% EA/90% hexanes); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 4.40 (t, *J* = 8.4 Hz, 2H), 3.87 (s, 3H), 1.13 (t, *J* = 8.3 Hz, 2H), 0.08 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 166.5, 163.2, 131.5, 123.2, 113.5, 62.9, 55.4, 17.4, −1.4.

Supplementary Materials: The following are available online at https://www.mdpi.com/2673-401X/2/1/2/s1, PDF file containing copies of NMR Spectra (^1H and ^{13}C) and chiral HPLC traces for Ester **15**.

Author Contributions: Conceptualization, J.D.C.; Investigation, W.L., S.T.M. and S.D.; Methodology, W.L., S.T.M. and S.D.; Project administration, J.D.C.; Writing—Original draft, W.L. and J.D.C.; Writing—Review and editing, J.D.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available in supplementary materials.

Acknowledgments: Christopher M. Russo is thanked for some preliminary experiments.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Wuts, P.G.M. *Greene's Protective Groups in Organic Synthesis*, 5th ed.; John Wiley & Sons: Hoboken, NJ, USA, 2014.
2. Kocienski, P.J. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, Germany, 2005.
3. Sieber, P. The 2-trimethylsilylethyl residue, a selectively cleavable carboxyl protecting group. *Helv. Chim. Acta* **1977**, *60*, 2711–2716. [CrossRef]
4. Gerlach, H. 2-(Trimethylsilyl)ethyl esters as a carboxyl protecting group; application in the synthesis of (-)-(S)-curvularin. *Helv. Chim. Acta* **1977**, *60*, 3039–3044. [CrossRef]

5. Wood, J.L.; Thompson, B.D.; Yusuff, N.; Pflum, D.A.; Matthaeus, M.S.P. Total Synthesis of (±)-Epoxysorbicillinol. *J. Am. Chem. Soc.* **2001**, *123*, 2097–2098. [CrossRef] [PubMed]
6. Serrano-Wu, M.H.; Regueiro-Ren, A.; St. Laurent, D.R.; Carroll, T.M.; Balasubramanian, B.N. Mild deprotection of 2-(trimethylsilyl)ethyl esters. *Tetrahedron Lett.* **2001**, *42*, 8593–8595. [CrossRef]
7. Allen, J.G.; Danishefsky, S.J. The Total Synthesis of (±)-Rishirilide B. *J. Am. Chem. Soc.* **2001**, *123*, 351–352. [CrossRef]
8. Forsch, R.A.; Rosowsky, A. Methotrexate analogs. 21. Selective cleavage of 2-(trimethylsilyl)ethyl esters in the presence of N-tert-butyloxycarbonyl groups during the synthesis of protected dilysine and trilysine derivatives of methotrexate. *J. Org. Chem.* **1984**, *49*, 1305–1309. [CrossRef]
9. Fustero, S.; Sancho, A.G.; Acena, J.L.; Sanz-Cervera, J.F. Fluorous TBAF: A Convenient and Selective Reagent for Fluoride-Mediated Deprotections. *J. Org. Chem.* **2009**, *74*, 6398–6401. [CrossRef]
10. Vedejs, E.; Larsen, S.D. Total synthesis of d,l-fulvine and d,l-crispatine. *J. Am. Chem. Soc.* **1984**, *106*, 3030–3032. [CrossRef]
11. Fustero, S.; Sanchez-Rosello, M.; Rodrigo, V.; Garcia, A.; Catalan, S.; del Pozo, C. Selective Formal Transesterification of Fluorinated 2-(Trimethylsilyl)ethyl α-Imino Esters Mediated by TBAF. *J. Org. Chem.* **2008**, *73*, 5617–5620. [CrossRef]
12. Reeves, C.M.; Behenna, D.C.; Stoltz, B.M. Development of (Trimethylsilyl)ethyl Ester Protected Enolates and Applications in Palladium-Catalyzed Enantioselective Allylic Alkylation: Intermolecular Cross-Coupling of Functionalized Electrophiles. *Org. Lett.* **2014**, *16*, 2314–2317. [CrossRef]
13. Bourne, G.T.; Horwell, D.C.; Pritchard, M.C. Synthesis of an α-CH_2CO_2H functionalized tryptophan and its incorporation into an analog of cholecystokinin. *Tetrahedron* **1991**, *47*, 4763–4774. [CrossRef]
14. Boger, D.L.; Yohannes, D. Total synthesis of OF4949-III and OF4949-IV: Unusual effects of remote substituents on the rate of macrocyclization reactions. *Tetrahedron Lett.* **1989**, *30*, 5061–5064. [CrossRef]
15. Nicolaou, K.C.; Namoto, K.; Ritzen, A.; Ulven, T.; Shoji, M.; Li, J.; D'Amico, G.; Liotta, D.; French, C.T.; Wartmann, M.; et al. Chemical synthesis and biological evaluation of cis- and trans-12,13-cyclopropyl and 12,13-cyclobutyl epothilones and related pyridine side chain analogues. *J. Am. Chem. Soc.* **2001**, *123*, 9313–9323. [CrossRef]
16. Baran, P.S.; Shenvi, R.A. Total Synthesis of (±)-Chartelline C. *J. Am. Chem. Soc.* **2006**, *128*, 14028–14029. [CrossRef] [PubMed]
17. Horning, B.D.; MacMillan, D.W.C. Nine-Step Enantioselective Total Synthesis of (-)-Vincorine. *J. Am. Chem. Soc.* **2013**, *135*, 6442–6445. [CrossRef]
18. Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guedin-Vuong, D. Total synthesis of a macrocyclic pyrrolizidine alkaloid, (±)-integerrimine, utilizing an activable protecting group. *J. Am. Chem. Soc.* **1984**, *106*, 2954–2961. [CrossRef]
19. Knutsen, L.J.S.; Judkins, B.D.; Newton, R.F.; Scopes, D.I.C.; Klinkert, G. Synthesis of imidazo-fused bridgehead-nitrogen 2′-deoxyribo-C-nucleosides: Coupling-elimination reactions of 2,5-anhydro-3,4,6-tri-O-benzoyl-D-allonic acid. *J. Chem. Soc. Perkin Trans.* **1985**, *1*, 621–630. [CrossRef]
20. White, J.D.; Amedio, J.C., Jr.; Gut, S.; Ohira, S.; Jayasinghe, L.R. Stereoselective synthesis of the pyrrolizidine alkaloids (-)-integerrimine and (+)-usaramine. *J. Org. Chem.* **1992**, *57*, 2270–2284. [CrossRef]
21. Jones, P.; Villeneuve, G.B.; Fei, C.; De Marte, J.; Haggarty, A.J.; Nwe, K.T.; Martin, D.A.; Lebuis, A.-M.; Finkelstein, J.M.; Gour-Salin, B.J.; et al. Synthesis and Structure-Activity Relationships of 2-Pyrazinylcarboxamidobenzoates and β-Ionylideneacetamidobenzoates with Retinoidal Activity. *J. Med. Chem.* **1998**, *41*, 3062–3077. [CrossRef]
22. Roush, W.R.; Madar, D.J.; Coffey, D.S. Synthesis of highly functionalized naphthoate precursors to damavaricin D—Observation of kinetically stable benzocyclohexadienones in the bromination reactions of highly functionalized β-naphthol derivatives. *Can. J. Chem.* **2001**, *79*, 1711–1726.
23. Fürstner, A.; Bindl, M.; Jean, L. Concise total synthesis of cruentaren A. *Angew. Chem. Int. Ed.* **2007**, *46*, 9275–9278. [CrossRef]
24. Reed, S.A.; White, M.C. Catalytic Intermolecular Linear Allylic C-H Amination via Heterobimetallic Catalysis. *J. Am. Chem. Soc.* **2008**, *130*, 3316–3318. [CrossRef]
25. Cheng, Y.; Tang, S.; Guo, Y.; Ye, T. Total synthesis of anti-tuberculosis natural products Ilamycins E1 and F. *Org. Lett.* **2018**, *20*, 6166–6169. [CrossRef]
26. Wallach, D.R.; Stege, P.C.; Shah, J.P.; Chisholm, J.D. Brønsted Acid Catalyzed Monoalkylation of Anilines with Trichloroacetimidates. *J. Org. Chem.* **2015**, *80*, 1993–2000. [CrossRef]
27. Wallach, D.R.; Chisholm, J.D. Alkylation of Sulfonamides with Trichloroacetimidates under Thermal Conditions. *J. Org. Chem.* **2016**, *81*, 8035–8042. [CrossRef] [PubMed]
28. Duffy, B.C.; Howard, K.T.; Chisholm, J.D. Alkylation of thiols with trichloroacetimidates under neutral conditions. *Tetrahedron Lett.* **2015**, *56*, 3301–3305. [CrossRef]
29. Howard, K.T.; Duffy, B.C.; Linaburg, M.R.; Chisholm, J.D. Formation of DPM ethers using O-diphenylmethyl trichloroacetimidate under thermal conditions. *Org. Biomol. Chem.* **2016**, *14*, 1623–1628. [CrossRef] [PubMed]
30. Thierry, J.; Yue, C.; Potier, P. 2-Phenylisopropyl and t-butyl trichloroacetimidates: Useful reagents for ester preparation of N-protected amino acids under neutral conditions. *Tetrahedron Lett.* **1998**, *39*, 1557–1560. [CrossRef]
31. Respondek, T.; Cueny, E.; Kodanko, J.J. Cumyl Ester as the C-Terminal Protecting Group in the Enantioselective Alkylation of Glycine Benzophenone Imine. *Org. Lett.* **2012**, *14*, 150–153. [CrossRef]
32. Shah, J.P.; Russo, C.M.; Howard, K.T.; Chisholm, J.D. Spontaneous formation of PMB esters using 4-methoxybenzyl-2,2,2-trichloroacetimidate. *Tetrahedron Lett.* **2014**, *55*, 1740–1742. [CrossRef]

33. Adhikari, A.A.; Shah, J.P.; Howard, K.T.; Russo, C.M.; Wallach, D.R.; Linaburg, M.R.; Chisholm, J.D. Convenient Formation of Diphenylmethyl Esters Using Diphenylmethyl Trichloroacetimidate. *Synlett* **2014**, *25*, 283–287.
34. Mahajani, N.S.; Meador, R.I.L.; Smith, T.J.; Canarelli, S.E.; Adhikari, A.A.; Shah, J.P.; Russo, C.M.; Wallach, D.R.; Howard, K.T.; Millimaci, A.M.; et al. Ester Formation via Symbiotic Activation Utilizing Trichloroacetimidate Electrophiles. *J. Org. Chem.* **2019**, *84*, 7871–7882. [CrossRef]
35. Ali, I.A.I.; Ashry, E.S.H.E.; Schmidt, R.R. Protection of Hydroxy Groups with Diphenylmethyl and 9-Fluorenyl Trichloroacetimidates—Effect on Anomeric Stereocontrol. *Eur. J. Org. Chem.* **2003**, *2003*, 4121–4131. [CrossRef]
36. Green, A.J.; Kuan, Y.L.; White, J.M. Rearrangement of r-5-methyl-c-2-(trimethylsilyl)cyclohexan-t-yl 2,4-dinitrobenzoate in chloroform. *J. Chem. Soc. Chem. Commun.* **1994**, 2023–2024. [CrossRef]
37. Schmidt, R.R.; Effenberger, G. O-glycosyl imidates. 29. Reaction of O-(glucopyranosyl) imidates with electron-rich heterocycles. Synthesis of C-glucosides. *Liebigs Ann. Chem.* **1987**, *19*, 825–831. [CrossRef]
38. Li, C.; Wang, J. Lewis Acid Catalyzed Propargylation of Arenes with O-Propargyl Trichloroacetimidates: Synthesis of 1,3-Diarylpropynes. *J. Org. Chem.* **2007**, *72*, 7431–7434. [CrossRef] [PubMed]
39. Devineau, A.; Pousse, G.; Taillier, C.; Blanchet, J.; Rouden, J.; Dalla, V. One-Pot Hydroxy Group Activation/Carbon-Carbon Bond Forming Sequence Using a Brønsted Base/Brønsted Acid System. *Adv. Synth. Catal.* **2010**, *352*, 2881–2886. [CrossRef]
40. Wiebe, C.; de la Sotilla, S.F.; Opatz, T. Synthesis of 1,3- and 2,3-diglycosylated indoles as potential trisaccharide mimetics. *Synthesis* **2012**, *44*, 1385–1397.
41. Adhikari, A.A.; Radal, L.; Chisholm, J.D. Synthesis of 3,3′-Disubstituted Indolenines Utilizing the Lewis Acid Catalyzed Alkylation of 2,3-Disubstituted Indoles with Trichloroacetimidates. *Synlett* **2017**, *28*, 2335–2339. [PubMed]
42. Suzuki, T.; Chisholm, J.D. Friedel-Crafts alkylation of indoles with trichloroacetimidates. *Tetrahedron Lett.* **2019**, *60*, 1325–1329. [CrossRef]
43. Lambert, J.B.; Wang, G.T.; Finzel, R.B.; Teramura, D.H. Stabilization of positive charge by β-silicon. *J. Am. Chem. Soc.* **1987**, *109*, 7838–7845. [CrossRef]
44. Chiavarino, B.; Crestoni, M.E.; Lemaire, J.; Maitre, P.; Fornarini, S. Communication: Infrared spectroscopy of protonated allyltrimethylsilane: Evidence for the β-silyl effect. *J. Chem. Phys.* **2013**, *139*, 071102. [CrossRef]
45. Sharma, P.K.; Dawid, M.; Warkentin, J.; Vestal, R.M.; Wudl, F. Mechanism of Migration of the Trimethylsilyl Group during Reactions of Methoxy[(trimethylsilyl)ethoxy]carbene with N-Phenylmaleimide and C60. *J. Org. Chem.* **2001**, *66*, 7496–7499. [CrossRef] [PubMed]
46. Green, A.J.; Issa, W.; White, J.M. Influence of trimethylsilyl substituents on primary C-O bond lengths at the β-position: Results from low-temperature x-ray structural studies. *Aust. J. Chem.* **1997**, *50*, 927–932. [CrossRef]