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Mechanism of β-Silyl Diacyl Peroxide Decomposition: A Mild and Stereoselective Synthesis of β-Silyl Esters

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A novel method for the formation of β-silyl esters is presented. Mechanistic studies were carried out on the formation and decomposition of β-silyl diacyl peroxides, showing that the decomposition pathway involves an ionic mechanism that is influenced by the presence of the β-silyl moiety. These studies exclude a free radical decomposition pathway as evidenced by the absence of chemically induced dynamic nuclear polarization (CIDNP) during the reaction and a strong correlation of the resulting regioisomeric product distribution to σ^+. This reaction allows for the formation of β-silyl esters in 45−50% isolated yield with predictable regioselectivity and good to excellent diastereoselectivity. Studies demonstrate that ester products which are formed at benzylic centers have the *erythro* configuration, whereas ester products formed at alkyl centers have the *threo* configuration.

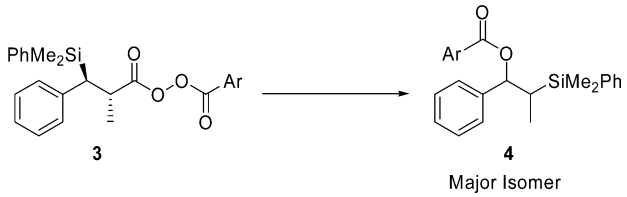
Introduction

Organic peroxides are known to undergo diverse transformations.[1] Although free radical mechanisms dominate the chemistry of peroxides, it has been known for some years that diacyl peroxides undergo ionic decomposition.[2−8] Diacyl peroxides, for example, undergo a carboxyinversion reaction when heated in a polar solvent[2,4−6] that generates products such as **2** shown in Scheme 1. Over the last 30 years there have been only a handful of reports dealing with the mechanism of this transformation.

Although the carboxyinversion reaction has been little studied, it is commonly accepted that diacyl peroxides simultaneously undergo ionic and free radical decomposition processes when heated in polar solvents.[6] A combination of chemically induced dynamic nuclear polarization (CIDNP) experiments and product identification has established that the products of diacyl peroxide decomposition arise through simultaneous electron transfer (e_t), radical, and ionic pathways.[2−4,6] Increasing the solvent polarity results in more products being formed through ionic pathways, whereas decreasing solvent polarity results in increased production of products derived from free radical decomposition. Carboxyinversion is believed to occur through a polar but concerted reaction mechanism as supported by studies with chiral substrates.[3,7]

SCHEME 1. Representative Carboxyinversion Reaction of Diacyl Peroxides

SCHEME 2. Attempted Preparation of 3 with Isolation of 4 (Ar = *m*-ClPh)



The known Criegee rearrangement is another example of a concerted rearrangement involving peroxy compounds. The Criegee rearrangement results from a concerted but polar rearrangement of peroxy esters. See ref 1 for examples of the Criegee rearrangement.

We had cause to prepare the previously unknown β-silyl diacyl peroxide compound **3** shown in Scheme 2 for possible use as a precursor to β-silyl free radicals. In the course of attempts to prepare compounds such as **3**, we discovered that β-silyl esters **4** are instead formed in reasonable yield and good to excellent diastereoselectivity. We report here on mechanistic studies that aim to elucidate the mechanism for the formation of the unexpected β-silyl esters **4** and explain the role that silicon plays in the decomposition of **3** (Scheme 2).

Results and Discussion

Initial attempts to prepare and isolate compound **3** involved the use of standard methods for the preparation

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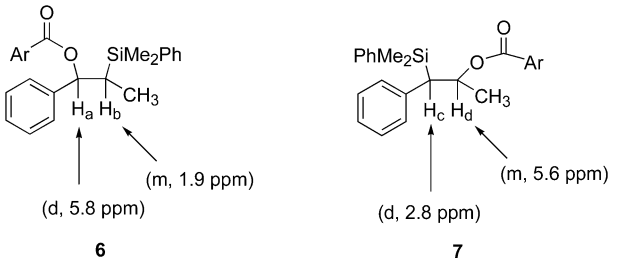
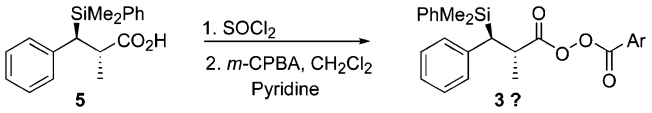


FIGURE 1. NMR evidence for regioisomeric esters **6** and **7** (relative stereochemistry not shown, Ar = *m*-ClPh).

SCHEME 3. Attempted Preparation of 3

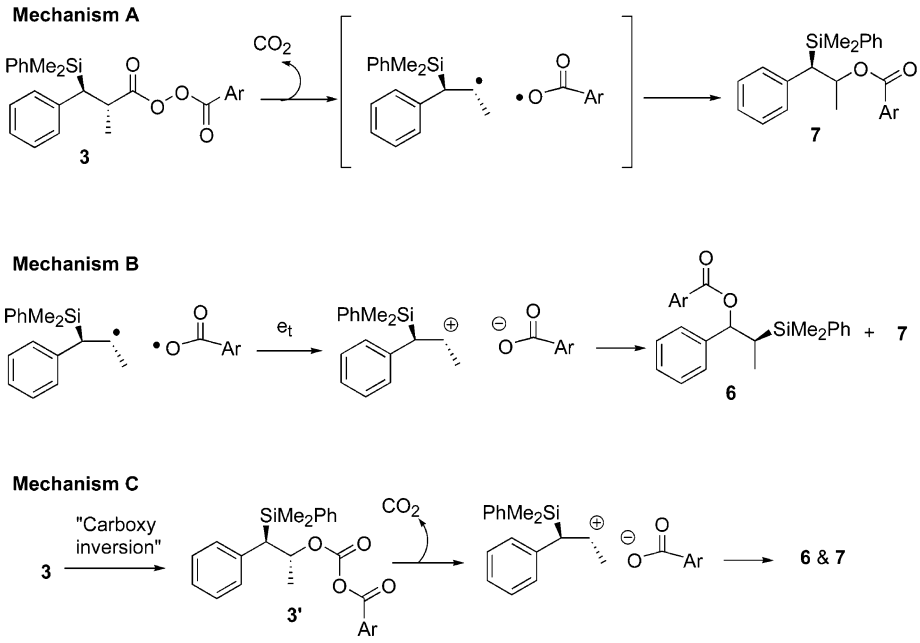


of diacyl peroxides.[9] The attempted synthesis of **3** made use of the known β-silyl carboxylic acid **5**,[10] which was transformed into the corresponding acid chloride by conventional methods. The acid chloride of **5** was then treated with a single equivalent of pure *m*-CPBA in dichloromethane at −10 °C. The reaction was monitored by thin-layer chromatography, which indicated that both the starting acid chloride and *m*-CPBA had been completely consumed. Chromatography also indicated the presence of two new products (Scheme 3), neither of which were peroxides as determined by the use of a peroxide-sensitive thin-layer stain.[11] The crude reaction mixture was subjected to chromatography and the more polar of the two products was isolated and subjected to IR, MS, and NMR spectral analysis. The IR analysis revealed the absence of the characteristic diacyl peroxide absorptions[12] and the presence of a single strong band at 1722 cm^{-1}, indicative of ester functionality.[12] MS analysis of the products generated by the chemistry described in Scheme 3 was consistent with loss of CO_2 from the desired diacyl peroxide **3**. Both 1D and 2D ^1H NMR analysis was performed and revealed that the isolated compound was in fact a mixture of two regioisomeric esters. The ^1H NMR analysis established that the major product was benzylic ester **6** and the minor product was the secondary alkyl ester **7**. Figure 1 shows the structures assigned to major product **6** and minor product **7** along with the diagnostic ^1H NMR signals used to assign the respective regioisomers. 2D NMR techniques were employed to unambiguously assign structures to the isomers **6** and **7**, shown in Figure 1. As illustrated from Scheme 3 and Figure 1, a formal migration of the silyl moiety must occur in order to obtain the major regioisomer **6**. Although a pair of regioisomers was formed during this transformation, it should be noted that each compound was produced as a single diastereomer as determined from ^1H and ^{13}C NMR experiments on the crude reaction mixture.

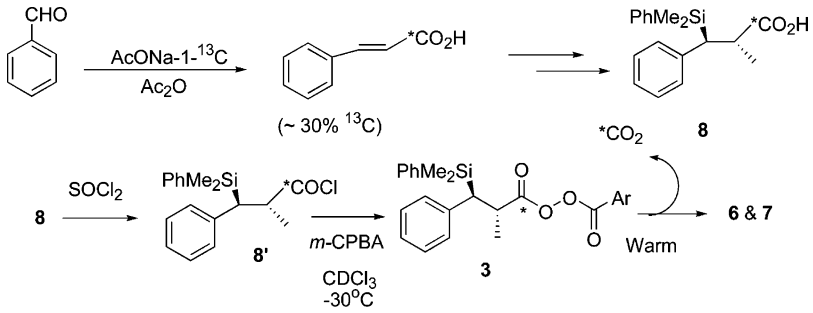
Three plausible mechanisms, shown in Scheme 4, could account for the formation of esters **6** and **7** from the reaction of **5** with thionyl chloride and *m*-CPBA. Mechanism A proceeds through an initially formed diacyl peroxide intermediate **3** that decomposes by a free radical mechanism to give loss of CO_2 and generate a solvent caged radical pair. The radical pair could then simply recombine, producing ester **7**. This mechanism can be discounted since a regioisomeric mixture of β-silyl esters is produced and there is no evidence from previous studies that β-silyl radicals undergo silyl rearrangement.[13,14]

Mechanism B also makes use of intermediate **3** but differs from mechanism A in that the initially formed radical pair undergoes electron transfer, a step that is reasonable on the basis both that decarboxylation of the aryl carboxyl radical is slow and that the ion pair may be energetically more stable than the radical pair (a β-silyl cation has a stabilization energy of ~38 kcal/mol,[15] whereas a β-silyl radical has a stabilization energy of only 3−4 kcal/mol[16,17]). Following electron transfer, the result-

SCHEME 4. Possible Mechanisms for the Formation of β-Silyl Esters (Ar = *m*-ClPh)



SCHEME 5. Preparation of ^{13}C-Labeled 8 and Use in CO_2 CIDNP Study (Ar = *m*-ClPh)



ing β-silyl cation could rearrange,[18] giving the observed regioisomeric mixture of ester products (**6** and **7**).

Mechanism C differs from mechanisms A and B in that **3** decomposes via a carboxyinversion process[2−4,6,7] instead of a free radical process. Loss of CO_2 from the intermediate **3′** could occur, giving an ion pair. The resulting β-silyl cation could then undergo facile rearrangement and trapping by the carboxylate anion to produce the observed regioisomeric mixture of esters. Having discounted mechanism A on the basis of the product distribution, we considered experiments that would discriminate between mechanisms B and C.

Mechanisms B and C differ in that B proceeds by a radical pair whereas C is polar-concerted and ionic. We devised a ^{13}C labeling experiment in order to determine whether CIDNP signals could be observed during the transformation. Detection of a significant ^{13}C CIDNP signal for the liberated CO_2 would be strong evidence for a mechanism involving radical pair intermediates as required for mechanism B.[6] Compound **8** was prepared as shown in Scheme 5 such that the carboxylic acid was approximately 30% enriched in ^{13}C label. Acid **8** was prepared by a known literature procedure[10] from labeled cinnamic acid, which was prepared by a Perkin reaction with ^{13}C-sodium acetate as the ^{13}C source.[19] The resulting acid **8** was converted to the acid chloride **8′** by standard methods.

The acid chloride **8′** in dry *d*-chloroform was placed in the NMR spectrometer and cooled to −30 °C. This solution was treated with a single equivalent of *m*-CPBA and the reaction was monitored by NMR at −30 °C. A sole signal in the carbon NMR spectrum at 171.98 ppm was observed and assigned to the suspected diacyl peroxide **3**. The compound appeared to be stable over the course of acquiring the spectrum at −30 °C. The temperature of the NMR probe was then raised to ambient and a signal corresponding to ^{13}C-labeled CO_2 was immediately observed. No evidence of an enhanced absorption or emission CIDNP signal was detected for the liberated CO_2. Absence of a CIDNP signal for CO_2 suggests the absence of free radical intermediates in the decomposition of diacyl peroxide **3** (see Supporting Information for ^{13}C spectra).

We consistently observed 45−50% yield of ester products with quantitative conversion of starting materials by both ^{1}H NMR and TLC analysis. To account for the remaining mass balance, a ^{13}C experiment was devised that would allow for straightforward detection of all products formed during this transformation. Labeled β-silyl acid **9** was prepared by conventional synthetic techniques as shown in Scheme 6. Acid **9** was then treated with *m*-CPBA/DCC[20] and ^{13}C NMR analysis was performed on the crude reaction mixture.

The NMR analysis of the product mixture revealed the presence of three products. The esters **6** and **7** had been previously identified in earlier experiments but were shown by this experiment to be only one diastereomeric form. Olefin **10** was the only other product observed, and it was found to comprise about 50% of the reaction mixture by comparison of the NMR signals. Olefin **10** was isolated from the reaction mixture and analyzed further by MS and ^{1}H NMR, confirming its structure compared to authentic material.[21]

The data gathered from both ^{13}C NMR experiments are taken as strong evidence against a free radical mechanism and for a carboxyinversion−ionic decomposition pathway. It is expected that in an ionic decomposition the ratio of ester products would be strongly dependent on phenyl substituents in the para position of the aromatic ring. A series of para-substituted β-silyl acids was therefore prepared in order to determine the dependence of the ester product ratio on the phenyl substituent. Table 1 presents product distributions from the reaction of substituted β-silyl acids with *m*-CPBA, and the data were subjected to a Hammett analysis. A strong correlation for the data exists only by the use of the σ^+ parameter. The Hammett analysis gives a ρ value of −1.2, which is taken as strong evidence of a cationic mechanism for the transformation (Figure 2).

Products **6** and **7** can also be accessed by the reaction of silyl carboxylic acid **11** with *m*-CPBA. Compound **11**

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SCHEME 6. ^{13}C Benzylic Labeling Experiment: Identification and Quantification of Olefin 10 and Esters 6 and 7 (Ar = *m*-ClPh)

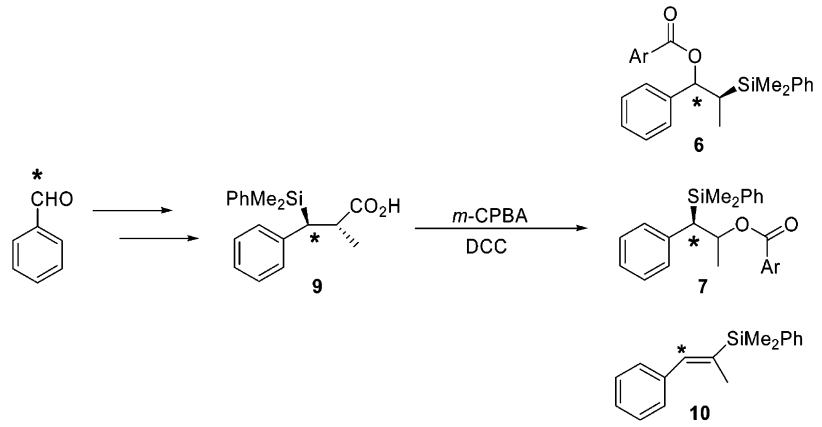
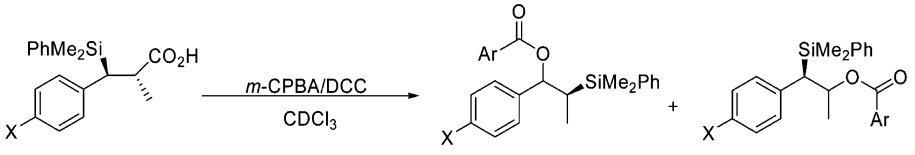


TABLE 1. Effect of Para Substituents on Regioselective Ester Ratio



3a X=H
3b X=Me
3c X=Cl
3d X=F
3e X=CF_3
3f X=$MeSO_2$

entry	substrate	% ester **6**[a]	% ester **7**[a]	yield[b] (%)
1	3a	85	15	50
2	3b	95	5	50
3	3c	86	14	42
4	3d	90	10	48
5	3e	56	44	39
6	3f	47	53	32

[a] Determined by ^{1}H NMR on crude reaction mixtures; average values of at least two experiments. [b] Determined by ^{1}H NMR relative to an internal standard of 1,1,2,2-tetrachloroethane; reported as the total yield of **6** and **7**.

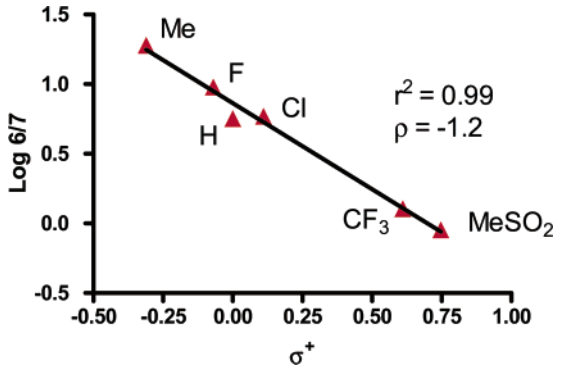


FIGURE 2. Hammett analysis of product ratio data from Table 1.

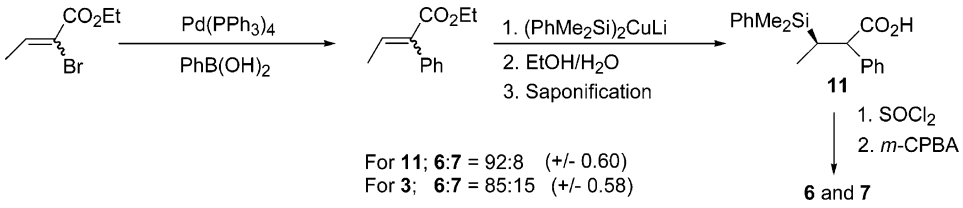
was prepared and converted to its acid chloride by conventional methods. The acid chloride of **11** was coupled with *m*-CPBA and the resulting product ester ratio was determined by ^{1}H NMR analysis of the crude reaction mixture as previously described (Scheme 7). The results suggest that **6** and **7** do not fully equilibrate since the product mixture obtained from acid **11** had measurably more **6** than that formed from the reaction of **3** with *m*-CPBA under identical conditions.

Reaction of **11** with *m*-CPBA gave a **6**:**7** ester ratio of 92:8, whereas an analogous reaction of **3** gave an ester ratio of 85:15. Both reactions gave ester products as about 50% of the product mixture, the remainder being the vinyl silane.

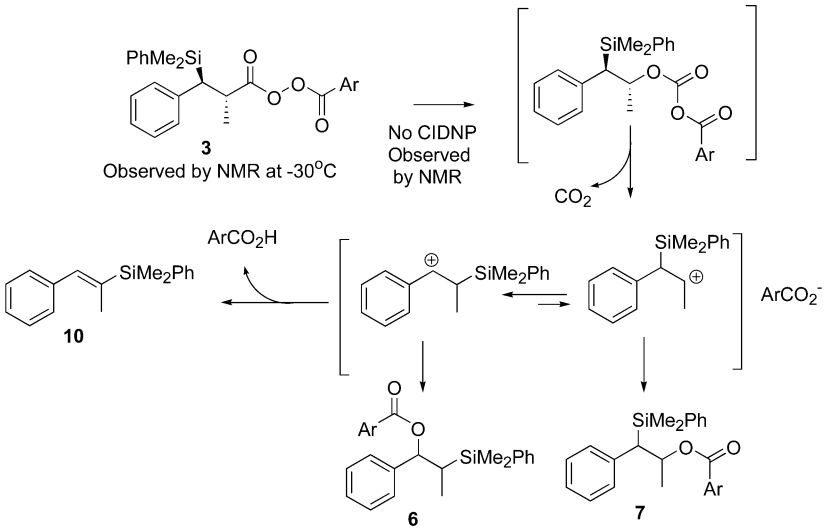
Scheme 8 presents a proposed mechanism for the conversion of **3** to esters **6** and **7** and olefin **10**. The carboxyinversion compound shown in the scheme was not observed in our NMR studies and is therefore not a required intermediate. Indeed, direct decomposition of the diacyl peroxide to form the stable β-silyl carbocation−carboxylate ion pair is a possible alternative. The carboxyinversion process is, however, a well-known pathway and we include it here based upon established precedent. Once the cationic intermediate is formed as a tight ion pair, rearrangement, β-elimination of a proton, and ion pair collapse produce the observed ester and olefin products.

The reaction illustrated in Scheme 8 produces a mixture of ester products but each product is produced as a single diastereomer. We prepared the acids **12** and

SCHEME 7. Preparation of 11 and Ester Ratio from Coupling 11 with *m*-CPBA



SCHEME 8. Proposed Decomposition Mechanism for Compound 3 (Ar = *m*-ClPh)



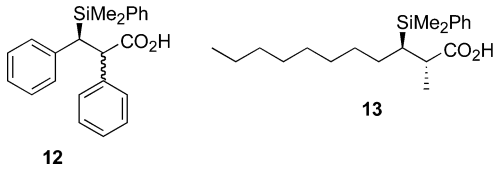


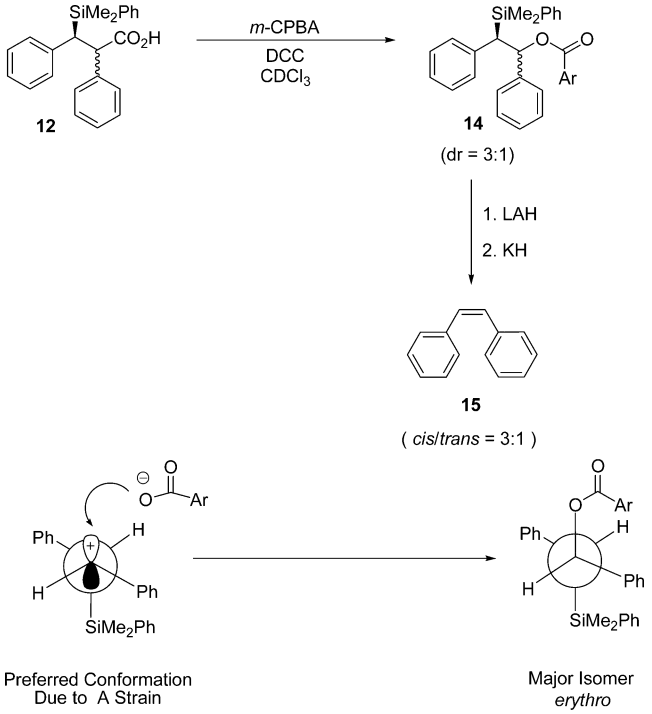
FIGURE 3. Compounds **12** and **13** for diastereoselectivity study.

13[13] (Figure 3) to further explore stereochemical questions raised by the transformation.

Compound **12** can only form benzylic cations after reaction with *m*-CPBA, while **13** can only form secondary alkyl cations. The *β*-silyl acid **12** was coupled with *m*-CPBA (DCC method) and the resulting esters (**14**) were isolated as a 3:1 mixture of diastereomers. The ester mixture **14** was then reduced to the corresponding *β*-silyl alcohol with LAH. The resulting alcohol mixture was immediately treated with an excess of KH to promote a syn-specific "Peterson-like" elimination (Scheme 9).[22] The resulting stilbene mixture obtained from the Peterson olefination reaction was analyzed by gas chromatography and found to contain a 3:1 mixture of cis/trans stilbene. The Peterson olefination, being syn-specific, could produce *cis*-stilbene as the major product only if the major diastereomer of **14** had the *erythro* relative configuration as illustrated in Scheme 9. Indeed, the major ester produced from the sequence would have the relative configuration shown in Scheme 9 if the stereocontrol element in the transformation was A-strain.

Compound **13** was coupled with *m*-CPBA and the resulting alkyl ester mixture (**16/17**) was isolated and

SCHEME 9. Determining the Configuration of the Major Isomer of 14 via Peterson Olefination (Ar = *m*-ClPh)



treated with TBAF to promote an anti-specific olefination reaction (Scheme 10).[22] Gas chromatographic analysis of mixture **16/17** resulted in an 8:1 ratio of cis/trans olefin by comparison to authentic samples. The major ester product obtained from **13** was expected to have a *threo* relative configuration as shown in Scheme 9. The major

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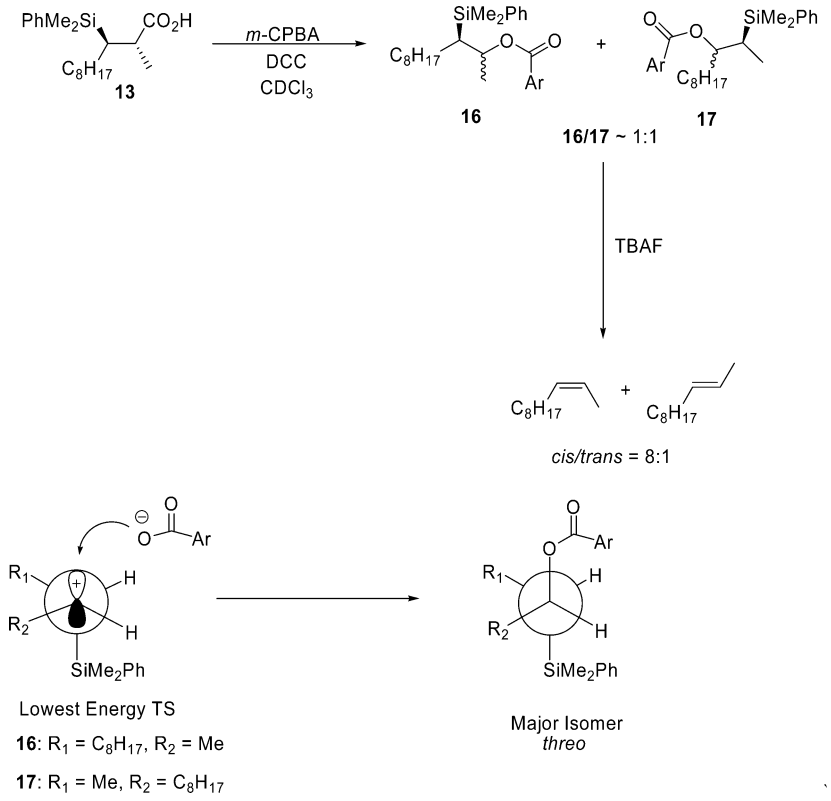
SCHEME 10. Determination of the Configuration of the Major Isomer of 16 and 17 via an Anti-Specific Elimination Sequence (Ar = *m*-ClPh)



ester from mixture **16/17** was shown to have the expected configuration since the cis olefin can only be produced from the *threo* configuration in an anti-specific elimination sequence (Scheme 10).

The result of the experiments, as illustrated in Schemes 9 and 10 above, demonstrates that the configurations of the ester products are controlled by elements that have been established by extensive investigations in analogous systems. In the case where the cation is trapped at a benzylic position, the resulting ester product has the *erythro* configuration that results from A-strain, which forces the two phenyl groups to obtain spatial arrangements that maximize their separation from one another (180°). In experiments where the cation is trapped at an alkyl position, the resulting ester product has the *threo* configuration as shown in Scheme 10 that results from minimizing interactions of the alkyl groups and the approaching nucleophile.

Conclusion

β-Silyl diacyl peroxides readily decompose to produce *β*-silyl esters in moderate yield with predictable regioselectivity and good to excellent diastereoselectivity. Decomposition of the *β*-silyl diacyl peroxide proceeds by an ionic process. The ionic decomposition produces silyl-stabilized cationic intermediates that readily undergo both trapping with a carboxylate anion and elimination producing an olefinic product. Configuration studies demonstrate that when the cation is a benzylic ion, trapping occurs to produce ester products of the *erythro* configuration. Alkyl cations are trapped to produce ester products having predominantly the *threo* configuration. This reaction allows for the mild and stereoselective formation of *β*-silyl esters from readily available materials. This procedure may find use for the in situ preparation of substrates used in the study of *β*-silyl cations.[23−26]

Experimental Section

Reaction of *β*-Silyl Acids with *m*-CPBA (Typical Procedure). A 25 mL round-bottom flask was charged with 0.10 g of (*RR*,*SS*)-2-methyl-3-phenyldimethylsilyl-3-phenylpropionic acid (**3**) (0.35 mmol), 10 mL of dry $CDCl_3$, and a stir bar. The resulting solution was cooled to −10 °C and 1 equiv of *m*-CPBA (60 mg) was added in one portion. After the *m*-CPBA had dissolved, 1.1 equiv of DCC (80 mg) was added. The solution was stirred for 2 h and allowed to reach 0 °C. Upon completion of the reaction, 0.5 equiv (relative to silyl acid) of 1,1,2,2-tetrachloroethane was added as an NMR standard and the resulting solution was filtered directly into an NMR tube. NMR analysis was performed immediately in order to obtain the ratio of ester products. NMR analysis revealed a 50% yield of ester products having an 85:15 ratio of regioisomers. Solvent was removed in vacuo and the residue was purified by preparative TLC (5% EtOAc/hexane trace triethylamine), giving an inseparable mixture of *β*-silyl esters. ^{1}H NMR (300 MHz, CD_2Cl_2) (major

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regioisomer) 0.28 (s, 3H), 0.30 (3, 3H), 0.90 (d, 3H, $J = 8$ Hz), 1.84−1.95 (m, 1H), 5.81 (d, 1H, $J = 10$ Hz), 7.20−7.40 (m, 9H), 7.50−7.53 (m, 3H), 7.60−7.70 (m, 1H), 7.75 (t, 1H, $J = 2$ Hz); (minor regioisomer) 0.09 (s, 3H), 0.10 (s, 3H), 1.21 (d, 3H, $J = 6$ Hz), 2.84 (d, 1H, $J = 10$ Hz), 5.61−5.68 (m, 1H). Aromatic protons of the minor isomer could not be accurately assigned and integrated due to overlap with aromatic signals of the major isomer. ^{13}C NMR (75 MHz, CD_2Cl_2) (major regioisomer) −4.1, −3.0, 12.2, 27.2, 80.9, 127.8, 128.3, 128.5, 128.8, 129.0, 129.5, 130.0, 130.2, 132.8, 133.3, 134.3, 134.7, 139, 141.3, 164.7. HRMS $C_{24}H_{25}ClO_2SiNa$ $(M + Na)^+$ 431.1204 calcd, 431.1197 found. IR (thin film) 1722 cm^{-1}.

Low-Temperature ^{13}C NMR Experiment. A 10 mL round-bottom flask was charged with 17 mg of **8** (0.06 mmol), 2 mL of dry CH_2Cl_2, and 1 mL of $SOCl_2$. The flask was connected to a reflux condenser and placed under an inert atmosphere. The solution was heated to reflux solvent overnight. The solution was cooled to room temperature and the solvent and excess $SOCl_2$ were removed in vacuo. The residue was taken up in 0.5 mL of dry $CDCl_3$ and placed in a dry NMR tube. The NMR tube was placed into the NMR and the probe was cooled to −30 °C. A ^{13}C NMR (100 MHz) was taken of the acid chloride, which gave an acid chloride signal at 177.7 ppm. The tube was quickly removed from the NMR and 1 equiv of *m*-CPBA was added along with 1 drop of pyridine-d_5. The sample was returned to the NMR and a spectrum was acquired at −30 °C, giving a signal at 172.0 ppm (consistent with a diacyl peroxide). The sample was then warmed to ambient temperature, whereupon the liberation of ^{13}C-CO_2 was immediately detected at 124.8 ppm.

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Supporting Information Available: NMR spectra of all new β-silyl acids and β-silyl esters **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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