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Polyphosphoric Acid Trimethylsilyl Ester Promoted Intramolecular Acylation of an Olefin by a Carboxylic Acid: Convenient Construction of C-18-Functionalized Δ^{14}-Hecogenin Acetate†

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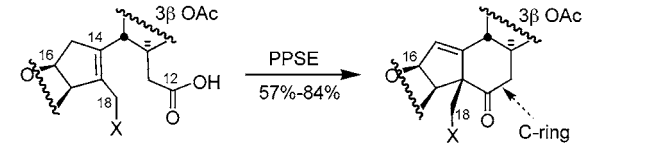
ABSTRACT



4: X = OCHO; **8a**: X = OAc;
8b: X = Cl; **8c**: X = Br; **8d**: X = SPh

5: X = OCHO; **9a**: X = OAc;
9b: X = Cl; **9c**: X = Br; **9d**: X = SPh

Polyphosphoric acid trimethylsilyl ester (PPSE)-promoted intramolecular Friedel–Crafts reactions on a nonaromatic carboxylic acid system have been investigated. Studies led to the synthesis of C-18 functionalized steroidal compounds 5 and 9a–d with strict retention of the spiroketals. Isomerization of spiroketal 9e was studied.

Polyphosphoric acid trimethylsilyl ester (PPSE) is a stable, colorless, viscous liquid that is soluble in most organic solvents. Although it was long known that phosphorus pentoxide reacted with excess hexamethyldisiloxane (HMDS) to give tris(trimethylsilyl) phosphate and tetrakis(trimethylsilyl) pyrophosphate,[1] while exploring the Beckmann rearrangement, Imamoto first reported the preparation of PPSE in 1981. This reagent is readily made by heating phosphorus pentoxide with HMDS in solvents such as dichloromethane, chloroform, or benzene under an argon atmosphere in the absence of acid.[2] Shortly thereafter, Yamamoto and Watanabe disclosed the composition of PPSE based on ^{31}P NMR.[3] The four components of PPSE are shown in Figure 1, and there was no tris(trimethylsilyl) phosphatedetectedunder the Imamoto conditions. The composition of PPSE was related to the solvent, and isocyclotetraphosphate (**1**) was held to be the most reactive species due to the presence of the branched phosphorus atoms.

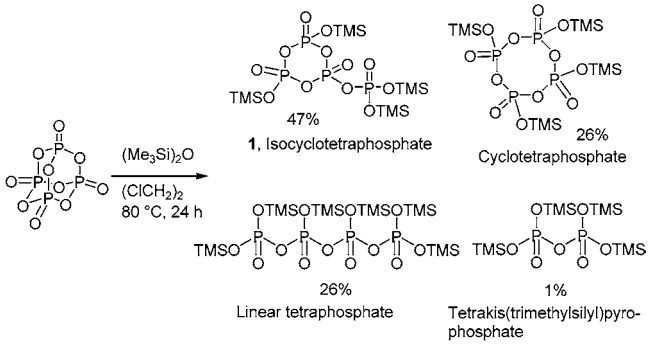


Figure 1. Composition of PPSE.

† Cephalostatin Support Studies. 29. For parts 26 and 27, see: Wei, L.; Fuchs, P. L. *Org. Lett.* **2003**, *5*, 2849, 2853.

(1) Sauer, R. O. *J. Am. Chem. Soc*. **1944**, *66*, 1707. (b) Voronkov, M. G. *Zh. Obshch. Khim*. **1955**, *25*, 437. (c) Mileshkevich, V. P.; Karlin, A. V. *Zh. Obshch. Khim* **1970**, *40*, 2573.

(2) Imamoto, T.; Yokoyama, H.; Yokoyama, M. *Tetrahedron Lett.* **1981**, *22*, 1803.

(3) Yamamoto, K.; Watanabe, H. *Chem. Lett*. **1982**, 1225.

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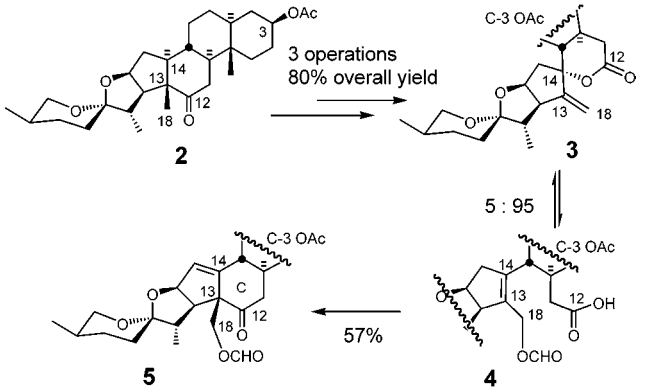
Halogenated solvents favored formation of **1** as the major component in the mixture.[3]

Since publication of these seminal observations, PPSE has been reported to promote reactions such as aldol condensations,[4] Beckmann rearrangements,[5] Pummerer rearrangements,[6] Meyer−Schuster rearrangements,[7] dehydration of amides into nitriles,[8] conversion of alcohols to iodides,[9] and cyclodehydrations leading to heterocycles.[10] However, PPSE-promoted Friedel−Crafts reactions of carboxylic acids have been essentially ignored. The only example prior to our studies[11] involved cyclization of aromatic carboxylic acids under strenuous reaction conditions (210 °C, P_2O_5, and PPSE syrup).[12]

Herein, we report our results of PPSE promoted Friedel−Crafts reactions of unsaturated steroidal acids under much milder conditions. The current study uses our recent protocol for oxidative functionalization of the C18 angular methyl group of hecogenin acetate **2** (Scheme 1).[11] PPSE-promoted

Scheme 1



Friedel−Crafts reaction to reclose the C-ring of acid **4** was a key step in the synthesis. The in situ procedure involves adding carboxylic acid **4** to a preformed solution of phosphorus pentoxide and hexamethyldisiloxane at reflux in K_2CO_3-dried 1,2-dichloroethane. This provided **5** in 57% yield along with 4% of **3** and 13% of C-15 side product **7** (Table 1, run 1), probably via C-15 acylation of intermediate **6** (Scheme 2).

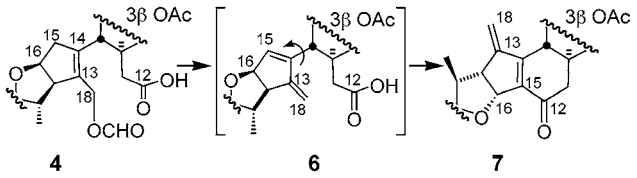
Table 1. Comparison of Friedel−Crafts Reactions of **4** Promoted by PPSE and PPE

run[a]	reagent	**5**[b] (%)	**7**[b] (%)	**3**[b] (%)
1	PPSE	57	13	4
2	PPE	26	40	10

[a] Both PPSE and PPE were made in situ and solution of acid **4** in 1,2-dichloroethane was added at reflux. [b] Isolated yield.

The unwanted compound **7** became the major product if the reaction was performed below reflux temperature, an indication that the formation of intermediate **6** was likely

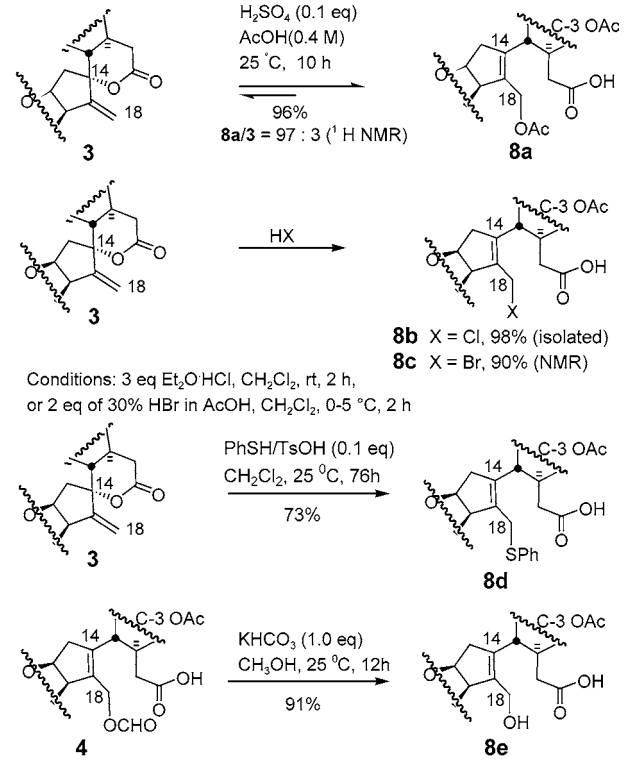
Scheme 2



kinetically controlled. When PPE was used instead of PPSE, compound **5** was formed in 26% yield with 40% of **7** and 10% of **3** (Table 1, run 2).

Table 1 shows that PPSE was a superior acylation promoter. The formation of **3** and **7** is apparently due to the sensitivity of the 18-formate to the PPSE reagent. To investigate this point, five additional substrates were prepared and subjected to the PPSE reaction. The substrate syntheses are outlined in Scheme 3.

Scheme 3



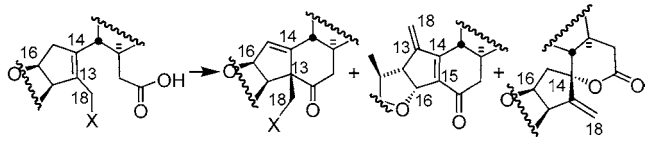
Treatment of olefinic lactone **3** with a catalytic amount of sulfuric acid in acetic acid gave an equilibrium mixture of **8a** and **3** (97:3) in 96% yield. In contrast, the reaction of **3** and hydrogen chloride etherate or hydrogen bromide (30%

(4) Imamoto, T.; Matsumoto, T.; Yokoyama, H.; Yokoyama, M.; Yamaguchi, K. I. *J. Org. Chem.* **1984**, *49*, 1105.
(5) Gawley, R. E.; Termine, E. J. *J. Org. Chem.* **1984**, *49*, 1946.
(6) Kakimoto, M.; Imai, Y. *Chem. Lett.* **1984**, *10*, 1831.
(7) Yoshimatsu, M.; Naito, M.; kawahigashi, M.; Shimizu, H.; Kataoka, T. *J. Org. Chem.* **1995**, *60*, 4798.
(8) Yokoyama, M.; Yoshida, S.; Imamoto, T. *Synthesis* **1982**, 591.

in AcOH) furnished **8b** (98% yield) or **8c** (90% yield) without a trace of **3**. The yield of **8c** was based on ^{1}H NMR integration because it suffered partial conversion to the starting material **3** during silica gel chromatography. Reaction of **3** with benzenethiol and catalytic *p*-toluenesulfonic acid furnished **8d** in 73% yield (80% based on recovered **3**). Selective hydrolysis of **4** with potassium bicarbonate in methanol gave **8e** in excellent yield.

With acids **8a**−**e** in hand, the in situ PPSE promoted intramolecular acylation reactions were performed, and the results are recorded in Table 2. Cyclized products **9a**−**d** were

Table 2. PPSE-Promoted Friedel−Crafts Reactions



8a, 8b, 8c, 8d, 8e **9a, 9b, 9c, 9d, 9e** **7** **3**

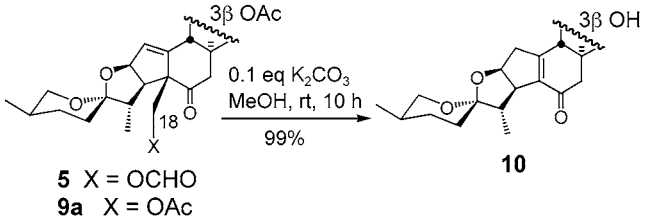
run[a]	substrate	product (%)	**7** (%)	**3** (%)
1	**8a**, X = OAc	**9a**, 70	8	2
2	**8b**, X = Cl	**9b**, 84	none[b]	none[b]
3	**8c**, X = Br	**9c**, 78	none[b]	none[b]
4	**8d**, X = SPh	**9d**, 74	none[b]	none[b]
5	**8e**, X = OH	**9e**, none	12	53

[a] The yields are isolated yield after chromatography except in run 5, which is based on ^{1}H NMR integration. [b] Based on crude ^{1}H NMR.

obtained in good yield for substrates **8a**−**d** (runs 1−4, respectively). Compounds **3** and **7** were not formed in runs 2 and 3 because *PPSE does not promote the elimination of halogens*. In contrast, substrate **8e** did not provide **9e**, presumably due to the strong interaction between 18-OH and PPSE (run 5).

Although **9a**−**c** were obtained in good yield, they could not be converted to **9e**. Both **5** and **9a** suffered retro-aldol reactions to give **10** (Scheme 4). As we described in a

Scheme 4

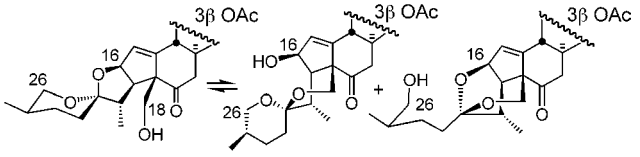


5 X = OCHO
9a X = OAc **10**

previous paper, **9e** was obtained in excellent yield by selective hydrolysis of **5** with catalytic $KHCO_3$ in methanol.[11]

The possible spiroketal equilibrium of **9e** is shown in Scheme 5. However, compound **11** was never detected.

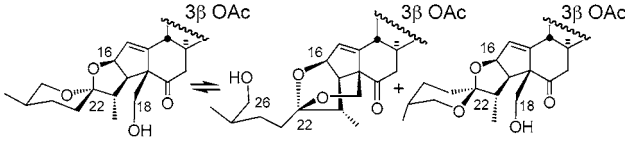
Scheme 5



9e **11** **12**

Studies of weak acid-catalyzed spiroketal equilibrium are shown in Table 3. The yield of component **12** appeared to be strongly related to the hydrogen-bonding ability of the solvent. Compound **13**, the C22 epimer of **9e**, featured a weak intramolecular hydrogen bond between 18-OH and the 22β oxygen. Consistent with the H-bond hypothesis, this compound was not detected in 75% aqueous acetic acid.

Table 3. Weak Acid-Catalyzed Spiroketal Equilibrium[a]



9e **12** (X-ray) **13**

catalyst	solvent[b]	*T* (°C)	ratio[c] **9e**/**12**/**13**
PPTS	CH_2Cl_2	25	67:28:5
PPTS	CH_2Cl_2/CH_3OH (1/1)	25	60:38:2
none	CH_2Cl_2/75% aq AcOH (2/1)	25	41:55:3
none	AcOH	25	37:61:2
none	75% aq AcOH	50−55	31:69:0

[a] For reactions under strong acidic conditions, see ref 11. [b] Compound **9e** is not soluble in methanol, ethyl acetate, diethyl ether, toluene, or 75% aq acetic acid at room temperature; however, it is soluble in dichloromethane and acetic acid (0.07 M). Both **12** and **13** have good solubility in most organic solvents. [c] Data are based on ^{1}H NMR integration.

In summary, mild *PPSE promoted Friedel−Crafts reactions of nonaromatic carboxylic acids are demonstrated for the first time.* This reaction provides a new and efficient route to C-18-functionalized, 12-keto steroids. Compared to the traditional Marker spiroketal degradation[13] followed by lead-mediated hypoiodite functionalization of C18 which required excision of the entire F-ring,[14] the approach described here retains the E- and F-rings. This enabled investigation of the spiroketal isomerization, which has led to the efficient

(9) Imamoto, T.; Matsumoto, T.; Kusumoto, T.; Yokoyama, M. *Synthesis* **1983**, 460.

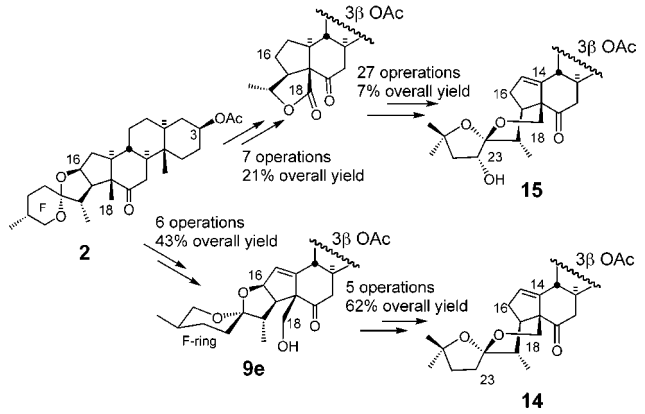
(10) (a) Müller, C. E. *J. Org. Chem.* **1994**, *59*, 1928. (b) Bennasar, M. L.; Vidal, B.; Lázaro, A.; Kumar, R.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 3541. (c) Garcia, M. B.; Orelli, L. R.; Magri, M. L.; Perillo, I. A. *Synthesis* **2002**, *18*, 2687. (d) Bergman, J.; Pelcman, B. *J. Org. Chem.* **1989**, *54*, 824. (e) Gawley, R. E.; Chemburkar, S. *Tetrahedron Lett.* **1986**, *27*, 2071.

(11) Li, W.; LaCour, T. G.; Fuchs, P. L. *J. Am. Chem Soc.* **2002**, *124*, 4548.

(12) Berman, E. M.; Hollis Showalter, H. D. *J. Org. Chem.* **1989**, *54*, 5642.

(13) *Chem. Eng. News* **1999**, Oct 25, 78.

Scheme 6



synthesis of C23-deoxy South 1 (**14**).[11] *The overall sequence is 23 operations shorter (Scheme 6*) than the previous approach to South 1 (**15**). Significantly, the GI_{50} values of the C23′-deoxy cephalostatin 1 were still in the nanomolar range in the NCI 10 cell line minipanel.[15]

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Supporting Information Available: Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra. The material is available free of charge via the Internet at http://pubs.acs.org.

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