Synthesis of Cyclic Ketones by Electrochemical Reduction of *S*-(2-Methoxycarbonyl)phenyl Thiolesters

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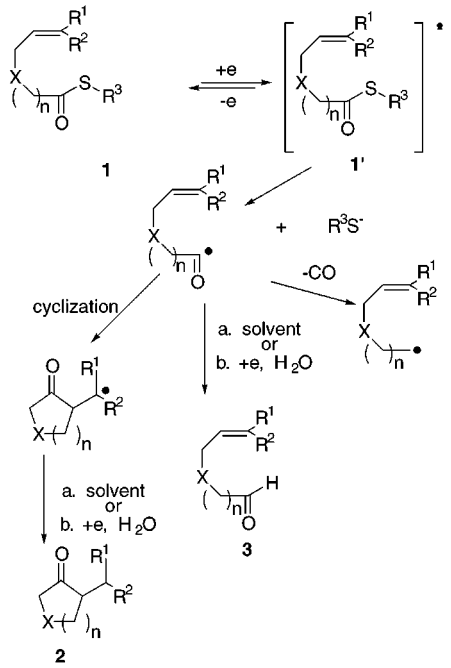
The generation of acyl radicals and their reaction with alkenes have been recognized as a useful and practical synthetic method for the formation of carbon−carbon bonds. Hitherto, synthetically useful acyl radicals have been generated by stannane-mediated chain sequences,[1] the chain reaction of S-acyl xanthate,[2] or photochemical methods.[3] The stannane-mediated methods, such as the reaction of *Se*-phenyl esters with tri-*n*-butyltin hydride (Bu_3SnH),[1a] intramolecular homolytic substitution at sulfur of thiolesters by aryl radicals generated by the reaction with tributyltin radical,[1b] or treatment of alk-4-enyl halides with the Bu_3SnH in the presence of carbon monoxide[1c] seem to be reliable methods. Though the tin hydride mediated approach to acyl radicals would be more reliable than photochemical methods, its utilization is not unproblematic. Tributyltin hydride is toxic and unstable. Furthermore, the tin byproducts represent ever increasing disposal problems.

In the course of the studies developing the catalytic electroreductive method of conducting radical reactions using nickel(II) complexes as an electron-transfer catalyst,[4] we reported recently on the studies of the synthesis of cyclic sulfides by S-heterocyclization by the ring closure of thiols to suitably placed multiple bonds[5a] or by intramolecular nucleophilic ring opening of epoxides by thiols,[5b] which are generated from the corresponding thiolacetates by the catalytic electroreduction.

In this note, we describe a synthetic method of cyclic ketones, which would proceed according to the reaction paths as shown in Scheme 1, i.e., by the intramolecular cyclization of the acyl radicals onto a suitably placed acceptor, which would be formed in pair with thiolates by the electroreduction of thiolesters.[6]

Scheme 1



Results and Discussion

In contrast with the catalytic electroreduction of thiolacetates,[5] both the catalytic and the direct electroreductions of *S*-phenyl 6-phenyl-5-hexenethioate, **X**, and *S*-butyl 6-phenyl-5-hexenethioate, **Y,** (Figure 1) were found to be very sluggish. For example, the electroreduction of **X** formed only 2% of cyclic ketone, 2-(phenylmethyl)cyclopentanone, and 14% of 6-phenyl-5-hexenal, while 35% of **X** remained unchanged after 4 F/mol of current was passed.

In seeking a thiolester that could undergo homolytic dissociation giving the acyl radicals on the electroreduction, a *S*-(2-methoxycarbonyl)phenyl 6-phenyl-5-hexenethioate, **1a,** which is slightly reducible (E_{pc} −2.06V vs SCE) compared to **X** (E_{pc} −2.28 V vs. SCE) and has a thiol group of higher acidity than that of **X** or **Y**,[7] was found to be reduced smoothly even without any electron-transfer catalyst, providing considerable amounts of the corresponding cyclopentanone.

Thus, *S*-(2-methoxycarbonyl)phenyl thiolesters **1** were used as precursors of acyl radicals. Typical electroreduction of thiolesters **1** was performed as descried in the Experimental Section. The results of the electroreduction are summarized in Table 1.

As shown in Table 1, the electroreduction of thiolesters **1a**,**d**,**e**,**f**, and **g** yielded the corresponding cycloketone **2** via **5**-*exo*- or 6-*exo* cyclization of the acyl radical onto alkenes in moderate to good yield. The yield tends to increase as the number of substituents at the acceptor alkene increases in accordance with the expectation of increased stability of cyclized radicals. The 6-*exo*-cyclization of the acyl radical (entry 3) to a phenyl-substituted alkene proceeded somewhat slower than the corresponding 5-*exo*-cylization (entry 1). A substrate **1b** afforded the corresponding aldehyde **3b** along with a cyclic product **2b**. This might be brought about by the fact that the acyl

(1) (a) Boger, D. L.; Mathvink, R. *J. Org. Chem.* **1992**, *57*, 1429−1443. (b) Crich, D.; Yao, Q. *J. Org. Chem.* **1996**, *61*, 3566−3570. (c) Ryu, I.; Kusano, K.; Hasegawa, M.; Kambe, N.; Sonoda, N. *J. Chem. Soc., Chem. Commun.* **1991**, 1018−1019. (d) Boeck, B. D.; Herbert, N.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 6971−6974.

(2) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672−685.

(3) (a) Penn, J. H.; Liu, F. *J. Org. Chem.* **1994**, *59*, 2608−2612. (b) Crich, D.; Chen, C.; Hwang, J.-T.; Yuan, H.; Papadatos, A.; Walter, R. I. *J. Am. Chem. Soc.* **1994**, *116*, 8937−8951.

(4) (a) Ozaki, S.; Matsushita, H.; Ohmori, H. *J. Chem. Soc., Chem. Commun.***1992**, 1120−1122. (b) Ozaki, S.; Matsushita, H.; Ohmori, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 649−651. (c) Ozaki, S.; Matsushita, H.; Ohomori, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2339−2344. (d) Ozaki, S.; Matsi, E.; Waku, J.; Ohmori, H. *Tetrahedron Lett.* **1997**, *38*, 2705−2708.

(5) (a) Ozaki, S.; Matsui, E.; Saiki, T.; Yoshinaga, H.; Ohmori, H. *Tetrahedron Lett.* **1998**, *39*, 8121−8124. (b) Ozaki, S.; Matsui, E.; Yoshinaga, H.; Kitagawa, S. *Tetrahedron Lett.* **2000**, *41*, 2621−2624.

(6) (a) Webster, R. D.; Bond, A. M. *J. Org. Chem.* **1997**, *62*, 1779−1787. (b) Gruber, L.; Camilo, A. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 127−129.

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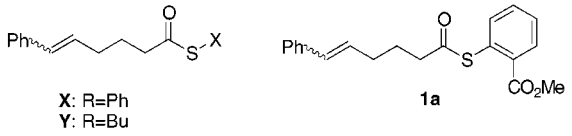
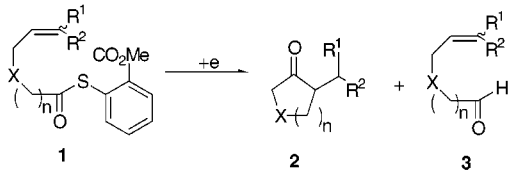
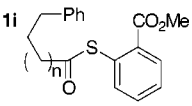
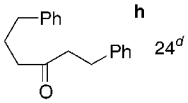


Figure 1.

Table 1. Cyclic Ketones Formed from *S*-(2-Methoxycarbonyl)phenyl Thiolesters by Electroreduction[a]



1 2 3

Entry	Substrate	R^1	R^2	X	n	Product, Yield %			
1	**1a**[c]	H	Ph	CH_2	1	**2a**	41	**3a**	0
2							61[d]		0
3	**1b**[c]	H	Ph	CH_2	2	**2b**	31	**3b**	10
4							39[d]		14
5	**1c**[e,f]	H	Ph	O	1	**2c**	27	**3c**	0
6	**1d**	Ph	Ph	CH_2	1	**2d**	67	**3d**	0
7	**1e**	Ph	Ph	O	1	**2e**	59	**3e**	0
8	**1f**	Ph	Ph	CH_2	2	**2f**	61	**3f**	0
9	**1g**[g]	Me	Ph	CH_2	1	**2g**	59[h]	**3g**	0
10	**1h**	H	H	CHPh	1	**2h**	31[d,i]	**3h**	
11[j]	**1i** 				1				24[d]
12	**1i**				1	**2i**	0	**3i**	34
13	**1j**				2	**2j**	0	**3j**	39

[a] For electrolysis conditions, see text. [b] Isolated yield. [c] 1:1 mixture of *E* and *Z* isomers. [d] Electrolysis at 60 °C. [e] *E* isomer. [f] Decomposed slowly at 60 °C. [g] 7:1 mixture of *E* and *Z* isomers, in which the *Z* isomer predominated. [h] 6:5 mixture of diastereomers. Stereochemistry of major isomer has not been determined. [i] 3.2:1 mixture of *cis* and *trans* isomers. Determined by NOE spectroscopy. [j] Electrolysis in the presence of 5 equiv of styrene.

radical derived from **1b** could accept the allylic proton by intramolecular 1,5-hydrogen transfer besides hydrogens from the solvent DMF prior to the cyclization, which is considered to be slow compared to 5-*exo*- or 6-*exo*-cyclization onto alkene bearing two substituents. The rate of 6-*exo*-cylization onto the diphenyl-substituted alkene (entry 8) was shown to be comparable with that of the 5-*exo*-cyclization (entry 6). The yields of the cyclohexanones **2f** suggest that the rate of 6-*exo*-cylization of the acyl radical derived from **1f** with the disubstituted alkene are higher than that of probable intramolecular 1,5-hydrogen transfer of allylic hydrogens to the acyl radicals. The yields of cyclopentanones **2d**,**e**,**g** and cyclohexanones **2f** indicate that the rates of 5-*exo*- and 6-*exo*-cyclization onto the alkene bearing two substituents are close to each other. The yields of the cyclic ketones **2a** and **2b** increased in the electrolysis at elevated temperature (60 °C) in accordance with expectation of the increased rate constant ratio k_c/k_{cHo}, where k_c and k_{cHo} denote the rate constant for each cyclization and hydrogen abstraction to give the aldehyde, respectively.[7] The electroreduction of **1h** at 60 °C led to a 3.2/1 mixture of *cis* and *trans* isomers of the cyclopentanone **2h** in which the *cis* isomer predominated. Such a *cis* selectivity is consistent with that predicted by both Beckwith's and Houk's force field models for intramolecular alkenyl radical addition.[9] Electroreduction of **1i** and **1j** afforded the corresponding aldehydes **3i** and **3j**, respectively, in similar yields of 34% and 39%. This suggests that the acyl radicals would be trapped mainly by hydrogen atom abstraction from the solvent rather than intramolecular 1,5-hydrogen transfer from benzylic hydrogens and that the decarbonylation of the acyl radicals proceeds at a rate slightly higher than that of hydrogenation of the acyl radicals by the solvent. However, products from decarbonylation of the intermediate acyl radicals were not detected in the electroreduction of all thiolesters used in this study. In the present electroreduction of thiolesters, around 4 F/mol of electricity was needed for consumption of the substrates. According to Scheme 1, the electricity required for the formation of a cyclic ketone of type **2** or an aldehyde of type **3** should be at most 2 F/mol per thiolester. This was the case for the catalytic elctroreduction of various halides.[3] In the present reductions electrolyses were performed without a catalyst at the potential −2.06 V vs SCE, which corresponds to reduction of the thiolester group and is at least 0.4 V more negative than the potentials applied in the previous catalytic electrolysis.[3] Then, the lower current efficiency observed in the present electroreduction of thiolesters could be partly attributed to the fact that competetive reduction of contaminants in the solvent DMF occurred.

In conclusion, we have developed an efficient method for the synthesis of five- and six-membered cyclic ketones through the intramolecular addition of acyl radicals generated by electroreduction of *S*-(2-methoxycarbonyl)-phenyl 5-hexene or 6-heptene thioates. In the field of organic synthesis achieved by free radical reactions, the avoidance of metal reagents and tin contamination is now urgent. In light of this situation, the present electroreductive method generating acyl radicals could be a useful alternative to the tin hydride method or other methods such as photolysis or thermolysis of the thiolesters or *S*-acyl xanthates.

Experimental Section

General. NMR spectra were taken on a JEOL JNM-EX 300 or JEOL GX-500 instrument. The *J* values are given in hertz (Hz). IR spectra were taken on a JASCO IR Report-100 instrument. Cyclic voltammetry was performed with a three-elecrode system employing a linear scanning unit (Huso Electronical System HECS 321B) equipped with a potentiostat (Hokuto Denko PS-55B). Constant current electrolysis was carried out with a potentio-galvanostat (Hokuto Denko HA105S), and the quantity of electricity was recorded with a coulometer (Hokuto Denko HF-201). All chemicals used were commercially available.

General Procedure for the Preparation of *S*-(2-Methoxycarbonyl)phenyl Thiolesters 1. *S*-(2-Methoxycarbonyl)-phenyl 6-Phenyl-5-hexenethioate 1a. 6-Pheny-5-hexenoic acid was prepared at room temperature by the reaction of benzaldehyde (2 equiv) with a phosphorus ylide, which had been prepared by the deprotonation of 4-carboxybutyl(triphenyl)-phosphonium bromide by NaH (2 equiv) at 65 °C in DMSO. Purification of the crude products by column chromatography provided 6-phenyl-5-hexenoic acid (64%) as a approximately 1:1

(7) Schwarzenbach, G; Rudin, E.; *Helv. Chim. Acta* **1939**, *22*, 360−370.

(8) Chatgilialoglu, C.; Ferreri, C.; Lucarini, M.; Venturini, A.; Zavitsas, A. A. *Chem. Eur. J.* **1997**, *3*, 376−387.

(9) (a) Beckwith, A. L. J. *Terahedron* **1981**, *37*, 3073−3100. Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925−3941. (b) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959−977.

mixture of *E* and *Z* isomers. Methyl thiosalicylate (1 equiv) was added at 0 °C to the dry methylene chloride including the acid, DCC (1 equiv), and DMAP (0.7 equiv), and the mixture was stirred for 2 h at room temperature. The resulting precipitate was removed from the reaction mixture after stirring for 3 h. The crude product obtained from the filtrate by concentration was purified by column chromatography to provide **1a** as an oil of a 1:1 mixture of *E* and *Z* isomers (85%). The detailed procedure of the preparation of **1a** and yields of other type **1** compounds and their characterization are given in the Supporting Information.

Procedure for the Electroreduction of the Thiolesters 1. The electroreduction was performed in DMF (10 or 20 mL) using 0.5 or 1.0 mmol of a thiolester **1**, 1 or 2 mmol of tetraethylammonium perchlorate (TEAP) as a supporting electrolyte, a graphite plate as a cathode, and an aluminum rod as an anode in an undivided cell at room temperature under an atmosphere of nitrogen. A constant current (6 mA) was passed until the substrate was consumed (determined by TLC). The electricity passed was 4 F/mol of the substrate **1**. The solution from the electrolysis was transferred to a brine solution (100 mL) and extracted with ether (40 mL × 3). The crude product obtained after concentration under vacuum was purified by silica gel column chromatography. Yields of products are given in Table 1; their characterizations based on the analytical and spectral data are given below.

2-Phenylmethylcyclopentanone 2a. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48−1.61 (1H, m), 1.67−1.78 (1H, m), 1.90−2.01 (1H, m), 2.04−2.17 (2H, m), 2.29−2.39 (2H, m), 2.50 (1H, dd, J = 13.6, 9.4, CH*H*Ph), 3.15 (1H, dd, J = 13.7, 4.0, C*H*HPh), 7.15−7.30 (5H, m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.5, 29.1, 35.6, 38.2, 51.0, 126.1, 128.4, 128.9, 140.0, 220.3; IR (thin film) cm^{-1} 1742; HRMS (FAB) calcd for $C_{12}H_{15}O$ 175.1123, found 175.1101.

2-Phenylmethylcyclohexanone 2b. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18−1.39 (1H, m), 1.43−1.68 (2H, m), 1.71−1.79 (1H, m), 1.90−2.04 (2H, m), 2.13−2.53 (4H, m, included CH*H*Ph), 3.16 (1H, dd, J = 13.7, 4.6, C*H*HPh), 7.15−7.30 (5H, m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.1, 28.0, 33.4, 35.4, 42.2, 52.5, 125.9, 128.3, 129.1, 140.3, 212.6.

3-Phenylmethyltetrahydrofuran-4-one 2c. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.65 (1H, dd, J = 13.7, 10.0, CH*H*Ph), 2.78 (1H, qd, J = 9.5, 4.3, C*H*CO), 3.16 (1H, dd, J = 13.7, 3.9, C*H*HPh), 3.84 [1H, d, J = 17.7, OCH*H*C(O)], 3.84−3.87 (1H, d, J = 8.8, OCH*H*CH), 4.06 [1H, d, J = 17.1, OC*H*HC(O)], 4.30 (1H, t, J = 8.8, OC*H*HCH), 7.14−7.32 (5H, m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 33.5, 48.8, 71.1, 71.8, 126.7, 128.6, 128.7, 138.5, 219.7; IR (thin film) cm^{-1} 1758.

2-Biphenylmethylcyclopentanone 2d. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60−1.72 (1H, m), 1.74−1.82 (2H, m), 1.87−1.96 (1H, m), 2.20−2.34 (2H, m), 2.90−2.98 (1H, m), 4.64 [1H, d, J = 4.9, C*H*Ph(Ph)], 7.06−7.30 (10H, m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.5, 27.3, 38.3, 50.0, 53.0, 126.3, 126.3, 128.2, 128.3, 128.3, 129.1, 142.5, 143.4, 219.2; IR (thin film) cm^{-1} 1738.

3-Biphenylmethyltetrahydrofuran-4-one 2e. The assignment of ^{1}H NMR spectra was confirmed by ^{1}H−^{1}H COSY examination. Solid, mp 72−74 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.36 (1H, q, J = 7.9, CH_2C*H*), 3.73 [1H, d, J = 17.0, OCH*H*C(O)], 3.90 (1H, t, J = 8.5, OCH*H*CH), 4.01 [1H, d, J = 17.1, OC*H*HC(O)], 4.42 (1H, t, J = 9.2, OC*H*HCH), 4.48 [1H, d, J = 7.3, C*H*Ph(Ph)], 7.12−7.34 (10H, m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 49.7, 50.7, 70.6, 71.3, 76.6, 77.0, 77.4, 126.7, 126.9, 128.0, 128.5, 128.5, 128.7, 141.5, 141.9, 214.5; IR (Nujol method) cm^{-1} 1750.

2-Biphenylmethylcyclohexanone 2f. Solid, mp 98−99 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.34−1.46 (1H, m), 1.59−1.71 (1H, m), 1.73−1.87 (3H, m), 1.99−2.04 (1H, m), 2.35−2.40 (2H, m), 3.31−3.40 (1H, m), 4.31 [1H, d, J = 10.3, C*H*Ph(Ph)], 7.10−7.29 (10H, m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 24.5, 29.1, 33.4, 42.5, 50.9, 54.8, 126.1, 126.3, 127.5, 128.3, 128.3, 128.5, 143.0, 143.8, 212.3; IR (Nujol method) cm^{-1} 1700; HRMS calcd for $C_{19}H_{20}O$ 264.1514, found 264.1485.

2-(1-Phenylethyl)cyclopentanone 2g. Yellow oil, obtained as 6:5 mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 300 MHz mixture of diastereomers) major isomer δ 1.41 (3H, d, J = 7.0, CHC*H*$_3$), 1.60−2.02 (4H, m), 2.17−2.40 (2H, m), 3.18−3.24 (1H, m, C*H*CH$_3$), 7.13−7.33 (5H, m, Ar*H*); minor isomer δ 1.19 (3H, d, J = 7.3, CHC*H*$_3$), 1.60−2.02 (4H, m), 2.17−2.40 (2H, m), 3.39−3.44 (1H, m, C*H*CH$_3$), 7.13−7.33 (5H, m, Ar*H*); IR (Nujol method) cm^{-1} 1736; HRMS calcd for $C_{13}H_{16}O$ 188.1201, found 188.1222.

2-Methyl-4-phenylcyclopentanone 2h. Yellow oil, obtained as 3.2:1 mixture of *cis* and *trans* isomers. Stereochemistry was determined on the basis of a positive NOE (3%) observed between 2H and 4H. The major isomer is the *cis* isomer. ^{1}H NMR ($CDCl_3$, 300 MHz *cis* and *trans* mixture) *cis* isomer δ 1.17 (3H, d, J = 6.7, CHC*H*$_3$), 1.63 (1H, q, J = 12.2, CHCH*H*CH), 2.24−2.39 (2H, m, CHC*H*HCH, CHCH*H*CO), 2.58−2.63 (1H, m, CHC*H*HCO), 2.77 (1H, dd, J = 18.3, 7.3, CH$_3$C*H*), 3.30−3.37 (1H, m, PhC*H*), 7.23−7.35 (5H, m, Ar*H*); *trans* isomer δ 1.17 (3H, d, J = 6.7, CHC*H*$_3$), 1.63 (1H, q, J = 12.2), 2.02−2.09 (1H, m), 2.42−2.53 (2H, m), 2.68 (1H, d, J = 7.9, CH$_3$C*H*), 3.52−3.58 (1H, m, PhC*H*), 7.23−7.35 (5H, m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz *cis* and *trans* mixture) δ 13.9, 39.9, 40.0, 45.3, 45.6, 126.5, 126.6, 126.7, 128.6, 143.0, 219.5; IR (thin film, *cis* and *trans* mixture) cm^{-1} 1740; HRMS calcd for $C_{12}H_{14}O$ 174.1045, found 174.1046.

4-Phenylbutanal 3i. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.91−2.01 (2H, m, CH_2C*H*$_2$CH$_2$), 2.45 (2H, td, J = 7.3, 1.6, C*H*$_2$CO), 2.66 (2H, t, J = 7.3, C*H*$_2$Ph), 7.13−7.31 (5H, m, Ar*H*), 9.75 (1H, t, J = 1.6, C*H*O).

5-Phenylpentanal 3j. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.51−1.65 (4H, m, CH_2C*H*$_2$CH$_2$, CH$_2$C*H*$_2$CH$_2$), 2.38 (2H, t, J = 7.8, C*H*$_2$CO), 2.57 (2H, t, J = 7.0, C*H*$_2$Ph), 7.08−7.23 (5H, m, Ar*H*), 9.69 (1H, t, J = 1.6, C*H*O).

Supporting Information Available: Characterization data (IR, ^{1}H NMR) for thiolesters **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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