JOC Article

Self-Protection: The Advantage of Radical Oligomeric Mixtures in Organic Synthesis

Hui Yu and Chaozhong Li*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,
354 Fenglin Road, Shanghai 200032, P. R. China

clig@mail.sioc.ac.cn

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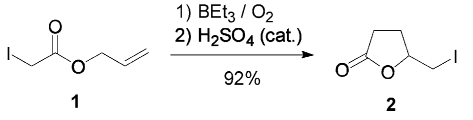
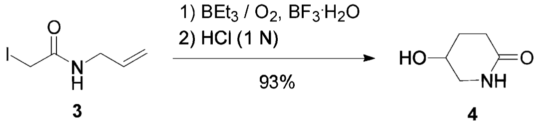
Atom-transfer radical oligomers of allyl iodoacetates were converted to 4-pentenoic acids upon treatment with zinc. Reactions of the radical oligomers of various ω-alkenyl iodoacetates with Grignard reagents afforded the corresponding substituted tetrahydrofuran derivatives. These results indicated that radical oligomeric mixtures not only serve as versatile intermediates in organic synthesis, but also exhibit unique advantages in that the oligomeric mixtures are self-protected and the deoligomerization functions as the simultaneous deprotection.

Introduction

The past two decades have witnessed enormous progress in free radical chemistry toward organic synthesis.[1] Among numerous methods developed, radical cyclizations have been well-established to be an indispensable tool in organic synthesis.[2] However, in the intramolecular radical cyclization reactions, the competing intermolecular radical oligomerizations, more or less, always occur.[3] In some cases, radical oligomerization predominates.[4] In our preliminary communications[5] we reported that radical oligomers of allyl iodoacetate (**1**) could be converted to the corresponding γ-lactone **2** via rearrangement deoligomerization (eq 1). In a similar fashion, Lewis acid-catalyzed radical oligomerization of *N*-allyliodoactamide (**3**) followed by acid treatment afforded γ-hydroxy-substituted δ-lactam **4** (eq 2). These results indicated that radical oligomeric mixtures could be utilized in organic synthesis and encouraged us to develop new synthetic strategies based on radical oligomerization.



(Eq 1)



(Eq 2)

Herein two novel deoligomerization methods are reported and the scope and limitation of the application of radical oligomerization in organic synthesis are discussed in detail. Further comparisons with the conventional methods are also conducted to reveal the unique characteristics of radical oligomers as synthetic intermediates.

Results and Discussion

Reaction of allyl iodoacetate (**1**) in CH_2Cl_2 (0.5 M) at room temperature (rt) with BEt_3 (0.1 equiv)/O_2 (trace) as the initiator gave the radical oligomeric mixture **5**. Treatment of **5** with magnesium metal in THF at refluxing temperature afforded 4-pentenoic acid (**6a**)[6] in 62% yield. Reaction of **5** with SmI_2 in THF at room temperature also led to the formation of **6a** in 78% yield. Satisfactory yield (85%) was achieved for **6a** when **5** was refluxed with zinc in THF for 2 h (Scheme 1). Other iodoacetates **7**−**10** underwent similar reactions to give the corresponding acids **6b**−**e** and the results are sum-

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* Corresponding author.

(1) For review articles, see: (a) Giese, B. *Radicals in Organic Synthesis*: *Formation of Carbon*−*Carbon Bonds*; Pergamon: Oxford, UK, 1986. (b) Curran, D. P. *Synthesis* **1988**, *417*, 489. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (d) Melikyan, G. G. *Synthesis* **1993**, 833. (e) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. (f) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (g) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, Germany, 1996. (h) Gansauer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771. (i) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001.

(2) For reviews, see: (a) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. In *Organic Reactions*; Wiley: New York, 1996; Vol. 48, p 301. (b) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747.

(3) *Free Radical Telomerization*; Starks, C. M., Ed.; Academic Press: New York, 1974.

(4) For examples, see: (a) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746. (b) Barth, F.; O-Yang, C. *Tetrahedron Lett.* **1990**, *31*, 1121.

(5) (a) Yu, H.; Wu, T.; Li, C. *J. Am. Chem. Soc.* **2002**, *124*, 10302. (b) Liu, L.; Wang, X.; Li, C. *Org. Lett.* **2003**, *5*, 361.

(6) For the synthesis of 4-pentenoic acids, see: (a) Cambie, R. C.; Hayward, R. C.; Roberts, J. L.; Rutledge, P. S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1864. (b) Eisch, J. J.; Merkley, J. H. *J. Am. Chem. Soc.* **1979**, *101*, 1148. (c) Hunter, D. H.; Patel, V.; Perry, R. A. *Can. J. Chem.* **1980**, *58*, 2271. (d) Evans, D. A.; Thomas, E. W.; Cherpeck, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 3695.

10.1021/jo035461s CCC: $27.50

SCHEME 1

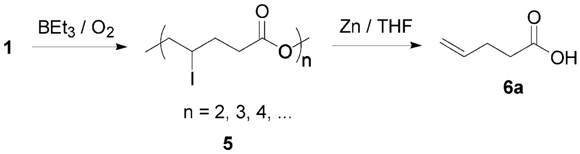
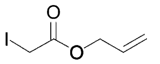
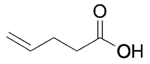
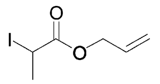
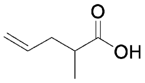
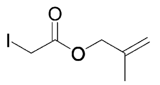
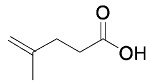
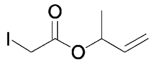
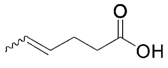
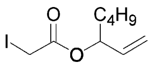
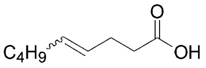


TABLE 1. Synthesis of Pentenoic Acids 6a–e via Deoligomerization

substrate		product		yield (%)[a]
	**1**		**6a**	85
	**7**		**6b**	86
	**8**		**6c**	80[b]
	**9**		**6d**	89[c]
	**10**		**6e**	91[d]

[a] Isolated yield based on the starting iodoacetates. [b] SmI_2 was used instead of Zn. [c] E:Z = 70:30. [d] E:Z = 75:25.

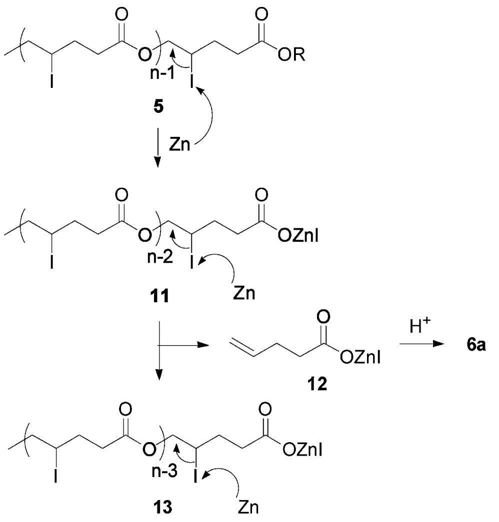
marized in Table 1. For substrates with internal C=C double bonds such as hex-2-en-1-yl iodoacetate or cyclohex-2-en-1-yl iodoacetate, no expected product **6** could be isolated because of the poor oligomerization under the above experimental conditions as indicated by ^{1}H NMR monitoring.

Apparently the mechanism of deoligomerization was that each unit of the oligomers **5** underwent β-scission[7,8] to give the same product **12**, which furnished **6a** upon acidification (Scheme 2).

The application of radical oligomeric mixtures in organic synthesis could be further extended to the preparations of functionalized tetrahydrofuran derivatives. The reaction of **5** with phenylmagnesium bromide in THF at rt led to the formation of 2,2-diphenyl-5-hydroxymethyltetrahydrofuran (**14a**) in 65% yield (Scheme 3). Thus, the atom-transfer radical oligomerization of various ω-alkenyl iodoacetates **15**–**18** followed by the subsequent treatment with phenylmagnesium bromide afforded the corresponding tetrahydrofuran derivatives **14**. Other Grignard reagents such as methyl- or allylmagnesium bromide behaved similarly and the results are summarized in Table 2.

A plausible mechanism could be drawn for the above deoligomerization process (Scheme 4). Upon treatment with a Grignard reagent, an ester group in **5** was attacked first by the Grignard reagent to break one end of the oligomer and generate an alkoxy anion **19**, which in turn underwent intramolecular nucleophilic substitution to generate **20** having a tetrahydrofuran skeleton. The same process was repeated in each unit of the oligomer, resulting in the deoligomerization of the oligo-

SCHEME 2



SCHEME 3

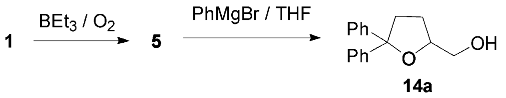
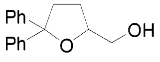
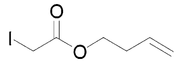
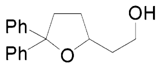
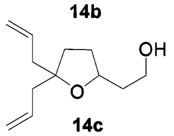
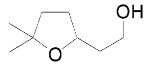
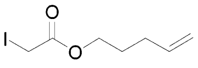
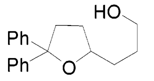
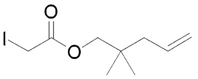
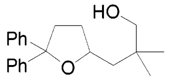
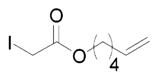
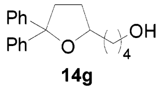


TABLE 2. Synthesis of Tetrahydrofurans 14 via Deoligomerization

substrate	RMgBr	product	yield (%)[a]
1	Ph	 **14a**	65
 **15**	Ph	 **14b**	78
15	allyl	 **14c**	85
15	Me	 **14d**	45
 **16**	Ph	 **14e**	86
 **17**	Ph	 **14f**	55
 **18**	Ph	 **14g**	64

[a] Isolated yield based on the starting iodoacetates.

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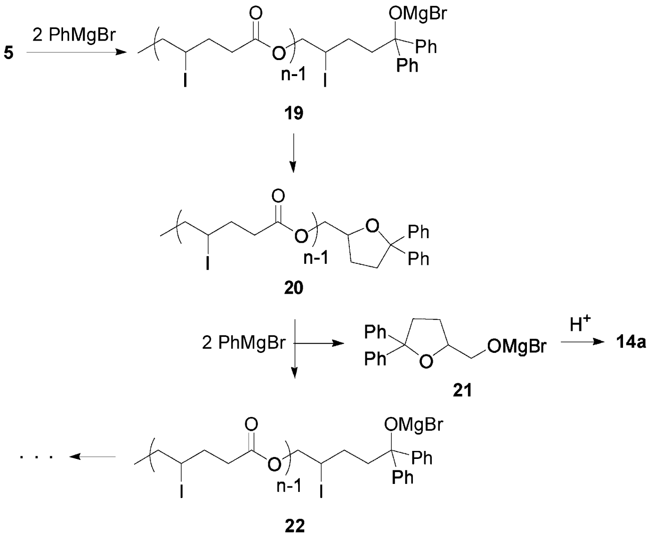
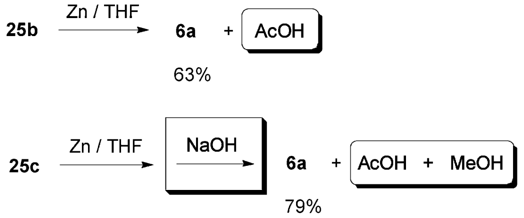
(7) Larock, R. C. In *Comprehensive Organic Transformations*; Wiley: New York, 1999; pp 266–268.

(8) For examples, see: (a) Semmelhack, M. F.; Heinsohn, G. E. *J. Am. Chem. Soc.* **1972**, *94*, 5139. (b) Adachi, T.; Iwasaki, T.; Inoue, I.; Miyoshi, M. *J. Org. Chem.* **1979**, *44*, 1404. (c) Rao, A. V. R.; Yadav, J. S.; Rao, C. S. *Tetrahedron Lett.* **1986**, *27*, 3297. (d) Florent, J. C.; Ughetto-Monfrin, J.; Monneret, C. *J. Org. Chem.* **1987**, *52*, 1051. (e) Cho, S.; Kang, S.; Keum, G.; Kang, S. B.; Han, S.-Y.; Kim, Y. *J. Org. Chem.* **2003**, *68*, 180.

SCHEME 4



SCHEME 5

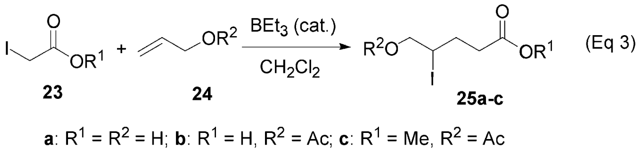


mer, along with the formation of the same single product **21**. Acidification of **21** afforded **14a**.

It should be mentioned that the reaction of ethyl 4-bromobutyrate with *o*-tolylmagnesium bromide gave the corresponding 2,2-disubstituted tetrahydrofuran in 14% yield as reported by Iqbal et al.[9] The reaction of phenyllithium with *O*-tosyl-protected 5-hydroxymethyldihydro-2(3*H*)-furanone also produced **14a**.[10] Compared to the literature methods, the oligomerization−deoligomerization route provided a general, atom-economical, and efficient approach to the synthesis of these compounds, which are important intermediates in organic synthesis.[11]

The results in Tables 1 and 2, together with those in eqs 1 and 2, demonstrate the versatility of radical oligomeric mixtures in organic synthesis.

To further elucidate the advantage of the deoligomerization method, we designed the following experiments (eq 3 and Scheme 5).



BEt$_3$-initiated atom-transfer radical addition of iodoacetic acid or methyl iodoacetate (**23**) to allyl alcohol or allyl acetate (**24**) gave the corresponding γ-iodo-substituted carboxylic acid derivatives **25a**−**c**. Compound **25c** is structurally equivalent to the unit of the oligomers **5**, while the latter can be regarded as the condensation oligomers of the monomer **25a**. Treatment of the unprotected hydroxy-acid **25a**[12] with zinc directly furnished 4-pentenoic acid **6a**. However, the reaction was not clean and the overall yield was low (35%). The yield of **6a** was increased to 63% when **25b** was employed to react with zinc. This is obvious in that OAc$^-$ is a better leaving group than OH$^-$. However, the 1,2-elimination of **25b** also produced acetic acid. For substrate **25c** as the structural analogue of oligomers **5**, its reaction with zinc afforded methyl 4-pentenoate. Further hydrolysis (deprotection) was required to give the acid **6a** along with the formation of methanol (Scheme 5). On the other hand, the oligomeric mixture **5** gave no such small molecules (acetic acid and methanol) as the byproducts, making the reaction not only clean, but also atom-economical in nature.

By comparison of **5** with **25c**, the advantage of radical oligomeric mixtures is clear in that the oligomeric mixture is *self-protected* and that the deoligomerization serves as the *simultaneous deprotection*.

The unique property of self-protection in oligomeric mixtures was also revealed in their reactions with Grignard reagents. To react with Grignard reagents, the acid group in **25** had to be protected. Thus, treatment of **25a** with PhMgBr failed to give **14a**. Reaction of **25c** gave **14a** along with the formation of Ph$_2$C(Me)OH and methanol. It could be expected that the *O*-benzyl-protected substrate **25** (R^1 = Me, R^2 = Bn) with PhMgBr would give *O*-benzyl-protected **14a** as well as methanol. Therefore, the only formations of **14a**−**g** bearing *free* hydroxy groups via deoligomerization again demonstrate the self-protection in oligomers and simultaneous deprotection during the deoligomerization process.

On the basis of the above results, it is certainly of interest to see if a similar strategy could be applied to substrates other than iodo compounds. We tested bromo and chloro analogues of **1** under similar conditions in eq 1. No corresponding product could be isolated because of the incomplete oligomerization of the substrates. In another case, 3-butenyl trichloroacetate underwent relatively efficient oligomerization. However, the subsequent deoligomerization with strong acid or by direct heating failed to give any meaningful product.

To apply radical oligomeric mixtures in organic synthesis, the oligomerization has to be complete and in a condensation mode. We have previously demonstrated that the completeness rather than the degree of oligomerization is essential.[5] High concentration and relatively low temperature significantly facilitate the oligomerization. In the meantime, the radical initiators have to be properly selected to meet the temperature requirement. BEt$_3$/O$_2$(trace) and (Bu$_3$Sn)$_2$/sunlamp turned out to be excellent choices for oligomerization. Other initiators such as AIBN, BPO, or copper are not suitable for the oligomerization of **1** because they usually require

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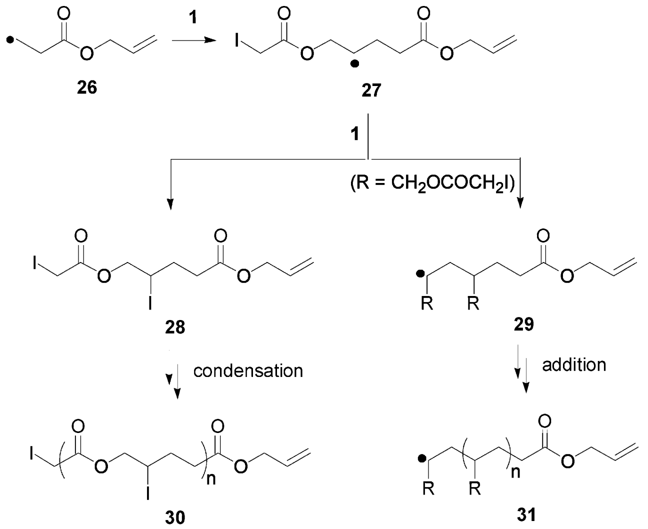
(9) Iqbal, N.; Wei, Z. Y.; Baker, G. B.; Knaus, E. E. *Can. J. Chem.* **1997**, *75*, 601.

(10) Harrow, D. C.; Dennison, S. T.; Hayward, J. S. *Tetrahedron Lett.* **1994**, *35*, 7467.

(11) For examples, see: (a) Monkovic, I.; Perron, Y. G.; Martel, R.; Simpson, W. J. *J. Med. Chem.* **1973**, *16*, 403. (b) Seebach, D.; Pohmakotr, M.; Weidmann, B. *Helv. Chim. Acta* **1982**, *65*, 419. (c) Erker, G.; Berlekamp, M.; Krieg, R. *Synthesis* **1994**, 212. (d) Macsari, I.; Szabo, K. J. *Chem. Eur. J.* **2001**, *7*, 4097.

(12) Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1999**, *40*, 519.

SCHEME 6



relatively high reaction temperature. For example, when copper was used as the radical initiator according to Metzger's procedure,[13] its reaction with **1a** at 140 °C afforded **2** and 4-iodomethyltetrahydro-2(3*H*)-furanone as the normal 5-exo cyclization product in a 3:1 ratio in an overall 45% yield. Apparently the high temperature required for the initiation also facilitates the intramolecular cyclization.

The other important factor is that the oligomers should be the *condensation* oligomers rather than the *addition* oligomers (Scheme 6).[14] This requires that the adduct radical **27** generated from the addition of a substarte radical **26** to a $C{=}C$ double bond of another substrate should be quenched by an iodine atom (to give **28**) rather than add to another $C{=}C$ double bond (to give **29**). The iodoacetates such as **1** meet this requirement because, in their oligomerization, the trapping rate of the adduct radicals by an iodine atom is significantly faster than that by a $C{=}C$ double bond. Curran and co-workers measured the rate constants for the halogen atom or aryl chalcogen (X) transfer from XCH_2CO_2Et to a primary alkyl radical in benzene at 50 °C to be about 7×10^4 (for Br), 1×10^5 (for PhSe), 2.3×10^7 (for PhTe), and 2.6×10^7 (for I) $M^{-1}\ s^{-1}$, respectively.[15] In the meantime, the rate constant for the addition of a primary radical to a simple alkene at 50 °C is roughly in the range of 10^3 to 10^4 $M^{-1}\ s^{-1}$.[16] On the basis of these kinetic data, iodo and phenyltelluro acetates should be excellent choices for the condensation oligomerization. On the other hand, one has to be careful in planning to use the bromo or phenylseleno analogues, while chloro derivatives are unlikely to be suitable in the condensation oligomerization.

Conclusion

The chemistry detailed above represents a considerable extension in scope of the novel deoligomerization methodology disclosed in our preliminary reports.[5] The unique characteristic of radical oligomeric mixtures as synthetic intermediates is that they are self-protected, making their reactions clean and atom-economical. Complete oligomerization in a condensation mode appears to be the condition for deoligomerization.

Experimental Section

Typical Procedure for the Oligomerization. Triethylborane (0.2 mL, 0.2 mmol, 1 M solution in hexane) was added to allyl iodoacetate (**1**, 452 mg, 2.0 mmol) in CH_2Cl_2 (4 mL) and the mixture was stirred at room temperature for 2 h. TLC monitoring showed that **1** was totally consumed. ^1H NMR monitoring indicated that no vinylic proton signals could be observed. The resulting solution, which contained the oligomeric mixture **5**, was then directly used in the following deoligomerization reactions. Characterization of **5**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.91–2.26 (2H, m), 2.44–2.68 (2H, m), 4.19–4.58 (3H, m). Anal. Calcd for $(C_5H_7IO_2)_n$: C, 26.57; H, 3.12. Found: C, 26.82; H, 3.18. The oligomeric mixture **5** was also characterized by HPLC analysis.[5a]

Typical Procedure for the Synthesis of Pentenoic Acids 6a–e via Deoligomerization. The oligomeric mixture **5** prepared from **1** (2 mmol) as outlined above was concentrated in vacuo and the residue was dissolved in THF (20 mL). Zinc powder (196 mg, 3 mmol) was added to the solution and the mixture was refluxed for 4 h. The resulting mixture was cooled to room temperature and hydrochloric acid (2 N) was added until the pH of the solution was close to 3. The solution was then extracted with ether (20 mL × 3) and the combined organic phase dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by flash chromatography on silica gel with ethyl acetate/hexane (1/4, v/v) as the eluent to give the pure product **6a** as a colorless liquid. Yield: 170 mg (85%).

2,2-Diphenyl-5-hydroxymethyltetrahydrofuran (14a). Typical Procedure. The oligomeric mixture **5** prepared from **1a** (2 mmol) as outlined above was concentrated in vacuo and the residue was dissolved in THF (10 mL). Phenylmagnesium bromide prepared from PhBr (1.26 g, 8 mmol) and magnesium powder (0.20 g, 8 mmol) in THF (20 mL) was added dropwise to the solution at rt and the mixture was further stirred at rt for 4 h. Hydrochloric acid (2 N) was added until the solution was slightly acidic. The resulting mixture was then extracted with ether (20 mL × 3) and the combined organic phase dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by flash chromatography on silica gel with ethyl acetate/hexane (1/4, v/v) as the eluent to give the pure product **14a** as a white solid. Yield: 305 mg (60%).

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Supporting Information Available: Characterizations of **10** and **14b–g**, preparations and characterizations of **25a–c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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