Preprint Title	Practical method to obtain α-acetoxyketones promoted by (diacetoxyiodo)benzene and acetic acid
Authors	Osvaldo J. Quintana-Romero, Jorge Camacho-Ruiz and Armando Ariza-Castolo
Publication Date	13 Nov 2019
Article Type	Full Research Paper
Supporting Information File 1	SI_JAVO_03_BJOC.pdf; 4.3 MB
ORCID® iDs	Armando Ariza-Castolo - https://orcid.org/0000-0003-2799-0764

Practical method to obtain α-acetoxyketones promoted by (diacetoxyiodo)benzene and acetic acid

Osvaldo J. Quintana-Romero, Jorge Camacho-Ruiz, Armando Ariza-Castolo

Address: Departamento de Química, Centro de Investigación y Estudios Avanzados del Instituto Politécnico Nacional, Av. IPN 2508, San Pedro Zacatenco, 07360, Ciudad de México

Email: Armando Ariza-Castolo, e-mail: aariza@cinvestav.mx

* Corresponding author

Abstract

By means of a simple procedure, we prepared α-acetoxyketones from a variety of enolizable ketones with $PhI(OAc)_2$ in the presence of acetic acid. The selectivity of the reactions depended on steric hindrance, and some other reactions were observed, such as the formation of N=N or C=C double bonds through an oxidation reaction.

Keywords

Functionalization α to a carbonyl group; α-acetoxyketones; (diacetoxyiodo)benzene; selectivity

Introduction

α-Hydroxyketones and α-acetoxyketones have great importance in organic chemistry because they can form part of an intermediate or structural subunit of compounds with biological activity. There are many procedures to obtain α-hydroxyketones, such as the Claisen-type reactions with β-dicarbonyl compounds and the use of organic peracids, oxaziridines and dioxiranes.[1] In addition, there are other methods in development that use [bis(triflouroacetoxy)]iodobenzene,[2] nitrosobenzene,[3] iodosobenzene,[4] 2-iodosylbenzoic acid,[5] or Oxone®/trifluoroacetic anhydride and are catalyzed by iodobenzene,[6] MoO_5•Py•HMPA,[7] or 2-sulfonyloxaziridines;[8,9] the oxidation of titanium enolates[10] or silyl enol ethers with *m*-chloroperbenzoic acid;[11] silyl enol ethers with osmium tetroxide/N-methylmorpholine-N-oxide;[12] and lithium enolates with molecular oxygen,[13] among others. In addition, some different methods have been developed to synthesize α-acetoxyketones, and some of the relevant examples are as follows: the catalysis of iodobenzene with hydrogen peroxide, acetic anhydride and boron trifluoride-diethyl ether;[14] palladium acetate as a catalyst and (diacetoxyiodo)benzene as an oxidant in acetic acid;[15] ketoxime derivatives with trimethyloxonium fluoroborate, triethylamine and aqueous acid;[16] (diacyloxyiodo)benzene with *m*-chloroperbenzoic acid[17] and thallium(III) triflate in amide solvents;[18] [hydroxy(*p*-nitrobenzene-sulfonyloxy)iodo]benzene[19] and terminal alkynes with (diacetoxyiodo)benzene catalyzed with silver(I);[20] and enone oxidation with Mn(III) acetate;[21] as well as the synthesis of 1-carbamoyl-2-oxopropyl acetate derivatives with the aid of (diacetoxyiodo)benzene.[22]

In the present research, we focus on the synthesis of α-acetoxyketones. One of the best methods to obtain these compounds is one that uses stable reactants with low toxicity that are easy to handle, and for this reason, hypervalent iodine derivatives have attracted attention.[23–26] The high necessity for diverse, easy, ecological and

safe methods motivated us to develop an efficient reaction of (diacetoxyiodo)benzene with ketones.

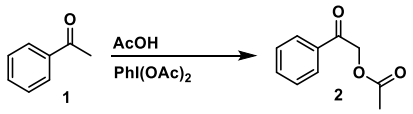
Results and Discussion

Acetophenone (**1**) was used as a model of reactivity. The initial exploration was to probe different solvents and the volume of solvent that was required. The best results were obtained with ethanol and acetonitrile (table 1, entries 1-4); this indicates that a polar medium is necessary. The diminution of solvent from 5 mL to 3 mL for 1.5 mmol of acetophenone increased the yield (table 1, entries 5-6). Acetonitrile is a better solvent than ethanol, and the ^{1}H NMR spectra of the crude reaction products show that when acetonitrile was used, the (diacetoxyiodo)benzene signals were observed. In contrast, with ethanol, there was no evidence of this compound, which indicates that the reaction could proceed in acetonitrile.

To determine the roll of the acetic acid, the volume used was probed from 0 to more than 0.85 mL in this experiment, and it was demonstrated that the presence of the acid is indispensable in this reaction (table 1, entry 7). The best results were obtained when 0.85 mL of acid was used, which corresponded to almost 10 chemical equivalents; if an excess of 3 mL was added, the reaction had similar results.

The reactions were performed at temperatures of 0 to 90°C (table 1, entries 11 and 14), and only traces of the product were found at 0 and 25°C. The best results were at 70 and 80°C, with a 40% yield in each case, and at 90°C, a yield diminution was observed; in addition, the observation of iodobenzene was attributed to the thermal, photochemical and free-radical decomposition of aryl iodine diacetates.[27,28]

Table 1. Optimization of reaction condition



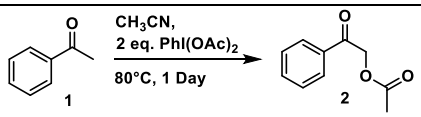
Entry	*Solvent*	*Amt of solvent*	*Amt of AcOH*	*Amt of $PhI(OAc)_2$ (Equiv)*	*Temperature (°C)*	*Time (Days)*	*Conversion[a] (%)*
1	MeCN	5	3	1.5	70	1	18
2	Toluene	5	3	1.5	70	1	16
3	EtOH	5	3	1.5	70	1	26
4	CH_2Cl_2	5	3	1.5	70	1	5
5	MeCN	3	3	1.5	70	1	37
6	EtOH	3	3	1.5	70	1	25
7	MeCN	3	-	1.5	70	1	0
8	MeCN	3	0.04	1.5	70	1	19
9	MeCN	3	0.08	1.5	70	1	27
10	MeCN	3	0.85	1.5	70	1	40
11	MeCN	3	0.85	1.5	0	1	Traze
12	MeCN	3	0.85	1.5	R. t.	1	Traze
13	MeCN	3	0.85	1.5	80	1	40
14	MeCN	3	0.85	1.5	90	1	14
15	MeCN	3	0.85	1.5	80	2	59
16	MeCN	3	0.85	1.5	80	3	67
17	MeCN	3	0.85	0.5	80	1	27
18	MeCN	3	0.85	1	80	1	29
19	MeCN	3	0.85	2.5	80	1	37
20	MeCN	3	0.85	5	80	1	45

a) The percent conversion was determined from the crude reaction product by ^{1}H NMR spectroscopy.

Amt = amount in mL

The best results were obtained with 1.5 equivalents of (diacetoxyiodo)benzene, and the optimized time was 3 days. The next objective was increasing the reaction rate and understanding the role of the acetic acid or other proton donors, and these experiments are summarized in table 2. The reaction yield with hydrochloric acid was null, and part of the explanation for this is the insolubility of the (diacetoxyiodo)benzene in water solution. To eliminate water, hydrogen chloride gas was bubbled into the solution, and the result was the decomposition of (diacetoxyiodo)benzene. The yield of the reaction with ethanol was 11% because it is a proton donor that induces keto-enol equilibrium. The use of benzoic acid only produces a trace of product **2**; in addition, the benzoate derivative was observed in major proportion compared to the acetate derivative. In agreement with previous reports, tosylation is a favorable reaction.[29] For this reason, the experiment was redesigned to tosylate the compound as a stable intermediate.

Table 2: Experiments with different acids.

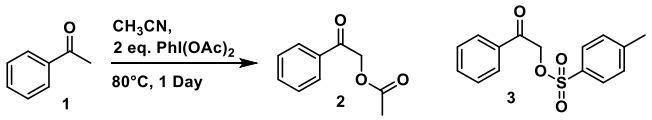


Entry	Acid	Amt of Acid (Equiv)	Conversion (%)[a]
1	TsOH	10	0
2	HCl	10	0
3	EtOH	10	11
4	Benzoic Acid	10	Traze

[a]The percent conversion was determined from each crude reaction product by ^{1}H NMR spectroscopy

Table 3 contains the experimental data with the quantities of *p*-toluenesulfonic acid and acetic acid used in each reaction. All experiments produced tosylate **3** as the principal product, but only when *p*-toluenesulfonic acid was at less than stoichiometric conditions was it possible to observe the acetylate derivative **2** in 8% yield. These results show that acetylation is slower than tosylation. Another strategy explored was to experiment with sodium acetate; the result was that the reaction yield was limited to 40% in 24 h, and this reaction did not progress if the same conditions were maintained for more time.

Table 3: Experiments with varying amounts of p-toluenesulfonic acid and acetic acid.



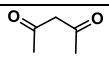
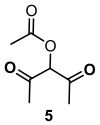
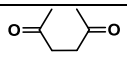
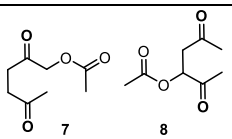
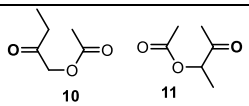
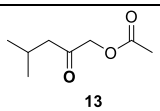
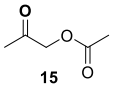
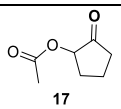
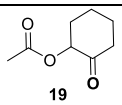
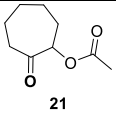
Entry	Amt of pTSO (Equiv)	Amt of AcOH (Equiv)	Conversion **2** (%)[a]	Conversion **3** (%)[a]
1	5	10	Traze	97
2	10	5	Traze	96
3	1	1	Traze	97
4	0.5	10	8	66

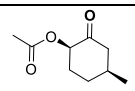
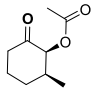
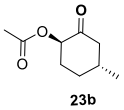
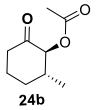
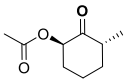
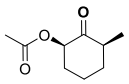
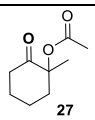
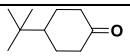
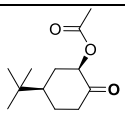
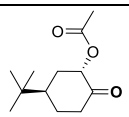
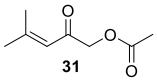
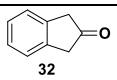
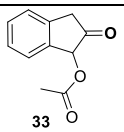
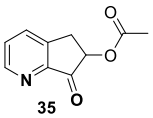
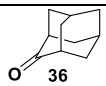
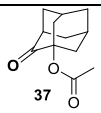
[a] The percent conversion was determined from the crude reaction product by 1H NMR spectroscopy

To determine the substituent effects on the reactivity of the ketones, the reaction was carried out under the optimum conditions. Compound **4** (2,4-pentanedione) only yielded the product with substitution at carbon 3 (compound **5**) with a conversion of 98% (table 4, entry 1). This compound is accessible by numerous procedures, including Claisen condensation.[1] In the case of 2,5-hexanedione **6**, two products with a 75% conversion were obtained. The major product had a methyl group (**7**), and the minor product had a methylene group (**8**), in a ratio of 18:7 (table 4, entry 2). To

understand the steric effects, butanone **9** was used, and the conversion was 95%, with methyl **10** as the major product relative to methylene **11** in a ratio of 7:2, and 3-hydroxybutanone as the subproduct in 28% yield (table 4, entry 3). The reaction of 4-methylpentan-2-one **12** produced only compound **13** in 80% yield (table 4, entry 4).

Table 4: Yield and selectivity with different ketones.

Entry	Compound	Product	Temperature (°C)	Conversion (%)[a]	Selectivity
1	 4	 5	70	98	
2	 6	 7 8	70	75	**7,**72% : **8,**28%
3	 9	 10 11	70	95	**10**,56% : **11**,16[b]
4	 12	 13	60	80	
5	 14	 15	60		
6	 16	 17	70	75	
7	 18	 19	70	91	
8	 20	 21	70	77	

9	 22	 23a  24a  23b  24b	70	93	**23a**,23 : **23b**,57 : **24b**,20
10	 25	 26a  26b  27	70	73	**26a**,38 : **26b**,62
11	 28	 29a  29b	70	90	**29a**,88 : **29b**,12
12	 30	 31	60	72	
13	 32	 33	40	60	
14	 34	 35	40	70	
15	 36	 37	70	0	

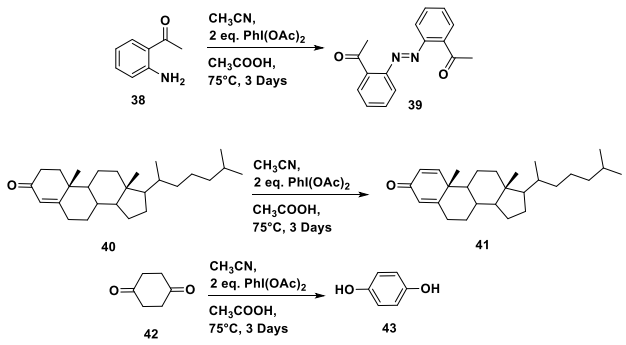
[a]The percent conversion was determined from the crude reaction product by 1H NMR spectroscopy

[b]3-hydroxybutanone was determined as hydrolysis product of **11** in 28%

Cyclic ketones **16**, **18** and **20** produced the expected six-membered ring compound with a high yield of 75% to 91%. For the cyclohexanone with an alkyl group, it was expected that all isomers would be observed, and the conversion was dependent on the steric effects of the substituent. The *cis* isomer is formed in lower yield than the *trans* isomer. The compounds with the substituents in the *equatorial* position were observed in higher yield than the compound with a conformational equilibrium between a substituent in the *equatorial* and *axial* positions (table 4, entries 6-8).

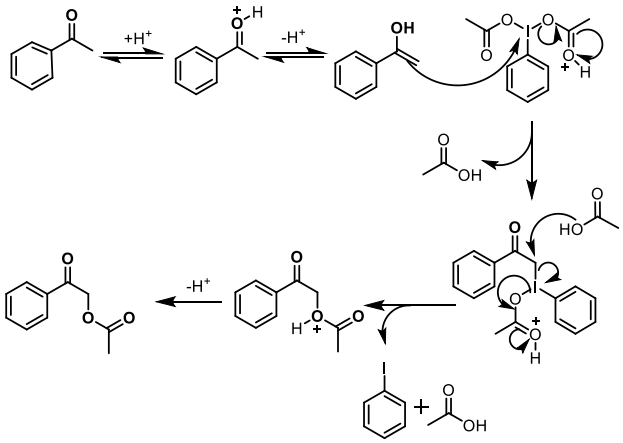
The reaction proceeds with ketones containing double bonds (**29**) and aromatic rings (**31** and **33**) (table 4, entries 12-14). The nonenolizable ketone **35** did not react under these conditions (table 4, entry 15).

To expand the scope of the reaction, a probe with 2'-aminoacetophenone **38** obtained 1,1'-[(*E*)-diazene-1,2-diyldibenzene-2,1-diyl]diethanone **39**. This product is similar to a previous report.[30] The reaction with (+)-4-cholesten-3-one **40** and 1,4-cyclohexanedione produced oxidative dehydrogenation product **41**, which is similar to the reaction of 1,4-cyclohexanedione **42**, whose product was 1,4-benzenediol **43** (Scheme 1).



Scheme 1: Reactions of compounds that have different reactivities with $PhI(OAc)_2$.

The proposed reaction mechanism (Scheme 2) is of the polar type because the reaction requires a favorable environment for the enolization of acetophenone. The first step is the keto-enol equilibrium, and the enol tautomer binds to the iodine atom of (diacetoxyiodo)benzene to liberate acetic acid. Following this, acetoxyiodobenzene functions as the leaving group in the nucleophilic substitution of acetate. Finally, the iodine is reduced to iodobenzene.



Scheme 2: Reaction mechanism proposed for α-acetoxylation.

Conclusion

We developed an easy method with moderate yields to obtain α-acetoxyketones. These compounds have great importance in industry. The participation of the reagents, solvent and conditions as well as the characteristics of each ketone was determined.

Experimental

General Information. All reagents were purchased from Sigma-Aldrich and were used without further purification. The NMR spectra were recorded using a JEOL ECA-500 spectrometer with a field strength of 11.75 T (^{1}H, 500.160 MHz; ^{13}C, 125.765 MHz). The unified scale[31] was used as a primary reference based on the ^{1}H resonance of TMS in a dilute solution (volume fraction φ < 1%) of chloroform ((CH3)4Si δ^{1}H, δ^{13}C = 0). The physical and spectroscopic properties are in agreement with previous reports: **2**,[32,33] **3**,[34–36] **5**,[37] **7**,[38] **10**,[39] **11**,[39] **13**,[40] **15**,[41] **17**,[38,42,43] **19**,[44] **21**,[45] **26a**,[16] **26b**,[16] **27**,[16] **29a**,[46] **29b**,[46] **31**,[47] **33**,[48] and **41**.[49,50]

Representative Procedure. In a flask, 1 equivalent of the corresponding ketone and 2.5 equivalents of PhI(OAc)2 were dissolved in the appropriate solvent, and 10 equivalents of acetic acid was added. The reaction mixture stirred for 3 days at 70°C. The solvent was evaporated, and the samples were purified by column chromatography using silica gel (60 Å, 200-240 mesh) and hexane/ethyl acetate 8:2 as the eluent.

Supporting Information

NMR and MS data, and NMR spectra can be found in the supporting information.

Acknowledgements

This work was supported by “Programa para el Desarrollo Profesional Docente, para el Tipo Superior (PRODEP).” O. J. Quintana-Romero thanks CONACyT for an awarded doctoral fellowship.

References

1. Chiristoffers, J.; Baro, A.; Werner, T. *Adv. Synth. Catal.* **2004**, *346*, 143–151.

2. Moriarty, R. M.; Berglund, B. A.; Penmasta, R. *Tetrahedron Lett.* **1992**, *33*, 6065–6068.

3. Bøgevig, A.; Sundén, H.; Córdova, A. *Angew. Chemie Int. Ed.* **2004**, *43*, 1109–1112.

4. Moriarty, M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett.* **1981**, *22*, 1283–1286.

5. Moriarty, R. M.; Hou, K. C. *Tetrahedron Lett*. **1984**, *25*, 691–694.

6. Chen, C.; Feng, X.; Zhang, G.; Zhao, Q.; Huang, G. *Synthesis*. **2008**, 3205–3208.

7. Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188–196.

8. Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *Org. Chem.* **1984**, *49*, 3241–3243.

9. Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919–934.

10. Adam, W.; Müller, M.; Prechtl, F. *J. Org. Chem.* **1994**, *59*, 2358–2364.

11. Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427–3429.

12. McCormick, J. P.; Tomasik, W.; Johnson, M. W. *Tetrahedron Lett*. **1981**, *22*, 607–610.

13. Wasserman, H. I. I.; Lipahutz, B. H. *Tetrahedron Lett.* **1975**, *16*, 1731–1734.

14. Sheng, J.; Li, X.; Tang, M.; Gao, B.; Huang, G. *Synthesis*. **2007**, 1165–1168.

15. Chen, T.; Ren, H.; Zhang, M.; Zhang, A. Q. *J. Chem. Res.* **2016**, *40*, 413–416.

16. House, H. O.; Richey, F. A. *J. Org. Chem.* **1969**, *34*, 1430–1439.

17. Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc.* **2005**, *127*, 12244–12245.

18. Lee, J. C.; Jin, Y. S.; Choi, J. H. *Chem. Commun.* **2001**, 956–957.

19. Chan Lee, J.; Hong, T. *Synth. Commun.* **1997**, *27*, 4085–4090.

20. Deng, G.; Luo, J. *Tetrahedron* **2013**, *69*, 5937–5944.

21 Demir, A. S.; Reis, Ö.; Igdir, A. C. *Tetrahedron* **2004**, *60* (15), 3427–3432.

22. Liu,W-B.; Chen, C.; Zhang, Q.; Zhu, Z-B. *Beilstein J. Org. Chem*., **2011**, *7*, 1436-1440

23. *Hypervalent Iodine Chemistry*; Wirth, T., Ed.; Topics in Current Chemistry; Springer International Publishing Switzerland, **2016**; Vol. *373*.

24. Viktor V. Zhdankin. *Hypervalent Iodine Chemistry Preparation , Structure and Synthetic Applications of Polyvalent Iodine Compounds*; John Wiley & Sons, Ltd: New Delhi, India, **2014**.

25. Moriarty, R. M.; Prakash, O. Oxidation of carbonyl compounds with organohypervalent iodine reagents. In *Organic Reactions*; **1999**; Vol. *54*, pp 277–412.

26. Prakash, O.; Saini, N.; Tanwar, M. P.; Moriarty, R. M. *Contemp. Org. Synth.* **1995**, *2*, 121–131.

27. Togo, H.; Katohgi, M. *Synlett* **2001**, 565–581.

28. Leffler, J. E.; Story1, L. J. *J. Am. Chem. Soc.* **1967**, *89*, 2333–2338.

29. Yusubov, M. S.; Wirth, T. *Org. Lett.* **2005**, *7*, 519–521.

30. Ma, H.; Li, W.; Wang, J.; Xiao, G.; Gong, Y.; Qi, C.; Feng, Y.; Li, X.; Bao, Z.; Cao, W.; Sun, Q; Veaceslav, C; Wang, F; Lei, Z. *Tetrahedron* **2012**, *68*, 8358–8366.

31. Harris, R. K.; Becker, E. D.; De Cabral Menezes, S. M.; Granger, P.; Hoffman, R. E.; Zilm, K. W. *Magn. Reson. Chem.* **2008**, *46*, 582–598.

32. Sabot, C.; Kumar, K. A.; Antheaume, C.; Mioskowski, C. *J. Org. Chem.* **2007**, *72*, 5001–5004.

33. Srinivas, B. T. V.; Supriya, P.; Rohithrao, V.; Naidu, N. V. S.; Sreedhar, B. *ChemistrySelect* **2017**, *2*, 2600–2604.

34. Guo, W.; Monge-Marcet, A.; Cattoën, X.; Shafir, A.; Pleixats, R. *React. Funct. Polym.* **2013**, *73*, 192–199.

35. Lex, T. R.; Swasy, M. I.; Whitehead, D. C. *J. Org. Chem.* **2015**, *80*, 12234–12243.

36. Yoshimura, A.; Klasen, S. C.; Shea, M. T.; Nguyen, K. C.; Rohde, G. T.; Saito, A.; Postnikov, P. S.; Yusubov, M. S.; Nemykin, V. N.; Zhdankin, V. V. *Chem. - A Eur. J.* **2017**, *23*, 691–695.

37. Bityukov, O. V.; Matveeva, O. K.; Vil, V. A.; Kokorekin, V. A.; Nikishin, G. I.; Terent'Ev, A. O. *J. Org. Chem.* **2019**, *84*, 1448–1460.

38. Stetter, H.; Mohrmann, K.; Schlenker, W. *Chem. Ber.* **1981**, *596*, 581–596.

39. Singh, M.; Murray, R. W. *J. Org. Chem.* **1992**, *57*, 4263–4270.

40. Hoffman, J.; Sarafidis, A.; Voss, J. *Electrochim. Acta* **1991**, *36*, 1165–1169.

41. Griesbaum, K.; Greinert, R. *Chem. Ber.* **1990**, *123*, 391–397.

42. Tanyeli, C.; Turkut, E.; Akhmedov, I. M. *Tetrahedron Asymmetry* **2004**, *15*, 1729–1733.

43. Rubottom, G. M.; Mott, R. C.; Juve, H. D. *J. Org. Chem.* **1981**, *46*, 2717–2721.

44. Lauktien, G.; Volk, F. J.; Frahm, A. W. *Tetrahedron Asymmetry* **1997**, *8*, 3457–3466.

45. Dave, V.; Warnhoff, E. W. *J. Org. Chem.* **1983**, *48*, 2590–2598.

46. Kuehne, M. E.; Giacobbe, T. J. *J. Org. Chem.* **1968**, *33*, 3359–3369.

47. Fristad, W. E.; Peterson, J. R. *J. Org. Chem.* **1985**, *50*, 10–18.

48. Dayan, S.; Bareket, Y.; Rozen, S. *Tetrahedron* **1999**, *55*, 3657–3664.

49. Kubota, T.; Yoshida, K.; Hayashi, F.; Takeda, K. *Chem. Pharm. Bull.* **1965**, *13*, 50–57.

50. Iida, T.; Shinohara, T.; Goto, J.; Nambara, T.; Chang, F. C. *J. Lipid Res.* **1988**, *29*, 1097–1101.