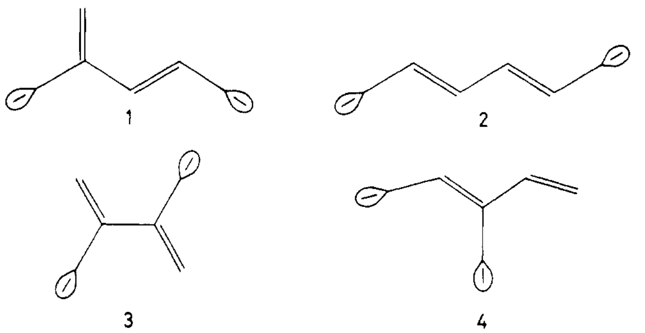

Figure 1. Structures of the isomers of $C_6H_8^{2-}$ which have been studied.

Table I. Calculated Average Polarizability, α, and the Second Hyperpolarizabiity, γ, (in au) of the Four Isomers of $C_6H_8^{2-}$ Considered. Relative Energies (in kcal/mol) Quoted from Ref 6 Are Also Tabulated

			relative energies	
molecule[a]	α^b	γ^b	STO-3G[6]	4-31G[6]
1	191	219000	−54.3	−34.8
2	648	−4790000	−52.1	−31.5
3	156	136000	−36.1	−18.5
4	237	348000	0.0	0.0

[a] Geometries of the molecules are from ref 6. The basis set employed is from ref 16. C: 2s (1.325), 2p (1.325). H: 1s (0.8), 2s (0.4), 2p (0.4). [b] Expressions for α and γ are given in ref 14–17.

invoked polarization mechanisms to interpret acidity trends, electronic and IR spectra, etc. (ref 13 and articles cited therein). However, the treatment presented here employs both polarizabilities and hyperpolarizabilities in the analysis of the anionic charge cloud's behavior; an extension which was very recently introduced.[14] The constants α and γ are computed by the CHF-PT-EB-CNDO method, the reliability of which has been established.[14-17] Further, since the character of this study is essentially comparative, any errors in the absolute values of these computed properties are not likely to change the conclusions. Details of the basis set are given in footnote a of Table I. It is worth noting that the accurate experimental measurement of the second hyperpolarizability of ions in solution encounters difficulties due to the environmental interactions which are hard to determine.[2b]

It is seen that the electric field due to the environment stabilizes, in general, the anions as is shown by the polarizabilities.[18] The same trend is also exhibited by the hyperpolarizabilities, with the notable exception of anion **2**, which has a negative value for γ. Further, one observes the pronounced effect of geometry changes on the properties and in particular changes in configuration cause enormous variations in the hyperpolarizability values; the maximum absolute value being associated with the "linear" configuration (anion **2**). These results may be rationalized by the following argument. $C_6H_8^{2-}$ can be considered as a set of interacting segments.[19] The total (effective) field at each unit is the sum of the external field plus the field due to the dipole moment induced at the other segments. Now, considering that the effective field is a vectorial quantity, it becomes clear why the overall property depends so extensively on the geometry of the molecule. Further since the "linear" configuration may be considered as having least vectorial cancellations, one qualitatively understands the difference in the properties observed between **2** and the other anions.

An important implication of the present results is that they provide evidence for a route by which the experimentally found lower stability of **2** with respect to **1**, is attained. Although the polarizability term stabilizes dianion **2** more than **1**, it is observed that anion **2** has a large negative value for the hyperpolarizability. Thus this nonlinearity's contribution will reduce (in absolute terms) the energy, while both the linearity and nonlinearity terms will increase the stability of **1**.[20]

It is finally noted that the four examined compounds are isoelectronic, with the same number and type of bonds. The geometry is the only variable. The considerable difference in the hyperpolarizability values illustrates the aptitude of γ to trace small changes in the intramolecular environment (more sensitively than the energy). We bring attention to the point that the deprotonated carbon does not in general correspond to the site of largest negative charge and Figure 1 should be considered as indicating the site of deprotonation and not that of highest charge concentration.[6]

In conclusion the close connection between molecular shape and the magnitude of the stabilizing interactions (the recipient of which is the anion and originates from the environment) has been demonstrated and the importance of the polarization terms illustrated.

Registry No. 1, 64080-78-0; 2, 64080-77-9; 3, 69780-62-7; 4, 78831-99-9.

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(13) Pellerite, M. J.; Brauman, J. I. "Comprehensive Carbanion Chemistry"; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1980; Part A, p 55.

(14) Waite, J.; Papadopoulos, M. G. *J. Comput. Chem.* **1983**, *4*, 578.

(15) Nicolaides, C. A.; Papadopoulos, M. G.; Waite, J. *Theoret. Chim. Acta* **1982**, *61*, 427.

(16) Papadopoulos, M. G.; Waite, J.; Nicolaides, C. A. *J. Chem. Phys.* **1982**, *77*, 2527.

(17) Waite, J.; Papadopoulos, M. G.; Nicolaides, C. A. *J. Chem. Phys.* **1982**, *77*, 2536.

(18) This is seen by considering that the energy, *E*, of a molecule in the presence of an electric field, *F*, is given by[11]

$$E(F) = E^\circ - \mu_\alpha F_\alpha - \frac{1}{2}\alpha_{\alpha\beta}F_\alpha F_\beta - \frac{1}{6}\beta_{\alpha\beta\gamma}F_\alpha F_\beta F_\gamma - \frac{1}{24}\gamma_{\alpha\beta\gamma\delta}F_\alpha F_\beta F_\gamma F_\delta \ldots$$

The symbols have their usual meaning (ref 11).

(19) Buckingham, A. D.; Sutter, H. *J. Chem. Phys.* **1976**, *64*, 364.

(20) It is noted that the order defined by the relative stabilities is completely different from that defined by the electric properties. This observation may be considered as an illustration of the different behavior exhibited by the inner and the outer regions of the charge cloud and thus our results are complementary to energy evaluations.

Metabolites of the Marine Pulmonate *Siphonaria australis*

Jill E. Hochlowski and D. John Faulkner*

Scripps Institution of Oceanography, La Jolla, California 92093

Received April 23, 1984

Marine pulmonates of the genus *Siphonaria* are air-breathing molluscs that resemble limpets in both form and habits. Nearly all specimens examined to date have contained "polypropionate" metabolites that are believed to be employed in a chemical defense against predators. *Siphonaria diemenensis*,[1] *S. pectinata*,[2] and *S. lessoni*[3] all contained α-pyrones exemplified by diemenensin A (**I**). Denticulatin A (**2**), a more complex cyclic hemiketal, was

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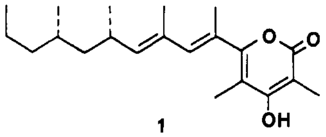
(1) Hochlowski, J. E.; Faulkner, D. J. *Tetrahedron Lett.* **1983**, *24*, 1917.

(2) Biskupiak, J. E.; Ireland, C. M. *Tetrahedron Lett.* **1983**, *24*, 3055.

(3) Capon, R. J.; Faulkner, D. J. *J. Org. Chem.* **1984**, *49*, 2506.



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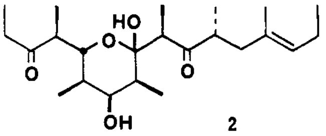

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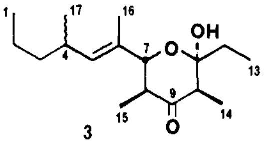

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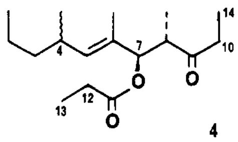

4

found in *S. denticulata*.[4] In this paper we describe a smaller cyclic hemiacetal (3) and an associated ketol ester (4) from *Siphonaria australis*.[5]

Specimens were collected near Auckland, New Zealand, and placed directly into acetone. The ethyl acetate soluble material from the decanted acetone extract was chromatographed by LC on Partisil using 1:1 ether–hexane as eluant to obtain the hemiacetal 3 (0.08 mg/animal) and the ester 4 (0.04 mg/animal).

The hemiacetal 3, $[\alpha]_D$ +22.3° (c 0.84, $CHCl_3$), had the molecular formula $C_{17}H_{30}O_3$.[6] The ^{13}C NMR spectrum provided signals for a carbonyl carbon at δ 207.3 (s), olefinic carbons at δ 136.5 (d) and 131.7 (s), a hemiketal carbon at δ 102.8 (s), and an ether carbon at δ 81.5 (d). Thus the three degrees of unsaturation were assigned to a ketone, a trisubstituted olefin, and a cyclic hemiketal. Infrared bands at 3560 and 1730 cm^{-1} confirmed the presence of hydroxyl and ketone groups. Analysis of the ^1H NMR spectrum (Table I) indicated that the ketone was on the six-membered hemiacetal ring. A signal at δ 4.00 (d, 1 H, J = 10.4 Hz) assigned to the C-7 proton was coupled to a methine proton signal at δ 2.33 (dqd, 1 H, J = 10.4, 6.5, 1.0 Hz) that was in turn coupled to a methyl signal at δ 0.80 (d, 3 H, J = 6.5 Hz). The methine proton signal was at the expected chemical shift for a proton adjacent to a ketone, as was a methine proton signal at δ 2.51 (br q, 1 H, J = 6.7 Hz) that was coupled to a methyl signal at δ 1.00 (d, 3 H, J = 6.7 Hz) and was W-coupled to the hydroxyl proton signal at δ 1.82 (br s, 1 H). These data defined the structure and stereochemistry of the tetrahydro-γ-pyrone ring.

The isolated ethyl group that gave rise to methylene proton signals at δ 1.80 (m, 1 H) and 1.65 (m, 1 H), both coupled to a methyl signal at δ 1.01 (t, 3 H, J = 7.4 Hz), must be attached at the hemiketal carbon. The remainder of the molecule must be attached by a bond between the ether carbon and the fully substituted olefinic carbon atom. A ^1H NMR signal at δ 1.63 (br s, 3 H) was assigned to an olefinic methyl group. An olefinic proton signal at δ 5.10 (d, 1 H, J = 9.6 Hz) was coupled to a methine signal at δ 2.39 (m, 1 H) that was in turn coupled to methyl signal at δ 0.91 (d, 1 H, J = 6.7 Hz). The remaining n-propyl group was attached to the methine carbon, completing the structural assignment. The relative stereochemistry at C-4 could not be determined by spectral analysis.

Table I. ^1H NMR Data (360 MHz, $CDCl_3$) for the Hemiacetal 3 and the Ester 4

H at C no.	3, δ	4, δ
1	0.91 (t, 3 H, J = 7 Hz)	0.90 (t, 3 H, J = 6.7 Hz)
2, 3	~1.3 (m, 4 H)	~1.3 (m, 4 H)
4	2.39 (m, 1 H)	2.03 (m, 1 H)
5	5.10 (d, 1 H, J = 9.6 Hz)	5.30 (d, 1 H, J = 9.7 Hz)
7	4.00 (d, 1 H, J = 10.4 Hz)	5.07 (d, 1 H, J = 10.3 Hz)
8	2.33 (dqd, 1 H, J = 10.4, 6.5, 1 Hz)	2.76 (dq, 1 H, J = 10.3, 6.9 Hz)
10	2.51 (br q, 1 H, J = 6.7 Hz)	2.40 (q, 2 H, J = 7.3 Hz)
12	1.65 (m, 1 H), 1.80 (m, 1 H)	2.16 (q, 2 H, J = 7.6 Hz)
13	1.01 (t, 3 H, J = 7.4 Hz)	1.06 (t, 3 H, J = 7.6 Hz)
14	1.00 (d, 3 H, J = 6.7 Hz)	1.00 (t, 3 H, J = 7.3 Hz)
15	0.80 (d, 3 H, J = 6.5 Hz)	0.89 (d, 3 H, J = 6.9 Hz)
16	1.63 (br s, 3 H)	1.54 (br s, 3 H)
17	0.91 (d, 3 H, J = 6.7 Hz)	0.91 (d, 1 H, J = 6.5 Hz)
OH	1.82 (br s, 1 H)	

The ester 4, $[\alpha]_D$ −7.1° (c 0.4, $CHCl_3$), was an isomer of the hemiketal 3. The ester and ketone groups were defined by ^{13}C NMR signals at δ 172.1 (s) and 210.8 (s) and IR bands at 1750 and 1730 cm^{-1}. The ^1H NMR spectrum revealed the presence of two ethyl groups. Signals at δ 1.06 (t, 3 H, J = 7.6 Hz) and 2.16 (q, 2 H, J = 7.6 Hz) were assigned to a propionate ester while those at δ 1.00 (t, 3 H, J, = 7.3 Hz) and 2.40 (q, 2 H, J = 7.3 Hz) were due to an ethyl ketone. A signal at δ 5.07 (d, 1 H, J = 10.3 Hz), assigned to the methine proton on the carbon bearing the propionate ester, was coupled to a methine proton signal at δ 2.76 (dq, 1 H, J = 10.3, 6.9 Hz) that was in turn coupled to a methyl signal at δ 0.89 (d, 3 H, J = 6.9 Hz). Since the ^1H and ^{13}C NMR spectra indicated an identical eight-carbon chain in each molecule, we could define the ester 4 as a propionate ester of a β-ketol.

The hemiacetal 3 and ester 4 are related by a fragmentation of the retroaldol type. This relationship was confirmed by treatment of the hemiacetal 3 with DBU in benzene to obtain the ester 4. This conversion allowed the assignment of the relative stereochemistry at C-7 and C-8 but the relative stereochemistry at C-4 was not determined.[7]

Experimental Section[8]

Isolation Procedures. A total of 110 specimens of *Siphonaria australis* were collected by hand in the intertidal zone near Auckland, New Zealand. The animals were stored in acetone for 5 months at 4 °C. The acetone was decanted and evaporated to obtain an aqueous suspension that was diluted with distilled water to 75 mL and extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried over sodium sulfate and the solvent was evaporated to obtain a green oil (45 mg). The oil was filtered through a silica gel plug in ether and the resulting oil separated by LC on μ-Partisil using ether/hexane (1:1) as eluant to obtain the hemiacetal 3 (8.4 mg, 0.08 mg/animal) and the ester 4 (4.0 mg, 0.04 mg/animal).

Hemiacetal 3: $[\alpha]_D$ +22.3° (c 0.84, $CHCl_3$); IR (CCl_4) 3690, 3560, 3000, 1730, 1460, 1450, 1370, 1330, 1160, 1135, 1010, 985, 950, 935 cm^{-1}; ^{13}C NMR (C_6D_6) δ 207.3 (s), 136.5 (d), 131.7 (s), 102.8 (s), 81.5 (d), 49.9 (d), 46.6 (d), 40.0 (t), 33.2 (t), 32.2 (d), 21.0 (q), 21.0 (t), 14.4 (q), 11.0 (q), 10.2 (q), 9.0 (q), 8.2 (q).

Ester 4: $[\alpha]_D$ −7.1° (c 0.404, $CHCl_3$); IR (CCl_4) 2990, 1750, 1730, 1450, 1370, 1350, 1170, 995 cm^{-1}; ^{13}C NMR (C_6D_6) δ 210.8 (s), 172.1 (s), 138.9 (d), 129.3 (s), 82.8 (d), 47.7 (d), 39.8 (t), 35.4 (t), 32.3 (d), 27.8 (t), 20.9 (t), 21.0 (q), 14.4 (q), 13.8 (q), 11.5 (q), 7.8 (q).

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(4) Hochlowski, J. E.; Faulkner, D. J.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1983**, *105*, 7413.

(5) Jenkins, B. S. *J. Malac. Soc. Aust.* **1983**, *6*, 1.

(6) The molecular formulae were derived primarily from ^{13}C NMR data since neither molecule gave a molecular ion in the mass spectrum.

(7) We anticipate that this stereochemical problem will be more easily solved by synthesis than by spectral or degradation studies.

(8) For general information, see: Cartê, B.; Faulkner, D. J. *J. Org. Chem.* **1983**, *48*, 2314.

Base-catalyzed rearrangement of hemiacetal 3: DBU (3 drops) was added to a solution of hemiacetal **3** (3 mg, 0.011 mmol) in dry benzene (10 mL) under a dry nitrogen atmosphere and the solution stirred for 15 min. After 15 min, the benzene was removed in vacuo and the residue dissolved in ether and filtered through a silica gel SEP-PAK to obtain ester **4** (1.7 mg, 57% yield).

Acknowledgment. We thank Bruce Jenkins for identifying the pulmonate and Dr. M. Taylor for assistance in collecting the organisms. The research was supported by a grant from the National Science Foundation (CHE-8121471).

Registry No. 3, 91466-58-9; 4, 91466-59-0.

Thallium in Organic Synthesis. 62. A Convenient Synthesis of α-Arylsuccinic Acids[1,2]

Edward C. Taylor,* Richard A. Conley, and Alan H. Katz

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

Alexander McKillop

School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, Norfolk, England

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The "acetophenone rearrangement" (eq 1),[3-5] which is carried out by treatment of aralkyl ketones with thallium(III) trinitrate (TTN) in a mixture of methanol and trimethyl orthoformate (TMOF), or with TTN absorbed

$$\mathrm{ArC(O)CH_2R} \xrightarrow[\text{MeOH/TMOF}]{\text{TTN}} \mathrm{R(Ar)CHCO_2Me} \quad (1)$$

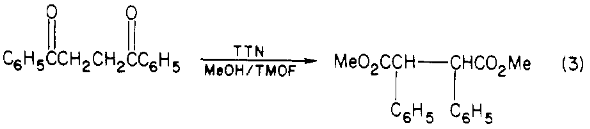
upon K-10 montmorillonite clay,[6] provides a high-yield, mild, one-step procedure for the synthesis of arylacetic acids and α-alkylarylacetic acids (as their methyl esters) which are of considerable interest as antiinflammatory, analgesic, and antipyretic agents.[7] We report in this paper details of a useful extension of the "acetophenone rearrangement" which leads to α-arylsuccinic acids (eq 2).

$$\mathrm{ArC(O)CH_2CH_2CO_2H} \xrightarrow[\text{MeOH/TMOF}]{\text{TTN}} \mathrm{MeO_2CC(Ar)HCH_2CO_2Me} \quad (2)$$

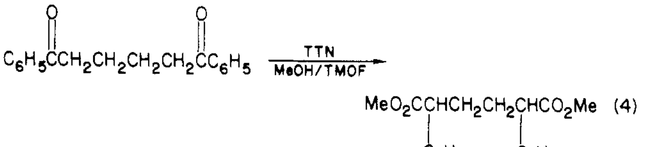
These latter compounds, which are precursors to the anticonvulsant α-arylsuccinimides,[8] are difficult to prepare in good yield by conventional routes.[9] Our new procedure involves TTN-mediated oxidative rearrangement of β-aroylpropionic acids (readily available by Friedel–Crafts acylation of arenes with succinic anhydride), and thus constitutes a two-step process for α-arylation of succinic acid. The same approach can be applied to the preparation of dimethyl α-phenylglutarate and dimethyl α-phenyladipate by oxidative rearrangement of γ-benzoylbutyric acid and δ-benzoylvaleric acid, respectively. Representative examples of this α-arylation process are given in Table I (method A).[10]

The reaction of β-benzoylpropionic acid with TTN in methanol alone gave only methyl β-benzoylpropionate (i.e., no oxidative rearrangement was observed), whereas the use of TMOF, free of added methanol,[11] led to a much lower yield of dimethyl α-phenylsuccinate, along with substantial amounts of the half-ester $\mathrm{C_6H_5CH(CO_2CH_3)CH_2CO_2H}$. Replacement of MeOH/TMOF by aqueous perchloric acid as the reaction medium gave a complex mixture of oxidation products.[12] These results suggest that β-benzoylpropionic acid is first converted to its methyl ester by methanol in the presence of TTN, a strong Lewis acid and an effective esterification catalyst, and that TMOF converts the latter to its enol ether, which then undergoes oxidative rearrangement.[13] In confirmation of this proposed pathway, methyl β-benzoylpropionate (prepared in situ from the acid) was converted with methanol/TMOF/TsOH to its enol ether, which rearranged cleanly to dimethyl α-phenylsuccinate within 15 min at room temperature (77% yield). Analogous results were obtained when this procedure was applied to other ω-aroylalkanoic acids (see Table I, method B).

Oxidative rearrangement of 1,2-dibenzoylethane and 1,4-dibenzoylbutane with 2 equiv of TTN in MeOH/TMOF gave dimethyl α,α′-diphenylsuccinate (65%) (eq 3) and dimethyl α,α′-diphenyladipate (73%) (eq 4), respectively.



$$\mathrm{C_6H_5\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}C_6H_5} \xrightarrow[\text{MeOH/TMOF}]{\text{TTN}} \mathrm{MeO_2C\underset{C_6H_5}{\underset{|}{C}H}{-}\underset{C_6H_5}{\underset{|}{C}H}CO_2Me} \quad (3)$$



$$\mathrm{C_6H_5\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}C_6H_5} \xrightarrow[\text{MeOH/TMOF}]{\text{TTN}} \mathrm{MeO_2C\underset{C_6H_5}{\underset{|}{C}H}CH_2CH_2\underset{C_6H_5}{\underset{|}{C}H}CO_2Me} \quad (4)$$

Unsymmetrical α,α′-diarylsuccinates can also be prepared by this procedure; thus, 1-(*p*-bromobenzoyl)-2-benzoylethane undergoes a double rearrangement under the above conditions to give dimethyl α-(*p*-bromophenyl)-α′-phenylsuccinate (51%). Existing methods for the preparation of α,α′-diarylsuccinic acid derivatives usually involve coupling of arylacetic acids and can only produce symmetrical products.[15]

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[1] For the preceding paper in this series, see: Taylor, E. C.; Andrade, J. G.; Rall, G. J. H.; Turchi, I. J.; Steliou, K.; Jagdmann, G. E., Jr.; McKillop, A. *J. Am. Chem. Soc.* **1981**, *103*, 6856.

[2] We are grateful to the National Science Foundation (Grant No. CHE 8215419) for its generous support of this work.

[3] McKillop, A.; Taylor, E. C. "Comprehensive Organometallic Chemistry", Wilkinson, G., Abel, E. W., Stone, F. G. A., Eds.; Pergamon Press: 1983; Vol. 7, p 465.

[4] McKillop, A.; Swann, B. P.; Taylor, E. C. *J. Am. Chem. Soc.* **1971**, *93*, 4919.

[5] McKillop, A.; Swann, B. P.; Taylor, E. C. *J. Am. Chem. Soc.* **1973**, *95*, 3340.

[6] Taylor, E. C.; Chiang, C.-S.; McKillop, A.; White, J. F. *J. Am. Chem. Soc.* **1976**, *98*, 6750.

[7] Lednicer, D.; Mitscher, L. A. "The Organic Chemistry of Drug Synthesis"; Wiley-Interscience: New York, 1980; Vol. 2, pp 63–64.

[8] Miller, C. A.; Long, L. M. *J. Am. Chem. Soc.* **1951**, *73*, 4895.

[9] (a) Lapworth, A.; Baker, W. "Organic Syntheses"; Wiley-Interscience: New York, 1941; Collect. Vol. 1, p 451. (b) Allen, C. F. H.; Johnson, H. B. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. 4, p 804. (c) Chigarev, A. G.; Ioffe, D. V. *Zh. Org. Khim.* **1967**, *3*, 85.

[10] A few examples of this process for α-arylation of carboxylic acids were previously reported without experimental details: (a) McKillop, A.; Taylor, E. C. *Endeavour* **1976**, 88. (b) Reference 3.

[11] There is some methanol present as a result of the reaction: $\mathrm{Tl(ONO_2)_3{\cdot}3H_2O + 3HC(OMe)_3 \rightarrow Tl(ONO_2)_3 + 6MeOH + 3HCO_2Me}$.

[12] Taylor, E. C.; Robey, R. L.; Liu, K. T.; Favre, B.; Bozimo, H. T.; Conley, R. A.; Chiang, C.-S.; McKillop, A.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 3037.

[13] Walker, J. A.; Pillai, M. D. *Tetrahedron Lett.* **1977**, 3707.

[14] We have also examined the effectiveness of the TTN/K-10 supported reagent (ref 6) for this transformation. The brown suspension of the reagent in $\mathrm{CCl_4}$ instantly turned white upon addition of the enol ether; results comparable to those reported in Table I were obtained. The TTN/K-10 supported reagent was not as effective, however, for oxidative rearrangement of the β-aroylpropionic acids; in these latter cases, the poor solubility of the substrates in $\mathrm{CCl_4}$ greatly slows the rate of reaction.

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