Further work is in progress to extent the scope of this method and to characterize the catalyst involved.

Experimental Section

In a typical experiment, finely powdered $Na_2WO_4 \cdot 2H_2O$ (1.65 g, 5 mmol), 40% w/v H_3PO_4 (2.45 mL, 10 mmol), and 8% aqueous H_2O_2 (51 g, 120 mmol) were introduced into a glass reactor. The pH of the aqueous solution was adjusted to 1.6 by 30% H_2SO_4, thereupon 1-octene (22.4 g, 200 mmol), 1,2-dichloroethane (15 mL), and Aliquat (0.82 g, ca. 2 mmol) were added. Under vigorous stirring the resultant biphase mixture was heated to 70 °C for 45 min. The water and 1,2-chloroethane layers were then separated. The amount of unreacted H_2O_2 was determined by iodometric titration of the aqueous phase. The organic layer was analyzed by GLC. In this way, 12.7 g (99 mmol) of 1,2-epoxyoctane was obtained (Table I, first entry).

The other olefins listed in Table I were epoxidized under similar conditions. In all cases combustion analyses, spectral data, and comparison with authentic samples confirmed the identity of the products.

Registry No. 3, 41272-12-2; WO_4^{2-}, 14311-52-5; PO_4^{3-}, 14265-44-2; Na_2HAsO_4, 7778-43-0; 1-octene, 111-66-0; 1-dodecene, 112-41-4; allyl chloride, 107-05-1; styrene, 100-42-5; α-methylstyrene, 98-83-9; cyclohexene, 110-83-8.

Improved Procedure for the Blaise Reaction: A Short, Practical Route to the Key Intermediates of the Saxitoxin Synthesis

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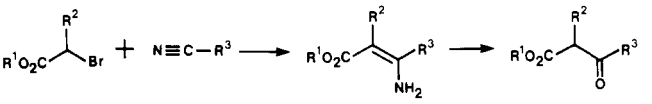
Since the discovery of the addition of zinc ester enolates to nitriles by Blaise in 1901,[1] this potentially useful β-keto ester synthesis has found little application in organic synthesis. The easy introduction of the functionalities and the straightforward nature of the conversion have been overshadowed by the problems of low yield, narrow scope, and competing side reactions.[2-5] We report a convenient modification of this reaction, which has proven surprisingly versatile and has provided a short, practical route to key intermediates in the total synthesis of the paralytic shellfish poisons, saxitoxin and gonyautoxins II and III.[6]

Table I



1 2 3 4

	R^1	R^2	R^3	yield of 3, %	yield of 4, %
a	Me	H	$(CH_2)_4Cl$	95	85
b	*t*-Bu	H	$(CH_2)_4Cl$	87	83
c	Me	H	$C(CH_3)_2(CH_2)_2Cl$	70	62
d	Me	H	C_6H_5	88	82
e	Me	Me	C_6H_5	84	79
f	Me	Me	$(CH_2)_4Cl$	54[a]	84

[a] The lower yield is due to facile hydrolysis of 3f to 4f.

Treatment of aliphatic or aromatic nitriles **2** with 3–5 molar excess of α-bromo esters **1** in the presence of activated zinc dust in refluxing tetrahydrofuran yielded the corresponding enamino esters **3**[7] or, after acid hydrolysis, the β-keto esters **4** as the only isolable products. Some representative examples are listed in Table I.[8] This procedure differs from the classical reaction conditions in the use of tetrahydrofuran as the solvent. In addition, two simple steps were found to be necessary to ensure the success of the reactions. First, the activated zinc was prepared by washing zinc dust sequentially with 3 N hydrochloric acid, distilled water, ethanol, and ether and drying under vacuum. Second, the α-bromo ester is added over 30–60 min to minimize self-condensation. The required excess of bromoacetate decreased in the order methyl ~ ethyl > isopropyl > *tert*-butyl esters.

One consequence of these modifications was a substantial improvement in the yield of α-monosubstituted β-keto esters, but most significant was the consistently successful reaction of bromo*acetates* to give α-unsubstituted products, e.g., **4a–4d**. These compounds were reported to be virtually unobtainable when using the classical reaction conditions.[1-3,9]

The possibility of in situ alkylation of the initial adduct offers an additional synthetic application for the Blaise reaction. In principle, the initial adduct **5** can cyclize in two different modes, leading to the N-alkylated product **6** or to the C-alkylated product **7** (Scheme I). As may be deduced from the principle of hard–soft acids and bases,[10] the course of the cyclization reaction depends primarily on the nature of the leaving group X. In the case of X = Br, the C-alkylated product **7** was found to be the major product. Among the conditions examined, heating the initial adduct in DMF for 30 min gave the cleanest results as a 15:85 mixture of **6** and **7** was isolated in about 80%

(1) Blaise, E. E. *C. R. Hebd. Seances Acad. Sci.* **1901**, *132*, 478.

(2) (a) Blaise, E. E. *C. R. Hebd. Seances Acad. Sci.* **1901**, *132*, 978. (b) Cason, J.; Rinehart, K. L. Jr.; Thornton, S. D., Jr. *J. Org. Chem.* **1953**, *18*, 1594. (c) Kagan, H. B.; Suen, Y.-H. *Bull. Soc. Chim. Fr.* **1966**, 1819. (d) Lhommet, G.; Eskenazi, C.; Maitte, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1974**, *279*, 263. (e) Konrad, J.; Jezo, I. *Chem. Zvesti* **1980**, *34*, 125.

(3) Kagan and Suen reported an improvement for the Blaise reaction.[2c] Their procedure involved use of slow addition of a benzene solution of α-bromo esters to a refluxing mixture of zinc and nitriles, providing excellent yields (70–83%) for α,α-di- and α-monosubstituted β-keto esters, but yields for α-unsubstituted β-keto esters exceeded 40% in only one case. Other workers have obtained only very low yields of α-mono- and α-unsubstituted β-keto esters by using this method.[2d,e]

(4) Twenty-seven representative examples reported in the papers quoted under ref 2 are summarized in the tables in the supplementary material.

(5) Since the completion of this work, Hiyama and Kobayashi (Hiyama, T.; Kobayashi, K. *Tetrahedron Lett.* **1982**, *23*, 1597) have reported the coupling of magnesium enolates of acetic acid esters. The reaction is limited to *tert*-butyl esters, and satisfactory reactions are reported for only a limited range of nitriles.

(6) For recent reviews on saxitoxins, see: (a) Schantz, E. J. *Pure Appl. Chem.* **1979**, *52*, 183. (b) LoCicero, V. R., Ed. "Proceedings of the 1st International Conferences on Toxic Dinoflagellate Blooms", Science and Technology Foundation: Wakefield, MA, 1975. (c) Shimizu, Y. In "Marine Natural Products"; Scheuer, P. J., Ed., Academic Press: New York, 1978; Vol. 1, pp 1–42. Also see: Koehn, F. E.; Hall, S.; Wichmann, C. F.; Schnoes, H. K.; Reichardt, P. B. *Tetrahedron Lett.* **1982**, *23*, 2247 and references cited therein.

(7) This type of enamino esters are known to exist predominantly as Z isomers. For example, see ref 13.

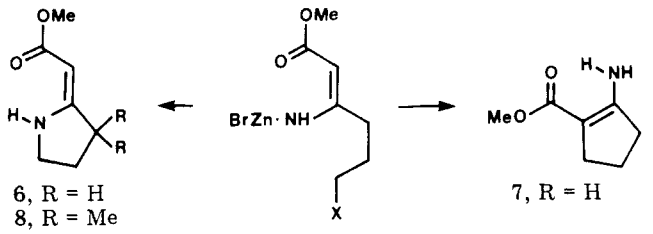
(8) Satisfactory spectroscopic data (^1H NMR, IR, UV, MS) were obtained for all the new substances. For crystalline compounds, satisfactory elemental analyses were obtained.

(9) The known procedures, in particular, the one described by Kagan and Suen,[2c] are very reliable for the preparation of α,α-disubstituted β-keto esters in excellent yield.

(10) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. Pearson, R. G., Songstad, J. *J. Org. Chem.* **1967**, *32*, 2899. Saville, R. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 928.

0022-3263/83/1948-3833$01.50/0

Scheme I



6, R = H
8, R = Me

5, X = Br or OMs

7, R = H

yield.[11] In contrast, when X = OMs the N-alkylated compound **6** was found to be the major product. Among the conditions examined, stirring of the initial adduct with powdered potassium carbonate in DMF at room temperature gave the cleanest result as a 95:5 mixture of **6** and **7** was isolated in about 80% yield.

For the synthesis of saxitoxins, we required heterocycles **10a** and **10b**, which were envisioned to result from addition of a zinc ester enolate to **9a** and **9b**, followed by cyclization of the resulting enamino esters. Although some reduction in yield might result due to the sterically crowded nature of these nitriles, we felt that the sp-hybridized electrophilic center would facilitate the required additions.[12] Indeed, the addition and subsequent cyclization were found to be surprisingly facile for α,α-disubstituted nitriles. This was first demonstrated by using $N{\equiv}CC(Me)_2CH_2CH_2OMs$. Treatment of this nitrile with methyl bromoacetate and zinc dust gave directly and exclusively the N-alkylated product **8** (mp 74–75 °C) in 61% isolated yield.[13]

The successful synthesis of **8** encouraged us to extend this reaction to the synthesis of the key intermediate **10a** (Scheme II) in our previous saxitoxin synthesis.[14,15] The cyano mesylate **9a** (colorless oil) was prepared from 2-cyano-1,3-dithiane[16] in two steps [(1) LDA/THF/−25 °C, followed by addition of ethylene oxide, and (2) MsCl/Et_3N/CH_2Cl_2/−25 °C] in 90% overall yield. Reaction of **9a** with methyl bromoacetate and zinc dust, followed by treatment of the crude adduct with powdered potassium carbonate in DMF at room temperature, yielded the desired vinylogous urethane **10a** (mp 175–176 °C) in 69% yield along with 23% recovery of the starting material. The heterocycle **10a** was converted to the saxitoxin intermediate **11a** (mp 161–163 °C) by the known method.[14] Compared with the previous route to **11a**, the current synthesis is shorter, more practical, and more suitable for large-scale preparation. In a synthetic approach to gonyautoxins II and III, the methoxy nitrile **9b** (colorless oil) was prepared from 2-cyano-1,3-dithiane in four steps [(1) LDA/THF/−10 °C, followed by addition of $THPOCH_2CHO$;[17] (2) *n*-BuLi/THF/−78 °C, followed by addition of $Me_3O^+BF_4^-$/−78 → −10 °C; (3) HCl/MeOH/room temperature; (4) MsCl/Et_3N/CH_2Cl_2/−25 °C → room temperature] in 52% overall yield. The nitrile **9b** was converted smoothly to the heterocycle **10b** (mp 117–118 °C) by the usual addition–cyclization sequence. Ten grams of **10b** could be conveniently prepared in 79% yield from the nitrile **9b**. Following the known procedure,[14] this monocyclic compound was converted to the tricyclic product **11b** (269–271 °C), the structure of which was confirmed by X-ray analysis.[18,19]

These results demonstrate the applicability of the classical Blaise reaction to contemporary synthetic problems. The facile addition of zinc ester enolates to nitriles is quite compatible with the functionalities and steric requirements often encountered in organic synthesis.

Experimental Section

General Procedure for the Preparation of Enamino Esters 3. To a suspension of 327 mg (5 equiv) of activated zinc dust (Fisher Scientific) in 3 mL of refluxing anhydrous THF under N_2 were added 4 drops of α-bromo ester. After the appearance of the green color (this color is very evident with bromoacetates; when substituted bromo esters are used, however, the color may not appear), 1 mmol of nitrile was added in one portion, and then 4 mmol of α-bromo ester were injected by syringe pump over 45 min. The mixture was refluxed for an additional 10 min, diluted with 9 mL of THF, and quenched with 1.3 mL of 50% aqueous K_2CO_3. Rapid stirring for 30 min gave two cleanly separated layers. The upper organic layer was decanted, the residue was washed three times with THF, and the combined organic layers were dried with $MgSO_4$. Concentration and purification by PTLC (SiO_2 developed with 1:1 hexanes:Et_2O, typically) gave the enamino ester product, contaminated with less than 25% of its β-keto ester hydrolysis product. Hydrolysis during purification could be minimized by avoiding contact of the enamino ester with dry

(11) Interest in the effect of replacing bromide by iodide led to the preparation of iodo nitriles, but they were, as might have been expected, reduced to the corresponding alkanes under the conditions used for preparation of zinc enolates. LiI added to the DMF solution had no apparent effect on the ratio of **6** to **7**.

(12) (a) Tenud, L.; Farooq, S.; Seibl, J.; Eschenmoser, A. *Helv. Chim. Acta* **1970**, *53*, 2059. (b) Bügi, H. B.; Dunitz, J. D.; Lehn. J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563. (c) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (d) Procter, G.; Britton D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 471.

(13) In studies on the total synthesis of vitamin B_{12}, the chemistry of this type of compounds was extensively investigated by Eschenmoser. For the synthesis of sterically hindered enamino esters similar to **8**, the sulfur contraction method is known to be effective; for example, see: Eschenmoser, A. *Q. Rev., Chem. Soc.* **1970**, *24*, 366.

(14) (a) Taguchi, M.; Yazawa, H.; Arnett, J. F.; Kishi, Y. *Tetrahedron Lett.* **1977**, 627. (b) Tanino, H.; Nakata, T.; Kaneko, T.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 2818. (c) Kishi, Y. *Heterocycles* **1980**, *14*, 1477.

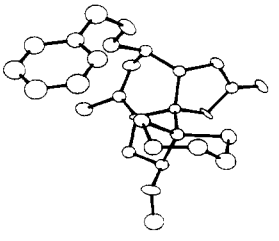
(15) For another synthetic approach to saxitoxin, see: Jacobi, P. A.; Brownstein, A.; Martinelli, M.; Grozinger, K. *J. Am. Chem. Soc.* **1981**, *103*, 239.

(16) This substance was prepared from $[O_3SS(CH_2)_3SSO_3]^{2-}2Na^+$ with a slight modification (i.e., 3 equiv of NaH in DMF rather than 2 equiv. of NaOEt in EtOH) of Hayashi's procedure. See: Hayashi, S.; Furukawa, M.; Fujino, Y.; Nakao, T.; Inoue, S. *Chem. Pharm. Bull.* **1971**, *19*, 1557.

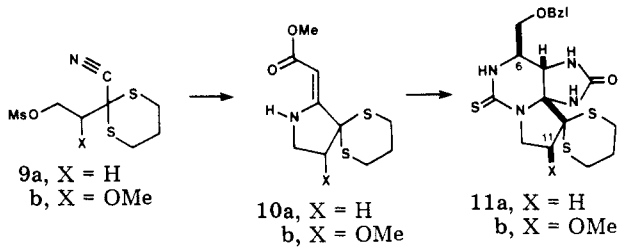
(17) Iwai, I.; Iwashige, T.; Asai, M.; Tomita, K.; Hiraoka, T.; Ide, J. *Chem. Pharm. Bull.* **1963**, *11*, 188.

(18) The diastereomers due to the C6 and C11 asymmetric centers were separated at the bicyclic thiourea urea stage, corresponding to the compound **7** reported in ref 14b, and then separately subjected to a cyclization reaction using the AcOH–TFA conditions.[14b] Each diastereomer yielded a single tricyclic thiourea urea. The stereochemistry of the tricyclic product of one diastereomer series was confirmed to be **11b** by X-ray analysis, while that of the other diastereomer series is under investigation.

(19) Crystals of **11b** were triclinic, space group P1, with a = 11.227 (3) Å, *b* = 13.764 (4) Å, *c* = 15.840 (5) Å, α = 92.13 (2)°, β = 90.54 (3)°, γ = 98.89 (2)°, and d_{calcd} = 1.33 g cm^{-3} for $Z = 2$ $(C_{20}H_{26}N_4O_3S_3)_2{\cdot}H_2O$, M_r = 466.64). The intensity data were measured on a Nicolet R3M diffractometer (graphite-filtered MoKα radiation, θ–2θ scans). A crystal measuring approximately 0.20 × 0.18 × 0.10 mm was used for data collection. A total of 2138 unique reflections ($3° < 2\theta < 38°$) were considered to be observed ($I > 2\sigma(I)$). The structure was solved by direct methods and was refined by the blocked-cascade least-squares procedure. In the final refinement, anisotropic thermal parameters were used for the hetereoatoms, and isotropic temperature factors were used for the carbon and hydrogen atoms. Except for the hydrogen atoms on N-1, which were located by difference map and refined, fixed hydrogen atom contributions were included with the carbon–hydrogen bond distances fixed at 0.96 Å and with isotropic thermal parameters set at 1.2 times those of the bonded carbon atoms. The final discrepancy indices that R = 0.083 and R_w = 0.072 for the 2138 reflections. The final difference map has no peaks greater than ±1 e Å^{-3}. A stereoscopic drawing is shown below.



Scheme II



silica gel. Column chromatography on solvent-wetted SiO_2 was an effective procedure for isolating pure enamino ester. Note that it was crucial to use the prescribed volumes of THF and K_2CO_3 solution. Otherwise, emulsions would form and the clear, Zn^{2+}-free THF layer would not separate, making the workup tedious and decreasing the yield. For each mole of zinc salt produced, the cooled reaction mixture should be diluted to a total volume of 3 mL, and then $^1/_3$ mL of 50% aqueous K_2CO_3 should be added with vigorous stirring.

General Procedure for the Preparation of β-Keto Esters 4. The THF solution of crude enamino ester obtained as described above was subjected to acid hydrolysis as follows. The THF solution was treated with 1 mL of 10% aqueous HCl at room temperature for 30 min, or a time sufficient for the UV-active enamino ester to be no longer detectable by TLC. The mixture was concentrated, diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and purified by PTLC (SiO_2 developed with 1:1 hexanes:Et_2O, typically) to yield the pure β-keto ester.

Synthesis of 10b. A suspension of 16.0 g (5 equiv) of activated zinc dust in 150 mL of THF was heated to reflux under N_2. Several 0.1-mL portions of methyl bromoacetate were added with vigorous stirring to initiate the reaction. When the green color appeared, 14.55 g (49.0 mmol) of cyano mesylate **9b** in 50 mL of THF were added. Then 18.9 mL (4 equiv) of methyl bromoacetate were added dropwise over 45 min to the refluxing mixture. The mixture was refluxed 10 min longer, cooled to room temperature, diluted with 430 mL of THF, and quenched with 70 mL of 50% aqueous K_2CO_3. Rapid stirring for 45 min gave two distinct layers. The THF layer was decanted, and the residue was rinsed with THF. The combined THF layers were dried over $MgSO_4$ and concentrated. This crude intermediate was then stirred with 14 g of powdered K_2CO_3 in 150 mL of DMF for 14 h. The reaction mixture was diluted with 150 mL of Et_2O, filtered through Celite, concentrated, and adsorbed on Florisil. The Et_2O eluate was concentrated and purified by MPLC (1.5:1 Et_2O:hexanes), giving 10.66 g (38.8 mmol, 79%) of 10b as colorless crystals from hexanes/EtOAc, mp 117–118 °C.

A procedure almost indentical with the above was used for the synthesis of 8 and **10a**.

Acknowledgment. Financial support from the National Institutes of Health (Grant No. NS 12108) and the National Science Foundation (Grant No. CHE 78-06296) is gratefully acknowledged.

Registry No. **1a**, 96-32-2; **1b**, 5292-43-3; **1e**, 5445-17-0; **2a**, 6280-87-1; **2c**, 64273-86-5; **2d**, 100-47-0; **3a**, 86971-58-6; **3b**, 86971-59-7; **3c**, 86993-51-3; **3d**, 86971-60-0; **3e**, 66213-66-9; **3f**, 86971-61-1; **4a**, 22977-45-3; **4b**, 86971-62-2; **4c**, 86971-63-3; **4d**, 614-27-7; **4e**, 29540-54-3; **4f**, 86971-64-4; **5** (X = Br), 86993-49-9; **5** (X = OMs), 86993-50-2; **6**, 86971-65-5; **7**, 52909-60-1; **8**, 86971-66-6; **9a**, 86971-67-7; **9b**, 86971-68-8; **10a**, 86971-69-9; **10b**, 86971-70-2; **11a**, 87037-54-5; **11b**, 86971-71-3; $N{\equiv}CC(Me)_2CH_2CH_2OMe$, 86971-72-4; $THPOCH_2CHO$, 699-13-8; $[O_3SS(CH_2)_3SSO_3]^{2-}{\cdot}2Na^+$, 37914-69-5; 2-cyano-1,3-dithiane, 33927-42-3; ethylene oxide, 75-21-8; saxitoxin, 35523-89-8; gonyautoxin, 77462-64-7.

Supplementary Material Available: Spectroscopic and crystallographic data and tables listing representative examples of the Blaise reaction (42 pages). Ordering information is given on any current masthead page.

Synthesis of Oxazolo[4,3-*a*]isoquinoline and Related Compounds through Intramolecular Arylation of α-Oxaacyl Iminium Ions

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π cyclization of *N*-acyl iminium ions has proven to be an important synthetic method for a wide variety of heterocyclic systems.[1] Several kinds of *N*-acyl iminium ions (**1a–f**) have been used for this purpose. Cyclization of **1d** and **1e**, followed by desulfurization of the cyclization products, is a valuable method for synthesis of α-substituted N-heterocycles.[1i] Recently, imidazo[2,1-*a*]isoquinolines were also obtained by annelation of imidazolidinones.[1j] We have now examined cyclization of α-oxaacyl iminium ions **1g** to provide oxazolo[4,3-*a*]isoquinolines and related compounds (Schemes I and II).

Starting materials **4a–g** were prepared by coupling the oxazolidinediones **2**, **3a**,[2] or **3b**[3] with the appropriate arylethanol by using the Mitsunobu procedure[4] with diisopropyl azodicarboxylate. Reduction of **4a–g** (DIBAH, toluene, −78 °C, 1 h) followed by treatment of the corresponding reduction products, without purification, with formic acid yielded the corresponding cyclization products **5a–g**, respectively, in moderate yields (Table I, Scheme III). In the formation of **5c–e,g**, arylation proceeded with high stereoselectivity. In the case of **5c**, thenylation proceeded from the side opposite the methyl group, and formation of the alternative stereoisomer was not observed. The ^1H NMR spectrum of **5a** exhibited two singlets attributable to 1-CH_3 in a different region (δ 0.97 and 1.76). The CH_3 cis to the benzene ring resonates at a higher field stemming from the shielding effect of the benzene ring. The trans-oriented CH_3 resonates at lower field because of the deshielding effect of benzene ring. In the case of **5g**, the higher 1-CH_3 signal disappeared and only the lower 1-CH_3 signal (δ 1.69, d, J = 6 Hz) remained. This fact strongly indicates that phenylation proceeds from the side opposite the methyl group and that the relative configuration of 1-H and 10b-H in **5g** is trans. Similarly, the relative configuration of **5d** and **5e** is also indicated to be trans. Reduction of **5d** ($LiAlH_4$, THF, room temperature) gave the trans-oriented 1-(α-hydroxybenzyl)isoquinoline **6** (Scheme IV). Although reduction of 1-benzoylisoquinoline **8** gives the 1-(α-hydrobenzyl)isoquinoline **7**,[5] the stereoisomer of **6**, the stereochemistry of **7** has not been determined. The stereochemistry of **5f**, obtained as a single product from one isomer of **4f**, was not determined from its spectral data at this stage.

(1) (a) Dijkink, D.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, 935. (b) Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345. (c) Speckamp, W. N.; Veenstra, S. J.; Dijkink, D.; Fortgens, R. *J. Am. Chem. Soc.* **1981**, *103*, 4643. (d) Veenstra, S. J.; Speckamp, W. N. *Ibid.* **1981**, *103*, 4645. (e) Dijkink, D.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 173. (f) Hart, D. G. *J. Org. Chem.* **1981**, *46*, 367. (g) Hart, D. G. *Ibid.* **1981**, *46*, 3576. (h) Nossin, P. M. M.; Hamersma, J. A. M.; Speckamp, W. N. *Tetrahedron Lett.* **1982**, *23*, 3807. (i) Hamersma, J. A. M.; Speckamp, W. N. *Ibid.* **1982**, *23*, 3811. (j) Kohn, H.; Liao, Z.-K. *J. Org. Chem.* **1982**, *47*, 2787.

(2) Aspelund, H. *Suom. Kemistiseuran Tied.* **1940**, *49*, 42.

(3) Shapiro, S. L.; Rose, I. M.; Roskin, E.; Freedman, L. *J. Am. Chem. Soc.* **1959**, *81*, 386.

(4) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679.

(5) MacMahon, R. M.; Thormer, C. W. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2163.

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