practical synthetic scheme to HETEs and analogues thereof.

Our synthetic strategy is centered on the preparation of the *cis-trans*-dienyl allylhydroxy unit A (Scheme I) which is common to all the HETEs. Disconnection of the C8–C9 olefin in 1 provides two convergent fragments, the C9–C20 aldehyde 11, and the C1–C8 phosphonium salt 16 which could be assembled via Wittig olefination. A flexible and efficient approach to the sensitive C9–C20 fragment 11 was conceived as arising from oxidative cleavage of an appropriately substituted furan 6.

Synthesis of the C9–C20 fragment 11 is outlined in Scheme I and described as follows.[6] Alkylation[7] of 2-methoxyfuran (5)[8] with *cis*-1-bromo-2-octene (4)[9] afforded the requisite substituted furan 6. Initial attempts to oxidatively cleave the furan[10] with pyridinium chlorochromate[11] gave complex product mixtures and a poor yield of the desired product. However, treatment of furan 6 with bipyridinium chlorochromate[12] effected smooth cleavage to a sensitive cis keto ester which was not isolated but directly isomerized to the trans configuration by treatment with a catalytic amount of iodine in ether solution[13] and then directly reduced with sodium borohydride to give the hydroxy ester 7. The hydroxy group was protected as a *tert*-butyldimethylsilyl ether and the ester group in 8 was reduced with diisobutylaluminum hydride to the corresponding alcohol which was oxidized by pyridinium chlorochromate[14] to the aldehyde 9.

Synthesis of the C1–C8 phosphonium salt 16 was accomplished by modification of known procedures.[15] The two convergent fragments 9 and 16 were coupled by using potassium *tert*-butoxide in tetrahydrofuran at −78 °C to give 17. Attempts to cleave the silyl ether to provide 12-HETE methyl ester resulted in low yields and significant amounts of byproducts. A satisfactory solution to this problem was found by deprotecting at an earlier stage in the synthetic sequence. Treatment of aldehyde 9 with aqueous HF in acetonitrile[17] and subsequent acetylation gave the aldehyde 11. Wittig olefination, as before, gave the desired cis coupling cleanly, providing 18. The title compound 1[18] was obtained quantitatively from 18 by treatment with excess LiOH in aqueous isopropyl alcohol. Treatment of 1 with an ether solution of diazomethane gave the corresponding methyl ester which exhibited identical ^{1}H NMR spectral parameters as that reported by Corey and co-workers for 12-HETE methyl ester.[3a]

This total synthesis of (±)-12-HETE (1) illustrates a simple and general synthetic approach to HETE syntheses which is operationally simple and amenable to scale-up. The key step in the synthetic strategy involves the oxidative cleavage of an appropriately substituted furan to prepare the requisite functionalized *trans*-allylhydroxy unit which is subsequently reacted in a cis-selective Wittig olefination reaction to complete the carbon skeleton.

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Supplementary Material Available: Experimental procedures and spectral data are provided (18 pages). Ordering information is given on any current masthead page.

(6) The experimental procedures and spectral data for pertinent compounds isolated and purified en route to 12-HETE and a copy of the 300-MHz ^{1}H NMR of 12-HETE is provided as supplementary material.

(7) For a related alkylation, see: Krause, G. A.; Sugimoto, H. *J. Chem. Soc., Chem. Commun.* **1978**, 30.

(8) Alkylation of furan with 4 proceeded smoothly; however, oxidative cleavage provided the corresponding cis keto aldehyde which was very unstable and difficult to manipulate further.

(9) Synthesis of *cis*-1-bromo-2-octene (4) was readily accomplished from 2-octyn-1-ol ((a) Pd/$BaSO_4$, H_2, quinoline poisoning, 90%; (b) PPh_3, Br_2, room temperature, 3 h, 95%).

(10) Oxidative cleavage of substituted furans to provide enediones has been demonstrated, for example, by Williams, P. D.; LeGoff, E. *Tetrahedron Lett.* **1985**, *26*, 1367.

(11) Antonioletti, R.; D'Auria, M.; DeMico, A.; Piancatelli, G.; Sceltri, A. *Synthesis* **1984**, 280.

(12) Guziec, F. S.; Luzzio, F. A. *Synthesis* **1980**, 691.

(13) Hirsch, J. A.; Szur, A. J. *J. Heterocycl. Chem.* **1972**, *9*, 523.

(14) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(15) Alkylation of 5-chloro-1-pentyne with ethylene oxide (*n*-BuLi, BF_3·Et_2O, −78 °C, 1 h, 45%) gave 7-chloro-3-heptyn-1-ol. The following sequence of reactions then provided 16: (a) NaCN, Me_2SO, 70 °C, 1 h, 93%; (b) EtOH/H_2O 1:1, NaOH, reflux, 18 h, 70%; (c) CH_2N_2, ether, 0 °C, 5 min, 100%; (d) Pd/$BaSO_4$, quinoline poisoning, H_2, 86%; (e) PPh_3, Br_2, CH_2Cl_2, room temperature, 2.5 h; (f) NaI, acetone, reflux, 1 h; (g) PPh_3, CH_3CN, 2.5 days, 80 °C, 80% (over three steps). A similar reaction sequence has been reported by Perchonock, C. D.; Finkelstein, J. A.; Uzinskas, I.; Gleason, J. G.; Sarau, H. M.; Cieslinski, L. B. *Tetrahedron Lett.* **1983**, *24*, 2457.

(16) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.

(17) Newton, R. F.; Reynolds, D. P.; Finch, M.; Kelly, D.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

(18) Spectral data for (±)-12-HETE (1): 300-MHz ^{1}H NMR ($CDCl_3$) δ 0.82 (t, *J* = 7.2 Hz, 3 H), 1.15–1.35 (m, 6 H), 1.63 (m, 2 H), 1.95–2.15 (m, 6 H), 2.28 (t, *J* = 7.2 Hz and m, 4 H), 2.80 (m, 1 H), 2.92 (m, 1 H), 4.23 (q, *J* = 5.4 Hz, 1 H), 5.20–5.45 (m, 4 H), 5.50 (m, 1 H), 5.65 (dd, *J* = 7.2, 16.2 Hz, 1 H), 5.91 (t, *J* = 10.8 Hz, 1 H), 6.53 (dd, *J* = 10.8, 16.2 Hz, 1 H); 75.5-MHz ^{13}C NMR ($CDCl_3$) 14.01; 22.53, 24.50, 26.18, 26.42, 27.40, 29.24, 31.49, 33.12, 35.24, 72.07, 124.12, 125.50, 127.59, 128.25, 129.26, 130.22, 133.66, 135.19, 177.99.

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Total Synthesis of Quadrone and Terrecyclic Acid A[1]

Summary: Syntheses of quadrone (1) and terrecyclic acid A (**2a**) are described which feature a Diels–Alder cycloaddition, ring expansion sequence for construction of their complex skeletal core and a nickel-mediated coupling reaction which serves as a preparatively useful enone γ-alkylation method.

Sir: The antitumor activity of the fungal metabolite quadrone (1)[2] coupled with its novel structural features and the more recent characterization of its biologically active congeners, terrecyclic acid A (**2a**)[3a] and terrecyclol (**2b**),[3b] have elicited considerable interest in synthetic approaches[4] to this new family of natural products. We describe in this communication syntheses of quadrone (1) and terrecyclic acid A (**2a**) which additionally provide general access to other analogues of biological interest in this series.

Our synthetic design for quadrone evolved from a long-standing interest[5] in the development of generic

(1) Presented in part at the 185th National Meeting of the American Chemical Society, March 1983, Seattle, WA. This work was taken, in part, from the Ph.D. dissertation of D. J. Wolanin, Harvard University, Cambridge, MA, 1983.

(2) (a) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, *19*, 499. (b) Calton, G. J.; Ranieri, R. L.; Espenshade, M. A. *J. Antibiot.* **1978**, *31*, 38.

(3) (a) Terrecyclic acid A: Hirota, A.; Nakagawa, M.; Sakai, H.; Isogai, A. *J. Antibiot.* **1982**, *35*, 783. (b) Terrecyclol: Nakagawa, M.; Sakai, H.; Isogai, A.; Hirota, A. *Agric. Biol. Chem.* **1984**, *48*, 117.

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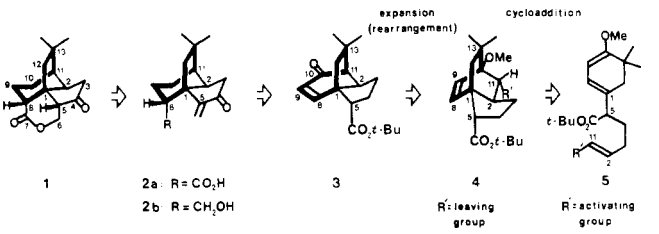
methods for the synthesis of complex seven-membered rings and the specific notion that such systems could be efficiently constructed through a Diels–Alder cycloaddition, ring expansion sequence. Application of this concept to the current problem (Scheme I) revealed that the seven-membered ring (boldface in **1**, **2**, and **3**) common to the quadrone family could, in principle, be obtained from the precursor **4** through migration of its C-13 center to C-11 directed by assisted departure of the antiperiplanar aligned, C-11 leaving group (R′). The attractiveness of this approach becomes apparent at the next stage of analysis where it is seen that **4** is formally the Diels–Alder endo cycloadduct of the relatively simple triene **5**. Thus, in two stages the complex tricyclic skeletal core of targets **1**, **2a**, and **2b** is reduced to the comparatively simple problem of preparing a monocyclic enone derivative **5**.

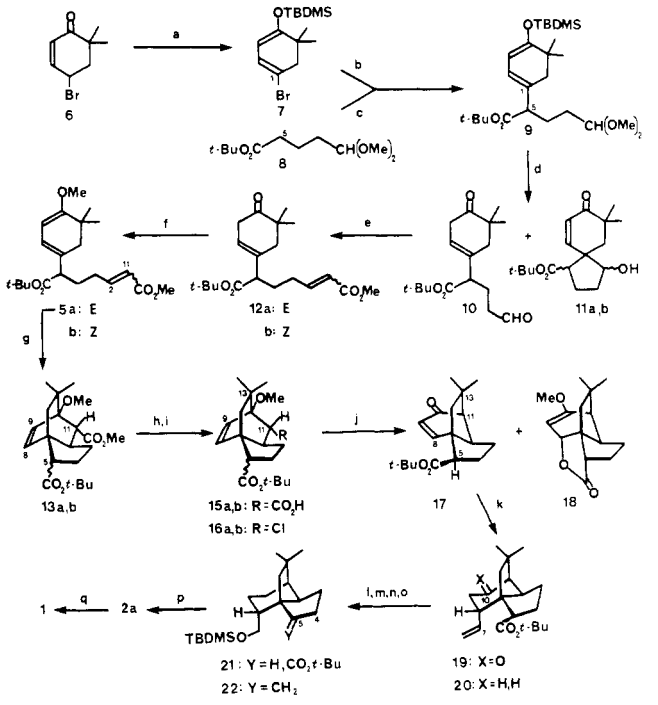
Implementation of the above strategy centered initially on the construction of cyclohexadiene **5**, which is formally derivable from γ-alkylation of enone **6** or its dienolonium ion equivalent[7] (**7**, Scheme II) with a suitable ester enolate. In practice, we found that this new approach to γ-alkylation was efficiently accomplished on a multigram scale by nickel-mediated coupling[8] in which active nickel was generated by addition of *n*-butyllithium (0.33 equiv) to a nickel(II) bromide (1 equiv) suspension in THF at −78 °, after which coupling was effected by sequential addition of bromo dienol ether **7**[9a] (1 equiv) and the ester enolate of **8**[9b] (1.5 equiv). Workup of the resultant mixture after it had reached room temperature provided the coupled product **9**[10] in 81% yield. Hydrolysis of the acetal in **9** as needed for introduction of the dienophile subunit was complicated by concomitant hydrolysis of the (*tert*-butyldimethylsilyl)oxy-activated diene. However, the desired diene and dienophile were instated, at the expense of one additional step, by submitting the product mixture of complete hydrolysis (**10**, **11a**, and **11b**)[11] to an olefination reaction, which produced unsaturated esters **12a,b** (*E*/*Z* = 12/1, 80%), and subsequently reacting this mixture with trimethyl orthoformate to afford chromatographically separable trienes **5a,b** (*E*/*Z* = 12/1, 81% yield).

The crucial test of the aforenoted cycloaddition produced mixed results initially in that thermolysis (162–165 °C 44 h) of triene **5a** gave not only the desired *endo*-carbomethoxy cycloadducts **13**[12] (68% yield) but also significant amounts of the corresponding *exo*-carbomethoxy adduct **14**[13] (13%) and unreacted starting material **5a**

Scheme I



Scheme II[a]



[a] (a) $(Me_3Si)_2NLi$, DME, −20 °C; TBDMSCl (100%); (b) $NiBr_2$, *n*-BuLi, THF, −78 °C; (c) LDA, THF, −78 °C to room temperature (81% yield of **9**); (d) SiO_2, CH_2Cl_2, $(CO_2H)_2$, room temperature (95%); (e) Ph_3PCHCO_2Me, $PhCH_3$, reflux (80%); (f) $HC(OMe)_3$, MeOH, *p*-TsOH, room temperature (81%); (g) $EtAlCl_2$, $PhCH_3$, 1 h, room temperature (88%); (h) NaOH, MeOH; (i) NCS, Pb $(OAc)_4$ (5:1, DMF:AcOH); (j) $AgNO_3$, DMF, 75 °C (45% of **17** from **13a,b**); (k) $(CH_2CH)_2CuLi$, −78 °C (76%); (l) $NaBH_4$; *N*,*N*′-thiocarbonyldiimidazole; *n*-Bu_3SnH, $PhCH_3$ (66%); (m) O_3, $MeOH/CH_2Cl_2$, −78 °C; $NaBH_4$ (85%); TBDMSCl (96%); (n) DIBAL, hexane (95%); (o) *o*-$NO_2C_6H_4SeCN$, $P(n\text{-}Bu)_3$, THF (93%); H_2O_2 (83%); (p) SeO_2, *t*-BuO_2H; Jones reagent (39%); (q) ref 4a.

(4) For total syntheses, see: (a) Danishefsky, S.; Vaughan, K.; Gadwood, R. C.; Tsuzuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 4262. Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981**, *103*, 4136. (b) Bornock, W. K.; Bagwat, S. S.; Ponton, J.; Helquist, P. *J. Am. Chem. Soc.* **1981**, *103*, 4647. (c) Burke, S. D.; Murtiashaw, C. W.; Saunders, J. O.; Dike, M. S. *J. Am. Chem. Soc.* **1982**, *104*, 872. Burke, S. D.; Murtiashaw, C. W.; Oplinger, J. A. *Tetrahedron Lett.* **1983**, *24*, 2949. Burke, S. D.; Murtiashaw, C. W.; Saunders, J. O.; Oplinger, J. A.; Dike, M. S. *J. Am. Chem. Soc.* **1984**, *106*, 4558. (d) Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 5808. (e) Takeda, K.; Shimono, Y.; Yoshii, Y. *J. Am. Chem. Soc.* **1983**, *105*, 563. (f) Schlessinger, R. H.; Wood, J. L.; Poss, A. J.; Nugent, R. A.; Parsons, W. H. *J. Org. Chem.* **1983**, *48*, 1146. (g) Dewanckele, J. M.; Zutterman, F.; Vandewalle, M. *Tetrahedron Lett.* **1983**, *24*, 3235. (h) Smith, A. B.; Konopelski, J. P. *J. Org. Chem.* **1984**, *49*, 4094. (i) Kon, K.; Ito, K.; Isoe, S. *Tetrahedron Lett.* **1984**, *25*, 3739. For approaches to the synthesis of quadrone, see: (j) Monti, S. A.; Dean, T. R. *J. Org. Chem.* **1982**, *47*, 2679. (k) Paquette, L. A.; Annis, G. D.; Schostarez, H. *J. Am. Chem. Soc.* **1982**, *104*, 6646. (l) Cooper, K.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1984**, *4*, 799. For syntheses of quadrone analogues, see: (m) Smith, A. B., III; Wexler, B. A.; Slade, J. *Tetrahedron Lett.*, **1982**, *23*, 1631. (n) Kakiuchi, K.; Nakao, T.; Takeda, M.; Tobe, Y.; Odaira, Y. *Tetrahedron Lett.* **1984**, *25*, 557.

(5) Wender, P. A.; Eissenstat, M. A.; Filosa, M. P. *J. Am. Chem. Soc.* **1979**, *101*, 2196. Wender, P. A.; Filosa, M. P. *J. Org. Chem.* **1976**, *41*, 3490.

(6) For related intramolecular cycloadditions, see: (a) Krantz, A.; Lin, C. Y. *J. Am. Chem. Soc.* **1973**, *95*, 5662. (b) Buchi, G.; Hauser, A.; Limacher, J. *J. Org. Chem.* **1977**, *42*, 3323.

(7) By analogy with enolonium (α-ketocarbonium) ion equivalents, the vinylogous grouping, $+CH_2CHCHCOR$, would be appropriately described in its formal function as dienolonium ion.

(8) Millard, A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 4833.

(9) (a) Compound **6** was prepared in 78% distilled yield by NBS bromination of 6,6-dimethylcyclohexenone (Marvell, E.; Magoon, E. *J. Am. Chem. Soc.* **1955**, *77*, 2542). (b) Compound **8** was prepared by reaction of the enolate of *tert*-butyl acetate with 3-bromo-1,1-dimethoxypropane.

(10) Satisfactory 300-MHz NMR, IR, and MS data and either elemental or exact mass analyses were obtained for all new compounds.

(11) Compounds **10**, **11a**, and **11b** were formed in a ratio which varied from run to run according to the time allowed for hydrolysis.

(12) The endo orientation of the C-11 ester group in **13a,b** was determined by the finding that the C-11 acid derivatives **15a,b** readily produced ($NaHCO_3$, KI_3, THF/H_2O) iodo lactones through addition to the C-9,C-8 double bond and that these lactones could be reconverted to **13a,b** by treatment with Zn/HOAc followed by diazomethane esterification. It follows that **13a,b** are epimeric at C-5 with the β ester favored by a factor of 3 to 1 in the noncatalyzed cycloaddition. Since our plan called for the eventual conversion of C-5 to an alkene center at the stage of compound **22**, both isomers were carried forward.

(9%). *Gratifyingly, these problems of efficiency and stereocontrol were readily rectified through the use of ethylaluminum dichloride catalyst*[14] *which resulted in complete conversion of triene* ***5a*** *in 1 h at room temperature and provided exclusively the endo adducts* ***13***[15] *in 88% yield.*

The next phase of our synthetic plan required the translation of the carbomethoxy group in adducts **13a,b** into a leaving group as required for the rearrangement (i.e., expansion) step. Accordingly, adducts **13a,b** (9:1, respectively) were selectively saponified and the resultant acids **15a,b** were halodecarboxylated.[16] Treatment of the crude chloride products **16a,b** with excess $AgNO_3$ in DMF at 75 °C gave **17** and **18** in 45% and 7% overall yields, respectively, from adducts **13a,b**. Importantly, products arising from migration of the synperiplanar aligned C-9 group (**16a,b**) or elimination were not observed.

For the completion of our synthesis, introduction of the only remaining skeletal carbon, C-7, and adjustment of functionality were required. Enone **17** proved well-suited for the former task since its reaction with divinylcopper lithium[17] produced exclusively the desired α-substituted product **19** (76% yield), as expected for conjugate addition to the sterically less-encumbered enone face through a chair-like cyclohexenyl transition state.[18] The ketone group, having served well in its prior activating and directing role, was then converted to a methylene unit in **20** (66% overall yield) by the Barton sequence.[19] Ozonolysis of **20** followed by a reductive workup and protection of the primary alcohol as its *tert*-butyldimethylsilyl ether produced **21** in 82% overall yield. The C-5 ester of **21** was then converted[20] to the exocyclic olefin in **22**. Subsequent regiospecific introduction of the C-4 oxygen through allyic oxidation with $SeO_2/t\text{-}BuO_2H$[21] followed by oxidation of the product with Jones reagent gave terrecyclic acid A (**2a**) which was identical (300-MHz NMR, capillary GC, MS, TLC) with an authentic sample of synthetic material.[22] The transformation of **2a** to quadrone (**1**) has been previously reported.[4a] Further studies are in progress.

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Registry No. **2a**, 98587-42-9; **5a**, 98587-31-6; **5b**, 98587-32-7; **6**, 98587-23-6; **7**, 98587-24-7; **8**, 98587-25-8; **9**, 98587-26-9; **10**, 98587-27-0; **11a**, 98587-28-1; **12a**, 98587-29-2; **12b**, 98587-30-5; **13a**, 98587-33-8; **13b**, 98673-84-8; **14a**, 98673-35-9; **14b**, 98673-38-2; **15a**, 98587-34-9; **15b**, 98673-36-0; **16a**, 98587-35-0; **16b**, 98673-37-1; **17**, 98611-59-7; **18**, 98587-36-1; **19**, 98587-37-2; **20**, 98587-38-3; **21**, 98611-60-0; **21** (alcohol), 98587-39-4; **22**, 98587-40-7; **22** (4-oxo), 98587-41-8; Ph_3PCHCO_2Me, 2605-67-6; Quadrone, 66550-08-1; 6,6-dimethylcyclohexenone, 6553-64-6; *tert*-butyl acetate, 540-88-5; 3-bromo-1,1-dimethoxypropane, 36255-44-4.

(13) Only one C-5 epimer of the exo adduct was produced. An unequivocal assignment of its C-5 stereochemistry could not be made, although models suggest that the β ester is sterically preferred.

(14) For other recent applications of Lewis acid catalysis to the intramolecular Diels–Alder reaction, see: (a) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269 and the references cited therein. (b) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, *47*, 4825. (c) Sakan, K.; Craven, B. M. *J. Am. Chem. Soc.* **1983**, *105*, 3732.

(15) The β to α C-5 ester ratio consistently fell in the range 6–8:1 and represented, at least, a twofold increase in selectivity over the uncatalyzed reaction.

(16) Becker, K. B.; Geisel, M.; Grob, C. A.; Kuhnen, F. *Synthesis* **1973**, 493.

(17) Vinyllithium in ether solution was produced according to the procedure of Seyferth and Weiner (Seyferth, D.; Weiner, M. A. *J. Am. Chem. Soc.* **1961**, *83*, 3583) and converted to the cuprate using dimethyl sulfide as an additive according the procedure of Clark and Heathcock (Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 1396).

(18) For a related example of steric and stereoelectronic control in vinyl cuprate additions, see: Harding, K. E.; Clement, B. A.; Moreno, L.; Peter-Katalinic, J. *J. Org. Chem.* **1981**, *46*, 940.

(19) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) Rasmussen, J. R.; Slinger, C. J.; Kordish, R. J.; Newman-Evans, D. D. *J. Org. Chem.* **1981**, *46*, 4843.

(20) (a) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *1485*. (b) Majetich, G.; Grieco, P. A.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 2327.

(21) Warpehowski, M. A.; Chabaud, B.; Sharpless, K. B. *J. Org.* Chem. **1982**, *47*, 2897.

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