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Theory-Guided Discovery of Unique Chemical Transformations of Cyclopropenes

Robin A. Weatherhead-Kloster and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

corey@chemistry.harvard.edu

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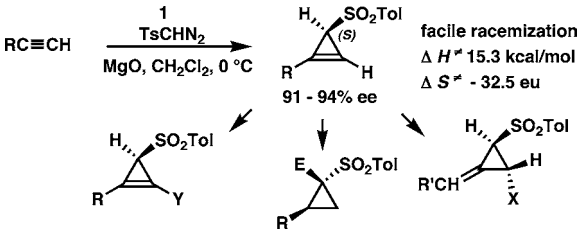
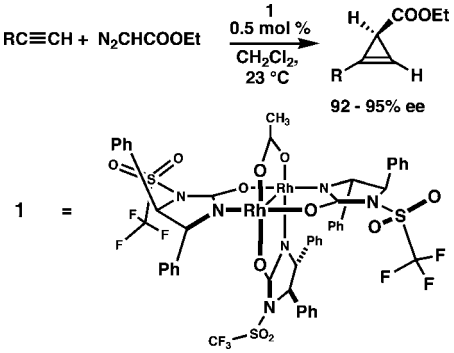
ABSTRACT



Chiral 2-cyclopropenyl-4-tolyl sulfones, available by the [2 + 1]-cycloaddition of tosyldiazomethane to acetylenes under catalysis by the Rh(II) complex 1, provide a number of unusual transformations and useful chiral products. This chemistry is dominated by the unusual strain and reactivity of the cyclopropene ring system.

We recently found that a mixed Rh_2(II) acetate complex containing three bridging *N*-triflyl (diphenylimidazolidinone) (DPTI) groups, $Rh_2(OAc)(DPTI)_3$ (**1**), is an extremely effective catalyst for the enantioselective generation of chiral cyclopropenes from ethyl diazoacetate and various terminal acetylenes, as illustrated in Scheme 1.[1,2] Syntheses of such chiral cyclopropenes have also been reported by other groups using different Rh_2(II) complexes as catalysts.[3] These chiral cyclopropenes are of great interest since they serve as versatile intermediates that can be elaborated to a wide variety of more complex chiral cyclopropanes, especially those having stereocenters at all three ring vertices.[1] This work was motivated not only by these considerations but also by the major advances in recent years in our understanding of strain effects in unsaturated cyclopropanes and of variations in individual bond strength.[4] The guidance from these new insights and the ready availability of a wide range of chiral cyclopropenes provide an excellent opportunity to discover new and unique aspects of the chemistry of cyclopropenes that can then further enrich mainstream synthetic methodology.[5]

Scheme 1. Catalyzed Enantioselective Addition of Ethyl Diazoacetate to Terminal Acetylenes



Studies with Cyclopropenyl 4-Tolyl Sulfones. We took advantage of the known 4-toluenesulfonyl (tosyl, Ts) diazomethane[6] and the highly selective catalyst **1** to synthesize

(1) Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8916−8918.

(2) See also: Lou, Y.; Remarchuk, T. P.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 14223−14230.

(3) (a) Doyle, M.; Protopopova, M.; Müller, P.; Ene, D.; Shapiro, E. *J. Am. Chem. Soc.* **1994**, *116*, 8492−8498. (b) Protopopova, M.; Doyle, M.; Müller, P.; Ene, D. *J. Am. Chem. Soc.* **1992**, *114*, 2755−2757. (c) Müller, P.; Imogaï, H. *Tetrahedron: Asymmetry* **1998**, *9*, 4419−4428.

(4) For an outstanding exposition of strain energies in unsaturated cyclopropanes and their origins, see: Bach, R. D.; Dmitrenko, O. *J. Am. Chem. Soc.* **2004**, *126*, 4444−4452.

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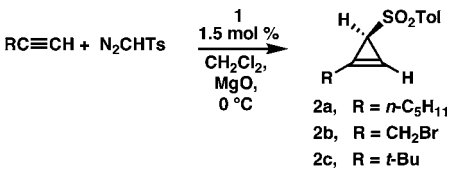
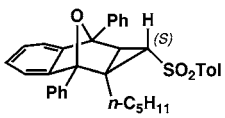
tosylcyclopropenes **2a**−**2c** from 1-heptyne, propargyl bromide, and *tert*-butylacetylene, respectively.[7] Most of our



research was carried out with **2a** and **2b** because these cyclopropenes were obtained in excellent enantiomeric purity (91% ee for **2a** and 94% ee for **2b**, as compared to 78% ee for **2c**). The molecular structures of **2a**, **2b**, and **2c** were proven to be as shown by single-crystal X-ray diffraction analysis (all were dextrorotatory).[7] In addition, (+)-**2a** was converted to the Diels−Alder adduct **3**, the structure and absolute configuration of which were demonstrated by X-ray crystallography.[7] The absolute configurations of **2a**−**2c** are the same as predicted by the mechanistic model previously proposed for catalyst **1**.[1] To the best of our knowledge these chiral 2-cyclopropenyl sulfones are the first such chiral compounds to have been synthesized. One interesting feature emerged from the X-ray crystal structures of **2a**, **2b**, and **2c**. In each case one of the oxygens attached to sulfur (a) is located above the cyclopropenyl ring and equidistant from the two olefinic carbons as shown in **4**. This geometry may



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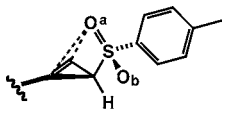
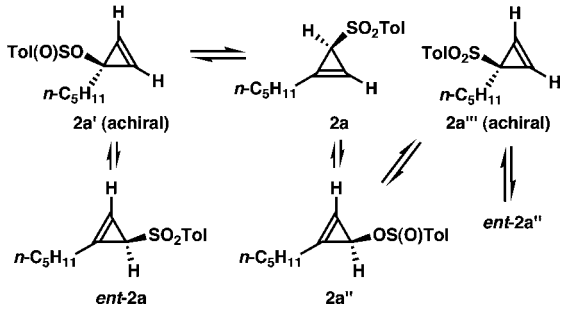


4

result from the simultaneous operation of two not unreasonable conditions: (1) staggering of substituents about the cyclopropenyl C−S bond and (2) location of oxygen above the three-membered ring in preference to tolyl because the larger bulk of the latter would lead to steric repulsion. The same conformational preference is also evident in (saturated) cyclopropyl tolyl sulfones.

A surprising observation was made initially with 2-*n*-amyl-2-cyclopropenyl 4-tolyl sulfone **2a**. When this sulfone of 91% ee was chromatographed on silica gel or stirred with a suspension of silica gel in benzene for 30 min at 30 °C, racemic sulfone **2a** was recovered in high yield. This unexpected finding prompted us to examine the kinetics of the racemization process in solution, where it was also found to be facile. The kinetics of thermal racemization of **2a** in benzene solution (without silica gel) were measured by HPLC analysis using a Chiralcel OD column (Chiral Technologies, Inc.) with *i*-PrOH−hexane as elution solvent at 23 °C and were found to be cleanly first order. From measurements of the first-order rate constant over the temperature range 30−70 °C and an Arrhenius plot of ln k_1 vs $1/T$ (strictly linear) the reaction activation parameters were found to be: E_a = 15.9 kcal/mol; $\Delta H^{\ddagger}$ = 15.3 kcal/mol; and $\Delta S^{\ddagger} = -32.5$ eu.[7] The Eyring plot of ln(k/T) vs $1/T$ was also linear and yielded $\Delta H^{\ddagger} = 14.9$ kcal/mol. The first-order rate constants were very close at 70 °C for the solvents benzene (3.6×10^{-5} s^{-1}), cyclohexane (2.6×10^{-5} s^{-1}), and acetonitrile (1.8×10^{-5} s^{-1}), indicating that a polar dissociation mechanism (e.g., to a cyclopropenium toluenesulfinate ion pair)[8] is improbable, especially since the rates were somewhat slower in CH_3CN than in C_6H_6 or cyclohexane. We believe that the most reasonable explanation for the facile thermal racemization reaction is a reversible 2,3-sulfone-sulfinate allylic rearrangement, a process that is very well-known in the allylic sulfinate to sulfone direction.[9,10] The pathway for racemization is outlined in Scheme 2. The

Scheme 2. Pathway for Racemization of **2a** via [2,3]-Sigmatropic Rearrangement



rates of such [2,3]-sigmatropic rearrangements are known not to be especially sensitive to solvent polarity. One possible explanation for the unique facility of the racemization of **2a** as compared to nonstrained allylic systems may be derived from the known weakening of allylic bonds in the cyclopropene system.[4] Thus, the allylic C−H bonds of cyclopropene are much weaker (100.4 kcal/mol) than the C−H bonds of cyclopropane (110.3 kcal/mol) (both BDEs).[4] If the bond weakening in the sulfone **2a** is greater than that in the sulfinate esters **2a′** and **2a″**, an acceleration of racemization would result.[11] Alternatively, there may be stabilization of the transition state by virtue of some three-center π-electron delocalization around the three-membered ring. In this possibility, there might be a slight degree of cyclopropenium cation character in the transition state.[8]

The observed silica-surface catalysis of the racemization could easily be explained by such slight charge separation

(5) For recent reviews of transformations on cyclopropenes, see: (a) Baird, M. S. *Cyclopropanes: Synthesis: From Cyclopropenes*. In Houben-Weyl; Thieme: Stuttgart, 1997; pp 114−255. (b) Nakamura, M.; Isobe, H.; Nakamura, E. *Chem. Rev.* **2003**, *103*, 1295−1326.

(6) (a) Van Leusen, A. M.; Strating, J. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 151−164. (b) Van Leusen, A. M.; Strating, J. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 140−151. (c) Van Leusen, A. M.; Strating, J. *Org. Synth.* **1977**, *VI*, 981−988.

(7) For full details, see Supporting Information.

(8) (a) Norden, T. D.; Staley, S. W.; Taylor, W. H.; Harmony, M. D. *J. Am. Chem. Soc.* **1986**, *108*, 7912−7918. (b) Breslow, R.; Groves, J. T.; Ryan, G. *J. Am. Chem. Soc.* **1967**, *89*, 5048−5048. (c) Breslow, R. *J. Am. Chem. Soc.* **1957**, *79*, 5318−5318.

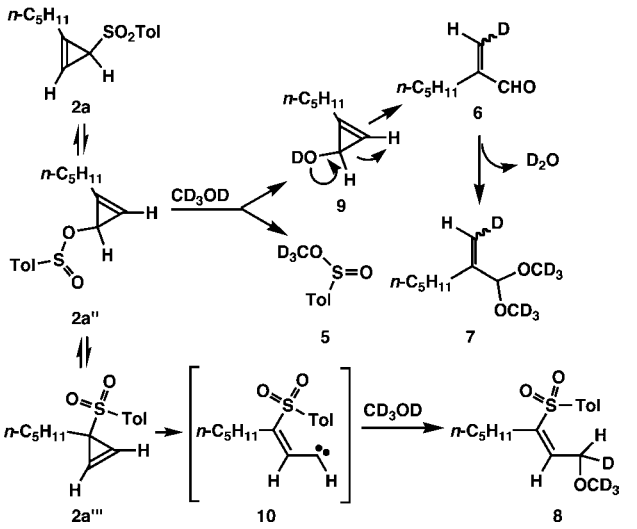
(9) For a review, see: Hoffmann, R. W. *Angw. Chem., Int. Ed. Engl.* **1979**, *18*, 563−640.

(10) (a) Braverman, S.; Mechoulam, H. *Tetrahedron* **1974**, *30*, 3883−3890. (b) Cope, A. C.; Morrison, D. E.; Field, L. *J. Am. Chem. Soc.* **1950**, *72*, 59−67.

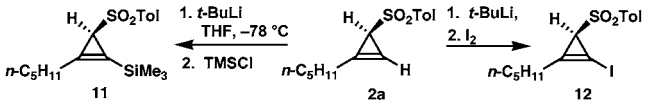
in the transition state. Since silica gel behaves effectively like a weak protic acid, hydrogen bonding to one oxygen of the migrating $TolSO_2$ group in the transition state would be an obvious source of acceleration of racemization by the pathway outlined in Scheme 2. Given the sizable magnitude of the acceleration of racemization by silica gel, it is even possible that this process occurs at the ion-pair extreme of the mechanistic spectrum. Deprotonation of **2a** α to the $TolSO_2$ group is clearly not a reasonable mechanistic pathway for the silica gel promoted racemization because silica gel is obviously not basic enough to form a high energy antiaromatic (4π-type) carbanion intermediate.

Strong confirmatory evidence for the pathway of (solution-phase) racemization of **2a** via a [2,3]-sigmatropic rearrangement to the achiral cyclopropenyl sulfinate **2a′** and achiral sulfone **2a‴** (Scheme 2) was obtained by a simple trapping experiment. When **2a** was heated at 55 °C in dry CD_3OD solution under an inert atmosphere the products **5**, **6**, **7**, and **8** shown in Scheme 3 were detected by ^1H NMR spectroscopy.[7] Methanolysis of **2a″** or *ent*-**2a″** produces $^2H_3$ methyl toluenesulfinate (**5**), which was also isolated, and cyclopropenol **9**, which was too unstable to isolate but which gave rise to the *β*-deuterated α,*β*-enal **6** and the corresponding $^2H_3$-methyl acetal **7**. The instability of 2-cyclopropenols, which has previously been noted,[12] is a consequence of the high strain energy (ca. 55 kcal/mol) and the availability of a carbonyl-forming elimination process which relieves that strain. Ring strain also accounts for the ring cleavage process that converts sulfone **2a‴** via intermediate **10** to the deuterated methoxy sulfone **8**.

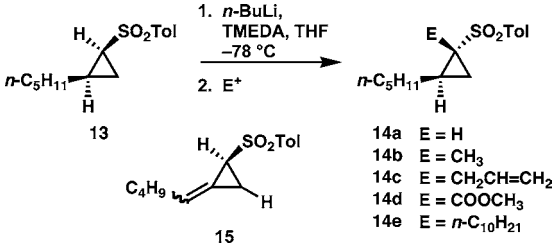
Scheme 3



The action of the strong base *t*-BuLi on the cyclopropenyl sulfone **2a** (91% ee) in THF at −78 °C results, as expected, not in deprotonation α to the $TolSO_2$ group, but at the other ring position as shown by subsequent reaction with Me_3SiCl to form the TMS derivative **11** (91% ee, 77% yield). Similarly, deprotonation of **2a** (91% ee) by *t*-BuLi in THF at −78 °C followed by treatment with iodine gave the chiral iodo sulfone **12** (91% ee, 64% yield). The enhanced acidity of the olefinic C−H of **2a** is in part a consequence of the considerably increased s-character (approaching an acetylenic C−H) of the olefinic carbon.



Hydrogenation of sulfone **2a** gave stereoselectively the corresponding *cis*-cyclopropyl sulfone **13**, which was readily deprotonated by *n*-BuLi-TMEDA in THF at −78 °C to give after treatment with NH_4Cl, methyl iodide, allyl bromide, methyl chloroformate, or *n*-decyl iodide the sulfones **14a**−**14e**, again stereoselectively. The results indicate that the conjugate base of **13** undergoes an inversion to the diastereomer in which the n-C_5H_{11} and $TolSO_2$ groups are *trans* to one another and that this more stable anion undergoes alkylation (or electrophilic attack) with stereochemical retention.



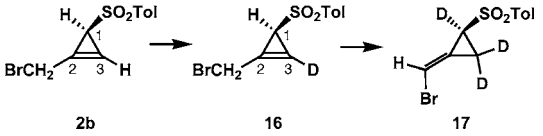
Yet another facet of the unusual chemistry of sulfone **2a** was revealed by its behavior when treated with tetra-*n*-butylammonium cyanide in THF at 23 °C. Under these conditions, it was readily converted to a mixture of *E* and *Z* forms of the exocyclic olefinic isomer **15**. Although this facile isomerization appears surprising at first glance, since cyanide ion is generally not considered to be sufficiently basic to effect allylic deprotonation of an olefin, it seems not unreasonable when it is recalled that the difference in strain energy between 1-methylcyclopropene and methylene cyclopropane is ca. 15 kcal/mol.[4]

Relief of ring strain as a driving force for reactions of cyclopropenes via carbanion intermediates adds to the richness and uniqueness of cyclopropene chemistry. With this in mind we have investigated the chemistry of 2-bromomethyl-2-cyclopropenyl 4-tolyl sulfone (**2b**). When this compound was treated with 1 equiv of Na_2CO_3 in CD_3OD at 23 °C in an NMR tube and analyzed by ^1H NMR spectroscopy, a very rapid exchange of the vinylic proton at

(11) It is highly relevant that (*S*)-(1,2,3-triphenylcyclopropenyl)-*O*-ethyldithiocarbonate undergoes [2,3]-sigmatropic rearrangement (degenerate) with $\Delta H^{\ddagger} = 14.8$ kcal/mol and $\Delta S^{\ddagger} = -10$ eu, $k_{298} = 0.43$ s^{-1}. (a) Mikhailov, I. E.; Dushenko, G. A.; Dorogan, I. V.; Minyaev, R. M.; Negrebetskii, V. V.; Zschunke, A.; Minkin, V. I. *Mendeleev Commun.* **1994**, 9−11. (b) Minkin, V. I.; Mikhailov, I. E.; Dushenko, G. A.; Kompan, O. E.; Zschunke, A. *Russ. Chem. Bull.* **1998**, *47*, 884−894.

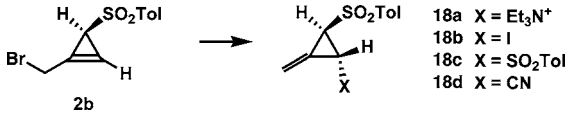
(12) For C−C cleavage as a consequence of the high strain energy of 2-cyclopropenols, see: Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1984**, *106*, 2363−2367.

C-3 to form **16** was observed (within 3 min). After 24 h, **16** was completely converted to the trideuterated exocyclic olefin **17** (reaction incomplete after 12 h). When chiral **2b**



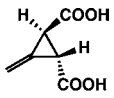
2b 16 17

of 91% ee was treated with 1 equiv of carbonate in CH_3OH under the same conditions, the nondeuterated isomer **17** of 89% ee was obtained. This result indicates that the kinetically controlled H/D exchange **16** → **17** occurs with retention of configuration at the carbon α to the tosyl group. Again, the driving force of endocyclic → exocyclic olefinic isomerization dominates cyclopropene chemistry. This effect also shows up in nucleophilic displacements of **2b**, which is converted to **18a**−**18d** upon treatment with the nucleophiles Et_3N/THF, NaI/acetone, $TolSO_2^-Na^+$/15-C-5/CH_3CN or $Bu_4N^+CN^-$/THF. Nucleophilic displacement at the secondary carbon in preference to the primary carbon is unusual but readily understandable because of the larger strain energy of a cyclopropene relative to a methylene cyclopropane.



2b

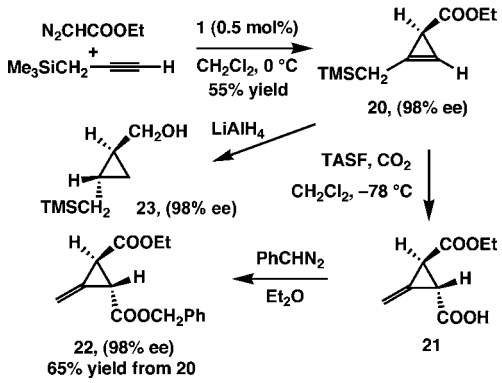
An Application: A Simple, Highly Enantioselective Route to the Feist Ester Series. The intriguing C_2-symmetric acid **19** and its esters, first prepared in racemic form by Feist in 1893, has been the subject of much research.[13] The (*R*,*R*)-(+)-enantiomer has been obtained either by



19

resolution of the quinine salt[14a] or by HPLC separation of the dimethyl ester using a chiral column.[14b] We have applied the fundamental knowledge described above to the development of a convenient enantioselective synthesis of differentiated diesters of **19** by the pathway outlined in Scheme 4.[15] We believe that this is the first enantioselective synthesis in the Feist ester/acid series.[15] Reaction of propargyltrimethylsilane with ethyl diazoacetate in the presence of 0.5% of the chiral Rh catalyst **1** afforded the cyclopropene carboxylate **20** in 98% ee.[7] Desilylation of **20** with tris(dimethylamino)-sulfonium difluorotrimethyl silicate (TASF) in dry CH_2Cl_2 under a CO_2 atmosphere at −78 °C yielded the monoethyl ester of Feist's acid (*S*,*S*-enantiomer) (**21**),[16] which upon esterification with phenyldiazomethane gave the (−)-(*S*,*S*)-enantiomer of Feist's acid ethyl, benzyl ester (**22** of 98% ee (65% overall from **20**)). Reduction of **20** by $LiAlH_4$ in ether produced the *trans*-(*S*,*S*)-(+)-cyclopropyl carbinol **23**.

Scheme 4



The ready availability of chiral 2-cyclopropenyl tosyl sulfones has allowed the exploration of the chemical behavior of this class of compounds and the discovery of several unusual transformations. These include (1) facile racemization at room temperature in benzene solution in the presence of silica gel or at temperatures in the range 50−70 °C in its absence; (2) identification of a reversible [2,3]-sigmatropic sulfone-sufinate ester rearrangement pathway as the likely reason for this racemization that is facilitated by the high strain energy of cyclopropenes and weakness of the allylic bonds; (3) stereoselective base-promoted alkylation of *cis*-2-substituted cyclopropyl sulfones with inversion of configuration due to the pyramidal character of the intermediate anion and a preference for *trans* geometry; and (4) an unusual preference for nucleophilic allylic displacement at the secondary versus primary carbon, another consequence of the thermodynamic driving force associated with greater strain for endocyclic cyclopropenes as compared to isomeric exocyclic structures.

Supporting Information Available: Experimental procedures and characterization data for all new products and X-ray diffraction data (CIF) for **2a**, **2b**, **2c**, **3**, **17**, **18c**, and **18d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Feist, F. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 747−764. (b) Feist, J. *Liebigs Ann. Chem.* **1924**, *436*, 125−153. (c) Ettlinger, M. G. *J. Am. Chem. Soc.* **1952**, *74*, 5805−5806. (d) Lloyd, D.; Downie, T. C.; Speakman, J. C. *Chem. Ind. (London)* **1954**, 222−223. (e) Lloyd, D.; Downie, T. C.; Speakman, J. C. *Chem. Ind. (London)* **1954**, 492−492. (f) Ettlinger, M. G.; Kennedy, F. *Chem. Ind. (London)* **1956**, 166−167. (g) Petersen, D. R. *Chem. Ind. (London*) **1956**, 904−905. (h) Kende, A. S. *Chem. Ind. (London*) **1956**, 437−437. (i) Bottini, A. T.; Roberts, J. D. *J. Org. Chem.* **1956**, 1169−1170. (j) Lloyd, D. In *Topics in Carbocyclic Chemistry*; Lloyd, D., Ed.; Plenum: New York, 1969; Vol. 1, pp 249−268. (k) Ramasubbu, N.; Venkatesan, K. *Acta Crystallogr.* **1982**, *B38*, 976−978.

(14) (a) Doering, W. v. E.; Roth, H. D. *Tetrahedron* **1970**, *26*, 2825−2835. (b) Baldwin, J. E.; Sakkab, D. H. *J. Org. Chem.* **1995**, *60*, 2635−2637.

(15) In general, methodology for the highly enantioselective synthesis of methylenecyclopropanes is poorly developed. See: (a) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1993**, *58*, 5037−5039. (b) Baldwin, J.; Adlington, R. M.; Bebbington, D.; Russell, A. T. *J. Chem. Soc., Chem. Commun*. **1992**, 1249−1251. (c) Achmatowicz, B.; Kabat, M.; Krajewski, J.; Wicha, J. *Tetrahedron* **1992**, *48*, 10201−10210. (d) Nemoto, T.; Ojika, M.; Sakagami, Y. *Tetrahedron Lett.* **1997**, *38*, 5667−5670.

(16) Approximately 9% of the *cis*-isomer of Feist's mono ester **21** was produced in the carboxylation of **20**. This *cis* impurity was removed by silica gel chromatography after conversion to the diester **22**.