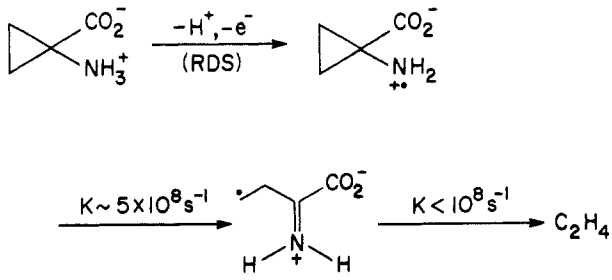

Figure 1.

Secondary isotope effects for the conversion of ACC and ACC-d_4[7] to C_2H_4/C_2D_4 by both mung bean hypocotyl segments and the electrochemical model[6] for ethylene biosynthesis were measured by the competition method. A 1:1[8] mixture of tetraprotio- and tetradeuterio-ACC was fed to mung bean.[9] After 72 h of feeding (<1% conversion), the head space was analyzed by GC/MS.[10] The observed ratio of isotopomers reveals $k_H/k_D = 0.990 \pm 0.014$.[11] Similarly, when the same mixture of tetraprotio- and tetradeuterio-ACC used above was converted to its tetrabutylammonium salt and oxidized at +0.8 V vs. SCE (<3% conversion) in CH_3CN, the observed isotope ratio reveals $k_H/k_D = 1.005 \pm 0.015$.

$$\text{ACC/ACC-}d_4 \xrightarrow{\text{mung bean}} \frac{C_2H_4}{C_2D_4} \Longleftrightarrow \frac{m/z = 27}{m/z = 30}$$

$$k_H/k_D = 0.990 \pm 0.014$$

The lack of an isotope effect for either oxidative conversion of ACC to ethylene when a significant effect might be expected[12] suggests that no step which would be isotope-sensitive contributes to the rate limitation. This is certainly true for the electrochemical oxidation, but because of the nature of competition experiments, only a V/K isotope effect is obtained from the in vivo experiment.[13] Such isotope effects do not reflect rate limitation, only the forward commitment for an isotope-sensitive step, which here must be great. This satisfies one's chemical intuition that once the cyclopropane ring has opened, conversion to products is highly favored over reclosure. This conclusion was also foreshadowed by data showing that *cis*-ACC-d_2 recovered from oxidations retains its stereochemistry.[14]

The inference that the initial one-electron oxidation of aminocyclopropanecarboxylic acid is rate limiting has precedent. Electrochemical and chemical oxidation of amines is known to have this characteristic.[15] In studying the mechanism-based inactivation of cytochrome P-450 by heteroatom-substituted cyclopropanes, Macdonald and Guengerich have found a linear correlation between the one-electron oxidation potential for the substrate and its log k_{inact}.[16] This implies that the rate-limiting step for inactivation events is the initial one-electron oxidation. The mechanistic similarities between inactivation of P-450, by cyclopropylamines, for example, and ethylene biosynthesis are striking.

The current data and recent studies on cyclopropyl-ACC[5] allow the proposal of a partial kinetic mechanism for ethylene biosynthesis (Figure 1). For the electrochemical model (and likely for the biosynthetic reaction, though no proof exists for this) the production of the amine radical cation is rate-limiting. Ring opening is assumed to occur at a rate similar to Ingold's measurements on cyclopropylaminyl radicals.[17] This ring-opened intermediate may not give nonradical products (i.e., ethylene) at a rate faster than that shown; otherwise, vinylcyclopropane would be expected as a product from cyclopropyl-ACC, a result contrary to fact in the biosynthetic and model[18] reactions. Other free-radical clocks may be used to more firmly define the lifetime of this intermediate.

Acknowledgment. Financial support from the U.S.-Israel Binational Agricultural Research & Development Fund (Grant I-643-83) is appreciated. M.C.P. is a Presidential Young Investigator (NSF CHE 84-51324).

(7) Prepared by applying a published procedure[6] to tetradeuteriodibromoethane.

(8) Determined by mass spectrometry of the methyl esters.

(9) Vegetative tissue such as mung bean does not have the capability to biosynthesize ACC in the absence of other phytohormones. Thus the only substrate present is what is provided. It was confirmed by adding compounds known to be inhibitors of ACC biosynthesis (e.g., aminooxyacetic acid) that no endogenous ethylene modified the isotope ratio.

(10) For a general description of the MS techniques used to analyze isotopically labeled gases, see: Pirrung, M. C. *Bioorg. Chem.* **1985**, *13*, 219. In this case, authentic C_2H_4/C_2D_4 mixtures were diluted to the same concentration of ethylene as in the sample and used for calibration. Isotope ratios were measured at the M - 1 ion of ethylene and M - 2 ion of perdeuterioethylene, obviating interference from N_2 and O_2.

(11) All errors given for these isotope effects refer to one standard deviation.

(12) The secondary isotope effect predicted (Streitweiser, A.; Jagow, R. H.; Fahey, R. C.; Suzuki, S. *J. Am. Chem. Soc.* **1968**, *80*, 2326) from IR data, using the stepwise mechanism previously proposed,[6] depends on which carbon–carbon bond cleavage is limiting. Radical additions to ethylene have $k_D/k_H \sim 1.1$ (Stefani, A. P.; Chuang, L. Y.; Todd, H. E. *J. Am. Chem. Soc.* **1970**, *92*, 4168). Olivella et al. (Olivella, S.; Canadell, E.; Poblet, J. M. *J. Org. Chem.* **1983**, *48*, 4696) have predicted isotope effects of approximately this magnitude. While ring opening is likely to have a very small isotope effect due to the countervailing influence of the hybridization changes at the two methylenes, this step is unlikely to be limiting. It is also important to note that good evidence exists that transport is not limiting in the processing of ACC analogues: Venis, M. A. *Planta* **1984**, *162*, 85.

(13) Northup, D. B. In *Isotope Effects on Enzyme-Catalyzed Reactions*; Cleland, W., O'Leary, M. H., Northrup, D. B., Eds.; University Park Press: Baltimore, 1977; p 122.

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(15) Hull, L. A.; Giordano, W.; Rosenblatt, D.; Davis, G.; Mann, C.; Milliken, S. *J. Phys. Chem.* **1969**, *73*, 2147.

(16) Guengerich, F. P.; Willard, R. J.; Shea, J. P.; Richards, L. E.; Macdonald, T. L. *J. Am. Chem. Soc.* **1984**, *106*, 6446.

(17) Griller, D.; Ingold, K. *Acc. Chem. Res.* **1980**, *13*, 317.

(18) McGeehan, G. M. Ph.D. Thesis, Stanford University, 1986.

Use of Chiral Single Crystals To Convert Achiral Reactants to Chiral Products in High Optical Yield: Application to the Di-π-Methane and Norrish Type II Photorearrangements

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A material that crystallizes in a chiral space group is characterized by the fact that the environment of the molecules is chiral. All optically pure compounds necessarily crystallize in chiral space groups, and a few examples are known of racemic mixtures that behave similarly, the most famous being that studied by Pasteur[1] of racemic sodium ammonium tartrate, which crystallizes below 28 °C as a mixture of enantiomeric crystals that can be differentiated by their morphology and separated by hand. In cases where the enantiomers are in equilibrium under the crystallization conditions, it is sometimes possible to convert the entire sample to crystals composed of a single enantiomer without the influence of an external asymmetric agent. An example of this genuine "spontaneous resolution" was provided by Pincock in his studies on binaphthyl.[2] Examples are also known of achiral molecules

(1) For an excellent discussion of Pasteur's work with sodium ammonium tartrate, see: Fieser, L. F.; Fieser, M. *Advanced Organic Chemistry*; Reinhold: New York, 1961; p 69.

(2) (a) Pincock, R. E.; Wilson, K. R. *J. Am. Chem. Soc.* **1971**, *93*, 1291–1292. (b) Pincock, R. E.; Perkins, R. R.; Ma, A. S.; Wilson, K. R. *Science (Washington, D.C.)* **1971**, *174*, 1018–1020. Other examples of spontaneous crystallization of one of two rapidly interconverting enantiomers from solutions are described by: (c) Havinga, E. *Biochim. Biophys. Acta* **1954**, *13*, 171–174. (d) Newman, A. C. D.; Powell, H. M. *J. Chem. Soc.* **1952**, 3747–3751.

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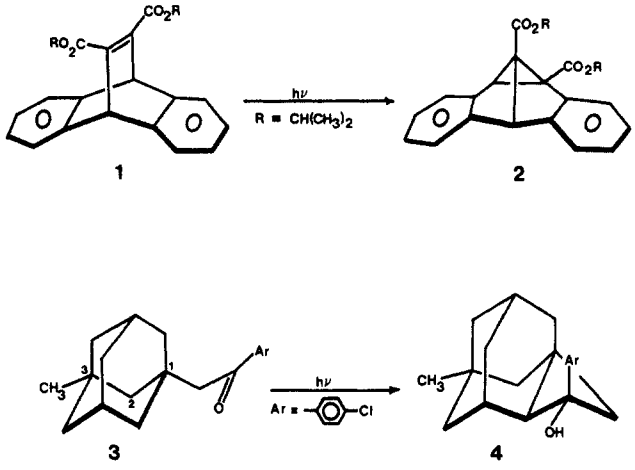
Scheme I



that crystallize in chiral space groups; in such a case, the molecule may (or may not) adopt a chiral conformation in the crystal lattice, but the molecular environment is chiral and may present an opportunity for the introduction of molecular chirality.

It has been recognized for some time that stereospecific solid-state chemical reactions of chiral crystals provide not only a plausible explanation for the prebiotic origin of optical activity but also an attractive general method of asymmetric synthesis.[3] Ideally, the solid-state reaction should transfer the crystal chirality to the product permanently in the form of new chemical bonds. These concepts have been realized experimentally and reported in a series of papers by the group at the Weizmann Institute.[3,4] Their studies have been concerned with the *bimolecular* reactions of chiral crystals in the solid state, primarily lattice-controlled [2 + 2] photocycloadditions. The enantiomeric yields achieved in these reactions varied from a few percent to (in one instance) quantitative. In the present paper, we report the first application of these principles to two very general classes of *unimolecular* photorearrangement, namely, the di-π-methane reaction[5] and the Norrish type II process.[6] In both instances, very high enantiomeric yields were obtained.

As shown by X-ray crystallography, crystals of diester **1**[7] (Scheme I) are dimorphic. Recrystallization from ethanol provides prisms, mp 135–136 °C, orthorhombic, space group *Pbca*, a = 9.738 (2) Å, b = 17.092 (3) Å, c = 25.080 (5) Å, Z = 8. The structure was solved by direct methods, R = 0.044 for 1302 reflections with $I > 3\sigma(I)$. Recrystallization from cyclohexane affords *Pbca* crystals plus a dimorph, mp 135–136 °C, orthorhombic, space group $P2_12_12_1$, a = 8.330 (1) Å, b = 11.689 (2) Å, c = 21.794 (3) Å, Z = 4, R = 0.058 for 1277 reflections with $I > 3\sigma(I)$. Both dimorphs crystallize in asymmetric conformations (the asymmetry resides in the ester groups), but only the $P2_12_12_1$ crystals are chiral; the *Pbca* crystals are racemic (enantiomeric conformations related by crystal symmetry).

In solution, diester **1** undergoes the di-π-methane photorearrangement to afford the dibenzosemibullvalene derivative **2**, which has four chiral centers (Scheme I). Ciganek[8] was the first to demonstrate this reaction for the corresponding dimethyl ester. An important experiment was to determine whether the transformation of **1** to **2** occurs in the solid state. It does, and the reaction appears to be general for diesters of general structure **1**. This set the stage for the key experiment. Large (20–85 mg) single crystals of both dimorphs of diester **1** were grown by slow evaporation and their identity was checked by infrared spectroscopy (the dimorphs have significantly different infrared spectra). In carrying out studies on the chiral polymorph, it is important to avoid inversion twinning or, at least, to be aware of the possibility of the occurrence of twinning.[9] Each dimorph was photolyzed by the output from a Molectron UV-22 nitrogen laser (337 nm, 330-mW average power); parallel irradiations were conducted in solution (0.1 M in benzene). At 337 nm, only the tail of the α,β-unsaturated diester n $\rightarrow \pi^*$ absorption (ϵ <10) is excited. The optical activity produced in each photolysis was determined by dissolving the sample in chloroform and measuring its rotation at the sodium D line. The specific rotation of photoproduct **2** was then calculated from the weight of the crystal, and the percent conversion as determined by capillary gas chromatography. The unreacted starting material contributes nothing to the rotation because it is achiral in solution. Both in solution and the solid state, the conversions were varied from a few percent up to 25%.

Measurable rotations were produced only in the case of the $P2_12_12_1$ crystals. The average specific rotation (ten separate irradiations) was 24.2 ± 2.9°; of these, one was dextrorotatory and nine were levorotatory (eight of the ten crystals studied were taken from the same batch and gave (−)-**2**). Neither the *Pbca* crystal irradiations nor the solution photolyses gave any trace of optical activity. Chiral NMR shift reagent studies at 300 MHz ($Eu(hfc)_3$, Aldrich) indicate that, within the limit of the method, the $P2_12_12_1$ crystals give **2** in 100% enantiomeric excess. Under conditions where racemic **2** gives rise to four very well-resolved signals (δ 5.08, 5.20, 5.63, and 5.73, due to $CH(CH_3)_2$), only two resonances are observed for samples of **2** obtained from the $P2_12_12_1$ crystal irradiations.

A second example of an absolute asymmetric photorearrangement in the solid state was discovered in the case of α-(3-methyladamantyl)-*p*-chloroacetophenone (**3**, Scheme I). This material, mp 44–45 °C,[7] forms very large prisms from ethanol that are also chiral, space group $P2_12_12_1$, a = 6.599 (1) Å, b = 12.028 (1) Å, c = 20.198 (2) Å, Z = 4. The structure was solved by Patterson methods, R = 0.038 for 1279 reflections with $I > 3\sigma(I)$. The molecule crystallizes in an asymmetric conformation (shown), whereas it has a mean plane of symmetry (the C(1)–C(2)–C(3) plane) in solution as shown by NMR. From our previous studies on the crystalline-phase Norrish type II reactions of substituted α-adamantylacetophenones,[10] we were confident that ketone **3** would react to give cyclobutanol-type photoproducts (e.g., **4**, six chiral centers); type II cleavage is precluded in the case of α-adamantyl ketones owing to the prohibitive strain energy involved in the formation of adamantene.[11] Laser irradiation of solutions of **3** led to mixtures of four of the six possible cyclo-

(3) (a) Green, B. S.; Lahav, M.; Rabinovich, D. *Acc. Chem. Res.* **1979**, *12*, 191–197. (b) Addadi, L.; Lahav, M. *Origins of Optical Activity in Nature*; Walker, D. C., Ed., Elsevier: New York, 1979; Chapter 14.

(4) (a) Addadi, L.; Lahav, M. *J. Am. Chem. Soc.* **1979**, *101*, 2152–2156. (b) Addadi, L.; van Mil, J.; Lahav, M. *J. Am. Chem. Soc.* **1982**, *104*, 3422–3429. (c) van Mil, J.; Addadi, L.; Gati, E.; Lahav, M. *J. Am. Chem. Soc.* **1982**, *104*, 3429–3434. The Weizmann group has also carried out asymmetric synthesis studies involving thermal gas/solid reactions as well as thermal and photochemical reactions in crystalline host/guest complexes. For reviews, see: (d) Addadi, L.; Ariel, S.; Lahav, M.; Leiserowitz, L.; Popovitz-Biro, R.; Tang, C. P. *Chemical Physics of Solids and Their Surfaces*; Roberts, M. W., Thomas, J. M., Ed., The Royal Society of Chemistry: London, 1980; Specialist Periodical Reports, Vol. 8, Chapter 7. (e) Arad-Yellin, R.; Green, B. S.; Knossow, M.; Tsoucaris, G. In *Inclusion Compounds III*, Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Ed.; Academic Press: London, 1984; Chapter 9.

(5) Review: Zimmerman, H. E. In *Molecular Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Wiley-Interscience: New York, 1980; Chapter 16.

(6) Review: Wagner, P. J. *Acc. Chem. Res.* **1971**, *4*, 168–177. The first asymmetric Norrish type II reaction of an achiral ketone complexed with deoxycholic acid has been reported recently: Aoyama, H.; Miyazaki, K.; Sakamoto, M.; Omote, Y. *J. Chem. Soc., Chem. Commun.* **1983**, 333–334. The photoproducts had enantiomeric excesses of 10–15%.

(7) Diester **1** was prepared by transesterification of the corresponding dimethyl ester prepared by the method of: Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1931**, *486*, 191–202. Ketone **3** was prepared by Friedel–Crafts acylation of chlorobenzene using the acid chloride of (3-methyladamantyl)-acetic acid (Aldrich).

(8) Ciganek, E. *J. Am. Chem. Soc.* **1966**, *88*, 2882–2883.

(9) See, for example: Rietz, R. R.; Zalkin, A.; Templeton, D. H.; Edelstein, N. M.; Templeton, L. K. *Inorg. Chem.* **1978**, *17*, 653–658.

(10) (a) Evans, S.; Omkaram, N.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1985**, *26*, 5903–5906. (b) Evans, S. V.; Omkaram, N.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1986**, *27*, 1419–1422.

(11) (a) Sauers, R. R.; Gorodetsky, M.; Whittle, J. A.; Hu, C. K. *J. Am. Chem. Soc.* **1971**, *93*, 5520–5526. (b) Gagosian, R. B.; Dalton, J. C.; Turro, N. J. *J. Am. Chem. Soc.* **1975**, *97*, 5189–5192. (c) Lewis, F. D.; Johnson, R. W.; Kory, D. R. *J. Am. Chem. Soc.* **1974**, *96*, 6100–6107.

butanols, and no trace of optical activity could be detected in these mixtures. However, when a single crystal of **3** weighing 313 mg was photolyzed at 8 °C to 8% conversion and the crude reaction mixture analyzed for optical activity, a specific rotation of −24.5° was observed. Cyclobutanol **4** comprises 70% of the crystal photoproduct mixture, and this material was isolated by column chromatography ($[\alpha]_D$ −21.6°) and its optical purity determined using the chiral NMR shift reagent Eu(hfc)$_3$. This indicated an enantiomeric excess of at least 80%. Following irradiation the crystal was sticky, and we attribute the less than quantitative optical yield to partial sample melting.

Mechanistically, these results indicate that the di-π-methane rearrangement of **1** and the Norrish type II reaction of **3** are stereospecific (albeit nonconcerted), topochemically controlled processes in the solid state. By determining the absolute configurations of the reactants and products and correlating them for a given crystal irradiation, the reaction stereochemistry can be mapped out in detail. This remains an important goal of future work. Unimolecular processes have at least two major advantages over bimolecular reactions for solid-state asymmetric synthesis studies. First, unimolecular reactions do not require specific crystal packing arrangements, and this increases the chances of finding a suitable chiral crystal structure. Second, each chemical event in a bimolecular solid-state reaction involves the disturbance of two lattice sites rather than one, and this may lead to a faster loss of topochemical control with a corresponding decrease in asymmetric induction.

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Total Synthesis of (+)-Methyl Homodaphniphyllate

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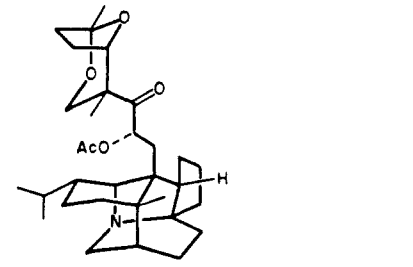
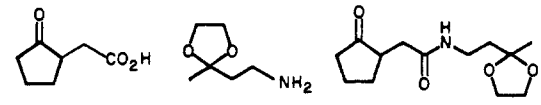
The oriental deciduous tree Yuzuriha (*Daphniphyllum macropodum* Miquel) contains a family of triterpene alkaloids, of which daphniphylline (**1**) is the prototypical member.[1] The structure of daphniphylline was elucidated by Hirata and Sakabe in 1966.[2] The *Daphniphyllum* alkaloid group now numbers some 20 compounds.[3] In this paper, we report the first total synthesis of a *Daphniphyllum* alkaloid, methyl homodaphniphyllate (**2**), a C-22 member of the group having the interesting pentacyclic nucleus of daphniphylline.

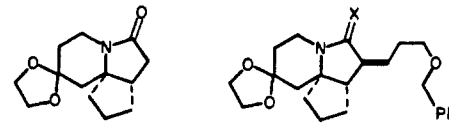
The known keto acid **3**[4] is treated sequentially with triethylamine, ethyl chloroformate, and amine **4**[5] to obtain keto amide **5** (89%). When this substance is heated in anhydrous toluene with *p*-toluenesulfonic acid, tricyclic lactam ketal **6** is formed in 83% yield. Alkylation of the derived lithium enolate, formed by treatment of **6** with lithium diisopropylamide (LDA) in THF, with the benzyl ether of 3-bromopropanol provides lactam **7** in 73% yield. Thiolactam **8** is formed from **7** in 76% yield by reaction with Lawesson's reagent[6] in THF with ultrasonication,[7] followed by sequential treatment of the initial product with aqueous base, aqueous acid, and finally, ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene.[8] The preformed lithium enolate of thiolactam **8** (LDA, THF) is allowed to react with pent-3-en-2-one (0 °C) to obtain the Michael adduct **9** in 84% yield. Although this reaction shows reasonably high stereoselectivity at the new side-chain stereocenter (4.8:1), we have not determined the stereochemistry at this point.



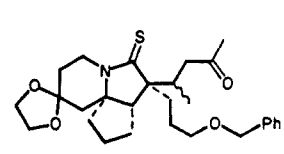
1



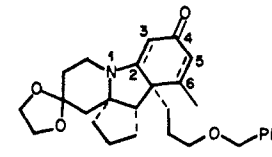
3 **4** **5**



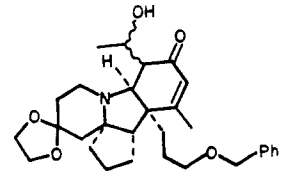
6 **7**: X = O; **8**: X = S



9



10: $\Delta^{2,3}$; 5,6-dihydro
11: 2,3,5,6-tetrahydro
12: $\Delta^{5,6}$; 2,3-dihydro



13

The fourth ring is closed by reaction of thiolactam **9** with triethyloxonium fluoborate in $CHCl_3$, followed by triethylamine. The tetracyclic vinylogous amide **10** is formed in 74% yield. Reaction of 10 sequentially with trimethyloxonium fluoborate in CH_2Cl_2 at 0 °C, $NaBH_4$ in methanol, and HCl in aqueous ether provides the saturated amino ketone **11** (87%). This material is treated with lithium 2,2,6,6-tetramethylpiperidide in THF at −78 °C and the resulting enolate selenylated with phenylselenyl chloride.[9] The resulting α-phenylseleno ketone is oxidized by *m*-chloroperoxybenzoic acid in methanol−CH_2Cl_2 at −20 °C to obtain enone **12** (59%).

The lithium enolate of enone **12** (LDA, THF, −78 °C) is treated with acetaldehyde in THF at −78 °C to obtain a mixture of diastereomeric aldols **13**, which is dissolved in acetone and treated with concentrated sulfuric acid. A complex series of transfor-

(1) Yamamura, S.; Hirata, Y. *Alkaloids (N.Y.)* **1975**, *15*, 41.
(2) Hirata, Y.; Sakabe, N. *Tetrahedron Lett.* **1966**, 965.
(3) (a) Hirata, Y.; Sasaki, K. *Tetrahedron Lett.* **1972**, *1275*. (b) Yamamura, S.; Hirata, Y. *Ibid.* **1974**, 3673. (c) Yamamura, S.; Hirata, Y.; Niwa, H.; Toda, M.; Ishimoru, S. *Tetrahedron* **1974**, *30*, 3031. (d) Yamamura, S.; Hirata, Y.; Irakawa, H.; Okamura, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2120. (e) Yamamura, S.; Hirata, Y.; Toda, M. *Ibid.* **1976**, *49*, 839. (f) Hirata, Y.; Sasaki, K. *Acta Crystallogr., Sect. B* **1973**, *29*, 547.
(4) Linstead, R. P.; Meade, E. M. *J. Chem. Soc.* **1934**, 935.
(5) Islam, A. M.; Raphael, R. A. *J. Chem. Soc.* **1955**, 3151.
(6) (a) Lawesson, S.-O.; Shabana, R.; Scheibye, S.; Clausen, K.; Olesen, S. O. *Nouv. J. Chim.* **1980**, *4*, 47. (b) Thompson, I.; Clausen, K.; Scheibye, S.; Lawesson, S.-O. *Org. Synth.* **1984**, *62*, 158.
(7) Raucher, S.; Klein, D. *J. Org. Chem.* **1981**, *46*, 3558.
(8) In the thiation reaction, surprisingly, one of the oxygens of the dioxolane ring is partially replaced by sulfur. Thus, the crude thiolactam, a mixture of a dioxolane (ca. 25%) and an oxothiolane (ca. 75%), is hydrolyzed and reconverted to dioxolane before continuing the synthesis. We have not investigated the mechanism of the intriguing transformation.
(9) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

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