Nonstereoselective Cyclopropanation of Olefins by Singlet Fluorenylidene

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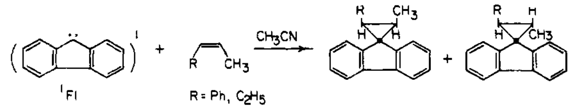
The postulate that the cyclopropanation of olefins by singlet carbenes occurs with retention of configuration of the olefin[1] has received considerable experimental support and is widely acknowledged to be generally true.[2] Our recent detection and characterization of singlet fluorenylidene (^{1}Fl) permits for the first time an unambiguous direct quantitative analysis of the stereochemistry of the addition of this carbene to olefins.[3] We find that in acetonitrile or in Freon solution the addition of ^{1}Fl to *cis*-β-methylstyrene, or *cis*-2-pentene, occurs with considerable loss of stereochemistry of the olefin component (eq 1), a result



(1)

which is in contrast to previous interpretations of the addition of singlet carbenes to olefins.

Irradiation of 9-diazofluorene (DAF) at 337 nm with a nitrogen laser[4] in oxygen-free acetonitrile solution generates a transient product that has a half-life of 17 ns which we have identified by spectroscopic, kinetic, and chemical trapping methods to be ^{1}Fl.[3] In dilute solution in the absence of a trapping reagent, ^{1}Fl intersystem crosses to triplet fluorenylidene (^{3}Fl) in high yield. Chemical reaction of ^{1}Fl with suitable reagents competes with intersystem crossing, and, therefore, as the concentration of trapping reagent increases, the yield of ^{3}Fl (ϕ_T) decreases. The rate constant for the reaction of ^{1}Fl with a trapping reagent (k_s) may thus be obtained by application of eq 2, where $\phi_T{}^0$ is the yield

$$\phi_T{}^0/\phi_T - 1 = k_s/k_{isc}[\text{reagent}] \tag{2}$$

of ^{3}Fl in the absence of trapping reagent, determined by measuring its absorbance at 400 nm following pulse irradiation, and k_{isc} is the previously determined rate constant for intersystem crossing to form ^{3}Fl.[3] Figure 1 shows the data for reaction of ^{1}Fl with *cis*- and *trans*-β-methylstyrene and *cis*- and *trans*-2-pentene plotted according to eq 2. The magnitudes of the bimolecular rate constant for reaction of ^{1}Fl with these olefins (k_s) are presented in Table I.

The rates for intersystem crossing and chemical reaction of ^{1}Fl determine the fraction of the reaction that originates from the singlet carbene. Irradiation of 1 × 10^{-2} M DAF at 337 nm in acetonitrile solution containing ca. 2.5 M olefin insures nearly complete reaction with ^{1}Fl before intersystem crossing to ^{3}Fl (Table I). The products of these reactions (Table I) are mainly cyclopropanes as determined by ^{1}H NMR spectroscopy and comparison with authentic samples independently prepared.[5] All of the reactions give some difluorenylidene. We suspect that this product is a result of the reaction of ^{3}Fl with DAF. Also, the pentenes give some allylic C–H insertion product,[6] the yield of which is dependent on the stereochemistry of the starting olefin.

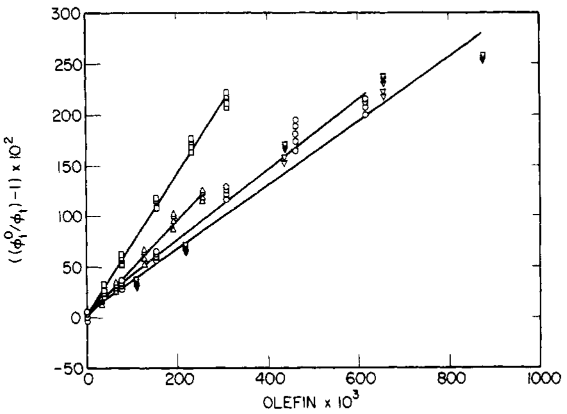


Figure 1. Stern–Volmer analysis of the reaction of the isomeric β-methylstyrenes and 2-pentenes with ^{1}Fl in CH_3CN at 23 °C. In order of decreasing slopes the lines correspond to *trans*-β-methylstyrene, *cis*-β-methylstyrene, *trans*-2-pentene, and *cis*-2-pentene.

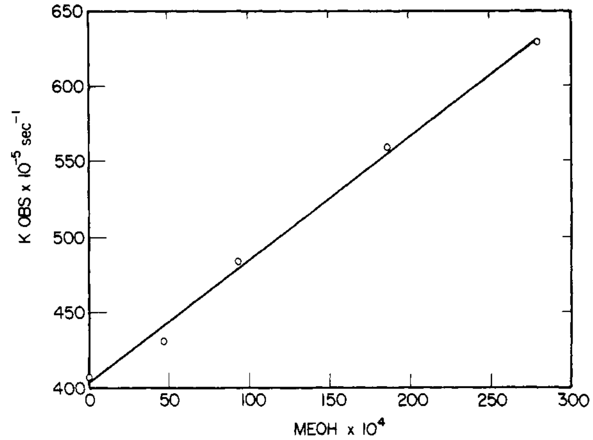


Figure 2. Effect of increasing methanol concentration on the rate of growth of ^{3}Fl following pulse irradiation at 337 nm in CH_3CN solution.

The surprising result is that the reaction of ^{1}Fl with *cis*-β-methylstyrene or *cis*-2-pentene does not occur stereoselectively. The ratio of *trans*- to *cis*-cyclopropane is 1.17 ± 0.06 for the styrene and 1.80 ± 0.17 for the pentene. In contrast, the reaction of ^{1}Fl with the trans-disubstituted olefins does occur stereoselectively. Within the 5% limit of detection of our analytical method, we can find none of the appropriate cis-disubstituted cyclopropanes from reaction of the trans-disubstituted olefins.

The apparent nonstereoselective reaction of ^{1}Fl with the cis-disubstituted olefins might have any one of several origins. We carried out a series of control experiments to examine these. Exposure of the olefins or the cyclopropane products to the conditions of the experiment does not cause isomerization.[7] Also, ground-state reaction of DAF with the olefins does not occur under the reaction conditions.[8] To show conclusively that the values of k_s we measured are for the cyclopropanation reaction we carried out a series of competitive trapping reactions between these olefins and methanol.

Methanol is widely regarded to react only with singlet carbenes to give ether products,[9] a conclusion that we have confirmed

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† Fellow of the Alfred P. Sloan Foundation (1977–1979) and the Dreyfus Foundation (1979–1984).

(1) This postulate is commonly referred to as the Skell–Woodworth hypothesis: R. C. Woodworth and P. S. Skell, *J. Am. Chem. Soc.*, **81**, 3383 (1958).

(2) P. P. Gaspar and G. S. Hammond, *Carbenes*, **2**, 293 (1975).

(3) J. J. Zupancic and G. B. Schuster, *J. Am. Chem. Soc.*, **102**, 5958 (1980).

(4) The spectroscopic apparatus has been described: J. J. Zupancic, K. A. Horn, and G. B. Schuster, *J. Am. Chem. Soc.*, **102**, 5279 (1980). The product studies were carried out on this apparatus by flashing at 4 Hz until the DAF was consumed. The solution was stirred continuously during the irradiation.

(5) The cyclopropanes were prepared by decomposition of DAF in neat olefin using a catalytic amount of $ZnBr_2$: S. H. Goh, L. E. Closs, and G. L. Closs, *J. Org. Chem.*, **34**, 25 (1969).

(6) The insertion product is composed entirely of stereoisomers of the trisubstituted olefin. Its yield follows directly the yield of the *trans*-disubstituted cyclopropane.

(7) The cyclopropane is transparent at 337 nm; however, irradiation at shorter wavelengths is known to cause isomerization: C. Decker, A. M. Braun, and J. Faure, *Nouv. J. Chem.*, **3**, 583 (1979), and references cited therein.

(8) At higher temperatures, however, we suspect that these olefins react with DAF, a fact which confounds our attempt to compare quantitatively thermally generated ^{1}Fl with the photochemically generated ^{1}Fl.

(9) W. Kirmse, "Carbene Chemistry", 2nd ed., Academic Press, New York, 1971; R. A. Moss and M. Jones, Jr., *Carbenes*, **1**, 2 (1973).

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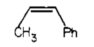
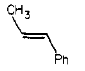
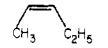
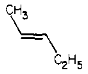
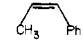
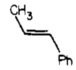
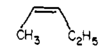
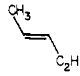
Table I. Kinetics and Products from the Reaction of ^{1}Fl with Olefins and Methanol

				products			
	$k_s \times 10^{-8}$, $M^{-1}\ s^{-1}$	reagent[a] concn, M	singlet carbene reaction,[b] %	*cis*-cyclopropane,[c] %	*trans*-cyclopropane, %	CH % insertion	other,[d] %
	1.94 2.24[e]	2.57 2.84	92 99	39 33	45 48		3 not determined
	2.86	2.60	93		82		3
	1.29	4.45	93	53	33	6	3
	1.43	3.25	92		65	18	3
CH_3OH	8.95 8.16[g]	2.68	98				85[f]

[a] The olefins were stereoisomerically pure (≥99%). [b] Calculated using $k_{isc} = 4.07 \times 10^7\ s^{-1}$ (ref 3). [c] The yields are computed by comparison with the total amount of DAF introduced at the start of the reaction and are absolute. The distribution of stereoisomeric cyclopropanes was determined by ^{1}H NMR spectroscopy at 220 MHz. [d] The major side products are fluorenone (1–2%) and difluorenylidene (1–2%). The olefin yield was determined spectrophotometrically. [e] These values were determined in Freon 113 solution. [f] This is the isolated yield of methyl fluorenyl ether. We suspect that the crude yield is higher. [g] This value for k_s^{MeOH} was determined by following the rate of ^{3}Fl at increasing methanol concentrations.

Table II. Analysis of Products of Competitive Trapping of ^{1}Fl by Olefins and Methanol

	concn, M	MeOH, M	$(k_s^{olefin} \times [olefin])/(k_s^{MeOH} \times [MeOH])$	$\frac{\text{cyclopropane}^b}{\text{ether}}$
	2.54	0.333	1.65 ± 0.05	1.79 ± 0.03
	2.38	0.333	2.28 ± 0.07	2.43 ± 0.05
	2.38 2.21	0.262 0.818	1.31 ± 0.04 0.38 ± 0.03	1.27 ± 0.03 0.39 ± 0.03
	2.70 2.13	0.298 0.818	1.44 ± 0.04 0.41 ± 0.04	1.39 ± 0.02[c] 0.36 ± 0.07

[a] The values of k_s are taken from Table I. The indicated errors are 1 SD. [b] The products were identified by ^{1}H NMR at 220 MHz and the relative yields determined by quantitative gas chromatography or quantitative NMR spectroscopy with *p*-dioxane or hexamethylbenzene as internal standard. [c] In this case the products from the olefin are the sum of the cyclopropane and carbon-hydrogen insertion.

spectroscopically for the fluorenylidene system.[3] We determined the rate constant for reaction of ^{1}Fl with methanol (k_s^{MeOH}) independently by monitoring the rate of appearance of the ^{3}Fl absorption at 400 nm following pulse irradiation at increasing methanol concentrations; these data are shown in Figure 2. The value of k_s^{MeOH} obtained by this method is the same within experimental error as that determined by monitoring ϕ_T. Table II contains a summary of the results of the irradiation of DAF in acetonitrile solution containing both methanol and an olefin. In all cases the ratio of cyclopropane to ether product observed is within the experimental error of the ratio predicted by consideration of the appropriate values for k_s and the olefin and alcohol concentrations. These observations confirm that the values of k_s used to estimate the extent of singlet reaction accurately reflect the actual chemical reactivity of ^{1}Fl and show also that ^{1}Fl is the precursor to the cyclopropane products. It should be noted that the ratio of stereoisomeric cyclopropanes obtained from the cis-disubstituted olefins is the same in the presence of methanol as in its absence.

Finally, it is possible that the nonstereoselectivity is a result peculiar to acetonitrile solutions.[10] To examine this, we investigated the reactions of ^{1}Fl in cyclopropane at −50 °C and Freon 113 at 22 °C. The rate constant for reaction of ^{1}Fl with *cis*-*β*-methylstyrene (Table I) is virtually solvent independent, and in the Freon this reaction gives a mixture of stereoisomeric cyclopropanes quite similar to that obtained in acetonitrile.

The findings described above force us to conclude that formation of cyclopropanes from ^{1}Fl and these cis-disubstituted olefins occurs with considerable loss of stereochemistry, an observation which is a clear violation of the widely accepted Skell–Woodworth postulate.[1] Fundamentally, these data require that there be an intermediate in the reaction of ^{1}Fl with these olefins that permits the conversion of the cis stereochemical arrangement of the olefin to the mixed stereochemistry observed in the cyclopropane products. The possible existence of such an intermediate was considered earlier by Gaspar and Hammond.[11]

Several previously reported investigations have dealt with the stereochemistry of the addition of fluorenylidene, and aryl substituted carbenes in general, to olefins. Jones and Rettig[12] examined the stereoselectivity of the addition of ^{1}Fl to *cis*-2-butene. They report that even in neat olefin a mixture of stereoisomeric cyclopropanes is formed. On dilution with hexafluorobenzene, thereby slowing the rate of reaction of ^{1}Fl with the olefin, the proportion of trans-disubstituted cyclopropane in the product mixture increases. They interpret these findings to indicate that reaction from ^{1}Fl is stereospecific and that from ^{3}Fl is not. However, the present values we obtain for k_s indicate that in neat olefin nearly all of the reaction is from ^{1}Fl. More recently Gaspar and co-workers[13] examined the stereospecificity of the addition of singlet diphenylmethylene to *cis*- and *trans*-1,2-dichloroethylene. Their experiments show nearly complete retention of configuration of olefin stereochemistry in the cyclopropane products. This finding is consistent with the earlier report of stereospecific addition of phenylmethylene to olefins.[14]

It appears that formation of an intermediate capable of stereoisomerization in the reaction of ^{1}Fl with olefins is exceptional. The possible causes for this unusual behavior may be linked to unique properties of the fluorenyl group. The enhanced stability of the fluorenyl compared to the diphenylmethyl system may increase the lifetime of the appropriate intermediate so that rotation about the remaining olefinic single bond is competitive with closure to the cyclopropane. Alternatively, the enhanced stability

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(10) We thank Professor Maitland Jones of Princeton University for suggesting this possibility.

(11) P. P. Gaspar and G. S. Hammond, "Carbon Chemistry", 1st ed., Chapter 12, W. Kirmse, Ed., Academic Press, New York, 1964.

(12) M. Jones, Jr., and K. R. Rettig, *J. Am. Chem. Soc.*, **87**, 4013 (1965).

(13) P. P. Gaspar, B. L. Whistle, M. Jones, Jr., and J. B. Lambert, *J. Am. Chem. Soc.*, **102**, 6108 (1980).

(14) C. D. Gutsche, G. L. Bachman, and R. S. Coffey, *Tetrahedron*, **18**, 617 (1962).

may encourage formation of an intermediate where none exists in less highly stabilized systems.

These results do not provide any direct information about the electronic nature of the reaction intermediate. In particular, three likely possibilities exist: a biradical, which may be a singlet or a triplet, a zwitterion, or a hybrid showing properties intermediate between these two extremes. We are continuing to investigate the chemical properties of this species in order to characterize it more precisely.

Acknowledgment. We thank Mr. James Wehmer for his efforts in the construction of the laser apparatus and Professor Peter Beak for a critical reading of the manuscript. This work was supported in part by the National Science Foundation and in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Total Synthesis of (±)-Trihydroxydecipiadiene

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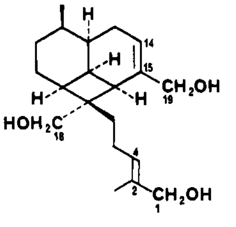
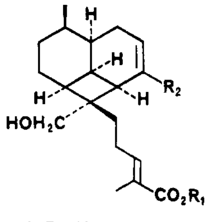
The decipiene diterpenes (**1**–**3**) possess a structurally unique skeleton based on the tricyclo[5.3.1.0^{3,11}]undecane ring system. These unusual compounds were isolated from the resinous coating of the Australian plant *Eremophila decipiens*, and their structures were established by a combination of chemical and X-ray studies.[1,2]



1, trihydroxydecipiadiene

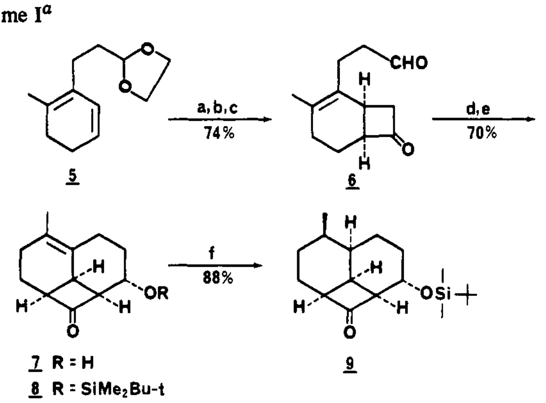


2 $R_1 = H; R_2 = CH_3$
3 $R_1 = H; R_2 = CH_2OH$
4 $R_1 = Et; R_2 = CH_2OH$

We describe an efficient approach to this novel tricyclic skeleton, and its application to the first total synthesis of a member of this interesting group of diterpenes, (±)-trihydroxydecipiadiene (**1**).

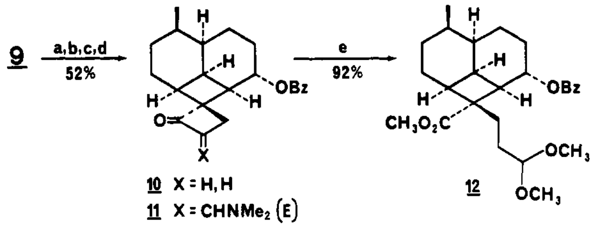
Our strategy for the construction of the decipiene ring system is illustrated in Scheme I by the synthesis of the key intermediate **9**. Cycloaddition of dichloroketene to the diene **5**,[3,4] followed by dechlorination and hydrolysis afforded the aldehyde **6** [bp 93–95 °C (0.02 mm); NMR ($CDCl_3$) δ 9.78 (1 H, t, $J = 1.4$ Hz), 1.67 (3 H, br s)] in 74% overall yield. Attempts to effect aldol cyclization of **6** were unsuccessful under a variety of conditions.[8] However, methanolic barium oxide was found to be a remarkably effective catalyst for this reaction, giving a single ketol **7**,[9] which was isolated in 70% yield after protection as its *tert*-butyldimethylsilyl ether **8** [mp 50–51 °C; NMR ($CDCl_3$) δ 4.08 (1 H, ddd, $J = 4.5$, 3.0, 3.0 Hz), 1.69 (3 H, d, $J = 2.3$ Hz); IR (neat) ν_{max} 1770 cm^{-1}]. Hydrogenation of **8** at atmospheric pressure occurred exclusively from the more accessible convex face of the molecule to give **9** [mp 59–60 °C; NMR ($CDCl_3$) δ 4.25 (1 H,

Scheme I[a]



[a] Reagents: (a) $Cl_2CHCOCl$, Et_3N, hexane, 25 °C, 16 h.[7] (b) Zn, NH_4Cl, MeOH, 25 °C. (c) 2 N HCl, THF. (d) 0.1 M BaO/MeOH, 25 °C, 10 h. (e) *t*-$BuMe_2SiCl$, 4-(dimethylamino)pyridine (DMAP), DMF, 25 °C.[11] (f) H_2 (1 atm), 10% Pd/Al_2O_3, MeOH.

Scheme II[a]



[a] Reagents: (a) 1-Lithiocyclopropyl phenyl sulfide, THF, −78 °C. (b) (1) MeOH, Dowex 50W-X8 resin; (2) benzoic anhydride, DMAP, CH_2Cl_2. (c) $SnCl_4$ (1 equiv), CH_2Cl_2, 0 °C, 10 min. (d) $(Me_2N)_2CHO$-*t*-Bu, PhH, 60 °C. (e) *p*-TsOH (1 equiv), MeOH, 50 °C, 12 h.

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* Address correspondence to the Department of Chemistry, Columbia University, New York, NY 10027.

(1) (a) Ghisalberti, E. L.; Jefferies, P. R.; Sheppard, P. *Tetrahedron Lett.* **1975**, 1775. (b) Indem, *Tetrahedron* **1980**, *36*, 3253. (c) Maslen, E. N.; Sheppard, P. N.; White, A. H.; Willis, A. C. *J. Chem. Soc., Perkin Trans. 2* **1976**, 263. (d) Recently, the structure of a new decipiene diterpene, which lacks the 2(4) unsaturation of **1**–**3**, has been determined: Croft, K. D.; Ghisalberti, E. L.; Jefferies, P. R.; Marshall, D. G.; Raston, C. L.; White, A. H. *Aust. J. Chem.* **1980**, *33*, 1529.

(2) The nomenclature for these compounds is based on the trivial name, decipiane, given to the parent hydrocarbon,[1a] and its assigned numbering system, which is shown (in part) in structure **1** of this paper. Thus, the complete name for **1** is 1,18,19-trihydroxydecipi-2(4),14-diene.[1b] We omit the number designations hereafter for convenience.

(3) Prepared in five steps from 4-carbethoxy-3-methyl-2-cyclohexen-1-one (Hagemann's ester): (i) 2-(2-bromoethyl)-1,3-dioxolane,[5] KO-*t*-Bu, THF, reflux; (ii) 2 N aqueous NaOH (1.5 equiv), MeOH, 25 °C; (iii) 75 °C, 1 mm, 12 h; (iv) H_2NNHTs, TsOH·Py, THF, 25 °C; (v) MeLi (2.5 equiv), Et_2O, 0 °C.[6] The overall yield of **5** [bp 60–62 °C (0.03 mm); NMR ($CDCl_3$) δ 5.79 (1 H, d, $J = 9.7$ Hz), 5.63 (1 H, m), 1.73 (3 H, br s)] was 35%.

(4) All new compounds were fully characterized by spectroscopic means (NMR, IR, MS) and gave satisfactory elemental analysis (crystalline compounds) or precise mass measurement. All yields correspond to isolated amounts of purified products.

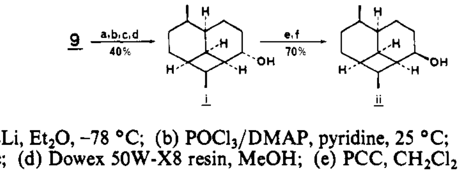
(5) Buchi, G.; Wuest, H. *J. Org. Chem.* **1969**, *34*, 1122.

(6) Dauben, W. G.; Lorber, M. E.; Vietmeyer, N. D.; Shapiro, R. H.; Duncan, J. H.; Tomer, K. *J. Am. Chem. Soc.* **1968**, *90*, 4762.

(7) Ghosez, L.; Montaigne, R.; Roussel, A.; Vanlierde, H.; Mollet, P. *Tetrahedron* **1971**, *27*, 615.

(8) Reaction of **6** under a number of aldol conditions led to either complex mixtures (e.g., KOH, NaOH, K_2CO_3, NaOMe, or $Mg(OMe)_2$ in MeOH; KO-*t*-Bu in Et_2O) or no reaction (pyrrolidine/HOAc in PhH; DBN in CH_2Cl_2).

(9) The orientation of the hydroxyl was assigned on the basis of the following observations. The alcohol ii, prepared as indicated from its more polar isomer i, showed a distinct downfield shift (0.15 ppm relative to i) of its ^1H NMR signal corresponding to the methyl group on the cyclobutane ring.[10]



(a) MeLi, Et_2O, −78 °C; (b) $POCl_3$/DMAP, pyridine, 25 °C; (c) H_2, Pd/C, EtOAc; (d) Dowex 50W-X8 resin, MeOH; (e) PCC, CH_2Cl_2; (f) DIBAH, Et_2O, −78 °C.

(10) For a similar deshielding effect, see: Cimarusti, C. M.; Wolinsky, J. *J. Org. Chem.* **1971**, *36*, 1871. See also: Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, 1969; p 71–72.

(11) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99.

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