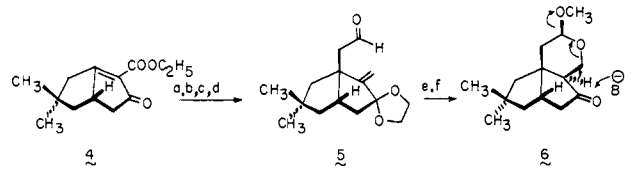
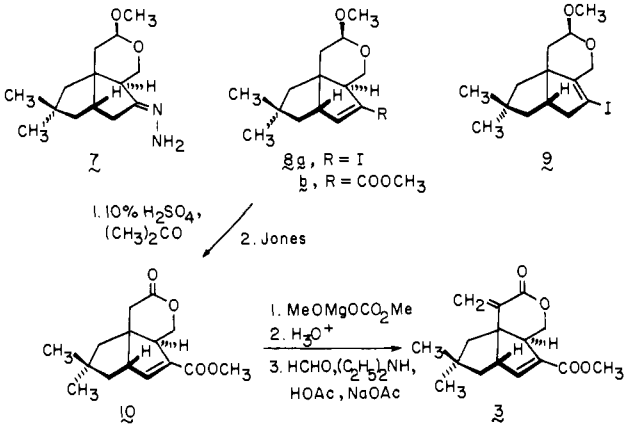
Chart I[a]



(a) $HOCH_2CH_2OH$, *p*-TsOH, C_6H_6. (b) $(i\text{-}Bu)_2AlH$, ether, −116 °C. (c) $CH_2{=}CHOCH_2CH_3$, $Hg(OAc)_2$. (d) decalin, 145–150 °C. (e) Py·HOTs, CH_3COCH_3, H_2O. (f) $NaOCH_3$ (catalytic), CH_3OH, 20 °C.

(see arrows). In view of the equatorial orientation of the methoxyl group, the resultant geometry is stereoelectronically appropriate for continuous overlap of the participating orbitals.[6] Furthermore, the adduct of **6** with trimethylsilyl cyanide is so disfavored in its equilibrium with the keto form that it proved not to be a serviceable intermediate. These complications were surmounted by heating **6** briefly with a solution of hydrazine hydrate in ethanol containing triethylamine. Oxidation of the resulting hydrazone (**7**, 95%) with iodine in the presence of trimethylamine (THF, 0°C)[8] provided in 74% yield a 2.2:1 mixture of the regioisomeric vinyl iodides **8a**[9] and **9**.[10] Although regiospecificity was not achieved in the formation of **8a**, extensive experimentation did reveal that trimethylamine reproducibly afforded the most favorable product ratio and that the relative distribution of vinyl iodides was more dependent upon the steric bulk of the base than its pK_a.[11] Chromatography on silica gel was successful in achieving separation of the positional isomers.

Reaction of **8a** with the nickel carbonyl–sodium methoxide reagent in methanol[12] gave rise in exceptionally high (93%) yield to methyl ester **8b** [IR (neat, cm^{-1}) 1720 and 1625; ^1H NMR ($CDCl_3$) δ 6.76 (br s, 1 H), 4.65 (t, J = 6.5 Hz, 1 H), 4.05 (B of ABX, J_{ab} = 12 Hz, J_{ax} = 7.5 Hz, 1 H), 3.70 (s, 3 H), 3.53–3.38 (m, 1 H) 3.33 (s, 3 H), 3.13–2.86 (m, 2 H), 1.9–1.1 (m, 6 H), and 1.03 (s, 6 H)] without any sign of double-bond equilibration or acetal destruction.



With the viability of our approach now on firm ground, attention turned to modification of the oxygen-containing ring. Unmasking of the lactone functionality was achieved uneventfully by sequential acidic hydrolysis in aqueous acetone solution and Jones oxidation (74% overall). Completion of the synthesis from **10**[13] was achieved in a straightforward manner. Because of the sterically encumbered nature of the methylene group α to the lactone carbonyl, *tert*-butoxybis(dimethylamino)methane[14] and its methoxy analogue proved ineffective in delivering the vinylogous amide. The need for more elevated temperatures was, however, conveniently and efficiently accommodated by methoxymagnesium carbonate[15] (large excess, 175 °C, 20 min). Subsequent treatment of the resulting lactonic acid with 37% formalin solution containing diethylamine, sodium acetate, and acetic acid[16] provided in 27% overall yield the target pentalenolactone E methyl ester, which was identical with the natural substance[17] by comparison of IR, ^1H NMR, and ^{13}C NMR spectra.

The concise, practical route reported here for the chemical synthesis of **3** can be expected to find application in other synthetic investigations, some of which we hope to report on in due course.

Acknowledgment. We are pleased to acknowledge the financial support of this research by the National Institutes of Health (GM-28468).

(6) D'Arcy, R.; Grob, C. A.; Kaffenberger, T.; Krasnobajew, V. *Helv. Chim. Acta* **1966**, *49*, 185.
(7) For an excellent recent review, consult: Groutas, W. C.; Felker, K. *Synthesis* **1980**, 861.
(8) Barton, D. H. R.; O'Brien, R. E.; Sternhell, S. *J. Chem. Soc.* **1962**, 470.
(9) ^1H NMR ($CDCl_3$) δ 6.11 (s, 1 H), 4.56 (dd, J = 7 and 6 Hz, 1 H), 3.86–3.41 (m, 2 H), 3.35 (s, 3 H), 2.91–2.63 (m, 2 H), 1.80–1.13 (m, 6 H), 1.05 (s, 3 H), and 1.01 (s, 3 H).
(10) ^1H NMR ($CDCl_3$) δ 4.47 (dd, J = 8 and 3 Hz, 1 H), 4.35 (d, J = 12 Hz, 1 H), 3.98 ($^1/_2$ABX, J_{ab} = 12 Hz, J_{ax} = 2.5 Hz, 1 H), 3.45 (s, 3 H), 3.1–2.81 (m, 1 H), 2.66–2.33 (m, 2 H), 2.0–1.1 (m, 6 H), and 1.01 (s, 6 H).
(11) Some exemplary product ratios follow: $(i\text{-}Pr)_2EtN$, 1:0.75; $Me_2NCH_2CH_2NMe_2$, 2.22:1; $Me_2N(C{=}NH)NMe_2$, 1.6:1; 4-(dimethylamino)pyridine, 1.42:1; Et_3N, 1.38:1; pyridine, 1.38:1.
(12) Corey, E. J.; Kirst, H. G.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 6314.
(13) ^1H NMR ($CDCl_3$) δ 6.83 (br s, 1 H), 4.45 (d, J = 4 Hz, 2 H), 3.73 (s, 3 H), 3.30–2.96 (m, 2 H), 2.56 (s, 2 H), 2.05–1.18 (m, 4 H), 1.03 (s, 3 H), and 1.00 (s, 3 H).
(14) (a) Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41. (b) Trost, B. M.; Preckel, M.; Leichter, L. M. *J. Am. Chem. Soc.* **1975**, *97*, 2224. (c) Greenlee, M. L. *Ibid.* **1981**, *103*, 2424.
(15) Finkbeiner, H. L; Stiles, M. *J. Am. Chem. Soc.* **1963**, *85*, 616.
(16) Parker, W. L.; Johnson, F. *J. Org. Chem.* **1973**, *38*, 2489. For a later example of the use of this reagent, see ref 2b.
(17) We are grateful to Professor David Cane for kindly providing us with the authentic spectra of **3** as obtained from natural resources.

12-s-Cis—A Novel Conformation of Retinoids

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Vitamin A has been considered to exist in extended transoid conformation of the polyene chain with a 6-s-cis conformation andd slight loss of coplanarity between the 5,6 and 7,8 double bonds.[1] A similar conformation has been deduced for *trans*-[2-4] and 13-*cis*-retinal,[4,5] but the conformation of 11-*cis*-retinal was ambiguous past C-12. Thus, neither Becker and Grant[4] nor Rowan and Sykes[3] were able to conclude unequivocally whether the preferred conformation of the 12,13 single bond was s-trans, s-cis, out of the polyene plane, or freely rotating. In the course of our investigation of 12-(carbomethoxy)retinoic acid methyl ester isomers we had prepared the trans, 13-cis, 11-cis, and 11-cis,13-cis isomers (**1**–**4**). The latter diester **4** had been reported by Robeson and Cawley[6] who, on the basis of UV studies, had concluded that

(1) Schwieter, V.; Isler, O. In "The Vitamins"; Sebrell, W. H., Jr., Harris, R. S., Eds.; Academic Press: New York, 1967.
(2) Honig, B.; Hudson, B.; Sykes, B. D.; Karplus, M. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1289–1293.
(3) Rowan, R., III; Warshel, A.; Sykes, B. D.; Karplus, M. *Biochemistry* **1974**, *13*, 970–980.
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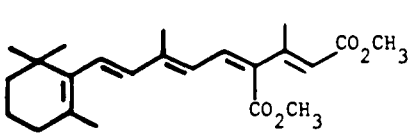
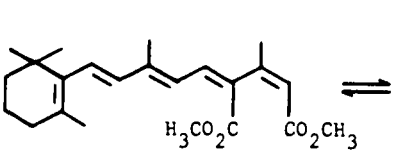
(5) Rowan, R., III; Sykes, B. D. *J. Am. Chem. Soc.* **1975**, *97*, 1024–1027.

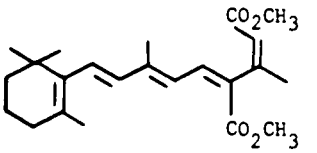
0002-7863/81/1503-6527$01.25/0



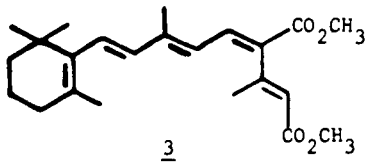
1



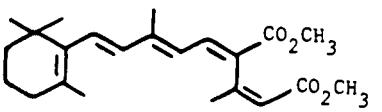
2t



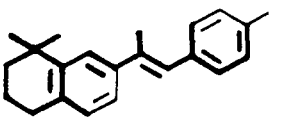
2c



3



4



5

Table I. Proton Chemical Shift Assignments[a-c]

compd	chemical shift, ppm, of proton on carbon no.							
	7	8	10	11	12	14	9a	13a
trans-retinoic acid	6.23	6.09	6.14	7.02	6.32	5.72	1.94	2.25
13-*cis*-retinoic acid	6.23	6.13	6.17	7.04	7.73	5.58	1.93	2.00
1	6.36	6.12	6.26	7.07		5.63	1.99	2.29
2	6.35	6.15	7.18	6.87		5.75	1.94	2.03
3	6.40	6.12	6.18	7.55		5.57	2.01	2.18
4	6.35	6.10	5.98	7.42		5.88	1.97	1.97

[a] 5 mg/0.6 mL of $(CD_3)_2CO$, degassed and sealed. [b] Bruker WM-250 NMR spectrometer. [c] Assignments were made by using selective decoupling.

Table II. Nuclear Overhauser Enhancements for Retinoids, %[a,b]

retinoid	group irradiated	proton obsd				
		14	11	10	7	15
trans-retinal	9-CH_3	0	26	0		0
	13-CH_3	0	24	0	0	36
trans-retinal[c]	9-CH_3	0	17	0	18	0
	13-CH_3	0	18	0	0	31
13-*cis*-retinal[d]	9-CH_3	0	17	0	11	0
	13-CH_3	24	14	0	0	0
11-*cis*-retinal[c]	9-CH_3	0	23	0	13	0
	13-CH_3	1	2	11	0	30
trans-retinoic acid	9-CH_3	0	26	0		
	13-CH_3	0	25	0		
13-*cis*-retinoic acid	9-CH_3	0	26	0		
	13-CH_3	39	23	0		
1[e]	9-CH_3	0	24	0	18	
	13-CH_3	0	21	0	0	
2[e]	9-CH_3	0	27	0	18	
	13-CH_3	30	14	0	0	
3	9-CH_3	0	25	0	15	
	13-CH_3	0	0	0	0	
4	9-CH_3	0	30	0	15	
	13-CH_3	30	0	0	0	

[a] 5 mg/0.6 mL of $(CD_3)_2CO$ degassed and sealed. [b] Bruker WM-250 NMR spectrometer. [c] Reference 3. [d] Reference 5. [e] No change from −50 to 50 °C.

the 13,14 double bond was out of conjugation in this stereoisomer. We were therefore interested in examining the effect of introducing a group with potential for cross-conjugation at C-12 on the conformations of the four retinoid isomers. For comparison, *trans*- and 13-*cis*-retinoic acid were included in our studies. Our investigations have revealed a heretofore unreported conformation for open chain 13-*cis*-retinoids.

The proton chemical shifts (Table I) and the NOE data (Table II) are consistent with the configurational assignments.[7] The 13-cis configuration of **2** and **4** is established by both the 0.25-ppm upfield shift of the 13a methyl (relative to **1**) and the observed NOEs at H-14; the 11-cis configuration of **3** and **4** is confirmed by the 0.4-ppm downfield shift (relative to **1** and **2**) of H-11, due to deshielding by the *syn*-carboxyl group at C-12.

The observed NOEs for *trans*- and 13-*cis*-retinoic acid are in good agreement with those reported for the analogous retinal isomers.[8] It therefore appears that Rowan and Sykes' method should be applicable to compounds **1**–**4**.

The NOEs observed for *trans*-12-carboxyretinoic acid dimethyl ester (**1**) are completely consistent with those observed for *trans*-retinoic acid. It follows that **1** exists in extended conformation. No NOEs are observed upon irradiation of the 13a methyl of the 11-cis isomer **3**, although irradiation at the 9a methyl resonance results in 25% and 15% NOEs at H-11 and H-7, respectively, consistent with the reported observations for 11-cis-retinal.[3] A similar situation obtains with the 11-cis,13-cis isomer **4** for which a 30% NOE at H-14 is observed upon irradiation of the 13a methyl resonance, but no NOE at any other resonance is detected. It therefore appears that in both **3** and **4** there is no conjugation in the polyene past C-12, as had been suggested by Rowan and Skyes[3] for 11-*cis*-retinal and by Robeson and Cawley[6] for **4** based on their UV investigations.

The most interesting situation was found with the 13-cis isomer **2**. Irradiation of the 13a methyl resonance gave 30% enhancement of H-14 but only 14% enhancement of H-11. It thus appears that the distance between H-11 and the 13a methyl protons must be larger in **2** than in either *trans*- or *cis*-retinoic acid or in the trans dimethyl ester **1**. Such a situation is accounted for by the existence of **2** as a rapidly equilibrating[9] mixture of transoid (**2t**) and 12-s-cis (**2c**) conformations. No NOE from irradiation of the 13a methyl group in **2c** is expected; therefore, the observed NOE arises from the extended conformation **2t**. The magnitude of this NOE suggests an approximately equal distribution of the two conformations (14/26 = 0.54), i.e., **2c** and **2t** must be about equal in energy. This is supported by the lack of a temperature effect on either the chemical shifts or the magnitude of the NOEs.

The existence of a 12-c-cis conformation (**2c**) for 13-*cis*-12-carboxyretinoic acid dimethyl ester (**2**) must be due to steric interference between the 1,3-carbomethoxy groups in the extended form **2t**. In **2c** this steric strain is relieved, partially offsetting the energy lost by deconjugation of the 13,14 double bond. Additional energy is regained in **2c** by conjugation with the 12-carbomethoxy group, as evidenced by the downfield shift of H-10. As a consequence, the energies of **2c** and **2t** are not greatly different.

The same steric interference as in **2** exists in the 11-cis,13-cis isomer **4**. Indeed, the lack of a NOE at H-10 upon irradiation

(6) Robeson, C. D.; Cawley, J. D.; Weisler, L.; Stern, M. H.; Eddinger, C. C.; Chechak, A. J. *J. Am. Chem. Sci.* **1955**, *77*, 4111–4119.

(7) The compounds were completely characterized by standard techniques.

(8) The fact that the actual enhancements obtained by us exceed the values reported[3] is probably not significant; it may be due to more complete deoxygenation of our samples, lesser protium content of the solvent, and/or variations in instrumental techniques. It is noteworthy that although the longest relaxation time reported for the protons in *trans*-retinal is 5.9 s,[3] our sample did not recover fully unless 60-s repetition time was used in the FT experiment, suggesting a relaxation time of 10–12 s. This observation is consistent with highly deuterated solvent and highly deoxygenated sample.

(9) Only a single set of ^{13}C NMR signals is observed for **1**–**4**.

at the resonance frequency of the 13a protons suggests that **4** does not possess an extended conformation. In fact, since the high field position of H-10 in **4** (5.98 ppm) relative to its position in the 13-cis analogue (7.18 ppm) is probably due to shielding by the 14-carbomethoxy group, the most likely conformation of **4** is one in which the C-12–C-15 moiety is twisted out of the polyene plane. Analogous conformations have been proposed for 11-*cis*-retinal, and since no NOE at H-10 is observed upon irradiation of the 13a protons of 11-*cis*-12-carboxyretinoic acid dimethyl ester (**3**), a similar situation probably obtains.

It has recently been suggested that the extraordinarily high activity of arotinoids in bringing about regression in papillomas may be associated with the s-cis nature of the polyene backbone (see bold lines in structure **5**).[10] To our knowledge, **2** is the only open-chain retinoid with the analogous conformation; whether it has biological activity similar to that of **5** is not known.

Acknowledgment. This work was supported in part by NCI Contract N01-CP-75932.

(10) Loeliger, P.; Bollag, W.; Mayer, H. *Eur. J. Med. Chem.* **1980**, *15*, 9–15.

Dimethyl(methylthio)sulfonium Fluoroborate. A Chemoselective Initiator for Thionium Ion Induced Cyclizations

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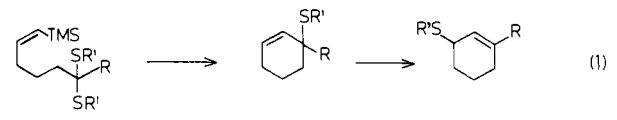
Thionium ions, α-aryl(or alkyl)thio carbocations, offer the possibility of overcoming some of the deficiencies of the carbonyl group in organic synthesis.[1,2] The discovery of a suitable set of conditions to generate such intermediates, which, in part, appear to depend upon the application, becomes critical if such a goal has to be reached. Thioketals represent one of the most useful precursors for thionium ions because (1) thioketals are available by metalation and alkylation of thioacetals[3] and (2) the normally inert thioketal group can be carried through many reactions before chemoselectively unmasking the reactive thionium ion. We wish to report that dimethyl(methylthio)sulfonium fluoroborate (**1**, DMTSF)[4,5] exhibits a remarkable thiophilicity for initiation of cyclization reactions of thioketals and provides an equivalent for a directed intramolecular aldol reaction.[6]

The general utility of allyl sulfides for further structural elaboration[7] led us to examine the cyclization of **2** (reaction 1). Use

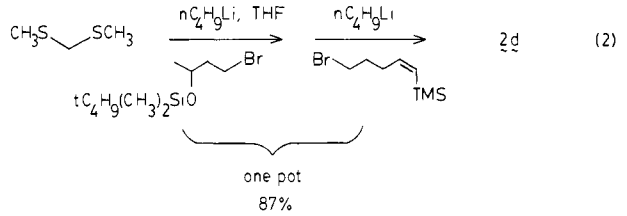


(1)

2 **3** **4**

a, R = H 37%
b, R = CH_3 68%
c, R = C_2H_5 64%
d, R = $CH_3CHCH_2CH_2$ (OSi) 67%

of mercuric chloride, mercuric trifluoroacetate, cupric trifluoromethanesulfonate, stannic chloride, cadmium trifluoroacetate, boron trifluoride, silver fluoroborate, silver trifluoromethanesulfonate, (trimethylsilyl)trifluoromethanesulfonate, among others all failed to effect the desired cyclization. Alternatively, treatment of substrates such as **2** ($R^1 = CH_3$) with salt **1** (1.1 equiv, CH_2Cl_2, room temperature, 20 h) initiated cyclization not to **3** but to **4**[8] in good yields.[9] The rearranged structure **4** was indicated by the NMR spectrum which showed a single vinyl proton, except for **2a** (**b**, δ 5.39; **c**, δ 5.43; **d**, δ 5.58), and a proton on a carbon bearing sulfur (**b**, δ 3.26; **c**, δ 3.31; **d**, δ 3.30). In the case of **2d**, the product **4d** was the free alcohol. The case of **2a** is noteworthy in that a thioacetal in contrast to a thioketal participates in the cyclization—the lower yield in this case attributed to mechanical losses due to volatility of the product during workup. The ready availability of substrates like **2** as shown in reaction 2 for **2d** via



(2)

a lynchpin one-pot sequence from bis(methylthio)methane combined with the flexibility of allyl sulfides gives special merit to this approach. The uniqueness of the cyclization reagent **1** is clearly established. Furthermore, the sulfur byproduct of the cyclization is dimethyl disulfide, which obviously can be recycled to DMTSF.

Extension of this cyclization to substrates such as **5** is particularly intriguing since (1) the high nucleophilicity of the enol silyl ether provides an extreme test of the chemoselectivity of the reagent **1** since it is known to readily add to olefins[10] and (2) cyclizations of diketones normally lead to the 2,3-disubstituted enones rather than the 3-monosubstituted ones.[11] Subjection of **5a** to 1 equiv of **1** (CH_2Cl_2, from −20 to −30 °C, 0.02 M) leads to excellent yields of the desired cyclization products **6**.[8] As the

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(2) Tamura, Y.; Choi, H. D.; Shindo, H.; Uenishi, J.; Ishibashi, H. *Tetrahedron Lett.* **1981**, *22*, 81. Oikawa, Y.; Tanaka, M.; Hirasawa, H.; Yonemitsu, O. *Heterocycles* **1981**, *15*, 207. Oikawa, Y.; Yonemitsu, O. *Ibid.* **1976** *5*, 233. *J. Chem. Soc. Perkin Trans. 1* **1976**, 1479. *J. Org. Chem.* **1976**, *41*, 1118. Paterson, I.; Fleming, I. *Tetrahedron Lett.* **1979**, 995, 2179.

(3) For reviews, see: Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18* 239. Grobel, B. T.; Seebach, D. *Synthesis* (*Washington, DC*) **1977**, 357. Lever, O. W., Jr. Tetrahedron **1976**, *32*, 1943.

(4) Smallcombe, S. H.; Caserio, M. C. *J. Am. Chem. Soc.* **1971**, *93*, 5826. Helmkamp, G. K.; Cassey, H. N.; Olsen, B. A.; Pettitii, D. J. *J. Org. Chem.* **1965**, *30*, 933. Meerwein, H.; Zenner, K. F.; Gipp, R. *Justus Liebigs Ann. Chem.* **1965**, *688*, 67.

(5) For a study of simple thioketals with this reagent, including an unsuccessful attempt to develop a mild hydrolysis procedure, see: Kim, J. K.; Paw, J. K.; Caserio, M. C. *J. Org. Chem.* **1979**, *44*, 1544.

(6) Mukaiyama, T.; Narasaka, K. *Chemistry* **1977**, *32*, 576. Witting, G. *Fortschr. Chem. Forsch.* **1976**, *67*, 1. Mukaiyama, T. *Org. React.* in press.

(7) For alkylation and reductive elimination, see: Biellman, J. F.; Ducep, J. B. *Org. React.* in press. For rearrangement to allylic alcohols, see: Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147. For rearrangement to allylic amines, see: Kakimoto, M.; Yamamoto, T.; Okawara, M. *Tetrahedron Lett.* **1979**, 623.

(8) This compound has been fully characterized by spectral analysis and for elemental composition by combustion analysis and/or high-resoltuion mass spectroscopy.

(9) The rearrangement of **3** to **4** is presumably initiated by **1**. Reaction of **2b**, $R^1 = C_2H_5$, with **1** leads to **4** where $R^1 = C_2H_5$ and CH_3 in a 1:1 ratio. For reactions of **1** and allyl sulfides, see: Kim, J. K.; Kline, M. L.; Caserio, M. C. *J. Am. Chem. Soc.* **1978**, *100*, 6243.

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