Stability of 2,4,6-Tri-*tert*-butylphenol in Acetic Acid. Sodium bismuthate (33.0 g, 0.118 mol) was added to a solution of III (8.73 g, 0.033 mol) in 50 ml of benzene. The mixture was stirred for 6 h at room temperature under nitrogen. The mixture was filtered rapidly. The dark blue filtrate was mixed with 100 ml of glacial acetic acid and kept under nitrogen for 2 weeks. The color persisted until the nitrogen supply was exhausted.

Stability of Hydroxycyclohexadienone IX in Acetic Acid. Compound IX was prepared from 2,4,6-tri-*tert*-butyl-4-nitrocyclohexadien-2,5-one[9] by the method of Müller and Ley.[10] In 5 ml of glacial acetic acid was dissolved 0.330 g of IX. The solution was kept at room temperature for 3 days. The solution was poured into 75 ml of water. The precipitate was filtered, dried, and weighed at 0.294 g (89%) and found to be identical with the starting material by an infrared spectrum and mixture melting point determination.

Registry No.—I, 7218-21-5; II, 4906-22-3; III, 732-26-3; IV, 2525-39-5; V, 20778-61-4; VI, 20778-58-9; VII, 1975-14-0; VIII, 719-22-2; IX, 4971-61-3; sodium bismuthate, 12125-43-8; 2,6-xylenol, 576-26-1; 2,4,6-tri-*tert*-butyl-4-nitrocyclohexadien-2,5-one, 1665-87-8.

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A Two-Step Synthesis of (*E*)-4-Chloro-2-methylcrotonaldehyde from Isoprene. An Unprecedented Oxidative Chlorination of a 1,3-Diene Monoepoxide by Cupric Chloride

Giancarlo Eletti-Bianchi, Felice Centini, and Luciano Re*

Snamprogetti S.p.A., L.P.M., 00015 Monterotondo (Rome), Italy

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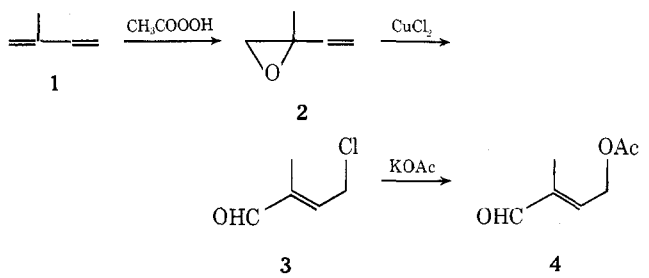
A key intermediate in the Pommer industrial synthesis of vitamin A acetate from β-ionone is (*E*)-4-acetoxy-2-methylcrotonaldehyde (**4**).[1] However, the known syntheses of the latter derivative are multistep and/or low-yield procedures.[1-4]

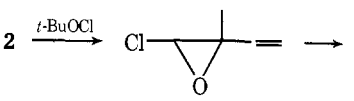
The scope of the present paper is to report a more efficient route to **4** involving epoxidation of isoprene (**1**) with peracetic acid to 3,4-epoxy-3-methyl-1-butene (**2**) followed by oxidative chlorination of the latter with cupric chloride to afford (*E*)-4-chloro-2-methylcrotonaldehyde (**3**), a known direct precursor of **4**.[2]



1 2 3 4

Although the peracetic acid epoxidation of **1** to **2** has been already described, the yield claimed is only 42%.[5] By using a modified procedure, i.e., carrying out the reaction at about 5 °C in chloroform solution in the presence of sodium bicarbonate (to neutralize the acetic acid formed which otherwise gave side reactions with **2**),[6] we could, however, increase the yield of **2** to 80% (VPC analysis of the reaction mixture). Furthermore, the resulting reaction mixture, containing also some residual **1** (87% conversion[7]), could be used, after filtration from the salts, directly for the reaction with cupric chloride.

In preliminary attempts to convert **2** to useful precursors of **4** we speculated that **2**, by free-radical reaction with *tert*-butyl hypochlorite, could give 4-chloro-3,4-epoxy-3-methyl-1-butene (**5**)[8] and that the latter, by rearrangement (possibly in situ),[9] could afford either **3** or its *Z* stereoisomer (**6**) or the constitutional isomer 2-chloro-2-methyl-3-butenal (**7**).



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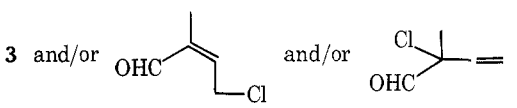
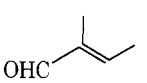


6 7

In fact, after gas-phase reaction[10] over alumina of an equimolar mixture of **2**[11] and *tert*-butyl hypochlorite (added dropwise, from the top, to a heated (125 °C) column charged with alumina pellets, using nitrogen as carrier gas and collecting the product at the bottom of the column in a liquid air cooled trap), VPC analysis of the reaction mixture revealed formation of a product (37% yield) with the same retention time as **3**. The same analysis revealed also formation of a product (37% yield) with retention time as for (*E*)-2-methylcrotonaldehyde (**8**). Structures **3** and **8** for

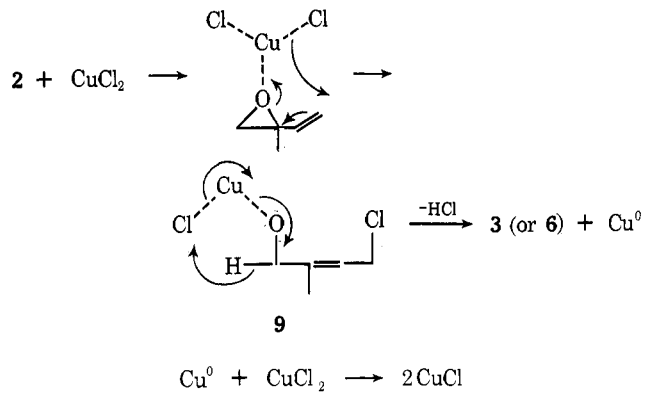


8

these two products were confirmed by the NMR and ir spectra and the boiling points of the compounds isolated, in low yields, by fractionation. Derivative **8**, the rearrangement product of **2**, was obtained in quantitative yields when the gas-phase reaction of **2** over alumina was carried out in the absence of the hypochlorite. On the other hand, when **8** was treated with the hypochlorite under the conditions used for **2**, no **3** was produced, supporting the intermediate formation of **5**, rather than **8**, in the reaction of **2** with the hypochlorite to give **3**.

Although it is known that by oxidative chlorination with cupric chloride **8** can be converted to **3** in moderate yields,[4] we thought that a more direct and possibly more efficient synthesis of **3** (or **6**) from **2** might be achieved by reaction of **2** itself with cupric chloride. To our knowledge, oxidative halogenation of an epoxide with a cupric halide has no precedent in the literature.[12] We speculated, however, that reaction of **2** with cupric chloride could afford **3** (or **6**), either via rearrangement in situ (cupric chloride acting as a Lewis acid catalyst) of **2** to **8** (or to its *Z* stereoisomer) or via cupric alcoholate **9**.

In fact, when the chloroform solution of **2** obtained from the peracetic acid epoxidation of **1** was treated, after addition of an equal volume of ethyl acetate,[13] with cupric chloride in the presence of lithium chloride,[14] VPC analysis of the organic extracts revealed formation of a major product (80% yield) with the same retention time as **3**. The retention time of the only by-product (20% yield) was as for **8**.



9

$Cu^0 + CuCl_2 \longrightarrow 2CuCl$

Structures 3 and 8 for these two products were confirmed by the NMR and ir spectra and the boiling points of the isolated pure compounds. However, for the acetoxylation[15] step the isolated crude 3 (78% pure, yield corrected for pure 3: 80%) was not distilled since the impurities consisted mainly of residual solvents and the distillation resulted in considerable decomposition of the product (57% yield). The acetoxylation afforded, after removal of low-boiling impurities from the isolated crude product, a 90% yield of 4, which did not require distillation, being already quite pure (95%).

When 2 was treated with cupric chloride in chloroform–ethyl acetate in the absence of lithium chloride the reaction was quite slower (2.5 h instead of 10–15 min), the amount of 8 formed was practically the same (23%), and the purity as well as the yield of the isolated crude 3 were somewhat lower (70% purity, 72% corrected yield). The yield of the distilled 3 was 50%.

By treatment of 8 with cupric chloride in the presence (or absence) of lithium chloride and in chloroform–ethyl acetate solution, using the same reaction conditions as for 2, the starting material was recovered practically unchanged.[16] Therefore, in the oxidative chlorination of 2 to 3 under these conditions the intermediacy of 8 can be excluded and the formation of the latter attributed only to a side reaction.

Finally, when the cuprous and lithium chlorides recovered together from the oxidative chlorination of 2 were submitted to air oxidation in aqueous hydrogen chloride (to regenerate the cupric chloride) and recycled several times, the yields of 3 (and 8) remained unchanged.

In conclusion, peracetic acid epoxidation of 1 followed by cupric chloride oxidative halogenation of the resulting solution and final acetoxylation of the crude 3 represents, on comparison with the previously known syntheses,[1-4] the most efficient route to 4.

Experimental Section

Materials. Isoprene obtained from Fluka (purum a) was purified by distillation over sodium; 82% peracetic acid was prepared according to Swern.[17]

General. Gas chromatography–mass spectrometry analysis was performed with a Varian MAT 111 instrument under the following conditions: 6 ft × 0.125 in. 3% OV-1 on Chromosorb W (80–100 mesh) column, at 40 °C for 3 min then 40 → 180 °C (20 °C/min) and with 24 ml/min of He; ionizing energy, 70 eV. Quantitative VPC analyses were performed with a Hewlett-Packard Model 7620-A gas chromatograph equipped with a thermal conductivity detector. The following columns were employed: (A) 10 ft × 0.125 in. 10% Carbowax 20M on silanized Chromosorb G (60–80 mesh); (B) 6 ft × 0.125 in. 4% SE-30 on silanized Chromosorb G (60–80 mesh). The 60-MHz NMR spectra were recorded on a Varian T-60 spectrometer with tetramethylsilane as internal standard. The following designations were used: s, singlet; dt, doublet of triplets; dq, doublet of quartets; tq, triplet of quartets; qq, quartet of quartets. The ir spectra were taken with a Perkin-Elmer 457 spectrometer.

3,4-Epoxy-3-methyl-1-butene (2). To a solution of 20.4 g (0.30 mol) of 1 in 240 ml of chloroform was added 30.2 g (0.36 mol) of $NaHCO_3$ and a trace of radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol. To the stirred suspension was added dropwise over a 6-h period under ice-bath cooling and N_2 atmosphere 27.8 ml of 82% peracetic acid (corresponding to 0.30 mol of peracid). After an additional 24 h of stirring under the same conditions, the undissolved salts were removed by filtration. Gas chromatography–mass spectrometry analysis of the filtrate confirmed structure 2 for the reaction products on comparing its mass spectrum, *m/e* 84 (9), 83 (14), 69 (16), 55 (98), 53 (42), 43 (96), 41 (22), 39 (100), 29 (61), and 27 (41), to the one of authentic 2 (prepared as cited under ref 11). Quantitative VPC analysis (column A at 70 → 180 °C (30 °C/min) and with 60 ml/min of He, using *n*-octane as internal standard) of the filtrate revealed that 2 was formed in 80% yield and that 13% of the charged 1 was still present in the solution. This solution was used directly for the preparation of 3 by reaction with cupric chloride.

(*E*)-4-Chloro-2-methylcrotonaldehyde (3). To the chloroform solution obtained from the epoxidation of 1 and containing 20.2 g (0.24 mol) of 2 was added 240 ml of ethyl acetate followed by 81.6 g (0.48 mol) of $CuCl_2 \cdot 2H_2O$ and 10.0 g (0.24 mol) of LiCl. The mixture was refluxed (90 °C bath temperature) for about 15 min and then poured onto 240 g of ice. After filtration from the CuCl, the organic phase was separated and the aqueous layer extracted with 240 ml of hexane. The combined organic extracts were washed to neutrality with water and dried (Na_2SO_4). Quantitative VPC analysis (column B at 60 °C for 1 min then 60 → 200 °C (30 °C/min) and with 15 ml/min of He, using *n*-octane as internal standard) of the organic solution revealed formation of 3 and 8 in 80 and 20% yield, respectively. The greater part of the solvents and the aldehyde 8 were then distilled from the organic solution by concentration, first at 10–20 mm and room temperature and finally at 120 mm and 40 °C bath temperature (in both cases the distillation was monitored by VPC to prevent distillation of 3), leaving a residue, 29 g, of crude 3 (78% pure by VPC, the balance to 100% being mainly residual solvents; corresponding to an 80% corrected yield). Distillation of the crude product gave 16.2 g (57%) of 95% pure (VPC) 3: bp 39–42 °C (0.5 mm) [lit.[18] 41–43 °C (0.5 mm)]; NMR ($CDCl_3$) τ 0.57 (s, CHO), 3.43 (tq, J = 6.5 and 1.5 Hz, C=CH), 5.67 (dq, J = 6.5 and 1 Hz, CH_2Cl), 8.23 (dt, J = 1.5 and 1 Hz, CH_3); ir (film) 2710, 1685, 1645 cm^{-1}.

When the distillates obtained in the isolation of the crude 3 (see above) from a few runs were combined and concentrated first at atmospheric pressure and 85 °C bath temperature (until incipient distillation of 8, VPC monitoring) and then at 40 mm and 0 °C (to a 1:1 mixture of 8 and ethyl acetate, VPC monitoring), and the residue distilled at atmospheric pressure, some pure 8 could be obtained: bp 116–117 °C (lit.[19] 116.2 °C); NMR and ir spectra identical with the ones reported in literature for 8.[20,21]

When the oxidative chlorination with $CuCl_2 \cdot 2H_2O$ of the chloroform solution of 2 was repeated in the absence of LiCl, 3 and 8 were formed, after 2.5 h reflux, in 72 and 23% yields, respectively (quantitative VPC analysis of the organic extracts). The yields of the isolated, 70% pure, 3 amounted to 72% (corrected for pure 3) and the one of distilled, 95% pure, 3 to 50%.

Acetoxylation of 11.85 g of the 78% pure 3 (corresponding to 0.078 mol of 3) dissolved in 100 ml of anhydrous ethanol was carried out with 8.42 g (0.086 mol) of potassium acetate keeping the mixture at reflux for 3 h. From the cooled (0 °C) mixture the precipitated KCl was removed by filtration, the filtrate concentrated under vacuum, and the residue taken up in ether in order to dissolve the product from residual KCl. Evaporation of the solvent from the filtered solution gave, after removal of low-boiling impurities at 2–3 mm and room temperature, 10.5 g (90%, based on 0.078 mol of 3) of 4, which did not require distillation, being already quite pure (95% by VPC using column B at 80 → 180 °C (10 °C/min) with 15 ml/min of He and *n*-decane as internal standard). The NMR and ir spectra and the boiling point of the product obtained were identical with the ones reported in the literature for 4.[22]

Acknowledgments. The authors wish to express their thanks to Mr. B. Biancini for his technical assistance in this investigation. Thanks are due to Dr. A. Robertiello for the gas chromatography–mass spectrometry analysis and to Dr. L. Settembri for the NMR spectra.

Registry No.—1, 78-79-5; 2, 1838-94-4; 3, 26394-25-2; 8, 497-03-0; $CuCl_2$, 7447-39-4.

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(6) For epoxidations with peracetic acid in the presence of bases see M. Korach, D. R. Nielsen, and W. H. Rideout, *J. Am. Chem. Soc.*, **82**, 4328 (1960).
(7) Use of excess peracetic acid in order to complete the conversion of **1** resulted in lower yields of **2**.
(8) Ethylene and propylene oxides give the corresponding chloro epoxides by liquid-phase photochlorination with *tert*-butyl hypochlorite; see C. Walling and P. S. Fredricks, *J. Am. Chem. Soc.*, **84**, 3326 (1962).
(9) For related rearrangements of chloro epoxides see H. O. House, "Modern Synthetic Reactions", 2d ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 313–314.
(10) Liquid-phase photochlorination of **2** with *tert*-butyl hypochlorite under various conditions was unsuccessful.
(11) For these experiments, because of difficulties in isolating the product from the solvent in the peracetic acid epoxidation of **1**, pure **2** was best prepared according to E. J. Reist, I. G. Junga, and B. R. Baker, *J. Org. Chem.*, **25**, 1673 (1960); the only modification being that the dehydrobromination was performed by treatment of the distilled isoprene bromohydrin (bp 60 °C, 10 mm) with solid sodium hydroxide at 90 °C and atmospheric pressure in a distillation flask equiped with a Vigreux fractionating column. Sodium sulfate drying of the distillate (bp 72–73 °C) afforded pure **2**.
(12) For a review on oxidative halogenations with cupric halides see W. G. Nigh in "Oxidation in Organic Chemistry", Vol. 5, Part B, W. S. Trahanovsky, Ed., Academic Press, New York, N.Y., 1973, pp 67–84.
(13) For the successful use of the chloroform–ethyl acetate solvent system in oxidative halogenations of carbonyl compounds with a cupric halide see literature cited under ref 12. The use of other solvents in the cupric chloride halogenation of **2**[11] gave less satisfactory results.
(14) Lithium chloride is a catalyst of oxidative halogenations of carbonyl compounds with cupric chloride; see literature cited under ref 12.
(15) For the acetoxylation of **3** to **4**, a procedure (see Experimental Section) different from the one cited under ref 2 gave more satisfactory results.
(16) The reaction conditions, especially with regard to solvents, used by the authors cited in ref 4 for the conversion of **8** to **3** with cupric chloride were quite different.
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Hydroxyl Assisted Epoxide Opening in Picrotoxins

Haldean C. Dalzell, Raj K. Razdan,* and Reuben Sawdaye

Sheehan Institute for Research, Inc., Cambridge, Massachusetts 02138

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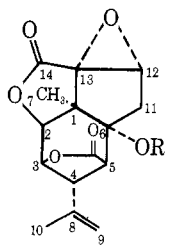
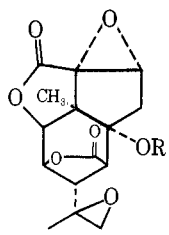
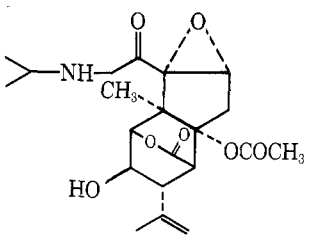
It is well documented that picrotoxinin (**1a**) is the potent analeptic component of picrotoxin.[1] In order to modify the analeptic properties of **1a**, we were interested in the introduction of a basic nitrogen moiety in the picrotoxinin molecule. Picrotoxinin possesses an epoxide ring which should theoretically be opened with amines or other nucleophiles, but is known to be very resistant to intermolecular nucleophilic attack. This unusual feature of the picrotoxinin structure is explained on the basis of shielding of the epoxide ring from rearward attack by the lactone groupings. However, the close proximity of the axial C-6 α-hydroxyl group to the C-4 α-isopropenyl group in **1** suggested to us that the 8,9-epoxide of picrotoxinin (i.e., **2a**) would be prone to nucleophilic attack due to participation by the C-6 hydroxyl group in oxirane ring opening. Indeed, this was found to be the case since epoxidation of **1a** with *m*-chloroperbenzoic acid in methylene chloride followed by aqueous work-up resulted in a mixture of the desired epoxide **2a** and the glycol **4d**. It is interesting to note that previous workers have reported similar problems in the synthesis of this epoxide.[2] In contrast, no difficulty was experienced in the epoxidation of picrotoxinin 6-acetate (**1b**) to give **2b** by the same procedure. Hence picrotoxinin epoxide (**2a**) appears to be much more reactive than **2b**. Because of this reactivity the epoxide **2a** was not isolated in pure form but was used, after a modified work-up procedure, directly in subsequent reactions with amines. On treatment of **2a** with pyrrolidine or diethylamine at room temperature, the corresponding amine derivatives **4a** and **4b** were obtained whereas chloroform reflux conditions were required to obtain **4c** from **2b** with diethylamine.



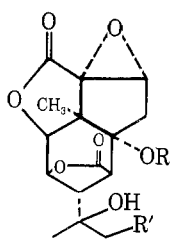
1a, R = H (picrotoxinin)
b, R = $COCH_3$



2a, R = H
b, R = $COCH_3$



3



4a, R = H; R′ = N⟨ ⟩
b, R = H; R′ = $N(C_2H_5)_2$
c, R = $COCH_3$; R′ = $N(C_2H_5)_2$
d, R = H; R′ = OH
e, R = H; R′ = H (picrotin)

The ease of opening of the epoxide in **2a** with amines to yield compounds of type **4** can be ascribed to the neighboring 6-hydroxyl group participation in an "anionic" process. Only a few examples of such participation are known such as the neighboring hydroxy group participation in the alkaline hydrolysis of esters[3–5] and more recently the opening of epoxides by nucleophiles in steroids.[6] Neighboring group participation in "cationic" reactions, on the other hand, has been known for many years and is well understood.[3,7,8]

The structural assignment of these compounds (**4a–c**) seems secure on the basis of spectral data. The NMR spectra of **4a** and **4b** are compared in Table I with those of picrotoxinin (**1a**) and picrotin (**4e**). The NMR spectra of the latter two important compounds have apparently not been reported previously. Infrared spectra of the amines show that the lactone groupings are maintained in the picrotoxinin epoxide molecule during reaction with amines. The mass spectrum of **4a** showed principal ions at *m/e* 380 $(M + 1)^+$, 379 $(M^{\cdot+})$, 280, 128, and 84 (base). The base peak at *m/e* 84 and the peak at *m/e* 128 correspond to the ions i and ii, respectively, both of which confirm the presence and