Registry No. 1 (R = H; R′ = Ph), 140-29-4; 1 (R = H; R′ = *n*-Bu), 628-73-9; 1 (R = R′ = Me), 78-82-0; 1 (R = R′ = $(CH_2)_4$), 4254-02-8; 2 (R = H; R′ = Ph; R″ = *n*-Bu), 73083-29-1; 2 (R = H; R′ = Ph; R″ = *n*-Bu) 2,4-DNP, 79792-46-4; 2 (R = H; R′ = Ph; R″ = Me), 93-53-8; 2 (R = H; R′ = Ph; R″ = Me) 2,4-DNP, 5530-36-9; 2 (R = H; R′ = *n*-Bu; R″ = *n*-C_5H_{11}), 998-62-9; 2 (R = H; R′ = *n*-Bu; R″ = *n*-C_5H_{11}) 2,4-DNP, 1243-29-4; 2 (R = H; R′ = *n*-Bu; R″ = $CH_2CH{=}CH_2$), 4456-87-5; 2 (R = H; R′ = *n*-Bu; R″ = $CH_2CH{=}CH_2$) 2,4-DNP, 30479-98-2; 2 (R = H; R′ = *n*-Bu; R″ = Me), 925-54-2; 2 (R = H; R′ = *n*-Bu; R″ = Me) 2,4-DNP, 23546-53-4; 2 (R = H; R′ = *n*-Bu; R″ = Me) semicarbazone, 1070-43-5; 2 (R = H; R′ = *n*-Bu; R″ = *i*-Pr), 79769-78-1; 2 (R = H; R′ = *n*-Bu; R″ = *i*-Pr) 2,4-DNP, 79769-79-2.

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Received September 2, 1981

A Total Synthesis of Racemic Senepoxide: Formal Syntheses of Crotepoxide and Pipoxide

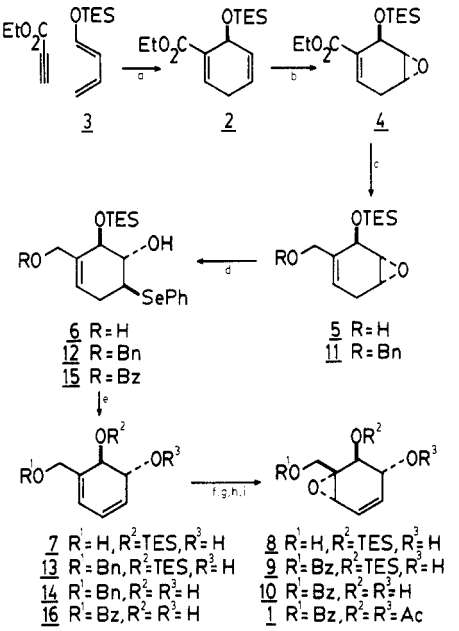
Summary: Diels–Alder reaction of 1-(triethylsiloxy)-buta-1,3-diene with ethyl propiolate affords an excellent yield of the dihydrobenzene adduct **2** which has been transformed into senepoxide. Formal syntheses of crotepoxide and pipoxide also have been carried out from **2**.

Sir: Senepoxide (**1**),[1] crotepoxide,[2] and pipoxide[3] belong to a small group of naturally occurring oxygenated cyclohexane derivatives. Our interest in these title substances arose from the realization that syntheses of them could be forthcoming from the dihydrobenzene derivative **2**. The ready tendency of substances like **2** to undergo thermal aromatization notwithstanding,[4] we report here the preparation of **2** using the Diels–Alder format. We also report the conversion of this adduct into the natural product **1**, as well as into synthetic intermediates which constitute formal syntheses of crotepoxide and pipoxide.[5]

Following the procedure used by Mukaiyama for the synthesis of 1-(trimethylsiloxy)buta-1,3-diene, we prepared the triethylsilyl analogue **3** (bp 120–125 °C).[6] Reaction of **3** with ethyl propiolate (1.1 equiv to 1.0 equiv, respectively; as a neat mixture to which had been added a crystal of methylene blue and then subjected to three freeze–thaw cycles at 10^{-6} torr and sealed under vacuum) at 80 °C for 120 h gave, after removal of the volatiles, crude **2** as a yellow oil in 87% yield (Scheme I). The structure of **2** followed from its ^1H spectrum recorded at 400 MHz.[7] This spectrum also indicated **2** to be 90% pure and as such its was used for all further reactions.[8]

In order to prepare senepoxide from **2**, we first monoepoxidized the diene using 95% *m*-chloroperbenzoic acid (*m*-CPBA) buffered with sodium bicarbonate in benzene solution to obtain the epoxide **4** contaminated with a small amount of its β isomer. This substance was then reduced with diisopropylaluminium hydride to give the corresponding allylic alcohol **5** which could be readily separated

Scheme I[a]



[a] (a) Compound **3** 1.1 equiv, ethyl propiolate 1.0 equiv, neat mixture, 10 mg of methylene blue, three freeze–thaw cycles at 10^{-6} torr, sealed under vacuum, 80 °C for 120 h, volatiles removed under vacuum. (b) Compound **2** 1.0 equiv, $NaHCO_3$ 3.1 equiv, *m*-CPBA 2.0 equiv, benzene (0.35 M), 22 °C, 48 h, standard workup. (c) Compound **4** 1.0 equiv, 0.1 M hexane, diisobutylaluminum hydride 2.1 equiv in hexane, −78 °C, 30 min, 0 °C quench with 2-propanol, standard workup. (d) Compound **5** 1.0 equiv, PhSeNa 2.0 equiv, EtOH 0.4 M, 80 °C, 3 h, standard workup, melting point of **6** 61–62 °C. (e) Compound **6** 1.0 equiv, CH_2Cl_2 0.1 M, $NaHCO_3$ 2.0 equiv, −78 °C, dropwise addition of *m*-CPBA 1.0 equiv in CH_2Cl_2 0.3 M, slowly warmed to 22 °C, stirred 8 h, standard workup. (f) Compound **7** 1.0 equiv, 0.1 M in CH_2Cl_2, −40 °C, *m*-CPBA 1.1 equiv in CH_2Cl_2 0.3 M added dropwise, −40 °C for 30 min, 0 °C for 30 min, standard workup. (g) Compound **8** 1.0 equiv, 0.04 M CH_2Cl_2, Et_3N 6 equiv, BzCl 3.0 equiv, −40 °C for 2 h, standard workup. (h) Compound **9** 1.0 equiv, MeOH 0.2 M at 0 °C add one drop of 5% HCl, 15 min at 0 °C standard workup. (i) Compound **10** 1.0 equiv, 0.5 M in C_5H_5N, 0 °C, Ac_2O 6.5 equiv, 10 mg of DMAP, warm to 22 °C, 15 min, filtration chromatography, white solid mp 97–98 °C.

(1) For the isolation of senepoxide, see Hollands, R.; Becker, D.; Gaudemar, A.; Polonsky, J. *Tetrahedron* **1968**, *24*, 1633. The X-ray structure of senepoxide has been determined by Ducruix, A.; Pascard, C.; Polonsky, J. *Acta Crystallogr., Sect. B* **1976**, *32*, 1589.

(2) For the isolation of crotepoxide, see (a) Kupchan, S. M.; Hemingway, R. J.; Coggon, P.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1968**, *90*, 2982. (b) Kupchan, S. M.; Hemingway, R. J.; Smith, R. M. *J. Org. Chem.* **1969**, *34*, 3898. (c) Takahashi, S. *Phytochemistry* **1969**, *8*, 321. For a description of the X-ray structure of crotepoxide, see Coggon, P.; McPhail, A. T.; Sim, G. A. *J. Chem. Soc. B* **1969**, 534.

(3) For the isolation and publication of the incorrect structure of pipoxide, see Singh, J.; Dhar, K. L.; Atal, C. K. *Tetrahedron* **1970**, *26*, 4403. For the correct structure of pipoxide as well as its synthesis, see Holbert, G. W.; Ganem, B.; Van Egen, D.; Clardy, J.; Borsub, K.; Chantrapromma, K.; Sadavongvivad, C.; Thebtaranonth, Y. *Tetrahedron Lett.* **1979**, 715. (b) Joshi, B. S.; Gawd, D. H.; Fuhrer, H. *Ibid.* **1979**, 2427.

(4) For a recent experimental description of this type of phenomenon, see Wolinsky, J.; Login, R. B. *J. Org. Chem.* **1970**, *35*, 3205.

(5) For syntheses of senepoxide, see (a) Ichihara, A.; Oda, K.; Kobayashi, M.; Sakamura, S. *Tetrahedron Lett.* **1974**, 4235. (b) Holbert, G. W.; Ganem, B. *J. Am. Chem. Soc.* **1978**, *100*, 352. (c) Ganem, B.; Holbert, G. W.; Weiss, L. B.; Ishizumi, K.; *Ibid.* **1978**, *100*, 6438. (d) Ganem, B. *Tetrahedron* **1978**, *34*, 3353. (e) Ichihara, A.; Oda, K.; Kobayashi, M.; Sakamura, S. *Tetrahedron* **1980**, *36*, 183. For syntheses crotepoxide, see (a) Oda, K.; Ichihara, A.; Sakamura, S. *Tetrahedron Lett.* **1975**, 3187. (b) Demuth, M. R.; Garrett, P. E.; White, J. D. *J. Am. Chem. Soc.* **1976**, *98*, 634. (c) Matsumoto, M.; Dobashi, S.; Kuroda, K. *Tetrahedron Lett.* **1977**, 3361. For the synthesis of pipoxide, see reference 3a.

(6) Ishida, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1161.

(7) We thank the National Science Foundation for funds that helped purchase the Bruker WH-400 spectrometer.

(8) Compound **2** could be purified only with great difficulty; however, this substance could be stored at −20 °C in the 90% pure state for long periods without decomposition.

0022-3263/81/1946-5252$01.25/0

from its β isomer by filtration chromatography.[9] Compound **5** was obtained from **2** in 85% overall yield. We next faced regiospecific ring opening of the epoxide residue in **5** which was accomplished by reaction of the epoxide with 2 equiv of sodium phenyl selenide in ethanol at 80 °C for 3 h—a process affording **6** in 82% yield from **5**.[10] Sodium bicarbonate buffered 95% *m*-CPBA oxidation of **6** in dilute methylene chloride solution at −78 °C followed by warming to 22 °C gave a 95% yield of the corresponding diene **7**. Submission of this material to further oxidation with 95% *m*-CPBA in methylene chloride at −40 °C selectively gave the epoxide **8** in 77% yield. Esterification of the primary alcohol present in **8** was accomplished with benzoyl chloride in methylene chloride at −40 °C in the presence of triethylamine to give an 85% yield of **9**. This substance was desilylated at 0 °C in methanol with 5% HCl, and the resulting diol **10** then reacted with acetic anhydride in pyridine to give after chromatography pure senepoxide (**1**), mp 97–98 °C in 83% yield from **9**. Senepoxide prepared in this manner agreed in all respects to both spectra and a sample of racemic **1** kindly provided by Professor B. Ganem.[11]

To complete a formal total synthesis of crotepoxide, we treated compound **5** as its lithium alkoxide salt with benzyl bromide and HMPA at −78 °C to obtain in 67% yield compound **11**. Treatment of **11** with 2 equiv of sodium phenyl selenide gave the ring-opened substance **12** (80% yield) which on oxidative-elimination with 95% *m*-CPBA afforded the diene **13** in 87% yield. Desilylation of **13** in methanol with 5% HCl gave the diene-diol **14** in essentially quantitative yield. This material proved identical in all respects with both a sample and spectra of this compound kindly provided by Professor J. D. White, who has reported the conversion of **14** into crotepoxide.[12]

Lastly, we carried out a formal synthesis of pipoxide by reacting compound **6** with benzoyl chloride in methylene chloride containing triethylamine at 22 °C to obtain **15** in 95% yield. Treatment of **15** with 95% *m*-CPBA resulted in the formation of the corresponding diene which was then desilylated in methanol with 5% HCl to give **16** in 78% yield from **15**. Compound **16** proved identical with both sample and spectra kindly provided by Professor B. Ganem, who has converted **16** into pipoxide.[11]

(9) All new compounds gave satisfactory spectral and physical data.
(10) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.
(11) We thank Professor B. Ganem for a sample of senepoxide as well as spectra of it. We also thank Professor Ganem for a sample and spectra of compound **16**.
(12) We thank Professor J. D. White for a sample and spectra of compound **14**.

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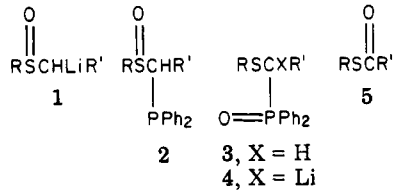
Thiol Esters from Sulfoxides via Rearrangement of Sulfoxide Phosphines to Sulfide Phosphine Oxides

Summary: Treatment of α-lithio sulfoxides with (1) $ClP(C_6H_5)_2$ and (2) I_2 (isolate sulfide phosphine oxide **3**) followed by (3) C_4H_9Li and (4) O_2 affords thiol esters.

Sir: The Pummerer oxidation converts sulfoxide α-carbon into the aldehyde or ketone oxidation state. However, there is no generally applicable method known for further oxidation to give carboxylic acid derivatives.[1] We report a method for conversion of sulfoxides into thiol esters that are versatile carboxylic acid equivalents. This technique depends on the observation that sulfoxide phosphines **2** rearrange readily to the isomeric sulfide phosphine oxides **3**. The latter can be oxygenated via the α-lithio derivatives **4** to give the thiol esters **5**.



Thiol esters have not previously been made by Horner–Bestmann oxygenation[2] of anions similar to **4** although other carbonyl compounds have been prepared from diphenylphosphine oxide or phosphonate anions.[3] Best results are obtained by bubbling oxygen into a THF solution of cold anion at individually optimized temperatures until the yellow-orange anion color fades. The readily available **4**[4] with R = CH_3 and R′ = $CH_2CH_2C_6H_5$ affords the thiol ester in 79% yield (93% based on recovered **3**) when oxygenation is performed at −100 °C.[5,6] This optimized procedure is generally effective when R = alkyl, but aryl sulfoxide anions (**4**, R = C_6H_5, R′ = alkyl) are less reactive and oxygenation at −44 °C is usually required.

The desired overall conversion of sulfoxides to thiol esters can now be achieved by combining the oxygenation process with a unique and effective method for introducing phosphorus at the correct oxidation state, **1** → **3**. Typical α-lithio sulfoxides react rapidly with $ClP(C_6H_5)_2$ to give sensitive sulfoxide phosphines **2** at −78 °C. The latter are reasonably stable when pure,[7] but rearrangement to **3** occurs slowly in the crude product at 20 °C (variable yield) or, more efficiently, in the presence of iodine at 0–20 °C.[8]

(1) Pummerer oxidation to orthoformic acid derivatives is a special case which succeeds because elimination pathways are not available to the Pummerer intermediate; Dinizo, S. E.; Watt, D. S. *Synthesis* **1977**, 181.
(2) Horner, L.; Hoffmann, H.; Klahre, G.; Toscano, V. G.; Ertel, H. *Chem. Ber.* **1961**, *94*, 1987. Bestmann, H. J. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 830.
(3) Davidson, A. H.; Warren, S. *J. Chem. Soc., Chem. Commun.* **1975**, 148. Zimmer, H.; Koenigkramer, R. E.; Cepulis, R. L.; Nene, D. M. *J. Org. Chem.* **1980**, *45*, 2019.
(4) Preparation: $Ph_2PLi + Br(CH_2)_3Ph \rightarrow Ph_2P(CH_2)_3Ph$; $H_2O_2 \rightarrow Ph_2PO(CH_2)_3Ph$; $LDA/CH_3SSCH_3 \rightarrow$ **4**; mp 139–142 °C.
(5) The intermediate oxygenation product fragments very rapidly to thiol ester at −78 °C according to quenching experiments. No peroxidic products have been detected.
(6) *CAUTION*: Oxygenation of THF solutions is inherently dangerous; the exit gases should be diluted with N_2 to minimize risks, and a good safety shield should be used.
(7) Isolation of sulfoxide phosphines **2** is possible by rapid chromatography or by crystallization but is not recommended due to losses induced by decomposition. The isomers **2** and **3** are most easily distinguished by systematic differences in the HCP coupling constant. Coupling is small in **2** (<4 Hz) and large in **3** (>7 Hz). Typical examples: **2** (R = *t*-C_4H_9, R′ = *i*-C_3H_7), mp 95–97 °C dec; δ(PCH) 2.88 (br s, J_{PH} < 2 Hz); **3** (R = *t*-C_4H_9, R′ = *i*-C_3H_7), sublimes without melting, 130 °C, δ(POCH) 3.04 (dd, J_{PH} = 13.6 Hz, J_{HH} = 2.6 Hz); **2** (R = *t*-C_4H_9, R′ = *n*-C_3H_7), mp 113–115 °C dec, δ(PCH) 3.0 (dt, J_{PH} = 4 Hz, J_{HH} = 7 Hz); **3** (R = *t*-C_4H_9, R′ = *n*-C_3H_7) mp 151–152.5 °C, δ(POCH) 3.02 (ddd, J_{PH} = 15.1 Hz, J_{HH} = 8.8, 4.0 Hz); **2** (R = C_6H_5, R′ = CH_3), oil after chromatography, TLC R_f 0.5 on silica gel (ether), δ(PCH) 2.88 (dq, J_{PH} = 1.5 Hz, J_{HH} = 7.0 Hz, q); **3** (R = C_6H_5, R′ = CH_3), mp 153–156 °C (lit.[8] mp 154–156 °C), δ(POCH) 2.79 (dq, J_{PH} = 9.2 Hz, J_{HH} = 7.4 Hz) (NMR spectra in $CDCl_3$; satisfactory elemental composition for all compounds).
(8) Representative procedure for conversion of sulfoxides into **3**: A solution of sulfoxide (5 mmol) in dry THF (10 mL or more if needed to dissolve anion) was cooled to −78 °C and alkyllithium (5.5 mmol) was added dropwise. After 30 min, the solution was added by cannula over 1–2 min to $ClP(C_6H_5)_2$ (5.5 mmol) in THF (5 mL) at −78 °C, with a N_2 atmosphere throughout. After 5 min, the mixture was warmed to 0 °C

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