allyl methyl systems, regardless of either the initial reactant ratio or the identity of the system originating as disulfide. Moreover, when an excess of disulfide is employed, higher disulfide/sulfide ratios are obtained for the system originating as the monosulfide than are possible from direct sulfurization with elemental sulfur, suggesting that S_8 is not an intermediate in the sulfur transfer reaction.

The above considerations suggest that nonallylic thioethers such as diethyl sulfide also react with elemental sulfur to a slight extent, and that the corresponding thiosulfoxides may thus be directly accessible, albeit in low concentrations.

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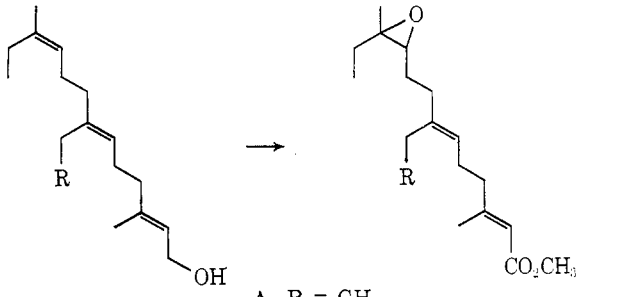
New Thiane Chemistry. The Conceptually Simple and Technically Practical Total Synthesis of *Cecropia* Juvenile Hormones

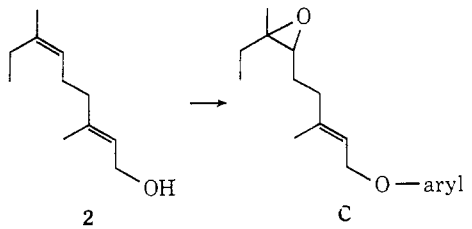
Sir:

In the last several years, much attention has been directed toward the chemistry and synthesis of *Cecropia* juvenile hormones A and B and related physiologically active analogs C. Many of the reported syntheses[1] of A and B describe ingeniously new general approaches to the stereoselective formation of unsymmetrically trisubstituted olefins, but these methods have often involved sequences too long and complicated for efficient construction of the structurally simple, acyclic terpenoids A and B. When the structural requirements of an effective synthesis were simplified even further by Corey's demnstration[1b] that farnesol homologs **1** are excellent precursors to A and B, we became convinced that a simple and effective total synthesis of the juvenile hormones should be demonstrable using a synthetic design specifically tailored to the preparation of trienols **1**. We now wish to report our observations that one such synthetic design makes possible, from *readily available* materials, the short, practical, and high-yield total synthesis of alcohols **1** and **2** and, consequently, of C_{18} and C_{17} *Cecropia* juvenile hormones and a number of active analogs.



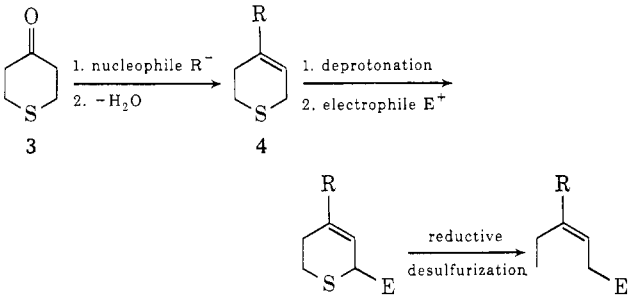
1a, R = CH_3
1b, R = H

A, R = CH_3
C_{18} *Cecropia* juvenile hormone
B, R = H
C_{17} *Cecropia* juvenile hormone



2 C

We chose to rely on a classically well-known method for fixing the geometry of acyclic olefins, that of forming the olefin as part of a ring and subsequently cleaving the ring; we also anticipated using a modification of Biellmann's elegant allylic coupling,[2,2c] involving the alkylation of allyl sulfide carbanions, for assembling the carbon skeleton. As the logical consequence of combining these two synthetic methods, we were led to an approach which would utilize the same sulfur functionality as a ring bridging member (thus allowing predictable double bond geometry) and as a carbanion stabilizing group (thus allowing new carbon–carbon bond formations at predictable sites).[3] Consequently, the readily available and symmetrical 4-thiacyclohexanone **3**[4] served as the precursor to olefin units having a cis ethyl substituent, as represented below.



3 4

In 90% yield, **3** was converted to the known 4-thia-1-methylcyclohexene-1 (**4a**) (R = CH_3)[5] (methylmagnesium chloride in ether followed by dehydration with $POCl_3$ in pyridine–benzene). Ketone **3** was also converted in greater than 75% yield to the crystalline epoxide **5**, mp 49–50°,[6] using dimethylsulfoxonium methylide[7] (in Me_2SO at room temperature[7b] for 3 hr);

(1) (a) For an extensive bibliography of syntheses of C-18 and C-17 juvenile hormones see C. A. Henrick, F. Schaub, and J. B. Siddall, *J. Amer. Chem. Soc.*, **94**, 5374 (1972); R. T. Anderson, C. A. Henrick, J. B. Siddall, and R. Zurfluh, *ibid.*, **94**, 5379 (1972); (b) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *J. Amer. Chem. Soc.*, **90**, 5618 (1968); E. J. Corey and H. Yamamoto, *J. Amer. Chem. Soc.*, **92**, 6636 (1970).

(2) (a) J. F. Biellmann and J. B. Ducep, *Tetrahedron Lett.*, 5629 (1968); 3707 (1969); *Tetrahedron*, **27**, 5861 (1971). (b) A Biellmann coupling was used in the final steps of a recent synthesis of **1a** by E. E. van Tamelen, P. McCurry, and N. Huber, *Proc. Nat. Acad. Sci. U. S.*, **68**, 1294 (1971).

(2c) NOTE ADDED IN PROOF. A synthetic approach similar to the one we now report has also been described recently by K. Kondo, A. Negishi, K. Matsui, D. Tunemoto, and S. Masamune, *J. Chem. Soc., Chem. Commun.*, 1311 (1972).

(3) A preliminary report of this research was made by the principal investigator at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972, Abstract ORGN-75.

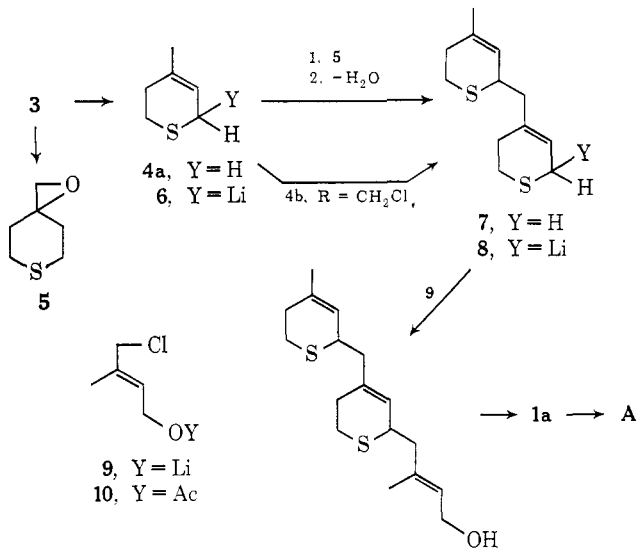
(4) Ketone **3** is derived *via* Dieckmann condensation of dimethyl thiodipropionate (from the commercially available diacid or by bis addition of methyl acrylate to hydrogen sulfide). Reproducibly satisfactory yields of **3** were obtained as reported by E. A. Fehnel and M. Cormack, *J. Amer. Chem. Soc.*, **70**, 1813 (1948).

(5) (a) A modification of the procedure reported by R. F. Naylor, *J. Chem. Soc.*, 2749 (1949). (b) The endocyclic olefin **4a** is contaminated by about 7% exocyclic isomer. This contaminant is inert during the generation and alkylation of the carbanion **6** and is sufficiently volatile to allow easy separation from alkylation products of **4a**.

(6) Satisfactory spectral and physical properties were observed for all new compounds; high-resolution mass spectrometric analyses confirm all structural assignments; satisfactory combustion analyses further confirm structural assignments of crystalline compounds.

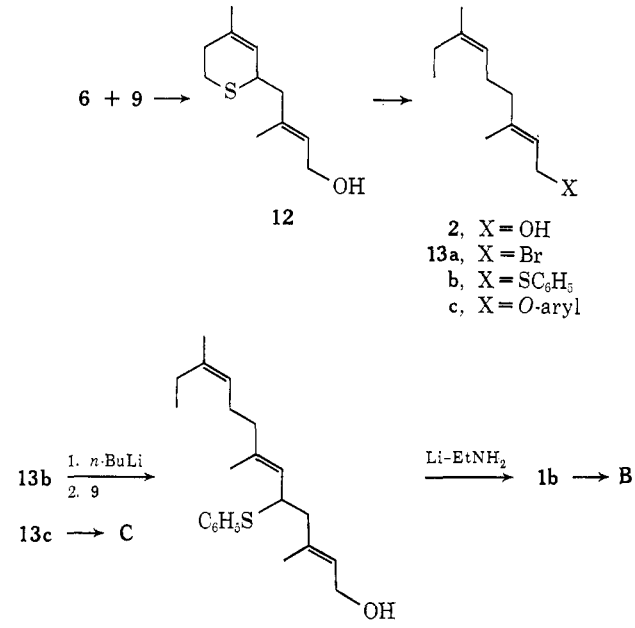
(7) (a) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965). (b) The procedure employed is a modification of ref 7a. Reaction at room temperature was necessary for satisfactory transformation

by a moderate-yield, six-step sequence, **3** could also be converted to 4-thia-1-chloromethylcyclohexene-1 (**4b**) (R = CH_2Cl).[8]



At −50°, *n*-butyllithium (TMEDA–THF)[2] was insufficiently basic to lithiate **4a** (R = CH_3) at any appreciable rate; however, dropwise addition at −50° of 1 equiv of *sec*-butyllithium (hexane) to **4a** (THF contining 1 equiv of TMEDA) quantitatively produced the desired anion **6**.[9] Preliminary studies with a variety of electrophiles showed that this ambident anion undergoes alkylation in almost quantitative yield, primarily α to sulfur.[9] Accordingly, addition of epoxide **5** (THF) to anion **6** (THF at −20°) produced a crude tertiary alcohol[6] which showed appropriate spectral characteristics and which could be directly dehydrated ($POCl_3$ in pyridine–benzene) to diene **7** (90% yield based on **5**). Diene **7** was identical with the major product of alkylation[8,9] of anion **6** by allylic chloride **4b**.[6]

Via a second alkylation, the completed carbon skeleton of **1a** was achieved. The addition of an appropriate C_5 unit to **7** was most effectively carried out at −20° by alkylating anion **8** (from **7**, at −50° in THF containing 3 equiv of TMEDA,[10] using 1 equiv of



sec-butyllithium) with a THF solution of lithium *trans*-4-chloro-3-methyl-2-buten-1-oxide (**9**)[11] (from 2 equiv of methyllithium in THF at low temperature on chloroacetate **10**, derived[12] from isoprene). Trienol **11**[6] was isolated in greater than 90% yield.

To complete the formal synthesis of the C_{18} juvenile hormone A there remained only the conversion of **11** to **1a**, since Corey has already converted **1a** to the natural product. We have found that reproducibly high-yield reductive desulfurizations[13] of 4-thia-1-cyclohexenes can be effected by reduction with excess lithium in ethylamine at −78°,[2] immediately followed by desulfurization using deactivated Raney nickel[13] in refluxing ethanol for 4 hr. Using these conditions, overreduction and double bond isomerization are suppressed. Accordingly, desulfurized[14] trienol **1a** was isolated in 55–70% yield from **11**. It showed appropriate physical and spectral properties and was specifically identified by comparison[15] (glc) with known samples of **1a** and its double bond isomers.[16]

When anion **6** was alkylated with **9**, dienol **12**[6] was isolated in essentially quantitative yield. Direct de-

of **3** to **5**; at elevated temperatures, epoxide **5** was isolated in less than 30% yield.

(8) Ketone **3** → cyanohydrin → α-hydroxy methyl ester → unsaturated ester **4c** (R = CO_2Me). Lithium aluminum hydride reduction of **4c** produced primary allylic alcohol **4d** (R = CH_2OH) in good overall yield from **3**. Thionyl chloride in ether at room temperature converted **4d** to **4b** in moderate yields; however, the product was contaminated with the isomeric secondary allylic chloride (by nmr). This contaminant was recovered unchanged from alkylation of anion **6** using crude **4b** at −20°; diene **7** was isolated in good yield, but contained about 8% of the γ-alkylation isomer (by nmr).

(9) That complete anion formation had occurred was proved by quenching with D_2O, allowing almost quantitative isolation of 3-deuterio-1-methyl-4-thiacyclohexene-1[6] (**4a**) (Y = D) containing a small amount of the γ-deuterated isomer. Using epoxide alkylating agents, no γ-alkylation products were observed by nmr (absence of high-field singlet for quaternary saturated methyl group). With methyl iodide and with several different primary allylic chlorides and bromides, α-alkylated products were produced in good yield, but usually contained varying amounts (3–15%) of γ-alkylation isomers [identified by nmr observation of saturated methyl singlet (δ 1.0–1.1)]. (See also footnote 8.) In contrast, aldehydes and ketones condensed *selectively* at the γ position. Further details concerning this positional selectivity will be described in a forthcoming publication.

(10) To assure effective alkylation of anion **6** or **8** by chloroalkoxide **9**, 3 equiv of TMEDA was necessary, since the method used for generating **9** produces two additional equivalents of lithium ions (as alkoxide counterions).

(11) Attempted alkylations of **6** or **8** using *trans*-4-chloro-3-methyl-2-butenyl 1-acetate (**10**) or esters of *trans*-4-bromo-3-methylbutenoic acid proved unsuccessful.

(12) W. Oroshnik and R. A. Mallory, *J. Amer. Chem. Soc.*, 72, 4608 (1950).

(13) (a) Freshly prepared, highly active Raney nickel was deactivated just prior to use by refluxing in EtOH for 1.5 hr. Unsatisfactory results were obtained from attempts to desulfurize 4-thiacyclohexenes directly with Raney nickel, without first reductively cleaving the allylic carbon–sulfur bond. Raney nickel desulfurizations of lithium mercaptides are apparently superior to desulfurizations of the mercaptans, making isolation of intermediate primary mercaptans unnecessary and perhaps detrimental. Primary mercaptans could, however, be isolated after initial lithium–ethylamine reduction. Their spectral properties were consistent with the structures anticipated.[6] (b) Although in slightly lower yield, lithium–ethylamine reductions of sulfoxides corresponding to thioethers **11** and **12** produced the same mercaptans as were derived from **11** and **12**.

(14) In this two-step desulfurization procedure, protection of the primary allylic hydroxyl was unnecessary.

(15) Known samples of **1a** and its isomers were provided for comparison by Professor Karl Dahm, Institute of Life Science, Texas A&M University.

(16) (a) Less than 5% isomeric trienols were observed. (b) Varying amounts (up to 8%) of 2,3-dihydro-**1a** were produced; however, separation of this material posed no difficulty after oxidation of allylic alcohol **1a** to its α,β-unsaturated ester using the procedure of E. J. Corey, N. W. Gilmann, and B. E. Ganem, *J. Amer. Chem. Soc.*, **90**, 5616 (1968).

sulfurization as described above produced dienol **2** (>70% overall yield from **3**) uncontaminated by over-reduced or isomerized materials.[17] Conversion of **2**, *via* the corresponding allylic bromide, to C_{17} juvenile hormone B or to a number of physiologically active insect juvenile hormone analogs C, can be readily accomplished in satisfactory yields.

Acknowledgments. The authors wish to acknowledge support of this research from the Research Corporation and The University of Texas Research Institute. The principal investigator also wishes to express his personal thanks to Dr. J. F. Biellmann for several most pertinent and informative discussions and to Dr. Karl Dahm and Dr. J. B. Siddall for authentic samples and glc data requisite for final identification of our synthetic alcohols. And, finally, the principal investigator thanks earlier coworkers, Dr. S. A. Roman, Dr. V. M. Kobal, and Mr. L. Cain, for their contributions to related studies of sulfur heterocycles.

(17) A mixture of 2 and its three geometric isomers was provided for comparison (nmr and glc) by Dr. John B. Siddall, Director of Research, Zoecon Corporation.

(18) University of Texas Postdoctoral Fellow, 1972.

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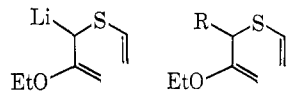
A New Route to γ-Ketoaldehydes. Application to the Synthesis of *cis*-Jasmone

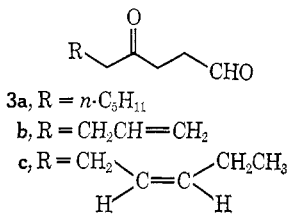
Sir:

The chain extension of alkyl halides by (1-vinylthio)-allyllithium has previously been applied to the simple synthesis of trans γ,δ-unsaturated aldehydes, including the key intermediate for the naturally occurring sex attractant of propylure.[1] It has now been found that this alkylation–thio-Claisen rearrangement process is also highly effective for the formation of γ-ketoaldehydes, an important class of organic substances for which there exists only a limited synthetic methodology.[2]

Addition of *sec*-butyllithium[1] (1.10 equiv in pentane) to the THF solution of 2-ethoxyallyl vinyl sulfide (1.20 equiv), bp 67° (16 mm),[3,4] under nitrogen at −78° produces the straw yellow solution of the anion **1**, which is stable at this temperature. This anion was alkylated immediately at −78° upon the addition of *n*-amyl bromide (1.00 equiv) to produce high yields of the corresponding sulfide **2** (R = n-C_5H_{11}). The crude sulfide thus obtained after extractive work-up is suitable for the thio-Claisen rearrangement, which is carried out by dissolving in DME–water (3:1) and heating at reflux for 12 hr[1] to afford, after preparative layer chromatography (plc) on silica gel, the desired 4-oxodecanal (**3a**)[5] in 66% over-all yield. The complete scheme is therefore a two-step operation requiring no purification of intermediates. In a similar experiment, allyl bromide and 1-bromo-*cis*-2-pentene gave the corresponding γ-ketoaldehyde **3b** (70% over-all yield) and **3c** (56% over-all yield), respectively.



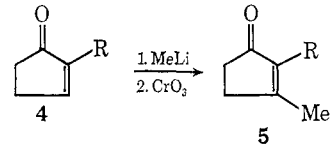
1 **2**



3a, R = n-C_5H_{11}
b, R = $CH_2CH{=}CH_2$
c, R = $CH_2C{=}CCH_2CH_3$ (H, H)

The efficiency of this synthetic process depends in part on the fact that the ethoxyl group in **2** does not interfere with the subsequent thio-Claisen rearrangement step,[6] and moreover the hydrolysis of vinyl ether is achieved after rearrangement.[7]

The anion **1** has been shown to serve effectively as an equivalent of the unknown enolate anion, $LiCH_2C(=O)CH_2CH_2CHO$, and the γ-ketoaldehyde units thus obtained are valuable intermediates for further elaboration into furan, pyrrole, and 2-cyclopentenone derivatives. As an example, we have carried out a simple synthesis of *cis*-jasmone from **3c**. The base catalyzed cyclization of **3c** (10% NaOH in methanol–water (1:1)) at 25° for 2 hr produced the cyclopentenone derivative **4c**[8,9] in 60% yield. Transformation of this cyclopentenone **4c** to *cis*-jasmone (**5c**)[8,10] followed the



4 **5**

a, R = n-C_5H_{11}
b, R = $CH_2CH{=}CH_2$
c, R = $CH_2C{=}CCH_2CH_3$ (H, H)

recorded procedure.[9] By a similar sequence we were able to convert the γ-ketoaldehydes **3a** and **3b** to **4a**[11] (71%) and **4b**[12] (71%), respectively, which in turn were

(1) K. Oshima, H. Takahashi, H. Yamamoto, and H. Nozaki, *J. Amer. Chem. Soc.*, **95**, 2693 (1973).

(2) Recently a variety of new synthetic methods for the preparation of 1,4-diketone has been developed; see (a) G. Stork and R. Borch, *ibid.*, **86**, 935 (1964); (b) G. Büchi and H. Wüest, *J. Org. Chem.*, **31**, 977 (1966); (c) E. J. Corey and L. S. Hegedus, *J. Amer. Chem. Soc.*, **91**, 4926 (1969); (d) E. Wenkert, R. A. Mueller, E. J. Reardon, Jr., S. S. Sathe, D. J. Scharf, and G. Tosi, *ibid.*, **92**, 7428 (1970); (e) J. E. McMurry and J. Melton, *ibid.*, **93**, 5309 (1971); (f) T. Mukaiyama, K. Narasaka, and M. Furusato, *ibid.*, **94**, 8641 (1972).

(3) This sulfide was prepared by the sequence 2-ethoxy-2-propen-1-ol [W. Grell and H. Mchleidt, *Justus Liebigs Ann. Chem.*, **699**, 53 (1966)] → 3-bromo-2-ethoxypropene (*n*-butyllithium–methanesulfonyl chloride–lithium bromide in ether: E. J. Corey, H. Yamamoto, D. K. Herron, and K. Achiwa, *J. Amer. Chem. Soc.*, **92**, 6635 (1970)) → 2-ethoxyallyl vinyl sulfide (lithium ethenethiolate in liquid ammonia: L. Brandsma, P. J. W. Schuijl, *Recl. Trav. Chim. Pays-Bas*, **88**, 513 (1969)) (30% over-all yield after distillation). Nmr (CCl_4, TMS) δ 1.30 (t, 3 H, J = 7.5 Hz), 3.23 (s, 2 H), 3.25 (q, 2 H, J = 7.5 Hz), 3.94 and 4.08 (2 d, 1 H each, J = 2 Hz), 5.08 (d, 1 H, J = 16 Hz), 5.13 (d, 1 H, J = 9 Hz), 6.32 (dd, 1 H, J = 9 and 16 Hz).

(4) All new compounds encountered in this work were characterized spectrometrically and analytically.

(5) Mass *m/e* 170 (M^+); ir (neat) 2735, 1735 (sh, CHO), 1710 cm^{-1} (C=O of ketone); nmr (CCl_4, TMS) δ 9.80 (1 H, CHO); homogeneous by tlc assay (R_f 0.30; SiO_2–CH_2Cl_2).

(6) Recently the Claisen rearrangement of 2-ethoxyallyl ester was reported: R. E. Ireland and R. H. Mueller, *J. Amer. Chem. Soc.*, **94**, 5897 (1972).

(7) α-Vinylthioketone was not detected in the crude reaction mixture after the rearrangement procedure.

(8) Identical in all respects with reported spectrometric data.

(9) (a) G. Büchi and B. Egger, *J. Org. Chem.*, **36**, 2021 (1971); (b) P. A. Grieco, *ibid.*, **37**, 2363 (1972).

(10) For references to other syntheses, see (a) ref 9b; (b) H. C. Ho, T.-L. Ho, and C. M. Wong, *Can. J. Chem.*, **50**, 2718 (1972).

(11) Mass *m/e* 152 (M^+); ir (neat) 1703 (C=O), 1634 cm^{-1} (C=C); nmr (CCl_4, TMS) δ 7.19 (bs, 1 H, olefinic proton); homogeneous by tlc.

(12) Mass *m/e* 122 (M^+); ir (neat) 1700 (C=O), 1640 (C=C), 1000 and 910 cm^{-1} (terminal olefin); nmr (CCl_4, TMS) δ 7.20 (bs, 1 H, olefinic proton); homogeneous by tlc.