**Supplementary Material Available.** The final values for the thermal parameters and the list of $h$, $k$, $l$, $|F_o|$, $|F_c|$, and $\alpha$ will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JACS-74-1205.

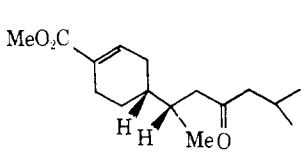
# Communications to the Editor

## Stereospecific Synthesis of *dl*-Juvabione

*Sir:*

We wish to describe in this communication the first stereospecific synthesis of *dl*-juvabione (**1**), a sesquiterpene which shows its juvenile hormone activity selectively on the insects of the Pyrrhocoridoe family. The absolute configuration of the natural enantiomer *d*-juvabione has been established by X-ray analysis[1] as 4(*R*) and 8(*S*), as shown in **1**.

Previous syntheses of juvabione[2] required separation of diastereoisomers, a reflection of the difficulty presented by the fact that one of the two asymmetric centers is in a free-rotating side chain. We have recently reported a method[3,4] which appeared suitable for the solution of this type of problem, since it allows the preparation of the keto acid **2**,[4b] free of its diastereo-

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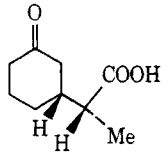
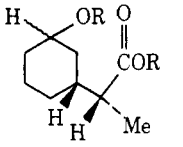



2

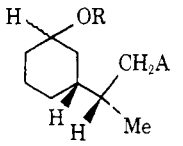
isomer. The application of our method to the synthesis of *dl*-juvabione is especially attractive as it resolves the problem of stereospecific construction at the very beginning of the synthesis.

Various strategies are conceivable for the transformation of the keto acid **2** to *dl*-juvabione (**1**). In the one we describe here, we first elaborate the side chain, and then the unsaturated ester component. To allow eventual differentiation of the ring carbonyl, which will serve to introduce the unsaturated ester function, from that which must be placed in the side chain of juvabione, the keto acid **2**[4b] (mp 76°; nmr[5] ($CDCl_3$) $\delta$ 1.15 ppm (d, 3)) was first reduced catalytically ($PtO_2$–$H_2$, dioxane, 25°, 1 atm, drop of hydrochloric acid) to produce in quantitative yield the hydroxy acid **3a** as a mixture of cyclohexanol epimers (ir (film) 3700–2300 and 1710 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 4.05 ppm (m, 1)); one of the epimers was obtained crystalline, mp 109° (chloroform–hexane). That **3a** is produced as an epimeric mixture is, of course, irrelevant to the overall stereospecificity since the center involved will again become trigonal. The cyclohexanol hydroxyl was, then, protected by reaction with ethyl vinyl ether (ether–HCl), which also esterified the carboxyl function, to give **3b** (bp 120–125° (0.1 mm); ir (film) 1730 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 4.65 (q, 1) and 5.8 ppm (q, 1)), which was then reduced ($LiAlH_4$, ether, reflux) to the alcohol **4a** (bp 90° (0.015 mm); ir (film) 3350 $cm^{-1}$ (broad), nmr ($CCl_4$) $\delta$ 4.65 ppm (q, 1)). The removal of the carboxyl function in the side chain, at this early stage, ensures that no subsequent epimerization of the adjacent center can take place. The stereochemical integrity at this stage was established by Jones oxidation of the glycol **4b** to the starting keto acid **2**.

Elaboration of the ketonic side chain of juvabione was achieved by the use of the Stork–Maldonado ketone synthesis,[6] starting with the bromide **4c** (bp



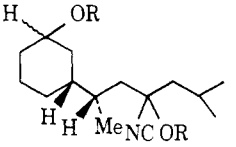

**3a**, R = H
**b**, R = CH(Me)OEt



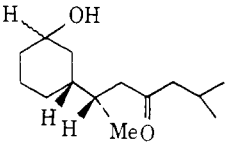

**4**

**4a**, R = CH(Me)OEt; A = OH
**b**, R = H; A = OH
**c**, R = CH(Me)OEt; A = Br

97–98° (0.2 mm); nmr ($CCl_4$) $\delta$ 3.85 (m, 1) and 4.65 ppm (q, 1)) derived from **4a**.[7] The sequence, initiated by reaction of **4c** with 1.5 equiv of the anion of the protected cyanohydrin of isovaleraldehyde, led, in quantitative yield, *via* **5a** and **5b** to the hydroxy ketone **6**: bp 130–135° (0.4 mm); ir (film) 3400 (broad) and 1710 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 4.05 ppm (m, 1).




**5a**, R = CH(Me)OEt
**b**, R = H




**6**

The synthesis of the hydroxy ketone **6**, thus available in 50% overall yield starting from the initial keto acid

(1) J. F. Blount, B. A. Pawson, and G. Saucy, *Chem. Commun.*, 715 (1969).

(2) (a) K. S. Ayyar and G. S. K. Rao, *Tetrahedron Lett.*, **43**, 4677 (1967); *Can. J. Chem.*, **46**, 1467 (1968); (b) K. Mori and M. Matsui, *Tetrahedron*, **24**, 3127 (1968; (c) B. A. Pawson, H. C. Cheung, S. Gurbaxani, and G. Saucy, *Chem. Commun.*, 1057 (1968); *J. Amer. Chem. Soc.*, **92**, 336 (1970); (d) A. J. Birch, P. L. Macdonald and V. H. Powell, *Tetrahedron Lett.*, 351 (1969); *J. Chem. Soc. C*, 1469 (1970); (e) G. Farges and H. Veschambre, private communication.

(3) J. Ficini and A. Krief, *Tetrahedron Lett.*, **18**, 1431 (1969); **17**, 1397 (1970).

(4) (a) J. Ficini and A. M. Touzin, *Tetrahedron Lett.*, **21**, 2093 (1972); (b) *ibid.*, **21**, 2097 (1972).

(5) The nmr spectra of all intermediates are recorded on a Varian T.60 (60 MHz) instrument.

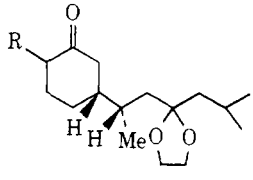
(6) G. Stork and L. Maldonado, *J. Amer. Chem. Soc.*, **93**, 5286 (1971).

(7) The bromide **4c** is prepared from **4a** by the procedure described by J. Hooz and S. S. H. Gilani, *Can. J. Chem.*, **46**, 86 (1968); using $CBr_4$ and $(C_6H_5)_3P$ in ether, with 1 equiv of pyridine, at 0°, then 3 hr at 25°.

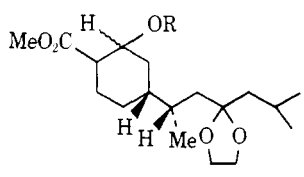
2, completes the construction of the side chain, and we now turn to the introduction of the unsaturated ester function.

Protection of the side-chain carbonyl of **6** by reaction with ethylene glycol (refluxing benzene, 30 hr) followed by chromic acid–pyridine oxidation of the ring hydroxyl led in 80% yield to the ketodioxolane **7a**: bp 130–131° (0.3 mm); ir (film) 1710 $cm^{-1}$; nmr ($C_6D_6$) $\delta$ 3.65 ppm (s, 4).

In that substance, the ring carbonyl is adjacent to, rather than at, the position eventually occupied by the carbomethoxy function of juvabione, thus preserving the chirality of the asymmetric center in the ring, as well as avoiding obvious problems of regiospecificity in the introduction of the double bond. This approach requires, however, that introduction of a suitable function (*cf.* R in formula **7**) take place selectively on the less hindered methylene of **7a**. We expected this to be the case of carbomethoxylation. Indeed, the acylation of **7a** (excess dimethyl carbonate, benzene, 2 equiv of sodium hydride, 60°, under nitrogen) led to the expected $\beta$ keto ester **7b**: ir (film) 1745, 1710, 1660, and 1610 $cm^{-1}$; nmr ($C_6D_6$) $\delta$ 3.5 (s, 3) and 3.65 (s, 4) ppm.



**7a**, R = H
**b**, R = $CO_2Me$



**8a**, R = H
**b**, R = Ts

Introduction of the required double bond was then achieved by initial reduction of **7b** (sodium borohydride, dimethylformamide–methanol, 1 hr, −10°) to give the hydroxy ester **8a** as a mixture of cyclohexanol epimers (ir (film) 3450 (broad) and 1735 $cm^{-1}$) obtained in 60% overall yield from **7a**, after purification by chromatography on neutral silica gel (95:5 benzene–ethyl acetate). There was also formed about 20% of the diols corresponding to the reduction of the ester function of **7b**.

Formation of the double bond is carried out by treatment of the crude tosylate **8b** (ir (film) 1735 $cm^{-1}$) with sodium methoxide in refluxing methanol containing 10% dimethyl sulfoxide. Acid hydrolysis of the dioxolane in the side chain then gave (55% from **8a**) *dl*-juvabione (**1**) (bp 122° (0.01 mm); $n^{24}D$ 1.4823; $uv_{max}$ (EtOH) 219 nm ($\epsilon$ 10,400); ir (film) 1710, 1650 $cm^{-1}$; mass spectrum[8] *m/e* 266 ($M^+$), 134 (base peak); nmr[9] ($CDCl_3$) $\delta$ 0.88 (d, 3), 0.92 (d, 6), 3.72 (s, 3) and 6.93 (s broad, 1)) in agreement with published values.[2b,d] Further confirmation of the structure of our synthetic *dl*-juvabione[10] was obtained by hydrolysis which gave *dl*-todomatuic acid (mp 66–67° (pentane), ir (Nujol) 1710, 1690, 1650 $cm^{-1}$; $uv_{max}$ (EtOH) 216 nm ($\epsilon$ 9700); nmr[9] ($CCl_4$) 0.87 (d, 3), 0.90 (d, 6), 7.02 (s, broad, 1)) in agreement with published values.[2b,d]

The stereospecific synthesis which we have described leads in 11 steps to *dl*-juvabione in a overall yield of 13%, starting from the keto acid **2** (6% starting from cyclohexenone). The general scheme presented here can, of course, be used for the synthesis of natural or modified sesquiterpenes structurally related to juvabione

(8) The mass spectrum was recorded on a A.E.I. (MS 30) instrument (70 eV) by Madame Besseyre, Laboratoire de spectroscopie, Paris.

(9) The nmr spectra of *dl*-juvabione and todomatuic acid were recorded on a Varian XL 100 (100 MHz) instrument (internal TMS) by Madame Platzer, Laboratoire de spectroscopie, Paris.

(10) *dl*-Juvabione, todomatuic acid, and the intermediates have correct elemental analysis.

**Jacqueline Ficini,* Jean d'Angelo, Jeanine Noiré**
*Laboratorie de Chimie Organique de Synthèse, Université Paris VI*
*8 Rue Cuvier, Paris (5e), France*
*Received October 19, 1973*

## Equilibrium Acidities of Carbon Acids. II.[1] Hydrocarbon Indicators, Phenylacetylene, and Other Carbon Acids in the 20–27 p*K* Region

*Sir:*

There has been general appreciation in recent years of the merits of dimethyl sulfoxide (DMSO) as a solvent for measuring equilibrium acidities. For acids in the 10–20 p*K* range measurements have been made potentiometrically,[2,3] spectrophotometrically,[4] and by $H_-$ techniques with $H_2O$–DMSO, MeOH–DMSO, and EtOH–DMSO using nitroaniline and nitrodiphenylamine indicators.[5] The latter method has been extended into the 20–30 p*K* range by Steiner, using hydrocarbon indicators.[6] During the past 6 years we have extended the investigation of the acidity of sulfones in pure DMSO[1] to a variety of other carbon acids including nitroalkanes, ketones, nitriles, sulfoxides, and hydrocarbons.[7] The Steiner method, which utilizes $CH_3SOCH_2K$ at low concentrations ($10^{-3}$–$10^{-4}$ *M*), has been modified in several ways in order to shorten the time required for each measurement and to increase the accuracy.[8] Standard deviations in a given titration are now routinely less than ±0.05 p*K* unit, and the reproducibility is generally within ±0.1 p*K* unit over the 10–27 p*K* range.

Steiner assigned p*K*'s to his indicators by extrapolating $H_-$ measurements into pure DMSO. We have checked the relative p*K*'s of these indicator standards by measuring acidities of each indicator pair against at least three carbon acids of intermediate acidity and found that only small adjustments need be made (Table I).

The data in Table I show that carbon acids of widely differing structure can be related by the same hydrocarbon indicators. Note, for example, that DDH and XH-9-Ph can be used for both phenyl methyl sulfone, where the negative charge on the carbanion is largely localized on carbon, and for benzyl methyl sulfoxide, where the negative charge is strongly delocalized to the benzene ring. Similarly, TPH and FH can be used for both acetophenone, where the charge is localized to

(1) For paper I in this series see F. G. Bordwell, R. H. Imes, and E. C. Steiner, *J. Amer. Chem. Soc.*, **89**, 3905 (1967).

(2) C. D. Ritchie and R. E. Uschold, *J. Amer. Chem. Soc.*, **89**, 1721 (1967).

(3) I. M. Kolthoff, M. K. Chantooni, Jr., and S. Bhowmik, *J. Amer. Chem. Soc.*, **90**, 23 (1968).

(4) R. Kuhn and D. Rewicki, *Justus Liebigs Ann. Chem.*, **704**, 79 (1967); **706**, 250 (1969).

(5) K. Bowden and R. Stewart, *Tetrahedron*, **21**, 261 (1965).

(6) (a) E. C. Steiner and J. M. Gilbert, *J. Amer. Chem. Soc.*, **87**, 382 (1965); (b) E. C. Steiner and J. D. Starkey, *ibid.*, **89**, 2751 (1967).

(7) We are greatly indebted to E. C. Steiner for providing us with the details of his method for measuring acidities in the 20–30 p*K* range.

(8) A description of the original Steiner titration method is given in the Ph.D. dissertation of R. H. Imes, Northwestern University, 1969. The modified method will be described in a later publication.