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SYNTHESES OF SHYOBUNONE AND RELATED SESQUITERPENES

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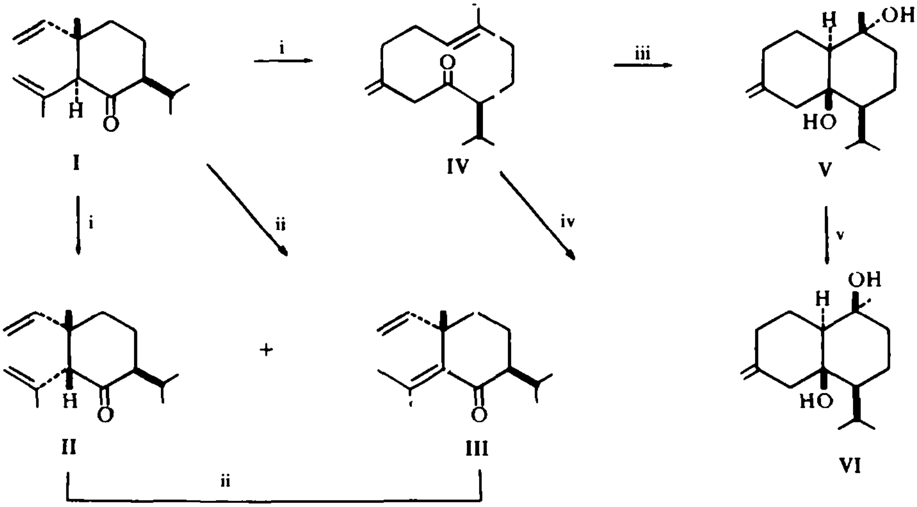
Abstract—Shyobunone, preisocalamendiol and related sesquiterpenes have been synthesized from (−)-santonin.

SEVERAL new sesquiterpenes have been isolated from *Acorus calamus* L. (Japanese name, Shyobu), and their structures have also been elucidated.[1] As shown in Scheme I, shyobunone (I) can be chemically converted into the other sesquiterpenes[2] isolated from *A. calamus.* The formation of preisocalamendiol (IV) provided shyobunone (I) in active form, because preisocalamendiol (IV), a germacrone-type sesquiterpene, was required for biogenetic reactions.[3] We report the syntheses of shyobunone (I) and related sesquiterpenes from the known dihydroxy-acetal (VII),[4] which has previously been obtained from (—)-santonin.

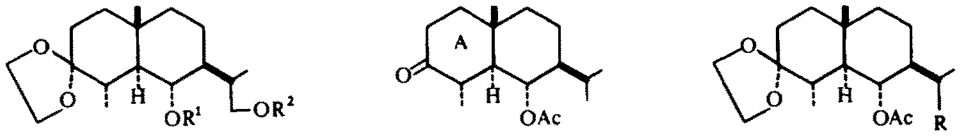
SCHEME I.
Chemical transformation of shyobunone (I)



(i) Δ at 160–180°. (ii) 100% HCOOH. (iii) 80% aq. AcOH. (iv) 1) Δ at 180°; (2) m-ClC_6H_4COOOH; (3) LAH. (v) (1) $POCl_3$-Pyridine; (2) m-ClC_6H_4COOOH; (3) LAH.

FIG 1.

Initially an acetoxy-ketone (VIII) was synthesised and converted into shyobunone (I) through a degradation of the ring A. Acetylation of the dihydroxy-acetal (VII) afforded a diacetate (IX) which was carefully hydrolysed to the hydroxy-monoacetate (X). Treatment of X with mesyl chloride–pyridine followed by substitution with excess of sodium iodide afforded an iodo-acetate (XII),* which was readily reduced to an acetoxy-acetal (XIII),[6] and then heated in aqueous acetic acid to produce, in 68% yield the acetoxy-ketone (VIII), m.p. 118–119°. The structure VIII was supported by its IR and NMR spectra (Experimental).



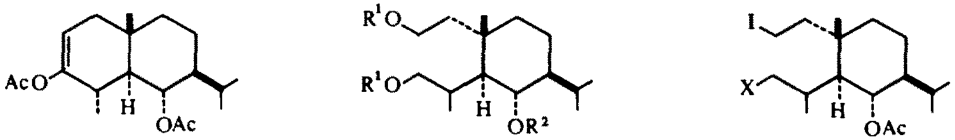
VII: $R^1 = R^2 = H$
IX: $R^1 = R^2 = Ac$
X: $R^1 = Ac, R^2 = H$
XI: $R^1 = Ac, R^2 = Ms$

VIII

XII: $R = -CH_2I$
XIII: $R = -Me$

FIG 2.

Degradation of the ring A of VIII and its conversion into shyobunone (I) was carried out as follows. An enol acetate (XIV), which was obtained by treatment of VIII was ozonized, and then carefully reduced with LAH to give a triol (XV) in high yield. In the next step, a secondary OH group in XV was protected from dehydration of ether-ring formation. The triacetate (XVI) obtained by acetylation of XV was hydrolysed to afford a dihydroxy-monoacetate (XVII),† which was then converted into a mono-acetoxy-dimesylate (XVIII). When treated with a large excess of sodium iodide under the same conditions as that of XI, XVIII afforded only a mono-iodide (XIX), indicating that one of two mesyl groups in XVIII was resistant to substitution by sodium iodide. In fact, the acetoxy-dimesylate (XVIII) could be quantitatively converted into the corresponding di-iodo-acetate (XX) when treated with sodium iodide under more vigorous conditions.



XIV

XV: $R^1 = R^2 = H$
XVI: $R^1 = R^2 = Ac$
XVII: $R^1 = H, R^2 = Ac$
XVIII: $R^1 = Ms, R^2 = Ac$

XIX: $X = OMs$
XX: $X = I$

FIG 3.

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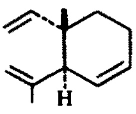
* An iodo-acetate (XII) is an important intermediate for syntheses of other elemene-type sesquiterpenes, e.g. geijerene (A),[5] has been synthesized from XII.

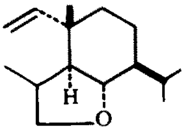


A

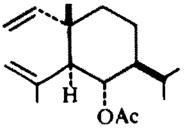
† When stirred in 5% methanolic KOH at room temp for 10 min, (XVI) was completely hydrolysed to XV.

Finally, treatment of XX with potassium t-butoxide afforded an ether (XXI) in high yield. However, dehydrohalogenation of XX was effected with 1,5-diazabicyclo-[5.4.0]undec-5-ene to give an oily acetoxy-diene (XXII), which was almost quantitatively converted into shyobunone (I) when treated with LAH followed by oxidation with Jones' reagent.[7] The synthetic compound thus obtained was identical with an authentic sample of shyobunone (I) (GLC, TLC and IR spectrum).

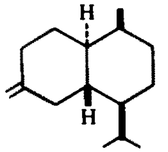
The synthesis of shyobunone (I) also means the syntheses of the other sesquiterpenes isolated from *Acorus calamus* L, as shown in Scheme I. Particularly, when I was heated in a sealed tube, preisocalamendiol (IV) was obtained, in *ca* 30% yield, in a pure state.[2] This is the first example of the synthesis of a naturally occurring germacrone-type sesquiterpene, from which ε-cadinene (XXIII) has been synthesized.[8] Furthermore, germacrene-D (XXIV) should also be synthesized from preisocalamendiol (IV).[9]



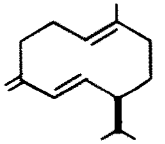
XXI



XXII



XXIII



XXIV

FIG 4.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded on a JASCO IR-S spectrophotometer. NMR spectra were taken on a Nihondensi JNM-C 60H spectrometer (60Mc) using $CDCl_3$ as a solvent, unless otherwise stated. Only prominent peaks are cited. Chemical shifts are given in ppm relative to internal TMS. Coupling constants are given in Hz (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet). Mass spectra were obtained on a Hitachi RMU-6D mass spectrometer operating with an ionization energy (70eV). Relative retentions *vs* calamenene as an internal standard were recorded on Shimazu GC-1C (Stationary phase: 5% PEG 20M on Celite 545 (100 Mesh); Column temp [Ø 3 mm × 1·5 m (stainless)]; 110; Carrier gas; Nitrogen; Inlet pressure: 1·5 Kg/cm^2). TLC and column chromatography were carried out on Merck Kieselgel GF_{254} and silicic acid (Mallincklodt, 100 Mesh) or neutral alumina (E. Merck, A. G., Germany), respectively.

Diacetoxy-acetal (IX). A soln of VII (10 g) in Ac_2O (50 ml) and pyridine (50 ml) was heated at 100° overnight, and then concentrated under reduced pressure to give a brown oil, which was dissolved in large amounts of ether. The ethereal soln was successively washed with sat $NaHCO_3$ aq, water, 2N HCl, water and sat NaCl aq, and then dried over $MgSO_4$. Removal of the solvent afforded 11 g of a viscous oil (86%), which crystallized, m.p. 83–85° (from n-hexane); ν_{max}(Nujol) 1730, 1245 and 1230 cm^{-1}; *m/e* 382 (M^+), 323, 322, 263 and 99. (Found: C, 65·86; H, 9·08. $C_{21}H_{34}O_6$ requires: C; 65·94; H, 8·96%).

Hydroxy-monoacetate (X). A soln of diacetoxy-acetal (7 g) in 5% methanolic KOH (21 g) was stirred at room temp for 10 min. and then poured into water (50 ml). The floating solid was extracted with ether.

The ethereal soln was washed with water and sat NaCl aq, and then dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded 5·5 g (88%) of a crystalline solid which was recrystallized from ether–n-hexane, m.p. 150–152°; ν_{max}(Nujol) 3580, 3360–3240 br, 1718 and 1250 cm^{-1}; δ 0·83 (6H, d, J = 6 Hz), 0·91 (3H, s), 2·00 (3H, s), 3·44 (2H, d, J = 6·9 Hz), 3·90 (4H, s) and 4·94 (1H, t, J = 9·7 Hz); *m/e* 340 (M^+), 322, 281, 280 and 99. (Found: C, 67·03; H, 9·47. $C_{19}H_{32}O_5$ requires: C, 66·57; H, 9·58%).

Monoacetoxy-mesylate (XI). To a soln of hydroxy-monoacetate (10 g) in pyridine (30 ml) was added dropwise 3·6 g mesyl chloride at 0°. The soln was stirred at 0° for 1 hr, and then at room temp for 30 min. The mixture was poured into ice-water, and extracted with ether. The ethereal soln was successively washed with 2N HCl, water and then sat NaCl aq. Evaporation of the solvent gave a crystalline solid (11·5 g, 93%), which was recrystallized from ether–n-hexane, m.p. 123–124°; ν_{max}(Nujol) 1725, 1360, 1250 and 1180 cm^{-1}; δ 0·83 (3H, d, J = 6·0 Hz), 0·93 (3H, s), 0·94 (3H, d, J = 6·3 Hz), 2·00 (3H, s), 2·98 (3H, s), 3·90 (4H, s), 3·99 (2H, d, J = 7·0 Hz) and 4·90 (1H, t, J = 9·7 Hz); *m/e* 418 (M^+), 359, 322, 263, 262 and 99 (Found: C, 57·07; H, 8·22. $C_{20}H_{34}O_7S$ requires: C, 57·40; H, 8·19%).

Iodo-acetate (XII). A mixture of monoacetoxy-mesylate (10 g) and NaI (20 g) in acetone (100 ml) was refluxed with stirring overnight. Evaporation of the solvent afforded a reddish oil, to which was added 30 ml water. The floating oil was extracted well with ether. The ethereal soln was washed with water and sat NaCl aq, and then dried over $MgSO_4$. Removal of the solvent afforded a red-brown oil, which was chromatographed on neutral alumina (30 g) and eluted with n-hexane to give 9·5 g (88%) of crystals, m.p. 108–109° (from n-hexane); ν_{max}(Nujol) 1720 and 1250 cm^{-1}; δ 0·83 (3H, d, J = 6·0 Hz), 0·92 (3H, s), 0·99 (3H, d, J = 6·4 Hz), 2·01 (3H, s), 3·08 (1H, d, J = 6·8 Hz), 3·10 (1H, fine splitted d, J = 6·8 Hz), 3·93 (4H, s) and 4·90 (1H, t, J = 9·7 Hz); *m/e* 450 (M^+), 392, 391, 390, 346, 329, 323, 307, 263 and 99. (Found: C, 50·66; H, 6·94. $C_{19}H_{31}O_4I$ requires: C, 50·90; H, 7·00%).

Acetoxy-acetal (XIII). A mixture of iodo-acetate (14 g) and $NaBH_4$ (3·54 g) in DMSO (280 ml) was stirred at room temp for 1 hr, and then heated at 80° for 15 min. The cooled mixture was poured into water, and extracted with ether. The ethereal soln was washed with water and sat NaCl aq, and then dried over $MgSO_4$. Removal of the solvent gave 9·0 g (90%) of XIII in crystalline form, m.p. 144–145° in a sealed tube (from n-hexane); ν_{max}(Nujol) 1720, 1390, 1380 and 1250 cm^{-1}; δ 0·84 (6H, d, J = 6·1 Hz), 0·89 (3H, d, J = 6·1 Hz), 0·92 (3H, s), 2·00 (3H, s), 3·95 (4H, s) and 4·95 (1H, br.t, J = 9·3 Hz); *m/e* 324 (M^+), 264, 181 and 99. (Found: C, 69·90; H, 10·39. $C_{19}H_{32}O_4$ requires: C, 70·33; H, 9·94%).

Acetoxy-ketone (VIII). A soln of acetoxy-acetal (12 g) in AcOH (120 ml) and water (40 ml) was stirred at 80° for 3 hr. After removal of the solvent under reduced pressure, the mixture was poured into water and extracted with ether. The ethereal soln was successively washed with sat $NaHCO_3$ aq, water and sat NaCl aq, and then dried over $MgSO_4$. Evaporation of the solvent afforded 9·5 g (92%) of white crystals, m.p. 118–119° (from n-hexane); ν_{max}(Nujol) 1725, 1695 and 1240 cm^{-1}; δ 0·83 (3H, d, J = 6·3 Hz), 0·95 (3H, d, J = 6·3 Hz), 0·98 (3H, s), 1·13 (3H, d, J = 6·7 Hz), 2·08 (3H, s) and 5·05 (1H, t, J = 9·7 Hz); *m/e* 280 (M^+), 265, 238, 237, 221 and 220. (Found: C, 72·53; H, 10·22. $C_{17}H_{28}O_3$ requires: C, 72·82; H, 10·06%).

Formation of an enol acetate (XIV). To a soln of acetoxy-ketone (3·1 g) in iso-propenyl acetate (12 ml) was added one drop of conc H_2SO_4. After refluxed for 1 hr under N_2, the soln was concentrated under reduced pressure, and then diluted with water. The resulting aqueous mixture was extracted with ether. The extracts were washed with water and sat NaCl aq, and then dried over $MgSO_4$. Evaporation of the solvent afforded an oily residue, which was chromatographed on neutral alumina and eluted with n-hexane to give 3·5 g (87%) of a colourless viscous liquid which was directly used for the next experiment. The compound XIV has the following spectral data: ν_{max}(Film) 1760, 1740, 1690, 1240 and 1215 cm^{-1}; δ 0·83 (3H, d, J = 6·3 Hz), 0·92 (3H, d, J = 6·3 Hz), 1·03 (3H, s), 1·09 (3H, d, J = 6·2 Hz), 2·05 (3H, s), 2·08 (3H, s), 5·03 (1H, br.t, J = ~9·0 Hz) and 5·23 (1H, q, J = 6·0, 3·1 Hz); *m/e* 280, 263, 262, 221 and 220.

Triol (XV). After the enol acetate (300 mg) in dry ether (15 ml) was ozonized at 0° until blue colour appeared, the soln was flashed with N_2 until excess amounts of O_3 dissolved in the soln was completely removed, and then added dropwise into a solution of LAH (600 mg) in dry ether (9 ml), with stirring, under ice cooling. The resulting mixture was stirred at 0° for 1 hr, at room temp for another 1 hr, and then refluxed for 2 hr. After destroying excess LAH with cold water and made acidic with 2N HCl, the aqueous layer was extracted with ether repeatedly. The combined ethereal soln was washed with water and sat NaCl aq, and then dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded white crystals, m.p. 140–141° (from MeOH-Et_2O); ν_{max}(Nujol) 3340–3320 br. cm^{-1}; *m/e* 258 (M^+), 240, 213 and 195. (Found: C, 69·50; H, 11·80. $C_{15}H_{30}O_3$ requires: C, 69·72; H, 11·70%).

Formation of triacetate (XVI). A soln of triol (2 g) in Ac_2O (5 ml) and pyridine (5 ml) was heated at 100° overnight, and then concentrated under reduced pressure and diluted with water. The floating oily material was extracted with ether, and then worked up as usual to give an oily residue, which was chromatographed on neutral alumina (10 g). Elution with benzene afforded 2·4 g (80%) of a colourless oil (XVI) which was directly used for the next experiment. This compound has the following spectral data: ν_{max} (Film) 1750–1720 br., 1250–1210 br. and 1030–1010 br. cm^{-1}; δ 0·82 (3H, d, J = 6·2 Hz), 0·88 (6H, d, J = 6·1 Hz), 0·93 (3H, s), 2·00 (3H, s), 2·03 (6H, s), 3·89 (2H, d, J = 7·3 Hz), 4·12 (2H, t, J = 7·2 Hz) and 4·93 (1H, br.t, J = 9·5 Hz); *m/e* 342, 324, 282 and 264.

Dihydroxy-monoacetate (XVII). A soln of triacetate (900 mg) in 5%-methanolic KOH (5·4 g) was stirred at room temp for 5 min, and then diluted with water (10 ml). After the aqueous soln had been extracted with ether, the extract was washed with sat NaCl aq, and then dried over $MgSO_4$. Evaporation of the solvent gave 620 mg (88%) of white crystals. m.p. 137–138° (from Et_2O); ν_{max} (Nujol) 3360–3240 br., 1735, 1235 and 1010 cm^{-1}; *m/e* 300 (M^+), 282, 257, 240 and 222. (Found: C. 67·93; H. 10·67. $C_{17}H_{32}O_4$ requires: C, 67·96; H. 10·74%).

Acetoxy-dimesylate (XVIII). Mesyl chloride (1 g) was added dropwise to a soln of dihydroxy-monoacetate (1·2 g) in dry pyridine (6 ml) at 0°. The mixture was stirred at 0° for 1 hr, at room temp for 30 min, and then poured into ice-water and extracted with ether. The extract was successively washed with 2N HCl, water and sat NaCl aq, and then dried over $MgSO_4$. Removal of the solvent gave a crystalline solid (1·7 g, 94%), m.p. 98–100° (from n-hexane–Et_2O); ν_{max}(Nujol) 1730, 1360, 1345, 1230, 1170 and 975 cm^{-1}; δ 0·83 (3H. d. J = 6·3 Hz), 0·90 (3H, d, J = 6·3 Hz), 0·94 (3H, d, J = 6·3 Hz), 0·95 (3H, s), 2·03 (3H. s), 2·96 (6H, s), 3·98 (2H, fine splitted d, J = 7·5 Hz), 4·25 (2H, t, J = 7·0 Hz) and 4·90 (1H, br.t, J = 9·5 Hz); *m/e* 456 (M^+), 413, 318 and 300. (Found: C. 49·78; H, 7·89. $C_{19}H_{36}O_8S_2$ requires: C. 49·98; H, 7·94%).

Di-iodo-acetate (XX). A mixture of acetoxy-dimesylate (800 mg) and NaI (5 g) in methyl ethyl ketone (20 ml) was refluxed. with stirring. for 3 days, and then concentrated under reduced pressure. The residue was diluted with water and extracted with ether. The extract was washed with water and sat NaCl aq, and then dried over $MgSO_4$. After removal of the solvent, an oily residue was chromatographed on neutral alumina and eluted with n-hexane to give 900 mg (99%) of a colourless oil which soon crystallized, m.p. 70–71° (from n-hexane); ν_{max}(Nujol) 1740 and 1235 cm^{-1}; δ 0·82 (3H, d, J = 6·3 Hz), 0·85 (3H, s), 0·90 (3H, d, J = 6·3 Hz), 1·01 (3H, d, J = 6·3 Hz), 2·02 (3H, s), 3·02–3·35 (4H. complex) and 4·95 (3H, br.t, J = 9·4 Hz): *m/e* 520 (M^+), 392, 349, 333 and 332 (Found: C, 39·11; H, 5·75. $C_{17}H_{30}O_2I_2$ requires: C, 39·24; H, 5·81%).

Formation of acetoxy-diene (XXII). Di-iodo-acetate (250 mg) was dissolved in 1·5 ml of 1,5:diazabicyclo-[5.4.0]undec-5-ene and heated at 80° for 24 hr. After cooling, the mixture was diluted with water, and then extracted with ether. The extracts were successively washed with 2N HCl, water and sat NaCl aq, and then dried over $MgSO_4$. Removal of the solvent gave a red-brown oily residue, which was chromatographed on neutral alumina and eluted with benzene to afford 50 mg (39%) of colourless liquid, relative retention 1·61; ν_{max}(Film) 3100, 1740, 1635, 1235, 905 and 890 cm^{-1}; δ 0·88 (3H, d, J = 6·5 Hz), 0·92 (3H, d, J = 6·5 Hz), 1·05 (3H, s), 1·70 (3H, br.s). 1·95 (3H. s). 4·50–5·30 (5H. m) and 5·75 (1H, q. J = 9·8, 11·0 Hz); *m/e* 264 (M^+), 222, 204, 189 and 161. This compound was directly used for the next experiment.

Reduction of the acetoxy-diene (XXII) *with LAH*. A soln of acetoxy-diene (50 mg) in dry ether (2 ml) was carefully added, with stirring, to dry ether (2 ml) containing 20 mg of LAH. The mixture was stirred at room temp for 1·5 hr, and then decomposed with water under ice cooling and made acidic with 2N HCl. The ethereal layer was washed with sat NaCl aq. and then dried over $MgSO_4$. Removal of the solvent afforded 38 mg (90%) of colourless liquid, relative retention 1·32; ν_{max} (Film) 3520–3400 br., 1635, 905 and 895 cm^{-1}; *m/e* 222 (M^+), 207, 179 and 137. (Found: $M^+ = 222{\cdot}1958$. $C_{15}H_{26}O$ requires: $M^+ = 222{\cdot}1984$).[7]

Shyobunone (I). Jones' reagent was carefully added to a soln of the above reduction product (38 mg) in acetone (1 ml) until a brown colour appeared continuously. The mixture was stirred at room temp for 30 min, and then poured into a soln of $NaHSO_3$ (20 mg) in water (1 ml) and extracted with ether. The ethereal soln was washed with water and sat NaCl aq, and then dried over $MgSO_4$. Removal of the solvent gave 35 mg (93%) of almost colourless oil, which was purified by silica gel chromatography using chloroform to give 25 mg of colourless liquid (I), relative retention 1·33; ν_{max}(Film) 3100, 1710. 1640, 910 and 890 cm^{-1}; *m/e* 220 (M^+), 205. 177 and 137. (Found: $M^+ = 220{\cdot}1826$; $C_{15}H_{24}O$ requires: $M^+ = 220{\cdot}1827$). The synthetic compound was completely identical with an authetic sample of the natural shyobunone (GLC, TLC and IR spectrum).

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REFERENCES

[1] M. Iguchi, A. Nishiyama, H. Koyama, S. Yamamura and Y. Hirata, *Tetrahedron Letters* 5315 (1968); *Ibid.* 3729 (1969); M. Iguchi, A. Nishiyama, S. Yamamura and Y. Hirata. *Ibid.* 855 (1970)

[2] M. Iguchi. A. Nishiyama. S. Yamamura and Y. Hirata, *Ibid.* 4295 (1969); M. Iguchi, A. Nishiyama, M. Niwa. S. Yamamura and Y. Hirata. *Chem. Comm.* 1323 (1970)

[3] To be published

[4] D. M. Simonovic. A. S. Rao and S. C. Bhattacharyya, *Tetrahedron* **19**, 1061 (1963)

[5] M. D. Sutherland, *Aust. J. Chem.* **17**, 75 (1964); R. V. H. Jones and M. D. Sutherland, *Ibid.* **21**, 2255 (1968)

[6] R. O. Hutchins, D. Hoke, J. Keogh and D. Koharski, *Tetrahedron Letters* 3495 (1969)

[7] G. H. Kulkarni, G. R. Kelkar and S. C. Bhattacharyya, *Tetrahedron* **20**, 1301 (1964)

[8] L. Westfelt, *Acta Chem. Scand.* **20**, 2865 (1966)

[9] K. Yoshihara, Y. Ohta, Y. Sakai and Y. Hirose, *Tetrahedron Letters* 2263 (1969)