Synthesis of Optically Pure (*R,Z*)-5-Dec-1-enyloxacyclopentan-2-one, the Sex Pheromone of the Japanese Beetle

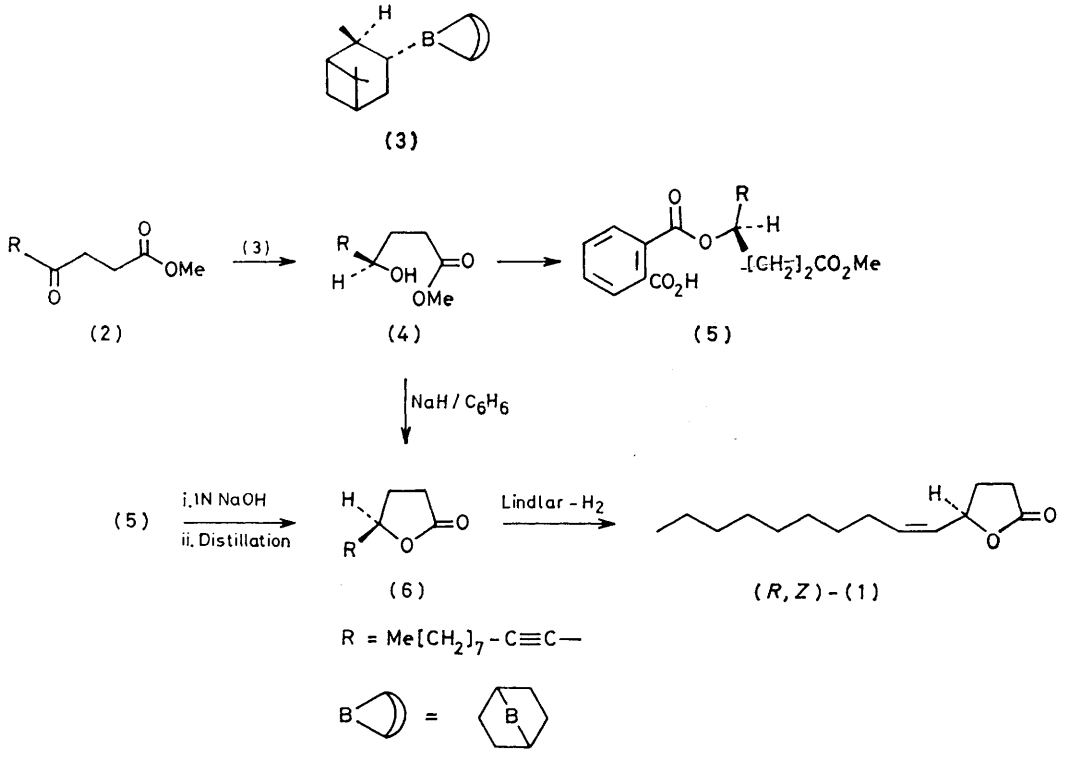
By **Raymond Baker** * and **V. Bhaskar Rao**, Department of Chemistry, The University, Southampton SO9 5NH

Optically pure (*R,Z*)-5-dec-1-enyloxacyclopentan-2-one (1) has been synthesised from methyl 4-oxotetradec-5-ynoate (2) by a chiral reduction with 9-(pinan-3-yl)-9-borabicyclo[3.3.1]nonane (3) which yielded the *R*-alcohol (4), in 74% enantiomeric excess. This was further purified by recrystallisation of the salt formed from the phthalate ester of compound (4) and (+)-α-methylbenzylamine and then hydrolysed and converted into (*R,Z*)-(−)-(1).

THE Japanese beetle *Popillia japonica* Newman is a devastating pest of a variety of ornamental trees and cultivated crops in the U.S.A. Its pheromone was isolated from virgin females and the structure assigned as (*R,Z*)-5-dec-1-enyloxacyclopentan-2-one (1). The unique feature of the compound is that even minute amounts of the (*S,Z*)-enantiomer decrease the male response to the pheromone under field conditions. Tests [1] showed that the pheromone with as little as 0.5% of the (*S,Z*)-enantiomer will reduce the number of the captured males from 168 to 106 in the traps. When the (*R,Z*)-derivative is contaminated with only 2% of its enantiomer, the mixture is three times less active than the optically pure pheromone and no activity is found with material of 94% enantiomeric excess (e.e.). The syntheses reported so far for this compound have been either from optically active starting material [1] or by a tedious synthetic route which includes resolution.[2] In the former case, *R*-glutamic acid was diazotized to yield γ-lactone carboxylic acid which gave the corresponding aldehyde from its acid chloride by Rosenmund reduction. A Wittig reaction was employed on this aldehyde to construct the olefinic linkage, which resulted in contamination by the (R,E)-isomer in the final product; this had to be removed by preparative high-pressure liquid chromatography (h.p.l.c.).[1] In a second approach, which involved a large number of steps, a resolution step was introduced in the early stages, so that the overall yield was low. The product was obtained in 85% e.e. ($[\alpha]_D$ −59.4°) which rendered it inactive for the insect control purposes. Similar problems have been encountered in recently reported syntheses.[3,4] We now report the synthesis of the optically pure compound (1) *via* a procedure which involves asymmetric reduction, followed by enhancement of optical purity by a simple resolution.

RESULTS AND DISCUSSION

Our synthetic strategy for the preparation of compound (1) involved the choice of methyl 4-oxotetradec-5-ynoate (2) as a suitable starting material. Acetylenic



ketones were earlier prepared [5] in two steps by the addition of lithium acetylide to the aldehydes and Jones oxidation of the resulting alcohols. In our hands, compound (2) has been made in a single step in 68% yield by the inverse addition of dec-1-ynylmagnesium bromide in tetrahydrofuran to a solution of β-methoxycarbonylpropionoyl chloride in the same solvent at −65 °C. This acetylenic ketone (2) was reduced with 9-pinan-3-yl-9-borabicyclo[3.3.1]nonane (3) [6] (3 mol equiv.) when stirred at room temperature for 3 d. After the usual work-up the residue was subjected to rapid chromatography [7] and the required alcohol (4) was obtained in *ca.* 70% yield. Examination of the n.m.r. spectrum in the presence of $Eu(tfmc)_3$ indicated the presence of an enantiomeric mixture of 87% *R* and 13% *S* (74% e.e.). The optical yields could not be improved further even by using 100% optically pure (+)-α-pinene. The alcohol (4) was stirred with sodium hydride in benzene and then distilled and the acetylenic bond *cis*-hydrogenated with Lindlar catalyst to give 5-decen-1-yloxacyclopentan-2-one (1) which was found to be 73.1% optically pure, $[\alpha]_D^{21}$ −51°.

To obtain optically pure (1) a resolution procedure was employed to enhance the percentage e.e. of compound (4). This was converted into its phthalic half ester (5) and resolved with (+)-α-methylbenzylamine. The white crystalline salt obtained was further purified by recrystallisation from diethyl ether–light petroleum to yield the pure dextrorotatory salt. The optically pure half ester (5) was liberated from the salt by acidification with dilute hydrochloric acid. Hydrolysis with 1N-NaOH gave the corresponding γ-hydroxy-acid which, on slow distillation, yielded pure (*R*)-(−)-(6). The overall yield of the lactone (6) from compound (4) was 24%, but further substantial amounts of the amine salt with high e.e. can be recovered from the mother liquor. The acetylenic lactone (6) was converted into the optically pure natural pheromone (*R*,*Z*)-(1), $[\alpha]_D^{21}$ −69.7° (lit.,[1] $[\alpha]_D^{26}$ −69.6°).

The final product obtained is, therefore, of sufficient purity to be used in pest management systems. It can also be stressed that the overall route is simple and capable of being conducted on a considerably larger scale.

EXPERIMENTAL

M.p.s were determined on electrothermal apparatus in sealed capillaries and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 157G spectrophotometer. Mass spectra were obtained with a Kratos MS 30 Spectrometer utilising the DS 50 S Data System. N.m.r. spectra were recorded with an XL 100 Fourier-Transform instrument with tetramethylsilane as an internal standard. Optical rotation measurements were obtained on a ETL-NPL automatic polarimeter type 143A. Rapid chromatography was performed with 230—400 mesh silica gel (Merck, type 60). G.l.c. analysis was performed on a Pye Unicam GCD Chromatograph, using a 1.7 m × 6 mm column with 5% FFAP and nitrogen (1 kg cm^{-2}) as carrier gas.

Methyl 4-Oxotetradec-5-ynoate (2).—A solution of ethylmagnesium bromide in tetrahydrofuran (THF) was prepared from magnesium (2.43 g), ethyl bromide (11 g, 0.1 mol), and dry THF (80 ml) under nitrogen. Dec-1-yne (13.8 g, 0.1 mol) in dry THF (40 ml) was added as drops to the Grignard reagent at room temperature and the stirred mixture was heated under reflux for 1 h. This solution of dec-1-ynylmagnesium bromide was added as drops to β-methoxycarbonylpropionyl chloride (15 g, 0.1 mole) in THF (80 ml) and the temperature was maintained at −65 °C. The mixture was stirred at this temperature for 3 h, brought to room temperature over a period of 20 h, after which time it was poured into ice (300 g) and saturated ammonium chloride solution (200 ml) and extracted with diethyl ether (3 × 150 ml). The combined diethyl ether extracts were washed with saturated sodium hydrogencarbonate (100 ml), brine, dried (anhydrous $MgSO_4$), filtered, and concentrated under reduced pressure. The residue was distilled to give compound (2) [4] (1.71 g, 68%), b.p. 125—126 °C/0.04 mmHg; t_R 4.8 min on 5% FFAP at 210 °C; $\nu_{max.}$ (CCl_4) 2 940s, 2 870s, 2 210s, 1 745s, 1 680s, 1 440s, and 1 160s cm^{-1}; δ ($CDCl_3$) 0.89 (3 H, distorted t, Me), 1.2—1.6 (12 H, m, 6 × CH_2), 2.16—2.8 (6 H, m, $H_2CC{\equiv}CCOCH_2CH_2$), and 3.65 (3 H, s, OMe); *m/e* (25 eV) 252 (M^+, 0.83%), 221 (5.9), 165 (100), 113 (10.7), and 115 (98.8) (Found: M^+, 252.1868. $C_{15}H_{24}O_3$ requires *M*, 252.1725).

Reduction of Compound (2) *with 9-Pinan-3-yl-9-borabicyclo*[3.3.1]*nonane* (3).—A THF solution of 9-borabicyclo-[3.3.1]nonane (9-BBN) (55.5 ml, 30 mmol) was refluxed with (+)-α-pinene (5.34 ml, 33 mmol) ($[\alpha]_D^{25}$ +47.7° distilled from $LiAlH_4$) for 2.5 h and cooled to room temperature. Methyl 4-oxotetradec-5-ynoate (2) (2.77 g, 11 mmol) was added and the mixture was stirred under nitrogen at room temperature for 3 d. Acetaldehyde (2 ml) was injected into the solution which was then stirred for 15 min. The solvent and α-pinene were then removed under reduced pressure (0.05 mmHg for 2 h) at 40 °C. The resulting yellow liquid was dissolved in dry diethyl ether (36 ml), and the solution cooled to 0 °C and treated with 2-hydroxyethylamine (1.98 ml, 33 mmol). A white precipitate was formed and the mixture was stirred for 15 min at 0 °C; it was then filtered and the residue washed with cold diethyl ether (12 ml). The combined filtrate was washed with brine (30 ml), dried, filtered, and concentrated to give a clear oil (3.39 g). This was subjected to rapid chromatography and eluted with 23% ethyl acetate in light petroleum (b.p. 40—60 °C) to yield compound (2) (0.5 g) and *methyl 4-hydroxytetradec-5-ynoate* (4) (1.9 g, 70%); $[\alpha]_D^{21}$ +7.4° (c 5, $CHCl_3$); t_R 5.0 min on 5% FFAP at 220 °C; $\nu_{max.}$ (CCl_4) 3 620m, 3 490br m, 2 975s, 2 940s, 2 215w, 1 745s, 1 440s, and 1 180s cm^{-1}; δ ($CDCl_3$) 0.88 (3 H, distorted t, Me), 1.2—1.6 (12 H, m, 6 × CH_2), 1.9—2.3 (5 H, m, O*H*, CH_2,CHOH, and $CH_2C{\equiv}C$), 2.51 (2 H, t, *J* 8 Hz, CH_2CO_2Me), 3.7 (3 H, s, CO_2CH_3), and 5.45 (1 H, t, *J* 6 Hz, *CH*OH); *m/e* (25 eV) 254 (M^+, 0%), 222 (3.5), 220 (52.0), 209 (2.7), 207 (2.8), 181 (2.8), 179 (7.1), 137 (17), and 117 (5.4).

5-Dec-1-ynyloxacyclopentan-2-one (6).—Sodium hydride (0.1 g) and a solution of compound (4) (0.5 g, 2 mmol) in dry benzene (15 ml) were stirred for 20 h. The mixture was diluted with water (10 ml) and acidified to pH 4 with glacial acetic acid followed by extraction with diethyl ether (3 × 40 ml). The combined ethereal layer was washed with brine (2 × 40 ml), dried, filtered, and solvent removed. The residual oil was distilled in a Kugelrohr oven slowly (pot temperature 110 °C at 0.1 mmHg) to yield *compound* (6) (0.362 g, 82%); t_R 6.6 min on 5% FFAP at 212 °C; $\nu_{max.}$ (CCl_4) 2945s, 2 870s, 2 250w, 1 790s, 1 460w, 1 190s, and

1 160s cm^{-1}; δ ($CDCl_3$) 0.89 (3 H, distorted t, Me), 1.2—1.6 (12 H, m, 6 × CH_2), 2.1—2.6 (6 H, m, CH_2CH_2CO and $CH_2C{\equiv}C$), and 5.1br (1 H, t, HCC=C); *m/e* (25 eV) 222 (M^+, 0.7%), 207 (0.4), 193 (1.7), 179 (2.2), 165 (11.1), 151 (4.2), 137 (23.4), 124 (100), 117 (7.1), 109 (15.8), and 85 (30.4) (Found: M^+, 222.1544. $C_{14}H_{22}O_2$ requires M, 222.1619).

(Z)-5-*Dec*-1-*enyloxacyclopentan*-2-*one*.—Palladium on calcium carbonate (5%), poisoned with lead (0.2 g) and quinoline (8 drops), was added to a solution of compound (6) (0.64 g) in pentane (50 ml). The mixture was hydrogenated at 0 °C by stirring under hydrogen atmosphere and, when the required amount of hydrogen had been taken up (*ca.* 62 ml), the catalyst was removed by filtration through a pad of Celite; the filtrate was then washed with 5% aqueous hydrochloric acid (4 × 15 ml) followed by brine. The pentane layer was dried, filtered, and solvent removed under reduced pressure to give a residue which was distilled in a Kugelrohr oven to yield (*R,Z*)-5-dec-1-enyloxacyclopentan-2-one (1) [2] (0.58 g, 90%), b.p. 110 °C at 0.1 mmHg; t_R 3.9 min on 5% FFAP at 218 °C; $[\alpha]_D^{21}$ −51° (c 5.01, $CHCl_3$); 73.1% e.e.; $\nu_{max.}$ (CCl_4) 2 940s, 2 865s, 1 790s, 1 460w, 1 326w, and 1 180s; δ ($CDCl_3$) 0.88 (3 H, distorted t, Me), 1.2—1.5br (12 H, s at δ 1.28, 6 × CH_2), 1.7—2.7 (6 H, m, CH_2CH_2CO and $CH_2CH{=}$), and 5.15—5.8 (3 H, m, CH=CHCH); *m/e* 224 (M^+, 2.8%), 167 (2.5), 153 (5.1), 139 (6.1), 125 (15.8), 111 (100), 85 (23), and 83 (19.4) (Found: M^+, 224.2029. $C_{14}H_{24}O_2$ requires M, 224.1776).

1-*Methoxycarbonyltridec*-4-*ol*-5-*ynyl Monophthalate* (5).—Phthalic anhydride (1.03 g) was added to a solution of compound (4) (1.75 g) in dry pyridine (4 ml) and the mixture was stirred for 2 h at 100 °C. After being cooled, the solution was diluted with diethyl ether (40 ml) and acidified to pH 3 with 10% hydrochloric acid. The ethereal layer was separated and the aqueous solution was extracted with diethyl ether. The combined diethyl ether solutions were then extracted with ammonia solution (3 × 30 ml). The alkaline aqueous extract was acidified with hydrochloric acid and the separated oil extracted with chloroform (3 × 40 ml). The combined chloroform solution was washed with brine, dried (anhydrous $MgSO_4$), and concentrated under reduced pressure to give compound (5) as a viscous oil which was directly employed for resolution without further purification (1.9 g, 65%); $[\alpha]_D^{21}$ −7.6° (*c* 5.1, $CHCl_3$); $\nu_{max.}$ (CCl_4) 3 600—3 100br, m, 2 200w, 1 740s, and 1 705s cm^{-1}; δ ($CDCl_3$) 0.88 (3 H, distorted t, Me), 1.2—1.6 (12 H, m, 6 × CH_2), 2.10—2.35 (4 H, m, $H_2CC{\equiv}C$ and $OCHCH_2$), 2.6 (2 H, t, *J* 3.5 Hz, CH_2CO_2Me), 3.65 (3 H, s, CO_2Me), 5.7br (1 H, m, $C{\equiv}CCHO$–), 7.5—8.00 (m, 4 H, aromatic), and 9.00 (1 H, br, CO_2H, deuterium exchangeable); *m/e* (25 eV) 402 (M^+, 0%), 253 (4.1%), 222 (1.7%), and 137 (23.1).

(R)(+)-α-*Methylbenzylamine Salt of the Phthalic Half Ester* (5).—(+)-α-Methylbenzylamine (0.52 g, 4.3 mmol) was added to a solution of compound (5) (1.75 g, 4.3 mmol) in dry diethyl ether (20 ml). This was gradually diluted, while being heated, with light petroleum (b.p. 40—60 °C) (180 ml); it was then cooled for 22 h at −25 °C. The crystalline salt thus obtained was filtered off and recrystallised three times from the above solvent mixture to yield the pure *salt*, m.p. 94 °C (0.96 g, 43%), $[\alpha]_D^{21}$ +27.1° (*c*, 5.86, $CHCl_3$) (Found: C, 71.2; H, 7.75. $C_{31}H_{41}NO_6$ requires C, 71.08; H, 7.89%).

(R)-(−)-5-*Dec*-1-*ynyloxacyclopentan*-2-*one* (6).—The above (*R*)-(+)amine salt (0.96 g) was added to 10% hydrochloric acid (20 ml) and the liberated phthalic half ester (5) was extracted with dichloromethane (2 × 15 ml). This was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give optically pure compound (5) (0.71 g, 97%), $[\alpha]_D^{21}$ −11.5° (*c*, 5.5, $CHCl_3$). The acid was dissolved in 1N-NaOH (20 ml), stirred for 20 h at room temperature, and acidified to pH 4 with glacial acetic acid. The resulting mixture was extracted with light petroleum (b.p. 40—60 °C) (4 × 30 ml). The organic layer was washed with brine, dried, filtered, and concentrated to yield an oily liquid. Slow distillation in a Kugelrohr oven (pot temperature 110 °C at 0.1 mmHg) gave pure (*R*)-(−)-(6) (0.363 g, 92.5%); $[\alpha]_D^{21}$ −6.5° (*c*, 5.5, $CHCl_3$). The spectral and analytical data were identical with those of the enantiomeric mixture (6).

(R,Z)-(−)-5-*Dec*-1-*enyloxacyclopentan*-2-*one* (1).—Optically pure compound (6) (0.363 g) was hydrogenated as described above and distilled to yield (*R,Z*)-(−)-(1) (0.287 g, 90%); $[\alpha]_D^{21}$ −69.7° (*c*, 1.0, $CHCl_3$) (lit.,[1] $[\alpha]_D^{26}$ −69.6°). The spectral and analytical data were similar to those of the enantiomeric mixture (1).

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