Synthesis of Optically Active δ-n-Hexadecalactone, the Proposed Pheromone from *Vespa orientalis*[1]

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Received April 20, 1976

The (R)-(+) and (S)-(−) enantiomers of δ-n-hexadecalactone (**3a** and **3b**) have been synthesized from (R)-(+)- and (S)-(−)-1,2-epoxytridecane (**1a** and **1b**), respectively, by reaction with propiolic acid dianion followed by reduction. The epoxides were prepared by resolution of 1-dimethylamino-2-tridecanol (**2**) using each enantiomer of dibenzoyltartaric acid, followed by Hofmann elimination. The absolute configuration of the epoxides was proven by conversion of (R)-(+)-1,2-epoxytridecane (**1a**) to (S)-(+)-3-tetradecanol (**5**), the absolute configuration of which is known. The method used represents a general route to many optically active δ-lactones.

In 1969 Ishay and co-workers[2] proposed that the pheromone responsible for some aspects of the social behavior of queens and workers of the Oriental hornet, *Vespa orientalis*, was δ-n-hexadecalactone. This proposal was based on an isolation of the active material from the heads of queen hornets and a comparison with authentic material. The comparison included chemical, spectral, and biological methods.

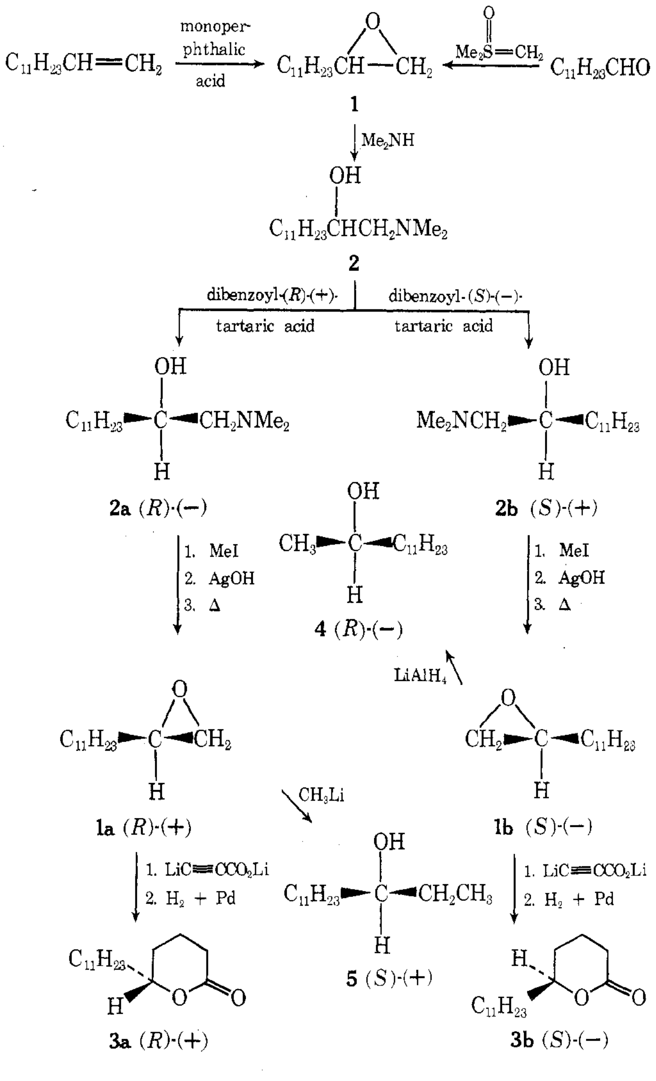
In an effort to further confirm the above work we have prepared both enantiomers of δ-n-hexadecalactone. Our method provides a convenient synthesis of material for biological testing to determine which enantiomer is the natural one. It also allows determination of the absolute configuration of both enantiomers and provides a general route to many optically active δ-lactones.

Our approach begins with racemic 1,2-epoxytridecane (**1**) and is shown in Chart I. Utilizing our earlier method[3] epoxide **1** was opened with dimethylamine and the resulting 1-dimethylamino-2-tridecanol (**2**) was resolved into the R and S isomers, **2a** and **2b**, respectively, using the two enantiomers of dibenzoyltartaric acid. The two amino alcohols were converted to the two optically active epoxides, **1a** and **1b**, by quaternization followed by Hofmann elimination. Using the method of Carlson and co-workers[4] the two optically active epoxides were allowed to react with the dianion of propiolic acid. The resulting acetylenic hydroxy acids were reduced with hydrogen and palladium to give the saturated hydroxy acids which spontaneously formed the two optically active lactones **3a** and **3b**. The use of dibenzoyl-(R)-(+)-tartaric acid as the resolving agent led ultimately to (R)-(+)-δ-n-hexadecalactone (**3a**) while use of dibenzoyl-(S)-(−)-tartaric acid led to (S)-(−)-δ-n-hexadecalactone (**3b**). The biological testing of compounds **3a** and **3b** on the Oriental hornet is being conducted by Professor Ishay and will be published at a later date.

The absolute configuration of the compounds shown in Chart I was determined by two methods. Reduction of (−)-1,2-epoxytridecane (**1b**) to (−)-2-tridecanol (**4**) indicated that the (−)-epoxide **1b** had the S configuration. This was based on the assumption that 2-butanol and 2-tridecanol of the same absolute configuration would show the same sign of rotation.[3a] A more rigorous proof of absolute configuration was carried out by reaction of the (+)-1,2-epoxytridecane (**1a**) with methyllithium to give (+)-3-tetradecanol (**5**), the absolute configuration of which has been proven to be S.[3a]

The resolution of amino alcohols similar to **2**, having a variety of alkyl groups in place of the C-11 side chain, appears to be a perfectly general method and both enantiomers of dibenzoyltartaric acid can be utilized. These optically active amino alcohols are readily converted to the corresponding optically active epoxides by Hofmann elimination.[3] Thus the above method represents a useful synthetic route to a wide variety of optically active molecules and other studies along these lines will be published shortly.

Chart I



Experimental Section[5]

1,2-Epoxytridecane (1). Method A. The following procedure, modified from a literature method,[6] was found to give the best yields. To a mixture of 1 g of anhydrous sodium sulfate and 36.4 g (0.2 mol) of tridecene in 150 ml of anhydrous ether was added a solution of monoperphthalic acid[7] (0.4 mol, 200 ml of a 2 M solution) in ether mixed with 30 ml of chloroform. The resulting mixture was stirred for 48 h at 25 °C. The solid phthalic acid was removed by filtration and the filtrate was washed several times with 10% aqueous sodium bicarbonate, dried with magnesium sulfate, and concentrated under vacuum. Distillation of the residue gave 39 g (98%) of 1,2-epoxytridecane, bp 119 °C (1 mmHg), n^{25}D 1.4362 [lit.[8] bp 138 °C (15 mm)].

Method B. Using the method of Clark and Goldsmith,[9] epoxide I was prepared from 38.7 g (0.21 mol) of dodecanal, 50 g (0.23 mol) of trimethylsulfoxonium iodide, and 11.0 g (0.22 mol) of sodium hydride dispersion (50% in oil). It was necessary to add the aldehyde as a 25% solution in a 60:40 mixture of dimethyl sulfoxide–tetrahydrofuran. The yield of epoxide 1 was 14.5 g (38%), bp 138 °C (15 mmHg).

1-Dimethylamino-2-tridecanol (2). By the procedure used earlier[3,10] 9.9 g (0.05 mol) of 1,2-epoxytridecane and 4.5 g (0.1 mol) of anhydrous dimethylamine gave 11.0 g (90%) of compound **2**, bp 168–174 °C (12 mmHg), n^{25}D 1.4462.

Anal. Calcd for $C_{15}H_{33}NO$: C, 74.01; H, 13.66; N, 5.76; O, 6.57. Found: C, 74.10; H, 13.64; N, 5.61.

Resolution of 1-Dimethylamino-2-tridecanol. (*R*)-(−)-1-Dimethylamino-2-tridecanol (2a). The resolution was started by mixing a warm solution of 10 g (0.041 mol) of racemic **2** in 20 ml of absolute ethanol with a warm solution of 15.4 g (0.041 mol) of dibenzoyl-(*R*)-(+)-tartaric acid monohydrate[11] in 60 ml of absolute ethanol. The solution was allowed to cool slowly to 10 °C and the salt which crystallized (called salt 1) was collected (25 g). Repeated crystallizations from absolute ethanol, with the solvent amounts shown, were as follows: salt 2, 50 ml, 10 g; salt 3, 40 ml, 8 g; salt 4, 30 ml, 7.5 g, mp 129–131 °C.

The solid salt 4, from the dibenzoyl-(*R*)-(+)-tartaric acid resolution, was shaken with a mixture of 50 ml of 20% aqueous hydrochloric acid and 150 ml of ether until all the solid had dissolved. The ether layer was separated and discarded.[12] The aqueous layer was cooled in ice while 8 g of sodium hydroxide was added slowly with stirring. The resulting basic mixture was saturated with sodium chloride and extracted repeatedly with ether. The ether solutions were combined, dried over magnesium sulfate, and evaporated under vacuum. The resulting liquid was distilled to yield 2.7 g (27% of the racemic amino alcohol) of (*R*)-(−)-1-dimethylamino-2-tridecanol (**2a**), bp 168–173 °C (12 mmHg), $[\alpha]^{26}$D −5.04° (*c* 1.032 g/100 ml, absolute ethanol).

(*S*)-(+)-1-Dimethylamino-2-tridecanol (2b). The filtrates from the above resolution were evaporated under vacuum and the amino alcohol was liberated from the salt and used in this resolution. By a procedure similar to the one above, 5.6 g (0.023 mol) of 1-dimethylamino-2-tridecanol (enriched in the *S* enantiomer) in 10 ml of absolute ethanol was mixed with 8.7 g (0.023 mol) of dibenzoyl-(*S*)-(−)-tartaric acid in 15 ml of absolute ethanol and slowly cooled to 10 °C to yield 11.1 g of salt 1. Repeated crystallizations from absolute ethanol, with the solvent amounts shown, were as follows: salt 2, 25 ml, 9.0 g; salt 3, 30 ml, 8.8 g; salt 4, 40 ml, 8.6 g; salt 5, 40 ml, 8.4 g, mp 129–131°. The resolved amino alcohol was liberated by the procedure given above[12] to yield 3.2 g (32% of the racemic amino alcohol) of (*S*)-(+)-1-dimethylamino-2-tridecanol (**2b**), bp 172 °C (12 mmHg), $[\alpha]^{25}$D +5.43° (*c* 1.142 g/100 ml, absolute ethanol).

Methiodide of (*R*)-(−)-1-Dimethylamino-2-tridecanol. The procedure of Coke and Rice[3a] was used to convert 2.7 g (12.4 mmol) of **2a** to the corresponding methiodide, yield 4.5 g (98%). A sample was crystallized from ethanol–ether, mp 170–172 °C, $[\alpha]^{25}$D −12.23° (*c* 1.022 g/100 ml, absolute ethanol).

Anal. Calcd for $C_{16}H_{36}INO$: C, 49.86; H, 9.42. Found: C, 50.02; H, 9.75.

Methiodide of (*S*)-(+)-1-Dimethylamino-2-tridecanol. As in the preceding method, 3.2 g (13.1 mmol) of **2b** was converted to 4.2 g (84%) of the corresponding methiodide, mp 170–172 °C, $[\alpha]^{22}$D +10.60° (*c* 1.205 g/100 ml, absolute ethanol).

(*R*)-(+)-1,2-Epoxytridecane (1a). The procedure of Coke and Rice[3a] was used to convert 4.5 g (11.7 mmol) of the methiodide of **2a** to 1.39 g (60%) of (*R*)-(+)-1,2-epoxytridecane, bp 138 °C (15 mmHg), $[\alpha]^{22}$D +9.61° (*c* 1.218 g/100 ml, tetrahydrofuran).

(*S*)-(−)-1,2-Epoxytridecane (1b). As in the preceding method 4.0 g (10.4 mmol) of the methiodide of **2b** was converted to 1.24 g (60%) of (*S*)-(−)-1,2-epoxytridecane, bp 138 °C (15 mmHg), $[\alpha]^{25}$D −9.55° (*c* 1.299 g/100 ml, tetrahydrofuran).

Racemic δ-*n*-Hexadecalactone. The procedure used was similar to that of Carlson and co-workers.[4] A solution of *n*-butyllithium (52 mmol, 21 ml of a 2.45 M solution in hexane) was added to a solution of 2.53 g (25 mmol) of diisopropylamine in 30 ml of dry tetrahydrofuran at −50 °C under nitrogen. After 10 min, 30 ml of hexamethylphosphoramide was added, followed by 1.75 g (25 mmol) of propiolic acid. The temperature was allowed to rise to −10 °C over 2 h. A solution of 5 g (25 mmol) of racemic 1,2-epoxytridecane in 5 ml of dry tetrahydrofuran was added and the solution was stirred for 50 h at 25 °C. The resulting solution was evaporated under vacuum and then was diluted with 100 ml of water. The aqueous mixture was washed with methylene chloride, acidified to pH 1 with concentrated hydrochloric acid, saturated with sodium chloride, and extracted with ether (3 × 150 ml). The ether extracts were combined, dried over magnesium sulfate, and evaporated. The crude material remaining was dissolved in 100 ml of absolute ethanol and hydrogenated over palladium (10% on carbon) until approximately 2 equiv of hydrogen had been absorbed. The mixture was filtered and evaporated and the residue was distilled in a Kugelrohr to give 4 g (60%) of racemic δ-*n*-hexadecalactone, bp 130 °C (0.75 mmHg), mp 26.5 °C (lit.[13] mp 29.5–30 °C).

(*R*)-(+)-δ-*n*-Hexadecalactone (3a). In a manner exactly analogous to the preceding method, 0.3 g (1.5 mmol) of (*R*)-(+)-1,2-epoxytridecane (**1a**) was converted to 0.2 g (53%) of (*R*)-(+)-δ-*n*-hexadecalactone (**3a**), bp 130 °C (0.75 mmHg), $[\alpha]^{24}$D +2.69° (*c* 0.371 g/100 ml, tetrahydrofuran).

(*S*)-(−)-δ-*n*-Hexadecalactone (3b). In a manner exactly analogous to the preceding method, 0.3 g (1.5 mmol) of (*S*)-(−)-1,2-epoxytridecane (**1b**) was converted to 0.2 g (53%) of (*S*)-(−)-δ-*n*-hexadecalactone (**3b**), bp 130 °C (0.75 mmHg), $[\alpha]^{23}$D −2.65° (*c* 1.130 g/100 ml, tetrahydrofuran).

(*R*)-(−)-2-Tridecanol (4). A solution of 0.3 g (1.5 mmol) of (*S*)-(−)-1,2-epoxytridecane (**1b**) in 10 ml of ether was added to a suspension of 0.8 g (2.0 mmol) of lithium aluminum hydride in 50 ml of ether. The mixture was heated at reflux under nitrogen for 14 h, and was then worked up by successive addition of 4 ml of water, 3 ml of 20% sodium hydroxide, and 14 ml of water. The ether was separated, dried over magnesium sulfate, and evaporated. The residue was distilled in a Kugelrohr to give 0.2 g (66%) of (*R*)-(−)-2-tridecanol (**4**), bp 106 °C (0.5 mmHg), $[\alpha]^{25}$D −6.01° (*c* 2.015 g/100 ml, absolute ethanol) [lit.[14] bp 156–157 °C (17 mm), $[\alpha]^{20}$D +7.22° for dextrorotatory enantiomer].

(*S*)-(+)-3-Tetradecanol (5). A solution of 0.30 g (1.51 mmol) of (*R*)-(+)-1,2-epoxytridecane in 10 ml of ether was cooled to 0 °C and a solution of methyllithium (3 mmol, 1.5 ml of 2 M solution) in ether was added. The solution was heated at reflux for 3 h and was then cooled in ice and worked up by slow addition of 10 ml of cold water. The ether layer was separated, dried over magnesium sulfate, and evaporated. The residue was distilled in a Kugelrohr to give 0.30 g (91%) of (*S*)-(+)-3-tetradecanol (**5**), bp 110 °C (0.05 mmHg), mp 31–38 °C, $[\alpha]^{25}$D +6.7° (*c* 3.61 g/100 ml, absolute ethanol) (lit.[3a] mp 30–38 °C, $[\alpha]^{25}$D +5.1°).

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—(±)-1, 59812-92-9; **1a**, 59829-81-1; **1b**, 59829-82-2; (±)-2, 59812-93-0; **2a**, 59829-83-3; **2a** methiodide, 59812-94-1; **2b**, 59829-84-4; **2b** methiodide, 59812-95-2; **3a**, 59812-96-3; **3b**, 59812-97-4; 4, 59812-98-5; **5**, 3760-98-3; tridecene, 2437-56-1; monoperphthalic acid, 2311-91-3; dibenzoyl-(*R*)-(+)-tartaric acid, 2743-38-6; dibenzoyl-(*S*)-(−)-tartaric acid, 17026-42-5.

References and Notes

(1) This work was presented at the Southeast–Southwest Regional Meeting of the American Chemical Society, Memphis, Tenn., Oct 1975.

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(5) All melting points and boiling points are uncorrected. Distillations were done with a 2-ft Podbielniak column unless otherwise stated. Optical rotations were taken with a Perkin-Elmer Model 141 polarimeter.

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(12) The optically active dibenzoyltartaric acid monohydrate can be recovered from these ether solutions simply by washing the ether solution with dilute hydrochloric acid, to remove traces of amino alcohol, followed by a water rinse. The ether is then removed under vacuum and the resulting syrup is stirred with water and seeded with the appropriate enantiomer. In this manner the resolving agent is recovered.

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