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EXPEDIENT SYNTHESIS OF QUADRILURE ANTIPODES, THE PHEROMONE OF SQUARE-NECKED GRAIN BEETLE

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Abstract: Both the enantiomers of the title pheromone, (*E*)-3-methyl-7-acetoxynon-3-ene (**I**) have been synthesized in high enantiomeric excess *via* a stereoselective route. Thus, easily accessible, 3-methylpent-1-en-3-ol (**2**) was converted *via* a Claisen orthoester rearrangement to the ester (**3**) with exclusive (*E*)-geometry. Its derivatization to the aldehyde (**5**) followed by reaction with ethylmagnesium bromide gave the racemic pheromone alcohol (**6**) in 27.7% overall yield. Its enantioselective lipase catalyzed *trans*-esterification directly afforded (*R*)-**I**, while its antipode was obtained from the resolved alcohol by chemical acetylation.

Stored grain pest pheromones have attracted wide attention due to their utility in selective suppression of these harmful insects. Many of these exhibit[1] an intriguing stereochemistry-activity relationship. One such insect, the square-necked grain beetle, *Cathartus quadricollis*, is a long-lived, cosmopolitan pest of stored products, the wild type attacking a large variety of plant seed pods[2]. This polished, reddish brown beetle is chiefly abundant in the Southern United States[3] and infests a large number of stored commodities such as corn and peanuts. The male species secretes[2] (3*R*, 6*E*)-7-methyl-6-nonen-3-yl acetate (**I**), trivally termed "quadrilure" as its aggregation pheromone, the (*S*)-enantiomer being inactive. In view of its practical importance, development of a practical synthesis of **I** seems desirable. So far, three asymmetric[4-6] and one racemic[7] synthesis of **I** have been reported. The first chiron[4] synthesis suffers from a multistep protocol for the generation of (*E*)-geometry and use of a volatile chiron which is difficult to handle. While the other chemoenzymatic syntheses[5,6] employed Cu (I) mediated conjugate addition and fractional crystallization for the preparation of the required olefinic geometry and hence seem less attractive for practical scale preparation.

The practical importance of the pheromone coupled with the inadequacy of the existing syntheses for this provided the fillip to the present synthesis. The challenge associated with the synthesis of **I** lies in the stereoselective construction of a trisubstuted olefin and asymmetric

generation of the required 3-carbinol function in high enantiomeric purity. Consequently, we developed a more efficient six step procedure for the same.

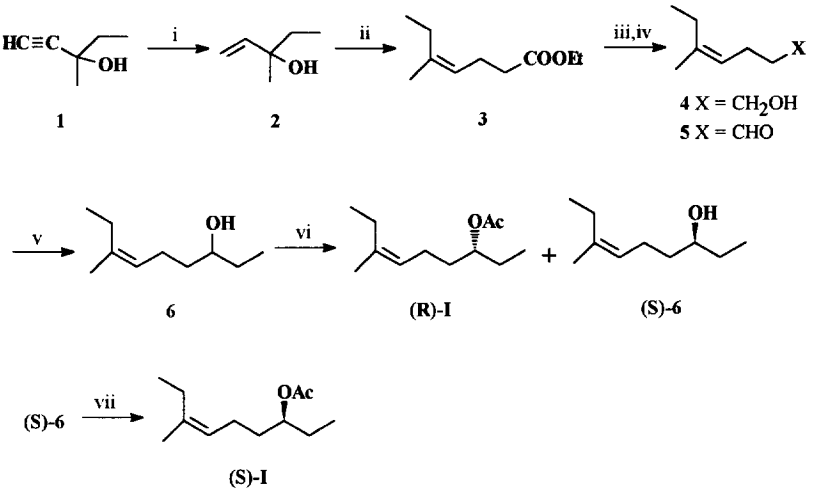
We envisaged that the most practical approach for the introduction of the required (*E*)-olefin geometry would be *via* Claisen orthoester rearrangement[8] of a suitable tertiary carbinol. Consequently, the primary job was the preparation of the desired carbinol, 3-methyl-penten-3-ol (**2**). The simplest route for this seems to be the reaction of ethylmagnesium bromide with methyl vinyl ketone (MVK). However, this led to a impure material from which the desired alcohol could be isolated in 12-15% yield only. Earlier, Takin and Rozkov[9] studied the action of different metal-alkyls with conjugated carbonyl compounds and suggested alkyl lithiums as the reagent of choice for exclusive 1,2-addition. However, attempted reaction of ethyl lithium with MVK furnished an equally disappointing result in the present case. These can be attributed to undesired 1,4-addition as well as polymerization of the reactant ketone. Finally, following a known procedure[10], the alkynol (**1**) was first prepared by reacting mono-lithium acetylide with methyl ethyl ketone (MEK). For its hydrogenation, the polar solvents generally employed, *viz.*, EtOAc, EtOH *etc.*, were unsuitable due to their comparable boiling points with the product **2**. Consequently, compound **1** was hydrogenated over freshly prepared Lindlar catalyst in the presence of powdered KOH[11] using *n*-pentane as the solvent to give **2.** This, on heating with triethyl orthoacetate in the presence of 1-propionic acid (catalyst) furnished the ester **3** which on reduction with LAH furnished the alcohol (**4**). Its PCC oxidation to the aldehyde (**5**) followed by reaction with ethylmagnesium bromide furnished the known alcohol [(±)-**6**].

The exclusive (*E*)-geometry of the olefinic bond in **6** was established by a NOSEY experiment using the following parameters, S12 = TD2 = 1K, TD = NE = 256, SI1 = 512 K and NS = 64 s. This showed spatial interaction of the olefinic proton (δ 5.05) with the allylic methylene signals (δ 1.9-2.1) while no interaction was evident with the allylic methyl singlet at δ 1.6.

For the resolution of **6**, we resorted to biocatalytic approach. Lipase catalyzed transesterification is extensively used[12-14] for the resolution of racemic secondary carbinols. However, most of these are restricted to 2-alkanols/alkenols and cycloalkanols as commercially available lipases are not generally capable of acylating 3-alkanols. This is generally attributed to the small size of one of the hydrophobic sites (H_f) of these enzymes which hinders efficient binding for substrates possessing the smaller alkyl which is bigger than a CH_3-group. Recently, resolution of alkyn-3-ols with *Pseudomonas* lipases has been reported[14,15]. This has been explained on the basis of linearity of the HC≡C-group which possibly does not exceed the size of a methyl group. Later, the same lipase was explored for successful esterifications of 3-alkanols also and in fact used for the synthesis of (**I**) in one of the earlier synthesis[6].

Realizing this, we, on our part investigated efficiency of several lipases in the same pursuit. It was gratifying to note that besides *Pseudomonas flourescence* lipase (PFL), the lipase from *Penicillium roqueforti* (PRL) can also acylate the alcohol (**6**) with vinyl acetate enantioselectively. Different reaction parameters *viz.* solvent polarity (hexane, toluene, diisopropyl ether and CH_2Cl_2), extent of conversion, enzyme concentration *etc.* were studied in order to optimize the reaction. Best result was obtained in diisopropyl ether and at 40% conversion, the (*R*)-acetate (**I**) and the (*S*)-alcohol (**6**) were obtained in 98% and 78% ee's respectively (**SCHEME**). A second enzymatic acetylation of

the partially resolved alcohol **6** led to its enantiomeric enrichment (97% ee). The configurations of the products were ascertained by comparing their chirooptical data with the reported values[5], while their %ee's estimated from the PMR analyses of their corresponding MTPA-esters. The spectral data of the synthetic pheromone antipodes were in good agreement with those reported[5,6] earlier.



i) H_2/Lindlar/KOH/*n*-Pentane, ii) Triethyl orthoacetate/*n*-Propionic Acid/Δ, iii) LAH/Ether, iv) PCC/CH_2Cl_2/ NaOAc, v) EtMgBr/Ether, vi) Vinyl acetate/PRL/Diisopropyl ether, vii) Ac_2O/Pyridine.

SCHEME

EXPERIMENTAL

All the bp's are uncorrected. The IR spectra were scanned with a Perkin-Elmer spectrophotometer, model 837 and only the pertinent bands are mentioned. The PMR spectra were recorded with a Bruker AC-200 (200 MHz) instrument in $CDCl_3$. The optical rotations were measured with a Jasco DIP-360 polarimeter. Anhydrous reactions were carried out under Ar using freshly distilled solvents kept over activated molecular sieves (4A°).

3-Methylpent-1-yn-3-ol (1): To a stirred solution of monolithium acetelyde (0.32 mol) at -78°C was added MEK (20.0 g, 0.28 mol) in ether (200 ml). After stirring for 4 h, the reaction mixture was quenched with solid NH_4Cl and NH_3 was allowed to evaporate. Water was added into it and the content extracted thoroughly with ether. The ether layer was washed with saturated NH_4Cl solution,

dried and carefully concentrated so as to remove the fraction collecting upto 60°C. The residue was then fractionated to furnish pure **1**. yield: 18.0 g (66.1%); bp 120°C (lit[10]. bp 120°C); IR: 3400, 3300, 2140, 1480 and 1390, 1050 cm^{-1}; PMR: δ 0.9-1.2 (m, 3H), 1.5-1.9 (m containing a s at δ 1.5, 5H), 2.3 (s, 1H), 3.25 (br. s, 1H, D_2O exchangeable). Anal. Calcd. for $C_6H_{10}O$: C, 73.43; H, 10.27. Found : C, 73.34; H, 10.12.

3-Methylpent-1-en-3-ol (2): A mixture of powdered KOH (5.6 g, 0.1 mol) and compound **1** (9.8 g, 0.1 mol) in pentane (40 ml) was stirred till dissolution (15-20 min). The resulting solution was transferred to the hydrogenation flask, freshly prepared Lindlar catalyst (0.5 g) added and the mixture shaken under a positive pressure of H_2. The hydrogenation was exothermic and required occasional cooling. A rapid uptake of H_2 took place immediately and the reaction was complete within 4 h. It was diluted with ether, passed through a small pad of celite to remove the catalyst and the clear solution concentrated on a water bath. Evaporative distillation of the residue gave pure **2**. yield: 8.8 g (88%); bp: 115°C; (lit[11]. bp 115-116°C); IR: 3400, 3100, 1640, 1480, 1390, 990 and 910 cm^{-1}; PMR: δ 0.8-1.1 (m, 3H), 1.3-1.8 (m containing a s at δ 1.4, 5H), 2.6 (br. s, 1H, D_2O exchangeable), 4.8-6.3 (m, 3H). Anal. Calcd. for $C_6H_{12}O$: C, 71.94; H, 12.08. Found : C, 71.84; H, 12.22.

Ethyl 5-methylhept-4(*E*)-enoate (3): A stirred mixture of **2** (10.0 g, 0.1 mol), triethyl orthoacetate (30 ml) and 1-propionic acid (1.0 ml) was heated in such a manner as to increase the bath temperature to 100°C in 2 h. Ethanol formed during the process, was continuously distilled. After ensuring cessation of any more distillate (2 h), the bath temperature was raised to 140°C and the mixture kept at that temperature for 4 h. The flask was fitted with a distillation assembly and the content carefully fractionated at normal pressure. After discarding first fraction containing the excess orthoester, the entire distillate (> 150°C) was collected and refractionated to afford **3**. yield: 12.0 g (70.6%); bp: 172°C; IR: 1740, 1480 and 1390 cm^{-1}; PMR: δ 0.96 (t, J = 7 Hz, 3H), 1.25 (t, J = 7 Hz, 3H), 1.72 (s, 3H), 1.9-2.3 (m, 6H), 4.15 (q, J = 7 Hz, 2H), 5.10 (t, J = 6 Hz, 1H). Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found : C, 70.34; H, 10.52.

5-Methyl-4(*E*)-hepten-1-ol (4): The ester **3** (3.9 g, 0.023 mol) was reduced with LAH (0.68 g, 0.018 mol) in ether (40 ml) to furnish **4** after usual isolation. yield: 2.54 g (86.1%); bp: 175°C; IR: 3340, 1470, 1390 and 780 cm^{-1}; PMR: δ 0.9-1.3 (m containing a t at δ 1.0, 5H), 1.6 (s, 3H), 1.9-2.3 (m, 4H), 2.7 (br. s, 1H, D_2O exchangeable), 3.68 (t, J = 7 Hz, 2H), 5.06 (t, J = 6 Hz, 1H). Anal. Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58. Found : C, 75.06; H, 12.42.

5-Methyl-4(*E*)-heptenal (5): Compound **4** (4.0 g, 0.031 mol) was oxidized with PCC (10.1 g, 0.47 mol) in presence of NaOAc (0.41 g, 0.005 mol) in CH_2Cl_2 (40 ml). Usual isolation followed by distillation furnished pure **5**. yield: 3.38 g (86%); bp: 175°C; IR: 2720, 1710 and 1610 cm^{-1}; PMR: δ 1.0 (m, 3H), 1.7 (s, 3H), 1.8-2.2 (m, 4H), 2.3-2.4 (m, 2H), 5.06 (t, J = 6 Hz, 1H), 9.8 (t, J = 1.5 Hz, 1H). Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found : C, 76.28; H, 11.36.

(*E*)-3-Methyl-3-nonen-7-ol (6): A solution of ethylmagnesium bromide (0.039 mol) in ether (40 ml) [prepared from ethyl bromide (4.25 g, 0.039 mol) and Mg-turnings (1.14 g, 0.047 mol)] was added to a stirred solution of the aldehyde **5** (3.3 g, 0.026 mol) at -20°C. After 1 h, the reaction was quenched with saturated NH_4Cl solution and extracted with ether. The ether layer was washed with water and brine and finally dried. Removal of solvent followed by distillation afforded (±)-**6**. yield: 3.7 g (91%);

bp: 150°C/ 20mm, (lit[4] 60-70°C (bath temp.)/ 0.5 mm); IR: 3400, 1480, 1380 and 1060 cm^{-1}; PMR: δ 0.8-1.1 (m, 6H), 1.3-1.7 (m containing a s at δ 1.6, 7H), 1.9-2.1 (m, 4H), 2.41 (s, D_2O exchangeable, 1H), 3.5-3.6 (m, 1H), 5.05 (t, J = 6 Hz, 1H). Anal. Calcd. for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found : C, 76.64; H, 12.81.

(R,*E*)-3-Methyl-7-acetoxynon-3-ene (I): A mixture of **6** (3.12 g, 0.02 mol), vinyl acetate (3.5 ml, 0.04 mol) and lipase from *Penicillium roqueforti* (Fluka, sp. act. 2 unit/g of solid) (3.0 g) in diisopropyl ether (40 ml) was magnetically stirred at room temperature. The reaction was stopped at desired conversion (40%) by monitoring with GLC. The mixture was filtered and the filtrate concentrated. Individual components of the reaction mixtures were obtained by column chromagraphy of the residue over silica gel (0-10% ether/hexane). compound **(R)-I**: yield: 1.44 g (36%); $[\alpha]^{25}$ +9.28 (c 1.46, $CHCl_3$), (lit[5]. $[\alpha]^{20}$ +9.59 (c 1.09, $CHCl_3$); IR: 1750, 1480, 1380, 1250 and 970 cm^{-1}; PMR: δ 0.9-1.2 (m, 6H), 1.4-1.7 (m containing a s at δ 1.6, 7H), 1.8-2.3 (m containing a s at δ 2.1, 7H), 4.5-4.9 (m, 1H), 5.1 (t, J = 6 Hz, 1H). Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.19. Found : C, 72.61; H, 11.33.

(S,*E*)-3-Methyl-7-acetoxynon-3-ene (I): Resolved **(S)-6** (1.65 g, 0.011 mol) was subjected to a second acetylation as above to produce optically pure **(S)-6**. yield: 1.2 g [38.4% based on (±)-**(6)**]; $[\alpha]^{25}$ +10.1 (c 1.24, $CHCl_3$), [lit[5]. $[\alpha]^{21}$ +10.4 (c 0.96, $CHCl_3$)]. Its spectral data were identical with those for (±)-**6**.

A mixture of the above alcohol (1.2 g, 0.008 mol), acetic anhydride (5.0 ml) and pyridine (5.0 ml) in CH_2Cl_2 (20 ml) was stirred at room temperature for 18 h. Usual isolation furnished **(S)-I**. yield: 1.34 g (88%); $[\alpha]^{25}$ -8.9 (c 1.16, $CHCl_3$), (lit[5]. $[\alpha]^{21}$ -9.05 (c 1.05, $CHCl_3$)). Its spectral data were similar to those of the antipode. Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.19. Found : C, 72.84; H, 11.36.

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