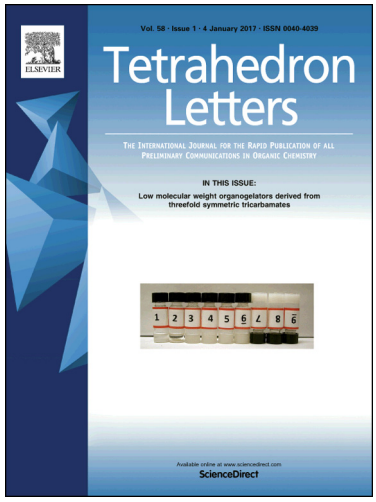

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Graphical Abstract

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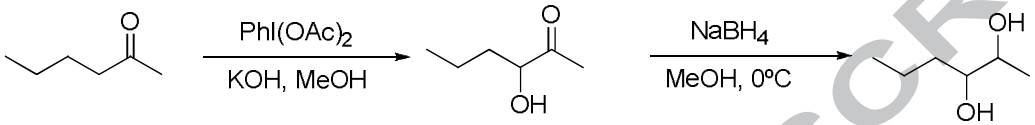

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Synthesis of aggregation pheromone components of cerambycid species through α-hydroxylation of alkylketones

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ABSTRACT

The synthesis of 3-hydroxy-2-hexanone and 2,3-hexanediol, two components of the aggregation pheromone of several cerambycid species, is disclosed in here. Starting from 2-hexanone, through an α-hydroxylation using (diacetoxyiodo)benzene, 3-hydroxy-2-hexanone is obtained in good yield. Further reduction of this compound, gives 2,3-hexanediol in excellent yield. A study of the α-hydroxylation reaction of several alkylketones using an hypervalent iodine reagent is also disclosed in here. The synthesis of optically active compounds (*R*)- and (*S*)-3-hydroxy-2-hexanone was achieved starting from 2-hexanone with nitrosobenzene and L- and D-proline respectively, in several reaction media.

Longhorn beetles (Insecta: Coleoptera: Cerambycidae) are a cosmopolitan and economically important group of insects. Cerambycids affect many agricultural crops and ornamental trees, causing millions of dollars in damage each year.[1] Therefore, it is essential to develop effective procedures for monitoring these cerambycid pests before they become established, by developing lures for pheromone-baited traps with cerambycid pheromones to attract a broad taxonomic diversity of these species.[2,3] As reported by Hanks *et al.*,[4] the 2,3-hydroxyketone is a highly conserved structural motif in male specific compounds among cerambycine species. Several species in the subfamily Cerambycinae produce male aggregation pheromones consisting of 3-hydroxy-2-hexanone and/or 2,3-hexanediol, as shown in Figure 1. These compounds can be used as generic pheromone blends to attract both sexes of this insects.[5] Furthermore, the attraction of multiple cerambycine species to (*R*)-3-hydroxy-2-hexanone, suggest that this compound is a widespread aggregation pheromone component in this family.[4] In addition, there are several reports on the variation of the chain lengths for the hydroxyketone and diol motifs in these male aggregation pheromones for this family.[6]

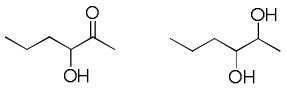

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Figure 1. 3-Hydroxy-2-hexanone and 2,3-hexanediol, major components of the aggregation pheromone of several cerambycids.

These compounds were synthesized by Schroder and coworkers using and a Corey-Seebach sequence,[7] starting from *n*-butanal and 2-methyl-l,3-dithiane in three steps. This report also describes the asymmetric synthesis of (*R*)-3-hydroxy-2-hexanone in 99% enantiomeric excess, starting from *E*-2-hexen-1-ol, through a Sharpless epoxidation followed by a Wacker oxidation, in seven steps with an overall yield of 24%. The synthesis of the four 2,3-hexanediol stereoisomers and the two 2-hydroxy-3-hexanone enantiomers from ethyl (*S*)-lactate and methyl (*R*)-lactate was achieved by Lacey and coworkers in a six steps methodology, in which the key step takes advantage of an alkylation with a lithium salt.[8] These authors also reported the production of (*R*)- and (*S*)-3-hydroxy-2-hexanone by kinetic resolution of the racemate with Amano lipase AK, reaching an enantiomeric excess of 94% for both cases.[9] More recently, Imrei *et al.*,[10] described the preparation of racemic 3-hydroxy-2-hexanone in a multigram scale by direct hydration of 1-hexyn-3-ol with boron trifluoride and highly toxic mercuric oxide as a catalyst.

In an attempt to shorten the synthetic strategy for these compounds to use them in monitoring pests in citrus, a methodology for the α-hydroxylation of 2-hexanone using hypervalent iodine chemistry was envisioned.[11-13] This chemistry has been extensively studied by Moriarty and coworkers,[14] particularly for acetophenone derivatives.[15] This transformation involves the use of (diacetoxyiodo)benzene in KOH/MeOH. The reaction occurs by attack of an enolate to *in situ* formed (dimethoxyiodo)benzene (Scheme 1). Reaction with methoxide, followed by intramolecular displacement of iodobenzene gives an

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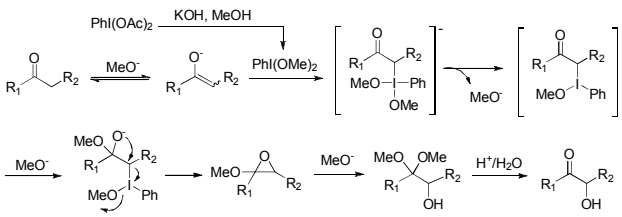
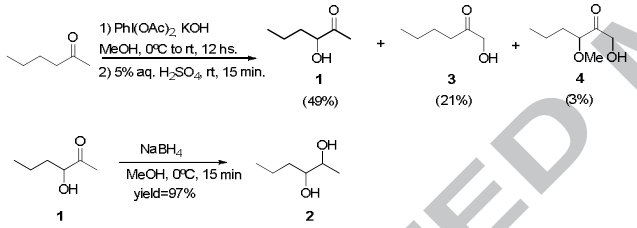
oxirane. Ring opening by methoxide renders an α-hydroxyketal, which is then treated with acid to obtain an α-hydroxyketone.



Scheme 1. Proposed mechanism for the α-hydroxylation of alkylketones with hypervalent iodine reagent.

Although few reports have been done with aliphatic ketones, experience shows that α-hydroxylation occurs preferentially at the more substituted position.[14]

As shown in Scheme 2, the synthesis of 3-hydroxy-2-hexanone and 2,3-hexanediol was performed starting from 2-hexanone. Through an α-hydroxylation of this compound using the hypervalent iodine reagent (diacetoxyiodo)benzene, 3-hydroxy-2-hexanone[7] and 1-hydroxy-2-hexanone[16] were obtained as a 7:3 mixture in 70% yield.[17] The fact that the α-hydroxylation occurs preferentially at the more substituted position reinforces the observation discussed above. Separation of the two products was easily achieved by flash column chromatography, leading to an isolated yield for 3-hydroxy-2-hexanone of 49%. As reported previously,[7,8] the volatility of this compound leads to moderate yields due to losses during purification.



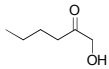
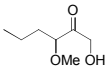
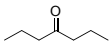
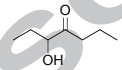
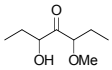
Scheme 2. Synthesis of 3-hydroxy-2-hexanone and 2,3-hexanediol.

In spite of previous reports of isomerization for these compounds,[18] upon fully characterization of the products by spectroscopy, there was no evidence of 2-hydroxy-3-hexanone formation. The formation of the byproduct 1-hydroxy-3-methoxy-2-hexanone could be explained in light of the mechanism described by Moriarty for the oxidation of ketones.[14,15] The formation of methoxyketones has already been observed in sterically hindred ketones under these conditions.[19-21]

To complete the synthesis of the second component of the aggregation pheromone, a reduction of 3-hydroxy-2-hexanone with sodium borohydride was performed. This led to the desired 2,3-hexanediol in excellent yield.[7] The product was obtained as a mixture of stereoisomers, and the two diastereomers could be readily separated by chromatography. This fact is relevant due to the evidence that *syn* and *anti* isomers proved to have different biological activity. The use of the mixture in some cases may not be effective for all cerambycid species that produce a 2,3-hexanediol stereoisomer, with reports of inhibitory effects for the unnatural isomer in some cases.[6]

With the aim of expanding the range of applicability of this strategy, several readily available alkylketones were subjected to the α-hydroxylation conditions described. Therefore, 2-pentanone, 3-pentanone and 4-heptanone reacted with (diacetoxyiodo)benzene to study regioselectivity patterns and formation of byproducts, and these results are shown in table 1.

Table 1. α-Hydroxylation of several alkylketones.[a]

Entry	Reagent	Product (isolated yield)		
1		 **1** (49%)	 **2** (21%)	 **4** (3%)
2		 **5** (23%)	 **6** (23%)	 **7** (5%)
3		 **8** (57%)	 **5** (9%)	
4		 **9** (22%)	 **10** (2%)	

[a]Reactions were conducted with 1.1 eq. of (diacetoxyiodo)benzene and 3 eq. of KOH in dry MeOH.

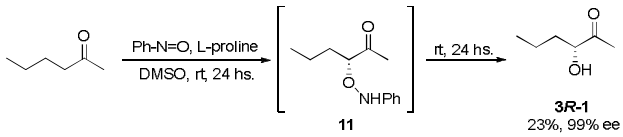
In all cases α-hydroxyketones were obtained by omitting isolation of the acetal, with direct hydrolysis of the reaction product. α-Hydroxylation of 2-pentanone occurred without regioselectivity (Table 1, entry 2), rendering 3-hydroxy-2-pentanone (**5**)[22] and 1-hydroxy-2-pentanone (**6**)[23] in 23% yield respectively. In this case, the formation of the methoxyketone byproduct (**7**) occurs in 5% yield, determined by NMR spectroscopy, due to the fact that **6** and **7** were not able to be isolated by column chromatography due to its similar retention factor. When 3-pentanone was used (entry 3), a mixture of 2-hydroxy-3-pentanone (**8**)[22] and 3-hydroxy-2-pentanone (**5**) was obtained as described previously by Moriarty.[24] This result suggests that the formed compound **8** could be isomerized under the reaction conditions, as already reported for these type of compounds.[6] No methoxyketone was observed in this case. Reaction of 4-heptanone (entry 4) rendered 3-hydroxy-4-heptanone (**9**)[25] in 22% yield, and also occurred the formation of a methoxylated byproduct (**10**) in 2% yield. No rearrangement was observed in this case.

In the case of unsymmetrical ketones (entries 1-2), a similar result was expected as the substrates are very similar, but the reaction proved to be erratic in this sense. For symmetrical ketones (entries 3-4), a different behavior was also observed. In general lines, it can be said that there is a regioselectivity of the hydroxylation at the more substituted position. This trend, although not quite evident, can be explained by the formation of the most stable enolate.[24] Also, the formation of the methoxyketone byproducts, although seen in a minor proportion, happens with a similar regioselectivity pattern.

The erratic distribution of the products for the different substrates tested may be attributed to subtle differences in the structure of the starting materials. These reactions occur in moderate yield. However, in our hands, other α-hydroxylation methods proved to be unsuccessful for alkylketones.[26,27]

The synthesis of optically active compound (*R*)-3-hydroxy-2-hexanone (***3R*-1**) was achieved starting from 2-hexanone with nitrosobenzene and L-proline in dimethylsulfoxide (Scheme 3).[28,29] This reaction renders intermediate aminooxyketone **11** in

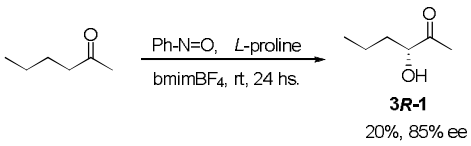
56% yield, and upon standing at room temperature for 24 hours affords ***3R*-1** in 23% isolated yield. The enantiomeric excess of the ***3R*-1** was estimated to be at least 99%, determined by chiral phase gas chromatography analysis.[30]



Scheme 3. Synthesis of (*R*)-3-(phenylaminooxy)-2-hexanone and (*R*)-3-hydroxy-2-hexanone.

The same strategy was employed using D-proline to afford ***3S*-1** in 30% yield. The enantiomeric excess was estimated to be at least 99%.

A survey of different solvents to improve the yield was not successful (*i.e.* $CHCl_3$, DMF, CH_3CN). This strategy was also employed using the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate,[31,32] with the aim of improving the reaction yield. Under these conditions (Scheme 4), the reaction afforded directly ***3*R-1** in 20% yield (based upon recovery of starting material). In this case, the enantiomeric excess was estimated to be at least 85%, determined by chiral phase gas chromatography analysis.



Scheme 4. Synthesis of (*R*)-3-hydroxy-2-hexanone in ionic liquid.

To summarize, a concise route for the synthesis of 2,3-hexanediol and 3-hydroxy-2-hexanone was achieved. The strategy, which involves the use of hypervalent iodine reagents in the α-hydroxylation of 2-hexanone, widens the scope of the method previously reported by Moriarty, and further demonstrates its applicability to aliphatic ketones.

The synthesis of optically active compounds *(R)*- and *(S)*-3-hydroxy-2-hexanone was achieved starting from 2-hexanone with nitrosobenzene and L- or D-proline respectively, in several reaction media, attaining better reaction yields in DMSO. Although these reactions occur with low yields, the products are obtained with excellent enantiomeric excess. Previous methods for preparing these compounds comprised larger routes,[7,8] had lower selectivity[9] or used toxic reagents[10] in comparison with the reported method. However, if large amounts of these compounds are needed for pest monitoring or control purposes, the low yields along with the formation of byproducts by the described methodology may become a disadvantage.

Results of the use of these synthetic pheromone components, in racemic and optically active form, to monitor cerambycid pests in field tests will be reported in due course.

Acknowledgements

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17. *Reaction of 2-hexanone with (diacetoxyiodo)benzene:* A solution of 2-hexanone (9.98 mmol) in methanol (20 mL) is added dropwise, under nitrogen, to a stirred solution of potassium hydroxide (29.9 mmol) in methanol (20 mL), cooled with an ice bath. The solution is stirred for 15 min and (diacetoxyiodo)benzene (10.9 mmol) is added in small portions for 30 min. The reaction mixture is warmed to room temperature and stirred for 12 hrs. A 5% aqueous solution of H_2SO_4 is added to the reaction mixture. Methanol is removed by distillation in a rotary evaporator. The residue was partitioned between water and CH_2Cl_2. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated in a rotary evaporator. Products were isolated by flash chromatography using hexane-EtOAc (4:1) as eluting solvent.
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30. Determination of optical purity was performed by chiral gas chromatography on a GC with split injector, flame ionization detector and nitrogen as carrier gas; enantiomers were separated on a Megadex DET TBS-β-(diethyl-tert-butyl-silyl β-cyclodextrin) 25 m x 0.25 mm i.d. x 0.25 µm column (temperature program: 50°C for 3 min, then at 5°C/min to 200°C).
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Supplementary Material

Supplementary data associated with this article can be found online at http://dx.doi.org/10.1016/j.tetlet.xxxx.xx.x

Highlights

- Synthesis of cerambycid pheromone: 3-hydroxy-2-hexanone and 2,3-hexanediol.
- α-Hydroxylation of several alkylketones using (diacetoxyiodo)benzene.
- Chiral synthesis of *(R)*-3-hydroxy-2-hexanone using L-proline as a catalyst.