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A New Synthesis of Alkylated 2*H*-Pyran-2-ones and Its Application to the Determination of the Relative and Absolute Configuration of Supellapyrone, Sex Pheromone of the Brownbanded Cockroach, *Supella longipalpa*

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Abstract: The sex pheromone of the brownbanded cockroach, *Supella longipalpa,* can be synthesized by direct coupling of a brominated pyrone with an alkylzinc reagent. The stereochemistry of the natural pheromone has been assigned as (*2'R, 4'R*)-5-(*2',4'*-dimethylheptanyl)-3-methyl-2*H*-pyran-2-one by a combination of synthesis, chiral gas chromatography, and electrophysiological measurement.

As the fruit of an impressive interdisciplinary collaboration, the volatile sex pheromone of the brownbanded cockroach, *Supella longipalpa*, has been isolated and characterized as 5-(*2',4'*-dimethyl heptanyl)-3-methyl-2*H*-pyran-2-one (**1**) (supellapyrone) with unknown stereochemistry.[1] The classical approach to determining the stereochemistry of chiral pheromones has required enantioselective syntheses of all possible isomers, coupled with a bioassay to identify the active form(s).[2] Even this systematic approach has its limitations, however, as shown by the example of the German cockroach (*Blattella germanica*) contact sex pheromone, where all four possible stereoisomers showed indistinguishable biological activity.[3]

Supellapyrone belongs to the family of 5-substituted 2*H*-pyran-2-ones, other members of which are well-known as cardiotonic agents,[4] insect defensive compounds,[5] and antiviral agents.[6] In spite of these biological activities, no general synthetic method for the direct attachment of alkyl groups to a pyrone ring has been reported, and syntheses in this area have all been cumbersome. We have now developed a convergent synthesis of alkylated pyrones, and we report its application to the synthesis of mixtures of stereoisomers of **1** (**Fig. 1**). Subsequent gas chromatographic separations and electrophysiological experiments (GC-EAD) allow us to define the stereochemistry of natural supellapyrone.

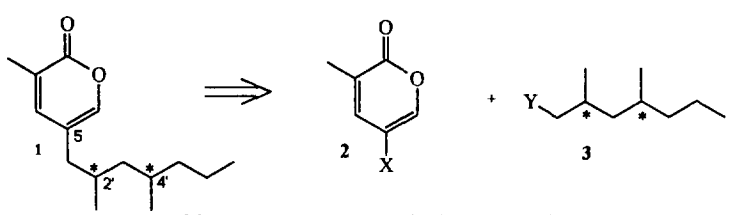
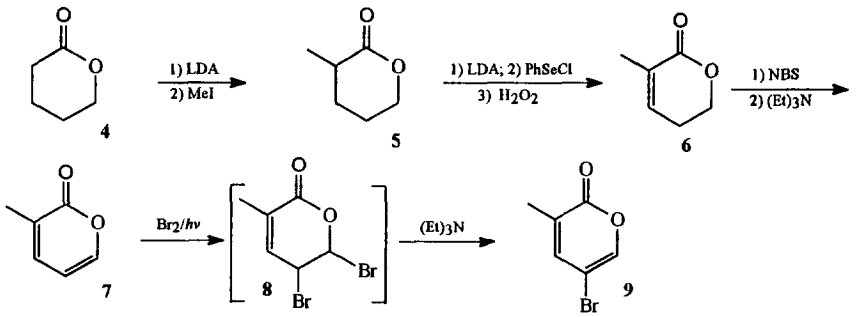


Fig. 1. Convergent synthetic strategy for supellapyrone

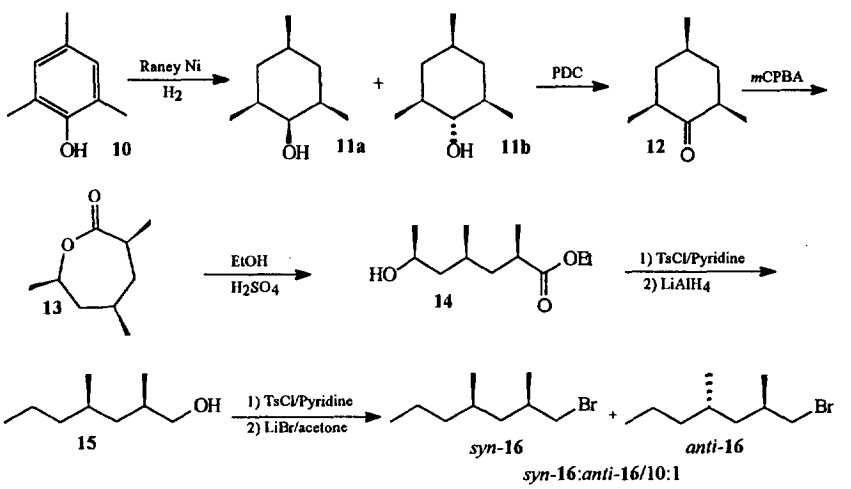
Scheme I



A convenient preparation of 5-bromo-3-methyl-2*H*-pyran-2-one is outlined in **Scheme I**. Methylation of δ-valerolactone (**4**) gave α-methyl-δ-valerolactone (**5**) in 76% yield. Selenylation of **5**, followed by oxidation and elimination introduced the desired α,β–double bond, giving **6** in 65% yield. Allylic bromination of **6** followed by elimination afforded pyrone **7** in 55% yield. Selective photochemical addition of bromine gave intermediate **8**, which was directly converted to crystalline **9** in 46% overall yield on treatment with base.[7]

The racemic side chain synthon **16** was synthesized using a minor variation of a reported procedure (**Scheme II**).[8] Mesitol was catalytically hydrogenated at high pressure to afford two major diastereomers **11a** and **11b** (90%) and other minor isomers (10%) in nearly quantitative yield. The mixture was oxidized to yield chiefly the all *cis*-ketone **12** (86%). Baeyer-Villiger oxidation of this cyclohexanone provided lactone **13**, which was ethanolyzed to the ester-alcohol **14** in 88% yield. Tosylation of the hydroxyl group followed by reduction afforded primary alcohol **15**. Further tosylation of this alcohol, followed by displacement of the sulfonyl moiety by bromide gave the

Scheme II

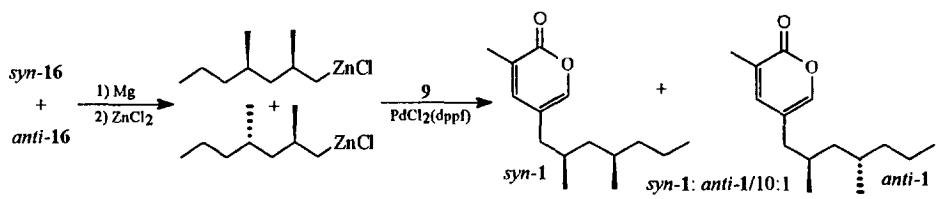


syn-16:*anti*-16/10:1

desired *syn*-**16** (91%) accompanied by *anti*-**16** (9%), reflecting the presence of minor stereoisomers in **11** and the subsequent intermediates. This mixture was of particular use in establishing the stereochemistry of natural supellapyrone.

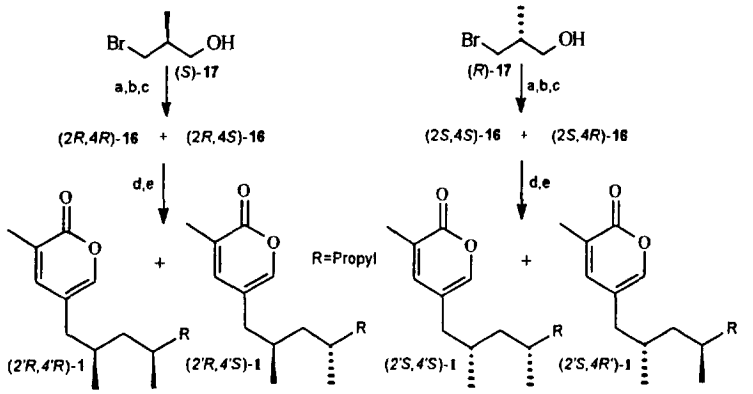
In the hope of preparing a reactive 2*H*-pyran-2-one synthon, we investigated the reaction of **9** with *t*-BuLi /-78 °C, but this gave a complex mixture instead of the desired lithium-bromine exchange product. Treatment of the Grignard reagent from **16** in the presence of catalysts, $Pd(PPh_3)_2Cl_2$ or $Ni(PPh_3)_2Cl_2$, with bromopyrone **9**, gave no trace of the desired coupling product, again because of the reactivity of the pyrone to the nucleophilic reagent. Fortunately, it was found that **9** is relatively stable to alkylzinc reagents. This made possible the dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II)-catalyzed coupling[9] of **9** with the organozinc chloride derived from **16** to give the expected mixture of *syn*-**1** and *anti*-**1** in 47% yield (unoptimized) (**Scheme III**). GC analysis (DB-5, 30 m) indicated that the coupled product contained *syn*-**1** and its diastereomer *anti*-**1** in the expected 10:1 ratio. GC-MS analysis showed both isomers to have mass spectra essentially indistinguishable from that of the cockroach pheromone. However, only the earlier eluting *syn*-**1** has a retention time identical to that of the natural product. ^1H NMR analysis also showed *syn*-**1** to have chemical shifts and coupling patterns identical to those of the natural pheromone, while *anti*-**1** was clearly different. Finally, a GC-EAD study demonstrated that a male *S. longipalpa* antenna responds to synthetic *syn*-**1** as well as to the natural pheromone.[10] These data establish the "*syn*" relative stereochemistry for the natural sex pheromone; the remaining question is that of its absolute configuration.

Scheme III



Gas chromatographic resolution of the synthetic mixture of racemic *syn*-**1** and *anti*-**1** was achieved on a cyclodextrin-based chiral capillary column, Chiraldex GTA , which gave baseline separation of all four stereoisomers (**Fig. 2A**). To assign the absolute stereochemistry to each peak, we prepared two additional diasteromeric mixtures. As outlined in **Scheme IV**, copper-assisted alkylation of the commercially available (*S*)-3-bromo-2-methylpropanol [(*S*)-**17**] (99% *e.e.*) with the Grignard reagent derived from 2-bromopentane afforded a diastereomeric mixture of two alcohols which was directly converted into the corresponding bromides (*2'R,4'R*)-**16** and (*2'R,4'S*)-**16**. The bromides were coupled with **9** to yield a 1:1 mixture of (*2'R,4'R*)-**1** and (*2'R,4'S*)-**1**. Chiral GC analysis indicated that these two compounds have retention times identical to those of peaks III and IV (**Fig. 2A**). Similarly, (*2'S,4'S*)-**1** and (*2'S,4'R*)-**1**, corresponding to peaks I and II, were prepared from (*R*)-**17** (88% *e.e.*). Thus, the absolute stereochemistry of all four peaks could be assigned as: I: (*2'S,4'S*)-**1**; II: (*2'S,4'R*)-**1**; III:(*2'R,4'R*)-**1** and IV: (*2'R,4'S*)-**1**.

Scheme IV



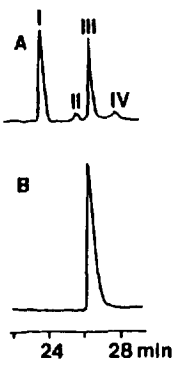


Fig. 2. Chiral GC separation of supellapyrone and its isomers

A small sample of natural pheromone re-isolated from 200 female *S. longipalpa* gave a single peak on the Chiraldex GTA column (**Fig. 2B**) with the same retention time as peak III. This correspondence was confirmed by coinjection. Both the naturally occurring pheromone and the synthetic (*2'R,4'R*)-**1** (peak III) were EAG-active.[10] The absolute configuration of supellapyrone is thus defined as (*2'R,4'R*)-5-(*2',4'*-dimethylheptanyl)-3-methyl-2*H*-pyran-2-one.

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