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An easy and versatile approach to the synthesis of chiral pheromone lactones via 4,4-dimethyl-2-oxazoline derivatives

Paulo H. G. Zarbin, Alfredo R. M. Oliveira,* Fabio Simonelli, José A. F. P. Villar and Orlando Delay, Jr.

Departamento de Química, Universidade Federal do Paraná, CP 19081, 81531-990 Curitiba-PR, Brazil

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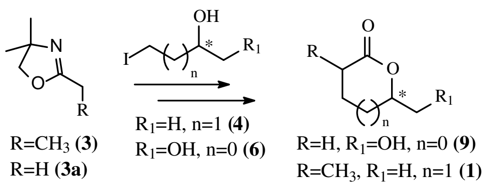
Abstract—As part of our ongoing investigation on the versatility of 4,4-dimethyl-2-oxazoline derivatives, we present a straightforward synthesis of chiral lactone pheromones from readily available starting materials. As an application, we describe the diastereoselective synthesis of *cis* and *trans*-2-methyl-5-hexanolide (**1**), a pheromone component of the carpenter bee *Xylocopa hirutissima*, and a formal synthesis of (4*R*,5*Z*)-5-tetradecen-4-olide (**2**), the sex pheromone of the Japanese beetle *Popillia japonica*.

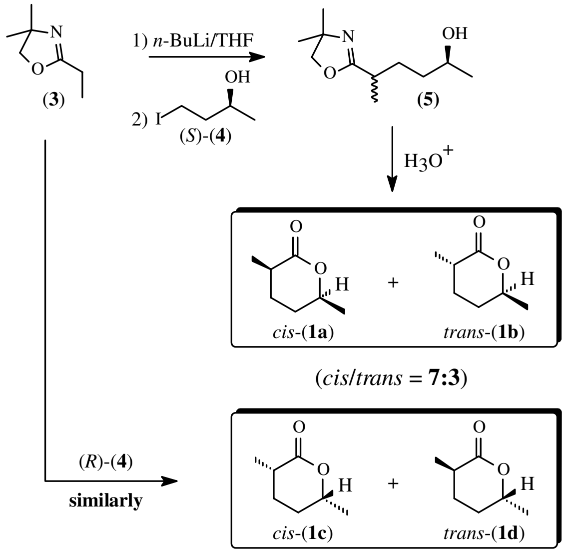
Lactone structures are found in many natural products among which there are a number with strong biological activity.[1] Lactones were isolated from insects and are part of the intriguing communication systems of bees, beetles and other taxa.[2] During previous years, several methodologies to synthesize lactones were developed.[3] Here we describe a way to synthesize chiral lactones, employing a coupling reaction of 4,4-dimethyl-2-oxazoline derivatives with alkyl iodides as the key step (Scheme 1). We choose *cis*- and *trans*-2-methyl-5-hexanolide (**1**) as an example of a diastereoselective synthesis, and a formal synthesis of (4*R*,5*Z*)-5-tetradecen-4-olide (**2**) as an enantioselective one.

While compound *cis*-2-methyl-5-hexanolide (**1**) is a component of the pheromone blend of the carpenter bee *Xylocopa hirutissima*[4] (4*R*,5*Z*)-5-tetradecen-4-olide (**2**) is the sex pheromone of the Japanese beetle *Popillia japonica*.[5]



Scheme 1. General strategy to chiral lactones.

All four possible isomers of (**1**) were synthesized using the optically pure hydroxy iodides (*R*)- and (*S*)-(**4**), obtained from PHB and by microbiological reduction of ethyl acetoacetate, respectively,[6] as electrophilic source. The reaction of 2-ethyl-4,4-dimethyl-2-oxazoline



Scheme 2. Synthesis of the lactones (2*R*,5*S*)-(**1a**)/(2*S*,5*S*)-(**1b**) and (2*S*,5*R*)-(**1c**)/(2*R*,5*R*)-(**1d**).

Keywords: Pheromones; Synthesis; Chiral lactones; Oxazoline.

* Corresponding author. Tel.: +55 41 361 3174; fax: +55 41 361 3186; e-mail: armo@quimica.ufpr.br

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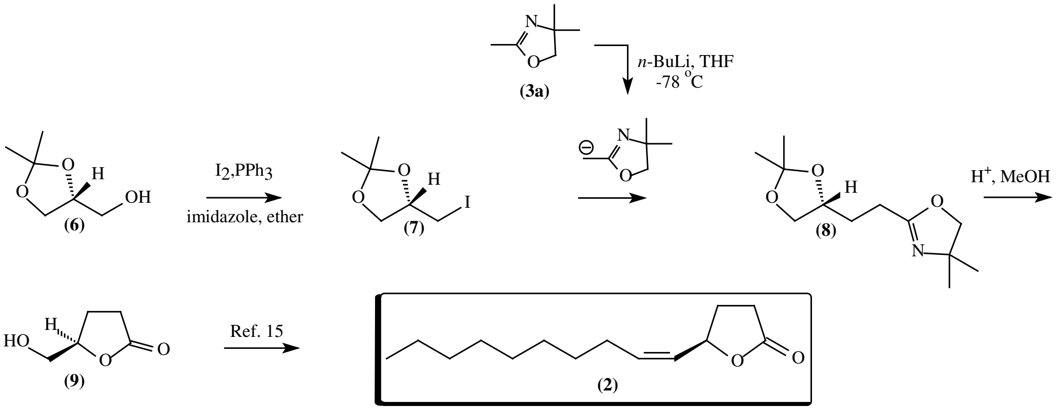

Scheme 3. Formal synthesis of lactone (**2**).

(**3**) with (*S*)-(**4**) afforded compound (**5**) in 92% isolated yield,[7] which was hydrolyzed and cyclized in acidic media ('one-pot'), to furnish compound (**1**) in 85% yield as a mixture of stereoisomers (**1a**) and (**1b**). Similarly, isomers (**1c**) and (**1d**) were synthesized in 87% yield using iodide (*R*)-(**4**) (Scheme 2). Mixtures of diastereoisomers were obtained in a ratio of 70:30 (**1a/b** or **1c/d**) as determined by GC and ^{1}H NMR analysis.[8]

Optimal yields (>90%) were obtained when compound (**5**) was not isolated, but rather hydrolyzed and cyclized straight from the alkylation step. Methods for the separation of diastereoisomers are largely described in the literature.[9]

A slightly different approach was used to synthesize (4*R*,5*Z*)-5-tetradecen-4-olide (**2**). In this case, (*R*)-4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (**6**) was employed as a chiral element. Iodide (**7**) was obtained from commercial (**6**) in 65% yield.[10] The lithium anion was generated from 2,4,4-trimethyl-2-oxazoline (**3a**) and alkylated in situ with iodide (**7**), yielding (**8**) in 85%.[11] 'One-pot' hydrolysis followed by cyclization under acidic conditions provided the known hydroxy lactone (**9**) ($[\alpha]_D$ −31.0 (*c* 0.4, EtOH); lit.[12] $[\alpha]_D$ −33 ± 2 (*c* 2.9, EtOH)) in 60% yield,[13] which can be employed in the syntheses of chiral pheromone lactones like (**2**) and others[14,15] (Scheme 3).

In conclusion, we have explored the versatility of oxazoline derivatives in the synthesis of five and six-membered ring lactones. The examples given here demonstrate a useful application of this methodology.

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7. Selected spectroscopic data for compound (**5**). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.2 (d, $J = 6.8$ Hz, 6H), 1.3 (s, 3H), 1.4–1.9 (m, 4H), 2.37–2.5 (m, 1H), 3.72–3.82 (m, 1H), 3.9 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 17.74, 18.18, 23.33, 23.53, 28.12, 28.29, 29.84, 29.89, 33.28, 33.43, 36.50, 36.93, 66.56, 66.95, 67.33, 78.80, 78.85, 169.68. IR (ν_{max} film, cm^{-1}) 3469, 2969, 2930, 1659. MS *m/z* (%) 200 (M^{+}+1, 17), 184 (12), 166 (21), 140 (48), 127 (100), 112 (32), 98 (21).
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11. Selected spectroscopic data for compound (**8**). ^{1}H NMR (80 MHz): δ 1.14 (s, 6H), 1.34 (s, 3H), 1.39 (s, 3H), 1.68–2.00 (m, 2H), 2.27–2.44 (m, 2H), 3.52–3.63 (m, 2H), 3.96 (s, 2H), 4.03–4.22 (m, 1H).
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