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Diastereoselective route to (2*R*,5*S*)- and (2*S*,5*S*)-2-methyl-1,6-dioxaspiro[4.5]decane, a pheromone component of the wasp *Paravespula vulgaris*

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Abstract—A diastereoselective approach to (2*R*,5*S*)- and (2*S*,5*S*)-2-methyl-1,6-dioxaspiro[4.5]decane **1** and **1a** is described. The route starts with an alkylation reaction among the cyclopentanone *N*,*N*-dimethylhydrazone **6** and the chiral iodides (*R*)-**3** or (*S*)-**3**, derived from the enantiomers of ethyl β-hydroxybutyrate, controlling the estereocenter at C-2 of the molecules. The alkylated products **7** and **7a** were easily transformed into the 1,8-*O*-TBS-1,8-dihydroxy-5-nonanones **9** and **9a** in four steps, and a subsequent stereoselective spiroketalization, in acidic media, afforded a *Z*:*E* mixture (1:2) of compounds **1** and **1a**.

Bicyclic acetals play an important role as volatiles signals in system of chemical communication between many insect species. Among the multitude of semiochemicals known today, this class of compounds appears as a distinct group.[1] The spiroketal 2-methyl-1,6-dioxaspiro[4.5]decane **1** (Fig. 1) was identified by Francke et al.[2,3] as a pheromone component of the common wasp *Paravespula vulgaris*. Since its identification, the number of racemic[4–6] and optically active[7–9] syntheses described in literature is remarkable, but even today, little is known about the stereochemistry of naturally occurring **1**.[10] Herein we wish to report an alternative and simple method for the synthesis of the titled compounds. Our plan was to utilize chiral building blocks [(*R*)-**3** and (*S*)-**3**] to control the stereocenter at C-2 of the molecule, while the stereoselctivity at C-5 must be attributed to stereoelectronic effects involved on the internal spiroketalization step.[11]

Optically pure (*R*)-**3** and (*S*)-**3** were obtained from PHB and by a microbiological reduction of ethyl acetoacetate, respectively[12] (see Schemes 1 and 2). Reduction of PHB with $LiAlH_4$ afforded diol (*R*)-**2** in 85% yield; $[\alpha]_D^{22} = -30.1$ (*c* 1.66, $CHCl_3$); lit.[13] $[\alpha]_D^{20} = -30.0$ (*c* 1.00, C_2H_5OH). Mono tosylation at the primary position of (*R*)-**2**, followed by halogenation with KI and protection of the free hydroxyl group with *t*-BDMSCl, yielded iodide (*R*)-**3**[14] in an e.e. >99%, as detected by chiral GC analysis $[\alpha]_D^{22} = -44.5$ (*c* 1.66, $CHCl_3$) (Scheme 1).

Microbiological reduction of ethyl acetoacetate with baker's yeast generated (*S*)-**4** in an e.e. <94%.[15] In order to improve the optical purity, we recrystalize its 3,5-dinitrobenzoate (*S*)-**5**.[16] The enantiomeric enhanced (*S*)-**4**, $[\alpha]_D^{22} = +43.8$ (*c* 1.35, $CHCl_3$); lit.[15] $[\alpha]_D^{20} = +43.9$ (*c* 1.66, $CHCl_3$), was reduced over $LiAlH_4$ to the diol (*S*)-**2**, $[\alpha]_D^{22} = +29.4$ (*c* 1.66, $CHCl_3$), which was straightforward transformed into iodide (*S*)-**3**,[14] $[\alpha]_D^{22} = +45.9$ (*c*

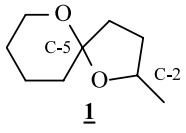

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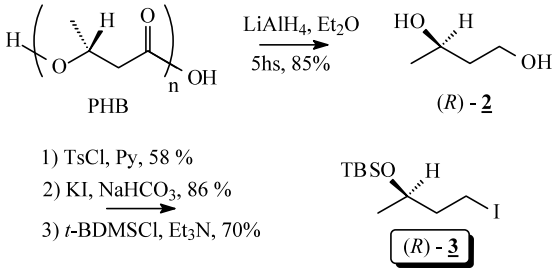
Figure 1.



Scheme 1. Synthesis of the chiral iodide (*R*)-**3**.

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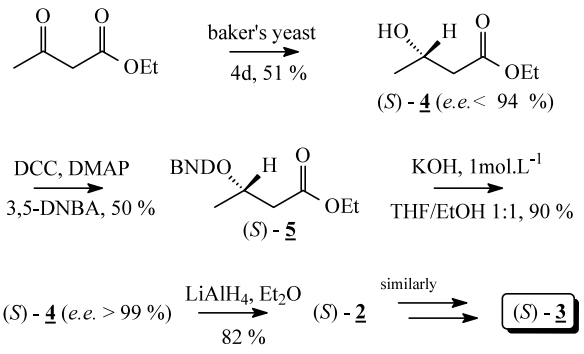

Scheme 2. Synthesis of the chiral iodide (*S*)-**3**.

1.66, $CHCl_3$), similarly as described for its enantiomer (Scheme 2).

Having a successful preparation of the chiral iodides (*R*)-**3** and (*S*)-**3**, the next step was to employ them as alkylating agents to the cyclopentanone *N*,*N*-dimethyl hydrazone **6**[17] carbanions (see Scheme 3). The carbonyl function of diastereoisomeric mixture of compounds **7** or **7a** was recovered by treatment with $CuCl_2$.[18] Formation of diols **8** or **8a** was accomplished by Bayer–Villiger oxidation and total reduction over $LiAlH_4$. These diols were protected with TBS group at the primary position and then oxidized (PCC) to the enantiomeric ketones **9** or **9a** {(*R*)-**9**, $[\alpha]_D^{22}=-37.8$ (*c* 1.66, $CHCl_3$); (*S*)-**9a**, $[\alpha]_D^{20}=+38.5$ (*c* 1.66, $CHCl_3$)}. Differently from the previous diastereoisomeric compounds, the signals in the ^{13}C NMR spectra of these molecules are not duplicated and could be easily attributed, as the carbinolics C-1 and C-8, at δ 62.85 and 67.57 ppm, and the carbonyl at δ 211.30 ppm.

Finally, removal of the TBS protecting groups of ketones **9** or **9a** under acidic conditions, gave rise to an intramolecular ketalization process,[10] affording the expected (2*R*,5*S*)-**1**,[19] $[\alpha]_D^{22}=-12.9$ (*c* 1.66, $CHCl_3$); lit.[20] $[\alpha]_D^{20}=-12.1$ (*c* 1.00, $CHCl_3$), or (2*S*,5*S*)-**1a**,[19] $[\alpha]_D^{22}=+13.4$ (*c* 1.66, $CHCl_3$); lit.[8] $[\alpha]_D^{20}=+13.9$ (*c* 1.04, $CHCl_3$), in a 1:2 mixture of *Z*:*E* isomers, attributable to anomeric effects.[11] This composition is identical with that reported for the natural material and with that observed after equilibration at the spiro center under acidic conditions.[6,20] All physical data[19] (MS, ^1H and ^{13}C NMR) were found identical in all respect with those reported in literature.[20,21]

In summary, we have introduced a new diastereoselective synthesis to the spiroketals **1** and **1a**. This convergent protocol has merits of the operational simplicity, and a complete description of the work will appear in due course.

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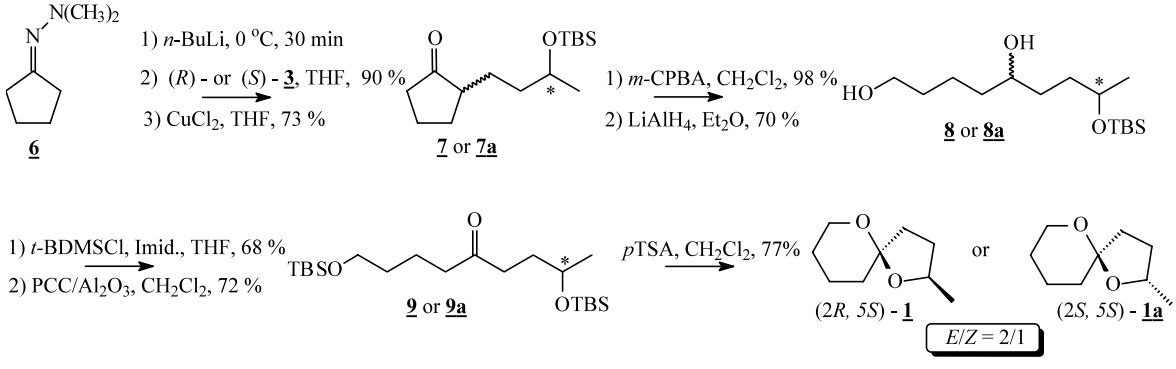

Scheme 3. Synthesis of the compounds **1** and **1a**.

14. Selected spectroscopic data for iodides (*R*)-**3** and (*S*)-**3**: IR (KBr): 2955, 2929, 1127, 1063, 967 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.12 (s, 3H), 0.14 (s, 3H), 0.93 (s, 9H), 1.20 (d, $J=6.8$ Hz, 3H), 1.95–1.97 (m, 2H), 3.24–3.29 (m, 2H), 3.89–3.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: −4.61, −4.23, 3.62, 18.00, 23.45, 25.84, 43.22, 68.24; MS *m*/*z* (%) 314 (M^+, 1), 271 (4), 257 (61), 229 (100), 215 (18), 185 (29), 129 (21), 75 (24), 59 (7) (ion trap).
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19. Selected spectroscopic data for compounds (2*R*,5*S*)-**1** and (2*S*,5*S*)-**1a** (*E*/*Z*=2/1): IR (KBr): 2937, 2870, 1080, 1042, 991 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.22 (d, $J=6.6$ Hz, 3H), 1.52–2.17 (m, 10H), 3.55–3.93 (m, 2H), 4.22 (sext, $J=6.6$ Hz, 1H) for *E* isomer; 1.32 (d, $J=6.6$ Hz, 1H), 4.20 (sext, $J=6.6$ Hz, 1H) for *Z* isomer; ^{13}C NMR (50 MHz, $CDCl_3$) δ: 105.81, 105.60, 76.73, 73.98, 61.56, 61.42, 38.97, 37.74, 34.14, 34.02, 31.68, 31.35, 25.35, 25.25, 23.18, 21.23, 20.33, 20.27; MS *m*/*z* (%) 157 (M^++1, 73), 141 (6), 128 (6), 112 (9), 111 (15), 101 (100), 100 (43), 98 (26), 85 (7), 83 (28), 71 (4), 59 (5), 57 (9), 56 (14), 55 (53), 43 (28), 41 (13) (ion trap).
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