Communications to the Editor

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SYNTHESIS OF (+)-7-ETHYL-5-METHYL-6,8-DIOXABICYCLO[3.2.1]OCT-3-ENE, An OPTICALLY ACTIVE FORM OF THE HOUSE MOUSE PHEROMONE

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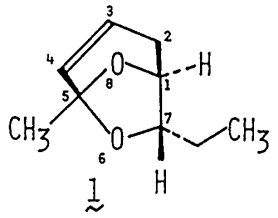
(+)-(1S,5R,7S)-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]oct-3-ene, an optically active form of the androgen-dependent pheromone of the adult male house mouse Mus musculus, was synthesized from (+)-(R,R)-diethyl tartrate via highly site-selective olefination of the 6,8-dioxabicyclo[3.2.1]octane intermediate.

KEYWORDS ——dehydro-exo-brevicomin; chiral synthesis; regioselective bromination; vicinal bromo-sulfone; reductive elimination

Exo-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]oct-3-ene (1) and 2-sec-butyl-2-thiazoline (2) have been characterized as androgen-dependent pheromonal constituents eliciting inter-male aggressive behavior.[1] Although the absolute stereochemistry of these compounds of the pheromonal activities has not been determined, biological testing of these synthetic racemates[1,2] revealed that they synergistically provoke male mice to fight. It is, therefore, necessary for detailed studies on the relationship of the absolute configuration of the compounds and the biological activities to synthesize their optically active forms. Recently, chiral syntheses of both enantiomers of dehydro-exo-brevicomin (1) have been reported by Wasserman[3a] and Mori.[3b]



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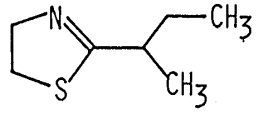

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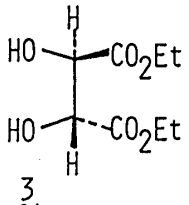

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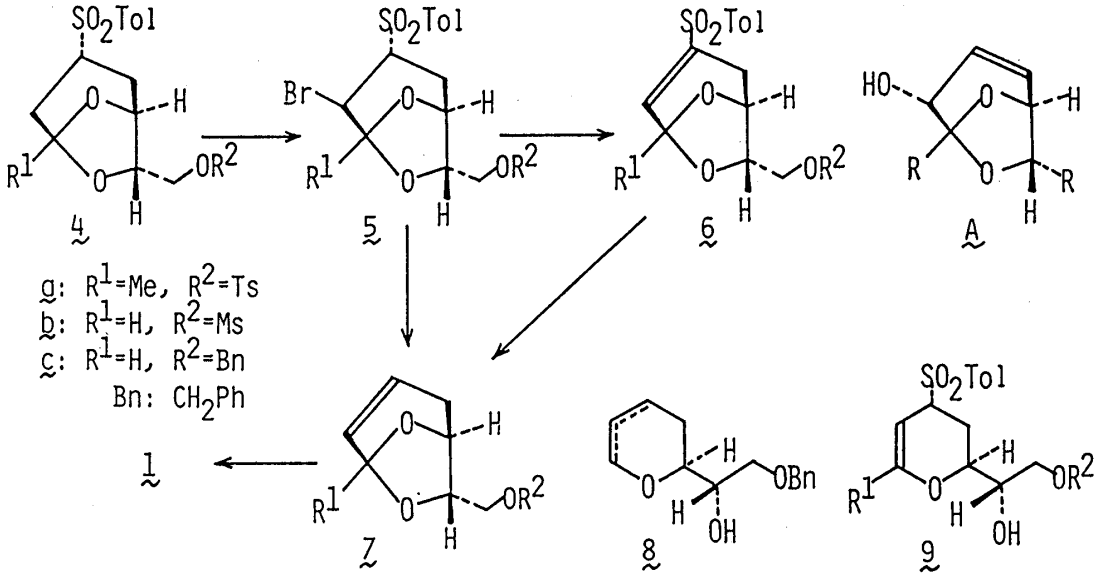
We report here a short-step synthesis of (+)-(1S,5R,7S)-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]oct-3-ene (1), one of the optically active forms of the pheromonal constituents starting with (+)-(R,R)-diethyl tartrate (3). The synthesis disclosed is featured by short-step synthesis of 1 including highly regioselective C(4)-bromination of the 6,8-dioxabicyclo[3.2.1]octane skeleton and chemoselective reductive elimination of the vicinal bromo-sulfone functionality in the contiguous triply functionalized system, α-bromo-β-sulfonyl acetal.

Highly site-selective olefination of the optically active 6,8-dioxabicyclo-[3.2.1]octane derivatives (4a) and (4b), prepared starting with (+)-diethyl tartrate (3) according to the reported method,[4] leading to the 3,4-dehydro-



bicyclics (7) must be potential not only for the present synthesis of 1 but also for access to the functionalized bicyclic skeleton such as the allylic alcohol (A),[5a] which appears to be a promising intermediate for sugar and pyranoid natural products.

Brown and coworkers reported bromination of unsubstituted 6,8-dioxabicyclo-[3.2.1]octane by treatment with an equimolar bromine in CCl_4 at the room temperature to give the C(4)-brominated product in high yield.[5b] The question in this work is the regioselectivity in the bromination of the C(5)-methyl substituted bicyclic compound (4a) which contains two α-methylenes to the acetal carbon C(5). Although the Brown's conditions did not work at all for bromination of the substituted bicyclics (4), the reaction was greatly accelerated by adding CF_3CO_2H. Thus, treatment of 4a or 4b with 1.2 eq of Br_2 in the presence of 4~5 eq of CF_3CO_2H (CH_2Cl_2/r.t/3 h) afforded nearly quantitatively and exclusively the C(4)-brominated product (5a) or (5b) respectively as a crystalline single stereoisomer.[6] It is noteworthy that no regioisomeric bromide, i.e. the 5-bromomethyl derivative, was detected in the bromination product of 4a.[7]

In the next olefination step, we first investigated reductive desulfurization of the vinyl sulfone (6) which was easily obtained quantitatively from the bromide (5) on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (benzene/r.t/1 h). Among the conditions examined extensively on the model compound (6c)[8] for desulfonylation, using 10 eq each of Na and EtOH (THF/0 °C/1 h)[9] was the only acceptable method, by which, however, the desired olefin (7c) was obtained in less than 55% yield together with a mixture of dihydropyran derivatives (8) in 20~25% yield as the side reaction products. In turn, we focused our attention on the direct route to the olefin (7) from the bromide (5) *via* chemoselective reductive elimination of the vicinal bromo-sulfone functionality in the contiguous triply functionalized system involved in the bromide (5). While it is well known that vicinal halogeno-ethers undergo reductive elimination providing olefins by means of metals such as zinc,[10] there has been no report concerning

behaviors either of vicinal halogeno-sulfones or of the contiguous functional system, α-halogeno-β-sulfonyl acetal toward metals. We have found that a zinc-copper couple (Zn-Cu)[11] was the reagent of choice for the desired chemoselective elimination of the vicinal bromo-sulfone functionality.[12] Thus, refluxing a mixture of the bromide (5b) and an excess of Zn-Cu in a solvent mixture of EtOH-EtOAc (4:1) for 2 h gave the desired olefin (7b) in 75% yield together with a minor amount (17%) of a dihydropyran derivative (9b) which might arise from the known elimination process of the vicinal bromo-ether system.[10] The by-product (9b) could be converted back to the bromide (5b) in high yield (88%) by treatment with N-bromosuccinimide (NBS) (CH_3CN/r.t/15 h). Under the same reaction conditions, the C(5)-methyl compound (5a) was also transformed to the desired olefin (7a) in 64% yield accompanied by the dihydropyran (9a) (10%), from which the bromide (5a) was recycled by means of NBS.

Synthesis of an optically active form of the mouse pheromone was achieved in 66% yield by methylation of the tosylate terminus of the olefin (7a) with five equivalents of Me_2CuLi in Et_2O at 0 °C for 4.5 h.[4] The fragrant oil (+)-(1S,5R,7S)-1 synthesized showed $[\alpha]_D^{20}$ +86.0° (c=1.20, $CHCl_3$) and the same IR and ^1H NMR spectra as those for the authentic compound 1.[3b]

For the biological testing, enantiosynthesis of the other pheromonal compound 2-sec-butyl-thiazoline (2) is in progress.

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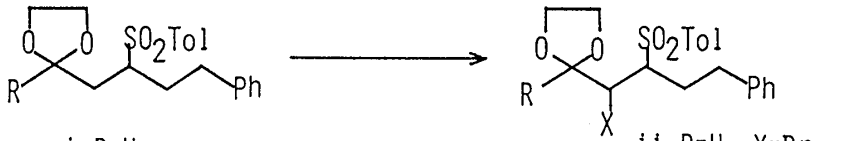
6) Selected physical data for 5a: mp 184-185 °C, $[\alpha]_D^{20}$ -64.6° (c=1.0, $CHCl_3$), $J_{3,4}$=9.83 Hz (270 MHz ^1H-NMR ($CDCl_3$)); 5b: mp 167-169 °C, $[\alpha]_D^{20}$ -124.2° (c=1.0, $CHCl_3$), $J_{3,4}$=10.68 Hz (270 MHz ^1H-NMR ($CDCl_3$)). Although the stereochemistry of the C(4)-position to which bromine atom attaches has not been

determined definitely, the C(4)-bromine and the C(3)-sulfonyl group appear to be arranged in trans-di-equatorial, i.e. trans-di-axial orientation of the C(3)-H and C(4)-H, on the basis that the coupling constants for the trans-di-axial C(2)-H and C(3)-H atoms of the analogous system 1,6-anhydro-hexopyranose skeleton are generally observed in the range of 9.0 to 9.9 Hz and that for the corresponding cis-axial-equatorial protons in the range of 4.2 to 5.8 Hz, respectively: M. Černy and J. Staněk, Jr., "Advances in the Carbohydrate Chemistry and Biochemistry" Tipson and Holton, ed., Academic Press, vol. 34, p. 23 (1977).

7) On the acyclic compounds which bear the same functionality as 4, while the aldehyde acetal (i) gave exclusively the monobrominated product (ii) under the conditions, the ketone acetal (iii) afforded a mixture of regioisomeric bromides (iv) and (v).



i R=H
iii R=Me

ii R=H, X=Br
iv R=Me, X=Br
v R=CH_2Br, X=H

8) The compound (6c), mp 161-163 °C, $[\alpha]_D^{20}$ +25.0° (c=1.0, $CHCl_3$), was prepared from 6b, mp 118-120 °C, $[\alpha]_D^{20}$ +19.2° (c=1.0, $CHCl_3$), in a three-step sequence of reactions including acetoxylation (AcOK/18-Crown-6 (cat.)/DMF/80 °C/15 h/92%), hydrolysis (K_2CO_3 (cat.)/EtOH-THF (1:1)/r.t/4 h/89%), and benzylation ($NaH/PhCH_2Br$/THF-DMF (1:3)/r.t/15 h/80%).

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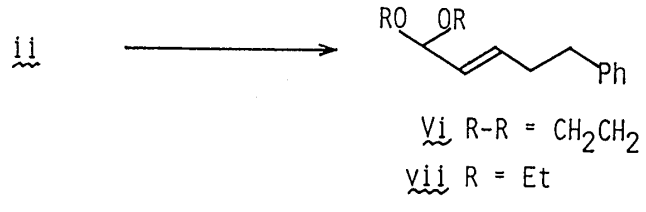
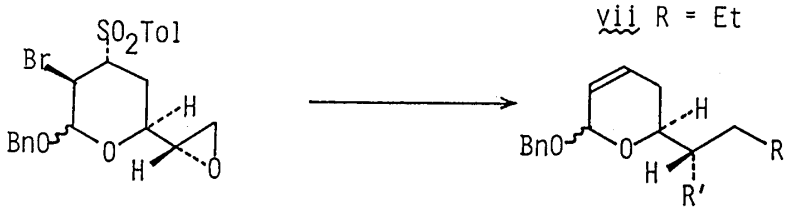
10) H.O. House, "Modern Synthetic Reactions" 2nd ed., W.A. Benjamin, Inc. (1972), p. 219.

11) E. LeGoff, J. Org. Chem., 29, 2048 (1964).

12) In the preliminary experiments, we observed that the acyclic substrate (ii) and the cyclic one (viii) gave exclusively a mixture of unsaturated acetals (vi) (63%) and (vii) (34%), and a mixture of dihydropyrans (ix) (55%) and (x) (17%) respectively on treatment with Zn-Cu in refluxing EtOH-EtOAc (1:1).



vi R-R = CH_2CH_2
vii R = Et



viii

ix R-R' = -O-
x R = OEt, R'= OH

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