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THE CARBONYL EPOXIDE REARRANGEMENT. A CHIRAL SYNTHESIS OF THE MUS MUSCULUS PHEROMONE

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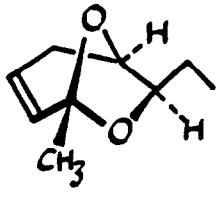
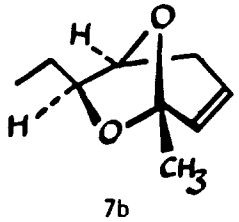
Abstract: The carbonyl-epoxide rearrangement in conjunction with the Sharpless asymmetric epoxidation procedure has been applied to an efficient synthesis of both enantiomers corresponding to the Mus musculus pheromone.

Since the isolation of the Mus musculus (house mouse) pheromone by Novotny,[1,2] several syntheses of this substance have been reported.[1,3,4,5] To date, none of these have afforded optically active products, and information regarding the absolute configuration of the active material has been unavailable.

We have previously described the stereospecific synthesis[6] of the (±)-Mus musculus pheromone (7ab) by a Lewis-acid catalyzed carbonyl epoxide rearrangement. The availability of both optical isomers in pure form would be most desirable in connection with biological testing of this pheromone and our procedure seemed to be particularly adaptable to an enantiomerically specific synthesis. We now report that this rearrangement,[6,7] in conjunction with the Sharpless asymmetric epoxidation,[8] may be applied to an efficient synthesis of both enantiomers 7a and 7b corresponding to the Mus musculus pheromone.

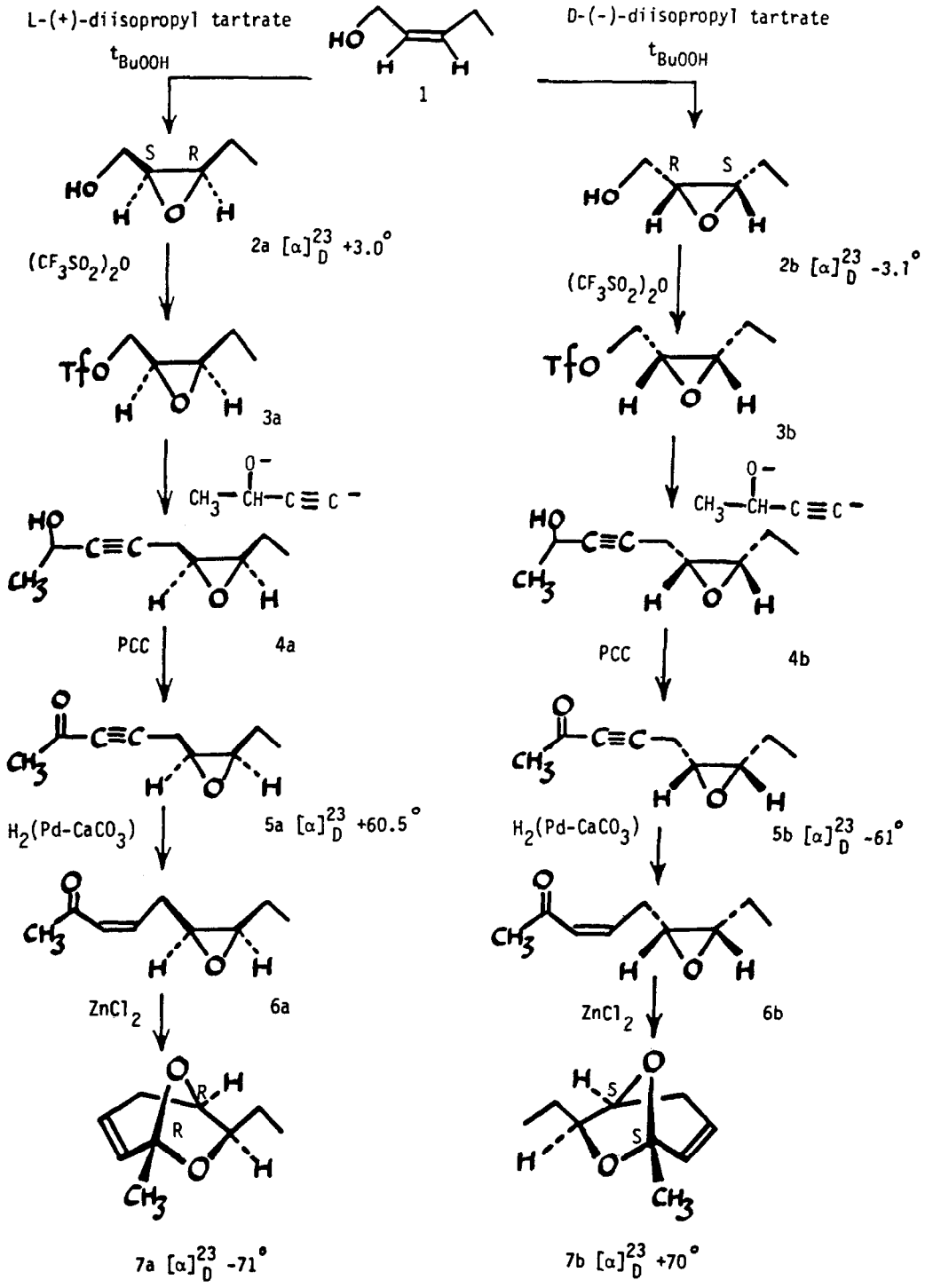


7a



7b

The (Z)-alcohol 1, prepared from commercially available 2-pentyn-1-ol by Lindlar reduction,[9] was epoxidized with t-butyl hydroperoxide in the presence of L-(+)-diisopropyl tartrate and titanium isopropoxide[8] to afford 2(S)-3(R)-epoxy-1-pentanol (2a) in moderate yield (42%, $[\alpha]_D^{23}$ +3.0°, (C=0.2, ether).[10] The alcohol (2a) was immediately treated with trifluoromethyl sulfonic anhydride in methylene chloride at -78°C for 20 min to yield triflate (3a) (95%, colorless oil).

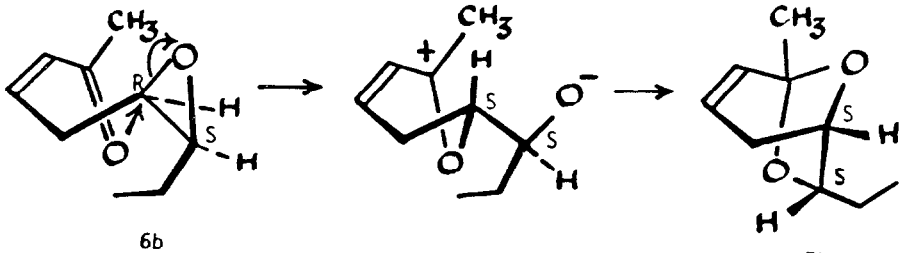

L-(+)-diisopropyl tartrate
tBuOOH
1
D-(-)-diisopropyl tartrate
tBuOOH
2a [α]D23 +3.0°
2b [α]D23 -3.1°
(CF3SO2)2O
3a
3b
4a
4b
PCC
5a [α]D23 +60.5°
5b [α]D23 -61°
H2(Pd-CaCO3)
6a
6b
ZnCl2
7a [α]D23 -71°
7b [α]D23 +70°

The freshly prepared triflate (3a) was treated with the dianion of 3-butyn-2-ol formed by n-BuLi in THF (-78°C, 1 h) to give the acetylenic alcohol (4a) (67%) as a diastereoisomeric mixture (colorless oil), which was oxidized to 5a by PCC (1.5 mol eq) (96%, colorless oil, $[\alpha]_D^{23}+60.5^0$, (C=0.077, ether). Reduction of 5a using Lindlar catalyst afforded 6a (45%) along with some 7a (11%) as observed in the racemic synthesis of the exo-isomer.[6]

The unsaturated epoxy ketone, (6a), which could be easily separated from 7a by flash column chromatography on silica gel, was treated with zinc chloride for 20 min at ambient temperature to afford the pure (-)-pheromone (7a) in nearly quantitative yield (colorless oil $[\alpha]_D^{23}-70.5^0$, (C=2.5, ether).

Using D-(-)-diisopropyl tartrate in the asymmetric epoxidation, the epoxy alcohol (2b) was prepared $[\alpha]_D^{23}-3.1^0$, (C=0.4, ether). Conversion of 2b to the triflate (3b) and then to the acetylenic alcohol (4b) was followed by PCC oxidation to the ketone (5b) $[\alpha]_D^{23}-61^0$, (C= 0.13, ether). Hydrogenation with Lindlar catalyst gave (6b) which, with zinc chloride, yielded the (+)-endo-enantiomer (7b) $[\alpha]_D^{23}+70.4^0$, (C=2.4, ether). Biological studies on both enantiomers (7a and 7b) are in progress.[10]

As observed in previous studies on the carbonyl-epoxide rearrangement,[6] the reaction takes place with remarkable specificity by a process (shown below in the 6b-7b conversion) which corresponds to epoxide ring opening by the ketone carbonyl group with inversion of configuration.



6b 7b

Acknowledgment: We are indebted to Dr. T.-J. Lu for his help in the last stages of this work involving accurate determination of the $[\alpha]_D^{23}$ values of products 7a and 7b.

References

1. Wieser, D.P.; Schwende, F.J.; Carmack, M.; Novotny, M. J. Org. Chem. 1984, 49, 882.

2. Novotny, M.; Schwende, F.J.; Wieser, D.P.; Jorgenson, J.W. Experientia 1984, 40, 217.

3. A synthesis of Mus musculus pheromone, recently reported by Danishefsky, illustrates diastereofacial control in the Lewis Acid cyclocondensation of aldehydes and dienes: Danishefsky, S.J.; Pearson, W.H.; Harvey, D.F. J. Am. Chem. Soc. 1984, 106, 2455.

4. For a non-stereospecific synthesis of the pheromone 1a, see Mundy, B.P.; Bornmann, W.G. J. Org. Chem. 1984, 49, 5264.

5. Bhupathy, M.; Cohen, T. Tetrahedron Letters 1985, 26, 2619, have recently reported stereoselective syntheses of 3a and 1a.

6. Wasserman, H.H.;Wolff, S.;Oku, T. previous communication.

7. Wasserman, H.H.; Barber, E.H. J. Am. Chem. Soc. 1969, 91, 3674.

8. a) Katsuki, T.; Sharpless, K.B.; J. Am. Chem. Soc. 1980, 102, 5974.
   b) Rossiter, B.E.; Katsuki, T.; Sharpless, K.B.; J. Am. Chem. Soc. 1981, 103, 464.

9. a) Jaenicke, L.; Seferiadis, K.; Chem. Ber. 1975, 108, 225.
   b) Smith, L.M.; Smith R.G.; Loehr, T.M.; Daves, G.D., Jr.; J. Org. Chem. 1978, 43, 2361.

10. All new compounds gave satisfactory spectroscopic values.

11. Samples of both enantiomers have been sent to Dr. Milos Novotny for biological tests.

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