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REMARKABLE STEREOCONTROL IN THE ADDITION OF AN ANION TO AN α-ALKOXYALDEHYDE BY ENCOURAGING OR DISCOURAGING INTERNAL COMPLEXATION. APPLICATIONS TO BRIEF SYNTHESES OF THE MUS MUSCULUS (HOUSE MOUSE) PHEROMONE AND EXO-BREVICOMIN

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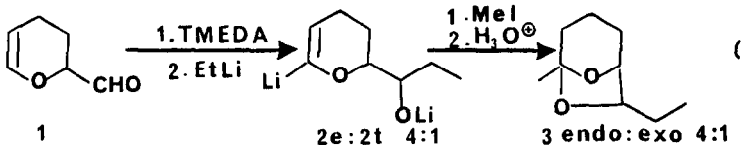
Abstract: Stereoselective addition of ethylmetallic reagents to acrolein dimer 1 and the conversion of the threo alchol **4t** to exo-brevicomin and the Mus musculus pheromone are reported.

We wish to report the first use of uncatalysed addition of diethylzinc to an aldehyde or the use of a complexing agent in the addition of ethyllithium to an aldehyde to achieve a high degree of threo or erythro selectivity, respectively, and the application of these findings to brief, high yield syntheses of the exo and endo isomers of brevicomin (3) and of the Mus musculus pheromone (7).

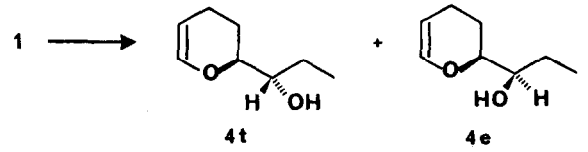
Endo-3, which is an aggregation pheromone of a European bark beetle[1] and an inhibitor of the aggregation behaviour of the Southern and Mountain Pine Beetles,[2,3] has recently been prepared in our laboratory by a one-flask, high-yield synthesis from commercially available acrolein dimer (1, eq 1).[4] In order to prepare exo-3, a component of the aggregation pheromone of the Western Pine Beetle,[5] and the Mus musculus (house mouse) pheromone (7),[6] we required an efficient synthesis of the threo alcohol **4t** and hence high stereochemical control in the addition of the ethylmetallic reagent to **1**. Ethyllithium, in the presence of TMEDA (Table I), evidently adds mainly according to the Felkin-Anh model[7] (TS I, to give **4e**), indicating that the degree of chelation of the metal ion by the carbonyl and ether oxygen atoms is minimal since such chelation should lead to the threo alcohol **4t** by nucleophilic attack from the less hindered side as suggested by Cram's cyclic model (TS II).[8] Experiments in the presence of the better complexing agent HMPA and in the absence of a complexing agent support this reasoning in that increased complexation of lithium ion by external reagents leads to a higher ratio of erythro to threo alcohol (Table I).

We reasoned that a reversal of the stereochemical preference may be brought about by the use of a metal which is capable of stronger chelation with the oxygen atoms of 1 to favor TS II and produce **4t**.[9] Indeed, the use of ethyl magnesium bromide provided a substantially improved threo : erythro ratio (Table I). In order to utilize the still greater complexing ability of zinc, the use of diethylzinc was contemplated despite the apparent absence in the literature of examples of uncatalysed addition of alkylzinc reagents to aldehydes;[10] it was hoped that the donation of electrons from the ether oxygen atom to the metal would facilitate the delivery of the ethyl anion. This strategy proved

particularly gratifying, delivering an alcohol 85% of which was the threo isomer.[11] There appears to be very few, if any, other studies in which sharp reversals of diastereoselectivity are attained by proceeding from the use of highly complexing metal ions to the use of powerful complexing agents for metals.



(1)

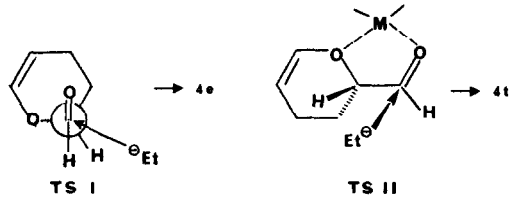


(2)

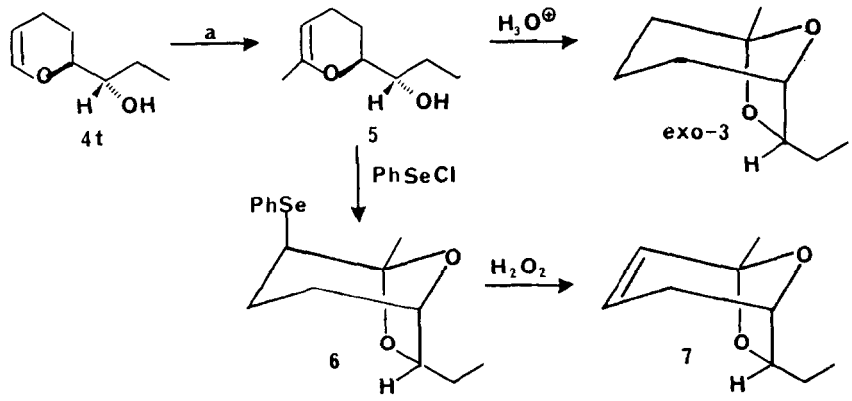
Table I. Stereochemistry of Addition of Ethylmetallics to 1

reagent[a]	yield	product ratio threo(4t) : erythro(4e)[b]
EtLi, HMPA,[c] -78 °C, 1 h	78%	.14
EtLi, TMEDA,[d] -78 °C, 1 h	81%	.25[e]
EtLi, -78 °C	[f]	.39
EtMgBr, 0 °C->RT 1 hr.	87%	2.3[g]
Et_2Zn, 0 °C->RT 5 hrs.	76%	5.7

[a]All reactions were performed in ether. The ethyllithium contains LiBr.[12] [b]The isomers were characterized by the method of Colonge.[13] The ratios were determined be GLC and NMR. [c]4 equiv per equiv of EtLi. [d]3.5 equiv per equiv of EtLi. [e]Ref 4. [f]The alcohols were not isolated; the ratio was determined from the ratio of the brevicomins (3) [g]The ratio (52:48) reported earlier[4] is in error.



The threo alcohol 4t, separated by flash chromatography or preparative HPLC, was converted[14] to 5 in 79% yield based on consumed alcohol (21% of 4t was recovered). Upon acid workup, 5 gave exo-3 quantitatively.[15]



[a]0.25 eq TMEDA, 2.5 eq BuLi (2.5 M in hexanes), over night, 0 to 25 °C, dilution with ether, addition of 2.5 eq TMEDA followed by 5 eq MeI at 0 °C, stir at 25 °C for 1 h.

Novotny, et al[6] have recently reported the isolation of a volatile component from the urine of male Mus musculus and identified it to be exo-3,4-dehydrobrevicomin (**7**). Considering the difficult accessibility of this compound from natural sources and its important role as a potential multipurpose male mouse pheromone, **7** becomes an attractive target for synthesis which we achieved as follows: Treatment[16] of **5** with 1.1 eq. of PhSeCl and 1.1 eq. of Et_3N in CH_2Cl_2 at -78 °C gave the phenylseleno compound **6**[17] in 91% yield after chromatographic purification. Upon treatment of **6** with 10 equiv. of hydrogen peroxide[18] in THF at 0 to 25 °C over 14 h gave the desired Mus musculus pheromone **7** in quantitative yield after flash chromatography using CH_2Cl_2 as eluant.[19] This synthesis of **7** is shorter and proceeds in higher yield than other reported syntheses.[6,15f,20,21]

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References and Notes

1. Kohnle, U.: Vité, J. P. Naturwissenschaften **1984**, 71, 47.

2. Vité , J. P.; Renwick, J. A. A. Naturwissenschaften **1971**, 58, 418. Payne, T. L. private communication.

3. Rudinsky, J. A.; Morgan, M. E.: Libbey, L. M.,; Putnam, T. B. Environmental Entymology **1974**, 3, 90.

4. Cohen, T.; Bhupathy, M. Tetrahedron Lett. **1983**, 24, 4163.

5. Silverstein, R. M.; Brownlee, R. G.; Bellas, T. E.; Wood, D. L.; Browne, L. E. Science (Washington, D. C.) **1968**, 159, 889. Wood, D. L.; Browne, L. E.; Ewing, B.; Lindahl, K.; Bedard, W. D.; Tilden, P. E.; Mori, K.; Pitman, G. B.; Hughes, P. R. Ibid. **1976**, 192, 896.

6. Novotny, M.; Schwende, F. J.; Wiesler, D.; Jorgenson, J. W.; Carmack, M. Experientia **1984**, 40, 217. Wiesler, D. P.; Schwende, F. J.; Carmack, M.; Novotny, M. J. Org. Chem. **1984**, 49, 882.

7. Cherest, M.; Felkin, H.; Prudent, N. Tetrahedron Lett. **1968**, 2199. Anh, N. T. Topics in Current Chem. **1980**, 88, 145.

8. Cram, D. J.; Kopecky, K. R. J. Am. Chem. Soc. **1959**, 81, 2748.

9. (a) Still, W. C.; McDonald, III, J. H. Tetrahedron Lett. **1980**, 21, 1031. (b) For examples of analogous studies on β-alkoxyaldehydes, see: Reetz, M. T.; Jung, A. J. Am. Chem. Soc. **1983**, 105, 4833 and references cited therein.

10. Allylzinc, however, does add to aldehydes: Nagaoka, H.: Rutsch, W.; Schmid, G.: Iio, H.; Johnson, M. R.; Kishi, Y. J. Am. Chem. Soc. **1980**, 102, 7962. For examples of addition of dialkylzinc to aldehydes in the presence of a Lewis acid, see: ref 9b and Jones, P. R.; Goller, E. J.; Kauffman, W. J. J. Org. Chem. **1971**, 36, 3311.

11. A reversal in the diastereoselectivity of addition to 2-benzyloxypropanal has been accomplished by Reetz using methyltitanium reagents of weaker or stronger Lewis acidity. Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B; Steinbach, R. Angew. Chem. Int. Ed. Engl. **1983**, 22, 989. Our attempts to add ethyltitanium derivatives to acid sensitive acrolein dimer did not give good yields.

12. Ethyllithium was prepared following the procedure for n-butyllithium from ethyl bromide and lithium in ether. Jones, R. G.; Gilman, H. Organic Reactions **1951**, 6, 339.

13. Colonge, J.; Buendia, J.; Guignard, H. Bull. Soc. Chim Fr. **1969**, 956.

14. Oakes, F. T.; Sebastian, J. F. J. Org. Chem. **1980**, 45, 4959.

15. For the earliest brevicomin syntheses, see: (a) Wasserman, H. H.; Barber, E. H. J. Am. Chem. Soc. **1969**, 91, 3674. (b) Bellas, T. E.; Brownlee, R. G.; Silverman, R. M. Tetrahedron **1969**, 25, 5149. Subsequent syntheses are cited in our earlier paper.[4] For some recent syntheses of exo-brevicomin, see: (c) Wuts, P. G. M.; Bigelow, S. S. J. Chem. Soc., Chem. Commun., **1984**, 736. (d) Reddy, P. S.; Vidyasagar, V.; Yadhav, J. S. Synth. Commun. **1984**, 14, 197. (e) Joshi, M. N.; Mandapur, V. R.; Chadha, M. S. J. Chem. Soc., Perkin Trans. I **1983**, 2963. (f) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F. J. Am. Chem. Soc. **1984**, 106, 2455; Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. Ibid. **1985**, 107, 1256. (g) Fuganti, C.; Grasselli, P.; Fantoni, G. P.; Servi, S.; Zirotti, C. Tetrahedron Lett. **1983**, 24, 5753. (h) Ferrier, R. J.; Prasit, P. J. Chem. Soc., Perkin Trans. I **1983**, 1645.

16. Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J.; Barnette, W. E.; Lysenko, Z.; Joullié, M. M. J. Am. Chem. Soc. **1980**, 102, 3784.

17. The structure of this compound is consistent with its ^{1}H NMR. IR, and mass spectra and its exact mass as determined by high resolution mass spectrometry.

18. Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. J. Org. Chem. **1978**, 43, 1697.

19. The 300 MHz ^{1}H NMR spectrum of 7 corresponds to the high field spectral data kindly supplied by Prof. S. J. Danishefsky.[15f]

20. This compound has been reported as an intermediate in a synthesis of exo-brevicomin. Chaquin, P.; Morizur, J.-P.; Kossanyi, J. J. Am. Chem. Soc. **1977**, 99, 903.

21. (a) A paper which appeared after the present work was prepared for publication reports a longer nonstereoselective synthesis involving a similar selenoetherification and elimination. Mundy, B. P.; Bornmann, W. G. J. Org. Chem. **1984**, 49, 5264. (b) We have been informed that H. H. Wasserman has completed syntheses of both enantiomers of this mouse pheromone.

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