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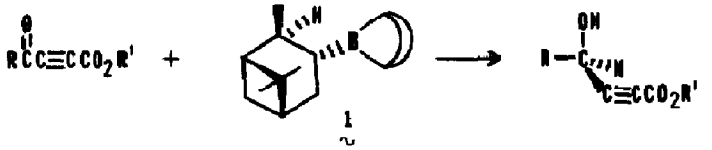
THE SYNTHESIS OF NATURALLY OCCURRING 4-ALKYL- AND 4-ALKENYL-γ-LACTONES USING THE ASYMMETRIC REDUCING AGENT B-3-PINANYL-9-BORABICYCLO[3.3.1]NONANE

M. Mark Midland* and Alfonso Tramontano
Department of Chemistry, University of California
Riverside, California 92521

ABSTRACT: 4-Hydroxy-2-alkynoates of high enantiomeric purity, available from the reduction of the corresponding ketones with B-3-pinanyl-9-BBN, are converted to 4-substituted-γ-lactones found in beetle and deer pheromones.

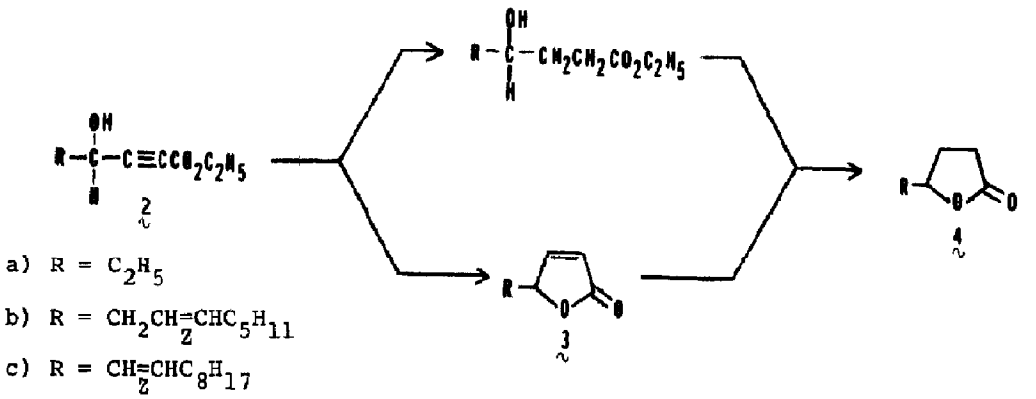
There is a great deal of interest in the synthesis of 4-substituted-γ-lactones of high optical purity. These are often found in nature as pheromonal constituents.[1] The biologically active lactone for Trogderma species of dermestid beetles, γ-caprolactone (4a) has the R-(+) configuration.[2] The black-tailed deer pheromone is composed of an 89% R, 11% S mixture of 6-(Z)-dodecen-4-olide, 4b.[3] The Japanese beetle pheromone consists of the pure R enantiomer of 5-(Z)-tetradecen-4-olide, 4c.[4] Synthetic approaches to such compounds are devised from methods of chiral resolution of intermediates,[5] from available optically-active starting materials,[4,6] and from asymmetric synthesis of an appropriate precursor.[7]

In the latter category we find that our recently reported synthesis of 4-hydroxy-2-alkynoates by the asymmetric reduction with B-3-pinanyl-9-BBN (1) can generate a new and general approach to these substances. The reduction of α,β-acetylenic ketones and 4-oxo-2-alkynoates with trialkylborane 1 provides chiral propargyl alcohols of high enantiomeric purity.[8]



Optically-active 4-alkyl-γ-lactones are prepared directly from 4-hydroxy-2-alkynoates by hydrogenation and acid-catalysed lactonization. Alternatively, the acetylene may be partially hydrogenated to provide the chiral butenolide upon acidification.[9] Saturated lactones are obtained from

butenolides by a conjugate reduction with "copper hydride".[10] This strategy will accommodate an unsaturated side chain in the preparation of 4-alkenyl-γ-lactones.



a) R = C_2H_5

b) R = $CH_2CH{=}CHC_5H_{11}$ (Z)

c) R = $CH{=}CHC_8H_{17}$ (Z)

We have explored both routes in the completion of synthesis of γ-caprolactone 4a, 6-(Z)-dodecen-4-olide 4b, and 5-(Z)-tetradecen-4-olide 4c, from the appropriate 4-hydroxy-2-alkynoates.

(+)-γ-Caprolactone (4a)

The reduction of ethyl 4-oxo-2-hexynoate[8,11] with 1 (prepared from (+)-α-pinene of 92% e.e.)(8 h., r.t.) gave ethyl 4-hydroxy-2-hexynoate (2a)(58%) of 88% e.e. as determined by NMR/LSR.[12] The lactone 4a was obtained by hydrogenation (Pd/C, MeOH) and acidification (70%, Kugelrohr distillation, 60° pot, 0.05 mm).[13] The enantiomeric purity was determined to be 87% e.e. by the method of Jones and Jakovac.[14]

(+) and (-)-6-(Z)-Dodecen-4-olide (4b)

3-Nonyn-1-ol[15] was converted to 3-(Z)-nonenal by partial hydrogenation (H_2,Pd/$BaSO_4$, quinoline) in methanol followed by oxidation (NCS, Me_2S, toluene).[16] The lithio salt of ethyl propiolate[11] was added to this aldehyde to give ethyl 4-hydroxy-5-(Z)-dodecen-2-ynoate (2b) in 60% yield. This was oxidized (Jones reagent, 15°C, 96%) and without purification reduced with a slight excess of reagent 1 (6 h., r.t.). The reagent from (+)-α-pinene (100% e.e.) gave (R)-2b of 90% e.e. We obtained (S)-2b of 78% e.e. using (-)-α-pinene (90% e.e.). The chemical yield for the oxidation reduction process ranged from 60-73%. The enantiomers of butenolide 3b were made from 2b in high yield (Pd/$BaSO_4$/quinoline, MeOH). These butenolides were quantitatively reduced to optically-active lactone 4b with "copper hydride"[10] (Kugelrohr distillation, 110° pot, 0.03 mm).[13] The enantiomeric purities were determined by NMR/LSR analysis of the diol obtained by the reaction with methyllithium.[14] R-2b gave S-(+)-4b of 88% e.e. and S-2b gave natural R-(-)-4b of 79% e.e. (coincidentally similar to the pheromone composition).

(-)-5-(Z)-Tetradecen-4-olide

2-Undecyn-1-ol[15] was partially hydrogenated as usual and oxidized ($DMSO/(COCl)_2/CH_2Cl_2$)[17] to 2-(Z)-undecenal. The addition of ethyl propiolate anion furnished the required 4-hydroxy-2-alkynoate 2c (82%). This was oxidized (MnO_2 15 eq., 6 h., r.t., pet. ether) and reduced without purification with a slight excess of 1 (6 h., r.t.). The reagent from 100% enantiomerically pure (+)-α-pinene gave essentially pure R-2a (>98% e.e.). The reagent from (-)-α-pinene (90% e.e.) gave alcohol of 87% e.e. The hydrogenation of these alcohols to the butenolide 3c gave ambiguous results. Most commercial catalysts are too active to selectively reduce 2c to butenolide only. We obtained a mixture of saturated and unsaturated products in the controlled addition of 1 equivalent of H_2. Using an aged, less active catalyst the reaction was successful (88% yield of 3c, Kugelrohr distillation, 110° pot, 0.02 mm). Butenolide S-3c is easily reduced[10] to the Japanese beetle lactone R-4c[13] but the chiral center is partly racemized in the process (38% e.e.). We attribute this to the action of HCl in the lactonization step.[5b] Other strategies for converting the nearly enantiomerically pure alcohol 2c to the 4-alkenyl-γ-lactone 4c are being investigated.

The chiral reducing agent, B-3-pinanyl-9-BBN is generally applicable to the efficient synthesis of 4-substituted-γ-lactones via the 4-hydroxy-2-alkynoates. Both (+) and (-)-α-pinene are readily available and can be obtained in essentially pure enantiomeric form.[18] The absolute configuration of the product is readily predicted from our proposed model for the transition state.[8] Reduction of the cross-conjugated alkenyl-acetylenic ketone from 2c demonstrates the remarkable enantiotopic discrimination which can be achieved in some synthetically useful substrates. The asymmetric synthesis of more elaborate lactonic natural products is underway.

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References:

1. Brand, J. M.; Young, J. Chr.; Silverstein, R. M. Fort. Chem. Org. Naturst. 1979, 37, 1. Rossi, R. Synthesis 1978, 413.

2. Silverstein, R. M.; Young, J. Chr. ACS Symposium series 1976, 23, 1. Also see ref. 6b.

3. Mueller-Schwarze, D.; Ravid, U.; Claesson, Alf.; Singer, A. G.; Silverstein, R. M.; Mueller-Schwarze, C.; Volkman, N. J.; Zemanek, K. F.; Butler, R. M. J. Chem. Ecol. 1978, 4, 247. Also see ref. 6b.

4. Tumlinson, J. H.; Klein, M. G.; Doolittle, R. E.; Ladd, T. L.;

Proveaux, A. T. Science 1977, 197, 789.

5. (a) Sato, K.; Nakayama, T.; Mori, K. Agric. Biol. Chem. 1979, 43, 1571. (b) Pirkle, W. H.; Adams, P. E. J. Org. Chem. 1979, 44, 2169.

6. (a) Smith, L. R.; Williams, H. J. J. Chem. Ed. 1979, 56, 696. (b) Ravid, U.; Silverstein, R. M.; Smith, L. R. Tetrahedron 1978, 34, 1449.

7. Vigneron, J. P.; Bloy, V. Tetrahedron Lett. 1980, 21, 1735.

8. Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. J. Am. Chem. Soc. 1980, 102, 867.

9. Vigneron, J. P.; Bloy, V. Tetrahedron Lett. 1980, 21, 1739. We found this sequence more efficient than the hydrolysis-hydrogenation sequence: Herrman, J. L.; Berger, M. H.; Schlessinger, R. H. J. Am. Chem. Soc. 1979, 101, 1544.

10. Procedure (C) of: Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. J. Org. Chem. 1977, 42, 3180.

11. Midland, M. M.; Tramontano, A.; Cable J. R. J. Org. Chem. 1980, 45, 28.

12. The chiral shift reagent tris[d,d-dicampholylmethanato]europium(III) is very effective for the resolution of enantiomers of 4-hydroxy-2-alkynoates by NMR/LSR: McCreary, M. D.; Lewis, D. W.; Wernick, D. L.; Whitesides, G. M. J. Am. Chem. Soc. 1974, 96, 1038.

13. All products exhibited satisfactory spectral properties in accord with the literature data.

14. Jackovac, I. J.; Jones, J. B. J. Org. Chem. 1979, 44, 2165.

15. Available from Farchan Acetylenes.

16. Corey, E. J.; Kim, C. U. J. Am. Chem. Soc. 1972, 94, 7586. For an alternative synthesis of 3-(Z)-nonenal see Kajiwara, T.; Odake, Y.; Hatanaka, A. Agric. Biol. Chem. 1975, 39, 1617.

17. Omura, K.; Swern, D. Tetrahedron 1978, 34, 1651.

18. Brown, H. C.; Yoon, N. M. Isr. J. Chem. 1976/1977, 15, 12. Cocker, W.; Shannon, P. V. R.; Staniland, P. A. J. Chem. Soc. C 1966, 41. Brown, C. A. Synthesis 1978, 754.

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