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1,2 ASYMMETRIC INDUCTION IN THE CYCLIC HYDROBORATION OF 1,5 - DIENES. A SYNTHESIS OF THE PRELOG-DJERASSI LACTONE[1]

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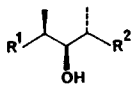
Cyclic hydroboration of an appropriately substituted 1,5-diene yields a 1,5 diol as the major product which can be converted to the racemic Prelog-Djerassi lactone.

The widespread occurrence of the three carbon unit 1 in natural products of current synthetic interest has prompted us to investigate methodology for the stereocontrolled construction of intermediates of this type. We are particularly interested in substances appropriately substituted at R^1 and R^2 to allow for transfer of stereochemical information present in 1 to distal prochial centers on the acyclic carbon chains R^1 and R^2. Diols such as 2 in principal meet this requirement and we have recently observed the stereocontrolled synthesis of 2a via a cyclic hydroboration route[1,2] described below. Subsequent transformations provided a structure proof for this substance and a practical illustration of the method for the preparation of the Prelog-Djerassi lactone 3[3] and its C-6 epimer.[4]



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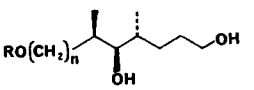
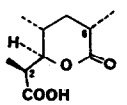


2a n=2
b n=3



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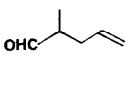
The requisite diene was constructed in a highly stereoselective fashion using Still's sigmatropic rearrangement route to Z-trisubstituted olefins.[5] Aldehyde 4[6] was treated with 2-propenylmagnesium bromide in THF to yield the alcohols 5 (88%).[7] Conversion of 5 to 6 was accomplished through a one-pot sequence (1-KH, THF 0^0; 2-ICH_2SnBu_3, THF; 3-n-BuLi, THF, -78^0) in 75% yield[7] after removal of a small amount of the E-diene by flash chromatography.[8] The isomeric purity of 6 was shown to be greater than 99.5% by VPC comparison[9] of the derived acetate with a sample of the E-acetate prepared by Johnson's method.[10]



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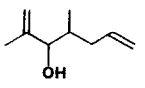

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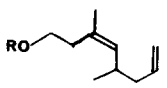
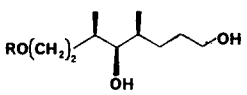


6 R=H

7 R=Si(CH$_3$)$_2$t-Bu



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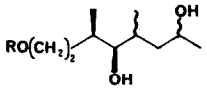

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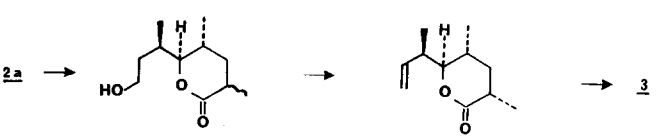
Silyl ether 7[7] (t-Bu(Me)$_2$SiCl, imidazole, DMF; 95%) upon hydroboration/oxidation (thexyl borane, THF, -78° to RT, 24 hrs then H_2O_2, NaOH, H_2O; 75%) yielded a diol mixture containing 2a[7], 8[7] and 9[7] (isolated ratio 2a:8:9 = 3.8:1:0.35) from which the desired isomer 2a could be efficiently separated by flash chromatography. Although isomers 2a and 8 were clearly distinguishable by ^1H and ^{13}C NMR,[11] no conclusion could be made concerning the relative configuration of the three chiral centers. Further transformation of 2a to 3 accomplished as shown in Scheme I defined the structure of diol 2a as well as providing a simple route for the construction of the Prelog-Djerassi-lactone.

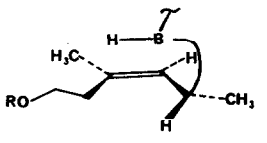
Oxidative cyclization to the lactone[7] (Fetizon's reagent,[12] C_6H_6, reflux, 1.5 hr; 86%), alkylation (LDA, THF, HMPA, -78° then MeI, -78°, 1 hr; 80%) and silyl ether hydrolysis (1:1 THF:10% HCl, 0°, 15 min; 90%) yielded hydroxy lactone isomers 10[7] (60:40 ratio) which could be efficiently separated by flash chromatography.[8] The major isomer, following one carbon degradation via the olefin 11[7] (o-nitrophenylselenocyanate, Bu_3P, CH_2Cl_2 then H_2O_2, THF;[13] 88% overall. 2- $NaIO_4$, catalytic $RuCl_3$, CCl_4, MeCN, H_2O;[14] 80%) afforded the Prelog-Djerassi lactone, 3, (m.p. (CCl_4) - 111-113°) identical in all respects with an authentic sample.[15] Similar degradation of the minor hydroxy lactone isomer yielded the 6-epi-lactonic acid (m.p.(CCl_4) 100-02) exhibiting spectral data in accord with the published[4f] parameters.

SCHEME 1



10 11

The observed stereoselectivity in the hydroboration step is apparently a reflection of the preference for a conformation as shown in 12 for the second intramolecular hydroboration step. These results thus demonstrate the application of such conformational constraints[16] to the intramolecular hydroboration reaction as well as providing a simple route to the Prelog-Djerassi lactone isomers. Although the lower stereoselectivity observed in the hydroboration step as compared with Still's report[1] may be due to subtle differences in substrate structure, other considerations[17] suggest that the stereochemical outcome of cyclic hydroborations is critically dependent on the age and history of the BH_3-THF solutions used.



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Acknowledgement - We wish to thank the Research Corporation and the Faculty Research Committee of the University of California for support of our work.

References and Notes:

1) While this work was in progress, another similar route to the Prelog-Djerassi lactone was brought to our attention:
Still, W. C. and Shaw, K. R., Tetrahedron Lett., preceeding paper, this issue. We thank Professor Still for providing us with a preprint describing this work.

2) For previous examples of intramolecular hydroborations applied to problems of acyclic asymmetric induction see: Still, W. C. and Darst, K. P., J. Am. Chem. Soc., *102*, 7385 (1980). A review of the cyclic hydroboration reaction has appeared. - Brown, H. C. and Negishi, E-I., Tetrahedron, *33*, 2331 (1977).

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4) For previous syntheses of this substance see ref. 1 and: a-Masamune, S.; Kim, C. U.; Wilson, K. E.; Spesard, G. O.; Georghiou, P. E. and Bates, G. S., J. Am. Chem. Soc., *97*, 3512 (1975). b-Herima, M.; Garvey, D. S.; Liu, L. C.-L. and Masamune, S. Tetrahedron Lett., 3937 (1979). c-White, J. D. and Fukuyama, Y., J. Am. Chem. Soc., *101*, 228 (1979). d-Stork, G. and Nair, V., ibid, *101*, 1315 (1979). e-Grieco, P. A.; Ohfune, Y.; Yokoyama, Y. and Owens W., ibid, *101*, 4749 (1979). f-Bartlett, P. A. and Adams, J. L., ibid, *102*, 337 (1980). g-Masamune, S.; Ali, S. A.; Sirdwan, D. L. and Garvey, D. S., Angew. Chem. Int. Ed., *19*, 557 (1980). h-Ireland, R. E. and Daub, J. P., J. Org. Chem., *46*, 479 (1981).

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6) Montgomery, L. K.; Matt, J. W. and Webster, J. R., J. Am. Chem. Soc., *89*, 923 (1967). This aldehyde was prepared in 52% overall yield from propylidenecyclohexylamine by alkylation (LDA, THF, 0^{o} then allyl bromide, -78^{o}) and hydrolysis (HOAc, H_2O, NaOAc).

7) All yields refer to chromatographically purified substances. Satisfactory analytical data (IR, NMR, MS.) was obtained for all compounds. Satisfactory combustion analysis was obtained for compounds 2a, the derived lactonic silyl ether and diene 6. NMR ($CDCl_3$) —— 6: δ 0.92 (d, 7, 3H), 1.45 (br s, 1H, exch.), 1.71 (d, 2, 3H), 1.80-2.74 (m, 5H), 3.66 (d, 6, 2H), 4.77-5.31 (m, 3H), 5.45-6.12 (m, 1H); 2a: 0.06 (s, 3H), 0.81-2.10 (m, s at 0.81, 0.89, 25H), 3.24 (d, 7, 1H), 3.54-4.03 (m, 4H); 7: 0.05 (s, 3H), 0.84-2.22 (m, s at 0.82, 0.92, 0.98, 25H), 3.24 (br t, 1H), 3.51-3.86 (m, 4H); 10 (Major): 0.89 (d, 6, 3H), 0.95 (d, 6, 3H), 1.25 (d, 7, 3H), 1.53-2.83 (m, 8H); 3.71 (t, 6, 2H); 3.96 (dd, 2, 9, 1H); 10 (Minor): 0.93 (d, 6, 3H), 0.97 (d, 6, 3H), 1.20 (d, 7, 3H), 1.41-2.85 (m, 8H); 3.72 (t, 6, 3H), 3.95 (dd, 2, 10, 1H); 11: 1.00 (d, 6, 3H), 1.04 (d, 6, 3H), 1.26 (d, 7, 3H), 1.52-2.72 (m, 5H), 3.94 (dd, 2, 9), 4.85-5.20 (m, 2H), 5.70-6.28 (m, 1H). IR ($CHCl_3$) 6: 3550, 3070, 2850, 1650, 1050, 990, 915 cm^{-1}; 2a: 3600, 3450, 2850, 1070 cm^{-1}; 10 (Major): 3600, 3450, 2850, 1730, 1200 cm^{-1}; 11: 3070, 1730, 1650, 990, 915 cm^{-1}.

8) Still, W. C.; Kahn, M. and Mitra, A., J. Org. Chem., *43,* 2923 (1978).

9) 50 m OV-101 capillary; temperature programmed run 70 —— 200° at 6.5°/min; retention times for Z and E-acetates were 26.4 and 26.8 min. respectively.

10) Brady, S. F.; Ilton, M. A. and Johnson, W. S., J. Am. Chem. Soc., *90,* 2882 (1968).

11) ^{13}C NMR ($CDCl_3$, 25 MH_z, ppm from TMS) 2a: 78.4, 62.9, 61.0, 37.5, 35.5, 32.2, 29.9, 29.1, 25.9, 16.1, 11.9. 8: 78.4, 63.1, 61.1, 36.9, 35.2, 32.7, 30.1, 29.6, 25.9, 14.8, 13.7.

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14) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S. and Sharpless, K. B., J. Am. Chem. Soc. submitted for publication. We thank Professor Sharpless for a preprint describing this improved method of oxidation.

15) Kindly provided by Professor Gilbert Stork.

16) Previous applications of this concept to stereocontrolled functionalization of acyclic systems for natural products synthesis in intermolecular hydroborations (Schmid, G.; Fukuyama, T.; Alaska, K. and Kishi, Y., J. Am. Chem. Soc., *101,* 259 (1979)) and intramolecular lactonizations (ref. 4f and Collum, D. B.; McDonald, J. H. and Still, W. C., J. Am. Chem. Soc., *102,* 2118 (1980)) have been described.

17) We used commercial samples (Aldrich) of BH_3-THF which had been opened for 4-8 weeks prior to use in the hydroborations while Still, et.al.[1] used freshly opened samples. Professor Still also notes that in all the cyclic hydroborations studied in his laboratories, substantial losses in stereoselectivity are observed unless freshly opened commercial samples of BH_3-THF were used within 7-10 days time. (Personal communication from W. C. Still).

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