Tetrahedron Letters, Vol.22, No.38, pp 3725 - 3728, 1981
Printed in Great Britain

0040-4039/81/383725-04$02.00/0

ACYCLIC STEREOSELECTION VIA CYCLIC HYDROBORATION. SYNTHESIS OF THE PRELOG-DJERASSI LACTONIC ACID.[1]

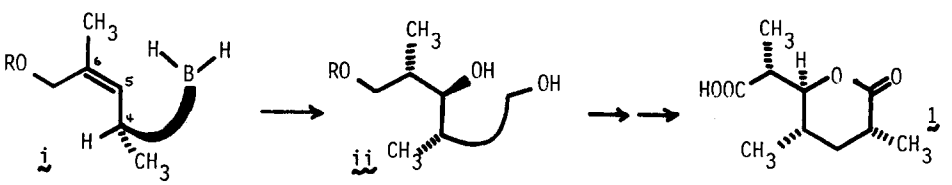
W. Clark Still and Kenneth R. Shaw

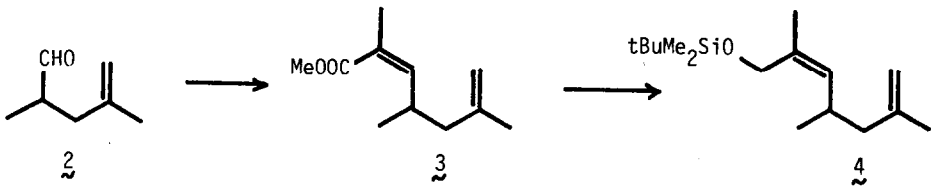
Department of Chemistry, Columbia University, New York, NY 10027

Summary: An intramolecularly directed hydroboration (4→5) provides high asymmetric induction for the construction of 1.

We recently reported that cyclic hydroboration of acyclic dienes provides an effective method for the stereoselective synthesis of acyclic molecules having widely separated asymmetric centers.[2] As it happens, that study was based on earlier unpublished work in our laboratory which demonstrated the utility of cyclic hydroboration for acyclic stereoselection and which involved a relatively concise synthesis of the well-known Prelog-Djerassi lactonic acid 1.[3,4] In this communication we describe our preparation of racemic 1 and further domonstrate the value of cyclic hydroboration in the construction of stereochemically complex acyclic molecules.

The key feature of our approach to 1 is illustrated in the following scheme and involves the conversion of i into ii. Assuming that hydroboration of i can be directed intramolecularly, the strong preference of the C4-C5 bond for the conformation shown should allow only the desired β-face intramolecular hydroboration of the C5-C6 olefin to occur.[5] Thus the required stereochemistry at C4-C6 should be readily produced by efficient 1,2-asymmetric induction from the preexisting C4 chiral center.

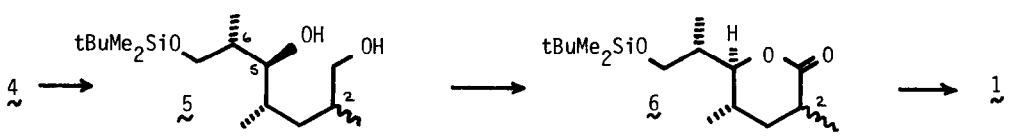




2 3 4

The synthesis itself starts from methallyl alcohol. Orthoester Claisen rearrangement[6] ($CH_3CH_2C(OEt)_3$, cat. HOAc; reflux, 4 hours) followed by reduction ($LiAlH_4$, Et_2O; 0^o C) proceeds in approximately 90% overall yield. A clean oxidation ($CrO_3 \cdot HCl \cdot C_5H_5N$, CH_2Cl_2; 25^o C; 1.5 hours) follows but yields only 60% of the known aldehyde 2[7] due to the volatility of the product. The remaining three carbons are then added via a stereoselective, kinetically-controlled Horner-Emmons-like olefination using the sodium salt of trimethyl phosphonopropionate[8] (a. THF, -78^o C, 30 sec.; b. HOAc-H_2O-THF quench) (81% yield). The Z-unsaturated ester 3 (^{1}H NMR ($CDCl_3$) δ 5.70 (1H, dq, J = 10, 1.5 Hz), 4.72 (1H, br s), 4.65 (1H, br s), 3.74 (3H, s), 3.37 (1H, m), 2.00 (2H, m), 1.89 (3H, d, J = 1.5 Hz), 1.70 (3H, br s), 0.97 (3H, d, J = 7 Hz)) predominates over the E-isomer to the extent of 18:1 and is readily freed of its isomer by simple flash chromatography[9] (R_f (silica gel, 5% EtOAc in C_5H_{12}) Z-3 0.69; E-3 0.65). Final preparation for the crucial cyclic hydroboration consists of reduction ($LiAlH_4$, Et_2O; 0^o C) and protection ($tBuMe_2SiCl$, $C_3H_4N_2$, DMF) to yield 4 (^{1}H NMR ($CDCl_3$) δ 5.01 (1H, br d, J = 9 Hz), 4.67 (1H, br s), 4.72 (1H, br s), 4.17 (2H, br s), 3.62 (1H, m), 1.96 (2H, br d, J = 7 Hz), 1.74 (3H, br s), 1.70 (3H, br s), 0.94 (9H, s), 0.93 (3H, d, J = 7 Hz), 0.09 (6H, s)) (96% yield for the two steps).

When a 0.5M solution of the diene 4 (THF, -78^o C) is (a) treated with 1.5 equivalents of fresh borane/THF, (b) allowed to warm slowly to 25^o C (2 hours) and (c) worked up in the usual way with alkaline hydrogen peroxide, a 1:1 mixture of two diols (5) is produced (92% yield). These two products can be shown to differ only in the asymmetry at C2 and result



4 5 6 1

from the stereorandom nature of the initial hydroboration. Synthetically, the mixture of isomers at C2 is merely an inconvenience since oxidation with Fetizon's reagent[10] (Ag_2CO_3-celite, C_6H_6; 80° C; 4 hours) smoothly yields the known lactone 6 in better than 90% yield. Compound 6 is then epimerized and separated (flash chromatography, 25% EtOAc-C_5H_{12}) as described previously by Grieco and coworkers.[4e,11] Careful 250 MHz ^1H NMR of 2α-6 ($(CDCl_3)$ 4.19 (1H, br d, J = 10 Hz), 3.68 (1H, dd, J = 8, 10 Hz), 3.50 (1H, dd, J = 6, 10 Hz), 2.47 (1H, m), 1.29 (3H, d, J = 7 Hz), 0.96 (3H, d, J = 7 Hz), 0.89 (9H, s), 0.85 (3H, d, J = 7 Hz), 0.09 (6H, s)) shows it to contain approximately 5% of an impurity which may have been derived from α-hydroboration of the C5-C6 olefin. Thus the key hydroboration of 4 appears to proceed with stereoselection for the desired β-face of the C5-C6 double bond to the extent of ≥20:1. Final conversion to (±)-Prelog-Djerassi lactone 1 follows Grieco's route (1. pTsOH, MeOH; 2. CrO_3-H_2O-H_2SO_4-CH_3COCH_3) and yields material (mp (CCl_4) 112-113° C[4], undepressed on mixing with authentic (±)-1; lit. 110-113° C,[4c] 113-114° C,[4e] 114-115° C,[4d] 116-117° C,[4f] 119-120° C[4a]) which is identical with an authentic sample of racemic 1 provided by Professor Gilbert Stork.

Finally we should mention that the entire sequence has also been carried out on enantiomerically pure 2 (prepared by a relatively lengthy route from (+)-β-hydroxyisobutyric acid) to yield (+)-2α-6 without loss of optical purity. Thus the primordial asymmetry at C4 is indeed capable of inducing all the other chiral centers in a relatively efficient way. Only the annoying equilibration at C2 detracts from what is otherwise a concise and efficient synthesis of 1.[12]

NOTES AND REFERENCES:

1. This work was first described at the Bürgenstock Stereochemical Conference at Bürgenstock, Switzerland on April 28, 1980.
2. W.C. Still and K.P. Darst, J. Am. Chem. Soc., 102, 7385 (1980). For a review of acyclic stereoselection see P.A. Bartlett, Tetrahedron, 36,2 (1980).
3. R. Anliker, D. Dvornik, K. Gubler, H. Huesser and V. Prelog, Helv. Chim. Acta, 39, 1785 (1956); C. Djerassi and J.A. Zderic, J. Am. Chem. Soc., 78, 6390 (1956); R.W. Rickards and R. M. Smith, Tetrahedron Lett., 1025 (1970); D.G. Manwaring, R.W. Rickards and R.M. Smith, ibid. , 1029 (1970).
4. (a) S. Masamune, C.U. Kim, K.E. Wilson, G.O. Spessard, P.E. Georghioll and G.S. Bates, J. Am. Chem. Soc., 97, 3512 (1975); (b) M. Hirama, D.S. Garvey, L. D.-L. Lu and S. Masamune, Tetrahedron Lett., 3937 (1979); (c) J.D. White and Y. Fukuyama,

J. Am. Chem. Soc., 101, 228 (1979); (d) G. Stork and V. Nair, ibid., 101, 1315 (1979); (e) P.A. Grieco, Y. Ohfune, Y. Yokoyama and W. Owens, ibid., 101, 4749 (1979); (f) P.A. Bartlett and J.L. Adams, ibid., 102, 337 (1980); (g) S. Masamune, S.A. Ali, D.L. Snitman and D.S. Garvey, Angew. Chem. Int. Ed., 19, 557 (1980); (h) R.E. Ireland and J.P. Daub, J. Org. Chem., 46, 479 (1981); (i) S. Masamune, M. Hirama, S. Mori, S.A. Ali and D.S. Garvey, J. Am. Chem. Soc., 103, 1568 (1981); (j) D.J. Morgans, Jr., Tetrahedron Lett., preceding paper in this issue.

5. This type of conformational approach to acyclic stereochemical control has been exploited previously. For recent examples see: G. Schmid, T. Fukuyama, K. Akasaka and Y. Kishi, J. Am. Chem. Soc., 101, 259 (1979); D.B. Collum, J.H. McDonald and W.C. Still, ibid., 102, 2118 (1980); reference 4f.
6. W.S. Johnson, L. Werthemann, W.R. Bartlett, T.J. Brocksom, T. Li, D.J. Faulkner and M.R. Peterson, J. Am. Chem. Soc., 92, 741 (1970).
7. For a simple and direct Claisen preparation of 2 see: J.M. Reuter and J.M. Salomon, J. Org. Chem., 42, 3360 (1977).
8. G. Schmid, T. Fukayama, K. Akasaka and Y. Kishi, J. Am. Chem. Soc., 101, 259 (1979).
9. W.C. Still, M. Kahn and A. Mitra, J. Org. Chem., 43, 2923 (1978).
10. M. Fetizon, M. Golfier and J.-M. Louis, Tetrahedron, 31, 171 (1975).
11. Starting with the undesired 2-β epimer of 6, we were unable to obtain more than a 1.3:1 ratio of 2-α:2-β by kinetic protonation under a variety of conditions (yield ≈80%).
12. This work and related studies were supported by grants from NSF (CHE 78 01769) and NIH (1R01 HL25634).

(Received in USA 5 June 1981)