Pergamon

Tetrahedron Letters 40 (1999) 7569–7572

TETRAHEDRON LETTERS

A New Asymmetric Synthesis of (+)-Grandisol *via* a Kinetic Resolution.

David P. G. Hamon* and Kellie L. Tuck

The Chemistry Department, The University of Adelaide, S.A. 5005, AUSTRALIA

Received 5 July 1999; accepted 24 August 1999

Abstract : A novel approach to the asymmetric synthesis of (+)-grandisol involves the use of catalytic kinetic resolution of a primary allylic alcohol. The allylic alcohol is prepared in 4 steps from simple achiral materials and the resolved alcohol (95%e.e.) is reduced in 2 steps to the corresponding methyl alkene. This alkene is converted to (+)-grandisol (95%e.e.).

(+)-Grandisol is the principle component of the aggregation pheromone produced by the male cotton boll weevil, *Anthonomus grandis* Boheman.[1] The cotton boll weevil is the most detrimental insect pest in cotton production in the USA. Due to the potential to use pheromones as alternatives to classical pesticides a large number of racemic[2] and enantiopure[3] syntheses of grandisol have been developed. The majority of syntheses of the enantiopure compound have a large number of synthetic steps, and the overall yields are low. All the earlier asymmetric syntheses of grandisol, achieved in high enantiopurity, have involved the use of chiral auxiliaries, and all have required the extensive separation of diastereomers.[4]

In an earlier synthesis of racemic grandisol, Rosini[5] used the endocyclic alkene **7** (racemic) as an intermediate. We recognized that the optically active alkene **7** could be formed from the optically active allylic alcohol **5r** and that this might be obtained by a Sharpless kinetic resolution of the primary allylic alcohol.[6] The key feature here is that the allylic alcohol **5** has both an open convex face and a much less readily accessible, concave face (figure 1). The Sharpless reagent should therefore attack preferentially one enantiomer of the racemate. We disclose that a catalytic kinetic resolution, involving a Sharpless asymmetric epoxidation of this primary allylic alcohol, gives one enantiomer in high optical purity. As far as we are aware[7] this is the first use of this compound in the synthesis of a natural product.

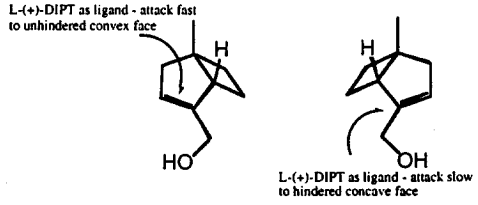
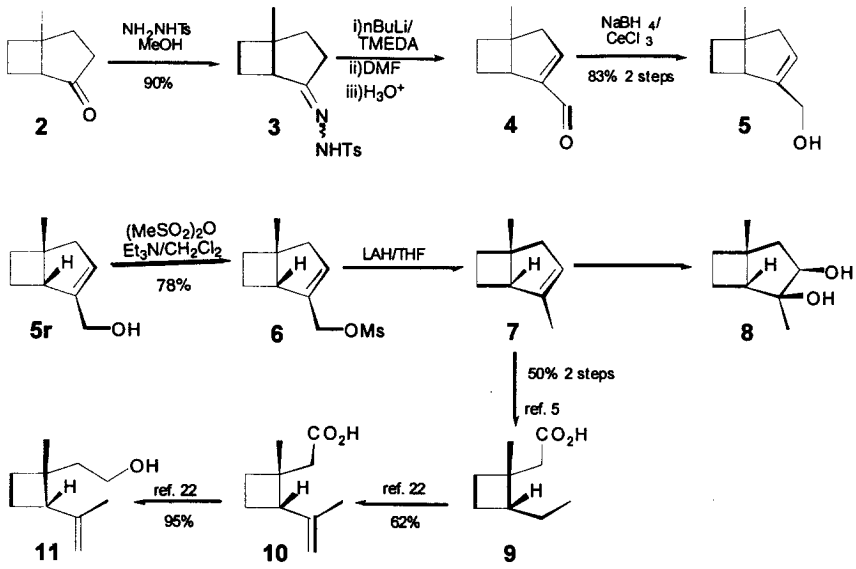


Figure 1. The proposed kinetic resolution of the allylic alcohol **5** by Sharpless asymmetric epoxidation

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01605-6

A photochemical [2+2] cycloaddition of 3-methyl-2-cyclopentene-1-one **1**[8] with ethylene[9] gave the bicyclic ketone **2** (77% yield, 98°C /56mm).[10] The allylic alcohol **5** could be formed in three steps from the bicyclic ketone (see Scheme 1). Conversion of the ketone **2** to the tosyl hydrazone **3** (90% crude yield) gives material that can be converted, without purification to the allylic alcohol **5** *via* a modified[11] Shapiro reaction. Treatment of the tosyl hydrazone **3** with 3 equivalents of *n*-BuLi, followed by reaction of the intermediate alkenyl anion with DMF gave, on acidic work up, the crude unsaturated aldehyde **4**. This was reduced immediately ($NaBH_4$, $CeCl_3.7H_2O$, MeOH) and the desired allylic alcohol **5**[12] was obtained in an 83% overall yield. Thus, a high yielding four-step synthesis of the key allylic alcohol **5** is available from commercially available material[13] without the need for chromatographic purification.

Sharpless has reported[14] extensive experimental details for kinetic resolution using the tartrate based epoxidation system. One aspect he stresses is the susceptibility of the reaction to water. The reaction we report is extremely sensitive to water and we have had to modify slightly[15] the way the reagents are added in able to obtain reproducible results. The reactions were monitored by capillary GC.



Scheme 1

A method for the determination of the enantiomeric enrichment, by this resolution, was difficult to find.[16] Eventually, however, it was discovered that for each diastereomer of the derived Mosher ester of the alcohol **5** ((+)MTPA, DCC, DMAP, CH_2Cl_2) one peak, of the overlapping ABq's, for the diastereotopic proton resonances of the methylene groups bearing oxygen, did separate from all other signals, at 600MHz. These peaks did not represent the same part in each ABq and so a correction factor was obtained from the spectrum of

the ester made from the racemate. In this way an estimate for the enantiomeric excess could be made.[17] The results are shown in Table 1. The absolute configuration for the resolved allylic alcohol **5r** was assumed from the Sharpless mnemonic.[18]

Temperature (°C)	% Conversion	Enantiomeric Excess	% Recovery
-20	80	>98%†	18
-40	60	95%	30
-60	55	90%	34

† Only one enantiomer detected by ^{1}H NMR.

Table 1. Kinetic resolution results at various temperatures.

Reaction of the allylic alcohol **5r** with methane sulfonic anhydride[19] gave the corresponding mesylate **6** (Ms_2O, Et_3N, CH_2Cl_2, 78% yield). Reduction of this mesylate ($LiAlH_4$, THF) gave exclusively the endocyclic alkene **7**, with no exocyclic alkene detected by ^{1}H NMR. To ensure that the method used to estimate the e.e. of the allylic alcohol was reliable, a determination of the e.e. of this alkene was made in the following way. A sample, prepared from allylic alcohol estimated to be 85% e.e., was treated according to the Sharpless dihydroxylation procedure[20] with the achiral ligand quinuclidine. The resultant diol **8** was then converted to the mono Mosher's ester ((+)MTPA, DCC, DMAP, CH_2Cl_2). A determination of 86% e.e. was obtained.[21]

The volatile alkene **7** was prepared from the mesylate **6** (from 95% e.e. allylic alcohol) on a larger scale. Then, without complete isolation from the solvent, it was treated with $RuCl_3/NaIO_4$ under essentially the conditions of Rosini[5] except that it was heated at 40°C for 15 h, to give in 50% yield for the two steps, the crude ketoacid **9**. Because of its tendency to epimerize this ketoacid was not purified but was treated, by the procedure of Webster and Silverstein,[22] with methylenetriphenylphosphorane to give the optically active olefinic acid **10** in 62% yield (76% for the racemate). Reduction of this acid (LAH/THF) gave, in 95% yield, (+)-grandisol **11**, $[\alpha]_D^{20} = +20.4$ (±2) (c=1.2 *n*-hexane)[lit. $[\alpha]_D^{20} = +18.4$ (c=1.1 *n*-hexane)]. The enantiopurity of the grandisol was established as 95% e.e. by conversion to the Mosher ester,[23] but in principle the enantiomeric excess could be made even higher.[24] This synthesis of grandisol[25] is accomplished in an 8% overall yield for 10 steps starting from achiral **1**.

Acknowledgment. We acknowledge the receipt of an Australian Postgraduate Research Award (to KLT), and thank Dr M.G. Banwell, A.N.U., Canberra for chiral GC experiments.

References

1. Tumlinson J. H., Gueldner, R. C., Hardee, D. D., Thompson, A. C., Hedin, P. A., and Minyard, J. P. *J. Org. Chem.* **1971**, 36, 2616.

2. Mori, K. In *The Total Synthesis of Natural Products*, ApSimon, J., ED., John Wiley: New York, **1981**, Vol 4, 120-2, 488-93.

3. Mori, K. In *The Total Synthesis of Natural Products*, ApSimon, J., ED., John Wiley: New York, **1992**, Vol 9, 303-12.

4. A catalytic Sharpless AE reaction has been used to prepare (+)-grandisol as a minor product. Martin, T., Rodriguez, C.M., Martin, V.S. *Tetrahedron Asymmetry* **1995**, 6, 1151.

5. Confalonieri, G., Marotta, E., Rama, F., Righi, P., Rosini, G., Serra, R., Venturelli, F., *Tetrahedron* **1994** 50, 10, 3235 and references within.

6. Burns, C.J., Martin, C.A., Sharpless, K.B. *J. Org. Chem.* **1989**, 54, 2826.

7. Johnson, R.A., Sharpless, K.B. in *Catalytic Asymmetric Synthesis* I. Ojima, VCH Publisher Inc., New York **1993**, 103-158.

8. Bagnell, L., Bliese, M., Cablewski, T., Strauss, C. R., Tsanaktsidis, J. *Aust. J. Chem.* **1997**, 50, 921.

9. Cargill, R. L., Wright, B. W. *J. Org. Chem.* **1975**, 40, 120, Cargill, R. L., Dalton, J. R., Morton, G. H., Caldwell, W. E. *Org. Synth.* **1984**, 62, 118.

10. Previous syntheses describe the proton NMR of the ketone as δ1.23 (s, 3H). Use of a 600MHz NMR allows the accurate assignment of protons. ^{1}H NMR ($CDCl_3$, 600MHz) : δ 1.26 (3H, s, CH_3), 1.55-1.8 (2H, complex, $H4_a$, $H6_a$), 1.81-1.95 (2H, complex, $H4_b$, $H7_a$), 2.0-2.1 (1H, complex, $H7_b$), 2.25-2.42 (3H, complex, H1, $H3_a$, $H6_b$), 2.68 (dt, 1H, $H3_b$, J= 9.0, 11.0, 18.5Hz). ^{13}C NMR ($CDCl_3$, 50MHz) : δ 18.70 (CH_2), 25.81 (CH_3), 30.64 (CH_2), 35.43 (CH_2), 38.30 (CH_2), 42.45 (quat), 50.22(CH), 222.5 (CO).

11. Shapiro, R. H., Heath, M. J. *J. Am.Chem. Soc.* **1967**, 89, 5734, Chamberlin, A. R., Bond, F. T. *Synthesis* **1979**, 44.

12. All new compounds gave satisfactory C and H microanalyses.

13. The enone **1** is commercially available from Aldrich but it may be contaminated with hexane-2,4-dione. The enone may be prepared essentially free of contaminants.[8]

14. Gao, Y., Hanson, R. A., Klunder, J. M., Ko, S.Y., Masamune, H., Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, 109, 5765.

15. E.g. Di-isopropyl tartrate (1.26mmol), titanium *i*-propoxide (0.69mmol) and powdered 4Å sieves (0.34g) were combined in anhydrous CH_2Cl_2 (4 mL) and cooled, under a small pressure of N_2, to –15°C. Previously dried *t*-BuOOH soln. (6.5mmol, 5.9M in CH_2Cl_2) was further dried over 3Å sieves for 15min and then added to the tartrate solution. This solution was aged at –40°C for 2h. A mixture of the allylic alcohol (11.8 mmol) and internal standard (*n*-decane), in CH_2Cl_2 (5 mL) were dried over 4Å sieves for 15min, and then added to the tartrate solution with further CH_2Cl_2 (2 mL washings). The reaction was stirred at –40°C for 15 h and then worked up.

16. No useful separation was seen with chiral shift NMR experiments on the alcohol or the derived acetate, nor for the diastereomeric urethanes derived from (S)-(-)-α-methylbenzyl isocyanate on either chromatography or NMR. Partial, but incomplete separation, of the alcohol enantiomers was found on chiral GC (SGE Cydex-B, 25m x 0.22mm).

17. From separate kinetic resolutions with both (+)DIPT and (-)DET highly enriched samples of the two enantiomers of the allylic alcohols were obtained. The Mosher ester for the alcohol from the DIPT resolution has peaks for the ABq at δ ~ 4.90, 4.88, 4.85 and δ 4.83. That from the DET resolution has peaks at δ ~ 4.93, 4.90, 4.85, and 4.83. In the ester from the racemic alcohol the peaks at 4.93 and 4.88 are in the ratio 1:2, close to the theoretical value calculated from the intensities for these ABq's. Almost complete separation of the methoxyl signals is also observed but because this region could be contaminated with reagent signals, it was only used for confirmation.

18. See Ref 7, pp. 227-272.

19. The use of methane sulfonyl chloride gave only a poor yield of the unstable allylic chloride.

20. VanNieuwenhze, M. S., Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, 115, 7864.

21. The ^{1}H NMR(600MHz) spectrum for the diasteromeric esters showed separate dd at δ 5.38 and 5.44 which were integrated.

22. Webster, F. X., Silverstein, R. M. *J. Org. Chem.* **1986** 51, 5226.

23. Mori, K., Miyake, M. *Tetrahedron* **1987**, 43, 2229.

24. Martin, V. S., Woodard, S. S., Katsuki, T., Yamada, Y., Ikeda, M., Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, 103, 6237.

25. The spectroscopic data obtained for grandisol was identical with that of the natural product.