Tetrahedron Letters,Vol.30,No.20,pp 2707-2708,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A USEFUL METHOD FOR PREPARING OPTICALLY ACTIVE SECONDARY ALCOHOLS: A SHORT ENANTIOSPECIFIC SYNTHESIS OF (R)- AND (S)-SULCATOL

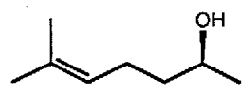
Carlos M. Afonso, M. Teresa Barros, Licio Godinho and Christopher D. Maycock*.

Faculdade de Ciência e Tecnologia, Departamento de Quimica, Universidade Nova de Lisboa, 2825 Monte de Caparica, Portugal.

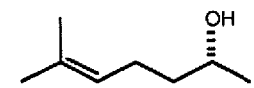
Abstract. The epimeric 2-(1-Hydroxyethyl)-5-methyl-4-hexenoic acids have been prepared by bakers yeast reduction of the corresponding oxo compound or by alkylation of an optically pure 3-hydroxybutanoate. Radical chain decarboxylation afforded the antipodes of sulcatol. The method is probably widely applicable to the synthesis of other optically pure alcohols.

Methyl ketones are readily prepared by the facile decarboxylation of 3-oxoesters. An analogous strategy for the production of methyl carbinols has not been feasible since an efficient method for carrying out the decarboxylation of a corresponding 3-hydroxyester has not been available. This latter route would provide an access to chiral methyl carbinols since a variety of 3-hydroxyesters with high optical purity are available cheaply . Barton's[1] method offered to overcome the decarboxylation problem at an otherwise nonactivated carboxyl group.

Here we apply this strategy to the preparation of the antipodes of Sulcatol **1**[2] which as a mixture constitute an aggregation pheromone of the insect pest *Gnathotrichus Sulcatis.* The species *Gnathotrichus retusus* responds in a positive manner only to the (S)-(+) enantiomer[3].



S - 1



R - 1

Three possible routes to the required 3-hydroxyacids were considered and studied.

1) Reduction by bakers yeast of a linear 3-oxoacid or ester. This would provide access to only one enantiomer, i.e. (S) -1. Since the enzymes involved do not differentiate efficiently for the esters the acid would be preferred, as shown recently[4].

2) Bakers yeast reduction of a 2-substituted 3-oxobutanoate. Again would only furnish one enantiomer. Results have shown that the reduction of these substrates leads to products having very high configurational purity at the newly formed carbinol carbon[5].

3) Alkylation at the 2-position of optically pure 3-hydroxybutanoates. Both of the enantiomers of the 3-hydroxybutanoates are available, the (R) -isomer in optically pure form by the depolimerisation[6] of the poly 3-hydroxybutanoic acid formed by bacterial fermentation[7], and the (S)-isomer is available (≈90% e.e.) by bakers yeast reduction of an appropriate acetoacetate. The ethyl (3S)-hydroxybutanoate used in this work was obtained in optically pure form by two routes. Bakers yeast reduction of ethyl 2-alkylthio-3-oxobutanoate followed by Raney nickel desulphurisation[8] or by recrystallisation of the amide resulting from the reaction of 90% e.e. ethyl (3S)-hydroxybutanoate with methanolic ammonia, the ester was regenerated by acid ethanolysis[9]. Both of these processes are efficient but in this case the second route was preferred because of the ready availability of the enantiomer enriched (3S)-hydroxybutanoate.

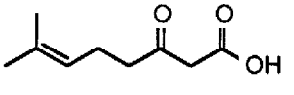
The 3-oxoacid **2** was prepared and reduced as per the method of Hirami[4] to afford the hydroxyacid **3**. The low yield (45%) for this step we attribute to competitive decarboxylation during the fermentation since no starting material was recovered or detected. Even the use of pH 7 buffer control during yeast reductions does not resolve the problem of the instability of acid labile functions under the fermentation conditions, implying that the environment inside the yeast cells is relatively acid. Acetylation ((a) Ac_2O, pyridine (b) aq.$NaHCO_3$) of **3** yielded the acetate **4** (84%). Decarboxylation by the Barton method did not afford the required acetate **5** but a volatile saturated compound which we tentatively assign the structure **6** on the basis of its nmr. Also mechanistically **6** would be expected from the intramolecular radical cyclisation of the intermediate **7.** This approach was abandoned in favour of options 2) and 3) since the formation of a cyclopropane by cyclisation of the expected radical intermediate appeared unlikely.

Bakers yeast reduction of the 2-acetylhexenoate **8** afforded starting ketone (42%) and the alcohol **9** (29%) with >97% stereeochemical integrity at the new carbinol center, as a mixture of diastereoisomers. Hydrolysis to the acid **10** (aq. NaOH, 98%) followed by acetylation (Ac_2O, pyridine) produced the substrate **11** (86%) which was subjected to Barton's decarboxylation conditions. These latter smoothly and cleanly produced the acetate **5** (71%) which could be hydrolised (NaOH) to afford (S)-sulcatol **1** (90%) in an optically pure state, as was shown by its optical rotation ($[\alpha]_D$ +14.8 (c. 0.95, EtOH),lit[10] +14.4 (c. 0.998, EtOH) and by nmr studies using chiral europium shift reagents.

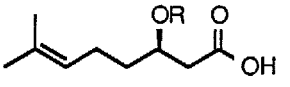
Alkylation of the dianion derived from ethyl (3S)-hydroxybutanoate with 4-bromo-2-methyl-2-butene afforded **10** (40%) as a mixture of diastereoisomers. Compound **10** was converted to optically pure (S)-**1** as above, the overall yield being 22%, mainly due to the inefficient alkylation step which was not optimised.

Similarly alkylation of the dianion of ethyl (3R)-hydroxybutanoate yielded **13** as a mixture of diastereoisomers. Subsequent treatment as for **9** afforded (R)-**1** in an optically pure form ($[\alpha]_D$ -14.3 (c. 1.22, EtOH).

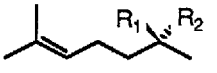
With this short enantioselective synthesis of both antipodes of sulcatol we have demonstrated a useful strategy for the preparation of methyl carbinols[11]. The application of strategy 3) to many of the large range of 3-hydroxyesters available should afford a general method for the enantioselective synthesis of a wide range of secondary alcohols and/or for the facile introduction of a chiral carbinol center during synthesis.



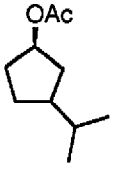
2



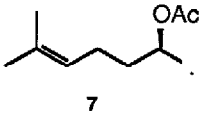
3 R = H
4 R = Ac



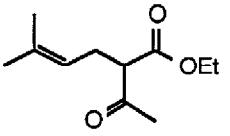
5 R_1 = OAc, R_2 = H
12 R_1 = H, R_2 = OAc



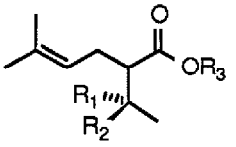
6



7



8



9 R_1 = OH , R_2 = H, R_3 = Et
10 R_1 = OH, R_2 = H, R_3 = H
11 R_1 = OAc, R_2 = H, R_3 = H
13 R_1 = H, R_2 = OH, R_3 = Et

Notes and references:

1. D. H. R. Barton, B. Garcia, H. Togo, S. Z. Zard, Tetrahedron Lett., 1986, **27**, 1327 and references therein.
2. For leading references see: A. Belan, J. Bolte, A. Fauve, J. G. Gourcy, H. Veschambre, J. Org. Chem., 1987, **52**, 256.
3. J. H. Borden, L. Chong, J. A. McLean, K. N. Slessa, K. Mori, Science, 1976, **192**, 894.
4. M. Hirama, M. Shimizu, M. Iwashita, J. Chem. Soc. Chem. Commun., 1983, 599.
5. G. Fráter, U. Muller, W. Gunther, Tetrahedron, 1984, **40**, 1269.
6. Several methods exist for this transformation. We use a mixture of PHB, ethanol, HCl, and chlorinated solvent. The nature of the chlorinated solvent determines the efficiency of the depolymerisation. A. G. O. Santos unpublished results.
7. P. J. Senior and E. A. Dawes, Biochem. J., 1973, **134**, 225.
8. T. Fujisawa, T. Itoh, T. Sato, Tetrahedron Lett., 1984, 5083.
9. C. M. Afonso and A. G. O. Santos, unpublished results. We have successfully applied this technique to the enantiomer enrichment of several β-hydroxyesters. The yields for this process are normally high.
10. K. Mori, Tetrahedron, 1975, **31**, 3011.
11. We have prepared other optically pure methyl carbinols using these approaches. We have no reason to believe that a large number of other functional groups would not be stable under the conditions used.

Acknowledgements: We thank **ICI** for a generous gift of PHB and **JNICT** Portugal for financial support.

(Received in UK 16 March 1989)