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Enantioselective Introduction of a Benzenesulfonylmethyl Substituent at an Unactivated Carbon Atom via Chemoenzymatic Methods

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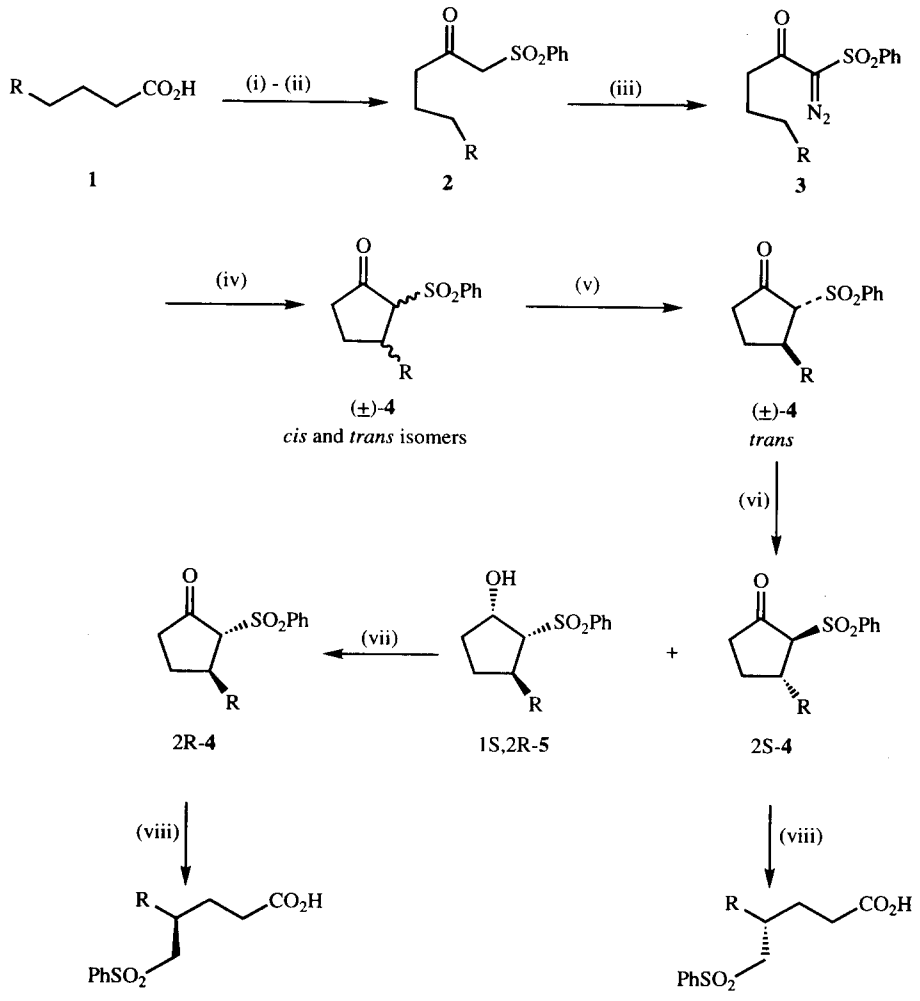
Abstract: Introduction of a benzenesulfonylmethyl group at the unactivated γ-carbon of carboxylic acid derivatives has been achieved through a combination of rhodium acetate catalysed carbenoid C-H insertion and baker's yeast mediated kinetic resolution. Access to the two complementary enantiomeric series of **6** with excellent enantiocontrol is possible. © 1997 Elsevier Science Ltd.

Advances in the development of new methodology for enantioselective synthesis in recent years have been extensive; for example, enantioselective functionalisation at positions α or β to a carboxylic acid moiety can be readily achieved by existing methods, the former by enantioselective enolate alkylation[1] and the latter by asymmetric conjugate addition,[2] among other methods. However, functionalisation at an unactivated γ–carbon of carboxylic acid derivatives in an enantioselective manner is much less readily achieved using existing synthetic methods.[3] We report here enantioselective introduction of benzenesulfonylmethyl groups at the unactivated γ-position of carboxylic acids, achieved through a synthetically powerful combination of a transition metal catalysed process and a kinetic resolution *via* biocatalysis.[4]

Regiospecific activation of the unactivated C-H bond at the γ-carbon was achieved under mild conditions *via* rhodium acetate catalysed carbenoid insertion[5] as illustrated in Scheme 1. Transformation of the carboxylic acids **1**, under standard conditions, *via* esters to β-keto sulfones **2**, followed by diazo transfer[6] led to the α-diazo-β-keto sulfones **3**. Rhodium(II) acetate catalysed decomposition of **3** resulted in essentially quantitative C-H insertion to form the α-benzenesulfonylcyclopentanones **4**. The carbenoid insertions were complete in just a few hours in refluxing dichloromethane. While the crude product in some reactions contained a mixture of *cis* and *trans* isomers of **4**, equilibration to form exclusively the thermodynamically more stable *trans* isomers was readily achieved.

With the racemic cyclopentanone derivatives in hand, the next challenge was to develop a method to obtain these compounds in enantiomerically pure (or enriched) form. Application of biocatalysis[7] leading to a kinetic resolution of the enantiomers of **4** was identified as an appropriate strategy. One of the micro-organisms which has been widely investigated in organic synthesis is baker's yeast, *Saccharomyces cerevisiae*, largely due to its ready availability, ease of use and the wide range of substrates which it accepts.[8] While



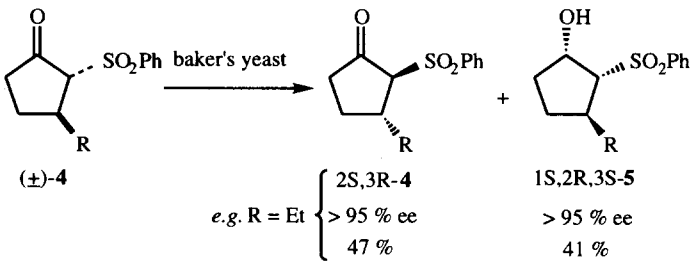
(i) esterification; (ii) $PhSO_2CH_3$, NaH, DMSO, THF, 70 - 90%; (iii) TsN_3, Et_3N, EtOH, 60 - 95%; (iv) $Rh_2(OAc)_4$, CH_2Cl_2, Δ, essentially quantitative; (v) a. aq. NaOH, b. aq. NH_4Cl, 75 - 95%; (vi) baker's yeast[10,12]; (vii) Dess-Martin oxidation, 60 - 90%; (viii) 0.5 M NaOH, Δ, < 1h, 92 - 100%

R = Me, Et, Pr, Bu, C_5H_{11}, Ph, CH_2Ph

Scheme 1

enantioselective reduction of β-keto esters with baker's yeast is an extremely successful transformation which has been widely exploited in asymmetric synthesis, reduction of β-keto sulfones with baker's yeast has been less successful.[9] Short chain derivatives were successfully reduced with yeast, but extension of the alkyl chain resulted in dramatic decreases in both the efficiency and the enantioselectivity of the yeast mediated reduction.

Despite this disappointing precedent, baker's yeast mediated reduction of the α-benzenesulfonylcyclopentanone derivatives **4** was attempted and, as illustrated in Scheme 2, resulted in extremely efficient kinetic resolution.[10] By variation of the conditions employed for the yeast reduction[11] (*e.g.* concentration of yeast and / or sucrose, reaction time, yeast immobilisation, use of organic solvents, additives) the efficiency, enantio- and diastereoselectivity of the transformation have been optimised for each of the cyclopentanone derivatives **4** so that it is possible to obtain samples of each of the cyclopentane derivatives 2S-**4** and 1S,2R-**5** in highly enantioenriched form (> 95 %ee).[12] The complementary series of the cyclopentanone derivatives could also be readily prepared; Dess-Martin oxidation of the cyclopentanols **5** recovered from the yeast reductions gave the 2R-**4** series.



Scheme 2

Treatment of β-keto sulfones with aqueous base leads to cleavage in a retro-Claisen type process.[13] Each of the two complementary enantiomeric series of α-benzenesulfonylcyclopentanones **4** was treated with aqueous sodium hydroxide resulting in efficient ring opening to form the corresponding carboxylic acid derivatives **6** as illustrated in Scheme 1. The enantiomeric purities of the carboxylic acids **6** isolated were determined by chiral HPLC analysis confirming that the stereochemical integrity at C-4 of the carboxylic acids **6** was, as expected, unaffected under these reaction conditions. For example, a sample of cyclopentanone 2R,3R-**4** (R = $PhCH_2$, 88 %ee) on treatment with aqueous base furnished the carboxylic acid 4R-**6** (87 %ee) in 93 % yield.

In summary, starting from the carboxylic acid derivatives **1**, conversion to the racemic cyclopentanones **4** is achieved in four steps, the key step involving a rhodium catalysed C-H insertion process which regiospecifically activates a remote unactivated C-H bond under mild reaction conditions, and is followed by kinetic resolution employing baker's yeast as the biocatalyst. Ring cleavage under basic conditions produces efficiently the 4-

(benzenesulfonylmethyl)carboxylic acids **6**. The overall transformation resulting from this reaction sequence is the enantioselective introduction of a benzenesulfonylmethyl substituent at the γ-position of the carboxylic acids **1**. Most significantly, access to the two complementary series with excellent enantioselectivity (> 95 %ee) is possible *via* this methodology. As the reaction conditions involved are quite mild, the sequence should be widely applicable. The benzenesulfonylmethyl substituent is a versatile group which can either be reductively desulfonylated to leave the methyl substituted compounds, or alternatively the sulfone can be used for further synthetic transformations leading to a range of valuable chiral synthons.

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References and Footnotes

1. Evans, D.A.; Ennis, M.D.; Mathre, D.J. *J. Am. Chem. Soc.*, 1982, **104**, 1737.
2. Lutomski, K.A.; Meyers, A.I. *Asymmetric Synthesis*, Vol. 3, Morrison, J.D. ed., Academic Press, Orlando, 1984, Chapter 3.
3. For an example of γ-functionalisation of carboxylic acids see Monteiro, H.J. *Synlett*, 1991, 990.
4. A few reports of the unusual combination of transition metal catalysis and biocatalysis in organic synthesis have appeared recently e.g. Allen, J.V.; Williams, J.M.J. *Tetrahedron Lett.*, 1996, **37**, 1859; Dinh, P.M.; Howarth, J.A.; Hudnott, A.R.; Williams, J.M.J.; Harris, W.*Tetrahedron Lett.*, 1996, **37**, 7623; Backvall, J.-E. *Acta Chem. Scand.*, 1996, **50**, 661.
5. Rhodium catalysed C-H insertion reactions to form cyclopentanone derivatives were originally developed by Taber using α-diazo-β-keto esters, Taber, D.F.; Petty, E.H *J. Org. Chem.*, 1982, **47**, 4808, and later extended to α-diazo-β-keto sulfones, Monteiro, H.J. *Tetrahedron Lett.*, 1987, **28**, 3459; Kennedy, M.; McKervey, M.A.; Maguire, A.R.; Roos, G.H.P. *J. Chem. Soc., Chem. Commun.*, 1990, 361; Monteiro, H.J.; Zukerman-Schpector, J. *Tetrahedron*, 1996, **52**, 3879.
6. Regitz, M.; Maas, G. *Diazo Compounds, Properties and Synthesis*, Academic Press, New York, 1986.
7. Poppe, L.; Novak, L.*Selective Biocatalysis*, VCH, Weinheim, 1992; Davies, H.G.; Green, R.H.; Kelly, D.R.; Roberts, S.M. *Biotransformations in Preparative Organic Chemistry*, Academic Press, London, 1989.
8. For reviews see Servi, S. *Synthesis*, 1990, 1; Csuk, R.; Glanzer, B.I. *Chem. Rev.*, 1991, **91**, 49; Sato, T.; Fujisawa, T. *Biocatalysis*, 1990, **3**, 1.
9. Crumbie, R.L.; Deol, B.S.; Nemorin, J.E.; Ridley, D.D. *Aust. J. Chem.*, 1978, **31**, 1965; Nakamura, K.; Ushio, K.; Oka, S.; Ohno, A.; Yasui, S. *Tetrahedron Lett.*, 1984, **25**, 3979; Robin, S.; Huet, F.; Fauve, A.; Veschambre, H. *Tetrahedron: Asymmetry*, 1993, **4**, 239; Tanikaga, R.; Hosoya, K.; Kaji, A. *J. Chem. Soc., Perkin Trans. 1*, 1987, 1799; Kozikowski, A.P.; Mugrage, B.B.; Li, C.S.; Felder, L. *Tetrahedron Lett.*, 1986, **27**, 4817; Svatos, A.; Hunkova, Z.; Kren, V.; Hoskovec, M.; Saman, D.; Valterova, I.; Vrkoc, J.; Koutek, B. *Tetrahedron: Asymm.*, 1996, **7**, 1285; also references in the reviews in ref. 8.
10. Maguire, A.R.; Kelleher, L.L.; Ferguson, G. *J. Mol. Catalysis B: Enzymatic*, 1996, **1**, 115; Maguire, A.R.; Lowney, D.G. *J. Chem. Soc., Perkin Trans. 1*, 1997, 235.
11. Nakamura, K. *Microbial Reagents in Organic Synthesis*, ed. Servi, S. 1992, 389 - 398, Kluwer Aacdemic Publishers, Dordrecht; Nakamura, K.; Kawai, Y.; Ohno, A. *Tetrahedron Lett.*, 1991, **32**, 2927; Nakamura, K.; Kawai, Y.; Nakajima, N.; Ohno, A. *J. Org. Chem.*, 1991, **56**, 4778.
12. Full details of the optimisation of the yeast mediated kinetic resolutions will be reported elsewhere.
13. Ficini, J.; Stork, G. *Bull. Soc. Chim. Fr.*, 1964, 723; Ballini, R.; Bosica, G.; Mecozzi, T. *Tetrahedron*, 1997, **53**, 7341; see also ref. 3.

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