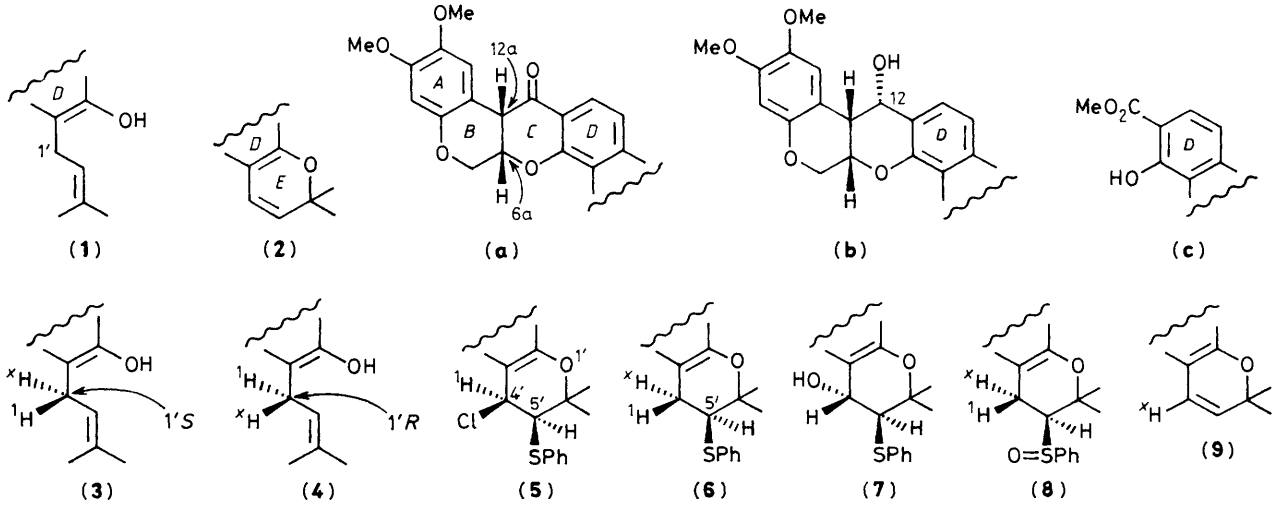
The Stereospecific Generation of Chirally Labelled Benzylic Centres in *o*-Prenylphenols: 1′-*R*- and 1′-*S*-[1′-^{3}H]-Rotenonic Acid

Prabha Bhandari, Leslie Crombie,* Mark H. Harper, M. Sanders, and Donald A. Whiting*

Department of Chemistry, The University of Nottingham, Nottingham NG7 2RD, U.K.

The problem of generating rot-2′-enonic acid stereospecifically with tritium in the 1′*R*- and 1′*S*-benzylic positions of the prenyl group is solved by a method generally applicable to *o*-prenylphenols: chiral centres are constructed on a ring system, with subsequent ring scission.

The *o*-prenylphenol sub-structure (**1**) is of common occurrence in natural products and is also found variously oxidised and cyclised in a range of natural product features. The mechanism and stereochemistry of such enzymic oxidations remain largely uninvestigated, and the availability of specifically 1′-*R*- and 1′-*S*-*o*-prenyl phenols would provide valuable enabling tools. Our own need arose during a study of the stereochemistry of the enzymic conversion of rot-2′-enonic acid (**1a**) into deguelin (**2a**)[1,2] and the method we have devised should have general applicability.



The strategy employed was to construct the desired chiral centre on a ring system where stereochemical control was more effective, followed by ring scission at a late stage. Accordingly, model chromen (**2c**) was allowed to react at −30 °C with phenylsulphenyl chloride to yield the highly reactive (±)-*cis*-chlorosulphide (**5c**),† $J_{4',5'}$ Hz (*cf. ca.* 9 Hz for *trans*-geometry). Aqueous work-up or silica chromatography gave only the 4',5'-*trans*-hydroxy-sulphide (**7c**), whilst borohydride reduction of (**5c**) afforded the 5'-thioether (**6c**, x = 1). Using deuterioborohydride clean deuteriation with 4'-inversion was observed, yielding the 5'-thioether (**6c**, x = 2), $J_{4',5'}$ 9 Hz; its stereochemical purity was checked by ^{2}H n.m.r. Finally, reductive ring opening with potassium naphthalenide unmasked both the phenol and the double bond to give the corresponding (±)-[1'-^{2}H]-dimethylallyl phenol (**3c**, x = 2).

The sequence was then adapted for the natural enzyme substrate rot-2'-enonic acid (**1a**). 6a*S*,12a*S*-Deguelin, $[\alpha]_D^{25}$ −30.4° (MeOH) was prepared from natural rotenone[4] and allowed to react with sodium cyanoborohydride to form the desired 5-*S*-5'-phenylthiochroman (**6a**, x = 1). Both diastereoisomers epimeric at 5' were expected but the addition was stereospecific in tetrahydrofuran or dichloromethane at various temperatures between −60 and +25 °C. The stereochemistry (**6a**, x = 1) was firmly established by n.m.r. comparison with the 5'-*R*- and 5'-*S*-phenylselenyl analogues[1b] and has been further confirmed by independent *X*-ray analysis.[5] Reductive cleavage of the chroman (**6a**, x = 1) could not be effected cleanly with either potassium naphthalenide or cathodic reduction. Although carbonyl groups have remained unaffected in certain model reactions,[6] it seemed possible that the rotenoid *B/C* system was the seat of the difficulty and would require protection. This was done by treatment of the chlorosulphide (**5a**) with sodium borohydride thus reducing both chloro and carbonyl functions, giving the 12-hydroxy thioether (**6b**, x = 1). The latter was smoothly reduced by potassium naphthalenide (−35 °C, 5 min) to give the acid-labile phenol (**1b**) which could be obtained in good yield by extraction from slightly alkaline medium. Finally, the 12-carbonyl was reconstituted using Dess–Martin reagent,[7] giving rotenonic acid (**1a**) in good overall yield. The sequence from (−)-deguelin was then repeated using sodium borodeuteride and borotritide to give the desired 1'-*S*-labelled compounds (**3a**, x = 2), $J_{4,5}$ 3.2 Hz, and (**3a**, x = 3).

The stereospecificity of the chlorosulphenylation of deguelin (**2a**) prevented access to the 5'-epimer of the thioether (**6a**) and hence the 1'-*R*-rotenonic acids (**4a**, x = 2 and 3). An indirect method was therefore devised. Oxidation (*m*-chloroperbenzoic acid) of the sulphide (**6a**, x = 3) to the sulphoxide (**8a**, x = 3), followed by elimination of phenylsulphenic acid gave [1'-^{3}H]-deguelin (**9a**, x = 3). No tritium was lost in this *syn*-elimination and a non-tritiated sample of deguelin (**9a**, x = 1) made by this route had $[\alpha]_D^{25}$ −30°, showing that *B/C* racemisation had not occurred. The sample of [1'-^{3}H]-deguelin was now used to prepare 1'-*R*-[1'-^{3}H]-rotenonic acid (**4a**, x = 3) by the route above.

These synthetic procedures should be adaptable to a wide range of similar structures, and in our case the tritiated 1'*S*- and 1'-*R*- pair (**3a**, x = 3) and (**4a**, x = 3) were used to study the deguelin cyclase enzyme in the following Communication.

Received, 28th February 1989; Com. 9/00875F

† *syn*-Electrophilic addition to aryl-conjugated double bonds *via* an ion pair mechanism is well precedented.[3]

References

1 (a) L. Crombie, J. Rossiter, and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 1986, 352; (b) M. J. Begley, L. Crombie, J. Rossiter, M. Sanders, and D. A. Whiting, *ibid.*, 1986, 353.
2 P. Bhandari, N. Van Bruggen, L. Crombie, and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 1989, following Communication.
3 G. E. Heasley, T. R. Bower, K. W. Dougharty, J. C. Easdon, V. L. Heasley, S. Arnold, T. L. Carter, D. B. Yaeger, B. T. Gipe, and D. F. Shellhamer, *J. Org. Chem.*, 1980, **45**, 5150 and references cited therein; M. J. S. Dewar, *Angew. Chem., Int. Ed. Engl.*, 1964, **3**, 245.
4 P. B. Anzeveno, *J. Org. Chem.*, 1979, **44**, 2578.
5 Personal communication, Dr. M. J. Begley.
6 S. E. Mohammed, P. Thomas, and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1987, 431.
7 D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155.