A New Enantioselective Route to Bisabolane Sesquiterpenes Phenols: Synthesis of (*S*)-(+)-Curcuphenol and (*S*)-(+)-Curcumene

Claudio Fuganti, Stefano Serra*

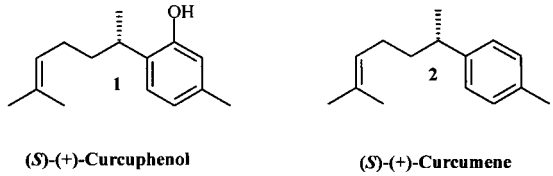
Dip. di Chimica del Politecnico, Centro CNR per la Chimica delle Sostanze Organiche Naturali,Via Mancinelli 7, 20131 Milano, Italy.

Fax: 39 2 23993080. E-mail: stud5412@dept.chem.polimi.it

Received 28 July 1998

Abstract: (*S*)-(+)-Curcuphenol **1** and (*S*)-(+)-curcumene **2** were synthesised starting from enantiopure (*R*)-(-)-3-furyl-2-methylpropanol **3** and building up the phenolic ring through a benzoannulation reaction.

In past years many different syntheses[1] of bisabolane sesquiterpenes have been developed allowing a whole availability of these natural products in their racemic form. In spite of this, few enantioselective approaches[2] have been reported in the literature due to the difficulty of introducing a stereogenic centre in the benzylic position. Moreover, opposite enantiomers show different biological activities, as in the case of curcuphenol where the (*S*)-(+)-enantiomer **1** (Scheme 1) inhibits the activity of gastric H, K-ATPase[3] while the (*R*)-(-)-enantiomer shows antibacterial activity.[4]



Scheme 1

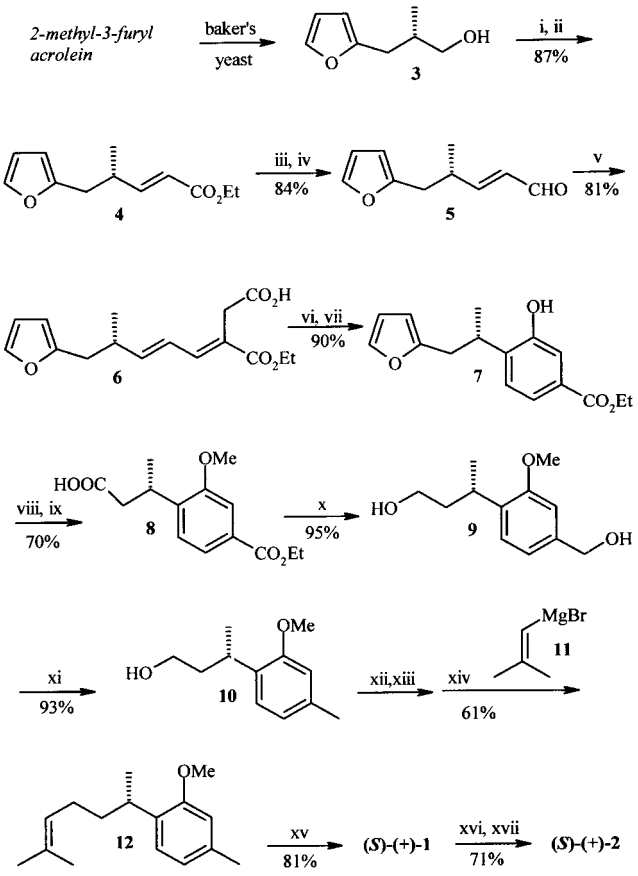
Until now, the only two methods that allow one to synthesise stereoselectively curcuphenol are described for (*R*)-(-)-enantiomer. Enzymatic resolution of a racemic intermediate[5] or use of enantiopure (*R*)-(+)-citronellal[6] are the methods for the introduction of the stereogenic centre. Troublesome separation of enantiomers or use of a precious enantiopure starting building block are then necessary. Otherwise, as in the previous syntheses of bisabolane sesquiterpenes[2], if the starting materials are aromatic the stereogenic centre is introduced with the difficulty mentioned above.

In our work we propose a different synthetic approach based on a stereoselective synthesis of a suitable chiral alicyclic framework which can be converted through a cyclisation reaction in a phenol derivative bearing a benzylic asymmetric centre. To effect our plan we used the benzoannulation procedure that we have recently developed,[7] based on the cyclisation of substituted 3-alkoxycarbonyl-3,5-hexadienoic acids. This latter process works under mild basic conditions and gives benzoannulate phenols in high yields starting from chiral aldehydes[7c] whilst preserving the configuration of the existing stereocentres.

We used (*R*)-(-)-3-furyl-2-methylpropanol **3** (99% e.e.) (Scheme 2), easily available by enzymatic reduction of 2-methyl-3-furylacrolein[8], as starting chiral building block. The hydroxyl group can be manipulated in order to obtain the hexadienoic acid and the furyl group is convertible into the acid group by ozonolysis.

The missing C-4 component of the whole C-15 bisabolane framework can be introduced through conversion of alcohol C-11 **10** in the related iodide followed by coupling with the Grignard reagent **11** in the presence of copper(I) iodide**.**

Thus, conversion of **3** (99% e.e.) in the 3-ethoxycarbonyl-3,5-hexadienoic acid **6** was performed through few straighforward reactions. Oxidation of **3** with pyridine-SO_3 system[9a] in dry DMSO



Scheme 2

Reagents and conditions: i) $PySO_3$/DMSO; ii) $Ph_3PCHCOOEt/CHCl_3$; iii) DIBAH/THF, 0°C; iv) $MnO_2/CHCl_3$; v) triphenyl(carbethoxycarboxy ethyl)phosphonium betaine/benzene; vi) $ClCOOEt/Et_3N$;vii) NaOH/EtOH; viii) K_2CO_3/DMF, MeI; ix) O_3/MeOH, $NaBH_4$; x) $LiAlH_4$/THF; xi) H_2, Pd/C, AcOEt; xii) $TsCl/Py/CH_2Cl_2$; xiii) NaI/acetone; xiv) **11**, CuI/THF; xv) NaI/CH_3CN, $ClSiMe_3$; xvi) $MsCl/Et_3N$; xvii) Li/NH_3.

afforded the related aldehyde without racemization of the vicinal stereocentre.[9b] Direct reaction of the crude product with carbethoxymethylenetriphenyl phosphonium betaine gives the ester **4** which was converted into the unsaturated aldehyde **5** through reduction with DIBAH followed by oxidation with MnO_2. Transformation of the latter aldehyde in acid **6** was achieved in good yields by Wittig olefination with triphenyl-(α-carbethoxy-β-carboxyethyl)-phosphonium betaine.[10] Benzannulation of the acid **6** with ethyl chloroformate in the presence of a slight excess of triethylamine followed by quick treatment with ethanolic NaOH afforded the chiral phenol **7**[11] in high yield (90%).

The phenolic group was protected by methylation and treatment of the resulting methyl ether with ozone at low temperature (-78°C) followed by $NaBH_4$ reduction gave the acid **8** in good yield. Simultaneous

reduction of the two carboxylic groups of **8** was performed by treatment with $LiAlH_4$ and the resulting diol **9** was deoxygenated at the benzylic position by hydrogenation affording the alcohol C-11 **10**.[12] Transformation of the latter alcohol to the corresponding iodide and the subsequent coupling[13] with the Grignard reagent **11** catalysed by CuI gave **12**,[14] allowing the whole bisabolane framework to be constructed. Hydrolysis of the phenolic methyl ether by treatment with Me_3SiCl/NaI[15] gave (*S*)-(+)-curcuphenol **1**[16] showing the same analytical data reported in the literature[3b]. To confirm that the absolute stereochemistry was unchanged we reduced the corresponding mesylate derivative using lithium in ammonia[4] to give (*S*)-(+)-curcumene **2**.[17]

Thus, the synthetic method that we proposed did not produce racemization. Moreover, the starting materials and reagents are inexpensive and the overall yield is good.

The present route may be applicable not only to curcuphenol, but also to other members of the bisabolane family. In effect, alcohol **10** can be a useful chiral precursor for the synthesis of natural sesquiterpene phenols[18] which show the same absolute configuration at the benzylic centre.

References and Notes

1) a) ApSimon, J.; '*The Total Synthesis of Natural Products*', vol. 5, *Wiley and Sons*, **1983**, p. 35.

2) a) Takano, S.; Goto, E.; Ogasawara, K. *Tetrahedron Lett.*, **1982**, *23*, 5567. b) Asaoka, M.; Shima, K.; Takei, H. *Tetrahedron Lett.*, **1987**, *28*, 5669. c) Takano, S.; Yanase, M.; Sugihara, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.*, **1988**, 1538.

3) a) Fusetani, N.; Sugano, M.; Matsunaga, S.; Hashimoto, K. *Experientia*, **1987**, *43*, 1234. b) Wright, A.E.; Pomponi, S.A.; McConnell, O.J.; Kohmoto, S.; McCarthy, P.J. *J. Nat. Prod.*, **1987**, *50*, 976.

4) McEnroe, F.J.; Fenical, W. *Tetrahedron*, **1978**, *34*, 1661.

5) Ono, M.; Ogura, Y.; Hatogai, K.; Akita, H. *Tetrahedron: Asymmetry*, **1995**, *6*, 1829.

6) Ghisalberti, E.L.; Jefferies, P.R.; Stuart, A.D. *Austr. J. Chem.*, **1979**, *32*, 1627.

7) a) Brenna, E.; Fuganti, C.; Perozzo, V.; Serra, S. *Tetrahedron*, **1997**, *53*, 15029. b) Brenna, E.; Fuganti, C.; Serra, S. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 901. c) Brenna, E.; Fuganti, C.; Serra, S. *Synlett*, **1998**, 365.

8) Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.*, **1982**, 205; Fuganti, C.; Grasselli, P.; Servi, S.; Högberg, H. E., *J. Chem. Soc., Perkin Trans.1*, **1988**, 3061

9) a) Parikh, J.R.; Doering, W.E. *J. Am. Chem. Soc.*, **1967**, *89*, 5505. b) Evans, D.A.; Bartroli, J. *Tetrahedron Lett.*, **1982**, *23*, 807.

10) Hudson, R.F.; Chopard, P.A. *Helv. Chim. Acta*, **1963**, *46*, 2178.

11) Ethyl chloroformate (50 mmoles) was added in one portion to a THF solution of acid **6** (20 mmoles, 0.2 M) and then Et_3N (60 mmoles) was added keeping the temperature under 20°C. The reaction mixture was stirred for 20 min. at room temperature, then treated with a excess of HCl 5% aq., and extracted with diethyl ether. The organic phase was concentrated under reduced pressure to give a residue which was a carboxyethyl derivative of phenol **7**. The latter was treated with ethanolic NaOH (50 mmoles) at room temperature for 10 min., diluted with an excess of HCl 5% and then extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on a silica gel column eluting with hexane-ethyl acetate (5:1 – 2:1) to give the phenol **7** in 90% yield and showing the following analytical data: Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.56. Found: C, 69.95; H, 6.58. $[\alpha]_D^{20}$ = +14.4° (c 5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.26 (d, 3H, J=6Hz, CH$\underline{CH_3}$), 1.37 (t, 3H, J=7.5Hz, COOCH$_2\underline{CH_3}$), 2.80-3.10 (m, 2H, furyl$\underline{CH_2}$CH), 3.47-3.53 (m, 1H, $\underline{CH}CH_3$), 4.35 (q, 2H, J=7.5Hz, COO$\underline{CH_2}CH_3$), 5.92 (m, 1H, furyl ring), 6.23 (m, 1H, furyl ring), 7.15-7.35 (2m, 2H, 1H furyl ring + 1H aromatic ring), 7.55 (m, 2H, aromatic ring); EI-MS *m/z* 275 (M^+ +1), 274 (M^+), 239, 193, 165, 81; FT-IR (nujol): (cm^{-1}) 733, 768, 1230, 1295, 1425, 1587, 1714, 2980, 3416.

12) The alcohol **10** shows the following analytical data: Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.18; H, 9.26. Found: C, 74.33; H, 9.20. $[\alpha]_D^{20}$ = +17.8° (c 4.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25 (d, 3H, J=6.5Hz, CH$\underline{CH_3}$), 1.55-1.72 (m, 1H, $CH_2\underline{CH_2}CH$), 1.80-1.98 (m, 1H, $CH_2\underline{CH_2}CH$), 2.20 (s, 1H, $CH_2\underline{OH}$), 2.33 (s, 3H, Ar$\underline{Me}$), 3.27-3.45 (m, 2H, $CH_2\underline{CH_2}OH$), 3.45-3.58 (m, 1H, $\underline{CH}CH_3$), 3.82 (s, 3H, O$\underline{Me}$), 6.69 (s, 1H, aromatic ring), 6.77 (d, 1H, J=8Hz, aromatic ring), 7.08 (d, 1H, J=8Hz, aromatic ring); EI-MS *m/z* 194 (M^+), 161, 149, 119, 91; FT-IR (nujol): (cm^{-1}) 812, 1042, 1259, 1462, 1612, 2959, 3376.

13) Deguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.*, **1976**, *36*, 3225.

14) The alcohol **10** in CH_2Cl_2 (15 mmoles, 0.3M solution) was treated with tosyl chloride (20 mmoles) and pyridine (30 mmoles) and stirred at room temperature until no more starting alcohol was detected by TLC analysis (4h). The mixture was then washed with an excess of HCl 5% aq., and extracted with CH_2Cl_2. The organic phase was concentrated under reduced pressure and the residue was treated with NaI (150 mmoles, 0.2M in dry acetone) at reflux for 3h. The reaction mixture was diluted with water, extracted with diethyl ether and the organic phase was washed with a solution of $Na_2S_2O_3$ (1%). The crude iodide was purified by chromatography and then dissolved in dry THF. The obtained solution (0.5M) was cooled to –40°C and treated under nitrogen with CuI (3 mmoles) and Grignard **11** (23 mmoles). The reaction was allowed to warm to 0°C and stirred at this temperature for 6h. Work-up with NH_4Cl aq., extraction with diethyl ether and purification of the crude product by chromatography on a silica gel column eluting with hexane-ethyl acetate (95:5) gave pure **12** in 61% overall yield and showing the following analytical data: Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.33. Found: C, 82.55; H, 10.26. $[\alpha]_D^{20}$ = +1.5° (c 4.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.17 (d, 3H, J=7Hz, CH$\underline{CH_3}$), 1.40-1.70 (m, 2H, C=CH$\underline{CH_2}$), 1.53 (s, 3H, $\underline{Me}$CMe), 1.68 (s, 3H, MeC$\underline{Me}$), 1.80-2.05 (m, 2H, $CH_2\underline{CH_2}CH$), 2.33 (s, 3H, Ar$\underline{Me}$), 2.98-3.20 (m, 1H, $\underline{CH}CH_3$), 3.80 (s, 3H, O$\underline{Me}$), 5.11 (bt, 1H, C=$\underline{CH}CH_2$), 6.67 (s, 1H, aromatic ring), 6.73 (d, 1H, J=7.5Hz, aromatic ring), 7.04 (d, 1H, J=7.5H, aromatic ring); EI-MS *m/z* 232 (M^+), 217 (M^+-Me), 175, 162, 149, 135, 119, 105, 91, 41; FT-IR (nujol): (cm^{-1}) 811, 1045, 1260, 1462, 1505, 1580, 1612, 2858.

15) Olah, G. A.; Narang, S. C.; Balaram Gupta, B. G.; Malhotra, R. *J. Org. Chem.*, **1979**, *44*, 1247.

16) To a stirred solution of the ether **12** (10 mmoles) and NaI (12 mmoles) in dry CH_3CN (40 ml) under nitrogen was added $ClSiMe_3$ (12 mmoles). The mixture was heated at reflux for 2 h, then quenched with water and extracted with diethyl ether. The organic layer was washed with a solution of $Na_2S_2O_3$ (1%), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on a silica gel column eluting with hexane-ethyl acetate (95:5 – 9:1) to give curcuphenol **1** in 81%

yield and showing the same analytical data reported in the Lit.[4] and $[\alpha]_D^{20}$ = +23.1° (c 4.5, $CHCl_3$). Lit.[3b] $[\alpha]_D^{20}$ = +24.6°

17) (*S*)-(+)-curcumene was obtained using the method described by Fenical[4] and shows $[\alpha]_D^{20}$ = +43.5° (c 1, $CHCl_3$). Natural curcumene shows $[\alpha]_D^{20}$ = +45.1° (c 0.75, $CHCl_3$) as reported by Damodaran, P. N. and Dev, S. *Tetrahedron*, **1968**, *24*, 4113.

18) Fraga, B. M. *Natural Product Report*, **1993**, 399.