

AN ENANTIOCONTROLLED FORMAL TOTAL SYNTHESIS OF (+)-IPOMEAMARONE, (-)-NGAIONE, AND THEIR EPIMERS

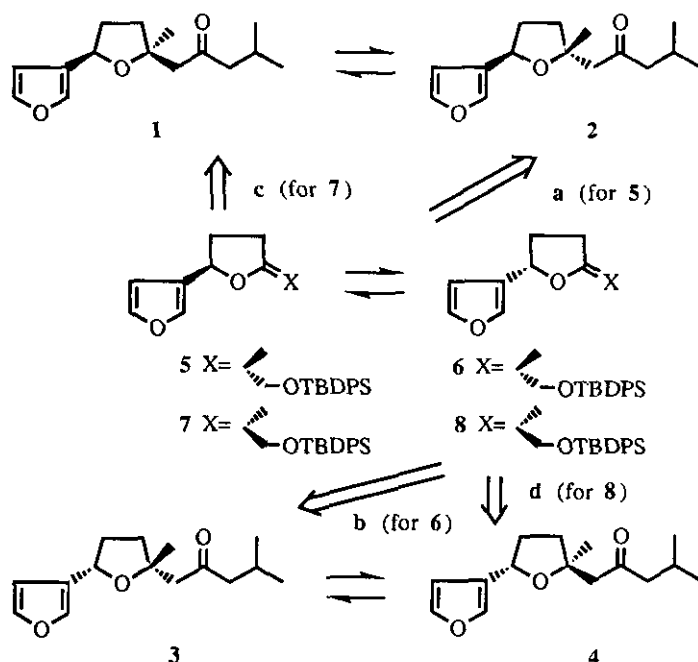
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Abstract--A concise enantiocontrolled synthesis of (+)-(5*S*, 2*R*)- and (+)-(5*R*, 2*R*)-5-(3-furyl)-2-iodomethyl-2-methyloxolanes, (6) and (5), was achieved starting from (+)-(R)-2-hydroxymethyl-2-methylcyclobutanone(11) which was efficiently prepared by the tandem asymmetric epoxidation and 1,2-rearrangement of 2-cyclopropylidenepropanol (9). This constitutes an enantiocontrolled formal total synthesis of (+)-ipomeamarone (1), (+)-epiipomeamarone (2), (-)-ngaione (3) and its epimer (4).

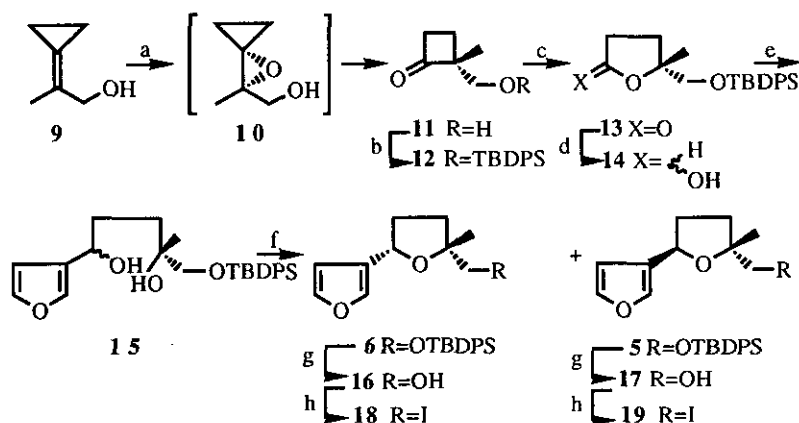
(+)-Ipomeamarone (1) is a well-known furanosesquiterpene as one of the first phytoalexins existing in mold-damaged sweet potatoes,¹ and 1, (+)-epiipomeamarone (2) and (-)-ngaione (3) were also isolated from *Myoporum deserti*.² Because of these interesting basic skeleton, 2,5-disubstituted tetrahydrofuran unit found in many naturally occurring antibiotics of monensin type³ and also interesting biological activity for the toxicological study,⁴ there have been growing interests in the synthesis⁵ of these compounds. In the course of our studies⁶ aimed at enantioselective synthesis of chiral cyclobutanes and its application to the synthesis of

biologically desirable compounds, we have disclosed a new enantiocontrolled formal total synthesis of (+)-ipomeamarone (1), (+)-epiipomeamarone (2), (-)-ngaione (3), and its epimer (4). The crucial point in our synthesis is that either enantiomer (1),(2),(3) or (4) can be obtained from either enantiomer (5),(6),(7) or (8) by taking advantage of the known^{2d} equilibration between 1 and 2 (hence 3 and 4) and our findings of the equilibration between 5 and 6 (hence 7 and 8) through the routes a, b, c, and d respectively. Herein we describe the results.⁷



The tandem asymmetric epoxidation of 2-cyclopropylidenepropanol (9)^{6d} and enantiospecific 1,2-rearrangement of the bicyclic oxacyclopentane (10) were effected with *tert*-butyl hydroperoxide (*tert*-BuOOH) in the presence of titanium tetrakisopropoxide [Ti(OⁱPr)₄] and 3 Å molecular sieves (3 ÅMS) using diisopropyl L-(+)-tartrate [(+)-DIPT] as the chiral auxiliary to afford the cyclobutanone alcohol (11) which on silylation [*tert*-butyldiphenylsilyl chloride (TBDPSCl), imidazole, dimethylaminopyridine (DMAP), DMF] gave the cyclobutanone silyl ether (12) in 51 % overall yield. Baeyer-Villiger oxidation (*tert*-BuOOH, 10 % NaOH, THF) of 12 followed by reduction [diisobutylaluminum hydride (DIBAL), Et₂O] of the resulting lactone (13) afforded the lactol (14) in 91 % overall yield which was then reacted with 3-lithiofuran⁸ generated by lithiation of 3-bromofuran [3-bromofuran, *n*-butyllithium (*n*-BuLi), Et₂O] to give the diol (15) as a

diastereoisomeric mixture (1:1 ratio) in 95 % yield. The cyclization of the diol (**15**) was achieved effectively either acidic [pyridinium *p*-toluenesulfonate (PPTS), CH_2Cl_2] or basic [*p*-toluenesulfonyl chloride (*p*-TsCl), pyridine] conditions to give the tetrahydrofurans (**6**)⁹ and (**5**)⁹ in a ratio of 11: 9 in 100 % yield (under the former conditions) and in a ratio of 1: 1 in 89 % yield (under the latter conditions) as an easily separable mixture. Then, the equilibration study was carried out by using pure **6** and **5** in the presence of a catalytic amount of *p*-toluenesulfonic acid and it was found that either pure **6** or **5** afforded a 1: 1 mixture of the two compounds. So, it would be possible to accumulate the either isomer through repeating equilibration and separation.¹⁰ Desilylation [tetra-*n*-butylammonium fluoride (TBAF), THF] of **6** and **5** afforded the alcohols (**16**)[$[\alpha]_{\text{D}}^{25} -5.9^\circ$ (c 3.8, CHCl_3); 81 % ee]¹¹ and (**17**)[$[\alpha]_{\text{D}}^{25} +15.8^\circ$ (c 3.5, CHCl_3); 82 % ee]¹¹ in 100 % and 100 % yields, respectively. Finally the alcohols (**16**) and (**17**) were converted (I_2 , imidazole, Ph_3P , THF) into the iodides (**18**)[$[\alpha]_{\text{D}}^{25} +6.7^\circ$ (c 0.9, CHCl_3)] and (**19**)[$[\alpha]_{\text{D}}^{25} +37.3^\circ$ (c 0.6, CHCl_3)] in 78 % and 74 % yields, respectively. Since racemic **18** and **19** have been converted^{5d} into racemic **1** and **2** respectively, this work constitutes the formal total synthesis of **1**, **2**, **3**, and **4**.



Steps: (a) *tert*-BuOOH, (+)-DIPT, $\text{Ti}(\text{O}^i\text{Pr})_4$, 3 ÅMS, CH_2Cl_2 , -50°C , 48 h; (b) TBDPSCl, imidazole, DMAP, DMF, room temperature, 12 h; (c) *tert*-BuOOH, 10 % NaOH, THF, room temperature, 7 h; (d) DIBAL, Et_2O , -78°C , 1 h; (e) 3-bromofuran, *n*-BuLi, Et_2O , -78°C ; then **14**, -78°C , 1 h $\rightarrow 0^\circ\text{C}$, 12 h; (f) PPTS, CH_2Cl_2 , reflux, 8.5 h; or TsCl, pyridine, room temperature, 12 h; (g) TBAF, THF, 60°C , 2 h; (h) I_2 , imidazole, Ph_3P , THF, 50°C , 12 h.

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7. All new substances exhibited spectroscopic data [ir, $^1\text{Hnmr}$ (500 MHz), and mass] in accord with the assigned structure and provided acceptable high resolution mass spectral data.
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9. The relative stereochemistry of the substituents at C₂ and C₅ on the oxolane ring of **6** was confirmed by the definite NOE enhancement (500 MHz) (5.5 %) observed for C₅-hydrogen upon irradiation of C₂-methyl group, while such NOE enhancement between C₅-hydrogen and C₂-methyl group of **5** could not be observed.
10. It has been confirmed that no detectable amount of epimerization at the quaternary carbon centers of the compounds (**15**) and (**6**) or (**5**) occurred under these conditions by showing the same enantiomeric excess of **16** and **17** as those derived independently from the cyclization of **15** under basic conditions.
11. The enantiomeric excess (ee) was estimated by $^1\text{Hnmr}$ analysis (500 MHz) of α -methoxy- α -trifluoromethylphenylacetates prepared under the modified procedure of Mosher's original procedure.¹² [(S)-(-)- α -methoxy- α -trifluoromethylphenylacetic acid, dicyclohexylcarbodiimide, dimethylaminopyridine, CH₂Cl₂, room temperature, 12 h].
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