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

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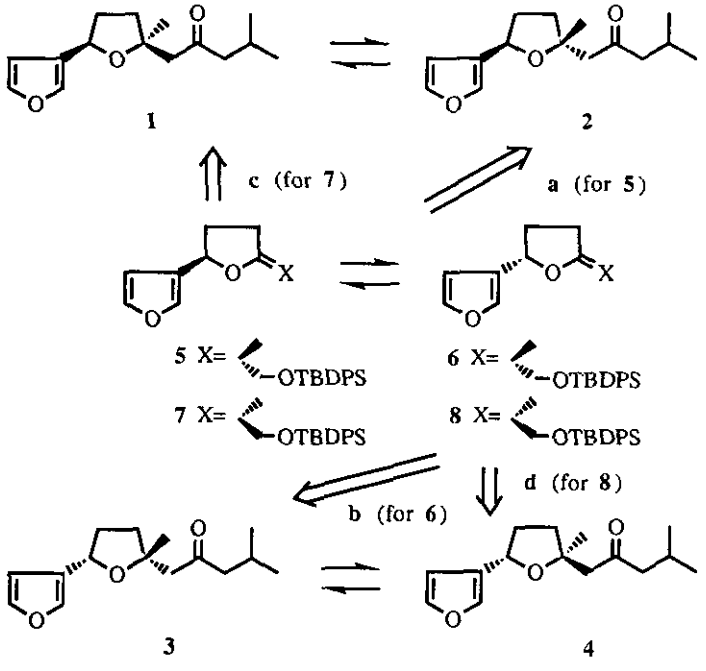
Abstract--A concise enantiocontrolled synthesis of (+)-(5S, 2R)- and (+)-(5R, 2R)-5-(3-furyl)-2-iodomethyl-2-methyloxolanes, (**6**) and (**5**), was achieved starting from (+)-(**R**)-2-hydroxymethyl-2-methylcyclobutanone(**11**) which was efficiently prepared by the tandem asymmetric epoxidation and 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**).

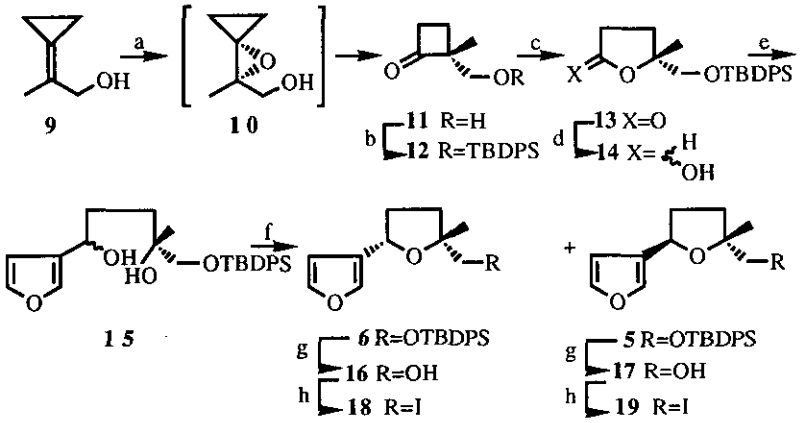
(+)-Ipomeamarone (**1**) is a well-known furanosesquiterpene as one of the first phytoalexins existing in mold-damaged sweet potatoes,[1] and **1**, (+)-epiipomeamarone (**2**) and (-)-ngaione (**3**) were also isolated from *Myoporum deserti*.[2] Because of these interesting basic skeleton, 2,5-disubstituted tetrahydrofuran unit found in many naturally occurring antibiotics of monensin type[3] and also interesting biological activity for the toxicological study,[4] there have been growing interests in the synthesis[5] of these compounds. In the course of our studies[6] 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 bicyclooxacyclopentane (**10**) were effected with *tert*-butyl hydroperoxide (*tert*-BuOOH) in the presence of titanium tetraisopropoxide [$Ti(O^iPr)_4$] and 3Å molecular sieves (3ÅMS) 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 [diisobutylaluminium hydride (DIBAL), Et_2O] of the resulting lactone (**13**) afforded the lactol (**14**) in 91 % overall yield which was then reacted with 3-lithiofuran[8] generated by lithiation of 3-bromofuran [3-bromofuran, n-butyllithium (n-BuLi), Et_2O] 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**)$[[\alpha]_D^{25}$-5.9° (c 3.8, $CHCl_3$); 81 % ee][11] and (**17**)$[[\alpha]_D^{25}$+15.8° (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**)$[[\alpha]_D^{25}$+6.7° (c 0.9, $CHCl_3$)] and (**19**)$[[\alpha]_D^{25}$+37.3° (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, $Ti(O^iPr)_4$, 3ÅMS, 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 → 0 °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}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 C_2 and C_5 on the oxolane ring of **6** was confirmed by the definite NOE enhancement (500 MHz) (5.5 %) observed for C_5-hydrogen upon irradiation of C_2-methyl group, while such NOE enhancement between C_5-hydrogen and C_2-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}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, CH_2Cl_2, room temperature, 12 h].
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Received, 25th December, 1992