Tetrahedron Letters, Vol. 34, No. 3, pp. 509-512, 1993
Printed in Great Britain

0040-4039/93 $5.00 + .00
Pergamon Press Ltd

Total Syntheses of (+)-Ipomeamarone and (-)-Ngaione

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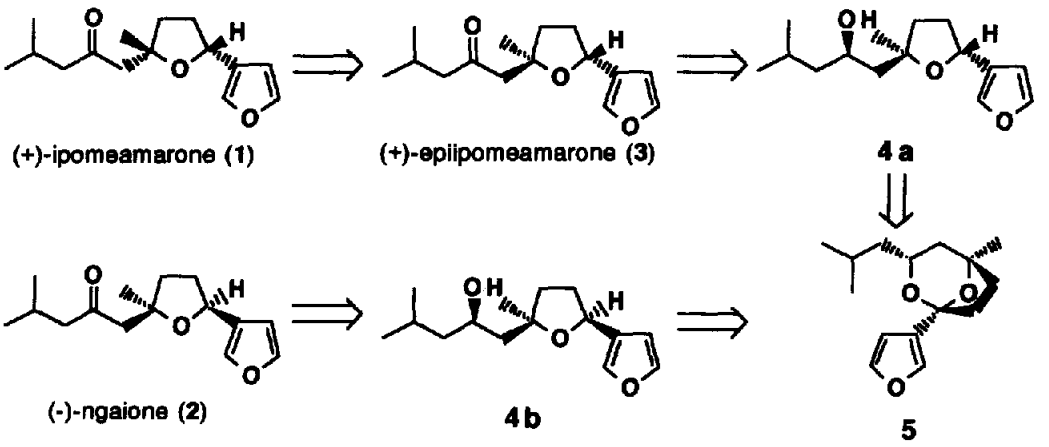
Abstract: Total syntheses of (+)-ipomeamarone and (-)-ngaione were achieved by using newly found stereoselective hydride transfer/ olefin addition process, and *syn* and *anti* hydride additions to optically active bicyclic acetal.

Toxicology and biosynthesis of (+)-ipomeamarone (**1**) and (-)-ngaione (**2**) have been extensively studied,[1,2] since these substances were essence of fatal toxins for domestic animals.[3,4] Although it has been known that two toxins were enantiomers each other, their absolute configurations have only recently been established by two independent groups as 1*R*,4*S* for **1** and 1*S*,4*R* for **2**.[5] In this communication, we wish to report the first total syntheses of optically active both toxins.[6]

The first key point in the present syntheses is that either enantiomer can be obtained from the same optically active intermediate (**5**), dihydro derivative of (+)-eremoacetal,[7] by *anti* hydride addition to ketal or by *syn* hydride addition followed by epimerization (Scheme 1).

Scheme 1.



The second key point is an application of the recently published novel method to construct chiral secondary and tertiary diol in an optically pure state from optically active 1,3-diol. (Scheme 2) In this process, R^1 and R^2 should be differentiated.

Scheme 2.

The route to obtain **5** is as follows(Scheme 3). Optically pure (2*R*,4*R*)-**6** was obtained by enantioface differentiating hydrogenation of 6-methyl-2,4-heptanedione over (*R*,*R*)-tartaric acid-NaBr-modified ultrasonicated Raney nickel[8] (100 °C, 100 atm, 43 hours) and four recrystallizations in 30% yield ($[\alpha]_D$=-25.5, c 1.0 methanol).[9] Acetalization of **6** with cyclohexanone and isomerization with triisobutylaluminum afforded **8a** and its regioisomer (**8b**) (**8a/8b**=81/19). This mixture was used in the next step without separation. Cyclopropanation to this with diethylzinc (5 eq.) and diiodomethane (10 eq.) in THF gave a mixture of **9a** and its regioisomer (**9b**), which were separated by MPLC on silica gel (49.8 and 13.7%, respectively). The diastereomeric excess of each regioisomer was 94 % d.e. and 87 % d.e., respectively.[11] The treatment of **9a** with mercuric acetate in acetic acid afforded a mixture of two products (**10a/10b**=2/1) in a quantitative yield.[11]

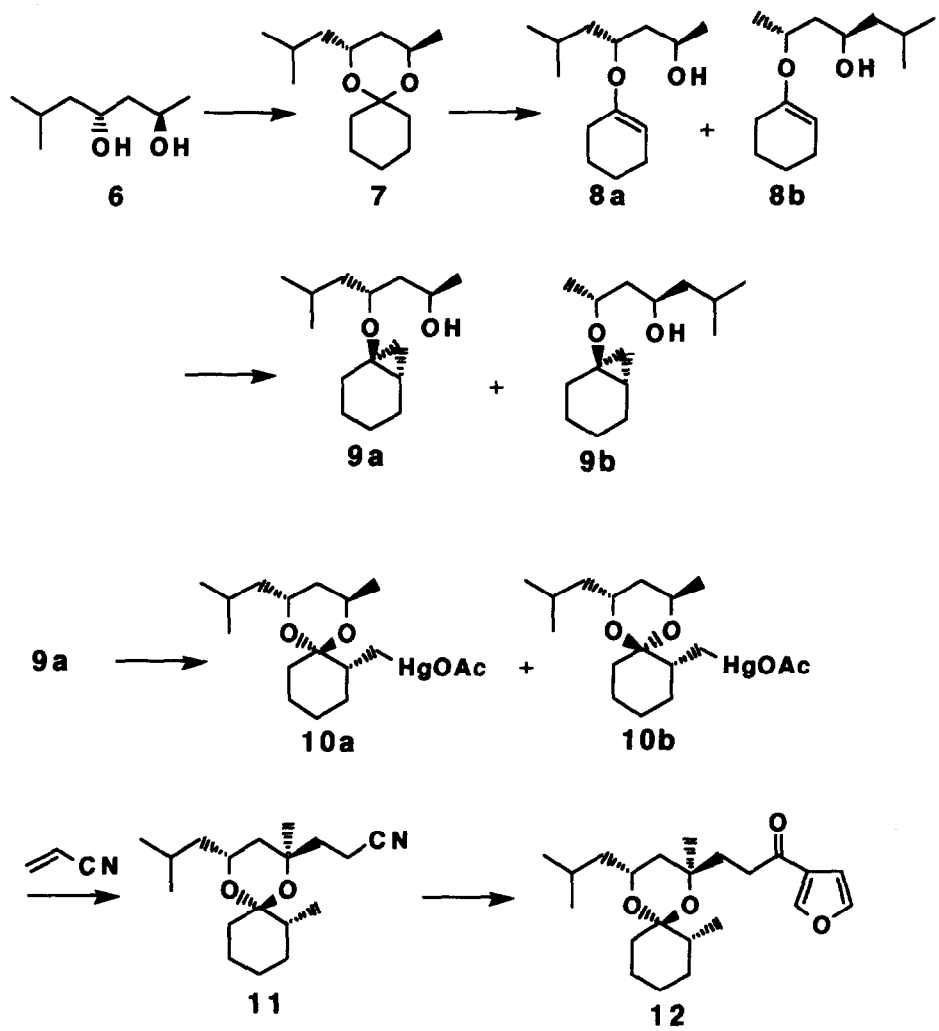
Reductive addition of acrylonitrile to this mixture (sodium borohydride and 3 eq. of acrylonitrile in dichloromethane-water) and following MPLC separation of the product gave diastereomerically pure **11** in 36.5% yield. Addition of 3-lithiofuran[12] to **11** at -40 °C gave **12** (51.8% yield) and treatment this with *p*-toluenesulfonic acid in methanol-benzene (1: 2) resulted in deacetalization and acetalization in one step to give bicyclic acetal (**5**) (73% yield).

Syn hydride addition to **5** with DIBAH at 0 °C in dichloromethane produced over 99% diastereomerically pure **4a** in a quantitative yield.[13] Oxidation of **4a** afforded (+)-epiipomeamarone (**3**), which was converted into a 1:1 mixture of (+)-ipomeamarone (**1**) and **3** with sodium methoxide without accompanying any decomposition.[14] Optically pure (+)-toxin (**1**) was completely separated from **3** by HPLC (preparative ODS column eluted with 35% water in methanol). Spectrum and optical rotation of the synthetic toxin were fully identical with those of reported natural ipomeamarone.[15]

On the other hand, *anti* hydride adduct (**4b**) could not be obtained preferentially. The reduction of **5** with triethylsilane and titaniumtetrachloride was not proceeded below -30 °C. When the reaction carried out at room temperature, over reduced compound was obtained as a sole product.

The best result so far obtained was a 1 to 1 mixture of **4a** and **4b** by the reaction of **5** with borane-dimethylsulfide and trimethylsilyltriflate in THF. The use of the other solvent such as diethyl ether or dichloromethane generally decreased the ratio of *anti* product. Oxidation of the mixture of **4b** and **4a** gave (-)-ngaione (**2**) and (+)-**3** in the same ratio (65% for two steps). Isolated (-)-toxin by HPLC had same spectrum with reported ones and those of (+)-toxin except levorotatory optical rotation.

Scheme 3.



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(9) The absolute configuration of (-)-**6** was assigned to be (2*R*,4*R*) by chemical correlation with (+)-(*S*)-methyl 3-hydroxybutanoate.

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(11) Diastereomer ratio of **10a** and **10b** was affected by the use of the solvent. When a nonpoler solvent such as dichloromethane was employed, the ratio was inverted to **10a/10b**=1/4. The mixture could not separate into each component in a preparative scale. The major product (**10a**) was found to have desired stereochemistry by NMR analysis.

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(15) We thank to Dr. Kazuo Yoshihara of SUNBOR, Osaka, Japan for supplying spectra of natural ipomeamarone.

(Received in Japan 29 September 1992)