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SYNTHESIS OF (*S*)-PLAKOLIDE A AND REVISION OF THE ABSOLUTE STEREOCHEMISTRY OF THE NATURAL (-)-PLAKOLIDE A

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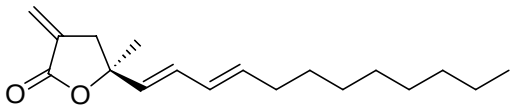
Abstract- (*S*)-Plakolide A, a γ–lactone from the marine sponge *Plakortis* sp., was synthesized starting from (*S*)-lactic acid by applying the chiral self-reproduction procedure. As the results of the synthetic research, the absolute stereochemistry of the natural product should be revised to *R*.

(*S*)-Plakolide A is a recently isolated γ–lactone from a shallow-water marine sponge of the genus *Plakortos* collected from La Palma, Canary Islands and shows significant inhibitory activity in a cell-based assay designed to detect inhibitors of inducible nitric oxide synthase (iNOS).[1] (*S*)-Plakolide A possesses an α–exomethylene and γ–disubstituted γ–lactone moieties (Figure 1).

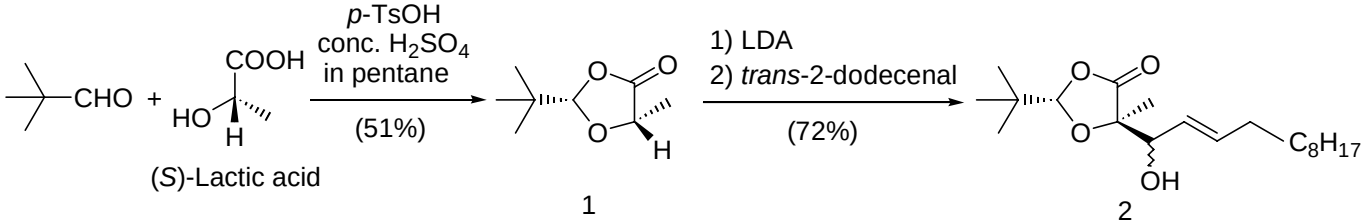
In the course of our synthetic studies on biologically active natural products, which possess chiral quaternary carbon center accompanying with one oxygen function, we have synthesized (+)-ipomeamarone,[2] (-)-vertinolide[3] and (*S*)-gregatin B[4] by adapting the chiral self-reproduction method developed originally by Seebach *et al*.[5] In continuation of that line, we planned to synthesize (*S*)-plakolide A.



(*S*)-Plakolide A

Figure 1

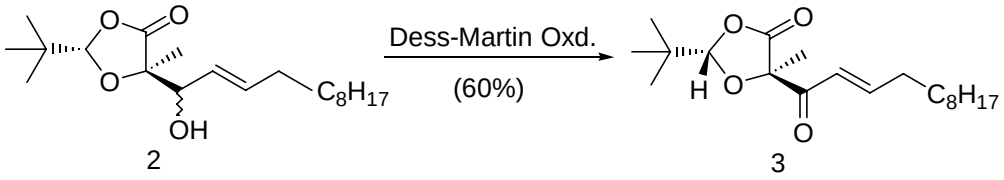
For the synthesis of (*S*)-plakolide A, (2*S*,5*S*)-2-(1,1-dimethylethyl)-5-methyl-1,3-dioxolan-4-one (**1**)[2, 5] was selected as the starting material, which was readily derived from (*S*)-lactic acid and 2,2-dimethyl-



Scheme 1

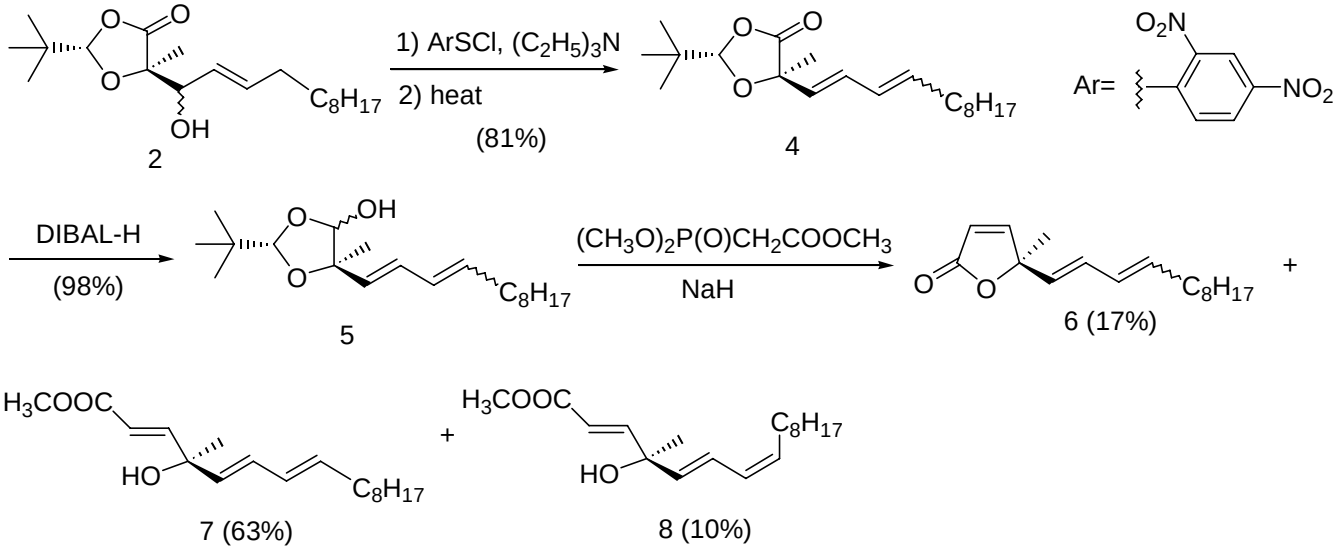
propanal. The addition of *trans*-2-dodecenal to the enolate derived from **1** occurred stereoselectively from β-side to give the alcohol (**2**) as a 1:1 mixture of diastereoisomers concerning with the orientation of the hydroxyl group (Scheme 1).[4]

In order to confirm the stereochemistry of the newly formed chiral center at C5 of **2**, it was converted to the enone (**3**) by oxidation with Dess-Martin periodinane.[6] In the ^{1}H-NMR spectrum of **3**, no NOE was observed between C2 methine proton and C5 methyl group (Scheme 2). This result indicates that the stereochemistry at C5 is *R*.



Scheme 2

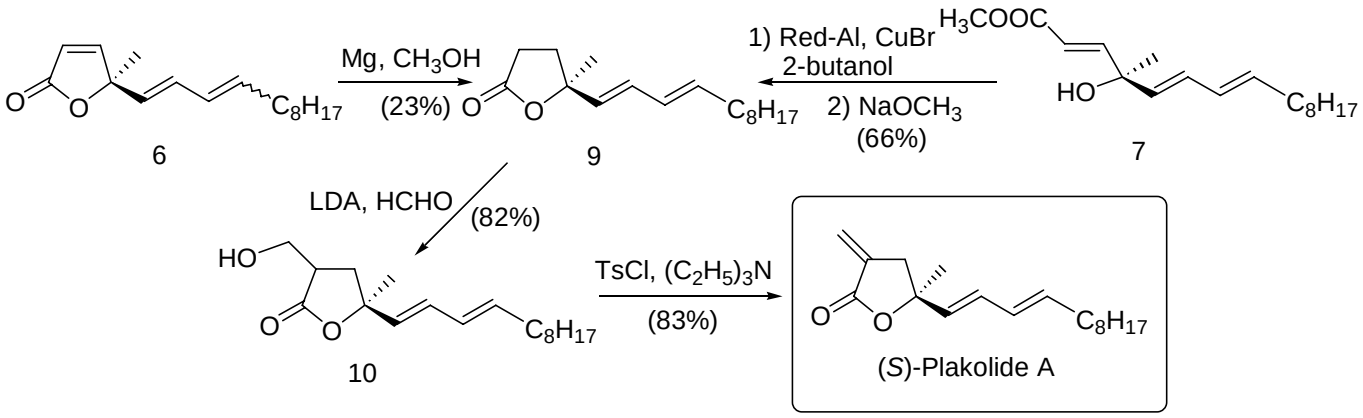
Transformation of the allyl alcohol (**2**) to 1,3-diene (**4**) was examined. [2,3] Sigmatropic rearrangement of the sulfenate of **2** to the sulfoxide and its thermal syn elimination[4, 7] were performed. Thus, the treatment of **2** with 2,4-dinitrophenylsulfenyl chloride in the presence of triethylamine gave the sulfenate, which rearranged to form the sulfoxide, and the successive thermal *syn* elimination of the sulfoxide occurred to afford an inseparable mixture of *E*,*E*-diene-**4** and *E*,*Z*-diene-**4** (86:14)[8] in 81% yield (Scheme 3). Successive DIBAL-H reduction[2] of **4** gave **5** in 98% yield which was treated with trimethyl phosphonoacetate in the presence of NaH (2.2 equiv.)[2, 9] at room temperature to afford **6**, **7**[10] and **8**[11] in 17, 63 and 10% yields, respectively, after purification of the products by silica gel column chromatography (C_6H_6:$CH_3CO_2C_2H_5$=49:1)(Scheme 3).



Scheme 3

For selective reduction of **6** and **7**, **6** was treated with Mg in methanol[12] to form only the *E*,*E*-diene (**9)** in 23% yield and **7** reacted with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®) in the presence

of CuBr and 2-butanol[13] to give **9**[14] in 66% yield. Successively, **9** was converted to hydroxymethyllactone (**10**)[15] by action of LDA (2.0 equiv.) and formaldehyde (-78 to -25 °C) in 82% yield. Finally, treatment of **10** with TsCl (1.2 equiv.) and triethylamine (2.5 equiv.) at 0 °C to room temperature furnished directly (*S*)-plakolide A in 83% yield (Scheme 4). IR, ^{1}H-NMR and MS spectral data are superimposable to those of the natural plakolide A.



Scheme 4

But, the specific rotation of the synthesized compound showed $[\alpha]_D^{25}$ +45° (*c* 0.12, CH_3OH). On the other hand, the reported value for the natural plakolide A is $[\alpha]_D^{24}$ -41° (*c* 0.1, CH_3OH). Furthermore, the CD spectrum (in CH_3OH) of the synthesized (*S*)-plakolide A showed a positive Cotton effect at 228 nm and a negative Cotton effect at 207 nm. This curve is just opposite to that of the natural (-)-plakolide A. Therefore, the absolute stereochemistry of the natural (-)-plakolide A should be revised to *R*-form as shown in Figure 2.

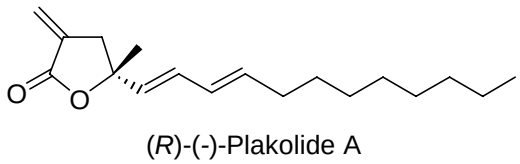


Figure 2

Synthesis of the natural (*R*)-(-)-plakolide A will be accomplished by the same manner as above, if the known enantiomeric **1**[3, 4, 5] is selected as the starting material.

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10. ^{1}H-NMR of **7**: δ: 5.66 (1H, d, *J*=15.3 Hz), 5.73 (1H, dt, *J*=15.0, 6.9 Hz), 6.00 (1H, dd, *J*=15.0, 10.3 Hz), 6.6.20 (1H, dd, *J*=15.3, 10.3 Hz).
11. ^{1}H-NMR of **8**: δ: 5.49 (1H, dt, *J*=10.7, 7.6 Hz), 5.71 (1H, d, *J*=15.3 Hz), 5.96 (1H, dt, *J*=11.0, 10.7 Hz), 6.53 (1H, ddd, *J*=15.3, 11.0, 1.0 Hz).
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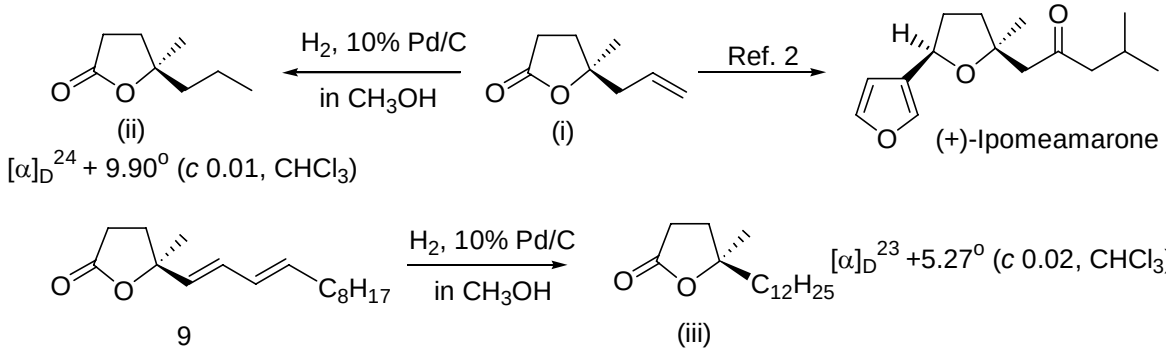
14. Previously, we have synthesized (+)-ipomeamarone using the lactone (i) as shown below. Catalytic hydrogenation of (i) gave (*R*)-lactone (ii), whose specific rotation was $[\alpha]_D^{24}$ +9.90°. The same reaction of **9** afforded (*R*)-lactone (iii), whose specific rotation was $[\alpha]_D^{23}$ +5.27°. Therefore, the absolute stereochemistry of **9** was confirmed again as *S*.



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