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STUDY OF SYNTHETIC ROUTES FOR THE SPIROKETAL FRAGMENT IN CALYCULIN A BASED ON CONFORMATIONAL ANALYSIS

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Abstract – The conformational analysis of the spiroketal fragment of calyculin A revealed that a series of the Wittig reaction by way of the Swern oxidation was suitable for the addition of the C_1-unit for the preparation of the spiroketal fragment. It also clarified that failure in the reaction of cyanide and the tetraol equivalents was attributed to the steric and electrostatic effects of the symmetrical structures.

INTRODUCTION

Calyculin A (**1**)[1,2] is one of structurally intriguing marine products as shown in Figure 1, which has the carcinogenic promoter action as the new class that specifically inhibits serine/threonine phosphatase 1 and 2A.[3-7] The total synthesis of **1** has been achieved by several research groups[8-16] including ours.[10] In order to prepare the spiroketal fragment (**2**) as the C_{20}-C_{25} part in **1** efficiently, Shioiri et al. tried to synthesize **3** by the addition of a C_1 building block to equivalents of a symmetrical tetraol (**4**) by way of a γ-lactone.[17] Their synthetic strategy was that the use of the symmetrical tetraol equivalents enabled to construct some enantiomers of the C_{20}-C_{25} part easily. As shown in Scheme 1, the addition of the CN ion as the C_1 building block using the S_N2 reaction did not succeed, and even the high reactive epoxide derivative **19** could not react with the CN ion. However, they finally got the desired compound **22** using the Wittig reaction via the Swern oxidation to add the C_1 building block in Scheme 2.[17] Their active synthetic

strategy using the symmetry of the reaction precursor has the potential synthetic diversity that can apply to other natural compounds. Therefore we investigated synthetic potential for the addition of the C_1 building block to the equivalents of the symmetrical alcohols.

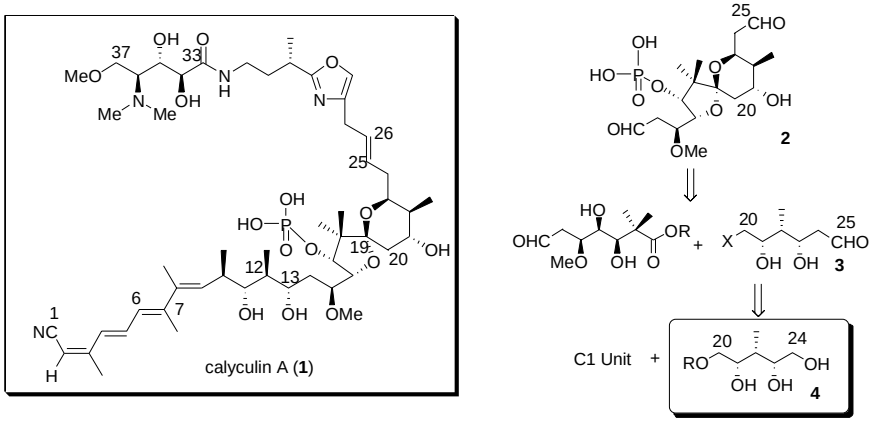
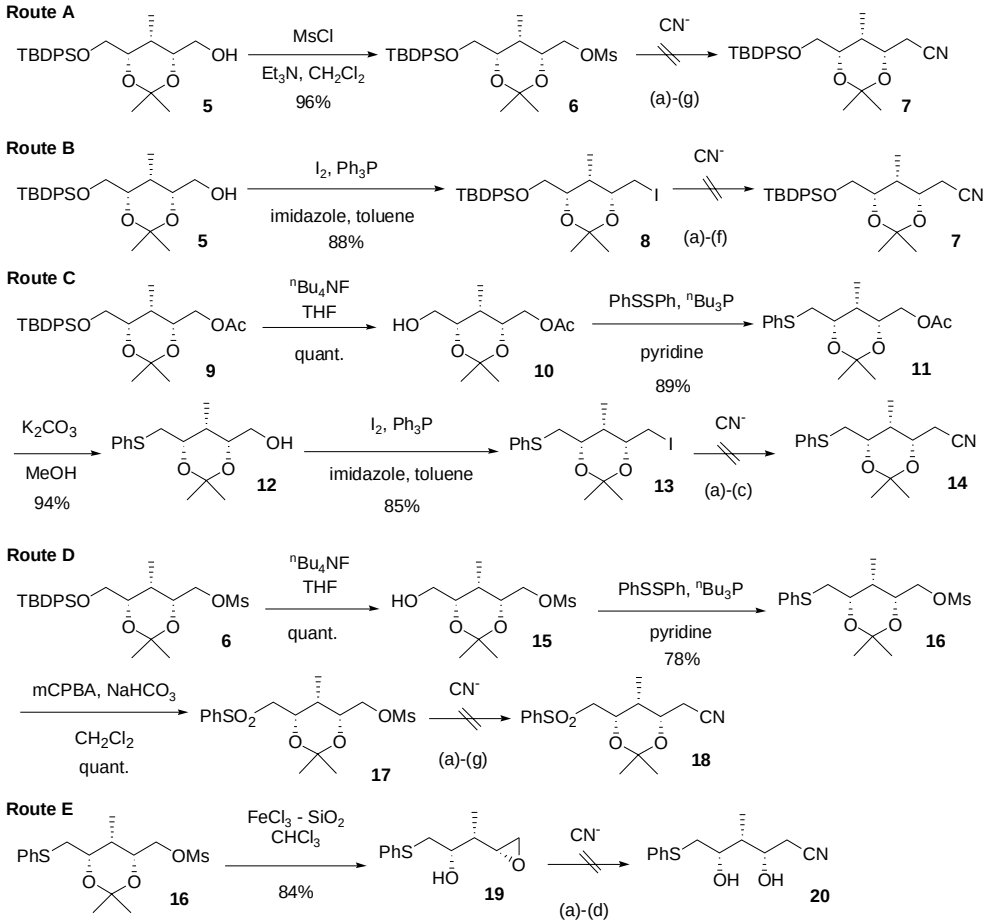
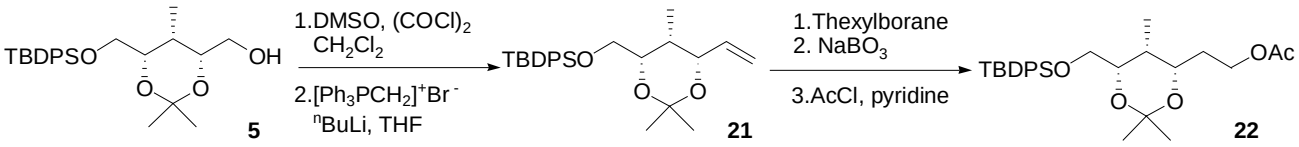


Figure 1. The structures of calyculin A(**1**), the spiroketal fragment **2** and its C_{20}-C_{25} building units **3** and **4**



Scheme 1. The reaction conditions in order to introduce the cyano group as a C_1 building block[17]: (a) KCN, DMF, rt, 48h, (b) KCN, DMSO, rt, 24h, (c) KCN, DMF, 100ºC, 13.5h, (d) KCN, DMSO, 100ºC, 2h, (e) KCN, 18-crown-6, toluene, 110ºC, 14h, (f) Bu_4NCN, toluene, 90ºC, 12h, (g) Bu_4NCN, DMF, 90ºC, 1.5h.



Scheme 2. The actual synthetic route to add the C_1 building block to **6** via **22**.[17]

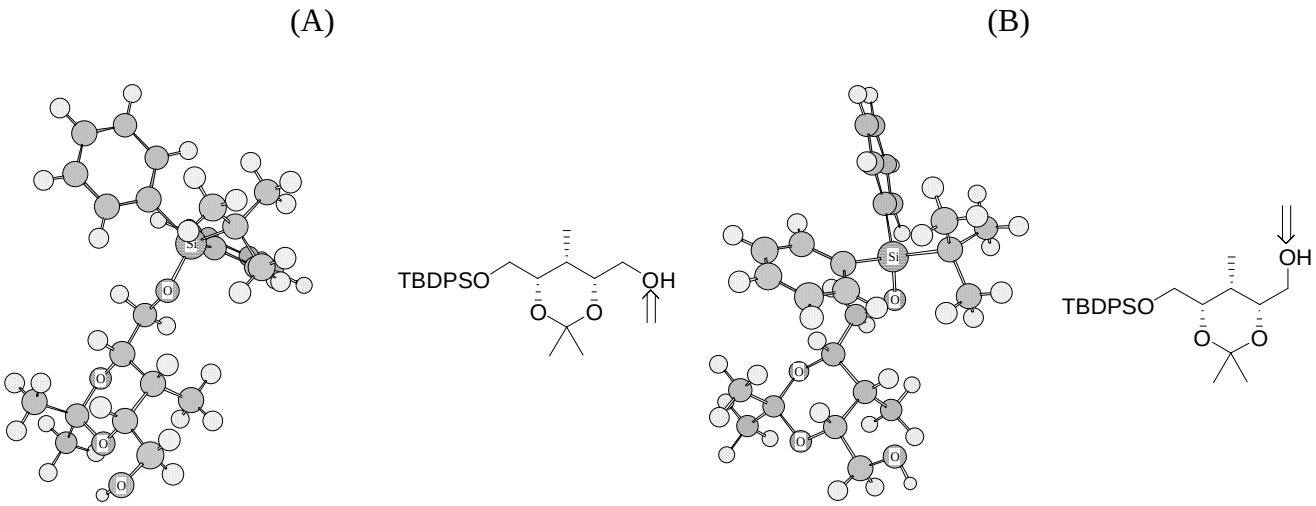


Figure 2. The structures of the global minimum (A) and the 29th minimum (B) of **5**

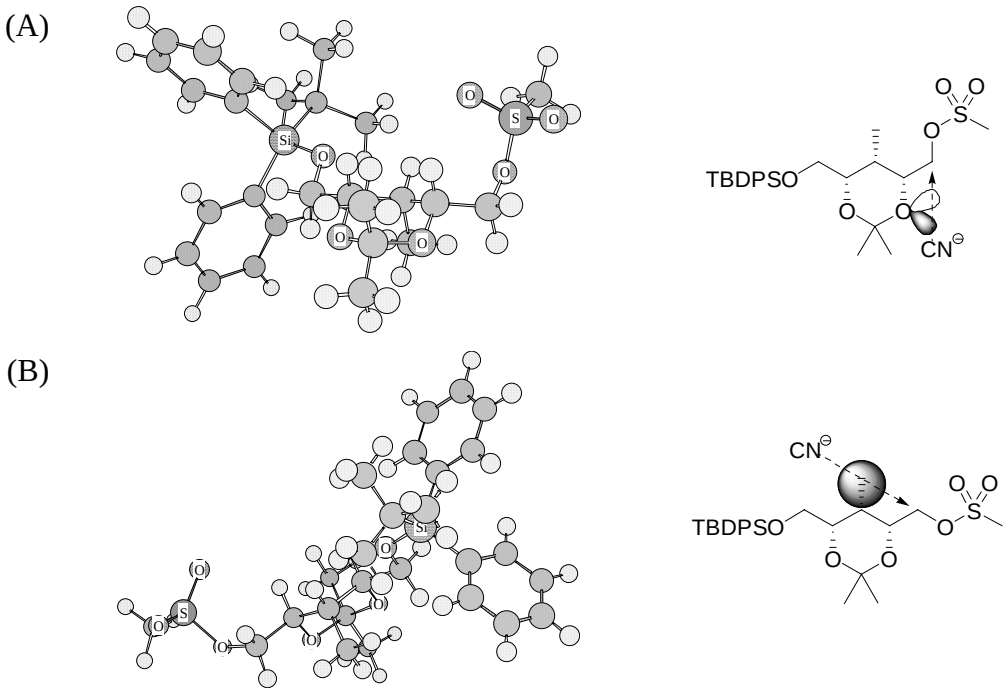


Figure 3. The structures of the global minimum (A) and the 4th minimum (B) of **6**

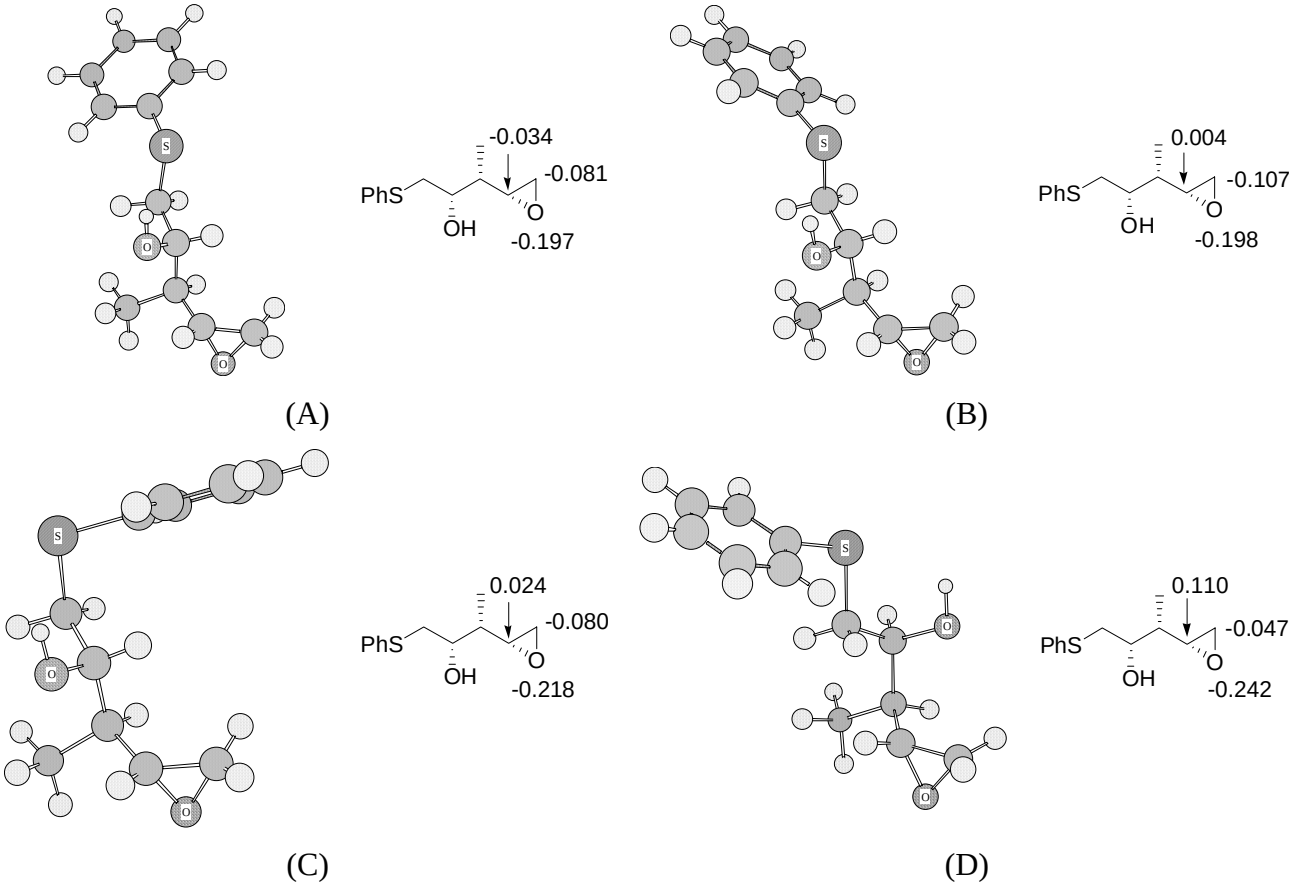


Figure 4. The structures of the global minimum (A), the 2nd minimum (B), the 3rd minimum (C) and the 4th minimum (D) of **19**

RESULTS AND DISCUSSION

First we investigated conformational properties of the precursor **5**, which is common in the introduction of the cyano group as a C_1 building block in Scheme 1 and in the actual synthetic route in Scheme 2. From the result of conformational analysis, 13 conformational isomers within 2 kcal/mol occupied 89.5% of all and took the chair form as a stable isomer. In Figure 2, the hydroxyl group in **5** was free from steric hindrance of methyl group and electrostatic repulsion from oxygen atoms in the acetonide. In fact, the protecting and the leaving groups could be added to the precursor **5** before the introduction of the cyano group, as shown in Scheme 1. Moreover the precursor was oxidized at the hydroxymethyl group, as shown in Scheme 2. Consequently this calculated result accorded with the experimental results.

The conformational analyses of reaction precursors in Scheme 1 were also performed. As for **6**, 45 conformers within 2 kcal/mol occupied 90.5% of all and took the chair form as a stable isomer. In Figure 3, the electrostatic repulsion from the oxygen atom in the acetonide and the steric hindrance from the methyl group existed, so that the CN ion could not approach the reaction site.[18] This is the reason why **6** did not substitute the CN ion for the methanesulfonyl group as a leaving group by the S_N2 reaction.[19] Furthermore the epoxide **19** could not react with the CN ion regardless of being the epoxide as a high

reactive group. From the calculated result of **19**, 13 conformers within 2 kcal/mol occupied 95.6% of all. As shown in Figure 4, there was nothing to disturb the approach of the CN ion to the reaction site. Thus the charge distribution of **19** was calculated. As compared with two carbon atoms in the epoxide group, the charge distribution was different definitely in Figure 4. The charge on the carbon with the substituent was more positive than the one on the carbon without the substituent. In brief, the charge on the target site without the substituent was δ- and then the CN ion could not approach the reaction site.

In summary, it was clear that the successful synthetic route was free from the steric hindrance and the electrostatic repulsion. On the other hand, the steric hindrance of the methyl group and the electric repulsion from the oxygen atom of the acetonide caused the failure of the addition of the CN ion as a C_1 unit. As for the more reactive epoxide, the charge on the reaction site was negative by contraries. In the event the synthetic strategy to prepare effective building blocks using the symmetry must be applied with caution.

EXPERIMENTAL

As for conformational analysis to cover all conformational spaces of target molecules, all conformational structures were searched and optimized by MMFF94[21-27] in CONFLEX5[28-33]. The conformational distribution was calculated from Gibbs free energy based on the vibrational calculations. In order to calculate electric charge and to take account of its application to bigger molecules without large calculation time cost, we decided the use of minimal basis function; RHF/STO-3G[34,35] in Gaussian 03 Rev. B.4.[36] The electric charge calculation was performed by Mertz-Singh-Kollman method.[37,38] All programs were performed in Windows 2000 on IMB PC mounted Pentium III. Supporting information will be directly available from the principal author, T.M.: matsu@tagen.tohoku.ac.jp.

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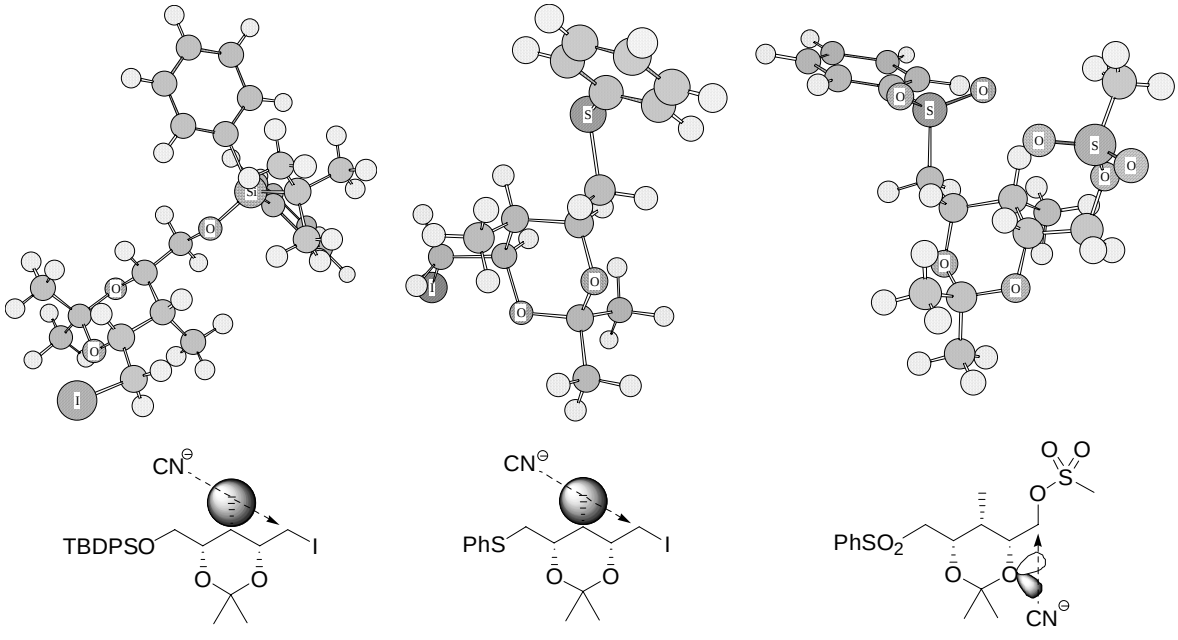
18. From the results of detailed conformational analyses for actual experimental reaction precursors (**8**, **13** and **17**), steric hindrance from the methyl group and influence from lone pairs of the oxygen atom in the acetonide unit affected the addition of the C_1-unit as same as the case of **6**. Consequently, it is impossible for the synthesis of the spiroketal fragment to use the symmetrical tetraol equivalent **4**.

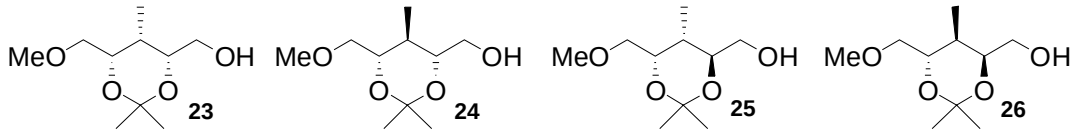


8 **13** **17**

The structures of the global minimum of **8**, **13** and **17**

19. The application of the symmetrical tetraol **4** must take potential effect of the stereo factor into consideration, because the symmetrical compound involves a steric problem. From the scrutinizing result of four model compounds (**23**, **24**, **25** and **26**), the models **23** and **26** include steric hindrance and electrostatic repulsion. Some conformers in **24** and **25** could ignore electrostatic repulsion except

steric hindrance, in which the ration of possible reactive conformers in **24** and **25** were 34.8% and 25.5%, respectively. So the addition of the C_1-unit seemed to be possible. In short, particular stereo systems have the potential possibilities to prepare enantiomers using the symmetry.[20]



The structures of four model compounds of **23**, **24**, **25** and **26**

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