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A Diels-Alder Reaction Approach to a Homoisocarbacyclin

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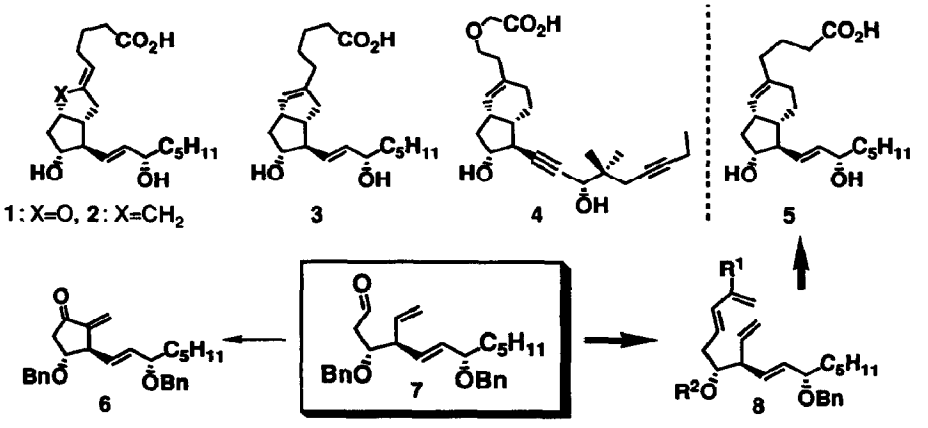
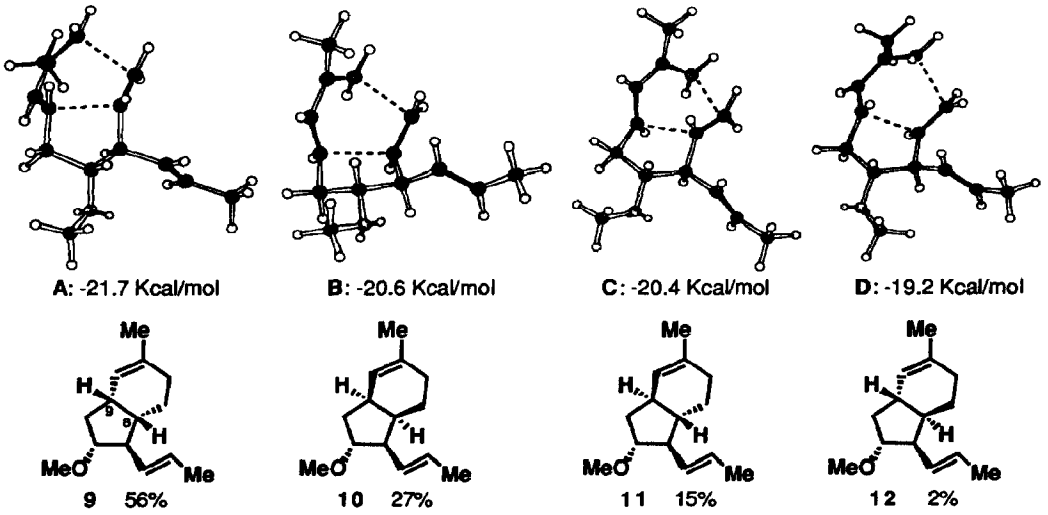
SUMMARY: Synthesis of a chiral homoisocarbacyclin by using intramolecular Diels-Alder reaction and its diastereoselectivity based on MM2 transition state model (flexible model) are described.

Prostacyclin (PGI_2) (**1**) is well known as a potent inhibitor of human platelet aggregation and a powerful vasodilator.[1] Despite its important biological profile, the potential therapeutic value of PGI_2 is limited by its chemical instability. Carbacyclin **2** and isocarbacyclin **3** are the most promising candidates because of their potent prostaglandin like activities and chemical stabilities. Moreover, in recent studies by Shibasaki on anti-aggregatory activity and hypotensive activity of homoisocarbacyclin analogues, especially the analogue **4** showed interesting properties in the selectivity of biological actions as compared to that of PGI_2.[2] These findings have stimulated significant efforts toward efficient syntheses of homoisocarbacyclin analogues having the *cis*-bicyclo[4.3.0]non-2-ene skeleton. Most syntheses of prostacyclin analogues have been accomplished by starting from the Corey lactone or primary prostaglandins (PGs).[3] Recently, we proposed the optically active aldehyde **7** as a new common synthetic intermediate for both primary PGs and prostacyclins, and succeeded in synthesis of the Stork's intermediate **6** by using [3+2] cycloaddition of the nitrile oxide derivative of **7**.[4] We report here synthesis of the chiral homoisocarbacyclin **5** by using intramolecular Diels-Alder reaction of triene **8** (Scheme 1).



(Scheme 1)

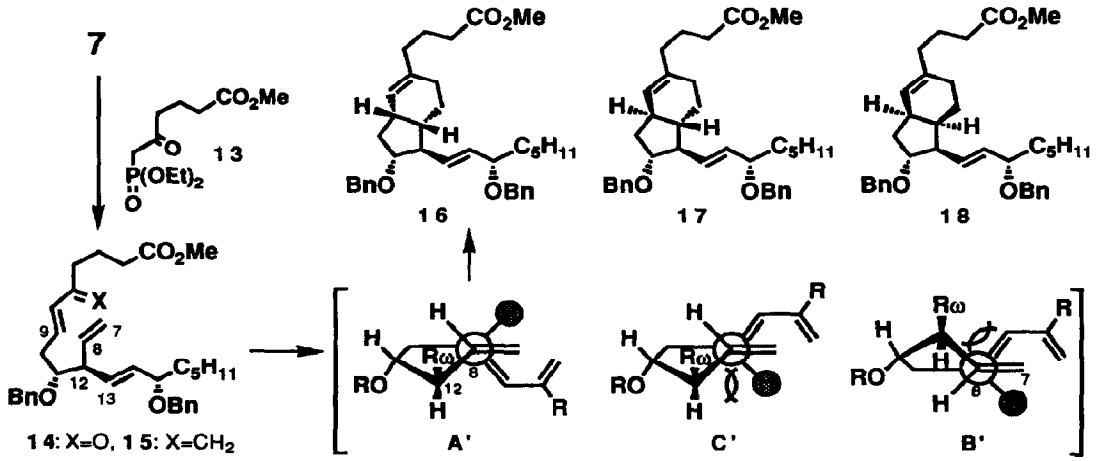
At first, we examined the stereoselectivity in the intramolecular Diels-Alder reaction of **8** by using MM2 transition-state model. "Transition-state modeling"[5] based on the MM2 and the *ab initio* calculations have proven useful in design for the synthetic key intermediate. Recently, we reported the MM2 transition state model (*rigid reactant model*)[6] to predict the stereoselectivity in the transannular Diels-Alder reaction of the 14-membered triene.[7] Now we applied the MM2 transition model (*flexible reactant model*)[8] to predict the diastereoselectivity in the intramolecular Diels-Alder reaction of triene **8** (R^1 and R^2 groups were replaced by methyls). Monte Carlo (MC) random-search method[9] was used to find the lower-energy "transition-state structures" of the Diels-Alder reaction of **8**. The structures generated by MC search were energy minimized by using extended MM2 parameters.[10] Thirty-three unique transition-state structures were found within 3.0 Kcal/mol of the global minimum. Figure 1 shows the lowest energy transition state structures **A**, **B**, **C** and **D** leading to **9**, **10**, **11** and **12** respectively. These calculations and a Boltzmann distribution based on the energy difference among the 33 transition state structures predict that the ratio of diastereomers **9**, **10**, **11** and **12** would be 56:27:15:2 and that the expected major product would be **9** having the desired $C_8(S)$ and $C_9(S)$ configurations.



(Fig. 1)

Aldehyde **7** was prepared from a readily available D-mannitol by our previous procedure.[4] Horner-Emmons reaction of aldehyde **7** at -70 °C with the anion of β-ketophosphonate **13**, generated with potassium *tert*-butoxide in THF at 25 °C, afforded *E*-enone **14** in 96% yield. Methylenation of **14** was carried out by using Nozaki-Lombardo's reagent (CH_2I_2, $TiCl_4$/Zn in THF)[11] to give diene **15** in 61% yield. Diels-Alder reaction of **15** (in bromobenzene at 150 °C) was completed within 5 h to give a mixture of bicyclo[4.3.0]non-2-enes **16**, **17** and **18** in 97% yield. HPLC analysis of the

reaction mixture indicated that the ratio of **16**, **17** and **18** was 56:27:17. The relative stereochemistry among C-8, -9 and -12 was determined on the basis of NMR and nOe studies.[12] The dominant formation of **16** compared with **17** and **18** can be explained as follows. The tether linking diene to dienophile occupies the less crowded endo position in the cis-fused transition structure **A'**, while the gauche interaction between C_9-H and C_8-C_{12} bond exists in the trans-fused transition structure **C'**.[13] Although the cis-fused transition structure **B'** possesses the tether in the less crowded endo position, the eclipsed interaction between the ω-chain and the C8-C7 double bond increases more distortions of the forming cyclopentane ring than that in both the cis-fused **A'** and the trans-fused **C'**. Hydrolysis of the ester moiety in **16** (NaOH/MeOH) followed by deprotection of the benzyl ether (Na/NH_3) afforded **5** in 95% overall yield.



(Scheme 2)

Thus an enantiospecific synthesis of the homoisocarbacyclin analogue **5** was accomplished from D-mannitol derivative by using intramolecular Diels-Alder reaction. While the predicting ratio of the minor products **17** and **18** was in disagreement with the experimental result, the major product in the experiment was in good agreement with the calculation results. Thus the described calculations might have predicting value in organic synthesis.

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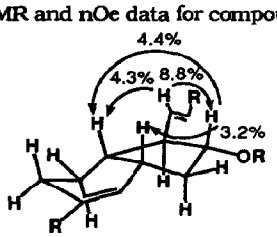

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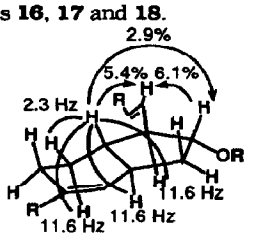

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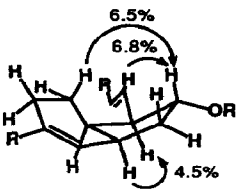

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