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Diastereoselective Conjugate Addition for Construction of Taxane Precursors

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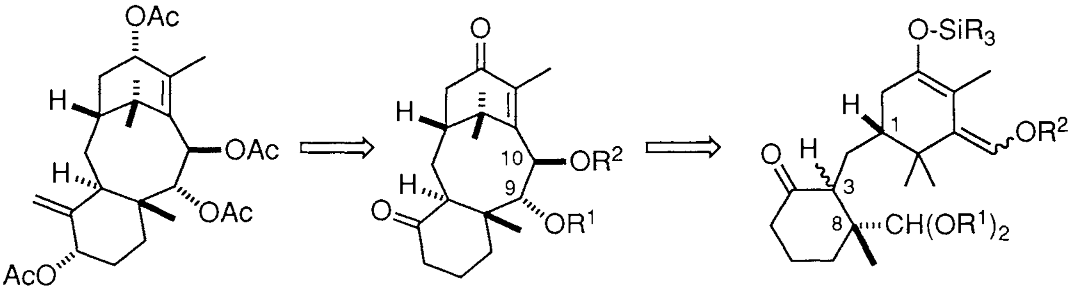
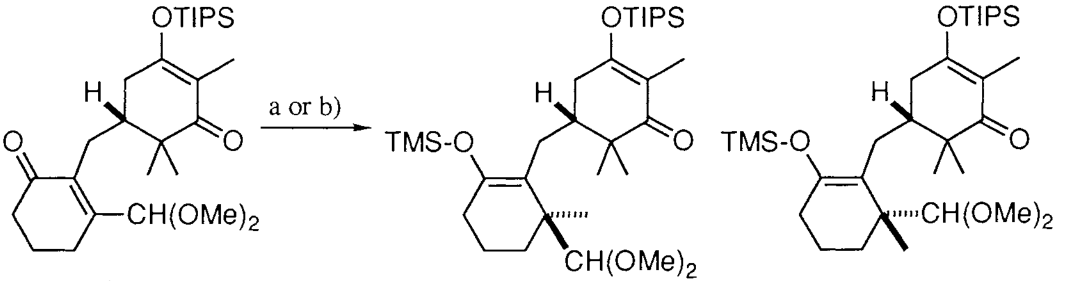
Copper catalyzed conjugate addition of Grignard reagents to enones was effected with high 1,4-diastereoinduction and was used for the preparation of taxane precursors.

Owing to the unique structural features as well as remarkable biological potential$^{1)}$ exhibited by taxol, a taxane family has attracted much attention in synthetic organic chemistry.$^{2)}$ In connection with synthetic study of taxusin, one of our plans was to connect carbon-carbon bond between C(9) and C(10)$^{3)}$ to make eight membered B ring (Scheme 1). For such purpose, it was required to prepare the cyclization precursor with diastereocontrol at C(1) and C(8) sites.$^{4)}$



Scheme 1.

According to such strategy, we examined diastereoselective introduction of methyl group on the enone **1** via conjugate addition. Use of a variety of organocopper$^{5)}$ failed to give the corresponding 1,4 addition product, although some of them gave 1,2 addition product. However, two types of reactions$^{6,7a)}$ recently developed in our laboratory allowed the desired transformation with high diastereoselectivity. Especially, a catalytic amount of Cu(II) N-isopropylsalicylaldimine complex$^{7b)}$ with stoichiometric amount of chlorotrimethyl-

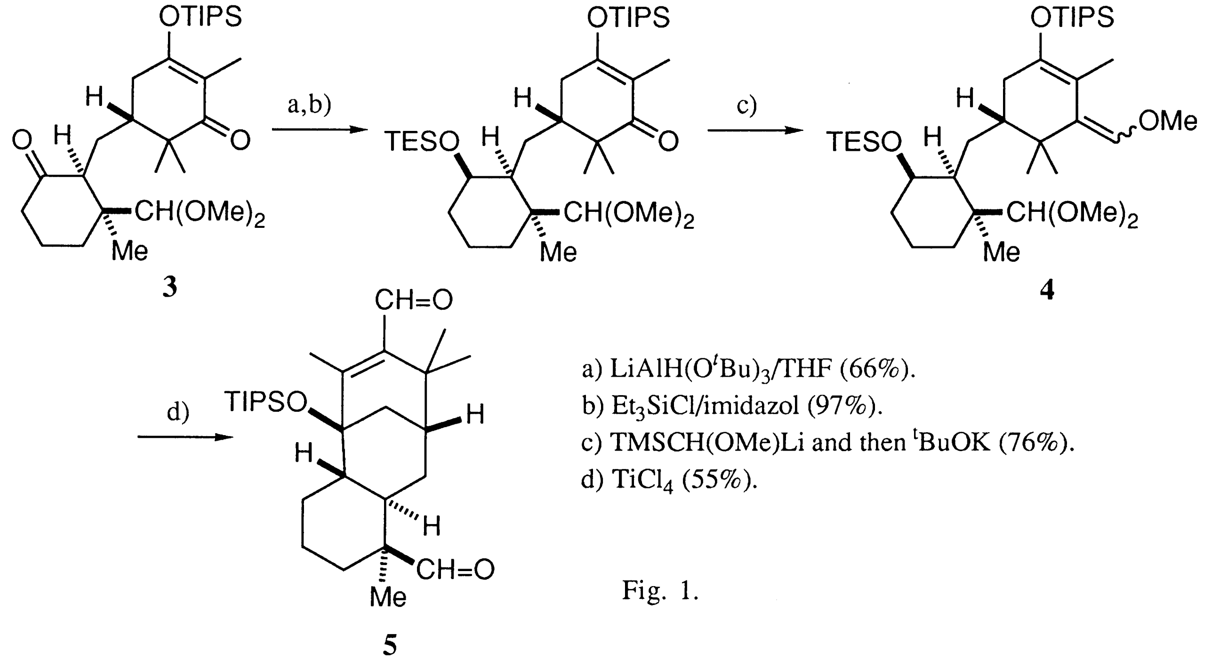


1 **2a** **2b** (1)

a) Me_2CuLi/TMS-Cl/HMPA; -78~-45 °C: 70% (**2a**:**2b** = 93:7)
b) MeMgBr/TMS-Cl/cat.Cu(II); -78~-45 °C: 100% (**2a**:**2b** = 94:6)

silane effected the conjugate addition of methylmagnesium bromide to **1** almost quantitatively.

However, the major diastereomer was proven to be not a desired **2b,** but its isomeric **2a** by the following experiments. In order to determine the stereochemical outcome, the ketone **3** was converted to **4**. The reduction took place stereoselectively to give the alcohol as a single product, but stereochemical relationship could not be assigned at this stage. After Peterson olefination, exposure of the dienol ether **4** to $SnCl_4$ unexpectedly gave the tricarbocycle **5** in 55% yield. Any spectroscopic methods did not help to determine the structure of this product, and finally structural identification and stereochemical assignment were performed by X-ray crystallographic analysis.8)

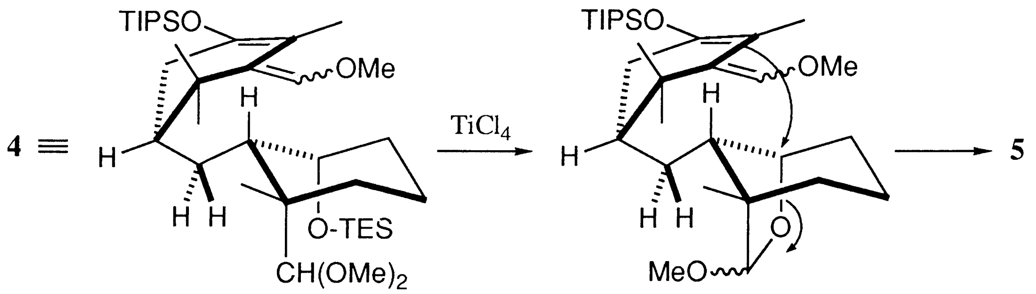


3 **4** **5**

a) $LiAlH(O^tBu)_3$/THF (66%).
b) Et_3SiCl/imidazol (97%).
c) $TMSCH(OMe)Li$ and then ^tBuOK (76%).
d) $TiCl_4$ (55%).

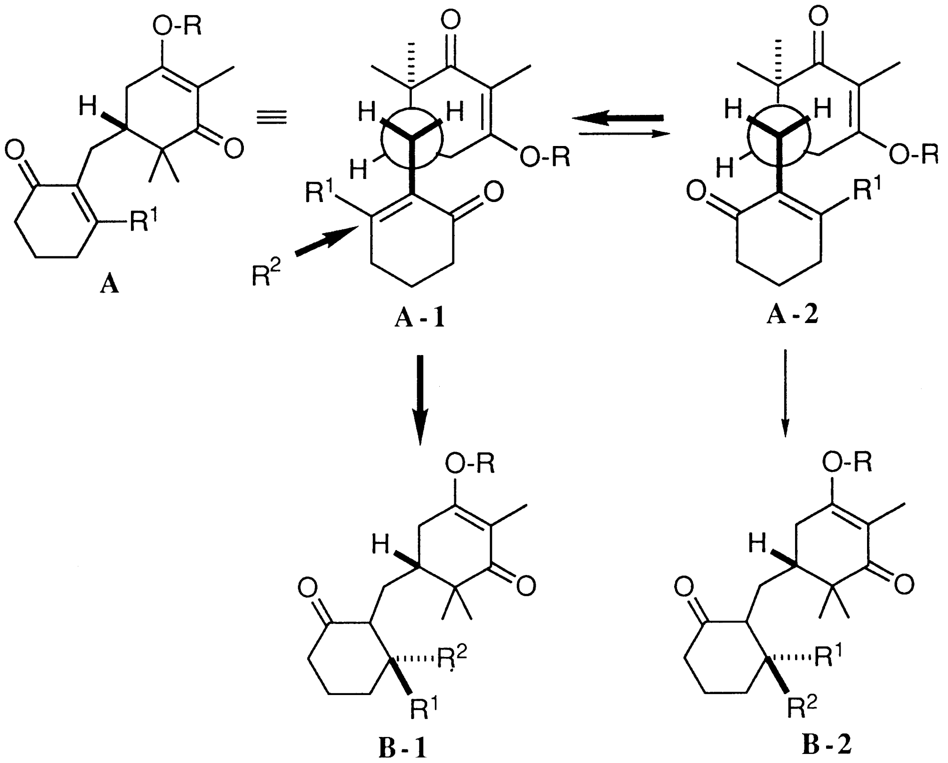
Fig. 1.

Based on the structure of **5**, the relative stereochemistry of the conjugate addition product could be deduced as **2a**. Thus, the formation of this complicated cyclization product can be explained by assuming an internal participation of the axial siloxy group followed by nucleophilic attack of vinyl carbon substituted with TIPSO.



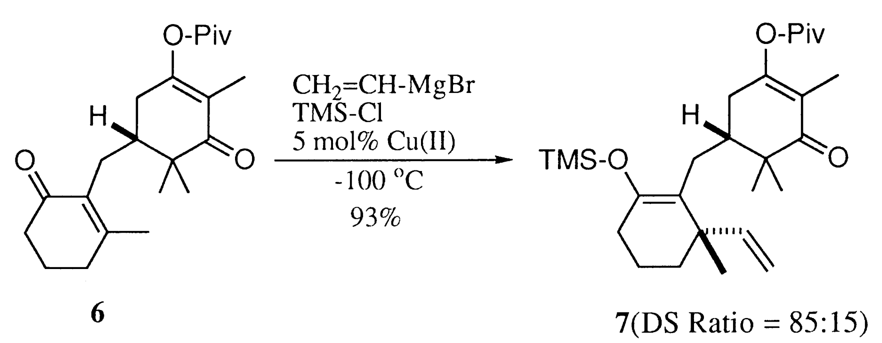
Scheme 2.

Further, the high diastereoselectivity observed in this conjugate addition reaction may be rationalized by comparing the two relatively stable conformers **A-1**9) and **A-2**. The conformer **A-1** seems to be generally more favored than conformer **A-2** due to steric repulsion between R^1 and cyclohexane-methylene group opposed to the latter, although the energy deference seems to be highly dependent on the bulkiness of R^1.10) Consequently, introduction of the alkyl group R^2 from the opposite side of A ring affords the product **B-1** preferentially.



Scheme 3.

In order to prepare the desired stereoisomer, we examined the conjugate addition of vinyl group to **6** under similar reaction conditions. At -100 °C for 10.5 h,11) the reaction completed to give **7** (a diastereomeric ratio 85:15) in 93% yield. After hydrolytic work up, conversion of vinyl group to the dimethylacetal followed by substitution of pivaloyl group with TIPS has been performed. Since the resulting minor product was assigned to be **3**, the major diastereomer was proven to possess the desired relative stereochemistry at C-1 and C-8.12)



(2)

Thus, the present methodology has not only allowed us to prepare the correct cyclization precursor, but also has disclosed an interesting stereochemical effect of remote stereocenter on conjugate addition of cyclohexenones. We are currently studying the total synthesis of taxusin by applying the present methodology.

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References

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2) Review on synthetic studies on the carbon frameworks: C. S. Swindell, *Org. Prep. Proced. Int*., **23**, 465 (1991).

3) Y. Horiguchi, T. Furukawa, and I. Kuwajima, *J. Am. Chem. Soc.*, **111**, 8277 (1989). T. Furukawa, K. Morihira, Y. Horiguchi, and I. Kuwajima, *Tetrahedron*, **48**, 6975 (1992).

4) Stereochemistry at C-3 site might also be important, but it seems to be controlled in a desired manner at a later stage via epimerization .

5) Neither Me_2CuLi nor $MeCuBF_3$ reacted with this enone, and the higher ordered cuprate $Me_2CuCNLi_2$ gave only 1,2 addition product.

6) E. Nakamura, S. Matsuzawa, Y. Horiguchi, and I. Kuwajima, *Tetrahedron Lett.*, **27**, 4029 (1986). S. Matsuzawa, Y. Horiguchi, E. Nakamura, and I. Kuwajima, *Tetrahedron*, **45**, 349 (1989).

7) a) H. Sakata, Y. Aoki, and I. Kuwajima, I. *Tetrahedron Lett.*, **31**, 1161 (1990). Y. Aoki and I. Kuwajima, *ibid.*, **31**, 7457 (1990). Although we previously reported the Cu(II) species survived the reaction conditions, reexamination has revealed the Cu(II) is reduced to Cu(I), but it still works very well for the conjugate addition. b) In this paper, the Cu(II) represents the N-isopropylsalicylaldimine complex.

8) S. Kamei, A. Uchida, Y. Ohashi, T. Furukawa, Y. Horiguchi, and I. Kuwajima, *Anal. Sci.* submitted for publication.

9) MM2 calculation shows this conformer having axial A-ring moiety is the most stable.

10) On conjugate addition of vinylmagnesium bromide under similar reaction conditions, the following diastereoselectivity was observed. **1**: 92:8 (98% yield), **A** (R^1 = CH_2OTIPS): 84:16 (76%). In contrary the substrate having ethylenedithioacetal moiety as R^1 gave 1,2 addition product exclusively.

11) In this case, the energy difference seems to be small and the diastereoselectivity was little observed when the reaction was performed at -45 °C.

12) Ozonolysis, TMS-OTf catalyzed acetalization, and removal of pivaloyl group followed by the silylation gave the desired product as a mixture of C-3 epimers together with **3** in the 45:43:12 ratio.

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