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CONTROL ELEMENTS IN THE ASYMMETRIC TANDEM ALKYLATION OF α-ALKYLIDENE-γ-BUTYROLACTONE DERIVATIVES

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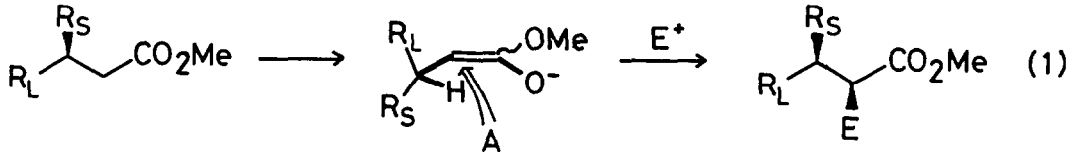
Summary: Control elements in the highly selective construction of contiguous tertiary and quaternary carbon centers by the tandem alkylation of α-alkylidene-γ-butyrolactone derivatives were studied. It is clarified that the stereochemical course of the reaction is rationalized by evaluating highly selective 1,2-, 1,3-, and 1,4-asymmetric inductions.

Development of new and efficient methodologies for the diastereoselective alkylation of chiral metal enolates is of great interest in relation to stereocontrol.[1] It is highly probable that allylic strain concepts serve as a basic understanding on the diastereoselective alkylation reactions of metal enolates with chirality at β-position.[2,3] When R_L and R_S are, respectively, sterically dominant and subordinate substituents in **1**, π-facial selection favoring path A is predicted in reactions of the enolate anion **2** with electrophiles affording **3** as a major diastereomer (equation 1).[2] As has been noted by Evans in the recent review on the stereoselective alkylations of chiral metal enolates,[4] it is rather surprising that no unambiguous cases have been reported that unequivocally provide documentation for this general case of 1,2-asymmetric induction.[3] We now report that in the asymmetric tandem alkylation of **4** and **9**, a sum of effects of two control elements, so called 1,2- and 1,3-asymmetric induction, is relevant to the alkylation of lactone enolates forming quaternary chiral carbon centers with excellently high to low level of diastereoselectivities.



1 **2** **3** (1)

Recently we reported highly efficient asymmetric tandem alkylation in the total synthesis of neolignan (-)-megaphone,[5] where nucleophile (2-lithio-2-(3,4,5-trimethoxyphenyl)dithiane: abbreviated as NuLi) and electrophile (allyl bromide: abbreviated as EBr) both reacted predominantly from the face of Z-ethylidene lactone **4** opposite to bulky trityloxymethyl substituent, giving major product **6** and two minor products **7** and **8** in the ratio of 23:1:1 (quant. yield) (equation 2). The structure of **6** was unambiguously established by x-ray analysis.[5] Two minor products **7** and **8** are now assigned to be the products arising from nucleophile attack from upper face of Z-ethylidene lactone **4** and subsequent electrophile

attack from bottom and upper face, respectively.[6] The same reaction sequence starting from E-ethylidene lactone **9**, however, afforded **6**, **7**, and **8** in the ratio of 15:31:52 (98% yield) (equation 3).

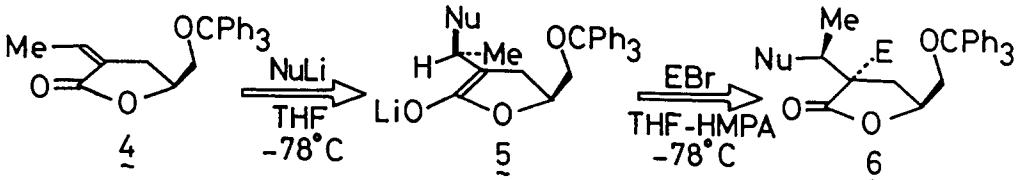
In these two reactions first attack of nucleophile to the ethylidene lactones **4** and **9** predominantly took place from the bottom face with selectivities of 92:8 for Z-**4** and 85:15 for E-**9**, respectively. High level of this 1,4-asymmetric induction is explainable from ^{1}H-NMR of **4** and **9** at 400 MHz in $CDCl_3$.[7] Figure 1A shows values of chemical shifts and coupling constants of **4** and these values indicate that trityloxymethyl group situates anti to C-H of lactone methine as visualized in Figure 1B and in almost axial conformation. The similar coupling constants were obtained for **9**. In this conformation benzene ring of trityl group may be placed just above double bond, so attack comes from bottom face of **4** and **9**.[8] On the other hand, the second attack of electrophile to the resulting lactone enolates took place with a rather different diastereoselectivity. It is surprising to note that the fourth possible isomer arising from enolate **5** with upper face attack of electrophile was not detected by usual analytical methods (NMR and HPLC).

Rationale of these diastereoselectivity to form chiral quaternary center is attainable on the basis of cooperative and competitive effects of two control elements, A-strain imposed π-facial diastereoselectivity (1,2-asymmetric induction)[9] and 1,3-asymmetric induction by trityloxymethyl substituent,[10] for the probable conformations of **5** and **10**.

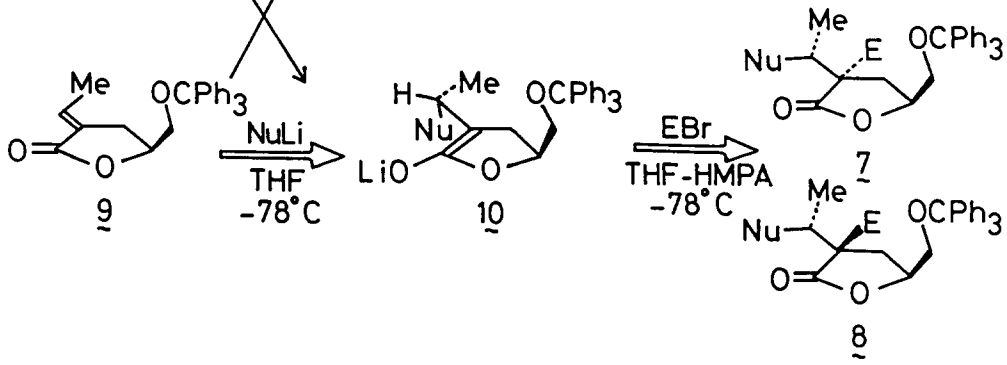
The reaction of chiral methylidene lactone **11** bearing trityloxymethyl substituent with nucleophile to produce enolate **12** and subsequent trapping with electrophile turned out to be highly diastereoselective, affording **13**[6] (48% yield) as a single isomer, in accord with Takano's[11] and our[12] previous observations (equation 4: 1,3-asymmetric induction).

Nucleophilic addition to achiral ethylidene lactone **14** and subsequent enolate trapping with electrophile gave rise to double alkylation product **16**[6] as a predominant isomer with diastereoselectivities of 18:1 (75% yield) at -78°C and 26:1 (62% yield) at -100°C (equation 5: 1,2-asymmetric induction). Relative configuration of **16** was unequivocally assigned by correlating with **6**.[6]

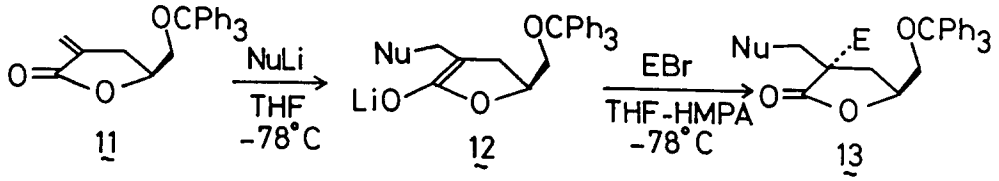
The high and low of stereoselectivity obtained in the alkylation of **5** and **10** in equations 2 and 3 are attributable to the sum of effects of the transition-state control elements that dictate enolate π-facial selectivity in equations 4 and 5. Without additional asymmetric center at the β-position stereochemical course of electrophile attack in enolate **12** is controlled by trityloxymethyl substituent as a 1,3-asymmetric induction (equation 4).[13] The explanation for the reaction in equation 5 follows from the steric influence in the low energy conformation **15**.[9] In this conformation, the hydrogen eclipses the double bond leaving the larger group staggered, in accord with allylic strain concepts.[4,9] Attack by electrophile then take place anti to the bulky dithioacetal based nucleophile group for steric reason (Nu serves as a severely larger group than methyl) giving **16**, in accord with theoretical predictions by Houk.[2] Chelation control by coordination of sulfur atom to lithium cation to form a seven membered chelate may not be important, because in alkylation of lactone enolate, a large excess of HMPA (2-10 eq.) is present in the reaction medium.[14] Consequently the 1,2- and 1,3-asymmetric inductions are favorably cooperative in the alkylation of enolate **5**, affording **6** as a predominant product without formation of any



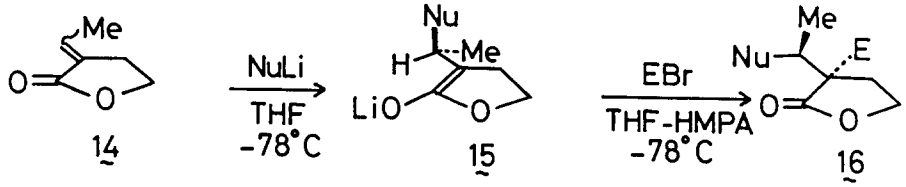
4 5 6 (2)



9 10 7 8 (3)

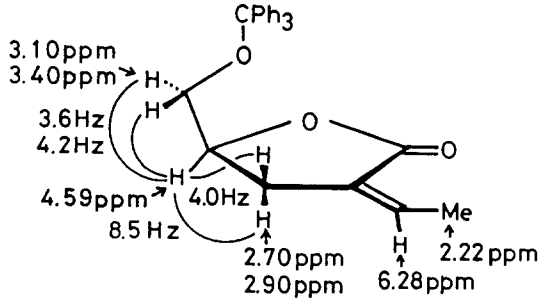


11 12 13 (4)



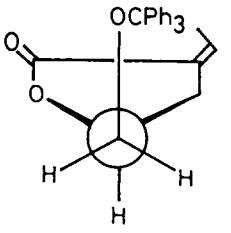
14 15 16 (5)

Nu : 3,4,5-(MeO)$_3$PhC(S,S) , E : CH_2=CH-CH_2



A

Fig.1



B

detectable isomer, whereas in the alkylation of enolate **10**, both control elements exhibit opposite trends giving **7** and **8** in comparable amounts.[15)]

A rather detailed understanding on the separate 1,2- and 1,3-asymmetric induction, and their cooperation and competition demonstrated in equations 2-5 will be useful in developing new and efficient diastereoselective reactions.

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6. Satisfactory analytical and spectroscopic data were obtained for all new compounds described in this communication. Compounds **6**, **7**, **8**, and **13** are optically pure and **16** is racemic. Correlation of **6**, **7**, **8**, **13**, and **16** were carried out as follows. Deprotection of thioacetal of **6** afforded the corresponding ketone **6'**. Deprotection of thioacetal of **13** and methylation of the corresponding ketone with MeI (LDA) gave **6'** and its isomer which was identical with ketone obtained from **7** by deprotection of thioacetal. Inversion of configuration of **6** at the carbon bearing trityloxymethyl (KOH-KH in THF, then MsCl) afforded the antipode of **8**. Reduction of **16** ($LiAlH_4$ in THF, then Na/NH_3-THF) gave a racemic diol which was obtained in optically active form from **6** (i. c. HCl-MeOH-THF; ii. $LiAlH_4$ in THF; iii. Na/NH_3-THF; iv. $NaIO_4$-aq. EtOAc; v. $LiAlH_4$ in THF).
7. The authors are grateful to Professors S. Okuda and S. Iwasaki for taking 400 MHz ^{1}H-NMR.
8. The similar conformation was observed by X-ray crystallographic analysis. See ref. 5.
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13. High diastereoselectivity may be explainable by the similar upper face shielding by trityloxymethyl group in **12** as shown in Figure 1A.
14. cf. C. Reichardt, "Solvent Effects in Organic Chemistry," ed. by H. F. Ebel, Verlag Chemie, Weinheim, 1979.
15. For the effects of another type of 1,2- and 1,3-asymmetric induction, see: K. Tomioka, T. Ishiguro, Y. Iitaka, and K. Koga, Tetrahedron, 40, 1303 (1984).

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