Tetrahedron Letters,Vol.27,No.28,pp 3247-3250,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A RATIONALE OF DIASTEREOFACIAL SELECTION IN THE ALKYLATION OF ENDOCYCLIC ENOLATES WITH CHIRALITY AT THE β-POSITION

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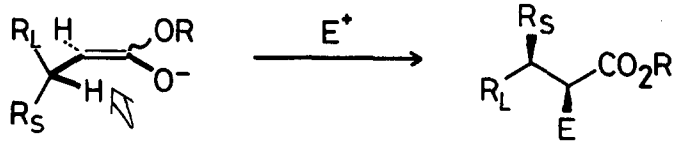
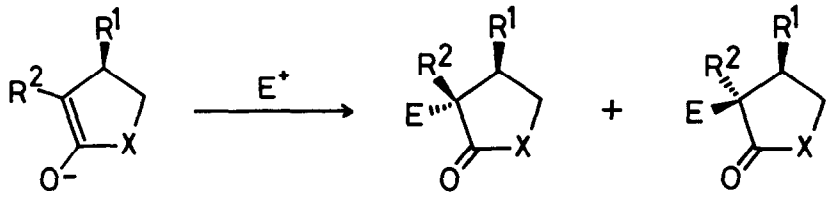
Summary: Ratios of the diastereomers **4** and **5** in the alkylation of the endocyclic enolates **3** with chirality at the β-position were highly dependent on the steric bulkiness of R^1 and R^2. It was clarified that, when the allylic strain considerations are acknowledged in **3**, the diastereofacial selection is successfully rationalized by evaluating two competitive 1,2-asymmetric inductions in the conformation **15**.

Understanding on the fundamental control elements in the diastereoselective alkylation of the metal enolates with chirality at the β-position has been the current focus in the synthetic organic chemistry.[1-13] In previous papers,[12,13] we have reported that allylic strain concepts serve as a basic understanding on the diastereoselective alkylation of the enolates. When R_L and R_S in **1**, respectively, represent the sterically dominant and subordinate substituents, alkylation of **1** is reasonably predictable to take place from the face opposite to R_L, giving **2** predominantly. The purpose of the present communication is to show that allylic strain concepts are also applicable to the rationale of the diastereofacial selection in the formation of quaternary carbon centers by the alkylation of endocyclic enolates **3** with chirality at the β-position.



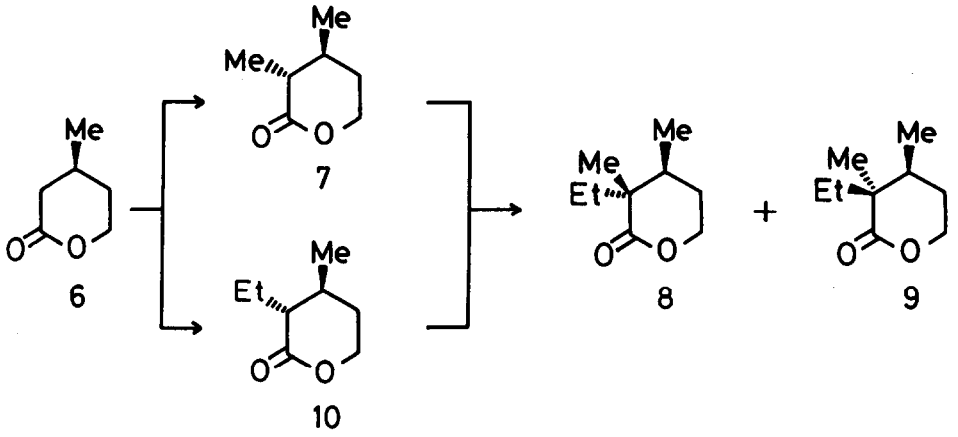
1 **2**

It is well recognized that alkylation of **3** with 1,2-asymmetric induction takes place, under the steric influence of the resident asymmetric center, from the less hindered α-face opposite to R^1 providing **4** as a major isomer. Indeed, many examples that appear to conform to

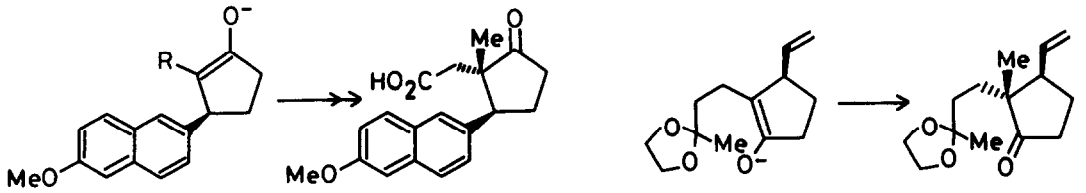


3 **4** **5**

this trend in the diastereofacial selection have been reported.[1] In our cases, methylation and ethylation of **6** (LDA-HMPA-THF, MeI or EtI, -78°∿-20°) afforded the corresponding products, **7**[14] and **10**[15], respectively, in an excellent diastereoselectivity (>20 : 1).[16,17] Ethylation of **7** (LDA-HMPA-THF, EtI, -20°) also proceeded smoothly to give a mixture of **8** and **9** in a reasonably anticipated ratio of 5 : 1 (56%).[16] However, it was found that methylation of **10** (LDA-HMPA-THF, MeI, -20°) provided a mixture of two isomers with an unexpected preference of **8** in a ratio of 2:1 (55%).[16] This type of unusual stereochemical behavior in the 1,2-asymmetric induction has also been reported by other authors. Birch[18] observed that methylation (MeI) of



11a afforded **12** as a major isomer in a ratio of 3 : 1, while Posner[19] reported that alkylation (ICH_2COOEt) of **11b** provided the expected product **12** exclusively. Tsuji and Takahashi[20] also observed similar unusual stereochemical outcome in the methylation (MeI) of **13** affording **14** as a major isomer in a ratio of 3.5 : 1. Thus, reversal of diastereofacial selection in **3** affording **5** as a major product appears to be general when R^2 is a group other than hydrogen or methyl.



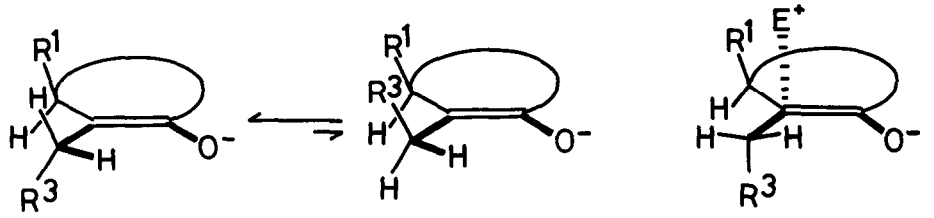
11a $R=CH_2CO_2Li$ **12** **13** **14**

11b R=Me

The unresolved issue is what is the transition-state control elements determining diastereofacial selection in the alkylation of **3**. We propose that allylic strain concepts[21] are applicable to the basic understanding on these unusual diastereofacial selection. It is highly probable that, when R^2 in **3** is a CH_2R^3 group, the conformation **15** in which the C-H of CH_2R^3 is placed to eclipse the double bond due to the allylic strain is favorable than **16** where steric repulsion between R^1 and R^3 exists.[22] It follows that in **15** a resident

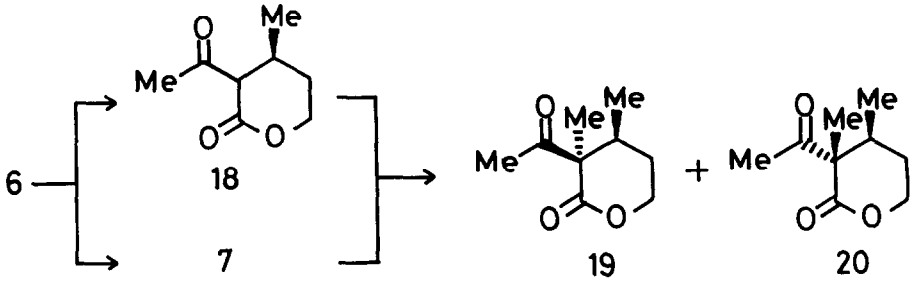
asymmetric center bearing R^1 dictates the α-face entry of electrophile, while exocyclic substituent CH_2R^3 allows entry from the β-face. Consequently diastereofacial selection in **15** may be governed by a couple of competitive 1,2-asymmetric inductions.

In general, the diastereofacial selection in **15** depends upon the balance of steric bulkiness between R^1 and R^3: i) When R^1 is bulkier than R^3 (**6**, **7**, **11b**), a resident asymmetric center plays a key role to dictate an attack from the α-face; ii) When R^3 is bulkier than R^1 (**11a**,[23] **13**), electrophile attacks from the β-face; iii) When R^1 and R^3 are of equal bulkiness (**10**), a readily accessible transition state, through the rotation of the σ-bond between CH_2R^3 and sp^2 carbon in **15**, would be the one similar to **17** where developing E-C bond takes the anti-relationship to the R^3-C bond as has been noted by Houk.[24]



15 **16** **17**

By changing a stereochemical character of the exocyclic substituents CH_2R^3 at the allylic position from tetrahedral sp^3 to planar sp^2 carbon, a usual diastereofacial selection controlled by the resident asymmetric center would be anticipated. In fact, methylation of **18**[25] (t-BuOK-PhH, MeI, 80°) and acetylation of **7** (LDA-THF, CH_3COCN,[26] -78°) afforded a mixture of **19** and **20** in a ratio of 5 : 1 (61%) and 1 : 60 (71%), respectively.[16]



18 **7** **19** **20**

The present analysis and demonstration of the diastereofacial selection exhibited by the endocyclic enolates **3** with chirality at the β-position are highly valuable in the sense that ,as shown in **15**, an induced conformational rigidity of CH_2R^3 substituents not bearing any asymmetric center plays a critical role in the stereoselection control. The successful rationale of the diastereofacial selection based on the allylic strain concepts may hold a great promise for the design of new and highly stereoselective alkylation reactions.[27]

References and Notes

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14. The ratio of **7** and its isomer was 20:1 (80%).
15. The ratio of **10** and its isomer was 26:1 (51%).
16. The compounds described in this paper are racemic. Satisfactory analytical and spectroscopic data were obtained for all new compounds. ^{1}H- and ^{13}C-NMR (quaternary Me, $CDCl_3$): **8** 1.16(s), 20.86(q); **9** 1.27(s), 22.74(q); **19** 1.57(s), 22.0(q); **20** 1.36(s), 16.9(q), respectively.
17. Diastereomeric ratio was determined by ^{1}H- and ^{13}C-NMR, and GLC analyses.
18. a) A. J. Birch and G. S. R. Subba Rao, Aust. J. Chem., **23**, 547 (1970); b) Idem, Tetrahedron Lett., **1967**, 2763. They explained unusual stereochemical outcome based on the concept of product development control: "Although in forming this isomer **12** the methyl group approaches from the more hindered side of the anion, the reaction proceeds with the adjacent large substituents on the anion becoming trans to each other."
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(Received in Japan 24 April 1986)