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Alkylation of 4-Hydroxyproline Ester Derivatives. Diastereoselectivity Guided by the Anomeric Effect and π-Interaction

Shinji Nagumo,* Megumi Mizukami, Noriaki Akutsu, Atsushi Nishida,[1] and Norio Kawahara*

Hokkaido College of Pharmacy, Katuraoka 7-1, Otaru 047-0264, Japan

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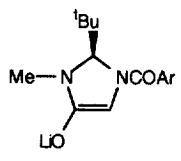
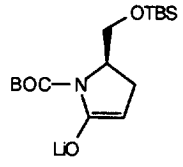
Abstract: The alkylation of 4-hydroxyproline derivatives **7** and **12** with a range of alkylating reagents was examined. The stereoselectivity was found to be dependent on the reagent and the N-protecting group. This was explained by a concept based on the stereoelectronic effect and π-interaction.

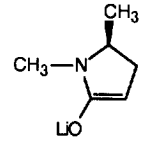
To modern organic chemistry, much interest has been shown in stereoselective alkylation of heterocyclic enolates. Endocyclic enolates (**1**-**3**) react with alkylating reagents from the face opposite to the remote substituent on the rings.[2,3,4] The diastereoselectivities appear to be correlated with steric hindrance. However, the value is too high to be rationalized by only a steric factor. Seebach has suggested that the stereochemical result of **1** might also be due to a stereoelectronic effect based on a slight pyramidalization of



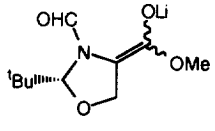
1 (97% α)



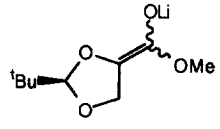
2 (93% α)



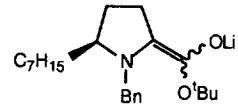
3 (99% α)



4 (>95% β)



5 (>90% β)



6 (89% β)

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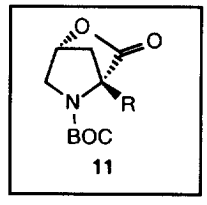
nitrogen.[2] The alkylation of exocyclic enolates has a more complex stereochemical problem. The alkylation of **4**, as well as endocyclic enolates **1-3**, shows trans attack to a large substituent with high selectivity.[5] On the other hand, enolates (**5-6**) react with alkylating reagents from the face *cis* to the substituent on the rings.[5,6] The stereoelectronic effect, the aggregation state of the reagent or the chelation effect of the metal should play an important role in the seemingly disfavorable selectivity in the alkylation of exocyclic enolates.[2a] Here, we report the unique diastereofacial differentiation, which is dependent on the reagent, in the alkylation of 4-hydroxyproline ester derivatives (**7**) and (**12**).

Table 1

7 **8** **9a-g** **10a-g**

Entry	Alkyl halides	Products	Yield (%)	Ratio (**9** : **10**)
1	$PhCH_2Cl$	**9a,10a**	74	71 : 29
2	$PhCH_2Br$	**9a,10a**	95	70 : 30
3	$4\text{-}MeOC_6H_4CH_2Cl$	**9b,10b**	83	66 : 34
4	$CH_2{=}CHCH_2Br$	**9c,10c**	78	40 : 60
5	$(CH_3)_2C{=}CCH_2Br$	**9d,10d**	84	36 : 64
6	$CH_2{=}C(CH_3)CH_2Br$	**9e,10e**	83	37 : 63
7	CH_3I	**9f,10f**	77	23 : 77
8	$CH_2{=}CHCH_2CH_2Br$	**9g,10g**	49	23 : 77
9	$CH_2{=}CHCH_2CH_2I$	**9g,10g**	74	27 : 73



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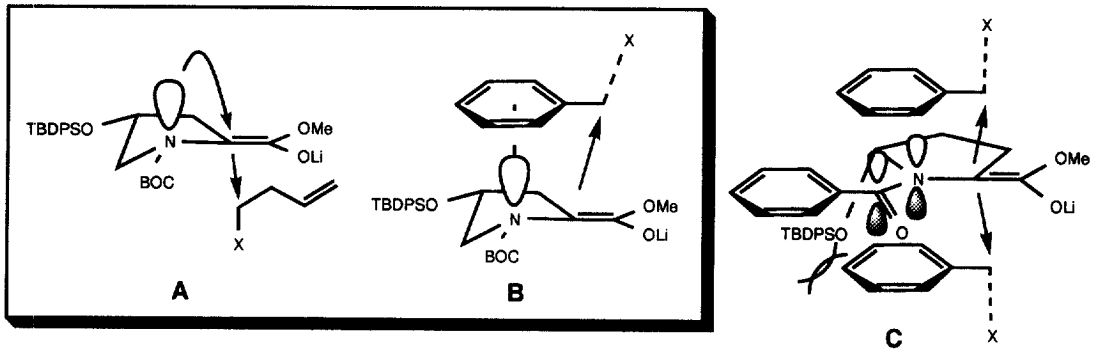
The alkylation of **7** with a range of alkyl halides was carried out by using LDA (1.2 eq.) and HMPA (10 eq.) at -78°C in THF as shown in Table 1. The addition of HMPA to the reaction mixture was essential for a good chemical yield. β-Alkylated products (**9a-g**, less polar) and α-alkylated products (**10a-g**, more polar) were separated by column chromatography on silica gel. The structures of products were assigned on the basis of spectroscopic data. The methyl proton peak of α-alkylated products **10** appeared at upper magnetic field (ca. 0.2 ppm) than that of β-alkylated products **9** in all cases. Furthermore, the proton peak at C_4 position for **9a** and **9b** appeared at upper magnetic field (ca. 1 ppm) than that for **10a** and **10b**. This finding suggested that the benzyl group in **9a** and **9b** were located over the pyrrolidine ring. To confirm the relative configuration, the conversion of **9** into bridgehead lactones (**11**) was carried out by a sequence of desilylation, hydrolysis and lactonization[7] using diphenylphosphoryl azide.

It was found that the diastereoselectivity is dependent on the alkylating reagent. Alkylation with benzylic halides (Entry 1-3) gave β-alkylated products preferentially. Conversely, α-alkylated epimers were major products by a ratio of 1.5-1.8 : 1 in the cases of using allylic halides (Entry 4-6). Furthermore, alkylation with non-activated alkyl halides showed a higher α-facial selectivity (Entry 7-9). We propose the following

hypothesis to rationalize these unique stereochemical results. The pyrrolidine ring in enolate (**8**) derived from **7** should prefer an envelope conformation (Figure, **A**,**B**), because three large substituents in the conformation are not coplanar with all adjacent C-H bonds. The nitrogen in the conformation would be pyramidalized to minimize the steric repulsion between the BOC group and enolate moiety. The resulting pseudoaxial lone pair could be considered to be essential for the stereochemical results. α-Facial alkylation of **8** is controlled by the anomeric effect, that is, the stereoelectronic interaction of N-lone pair with the forming C-C bond orbital (Figure, **A**). The strength of the effect is unchanged by the type of alkylating reagents. On the other hand, the partial breaking of benzylic or allylic carbon-halogen bond at the transition state is thought to induce the positive character in the π-system. Thus, a lone pair on nitrogen of **8** interacts electrostatically with the benzylic or allylic halide (n-π interaction) to lower the energy of the transition state involved in a β-facial alkylation (Figure, **B**).[8] The strength of electrostatical interaction in the alkylation of **8** with benzilic halide is higher than that with allylic halide. Consequently, the stereochemical results shown in Table 1 can be attributed to the respective balance between the anomeric effect and the n-π interaction.

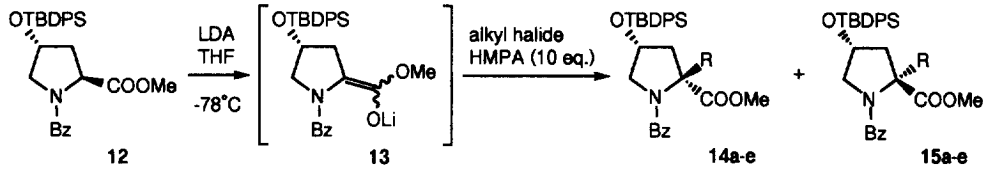
Figure



Next, we carried out alkylation of **12** to examine the effect of the N-protecting group. A series of results are presented in Table 2. A remarkable difference between alkylations of **7** and **12** in aspect of stereoselectivity was observed. β-Facial selectivity of (**13**) with benzilic halides was much higher than that of **8**. It was found that the stereoselectivity in the case of using allyl bromide was reversed by changing the N-protecting group. That is, the alkylation of **12** with allyl bromide afforded β-alkylated compound (**14b**) as a major product. In the case of using butenyl iodide, α-facial selectivity of **13** was lower than that of **8**. These stereochemical results could be rationalized as following. The benzoyl group in **13** increases delocalization of the lone pair on nitrogen to inhibit the anomeric effect. It's suggested by the low reactivity in the case of using butenyl iodide, which are not controlled by π-interaction (Entry 5). Furthermore, the decreased α-facial selectivity in Entry 5 can be attributed to the lowering of the anomeric effect. In the case of using benzilic halides and allyl bromide (Entry 1-4), because of the lowering of the anomeric effect, the π-interaction is more dominant factor determining the diastereofacial differentiation. Nitrogen in **13** may be not pyramidalized owing to

delocalization (Figure, C). The π-system of benzylic halides and allyl bromide should associate electrostatically with the N-Bz moiety of **13** (π-π interaction). The interaction leads to a transition state in which the π-system of the reagents and the N-Bz moiety of the enolate lies close together. In such a situation, the bulky silyloxy group inhibits the α-facial attack of benzilic halides and allyl bromide.

Table 2



12 **13** **14a-e** **15a-e**

entry	alkylating reagent	products	yield (%)	ratio (**14** : **15**)
1	$C_6H_5CH_2Br$	**14a,15a**	66	>95 : 5
2	4-$MeC_6H_4CH_2Cl$	**14b,15b**	79	91 : 9
3	4-$MeOC_6H_4CH_2Cl$	**14c,15c**	56	>95 : 5
4	CH_2=$CHCH_2Br$	**14d,15d**	69	77 : 23
5	CH_2=$CHCH_2CH_2I$	**14e,15e**	14	37 : 63

In conclusion, it was found that the stereoselectivity of 4-hydroxyproline derivatives is dependent on the reagent and N-protecting group. Highly selective benzylation has been realized by using the benzoyl group as a protecting group. Such a high selectivity has not previously been reported in the alkylation of monocyclic enolates of 4-hydroxyproline derivatives.[9,10] Needless to say, other controlling factors should be considered as an origin of the unique stereochemical results. Further work is in progress to clarify the origin of stereoselectivity in more detail.

References and Notes

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