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Factors That Cause Contrasteric Alkylation of a Cyclopentane-1,2-dicarboxylic Acid Monoester

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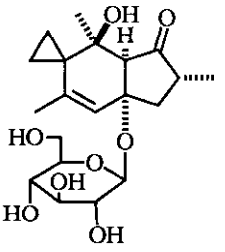
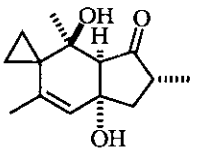
Summary: The stereochemical outcome in the alkylation of the enolate generated from a cyclopentane-1,2-dicarboxylic acid monoester is described. The alkylation of the Li enolate with an alkylating reagent having a hard leaving group such as Cl gave a contrasteric alkylation (alkylation from the more hindered side of the enolate) product, predominantly. An important factor effecting contrasteric alkylation was found to be complexation of the hard leaving group of the alkylating reagent to the carboxylate Li counterion in the enolate.

Stereoselective construction of quaternary carbon centers is an important synthetic operation and a number of methods have been developed.[1] Of those, alkylation of ester enolates is one of the most widely employed procedures. In the course of the total synthesis of ptaquilosin (**2**), the aglycone of ptaquiloside (**1**) a bracken carcinogen, we have investigated stereoselectivity of the alkylation of a cyclopentane-1,2-dicarboxylic acid monoester and have found that contrasteric[2] alkylation occurred:[3] the ester enolate generated from (1*R*,2*R*)-cyclopentane-1,2-dicarboxylic acid mono-(+)-menthyl ester (**3**) with LDA (THF, -25 °C) was alkylated with methallyl chloride to afford a 4:1 mixture of diastereomeric esters, **4a** and **4b**, the predominant isomer **4a** being the one that was alkylated from the sterically more hindered side of the enolate (Scheme I, R = Me, X = Cl). This interesting observation has prompted us to investigate factors causing contrasteric alkylation. This paper describes the stereochemical outcome in the alkylation of the ester enolate generated from **3**.



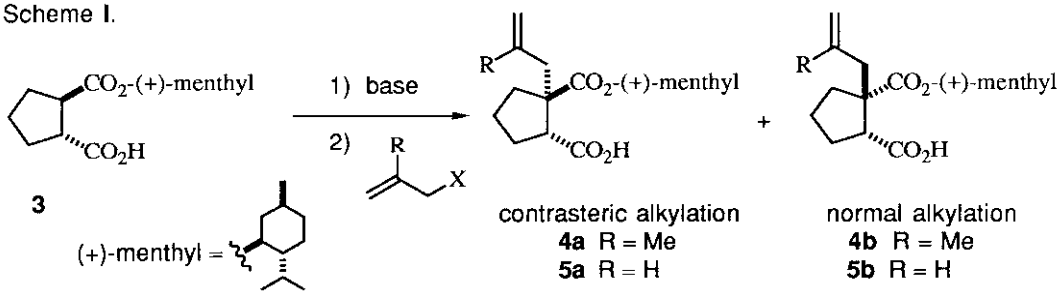
ptaquiloside (**1**)



ptaquilosin (**2**)

(1*R*,2*R*)-Cyclopentane-1,2-dicarboxylic acid mono-(+)-menthyl ester (**3**) was treated with 2.4 equiv of an appropriate base [LDA, $NaN(TMS)_2$, or $KN(TMS)_2$] in THF (-25 °C, 1 h) to generate the ester enolate, which was alkylated with various alkylating reagents (methallyl halides, allyl halides, or allyl tosylate) in the absence or presence of HMPA (Scheme I). The results of the alkylation are summarized in Table 1. The alkylation of the Li enolate with methallyl chloride, allyl chloride, and allyl tosylate in the absence of HMPA proceeded in the contrasteric mode to give **4a** and **5a**[4, 5] as the major products (entry 1, 6, and 12), while the alkylation with

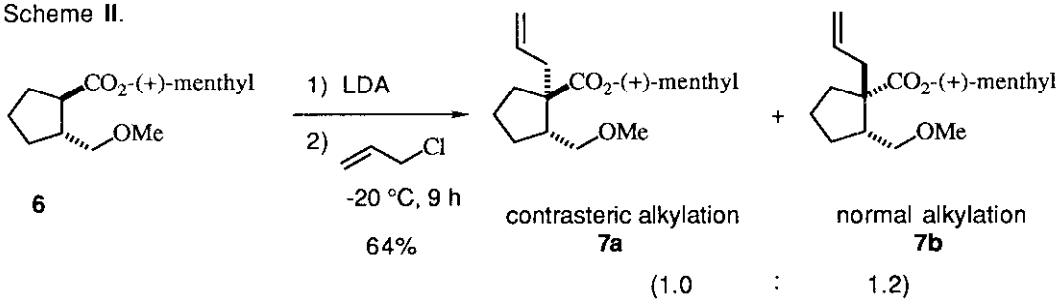
Scheme I.



methallyl bromide, allyl bromide, and allyl iodide gave normal alkylation products, **4b** and **5b**,[4, 5] predominantly (entry 3, 8, and 10). These results can be explained by the HSAB theory.[6] The stereochemical outcome in the present alkylation reactions may depend on the hardness of the leaving groups in the alkylating reagents. The formation of contrasteric alkylation products, **4a** and **5a**, increased with increasing the hardness of the leaving groups (OTs, Cl > Br > I). This trend is consistent with the ability of the leaving groups for complexation to Li cation (OTs, Cl > Br > I). Thus, the harder leaving groups such as Cl and OTs may coordinate more tightly to *the Li counterion of the carboxylate group* adjacent to the enolate moiety. The tighter complexation may cause the contrasteric alkylation (alkylation from the side syn to the carboxylate group) to a larger extent. A powerful cation-complexing agent HMPA may interfere complexation of the leaving group to the Li cation of the carboxylate group, and this ability of HMPA may affect the stereochemical outcome in the alkylation. Thus, we conducted the alkylation of the Li enolate in the presence of HMPA (entry 2, 4, 7, 9, 11, 13, and 14). Compared with the alkylation in the absence of HMPA, the formation of contrasteric alkylation products, **4a** and **5a**, decreased in all cases. The amounts of normal alkylation products, **4b** and **5b** increased with decreasing the hardness of the leaving groups (OTs, Cl > Br > I). In particular, the alkylation with methallyl bromide in the presence of HMPA proceeded with surprisingly high degree of normal alkylation; **4a** and **4b** were obtained in a ratio of 1:45 (entry 5). These results support the above explanation for the factor effecting contrasteric alkylation.

In order to investigate the effect of metal counterions on stereoselectivity, the alkylation of the Na and K enolates with allyl chloride and allyl bromide was performed in the absence of HMPA (entry 15, 16, 17, and 18). Compared with the alkylation of the Li enolate (entry 6), the extent of contrasteric alkylation decreased even in the alkylation with allyl chloride possessing a hard, Cl leaving group (entry 15 and 17). These results may reflect the fact that the affinity of Na and K cations for halide ions is weaker than that of Li cation.

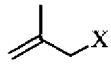
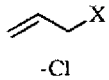
Scheme II.



As was expected, the extent of contrasteric alkylation of the Li enolate derived from **6**[4,7] (Scheme II)[8] is less than that of Li enolate derived from **3** (compare with entry 6 in Table 1), supporting that the carboxylate Li counterion in the enolate molecule plays an important role for contrasteric alkylation.[9]

In conclusion, an important factor causing contrasteric alkylation of the Li enolate derived from **3** is complexation of the leaving group of the reagent to the Li counterion of the carboxylate group in the enolate: Complexation of the harder leaving groups (Cl, OTs) to the carboxylate Li counterion causes the contrasteric alkylation to a larger extent.

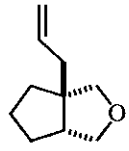
Table 1. Alkylation of Alkali Metal Enolates Generated from (1*R*,2*R*)-Cyclopentane-1,2-dicarboxylic Acid Mono-(+)-menthyl Ester (**3**)

entry	base[a]	R-X	HMPA (equiv)[b]	time (h)[c]	yield (%),[d] ratio of contrasteric : normal[e]
					**4a : 4b**
1	LDA	-Cl	-	8.0[f]	89	4.0 : 1.0
2			2.3	6.5[f]	72	1.0 : 2.5
3		-Br	-	4.7	91	1.0 : 3.4
4			2.3	3.0	92	1.0 : 11.5
5			2.3	g	94	1.0 : 45.0
					**5a : 5b**
6		-Cl	-	3.7[f]	96	4.9 : 1.0
7			2.3	5.0[f]	95	1.0 : 1.4
8		-Br	-	4.5	74	1.0 : 1.7
9			2.3	1.7	86	1.0 : 3.9
10		-I	-	0.9	95	1.0 : 3.9
11			2.3	0.5	92	1.0 : 6.2
12		-OTs	-	2.2	76[h]	4.0 : 1.0
13			2.3	2.2	80[h]	2.4 : 1.0
14			23	3.0	51[h]	1.2 : 1.0
15	$NaN(TMS)_2$	-Cl	-	2.0[f]	90	1.3 : 1.0
16		-Br	-	4.0[f]	66[e]	1.0 : 11.2
17	$KN(TMS)_2$	-Cl	-	7.0[f]	57[e]	1.0 : 2.0
18		-Br	-	3.0	81[e]	1.0 : 6.7

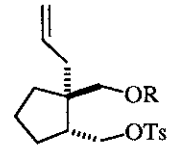
a) The ester enolate was generated with 2.4 equiv of the base in THF at -25 °C for 1 h.
b) HMPA was added after generation of the enolates.
c) Unless otherwise stated, the reaction was performed at -25 ~ -15 °C for a period of the indicated time.
d) Unless otherwise noticed, yields refer to isolated materials.
e) Determined by ^1H NMR spectra.
f) After addition of the alkylating reagent at -25 °C, the reaction mixture was warmed to room temperature and was stirred for a period of the indicated time.
g) Methallyl bromide was added at -78 °C and the reaction mixture was gradually warmed to -20 °C over a period of 3 h.
h) Isolated as the corresponding methyl ester.

References and Notes

1. Martin, S. F. *Tetrahedron* **1980**, *36*, 419.
2. Other examples for contrasteric alkylation, see Naef, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1030: Ladner, W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 449: Ladner, W. *Chem. Ber.* **1983**, *116*, 3413. Related studies: Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934: Takahashi, T.; Nisar, M.; Shimizu, K.; Tsuji, J. *Tetrahedron Lett.* **1986**, *27*, 5103: Tomioka, K.; Kawasaki, H.; Yasuda, K.; Koga, K. *J. Am. Chem. Soc.* **1988**, *110*, 3597.
3. Kigoshi, H.; Imamura, Y.; Niwa, H.; Yamada, K. *J. Am. Chem. Soc.* **1989**, *111*, 2302.
4. Satisfactory spectral (IR, ^{1}H NMR, mass) and analytical data were obtained for this compound.
5. Stereochemistry of **5a** and **5b** was determined as follows: **5b** could be converted into 5-membered ether **8**[4] by a three-step sequence [(1) CH_2N_2; (2) $LiAlH_4$, THF; (3) TsCl, pyridine], whereas **5a** gave monotosylate **9a**[4] and ditosylate **9b**[4] by the same reaction sequence.

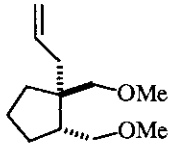


8

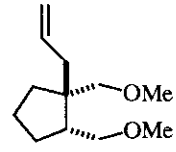


9a R = H
9b R = Ts

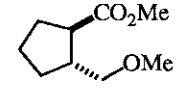
6. Ho, T.-L. *Hard and Soft Acids and Bases Principle in Organic Chemistry*; Academic Press: New York, 1977.
7. Compound **6** was prepared from **3** by a two-step sequence: (1) BH_3·THF, THF; (2) MeI, NaH, DME.
8. Stereochemistry of **7a** and **7b** was determined by comparing the ^{1}H NMR spectra of **10a**[4] and **10b**[4] [derived from **7a** and **7b**, respectively, by a two-step sequence: (1) $LiAlH_4$, THF; (2) MeI, NaH, DME] with those of authentic **10a** and **10b** [derived from **5a** and **5b**, respectively, by a three-step sequence: (1) CH_2N_2; (2) $LiAlH_4$, THF; (3) MeI, NaH, DME].



10a



10b



11

9. Alkylation of monomethyl ester **11**[4] [prepared from **6** by a two-step sequence: (1) KOH-30% H_2O_2, MeOH; (2) CH_2N_2] gave a similar results with a small preference for normal alkylation, indicating that contrasteric alkylation discussed here is not affected by bulkiness and chirality of the *O*-alkyl group in the ester moiety.

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