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Regioselective Baeyer–Villiger Reaction of Polyhydroxycyclohexanone Derivatives

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Abstract: The regioselectivities observed in Baeyer–Villiger reaction of polyhydroxycyclohexanone derivatives possessing various substituents at adjacent carbons to the ketone carbonyl are reported. This study suggested that the trend of the migratory aptitude of substituted carbons would be a carbon with benzyloxy > methoxy > ketal oxygen >> acyloxy ~ methyl.

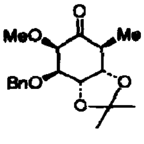
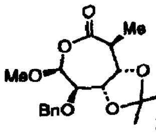
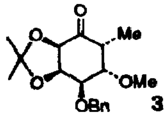
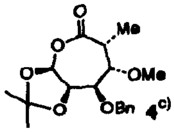
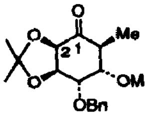
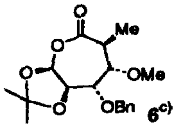
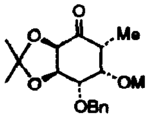
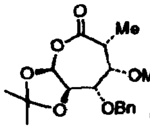
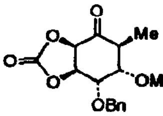
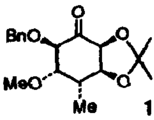
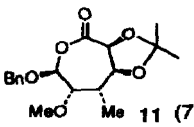
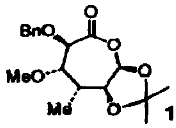
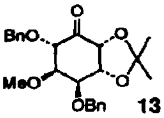
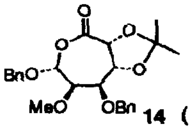
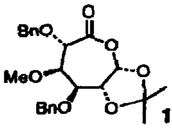
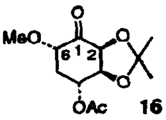
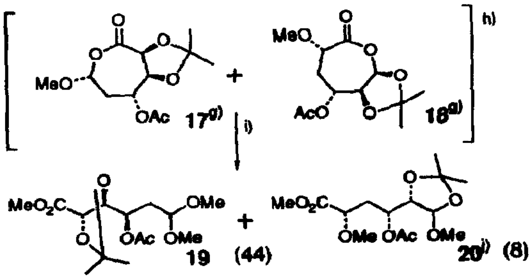
We have been engaged in the development of a new methodology in natural product synthesis by using cyclitols as chiral starting materials, and have demonstrated their versatility in the synthesis of several natural products.[1] The key feature of this approach resides in the regioselectivity in the Baeyer–Villiger reaction of polyhydroxycyclohexanone derivatives,[1] which effectively transfers an array of chiral centers in cyclitols into the stereogenic centers of acyclic or heterocyclic compounds. There have been numerous data on Baeyer–Villiger reaction[2] of unsymmetrical ketones, establishing the relative migratory aptitudes of alkyl and aryl groups in the reaction. However, study on the reaction of polyhydroxycyclohexanone derivatives possessing oxygen or other functionalities at α-carbons are limited,[1,3] and the migratory preference of such substituted carbons is still beyond prediction.[2,4] In order to expand the scope of our methodology, we undertook a study to clarify the governing factor to control the regioselectivity. In this letter, we wish to report the outcome of the experiments for a series of unsymmetrical polyhydroxycyclohexanone derivatives.

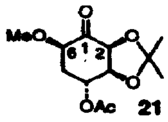
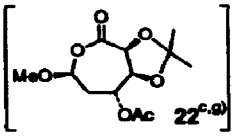
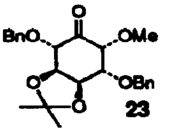
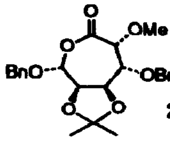
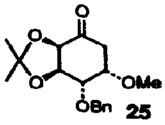
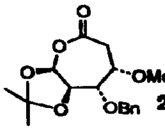
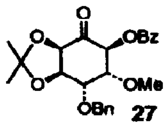
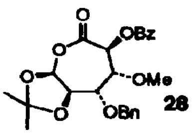
The substrates listed in Table 1[5,6] were synthesized by the PCC oxidation of the corresponding alcohols[5] which in turn were prepared from a naturally occurring optically active cyclitol, L-quebrachitol.[7]

These substrates were subjected to Baeyer–Villiger reaction[8] with m-chloroperbenzoic acid (mCPBA), and the results are summarized in Table 1. Reaction of ketones having a methyl at α and an ether or a ketal oxygen at α' position (run 1-4) always afforded the products in which the carbon bearing the oxygen atom had migrated. The regioisomeric products could not be detected in the crude reaction mixture. Reaction did not proceed for the ketone possessing a carbonate, more electron-withdrawing than ether and ketal functions (run 5).

On the other hand, in the case of ketones having an ether and a ketal oxygen at adjacent carbons to carbonyl (run 6-9), the ether-bearing carbons migrated in preference to those bearing ketal oxygen. In run 8 and 9, the products, 7-membered lactones (17, 18 and 22), were unstable to the purification with silica gel, so that the crude lactones were converted into ring-opened products for isolation. Interestingly, the migratory aptitude of a benzyloxy-substituted carbon is greater than that of a methoxy-substituted carbon (run 10). The carbon having a ketal oxygen, even though a rather poor migrator (*vide supra*), however, takes part in the migration in preference to a methylene (run 11) and a carbon with an acyloxy group (run 12).

Table 1. Baeyer–Villiger Reaction of Substituted Cyclohexanones[a]

Run	Ketone	Time / h	Product (yield /%)[b]
1	 1	2	 2[c] (74)
2	 3	3	 4[c] (62)
3	 5	3	 6[c] (48)[d]
4	 7	4	 8[c] (27)[d]
5	 9	2	No reaction[e]
6	 10	1	 11 (79) +  12 (2)
7[f]	 13	3	 14 (70) +  15 (5)
8	 16	2	

9	 21	1	 22[c,g] $\xrightarrow{i)}$ 19	(63)
10	 23	1	 24[c)]	(69)
11	 25	2	 26[c)]	(63)
12	 27	3	 28	(40)[d)]

Bn = -CH_2Ph
Bz = -C(O)Ph

a) All reactions were carried out at room temperature in the presence of mCPBA (3 equiv) and $KHCO_3$ (3 equiv). b) Isolated yield after silica gel chromatography. c) No regioisomer could be detected in the crude reaction mixture by ^1H NMR analysis. d) Partial decomposition of the product during chromatographic separation, which lowered the isolated yield, was observed. e) Starting ketone was recovered unchanged. Prolonged reaction (70 h) using excess mCPBA (20 equiv) and $KHCO_3$ (20 equiv) resulted in the decomposition of the ketone. f) 6 equiv of mCPBA and $KHCO_3$ were used. g) This compound could not be isolated due to its instability toward silica gel chromatography. h) ^1H NMR analysis of the crude reaction mixture revealed the ratio of 17 and 18 is 4.5:1. i) The crude reaction mixture was treated with 1) $CH(OMe)_3$, p-TsOH in MeOH, 5 °C, 2) $TMSCHN_2$, MeOH. Chromatographic separation afforded the pure ring-opened product(s). j) This was obtained as a single diastereomer. The stereochemistry at C(1) has not been determined.

The structures of the 7-membered lactones are nicely deducible by comparing their ^1H NMR spectra with those of the starting ketones; for example, in compound 5 and 6, the methine proton attached to the carbon bearing a methyl group was observed at δ 2.84 in ketone 5 and at δ 2.56 in the product 6, whereas the proton attached to the carbon possessing a ketal oxygen was observed at δ 4.57 in 5 and δ 5.97 in 6. The remarkable downfield shift of the methine proton of the carbon with a ketal oxygen clearly suggests the insertion of an oxygen between C(1) and C(2) of the ketone 5.

It is known that the migratory aptitude in Baeyer–Villiger reaction is attributed to electronic and conformational factors,[2] and the preferential migration occurs for the groups which can best support a positive charge by inductive effect or hyperconjugation, provided that no special conformational factors are involved.[2] It was suggested that the electronic effect is predominant in the substituted cyclohexanone system examined in this study, since the observed regioselectivity appears to be affected not by the configuration of the substrates, but the kind of substituents on the α-carbon. The inductive effect fails to account for the observed regioselectivity considering the lower migratory ability of methyl-substituted carbons compared to the oxygen-substituted ones.[9] A possible rationale is that the lone pair electrons on the oxygen attached to the α-carbon play an important role for directing migration. This view is consistent with the migratory trend of the oxygen-substituted carbons (ether > ketal > ester), suggesting that the n-electron density on the oxygen atom attached to the adjacent carbon to the carbonyl is of significance. Decrease in the regioselectivity observed in run 8 indicates that the conformational factor is important in some cases.[10] The results presented here as well as previous study[1a,b,2,3,9] show that the migratory aptitudes of substituted carbons adjacent to the carbonyl in the polyhydroxycyclohexanone system are: a carbon possessing benzyloxy > methoxy > ketal oxygen >> acyloxy ~ methyl > hydrogen.

In summary, regioselectivities observed in Baeyer–Villiger reactions of polyhydroxycyclohexanones derived from L-quebrachitol are reported. The optically pure 7-membered lactones, thus obtained, are useful chiral building blocks for natural product synthesis and, more importantly, it would be now possible to design polyhydroxycyclohexanone derivatives which undergo regioselective Baeyer–Villiger reaction.

REFERENCES AND NOTES

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2. For recent reviews of Baeyer–Villiger reaction, see: (a) Krow, G. R. *Organic Reactions;* Paquette, L. A. Eds.; John Wiley and Sons: New York. 1993, vol. 43; pp. 251–798; (b) Krow, G. R. *Tetrahedron* **1981**, *37*, 2697–2724; (c) Krow, G. R. *Comprehensive Organic Synthesis;* Trost, B. M. Eds.; Pergamon Press: Oxford. 1985, vol. 7; pp. 671–688. (d) Hudlicky, M. *Oxidation in Organic Chemistry, ACS Monograph 186*, American Chemical Society 1990, pp. 186–195.
3. Fukami, H.; Koh, H.-S.; Sakata, T.; Nakajima, M. *Tetrahedron Lett.* **1967**, 4771–4776; **1968**, 1701–1704.
4. Köll, P.; Dürrfeld, R.; Wolfmeier, U.; Heyns, K. *Tetrahedron Lett.* **1972**, 5081–5084.
5. The details of the preparation of these compounds will be reported in due course.
6. Ketone **21** was prepared by the base-induced epimerization of compound **16**.
7. van Alphen, J. *Ind. Eng. Chem.* **1951**, *43*, 141–145. See also ref. 1b. For utilization of L-quebrachitol in natural product synthesis, see Chida, N.; Yamada, K.; Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1957–1962, and references therein.
8. Typical experimental procedure: To a stirred suspension of ketone (0.1 mmol) and KHCO$_3$ (15 mg, 0.15 mmol) in 1,2-dichloroethane (2 mL) was added mCPBA (26 mg, 0.15 mmol) at room temperature. After being stirred for 1 h, additional mCPBA (26 mg, 0.15 mmol) and KHCO$_3$ (15 mg, 0.15 mmol) were added and the mixture was further stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc and then washed successively with 10% aqueous NaHSO$_3$ solution, saturated aqueous NaHCO$_3$ solution and brine, and dried over Na$_2$SO$_4$. Removal of the solvent afforded a residue, which was purified by silica gel chromatography with EtOAc–toluene (1:3) to give the product. In run 8 and 9, washing with NaHSO$_3$ and NaHCO$_3$ solution was omitted to avoid the decomposition of the product(s).
9. The preferential migration of the carbon with trimethylsilyloxy group over the carbon with methyl group in a cyclohexanone system (Rubottom, G. M.; Gruber, J. M.; Boeckman, Jr., R. K.; Ramaiah, M.; Medwid, J. B. *Tetrahedron Lett.* **1978**, 4603–4606) and an acetate-substituted carbon over a methylene carbon in the steroidal skeleton (Dave, V.; Warnhoff, E. W. *J. Org Chem.* **1983**, *48*, 2590–2598) have been reported.
10. The axially oriented oxygen substituent at α-carbon (C-2) in compound **16** should be responsible for the lower regioselectivity. Note that its 6-epimer **21** (run 9), which has equatorial oxygens at α- and α'-carbons, showed the high selectivity. These results suggest the possibility that the axially oriented oxygen substituent at the α-carbon accelerates the migration.

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