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Steric Control of the Epoxidation of 1-Hydroxymethyl-3-Cyclopentene Using Aryl or Silyl Hydroxyl Protecting Groups.

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Abstract *: A good anti-stereoselectivity is observed in the epoxidation of 1-hydroxymethyl-3-cyclopentene using tert-butyldimethylsilyl chloride as an hydroxyl protecting group (ratio anti:syn 8.2:1).*

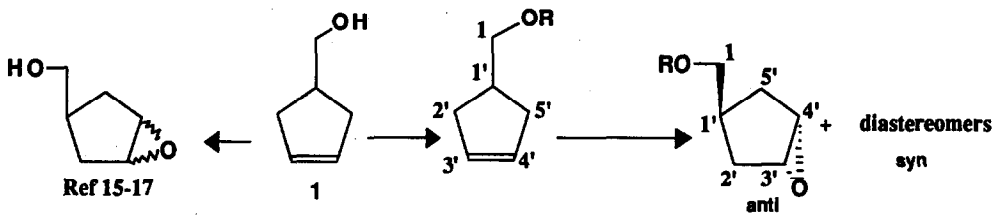
The well-known epoxidation of allylic and homoallylic alcohols [1-5] by organic peracids (3-chloroperbenzoic acid (MCPBA) or monoperoxyphtalic acid magnesium salt hexahydrate (MMPP) exclusively leads to the syn isomer. This result is due to hydrogen bonding between the hydroxyl group and the oxygen of the peracid [6-8].

The regioselectivity of epoxidation with organic peracids depends on electronic and steric interactions, favorising the approach of the peracid by one or another side of the plane which contains the alkene [8-11].

The 1-hydroxymethyl-3-cyclopentene epoxidation led to syntheses of functionalized cyclopentanes, precursors of carbocyclic analogues of nucleosides. These drugs are interesting because of their potential antiviral properties [12-14]. This epoxidation provided a 1.1:1 ratio [15-17] of anti:syn epoxides. Now, only the anti isomer is used in the course of synthetic studies on carbocyclic analogues.

Here, we describe studies comparing the influence of electronic and steric interactions of some hydroxyl protecting groups on the regioselectivity of the epoxidation by MCPBA.

The rigidity and the almost planeity of cyclopentenes and also the steric hindrance of the syn side by a free rotation of the hydroxyl protecting groups, favorise the majority formation of the anti isomer. Our aim was the study of epoxidation of 1-hydroxymethyl-3-cyclopentene (**1**), in which the hydroxyl group was protected with some functional groups. In this way, the (3'-cyclopentene)-1-methylbenzoate (**2**) R = Bz; the (3'-cyclopentene)-1-methyl-9-fluorenylmethyloxycarbonate (**3**) R = Fmoc; the (3'-cyclopentene)-1-methyl-triphenylsilylether (**4**) R = (Ph)3Si, and the (3'-cyclopentene)-1-methyl *tert*-butyldimethylsilylether (**5**) R = tBDMSi have been synthesized, then submitted to the epoxidation (see scheme 1).



2 R = Bz
3 R = Fmoc
4 R = (Ph)3Si
5 R = tBDMSi

6 R = Bz
7 R = Fmoc
8 R = (Ph)3Si
9 R = tBDMSi

Scheme 1

Experimentally, the alkenes **2** - **5** were treated with MCPBA in an aprotic solvent at gentle reflux (CH_2Cl_2, THF). Usual work-up afforded the corresponding epoxides **6** - **9** in fair yields [18-19].

After purification of the diastereomeric mixture, the anti isomer has been identified by the CH_2OR ^1H NMR analysis (chemical shifts and J-coupling constants). The constants and the chemical shifts were found to vary considerably from the syn or anti isomers; this variation is a characteristic of the quadrupolary effect of the O atom of the epoxide on the CH_2OR; for instance, when R = $(Ph)_3Si$-, $\delta_{CH_2OR\ anti}$ = 3.82-3.80 ppm , $^3J_{anti}$ = 4.6 Hz, and $\delta_{CH_2OR\ syn}$ = 3.67-3.63 ppm, $^3J_{syn}$ = 8.1 Hz.

Table I represents the ratio of anti:syn epoxides determined from ^1H NMR spectra and HPLC chromatograms.

R	ratio anti:syn
H	1.1:1 Ref 15-17
Bz	2.3:1
Fmoc	3:1
(Ph)3Si	4:1
tBDMSi	8.2:1

Table I : Ratios of Anti:Syn Epoxides

The predominance of anti products which we have obtained, is attributed to the steric hindrance of the syn side. The decrease of electronic interactions, using some silyl hydroxyl-protecting groups, favorises the anti epoxides. The most pronounced anti directive effect (8.2:1 anti:syn) is achieved by means of *tert*-butyldimethylsilylether.

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18 All new compounds **2 - 9** were purified by column chromatography or HPLC and product structures were determined by infrared, high resolution ms, 200 MHz ^1H NMR and ^{13}C NMR.
19 Selected spectroscopic data for (**5**) : *^1H NMR $\delta(CDCl_3)$ 5.63 (s, 2H, C_3-H, C_4-H), 3.51-3.45 (d, ^3J = 5.7 Hz, C_1-H_2), 2.50-2.05 (m, 5H, C_2-H_2, C_5-H_2, C_1-H), 0.90 (s, 9H, tBu), 0.04 (s, 6H, $(CH_3)_2Si$). ^{13}C NMR (DEPT) $\delta(CDCl_3)$ 129.4 (C_3, C_4), 64.8 (C_1), 39.2 (C_1), 35.3 (C_2, C_5), 25.6 (tBu), -5.3 ($(CH_3)_2Si$). IR ν (cm^{-1}) 3049, 1612, 1472-1464. MS : (M+) 212.*
Selected spectroscopic data for (**9**) : *^1H NMR δ $(CDCl_3)$ 3.54-3.51 (d, 2H, ^3J = 4.6 Hz, C_1-H_2), 3.44 (s, 1H, C_3-H, C_4-H), 2.11-1.94 (m, 3H, C_1-H, C_2-H_β, C_5-H_β), 1.52-1.41 (m, 2H, C_2-H_α, C_5-H_α), 0.87 (s, 9H, tBu), 0.01 (s, 6H, $(CH_3)_2Si$.). ^{13}C NMR (DEPT) $\delta(CDCl_3)$ 64.6 (C_1), 57.2 (C_3, C_4), 35.2 (C_1), 30.5 (C_2, C_5), 25.8 (tBu), -5.4 ((Me)2Si)). IR ν (cm^{-1}) 3028, 2955-2958, 1472, 1258, 1090, 837. MS : (M^+) 228.*

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