Tetrahedron Letters, Vol.32, No.47, pp 6943-6946, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Stereoselective Epoxidation of Asymmetrized 2-Alkenyl-1,3-Propanediols.

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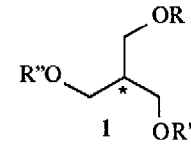
Summary: Asymmetrized 2-alkenyl 1,3-propanediols are stereoselectively epoxidized to the same main diastereoisomer both with 3-chloroperbenzoic acid and the $VO(acac)_2$ / t-butyl hydroperoxyde system. Using the latter epoxidating reagent in combination with a protection-deprotection sequence involving the two homoallylic hydroxy groups, all the four *cis* epoxides were easily achieved in stereoisomeric pure form starting from a single common *(Z)* precursor.

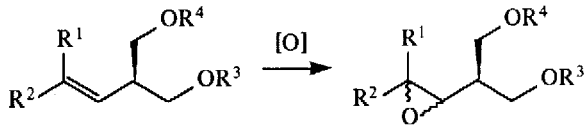
Epoxides are highly versatile intermediates useful for the synthesis of many biological targets[1] and the stereoselective epoxidation reaction of allylic and homoallylic alcohols[2] is one of the most general way for the achievement of these compounds. Actually the importance of the epoxidation in asymmetric synthesis is strictly linked to the possibility of constructing, through these intermediates, polystereogenic organic molecules of any desired configuration at the new asymmetric centres.

Recently we reported[3] on the preparation (by a chemoenzymatic procedure, e.e. > 95%) and the synthetic exploitation of asymmetrized *tris*(hydroxymethyl)methane (THYM*) **1**, which is a new polyfunctionalized chiral C_4 building block endowed with high latent symmetry and useful for the synthesis of many natural products.[3e]



In connection with these studies, we now report the results of stereoselective epoxidation of variously monoprotected *(E)*(**2a-c**) or *(Z)*(**3a-g**) 2-(1-pentenyl)-1,3-propanediols,[4] which are homoallylic diols having both hydroxyls at the same distance and on the same side with respect to the double

Scheme 1



2a-c: R^1 = H, R^2 = Pr

3a-g: R^1 = Pr, R^2 = H

Pr = $MeCH_2CH_2$

	R^3	R^4
a	Ac	H
b	Bn	H
c	H	TBDMS
d	H	TBDPS
e	H	TIPS
f	H	Tr
g	H	PMBOM

Bn = $PhCH_2$ TBDMS = Bu^tMe_2Si TBDPS = Bu^tPh_2Si TIPS = $(Me_2CH)_3Si$
Tr = Ph_3C PMBOM = 4-$MeOC_6H_4CH_2OCH_2$

Table 1. Epoxidation of mono-protected homoallylic diols (E) 2a-c and (Z) 3a-g

Entry	Subs	Configuration	R^3	R^4	Method	Yield (%)[a]	*anti : syn* ratio[b, c]
1	**2a**	*(E)-(S)*	Ac	H	A	84	54 : 46
2	**2b**	*(E)-(S)*	Bn	H	A	86	51 : 49
3	**2c**	*(E)-(R)*	H	TBDMS	A	77	57 : 43
4	**2a**	*(E)-(S)*	Ac	H	B	58	50 : 50
5	**2c**	*(E)-(R)*	H	TBDMS	B	96	68 : 32
6	**3a**	*(Z)-(S)*	Ac	H	A	82	64 : 36
7	**3b**	*(Z)-(S)*	Bn	H	A	71	80 : 20
8	**3c**	*(Z)-(R)*	H	TBDMS	A	79	70 : 30
9	**3d**	*(Z)-(R)*	H	TBDPS	A	72	85 : 15
10	**3f**	*(Z)-(R)*	H	Tr	A	95	79 : 21[d]
11	**3a**	*(Z)-(S)*	Ac	H	B	38	72 : 28
12	**3b**	*(Z)-(S)*	Bn	H	B	56	> 95 : 5
13	**3c**	*(Z)-(R)*	H	TBDMS	B	63	> 95 : 5
14	**3d**	*(Z)-(R)*	H	TBDPS	B	57	> 95 : 5
15	**3e**	*(Z)-(R)*	H	TIPS	B	61	> 95 : 5
16	**3f**	*(Z)-(R)*	H	Tr	B	90	> 95 : 5[d]
17	**3g**	*(Z)-(R)*	H	PMBOM	B	74	> 95 : 5

Method A: MCPBA, anhydrous CH_2Cl_2, r.t. **Method B**: $VO(acac)_2$, *t*-BuOOH, anhydrous CH_2Cl_2, r.t.

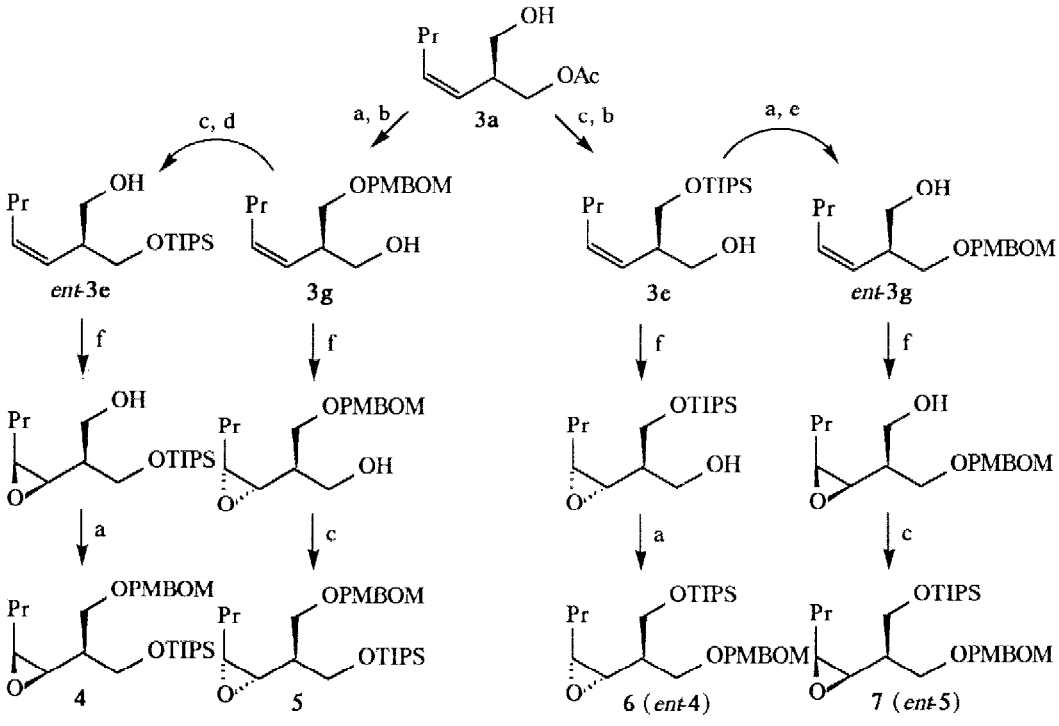
[a] Isolated (*anti* + *syn*) yields. [b] Determined by ^1H n.m.r. spectroscopy. In some cases, diastereoisomeric ratio was confirmed by isolating (flash chromatography) and weighing single diastereoisomers. [c] For a definition of *anti* isomer, see note 5. Stereochemistry of products was established for epoxides obtained from **3c** and **3f**, through n.m.r. analysis of 1,3-dioxanes obtained after chromatographic separation of diastereoisomeric epoxides, their reductive opening, and cyclic protection of the resulting diols (see note 6). Chromatographic and spectroscopic analogies were used in other cases. The enantiomeric purity of substrates and products was checked on compounds **3c**, **3d**, and the epoxide from **3f** by ^1H n.m.r. analysis of the corresponding *(S)* and *(R)* Mosher's esters, which showed that no appreciable variation of e.e. occurred during the reactions. With regard to **3b**, when **3a** was directly subjected to benzylation under basic conditions only racemic **3b** was obtained, while procedure reported in note 4 afforded partially racemized **3b** (e.e. ≈ 60%). [d] Determined by t.l.c. spectrodensitometry (λ 254 nm).

bond (Scheme 1). The reaction was studied with two different oxidation reagents (Method A: 3-chloroperbenzoic acid, anhydrous CH_2Cl_2, r.t.;[2d] Method B: $VO(acac)_2$, *t*-BuOOH, anhydrous CH_2Cl_2, r.t.[2e]) and the chemical and stereochemical results are reported in Table 1.

The general preference for the *anti*[5, 6] product and the higher selectivity observed for *(Z)* homoallylic alcohols especially with Method B is in accordance with the models normally accepted for this type of reactions.[2d, e]

With regard to the achievement of the *syn* product in the epoxidation of *(Z)* unsaturated alcohols, it must be stressed that the problem has been object of interest from different research groups and only recently some suitable practical solutions have been proposed.[2f, h] Here we wish to show that in the case of our *(Z)* substrates, thanks to the high latent symmetry present in the propanediol moiety of the molecule, the stereoselective obtainment of the *anti* product enables the straightforward achievement of the *syn* one as well, through a simple protection-deprotection trick applied to the two homoallylic OH groups. Moreover, since starting from monoacetate **3a** each monoprotected alcohol **3b-g** and his enantiomer[7] can be easily achieved (in Scheme 2 the case of **3g** and **3e** is exemplified), it follows that a suitable combination of protection-deprotection and epoxidation reactions allows the preparation of all the four stereoisomeric *cis* epoxides starting from a single common precursor. Since compounds **4-7** are highly versatile intermediates that can be elaborated in different ways, the herein reported strategy for a predictable construction of contiguous chiral centres can find useful application in asymmetric synthesis of many polystereogenic natural compounds.

Scheme 2



a) PMBOM-Cl, *i*-Pr_2NEt, CH_2Cl_2. b) KOH, MeOH. c) *i*-Pr_3SiCl, 2,6-lutidine, CH_2Cl_2, 0°C.
d) DDQ, CH_2Cl_2, *t*-BuOH, pH 7 buffer. e) *n*-Bu_4NF, THF. f) TBHP, $VO(acac)_2$, CH_2Cl_2.

Researches are in progress in our laboratory and the results will be soon published.

We wish to thank Miss Valeria Merlo for her enthusiastic and valuable collaboration in this w MURST and Progetto Finalizzato Chimica Fine II for financial support.

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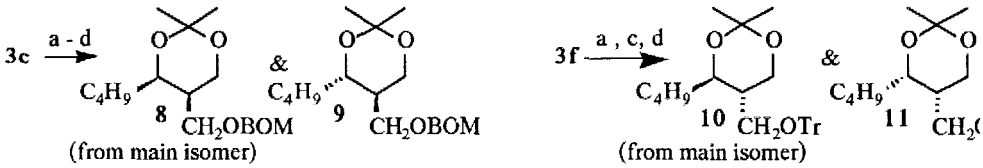
4) Homoallylic alcohols **2b-c** and **3b-g** were prepared starting from *(E)-(S)* or *(* 2-(acetoxymethyl)hept-3-en-1-ol (**2a** or **3a**)[3b,d] [**2b** & **3b**: i, TBDMS-Cl, imidazole, DMF; ii, KOH, iii, BnBr, NaH, DMF; iv, *n*-Bu4NF, THF; **2c** & **3c**: i, TBDPS-Cl, imidazole, DMF; ii, KOH, MeOH TBDPS-Cl, imidazole, DMF; ii, KOH, MeOH; **3c**: i, TIPS-Cl, 2,6-lutidine, CH_2Cl_2, 0°C; ii, KOH, **3f**: i, Tr-Cl, Et_3N, DMAP, CH_2Cl_2; ii, KOH, MeOH; **3g**: i, PMBOM-Cl, *i*-Pr_2NEt, CH_2Cl_2; ii, MeOH].

5) *Anti* isomer is here defined as the one having the oxiranic ring and the alkoxymethyl substitue opposite side in the zigzag drawing of epoxides.

6) ^1H N.m.r. spectra for 1,3-dioxanes (see note c in Table 1) show that coupling constant of pr the ring are quite low for **8** [$J_{5,6}$ = 1.6 & 2.8 Hz ($CDCl_3$)] and **11** [$J_{4/5}$ = 2.5 Hz, $J_{5/6}$ = 1.6 & ($CDCl_3$), $J_{5/6}$ = 1.5 & 2.7 Hz (C_5D_5N)], while for **9** and **10** they were not determined (complex multi $CDCl_3$, but spectra patterns indicates that they are certainly higher; moreover, in C_5D_5N **10** shows J_5 & 12.1 Hz. In connection with ^{13}C n.m.r. data ($CDCl_3$) for methyl groups at C-2 (19.19 & 29.87 for & 29.23 for **9**, 19.07 & 29.62 for **10**, 19.63 & 29.36 for **11**), which confirm a preferred chair confo for all examined 1,3-dioxanes (see D.A. Evans, D.L. Rieger, J.R. Cage, *Tetrahedron Lett.*, **1990**, *31* S.D. Rychnovsky, D.J. Skalitzky, *Tetrahedron Lett.*, **1990**, *31*, 945), these data indicate a *cis* 4,5-eq axial substitution for **8** and **11** and a *trans* 4,5-diequatorial substitution for **9** and **10**.



a) Epoxidation & diastereoisomers chromatographic separation. b) $PhCH_2OCH_2Cl$ (BOM-(*i*-Pr_2NEt, CH_2Cl_2. c) $LiAlH_4$, THF / Et_2O, reflux. d) 2-Methoxypropene, PTSA, CH_2Cl_2.

7) See note c in Table 1.

(Received in UK 30 July 1991)