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THE OSMYLATION OF FLEXIBLE 3-SUBSTITUTED CYCLOPENTENES

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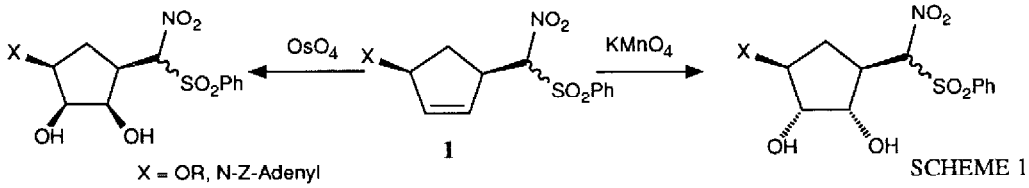
Summary: The osmylation of several 3-substituted cyclopentenes has been studied. A preference for OsO_4 addition *syn* to an allylic CHR_2 substituent is observed. By contrast, bulkier substituents of type $CMeR_2$ give rise to a striking reversal of selectivity. These results are interpreted in terms of the stereodivergent nature of the two differently reactive envelope conformations.

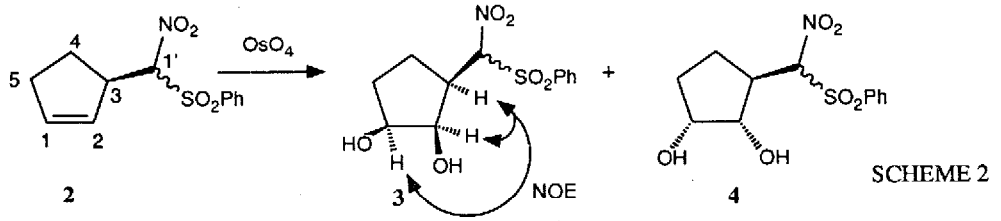
The understanding of the stereochemical outcome in the osmylation of 3-substituted cyclopentenes is a challenging problem. Only a few examples[1] have been reported in the literature to date, and no clear trends can be formulated yet.

Trost and coworkers[2], for example, have recently shown that osmylation of nitrosulfone **1** takes place with complete *syn* selectivity. Since the opposite preference was observed with $KMnO_4$, the hypothesis of an osmium-coordinating nitro group has been put forward (Scheme 1).



SCHEME 1

In order to obtain a deeper insight into this problem, nitrosulfone **2**[3] has been tested as a simpler model. *Cis*-dihydroxylation of **2** under several different conditions gave the expected diastereomeric diols **3** and **4** as 50 : 50 epimeric mixtures at C-1' (Scheme 2, Table 1).



2 3 4

SCHEME 2

The stereochemical assignment of the epimeric mixtures is based upon:

- Selective crystallization ($CDCl_3$) of **3** as a single epimer at C-1' and subsequent NEt_3 mediated re-equilibration
- NOE difference experiments as shown on scheme 2

TABLE 1 Cis-dihydroxylation of nitrosulfone **2**[4]

EXP	OXID 1	EQUIV.	OXID 2	SOLV	3:4
1	OsO_4	0.01	NMO H_2O	THF:H_2O 10:1	***69:31***
2	OsO_4	0.01	Me_3NO $2H_2O$	Me_2CO:H_2O 8:1	***65:35***
3	OsO_4	0.01	Me_3NO $2H_2O$	THF:H_2O 10:1	***75:25***
4	OsO_4	1.0		THF:H_2O 10:1	***64:36***
5	OsO_4py	1.0		THF:H_2O 10:1	***57:43***
6	OsO_4	0.01	Me_3NO $2H_2O$	$CHCl_3$	***91:9***
7	$OsCl_3$	0.01	Me_3NO $2H_2O$	$CHCl_3$	***94:6***
8	OsO_4	1.0		$CHCl_3$	***90:10***
9	OsO_4	0.01	Me_3NO $2H_2O$	CH_2Cl_2	***92:8***

The results in table 1 deserve some comments:

In line with Trost's results, stereoselectivity is always in favor of the *syn* isomers. A marked solvent effect is noticeable, apolar media giving better selectivities. Catalytic and stoichiometric conditions afford comparable results.

Directed osmylations have been reported in the literature.[5] In these cases a complexation between OsO_4 and a "hard" oxygen has been proposed or is reasonably envisageable. In light of the known affinity of amine N-oxides for osmium VI,[6] an analogous RNO_2-osmium interaction was initially considered. However, ^{1}H-, ^{13}C-, ^{17}O-NMR, and I.R. spectra of $O_2NCH(R)SO_2Ph$ (R = H or Me) in the presence of OsO_4 did not show any apparent complexation.

Additional information came from the investigation of other analogues. Accordingly, cyclopentenes **5-11** were synthesized[3] and tested towards osmylation.

As can be seen from scheme 3, *syn* selectivity is not a peculiarity of the phenylsulfonylnitromethane moiety. Indeed, exchanging the NO_2 with CN (compare **2** with **5**) or removing the sulfonyl group (compare **2** with **6**) did not reverse but lowered the *syn* selectivity, whereas replacing the NO_2 group for SO_2Ph gave a stereorandom result.

By contrast, osmylation of the methyl analogues **7**, **9**, and **11**, brought about a striking inversion in the π-face differentiation affording the *anti* products with very high selectivities.

It is known that cyclopentenes adopt envelope conformations with a very low barrier to inversion through the planar form.[7] Applying the Karplus equation[8] to the $J_{5\text{-}6(cis)}$ and $J_{5\text{-}6(trans)}$ (see scheme 2 for numbering) of their ^{1}H-NMR spectra, allows estimation of the degree of pucker and of the conformational population respectively. In all the cases where such an analysis was possible a virtually even population for the two possible envelopes was found. Moreover, the $J_{1\text{-}2}$= 9-10 Hz in compounds **2** and **10** suggests a strong preference for a staggered anti H-C1-C2-H disposition, which is not the case for disulfone **8** ($J_{1\text{-}2}$= 3 Hz).

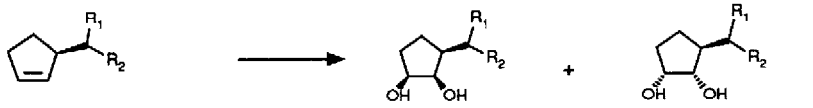
The stereochemical results of these osmylations can be interpreted in terms of the stereodivergent nature of the equilibrating, but differently reactive,[9] conformers A and B (Scheme 4). Maximum staggering reasons[10] as well as the expected deplanarization[11] of the olefinic hydrogen atoms in the ground states allow to anticipate reactivity in the directions described.[12]

The *syn* preference observed with the 3-CHR_2-substituted cyclopentenes **2**, **5**, **6**, and **10** (entries 3, 1, 2, and 7) is clearly against simple steric factors, and coordination (compare **2** with **7**) is unlikely.

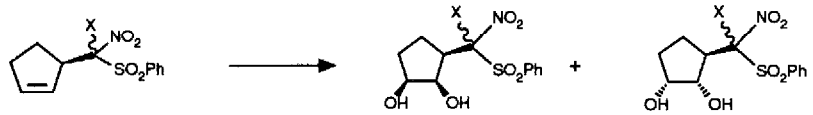
On the other hand, we suggest that the differential H_2/H_3 versus H_2/C_1, eclipsing experienced in the progressive pyramidalization of A and B along the reaction coordinate towards a rather late transition state,[13] may be important.

SCHEME 3 Cis - Dihydroxylation of 3-substituted cyclopentenes [a]

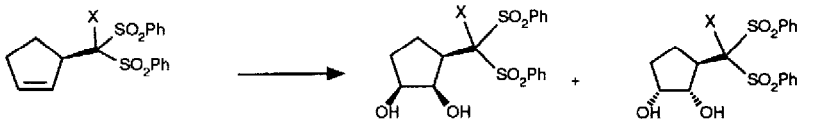
ENTRY



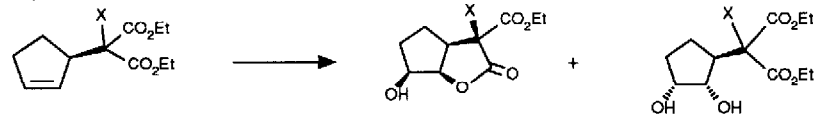
1. [b]	**5** $R^1 = CN$; $R^2 = SO_2Ph$	*73*	*27*
2. [c,d]	**6** $R^1 = H$; $R^2 = NO_2$	*73*	*27*



3. [c]	**2** X = H	*92*	*8*
4. [c,f]	**7** X = Me	*≤ 5*	*≥ 95*



5.	**8** X = H	*50*	*50*
6. [c]	**9** X = Me	*≤ 1*	*≥ 99*



7. [b]	**10** X = H	*75*	*25*
8. [e]	**11** X = Me	*≤ 1*	*≥ 99*

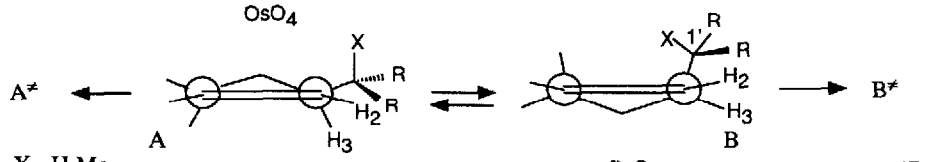
Notes: a] See ref. 4; isolated chemical yields 90-95%. b] Immediate lactonization of the *syn* diastereomers can be obtained by addition of cat. PTSOH just before work-up or by dil. HCl washing during work-up. c] NOE difference experiments allowed the stereochemical attributions. d] Bu_3SnH reduction of **3** gave the same major diol of this exp. e] No lactonization under the conditions described in b. allowed assignment of the *anti* stereochemistry. f] $KMnO_4$ dihydroxylation gave the same stereochemical result.

Such a torsional effect, which favors A$^{\neq}$over B$^{\neq}$, will be at work with 3-CHR_2 substituted cyclopentenes featuring anti HC_3-C_1-H disposition, since neither π face is particularly hindered.[14]

By contrast, in the 3-$CMeR_2$ substituted derivatives, the top face of both conformers is heavily congested. As a result, allylic group-reagent steric interactions become dominant and OsO_4 addition can proceed only *via* B.

Although this model is consistent with the observed results, it should be kept in mind that subtle changes in such flexible rings may heavily affect the relative reactivities and populations of the conformers in a rather complex way. So for example, the reasons dictating the *anti* selectivity in the osmylation of 3-heterosubstituted cyclopentenes[1] have necessarily to be of different nature.[15]

From a synthetic point of view it is worth mentioning that the catalytic osmylations described in scheme 3 can be performed under virtually anhydrous conditions. Indeed, $Me_3NO\ 2H_2O$, although sparingly soluble in CH_2Cl_2 at the beginning of the reaction, is capable of bringing about the osmate oxidation/hydrolysis with excellent osmium turnover thereby avoiding the traditional use of H_2O as co-solvent. Such a simple but relevant modification should prove of value when *in-situ* diol protection is desired.[16]



SCHEME 4

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Present address: Dipartimento di Chimica Organica e Industriale, Università di Milano, Italy

1.a) Christ W.J., Cha J.K., Kishi Y., Tetrahedron Lett., **1983**, *24*, 3943, and 3947; b) Deardorff D.R., Shambayati S., Myles D.C., Heerding D., J.Org.Chem., **1988**, *53*, 3614; c) Wolkzunowicz G., Cocu F.C., Posternak Th., Helv. Chim. Acta, **1970**, *53*, 2275 and 2286; d) Steyn R., Sable H.Z., Tetrahedron, **1969**, *25*, 3579; e) Vince R, Daluge S., J.Org.Chem, **1980**, *45*, 531; f) Whitten J.P., Mc Carthy J.R., Whalon M.R., J.Org.Chem., **1985**, *50*, 4399; g) Hanselaer R., Samson M., Vandewalle M., Tetrahedron, **1978**, *34*, 2393; h) Hacksell U., Daves G.D. Jr., J.Org.Chem., **1983**, *48*, 4144; i) Johnson C.R., Penning T.D., J.Am.Chem.Soc., **1988**, *110*, 4726.

2.Trost B.M., Kuo G.H., Benneche T., J.Am.Chem.Soc., **1988**, *110*, 621.

3.Except for compound **10** (Kozikowski A.P., Mugrage B.B., Wang B.C., Xu Z.B., Tetrahedron Lett., **1983**, *24*, 3705 and ref. quoted) the cyclopentenes described in this work were unknown. All new compounds gave satisfactory spectral and analytical data. A detailed preparation of the cyclopentenes will be reported in a full paper.

4.In a typical procedure to a 0.05 molar solution of the substrate in dry CH_2Cl_2, $Me_3NO\ 2H_2O$ (1.3 equiv.) and OsO_4(0.01 equiv, 2.5% soln. in CCl_4) were added. After 4-15 hrs. stirring the rxns were over. Direct filtration through a small pad of silica gel (AcOEt elution) gave the desired alcohols.

5.a) Hauser F.M., Ellenberger S.R., Clardy J.C., Bass, L.S., J.Am.Chem.Soc, **1984**, *106*, 2458; b) Johnson C.R., Barbachyn M.R., J.Am.Chem.Soc., **1984**, *106*, 2459.

6.Jacobsen E.N., Marko I., France M.B., Svendsen J.S., Sharpless K.B., J.Am.Chem.Soc., **1989**, *111*, 737.

7.See for example: Allinger N.L., Dodziuk H., Rogers D.W., Naik S.N., Tetrahedron, **1982**, *38*, 1593. Force field calculations performed on compounds **10** and **11** indicated the two expected envelopes as the most stable and virtually isoenergetic forms (δE=0.1-0.3 Kcal/mol).

8.The following equation was used: $^3J=12.9\ \cos^2\varphi - 0.32\ \cos\varphi$ (Bakke J.M., Schie A.M., Skjetne T., Acta Chem Scand., **1986**, *B40*, 703) see also ref. 1g.

9.Seeman J.I., Chem.Rev., **1983**, *83*, 83.

10.Paddon-Row M.N., Rondan N.G., Houk K.N., J.Am.Chem.Soc, **1982**, *104*, 7162.

11.*a)* Seebach D., Zimmermann J., Gysel U., Ziegler R., Ha T-K., J.Am.Chem.Soc., **1988**, *110*, 4763; *b)* Burkert U., Angew.Chem.Int.Ed. **1981**, *20*, 572; Houk K.N., Rondan N.G., Brown F.K., Jorgensen W.L., Madura J.P., Spellmeyer D.C., J.Am.Chem.Soc., **1983**, *105*, 5980.

12.This assumption is also in line with the study on the suprafacial cis-addition to cyclopentenes using the torsion angle notation: Toromanoff E., Tetrahedron, **1980**, *36*, 2809, ibidem **1979**, *35*, 893.

13.a)Vedejs E., Mc Clure C.K., J.Am.Chem.Soc., **1986**, *108*, 1094; b) Vedejis E., Dent III W.H., Gapinski D.M., McClure C.K., J.Am.Chem.Soc., **1987**, *109*, 5437.

14.An alternative rationale based on the preferred antiperiplanar disposition OsO_4/C-H versus OsO_4/C-C in the two competing transition states seems unlikely also in view of the observed absence of hyperconjugative effects in osmylations. Ref 13a.

15.An axial orientation of the reactive form has been noticed in nitrile oxide 1.3-dipolar cycloadditions to 3-methoxy-cyclopentene: Caramella P., Cellerino G., Tetrahedron Lett., **1974**, 229; and ref. 12. See also Chamberlin R., Mullholland R.L., Kahn S.D., Hehre W.J., J.Am.Chem.Soc., **1987**, *109*, 672.

16.Preliminary experiments showed succesful acetylations as well as cyclic sulfites formation.

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