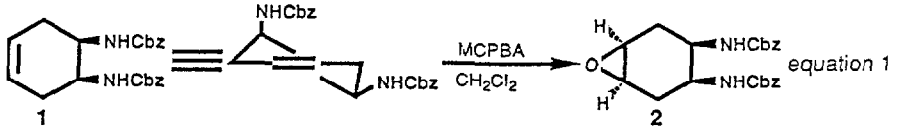
Tetrahedron Letters,Vol.30,No.15,pp 1913-1916,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

HOMOALLYLICALLY CONTROLLED EPOXIDATION OF Δ^4-CIS-1,2-DISUBSTITUTED CYCLOHEXENES

David P. Rotella
Department of Pharmacognosy
School of Pharmacy
University of Mississippi
University, MS 38677

ABSTRACT: Stereochemical control during the epoxidation of *cis*-1-[N-Cbz]-2-[hydroxymethyl]-cyclohex-4-enes with MCPBA is dependent on hydroxyl functionalization which apparently determines ring conformation. Unprotected or acetate-derivatized compounds afford exclusively syn epoxide products. Silyl ether protected analogs furnish predominantly products derived from anti delivery of oxygen. Respective 2-carbomethoxy and benzyl carbamate-protected aminomethyl derivatives show stereospecificity similar to the free hydroxyl and acetate-protected substrates.

The stereoelectronic directing effect of an allylic alcohol or protected amine during peracid-mediated epoxidation of olefins is well documented[1] and has been attributed to hydrogen bonding between the oxidant and polar moiety[2]. Recently we[3] and others[4] have demonstrated that homoallylic carbamate-protected nitrogen atoms that occupy pseudoaxial positions on a cyclohexene ring may also direct syn oxygen delivery to the olefin as shown in equation 1.[5]

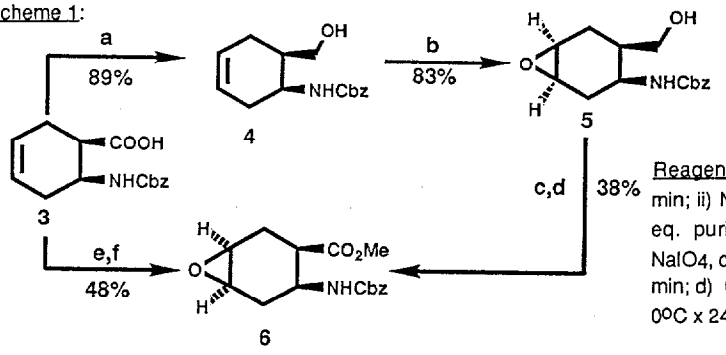


1 2 equation 1

Obviously a compound such as **1** represents a best case scenario for observation of this electronic influence by virtue of the symmetrical orientation of nitrogen in the molecule. It was of interest, therefore, to examine dissymmetric systems in order to determine the extent of the generality of this nitrogen-mediated directing effect and develop stereocontrolled routes to highly substituted and functionalized cyclohexane rings.

Thus, epoxidation of alcohol **4**, derived from *cis* β-amino acid **3**, gave in 83% yield a single epoxide **5** as demonstrated by ^1H and ^{13}C spectroscopy.[6] Although it was not possible to assign the relative stereochemistry of the product by NMR methods, the compound was transformed into epoxy ester **6** by ruthenium-catalyzed oxidation[7] followed by esterification with diazomethane in 38% overall yield. This material proved to be identical in all respects to the epoxy ester obtained by iodolactonization of **3** (73%), followed by treatment with K_2CO_3 in MeOH at room temperature overnight (66%) (Scheme 1).

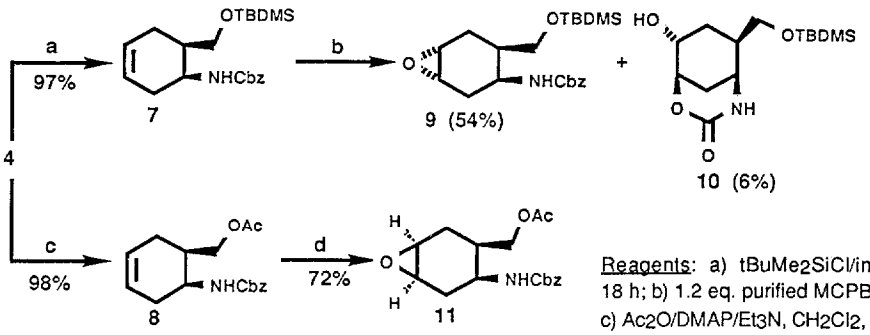
Scheme 1:



Reagents: a) i) iBuOCOCl/Et3N, THF, 0°C x 45 min; ii) $NaBH_4/H_2O$, 0°C to RT overnight; b) 1.2 eq. purified[8] MCPBA, CH_2Cl_2, RT x 17 h; c) $NaIO_4$, cat. $RuCl_3$-H_2O/CH_3CN-CCl_4-H_2O, RT x 40 min; d) CH_2N_2/THF; e) I_2/$NaHCO_3$; $CHCl_3$-H_2O, 0°C x 24 h; f) 1.05 eq. K_2CO_3/MeOH, RT x 16 h.

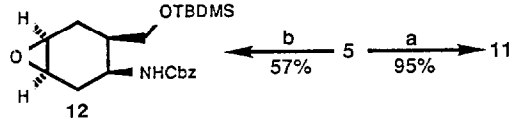
Interestingly, similar treatment of acetate **8** also led exclusively to syn epoxidation, affording **11** in 72% yield, while TBDMS ether **7** furnished predominantly products **9**[6] and **10**[6] derived from *anti* addition of oxygen (Scheme 2). The stereochemistry of epoxides **9** and **11** were assigned by correlation with epoxy alcohol **5** according to the transformations outlined in Scheme 3. Epoxy acetate **11** proved to be identical to the product derived from acetylation of **5**; silylation of **5** produced **12**, an epoxide diastereomeric with **9**.[6]

Scheme 2:



Reagents: a) $tBuMe_2SiCl$/imidazole, DMF, RT x 18 h; b) 1.2 eq. purified MCPBA,CH_2Cl_2, RT x 18h; c) Ac_2O/DMAP/Et_3N, CH_2Cl_2, 0°C x 1 h; d) 1.2 eq. purified MCPBA, CH_2Cl_2, RT x 16 h.

Scheme 3:



Reagents: a) Ac_2O/DMAP/Et_3N, CH_2Cl_2, 0°C x 30 min; b) $tBuMe_2SiCl$/imidazole, DMF, RT x 17 h.

The outcome of these experiments can be understood based on the conformational disposition of the amino group in olefins **4**, **7** and **8**. It was not possible to directly ascertain the orientation of the carbamate moiety by analysis of the coupling constants for the associated methine hydrogen. This resonance signal was observed in all three compounds as

a complex multiplet not readily simplified by homonuclear decoupling experiments. However, chemical shift comparisons (Table 1, recorded at ambient temperature) for this proton and the adjacent methine hydrogen provide evidence consistent with the notion that upon silylation, but not acetylation or in the free alcohol, the molecule adopts a conformation with the benzyl urethane moiety in a pseudoequatorial disposition. As a consequence of this shift, the nitrogen would be unavailable to stereoelectronically control epoxidation of the olefin by MCPBA.[9]

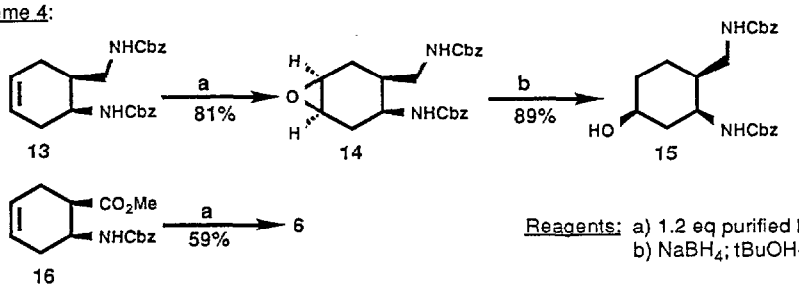
Table 1 ^{1}H CHEMICAL SHIFT DATA[a]

compound	NHCbz methine proton	CH_2OR' methine proton
4 (R=H)	4.25	1.96
7 (R=Ac)	4.18	2.12
8 (R=TBDMS)	4.06	2.14

[a]Spectra were recorded at 300 MHz in $CDCl_3$ solution at ambient temperature.

The generality of these results have been extended to include other 1,2-disubstituted-Δ^4-cyclohexenes. Diamine **13** affords solely **14** in 81% yield. The stereochemical outcome of this reaction was determined by conversion to alcohol **15** and observation of a 1,3-interaction between the methine protons at C1 and C3 in the NOESY spectrum. Epoxidation of ester **16** provided a single oxirane product in 59% yield which was identical in all respects to **6** prepared unambiguously as described above.

Scheme 4:



We are currently exploring the opportunities presented by these observations within the context of the synthesis of modified aminocyclitol antibiotics[10] as well as in the preparation of novel functionalized diamines for use as ligands for antineoplastic Pt (II) complexes[3].

ACKNOWLEDGEMENTS: *This research was assisted in part by a Faculty Research Grant from the University of Mississippi. The author wishes to thank Mr. Frank Wiggers for recording the NMR spectra, Dr. Charles D. Hufford for helpful discussions and Mrs. Jane Bryan for typing this manuscript.*

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6. Spectroscopic data ($CDCl_3$, ^1H 300 MHz, ^{13}C 75 MHz): **5**:$^1H\delta$ 7.36 (s, 5H), 5.67-5.72 (m, 1H), 5.55-5.63 (m, 1H), 5.11 (s, 2H), 4.81-4.92 (br d, 1H J=10 Hz), 4.20-4.29 (m, 1H), 3.63 exchange with D_2O, dd, 1H, J=5, 10 Hz), 3.50 (dd, 1H, J=5, 12 Hz), 3.27 (dd, 1H, J=10, 12 Hz), 2.39-2.50 (m, 1H), 1.90-2.15 (m, 3H), 1.52-1.64 (m, 1H). ^{13}C:δ 158, 136, 128.6, 128.5, 128.4, 128.3, 128.2, 126, 123, 67, 63, 44, 39, 31, 23. **6** ^1H δ 7.34 (s, 5H), 5.77 (br d, 1H, J=10 Hz), 5.06 (s, 2H), 4.06-4.15 (m, 1H), 3.67 (s, 3H), 3.18 (br s, 2H), 2.62 (dd, 1H, J=7, 15 Hz), 2.50 (ddd, 1H, J=3,7,8 Hz), 2.19 (dd, 1H, J=3,6 Hz), 2.13 (dd, 1H, J=3,6 Hz), 2.08 (dd, 1H, J=3,6 Hz). ^{13}C: 173, 156, 136, 128.4, 128, 67, 52, 51.5, 50.8, 46, 40, 29, 24. **9**:^1H δ: 7.34 (s, 5H), 5.72 (d, 1H, J=9 Hz), 5.06 (AB quartet, 2H, J=12 Hz), 3.92-4.01 (m, 1H), 3.68 (dd, 1H, J=6,9 Hz), 3.29 (dd, 1H, J=6,11 Hz), 3.21 (br s, 2H), 2.02-2.22 (m, 3H), 1.60-1.79 (m, 2H), 0.88 (s, 9H), 0.20 (s, 6H). ^{13}C: 156, 137, 128.4, 127.9, 66, 65, 52, 51, 45, 38, 30, 25, 24, 18, -5.4, -5.7. **10** ^1H (pyridine-d_5) δ: 4.71 (br s, 1H), 4.44 (br s, 1H), 3.82 (br s, 1H), 3.68 (dd, 1H, J=8, 10 Hz), 3.50 (dd, 1H, J=6,10 Hz), 2.34-2.49 (m, 2H), 1.89-2.00 (m, 2H), 1.65-1.86 (m, 1H), 0.86 (s, 9H), 0.18 (s, 6H). ^{13}C: 159, 81, 72, 70, 51, 45, 33, 31, 30, 23, -5.3, -5.5. **11** ^1H δ: 7.34 (s, 5H), 5.59 (d, 1H, J=10 Hz), 5.06 (AB quartet, 2H, J=15 Hz), 4.08-4.15 (m, 1H), 3.96 (dd, 1H, J=8,11 Hz), 3.83 (dd, 1H, J=6, 11 Hz), 3.20-3.27 (m, 2H), 2.25 (br d, J=15 Hz), 2.02-2.10 (m, 4H), 1.83-1.95 (m, 1H), 1.68 (dd, 1H, J=12, 15 Hz). ^{13}C: 171, 156, 136, 128.5, 128, 66, 65, 52, 51, 44, 35, 30, 22, 20. **12** ^1H δ: 7.34 (s, 5H), 6.16-6.22 (br s, 1H), 5.08 (AB quartet, 2H, J=12 Hz), 3.74-4.00 (m, 4H), 3.59 (dd, 1H, J=6, 11 Hz), 2.20-2.33 (m, 2H), 2.06-2.18 (m, 1H), 1.84-1.93 (m, 1H), 1.69-1.80 (m, 1H), 0.88 (s, 9H), 0.56 (s, 6H). ^{13}C: 156, 136, 128, 127.9, 66, 63, 61, 49, 38, 33, 25, 18, -5.56, -5.58.

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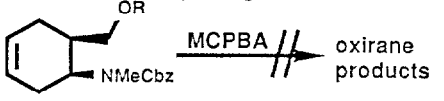
9. Additional support for the critical role of the NH moiety can be found in the following observations. Neither N-methyl alcohol **17a** nor its derived acetate **17b** produced significant amounts of epoxide products under conditions similar to those employed in the nor series (**4** and **8**). Surprisingly even after refluxing for 24 hours in CH_2Cl_2 or $CHCl_3$ little conversion of these olefins to the corresponding oxiranes could be observed by tlc analysis. The basis for these results is under study.



17a) R=H
b) R=Ac

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(Received in USA 20 October 1988)