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Stereoselective Dihydroxylation of 2-Alkyl- and 2,4-dialkyl-2-amido-3-cyclohexen-1-ones. Synthesis of Enantiomerically Related 2-Alkyl- and 2,4-dialkyl-3-hydroxy-1-oxocyclohexan-2,4-carbolactones by Complementary Butyrolactonization Reactions

Arthur G. Schultz,* Mingshi Dai, Fook S. Tham and Xuqing Zhang

Department of Chemistry
Rensselaer Polytechnic Institute
Troy, NY 12180-3590

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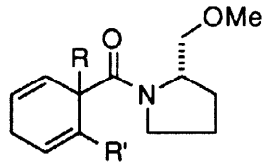
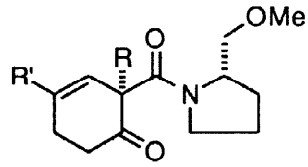
Abstract: Stereoselective dihydroxylation of **2a-2f** gives cis-diols **3a-3f**, from which hydroxylactones **5a-5f** are obtained by an acid-catalyzed process involving retro aldol-realdolization prior to transesterification.

Keywords: Asymmetric Synthesis; Epimerization; Hydroxylation; Lactonization

In connection with the development of the asymmetric Birch reduction-alkylation method,[1] we have been involved with the study of facial selective addition reactions of 1,4-cyclohexadienes **1**. For example, hydrogenation of **1** and related substrates with the homogeneous catalyst/solvent system $[Ir(cod)py(PCy_3)]PF_6/CH_2Cl_2$[2] occurs with outstanding facial selectivity syn to the amide carbonyl group.[3] Opposite stereoselectivity has been observed with heterogeneous hydrogenation catalysts, presumably a result of steric approach control.[3] The regio- and stereoselective epoxidations of **1** also have been reported.[4] We now describe the highly stereoselective dihydroxylation of 2-alkyl- and 2,4-dialkyl-2-[[2'-(methoxymethyl)pyrrolidinyl]carbonyl]-3-cyclohexen-1-ones **2** with OsO_4 to give **3** and chemistry that provides butyrolactone derivatives of **3** in both enantiomeric modifications; e.g., **5** and **8**.



1, R' = OMe, alkyl



2

Stereodirected dihydroxylation of alkenes using OsO_4 with assistance from polar functional groups has been a topic of exceptional interest during the past two decades.[5] Although amides derived from acyclic allylic amines have not provided useful stereodirection by way of coordination or steric effects,[6] the high level of stereocontrol displayed in the epoxidation reactions of 1,4-cyclohexadienes **1** (R' = OMe and Me; R = Me) anti to the sterically demanding amido group[4] suggested that a study of the dihydroxylation reactions of **2** would be worthwhile.

Treatment of **2a-2f**[7] with OsO_4 (0.05-0.1 equiv) and 4-methylmorpholine N-oxide (NMO) in acetone-water solution gave cis-diols **3a-3f** in good to excellent yields.[8] NMR spectral data did not allow for unambiguous configurational assignments in the series **3a-3f**, especially in light of the potential for

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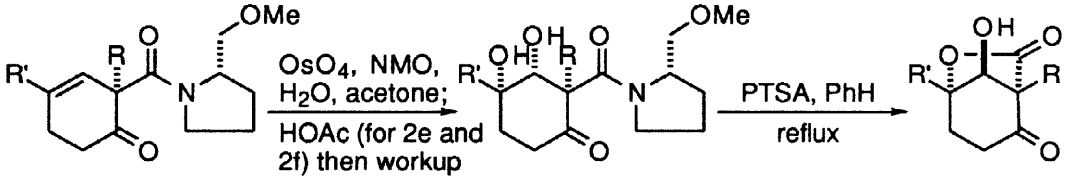
epimerization at C(2) and C(3) by a retro-aldol process; consequently, X-ray diffraction data were obtained for crystals of **3a** and **3e**. The molecular structure of **3a** (Figure 1) shows the hydroxyl group at C(3) and the amido group at C(2) to be in axial environments. It is noteworthy that the carbonyl oxygen atom in **3a** is directed away from the C(1) carbonyl group as would be expected on the basis of dipole minimization. The molecular structure of **3e** (Figure 2) shows the hydroxyl group at C(3) and the amide at C(2) to be in equatorial orientations, consistent with the relief of 1,3-diaxial interactions between these two large substituents that would be present in the chair conformation corresponding to that shown for **3a** in Figure 1.

Scheme I



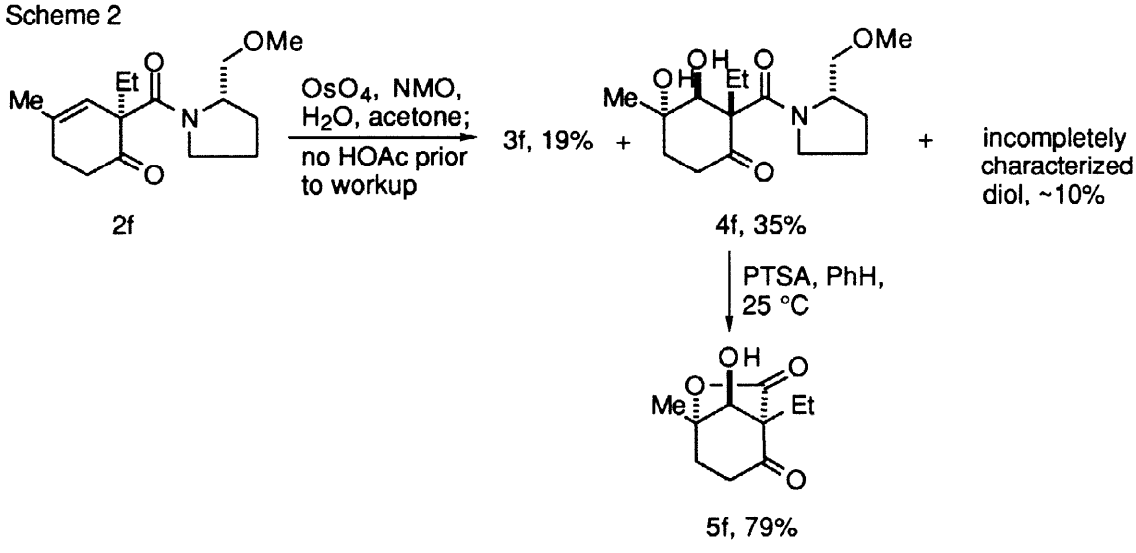
2a, R' = H; R = Me
b, R' = H; R = CH_2Ph
c, R' = H; R = $(CH_2)_3N_3$
d, R' = H; R = $(CH_2)_3Cl$
e, R' = CH_2Ph; R = Et
f, R' = Me; R = Et

3a, 91%
b, 86%
c, 88%
d, 94%
e, 73%
f, 76%

5a, 65%
b, 70%
c, 42%
d, 76%
e, 61%
f, 46%

When acetic acid was not added to the reaction mixture containing cis-diol **3f** prior to workup, a mixture of **3f** (19%), **4f** (35%) and a third incompletely characterized diol (~10%) was obtained (Scheme 2). Presumably **4f** is generated from **3f** by a retro aldol-realdolization process involving catalysis by 4-methylmorpholine; addition of acetic acid prior to workup effectively prevents the amine-catalysis. This requirement for an acetic acid quench was observed for dihydroxylations of **2e**, but was unnecessary for the C(4)-unsubstituted enones **2a-2d**.

Scheme 2



2f

The molecular structure of the trans-diol **4f** is shown in Figure 3. A prominent feature of the structure of **4f** is a hydrogen bond between the hydroxyl group at C(4) and the amide carbonyl group. Assuming that this conformational preference in the solid-state is representative of solution-state behavior, it would appear that intramolecular hydrogen bonding in **4f** might be the driving force for an equilibration that favors **4f**. In any event, the close proximity of the amide and C(4) hydroxyl group results in efficient acid-catalyzed lactonization at room temperature to give **5f** in 79% isolated yield.

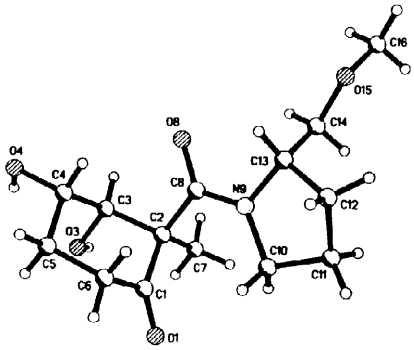


Figure 1. Molecular Structure of **3a**.

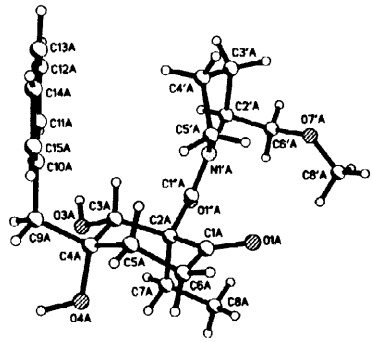


Figure 2. Molecular Structure of **3e**.

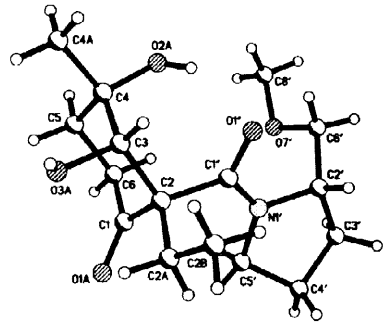
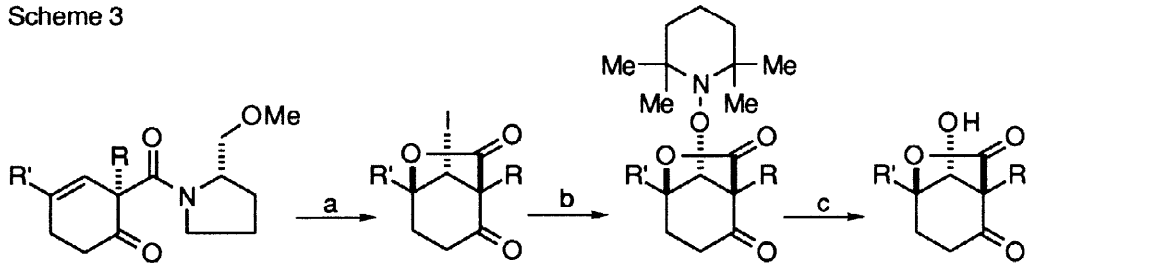


Figure 3. Molecular Structure of **4f** showing an H-bond between the OH at C(4) and O(1"): 1.988Å, < 146°.

Diols **3a-3f** were converted to lactones **5a-5f** by treatment with p-toluenesulfonic acid (PTSA) in refluxing benzene solution. Thus, under these more strongly acidic conditions, **3a-3f** undergo acid-catalyzed retro aldol-realdolization to give trans-diols of type **4**, which very rapidly convert to hydroxy lactones **5a-5f**.

The enantiomeric hydroxy lactones **8a** and **8d-8f** were prepared as shown in Scheme 3. Conversions of **2a** and **2d-2f** to iodolactones **6** were followed by exchange of iodide with 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (TEMPO) and Bu_3SnH in refluxing benzene solution to give the TEMPO derivatives 7.[9] Two diastereomeric TEMPO derivatives were obtained from **6a** and **6d**; these diastereomers were separated by chromatography on silica gel. Iodolactones **6e** and **6f** gave only the axial TEMPO derivatives **7e** and **7f**. Reductive cleavage of **7a** and **7d-7f** with Zn in HOAc gave the hydroxy lactones **8a** and **8d-8f**.

Scheme 3



2a, R' = H; R = Me	6a, 90%	7a, 71% (1:1)	8a, 83%
d, R' = H; R = $(CH_2)_3Cl$	d, 75%	d, 81% (1.7:1)	d, 81%
e, R' = CH_2Ph; R = Et	e, 81%	e, --	e, 42% (two steps)
f, R' = Me; R = Et	f, 80%	f, 50%	f, 62%

Reaction conditions: (a) I_2, THF, H_2O; (b) TEMPO, Bu_3SnH, PhH, reflux; (c) Zn, HOAc, THF, reflux.

That hydroxylactones **5** and **8** are enantiomers was clearly evident from their opposite signs of optical rotation.[10] Enantiomeric purity was determined by conversion of **5d/8d** and **5f/8f** to the Mosher esters and integration of resonances in the ^{19}F NMR spectra of the derivatives: **5d**, 95% ee; **8d**, 98% ee; **5f**, 95% ee; **8f**, 96%.[11]

In summary, we have demonstrated what appears to be complete facial selectivity for the dihydroxylation of several 2-alkyl- and 2,4-dialkyl-2-amido-3-cyclohexen-1-ones, **2a-2f**. The resulting cis-diols, **3a-3f**, should be useful in synthetic applications as shown here by the acid-catalyzed conversions to hydroxylactones, **5a-5f**. The availability of enantiomerically related hydroxylactones, **5** and **8**, from a single chiral auxiliary adds additional value to these developments.

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References and Notes

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8. A representative procedure for dihydroxylation of **2e** follows. To a solution of **2e** (0.600 g, 1.69 mmol) in acetone-H_2O (5:1, 24 mL) was added NMO (0.620 g, 5.07 mmol) and OsO_4 (2.5 wt % in *t*-BuOH, 2.12 mL, 0.169 mmol) at room temperature. The reaction mixture was stirred for 48 h. HOAc (0.5 mL) was added, then saturated aqueous $Na_2S_2O_3$ (2 mL) and then the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. Flash column chromatography (hexane:EtOAc, 1:1) gave **3e** (0.48 g, 73%). mp = 132-3 °C. $[\alpha]^{30}_D$ -13.1 (*c* 0.99, $CHCl_3$). R_f = 0.27 (1:1 hexane/EtOAc). ^1H NMR ($CDCl_3$) δ 7.24-7.14 (m, 5 H), 4.20 (m, 1 H), 4.14 (d, J = 5.3 Hz, 1 H), 4.02 (d, J = 5.3 Hz, 1 H), 3.52 (dd, J = 7.1, 2.1 Hz, 1 H), 3.34 (dd, J = 7.1, 2.1 Hz, 1 H), 3.25 (s, 3 H), 3.04 (d, J = 3.1 Hz, 1 H), 2.93 (m, 1 H), 2.89 (d, J = 3.1 Hz, 1 H), 2.68 (m, 2 H), 2.50 (m, 1 H), 2.08 (dd, J = 9.8, 4.4 Hz, 1 H), 1.80 (m, 6 H), 1.40 (m, 1 H), 0.75 (t, J = 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 208.0, 169.0, 136.5, 130.2, 127.9, 126.3, 73.9, 72.7, 71.8, 66.1, 58.7, 57.6, 47.9, 46.4, 34.6, 29.9, 26.2, 24.3, 21.7, 8.9. IR (film) 3430, 1706, 1607 cm^{-1}. Anal. Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02. Found: C, 67.72; H, 8.07.
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10. For example, **5e** $[\alpha]^{31}_D$ +281 (*c* 0.88, $CHCl_3$) and **8e** $[\alpha]^{25}_D$ -230 (*c* 0.57, $CHCl_3$).
11. The ^{19}F chemical shifts of the Mosher esters are (CF_3CO_2H reference): **5d**, δ 4.70; **8d**, 4.35; **5f**, 4.70; **8f**, 4.56.