Diastereoselective Osmylation and Hydroboration of \(\beta,\gamma\)-Unsaturated \(N,N\)-Diisopropylamides and Acid-Catalyzed Conversion to \(\delta\)-Lactones

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The title reactions of \(\beta,\gamma\)-unsaturated \(N,N\)-diisopropylamides occur with useful diastereofacial selectivity. The major diol isomer from osmylation of alkenes 1, 10, 11, and 12 in the presence of TMEDA at \(-78^\circ C\) corresponds to the facial preference shown in transition state model 41 (\(R_2 = H\)), while the opposite preference for 42 is observed with the Z-alkene 13. (Table 1). Hydroboration with 9-BBN does not show this inversion of diastereofacial selectivity for the Z-alkene. All of the results in Table 2 correspond to the usual preference for a transition state such as 45. Acid-catalyzed lactonization of the alcohols obtained in Tables 1 and 2 can be carried out with overall retention of configuration to afford \(\delta\)-lactones. Butenolide 5 was prepared with 90% ee from alcohol 2a via osmylation followed by acid-catalyzed lactonization to 3 and elimination using SOCl\(_2\)/pyridine.

Previous studies in our laboratory have shown that the \(\beta,\gamma\)-unsaturated amide 1 can be obtained with a high level of enantiomeric excess by asymmetric protonation of the corresponding enolate. We were therefore interested in determining whether 1 can be converted into potentially useful chiral products by relying on the \(\alpha\)-carbon to direct electrophilic addition reactions by sterically demanding reagents. Osmium tetroxide hydroxylation is one possibility for olefin functionalization where the bulky allylic diisopropyl carboxamide group might control facial selectivity. If either diol diastereomer 2a or 2b can be obtained with high selectivity, then subsequent lactonization to 3 or 4 followed by \(\beta\)-elimination should afford the chiral butenolide 5 (from 3) or ent-5 (from 4). In principle, the analogous sequence would be possible from other chiral \(\beta,\gamma\)-unsaturated amines as an entry into butenolide target structures. To test the feasibility of this approach, we began with an investigation of the osmium tetroxide hydroxylation using racemic 1 as a representative substrate. The initial goal was to learn whether alkene hydroxylation is possible with an acceptable level of diastereofacial control. We also hoped to demonstrate stereospecific conversion from the amide 1 to the butenolide product 5 via a simple acid-catalyzed lactonization—elimination sequence. If this can be done without loss of enantiomeric purity starting from (R)-1, then the bulky \(N,N\)-disopropylcarboxamide substituent might be used in a dual role to promote the decarboxamidation of \(\beta,\gamma\)-unsaturated amides and then to direct the subsequent introduction of versatile oxygen functionality.

Results

Osmylation of rac-1 using the catalytic conditions of Van Rheenen and Kelly et al. proceeded smoothly at 0 °C and gave a 5:1 mixture of diols. The diastereomers 2a and 2b were separated by chromatography and were converted into diastereomeric lactones 3 and 4, respectively, by heating in the presence of acid catalysts. Similar results were obtained with camphorsulfonic acid (CSA) in refluxing toluene or with refluxing 10% H\(_2\)SO\(_4\). The latter procedure proved to be effective with a number of simpler substrates to be described shortly. The 10% H\(_2\)SO\(_4\) method was also successful with the minor diol 2b, although the lactone 4 was obtained in modest 60% yield together with a byproduct derived from pinacol rearrangement. No attempt was made to optimize the lactonization in the minor diol series. However, in the case of 2a, the 10% H\(_2\)SO\(_4\) method gave 3 together with a minor (uncharacterized) byproduct containing vinylic signals in the \(^1H\) NMR spectrum. Late in the study, after nearly all of the correlation work had been completed, it was found that the lactonization proceeds best when performed with 10% H\(_2\)SO\(_4\) in refluxing aqueous dioxane. This method gave crystalline 3 as the sole product detected by \(^1H\) NMR upon removal of solvent (81% yield).


(4) The structure i was established for the minor product by correlation with 29b via Swern oxidation to the corresponding ketone ii. The latter was not identical with the pinacol product, but treatment with K\(_2\)CO\(_3\)/MeOH resulted in a 1:1 mixture of i and ii. Thus, the pinacol product differs in the configuration of the enolizable carbon, as expected from the assigned configurations of 29b and 2a if the pinacol rearrangement occurs with stereospecific hydride migration to the backside of the protonated tertiary hydroxyl group.

![Diagram](https://example.com/diagram.png)
isolated yield). Thus, optimization was necessary to control side reactions, but the acid-catalyzed lactonization pathway starting from 2a was stereospecific under all of the conditions examined.

The osmylation diastereoselectivity at 0 °C (5:1 2a:2b) is sufficiently high to allow purification of the major diol by crystallization. However, higher selectivity is important for other substrates where isomer separation is difficult (see below), so several other experimental procedures were evaluated. The best diastereoselectivity (11:1 2a:2b; 82% isolated yield of 2a) resulted when the osmylation was performed using a TMEDA-accelerated stoichiometric OsO4 procedure at −78 °C (Scheme 1).5 At room temperature, the TMEDA/OsO4 reagent gave a product ratio of ca. 3:1:1, nearly the same as that obtained under the catalytic osmylation conditions (3.4:1).

The TMEDA-accelerated osmylation was repeated with enantiomerically enriched (R)-1 (96% ee), and the resulting major diol was subjected to the aqueous dioxane (H2O-enriched) lactonization conditions, followed by treatment with SOCl2/pyridine at 0 °C to convert 3 into the butenolide 5 (75% yield based on 2a). A small amount of isomeric lactone 6 was also isolated (5%). The structure of the minor lactone was assigned on the basis of a characteristic olefinic proton signal at 5.55 ppm in the 1H NMR spectrum as well as the infrared frequency of 1756 cm−1. A similar sequence was carried out from rac-2a to provide a reference sample of 5/ent-5 (81%). Analysis by HPLC on a chiral stationary phase proved difficult, but conditions were found that gave near-baseline resolution and that were shown to detect 5% of the enantiomeric lactone in an authentic mixture as an inflection point in the major peak. No inflection point was detected in the sample of 5 obtained starting from (R)-1 with 96% ee, so the product 5 is formed with >90% ee, suggesting that there is no loss of configuration over the sequence of lactonization and elimination steps. The same sequence was also tested on a small scale starting with enantiomerically enriched minor diol diastereomer 2b. However, attempted elimination from 4 gave a mixture of three lactones with ent-5 as the minor component (3–5%). Assay of this material was problematic because of the order of peak elution. Significant racemization was detected, and the major enantiomer was clearly ent-5 as expected from the stereochemistry of 2b and 4. However, only a qualitative assay for enantiomeric purity was feasible (>60% ee and <80% ee) due to partial peak overlap. In view of the limited availability of 2b, no attempt was made to optimize this sequence or to determine the source of partial racemization at the stage of ent-5 in the minor isomer series.

The relative stereochemistry of the crystalline lactone 3 (from the major diol 2a) was established using X-ray techniques (see Supporting Information). Because the C–O bonds in 3 are cis with respect to the six-membered ring, it is likely that the lactonization process occurs with retention of diol stereochemistry from 2a. This would implicate a precedented acid-catalyzed acyl transfer via 7 as the lactonization mechanism (path a)7 and would argue against an alternative (path b) involving backside displacement of the protonated alcohol 8 by the amide carbonyl. The latter sequence should produce the diffused lactone 9, but no evidence to suggest formation of this diastereomer was detected in any of the experiments. Furthermore, the absence of lactone crossover products in the two lactonizations (2a to 3, 2b to 4) indicates that there is no enolization at the α-carbon under the lactonization conditions. Thus, formation of 3 from 2a takes place with retention of configuration at each of the asymmetric carbons. This outcome is consistent with earlier precedents for acid-catalyzed conversion of γ-hydroxyamides into lactones in hydroxylic solvents.7

The low-temperature TMEDA hydroxylation of 3 proceeds with useful diastereofacial selectivity under control of the amide α-carbon. It was therefore of interest to determine whether similar results would be seen with other β,γ-unsaturated amides. The prospects were evaluated with the substrates 10–13 (Table 1).8 As expected from the structural similarity, 12 gave essentially the same product ratios as obtained from 1. All of the other osmylations proved to be more highly selective, and the low-temperature TMEDA procedure was consistently superior to the catalytic method. However, one of the osmylations (Z-trisubstituted alkene 13) was found to proceed with opposite facial selectivity by comparison

with 1 or with the other acyclic entries. This conclusion did not come easily because of difficulties encountered due to similar chromatographic behavior for the isomers in several cases. Fortunately, the products 17a and 17b could be separated from each other, and from a minor contaminant (16a) resulting from the presence of 9% of 12 in the starting 13. On the other hand, the minor diol diastereomers could not be obtained pure starting from alkenes 10–12. The major diol 14a from 10 could be separated from 14b, but the latter was not obtained pure and the NMR signals did not differ sufficiently to assay the mixture. Fortunately, assay was possible after conversion of the initial mixture of 14a and 14b to the separable acetonides 18a and 18b (Scheme 2). In the other osmylations, only the major diol diastereomers (15a, 16a) could be purified and product ratios were estimated from NMR integral comparisons of characteristic signals assigned to the minor diol diastereomers (15b δ 5.00, 3.65, 2.85 ppm; 16b δ 3.9, 2.7 ppm). These assignments were guided by comparing fractions where the minor diastereomers had been enriched by partial separation or by osmylation at higher temperatures.

In the course of attempts to prove diol relative stereochemistry, the purified major isomer 14a + ent-14a (obtained from racemic 10) was converted into the diastereomeric esters 19 and 20 by reaction with (S)-naproxen in the presence of DMAP and N-ethyl-N-dimethylaminopropylcarbodiimide (EDCI). One diastereomer, 19, was characterized and crystallized, and X-ray structure determination established the stereochemistry. This information defines the relative configuration of the major diol from 10 as shown in 14a/ent-14a. The structures of diols 17a and 17b (from 13) were also defined by X-ray crystallography. In this case, the minor diastereomer 17a could be crystallized without derivatization, and the knowledge of its relative stereochemistry defined the major diastereomer as 17b. However, direct evidence for the structures of 15a and 16a could not be obtained. These assignments were made on the basis of NOE effects (GOESY method; gradient enhanced nuclear Overhauser effect spectroscopy) after acid-catalyzed conversion to the corresponding lactones 21 and 22. For purposes of comparison, GOESY experiments were also performed with the lactone 23, obtained from 17b, and self-consistent results were obtained.

The acid-catalyzed cyclizations from diols 15a, 16a, and 17b were somewhat slower than the corresponding lactonization of 2a to 3. Relatively forcing conditions were necessary (hours at 100 °C, 10% sulfuric acid), and this raised the same concerns about retention of hydroxyl stereochemistry as in the lactonizations of 2a and 2b. Fortunately, the availability of diol diastereomers 16a and 17b that differ only in the configuration at the tertiary hydroxyl-bearing carbon (different rotamers are shown at the secondary carbon) simplifies the arguments.

(a) Minor isomer not isolated unless specified (b) Catalytic OsO₄/NMMO at RT (c) Stoichiometric OsO₄/TMEDA, -78 °C. (d) Recovery of diol, >90% conversion by 1H NMR assay (e) Isolated yield of diols after chromatography. (f) Isomer 17a was isolated in 6% yield.
Because 16a and 17b afford unique products 22 and 23, reversible S_{N}1 cleavage of the tertiary C–O bond before or after cyclization can be ruled out. According to the NOE relationships summarized in Scheme 2, both 22 and 23 retain the oxygen stereochemistry expected from cis-hydroxylation of the starting 

E- or Z-alkenes. The configuration of 17b is known from the X-ray structure determination for 17a. Thus, conversion to 23 must take place with retention of relative stereochemistry at both oxygenated carbons. Therefore, the configuration at the secondary hydroxyl of 16a can be deduced from the stereochemistry of 22, assuming retention in the lactonization step by analogy to the conversion from 17b to 23. Finally, the relative stereochemistry at tertiary hydroxyl in 15a can be assigned from the NOE results and from the survival of tertiary hydroxyl configuration in the related lactones 22 and 23 made under similar conditions.

A comparison of the major diol products obtained from the \( \beta,\gamma \)-unsaturated amides in Table 1 reveals that the relative stereochemistry follows the same pattern with respect to the asymmetric \( \alpha \)-carbon in all cases except for the Z-trisubstituted alkene example 13. A similar inversion of osmylation facial preferences in Z- vs E-alkenes has been observed in certain enoates \(^{26a} \) and in 4-substituted 2-pentenes.\(^{23} \) However, the amide substituent differs in its potential for osmium complexation compared to the examples explored previously. The constrained Z-trisubstituted alkene \(^{24c} \) (Scheme 3) was therefore studied to help determine whether the stereochemical outcome in the unconstrained analogue 13 could involve directed osmylation mediated by the amide carbonyl group. Internal complexation of osmium by the amide carbonyl would be expected to form the syn hydroxylation product 25b, a substance that is analogous to 17b in relative configuration. However, the reaction gave 25a as a single diastereomer, even at room temperature, and the configuration of the secondary hydroxyl was anti with respect to the amide according to the vicinal coupling, \( J_{1,2} = 9.6 \) Hz. This result is consistent with an earlier report of osmylation anti to an allylic carboxamide group in a cyclopentene environment.\(^{15a} \) We could find no reports of specific directing effects involving amide carbonyl in other studies where amide nitrogen is in the allylic position, although a variety of interesting methods for controlling diastereoselectivity are described in this series.\(^{10b-d} \) We conclude that the osmylation reagent prefers to avoid the bulky allylic carboxamide group. The results indicate that the favored geometry for osmylation of 13 differs from that of the more constrained analogue 24, presumably due to the conformational freedom at the allylic C–C bond.

Several other comparisons were made that suggest a dominant role for steric factors in the osmolyations. The N,N-dimethyl analogue of 1 was explored briefly under the TMEDA conditions. Osmylation selectivity was lower (7.1 at \(-78^\circ C\), but the major product had the same relative configuration, as shown by acid-catalyzed lactonization to 4. Furthermore, osmylation of the corresponding ester \(^{261} \) (Scheme 3) proceeded with almost no selectivity (1.2:1 diastereomer ratio; major product not assigned). Thus, the isopropyl groups are important for obtaining a practical level of diastereoselectivity.

It was also of interest to compare the osmylation results with hydroborations conducted with 9-BBN, a sterically discriminating electrophile that reacts with a well-precedented facial selectivity pattern.\(^{12} \) Product configurations can easily be established via oxidative workup followed by the same acid-catalyzed lactonization procedure as used in the osmylation series. This system has the advantage that both of the diastereomeric lactones expected from the alkenes 1, 12, and 13 are already described in the literature.\(^{13} \) The hydroborations proved to be relatively slow, and heating was necessary (3–24 h in refluxing THF). However, each of the three test substrates reacted with a dear preference for one major alcohol diastereomer (Table 2). The purified hydroxymides 27, 28, and 29 were lactonized using 10% \( \text{H}_{2}\text{SO}_{4} \) as before, and the resulting 30, 31, and 32 were identified by comparisons with literature NMR data.\(^{23} \) All three lactones have the same relative stereochemistry. Thus, hydroboration occurs with the same facial preference with the E- or the Z-trisubstituted alkene 12 and 13, in contrast to the osmylations. The major diastereomers obtained with 9-BBN correspond to the osmylation facial preference seen with the Z-alkene 13, but the hydroboration facial preferences for alkenes 10, 11, and 12 are inverted compared to those found for the corresponding osmylations.

Discussion

In a prior study, the inversion of osmylation diastereofacial preferences from E-alkenes 33 to the Z-alkenes 35 was attributed to steric factors in the competing transition states (Figure 1). Essentially identical selectivities were found in the case of 35a and 35b despite the expected difference in substituent donor/acceptor properties, and the pathway corresponding to a proposed transition state geometry 36 was favored by a 4:1 ratio at room temperature.2b The isomeric E-alkenes 33a and 33b reacted with the inverted facial preference, corresponding to a favored geometry such as 34. Key geometrical details were left unspecified in the prior report because a consensus for the 5-center rather than the 4-center (osmaoxetane) mechanisms had not yet emerged.14 Despite these uncertainties, the results suggested that allylic SiMe2Ph or SO2Ph substituents control facial selectivity due primarily to their steric bulk. In the current study involving the osmylation of the trisubstituted analogues 12 and 13, the same selectivity trends are apparent and a similar sterically based rationale is plausible for 13 if the hindered N,N-diisopropylamide environment can be accommodated within a transition state geometry analogous to 36. The role of 34 is less clear and must be reevaluated in light of recent mechanistic findings. Differences due to the potential involvement of amide carbonyl as a ligand that might coordinate to osmium must also be considered. However, literature precedents10a as well as the anti osmylation observed with the cyclic alkene 24 argue against internal coordination by amide carbonyl oxygen.

The issue of amide steric effects in the acyclic substrates is potentially complicated, but crystal structure evidence suggests a simplifying approximation as outlined below. The X-ray structure of diol 17a reveals an interesting arrangement of staggered isopropyl substituents (Figure 2). In one of the isopropyl groups, the C7-C6,C8 angle is bisected by the plane of the amide NCdO subunit. The other isopropyl is turned so that the C10,C9,C11 angle is bisected by the C6-H bond. This arrangement places the C9-H near the C2-H and close to the plane defined by the carbonyl carbon (C1) and the C2-H bond, resulting in the effective separation of methyl groups and the proximity of the C9 and C2 hydrogens (shown in bold font). While the structure 17a may reflect crystal lattice effects or contributions by hydrogen bonding, a search of the Cambridge crystallographic database turned up three other examples of R-branched N,N-diisopropylamides, all of which have a similar local conformation.15 The proximity of the α-hydrogen (corresponding to C2−H) and one of the isopropyl

Table 2. Hydroborylation of \( \beta,\gamma \)-Unsaturated Amines with 9-BBN

<table>
<thead>
<tr>
<th>Alkene Substrate</th>
<th>Hydroboration; major product</th>
<th>Ratio of ( \text{a} : \text{b}^a ) (yield)</th>
<th>Lactonization product ( \text{b} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>27b</td>
<td>1 : 5.7 (94%)</td>
<td>30 (80%)</td>
</tr>
<tr>
<td>13</td>
<td>28b</td>
<td>&lt;1 : 10 (63%)</td>
<td>31 (40%)</td>
</tr>
<tr>
<td>1</td>
<td>29b</td>
<td>&lt;1 : 15 (69%)</td>
<td>32 (52%)</td>
</tr>
</tbody>
</table>

(a) The amide was refluxed with 9-BBN in THF. The minor isomer was not isolated; product ratio estimated by \( ^1H \) NMR assay. (b) Lactonization conditions: 10% \( \text{H}_2\text{SO}_4 \) reflux. (c) Competing elimination occurred to give 12 (20%) as a byproduct.

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Figure 1. Major pathways for osmylation of 4-substituted pent-2-enes.

Figure 2. Crystal structure of 17a.

4-center (osmaoxetane) mechanisms had not yet emerged.14 Despite these uncertainties, the results suggested that allylic SiMe2Ph or SO2Ph substituents control facial selectivity due primarily to their steric bulk. In the current study involving the osmylation of the trisubstituted analogues 12 and 13, the same selectivity trends are apparent and a similar sterically based rationale is plausible for 13 if the hindered N,N-diisopropylamide environment can be accommodated within a transition state geometry analogous to 36. The role of 34 is less clear and must be reevaluated in light of recent mechanistic findings. Differences due to the potential involvement of amide carbonyl as a ligand that might coordinate to osmium must also be considered. However, literature precedents\(^{10a}\) as well as the anti osmylation observed with the cyclic alkene 24 argue against internal coordination by amide carbonyl oxygen.

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The catalytic osmylations at room temperature are not likely to follow an early transition state model such as that described above for the TMEDA-accelerated (stochiometric Os) reactions. Carbon isotope effect studies indicate that the five-center transition state has significant C-O bonding at both olefinic carbons. The catalytic process therefore involves substantial rehybridization at carbon, and there are differences in the arrangement and number of osmium ligands relative to the TMEDA reactions. However, the diastereofacial selectivity is similar (Table 1) if the difference in reaction temperature is taken into account. The consistent selectivity pattern indicates that rehybridization at the olefinic carbons does not strongly affect the relative energies of competing transition states even though there must be some change in transition state geometries due to bond angle changes and the differences in ligand geometry. A consistent selectivity pattern in early as well as relatively advanced transition states is easy to understand in the Z-alkene case. A comparison of the reactant-

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**Figure 3.** Selected ground state geometries.

hydrogens (corresponding to C9–H) is characteristic, and the amide geometries can be represented by dihedral angle variations between the two limiting cases 37a and 37b (Figure 3). Within this range of geometries, the osmium tetroxide amine complex can interact with an adjacent alkene (R' = R1R2C = CR) without encountering the isopropyl methyls while the latter avoid interactions with the C2 substituents. Similar local conformers will be used to represent the amide environment in subsequent drawings, as in the ground state structures 38–40. These geometries represent the three alkene rotamers around the allylic C2–C3 bond that have the olefinic C=C subunit eclipsed with one of the allylic bonds and therefore correspond to the local energy minima.

The favored transition state geometries for osmylation need not be similar to the favored ground state geometries, depending on the extent of rehybridization and the nature of substrate interactions with developing bonds and osmium ligands. However, recent developments in the mechanistic interpretation of osmium tetroxide reactions suggest that ground state preferences can be quite important for the TMEDA-accelerated reactions at low temperature. According to the mechanistic proposal by Corey et al., the stereochemistry-determining step in diamine-accelerated reactions is olefin complexation to produce a labile 20-electron complex that undergoes subsequent rearrangement to an osmate ester. Possible transition structures based on the Corey geometry are shown in Figure 4. Structure 41 assumes relatively little carbon rehybridization in the olefin subunit, corresponding to the t -interaction of the OsO4–TMEDA complex with one of the local energy minima for the alkene (structure 38'). Geometry 41 encounters no interactions between osmium ligands with the allylic (C2) methyl or amide isopropyl substituents and accounts for the facial preference seen in all of the osmylations of Table 1 with the single exception of the Z-alkene 13. Alternative transition structure 42 corresponding to another alkene local energy minimum (39') in Figure 3 also avoids isopropyl–osmium ligand interactions if bonding occurs from below, but in this case ligand interactions with the allylic methyl are possible. Therefore, 41 is favored over 42 with R2 = H. On the other hand, 41 is destabilized when R2 = CH3 and 42 becomes the preferred transition state. Analogous structures derived from the ground state rotamer 40/40 (Figure 3) are unlikely because they would encounter osmium ligand interactions with isopropyl groups on one side of the olefin (complex formation from below) or ligand interactions with the carbonyl oxygen and C2 methyl on the other side (complex formation from above). In the case of the Z-alkene, there would also be a severe interaction between R2 (C4 methyl) and the amide. Any single one of these interactions can be reduced by turning the isopropyl or the C1–C2 bond, but such conformational changes would result in increased isopropyl interactions with other groups because the amide geometry would have to deviate from the arrangements shown in Figure 3.

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**References**


like 42 with the more advanced transition state 44 (monodentate amine; room-temperature osmylation) shows dihedral angle changes along the C4—C3—C2—H segment, but the geometry remains near the expected local energy minimum (nearly eclipsed in alkene-like; more staggered in the partly rehybridized). There are other subtle changes, but the geometry of 44 retains the important features that favor 42 vs alternative geometries as discussed earlier. A similar argument can be made in the E-alkene series, but there are additional geometries to consider. The partially rehybridized transition state geometry 43a corresponds closely to that of 34 in the earlier proposal that focused on minimal C2 substituent interactions with osmium ligands. These factors would be more important in an osmaoxetane transition state than in the currently favored 5-center mechanism. Depending on the extent of rehybridization, 43a will be somewhat destabilized by eclipsing effects. If the C2 carbon is turned counterclockwise to increase the degree of staggering as shown in 43b, then isopropyl interactions with osmium ligands are increased unless the amide geometry is restricted to resemble local conformer 37b. An alternative dockwise rotation produces 43c, a geometry that would also increase staggering of bonds, but at the cost of C2-methyl interactions with osmium ligands. Structure 43c has the C2 methyl “inside” the developing bonds, a situation that is energetically unfavorable according to recent calculations for the osmylation of allylic alcohol analogues. Transition state geometries between 43a and 43b are therefore considered most likely for the E-alkene osmylations in Table 1, depending on the extent of transition state rehybridization.

No inversion of facial selectivity is seen in the hydroborations. All of the examples in Table 2 correspond to favored transition state 45, an arrangement that follows the well-known pattern with the bulky group anti to the developing bonds in a staggered geometry with the smallest group “inside.” Reagent bulk in the case of 45 is confined to an area near the substituents R1 and R2, and only the compact B—H bond approaches the C2 methyl regardless of olefin geometry. In short, both the osmylations and the hydroborations are controlled largely by steric factors, but the results are different because the reagents differ in shape and in the nature of the reacting bonds.

**Conclusion**

Osmylation or hydroboration of the \( \beta,\gamma \)-unsaturated N,N-diisopropylamides (Table 1, Table 2) occurs with useful diastereoselectivity. As observed in several earlier osmylations, the Z-alkene 13 reacts with the opposite diastereofacial preference compared to the E-isomer 12. Acid-catalyzed lactonization of the alcohols described in Tables 1 and 2 can be carried out with overall retention of configuration to afford \( \delta \)-lactones. Starting with the alcohol 2a, the sequence provides access to the hydroxy lactone 3 and elimination affords the butenolide 5 with >90% enantiomer excess.

**Experimental Section**

**General.** Materials were purified as follows. TMEDA was dried over CaH2 and distilled. CH2Cl2 was distilled from P2O5. All other reagents were used as received. Osmylation substrates 1, the N,N-dimethyl analogue of 1, 10, 11, 12, 13, 24 and 26 were prepared according to literature procedures.

**General NMO-Mediated Osmylation Procedure.** The procedure is a modification of the method of Van Rheenen. To a stirred solution of N-methylmorpholine N-oxide (1.5 equiv) and the alkene (1.0 equiv) in 10:1 acetone/H2O at 0°C or room temperature was added OsO4 (0.02–0.05 equiv, 2.5% w/v solution in t-BuOH, Aldrich). After TLC analysis indicated consumption of the alkene, excess Na2HSO3/Na2S2O5 was added and the darkened reaction was stirred for 30 min at 0°C.

room temperature. To this solution was added ether, and the solution was dried (MgSO4) and the solvent removed (aspirator).

**General TMEDA-Mediated Osylation Procedure.** To a stirred solution of the alkene and TMEDA (1.1–1.5 equiv) at −78 °C was added OsO4 (solution in CH2Cl2), and the solution turned dark. After stirring for 2 h the reaction was tested for the presence of the starting alkene by TLC. Once the alkene was consumed, the ester ester was reduced with 1:1 saturated NaHSO3/THF (10 mL) (reflux, 2 h). Brine was added, and the resulting solution was extracted with EtOAc (3×). The combined organic extracts were then dried (MgSO4) and evaporated (aspirator) to give the crude product.

**Diols 2a (Major) and 2b (Minor).** The general NMO procedure (rt) using 1° (213 mg, 0.90 mmol), NMO (126 mg, 1.1 mmol), and OsO4 (0.25 mL of a 2.5% v/v solution in BuOH, 0.02 mmol) to afford 101 mg (81%) as a white crystalline solid. The same procedure was used for the preparation of 2b.

**Elaboration of 2a Using TMEDA/OSO4.** To a solution of 1° (272 mg, 1.15 mmol) and TMEDA (208 µL, 1.38 mmol) in 2.0 mL of CH2Cl2 at −78 °C was added OsO4 (350 mg, 1.38 mmol) in CH2Cl2 (2.0 × 1.0 mL). After 2 h, TLC analysis indicated 1 had been consumed. The solution was allowed to warm to room temperature, and the solvent was evaporated to produce a brown residue. After the addition of 10 mL of THF, 1.6 g of NaHSO3, and 0.75 mL of water, the solution was heated to reflux for 2 h. The resulting mixture was heated (aspirator) to give 253 mg (82%) of pure 2a.

**Lactonization of Diol 2a.** rac-(3R,3aS,7aS)-3a-Hydroxy-3-methylhexahydrobenzofuran-2-one (3) and (3R,3aS,7aS)-3a-Hydroxy-3-methylhexahydrobenzofuran-2-one (3). To rac-2a (200 mg, 0.74 mmol) in 1.8 mL of dioxane was added 1.6 mL of a 10% H2SO4 solution (v/v) (4 equiv), and the solution was heated to reflux for 9 h. The acid layer was extracted with ether (3 × 10 mL). The combined organic layers were dried (MgSO4) and evaporated (aspirator) to give 126 mg of a white solid. The procedure (rt) using 3 was identical.

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