Diastereoselective Osmylation and Hydroboration of β,γ-Unsaturated *N,N*-Diisopropylamides and Acid-Catalyzed Conversion to δ-Lactones

E. Vedejs* and A. W. Kruger

Chemistry Department, University of Wisconsin, 53706

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The title reactions of β,γ-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 °C corresponds to the facial preference shown in transition state model **41** (R_Z = 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 δ-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 β,γ-unsaturated amide **1** can be obtained with a high level of enantiomeric excess by asymmetric protonation of the corresponding enolate.[1] We were therefore interested in determining whether **1** can be converted into potentially useful chiral products by relying on the α-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.[2] If either diol diastereomer **2a** or **2b** can be obtained with high selectivity, then subsequent lactonization to **3** or **4** followed by β-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 β,γ-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 deracemization of β,γ-unsaturated amides and then to direct the subsequent introduction of versatile oxygen functionality.

(1) Vedejs, E.; Lee, N.; Sakata, S. T. *J. Am. Chem. Soc.* **1994**, *116*, 2175.

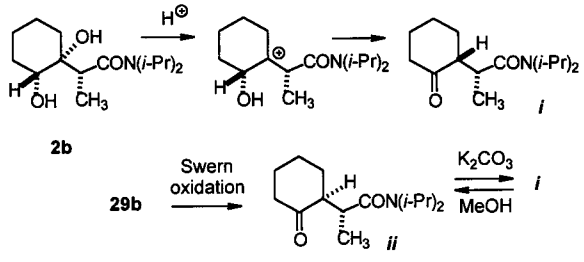
(2) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947. Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247. (b) Vedejs, E.; McClure C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094. (c) Fleming, I.; Lawrence, N. J.; Sarkar, A. K.; Thomas, A. P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3303. (d) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951. (e) Brimacombe, J. S.; Hanna, R.; Kabir, A. K. M. S.; Bennett, F.; Taylor, I. D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 815. DeNinno, M. P.; Danishefsky, S. J.; Schulte, G. *J. Am. Chem. Soc.* **1988**, *110*, 3925. (f) Evans, D. A.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 1698. Panek, J. S.; Cirillo, P. F. *J. Am. Chem. Soc.* **1990**, *112*, 4873. Vedejs, E.; Dent, W. H., III, Kendall, J. T.; Oliver, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 3556.

Results

Osmylation of **rac-1** using the catalytic conditions of Van Rheenen and Kelly et al.[3] 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_2SO_4. The latter procedure proved to be effective with a number of simpler substrates to be described shortly. The 10% H_2SO_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.[4] No attempt was made to optimize the lactonization in the minor diol series. However, in the case of **2a**, the 10% H_2SO_4 method gave **3** together with a minor (uncharacterized) byproduct containing vinylic signals in the ^{1}H 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_2SO_4 in refluxing aqueous dioxane. This method gave crystalline **3** as the sole product detected by ^{1}H NMR upon removal of solvent (81%

(3) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

(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_2CO_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.



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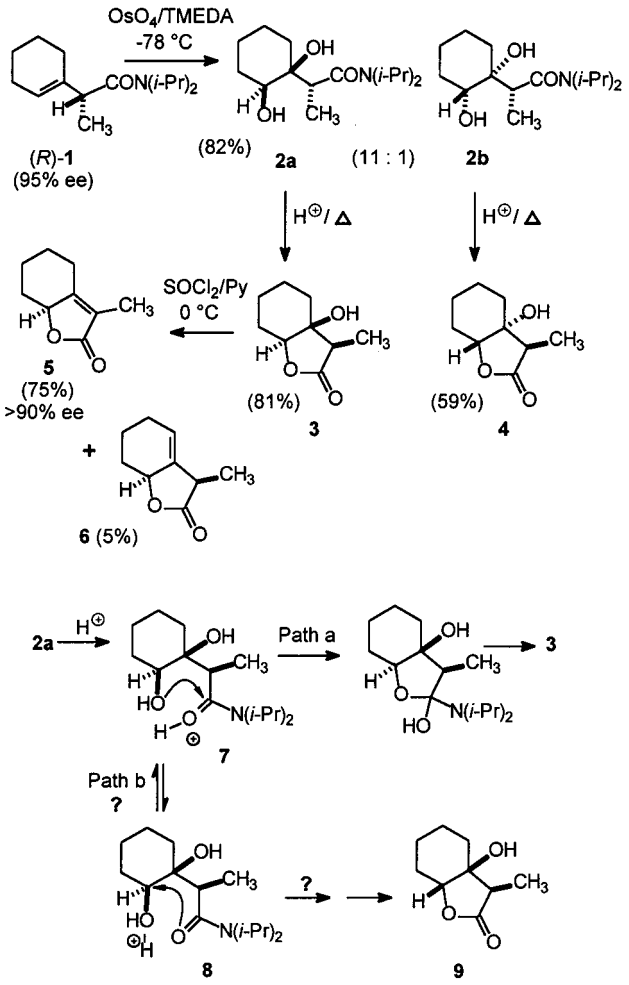
Scheme 1



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 OsO_4 procedure at −78 °C (Scheme 1).[5] At room temperature, the TMEDA/OsO_4 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 (H_2SO_4-catalyzed) lactonization conditions, followed by treatment with $SOCl_2$/pyridine at 0 °C to convert **3** into the butenolide **5**[6] (75% yield based on **2**). A small amount of isomeric lactone **6** was also isolated (5%). The structure of the minor lactone was assigned on the basis of the presence of a characteristic olefinic proton signal at δ 5.55 ppm in the ^{1}H 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 cis-fused 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]

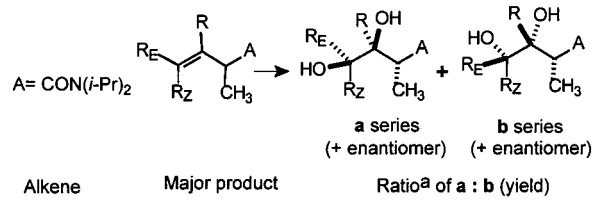
The low-temperature TMEDA hydroxylation of **1** proceeds with useful diastereofacial selectivity under control of the amide α-carbon. It was therefore of interest to determine whether similar results would be seen with other β,γ-unsaturated amides. The prospects were evaluated with the substrates **10**−**13** (Table 1).[1] 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*-trisubtituted alkene **13**) was found to proceed with opposite facial selectivity by comparison

(5) (a) Tomioka, K.; Nakajuma, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213. (b) Oishi, T.; Iida, K−i.; Hirama, M. *Tetrahedron Lett.* **1993**, *34*, 3573. (c) Donohoe, T. J.; Moore P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027. (c) Vedejs, E.; Galante, R. J.; Goekjian, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 3613.

(6) Aben, R. W.; Hofstraat, R.; Scheeren, J. W. *Recl.; J. R. Neth. Chem. Soc.* **1981**, *100*, 355.

(7) Martin, R. B.; Hedrick, R.; Parcell, A. *J. Org. Chem.* **1964**, *29*, 158. Hauser, C. R.; Adams, T. C., Jr. *J. Org. Chem.* **1977**, *42*, 3029.

Table 1. Osmylation of Acyclic β,γ-Unsaturated Amides



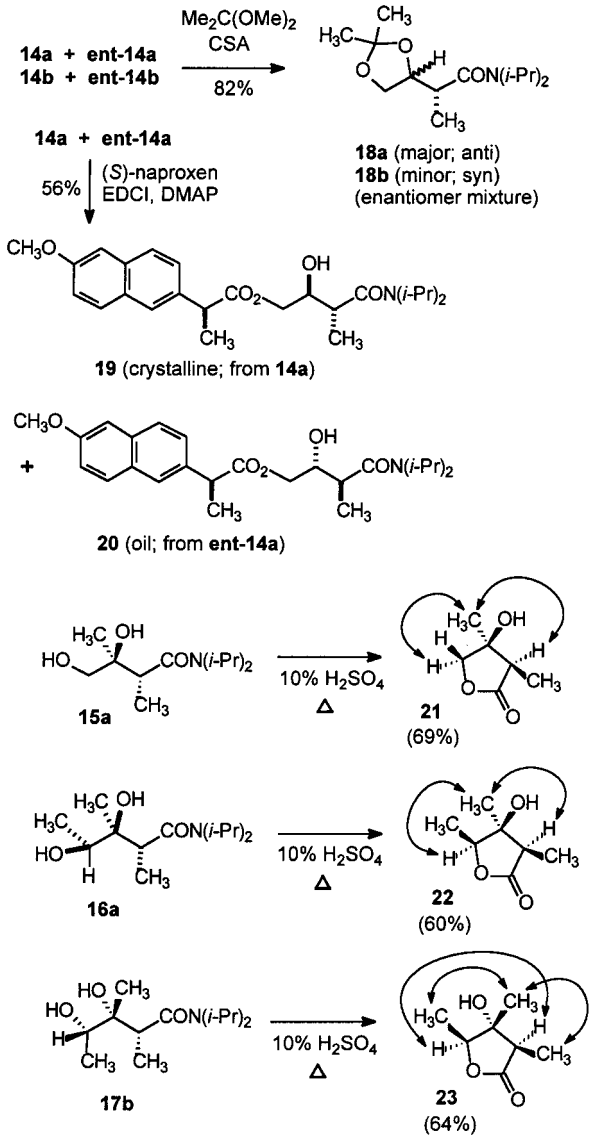
Alkene	Major product	Ratio[a] of **a** : **b** (yield) Room Temperature[b]	-78 °C[c]
10	**14a**	5:1 (98%)[d]	19:1 (87%)[d] (69%)[e]
11	**15a**	6:1 (90%)[d]	>20:1 (94%)[d] (88%)[e]
12	**16a**	6:1 (81%)[d]	11:1 (91%)[d] (80%)[e]
13	**17b**	1:7 (82%)[d,f]	1:>20 (71%)[e]

(a) Minor isomer not isolated unless specified (b) Catalytic OsO_4/NMMO at RT (c) Stoichiometric OsO_4/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.

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**.[1] 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)[8] 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.

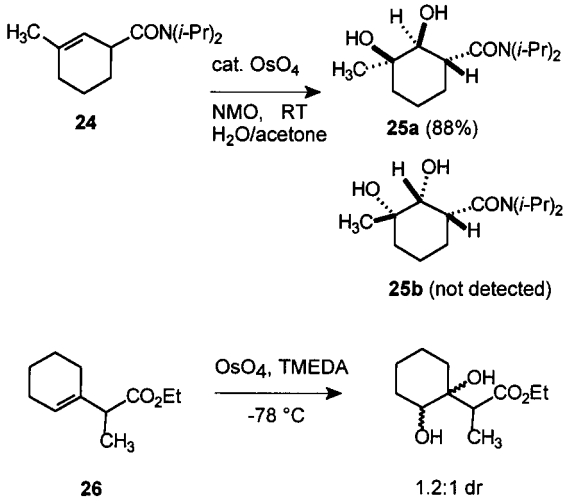
Scheme 2



The acid-catalyzed cyclizations from diols **15a**, **16a**, and **17b** were somewhat slower than the corresponding laconization 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.

(8) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037.

Scheme 3



Because **16a** and **17b** afford unique products **22** and **23**, reversible S_N1 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 β,γ-unsaturated amides in Table 1 reveals that the relative stereochemistry follows the same pattern with respect to the asymmetric α-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[2d,e] and in 4-substituted 2-pentenes.[2b] However, the amide substituent differs in its potential for osmium complexation compared to the examples explored previously. The constrained *Z*-trisubstituted alkene **24**[9] (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.[10a] 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 osmylations. The *N*,*N*-dimethyl analogue of **1** was explored briefly under the TMEDA conditions. Osmylation selectivity was lower (7:1 at −78 °C), but the major product had the same relative configuration, as shown by acid-catalyzed lactonization to **4**. Furthermore, osmylation of the corresponding ester **26**[11] (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 clear preference for one major alcohol diastereomer (Table 2). The purified hydroxyamides **27**, **28**, and **29** were lactonized using 10% H_2SO_4 as before, and the resulting **30**, **31**, and **32** were identified by comparisons with literature NMR data.[13] All three lactones have the same relative stereochemistry. Thus, hydroboration occurs with the same facial preference with the *E*- or the *Z*-trisubstituted alkenes **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.

(9) Vedejs, E.; Sakata, S. Unpublished Results.

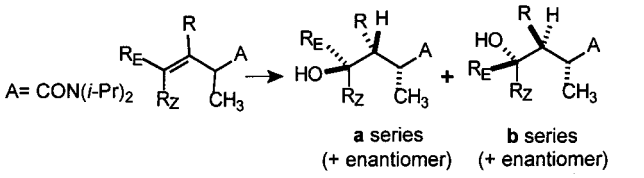
(10) (a) Palmer, C. F.; McCague, R.; Ruecroft, G.; Savage, S.; Taylor, S. J. C.; Ries, C. *Tetrahedron Lett.* **1996**, *37*, 4601. (b) Osmylation syn to allylic N−H is known in an amide example, but this selectivity may be influenced by additional factors: King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089 and references therein. For leading references to syn direction by other allylic heteroatoms, see ref 5c. (c) Krysan, D. J.; Rockway, T. W.; Haight, A. R. *Tetrahedron: Asymmetry* **1994**, *5*, 625 and references therein. (d) Reetz, M. T.; Strack, T. J.; Mutulis, F.; Goddard, R. *Tetrahedron Lett.* **1996**, *37*, 9293. Paz, M. M.; Sardina, F. J. *J. Org. Chem.* **1993**, *58*, 6990. Hauser, F. M.; Ellenberger, S. R. *J. Am. Chem. Soc.* **1984**, *106*, 2458. Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1981**, *46*, 227.

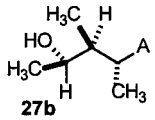
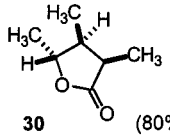
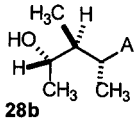
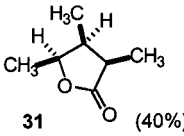
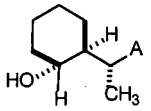
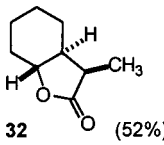
(11) Chavan, S. P.; Zubaidha, P. K.; Ayyangar, N. R. *Tetrahedron Lett.* **1992**, *33*, 4605.

(12) (a) Transition state proposal: Evans, D. A.; Bartroli, J.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4577. Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row: M. N. *Tetrahedron* **1984**, *40*, 2257. (b) Examples: Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259. Midland, M. M.; Kwon, Y. C. *J. Am. Chem. Soc.* **1983**, *105*, 3725. Burgess, K.; Cassidy, J.; Ohlmeyer, M. J. *J. Org. Chem.* **1991**, *56*, 1020. Burgess, K.; Ohlmeyer, M. J. *J. Org. Chem.* **1991**, *56*, 1027.

(13) (a) Petrzilka, M.; Felix, D.; Eschenmoser, A. *Helv. Chim. Acta* **1973**, *56*, 2950. (b) Forzato, C.; Nitti, P.; Pitacco, G. *Tetrahedron Asymmetry* **1997**, *8*, 4101.

Table 2. Hydroborylation of β,γ-Unsaturated Amines with 9-BBN



Alkene Substrate	Hydroboration; major product	Ratio of a : b[a] (yield)	Lactonization product[b]
12	 **27b**	1 : 5.7 (94%)	 **30** (80%)
13	 **28b**	<1 : 10 (63%)	 **31** (40%)[c]
1	 **29b**	<1 : 15 (69%)	 **32** (52%)

(a) The amide was refluxed with 9-BBN in THF. The minor isomer was not isolated; product ratio estimated by ^{1}H NMR assay (b) Lactonization conditions: 10% H_2SO_4, reflux. (c) Competing elimination occurred to give **12** (20%) as a byproduct

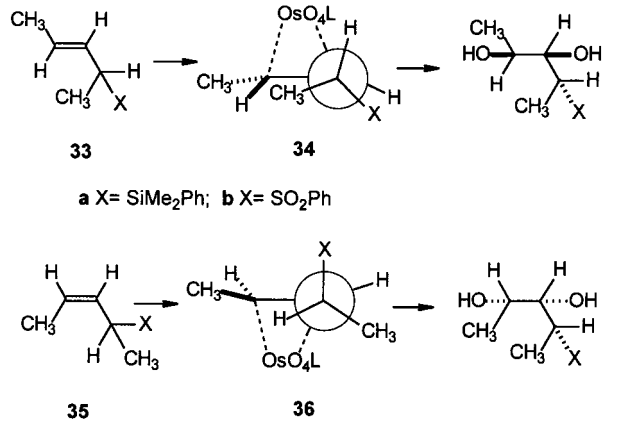


Figure 1. Major pathways for osmylation of 4-substituted pent-2-enes.

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 $SiMe_2Ph$ or SO_2Ph 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 steric 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.

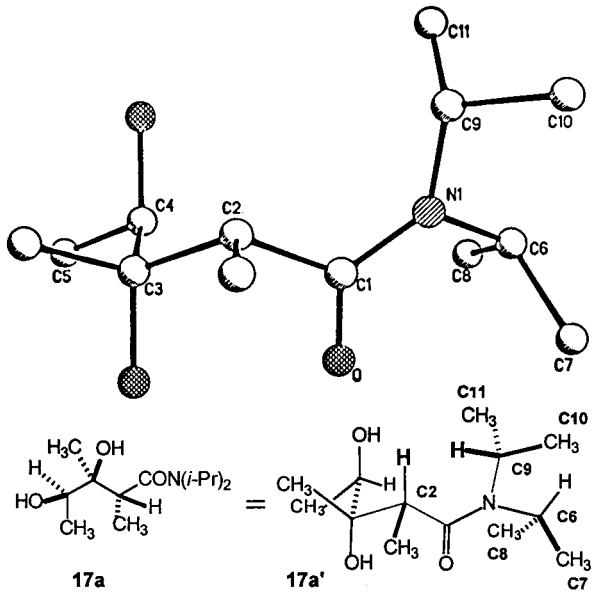


Figure 2. Crystal structure of **17a**.

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 NC=O 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 α-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

(14) (a) Corey, E. J.; Noe, M. C.; Grogan, M. J. *Tetrahedron Lett.* **1996**, *37*, 4899. (b) DelMonte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Strassner, T.; Thomas, A. A. *J. Am. Chem. Soc.* **1997**, *119*, 9907.

(15) For an example, see: Lutz, G. P.; Wallin, A. P.; Kerrick, S. T.; Beak, P. *J. Org. Chem.* **1991**, *56*, 4938.

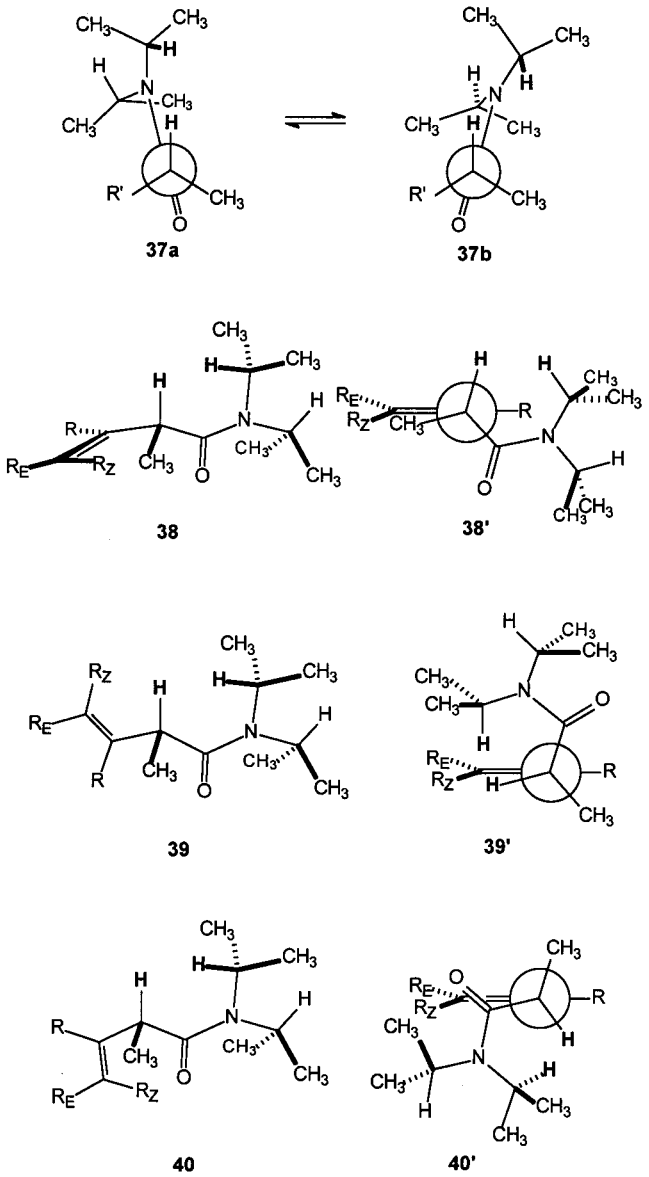


Figure 3. Selected ground state geometries.

hydrogens (correponding 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′ = R_ER_ZC = 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.[16]

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.,[17] 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 π-interaction of the OsO_4−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 R_Z = H. On the other hand, **41** is destabilized when R_Z = CH_3 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 R_Z (C4 methyl) and the amide. Any single one of these interactions can be reduced by turning the isopropyls 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.

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 (stoichiometric Os) reactions. Carbon isotope effect studies indicate that the five-center transition state has significant C−O bonding at both olefinic carbons.[14] 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-

(16) Allinger, N. L.; Hirsch, J. A.; Miller, M. A.; Tyminski, I. J. *J. Am. Chem. Soc.* **1968**, *90*, 5773. Lowe, J. P. *Prog. Phys. Org. Chem.* **1968**, *6*, 1. Wiberg, K. B. *J. Am. Chem. Soc.* **1986**, *108*, 5817. Dorigo, A. E.; Pratt, D. W.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 6591. Bader, R. F. W.; Cheeseman, J. R.; Laidig, K. E.; Wiberg, K. B.; Breneman, C. *J. Am. Chem. Soc.* **1990**, *112*, 6530.

(17) Corey, E. J.; Sarshar, S.; Azimioara, M. D.; Newbold, R. C.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 7851.

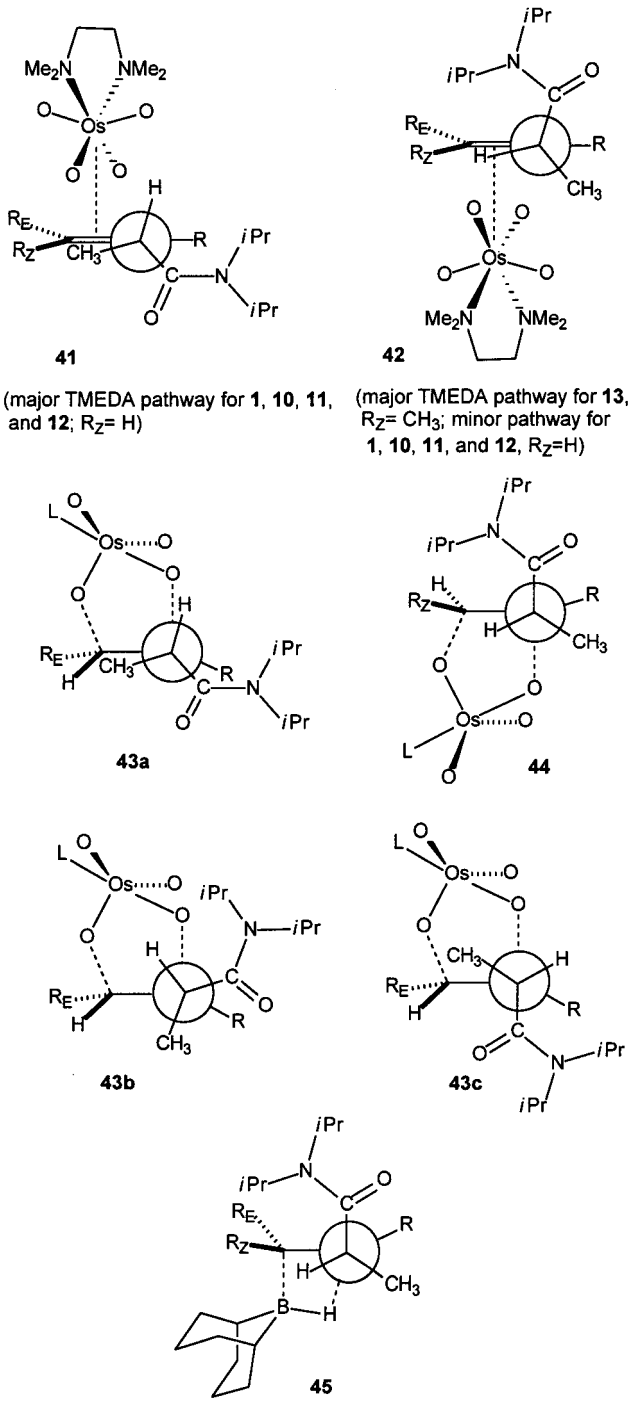


Figure 4. Proposed transition state geometries.

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 **42**; more staggered in the partly rehybridized **44**). 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 clockwise 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.[18] 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".[12a] Reagent bulk in the case of **45** is confined to an area near the substituents R_E and R_Z, 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 β,γ-unsaturated *N*,*N*-diisopropylamides (Table 1, Table 2) occurs with useful diastereoselectivity. As observed in several earlier osmylations,[2b,d,e] 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 δ-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 CaH_2 and distilled. CH_2Cl_2 was distilled from P_2O_5. All other reagents were used as received. Osmylation substrates **1**,[1] the *N*,*N*-dimethyl analogue of **1**,[1] **10**,[19] **11**,[19]**12**,[1] **13**,[1] **24**,[9] and **26**[20] were prepared according to literature procedures.

General NMO-Mediated Osmylation Procedure. The procedure is a modification of the method of Van Rheenen.[3] To a stirred solution of *N*-methylmorpholine *N*-oxide (1.5 equiv) and the alkene (1.0 equiv) in 10:1 acetone/H_2O at (0 °C or room temperature) was added OsO_4 (0.02−0.05 equiv, 2.5% w/v solution in *t*-BuOH, Aldrich). After TLC analysis indicated consumption of the alkene, excess $Na_2HSO_3/Na_2S_2O_5$ was added and the darkened reaction was stirred for 30 min at

(18) Haller, J.; Strassner, T.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 8031.
(19) Majewski, M.; Mpango, G. B.; Thomas, M. T.; Wu, A.; Snieckus, V. *J. Org. Chem.* **1981**, *46*, 2029.
(20) Henin, F.; Mortezaei, R.; Muzart, J.; Pete, J.-P.; Piva, O. *Tetrahedron* **1989**, *45*, 6171.

room temperature**.** To this solution was added ether, and the solution was dried ($MgSO_4$) and the solvent removed (aspirator).

General TMEDA-Mediated Osmylation Procedure.[5] To a stirred solution of the alkene and TMEDA (1.1−1.5 equiv) at −78 °C was added OsO_4 (solution in CH_2Cl_2), 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 osmate ester was reduced with 1:1 saturated $NaHSO_3$/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 ($MgSO_4$) and evaporated (aspirator) to give the crude product.

Diols 2a (Major) and 2b (Minor). The general NMO procedure (rt) using **1**[1] (213 mg, 0.90 mmol), NMO (126 mg, 1.1 mmol), and OsO_4 (0.25 mL of a 2.5% v/v solution in *t*-BuOH, 0.02 mmol, Aldrich) afforded 254 mg (99%) of a 3.2:1 diastereomer ratio (**2a** (major):**2b** (minor)) that was >90% diols. The residue was purified by flash chromatography on EM silica gel 60 (33 × 1.6 cm, 50 mL and then 8 mL fractions). Fractions 13−16 gave 52 mg of **2b** (21%) and fractions 18−25 afforded 165 mg of **2a** (68%); 4:1 CH_2Cl_2/ether eluent; analytical TLC on EM silica gel 60, 4:1 CH_2Cl_2/ether, R_f = 0.50 (**2b**, minor), R_f = 0.45 (**2a**, major). **Major diastereomer 2a. *rac*-(2*R*,1′*S*,2′*S*)-2-(1′,2′-Dihydroxycyclohexyl)-*N*,*N*-diisopropylpropanamide:** solid; molecular ion calcd for $C_{15}H_{29}NO_3$ 271.21470, found *m*/*e* = 271.2146, error = 0 ppm; IR (neat, cm^{-1}) 3442, O−H; 3236, O−H; 1604, C═O; 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 6.46 (1H, s) 4.08 (1H, sept, *J* = 6.6 Hz) 3.60−3.39 (2H, m) 2.82 (1H, q, *J* = 7.2 Hz) 2.50 (1H, br s) 1.90−1.42 (6H, m) 1.41−1.22 (14H, m) 1.18 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 177.5 s, 74.7 s, 73.4 d, 48.5 d, 45.9 d, 37.2 d, 30.8 t, 29.9 t, 21.2 t, 21.2 t, 20.9 q, 20.8 q, 20.2 q, 20.2 q, 12.7 q. **Minor diastereomer 2b. *rac*-(2*R*,1′*R*,2′*R*)-2-(1′,2′-Dihydroxycyclohexyl)-*N*,*N*-diisopropylpropanamide:** colorless oil; molecular ion calcd for $C_{15}H_{29}NO_3$ 271.21470, found *m*/*e* = 271.2155, error = 3 ppm; IR (neat, cm^{-1}) 3419, O−H; 3263, O−H; 1604, C═O; 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 5.20 (1H, br s) 4.25−4.05 (1H, m) 3.80−3.40 (2H, m) 3.71 (1H, ddd, *J* = 9.9, 4.4, 2.2 Hz) 2.91 (1H, q, *J* = 7.2 Hz) 1.79−1.32 (14H, m) 1.29−1.19 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 176.7 s, 74.4 s, 70.2 d, 49.2 d, 46.3 d, 35.5 d, 29.8 t, 23.1 t, 21.3 t, 21.1 q, 20.6 q, 20.5 q, 14.5 q.

Preparation of 2a Using TMEDA/OsO_4. To a solution of **1**[1] (272 mg, 1.15 mmol) and TMEDA (208 μL, 1.38 mmol) in 2.0 mL of CH_2Cl_2 at −78 °C was added OsO_4 (350 mg, 1.38 mmol) in CH_2Cl_2 (2 × 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 $NaHSO_3$, and 0.75 mL of water, the solution was heated to reflux for 2 h. The solution was then diluted with ether (30 mL), dried ($MgSO_4$), and evaporated to a green oil (314 mg). ^{1}H NMR assay of this residue indicated a 11:1 diastereomer ratio and >95% conversion to diols. The residue was purified by flash chromatography on EM silica gel 60 (23 × 1.6 cm, 7 mL fractions; 4/1, CH_2Cl_2/ether eluent). Fraction 11 gave 11 mg of a mixture of **2a** and **2b**. Fractions 12−33 gave 253 mg (82%) of pure **2a**.

Lactonization of Diol 2a. *rac*-(3*R*,3a*S*,7a*S*)-3a-Hydroxy-3-methylhexahydrobenzofuran-2-one (3) and (3*R*,3a*S*,-7a*S*)-3. To **rac-2a** (200 mg, 0.74 mmol) in 1.8 mL of dioxane was added 1.6 mL of a 10% H_2SO_4 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 ($MgSO_4$) and evaporated (aspirator) to give 126 mg of a white solid. ^{1}H NMR analysis indicated >90% conversion to product. Crystallization of the initial product from ether afforded 77 mg of **3** (62%). The mother liquor (44 mg) was purified by flash chromatography on EM silica gel 60 (11 × 1 cm, 4:1 CH_2Cl_2/ether eluent, 3 mL fractions, 25 mL prerun). Fractions 4−7 gave 24 mg of **3** (19%). The materials were combined to afford 101 mg (81%) as a white crystalline solid.

Pure **rac-3** was obtained by crystallization from ether/hexane, mp 120.0−121.0 °C. X-ray crystallography confirmed the structural assignment. Molecular ion calcd for $C_9H_{14}O_3$ 170.09430, found *m*/*e* = 170.0957, error = 8 ppm; IR (neat, cm^{-1}) 3508, O−H; 1759, C═O; 300 ^{1}H MHz NMR ($CDCl_3$, ppm) δ 3.97 (1H, dd, *J* = 11.6, 5.2 Hz) 2.46 (1H, q, *J* = 7.0 Hz) 2.01−1.87 (4H, m) 1.69−1.62 (3H, m) 1.52−1.25 (2H, m) 1.20 (3H, d, *J* = 7.0 Hz).

Enantiomerically enriched **3** was prepared by the same sequence starting from (*R*)-**1** of 96% ee and performing the lactonization on 98 mg of enantiomerically enriched diol **2a** to give 50 mg (82%) of (3*R*,3a*S*,7a*S*)-**3** after chromatography as described above, oil, ($[\alpha]^{25}_D$ = −46, *c* = 0.05).

Lactonization of the Minor Diol 2b. *rac*-(3*R*,3a*R*,7a*R*)-3a-Hydroxy-3-methylhexahydrobenzofuran-2-one (4). To **rac-2b** (25 mg, 0.09 mmol) was added 0.27 mL of a 10% H_2SO_4 solution (v/v) (5 equiv), and the mixture was heated to reflux for 2 h. The acid layer was extracted with ether (3 × 2 mL). The combined organic layers were dried ($MgSO_4$) and evaporated (aspirator) to give 13 mg of an oil. ^{1}H NMR analysis indicated a 3.5:1 ratio of **4**:**2b** with no sign of **3**. An isomeric product was also present (ca. 10%; R_f = 0.47 in 1:1 EtOAc:hexane), identified as the ketone derived from pinacol rearrangement of **2b**. The structure of the pinacol contaminant was confirmed by correlation with **29b** (see Supporting Information).[4] The residue was purified by preparative layer chromatography on EM silica gel 60 (20 × 20 × 0.02 cm), 4:1 CH_2Cl_2/ether eluent (R_f = 0.36), which afforded 9 mg (60%) of **4** as an oil. Analytical TLC on EM silica gel 60, R_f = 0.37. Molecular ion calcd for $C_9H_{14}O_3$ 170.09430, found *m*/*e* = 170.0944, error = 1 ppm; IR (neat, cm^{-1}) 3482, O−H; 1757, C═O; 300 MHz NMR ($CDCl_3$, ppm) δ 4.11 (1H, dd, *J* = 11.8, 4.8 Hz) 2.55 (1H, q, *J* = 7.7 Hz) 2.04−1.25 (9H, m) 1.20 (3H, d, *J* = 7.7 Hz).

Elimination of Enantiomerically Enriched 3 to 5[7] Using $SOCl_2$/Pyridine. To a solution of (3*R*,3a*S*,7a*S*)-**3** (45 mg, 0.26 mmol) in 0.5 mL of pyridine at 0 °C was added thionyl chloride (60 μL, 0.79 mmol). After 15 min the reaction was warmed to room temperature and the solution was stirred for 30 min. Ether (5 mL) was added, and the resulting solution was extracted with 1.5 N HCl (3 × 3 mL). The ether layer was dried ($MgSO_4$) and evaporated to an oil. The initial residue was purified by flash chromatography (13 × 1 cm, 2 mL fractions), 9:1 hexane:ether. Fractions 8−10 gave 2 mg of the minor lactone **6**. Fractions 13−17 gave 30 mg (75%) of pure (*S*)-**5** ($[\alpha]^{25}_D$ = +54, *c* = 0.03). Comparison of a racemic sample of **5**[7] and the enantiomerically enriched (*S*)-**5** by HPLC on a chiral stationary phase (93:3 hexane/EtOH, (*R*,*R*)-Whelk-O 1 (Regis), flow = 1.0 mL/min, t_R19.3 min (*R*), 20.1 min (*S*)) established that the ee was greater than 90% favoring the (*S*) enantiomer. Baseline resolution could not be achieved, but an authentic 95:5 mixture of enantiomers prepared from the enriched and racemic samples showed a clear inflection point for 90% ee that was absent in the enriched sample (>90% ee). To establish the structure of **6**, a similar experiment was performed starting with racemic racemic **3** and **rac-6** was obtained as an oil; analytical TLC on EM silica gel 60, 1:1 hexane/ether, R_f = 0.59. Molecular ion calcd for $C_9H_{12}O_2$ 152.08370, found *m*/*e* = 151.0758; M − 1, 151.0758; IR (neat, cm^{-1}) 1756, C═O; 300 MHz ^{1}H NMR ($CDCl_3$, ppm) δ 5.55 (1H, br s) 4.86−4.76 (1H, m) 3.20−3.09 (1H, m) 2.36−2.27 (1H, m) 2.19−2.09 (2H, m) 2.00−1.89 (1H, m) 1.69−1.52 (1H, m) 1.47−1.33 (1H, m) 1.31 (3H, d, *J* = 6.9 Hz).

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Supporting Information Available: X-ray data tables for **3**, **17a**, and **19**. NMR spectra. Procedures and characterization for **14a**, **18a**,**b 19**, **15**−**17**, **21**−**23**, and **25**−**29**, and correlations with **30**−**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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