Investigations on 1,2-, 1,3-, and 1,4-Asymmetric Induction in Intramolecular Reformatsky Reactions Promoted by Samarium(II) Iodide

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Abstract: A series of β- and γ-haloacetoxy ketones and aldehydes bearing substituents at various positions were cyclized with samarium(II) iodide (SmI_2), providing the corresponding hydroxy lactones. Excellent 1,2- and 1,3-asymmetric inductions were demonstrated in the cyclization of β-haloacetoxy carbonyl substrates. Although 1,2-asymmetric induction was also exceptional with the γ-bromoacetoxy ketones, 1,3-asymmetric induction was in general far less impressive. Low levels of 1,4-asymmetric induction were achieved in cyclization of the γ-haloacetoxy substrates. Despite the varying levels of asymmetric induction demonstrated with the γ-haloacetoxy substrates examined, this method provides a useful, general route to stereodefined 4-hydroxy-1-oxacyclohexan-2-ones and 4-hydroxy-1-oxacycloheptan-2-ones, which can be carried out under very mild conditions.

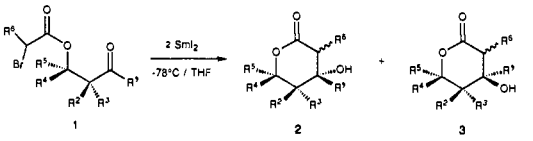
Introduction

Although the traditional and most often utilized protocol for promoting the Reformatsky reaction employs zinc metal, there are problems inherent in this method. The necessity for long reaction times in solvents heated to reflux often leads to products resulting from the desired reaction followed by elimination to the α,β-unsaturated ester or self-condensation of the carbonyl substrate.[2] In addition, attempts at stereoselective zinc-promoted intermolecular Reformatsky reactions have been thwarted by low yields and poor diastereoselectivities. In a search for other metals that could promote the Reformatsky reaction, magnesium, lithium, aluminum, and cadmium have been employed with varying results.[3]

In 1980, Kagan reported that treatment of cyclohexanone with SmI_2 and ethyl α-bromopropionate resulted in a 90% yield of the desired Reformatsky product.[4] Diastereoselective processes were not examined in this initial study. Subsequent to this early study, lanthanide reagents have been used to promote both intermolecular and intramolecular Reformatsky-type reactions. For example, the utility of SmI_2 in the formation of 8- through 14-membered lactones has been demonstrated, although little mention was made of the diastereoselectivity of the reaction.[5] Cerium reagents have also been applied to Reformatsky-type processes, providing the desired condensation products in high yields but with low levels of diastereoselectivity.[6] Finally, a $LaBr_3$-assisted Reformatsky reaction of α-bromopropiophenone and benzaldehyde under electrochemical conditions has also been reported.[7] In this example, an equilibrium mixture of the diastereomeric condensation products was formed.

We were intrigued with the possibility of achieving 1,2-, 1,3-, and perhaps even 1,4-asymmetric induction during the course of SmI_2-promoted intramolecular Reformatsky-type reactions. The oxophilic nature of Sm(III) and the chelating ability of this ion[8] led us to propose a simple, empirical model for intramolecular Reformatsky-type reactions promoted by SmI_2. On the basis of this six-membered chair transition structure (Figure 1, **1A**) and the high level of organization engendered therein, excellent diastereoselectivities in these processes were anticipated.

Indeed, preliminary work demonstrated the utility of SmI_2 in the stereoselective intramolecular Reformatsky-type cyclization of β-bromoacetoxy ketones and aldehydes, yielding substituted δ-valerolactones in high yield.[9] In these transformations, excellent 1,2- and 1,3-asymmetric inductions were achieved in nearly all cases, and the sense of this asymmetric induction was fully in accord with the proposed model (eq 1).



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Systematic investigation of the cyclization encompassing a wider range of substrates was undertaken to delineate specific factors involved in the stereoselectivity of SmI_2-promoted intramolecular Reformatsky-type reactions. In addition, it was our intent to extend this method to the cyclization of γ-haloacetoxy ketones and aldehydes in order to examine the possibility of 1,4-asymmetric induction in this reaction. The results of these investigations are outlined below.

Results and Discussion

Many general approaches to 1,2-asymmetric induction have been developed in recent years. In particular, the stereoselective addition of carbon-centered nucleophiles to aldehydes and ketones bearing a stereogenic α-carbon has been extensively explored. Steric and electronic properties of both the nucleophile[10] and the electrophile can often be manipulated to accomplish selective facial attack in carbonyl addition reactions.[11] In what are perhaps the

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Table I. Cyclization of Haloacetoxy Aldehydes and Ketones with 2 equiv of SmI_2 (Eq 1)

substrate	R^1	R^2	R^3	R^4	R^5	R^6	% isoltd yield	diastereomeric ratio **2:3**[a]
1a	Ph	H	Me	H	H	H	76	>200:1
1b	isopropenyl	H	Me	H	H	H	66	>200:1
1c	*t*-Bu	H	Me	H	H	H	85	>200:1
1d	Et	H	Me	H	H	H	99	3:1
1e	*i*-Pr	H	OBn	H	H	H	57	1:6
1f	$-(CH_2)_4-$		H	H	H	H	68	1.6:1
1g	H	H	H	*n*-Pr	H	H	69	>200:1
1h	Me	H	H	*n*-Pr	H	H	70	>200:1
1i	Me	H	H	Ph	H	H	95	>200:1
1j	*t*-Bu	H	H	Ph	H	H	98	>200:1
1k	H	H	Me	Ph	H	H	65[b]	>200:1
1l	Et	H	Me	*n*-Pr	H	H	86[c]	>200:1
1m	*t*-Bu	H	Me	Ph	H	H	71[c]	>200:1
1n	H	Me	H	Ph	H	H	62[b]	>200:1
1o	Et	Me	H	*n*-Pr	H	H	97[d] (65[e])	8:1
1p	Ph	Me	H	Ph	H	H	17[b]	1.4:1
1q	*t*-Bu	Me	H	Ph	H	H	88	1:>200
1r	H	H	H	Me	Et	H	17	1:1
1s	H	H	H	Me	Ph	H	56[f]	20:1
1t	Me	H	H	Me	Ph	H	79[f]	29:1
1u	*t*-Bu	H	H	H	H	Me	63[g]	1.8:1

[a] Determined by GC analysis on the crude reaction mixture with fused silica GC capillary columns. [b] Reaction performed at ambient temperature. [c] Reaction performed at 0 °C. [d] Diastereomeric ratio was 8:1 when performed at −20 °C. [e] Reaction performed at −78 °C provided a 13:1 mixture of diasteromers. [f] Produced from corresponding iodo ester. [g] Reaction performed at −100 °C.

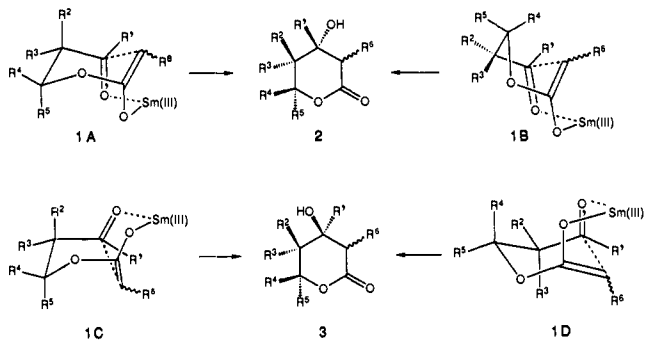
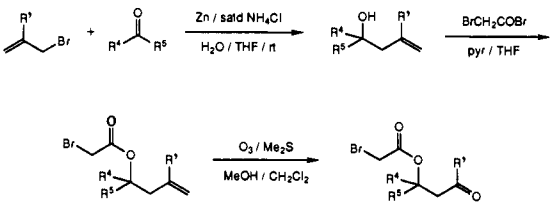


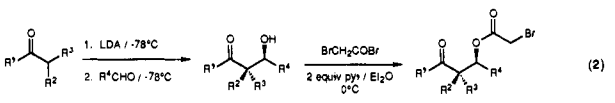
Figure 1. Empirical transition-structure models for SmI_2-promoted cyclization of β-bromoacetoxy ketones and aldehydes.

most reliable and effective methods, chelation of heteroatom substituents α to the carbonyl with a Lewis acid is exploited in order to "lock" the substrate into a conformation that greatly favors one mode of attack.[11,12]

Intramolecular carbonyl addition reactions in which a latent nucleophile is incorporated within the substrate (to be activated at an opportune time by addition of a "triggering" reagent) represent an important subset of "directed reactions". In these procedures, one can exploit both the highly ordered nature inherent in intramolecular reactions[13] and the enthalpic and entropic advantages of chelation[14] to control relative asymmetric induction. This strategy has been employed very effectively in the current study. The β-bromoacetoxy ketone substrates used in the first part of this investigation were generally available through a two-step sequence (eq 2). An appropriate ketone enolate was condensed with an aldehyde or ketone uner typical aldol conditions.[15] The resulting β-hydroxy ketone was treated with bromoacetyl bromide in the presence of pyridine at 0 °C to provide the desired substrate.

Scheme I





(2)

Substrates **1l** and **1o** were prepared in diastereomerically pure form from the corresponding diastereomers of 5-hydroxy-4-methyl-3-octanone. The latter were generated as a mixture and separated by chromatography.[16] Substrate **1m** was prepared by the method of Heathcock, in which the trimethylsilyl enol ether of 2,2-dimethyl-3-pentanone was added to a solution of benzaldehyde and $BF_3{\cdot}OEt_2$ in CH_2Cl_2.[17]

Other substrates that were not directly accessible from this route, in particular the aldehyde substrates, were available through ozonolysis of the corresponding homoallylic bromoacetates (Scheme I). *threo*- and *erythro*-2-Methyl-1-phenylbut-3-en-1-ol were prepared as a mixture by the method of Brown[18] and then separated by flash chromatography on $AgNO_3$-impregnated silica gel. The two compounds were subsequently acylated with bromoacetyl bromide and then ozonolyzed to provide substrates **1k** and **1n**.

The results obtained in studies of 1,2-asymmetric induction in the intramolecular Reformatsky-type process were generally quite favorable. In Table I, substrates **1a–1f** reveal that the diastereoselectivity was dependent to a large extent on the steric bulk of R^1.

In assessing the contribution of various transition structures to the observed diastereoselectivities, we have postulated that the

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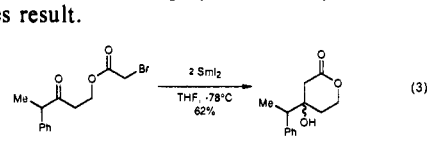
boat transition structures (Figure 1, **1B** and **1C**) are unfavorable relative to the chair transition structures (**1A** and **1D**) because of the usual unfavorable interactions associated with the former conformations. However, another compelling reason to believe that only the two competing chair transition structures must be considered relates to the conformation of the enolate in the respective chair and boat conformations. Conformational analyses have established that *Z* ester rotamers are substantially favored over the corresponding *E* ester rotamers.[19] To the extent that this preference asserts itself in the transition state of the intramolecular Reformatsky reactions, exclusive involvement of the chair transition structures should be even more highly favored. It should be noted that these transition structures must be modified from that of the usual (Zimmerman–Traxler) chairs because of the bicyclic nature of the transition structures in this particular transformation.[14a]

As mentioned above, the effect of R^1 on the diastereoselectivity of 1,2-asymmetric induction was striking. When R^1 was sterically imposing, as in **1a–c** (R^1 = isopropenyl, phenyl, and *t*-Bu, respectively), the diastereoselectivity was very high. The stereochemistry of the major product (**2**) derived from substrate **1c** was determined by single-crystal X-ray diffractometry, and the stereochemistry of the products from **1a** and **1b** was assigned by analogy. The sense of 1,2-asymmetric induction observed is consistent with the model (Figure 1, **1A**) originally proposed for the cyclization, and the correlation between the steric bulk of R^1 and the diastereoselectivity of the cyclization reinforces this proposal. Thus, when R^1 and R^3 are large alkyl groups (R^2 = R^{4-6} = H), a chair transition structure in which R^3 occupies an equatorial position should be preferred. Structure **1A** is preferable to that of **1D** because the latter leads to $A^{1,2}$ strain[20] between R^1 and R^3. These interactions become particularly severe as the size of R^1 is increased. Diastereoselectivities for the reaction track accordingly. In substrate **1d**, where only an ethyl and methyl group are present to force the substrate into the desired chair transition structure (**1A**), diastereoselectivity is low. In this case, a structure such as **1D** is closer in energy to **1A** (there being but a single gauche propyl ether interaction[21] with R^3 and the gauche butane interaction between axially oriented R^3 and the developing bond). It is apparent from these results and those that follow that substituents in the α-position are relatively weak stereodirectors, and that a large substituent at R^1 is required for high levels of 1,2-asymmetric induction in this process.

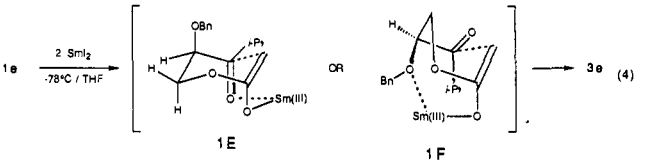
Other significant features of the reaction bear mentioning. The first is that the incorporation of the controlling stereocenter within the Sm(III) chelate appears to be crucial to the attainment of high diastereoselectivities. As evidence of this, cyclization of 5-(bromoacetoxy)-2-phenylpentan-3-one provides only a 2:1 mixture of diastereomers (eq 3). In this substrate, the stereocenter is placed outside of the proposed chelate ring, with free rotation about the carbon–carbon bond linking the carbonyl unit to the stereocenter. As expected from such a highly fluxional system, low diastereoselectivities result.



(3)

Another interesting observation is that virtually no unsaturated lactones are generated as byproducts in these reactions. Even in those cases where tertiary benzylic (**2a**) and tertiary allylic (**2b**) alcohols are generated β to the lactone carbonyl, excellent yields of the desired products are obtained. This is in stark contrast to the situation with zinc-promoted Reformatsky reactions where significant elimination occurs.[2] Furthermore, substrate **1b** dramatically demonstrates the chemoselectivity of the reaction with regard to α,β-unsaturated carbonyl substrates. In spite of the fact that the conjugated ketone might be expected to suffer facile reduction or polymerization,[4] the mild reaction conditions permit selective 1,2-carbonyl addition to occur with surprising ease.

Substrate **1e** possesses a heterosubstituent α to the ketone. In this example, the stereochemistry of the major diastereomer was shown by X-ray crystallography to be that represented by **3**, in which the benzyloxy group is trans to the hydroxyl group in the product. It is interesting to note that the stereochemistry of this product is opposite that derived from **1b**, even though R^1 is nearly identical in the two substrates (i.e., the steric bulk of the isopropyl and isopropenyl groups is very similar). Stereoelectronic effects seem important in this stereochemical reversal. A transition structure in which the benzyloxy group (R^3) occupies an axial position, antiperiplanar to the carbonyl undergoing attack (eq 4, **1E**), may be energetically favorable from the standpoint of minimizing dipole–dipole interactions. The *A* value of the



(4)

benzyloxy group (on the order of 0.60) would not necessarily preclude its axial disposition, and the presence of a smaller gauche propyl ether interaction[21] replacing the normal gauche butane interaction in such a structure might further reinforce this supposition.[22] The benzyloxy group may also act to break up the Sm(III) chelate between the two carbonyl moieties (eq 4, **1F**). If Sm(III) chelation between the enolate oxygen and the benzyloxy group occurs, and in addition the ketone carbonyl is antiperiplanar to the benzyloxy group in order to minimize dipole interactions, then diastereomer **3** would again be expected to predominate. The latter explanation seems less likely because a highly strained boat transition structure would be required.[23]

Substrate **1f** introduces a slight twist to the notion of 1,2-asymmetric induction in the cyclization. The cyclohexanone substrate raises the question of whether equatorial versus axial attack of the samarium ester enolate on the carbonyl or other factors are the stereocontrolling elements in this particular cyclization. As shown in Table I, diastereoselectivity in the cyclization is in fact quite low. These results are consistent with the observation that substrate **1d** also provides cyclized product with low diastereoselection. This implies that $A^{1,2}$ strain (or specifically, the lack thereof) and not axial versus equatorial preference is the stereocontrolling element in the cyclization of the substituted cyclohexanone derivative.

Relatively few examples of 1,3-asymmetric induction in intermolecular carbon–carbon bond-forming reactions have been reported.[11,12e,24] Still fewer studies of intramolecular carbon–carbon bond-forming processes of this type have been documented.[13] The SmI_2-promoted intramolecular Reformatsky reaction has proven to be equally successful as these previously reported methods in terms of its general applicability and its

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(23) Attempts to clarify the issue by preparing the corresponding *tert*-butyldimethylsilyl ether (which would presumably not be involved in chelation: Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697 and references therein) were unsuccessful. We are therefore resigned to conclude only that the effect of the alkoxy group is due to the stereoelectronic properties of the substituent and is unlikely to be associated with steric effects.

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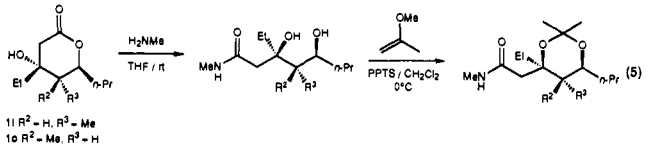
attainment of uniformly high diastereoselectivity. In fact, the 1,3-asymmetric induction achieved in the cyclization of the β-bromoacetoxy ketones and aldehydes was more impressive and even more general than the 1,2-asymmetric induction described above. This is depicted in Table I with substrates **1g** through **1j**. In all cases, the diastereoselectivities were >200:1 regardless of the steric bulk of R^1, with yields in the range of 69–98%. The stereochemistry of the product from **1g** was established by comparison with ^{13}C NMR chemical shifts reported in the literature,[25] and the stereochemistry of the major product from **1i** and **1j** was determined by single-crystal X-ray diffractometry. The stereochemistry of **2h** was assigned by analogy.

These transformations not only provide an extraordinary means for 1,3-acyclic stereochemical control (after ring opening of the lactone), but they also provide entry to stereodefined β-hydroxy valerolactones. Molecules possessing this functional array, structurally analogous to compactin lactone, are potent inhibitors of HMG-CoA reductase, an important enzyme involved in the biosynthesis of cholesterol.[26]

It appears from the preceding results that the β-stereocenter has a stronger influence on stereoinduction than the α-stereocenter. The empirical chair transition structure suggests a reason as to why this might be so. A transition structure placing R^4 in a favorable equatorial position (**1A**) correctly predicts the formation of the observed products. On the other hand, structure **1D**, placing R^4 in an axial orientation, suffers not only from the usual gauche butane interactions of axially oriented substituents, but also from severe *syn*-pentane interactions between this substituent and the Sm(III) chelate. This highly unfavorable situation is likely to be exacerbated by the short carbon–oxygen bonds found in the incipient ring, which brings the axial substituents even closer together. In fact, the steric interactions described are proposed to be the predominant stereochemical control elements in establishing relative asymmetric induction in more highly substituted substrates.

Substitutionally elaborated substrates were prepared in order to determine the extent to which an α-stereocenter would influence 1,3-asymmetric induction in the cyclization of β-bromoacetoxy ketones and aldehydes. Diastereomerically pure substrates **1k–m** were thus subjected to typical cyclization conditions in order to investigate the possibility of establishing three contiguous stereocenters in a 6-membered lactone. In fact, all three substrates demonstrated that 1,3-asymmetric induction could be reinforced by the presence of a substituent at the α-position; i.e., a single diastereomer was generated in each case. In such substrates, substituents R^3 and R^4 can both assume equatorial positions in the empirical transition structure **1A** (Figure 1). In this structure, there are no severe gauche butane or *syn*-pentane interactions as there would be in **1D**, and furthermore, the eclipsing R^1–R^3 interactions are absent. The stereochemistry of the products derived from cyclization of **1k** and **1m** was established by single-crystal X-ray diffractometry. The stereochemistry of **2l** was determined by converting the product lactone to the corresponding 3,5-dihydroxy amide with methylamine, followed by acetonide formation with pyridinium *p*-toluenesulfonate (PPTS) and 2-methoxypropene (eq 5). Single-crystal X-ray diffractometry of the resulting acetonide allowed assignment of the lactone stereochemistry.

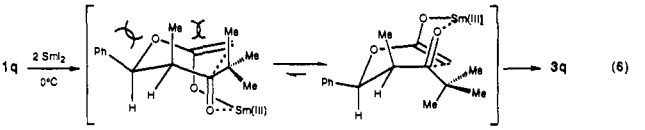


1l R^2 = H, R^3 = Me
1o R^2 = Me, R^3 = H

Substrates **1n–q** were also prepared as single diastereomers and subjected to the standard cyclization conditions. In each of these substrates, substituents at R^2 and R^4 must compete for equatorial positions in the proposed transition structures. That is, if a chair transition structure is operative, then one of the substituents must assume an axial orientation. It is interesting to note that with substrates **1n** and **1o**, the effect of the substituent at the β-carbon *overcomes* the influence of the methyl group at the α-carbon, and a predominance of product **2** is still observed. A single diastereomeric product was isolated from reductive cyclization of **1n**, and its stereochemistry was determined by single-crystal X-ray diffractometry. The stereochemistry of **2o** was established by X-ray diffractometry in the same way as that of **2l** above (eq 5).

The bias for stereochemical control being derived from the stereocenter distal to the prochial reaction center in preference to that of the proximal stereocenter has been recorded in other studies involving intramolecular reactions. For example, asymmetric reduction of β-hydroxy ketones employing tetramethylammonium triacetoxyborohydride,[27] SmI_2-promoted intramolecular Tischenko reduction of β-hydroxy ketones,[28] and iodolactonization reactions of homoallylic phosphonates[29] all exhibit strong stereocontrol by a β-stereocenter in preference to the α-stereocenter in facial addition to reactive π-systems. In Evan's studies,[27,28] the intramolecular nature of the reaction, coupled with strong chelation between the hydroxyl and carbonyl moieties with either boron or samarium(III), allowed the effects of remote (β) stereogenicity to almost completely outweigh any effects of α-substituents. In the present study, the bias for 1,3-asymmetric induction can again be rationalized on the basis of the proposed model. Thus, although R^4 experiences severe *syn*-pentane interactions with the Sm(III) chelate in chair structure **1D**, R^2 would experience far fewer unfavorable interactions when it is axially disposed, as in **1A**. Consequently, the remote (β) stereocenter can be expected to dictate facial selectivity through transition structure **1A** in these and related carbonyl addition reactions.

There is, however, a limit to this phenomenon. As the steric bulk of substituents at the α- and β-stereocenters increases, the diastereoselectivity decreases (substrate **1p**). Eventually, a complete reversal in stereochemistry is observed (substrate **1q**). Single-crystal X-ray diffractometry established the stereochemistry of the major product derived from the reaction of **1q** with SmI_2. The former compound is believed to have cyclized through the boat transition state **1C**, thereby eliminating the *syn*-pentane and gauche butane interactions present in the chair transition structure **1A** and the severe 1,3-diaxial interactions inherent in **1D** (eq 6). Thus, when the steric demands of substituents R^1, R^2, and R^4 become great enough, a significant decrease in steric interactions is realized by passing through such a boat transition state. Analogous changes from chair to boat-like transition states have also been observed in ester enolate Claisen rearrangements.[30]



Substrates **1r–t** illustrate attempts to achieve 1,3-asymmetric induction from a quaternary β-center. Because this substitution pattern does not permit both R^4 and R^5 to be oriented equatorially, both chair transition structures (**1A** and **1D**) are equally accessible when R^4 and R^5 are similar in size. This is reflected in the lack of diastereoselectivity observed with **1r**. On the other hand, geminally disubstituted substrates **1s** and **1t** provided excellent diastereoselectivity. The stereochemistry of the major product from **1s** was determined by X-ray crystallography. The stereochemistry of the major product from **1t** has been assigned by analogy to that of **1s**. In light of the stereochemistry of the product, this places the phenyl group in an axial orientation in

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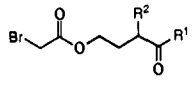
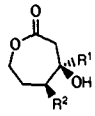
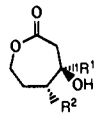
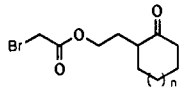
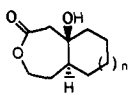
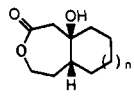
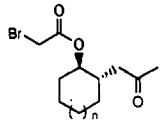
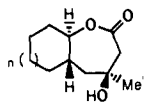
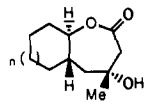
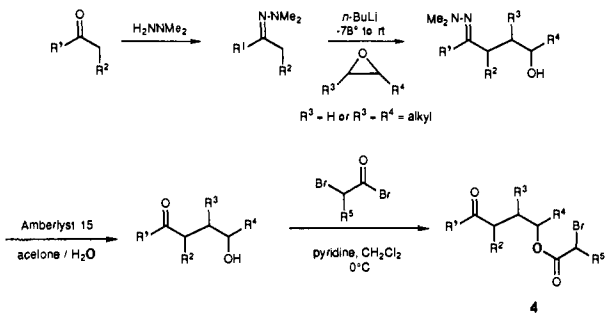
Table II. Cyclization of Substrates **4a–f** (Eq 7)

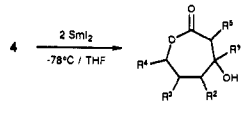
substrate	products		diastereomeric ratio (**5**:**6**)	% isoltd yield
				
4a R^1 = Et, R^2 = Me	**5a**	**6a**	>200:1	39
4b R^1 = Ph, R^2 = Me	**5b**	**6b**	>200:1	65
				
4c n = 1	**5c**	**6c**	>200:1	44
4d n = 3	**5d**	**6d**	29:1	72
				
4e n = 0	**5e**	**6e**	>200:1	73
4f n = 1	**5f**	**6f**	29:1	68

Scheme II



the proposed transition structure. In fact, conformational analyses have shown that the preferred conformation of 1-methyl-1-phenylcyclohexane is that in which the phenyl group maintains an axial orientation with an energy difference between the two limiting conformers of 0.30–0.34 kcal/mol.[31]

Virtually all of the results from the SmI_2-promoted cyclization of β-bromoacetoxy carbonyl substrates could be rationalized on the basis of the simple empirical model proposed. At the outset, the situation that would be encountered in the cyclization of γ-bromoacetoxy ketones was not as clear. Preparation of requisite substrates for this aspect of the study was straightforward. The appropriate ketone hydrazones were prepared and converted to the metalated hydrazone with *n*-BuLi.[32] Alkylation of these metalated hydrazones with monosubstituted or symmetrically disubstituted epoxides provided the desired hydroxy hydrazones,[33] which were hydrolyzed to the corresponding γ-hydroxy ketones in the presence of Amberlyst 15 and acetone.[34] Subsequent treatment with bromoacetyl bromide in the presence of pyridine afforded the requisite γ-bromoacetoxy ketones (Scheme II). Cyclizations of γ-bromoacetoxy ketones were carried out under the same conditions as for the β-bromoacetoxy ketones and aldehydes above. Substrates were treated with 2 equiv of SmI_2 at −78 °C and allowed to react for approximately 1 h (eq 7).



(7)

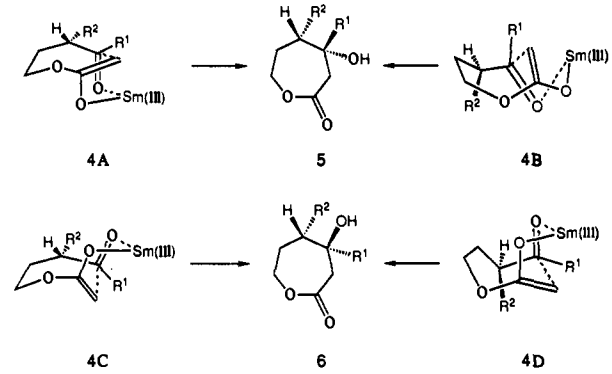


Figure 2. Empirical transition-structure models for SmI_2-promoted cyclization of γ-bromoacetoxy ketones and aldehydes.

The 1,2-asymmetric induction observed in the cyclization of appropriately substituted γ-bromoacetoxy ketones is represented by substrates **4a** and **4b** in Table II. The relative stereochemistry of the major product (**5b**) from the reaction of substrate **4b** with SmI_2 was established by X-ray diffractometry. The structure of **5a** was assigned by analogy.

At least four empirical transition structures leading to the observed products must be considered for the γ-bromoacetoxy ketone substrates. As with the β-bromoacetoxy ketones and aldehydes, all of these incorporate the concept of Sm(III) coordination to both carbonyl functionalities (Figure 2). The most favorable structure would place R^2 away from the approaching enolate (**4A** and **4C**), allowing attack of the nucleophile from the less hindered face of the carbonyl. Placing R^2 at the "inside" position of the developing ring (**4B** and **4D**) would be highly unfavorable because of developing transannular interactions between this substituent and the oxygen lone pair and carbon center across the ring. In analogy with the β-bromoacetoxy carbonyl substrates, the enolate rotameric geometry should also be considered. From this standpoint, transition structures **4B** and **4C** should be considerably less favorable than the analogous structures **4A** and **4D**. The combination of these considerations leads to the conclusion that transition structure **4A** is perhaps the most favorable among those depicted.

It is interesting to compare the diastereoselectivity demonstrated in the cyclization of **4a** with that of **1d**. Surprisingly, although the diastereomeric ratio of products was 3:1 in forming a six-membered lactone from **1d**, a single diastereomeric seven-membered ring was formed from **4a**, even though the substitution pattern is identical in both substrates. We postulate that the difference can be attributed to discrete stereochemical control elements. In contrast to the situation with β-bromoacetoxy

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Table III. Cyclization of Substrates **4g–q** (Eq 7)

substrate	R^1	R^2	R^3	R^4	R^5	% isoltd yield	diastereomeric ratio[a]
4g	Me	H	Me	H	H	39	3:1
4h	Me	H	Ph	H	H	64	4:1
4i	Me	H	H	*t*-Bu	H	79	3:1
4j	Me	H	H	Ph	H	75	3:1
4k	*n*-Pr	H	H	Me	H	90	2:1
4l	*t*-Bu	H	H	Me	H	53	1.5:1
4m	*t*-Bu	H	H	Ph	H	46	1:1
4n	Me	H	H	H	Me	28	1:1
4o	Ph	H	H	H	Me	75	10:1
4p	Et	Me	H	H	Me	43	1:1:0:0
4q	Ph	Me	H	H	Me	66	1.5:1:0:0

[a] Diastereomeric ratio determined by GLC analysis of crude reaction mixture where possible, otherwise, by ^{1}H NMR spectrum of crude material. Relative stereochemistry was not assigned, with the exception of the major diastereomer derived from substrate **4o**.

carbonyl substrates where $A^{1,2}$ strain is the controlling element, in the γ-bromoacetoxy carbonyl substrates we propose that avoidance of transannular interactions dictates the sense and to a large extent the magnitude of 1,2-asymmetric induction. Thus, one would not necessarily expect diastereoselectivities to be similar for analogous substitution patterns in homologous substrates.

Substrates **4c** and **4d** further elucidate this point. As in **1f**, the carbonyl undergoing attack is embodied in a ring. However, unlike the results described with **1f** above, substrate **4c** generates a single diastereomeric bicyclic product in modest yield. The stereochemistry was established by X-ray diffractometry. The major product from cyclization of **4d** has been assigned as trans at the ring juncture in analogy with **4c**. The major diastereomer derived from **4c** undoubtedly arises as the result of the side chain assuming an equatorial position on the cyclohexanone ring, with the enolate attacking the carbonyl from the equatorial direction.[35] These findings, taken together with those of the 6-membered lactones described above, again support the notion that transannular interactions and not $A^{1,2}$ strain are the principal factors controlling 1,2-asymmetric induction in the synthesis of 7-membered lactones via the SmI_2-promoted Reformatsky reaction.

Cyclization of substrates **4e** and **4f** in Table II are interesting in that both the haloacetoxy and carbonyl moieties are present as side chains on 5- and 6-membered rings, respectively. It should be noted that the two side chains bear a trans relationship on the ring as a result of the manner in which they were prepared. Incorporation of a ring limits the number of degrees of freedom available to these substrates. Observed diastereoselectivities in the cyclization reactions are excellent in both cases. The stereochemistry of **5f** was determined by single-crystal X-ray diffractometry, and the major diastereomer from cyclization of **4e** was assumed to possess the same relative stereochemistry.

The 1,3-asymmetric induction achieved in the cyclization of γ-bromoacetoxy ketones proved to be far less impressive than that observed in the cyclization of β-haloacetoxy ketones. Substrates **4g** and **4h** (Table III) showed diastereoselectivities of 3:1 and 4:1, respectively. Most likely, this dramatic decrease in diastereoselectivity from that observed with the β-bromoacetoxy substrates is due to greater flexibility in the transition state leading to the formation of the 7-membered ring and less rigid positioning of the substituents about the ring in this transition state (i.e., the substituents no longer maintain a strict "axial" or "equatorial" orientation, and perhaps a boat-type transition structure is involved).

Attempts at 1,4-asymmetric induction in the cyclization of the γ-bromoacetoxy ketones proved even less promising, with diastereomeric ratios only in the range of 1:1 to 3:1 at best. Results of the cyclization of substrates **4i–m** reflect such attempts. These results are again indicative of the lack of rigidity in the transition state associated with the closure of a 7-membered ring. Even with rather bulky substituents R^1 and R^4, such as in **4m**, there was negligible preference shown for the formation of either diastereomer.

Appropriately functionalized bromopropionate esters of various carbonyl electrophiles were next examined as cyclization substrates. This introduced the possibility of establishing a stereocenter adjacent to the ester carbonyl in the final product. Substrates **1u** (Table I) and **4n–q** (Table III) contain methyl groups on the α-carbon of the halo ester portion of the molecule. The diastereomeric ratios were less than 2:1 in all cases except **4o**, in which a 10:1 ratio of diastereomers was found. The major product from this reaction was determined by X-ray crystallography to be (3*R**,4*S**)-4-hydroxy-3-methyl-4-phenyl-1-oxacycloheptan-2-one. Although several detailed studies have been performed on the stereoselectivity of the Reformatsky reaction with secondary bromoesters, the diastereomeric ratios reported for intermolecular examples are generally quite low. Most studies indicate that the product mixtures are kinetically formed and that the diastereomeric ratios vary to some extent with the steric bulk of the alkyl substituent on the α-carbon of the ester.[36] The intermolecular reaction between α-bromopropionate and acetophenone utilizing zinc as the reductive coupling agent has been shown to provide a 2:1 mixture of diastereomers. Although this substitution pattern is similar to that of **4o**, the intramolecular nature of the reaction of the latter, as well as the replacement of zinc by SmI_2, may greatly influence the geometry of the forming enolate and lead to higher selectivity.

Finally, one attempt at promoting a stereoselective *intermolecular* Reformatsky reaction with SmI_2 was unsuccessful. The reaction between ethyl α-bromopropionate and 2-methylpropiophenone provided a 3:1 mixture of diastereomers in only 40% yield. This again implies that the high degree of stereoselectivity observed in the intramolecular examples described above must be a manifestation of the intramolecular nature of the reaction and likely the chelation of Sm(III) with the two carbonyl moieties in the substrate.

Conclusions

A wide range of substituted β- and γ-haloacetoxy ketones and aldehydes was efficiently cyclized with SmI_2, providing the corresponding hydroxy lactones. In many examples, virtually complete diastereoselectivity was achieved. This method represents a mild, selective, and efficient alternative to standard Reformatsky reaction conditions.

In general, far better 1,2- and 1,3-asymmetric inductions were achieved in the cyclization of the β-haloacetoxy ketones than with homologous substrates. In addition, in several of these cases it was possible to overcome the influences of an adjacent stereocenter to achieve 1,3-asymmetric induction, thereby producing δ-valerolactones containing three contiguous stereocenters. In all but one example of this sort a single diastereomeric product was isolated, and all of these appear to result from a Sm(III) chelated chair transition structure. The substrate that proved to be an

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exception also formed a single diastereomeric product, but it is proposed to have resulted from a boat transition state in order to minimize severe steric interactions.

Although high 1,2-asymmetric induction could be achieved in the formation of seven-membered ring lactones, attempts at 1,3- and 1,4-asymmetric induction in the cyclization of γ-bromoacetoxy ketones proved disappointing. Despite the lack of stereoselectivity, these cyclizations still proceeded quite efficiently to provide the corresponding ε-lactones. The use of bromopropionate esters in the cyclizations in general provided stereoselectivities no greater than 1.5:1, although in one case the diastereoselectivity reached 10:1.

Experimental Section

IR spectra were recorded on an FT-IR spectrophotometer. $CDCl_3$ was employed as the solvent for both ^1H and ^{13}C NMR, with $CHCl_3$ as the reference for ^1H NMR and $CDCl_3$ as the reference for ^{13}C NMR. Capillary GC analyses were performed with a 25 m × 320 μm 5% phenyl SE-54 fused silica column. Low-resolution and exact mass spectra were recorded with perfluorokerosene as the internal standard. Elemental analyses were performed by Galbraith Laboratories, Inc. Standard flash chromatography procedures were followed with silica gel.[37] Tetrahydrofuran was distilled immediately prior to use from sodium benzophenone ketyl under Ar. Standard bench-top techniques were employed for handling air-sensitive reagents, and all reactions were carried out under Ar.[38]

General Procedure for the Cyclization of Haloacetoxy Ketones and Aldehydes. To a slurry of samarium metal powder (0.33 g, 2.1 mmol, flamed for several minutes and cooled to room temperature under slow flow of Ar) in 15 mL of THF at 0 °C was added 2.0 mmol of CH_2I_2. The mixture was stirred at 0 °C for 15 min and allowed to warm to room temperature for 1 h. The substrates were added at the appropriate temperature (−78 °C unless otherwise indicated) and the mixture was stirred for approximately 1 h before being partitioned between saturated aqueous NH_4Cl (15 mL) and Et_2O (15 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL), and the combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, concentrated, and isolated by flash chromatography on silica gel or by recrystallization.

(4*R,5*S**)-4-Hydroxy-5-methyl-4-phenyl-1-oxacyclohexan-2-one (2a),** Isolated in 76% as a single diastereomer after recrystallization in 10:1 $CCl_4/CHCl_3$ at −18 °C: mp 103.5–104.5 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.50–7.26 (m, 5 H), 4.49–4.29 (m, 2 H), 2.99 (d, J = 18.0 Hz, 1 H), 2.8 (d, J = 18.0 Hz, 1 H), 2.57–2.40 (m, 1 H), 2.18 (s, 1 H), 0.73 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 170.52, 143.77, 128.68, 127.53, 124.55. 73.66, 71.61, 45.62, 37.09, 9.52; IR ($CHCl_3$) 3600, 3446, 3070, 3032, 3011, 2989, 2909, 1729, 1473, 1312, 1237, 1100, 1000 cm^{-1}; HRMS calcd for $C_{12}H_{15}O_3$ (M + 1) 207.1021, found 207.1016: LRMS (EI) m/e 207 (M + 1), 165 (31), 147 (21), 120 (9), 105 (100), 91 (10), 77 (22).

(4*R,5*S**)-4-Hydroxy-5-methyl-4-isopropenyl-1-oxacyclohexan-2-one (2b),** Isolated in 66% yield as a single diastereomer after recrystallization in $CCl_4/CHCl_3$/*n*-pentane 20:1:1 at 25 °C: mp 94–97 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 5.15 (bs, 1 H), 5.05 (m, 1 H), 4.38–4.20 (m, 2 H), 2.81 (d, J = 17.8 Hz, 1 H), 2.53 (d, J = 17.8 Hz, 1 H), 2.37–2.20 (m, 1 H), 1.79 (m, 3 H), 1.70 (s, 1 H), 0.82 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.60, 146.32, 112.31, 74.35, 70.95, 42.31, 33.49, 18.96, 9.18; IR ($CHCl_3$) 3600, 2984, 2930, 1734, 1470, 1317, 1234, 1100, 906 cm^{-1}; HRMS calcd for $C_9H_{15}O_3$ (M + 1) 171.1021, found 171.1013; LRMS (EI) m/e 171 (M + 1), 153 (25), 129 (15), 111 (40), 83 (17).

4-Ethyl-4-hydroxy-5-methyl-1-oxacyclohexan-2-one (2d and 3d). Isolated in 99% yield as a 3:1 mixture of diastereomers after flash chromatography in 1:2 hexanes/EtOAc: ^1H NMR (300 MHz, $CDCl_3$) δ (mixture) 4.77 (dd, J = 4, 11.2 Hz, 1 H), 4.33–4.15 (m, 2 H), 4.07 (dd, J = 3.2, 11.2 Hz, 1 H), 2.67–2.47 (m, 4 H), 2.10–1.93 (m, 2 H), 1.70–1.40 (m, 6 H), 1.08 (d, J = 7.2 Hz, 3 H), 1.02–0.90 (m, 9 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (major) 171.49, 72.1, 70.8, 41.26, 34.60, 31.92, 8.61, 7.37; IR (neat) 3462, 2978, 2945, 2890, 1717, 1470, 1400, 1261, 1245, 1077, 1050, 1008, 992, 920, 819 cm^{-1}; HRMS calcd for $C_8H_{15}O_3$ (M + 1) 159.1021, found 159.1008; LRMS (EI) m/e 159 (M + 1), 141 (18), 129 (62), 117 (55), 99 (72), 85 (22), 75 (52), 67 (100).

(4*R,5*S**)-4-*tert*-Butyl-4-hydroxy-5-methyl-1-oxacyclohexan-2-one (2c).** Isolated in 85% yield after flash chromatography with 45% EtOAc in hexanes: mp 72–73 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 4.10–4.00 (m, 2 H), 2.77 (d, J = 16 Hz, 1 H), 2.41 (d, J = 16 Hz, 1 H), 2.30–2.20 (m, 1 H), 1.98 (bs, 1 H), 1.00 (d, J = 6 Hz, 3 H), 0.92 (s, 9 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.07, 71.56, 39.61, 39.55, 33.48, 25.87, 24.64 (3), 13.07; IR ($CHCl_3$) 3610, 3500, 2980, 1745, 1475, 1275, 1055 cm^{-1}; HRMS calcd for $C_{10}H_{19}O_3$ (M + 1) 187.1334, found 187.1330; LRMS (EI) m/e 187 (M + 1), 145 (10), 130 (28), 112 (48), 97 (10), 85 (82), 70 (100).

(4*R,5*S**)-5-(Benzyloxy)-4-hydroxy-4-isopropyl-1-oxacyclohexan-2-one (2e),** Isolated as a 6:1 mixture of diastereomers in 57% yield after flash chromatography with 2:1 hexanes/EtOAc. Major diastereomer recrystallized from $CDCl_3$: mp 103–105 °C; ^1H NMR (300 MHz, $CDCl_3$) δ (major) 7.38–7.24 (m, 5 H), 4.74 (d, J = 11.5 Hz, 1 H), 4.63 (dd, J = 12.7, 1.7 Hz, 1 H), 4.55 (dd, J = 12.5, 1.5 Hz, 1 H), 4.46 (d, J = 11.5 Hz, 1 H), 3.53 (d, J = 1.0 Hz, 1 H), 2.73 (d, 17.8 Hz, 1 H), 2.59 (dd, J = 18.1, 1.0 Hz, 1 H), 2.15–2.06 (m, 1 H), 1.61 (bs, 1 H), 0.88 (d, J = 6.8 Hz, 3 H), 0.78 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (major) 170.26, 137.10, 128.56, 128.14, 127.92, 73.96, 72.61, 70.94, 66.23, 39.05, 31.41, 15.44, 14.91; IR ($CDCl_3$) 3608, 3468, 3032, 2969, 1729, 1654, 1456, 1257, 1117, 1083, 920, 906 cm^{-1}; HRMS calcd for $C_{15}H_{21}O_4$ (M + 1) 265.1440, found 265.1439.

1-Hydroxy-4-oxabicyclo[4.4.0]decan-3-one (2f and 3f). Isolated in 68% yield as a 1.6:1 mixture of diastereomers, which were separated by flash chromatography with 1:2 hexanes/EtOAc: mp major 100–103 °C, minor 106–111 °C; ^1H NMR (250 MHz, $CDCl_3$) δ (major) 4.37–4.12 (m, 2 H), 2.64 (d, J = 17.5 Hz, 1 H), 2.43 (d, J = 17.5 Hz, 1 H), 2.00–1.50 (m, 10 H), (minor) 4.84 (dd, J = 3.8, 11.3 Hz, 1 H), 4.11 (dd, J = 2.0, 11.3 Hz, 1 H), 2.86 (d, J = 18.3 Hz, 1 H), 2.42 (dd, J = 1.3, 18.3 Hz, 1 H), 1.95–1.20 (m, 10 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (major) 170.89, 70.55, 67.41, 45.07, 39.23, 37.38, 24.73, 22.06, 20.23, (minor) 171.10, 70.80, 70.40, 40.55, 38.53, 38.37, 26.64, 24.36, 23.47; IR ($CDCl_3$) (major) 3626, 3467, 2940, 2874, 1734, 1481, 1467, 1234, 1050, 1033, 995, (minor) 3600, 3478, 2950, 2878, 1733, 1483, 1461, 1272, 1244, 1200, 1078, 1011, 989 cm^{-1}; LRMS (EI) m/e (major) 171 (M + 1), 152 (11), 111 (44), 93 (14), 83 (22), 68 (43), 55 (26), 41 (24), (minor) 171 (M + 1), 152 (16), 111 (94), 102 (27), 93 (22), 83 (32), 68 (100), 55 (60), 41 (60). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.44; H, 8.31.

(4*R,6*R**)-4-Hydroxy-6-*n*-propyl-1-oxacyclohexan-2-one (2g).** Isolated in 69% yield by flash chromatography with 4:1 EtOAc/hexanes: ^1H NMR (90 MHz, $CDCl_3$) δ 4.80–4.50 (m, 1 H), 4.40–4.10 (m, 1 H), 2.75–2.45 (m, 3 H), 2.10–1.10 (m, 6 H), 1.00–0.70 (m, 3 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 171.55, 75.99, 62.18, 38.42, 37.41, 35.57, 17.97, 13.67; IR (CCl_4) 3450, 2980, 1725, 1345, 1255, 1090, 1035 cm^{-1}; LRMS (EI) m/e 159 (M + 1), 141 (15), 115 (68), 97 (59), 86 (13), 73 (100); HRMS calcd for $C_8H_{15}O_3$ (M + 1) 159.1021, found 159.1042.

(4*R,6*R**)-4-Hydroxy-4-methyl-6-*n*-propyl-1-oxacyclohexan-2-one (2h).** Isolated as a single diastereomer in 70% yield after flash chromatography with 1:3 hexanes/EtOAc: ^1H NMR (250 MHz, $CDCl_3$) δ 4.75–4.61 (m, 1 H), 2.66 (dd, J = 2.3, 17.5 Hz, 1 H), 2.47 (d, J = 17.5 Hz, 1 H), 1.91 (dm, J = 14.4 Hz, 1 H), 1.8–1.41 (m, 6 H), 1.38 (s, 3 H), 0.96 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.39, 77.00, 67.97, 44.22, 41.71, 37.56, 30.05, 18.03, 13.73; IR (neat) 3441, 2962, 2932, 2873, 1712, 1475, 1390, 1263, 1131, 1030, 941, 800 cm^{-1}; HRMS Calcd for $C_9H_{16}O$ 172.1099, found 172.1098; LRMS (EI) m/e 172 (M), 154 (4), 129 (35), 111 (35), 87 (100), 71 (46).

(4*R,6*S**)-4-Hydroxy-4-methyl-6-phenyl-1-oxacyclohexan-2-one (2i).** Isolated in 95% yield after flash chromatography with 55% EtOAc in hexanes: ^1H NMR (200 MHz, $CDCl_3$) δ 7.33 (s, 5 H), 5.71 (dd, J = 11, 3 Hz, 1 H), 3.01 (bs, 1 H), 2.78 (dd, J = 17, 2 Hz, 1 H), 2.54 (d, J = 17 Hz, 1 H), 2.14 (m, 1 H), 1.89 (m, 1 H), 1.38 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.07, 139.30, 128.53 (2), 128.23, 125.83 (2), 78.60, 68.12, 44.06, 43.90, 29.78; IR (CCl_4) 3420, 3030, 2965, 2860, 1715, 1380, 1245, 1115, 1065, 1015 cm^{-1}; HRMS calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0945; LRMS (EI) m/e 206 (M^+), 188 (31), 160 (17), 105 (100), 82 (32), 77 (23).

(4*R,6*S**)-4-*tert*-Butyl-4-hydroxy-6-phenyl-1-oxacyclohexan-2-one (2j).** Isolated in 98% yield after flash chromatography on silica gel with 3:2 EtOAc/hexanes: mp 133–134 °C; ^1H NMR ($CDCl_3$) δ 7.35 (s, 5 H), 5.87 (dd, J = 10.9, 3.9 Hz, 1 H), 2.74 (bs, 1 H), 2.51 (s, 2 H), 1.95 (d, J = 10.9 Hz, 2 H), 0.97 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 171.37, 139.79, 128.57 (2), 128.22, 125.92 (2), 78.14, 74.94, 39.05, 38.67, 37.59, 24.45 (3); HRMS calcd for $C_{15}H_{18}O_2$ (M − 18) 230.1307, found 230.1305.

(4*R,5*R**,6*R**)-4-Hydroxy-5-methyl-6-phenyl-1-oxacyclohexan-2-one (2k).** Isolated in 65% yield after cyclization at room temperature and flash chromatography with 3:1 EtOAc/hexanes: mp 133.5–135 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.34 (s, 5 H), 5.34 (d, J = 10.6 Hz, 1 H), 4.20–4.00 (m, 1 H), 3.28 (bs, 1 H), 2.82 (d, J = 3.4 Hz, 2 H), 2.20–1.90 (m, 1 H), 0.87 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.45, 138.12, 128.63, 128.50 (2), 127.24 (2), 83.10, 67.27, 39.51, 39.00, 13.28; IR (CCl_4) 3600, 3460, 3025, 3010, 2980, 2920, 1730, 1245, 1070

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cm^{-1}; LRMS (EI) *m/e* 206 (M^+), 178 (11), 117 (17), 107 (100), 91 (18), 79 (22).

(4*R,5*S**,6*S**)-4-Ethyl-4-hydroxy-5-methyl-6-*n*-propyl-1-oxacyclohexan-2-one (2l).** Isolated in 86% yield after flash chromatography with 45% EtOAc in hexanes: ^1H NMR (90 MHz, $CDCl_3$) δ 4.40–4.20 (m, 1 H), 2.50–2.40 (m, 2 H), 2.19 (bs, 1 H), 1.80–1.10 (m, 7 H), 1.00–0.70 (m, 9 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 171.72, 81.46, 71.83, 41.35, 38.87, 35.21, 32.28, 17.60, 13.80, 9.45, 7.80; IR (CCl_4) 3460, 2960, 1715, 1255, 990 cm^{-1}; HRMS calcd for $C_9H_{15}O_3$ (M − 29) 171.1021, found 171.1024; LRMS (EI) *m/e* 171 (M − 29), 158 (5), 139 (10), 128 (9), 117 (30), 99 (45), 86 (80), 71 (45), 57 (100).

(4*R,5*S**,6*R**)-4-*tert*-Butyl-4-hydroxy-5-methyl-6-phenyl-1-oxacyclohexan-2-one (2m).** Isolated in 71% yield after flash chromatography with 45% EtOAc in hexane: mp 164–165.5 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35 (s, 5 H), 4.97 (d, J = 10.8 Hz, 1 H), 3.06 (d, J = 15.3 Hz, 1 H), 2.59 (d, J = 16.2 Hz, 1 H), 2.40–2.20 (m, 1 H), 2.08 (bs, 1 H), 1.02 (s, 9 H), 0.76 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.62, 137.54, 128.69, 128.45 (2), 127.38 (2), 83.55, 75.85, 40.58, 40.34 (2), 24.89 (3), 12.59; IR (CCl_4) 3460, 3020, 2980, 1730, 1330, 1250, 1210, 1045 cm^{-1}; HRMS calcd for $C_{16}H_{23}O_3$ (M + 1) 263.1647, found 263.1660; LRMS (EI) *m/e* 263 (M + 1), 205 (32), 188 (15), 145 (74), 118 (91), 107 (100), 99 (84), 91 (68), 71 (83).

(4*R,5*S**,6*R**)-4-Hydroxy-5-methyl-6-phenyl-1-oxacyclohexan-2-one (2n).** Isolated in 62% yield after cyclization at room temperature and flash chromatography with 3:1 EtOAc/hexanes: mp 100.5–101.5 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.25 (m, 5 H), 5.90 (d, J = 2.7 Hz, 1 H), 4.20–4.15 (m, 1 H), 2.93 (dd, J = 5.4, 18.6 Hz, 1 H), 2.67 (dd, J = 2.18, 18.4 Hz, 1 H), 2.24–2.18 (m, 1 H), 2.15 (d, J = 3.2 Hz, 1 H), 0.72 (d, J = 7.4 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.26, 137.58, 128.22 (2), 127.53, 125.32 (2), 78.96, 67.87, 39.71, 35.41, 10.07; IR (CCl_4) 3620, 3450, 3020, 3010, 2980, 2930, 1730, 1240, 1040, 990 cm^{-1}; LRMS (EI) *m/e* 206 (M^+), 178 (22), 164 (50), 134 (13), 107 (100), 91 (31), 79 (68); HRMS calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0945.

(4*R,5*R**,6*S** and 4*R**,5*S**,6*R**)-4-Ethyl-4-hydroxy-5-methyl-6-*n*-propyl-1-oxacyclohexan-2-one (2o and 3o).** Isolated by flash chromatography with 65% EtOAc in hexanes, providing an 8:1 mixture of diastereomers in 97% combined yield: ^1H NMR (90 MHz, $CDCl_3$) δ (major) 5.00–4.80 (m, 1 H), 2.60–2.40 (m, 2 H), 2.15 (bs, 1 H), 1.80–1.10 (m, 7 H), 1.00–0.70 (m, 9 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ (major) 171.60, 79.07, 72.86, 39.82, 37.78, 34.38, 31.78, 18.76, 13.86, 7.89, 6.18; IR ($CDCl_3$) 3610, 3450, 2975, 1715, 1260, 1145, 1000 cm^{-1}; HRMS calcd for $C_9H_{15}O_3$ (M − 29) 171.1021, found 171.1024; LRMS (EI) *m/e* 171 (M − 29), 158 (8), 128 (8), 110 (10), 99 (20), 86 (100), 71 (38).

(4*R,5*R**,6*R** and 4*R**,5*S**,6*S**)-4-Hydroxy-5-methyl-4,6-diphenyl-1-oxacyclohexan-2-one (2p and 3p).** Isolated by flash chromatography with 2:1 hexanes/EtOAc after cyclization at −78 to 0 °C, providing a 1.4:1 mixture of diastereomers in 17% combined yield: ^1H NMR (300 MHz, $CDCl_3$) δ (mixture) 7.58–7.11 (m, 20 H), 6.31 (d, J = 2.9 Hz, 1 H), 5.03 (d, J = 2.9 Hz, 1 H), 3.40 (d, J = 17.7 Hz, 1 H), 3.30 (dd, J = 1.5, 17.7 Hz, 1 H), 3.04 (d, J = 17.7 Hz, 1 H), 2.94 (dd, J = 1.5, 17.7 Hz, 1 H), 2.49 (m, 2 H), 2.31 (s, 1 H), 2.19 (s, 1 H), 0.93 (d, J = 8.3 Hz, 3 H), 0.45 (d, J = 8.3 Hz, 3 H); IR ($CHCl_3$) 3600, 3456, 3100, 3066, 3039, 3017, 1734, 1492, 1448, 1250, 1000, 915 cm^{-1}; HRMS calcd for $C_{18}H_{16}O_2$ (M − 18) 264.1150, found 264.1159; LRMS (EI) *m/e* 264 (M − 18), 209 (33), 118 (100), 91 (10), 77 (23).

(4*R,5*S**,6*S**)-4-*tert*-Butyl-4-hydroxy-5-methyl-6-phenyl-1-oxacyclohexan-2-one (3q).** Isolated in 88% yield after flash chromatography on silica gel with 3:2 hexanes/EtOAc: mp 170–171 °C; ^1H NMR ($CDCl_3$) δ 7.34 (s, 5 H), 5.31 (d, J = 3.4 Hz, 1 H), 2.97 (d, J = 14.8 Hz, 1 H), 2.70–2.50 (m, 2 H), 1.06 (s, 9 H), 0.72 (d, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.62, 138.95, 128.32 (2), 127.62, 125.44 (2), 81.17, 77.00, 39.58 (2), 39.11, 24.45 (3), 9.25; IR ($CHCl_3$) 3580, 3010, 2980, 1750, 1300, 1275 cm^{-1}; HRMS calcd for $C_{16}H_{23}O_3$ (M + 1) 263.1647, found 263.1644.

6-Ethyl-4-hydroxy-6-methyl-1-oxacyclohexan-2-one (2r and 3r), Isolated in 17% yield as a 1:1 mixture of diastereomers after flash chromatography with 1:3 hexanes/EtOAc: ^1H NMR (250 MHz, $CDCl_3$) δ (mixture) 4.40–4.20 (m, 2 H), 3.06–2.86 (m, 2 H), 2.50–2.30 (m, 2 H), 2.17–2.03 (m, 2 H), 1.87–1.62 (m, 6 H), 1.58 (s, 2 H), 1.45 (s, 3 H), 1.36 (s, 3 H), 0.98 (t, J = 7.6 Hz, 3 H), 0.96 (t, J = 7.6 Hz, 3 H); HRMS calcd for $C_8H_{15}O_3$ 159.1021, found 159.1022; LRMS (EI) *m/e* 159 (M + 1), 141 (100), 128 (8), 111 (8), 95 (10), 89 (10).

(4*R,6*R**)-4-Hydroxy-6-methyl-6-phenyl-1-oxacyclohexan-2-one (2s),** Isolated in 56% yield after flash chromatography with 7:1 EtOAc/hexanes: ^1H NMR (250 MHz, $CDCl_3$) δ 7.47–7.18 (m, 5 H), 3.92–3.74 (m, 1 H), 2.90–2.70 (m, 2 H), 2.43 (dd, J = 8.5, 17.5 Hz, 1 H), 2.11 (bs, 1 H), 1.99 (dd, J = 10.5, 13.5 Hz, 1 H), 1.72 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.97, 144.37, 129.25, 127.93, 124.50, 83.78, 62.36, 44.15, 39.74, 32.23; IR (neat): 3441, 3068, 3038, 3004, 2949, 1742, 1453, 1271, 1182, 1081, 1047, 771, 703 cm^{-1}; HRMS calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.9044.

(4*R,6*R**)-4,6-Dimethyl-4-hydroxy-6-phenyl-1-oxacyclohexan-2-one (2t).** Isolated in 79% yield after flash chromatography with 1:7 hexanes/EtOAc: ^1H NMR (250 MHz, $CDCl_3$) δ 7.47–7.23 (m, 5 H), 2.59 (dd, J = 1.5, 16.5 Hz, 1 H), 2.53 (d, J = 15.0 Hz, 1 H), 2.37 (dd, J = 1.5, 15.0 Hz, 1 H), 2.34 (d, J = 16.5 Hz, 1 H), 1.90 (s, 1 H), 1.77 (s, 3 H), 1.27 (s, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.05, 145.75, 128.72, 127.35, 123.97, 83.99, 69.29, 47.81, 44.41, 32.64, 30.78; IR (neat) 3452, 3077, 3030, 2988, 2946, 1720, 1500, 1452, 1384, 1271, 1176, 1122, 1054, 994, 771, 702 cm^{-1}; HRMS calcd for $C_{13}H_{16}O_3$ 220.1099, found 220.1089; LRMS (EI) *m/e* 220 (M), 205 (40), 187 (30), 163 (13), 121 (47), 118 (31), 105 (100).

4-*tert*-Butyl-4-hydroxy-3-methyl-1-oxacyclohexan-2-one (2u and 3u). Isolated in 63% yield as a 1.8:1 mixture of diastereomers, which were separated by flash chromatography with 1:1 EtOAc/hexanes: mp 170–171 °C; ^1H NMR (200 MHz, $CDCl_3$) δ (major) 4.60–4.30 (m, 2 H), 3.00–2.80 (m, 1 H), 2.30–1.50 (m, 2 H), 1.37 (d, J = 7 Hz, 3 H), 0.98 (s, 9 H), (minor) 4.60–4.40 (m, 2 H), 2.20–1.50 (m, 2 H), 1.37 (d, J = 7 Hz, 3 H), 1.02 (s, 9 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (major) 175.81, 64.33, 42.02, 39.17, 33.39, 26.18, 24.60 (3), 15.09, (minor) 175.59, 65.43, 47.77, 37.84, 25.80, 25.39 (3), 24.70, 16.74; IR ($CHCl_3$) 3620, 2480, 2980, 1730, 1485, 1275, 1105 cm^{-1}; HRMS calcd for $C_{10}H_{19}O_3$ (M + 1) 187.1334, found 187.1331; LRMS (EI) *m/e* 187 (M + 1), 186 (trace), 160 (8), 131 (12), 115 (86), 113 (84), 97 (42), 73 (28), 69 (42), 57 (100).

(4*R,5*S**)-4-Ethyl-4-hydroxy-5-methyl-1-oxacycloheptan-2-one (5a).** Isolated in 39% yield as a single diastereomer after flash chromatography with 3:1 EtOAc/hexanes. The product was a white crystalline solid: mp 89–92 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.29–4.11 (m, 2 H), 2.93 (d, J = 13.7 Hz, 1 H), 2.70 (d, J = 13.4 Hz, 1 H), 2.08–1.47 (m, 6 H), 0.91 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 173.47, 72.40, 67.96, 45.30, 39.97, 35.04, 32.87, 15.30, 8.19; IR ($CDCl_3$) 3603, 3448, 2972, 1729, 1435, 1395, 13312, 1285, 1112, 1075 cm^{-1}. Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.67; H, 9.37.

(4*R,5*S**)-3-Hydroxy-4-methyl-3-phenyl-1-oxacycloheptan-2-one (5b).** Isolated in 65% yield as a single diastereomer after flash chromatography with 5:1 hexanes/EtOAc. The product was a white crystalline solid: mp 180–182 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.24 (m, 5 H), 4.41–4.33 (m, 2 H), 3.47 (d, J = 13.7 Hz, 1 H), 2.89 (d, J = 13.7 Hz, 1 H), 2.36 (s, 1 H), 2.18–1.03 (m, 2 H), 1.86–1.81 (m, 1 H), 0.67 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.86, 147.29, 128.64, 127.23, 124.03, 74.06, 68.49, 48.09, 44.64, 32.86, 32.86, 16.01; IR ($CDCl_3$) 3585, 3432, 2981, 2914, 1733, 1437, 1394, 1307, 1283 cm^{-1}; HRMS calcd for $C_{13}H_{17}O_3$ (M + 1) 221.1178, found 221.1167. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.85; H, 7.32.

(1*R,7*S**)-1-Hydroxy-4-oxabicyclo[5,4.0]undecan-3-one (5c).** Isolated in 44% yield as a single diastereomer after flash chromatography with 1:1 hexanes/EtOAc. The product was a white crystalline solid: mp 151–152 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.31–4.09 (m, 2 H), 2.94 (d, J = 13.7 Hz, 1 H), 2.63 (d, J = 13.7 Hz, 1 H), 2.00 (m, 2 H), 1.72–1.14 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.64, 69.18, 68.74, 48.80, 47.76, 40.34, 31.75, 28.63, 25.31, 21.06; IR ($CDCl_3$) 3678, 3596, 2935, 2857, 1730, 1301, 1284, 1256, 1080, 1021 cm^{-1}; HRMS calcd for $C_{10}H_{16}O_3$ 184.1099, found 184.1104. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.20; H, 8.75. Found: C, 65.05; H, 8.69.

(1*R,7*S**)-1-Hydroxy-4-oxabicyclo[6,5.0]tridecan-3-one (5d),** Isolated in 72% yield as a 30:1 mixture of diastereomers after flash chromatography on silica gel in 10:1 hexanes/EtOAc: ^1H NMR (300 MHz, $CDCl_3$) δ 4.29–4.11 (m, 2 H), 3.08 (d, J = 13.1 Hz, 1 H), 2.62 (d, J = 13.7 Hz, 1 H), 2.21–1.12 (m, 16 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.78, 72.37, 68.83, 47.56, 45.99, 33.46, 30.28, 28.87, 26.69, 24.82, 22.17; HRMS calcd for $C_{12}H_{20}O_3$ 212.1389, found 212.1412.

(1*R,5*S**,7*S**)-5-Hydroxy-5-methyl-2-oxabicyclo[5,3.0]decan-3-one (5e).** Isolation in 73% yield as a single diastereomer by flash chromatography with 1:1 hexanes/EtOAc. The product was a white crystalline solid: mp 145–146 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.41–4.33 (m, 1 H), 3.04 (bs, 1 H), 2.96 (d, J = 13.7 Hz, 1 H), 2.74 (dd, J = 13.7, 2.1 Hz, 1 H), 2.33–1.54 (m, 7 H), 1.41–1.16 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.41, 84.24, 69.29, 47.94, 46.57, 40.48, 32.28, 31.37, 30.79, 20.44; IR ($CDCl_3$) 3588, 3450, 2970, 1714, 1454, 1320, 1095 cm^{-1}; HRMS calcd for $C_{10}H_{17}O_3$ (M + 1) 185.1194, found 185.1170.

(1*R,5*S**,7*S**)-5-Hydroxy-5-methyl-2-oxabicyclo[5.4.0]undecan-3-one (5f).** Isolation by flash chromatography with 2:1 EtOAc/hexanes, followed by recrystallization from 3:1 $CCl_4/CHCl_3$ provided a 68% yield 29:1 mixture of diastereomers (as indicated by GLC analysis). The product was a colorless solid: mp 169–172 °C; ^1H NMR (300 MHz, $CDCl_3$) δ (major) 4.13–4.04 (m, 1 H), 2.97 (d, J = 14.0 Hz, 1 H), 2.75 (dd, J = 13.5, 3.5 Hz, 1 H), 2.19–0.88 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 172.32, 81.84, 68.16, 50.84, 47.61, 37.20, 33.19, 32.71,

32.60, 24.65, 24.20; IR ($CHCl_3$) 3605, 2950, 2870, 1725, 1455, 1380, 1330, 1300, 1030 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_3$: C, 66.64; H, 9.15. Found: C, 66.42; H, 9.30.

4,6-Dimethyl-4-hydroxy-1-oxacycloheptan-2-one (5g and 6g). Isolated in 39% yield as a 3:1 mixture of diastereomers after flash chromatography with 3:1 hexanes/EtOAc: ^1H NMR (300 MHz, $CDCl_3$) δ (mixture) 4.03–3.89 (m, 4 H), 3.00–2.65 (m, 4 H), 2.35–2.18 (m, 4 H), 1.91–1.86 (m, 4 H), 1.31 (s, 3 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.87 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (mixture) 172.90, 171.94, 74.18, 74.02, 69.37, 68.77, 51.59, 50.36, 48.05, 47.11, 32.71, 31.21, 29.45, 26.96, 18.44; HRMS calcd for $C_8H_{15}O_3$ (M + 1) 159.1021, found 159.1035.

4-Hydroxy-4-methyl-6-phenyl-1-oxacycloheptan-2-one (5h and 6h). Isolated in 64% yield as a 4:1 mixture of diastereomers after flash chromatography with 3:1 hexanes/EtOAc. The product was a white crystalline solid: mp 165–167 °C; ^1H NMR (300 MHz, $CDCl_3$) δ (mixture) 7.37–7.17 (m, 10 H), 4.47–4.28 (m, 4 H), 3.68–3.44 (m, 2 H), 3.26–2.80 (m, 4 H), 2.37 (bs, 2 H), 2.21–1.91 (mm, 4 H), 1.48 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (mixture) 172.31, 171.46, 141.25, 129.06, 128.98, 128.75, 127.64, 127.42, 127.18, 126.99, 126.94, 73.39, 69.39, 68.65, 50.80, 49.54, 48.16, 47.20, 42.80, 40.94, 32.76, 26.30; IR ($CDCl_3$) 3589.1, 3424.6, 3025, 2966.2, 2931.0, 1731.0, 1266.8 cm^{-1}; HRMS calcd for $C_{13}H_{16}O_3$ (M^+) 220.1099, found 220.1081.

7-*tert*-Butyl-4-hydroxy-4-methyl-1-oxacyclononan-2-one (5i and 6i). Isolated in 79% yield as a 3:1 mixture of diastereomers after flash chromatography with 3:1 hexanes/EtOAc followed by Kugelrohr distillation. The product was a clear colorless oil: bp 80–90 °C (0.03 mmHg); ^1H NMR (300 MHz, $CDCl_3$) δ (mixture) 4.63–4.57 (m, 1 H), 4.40–4.34 (m, 1 H), 4.19–4.11 (m, 1 H), 3.92–3.83 (m, 1 H), 2.53–1.44 (m, 16 H), 1.23 (s, 3 H), 1.22 (s, 3 H), 1.15–0.80 (m, 4 H), 0.77 (s, 9 H), 0.76 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (mixture) 172.38, 172.19, 72.89, 72.32, 65.00, 64.32, 50.25, 49.43, 48.46, 48.35, 41.93, 41.76, 33.99, 33.88, 31.57, 29.70, 29.43, 28.92, 27.35, 27.19, 25.98, 25.95; IR ($CDCl_3$) 3592.1, 3459.2, 2963.0, 2865.6, 1719.6, 1471.5, 1458.2, 1365.2, 1307.6, 1232.3 cm^{-1}; HRMS calcd for $C_{13}H_{24}O_3$ (M + 1) 229.1804, found 229.1823.

4-Hydroxy-4-methyl-7-phenyl-1-oxacycloheptan-2-one (5j and 6j). Isolated in 75% yield as a 3:1 mixture of diastereomers after flash chromatography with 3:1 EtOAc/hexanes. The product was a white crystalline solid, 95% pure as indicated by GLC analysis: mp 116–118 °C; ^1H NMR (300 MHz, $CDCl_3$) δ (major) 7.29–7.16 (m, 5 H), 5.28–5.18 (m, 1 H), 3.11–3.02 (m, 1 H), 2.70–2.65 (m, 1 H), 2.18–1.75 (m, 5 H), 1.38 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (mixture) 172.09, 171.75, 140.69, 140.32, 128.77, 128.39, 126.09, 125.98, 82.26, 81.69, 75.50, 69.04, 68.20, 48.67, 47.56, 41.43, 33.41, 32.44, 32.35, 26.24; IR ($CDCl_3$) 3588, 3450, 2970, 1714, 1454, 1320, 1095 cm^{-1}; HRMS calcd for $C_{13}H_{14}O_2$ (M − 18) 202.1001, found 202.0994.

4-Hydroxy-7-methyl-4-propyl-1-oxacycloheptan-2-one (5k and 6k). Isolated in 90% yield as a 2:1 mixture of diastereomers, which were separated by flash chromatography with 2:1 EtOAc/hexanes: ^1H NMR (250 MHz, $CDCl_3$) δ (major) 4.58–4.44 (m, 1 H), 3.02 (d, J = 13.2 Hz, 1 H), 2.76 (dd, J = 2.3, 13.2 Hz, 1 H), 2.09–1.23 (m, 9 H), 1.38 (d, J = 6.6 Hz, 3 H), 0.97 (t, J = 7.2 Hz, 3 H), (minor) 4.54–4.38 (m, 1 H), 2.93 (d, J = 13.4 Hz, 1 H), 2.71 (dd, J = 2.3, 13.4 Hz, 1 H), 2.22–2.02 (m, 1 H), 1.95–1.23 (m, 8 H), 1.38 (d, J = 6.6 Hz, 3 H), 0.96 (t, J = 7.2, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (major) 171.80, 76.41, 70.67, 47.65, 40.52, 40.17, 32.05, 22.19, 15.58, 14.17, (minor) 172.65, 76.55, 70.04, 47.32, 46.13, 38.7, 31.2, 22.3, 16.67, 14.27; IR (neat) (major) 3456, 2984, 2951, 2885, 1722, 1464, 1442, 1291, 1200, 1137, 1100, 1017, 912, 824, (minor) 3461, 2973, 2945, 2907, 1714, 1437, 1387, 1294, 1223, 1118, 1100, 931 cm^{-1}; HRMS calcd for $C_{10}H_{19}O_3$ (M + 1) 187.1334, found 187.1342.

4-*tert*-Butyl-4-hydroxy-7-methyl-1-oxacycloheptan-2-one (5l and 6l). Isolated in 64% yield as a 1.5:1 mixture of diastereomers after flash chromatography with 1:1 hexanes/EtOAc. The product was a white crystalline solid: mp 115–132 °C, with >95% purity as determined by ^{13}C NMR; ^1H NMR (300 MHz, $CDCl_3$) δ (mixture) 4.75–4.60 (m, 1 H), 4.52–4.40 (m, 1 H), 3.11 (d, J = 15 Hz, 1 H), 2.87 (s, 2 H), 2.78 (d, J = 15 Hz, 1 H), 2.13–1.67 (m, 10 H), 1.39 (d, J = 3.5 Hz, 3 H), 1.36 (d, J = 3.5 Hz, 3 H), 1.00 (s, 9 H), 0.97 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (mixture) 173.84, 173.65, 76.51, 75.15, 73.87, 73.66, 44.21, 41.26, 39.77, 38.54, 33.52, 31.24, 30.50, 28.64, 24.58, 24.47, 22.28, 13.94; IR ($CDCl_3$) 3588, 3450, 2933, 1734, 1262 cm^{-1}; HRMS calcd for $C_{11}H_{20}O_3$ 201.1491, found 201.1479.

4-*tert*-Butyl-4-hydroxy-7-phenyl-1-oxacycloheptan-2-one (5m and 6m). Isolated in 46% yield as a 1:1 mixture of diastereomers after flash chromatography with 1:1 hexanes/EtOAc. The product was a white crystalline solid: mp 116–118 °C, with >90% purity as indicated by ^{13}C NMR analysis; ^1H NMR (300 MHz, $CDCl_3$) δ (mixture) 7.28–7.12, (m, 10 H), 5.51 (dd, J = 9.7, 3.9 Hz, 1 H), 5.17 (d, J = 9.7, 3.9 Hz, 1 H), 2.97–2.76 (m, 4 H), 2.47–1.60 (m, 10 H), 1.19–0.77 (m, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (mixture) 173.31, 172.91, 140.90, 139.67, 128.85, 128.78, 128.38, 128.11, 126.56, 126.50, 126.15, 125.92, 82.02, 78.89, 78.34, 73.87, 44.16, 41.29, 39.54, 38.62, 34.02, 32.67, 30.12, 28.73, 26.24, 24.62, 24.42; IR ($CDCl_3$) 3603, 3052, 2971, 1724, 1265 cm^{-1}; HRMS calcd for $C_{16}H_{20}O_2$ 244.1463, found 244.1461.

4-Hydroxy-3,4-dimethyl-1-oxacycloheptan-2-one (5n and 6n). Isolated in 28% yield as a 1:1 mixture of diastereomers after flash chromatography with 5:1 hexanes/EtOAc. The product was a clear, colorless oil with >94% purity as indicated by GLC analysis: ^1H NMR (300 MHz, $CDCl_3$) δ (mixture) 4.29–4.20 (m, 4 H), 3.07–2.95 (m, 2 H), 2.16–1.62 (m, 10 H), 1.28–1.18 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (mixture) 175.57, 175.45, 70.97, 70.43, 68.05, 67.77, 47.38, 45.84, 43.40, 42.65, 28.72, 25.65, 24.40, 22.72, 12.69, 11.71; IR ($CDCl_3$) 3604, 2984, 2944, 1728, 1389, 1283, 1179, 1094, 902; HRMS calcd for $C_8H_{15}O_3$ (M + 1) 159.1012, found 159.1012.

(3*R,4*S**)-4-Hydroxy-3-methyl-4-phenyl-1-oxacycloheptan-2-one (5o).** Isolated from cyclization of 4o in 75% yield, initially as a 10:1 mixture of diastereomers by flash chromatography with 1:1 hexanes/EtOAc. The major product was a white crystalline solid: mp 144–146 °C (the major diastereomer was purified by several recrystallizations from CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ (major) 7.48–7.22 (m, 5 H), 4.42 (t, J = 5.85 Hz, 2 H), 3.28 (q, J = 7.4 Hz, 4 H), 2.58–1.90 (m, 5 H), 1.00 (d, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 175.20, 144.86, 128.07, 127.33, 125.11, 75.07, 66.89, 50.74, 36.52, 22.80, 11.92; IR ($CDCl_3$) 3591, 3462, 2935, 1717, 1398, 1256, 1093, 999, 908, 739 cm^{-1}; HRMS calcd for $C_{13}H_{16}O_3$ (M^+) 220.1099, found 220.1105. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.61; H, 7.35.

4-Ethyl-4-hydroxy-3,5-dimethyl-1-oxacycloheptan-2-one (5p and 6p). Isolated in 43% yield as a 1:1 mixture of diastereomers after flash chromatography with 1:1 hexanes/EtOAc. The product was an off-white crystalline solid: mp 65–81 °C; ^1H NMR (300 MHz, $CDCl_3$) δ (mixture) 4.55–4.19 (m, 4 H), 3.39–3.32 (m, 1 H), 2.37–1.61 (m, 12 H), 1.32–1.29 (m, 6 H), 1.20 (d, J = 6.4 Hz, 3 H), 1.06 (d, J = 6.4 Hz, 3 H), 1.02–0.92 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (mixture) 176.29, 175.77, 74.26, 73.73, 66.99, 63.41, 43.73, 40.11, 35.49, 32.98, 31.89, 29.70, 27.88, 16.05, 13.41, 12.97, 11.52, 8.78, 6.69; IR ($CDCl_3$) 3610, 2972, 1725, 1265, 1182 cm^{-1}; HRMS calcd for $C_{11}H_{18}O_3$ 187.1334, found 187.1325.

4-Hydroxy-3,5-dimethyl-4-phenyl-1-oxacycloheptan-2-one (5q and 6q). Isolation by flash chromatography with 5:1 hexanes/EtOAc provided a 66% yield as a 1:1 mixture of diastereomers (as determined by ^1H NMR and ^{13}C NMR). The product was a white crystalline solid: mp 106–139 °C; ^1H NMR (300 MHz, $CDCl_3$) δ (mixture) 7.30–7.14 (m, 10 H), 4.48–4.23 (m, 4 H), 3.38 (q, J = 6.8 Hz, 1 H), 3.23–3.17 (m, 1 H), 2.49–1.72 (m, 8 H), 0.83 (d, J = 6.8 Hz, 3 H), 0.68 (d, J = 6.8 Hz, 3 H), 0.62 (d, J = 6.8 Hz, 3 H), 0.53 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (mixture) 175.67, 175.41, 144.82, 143.11, 128.30, 128.15, 127.14, 126.74, 125.23, 124.96, 78.16, 77.45, 67.28, 65.36, 46.19, 45.50, 37.03, 33.19, 33.10, 29.87, 16.65, 15.73, 14.78, 12.16; IR ($CDCl_3$) 3592, 2984, 2940, 1727, 1458, 1394, 1186, 1097, 1064 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.81; H, 7.69.

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Registry No. 1a, 135973-71-6; **1b**, 135973-72-7; **1c**, 135973-73-8; **1d**, 135973-74-9; **1e**, 135973-75-0; **1f**, 135973-76-1; **1g**, 135973-77-2; **1h**, 135973-78-3; **1i**, 135973-79-4; **1j**, 135973-80-7; **1k**, 135973-81-8; **1l**, 135973-82-9; **1m**, 135973-83-0; **1n**, 135973-84-1; **1o**, 135973-85-2; **1p**, 135973-86-3; **1q**, 135973-87-4; **1r**, 135973-88-5; **1s**, 135973-89-6; **1t**, 135973-90-9; **1u**, 135973-91-0; **2a**, 135973-92-1; **2b**, 135973-93-2; **2c**, 136085-25-1; **2d**, 135973-94-3; **2e**, 135973-95-4; **2f**, 135973-96-5; **2g**, 114431-79-7; **2h**, 135973-97-6; **2i**, 128720-73-0; **2j**, 135973-98-7; **2k**, 136031-58-8; **2l**, 135973-99-8; **2m**, 136031-59-9; **2n**, 136031-60-2; **2o**, 135974-00-4; **2p**, 135974-01-5; **2r**, 135974-02-6; **2s**, 135974-03-7; **2t**, 135974-04-8; **2u**, 135974-05-9; **3d**, 135974-06-0; **3e**, 135974-07-1; **3f**, 135974-08-2; **3o**, 135974-09-3; **3p**, 136031-61-3; **3q**, 136031-62-4; **3r**, 135974-10-6; **3u**, 136031-63-5; **4a**, 135974-11-7; **4b**, 135974-12-8; **4c**, 135974-13-9; **4d**, 135974-14-0; **4e**, 135974-15-1; **4f**, 135974-16-2; **4g**, 135974-17-3; **4h**, 135974-18-4; **4l**, 135974-19-5; **4j**, 135974-20-8; **4k**, 135974-21-9; 4l, 135974-22-0; **4m**, 135974-23-1; **4n**, 135974-24-2; **4o**, 135974-25-3; **4p**, 135974-26-4; **4q**, 135974-27-5; **5a**, 135974-28-6; **5b**, 135974-29-7; **5c**, 135974-30-0; **5d**, 135974-31-1; **5e**, 135974-32-2; **5f**, 135974-33-3; **5g**, 135974-34-4; **5h**, 135974-35-5; **5l**, 135974-36-6; **5j**, 135974-37-7; **5k**, 135974-38-8; **5l**, 135974-39-9; **5m**, 135974-40-2; **5n**, 135974-41-3; **5o**, 135974-42-4; **5p**, 135974-43-5; **5q**, 135974-44-6; **6d**,

135974-45-7; **6f**, 136031-64-6; **6g**, 135974-46-8; **6h**, 135974-47-9; **6i**, 135974-48-0; **6j**, 135974-49-1; **6k**, 135974-50-4; **6l**, 135974-51-5; **6m**, 135974-52-6; **6n**, 135974-53-7; **6o**, 135974-54-8; **6p**, 136031-65-7; **6q**, 136031-66-8; samarium iodide, 13813-25-7.

Supplementary Material Available: Details of the X-ray crystallographic structure determinations described within the paper, including structure data, atomic coordinates, bond lengths and angles, and isotropic and anisotropic thermal parameters (108 pages). Ordering information is given on any current masthead page.

Synthesis and Analysis of 506BD, a High-Affinity Ligand for the Immunophilin FKBP

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Abstract: The design, synthesis, and analysis of a high-affinity ligand, 506BD, for the human immunophilin FKBP is described. The synthesis illustrates a novel hydroboration reaction that proceeds with unusual regio- and stereochemical control. In accord with expectations regarding the structural requirements for FKBP binding, 506BD potently inhibits the rotamase activity of FKBP (inhibitory constant K_i = 5 nM). The significance of these and other findings with regard to a biological model for immunophilin–ligand actions is described.

Investigations of FK506, rapamycin, and cyclosporin A (CsA) are providing insights into the mechanisms of signal transduction in the cytoplasm of cells, the "black box" of the signal transduction pathway (Figure 1).[1] FK506 and CsA inhibit the exocytosis of secretory vesicles in mast cells following stimulation of the IgE receptor[2] as well as the transcription of the interleukin-2 (IL-2) gene in T cells following stimulation of the T-cell receptor.[3,4] The ability of rapamycin to inhibit the actions of FK506 but not CsA in both cell lines implies that these signaling pathways share common features.[2] We have suggested that complexes of these three molecules with cytosolic receptors termed immunophilins (immunosuppressant binding proteins) function as the inhibitory agents.[1,4,5] Whereas complexes of CsA with a cyclophilin (cyclosporin A binding protein) and FK506 with an FKBP (FK506 and rapamycin binding protein) inhibit the aforementioned signaling pathways in mast cells and T cells, a complex of rapamycin with an FKBP (possibly the same FKBP associated with FK506) inhibits lymphokine receptor mediated pathway in the T cell that results in cell proliferation.[4,6] Recently, the "immunophilin complex" hypothesis received strong support from studies on *Saccharomyces cerevisiae*, an organism that is highly sensitive to the antiproliferative actions of rapamycin. Deletion of the yeast FKBP gene resulted in a mutant strain that is resistant to rapamycin; transfection of either yeast or human FKBP into the mutant strain returned rapamycin sensitivity.[7] Related findings on *S. cerevisiae* have been reported with FK506[8] (see Note Added in Proof).

Following the discovery of cyclophilin[9] and FKBP,[10,11] the use of the expression cassette polymerase chain reaction (ECPCR) method[12,13] led to the overexpression of the human forms of both proteins in *Escherichia coli*.[14,15] The availability of these recombinant proteins has facilitated investigations of binding interactions with ligands,[16] enzyme properties,[17,18] and structure determinations.[19–22] Cyclophilin and FKBP are rotamase enzymes: they catalyze the interconversion of the cis and trans rotamers of peptidyl–prolyl amide bonds of peptide and protein substrates in vitro.[10,11,23,24] This functional property encouraged an alternative biological proposal. It had been suggested that immunophilins constitute a component of signaling pathways and that the T-cell-inhibitory properties of immunophilin ligands may be associated with their ability to inhibit the actions of immunophilins.[25,26] The studies reported in this article resulted in the

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