Stereocontrolled Cyclization Reactions Mediated by Samarium Diiodide[1]

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Abstract: Stereocontrolled cyclization of 2-(ω-iodoalkyl)-β-keto ester and 2-(ω-iodoalkyl)-β-keto amide substrates induced by samarium diiodide is described. Excellent diastereoselectivity is achieved in these reactions in a predictable sense, affording highly substituted *cis*-2-hydroxycycloalkanecarboxylates and *cis*-2-hydroxycycloalkanecarboxamides, respectively, in high yields. Corresponding allylic halide substrates have also been examined and provide access to further functionalized five-, six-, and seven-membered ring systems in excellent yields.

Intramolecular Barbier-type syntheses[2] are conceptually among the most simple approaches to carbocyclic ring structures. Unfortunately, utilization of alkali and alkaline-earth metals as reductants for this process encounters several serious limitations. For example, six-membered rings appear difficult to access by employing these metal reductants.[3] Although few pertinent studies have been performed, it seems unlikely that use of these metals will allow incorporation of sensitive functional groups such as alkyl chlorides, esters, or nitriles. Furthermore, elevated temperatures required to effect cyclization under heterogeneous reaction conditions with these metals would also seem to preclude any hope of achieving highly diastereoselective intramolecular carbon–carbon bond formation.[3,4] Five, six, seven, and even larger membered rings have been generated from intramolecular coupling of allylic halides with carbonyls utilizing Cr(II) reagents and other chemoselective reductants.[5] However, few detailed studies delineating relative asymmetric induction in generation of carbocycles have been reported by utilizing these techniques.

We have focused on use of soluble lanthanide-based reductants to resolve the aforementioned concerns. Pioneering work by Kagan and co-workers with samarium diiodide (SmI_2) has served to outline use of this reagent in intermolecular Barbier-type syntheses.[6] These initial studies have also revealed the potential for SmI_2 to accomplish such transformations in a highly chemoselective fashion. Esters, nitriles, amides, and many organic halides are virtually inert under the mild reaction conditions required for coupling of alkyl iodides with ketone substrates. Kagan's investigations have been followed by reports from other laboratories,[7] and our own,[8] further substantiating the unique role that SmI_2 can play in promoting organic reactions difficult to accomplish by any other available methodologies.

Table I. Samarium Diiodide Promoted Cyclization of 2-(ω-Iodoalkyl)-Substituted β-Keto Amides (**1**, R′ = H)

starting material	R	R″	*n*	% isolated yield (**2**)
1a	H	Me	1	72[a]
1b	Me	Et	1	89
1c	Et	Me	1	79
1d	*i*-Pr	Me	1	87
1e	*t*-Bu	Me	1	77
1f	Ph	Me	1	49
1g	Me	Et	2	49
1h	*i*-Pr	Me	2	34[b]
1i	*t*-Bu	Me	2	62[c]

[a] A 21:1 mixture of diastereomers was generated. [b] Uncyclized iodo alcohol was obtained in 34% yield. [c] Uncyclized unsaturated alcohol was obtained in 29% yield.

An important area that has yet to be addressed concerns stereochemical control accessible in SmI_2-promoted Barbier reactions. As part of a program to develop novel, stereocontrolled approaches to highly functionalized carbocycles,[8b,9] we sought to utilize SmI_2 as a template upon which intramolecular coupling of organic halides with carbonyl substrates could be accomplished with substantial control of stereochemistry in a predictable sense. Herein we describe our efforts in this area, which have resulted in a unique route to highly substituted, stereodefined carbocyclic ring systems difficult to access by existing synthetic strategies.

Results and Discussion

Data we[8a,c] and others[10] have gathered from a variety of systems indicate that ketyls are the initial intermediates formed by electron transfer from SmI_2 to the ketone in SmI_2-promoted Barbier reactions. On the basis of these observations and other mechanistic studies of the Barbier reaction,[11] we postulated that Lewis basic functional groups could be incorporated into suitable haloalkyl ketone substrates, serving as stereochemical control elements for subsequent cyclization.

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(2) Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18.
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(11) (a) Pearce, P. J.; Richards, D. H.; Scilly, N. F. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1655. (b) Garst, J. F.; Smith, C. D. *J. Am. Chem. Soc.* **1976**, *98*, 1520. (c) Molle, G.; Bauer, P. *J. Am. Chem. Soc.* **1982**, *104*, 3481. (d) Molle, G.; Briand, S.; Bauer, P.; DuBois, J.-E. *Tetrahedron* **1984**, *40*, 5113.

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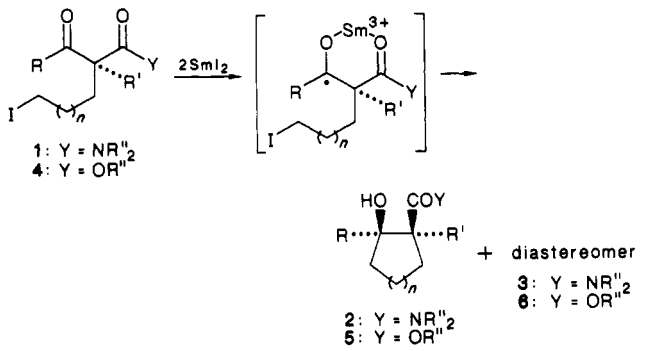
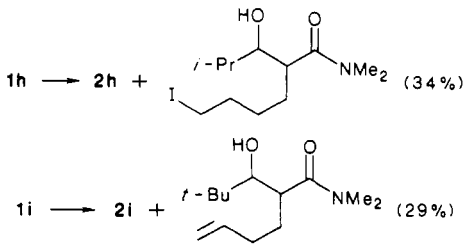


The empirical model thus envisioned would permit control of stereochemistry by virtue of a kinetically favored ring closure from the most accessible face of the chelated ketyl intermediate.

We chose *N,N*-dialkyl-2-(ω-iodoalkyl)-β-keto amides (**1**) as substrates for our initial study. These were considered to be ideal starting materials since they are readily prepared by simple alkylation reactions,[12] and, furthermore, we expected that the amide functionality would serve as an effective chelator of Sm^{3+} generated after electron transfer.[13] Through chelation, we anticipated strict control of transition-state geometry during cyclization, affording a single diastereomeric cyclized product.

A series of suitably functionalized β-keto amides was therefore prepared and treated with 2 equiv of SmI_2 in THF at −78 °C. Reactions were generally complete within 2 h at this temperature but were typically allowed to warm to room temperature. Aqueous workup, followed by simple bulb-to-bulb distillation, provided excellent isolated yields of cyclopentanoid products in nearly all cases (Table I). Steric encumbrance about the carbonyl has little, if any, effect on yields in the cyclization. Unlike intermolecular SmI_2-induced Barbier reactions,[6] aldehydes (**1a**) are effective substrates for reaction and provide excellent yields of product. Lower yields are observed in generation of cyclohexanoids, due to generation of uncyclized side products.

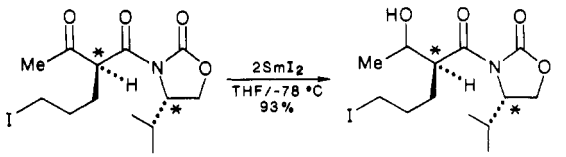


However, the desired cyclic products (**2h** and **2i**) are readily isolated in pure form from these reactions as well. Careful capillary gas chromatographic and GC/MS analyses of crude reaction mixtures reveal that, with one exception (**1a**), no detectable amounts of diastereomers are formed at any time during the course of the reactions.

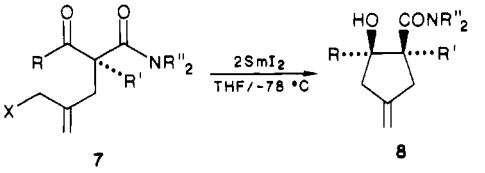
As far as we are able to determine, the reaction is under kinetic control. Our efforts to establish this on a firm basis have been thwarted by a number of experimental difficulties. For example, we have been unable to access diastereomers **3** by deprotonation of **2** (utilizing LDA, MeLi, BuLi, etc.) followed by reprotonation, or by performing the SmI_2-induced reaction in other, more highly solvating solvent systems (vide infra).

A single-crystal X-ray structure of **2e** confirmed the assigned stereochemistry of that particular product. All other compounds were correlated to **2e** by comparison of ^1H NMR, ^{13}C NMR, and IR spectra.

An attempt to generate chiral, nonracemic carbocycles proved unsuccessful when attempts to cyclize the corresponding oxazolidone[14] failed. In this instance, iodo alcohol was isolated in 93% yield as a 2:1 mixture of diastereomers.

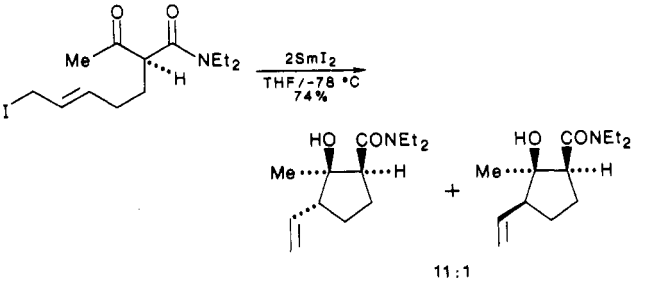


Allylic halide substrates (**7**) have also been successfully cyclized (Table II).



In these cases, cyclization is complete in less than 5 min at −78 °C after addition of substrates to SmI_2 in THF. Capillary GC and GC/MS analyses performed on crude reaction mixtures again reveal that, with a single exception (substrate **7f**), no detectable amounts of diastereomers are formed at any time. Small amounts of trans diastereomer (6%) could be detected by GC/MS when **7a** was treated with SmI_2 in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU). Allylic bromide substrates provide yields comparable to those of the allylic iodides in all cases and better yields than corresponding allylic iodides as steric hindrance about the ketone carbonyl increases.

Stereodefined vinyl-substituted carbocycles can be accessed by utilizing appropriately substituted allylic halide substrates. In formation of cyclopentanoids with an allylic iodide substrate, excellent diastereoselectivity (11:1) is achieved at three stereocenters,[15] the desired product being isolated in 74% yield.



The structure of the major diastereomer was determined by single-crystal X-ray diffractometry of its *m*-dinitrobenzoate ester. Spectral data of the minor diastereomer are consistent with a product that is epimeric about the vinyl-substituted carbon. By utilizing the corresponding allylic bromide as starting material for the reaction, three of the four possible diastereomers were detected by GC/MS studies in the ratio of 37.6:1.4:1. Although diastereoselectivity in this instance is somewhat higher than for

Table II. Samarium Diiodide Promoted Cyclization of 2-(2-Halomethyl-2-propenyl)-Substituted β-Keto Amides (**7**)

starting material	R	R′	R″	X	% isolated yield (**8**)
7a	Me	H	Et	I	80
7b	Et	H	Me	I	70
7c	*n*-Hex	H	Me	I	56
7d	*i*-Pr	H	Me	Br	50
7e	*t*-Bu	H	Me	Br	43
7f	Me	Me	Et	I	91[a]

[a] A 5.7:1 ratio of diastereomers was generated in this case.

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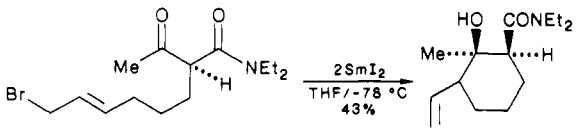
Table III. Samarium Diiodide Induced Cyclization of 2-Alkyl-2-(3-iodopropyl)-β-keto Ester Substrates (**4**)

starting material	R	R′	% isolated yield	diasteromer ratio (**5**:**6**)
4a	H	Me	96	8:1
4b	Me	Me	75	36:1
4c	Et	Me	83	>200:1
4d	*i*-Pr	Me	87	>200:1
4e	*t*-Bu	Me	83	>200:1
4f	Ph	Me	39	>200:1
4g	Me	Et	78	10:1
4h	Me	*i*-Pr	74	7:1
4i	Me	Ph	83	>200:1

the allylic iodide substrate, yields are lower (59%) due primarily to problems encountered in obtaining pure allylic bromide starting material.

Cyclization of the homologous allylic bromide led to generation of the β-hydroxycyclohexanecarboxamide in 43% yield as a 1.3:1 mixture of diastereomers.

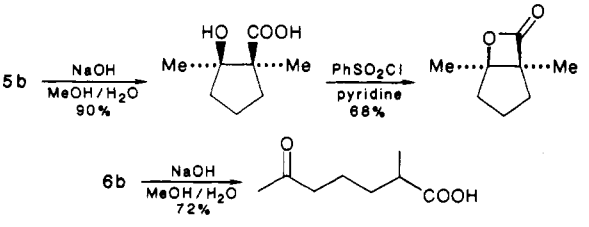


It appears likely on the basis of the analogous five-membered ring system and comparison of spectra that these are both *cis*-β-hydroxycarboxamide derivatives, epimeric about the vinyl-substituted carbon center. However, rigorous studies to establish this have not been undertaken.

On the basis of these studies in the β-keto amide series, we anticipated that SmI_2-induced cyclization of 2-(ω-iodoalkyl)-β-keto ester substrates (**4**, $n = 1$) would result in highly diastereoselective syntheses of cyclized products as well. We were surprised to discover that the ratio of products formed with substrate **4b** (R, R′ = Me, R″ = Et) at −78 °C was only about 3:1. However, by allowing reactions to warm to room temperature and to stir for approximately 3 h, diastereomeric ratios improved dramatically in many cases (Table III).

That SmI_2 is perhaps unique in its ability to promote this type of reaction was established by attempting cyclization of **4b** with Mg metal. In our hands, even use of activated Mg[16] in THF at room temperature for 24 h failed to provide cyclized product, and starting material remained largely unchanged in the reaction mixture.

Stereochemistry of the major diastereomers generated in the SmI_2 cyclization reaction was established by hydrolysis of **5b** to the carboxylic acid, followed by generation of the corresponding β-lactone.[17] Saponification of **6b** under the same reaction conditions led to formation of an acyclic keto acid. All other diastereomers were correlated to **5b** and **6b** by comparison of ^1H NMR, ^{13}C NMR, and IR spectra, as well as by physical properties (relative GC retention times and R_f on TLC).[18]

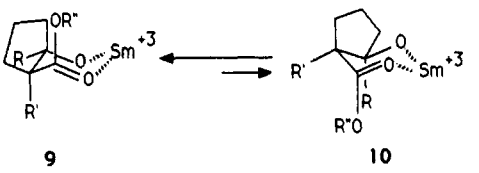


(16) (a) Rieke, R. D.; Li, P. T.-J.; Burns, T. P.; Uhm, S. T. *J. Org. Chem.* **1981**, *46*, 4323. (b) Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1983**, *48*, 4141.

(17) Adam, W.; Baeza, J.; Liu, J. *J. Am. Chem. Soc.* **1972**, *94*, 2000.

(18) Strong intramolecular H bonding in the cis series of compounds had the expected effect on the IR O—H and C=O stretching frequencies (both falling at lower wavenumbers relative to corresponding trans isomers). Shorter relative GC retention times and higher relative R_f values were also observed for the cis compounds.

cis Diastereomer Conformations



trans Diastereomer Conformations

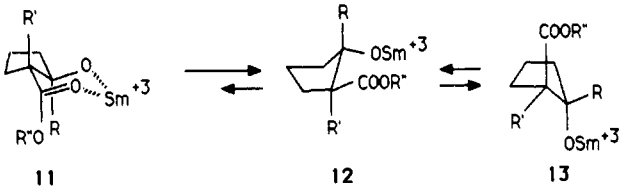
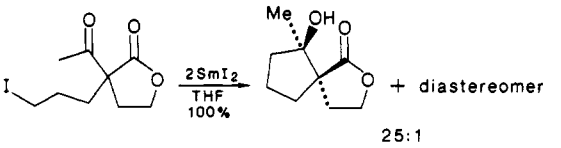
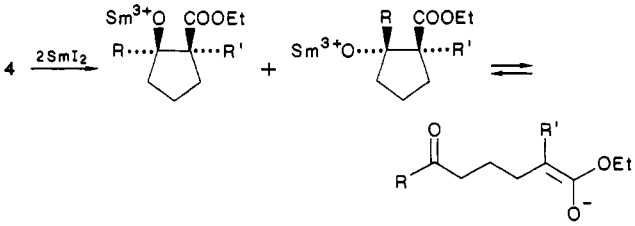


Figure 1.

A highly diastereoselective route to a spirocyclic system can be realized by utilizing 2-(3-iodopropyl)-2-acetylbutyrolactone as a substrate for the reaction.



A logical explanation for the phenomena observed in cyclization of β-keto ester substrates involves invocation of a retroaldol–aldol process which serves to equilibrate initially formed aldolates.[19]



Intermolecular reverse aldolizations leading to thermodynamic stereoselection have been observed in various systems.[20] Several highly diastereoselective processes leading to cyclic aldolate products by a variety of methods have also been described recently.[21] Well-precedented factors make it reasonable that intramolecular retroaldol–aldol processes might occur with ease in cyclic ester aldolates, but less readily in corresponding cyclic amide aldolates described above. For example, steric crowding is known to promote retroaldol reactions.[20a] In the present case, aldolates derived from 1,2-disubstituted β-hydroxy ester substrates (**4**: R′ = alkyl) are therefore more susceptible to reverse aldolization than those derived from β-monosubstituted β-hydroxy amides (**1**: R′ = H) described above. In fact, in this regard it is interesting to

(19) This retroaldol–aldol process is particularly surprising in view of the report that use of Ce^{3+} counterion suppresses retroaldol reactions in ketone aldolates due to formation of stable chelates. Imamoto, T.; Kusomoto, T.; Yokoyama, M. *Tetrahedron Lett.* **1983**, *24*, 5233.

(20) (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, **1984**; Vol. 3. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

(21) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Cohen, N. *Acc. Chem. Res.* **1976**, *9*, 412. (c) Agami, C.; Sevestre, H. *J. Chem. Soc., Chem. Commun.* **1984**, 1385. (d) Jackson, A. C.; Goldman, B. E.; Snider, B. B. *J. Org. Chem.* **1984**, *49*, 3988. (e) Nokami, J.; Wakabayashi, S.; Okawara, R. *Chem. Lett.* **1984**, 869. (f) Stevens, R. W.; Mukaiyama, T. *Chem. Lett.* **1985**, 851.

Table IV. Solvent Effects in SmI_2-Promoted Cyclization of Substrate **4b**

solvent	additive	yield (%)	ratio (**5b**:**6b**)
THF		84	20:1
THF	$Fe(DBM)_3$/5%	60	7:1
THF	*N*,*N*-diethylacetoacetamide (10%)	65	7.5:1
THF	tetraglyme (1 equiv)	67	2.3:1
THF	18-crown-6 (1 equiv)	62	1.7:1
DME		75	3:1

note that the one β-formyl ester substrate studied (**4a**) showed no signs of equilibration under reaction conditions employed.

Retroaldol reactions are also facilitated by structural modifications that make the enolate less basic (i.e., ester enolate vs. amide enolate).[20a] Finally, enhanced basicity of amide carbonyls (relative to those of esters) should further inhibit the retroaldol process in amide aldolates by forming tighter chelates with Lewis acidic metal ions than is possible in corresponding ester aldolates.

Preferred formation of cis products can be rationalized by consideration of structures depicted in Figure 1. Conformation **11** for the trans diastereomer intermediate begins to suffer by having both alkyl groups (R and R′) axial on the six-membered ring defined by the chelate as the steric bulk of these substituents increases. As a consequence, structures **12** and, in particular, **13** may more accurately reflect the most stable conformations of this diastereomer when R or R′ is relatively large. In **12** and **13**, any stability ascribed to formation of a chelate is obviously forsaken.

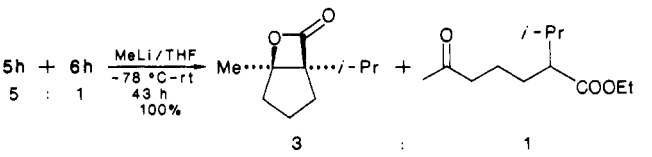
Of the two favorable cis (chelated) conformations, **9** perhaps more accurately reflects the nature of this intermediate. Only **9** can be used to rationalize the increase in diastereoselectivity seen when alkyl substituents on the ketone (R) become sterically demanding (**4a–e**), and the trend toward decreased diastereoselectivity when substituents at the 2-position (R′) become larger (**4b**, **4g**, **4h**).

Also consistent with this picture is the fact that while methyl and ethyl esters (**4**: R, R′ = Me; R″ = Me, Et) provide excellent diastereoselectivities (13:1, 95% and 36:1, 75%, respectively) in cyclization processes after equilibration, *tert*-butyl ester **4** (R, R′ = Me; R″ = *t*-Bu) provided only a 3:1 mixture of diastereomers in 97% yield under identical conditions. It may well be that in this instance the relative preponderance of the trans diastereomer is a direct result of the ability of the *tert*-butyl ester group to prevent severe 1,3-diaxial interactions present in cis diastereomer conformations by equilibration to the trans diastereomer through the retroaldol–aldol process.

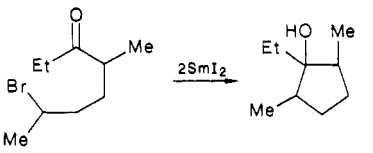
That the metal counterion is intimately involved in control of stereochemistry in these processes was demonstrated by a study of solvent effects in cyclization of **4b** (Table IV). If chelation is a major factor in stabilization of cis diastereomer intermediates over trans diastereomer intermediates in equilibrating reaction mixtures, use of highly coordinating solvents or additives that serve to strip the metal ion away from the chelating center should radically alter observed diastereoselectivity. This phenomenon is indeed observed, and nearly equal proportions of **5b** and **6b** are generated under such circumstances.

We have also taken a brief look at the retroaldol–aldol process in aldolates of **5b** and **6b** utilizing a number of different metal counterions. Curiously, lithium aldolates (generated by addition of MeLi to either **5b** or **6b** in THF) equilibrate to provide a 6:1 ratio of diastereomers in which **6b** predominates. Sodium and potassium aldolates (generated by addition of NaH or KH, respectively, to **5b**) afford at best a 1:1 equilibrated mixture of diastereomers from **5b** before yields in the process begin to erode due to side reactions. We have seen no evidence for equilibration when magnesium, zinc, or Sm^{3+} aldolates (the latter two generated by addition of MeLi to **6b** in THF, followed by $ZnCl_2$ and SmI_3, respectively) were generated from **6b**. Results from the experiment in which the Sm^{3+} aldolate was generated via the MeLi/SmI_3 protocol indicate that we are unable to mimic cyclization reaction conditions by simply generating a Sm^{3+} aldolate from the product β-hydroxycarboxylate in this manner.

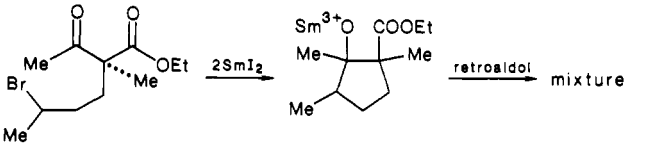
Unfortunately, lithium aldolate equilibration does not provide a general method for diastereoselective preparation of *trans*-β-hydroxycyclopentanecarboxylate products. As might be expected, the reaction is highly sensitive to substitution about the β-hydroxy ester, as exemplified by reaction of **5h** and **6h** with MeLi. Only β-lactone and acyclic keto ester could be isolated from the reaction mixture.



Cyclization of a simple ketone substrate incorporating a secondary alkyl halide proceeds in reasonable yields, although at least three diastereomers are produced in a nonselective fashion.



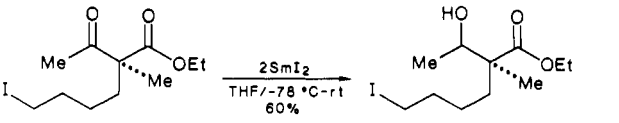
However, only minor amounts of cyclized product could be isolated from reaction mixtures by utilizing secondary halide β-keto ester substrates.



While cyclized product is clearly formed at −78 °C, it is rapidly consumed under the reaction conditions to form a variety of products. We believe that this phenomenon is again related to the retroaldol–aldol equilibration. In this particular instance, the retroaldol process is enhanced (and the intramolecular aldol inhibited) due to increased steric encumbrance in the intermediates.[20a] As a consequence, SmI_2-induced cyclization initially occurs; however, the resulting aldolate product is unstable under the reaction conditions and leads to an intractable mixture of products.

Substituted β-diketone substrates may be another casualty of the retroaldol reaction manifold. Attempts to cyclize 3-methyl-3-(3-iodopropyl)-2,4-pentanedione with SmI_2 failed, and unidentifiable products were generated in the process. In this instance, the retroaldol reaction is particularly favorable since a relatively stable acyclic ketone enolate is generated. However, we cannot rule out other processes which might compete with cyclization in this instance.

Attempts to generate six-membered ring carbocycles in the β-keto ester series were unsuccessful. Treatment of appropriate substrates results in formation of ketone-reduced alcohols as a mixture of diastereomers.



This result again points to the fact that initial electron transfer

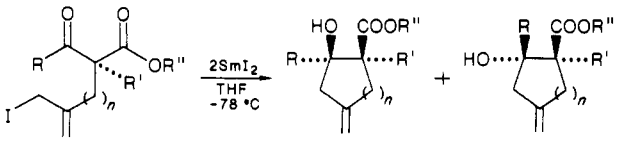
(22) IR absorption frequencies of the O—H and C=O stretches were again diagnostic of the intramolecularly H-bound cis isomers relative to the corresponding trans isomers. In addition, in this series the trans isomers gave a characteristic M − 28 ion in the mass spectrum from a McLafferty rearrangement, whereas the cis isomers showed no such fragmentation pattern. (a) Deutsch, J.; Mandelbaum, A. *J. Am. Chem. Soc.* **1970**, *92*, 4288. (b) Green, M. M. *Top. Stereochem.* **1976**, *9*, 35. (c) Green, M. M. *Pure Appl. Chem.* **1978**, *50*, 185. (d) Mandelbaum, A. *Mass Spectrom. Rev.* **1983**, *2*, 223. (e) Tabet, J. C.; Bertronne, M.; Beloeil, J. C.; Stahl, D. *Org. Mass Spectrom.* **1984**, *19*, 363.

Table V. Samarium Diiodide Promoted Cyclization of Allylic Halide β-Keto Ester Substrates (**14**)

starting material	R	R′	R″	*n*	% isolated yield	ratio (**15**:**16**)
14a	Me	Me	Me	1	91	6:1
14b	Me	Me	Et	1	84	6:1
14c	Me	Me	*t*-Bu	1	76	2:1
14d	Et	Me	Et	1	73	16:1
14e	*i*-Pr	Me	Et	1	74	41:1
14f	*t*-Bu	Me	Et	1	63	>200:1
14g	Me	Et	Et	1	78	2:1
14h	Me	*i*-Pr	Et	1	77	1:1.2
14i	Me	Ph	Et	1	68	>200:1
14j	Me	Me	Et	2	73	1.8:1
14k	Me	Me	Et	3	64	1:1

takes place from SmI_2 to the ketone carbonyl rather than organic halide in SmI_2-promoted Barbier reactions.[10] It is disheartening to find, however, that in these cases even the enhanced ability of SmI_2 to effect generation of six-membered rings is not enough to make up for entropic factors which preclude efficient cyclization.

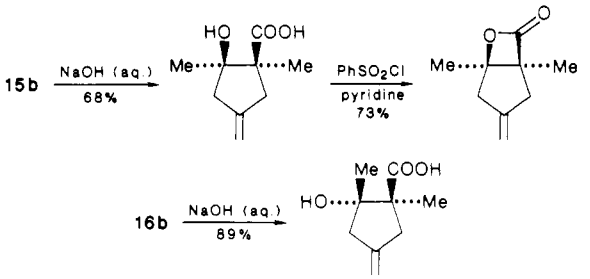
Allylic halides in the β-keto ester series provide excellent substrates for cyclization (Table V).



14 **15** **16**

Reaction occurs smoothly in less than 5 min upon treatment of these substrates with 2 equiv of SmI_2 in THF at −78 °C. Simple aqueous workup followed by flash chromatography allows isolation of products in excellent yields. Five-, six-, and seven-membered rings can all be accessed in this series, although diastereoselectivity for six- and seven-membered rings is not optimal.

Stereochemistry in this series, too, was established by conversion of **15b** to the corresponding β-lactone[17] through a two-step procedure. Diastereomer **16b** could be hydrolyzed to the corresponding hydroxy acid, which is incapable of forming a β-lactone. (Under essentially the same conditions, the haloalkyl-derived cyclopentanecarboxylate provided acyclic keto acid, vide supra).



All other products were correlated to **15b** or **16b** by spectra data[22] as well as physical characteristics (e.g., relative R_f on TLC, relative GC retention times, etc.).

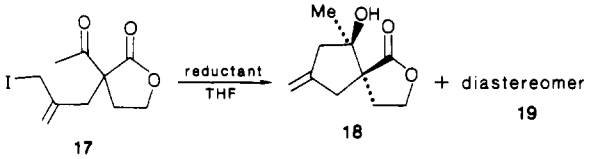
Curiously, we have seen no evidence for equilibration of diastereomers in this series. Reactions quenched immediately after addition of substrate to SmI_2 at −78 °C show essentially the same ratio of diastereomers as those allowed to warm to room temperature (or heated at reflux in THF) for long periods of time. Furthermore, a synthetic 1.4:1 mixture of **15b** and **16b**, when treated at −78 °C with MeLi followed by 2 equiv of SmI_3, showed no signs of equilibration when allowed to warm to room temperature. (However, it must be remembered that these conditions probably do not mimic the reaction conditions, as noted for the iodoalkyl substrates above.) When MeLi itself is added to a 6:1 mixture of **15b**:**16b**, slow equilibration ensues to provide the diastereomers in a ratio of 1:3.6.

Allylic halide substrates ultimately derived from 2-acetylbutyrolactone cyclized to provide corresponding spirocyclic products and provided an opportunity to examine the efficiency of SmI_2 relative to a number of other reductants in this process (Table VI).

Table VI. Effect of Reductant on Yield and Diastereoselectivity in Cyclization of Substrate **17**

entry	reductant	% isolated yield	diastereomer ratio (**18**:**19**)
1	SmI_2	94	6.2:1
2	$CrCl_2$	84	6.8:1
3	Mg	71	5.1:1
4	Sm	94	2.4:1
5	Ce(Hg)	99	1.9:1
6	SnF_2	76	1:33.5
7	Zn	71	1:10.3
8	Mn	0[a]	

[a] Starting material was recovered unchanged.



17 **18** **19**

Samarium diiodide, $CrCl_2$,[23] and Mg[15,16] all provide essentially the same ratio of diastereomers (entries 1–3), the "chelation-controlled" product predominating. Samarium diiodide provides somewhat cleaner reaction mixtures and, in our hands, higher isolated yields were obtained by utilizing this reagent.

In many cases, chelation-controlled cyclization of allylsilanes provides perhaps the most efficient entry into stereodefined carbocycles with this particular substitution pattern.[9a] However, other organometallics derived from allylic halides provide the opportunity to generate carbocycles with complementary stereochemistry. Indeed, SnF_2[9b,24] and Zn[16a] (entries 6 and 7) provide predominantly the opposite diastereomer in good yields. For SnF_2, at least, this trend carried over to other substrates, although not so dramatically as in the spirocyclic system.

$$\mathbf{14b} \xrightarrow[\text{THF}\ 98\%]{SnF_2} \mathbf{15b} + \mathbf{16b}\quad 1:3$$

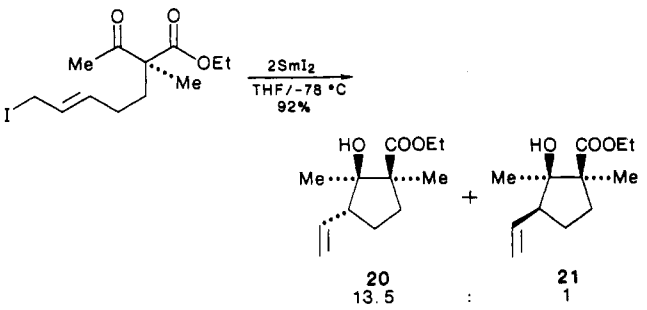
Efforts continue to determine conditions for diastereoselective generation of the "nonchelation-controlled" product in the allylic halide series.

Different configurations about the allylic halide were briefly examined to determine the effect on the cyclization reaction. In spite of increased steric crowding in the aldolate products, vinyl-substituted products could be accessed in a highly stereoselective fashion by employing a 2-(*trans*-5-iodo-3-pentenyl)-substituted β-keto ester for cyclization. Again, no evidence for a retroaldol–aldol process which would attenuate yields in these instances was evident. Only two of four possible diastereomers could be detected by GC/MS in this particular case, being formed in a ratio of 13.5:1.

(23) (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. (b) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685. (c) Hiyama, T.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1037. (d) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561. (e) Lewis, M. D.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343. (f) Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G.; Zirotti, C. *Chem. Lett.* **1984**, 335.

(24) (a) Gambaro, A.; Peruzzo, V.; Plazzogna, G.; Tagliavini, G. *J. Organomet. Chem.* **1980**, *197*, 45. (b) Mukaiyama, T.; Harada, T.; Shoda, S. *Chem. Lett.* **1980**, 1507. (c) Harada, T.; Mukaiyama, T. *Chem. Lett.* **1981**, 1109. (d) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (e) Mukaiyama, T.; Harada, T. *Chem. Lett.* **1981**, 621. (f) Mukaiyama, T.; Suzuki, K.; Yamada, T. *Chem. Lett.* **1982**, 929. (g) Auge, J.; David, S. *Tetrahedron Lett.* **1983**, *24*, 4009. (h) Auge, J. *Tetrahedron Lett.* **1985**, *26*, 753.

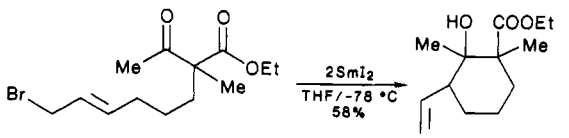
(25) (a) Tsutsui, M.; Ely, N. *J. Am. Chem. Soc.* **1975**, *97*, 3551. (b) Mazzei, A. In *Organometallics of the f-Elements*; Marks, T. J., Fischer, R. D., Eds.; Reidel: Dordrecht, 1979.



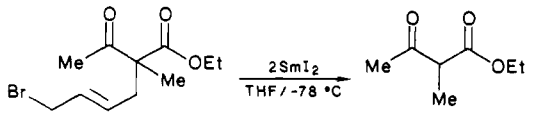
Relative stereochemistry of the hydroxyl and carboxylate stereocenters in the major diastereomer was established by generation of the β-lactone[17] from **20** as described above. On the basis of all spectral data,[22] it appears that the relative stereochemistry of the vinyl substituent in the major diastereomer is the same as that established for analogous β-keto amide substrates described above,[15] and the minor diastereomer is epimeric about the vinyl-substituted carbon center.

By utilizing the corresponding bromide substrate, all four diastereomers were detected by GC/MS in a ratio of 89:1.4:1.2:1 (**20** and **21** the major isomers). Unfortunately, the process is not stereospecific. Cyclization of the corresponding 2-(*cis*-5-iodo-3-pentenyl)-β-keto ester derivative resulted in formation of three diastereomers in ratio of 38:5:1 in 73% yield, with the major isomers again being **20** and **21**.

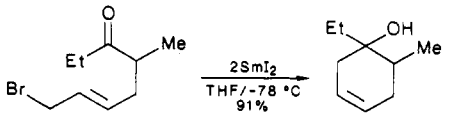
Cyclization of the homologous allylic bromide provides vinyl-substituted cyclohexanecarboxylates as a mixture of all four diastereomers in a ratio of 3.8:1.8:1.2:1.



Curiously, attempts to cyclize ethyl 2-methyl-2-(*trans*-4-bromo-2-butenyl)-3-oxobutanoate were unsuccessful, with ethyl 2-methyl-3-oxobutanoate isolated as the major product of the reaction.



Loss of butadiene as required for this transformation is clearly facilitated by the ability of a β-keto ester stabilized (anion or radical) intermediate to serve as an effective leaving group in the reaction. Thus, cyclization of *trans*-8-bromo-4-methyl-6-octen-3-one proceeds smoothly to provide 1-ethyl-6-methyl-3-cyclohexen-1-ol in 91% isolated yield.



These examples have some mechanistic implications in that they appear to rule out cyclization via S_N2 displacement of the halide by a samarium ketyl. However, one cannot distinguish between a mechanism based on "allylsamarium"[25] addition to the carbonyl vs. an electron-transfer mechanism as outlined for alkyl halide substrates above. Both mechanisms allow for isomerization required of the double bond (via 1,3-allylic transposition in the case of an organometallic,[26] or configurational instability in an allylic radical[27] in a diradical coupling mechanism) and also provide reasonable routes for generation of butadiene. As a consequence, further mechanistic work is clearly required in order to provide a more detailed understanding of reactions in the allylic halide series.

Conclusions

Samarium diiodide has been demonstrated to be an exceedingly effective reagent in inducing stereocontrolled intramolecular Barbier-type reactions. Highly functionalized five-, six-, and, in some cases, seven-membered rings can be accessed in synthetically useful yields from β-keto ester and β-keto amide substrates. Cyclization of alkyl halide as well as allylic halide substrates has been described. Reactions proceed under very mild conditions and are therefore anticipated to allow incorporation of a variety of different functional groups within the same molecules. Stereochemical aspects of the reaction have been delineated. In most cases, products based on a "chelation-controlled" model can be anticipated. Although further development is required, access to diastereomeric products has also been accomplished in several cases. Mechanistic aspects of the reaction revealed through these studies appear consistent with electron transfer from SmI_2 to the carbonyl generating a ketyl, followed by coupling to provide cyclized product. However, other mechanistic interpretations, particularly in the allylic halide series, certainly cannot be ruled out.

We continue to explore the utility of SmI_2 in providing stereocontrolled access to carbocycles inaccessible by existing methodologies and as a reducing agent for other unique synthetic transformations.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus. All melting points and boiling points are reported uncorrected. IR spectra were recorded on a Perkin-Elmer 727B infrared spectrophotometer and calibrated by comparison with a standard 0.05 mm thick polystyrene film. FTIR spectra were performed on an IBM IR/30 Series FTIR spectrometer. ^1H NMR were recorded at 200 MHz with $CDCl_3$ as solvent and with $CHCl_3$ as internal standard (δ 7.24). ^{13}C NMR spectra were recorded at 50 MHz with $CDCl_3$ as both solvent and internal standard. Low resolution and exact mass spectra were recorded on a VG-7070EQ-HF mass spectrometer employing perfluorokerosene as internal standard. All mass spectra utilized a 70-eV ionizing potential. Gas–liquid chromatographic analyses were conducted on either a Hewlett-Packard Model 5750 or Model 5890A chromatograph equipped with a Hewlett-Packard Model 3390 digital integrator. GLC columns (10 × $^1/_8$ in.) were packed with 3% Carbowax 20M on 100/120 AW-DMCS Chromosorb W. Capillary gas–liquid chromatographic analyses were performed by utilizing 25 m × 320 μm 5% phenyl SE-54 fused silica capillary columns. Flash chromatography was carried out with standard procedures.[28]

Reagents. THF was distilled from $LiAlH_4$, stored over sodium benzophenone ketyl, and distilled from benzophenone ketyl immediately prior to use. 1,2-Diiodoethane was purified by dissolving it in ether, washing it with saturated aqueous $Na_2S_2O_3$, drying it over $MgSO_4$, and removing the ether in vacuo to yield a white crystalline solid. All reactions were conducted under an argon atmosphere and employing standard bench-top techniques for handling air-sensitive materials.[29] Samarium metal powder (99.9%) was purchased from Research Chemicals (P.O. Box 14588, Phoenix, AZ 85063-4588).

Starting Materials. All commercially unavailable β-keto amides and β-keto esters were prepared by the method of Smith.[30] Substrates for cyclization were typically prepared by alkylation of these β-keto esters or β-keto amides with appropriate dihalides, followed by Finkelstein reactions with NaI in acetone. The β-formyl amide and β-formyl ester substrates were prepared by hydroxymethylation of the corresponding 5-chloro amide or 5-chloro ester sodium enolate with monomeric formaldehyde, followed by Swern oxidation and Finkelstein reaction.

Cyclization of 2-(3-Iodopropyl)-β-formyl Amides and 2-(3-Iodopropyl)-β-formyl Esters with SmI_2. General Procedure. To a slurry of samarium metal power (0.30 g, 2.0 mmol, flamed and cooled under argon) in THF (1 mL) at room temperature was added a solution of 1,2-diiodoethane (0.42 g, 1.5 mmol) in THF (2 mL). The mixture was

(26) Fedorov, L. A. *Russ. Chem. Rev.* **1970**, *39*, 655.
(27) Korth, H.-G.; Lommes, P.; Sustmann, R. *J. Am. Chem. Soc.* **1984**, *106*, 663.
(28) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(29) Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, **1975**.
(30) Smith, A. B., III; Levenburg, P. A. *Synthesis* **1981**, 567.

stirred at ambient temperature for 1 h during which time the reaction's color changed from olive-green to deep blue. The resulting solution was cooled to −78 °C in a dry ice–acetone bath, and the 2-(3-iodopropyl)-β-formyl amide or 2-(3-iodopropyl)-β-formyl ester (0.75 mmol) was slowly added neat. The reaction was allowed to stir at −78 °C for 0.5 h before being quenched with saturated aqueous K_2CO_3. The reaction was then warmed to room temperature and separated between saturated aqueous K_2CO_3 (5 mL) and ether (5 mL). The aqueous layer was extracted with ether (3 × 3 mL). The organic extracts were washed with brine (2 mL) and dried over $K_2CO_3/MgSO_4$.

Cyclization of *N,N*-Dimethyl-2-formyl-5-iodopentanamide (1a). By using the general procedure described above, **1a** (0.212 g) was cyclized to provide **2a** (0.085 g), 72%, isolated by Kugelrohr distillation: bp 120–125 °C (0.20 mmHg); ^{1}H NMR ($CDCl_3$) δ 4.53 (br s, 1 H), 4.4–4.3 (m, 1 H), 2.98 (s, 3 H), 2.88 (s, 3 H), 2.61 (dt J = 9.0, 4.0 Hz, 1 H), 2.0–1.5 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 175.91, 74.09, 44.59, 37.02, 35.10, 33.84, 26.62, 21.86; IR (CCl_4) 3360, 2950, 2880, 1625, 1505, 1415, 1250, 1185, 1145 cm^{-1}; FTIR ($CHCl_3$) 3399.0, 1616.5 cm^{-1}; calcd for $C_8H_{15}NO_2$ 157.1103, found 157.1108.

Cyclization of Ethyl 2-Formyl-5-iodo-2-methylpentanoate (4a). By using the general procedure described above, **4a** (0.244 g) was cyclized to provide a mixture of **5a** and **6a** (0.124 g), 96%, isolated by flash chromatography (25% EtOAc in hexane on silica gel). **5a**: ^{1}H NMR ($CDCl_3$) δ 4.10 (q, J = 7.0 Hz, 2 H), 3.93 (t, J = 4.0 Hz, 1 H), 2.3–1.4 (m, 6 H), 1.21 (t, J = 7.0 Hz, 3 H), 1.11 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.17, 79.83, 60.56, 53.95, 33.07, 31.78, 22.26, 20.31, 14.05; IR (CCl_4) 3500, 2950, 2880, 1710, 1470, 1385, 1305, 1125, 1055 920 cm^{-1}; FTIR ($CHCl_3$) 3530.2, 1703.4 cm^{-1}; calcd for $C_9H_{16}O_3$ 172.1099, found 172.1096. **6a**: ^{1}H NMR ($CDCl_3$) δ 4.30 (t, J = 7.0 Hz, 1 H), 4.12 (q, J = 7.0 Hz, 2 H), 2.3–1.4 (m, 6 H), 1.19 (t, J = 7.0 Hz, 3 H), 1.14 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.75, 79.93, 60.56, 33.69, 31.89, 30.80, 18.96, 17.19, 14.16; IR (CCl_4) 3500, 2970, 2865, 1710, 1465, 1375, 1265, 1180, 1130, 1080 cm^{-1}; FTIR ($CHCl_3$) 3622.8, 3437.6, 1711.1 cm^{-1}; calcd for $C_9H_{16}O_3$ 172.1099, found 172.1096.

Cyclization of 2-(3-Iodopropyl)-β-keto Amides and 2-(3-Iodopropyl)-β-keto Esters with SmI_2. General Procedure. To samarium metal powder (0.30 g, 2.0 mmol), flamed and cooled under a slow flow of argon, was added THF (1 mL) followed by a solution of 1,2-diiodoethane (0.42 g, 1.5 mmol) in THF (2 mL). The mixture was stirred at ambient temperature for 1 h. The resulting solution was cooled to −78 °C in a dry ice–acetone bath, and the 2-(3-iodopropyl)-β-keto amide or ester (0.75 mmol) was slowly added neat. The reaction was allowed to stir and warm to room temperature overnight before being separated between saturated aqueous K_2CO_3 (5 mL) and ether (5 mL). The aqueous layer was extracted with ether (3 × 3 mL). The organic extracts were washed with brine (2 mL) and dried over $K_2CO_3/MgSO_4$.

Cyclization of *N,N*-Diethyl-5-iodo-2-acetylpentanamide (1b). By using the general procedure described above, **1b** (0.244 g) was cyclized to provide **2b** (0.127 g), 85% by Kugelrohr distillation: bp 70–80 °C (0.01 mmHg); ^{1}H NMR ($CDCl_3$) δ 5.95 (br s, 1 H), 3.5–3.1 (m, 4 H), 2.6–1.3 (m, 7 H), 1.23 (s, 3 H), 1.08 (q, J = 7.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 175.19, 79.83, 48.28, 41.97, 40.13 (2), 28.81, 26.17, 21.73, 14.80, 13.01; IR (CCl_4) 3350, 2965, 2855, 1610, 1460, 1260, 1145, 940 cm^{-1}; FTIR ($CHCl_3$) 3346.9, 1608.8 cm^{-1}; calcd for $C_{11}H_{21}NO_2$ 199.1572, found 199.1578.

Cyclization of *N,N*-Dimethyl-2-(3-iodopropyl)-3-oxopentanamide (1c). By using the general procedure described above, **1c** (0.233 g) was cyclized to provide **2c** (0.129 g), 93%, by Kugelrohr distillation: bp 55–60 °C (0.05 mmHg); ^{1}H NMR ($CDCl_3$) δ 5.75 (d, J = 2.4 Hz, 1 H), 2.99 (s, 3 H), 2.89 (s, 3 H), 2.52 (t, J = 9.0 Hz, 1 H), 2.0–1.3 (m, 8 H), 0.86 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.37, 82.80, 46.86, 37.21, 37.13, 35.15, 32.69, 28.09, 21.51, 9.03; IR (CCl_4) 3375, 2965, 2880, 1620, 1460, 1405, 1325, 1140 cm^{-1}; FTIR ($CHCl_3$) 3360.4, 1616.5 cm^{-1}; calcd for $C_{10}H_{19}NO_2$ 185.1416, found 185.1427.

Cyclization of *N,N*-Dimethyl-2-(3-iodopropyl)-4-methyl-3-oxopentanamide (1d). By using the general procedure described above, **1d** (0.244 g) was cyclized to provide **2d** (0.132 g), 88%, by Kugelrohr distillation: bp 80–85 °C (0.10 mmHg); ^{1}H NMR ($CDCl_3$) δ 5.95 (br s, 1 H), 3.02 (s, 3 H), 2.90 (s, 3 H), 2.63 (t, J = 10.0 Hz, 1 H), 2.0–1.4 (m, 7 H), 0.84 (d, J = 6.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 177.06, 85.50, 44.59, 37.18, 36.60, 35.69, 35.31, 28.84, 21.60, 18.39, 18.09; IR (CCl_4) 3325, 2955, 2860, 1620, 1465, 1420, 1400, 1330, 1135 cm^{-1}; FTIR ($CHCl_3$) 3346.9, 1616.5 cm^{-1}; calcd for $C_{11}H_{21}NO_2$ 199.1572, found 199.1574.

Cyclization of *N,N*-Dimethyl-4,4-dimethyl-2-(3-iodopropyl)-3-oxopentanamide (1e). By using the general procedure described above, **1e** (0.254 g) was cyclized to provide **2e** (0.142 g), 89%, isolated by Kugelrohr distillation: bp 70–75 °C (0.02 mmHg), mp 86.0–87.5 °C; ^{1}H NMR ($CDCl_3$) δ 6.43 (s, 1 H), 3.06 (s, 3 H), 2.91 (s, 3 H), 2.81 (t, J = 9.4 Hz, 1 H), 2.0–1.5 (m, 6 H), 0.87 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 177.92, 88.02, 40.98, 37.45, 37.24, 35.50, 35.13, 29.91, 26.33 (3), 21.78; IR (CCl_4) 3310, 2950, 2875, 1620, 1470, 1400, 1385, 1325, 1185, 1135, 995, 880 cm^{-1}; FTIR ($CHCl_3$) 3319.9, 1616.5 cm^{-1}; calcd for $C_{12}H_{23}NO_2$ 213.1729, found 213.1721.

Cyclization of *N,N*-Dimethyl-2-(3-iodopropyl)-3-oxo-3-phenylpropanamide (1f). By using the general procedure described above, **1f** (0.281 g) was cyclized to provide **2f** (0.086 g), 49%, isolated by Kugelrohr distillation: bp 90–100 °C (0.01 mmHg); ^{1}H NMR ($CDCl_3$) δ 7.5–7.2 (m, 5 H), 6.63 (s, 1 H), 3.3–3.1 (m, 1 H), 2.91 (s, 3 H), 2.83 (s, 3 H), 2.2–1.8 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 177.59, 138.92, 128.36 (2), 128.00 (2), 126.85, 83.48, 49.61, 41.85, 36.98, 35.17, 28.14, 22.28; IR (CCl_4) 3300, 3060, 3015, 2925, 2865, 1625, 1490, 1450, 1400, 1325, 1180, 1140, 1065, 1030 cm^{-1}; FTIR ($CHCl_3$) 3391.3, 1624.3 cm^{-1}; calcd for $C_{14}H_{19}NO_2$ 233.1416, found 233.1404.

Cyclization of Ethyl 2-Acetyl-5-iodo-2-methylpentanoate (4b). By using the general procedure described above, **4b** (0.234 g) was cyclized to provide a mixture of **5b** and **6b** (0.105 g), 75%, isolated by Kugelrohr distillation: bp 30 °C (0.01 mmHg). **5b**: ^{1}H NMR ($CDCl_3$) δ 4.13 (q, J = 7.1 Hz, 2 H), 3.23 (br s, 1 H), 2.6–1.3 (m, 6 H), 1.31 (s, 3 H), 1.22 (t, J = 7.1 Hz, 3 H), 1.12 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.74, 82.02, 60.11, 55.08, 38.13, 34.97, 22.59, 21.26, 19.11, 13.80; IR (CCl_4) 3540, 2975, 2875, 1710, 1470, 1457, 1375, 1290, 1265, 1145, 1180, 1020, 935 cm^{-1}; FTIR ($CHCl_3$) 3618.9, 3485.8, 1707.2 cm^{-1}; calcd for $C_{10}H_{19}O_3$ (M + 1) 181.1264, found 181.1261. **6b**: ^{1}H NMR ($CDCl_3$) δ 4.11 (q, J = 7.1 Hz, 2 H), 2.3–1.5 (m, 7 H), 1.22 (t, J = 7.1 Hz, 3 H), 1.20 (s, 3 H), 1.16 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.65, 80.66, 60.28, 55.38, 37.57, 33.35, 25.10, 19.58, 18.22, 14.15; IR (CCl_4) 3560, 2970, 2875, 1720, 1535, 1465, 1380, 1290, 1250, 1133, 1080, 980, 930 cm^{-1}; FTIR ($CHCl_3$) 3588.0, 1716.9 cm^{-1}; calcd for $C_{10}H_{19}O_3$ (M + 1) 181.1264, found 181.1261.

Cyclization of Ethyl 2-(3-Iodopropyl)-2-methyl-3-oxopentanoate (4c). By using the general procedure described above, **4c** (0.245 g) was cyclized to provide **5c** (0.125 g), 83%, isolated by Kugelrohr distillation: bp 40–45 °C (0.05 mmHg); ^{1}H NMR ($CDCl_3$) δ 4.06 (q, J = 7.2 Hz, 3 H), 3.30 (br s, 1 H), 2.6–1.3 (m, 8 H), 1.70 (t, J = 7.1 Hz, 3 H), 1.05 (d, J = 0.7 Hz, 3 H), 0.84 (t, J = 7.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 177.68, 85.02, 60.45, 54.95, 36.34, 35.58, 28.46, 20.69, 19.38, 13.94, 8.39; IR (CCl_4) 3450, 2960, 2870, 1700, 1465, 1370, 1270, 1130, 1090, 1025 cm^{-1}; FTIR ($CHCl_3$) 3468.4, 1701.4 cm^{-1}; calcd for $C_{11}H_{20}O_3$ 200.1412, found 200.1412.

Cyclization of Ethyl 2,4-Dimethyl-2-(3-iodopropyl)-3-oxopentanoate (4d). By using the general procedure described above, **4d** (0.255 g) was cyclized to provide **5d** (0.140 g), 87%, isolated by Kugelrohr distillation: bp 45–50 °C (0.05 mmHg); ^{1}H NMR ($CDCl_3$) δ 4.69 (br s, 1 H), 4.07 (q, J = 7.1 Hz, 2 H), 2.5–1.3 (m, 7 H), 1.18 (t, J = 7.1 Hz, 3 H), 0.65 (d, J = 6.8 Hz, 3 H), 1.05 (s, 3 H), 0.84 (d, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.43, 87.99, 60.93, 53.05, 39.28, 37.39, 33.02, 19.91, 19.20, 17.93, 16.98, 13.77; IR (CCl_4) 3540, 3450, 2970, 2875, 1725, 1690, 1470, 1385, 1360, 1290, 1260, 1150, 1110, 1020, 930 cm^{-1}; FTIR ($CHCl_3$) 3437.6, 1686.0 cm^{-1}; calcd for $C_{12}H_{22}O_3$ 214.1569, found 214.1579.

Cyclization of Ethyl 2-(3-Iodopropyl)-3-oxo-2,4,4-trimethylpentanoate (4e). By using the general procedure described above, **4e** (0.266 g) was cyclized to provide **5e** (0.134 g), 83%, isolated by Kugelrohr distillation: bp 50–55 °C (0.05 mmHg); ^{1}H NMR ($CDCl_3$) δ 5.17 (br s, 1 H), 4.09 (q, J = 7.1 Hz, 2 H), 2.6–1.3 (m, 6 H), 1.21 (s, 3 H), 1.20 (t, J = 7.1 Hz, 3 H), 0.91 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 179.82, 90.71, 61.15, 54.44, 41.06, 38.46, 31.85, 27.76 (3), 22.04, 19.44, 13.78; IR (CCl_4) 3540, 3440, 2950, 2875, 1725, 1690, 1465, 1395, 1360, 1290, 1260, 1120, 1020, 925 cm^{-1}; FTIR ($CHCl_3$) 3433.7, 1687.9 cm^{-1}; calcd for $C_{13}H_{24}O_3$ 228.1725, found 228.1710.

Cyclization of Ethyl 2-(3-Iodopropyl)-3-oxo-3-phenylpentanoate (4f). By using the general procedure described above, **4f** (0.281 g) was cyclized to provide **5f** (0.073 g), 39%, isolated by Kugelrohr distillation: bp 100–110 °C (0.05 mmHg); ^{1}H NMR ($CDCl_3$) δ 7.6–7.1 (m, 5 H), 4.17 (q, J = 7.0 Hz, 2 H), 2.7–1.4 (m, 7 H), 1.21 (t, J = 7.0 Hz, 3 H), 0.96 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.75, 142.44, 127.54 (2), 126.92, 126.45 (2), 86.27, 60.95, 37.05, 36.88, 29.58, 21.56, 19.95, 13.93; IR (CCl_4) 3480, 2960, 2875, 1695, 1445, 1365, 1285, 1125, 1030 cm^{-1}; FTIR ($CHCl_3$) 3443.4, 1699.5 cm^{-1}; calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1429.

Cyclization of Ethyl 2-Acetyl-2-ethyl-5-iodopentanoate (4g). By using the general procedure described above, **4g** (0.245 g) was cyclized to provide a mixture of **5g** and **6g** (0.117 g), 78%, isolated by Kugelrohr distillation: bp 45–50 °C (0.05 mmHg); ^{1}H NMR ($CDCl_3$) (mixture) δ 4.08 (q, J = 7.0 Hz, 2 H), 2.50 (br s, 1 H), 2.4–1.4 (m, 8 H), 1.27 (s, 3 H), 1.18 (t, J = 7.0 Hz, 3 H), 0.74 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$), **5g** (major), δ 175.44, 82.66, 60.72, 60.18, 39.62, 30.30, 26.86, 22.96, 19.36, 14.11, 9.58; ^{13}C NMR ($CDCl_3$) **6g** (minor), δ 80.75, 37.48, 28.60, 25.62, 24.48, 17.92, 11.67, 9.31; IR (CCl_4) (mixture) 3500, 2965, 2875, 1710, 1465, 1370, 1235, 1130, 1035, 940, 910 cm^{-1}; FTIR ($CHCl_3$)

(mixture) 3609.3, 1716.9 cm^{-1}; calcd for $C_{11}H_{20}O_3$ 200.1412, found 200.1423.

Cyclization of Ethyl 2-Acetyl-5-iodo-2-isopropylpentanoate (4h). By using the general procedure described above, **4h** (0.255 g) was cyclized to provide a mixture of **5h** and **6h** (0.119 g), 74%, isolated by flash chromatography (15% EtOAc in hexane on silica gel). **5h** (major isomer): ^1H NMR ($CDCl_3$) δ 4.11 (q, J = 7.2 Hz, 2 H), 3.63 (br s, 1 H), 2.6–1.4 (m, 7 H), 1.27 (s, 3 H), 1.21 (t, J = 7.2 Hz, 3 H), 0.90 (d, J = 4.4 Hz, 3 H), 0.82 (d, J = 4.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.19, 82.23, 61.97, 60.32, 40.65, 31.71, 29.76, 23.04, 19.49, 19.03, 18.74, 14.11; IR (CCl_4) 3475, 2975, 2880, 1695, 1465, 1375, 1240, 1195, 1140, 1040, 920 cm^{-1}; FTIR ($CHCl_3$) 3609.3, 1716.9 cm^{-1}; calcd for $C_{12}H_{22}O_3$ 214.1569, found 214.1575.

Cyclization of Ethyl 2-Acetyl-5-iodo-2-phenylpentanoate (4i). By using the general procedure described above, **4i** (0.281 g) was cyclized to provide **5i** (0.155 g), 83%, isolated by flash chromatography (15% EtOAc in hexane on silica gel): ^1H NMR ($CDCl_3$) δ 7.4–7.2 (m, 5 H), 4.38 (br s, 1 H), 4.13 (dq, J = 7.2, 2.7 Hz, 2 H), 2.7–1.6 (m, 6 H), 1.14 (t, J = 7.1 Hz, 3 H), 1.04 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.95, 140.22, 128.00 (2), 127.00 (3), 82.61, 62.91, 60.86, 38.05, 32.60, 24.32, 19.30, 13.81; IR (CCl_4) 3525, 3060, 2975, 2870, 1710, 1450, 1370, 1300, 1240, 1190, 1105, 1050, 940 cm^{-1}; FTIR ($CHCl_3$) 3509.0, 1701.4 cm^{-1}; calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1403.

Cyclization of 3-Acetyl-3-(3-iodopropyl)oxacyclopentan-2-one. With the general procedure described above, the iodo ketone (0.222 g, 0.75 mmol) was cyclized to provide 0.128 g (0.75 mmol), 100%, of **(5*R**,6*S**)-6-hydroxy-6-methyl-2-oxaspiro[4.4]nonan-1-one** isolated by Kugelrohr distillation: bp 50–60 °C (0.005 mmHg). ^1H NMR ($CDCl_3$) δ 4.4–4.2 (m, 2 H), 3.67 (br s, 1 H), 2.4–2.3 (m, 2 H), 2.1–1.6 (m, 6 H), 1.26 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 181.63, 81.77, 65.43, 54.59, 38.54, 33.64, 31.97, 22.87, 20.21; IR (CCl_4) 3475, 2970, 1755, 1370, 1195, 1150, 1035 cm^{-1}; FTIR ($CHCl_3$) 3487.7, 1749.7; calcd for $C_9H_{14}O_3$ 170.0943, found 170.0942.

Hydrolysis of Ethyl 2-Hydroxycyclopentanecarboxylates. General Procedure. To a 1:1 mixture of MeOH/H_2O (2 mL) was added NaOH (0.4 g, 10 mmol). The substrate (1.0 mmol) was added neat and the reaction temperature brought to 50 °C for 1.5 h. The mixture was cooled and neutralized with 3 M HCl and extracted with a 1:1 mixture of $Et_2O/CHCl_3$ (10 × 3 mL). The organic extracts were dried over $MgSO_4$.

Hydrolysis of Ethyl (1*R,2*S**)-1,2-Dimethyl-2-hydroxycyclopentanecarboxylate (5b).** By using the general procedure described above, **5b** (0.186 g) was hydrolyzed to provide **(1*R**,2*S**)-1,2-dimethyl-2-hydroxycyclopentanecarboxylic acid** (0.125 g), 79%, isolated by flash chromatography (10% MeOH in CH_2Cl_2 on silica gel): ^1H NMR ($CDCl_3$) δ 7.72 (br s, 2 H), 2.6–1.4 (m, 6 H), 1.32 (s, 3 H), 1.16 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 182.21, 83.00, 55.35, 38.46, 35.30, 22.68, 21.50, 19.38; IR (CCl_4) 3610–2260, 1690, 1465, 1380, 1300, 1140, 1060, 940 cm^{-1}; MS (EI) 141 (M + 1, 3), 140 (M^+, 4), 120 (5), 112 (100), 97 (21), 82 (56), 69 (35).

Hydrolysis of Ethyl (1*R,2*R**)-1,2-Dimethyl-2-hydroxycyclopentanecarboxylate (6b).** By using the general procedure described above, **6b** (0.186 g) was hydrolyzed to provide **2-methyl-6-oxoheptanoic acid** (0.145 g), 92%, isolated by flash chromatography (10% MeOH in CH_2Cl_2 on silica gel): ^1H NMR ($CDCl_3$) δ 11.19 (br s, 1 H), 2.6–2.2 (m, 3 H), 2.13 (s, 3 H), 1.9–1.3 (m, 4 H), 1.14 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 203.82, 182.24, 43.21, 39.08, 32.64, 29.66, 21.15, 16.66; IR (CCl_4) 3450–2375, 1705, 1470, 1420, 1360, 1280, 1240, 1165, 1080, 940 cm^{-1}; FTIR ($CHCl_3$) 3688.4–2368.9, 1709.1 cm^{-1}; MS (EI) 158 (M^+, 4), 140 (13), 112 (68), 97 (50), 86 (37), 69 (100).

Lactonization of 2-Hydroxycyclopentanecarboxylic Acids. General Procedure. The 2-hydroxycyclopentanecarboxylic acid (1.0 mmol) was dissolved in dry pyridine (3.0 mL) and cooled to 0 °C. Benzenesulfonyl chloride (0.53 g, 3.0 mmol) was added and the reaction temperature maintained between 0 and −5 °C overnight. The mixture was poured over several volumes of ice and extracted with ether (3 × 5 mL). The organic extracts were washed with saturated aqueous $CuSO_4$ (2 × 3 mL), saturated aqueous $NaHCO_3$ (1 × 3 mL), and brine (1 × 3 mL) and dried over $MgSO_4$.

Lactonization of (1*R,2*S**)-1,2-Dimethyl-2-hydroxycyclopentanecarboxylic Acid.** By using the general procedure described above, (1*R**,2*S**)-1,2-dimethyl-2-hydroxycyclopentanecarboxylic acid (0.140 g) was lactonized to provide **(1*R**,4*S**)-*cis*-1,5-dimethyl-6-oxabicyclo[3.2.0]heptan-7-one** (0.100 g), 71%, isolated by flash chromatography (10% EtOAc in hexane on silica gel): ^1H NMR ($CDCl_3$) δ 2.2–1.2 (m, 6 H), 1.45 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.50, 89.67, 62.05, 36.57, 35.03, 21.89, 18.58, 13.62; IR (CCl_4) 2955, 1800, 1465, 1385, 1330, 1152, 1100, 1030, 850 cm^{-1}; FTIR ($CHCl_3$) 1813.3 cm^{-1}; calcd for $C_8H_{13}O_2$ (M + 1) 141.0916, found 141.0917.

Cyclization of 2-(4-Iodobutyl)-β-keto Amides with SmI_2. General Procedure. To samarium metal powder (0.30 g, 2.0 mmol), flamed and cooled under a slow flow of argon, was added THF (5 mL) followed by a solution of 1,2-diiodoethane (0.42 g, 1.5 mmol) in THF (10 mL). The mixture was stirred at ambient temperature for 1 h. The resulting solution was cooled to −78 °C in a dry ice–acetone bath, and the 2-(4-iodobutyl)-β-keto amide (0.75 mmol) was slowly added neat. The reaction was allowed to stir and warm to room temperature overnight before being separated between saturated aqueous K_2CO_3 (15 mL) and ether (15 mL). The aqueous layer was extracted with ether (3 × 5 mL). The organic extracts were washed with brine (5 mL) and dried over $K_2CO_3/MgSO_4$.

Cyclization of *N*,*N*-Diethyl-2-acetyl-6-iodohexanamide (1g). By using the general procedure described above, **1g** (0.254 g) was cyclized to provide **2g** (0.078 g), 49%, isolated by Kugelrohr distillation: bp 60–70 °C (0.01 mmHg); ^1H NMR ($CDCl_3$) δ 5.65 (br s, 1 H), 3.5–3.2 (m, 4 H), 2.35 (dd, J = 12.4, 3.1 Hz, 1 H), 2.0–1.3 (m, 8 H), 1.20 (t, J = 6.0 Hz, 6 H), 1.14 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.36, 69.20, 46.64, 42.38, 40.49, 38.81, 29.65, 26.26, 25.46, 21.18, 15.00, 13.08; IR (CCl_4) 3375, 2965, 2940, 2865, 1620, 1460, 1385, 1270, 1135 cm^{-1}; FTIR ($CHCl_3$) 3372.0, 1608.8 cm^{-1}; calcd for $C_{12}H_{23}NO_2$ 213.1729, found 213.1737.

Cyclization of *N*,*N*-Dimethyl-2-(iodobutyl)-4-methyl-3-oxopentanamide (1h). By using the general procedure described above, **1h** (0.245 g) was cyclized to provide **2h** (0.054 g), 34%, isolated by flash chromatography (50% EtOAc in hexane on silica gel): ^1H NMR ($CDCl_3$) δ 5.36 (d, J = 2.0 Hz, 1 H), 3.02 (s, 3 H), 2.89 (s, 3 H), 2.63 (dd, J = 12.0, 2.0 Hz, 1 H), 1.9–0.9 (m, 9 H), 0.88 (d, J = 6.0 Hz, 3 H), 0.76 (d, J = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.14, 74.01, 42.80, 37.16, 36.38, 35.21, 28.55, 25.87, 25.55, 20.63, 18.07, 16.54; IR (CCl_4) 3375, 2945, 2860, 1630, 1450, 1415, 1395, 985, 910 cm^{-1}; FTIR ($CHCl_3$) 3381.6, 1616.5 cm^{-1}; calcd for $C_{12}H_{23}NO_2$ 213.1729, found 213.1737.

Cyclization of *N*,*N*-Dimethyl-4,4-dimethyl-2-(4-iodobutyl)-3-oxopentanamide (1i). By using the general procedure described above, **1i** (0.265 g) was cyclized to provide **2i** (0.106 g), 62%, isolated by flash chromatography (45% EtOAc in hexane on silica gel). ^1H NMR ($CDCl_3$) δ 5.94 (d, J = 2.0 Hz, 1 H), 3.00 (s, 3 H), 2.81 (s, 3 H), 2.59 (dd, J = 12.0 Hz, J = 4.0 Hz, 1 H), 1.9–0.9 (m, 8 H), 0.78 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 178.58, 75.98, 39.46, 39.22, 37.16, 35.37, 31.54, 28.07, 26.43 (3), 25.23, 21.22; IR (CCl_4) 3350, 2940, 2865, 1625, 1450, 1400, 1155, 985 cm^{-1}; FTIR ($CHCl_3$) 3350.8, 1616.5 cm^{-1}; calcd for $C_{13}H_{25}NO_2$ 227.1885, found 227.1866.

General Procedure for Cyclization of Allylic Halides in β-Keto Ester and β-Keto Amide Series. To the samarium metal (0.33 g, 2.2 mmol, flamed and cooled under Ar) was added ICH_2CH_2I (0.56 g, 2.0 mmol) in THF (10 mL). The resultant solution was stirred at 25 °C for 2 h. The dark blue mixture was cooled to −78 °C with a dry ice–acetone bath, and a solution of the allylic halide (1 mmol) in THF (10 mL) was added and the reaction mixture allowed to warm to 25 °C. The mixture was decanted into saturated Na_2CO_3, extracted with EtOAc:ether (1:3, 3 × 30 mL), washed with saturated Na_2CO_3, dried over $MgSO_4$, and concentrated in vacuo.

Cyclization of *N*,*N*-Diethyl-2-acetyl-4-iodomethyl-4-pentenamide (7a). With the general procedure described above, **7a** (0.337 g, 1.0 mmol) was cyclized to provide **8a** (0.169 g, 0.80 mmol), 80%, as a clear colorless liquid isolated by flash chromatography (50% EtOAc in hexane): ^1H NMR ($CDCl_3$) δ 6.07 (d, J = 1.5 Hz, 1 H), 4.94 (br s, 2 H), 3.38 (m, J = 7.0 Hz, 4 H), 2.73–2.07 (m, 5 H), 1.29–1.07 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 174.41, 148.19, 107.55, 79.11, 47.91, 47.64, 42.22, 40.43, 36.05, 26.24, 14.97, 13.13; IR ($CHCl_3$) 3300, 2950, 1605, 1450, 1370, 1295, 1255, 1130, 890 cm^{-1}; calcd for $C_{12}H_{21}NO_2$ 211.1572, found 211.1562.

Cyclization of *N*,*N*-Dimethyl-2-(2-iodomethyl-2-propenyl)-3-oxopentanamide (7b). With the general procedure described above, **7b** (0.323 g, 1.0 mmol) was cyclized to provide **8b** (0.138 g, 0.70 mmol), 70%, as a clear colorless liquid isolated by flash chromatography (50% EtOAc in hexane): ^1H NMR ($CDCl_3$) δ 5.82 (s, 1 H), 4.94 (br s, 2 H), 3.08 (s, 3 H), 2.97 (s, 3 H), 2.80–2.05 (m, 5 H), 1.80–1.20 (q, J = 7.3 Hz, 2 H), 0.94 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.33, 147.86, 107.45, 81.88, 46.39, 44.77, 37.18, 35.23, 32.63, 8.91; IR ($CHCl_3$) 3300, 2950, 1610, 1405, 1320, 1250, 1140, 880 cm^{-1}; calcd for $C_{11}H_{19}NO_2$ 197.1416, found 197.1428.

Cyclization of *N*,*N*-Dimethyl-2-(2-iodomethyl-2-propenyl)-3-oxononanamide (7c). With the general procedure described above, **7c** (0.379 g, 1.0 mmol) was cyclized to provide **8c** (0.141 g, 0.56 mmol), 56%, as a clear colorless liquid isolated by flash chromatography (50% EtOAc in hexane): ^1H NMR ($CDCl_3$) δ 5.76 (s, 1 H), 4.89 (br s, 2 H), 3.03 (s, 3 H), 2.94 (s, 3 H), 2.75–2.05 (m, 5 H), 1.7–1.1 (m, 10 H), 0.9–0.7 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.41, 148.00, 107.45, 81.63, 46.91, 45.28, 40.24, 37.24, 35.29, 35.12, 31.79, 29.84, 22.58, 14.05; IR

($CHCl_3$) 3420, 2920, 1615, 1495, 1415, 1325, 1265, 1140, 1065, 980 cm^{-1}; calcd for $C_{15}H_{27}NO_2$ 253.2042, found 253.2051.

Cyclization of *N,N*-Dimethyl-2-(2-bromomethyl-2-propenyl)-3-oxo-4-methylpentanamide (7d). With the general procedure described above, **7d** (0.290 g, 1.0 mmol) was cyclized to provide **8d** (0.104 g, 0.49 mmol), 49%, as a clear colorless liquid isolated by flash chromatography (50% EtOAc in hexane): ^1H NMR ($CDCl_3$) δ 6.06 (s, 1 H), 4.94 (br s, 2 H), 3.09 (s, 3 H), 2.97 (s, 3 H), 3.02–2.10 (m, 6 H), 0.91 (d, J = 6.7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 175.98, 147.86, 107.34, 84.58, 44.06, 43.03, 37.02, 36.43, 35.83, 18.28, 17.84; IR ($CHCl_3$) 3320, 2900, 1620, 1485, 1330, 1215, 1010, 930, 890 cm^{-1}; calcd for $C_{12}H_{21}NO_2$ 211.1572, found 211.1581.

Cyclization of *N,N*-Dimethyl-2-(2-bromomethyl-2-propenyl)-3-oxo-4,4-dimethylpentanamide (7e). With the general procedure described above, **7e** (0.304 g, 1.0 mmol) was cyclized to provide **8e** (0.0968 g, 0.43 mmol), 43%, as a clear colorless liquid isolated by flash chromatography (50% EtOAc in hexane). ^1H NMR ($CDCl_3$) δ 6.33 (s, 1 H), 4.82 (br s, 2 H), 3.05 (s, 3 H), 3.01–2.35 (m, 5 H), 2.88 (s, 3 H), 0.84 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 176.79, 147.91, 106.85, 87.02, 42.49, 40.49, 37.40, 37.13, 36.75, 35.40, 26.62, 26.13; IR ($CHCl_3$) 3305, 3000, 1620, 1480, 1420, 1345, 1210, 1165, 1010, 935, 820 cm^{-1}; calcd for $C_{13}H_{23}NO_2$ 225.1729, found 255.1743.

Cyclization of *N,N*-Diethyl-2-acetyl-4-iodomethyl-2-methyl-4-pentenamide (7f). With the general procedure described above, **7f** (0.351 g, 1.0 mmol) was cyclized to provide **8f** (0.205 g, 0.91 mmol), 91%, as a clear colorless liquid isolated by flash chromatography (50% EtOAc in hexane): ^1H NMR ($CDCl_3$) δ 4.95 (br s, 2 H), 3.55–3.10 (m, 4 H), 3.00–2.35 (m, 5 H), 1.46 (s, 3 H), 1.20 (s, 3 H), 0.95 (t, J = 6.5 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 176.55, 147.38, 107.55, 83.68, 54.15, 44.37, 42.69, 41.53, 23.20, 21.49, 14.00; IR ($CHCl_3$) 3450, 3000, 1605, 1470, 1390, 1370, 1120, 1090, 895 cm^{-1}; calcd for $C_{13}H_{23}NO_2$ 225.1729, found 225.1725.

Cyclization of (*E*)-*N,N*-Diethyl-2-acetyl-7-iodo-5-heptenamide. With the general procedure described above, the iodo keto amide (0.351 g, 1.0 mmol) was cyclized to provide **(1*R*,2S*,3S**)-*N,N*-diethyl-2-methyl-2-hydroxy-3-ethenylcyclopentanecarboxamide** (0.167 g, 0.74 mmol), 74%, isolated as a clear colorless liquid by flash chromatography (40% EtOAc in hexane on silica gel): ^1H NMR ($CDCl_3$) δ 5.68–5.49 (m, 1 H), 5.02 (m, 1 H), 4.86 (m, 1 H), 3.29 (q, J = 7.0 Hz, 4 H), 2.72–2.49 (m, 4 H), 2.31–1.85 (m, 3 H), 1.15 (q, J = 7.0 Hz, 6 H), 1.11 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.33, 139.49, 114.68, 81.71, 54.71, 47.45, 42.14, 40.35, 28.30, 27.67, 23.86, 14.76, 13.02; IR (neat) 3320, 2980, 1610, 1455, 1375, 1260, 1220, 1145, 1090, 995, 915, 875 cm^{-1}; calcd for $C_{13}H_{23}NO_2$ 225.1735, found 225.1729.

Cyclization of (*E*)-*N,N*-Diethyl-2-acetyl-8-bromo-6-octenamide. With the general procedure described above, the bromo keto amide (0.318 g, 1.0 mmol) was cyclized to provide a mixture of two diastereomers (1:1, 0.103 g, 0.43 mmol), 43%, isolated as a clear colorless liquid by flash chromatography (40% EtOAc in hexane on silica gel). **(1*R*,2S*,3S**)-*N,N*-Diethyl-2-methyl-2-hydroxy-3-ethenylcyclohexanecarboxamide**: ^1H NMR ($CDCl_3$) δ 6.1–5.8 (m, 1 H), 5.52 (s, 1 H), 5.03–4.94 (m, 2 H), 3.32 (m, 4 H), 2.29–1.43 (m, 8 H), 1.19 (m, 6 H), 1.10 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.27, 139.77, 115.24, 70.52, 52.44, 47.21, 42.41, 40.53, 28.14, 27.08, 26.20, 25.21, 14.98, 13.04; IR ($CHCl_3$) 3340, 2970, 1605, 1450, 1220, 1000, 910 cm^{-1}; calcd for $C_{14}H_{25}NO_2$ 239.1881 found 239.1885.

(1*R*,2S*,3R)-*N,N*-Diethyl-2-methyl-2-hydroxy-3-ethenylcyclohexanecarboxamide**: ^1H NMR ($CDCl_3$) δ 6.1–5.8 (m, 1 H), 5.59 (s, 1 H), 5.27–5.03 (m, 2 H), 3.35 (m, 4 H), 2.49 (m, 1 H), 2.35–1.15 (m, 7 H), 1.18 (m, 6 H), 1.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.11, 137.83, 116.72, 70.98, 49.54, 42.80, 42.44, 40.53, 27.48, 26.72, 26.16, 20.15, 14.92, 12.98; IR (neat) 3290, 2910, 1600, 1450, 1250, 1135, 1075, 1030, 980, 840 cm^{-1}; calcd for $C_{14}H_{25}NO_2$ 239.1881, found 239.1885.

Cyclization of Methyl 2-Acetyl-2-methyl-4-iodomethyl-4-pentenoate (14a). With the general procedure described above, **14a** (0.310 g, 1.0 mmol) was cyclized to provide a 6:1 mixture of **15a** and **16a** (0.167 g, 0.91 mmol), 91%, as a clear, colorless liquid by flash chromatography (20% EtOAc in hexane on silica gel). **15a**: ^1H NMR ($CDCl_3$) δ 4.94 (br s, 2 H), 3.73 (m, 3 H), 3.18 (m, 2 H), 2.51–2.15 (m, 3 H), 1.41 (s, 3 H), 1.20 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.63, 146.13, 108.04, 81.39, 55.01, 51.70, 45.47, 42.60, 22.45, 21.36; IR ($CHCl_3$) 3490, 2970, 1715, 1450, 1380, 1305, 1255, 1085, 880 cm^{-1}; calcd for $C_{10}H_{16}O_3$ 184.1099, found 184.1108.

Cyclization of Ethyl 2-Acetyl-2-methyl-4-iodomethyl-4-pentenoate (14b). With the general procedure described above, **14b** (0.324 g, 1.0 mmol) was cyclized to provide a 6.2:1 mixture of **15b** and **16b** (0.166 g, 0.84 mmol), 84%, as a clear colorless liquid by flash chromatography (20% EtOAc in hexane on silica gel). **15b** (major): ^1H NMR ($CDCl_3$) δ 4.94 (m, 2 H), 4.18 (q, J = 7.1 Hz, 2 H), 3.25–3.08 (m, 2 H), 2.50–2.05 (m, 3 H), 1.41 (s, 3 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.21 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.45, 146.28, 108.15, 81.44, 60.69, 54.91, 45.61, 42.80, 22.64, 21.54, 14.31; IR ($CHCl_3$) 3540, 2970, 2870, 1710, 1450, 1385, 1305, 1110, 1015, 890, 870 cm^{-1}; FTIR ($CHCl_3$) 3538.9, 1710.1 cm^{-1}; calcd for $C_{11}H_{18}O_3$ 198.1256, found 198.1252. **16b** (minor): ^1H NMR ($CDCl_3$) δ 4.85 (br s, 2 H), 4.14 (q, J = 7.0 Hz, 2 H), 3.05–2.05 (m, 5 H), 1.25 (s, 3 H), 1.25 (m, 3 H), 1.20 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.09, 145.31, 108.23, 79.46, 60.45, 55.33, 45.61, 41.63, 25.13, 19.58, 14.19; IR (neat) 3500, 2990, 1720, 1660, 1460, 1385, 1305, 1270, 1230, 1140, 1090, 975, 935, 980 cm^{-1}; FTIR ($CHCl_3$) 3582.3, 1713.0 cm^{-1}; calcd for $C_{11}H_{18}O_3$ 198.1256, found 198.1267.

Cyclization of *tert*-Butyl 2-Acetyl-2-methyl-4-iodomethyl-4-pentenoate (14c). With the procedure described above, **14c** (0.352 g, 1.0 mmol) was cyclized to provide a 1.8:1 mixture of **15c** and **16c** (0.171 g, 0.76 mmol), 76%, as a clear colorless liquid isolated by flash chromatography (20% EtOAc in hexane on silica gel). **15c** (major): ^1H NMR ($CDCl_3$) δ 4.94 (br s, 2 H), 3.34–2.98 (m, 2 H), 2.48–2.03 (m, 3 H), 1.47 (s, 9 H), 1.38 (s, 3 H), 1.17 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.76, 146.45, 107.77, 81.23, 80.90, 55.22, 45.69, 42.87, 27.92, 22.61, 21.53; IR ($CHCl_3$) 3500, 2975, 1705, 1455, 1370, 1310, 1250, 1145, 1085, 890 cm^{-1}; calcd for $C_{13}H_{23}O_3$ (M + 1) 227.1647, found 227.1646. **16c** (minor): ^1H NMR ($CDCl_3$) δ 4.94 (br s, 2 H), 3.05–2.10 (m, 5 H), 1.48 (br s, 12 H), 1.26 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.32, 144.84, 108.47, 80.98, 79.03, 55.29, 44.83, 40.98, 28.01, 25.18, 19.94; IR ($CHCl_3$) 3570, 2970, 1705, 1455, 1365, 1290, 1135, 1080, 965, 885, 840 cm^{-1}; calcd for $C_{13}H_{21}O_3$ (M - 1) 225.1491, found 225.1481.

Cyclization of Ethyl 2-(2-Iodomethyl-2-propenyl)-2-methyl-3-oxopentanoate (14d). With the procedure described above, **14d** (0.338 g, 1.0 mmol) was cyclized to provide a 15.7:1 mixture of **15d** and **16d** (0.155 g, 0.73 mmol), 73%, as a clear, colorless liquid isolated by flash chromatography (20% EtOAc in hexane on silica gel). **15d**: ^1H NMR ($CDCl_3$) δ 4.89 (br s, 2 H), 4.13 (q, J = 7.2 Hz, 2 H), 3.35–2.15 (m, 5 H), 1.67 (m, J = 7.3 Hz, 2 H), 1.23 (t, J = 7.3 Hz, 3 H), 1.14 (d, J = 0.5 Hz, 3 H), 0.91 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.82, 146.53, 108.10, 84.12, 60.69, 54.60, 43.77, 42.97, 28.22, 20.82, 14.03, 8.31; IR ($CHCl_3$) 3470, 3000, 1715, 1490, 1410, 1390, 1325, 1260, 1230, 1170, 1150, 1080, 1040, 900 cm^{-1}; calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1425.

Cyclization of Ethyl 2-(2-Iodomethyl-2-propenyl)-3-oxo-2,4-dimethylpentanoate (14e). With the procedure described above, **14e** (0.352 g, 1.0 mmol) was cyclized to provide a 41.2:1 mixture of **15e** and **16e** (0.167 g, 0.74 mmol), 74%, as a clear, colorless liquid isolated by flash chromatography (20% EtOAc in hexane on silica gel). **15e**: ^1H NMR ($CDCl_3$) δ 4.87 (br s, 2 H), 4.14 (q, J = 7.2 Hz, 2 H), 3.15–2.10 (m, 5 H), 1.80 (m, J = 6.8 Hz, 1 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.13 (d, J = 0.8 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H), 0.74 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.66, 147.07, 107.96, 86.94, 61.21, 52.27, 46.74, 44.61, 32.99, 19.25, 17.79, 16.81, 13.84; IR (neat) 3450, 2975, 1695, 1475, 1390, 1370, 1300, 1275, 1215, 1150, 1120, 1025, 980 cm^{-1}; calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1575.

Cyclization of Ethyl 2-(2-Iodomethyl-2-propenyl)-3-oxo-2,4,4-trimethylpentanoate (14f). With the procedure described above, **14f** (0.366 g, 1.0 mmol) was cyclized to provide **15f** (0.151 g, 0.63 mmol), 63%, as a clear, colorless liquid isolated by flash chromatography (20% EtOAc in hexane on silica gel): ^1H NMR ($CDCl_3$) δ 5.24 (q, J = 0.7 Hz, 1 H), 4.90 (br s, 2 H), 4.16 (q, J = 7.0 Hz, 2 H), 3.31–2.05 (m, 4 H), 1.27 (t, J = 7.0 Hz, 3 H), 1.26 (s, 3 H), 0.97 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 178.98, 147.13, 107.99, 89.49, 61.43, 53.95, 48.50, 39.59, 38.67, 27.67, 22.04, 13.86; IR (neat) 3450, 2975, 1700, 1480, 1405, 1375, 1305, 1280, 1200, 1125, 1190, 1035, 990, 885 cm^{-1}; calcd for $C_{14}H_{24}O_3$ 240.1725, found 240.1727.

Cyclization of Ethyl 2-Acetyl-2-ethyl-4-iodomethyl-4-pentenoate (14g). With the general procedure described above, **14g** (0.338 g, 1.0 mmol) was cyclized to provide a 2.1:1 mixture of **15g** and **16g** (0.165 g, 0.78 mmol), 78%, as a clear, colorless liquid isolated by flash chromatography (20% EtOAc in hexane on silica gel). **15g** (major): ^1H NMR ($CDCl_3$) δ 4.88 (br s, 2 H), 4.15 (q, J = 7.2 Hz, 2 H), 3.25–1.65 (m, 7 H), 1.38 (s, 3 H), 1.33 (t, J = 7.0 Hz, 3 H), 0.81 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.81, 146.29, 107.74, 81.90, 60.45, 46.85, 37.97, 26.56, 22.58, 14.19, 9.61; IR (neat) 3480, 2975, 1710, 1460, 1370, 1325, 1245, 1135, 1035, 955, 880 cm^{-1}; calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1449.

Cyclization of Ethyl 2-Acetyl-4-iodomethyl-2-isopropyl-4-pentenoate (14h). With the procedure described above, **14h** (0.352 g, 1.0 mmol) was cyclized to provide a 1:1 mixture of **15h** and **16h** (0.174 g, 0.77 mmol), 77%, as a clear, colorless liquid by flash chromatography (15% EtOAc in hexane on silica gel). **15h** (major): ^1H NMR ($CDCl_3$) δ 4.83 (br s, 2 H), 4.15 (q, J = 7.0 Hz, 2 H), 3.59–2.00 (br m, 5 H), 1.36 (s, 3 H), 1.21 (m, 4 H), 0.94 (m, 6 H); ^{13}C NMR ($CDCl_3$) 175.71, 175.49, 146.26, 146.13, 107.20, 106.93, 81.50, 80.25, 62.62, 60.59, 48.59, 47.48, 37.43, 35.02, 31.68, 31.47, 28.27, 19.87, 19.28, 19.06, 18.87, 14.13; IR (neat) 3475, 2975, 1715, 1450, 1375, 1250, 1040, 960, 880 cm^{-1}; calcd for

$C_{13}H_{22}O_3$ 226.1569, found 226.1563.

Cyclization of Ethyl 2-Acetyl-4-iodomethyl-2-phenyl-4-pentenoate (14i). With the general procedure described above, **14i** (0.386 g, 1.0 mmol) was cyclized to provide **15i** (0.176 g, 0.68 mmol), 68%, as a clear, colorless liquid isolated by flash chromatography (10% EtOAc in hexane on silica gel): ^{1}H NMR ($CDCl_3$) δ 7.33 (br m, 5 H), 5.09 (m, 1 H), 5.00 (m, 1 H), 4.16 (q, J = 7.0 Hz, 2 H), 3.50–2.95 (m, 3 H), 2.51 (br s, 2 H), 1.16 (t, J = 7.0 Hz, 3 H), 1.11 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.19, 145.99, 139.82, 128.82, 127.19, 126.89, 107.85, 81.88, 62.94, 61.07, 45.55, 40.76, 24.04, 13.84; IR (neat) 3350, 2900, 1710, 1610, 1510, 1460, 1440, 1380, 1315, 1250, 1160, 1090, 1075, 970, 935, 895, 875, 765, 715 cm^{-1}; calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1410.

***Cyclization of Ethyl 2-Acetyl-5-iodomethyl-2-methyl-5-pentenoate* (14j).** With the general procedure described above, **14j** (0.338 g, 1.0 mmol) was cyclized to provide **15j** and **16j** (0.155 g, 0.73 mmol), 73%, isolated as a clear colorless liquid by flash chromatography (40% EtOAc in hexane on silica gel): ^{1}H NMR ($CDCl_3$) δ 4.67 (m, 2 H), 4.46 (s, 1 H), 4.16 (q, J = 7.2 Hz, 2 H), 2.30–1.65 (m, 6 H), 1.33–1.11 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 178.47, 177.55, 145.36, 145.13, 110.34, 109.91, 73.91, 73.15, 60.89, 60.69, 49.74, 49.61, 44.09, 33.56, 32.05, 31.03, 30.05, 29.65, 24.85, 23.17, 19.79, 18.41, 14.06; IR (neat) 3500, 2950, 1705, 1460, 1380, 1270, 1220, 1180, 1105, 1020, 960, 890, 780 cm^{-1}; calcd for $C_{12}H_{20}O_3$ 212.1411, found 212.1412.

Cyclization of Ethyl-2-acetyl-2-methyl-6-iodomethyl-6-hexenoate (14k). With the general procedure described above, **14k** (0.351 g, 1.0 mmol) was cyclized to provide a (1:1) mixture of **15k** and **16k** (0.145 g, 0.64 mmol), 64%, isolated as a clear colorless liquid by flash chromatography (10% EtOAc in hexane on silica gel): ^{1}H NMR ($CDCl_3$) δ 4.80 (s, 1 H), 4.75 (s, 1 H), 4.14 (q, J = 7.0 Hz, 2 H), 2.7–1.9 (m, 5 H), 1.8–1.4 (m, 4 H), 1.24 (s, 3 H), 1.22 (s, 3 H), 1.12 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.52, 146.37, 145.45, 115.41, 113.73, 74.54, 73.02, 60.69, 60.59, 53.65, 53.22, 47.85, 45.23, 34.50, 33.77, 26.02, 25.10, 23.23, 20.42, 19.66, 14.08; IR (neat) 3490, 2980, 2940, 1695, 1625, 1455, 1370, 1295, 1250, 1175, 1090, 1020, 940, 890 cm^{-1}; calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1562.

Saponification of Ethyl (1*R,2*S**)-1,2-Dimethyl-2-hydroxy-4-methylenecyclopentanecarboxylate (15b).** To a 25-mL flask was added MeOH (10 mL), 1 M NaOH (1.0 mL), and **15b** (0.099 g, 0.50 mmol). The solution was stirred for 12 h at 25 °C and then made acidic (pH 3) by addition of 1 M HCl, extracted into $CHCl_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (10% MeOH in CH_2Cl_2 on silica gel) to provide **(1*R**,2*S**)-1,2-dimethyl-2-hydroxy-4-methylenecyclopentanecarboxylic acid** (0.058 g, 0.34 mmol), 68%, as a clear, colorless liquid: ^{1}H NMR ($CDCl_3$) δ 6.9 (br s, 1 H), 4.91 (br s, 2 H), 3.3–2.1 (m, 5 H), 1.40 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 180.82, 145.76, 108.22, 81.82, 54.88, 45.50, 42.50, 22.27, 21.27; IR (neat) 3450, 2980, 1715, 1460, 1380, 1250, 1090, 935, 885 cm^{-1}; calcd for $C_9H_{14}O_3$ 170.0943, found 170.0957.

Saponification of Ethyl (1*R,2*R**)-1,2-Dimethyl-2-hydroxy-4-methylenecyclopentanecarboxylate (16b).** With the procedure described above, **16b** (0.099 g, 0.50 mmol) was hydrolyzed to provide **(1*R**,2*R**)-1,2-dimethyl-2-hydroxy-4-methylenecyclopentanecarboxylic acid** (0.076 g, 0.45 mmol), 89%, as a clear, colorless liquid isolated by flash chromatography (10% MeOH in CH_2Cl_2 on silica gel): ^{1}H NMR ($CDCl_3$) δ 8.0 (br s, 1 H), 4.95 (br s, 2 H), 3.1–1.5 (m, 5 H), 1.41 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR ($CDCl_3$) 181.42, 145.84, 108.77, 81.79, 53.95, 45.75, 42.61, 22.44, 21.47; IR (neat) 3490, 2950, 1730, 1460, 1320, 1190, 890 cm^{-1}; MS 170 (M^+), 152, 109, 95, 82, 67, 55, 43.

Lactonization of (1*R,2*S**)-1,2-Dimethyl-2-hydroxy-4-methylenecyclopentanecarboxylic Acid.** With the method described by Adam,[17] the hydroxy acid (0.058 g, 0.34 mmol) was lactonized to provide **(1*R**,2*S**)-1,5-dimethyl-3-methylene-6-oxabicyclo[3.2.0]heptan-7-one** (0.038 g, 0.25 mmol), 73%, as a white solid isolated by flash chromatography (10% EtOAc in hexane on silica gel): mp 42–43 °C; ^{1}H NMR ($CDCl_3$) δ 4.95 (br s, 2 H), 2.8–1.9 (m, 4 H), 1.54 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.66, 143.69, 111.10, 88.26, 62.48, 43.73, 42.53, 18.66, 13.81; IR ($CHCl_3$) 2940, 1810, 1450, 1380, 1320, 1255, 1150, 1120, 1090, 915, 825 cm^{-1}; calcd for $C_9H_{12}O_2$ 152.0837, found 152.0835.

Lactonization of (1*R,2*S**,3*S**)-1,2-Dimethyl-2-hydroxy-3-ethenylcyclopentanecarboxylic Acid.** With the two-step procedure described above, the hydroxy ester (0.092 g, 0.50 mmol) was hydrolyzed and lactonized[17] to provide **(1*R**,4*S**,5*S**)-1,5-dimethyl-4-ethenyl-6-oxabicyclo[3.2.0]heptan-7-one** (0.053 g, 0.32 mmol), 63%, isolated as a clear colorless liquid by flash chromatography (25% EtOAc in hexane on silica gel): ^{1}H NMR ($CDCl_3$) δ 5.66–4.99 (m, 3 H), 2.90 (m, 1 H), 2.19–1.65 (m, 4 H), 1.42 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.44, 135.43, 117.15, 91.19, 62.54, 51.48, 33.52, 28.23, 17.36, 14.14; IR (neat) 2850, 1810, 1455, 1385, 1330, 1295, 1210, 1155, 1040, 925, 830 cm^{-1}; calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0999.

Cyclization of 3-Acetyl-3-(2-iodomethyl-2-propenyl)oxacyclopentan-2-one (17). With the procedure described above, **17** (0.308 g, 1.0 mmol) was cyclized to provide a 6.2:1 mixture of **18** and **19** (0.171 g, 0.94 mmol), 94%, isolated by flash chromatography (40% EtOAc in hexane on silica gel). **18** (major): ^{1}H NMR ($CDCl_3$) δ 5.00 (br s, 2 H), 4.3 (m, 2 H), 3.76 (d, J = 1 Hz, 1 H), 3.1–2.7 (m, 2 H), 2.40 (m, 2 H), 2.0 (m, 2 H), 1.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 180.70, 145.05, 109.22, 80.56, 65.42, 54.24, 45.85, 40.85, 31.68, 22.72; IR ($CHCl_3$) 3490, 2900, 1725, 1450, 1360, 1275, 1135, 1060, 1020, 885 cm^{-1}; FTIR ($CHCl_3$) 3489.7, 1725.5 cm^{-1}; calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0938. **19** (minor): ^{1}H NMR ($CDCl_3$) δ 4.98 (br s, 2 H), 4.28 (m, 2 H), 2.81–1.99 (m, 7 H), 1.36 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.63, 145.32, 108.90, 80.69, 65.77, 56.09, 47.21, 41.68, 30.37, 22.48; IR ($CHCl_3$) 3590, 2950, 1760, 1380, 1260, 1200, 1080, 1040, 880 cm^{-1}; FTIR ($CHCl_3$) 3590.0, 1762.2 cm^{-1}; calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0958.

Cyclization of (*E*)-8-Bromo-4-methyl-6-octen-3-one. With the procedure described above, the bromo ketone (0.219 g, 1.0 mmol) was cyclized to provide a 1:1 mixture of diastereomers (0.127 g, 0.91 mmol), 91%, as a clear colorless liquid isolated by flash chromatography (10% EtOAc in hexane on silica gel). **(1*R**,2*S**)-1-Ethyl-2-methyl-4-cyclohexen-1-ol**: ^{1}H NMR ($CDCl_3$) δ 6.1–5.7 (m, 2 H), 2.8–2.6 (m, 1 H), 2.2–2.0 (m, 2 H), 1.7–0.8 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 137.14, 116.76, 79.30, 45.58, 36.48, 34.53, 28.44, 14.03, 7.59; IR ($CHCl_3$) 3570, 2920, 1700, 1630, 1460, 1380, 1260, 1110, 1000, 920 cm^{-1}. **(1*R**,2*R**)-1-Ethyl-2-methyl-4-cyclohexen-1-ol**: ^{1}H NMR ($CDCl_3$) δ 6.2–5.8 (m, 1 H), 5.35–5.0 (m, 1 H), 2.9–2.7 (m, 1 H), 2.4–0.8 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 137.73, 116.76, 77.65, 45.58, 40.79, 27.62, 26.61, 14.45, 6.83; IR ($CHCl_3$) 3490, 2980, 1710, 1620, 1455, 1385, 1275, 1190, 1095, 1005, 915 cm^{-1}.

Cyclization of Ethyl (*E*)-2-Methyl-2-acetyl-7-iodo-5-heptenoate. With the general procedure described above, the iodo keto ester (0.338 g, 1.0 mmol) was cyclized to provide **ethyl (1*R**,2*S**,3*S**)-1,2-dimethyl-2-hydroxy-3-ethenylcyclopentanecarboxylate** (0.193 g, 0.91 mmol), 91%, isolated as a clear colorless liquid by flash chromatography (40% EtOAc in hexane on silica gel): ^{1}H NMR ($CDCl_3$) δ 5.97–5.58 (m, 1 H), 5.07 (s, 1 H), 4.94 (m, 1 H), 4.13 (q, J = 7.2 Hz, 2 H), 3.61 (br s, 1 H), 2.75–1.20 (m, 5 H), 1.31 (t, J = 7.2 Hz, 3 H), 1.23 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.04, 138.82, 115.73, 82.59, 60.79, 55.00, 53.13, 33.00, 25.38, 19.65, 19.39, 14.06; IR (neat) 3460, 2970, 1705, 1635, 1465, 1375, 1270, 1190, 1140, 1090, 1020, 910, 860 cm^{-1}; calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1428.

Cyclization of Ethyl (*E*)-2-Methyl-2-acetyl-8-bromo-6-octenoate. With the general procedure described above, the bromo keto ester (0.352 g, 1.0 mmol) was cyclized to provide **ethyl 1,2-dimethyl-2-hydroxy-3-ethenylcyclohexanecarboxylate** (0.131 g, 0.58 mmol), 58%, isolated as a clear colorless liquid by flash chromatography (40% EtOAc in hexane on silica gel): ^{1}H NMR ($CDCl_3$) δ 5.9 (m, 1 H), 5.27 (s, 1 H), 5.01 (s, 1 H), 4.94 (m, 1 H), 4.28 (d, J = 1.6 Hz, 1 H), 4.14 (q, 2 H), 2.14 (m, 2 H), 1.58–1.39 (m, 4 H), 1.24 (t, J = 7.0 Hz, 3 H), 1.24 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR ($CDCl_3$) 178.83, 140.00, 115.32, 73.07, 60.85, 49.81, 47.27, 32.26, 27.83, 24.48, 20.04, 18.23, 14.08; IR (neat) 3450, 2920, 1700, 1450, 1380, 1365, 1260, 1220, 1180, 1120, 1075, 1015, 905 cm^{-1}; calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1573.

Acknowledgment. We thank the National Institutes of Health for their generous support of our programs and Curt Haltiwanger for performing the single-crystal X-ray structure determinations.

Registry No. 1a, 105664-94-6; **1b**, 105664-95-7; **1c**, 105664-96-8; **1d**, 105664-97-9; **1e**, 105664-98-0; **1f**, 105664-99-1; **1g**, 105665-00-7; **1h**, 105665-01-8; **1i**, 105665-02-9; **2a**, 105665-03-0; **2b**, 105665-05-2; **2c**, 105665-06-3; **2d**, 105665-07-4; **2e**, 105665-08-5; **2f**, 105665-09-6; **2g**, 105665-10-9; **2h**, 105665-11-0; **2h** (uncyclized iodo alcohol), 105665-13-2; **2i**, 105665-12-1; **2i** (uncyclized unsaturated alcohol), 105694-13-1; **3a**, 105665-04-1; **4a**, 105665-26-7; **4b**, 105665-27-8; **4c**, 105665-28-9; **4d**, 105665-29-0; **4e**, 105665-30-3; **4f**, 105694-15-3; **4g**, 105665-31-4; **4h**, 105665-32-5; **4i**, 105665-33-6; **5a**, 22886-57-3; **5b**, 105665-34-7; **5c**, 105665-36-9; **5d**, 105665-37-0; **5e**, 105665-38-1; **5f**, 105665-39-2; **5g**, 105665-40-5; **5h**, 105665-42-7; **5i**, 105665-44-9; **6a**, 22886-56-2; **6b**, 105665-35-8; **6g**, 105665-41-6; **6h**, 105665-43-8; **7a**, 105665-14-3; **7b**, 105665-15-4; **7c**, 105665-16-5; **7d**, 105694-14-2; **7e**, 105665-17-6; **7f**, 105665-18-7; **8a**, 105665-19-8; **8b**, 105665-20-1; **8c**, 105665-21-2; **8d**, 105665-22-3; **8e**, 105665-23-4; **8f**, 105665-24-5; **8f** (trans isomer), 105665-25-6; **14a**, 105665-50-7; **14b**, 105665-51-8; **14c**, 105665-52-9; **14d**, 105665-53-0; **14e**, 105665-54-1; **14f**, 105665-55-2; **14g**, 105665-56-3; **14h**, 105665-57-4; **14i**, 105665-58-5; **14j**, 105665-59-6; **14k**, 105665-60-9; **15a**, 105665-61-0; **15b**, 105665-63-2; **15c**, 105665-65-4; **15d**, 105665-67-6; **15e**, 105665-69-8; **15f**, 105665-70-1; **15g**, 105665-71-2; **15h**, 105665-73-4; **15i**, 105665-75-6; **15j**, 105665-76-7; **15k**, 105665-78-9; **16a**, 105665-62-1; **16b**, 105665-64-3; **16c**, 105665-66-5;

16d, 105665-68-7; **16g**, 105665-72-3; **16h**, 105665-74-5; **16j**, 105665-77-8; **16k**, 105665-79-0; **17**, 105665-89-2; **18**, 105665-90-5; **18** (demethylene), 105666-08-8; **19**, 105665-91-6; **20**, 105665-84-7; **21**, 105761-20-4; 3-acetyl-3-(3-iodopropyl)tetrahydro-2-furanone, 105666-07-7; (1*R**,2*R**)-1-isopropyl-5-methyl-6-oxabicyclo[3.2.0]heptan-7-one, 105666-00-0; ethyl 2-isopropyl-6-oxoheptanoate, 105666-01-1; 7-bromo-4-methyl-3-oxooctane, 105666-02-2; 2-ethyl-1,3-dimethyl-2-cyclopentanol, 105666-03-3; ethyl 2-acetyl-6-iodo-2-methylhexanoate, 105666-04-4; (*R**,*R**)-ethyl 6-iodo-2-(1-hydroxyethyl)-2-methylhexanoate, 105666-05-5; (*R**,*S**)-ethyl 6-iodo-2-(1-hydroxyethyl)-2-methylhexanoate, 105666-06-6; ethyl 2-methyl-2-(*trans*-4-bromo-2-butenyl)-3-oxobutanoate, 105665-94-9; ethyl 2-methyl-3-oxobutanoate, 609-14-3; (1*R**,2*S**)-1,2-dimethyl-2-hydroxycyclopentanecarboxylic acid, 105665-97-2; 2-methyl-6-oxoheptanoic acid, 2570-68-5; (1*R**,4*S**)-*cis*-1,5-dimethyl-6-oxabicyclo[3.2.0]heptan-7-one, 105665-98-3; (*E*)-*N*,*N*-diethyl-2-acetyl-7-iodo-5-heptenamide, 105665-46-1; (1*R**,2*S**,3*S**)-*N*,*N*-diethyl-2-methyl-2-hydroxy-3-ethenylcyclopentanecarboxamide, 105665-45-0; (1*R**,2*S**,3*R**)-*N*,*N*-diethyl-2-methyl-2-hydroxy-3-ethenylcyclopentanecarboxamide, 105761-18-0; (*E*)-*N*,*N*-diethyl-2-acetyl-8-bromo-6-octenamide, 105665-47-2; (1*R**,2*S**,3*S**)-*N*,*N*-diethyl-2-methyl-2-hydroxy-3-ethenylcyclohexanecarboxamide, 105665-48-3; (1*R**,2*S**,3*R**)-*N*,*N*-diethyl-2-methyl-2-hydroxy-3-ethenylcyclohexanecarboxamide, 105761-19-1; (1*R**,2*S**,3*S**)-*N*,*N*-diethyl-2-methyl-2-hydroxy-3-ethenylcyclopentanecarboxamide (*m*-dinitrobenzoate ester), 105665-49-4; (1*R**,2*S**)-1,2-dimethyl-2-hydroxy-4-methylenecyclopentanecarboxyliic acid, 105665-80-3; (1*R**,2*R**)-1,2-dimethyl-2-hydroxy-4-methylenecyclopentanecarboxylic acid, 105665-82-5; (1*R**,2*S**)-1,5-dimethyl-3-methylene-6-oxabicyclo[3.2.0]heptan-7-one, 105665-81-4; (1*R**,2*S**,3*S**)-1,2-dimethyl-2-hydroxy-3-ethenylcyclopentanecarboxylic acid, 105665-87-0; (1*R**,4*S**,5*S**)-1,5-dimethyl-4-ethenyl-6-oxabicyclo[3.2.0]heptan-7-one, 105665-88-1; (*E*)-8-bromo-4-methyl-6-octen-3-one, 105665-95-0; (1*R**,2*S**)-1-ethyl-2-methyl-4-cyclohexen-1-ol, 105665-96-1; (1*R**,2*R**)-1-ethyl-2-methyl-4-cyclohexen-1-ol, 105665-99-4; ethyl (*E*)-2-methyl-2-acetyl-7-iodo-5-heptenoate, 105665-83-6; ethyl (*E*)-2-methyl-2-acetyl-7-bromo-5-heptenoate, 105665-85-8; (1*R**,2*R**,3*R**)-1,2-dimethyl-2-hydroxy-3-ethenylcyclopentanecarboxylate, 105761-21-5; (1*R**,2*S**,3*R**)-1,2-dimethyl-2-hydroxy-3-ethenylcyclopentanecarboxylate, 105761-22-6; ethyl (*Z*)-2-methyl-2-acetyl-7-iodo-5-heptenoate, 105665-86-9; ethyl (*E*)-2-methyl-2-acetyl-8-bromo-6-octenoate, 105665-92-7; (1*R**,2*S**,3*S**)-ethyl 1,2-dimethyl-2-hydroxy-3-ethenylcyclohexanecarboxylate, 105665-93-8; (1*R**,2*S**,3*R**)-ethyl 1,2-dimethyl-2-hydroxy-3-ethenylcylohexanecarboxylate, 105761-23-7; (1*R**,2*R**,3*S**)-ethyl 1,2-dimethyl-2-hydroxy-3-ethenylcyclohexanecarboxylate, 105761-24-8; (1*R**,2*R**,3*R**)-ethyl 1,2-dimethyl-2-hydroxy-3-ethenylcyclohexanecarboxylate, 105761-25-9; samarium diiodide, 32248-43-4.

Cooperativity and Anticooperativity in Solvation by Water: Imidazoles, Quinones, Nitrophenols, Nitrophenolate, and Nitrothiophenolate Ions†

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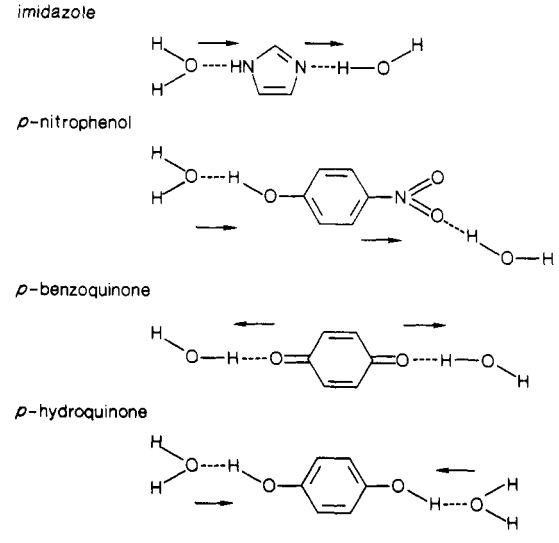
Abstract: Equilibrium constants for transfer from water to vapor, determined by dynamic vapor pressure measurements, show that the hydrophilic character of imidazole (log K(v/w) = −7.2) is no greater than might be expected on the basis of its constituent groups, whereas *p*-nitrophenol (log K(v/w) = −8.6) is about 30-fold more hydrophilic than would be the case if the effects of its constituent groups were additive. In contrast, the *p*-nitrophenolate ion (estimated log K(v/w) = −46) is less hydrophilic, by approximately 15 orders of magnitude, than might be expected if there were no interactions between its substituent groups. Thiopicric acid yields the most hydrophobic benzenoid anion that appears to have been reported thus far, its dissociated tetraethylammonium salt entering methylene chloride from water with an equilibrium constant approaching unity. The hydrophilic character of *p*-benzoquinone (log K(v/w) = −4.3) is much exceeded by that of *p*-hydroquinone (log K(v/w) = −7.5), so that solvent water exerts a major effect on the redox potential of this system. Comparison with model compounds indicates that in both *p*-benzoquinone and *p*-hydroquinone, solvation requirements of the symmetrical polar substituents are in conflict.

When two or more polar groups are present within the same molecule, their combined influence on its equilibrium of transfer from water to vapor, expressed in terms of free energy, if often found to be approximately additive. The regularity of these effects, first noticed by Butler,[1] has been amply confirmed by later investigators.[2-4]

Departures from additivity, observed occasionally, may indicate the presence of special interactions involving different parts of the solute molecule and the solvent that surrounds it. *p*-Nitrophenol[2] and imidazole,[5] for example, might be expected to be exceptionally hydrophilic if hydrogen bonds to solvent water from different parts of these solutes tended to reinforce each other by electronic effects transmitted through the solute molecules themselves (see arrows in Scheme I). For similar reasons, *p*-benzoquinone and hydroquinone might be less hydrophilic than would be anticipated if the effects of their polar substituents were additive.

Each of these potential effects is of biological interest. Side-chain imidazole groups are frequently involved in catalytic processes at the active sites of enzymes; if hydrogen bonding to solvent water were cooperative, then the chemical reactivity of histidine residues in proteins would be sensitive to the detailed environment of their nonreacting portions. The toxic effects of 2,4-dinitrophenol

Scheme I. Potential Electronic Interactions between Solvation Sites



†Supported by Grant No. PCM 7823016 from the National Science Foundation.

0002-7863/87/1509-0463$01.50/0