mixture was warmed to room temperature. After 30 min, excess NaH was destroyed by addition of 5% aqueous HCl (2 mL). The layers were separated, the aqueous layer was extracted three times with CH_2Cl_2 (2 mL), and the combined organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified by dissolving in 1 N NaOH solution (2 mL) and washing twice with 5:1 hexane–CH_2Cl_2 (2 mL). The aqueous layer was acidified to pH 1 with 5% HCl solution and extracted five times with CH_2Cl_2 (2 mL). The combined acid extracts were dried over $MgSO_4$ and evaporated to afford 12.5 mg (100%) of synthetic equisetin (**1**) as a colorless foam: $[\alpha]^{23}_D$ −253° (c = 0.038, $CHCl_3$);[18] IR ($CDCl_3$) 3600–3100 (OH), 3020, 2940, 2910, 2840, 1560, 1405, 1265 cm^{-1}; ^{1}H NMR (490 MHz, $CDCl_3$) δ 5.40 (m, 2 H), 5.30–5.10 (m, 2 H), 4.07 (dd, J = 3.5, 12.0 Hz, 1 H), 3.90 (dd, J = 5.0, 12.0 Hz, 1 H), 3.67 (app t, J = 5.0 Hz, 1 H), 3.32 (br, 1 H), 3.07 (s, 3 H), 2.00–1.70 (m, 4 H), 1.56 (d, J = 6.5 Hz, 3 H), 1.60–1.40 (m, 7 H), 1.30–0.90 (m, 3 H), 0.92 (d, J = 6.5 Hz, 3 H); mass spectrum (EI, 20 eV), m/z (relative intensity) 373 (M^+, 8), 355 (20), 210 (68), 200 (71), 199 (100), 170 (88), 149 (52), 143 (37); HRMS exact mass calcd for $C_{22}H_{31}O_4N$ 373.2254, found 373.2241.

Ent-Epimer 18: IR ($CDCl_3$) 3600–3100 (OH), 3020, 2940, 2910, 2840, 1560, 1405, 1265 cm^{-1}; ^{1}H NMR (490 MHz, $CDCl_3$) δ 5.42 (m, 2 H), 5.30–5.10 (m, 2 H), 4.06 (dd, J = 3.5, 12.0 Hz, 1 H), 3.85 (dd, J = 5.0, 12.0 Hz, 1 H), 3.66 (app t, J = 3.5 Hz, 1 H), 3.36 (br, 1 H), 3.05 (s, 3 H), 2.00–1.70 (m, 4 H), 1.56 (d, J = 6.5 Hz, 3 H), 1.60–1.40 (m, 7 H), 1.30–0.90 (m, 3 H), 0.92 (d, J = 6.5 Hz, 3 H); mass spectrum (EI, 20 eV), m/z (relative intensity) 373 (M^+, 8), 355 (20), 210 (68), 200 (71), 199 (100), 170 (88), 149 (52), 143 (37).

Acknowledgment. This research was financially supported by PHS Grant HL 25848. PHS Postdoctoral Fellowships to E.T. (PHS Grant 5 F32 CA08301-02) and J.E.A. (PHS Grant 1 F32 CA11104-01) are gratefully acknowledged. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Chemistry Division Grant CHE 7916210 at Yale University. We are especially grateful to Professor David Lynn for disclosing to us unpublished material as well as for providing a sample of natural *Fusarium* toxin.

Intramolecular Reductive Coupling Reactions Promoted by Samarium Diiodide

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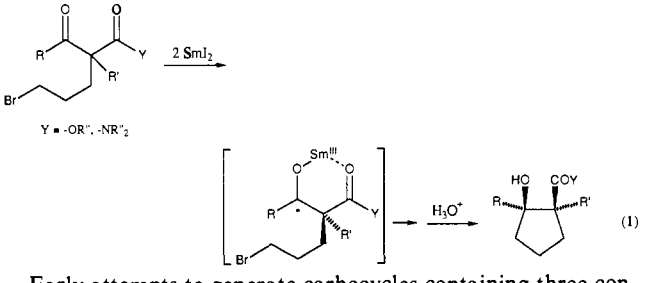
Abstract: Samarium diiodide is a useful reagent for promoting intramolecular reductive coupling reactions, generating functionalized carbocycles. Ketone–olefin coupling, pinacolic coupling, and other related reductive coupling reactions are accomplished under mild conditions with samarium diiodide. Products are accessed in high yield, and in many cases excellent stereochemical control is achieved at three contiguous stereocenters. Factors controlling the stereochemical outcome of these reactions are discussed, and mechanistic considerations are also outlined.

Samarium diiodide (SmI_2) has become an extremely useful reagent to organic chemists.[2] Recent applications, including intramolecular Barbier reactions,[3] intramolecular Reformatsky reactions,[4] and ketyl coupling reactions[5] reveal the outstanding versatility of this reagent. We have demonstrated that SmI_2 is particularly efficient and perhaps unique in promoting highly selective, stereocontrolled reductive coupling reactions. The continued development of SmI_2-mediated stereoselective reactions has thus allowed entry into highly functionalized organic molecules inaccessible by more conventional methods.

Initial studies performed by Kagan and co-workers demonstrated that SmI_2 was a useful reagent for promoting intermolecular Barbier coupling reactions.[6] Our earliest studies utilized SmI_2 to promote intramolecular Barbier coupling reactions.[3a] This route to functionalized carbocycles permits excellent stereochemical control at two adjacent stereocenters utilizing 2-(ω-haloalkyl)-β-keto esters and 2-(ω-haloalkyl)-β-keto amides as cyclization substrates. Highly functionalized five- and (in some instances) six-membered carbocycles can be generated by this method in high yield and with excellent stereochemical control. In our studies, the Sm(III) Lewis acid generated during the reduction was utilized as a template for stereochemical control during the ensuing cyclization (eq 1).[3b,4a]



(1)

Early attempts to generate carbocycles containing three contiguous stereocenters via the SmI_2-mediated intramolecular Barbier coupling reaction were thwarted by the instability of the cyclic intermediate generated from secondary haloalkyl β-keto ester substrates.[3b] Presumably, a carbocyclic intermediate is initially

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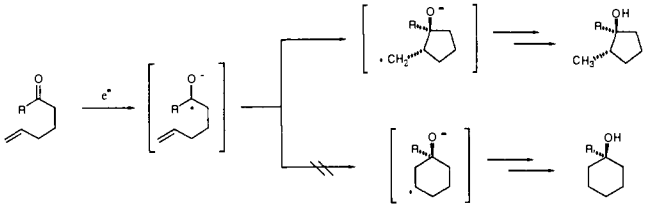
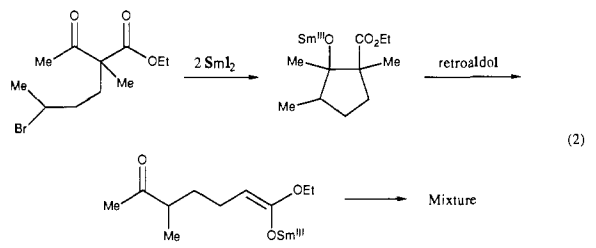


Figure 1. Regioselectivity and stereoselectivity for reductive cyclizations of 6-hepten-2-one.

formed at −78 °C, but under the aprotic reaction conditions quickly decomposes via a retro-aldol pathway to provide a mixture of products. The retro-aldol pathway becomes highly favored because of increased steric interactions in the cyclized intermediate, and the resulting acyclic enolate leads to the observed mixture (eq 2).



(2)

We describe here our efforts to develop intramolecular reductive coupling reactions with the goal of achieving high stereochemical control at three contiguous stereocenters on carbocyclic frameworks. In addition to expanding synthetic utility, these studies have allowed us to gain further understanding of the mechanism of SmI_2-promoted reactions. Substantial evidence implicates ketyls as key intermediates in SmI_2-promoted reactions involving aldehyde and ketone substrates.[6b] We have revealed in preliminary accounts that these SmI_2-generated ketyls can be intramolecularly trapped by a number of functional groups.[3a-c,5b,c] The full scope of these reductive coupling reactions utilizing substrates containing a variety of ketyl-trapping substituents is now outlined.

Results and Discussion

Ketone–Olefin and Related Reductive Coupling Reactions. There are many reactions in which photochemical,[7] electrochemical,[8] and chemical methods[5b,f,9] have been utilized to generate ketyls that are subsequently trapped by olefins. In reductive cyclization reactions of 6-hepten-2-one and related systems, the major observed product (1,2-dimethylcyclopentanol) is derived from the thermodynamically less favored radical intermediate.[10] Regioselective cyclization of 6-hepten-2-one and similar derivatives under reductive conditions is thus strikingly similar to the extensively studied 5-hexenyl radical. The 5-hexenyl radical undergoes exo cyclization to afford the primary methylcyclopentyl radical, rather than endo cyclization to generate a more stable secondary cyclohexyl radical. According to Beckwith,[10a] alkyl radicals preferentially attack π systems through an unsymmetrical transition state to maximize orbital overlap between the semioccupied orbital (SOMO) and the empty π^* orbital (LUMO) of the olefin. Thus, requirements of the three reacting centers for stereoelectronic orbital alignment outweigh thermodynamic influences. Similar factors are presumably operative in the reductive cyclization of 6-hepten-2-one (Figure 1).

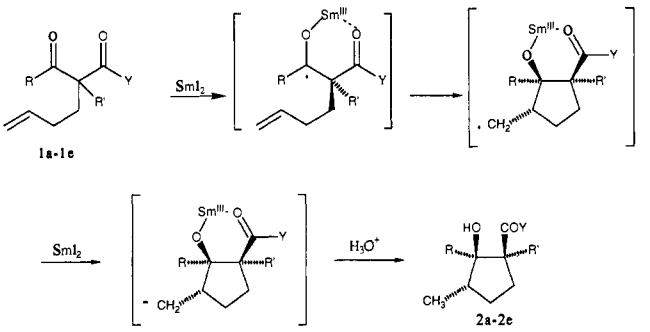


Figure 2. SmI_2-mediated cyclization of unsaturated β-keto esters.

Scheme I

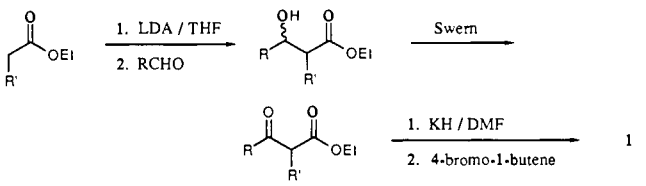


Table I. Samarium Diiodide Promoted Cyclization of Unsaturated β-Keto Esters

substr	Y	R	R′	isol yield of **2**, %	diastereoselectivity
1a	OEt	Me	Me	75	25:1
1b	OEt	Et	Me	66	30:1
1c	OEt	*i*-Pr	Me	63	30:1
1d	OEt	Me	Et	51	200:1
1e	OMe	Me	H	60	20:1

In addition to excellent regiochemical control, reductive cyclizations of 6-hepten-2-one have also demonstrated good stereoselectivity at two stereocenters.[7a,b,8a,b] The major diastereomer produced is (1*R**,2*S**)-1,2-dimethylcyclopentanol (see Figure 1). Stereochemical control has been ascribed to favorable secondary orbital overlap interactions between the developing methylene radical and the adjacent alkyl substituent in the transition state.[7a,8c,10a] Important electrostatic interactions may also contribute to formation of the trans product. According to calculation, the oxygen of the nucleophilic ketyl and the developing methylene radical center both carry partial negative charge in the transition state leading to carbon–carbon bond formation.[10] As a consequence, these two centers repel one another, assuming orientations that reinforce generation of (1*R**,2*S**)-1,2-dimethylcyclopentanol.[7a,8a,10]

We postulated that we could take advantage of the inherent stereochemical control exhibited in intramolecular ketone–olefin coupling reactions and extend stereochemical control to a third center through chelation utilizing SmI_2 as the reducing agent. As previously observed, the Sm(III) ion generated was expected to serve as a template for control of stereochemistry about the third stereocenter. Readily available β-keto ester and β-keto amide substrates possessing unsaturated side chains provided the requisite features for the cyclization we envisioned (Figure 2).

We began our study by investigating SmI_2-promoted reductive cyclization of a series of unsaturated β-keto esters. Starting materials for our study were prepared by condensation of ethyl propanoate with various aldehydes. Swern oxidation and alkylation with 4-bromo-1-butene led to the desired substrates **1a–1e**,[11] (Scheme I).

In initial attempts, the SmI_2-promoted reaction was performed without an added proton source. This resulted in large amounts

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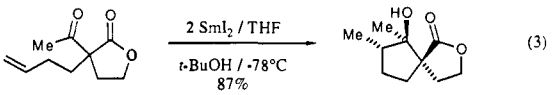
of unreacted starting material and a mixture of unidentified products. Presumably, the retro-aldol process mentioned above is operative under these conditions. However, upon performing the reaction in the presence of 2 equiv of a proton source the desired products were generated very cleanly. Thus, standard reaction conditions involved treatment of unsaturated β-keto esters with 2 equiv of SmI_2 and 2 equiv of *t*-BuOH (or MeOH) in THF at −78 °C. After stirring for 2 hours at −78 °C and then slowly warming to room temperature, reactions were quenched with pH 8.0 phosphate buffer. This protocol typically provided very clean products (**2a–2e**) in good yields, with excellent stereochemical control at three stereocenters (Table I). The products could be isolated by flash chromatography or by Kugelrohr distillation. Ratios of diastereomers were determined by fused silica capillary GC analysis of crude reaction mixtures. Generally, yields and diastereomeric ratios of the products **2a–2e** were not affected greatly by changing the size of the alkyl substituent (R in Figure 2) on the ketone.

The versatility of SmI_2 reductions has been demonstrated by utilization of a wide range of substrates. For example, we have found it possible to perform the reductive cyclization on an enolizable substrate. The α-monosubstituted β-keto ester (**1e**) was cyclized to provide **2e** in 60% yield as a 20:1 ratio of diastereomers.

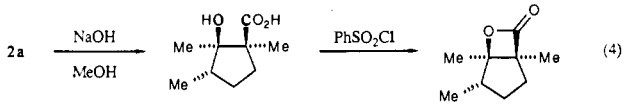
A spirocyclic system was also very efficiently generated with SmI_2. As shown below, the γ-lactone **3** was treated with SmI_2 in THF at −78 °C to afford (5*R**,6*R**,7*S**)-6-hydroxy-6,7-dimethyl-2-oxaspiro[4.4]nonan-1-one (**4**) in 87% yield as a single diastereomer (eq 3).



(3)

3 4

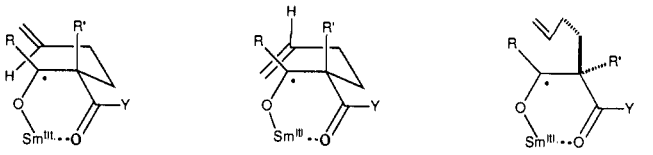
A critical component of these studies was the assignment of relative stereochemistry in the products. The relative stereochemistry of the products in Table I was determined by a combination of ^1H NMR, IR (vide infra), and X-ray crystallographic data, combined with chemical derivatization. For example, the relative cis stereochemistry of the carboxylate and the hydroxyl group of **2a** was determined by saponification to the β-hydroxy acid, followed by treatment with benzenesulfonyl chloride to generate the β-lactone (eq 4).[12] It had been shown in previous



(4)

studies that *trans*-2-hydroxycycloalkanecarboxylic acids do not lead to β-lactones under these conditions.[3b] An NOE difference ^1H NMR experiment[13] demonstrated that all three methyl groups of **2a** were positioned on the same face of the molecule, thereby confirming the relative stereochemistry of this molecule. The stereochemistry of the spirocyclic product (**4**) was established by single-crystal X-ray diffractometry.

A straightforward mechanism for these reductive cyclization processes can be envisioned. Single-electron reduction of the ketone by SmI_2 first generates a ketyl intermediate. Chelation of the Lewis acid, Sm(III), then produces a six-membered ring ketyl intermediate, which adds irreversibly to the olefin.[14] The second equivalent of SmI_2 reduces the cyclic radical intermediate to a transient carbanion, which is immediately protonolyzed to provide the carbocyclic products (see Figure 2). We were able to provide further evidence that the overall cyclization process is a two-electron process. Stoichiometry studies revealed that reactions did not go to completion when less than 2 equiv of SmI_2 was utilized, and large amounts of starting material could be



A B C

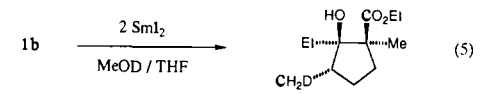
Figure 3. Plausible transition structures for cyclization of **1**, generating **2**.

Table II. Samarium Diiodide Promoted Cyclization of Unsaturated β-Keto Esters Substituted with an Electron-Withdrawing Group (EWG)

substr	R	R′	EWG	isol yield of **6**, %	diastereoselectivity
5a	Me	Me	CO_2Et	88	200:1
5b	Me	Me	COSEt	69	1.4:1
5c[a]	Me	Me	SPh		

[a] Substrate not obtained in sufficient purity for meaningful results.

recovered. Furthermore, when β-keto ester **1b** was treated under our standard reduction conditions with SmI_2, but MeOD was added as the proton source, the product contained greater than 90% deuterium incorporation at the C-3 methyl position (eq 5).



(5)

The amount of deuterium incorporation was determined by GC/MS and confirmed by ^1H NMR data. A similar two-electron process has been invoked by Kariv-Miller and Mahachi in the electrochemical cyclization of 6-hepten-2-one promoted by tetraalkylammonium electrolytes.[8c]

Three plausible cyclization transition structures leading to the observed products are diagramed in Figure 3. After the initial reduction and chelation of Sm(III), the resulting ketyl attacks the olefin following the geometric constraints described by Beckwith.[10a,b] The LUMO of the olefin and the SOMO of the ketyl align to attain an appropriate angle maximizing orbital overlap. As a result, an intermediate in which the hydroxyl group and the carboxylate group are situated cis on the ring is generated (A or B). The transition structure leading to the diastereomer with trans stereochemistry about the hydroxyl and carboxylate groups (C) is less favorable because of inherent limitations of the four-carbon olefinic side chain, which cannot attain the correct orbital alignment without significant distortion and ensuing strain. The third stereocenter is established by favorable electrostatic and secondary orbital interactions in the transition state as mentioned above (i.e., transition structure A is favored over that of B).[10] In addition, steric interactions may further reinforce this stereochemistry, directing the developing methylene center away from the face of the molecule with the large chelated ring.

The rate of addition of free radicals to alkenes is greatly affected by substituents on the alkene.[10c,15] Rates of radical addition to alkenes have been observed to increase up to 4 orders of magnitude when an electron-withdrawing group is positioned β to the carbon of the olefin undergoing radical attack. The observed rate increase is ascribed to polar effects, which increase the stability of the developing radical. Such phenomena can be adequately described by frontier molecular orbital theory.[10c,16] We postulated that an electron-withdrawing substituent at the terminal olefinic carbon of the unsaturated β-keto ester substrates would increase the rate (and perhaps yield) of the ketone–olefin coupling reactions (eq 6). To test this idea, several cyclization substrates were prepared by Horner–Emmons methodology.[17] For example, **5a** was easily prepared by reaction of triethyl phosphonoacetate/NaH with the

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(15) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753.
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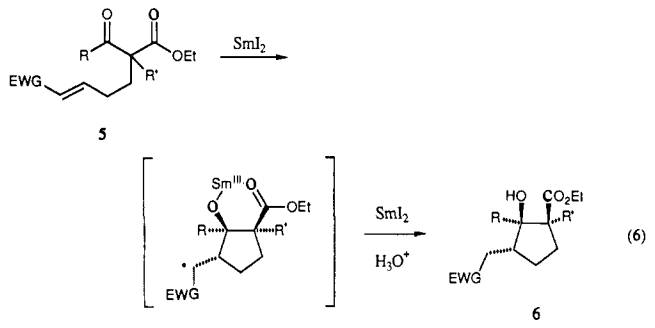
(17) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985 and references therein.

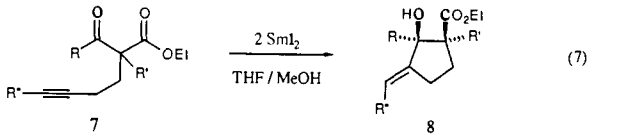


5 6 (6)

aldehyde derived from ozonolysis of **1a**. Treatment of **5a** with SmI_2 provided the desired cyclic product **6a** in 88% yield as a 200:1 mixture of diastereomers. An NOE difference ^1H NMR experiment[13] determined that the relative stereochemistry of **6a** was consistent with the stereochemistry determined for **2a**. The major setback in pursuing this study further was that many of the desired olefinic starting materials could not be readily accessed in pure form (see Table II). For example, the results of cyclization of substrate **5c** were very poor because of the impurity of the starting material. As a consequence, we did not intensively pursue this line of research.

There is an inherent competition between simple reduction of the ketone and the reductive cyclization process in these unsaturated carbonyl substrates. When the rate of cyclization is slow, one expects lower yields of carbocycles and correspondingly higher yields of simple (acyclic) alcohols or other undesired byproducts. In exploring the scope of the SmI_2-promoted reductive cyclization, we encountered several classes of molecules where these alternative pathways begin to compete with the desired cyclization.

Although there have been few rate studies dealing with intramolecular addition of radicals to alkynes, it has been established that the rate constant for cyclization of 5-hexynyl radical is somewhat slower than that for the 5-hexenyl radical (1×10^5 vs 5×10^5 s^{-1}).[10b] Nevertheless, several important examples of ketone–alkyne reductive cyclizations have been reported to proceed in good yields.[7b,9a,18] We hoped that cyclization of β-keto esters substituted with an alkyne would also be a facile process utilizing SmI_2 chemistry (eq 7). However, only one successful substrate



7 8 (7)

was found in our brief examination (Table III). Ethyl 2-acetyl-2-methyl-6-(trimethylsilyl)-5-hexynoate (**7a**) was prepared and subjected to SmI_2 reductive cyclization at −78 °C. The reaction was complete after warming to room temperature and stirring at that temperature for 1 h, and the desired product **8a** was isolated in 51% yield as a single diastereomer (eq 7). Attempted cyclization of the unprotected alkyne **7b** led to uncyclized alkynyl β-hydroxy ester as the major product.

We postulated that an electron-withdrawing substituent at the terminal alkyne carbon would enhance the cyclization process. We prepared **7c** with an ester substituent positioned to stabilize the intermediate vinyl radical. We were unable to isolate cyclized material in satisfactory yield or purity and therefore did not pursue related substrates.

The rate of cyclization of the 6-heptenyl radical (generating methylcyclohexane) is over 40 times slower than cyclization of the 5-hexenyl radical (approximately 1.1×10^4 vs 5×10^5 s^{-1}).[10a] Thus, it was not clear whether six-membered rings could be accessed by reductive coupling. Indeed, in the intramolecular Barbier

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Table III. Samarium Diiodide Promoted Cyclization of Alkynyl Ketones

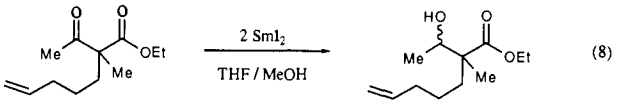
substr	R	R′	R″	isol yield of **8**, %	diastereoselectivity
7a	Me	Me	Me_3Si	51	200:1
7b[a]	Me	Me	H	0	
7c	Me	Me	CO_2Et	0	

[a] The major product was the uncyclized reduction product.

Table IV. Samarium Diiodide Promoted Cyclization of Unsaturated β-Keto Amides

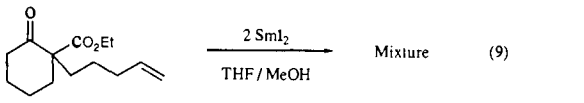
substr	R	R′	isol yield of **13**, %	diastereoselectivity
12a	Me	Et	78	>200:1
12b	Et	Me	35	>120:1
12c	*i*-Pr	Me	22	30:1

coupling study, generation of six-membered carbocycles from 2-(4-halobutyl)-β-keto ester substrates was unsuccessful.[3b] The major product obtained in this case was uncyclized 2-(4-halobutyl)-β-hydroxy ester, resulting from simple reduction of the ketone to the alcohol. With the hopes of being able to access six-membered carbocycles by a SmI_2-promoted process, the pentene-substituted β-keto ester **9** was prepared and subjected to SmI_2 reductive cyclization conditions. As expected, the simple intermolecular reduction process was again more rapid; the only product observed was uncyclized alcohol **10** (eq 8). Unsaturated



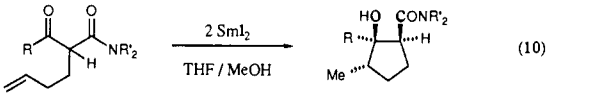
9 10 (8)

cyclohexanonecarboxylate **11** was then prepared, with the intent of decreasing the number of degrees of freedom in the cyclization transition state, thereby entropically facilitating cyclization to the six-membered ring. However, upon subjecting **11** to SmI_2 reduction conditions the desired bicyclic product could not be isolated (eq 9).



11 (9)

Previous studies from our laboratory had demonstrated that, in addition to β-keto esters, β-keto amides were also excellent chelating substrates for intramolecular reductive coupling reactions promoted by SmI_2.[3b] Amides are stronger Lewis bases than esters and therefore provide stronger chelation to Lewis acids. We presumed that excellent stereochemical control would be observed for ketone–olefin cyclization of β-keto amides (eq 10).



12 13 (10)

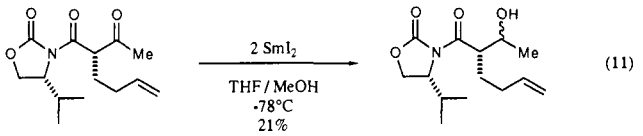
β-Keto amide substrates were prepared by an analogous sequence used for preparation of the β-keto ester starting materials. Appropriately functionalized β-keto amides were treated with 2 equiv of SmI_2 and 2 equiv of *t*-BuOH in THF at −78 °C, with reactions proceeding to completion within 2 h at −78 °C (Table IV). Crude reaction mixtures in these cases were not as clean as crude mixtures in the β-keto ester series, and isolated yields were correspondingly lower. Ratios of diastereomers were determined by fused silica capillary GC analysis of crude reaction mixtures, and the cyclized products were isolated by flash chromatography.

Diastereoselectivity of the products was excellent and generally higher than that observed for the β-keto esters. However, the

diastereoselectivity of the cyclization in this series appears to be more sensitive to the size of the substituent on the ketone of the β-keto amide. Thus, diastereoselectivity dramatically erodes as the size of this substituent (R) increases. We cannot really pinpoint the subtle factors that contribute to this phenomenon, and without more intimate knowledge of the nature of the intermediates involved we hesitate to speculate on the matter.

On the basis of similar steric and electronic arguments described for assigning the relative stereochemistry of products **2a–2e**, we assigned the same relative stereochemistry to the 2-hydroxycyclopentanecarboxamides. We attempted preparation of several derivatives of the products (**13a–13c**) for X-ray analysis but were unable to prepare suitable crystals. An NOE difference experiment established that the methyl groups and hydrogen α to the carboxamide were on the same face of **13a**.[13]

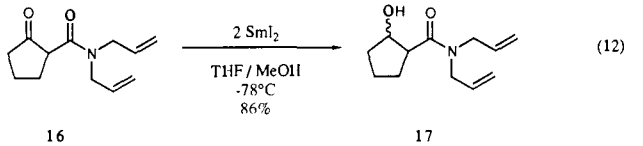
Encouraged by our observations that SmI_2 was an extremely efficient reagent for promoting ketone–olefin reductive cyclizations, we sought to employ a chiral, nonracemic substrate. Synthesis of one such substrate was accomplished utilizing Evans' oxazolidinone chemistry.[19] The oxazolidinone derived from L-valinol was alkylated with 5-hexenoyl chloride. Condensation of the enolate derived from this substrate with acetaldehyde, followed by Swern oxidation, provided **14**. Upon subjecting **14** to our standard SmI_2 reduction conditions the only product recovered was the uncyclized reduction product **15** in 21% yield, isolated as a single diastereomer (eq 11). Although the reasons are unclear, once again the overall simple reduction process effectively competes with efficient cyclization.



(11)

14 15

Throughout our studies we have invoked the idea that a six-membered Sm(III) chelated ring is generated in these processes, providing a rigid template for subsequent cyclization. Solvent and counterion studies performed previously on the SmI_2-promoted Barbier reaction certainly provide support for such a postulate in related systems.[3b] To further test this hypothesis, we attempted a reductive cyclization of *N,N*-di-(2-propenyl)-2-oxocyclopentanecarboxamide (**16**). Under reductive photochemical conditions established by Cossy and co-workers, this substrate had been shown to undergo smooth cyclization.[7] We surmised that a chelated Sm(III) complex generated from **16** would be unable to attain a conformation favorable for cyclization, and therefore simple reduction of the ketone to an alcohol would become the favored pathway. When substrate **16** was subjected to reduction by SmI_2 at −78 °C, an extremely rapid reaction was observed. The only product isolated was the uncyclized reduced cyclopentanol **17** in 86% yield, isolated as a single diastereomer (eq 12). This result provides further evidence that a Sm(III) chelate

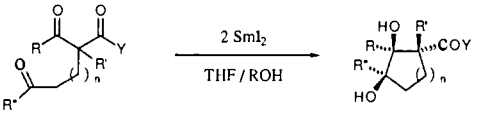


(12)

16 17

may be a key intermediate in the SmI_2-promoted reductive cyclizations. Clearly, if a chelated intermediate was not generated, free rotation in the ketyl intermediate should permit smooth cyclization of **16**.

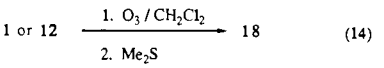
Intramolecular Pinacolic Coupling Reactions. Intramolecular pinacolic coupling reactions represent another potential reaction pathway for ketyl intermediates. A number of reagents are known to promote intermolecular pinacolic coupling of simple ketones or aldehydes.[20] There exists a limited number of examples of intramolecular pinacolic couplings as well.[21] These reactions are generally not synthetically useful because of the poor stereoselectivity observed under conditions required for cyclization. Our success in utilizing Sm(III) ion as a stereochemical control element encouraged us to develop a method for generation of stereochemically defined, functionalized 2,3-dihydroxycycloalkanecarboxylates (eq 13).



(13)

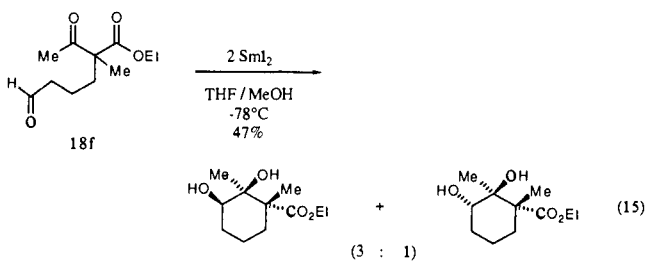
18 19

Appropriate starting materials to initiate our investigation were easily prepared from ozonolysis of the unsaturated β-keto esters (**1**) and β-keto amides (**12**) utilized above. Upon reductive workup with Me_2S and flash chromatography on silica gel, the desired substrates were prepared in excellent yield and purity (eq 14).



(14)

Propionaldehyde-substituted starting materials (**18a–18f**) were treated with 2 equiv of SmI_2 and 2 equiv of MeOH in THF at −78 °C. Reactions were generally complete soon after addition of the substrate to SmI_2 at −78 °C. The desired cyclic diols (Table V) were isolated by flash chromatography. Reaction mixtures were very clean and the products (**19a–19f**) were obtained in high yields with excellent stereochemical control at three contiguous stereocenters. Under the same conditions substrate **18g** left large amounts of unreacted starting material and produced many by-products. Replacing MeOH with *t*-BuOH resulted in the reaction proceeding cleanly to the desired cyclic diol in 46% yield. As was observed in the ketone–olefin reductive coupling study, an enolizable substrate (**18j**) could be cyclized in lower yield utilizing this method. Somewhat surprisingly, the cyclohexanediol (**19f**) was successfully generated in 47% yield and isolated as a 3:1:<0.1 mixture of diastereomers (eq 15). This indicates that the rate



(15)

18f 19f 20

Table V. Intramolecular Pinacolic Coupling Reactions Promoted by Samarium Diiodide

substr	*n*	Y	R	R′	R″	isol yield of **19**, %	diastereoselectivity
18a	1	OEt	Me	Me	H	77	200:1
18b	1	OEt	Et	Me	H	82	120:1
18c	1	OEt	*i*-Pr	Me	H	73	35:1
18d	1	OEt	Ph	Me	H	66	200:1
18e	1	OEt	Me	Et	H	75	>120:1
18f	2	OEt	Me	Me	H	47	3:1:<0.1
18g[a]	1	OEt	H	Me	H	46	>200:1
18h[a]	1	OEt	H	Me	Me	47	>200:1
18i	1	OEt	Me	Me	Me	30	3:1
18j	1	OMe	Me	H	H	31	5:1

[a] *t*-BuOH required as a proton source.

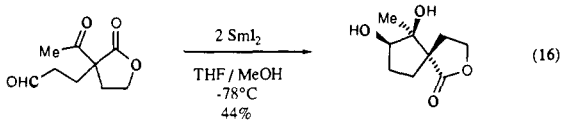
(19) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(20) (a) Clerici, A.; Porta, O. *Tetrahedron Lett.* **1982**, *23*, 3517. (b) Imamoto, T.; Kusumoto, T.; Hatanaka, Y.; Yokoyama, M. *Tetrahedron Lett.* **1982**, *23*, 1353. (c) Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765. (d) Clerici, A.; Porta, O. *J. Org. Chem.* **1987**, *52*, 5099. (e) Kahn, B. E.; Rieke, R. D. *Chem. Rev.* **1988**, *88*, 733.

(21) (a) Griffin, G. W.; Hager, R. B. *J. Org. Chem.* **1963**, *28*, 599. (b) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260. (c) Nakayama, J.; Yamaoka, S.; Hoshino, M. *Tetrahedron Lett.* **1987**, *28*, 1799.

of reductive pinacolic coupling providing six-membered rings is at least competitive with simple reduction and is certainly faster than corresponding intramolecular ketyl–olefin coupling reactions or the intramolecular Barbier-type coupling reactions.

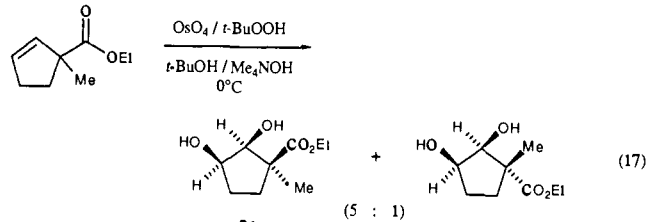
A spirocyclic diol was also prepared as a single diastereomer in somewhat lower yield (eq 16).



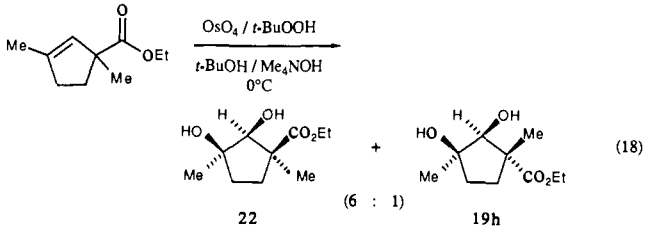
(16)

Diastereomeric ratios of products **19a–19j** were again determined by fused silica capillary GC analysis of crude reaction mixtures. It was determined that the major product diastereomers were cis diols in three examples by their ability to form acetonides with acetone (**19a**, **19c**, **19g**).[22] Two products (**19b**, **19f**) were suitable for X-ray analysis, and the relative stereochemistry of all three stereocenters was therefore firmly established. In addition, the second most preponderant diastereomer derived from reductive cyclization of substrate **18f** (**20**) was isolated and the stereochemistry determined by X-ray diffractometry.

Determination of the relative stereochemistry of diols **19g** and **19h** was particularly important. The diastereoselectivity of the cyclization was excellent, but it was unclear whether the major product was a cis diol or a trans diol. Consequently, rigorous efforts were taken to determine unambiguously that the products were the cis diols. Though the acetonide had been prepared from **19g**, less ambiguous data were required. ^{1}H NMR NOE difference experiments were attempted on **19g** and **19h** to determine the relative stereochemistry, but the NOE data could not be used to confirm the stereochemistry. We proceeded to prepare authentic cis diols from OsO_4 oxidation of suitably substituted cyclopentene derivatives, as shown in eq 17 and 18. In both reactions, the two



(17)



(18)

cis diol diastereomers were readily separated by flash chromatography. The minor cis diol of eq 17 corresponded to **19g** and the minor cis diol diastereomer of eq 18 corresponded to **19h** by capillary GC, TLC, ^{1}H NMR, and FT-IR data. We have used several lines of evidence to assign the major and minor products of the OsO_4 cis dihydroxylation reaction. First, the major product in each case was the more polar product as determined by its thin-layer chromatographic behavior. Second, OsO_4 vicinal hydroxylation reactions are known to be directed by steric factors.[23] Because ester groups are generally regarded as less sterically demanding than methyl groups,[24] it is expected that dihydroxylation will take place from the face of the olefin occupied by the carboxylate. Finally, IR data also strongly support the

Table VI. FT-IR Absorption Frequencies of *trans*-2-Hydroxycycloalkanecarboxylates

compd	OH stretch, cm^{-1}	C=O stretch, cm^{-1}	compd	OH stretch, cm^{-1}	C=O stretch, cm^{-1}
19a	3560	1710	**19g**	3555	1713
19b	3550	1709	**19h**	3560	1715
19c	3500	1700	**19j**	3570	1725
19f	3560	1715			

Table VII. FT-IR Absorption Frequencies of *cis*-2-Hydroxycycloalkanecarboxylates

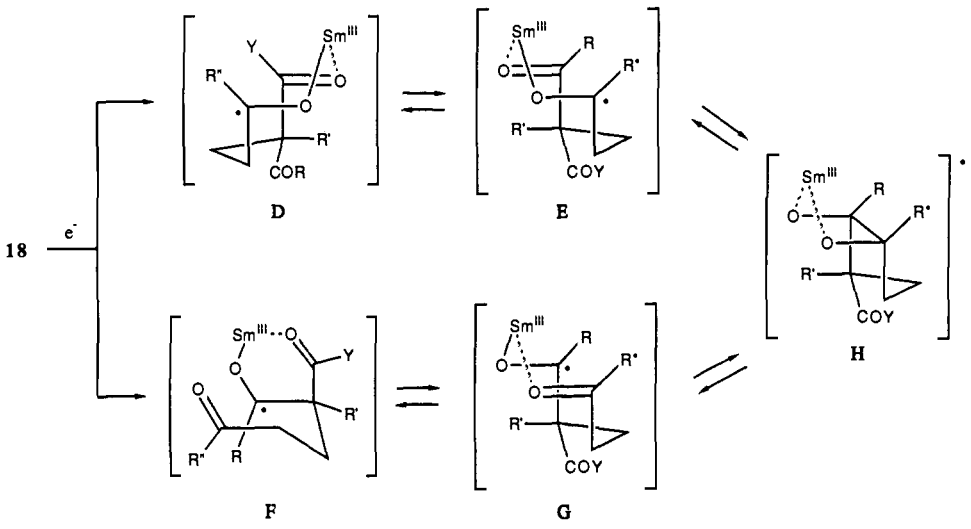
compd	OH stretch, cm^{-1}	C=O stretch, cm^{-1}	compd	OH stretch, cm^{-1}	C=O stretch, cm^{-1}
2a	3450	1693	**2e**	3495	1700
2b	3400	1690	**20**	3540	1700
2c	3400	1680	**21**	3327	1690
2d	3450	1690	**22**	3371	1688

stereochemical assignments made for the cyclic products. There is strong intramolecular hydrogen bonding in cyclic compounds possessing a carboxylate group and adjacent hydroxyl group cis on the carbocycle. Therefore, lower IR absorption frequencies for the carbonyl stretch and hydroxyl stretch relative to the trans compound should be expected.[25] For the products in which the carboxylate and the adjacent hydroxy group are trans on the ring, the carbonyl stretch of the ester occurs at 1710–1725 cm^{-1} and the hydroxyl stretch at 3555–3590 cm^{-1}. The IR frequencies were significantly lower in all cyclic products containing the *cis*-2-hydroxycycloalkanecarboxylate stereochemistry. The carbonyl stretch was typically observed at 1680–1690 cm^{-1} and the hydroxyl stretch was observed at 3330–3450 cm^{-1} in these diastereomers. This trend was consistent throughout the ketone–olefinic coupling series as well as the pinacolic coupling series (Tables VI and VII).

The relative stereochemistry (trans) between the carboxylate and adjacent hydroxyl group in the intramolecular pinacolic coupling reactions is notable. In other cases of SmI_2-mediated reductive cyclizations of substituted β-keto esters and β-keto amides studied to date (e.g., intramolecular Barbier reactions[3b] and ketone–olefin reductive coupling reactions, vide supra), the relative stereochemistry about these two centers has been cis. Not only does this methodology provide access to the manifold of products with complementary stereochemistry, it also presents interesting mechanistic implications as well. Unlike potential substrates for ketone–olefin reductive coupling reactions, precursors for the pinacolic coupling reaction contain two nearly equally reducible functional groups. This complicates any rational assessment of the stereochemical outcome of these reactions. Furthermore, several different mechanisms can be proposed for the intramolecular pinacolic coupling reaction. One scenario involves two-electron reduction followed by cyclization. Thus, after initial reduction of one of the carbonyl substituents to a ketyl, intermolecular reduction to generate a dianion could ensue. Subsequent nucleophilic attack by this dianion at the carbonyl and hydrolysis would provide the observed product. A mechanism of this type can be ruled out rather easily. A great deal of evidence suggests that such ketyl dianions are inaccessible, even under the most brutal reducing conditions. Reduction of a ketyl is highly endothermic,[26] and certainly SmI_2 is not a strong enough reducing agent to generate such a species. Furthermore, a dianion intermediate would quickly become protonated under our reaction conditions (pK_a *t*-BuOH, 17; pK_a MeOH, 16; pK_a carbonyl di-

(22) (a) Larson, G. L.; Hernandez, A. *J. Org. Chem.* **1973**, *38*, 3935. (b) Clode, D. M. *Chem. Rev.* **1979**, *79*, 491.
(23) Schröder, M. *Chem. Rev.* **1980**, *80*, 187.
(24) Eliel, E.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; American Chemical Society: Washington, DC, 1961.
(25) (a) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 4th ed.; Wiley: New York, 1981. (b) Nakanishi, K.; Solomon, P. H. *Infrared Absorption Spectroscopy*; Holden Day: San Francisco, 1977.
(26) (a) Rautenstrauch, V. *Tetrahedron* **1988**, *44*, 1613. (b) Huffman, J. W.; Wallace, R. H.; Pennington, W. T. *Tetrahedron Lett.* **1988**, *29*, 2527. (c) Huffman, J. W.; Liao, W.-P.; Wallace, R. H. *Tetrahedron Lett.* **1987**, *28*, 3315.

Scheme II



anion, 49–51), resulting in large amounts of uncyclized reduction products.[26a]

The most feasible pathway to coupled products is intramolecular ketyl addition to the Sm(III)-coordinated ketone (see Scheme II). Several examples of ketyl addition to Lewis acid activated carbonyls have been reported in the literature.[20d,21b,27] Clerici and Porta demonstrated in detailed experiments that intermolecular addition of ketyls to carbonyls can even be a rapid process.[20d,27] Generally, ketyl addition to carbonyls is a reversible reaction. However, reversibility is undoubtedly greatly affected by Lewis acid chelation of the complex, and further reduction of H by the second equivalent of SmI_2 would serve to make the process irreversible.[26a,27b]

In the SmI_2-promoted reductive coupling, two different ketyls can be generated initially. We propose that in either of these intermediates, chelation of the resulting Sm(III) ion with the carboxylate or carboxamide moiety (structures D and F) is of minimal consequence. That is, Lewis acid activation of the unreduced aldehyde or ketone (structures E and G) may be *required* for efficient cyclization. Again, a frontier molecular orbital approach is useful in thinking about the effects of Lewis acid complexation on the rate of radical addition to activated carbonyl substrates vs their unactivated counterparts.[16] Reetz quantitatively measured the effect of Lewis acid complexation on the HOMO (π_{CO}) and LUMO (π^*_{CO}) of carbonyl substrates.[28] Calculations indicate that the LUMO energy decreases by ≅50 kcal upon coordination with BF_3. Thus, the electrophilicity of the carbonyl is enhanced, making it more susceptible to nucleophilic radical addition. In our case, the rate of ketyl addition may be substantially increased by complexation of Sm(III) to the ketone as in intermediates E and G. If complexation is *required* for efficient cyclization, this would explain the cis diol stereochemistry observed in all of our substrates, regardless of which carbonyl is first reduced to initiate the reductive cyclization process.

Dipolar repulsion between the carboxylate moiety and the developing diol centers in intermediates E and G would account for the (trans) relative stereochemistry between these stereocenters. Following cyclization, intermolecular reduction of the Sm(III) chelated complex (H) and protonolysis by alcohol irreversibly drives the reaction to completion, generating the observed products.

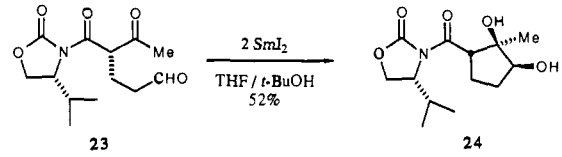
Certainly another plausible mechanism must also be considered. After initial ketyl formation, a second intermolecular reduction could follow, generating a diketyl intermediate. Subsequent carbon–carbon bond formation and protonolysis would again provide the observed products. We cannot unambiguously distinguish between this mechanism and the ketyl addition mechanism. However, both cis and trans diols might be expected from a diketyl coupling reaction. Corey investigated intramolecular pinacolic coupling reactions promoted by Ti^{+2} (which also lead to generation of cis diols) and argued that a diketyl coupling mechanism was unlikely.[21b] Strong dipolar repulsion between the Ti^{+3}-complexed ketyls would appear to favor generation of trans diols. The same argument may apply in our case; exclusive formation of cis diols would not seem likely from coupling of a di-Sm(III) complexed diketyl. Furthermore, one might speculate that Lewis acid catalyzed intramolecular carbonyl addition (by the ketyl) may be faster than intermolecular reduction of a ketone to a ketyl by SmI_2.

Table VIII. Intramolecular Pinacolic Coupling Reaction of β-Keto Amides

substr	*n*	Y	R	R′	R″	isol yield of **19**, %	diastereoselectivity
18k	1	NEt_2	Me	H	H	50	200:1
18l	1	NMe_2	Et	H	H	35	>120:1
18m	1	NMe_2	*i*-Pr	H	H	44	3:1

A short series of β-keto amides (Table VIII) was also included in the intramolecular pinacolic coupling study. This series follows a reactivity pattern similar to that observed in the unsaturated β-keto amide cyclizations (Table IV). The overall yields are somewhat lower than the yields for the corresponding β-keto esters, and both the yield and diastereoselectivity of **19k–19m** decreases as the size of R increases.

Because the pinacolic coupling reactions proceeded extremely quickly at −78 °C, we were again prompted to attempt cyclization of a chiral, nonracemic substrate. Simple ozonolysis of nonracemic oxazolidinone **14** provided **23** very cleanly. Treatment of **23** with SmI_2 under standard reaction conditions led to isolation of the chiral cyclic diol **24** in 52% yield (eq 19). Several flash chromatographies followed by recrystallization from diethyl ether provided crystals suitable for X-ray analysis, establishing the absolute configuration of this molecule. The ability to generate nonracemic diols may provide tremendous opportunities for natural product synthesis or construction of pharmacologically important target molecules.



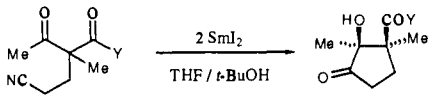
23 24 (19)

Miscellaneous Reductive Cyclizations. Nitriles have also been shown to trap ketyls.[7b,18c] The rate of cyclization of the 4-cyanobutyl radical, generating 2-hydroxycyclopentanone (after

(27) (a) Clerici, A.; Porta, O. *Tetrahedron Lett.* **1983**, *39*, 1239. (b) Clerici, A.; Porta, O. *J. Org. Chem.* **1983**, *48*, 1690.

(28) Reetz, M. T.; Hullmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405.

hydrolysis), is 4.0×10^3 s^{-1} at 25 °C.[10a,b] This is approximately 2 orders of magnitude slower than corresponding 5-hexenyl radical cyclizations. We prepared a cyano-substitued β-keto ester (**25a**) and β-keto amide (**25b**) and submitted these to SmI_2 reduction conditions (eq 20). Small amounts of the desired product along



(20)

25a Y = OEt
25b Y = NEt_2

26a Y = OEt (45%)
26b Y = NEt_2 (30%)

with major amounts of unreacted starting material were observed. In both substrates under varying reaction conditions the product yields were low, although the diastereoselectivity appeared to be very good (>120:1). Though we could obtain cyclized product, the lower reactivity of nitriles as ketyl traps was demonstrated by these two examples and we chose not to investigate other nitrile-substituted compounds.

Conclusions

Samarium diiodide has been shown to be an extremely reliable reagent for promoting intramolecular reductive coupling reactions. Methods to prepare highly functionalized five- and six-membered carbocycles with high diastereoselectivity at three contiguous stereocenters have been demonstrated. Generation of a chiral, nonracemic product was achieved. The reaction conditions are exceptionally mild and therefore allow generation of products that would not be accessible by other reduction methods. We described methods for cyclization of various δ,ε-unsaturated ketone substrates and intramolecular pinacolic coupling reactions. These processes provide stereochemically complementary carbocycles and therefore may have great synthetic utility. The diastereoselectivity of SmI_2 processes is dependent on chelation of Lewis acidic Sm(III) generated during the reduction, providing a stereochemical control template for subsequent cyclization. Through this methodology, relatively simple substrates are rapidly converted to products of high molecular complexity, both in terms of functionality and stereochemistry. As a consequence, samarium diiodide once again presents itself as a very useful tool for synthetic organic chemists.

Experimental Section

IR spectra were recorded on a Mattson-Polaris FT-IR spectrophotometer. ^1H NMR and ^{13}C NMR were recorded on either a Magnachem A-200 or Gemini-300 NMR, operating at 200 and 300 MHz, respectively. $CDCl_3$ was employed as the solvent for both ^1H and ^{13}C NMR, with $CHCl_3$ as reference for ^1H NMR and $CDCl_3$ as internal standard for ^{13}C NMR. Capillary GC traces were obtained from Hewlett-Packard Model 5890A gas–liquid chromatographs containing either a 25 m × 320 μm 5% phenyl SE-54 fused silica or 10% fused silica Carbowax column, with a Hewlett-Packard Model 3390 digital integrator. Low-resolution and exact mass spectra were recorded on a VG7070 EQ-HF instrument with perfluorokerosene as internal standard. Standard flash chromatography procedures were followed.[29]

Reagents. Tetrahydrofuran was distilled immediately prior to use from benzophenone ketyl under argon. Samarium metal was purchased from Research Chemicals, Phoenix, AZ, and was weighed and stored under an inert atmosphere. Diiodomethane was purchased from Fluka Chemicals and distilled prior to use. Standard benchtop techniques were employed for handling air sensitive reagents[30] and all reactions were carried out under an argon atmosphere.

Ethyl (1*R,2*S**,3*S**)-2-Hydroxy-1,2,3-trimethylcyclopentanecarboxylate (2a).** Samarium diiodide (2.0 mmol) was prepared in 10.0 mL of dry THF according to the general procedure described in the supplementary material. The SmI_2 solution was cooled to −78 °C, and a solution of ethyl 2-acetyl-2-methyl-5-hexenoate (**1a**; 0.1984 g, 1.00 mmol) and 2 equiv of *t*-BuOH in 10.0 mL of dry THF was added dropwise. The resulting solution was stirred at −78 °C for 1.5–2 h and then slowly warmed to room temperature before quenching with pH 8.0 phosphate buffer. The mixture was filtered through Celite and the layers were separated. The aqueous layer was extracted with Et_2O and the combined organic extracts were washed with saturated NaCl, filtered, and concentrated in vacuo. The crude mixture was purified by flash chromatography on neutral alumina (activity III, 7:1 hexanes/EtOAc) to provide **2a** (0.1403 g, 0.700 mmol, 70%) as a 25:1 mixture of diastereomers: ^1H NMR ($CDCl_3$) δ 4.15 (q, *J* = 7.01 Hz, 2 H), 3.50 (br s, 1 H), 2.30 (m, 1 H), 2.02–1.8 (m, 2 H), 1.55 (m, 1 H), 1.25 (t, *J* = 7.01 Hz, 3 H), 1.18 (s, 3 H), 1.16–1.10 (m, 1 H), 1.06 (s, 3 H), 0.945 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.5, 81.9, 60.16, 54.68, 42.98, 32.41, 28.51, 19.54, 17.20, 14.86, 13.30; IR ($CHCl_3$) 3460 (br s), 2980 (s), 2920 (s), 2875, 1700 (s), 1490, 1390, 1250 (s), 1110 (s), 950 (m) cm^{-1}; exact mass calcd for $C_{11}H_{20}O_3$ 200.1412, found 200.1431.

Ethyl (1*R,2*S**,3*R**)-2-Ethyl-2-hydroxy-1,3-dimethylcyclopentanecarboxylate (2b).** Following the general procedure outlined above, ethyl 2-(1-oxopropyl)-2-methyl-5-hexenoate (**1b**) (0.088 g, 0.41 mmol) was treated with SmI_2 in 9.0 mL of THF. After stirring at room temperature for 30 min, **2b** was generated as a 30:1 mixture of diastereomers. The product was isolated as a yellow oil (0.0581 g, 0.271 mmol, 66%) by Kugelrohr distillation: bp 40 °C (0.05 mmHg); ^1H NMR ($CDCl_3$) δ 4.10 (q, *J* = 7.2 Hz, 2 H), 2.4–2.3 (m, 1 H), 2.15–2.01 (m, 2 H), 1.8–1.6 (m, 3 H), 1.57 (q, *J* = 7.2 Hz, 2 H), 1.22 (t, *J* = 7.2 Hz, 3 H), 1.15 (s, 3 H), 0.99 (d, *J* = 7.2 Hz, 3 H), 0.91 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.84, 85.66, 60.60, 55.98, 43.69, 35.25, 30.32, 25.43, 20.65, 18.95, 14.08, 8.27; IR ($CHCl_3$): 3400 (br), 3000, 2900, 2880, 1690, 1450, 1390, 1340, 1250, 1130, 975 cm^{-1}; exact mass calcd for $C_{11}H_{22}O_3$ 214.1569, found 214.1563.

Ethyl (1*R,2*S**,3*S**)-2-Hydroxy-2-isopropyl-1,3-dimethylcyclopentanecarboxylate (2c).** Following the general procedure outlined above, ethyl 2-(2-methyl-1-oxopropyl)-5-hexenoate (**1c**; 0.0882 g, 0.390 mmol) was treated with SmI_2 in 16.0 mL of THF. After stirring at room temperature for 2 h, **2c** was generated as a 30:1 mixture of diastereomers. The product was isolated as a pale yellow liquid (0.0561 g, 0.245 mmol, 63%) by Kugelrohr distillation: bp 57–62 °C (0.05 mmHg); ^1H NMR ($CDCl_3$) δ 5.03 (s, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 2.28–2.20 (m, 2 H), 2.15–2.0 (m, 1 H), 1.95–1.8 (sept, *J* = 6.5 Hz, 1 H), 1.65–1.52 (m, 1 H), 1.45–1.35 (m, 1 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.17 (s, 3 H), 1.04 (d, *J* = 7.3 Hz, 3 H), 0.91 (d, *J* = 6.4 Hz, 3 H), 0.74 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.77, 88.98, 61.04, 53.90, 44.13, 38.48, 30.83, 29.85, 20.24, 18.57, 18.13, 17.34, 13.83; IR (neat) 3430 (br s), 3500 (w), 2980 (s), 2880 (m), 1688 (s), 1490, 1410, 1235, 1100, 1020 cm^{-1}; exact mass calcd for $C_{13}H_{24}O_3$ 228.1746, found 228.1719.

Cyclization of Ethyl 2-Acetyl-2-ethyl-5-hexenoate (1d). Following the general procedure outlined above, **1d** (0.0678 g, 0.319 mmol) was treated with SmI_2 (0.7026 mmol) in 14 mL of dry THF to provide ethyl (1*R**,2*S**,3*R**)-1-ethyl-2-hydroxy-2,3-dimethylcyclopentanecarboxylate (**2d**) as a 200:1 mixture of diastereomers. The product was isolated as a clear, colorless liquid (0.0348 g, 0.309 mmol, 51%) by flash chromatography on silica gel (4:1 hexanes/EtOAc): ^1H NMR ($CDCl_3$) δ 4.2 (q, *J* = 7.26 Hz, 2 H), 3.54 (s, 1 H), 2.5–2.0 (m, 2 H), 1.95–1.4 (m, 5 H), 1.24 (t, *J* = 7.01 Hz, 3 H), 1.00 (s, 3 H), 1.0–0.7 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.3, 80.60, 59.22, 58.16, 41.94, 28.23, 26.23, 25.46, 16.03, 13.15, 12.73, 8.45; IR ($CHCl_3$) 3500 (br), 2900 (s), 2880 (m), 1680 (s), 1475 (m), 1250 (s), 1200 (s), 1140 (s), 1030 (s), 980 (m) cm^{-1}; exact mass calcd for $C_{12}H_{22}O_3$ 214.1550, found 214.1562.

Cyclization of Methyl 2-Acetyl-5-hexenoate (1e). Following the general procedure described above, **1e** (0.060 g, 0.35 mmol) was treated with SmI_2 (0.733 mmol) at −78 °C to provide methyl (1*R**,2*S**,3*R**)-2-hydroxy-2,3-dimethylcyclopentanecarboxylate (**2e**; 0.035 g, 58%, 0.20 mmol) as a 19:1 mixture of diastereomers. The crude product was purified by flash chromatography on silica gel (3:1 hexanes/EtOAc) followed by flash chromatography on neutral alumina (activity III, 5:1 hexanes/EtOAc): ^1H NMR ($CDCl_3$) δ 3.67 (s, 3 H), 3.08 (br s, 1 H), 2.62 (dd, 1 H), 2.1–1.8 (m, 5 H), 1.2 (s, 3 H), 0.85 (d, *J* = 7.25 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.51, 80.06, 50.48, 50.0, 42.98, 29.54, 24.88, 21.85, 15.19; IR ($CHCl_3$) 3500 (br), 3000 (m), 2960 (s), 2880 (m), 1715 (s), 1430 (s), 1350 (s), 1180 (s), 930 (m) cm^{-1}; exact mass calcd for $C_9H_{17}O_3$ (M + 1) 173.1019, found 173.1021.

Ethyl (1*R,2*S**,3*R**)-2-Ethyl-2-hydroxy-1-methyl-3-methyl-(*d*)-cyclopentanecarboxylate (2f).** Samarium diiodide (1.935 mmol) in 11 mL of THF was prepared according to the general procedure described in the supplementary material. The solution was cooled to −78 °C, and a solution of ethyl 2-(1-oxopropyl)-2-methyl-5-hexenoate (**1b**; 0.187 g, 0.845 mmol) and MeOD (2 equiv) in 11 mL of THF was added dropwise. The resulting mixture was stirred at −78 °C for 1.5 h, then slowly warmed to room temperature, and quenched with pH 8.0 buffer. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with saturated NaCl, dried (Na_2SO_4), filtered, and concentrated in vacuo to provide **2f**. The product was isolated as a pale yellow liquid (0.157 g, 0.729 mmol, 86%) by Kugelrohr distillation: bp 40–42 °C (0.05 mmHg); ^1H NMR ($CDCl_3$) δ 4.1 (t, *J* = 7.01 Hz, 2 H), 3.43 (s, 1 H), 2.5–1.9 (m, 3 H), 1.7–1.4 (m,

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3 H), 1.20 (t, J = 7.01 Hz, 3 H), 1.13 (s, 3 H), 0.89 (t, J = 7.01 Hz, 3 H), 1.0–0.8 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.5, 83.47, 58.03, 54.03, 41.52, 33.09, 28.24, 23.13, 18.68, 15.68 (t), 12.02, 6.2; IR ($CHCl_3$) 3470.4 (s), 2932.2 (s), 2876.2 (s), 1707.2 (s), 1280.9 (m), 1379.3 (m), 1462.2 (s), 1128.5 (w), 1020.5 (s) cm^{-1}.

Hydrolysis of Ethyl (1*R,2*S**,3*R**)-2-Hydroxy-1,2,3-trimethylcyclopentanecarboxylate (2a).** In an oven-dried round-bottom flask equipped with magnetic stirring bar and septum inlet were placed **2a** (0.166 g, 0.827 mmol) and 1.5 mL of MeOH. To the solution was added 2.0 mL of 1.0 M NaOH. The resulting solution was heated at 50 °C for 2 h and then cooled, and 3 N HCl was added until the solution had a slightly acidic pH. The crude solution was extracted with 1:1 CH_2Cl_2/Et_2O. The combined organic extracts were washed with saturated NaCl, dried (Na_2SO_4), filtered, and concentrated in vacuo to provide (1*R**,2*S**,3*R**)-2-hydroxy-1,2,3-trimethylcyclopentanecarboxylic acid. The product was isolated as a yellow oil (0.1148 g, 0.667 mmol, 80%) by flash chromatography on silica gel (10:1 CH_2Cl_2/MeOH): ^{1}H NMR ($CDCl_3$) δ 8.75 (br s, 1 H), 2.5–2.2 (m, 1 H), 2.05 (s, 3 H), 2.0–1.3 (m, 5 H), 1.3 (s, 3 H), 0.9 (d, 3 H).

Lactonization of (1*R,2*S**,3*R**)-2-Hydroxy-1,2,3-trimethylcyclopentanecarboxylic Acid.** To an oven-dried round-bottom flask was added the hydroxy carboxylic acid (0.1238 g, 0.719 mmol) in 3.0 mL of triethylamine. The solution was cooled to 0 °C and benzenesulfonyl chloride (0.265 g, 1.5 mmol) was added neat. The reaction was stirred at 0 °C for 10 min and then placed in a freezer at −20 °C for 16 h. The crude reaction mixture was poured over ice, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with H_2O, saturated $NaHCO_3$, and saturated NaCl, then dried ($MgSO_4$), filtered, and concentrated in vacuo to provide (1*R**,2*S**,3*R**)-1,2,3-trimethyl-6-oxabicyclo[3.2.0]heptan-7-one. The product was isolated as a pale yellow oil (0.100 g, 0.649 mmol, 90%) by flash chromatography on silica gel (3:1 hexanes/EtOAc). GLC analysis indicated a purity of 97%: ^{1}H NMR ($CDCl_3$) δ 2.5–2.3 (m, 1 H), 1.6–1.8 (m, 2 H), 1.7–1.5 (m, 2 H), 1.4 (s, 3 H), 1.3 (s, 3 H), 0.8 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.91, 92.39, 62.27, 40.43, 32.84, 29.51, 16.23, 15.56, 14.30; IR ($CHCl_3$) 2990 (s), 2900, 2850, 1820 (s), 1450, 1390, 1190 cm^{-1} Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.62; H, 9.36.

(5*R,6*S**,7*S**)-6-Hydroxy-6,7-dimethyl-2-oxaspiro[4.4]nonan-1-one (4).** Following the general procedure outlined above, 2-acetyl-2-(3-butenyl)-γ-butyrolactone (**3**; 0.715 g, 0.392 mmol) was treated with SmI_2 in 8.0 mL of THF. After stirring at room temperature for 4 h, **4** was obtained as a 200:1 mixture of diastereomers. The product was isolated as a white solid (0.063 g, 0.34 mmol, 87%, mp 63–64 °C) by flash chromatography on silica gel (1:1 hexanes/EtOAc): ^{1}H NMR ($CDCl_3$) δ 4.4–4.15 (m, 2 H), 4.14 (s, 1 H), 2.4–2.2 (m, 2 H), 2.0–1.8 (m, 2 H), 1.75–1.6 (m, 3 H), 1.26 (s, 3 H), 1.0 (d, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 203.45, 179.33, 62.27, 51.94, 39.88, 30.08, 29.55, 26.56, 17.71, 9.10; IR ($CHCl_3$) 3495 (br), 3000, 2950, 2900, 2850, 1755 (s), 1400 (s), 1250 (s), 1050, 960, 845 cm^{-1}; exact mass calcd for $C_{10}H_{16}O_3$ 184.1099, found 184.1104. The structure was confirmed by X-ray diffractometry.

Cyclization of Ethyl 6-Carbethoxy-6-methyl-7-oxo-2-octenoate (5a). Following the general procedure described above, **5a** (0.1091 g, 0.4036 mmol) was treated with SmI_2 (0.2504 mmol) in 15 mL of dry THF. The reaction was complete upon addition of **5a** to SmI_2 at −78 °C to provide ethyl (1*R**,2*S**,3*S**)-3-[(ethylcarboxy)methyl]-2-hydroxy-1,2-dimethylcyclopentanecarboxylate (**6a**) as a 200:1 mixture of diastereomers. The product was isolated as a clear yellow liquid (0.0973 g, 0.3575 mmol, 88%) by flash chromatography on silica gel (1:1 hexanes/EtOAc): ^{1}H NMR ($CDCl_3$) δ 4.1 (q, J = 7.01 Hz, 2 H), 4.01 (q, J = 7.25 Hz, 2 H), 3.24 (s. 1 H), 2.7–1.4 (m, 7 H), 1.21 (t, J = 7.00 Hz, 3 H), 1.18 (t, J = 7.0 Hz, 3 H), 1.15 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.31, 173.49, 81.31, 60.9, 59.0, 44.63, 35.89, 32.0, 26.30, 19.46, 18.7, 14.15; IR ($CHCl_3$) 3500 (br), 3000 (m), 2975 (s), 2910 (m), 2880 (w), 1710 (s), 1500 (m), 1400 (s), 1300 (s), 1260 (s), 1050 (s), 990 (m), 940 (m) cm^{-1}; exact mass calcd for $C_{14}H_{25}O_5$ (M + 1) 273.1623, found 273.1640.

Cyclization of Ethyl 2-Acetyl-2-methyl-6-(*S*-ethylthiocarboxy)-5-hexenoate (5b). Following the general procedure described above, **5b** (0.072 g, 0.25 mmol) was treated with SmI_2 (0.55 mmol) in 5.0 mL of THF at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, slowly warmed to room temperature, and stirred an additional 30 min to provide ethyl (1*R**,2*S**,3*S**)-3-[(*S*-ethylthiocarboxy)methyl]-2-hydroxy-1,2-dimethylcyclopentanecarboxylate (**6b**) as 1:1.4 mixture of diastereomers. The product was isolated as a yellow oil (0.05 g, 79%, 0.200 mmol) by flash chromatography on silica gel (3:1 hexanes/EtOAc): ^{1}H NMR ($CDCl_3$) (two diastereomers) δ 4.17 (q, J = 7.00 Hz, 2 H), 4.03 (q, J = 7.00 Hz, 2 H), 2.85 (q, J = 7.6 Hz, 2 H), 2.72 (q, J = 7.1 Hz, 2 H), 2.5–2.1 (m, 1 H), 2.05–1.7 (m, 2 H), 1.6–1.35 (m, 1 H), 1.27 (t, J = 7.0 Hz, 3 H), 1.25 (s, 3 H), 1.19 (t, J = 7.0 Hz, 3 H), 1.11 (s, 3 H); ^{13}C NMR ($CDCl_3$) (two diastereomers) δ 199.0, 198.9, 178.00, 176.2, 81.17, 79.68, 60.84, 60.36, 45.29, 44.97, 44.74, 42.01, 32.25, 30.08, 25.66, 24.14, 23.23, 20.93, 20.03, 19.33, 18.04, 14.57, 14.10, 13.93; exact mass calcd for $C_{14}H_{23}O_4S$ (M − 1) 287.1317, found 287.1317.

Ethyl (1*R,2*R**)-2-Hydroxy-1,2-dimethyl-3-[(trimethylsilyl)-methylene]cyclopentanecarboxylate (8a).** Following the general procedure outlined above, ethyl 2-acetyl-2-methyl-6-(trimethylsilyl)-5-hexenoate (**7a**; 0.0684 g, 0.2548 mmol) was treated with SmI_2 in 6.0 mL of THF. After reaction at room temperature for 1 h, **8a** was generated as a 200:1 mixture of diastereomers. The product was isolated as a pale yellow solid (0.0353 g, 0.130 mmol, 51%) by flash chromatography on neutral alumina (activity III, 9:1 hexane/EtOAc), followed by a second flash chromatography on silica gel (5:1 hexanes/EtOAc): ^{1}H NMR ($CDCl_3$) δ 5.26 (m, 1 H), 4.15 (q, J = 7.5 Hz, 2 H), 2.5–2.0 (m, 3 H), 2.3 (s, 1 H), 1.7–1.4 (m, 1 H), 1.24 (s, 3 H), 1.22 (s, 3 H), 1.19 (t, J = 7.01 Hz, 3 H), 0.124 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 175.6, 163.6, 140.3, 119.53, 80.54, 59.49, 53.01, 29.91, 28.30, 27.94, 21.68, 16.48, 12.64, 0.180; IR ($CHCl_3$) 3510 (w), 3460 (s), 2990, 2950, 2900, 2820, 1700, 1600, 1560, 1400, 1270, 1100 (s), 1020, 860 (s) cm^{-1}; exact mass calcd for $C_{14}H_{26}O_3Si$ 270.1651, found 270.1658.

(1*R,2*S**,3*R**)-*N*,*N*-Diethyl-2-hydroxy-2,3-dimethylcyclopentanecarboxamide (13a).** Following the general procedure outlined above, *N*,*N*-diethyl-2-acetyl-5-hexenamide (**12a**) (0.0868 g, 0.429 mmol) was treated with SmI_2 in 8.0 mL of THF to provide **13a** as a 200:1 mixture of diastereomers. The product was isolated as a pale yellow liquid (0.0664 g, 0.313 mmol, 78%) by flash chromatography on silica gel (1:1 hexanes/EtOAc): ^{1}H NMR ($CDCl_3$) δ 5.57 (s, 1 H), 3.45–3.25 (m, 4 H), 2.61 (t, J = 9.4 Hz, 1 H), 2.4–2.1 (m, 2 H), 2.0–1.7 (m, 3 H), 1.18–1.02 (m, 6 H), 1.13 (s, 3 H), 0.80 (d, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.5, 80.1, 46.3, 44.7, 42.5, 40.3, 32.3, 28.8, 24.1, 22.3, 13.1, 12.5; IR ($CHCl_3$) 3379 (br), 3000 (s), 2950, 2850, 1622 (s), 1450, 1375, 1230, 1150, 980 (s) cm^{-1}; exact mass calcd for $C_{12}H_{23}NO_2$ 213.1729, found 213.1759.

(1*R,2*S**,3*R**)-*N*,*N*-Dimethyl-2-ethyl-2-hydroxy-3-methylcyclopentanecarboxamide (13b).** Following the general procedure outlined above, *N*,*N*-dimethyl-2-(1-oxopropyl)-5-hexenamide (**12b**; 0.1443 g, 0.800 mmol) was treated with SmI_2 in 16.0 mL of THF to provide **12b** as a 120:1 mixture of diastereomers. The product was isolated as a pale yellow liquid (0.0558 g, 0.228 mmol, 35%) by Kugelrohr distillation: bp 78–83 °C (0.05 mmHg); ^{1}H NMR ($CDCl_3$) δ 5.7 (br s, 1 H), 2.99 (s, 3 H), 2.89 (s, 3 H), 2.68 (t, J = 9.6 Hz, 1 H), 2.4–2.1 (m, 1 H), 2.02–1.75 (m, 3 H), 1.5–1.4 (m, 2 H), 1.3–1.19 (m, 2 H), 0.87 (t, J = 7.0 Hz, 3 H), 0.78 (d, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.73, 84.55, 44.70, 41.86, 37.21, 35.22, 30.86, 28.49, 26.63, 17.56, 8.01; IR ($CHCl_3$) 3400 (br), 3000, 2970, 2900, 1600, 1490, 1400, 1310, 1190, 990 cm^{-1}; exact mass calcd for $C_{11}H_{21}NO_2$ 199.1201, found 199.1576.

(1*R,2*S**,3*R**)-*N*,*N*-Dimethyl-2-hydroxy-2-isopropyl-3-methylcyclopentanecarboxamide (13c).** Following the general procedure outlined above, *N*,*N*-dimethyl-2-(2-methyl-1-oxopropyl)-5-hexenamide (**12c**; 0.074 g, 0.3525 mmol) was treated with SmI_2 in 7.0 mL of THF to provide **13c** as a 30:1 mixture of diastereomers. The product was isolated as a white solid (0.015 g, 0.070 mmol, 22%) by flash chromatography on silica gel (1:1 hexanes/EtOAc): ^{1}H NMR ($CDCl_3$) δ 6.51 (s, 1 H), 3.05 (s, 3 H), 2.92 (s, 3 H), 2.74 (br t, J = 8.5 Hz, 1 H), 2.5–1.5 (m, 6 H), 0.9 (d, J = 6.77 Hz, 3 H), 0.834 (d, J = 6.77 Hz, 3 H), 0.762 (d, J = 6.52 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.77, 85.74, 42.30, 40.91, 35.92, 34.03, 32.17, 29.60, 26.35, 16.36, 16.18, 15.72; IR ($CHCl_3$) 3350 (br), 3000 (w), 2950 (s), 2870 (m), 2800 (m), 1620 (s), 1480 (m), 1450 (s), 1400 (s), 1390 (s), 1250 (w), 1140 (m), 980 (s) cm^{-1}; exact mass calcd for $C_{12}H_{23}NO_2$ 213.1728, found 213.1718.

Cyclization of Ethyl 2-Acetyl-2-methyl-5-oxopentanoate (18a). The following general procedure was utilized for SmI_2-promoted pinacolic coupling reactions of β-keto esters and β-keto amides. Samarium diiodide (2.0 mL) was prepared in 10 mL of THF according to the general procedure described in the supplementary material. The SmI_2 mixture was cooled to −78 °C, and a solution of **18a** (0.200 g, 1.00 mmol) and MeOH (2 equiv) in 10.0 mL of dry THF was added dropwise. The resulting solution was stirred at −78 °C for 1–2 h and then slowly warmed to room temperature before quenching with saturated $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with saturated NaCl, dried (Na_2SO_4), filtered, and concentrated in vacuo to provide ethyl (1*R**,2*S**,3*R**)-2,3-dihydroxy-1,2-dimethylcyclopentanecarboxylate (**19a**) as a 200:1 mixture of diastereomers. The product was isolated as a clear colorless liquid (0.154 g, 0.77 mmol, 77%) by flash chromatography on silica gel (2:1 EtOAc/hexanes): ^{1}H NMR ($CDCl_3$) δ 4.1 (q, J = 7.01 Hz, 2 H), 2.5 (br s, 2 H), 2.2–2.0 (m, 2 H), 1.9–1.8 (m, 1 H), 1.7–1.55 (m, 2 H), 1.28 (s, 3 H), 1.3 (t, J = 7.01 Hz, 3 H), 1.11 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.00, 78.49, 76.82, 59.18, 53.51, 30.65, 28.27, 20.64, 17.33, 12.70; IR ($CHCl_3$) 3620 (br), 3560 (br), 3000 (m), 2980 (s), 2900 (m), 2810 (w), 1710 (s), 1450 (s), 1400 (s), 1285 (s), 1250

(s), 1110 (s), 1050 (s), 950 (m) cm^{-1}; exact mass calcd for $C_{10}H_{17}O_4$ (M − 1) 201.1127, found 201.1120.

Cyclization of Ethyl 2-Methyl-3-oxo-2-(3-oxopropyl)pentanoate (18b). Following the general procedure outlined above, **18b** (0.0673 g, 0.314 mmol) was treated with SmI_2 (0.6282 mmol) in 7.0 mL of THF to provide ethyl (1*R**,2*S**,3*R**)-2-ethyl-2,3-dihydroxy-1-methylcyclopentanecarboxylate (**19b**) as a 120:1 mixture of diastereomers. The product was isolated as a white solid (0.0617 g, 0.285 mmol, 90%, mp 65 °C) by Kugelrohr distillation: bp 95–100 °C; ^1H NMR ($CDCl_3$) δ 4.15 (q, *J* = 7.01 Hz, 2 H), 2.76 (br s, 1 H), 2.4–2.25 (m, 1 H), 2.2–2.05 (m, 3 H), 2.0–1.4 (m, 4 H), 1.24 (t, *J* = 7.01 Hz, 3 H), 1.29 (s, 3 H), 0.946 (t, *J* = 7.01 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.06, 79.58, 75.58, 59.10, 54.52, 31.22, 29.12, 26.94, 17.93, 12.70, 6.38; IR ($CHCl_3$) 3600, 3500 (br), 2970 (s), 2900 (m), 2850 (w), 1700 (s), 1450 (m), 1360 (m), 1220 (s), 1180 (s), 1100 (m), 1020 (m), 990 (m) cm^{-1}. The structure was confirmed by X-ray diffractometry.

Cyclization of Ethyl 2,4-Dimethyl-3-oxo-2-(3-oxopropyl)pentanoate (18c). Following the general procedure outlined above, **18c** (0.1638 g, 0.7175 mmol) was treated with SmI_2 (1.430 mmol) in 20 mL of THF to provide ethyl (1*R**,2*S**,3*R**)-2,3-dihydroxy-1-methyl-2-isopropylcyclopentanecarboxylate (**19c**) as a 35:1 mixture of diastereomers. The product was isolated as a clear colorless liquid (0.111 g, 0.717 mmol, 67%) by flash chromatography on silica gel (1:1 hexanes/EtOAc): ^1H NMR ($CDCl_3$) δ 4.1 (q, *J* = 7.01 Hz, 2 H), 2.65 (br s, 1 H), 2.47–2.32 (m, 1 H), 2.30–2.0 (m, 3 H), 1.9–1.45 (m, 3 H), 1.32 (s, 3 H), 1.25 (t, *J* = 7.25 Hz, 3 H), 1.17 (d, *J* = 1.55 Hz, 3 H), 0.96 (d, *J* = 1.69 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.13, 76.19, 59.04, 51.25, 33.88, 32.93, 30.52, 28.27, 18.76, 16.95, 16.46, 12.64; IR ($CHCl_3$) 3500 (br), 2960 (s), 2910 (s), 2870 (s), 2800 (w), 1710 (s), 1460 (s), 1390 (s), 1250 (s), 1100 (s), 1050 (s), 960 (m), 840 (m) cm^{-1}; exact mass calcd for $C_{12}H_{22}O_4$ 230.1518, found 230.1538.

Cyclization of Ethyl 2-Benzoyl-2-methyl-5-oxopentanoate (18d). Following the general procedure outlined above, **18d** (0.1159 g, 0.4422 mmol) was treated with SmI_2 (0.8932 mmol) in 10.0 mL of THF to provide ethyl (1*R**,2*S**,3*R**)-2,3-dihydroxy-1-methyl-2-phenylcyclopentanecarboxylate (**19d**) as a 200:1 mixture of diastereomers. The product was isolated as a pale yellow liquid (0.0771 g, 0.292 mmol, 66%) by flash chromatography on silica gel (1:1 hexanes/EtOAc): ^1H NMR ($CDCl_3$) δ 7.32–7.15 (m, 5 H), 5.1–4.8 (m, 1 H), 3.44 (q, *J* = 7.25 Hz, 2 H), 3.01 (s, 1 H), 2.35–2.0 (m, 2 H), 1.95–1.75 (m, 1 H), 1.7–1.5 (m, 2 H), 1.21 (s, 3 H), 0.80 (t, *J* = 7.25 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.62, 139.49, 126.92, 125.92, 124.86, 81.77, 74.67, 58.91, 56.12, 31.77, 27.78, 16.24, 12.05; IR ($CHCl_3$) 3600 (br), 3510 (br), 3000 (s), 2030 (s), 2800 (m), 1700 (s), 1460 (m), 1330 (s), 1250 (w), 1190 (s), 1110 (s), 1025 (s) cm^{-1}; exact mass calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1365.

Cyclization of Ethyl 2-Acetyl-2-ethyl-5-oxopentanoate (18e). Following the general procedure outlined above, **18e** (0.1133 g, 0.5286 mmol) was treated with SmI_2 (1.0594 mmol) in 12.0 mL of THF to provide ethyl (1*R**,2*S**,3*R**)-1-ethyl-2,3-dihydroxy-2-methylcyclopentanecarboxylate (**19e**) as a 120:1 mixture of diastereomers. The product was isolated as a pale yellow liquid (0.0856 g, 0.396 mmol, 75%) by flash chromatography on silica gel (2:1 EtOAc/hexanes): ^1H NMR ($CDCl_3$) δ 4.1 (q, *J* = 6.29 Hz, 2 H), 3.9–3.8 (m, 1 H), 2.95 (d, *J* = 5.07 Hz, 1 H), 2.79 (br s, 1 H), 2.25–1.5 (m, 6 H), 1.25 (t, *J* = 7.01 Hz, 3 H), 1.09 (s, 3 H), 0.74 (t, *J* = 7.25 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.03, 78.65, 76.70, 58.93, 58.31, 27.78, 26.64, 23.04, 21.20, 12.64, 7.79; IR ($CHCl_3$) 3600, 3500 (br), 3000 (m), 2950 (s), 2900 (m), 2820 (w), 1710 (s), 1470 (s), 1400 (s), 1240 (s), 1340 (m), 1300 (s), 1080 (m), 1020 (m), 940 (m) cm^{-1}; exact mass calcd for $C_{11}H_{20}O_4$ 216.1362, found 216.1362.

Cyclization of Ethyl 2-Acetyl-2-methyl-6-oxohexanoate (18f). Following the general procedure outlined above, **18f** (0.1358 g, 0.6339 mmol) was treated with SmI_2 (1.3702 mmol) in 15.0 mL of THF to provide ethyl (1*R**,2*S**,3*R**)-2,3-dihydroxy-1,2-dimethylcyclohexanecarboxylate (**19f**) as a 3:1:<0.1 mixture of diastereomers. The product was isolated as a white solid (0.060 g, 0.28 mmol, 47%, mp 89–90 °C) by flash chromatography on silica gel (3:1 EtOAc/hexanes): ^1H NMR ($CDCl_3$) δ 4.3 (q, *J* = 7.01 Hz, 2 H), 4.1–4.0 (m, 1 H), 3.2 (br s, 1 H), 2.0–1.75 (m, 7 H), 1.35 (s, 3 H), 1.23 (t, *J* = 7.0 Hz, 3 H), 1.21 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.85, 72.31, 59.28, 49.05, 30.63, 27.62, 21.50, 18.30, 16.81, 12.89, 12.75; IR ($CHCl_3$) 3540 (br), 3000 (s), 2940 (s), 2830 (w), 1730 (m), 1700 (s), 1450 (s), 1400 (m), 1260 (s), 1140 (s), 1150 (s), 975 (m) cm^{-1}. The structure was confirmed by X-ray diffractometry.

Cyclization of Ethyl 2-Formyl-2-methyl-5-oxopentanoate (18g). Following the general procedure outlined above, **18g** (0.0341 g, 0.1832 mmol) was treated with SmI_2 (0.3664 mmol) in 4.0 mL of dry THF to provide ethyl (1*R**,2*S**,3*R**)-2,3-dihydroxy-1-methylcyclopentanecarboxylate (**19g**) as a 200:1 mixture of diastereomers. The product was isolated as a clear yellow oil (0.0160 g, 0.085 mmol, 46%) by flash chromatography on silica gel (1:1 hexanes/EtOAc): ^1H NMR ($CDCl_3$) δ 4.25–4.15 (m, 2 H), 4.1 (q, *J* = 7.01 Hz, 2 H), 2.78 (s, 1 H), 2.55 (s, 1 H), 2.07–1.9 (m, 2 H), 1.8–1.65 (m, 2 H), 1.31 (s, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.92, 76.5, 72.87, 60.70, 51.12, 32.65, 29.82, 18.56, 13.87; IR ($CHCl_3$) 3620 (w), 3555 (m), 2957 (s), 2905 (m), 2862 (m), 1713 (s), 1449 (m), 1302 (s), 1260 (s), 1118 (s), 1074 (s), 1025 (s) cm^{-1}; exact mass calcd for $C_9H_{16}O_4$ 189.1127, found 189.1127.

Cyclization of Ethyl 2-Formyl-2-methyl-5-oxohexanoate (18h). Following the general procedure outlined above, **18h** (0.0200 g, 0.099 mmol) was treated with SmI_2 in 4.0 mL of dry THF to provide ethyl (1*R**,2*S**,3*R**)-2,3-dihydroxy-1,3-dimethylcyclopentanecarboxylate (**19h**) as a 200:1 mixture of diastereomers. The product was isolated as a clear yellow oil (0.0096 g, 0.0475 mmol, 47%) by flash chromatography on silica gel (1:1 hexanes/EtOAc): ^1H NMR ($CDCl_3$) δ 4.17 (q, *J* = 7.13 Hz, 2 H), 3.99 (d, *J* = 6.16 Hz, 1 H), 2.55 (s, 1 H), 2.2–2.02 (m, 2 H), 1.9–1.65 (m, 3 H), 1.34 (s, 3 H), 1.3 (s, 3 H), 1.27 (t, *J* = 7.13 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.01, 81.08, 78.45, 60.86, 51.49, 36.07, 33.06, 26.99, 18.96, 14.10; IR ($CHCl_3$) 3560 (s), 3525 (s), 3000 (s), 2920 (s), 2800 (s), 1700 (s), 1450 (s), 1375 (s), 1260 (s), 1100 (s), 920 (s) cm^{-1}; exact mass calcd for $C_{10}H_{17}O_3$ (M − 17) 185.1178, found 185.1184.

Cyclization of Ethyl 2-Acetyl-2-methyl-5-oxohexanoate (18i). Samarium diiodide (1.969 mmol) in 10 mL of THF was prepared according to the general procedure described above. The solution was cooled to −78 °C, and a solution of **18i** (0.1405 g, 0.6560 mmol) and *t*-BuOH (2 equiv) in 10.0 mL of THF was added. The resulting mixture was stirred 2 h at −78 °C and then slowly warmed to room temperature while stirring overnight. The mixture was quenched with saturated $NaHCO_3$, the layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with saturated NaCl, dried (Na_2SO_4), filtered, and concentrated in vacuo to provide ethyl (1*R**,2*S**,3*R**)-2,3-dihydroxy-1,2,3-trimethylcyclopentanecarboxylate (**19i**) as a 3:1 mixture of diastereomers. The product was isolated as a white solid (0.0394 g, 0.1968 mmol, 30%) by flash chromatography on neutral alumina (activity III, 3:1 hexanes/EtOAc): ^1H NMR ($CDCl_3$) δ 4.17 (q, *J* = 7.01 Hz, 2 H), 2.68 (br s, 1 H), 2.6–2.38 (m, 1 H), 2.1–1.5 (m, 4 H), 1.38 (s, 3 H), 1.31 (s, 3 H), 1.2 (t, *J* = 7.25 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.92, 82.40, 82.20, 59.19, 55.38, 35.77, 31.19, 23.21, 21.29, 15.86, 12.76; IR ($CHCl_3$) 3600 (s), 3500 (s), 3000 (s), 2940 (s), 2850 (w), 1700 (s), 1460 (s), 1375 (s), 1260 (s), 1150 (m), 1050 (m), 950 (m) cm^{-1}; exact mass calcd for $C_{11}H_{20}O_4$ 216.1048, found 216.1055.

Cyclization of Methyl 2-Acetyl-5-oxopentanoate (18j). Following the general procedure described above, **18j** (0.087 g, 0.506 mmol) was treated with SmI_2 (1.0116 mmol) at −78 °C in 15 mL of THF to provide methyl (1*R**,2*S**,3*R**)-2,3-dihydroxy-2-methylcyclopentanecarboxylate (**19j**) (0.027 g, 0.15 mmol, 31%). Impure product was isolated by flash chromatography on silica gel (1:1 hexanes/EtOAc). The impurities could not be removed by further chromatographies: ^1H NMR ($CDCl_3$) δ 4.6 (s, 3 H), 3.1–2.8 (m, 2 H), 2.65 (m, 1 H), 2.1–1.6 (m, 4 H), 1.3–1.18 (m, 1 H), 1.15 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.8, 78.65, 65.4, 50.32, 52.00, 27.43, 22.00, 20.93; IR ($CHCl_3$) 3500 (br), 3000 (s), 2950 (m), 2900 (m), 1730 (s), 1450 (m), 1400 (s), 1280 (s), 1150 (m), 1110 (m), 1000 (m), 980 (w), 850 (w) cm^{-1}.

Cyclization of *N*,*N*-Diethyl-2-acetyl-5-oxopentanamide (18k). Following the general procedure outlined above, **18k** (0.070 g, 0.33 mmol) was treated with SmI_2 (0.3564 mmol) in 8.0 mL of THF to provide (1*R**,2*S**,3*R**)-*N*,*N*-diethyl-2,3-dihydroxy-2-methylcyclopentanecarboxamide (**19k**) as a 200:1 mixture of diastereomers. The product was isolated as a clear yellow liquid (0.0353 g, 0.164 mmol, 50%) by flash chromatography on neutral alumina (activity III, 1:1 hexanes/EtOAc): ^1H NMR ($CDCl_3$) δ 6.26 (s, 1 H), 3.8 (br d, *J* ≅ 5.0 Hz, 1 H), 3.5–3.15 (m, 4 H), 2.8 (t, *J* = 8.46 Hz, 1 H), 2.5–2.2 (m, 1 H), 2.05–1.8 (m, 2 H), 1.65–1.4 (m, 2 H) 1.24 (s, 3 H), 1.2–1.0 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 174.0, 80.90, 78.24, 43.30, 40.79, 38.87, 30.87, 25.43, 19.91, 13.47, 11.61; IR ($CHCl_3$) 3600, 3440 (br), 3000 (s), 2975 (s), 2880 (s), 2800 (m), 1610 (s), 1470 (m), 1450 (s), 1375 (m), 1250 (s), 1190 (s), 1080 (s), 990 (m) cm^{-1}; exact mass calcd for $C_{11}H_{21}NO_3$ 215.1521, found 215.1526.

Cyclization of *N*,*N*-Dimethyl-3-oxo-2-(3-oxopropyl)pentanamide (18l). Following the general procedure outlined above, **18l** (0.0922 g, 0.463 mmol) was treated with SmI_2 (0.900 mmol) in 10.0 mL of THF to provide (1*R**,2*S**,3*R**)-*N*,*N*-dimethyl-2-ethyl-2,3-dihydroxycyclopentanecarboxamide (**19l**) as a 120:1 mixture of diastereomers. The product was isolated as a pale yellow liquid (0.033 g, 0.16 mmol, 35%) by flash chromatography on silica gel (3:1 hexanes/EtOAc): ^1H NMR ($CDCl_3$) δ 5.96 (s, 1 H), 3.9 (br d, *J* ≅ 6.0 Hz, 1 H), 3.04 (s, 3 H), 2.93 (s, 3 H), 2.5–2.3 (m, 2 H), 2.05–1.8 (m, 3 H), 1.75 (br s, 1 H), 1.6 (q, *J* = 6.75 Hz, 2 H), 0.95 (t, *J* = 7.25 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.21, 83.41, 76.02, 42.83, 35.98, 33.88, 30.92, 25.96, 24.90, 6.89; IR ($CHCl_3$) 3400 (br), 3000 (s), 2890 (s), 2320 (w), 1610 (s), 1460 (s), 1440

(s), 1390 (s), 1250 (m), 1230 (s), 1130 (m), 970 (s) cm^{-1}; exact mass calcd for $C_{10}H_{19}NO_3$ 201.1365, found 201.1375.

Cyclization of *N*,*N*-Dimethyl-4-methyl-3-oxo-2-(3-oxopropyl)pentanamide (18m). Following the general procedure outlined above, **18m** (0.1293 g, 0.6093 mmol) was treated with SmI_2 (1.2235 mmol) in 15.0 mL of THF to provide (1*R**,2*S**,3*R**)-*N*,*N*-dimethyl-2,3-dihydroxy-2-isopropylcyclopentanecarboxamide (**19m**) as a 3:1 mixture of diastereomers. The product was isolated as a white solid (0.0572 g, 0.267 mmol, 44%) by flash chromatography on neutral alumina (activity III, 1:1 hexanes/EtOAc): ^1H NMR ($CDCl_3$) δ 6.55 (s, 1 H), 4.1–3.91 (m, 1 H), 3.04 (s, 3 H), 2.89 (s, 3 H), 2.5–2.05 (m, 2 H), 2.0–1.5 (m, 4 H), 1.3–1.1 (m, 1 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.75 (d, J = 7.01 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.27, 85.51, 76.90, 40.67, 35.80, 33.76, 30.72, 30.54, 25.90, 16.30, 15.63; IR ($CHCl_3$) 3500 (br), 2975 (s), 2900 (m), 2880 (m), 1610 (s), 1410 (m), 1380 (m), 1220 (s), 1130 (m), 950 (m) cm^{-1}; exact mass calcd for $C_{11}H_{21}NO_3$ 215.1521, found 215.1525.

Cyclization of 2-Acetyl-2-(3-oxopropyl)-γ-butyrolactone. Following the general procedure outlined above, the butyrolactone (0.1257 g, 0.6828 mmol) was treated with SmI_2 (1.3659 mmol) in 18.0 mL of THF to provide (5*R**,6*S**,7*R**)-6,7-dihydroxy-6-methyl-2-oxaspiro[4.4]nonan-1-one as a 200:1 mixture of diastereomers. The product was isolated as a light yellow solid (0.056 g, 0.30 mmol, 44%) by flash chromatography on silica gel (6:1 EtOAc/hexanes): ^1H NMR ($CDCl_3$) δ 4.23–4.15 (m, 3 H), 2.92 (br s, 1 H), 2.9–2.65 (m, 2 H), 2.4–1.5 (m, 5 H), 1.21 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.48, 76.94, 74.49, 63.86, 52.54, 29.21, 28.38, 26.73, 17.96; IR ($CHCl_3$) 3600, 3500 (br), 3000 (s), 2920 (m), 2800 (m), 1750 (s), 1450 (m), 1360 (m), 1250 (m), 1110 (s), 1050 (s), 980 (s) cm^{-1}; exact mass calcd for $C_9H_{14}O_4$ 186.0892, found 186.0888.

Cyclization of (4*S*)-3-[(2*S*)-2-Acetyl-5-oxopentanoyl]-4-isopropyloxazolidin-2-one (23). Following the general procedure outlined above, **23** (0.0866 g, 0.3217 mmol) was treated with SmI_2 in 6.0 mL of dry THF to provide chiral diol **24** as a single enantiomer. The product was isolated as a white solid (0.0452 g, 0.1667 mmol, 52%) by flash chromatography on silica gel (1:1 hexanes/EtOAc) followed by recrystallization in Et_2O: mp 157 °C; ^1H NMR ($CDCl_3$) δ 4.58–4.48 (m, 2 H), 4.45–4.2 (m, 2 H), 4.17–4.15 (m, 1 H), 3.7 (s, 1 H), 2.7 (s, 1 H), 2.4–2.3 (m, 1 H), 2.2–1.8 (m, 3 H), 1.7–1.6 (m, 1 H), 1.1 (s, 3 H), 0.95 (d, J = 7.5 Hz, 3 H), 0.90 (d, J = 7.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.20, 160.50, 81.60, 79.50, 64.08, 59.54, 50.11, 31.87, 29.60, 23.32, 22.93, 18.31, 14.89; IR ($CHCl_3$) 3600 (m), 3500 (br), 3030 (m), 2990 (m), 1760 (s), 1700 (s), 1640 (m), 1380 (s), 1240 (s), 1200 (s), 1100 (m), 1030 (m), 940 (w) cm^{-1}. The structure was confirmed by X-ray diffractometry.

Cyclization of Ethyl 2-Acetyl-2-methyl-5-cyanopentanoate (25a). Following the general procedure described above, **25a** (0.1013 g, 0.5135 mmol) was treated with SmI_2 (1.03 mmol) to provide ethyl (1*R**,2*R**)-2-hydroxy-1,2-dimethyl-3-oxocyclopentanecarboxylate (**26a**) as 120:1 mixture of diastereomers. The product was isolated as a clear colorless liquid (0.0278 g, 0.139 mmol, 30%) by flash chromatography on silica gel (9:1 hexanes/EtOAc): ^1H NMR ($CDCl_3$) δ 4.2 (q, J = 7.25 Hz, 2 H), 3.0 (br s, 1 H), 2.6–1.4 (m, 4 H), 2.37 (s, 3 H), 1.2 (t, J = 7.01 Hz, 3 H), 1.16 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 215.67, 173.73, 79.30, 59.69, 50.68, 30.25, 27.74, 17.93, 16.04, 12.55; exact mass calcd for $C_{10}H_{16}O_4$ 200.1048, found 200.1055.

Cyclization of *N*,*N*-Diethyl-2-acetyl-5-cyanopentanamide (25b). Samarium diiodide (1.223 mmol) in 10 mL of THF was prepared according to the general procedure described in the supplementary material. The solution was cooled to −78 °C, and a solution of **25b** (0.1274 g, 0.6059 mmol) and *t*-BuOH (2 equiv) in 10.0 mL of dry THF was added. The resulting mixture was stirred at −78 °C for 2 h and then slowly warmed to room temperature while stirring overnight. The mixture was quenched with saturated $NaHCO_3$, the layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with saturated NaCl, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel (100% EtOAc) to provide (1*R**,2*R**)-*N*,*N*-diethyl-2-hydroxy-2-methyl-3-oxocyclopentanecarboxamide (**26b**) as a 200:1 mixture of diastereomers (0.0582 g, 0.2726 mmol, 45%): ^1H NMR ($CDCl_3$) δ 4.86 (s, 1 H), 3.4 (br q, J = 7.2 Hz, 4 H), 2.9 (br t, 1 H), 2.6–1.9 (m, 4 H), 1.21 (s, 3 H), 1.0 (br t, J = 7.25 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 213.16, 171.78, 76.23, 45.34, 40.70, 38.84, 30.87, 20.70, 19.79, 13.20, 11.43; IR ($CHCl_3$) 2985 (s), 2900 (m), 2840 (w), 1750 (s), 1610 (s), 1470 (m), 1450 (s), 1400 (m), 1360 (m), 1250 (s), 1140 (s), 1050 (s), 950 (m) cm^{-1}.

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Supplementary Material Available: Preparation of starting materials, general procedure for preparation of SmI_2, other attempted cyclization reactions and X-ray crystallographic structural data for those compounds whose structures were determined by X-ray diffractometry (**4**, **19b**, **19f**, **20**, **24**) (39 pages). Ordering information is given on any current masthead page.