Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.36; H, 11.75.

Acknowledgment. J.R.A. and D.G.K. thank CSIR, India, for fellowship; the authors appreciate Prof. M. S. Wadia's (Poona University) stimulating discussions.

Registry No. (±)-**1a**, 131131-42-5; (±)-**1b**, 131131-44-7; (±)-**1b** (acid precursor), 131131-59-4; (±)-**1c**, 131131-46-9; (±)-**1c** (acid precursor), 131131-61-8; (±)-**1d**, 131131-47-0; (±)-**1d** (acid precursor), 131131-63-0; (±)-**2a**, 131131-50-5; (±)-**2a** (acid precursor), 85506-67-8; (±)-**2b**, 131131-52-7; (±)-**2b** (acid precursor), 131131-58-3; (±)-**2c**, 131131-54-9; (±)-**2c** (acid precursor), 131131-60-7; (±)-**2d**, 131131-55-0; (±)-**2d** (acid precursor), 131131-62-9; (+)-**3a**, 131232-88-7; (±)-**3a**, 131131-43-6; (±)-**3b**, 131131-45-8; (±)-**3b** enone, 131131-64-1; (±)-**3c**, 131232-81-0; (±)-**3c** enone, 131131-65-2; (±)-**3d** (isomer 1), 131131-48-1; (±)-3d (isomer 2), 131131-49-2; (±)-**4a**, 131131-51-6; (±)-**4a′**, 131232-82-1; (±)-**4a′** enone, 131232-86-5; (±)-**4b**, 131232-83-2; (±)-**4b′**, 131131-53-8; (±)-4c, 131232-84-3; (±)-4c enone, 13232-87-6; (±)-4d (isomer 1), 131131-56-1; (±)-**4d** (isomer 2), 131131-57-2; (+)-**5**, 67518-96-1; (±)-**5**, 67519-00-0; (+)-**6**, 13232-77-4; (±)-**6**, 131232-85-4; (+)-**7**, 66701-34-6; (+)-7 enone, 131232-89-8; (+)-7 tosylhydrazone, 131232-90-1; (+)-7 oxime, 131232-91-2; (+)-**8**, 131232-78-5; (−)-**9**, 131232-79-6; (−)-**10**, 131232-80-9; (−)-**11**, 511-59-1.

Supplementary Material Available: NMR spectra of the homologated acids, (+)-albene and (−)-β-santalene and mass spectra of the homologated acids (17 pages). Ordering information is given on any current masthead page.

Sequential Radical Cyclization/Intermolecular Carbonyl Addition Reactions Initiated by Samarium(II) Iodide

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A sequential reductive coupling process promoted by samarium(II) iodide (SmI_2) is described. Thus, ethyl 2-acetyl-2-methyl-5-hexenoate, upon treatment with SmI_2 in the presence of a variety of aldehydes or ketones, undergoes an initial radical (ketyl) olefin cyclization. Subsequent reduction of the intermediate radical generated in this process produces a transient organosamarium species which can be trapped in situ by the added aldehyde or ketone electrophiles. Through this sequential radical cyclization/intermolecular carbonyl addition reaction, two new carbon–carbon bonds are generated in a one-pot process. Furthermore, a high degree of stereochemical control is established over three contiguous stereocenters, markedly increasing molecular complexity from the starting materials to the observed products.

Samarium(II) iodide (SmI_2) is an exceptional reagent for promoting intramolecular reductive cyclization reactions.[2] This reagent has been utilized in a variety of such processes, including ketone–olefin[3] and pinacolic coupling reactions.[3a] Intramolecular variants of these transformations proceed smoothly to provide densely functionalized carbocycles in many cases. In earlier studies, excellent stereoselectivity was achieved at up to three contiguous stereocenters,[3a] and products were generally obtained in good yields utilizing standard purification techniques.

The mechanism of the intramolecular ketone–olefin reductive coupling reaction was postulated to proceed via chelation-controlled ketyl addition to an unsaturated substituent, generating a cyclized radical intermediate.[3a] Intermolecular reduction of the cyclized radical intermediate by a second equivalent of SmI_2 led to formation of a transient organosamarium intermediate. The sequence was terminated by protonation of the organometallic utilizing an in situ proton source (MeOH or *t*-BuOH) (Scheme I, path A). Use of MeOD provided >95% deuterium incorporation at the methyl group in the final product and confirmed the existence of an intermediate organosamarium species.[3a] Based on the proposed mechanism, intermolecular entrapment of this organometallic with a variety of electrophiles was envisioned as a useful extension of the methodology (Scheme I, path B). The proposed sequential reaction process (radical cyclization/organometallic coupling) would place additional functionality in the cyclized products, thereby further in-

Table I. Sequential Radical Cyclization/Carbanion Carbonyl Addition Reactions Promoted by SmI_2 Utilizing Ethyl 2-Acetyl-2-methyl-5-hexenoate (1) as a Substrate

entry	carbonyl electrophile	product	% isolated yield[a]	diastereomeric ratio[b]
1	acetone	**2a**	79	31:1
2	3-pentanone	**2b**	73	65:1
3	diisopropyl ketone	**2c**	32	>200:1
4	cyclohexanone	**2d**	58	200:1
5	cyclopentanone	**2e**	65	60:1
6	2-methylcyclohexanone	**2f**	75	1:1
7	4-*tert*-butylcyclohexanone	**2g**	61	10:1
8	5-chloro-2-pentanone	**2h**	65	1:1
9	5-(diethylamino)-2-pentanone	**2i**	33	1:1
10	butanal	**2j**	55	17:17:1:1
11	isobutyraldehyde	**2k**	56	30:15:1:1
12	pivalaldehyde	**2l**	35	2:1
13	benzaldehyde	**2m**	0	–

[a] Refers to yields of purified material. All of these compounds have been fully characterized spectroscopically (^1H NMR, ^{13}C NMR, IR) and elemental composition has been established by high-resolution mass spectrometry and/or combustion analysis. [b] Determined on crude reaction mixture.

(1) Alfred P. Sloan Foundation Fellow, 1987–1991, American Cyanamid Academic Awardee, 1989.

(2) Molander, G. A. In *Chemistry of the Metal–Carbon Bond*; Hartley, F. R., Patai, S., Eds; Wiley: New York, 1989 and references therein.

(3) (a) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236. (b) Fevig, T. L.; Elliott, R. L.; Curran, D. P. *Ibid.* **1988**, *110*, 5064. (c) Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1989**, *30*, 1063. (d) Enholm, E. J.; Satici, H.; Trivellas, A. *J. Org. Chem.* **1989**, *54*, 5841. (e) Enholm, E. J.; Trivellas, A. *J. Am. Chem. Soc.* **1989**, *111*, 6463.

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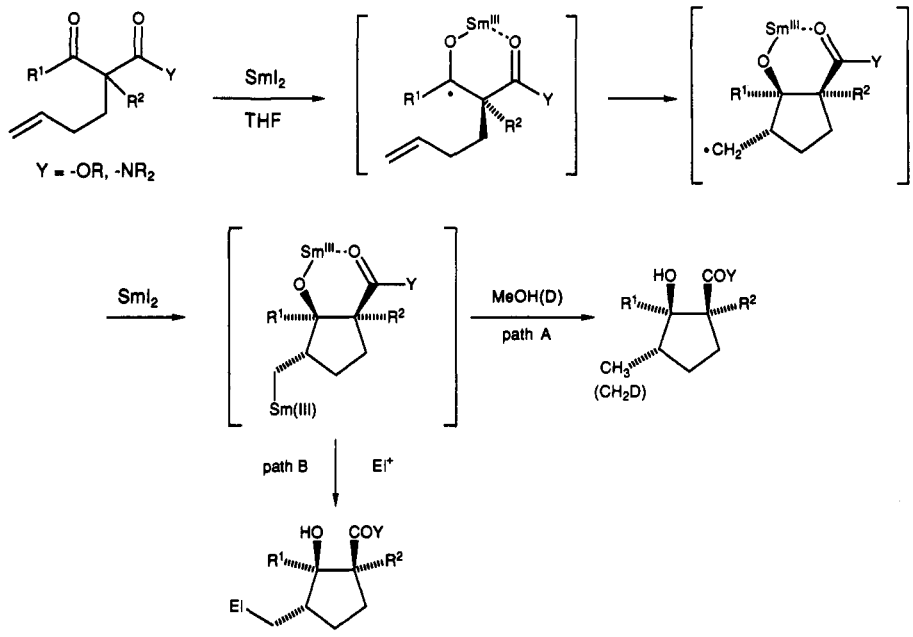
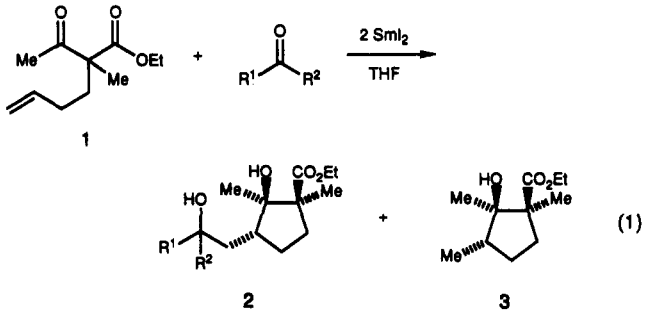
Scheme I



creasing the level of molecular complexity embodied in the overall transformation. Herein we document the realization of this process, whereby ketones and aldehydes serve as terminating electrophiles for this two-step sequential reaction.[4]

Results and Discussion

Unsaturated β-Keto Ester Substrates. Initial studies were carried out by treating β-keto ester 1 with 2.1–2.2 equiv of SmI_2 in tetrahydrofuran (THF) in the presence of a variety of aldehydes and ketones (eq 1). As revealed



1

2 3 (1)

in Table I, these studies proved extremely fruitful. Highest yields of the desired products were achieved by adding a THF solution of the β-keto ester and 1.0–1.5 equiv of the carbonyl substrate to a solution of SmI_2 in THF at −30 °C. The resulting mixtures were stirred for 2 h at −30 °C. In some cases, it was necessary to warm the reaction mixtures to room temperature and then stir for several additional hours before the reaction was complete. The reaction mixtures were subsequently quenched with saturated aqueous $NaHCO_3$. A simple extractive workup, followed by flash chromatography and/or Kugelrohr distillation, provided the desired products (**2a–l**).

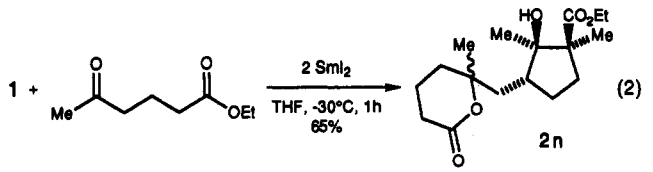
For this sequential transformation, the organosamarium intermediates could not be trapped by simply quenching the reaction mixture with an electrophile after completion of the cyclization process. Attempts to quench the reaction mixture at −30 °C with acetone did not generate the desired product in significant yields. The major product in this case was the untrapped cyclic compound (**3**), but there were also numerous other byproducts. Simply quenching the reaction mixture with MeOH was also attempted, but again the desired protonated product could not be isolated in significant yields. Apparently, it is critical that the electrophile be present in situ during the entire reaction sequence in order to trap the reactive organometallic intermediate. Therefore, any potential electrophiles must be stable to the reduction conditions. This explains the modest yields obtained utilizing aldehydes as the electrophiles (entries 10–13). Presumably, competitive reduction of the aldehyde by SmI_2 depletes the electrophile source. In particular, treatment of 1 with SmI_2 in the presence of benzaldehyde (readily reduced by SmI_2[5]) did not provide any of the desired product; the β-keto ester starting material was recovered intact, and all of the SmI_2 had reacted with the benzaldehyde. Nevertheless, the selectivity demonstrated by SmI_2 in the initial reduction is still rather striking in most cases. It is clear that the electron-withdrawing effect of the carboxylate, along with a chelation effect inherent in this β-dicarbonyl system, combine to insure facile reduction of the ketone in the unsaturated β-keto ester in preference to isolated ketones and even most aldehydes.

A number of other functional groups can be tolerated in the reaction. For example, alkyl chlorides are readily accommodated (entry 8), as well as carboxylic acid esters (eq 2). The single amino ketone utilized as an electrophilic substrate also furnished the desired product (entry 9), although in modest yield.

The efficiency of the process was determined to be highly dependent on steric effects of the added carbonyl substrates. Sterically hindered electrophiles provided

(4) Similar processes of this nature utilizing unsaturated organic halides as the radical precursor and aldehydes or ketones as the terminating electrophiles have been described previously. These reactions were promoted by $CrCl_2$ in conjunction with cobalt catalysts [(a) Takai, K.; Nitta, K.; Fujimura, O.; Utimoto, K. *J. Org. Chem.* **1989**, *54*, 4732] as well as by SmI_2 [(b) Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron* **1981**, *37*, 175, Supplement No. 1. (c) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1990**, *55*, 6171]. Samarium(II) iodide has also been utilized as the reducing agent in related conversions using acyl halide precursors [(d) Saski, M.; Collin, J.; Kagan, H. B. *Tetrahedron Lett.* **1988**, *29*, 6105].

(5) Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet. Chem.* **1983**, *250*, 227.



products in significantly diminished yields (entries 3 and 12). This perhaps explains why little, if any, self-condensation occurs in the carbonyl addition component of the process. The ketone carbonyl of the β-keto ester substrate must be considered as a reasonably hindered electrophile, and thus it is reluctant to undergo attack by the organosamarium intermediate generated in the cyclization reaction.

The major byproduct encountered in the reactions was the cyclic untrapped material (**3**). Generally, 5–12% of **3** could be detected in the crude reaction mixtures. Fortunately, **2** and **3** were trivial to separate by flash chromatography. Performing the reaction with larger excesses of the carbonyl electrophile (3–5 equiv) did not improve the ratio of **2** to **3**. In fact, in most cases addition of more than 2 equiv of ketone in the reaction mixtures was detrimental and the amount of **3** actually increased.

There are several pathways by which **3** could be generated. The cyclized organosamarium intermediate may be basic enough to enolize the carbonyl electrophile at rates competitive to nucleophilic addition, thus generating the cyclized uptrapped material and the corresponding samarium enolate of the ketone. This possibility was explored by treating **1** with SmI_2 in the presence of acetone-d_6 under the standard reaction conditions. The cyclized uptrapped material (**3**) was isolated by flash chromatography and had no deuterium incorporated at the C-3 methyl group within the limits of detection of ^{13}C NMR and GC/MS analyses. Thus it seems unlikely that the electrophiles are becoming enolized under the reaction conditions.

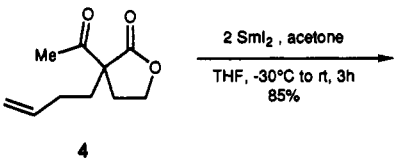
The cyclized untrapped product may also arise simply by quenching of the carbanion intermediate with adventitious water which was not removed during the drying procedures for the carbonyl electrophile. The final possibility is that the cyclic radical species abstracted a hydrogen atom from THF. The rate of hydrogen atom abstraction from THF by alkyl radicals is 6×10^3 mol^{-1} s^{-1}.[6] The rate of the second intermolecular reduction of the cyclized radical intermediate leading to the organosamarium species has not been accurately determined but has been estimated at 2×10^4 mol^{-1} s^{-1}.[7] Given the uncertainty of the latter rate, it is not entirely clear whether hydrogen abstraction or adventitious water is responsible for the presence of the byproduct which has simply been protonated.

The relative stereochemistry between the carboxylate group and the hydroxyl group on the cyclopentane ring was expected to be cis, and the third substituent trans relative to these two functional groups. This assumption was based on the stereochemical results elucidated previously for cyclization of unsaturated 1,3-dicarbonyl compounds.[3a] Compounds **2f** formed crystals suitable for single-crystal X-ray analysis, and the stereochemistry of this compound was proven to be as speculated.

Infrared data for all of the products reinforce the stereochemical assignments. Both the hydroxyl and carbonyl stretching frequencies of the products are lowered due to intramolecular hydrogen bonding between the cis hydroxyl and carboxylate groups.[3a,8] The carbonyl stretching frequencies, measured in dilute solution by FT-IR, appear to be the most diagnostic. Products consistently have carbonyl absorption peaks in the range in 1685–1696 cm^{-1}, characteristic of *cis*-2-hydroxycyclopentanecarboxylates. Structurally related trans diastereomers typically absorb at 1700–1725 cm^{-1}.[3a] The hydroxyl absorption frequencies for the cis compounds show a broader range but are typically observed between 3374 and 3500 cm^{-1}, while for related trans diastereomers values of 3500–3570 cm^{-1} are commonly observed.[3a]

Mixtures of diastereomers were generated with chiral ketones (entry 6), prochiral ketones (entries 7–9), and aldehydes (entries 10–12), presumably as a result of the fourth stereogenic center created in the process. Although the relative stereochemistry of these products was not rigorously assigned, it is reasonable to assume that the relative stereogenicity of the three stereocenters about the ring of the cyclopentanecarboxylate correlate with the relative stereochemistry of the products trapped with symmetrical ketones, while the stereochemistry of the exocyclic stereocenter is not controlled in the process and thus leads to the observed mixture of diasteromers.

In addition to acyclic carbonyl electrophiles, ketone substrates were examined that led to spirocyclic and bicyclic products. The three substrates investigated (eqs 3–4) reacted extremely well, and the crude reaction mixtures were very clean. In each case a single diastereomer was generated in great excess as determined by GC/MS analysis of crude reaction mixtures, and the isolated yields of the trapped products in all three cases were high. Relatively small amounts (<5%) of the cyclized untrapped products were observed.



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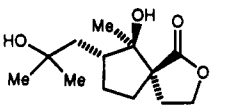
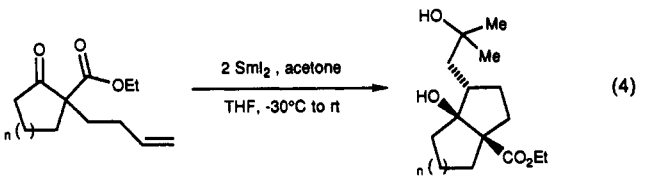


11 : 1

5



6, n = 1
8, n = 2

7, n = 1 (66%)
9, n = 2 (75%)

Compound **5** was a crystalline solid, and the stereochemistry was confirmed by X-ray diffractometry. Though the stereochemistry was not rigorously assigned for products **7** or **9**, the cis relative stereochemistry of the bicyclic hydroxyl and carboxylate groups seems plausible based upon the results described above and previous investigations.[3a] The IR absorption frequencies of the carbonyl

(6) (a) Newcomb, M.; Kaplan, J. *Tetrahedron Lett.* **1988**, *29*, 3449. (b) Curran, D. P. *Synthesis* **1988**, 489.

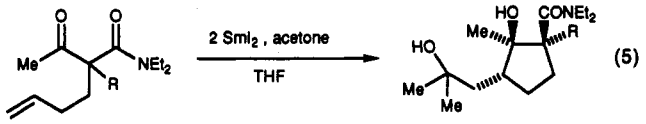
(7) (a) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485. (b) Ujikawa, O.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2837.

(8) (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.

stretches for compounds **7** and **9** (1698.2 and 1688.8 cm^{-1}, respectively) followed the same patterns as outlined earlier and are indicative of strong intramolecular hydrogen bonding between the cis hydroxyl and carboxylate groups.[3a,8]

β-Keto Amide Cyclizations. Results from previous studies indicated that SmI_2-mediated reductive cyclization of unsaturated β-keto amide substrates were more troublesome than the corresponding β-keto esters.[3a] Though the yields of the hydroxycycloalkanecarboxamide products were somewhat depressed, the diastereoselectivity was outstanding for the majority of examples.

To examine the sequential process with these substrates, β-keto amide **10** was treated with SmI_2 in the presence of acetone at −78 °C (eq 5). The crude reaction mixture was



(5)

10, R = H
12, R = Me

11, R = H (46%)
13, R = Me (46%)

considerably more complex than corresponding B-keto ester reaction mixtures. The product (**11**) was isolated in pure form after several flash chromatographies; however, the yield suffered greatly. The product proved to be somewhat sensitive to chromatography, and there was significant loss of material after each successive pass through the column. Although it was isolated in modest yield, the product was generated as a single diastereomer as determined by analysis of the crude reaction mixture.

Enolization of the α-monosubstituted β-keto amide substrate under the reaction conditions was considered as one possible reason for the disappointing yields with this series of compounds. To alleviate this potential problem, methylation of the α-position of **10** was undertaken to provide a substrate (**12**) incapable of enolization. Unfortunately, treatment of **12** under the same reaction conditions as described for **10** led to the desired product in the same moderate yield. The reaction again proceeded with complete diastereoselectivity, providing **13** as a single diastereomer (eq 5).

Conclusions

The advantages of SmI_2-promoted sequential reductive cyclization/intermolecular carbonyl addition reactions are evident from the brief survey described. The primary goal of outlining a stereoselective and regioselective cyclization reaction followed by intermolecular addition to the added electrophilic substrate was successfully achieved. Utilizing the very simple protocol described herein, generation of complex carbocycles through two consecutive carbon–carbon bond forming reactions is possible. In addition, a considerable increase in molecular complexity is engendered: control of relative stereochemistry at three contiguous stereocenters can be achieved in the sequential process. Starting materials for the reaction were readily prepared by simple alkylation procedures,[3a] and crude reaction mixtures were very clean in most cases. Isolation of the desired products was achieved utilizing standard procedures.

The list of electrophiles which might be suited for this reaction pathway is fairly extensive and has yet to be fully explored. Further investigation will be required to outline the reactivity patterns and the reaction conditions necessary to provide a wider variety of suitable electrophiles and expand the nucleophilic addition segment of the tandem reaction process.

Although the use of sequential reactions is still in its infancy in organic chemistry, the SmI_2-promoted process demonstrated herein lays the groundwork for still further consecutive reactions utilizing SmI_2 as well as other reductive coupling agents.

Experimental Section

^1H NMR spectra were recorded at 200 or 300 MHz. ^{13}C NMR spectra were recorded at 50 or 75 MHz. Capillary GC analyses were performed on a 25 m × 320 μm 5% phenyl SE-54 fused silica capillary column. Low-resolution and exact mass spectra were recorded utilizing perfluorokerosene as internal standard. Standard flash chromatography procedures were followed.[9]

Reagents. Tetrahydrofuran (THF) was distilled immediately prior to use from benzophenone ketyl under argon. Ketone and aldehyde electrophiles were distilled prior to use. 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,[10] and all reactions were carried out under an argon atmosphere.

General Procedure for Preparation of SmI_2. Samarium metal (0.15 g, 1.0 mmol) was added under a flow of argon to an oven-dried round-bottom flask containing a magnetic stirring bar and a septum inlet. The flask and samarium were flame-dried and cooled under an argon atmosphere. THF (10 mL) was added. The slurry of samarium metal in THF was cooled to 0 °C, and CH_2I_2 (0.228 g, 0.85 mmol) was added neat. The resulting green solution was stirred at 0 °C for 15 min, allowed to warm to room temperature, and stirred for an additional 1 h. The resulting SmI_2 solution was a deep blue-green.

Ethyl (1*R,2*S**,3*S**)-2-Hydroxy-3-(2-hydroxy-2-methylprop-1-yl)-1,2-dimethylcyclopentanecarboxylate (2a).** The following describes the general procedure utilized for the cyclization/intermolecular carbonyl addition reactions. Samarium(II) iodide (0.150 g, 1.00 mmol) was prepared as described above in 10.0 mL of dry THF. The SmI_2 solution was cooled to −30 °C, and to it was added a solution of **1** (0.802 g, 0.405 mmol) and dry acetone (0.282 g, 0.486 mmol) in 10.0 mL of THF. The resulting reaction mixture was slowly warmed to room temperature over 2–3 h and then quenched with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to provide (**2a**) as a 31:1 mixture of diastereomers. The product was isolated as a clear colorless liquid (0.083 g, 0.32 mmol, 79%) by flash chromatography on silica gel (3:1 hexanes–EtOAc) followed by Kugelrohr distillation (90 °C at 0.1 mmHg): ^1H NMR ($CDCl_3$) δ 4.99 (br s, 1 H), 4.16 (q, J = 7.5 Hz, 2 H), 3.88 (br s, 1 H), 2.40–2.20 (m, 2 H), 1.85–1.71 (m, 2 H), 1.47–1.35 (m, 2 H), 1.25 (t, J = 7.5 Hz, 3 H), 1.23–1.10 (m, 1 H), 1.19 (s, 3 H), 1.18 (s, 3 H), 1.17 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.36, 81.45, 70.04, 61.10, 54.36, 43.68, 43.17, 31.70, 31.11, 28.47, 27.13, 19.34, 16.97, 14.01; IR ($CHCl_3$) 3583.9 (w), 3384.9 (br), 2976.8 (s), 2927.1 (m), 2877.2 (w), 1692.3 (s), 1602.7 (w), 1468.3 (m), 1398.7 (m), 1373.8 (m), 1294.2 (m), 1284.2 (m), 1179.7 (m), 1144.9 (s), 1085.2 (m), 1015.0 (m), 965.8 (w), 935.9 (m) cm^{-1}; exact mass calcd for $C_{14}H_{24}O_3$ (M − 18) 240.1725, found 240.1723.

The following reactions were carried out according to the preceding procedures. The reactants, time, and temperature are given first in abbreviated format.

Ethyl (1*R,2*S**,3*S**)-3-(2-Ethyl-2-hydroxybut-1-yl)-2-hydroxy-1,2-dimethylcyclopentanecarboxylate (2b).** **1** (0.0723 g, 0.365 mmol), 3-pentanone (0.028 g, 0.33 mmol), SmI_2 (0.8192 mmol), 4 h, 25 °C. Ester **2b** was isolated as a clear colorless liquid (0.0762 g, 0.266 mmol, 73%) by flash chromatography on silica gel (3:1 hexanes–EtOAc). Capillary GLC analysis of the crude reaction mixture indicated the product was formed as a 65:1 mixture of diastereomers: ^1H NMR ($CDCl_3$) δ 4.92 (br s, 1 H), 4.23–4.14 (m, 2 H), 3.60 (br s, 1 H), 2.40–2.32 (m, 1 H), 2.28–2.15

(9) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(10) Brown, H. C. *Organic Syntheses via Boranes*: Wiley: New York, 1975.

(m, 1 H), 1.85–1.75 (m, 1 H), 1.70–1.60 (m, 1 H), 1.55–1.35 (m, 6 H), 1.27 (t, J = 7.0 Hz, 3 H), 1.21 (s, 3 H), 1.20–1.12 (m, 1 H), 1.08 (s, 3 H), 0.85 (t, J = 7.4 Hz, 3 H), 0.76 (t, J = 7.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.31, 81.42, 74.00, 61.08, 54.41, 42.30, 38.61, 31.74, 31.62, 30.29, 27.30, 19.41, 17.11, 14.04, 8.44, 7.79; IR ($CHCl_3$) 3600.9 (w), 3405.8 (br), 2976.5 (s), 2937.5 (s), 2869.2 (w), 1688.3 (s), 1459.0 (s), 1376.1 (m), 1293.2 (s), 1171.2 (m), 1141.9 (s), 1088.3 (m), 1020.0 (w), 966.3 (w), 907.8 (w) cm^{-1}; exact mass calcd for $C_{16}H_{28}O_3$ (M − 18) 268.2038, found 268.2028.

Ethyl (1*R,2*S**,3*S**)-2-Hydroxy-3-(2-hydroxy-3-methyl-2-isopropylbut-1-yl)-1,2-dimethylcyclopentanecarboxylate (2c).** 1 (0.060 g, 0.31 mmol), 2,4-dimethyl-3-pentanone (0.041 g, 0.36 mmol), SmI_2 (0.633 mmol), 3 h, 25 °C. Ester **2c** was isolated as a white solid (0.0312 g, 0.094 mmol, 32%, mp 51–52 °C) by flash chromatography on silica gel (8:1 hexanes–EtOAc). Capillary GLC analysis of the crude reaction mixture indicated the product was formed as a single diastereomer: ^{1}H NMR ($CDCl_3$) δ 4.87 (s, 1 H), 4.22–4.09 (m, 2 H), 3.28 (s, 1 H), 2.38–2.20 (m, 2 H), 1.90–1.81 (m, 3 H), 1.75–1.65 (m, 1 H), 1.47–1.31 (m, 2 H), 1.26 (t, J = 7.08 Hz, 3 H), 1.23 (s, 3 H), 1.17–1.11 (m, 1 H), 1.09 (s, 3 H), 0.95 (d, J = 6.84 Hz, 3 H), 0.92 (d, J = 5.61 Hz, 3 H), 0.91 (d, J = 6.11 Hz, 3 H), 0.89 (d, J = 6.69 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.10, 81.88, 76.61, 61.04, 54.58, 42.34, 36.20, 34.60, 31.87, 31.64, 27.58, 19.45, 18.39, 18.15, 17.95, 17.21(2), 14.01; IR ($CHCl_3$) 3391.0 (br), 2969.8 (s), 2874.1 (m), 1690.4 (s), 1537.2 (m), 1503.7 (m), 1470.2 (m), 1451.1 (m), 1379.3 (w), 1277.9 (w), 1163.9 (w), 1082.5 (m), 1020.3 (m), 938.0 (w) cm^{-1}; exact mass calcd for $C_{18}H_{33}O_4$ (M − 1) 313.2379, found 313.2390.

Ethyl (1*R,2*S**,3*S**)-2-Hydroxy-3-[(1-hydroxycyclohex-1-yl)methyl]-1,2-dimethylcyclopentanecarboxylate (2d).** 1 (0.045 g, 0.23 mmol), cyclohexanone (0.023 g, 0.23 mmol), SmI_2 (0.452 mmol), 2 h, −30 °C. Ester **2d** was isolated as a clear colorless oil (0.039 g, 58%) by flash chromatography on silica gel (3:1 hexanes–EtOAc) followed by Kugelrohr distillation (110 °C at 0.07 mmHg). Capillary GLC analysis of the crude reaction mixture indicated the product was formed as a 200:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 4.92 (br s, 1 H), 4.14 (q, J = 7.01 Hz, 2 H), 3.66 (br s, 1 H), 2.38–2.26 (m, 2 H), 1.82–1.70 (m, 2 H), 1.60–1.30 (m, 12 H), 1.24 (t, J = 7.01 Hz, 3 H), 1.18 (s, 3 H), 1.14–1.13 (m, 1 H), 1.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.46, 81.48, 70.60, 61.06, 54.38, 42.41, 41.96, 39.19, 36.61, 31.79, 27.34, 26.04, 22.33, 22.09, 19.36, 17.02, 13.98; IR ($CHCl_3$) 3583.9 (w), 3384.9 (br), 2927.1 (s), 2857.4 (m), 1692.0 (s), 1602.7 (w), 1453.4 (m), 1378.9 (m), 1363.8 (m), 1299.2 (m), 1284.2 (m), 1149.9 (m), 1095.1 (m), 990.7 (w), 940.9 (w) cm^{-1}; exact mass calcd for $C_{17}H_{29}O_4$ (M − 1) 297.2066, found 297.2055.

Ethyl (1*R,2*S**,3*S**)-2-Hydroxy-3-[(1-hydroxycyclopent-1-yl)methyl]-1,2-dimethylcyclopentanecarboxylate (2e).** 1 (0.099 g, 0.50 mmol), cyclopentanone (0.046 g, 0.55 mmol), SmI_2 (1.00 mmol), 4 h, 25 °C. Ester **2e** was isolated as a clear colorless oil (0.0817 g, 0.287 mmol, 60%) by flash chromatography on silica gel (3:1 hexanes–EtOAc) followed by Kugelrohr distillation (93 °C at 0.2 mmHg). Capillary GLC analysis of the crude reaction mixture indicated the product was formed as a 60:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 5.03 (br s, 1 H), 4.18 (q, J = 7.1 Hz, 2 H), 3.95 (br s, 1 H), 2.40–2.30 (m, 1 H), 2.25–2.15 (m, 1 H), 2.03–1.90 (m, 1 H), 1.85–1.40 (m, 11 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.21 (s, 3 H), 1.20–1.12 (m, 1 H), 1.09 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.29, 81.52, 81.32, 61.05, 54.41, 44.54, 41.73, 41.00, 39.02, 31.60, 27.20, 23.81, 23.59, 19.31, 16.97, 13.20; IR ($CHCl_3$) 3583.9 (w), 3384.9 (br), 2947.0 (s), 2857.4 (m), 1692.3 (m), 1453.4 (m), 1378.8 (m), 1363.8 (m), 1090.2 (s), 1010.6 (s), 896.1 (m) cm^{-1}. Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.26; H, 9.93.

Ethyl (1*R,2*S**,3*S**)-2-Hydroxy-3-[(1-hydroxy-2-methylcyclohex-1-yl)methyl]-1,2-dimethylcyclopentanecarboxylate (2f).** 1 (0.068 g, 0.34 mmol), 2-methylcyclohexanone (0.038 g, 0.34 mmol), SmI_2 (0.686 mmol), 2 h, 25 °C. Ester **2f** was isolated as a white solid (0.0545 g, 0.715 mmol, 75%, mp 73–76 °C), by flash chromatography on silica gel (5:1 hexanes–EtOAc). Capillary GLC analysis of the crude reaction mixture indicated the product was formed as a 1:1 mixtue of diasteromers: ^{1}H NMR ($CDCl_3$) δ 4.42 (s, 1 H), 4.20 (q, J = 7.01 Hz, 2 H), 3.48 (s, 1 H), 2.42–2.30 (m, 2 H), 2.06–1.95 (m, 2 H), 1.88–1.72 (m, 2 H), 1.69–1.54 (m, 3 H), 1.53–1.45 (m, 4 H), 1.30 (t, J = 7.01 Hz, 3 H), 1.24 (s, 3 H), 1.10 (s, 3 H), 1.22–1.15 (m, 3 H), 0.95 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.40, 81.50, 71.95, 61.04, 54.49, 41.70, 40.69, 40.61, 36.26, 31.80, 30.93, 27.54, 25.80, 21.72, 19.41, 17.03, 15.25, 14.01; IR ($CHCl_3$) 3610.6 (w), 3425.3 (br), 2976.5 (s), 2927.7 (s), 2859.4 (m), 1685.9 (s), 1463.9 (m), 1444.4 (m), 1376.1 (m), 1293.2 (m), 1176.1 (m), 1151.7 (m), 1088.7 (m), 1000.0 (m), 956.6 (w) cm^{-1}. Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.18; H, 10.32. Found: C, 69.22; H, 10.36.

Ethyl (1*R,2*S**,3*S**)-2-Hydroxy-3-[(4-*tert*-butyl-1-hydroxycyclohex-1-yl)methyl]-1,2-dimethylcyclopentanecarboxylate (2g).** 1 (0.0594 g, 0.300 mmol), 4-*tert*-butylcyclohexanone (0.509 g, 0.330 mmol), SmI_2 (0.629 mmol), 1 h at −30 °C. Ester **2g** was isolated as a clear colorless oil (0.0647 g, 0.140 mmol, 61%) by flash chromatography on silica gel (7:1 hexanes–EtOAc). Capillary GLC analysis of the crude reaction mixture indicated the product was formed as a 10:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 4.89 (br s, 1 H), 4.16 (q, J = 7.0 Hz, 2 H), 3.55 (br s, 1 H), 2.42–2.25 (m, 2 H), 1.82–1.65 (m, 4 H), 1.60–1.19 (m, 9 H), 1.25 (t, J = 7.0 Hz, 3 H), 1.19 (s, 3 H), 1.07 (s, 3 H), 0.95–0.82 (m, 1 H), 0.81 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 179.48, 81.52, 69.80, 61.08, 54.40, 48.21, 44.51, 42.20, 39.49, 36.79, 32.37, 31.77, 27.56, 27.36, 22.53, 22.31, 19.34, 16.99, 14.02; IR ($CHCl_3$) 3603.4 (w), 3393.0 (br), 2943.5 (s), 2867.0 (s), 1687.5 (s), 1467.6 (m), 1443.7 (m), 1376.7 (m), 1367.1 (m), 1295.4 (m), 1238.0 (m), 1175.9 (m), 1152.0 (m), 1089.8 (m), 1018 (m), 936.8 (w), 917.7 (w) cm^{-1}. Anal. Calcd for $C_{21}H_{38}O_4$: C, 71.14; H, 10.80. Found: C, 71.44; H, 10.98.

Ethyl (1*R,2*S**,3*S**)-2-Hydroxy-3-(5-chloro-2-hydroxy-2-methylpent-1-yl)-1,2-dimethylcyclopentanecarboxylate (2h).** 1 (0.1200 g, 0.606 mmol), 5-chloro-2-pentanone (0.0730 g, 0.606 mmol), SmI_2 (1.333 mmol), 1 h at −30 °C, warming to 25 °C over 2 h. Ester **2h** was isolated as a clear colorless oil (0.127 g, 0.396 mmol, 65%) by flash chromatography on silica gel (3:1 hexanes–EtOAc). The product readily eliminates H_2O upon distillation. Capillary GLC analysis of the crude reaction mixture indicated the product was formed as a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 5.13 (br s, 1 H), 5.06 (br s, 1 H), 4.28 (br s, 1 H), 4.19 (q, J = 7.0 Hz, 2 H), 4.10 (q, J = 7.0 Hz, 2 H), 4.02 (br s, 1 H), 3.61–3.47 (m, 4 H), 2.41–2.39 (m, 2 H), 2.27–2.12 (m, 2 H), 1.94–1.80 (m, 4 H), 1.79–1.65 (m, 4 H), 1.63–1.51 (m, 4 H), 1.49–1.32 (m, 4 H), 1.30–1.25 (m, 8 H), 1.21 (s, 6 H), 1.14 (s, 3 H), 1.14 (s, 3 H), 1.10 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.44, 179.30, 81.42, 71.54, 71.38, 65.75, 61.17, 61.14, 54.35, 54.29, 45.86, 45.73, 42.64, 42.57, 42.05, 41.72, 41.10, 38.15, 31.57, 31.48, 27.74, 27.71, 27.29, 27.12, 27.01, 26.31, 19.30, 16.99, 16.91, 15.16, 13.97; IR ($CHCl_3$) 3373.5 (s), 2982.9 (s), 2933.0 (m), 2866.5 (w), 1689.3 (s), 1535.6 (w), 1506.5 (w), 1469.1 (m), 1452.4 (m), 1381.8 (m), 1365.2 (m), 1107.5 (m), 1086.7 (s), 1016.7 (m), 937.1 (w); exact mass calcd for $C_{16}H_{27}O_3Cl$ (M − 18) 302.1657, found 302.1649. Anal. Calcd for $C_{16}H_{29}O_4Cl$: C, 59.89; H, 9.11. Found: C, 59.81; H, 9.22.

Ethyl (1*R,2*S**,3*S**)-2-Hydroxy-3-[5-(diethylamino)-2-hydroxy-2-methylpent-1-yl]-1,2-dimethylcyclopentanecarboxylate (2i).** 1 (0.0947 g, 0.478 mmol), 5-(diethylamino)-2-pentanone (0.0751 g, 0.478 mmol), SmI_2 (1.004 mmol), 1 h at −30 °C, warming to 25 °C over 2 h. Ester **2i** was isolated as a clear colorless oil (0.0550 g, 0.154 mmol, 32.5%) by flash chromatography on silica gel (100% EtOAc), followed by Kugelrohr distillation (103–105 °C at 0.03 mmHg). Capillary GLC analysis of the crude reaction mixture indicated the product was formed as a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 5.82 (br s, 1 H), 5.22 (br s, 1 H), 4.22–4.09 (m, 4 H), 2.66–2.50 (m, 4 H), 2.49–2.36 (m, 8 H), 2.35–2.23 (m, 3 H), 1.91–1.78 (m, 4 H), 1.75–1.50 (m, 8 H), 1.44–1.30 (m, 3 H), 1.37 (t, J = 7.0 Hz, 6 H), 1.40–1.30 (m, 2 H), 1.22 (s, 6 H), 1.12 (s, 6 H), 1.08 (s, 6 H), 1.01 (t, J = 7.0 Hz, 12 H), 1.02–0.80 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 178.70, 178.33, 81.25, 80.87, 70.68, 70.34, 60.49, 60.36, 60.33, 55.32, 54.81, 54.06, 46.11, 46.04, 45.95, 43.63, 43.22, 42.92, 42.85, 42.74, 40.47, 32.87, 32.74, 28.65, 28.59, 28.19, 26.32, 21.72, 21.43, 19.89, 19.68, 18.20, 17.97, 14.12, 14.10, 10.72, 10.60; IR ($CHCl_3$) 3335.1 (br), 2964.6 (s), 2938.1 (s), 2823.4 (w), 1705.0 (s), 1463.2 (s), 1479.4 (s), 1286.7 (s), 1150.0 (m), 1110.3 (m), 1092.6 (m), 1022.0 (m), 1000.0 (w), 933.0 (w), 858.8 (w); exact mass calcd for $C_{20}H_{39}NO_4$ 357.2880, found 357.2880. Anal. Calcd for $C_{20}H_{39}NO_4$: C, 67.18; H, 10.99. Found: C, 67.42; H, 11.15.

Ethyl (1*R,2*S**,3*S**)-2-Hydroxy-3-(2-hydroxypent-1-yl)-1,2-dimethylcyclopentanecarboxylate (2j).** 1 (0.1665 g,

0.8440 mmol) and butanal (0.0910 g, 1.26 mmol), SmI_2 (1.7664 mmol), 2 h, 25 °C. Ester **2j** was isolated as a clear colorless liquid (0.1270 g, 0.4662 mmol, 55%) by flash chromatography on silica gel (5:1 hexanes–EtOAc) followed by Kugelrohr distillation (87–90 °C at 0.07 mmHg). Capillary GLC analysis of the crude reaction mixture indicated the product was formed as a 17:17:1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, two diastereomers) δ 5.15 (s, 1 H), 4.48 (s, 1 H), 4.25–4.12 (m, 4 H), 3.82–3.73 (m, 1 H), 3.61 (br s, 1 H), 3.44 (br s, 1 H), 2.67–2.61 (m, 1 H), 2.43–2.31 (m, 1 H), 2.20–2.12 (m, 1 H), 2.10–2.01 (m, 3 H), 1.43–1.31 (m, 2 H), 1.74–1.66 (m, 1 H), 1.55–1.30 (m, 14 H), 1.25 (t, J = 7.0 Hz, 3 H), 1.24 (t, J = 7.05 Hz, 3 H), 1.21 (s, 3 H), 1.20 (s, 3 H), 1.13 (s, 3 H), 1.02 (s, 3 H), 0.92–0.85 (m, 6 H); ^{13}C NMR ($CDCl_3$, two diastereomers) δ 179.29, 178.95, 81.72, 81.68, 74.36, 74.18, 71.55, 70.12, 61.14, 61.04, 54.58, 47.04, 43.59, 40.03, 39.98, 39.19, 38.31, 37.72, 35.65, 33.27, 32.08, 31.60, 26.82, 26.63, 19.15, 19.03, 18.94, 18.85, 17.51, 14.03; IR ($CHCl_3$) 3555.9 (w), 3379.3 (br), 2990.7 (w), 2964.2 (s), 2928.8 (s), 1696.0 (s), 1515.0 (m), 1470.8 (m), 1453.2 (s), 1378.1 (s), 1364.9 (m), 1289.8 (s), 1170.6 (s), 1135.2 (s), 1086.7 (s), 1016.0 (s) cm^{-1}; exact mass calcd for $C_{15}H_{26}O_3$ (M − 18) 254.1882, found 254.1911.

Ethyl (1*R,2*S**,3*S**)-2-Hydroxy-3-(2-hydroxy-3-methylbut-1-yl)-1,2-dimethylcyclopentanecarboxylate (2k).** **1** (0.0385 g, 0.194 mmol), isobutyraldehyde (0.0144 g, 0.200 mmol), SmI_2 (0.4076 mmol), 1.5 h, −30 °C. Ester **2k** was isolated as a white solid (0.0279 g, 0.0987 mmol, 56%, mp 56–64.5 °C) by flash chromatography on silica gel (5:1 hexanes–EtOAc). Capillary GLC analysis of the crude reaction mixture indicated the product was formed as a 30:15:1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 4.45 (br s, 1 H), 4.23 (q, J = 7.0 Hz, 2 H), 3.50 (br s, 1 H), 2.45–2.30 (m, 2 H), 2.23–2.05 (m, 1 H), 2.00–1.55 (m, 4 H), 1.50–1.42 (m, 2 H), 1.31 (t, J = 7.0 Hz, 3 H), 1.27 (s, 3 H), 1.12 (s, 3 H), 0.85 (d, J = 7.0 Hz, 3 H), 0.73 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, two diastereomers) δ 179.19, 178.93, 81.74, 81.32, 77.22, 76.45, 75.25, 61.09, 61.02, 54.64, 47.04, 43.94, 34.82, 34.66, 33.98, 33.94, 32.06, 31.62, 26.89, 26.72, 19.39, 19.36, 18.96, 18.74, 17.83, 17.77, 17.58, 17.49, 14.00; IR ($CHCl_3$) 3589.1 (w), 3388.5 (br), 2968.1 (s), 2872.5 (m), 1691.0 (s), 1466.0 (m), 1447.4 (m), 1380.5 (m), 1366.2 (m), 1294.5 (s), 1175.1 (s), 1084.3 (s), 1017.0 (m), 984.0 (w), 941.0 (w) cm^{-1}; exact mass calcd for $C_{15}H_{27}O_4$ (M − 1) 271.1909, found 271.1917.

Ethyl (1*R,2*S**,3*S**)-2-Hydroxy-3-(2-hydroxy-3,3-dimethylbut-1-yl)-1,2-dimethylcyclopentanecarboxylate (2l).** **1** (0.0658 g, 0.332 mmol), pivalaldehyde (0.0364 g, 0.423 mmol), SmI_2 (0.740 mmol), 1 h, −30 °C. Ester **2l** was isolated as a white solid (0.0333 g, 0.116 mmol, 35%, mp 101.5–104 °C) by flash chromatography on silica gel (3:1 hexanes–EtOAc). Capillary GLC analysis of the crude reaction mixture indicated the product was formed as a 2:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 4.30 (br s, 1 H), 4.14 (q, J = 7.01 Hz, 2 H), 3.50 (br s, 1 H), 2.43–2.28 (m, 1 H), 2.21–2.05 (m, 2 H), 1.97–1.84 (m, 1 H), 1.67–1.58 (m, 2 H), 1.45–1.28 (m, 2 H), 1.26 (t, J = 7.05 Hz, 3 H), 1.19 (s, 3 H), 1.05 (s, 3 H), 0.88 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 178.86, 82.00, 77.54, 61.03, 54.74, 44.62, 34.90, 32.46, 32.04, 27.08, 25.68, 19.31, 17.48, 14.02; IR ($CHCl_3$) 3629.9 (w), 3430.9 (br), 2953.2 (s), 2863.6 (s), 1690.4 (s), 1471.5 (m), 1376.9 (m), 1362.0 (m), 1292.3 (m), 1242.6 (w), 1167.9 (m), 1158.0 (m), 1088.3 (m), 1013.7 (m), 964.2 (w) cm^{-1}; exact mass calcd for $C_{16}H_{29}O_4$ (M − 1) 285.2066, found 285.2067.

Ethyl (1*R,2*S**,3*S**)-2-Hydroxy-3-[(6-methyl-2-oxo-1-oxacyclohex-6-yl)methyl]-1,2-dimethylcyclopentanecarboxylate (2n).** **1** (0.1054 g, 0.5320 mmol), ethyl 5-oxohexanoate (0.0925 g, 0.585 mmol), SmI_2 (1.117 mmol), 1 h, −30 °C. Ester **2n** was isolated as a clear colorless oil (0.1082 g, 0.3464 mmol, 65%) by flash chromatography on silica gel (1:1 hexanes–EtOAc), followed by Kugelrohr distillation (90–93 °C at 0.03 mmHg). Capillary GLC analysis of the crude reaction mixture indicated the product was formed as a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 4.21–4.08 (m, 2 H), 4.02 (br s, 1 H), 2.58–2.42 (m, 3 H), 2.40–2.27 (m, 3 H), 2.13–2.02 (m, 4 H), 2.00–1.80 (m, 7 H), 1.79–1.71 (m, 3 H), 1.69–1.55 (m, 4 H), 1.54–1.41 (m, 5 H), 1.39 (s, 3 H), 1.35 (s, 3 H), 1.27 (t, J = 7.0 Hz, 6 H), 1.21 (s, 6 H), 1.01 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.09, 178.74, 171.18, 171.05, 84.49, 84.47, 81.74, 81.70, 65.73, 60.89, 53.62, 53.43, 43.04, 42.88, 42.55, 42.02, 33.07, 32.58, 32.51, 31.52, 29.23, 29.10, 27.42, 27.31, 27.26, 26.28, 19.22, 19.19, 17.63, 17.16, 16.55, 16.32, 15.15, 13.94; IR ($CHCl_3$) 3449.8 (br), 2982.2 (s), 2955.7 (s), 1714.7 (s), 1697.0 (s), 1467.6 (m), 1450.0 (m), 1410.2 (m), 1379.4 (s), 1326.4 (m), 1291.1 (s), 1260.3 (m), 1150.0 (s), 1088.2 (s), 1052.9 (m), 1017.6 (m), 991.1 (m), 938.2 (s), 959.8 (s); exact mass calcd for $C_{17}H_{28}O_5$ 312.1937, found 312.1942. Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.35; H, 9.03. Found: C, 65.41; H, 9.17.

(5*R,6*S**,7*S**)-6-Hydroxy-6-methyl-7-(2-hydroxy-2-methylprop-1-yl)-2-oxaspiro[4.4]nonan-1-one (5).** **4** (0.0639 g, 0.351 mmol), acetone (0.0305 g, 0.526 mmol), SmI_2 (0.7361 mmol), 3 h, 25 °C. Lactone **5** was isolated as a white solid (0.0721 g, 0.288 mmol, 85%) by flash chromatography on silica gel (7:1 hexanes–EtOAc). Capillary GC analysis of the crude reaction mixture indicated that the product was formed as an 11:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 4.32–4.25 (m, 1 H), 4.18–4.06 (m, 2 H), 3.03–2.90 (m, 1 H), 2.56–2.43 (m, 2 H), 2.17–2.05 (m, 2 H), 2.01–1.93 (m, 2 H), 1.80–1.72 (m, 1 H), 1.62–1.51 (m, 1 H), 1.42–1.29 (m, 1 H), 1.23 (s, 3 H), 1.21 (s, 2 H), 1.12 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 181.31, 80.79, 71.41, 65.57, 55.87, 42.66, 42.49, 31.84, 31.72, 30.84, 28.45, 28.30, 18.36; IR ($CHCl_3$) 3599.2 (w), 3403.5 (br), 2967.7 (s), 2914.4 (m), 2869.8 (w), 1754.5 (s), 1465.5 (m), 1372.0 (s), 1269.7 (w), 1185.2 (s), 1149.7 (m), 1122.4 (m), 1100.7 (m), 1025.5 (s), 967.3 (w), 940.6 (w), 905.1 (w) cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.43; H, 9.15. Found: C, 64.17; H, 9.14. The structure was confirmed by X-ray diffractometry.

Ethyl (1*R,4*S**,5*S**)-5-Hydroxy-4-(2-hydroxy-2-methylprop-1-yl)bicyclo[3.3.0]octanecarboxylate (7).** **6** (0.0640 g, 0.303 mmol) and acetone (0.0377 g, 0.650 mmol), SmI_2 (0.6369 mmol), 2 h, 25 °C. Ester **7** was isolated as a thick pale yellow oil (0.0541 g, 0.200 mmol, 66%) by flash chromatography on silica gel (3:1 hexanes–EtOAc). Capillary GC analysis of the crude reaction mixture indicated that the product was formed as a >90:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 4.18–4.06 (m, 2 H), 3.90 (br s, 1 H), 3.46 (br s, 1 H), 2.42–2.33 (m, 1 H), 2.29–2.16 (m, 2 H), 1.68–1.55 (m, 6 H), 1.54–1.37 (m, 3 H), 1.24 (t, J = 7.0 Hz, 3 H), 1.22 (s, 3 H), 1.20 (s, 3 H), 1.22–1.15 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 176.87, 93.12, 70.06, 61.44, 60.66, 45.42, 43.20, 37.87, 36.04, 34.80, 31.13, 30.18, 28.33, 24.44, 14.06; IR ($CHCl_3$) 3599.5 (w), 2962.0 (s), 2868.2 (w), 1698.2 (s), 1463.8 (w), 1388.8 (w), 1365.3 (m), 1332.5 (w), 1281.0 (s), 1149.7 (s), 1116.9 (m), 1018.5 (m), 971.6 (w), 901.3 (w) cm^{-1}; exact mass calcd for $C_{15}H_{26}O_4$ (M − 1) 269.1753, found 269.1754.

Ethyl (1*R,6*S**,7*S**)-6-Hydroxy-7-(2-hydroxy-2-methylprop-1-yl)bicyclo[4.3.0]nonanecarboxylate (9).** **8** (0.0748 g, 0.354 mmol), acetone (0.0311 g, 0.531 mmol), SmI_2 (0.7440 mmol), 4 h, 25 °C. Ester **9** was isolated as a clear colorless oil (0.731 g, 0.257 mmol, 75%) by flash chromatography on silica gel (3:1 hexanes–EtOAc). ^{1}H NMR of the crude reaction mixture indicated that the product was formed as a single diastereomer: ^{1}H NMR ($CDCl_3$) δ 5.29 (s, 1 H), 4.24 (s, 1 H), 4.15 (q, J = 7.1 Hz, 2 H), 2.28–2.14 (m, 1 H), 2.12–2.00 (m, 2 H), 1.89–1.65 (m, 7 H), 1.59–1.48 (m, 3 H), 1.34–1.29 (m, 1 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.16 (s, 6 H), 1.17–1.13 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 180.13, 78.74, 69.76, 61.06, 54.22, 43.42, 42.63, 31.01, 28.80, 27.78, 26.30, 25.58, 20.49, 19.89, 13.91 cm^{-1}; IR ($CHCl_3$) 3674.5 (w), 3590.1 (w), 3374.5 (s), 2971.0 (s), 2933.9 (s), 2858.9 (m), 1688.8 (m), 1440.0 (m), 1398.2 (m), 1327.8 (m), 1290.3 (s), 1271.6 (s), 1177.8 (s), 1149.7 (s), 1060.7 (m), 1027.8 (m). Anal. Calcd for $C_{16}H_{28}O_4$: C, 66.63; H, 9.69. Found: C, 66.56; H, 9.84.

(1*R,2*S**,3*S**)-*N*,*N*-Diethyl-2-hydroxy-3-(2-hydroxy-2-methylpropyl)-2-methylcyclopentanamide (11).** **10** (0.0736 g, 0.349 mmol), acetone (0.0200 g, 0.523 mmol), SmI_2 (0.7321 mmol), 4 h, −78 °C. Amide **11** was isolated (0.0395 g, 0.146 mmol, 46%) as a cloudy white oil by flash chromatography on silica gel (2:1 EtOAc–hexanes). Capillary GC analysis of the crude reaction mixture indicated that the product was formed as a single diastereomer: ^{1}H NMR ($CDCl_3$) δ 5.69 (br s, 1 H), 3.92 (br s, 1 H), 3.45–3.32 (m, 2 H), 3.30–3.16 (m, 2 H), 2.72–2.68 (m, 1 H), 2.51–2.43 (m, 1 H), 2.09–1.45 (m, 1 H), 1.82–1.63 (m, 3 H), 1.45–1.23 (m, 2 H), 1.22 (s, 3 H), 1.18 (s, 6 H), 1.17–1.03 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 175.96, 80.86, 70.06, 48.84, 45.49, 42.91, 42.03, 40.10, 30.77, 30.35, 28.94, 27.23, 22.88, 14.43, 12.89; IR ($CHCl_3$) 3599.5 (w), 3365.1 (s), 2971.4 (s), 2933.9 (m), 2877.4 (w), 1604.4 (s), 1459.1 (s), 1435.7 (m), 1402.8 (m), 1379.4 (m), 1332.5 (w), 1252.8 (s), 1149.7 (m), 1135.7 (m), 1079.4 (w), 1004.4 (w), 943.5 (w) cm^{-1}; exact mass calcd for $C_{15}H_{25}NO_2$ (M − 18) 253.2041, found 253.2045.

(1*R,2*S**,3*S**)-*N*,*N*-Diethyl-2-hydroxy-2-methyl-3-(2-hydroxy-2-methylpropyl)-1,2-dimethylcyclopentanamide**

(13). 12 (0.0549 g, 0.244 mmol) and acetone (0.0297 g, 0.512 mmol), SmI_2 (0.5121 mmol), 5 h, −78 to 25 °C. Amide 13 was isolated (0.0161 g, 46%) as a yellow oil by flash chromatography on silica gel (2:1 EtOAc–hexanes). Capillary GC analysis indicated that the product was formed as a single diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.78 (s, 1 H), 5.82 (s, 1 H), 3.51–3.38 (m, 2 H), 3.37–3.15 (m, 2 H), 2.63–2.50 (m, 1 H), 2.19–2.08 (m, 1 H), 1.78–1.57 (m, 4 H), 1.44–1.39 (m, 1 H), 1.22 (s, 3 H), 1.21 (s, 3 H), 1.09 (s, 3 H), 1.23–1.04 (m, 6 H), 1.03 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 180.25, 83.99, 77.21, 69.85, 50.60, 43.99, 41.46, 32.42, 31.18, 28.60, 27.79, 19.81, 17.09; IR ($CHCl_3$) 3331.2 (br), 2968.4 (s), 2933.0 (m), 2879.9 (w), 1590.5 (s), 1453.3 (m), 1395.8 (m), 1382.5 (m), 1356.0 (m), 1263.1 (w), 1152.1 (m), 1121.5 (m), 1064.0 (w), 962.2 (w), 895.8 (w) cm^{-1}; exact mass calcd for $C_{16}H_{29}NO_2$ (M − 18) 267.2198, found 267.2213.

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Supplementary Material Available: Experimental data for X-ray structure determination of compounds **2f** and **5** and ^{1}H and/or ^{13}C NMR spectra for compounds **2a–d,k–l**, **7**, **11**, and **13** (41 pages). Ordering information is given on any current masthead page.

The Direct Formation of Functionalized Alkyl(aryl)zinc Halides by Oxidative Addition of Highly Reactive Zinc with Organic Halides and Their Reactions with Acid Chlorides, α,β-Unsaturated Ketones, and Allylic, Aryl, and Vinyl Halides

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Highly reactive zinc, prepared by the lithium naphthalenide reduction of $ZnCl_2$, readily undergoes oxidative addition to alkyl, aryl, and vinyl halides under mild conditions to generate the corresponding organozinc compounds in excellent yields. Significantly, the reaction will tolerate a spectrum of functional groups on the organic halides. Accordingly, this approach can now be used to prepare a wide variety of highly functionalized organozinc compounds. In the presence of Cu(I) salts, the organozinc compounds cross-couple with acid chlorides, conjugatively add to α,β-unsaturated ketones, and regioselectively undergo S_N2' substitution reactions with allylic halides. They also cross-couple with aryl or vinyl halides with Pd(0) catalysts.

Introduction

Organozinc compounds were first prepared by Frankland[1] in 1848 by oxidative addition of zinc metal to alkyl iodides. The reaction was limited due to the low reactivity of the metal. Several methods have been used to activate zinc, such as washing with HCl solution,[2] ultrasound irradiation,[3] using a Zn–Cu couple,[4] adding 1,2-dibromoethane[5] or trimethylchlorosilane[6] to the reaction mixture, and metal–solvent cocondensation.[7] In spite of these methods, the direct oxidative addition of zinc metal to organic halides has been limited to relatively reactive halides such as alkyl iodides or α-halo esters.[8] Recently, zinc homoenolates of alkyl propionates were prepared by ring-opening reactions of 1-siloxy-1-alkoxycyclopropanes.[9] However, most alkyl bromides and chlorides and all vinyl and aryl halides have been totally useless for the direct reaction with zinc metal. For these substrates, the only option was a metathesis reaction with a Grignard reagent or organolithium reagent which precluded the presence of most functional groups.

Table I. Preparation of Organozinc Compounds[a]

$$RX + Zn^* \xrightarrow[THF]{\text{temp, time}} RZnX$$

entry	organic halide	Zn*:RX ratio	time, °C	time, h	yield,[b] %
1	$Br(CH_2)_6Cl$	1.2:1	23	4	100
2	$Br(CH_2)_7CH_3$	1.2:1	23	6	100
3	$Br(CH_2)_3CO_2Et$	1:1	23	3	100
4	p-IC_6H_4Cl	2:1	23	3	100
5	p-BrC_6H_4CN	2:1	reflux	3	90
6	p-BrC_6H_6CN	3:1	reflux	3	100
7	p-$BrC_6H_4CO_2Et$	2:1	reflux	2	100
8	o-$BrC_6H_4CO_2Et$	2:1	reflux	2	100
9	m-$BrC_6H_4CO_2Et$	3:1	reflux	4	100
10	$Cl(CH_2)_3CO_2Et$	3:1	reflux	4	100[c]

[a] THF was used as solvent. [b] The percent yield was determined by GC after hydrolysis with dilute HCl solution. [c] In the presence of 2 equiv of KI.

In this paper, we would like to report that highly reactive zinc[10] prepared by the lithium naphthalenide reduction of $ZnCl_2$ readily undergoes oxidative addition to alkyl, aryl, and vinyl halides under mild conditions to generate the corresponding organozinc compounds. Significantly, the reaction will tolerate a wide spectrum of functional groups on the organic halides. We also report a variety of cross-coupling reactions of the functionalized organozinc

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