Intramolecular Nucleophilic Acyl Substitution Reactions Mediated by Samarium(II) Iodide: A Convergent Approach to the Preparation of Enantiomerically Enriched 4-Hydroxy Ketones from 3-Iodopropyl Carboxylates

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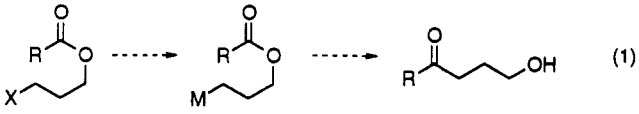
Received January 25, 1994®

Intramolecular nucleophilic acyl substitution (INAS) reactions of substituted 3-iodopropyl carboxylates have been achieved using samarium(II) iodide (SmI_2) in the presence of an iron(III) catalyst. Diverse ester starting materials containing stereogenic centers placed in varying positions on the substrates have been converted to acyclic 4-hydroxy ketone derivatives in good yields using this method. No racemization of stereogenic centers α to the carbonyl was observed in any of the reactions examined. Consequently, the method serves as a convenient, high-yield synthesis of functionalized, enantiomerically enriched acyclic ketones possessing stereogenic centers far removed from one another.

Introduction

Synthetic sequences involving the transfer of carbon fragments from oxygen to carbon have emerged as important methods for the formation of carbon–carbon bonds. Claisen rearrangements[1] and 2,3-sigmatropic Wittig rearrangements[2] are typical examples of this type of transformation that have been extensively exploited. At the same time, intramolecular nucleophilic acyl substitution (INAS) reactions (eq 1) have received rather limited attention. Difficulties associated with the enhanced reactivity of the ketone product relative to that of the ester starting material have made this conceptually simple transformation a rather difficult one to carry out in practice.[3] This is particularly unfortunate in view of the potential of this process for the convergent construction of enantiomerically enriched acyclic ketones and especially those ketones possessing stereogenic centers far removed from one another and the ketone functional group itself.[4]

The importance of this process is illustrated by the fact that a variety of 4-hydroxy ketones (one class of products potentially accessible by such a synthetic process) can be transformed into dihydrofurans,[5] tetrahydrofuran derivatives,[6] spiroketals,[7] dicarbonyl compounds,[8] diols,[9] and cyclopropyl ketones.[10] Moreover, the synthesis of chiral, nonracemic 4-hydroxy ketones can lead to a variety of important natural products. In addition to the classical examples of furanosides, substituted 4-hydroxy ketones are key building blocks for biologically active compounds such as polyether antibiotics,[11] insect pheromones,[12] acetogenins,[13] and C-glycosides.[14]



(1)

One of the difficulties associated with INAS reactions is that a fairly reactive nucleophilic species must be generated in the presence of an ester electrophile. At the same time, this nucleophile must be prevented from undergoing nucleophilic addition to the hydroxy ketone product. These criteria rule out the use of many orga-

® Abstract published in *Advance ACS Abstracts,* May 15, 1994.

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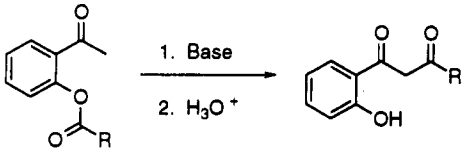
nometallics, such as organozincs[15] and organocuprates,[16] which lack the nucleophilicity to undergo reaction with ester electrophiles, as well as organolithiums and organomagnesiums, which are apparently too reactive.[3,17] INAS reactions of aryl or vinyl anions, generated by the reaction of CsF or TASF with alkenyl iodides, have been achieved,[18] but the esters utilized in these studies did not contain enolizable protons. It is not surprising, then, that most of the published examples of INAS reactions involve the use of stabilized carbanions (eq 2).[19]

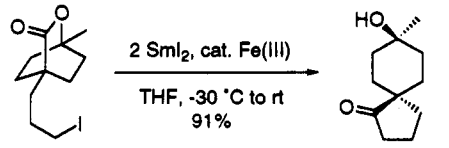


(2)

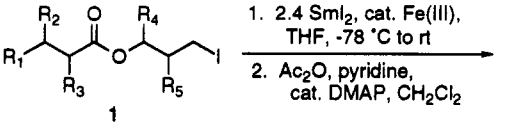
An even more rigorous criterion for success is demanded in INAS reactions of nonracemic ester substrates possessing a stereogenic center α to the carbonyl. In these cases, neither the carbanion nor the alkoxide product should competitively deprotonate acidic protons α to the carbonyl functional group of the starting material or the final product.

Among the few organometallics that appear capable of meeting all of the demanding criteria outlined above for INAS reactions are organolanthanides.[20] In particular, organosamarium reagents appear to be ideal candidates. Although under some reaction conditions organosamariums undergo neither intermolecular[21] nor intramolecular[22] nucleophilic acyl substitution (NAS) reactions with esters, recent studies have clearly established that alkylsamariums do react intramolecularly with esters or lactones in the presence of tris(dibenzoylmethido)iron(III) [$Fe(DBM)_3$], providing four-, five-, or six-membered carbocyclic ketones in excellent yields (eq 3).[23]

Herein we report a useful extension of our original study on SmI_2-promoted NAS reactions in which acyclic 3-iodopropyl carboxylates have been utilized as substrates (eq 4). This transformation complements existing methods of preparation of 4-hydroxy ketones[24] and thereby provides an efficient entry to enantiomerically enriched ketones of considerable use for the construction of a variety of useful organic compounds.



(3)



(4)

Results and Discussion

In order to probe the feasibility and scope of the SmI_2-promoted NAS reaction, several 3-iodopropyl carboxylates possessing varying substitution patterns were synthesized (Table 1). Compounds **1a–e** were prepared by reacting commercially available 3-phenylpropionyl chloride with 3-iodopropanol,[25] (2*S*)-3-iodo-2-methylpropanol, (2*R*)-3-iodo-2-methylpropanol,[26] (1*S*)-3-iodo-1-phenylpropanol, or (1*R*)-3-iodo-1-phenylpropanol,[27] respectively. Iodides **1i–l** and **1o,p** were obtained by the same method using carboxylic acid chlorides prepared from readily available carboxylic acids. Both enantiomers of 2-methyl-3-phenylpropanoic acid[28] and 3-(benzyloxy)-2-methylpropanoic acid[29] were converted to their acid chlorides by azeotropic drying and subsequent treatment with oxalyl chloride. Gas chromatographic analysis of iodo esters **1i,j** prepared in this fashion revealed that these compounds were 96–98% diastereomerically pure. (±)-Dihydrocitronellic acid

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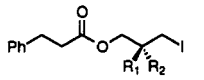
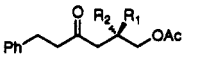
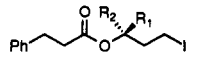
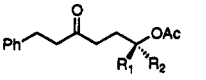
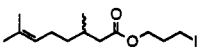
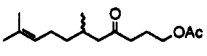
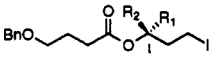
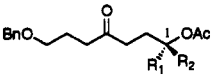
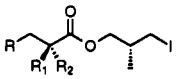
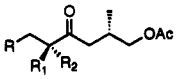
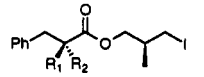
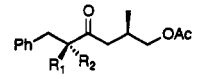
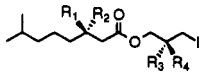
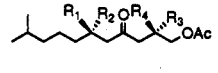
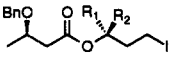
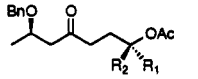
(25) 3-Iodopropanol was obtained by Finkelstein reaction of 3-bromopropanol with sodium iodide in acetone. In an attempt to avoid this additional step, analogous bromo esters of 3-bromopropanol were treated with SmI_2 in the presence of HMPA or $Fe(DBM)_3$ under a variety of conditions. Generally reaction times were longer and yields were inferior compared to those of iodo esters, presumably because of the competitive reduction of the ketone in the product by SmI_2.

(26) Both (2*R*)- and (2*S*)-3-iodo-2-methylpropanol were obtained by Finkelstein reaction of 3-bromo-2-methylpropanol (Aldrich) with sodium iodide in acetone. For the preparation of benzyl or silyl ethers of 3-iodo-2-methylpropanol: Evans, D. A.; Sacks, C. E.; Kleschich, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789.

(27) Prepared by Finkelstein reaction of (1*S*)- and (1*R*)-3-chloro-1-phenylpropanol (Aldrich): (a) (1*S*) isomer: Chenevert, R.; Fortier, G.; Rhlid, R. B. *Tetrahedron* **1992**, *48*, 6769. (b) (1*R*) isomer: Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207.

(28) Both enantiomers were prepared by following the Evans procedure, which provided material >98% enantiomerically pure: (a) asymmetric alkylation: Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (b) $LiOH/H_2O_2$ hydrolysis: Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

Table 1. Samarium(II) Iodide-Promoted Conversion of 3-Iodopropyl Esters 1 to Acetoxy Ketones 2 (eq 4)

entry	substrate	product	% overall yield[a]
			
1	**1a** $R_1 = R_2 = H$	**2a** $R_1 = R_2 = H$	60
2	**1b** $R_1 = Me$, $R_2 = H$	**2b** $R_1 = Me$, $R_2 = H$	70
3	**1c** $R_1 = H$, $R_2 = Me$	**2c** $R_1 = H$, $R_2 = Me$	90
			
4	**1d** $R_1 = H$, $R_2 = Ph$	**2d** $R_1 = H$, $R_2 = Ph$	75 (95% ee)[b]
5	**1e** $R_1 = Ph$, $R_2 = H$	**2e** $R_1 = Ph$, $R_2 = H$	71 (98% ee)[b]
			
6	**1f**	**2f**	71
			
7	**1g** $R_1 = H$, $R_2 = Me$ and $R_1 = Me$, $R_2 = H$ (1*RS*)	**2g** racemic (1*RS*)	71[c]
8	**1h** $R_1 = Me$, $R_2 = H$ (1*R*)	**2h** $R_1 = Me$, $R_2 = H$ (1*R*)	71
			
9	**1i**[d] R = Ph, $R_1 = H$, $R_2 = Me$	**2i** R = Ph, $R_1 = H$, $R_2 = Me$	76 (98:2 dr)[e]
10	**1j**[d] R = Ph, $R_1 = Me$, $R_2 = H$	**2j** R = Ph, $R_1 = Me$, $R_2 = H$	80 (97:3 dr)
11	**1k** R = OBn, $R_1 = Me$, $R_2 = H$	**2k** R = OBn, $R_1 = Me$, $R_2 = H$	64 (97:3 dr)
12	**1l** R = OBn, $R_1 = H$, $R_2 = Me$	**2l** R = OBn, $R_1 = H$, $R_2 = Me$	60 (96:4 dr)
			
13	**1m** $R_1 = H$, $R_2 = NBn_2$	**2m** $R_1 = H$, $R_2 = NBn_2$	34[f]
14	**1n** $R_1 = H$, $R_2 = NBn_2$ and $R_1 = NBn_2$, $R_2 = H$	**2n** $R_1 = H$, $R_2 = NBn_2$ and $R_1 = NBn_2$, $R_2 = H$	53[g]
			
15	**1o** $R_1 = H$, $R_2 = Me$ and $R_1 = Me$, $R_2 = H$; $R_3 = Me$, $R_4 = H$	**2o** $R_1 = H$, $R_2 = Me$ and $R_1 = Me$, $R_2 = H$; $R_3 = Me$, $R_4 = H$	91
16	**1p** $R_1 = Me$, $R_2 = H$, $R_3 = H$, $R_4 = Me$	**2p** $R_1 = Me$, $R_2 = H$, $R_3 = H$, $R_4 = Me$	75
			
17	**1q** $R_1 = H$, $R_2 = Ph$	**2q** $R_1 = H$, $R_2 = Ph$	64
18	**1r** $R_1 = Ph$, $R_2 = H$	**2r** $R_1 = Ph$, $R_2 = H$	68

[a] Overall yield of **2** from **1** after purification. [b] Determined by ^{19}F NMR analysis of the Mosher esters of corresponding hydroxy ketones. [c] The SmI_2 reaction provided a 77% yield of hydroxy ketone, which upon acetylation gave **2g** in 71% overall yield (92% conversion during the acetylation reaction). [d] The diastereomeric purity was determined to be 96–98% by GLC analysis. [e] The diastereomeric ratio (dr) was determined by GLC analysis. [f] At rt (35% at −20 °C). [g] At 0 °C.

and (3*R*)-dihydrocitronellic acid[30] were converted to their respective acid chlorides by treatment with oxalyl chloride. The crude acid chlorides, obtained after the removal of solvent and excess oxalyl chloride, were used in a subsequent esterification reaction. When (±)-citronellic acid chloride obtained in this fashion was subsequently treated with 3-iodopropanol, a complex mixture was obtained. However, use of dicyclohexylcarbodiimide (DCC) in the presence of a catalytic amount of *N,N*-(dimethylamino)pyridine (DMAP) in THF provided a better yield of the 3-iodopropyl ester of citronellic acid, **1f**. One drawback of this method of preparation of the esters was that excess DCC was required to effect the condensation. The separation of residual DCC from the product often proved difficult. This problem was alleviated to a certain extent by the removal of DCC under vacuum at elevated temperature. A more satisfactory solution proved to be the use 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide methiodide (EDCI)–a water soluble analog of DCC.

Because 4-(benzyloxy)butyryl chloride was known to be readily converted to butyrolactone,[31] esterifications involving this acid chloride were avoided. Consequently, the condensation of 4-(benzyloxy)butanoic acid[32] with racemic 4-iodobutan-2-ol and (2*R*)-4-iodobutan-2-ol[33] was accomplished by using excess EDCI to provide **1g** and **1h**.

(29) Methyl (2*S*)-3-hydroxy-2-methylpropionate (Aldrich) was benzylated using benzyl trichloroacetimidate (Widmer, U. *Synthesis* **1987**, 568) and a catalytic amount of TfOH to provide the corresponding benzyl derivative which was hydrolyzed with LiOH in 4:1 THF/water to give (2*S*)-3-(benzyloxy)-2-methylpropionic acid. The enantiomer of this acid was prepared in similar manner.

(30) Reduction of citronellic acid with hydrogen and catalytic Pd–C (10%) in ethanol affords the desired dihydrocitronellic acid.

(31) Sudo, R.; Kaneda, A.; Itoh, N. *J. Org. Chem.* **1967**, *32*, 1844.

(32) Wieler, L.; Lermer, L.; Neeland, E. G.; Ounsworth, J. P.; Sims, R. J.; Tischler, S. A. *Can. J. Chem.* **1992**, *70*, 1427.

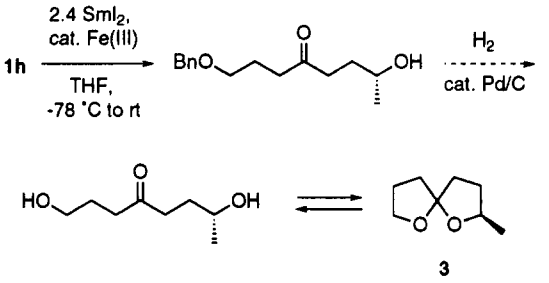
(2R)-3-(Benzyloxy)butanoic acid[34] was condensed with either (1S)- or (1R)-3-iodo-1-phenylpropanol[27] by using the EDCI method to provide 3-iodopropyl esters **1q** and **1r**. Both racemic *N,N*-dibenzylphenylalanine and (2R)-*N,N*-dibenzylphenylalanine,[35] upon condensation with (2S)-3-iodo-2-methylpropanol under similar conditions, afforded the corresponding 3-iodopropyl esters **1m,n**.

With the requisite substrates in hand, the task of exploring the scope and limitations of the SmI_2-promoted reactions was initiated (Table 1). In a typical reaction, a solution of iodide **1a** in THF was slowly added to a solution of SmI_2 and a catalytic amount of Fe(III) in THF at −78 °C. The reaction mixture was then gradually warmed to room temperature. Most of the reactions were complete within 0.5–1 h under these conditions. The products generated by this reaction exist as an equilibrium mixture of acyclic 4-hydroxy ketones and the cyclic hemiacetals.[36] In order to facilitate analysis, the 4-hydroxy ketones were converted to the corresponding acyloxy ketones. When the resultant 4-hydroxy ketone derived from **1a** was acetylated in situ using acetic anhydride, pyridine, and a catalytic amount of *N,N*-(dimethylamino)pyridine (DMAP), compound **2a** was obtained in 80% overall yield but in somewhat impure state. To circumvent this purification problem, the initially formed 4-hydroxy ketone product was isolated, purified by flash column chromatography and then acetylated to afford **2a** in 60% overall yield.

Having established a standard general procedure and carried it out on a simple substrate, we then applied the method to the synthesis of enantiomerically enriched ketones. In fact, nonracemic iodides **1b,c** provided an excellent yield of their respective acetoxy ketones **2b** and **2c** upon treatment with SmI_2 and subsequent acetylation. On the basis of the facts that the process offers no obvious means for racemization and that optical activity was indeed observed in the final products, one can infer that complete stereochemical fidelity was maintained in the transformation. The iodo esters **1d** and **1e** provided the corresponding 4-hydroxy ketones, analytical aliquots of which were converted to the corresponding Mosher esters. The enantiomeric excesses of these compounds were found to be 95 and 98%, respectively, as assessed by ^{19}F NMR of the Mosher esters.

Substrate **1f** was converted to **2f** in 71% yield, indicating that SmI_2-promoted one-electron reduction of the ketone carbonyl in the final product followed by reaction of the resultant ketyl with the double bond (generating a six-membered carbocycle by a radical cyclization process)[37] is not a major concern. Normally, these ketyl cyclization

Scheme 1. Synthesis of Enantiomerically Enriched Spiroketals



reactions are performed using SmI_2 in THF/HMPA. The milder reducing conditions utilized in the present study, perhaps in combination with a low concentration of the ketone as a result of in situ protection by intramolecular reaction with the samarium alkoxide, is likely to be responsible for the lack of cyclization observed.

Compound **3** (Scheme 1, R = Et) is the simplest member of a class of insect pheromones possessing a spiroketal ring system.[38] Seebach and co-workers synthesized this compound and some analogs in five steps by sequential alkylation of a dithiane (35% overall yield).[39] The current approach to this class of compounds requires just three steps from readily available (2R)-4-iodo-2-butanol.[33] Keto acetates **2g** and **2h** are key synthons for the preparation of the spiroketal **3** (racemic or enantiomerically enriched). Debenzylation and acid-catalyzed annulation of the corresponding 4-hydroxy ketones would be expected to furnish the desired target (Scheme 1).

As mentioned previously, one of the most demanding requirements of the desired synthetic procedure is the ability to accomplish the INAS reaction under conditions that prevent epimerization of stereocenters α to the carbonyl in the final product. Several substrates were synthesized and subjected to the SmI_2-promoted reaction to examine this issue. In the event, **2i** was prepared from **1i** in 76% yield and 98% diastereomeric purity (Table 1). Similarly, compound **2j** was obtained from **1j** in 80% yield and 97% diastereoselectivity. Based on several control experiments, it appeared that the use of a large excess of pyridine during the acetylation process could lead to epimerization of the final product. For example, when the hydroxy ketone of **2i**, obtained by SmI_2 reaction of 1 mmol of **1i**, was acetylated using 2.97 mmol of Ac_2O, 2 mg of DMAP, and 1.49 mmol of pyridine in 5 mL of CH_2Cl_2 for 1 h at 25 °C, a 91:9 ratio of diastereomers was isolated. The same ratio of reagents under more dilute conditions (12 mL of CH_2Cl_2) provided a 94:6 ratio of diastereomers. Only by using near equimolar quantities of pyridine and excess acetic anhydride (≥2 equiv) in 12 mL of CH_2Cl_2 could **2i** be isolated with no observable epimerization in the overall transformation from **1i**.

Compound **1k** and its epimer **1l** were also subjected to the SmI_2 reaction, furnishing the acetoxy derivatives **2k** and **2l** in 64 and 60% overall yields, respectively. The diastereomeric ratios were found to be 97:3 and 96:4, respectively, by GC analysis of the crude reaction mixtures. The ability to access products **2i–l** in high diastereoselectivities attests further to the near-neutral reaction conditions provided by the SmI_2 reactions. This permits

(33) Racemic 4-iodo-2-butanol: Ferreira, J. T. B.; Simonelli, F. *Tetrahedron* **1990**, *46*, 6311. (2R)-4-iodo-2-butanol: Braun, M.; Mahler, U.; Houben, S. *Liebigs Ann. Chem.* **1990**, 513. Prepared from ethyl (3R)-3-hydroxybutanoate via $LiAlH_4$ reduction in THF and subsequent treatment with Ph_3P, I_2, and imidazole in acetonitrile.

(34) Ethyl (3R)-3-hydroxybutanoate (92% ee determined by Mosher ester formation and analysis by ^{19}F NMR), obtained by acid-catalyzed depolymerization of polyhydroxybutanoate (Fluka), (Seebach, D.; Beck, A. K.; Breitschud, R.; Job, K. *Org. Synth.* **1992**, *71*, 39), was benzylated by using benzyl trichloroacetimidate (ref 29) and hydrolyzed with LiOH in THF/H_2O to afford (3R)-3-(benzyloxy)butanoic acid.

(35) Preparation of benzyl dibenzylphenylalanine: (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. (b) Reetz, M. T.; Drewes, M. W.; Matthews, B. R.; Lennick, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1479. Because the dibenzylphenylalanine is contaminated with benzyl alcohol, the benzyl ester of dibenzylphenylalanine was selectively debenzylated: (c) Bajwa, J. S. *Tetrahedron Lett.* **1992**, *33*, 2299.

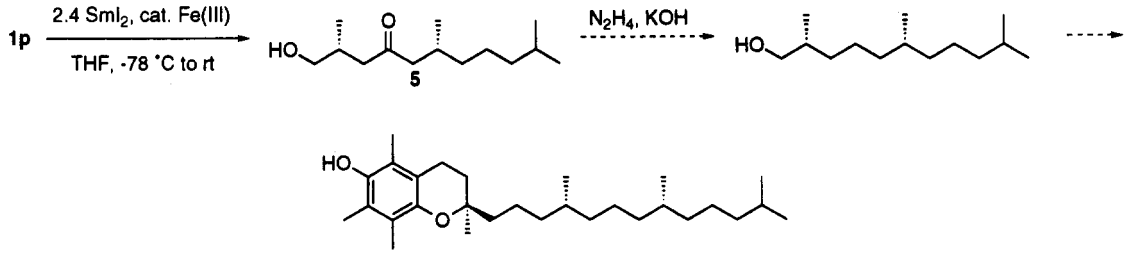
(36) Whiting, J. E.; Edward, J. T. *Can. J. Chem.* **1971**, *49*, 3799.

(37) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132.

(38) Chalcogran and related spiroketals: Francke, W.; Hindorf, G.; Reith, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 862.

(39) Seebach, D.; Hungerbuhler, E.; Naef, R.; Wasmuth, D.; Loosli, H. R.; Wehrli, A. *Helv. Chim. Acta* **1980**, *63*, 1960.

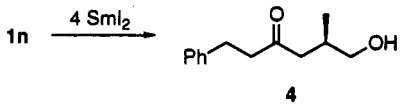
Scheme 2. Synthesis of the Vitamin E Side Chain



Vitamin E (α-Tocopherol)

the acquisition of products with stereocenters α to the carbonyl and also provides a means to synthesize materials with stereocenters far removed from one another and from the carbonyl unit itself.

Heteroatoms situated α to the carbonyl do not fare well in these reactions because of a competing reductive elimination process.[40] Although α alkoxy substituents were known to rapidly eliminate under the reaction conditions,[23] we had hoped that less nucleofugic leaving groups (like amines) could be retained α to the carbonyl in the final product. Consequently, iodo esters **1m** and **1n** were prepared and subjected to the reaction conditions. Although both could be converted to the desired keto esters **2m** and **2n**, respectively, the yields of these products were significantly lower than those previously described, and competing deamination of the resultant 4-hydroxy ketones was still evident (eq 5). Lowering the reaction temperature from room temperature to 0 °C improved the formation of the desired product by 20%, but further lowering to −20 °C did not increase the yield further. No racemization of the α stereocenter was observed in any of these cases. The reductive deamination must result from reduction of the amino ketone product and not the amino ester starting material, because subjection of the benzyl ester of *N,N*-dibenzylphenylalanine to SmI_2 and a catalytic amount Fe(III) under the reaction conditions utilized for the INAS reactions led to 93% recovery of the starting ester.



(5)

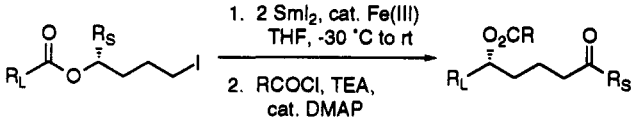
To illustrate further the utility of this synthetic method for the construction of enantiomerically enriched organic molecules with remote stereocenters, we chose to investigate the application of this strategy to the synthesis of the vitamin E side chain. The vitamin E side chain possesses 1,5-dimethyl-substituted stereogenic centers which have posed a significant challenge for efficient synthesis. This substitution pattern is also present in other biologically important molecules such as phytol,[41] vitamin K,[42] archaebacterial lipids,[43] and insect pheromones.[44] Some key approaches to this substitution pattern include acyclic stereoselection followed by resolution,[45] asymmetric induction,[46] a "chiron" approach,[47] chirality transfer,[48] and a combination of chirality transfer and "chiron" methods.[49] Most of these approaches were linear, and the syntheses were thus accomplished only through many steps. We have chosen to prepare a known synthetic intermediate to the vitamin E side chain, **5**, in a concise and convergent manner from readily available starting materials (Scheme 2). Reaction of readily available iodo ester substrates **1o** and **1p** with SmI_2, followed by acetylation afforded excellent yields of keto acetates **2o** and **2p** (Table 1). Comparative examination of the ^1H NMR and ^{13}C NMR of **2o** (as a mixture of diastereomers) with that of **2p** revealed that the latter was a single diastereomer. Because the intermediate hydroxy ketone of **2p** has already been converted to its alcohol by Wolff–Kishner reduction in 60% yield by Saucy and co-workers, this route constitutes a formal synthesis of the vitamin E side chain.[50]

It is clear that stereogenic centers virtually any distance apart can be generated by this technique. The only potential limitations would appear to be the proficiency to synthesize the appropriate substrates and to some extent the ability to analyze the final products for their enantiomeric or diastereomeric purity. The furthest point to which we have taken this concept is in the synthesis of keto acetates **2q** and **2r** possessing a 1,6 relationship between the two stereogenic centers (Table 1).

The sum of the results documented herein indicate that the NAS reaction is exceedingly general for the conversion of 3-iodopropyl carboxylates to the corresponding 4-hydroxy ketones. The only limitation with such substrates would appear to be with those that place a heterosubstituent α to the carbonyl in the final product. In these instances, rapid reductive α elimination competes,[40] leading to dramatically lower yields. It should also be noted that this particular type of NAS reaction appears strictly limited to conversions of 3-iodopropyl carboxylates. As was reported in one of the initial studies of SmI_2-promoted NAS reactions, the reaction of 4-iodobutyl carboxylates with SmI_2 proceeds via an initial NAS

(40) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.
(41) (a) Fujisawa, T.; Sato, T.; Kawara, T.; Ohashi, K. *Tetrahedron Lett.* **1981**, *22*, 4823. (b) Schmid, M.; Gerber, G.; Hirth, G. *Helv. Chim. Acta* **1982**, *65*, 684.
(42) (a) Isler, W. *Angew. Chem.* **1959**, *71*, 7. (b) Schmid, M.; Gerber, G.; Hirth, G. *Helv. Chim. Acta* **1982**, *65*, 684.
(43) Sita, L. R. *J. Org. Chem.* **1993**, *58*, 5285.
(44) (a) Mori, K.; Kuwahara, S.; Ueda, H. *Tetrahedron* **1983**, *39*, 2439. (b) Mori, K.; Harada, H.; Zagatti, P.; Cork, A.; Hall, D. R. *Liebigs Ann. Chem.* **1991**, 259.
(45) (a) Berube, G.; Deslongchamps, P. *Can. J. Chem.* **1984**, *62*, 1558. (b) Berube, G.; Deslongschamps, P. *Bull. Soc. Chim. Fr.* **1987**, 103.
(46) (a) Harada, T.; Hayashiya, T.; Wada, I.; Iwa-ake, N.; Oku, A. *J. Am. Chem. Soc.* **1987**, *109*, 527. (b) Heathcock, C. H.; Jarvi, E. T. *Tetrahedron Lett.* **1982**, *23*, 2825.
(47) (a) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505. (b) Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1979**, 995. (c) Takano, S.; Shimazaki, Y.; Iwabuchi, Y.; Ogasawa, K. *Tetrahedron Lett.* **1990**, *31*, 3619.
(48) (a) Chan, K.; Cohen, N.; DeNoble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497. (b) Chan, K.; Saucy, G. *J. Org. Chem.* **1977**, *42*, 3828. (c) Chan, K.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1978**, *43*, 3435. (d) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3512.
(49) Cohen, N.; Scott, C. G.; Neukom, C.; Lopresti, R. J.; Weber, G.; Saucy, G. *Helv. Chim. Acta* **1981**, *64*, 1158.
(50) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505.

reaction, followed by a Meerwein–Ponndorf–Verley (MPV) redox reaction (eq 6).[51] Furthermore, neither iodomethyl carboxylates, 2-iodoethyl carboxylates, nor higher analogs than the 4-iodobutyl carboxylates would appear to be suitable substrates for the reaction.



(6)

Conclusions

A variety of chiral compounds possessing a 1,4-, 1,5-, or 1,6-relationship between the two stereogenic centers have been prepared using a mild, simple, and efficient procedure. The ready availability of enantiomerically enriched starting materials (carboxylic acid and alcohol partners), combined with the high yields of these reactions, make this convergent approach highly appealing and very practical. Furthermore, because the optically active starting materials are often readily available in both enantiomeric forms, all possible combinations of stereoisomers can be easily prepared. This synthetic method should thus find broad application in the synthesis of synthetic intermediates and complex natural products.

Experimental Section

Tetrahydrofuran (THF) was purchased from Mallinckrodt, distilled from $LiAlH_4$ under argon, and stored over sodium–benzophenone ketyl. The THF was then redistilled from sodium–benzophenone ketyl immediately prior to use. Dichloromethane was distilled from P_2O_5 and stored over 4-Å molecular sieves prior to use. Acetic anhydride and pyridine were distilled before use.

Preparation of Samarium(II) Iodide Solution. Diiodomethane (0.632 g, 2.36 mmol) was added dropwise to a suspension of samarium metal (0.45 g, 3.00 mmol) in 15 mL of dry THF under argon. When the reaction mixture developed a blue color, a solution of $Fe(DBM)_3$ (0.015 g, 2.06×10^{-5} mmol) in 3 mL of THF was added by cannula. The reaction mixture was stirred at ambient temperature for 1.5 h.

6-Acetoxy-1-phenylhexan-3-one (2a). General Procedure for the Intramolecular Nucleophilic Acyl Substitution Reactions. A solution of **1a** (0.318 g, 1 mmol) in 8 mL of THF was added to the solution of SmI_2, prepared as described above, at −78 °C by a syringe pump at a rate of 0.5 mL/min. The reaction mixture was gradually warmed to room temperature over 30 min and stirred for a further 1.5 h. TLC analysis (1:10 EtOAc/hexanes, $KMnO_4$ + heat development) showed complete reaction. The reaction was quenched by adding 20 mL of a saturated solution of $NaHCO_3$. After stirring for about 5 min, the organic layer was decanted and the resultant yellowish slurry was washed six times with 20 mL of EtOAc. The combined organic extracts were dried with anhydrous $MgSO_4$. The residue obtained after evaporation of the solvent was purified by flash silica gel column chromatography (1:1 EtOAc/hexanes) to afford 140 mg (73%) of the hydroxy ketone as a yellowish oil. This compound was acetylated without further characterization.

General Method of Acetylation. *N,N*-(Dimethylamino)-pyridine (DMAP, approximately 3 mg, catalytic quantity) and pyridine (0.235 g, 2.98 mmol) were added to a CH_2Cl_2 solution (10 mL) of the crude hydroxy ketone obtained as described above. After cooling to 0 °C under argon, Ac_2O (0.206 g, 2.01 mmol) was added dropwise to this solution. The bath was removed immediately after completion of the addition of Ac_2O and the reaction mixture was stirred for 1.75 h. TLC analysis (1:1 EtOAc/hexanes, anisaldehyde + heat or ceric ammonium molybdate + heat) revealed that the reaction was complete. The reaction mixture was diluted with 25 mL of dichloromethane and washed with 10 mL each of 10% HCl, 5% $NaHCO_3$, and brine. The organic phase was dried with anhydrous $MgSO_4$ and concentrated in vacuo. The crude product obtained was purified by flash silica gel column chromatography to provide 140 mg (82%) of **2a** as a yellowish oil: Kugelrohr distilled ot 140–145°/1 mmHg; R_f 0.3 (1:5 EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (pentet, J = 6.8 Hz, 2H), 2.02 (s, 3H), 2.46 (t, J = 7.1 Hz, 2H), 2.74 (t, J = 7.5 Hz, 2H), 2.90 (t, J = 7.5 Hz, 2H), 4.04 (t, J = 6.3 Hz, 2H), 7.16–7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 22.9, 30.0, 39.4, 44.6, 63.9, 126.4, 128.6, 128.8, 141.3, 171.3, 209.2; IR (neat) 1737, 1714 cm^{-1}; HRMS calcd for $C_{14}H_{18}O_3$: 234.1256, found 234.1267; LRMS (EI) m/e 234 (5), 174 (100), 146 (13), 133 (14), 105 (60).

(5*R*)-6-Acetoxy-5-methyl-1-phenylhexan-3-one (2b). The general methods described for the preparation of **2a** was applied with following modifications. Compound **1b** (0.326 g, 0.98 mmol) in 12 mL of THF was added to the SmI_2 solution. The reaction mixture was stirred at room temperature for 2.5 h. The purification of the intermediate hydroxy ketone was accomplished by flash silica gel column chromatography (1:1 EtOAc/hexanes) to afford 0.172 g (86%) of a yellowish oil. Acetylation was carried out using 3 mg of DMAP, pyridine (0.157 g, 1.98 mmol), and Ac_2O (0.151 g, 1.48 mmol). However, the reaction was incomplete even after stirring for 4 h at ambient temperature. Thus, a further excess of Ac_2O (0.649 g, 6.36 mmol) was added and the reaction mixture was stirred for 0.5 h. The reaction was complete after this treatment based on a TLC analysis of the reaction mixture. The crude product was purified by flash chromatography to afford 0.168 g (81%) of **2b** as a colorless oil: Kugelrohr distilled ot 155–160°/1 mmHg; R_f 0.2 (1:10, EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, J = 6.6 Hz, 3H), 2.02 (s, 3H), 2.25 (dd, J = 7.1, 15.9 Hz, 1H), 2.33–2.44 (m, 1H), 2.48 (dd, J = 5.4, 15.9 Hz, 1H), 2.70–2.75 (m, 2H), 2.90 (t, J = 7.3 Hz, 2H), 3.84 (dd, J = 6.6, 11.0 Hz, 1H), 3.94 (dd, J = 5.6, 10.8 Hz, 1H), 7.16–7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 20.7, 28.5, 29.5, 44.7, 46.5, 68.4, 126.0, 128.2, 128.4, 140.9, 170.9, 208.6; IR (neat) 1738, 1714 cm^{-1}; HRMS calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1422; LRMS (EI) m/e 248 (3), 188 (72), 173 (6), 133 (19), 105 (67); $[\alpha]^{22}_D$ +6.6° (c = 0.40, $CHCl_3$).

(5*S*)-6-Acetoxy-5-methyl-1-phenylhexan-3-one (2c). Iodide **1c** (0.323 g, 0.973 mmol) was converted to **2c** in 90% overall yield (0.217 g) by following the general procedures described for **2b**: Kugelrohr distilled ot 155–160°/1 mmHg; R_f 0.35 (1:5 EtOAc: hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, J = 6.6 Hz, 3H), 2.03 (s, 3H), 2.25 (dd, J = 6.9, 15.9 Hz, 1H), 2.33–2.44 (m, 1H), 2.47 (dd, J = 5.4, 15.6 Hz, 1H), 2.73 (t, J = 6.3 Hz, 2H), 2.89 (t, J = 7.5 Hz, 2H), 3.84 (dd, J = 6.6, 10.8 Hz, 1H), 3.94 (dd, J = 5.4, 10.5 Hz, 1H), 7.16–7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 20.9, 28.6, 29.7, 44.8, 46.7, 68.5, 126.1, 128.3, 128.5, 140.9, 171.0, 208.7; IR (neat) 1738 cm^{-1}; HRMS calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1411; LRMS (EI) m/e 248 (4), 188 (100), 173 (10), 146 (100), 133 (19); $[\alpha]^{22}_D$ −5.3° (c = 0.74, $CHCl_3$).

(6*S*)-6-Acetoxy-1,6-diphenylhexan-3-one (2d). Iodide **1d** (0.394 g, 1.00 mmol) afforded **2d** in 75% overall yield. Acetylation of the intermediate hydroxy ketone (0.213 g, 0.795 mmol) was carried out using 0.24 g (2.385 mmol) of Ac_2O, 0.19 g (2.385 mmol) of pyridine and 5 mg (cat) of DMAP: Kugelrohr distilled ot 170–180°/0.5 mmHg; R_f 0.23 (1:3 ether/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.05–2.20 (m, 2H), 2.34–2.39 (m, 2H), 2.67 (t, J = 6.8 Hz, 2H), 2.85 (t, J = 7.6 Hz, 2H), 5.7 (t, J = 7.3 Hz, 1H), 7.12–7.34 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 29.6, 29.9, 38.6, 44.2, 75.0, 126.1, 126.4, 128.0, 128.3, 128.48, 128.52, 140.0, 140.9, 170.2, 208.7; IR (neat) 1740, 1712 cm^{-1}; LRMS (CI) m/e 309 (M − 1): (EI) m/e 267 (7), 105 (52), 91 (100); $[\alpha]^{22}_D$ −47° (c = 0.76, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.33; H, 7.30.

(1*R*)-6-Acetoxy-1,6-diphenylhexan-3-one (2e). Iodide **1e** (0.394 g, 1.00 mmol) afforded **2e** in 71% overall yield, after acetylation of the hydroxy ketone as described for **2d**: Kugelrohr distilled ot 170–180°/5 mmHg; R_f 0.27 (1:3 ether/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.06–2.14 (m, 2H), 2.34–2.38 (m, 2H), 2.65–2.69 (m, 2H), 2.84 (t, J = 7.6 Hz, 2H), 5.70 (t, J = 6.4 Hz, 1H), 7.12–7.32 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$)

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δ 21.2, 29.6, 30.0, 38.6, 44.3, 75.0, 126.1, 126.3, 128.0, 128.2, 128.4, 128.5, 139.9, 140.9, 170.2, 208.6; IR (neat) 1732, 1714 cm^{-1}; LRMS (CI) *m/e* 309 (M − 1): (EI) *m/e* 267 (71), 250 (46), 91 (100); $[\alpha]^{22}_D$ +48.9° (*c* = 0.62, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.19; H, 7.18.

1-Acetoxy-6,10-dimethylundec-9-en-4-one (2f). Compound **2f** was isolated in 71% yield (0.180 g) starting from 0.338 g (1 mmol) of **1f** following general methods described above: Kugelrohr distilled ot 110–120°/0.5 mmHg; R_f 0.3 (1:10 ether/hexanes); ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (d, *J* = 6.6 Hz, 3H), 1.15–1.32 (m, 2H), 1.58 (s, 3H), 1.66 (s, 3H), 1.84–2.04 (m, 5H), 2.02 (s, 3H), 2.20 (dd, *J* = 8.3, 15.9 Hz, 1H), 2.35–2.47 (m, 3H), 4.04 (t, *J* = 6.3 Hz, 2H), 5.03–5.08 (m appearing as a broad t, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 19.7, 20.9, 22.6, 25.4, 25.7, 28.9, 36.9, 39.5, 50.3, 63.7, 124.2, 131.6, 171.0, 209.8; IR (neat) 1745, 1710 cm^{-1}; HRMS calcd for $C_{15}H_{26}O_3$ 254.1882, found 254.1884; LRMS (EI) *m/e* 254 (1), 236 (4), 194 (23), 179 (8), 111 (100). Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.93; H, 10.27.

7-Acetoxy-1-(benzyloxy)octan-4-one (2g). Iodide **1g** (0.379 g, 1.013 mmol) upon reaction with SmI_2 and subsequent acetylation of hydroxy ketone (0.25 g, 1.0 mmol) using Ac_2O (1.461 g, 14.306 mmol), pyridine (1.284 g, 16.251 mmol), and 5 mg of DMAP for 18 h, provided 0.210 g (71% overall yield) of **2g** (30 mg of the intermediate hydroxy ketone was recovered): Kugelrohr distilled ot 150–160°/0.5 mmHg; R_f 0.25 (1:5 EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.2 Hz, 3H), 1.71–1.90 (m, 4H), 2.00 (s, 3H), 2.35–2.47 (m, 2H), 2.50 (t, *J* = 7.3 Hz, 2H), 3.46 (t, *J* = 6.1 Hz, 2H), 4.45 (s, 2H), 4.81–4.89 (m, 1H), 7.26–7.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 21.3, 23.8, 29.6, 38.6, 39.4, 69.2, 70.2, 72.8, 127.5, 127.6, 128.3, 138.3, 170.7, 209.6; IR (neat) 1732, 1714 cm^{-1}; LRMS (EI) *m/e* 293 (6), 232 (25), 185 (25), 141 (70), 91 (100). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.59; H, 8.47.

(7*R*)-7-Acetoxy-1-(benzyloxy)octan-4-one (2h). Iodide **1h** (0.374 g, 0.995 mmol) provided 0.205 g (71%) of **2h.** Acetylation was carried out as described for **2g**: Kugelrohr distilled ot 150–160°/0.5 mmHg; R_f 0.25 (1:5 EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.3 Hz, 3H), 1.71–1.90 (m, 4H), 1.99 (s, 3H), 2.35–2.46 (m, 2H), 2.50 (t, *J* = 7.2 Hz, 2H), 3.46 (t, *J* = 6.1 Hz, 2H), 4.45 (s, 2H), 4.81–4.89 (m, 1H), 7.26–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 21.2, 23.8, 29.5, 38.5, 39.3, 69.2, 70.1, 72.8, 127.5, 127.6, 128.3, 138.3, 170.6, 209.6; IR (neat) 1732, 1711 cm^{-1}; LRMS (EI) *m/e* 293 (0.1), 265 (0.3), 232 (5), 141 (22), 91 (100). $[\alpha]^{22}_D$ −3.68° (*c* = 0.50, $CHCl_3$). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 70.08; H, 8.45.

(2*R*,5*S*)-6-Acetoxy-2,5-dimethyl-1-phenylhexan-3-one (2i). The hydroxy ketone intermediate, obtained by SmI_2 reaction of **1i** (0.349 g, 1.01 mmol), was treated with Ac_2O (0.227 g, 2.22 mmol), catalytic DMAP, and pyridine (0.064 g, 0.81 mmol) at 0 °C to room temperature for 3 h to afford **2i** in 76% yield (0.200 g): ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 2.00 (s, 3H), 2.25–2.34 (m, 3H), 2.54 (dd, *J* = 7.4, 13.5 Hz, 1H), 2.75–2.83 (m, 1H), 2.95 (dd, *J* = 7.3, 13.4 Hz, 1H), 3.78–3.87 (m, 2H), 7.11–7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.8, 20.8, 28.2, 38.9, 45.6, 48.4, 68.4, 126.2, 128.4, 128.9, 139.6, 171.0, 212.7; IR (neat) 1739, 1712 cm^{-1}; LRMS (EI, GCMS) *m/e* 262 (2), 202 (20), 187 (26), 147 (7), 101 (100); $[\alpha]^{22}_D$ −47.3° (*c* = 0.35, $CHCl_3$). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.11; H, 8.42.

(2*S*,5*S*)-6-Acetoxy-2,5-dimethyl-1-phenylhexan-3-one (2j). The hydroxy ketone intermediate, obtained by SmI_2 reaction of **1j** (0.345 g, 0.997 mmol), was acetylated as described for **2i** to afford **2j** in 80% yield (0.210 g): Kugelrohr distilled ot 110–120°/0.5 mmHg; R_f 0.35 (1:5 EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 2.01 (s, 3H), 2.09 (dd, *J* = 7.3, 17.1 Hz, 1H), 2.24–2.39 (m, 1H), 2.47 (dd, *J* = 5.6, 17.3 Hz, 1H), 2.54 (dd, *J* = 7.3, 13.4 Hz, 1H), 2.64–2.86 (m, 1H), 2.94 (dd, *J* = 7.3, 13.2 Hz, 1H), 3.79 (dd, *J* = 6.6, 11.0 Hz, 1H), 3.88 (dd, *J* = 5.9, 11.0 Hz, 1H), 7.11–7.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 16.8, 20.8, 28.1, 39.1, 45.7, 48.4, 68.4, 126.3, 128.4, 128.9, 139.6, 171.0, 212.8; IR (neat) 1738, 1711 cm^{-1}; LRMS (EI) *m/e* 262 (5), 202 (75), 187 (62), 147 (20), 101 (92); $[\alpha]^{22}_D$ +35.8° (*c* = 0.60, $CHCl_3$). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.35; H, 8.59.

(2*S*,5*S*)-6-Acetoxy-1-(benzyloxy)-2,5-dimethylhexan-3-one (2k). Iodide **1k** (0.368 g, 0.979 mmol), upon reaction with SmI_2, provided the hydroxy ketone (0.187 g, 76%) which was treated with Ac_2O (0.26 g, 2.54 mmol), catalytic DMAP (ca. 1 mg), and pyridine (58.8 mg, 0.744 mmol) at 0 °C for 1 h and 3 h at room temperature to yield 0.183 g of **2k** (64% overall yield from **1k**): Kugelrohr distilled ot 130–135°/0.5 mmHg; R_f 0.2 (1:5 ether/hexanes); ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.4 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 3H), 2.01 (s, 3H), 2.34–2.39 (m, 2H), 2.52–2.57 (m, 1H), 2.82–2.87 (m, 1H), 3.45 (dd, *J* = 5.3, 9.0 Hz, 1H), 3.59 (t, *J* = 8.7 Hz, 1H), 3.85 (dd, *J* = 6.1, 10.8 Hz, 1H), 3.93 (dd, *J* = 5.5, 10.8 Hz, 1H), 4.44 (d, *J* = 12.1 Hz, 1H), 4.48 (d, *J* = 12.1 Hz, 1H), 7.26–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 16.9, 20.8, 28.1, 45.8, 46.6, 68.5, 72.2, 73.2, 127.5, 127.6, 128.3, 137.9, 171.0, 211.7; IR (neat) 1738, 1714 cm^{-1}; LRMS (EI) *m/e* 292 (<1), 232 (4), 186 (5), 141 (13), 126 (97), 91 (100); $[\alpha]^{22}_D$ +13.3° (*c* = 0.35, $CHCl_3$). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.10.

(2*R*,5*S*)-6-Acetoxy-1-(benzyloxy)-2,5-dimethylhexan-3-one (2l). Iodide **1l** (0.375 g, 0.997 mmol) provided 0.174 g (60%) of **2l** as a colorless oil, under conditions similar to those used for the preparation of **2k**: Kugelrohr distilled ot 130–140°/0.5 mmHg; R_f 0.26 (1:5 EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 7.1 Hz, 3H), 2.00 (s, 3H), 2.31–2.40 (m, 2H), 2.58 (dd, *J* = 4.5, 16.4 Hz, 1H), 2.81–2.86 (m, 1H), 3.43 (dd, *J* = 5.3, 9.1 Hz, 1H), 3.60 (dd/apparent t, *J* = 8.2, 8.9 Hz, 1H), 3.86 (dd, *J* = 6.2, 10.7 Hz, 1H), 3.92 (dd, *J* = 5.7, 10.8 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 7.26–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 16.9, 20.9, 28.1, 45.8, 46.7, 68.5, 72.1, 73.2, 127.6, 127.6, 128.4, 138.0, 171.1, 211.7; IR (neat) 1738, 1711 cm^{-1}; LRMS (EI) *m/e* 293 (<1), 233 (4), 186 (6), 141 (20), 126 (80), 91 (100); $[\alpha]^{22}_D$ −8.9° (*c* = 0.24, $CHCl_3$). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.63; H, 8.31.

(2*R*,5*R*)-6-Acetoxy-2-(dibenzylamino)-5-methyl-1-phenylhexan-3-one (2m). Iodide **1m** (0.523 g, 0.992 mmol) was subjected to SmI_2 reaction as described in the general method section, and the resultant hydroxy ketone (0.208 g, 0.519 mmol) was treated with Ac_2O (0.159 g, 1.557 mmol) and a catalytic amount of DMAP to furnish 0.148 g (34%) of **2m.** [When the SmI_2 reaction was carried out at −20 °C bath temperature for 6 h and the intermediate hydroxy ketone was acetylated under similar conditions, 35% of the desired product was obtained]: R_f 0.3 (1:8 EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 0.62 (d, *J* = 6.8 Hz, 3H), 1.97 (s, 3H), 2.08 (dd, *J* = 7.6, 16.5 Hz, 1H), 1.98–2.13 (m, 1H), 2.67 (dd, *J* = 5.5, 16.7 Hz, 1H), 2.90 (dd, *J* = 3.5, 13.1 Hz, 1H), 3.15 (dd, *J* = 9.6, 13.2 Hz, 1H), 3.50 (dd, *J* = 3.9, 9.6 Hz, 1H), 3.57 (d, *J* = 13.6 Hz, 2H), 3.73–3.82 (m, 4H), 7.07–7.33 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 20.8, 28.6, 29.1, 44.8, 54.6, 68.3, 68.4, 126.0, 127.3, 128.3, 128.4, 128.8, 129.4, 139.1, 139.3, 171.0, 208.9; IR (neat) 1738, 1712 cm^{-1}; HRMS calcd for $C_{29}H_{34}NO_3$ (M + 1) 444.2539, found 444.2547; LRMS (EI) *m/e* 444 (0.2), 352 (2), 300 (85), 208 (14), 91 (100); $[\alpha]^{22}_D$ 62.5° (*c* = 0.6, $CHCl_3$).

(5*R*)-6-Acetoxy-2-(dibenzylamino)-5-methyl-1-phenylhexan-3-one (2n). Iodide **1n** (0.54 g, 1.025 mmol) was treated with a solution of SmI_2 in THF at −78 °C as described in the general section, but the reaction was subsequently warmed to 0 °C. The resultant hydroxy ketone (0.240 g, 0.598 mmol) was treated with Ac_2O (0.244 g, 2.332 mmol), pyridine (0.47 g, 0.598 mmol), and a catalytic amount of DMAP to provide 0.24 g (53% overall yield) of **2n**: R_f 0.3 (1:8 EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 0.63 (d, *J* = 6.8 Hz, 1.5H), 0.75 (d, *J* = 6.8 Hz, 1.5H), 1.89 (s, 1.5H), 1.97 (s, 1.5H), 1.98–2.04 (dd, *J* = 7.6, 16.9 Hz, 0.5H), 2.07–2.15 (m, 1H), 2.26 (dd, *J* = 5.0, 16.9 Hz, 0.5H), 2.44 (dd, *J* = 8.6, 16.9 Hz, 0.5H), 2.67 (dd, *J* = 5.5, 16.9 Hz, 0.5H), 2.90 (dd, *J* = 3.7, 13.2 Hz, 1H), 3.15 (dd, *J* = 9.5, 13.1 Hz, 1H), 3.48–3.53 (m, 1H), 3.56 (2 sets of overlapping d, *J* = 13.6 Hz, 2H), 3.65–3.76 (m, 2H), 3.80 (2 sets of overlapping d, *J* = 13.3 Hz, 2H), 7.07–7.34 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 16.74, 20.7, 20.8, 28.3, 28.5, 28.8, 29.0, 44.66, 44.68, 54.5, 67.64, 68.24, 68.38, 68.46, 125.96, 125.97, 127.28, 128.32, 128.34, 128.39, 128.40, 128.81, 129.42, 129.43, 139.04, 139.07, 139.33, 170.93, 170.98, 208.71, 208.94; IR (neat) 1738, 1712 cm^{-1}; HRMS calcd for $C_{29}H_{34}NO_3$ (M + 1) 444.2538, found 444.2504; LRMS (EI) *m/e* 444 (0.3), 352 (2), 300 (81), 181 (6), 91 (100).

(2*S*)-1-Acetoxy-2,6,10-trimethylundecan-4-one (2o). Iodide **1o** (1.222 g, 3.452 mmol) in 10 mL of THF was added to a

solution of SmI_2 prepared from diiodomethane (2.25 g, 8.4 mmol) and Sm (1.604 g, 10.7 mmol) at −78 °C. Purification of the crude product by flash silica gel chromatography (1:1.5 EtOAc/hexanes, R_f = 0.4) provided 0.72 g (91%) of hydroxy ketone which was not characterized. A portion of this product (84.5 mg, 0.371 mmol) in 2 mL of CH_2Cl_2 was acetylated with Ac_2O (0.27 g, 2.65 mmol), catalytic DMAP, and pyridine (58.8 mg, 0.742 mmol) for 18 h. Purification of the crude product by flash silica gel chromatography afforded 0.100 g (>99%, 91% overall yield) of **2o**: Kugelrohr distilled ot 100–110°/0.5 mmHg; R_f 0.12 (1:6 ether/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, J = 6.8 Hz, 6H), 0.85 + 0.86 (2 sets of d, J = 6.8, 6.7 Hz, 3H), 0.92 (2 sets of d, J = 6.7 each Hz, 3H), 1.09–1.28 (m, 6H), 1.46–1.54 (m, 1H), 1.96–1.99 (m, 1H), 2.03 (s, 3H), 2.14–2.48 (m, 5H), 3.86 (dd, J = 6.4, 9.8 Hz, 1H), 3.91–3.95 (2 sets of overlapping dd, J = 5.8, 12.3 each Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.90, 16.94, 19.80, 19.83, 20.89, 22.55, 22.65, 24.67, 24.69, 27.90, 28.48, 28.51, 29.19, 37.10, 37.16, 39.03, 46.94, 46.96, 50.86, 50.91, 68.56, 68.58, 171.07, 209.73; IR (neat) 1742, 1713 cm^{-1}; HRMS calcd for $C_{16}H_{31}O_3$ (M + 1) 271.2273, found 271.2270; LRMS (EI) m/e 270 (2), 241 (1), 227 (2), 210 (4), 98 (100).

(2*R*,6*R*)-1-Acetoxy-2,6,10-trimethylundecan-4-one (2p). Compound **2p** was prepared in 75% yield (0.184 g) starting from 0.321 g (0.907 mmol) of **1p** by following a procedure similar to that used for **2o**: Kugelrohr distilled ot 100–110°/0.5 mmHg; R_f 0.125 (1:6 ether/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, J = 6.7 Hz, 6H), 0.86 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H), 1.09–1.29 (m, 6H), 1.44–1.53 (m, 1H), 1.86–1.99 (m, 1H), 2.03 (s, 3H), 2.15–2.26 (m, 2H), 2.33–2.42 (m, 2H), 2.46 (dd, J = 5.5, 16.4 Hz, 1H), 3.86 (dd, J = 6.4, 10.6 Hz, 1H), 3.94 (dd, J = 5.6, 10.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.93, 19.83, 20.85, 22.54, 22.64, 24.66, 27.90, 28.54, 29.21, 37.11, 39.03, 46.96, 50.91, 68.56, 171.02, 209.65; IR (neat) 1742, 1715 cm^{-1}; LRMS (EI) m/e 271 (3), 241 (<1), 227 (2), 211 (44), 98 (100); $[\alpha]^{22}_D$ +7.1° (c = 0.24, $CHCl_3$). Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.16; H, 10.76.

(1*R*,6*R*)-1-Acetoxy-6-(benzyloxy)-1-phenylheptan-4-one (2q). Iodide **1q** (0.428 g, 0.977 mmol) was treated with SmI_2 as described in the general section. The intermediate hydroxy ketone (0.270 g, 0.865 mmol) was treated with Ac_2O (0.519 g, 5.083 mmol), pyridine (0.078 g, 0.99 mmol), and a catalytic amount of DMAP to afford 0.220 g (64% overall yield) of **2q**: R_f 0.42 (1:1 ether/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 6.1 Hz, 3H), 2.02 (s, 3H), 2.04–2.18 (m, 2H), 2.36–2.41 (m, 3H), 2.71 (dd, J = 7.4, 15.6 Hz, 1H), 4.06–4.04 (m, 1H), 4.39 (d, J = 11.4 Hz, 1H), 4.51 (d, J = 11.5 Hz, 1H), 5.70 (t, J = 6.3 Hz, 1H), 7.23–7.50 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 21.2, 29.8, 39.6, 49.9, 70.8, 71.6, 75.1, 126.4, 127.56, 127.64, 128.0, 128.3, 128.5, 138.4, 139.9, 170.2, 208.1; IR (neat) 1732, 1715 cm^{-1}; LRMS (CI) m/e 353 (M − 1) (EI) m/e 294 (3), 203 (31), 91 (100); $[\alpha]^{22}_D$ −28.98° (c = 0.535, $CHCl_3$). Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.29; H, 7.56.

(1*S*,6*R*)-1-Acetoxy-6-(benzyloxy)-1-phenylheptan-4-one (2r). Iodide **1r** (0.438 g, 1.00 mmol) afforded 0.240 g (68% overall yield) of **2r** under reaction conditions similar to those used for **2q**: R_f 0.43 (1:1 ether/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (d, J = 6.1 Hz, 3H), 2.03 (s, 3H), 2.05–2.19 (m, 2H), 2.33–2.49 (m, 3H), 2.71 (dd, J = 7.7, 15.7 Hz, 1H), 3.96–4.04 (m, 1H), 4.39 (d, J = 11.4 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 5.70 (t, J = 6.0 Hz, 1H), 7.10–7.94 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 21.2, 29.9, 39.7, 49.9, 70.9, 71.7, 75.0, 126.3, 127.5, 127.7, 128.0, 128.3, 128.5, 138.4, 140.0, 170.2, 208.1; IR (neat) 1732, 1713 cm^{-1}; LRMS (EI) m/e 294 (2), 203 (15), 91 (100); $[\alpha]^{22}_D$ −56.03° (c = 0.68, $CHCl_3$). Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.32; H, 7.27.

Acknowledgment. We thank the National Institutes of Health for their generous support of our research program and Hauser Chemical Research for providing us with the facilities to measure the optical rotations reported herein.

Supplementary Material Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds for which no elemental analysis was obtained, and experimental details of the preparation of 3-iodopropyl carboxylates **1a–r** (57 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.