# Conjugate Addition Reactions Mediated by Samarium(II) Iodide

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Samarium(II) iodide in conjunction with a catalytic low-valent transition metal species has been employed to promote the conjugate addition reaction of primary and secondary alkyl halides onto α,β-unsaturated esters and amides. The method has been determined to be quite general and hence has been extended to the cyclization reactions of alkyl halides onto α,β-unsaturated lactones, lactams, and nitriles. The cyclization reactions described herein provide a very general approach to the synthesis of functionalized carbocycles from simple acyclic precursors with excellent diastereoselectivity and under very mild reaction conditions.

## Introduction

In the past decade, there have been numerous reports of radical or anionic cyclization processes in which alkyl halides were used as precursors in the addition to electron deficient olefinic systems (Figure 1). The radical cyclizations have been initiated primarily with tri-*n*-butyltin hydride[1] and related agents, while the anionic pathway typically occurs through a lithium−halogen exchange mediated process initiated with an alkyllithium species.[2] Although these types of reactions are conceptually very simple, there are significant limitations in their execution utilizing the traditional methods mentioned above, making them of limited utility within the scope of synthetic organic chemistry.

Tin hydride mediated cyclization reactions represent the most common method for promoting radical cyclization processes of alkyl halides with α,β-unsaturated systems,[1,3] but this method is less than ideal because of the frequent inability to remove fully the desired reaction products from the residual, toxic organotin species.[4] Removal of large amounts of tin byproducts on a preparatory scale is quite inconvenient, and this becomes particularly problematic when the desired reaction products are very nonpolar. The tin hydride mediated process is encumbered further by the inconvenience of long addition times, usually requiring the use of a syringe pump to ensure the maintenance of a low concentration of radicals over the course of the reaction. Furthermore, the tin hydride mediated processes often require more vigorous reaction conditions such as heating. These problems have been circumvented, albeit partially, by utilizing a catalytic amount of the tri-*n*-butyltin species and stoichiometric $NaBH_4$ or $Na(CN)BH_3$,[5] which allows one to keep the tin hydride concentration low but concomitantly limits the types of functionality that may be present in the substrate because of the reducing conditions of the reaction.

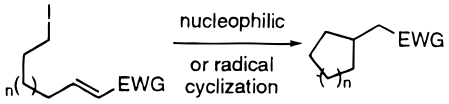


**Figure 1.** Nucleophilic or radical cyclization reactions of alkyl halides with activated olefins.

Lithium−halogen exchange mediated cyclizations have been utilized to achieve analogous results.[2] However, it too is of limited synthetic utility because of functional group incompatibilities. Reaction conditions required for the generation of the highly reactive nucleophilic center are not generally compatible with the functional groups commonly employed to predispose alkenes or alkynes to such nucleophilic attack. Specifically, the lithium−halogen exchange process works well only when the rate of the metal−halogen exchange with the primary alkyl halide and alkyllithium species is greater than competing reactions of the lithiated agents. Additionally, intramolecular ring closure must also be more rapid than other competing reactions involving the newly generated C−Li center formed after the lithium−halogen exchange reaction. Other competing reactions include addition of alkyllithium to the activated olefin, nucleophilic addition of the alkyllithium to the carbonyl, or simple deprotonation of acidic protons present in the substrate. Hence, the lithium−halogen exchange process is limited largely to primary alkyl halides coupling with α,β-unsaturated carbonyl systems possessing either doubly activated olefins such as charge-protected unsaturated acyl phosphoranes or sterically hindered ester groups that are resistant to 1,2-carbonyl additions. Although moderate success has been acheived in the preparation of 3- and 4-membered rings, the lithium−halogen exchange pro-

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(1) (a) Thebtaranouth, C.; Thebtaranouth, Y. *Tetrahedron* **1990**, *46*, 1385 and references therein. (b) Curran, D. P. *Synthesis* **1988**, 417 and 489 and references therein. (c) Hanessian, S.; Dhanoa, D. S.; Beaulieu, P. L. *Can. J. Chem.* **1987**, *65*, 1859. (d) Ihara, M.; Taniguchi, N.; Fukumoto, K.; Kametaui, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1438. (e) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992. (f) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (g) Giese, B. *Radicals in Organic Synthesis*: *Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986.

(2) (a) Cooke, M. P., Jr. *J. Org. Chem.* **1993**, *58*, 6833. (b) Cooke, M. P., Jr. *J. Org. Chem.* **1993**, *58*, 2910. (c) Cooke, M. P., Jr.; Jaw, J.-Y. *J. Org. Chem.* **1993**, 267. (d) Cooke, M. P., Jr. *J. Org. Chem.* **1992**, *57*, 1495. (e) Cooke, M. P., Jr.; Widener, R. K. *J. Org. Chem.* **1987**, *52*, 1381. (f) Cooke, M. P., Jr. *J. Org. Chem.* **1984**, *49*, 1144.

(3) Curran, D. P. In *Comprehensive Organic Synthesis*, Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vols. 4.1 and 4.2.

(4) (a) Motherwell, W. B.; Crich, D. In *Free Radical Chain Reactions in Organic Synthesis, Best Synthetic Methods*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: London, 1992; pp 131−145. (b) Neumann, W. P. *Synthesis* **1987**, 665. (c) Hamon, D. P. G.; Richards, K. P. *Aust. J. Chem.* **1983**, *36*, 2243. (d) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (e) Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449. (f) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.

(5) Kuivila, H. G.; Menapace, L. W. *J. Org. Chem.* **1963**, *28*, 2165. (b) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554. (c) Gerth, D. B.; Giese, B. *J. Org. Chem.* **1986**, *51*, 3726.

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tocol is largely limited to the preparation of 5-membered ring systems. The competing reactions described above occur much more rapidly than does the formation of 6-membered rings under these strongly reducing and highly nucleophilic reaction conditions.

The fundamental importance of conjugate addition reactions in organic synthesis demands a more general and efficient solution. The application of samarium(II) iodide to the problem was perceived as a potentially useful alternative. Samarium(II) iodide is a very mild reagent with a reduction potential that may be manipulated *via* the addition of an appropriate cosolvent[6] or catalyst.[7] Furthermore, $SmI_2$ is highly tolerant of other functionality in spite of its strong reducing ability, and thus it provides an excellent alternative to more traditional reductive coupling methods. Although there have been isolated reports[8] of $SmI_2$-mediated intramolecular cyclization of alkyl halides with α,β-unsaturated carbonyl systems, suprisingly there have been no reports of a truly general method for the preparation of functionalized carbocycles from both cyclic and acyclic substrates *via* an intramolecular conjugate addition process mediated by this reagent.

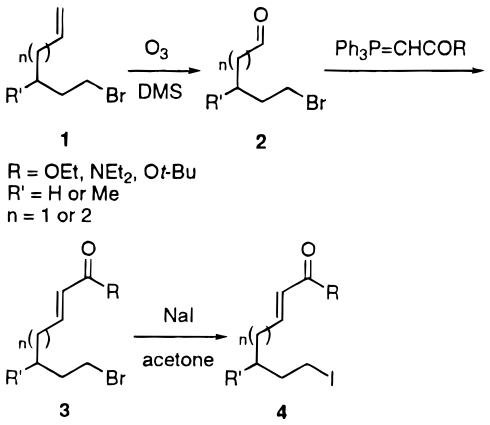
One inherent difficulty that might be anticipated in constructing these carbocyclic systems through an intramolecular cyclization reaction of an alkyl halide with an α,β-unsaturated carbonyl system is the well−demonstrated ability of $SmI_2$ to promote the 1,4-reduction of α,β-unsaturated systems.[9] However, as mentioned previously, the reduction potential of $SmI_2$ may be modulated through the addition of an appropriate cosolvent or catalyst. We report here that samarium(II) iodide, in conjunction with a catalytic amount of a low-valent transition metal salt [e.g., $NiI_2$,[7a] $Fe(acac)_3$, $Fe(DBM)_3$, or $FeCl_3$],[7b] promotes the intramolecular cyclization reaction of both primary and secondary alkyl halides with a variety of α,β-unsaturated olefinic systems including esters, lactones, amides, and lactams in high yield and under mild reaction conditions.

Under optimized reaction conditions, our anticipation of the unwanted 1,4-reduction of the α,β-unsaturated systems proved to be unfounded, and the desired carbocyclic products could be obtained readily in high yield with little, if any, products resulting from the simple 1,4-reduction of the α,β-unsaturated systems. Additionally, α,β-unsaturated alkynyl esters and amides and α,β-unsaturated nitriles were also found to be willing substrates under the standard reaction conditions, providing the corresponding cyclized vinyl esters, vinyl amides, and carbocyclic nitriles in high yield.

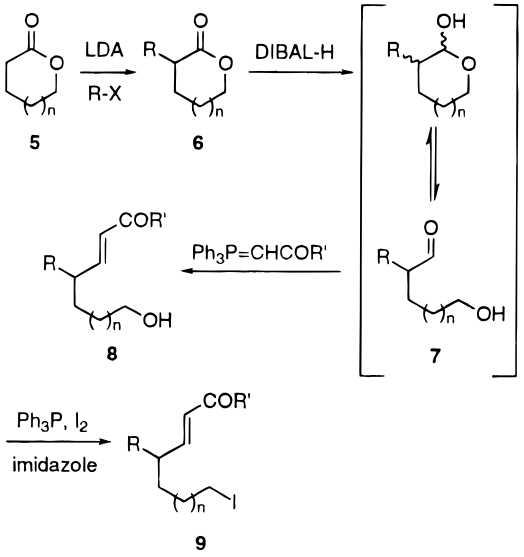
## Results and Discussion

At the outset, studies directed toward the development of the samarium(II) iodide ($SmI_2$) mediated conjugate addition reaction process began with a series of simple α,β-unsaturated esters containing a pendant haloalkyl chain. This series was prepared to test the feasibility of this cyclization process.

**Scheme 1**




**Scheme 2**




Access to the requisite substrates was achieved through either one of two related methods as outlined in Schemes 1 and 2. The first route to the required substrates (Scheme 1) involved Wittig olefination of an aldehyde, **2**, that was obtained by ozonolysis of an appropriate olefin, **1**. Subsequent Finkelstein reaction with NaI in acetone afforded the desired cyclization substrates, **4**, in a relatively few steps and in overall good yield.

Alternatively, the more functionalized substrates in this series were prepared from either the δ- or γ-lactones. In this case, the lactol precursors **7** (Scheme 2) were prepared from DIBAL-H reduction of a suitably alkylated lactone, **6**.[10] Subsequent iodination[11] of the resultant alcohol, **8**, afforded the desired halo olefins, **9**, suitable for cyclization.

Optimum reaction conditions for cyclization of these substrates involved the rapid addition of the iodoalkyl α,β-unsaturated esters or α,β-unsaturated amides (0.5 M in THF) with *t*-BuOH (1.5 equiv) to a vigorously stirred solution of 3 equiv of $SmI_2$ (0.11 M in THF) with catalytic (4 mol %) $NiI_2$[7a] cooled to −78 °C in a dry ice/acetone bath.

(6) (a) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485. (b) Ruder, S. M. *Tetrahedron Lett.* **1992**, *33*, 2621. (c) Hasegawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008. (d) Namy, J.-L.; Colomb, M.; Kagan, H. B. *Tetrahedron Lett.* **1994**, *35*, 1723. (e) Cabri, W.; Candiani, I.; Colombo, M.; Franzoi, L.; Bedeschi, A. *Tetrahedron Lett.* **1995**, *36*, 949. (f) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

(7) (a) Machrouhi, F.; Hamann, B.; Namy, J.-L.; Kagan, H. B. *Synlett* **1996**, 633. (b) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *57*, 3132.

(8) (a) Curran, D. P.; Wolin, R. L. *Synlett* **1991**, 317. (b) Zhou, Z.; Larouche, D.; Bennett, S. M. *Tetrahedron* **1995**, *51*, 11623. (c) Zhou, Z.; Bennett, S. M. *Tetrahedron Lett.* **1997**, *38*, 1153.

(9) Molander, G. A. *Org. React.* **1994**, *46*, 211.

(10) Hermann, J. L.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun.* **1973**, 711.

(11) Miller, J. G.; Underhill, E. W. *J. Org. Chem.* **1986**, *51*, 4726.

The reaction mixture was typically maintained at −78 °C for 30 min, and then the cold bath was removed and the reaction mixture was allowed to warm to ambient temperature. The reactions were complete upon reaching room temperature (ca. 30−45 min), and the products were isolated analytically pure and in high yield after either bulb-to-bulb distillation or flash column chromatography. Performing these cyclization reactions in the absence of *t*-BuOH (a proton source) produced none of the desired cyclization products. The sole products obtained under these reaction conditions were the result of rapid product decomposition owing to subsequent Claisen reaction of the resultant samarium(III) enolate with unreacted starting material or other cyclization products.

Interestingly, attempting the cyclization reaction of α,β-unsaturated olefinic alkyl bromides under the standard reaction conditions (3 equiv of $SmI_2$, 4 mol % catalyst, *t*-BuOH, −78 °C to rt, 30 min) required for the cyclization of the corresponding alkyl iodides provided a near quantitative yield of reisolated starting material with no apparent 1,4-reduction of the α,β-unsaturated ester or reduction of the bromide after stirring for 18 h at ambient temperature. Performing the desired cyclization process in the presence of $SmI_2$ and HMPA, a more strongly reducing system[9] that is known to reduce the C−I bond rapidly to the organosamarium species and also promote the rapid reduction of α,β-unsaturated carbonyl systems, provided no cyclization products.[12,13] The reaction products obtained under these conditions were largely the result of 1,4-reduction of the α,β-unsaturated system and reduction of the carbon−halogen bond to the uncyclized alkyl-substituted enoate. These observations attest to the remarkable ability for the reduction potential of $SmI_2$ to be modulated through the use of an appropriate solvent or catalyst.

The cyclization reactions discussed below were found to proceed equally well in the presence of either $NiI_2$,[7a] $Fe(acac)_3$, $Fe(DBM)_3$, or $FeCl_3$.[7b] The cyclization reactions were also found to proceed in the absence of the transition metal catalyst. However, the uncatalyzed reactions took more than 10 h to proceed to completion and would often result in a small amount of uncyclized, reduced iodide (<5%) that was difficult to remove from the desired cyclization product by flash column chromatography or distillation. Consequently, all cyclization reactions were performed in the presence of 4 mol % $NiI_2$ catalyst.

The $SmI_2$-induced cyclization reactions proceeded in high yields under the standard cyclization conditions described previously to provide the desired cyclized cyclopentaneacetic acid and cyclohexaneacetic acid derivatives **10a**−**e**, **11a**−**d**, and **13** in high yields and with good diastereoselectivity. Often only one diastereomer was detected by inspection of the $^1H$ NMR spectrum of the unfractionated, crude reaction mixture. The results of these initial studies are presented in Table 1.

Remarkably, the cyclization of the unsaturated Weinreb's amide, **9d**, proceeded very well although $SmI_2$ is known to readily reduce N−O bonds.[9,14] However, a larger excess of $SmI_2$ was required to effect this cyclization. Subjection of the unsaturated Weinreb amide substrate, **9d**, to 2 equiv of $SmI_2$ and catalytic $NiI_2$ afforded solely reduction of the amide N−OMe bond to N−H in near quantitative yield, with no cyclization products evident. Performing the reaction of **9d** with 5 equiv of $SmI_2$ afforded the desired cyclized material **11d** (with the N−OMe bond reduced) in high yield as a 30:1 mixture of diastereomers.

The rationalization for the high diastereoselectivities obtained for the 5-*exo* cyclization reactions in entry 2 (Table 1), **9a**−**d**, has been described previously.[15] They may be accounted for by comparing the two chairlike conformations corresponding to the two possible rotamers [R equatorial (**I**) and R axial (**II**)] in the transition structures of the *E*-olefin esters leading to the observed products as depicted in Figure 2. Thus, positioning the R group equatorially relieves both the 1,3-allylic strain ($A^{1,3}$-strain) and a butane-gauche interaction that are present in **II** but absent in **I** (Figure 2) to provide predominantly the *trans*-cyclization products.

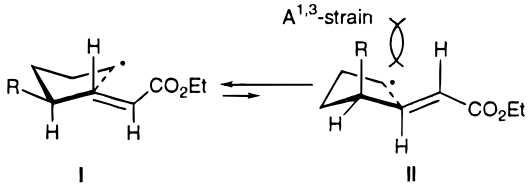
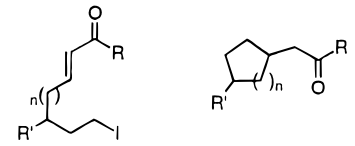
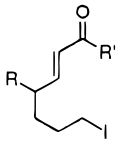
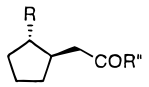
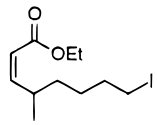
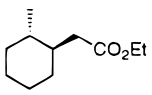



**Figure 2.** Stereodrawing depicting the source of stereocontrol for radical cyclizations in entry 2, Table 1.

**Table 1. Conjugate Addition Reactions of α,β-Unsaturated Esters and Amides**

| entry | substrate | product | % isolated yield (ds) |
|---|---|---|---|
| 1 |  |  | **4a**, R = OEt, R' = H, n = 1 — **10a**, 84%<br>**4b**, R = O*t*-Bu, R' = H, n = 1 — **10b**, 100%<br>**4c**, R = $NEt_2$, R' = H, n = 1 — **10c**, 100%<br>**4d**, R = OEt, R' = $CH_3$, n = 2 — **10d**, 84% (1.8 : 1)<br>**4e**, R = $NEt_2$, R' = $CH_3$, n = 2 — **10e**, 86% (5 : 1) |
| 2 |  |  | **9a**, R = allyl , R' = R" = OEt — **11a**, 87% (>100 : 1)<br>**9b**, R = $(CH_2)_3Cl$, R' = R" = OEt — **11b**, 74% (>100 : 1)<br>**9c**, R = ethyl, R' = R" = OEt — **11c**, 92% (>100 : 1)<br>**9d**, R = allyl , R' = N(OMe)Me, R" = NHMe — **11d**, 78% (30 : 1) |
| 3 |  |  | **12** — **13** — 85% (>100 : 1) |

(12) (a) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307 and references therein. (b) Molander, G. A.; Harris, C. R. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons Ltd: Chichester, England, 1995; Vol. 6, pp 4428−4432. (c) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. (d) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (e) Sasaki, M.; Collin, J.; Kagan, H. B. *New J. Chem.* **1992**, *16*, 89. (f) Soderquist, J. A. *Aldrichim. Acta* **1991**, *24*, 15.

(13) Shabangi, M.; Flowers, R. A. *Tetrahedron Lett.* **1997**, *38*, 1137.

(14) Chiara, J. L.; Destabel, C.; Gallego, P.; Marco-Contelles, J. *J. Org. Chem.* **1996**, *61*, 359.

(15) The *trans* stereochemisty of the cyclization products in entry 2 were determined by comparison of **9c** to the known *cis* and *trans* diastereomers; refs 1c and 2d,e.

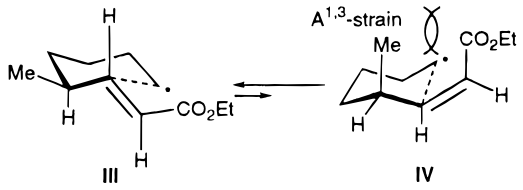
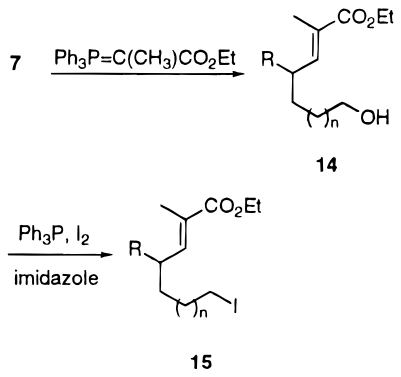



**Figure 3.** Stereodrawing depicting the source of stereocontrol for radical cyclization in entry 3, Table 1.

**Scheme 3**

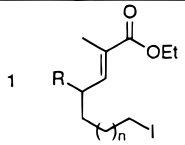
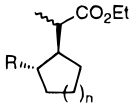
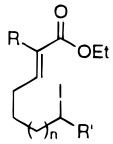
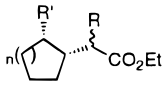
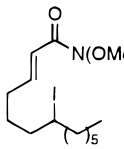
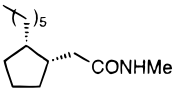



The *Z*-olefin isomer **12** was prepared as described above in Scheme 2, but through a modified Horner−Emmons Wittig in which the Wittig olefination reaction was performed under conditions wherein elimination of the initial adduct was faster than adduct equilibration, thus providing a larger ratio of the *Z*-olefin isomer. This protocol involved the use of the diethyl phosphonoester, $(EtO)_2P(O)CH_2CO_2Et$, and the strongly dissociating base system $KN(TMS)_2$ with 18-crown-6.[16]

The $SmI_2$-induced 6-*exo* cyclization reaction of **12** proceeded in high yield and high diastereoselectivity. Attempts to perform the cyclization on the corresponding *E*-olefin isomer provided respectable yields of the desired cyclization product.[17] However, the diastereoselectivity in the reaction was quite poor, resulting in a 1:1 mixture of diastereomeric products. The source of the high *trans*-stereoselectivity for the *Z*-isomer has also been described previously[2] and is believed to result from the large difference in $A^{1,3}$-strain present in the two rotamers **III** and **IV**, Figure 3, leading to the *trans*- and *cis*-cyclization products, respectively. The $A^{1,3}$-strain present in the corresponding *E*-olefin isomer is not so dramatic in this instance, thus resulting in a 1:1 mixture of *cis*- and *trans*-cyclization products.

After the initial set of experiments designed to determine the appropriate reaction conditions for the cyclization of these iodoalkyl enoates was complete, a second series of substrates was synthesized to determine the scope and limitations of this $SmI_2$-induced radical cyclization protocol. Specifically, an examination of the substitution tolerated about the olefinic portion of the molecule was performed. This series of cyclization substrates was prepared as outlined in Scheme 3 (*vide infra*). Thus, an appropriately alkylated lactone, **7**, was subjected to a Wittig olefination reaction with a suitable ylide. Subsequent iodination of **14** afforded the desired cyclization substrates, **15**, in overall good yield and in a relatively few steps.

**Table 2. Conjugate Addition Reactions of α,β-Unsaturated Esters and Amides**

| entry | substrate | product | % isolated yield (ds) |
|---|---|---|---|
| 1 |  |  | |
| | **15a**, R = H, n = 1<br>**15b**, R = Me, n = 1<br>**15c**, R = H, n = 2 | | **16a**, 91%<br>**16b**, 87% (5.3 : 1)<br>**16c**, 38% |
| 2 |  |  | |
| | **21a**, R = H, R' = *n*-pentyl, n = 1<br>**21b**, R = Me, R' = *n*-pentyl, n = 1<br>**21c**, R = H, R' = Me, n = 2 | | **22a**, 82% (4.3 : 1)<br>**22b**, 95% (10 : 2.8 : 1)<br>**22c**, 79% (1 : 1) |
| 3 |  |  | |
| | **21d** | | **22d**, 85%, (31 : 1) |

Cyclization of these substrates, **15a−c**, proceeded in both high yield and suprisingly high diastereoselectivity as outlined in entry 1, Table 2. Thus, cyclization of the α-methylated iodoalkyl enoate, **15a**, provided the corresponding α-methyl-substituted cyclopentaneacetic acid derivative, **16a**, in very good yield. Cyclization of the 2,4-dimethyl-substituted derivative, **15b**, provided the desired cyclized material, **16b**, as a 5.3:1 mixture of diastereomeric products (epimeric at the α-methyl stereocenter). Although the relative configuration of the three stereocenters present in **16b** was not proven rigorously, the *trans*-stereochemistry about the cyclopentane ring is a well-precedented observation in these types of radical cyclizations.[18] Cyclization of the α-methyl-substituted substrate in the 6-*exo* mode, **15c**, is evidently a limiting substrate in this cyclization process, affording only a very low yield of the desired cyclization product **16c**. Simple reduction of the C−I bond competes in this instance. Additionally, substrates containing a *β*-methyl group (not shown) on the olefin suffered a similar fate, affording virtually none of the desired cyclization products under the standard reaction conditions. It is well documented that the presence of an alkyl group on the *β*-position reduces dramatically the rate of 5-*exo* cyclization such that the 6-*endo* cyclization pathway becomes significant.[3,4]

Next, the ability of the α,*β*-unsaturated esters and amides to undergo intramolecular cyclization with secondary alkyl halides was investigated (Table 2, entry 3).

(16) Still, C. W.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(17) Unexplainably, the cyclization product in the cyclization of the *E*-olefin isomer invariably contained a small amount of unreacted starting α,*β*-unsaturated olefinic material even in the presence of excess $SmI_2$.

(18) (a) Hart, D. J.; Huang, H.-C. *Tetrahedron Lett.* **1985**, *26*, 3749. (b) Chaung, C.-P.; Hart, D. J. *J. Org. Chem.* **1983**, *48*, 1782. (c) Burnett, D. A.; Choi, J.-K.; Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8201. (d) Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1982**, *104*, 1430. (e) Ladlow, M.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 4413. (f) Wilcox, C. S.; Thomasco, L. M. *J. Org. Chem.* **1985**, *50*, 547.

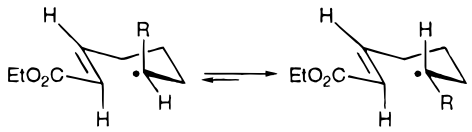
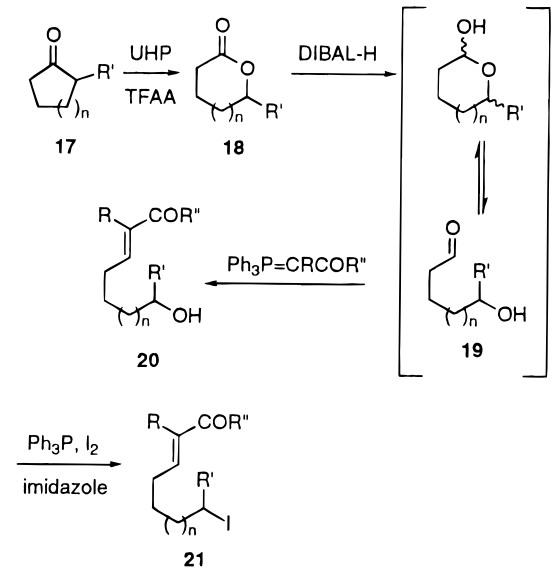


**Figure 4.** Stereodrawing for the cyclization of secondary alkyl halides.

**Scheme 4**



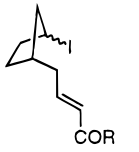
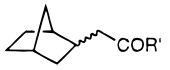
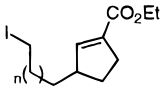
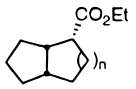
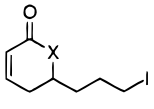
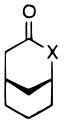
The substrates in this series were prepared as outlined in Scheme 4 from the appropriately substituted lactone, **18**, available either commercially or prepared through a Baeyer−Villiger oxidation utilizing urea hydrogen peroxide (UHP) with trifluoroacetic anhydride in high yield.[19] Subsequent DIBAL-H reduction of the resultant lactone afforded the desired substrates, **19**, for Wittig olefination with either commercially available (carbethoxymethylidene)triphenylphosphorane or *N*-methoxy-*N*-methyl-2-(triphenylphosporanylidene)acetamide. Finally, iodination of the resultant secondary alcohol, **20**, afforded the requisite secondary alkyl iodides **21** for the cyclization survey.

Fortunately, the secondary iodoalkyl enoate and enamide substrates provided the desired conjugate addition products, **22a**−**d**, in high yield. As before, treatment of the Weinreb's amide, **21d**, with 5 equiv of $SmI_2$, but under otherwise standard reaction conditions, provided the expected cyclization product, with the N−O bond reduced to N−H, in excellent yield and with suprisingly high diastereoselectivity (entry 2, Table 3). Although not determined rigorously, the major diastereomers obtained in the cyclizations in this series are presumably the *cis*-diastereomers resulting from equatorial placement of the alkyl group (R′) in the transition structure leading to the observed products (Figure 4).[1c]

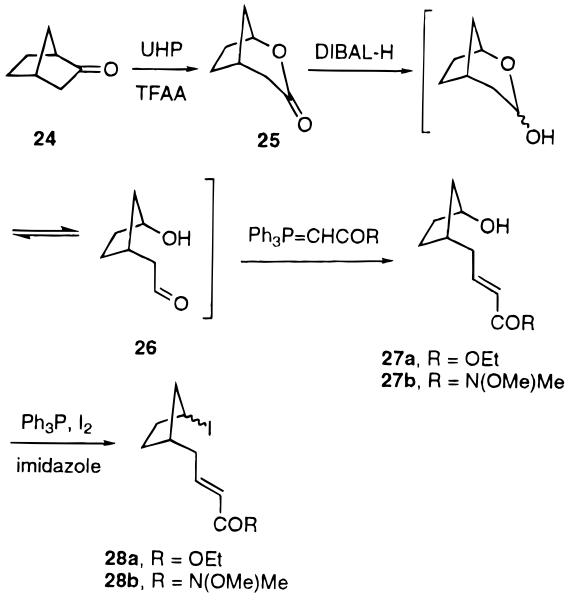
Cyclization reactions performed on a corresponding tertiary alkyl halide, **23**, were also investigated. Upon subjection of the tertiary alkyl halide to the standard cyclization reaction conditions, **23** provided a complex mixture of products, inseparable by column chromatography, as outlined in eq 1. Proton NMR of the unfractionated, crude reaction mixture revealed what appeared to be a mixture of the desired cyclization product,

(19) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533.

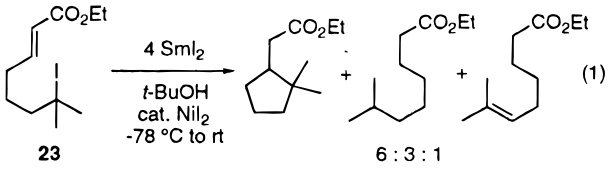
**Table 3. Radical Cyclization of Olefinic Halo Esters To Prepare Bicyclic Systems**

| entry | substrate | product | % isolated yield |
|---|---|---|---|
| 1 |  |  | **28a**, R = R' = OEt<br>**28b**, R = N(OMe)Me, R' = NHMe |
| | | | **29a**, 85% (2 : 1)<br>**29b**, 79% (1 : 1) |
| 2 |  |  | **33a**, n = 1<br>**33b**, n = 2 |
| | | | **34a**, 93% (4.7 : 1) complex |
| 3 |  |  | **38a**, X = NMe<br>**38b**, X = O |
| | | | **39a**, 88%<br>**39b**, 78% |

**Scheme 5**

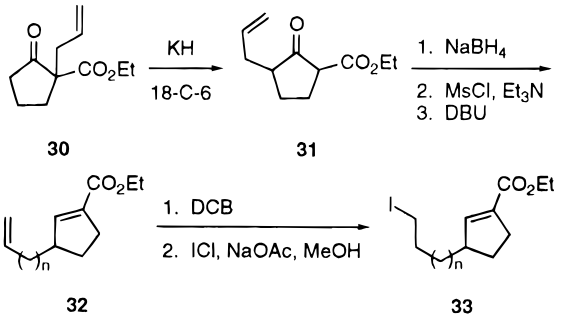


elimination of the iodide without cyclization (probably from disproportionation of the tertiary alkyl radical), and 1,4-reduction of the α,β-unsaturated ester in a 6:1:3 ratio of products, respectively.

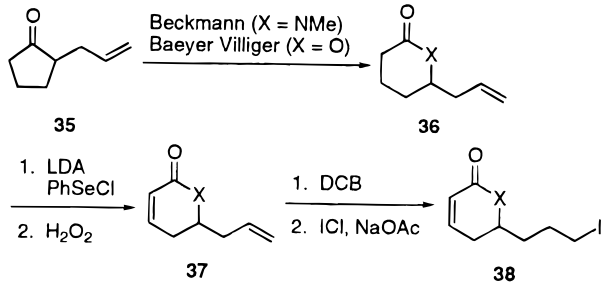


A series of selected substrates was designed to investigate the ability of this $SmI_2$-mediated cyclization protocol to promote the formation of more highly strained bicyclic systems. The substrates in this series were prepared as outlined in Schemes 5−7. Thus, as shown in Scheme 5, the cyclization precursors **28a,b** were prepared beginning with commercially available norcam-

**Scheme 6**




**Scheme 7**

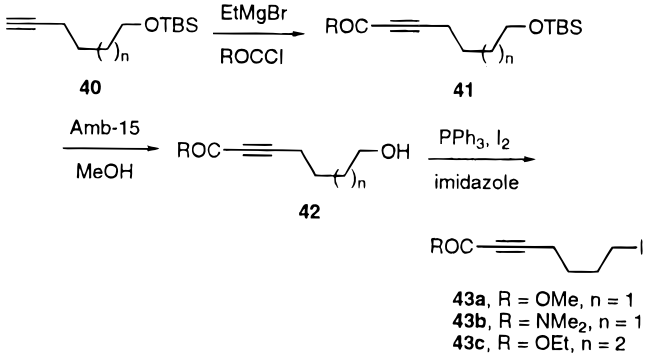



phor. Baeyer−Villiger oxidation of norcamphor, **24**, with UHP followed by DIBAL-H reduction of the resultant lactone, **25**, afforded the desired lactol, in equilibrium with its hydroxy aldehyde. The latter could be olefinated with an appropriate Wittig reagent to afford the desired hydroxy olefin, **27**. The hydroxy olefin was subjected to further iodination to afford the desired iodoalkyl enoate and enamide, **28**, for cyclization. Samarium(II) iodide mediated cyclization of the norcamphor-derived substrate provided excellent yields of both the amide- and ester-substituted bicyclo[2.2.1] systems, **29a** and **29b** (entry 1, Table 3).

Other substrates for bicyclic ring formation were prepared as outlined in Scheme 6, beginning with alkylation of commercially available ethyl 2-oxocyclopentanecarboxylate under standard conditions (NaH, allyl bromide). Next, the α-alkylated β-keto ester **30** was subjected to a rearrangement induced by KH/18-crown-6 to afford the α′-alkylated β-keto ester **31** in quantitative yield.[20] Chemoselective reduction of the ketone carbonyl with sodium borohydride followed by elimination to the conjugated olefin afforded the diene **32**, which was subjected to a regioselective one-pot hydroboration−iodination sequence[21] to afford the requisite substrate, **33**, for cyclization. Cyclization of **33a** with $SmI_2$ provided a 93% yield of the bicyclo[3.3.0] product, **34a** (entry 2, Table 3). The major diastereomer provided in this cyclization is consistent with protonation from the less sterically encumbered top face of the bicyclo[3.3.0] system.[22] Unfortunately, cyclization in the 6-*exo* mode as required for substrate **33b** afforded only a very small amount of the desired cyclization product as revealed by $^1$H NMR of the crude, unfractionated reaction material.

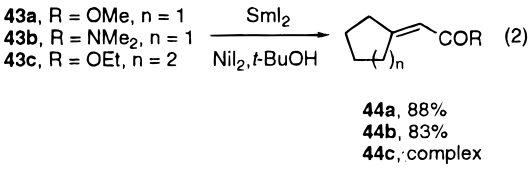
Access to the cyclization substrates **38a,b**, in entry 3, Table 3, was gained by starting with readily prepared 2-(2-propenyl)cyclopentanone, **35** (Scheme 7). Introduction of the heteroatom was acheived through either a Beckmann rearrangement[23] (**36a**, X = NMe) or a Baeyer−Villiger oxidation (**36b**, X = O) of 2-(2-propenyl)cyclopentanone. Introduction of the α,β-unsaturated olefin was gained through a PhSeCl alkylation−$H_2O_2$ oxidation sequence.[24] Finally, a one-pot regioselective hydroboration−iodination sequence was performed to provide the requisite substrates **38a,b** in overall good yield. Cyclization of these lactone and lactam substrates proceeded uneventfully and in good yield to afford the expected bicyclic[3.3.1] systems, **39a,b** (entry 3, Table 3).

**Scheme 8**




The ability of alkynyl esters and amides to undergo the desired cyclization reaction was subsequently investigated.[8b] Preparation of the alkynyl substrates, **43a,b**, proceeded in a straightforward manner (Scheme 8) beginning with the *tert*-butyldimethylsilyl-protected alkyn-1-ol, **40**, followed by carbonylation with ethylmagnesium bromide and an appropriate acid chloride. Next, deprotection of **41** proceeded smoothly with Amberlyst-15 resin in methanol, and subsequent iodination of **42** afforded the requisite iodide, **43**, for cyclization.

Upon treatment with $SmI_2$ under the standard reaction conditions, the unsaturated alkynyl systems, **43a** and **43b**,[25] cyclized to provide the exocyclic vinyl esters and amides **44a,b** in high yield (eq 2). Precautions were

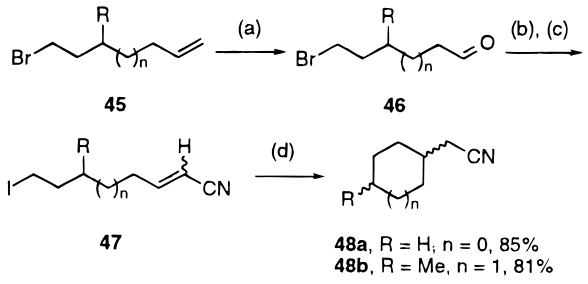



taken to ensure that no more that 2 equiv of $SmI_2$ was present during the reaction to prevent unwanted reduction of the enoate or enamide cyclization product to the corresponding saturated system. Attempts to form the corresponding six-membered exocyclic enoate proved futile. Reaction of **43c** with $SmI_2$ provided a 1:1 mixture of the reduced, uncyclized alkane and desired cyclization products plus several other unidentified products that were inseparable by flash column chromatography.

Interestingly, a previous investigation performed by Bennett et al.[8b] demonstrated the successful cyclization of **43b** mediated by $SmI_2$. However, the reaction conditions to accomplish this conversion were more vigorous, requiring heating substrate **43b** overnight in THF in the presence of a proton source to provide an 88% yield of **44b**. Similar attempts by Bennett and co-workers[8b] to

(20) Habi, A.; Gravel, D. *Tetrahedron Lett.* **1994**, *35*, 4315.
(21) Gooch, E. E.; Kabalka, G. W. *Synth. Commun.* **1981**, *11*, 521.
(22) Whitesell, J, K.; Matthews, R. S. *J. Org. Chem.* **1977**, *42*, 3878.
(23) Olah, G. A.; Fung, A. P. *Synthesis* **1979**, 537.
(24) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.
(25) (a) Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron* **1989**, *45*, 363. (b) Kita, Y.; Okunaka, R.; Honda, T.; Shindo, M.; Taniguchi, M.; Kondo, M.; Sasho, M. *J. Org. Chem.* **1991**, *56*, 119.

**Scheme 9**[a]




[a] (a) $O_3$ DMS; (b) $(EtO)_2P(O)CH_2CN$; (c) NaI, acetone (d) $SmI_2$, cat. $NiI_2$, *t*-BuOH, −78 °C to rt.

perform the cyclization of the analogous iodoalkyl alkynoate **43a** were unsuccessful under these and other attempted reaction conditions.

Finally, an investigation of other activating groups was initiated to determine fully the scope and limitations of this cyclization protocol. The olefinic activating groups that were investigated included nitriles, ketones, and nitro functionalities. The requisite substrates for this cyclization series were readily available through a modified Horner−Emmons Wittig reaction on the appropriate aldehyde as outlined in Scheme 9. As indicated, the nitrile group was found to be strongly activating toward cyclization (without undergoing simple 1,4-reduction of the olefin), providing yields of the desired product comparable to the ester and amide substrates investigated previously. For example, 5-*exo* cyclization of the 6-bromohexene derived substrate (**47a**, Scheme 9) provided the desired cyclopentane derivative, **48a**, in 85% yield. Likewise, cyclization of the citronellyl bromide−derived substrate (**47b**, a 1:1 mixture of olefinic diastereomers) provided the cyclohexane derivative **48b** in 81% yield as a 3:1 mixture of diastereomeric products.

Investigation of the corresponding α,β-unsaturated nitro compounds proved, as expected, to be a futile effort, providing only a very complex reaction mixture. The only isolable products from this effort appeared to result from reduction of both the nitro and olefin functionality to provide uncyclized, fully reduced product. Further efforts with these substrates were not pursued. Likewise, cyclization of the corresponding α,β-unsaturated ketone systems also failed and were not pursued further.[8a]

One of the unique traits of $SmI_2$ that differentiates it from other reagents in synthetic organic chemistry is its ability to sustain both radical and carbanionic processes in a single reaction vessel.[26] The ability of $SmI_2$ to promote both radical and carbanionic processes warranted an investigation into the mechanism of this conjugate addition process. The cyclization could well proceed through a mechanism involving either nucleophilic attack of an organosamarium species on the α,β-unsaturated carbonyl system or a radical addition (Figure 5). Thus, a series of experiments was designed to establish more fully the exact mechanism by which this transformation occurs.

Clearly, the empirical evidence presented thus far implied a radical-type process. This evidence includes the very high diastereoselectivities obtained for the *E*-olefins in cyclopentane formation (**11a**−**d**, Table 1). Stereoselectivity is generally higher for the radical cyclization process[1−4] and generally poor for the carbanionic

(26) (a) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1996**, *118*, 4059. (b) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 2944.

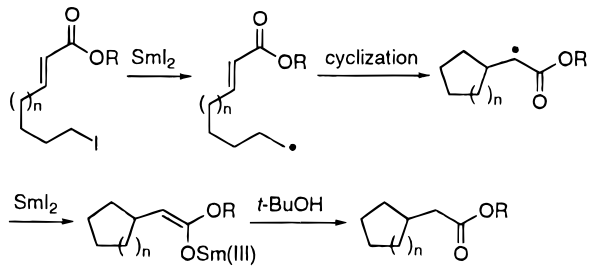
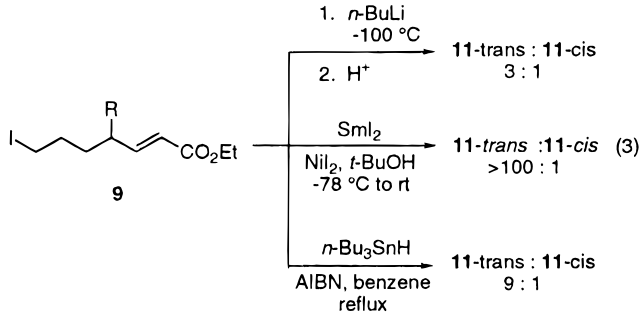
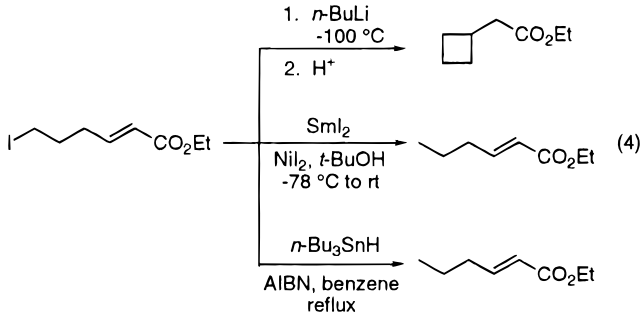



**Figure 5.** Proposed mechanism for the conjugate addition reactions of iodoalkyl enoates.

counterparts in these particular systems (eq 3).[1−4] Furthermore, the standard reaction conditions that were developed for successful cyclization required the addition of a proton source. That these cyclization reactions proceed in the presence of a proton source tends to rule out the possibility of the generation of an initial organosamarium species before cyclization occurs.

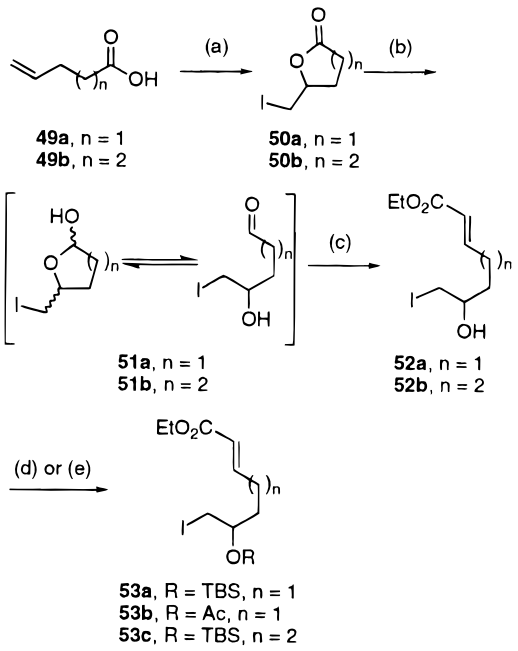



Additional circumstantial evidence supporting the radical cyclization pathway was gained by performing the reactions outlined in eq 4. Subjection of the iodoalkyl enoate in eq 4 to the standard $SmI_2$ cyclization reaction conditions described previously provides the reduced, uncyclized alkane in quantitative yield. Likewise, *n*-$Bu_3SnH$/AIBN, which is known to occur through a radical-mediated process, affords no apparent cyclobutane formation and only reduced, uncyclized alkane is isolated.[2d,e] Treatment of the same cyclization substrate under the carbanionic cyclization reactions conditions (*n*-BuLi, −100 °C) has been shown to form the cyclized cyclobutane product, and this cyclization process is believed to occur through a carbanionic intermediate.[2d,e] Thus, this experiment would point toward a radical cyclization process operating under the present $SmI_2$/catalytic $NiI_2$ reaction conditions.




Further evidence for the absence of an organosamarium (carbanion) intermediate generated either at the C−I bond or at the β-position relative to the ester was provided in the following experiments. Appropriate cyclization substrates (**52a,b** and **53a,b**) were designed

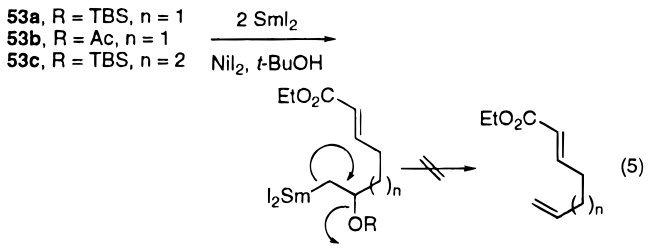
**Scheme 10**[a]



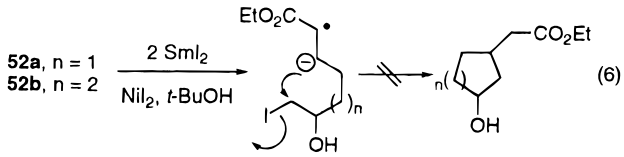

[a] (a) $I_2$, $NaHCO_3$; (b) DIBAL-H; (c) $EtO_2CCH{=}PPh_3$; (d) $Ac_2O$ DMAP, pyridine; (e) TBSCI, $Et_3N$, $CH_2Cl_2$.

such that the cyclization reaction would fail if an organosamarium intermediate was generated during the course of the reaction.[27] The cyclization substrates designed to help elucidate the mechanism of this cyclization process were prepared as outlined in Scheme 10. Beginning with the commercially available 4-pentenoic acid or 5-hexenoic acid,[28] an iodolactonization reaction provided the requisite iodo lactone, **50a,b**, in near quantitative yield. Subsequent DIBAL-H reduction, to afford **51a,b**, followed by a modified Horner−Wittig reaction provided the desired α,β-unsaturated system, **52a,b**, in good yield. Finally, the liberated hydroxyl group in either **52a** or **52b** could be protected to afford the *tert*-butyldimethylsilyl ethers, **53a** and **53c**, and acetate **53b** in near quantitative yield.

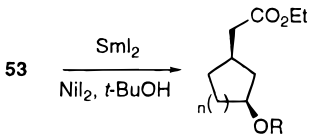
The two carbanionic reaction mechanisms that may be envisioned involve an organosamarium formed at the carbon−iodide bond (followed by nucleophilic attack on the α,β-unsaturated system, eq 5) or radical anion formation followed by $S_N2$ attack on the iodide to generate the observed carbocyclic product (eq 6). Thus, as depicted in eq 5 the cyclization reaction of the substrate should fail if there is an organosamarium intermediate formed at the C−I bond because β-elimination of the OR group should occur more rapidly than cyclization.[29]




The substrate **52a** in eq 6 should not undergo cyclization if a carbanion is formed at the β-position relative to the ester group because in this substrate there is an intramolecular proton source. Intramolecular proton transfer should be able to compete effectively in this instance to provide the protonated acyclic product.

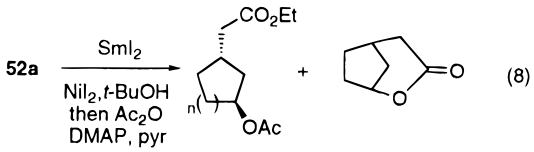



In the event, the designed substrates (**52a** and **53a**−**c**) proceeded to provide the cyclized material in excellent yield with modest diastereoselectivity as depicted in eqs 7 and 8. These results indicate that organosamarium formation is not a significant reaction pathway in these cyclizations and further suggests that a radical cyclization process must be largely operative under these reaction conditions.



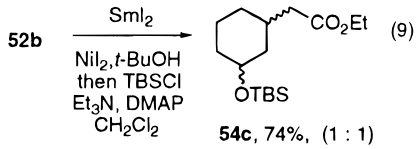

**54a**, R =TBS, n = 1, 81% (3.5 : 1)
**54b**, R = Ac, n = 1, 77% (2.5 : 1)
**54c**, R = TBS, n = 2, 88% (1.3 : 1)

Cyclization of the unprotected alcohol (**52a**) provided a mixture of *cis*- and *trans*-hydroxy esters. The *cis*-hydroxy ester underwent lactonization upon workup and chromatography to form the previously prepared **25** (eq 8). The products were best characterized after acetylation of the reaction mixture. Thus, the crude reaction mixture was subjected to acetylation to afford **54b** (as a 1.4:1 mixture of *trans* and *cis* diastereomers) and **25** in 79% combined yield (eq 8). The major diastereomer, *trans*-**54b** (resulting from unprotected alcohol cyclization), corresponds to the *minor* product obtained in the cyclization reaction of the acetate and *tert*-butyldimethylsilyl-protected alcohols above. This provided an internal proof of the stereochemistry of the cyclization products.




***trans*-54b**, 71% (1.4 : 1) **25**, 8%

Likewise, cyclization of the unprotected alcohol (**52b**) under the standard conjugate addition cyclization reaction conditions afforded a 1:1 mixture of diastereomeric alcohols in good yield. The diastereomeric products in this reaction were best characterized as the previously prepared TBS ether **54c** (eq 9).




**54c**, 74%, (1 : 1)

## Conclusions

The $SmI_2$-promoted intramolecular conjugate addition reaction has been utilized to convert a variety of cyclic and acyclic substrates to monocyclic and bicyclic carbocycles in excellent yield and fair to excellent diastereoselectivity. The substrates for these cyclization reactions are prepared readily in only a relatively few steps. The overall transformation represents a general method for the conjugate addition of alkyl halides onto α,β-unsaturated systems including esters, amides, lactones, lactams, and nitriles, thus permitting the use of more functionalized substrates and allowing for more readily isolated cyclization products than the more traditional tin hydride or alkyllithium-mediated processes. The method has also been extended to the cyclization of α,β-unsaturated alkynyl esters and -amides, providing ready access to the corresponding vinyl esters and amides.

## Experimental Section

**Reagents.** Tetrahydrofuran (THF) was distilled immediately prior to use from benzophenone ketyl under Ar. Samarium metal was purchased from Cerac Inc., Milwaukee, WI, and was stored under an inert atmosphere. $CH_2I_2$ was purchased from Aldrich Chemicals and was distilled prior to use and stored under argon over copper turnings. Standard benchtop techniques were employed for handling air sensitive reagents,[30] and all reactions were carried out under argon.

**Ethyl Cyclopentylacetate (10a). General Procedure for the Preparation of Esters from 7-Iodo and 8-Iodo α,β-Unsaturated Esters/Amides by Conjugate Addition Reactions Mediated by $SmI_2/NiI_2$.** $CH_2I_2$ (0.401 g, 1.50 mmol) was added to a vigorously stirred solution of Sm metal (0.25 g, 1.67 mmol) in 14 mL of dry THF. The resultant blue-green reaction mixture was stirred at ambient temperature for 1.5 h. After this period of stirring, $NiI_2$ (14 mg, 0.045 mmol) was added in one portion (under a flow of Ar) to the vigorously stirred $SmI_2$ solution. The resultant blue-green reaction mixture was then cooled to −78 °C in a dry ice/acetone bath, and then **4a** (0.141 g, 0.50 mmol) and *t*-BuOH (74.4 mg, 1.0 mmol) in 5 mL of dry THF were added rapidly to the vigorously stirred solution of $SmI_2/NiI_2$. After the addition of the substrate was complete, the reaction mixture was stirred an additional 30 min at −78 °C and then allowed to warm to rt. TLC at this time showed the complete consumption of the starting material and formation of a single new product. The reaction was then quenched with saturated aqueous $NaHCO_3$, filtered through a plug of Celite to remove the precipitated salts, and concentrated *in vacuo* to remove the THF solvent, and then the resultant aqueous layer was subjected to an aqueous workup. Kugelrohr distillation of the crude product afforded **10a** (65.4 mg, 0.42 mmol) in 84% yield: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.09 (q, $J$ = 7.08 Hz, 2H), 2.28 (m, 2H), 2.20 (m, 1H), 1.80 (m, 2H), 1.56 (m, 4H), 1.23 (t, $J$ = 7.08 Hz, 3H), 1.13 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.44, 60.05, 40.46, 36.51, 32.41 (2), 24.96 (2), 14.26; IR (neat) 1732.5 cm$^{-1}$; HRMS calcd for $C_9H_{16}O_2$ 156.1150, found 156.1149; LRMS (EI$^+$) $m/z$ 156 (96), 128 (100), 111 (36), 88 (98), 83 (34), 60 (47), 55 (41), 41 (51), 29 (42).

***tert*-Butyl Cyclopentylacetate (10b). 10b** was prepared from **4b** according to the general procedure for the preparation of **10a** in 100% yield after Kugelrohr distillation of the crude product (ot 110−130 °C, 0.05 mmHg): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.19 (m, 3H), 1.78 (m, 2H), 1.55 (m, 4H), 1.41 (s, 9H), 1.13 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.86, 79.82, 41.81, 36.71, 32.32 (2), 28.09 (3), 24.98 (2); IR (neat) 1731.6 cm$^{-1}$.

***N,N*-Diethylcyclopentylacetamide (10c). 10c** was prepared from **4c** according to the general procedure outlined for the preparation of **10a** in 100% yield after Kugelrohr distillation of the crude product (ot 100−120 °C, 0.05 mmHg): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.35 (q, $J$ = 7.08 Hz, 2H), 3.28 (q, $J$ = 7.08 Hz, 2H), 2.28 (m, 3H), 1.82 (m, 2H), 1.62−1.51 (m, 4H), 1.11 (m, 2H), 1.14 (t, $J$ = 7.08 Hz, 3H), 1.08 (t, $J$ = 7.08 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.87, 41.92, 39.92, 38.99, 36.83, 32.66 (2), 24.96 (2), 14.42, 13.11; HRMS calcd for $C_{11}H_{21}NO$ 183.1623, found 183.1616; LRMS (EI$^+$) $m/z$ 183 (74), 154 (83), 126 (100), 115 (100), 100 (62), 72 (41), 58 (88).

**Ethyl (4-Methylcyclohexyl)acetate (10d). 10d** was prepared from **4d** according to the general procedure outlined for the preparation of **10a** in 84% yield as a 1.8:1 mixture of diastereomeric products after Kugelrohr distillation of the crude product (ot 100−120 °C, 0.05 mmHg): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.09 (q, $J$ = 6.35 Hz, 2H), 2.25 (d, $J$ = 7.57 Hz, 0.7H), 2.14 (d, $J$ = 6.59 Hz, 1.3H), 1.67 (m, 3H), 1.45 (m, 3H), 1.23 (t, $J$ = 6.35 Hz, 3H), 1.22 (m, 4H), 0.88 (d, $J$ = 6.84 Hz, 1.1H), 0.84 (d, $J$ = 6.35 Hz, 1.9H); (major diastereomer) $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.22, 60.06, 42.17, 34.89 (2), 32.96 (2), 30.49, 28.58, 22.57, 14.28; (minor diastereomer) $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.44, 60.06, 42.17, 34.70 (2), 32.39 (2), 30.49, 28.58, 22.57, 14.28; IR (neat) 1742.2 cm$^{-1}$; HRMS calcd for $C_{11}H_{20}O_2$ 185.1546, found 185.1541; LRMS (EI$^+$) $m/z$ 184 (98), 171 (10), 165 (11), 155 (16), 139 (20), 88 (100), 70 (24), 61 (42), 55 (38), 41 (39), 29 (30).

***N,N*-Diethyl-2-(4-methylcyclohexyl)acetamide (10e). 10e** was prepared from **4e** according to the general procedure outlined for the preparation of **10a** as a 5:1 mixture of diastereomers in 86% yield after Kugelrohr distillation (ot 110−120 °C, 0.5 mmHg): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.35 (q, $J$ = 7.13 Hz, 2H), 3.28 (q, $J$ = 7.08 Hz, 2H), 2.22 (d, $J$ = 7.14 Hz, 0.33H), 2.14 (d, $J$ = 6.64 Hz, 1.67H), 1.73 (m, 2H), 1.64 (m, 2H), 1.49 (m, 1H), 1.35−1.18 (m, 2H), 1.14 (t, $J$ = 7.13 Hz, 3H), 1.08 (t, $J$ = 7.08 Hz, 3H), 0.96−0.89 (m, 3H), 0.87 (d, $J$ = 6.91 Hz, 0.5H), 0.84 (d, $J$ = 6.51 Hz, 2.5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.61, 42.05, 40.43, 34.99 (2), 34.91, 33.29 (2), 32.56, 30.92, 28.93, 22.60, 14.49, 13.16; IR (neat) 1643.9 cm$^{-1}$; HRMS calcd for $C_{13}H_{25}NO$ 211.1936, found 211.1938; LRMS (EI$^+$) $m/z$ 211 (100), 196 (20), 182 (19), 115 (98), 100 (62), 72 (34), 58 (50), 41 (23), 29 (31).

**Ethyl (1*R**,2*R**)-2-(2-Propenyl)cyclopentaneacetate (11a). 11a** was prepared from **9a** according to the general procedure outlined for the preparation of **10a** as a single diastereomer in 87% yield after flash chromatography with 3% EtOAc/hexanes: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.76 (m, 1H), 4.95 (m, 2H), 4.10 (q, $J$ = 6.96 Hz, 2H), 2.45 (dd, $J$ = 4.82, 14.72 Hz, 1H), 2.20 (m, 1H), 2.12 (m, 1H), 1.93−1.76 (m, 4H), 1.56−1.48 (m, 3H), 1.27−1.20 (m, 2H), 1.23 (t, $J$ = 6.96 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.38, 137.66, 115.33, 60.10, 45.00, 41.71, 39.64, 38.82, 32.28, 31.55, 23.47, 14.25; IR (neat) 1732.1, 1640.2 cm$^{-1}$; HRMS calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1457; LRMS (EI$^+$) $m/z$ 196 (10), 167 (13), 252 (38), 133 (22), 108 (40), 81 (51), 67 (52), 53 (21), 41 (74), 29 (100).

**Ethyl (1*R**,2*R**)-2-(3-Chloropropyl)cyclopentaneacetate (11b). 11b** was prepared from **9b** according to the general procedure outlined for the preparation of **10a** as a single diastereomer in 74% yield; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.10 (q, $J$ = 7.08 Hz, 2H), 3.51 (t, $J$ = 6.59 Hz, 2H), 2.43 (dd, $J$ = 5.13, 14.65 Hz, 1H), 2.12 (dd, $J$ = 8.79, 14.65 Hz, 1H), 1.94−1.54 (m, 11H), 1.39 (m, 1H), 1.24 (t, $J$ = 7.08 Hz, 3H), 1.18 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 173.34, 60.17, 45.28, 44.94, 42.26, 39.61, 32.20, 31.89, 31.84, 31.46, 23.48, 14.26; IR (neat) 1731.8 cm$^{-1}$; HRMS calcd for $C_{12}H_{24}ClO_2$ (M + H) 233.1308, found 233.1312; LRMS (EI$^+$) $m/z$ 233 (100), 197 (14), 187 (68), 144 (38), 123 (23), 109 (31), 88 (98), 81 (40), 67 (62), 55 (51), 41 (84), 29 (100).

**Ethyl 2-Ethylcyclopentaneacetate (11c). 11c** was prepared from ethyl (2*E*)-2-ethyl-7-iodo-2-heptenoate according to the general cyclization procedure outlined for the preparation of **10a** as a single diastereomer in 92% yield after Kugelrohr

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(29) (a) Grove, J. J.; Holzapfel, C. W.; Williams, D. B. G. *Tetrahedron Lett.* **1996**, *37*, 5817. (b) Chiara, J. L.; Martinez, S.; Bernabe, M. *J. Org. Chem.* **1996**, *61*, 6488.

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distillation (ot 100−120 °C, 10 mmHg): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.10 (q, $J$ = 7.15 Hz, 2H), 2.42 (dd, $J$ = 14.69, 4.96 Hz, 1H), 2.10 (dd, $J$ = 14.69, 9.13 Hz, 1H), 1.86−1.78 (m, 3H), 1.56−1.48 (m, 3H), 1.31−1.28 (m, 1H), 1.23 (t, $J$ = 7.15 Hz, 3H), 1.21−1.10 (m, 3H), 0.87 (t, $J$ = 7.44 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.57, 60.06, 47.38, 42.01, 39.82, 32.38, 31.48, 27.29, 23.52, 14.26, 12.65; IR (neat) 1731.8 cm$^{-1}$; HRMS calcd for $C_{11}H_{20}O_2$: 184.1463, found 184.1460; LRMS (EI$^+$) $m/z$ 184 (21), 139 (100), 109 (43), 96 (39), 88 (98), 67 (41), 61 (32), 55 (47), 41 (41).

***N*-Methyl-2-(2-Propenyl)cyclopentaneacetamide (11d). 11d** was prepared from *N*-methoxy-*N*-methyl-(2*E*)-7-iodo-4-(2-propenyl)-2-heptenamide, **9d**, according to the general procedure outlined for the preparation of **10a** (except 5 equiv of $SmI_2$ were employed) in 78% yield as a 30:1 mixture of diastereomers after flash column chromatography with 70% EtOAc/hexanes: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.81 (m, 1H), 5.44 (m, 1H), 5.02 (m, 2H), 2.83 (d, $J$ = 4.86 Hz, 3H), 2.40 (dd, $J$ = 4.56, 13.80 Hz, 1H), 2.26 (m, 1H), 2.02−1.81 (m, 5H), 1.63−1.50 (m, 5H), 1.27 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ 173.28, 137.76, 115.25, 45.16, 42.25, 42.03, 38.86, 32.38, 31.55, 26.19, 23.45; IR (neat) 3465.5, 1664.1, 1522.0 cm$^{-1}$; HRMS calcd for $C_{11}H_{22}NO$ 181.1467, found 181.1457; LRMS (EI$^+$) $m/z$ 181 (42), 140 (100), 123 (30), 73 (98), 58 (30), 40 (22). Anal. Calcd for $C_{11}H_{22}NO$: C, 72.88; H, 10.56. Found: C, 72.68; H, 10.86.

**Ethyl (1*R**,2*S**)-2-Methylcyclohexaneacetate (13). 13** was prepared from ethyl (2*Z*)-8-iodo-4-methyl-2-octenoate, **12**, according to the general procedure outlined for the preparation of **10a** as a single diastereomer ($^1$H NMR) in 85% yield after Kugelrohr distillation (ot 110−120 °C, 15 mmHg); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.10 (q, $J$ = 6.96 Hz, 2H), 2.50 (dd, $J$ = 14.46, 4.28 Hz, 1H), 1.98 (dd, $J$ = 14.72, 9.10 Hz, 1H), 1.71−1.62 (m, 4H), 1.41 (m, 1H), 1.23 (t, $J$ = 7.23 Hz, 3H), 1.96 (m, 2H), 1.16−0.92 (m, 3H), 0.87 (d, $J$ = 6.42 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.74, 60.05, 41.35, 39.63, 37.23, 35.55, 32.58, 26.37, 26.28, 20.17, 14.26; IR (neat) 1738.0 cm$^{-1}$; HRMS calcd for $C_{11}H_{20}O_2$ 184.1455, found 184.1463; LRMS (EI$^+$) $m/z$ 184 (20), 139 (100), 96 (20), 88 (99), 81 (12), 70 (21), 61 (40), 55 (39), 41 (29), 29 (30).

**Ethyl 2-Cyclopentylpropionate (16a). 16a** was prepared from **15a** according to the general cyclization procedure outlined for the preparation of **10a** in 91% yield after flash column chromatography with 5% EtOAc/hexanes: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.10 (dq, $J$ = 1.87, 7.23 Hz, 2H), 2.21 (m, 1H), 1.94 (m, 1H), 1.76 (m, 1H), 1.68 (m, 1H), 1.61−1.46 (m, 4H), 1.23 (t, $J$ = 7.23 Hz, 3H), 1.18 (m, 2H), 1.12 (t, $J$ = 6.96 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 176.77, 59.94, 45.10, 43.48, 30.83, 30.27, 25.17, 25.08, 16.17, 14.28; IR (neat) 1731.9, 1455.3, 1373.5 cm$^{-1}$; HRMS calcd for $C_{10}H_{18}O_2$ 170.1307, found 170.1302; LRMS (EI$^+$) $m/z$ 170 (11), 155 (99), 127 (76), 102 (100), 97 (34), 74 (50), 67 (21), 55 (83), 41 (70), 29 (99). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.98; H, 10.78.

**Ethyl 2-[(1*R**,2*R**)-2-Methylcyclopentyl]propionate (16b). 16b** was prepared from **15b** according to the general cyclization procedure for **10a** in 87% yield as a 5.3:1 mixture of diastereomers epimeric at C-2 and isolated by flash column chromatography with 5% EtOAc/hexanes: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.09 (dq, $J$ = 7.23, 2.14 Hz, 2H), 2.40 (m, 1H), 1.79−1.63 (m, 3H), 1.59−1.48 (m, 3H), 1.34 (m, 1H), 1.23 (t, $J$ = 7.23 Hz, 3H), 1.19 (m, 1H), 1.13 (d, $J$ = 6.96 Hz, 3H), 0.97 (d, $J$ = 6.43 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 176.28, 59.89, 50.23, 43.12, 37.21, 35.21, 30.28, 24.00, 20.93, 15.69, 14.29; IR (neat) 1731.8, 1548.1, 1512.6, 1462.0, 1377.7, 1333.1, 1255.1, 1158.7 cm$^{-1}$; HRMS calcd for $C_{11}H_{20}O_2$ 184.1477, found 184.1463; LRMS (EI$^+$) $m/z$ 184 (13), 169 (98), 139 (71), 111 (46), 102 (100), 95 (21), 81 (25), 74 (72), 69 (53), 55 (81), 41 (90).

**Ethyl 2-Methylcyclohexaneacetate (16c). 16c** was prepared from ethyl (2*E*)-8-iodo-2-methyl-2-octenoate according to the general procedure outlined for the preparation of **10a** in 38% yield after flash column chromatography with 2% EtOAc/hexanes: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.10 (dq, $J$ = 6.69, 2.67 Hz, 2H), 2.20 (m, 1H), 1.72−1.39 (m, 6H), 1.23 (t, $J$ = 6.96 Hz, 3H), 1.21−1.12 (m, 3H), 1.07 (d, $J$ = 6.96 Hz, 3H), 0.81−1.01 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 176.56, 59.91, 45.48, 40.74, 31.14, 29.60, 26.33, 26.28, 26.24, 14.29, 13.99; IR (neat) 1732.1 cm$^{-1}$; HRMS calcd for $C_{11}H_{20}O_2$ 184.1463, found 184.1476; LRMS (EI$^+$) $m/z$ 184 (21), 139 (99), 102 (100), 111 (39), 74 (77), 69 (51), 55 (60), 41 (58), 29 (49). Anal. Calcd for $C_{11}H_{20}O_2$: C, 72.70; H, 10.94; Found: C, 72.48; H, 11.16.

**Ethyl (1*R**,2*S**)-2-*n*-Pentylcyclopentaneacetate (22a). 22a** was prepared from ethyl (2*E*)-7-iodo-2-dodecenoate, **21a**, according to the general procedure for the preparation of **10a** in 82% yield as a 4.3:1 mixture of diastereomeric products (capillary GC) after flash column chromatography with 2% EtOAc/hexanes: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.58 (m, 2H), 2.78 (m, 2H), 2.53 (m, 1H), 2.31 (m, 1H), 2.22−1.92 (m, 4H), 1.83−1.63 (m, 9H), 1.73 (m, 3H), 1.56 (m, 1H), 1.34 (m, 3H); (major diastereomer) $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.98, 60.07, 42.44, 38.96, 34.87, 32.15, 30.74, 29.95, 29.91, 28.17, 22.64, 22.35, 14.26, 14.07; IR (neat) 1738.0, 1465.6 cm$^{-1}$; LRMS (EI$^+$) $m/z$ 226 (42), 197 (13), 181 (100), 155 (37), 138 (24), 127 (13), 88 (98), 81 (32), 67 (41), 55 (43), 41 (45), 25 (42). Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.50; H, 11.67.

**Ethyl (1*R**,2*S**,2′*R**/*S**)-2-(2′-*n*-Pentylcyclopentyl)propionate (22b).** Prepared from ethyl (2*E*)-7-iodo-2-methyl-2-dodecenoate, **21b**, according to the general procedure for the preparation of **10a** to afford the desired cyclized product in 95% yield as a 10:2.8:1 mixture of diastereomers (capillary GC) after flash column chromatography with 2% EtOAc/hexanes: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.09 (m, 2H), 2.32 (m, 1H), 1.88 (m, 2H), 1.75−1.48 (m, 5H), 1.36−1.05 (m, 8H), 1.23 (t, $J$ = 7.23 Hz, 3H), 1.13 (d, $J$ = 6.69 Hz, 3H), 0.86 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 177.21, 59.96, 47.74, 40.92, 39.55, 32.12, 29.32, 27.72, 27.61, 26.63, 22.71, 21.85, 16.66, 14.26, 14.08; IR (neat) 1735.7, 1460.3 cm$^{-1}$; LRMS (EI$^+$) $m/z$ 240 (99), 225 (100), 197 (89), 167 (41), 102 (96), 95 (32), 83 (30), 69 (36), 55 (25), 41 (13), 28 (14). Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.90; H, 11.89.

**Ethyl 2-Methylcyclohexaneacetate (22c).** Prepared from ethyl (2*E*)-8-iodo-2-nonenoate, **21c**, according to the general procedure outlined for the preparation of **10a** to afford the desired cyclized product as a 1:1 mixture of diastereomers (capillary GC and $^1$H NMR) in 77% combined yield after flash column chromatography with 3% EtOAc/hexanes: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.09 (q, $J$ = 7.23 Hz, 2H), 2.50 (dd, $J$ = 4.55, 14.72 Hz, 0.5H), 2.28−2.12 (m, 1.5H), 2.06 (m, 0.5H), 1.97 (dd, $J$ = 8.83, 14.72 Hz, 0.5H), 1.78 (m, 0.5H), 1.71−1.59 (m, 1H), 1.52 (m, 0.5H), 1.48−1.28 (m, 4H), 1.23 (t, $J$ = 7.23 Hz, 3H), 1.19 (m, 1H), 1.12−0.96 (m, 2H), 0.87 (d, $J$ = 6.43 Hz, 1.5H), 0.82 (d, $J$ = 6.43 Hz, 1.5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.74, 60.06, 41.33, 39.62, 37.22, 36.99, 35.53, 32.56, 32.51, 31.95, 27.97, 26.36, 26.26, 24.28, 22.19, 20.17, 14.72, 14.25; IR (neat) 1737.9 cm$^{-1}$; HRMS calcd for $C_{11}H_{20}O_2$ 184.1463, found 184.1477; LRMS (EI$^+$) $m/z$ 184 (11), 139 (100), 97 (41), 88 (98), 81 (26), 70 (31), 61 (50), 55 (53), 41 (38), 29 (33). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 72.11; H, 11.09.

***N*-Methyl-(1*R**,2*R**)-2-*n*-pentyl-1-cyclopentaneacetamide (22d). 22d** was prepared from *N*-methoxy-*N*-methyl-(2*E*)-7-iodo-2-dodecenamide, **21d**, according to the general procedure for the preparation of **10a** (except 5 equiv of $SmI_2$ were employed in this reaction) in 85% of yield as a 30:1 mixture of diastereomeric products (capillary GC) of undetermined stereochemistry. The product was isolated using flash column chromatography with 50% EtOAc/hexanes: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.42 (s, 1H), 2.78 (d, $J$ = 4.88 Hz, 3H), 2.31 (m, 1H), 2.22 (dd, $J$ = 13.92, 5.13 Hz, 1H), 1.84 (dd, $J$ = 10.50, 13.92 Hz, 1H), 1.83 (m, 1H), 1.76−1.42 (m, 4H), 1.36−1.02 (m, 10H), 0.86 (t, $J$ = 6.84 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.90, 42.47, 39.31, 36.79, 32.13, 30.51, 29.24 (2), 28.11, 26.09, 22.60, 22.32, 14.03; IR (neat) 3299.2, 1659.0, 1643.7, 1567.2, 1555.7, 1453.9 cm$^{-1}$; LRMS (EI$^+$) $m/z$ 211 (34), 196 (8), 182 (32), 168 (100), 140 (54), 154 (43), 73 (50), 58 (42), 41 (30). Anal. Calcd for $C_{13}H_{25}NO$: C, 73.88; H, 11.84. Found: C, 73.61; H, 12.19.

**Ethyl (1*R**/*S**,2*R**,5*R**)-Bicyclo[2.2.1]heptane-1-acetate (29a).**[31] **29a** was prepared from ethyl (*E*)-4-[(1*R**,3*R**/*S**)-3-iodocyclopentyl]-2-butenoate, **28a**, according to the general cyclization procedure outlined for the preparation of **10a** to afford the desired cyclized product as a 2:1 mixture of diastereomers in 85% yield after flash column chromatography with 2% EtOAc/hexanes: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.09 (q, $J$ = 7.23 Hz, 2H), 2.30−2.19 (m, 2H), 2.14−2.06 (m, 2H), 1.86 (m, 2H), 1.48 (m, 3H), 1.33−1.20 (m, 2H), 1.23 (t, $J$ = 7.23 Hz, 3H), 1.14−1.01 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.58, 173.15, 60.02, 41.27, 41.07, 40.12, 39.72, 38.40, 37.66, 37.60, 37.04, 36.67, 36.56, 36.39, 35.15, 29.30, 29.72, 28.50, 22.56, 14.23; IR (neat) 1731.9 cm$^{-1}$; LRMS (EI$^+$) *m*/*z* 182 (64), 153 (63), 137 (100), 113 (81), 95 (98), 88 (99), 79 (40), 67 (98), 61 (23), 55 (30), 41 (52), 29 (62). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.29; H, 10.19.

***N*-Methyl-(1*R**/*S**,2*R**,5*R**)-bicyclo[2.2.1]heptane-1-acetamide (29b). 29b** was prepared from *N*-methoxy-*N*-methyl-(2*E*)-[(1*R**,3*R**/*S**)-3-iodocyclopentyl]-2-butenamide, **28b**, according to the general procedure outlined for the preparation of **10a** (except 5 equiv of $SmI_2$ were employed) in 79% yield as a ca. 1:1 mixture of diastereomers after flash column chromatography with 70% EtOAc/hexanes: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.40 (s, 1H), 2.78 (d, $J$ = 4.86 Hz, 3H), 2.24−2.09 (m, 3H), 1.99−1.95 (m, 1H), 1.89−1.78 (m, 1H), 1.61 (m, 0.4H), 1.51−1.40 (m, 2.6H), 1.35 (m, 1H), 1.27−1.19 (m, 2H), 1.13−1.00 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.57, 173.10, 60.65, 43.66, 41.07, 40.26, 39.81, 39.73, 38.95, 37.77, 37.08, 36.99, 36.71, 36.61, 35.20, 30.07, 29.77, 28.53, 26.20, 26.17, 22.67, 14.15; IR ($CHCl_3$) 3465.1, 1663.3, 1521.2 cm$^{-1}$; HRMS calcd for $C_{10}H_{17}NO$ 167.1310, found 167.1320; LRMS (EI$^+$) *m*/*z* 167 (12), 138 (7), 109 (8), 98 (12), 81 (12), 73 (100), 58 (34), 41 (18), 28 (26). Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.24. Found: C, 71.65; H, 10.45.

**Ethyl (1*R**,2*R**/*S**,5*S**)-2-Bicyclo[3.3.0]octanoate (34a). 34a** was prepared from ethyl 3-(3-iodopropyl)-1-cyclopentenecarboxylate according to the general procedure for the preparation of **10a** in 93% yield as a 4.7:1 mixture of diastereomeric products (capillary GC) after Kugelrohr distillation (ot 110−120 °C): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.11 (m, 2H), 2.69 (m, 2H), 2.45 (m, 0.80H), 2.26 (m, 0.2H), 1.90−1.82 (m, 1H), 1.78−1.41 (m, 6H), 1.27 (m, 1H), 1.26 (t, $J$ = 6.96 Hz, 3H), 1.11 (m, 2H); (major diastereomer) $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 174.59, 59.86, 48.69, 45.49, 42.77, 34.95, 31.76, 29.82, 27.45, 26.26, 14.33; (minor diastereomer) $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 176.30, 60.07, 51.87, 47.77, 43.26, 33.49, 33.41, 32.89, 31.37, 25.31, 14.25; IR (neat) 1731.7 cm$^{-1}$; LRMS (EI$^+$) *m*/*z* 182 (13), 154 (12), 136 (67), 109 (48), 94 (50), 67 (100), 55 (23), 41 (54), 29 (49). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.53; H, 9.93.

**2-(*N*-Methylamino)bicyclo[3.3.1]nonan-3-one (39a). 39a** was prepared from dihydro-*N*-methyl-6-(3-iodopropyl)pyridin-2-one according to the general procedure outlined for the preparation of **10a** to afford the desired bicyclic lactam in 88% yield after flash column chromaography with EtOAc and Kugelrohr distillation (ot 110−120 °C, 0.05 mmHg): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.44 (m, 1H), 2.90 (s, 3H), 2.57 (dd, $J$ = 18.20, 7.23 Hz, 1H), 2.21 (dd, $J$ = 18.20, 1.60 Hz, 1H), 2.18 (m, 1H), 1.91−1.82 (m, 2H), 1.70 (dq, $J$ = 12.58, 2.41 Hz, 1H), 1.62−1.50 (m, 3H), 1.47−1.38 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.47, 54.75, 37.61, 33.66, 31.89, 31.87, 28.14, 27.21, 16.51; IR (neat) 1643.8 cm$^{-1}$; HRMS calcd for $C_9H_{14}N$ (M − H)$^+$ 136.1126, found 136.1135; LRMS (EI$^+$) *m*/*z* 136 (8), 122 (9), 108 (68), 97 (92), 81 (81), 69 (31), 55 (100), 41 (74).

**2-Oxabicyclo[3.3.1]nonan-3-one (39b).** Prepared from dihydro-6-(3-iodopropyl)pyran-2-one according to the general procedure outlined for the preparation of **10a** to afford the desired cyclized product in 78% yield after flash column chromatography with 13% EtOAc/hexanes: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.73 (m, 1H), 2.72 (dd, $J$ = 18.56, 6.64 Hz, 1H), 2.46 (m, 1H), 2.26 (m, 1H), 2.08−1.94 (m, 2H), 1.74−1.54 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.01, 75.45, 36.01, 30.98, 30.33, 25.99, 15.95.

(31) Trecker, D. J.; Foote, R. S. *J. Org. Chem.* **1968**, *33*, 3527.

**Methyl 2-Methylenecyclopentaneacetate (44a). 44a** was prepared from **43a** according to the general procedure outlined for the preparation of **10a** in 88% yield after Kugelrohr distillation (ot 90−110 °C, 15 mmHg): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.78 (m, 1H), 3.66 (s, 3H), 2.74 (m, 2H), 2.41 (m, 2H), 1.75−1.61 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.51, 167.31, 111.18, 50.76, 35.94, 32.64, 26.39, 25.49; IR (neat) 1714.3, 1651.7 cm$^{-1}$; HRMS calcd for $C_8H_{12}O_2$ 140.0838, found 140.0832; LRMS (EI$^+$) *m*/*z* 140 (100), 109 (77), 105 (52), 79 (13), 57 (22), 41 (31), 32 (22), 28 (100).

***N*,*N*-Dimethyl-2-methylenecyclopentaneacetamide (44b). 44b** was prepared from **43b** according to the general procedure outlined for the preparation of **10a** in 83% yield after Kugelrohr distillation (ot 100−120 °C, 15 mmHg): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.05 (m, 1H), 3.00 (s, 3H), 2.94 (s, 3H), 2.68 (m, 2H), 2.39 (m, 2H), 1.69 (m, 2H), 1.61 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 167.98, 162.54, 111.27, 37.48, 35.57, 35.04, 31.85, 26.51, 25.50; IR (neat) 1651.1, 1614.0 cm$^{-1}$; HRMS calcd for $C_9H_{15}NO$ 153.1154, found 153.1149; LRMS (EI$^+$) *m*/*z* 153 (84), 124 (11), 109 (100), 87 (26), 81 (67), 72 (49), 53 (27), 41 (28), 27 (18).

**Cyclopentaneacetonitrile (48a). 48a** was prepared from (1*E*/1*Z*)-1-cyano-6-iodo-1-hexene according to the general procedure outlined for the preparation of **47** in 85% yield after flash column chromatography with 2% EtOAc/hexanes; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 2.08 (d, $J$ = 6.85 Hz, 2H), 1.95−1.87 (m, 1H), 1.63 (m, 2H), 1.43 (m, 2H), 1.34 (m, 2H), 1.04 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 119.34, 36.24, 32.02 (2), 24.97 (2), 22.72; IR (neat) 2245.9 cm$^{-1}$; HRMS calcd for $C_7H_{11}N$ 108.0813, found 108.0805; LRMS (EI$^+$) *m*/*z* 108 (17), 94 (11), 80 (20), 69 (100), 55 (27), 41 (99), 27 (35).

**(*cis*/*trans*)-4-Methylcyclohexaneacetonitrile (48b). 48b** was prepared from a 1:1 mixture of (1*E*/1*Z*)-1-cyano-5-methyl-7-iodo-1-heptene according to the general procedure for the preparation of **10a** to afford a 3:1 mixture of diastereomers (stereochemistry undetermined) in 81% yield after flash chromatography with 1% EtOAc/hexanes: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 2.29 (d, $J$ = 7.35 Hz, 0.4H), 2.22 (d, $J$ = 6.65 Hz, 1.6H), 1.83 (m, 1H), 1.71 (m, 1H), 1.58 (m, 1H), 1.48 (m, 1H), 1.28 (m, 2H), 1.08 (dq, $J$ = 12.90, 3.37 Hz, 2H), 0.94 (m, 2H), 0.91 (d, $J$ = 6.85 Hz, 0.6H), 0.87 (d, $J$ = 6.55 Hz, 2.4H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 118.89, 34.60, 34.48, 32.85, 32.41, 32.05, 30.18, 27.81, 24.65, 22.33, 19.75; IR (neat) 2245.5 cm$^{-1}$; HRMS calcd for $C_9H_{14}N$ (M − H)$^+$ 136.1126; found 136.1135; LRMS (EI$^+$) *m*/*z* 136 (8), 122 (9), 108 (68), 97 (92), 81 (81), 69 (31), 55 (100), 41 (74).

**Ethyl (1*R**,2*R**/*S**)-3-[[(*tert*-Butyldimethylsilyl)oxy]cyclopentaneacetate (54a). 54a** was prepared from ethyl (2*E*)-7-[(*tert*-butyldimethylsilyl)oxy]-7-iodo-2-heptenoate according to the general procedure outlined for the preparation of **47** to afford the desired cyclized product in 81% yield as a 3:1 mixture of diastereomers (cis diastereomer major) after flash column chromatography with 2% EtOAc/hexanes: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.25 (m, 0.25H), 4.20 (m, 0.75H), 4.09 (q, $J$ = 7.15 Hz, 1.5H), 4.08 (q, $J$ = 7.05 Hz, 0.5H), 2.52 (m, 0.25H), 2.38−2.36 (m, 1.5H), 2.25 (m, 0.5H), 2.22 (m, 0.75H), 2.02 (m, 0.75H), 1.95 (m, 0.25H), 1.84 (m, 0.25H), 1.77 (m, 0.75H), 1.69 (m, 0.75H), 1.61−1.55 (m, 0.75H), 1.51 (m, 0.25H), 1.44−1.39 (m, 0.75H), 1.33 (m, 0.25H), 1.23 (t, $J$ = 7.05 Hz, 0.75H), 1.23 (t, $J$ = 7.05 Hz, 2.25H), 1.19 (m, 1H), 1.11 (m, 0.25H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.29, 173.11, 73.93, 73.72, 60.07, 60.03, 42.36, 42.20, 41.24, 40.62, 35.54, 35.36, 34.12, 33.86, 30.14, 29.83, 25.85, 18.09, 18.07, 14.25, −4.76, −4.80; IR (neat) 1738.1, 836.1 cm$^{-1}$; HRMS calcd for $C_{15}H_{30}SiO_2$ 285.1886, found 285.1873; LRMS (EI$^+$) *m*/*z* 241 (97), 229 (100), 183 (90), 155 (31), 109 (48), 67 (81), 41 (31), 29 (42). Anal. Calcd for $C_{15}H_{30}SiO_2$: C, 62.89; H, 10.55. Found: C, 63.34; H, 10.67.

**Ethyl (1*R**,2*R**/*S**)-3-Acetoxycyclopentaneacetate (54b). 54b** was prepared from ethyl (2*E*)-6-acetoxy-7-iodo-2-heptenoate according to the general procedure outlined for the preparation of **10a** to afford the desired cyclized product in 77% yield as a 2.5:1 mixture of diastereomers (*cis* isomer major) after flash column chromatography with 20% EtOAc/hexanes: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.14 (m, 0.4H), 5.11 (m, 0.6H), 4.10 (q, $J$ = 7.15 Hz, 2H), 2.48 (m, 0.4H), 2.37 (m, 1.2H), 2.29 (m, 0.8H), 2.28−2.23 (m, 0.6H), 2.06 (m, 0.3H), 1.99

(s, 3H), 1.98−1.91 (m, 1.5H), 1.88−1.80 (m, 1.5H), 1.77−1.71 (m, 0.6H), 1.66 (m, 0.4H), 1.48−1.29 (m, 1.7H), 1.23 (t, $J$ = 7.15 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 172.74, 170.23, 76.29, 76.21, 60.19, 40.51, 39.89, 39.19, 38.71, 34.71, 34.34, 32.32, 32.02, 30.33, 30.30, 21.28, 14.20; IR (neat) 1731.5 cm$^{-1}$; LRMS (EI$^+$) $m/z$ 214 (22), 189 (100), 171 (51), 154 (71), 127 (90), 108 (80), 88 (83), 81 (72), 67 (82), 61 (51), 43 (98), 29 (79). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.70; H, 8.59.

**2-Oxabicyclo[3.2.1]octan-3-one and Ethyl (1*R**,2*R**)-3-Acetoxycyclopentaneacetate (54b, *trans*).**[32] **54b** was prepared from ethyl (2*E*)-7-iodo-6-hydroxy-2-heptenoate (**52**) according to the general procedure outlined for the preparation of **10a** to afford the expected *cis*- and *trans*-cyclized products (as a 2:1 mixture of *trans* and *cis* diastereomers, respectively) along with a small amount bicyclic lactone. The crude product mixture was subjected directly to acetylation ($Ac_2O$, DMAP, pyridine, 18 h at rt) to afford a similar mixture of bicyclic lactone (8%) and *cis*- and *trans*-acetoxy esters (trans acetoxy ester major, 71% combined) after flash column chromatography with 15% EtOAc/hexanes: (major diastereomer, trans) $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.14 (m, 1H), 4.10 (q, $J$ = 6.96 Hz, 2H), 2.48 (m, 1H), 2.30 (m, 2H), 2.08−1.91 (m, 3H), 1.99 (s, 3H), 1.65 (m, 1H), 1.45 (ddd, $J$ = 13.92, 9.91, 6.61 Hz, 1H), 1.23 (t, $J$ = 6.96 Hz, 3H), 1.19 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 172.80, 170.82, 76.32, 60.24, 39.90, 39.22, 34.36, 32.04, 30.35, 21.33, 14.22; IR (neat) 1731.7 cm$^{-1}$; HRMS calcd for $C_{11}H_{17}O_4$ (M − H$^+$) 213.1127, found 213.1152; LRMS (EI$^+$) $m/z$ 213 (72), 185 (100), 171 (41), 154 (52), 127 (62), 108 (61), 88 (72), 67 (71), 43 (98), 29 (71).

(32) (a) House, H. O.; Haack, J. L.; McDaniel, W. C.; VanDerver, D. *J. Org. Chem.* **1983**, *48*, 1643. (b) Schaefer, J. P.; Higgins, J. *J. Org. Chem.* **1967**, *32*, 553.

**Ethyl (1*R**,3*R**/*S**)-3-[(*tert*-Butyldimethylsilyl)oxy]cyclohexaneacetate (54c).** **54c** was prepared from **53c** according to the general procedure outlined for the preparation of **10a** to afford a 1.3:1 mixture of diastereomeric **54c** in 88% yield after flash column chromatography with 2% EtOAc/hexanes: (low $R_f$) $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.10 (q, $J$ = 7.05 Hz, 2H), 3.54 (m, 1H), 2.18 (d, $J$ = 7.05 Hz, 2H), 1.87−1.76 (m, 3H), 1.72 (m, 1H), 1.61 (m, 1H), 1.24 (t, $J$ = 7.05 Hz, 3H), 1.20−1.09 (m, 2H), 1.01 (m, 1H), 0.85 (s, 9H), 0.81 (m, 1H), 0.02 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 172.83, 71.05, 60.16, 42.57, 41.75, 35.72, 33.63, 31.78, 25.90 (3), 23.84, 18.20, 14.28, −4.61 (2); IR (neat) 1735.1 cm$^{-1}$; (high $R_f$) $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.09 (q, $J$ = 7.15 Hz, 2H), 3.99 (m, 1H), 2.26 (m, 1H), 2.16 (dd, $J$ = 14.19, 6.85 Hz, 1H), 2.09 (dd, $J$ = 14.09, 7.74 Hz, 1H), 1.71 (m, 1H), 1.67−1.62 (m, 2H), 1.55 (m, 1H), 1.43−1.39 (m, 1H), 1.36−1.30 (m, 1H), 1.23 (t, $J$ = 7.15 Hz, 3H), 1.15 (m, 1H), 0.96 (m, 1H), 0.86 (s, 9H), 0.00 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 172.96, 66.74, 60.05, 41.82, 39.98, 33.48, 32.38, 29.10, 25.81 (3), 19.90, 18.08, 14.28, −4.89 (2); IR (neat) 1738.1 cm$^{-1}$.

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**Supporting Information Available:** $^1$H NMR and $^{13}$C NMR spectra of compounds synthesized and the remainder of experimental section (273 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.

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