Samarium(II) Iodide-Mediated Intramolecular Conjugate Additions of α,β-Unsaturated Lactones

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Samarium(II) iodide, in the presence of catalytic amounts of nickel(II) iodide, has been used to promote intramolecular conjugate additions of alkyl halides onto α,β-unsaturated lactones. This process has been shown to be applicable to a number of α,β-unsaturated lactones, including tetrasubstituted olefins, and has been demonstrated to be quite general for the formation of saturated bicyclic and tricyclic lactones. The method presented herein provides a mild, efficient process to form structurally complex lactones from simple precursors.

Introduction

Only a handful of examples have been reported in which an alkyl halide was a precursor in the intramolecular conjugate addition onto α,β-unsaturated lactones.[1] Although these cyclizations, promoted almost exclusively by Bu_3SnH, yielded the desired lactones in good overall yield, they are burdened with several disadvantages. Tin-mediated cyclizations typically require elevated temperatures, usually boiling ethyl acetate[1a−c] or benzene.[1f] The difficulty of removal as well as the toxicity of the residual tin species[2] makes the use of these reagents undesirable, especially when compared to the rather benign nature of SmI_2.[3] Furthermore, to maintain a low radical concentration during the reaction, tin-mediated cyclizations are often encumbered by the inconvenience of long addition times, sometimes as long as 5 h.[1a]

Since the initial report by Kagan and co-workers[4] on the convenient synthesis of SmI_2 and its use in various reductive transformations, this reagent has been used in a variety of intramolecular conjugate addition reactions.[5] Molander and Harris reported that SmI_2, in conjunction with a catalytic amount of NiI_2,[6] was able to effect conjugate additions of alkyl iodides onto a variety of electron-deficient olefins.[5d] However, to the best of our knowledge, only one example of cyclization onto an α,β-unsaturated lactone with SmI_2 has been reported.[5d] Herein we report a general procedure for the SmI_2-mediated, nickel(II)-catalyzed cyclization of alkyl halides onto α,β-unsaturated lactones. Under optimized conditions, conjugate additions were achieved using a variety of primary iodides and various lactones. This method was expanded to include tri- and tetrasubstituted olefins, which provided the desired cyclized lactones in high yields under mild reaction conditions.

Results and Discussion

To determine the generality of the SmI_2-mediated cyclization, a number of suitable substrates were prepared. Compounds **8**−**10** were prepared from the same intermediate, bromo amide **1** (Scheme 1).

Coates reported that bromo amide **1** could be lithiated and trapped with various carbonyl electrophiles to form, after acidic hydrolysis, bicyclic lactones.[7] Under optimized conditions, 1.3 equiv of *t*-BuLi cleanly effected the lithiation. Addition of the appropriate chloro ketone [(5-chloropentan-2-one (**2**), 6-chlorohexan-2-one (**3**), or 4′-chlorobutyrophenone (**4**)] yielded, after hydrolysis, the desired chloro lactones. Conversion to the iodo lactone derivatives **8**−**10** was achieved using standard Finkelstein procedures. Unfortunately, the cyclopentene derivative **13** could not be made via the route described above. However, reaction of bromo acid **11** with 3 equiv of *t*-BuLi yielded, after benzenesulfonyl chloride-mediated ring closure,[8] the desired lactone **12**, albeit in low yield (Scheme 2). The resultant chloro lactone was converted to the iodo derivative **13** in high yield by a Finkelstein reaction.

To determine the effect of substitution on this intramolecular conjugate addition, monocyclic lactones with and

(1) (a) Lundt, I.; Horneman, A. M. *Tetrahedron* **1997**, *53*, 6879. (b) Lundt, I.; Horneman, A. M. *J. Org. Chem.* **1998**, *63*, 1919. (c) Lundt, I.; Horneman, A. M. *Synthesis* **1999**, 317. (d) Hsia, K. Y.; Ward, P.; Lamont, R. B.; de Q. Lilley, P. M.; Watkin, D. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1994**, *35*, 4823. (e) Morikawa, T.; Uchida, J.; Hasegawa, Y.; Taguchi, T. *Chem. Pharm. Bull.* **1991**, *39*, 2462. (f) Schultz, A. G.; Dai, M. D.; Khim, S.-K.; Pettus, L.; Thakker, K. *Tetrahedron Lett.* **1998**, *39*, 4203.

(2) (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; p 131. (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. *J. Org. Chem.* **1979**, *44*, 449. (f) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.

(3) Molander, G. A. In *The Chemistry of the Metal−Carbon Bond*; Hartley, F. R., Patai, S., Eds.; John Wiley and Sons: Chichester, 1989; Vol. 5.

(4) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

(5) (a) Molander, G. A. *Chem. Rev.* **1996**, *96*, 307. (b) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321. (c) Krief, A.; Laval, A. M. *Chem. Rev.* **1999**, *99*, 745. (d) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 7418 and references therein. (e) Salari, B. S. F.; Biboutou, R. K.; Bennett, S. M. *Tetrahedron* **2000**, *56*, 6285.

(6) Machrouhi, F.; Hamann, B.; Namy, J. L.; Kagan, H. B. *Synlett* **1996**, 633.

(7) Baker, W. R.; Coates, R. M. *J. Org. Chem.* **1979**, *44*, 1022.

(8) Sauter, F.; Stanetty, P.; Fröhlich, H.; Ramer, W. *Heterocycles* **1987**, *26*, 2639.

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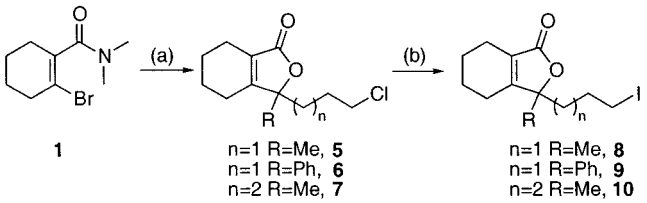
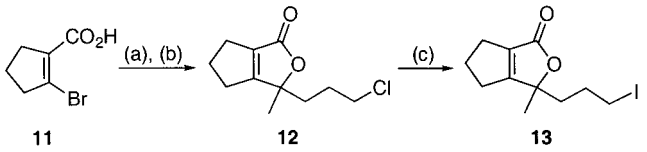
Scheme 1[a]



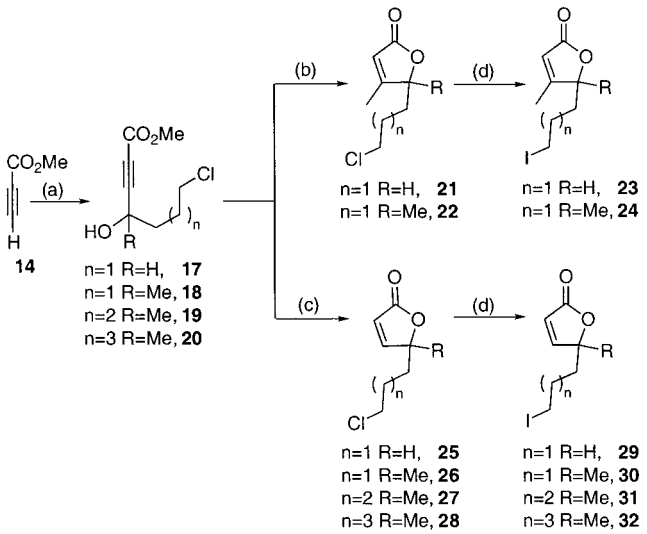
[a] Key: (a) (i) 1.3 equiv of *t*-BuLi, −78 °C, (ii) **2**, **3**, or **4**, (iii) THF/aq HOAc; (b) NaI, acetone, Δ.

Scheme 2[a]



[a] Key: (a) (i) 3.1 equiv of *t*-BuLi, −78 °C, (ii) **2**; (b) benzenesulfonyl chloride, pyr; (c) NaI, acetone, Δ.

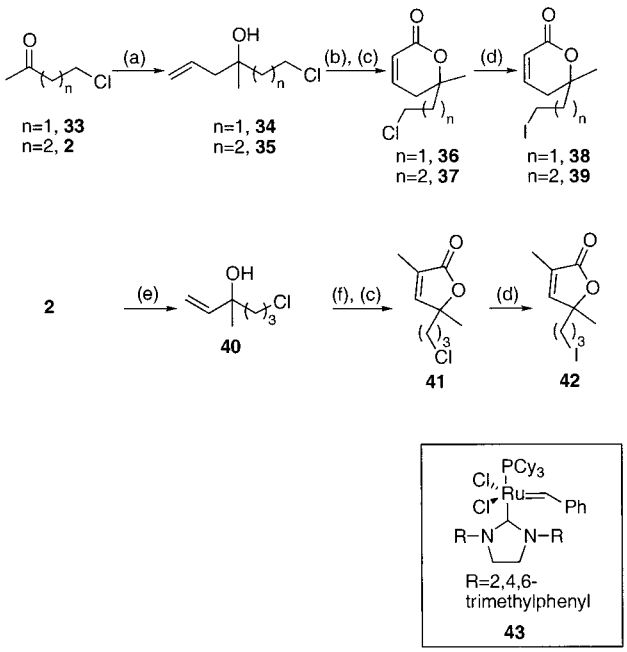
Scheme 3[a]



[a] Key: (a) (i) LDA, −78 °C, (ii) **2**, **3**, **15**, or **16**; (b) 2 equiv of Me_2CuLi, 0 °C to rt; (c) H_2, Lindlar's catalyst, C_6H_6, quinoline; (d) NaI, acetone, Δ.

without substitution at the *β*-position were prepared. The synthesis of iodo lactones **23**, **24**, and **29**−**32** began with the addition of lithium methyl propynoate[9a,b] to the appropriate chloro ketone [(**2**, **3**, 4-chlorobutanal (**15**), or 7-chloroheptan-2-one (**16**)] (Scheme 3). With the appropriate alkynyl alcohols in hand, two routes to the desired lactones were available. The addition of 2 equiv of dimethylcuprate to alcohols **17** and **18** provided the desired *β*-methyl-substituted chloro butenolides in high yields.[9a] Alternatively, alcohols **17**−**20** could be carefully hydrogenated using Lindlar's catalyst in the presence of quinoline to yield, after acid-catalyzed lactonization, the unsubstituted chloro lactones (Scheme 3).[10] Exposing the chloro lactones **21**, **22**, and **25**−**28** to an acetone/NaI mixture heated at reflux yielded the desired iodo lactones in good yield.

Scheme 4[a]



[a] Key: (a) allylmagnesium bromide, THF; (b) acryloyl chloride, NEt_3, DMAP, CH_2Cl_2; (c) **43**, C_6H_6; (d) NaI, acetone, Δ; (e) vinylmagnesium chloride, THF; (f) methacryloyl chloride, NEt_3, DMAP, CH_2Cl_2.

Iodo lactones **38**, **39**, and **42** were also synthesized (Scheme 4). These lactones, which were designed to test the effect of substitution α to the carbonyl as well as the lactone ring size, were constructed by the following sequence. Addition of a magnesium-based nucleophile to the appropriate chloro ketone yielded alcohols **34**, **35**, and **40**.[11] Protection of the tertiary alcohols as their acrylate derivatives,[12] followed by ring-closing metathesis (RCM) in boiling benzene with the commercially available ruthenium carbene complex **43**, yielded the desired chloro lactones **36**, **37**, and **41**.[13a,b] Conversion to the iodides was accomplished using the standard Finkelstein conditions reported above.

Iodo lactone **47**, a potential precursor to a lactone containing a spiro ring junction, was generated via a three-step sequence (Scheme 5). The synthesis began with a conjugate addition/elimination reaction involving vinyl triflate[14] **44** and the Grignard-derived cuprate of *tert*-butyl-(4-chlorobutoxy)dimethylsilane.[15] The resulting *β*-substituted butenolide **45** was then deprotected using a CH_3CN/1 M HCl mixture and converted to iodide **47** in high overall yield using standard methods.

The final class of substrates synthesized was heteroaromatic iodo lactones **50**, **51**, and **55**−**57** (Scheme 6).

(9) (a) Krause, N. *Liebigs Ann. Chem.* **1990**, 603. (b) Midland, M. M.; Tramontano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28.

(10) Takano, S.; Setoh, M.; Yamada, O.; Ogasawara, K. *Synthesis* **1993**, 1253.

(11) Hoffman, W.; Baumann, M.; Pommer, H. *Liebigs Ann. Chem.* **1976**, 1626.

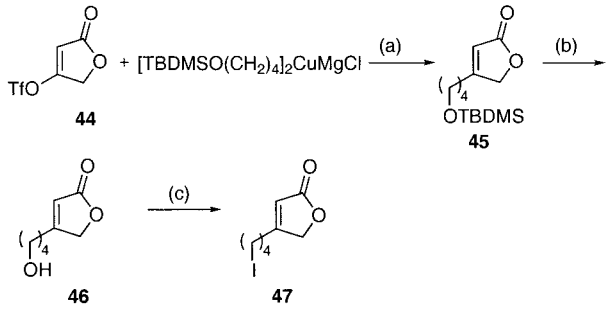
(12) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651.

(13) (a) Grubbs, R. H.; Chatterjee, A. K. *Org. Lett.* **1999**, *1*, 1751. (b) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204. For other examples of RCM reactions leading to α,*β*-unsaturated lactones, see: (c) Carda, M.; Castillo, E.; Rodriguez, S.; Uriel, S.; Marco, J. A. *Synlett* **1999**, 1639. (d) Ghosh, A. K.; Bilcer, G. *Tetrahedron Lett.* **2000**, *41*, 1003. (e) Ghosh, A. K.; Liu, Ch. *Chem. Commun.* **1999**, 1743.

(14) Grigg, R.; Kennewell, P.; Savic, V. *Tetrahedron* **1994**, *50*, 5489.

(15) Hanson, R. L.; Schwinden, M. D.; Banerjee, A.; Brzozowski, D. B.; Chen, B.-C.; Patel, B. P.; McNamee, C. G.; Kodersha, G. A.; Kronenthal, D. R.; Patel, R. N.; Szarka, L. J. *Bioorg. Med. Chem.* **1999**, *7*, 2247.

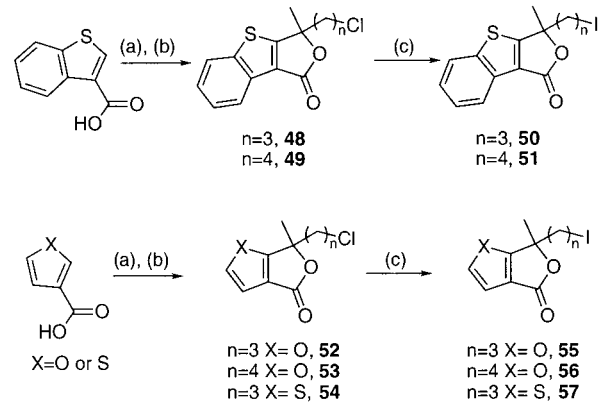
Scheme 5[a]



44 45 46 47

[a] Key: (a) Et_2O, −78 °C, 5 min; (b) 1 M HCl/MeCN, 5:1; (c) PPh_3, imidazole, I_2.

Scheme 6[a]



[a] Key: (a) (i) 2.1 equiv of LDA, (ii) **2** or **3**; (b) benzenesulfonyl chloride, pyr; (c) NaI, acetone, Δ.

The synthesis of the heteroaromatic iodo lactones began with a deprotonation/lithiation of the appropriate heteroaromatic carboxylic acid.[16a,b] This dianion was trapped with carbonyl compounds to form intermediate hydroxy acids, which were then lactonized with a benzenesulfonyl chloride/pyridine mixture to produce chloro lactones **48**, **49**, and **52**−**54** in good overall yields.[8] Conversion of the chloro lactones to the corresponding iodides completed the synthetic sequence.

With the requisite substrates in hand, studies were initiated on the development of the conjugate addition process. Initially, we envisioned that the resultant chloro lactone **5** could be directly converted to tricyclic lactone **58** via the combination of SmI_2, catalytic NiI_2,[6] and photochemical irradiation (Table 1, entry 1).[17] Although these reaction conditions did yield the desired lactone, long reactions times (usually greater than 10 h) and a large excess of SmI_2, often as much as 5 equiv, were required.[17a] Consequently, the intermediate chloro lactone was converted to the more reactive iodide.[17b] The resultant iodo derivative **8**, in addition to requiring fewer equivalents of SmI_2, underwent facile cyclization at low temperatures (−78 °C to room temperature) to give the desired lactones in high yield and with good diastereoselectivity (Table 1, entry 2).

On the basis of earlier studies,[5d] a mechanism can be postulated for this SmI_2-mediated 1,4-addition (Scheme 7). After a dissociative electron transfer, the resultant radical undergoes cyclization onto the α,β-unsaturated lactone. It appears that when forming five-membered rings, even with sterically crowded electrophilic centers, the cyclization occurs faster than reduction of the initially formed radical to the corresponding samarium anion, an observation previously reported by Curran.[18] After cyclization, the resultant radical is reduced to the samarium enolate, which is then quenched in situ by the *t*-BuOH additive. This radical cyclization, rather than an anionic variant, is supported by the fact that, even with a proton source (*t*-BuOH) present in the reaction medium, the reaction succeeds (Table 1, entry 3). If the cyclization involved an intermediate organosamarium species or carbanion, one would expect to recover reduced starting material as a result of the basicity of the anion.

Conducting this conjugate addition in the presence of a proton source, specifically *t*-BuOH, provided higher diastereoselectivities than reactions performed in the absence of a proton source (entry 3). This increase most likely resulted from immediate, low-temperature protonation of the organosamarium enolate (Scheme 7). Because the enolate could be quenched in situ under these conditions, one might anticipate this enhancement of diastereoselectivity.

Formation of a six-membered ring proved to be problematic in this series of substrates (entries 5 and 6). Under the optimized protic cyclization conditions, only reduced starting material was recovered (Scheme 7). This most likely resulted from the comparatively slow ring formation, exacerbated by the steric bulk around the reaction center. In contrast to entry 2, it seems that the intermediate radical is reduced to the organosamarium species faster than the cyclization event. This basic intermediate is then quenched by the *t*-BuOH present in solution. However, when no proton source is present, the intermediate organosamarium species cyclizes to form tricyclic hemiacetal **60** exclusively via a nucleophilic acyl substitution[5b] (entry 5). The structure of this 1,2-adduct was confirmed by X-ray analysis.

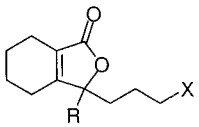
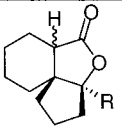
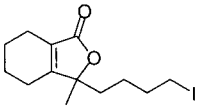
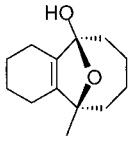
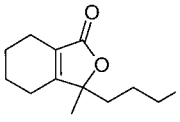
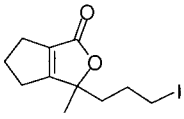
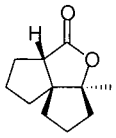
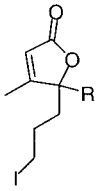
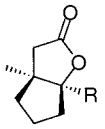
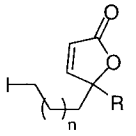
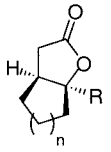
Under optimal conditions (3.0 equiv of SmI_2, 4 mol % NiI_2, 2 equiv of *t*-BuOH), cyclization of the monocyclic lactones proceeded to form the desired bicyclic lactones in good to high yields (entries 4−12, 14, Table 1). This method proved to be reasonably general for the formation of five-membered rings, regardless of substitution pattern. Also, it should be noted that the formation of six-membered rings could be achieved if the steric bulk around the electrophilic center was kept to a minimum (entries 12 and 15). For example, reaction of iodo lactone **31** under optimal conditions did form the desired 5,6-bicyclic lactone **67** in 63% yield with moderate diastereoselectivity. In addition, iodo lactone **39** yielded bridged bicyclic lactone **70** in high yield. Although some six-membered rings could be successfully constructed using this method, all attempts to form a seven-membered ring (entry 13) resulted in reduced starting material.

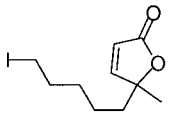
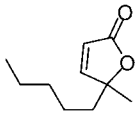
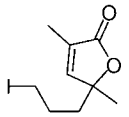
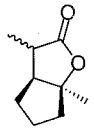
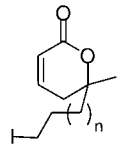
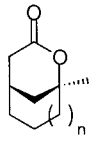
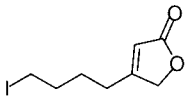
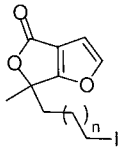
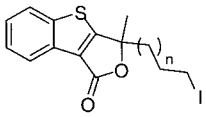
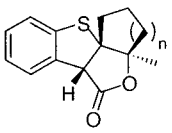
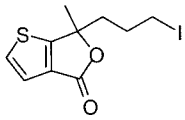
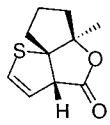
(16) (a) Knight, D. W.; Nott, A. P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1125. (b) Knight, D. W.; Nott, A. P. *Tetrahedron Lett.* **1980**, *21*, 5051.

(17) (a) Molander, G. A.; Köllner, C. *J. Org. Chem.* **2000**, *65*, 8333. (b) Molander, G. A.; Machrouhi, F. *J. Org. Chem.* **1999**, *64*, 4119. (c) Skene, W. G.; Scaiano, J. C.; Cozens, F. L. *J. Org. Chem.* **1996**, *61*, 7918. (d) Ogawa, A.; Sumino, Y.; Nanke, T.; Ohya, S.; Sonoda, N.; Hirao, T. *J. Am. Chem. Soc.* **1997**, *119*, 2745. (e) Ogawa, A.; Ohya, S.; Hirao, T. *Chem. Lett* **1997**, 275.

(18) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943.

Table 1. Intramolecular Samarium(II) Iodide-Mediated Conjugate Additions Involving α,β-Unsaturated Lactones[a]

entry	substrate	product	isolated yield (%)
1	 R=Me X=Cl, **5**	 **58**	73[b,c,d]
2	R=Me X=I, **8**	**58**	95[b,d]
3	**8**	**58**	100[e]
4	R=Ph X=I, **9**	**59**	93[f]
5	 **10**	 **60**	60[b]
6	**10**	 **61**	74
7	 **13**	 **62**	100
8	 R= H, **23** R= Me, **24**	 R= H, **63** R= Me, **64**	61
9			85
10	 R= H n=1, **29**	 R= H n=1, **65**	59
11	R= Me n=1, **30**	R= Me n=1, **66**	80
12	R= Me n=2, **31**	R= Me n=2, **67**	63[g]

entry	substrate	product	isolated yield (%)
13	 **32**	 **68**	47[h]
14	 **42**	 **69**	77[i]
15	 n=1, **39** n=0, **38**	 **70**	86
16		[j]	–
17	 **47**	[j]	–
18	 n=1, **55** n=2, **56**	[j]	–
19		[j]	–
20	 n=1, **50**	 n=1, **71**	73[b]
21	n=2, **51**	[j]	–
22	 **57**	 **72**	23[k]

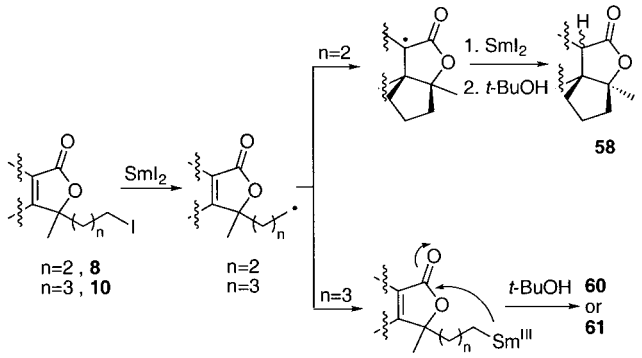
[a] All reactions were carried out with 3.0 equiv of SmI_2, 2.0 equiv of *t*-BuOH, and 4 mol % NiI_2 unless otherwise stated. [b] No *t*-BuOH used. [c] Light was used (250 W krypton lamp). [d] Isolated as a 10:1 mixture of diastereomers by ^{1}H NMR. [e] Isolated as a 20:1 mixture of diastereomers by ^{1}H NMR. [f] Isolated as a 15:1 mixture of diastereomers by GC. [g] Isolated as a 3:1 mixture of diastereomers by ^{1}H NMR. [h] 90% based on recovered starting material. [i] Isolated as a 6.3:1 mixture of diastereomers by ^{1}H NMR. [j] Complex mixture. [k] Based on recovered starting material.

Unfortunately, all attempts to form lactones with a spiro ring junction also failed (entry 17). In each case, a complex mixture was obtained.

The last substrates tested were heteroaromatic iodo lactones (entries 18−22). Ironically, these substrates were originally designed to undergo selective 1,2-addition because we believed that the aromatic character of the electrophilic center would prevent 1,4-addition. Interestingly, when aromatic iodo lactone **50** was exposed to SmI_2 (cat. NiI_2), tetracyclic lactone **71** was formed in high yield (entry 20).[19] The structure of this aromatic lactone was confirmed by X-ray analysis. Extension of the alkyl chain by one methylene unit, however, resulted in a complex mixture of products, with no detectable products resulting from 1,2-addition. Surprisingly, exposing thiophene derivative **57** to the aprotic annulation conditions yielded tricylic lactone **72**, albeit in low yield and with poor conversion (entry 22). Although some success was achieved with the benzothiophene and thiophene derivatives, other aromatic iodo lactones proved to be problematic. All attempts to facilitate a 1,4-addition with the furan iodo lactones of various chain lengths resulted in complex mixtures of unidentified compounds (entries 18 and 19).

(19) For a review on radical cyclizations involving aromatic rings see Bowman, W. R.; Cloonan, M. O.; Krintel, S. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2885.

Scheme 7



To compare the current method to established conjugate addition protocols is difficult, because to the best of our knowledge only one example has been previously reported for the construction of identical compounds (entry 10).[20] In that case, an appropriately substituted phenyl selenide was cyclized to form **65.** That cyclization, mediated by tributyltin hydride, not only required long addition times and high dilution, but also necessitated heating. The isolated yield of the desired lactone was 66%, roughly comparable (58%) to that obtained by the method reported herein.

Conclusion

A samarium(II) iodide-mediated conjugate addition protocol for the addition of alkyl iodides onto various α,β-unsaturated lactones has been realized. This method is reasonably general for alkenes with varying substitution patterns, including tetrasubstituted olefins, and provides a mild and efficient preparation of polycyclic saturated lactones.

Experimental Section

Reagents. Tetrahydrofuran (THF) was distilled immediately prior to use from benzophenone ketyl under N_2. Samarium metal was purchased from a commercial supplier (99.9%, 40 mesh). CH_2I_2 was purchased, distilled under N_2, and stored over copper turnings. Standard flash chromatography procedures were followed using 32−63 mm silica gel.[21] All chloro ketones and chloro aldehydes[22] were either purchased or made following literature procedures.[23a,b] Standard benchtop techniques were employed for handling air-sensitive reagents.[24]

General Finkelstein Procedure for the Formation of Iodo Lactones. Synthesis of 3-(3-Iodopropyl)-3-methyl-4,5,6,7-tetrahydro-3*H*-isobenzofuran-1-one (8). To a solution of 850 mg (3.72 mmol) of chloro lactone **5** in 20 mL of HPLC-grade acetone was added 2.78 g (18.6 mmol) of NaI. This yellow solution was heated at reflux for 15 h under N_2. After cooling to room temperature, 20 mL of CH_2Cl_2 was added along with 20 mL of H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), dried with $MgSO_4$, and concentrated under reduced pressure to give 1.077 g (91%) of the iodo lactone **8** as an oil that solidified on standing: mp 75−77 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.23−3.03 (m, 2H), 2.24−2.07 (m, 4H), 1.90−1.83 (m, 1H), 1.81−1.62 (m, 6H), 1.55−1.48 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.82, 166.68, 126.38, 87.27, 38.04, 27.31. 24.01, 22.37, 21.83, 21.75, 20.01, 6.53; IR (neat) 2931, 2858, 1750, 1679 cm^{-1}; HRMS calcd for $C_{12}H_{18}IO_2$ $(M + H)^+$ 321.0352, found 321.0344; LRMS (CI) *m*/*z* 320 (100), 196 (37).

General Procedure for SmI_2/NiI_2 (cat.) Conjugate Addition onto α,β-Unsaturated Lactones. Synthesis of 3a-Methyloctahydro-4-oxacyclopenta[*c*]inden-5-one (58). To a suspension of 410 mg (2.73 mmol) of samarium metal in 25 mL of THF at 0 °C was added 615 mg (2.34 mmol) of freshly distilled CH_2I_2. The resultant blue solution was warmed to room temperature and stirred for 1.5 h. To the SmI_2 solution was added 29.3 mg (0.094 mmol) of NiI_2, and the mixture was subsequently cooled to −78 °C. A THF solution (15 mL) of 250 mg (0.781 mmol) of iodo lactone **8** and 116 mg (1.56 mmol) of *t*-BuOH was then added. After the addition of the substrate was complete, the reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was hydrolyzed with saturated aqueous $NaHCO_3$. The organic phase was separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine and dried with $MgSO_4$. Removal of the solvent followed by column chromatography (SiO_2, 5:1 hexanes: ethyl acetate) yielded 151 mg of **58** (100%) as a 20:1 mixture of diastereomers: ^{1}H NMR (major isomer) (500 MHz, $CDCl_3$) δ 2.50 (t, J = 5.54 Hz, 1H), 1.94 (m, 1H), 1.93−1.92 (m, 2H), 1.81−1.77 (m, 2H), 1.78−1.60 (m, 3H), 1.51−1.47 (m, 4H), 1.33 (s, 3H), 1.26−1.22 (m, 2H); ^{13}C NMR (125 MHz) δ 178.20, 94.01. 50.61, 45.57, 38.63, 36.13, 31.01, 22.83, 22.57, 22.39, 21.71, 21.58; IR (neat) 2933, 2857, 1769 cm^{-1}; HRMS calcd for $C_{12}H_{19}O_2$ $(M + H)^+$ 195.1385, found 195.1384; LRMS (CI) *m*/*z* 195 (100), 177 (8), 149 (27).

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Supporting Information Available: Experimental detail and structural data for all new compounds not described within the text, as well as X-ray structure data for compounds **60** and **71**. This material is available free of charge via the Internet at http://pubs.acs.org.

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