Development of a Protocol for Eight- and Nine-Membered Ring Synthesis in the Annulation of sp^2,sp^3-Hybridized Organic Dihalides with Keto Esters

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A protocol has been developed in which annulation reactions of various dihalides with keto esters can be carried out to provide entry to eight- and nine-membered carbocycles. In this process wherein one alkenyl- or aryl bromide and a tethered alkyl chloride comprise the organic dihalide, a selective metal−halogen exchange reaction between the sp^2-hybridized bromide and an organolithium initiates the process. Transmetalation to an organoytterbium reagent generates a species that undergoes selective carbonyl addition to the ketone of the keto ester, creating a lactone intermediate. Subjection of the resulting chloroalkyl lactone to intramolecular reductive coupling with samarium(II) iodide completes the desired annulation.

Introduction

Since the first use of samarium(II) iodide (SmI_2) as a reducing agent in organic synthesis 20 years ago,[1] this remarkable reductant has been utilized in a variety of selective reactions.[2] Although many of the early studies focused on single transformations, it subsequently became evident that SmI_2 was an ideal reductive coupling agent for sequential processes.[3] This provides a major advantage compared to other reductants such as Mg, Zn, Cr(II), and Bu_3SnH. In addition to its ability to promote a wide array of useful organic reactions (both radical and anionic processes), one of the unique benefits of SmI_2 is its adjustable reactivity through solvent effects,[4] by the addition of catalysts,[1,5] and even through irradiation of reaction mixtures.[6] This feature greatly facilitates the sequencing of reactions because the reductant can be selectively tuned for each individual step of a multistep process.

Samarium(II) iodide has proven to be a useful reagent in the synthesis of medium-sized carbocycles. These carbocycles are structural units present in a wide range of natural products, existing either as isolated rings or forming a part of bicyclic or tricyclic frameworks.[7] The synthesis of such structures often requires application of carbon−carbon bond-forming reactions and is still considered quite challenging. Entropic factors, together with transannular interactions that inhibit cyclization, conspire to make the construction of medium-sized rings difficult.[8] As evidence of this, the number of general methods for preparing medium-sized carbocycles by cyclization or cycloaddition (annulation) reactions from acyclic precursors is relatively small.[7a,9]

We have previously employed SmI_2 to promote a sequential intermolecular carbonyl addition/intramolecular nucleophilic acyl substitution sequence, generating seven- through nine-membered monocyclic, bicyclic, and tricyclic ring systems with good yields and high diastereoselectivities.[10] This domino process consisted of an intermolecular reaction followed by an intramolecular ring expansion that resulted in a formal [$m + n$] cycloaddition, starting from extremely simple, readily available substrates. We have shown that the intermolecular reaction between a chloroiodoalkane and a keto ester leads to a chloroalkyl-substituted lactone via an initial carbonyl addition reaction (Scheme 1).

Preferential reactivity of the iodide over the chloride provided high regioselectivity in the initial step. High chemoselectivity for reaction of the initially formed organosamarium species at the aldehyde or ketone in preference to the ester was observed. Reaction of the chloroalkyl-substituted lactone via an intramolecular nucleophilic acyl substitution ended the sequential reaction pathway and afforded the desired carbocyclic hydroxy ketones. We also demonstrated that a complementary construction of medium-sized carbocycles was feasible

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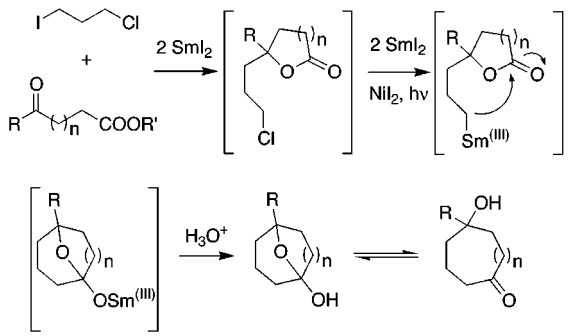
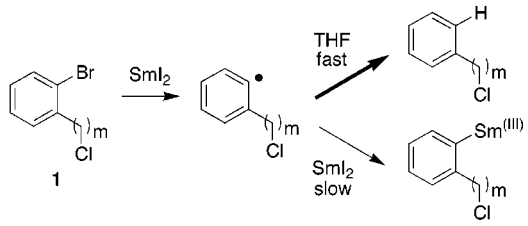
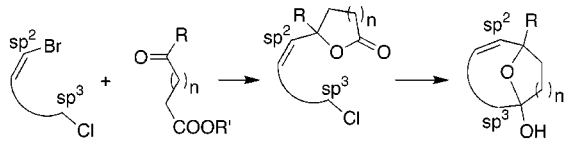
Scheme 1



Scheme 2



Scheme 3



using iodo esters and (chloroalkyl)cycloalkanones in an efficient one-pot annulation reaction.[11] This reaction sequence also involved intermolecular carbonyl addition followed by an intramolecular nucleophilic acyl substitution reaction.

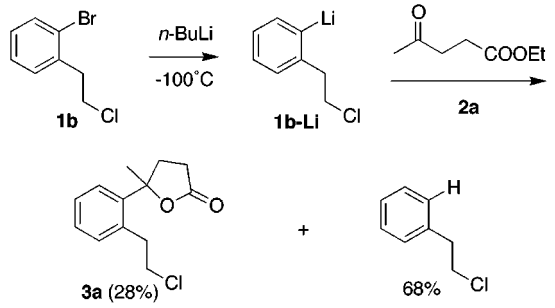
The drawback of both of these processes was that only alkyl halides could be employed. Aryl and alkenyl halides are relatively resistant to reduction by SmI_2,[12] and the sp^2-hybridized radicals generated under these conditions typically abstract hydrogen from THF more rapidly than electron transfer from SmI_2 can produce the corresponding organosamarium.[4a,13] Consequently, only reduction products are observed (Scheme 2).

In the present contribution we outline a means to circumvent this problem using a two-step synthetic approach (Scheme 3). We have developed a procedure whereby organoytterbiums are generated in situ from easy accessible organolithiums and are utilized as nucleophiles in the first step of a two-step reaction, with a SmI_2-promoted process completing the transformation.

Results and Discussion

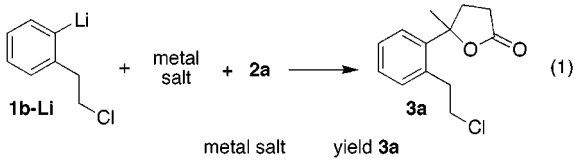
The desired process was initially tested with readily available aryl dihalide **1b** and keto ester **2a**. Parham et al.[14] have shown that selective metalation of 1-bromo-2-(2-chloroethyl)benzene **1b** at low temperatures (−100 °C) is virtually quantitative. However, reaction of the organolithium compound **1b-Li** with ethyl levulinate **2a** afforded the desired lactone in a yield of only 28% (Scheme 4).

Scheme 4



Unfortunately, these initial reaction conditions appeared nearly optimal in terms of the organolithium nucleophile. For example, we varied the concentration of **2a** added (neat or as a solution in THF) and the order of the addition (**2a** added to **1b-Li** or the inverse addition). Use of other solvents such as Et_2O and other bases (*t*-BuLi) did not increase the yield. The major product isolated was always (2-chloroethyl)benzene. Thus it seems likely that deprotonation of the keto ester is occurring under these conditions to form an enolate and (2-chloroethyl)benzene. The enolate is subsequently protonated in the aqueous workup to give the starting keto ester. A brief survey of the literature uncovered few successful reactions of organolithiums with ethyl levulinate,[15] and in none of these reports were aryllithiums employed.

Literature precedent indicated that more success might be achieved with organomagnesium reagents.[16] Thus a Li−Mg-exchange reaction was effected by treating the organolithium with solid anhydrous $MgBr_2$.[17] After the $MgBr_2$ was completely dissolved the keto ester was added, but only a small amount of the product could be isolated in this unoptimized procedure (eq 1). Most of the material obtained was again (2-chloroethyl)benzene. We did not explore the direct reaction between the dihalide **1b** and Mg metal to obtain a Grignard solution. The lack of chemoselectivity of Mg toward the dihalide was perceived to be a significant potential problem.



(1)

metal salt	yield **3a**
$MgBr_2$	**5%**
$CeCl_3$	**56%**
$Yb(OTf)_3$	**70%**

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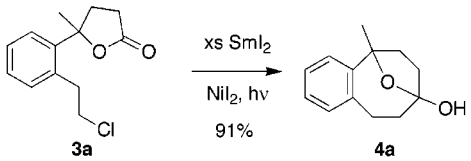
Although the reaction of **1b-Li** with $MgBr_2$ and **2a** was not subjected to exhaustive optimization, the initial result was significantly discouraging that other organometallic compounds were explored. Organolanthanide reagents have made a significant impact on selective organic synthesis and in particular on those reactions involving carbonyl addition reactions. For example, organocerium reagents derived from a variety of organolithium reagents show little enolization in their reactions with carbonyl substrates.[18] The Li−Ce-exchange reaction is well-known and has been applied to many organic transformations.[2c] Reaction of anhydrous $CeCl_3$ with organolithium or organomagnesium reagents leads to organocerium intermediates that are less basic than their organometallic precursors. One advantage of the cerium reagents compared to the lithium or magnesium reagents is that it is easy to follow the reaction as it proceeds to completion. The organocerium compounds are in most cases bright orange or yellow. After the reaction with an electrophile is complete, the color fades, leaving a white suspension. After reaction of **1b-Li** with solid $CeCl_3$ and subsequent addition of a solution of **2a** in THF, the desired chloroalkyl lactone **3a** was obtained in a respectable yield of 56% (eq 1). The best yield, however, was achieved employing another lanthanide salt, tris(trifluoromethanesulfonato)ytterbium [$Yb(OTf)_3$, ytterbium(III) triflate]. In an earlier study[19] we had used organoytterbium reagents derived from $Yb(OTf)_3$ and organolithium or Grignard reagents in carbonyl addition reactions. When the organoytterbium reagents were added to the chiral aldehydes or ketones, exceptionally high diastereofacial selectivities were observed. One further advantage of $Yb(OTf)_3$ is its relatively good solubility in THF, which ensures a fast and complete reaction with the organolithium reagents. When $Yb(OTf)_3$ in THF at −78 °C was treated with 1 equiv of **1b-Li**, an intensely colored burgundy solution of the organoytterbium was produced. Upon addition of a solution of **2a** in THF and slow warming to room temperature the color faded at ca. −30 °C, providing a nearly colorless solution. Aqueous workup and silica gel chromatography provided the lactone **3a** in an isolated yield of 70% (eq 1). This was by far the best result under all tested conditions with different metal exchange reactions.

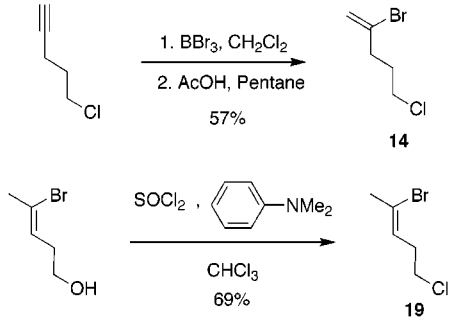
It should be noted at this point that all attempts to complete the annulation process in a "one-pot" transformation were unsuccessful. Thus direct addition of SmI_2 to the chloroalkyl lactone generated in situ by the $Yb(OTf)_3$ method failed to produce the desired annulated product. Additionally, all attempts to utilize an intermediate organosamarium species generated by addition of SmI_3 to the initial organolithium reagent failed to provide the selectivities necessary for a clean conversion to the intermediate lactone.

To complete the annulation reaction, therefore, the isolated lactone **3a** was subjected to a SmI_2-promoted reaction under similar conditions to those previously utilized.[10,11] Reduction of the chloroalkyl lactone with SmI_2 and subsequent nucleophilic acyl substitution in the presence of a catalytic amount of NiI_2 and irradiation with visible light proved to be the most successful conditions (eq 2). Although theoretically only 2 equiv of SmI_2 were necessary to complete the reaction, an excess of SmI_2 increased the yield. Therefore in this study 4 equiv of SmI_2 were typically used for the second step of the reaction sequence. Under these conditions **3a** was transformed in the annulated product **4a** in a yield of 91%.



To explore the scope and limitations of the two-step annulation reaction, a diverse array of substrates were subjected to the protocol. All dihalides in this study had as a common feature a bromo substituent attached to an sp^2-center and a chloroalkyl side chain. The keto esters were acyclic or cyclic, and both chiral and achiral examples were examined. The different substrate combinations tested for this study are outlined in Table 1.

All of the substrates were either commercially available or were prepared using literature procedures (see Experimental Section). The two exceptions were the dihalides **14**[20] and **19**. Substrate **14** was generated by reaction of 5-chloropent-1-yne with BBr_3 at −78 °C, which afforded a (*Z*/*E*)-mixture of the bromoboration product.[21] Subsequent cleavage of the boron−vinyl bond was achieved using acetic acid in pentane. This two-step procedure provided **14** in an overall yield of 57% (eq 3). Substrate **19** was generated in 69% yield from (*Z*)-4-bromopent-3-en-1-ol[22] using thionyl chloride and *N*,*N*-dimethylaniline as base (eq 4).



With regard to the results displayed in Table 1, a few general comments are in order. First, all of the annulation products in Table 1 were isolated in their hemiketal form, with no detectable evidence (NMR) for equilibration with the open hydroxy ketone. With a few exceptions, the yields were good to excellent. As might be expected, formation of the nine-membered rings proved more troublesome than the eight-membered rings. All of the products where a new stereocenter was formed were obtained as single diastereomers. This was demonstrated by ^1H and ^{13}C NMR analysis as well as by fused silica capillary GC analysis of the crude reaction mixtures. Because all of the stereochemistry of the annulation process is determined in the initial carbonyl addition reaction, these results provided further evidence of the

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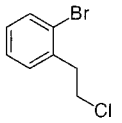
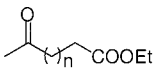
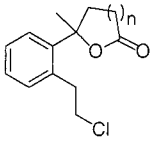
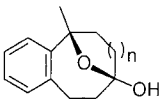
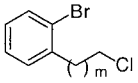
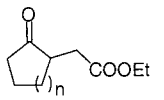
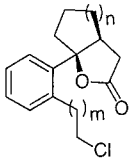
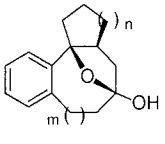
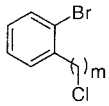
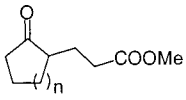
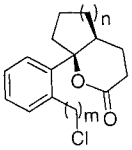
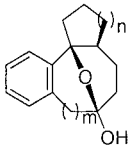
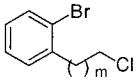
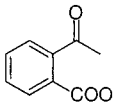
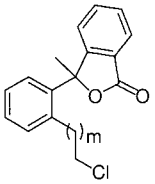
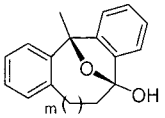
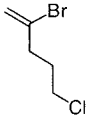
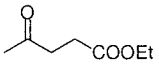
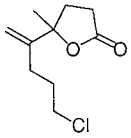
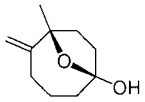
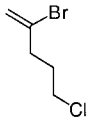
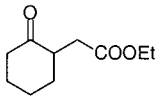
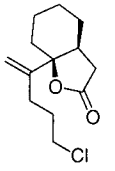
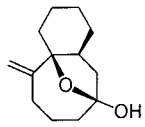
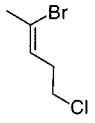
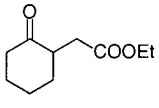
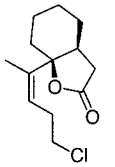
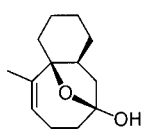
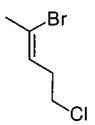
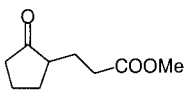
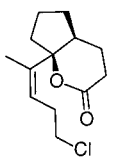
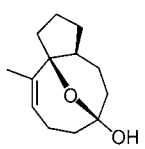
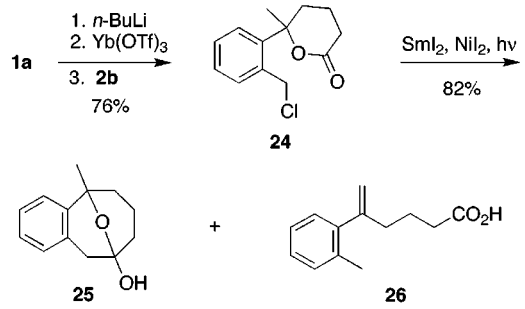
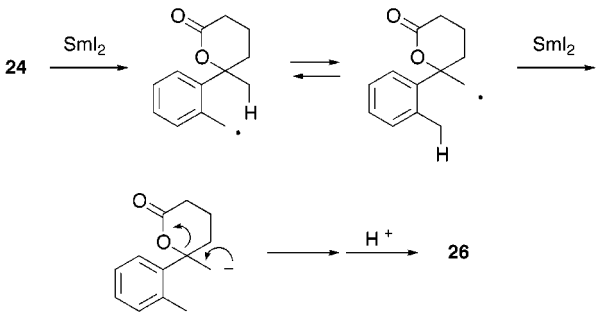
Table 1. Lanthanide-Promoted Two-Step Annulation Reactions between Dihalides and Keto Esters

entry	dihalide	keto ester	lactone (% isolated yield)	annulated product (% isolated yield)
				
1	**1b**	**2a**, n = 1	**3a** (70)	**4a** (91)
2	**1b**	**2b**, n = 2	**3b** (87)	**4b** (63)
				
3	**1b**, m = 1	**5a**, n = 1	**6a** (77)	**7a** (63)
4	**1b**, m = 1	**5b**, n = 2	**6b** (65)	**7b** (65)
5	**1c**, m = 2	**5a**, n = 1	**6c** (75)	**7c** (73)
6	**1c**, m = 2	**5b**, n = 2	**6d** (59)	**7d** (42)
				
7	**1a**, m = 1	**8b**, n = 2	**9a** (69)	**10a** (53)
8	**1b**, m = 2	**8a**, n = 1	**9b** (83)	**10b** (71)
9	**1b**, m = 2	**8b**, n = 2	**9c** (72)	**10c** (63)
				
10	**1b**, m = 1	**11**	**12a** (85)	**13a** (55)
11	**1c**, m = 2	**11**	**12b** (86)	**13b** (27)
				
12	**14**	**2a**	**15** (84)	**16** (40)
				
13	**14**	**5b**	**17** (72)	**18** (68)
				
14	**19**	**5b**	**20** (74)	**21** (72)
				
15	**19**	**8a**	**22** (64)	**23** (11)

Scheme 5



Scheme 6



exceptionally good diastereoselectivity engendered by organoytterbium reagents in carbonyl addition reactions.[19] Single-crystal X-ray structural analysis of compounds **7d**, **10c**, and **21** confirmed the expected trans fusion between the two carbocyclic rings resulting from attack of the organoytterbium species trans to the side chain on the cyclic keto ester in the first step of the two-step reaction sequence. This expected stereochemical outcome is in agreement with our earlier study.[10]

Use of substrate **8b** for the first step synthesis of **9a** and **9c** (entries 7 and 9) yielded products that showed very broad signals in the ^{1}H NMR spectra at room temperature. Hindered rotation about the aryl−lactone single bond in the molecule appeared to be responsible for these broad signals, because at higher temperatures (80 °C in DMSO-d_6) the rotation barrier was exceeded and sharp signals in the ^{1}H as well as in the ^{13}C NMR spectra were obtained. As expected the NMR spectra of the two corresponding annulation products **10a** and **10c** showed no such abnormal behavior and were clearly resolved at room temperature in $CDCl_3$.

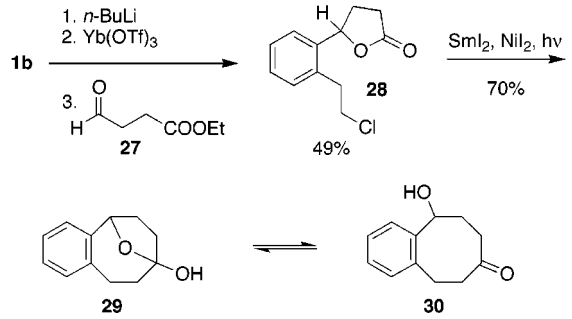
Intermediate **9a** could not be obtained analytically pure, as we were not able to remove one impurity despite several attempts with column chromatography. In the end, **9a** was subjected to the SmI_2-promoted annulation reaction as obtained after the purification (87% pure as measured by GC). After the annulation reaction and column chromatography, only a single product (the expected **10a**) was isolated.

The Br−Li-exchange reaction of the alkenyl bromide substrates **14** and **19** (entries 12−15) were performed using 2 equiv of *t*-BuLi according to a known procedure.[23] Although the yield of the SmI_2 reaction to form **16** and **23** (entries 12 and 15) were lower than those generally observed, no significant differences in the use of alkenyl bromide derivatives compared to their aryl bromide counterparts were noted.

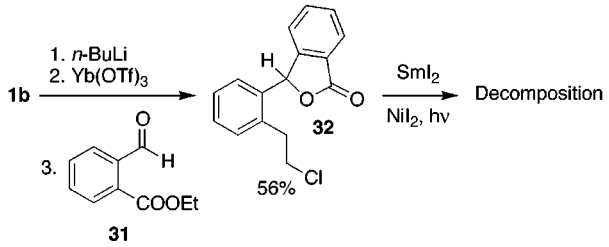
Reaction of **1a** with **2b** led cleanly to the chloroalkyl lactone **24**, but the subsequent SmI_2 reaction gave a surprising result (Scheme 5). The reaction resulted in a mixture of the desired annulation product **25** and the unexpected unsaturated acid **26**.

(23) Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785.

Scheme 7



Scheme 8



Although we have no evidence to confirm the mechanism of this transformation, it may result from an unusual 1,5-hydrogen atom transfer to afford a primary, α-alkoxy radical. Subsequent reduction of this radical by SmI_2 and *β*-elimination would lead to the observed product (Scheme 6).

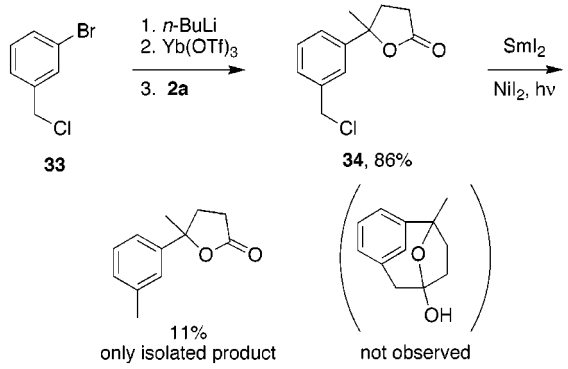
In addition to the keto esters, we also employed two aldehyde esters in the annulation process. Reaction of the dihalide **1b** with aldehyde ester **27** gave only a moderate yield of the lactone **28** (Scheme 7). Subsequent reaction with SmI_2 provided a 70% yield of the expected product **29** that was in equilibrium with its opened hydroxy ketone isomer **30**. The ratio of the two isomers was approximately 4:1 (**29**:**30**). This was the only compound where such an equilibrium was observed. As pointed out above all of the keto ester annulated products appeared to exist exclusively in the hemiketal form.

We also employed aldehyde ester **31** in the reaction with the dihalide **1b** to afford lactone **32** in moderate yield (56%, Scheme 8). Unfortunately, reaction of **32** with SmI_2 provided a complex reaction mixture from which no annulation product could be isolated.

Finally, reaction of the 1,3-substituted dihalide **33** with **2a** cleanly delivered the lactone **34**. However, after reaction with SmI_2, only the (*m*-tolyl)lactone was isolated and this in a yield of only 11% (Scheme 9). Much of the crude material from this reaction after aqueous workup could not be eluted from the silica gel column. Presumably, after reduction of the chloroalkyl chain to the organosamarium an intermolecular rather than an intramolecular nucleophilic acyl substitution reaction took place, yielding polymeric material. Although eight-membered ring systems incorporating a 1,3-substituted benzene ring are known,[17,24] undoubtedly the strain of

(24) (a) Jenneskens, L. W.; de Kanter, F. J. J.; Turkenburg, L. A. M.; de Boer, H. J. R.; de Wolf, W. H.; Bickelhaupt, F. *Tetrahedron* **1984**, *40*, 4401. (b) Wijsman, G. W.; van Es, D. S.; de Wolf, W. H.; Bickelhaupt, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 726.

Scheme 9



the desired eight-membered ring is too high to permit its formation by the current technique.

Conclusions

A two-step annulation process to synthesize eight- and nine-membered monocyclic, bicyclic, and tricyclic hydroxy ketones has been developed. In contrast to earlier reports this method allows one to employ sp^2-hybridized bromo derivatives for the incorporation of alkenyl or aryl moieties in the carbocycles. This extension was made possible by using organoytterbium reagents prepared in situ from organolithiums and $Yb(OTf)_3$ in a carbonyl addition reaction followed by a SmI_2-promoted nucleophilic acyl substitution reaction. Use of these organoytterbium species provided the products with complete diastereoselection. Consequently, this method seems promising for the synthesis of a variety of medium-sized ring platforms.

Experimental Section

Reagents. Tetrahydrofuran (THF) was distilled immediately prior to use from benzophenone ketyl under N_2. Ytterbium(III) triflate ($Yb(OTf)_3$ hydrate), 1.6 M *n*-BuLi solution in hexanes, 1.7 M *t*-BuLi solution in pentane, samarium metal, diiodomethane, nickel(II) iodide (NiI_2), 5-chloropent-1-yne, 1.0 M BBr_3 solution in CH_2Cl_2, thionyl chloride, *N*,*N*-dimethylaniline, as well as the substrates **2a**, **2b**, **5b**, and **33** were purchased from Aldrich Chemicals. Anhydrous $Yb(OTf)_3$ was obtained according to a literature procedure.[25] The substrates **1a**−**c**,[14a,26] **5a**,[27] **8a**,**b**,[28] **11**[29] and (*Z*)-4-bromopent-3-en-1-ol[22] were synthesized as reported earlier. Standard benchtop techniques were employed for handling air-sensitive reagents,[30] and all reactions were carried out under N_2.

5-[2-(2-Chloroethyl)phenyl]-5-methyldihydrofuran-2-one (3a). General Procedure for the Synthesis of Chloroalkyl Lactones. To a solution of 265 mg (1.21 mmol) of 1-bromo-2-(2-chloroethyl)benzene (**1b**) in 10 mL of THF at −100 °C was added dropwise 0.76 mL of a 1.6 M *n*-BuLi-solution in hexanes. The resulting clear solution was stirred at −100 °C for 10 min and then transferred via a dry-ice-cooled cannula to a solution of 758 mg (1.21 mmol) of anhydrous $Yb(OTf)_3$ in 25 mL of THF at −78 °C. The solution turned to a deep burgundy color and was stirred at −78 °C for 30 min. Addition of a solution of ethyl levulinate (**2a**) in 10 mL of THF via cannula yielded a lighter red color. While warming to room temperature during 3 h, the color of the solution changed to pale yellow. After an additional 2 h at room temperature, the reaction 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 over $MgSO_4$. After removal of solvent, the residue was purified by flash chromatography (silica gel, 3:1 hexanes−ethyl acetate) to provide 182 mg (70%) of **3a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 1H), 7.25 (m, 3H), 3.79 (m, 1H), 3.70 (m, 1H), 3.31 (m, 1H), 3.13 (m, 1H), 2.59−2.74 (m, 2H), 2.47−2.56 (m, 2H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 142.1, 134.8, 131.9, 128.0, 127.1, 125.2, 87.5, 44.8, 37.2, 35.8, 29.3, 28.4; IR (neat) 2974, 1770 cm^{-1}; HRMS calcd for $C_{13}H_{16}ClO_2$ (MH^+): 239.0839, found 239.0841; LRMS (CI) *m*/*z* 239 MH^+ (100), 173 (57), 137 (67).

1-Methyl-13-oxatricyclo[8.2.1.0^{2,7}]trideca-2(7),3,5-trien-10-ol (4a). General Procedure for the Synthesis of Hydroxy Cycloalkanones. To a suspension of 537 mg (3.57 mmol) of samarium metal in 25 mL of THF at 0 °C was added 911 mg (3.40 mmol) of diiodomethane. The suspension was stirred 1 h at 0 °C and 2 h at room temperature. To the resulting deep blue SmI_2 solution was added 21 mg (0.068 mmol) of NiI_2 and then a solution of 204 mg (0.85 mmol) of **3a** in 10 mL of THF via cannula. After the addition of the substrate, the reaction mixture was irradiated with visible light (250 W krypton lamp) for 4 h while the temperature was maintained below 25 °C. The resultant mixture was hydrolyzed with a saturated aqueous solution of Rochelle's salt. The organic phase was separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine and dried over $MgSO_4$. After removal of solvent, the residue was purified by flash chromatography (silica gel, 3:1 hexanes−ethyl acetate) to provide 159 mg (91%) of **4a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 1H), 7.14 (m, 3H), 3.12 (m, 1H), 2.89 (m, 1H), 2.72 (s, 1H), 2.11−2.22 (m, 5H), 2.03 (m, 1H), 1.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8, 138.7, 131.4, 127.0, 126.1, 124.6, 107.6, 83.5, 39.7, 39.0, 38.5, 31.9, 28.4; IR (neat) 3395 cm^{-1}; HRMS calcd for $C_{13}H_{17}O_2$ (MH^+): 205.1229, found 205.1227; LRMS (CI) *m*/*z* 205 MH^+ (14), 187 (100), 169 (18).

2-Bromo-5-chloropent-1-ene (14). To a solution of 4.43 g (43.2 mmol) of 5-chloropent-1-yne in 25 mL of CH_2Cl_2 at −78 °C was added 43.2 mL of a 1.0 M solution of BBr_3 in CH_2Cl_2 during 20 min. The solution was warmed to room temperature and stirred for an additional 1 h. After careful hydrolysis with water, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$. After removal of solvent, the residue (a mixture of the title compound and an *E*/*Z*-mixture of 2-bromo-5-chloropent-1-en-1-yl)dibromoborane was suspended in 300 mL of pentane. After addition of 10 mL of AcOH, the suspension was heated to reflux for 4 h. After careful neutralization with saturated $NaHCO_3$ solution, the organic phase was separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed first with saturated $NaHCO_3$ solution and then with brine and dried over $MgSO_4$. After removal of solvent, the residue was purified via Kugelrohr distillation (10 mmHg, 70 to 80 °C) to provide 4.50 g (57%) of the title compound **14**, which rapidly turned brown on standing. No correct elemental analysis nor HRMS could be obtained. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (m, 1H), 5.44 (d, J = 1.6 Hz, 1H), 3.54 (t, J = 6.3 Hz, 2H), 2.58 (m, 2H), 2.01 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.4, 118.1, 43.3, 38.3, 30.3; IR (neat) 2958, 1629 cm^{-1}; LRMS (CI) *m*/*z* 184 (24), 120 (82), 103 (100).

(*Z*)-2-Bromo-5-chloropent-2-ene (19). A solution of 210 mg (1.27 mmol) of (*Z*)-4-bromopent-3-en-1-ol, 257 mg (2.16 mmol) of thionyl chloride and 262 mg (2.16 mmol) of *N*,*N*-dimethylaniline in 4 mL of $CHCl_3$ was heated to reflux

(25) Forsberg, J. H.; Spaziano, V. T.; Balasubramanian, T. M.; Liu, G. K.; Kinsley, S. A.; Duckwort, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *J. Org. Chem.* **1987**, *52*, 1017.

(26) Ponton, J.; Helquist, P.; Conrad, P. C.; Fuchs, P. L. *J. Org. Chem.* **1981**, *46*, 118.

(27) (a) Marschall, H.; Vogel, F.; Weyerstahl, P. *Chem. Ber.* **1974**, *107*, 2852. (b) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705.

(28) (a) Cotarca, L.; Delogu, P.; Maggioni, P.; Nardelli, A.; Bianchini, R.; Sguassero, S. *Synthesis* **1997**, 328. (b) Andrew, D.; Hastings, D. J.; Weedon, A. C. *J. Am. Chem. Soc.* **1994**, *116*, 10870. (c) Lee, G. H.; Choi, E. B.; Lee, E.; Pak, C. S. *J. Org. Chem.* **1994**, *59*, 1428.

(29) de Diesbach, H.; Klement, O. *Helv. Chim. Acta* **1941**, *24*, 158.

(30) Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975.

overnight. The cooled solution was hydrolyzed with 2 N HCl. The organic phase was separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed first with 2 N HCl and then with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified via Kugelrohr distillation (10 mmHg, 50 to 60 °C) to provide 160 mg (69%) of the title compound **19**, which rapidly turned brown on standing. No correct elemental analysis nor HRMS could be obtained. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (m, 1H), 3.53 (t, J = 6.8 Hz, 2H), 2.60 (m, 2H), 2.30 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 125.2, 124.7, 43.0, 34.7, 28.8; IR (neat) 2958 cm^{-1}; LRMS (CI) *m*/*z* 184 (4), 154 (100), 135 (12), 133 (11).

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Supporting Information Available: Experimental procedures and structural data for all compounds not described within the text. X-ray crystal structure data for compounds **7d**, **10c**, and **21**. ^{1}H and ^{13}C NMR spectra from all compounds for which no elemental analyses were obtained. This material is available free of charge via the Internet at http://pubs.acs.org.

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