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A New Strategy for the Preparation of an Active Mn(0) and its Use for Radical Cyclization Reactions

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Abstract: Reduction of Li_2MnCl_4 with magnesium in THF afforded a fairly active manganese species which readily initiated radical cyclization of 2-iodoethanal allylic acetals at room temperature. The corresponding 2-bromoethanal acetals also provided the same cyclized products upon treatment with the activated manganese reagent at reflux in THF. This reagent can also be used to induce tandem radical cyclizations, and the 5-*exo*/6-*endo* and 5-*exo*/6-*exo* modes are both available to give the products with *trans*-stereochemistry with regard to ring-junction. Further, the intramolecular type of sequential generation and utilization of radical and anionic species with this reagent have also been studied.

Recently, organomanganese reagents have received much more attention not only because they have an important role for the understanding of the mechanisms of fundamental organometallic reactions, but also recent research indicates that certain types of manganese-mediated reactions have great synthetic potential in organic chemistry.[1] Among them, Mn(III) as an oxidative radical initiator has been of primary importance in the construction of cyclic compounds, which have even been widely used in the synthesis of natural compounds.[2] Lately, some research work has shown that the reductive metal Mn(0) in combination with TMSCl and $PbCl_2$ could also act as a radical initiator to promote multi-component coupling reactions.[3] At the same time, we have reported an effective method for the preparation of indoline, dihydrobenzofuran and 2-alkoxytetrahydrofuran derivatives by means of tributylmanganate(II) which have also been considered to be a reductive radical initiator.[4] To date, numerous radical reactions have been reported and employed routinely by synthetic organic chemists.[5,6] In addition, transition metal species[2b,7] and samarium(II) iodide[8] have also been used in the construction of heteroatom ring compounds via a radical process. Herein, we disclose in detail another effective method for the preparation of low-valent manganese and its mediated radical cyclization[9] of 2-haloethanal acetals. This new method provides an alternative route to reach the same aim as the above reagents.[10]

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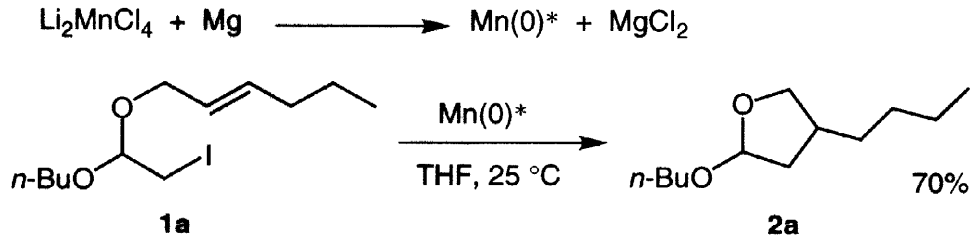
A new manganese reagent was obtained upon reduction of the well soluble ate-complex Li_2MnCl_4 with magnesium turnings activated by 1,2-dibromoethane. 1,2-Dibromoethane (5.0 mmol) was added to a suspension of magnesium[11] (40 mmol) in THF (4 mL). Exothermic reaction took place. After being stirred for another 5 min, THF and the produced $MgBr_2$ were removed with a syringe and the resulting magnesium turnings were washed by THF (3 x 4 mL).[12] Then, a pale yellow-green solution of Li_2MnCl_4[13] (15 mmol), derived from $MnCl_2$ (15 mmol) and LiCl (30 mmol), in THF (40 mL) was added to the above magnesium turnings. The mixture was stirred for 24 h at room temperature. The original pale yellow-green color gradually turned dark, affording a extremely divided black powder[14,15] which was partially soluble in THF. Hence, a clear dark supernatant manganese in THF (5.0 mL, ~1.8 mmol) was added with a syringe to a solution of 2-iodoethanal acetal **1a** (1.0 mmol) in THF (2.0 mL) at 25 °C under argon atmosphere. After stirring the mixture for 6 h at 25 °C, the resulting mixture was quenched with sat. NH_4Cl, extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were washed with NaCl solution, dried over anhydrous Na_2SO_4, and concentrated. Silica gel column chromatography provided a cyclized product **2a** in 70% yield as a mixture of two stereoisomers (1:1) (Scheme 1).

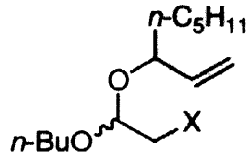
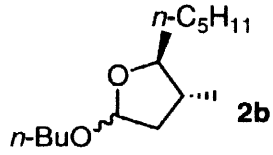
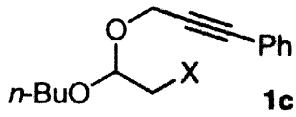
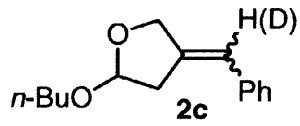
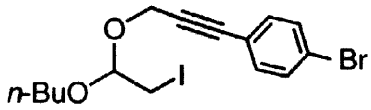
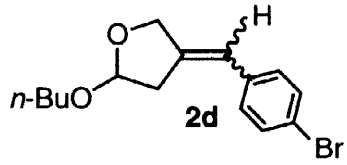
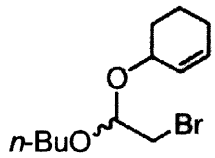
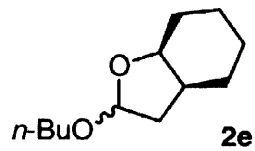
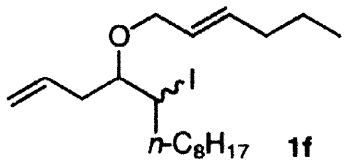
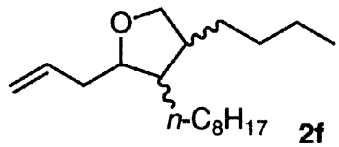
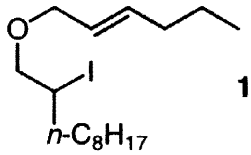
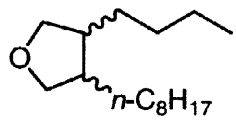
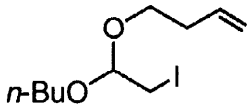
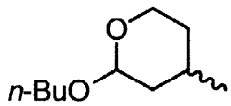
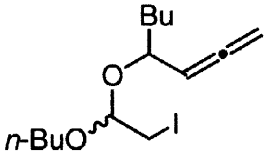
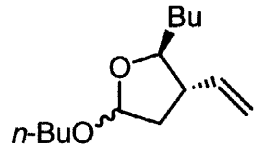
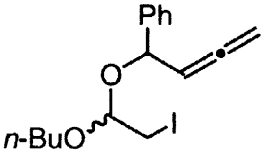
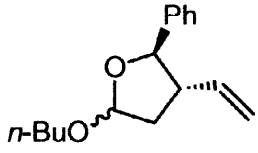
Scheme 1



1a **2a**

The representative results of the reaction of various acetals and the others with low-valent manganese are shown in Table 1. 2-Haloethanal acetal derivatives were prepared by the reactions of allylic or 2-propynylic alcohols with butyl vinyl ether in the presence of *N*-iodosuccinimide or *N*-bromosuccinimide in dichloromethane.[4b,16] The derivatives which have the allenyl moiety were synthesized from the corresponding allenyl alcohols which could be attained according to the published method.[17] This new cyclization method has some characteristic features compared to the reaction with *n*-$Bu_3MnMgBr$ and several comments are worth noting. (1) In the case of the substrates (**1a**, **1b**, **1e**,**1f**, and **1g**) which have a terminal alkene or a disubstituted olefin as radical acceptor, in all cases, 4-alkyl-substituted tetrahydrofuran derivatives were obtained principally with this new procedure. These results show sharp contrast to those of the reaction with *n*-$Bu_3MnMgBr$ which provides alkenyl-substituted tetrahydrofuran products exclusively in the case of the substrates which have disubstituted or trisubstituted alkenic moieties.[4b] We are tempted to assume that a hydrogen abstraction of the intermediary carbon radical is the major pathway in the reaction with Mn(0), whereas recombination with *n*-BuMn(I) followed by β-elimination of Mn–H producing an alkenyl substituent becomes the main route in the reaction with *n*-$Bu_3MnMgBr$. (2) The bromo acetals (**1b**, **1c** (X=Br), and **1e**) reacted with Mn(0) smoothly as well as the iodo acetals and provided comparable yields of the desired tetrahydrofuran derivatives, although the reaction of bromo acetals required heating of the reaction mixture at reflux in THF. (3) Acetylenic triple bonds were equally effective as carbon-carbon double bonds for trapping

Table 1. The Active Manganese Mediated Cyclization Reactions[a)]

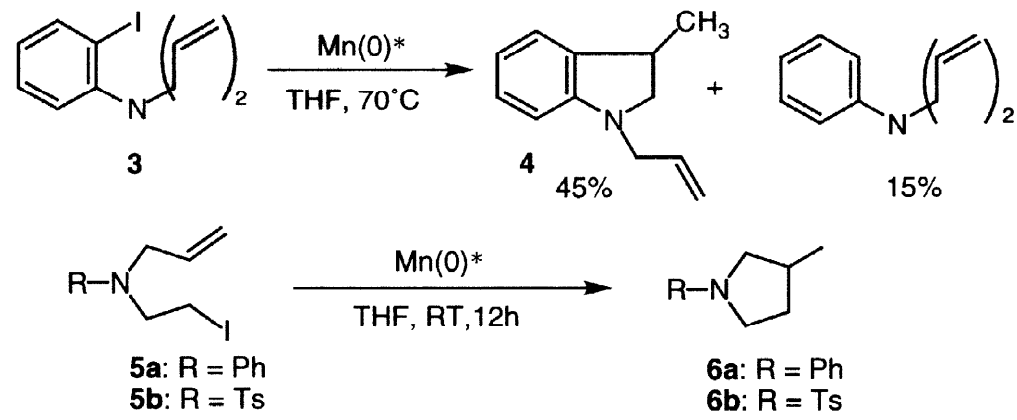
Entry	Starting material	Product	Yield
1	 **1b**	 **2b**	X = I 72%[b)] X = Br 61%[b)]
2	 **1c**	 **2c**	X = I 85%[c)] X = Br 80%[c)]
3	 **1d**	 **2d**	65%[c)]
4	 **1e**	 **2e**	62%[b)]
5	 **1f**	 **2f**	60%[d)]
6	 **1g**	 **2g**	62%[e)]
7	 **1h**	 **2h**	35%[d)]
8	 **1i**	 **2i**	68%[b)]
9	 **1j**	 **2j**	70%[b)]

a) The reaction was performed at 25 °C (X=I) or 70 °C (X=Br). b) Diastereomeric ratio = 1/1. c) *E*/*Z* = 45/55. d) Diastereomeric ratio could not be determined. e) Diastereomeric ratio = 52/48.

the radical intramolecularly. Quenching the reaction mixture with D_2O afforded a mixture of deuterated alkene (**2c**-*d*) and **2c** (**2c**-*d*:**2c** = 35:65). (4) The bromo group in the aromatic ring proved to be completely tolerated in this kind of transformation (Entry 3). (5) The reaction of 2-iodoethanal butyl homoallyl ether **1h** with Mn(0) provided **2h** in only 35% yield in a 6-*exo* pattern. (6) The allenyl moiety is as effective as olefinic linkage to trap the radical intramolecularly (Entries 8 and 9). In these cases, only the favorable 5-*exo* products were acquired. The resulting vinyl radical intermediates have higher reactivity and easily pick up a hydrogen from the solvent.[18,19,20] Additionally, the cyclization of allenyl derivatives has a chemically valuable feature, namely, that the resulting ring has a double bond substituent in a predetermined position. Moreover, this kind of substrate shows high stereoselectivity between C(4) and C(5), affording only *trans*-products.[21]

The reagent Mn(0) also reacted with the most reactive substrates such as allylic bromides or α-bromoesters at 25 °C. In contrast, a simple secondary iodide such as 2-iodotridecane[3] was recovered unchanged upon treatment with Mn(0) at 25 °C even for 12 h. The cyclization of *N*,*N*-diallyl-2-iodoaniline with Mn(0) was not so effective. For instance, treatment of 2-iodoaniline **3** (1.0 mmol) with Mn(0) (5 mL, ~1.8 mmol) in THF at reflux for 6 h afforded an indoline derivative **4** in only 45% yield along with reduced *N*,*N*-diallylaniline (15%). However, the allylic amine derivatives **5** provided pyrrolidine derivatives **6** in much better yields (**6a**, 60% or **6b**, 70%) (Scheme 2) compared to the reaction with *n*-$Bu_3MnMgBr$ which afforded the desired product **6a** or **6b** in only 7% or 35%, respectively, and the starting allylic amines (CH_2=$CHCH_2NHR$) were obtained as the main products. The latter compound could be formed *via* E2 elimination by the attack of an ate complex (probably butyl anion) on iodine.

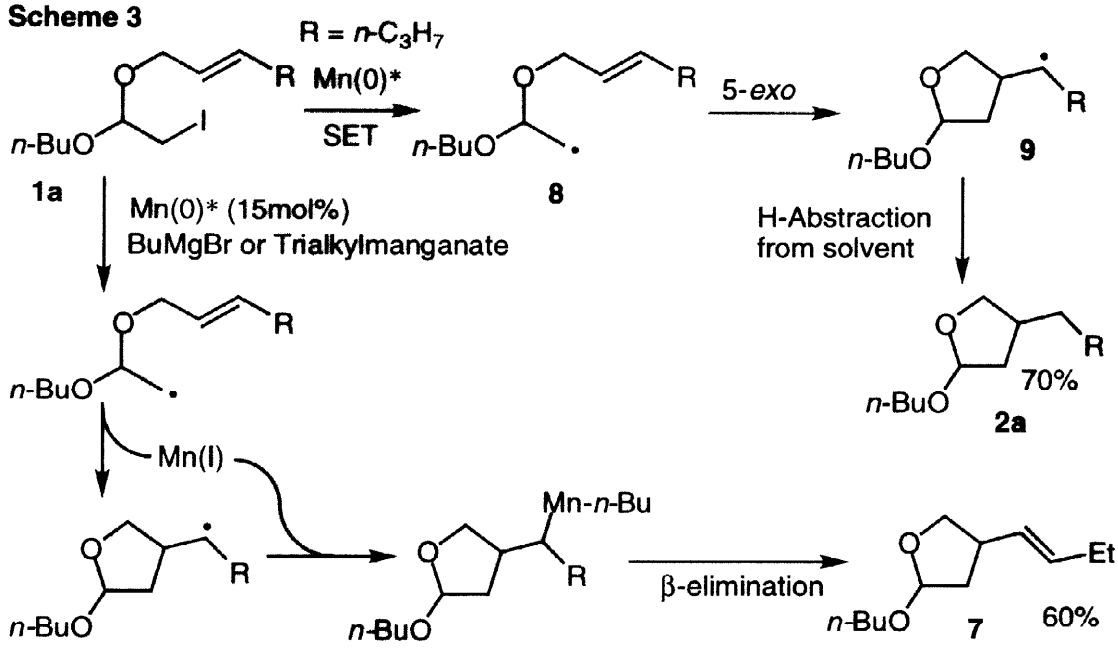
Scheme 2



Next, Mn(0)-catalyzed reaction of acetals **1a** was examined. Treatment of a solution of **1a** (1.0 mmol) in THF (5 mL) with butylmagnesium bromide (1.0 M THF solution, 2 mL, 2 mmol) in the presence of Mn(0) (0.4 mL of a clear dark supernatant, ~0.15 mmol) gave **7** which was identical with a sample prepared by the reaction of **1a** with *n*-$Bu_3MnMgBr$.

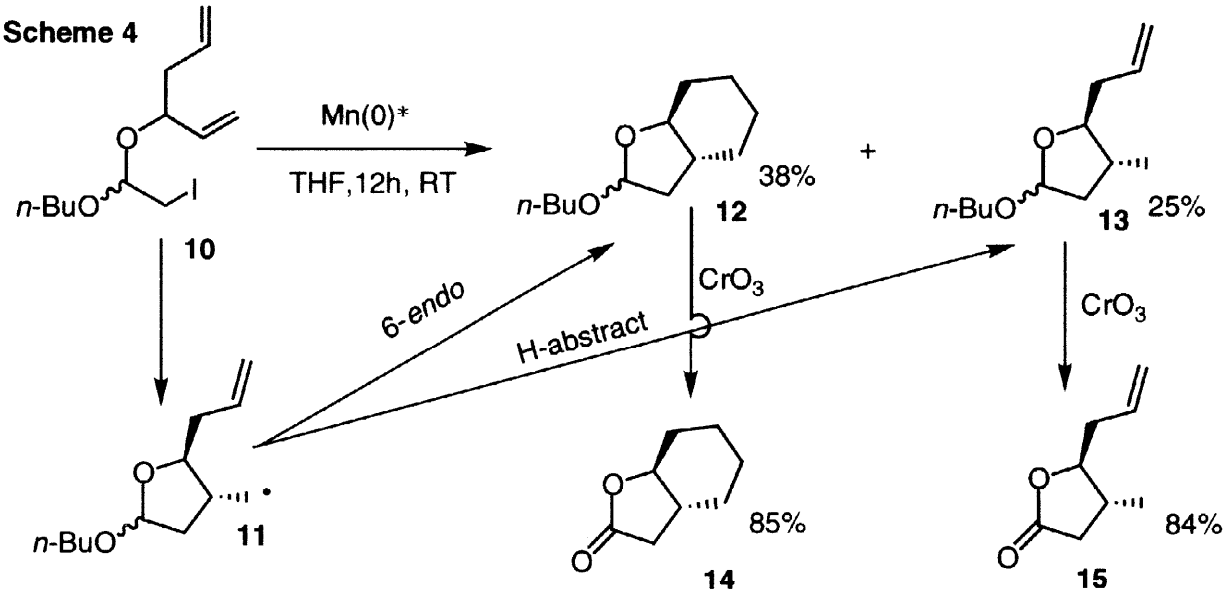
Based on these facts, we are tempted to assume the following reaction mechanism. Single-electron transfer from Mn(0) to 2-iodoethanal acetals would give an anion radical which provides a radical **8** after departure of iodide. 5-*Exo* mode cyclization could afford a carbon radical **9** which abstracts a hydrogen from the solvent THF[18] (Scheme 3).

Scheme 3



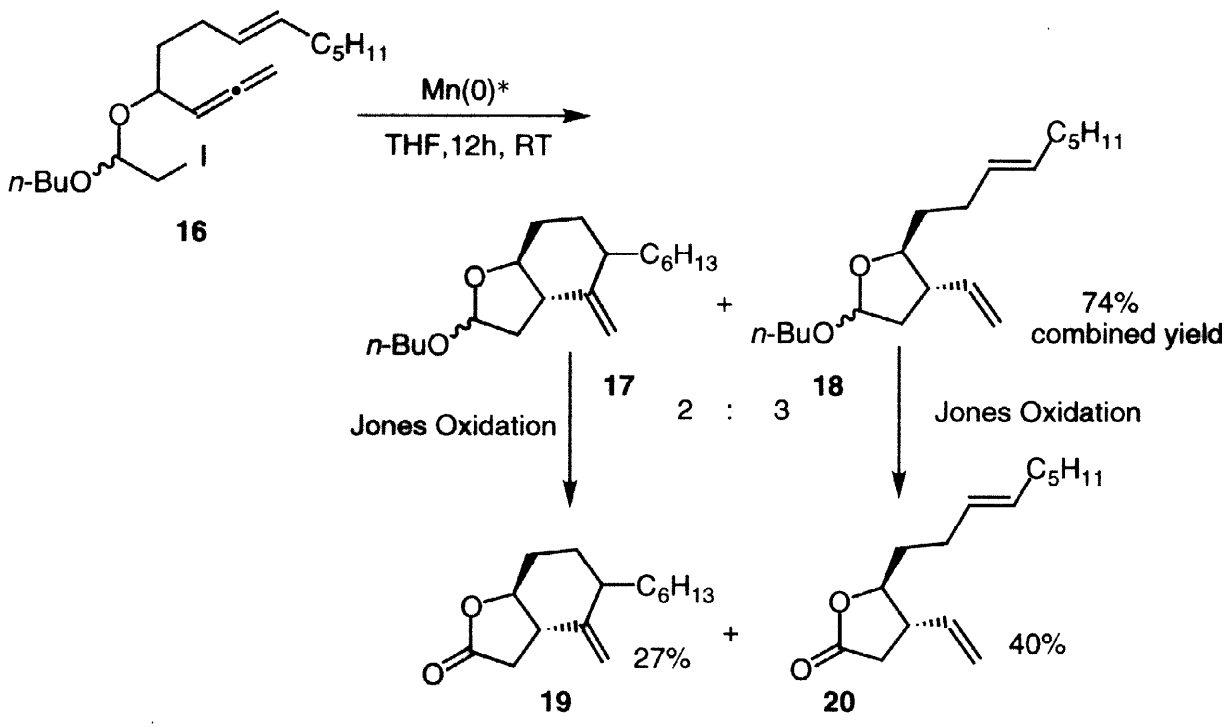
In light of the findings cited above, we tried to carry out the same reaction with a more complex substrate like **10**. The reaction proceeded smoothly under the standard mild conditions, and the compounds **12** and **13**[22] were obtained in 38% and 25% isolated yield, respectively. Upon careful Jones oxidation,[23] we were quite surprised to find that, in addition to monocyclic lactone **15**, the main product **14** was a bicyclic lactone, a product of 5-*exo*/6-*endo*[24] tandem radical cyclizations (Scheme 4). Both products obtained have high stereoselectivity between C(4) and C(5) giving the *trans*-conformation only.[21] This forms a sharp contrast with the result of the reaction of **1e** (Table 1. Entry 4). Treatment of **1e** with Mn(0) provided the cyclized products **2e** showing *cis*-stereochemistry with regard to the ring junction. Thus, we have achieved methods to prepare both *cis*-fused and *trans*-fused 7-oxa-8-oxobicyclo[4.3.0]nonane.

Scheme 4



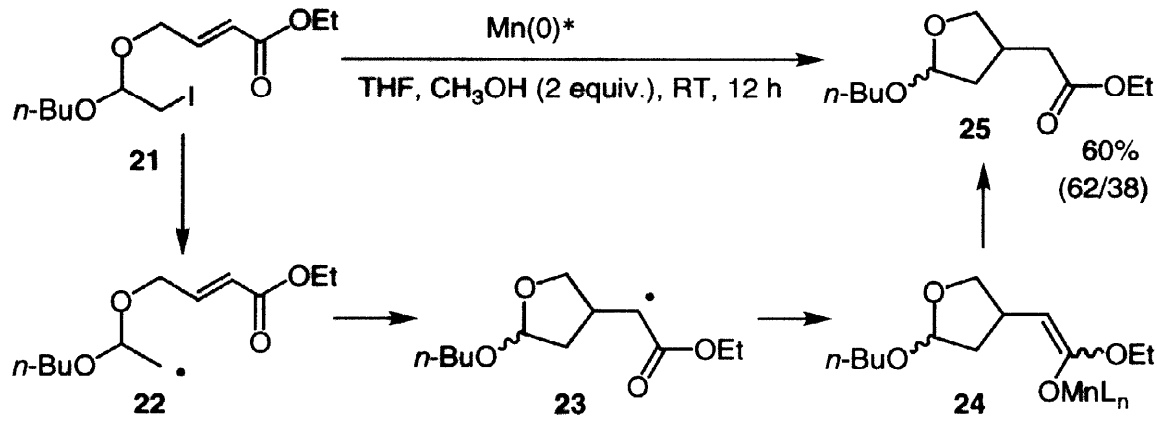
Then, we carried out the following reaction with compound **16**. After standing a reaction mixture of **16** and Mn(0) in THF at room temperature for 12 h, compounds **17** and **18**[22] were isolated in 74% combined yield in a ratio about 2 to 3. Jones oxidation gave a bicyclic lactone **19** in 27% isolated yield with a stereoisomeric ratio about 1.66:1 and monocyclic lactone **20** in 40% isolated yield as a single diastereoisomer. It is obvious that the bicyclic lactone is formed via a successive 5-*exo* and 6-*exo* process (Scheme 5). The vinyl radical thus formed might abstract a hydrogen more easily, giving the monocyclized product **18** compared to the methyl radical **11** in the case of substrate **10**.

Scheme 5



Finally, we examined the reaction of **21** which has an α,β-unsaturated ester moiety as the radical acceptor. Treatment of **21** with Mn(0) under the same reaction conditions gave a complex mixture. Fortunately, this intermolecular radical 1,4-addition to α,β-unsaturated ester could be achieved by carrying out the reaction in the coexistence of a proton source such as methanol (Scheme 6). The critical role of methanol might be in the facile and quick trapping of the manganese enolate **24**,[25] which is produced by a second single-electron transfer from Mn(0) or Mn(I) to **23**.

Scheme 6



In conclusion:

Many kinds of 2-haloethanal acetal derivatives with a radical acceptor in a proper position undergo cyclization reactions smoothly under very mild conditions with a new active Mn(0) reagent. This reagent can also be applied to induce tandem radical cyclizations, and in this case, the 5-*exo*/6-*endo* and 5-*exo*/6-*exo* mode cyclizations are both available to give the products with *trans*-stereochemistry with regard to the ring-junction. Further, the results of an intramolecular type of sequential generation and utilization of radical and anionic species with this reagent would provide an alternative route to synthesize functionalized latone when methanol is replaced by other electrophiles.

Experimental

Distillation of the products was performed by the use of Kugelrohr (Büchi), and boiling points are indicated by air-bath temperature without correction. ^{1}H NMR and ^{13}C NMR spectra were taken on a Varian GEMINI 300 spectrometer, $CDCl_3$ was used as a solvent, and chemical shifts are given in δ with tetramethylsilane as an internal standard. IR spectra were determined on a JASCO IR-810 spectrometer. The analyses were carried out at the Elemental Analysis Center of Kyoto University.

Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl before use. Anhydrous manganese(II) chloride purchased from Aldrich was heated at 160 °C for 2h prior to use. All reactions were carried out in dry argon atmosphere.

Generation of the Low-Valent Manganese. Magnesium turnings were activiated by treatment with a solution of 1,2-dibromoethane in THF, followed by washing with THF (3x4 mL). Then, a pale yellow-green solution of Li_2MnCl_4 (15 mmol), derived from $MnCl_2$ (15 mmol) and LiCl (30 mmol), in THF (40 mL) was added to the above magnesium turnings. The mixture was stirred for 24 h at room temperature.[26] The original pale yellow-green color turned dark. This resulting, extremely divided black powder[14,15] was partially soluble in THF and the clear dark supernatant manganese in THF[27] was transferred with a syringe when using.

Typical Procedure for the Manganese(0)-Mediated Cyclization Reaction. The supernatant manganese in THF (5mL, ~1.8mmol) was added with a syringe to a solution of substrate **1a** (1.0 mmol) in THF (2.0 mL) at 25 °C under argon atmosphere. The progress of the reaction was monitored by TLC (hexane/ethyl acetate = 20/1). When the starting material was no longer present (c.a. 6h), the resulting

mixture was quenched with sat. NH_4Cl, extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were washed with NaCl solution, dried over anhydrous Na_2SO_4, and concentrated to dryness. Silica gel column chromatography provided the cyclized product 2-Butoxy-4-butyltetrahydrofuran (**2a**, 1:1 Mixture of Stereoisomers) in 70% yield: **Bp**: 100 °C (3 torr); IR (neat) 2910, 2860, 1459, 1379, 1347, 1263, 1239, 1191, 1097, 1021, 931, 734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 7.5 Hz, 3H), 1.18–1.56 (m, 11H), 2.04–2.27 (m, 2H), 3.34 (dt, J = 6.6, 9.6 Hz, 1H), 3.41 (t, J = 8.4 Hz, 1H), 3.64 (dt, J = 6.6, 9.6 Hz, 1H), 3.90 (t, J = 7.5 Hz, 1H), 5.06 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.73, 13.87, 19.26, 22.67, 30.78, 31.77, 32.65, 38.54, 39.02, 67.38, 71.81, 104.56. Found: C, 71.68; H, 12.35%. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08%.

2-Butoxy-4-(4-bromophenyl)[^{2}H]methylenetetrahydrofuran (2d, *E/Z* = 45/55 mixture of stereoisomers): IR (neat) 2954, 2924, 2862, 1731, 1663, 1586, 1489, 1459, 1423, 1406, 1378, 1334, 1182, 1146, 1097, 1074, 1036, 1007, 926, 861 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 3H), 1.33 (tq, J = 7.2, 7.5 Hz, 2H), 1.52 (tt, J = 7.2, 8.1 Hz, 2H), 2.64–2.92 (m, 2H), 3.37–3.45 (m, 1H), 3.65–3.72 (m, 1H), 4.46–4.61 (m, 2H), 5.19 (d, J = 4.8 Hz, 0.44H), 5.31 (d, J = 4.5 Hz, 0.56H), 6.28 (s, 0.56H), 6.33 (s, 0.44H), 6.95–7.44 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.72(x2), 19.22(x2), 31.59(x2), 37.83, 41.09, 67.08, 67.15, 67.74, 70.77, 102.19, 104.27, 119.15, 120.35, 120.39, 120.53, 129.43, 129.57, 131.54, 131.64, 136.39, 136.44, 139.88, 140.36. HRMS, Calcd for $C_{15}H_{19}O_2Br$: M, 310.0568, 312.0549. Found: *m/z* 310.0566, 312.0569.

2-Allyl-4-butyl-3-octyltetrahydrofuran (2f, mixture of stereoisomers, isomeric ratio could not be determined): Bp: 187–189 °C (0.5 torr); IR (neat) 2922, 2850, 1467, 1460, 1378, 1037, 990, 911, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (m, 6H), 1.16–1.40 (m, 20H), 1.73–2.33 (m, 4H), 3.28–4.05 (m, 3H), 5.01–5.09 (m, 2H), 5.76–5.91 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.94, 13.96, 22.55, 22.81, 26.41, 27.15, 28.00, 29.20, 29.43, 29.78, 30.56, 31.78, 39.89, 41.38, 46.13, 71.86, 82.60, 116.60, 135.63. Found: C, 81. 6; H, 12.80%. Calcd for $C_{19}H_{36}O$: C, 81.36; H, 12.94%.

3-Butyl-4-octyltetrahydrofuran (2g, 1:1 mixture of stereoisomers) faster moving band (R_f = 0.45, hexane/ethyl acetate = 20/1): Bp: 116 °C (1 torr); IR (neat) 2952, 2920, 2850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86–0.92 (m, 6H), 1.21–1.34 (m, 20H), 1.45–1.60 (m, 1H), 1.68–1.80 (m, 1H), 3.38 (dd, J = 7.5, 7.5 Hz, 2H), 3.9 (dd, J = 6.9, 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.90, 13.98, 22.55, 22.82, 28.41, 29.19, 29.43, 29.79, 30.61, 31.78, 32.82, 33.14, 45.56, 45.58, 73.87(x2). Found: C, 80.03; H, 13.45%. Calcd for $C_{16}H_{32}O_2$: C, 79.93; H, 13.41%. **slower moving band (R_f = 0.43, hexane/ethyl acetate = 20/1)**: Bp: 116 °C (1 torr); IR (neat) 2952, 2920, 2850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 0.91 (t, J = 6.6 Hz, 3H), 1.20–1.40 (m, 20H), 2.06–2.18 (m, 2H), 3.50 (dd, J = 6.0, 8.1 Hz, 2H), 3.85 (dd, J = 6.6, 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.96, 13.99, 22.57, 22.84, 26.64, 26.96, 28.44, 29.20, 29.48, 29.81, 30.66, 31.79, 41.95, 41.97, 72.44(x2). Found: C, 80.03; H, 13.45%. Calcd for $C_{16}H_{32}O_2$: C, 79.93; H, 13.41%.

2-Butoxy-4-methyltetrahydropyran (2h, mixture of stereoisomers, isomeric ratio could not be determined): Bp: 102–105 °C (7 torr); IR (neat) 2916, 2856, 2790, 1460, 1444, 1412, 1381, 1371, 1351, 1258, 1164, 1141, 1075, 1003, 988, 973, 915, 886 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.2 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 1.01–1.79 (m, 9H), 3.34–3.44 (m, 2H), 3.82 (dt, J = 6.6, 9.6 Hz, 1H), 3.97 (ddd, J = 1.8, 4.2, 11.7 Hz, 1H), 4.29 (dd, J = 2.4, 9.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.77, 19.18, 21.73, 29.28, 31.80, 33.68, 39.96, 65.22, 68.53, 101.88. Found: C, 69.42; H, 11.41%. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70%.

2-Butoxy-5-butyl-4-vinyltetrahydrofuran (2i, 1:1 mixture of stereoisomers) faster moving band (R_f = 0.43, hexane/ethyl acetate = 20/1): Bp: 123–125 °C (0.5 torr); IR (neat) 2928, 2858,

1643, 1467, 1380, 1341, 1300, 1156, 1099, 1034, 996, 914, 882, 669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 6H), 1.23–1.70 (m, 11H), 2.23–2.37 (m, 2H), 3.36 (dt, J = 6.6, 9.6 Hz, 1H), 3.62–3.70 (m, 2H), 4.94–5.12 (m, 3H), 5.73 (ddd, J = 8.1, 9.9, 17.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.72, 13.88, 19.26, 22.68, 28.41, 31.80, 32.99, 39.84, 49.14, 67.28, 81.56, 103.42, 115.72, 139.29. Found: C, 74.22; H, 11.34%. Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58%. **slower moving band (R_f = 0.40, hexane/ethyl acetate = 20/1)**: Bp: 123–125 °C (0.5 torr); IR (neat) 2924, 2860, 1644, 1466, 1379, 1349, 1321, 1187, 1161, 1087, 1032, 993, 914, 661 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 6H), 1.27–1.62 (m, 10H), 1.80 (ddd, J = 4.8, 11.7, 11.7 Hz, 1H), 2.04 (dd, J = 6.9, 12.6 Hz, 1H), 2.71 (m, 1H), 3.31 (dt, J = 6.3, 9.6 Hz, 1H), 3.62–3.70 (m, 2H), 4.96–5.10 (m, 3H), 5.65 (ddd, J = 8.4, 10.2, 17.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.75, 13.90, 19.32, 22.61, 28.44, 31.76, 35.36, 40.32, 47.51, 66.63, 84.48, 103.21, 115.97, 138.87. Found: C, 74.22; H, 11.34%. Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58%.

2-Butoxy-5-phenyl-4-vinyltetrahydrofuran (2j, 1:1 mixture of stereoisomers) faster moving band (R_f =0.41, hexane/ethyl acetate = 20/1): Bp: 175 °C (0.5 torr); IR (neat) 3064, 3030, 2954, 2868, 1642, 1453, 1350, 1333, 1191, 1098, 1003, 916, 753, 697, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3H), 1.38 (tq, J = 7.2, 7.8 Hz, 2H), 1.53–1.63 (m, 2H), 1.88 (ddd, J = 3.0, 7.8, 13.2 Hz, 1H), 2.50 (ddd, J = 5.4, 9.0, 12.9 Hz, 1H), 2.63 (ddt, J = 8.4, 8.4, 8.4 Hz, 1H), 3.44 (dt, J = 6.6, 9.6 Hz, 1H), 3.77 (dt, J = 6.9, 9.6 Hz, 1H), 4.68 (d, J = 8.4 Hz, 1H), 4.90 (d, J = 17.1 Hz, 1H), 4.99 (d, J = 10.2 Hz, 1H), 5.33 (dd, J = 3.3, 5.7 Hz, 1H), 5.84 (ddd, J = 8.1, 10.2, 17.1 Hz, 1H), 7.24–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.76, 19.26, 31.74, 39.76, 52.00, 67.68, 83.55, 103.92, 116.44, 126.45, 127.73, 128.34, 137.84, 140.34. Found: C, 77.71; H, 9.20%. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00%. **slower moving band (R_f = 0.39, hexane/ethyl acetate = 20/1)**: Bp: 175 °C (0.5 torr); IR (neat) 3028, 2954, 2928, 2866, 1644, 1493, 1455, 1443, 1351, 1322, 1183, 1097, 1056, 1028, 982, 939, 913, 888, 752, 698, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, J = 7.5 Hz, 3H), 1.44 (tq, J = 7.2, 7.5 Hz, 2H), 1.60–1.70 (m, 2H), 2.04 (ddd, J = 5.1, 12.3, 17.4 Hz, 1H), 2.22 (dd, J = 6.6, 12.6 Hz, 1H), 3.00 (m, 1H), 3.46 (dt, J = 6.6, 9.3 Hz, 1H), 3.89 (dt, J = 6.6, 9.6 Hz, 1H), 4.64 (d, J = 9.3 Hz, 1H), 4.96 (d, J = 17.1 Hz, 1H), 5.03 (d, J = 10.5 Hz, 1H), 5.20 (d, J = 5.1 Hz, 1H), 5.75 (ddd, J = 7.8, 10.5, 17.1 Hz, 1H), 7.26–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.82, 19.35, 31.76, 40.35, 50.60, 67.38, 86.92, 103.70, 116.94, 126.78, 127.55, 128.24, 136.81, 141.73. Found: C, 77.71; H, 9.20%. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00%.

N-phenyl-3-methylpyrrolidine (6a): Bp: 127–130 °C (0.1 torr); IR (neat) 2954, 2922, 2888, 2866, 2824, 1600, 1510, 1504, 1483, 1365, 1185, 991, 744, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (d, J = 6.9 Hz, 3H), 1.61 (ddt, J = 8.1, 8.4, 12.3 Hz, 1H), 2.06–2.15 (m, 1H), 2.36 (tq, J = 6.9, 8.4 Hz, 1H), 2.84 (dd, J = 7.8, 7.8 Hz, 1H), 2.23–3.38 (m, 2H), 3.42 (dd, J = 7.5, 9.0 Hz, 1H), 6.52 (d, J = 7.8 Hz, 1H), 6.63 (t, J = 7.5 Hz, 1H), 7.17–7.23 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 18.31, 33.16, 33.43, 47.34, 54.84, 111.39, 115.23, 129.17, 148.01. Found: C, 81.80; H, 9.41%. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38%.

N-tosyl-3-methylpyrrolidine (6b): Mp: 66.0–67.5 °C; IR (nujol) 2850, 1337, 1302, 1163, 1092, 1040, 764, 659 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (d, J = 6.9 Hz, 3H), 1.31 (ddt, J = 8.1, 8.4, 12.3 Hz, 1H), 1.86 (ddt, J = 4.8, 6.9, 12.3 Hz, 1H), 2.07 (ttq, J = 6.9, 6.9, 6.9 Hz, 1H), 2.39 (s, 3H), 2.70 (dd, J = 7.8, 9.6 Hz, 1H), 3.18 (ddd, J = 7.5, 8.1, 9.6 Hz, 1H), 3.29 (ddd, J = 4.2, 8.1, 9.6 Hz, 1H), 3.38 (dd J = 7.2, 9.6 Hz, 1H), 7.28 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 17.46, 21.35, 33.08, 33.14, 47.49, 54.65, 127.52, 129.62, 134.01, 143.31. Found: C, 59.98; H, 7.07%. Calcd for $C_{12}H_{17}NO_2S$: C, 60.21; H, 7.17%.

***trans* -7-Oxabicyclo[4.3.0]nonan-8-one (14)**: IR (neat) 2932, 2864, 1745, 1449, 1426, 1299, 1255, 1212, 1189, 1172, 1130, 1114, 1091, 1076, 1028, 932, 876 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12–2.52

(m, 11H), 3.75 (dt, J = 3.9, 10.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.94, 25.19, 28.22, 30.07, 35.77, 44.70, 85.17, 176.78. HRMS, Calcd for $C_8H_{12}O_2$: M, 140.0837. Found: *m/z* 140.0839.

***trans*-4-Methyl-5-(2-propenyl)tetrahydro-2-furanone (15)**: IR (neat) 2962, 2930, 1776, 1421, 1210, 1157, 1069, 988, 942, 914 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (d, J = 6.6 Hz,3H), 2.12–2.50 (m, 4H), 2.65 (dd, J = 7.5, 16.8 Hz, 1H), 4.06 (dt, J = 5.4, 6.6 Hz, 1H), 5.11–5.18 (m, 2H), 5.73–5.87 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17.42, 35.02, 36.84, 37.81, 86.18, 118.74, 132.56, 176.48. HRMS, Calcd for $C_8H_{12}O_2$: M, 140.0837. Found: *m/z* 140.0833.

***trans*-3-Hexyl--2-methylene-7-oxabicyclo[4.3.0]nonan-8-one (19, 1.66:1 Mixture of Stereoisomers)**: IR (neat) 2922, 2856, 1784, 1459, 1450, 1214, 1185, 1086, 1038, 1007, 986, 927, 894 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82–0.90 (m, 3H), 1.00–2.88 (m, 18H), 3.68 (ddd, J = 4.2, 10.5, 10.5 Hz, 0.62H), 3.84 (ddd, J = 4.5, 10.8, 10.8 Hz, 0.38H), 4.60–4.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.90, 13.93, 22.46, 22.51, 26.38, 27.13, 27.59, 29.46, 29.91, 30.73, 31.34, 31.69(x2), 31.99, 32.14, 32.27, 32.73, 33.80, 34.60, 36.91, 44.22, 46.19, 85.41, 87.78, 104.52, 111.45, 147.45, 148.13, 176.17, 176.34. HRMS, Calcd for $C_{15}H_{24}O_2$: M, 236.1777. Found: *m/z* 236.1780. Found: C, 76.33; H, 10.38%. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24%.

***trans*-4-(3-Nonenyl)-3-vinyltetrahydro-2-furanone (20)**: IR (neat) 2918, 2850, 1779, 1460, 1448, 1424, 1273, 1204, 1150, 1084, 1062, 1042, 993, 968, 949, 922 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (t, J = 6.9 Hz, 3H), 1.15–1.35 (m, 6H), 1.58–1.78 (m, 2H), 1.93 (q, J = 6.9 Hz, 2H), 2.01–2.25 (m, 2H), 2.40 (dd, J = 10.2, 17.1 Hz, 1H), 2.65 (dd, J = 8.1, 17.1 Hz, 1H), 2.75 (tt, J = 8.1, 8.4 Hz, 1H), 4.12 (dt, J = 3.6, 8.4 Hz, 1H), 5.11–5.18 (m, 2H), 5.27–5.47 (m, 2H), 5.68 (ddd, J = 7.8, 10.2, 17.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.88, 22.35, 28.55, 29.00, 31.22, 32.34, 35.50, 35.34, 46.20, 83.91, 118.06, 128.24, 132.06, 135.74, 175.82. HRMS, Calcd for $C_{15}H_{24}O_2$: M, 236.1777. Found : *m/z* 236.1765.

Typical Procedure for the Manganese(0)-Mediated Cyclization Reaction of 21. The supernatant manganese in THF (5mL, ~1.8mmol) was added with a syringe to a solution of substrate **21** (1.0 mmol) and methanol (2.5mmol) in THF (5.0 mL) at 25 °C under argon atmosphere. The progress of the reaction was monitored by TLC (hexane/ethyl acetate = 10/1). When all of the starting material were consumed (c.a. 12h), the resulting mixture was quenched with sat. NH_4Cl, extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were washed with NaCl solution, dried over anhydrous Na_2SO_4, and concentrated to dryness. Silica gel column chromatography provided the cyclized product 2-Butoxy-4-ethoxycarbonylmethyltetrahydrofuran (**25,** 1.65:1 Mixture of Stereoisomers) in 60% yield. Bp: 170 °C (0.5 torr); IR (neat) 2930, 2870, 1737, 1370, 1350, 1310, 1229, 1166, 1068, 1019, 933 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H), 1.26–1.38 (m, 2H), 1.45–1.62 (m, 3H), 2.02–2.82 (m, 4H), 3.32 (dt, J = 6.6 Hz, 9.3 Hz, 1H), 3.47–3.52 (m, 1H), 3.57–3.66 (m, 1H), 4.00–4.12 (m, 3H), 5.06 (d, J = 5.1 Hz, 0.38H), 5.07 (d, J = 5.4 Hz, 0.62H); ^{13}C NMR ($CDCl_3$) δ 13.69, 14.05, 19.20, 19.23, 31.65, 31.69, 33.56, 33.91, 38.20, 38.48(x2), 38.75, 60.31, 60.37, 66.98, 67.18, 71.45, 71.54, 103.73, 104.11, 172.45, 172.72. Found: C, 62.85; H, 9.63%. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63%. The cyclized compound **25** was easily transformed into 4-Ethoxycarbonylmethyl-2-furanone by Jones Oxidation in 85% yield. Bp: >200 °C (0.5 torr); IR (neat) 2974, 2912, 1779, 1719, 1420, 1375, 1333, 1299, 1259, 1162, 1096, 1017 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7.2 Hz, 3H), 2.23 (dd, J = 7.8, 17.7 Hz, 1H), 2.48 (dd, J = 6.6, 8.7 Hz, 2H), 2.69 (dd, J = 8.4, 17.7 Hz, 1H), 2.94 (heptet, J = 7.8 Hz, 1H), 3.97 (dd, J = 6.6, 9.3 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 4.48 (dd, J = 7.2, 9.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.98, 31.75, 33.87, 37.17, 60.88, 72.57, 171.12, 176.42. HRMS, Calcd for $C_8H_{12}O_4$: M, 172.0735. Found: *m/z* 172.0727.

Physical data for **2b**, **2c**, **2e**, **4** and **7** were identical with those which have been described in a

literature.[4b]

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11. Metal granules 1–3 mm purchased from Mitsuwa's pure chemicals.
12. The blank test without manganese species was performed as follows: The fully activated magnesium

turnings were stirred in THF for 24 h, and the supernatant (5 mL) was added to the flask containing **1b** (X=I, 1.0 mmol) in THF (2 mL). No reaction took place after 24 h from which 90% of the starting material was recovered unchanged.

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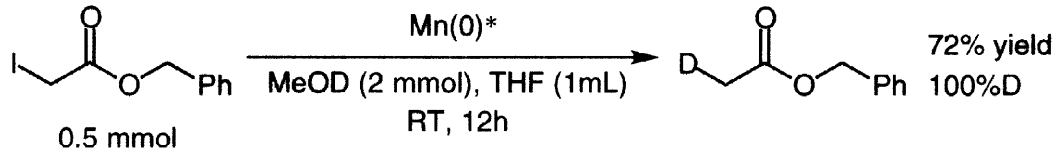
14. We are tempted to assume the manganese species to be an active metallic manganese (Mn(0)). Several reductive procedures have been reported for the preparation of active manganese from manganese(II) halides. $LiAlH_4$: Hiyama, T.; Obayashi, M.; Nakamura, A. *Organometallics* **1982**, *1*, 1249; Li-naphthalene: Kim, S.-H.; Hanson, M. V.; Rieke, R. D. *Tetrahedron Lett.* **1996**, *37*, 2197; C_8K: Fürstner, A.; Brunner, H. *Tetrahedron Lett.* **1996**, *37*, 7009.
15. Treatment of **1b** (X=I) with commercially available manganese powder (Kanto Chemical Co. Inc) at 25 °C for 36 h resulted in a complete recovery of the starting material. Several procedure for an activation of Mn metal has been reported: (a) Hiyama. T.; Sawahata, M.; Obayashi, M. *Chem. Lett.* **1983**, 1237. (b) Cahiez, G.; Chavant, P. Y. *Tetrahedron Lett.* **1989**, *30*, 7373. (c) Takai, K.; Ueda, T.; Hayashi, T.; Moriwake, T. *Tetrahedron Lett.* **1996**, *37*, 7049.
16. Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384.
17. Shimizu, I.; Sugiura, T.; Tsuji, J. *J. Org. Chem.* **1985**, *50*, 537.
18. THF is a better H-donor in radical reaction ($K_H = 10^4 s^{-1}$). For the detail please see: Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206. and references therein.
19. Stork, G.; Jr. Mook, R. *J. Am. Chem. Soc.* **1983**, *105*, 3720.
20. Treatment of **1i** with Et_3B/Bu_3SnH afforded **2i** in 85% yield, however the workup and purification of the products were troublesome.
21. Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.
22. Diastereomeric ratio could not be determined because of their complex ^1H NMR spectra. Characterization of the products is based on the corresponding lactones after Jones oxidation.
23. Morikawa, T.; Nishiwaki, N.; Iitake, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1987**, *28*, 671.
24. 5-*exo* mode cyclization of **11** to form *trans*-fused 2-oxabicyclo[3.3.0]octane might be unfavorable.
25. The presence of the manganese enolate could also be supported by the following reaction.

Scheme 7



26. If the magnesium turnings were not fully activiated, this reductive reaction shoud not be initiated. In such case, a small amount of 1,2-dibromoethane (ca. 3 mmol) was added to the above suspension and the reductive reaction should take place at once.
27. The content of manganese in this supernatant could be simplely determined by acid-base titration method and the details are as follows: supernatant (2 mL) was transfered with a syringe to a flask under argon atmosphere, and quenched it with standard hydrochloric acid (0.100 mmol/mL, 10 mL) at 0 °C. The excess hydrochloric acid was titrated by a standard sodium hydroxide (0.100 mmol/mL) with phenol phthalein as an indicator. Upon this method, the factor is about 0.29 mmol Mn(0)/mL.