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A Facile Approach to the Synthesis of Allylic Spiro Ethers and Lactones

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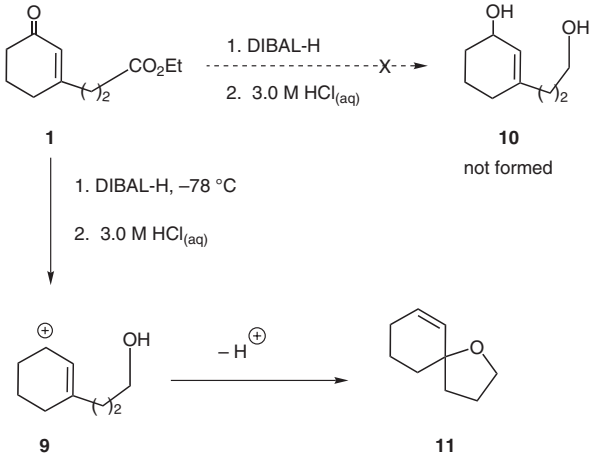
Dedicated to Marty Semmelhack on the occasion of his 65th birthday

Abstract: Treatment of 3-[(alkoxycarbonyl)alkyl]-substituted conjugated cycloalkenones with diisobutylaluminum hydride at –78 °C followed by acid quenching furnishes spiro ethers, whereas the corresponding 3-(carboxyalkyl)-substituted cycloalkenones generate spiro lactones upon reaction with sodium borohydride at 30 °C followed by acid quenching.

Key words: enones, heterocycles, lactones, spiro compounds

Oxygen heterocycles constitute an important class of molecules owing to their frequent occurrence in many natural products.[1] A number of synthetic methods have been developed for the construction of oxaspirocycles.[2] For spiro ethers, 1-(hydroxyalkyl)cycloalka-1,3-dienes have been used as starting materials,[3] and for spiro lactones, cyclic tertiary alcohols substituted at C-1 with a carboxyalkyl side chain[4] or cyclic carboxylic acids bearing a hydroxyalkyl side chain at the α-carbon[5] have often been used as building blocks. In most cases, these substrates require lengthy preparations and transition metals need to be employed for the intramolecular cyclization reactions. For example, palladium acetate has been used to catalyze the intramolecular oxaspirocyclization of 1-(hydroxyalkyl)cycloalka-1,3-dienes to produce allylic spiro ethers.[3] Similarly, tricarbonyliron was needed for the intramolecular coupling of cyclohexa-1,3-dienes with a pendant (alkoxycarbonyl)alkenyl group to afford heterospirocycles.[6] Therefore, inexpensive reagents and mild reaction conditions are still needed for the preparation of spiro ethers and spiro lactones.

We now report a facile approach to the synthesis of allylic spiro ethers by treatment of 3-[(alkoxycarbonyl)alkyl]cycloalk-2-enones with diisobutylaluminum hydride followed by quenching of the reaction mixture with hydrochloric acid. In addition, spiro lactones can be obtained by reaction of cyclic 3-(carboxyalkyl)cycloalk-2-enones with sodium borohydride followed by acid quenching. It was expected that the allylic cation, e.g. **9**, generated in situ upon reduction of a 3-[(alkoxycarbonyl)alkyl]cycloalk-2-enone, e.g. **1**, with diisobutylaluminum hydride followed by acid quenching, would be attacked by the tethered hydroxy group to generate the allylic spiro ether **11** (Scheme 1).



Scheme 1

3-[(Alkoxycarbonyl)alkyl]cycloalk-2-enones **1**–**4** (Table 1) were synthesized from 3-iodocyclohex-2-enone or 3-iodocyclopent-2-enone according to literature procedures.[7] Ethyl 3-(6-oxocyclohex-1-enyl)propanoate (**5**) was obtained by treating cyclohex-2-enone with ethyl acrylate and 1,8-diazabicyclo[5.4.0]undec-7-ene under Baylis–Hillman reaction conditions.[8] Acids **6**–**8** were obtained by treatment of the corresponding esters with aqueous potassium hydroxide at 30 °C for three hours.

We recently reported an efficient method for the construction of benzofurans by intramolecular cyclization catalyzed by $CeCl_3 \cdot 7H_2O$–NaI of cyclohexa-1,3-dienes bearing a hydroxy group at C-7.[9] A suitable substrate for the extension of this chemistry to the synthesis of spiro ethers would be 3-(3-hydroxypropyl)cyclohex-2-en-1-ol (**10**) (Scheme 1). Thus, ethyl 3-(3-oxocyclohex-1-enyl)propanoate (**1**)[7] was treated with diisobutylaluminum hydride at –78 °C for one hour, after which the reaction mixture was quenched with 3 M hydrochloric acid. Surprisingly, allylic spiro ether **11**[10] was isolated in 74% yield after aqueous workup and flash column chromatography on silica gel. The yield of **11** was optimized to 82% by treatment of compound **1** with four equivalents diisobutylaluminum hydride for one hour followed by quenching of the reaction mixture with 6 M hydrochloric acid for ten minutes (Scheme 2). This straightforward synthesis of 1-oxaspiro[4.5]dec-6-ene (**11**) is more effective than the oxaspirocycle syntheses reported in the literature.[3,6]

Increasing the tether length by one with ethyl 4-(3-oxocyclohex-1-enyl)butanoate (**2**) (Table 1, entry 2) led to 1-

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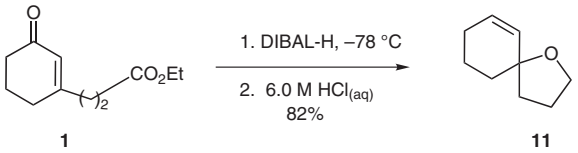
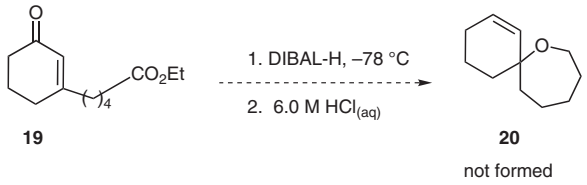


Scheme 2

oxaspiro[5.5]undec-7-ene (**12**) in 75% yield under the same reaction conditions. Five-membered-ring analogues **3** and **4** (Table 1, entries 3 and 4) also underwent intramolecular cyclization to produce 1-oxaspiro[4.4]non-6-ene (**13**) and 6-oxaspiro[4.5]dec-1-ene (**14**), in 66% and 72% yields, respectively. Under the same reaction conditions, the cyclohex-2-enone derivative **5** afforded hexahydrochromene derivative **15** in 60% yield (Table 1, entry 5). Unlike oxaspirocycles **11**–**14**, larger oxaspirocycles, e.g. **20**, cannot form under these conditions (Scheme 3). Thus, ethyl 5-(3-oxocyclohex-1-enyl)pentanoate (**19**) gave unidentified mixtures after being treated with diisobutylaluminum hydride at –78 °C followed by acid quenching (Scheme 3). The difficulty in forming 7-oxaspiro[5.6]dodec-1-ene (**20**) might be attributed to unfavorable formation of the seven-membered ring.

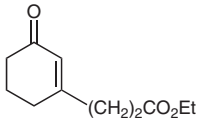
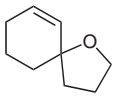
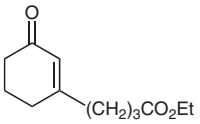
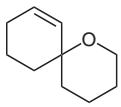
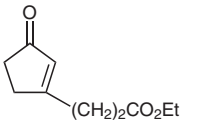
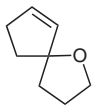
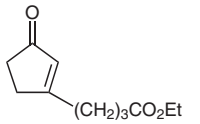
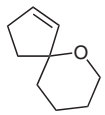
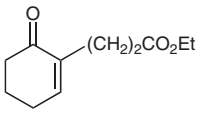
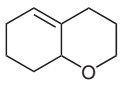
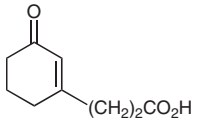
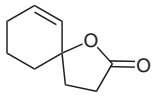
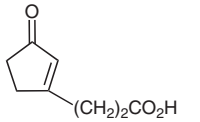
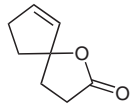
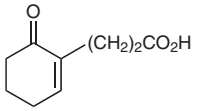
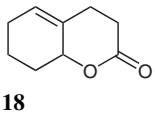


Scheme 3

Next, we applied this reaction to the synthesis of allylic spiro lactones. Treatment of 3-(3-oxocyclohex-1-enyl)propanoic acid (**6**) with four equivalents of diisobutylaluminum hydride at –78 °C followed by quenching of the reaction mixture with 6 M hydrochloric acid produced the spiro lactone **16** in only 10% yield. However, the yield of **16** can be improved to 67% when sodium borohydride is used as the reducing agent along with a catalytic amount of a Lewis acid. Thus, the best reaction conditions for the reduction of **6** was the use of ten equivalents sodium borohydride in the presence of a catalytic amount of $CeCl_3 \cdot 7H_2O$ at 30 °C for 30 minutes. The reaction mixture was then quenched with 6 M hydrochloric acid to afford the spiro lactone **16** in 67% isolated yield. The five-membered-ring substrate **7** (Table 1, entry 7) also underwent intramolecular cyclization ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, 6 M aq HCl) to produce 1-oxaspiro[4.4]non-6-en-2-one (**17**) in 40% yield. Cyclohex-2-enone derivative **8** bearing a carboxyalkyl side chain at C-2 generated hexahydrochromenone derivative **18** in 44% yield (Table 1, entry 8).

In conclusion, conjugated cyclic enones containing an (alkoxycarbonyl)alkyl- or carboxyalkyl side chain were found to readily react with hydrides to give allylic spiro ethers and lactones after acid quenching. This method can also be applied to the synthesis of fused oxabicycles. This synthesis of oxaspirocycles by reduction/dehydration of conjugated cyclic enones is more efficient than the previously reported methods.[3]

Table 1 Synthesis of Oxaspirocycles and Fused Oxabicycles from 3-(Ethoxyalkyl)- and 3-(Carboxyalkyl)-Substituted Cycloalk-2-enones

Entry	Starting material	Product	Yield[a] (%)
1[b]	 **1**	 **11**	82
2[b]	 **2**	 **12**	75
3[b]	 **3**	 **13**	66
4[b]	 **4**	 **14**	72
5[b]	 **5**	 **15**	60
6[c]	 **6**	 **16**	67
7[c]	 **7**	 **17**	40
8[c]	 **8**	 **18**	44

[a] Isolated yields. Satisfactory spectral data were obtained for all compounds.
[b] DIBAL-H was used for the cyclization.
[c] Cyclization in the presence of $NaBH_4$ and $CeCl_3 \cdot 7H_2O$.

^{1}H (400 MHz) and ^{13}C (100.4 MHz) NMR spectra were recorded on a Bruker-AC 400 spectrometer. IR spectra were recorded on a JASCO IR-700 spectrometer. Mass spectra were acquired on a JEOL JMS-D 100 spectrometer. High-resolution mass spectra were obtained on an AEI MS-9 double-focusing mass spectrometer and a JEOL JMS-HX 110 spectrometer using the EI method.

1-Oxaspiro[4.5]dec-6-ene (11);[11] Typical Procedure
A soln of **1** (0.50 g, 2.55 mmol) in THF (10 mL) was added slowly by syringe to 1.0 M DIBAL-H in cyclohexane (10 mL) at –78 °C. The mixture was stirred at –78 °C for 1 h. A homogeneous soln was obtained after slow addition of 6 M aq HCl (ca. 5.0 mL) to the mixture and subsequent removal of the cooling bath. The mixture was stirred for 10 min and diluted with Et_2O (150 mL). The resultant soln was washed with H_2O (3 × 200 mL) and brine (3 × 200 mL), dried ($MgSO_4$; 10 g), filtered through a bed of Celite, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes–EtOAc, 10:1).

Yield: 0.29 g (82%).

IR (CH_2Cl_2): 3049, 2983, 1726, 1605, 1445 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77 (dt, *J* = 10.0, 3.7 Hz, 1 H), 5.58 (d, *J* = 10.0 Hz, 1 H), 3.81–3.88 (m, 2 H), 1.93–1.97 (m, 4 H), 1.61–1.78 (m, 4 H), 1.58–1.60 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.98, 128.98, 79.65, 67.02, 37.93, 34.97, 26.00, 24.97, 20.45.

1-Oxaspiro[5.5]undec-7-ene (12)[12]
Spiro ether **12** was prepared by the same method as that described above for **11**.

Yield: 0.27 g (75%).

IR (CH_2Cl_2): 3531, 3431, 3388, 1667, 1438 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.74–5.81 (m, 2 H), 3.61–3.69 (m, 2 H), 2.00–2.04 (m, 1 H), 1.90–1.93 (m, 1 H), 1.79–1.84 (m, 1 H), 1.67–1.74 (m, 1 H), 1.59–1.66 (m, 2 H), 1.46–1.53 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.42, 129.84, 69.93, 61.26, 35.69, 32.90, 25.89, 25.63, 18.93, 18.48.

1-Oxaspiro[4.4]non-6-ene (13)[13]
Spiro ether **13** was prepared by the same method as that described above for **11**.

Yield: 0.18 g (66%).

IR (CH_2Cl_2): 3493, 3407, 3388, 1851, 1663, 1365 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87–5.89 (m, 1 H), 5.66–5.68 (m, 1 H), 3.83 (t, *J* = 6.75 Hz, 2 H), 2.44–2.50 (m, 1 H), 2.24–2.31 (m, 1 H), 1.93–1.99 (m, 3 H), 1.83–1.89 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.73, 133.25, 93.91, 66.97, 36.60, 36.38, 30.80, 26.19.

6-Oxaspiro[4.5]dec-1-ene (14)[11,13]
Spiro ether **14** was prepared by the same method as that described above for **11**.

Yield: 0.24 g (72%).

IR (CH_2Cl_2): 3856, 3431, 3406, 1870, 1655 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.89–5.93 (m, 2 H), 3.71–3.76 (m, 1 H), 3.64–3.69 (m, 1 H), 2.45–2.52 (m, 1 H), 2.24–2.32 (m, 1 H), 1.94–2.00 (m, 1 H), 1.86–1.92 (m, 1 H), 1.53–1.73 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.39, 133.68, 87.15, 63.43, 34.96, 34.53, 30.74, 25.84, 20.89.

3,4,6,7,8,8a-Hexahydro-2*H*-chromene (15)
Chromene **15** was prepared by the same method as that described above for **11**.

Yield: 0.17 g (60%).

IR (CH_2Cl_2): 3431, 3407, 3387, 1870, 1659, 1459 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.46 (s, 1 H), 3.96–4.01 (m, 1 H), 3.85–3.88 (m, 1 H), 3.53 (td, *J* = 11.52, 2.68 Hz, 1 H), 1.64–2.17 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.09, 122.22, 74.75, 67.95, 31.92, 30.02, 28.14, 25.30, 20.54.

MS (EI): *m*/*z* (%) = 138 (20) [M$^+$], 137 (100), 119 (63), 107 (51), 95 (55), 93 (89), 79 (51), 71 (100), 57 (83), 55 (63).

HRMS (EI) *m*/*z* calcd for $C_9H_{14}O$: 138.1045; found: 138.1041.

1-Oxaspiro[4.5]dec-6-en-2-one (16);[14] Typical Procedure
$CeCl_3·7H_2O$ (3.62 g, 9.72 mmol) and $NaBH_4$ (1.23 g, 32.4 mmol) were added separately in five portions to a stirring soln of **6** (0.50 g, 3.24 mmol) in MeOH (100 mL) at 0 °C. The mixture was stirred at 30 °C for 30 min, and the addition of 6 M aq HCl (5.0 mL) followed. The mixture was stirred for 10 min and was concentrated in vacuo. The residue was diluted with H_2O (100 mL). The aqueous solution was extracted with EtOAc (3 × 50 mL). The combined organic soln was washed with H_2O (3 × 200 mL) and brine (3 × 200 mL), dried ($MgSO_4$; 10 g), filtered through a bed of Celite, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes–EtOAc, 5:1).

Yield: 0.15 g (67%).

IR (CH_2Cl_2): 3431, 3407, 3387, 2666, 1664 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.94–5.98 (m, 1 H), 5.64 (d, *J* = 10.0 Hz, 1 H), 2.61 (t, *J* = 8.2 Hz, 2 H), 2.10–2.17 (m, 3 H), 1.96–2.01 (m, 2 H), 1.81–1.85 (m, 1 H), 1.65–1.77 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.67, 132.56, 128.45, 83.56, 34.53, 34.03, 28.72, 24.56, 19.30.

1-Oxaspiro[4.4]non-6-en-2-one (17)[8,14,15]
Bicyclic lactone **17** was prepared by the same method as that described above for **16**.

Yield: 0.18 g (40%).

IR (CH_2Cl_2): 3856, 3431, 3387, 1774, 1663, 1459 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08–6.10 (m, 1 H), 5.72–5.75 (m, 1 H), 2.60–2.64 (m, 3 H), 2.39–2.42 (m, 1 H), 2.21–2.30 (m, 3 H), 2.04–2.06 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.54, 137.44, 131.74, 97.74, 36.26, 33.44, 31.11, 29.68.

3,4,6,7,8,8a-Hexahydro-2*H*-chromen-2-one (18)
Chromenone **18** was prepared by the same method as that described above for **16**.

Yield: 0.13 g (44%).

IR (CH_2Cl_2): 3856, 3432, 3387, 2867, 1667, 1560, 1438 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.72 (s, 1 H), 4.82 (s, 1 H), 2.43–2.74 (m, 4 H), 2.04–2.15 (m, 3 H), 1.72–1.81 (m, 2 H), 1.55–1.60 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.48, 130.56, 126.15, 76.03, 30.47, 29.10, 25.84, 24.90, 19.55.

MS (EI): *m*/*z* (%) = 152 (83) [M$^+$], 124 (55), 110 (23), 97 (45), 96 (58), 91 (36), 82 (61), 79 (72), 67 (100), 55 (92).

HRMS (EI): *m*/*z* calcd for $C_9H_{12}O_2$: 152.0837; found: 152.0840.

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