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# A Simple Preparation of (*R*)-(2-Cyclopentenyl)acetic Acid and (*R*)-(2-Cyclohexenyl)acetic Acid Using β-Diastereoselective Radical Cyclization in the Presence of Lewis Acid

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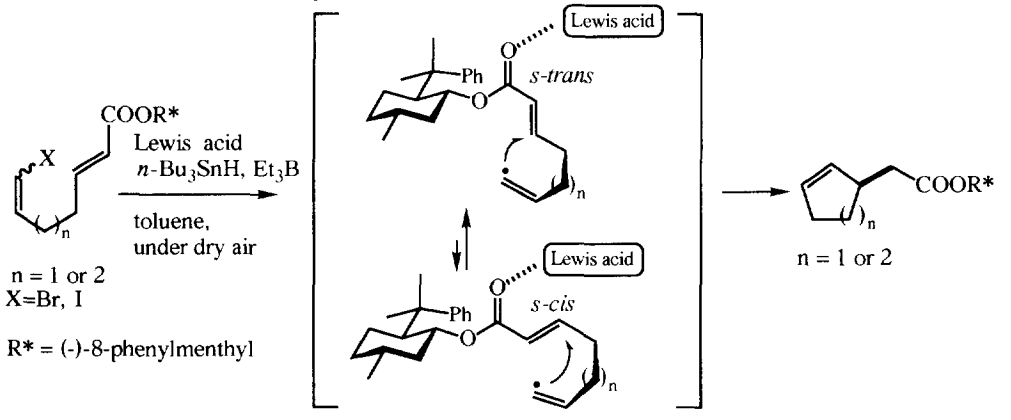
***Abstract***: The alkenyl radical generated from (-)-8-phenylmenthyl 7-iodo-2,6-heptadienoate smoothly cyclized to afford (*R*)-(2-cyclopentenyl)acetate with 88% *de* in 90% yield. (*R*)-(2-Cyclohexenyl)acetate was also obtained with 84% *de* in 72% yield under the same conditions. The presence of Lewis acid is essential for high diastereoselectivity and chemical yield.

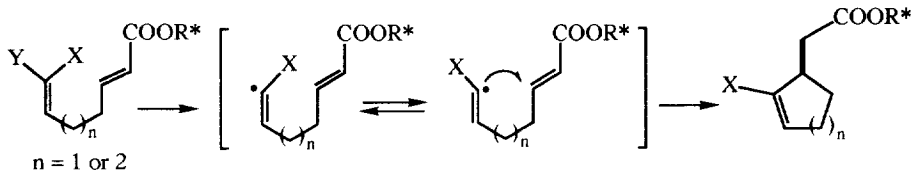
Despite a large number of investigations on the β-addition reaction of carbon radicals toward the α,β-unsaturated carbonyl system,[1] little is known about the β-diastereoselective radical addition to chiral alkenes with β-attached chiral auxiliaries.[2] Recently we reported the Lewis acid promoted β-diastereoselective radical cyclizations using α,β-unsaturated (-)-8-phenylmenthyl ester as a chiral radical acceptor.[3,4]

Here, we report that the terminal alkenyl radical could cyclize to afford (*R*)-(2-cyclopentenyl)acetate and (*R*)-(2-cyclohexenyl)acetate with high *de* in high yield under similar conditions. Because alkenyl radicals have low barriers to inversion, we expected equilibration to exist and cyclization to proceed preferentially (Schemes 1 and 2). Bulky Lewis acid seemed to fix the conformation of α,β-unsaturated ester as *s-trans* at a low temperature and the cyclization from *s-trans* rotamer would be increased.[5] Furthermore, the chelation of the Lewis acid with a carbonyl group would enhance the reactivity of α,β-unsaturated ester as a radical acceptor.




**Scheme 1**

First we chose dibromoolefin as a radical generator, because dibromoolefin was readily available from aldehyde under mild conditions and the cyclized product would possess the alkenyl bromide function on the cyclopentene ring which is useful for further transformations.




n = 1 or 2

X, Y = Br, Br ; X, Y = H , Br ; X, Y = H , I

R* = (-)-8-phenylmenthyl

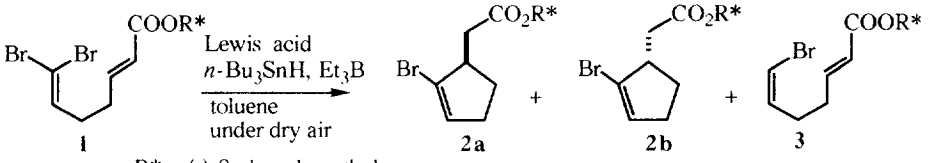
**Scheme 2**

The reaction of **1** without Lewis acid provided the cyclized product **2** only in 36% yield with the monobromoolefin **3** in 61% yield (Table 1, run 1). This shows that the α-bromoalkenyl radical is rapidly generated from the dibromoolefin at -20 °C.[6] However, the cyclization step is inefficient.[7] The presence of Lewis acid did not improve the yield of **2**, but the diastereoselectivity increased with increasing bulkiness of Lewis acid (runs 2-4). The reaction at a lower temperature (-78°C) showed a similar tendency.

The reaction of the terminal *cis*-alkenyl bromide **3** without Lewis acid provided the cyclized product **6** in low yields and most of **3** was recovered (Table 2, runs 1 and 2). Lewis acid could not improve the yield of **6** (run 3). Apparently the alkenyl radical could not be generated in these cases.[6,8]

On the other hand, the terminal alkenyl iodide **4** afforded the cyclized product in 85% yield at 0°C without Lewis acid (run 4). Furthermore the reaction proceeded smoothly even at -78°C to afford **6** in

**Table 1. Reactions Using Dibromoolefin as a Radical Generator[a]**



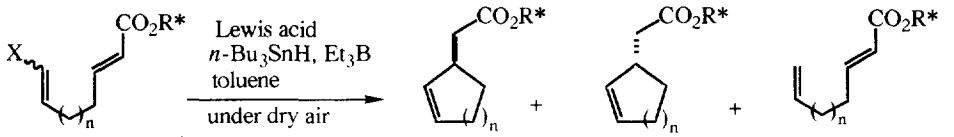

**1** **2a** **2b** **3**

R* = (-)-8-phenylmenthyl

| run | Lewis acid | eq. | M | temp. (°C) | time (min.) | yield (%) **2** | ratio *R* : *S* | yield (%) **3** |
|---|---|---|---|---|---|---|---|---|
| 1 | none | | | -20 | 60 | 36 | 63 : 37 | 61 |
| 2 | *i*-Bu3Al | 2 | 0.18 | -20 | 60 | 35 | 73 : 27 | 50 |
| 3 | *i*-Bu3Al | 4 | 0.36 | -20 | 60 | 32 | 76 : 24 | 38 |
| 4 | MAD[b] | 2 | 0.18 | -20 | 60 | 26[c] | 91 : 9 | 73 |
| 5 | none | | | -78 | 60 | 34 | 60 : 40 | 49 |
| 6 | *i*-Bu3Al | 2 | 0.18 | -78 | 60 | 23 | 74 : 26 | 37 |
| 7 | *i*-Bu3Al | 4 | 0.36 | -78 | 60 | 28 | 86 : 14 | 40 |
| 8 | MAD[b] | 2 | 0.18 | -78 | 60 | 29[c] | 97 : 3 | 71 |

a) Representative procedure (run 2): To a solution of **1** (109 mg, 0.22 mmol) in toluene (1.4 ml), were added *n*-$Bu_3SnH$ (59 μl, 0.22 mmol), *i*-Bu3Al (0.83 ml, 0.53 M in hexane, 0.44 mmol) and $Et_3B$ (0.23 ml, 1M in hexane, 0.23 mmol) in sequence at -20°C under dry air. The concentration of **1** (90 mM) was kept constant in the other reactions. The reaction was quenched by 1N HCl. The diastereoselectivity was determined by $^1$H-NMR. b) Methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide).[9] c) To a solution of **1** (109 mg, 0.22 mmol) in toluene (0.87 ml), were added a solution of MAD (0.4 M solution, 1.1 ml, 0.44 mmol), *n*-$Bu_3SnH$ (0.53 mmol) and $Et_3B$ (0.46 mmol) in this sequence.

**Table 2. Reactions using monohaloolefin**[a]




**3** : n = 1 (X = Br)[b] **(*R*)-6** : n = 1 **(*S*)-6** : n = 1
**4** : n = 1 (X = I)[c] **(*R*)-7** : n = 2 **(*S*)-7** : n = 2 **8** : n = 2
**5** : n = 2 (X = I)[d] R* = (-)-8-phenylmenthyl

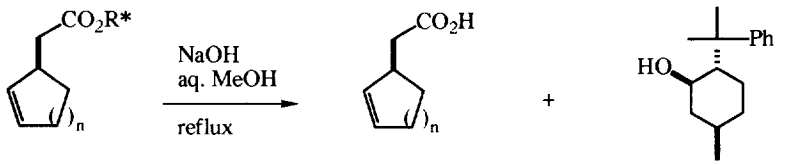
| run | substrate | Lewis acid | eq. | M | temp. (°C) | time (min.) | product **6** or **7** (%) | ratio *R* : *S* | **3** (%) | **8** (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **3** | none | | | 0 | 60 | 13 | 55 : 45 | 85 | |
| 2 | **3** | none | | | -20 | 60 | 4 | 60 : 40 | 96 | |
| 3 | **3** | *i*-Bu3Al | 2 | 0.16 | -20 | 60 | 4 | 61 : 39 | 79 | |
| 4 | **4** | none | | | 0 | 10 | 85 | 62 : 38 | | |
| 5 | **4** | none | | | -78 | 15 | 76 | 60 : 40 | | |
| 6 | **4** | $BF_3$•$OEt_2$ | 32 | 2.9 | -78 | 10 | 81[e] | 80 : 20 | | |
| 7 | **4** | *i*-Bu3Al | 4 | 0.36 | -78 | 10 | 80 | 84 : 16 | | |
| 8 | **4** | MAD | 1 | 0.09 | -78 | 120 | 89 | 86 : 14 | | |
| 9 | **4** | MAD | 4 | 0.36 | -78 | 120 | 87 | 90 : 10 | | |
| 10 | **4** | MAD | 4 | 0.36 | -98 | 120 | 90 | 94 : 6 | | |
| 11 | **5** | none | | | -20 | 10 | 59 | 69 : 31 | | 18 |
| 12 | **5** | $BF_3$•$OEt_2$ | 32 | 2.9 | -20 | 30 | 72[f] | 88 : 12 | | 3 |
| 13 | **5** | *i*-Bu3Al | 4 | 0.36 | -20 | 10 | 52 | 88 : 12 | | 2 |
| 14 | **5** | MAD | 1 | 0.09 | -20 | 60 | 72[g] | 92 : 8 | | 0 |
| 15 | **5** | none | | | -40 | 30 | 50 | 74 : 26 | | 31 |
| 16 | **5** | $BF_3$•$OEt_2$ | 32 | 2.9 | -40 | 20 | 52[f] | 90 : 10 | | 8 |
| 17 | **5** | *i*-Bu3Al | 4 | 0.36 | -40 | 10 | 52 | 88 : 12 | | 14 |
| 18 | **5** | MAD | 1 | 0.09 | -40 | 50 | 53[g] | 96 : 4 | | 15 |

a) The reactions were carried out using the same procedure described in Table 1 except for the amount of *n*-$Bu_3SnH$ (0.33 mmol) b) *cis* isomer. c) *cis* : *trans* = 1 : 1.6. d) *cis* : *trans* = 1 : 4. e) The reaction was carried out using 0.99 mmol of *n*-$Bu_3SnH$. f) Additional *n*-$Bu_3SnH$ (0.33 mmol) and $Et_3B$ (0.23 mmol) were added after 15 min. g) Additional $Et_3B$ (0.23 mmol) was added after 30 min.

76% yield (run 5).[6] The diastereoselectivity was increased in the presence of bulky Lewis acid (runs 7-9). The reaction with methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)[9] at -98°C provided the highest diastereoselectivity (88 % *de*, run 10).

The cyclohexene ring formation was relatively inefficient compared to the cyclopentene ring formation and (2-cyclohexenyl)acetate **7** was obtained in 59% without Lewis acid at -20°C (run 11). Both chemical yield and diastereoselectivity were improved when the reaction was carried out in the presence of Lewis acid and the bulkiness of Lewis acid was also important to provide high diastereoselectivity (runs 12-14). However, the chemical yield of **7** decreased in the reaction at -40°C although a slightly higher diastereoselectivity was observed. Practically, in respect to the cyclohexene formation, the reaction in the presence of MAD at -20°C provided a satisfactory result (84% *de*, 72%, run 14).

The absolute configurations of the major diastereoisomers, **(*R*)-6** and **(*R*)-7**, were determined by hydrolysis of these compounds to the known chiral acids (Scheme 3).[10] The acids, **(*R*)-9** and **(*R*)-10**, were obtained in 97% and 94% yield respectively. (-)-8-Phenylmenthyl alcohol could be recovered and reused.




**(*R*)-6** (n = 1, 88% *de*)
**(*R*)-7** (n = 2, 72% *de*)

**(*R*)-9** (n = 1, 97% yield)
$[\alpha]_D^{18}$= -87° (*c* 0.59, $CHCl_3$)
**(*R*)-10** (n = 2, 94% yield)
$[\alpha]_D^{18}$= -43° (*c* 1.04, $CHCl_3$)

**11**
(90 - 93% yield)

**Scheme 3**

In conclusion we have reported here a simple preparation of (*R*)-(2-cyclopentenyl)acetic acid and (*R*)-(2-cyclohexenyl)acetic acid using β-diastereoselective radical cyclization in the presence of Lewis acid. We found that Lewis acid played an essential role for high diastereoselectivity and chemical yield. Generally higher diastereoselectivity was observed when bulky Lewis acid was used at a low temperature. Chelation of the Lewis acid to the carbonyl oxygen fixed the conformation of α,β-unsaturated ester as *s-trans* and activated the unsaturated ester as a radical acceptor. Further applications for the preparation of chiral heterocyclic compounds will be reported in due course.

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