

Synthesis of α -Methylene- γ -lactone Fused to Seven, Eight, and Fourteen-membered Carbocycle through Intramolecular Cyclization of Functionalized Allylsilane with Acid Chloride

Chiaki Kuroda* and Shuzo Anzai

Department of Chemistry, Rikkyo University, Nishi-Ikebukuro, Toshima-ku, Tokyo 171-8501

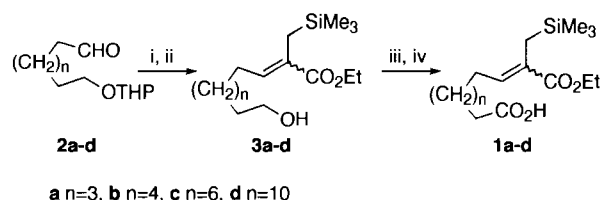
(Received May 27, 1998; CL-980402)

α -Methylene- γ -lactone fused to cycloheptane ring was synthesized by intramolecular cyclization of 8-(ethoxycarbonyl)- or 8-(acetoxymethyl)-9-(trimethylsilyl)non-7-enoyl chloride followed by lactonization. α -Methylene- γ -lactone fused to cyclooctane and cyclotetradecane ring were also synthesized from 9-(acetoxymethyl)-10-(trimethylsilyl)dec-8-enoyl chloride and 15-(acetoxymethyl)-16-(trimethylsilyl)hexadec-14-enoyl chloride, respectively.

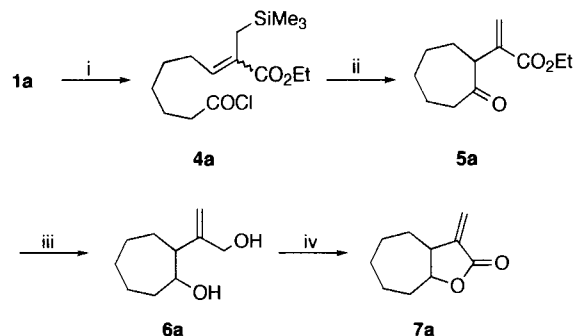
We previously reported that intramolecular Hosomi-Sakurai reaction of β -(ethoxycarbonyl)allylsilane is an excellent method to synthesize α -methylene- γ -lactone fused to terpenoid-type of carbocycles.¹⁻⁶ This process includes carbocyclization, lactonization, and α -methylenation in a single concept. However, a problem stays on the yields when this method is applied to the synthesis of seven-membered carbocycle, which is one the major class of sesquiterpenes. Thus guaianolide-type of compounds were obtained in only 10-30% yields.^{3,4} In contrast, eudesmanolide- or cadinanolide-type of compounds were obtained in good yields.^{1,2,5} Nishitani *et al.* reported that seven-membered carbocyclization does not proceed at all from acyclic compound.⁷ While Majetich *et al.* obtained seven-membered ring in good yields by intramolecular cyclization of non-functionalized allylsilane with unsaturated carbonyl.^{8,9} From this we supposed that the conjugation of ethoxycarbonyl group to the allylsilane reduces the nucleophilicity. Here we report that seven-membered carbocyclization from functionalized allylsilane proceeds in good yield by the use of acid chloride as an electron acceptor.

The cyclization precursor **1a** was synthesized according to Scheme 1. Thus to the aldehyde **2a**⁷ was introduced functionalized allylsilane moiety giving **3a** (*Z:E*=2:1) after hydrolysis. Swern oxidation followed by chlorite oxidation afforded **1a**. After conversion into acid chloride **4a**, cyclization reaction was carried out with AlCl_3 in refluxing CH_2Cl_2 for 2 h¹⁰ giving expected product **5a** in 70% yield from **1a** (Scheme 2). Ketone **5a** was reduced with DIBAL-H giving diol **6a** (73%) as a mixture of *cis*- and *trans*-isomers (ratio 6:1). Some other reducing agents such as L-Selectride[®] or LiAlH_4 were used but unsuccessful. The lactone **7a** was then obtained in 80% yield by oxidation with MnO_2 ¹¹ (*cis:trans*= 6:1). Cyclizations towards eight-, ten-, and fourteen-membered rings were also examined; these substructures are also found in natural sesquiterpenes.^{12,13} However, the acids **1b-d**, prepared from **2b-d**, were recovered without cyclization on treatment with AlCl_3 .

There were two problems on the above pathway. One is the limitation of the reducing agents (**5a** to **6a**) and the other is the failure of the cyclization towards larger sized rings. Then, another route involving reduction of ethoxycarbonyl group prior



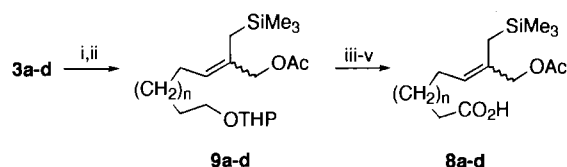
Scheme 1. Reagents and conditions: i, $(\text{EtO})_2\text{P}(\text{O})\text{CH}(\text{CO}_2\text{Et})\text{CH}_2\text{SiMe}_3$, NaH, DME, rt, 58-58%; ii, HCl, THF aq, rt, 80-91%; iii, $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , -60°C ; iv, NaClO_2 , NaH_2PO_4 , 2-methyl-2-butene, *t*-BuOH aq, rt, 80-93% (two steps).



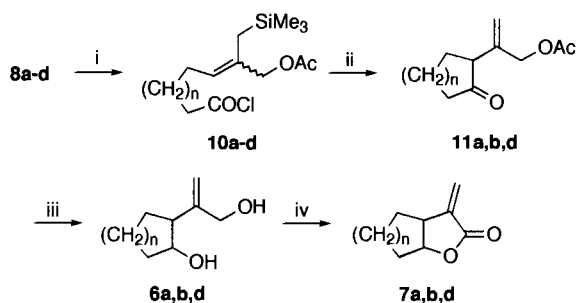
Scheme 2. Reagents and conditions: i, $(\text{COCl})_2$, CH_2Cl_2 , reflux; ii, AlCl_3 , CH_2Cl_2 , reflux; iii, DIBAL-H, Et_2O , rt; iv, MnO_2 , CH_2Cl_2 , rt.

to the cyclization was explored, which would result in cyclization of protected β -(hydroxymethyl)allylsilane. The substrate **8a** was prepared from **3a** according to Scheme 3. Thus after reduction of ethoxycarbonyl group with LiAlH_4 , the resultant hydroxy group was protected as an acetate to give **9a**. Hydrolysis of THP group followed by two-step oxidation gave carboxylic acid **8a**. The cyclization of acid chloride **10a** proceeded at lower temperature (rt, 18 h) than **4a** when treated with AlCl_3 , giving seven-membered carbocycle **11a** in 50% yield from **8a** (Scheme 4). Reduction of **11a** with DIBAL-H gave the same mixture of diol **6a** (*cis:trans*=6:1; 90%), while the reduction with L-Selectride[®] afforded only *cis*-**6a** (76%), which could be converted to *cis*-**7a**.

Carbocyclization towards larger sized ring was carried out using **8b-d** as the substrates. On treatment with AlCl_3 , the acid



Scheme 3. Reagents and conditions: i, DIBAL-H, CH_2Cl_2 , rt, 78-93%; ii, Ac_2O , pyridine, rt, 88-98%; iii, HCl, THF aq, rt, 70-90%; iv, $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , -60°C ; v, NaClO_2 , NaH_2PO_4 , 2-methyl-2-butene, *t*-BuOH aq, rt, 82-91% (two steps).



Scheme 4. Reagents and conditions: i, (COCl)₂, CH₂Cl₂, reflux; ii, AlCl₃, CH₂Cl₂, rt; iii, L-Selectride, Et₂O, rt; iv, MnO₂, CH₂Cl₂, rt.

chlorides **10b** and **10d** afforded eight- (**11b**) and fourteen-membered ring (**11d**) in 34% and 16% yields, respectively. However, ten-membered carbocycle was not obtained from **10c**. Reduction of **11b** and **11d** with L-Selectride[®] produced **6b** (56%; *cis* only) and **6d** (98%; *cis:trans* = 3:2), respectively, which were converted to fused α -methylene- γ -lactones **7b** (82%) and **7d** (90%).

In conclusion, α -methylene- γ -lactones fused to seven-membered carbocycle was obtained through intramolecular cyclization of both β -(ethoxycarbonyl)allylsilane (**1a**) and β -(acetoxymethyl)allylsilane (**8a**). The former afforded the cyclization product in better yield, but the latter has an advantage on both lactonization-step and the synthesis of eight- and fourteen-membered carbocycles.

References

1 C. Kuroda, S. Shimizu, and J. Y. Satoh, *J. Chem. Soc.*,

Chem. Commun., **1987**, 286; *J. Chem. Soc., Perkin Trans. 1*, **1990**, 519.

2 C. Kuroda, S. Shimizu, T. Haishima, and J. Y. Satoh, *Bull. Chem. Soc. Jpn.*, **66**, 2298 (1993).

3 C. Kuroda, S. Inoue, S. Kato, and J. Y. Satoh, *J. Chem. Res. (S)*, **1993**, 62.

4 C. Kuroda, S. Inoue, R. Takemura, and J. Y. Satoh, *J. Chem. Soc., Perkin Trans. 1*, **1994**, 521.

5 C. Kuroda and K. Ito, *Bull. Chem. Soc. Jpn.*, **69**, 2297 (1996).

6 For reviews regarding the reaction of allylsilane: E. Langkopf and D. Schinzer, *Chem. Rev.*, **95**, 1375 (1995); I. Fleming, A. Barbero, and D. Walter, *Chem. Rev.*, **97**, 2063 (1997); Y. Yamamoto and N. Asao, *Chem. Rev.*, **93**, 2207 (1993).

7 K. Nishitani, Y. Nakamura, R. Orii, C. Arai, and K. Yamakawa, *Chem. Pharm. Bull.*, **41**, 822 (1993).

8 G. Majetich and K. Hull, *Tetrahedron*, **43**, 5621 (1987).

9 G. Majetich, R. W. Desmond, Jr., and J. J. Soria, *J. Org. Chem.*, **51**, 1753 (1986).

10 For intermolecular reaction of allylsilane with acid chloride, see: K.-T. Kang and J. S. U, *Synth. Commun.*, **24**, 1507 (1994); K.-T. Kang and J. S. U, *Synth. Commun.*, **25**, 2647 (1995).

11 J. A. Marshall, N. Cohen, and A. R. Hochstetler, *J. Am. Chem. Soc.*, **88**, 3408 (1966).

12 B. M. Fraga, *Nat. Prod. Rep.*, **15**, 73 (1998); **14**, 145 (1997); **13**, 307 (1996); **12**, 303 (1995); **11**, 533 (1994).

13 For an example of natural α -methylene- γ -lactone fused to eight-membered carbocycle: G. Chiari, G. Appendino, and G. M. Nano, *J. Chem. Soc., Perkin Trans. 2*, **1986**, 263.