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Efficient and connective synthesis of substituted butyrolactones and *exo*-methylene butyrolactones

Bernard Leroy, Raphaël Dumeunier and István E. Markó*

Université catholique de Louvain, Département de Chimie, Bâtiment Lavoisier, Place Louis Pasteur 1, B-1348 Louvain-la-Neuve, Belgium

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Abstract

A variety of α-(trimethylsilylmethyl)-substituted butyrolactones are readily accessed by a novel tandem ene-reaction/oxidative desilylation of a range of aldehydes. Subsequent functionalisation led to an efficient methodology for the preparation of *exo*-methylene butyrolactones. © 2000 Published by Elsevier Science Ltd.

Keywords: ene reactions; oxidation; silicon; lactones; *exo*-methylene lactones.

Butyrolactones and *exo*-methylene lactones are widespread in a large variety of biologically active natural products.[1] Their occurrence coupled with their pharmacophoric activity has spurred the development of numerous elegant procedures for their preparation.[2] In this communication, we wish to disclose some of our preliminary results in the establishment of a concise and stereocontrolled methodology for the efficient assembly of these important subunits.

Recently, we have reported that the tandem ene-reaction/**I**ntra**M**olecular **S**akurai **C**yclisation (IMSC) of aldehydes **1** was a particularly efficient procedure for the preparation of a variety of diastereomerically pure *exo*-methylene tetrahydropyrans **4** (Fig. 1).[3]

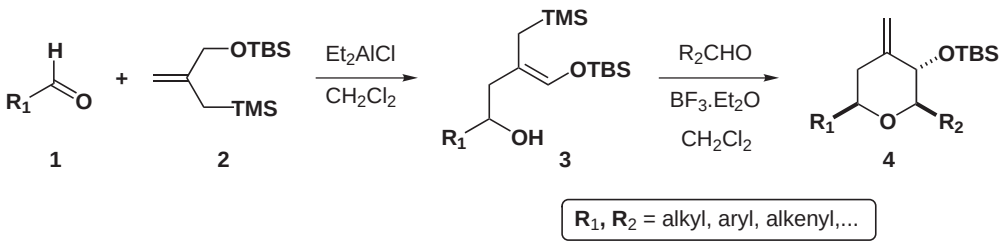

Figure 1.

* Corresponding author.

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During the course of the total synthesis of amphidinol, we had the opportunity to examine the ene-IMSC reaction of the model α-bromoaldehyde **5** with allylsilane **2** (Fig. 2).

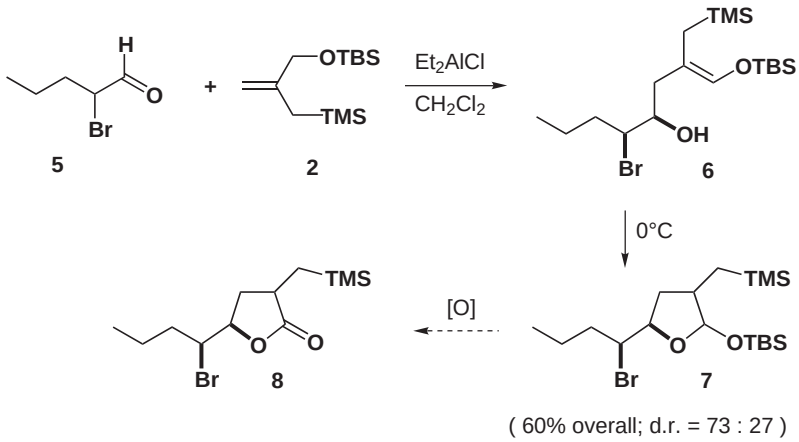


Figure 2.

Whilst both the initial ene reaction and the subsequent IMSC cyclisation proceeded smoothly, we were surprised to find that the ene adduct **6** was unstable to storage, even at 0°C, and rearranged readily into the silylated lactol **7**. This unexpected observation triggered our interest and we surmised that a simple oxidation of adduct **7** should provide us with a novel and rapid entry into the largely unexplored family of α-(trimethylsilylmethyl)-lactones.[4] A plausible rationale for the formation of **7** might involve the initial intramolecular cyclisation of a catalytic amount of bromohydrin **6** into the corresponding *trans*-epoxide with concomitant production of minute quantities of HBr. The in situ generated HBr could subsequently protonate the enol ether portion of **6**, affording an oxocarbenium ion, which would be rapidly and intramolecularly intercepted by the incipient hydroxyl function, ultimately leading to the observed product **7**.[5]

In order to widen the scope of this novel transformation, a series of ene adducts **3** were prepared and submitted to a variety of acid-catalysed conditions. Unfortunately, either recovered starting material or complete degradation of these homoallylic alcohols **3** was observed.

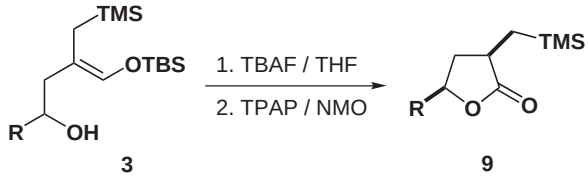
Gratifyingly, we found that treatment of the ene adducts **3** with TBAF (tetra *n*-butyl ammonium fluoride), followed by the addition of catalytic amounts of TPAP (tetra *n*-propyl ammonium perruthenate) and NMO (*N*-methyl morpholine-*N*-oxide)[6] led to the desired α-(trimethylsilylmethyl)-lactones **9** in good overall yields and in a single pot operation (Table 1).

These lactones are obtained as diastereomeric mixtures; their ratios depending upon the steric bulk of the C5-substituent and varying from 45 to 70% d.e. in favour of the *syn*-isomer.

With rapid access to α-(trimethylsilylmethyl)-lactones in hands, we turned our attention to their further transformation into the useful class of *exo*-methylene butyrolactones. In his seminal contribution, Fleming has already reported such a protocol. Unfortunately, this conversion proceeded only with modest overall yields.[4] We were pleased to find that a one-pot procedure, based upon the initial formation of the derived silylenol lactones of **9** followed by the rapid addition of NBS and TBAF provided us with the desired *exo*-methylene lactones **10** in excellent overall yield (Fig. 3).

In summary, we have uncovered a novel methodology for the efficient construction of α-(trimethylsilylmethyl)-butyrolactones and their *exo*-methylene analogues[7] based upon an

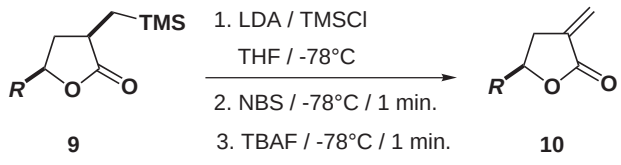
Table 1
Oxidative lactonisation of ene adducts **3**



3 **9**

Entry	R	Yields[a] (%)	D.e. (%)
1	n-C_3H_7	80	45
2	c-C_6H_{11}	60	50
3	t-C_4H_9	55	70

[a] All yields are for pure, isolated products.



9 **10**

a : R = n-C_3H_7 : 80%; **b** : R = c-C_6H_{11} : 70%

Figure 3.

initial ene reaction between an aldehyde and the allylsilane reagent 2. Current efforts are now being directed towards delineating the full scope of this connective methodology and defining an enantioselective version. The results of these investigations will be reported in due course.

Acknowledgements

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2. For excellent reviews, see: (a) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 94. (b) Petragnani, N.; Ferraz, H. M. C.; Silva, G. V. J. *Synthesis* **1986**, 157.
3. (a) Markó, I. E.; Bayston, D. J. *Tetrahedron Lett.* **1993**, *34*, 6595. (b) Markó, I. E.; Bayston, D. J. *Tetrahedron* **1994**, *50*, 7141. (c) Markó, I. E.; Plancher, J.-M. *Tetrahedron Lett.* **1999**, *40*, 5259, and references cited therein.
4. To the best of our knowledge, only a single article is explicitly devoted to the synthesis and reactions of α-(trimethylsilylmethyl)-ketones and lactones: (a) Fleming, I.; Goldhill, J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1493. Three other limited examples of such compounds also appeared in: (b) Paterson, I. *Tetrahedron* **1988**, *44*, 4207. (c) Bertrand, M.; Dulcere, J.-P.; Gil, G. *Tetrahedron Lett.* **1980**, *21*, 1945. (d) Bachi, M. D.; Bosch, E. *Tetrahedron Lett.* **1988**, *29*, 2581.
5. It is interesting to note that the *anti*-diastereoisomer of bromohydrin **6**, which would afford the corresponding *cis*-epoxide upon ring closure, is stable to be stored for months. No silylated lactol is formed in this case. This observation reinforces our proposal that acid-catalysis is responsible for the spontaneous generation of **7** from **6**.
6. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
7. Typical experimental procedure. Preparation of **10a**.
   To a solution of ene adduct **3** (R = *n*-C_3H_7; 0.58 g; 1.75 mmol) dissolved in 10 mL of anhydrous THF is added dropwise, at room temperature, 3.51 mL of a 1.0 M THF solution of TBAF (2 equiv.; 3.51 mmol). The resulting pale-yellow solution is stirred at 20°C for 15 h. The reaction mixture is poured into a saturated NaCl solution. The organic layer is separated and the aqueous phase is extracted three times with Et_2O. The combined organic layers are dried over $MgSO_4$, filtered and the solvent is evaporated under reduced pressure. The crude product is dissolved in 2 mL of CH_2Cl_2 and added dropwise to a suspension of 1.8 g of 4 Å MS in 3 mL CH_2Cl_2. NMO (0.308 g; 1.5 equiv.; 2.63 mmol) is then added and the heterogeneous mixture cooled to 0°C before adding the TPAP (20 mg; 0.06 mmol; 3%). The cooling bath is removed and the black suspension is stirred at room temperature during 1 h. The crude reaction mixture is directly filtered through a pad of silica and the product further purified by silica gel column chromatography (petroleum ether/EtOAc: 15/1) affording 304 mg (80%) of **9a** (R = *n*-C_3H_7, colourless oil) as a 2:1 diastereoisomeric mixture. To a cold (0°C) solution of diisopropyl amine (0.174 mL; 1.1 equiv.; 1.05 mmol) in 6 mL of anhydrous THF is added dropwise 0.627 mL (1.05 equiv.; 1 mmol) of a 1.6 M solution of *n*-BuLi in hexanes and the reaction mixture is stirred at 0°C for 30 min. The faint yellow solution is then cooled at −78°C and 205 mg (1 equiv.; 0.96 mmol) of lactone **9a** (R = *n*-C_3H_7) is added. The reaction mixture is stirred at −78°C for 1 h then 0.212 mL (1.75 equiv.; 1.68 mmol) of TMSCl are added at once. After stirring for another 5 h at −78°C, 274 mg (1 equiv.; 0.96 mmol) of NBS is added followed, after 1 min, by 1.15 mL (1.2 equiv.) of a 1 M solution of TBAF in THF. After 1 min, the crude reaction mixture is poured onto a saturated solution of $NaHCO_3$/NaCl and extracted three times with Et_2O. The organic layers are dried over $MgSO_4$ and the solvent removed in vacuo. The crude product is purified by silica gel column chromatography (Petroleum ether/EtOAc: 13/1) affording 107 mg (80%) of **10a** as a colourless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.20 (t, J = 2.8 Hz, 1H), 5.61 (t, J = 2.7 Hz, 1H), 4.56–4.47 (m, 1H), 3.0 (ddt, J^1 = 17 Hz, J^2 = 7.6 Hz, J^3 = 2.5 Hz, 1H), 2.56 (ddt, J^1 = 17 Hz, J^2 = 5.9 Hz, J^3 = 2.8 Hz, 1H), 1.48–1.33 (m, 4H), 0.95 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 170.2, 134.86, 121.67, 77.23, 38.36, 33.60, 18.18, 13.72. IR (Film) ν_{max}: 2961, 1765, 1666, 1187 cm^{-1}. MS (EI) 141 (M^+), 97, 68, 43. This compound has been reported earlier: Adlington, R. M.; Barrett, A. G. M. *J. Chem. Soc., Perkin Trans 1* **1981**, *11*, 2848.