Pergamon

Tetrahedron Letters 43 (2002) 2307–2311

TETRAHEDRON LETTERS

Concise and connective synthesis of *exo*-methylene-γ-butyrolactones

Raphaël Dumeunier, Cédric Leclercq and István E. Markó*

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

Received 12 November 2001; revised 24 January 2002; accepted 31 January 2002

Abstract—A novel sequence, combining an ene-reaction of the substituted allylsilane **2** with a variety of aldehydes, followed by an oxidative double desilylation, provides an efficient access to a wide range of *exo*-methylene-γ-butyrolactones.

Exo-methylene-γ-butyrolactones are ubiquitous fragments in a wide range of biologically active natural products.[1] Their remarkable physiological properties, and their versatile synthetic utility, has prompted considerable interest in their preparation and subsequent transformation.[2]

In a previous communication, we have disclosed some of our results on a new synthesis of α-(trimethylsilylmethyl)-γ-butyrolactones **4**, and on their subsequent conversion into functionalised *exo*-methylene-γ-butyrolactones **5** (Fig. 1).[3]

This approach embodied an initial ene-reaction between aldehyde **1** and allylsilane **2**, followed by a chemoselective desilylation/oxidative cyclisation of **3**, affording **4** as a mixture of diastereoisomers. Subsequent silyl enol ether formation, bromination and fragmentation provided the desired *exo*-methylene-γ-butyrolactones **5**. Although the final three steps could be performed sequentially, in the same reaction vessel, this initial route proved to be rather lengthy and to require an extremely precise control of the experimental protocol.

We reasoned that a shorter and more efficient access to *exo*-methylene-γ-butyrolactones **5** might involve the conversion of readily available ene-adducts **3** into the cyclic silylated acetals **6**. Oxidative desilylation would then provide, in a two-step operation, the desired lactones **5**. In this article, we wish to report the successful implementation of this strategy.

A variety of ene adducts **3** were prepared according to our previously reported procedure[4] and submitted to

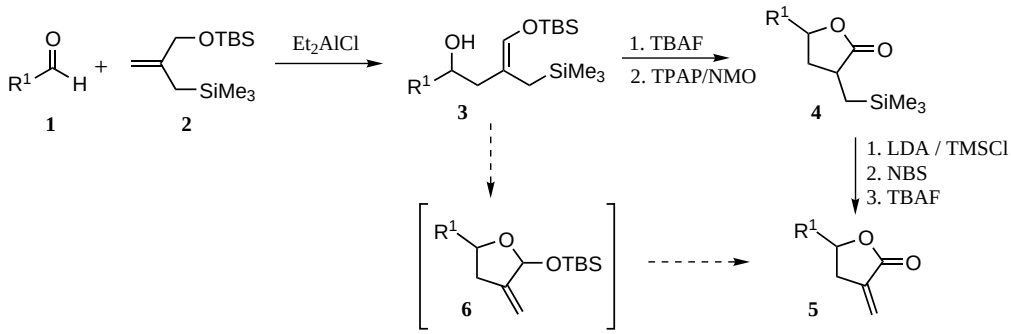


Figure 1.

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

* Corresponding author.

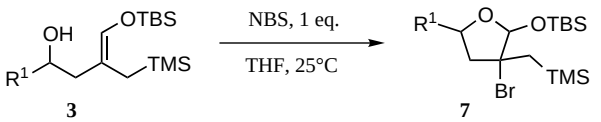
PII: S0040-4039(02)00240-X

various cyclisation/desilylation conditions. Though initial attempts proved frustrating, we were gratified to find that the reaction of NBS with ene-adducts **3** proceeded smoothly and afforded, in essentially quantitative yields, the corresponding brominated acetals **7** (Table 1).[5]

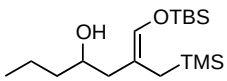
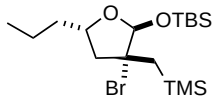
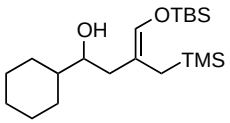
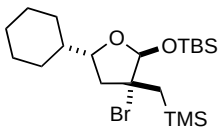
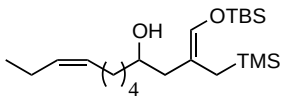
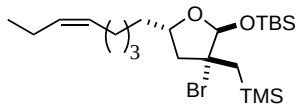
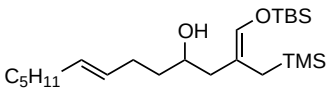
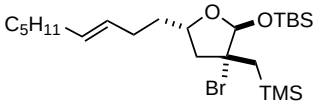
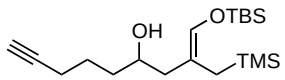
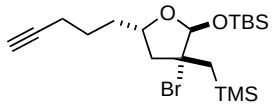
This intramolecular bromoetherification displays several noteworthy features. Not only are the corresponding bromoacetals produced in quantitative yields but the reaction is complete within 5 min. The cyclisation also tolerates a range of functionalities and, in all cases, only the silyl enol ether function undergoes electrophilic addition.[6] Carbon–carbon double and triple bonds are unaffected, even when suitably positioned to undergo intramolecular cyclisation (entries 4 and 5). Moreover, this transformation proceeds in a highly stereoselective manner, resulting in the exclusive formation of a single diastereoisomer, possessing the relative stereochemistry depicted in Table 1.[7] The sole generation of this isomer can be rationalised by considering the intermediate of the bromocyclisation, as shown in Fig. 2.

In this intermediate, both the silyl ether and trimethylsilylmethyl substituents are locked in a *syn* relationship, due to the initial enol ether double bond geometry. The substituent located α to the hydroxyl function controls the folding of the five-membered ring envelope conformation and preferentially positions itself in a pseudo-equatorial orientation. In the other possible conformer,

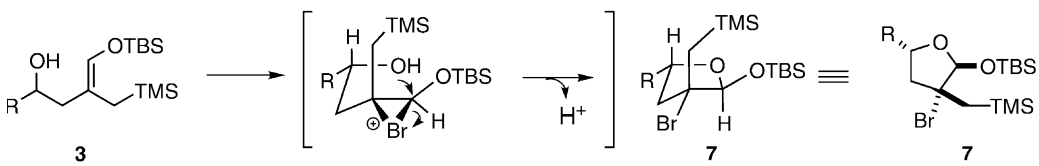
Table 1. Bromocyclisation of ene-adducts **3**



3 **7**

Entry	Substrate	Product	Yields[a]
1			> 95 %
2			> 95 %
3			> 95 %
4			> 95 %
5			> 95 %

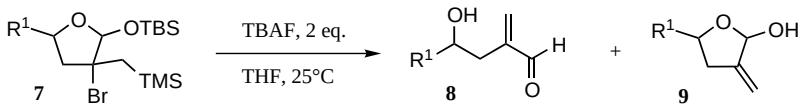
[a] All yields are for crude compounds. These can be purified but substantial decomposition occurs resulting in significant losses in yields. The crude products are sufficiently pure (>95%) to be engaged as such in the next step. The stereochemistry of adducts **7** has been established by careful NMR studies including selective irradiations.

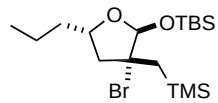
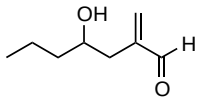
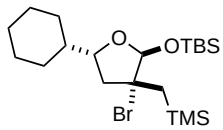
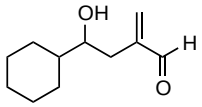
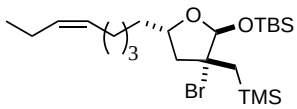
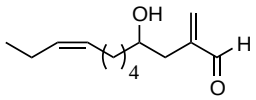
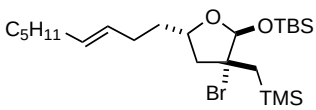
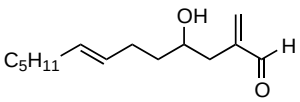
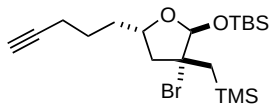
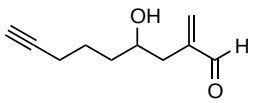


3 **7** **7**

Figure 2.

Table 2. Double desilylation of acetals **7**



Entry	Substrate	Product (major)	Yields[a] [**8**:**9**]
1			73 % [89:11]
2			88 % [64:36]
3			65 % [80:20]
4			72 % [78:22]
5			90 % [78:22]

[a] Isolated yields after purification by column chromatography. The ratios of **8**:**9** were determined by ^{1}H NMR spectroscopy.

this substituent would be disposed in a pseudoaxial orientation, encountering severe 1,3-diaxial interactions with the trimethylsilylmethyl group. It is also probable that the silyloxy function assists the halocyclisation by electron-donation towards the bromonium ion; hence this type of cyclisation is likely a 5-*exo*- rather than a 5-*endo*-process.[8]

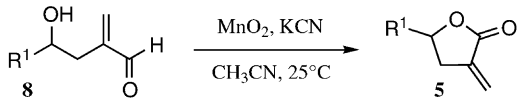
Whilst bromoacetals **7** can be readily and quantitatively obtained, they proved to be rather unstable, undergoing significant decomposition under purification conditions or simple storage. It was therefore found more convenient and higher yielding to use the crude reaction product (>95% pure) immediately for the subsequent transformation (Table 2).

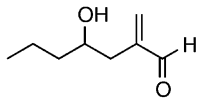
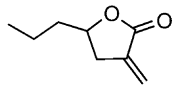
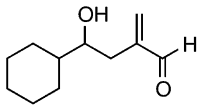
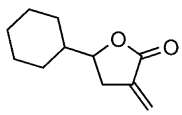
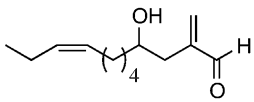
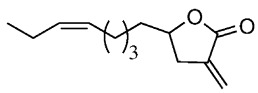
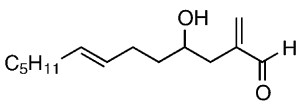
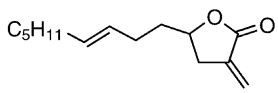
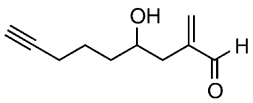
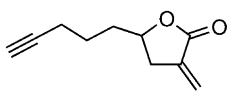
Addition of 2 equiv. of TBAF to a THF solution of crude bromoacetals **7** resulted in a smooth double desilylation/elimination reaction affording, rather unexpectedly, the corresponding β′-hydroxy enals **8**. Careful analysis of the NMR spectra of **8** revealed the presence of variable amounts of the cyclic lactols **9**. The ratio of **8** to **9** remained constant for a given pair, even after several purifications, implying that a dynamic equilibrium is established between the open and closed forms of enal **8**.[9] The preference in favour of the open form **8** probably reflects an increased Pitzer strain in the closed form **9** coupled with the loss of conjugation present in enal **8**.

The existence of this equilibrium is, however, of no consequence for the subsequent step. Indeed, oxidative cyclisation to form the desired *exo*-methylene-γ-butyrolactones **5** proceeded smoothly upon treatment of a mixture of aldehyde **8** and lactol **9** with freshly prepared MnO_2, in the presence of catalytic amounts of cyanide ion.[10] The final lactones were obtained in good to excellent yields, as shown in Table 3.

In summary, we have developed a simple and efficient route to *exo*-methylene-γ-butyrolactones from readily available ene adducts **3**. This novel procedure, which involves a three-step sequence starting from easily accessible aldehydes, displays excellent tolerance towards a variety of functional groups and is amenable to the synthesis of large quantities of the desired lac-

Table 3. Oxidative cyclisation of enals **8**



Entry	Substrate[a]	Product	Yields[b]
1			84 %
2			86 %
3			88 %
4			83 %
5			82 %

[a] All the reactions were performed on the equilibrating mixture of enals and cyclic lactols.
[b] Isolated yields after purification by column chromatography.

tones.[11] Furthermore, a wide variety of substituents can be readily incorporated on the heterocyclic ring system. Current efforts are now being directed towards delineating the full scope of this connective methodology, uncovering an enantioselective version of this new *exo*-methylene-γ-butyrolactones synthesis and applying this novel approach to the total synthesis of complex natural products. The results of these investigations will be reported in due course.

Acknowledgements

Financial support of this work by the Université catholique de Louvain, the Actions de Recherche Concertées (convention 96/01-197), the Fonds pour la Formation à la Recherche dans l'Industrie et dans l'Agriculture (FRIA), the Fonds de la Recherche Fondamentale Collective (dossier n° 2.4571.98) and the Fond National de la Recherche Scientifique (FNRS) for R. Dumeunier (Aspirant FNRS) is gratefully acknowleged. I.E.M. is thankful to Merck & Co. for its continuing support and for receiving the Merck Young Investigator Award.

References

1. (a) Matsuda, H.; Shimoda, H.; Uemura, T.; Yoshikawa, M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2647; (b) Fardella, G.; Barbetti, P.; Grandolini, G.; Chiappini, I.; Ambrogi, V.; Scarcia, V.; Candiani, A. F. *Eur. J. Med. Chem.* **1999**, *34*, 515 and references cited therein.
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**, 57.
3. Leroy, B.; Dumeunier, R.; Marko, I. E. *Tetrahedron Lett.* **2000**, *41*, 10215.
4. Marko, I. E.; Bayston, D. J. *Tetrahedron Lett.* **1993**, *34*, 6595.
5. Takano, S.; Sekiguchi, Y.; Shimazaki, Y.; Ogasawara, K. *Tetrahedron Lett.* **1989**, *30*, 4001. For a review on the synthesis of substituted tetrahydrofurans by 5-*exo* and 5-*endo* type cyclisations, see: Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.
6. It is interesting to note that this ambident silyl enol ether/allylsilane function typically reacts with electrophiles as an allylsilane and not as an enol ether. The bromocyclisation reported above is a rare example of the

chemoselective involvement of the enol silane system in electrophilically-induced cyclisations.

7. (a) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950; (b) Bedford, S. B.; Bell, K. E.; Bennett, F.; Hayes, C. J.; Knight, D. W.; Shaw, D. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, *15*, 2143; (c) Jung, M. E.; Karama, U.; Marquez, R. *J. Org. Chem.* **1999**, *64*, 663; (d) For mechanistic studies, see: Barks, J. M.; Knight, D. W.; Seaman, C. J.; Weingarten, G. G. *Tetrahedron Lett.* **1994**, *35*, 7259.
8. See for example: Galatsis, P.; Manwell, J. J. *Tetrahedron Lett.* **1995**, *36*, 8179 and references cited therein.
9. (a) Morton, D. R.; Lee-Ruff, E.; Southam, R. M.; Turro, N. J. *J. Am. Chem. Soc.* **1970**, *92*, 4349; (b) Wood, W. W.; Watson, G. M. *J. Chem. Soc., Chem. Commun.* **1986**, *21*, 1599.
10. Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.
11. **Typical experimental procedure**: To a solution of 0.40 g of ene adduct **3** [Table 1, entry 1, 1.22 mmol] in 10 mL of THF was added 0.22 g of *N*-bromosuccinimide (1.22 mmol). The mixture was stirred at 25°C for 5 min. Volatiles were then removed under reduced pressure. The residue, a white solid, was stirred with pentane (10 mL) for 1 min and filtered. The resulting solution was concentrated in vacuo, giving 0.51 g of pure bromoacetal **7** (>99%). To a solution of **7** [Table 2, entry 1, 1.22 mmol] in 15 mL of THF was added Bu_4NF in THF (2.44 mL of 1 M, 2.44 mmol). A yellow colour appeared immediately. The mixture was stirred for 5 min at 25°C, diluted with 20 mL of diethyl ether and washed with 20 mL of brine. The aqueous layer was extracted twice with 20 mL of diethyl ether. The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. Chromatography of the residue over silica gel (eluted with EtOAc–hexane, 1:3) gave 125 mg of the corresponding aldehyde **8** (73%) as a thick oil. This sensitive material was directly used in the oxidation step. Thus, to a cold solution (0°C) of aldehyde **8** (0.33 g, 2.30 mmol) in 20 mL of acetonitrile were added successively, MnO_2 (4 g, 46 mmol) and KCN (15 mg, 0.23 mmol). The mixture was stirred for 25 min at 0°C and filtered over silica-gel. The filtrate was concentrated under reduced pressure and the resulting oil purified by silica-gel column chromatography (with EtOAc–hexane, 1:13), giving 275 mg (84%) of pure α-methylene-γ-butyrolactone **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm): 6.20 (1H, t, $J=2.8$ Hz), 5.61 (1H, t, $J=2.7$ Hz), 4.56–4.47 (1H, m), 3.00 (1H, ddt, $J=17$, 7.6, 2.5 Hz), 2.56 (1H, ddt, $J=17$, 5.9, 2.8 Hz), 1.48–1.33 (4H, m), 0.95 (3H, t, $J=7.2$ Hz).^{13}C NMR (50 MHz, $CDCl_3$) δ_C (ppm): 170.20, 134.86, 121.67, 77.23, 38.36, 33.60, 18.18, 13.72. MS (EI) m/z: 141 ($M^{+\bullet}+H^+$, 80), 140 ($M^{+\bullet}$, 36). IR (film): 2961–2874, 1765, 1666, 1466, 1399, 1273, 1187, 1001, 940, 813 cm^{-1}. RN: [58557-51-3].