Diastereoselective thiol conjugate addition on δ-alkylated-γ-silylated-α,β-unsaturated-δ-lactones

Sandrine Calvet, Christine Courillon, and Max Malacria*

Université Pierre et Marie Curie, Laboratoire de Chimie Organique de Synthèse, associé au CNRS, Tour 44-54,2ème, B. 229, 04 place Jussieu, 75252 Paris cedex 05, France
E-mail: malacria@ccr.jussieu.fr, courillo@ccr.jussieu.fr

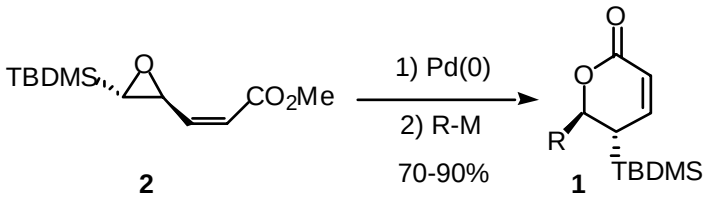
Dedicated to Professor Marcial Moreno-Mañas on the occasion of his 60th birthday
(received 06 Mar 02; accepted 17 May 02; published on the web 25 May 02)

Abstract
The silicon atom at the γ position of α-pyrone **1a** plays a dramatic role in directing thiol conjugate additions in a diastereoselective way. We describe here a stereoselective access to γ-silylated-β-thio-δ-lactones.

Keywords: Diastereoselective conjugate addition, silylated unsaturated thiolactones

Introduction

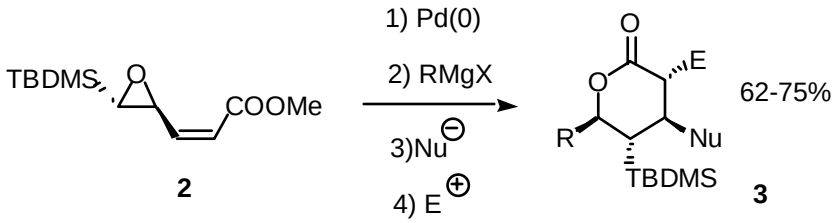
As we have reported recently,[1] our group is currently involved in investigating the reactivity field of δ-alkylated-γ-silylated-α,β-unsaturated δ-lactones **1**. These compounds are easily synthesized in enantiomerically pure forms and in a highly diastereoselective manner by a tandem rearrangement / alkylation-lactonization sequence starting from α,β-epoxy-γ,δ-vinyl-silanes **2**.[2] (Scheme 1)



Scheme 1

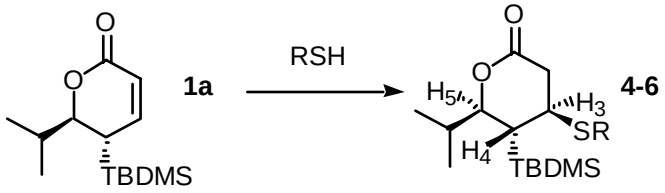
Since the palladium(0) catalyzed first step totally transfers the chirality[3] and the alkylation second step is highly distereoselective,[4] this stereoselective one-pot transformation is a valuable synthetic tool.

Of course δ-lactones **1** are interesting because of the wide occurrence of this skeleton among pharmacological and / or natural compounds[5-7] and also because they display different highly reactive chemical functionalities. In particular, we focused recently on diastereoselective conjugate additions which may be followed by electrophilic trapping.[1] We demonstrated that these two former reactions can be included in a four-step one-pot transformation of α,β-epoxy-γ,δ-vinyl-silanes **2**, directly into tetra-substituted δ-lactones **3**.[1] (Scheme 2)



Scheme 2

We are also interested in the conjugate addition of nucleophiles, other than carbanions, on δ-lactone **1a.** In this paper we describe the conjugate addition of various thiols derivatives and the confirmation of the structural assessment of the 1,4-adducts with the *anti* relative configuration of the silicon and the sulfur atoms. (Scheme 3)



Scheme 3

Results and Discussion

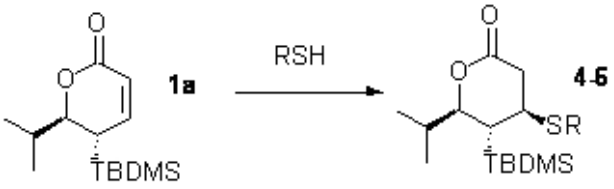
Conjugate thiol additions on unsaturated β-, γ- or δ-lactones have been described in the literature.[8-10] Some of the studies, especially with the cysteine system are closely related to the investigation of the biological mechanism responsible for the carcinogenicity of lactones.[11] The thiol reagent often plays the role of solvent in thiol conjugate additions on δ-lactones in the presence of a basic amine. Piperidine is used at high temperature to perform the addition of aromatic thiols on aromatic δ-lactones.[12] Mevilonin and its analogs could react on thio-acids,

thio-alcohols or thiols at room temperature with triethylamine to afford δ-lactones bearing a sulfur atom on the β position.[13] Recently high stereoselectivity of these thiol 1,4-additions has been observed on α,β-unsaturated esters by using external chiral ligands which give the adducts with high ees.[14]

In the case of the δ-lactone **1a**, the presence of the trialkylsilyl substituent should again direct the incoming of the heteronucleophile, then unequivocally creating an *anti*/*anti* relationship between the three substituents. Independent from the structural interest, this brought the advantage of functionalizing our substrate with an heteroatom which could be oxidized[15], eliminated or reduced, for instance by a radical transformation.[16] Therefore, we ran some experiments consisting of adding thiols in a 1,4-process on lactone **1a**. Table 1 shows that the same diastereomer is obtained either exclusively (entries 1,2,4,5,7) or as the major product (entry 3). Yields of the thiophenol addition depend very much on the basic conditions. Use of butyllithium (entry 1) may be optimized in the presence of ether / boron trifluoride complex, but still the yield does not reach beyond 28% (entry 2). Triethylamine gives a better yield of 81% at 90°C (entry 3) and lowering the temperature to 70°C improves the diastereomeric excess to 98% (entry 4). The absence of reactivity for *tert*-butyl-thiol (entry 6) indicates some steric control of the reaction and *p*-nitro-thiophenol (entry 8) fails to react probably because of its weak nucleophilicity. In the case of *n*-butyl-thiol and *p*-methoxy-thiophenol (entries 5,7) the conjugate addition is probably reversible as formerly reported.[17]

^{1}HNMR experiments, especially NOE studies, did not allow us to elucidate the relative configuration of the sulfur and the silicon atoms in thioethers **4-6**. Structural determination of the diastereomer obtained in the experiments outlined in table 1 was accomplished with the X-ray analysis of compound **4**. These X-ray results show the sulfur atom clearly in an *anti* relative configuration to the silicon atom, therefore *syn* to the *iso*-propyl group (Figure 1). Dihedral angles between C_5-H_5 and C_4-H_4 bonds and between C_3-H_3 and C_4-H_4 bonds are respectively 166° and 129°, which proves important distortion of this conformationaly stable δ-lactone compared to a cyclohexane chair. Therefore, we were not surprised by the value of the ^{1}HNMR coupling constants for protons H_4 and H_5 (J = 10.83Hz) and for protons H_4 and H_3 (J = 2.46Hz).

Table 1. 1,4-Conjugate addition of RSH on δ-Lactone **1a**



Entry	Product	R	Exp. Conditions	Yield(%)	D.E.(%)[d]
1	**4**	Ph	*n*-BuLi, -78°C	14	>98
2	**4**	Ph	*n*-BuLi, -78°C BF_3-Et_2O	28	>98
3	**4**	Ph	NEt_3, 90°C	81	72
4	**4**	Ph	NEt_3, 70°C	73	>98
5	**5**	*n*-Bu	NEt_3, 70°C	96[a,b]	>98
6	-	*t*-Bu	NEt_3, 70°C	-	-
7	**6**	*p*-CH_3O-Ph	NEt_3, 70°C	90[a,c]	>98
8	-	*p*-NO_2-Ph	NEt_3, 70°C	-	-

[a] Corrected yields [b] 33% Recovery of starting material
[c] 27% recovery of starting material, d: d.e. are measured by ^{1}HNMR experiments

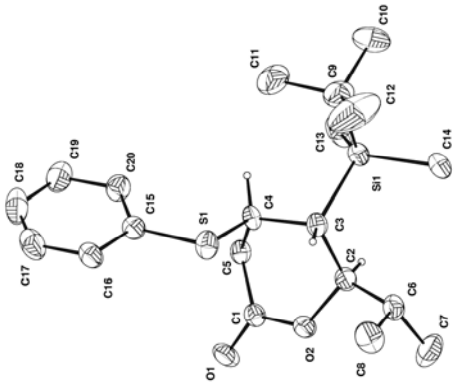


Figure 1. X-Ray Analysis of Compound 4.

Our conclusion points out the directing effect of the silicon group at the γ-position of the δ-lactone **1a** and the possibility of reacting it with thiols in a diastereoselective conjugate addition. This links a sulfur atom, *anti* to the silicon atom and creates a new stereogenic center on the lactone ring which bears a heteroatom. We have previously studied the desilylation of our substrates and ascertained that, after desilylation, we obtained tri-substituted δ-lactones with substituents at the β and the δ positions which are *syn* to each other. This is interesting according to the existing literature providing the *anti* relative configuration of these substituents.[18] Synthetic developments of our γ-silylated-β-thio-δ-lactones **4-6** are currently under investigation in our group.

Experimental Section

General Procedure. Compounds 4-6. δ-Lactone 1a (1 equiv), thiol (5 equiv) and triethylamine (0.3 equiv) are successively introduced in a flask equipped with a condenser. The mixture is heated at 70°C and stirred for 48 hours. Hydrolysis with a saturated aqueous solution of ammonium chloride, followed by extraction with dichloromethane and washing of the organic phase with brine leads to a crude material which was purified on silica gel by flash chromatography with petroleum ether / ethyl acetate 95 /5.

5-*tert*-Butyldimethylsilyl-4-phenylsulfanyl-6-*iso*-propyl-3,4,5,6-tetrahydropyran-2-one (4). yield 73%, white solid, m.p. 109-110°C; ^{1}HNMR (200 MHz; $CDCl_3$) δ (ppm) : 7.30 (m, 5H); 4.15 (dd, 1H, *J* = 10.83 Hz, *J* = 2.2 1 Hz); 3.58 (dt, 1H, *J* = 3.94 Hz, *J* = 2.46 Hz); 2.53 (d, 2H, *J* = 3.94 Hz); 1.85 (hpd, 1H, *J* = 6.89 Hz, *J* = 2.21 Hz); 1.40 (dd, 1H, *J* = 10.83 Hz, *J* = 2.46 Hz); 1.04 (d, 1H, *J* = 6.89 Hz); 0.98 (d+s, 12H); 0.12 (s, 3H); 0.09 (s, 3H). ^{13}CNMR (400 MHz; $CDCl_3$) δ (ppm) : 172.6; 135.2-129.5 (4C); 83.8; 44.03; 35.6-13.4 (7C); -4.5; -5.2. IR (cm^{-1}) : 2870-2980, 1740, 1480, 1370, 1250, 850, 830, 810. HRMS calcd for $C_{20}H_{32}O_2SSi$ 365.1971, found m/z (relative intensity) 365.1968 (MH^+, 5), 255 (100), 239 (12), 225 (18).
The crystal structure of compound **4** has been deposited at the Cambridge Crystallographic Data Centre and was allocated the deposition number CCDC 173436.
5-*tert*-Butyldimethylsilyl-4-butylsulfanyl-6-*iso*-propyl-3,4,5,6-tetrahydropyran-2-one (5). yield 83%. ^{1}HNMR (200 MHz; $CDCl_3$) δ (ppm) : 4.11 (dd, 1H, *J* = 10.34 Hz, *J* = 2.46 Hz); 3.30 (dt, 1H, *J* = 4.18 Hz; *J* = 2.46 Hz); 2.68 (d, 2H, *J* = 4.18 Hz); 2.48 (dt, 2H, *J* = 7.39 Hz; *J* = 1.47 Hz); 1.80 (hd, 1H, *J* = 6.89 Hz; *J* = 2.46 Hz); 1.1-1.5 (m, 8H); 1.04 (d, 3H, *J* = 6.89 Hz); 0.96 (d+s, 12H); 0.08 (s, 3H); 0.06 (s, 3H). ^{13}CNMR (400 MHz; $CDCl_3$) δ (ppm) : 171.7; 83.1; 38.7-14.6 (14C); -4.8; -5.3. IR (cm^{-1}) : 2860-2980, 1740, 1480, 1370, 1270-1300, 850. HRMS calcd for $C_{18}H_{36}O_2SSi$ 345.2284, found m/z (relative intensity) 345.2286 (MH^+, 43), 255 (100), 231 (65), 205 (32), 141 (25).

5-*tert*-Butyldimethylsilyl-4-(4-methoxyphenylsulfanyl)-6-*iso*-propyl-3,4,5,6-tetrahydro-pyran-2-one (6). yield 89%. ^{1}HNMR (200 MHz; $CDCl_3$) δ (ppm) : 7.41 (m, 2H); 6.83 (m, 2H); 4.14 (dd, 1H, *J* = 10.83 Hz, *J* = 1.97 Hz); 3.77 (s, 3H); 3.43 (dt, 1H, *J* = 3.94 Hz, *J* = 2.46 Hz); 2.49 (d, 2H, *J* = 3.94 Hz); 1.79 (hd, 1H, *J* = 6.89 Hz, *J* = 1.97 Hz); 1.36 (dd, 1H, *J* = 10.83 Hz, *J* = 2.46 Hz); 1.06 (d, 3H, *J* = 6.89 Hz); 0.89 (d+s, 12H); 0.11 (s, 3H); 0.06 (s, 3H). ^{13}CNMR (400 MHz; $CDCl_3$) δ (ppm) : 171.9; 160.3; 136.9; 135.9; 133.0; 124.1; 114.8; 82.9; 74.0; 55.4; 43.8; 39.9; 34.5-14.5(6C); -5.4; -6.1. IR (cm^{-1}) : 2880-2980, 1740, 1600, 1480, 1270, 1110, 850, 830, 810. HRMS calcd for $C_{21}H_{34}O_3SSi$ 395.2076, found m/z (relative intensity) 395.2075 (MH^+, 162), 379 (42), 353 (214), 379 (42), 337 (94).

References

1. Marion, F.; Calvet, S.; Courillon, C.; Malacria, M. *Tetrahedron Lett.* **2002**, *43*, 3369
2. Marion, F.; Le Fol, R.; Courillon, C.; Malacria, M. *Synlett* **2001**, 138.
3. (a) Le Bideau, F.; Aubert, C.; Malacria, M. *Tetrahedron: Asymmetry* **1995**, *6*, 697. (b) Gilloir, F.; Malacria, M. *Tetrahedron Lett*. **1992**, *33*, 3859. (c) Courillon, C.; Le Fol, R.; Vandendris, E.; Malacria, M. *Tetrahedron Lett*. **1997**, *38*, 5493.
4. (a) Le Bideau, F.; Gilloir, F.; Nilsson, Y.; Aubert, C.; Malacria, M. *Tetrahedron Lett*. **1995**, *36*, 1641. (b) Le Bideau, F.; Gilloir, F.; Nilsson, Y.; Aubert, C.; Malacria, M. *Tetrahedron* **1996**, *52*, 7487.
5. (a) Davies-Coleman, M.T.; Rivett D.E.A. *Fortschr. Chem. Org. Naturst.* **1989**, *55*, 1. (b) Ohloff, G. *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 431.
6. Takano, S.; Kamikubo, T.; Sugihara, T.; Ogasawara, K. *Tetrahedron: Asymmetry* **1992**, *3*, 853.
7. Grove, J. F. *J. Chem. Soc., Perkin Trans. I* **1985**, 865.
8. Adam, W.; Nava-Salgado, V. O. *J. Org. Chem*. **1995**, *60*, 578.
9. Kupchan, S. M.; Giacobbe, T. J.; Krull, I. S.; Thomas, A. M.; Eakin, M. A.; Fessler, D. C. *J. Org. Chem*. **1970**, *35*, 3539.
10. Kupchan, S. M.; Giacobbe, T. J.; Krull, I. S. *Tetrahedron Lett*. **1970**, *33*, 2859.
11. Jones, J. B.; Young, J. M. *J. Med. Chem*. **1968**, *11*, 1176.
12. Asker, W.; Shalaby, A. F. A. M.; Zayed, S. M. A. D. *J. Org. Chem*. **1958**, *23*, 1781.
13. Bartmann, W.; Beck, G.; Granzer, E.; Jendralla, H.; Kerekjarto, B.; Wess, G. *Tetrahedron Lett.* **1986**, *39*, 4709.
14. (a) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc*. **1997**, *119*, 12974. (b) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc*. **1998**, *120*, 4043.
15. Khan, H. A.; Paterson, I. *Tetrahedron Lett*. **1982**, *48*, 5083.
16. Lopez, J. C.; Gomez, A. M.; Valverde, S. *J. Chem. Soc., Chem. Commun*. **1992**, 613.
17. Khan, H. A.; Paterson, I. *Tetrahedron Lett*. **1982**, *48*, 5083.

18. Deslongchamps, P. In *Organic Chemistry Series, Vol.1 Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; p 221.