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Highly stereoselective generation of α-pyrones displaying four contiguous stereogenic centers

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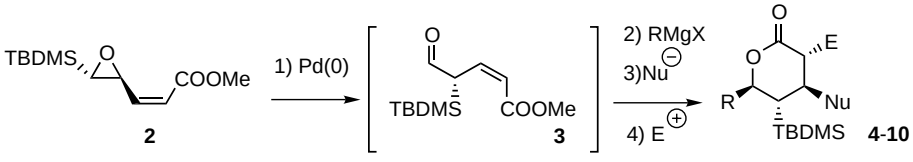
Abstract—We report here an efficient one-pot diastereoselective procedure which transforms silylated vinyloxiranes **2** into enantiomerically pure tetrasubstituted δ-lactones **7**, **10**. This transformation includes four steps: palladium(0)-catalyzed rearrangement/alkylation-lactonization/1,4-conjugated addition/electrophilic trapping of the intermediary enolate. These reactions allow efficient control of four contiguous stereogenic centers, and even of a fifth one when the electrophile is the prochiral benzaldehyde.

We have recently reported a short diastereoselective route to diastereomerically pure δ-alkylated-γ-silylated-α-pyrones **1**.[1] Our interest in compounds **1** is directly due to their functionalization and therefore their potential reactivity. The wide occurrence of β-substituted-δ-lactones in nature[2,3] as well as their being part of more sophisticated therapeutic molecules[4–6] raise interesting synthetic applications.

We report here an efficient one-pot procedure which transforms α,β-epoxy-γ,δ-vinyl-silane **2** into enantiomerically pure tetrasubstituted δ-lactones **7** and **10**. These highly functionalized substrates are isolated in high yields via a four-step transformation of compound **2**, which first rearranges[7] under zerovalent palladium catalysis into α-silylated-β,γ-unsaturated aldehydes **3** with a total chirality transfer and retention of the double bond configuration.[8,9] The presence of the silylated tertiary center in the α position to the aldehyde function is responsible for the control of the diastereoselectivity[10] of the second step. This alkylation step creates the second stereogenic center according to the Felkin–Ahn model. Then, after lactonization, the next two stereogenic carbon atoms are consecutively and efficiently controlled in the 1,4-addition step and in the electrophilic trapping of the intermediary ester enolate.

Since the two first steps have already been described,[7,10] we focus our attention on the 1,4-addition/enolate trapping sequence in which the silicon atom, bound to the lactone on the γ-position, plays a dramatic role. Indeed it directs the stereochemical fate of this conjugate addition which occurs *anti* to the silyl group and therefore *syn* to the *iso*-propyl substituent, in the equatorial position on the six-membered ring, as described in Scheme 1.

Copper derivatives are reported[11] as versatile reagents for conjugate additions on enoate type acceptors. According to Yamamoto's procedure,[12] we added cuprous derivatives, cuprates and cyanocuprates[13] on the δ-lactone **1a**. No reaction occurred unless the ester moiety was activated with boron trifluoride–ether com-



Scheme 1.

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plex and then reacted with any of the three former reagents yielding 10–30% of the 1,4-adduct in the case of cuprous derivatives and cyanocuprates. As shown in Table 1, dialkylcuprates gave the best results with 93% yield of the adduct **4** (entry 1). Conjugate addition of vinylcuprates, prepared from the tributylvinyltin derivatives, with or without boron trifluoride failed on δ-lactone **1a**. Finally compound **1a** was reacted under Lipshutz' conditions[14] and the hexenyl-adduct **6** was isolated in 72% yield and with a high diastereomeric purity (entry 4). We experienced that preparation of alkynyl adducts could not be achieved through Nilsson's conditions,[15] neither does a phenyl Grignard reagent add to the unsaturated lactone in the presence of cuprous iodide.

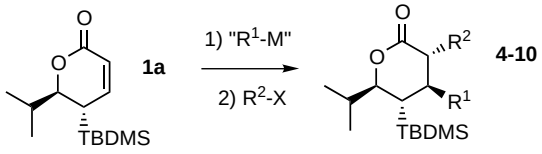
Conjugate addition of nucleophiles on conformationally stable α-pyrones, is very well documented[16–20] in literature and the reported studies show an axial approach of the nucleophile which adds *anti* to the δ-substituent.[21] This mechanistic conclusion is drawn in the case of carbanions or heteroatomic nucleophiles adding to δ-lactones substituted/or not on the γ-position. This stereoelectronic control may be explained by the stability of the energetically favored chair-like transition state. In our case the silicon atom directs the reaction and yields a compound with the β and the δ substituents *syn* to each other. The transition state has probably the twist form imposed by steric hindrance from the *tert*-butyldimethylsilyl group. Since we are able to operate desilylation of these lactonic substrates, we demonstrate here the possibility of binding a substituent *syn* to the *iso*-propyl or to any other substituent linked in the δ-position of the δ-lactones.[1] The newly formed stereogenic center may bear alkyl, vinyl and benzyl substituents which opens a wide range of further synthetic developments.

The electrophilic enolate trapping failed when tried on various copper enolates, whereas the use of zincates allowed this reaction with high selectivity.[23] Prostaglandin synthesis[24] shows a convincing example of the high reactivity of zinc enolates[25] obtained from the conjugate addition of zincates on cyclopentenones. On compound **1a**, tributylzincate adds with 86% yield and the same high diastereoselectivity as dibutylcuprate. Reaction with allylbromide (entry 5) gave 77% yield of the tetrasubstituted lactone **7**, in which the α-carbon has the relative *anti* configuration to the β-carbon. Trapping with acyl chloride afforded 12% of ketyl derivative **8a** and 66% of the ylidene derivative **8b** obtained probably by reaction of **8a** with an excess of acylchloride (entry 6). We were also able to control an extracyclic carbon center by adding a prochiral aldehyde (benzaldehyde) on the zinc enolate. Compound **9** was therefore isolated in only one diastereomeric form with 79% yield.

The conjugate addition and the electrophilic trapping could be performed as the third and fourth steps of a four-step one-pot procedure which creates and controls three new C–C bonds, starting from α,β-epoxy-γ,δ-vinyl-silane **2**. Entries 5 and 8 show the transformation of compound **2** giving **7** and **10**, respectively, in good overall yields of 62 and 75%.[22]

Our conclusion stresses that the enantioselective rearrangement of silylated vinyloxiranes takes place here as the first among four steps, all successively accomplished in a one-pot diastereoselective procedure. This work leads to creating four contiguous stereogenic centers and therefore brings a highly versatile tool to asymmetric synthesis. Furthermore, after desilylation of the compounds that are described in this study (**4–10**), we can prepare di- (**4–6** and **10**) or tri- (**7–10**) substituted

Table 1.



Entry	R^1-M	R^2-X	Product: R^1, R^2	D.e. (%)	Yield (%)	One-pot[e] from **2** yield (%)
1	[a]	H_2O	**4**: *n*-Bu, H	>98	93	–
2	[b]	H_2O	**4**: *n*-Bu, H	>98	86	–
3	[c]	H_2O	**5**: CH_2–Ph, H	>98	75	–
4	[d]	H_2O	**6**: $CH{=}CH(CH_2)_2CH_3$, H	>98	72	–
5	[b]	$CH_2{=}CHCH_2Br$	**7**: *n*-Bu, $CH_2CH{=}CH_2$	>98	77	62
6	[b]	CH_3COCl	**8a**: *n*-Bu, $COCH_3$	–	**8a**: 12	–
			8b: *n*-Bu, $=C(CH_3)(OCOCH_3)$		**8b**: 66	
7	[b]	PhCHO	**9**: *n*-Bu, PhCHOH	>98	79	–
8	[b]	CH_3I	**10**: *n*-Bu, CH_3	70	89	75

[a] *n*-Bu_2CuLi, BF_3–Et_2O.
[b] *n*-BuLi, $ZnCl_2$ in a 3/1 ratio.
[c] $PhCH_2Li$, $ZnCl_2$.
[d] Cp_2ZrHCl, hexyne, CuCN, MeLi, BF_3–Et_2O.
[e] Addition of HMPT is required in the one-pot procedure.[22]

δ-lactones in which the δ-and β-substituents are *syn* to each other. This last statement offers a novel and interesting access to enantiomerically pure δ-lactones, compared to the existing methods which give the δ-and β-substituents *anti* to each other.

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References

1. Marion, F.; Le Fol, R.; Courillon, C.; Malacria, M. *Synlett* **2001**, 138–140.
2. Davies-Coleman, M. T.; Rivett, D. E. A. *Fortschr. Chem. Org. Naturst.* **1989**, *55*, 1–35.
3. Ohloff, G. *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 431–527.
4. Cazelles, J.; Robert, A.; Meunier, B. *J. Org. Chem.* **1999**, *64*, 6776–6781.
5. Smith, A. B., III; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999**, 1823–1826.
6. Olagbemiro, T. O.; Birkett, M. A.; Mordue, A. J.; Pickett, J. A. *J. Agric. Food Chem.* **1999**, *47*, 3411–3415.
7. (a) Le Bideau, F.; Aubert, C.; Malacria, M. *Tetrahedron: Asymmetry* **1995**, *6*, 697–700; (b) Gilloir, F.; Malacria, M. *Tetrahedron Lett.* **1992**, *33*, 3859–3862.
8. Courillon, C.; Le Fol, R.; Vandendris, E.; Malacria, M. *Tetrahedron Lett.* **1997**, *38*, 5493–5496.
9. Le Bideau, F.; Gilloir, F.; Nilsson, Y.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1995**, *36*, 1641–1644.
10. Le Bideau, F.; Gilloir, F.; Nilsson, Y.; Aubert, C.; Malacria, M. *Tetrahedron* **1996**, *52*, 7487–7510.
11. (a) Nakamura, E. In *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press, 1994; pp. 129–142; (b) Ibuka, T.; Yamamoto, Y. In *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press, 1994; pp. 143–158; (c) Alexakis, A. In *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press, 1994; pp. 159–184; (d) Suzuki, M.; Noyori, R. In *Organocopper Reagents*; Taylor, R. J. K., Ed.; Oxford University Press, 1994; pp. 185–216.
12. Yamamoto, Y.; Yukiyasu, C.; Nishii, S.; Ikuba, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652–7660.
13. Burke, S. D.; Kort, M. E.; Strickland, S. M. S.; Organ, H. M.; Silks, L. A., III. *Tetrahedron Lett.* **1994**, *35*, 1503–1506.
14. Lipshutz, B.; Wood, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 12625–12626.
15. Eriksson, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1997**, *62*, 182–187.
16. Chmielewski, M.; Jurczak, J.; Zamojski, A. *Tetrahedron* **1978**, *34*, 2977–2981.
17. Takano, S.; Shimazaki, Y.; Moriya, M.; Ogasawara, K. *Chem. Lett.* **1990**, 1177–1180.
18. Panfil, I.; Chmielewski, M. *Heterocycles* **1993**, *36*, 2267–2272.
19. Jurczak, M.; Socha, D.; Chmielewski, M. *Tetrahedron* **1996**, *52*, 1411–1424.
20. Herradon, B.; Fenude, E.; Bao, R.; Valverde, S. *J. Org. Chem.* **1996**, *61*, 1143–1147.
21. Deslongchamps, P. *Organic Chemistry Series*; Pergamon Press: Oxford, 1983; Vol. 1, pp. 221–242.
22. One-pot general procedure: To a neat sample of vinylepoxide (1 mmol, 1 equiv.) is added at room temperature a solution of palladium acetate (0.05 mmol) and triphenylphosphite (0.2 mmol) in THF (1 ml). After checking completion of the reaction by TLC, the temperature is lowered at −78°C and the Grignard reagent (1.1 mmol, 1.3 M in THF) is added dropwise. After stirring for 30 min, the solution is warmed to room temperature. The resulting mixture is then added at −78°C to a white slurry of zinc chloride (3.0 mmol, 1.6 M in THF) and lithium reagent (8.9 mmol, 2.3 M in hexane) and stirred at this temperature until the TLC indicates the end of the reaction. Then, hexamethyl phophoramide (3 ml) is added at −78°C followed by the electrophile (5.0 mmol). The mixture is then slowly warmed up to 0°C. The reaction is quenched with a saturated aqueous solution of ammonium chloride and extracted with ether. The organic layer is dried over sodium sulfate and concentrated under reduced pressure. Flash chromatography petroleum ether/diethyl oxide (95/5) afforded lactones **7** and **10** (fully characterized), respectively, with yields of 75 and 62%.
23. To a refrigerated (0°C) and saturated solution of zinc chloride in THF (1.6 M, 1.2 mmol, 3 equiv.) was added *n*-butyllithium (3.6 mmol, 9 equiv.) and the resulting heterogeneous mixture was stirred at 0°C for 1 h. After lowering the temperature to −78°C, a solution of **1a** (100 mg, 0.41 mmol, 1 equiv.) in 5 ml of THF is added. The reaction medium is kept for 30 min at −78°C and warmed up at 0°C for 1 h. Before adding an excess of the electrophile (5 equiv.), temperature was lowered back to −78°C, and then the reaction was kept at 0°C for 1 h. Hydrolysis with a saturated aqueous solution of ammonium chloride is followed by extractions and flash chromatography with petroleum ether/ethyl acetate: 95/5.
24. Suzuki, M.; Morita, Y.; Koyano, H.; Koga, M.; Noyori, R. *Tetrahedron* **1990**, *46*, 4809–4822.
25. Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38*, 225–654.