Tandem Michael-aldol induced ring closure of dimethyl 2-phenylselenofumarate: a diastereoselective entry to novel 4-phenylseleno butano-4-lactone derivatives, versatile precursors of naturally occurring compounds

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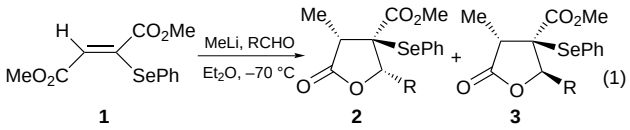
Tandem Michael-aldol induced ring closure of dimethyl 2-phenylsenofumarate gives, with good yields and diastereoselectivities, highly substituted 4-phenylselenobutano-4-lactones, which can be further transformed into naturally occurring substances.

The synthesis of trisubstituted butenolides and butano-4-lactones, in particular of their 4-carboxy-derivatives (paraconic acids), has attracted considerable attention in recent years, because of the wide range of biological activities exhibited by this class of compounds,[1] which includes substances such as lichesterinic, protolichesterinic, dihydroprotolichesterinic,[1b,2h,i] roccellaric,[2j] nephromopsinic,[2f] pertusarinic[2k] and phaseolinic[2l] acids. Many synthetic approaches to these molecules have been developed by a number of research groups over the past decades.[2,3]

In connection with our previous studies on the reactivity of dimethyl 2-phenylselenofumarate **1** as a Michael acceptor,[4b,c] we describe here a simple method for the diastereocontrolled synthesis of the novel highly functionalized 4-phenylselenobutano-4-lactones **2a–d**, **3a–d**, which involves a tandem Michael-Aldol induced ring closure [reaction (1), Table 1]. We



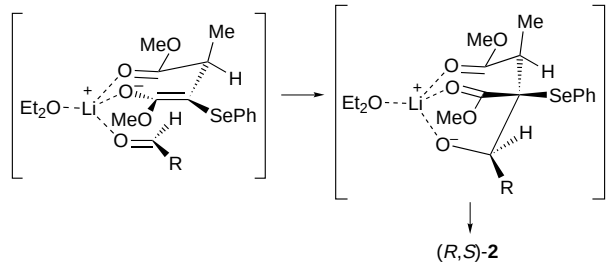
1 **2** **3**

also show the synthetic utility of the new molecules, which can be easily transformed into naturally occurring products, such as saturated and unsaturated paraconic acids.

As we described in a previous paper, the diester **1**, which is easily available from dimethyl maleate,[4a] reacts with MeLi in a Michael reaction, with no trace of the 1,2 addition products.[4b]

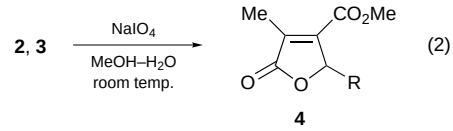
The anion resulting from this Michael addition can be easily trapped by adding an aldehyde to the reaction mixture; the resulting aldol adduct then instantaneously undergoes lactonization affording 4-phenylselenobutano-4-lactones **2a–d**, **3a–d** with good overall process yields [reaction (1), Table 1].†

As summarized in Table 1, the reaction proceeds with excellent diastereoselectivities when R = *n*-alkyl, aryl or 2-furyl; a lower diastereoselectivity is observed when an α,β-unsaturated aldehyde is used. The stereochemistry of the process could be rationalised assuming the formation of the chelated intermediate **A** resulting from the attack of MeLi and the subsequent approach of the aldehyde from the favoured *si*-face (Scheme 1).[5] However, the assignment of the relative stereochemistries of diastereoisomers **2** and **3** is based upon the following chemical evidence arising from further transformations of these compounds.



Scheme 1

First, **2** and **3** gave butenolides **4** *via* selenoxide *syn*-elimination when treated with $NaIO_4$,[6] [reaction (2), Table 2],



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indicating that the phenylselenenyl and methyl groups in **2** and **3** must be in a *trans* relative configuration. Using **2a** and **3a** as starting compounds in this reaction allowed the synthesis of (*R*,*S*)-lichesterinic acid methyl ester **4a**; (*R*,*S*)-lichesterinic acid has been isolated from Icelandic moss *Cetraria islandica*.[7] This paraconic acid shows antibacterial activity towards Gram positive organisms,[7c] and various syntheses have already been reported in the literature.[3d,7c,8]

Secondly, in order to determine the relative configurations at C-5 in lactones **2** and **3**, hydrogenolysis of the C–Se bond of **2a**,**b** was carried out.[9] The resulting products were identified as

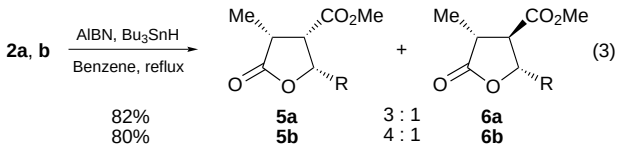
Table 1 Synthesis of γ-lactones **2a–d**, **3a–d**

R	**2** + **3**	Yield (%)	**2** : **3**
n-$C_{13}H_{27}$	**a**	71	93 : 7
Ph	**b**	58	89 : 11
2-Furyl	**c**	55	91 : 9
CH_3CH=CH	**d**	66	71 : 29

Table 2 Transformation of γ-lactones **2a–d**, **3a–d** to butenolides **4a–d**

R	**4**	Yield (%)
n-$C_{13}H_{27}$	**a**	92
Ph	**b**	73
2-Furyl	**c**	81
CH_3CH=CH	**d**	82

5a,**b**, **6a**,**b** by comparison with the literature data [reaction (3)];[2k] this outcome was interpreted in terms of a structure for



(3)

82% **5a** 3 : 1 **6a**
80% **5b** 4 : 1 **6b**

compound **2** in which the substituent at C-5 and the methyl group at C-3 are in a *cis* relative configuration. Consequently, the lactone **3** must have the same groups in a *trans* configuration.

In addition, as the predominant isomer **5a** can be easily epimerized to **6a**,[2k] this transformation also has synthetic relevance, as **6a** is the methyl ester of the naturally occurring roccellaric acid, isolated from the chilenic lichen species *Roccellaria mollis*.[2b]

In conclusion, we have described a facile diastereoselective synthesis of novel highly functionalized 4-phenylselenobutano-4-lactones and their application in the synthesis from **1** of racemic paraconic acids esters *e.g.* **4a** and **6a**, with good overall yields (65 and 58%, respectively). Furthermore, this strategy allows good flexibility with respect to the substituent at C-5, which is characteristic of paraconic acids.

Development of a stereocontrolled methodology to prepare enantiomerically pure compounds[2] *via* this sequential process and extension of the methodology are underway in our laboratory.

Footnotes and References

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† Typical experimental procedure: MeLi (1.1 mmol) was added to a stirred solution of **1** (1 mmol, 300 mg) at −70 °C in 10 ml of dry Et_2O, under argon atmosphere; the reaction mixture was allowed to react for 10 min and then the aldehyde (1.2 mmol), dissolved in 2 ml of dry Et_2O, was added. The resulting mixture was stirred at −70 °C for 1 h after which the temperature was raised to 0 °C and water was added. The solution was then extracted with ethyl acetate and the combined organic extracts were washed with aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Column chromatography on SiO_2 (hexane–ethyl acetate 9 : 1) afforded pure products **2** and **3**. Representative ^1H NMR; spectra δ($CDCl_3$); **2a**: 0.86 (3 H, m), 1.23 (3 H, d, *J* 7.0 Hz), 1.2–1.5 (22 H, m), 1.8–2.1 (2 H, m), 2.34 (1 H, q, *J* 7.0 Hz), 3.77 (3 H, s), 4.10 (1 H, dd, *J* 2.3 Hz, J_2 9.9 Hz); 7.3–7.5 (3 H, m), 7.5–7.6 (2 H, m). **2b**: 1.31 (3 H, d, *J* 7.0 Hz), 2.52 (1 H, q, *J* 7.0 Hz), 3.38 (3 H, s), 5.38 (1 H, s), 7.3–7.8 (10 H, m). Representative IR spectra; ν($CDCl_3$)/cm^{-1}. **2a**: 1773 (C=O, br), 1728 (C=O, br). **2b**: 1781 (C=O, br), 1731 (C=O, br).

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