

Stereoselective routes to aryl substituted γ -butyrolactones and their application towards the synthesis of highly oxidised furanocembranoids†

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Received 21st January 2011, Accepted 8th March 2011

DOI: 10.1039/c1ob05113j

Titanium chelate addition of aryl nucleophiles to cyclopropyl aldehyde **6** followed by a tin-catalyzed one-pot *retro*-aldol, acetalisation and lactonisation sequence afforded *cis* and *trans* γ -aryllactone acetals. A γ -furyllactone derived by this approach was further transformed in two steps to model compounds for the oxidised northeastern sectors of selected *Pseudopterogorgia* diterpenoids.

Highly substituted γ -butyrolactone motifs are profusely present in many synthetic intermediates and biologically active structures.¹ In general, their enantiomeric purity and absolute configuration play a significant role on their purported pharmacological properties.² Thus, much effort has been invested in their asymmetric synthesis.³ Among the derivatives thus far reported, less attention has been devoted to the stereoselective synthesis of *trans* and especially, *cis* γ -aryl- or heteroarylbutyrolactones.⁴ Such lactone-based synthons may serve as intermediates for the synthesis of highly oxidised furanocembranoids (e.g. **1–3**) and lignan natural products (e.g. **4**) (Fig. 1).⁵

We previously reported that Hosomi–Sakurai allylation of furan ester **5** derived cyclopropyl aldehyde **6** affords *trans* lactones **7** with high diastereoselectivity following the Felkin–Ahn paradigm as the operating addition pathway.⁶ A useful alternative would appear to be the addition of nucleophiles through a substrate-controlled Cram chelate addition pathway that should lead to the corresponding *cis*-lactones. In this study, we wish to disclose the addition of aryl- and heteroaryl-titanium nucleophiles to **6** leading to either *cis*- or *trans*-lactones **9**, which appear to be useful building blocks towards the synthesis of **1–4** (Scheme 1).

We initiated our experiments by screening furyl nucleophiles taking into consideration the sensitive nature of the methyl oxalate moiety in **6** under basic nucleophilic conditions. Initial attempts to add several different 2-furyl metal reagents (ArCeCl₂, ArCuCl, ArZnCl) alone or in combination with BF₃·OEt₂ to aldehyde **6** were unsuccessful (Scheme 2). Either decomposition or no reaction of the starting material was observed. Organotitanium

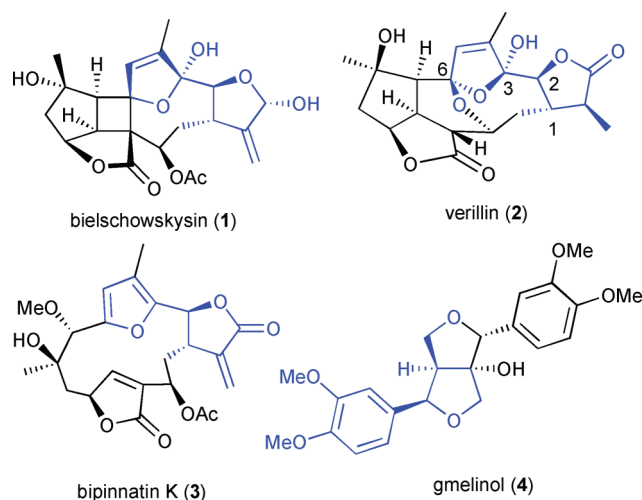
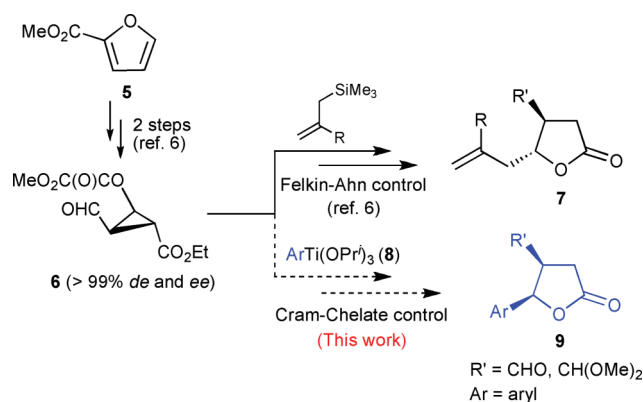


Fig. 1 Representative natural products that can be derived from γ -aryllactones.

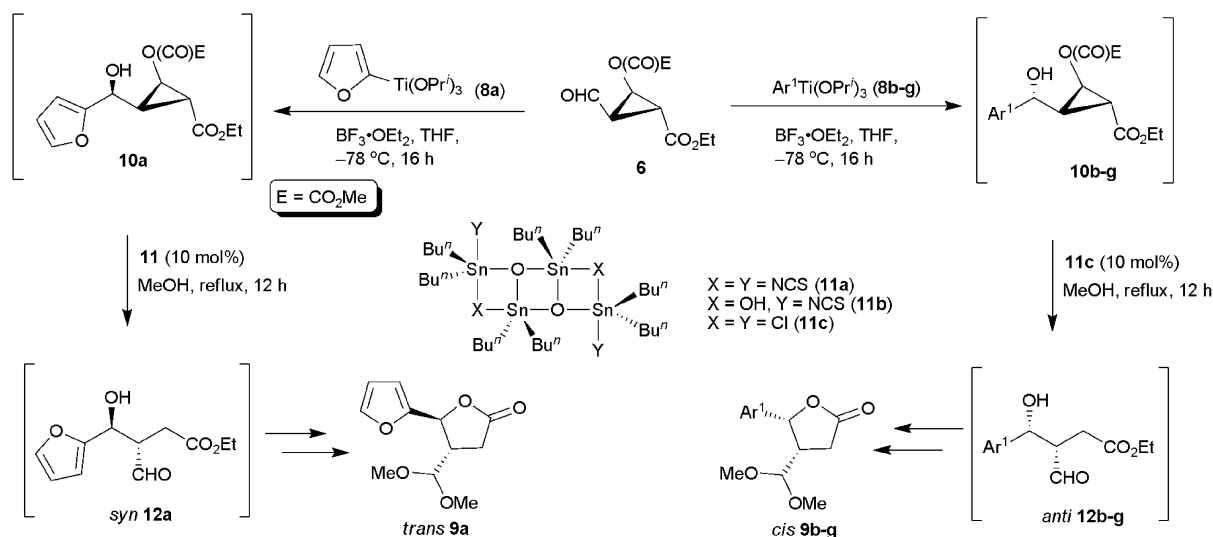


Scheme 1

reagents display high chemo- and diastereoselectivity towards aldehydes in comparison to other carbonyl functionalities and are considered as “well-behaved reagents” because of their ability to mitigate chemical reactivity and basicity.⁷ Nevertheless, reaction of the 2-furyltitanium reagent **8a** with **6** was also unsuccessful, however, when BF₃·OEt₂ was additionally employed, the desired furyl transfer was finally achieved to give rise to **10a**

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† Electronic supplementary information (ESI) available: Experimental procedures, ¹H and ¹³C NMR spectra. CCDC reference numbers 809453 and 809454. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05113j



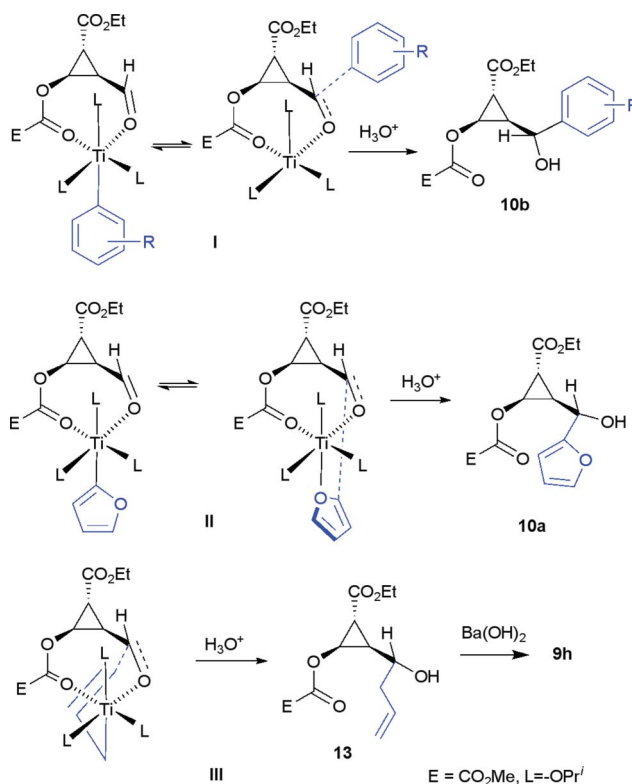
(>90% conversion). While **10a** can be isolated, due to its sensitive nature we opted to directly convert it to the corresponding lactone **9a** through a retro-aldol and lactonisation sequence upon saponifying the oxalylic ester, making use of the 1,2-donor-acceptor relationship⁸ in the cyclopropane ring (Scheme 2). Previously, we reported $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ and Otera stannoxanes^{6,9} as effective reagents to carry out this transformation for allylated derivatives of **6**. Treatment of **10a** with $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ however, failed to give the expected furyllactone carbaldehyde. Gratifyingly, stannoxane **11a** furnished the desired lactone acetal **9a**, albeit in only 23% overall yield based on **6**. Screening of other stannoxane derivatives revealed **11c** to be more effective, improving the overall yield of the two-step sequence from **6** to **9a** to 40% (Table 1, entry 1–3).

Subsequently, a representative number of other aryltitanium reagents, being readily prepared by dehydrolithiation or dehalolithiation of aryl derivatives followed by titaniation with $\text{ClTi}(\text{OPr}^i)_3$, were tested for the synthesis of lactones **9** (Scheme 2).¹⁰ Besides 2-thienyl (entry 4) and phenyl (entry 5), alkoxy substituted aryl groups (entries 6–9) being especially relevant towards naturally occurring compounds such as **4** could be successfully introduced. However, aryltitanium nucleophiles bearing substitutions at the *ortho*-position, e.g. those derived from 2-bromoanisole and 2-bromotoluene, were not amenable with this reaction sequence, which is most likely due to steric hindrance.

The stereochemistry of **9a–g** was confirmed through 2D-NOESY correlation experiments and X-ray analysis of **9c** (see supporting information). Thus, it was revealed that the diastereoselectivity of this reaction sequence was greatly influenced by the type of aryl nucleophile being used. While the 2-furyltitanium **8a** gave rise predominantly to the *trans*-lactone **9a** (86:14), the aryl substituted lactones **9c–9g** were obtained with moderate to excellent *cis*-selectivity (3:1 to >99:1), demonstrating for the first time that addition of nucleophiles to **6** can ultimately lead to *cis*-lactone of type **9** as the major products.

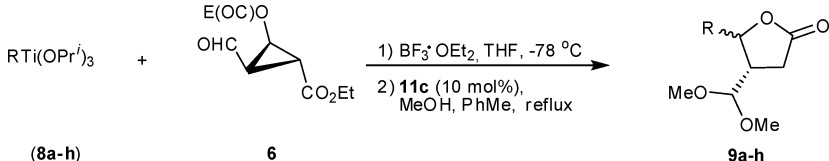
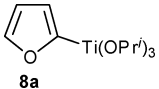
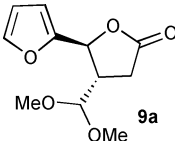
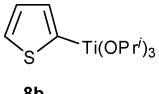
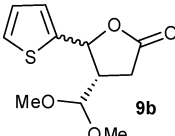
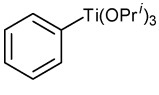
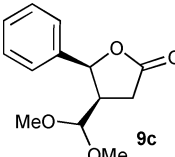
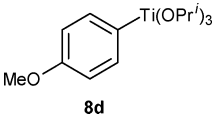
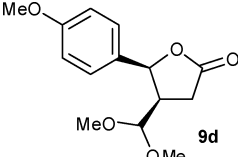
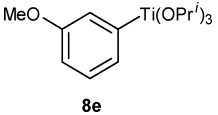
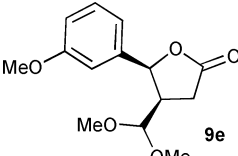
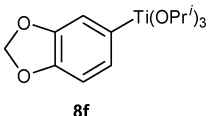
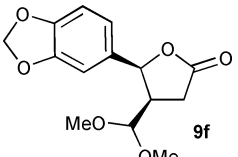
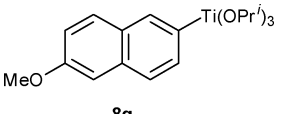
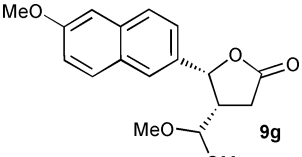
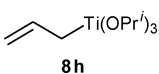
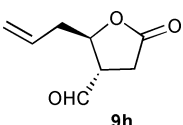
The *cis*-selectivity observed in the formation of **9c–9g** with aryltitanium/ $\text{BF}_3 \cdot \text{OEt}_2$ reagents, contrasting the high *trans*-selectivity achieved in the corresponding transformations with

allylsilanes/ $\text{BF}_3 \cdot \text{OEt}_2$,⁶ and the excellent oxygen-chelating capabilities of titanium reagents make us propose a cyclic Cram chelate-type featuring a rather unusual 8-membered titanium complex (Scheme 3, pathway I).¹¹ The aryl nucleophile is delivered externally from the sterically less hindered face of the carbonyl group, giving rise to **10c–g** as the major diastereomer.



In contrast, the *syn*-selectivity observed with furan titanate **8a** results through the formation of an incipient bond between the furyl nucleophile and the electrophilic aldehyde carbon while

Table 1 γ -Aryl and allyl lactone synthesis from cyclopropane aldehyde, **6**

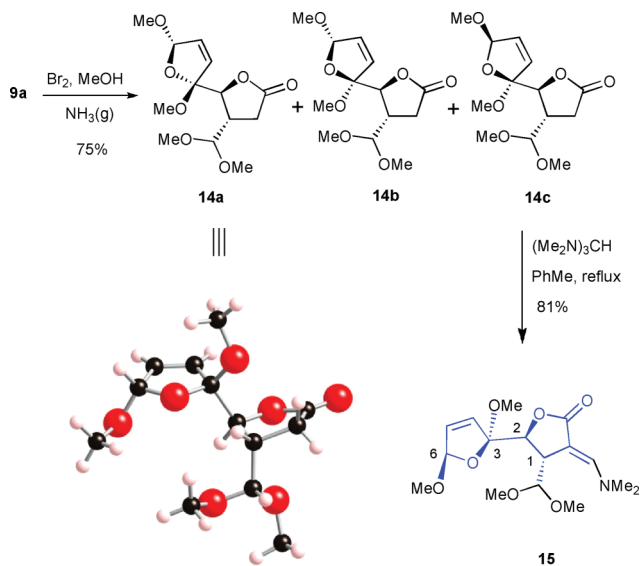
Entry	Organotitanium nucleophile	Aldehyde	Lactone ^a	Yield ^b	<i>cis</i> : <i>trans</i> ratio ^c
		6	9a-h		
1	 8a	6	 9a	23 ^c	14 : 86
2				29 ^d	
3				40	
4	 8b	6	 9b	38	54 : 46
5	 8c	<i>ent</i> - 6	 9c	45	>99 : 1
6	 8d	<i>ent</i> - 6	 9d	38	82 : 18
7	 8e	<i>ent</i> - 6	 9e	40	74 : 26
8	 8f	<i>ent</i> - 6	 9f	33	76 : 24
9	 8g	6	 9g	37	92 : 8
10	 8h	6	 9h	29 ^f	6 : 94

^a Major diastereomer shown. ^b Unless otherwise stated, **11c** was used as catalyst. Overall yield in two steps. ^c **11a** was used. ^d **11b** was used. ^e Based on relative integrals in the ¹H NMR spectrum. ^f Lactonisation was carried out with Ba(OH)₂·8H₂O.

the oxygen atom in the furan ring is coordinated with titanium, favoring the formation *syn* addition product **10a** (Scheme 3, pathway II).

The poor diastereoselectivity achieved with the thienyl nucleophile **8b** could be explained by the weaker coordination ability of sulfur to titanium, thus resulting in no preference either for pathway I or II. The lower diastereoselectivity for oxygenated aryltitanium reagents leading to **9d–9g** compared to **9a** might reflect different degrees of internal delivery of the nucleophile *via* coordination of titanium to the oxygen substituents in the aryl rings. In agreement with this proposal is the highly selective addition of allyltitanium **8h** to **6** (Table 1, entry 10), leading to **13** by directed delivery of the allyl nucleophile *via* a Zimmerman–Traxler-like transition state (Scheme 3, pathway III).

Lactone **9a** seemed to be a suitable precursor to study the synthesis of the northeastern segments of diterpenoids **1** and **2** (Scheme 4). Initial attempts to perform oxidative transformations on the furan ring using a number of methods known for that moiety, *i.e.* singlet oxygen oxidation, mCPBA or Jones oxidation¹² to furnish a γ -hydroxybutenolide were unsuccessful. Using bromine¹³ in methanol, however, afforded the 2,5-dimethoxy-2,5-dihydrofuran **14** in 75% yield, albeit as a mixture of three diastereomers in a 1:1:2 ratio, from which **14c** could be separated by chromatography. From the mixture of **14a** and **14b** the former was obtained in pure form by crystallisation and its structure could be assigned unambiguously by X-ray structural analysis. The major diastereomer **14c** was heated with Bredereck's reagent¹⁴ to install the α -dimethylaminomethylene handle, furnishing **15** in good yield (81%). The model precursor product thus obtained satisfies the 1*S*,2*S*,3*S* (and 6*S*) configurations required in furanocembranoids **1** and **2**.



Scheme 4

In conclusion, we have developed a new diastereoselective approach towards γ -aryl lactones utilising aryltitanium reagents in combination with the readily available cyclopropanecarbaldehyde **6**. This methodology extends the previously reported functional-

sation of **6** with allylsilanes in substrate scope, but also offers for the first time a reversal of stereochemistry. Thus, *cis*-disubstituted γ -aryl- β -methyl acetal lactones with good diastereoselectivity in enantiomerically pure form can be obtained, which compares well with previously reported methods.^{3–4}

Acknowledgements

A.P.G.M. is grateful to the Deutscher Akademischer Austauschdienst (DAAD) for a graduate fellowship.

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