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COMMUNICATION

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

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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]

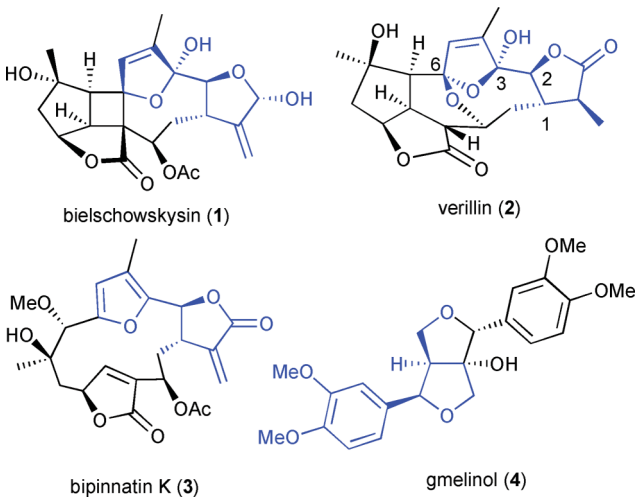
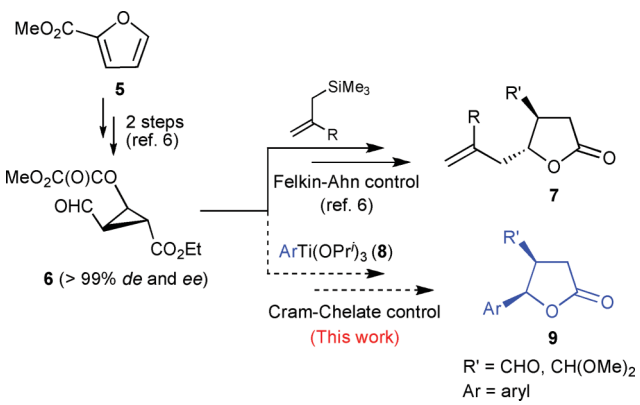


Fig. 1 Representative natural products that can be derived from γ-aryllactones.

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 heteroarylltitanium 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).



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 ($ArCeCl_2$, ArCuCl, ArZnCl) alone or in combination with $BF_3{\cdot}OEt_2$ to aldehyde **6** were unsuccessful (Scheme 2). Either decomposition or no reaction of the starting material was observed. Organotitanium 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 $BF_3{\cdot}OEt_2$ was additionally employed, the desired furyl transfer was finally achieved to give rise to **10a**

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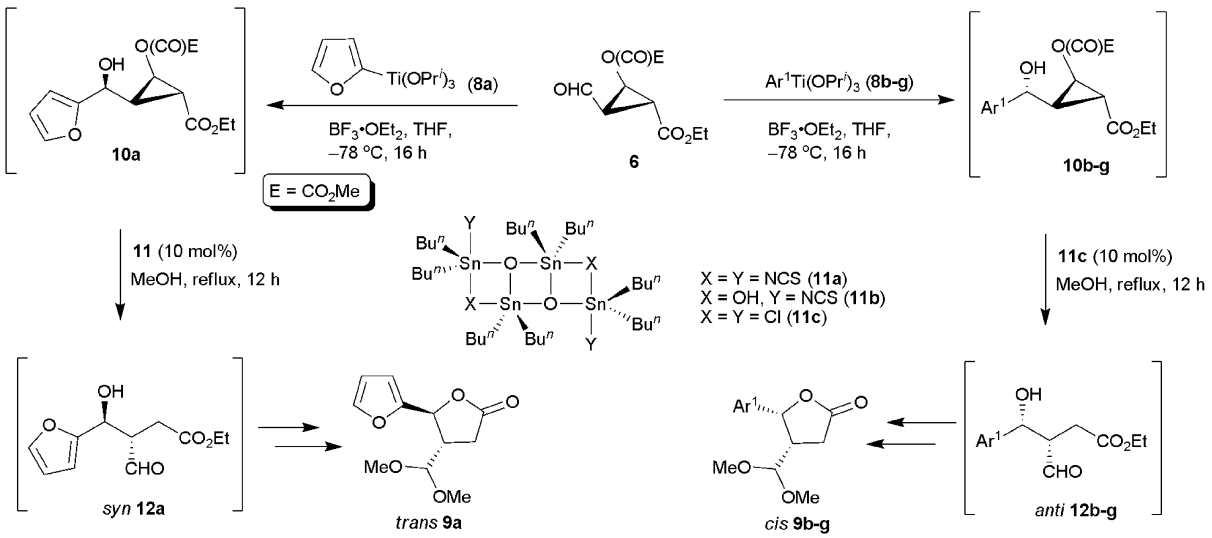


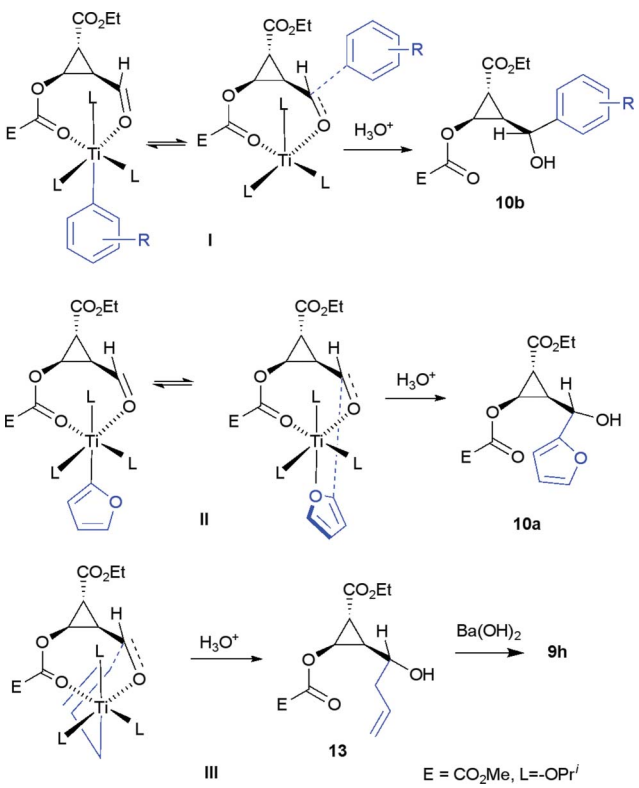
Scheme 2

(>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 relationship[8] in the cyclopropane ring (Scheme 2). Previously, we reported $Ba(OH)_2{\cdot}8H_2O$ and Otera stannoxanes[6,9] as effective reagents to carry out this transformation for allylated derivatives of **6**. Treatment of **10a** with $Ba(OH)_2{\cdot}8H_2O$ 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 titanation with ClTi(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.

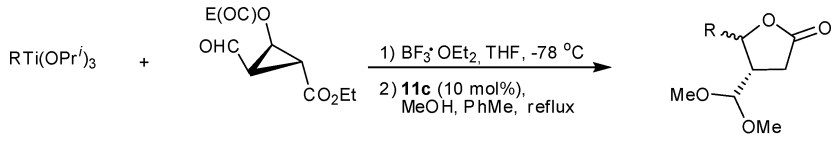
The *cis*-selectivity observed in the formation of **9c–9g** with aryltitanium/$BF_3{\cdot}OEt_2$ reagents, contrasting the high *trans*-selectivity achieved in the corresponding transformations with allylsilanes/$BF_3{\cdot}OEt_2$,[6] and the excellent oxygen-chelating capabilities of titanium reagents 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.



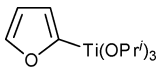
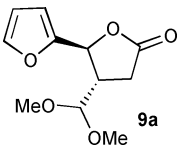
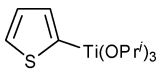
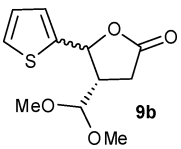
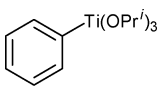
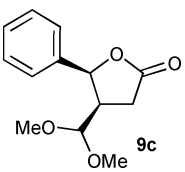
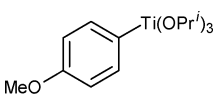
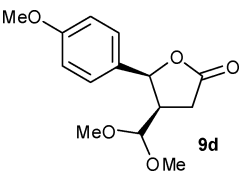
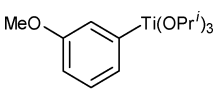
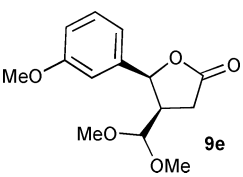
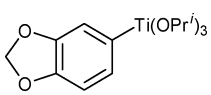
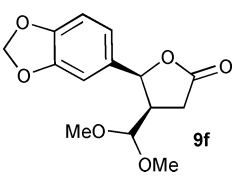
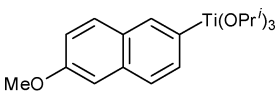
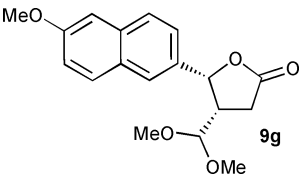
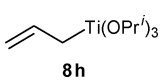
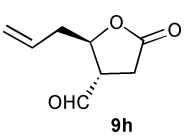
Scheme 3

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**



(**8a-h**) **6** **9a-h**

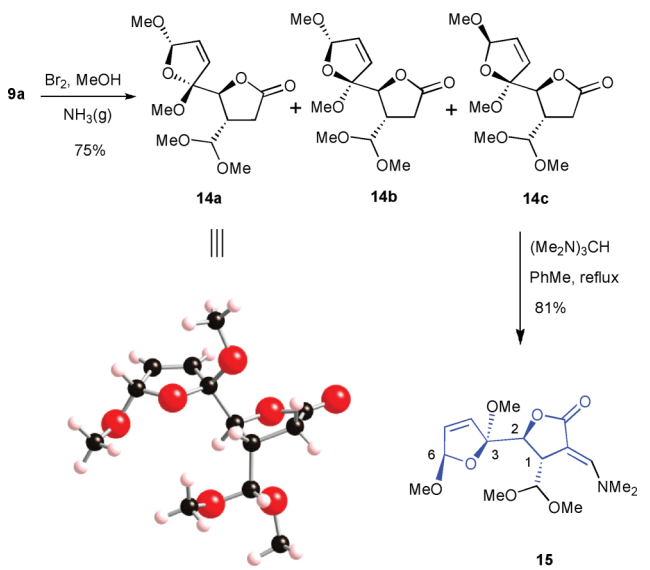
Entry	Organotitanium nucleophile	Aldehyde	Lactone[a]	Yield[b]	*cis* : *trans* ratio[e]
1	 **8a**	**6**	 **9a**	23[c]	14 : 86
2				29[d]	
3				40	
4	 **8b**	**6**	 **9b**	38	54 : 46
5	 **8c**	*ent*-**6**	 **9c**	45	>99 : 1
6	 **8d**	*ent*-**6**	 **9d**	38	82 : 18
7	 **8e**	*ent*-**6**	 **9e**	40	74 : 26
8	 **8f**	*ent*-**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 ^{1}H NMR spectrum. [f] Lactonisation was carried out with $Ba(OH)_2 \cdot 8H_2O$.

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 oxidation[12] to furnish a γ-hydroxybutenolide were unsuccessful. Using bromine[13] 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 reagent[14] 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 functionalisation 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

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