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Facile Asymmetric Synthesis of the Core Nuclei of Xanthanolides, Guaianolides, and Eudesmanolides

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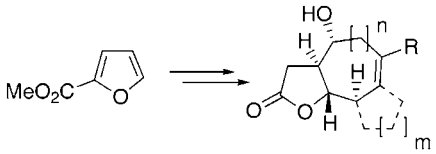
ABSTRACT



Bicyclic and tricyclic γ-butyrolactones with 5,7-, 5,6,5-, 5,6,6-, or 5,7,5-fused ring systems, being found in xanthanolides, eudesmanolides, and guaianolides, were readily synthesized from methyl furan-2-carboxylic acid. Key steps were a copper(I)-catalyzed asymmetric cyclopropanation, Sakurai allylations, intramolecular ene reactions, and ring-closing metathesis reactions.

γ-Butyrolactones are prominent constituents in biologically active compounds and are found in about 10% of all natural products.[1] In particular, there are many examples in which the γ-butyrolactone is part of a more complex ring system, e.g. in sesquiterpene lactones as depicted in Figure 1.[2] An example for the bicyclic xanthanolides includes xanthatin **1**,[3] having extraordinarily high antibacterial activity against methicillin-resistant *staphylococcus aureus*. The sesquiterpene Saussureal (**2**),[4] a potent plant regulator that was isolated from *Saussurea Lappa*, belongs to the class of eudesmanolides, being characterized by a 5,6,5-tricyclic ring system. Ixerin Y[5] (**3**) and Arglabin[6] (**4**), having the 5,7,5-tricyclic ring system of the guaianolides, display strong activities against breast, colon, ovarian, and lung cancer. Arglabin (**4**), being currently under clinical evaluation in Kazakhstan and the US, inhibits the farnesyl transferase and by this mode the activation of the RAS proto-oncogene, a process that is believed to play a pivotal role in 20−30% of all human tumors.

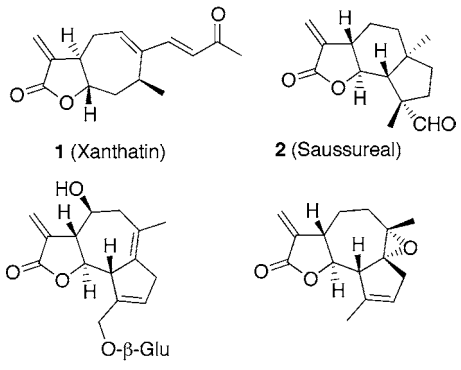


Figure 1. Biologically active xanthanolides, guaianolides, and eudesmanolides.

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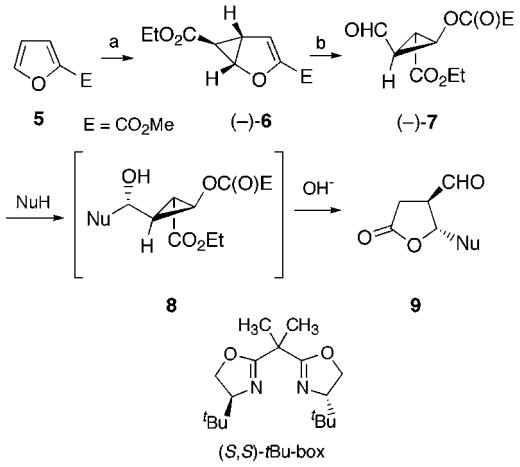
Very few strategies toward the total synthesis of eudesmanes, xanthanolides, and guaianolides have been reported,[7] but especially Ixerin Y (**3**) and Arglabin (**4**) are only available from natural sources so far.

We have recently developed an asymmetric route to disubstituted γ-butyrolactones **9** starting with the copper(I)-bis(oxazolines)-catalyzed cyclopropanation of furan-2-carboxylic esters **5** (Scheme 1).[8] This way, either enantiomer

Scheme 1. Synthesis of *anti*-Disubstituted γ-Butyrolactones **9**[8b,c]

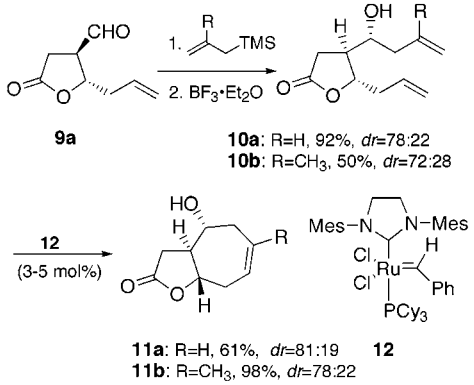


[a] Conditions: (a) (i) ethyl diazoacetate, $Cu(OTf)_2$ (2 mol %), (*S*,*S*)-*t*Bu-box (2.5 mol %), $PhNHNH_2$ (2 mol %), CH_2Cl_2, 91% ee; (ii) recrystallization (pentane), >99% ee, 53%. (b) (i) O_3, CH_2Cl_2, −78 °C, (ii) dimethyl sulfide, 94%.

of **6** can be readily prepared on a multigram scale in pure form. Ozonolysis of **6** followed by reductive workup leads to the aldehyde **7**, which undergoes highly diastereoselective additions with nucleophiles to **8** followed by a retroaldol/lactonization cascade to **9**. Here we would like to report the application of this strategy toward bi- and tricylic γ-butyolactones as a facile entry to the core nuclei of xanthanolides, eudesmanolides, and guaianolides.

The lactone **9a**, which can be obtained following the general strategy outlined in Scheme 1 by using allylsilane as the nucleophile (anti/syn ratio 95:5),[8b,c] seemed to be an ideal starting point for a subsequent annulation of a seven-membered ring (Scheme 2).

Scheme 2. Synthesis of the Core Nucleus of Xanthanolides



Introduction of a second allyl group by BF_3-mediated reaction with allylsilanes takes place with moderate diastereoselectivity (3:1 to 4:1) to **10** (major diastereomers shown), which was set up for ring-closing metathesis (RCM).

By using the ruthenium catalyst **12**, which is especially effective in RCM reactions,[9] both **10a** and **10b** could be directly converted to the bicyclic derivatives **11a** and **11b**, respectively, with no protection of the free hydroxyl group being necessary. In the course of the ring closure, the diastereoselectivity changed very little, indicating that both diastereomers **10a** and **10b** undergo equally well the metathesis reaction. The major diastereomer of **11b** could be obtained in pure form by recrystallization, and its relative stereochemistry was established by X-ray crystallography (Figure 2).

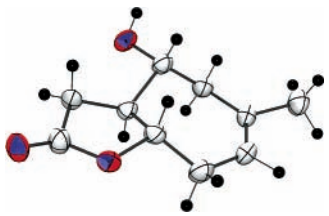


Figure 2. X-ray structure of (*rac*)-**11b**.

The synthesis of the tricyclic 5,7,5 framework with all-trans stereochemistry at the ring junctions, found in guaianolides such as **3** and **4**, posed an additional challenge for our synthetic route. Addition of the allylsilane **13**[10] to **7** does not only have to proceed under Felkin-Anh control[11] at the aldehyde with respect to the cyclopropyl group, but also must

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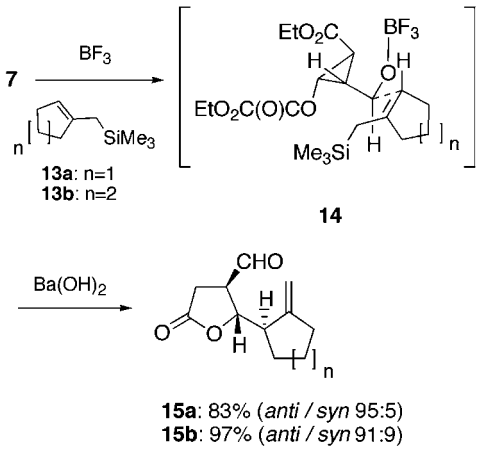
be *anti*-selective between the prochiral centers of the two reaction partners. Indeed, **15a** was obtained with excellent stereocontrol, giving again good *anti*-selectivity (95:5) of the substituents placed on the lactone ring, while the *anti*-relationship was observed between the two five-membered rings exclusively (Scheme 3).

Scheme 3. Addition of Cyclic Allyl Silanes **13** to **7**

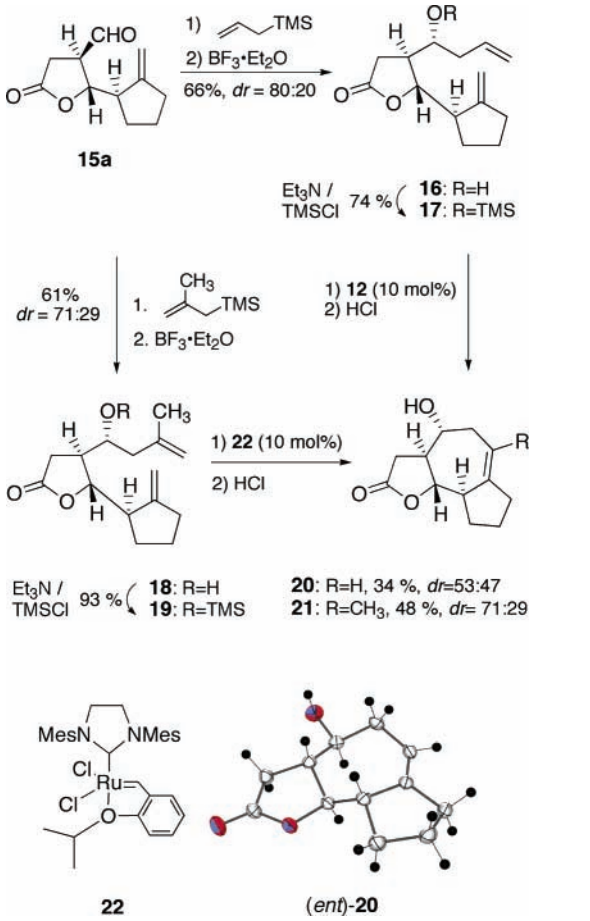


The stereochemical outcome of the reaction can be rationalized by the transition state **14**, in which both, the Felkin-Anh[11] as well as the antiperiplanar orientation with the least sterical hindrance of the carbonyl group and the C−C double bond of the allylsilane is observed.[12] Likewise, the six-membered allylsilane **13b** gave good results, resulting in the formation of **15b** with only minute amounts of the *syn*-diastereomer present.

15a proved to be somewhat unstable and was therefore used as the crude material obtained directly from the reaction. For the synthesis of the core nucleus of guaianolides, allylations in the presence of boron trifluoride were carried out to yield the 1,8-dienes **16** and **18**, respectively (Scheme 4, major diastereomer shown). However, it was imperative to add the allylsilane before introducing the Lewis acid to prevent an intramolecular carbonyl-ene reaction (vide infra). Ring-closing metathesis could not be achieved with either **16** or **18**, but after conversion to their corresponding trimethylsilyl ethers **17** and **19** cyclization became possible.

Unfortunately, **17** gave rise to **20** in the presence of the catalyst **12** in only low yields (34%). It was interesting to note, however, that apparently the minor diastereomer in **17** reacted preferentially, since the diastereoselectivity changed from 4:1 in **17** to 1:1 in **20**. The diastereomers could be separated by crystallization, and their relative stereochemistry

Scheme 4. Synthesis of the Core Nucleus **21** of Guaianolides



was assigned by X-ray structure analysis of (*ent*)-**20**, being prepared from (+)-**6** in an analogous way to **20**. Attempts to improve upon the RCM of **17** by employing **22**[13] as catalyst were not successful. **20** was obtained in 28% yield; however, with catalyst **22** the ratio of diastereomers did not change in the course of the cyclization.

Even more challenging was the RCM of **19**, creating a tetrasubstituted double bond. Indeed, no reaction was observed employing **12**, but in the presence of the catalyst **22** the tricylic lactone **21** could be obtained in moderate yield (48%).

For the synthesis of the core nucleus of eudesmanolides, the direct ring closure of **15** by an intramolecular carbonyl ene reaction[14] was envisioned. Lewis acids such as $SnCl_4$ or $MeAlCl_2$ most commonly mediate such coupling reactions.[15] In our hands boron trifluoride etherate at room temperature gave the best results, leading in a remarkably regio- and stereoselectivereaction to **24** as a single stereoisomer. Their relative stereochemistry was established by X-ray structure analysis of **24a**. The stereochemical course[16] of the reaction could be rationalized by the transition state **23**, in which the least steric interactions are encountered in the attack of the carbonyl group.

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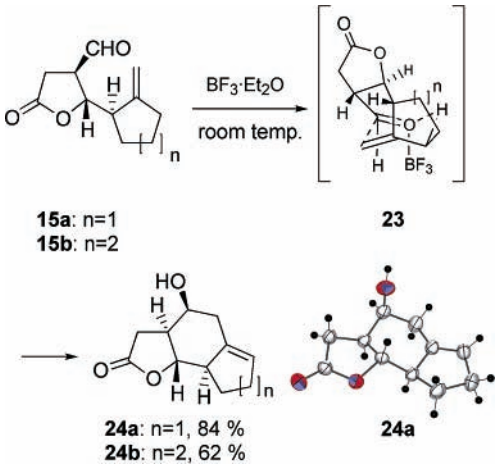
Scheme 5. Synthesis of the Core Nucleus of Eudesmanes



In conclusion, a variety of bi- and tricyclic lactones, representing the core structures of important natural products, can be readily prepared by using the asymmetric cyclopropanation of furan-2-carboxylic methyl ester as the key step for the enantioselective preparation of γ-butyrolactones. On the basis of this strategy, further studies toward the total synthesis of **1**−**4** are being carried out in our laboratories.

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Supporting Information Available: Experimental and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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