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Enantioselective Synthesis of Furo[2,3-*b*]furans, a Spongiane Diterpenoid Substructure

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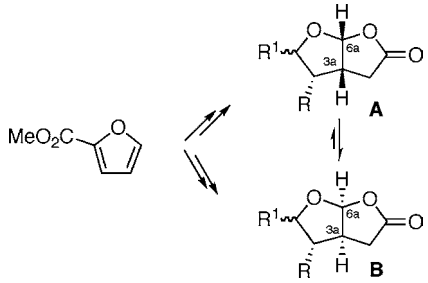
ABSTRACT



A short and enantioselective synthesis of *cis*-fused 5-oxofuro[2,3-*b*]furans, being found in many spongiane diterpenoid natural products, is reported starting from inexpensive methyl 2-furoate. Moreover, the acid-catalyzed rearrangement of the furo[2,3-*b*]furan framework A to B is observed for some derivatives, suggesting a simple connection between natural products differing in the absolute configuration of the 3a,6a ring junction.

Sponges are marine organisms expressing a large number of natural compounds, which display interesting biological properties such as antibacterial or cytotoxic activities.[1] A scarcely explored subgroup of spongiane diterpenoids shares the structural motive of a *cis*-fused 5-oxofuro[2,3-*b*]furan unit **1**, found, e.g., in macfarlandin C (**2**)[2] or in norrisolide (**3**), which shows a unique interference with the Golgi complex (Figure 1).[3] Especially challenging in the latter two structures is the placement of a bulky group in 3-position on the concave face of the bicyclic system.

In contrast, the cheloviolenes A (**4a**) and B (**4b**),[4] which differ from all of the other known 5-oxofuro[2,3-*b*]furans in their absolute stereochemistry at the 3a,6a ring junction, and many other spongiane diterpenoids have not yet been examined for biological activity at all, which is probably due to their limited availability.

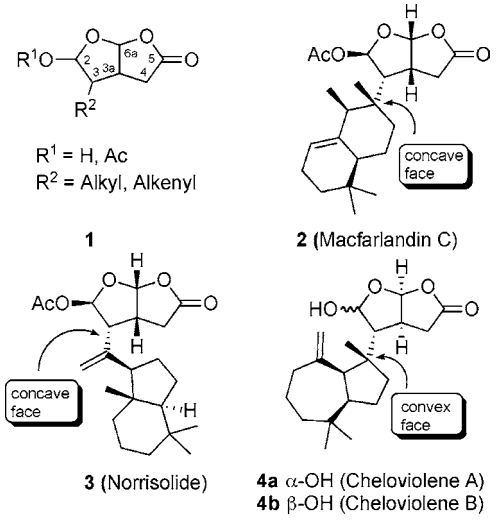


Figure 1. Natural products with 5-oxofuro[2,3-*b*]furan unit.

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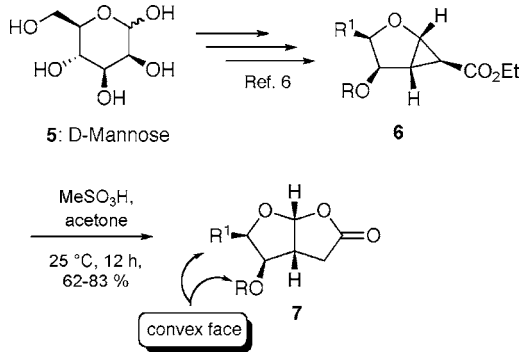
Few strategies for the synthesis of furo[2,3-*b*]furans have been reported,[5,6] with only one report making use of asymmetric catalysis.[5a] Most related to our work, Theodorakis and co-workers developed an elegant method to convert cyclopropanes **6** to the 5-oxofuro[2,3-*b*]furan **7** (Scheme 1);

Scheme 1

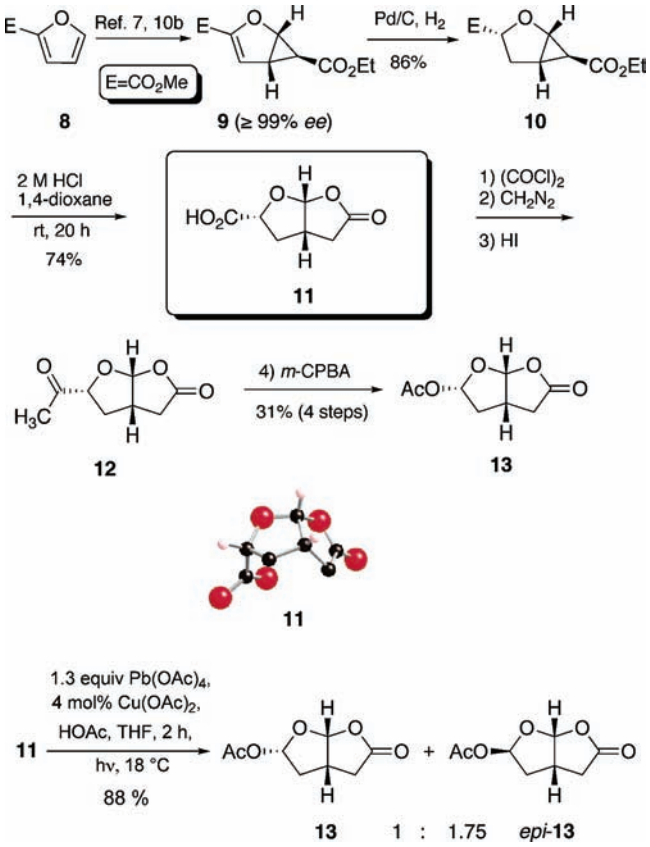


however, in all derivatives reported subsituents in 3-position are located on the *convex face* of the bicyclic ring system.[6] We report here a different strategy to compounds of type **6** and their subsequent rearrangement, giving not only access to the 5-oxofuro[2,3-*b*]furan framework with substituents in the 3-position on the *concave face* of the bicyclic framework, a pattern being found in most spongiane diterpenoids such as **2** or **3**, but also to 3a,6a-epimers, a pattern being found in the cheloviolenes **4**.

We recently reported the copper−bisoxazoline-catalyzed, enantioselective cyclopropanation of methyl 2-furoate (**8**) to **9**[7] as a starting point toward the synthesis of γ-butyrolactone natural products such as paraconic acids,[8,9] xanthanolides, guaianolides, and eudesmanolides.[10] We envisioned **9** to be a versatile building block toward a broad variety of derivatives of **6**, which could be subsequently converted to 5-oxofuro[2,3-*b*]furans.

As a proof of concept, **9** was hydrogenated, which proceeded exclusively from the convex face of the bicyclic framework to yield **10** as a single stereoisomer in 86% yield. Subsequent rearrangement to **11** (74%) using 2 M hydrochloric acid in 1,4-dioxane gave rise to the parent 5-oxofuro-[2,3-*b*]furan framework in only three steps from inexpensive methyl 2-furoate (**8**) in enantiomerically pure form (Scheme 2).

Scheme 2



The structure of **11**, having the carboxylic acid group positioned on the concave face of the bicyclic system, was unambiguously assigned by NOE experiments and by X-ray structure analysis. Conversion of the carboxylic acid to the acetoxy derivative **13**, being typical in many spongiane diterpenoids, was accomplished in a four-step sequence from **11** via its methyl ketone **12**, which underwent diastereoselective Baeyer−Villiger oxidation under retention of configuration. Alternatively, **11** could be photochemically decarboxylated[11] with lead tetraacetate under copper(II) catalysis following a radical pathway to directly yield a mixture of **13** and *epi*-**13**, which could be easily separated by chromatography.

Following this general strategy, we were next looking for flexible ways to stereoselectively introduce substituents into the 3-position of 5-oxofuro[2,3-*b*]furans (Scheme 3).

Thus, the vinylbromide **15**, which we anticipated to be a versatile building block for functionalization via palladium-

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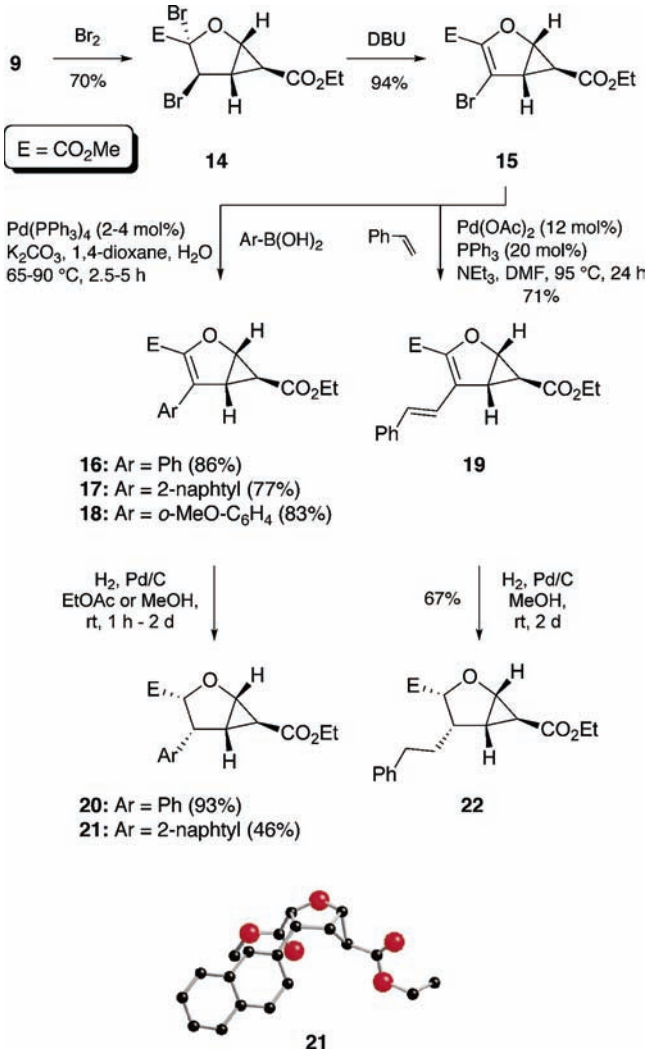
Scheme 3

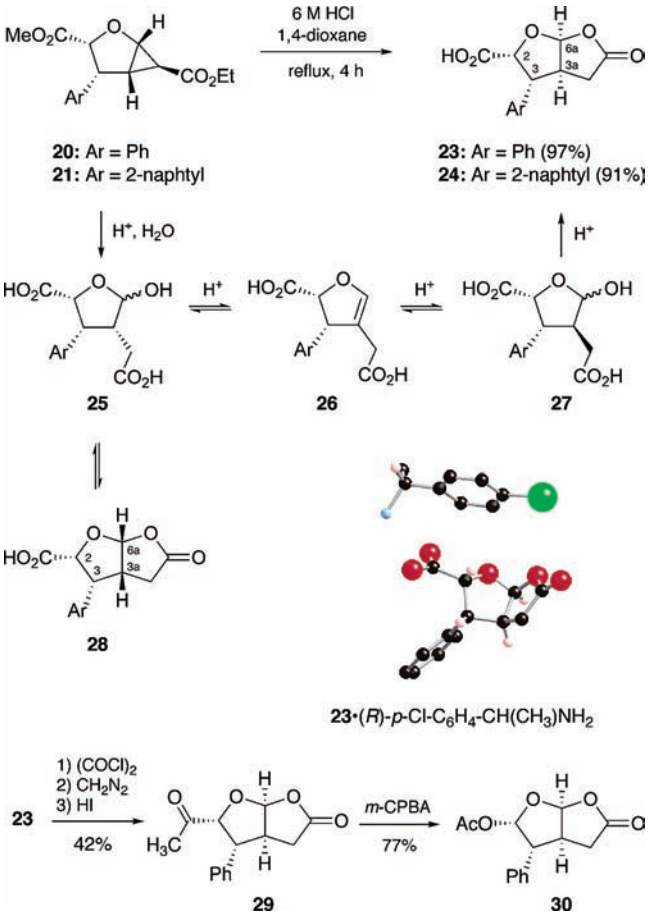


catalyzed cross-coupling reactions, was synthesized from **9** by a bromination/dehydrobromination sequence. Indeed, **15** proved to be amenable for both Suzuki-couplings of arylboronic acids and for Heck-coupling of styrene to give rise to **16**−**19** in good yields. Subsequent hydrogenation of the tetrasubstituted double bond was quite substrate dependent: While **16** gave excellent yields already in ethyl acetate after only 1 h, the use of methanol as a solvent and considerable longer reaction times (2 d) were necessary to achieve at least satisfying yields in the case of **17** and **19**.

Hydrogenation of **18** failed completely under various conditions, probably due to the additional steric hindrance of the methoxy group. Nevertheless, in all successful cases hydrogenation occurred exclusively from the *exo*-face of the bicyclus, resulting in highly congested derivatives in which the aryl and the ester group are forced on the concave side. X-ray structure analyses of **20** (not shown) and **21** as well as NOE experiments unambiguously proved these structural assignments.

Similar to **10**, acid-induced hydrolysis of **20** or **21** with concomitant rearrangement to the 5-oxofuro[2,3-*b*]furan framework could again be initiated at room temperature. However, the expected **28** was accompanied by uncyclized compounds, and already by small amounts of **23** or **24**. Compound **28** could not be isolated in pure form but was identified by ^{1}H NMR of the mixtures (Scheme 4). Upon

Scheme 4

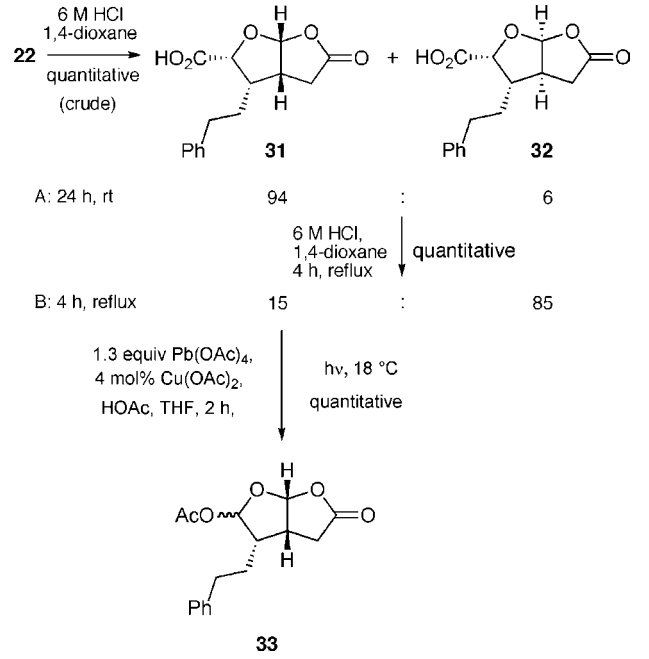


refluxing of these mixtures, **23** or **24**, respectively, could be isolated in high yields. Following these conversions by NMR, signals were observed in agreement with the 2,3-dihydrofuran **26**, which could explain the inversion of stereochemistry on the centers 3a,6a.

The relative stereochemistry of **23** and **24** was assigned from NOE data, and the absolute stereochemistry of **23** was proved by an X-ray structure analysis of its (1*R*)-1-(4-chlorophenyl)ethylammonium-salt. The latter analysis allowed ruling out that instead of the centers at position 3a and 6a the positions 2 and 3 were inverted, which would have also been conceivable under the acidic reaction conditions. Again, **23** could be converted to **30** in a straightforward manner as previously described for the transformation of **11** to **13** (cf. Scheme 2).

The stereochemistry for the rearrangement of **22**, having a medium sized substituent in 3-position, could be controlled to some extent (Scheme 5). At room temperature, along with

Scheme 5



some ring opened, not lactonized products, mainly **31** was formed, which could be isolated in pure form by crystallization in moderate yield (37%). Under refluxing conditions **32** was predominantly formed, which unfortunately could not be separated from **31**. Moreover, refluxing **31** in 6 M HCl and 1,4-dioxane resulted in the predominant formation of **32** in quantitative yield.

Oxidative decarboxylation of **31** proceeded quantitatively to give rise to **33** as an inseparable 1:3 α/β-mixture.

There had been considerable difficulties in the structure elucidation of 5-oxofuro[2,3-*b*]furan natural products with respect to the stereocenters at the 3a,6a ring junction. For example, for both cheloviolene A (**4a**) as well as dendrillolide A (**33**) the original structural assignment[12] had to be revised later on.[4,13] Our findings in the synthesis of **23**, **24**, **31**, and **32** suggest the close relation between the two 5-oxofuro-[2,3-*b*]furan frameworks found in nature and that under acidic conditions their rearrangement, e.g., that of dendrillolide A (**34**) to cheloviolene A (**4a**), should be feasible (Figure 2).

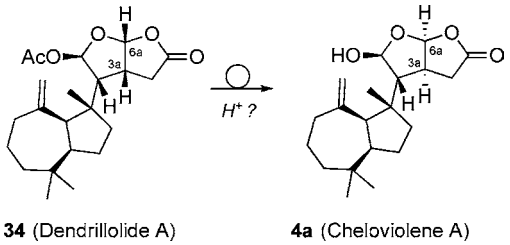


Figure 2. Possible chemical relation between cheloviolene A and dendrillolide A.

In conclusion, a synthetic strategy to 5-oxofuro[2,3-*b*]-furans was developed that allows the versatile introduction of carbon substituents in 3-position. The steric size of these groups has a decisive influence on the stereochemistry of the 3a,6a-ring junction, giving rise to bicyclic frameworks found in spongian diterpenoids such as **2**−**4**. The biological evaluation of the analogues of these natural products presented here and the application of the synthetic strategy toward spongians is currently underway.

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Supporting Information Available: Analytical data, CIF files of all X-ray structures, and copies of spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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