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An Unexpected Transannular [4+2] Cycloaddition during the Total Synthesis of (+)-Norcembrene 5

Michael Breunig[‡], Po Yuan[‡], and Tanja Gaich*

Dedicated to Prof. Dr. Johann Mulzer on the occasion of his 75th birthday

Abstract: We report a concise and versatile total synthesis of the diterpenoid (+)-norcembrene 5 from simple building blocks. A ring-closing metathesis as well as an auxiliary-directed 1,4-addition represent the key steps of our synthetic route. During the synthesis, an unprecedented, highly oxidized pentacyclic structure motif was established from a furanocembranoid via transannular [4+2] cycloaddition.

Norcembrenolides represent a large and diverse family of norditerpene natural products. The main source for isolation of norcembrenolides are gorgonian soft corals found in the Western Atlantic Ocean.[1] Most of these natural products were isolated from soft corals of the genus *Sinularia* (family: *Alcyoniidae*). Representative norcembrenolides **1**–**8** exhibit a variety of different functional group patterns embedded in a macrocyclic ring, which is present in all congeners (Figure 1).[2] Several of these compounds showed biological and pharmacological activities such as cytotoxicity or antiviral properties. Gyrosanin A[2d] (**2**) was tested positive on cytotoxicity against P-388 cancer cell lines (mouse lymphocytic leukemia). Sinuleptolide[2c] (**3**), norcembrenolide/5-episinuleptolide[2c] (**4**), scabrolide E[2e] (**5**), leptocladolide A[2f] (**6**) and 7*E*-leptocladolide A[2f] (**7**) showed strong to moderate cytotoxic activity both against KB (human oral epidermoid carcinoma) and Hepa59T/VGH (human liver carcinoma) cancer cell lines. Sinuleptolide (**3**) furthermore exhibited antiviral activity against HCMV (human cytomegalovirus) cells.[2d]

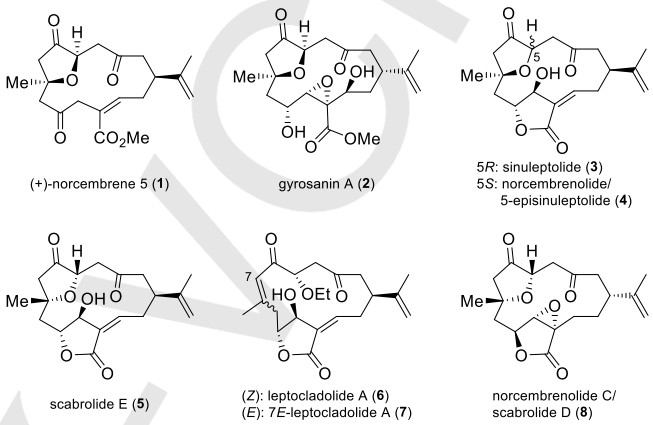

Figure 1. Representative norcembrenolide natural products.

Despite their unique molecular structure featuring a 14-membered cembrane ring, a bridging dihydrofuranone, and a lactone or ester motif, only a few accomplished (semi-)syntheses of norcembrenolides have been reported so far.[2b, 3]

Norcembrene 5 (**1**) was first isolated in 1985 by the groups of W. Fenical and J. Clardy.[2a] Its absolute configuration was not determined so far, and both enantiomeric structures of norcembrene 5 were reported in later isolations of this compound in literature, all referring to the original publication.[2c, 4] Therefore, its absolute configuration remained ambiguous.

Herewith, we report the total synthesis of norcembrene 5 as well as the elucidation of its absolute configuration. Comparison of the optical rotation of our synthesized material with literature revealed opposite signs (synthetic +51.4 vs. –77 for the isolated material), thus establishing the natural product as (–)-norcembrene 5.[2a] In a retrosynthetic fashion, (+)-norcembrene 5 (**1**) is assembled from furanocembranoid **9** (Scheme 1). In a biomimetic[3a] oxidation/transannular cyclization cascade the furan moiety is cleaved to the 3-furanone motif present in the natural product. In addition, methanolysis of the butenolide completes the transformations that convert **9** into **1**. The macrocycle of **9** is constructed via ring-closing metathesis (RCM) from triene **10**, which is accessible from aldehyde **11** and selenolactone **12** by aldol reaction. The stereocenter of **11** is introduced via an auxiliary-directed 1,4-addition on compound **13**, available from 2-allylfuran (**14**) by cross metathesis.

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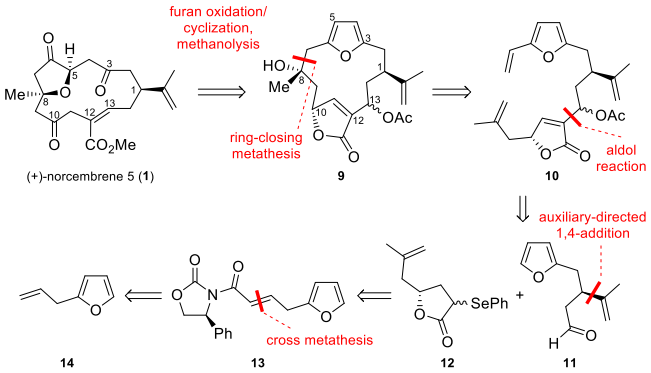
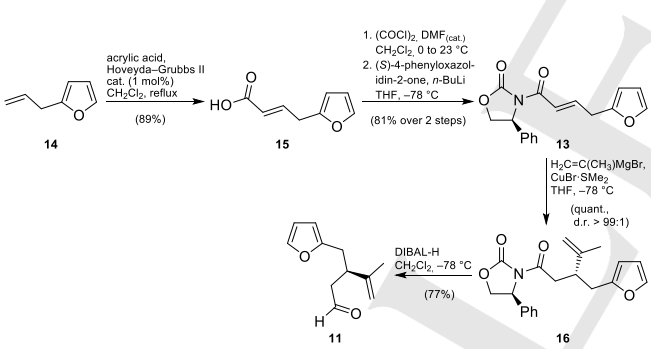


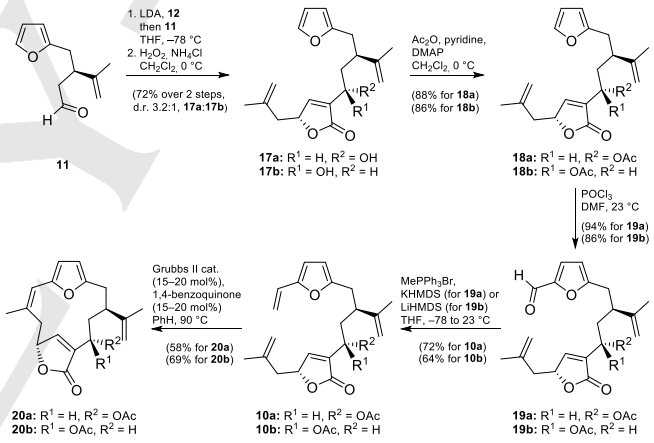
Scheme 1. Retrosynthetic analysis of (+)-norcembrene 5 (**1**).

Our synthesis began with the preparation of enantiopure aldehyde **11** (Scheme 2). Cross metathesis of 2-allylfuran[5] (**14**) with acrylic acid and Hoveyda–Grubbs II catalyst afforded unsaturated carboxylic acid **15** in high yields.[6] The Evans auxiliary for the stereoselective 1,4-addition was attached via amidation of the lithiated oxazolidinone with the in situ formed acid chloride from **15** furnishing enone **13** in 81% yield.[7] Diastereoselective installation of the isopropenyl moiety was performed using freshly recrystallized CuBr·SMe_2 as copper source.[8] Under optimized conditions, compound **16** was obtained in quantitative yield as single diastereomer. With this auxiliary-controlled 1,4-addition we introduced optical activity into the molecule. Subsequent reductive cleavage of the auxiliary directly afforded aldehyde **11** in 77% yield.



Scheme 2. Synthesis of enantiopure aldehyde **11**.

In the next sequence, the macrocycle of the furanocembranoid scaffold was established (Scheme 3). First, aldehyde **11** was assembled with selenolactone **12** (available in three steps from (*S*)-(–)-glycidol) via aldol reaction and subsequent oxidation/elimination under the conditions reported by Mulzer and co-workers.[9] The two diastereomeric butenolides **17a** and **17b** were obtained in a ratio of 3.2:1, were separated and used independently for further transformations. Acetylation of the secondary alcohol followed by Vilsmeier–Haack formylation[10] of the furan ring furnished aldehydes **19a** and **19b** both in high yields. Subsequent olefination of the aldehyde functionality initially caused synthetic drawbacks. After extensive experimentation, we found that the diastereomers **19a** and **19b** behaved differently in the Wittig olefination. **19a** was successfully converted to **10a** by using KHMDS as a base for ylide formation in 72% yield. By contrast, for the conversion of diastereomer **19b** LiHMDS gave better yields (64%) than the use of KHMDS (47%). With compounds **10a** and **10b** in hand, ring-closing metathesis as key step of the synthetic route could be performed. Initial studies for this transformation applying a continuous addition of Grubbs II catalyst to the starting material in refluxing benzene resulted in very inconsistent reaction yields varying from 9–53% of product. After screening a number of different reaction parameters, two distinct changes eventually gave reasonable access to the desired macrocycles **20a** and **20b**. First, 1,4-benzoquinone was added to the reaction mixture in catalytic amounts. In literature it is reported to prevent isomerization during olefin metathesis[11], but we suppose that it operated as scavenger for decomposition species formed by the catalyst at high temperatures. Secondly, the catalyst was added in several portions to the reaction mixture instead of a continuous addition. Under these optimized conditions, furanocembranoids **20a** and **20b** could be prepared in 58% and 69% yield, respectively.



Scheme 3. Synthesis of furanocembranoids **20a/b** via RCM reaction.

For further functionalization, the trisubstituted double bond of the macrocycle needed to be hydrated stereo- and regioselectively (Markovnikov). Since direct hydration such as Mukaiyama hydration failed, a two-step sequence consisting of Upjohn dihydroxylation[12] followed by deoxygenation of the secondary alcohol was applied (Scheme 4). Under similar conditions as established by Theodorakis and co-workers, furanocembranoid **20a** was treated with a mixture of OsO_4 and NMO to perform site-selective dihydroxylation of the cyclic C–C double bond.[2b] In doing so, diol **21a** could be afforded as single diastereomer in 46% yield. After preparation of **21a** we observed slow but spontaneous reaction of this compound to another product when stored in solution. Thorough characterization via 2D-NMR spectroscopy revealed, that **21a** underwent a transannular [4+2] cycloaddition between the furan and the butenolide moiety. In this transformation, pentacyclic compound **22** was formed as single diastereomer representing the *exo*-Diels–Alder product, which could be confirmed by NOESY experiments. This unprecedented

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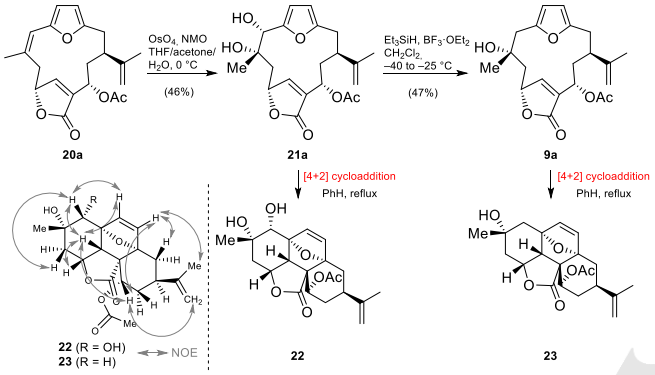
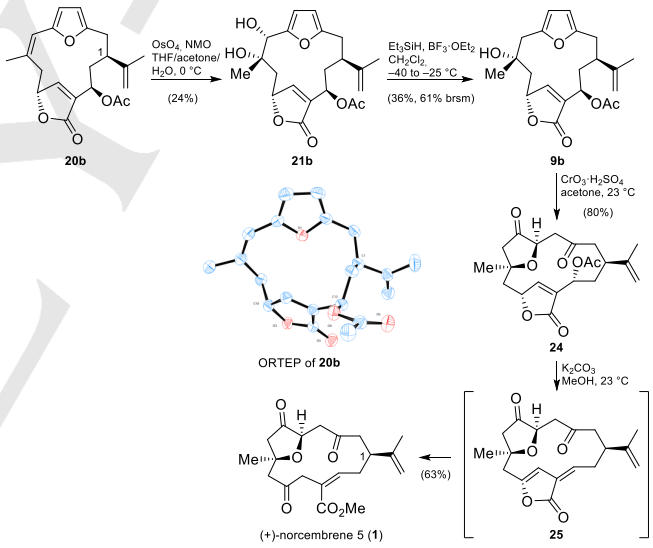
structure motif features a highly oxygenated and congested compound bearing eight stereocenters (five of them contiguous) and one quaternary carbon center. This motif is of interest for further SAR studies in the future. For better characterization, full conversion of **21a** to **22** was achieved by heating the starting material in refluxing benzene. Despite this unexpected transannular reaction we were able to convert diol **21a** into **9a** by deoxygenation of the secondary alcohol moiety. Treatment of **21a** with Et_3SiH and $BF_3{\cdot}OEt_2$ was fast enough to furnish alcohol **9a** in 47% yield[2b], before **21a** was able to undergo the undesired transannular [4+2] cycloaddition. Likewise, **9a** was prone to undergo transannular [4+2] cycloaddition to give pentacycle **23** as single product featuring identical stereochemical relationships.



Scheme 4. Site-selective hydration of furanocembranoid **20a** and [4+2] cycloaddition products **22**/**23** with key NOESY correlations.

This transannular [4+2] cycloaddition is of general interest, since similar transannular cycloadditions on these natural products have previously been reported and seem to reflect a general reactivity trend in this natural product family. In his synthesis of intricarene, D. Trauner relied on a transannular [5+2] oxidopyrylium cycloaddition of similar furanocembranoid bipinnatin J to obtain the natural product.[13] Another example is the transannular [2+2] photocycloaddition in an approach to bielschowskysin accomplished by L. West and S. P. Roche via a dearomatization of the furan ring with concomitant transannular [2+2] cycloaddition reaction.[14] These previously reported transannular cyclizations are considered to act in the actual biosynthesis of these natural products, thus contributing largely to the architectural diversity in the molecular scaffolds present in furanocemranoid diterpenes. Therefore, it is highly likely that in future isolation efforts novel natural product congeners with a molecular architecture of **22** and **23** will be discovered from *Sinularia* type soft corals, thus comprising an additional case of "natural product anticipation".[15]

The two-step sequence for hydration of the C–C double bond was also applied to diastereomeric furanocembranoid **20b** (Scheme 5), since direct Mukaiyama hydration proved to be unsuccessful as previously described for Scheme 4. However, applying the same reaction conditions for dihydroxylation (OsO_4/NMO) as for **20a** only gave unsatisfactory yields. The best results that could be obtained was 24% yield of diol **21b** despite screening different temperatures, solvent systems and concentrations. Other reagents for dihydroxylation such as AD-mix, K_2OsO_4/NMO or $RuCl_3/NaIO_4$ showed no reaction at all. Nevertheless, the synthesis was continued and by treatment of **21b** with $Et_3SiH/BF_3{\cdot}OEt_2$, alcohol **9b** was afforded in 36% yield (61% brsm). To our surprise, neither compound **21b** nor compound **9b** showed any tendency for transannular cycloaddition at all (see Figure 2 for further details). With **9b** in hand, oxidation of the furan moiety followed by 5-*exo*-trig cyclization of the tertiary alcohol was triggered upon treatment with Jones reagent to afford norcembrenolide **24** in high yields.[2b, 16] Finally, a sequence of deprotonation of the butenolide and elimination of the acetate group via intermediate **25**, followed by methanolysis of the lactone gave access to (+)-norcembrene 5 (**1**) in good yields. The absolute stereochemistry of **1** was established with the help of single crystal X-ray analysis of furanocembranoid **20b**. Since the absolute configuration at C1 was introduced earlier in the synthesis via the enantioselective 1,4-addition, all other stereocenters could be correlated.



Scheme 5. Preparation of (+)-norcembrene 5 (**1**) from furanocembranoid **20b**.

Since there was no obvious reason that could explain the different reactivity of compounds **21a**/**9a** (transannular [4+2] cycloaddition) and their diastereomeric compounds **21b**/**9b** (no transannular reaction), we performed DFT calculations for further clarification (Figure 2, for experimental details and calculated structures see Supporting Information). Therefore, we decided to calculate the Gibbs free energies of diol **21a** and its reaction product **22** via transition state **21a**‡. On the other hand, the free energies of diol **21b** and its (not observed) reaction product **22b** via transition state **21b**‡ were calculated. In doing so, the first interesting result was the clearly higher free energy and therefore higher reactivity of **21a** in comparison to **21b** (ΔG = 11.9 kcal/mol) in the ground state. As second result we observed the lower free energy of transition state **21a**‡ compared to possible transition state **21b**‡

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(ΔG = 4.47 kcal/mol). Both results further imply activation energies of 22.8 kcal/mol for the transition of **21a** to **21a**‡ (black dash) and 39.2 kcal/mol for the transition of **21b** to **21b**‡ (red dash). In conclusion, the activation barrier for diol **21b** is almost twice the amount as for **21a**. For this reason, it is very plausible that transannular Diels–Alder reaction of **21a** takes place, whereas compound **21b** fails to undergo the transannular reaction. Since compounds **9a**, **9b**, and **23** have the same molecular scaffolds and only differ in substitution pattern from **21a**, **21b**, and **22**, analogous behavior can be presumed.

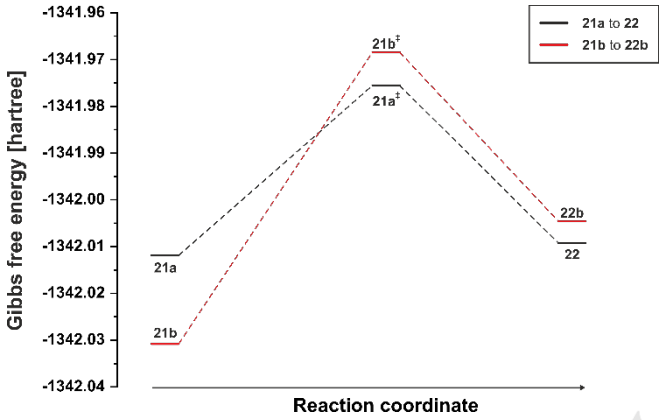

Figure 2. Comparison of Gibbs free energies of compounds **21a**/**b** and **22**/**22b** via **21a**/**b**‡ concerning transannular [4+2] cycloaddition based on DFT calculations.

In conclusion, we have established the absolute configuration of (–)-**1** and accomplished a concise synthetic route to its enantiomer (+)-norcembrene 5 (**1**) in 13 isolated steps from 2-allylfuran (**14**). An optimized ring-closing metathesis reaction was applied as a key step to assemble the 14-membered carbocyclic scaffold. Our route is very versatile and can be adopted for the synthesis of further furanocembranoids and norcembrenolides. In addition, we demonstrated the formation of the unprecedented and highly congested pentacyclic structure motifs **22** and **23** via transannular [4+2] cycloaddition. The frequent occurrence of transannular cycloaddition reactions in furanocembranoid (bio)-synthesis ([5+2] and [2+2]) strongly suggests that the molecular scaffold obtained from our transannular [4+2] cycloaddition is yet another case of natural product anticipation.

Acknowledgements

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Keywords: furanocembranoid • norcembrenolide • ring-closing metathesis • total synthesis • transannular [4+2] cycloaddition

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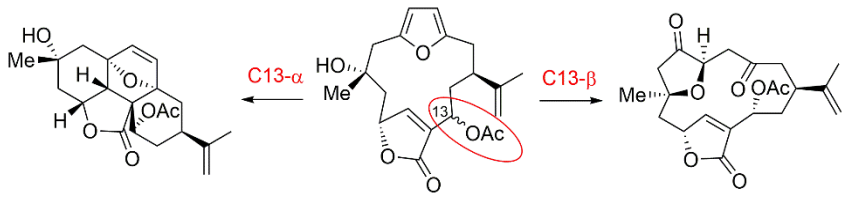

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An Unexpected Transannular [4+2] Cycloaddition during the Total Synthesis of (+)-Norcembrene 5

Different reactivities of diastereomeric compounds (at C13) were observed. The α-isomer underwent clean and spontaneous Diels–Alder reaction at room temperature, whereas the β-isomer did not undergo any Diels–Alder reaction, but was oxidized to the corresponding furanone, and was further transformed to norcembrene 5.