Natural Products Synthesis

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

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Dedicated to Professor 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. Ring-closing metathesis and an auxiliary-directed 1,4-addition are the key steps of our synthetic route. During the synthesis, an unprecedented, highly oxidized pentacyclic structural motif was established from a furanocembranoid through transannular [4+2] cycloaddition.*

Norcembrenolides are a large and diverse family of norditerpene natural products. The main source for the 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 show biological and pharmacological activity, such as cytotoxicity or antiviral properties. Gyrosanin A[2d] (**2**) tested positive for cytotoxicity against P-388 cancer cell lines (mouse lymphocytic leukemia). Sinuleptolide[2c] (**3**), norcembrenolide/5-epis-inuleptolide[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] 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 Fenical and 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, all referring to the original publication.[2c,4] Therefore, its absolute configuration remained ambiguous.

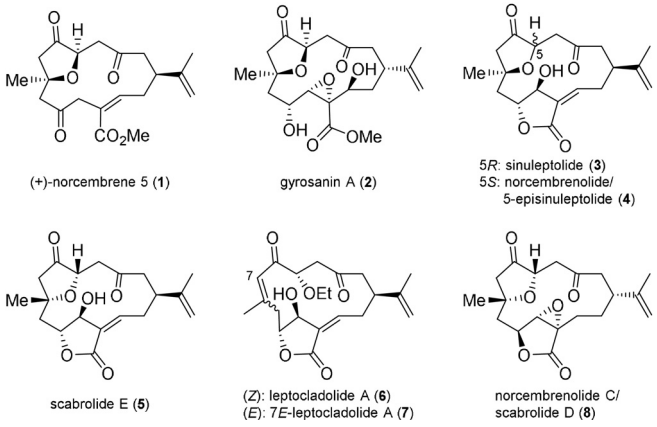
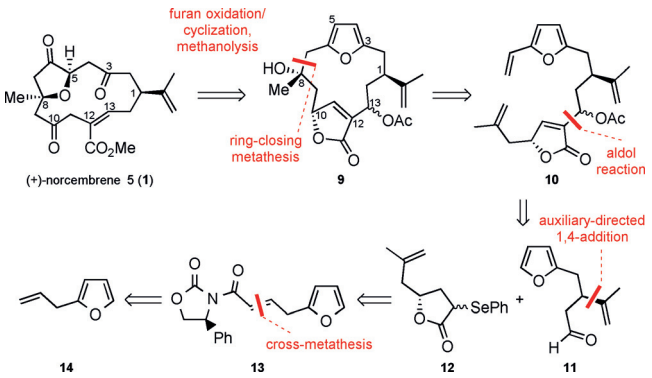


Figure 1. Representative norcembrenolide natural products.

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 the literature value revealed opposite signs (synthetic +51.4 vs. −77 for the isolated material), thus establishing the natural product as (−)-norcembrene 5.[2a] Retrosynthetically, (+)-norcembrene 5 (**1**) can be 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. Methanolysis of the butenolide completes the transformation of **9** into **1**. The macrocycle of **9** is constructed by ring-closing metathesis (RCM) from triene **10**, which is



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

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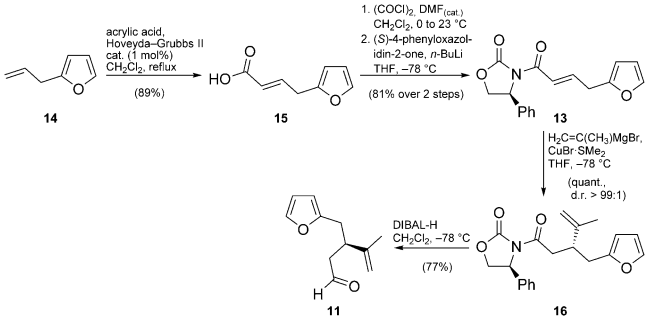
accessible from aldehyde **11** and selenolactone **12** by an aldol reaction. The stereocenter of **11** is introduced through auxiliary-directed 1,4-addition to compound **13**, available from 2-allylfuran (**14**) by cross-metathesis.

Our synthesis began with the preparation of enantiomerically pure aldehyde **11** (Scheme 2). Cross-metathesis of 2-allylfuran[5] (**14**) with acrylic acid and the Hoveyda–Grubbs II



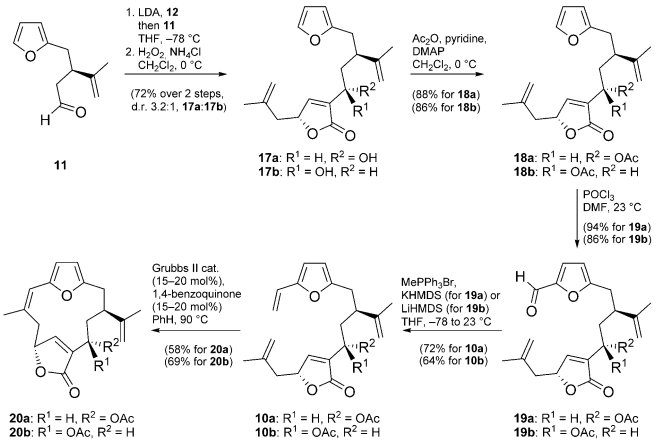
Scheme 2. Synthesis of enantiomerically pure aldehyde **11**. DIBAL-H = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide.

catalyst afforded unsaturated carboxylic acid **15** in high yield.[6] The Evans auxiliary for the stereoselective 1,4-addition was attached by amidation of the lithiated oxazolidinone with the acid chloride formed in situ from **15** to furnish enone **13** in 81 % yield.[7] Diastereoselective installation of the isopropenyl moiety was performed using freshly recrystallized $CuBr{\cdot}SMe_2$ as the copper source.[8] Under optimized conditions, compound **16** was obtained in quantitative yield as a single diastereomer. Subsequent reductive cleavage of the auxiliary directly afforded aldehyde **11** in 77 % yield.

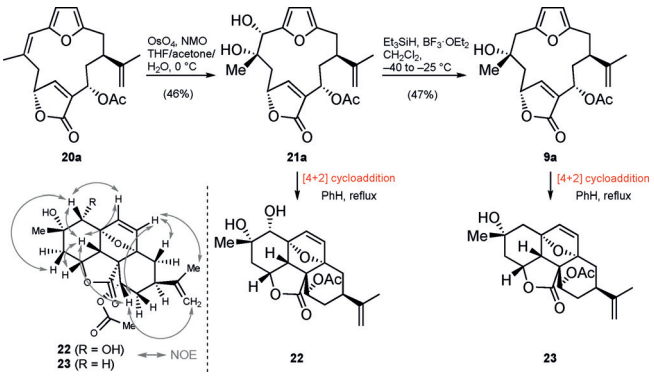
In the next sequence, the macrocycle of the furanocembranoid scaffold was established (Scheme 3). First, aldehyde **11** was assembled with selenolactone **12** (available in three steps from (*S*)-(−)-glycidol) through an aldol reaction and subsequent oxidation/elimination under the conditions reported by Mulzer and co-workers.[9] The two diastereomeric butenolides **17a** and **17b** were obtained in a ratio of 3.2:1, and 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 yield. 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. Compound **19a** was successfully converted into **10a** by using KHMDS as a base for ylide formation in 72 % yield. By contrast, for the conversion of diastereomer **19b**, LiHMDS gave **10b** in better yield (64 %) than the use of KHMDS (47 %).

With compounds **10a** and **10b** in hand, ring-closing metathesis as the key step of the synthetic route could be performed. Initial studies for this transformation involving the continuous addition of Grubbs II catalyst to the starting material in refluxing benzene resulted in very inconsistent product yields varying from 9 to 53 %. 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. This additive has been 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. Second, the catalyst was added in several portions to the reaction mixture instead of being added continuously. Under these optimized conditions, furanocembranoids **20a** and **20b** could be prepared in 58 and 69 % yield, respectively.

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 enable site-selective dihydroxylation of the C–C double bond[2b] to give diol **21a** as a single



Scheme 3. Synthesis of furanocembranoids **20a**/**b** by a ring-closing metathesis reaction. DMAP = 4-dimethylaminopyridine, HMDS = hexamethyldisilazide, LDA = lithium diisopropylamide.

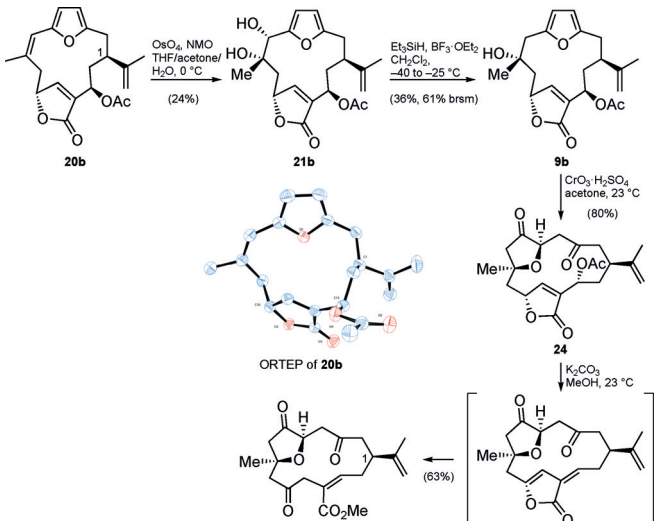


Scheme 4. Site-selective hydration of furanocembranoid **20a** and [4+2] cycloaddition products **22**/**23** with key NOESY correlations. NMO = 4-methylmorpholine *N*-oxide.

diastereomer in 46% yield. After the preparation of **21a**, we observed slow but spontaneous conversion of this compound into another product when stored in solution. Thorough characterization by 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**, the *exo*-Diels–Alder product, was formed as a single diastereomer, as confirmed by NOESY experiments. This unprecedented highly oxygenated and congested structure contains a quaternary carbon center and eight other stereocenters (five of them contiguous). This motif is of interest for further structure–activity relationship (SAR) studies in the future. For better characterization, we heated **21a** in benzene at reflux to promote full conversion into **22**. 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. Similarly, **9a** was prone to undergo transannular [4+2] cycloaddition to give pentacycle **23** as a single product featuring identical stereochemical relationships.

This transannular [4+2] cycloaddition is of general interest, since similar transannular cycloadditions of these natural products have been reported previously and seem to reflect a general reactivity trend in this natural product family. In their synthesis of intricarene, Trauner and co-workers relied on a transannular [5+2] oxidopyrylium cycloaddition of the similar furanocembranoid bipinnatin J to obtain the natural product.[13] Another example is the transannular [2+2] photocycloaddition in an approach to bielschowskysin by West, Roche, and co-workers through dearomatization of a furan ring with a concomitant transannular [2+2] cycloaddition reaction.[14b] These previously reported transannular cyclizations are considered to occur 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 the 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 described for **20a**. However, applying the same reaction conditions for dihydroxylation (OsO_4/NMO) as for **20a** only gave unsatisfactory yields. The best result that could be obtained was a 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 to undergo transannular cycloaddition at all (see Figure 2 for further details). Oxidation of the furan moiety of **9b**, followed by 5-



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

exo-trig cyclization of the tertiary alcohol, was triggered by treatment with the Jones reagent to afford norcembrenolide **24** in high yield.[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 yield. The absolute configuration of **1** was established with the help of single-crystal X-ray analysis of furanocembranoid **20b**. Since the C1 stereocenter was introduced earlier in the synthesis through the enantioselective 1,4-addition, the configuration of all other stereocenters could be deduced by correlation.

Since there was no obvious explanation for the different reactivity of compounds **21a**/**9a** (transannular [4+2] cycloaddition) and their diastereomers **21b**/**9b** (no transannular reaction), we performed DFT calculations for further clarification (Figure 2; for experimental details and calculated structures, see the Supporting Information). We calculated the Gibbs free energies of diol **21a** and its reaction product **22**

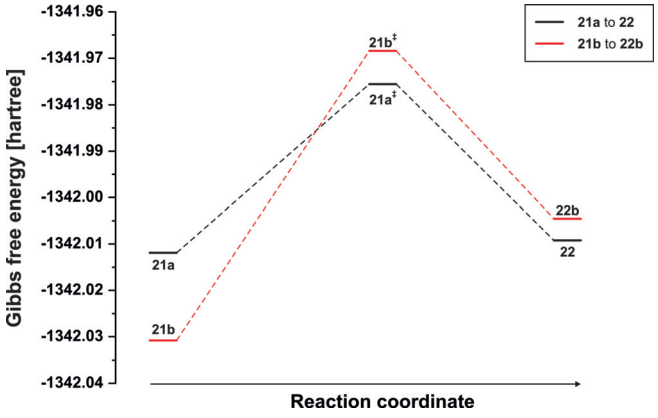


Figure 2. Comparison of the Gibbs free energies of compounds **21a/b** and the corresponding products of transannular [4+2] cycloaddition **22**/**22b** via **21a/b**$^{+}$ as based on DFT calculations.

via transition state **21a**$^+$, as well as the Gibbs free energies of diol **21b** and its (not observed) reaction product **22b** via transition state **21b**$^+$. The first interesting result was the clearly higher free energy and therefore higher reactivity of **21a** in comparison to **21b** ($\Delta G = 11.9$ kcal mol^{-1}) in the ground state. We also observed a lower free energy of transition state **21a**$^+$ as compared to the possible transition state **21b**$^+$ ($\Delta G = 4.47$ kcal mol^{-1}). These results imply activation energies of 22.8 kcal mol^{-1} for the transition of **21a** to **21a**$^+$ (black dash) and 39.2 kcal mol^{-1} for the transition of **21b** to **21b**$^+$ (red dash). In conclusion, the activation barrier for diol **21b** is almost twice that for **21a**. It appears that for this reason, the 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 their substitution pattern from **21a**, **21b**, and **22**, analogous behavior can be presumed.

In conclusion, we have established the absolute configuration of (−)-**1** and completed a concise synthetic route to its enantiomer (+)-norcembrene 5 (**1**) in 13 steps (requiring isolation of the product) 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 could be adopted for the synthesis of further furanocembranoids and norcembrenolides. In addition, we demonstrated the formation of the unprecedented and highly congested pentacyclic structures **22** and **23** through transannular [4+2] cycloaddition. The frequent occurrence of transannular ([5+2] and [2+2]) cycloaddition reactions in furanocembranoid (bio)synthesis strongly suggests that the molecular scaffold obtained from our transannular [4+2] cycloaddition may be yet another case of natural product anticipation.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Diels–Alder reaction · ring-closing metathesis · terpenoids · total synthesis · transannular cycloaddition

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