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Transannular *O*-Heterocyclization: A Useful Tool for the Total Synthesis of Murisolin and 16,19-*cis*-Murisolin

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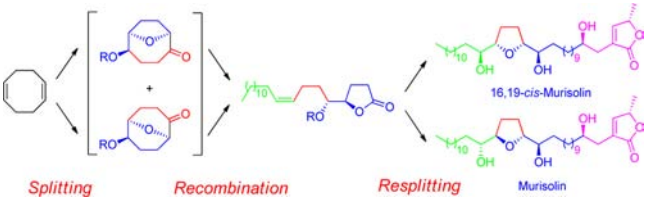
ABSTRACT



Transannular *O*-heterocyclization is applied as a key step in a total synthesis. This highly stereoselective and metal-free transformation introduces four stereocenters in one step. It was chosen to be the pivotal step in the synthesis of Murisolin and 16,19-*cis*-Murisolin, two annonaceous acetogenins. The efficiency of this synthesis is further illustrated by a stereodivergent late-stage separation of both synthetic routes.

Annonaceous acetogenins (ACGs) belong to a class of polyketide natural products whose structural diversity and manifold biological activity have drawn scientific attention since their discovery in 1982.[1,2] Special interest is attracted by the conspicuously high cytotoxicity of these compounds which rivals that of taxol.[3] Thus, ACGs might serve as lead structures for potential drugs in e.g. cancer therapy. Inhibition of the mitochondrial NADH dehydrogenase complex I is thought to be the specific mode of action.[4] Recent results show that the efficiency of Ca^{2+} chelation by ACGs correlates with their cytotoxicity.[5] Typically, their structure consists of an unbranched C_{32} or C_{34} chain with a terminal γ-lactone ring. Different oxygen-containing functional groups are located along the carbon chain, such as epoxides, ketones, and especially hydroxyl-flanked THF motifs. Both moieties are active pharmacophores.[4,5]

Up to now, more than 500 ACGs were isolated from *Annonaceae*;[6] in many cases a different relative and absolute configuration is the only distinction. This unique structural diversity reveals the challenges in the synthesis of these compounds despite their apparent simple structure. A high versatility and elegance for the introduction of stereocenters and for the connection of different functional structure elements along the carbon chain is desirable.

For the synthesis of the central hydroxyalkyl-flanked THF moiety, different strategies have been developed. These

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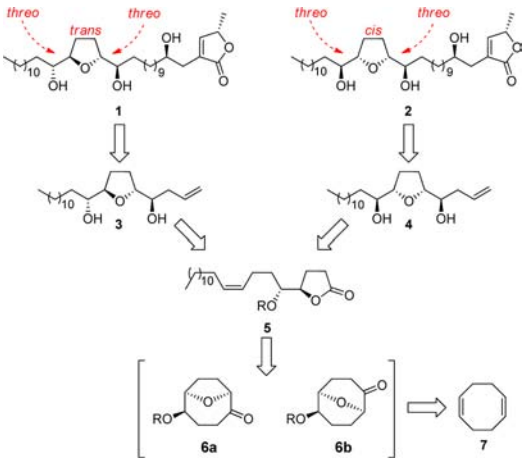
include enantioselective dihydroxylation[7] or epoxidation and adjacent epoxide opening/THF closing sequences,[8] RuO_4-catalyzed oxidative cyclizations of 1,5-dienes,[9] exploitation of the chiral pool,[10] the use of chiral auxiliaries,[11] asymmetric alkynylations,[12] cyclizing iodoetherifications[13] and oxymercurations[14] of unsaturated alcohols, or the application of stereoselective stannylation chemistry,[15] among others.

Encouraged by our former work on different transannular *O*-heterocyclizations[16] we have chosen this type of reaction as the pivotal step for the synthesis of Murisolin (**1**)[17] and its stereoisomer 16,19-*cis*-Murisolin (**2**).[18] We identified these two compounds as exemplary targets for the development of a novel Lego-like building block strategy and promising approach toward the total synthesis of ACGs.[19]

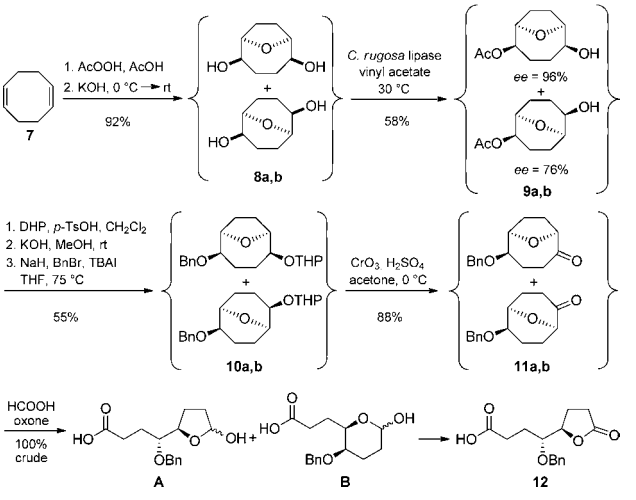
Retrosynthetically, an alkene cross-metathesis was destined for the introduction of the terminal butenolide fragment, whereas precursors **3** and **4** should be available from the common intermediate **5** by stereoselective dihydroxylation and cyclization. Connected to this is the late stage separation of both synthetic routes, which minimizes the total number of transformations. **5** was supposed to be obtained by a Wittig reaction after Baeyer–Villiger oxidation of bicyclic ketones **6a,b**. These are accessible as a mixture from the products of a transannular *O*-heterocyclization of cycloocta-1,5-diene (**7**)[16d–f] (Scheme 1). To the best of our knowledge, it is the first application of a transannular *O*-heterocyclization in total synthesis.

Scheme 1. Retrosynthetic Analysis of Murisolin (**1**) and 16,19-*cis*-Murisolin (**2**)



In the first step, inexpensive **7** and 40% peracetic acid were used for a highly stereoselective metal-free formal introduction of four stereocenters. Diols **8a,b** were obtained as an inseparable 45:55 mixture in 92% yield.[16d–f,20] Kinetic resolution or desymmetrization, respectively, gave a 62:38 mixture of acetates **9a** (96% *ee*) and **9b** (76% *ee*) (^{1}H NMR of Mosher esters) by using lipase from *Candida rugosa* (Scheme 2).

Scheme 2. Synthesis and Oxidative Ring Opening of Bicyclic Precursors



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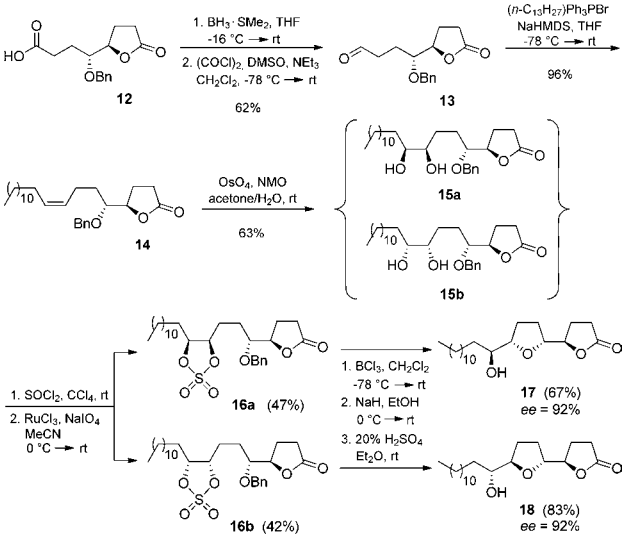
After protecting group operations, the protected diols **10a,b** were transferred into the bicyclic ketones **11a,b** by *in situ* deprotection and Jones oxidation. Baeyer–Villiger oxidation of **11a,b** leads convergently to just one single γ-lactone **12** via lactol intermediate **A**. In a previous work we revealed that intermediates of type **B** rearranged to type **A** without loss of optical purity.[16b] Here, the formerly applied reagents TFA and sodium percarbonate[16f] caused additional oxidation of the benzyl group and hydrolysis of the formed benzoyl group, whereas the milder acetic acid/percarbonate system left the ketone moiety untouched. Finally, formic acid and oxone were found as an appropriate oxidizing system to obtain the desired carboxylic acid **12**.

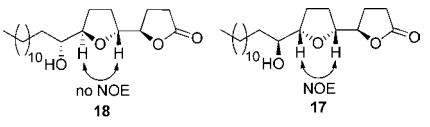
Chemoselective reduction of **12** and Swern oxidation of the formed alcohol gave aldehyde **13** as a precursor for the following Wittig reaction to receive the *Z*-alkene **14** contaminated with 4% of the *E*-isomer. The following *cis*-dihydroxylation and subsequent formation of cyclic sulfates **16a,b** was followed by the separation of the diastereomers by simple column chromatography and hence splitting of the synthetic routes toward Murisolin and 16,19-*cis*-Murisolin (Scheme 3).

Benzyl deprotection led to spontaneous cyclization and formation of the central THF core for both natural products. Final hydrolysis of the sulfates with 20% H_2SO_4 furnished the key intermediates **17** and **18** in 67% and 83%, respectively, over these three steps. Both compounds were received with each 92% *ee* and the required *threo-cis-threo* and *threo-trans-threo* relative configuration, which was confirmed by NOE-NMR experiments[21] and X-ray analysis (Figure 1).[22]

Scheme 3. Stereodivergent Separation of the Routes towards the Key Intermediates **17** and **18**



(21) The relative configuration of diastereomers **17** and **18** was assigned by NOE NMR measurements, and the enantiomeric excess was determined by chiral HPLC (see Supporting Information):



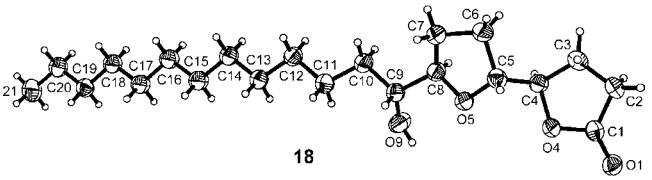
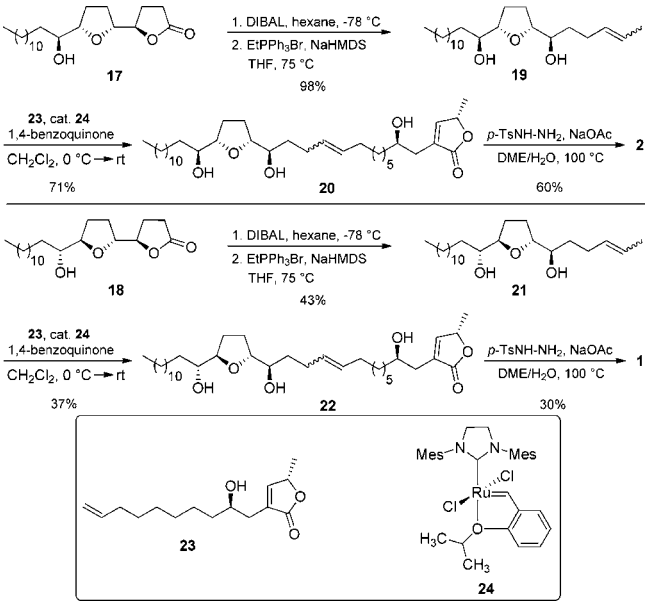


Figure 1. X-ray structure of compound **18**.

To complete the synthesis of **1** and **2**, the lactones **17** and **18** were transferred to alkenes **19** and **21** in a one-pot DIBAL reduction and a subsequent Wittig reaction. In the first attempt the methyl Wittig reagent was used and terminal alkenes were obtained instead of internal alkenes **19** and **21**. Unfortunately, the terminal alkenes under went a double-bond isomerization catalyzed by **24** to form 2-alkenes resulting in a partial chain shortening during the following cross-metathesis step with the known butenolide bearing alkene **23**.[23] Therefore, the expected products **20** and **22** were isolated together with their analogues shortened by one CH_2 group as inseparable mixtures. The use of internal alkenes **19** and **21** and 1,4-benzoquinone as an additive for the metathesis[24] nicely solved this problem. Despite this optimization, the metathesis steps remained erratic yielding 71% or 37% of the product (Scheme 4). After final diimide reduction[25] of the internal double bond both natural products Murisolin (**1**) and 16,19-*cis*-Murisolin (**2**) were obtained. For both compounds NMR and mass spectra as well as analytical data were in agreement with those reported.[26]

Scheme 4. Final Steps towards Murisolin (**1**) and 16,19-*cis*-Murisolin (**2**)[a]



In summary, a transannular *O*-heterocyclization was applied for the selective construction of stereocenters in a

total synthesis for the first time. By means of this key step a synthetic access to ACGs was developed. In 18 steps Murisolin (**1**) and 16,19-*cis*-Murisolin (**2**) were prepared exemplarily in 1.6% or 0.2% overall yields. Especially key compounds **17** and **18** are useful for the synthesis of similar ACGs. A late stage splitting of both synthetic routes depicts another special feature of this synthesis. Because transannular *O*-heterocyclization seems to be superior to the stepwise introduction of single stereocenters, studies toward the synthesis of other ACGs and more complex target molecules are ongoing. The exploitation of such a facile and inexpensive tool in future syntheses might be an option to metal-mediated operations.

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Supporting Information Available. Experimental procedures, analytical and spectral data, determination of enantiomeric excesses, and copies of the NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(22) X-ray crystal structure analysis for **18**: formula $C_{21}H_{38}O_4$, M = 354.51, colorless crystal 0.80 × 0.10 × 0.03 mm^3, a = 5.2688(2) Å, b = 7.4978(5) Å, c = 52.7860(20) Å, V = 2085.28(18) Å^3, ρ_{calc} = 1.129 g cm^{-3}, μ = 0.600 cm^{-1}, empirical absorption correction (0.645 ≤ T ≤ 0.982), Z = 4, orthorhombic, space group $P2_12_12_1$ (No. 19), λ = 1.54178 Å, T = 223 K, ω and φ scans, 28 582 reflections collected (±h, ±k, ±l), [(sin θ)/λ] = 0.60 Å^{-1}, 3345 independent (R_{int} = 0.058) and 3345 observed reflections [$I \geq 2\sigma(I)$], 228 refined parameters, R = 0.037, wR^2 = 0.105, max. residual electron density 0.12 (−0.14) e Å^{-3}, Flack parameter −0.1(2), hydrogens calculated and refined as riding atoms. CCDC 905530 contains the supplementary crystallographic data for compound **18**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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