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Total Syntheses of 7,20-Oxa-Bridged Dinorditerpenes: Antihepatitis C Virus Active (+)-Elevenol from *Flueggea virosa* and (+)-Przewalskin

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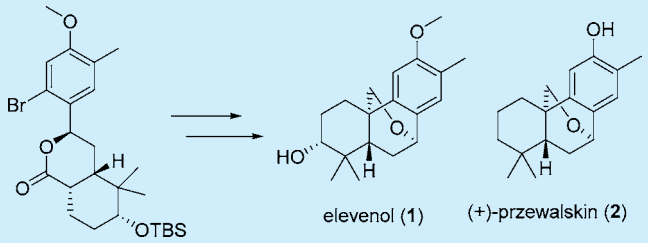
Supporting Information

ABSTRACT: An efficient stereoselective synthetic approach to 7−20 oxa-bridged abietane type natural products is reported. Key steps are an asymmetric Mukaiyama aldol addition to construct the C3 stereocenter and an intramolecular organocatalyzed Stetter-type Michael addition followed by a Tishchenko reaction. An intramolecular lactone−enolate arylation delivers the tetracyclic skeleton. This synthetic strategy was applied for the first total synthesis of (+)-elevenol, an antihepatitis C active compound from *Fluegga virosa*, and the first total synthesis of (+)-przewalskin.



In 2014 Chao, Wu et al. reported a novel antihepatitis C virus dinorditerpene from the roots of *Fluegga virosa*.[1] Using a J6JFH-based hepatitis C virus cell culture infection system, promising antiviral activity was observed (EC_{50} 7.5 μm, IC_{50} 419 μM, TI 55.9). Based on NMR spectroscopic data including Mosher's ester analysis structure **1** was proposed for the new compound (Figure 1). The new natural product with the

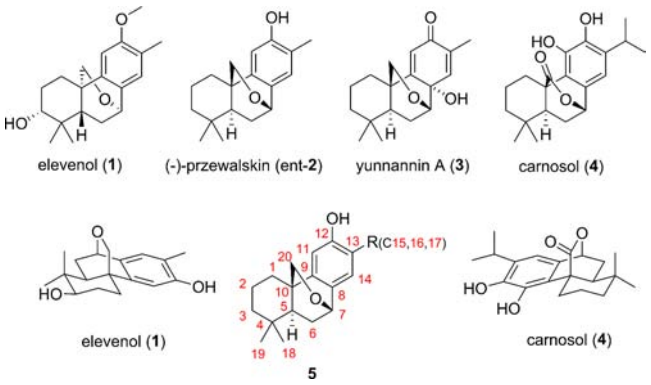


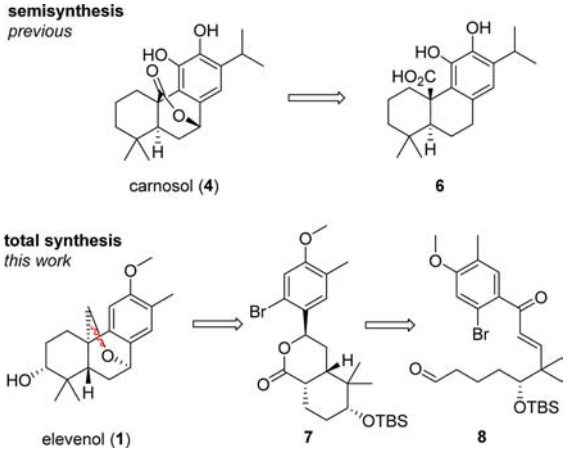
Figure 1. Structure of 7−20 oxa-bridged abietane type natural products.

systematic name 7α,20-epoxy-3α-hydroxy-12-methoxy-13-methyl-*ent*-podocarp-8,11,13-triene was named "compound 11" by the authors. For reasons of brevity, we propose the use of the name elevenol.

Together with przewalskin (**2**),[2] yunnanin A (**3**),[3] and carnosol (**4**),[4] elevenol (**1**) belongs to a group of 7−20 oxa-bridged dinorditerpenes and diterpenes. According to the majority of publications in this area the abietane based numbering illustrated in the common basic structure **5** is used within this work.

Semisynthetic access toward these natural products has so far been limited to carnosol (**4**) and used a benzylic C7 oxidation of the precursor **6** (Scheme 1).[5−7] Synthetic studies with model

Scheme 1. Retrosynthetic Analysis



systems were reported.[8] Here, we present a strategy for the total synthesis of elevenol (**1**) which can be adopted for all 7−20 oxa-bridged abietane type compounds. Key steps are construction of the C9,10 bond via an intramolecular lactone arylation of compound **7** which we considered could derive from an intramolecular Stetter-type Michael addition on the aldehyde **8** followed by proper redox manipulation.

The starting point for the synthesis of aldehyde **13** was the aldehyde **9** (Scheme 2), which can be prepared in two steps from 1,5-pentane diol.[9] An asymmetric Mukaiyama aldol

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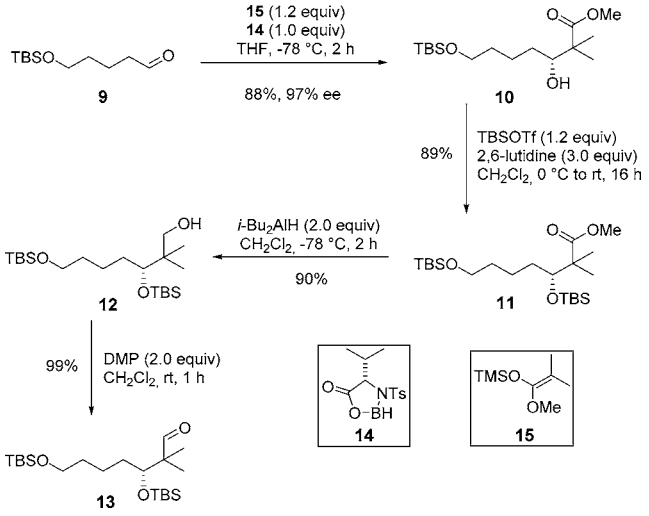
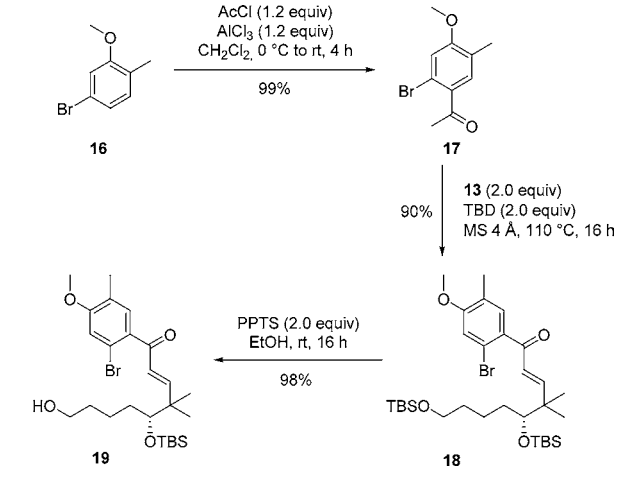
Scheme 2. Synthesis of Aldehyde 13



addition with silyl ketene acetal **15** and the Kiyooka chiral borane reagent **14**[10] provided the alcohol **10** in good yield and excellent enantiomeric excess. The protection of alcohol **10** using TBSOTf and 2,6-lutidine gave ester **11** in 89% yield. Reduction of ester **11** with DIBAH led to alcohol **12** which was transformed almost quantitatively into aldehyde **13** with Dess-Martin periodinane (DMP).

However, the sensitive aldehyde **13** was used directly for the following aldol condensation (Scheme 3). Friedel–Crafts

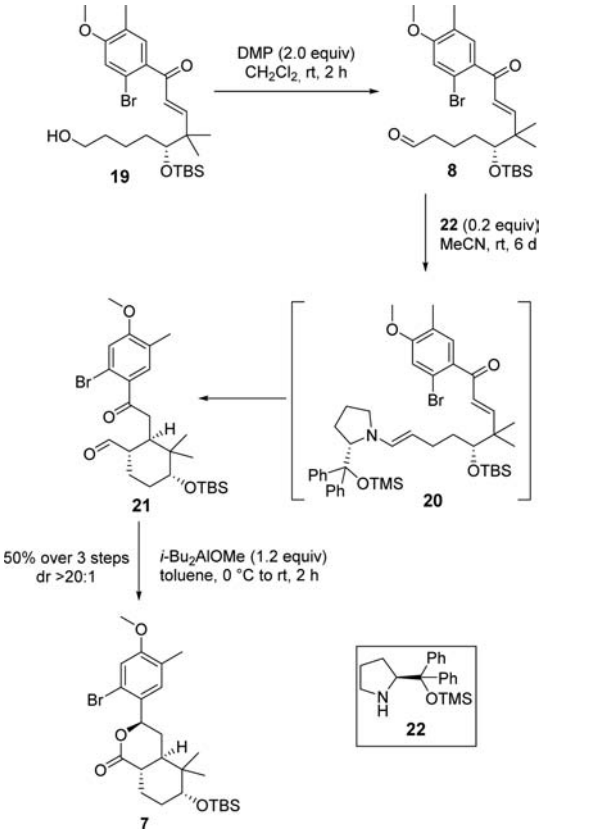
Scheme 3. Synthesis of Alcohol 19



acylation of **16** gave acetophenone **17** in excellent yield. Subsequent aldol condensation with aldehyde **13** gave the enone **18**. However, the use of KOH in methanol to mediate the reaction resulted in incomplete conversion of the starting material. Changing the base to the bicyclic guanidine base, 1,3,5-triazabicyclo[4.4.0]dec-5-ene (TBD), and addition of molecular sieves did however improve the yield of enone **18** up to 90%. The deprotection of the primary TBS-ether of **18** under acidic condition gave the desired alcohol **19**.

Oxidation of the alcohol **19** with DMP provided the unstable aldehyde **8** (Scheme 4) which was directly used in the next step to construct cyclohexane derivate **21** diastereoselectively (Scheme 4). Related enantioselective enamine-catalyzed intramolecular Michael additions have been reported by several

Scheme 4. Synthesis of Lactone 7



groups.[11] Therefore, different catalysts such as proline or the MacMillan catalyst were tested, but only the diphenylprolinol derivate **22** gave via the enamine intermediate **20** the *trans* product **21** in an excellent diastereomeric ratio of >20:1. Literature additives, such as TFA, were tested but did not improve neither yield nor reaction time. An intramolecular Tishchenko reaction of the keto aldehyde **21** produced the desired lactone **7** as a single diastereomer.[12]

With lactone **7** in hand the palladium catalyzed intramolecular lactone arylation was investigated to obtain **23** (Scheme 5). This α-arylation is an important tool to form C–C bonds[13] and required careful optimization of the base for enolate generation and the Pd-catalyst. Different bases were tested to generate the enolate. With LDA decomposition of the lactone, functionality was observed. Weaker bases such as KO*t*Bu gave no turnover. NaHMDS was the only base tested which gave the product in very good yield and as a single diastereomer. The countercation is important for the reaction. For instance, switching the base to KHMDS or LiHMDS leads to no formation of the desired product **23**. After testing different literature known palladium catalyst systems for α-arylation of esters,[14] such as $[(t\text{-}Bu_3P)PdBr]_2$, $Pd(dba)_2/t\text{-}Bu_3P$, and $Pd(OAc)_2$/DavePhos, $Pd(dba)_2$/SIPr **25** was identified as the best catalyst, giving the desired product **23** in 98% yield. The arylated lactone **23** was unstable under aqueous acidic or basic conditions. Attempts to purify **23** directly by silica chromatography resulted in decomposition of the product. The product was therefore purified by chromatography on alumina (neutral III). The hydrolytic instability of compound **23** could be explained by steric strain resulting from the 1,3-diaxial interaction between the methyl group and the lactone.

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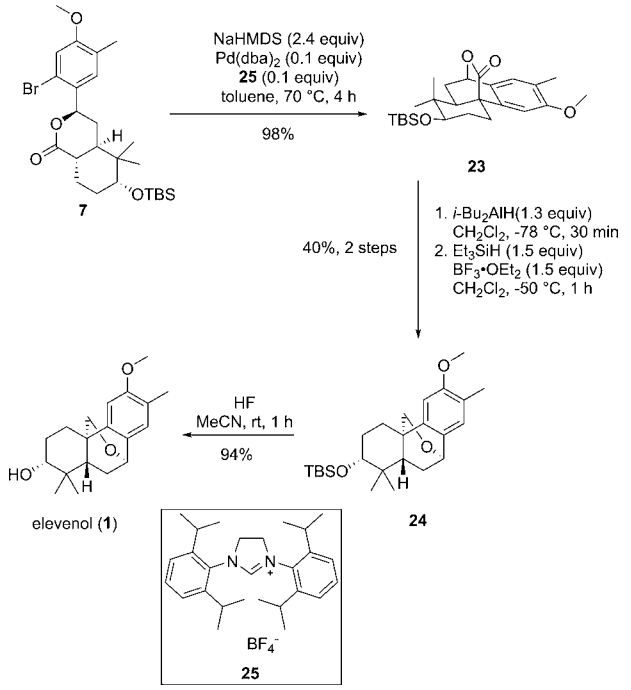
Scheme 5. Synthesis of (+)-Elevenol (1)



DIBAL-H-reduction of the lactone **23** gave the corresponding lactol which was subjected to ionic reduction[15] to yield the tetrahydropyran **24**. TBS-deprotection of **24** yielded the natural product elevenol (**1**) which was identical in its spectroscopic data with the data reported by Chao, Wu et al.[1] (optical rotation (*c* 0.50, $CHCl_3$) $[\alpha]_D^{25}$= +57, $[\alpha]_D^{25}$= +54 (*c* 0.25, $CHCl_3$)[1]).

An X-ray crystal structure analysis of synthetic elevenol (**1**) confirmed the structural assignment and the stereochemical course of the synthesis (Figure 2)

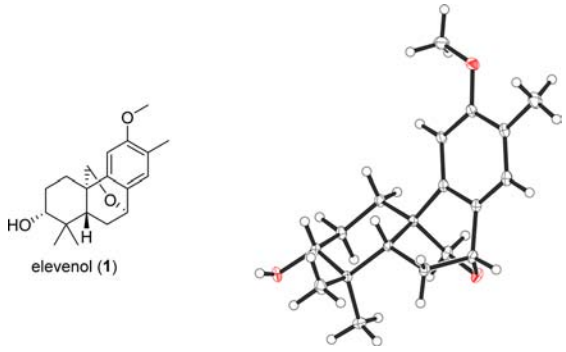
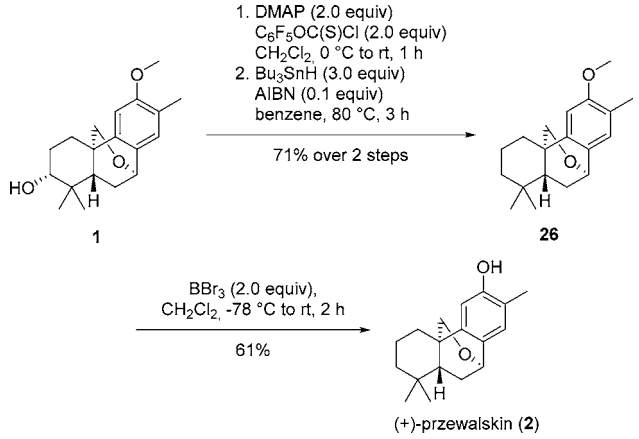


Figure 2. X-ray crystal structure of (+)-elevenol (**1**).

The synthetic route developed for elevenol (**1**) should be applicable for accessing other 7−20 oxa-bridged abietane type natural products. One such target is the structurally related przewalskin (**2**). Przewalskin (**2**) was isolated from the roots of *Salvia Przewalskii* by Sun et al. in 1991.[2] Its relative configuration was deduced from NMR studies and its absolute configuration by analogy with the carnosol type compounds. The relative configuration was confirmed later by X-ray analysis.[16] The conversion of elevenol (**1**) into przewalskin (**2**) required the deoxygenation of the C3-alcohol and the cleavage of the methyl ether (Scheme 6). Barton−McCombie

Scheme 6. Synthesis of (+)-Przewalskin (2)



deoxygenation[17] of elevenol (**1**) gave the cyclohexane **26**. Deprotection of the methyl ether was achieved using BBr_3 to deliver (+)-przewalskin (**2**) ($[\alpha]_D^{25}$= +37, *c* 0.55, CH_2Cl_2). Synthetic (+)-przewalskin (**2**) was spectroscopically identical to the natural product. Since no optical rotation was given for the natural product,[2] the absolute configuration of natural przewalskin from *Salvia Przewalskii* remains to be clarified.

In conclusion, an efficient synthetic route to 7−20 oxa-bridged abietane type natural products has been developed. Key steps are an asymmetric Mukaiyama aldol addition to construct the C3 stereocenter. An organocatalyzed intramolecular Stetter-type Michael addition followed by a Tishchenko reaction elaborates the tricyclic skeleton. An intramolecular lactone−enolate arylation delivers the tetracyclic skeleton. The efficiency of the synthetic concept was demonstrated by the first total synthesis of (+)-elevenol (**1**), an antihepatitis C active compound from *Flueggea virosa*, and the first total synthesis of (+)-przewalskin (**2**). The present work should be adaptable to the synthesis of derivatives of pharmaceutical interest.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02922.

Experimental details, spectroscopic and analytical data of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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