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Synthesis of the Core Structure of Apicularen A by Transannular Cyclization

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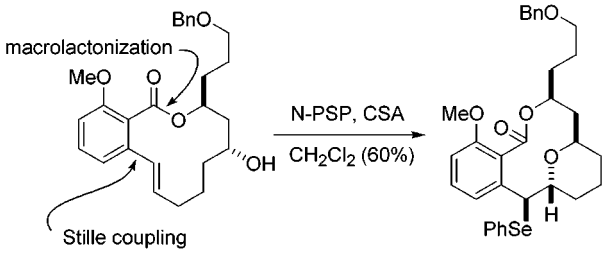
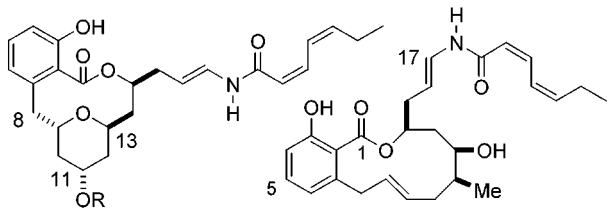
ABSTRACT



An approach to the macrocyclic core of apicularen A is described. Thus, cross-coupling of the aryl triflate 7 with the vinylstannane 19 provided the styrene 20. Deprotection led to the dihydroxy acid 22. Through a size-selective macrolactonization, the 12-membered macrolactone 23 was obtained. Treatment of 24 with *N*-phenyl selenophthalimide gave the desired *trans*-pyran 24. This approach might parallel the biosynthetic pathway.

Recently a number of natural products were isolated that contain a salicylic acid substructure, a macrolactone, and an enamide side chain. This class of compounds comprises the apicularens (**1**, **2**),[1] the salicylihalamides (**3**) (Figure 1),[2] the lobatamides, the oximidines, and CJ-12,950. All of these compounds show potent antitumor activity. Of particular interest was the fact that the screening profiles of these compounds differed significantly from those of other known antitumor compounds. In the meantime, it turned out that the molecular targets of the benzolactone enamides are mammalian vacuolar-type(H^+)-ATPases.[3] These membrane-bound proton-translocating pumps are responsible for regulation of pH in cellular spaces. A unique property of the benzolactone enamides is their selectivity toward certain V-ATPases.

As a result of their structural and biochemical features, these compounds became prominent synthetic targets. Thus,



salicylihalamide A (17E) (**3E**)

salicylihalamide B (17Z) (**3Z**)

apicularen A (R = H) (**1**)

apicularen B (R = *N*-acetyl-β-D-glucosamine) (**2**)

Figure 1. Structures of representative benzolactone enamides.

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total synthesis of apicularen A[4] and salicylihalamide[5] were reported. In addition, a range of analogues[6,7] and studies concerning the enamide side chains[8] have appeared in the literature.

Apicularen differs from the other benzolactone enamides in that it contains a pyran ring, probably being formed through a transannular cyclization. Figure 2 depicts some

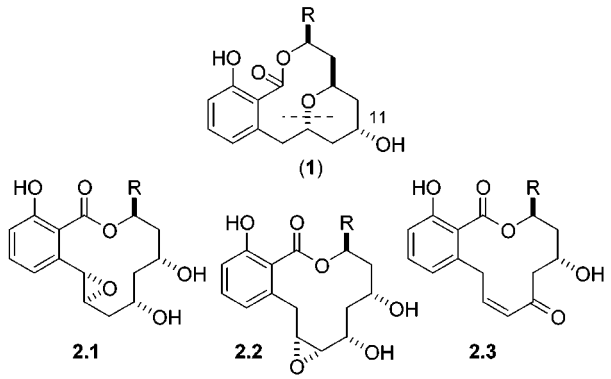


Figure 2. Potential biosynthetic precursors for apicularen A.

potential precursors. We reasoned that a similar strategy might also work in a laboratory setting. In this paper we demonstrate the feasibility of this approach.

The corresponding retrosynthetic analysis is shown in Figure 3. According to this plan, the triflate **3.3** and a vinylstannane, such as **3.4**, appear as possible starting materials. Initially we confined ourselves to the 11-deoxy compound **3.1**.

In related work[9] we have used the triflate **3.3** (R^1 = Me), which was prepared from commercially available 2-hydroxy-6-methoxybenzoic acid **5**. Because compounds of this type are quite costly, we developed a new synthesis for this benzoic acid. In the literature, the acid **5** or its methyl ester

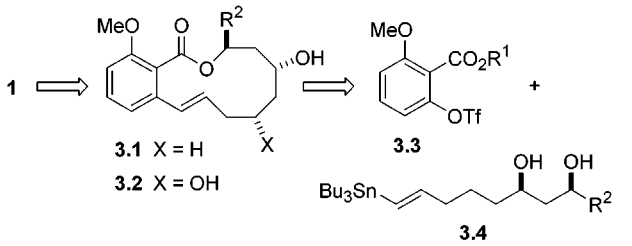
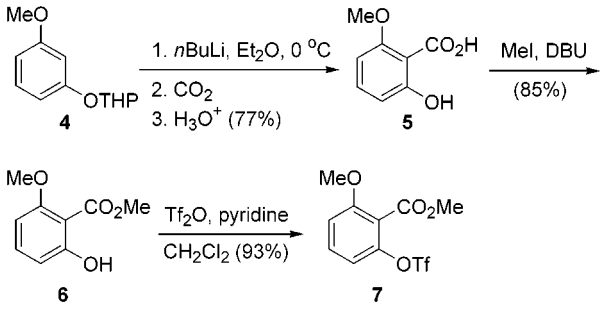


Figure 3. Retrosynthetic analysis for apicularen A based on a transannular etherification reaction

6 are usually prepared by monoetherification of a 2,6-dihydroxy precursor[10] or a mono cleavage of a dimethoxy precursor.[11] These steps are problematic and lead to mixtures. The following route is based on a carboxylation reaction of 1-methoxy-3-tetrahydropyran-2-yloxybenzene **4** (Scheme 1).

Scheme 1. Facile Synthesis of the Ester **6**



As it is described in the literature,[12] the O-THP protected 3-methoxyphenol can be deprotonated at the 2-position, the common *ortho*-site. On this basis, we subjected **4** to a metalation reaction with *n*-butyllithium in dry diethyl ether. The resulting anion was quenched by adding solid carbon dioxide. After acidification of the reaction mixture and extractive workup the acid **5** was obtained directly in good yield. A subsequent methylation of the carboxylic group using 1,8-diazabicyclo[5.4.0] undec-7-en (DBU) and iodomethane[13] gave the methyl ester **6**. The latter could be converted in the usual way (Tf_2O, pyridine, 23 °C) to the triflate **7**.

The other building block was constructed by connecting two fragments via dithiane coupling (Scheme 2).[14] The synthesis of the epoxide began with the triol **8**, which is

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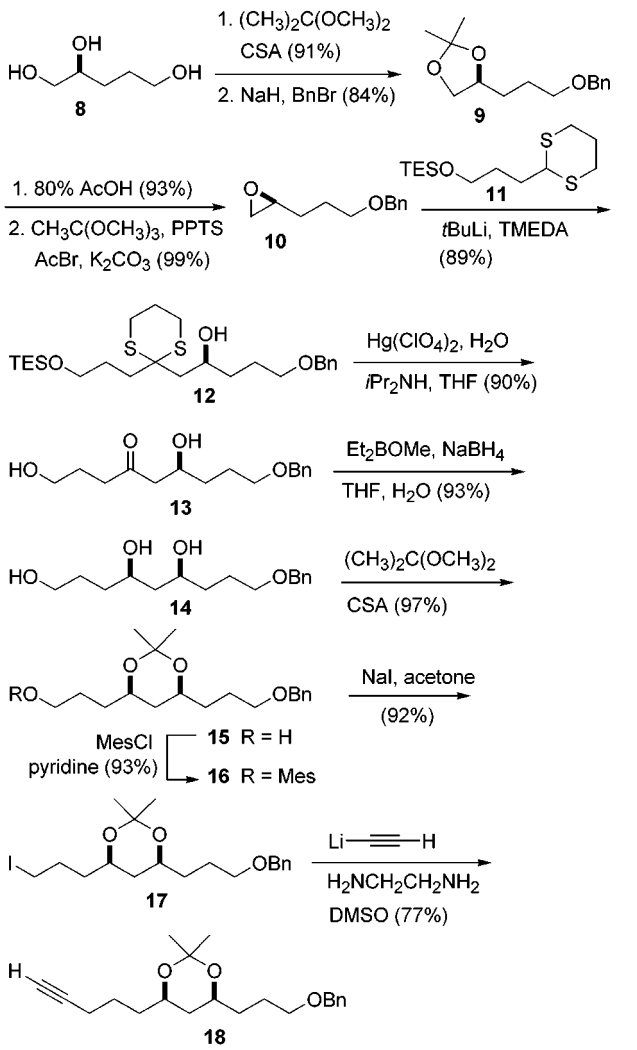
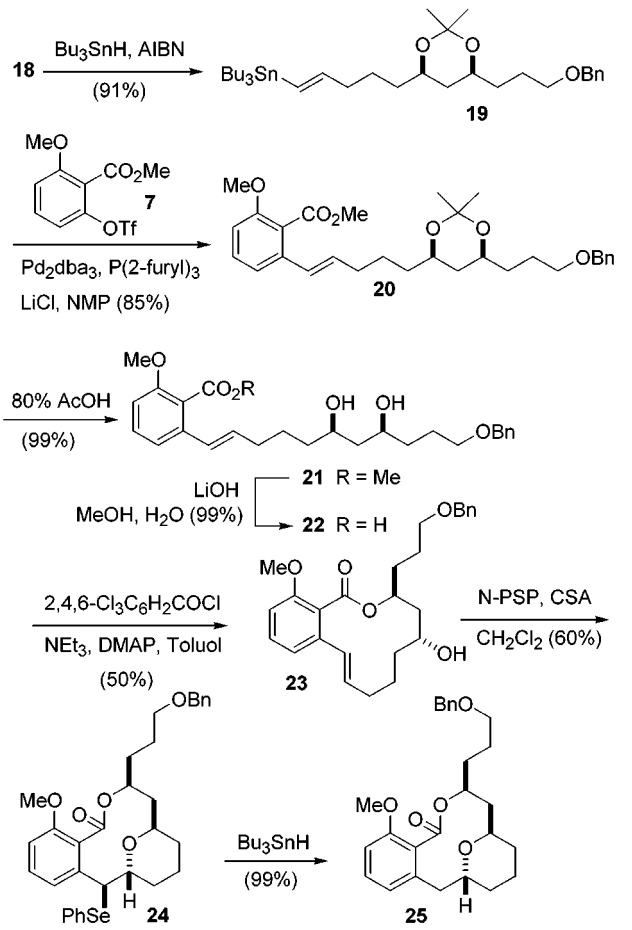
Scheme 2. Synthesis of the Alkynediol **18** via Dithiane Coupling



Scheme 3. Coupling, Macrolactonization, and Transannular Etherification



available from d-glutamic acid.[15] After differentiation of the 1,2-diol as the acetonide, benzylation[16] of the primary hydroxyl group gave compound **9**. The isopropylidene protecting group was then removed, and the resulting diol was converted to the epoxide **10** with the Sharpless method.[17] The other fragment, the dithiane **11**, was prepared from dihydrofuran in a two-step sequence.[18] The crucial alkylation of the 1,3-dithiane **11** with the epoxide **10** took place with *tert*-butyllithium as base in the presence of tetramethylethylenediamine (TMEDA) to provide compound **12** in good yield.[19] The subsequent hydrolysis of the dithiane necessitated some optimization studies in order to prevent elimination of the hydroxyl group. The combination of mercury(II) perchlorate in the presence of diisopropylamine turned out to be suitable.[20] These conditions not only affected hydrolysis of the dithiane but also cleavage of the triethylsilyl ether. The resulting β-hydroxyketone **13** was then reduced to the *syn*-1,3-diol **14**.[21] Again, acetal formation was used to protect the neighboring hydroxyl groups. The primary alcohol **15** was extended to the alkyne **18** via the mesylate **16** and the iodide **17**. The direct substitution of the mesylate with lithium acetylide was less efficient.

Before the cross-coupling, the alkyne **18** was converted via a hydrostannylation to the vinyl stannane **19** in good yield (Scheme 3). The merging of the fragments **7** and **19** was realized by a palladium-catalyzed cross-coupling using Pd_2dba_3 as a catalyst and tri-(2-furyl)-phosphine as a ligand, which formed the styrene derivative **20**.[22] After hydrolysis of the isopropylidene group under acidic conditions, the ester **21** was cleaved with lithium hydroxide to provide the dihydroxy acid **22.** The macrolactonization under Yamaguchi conditions allowed for a clear-cut differentiation of the two

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secondary hydroxy groups.[23] Essentially only the 12-membered macrolactone **23** was formed under these conditions. With the macrolactone **23** in hand, we were now in the position to study the crucial transannular etherification. Initial experiments using iodine (I_2, CH_2Cl_2, 0 °C) only caused oxidation of the alcohol to the corresponding ketone. The same product was observed with trifluoroacetyl perrhenate.[24] Gratifyingly however, the pyran formation could be realized with *N*-phenylselenophthalimide to give with compound **24** as only one isomer.[25] Reductive removal of the phenylselenyl group with tributyltin hydride gave compound **25**.

The relative stereochemistry of the pyran ring was determined on the basis of NOE data. Thus, there was no cross-peak between H-9 and H-13, which would be the case for a *cis* stereochemistry. Instead, cross-peaks were observed for H-13/H-15 and H-10/H-13. The calculated conformation, which is in accordance with these NOE results, corresponds to the right structure (**model26trans)** of Figure 4 (MacroModel 7.0,[26] calculated energy 278.14 kJ mol^{-1}). In this compound the selenium atom was replaced with a sulfur atom because of the lack of parameters. In addition, the side-chain was truncated. This conformation corresponds to the one found for apicularen A.[1b] The C═O bond is eclipsed to H-15 in this conformer. Further experiments and calculations will be performed to elucidate the origin of the selectivity.

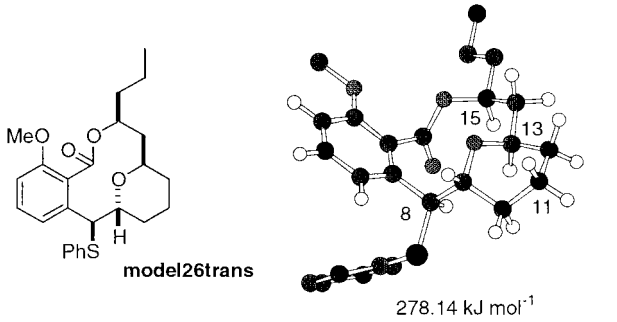

Figure 4. Low energy conformations of compound **model26trans** calculated by conformational search using MacroModel 7.0.

In summary, we have described a synthesis of a model system for the macrocyclic subunit of the apicularens. Key reactions include the cross-coupling of the aryl triflate **7** with the vinyl stannane **19**, a size-selective macrolactonization, and a final diastereoselective transetherification. This strategy is also of interest, in that it might resemble the biochemical pathway. Studies to include the 11-hydroxy group into this scheme are underway in our laboratory.

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Supporting Information Available: Experimental procedures and characterization for all new compounds reported and copies of NMR spectra for important intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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