Natural Products Synthesis

Total Synthesis of Apicularen A through Transannular Pyran Formation**

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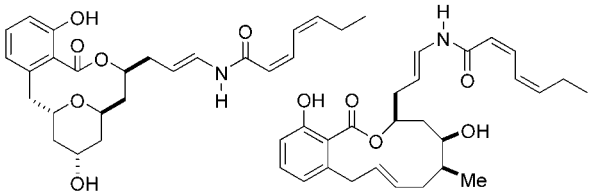
Natural products that show cytotoxic effects are important in cancer treatment. As resistance can occur, and not all tumor cells are equally sensitive to a certain drug, there is a need for compounds that have novel modes of action. Such compounds include the benzolactone enamides,[1] for example, apicularen A (**1**) and salicylihalamide A (**2**). Salicylihalamide A was



isolated from the sponge *Haliclona* sp.,[2] whereas apicularen A has been found in various myxobacteria strains.[3] Both compounds were shown to be selective inhibitors of mammalian V-ATPases, which are important as proton pumps for regulating intracellular pH.[4] Depending on the cell type studied, other downstream effects were observed, such as the phosphorylation of mitogen-activated protein kinases, which results in apoptosis.[5,6] The structure of apicularen A is characterized by the salicylic acid portion, a *trans* tetrahydropyran embedded in a macrolactone, and an enamide side chain. Several total syntheses of apicularen A,[7] formal total syntheses,[8] and synthetic studies[9,10] have been reported.

Some time ago we proposed that the pyran ring of apicularen A is probably formed by a transannular reaction of a macrolactone precursor through the opening of an epoxide or addition to an enone.[10a] Herein we describe the application of the transannular etherification strategy for the total synthesis of apicularen A (**1**).

As described previously,[10b] the dithiane **3**, the epoxides **4** and **5**, and trimethylsilylacetylene (**6**) were combined in a four-component coupling[11,12] to give the alkyne **7**

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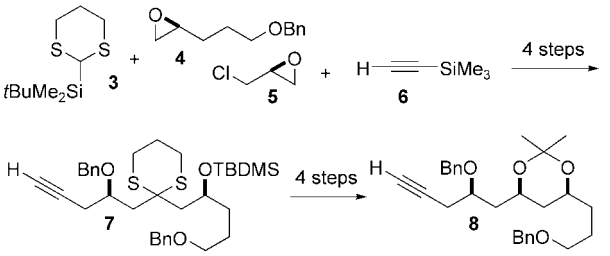
[**] Financial support by the Deutsche Forschungsgemeinschaft (grant Ma 1012/10-1) and the Fonds der Chemischen Industrie is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

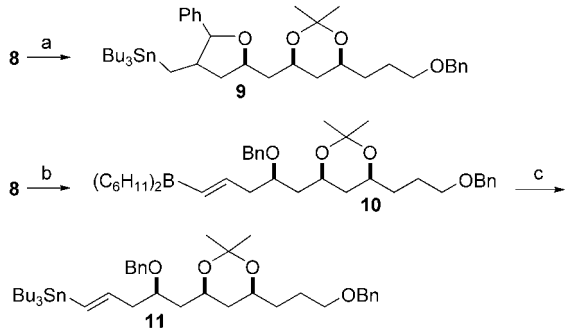
 DOI: 10.1002/anie.200460760

(Scheme 1). Hydrolysis of the dithiane and desilylation yielded a β-hydroxyketone, which was converted by *syn* reduction and acetalization into the alkyne **8**.



Scheme 1. Synthesis of the alkyne **8** by a four-component coupling strategy. Bn = benzyl, TBDMS = *tert*-butyldimethylsilyl.

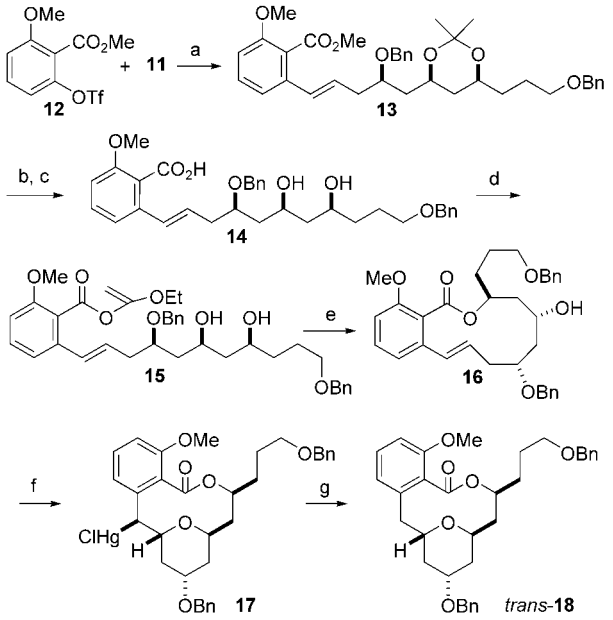
The conversion of the alkyne **8** into a suitable vinyl metal species for cross-coupling turned out to be quite challenging (Scheme 2). For example, the palladium-catalyzed hydro-



Scheme 2. Synthesis of the vinylstannane **11** via an intermediate vinyl borane: a) nBu$_3$SnH, AIBN (cat.), toluene, reflux (56%); b) (C$_6$H$_{11}$)$_2$BH, THF, 0°C, 1 h; c) NaOH, [Cu(acac)$_2$] (cat.), nBu$_3$SnCl, −15→23°C (>93%).

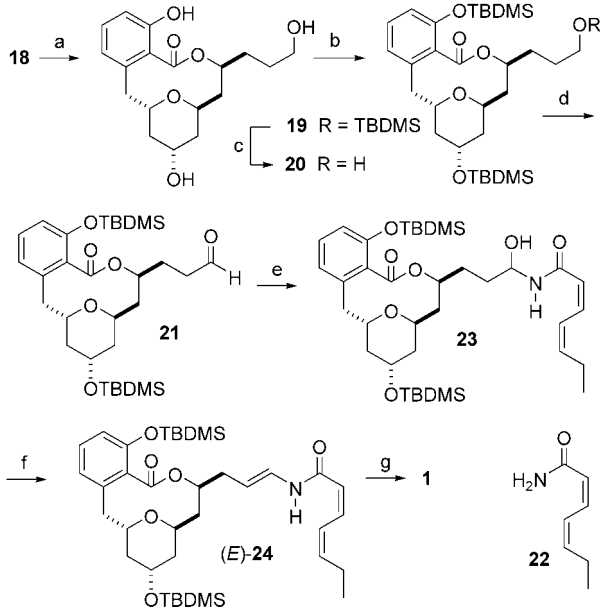
stannylation[13] of **8** gave an inseparable mixture of the internal and terminal stannane. The hydrostannylation under radical conditions led to the tetrahydrofuran **9** through an atom-transfer and cyclization process. This difficulty was overcome by generation of the vinyl borane **10**[14] followed by transmetalation to the stannane **11**.[15] In this way the vinyl stannane was obtained exclusively as the *E* isomer in excellent yield.

The subsequent cross-coupling reaction of the triflate **12**[10a] with the stannane **11** proceeded smoothly to furnish the salicylate **13** in excellent yield (Scheme 3). Hydrolysis of the acetal and ester functionalities then gave the dihydroxy acid **14**. As we had observed in this and related cases,[10] the size-selective macrolactonization under Yamaguchi conditions[16] gave selectively the larger of the two macrolactones, but the chemical yield was only in the range of 50%. Therefore, the method of Trost and Chisholm was investigated.[17] In this case, an ethoxyvinyl ester, prepared by the ruthenium-catalyzed addition of the carboxylic acid **14** to ethoxyacetylene, serves as the precursor. The best results for the macrolactonization were obtained at 80°C (5 mM, 63% yield). In contrast to the results of our previous model study,[10a] the treatment of the macrolactone **16** with *N*-(phenylseleno)phthalimide left the starting material unchanged.[18] Eventually, it was found that treatment with mercuric trifluoroacetate in dichloromethane gave the cyclized organomercurial intermediate within minutes. To suppress the undesired retrocyclization[19] of the mercurial intermediate during the reductive demercuration, it was necessary to change the solvent from CH_2Cl_2 to THF and to perform the reduction with $LiBH_4$ in the presence of Et_3B.[20] The origin of the high selectivity in the transannular etherification has not yet been clearly ascertained. However, on the basis of previous work, we believe that the transition state of the kinetically controlled reaction is productlike, thus leading to the less strained product.[8d,10a]



Scheme 3. Cross-coupling, size-selective macrolactonization, and transannular etherification to yield the building block *trans*-**18**: a) P(furyl)$_3$, [Pd$_2$(dba)$_3$], LiCl, NMP, 60°C, 48 h (93% from **8**); b) 80% AcOH, 23°C, 80 min (99%); c) LiOH, MeOH/H$_2$O, 60°C, 72 h (99%); d) [{RuCl$_2$(*p*-cymene)}$_2$], ethoxyacetylene, toluene, 0°C; e) CSA, toluene, 80°C (63% from **14**); f) Hg(O$_2$CCF$_3$)$_2$, CH$_2$Cl$_2$, 23°C, 30 min, then NaCl, 23°C; g) Et$_3$B, LiBH$_4$, THF, −78°C, 1 h (89% from **16**). CSA = camphorsulfonic acid, NMP = 1-methyl-2-pyrrolidinone, Tf = trifluoromethanesulfonyl.

The synthesis continued with the cleavage of all ether protecting groups with 9-iodoborabicyclononane (9-I-9-BBN; Scheme 4).[21] A sequence of complete silylation and selective desilylation generated the primary alcohol **20**, which was oxidized to the aldehyde **21**[7c] with tetra-*n*-propylammonium perruthenate (TPAP).[22] The stage was set for the attachment of the enamide side chain.[23] The addition of the aluminum carboximidoate derived from the amide **22**[23b] and diisobutylaluminum hydride[24] to the aldehyde **21** provided the hemiaminal **23** in 86% yield (1:1 mixture of diastereomers). When a solution of the hemiaminal **23** in THF was heated at reflux in the presence of acetic anhydride and pyridine, the enamide **24** was obtained as a separable *E*/*Z* mixture (*E*/*Z* = 75:25). The removal of the silicon protecting groups from (*E*)-**24** with



Scheme 4. Synthesis of apicularen A via the hemiaminal **23**: a) 9-I-9-BBN, CH_2Cl_2, 23 °C, 90 s, MeOH; b) TBDMSCl, imidazole, DMAP (cat.), DMF, 23 °C, 48 h (72% from **18**); c) CSA (cat.), CH_2Cl_2/MeOH, 0 °C, 3 h (85%); d) TPAP, NMO, 0 °C, 1 h (98%); e) **22**, DIBAL, THF, 0 °C, 30 min, add **21**, 0 °C, 18 h (86%); f) THF, pyridine, Ac_2O, reflux, 48 h ((*E*)-**24**: 46%, (*Z*)-**24**: 15%); g) TASF, DMF, 23 °C, 21 h (75%). DIBAL = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide, NMO = 4-methylmorpholine *N*-oxide, TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate.

TASF[25] gave pure apicularen A (**1**). Another method for the conversion of an aldehyde into the corresponding enamide via a bisamide derivative through a base-induced elimination[26] proved unsuccessful in the case of apicularen.[7b,c]

In summary, we have developed a concise total synthesis of apicularen A, featuring a number of key transformations: a) a four-component coupling that combines a 1,3-dithiane, a terminal epoxide, an acetylide, and epichlorohydrin, b) a Stille cross-coupling reaction with the vinylstannane generated from a vinylborane, c) a size-selective macrolactonization of an ethoxyvinyl ester, d) a transannular etherification, and e) formation of the enamide from a hemiaminal. This successful strategy underscores the close relationship between salicylihalamide and apicularen.

Received: May 24, 2004

Keywords: cross-coupling · enamides · macrolactonization · total synthesis · transannulation

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