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Synthesis of the core of apicularen A by transannular conjugate addition

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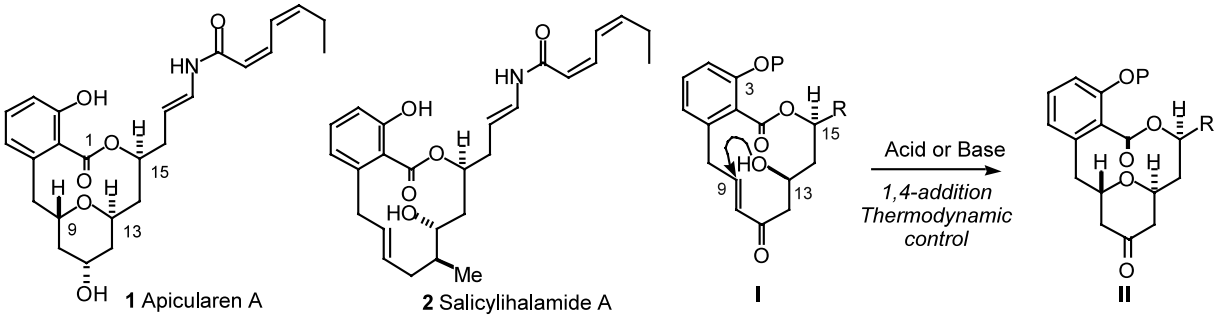
Abstract—The synthesis of the core of the myxobacteria metabolite apicularen A by a novel transannular 1,4-addition is described. The key step involved acid mediated transannular conjugate addition of the C13 hydroxyl into the α,β-unsaturated ketone in macrolactone **18** to provide the *trans*-pyranone **19** and the *cis*-isomer **20** in a ratio of 9:1, respectively.

Extracts of the myxobacterium *Chondromyces robustus* (Cm a13) showed high cytotoxicity against cultivated mammalian cells and bioassay-guided fractionation revealed the cytotoxicity was due to one main metabolite identified as the novel macrolide apicularen A (**1**).[1] Along with this compound another less cytotoxic metabolite was found and identified as the *N*-acetyl-β-D-glucosamine glycoside of **1** named apicularen B. Interestingly, the apicularens are structurally similar to salicylihalamide A (**2**),[2] a novel metabolite isolated from the Western Australian marine sponge *Haliclona* sp., and it is possible that the pyran ring in the apicularens may form by transannular cyclization of a salicylihalamide type precursor. Like the salicylihalamides, the apicularens contain a novel secondary enamide functionality which is probably critical for the biological activity[3] and also is found in other myxobacteria metabolites.[4] Apicularen A (**1**) shows highly effective growth inhibition of several human tumor cell lines originating from cervix (IC_{50} 0.4 ng mL^{-1}), kidney (IC_{50} 0.3 ng mL^{-1}), lung (IC_{50} 0.1 ng mL^{-1}) and prostate (IC_{50} 0.5 ng mL^{-1}) carcinomas.[1a]

The first total synthesis of apicularen A (**1**) was reported by De Brabander and co-workers[5] and relied on the construction of the tetrahydropyran ring by an asymmetric hetero-Diels–Alder reaction prior to macrolactonization. A formal total synthesis has been also been described which again involved formation of the tetrahydropyran first.[6] We envisaged that the pyran ring could be formed via a possible biomimetic transannular conjugate addition from the salicylihalamide type precursor **I** as shown above and, during the course of this work, Maier and Kühnert reported that the electrophilic *N*-PSP mediated transannular cyclization of a C8–C9 alkene isomer related to the salicylihalamide ring forms the *trans*-pyran apicularen type ring devoid of the C11 oxygenation.[7] In the current approach, an intramolecular conjugate addition of the C13 oxygen into the C9–C10 α,β-unsaturated ketone in precursor **I** could produce the pyranone **II** with stereocontrol resulting from strain due to the pre-formed benzlactone. In fact, MM2 calculations (PC MODEL) conducted on a truncated apicularen type ring system indicated that the 9,13-*trans*-13,15-*syn*-pyranone (*twist*-



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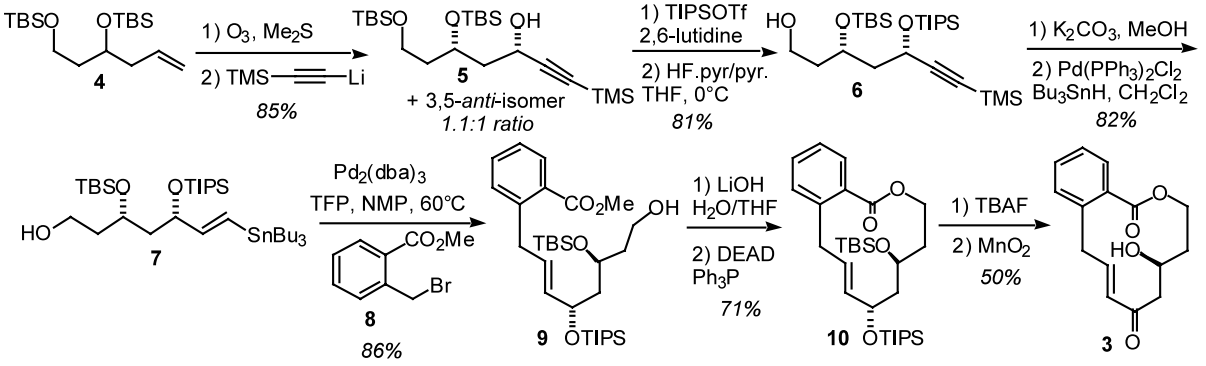
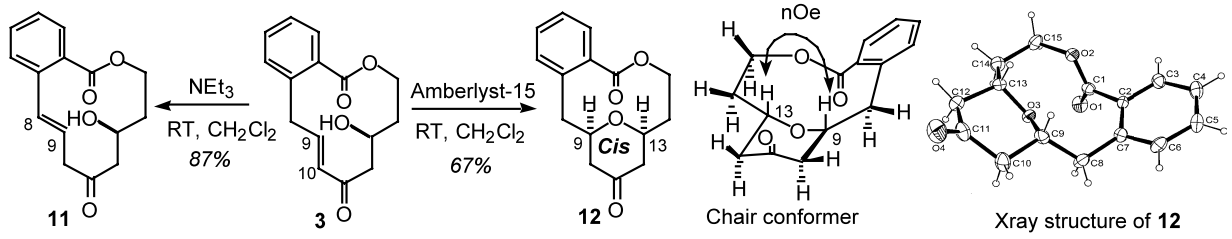
boat conformer)[8] is more stable than the 9,13-*cis*-13,15-*syn*-pyranone (*chair* conformer) by more than 10 kJ mol^{-1}. Therefore, if an equilibrium could be established under either basic or acidic conditions,[9,10] formation of the 9,13-*trans*-isomer **II** should be strongly favored.

To test this proposal we first targeted the cyclization precursor **3** which does not possess the C3 or C15 substituents (Scheme 1) using our recently reported Stille coupling–macrolactonization sequence which provided the macrolactone core of the salicylihalamides.[11] The racemic bis-silyl ether **4**[12] was converted into the alkyne **5**[13] by ozonolysis and acetylide anion addition followed by separation of the diastereoisomers (*syn*:*anti* = 1.1:1). Although the stereochemistry at the propargylic center is not relevant, as it will be destroyed upon oxidation, we proceeded with the *syn*-isomer **5**. Thus, alcohol **5** was protected as the TIPS ether and the primary TBS ether was selectively removed. Deprotection of the alkyne **6** followed by catalytic hydrostannylation[14] provided the stannane **7** which smoothly underwent Stille coupling[15] with the benzyl bromide **8**. Hydrolysis of **9** followed by Mitsunobu macrolactonization[16] then gave lactone **10** which upon global desilylation and allylic oxidation with MnO_2 afforded the cyclization precursor **3**.

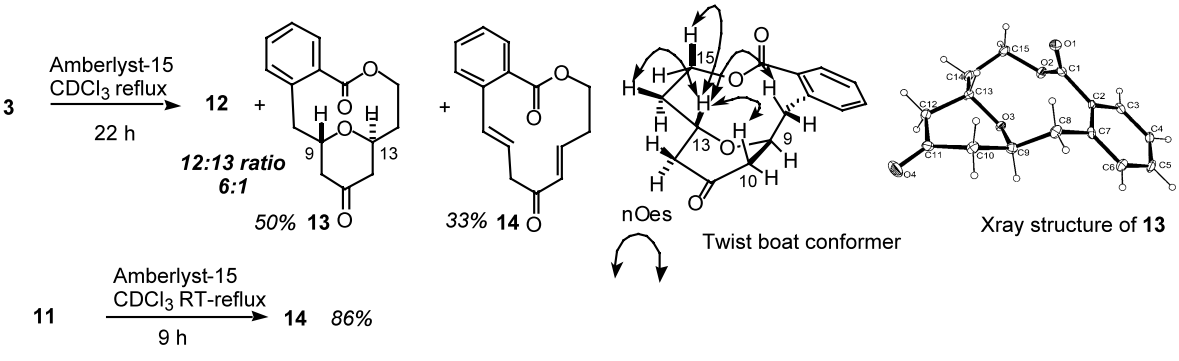
Treatment of **3** with NEt_3 afforded the C8–C9 alkene isomer **11** only with no detectable pyranone product (Scheme 2). However, exposure of **3** to acidic ion-exchange resin[10] resulted in the formation of a higher R_f compound which was identified as the *cis*-pyranone **12** by ^1H NMR spectroscopy. Compound **12** was crystalline and a single-crystal X-ray structure[17] revealed the *cis*-pyranone assignment was correct. A small amount of alkene **11** was also isolated from the acid-mediated reaction. At this stage, we concluded that *cis*-pyranone **12** was the kinetic product and so we elected to examine acid induced cyclization under slightly more forcing conditions. To our delight, when **3** was heated in boiling deuterochloroform in the presence of Amberlyst-15, two new compounds began to form as indicated by NMR analysis along with the *cis*-pyran **12** and alkene isomer **11** (Scheme 3). After 22 h, only a mixture of *trans*-



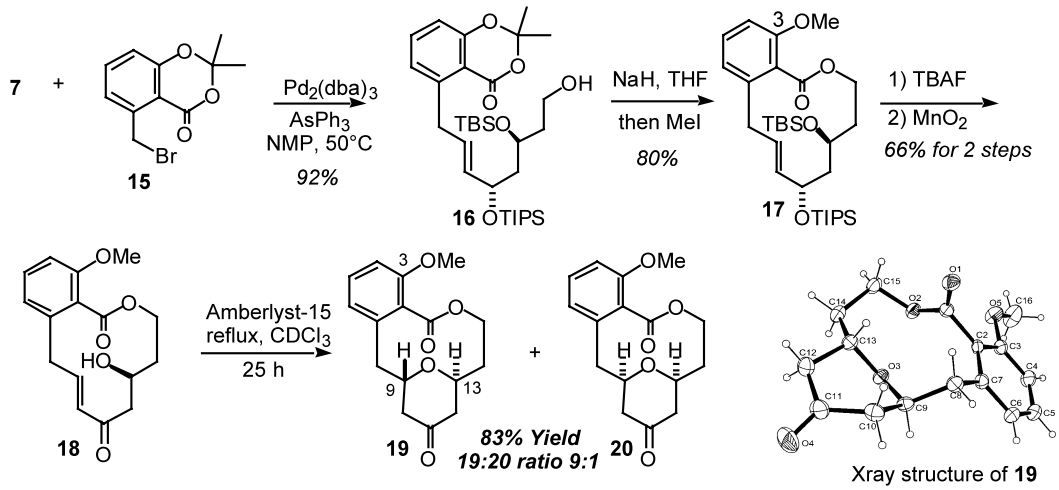
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

pyranone **13** and *cis*-pyranone **12** (6:1 ratio, respectively) and diene **14** could be identified in the ^{1}H NMR spectrum and each was isolated from the reaction mixture with no alkene isomer **11** remaining. The stereochemistry of compound **13** was confirmed by NOE analysis[1b] as shown and a single-crystal X-ray structure[18] was also obtained. It is worth noting that the pyranone is in a *twist-boat* conformation in the solid state which is similar to that observed in solution.

It is possible that the isomerized alkene **11** could also undergo transannular cyclization to pyrans **12** or **13** under the acidic conditions. However, exposure of pure **11** to acid ion-exchange resin in deuterochloroform at room temperature provided no pyranone (Scheme 3). Upon heating the solution to reflux, the diene **14** was the only product formed in 86% yield. These results demonstrate that C8–C9 isomerization is an unproductive pathway which does not cyclize to the desired pyranone.

We next examined the influence of the C3 oxygen substituent of the aromatic ring (Scheme 4). Stille coupling between the bromide **15**[19] and stannane **7** gave alkene **16** and subsequent novel base-induced macrolactonization[5a] followed by methylation of the resultant phenoxide anion in situ provided the macrolactone **17** in good yield. This cyclization is noteworthy since it results in the formation of the 12-membered benzlactone without recourse to other methods or migration of the silicon protecting groups. Desilylation and allylic oxidation then gave the cyclization precursor **18**. We were again pleased to find that acid treatment of **18** under thermodynamic conditions gave the *trans*-pyranone **19** and *cis*-pyranone **20** in good yield in a 9:1 ratio, respectively. In this case, the presence of the C3 electron donating group now thwarts the unproductive C8–C9 isomerization to give the desired pyranone as the only product. The *trans*-pyranone **19** also provided crystals suitable for X-ray analysis[20] which confirmed the structure. While these results do not confirm this mode of cyclization as biomimetic, the facile cyclization of **18** lends support to this proposal.

In conclusion, we have synthesized the novel macrolactone core of apicularen by transannular conjugate addition whereby the stereochemical outcome is under thermodynamic control. The asymmetric synthesis of the macrolactone which includes an appropriate C15 substituent for the production of apicularen A (**1**) is underway and will be reported in due course.

Acknowledgements

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19. 1,3-Benzodioxin-4-one **15** was prepared from 5-methylsalicylic acid by acetonide formation (acetone, DMAP, $SOCl_2$ see: Hadfield, A.; Scweitzer, H.; Trova, M. P.; Green, K. *Synth. Commun.* **1994**, *24*, 1025) followed by benzylic bromination (NBS, benzoyl peroxide, CCl_4, reflux).
20. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC no. 190400.