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Formal Synthesis of (−)-Apicularen A

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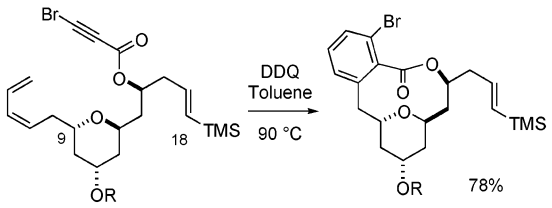
ABSTRACT



A formal synthesis of (−)-apicularen A has been completed. The synthesis features a cyanohydrin acetonide coupling as a convergent approach to the C9−C18 segment and an intramolecular Diels−Alder addition sequence to create both the 10-membered macrocycle and the aromatic ring.

Isolated in a screening of the myxobacterial genus *Chondromyces*, (−)-apicularen A (**1**) was found to be a potent inhibitor of human cancer cell lines.[1] Additionally, apicularen was found to be active against the drug-resistant cell line KB-V1.[1b] Apicularen A and the related salicylihalamides appear to function by inhibiting growth-factor-induced angiogenesis, a mode of action distinct from that of other known antitumor compounds.[2] The structure of apicularen A is characterized by a macrocyclic salicylate, a *trans*-tetrahydropyran, and an unusual enamide side chain. Because of its potent biological activity and interesting structure, the synthesis of apicularen A has been investigated by a number of groups,[3] and three total or formal syntheses have been reported.[4] We describe a formal synthesis of (−)-apicularen A based on an intramolecular Diels−Alder reaction that simultaneously closes the macrocycle and assembles the salicylate ring.

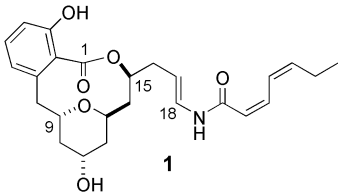


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Figure 1. Structure of (−)-apicularen A.

Initially, a total synthesis was envisioned in which the enamide would be introduced in the final step by coupling of the amide **2**[5] and the vinyl iodide **3** (vide infra), Figure 2. An alternative route to a formal synthesis was envisioned that proceeded through the macrolactone **4**, synthesized by De Brabander en route to apicularen A.[4a] In a retrosynthetic analysis, the macrolactone would be generated from a sequence involving a transesterification of methyl 3-bromopropiolate[6] with diol **6**. The transesterification would

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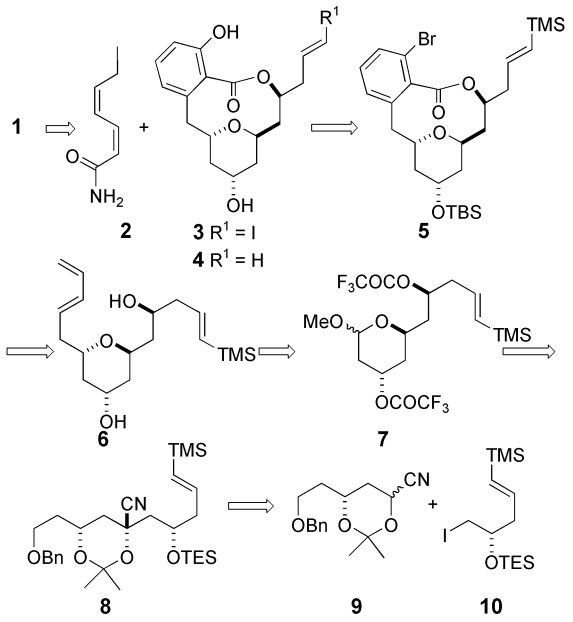
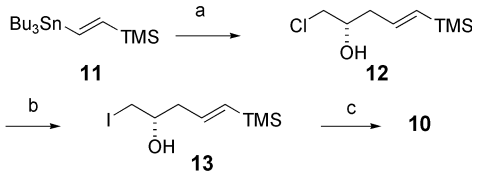


Figure 2. Retrosynthetic analysis of apicularen A.

be mediated by Otera's distannoxane catalyst[7] with concomitant Diels−Alder cyclization of one of the newly formed alkynoate to generate the desired 10-membered macrolactone preferentially over the alternative eight-membered Diels−Alder product. The diene for the Diels−Alder reaction would be generated from the addition of 2,4-pentadienyltrimethylsilane[8] to an oxocarbenium ion generated from the methyl acetal **7**, setting the *trans*-tetrahydropyran geometry. Methyl acetal **7** itself would be prepared by dissolving metal reduction of nitrile **8**, followed by oxidation of the resultant primary alcohol and acidic deprotection. Nitrile **8** would result from a cyanohydrin acetonide coupling between iodide **10** and nitrile **9**. A cyanohydrin acetonide[9] was envisioned as an appropriate synthon for the requisite *syn*-1,3-diol embedded in the structure of apicularen. The cyanohydrin acetonide coupling[10] facilitates a convergent synthesis of the core of the molecule.

The synthesis of the electrophile for the cyanohydrin acetonide coupling began with a tin−lithium exchange of **11**[11] followed by treatment with $BF_3{\cdot}OEt_2$ and (*S*)-epichlorohydrin to produce enantiopure chlorohydrin **12** in 60% yield as a single olefin isomer, Scheme 1. Finkelstein reaction followed by protection of the secondary alcohol as the TES ether was achieved in >95% yield over two steps to provide iodide **10**.

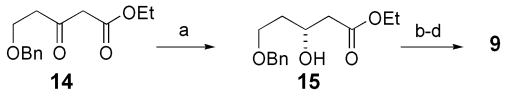
Scheme 1. Synthesis of Cyanohydrin Acetonide Electrophile[a]



[a] Reagents and conditions: (a) (i) *n*-BuLi, THF, −78 °C, (ii) $BF_3{\cdot}OEt_2$, (*S*)-epichlorohydrin, 60%; (b) NaI, acetone, △, 99%; (c) TESOTf, Et_3N, CH_2Cl_2, 99%.

The synthesis of the cyanohydrin acetonide employed a Noyori hydrogenation[12] of *β*-ketoester **14**[13] and was achieved in 96% yield and 94% ee, as determined by HPLC analysis on a chiral column, Scheme 2. The cyanohydrin acetonide

Scheme 2. Synthesis of Cyanohydrin Acetonide[a]



[a] Reagents and conditions: (a) [(*R*)-(+)-BINAP]-$RuCl_2(C_6H_6)$, H_2, EtOH, 1200 psi, 96%, 94% ee; (b) TMSCl, Et_3N, CH_2Cl_2; (c) DIBAL-H, Et_2O, −78 °C; (d) (i) TMSCN, 18-crown-6/KCN (cat.), CH_2Cl_2, (ii) 2,2-dimethoxypropane, acetone, CSA (cat.), 80% from **15**.

9 was synthesized in a four-step, three-pot procedure starting with protection of the secondary alcohol in **15** as a TMS ether. Reduction of the ester to the aldehyde with DIBALH, cyanohydrin formation with TMSCN and catalytic 18-crown-6/KCN complex, and acetonide formation by treatment with acetone, 2,2-dimethoxypropane, and catalytic camphorsulfonic acid provided **9** as a 1:1 mixture of diastereomers in 80% yield from ester **15**.

With both coupling partners in hand, the polyol segment of apicularen was ready for assembly, Scheme 3. Treatment of cyanohydrin acetonide **9** with LDA in the presence of iodide **10** and *N*,*N*-dimethylpropyleneurea (DMPU) provided **8** as a single diastereomer in 92% yield on a gram scale. The nitrile and the benzyl protecting group of the coupled product were reduced under dissolving metal conditions, generating **16** as a single diastereomer in 88% yield. It was important that the excess lithium in the reduction be quenched with isoprene; otherwise reduction of the vinyl silane to the saturated silane was observed. Additionally, the ammonia solution required rapid neutralization to avoid loss of the TES ether. Alcohol **16** was converted to methyl acetal

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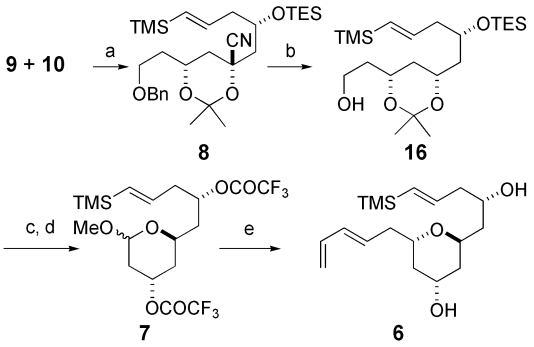
Scheme 3. Synthesis of Macrocycle Precursor[a]



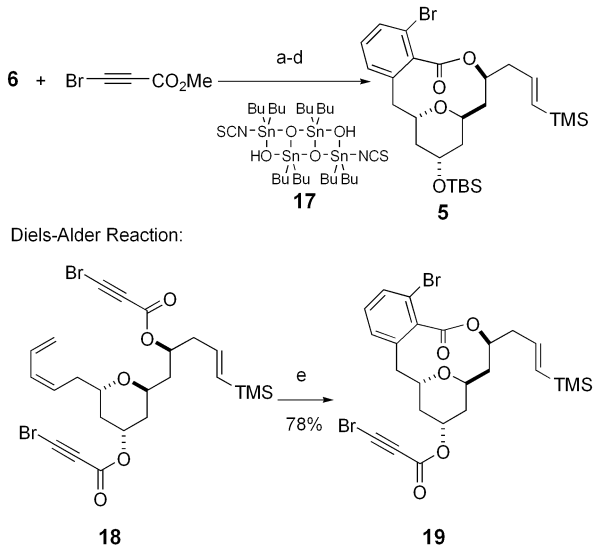
[a] Reagents and conditions: (a) LDA, DMPU, THF, −78 to −40 °C, 92%; (b) (i) Li^0, NH_3(l), (ii) isoprene quench, 88%; (c) Dess−Martin periodinane, CH_2Cl_2; (d) (i) DOWEX, MeOH, (ii) TFAA, DMAP, pyridine, CH_2Cl_2, 89% from **16**; (e) (i) 2,4-pentadienyltrimethylsilane, $BF_3{\cdot}OEt_2$, CH_3CN, 0 °C, (ii) K_2CO_3, MeOH, H_2O, 98%.

7 with a three-step sequence. The primary alcohol was oxidized to the aldehyde with Dess−Martin periodinane. The TES ether and the acetonide were removed with DOWEX in methanol, and the revealed secondary alcohols were protected as trifluoroacetates, producing acetal **7** in 89% yield over the three steps. THP acetal **7** was treated with 2,4-pentadienyltrimethylsilane[8] and $BF_3{\cdot}OEt_2$ to provide exclusively the *trans*-tetrahydropyran[14] **6** in 98% yield.

After initial screening of a variety of methods to esterify diol **6** with 3-bromopropiolic acid, it was discovered that 3-bromopropiolic acid decomposed under most standard coupling conditions and that none of the desired ester was detected. Otera has shown that a number of sensitive esters can be prepared with his distannoxane catalyst **17**, which requires only heat to promote transesterification.[7] Otera's method seemed ideal for our system since the next step would involve a Diels−Alder reaction under thermal conditions followed by oxidation with DDQ, all of which might be carried out in the same flask, Scheme 4. Although this proved to be true, namely, diol **6** in the presence of methyl 3-bromopropiolate and distannoxane catalyst **17** could be heated in toluene followed by addition of DDQ to provide the macrocyclic salicylate **19** in low yield (ca 10−20%), in practice, yields were improved if the excess methyl 3-bromopropiolate was removed by passing the reaction through a plug of silica after the transesterification step. The mixture could then be heated with DDQ in toluene to cyclize the diester and to aromatize the Diels−Alder adduct. Once the aromatic moiety was formed, removal of the extraneous alkynoate on the THP was achieved with NaOH in methanol. The resultant alcohol was protected as the TBS ether in 44% yield from diol **6**.

The moderate overall yield in the transformation of diol **6** to macrolide **5** is primarily a function of the inefficient esterification. We found that diester **18** could be isolated in

Scheme 4. Construction of the Macrocycle via Intramolecular Diels−Alder Reaction[a]

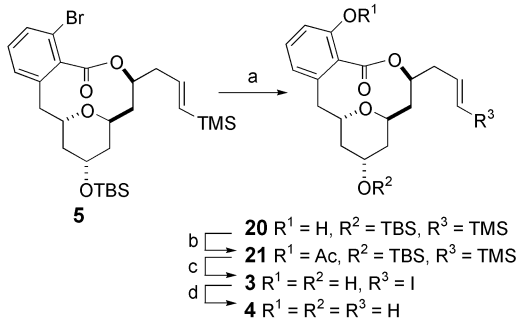


[a] Reagents and conditions: (a) toluene, 110 °C; (b) toluene, DDQ, 100 °C; (c) NaOH, MeOH; (d) TBSOTf, Et_3N, CH_2Cl_2, 44% from **6**; (e) DDQ, toluene, 90 °C, 8 h.

15% yield from an Otera esterification reaction (in addition to the expected Diels−Alder adduct). Cyclization of **18** in toluene with DDQ at 90 °C produced the aromatized macrolide in a remarkable 78% yield. Cyclization in the absence of DDQ did not proceed to completion under the same conditions, suggesting that the DDQ played a catalytic role in the Diels−Alder reaction. The intramolecular Diels−Alder reaction itself is very efficient.

To complete the synthesis it was necessary to convert the aryl bromide to a phenol, Scheme 5. This transformation was

Scheme 5. Completion of Formal Synthesis of Apicularen A[a]



[a] Reagents and conditions: (a) (i) *n*-BuLi, THF, −78 °C, (ii) $(TMSO)_2$, 50%; (b) Ac_2O, DMAP, pyridine, CH_2Cl_2, 94%; (c) (i) *N*-iodosuccinimide, CH_3CN, (ii) K_2CO_3, MeOH, (iii) DOWEX, MeOH, 78%; (d) Bu_3SnH, AIBN, PhH, 80%.

achieved by halogen−lithium exchange followed by treatment with trimethylsilyl peroxide[15] to provide phenol **20** in 50% yield. Interestingly, treatment of phenol **20** with a

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number of desilylation reagents such as TBAF or HF, which would have generated alkene **4** directly, only removed the TBS ether and not the vinyl silane. The vinyl silane could be converted to a vinyl iodide in a two-step process. First, the phenol **20** was protected as an acetate in quantitative yield. The vinyl silane was converted to a vinyl iodide by treatment with *N*-iodosuccinimide,[16] and the acetate and TBS protecting groups were removed with K_2CO_3 and then DOWEX in methanol in 78% overall yield. Unfortunately, attempts to couple the vinyl iodide **3** with the amide side chain **2** using Porco's conditions,[17] which would have completed the synthesis of apicularen A, were unsuccessful. Removal of the iodine atom with Bu_3SnH and AIBN produced macrolide **4** in 80% yield. Macrolide **4** was an intermediate in De Brabander's total synthesis of apicularen A, and this work thus constitutes a formal synthesis of apicularen A.

A formal synthesis of (−)-apicularen A has been completed. The synthesis provides another example of the utility of the convergent cyanohydrin acetonide coupling strategy for the synthesis of oxygenated natural products. The key transformation in the synthesis is an interesting intramolecular Diels−Alder sequence that assembled the aromatic ring and the macrocycle in a single laboratory operation.

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Supporting Information Available: Preparation and characterization of the compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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