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Synthesis of (*S*)-2-amino-8-oxodecanoic acid (Aoda) and apicidin A

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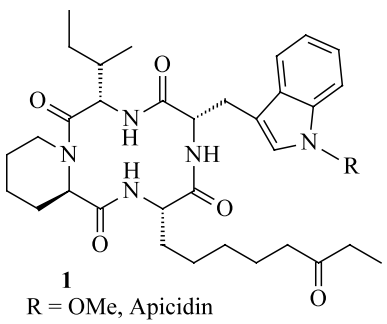
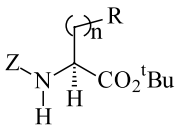
Abstract—The synthesis of (*S*)-2-amino-8-oxodecanoic acid, a constituent of the cyclic tetrapeptides, the apicidins, was accomplished under photolytic conditions in the presence of tri-*n*-butyltin hydride using glutamic acid. This enabled a total synthesis of apicidin A to be completed.

The challenge to the well-being of humans and animals represented by parasitic diseases caused by protozoa of the sub-phylum Apicomplexa which include malaria, cryptosporidiosis, toxoplasmosis and coccidiosis has resulted in increased activity in the search to find new agents to combat these life-threatening organisms. The onset of rapid resistance towards widely used medicinal agents for the treatment of these diseases has given further impetus to the discovery of agents that are based on new mechanisms of action to allow control of epidemics caused by these parasites. Singh and co-workers at Merck[1] have isolated novel cyclic peptides that they named as apicidins **1** from *Fusarium pallidoroseum*. These natural products have shown both in vitro and in vivo efficacy against *Plasmodium berghei* malaria at less than 10 mg/kg.[2] This biological efficacy is due to the apicidins being inhibitors of histone deacetylase. Histone deacetylase is an integral component in the regulation of gene transcription that contributes to the acetylation/deacetylation found on specific lysine residues in histones.[2]

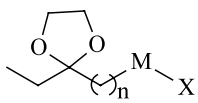


1
R = OMe, Apicidin
R = H, Apicidin A

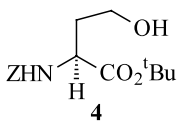
The limited availability of these biologically significant peptides from natural sources render them as attractive targets for synthesis and also provides impetus for the synthesis of structural variants for biological evaluation. The incorporation of the unusual keto amino acid, (*S*)-2-amino-8-oxodecanoic acid (Aoda), in apicidins presents a challenge for synthesis of this unusual amino acid. Recently there have been reports by Meinke and co-workers at Merck on the side chain modification of apicidin with the aim of obtaining more potent inhibitors of histone deacetylase,[3] however, there have been no reports regarding the synthesis of apicidin and of apicidin A. In this letter we report our endeavours in this area.



2
R = I, OTs, CO_2H
n = 1-3



3
n = 3 or 4



4

A prerequisite to the synthesis of apicidin A is the synthesis of the unusual keto amino acid Aoda. There are a number of reports in the literature concerning the homologation of amino acids[4] with organocuprates[5] and Grignard reagents[6] of type **3** and of those derived from **2**. However, all of our attempts at using these strategies resulted in the formation of the corresponding dehydroamino acids. The use of the organozinc reagent formed from *N*-benzyloxycarbonyl-L-serine-

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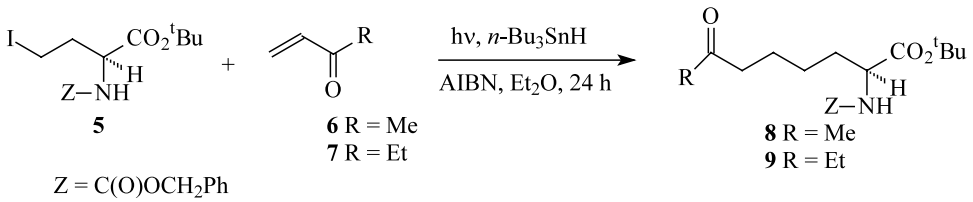
tert-butyl ester has resulted in the successful coupling with aryl iodides and aroyl chlorides by Jackson and other groups.[7] Our extensive studies focused on the chemistry of organozinc reagents formed from **2** with a range of aliphatic acid chlorides, which included ultrasonication and the use of palladium catalysts. Unfortunately, all reactions led to the formation of the dehydroamino acids. A similar outcome resulted from the application of the decarboxylative procedure used by Barton and co-workers.[8]

As a result of these studies we proceeded to investigate the coupling reaction of the radical generated from the iodide **5**, prepared from the appropriately protected D-homoserine **4**,[9] under photolysis in the presence of tri-*n*-butyltin hydride and AIBN. Reaction of **5** with methyl vinyl ketone **6** resulted in the isolation of the coupled keto amino acid **8** in 31% yield after chromatographic purification. This procedure was an improvement on the previous reaction wherein the requisite radical is generated using thermolysis with tri-*n*-butyltin hydride with a yield of 19%.

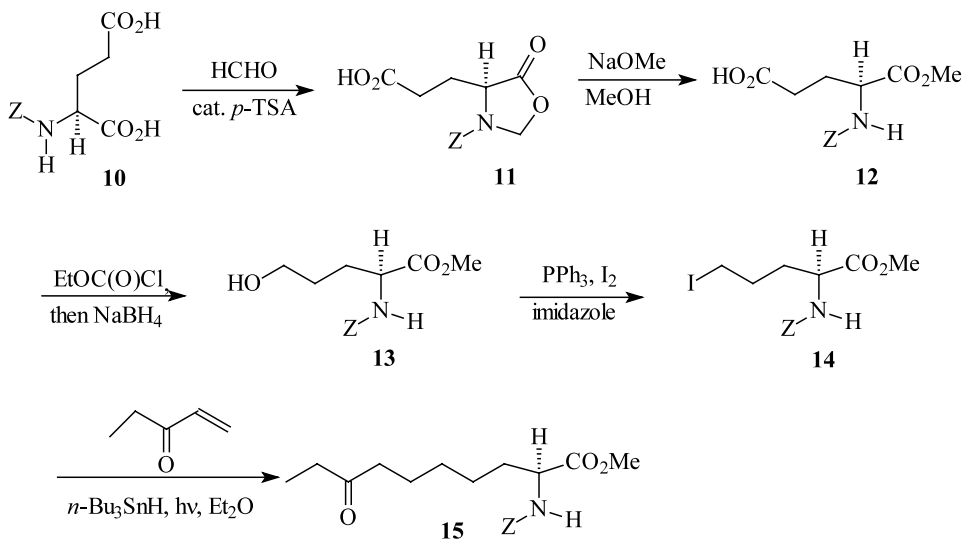


Next, we reacted ethyl vinyl ketone **7** with **5** under similar reaction conditions which resulted in the isolation of the corresponding amino acid **9** in a yield of 50%. For the synthesis of Aoda, L-glutamic acid was selected as the starting material to prepare the required iodo ester **14**, Scheme 1.

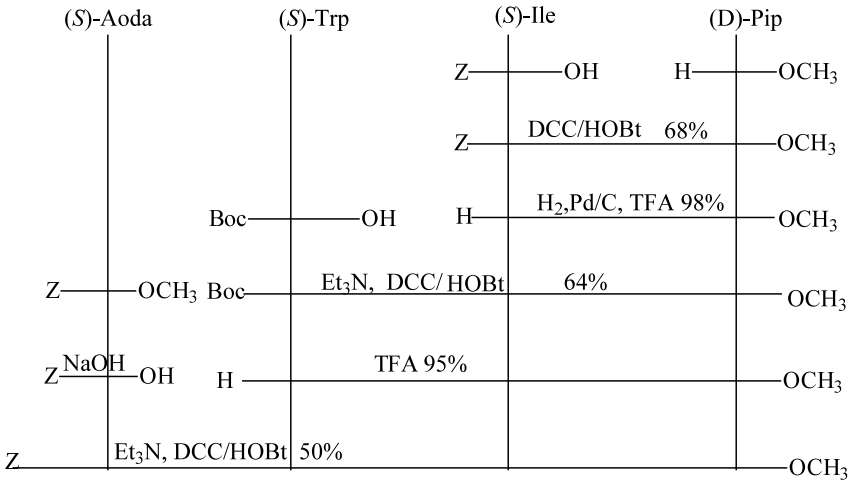
The monomethyl ester **12** was prepared in 90% overall yield from L-glutamic acid. Reduction of the mixed anhydride formed from **12** and ethyl chloroformate with sodium borohydride gave the alcohol **13** in 67% yield, which was transformed to the iodoamino ester **14** in 83% yield on treatment with iodine in the presence of triphenylphosphine and imidazole. The coupling of **7** with the primary radical formed by treatment of **14** with tri-*n*-butyltin hydride under photolysis resulted in the formation of the *N*- and *C*-protected Aoda **15** in 46% yield.[10]

Although the macrocyclic peptide could be disconnected at one of four amide bonds, we chose disconnection at the D-pip residue as there was literature precedent for good yields for cyclisation of other peptides incorporating D-pro.[11] The synthesis of the linear tetrapeptide apicidin A is detailed in Scheme 2. Chiral D-pipecolic acid, was obtained by resolution from D,L-pipecolic acid using (+)-tartaric acid[12] and then converted to its methyl ester. All the couplings were carried out in good yields using DCC/HOBt as the condensing reagents.

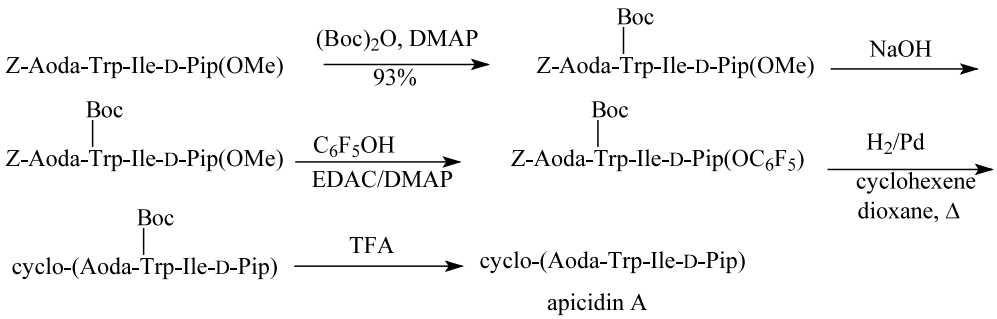
Saponification of the linear tetrapeptide and removal of the *Z* group by hydrogenolysis gave the corresponding deprotected tetrapeptide. All attempts to effect macrocyclisation of the latter using diphenylphosphoryl azide (DPPA),[13] benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP),[14] or DCC/HOBt in dilute solution proved to be unsuccessful leading to decomposition or polymeric products. We then examined the procedure developed by Schmidt that activates the acid function as a pentafluorophenyl ester.[15] This procedure has been widely used in the synthesis of 13-,14- and 15-membered macrocycles. Saponification of the linear tetrapeptide followed by treatment with



Scheme 1.



Scheme 2. Synthesis of linear tetrapeptide *Z*-Aoda-Trp-Ile-D-Pip(OMe).



Scheme 3.

pentafluorophenol, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC) and a catalytic amount of DMAP led to the formation of the corresponding pentafluorophenyl ester. This ester was found to decompose on silica and subsequent cyclisation attempts which included slow addition via a syringe pump to a refluxing suspension of 10% palladium on carbon in dioxane at 95°C with hydrogen bubbling through the reaction mixture proved to be unsuccessful.

Based on these investigations, we reasoned that the problems with the cyclisation reaction may be due to the free indole nitrogen atom in the side chain of Trp. Thus, we protected the *NH*-indole of the tetrapeptide as a Boc carbamate (Scheme 3) in 93% yield, using $(Boc)_2O$ and DMAP. The tetrapeptide was saponified and then converted to pentafluorophenyl ester, which was used directly without purification. Cyclisation of the activated ester was carried out using the modified Schmidt protocol wherein cyclohexene was added as the hydrogen source to produce a slow evolution of hydrogen in the presence of 10% palladium on carbon as catalyst. Gratifyingly, this resulted in the formation of the cyclic tetrapeptide, which on removal of the Boc indole protecting group using TFA gave apicidin A in 54% yield, for these steps, after chromatographic purification.

The synthetic apicidin A exhibited physical and spectroscopic properties in agreement with a sample kindly provided by Merck.

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10. *Physical data*. All new compounds gave satisfactory spectral, microanalytical and/or high-resolution mass spectral data. **15**, $[\alpha]_D$ +10.0 ($c=0.4$, $CHCl_3$); δ_H (270 MHz, $CDCl_3$): 1.04 (t, 3H, *J* 7.2 Hz), 1.22–1.32 (m, 4H), 1.59–1.80 (m, 4H), 2.36–2.45 (m, 4H), 3.74 (s, 3H), 4.31–4.38 (m, 1H), 5.11 (s, 2H), 5.25 (br. d, 1H, *J* 8.5 Hz), 7.28–7.37 (m, 5H); δ_C (67.8 MHz, $CDCl_3$): 7.70, 23.37, 24.87, 28.58, 32.33, 35.79, 41.99, 52.27, 53.62, 66.85, 128.03, 128.10, 128.42, 128.44, 128.45, 136.13, 155.80, 172.95, 211.62; ν_{max} (thin film) 3347, 1735, 1712, 1527, 1214, 732; *m*/*z* [found (MH^+) 350.1973, $C_{19}H_{28}NO_5$ requires 350.1967].
Cyclic peptide **1** (R = Boc): mp: 72–74°C, $[\alpha]_D$ −28.3 ($c=0.6$, $CHCl_3$); δ_H (270 MHz, $CDCl_3$): 0.85 (d, 3H, *J* 7.1 Hz, Ile); 0.92 (t, 3H, *J* 7.2 Hz, Ile); 1.00 (t, 3H, *J* 10.5Hz, Aoda);1.21–2.15 (m, 17H, 6Pip+3Ile+8Aoda), 1.68 (s, 9H, Boc), 2.33 (t, 2H, *J* 7.2 Hz, Aoda), 2.38 (q, 2H, *J* 7.4 Hz, Aoda), 3.02 (brt, 1H, *J* 13.1 Hz, Pip), 3.43 (dd, 1H, *J* 14.5, 5.8 Hz, Trp), 3.76 (dd, 1H, *J* 15.0,10.0 Hz, Trp), 4.01–4.06 (m, 1H, Trp), 4.20 (brt, 1H, *J* 10.0 Hz, Aoda), 4.28–4.41 (m, 1H, Pip), 4.73 (t, 1H, *J* 10.0 Hz, Ile), 5.08 (brd, 1H, *J* 4.0 Hz, Pip), 6.47 (d, N*H*, *J* 10.5 Hz), 6.66 (d, N*H*, *J* 10.0 Hz), 7.22 (dt, 1H, *J* 7.5, 1.5 Hz, Trp), 7.30 (dt, 1H, *J* 8.4,1.6 Hz, Trp), 7.38 (d, 1H, *J* 8.4 Hz, Trp), 7.43 (brs, 1H, Trp), 7.52 (d, 1H, *J* 8.4 Hz, Trp), 8.1 (d, 1H, N*H*, *J* 7.8 Hz); *m*/*z* [Found (MH^+) 694.4171 $C_{38}H_{56}N_5O_7$ requires 694.4180].
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