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SYNTHESIS OF APICIDIN

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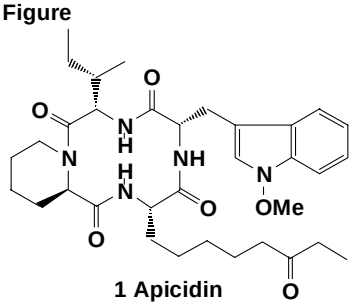
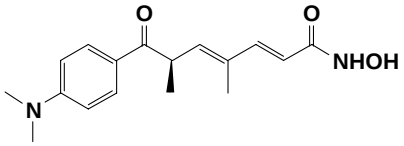
Abstract – Tetrapeptide containing L-2-amino-8-protected hydroxydecanoic acid, L-*N*-*O*-methyltryptophan, L-isoleucine and D-pipecolinic acid was cyclized with pentafluorophenyl diphenylphosphinate. The cyclic tetrapeptide was deprotected and oxidized to apicidin [cyclo-(*N*-*O*-methyl-L-Trp-L-Ile-D-Pip-L-2-amino-8-oxodecanoyl)].

Apicidin (**1**) was first isolated from *Fusarium pallidoroseum* by the Merck Research Group.[1,2] It shows *in vitro* antiapicomplexan and *in vivo* antimalarial activity.[1,2] Its apicomplexan activity appears to be due to the mechanism of the apicomplexan histone deacetylase (HDA) inhibiting activity.[1,2] The known mammalian histone deacetylase inhibitor, trichostatin[3] (**2**) and structually related compound, HC toxin,[4] (**3**) also have apicomplexan activity.[1] (**Figure**)

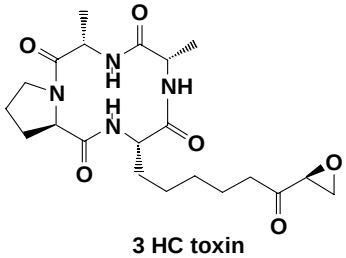
Figure



1 Apicidin



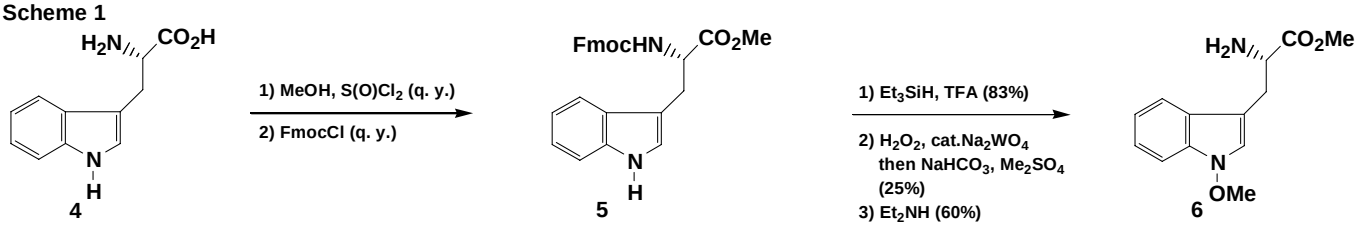
2 Trichostatin



3 HC toxin

Some cyclic tetrapeptides with (2*S*,9*S*)-2-amino-8-oxo-9,10-epoxydecanoic acid and its analogues which have mammalian histone deacetylase inhibiting activity have been synthesized[5-8] and the histone deacetylase function was explored.[8] We are interested in the synthesis of apicidin and related analogues because apicidin possesses the same inhibiting activity as HC toxin without epoxide linkage in the side chain. Herein, we report the synthesis of apicidin. The cyclization site was determined by hydrogen bond analysis.[2] The carbonyl groups of pipecolinic acid and 2-amino-8-oxodecanoic acid and the amino group of the latter play an important role in the apicidin conformation. *N*-*O*-Methyl-L-tryptophan (**6**) was synthesized as follows. (**Scheme 1**)

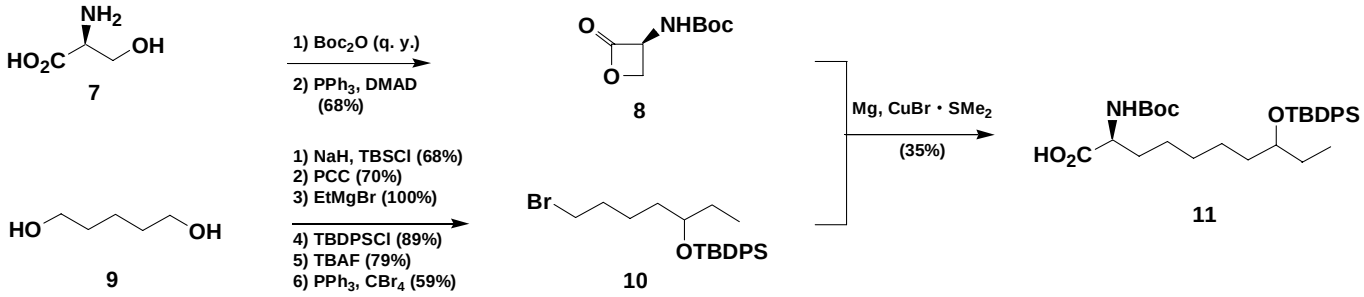
Scheme 1



When the Fmoc protected amino group is substituted with other alkyl groups (in the case of methyl), the yield of each step is good.[9] But in our case, perhaps due to overoxidation of the amino group, the yield of the oxidation step was poor. In the case of $MeReO_3$ and urea・H_2O_2, the yield was up to 40%.

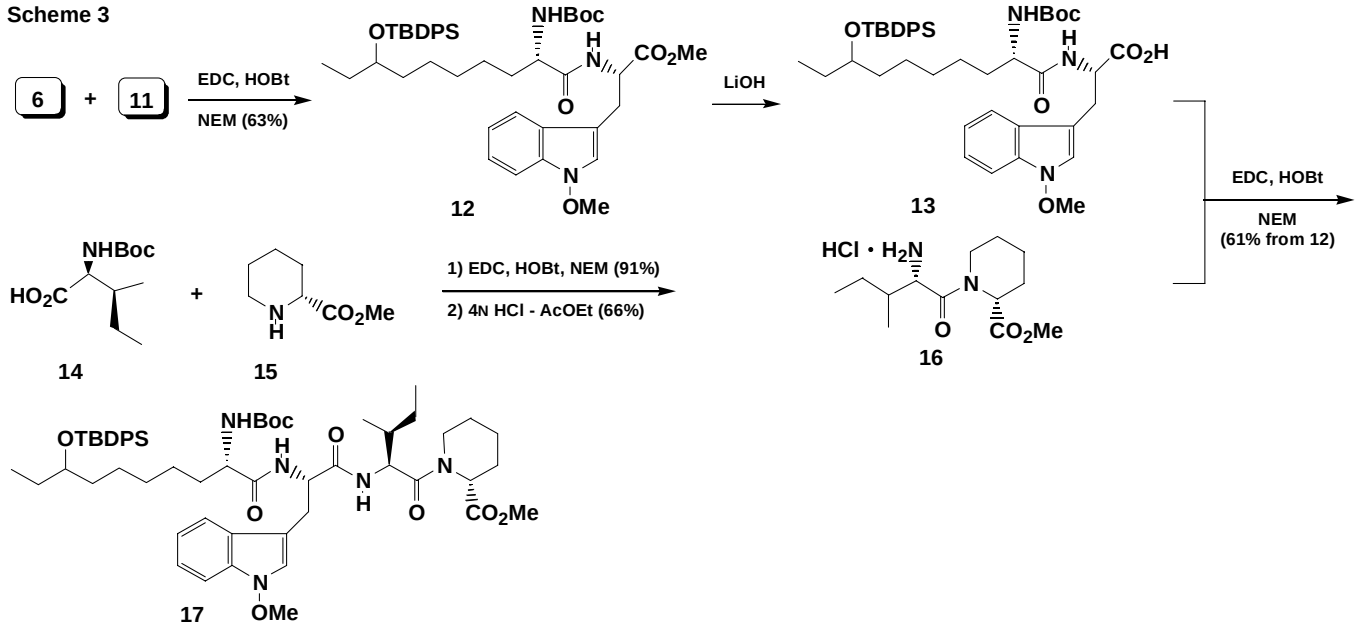
Synthesis of 2-amino-8-oxodecanoic acid [2-amino-8-protected hydroxydecanoic acid (**11**)] is outlined in **Scheme 2**. During the Grignard reaction in the presence of cuprous bromide, the racemization rate is very low between 2-amino-β-lactone and alkylmagnesium bromide.[10] 2-Boc-amino-β-lactone (**8**) was synthesized from L-serine (**7**) *via* cyclization step under modified Mitsunobu conditions using dimethyl azodicarboxylate,[10,11] and alkyl bromide (**10**) was obtained from 1,5-pentanediol (**9**) *via* a monoprotection procedure.[12]

Scheme 2



Each amino acid [(**6**), (**11**) and (**13**), (**14**)] was condensed to give dipeptides (**12**) and (**15**), which were condensed again to give open-chained tetrapeptide (**16**). (**Scheme 3**)

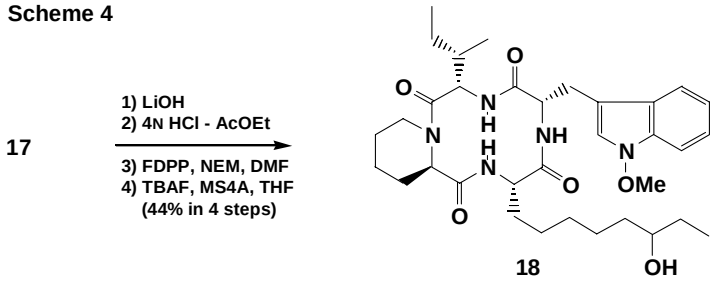
Scheme 3



The ring closure was successfully achieved with the use of FDPP (pentefluorophenyl diphenylphosphinate).[13] (**Scheme 4**) Under normal conditions such as using some carbodiimide and base, ring closure did not proceed. Deprotection of TBDPS proceeded very slowly (with 50 eq. TBAF・H_2O, for one week, the starting material was still remained).

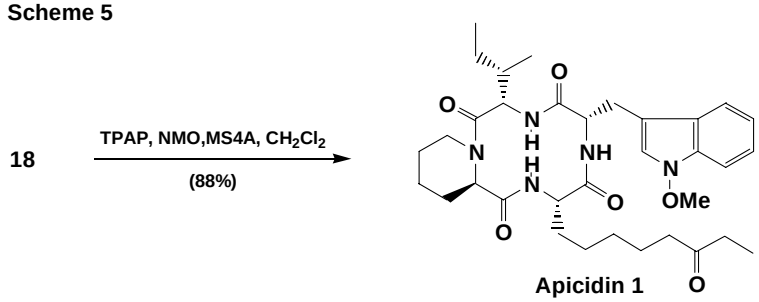
However, in the presence of powdered molecular sieves 4A to remove water in the reaction mixture, TBDPS was easily cleaved over one day. Each diastereomer of **11**, **12**, **17**, and **18** was inseparable.

Scheme 4



Finally, oxidation was achieved with TPAP and NMO.[14] Moffat oxidation[15] or Dess-Martin periodinane[16] did not effect the oxidation and only the starting material was recovered. (**Scheme 5**)

Scheme 5



The synthetic compound was identical to the natural product in all respects. (^{1}HNMR, IR, $[\alpha]_D$ and Rf value).[17]
In conclusion, the synthesis of apicidin, a cyclic tetrapeptide containing an abnormal amino acid, was achieved. Syntheses of apicidin analogues, histone deacethylase inhibitors are now in progress, and will be discussed precisely in a full account.

ACKNOWLEDGEMENTS

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   mp 186-188^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.56 (1H, d, *J* = 7.8 Hz), 7.39 (1H, d, *J* = 8.1 Hz), 7.00 - 7.30 (4H, m), 6.46 (1H, d, *J* = 10.2 Hz), 6.42 (1H, d, *J* = 6 Hz), 5.06 (1H, d, *J* = 4.5 Hz), 4.73 (1H, t, *J* = 10.5 Hz), 4.18 (1H, dt, *J* = 7.5, 10.0 Hz), 3.90 - 4.10 (2H, m), 4.03 (3H, s), 3.79 (1H, dd, *J* = 10.5, 10 Hz), 3.45 (1H, dd, *J* = 6.0, 15.0 Hz), 3.05 (1H, dt, *J* = 2.4, 13.0 Hz), 2.39 (2H, q, *J* = 7.5 Hz), 2.36 (2H, t, *J* = 7.5 Hz), 1.05 - 2.20 (17H, m), 1.04 (3H, t, *J* = 7.5 Hz), 0.92 (3H, t, *J* = 7.5 Hz), 0.86 (3H, d, *J* = 6.6 Hz); IR (film) 3271, 1713, 1694, 1667, 1616 cm^{-1}; HRMS (FAB, NBA) MH^+ calcd for $C_{34}H_{50}N_5O_6$ 624.3761, found 624.3718; $[\alpha]_D^{28}$ -82.6^{o} (*c* 0.25, $CHCl_3$)