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First total synthesis of (±)-Stachyflin

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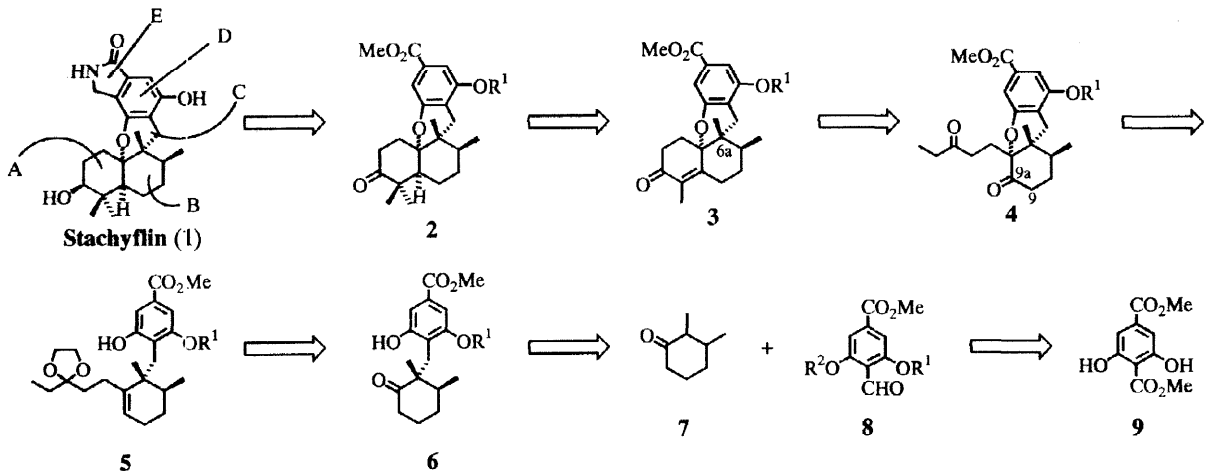
Abstract

We achieved the first total synthesis of (±)-stachyflin in 29 steps, including the construction of *cis*-fused decalin and the formation of an etheral bond at its bridgehead as key transformations.

Keywords: Antivirals; Terpenoids

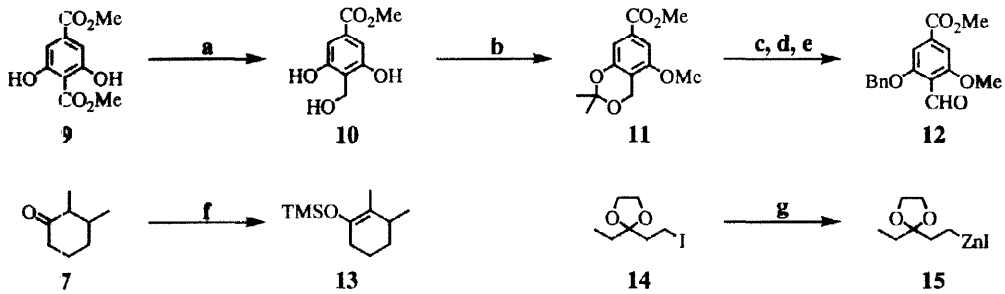
Stachyflin (**1**) is a new natural product isolated in our laboratories from the culture of *Stachybotrys sp.* RF-7260. It exhibits potent anti-influenza A virus activity (EC_{50} = 0.003 μM; virus: A/WSN/33(H1N1), cell: MDBK) [1] and has a novel skeleton. The AB rings and the BC rings of stachyflin are *cis*-fused and there is an etheral bond at the bridgehead of the AB ring junction. Its characteristic structure and biological activity made it an interesting synthetic target.



Scheme 1

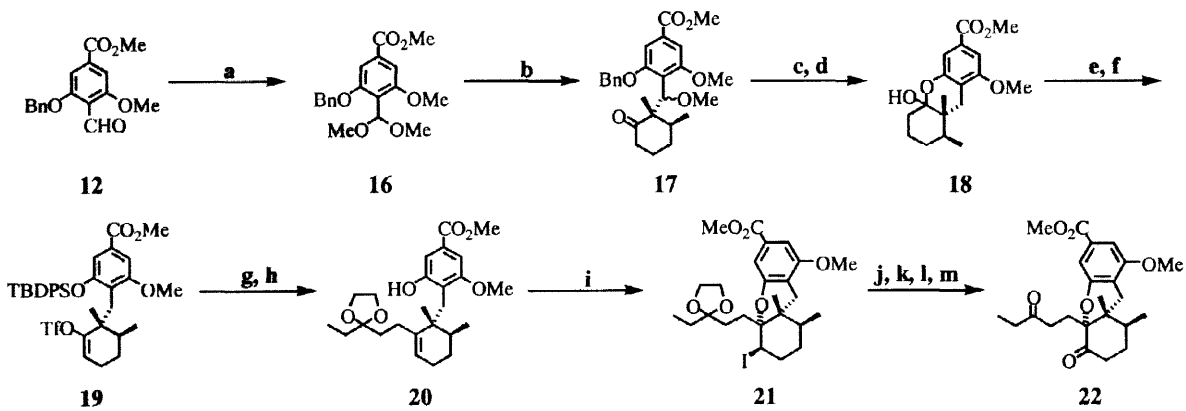
PII: S0040-4039(98)00769-2

The retrosynthetic analysis, shown in Scheme 1, includes two key transformations. One is the construction of the *cis*-fused AB ring and the other is the formation of the etheral bond at the bridgehead. For the former, reduction of enone (**3**) was expected to afford the *cis*-fused decalin because of the steric hindrance caused by the methyl group at the C6a position. For the latter, C ring construction *via* iodoetherification was selected.



Reagents and Conditions: **a**) $NaBH_4$, THF; **b**) *p*-TsOH, acetone; K_2CO_3, $(MeO)_2SO_2$, 61% for a, b; **c**) 1N HCl, MeOH, THF; **d**) BnBr, K_2CO_3, acetone; **e**) PCC, CH_2Cl_2, 74% for c, d, e; **f**) TMSCl, $(TMS)_2NH$, NaI, CH_3CN; **g**) Zn, TMSCl, THF

Scheme 2



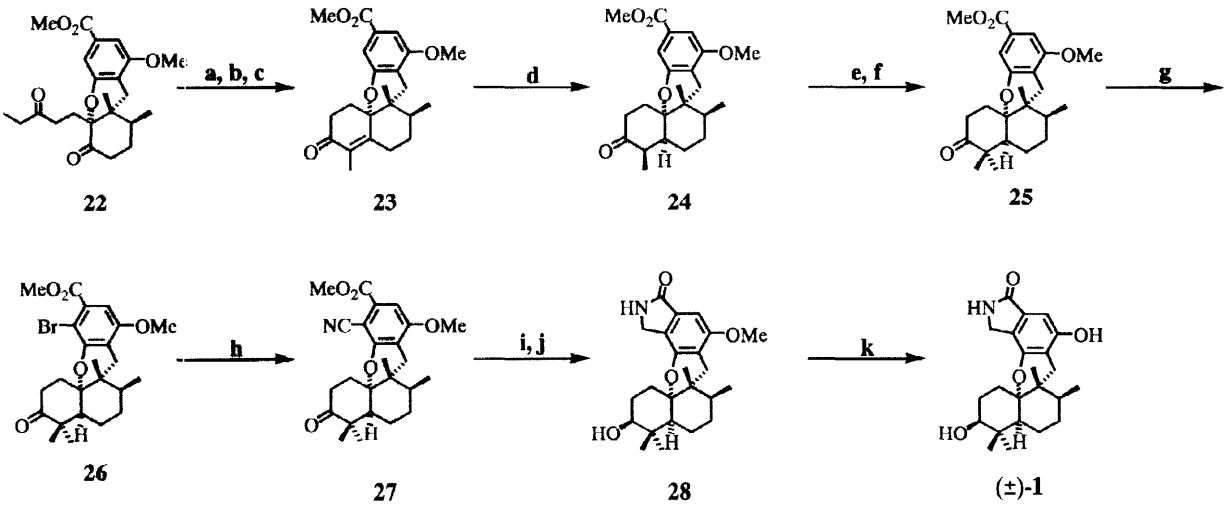
Reagents and Conditions: **a**) $(MeO)_3CH$, *p*-TsOH, MeOH; **b**) **13**, TMSOTf, CH_2Cl_2; **c**) H_2, 10%Pd-C, 1N HCl, acetone; **d**) H_2, 10%Pd-C, AcOH, 65% for a, b, c, d; **e**) TBDPSCl, *t*-BuOK, THF, 81%; **f**) 2-[*N*,*N*-Bis(trifluoromethylsulfonyl)amino]-5-chloro-pyridine [2], KHMDS, THF, 82%; **g**) **15**, $Pd(PPh_3)_4$, HMPA, THF, 85%; **h**) Bu_4NF, THF, 91%; **i**) I_2, propylene oxide, THF, 87%; **j**) DBU, DMSO, 92%; **k**) BH_3·THF, THF; H_2O_2, NaOH; **l**) PCC, CH_2Cl_2, 45% for k, l; **m**) 0.5 N HCl, acetone, 90%

Scheme 3

The six-step conversion to aldehyde (**12**) from dimethyl 3,5-dihydroxytelephthalate (**9**) [3] is outlined in Scheme 2. Noyori's aldol condensation [4] of dimethylacetal (**16**) with TMS enolether (**13**) prepared from ketone (**7**) (Scheme 2) [5] afforded adducts (**17**) as a 1:1 diastereomixture of the benzylic methoxy group, which was converted to **18** by stepwise hydrogenolysis of the benzyl ether and the methoxy group (Scheme 3). Protection of the phenolic hydroxy group of **18** with TBDPSCl followed by conversion of the ketone group to the enoltriflate afforded **19**. Subsequently, the A ring moiety was introduced by palladium-

catalyzed coupling [6] of enoltriflate (**19**) with alkylzinc reagent (**15**) [7] derived from **14** (Scheme 2) [8] and following deprotection of TBDPS afforded **20**. In the first key step, C ring construction succeeded *via* iodoetherification. In this reaction, propylene oxide proved to be an effective HI scavenger. Direct conversion of the iodine function of **21** to the oxygen function failed because of predominant elimination of HI. We then conducted hydroboration [9] and subsequent PCC oxidation[1] to the olefin formed by β-elimination of **21**. Subsequent ethyleneketal deprotection afforded the diketone **22**.

A ring construction was achieved *via* intramolecular aldol cyclization (Scheme 4). The dehydration gave a mixture of α,β- and β,γ-unsaturated ketones, then isomerization under the basic condition afforded the α,β-unsaturated ketone (**23**) as a single isomer.



Reagents and Conditions: **a**) NaOMe, MeOH, THF; **b**) $SOCl_2$, pyridine, CH_2Cl_2; **c**) NaOMe, MeOH, 75% for a, b, c; **d**) H_2, 5%Rh-C, acetone, 52%; **e**) TMSCl, $(TMS)_2NH$, CH_3CN, 80 °C, then NaI[2]; **f**) MeI, tris(dimethylamino)sulfur (trimethylsilyl)difluoride [10], CH_2Cl_2, 75% for e, f; **g**) NBS, DMF, 76% based on recovery; **h**) CuCN, DMF, 80%; **i**) H_2, PtO_2, EtOH, $CHCl_3$; **j**) NaOMe, MeOH, 87% for i, j; **k**) BuSLi, HMPA, 83%

Scheme 4

Next, we tried to construct the *cis*-fused AB ring by 1,4-reduction of the α,β-unsaturated ketone (**23**) with hydrides, but this was unsuccessful because of the steric hindrance. We then tried the hydrogenation after screening catalysts and solvents. We found that Rh-C in acetone was the only conditions that gave the desirable *cis*-fused decalin (**24**) as the major product (*cis*/*trans* = 1.6). After construction of the *cis*-decalin, regioselective introduction of the methyl group to **24** was achieved by methylation of the thermodynamically stable TMS enolether of **24** to afford **25**.

1) Undesirable C9 ketone derivative was also obtained in 25% yield.

2) TMS enolether formation of **24** in this condition provided ca. 15:1 ratio of thermodynamic to kinetic product while a 1:1 ratio mixture was obtained in the usual manner (TMSI, $(TMS)_2NH$, $ClCH_2CH_2Cl$, 0 °C) [11].

In the last stage, the lactam structure was constructed as follows [12]. Bromination of the aromatic ring of **25** with NBS gave **26** in 36% yield, together with the regioisomer and the dibromide. However, these byproducts were quantitatively reduced to **25** ($Pd(PPh_3)_4$, HCO_2Na/DMF) [13] and the yield of **26** was 76% based on recovery. The bromine function of **26** was converted to the nitrile function with CuCN to afford **27**. The nitrile group and the ketone group of **27** were reduced to the amine group and the alcohol group, respectively, by catalytic hydrogenation, in which the reduction of ketone proceeded stereoselectively to the β-alcohol, and subsequent treatment with NaOMe afforded **28**. Finally, demethylation of **28** with BuSLi [14, 15] completed the total synthesis of (±)-stachyflin (**1**). Our synthetic stachyflin was shown to be identical with the natural compound from its 600 MHz ^1H NMR spectrum. Its anti-influenza A virus activity was about half of that of natural (+)-stachyflin.

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