

Tetrahedron Letters 39 (1998) 4347-4350

TETRAHEDRON LETTERS

# First total synthesis of (±)-Stachyflin

## Teruhiko Taishi, Shozo Takechi, and Sachio Mori\*

Shionogi Research Laboratories, Shionogi & Co., Ltd. Fukushima-ku, Osaka 553-0002 Japan

Received 18 March 1998; accepted 8 April 1998

### 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. © 1998 Elsevier Science Ltd. All rights reserved. *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 ( $EC_{50} = 0.003$ )

Stachybotrys sp. RF-7260. It exhibits potent anti-influenza A virus activity (EC<sub>50</sub> = 0.003  $\mu$ M; 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

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<sub>4</sub>, THF; b) *p*-TsOH, acetone;  $K_2CO_3$ , (MeO)<sub>2</sub>SO<sub>2</sub>, 61% for a, b; c) 1N HCl, MeOH, THF; d) BnBr,  $K_2CO_3$ , acetone; e) PCC, CH<sub>2</sub>Cl<sub>2</sub>, 74% for c, d, e; f) TMSCl, (TMS)<sub>2</sub>NH, NaI, CH<sub>3</sub>CN; g) Zn, TMSCl, THF

Scheme 2



**Reagents and Conditions: a)** (MeO)<sub>3</sub>CH, *p*-TsOH, MeOH; b) **13**, TMSOTf, CH<sub>2</sub>Cl<sub>2</sub>; c) H<sub>2</sub>, 10%Pd-C, 1N HCl, acetone; d) H<sub>2</sub>, 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<sub>3</sub>)<sub>4</sub>, HMPA, THF, 85%; h) Bu<sub>4</sub>NF, THF, 91%; i) I<sub>2</sub>, propylene oxide, THF, 87%; j) DBU, DMSO, 92%; k) BH<sub>3</sub>·THF, THF; H<sub>2</sub>O<sub>2</sub>, NaOH; l) PCC, CH<sub>2</sub>Cl<sub>2</sub>, 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<sup>1)</sup> to the olefin formed by  $\beta$ -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  $\alpha$ , $\beta$ - and  $\beta$ , $\gamma$ -unsaturated ketones, then isomerization under the basic condition afforded the  $\alpha$ , $\beta$ -unsaturated ketone (23) as a single isomer.



**Reagents and Conditions: a)** NaOMe, MeOH, THF; **b)** SOCl<sub>2</sub>, pyridine, CH<sub>2</sub>Cl<sub>2</sub>; **c)** NaOMe, MeOH, 75% for a, b, c; **d)** H<sub>2</sub>, 5%Rh-C, acetone, 52%; **e)** TMSCl, (TMS)<sub>2</sub>NH, CH<sub>3</sub>CN, 80 °C, then NaI<sup>2</sup>; **f)** MeI, tris(dimethylamino)sulfur (trimethylsilyl)difluoride [10], CH<sub>2</sub>Cl<sub>2</sub>, 75% for e, f; **g)** NBS, DMF, 76% based on recovery; **h)** CuCN, DMF, 80%; **i)** H<sub>2</sub>, PtO<sub>2</sub>, EtOH, CHCl<sub>3</sub>; **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  $\alpha,\beta$ 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.

<sup>1)</sup> Undesirable C9 ketone derivative was also obtained in 25% yield.

<sup>2)</sup> 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)<sub>2</sub>NH, ClCH<sub>2</sub>Cl, 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<sub>3</sub>)<sub>4</sub>, HCO<sub>2</sub>Na/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  $\beta$ -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 <sup>1</sup>H NMR spectrum. Its anti-influenza A virus activity was about half of that of natural (+)-stachyflin.

Acknowledgment: We are grateful to Dr. T. Fujiwara for measuring activity against the influenza A virus.

#### References

- Kamigauchi T, Fujiwara T, Tani H, Kawamura Y, Horibe I. (Shionogi & Co., Ltd): Sesquiterpene derivatives having antiviral activity. PCT WO 9711947 A1, April 3, 1997.
- [2] Comins DL, Dehghani A. Tetrahedron Lett. 1992;42:6299-6302.
- [3] Brunner K. Monatsh. Chem. 1928;50:216-224.
- [4] Murata S, Suzuki M, Noyori R. J. Am. Chem. Soc. 1980;102:3248-3249.
- [5] Ulery HE, Richards JH. J. Am. Chem. Soc. 1964;86:3113-3117.
- [6] Tamaru Y, Ochiai H, Nakamura T, Yoshida Z. Tetrahedron Lett. 1986;27:955-958.
- [7] Takai K, Kakiuchi T, Utimoto K. J. Org. Chem. 1994;59:2671-2673.
- [8] Hamilton RJ, Mander LN, Sethi SP. Tetrahedron 1986;42:2881-2892.
- [9] For information on regioselectivity in hydroboration of olefins that have a functional group at the allylic position, see Pelter A, Smith K, Brown HC: Katritzky AR, Meth-Cohn O, Rees CW, editors. Borane Reagent. Academic Press: London, 1988:168-170.
- [10] Noyori R, Nishida I, Sakata J. Tetrahedron Lett. 1980;21:2085-2088.
- [11] Miller RD, McKean DR. Synthesis;1979:730-732.
- [12] Wrobel J, Dietrich A, Gorham BJ, Sestanj K. J. Org. Chem. 1990;55:2694-2702.
- [13] Helquist P. Tetrahedron Lett. 1978:1913-1914.
- [14] Welch SC, Rao ASCP Tetrahedron Lett. 1977:505-508.
- [15] Aristoff PA, Harrison AW, Huber M. Tetrahedron Lett. 1984;25:3955-3958.