Pergamon

Tetrahedron Letters, Vol. 38, No. 22, pp. 3973-3976, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00793-4

Total Syntheses of $O^{4,9}$-Dimethyl Stealthins A and C

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Abstract: $O^{4,9}$-Dimethylstealthin A (11-amino-5-hydroxy-2-hydroxymethyl-4,9-dimethoxybenzo[*b*]fluoren-10-one) and $O^{4,9}$-dimethylstealthin C (11-amino-5-hydroxy-4,9-dimethoxy-2-methylbenzo[*b*]fluoren-10-one), methylated derivatives of radical scavengers produced by *Stereptomyces viridochromogenes*, were synthesized using the Suzuki coupling reaction as a key step.
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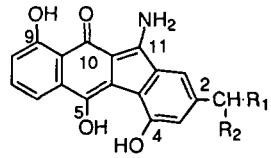
In 1992, the Seto group reported the isolation of stealthin A and B (**1** and **2**, Fig. 1) as potent radical scavengers from *Streptomyces viridochromogenes*.[1] The Gould group synthesized stealthin C (**3**, Fig. 1) and demonstrated its existence in kinamycin biosynthesis.[2,3]

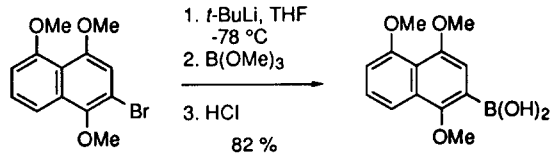


1: R_1 = OH, R_2 = H
2: R_1 , R_2 = O
3: R_1 = R_2 = H

Figure 1. Structures of Stealthins A, B and C

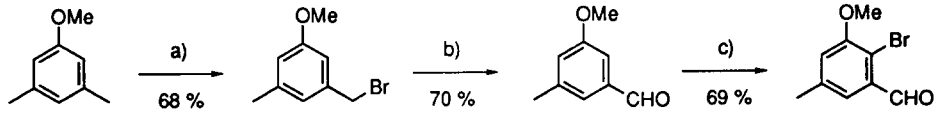
The strong biological activities as well as the unique skeleton of these compounds prompted us to synthesize them. In this communication, we describe the efficient synthesis of $O^{4,9}$-dimethylstealthin C and $O^{4,9}$-dimethylstealthin A. Our plan for constructing the benzo[*b*]fluoren-11-one skeleton was by using Friedel-Crafts cyclization of biaryl carboxylic acid, obtained by using the Suzuki coupling reaction of naphthyl boronic acid and aryl halide.

The boronic acid **5** required for the biaryl synthesis was available in a few steps from the known 2-bromo-1,4,5-trimethoxynaphthalene **4**,[4] by lithiation, boration and hydrolysis (Scheme 1). The partner of the biaryl synthesis was prepared by the following reaction sequence. Monobromination of 3,5-dimethylanisole **6** with *N*-bromosuccinimide (NBS) yielded the benzyl bromide **7** which when oxidized by the Hass procedure[5] using 2-nitropropane and sodium ethoxide afforded the aldehyde **8**. This aldehyde **8** was



4 5

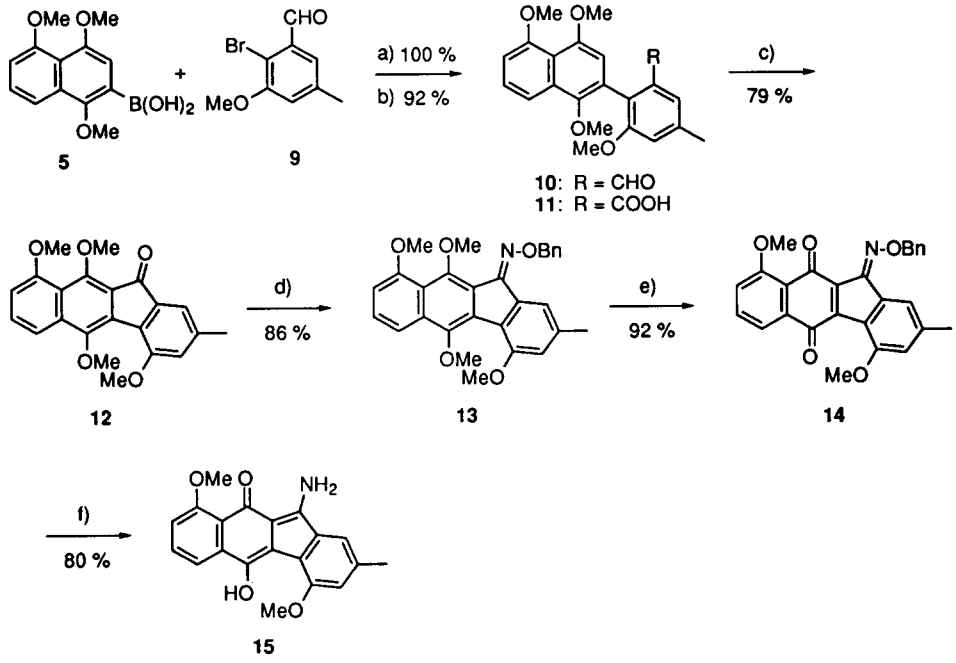
Scheme 1



6 7 8 9

Conditions: a) NBS, $(PhCO_2)_2$, CCl_4, reflux, b) Me_2CHNO_2, EtONa, 90 °C, c) *N,N,N'*-trimethylethylenediamine, *n*-BuLi, THF, -65 °C; *n*-BuLi, -65~-25 °C; $BrCF_2CF_2Br$, -78 °C.

Scheme 2



5 9 12 13 14 15

Conditions: a) $Pd(PPh_3)_4$, DME, 2M Na_2CO_3, b) 35% H_2O_2, 15% NaOH, MeOH, 90 °C, c) i) $(COCl)_2$, CH_2Cl_2, DMF (cat), ii) $TiCl_4$, CH_2Cl_2, 0 °C, d) $BnONH_2HCl$, $MeOH/H_2O$, AcONa, reflux, e) CAN, $MeCN/H_2O$, 2,6-pyridine dicarboxylic acid *N*-oxide, f) Zn, AcOH, 140 °C.

Scheme 3

subjected to ortho directed metalation using the Comins procedure[6] with lithium *N,N,N'*-trimethylethylenediamide. Treatment of the resulting lithium α-amino alkoxide with 1,2-dibromotetrafluoroethane afforded the bromide **9** (Scheme 2).

For the synthesis of benzo[*b*]fluoren-11-one, the naphthyl boronic acid **5** and the bromide **9** were coupled under the modified Suzuki conditions[7] to give the biaryl aldehyde **10** in good yield. Attempts at oxidation of the aldehyde **10** using Jones' reagent, pyridinium dichromate, potassium permanganate or silver oxide did not give satisfactory results. Finally, alkaline hydrogen peroxide oxidation was found to give the carboxylic acid **11** in good yield (91%). Friedel-Crafts cyclization of **11** with titanium(IV) chloride as a catalyst gave the benzo[*b*]fluoren-11-one **12** in excellent yield. The physical data of **12** were in good agreement with the reported values.[8]

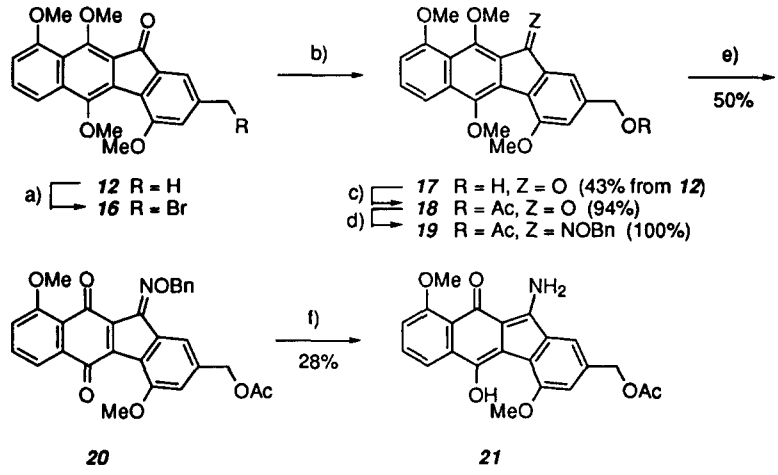
As the attempted demethylation of **12** with boron tribromide gave a complex mixture of partially demethylated products, we proceeded to the functionalization of **12** without complete demethylation followed by reprotection with removable protecting groups. Thus, the benzofluorenone **12** was treated with *O*-benzylhydroxylamine to give *O*-benzyloxime **13**, which upon oxidation with ammonium cerium(IV) nitrate (CAN) gave the benzo[*b*]fluoren-9,10,11-trione derivative **14**. Reduction of **14** with zinc and acetic acid afforded 11-amino-5-hydroxy-4,9-dimethoxy-2-methylbenzo[*b*]fluoren-10-one **15** ($O^{4,9}$-dimethylstealthin C) (Scheme 3).[9] Although the ^{13}C NMR, nOe NMR, IR and UV spectra of **15** were consistent with the structure proposed, the FAB mass spectrum showed the molecular peak at m/z 639 (2M-31). The reason for this discrepancy remains unknown. The hydrolysis of protecting groups of **15** with boron tribromide gave a photo- and oxygen-sensitive product, which upon immediate acetylation gave a mixture of partially acetylated products.

Having established the construction of the stealthin C framework, we next carried out the synthesis of stealthin A. Compound **12** was transformed into **19** by the following reaction sequence: a) bromination to **16**, b) hydrolysis to **17**, c) acetylation to **18** and d) oximation to **19**. The benzyl oxime **19** was oxidized with CAN to give the fluorenequinone **20**, which was then reduced with zinc and acetic acid to give 2-acetoxymethyl-11-amino-5-hydroxy-4,9-dimethoxy-benzo[*b*]fluoren-10-one **21** (O^{12}-acetyl-$O^{4,9}$-dimethylstealthin A) (Scheme 4). The physical data of **21**[10] supported the structure proposed but, again, the FAB MS spectrum showed a discrepansy (m/z 755, 2M-31). However, the FAB MS spectrum of the *N,O,O*-triacetate of **21** showed the normal molecular peak at m/z 479 (M+2). The attempted hydrolysis of protecting groups of **21** with boron tribromide failed owing to partial decomposition, and photo-lability of the demethylated products.

Although the final demethylation was not achieved, the present work offers new, rather stable and useful compounds to study radical scavenging action.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Science Research from the Ministry of Education (Grant No. C-08680640), Science and Culture of Japan and by financial support from Kinki University.



Conditions: a) NBS, $(PhCO_2)_2$, CCl_4, reflux, b) $CaCO_3$, 1,4-dioxane-H_2O, reflux, c) Ac_2O, py, DMAP (cat), d) $BnONH_2HCl$, AcONa, MeOH-H_2O, e) CAN, 2,6-pyridinedicarboxylic acid *N*-oxide, MeCN-H_2O, f) Zn, AcOH, reflux

Scheme 4

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8. Gore, M.P.; Gould, S.J.; Weller, D.D. *J. Org. Chem.* **1992**, 57, 2774-2783. The IR absorpton bands were in good agreements with those reported except a band at 1733 cm^{-1}. From the structure of **12** this band is not explicable, so it may be a mistake.
9. Spectral data for **15**: Mp >300 ℃; IR (KBr disk) 3197, 2922, 1642, 1625, 1581, 1463, 1313, 1296 cm^{-1}; UV (EtOH) λ_{max} 205, 280, 472, 507 nm; ε_{max} 1.07×10^4, 1.11×10^4, 2.67×10^3,2.61×10^3; ^1H NMR (270 MHz, $CDCl_3$) δ 1.58 (br. 2H), 2.22 (s, 3H), 3.82 (s, 3H), 4.10 (s, 3H), 6.61 (s, 1H), 6.63 (s, 1H), 6.97 (dd, 1H, J = 8.1, 1.1 Hz), 7.47 (t, 1H, J = 8.1 Hz), 7.59 (dd, 1H, J = 8.1, 1.1 Hz), 10.67 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.5, 55.9, 56.4, 111.1, 114.7, 114.8, 117.3, 118.1, 120.0, 121.2, 131.0, 133.6, 136.5, 138.1, 140.6, 142.5, 150.1, 51.5, 161.0, 180.3. Among the three tautomers assumed, the one corresponding to the natural product was shown to be the most stable by means of MOPAC calculation.
10. Spectral data for **21**: Mp 288 ℃; IR (KBr disk) 3205, 1739, 1641, 1622, 1581, 1463, 1309, 1288, 1267, 1224, 1122, 1039, 1022, 704 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.01 (s, 3H), 3.83 (s, 3H), 4.15 (s, 3H), 4.93 (d, 1H, J = 11.9 Hz), 4.99 (d, 1H, J = 11.9 Hz), 6.79 (d, 1H, J = 1.1 Hz), 6.85 (d, 1H, J = 1.1 Hz), 7.01 (dd, 1H, J = 8.1, 1.1 Hz), 7.50 (t, 1H, J = 8.1 Hz), 7.63 (dd, 1H, J = 8.1, 1.1 Hz), 10.81 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.0, 56.1, 56.7, 66.4, 110.2, 114.6, 114.9, 117.6, 118.2, 121.2, 122.6, 131.5, 134.0, 135.7, 136.3, 139.8, 142.5, 151.7, 151.8, 161.2, 170.8, 180.7.

(*Received in Japan* 31 *March* 1997; *revised* 14 *April* 1997; *accepted* 21 *April* 1997)