JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

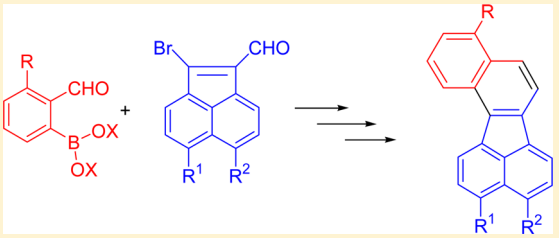
Total Synthesis of the Natural Product Benzo[*j*]fluoranthene-4,9-diol: An Approach to the Synthesis of Oxygenated Benzo[*j*]fluoranthenes

Santosh Lahore,[†] Umesh Narkhede,[†] Lucio Merlini, and Sabrina Dallavalle*

Department of Food, Environmental and Nutritional Sciences, Division of Chemistry and Molecular Biology, Università di Milano, Via Celoria 2, 20133 Milano, Italy

Supporting Information

ABSTRACT: A synthetic sequence to the benzo[*j*]fluoranthene nucleus is described. Crucial steps of the procedure include a Suzuki coupling between appropriately substituted 2-bromo-acenaphthylene-1-carbaldehydes and 2-formylbenzeneboronates followed by McMurry ring closure. The synthesis represents a new approach to the benzo[*j*]fluoranthene ring system and specifically provides a method for the rapid preparation of differently substituted derivatives. Following this strategy, the first total synthesis of the recently isolated natural product benzo[*j*]fluoranthene-4,9-diol was carried out.



INTRODUCTION

Small molecules produced in biological contexts have been, and still are, a large reservoir of new biologically active substances, which can become scaffolds for the discovery of drugs, agrochemicals, or can be utilized in other applications.[1]

The fluoranthene carbon skeleton with annelated rings is of interest for different areas of chemistry, including medicinal chemistry and material science for organic electronics as well as sensing.[2]

A number of polyketide-derived fungal metabolites, mostly from xylariaceous fungi,[3] possess a differently oxygenated and/or reduced benzo[*j*]fluoranthene nucleus. Examples are bulgarein,[4] bulgarhodin,[4] hortein,[5] daldinones A–D,[6,7] truncatone,[8] hypoxylonols A,B,[9] and xylarenol.[10] There are also some unnamed analogues,[11] among which is benzo[*j*]fluoranthene-4,9-diol, recently isolated by Tan and co-workers[12] as one of the metabolites of Mantis-associated *Daldinia eschscholzii* fungus (Figure 1).

It is quite likely that these compounds derive from an oxidative phenol coupling of two hydroxylated naphthalene units, followed by further oxidative condensation.[7] This hypothesis is supported by the fact that in most of the metabolites, the carbon atoms 3, 4, 9, 10 are oxygenated.

Some of them exhibit significant biological activity, e.g., topoisomerase I inhibition for bulgarein,[13] cytotoxicity for daldinone C and D,[7] immunosuppressive activity for benzo[*j*]-fluoranthene-4,9-diol[12] and tyrosine kinase inhibition[10] for other compounds.

To the best of our knowledge, no attempt to synthesize any of these compounds has been reported in literature so far.

The benzo[*j*]fluoranthene nucleus has been little studied from a synthetic point of view. Apart from the parent hydrocarbon, which can be obtained by gas phase high temperature reactions,[14] few syntheses of substituted benzo-[*j*]fluoranthenes have been reported in the literature so far.

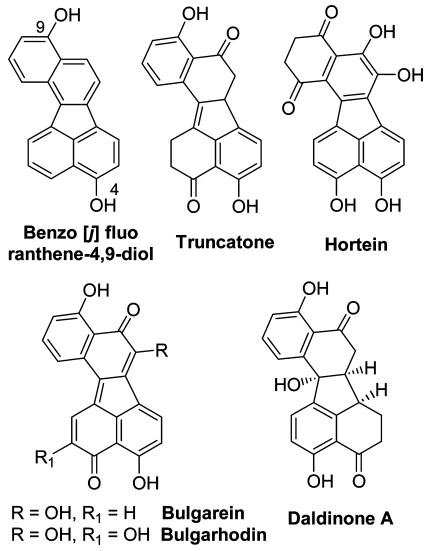


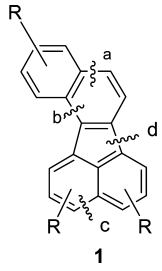
Figure 1. Polyketide-derived fungal metabolites with benzo[*j*]-fluoranthene nucleus.

Ring closures with Friedel–Crafts reactions according to disconnections *a*,[15] *b*,[16,17] and *c*[15,16] (Scheme 1) or with a Suzuki reaction (disconnection *d*[18]) have been reported to prepare fluoro, methoxy, and methylthio derivatives by Rice[15,16,18] and Panda.[17] The recent synthesis of 10,11-dihydrobenzo[*j*]fluoranthen-12-one by Chang[19] mimics the last steps of the putative biosynthetic scheme.[7]

Continuing our interest in potential antitumor compounds, we developed a convergent and efficient synthetic pathway to prepare oxygenated natural metabolites, as well as their

Received: August 20, 2013
Published: September 30, 2013

Scheme 1. Retrosynthetic Disconnections of Benzo[*j*]fluoranthene Ring (1)



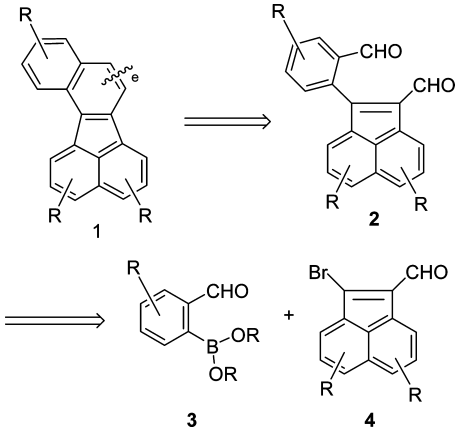
1

analogues. Following this procedure, the first total synthesis of the recently isolated benzo[*j*]fluoranthene-4,9-diol[12] was carried out and is reported here.

RESULTS AND DISCUSSION

As we needed a rapid and versatile way for the construction of the benzo[*j*]fluoranthene skeleton, in which the introduction of substituents could be easily modulated, we developed a retrosynthetic sequence following a different disconnection (*e*) (Scheme 2).

Scheme 2. Retrosynthetic Analysis for Benzo[*j*]fluoranthene



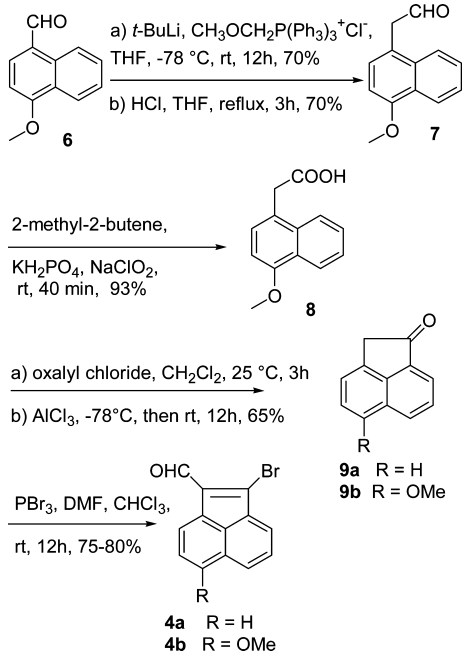
The crucial step of our strategy was an intramolecular McMurry coupling reaction of a dialdehyde **2**, which would allow the construction of the pentacyclic system.[20] In turn, compounds **2** could be obtained by Suzuki reaction of a boronate (**3**) with a bromoacenaphthylenecarbaldehyde (**4**).

To test the feasibility of our approach, we first synthesized the unsubstituted benzo[*j*]fluoranthene. The strategy was then applied to the preparation of oxygenated compounds.

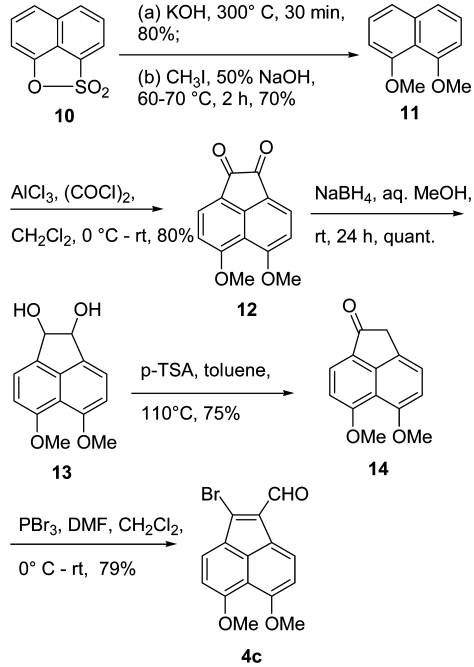
Initially, we concentrated on the synthesis of the building blocks **4** (Schemes 3 and 4). Compound **4a** was prepared starting from acenaphthene **5**, according to a reported procedure.[21]

The synthesis of 2-bromo-6-methoxyacenaphthylene-1-carbaldehyde **4b**, required for the preparation of the natural compound benzo[*j*]fluoranthene-4,9-diol, was accomplished from ketone **9b**. This was obtained in four steps from **6** by a cleaner and shorter sequence than the one described in the literature.[22] Reaction of commercially available 4-hydroxy-1-naphthaldehyde **6** with $Ph_3P{=}CHOCH_3$ and subsequent acidic hydrolysis gave the homologous aldehyde **7**. Oxidation to acid **8** followed by intramolecular Friedel–Crafts acylation gave ketone **9b** in good yield. Compounds **9a,b** were converted

Scheme 3. Synthesis of Acenaphthylen-1(2*H*)-ones



Scheme 4. Synthesis of 2-Bromo-5,6-dimethoxyacenaphthylene-1-carbaldehyde



into the bromoaldehydes **4a,b** by an Arnold-modified Vilsmeier–Haack reaction.[23] (Scheme 3).

As in most naturally occurring benzo[*j*]fluoranthenes, carbons 3 and 4 are oxygenated, the synthesis of a compound with two methoxy groups in those position was undertaken, starting from 2-bromo-5,6-dimethoxyacenaphthylene-1-carbaldehyde **4c** (Scheme 4).

Naphthosultone **10** was thermally hydrolyzed[24] with KOH at 300 °C for 30 min to give 1,8-dihydroxynaphthalene in 80% yield. Methylation by methyl iodide under phase transfer conditions[25] with Aliquat336, followed by Friedel–Crafts acylation with oxalyl chloride and $AlCl_3$ in dry dichloro-

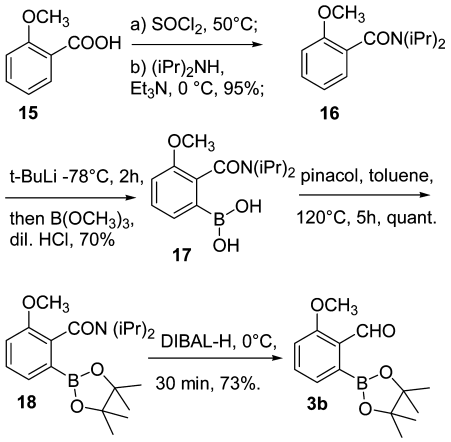
dx.doi.org/10.1021/jo401887t | J. Org. Chem. 2013, 78, 10860–10866

methane[25] afforded cyclic diketone **12** in high yield. Subsequently, reduction with sodium borohydride in ethanol−water medium, gave quantitatively 5,6-dimethoxyacenaphthene-1,2-diol **13**, which was dehydrated smoothly by *p*-TSA in dry toluene to give 5,6-dimethoxyacenaphthenone **14** in 75% yield.[26] Applying Arnold-modified Vilsmeier−Haack conditions[23] to **14**, the requested intermediate *β*-bromovinylaldehyde **4c** was obtained using PBr_3-DMF in chloroform at 0 °C.

With aldehydes **4a−c** in our hands, we turned to the second building block required for the Miyaura−Suzuki coupling, e.g., compound **3**.

Boronate **3b** was synthesized starting from 2-methoxybenzoic acid **15**, which was converted in 95% yield into the *N*-diisopropylamide **16**[27] via the acid chloride. The conversion to the amide group allowed both directed ortho-metalation to insert the boronic acid group, and the synthesis of the aldehyde by reduction. Thus, generation of a carbanion ortho to the *N*,*N*-diisopropyl amide group by *tert*-BuLi in THF at −78 °C for 2 h, followed by quenching with trimethyl borate and acidic workup, gave regiospecifically *N*,*N*′-diisopropylcarbamoyl-3-methoxy-1-phenylboronic acid **17**.[28] This was protected by reaction with pinacol in toluene under azeotropic distillation conditions, to give pinacolate **18**, which afforded aldehyde **3b** in 73% yield by treatment with DIBAL-H at 0 °C (Scheme 5).

Scheme 5. Synthesis of 3b

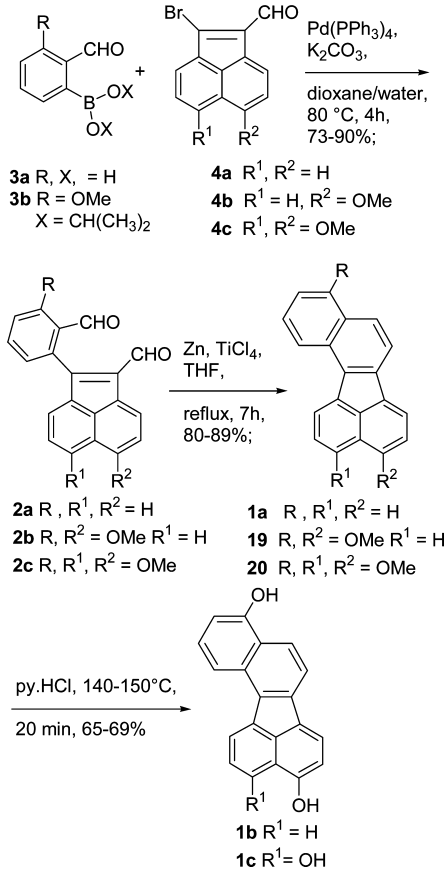


The two building blocks **3** and **4** were subjected to a Suzuki condensation for the construction of the polycyclic system. Several attempts were made to couple model intermediates **3a** and **4a** by using various bases and solvents. Use of $Pd(PPh_3)_4$ as a palladium source and aq. Na_2CO_3, KOAc, or CsF as a base in DMF, toluene, DMSO, or DME gave undesirable hydrolytic deboronation products and the homocoupled product of *β*-bromovinyl aldehyde. By using $Pd(OAc)_2$ with K_2CO_3 as a base under phase transfer catalysis, a small amount of the expected dialdehyde occurred. A satisfactory conversion, though, was finally obtained by $Pd(PPh_3)_4$ with K_2CO_3 in 1,4-dioxane:water medium. Under these optimized conditions, **2a** was synthesized in 73% yield .

Boronate **3b** was coupled under the same conditions with **4b** and **4c** to give dialdehydes **2b** and **2c**, respectively, in high yields (Scheme 6).

Finally, treatment of the dialdehydes **2a−c** with $Zn/TiCl_4$ in THF[29] under McMurry conditions, followed by deprotection of hydroxy groups using pyridine hydrochloride at 140−150 °C gave benzo[*j*]fluoranthenes **1a−c**. The ^1H and ^{13}C NMR

Scheme 6. Synthesis of Benzo[*j*]fluoranthene



spectra of **1b** completely matched the spectra reported for the natural compound.

CONCLUSION

In conclusion, a synthetic sequence to the benzo[*j*]fluoranthene nucleus has been developed, which could be adopted for the synthesis of variously substituted compounds with this skeleton. Crucial steps for our strategy include a Suzuki coupling followed by a McMurry ring closure. The approach is modular and rapid and can be utilized to synthesize natural products, biologically active analogues or building blocks for the preparation of materials.

Work is in progress to synthesize C-7 and/or C-8 oxygenated compounds by coupling the dialdehydes under different conditions.

EXPERIMENTAL SECTION

General Experimental Method. All reagents and solvents were reagent grade or were purified by standard methods before use. Melting points were determined in open capillaries and are uncorrected. NMR spectra were recorded at 300 MHz. Chemical shifts (*δ* values) and coupling constants (*J* values) are given in ppm and Hz, respectively. Solvents were routinely distilled prior to use; anhydrous tetrahydrofuran (THF) and ether (Et_2O) were obtained by distillation from sodium-benzophenone ketyl; dry methylene chloride was obtained by distillation from phosphorus pentoxide. All reactions requiring anhydrous conditions were performed under a positive nitrogen flow, and all glassware were oven-dried and/or flame-dried. Isolation and purification of the compounds were performed by flash column chromatography on silica gel 60 (230−400 mesh). Analytical thin-layer chromatography (TLC) was conducted on Fluka TLC plates (silica gel 60 F_{254}, aluminum foil).

dx.doi.org/10.1021/jo401887t | J. Org. Chem. 2013, 78, 10860−10866

Compounds **9a**,[30] 1,8-naphthalendiol,[24] **11**,[31] and **16**[27] were synthesized according to literature procedures.

(4-Methoxy-naphthalen-1-yl)acetaldehyde (7).[32] *t*-Butyl lithium (1.7 M in hexane, 4 mL, 6.80 mmol) was added dropwise to a suspension of methoxymethyltriphenylphosphonium chloride (2.20 g, 6.50 mmol) in dry THF (60 mL) at −78 °C in a round-bottom flask under nitrogen. The color of solution turned to red. After stirring for 30 min, 4-methoxy-naphthalene-1-carbaldehyde (1 g, 5.35 mmol) was added in a single lot. The solution was allowed to gradually warm to room temperature, and the color changed to pale yellow. The reaction was stirred at room temperature for 12 h, and then it was quenched by adding diethyl ether (100 mL) and water (50 mL). The aqueous layer was extracted with ether (2 × 25 mL). Evaporation of solvent and purification by flash column chromatography provided a viscous oil. NMR analysis showed it was a 1:1 mixture of (*E*)- and (*Z*)-1-methoxy-4-(2-methoxyvinyl)naphthalene isomers (0.815 g, 70%), which were not separated and were directly used for the next step.

(*E*/*Z*)-1-methoxy-4-(2-methoxyvinyl)naphthalene (0.50 g, 2.30 mmol) was dissolved in 50 mL of THF. A 2.0 M HCl (2.3 mL, 4.60 mmol) solution was added, and the reaction was refluxed for 3 h. The reaction was diluted with ethyl acetate (75 mL), washed with a satd. solution of $NaHCO_3$ (50 mL × 2) water (25 mL), and finally with brine (25 mL). The organic layer was evaporated to give a crude that was purified by flash column chromatography to provide **7** (0.320 g, 70% yield) as a white solid after refrigeration: mp = 55−56 °C; ^{1}H NMR ($CDCl_3$) δ 9.76 (1H, s), 8.37 (1H, d, J = 7.9 Hz), 7.82 (1H, d, J = 7.9 Hz), 7.64−7.50 (2H, m), 7.32 (1H, d, J = 7.9 Hz), 6.82 (1H, d, J = 7.9 Hz), 4.03 (3H, s); ^{13}C NMR ($CDCl_3$) δ 200.4, 155.7, 133.2, 128.7, 127.3, 126.2, 125.5, 123.5, 123.0, 120.3, 103.6, 55.7, 48.1. Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.84; H, 6.06.

2-(4-Methoxynaphthalen-1-yl)acetic acid (8).[33] Compound **7** (0.30 g, 1.50 mmol) was dissolved in a 1:1 solution of H_2O:*t*-BuOH (0.1 M). To this suspension 2-methyl-2-butene (2.10 g, 30 mmol), KH_2PO_4 (0.41 g, 3.0 mmol) and sodium chlorite (0.34 g, 3.75 mmol) were added in sequence, and the mixture was stirred for 40 min at room temperature.[34] The reaction mixture was diluted with ethyl acetate (50 mL), the aqueous layer was re-extracted by ethyl acetate (2 × 15 mL), and the combined organic layers were then treated with saturated aq. $NaHCO_3$ (2 × 20 mL). The basic layer was then washed with ethyl acetate (2 × 15 mL), and then cooled and carefully acidified by dil. HCl. The precipitate formed was filtered, and then dissolved in ethyl acetate and washed with water and with brine. The organic layer was dried and concentrated to give compound **8** (0.30 g, 93% yield) as a white solid: mp = 147−148 °C (lit.[32] 144 °C); ^{1}H NMR ($CDCl_3$) δ 8.32 (1H, d, J = 8.4 Hz), 7.88 (1H, d, J = 8.4 Hz), 7.59−7.46 (2H, m), 7.31 (1H, d, J = 7.8 Hz), 6.76 (1H, d, J = 7.8 Hz), 3.99 (5H, s);^{13}C NMR ($CDCl_3$) δ 178.5, 155.6, 133.0, 128.4, 127.2, 126.1, 125.4, 123.7, 122.9, 121.9, 103.5, 55.7, 38.5. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.10; H, 5.61.

5-Methoxyacenaphthylen-1(2*H*)-one (9b).[22] Oxalyl chloride (38 mg, 0.30 mmol) was added dropwise to a solution of **8** (50 mg, 0.23 mmol) in dry CH_2Cl_2 (1.5 mL) at 0 °C under nitrogen. The solution was stirred at 25 °C for 3 h. The solvent was evaporated to give a colorless oil that was added with dry CH_2Cl_2 (1.5 mL) under nitrogen. The solution was cooled to −78 °C, and then pulverized $AlCl_3$ (52 mg, 0.39 mmol) was added portionwise, and stirring was continued for 12 h at room temperature. The reaction was quenched at −78 °C by dropwise addition of 4 N HCl (0.24 mL), and then it was diluted with CH_2Cl_2 (15 mL), and the aqueous layer was extracted by CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried to give a crude that was purified by flash column chromatography to provide **9b** (30 mg, 65% yield) as a colorless off-white solid: mp = 163−164 °C ; ^{1}H NMR ($CDCl_3$) δ 8.32 (1H, d, J = 7.9 Hz), 7.96(1H, d, J = 7.1 Hz), 7.66 (1H, dd, J = 7.1, 7.9 Hz), 7.33 (1H, d, J = 7.5 Hz), 6.85 (1H, d, J = 7.5 Hz), 4.02 (3H, s), 3.73 (2H, s);^{13}C NMR ($CDCl_3$) δ 204.0, 154.2, 144.2, 134.5, 127.3, 127.2, 126.5, 123.9, 122.1, 121.5, 105.8, 55.8, 41.7. Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09. Found: C, 78.96; H, 5.07.

2-Bromo-6-methoxyacenaphthylene-1-carbaldehyde (4b). PBr_3 (0.22 g, 0.07 mL, 0.81 mmol) was added dropwise at 0 °C to a solution of dry DMF (66 mg, 0.07 mL, 0.91 mmol) and dry chloroform (3 mL), and the resulting white suspension was stirred at room temperature for 30 min. A solution of **9b** (60 mg, 0.30 mmol) in anhydrous chloroform (1.5 mL) was added dropwise over 10 min at 0 °C. After stirring at room temperature for 12 h, the solution was poured into ice cold water. Sodium bicarbonate was carefully added to neutralize the acid, and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with water (2 × 10 mL) and dried to give a residue, which was purified by flash column chromatography to afford **4b** (70 mg, 80% yield) as a orange red solid: mp = 187−188 °C; ^{1}H NMR ($CDCl_3$) δ 10.28 (1H, s), 8.28 (1H, d, J = 8.2 Hz), 8.18 (1H, d, J = 7.9 Hz), 7.91 (1H, d, J = 7.2 Hz), 7.62 (1H, dd, J = 7.2, 8.2 Hz), 6.76 (1H, d, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 188.1, 158.1, 135.5, 133.3, 130.8, 128.5, 128.2, 127.1, 126.6, 126.5, 126.2, 121.4, 105.5, 55.6. Anal. Calcd for $C_{14}H_9BrO_2$: C, 58.16; H, 3.14. Found: C, 58.31, H, 3.12.

5,6-Dimethoxy-acenaphthylene-1,2-dione (12). In an oven-dried flask, 1,8-dimethoxynaphthalene **11** (2 g, 10.64 mmol) was dissolved in dry dichloromethane (35 mL) under argon atmosphere. The resulting solution was cooled to 0−5 °C. After 30 min anhydrous $AlCl_3$ (1.71 g, 12.80 mmol) was added in a single lot, followed by dropwise addition of oxalyl chloride (0.68 g, 480 μL, 5.30 mmol). The reaction mixture was allowed to reach room temperature overnight, and then poured slowly into ice−water (200 mL) containing 40 mL of conc. HCl under stirring. After addition of 50 mL of *n*-hexane, the above mixture was stirred for further 35−40 min. The resultant mixture was filtered through a sintered funnel, and the residue was washed with water (100 mL) and 2% EtOAc/*n*-Hexane (30 mL). Purification by flash column chromatography using acetone−DCM (1:99) as an eluent afforded the diketone as an orange solid (2.06 g, 80% yield): mp = 262−265 °C (dec.); ^{1}H NMR ($CDCl_3$ + TFA) δ 8.06 (2H, d, J = 8.4 Hz), 7.03 (2H, d, J = 8.4 Hz); 4.12 (6H, s); ^{13}C NMR ($CDCl_3$ + TFA) δ 188.3, 163.4, 152.9, 127.1, 120.3, 114.4, 107.6, 57.0. Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.25; H, 4.18.

5,6-Dimethoxyacenaphthene-1,2-diol (13). To a suspension of diketone **12** (2 g, 8.26 mmol) in ethanol (334 mL) and water (71 mL), $NaBH_4$ (6.25 g, 165.30 mmol) was added in portions with stirring at room temperature. The reaction was stirred for further 21 h at room temperature, and then poured into ice-cold water (400 mL), and treated with solid NH_4Cl (16.70 g). DCM (400 mL) was added, and the mixture stirred for 30 min. The organic layer was separated, and the aqueous layer was extracted with DCM (3 × 100 mL). The combined organic layers were dried and evaporated. The obtained residue was washed with EtOAc:hexane (1:99) and filtered through a sintered funnel to give diol **13** in quantitative yield: ^{1}H NMR (DMSO-d_6) Mixture of diastereomers 2:1, Major δ 7.30 (2H, d, J = 7.9 Hz), 6.90 (2H, d, J = 7.9 Hz), 5.60 (2H, d, J = 5.8 Hz, exchanges with D_2O), 5.03 (2H, d, J = 5.8 Hz), 3.84 (6H, s), minor δ 7.46 (2H, d, J = 7.9 Hz), 6.95 (2H, d, J = 7.9 Hz), 5.89 (2H, s), 3.87 (6H, s); ^{13}C NMR (DMSO-d_6) Major δ 155.0, 132.7, 121.2, 107.4, 82.1, 56.0, minor δ 156.1, 139.0, 135.3, 123.0, 80.0, 56.0. Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.45; H, 5.76.

5,6-Dimethoxy-2*H*-acenaphthylen-1-one (14). To a suspension of diol **19** (1.5 g, 6.10 mmol) in dry toluene (150 mL), *p*-toluenesulfonic acid (0.25 g, 1.31 mmol) was added under N_2 atmosphere. The reaction mixture was heated at 80 °C for 2 h. and then cooled to room temperature and washed with aq. satd. $NaHCO_3$ (100 mL). The separated organic layer was sequentially washed with brine (2 × 100 mL) and water (2 × 100 mL). The separated organic layer was dried, and the solvent evaporated to a crude product that was purified by chromatography using acetone:DCM (1:99) as an eluent to give ketone **14** (1.04 g, 75% yield) as an orange colored powder: mp = 133 °C; R_f 0.23 (1% acetone in DCM); ^{1}H NMR ($CDCl_3$) δ 7.94 (1H, d, J = 7.9 Hz), 7.34 (1H, d, J = 7.9 Hz), 7.01 (1H, d, J = 7.9 Hz), 6.87 (1H, d, J = 7.9 Hz), 4.10 (3H, s), 4.01 (3H, s), 3.71 (2H, s); ^{13}C NMR ($CDCl_3$) δ 201.8, 161.2, 154.8, 146.1, 129.3, 127.1, 125.9, 125.7, 123.7, 122.9, 121.8, 114.1, 107.0, 106.2, 56.2, 55.8, 41.5. Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.89; H, 5.27.

dx.doi.org/10.1021/jo401887t | *J. Org. Chem.* 2013, 78, 10860−10866

2-Bromo-5.6-dimethoxyacenaphthylene-1-carbaldehyde (4c). To a precooled solution of dry DMF (0.91 g, 957 μL, 12.30 mmol) in dry chloroform (13.75 mL) under argon atmosphere, PBr_3 (3.03 g, 1.06 mL, 11.19 mmol) was added dropwise at 0 °C over 20 min. The reaction was stirred for 1 h at the same temperature, and then the solution of ketone **14** (0.85 g, 3.73 mmol) in anhydrous chloroform (12.2 mL) was added over 30 min maintaining the temperature to 0 °C. The reaction mixture was allowed to reach room temperature overnight, and then was poured slowly into ice−water mixture (100 g to 100 mL) to avoid emulsion, and neutralized by solid $NaHCO_3$ to pH 7. The organic layer was separated, and the aqueous layer was again extracted with EtOAc (2 × 100 mL). The combined organic layers were dried on Na_2SO_4. Evaporation of solvent gave a crude product that was purified by chromatography using EtOAc:*n*-hexane (30:70) as an eluent to give **4c** (0.22 g, 79% yield) as an orange colored powder: mp = 132−136 °C; ^{1}H NMR ($CDCl_3$ + TFA) δ. 9.91 (1H, s), 8.29 (1H, d, J = 8.2 Hz), 8.05 (1H, d, J = 8.2 Hz), 7.11 (1H, d, J = 8.2 Hz), 6.96 (1H, d, J = 8.2 Hz), 4.16 (3H, s), 4.09 (3H, s); ^{13}C NMR ($CDCl_3$ + TFA) δ 190.6, 165.1, 159.2, 138.0, 132.1, 131.4, 130.6, 129.6, 129.0, 126.0, 112.8, 109.2, 108.2, 57.2, 56.9. Anal. Calcd for $C_{15}H_{11}BrO_3$: C, 56.45; H, 3.47. Found: C, 56.63; H, 3.45.

2-*N*,*N*-Biisopropylcarbamoyl-3-methoxyphenyl-1-boronic acid (17).[28] In an oven-dry flask, *N*,*N*-di-isopropyl-2-methoxybenzamide **16**[27] (2 g, 8.51 mmol) was dissolved in dry THF (50 mL) under argon atmosphere, and the resulting solution was cooled to −78 °C. To the solution ^{t}BuLi (1.7 M solution in hexane, 8.34 mL, 14.13 mmol) was added dropwise over 30 min to avoid rise in temperature. The reaction mixture was stirred at −78 °C for additional 2 h resulting in a thick slurry that was quenched with trimethyl borate (3.42 g, 3.75 mL, 32.87 mmol). The solution was warmed to 25 °C, and THF removed under reduced pressure. The residue was rinsed with DCM (100 mL), and then washed with 10% HCl (3 × 30 mL). The aqueous washings were back extracted with DCM (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, the solvent evaporated under reduced pressure, and the resulting residue was purified by acid−base extraction, to give **17** as a white solid (1.66 g, 70% yield): mp = 149−150 °C; ^{1}H NMR ($CDCl_3$) δ 7.47 (1H, d, J = 7.3 Hz), 7.33 (1H, dd, J = 7.3, 8.2 Hz), 6.96 (1H, d, J = 8.2 Hz), 6.40 (2H, brs), 3.81 (3H, s), 3.62 (1H, sept, J = 6.7 Hz), 3.52 (1H, sept, J = 6.7 Hz), 1.57 (6H, d, J = 6.7 Hz), 1.08 (6H, d, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 171.5, 154.6, 132.0, 129.3, 127.7, 127.2, 112.8, 55.5, 51.7, 46.4, 20.7, 20.5, 20.4. Anal. Calcd for $C_{14}H_{22}BNO_4$: C, 60.24; H, 7.94. Found: C, 60.11; H, 7.96.

***N*,*N*-Diisopropyl-2-methoxy-6-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-benzamide (18).** In a flask fitted with azeotropic distillation condenser under N_2 atmosphere, a suspension of boronic acid **17** (1 g, 3.58 mmol) and pinacol (466 mg, 3.94 mmol) in dry toluene (50 mL) was heated to 120 °C for 5h. Toluene was removed to give the boronate **18** as a white solid (1.23 g, 95% yield): mp = 136−137 °C; R_f 0.35 (30% EtOAc:Hexane); ^{1}H NMR ($CDCl_3$) δ 7.40 (1H, d, J = 7.3 Hz), 7.27 (1H, dd, J = 7.3 Hz), 6.96 (1H, d, J = 8.2 Hz), 3.79 (3H, s), 3.62 (1H, sept., J = 6.7 Hz), 3.49 (1H, sept., J = 6.7 Hz), 1.59 (6H, d, J = 6.7 Hz), 1.31 (12H, s), 1.11 (6H, d, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 168.3, 155.0, 134.7, 128.4, 128.1, 113.8, 84.1, 55.7, 51.1, 45.8, 25.0, 20.6, 20.4. Anal. Calcd for $C_{20}H_{32}BNO_4$: C, 66.49; H, 8.93. Found: C, 66.65; H, 8.90.

2-Methoxy-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde (3b). Under argon atmosphere, to a precooled solution of boronate **24** (430 mg, 1.19 mmol) in anhydrous THF (20 mL) at 0 °C, a solution of DIBAL-H (1 M in hexane, 170 mg, 1.2 mL, 1.19 mmol) was added slowly at 0 °C over 30 min to avoid rise in temperature. The reaction was quenched with 1 M HCl (1.5 mL), pH 7 buffer (10 mL). The organic layer was separated, and the aqueous layer was extracted with saturated brine:ether:DCM (2 × 100 mL). The combined organic layer was dried on Na_2SO_4 and concentrated. The obtained residue was dissolved in minimum amount of hot *n*-hexane, filtered, and concentrated under reduced pressure to give **3b** as a white powder (230 mg, 73% yield): mp = 107−108 °C; R_f 0.30 (30% EtOAc:Hexane); ^{1}H NMR ($CDCl_3$) δ 10.43 (1H, s), 7.52 (1, dd, J = 7.6, 8.8 Hz), 7.05 (1H, d, J = 7.6 Hz), 6.96 (1H, d, J = 8.8 Hz), 3.90 (3H, s); ^{13}C NMR ($CDCl_3$) δ191.0, 161.7, 135.6, 128.3, 124.6, 112.4, 84.2, 55.8, 29.9, 25.0. Anal. Calcd for $C_{14}H_{19}BO_4$: C, 64.15; H, 7.31. Found: C, 64.32; H, 7.28.

2-(2-Formylphenyl)acenaphthylene-1-carbaldehyde (2a). A solution of 2-formylboronic acid **3a** (58 mg, 0.39 mmol), bromoaldehyde **4a** (100 mg, 0.386 mmol) and K_2CO_3 (319 mg, 2.31 mmol) in 1,4-dioxane/water (4/1) was degassed by purging N_2 for 30 min. $Pd(PPh_3)_4$ (8.8 mg, 0.0076 mmol) was added, and the resulting reaction mixture was refluxed at 80 °C for 4 h under N_2 atmosphere, and then cooled to room temperature, diluted with diethyl ether (10 mL) and filtered through a small silica gel bed. The bed was washed with diethyl ether (3 × 10 mL). The resulting mixture was dried and evaporated. Purification by chromatography using EtOAc:*n*-hexane (4:96) as an eluent gave dialdehyde **2a** as a bright orange colored powder (73 mg, 73% yield): mp = 150−151 °C; ^{1}H NMR ($CDCl_3$) δ 10.08 (1H, s), 10.05 (1H, s), 8.49 (1H, d, J = 7.1 Hz), 8.19 (1H, dd, J = 1,5, 8.2 Hz), 8.09 (1H, m), 7.96 (1H, d, J = 8.2 Hz), 7.81−7.57 (6H, m); ^{13}C NMR ($CDCl_3$) δ 190.9, 188.7, 151.4, 139.4, 136.1, 135.7, 135.6, 135.1, 134.0, 132.23, 132.17, 129.9, 129.1, 128.9, 128.74, 128.69, 128.51, 128.48, 128.0, 127.8. Anal. Calcd for $C_{20}H_{12}O_2$: C, 84.49; H, 4.25. Found: 84.62; H, 4.27.

2-(2-Formyl-3-methoxyphenyl)-6-methoxyacenaphthylene-1-carbaldehyde (2b). The compound was prepared following the procedure described for the synthesis of **2a** from **3b** (55 mg, 0.19 mmol) and **4c** (55 mg, 0.19 mmol). Purification by flash column chromatography using EtOAc:*n*-hexane (30:70) as an eluent gave compound **2b** as a bright orange colored solid (70 mg, 80% yield): mp = 82−83 °C; ^{1}H NMR ($CDCl_3$) δ 10.41 (1H, s), 9.96 (1H, s), 8.30 (1H, d, J = 7.7 Hz), 8.25 (1H, m), 7.61 (1H, m), 7.58−7.49 (2H, m), 7.15 (1H, d, J = 8.6 Hz), 7.07 (1H, d, J = 7.7 Hz), 6.85 (1H, d, J = 7.7 Hz), 4.04 (3H, s), 4.01 (3H, s); ^{13}C NMR ($CDCl_3$) δ 190.0, 189.2, 162.1, 158.8, 152.5, 138.1, 135.8, 134.7, 134.3, 129.64, 129.58, 127.8, 127.14, 127.11, 126.5, 124.8, 124.6, 122.3, 112.6, 106.3, 56.3, 56.2. Anal. Calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68. Found: C, 76.89; H, 4.66.

2-(2-Formyl-3-methoxy-phenyl)-5,6-dimethoxy-acenaphthylene-1-carbaldehyde (2c). To a solution of boronate **3b** (166 mg, 0.634 mmol), bromoaldehyde **4c** (200 mg, 0.627 mmol) and K_2CO_3 (518 mg, 3.746 mmol) in 1,4-dioxane/water (11 mL/2.6 mL), previously degassed by purging N_2 for 30 min, $Pd(PPh_3)_4$ (14.5 mg, 0.01 mmol) was added, and the resulting reaction mixture was refluxed at 80 °C for 4 h under N_2 atmosphere. The reaction was cooled to room temperature, diluted with diethyl ether (10 mL), and filtered through a short silica gel bed. The silica gel bed was washed with diethyl ether (3 × 20 mL), and the resulting mixture was dried and evaporated. Purification by flash column chromatography using EtOAc:DCM (2:98) as an eluent, afforded dialdehyde **2c** as a red colored powder (210 mg, 89% yield): mp = 128.4−129 °C; ^{1}H NMR ($CDCl_3$) δ 10.34 (1H, s), 9.92 (1H, s), 8.42 (1H, d, J = 7.9 Hz), 7.64 (1H, dd, J = 7.9, 8.2 Hz), 7.53 (1H, d, J = 7.9 Hz), 7.17 (1H, d, J = 8.2 Hz), 7.11 (1H, d, J = 7.9 Hz), 6.98 (1H, d, J = 7.9 Hz), 6.90 (1H, d, J = 7.9 Hz), 4.10 (3H, s), 4.09 (3H, s), 4.04 (3H, s); ^{13}C NMR ($CDCl_3$) δ 190.3, 188.7, 162.4, 161.6, 159.4, 151.0, 136.7, 134.5, 132.7, 131.3, 130.9, 129.8, 129.7, 127.4, 124.9, 124.8, 112.4, 107.7, 107.5, 107.1, 56.8, 56.7, 56.3. Anal. Calcd for $C_{23}H_{18}O_5$: C, 73.79; H, 4.85. Found: C, 73.92; H, 4.82.

Benzo[*j*]fluoranthene (1a).[18] $TiCl_4$ (55 mg, 316 μL, 2.87 mmol) was carefully added under N_2 atmosphere to dry THF (10 mL) at 0 °C, giving a bright-yellow mixture of $TiCl_4$·2THF complex. The solution was refluxed for 20 min and cooled to room temperature. Zinc dust (406 mg, 6.21 mmol, not activated) was added, and the mixture was refluxed for 2 h, during which the color changed from yellow to dark greenish blue. The mixture was cooled, and pyridine (227 mg, 231 μL, 2.88 mmol) was added. Refluxing continued for 30 min.

A solution of dialdehyde **2a** (40 mg, 0.145 mmol) in dry THF (10 mL) was added, the reaction mixture was refluxed for a further 4 h, and then it was cooled. Saturated aqueous K_2CO_3 solution was added until the aqueous layer became almost colorless and transparent, and then the aqueous layer was extracted with ethyl acetate (2 × 20 mL). Evaporation of the solvent and purification by flash column chromatography on silica gel column provided benzo[*j*]fluoranthene

dx.doi.org/10.1021/jo401887t | J. Org. Chem. 2013, 78, 10860−10866

1a (30 mg, 83% yield): mp = 164 °C (lit.[18] 165 °C). ^{1}H, ^{13}C NMR and analytical data as reported in the literature.[18]

4,9-Dimethoxybenzo[*j*]fluoranthene (19). Prepared from dialdehyde **2b** (50 mg, 145 mmol) following the procedure described for **1a**. The residue was purified by flash column chromatography on silica gel column to provide 3,10-dimethoxybenzo[*j*]fluoranthene as a yellow solid (40 mg, 89% yield): mp = 164−165 °C; ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, d, J = 7.2 Hz), 8.32 (1H, d, J = 8.6 Hz), 8.28 (1H, d, J = 8.6 Hz), 8.13 (1H, d, J = 8.6 Hz), 7.98 (1H, d, J = 8.6 Hz), 7.90 (1H, d, J = 7.6 Hz), 7.67 (1H, m), 7.52 (1H, m), 6.88 (1H, d, J = 7.6 Hz), 6.81 (1H, d, J = 7.6 Hz), 4.07 (3H, s), 4.05 (3H, s); ^{13}C NMR ($CDCl_3$) δ 158.0, 156.5, 138.3, 137.5, 133.4, 133.3, 131.8, 129.7, 127.4, 127.2, 125.4, 124.5, 122.7, 122.3, 122.2, 121.9, 118.8, 116.7, 105.7, 103.2, 56.0, 55.7. Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.73; H, 5.14.

3,4,9-Trimethoxybenzo[*j*]fluoranthene (20). Prepared from dialdehyde **2c** (140 mg, 0.374 mmol) following the procedure described for **1a**. The obtained residue was purified by column chromatography using DCM:Hexane (50:50) as an eluent, to give 3,4,9-trimethoxy-benzo[*j*]fluoranthene as a yellow colored powder (103 mg, 80% yield): mp = 168 °C; ^{1}H NMR ($CDCl_3$) δ 8.37 (1H, d, J = 7.8 Hz), 8.31−8.20 (2H, m), 8.02−7.93 (2H, m), 7.50 (1H, dd, J = 7.8, 7.8 Hz), 7.03−6.92 (2H, m), 6.81 (2H, d, J = 7.3 Hz), 4.10 (3H, s), 4.09 (3H, s), 4.04 (3H, s); ^{13}C NMR ($CDCl_3$) δ 158.7, 158.0, 156.5, 137.3, 135.2, 132.8, 131.3, 130.3, 129.3, 127.0, 125.8, 125.3, 122.6, 120.9, 118.7, 116.7, 114.4, 107.0, 106.8, 103.2, 56.7, 56.6, 55.7. Anal. Calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.84; H, 5.32.

Benzo[*j*]fluoranthene-4,9-diol (1b). A mixture of 4,9-dimethoxybenzo[*j*]fluoranthene (40 mg, 0.128 mmol) and pyridine hydrochloride (537 mg, 4.65 mmol) was heated under N_2 at 140−150 °C for 30 min, during which the solid mixture became homogeneous. After complete conversion, the reaction was allowed to cool to room temperature. The reaction was poured in ice cold water and was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with water (2 × 10 mL) and dried over sodium sulfate to give a residue, which was purified by flash column chromatography to afford **1b** as a dark greenish yellow solid (24 mg, 65% yield): mp = 164−165 °C; ^{1}H NMR (acetone-d_6) δ 9.62 (1H, brs), 9.17 (1H, brs), 8.63 (1H, d, J = 7.0 Hz), 8.38 (1H, d, J = 8.6 Hz), 8.33 (1H, dd, J = 8.5, 0.8 Hz), 8.25 (1H, d, J = 8.0 Hz), 8.09 (1H, d, J = 8.6 Hz), 8.03 (1H, d, J = 7.5 Hz), 7.78 (1H, dd, J = 8.0, 7.0 Hz), 7.50 (1H, dd, J = 8.5, 7.5 Hz), 7.08 (1H, d, J = 7.5 Hz), 6.96 (1H, dd, J = 7.5, 0.8 Hz); ^{13}C NMR (acetone-d_6) δ 157.0, 155.1, 139.2, 138.2, 134.1, 133.3, 133.0, 129.3, 128.6, 127.8, 125.3, 123.9, 123.4, 122.9, 122.7, 119.0, 116.2, 111.2, 108.2. Anal. Calcd for $C_{20}H_{12}O_2$: C, 84.49; H, 4.25. Found: C, 84.65; H, 4.27.

Benzo[*j*]fluoranthene-3,4,9-triol (1c). Prepared following the procedure described for **1b**. Dark green colored powder (75 mg, 69% yield): mp = 175 °C; R_f 0.33 (4% MeOH:DCM); ^{1}H NMR (acetone-d_6) δ 9.97 (1H, brs), 9.06 (1H, brs), 8.43 (1H, d, J = 7.8 Hz), 8.25 (1H, d, J = 8.5 Hz), 8.21 (1H, d, J = 8.5 Hz), 8.07−8.02 (2H, m), 7.42 (1H, d, J = 7.6 Hz), 7.39 (1H, d, J = 7.6 Hz), 7.05 (1H, d, J = 7.8 Hz), 7.00 (1H, d, J = 7.6 Hz), 6.89 (1H, dd, J = 7.6, 0.8 Hz); ^{13}C NMR (acetone-d_6) δ156.8, 156.2, 155.1, 137.9, 132.5, 129.9, 128.1, 128.0, 127.5, 127.4, 124.4, 124.3, 121.7, 121.3, 119.0, 116.4, 111.2, 110.9, 108.2, 104.1. Anal. Calcd for $C_{20}H_{12}O_3$: C, 79.99; H, 4.03. Found: C, 80.16; H, 4.00.

■ ASSOCIATED CONTENT

Supporting Information

Copies of the ^{1}H and ^{13}C NMR spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sabrina.dallavalle@unimi.it.

Author Contributions

†S. Lahore and U. Narkhede contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are indebted to MIUR (PRIN 2009 project) for financial support.

■ REFERENCES

(1) (a) Lachance, H.; Wetzel, S.; Kumar, K.; Waldmann, H. *J. Med. Chem.* **2012**, *55*, 5989−6001. (b) Li, J. W. H.; Vederas, J. C. *Science* **2009**, *325*, 161−165. (c) Ganesan, A. *Curr. Opin. Chem. Biol.* **2008**, *12*, 306−317. (d) Grabowski, K.; Baringhaus, K. H.; Schneider, G. *Nat. Prod. Rep.* **2008**, *25*, 892−904.

(2) For reviews on benzannulated fluoranthenes, see: (a) Scott, L. T. *Pure Appl. Chem.* **1996**, *68*, 291−302. (b) Rabideau, P. W.; Sygula, A. *Acc. Chem. Res.* **1996**, *29*, 235−242. (c) Okujima, T.; Tomimori, Y.; Nakamura, J.; Yamada, H.; Uno, H.; Ono, N. *Tetrahedron* **2010**, *66*, 6895−6900. (d) Xia, Z.-Y.; Su, J.-H.; Fan, H.-H.; Cheah, K.-W.; Tian, H.; Chen, C.-H. *J. Phys. Chem. C* **2010**, *114*, 11602−11606. (e) Yan, Q.; Zhou, Y.; Ni, B.-B.; Ma, Y.; Wang, J.; Pei, J.; Cao, Y. *J. Org. Chem.* **2008**, *73*, 5328−5339.

(3) Stadler, M.; Fournier, J.; Quang, D. N.; Akulov, A. Y. *Nat. Prod. Comm.* **2007**, *2*, 287−304.

(4) (a) Edwards, R. L.; Lockett, H. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2149−2155. (b) Bao, H.; Li, Y. *Junwu Xitong* **2003**, *22*, 303−307.

(5) Brauers, G.; Ebel, R.; RuAngelie, E.; Wray, V.; Berg, A.; Graefe, U.; Proksch, P. *J. Nat. Prod.* **2001**, *64*, 651−652.

(6) Quang, D. N.; Hashimoto, T.; Tanaka, M.; Baumgartner, M.; Stadler, M.; Asakawa, Y. *J. Nat. Prod.* **2002**, *65*, 1869−1874.

(7) Gu, W.; Ge, H. M.; Song, Y. C.; Ding, H.; Zhu, H. L.; Zhao, X. A.; Tan, R. X. *J. Nat. Prod.* **2007**, *70*, 114−117.

(8) (a) Buchanan, M. S., Hashimoto, T., Yasuda, A., Takaoka, S., Kan, Y., Asakawa, Y. *Proc. 37th Symp. Chem. Nat. Prod.*, Tokushima, Japan, 1995, pp 409−414. (b) Hashimoto, T.; Asakawa, Y. *Heterocycles* **1998**, *47*, 1067−1110.

(9) Koyama, K.; Kuramochi, D.; Kinoshita, K.; Takahashi, K. *J. Nat. Prod.* **2002**, *65*, 1489−1490.

(10) Rukachaisirikul, V.; Sommart, U.; Phongpaichit, S.; Hutadilok-Towatana, N.; Rungjindamai, N.; Sakayaroj, J. *Chem. Pharm. Bull.* **2007**, *55*, 1316−1318.

(11) (a) Wrigley, S. K.; Ainsworth, A. M.; Kau, D. A.; Martin, S. M.; Bahl, S.; Tang, J. S.; Hardick, D. J.; Rawlins, P.; Sadheghi, R.; Moore, M. *J. Antibiot.* **2001**, *54*, 479−488. (b) Assante, G.; Bava, A.; Nasini, G. *Appl. Microbiol. Biotechnol.* **2006**, *69*, 718−721.

(12) Zhang, Y. L.; Zhang, J.; Jiang, N.; Lu, Y. H.; Wang, L.; Xu, S. H.; Wang, W.; Zhang, G. F.; Xu, Q.; Ge, H. M.; Ma, J.; Song, Y. C.; Tan, R. X. *J. Am. Chem. Soc.* **2011**, *133*, 5931−5940.

(13) Fujii, N.; Yamashita, Y.; Saitoh, Y.; Nakano, H. *J. Biol. Chem.* **1993**, *268*, 13160−13165.

(14) (a) Mouri, M.; Kuroda, S.; Oda, M.; Miyatake, R.; Kyogoku, M. *Tetrahedron* **2003**, *59*, 801−811. (b) Cho, H. Y.; Ajaz, A.; Himali, D.; Waske, P. A.; Johnson, R. P. *J. Org. Chem.* **2009**, *74*, 4137−4142.

(15) Rice, J. E.; He, Z.-M. *J. Org. Chem.* **1990**, *55*, 5490−5494.

(16) Rice, J. E.; Shih, H.-C.; Hussain, N.; LaVoie, E. G. *J. Org. Chem.* **1987**, *52*, 849−855.

(17) Panda, K.; Venkatesh, C.; Ila, H.; Junjappa, H. *Eur. J. Org. Chem.* **2005**, 2045−2055.

(18) Rice, J. E.; Cai, Z.-W. *J. Org. Chem.* **1993**, *58*, 1415−1424.

(19) Chang, M.-Y.; Lee, T.-W.; Wu, M. H. *Org. Lett.* **2012**, *14*, 2198−2201.

(20) Some, S.; Dutta, B.; Ray, J. K. *Tetrahedron Lett.* **2006**, *47*, 1221−1224.

(21) Jana, R.; Chatterjee, I.; Samanta, S.; Ray, J. K. *Org. Lett.* **2008**, *10*, 4795−4797.

(22) Zhao, C.; Whalen, D. L. *Chem. Res. Toxicol.* **2006**, *19*, 217−222.

(23) Arnold, Z.; Holy, A. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3059−3073.
(24) Parker, K. A.; Iqbal, T. *J. Org. Chem.* **1980**, *45*, 1149−1151.
(25) Eynde, J.; Mailleux, I. *Synth. Commun.* **2001**, *31*, 1−7.
(26) Sangaiah, R.; Gold, A. *J. Org. Chem.* **1987**, *52*, 3205−3211.
(27) Honda, A.; Karen, M.; Waltz, K. M.; Carroli, P. J.; Walsh, P. J. *Chirality* **2003**, *15*, 615−621.
(28) Fu, J. M.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1665−1668.
(29) Lenoir, D. *Synthesis* **1977**, 553−554.
(30) Li, W.-S.; Liu, L. K. *Synthesis* **1989**, 293−295.
(31) Yang, Y.; Lowry, M.; Xu, X.; Escobedo, J. O.; Sibrian-Vazquez, M.; Wong, L.; Schowalter, C. M.; Jensen, T. J.; Fronczek, F. R.; Warner, I. M.; Strongin, R. M. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 8829−8834.
(32) Liu, H.-J; Duong Duc-Phi, T. *Tetrahedron Lett.* **1999**, *40*, 3827−3830.
(33) Inamdar, A. R.; Kulkarni, S. N.; Nargund, K. S. *J. Indian Chem. Soc.* **1967**, *44*, 398−399.
(34) Chakor, J. N.; Merlini, L.; Dallavalle, S. *Tetrahedron* **2011**, *67*, 6300−6307.