Studies toward the synthesis of angularly-oxygenated angucyclines antibiotics

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Dedicated to Professor Karsten Krohn on the occasion of his 60th birthday
(received 31 Mar 04; accepted 17 Aug 04; published on the web 23 Aug 04)

Abstract
The [bis(trifluoroacetoxy)]iodobenzene-mediated oxidative dearomatization of 2-alkoxyarenols, followed *in situ* by trapping of the resulting arenoxenium ions by soft external carbon-based nucleophiles, constitutes a rapid access to highly functionalized naphthoid cyclohexa-2,4-dienones. These synthons can serve as valuable intermediates in the construction of the angularly-oxygenated benz[*a*]anthraquinone ABCD tetracyclic ring system of aquayamycin-like angucyclinones. This methodology so far has led to the elaboration of five-membered ring analogues of the ABC tricyclic unit of these natural products.

Keywords: Angucyclines, aquayamycin, dearomatization, cyclohexa-2,4-dienones, λ^3-iodane

Introduction

Angucyclines along with tetracyclines and anthracyclines are the third class of natural antibiotics featuring a carbotetracyclic skeleton.[1,2] These natural products are isolated from the fermentation broth of *Actinomycetes*; they feature a benz[*a*]anthraquinone framework with varying degree of insaturation and oxygenation, and display a broad spectrum of biological activities including antitumor, antifungal and antiviral properties.[1,2] Their structural diversity has provided organic chemists with attractive targets for the development of various synthetic methodologies. Until now, most synthetic efforts have been directed toward angucyclines with an aromatic B ring. In most cases, the strategy used for constructing the benz[*a*]anthracene framework is based on the Diels-Alder reaction,[3–12] but other synthetic approaches also have been described.[13–22] However, angucyclines bearing two hydroxy groups at the AB ring junction positions (Figure 1) hold a

special status among these targets because (1) their total synthesis still constitutes a real challenge and (2) their biological activities[23–29] are the most therapeutically significant ones e.g., exhibiting antitumor activity against adriamycin- and doxorubicin-resistant P388 leukemia cells.[1,30] In this subclass, two groups are distinguished: angucyclines without and with a C-glycosidic moiety, exemplified by the angucyclinones SS-228Y (**1**) and aquayamycine (**2**), respectively. Inhibition of dopamine β-hydrolase has been reported for both **1** (62.5% at 0.29 μM)[31] and **2** (50% at 0.40 μM).[23] Aquayamycin (**2**) is also known as an inhibitor of tyrosine hydroxylase (50% at 0.37 μM).[24] Vineomycin A_1 (**3**)[32] exhibits antitumour activity against Sarcoma 180 solid tumour in mice, and SS-228Y (**1**) also was found to show cytotoxic activity *in vivo*.[31,33] Saquayamycin A (**4**)[28] and ritzamycin A (**5**) display remarkable activities against L-1210 and HT-29 tumor cells, even though certain saquayamycins have shown some levels of toxicity *in vivo*.

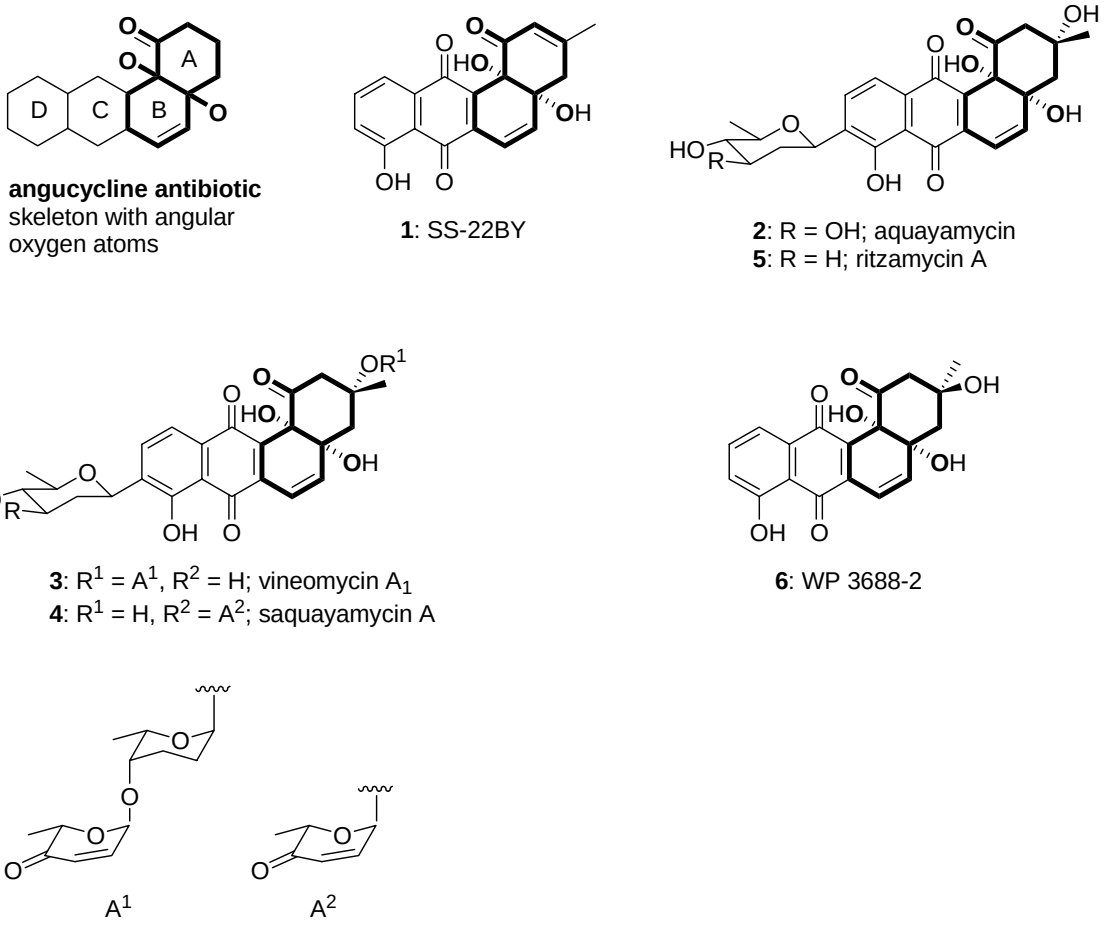
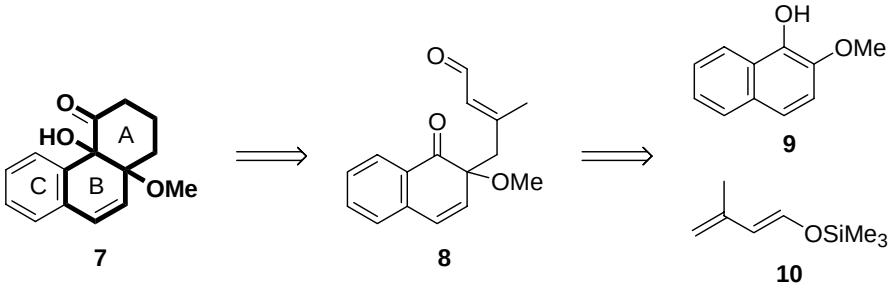


Figure 1

Only two total syntheses of such angucyclines have been reported: Krohn's synthesis of the racemic 8-deoxy analogue of WP 3688-2 (**6**)[34] and the first total synthesis of aquayamycin (**2**),

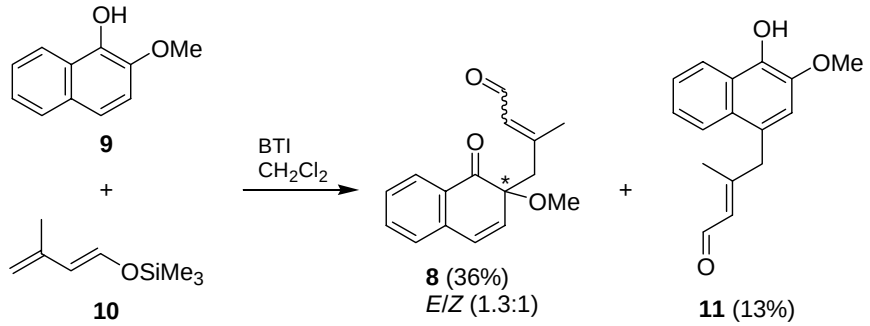
described by the Suzuki group.[35–37] In both cases, the key A ring annulation step was a pinacol-type coupling. Our previous investigation[38,39] on the formation of naphthoid cyclohexane-2,4-dienones via λ^3-iodane-mediated oxidation of 2-alkoxynaphthols such as **9** followed *in situ* by regioselective attack of a carbon-based nucleophile such as **10**, led us to design a new synthetic approach toward the benz[*a*]naphthalene ABC unit of *angularly oxygenated angucyclines* (Scheme 1). We report herein some preliminary results from this novel approach that led to the elaboration of five-membered ring-containing analogues of this angucyclinone unit.



Scheme 1

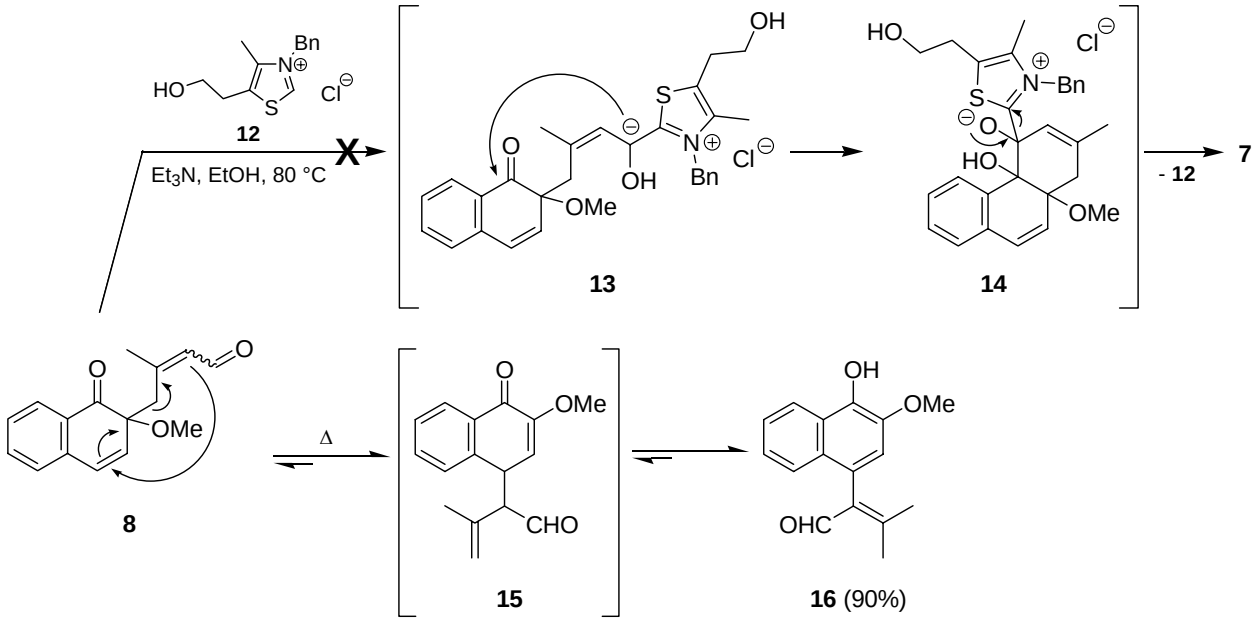
Results and Discussion

The regioselective formation of naphthoid cyclohexa-2,4-dienones by [bis(trifluoroacetoxy)]-iodobenzene-mediated (BTI) oxidative dearomatization of 2-alkoxynaphthols in the presence of external carbon-based nucleophiles is a synthetically valuable process that we have recently introduced.[38,39] The presence of a strong electron-releasing group, like an alkoxy group at the 2-position of the starting naphthol, is essential for regiochemical control of this reaction. In the context of the synthesis of aquayamycin (**2**) and its congeners, we used the silyl enol ether **10**, which presents the advantage of furnishing in one step a four-carbon side-chain adequately functionalized for the A ring annulation. A mixture of 2-methoxynaphthol (**9**) and diene **10** was thus treated with BTI (1.8 equiv) in CH_2Cl_2 at 0 °C for two hours to furnish both the C-2 (**8**) and the C-4 (**11**) adducts in 36% and 13%, respectively (Scheme 2).



Scheme 2

The desired *ortho*-quinol ether **8** was obtained in 36% yield as a 1.3:1 mixture of (*E*)- and (*Z*)-isomers as determined by NOE spectroscopy. We must emphasize the conciseness of this approach to highly functionalized *ortho*-quinol ethers that can then be used for annulation to the ABC ring system of angucyclinones. The first annulating strategy we considered was an intramolecular thiazolium ion-catalyzed aldehyde-ketone benzoin-type condensation (Scheme 3).[40,41] No cyclization was observed under the conditions applied, the only product isolated after heating **8** at 80 °C in absolute ethanol and in the presence of thiazolium chloride **12** and triethylamine was the thermally-induced Cope rearrangement product **16** (90%) (Scheme 3). The reaction performed at lower temperature only led to the recovery of starting material.

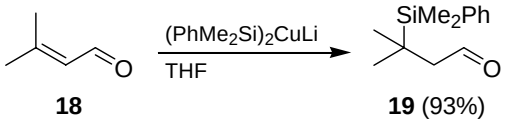


Scheme 3

The next strategy we examined was derived from Kraus' synthesis of an aquayamycin-type ABC ring system;[22] the construction of the A ring was based on the conversion of a B ring-tethered aldehyde into a cyclizing acyl carbanion equivalent. Thus, trimethylsilyl cyanide was added to **8** in the presence of catalytic amounts of potassium cyanide and 18-crown-6, thereby furnishing the protected cyanohydrin **17** in 37% yield (Scheme 5). Treatment of **17** with LDA in THF at –78 °C restored the aldehyde **8**. This somewhat surprising recovery can be explained simply by deprotonation at one of the γ-allylic positions in place of the cyanohydrin group. Since the double bond in the carbon side-chain would allow other reactions to compete with the desired cyclization, we introduced the A ring tertiary 3-OH group, or a function convertible into it before carrying out the cyclization.

Inspired by Krohn's work on the synthesis of angucyclinones,[6,7,42] we wanted to install a silyl group as a hydroxyl group surrogate at position 3 (Scheme 5).[43] We first verified the feasibility of the conjugate addition of a silyl cuprate onto a β,β'-disubstituted enal: Mesityloxide **18** was

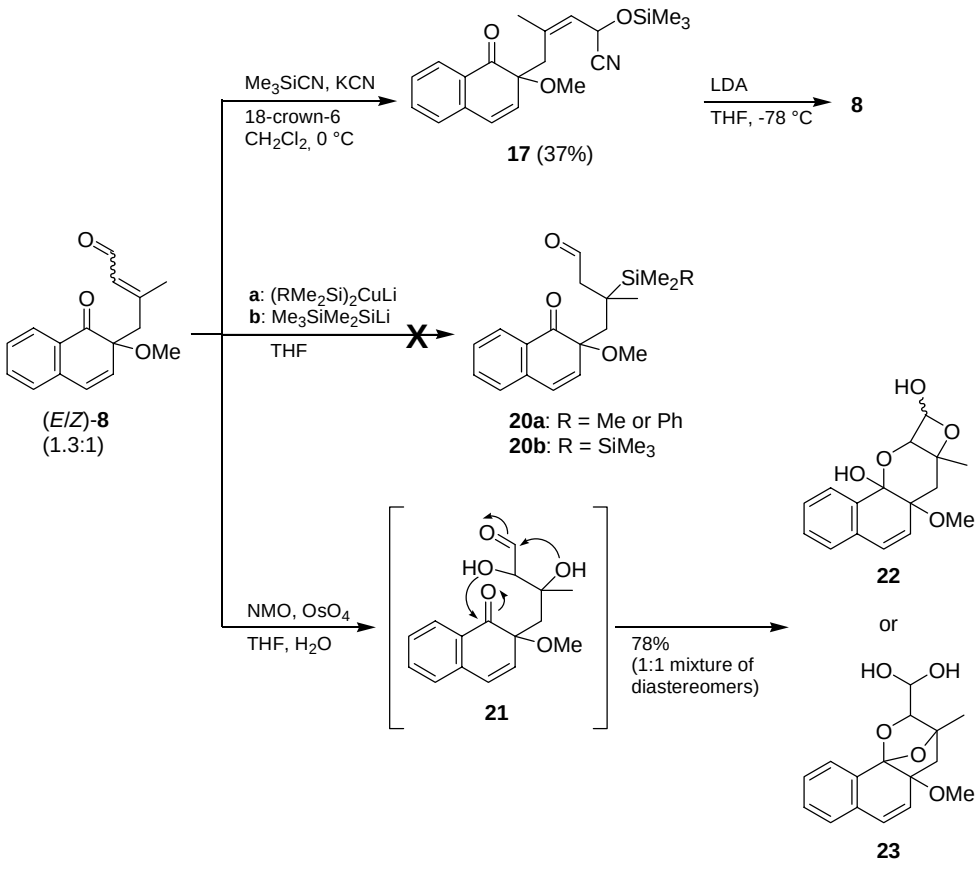
treated with $(PhMe_2Si)_2CuLi$ to furnish the expected 3-(dimethylphenylsilanyl)-3-methylbutanal (**19**) in high yield (Scheme 4).



18 **19** (93%)

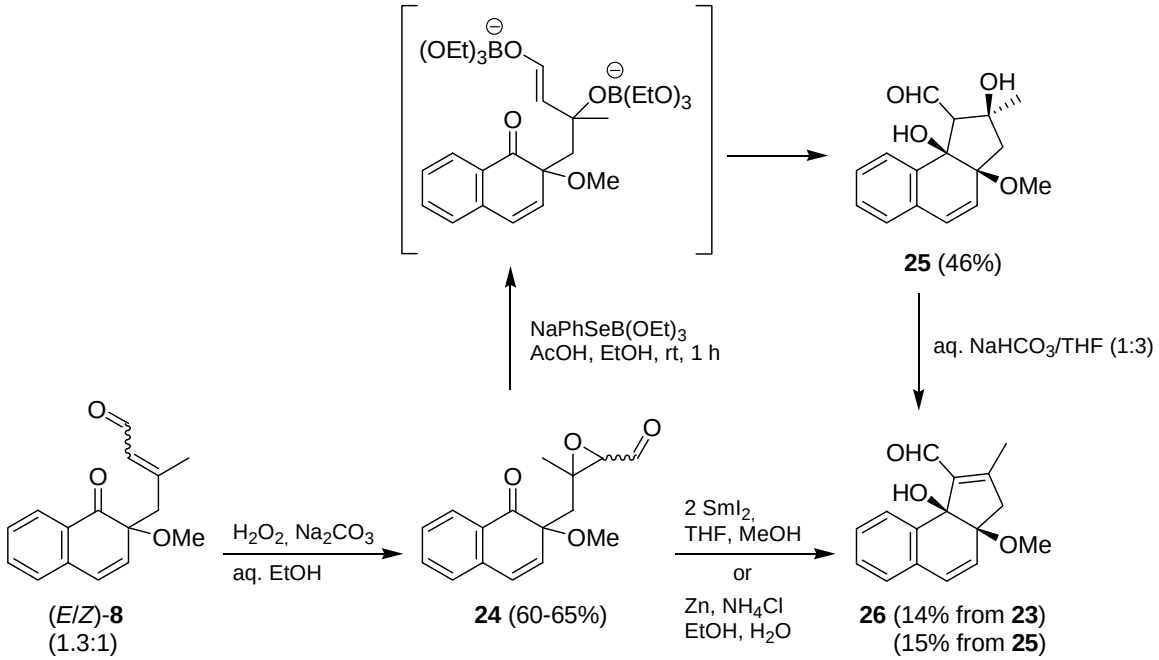
Scheme 4

However, all attempts to perform similar conjugate additions of silyl cuprates[6,7] or pentamethyldisilane[42] onto **8** only led to the recovery of the starting material (Scheme 5). Another option to oxygenate the exocyclic C=C double bond of **8** was dihydroxylation into diols **21** using catalytic amounts of osmium tetroxide and *N*-methylmorpholine-*N*-oxide (NMO). However, we did not isolate the expected diols **21**; instead, two diastereoisomers of an unassigned product, [bis(hemiacetal) **22** or ketal-carbaldehyde hydrate **23**] in a combined yield of 78% were obtained (Scheme 5).



Scheme 5

The most promising approach of introducing only one oxygen atom relied on epoxydation and responded to our expectations in part. Treatment of **8** with H_2O_2 in the presence of Na_2CO_3 in aqueous EtOH[44] afforded the α,β-epoxyaldehyde **24** (60–65%) (Scheme 6). This epoxide rapidly decomposed on silica gel, and it was very difficult to obtain it in higher yields with satisfactory purity. Its regioselective opening was accomplished by using the organoselenium reagent developed by Miyashita[45] to limit dehydration of the β-hydroxyaldehyde. Treatment of **24** with the phenylseleno(triethyl)borate complex, prepared by reduction of $(PhSe)_2$ with $NaBH_4$ in EtOH, gave the five-membered cyclization product **25** (46%) (Scheme 6). Reductive opening of **24** using zinc or samarium diiodide furnished only the dehydrated product **26** in low yield. We treated **25** under mildly basic conditions (i.e., saturated aq. $NaHCO_3$, THF, rt, 19 h) with the expectation of converting the five-membered A ring into a six-membered one via a retro-aldol reaction, but the only product isolated was the dehydrated compound **26** (15%), together with recovered starting material **8** (85%).



Scheme 6

Although we were not yet able to generate the aquayamycin-type angucyclinone six-membered A ring by this approach, the BTI-mediated oxidative nucleophilic substitution of the 2-alkoxynaphthol **9** with the silyl enol ether **10** constitutes a concise route to the highly functionalized naphthoid cyclohexa-2,4-dienone **8**. This synthon was transformed into five-membered ring-containing ABC models of the angularly-oxygenated benz[*a*]naphthalene unit of aquayamycin-type angucyclinones. The exploitation of these intermediates in the synthesis of full analogues of aquayamycin (**2**) is in progress.

Experimental Section

General Procedures. Tetrahydrofuran (THF) and diethyl ether were purified by distillation from sodium/ benzophenone under N_2 immediately before use. CH_2Cl_2 was distilled from CaH_2. Light petroleum refers to the 40–60 °C boiling range. Moisture and oxygen sensitive reactions were carried out in flame-dried glassware under N_2. Evaporations were conducted under reduced pressure at temperatures less than 45 °C unless otherwise noted. Column chromatography was carried out under positive pressure using 40–63 μm silica gel (Merck) and the indicated solvents. Melting points were determined on an Electrothermal IA9100 Digital apparatus. NMR spectra of samples in the indicated solvent were run at 200, 250 or 300 MHz. Carbon multiplicities were determined by DEPT-135 experiments. Electron impact mass spectra (EIMS) were obtained at 50–70 eV. Electron impact and liquid secondary ion mass spectrometry at low and high resolution (EIMS, and LSIMS, HRMS) were obtained using a VG-autospec-Q intrument at the CESAMO mass spectrometry laboratory, Université Bordeaux 1.

(2*E*/*Z*)-4-(2-Methoxy-1-oxo-1,2-dihydronaphthalen-2-yl)-3-methylbut-2-enal [(*E*/*Z*)-8] and (2*E*)-4-(4-hydroxy-3-methoxy-1-naphthyl)-3-methylbut-2-enal [(*E*)-11]. To a stirred ice-cold solution of **9**[39] (1.0 g, 5.74 mmol) and **10**[46] (2.6 g, 16.6 mmol) in CH_2Cl_2 (17 mL) was added BTI (4.4 g, 10.2 mmol) in one portion. After continued stirring at room temperature for 2 h, the mixture was diluted with CH_2Cl_2 (20 mL), washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), 1M H_3PO_4 (20 mL), brine (20 mL), dried over Na_2SO_4, and evaporated. The resulting brownish oil was purified by column chromatography, eluting with light petroleum/Et_2O (1:1), to furnish a 1.3:1 *E*/*Z* mixture of 8 (532 mg, 36%) as red oil, and 11 as pale yellow gum (192 mg, 13%).
(*E*/*Z*)-8. IR (KBr): 2938, 1670, 1596, 1120 cm^{-1}.
(*E*)-8: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.57 (s, 2H), 3.16 (s, 3H), 5.74 (d, *J* = 6.6 Hz, 1H), 6.08 (d, *J* = 10.1 Hz, 1H), 6.76 (d, *J* = 10.1 Hz, 1H), 7.23 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.37 (m, 1H), 7.58 (m, 1H), 7.98 (m, 1H), 9.89 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 199.5, 190.8, 157.8, 136.9, 135.3, 134.8, 131.3, 129.8, 129.6, 128.7, 127.9, 127.2, 82.3, 53.7, 49.6, 19.7.
(*Z*)-8. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.79 (d, *J* = 13.2 Hz, 1H), 2.91 (d, *J* = 13.2 Hz, 1H), 3.09 (s, 3H), 5.69 (d, *J* = 8.6 Hz, 1H), 6.02 (d, *J* = 9.8 Hz, 1H), 6.71 (d, *J* = 9.8 Hz, 1H), 7.17 (m, 1H), 7.30 (m, 1H), 7.52 (m, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 9.61 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 199.4, 190.7, 156.8, 136.7, 135.3, 134.8, 131.3, 129.7, 129.5, 128.7, 127.9, 127.1, 82.0, 53.7, 41.3, 27.7. LSIMS: *m/z* (rel intensity) 279 (58) [MNa^+], 257 (41) [MH^+], 256 (35) [M^+], 225 (59); HMRS (LSIMS): Calcd for $C_{16}H_{16}O_3$ 256.1099. Found 256.1091.
(*E*)-11. IR (KBr): 3292, 1649 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.20 (s, 3H), 3.88 (s, 2H), 3.94 (s, 3H), 5.75 (br d, *J* = 8.1 Hz, 1H), 6.20 (s, 1H), 7.07 (s, 1H), 7.41 (m, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 8.20 (d, *J* = 7.9 Hz, 1H), 9.98 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 191.4, 162.9, 140.6, 139.4, 131.9, 128.3, 127.9, 125.4, 124.8, 124.6, 123.6, 122.0, 115.6, 57.3,

43.7, 17.8; LSIMS: *m/z* (rel intensity) 279 (18) [MNa^+], 256 (100) [M^+]; HMRS (LSIMS): Calcd for $C_{16}H_{16}O_3$ 256.1099. Found 256.1098.

2-(4-Hydroxy-3-methoxy-1-naphthyl)-3-methylbut-2-enal (16). 3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (**12**, 1.4 mg, 0.005 mmol) and Et_3N (4 μL, 0.03 mmol) were successively added to a solution of **8** (25 mg, 0.098 mmol) in absolute ethanol (2 mL). The reaction mixture was heated at 80 °C for 2.5 h, after which time ethanol was evaporated. The residue was then diluted with CH_2Cl_2 (10 mL), washed with saturated aqueous Na_2CO_3 (10 mL), brine (20 mL), dried over Na_2SO_4, and evaporated. The resulting crude oil was purified by column chromatography, eluting with light petroleum/Et_2O (1:1), to give **16** as light red gum (23 mg, 90%). IR (NaCl) 3408, 2928, 1694, 1350 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.71 (s, 3H), 2.47 (s, 3H), 3.97 (s, 3H), 6.03 (s, 1H), 6.94 (s, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 7.42 (m, 2H), 8.17 (d, *J* = 7.6 Hz, 1H), 10.36 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 190.7, 158.7, 140.8, 139.5, 137.1, 128.0, 125.8, 125.4, 124.8, 124.7, 124.3, 121.8, 115.0, 57.2, 25.3, 19.9; LSIMS: *m/z* (rel intensity) 279 (28) [MNa^+], 256 (100) [M^+]; HMRS (LSIMS): Calcd for $C_{16}H_{16}O_3$ 256.1099. Found 256.1101.

(3*Z*)-5-(2-Methoxy-1-oxo-1,2-dihydronaphthalen-2-yl)-4-methyl-2-[(trimethylsilyl)oxy] hyphen: pent-3-enenitrile (17). To a stirred solution of **8** (150 mg, 0.59 mmol), KCN (3 mg, 0.08 mmol) and 18-crown-6 (8 mg, 0.05 mmol) in CH_2Cl_2 (6 mL) was added dropwise at 0 °C Me_3SiCN (94 μl, 0.71 mmol). The reaction mixture was stirred at 0°C for 45 min; after evaporation of the solvent the residue was submitted to column chromatography, eluting with light petroleum/Et_2O (2:1) to give **17** as a pale yellow oil (77 mg, 37%). ^1H NMR (250 MHz, $CDCl_3$): δ 0.16 (s, 9H), 1.67 (s, 3H), 1.79 (s, 3H), 2.46 (s, 2H), 2.50 (s, 2H), 3.17 (s, 3H), 3.18 (s, 3H), 4.93 (d, *J* = 8.5, 1H), 4.99 (d, *J* = 7.9 Hz, 1H), 5.26 (d, *J* = 8.5 Hz, 1H), 5.32 (d, *J* = 7.3 Hz, 1H), 6.09 (d, *J* = 10.1 Hz, 1H), 6.79 (d, *J* = 10.1 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 200.0, 137.1, 136.9, 135.0, 135.0, 134.9, 134.9, 129.9, 129.3, 129.1, 128.3, 126.9, 126.8, 125.8, 82.3, 57.9, 53.4, 48.6, 48.3, 18.7, 18.5, -0.4; EIMS: *m/z* (rel intensity) 355 (7) [M^+]; HMRS (EIMS): Calcd for $C_{20}H_{25}NO_3Si$ 355.1603. Found 355.1601.

3-[Dimethyl(phenyl)silyl]-3-methylbutanal (19). Dimethylphenylsilyl lithium in THF (0.48 M, 2.3 mL, 1.1 mmol) was added dropwise to a suspension of copper iodide (105 mg, 0.55 mmol) in THF (1 mL) at - 78 °C. The reaction mixture was stirred at - 25 °C for 30 min, recooled to - 78 °C, and the mesityloxide (**18**, 42 mg, 0.5 mmol) was added. After stirring at - 60 °C for 2.5 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with 10% HCl (5 mL), brine (10 mL), dried over Na_2SO_4, and evaporated. The resulting oil was purified by column chromatography, eluting with light petroleum/Et_2O (6:1), to afford **19** (102 mg, 93%). IR (NaCl) 2958, 2866, 1717, 1468, 1111 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 0.33 (s, 6H), 1.11 (s, 6H), 2.23 (d, *J* = 3.3 Hz, 2H), 7.38 (m, 3H), 7.48 (m, 2H), 9.78 (t, *J* = 3.3 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 204.5, 134.5, 129.3, 127.7, 51.7, 23.4, -6.1.

6a-Methoxy-7a-methyl-7,7a,9,9a-tetrahydrobenzo[*h*]oxeto[3,2-*b*]chromene-9,10a(6a*H*)- diol (22) or (4a-methoxy-3-methyl-2,3,4,4a-tetrahydro-3,10b-epoxybenzo[*h*]chromen-2-yl) methanediol (23). To a solution of **8** (160 mg, 0.62 mmol) in THF (6 mL) and H_2O (1 mL) were added at rt OsO_4 (7.9 mg, 0.03 mmol) and NMO (210 mg, 1.56 mmol). After 24 h the mixture was treated with aqueous $Na_2S_2O_3$ and stirred for 40 min, after which time it was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and evaporated. The resulting oil was purified by column chromatography, eluting with light petroleum/acetone (2:1), to furnish two separate but unassigned diastereoisomers as yellow oils, the faster moving isomer **22a** or **23a** (69 mg, 38%) and the slower one **22b** or **23b** (72 mg, 40%).

22a/23a. IR (KBr): 3420 (br), 2930, 1469, 1064 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 1.34 (s, 3H), 2.10 (d, *J* = 13.7 Hz, 1H), 2.62 (d, *J* = 8.5 Hz, 1H), 3.04 (s, 3H), 3.48 (d, *J* = 7.2 Hz, 1H), 5.62 (d, *J* = 7.2 Hz, 1H), 5.73 (d, *J* = 9.7 Hz, 1H), 6.67 (d, *J* = 9.7 Hz, 1H), 7.26 (m, 1H), 7.34 (m, 2H), 7.89 (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 132.7, 131.0, 129.4, 129.3, 128.4, 127.9, 127.3, 125.8, 101.6, 95.5, 81.9, 79.0, 75.2, 52.0, 44.9, 22.8; LSIMS: *m/z* (rel intensity) 313 (100) [MNa^+]; HMRS (LSIMS): Calcd for $C_{16}H_{18}O_5Na$ 313.1052. Found 313.1058.

22b/23b. mp 138 °C, IR (KBr): 3414 (br), 2926, 1706, 1066 cm^{-1}; ^1H NMR (250 MHz, acetone-d_6): δ 1.35 (s, 3H), 1.93 (d, *J* = 13.1 Hz, 1H), 2.18 (d, *J* = 8.5 Hz, 1H), 2.98 (s, 3H), 3.75 (d, *J* = 2.1 Hz, 1H), 5.85 (s, 1H), 6.02 (d, *J* = 9.7 Hz, 1H), 6.67 (d, *J* = 9.7 Hz, 1H), 7.18 (m, 1H), 7.30 (m, 2H), 7.73 (m, 1H); ^{13}C NMR (acetone-d_6, 62.9 MHz): *δ* 135.1, 134.8, 132.0, 131.2, 129.8, 128.6, 127.3, 126.0, 108.5, 97.0, 87.2, 73.6, 67.6, 50.3, 44.1, 27.3; LSIMS: *m/z* (rel intensity) 313 (100) [MNa^+]; HMRS (LSIMS): Calcd for $C_{16}H_{18}O_5Na$ 313.1052. Found 313.1059.

3-[(2-Methoxy-1-oxo-1,2-dihydronaphthalen-2-yl)methyl]-3-methyloxirane-2-carbaldehyde (24). To a suspension of 8 (120 mg, 0.47 mmol) and Na_2CO_3 (49.8 mg, 0.47 mmol) in EtOH/H_2O (4:1, 7 mL) was added dropwise at 0 °C an aqueous solution of H_2O_2 (30%, 400 μL). After the addition was complete, the ice-bath was removed, and the mixture was stirred at room temperature for 3 h. The mixture was then evaporated, and the residue was diluted with CH_2Cl_2 (10 mL), washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4, and evaporated at rt. The resulting oil was purified by column chromatography, eluting with ligth petroleum/Et_2O (2:3), to afford a 1:1 mixture of epoxide diastereosomers **24** as a light yellow oil (85 mg, 67%). Preparative TLC, eluting with light petroleum/acetone (3:1), furnished **24a** as the faster moving isomer and **24b**.

24a. ^1H NMR (250 MHz, $CDCl_3$): δ 1.42 (s, 3H), 2.10 (d, *J* = 14.6 Hz, 1H), 2.31 (d, *J* = 14.6 Hz, 1H), 3.18 (s, 3H), 6.13 (d, *J* = 10.0 Hz, 1H), 6.72 (d, *J* = 10.0 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.39 (m, 1H), 7.60 (t, *J* = 1.5, 7.8 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 9.28 (d, *J* = 5.2 Hz, 1H); EIMS: *m/z* (rel intensity) 272 (M^+, 15), 157 (100).

24b. ^1H NMR ($CDCl_3$, 250 MHz) *δ*1.48 (s, 3H), 1.88 (d, *J* = 14.6 Hz, 1H), 2.20 (d, *J* = 14.6 Hz, 1H), 3.18 (s, 3H), 6.18 (d, *J* = 10.0 Hz, 1H), 6.82 (d, *J* = 10.0 Hz, 1H), 7.24 (d, *J* = 6.1 Hz, 1H), 7.39 (m, 1H), 7.60 (t, *J* = 1.5, 7.8 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 9.37 (d, *J* = 4.9 Hz, 1H); EIMS: *m/z* (rel intensity) 272 (15) [M^+], 157 (100).

(3a*S,9b*R**)-2,9b-Dihydroxy-3a-methoxy-2-methyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*a*]-naphthalene-1-carbaldehyde (25).** $NaBH_4$ (38 mg, 1.00 mmol) was added portionwise to a solution of diphenyldiselenide (160 mg, 0.51 mmol) in absolute EtOH (2 mL). Once the gas evolution ceased, the yellow solution was cooled to 0 °C using an ice-water bath, treated with AcOH (9.8 µL), and then added at rt to a solution of epoxide 24 (90 mg, 0.33 mmol) in EtOH (2 mL). The reaction mixture turned blue and was stirred for 2.5 h, after which time it was diluted with EtOAc and bubbled with oxygen gas for several minutes to convert the remaining selenium reagent to $(PhSe)_2$. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated at rt. The resulting crude oil was purified by column chromatography, eluting with ligth petroleum/acetone (3:1), to furnish **25** as a yellow oil (42 mg, 46%): IR (KBr) 3447, 2933, 1716 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.39 (s, 3H), 2.40 (d, *J* = 14.9 Hz, 1H), 2.54 (d, *J* = 2.1 Hz, 1H), 2.58 (d, *J* = 15.5 Hz, 1H), 3.08 (s, 3H), 3.88 (s, 1H), 3.88 (s, 1H), 4.08 (s, 1H), 5.75 (d, *J* = 9.8 Hz, 1H), 6.73 (d, *J* = 9.8 Hz, 1H), 7.16 (d, *J* = 7.1 Hz, 1H), 7.26-7.30 (m, 2H), 7.70 (d, *J* = 7.5 Hz, 1H), 9.90 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 203.3, 137.7, 131.2, 129.9, 129.1, 128.6, 128.2, 127.8, 125.1, 82.4, 80.3, 78.1, 66.3, 54.8, 52.0, 28.2; LSIMS: *m/z* (rel intensity) 297 (MNa^+, 100); HMRS (LSIMS): Calcd for $C_{16}H_{18}O_4Na$ 297.1103. Found 297.1106.

(3a*S,9b*S**)-9b-Hydroxy-3a-methoxy-2-methyl-3a,9b-dihydro-3*H*-cyclopenta[*a*] naphthalene-1-carbaldehyde (26).** A suspension of **24** (17 mg, 0.06 mmol), zinc powder (20 mg, 0.31 mmol), ammonium chloride (10 mg, 0.18 mmol) in a 4:1 mixture of $EtOH/H_2O$ (7 mL) was heated at 80 °C for 20 min, after which time it was filtered. The filtration pellet was rinsed with Et_2O, and the filtrates were washed with brine (10 mL), dried over Na_2SO_4 and evaporated at rt. The residue was purified by PLC, eluting with light petroleum/Et_2O (2:3), to afford **26** as yellow oil (17 mg, 14%). IR (KBr) 3430, 2930, 1680, 1608, 753 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 2.19 (s, 3H), 2.63 (d, *J* = 17.4 Hz, 1H), 3.12 (d, *J* =17.4 Hz, 1H), 3.17 (s, 3H), 3.48 (s, 1H), 5.73 (d, *J* = 9.8 Hz, 1H), 6.73 (d, *J* = 9.8 Hz, 1H), 7.25-7.28 (m, 1H), 7.32-7.36 (m, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 9.51 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 189.4, 160.9, 136.6, 136.3, 132.7, 130.4, 128.7, 128.1, 127.3, 127.1, 126.9, 80.9, 80.2, 52.3, 49.8, 16.4; EIMS: *m/z* (rel intensity) 256 (55) [M^+], 224 (100), 195 (73); HMRS (EIMS): Calcd for $C_{16}H_{16}O_3$ 256.1099. Found 256.1103.

Acknowledgements

The support of the Centre National de la Recherche Scientifique (French part of the IGERT Program) is gratefully acknowledged. The authors also wish to thank the Ministère délégué à la Recherche et aux Nouvelles Technologies for G.-J.F.'s postdoctoral fellowship and for N.L.'s graduate research assistantship (N.L. was awarded with this assistantship through the French part of the IGERT Program) and Simafex (www.simafex.com) for the gift of BTI reagent.

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