Synthesis of espicufolin based on 6-*endo* ring closure of *o*-alkynoylnaphthols †

Hidemitsu Uno,*[a] Katsuji Sakamoto,[a] Erina Honda,[a] Kaori Fukuhara,[a] Noboru Ono,[b] Junya Tanaka[c] and Masahiro Sakanaka[c]

[a] *Advanced Instrumentation Center for Chemical Analysis, Ehime University, Bunkyo-cho 2-5, Matsuyama 790-8577, Japan*
[b] *Department of Chemistry, Faculty of Science, Ehime University, Bunkyo-cho 2-5, Matsuyama 790-8577, Japan*
[c] *Department of Physiology and Anatomy, Ehime University School of Medicine, Shigenobu, Ehime 791-0295, Japan. E-mail: uno@dpc.ehime-u.ac.jp; Fax: +81-89-927-9670*

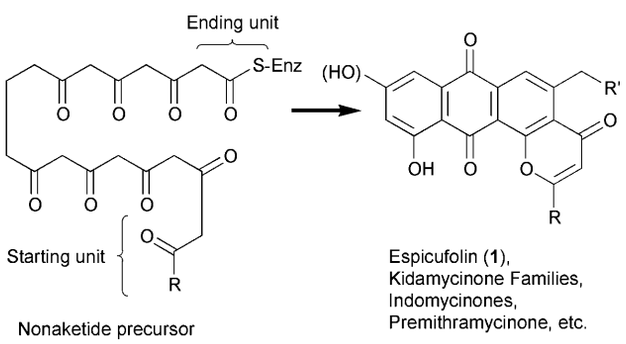
Received (in Cambridge, UK) 27th September 2000, Accepted 27th November 2000
First published as an Advance Article on the web 10th January 2001

Regioselective halogenation of 3-acetoxymethyl-7-chloro-5,8-dimethoxy-1-naphthol **5** was achieved by DBH or I_2/*N*-methylmorpholine to give the corresponding 2-halogeno-1-naphthols **8** and **11**, which were converted to 1-methoxymethoxy-3-(alk-2-ynoyloxymethyl)-2-halogenonaphthalenes **17** and **18** in good yields. An intramolecular acyl-transfer reaction of the 2-halogenonaphthalenes triggered by halogen–lithium exchange with BuLi at −78 °C gave 1-methoxymethoxy-2-alkynoyl-3-(hydroxymethyl)naphthalenes **21** in high yields. After protection of the hydroxymethyl group as a benzoate, formation of a γ-pyrone ring was easily achieved by deprotection of the methoxymethyl group followed by spontaneous 6-*endo* ring closure under mildly acidic conditions. The pyrone derivative having a 1-methylpropyl group was successfully converted to espicufolin **1**.

Introduction

Neuronal cell-protecting substances in the event of ischemia have attracted increasing attention from scientists in many fields. Many kinds of such compounds have been reported.[1] In the event of ischemia, L-glutamic acid existing as an excitatory neurotransmitter in the brain is believed to play the important role of increasing the level of oxidants such as superoxide anion and oxygen radicals in the neuronal cells, which then cause neuronal cell death.[2] In 1996, Seto *et al.* found a novel neuronal cell-protecting substance, espicufolin **1**, in the culture broth of *Streptomyces sp. cu39* in the course of their screening for suppressors of glutamate toxicity using neuronal hybridoma N18-RE-105 cells.[3] However, the mechanism of action of espicufolin was suggested not to relate to antioxidative activity following an investigation of buthionine sulfoximine toxicity.[3] During the course of our project exploring efficient neuronal-cell-protecting substances, we were interested in the mechanism of action and *in vivo* activity of espicufolin **1**.

Espicufolin **1** has a 1,8-dihydroxyanthraquinone skeleton fused with a γ-pyrone ring and one unknown stereogenic center at the 14-position, and is considered as a new member of the pyranoanthraquinone family. Some of these family members were reported to show important properties such as antitumor and antibiotic activities.[4] These pyranoanthraquinone families are thought to be biosynthesized from a nonaketide having an appropriate starting unit (Scheme 1).[5] In the biosynthesis of espicufolin and premithramycinone,[6] 2-methylbutanoyl and acetyl groups are used as the starting unit, and the ending acetyl group is modified to hydroxymethyl and methoxycarbonyl groups, respectively. We have planned to synthesize espicufolin **1** *via* the route in which the two parts can be easily modified for syntheses of other family members in addition to espicufolin analogues. We have devised a novel approach to naphtho-[1,2-*b*]pyrantriones based on an intramolecular alkynoyl transfer followed by 6-*endo* closure under acidic conditions,[7] and succeeded in preparing (*S*)-espicufolin.[8] In this paper, we describe the detailed study for the preparation of espicufolin. The *in vitro* study of espicufolin using rat neuronal cells of 17-day embryos is also described.



Scheme 1 Biosynthesis of pyranoanthraquinone families.

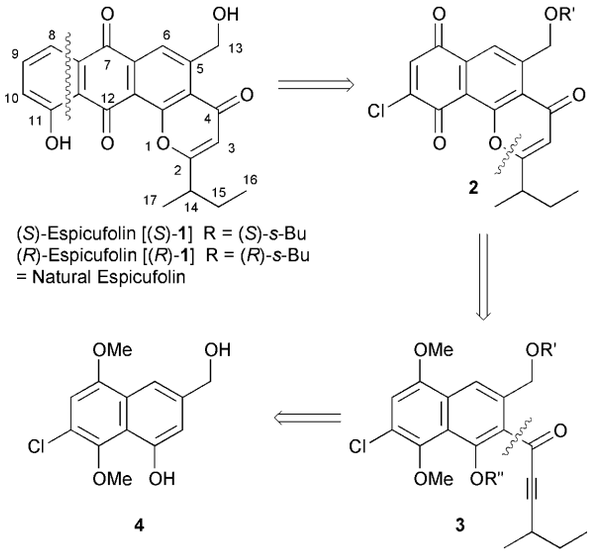
Results and discussion

Retro-synthesis

Our retrosynthetic pathway is shown in Scheme 2. Since the regioselective Diels–Alder reaction of chloronaphthoquinone with 1-methoxycyclohexa-1,3-diene has been established as one of the most reliable methods for construction of anthraquinones bearing hydroxy groups,[9] we focused our attention on the preparation of pyranonaphthoquinone **2**. This pyranonaphthoquinone **2** could be prepared by the intramolecular cyclization of *o*-alkynoylnaphthalene **3**; a similar and successful method using such a reaction was reported for the preparation of the kapurimycin A_3 analogue.[10] The *o*-alkynoylnaphthalene **3** would be prepared from the known naphthol **4**.[11]

† Experimental details for **13**, **15**, **17a**, **18c**, **18d**, **18e**, **21c**, **21d**, **21e**, **25c**, **25d**, **25e**, **26c**, **26e**, **27e**, **28** and **29** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b007859j/

DOI: 10.1039/b07859j

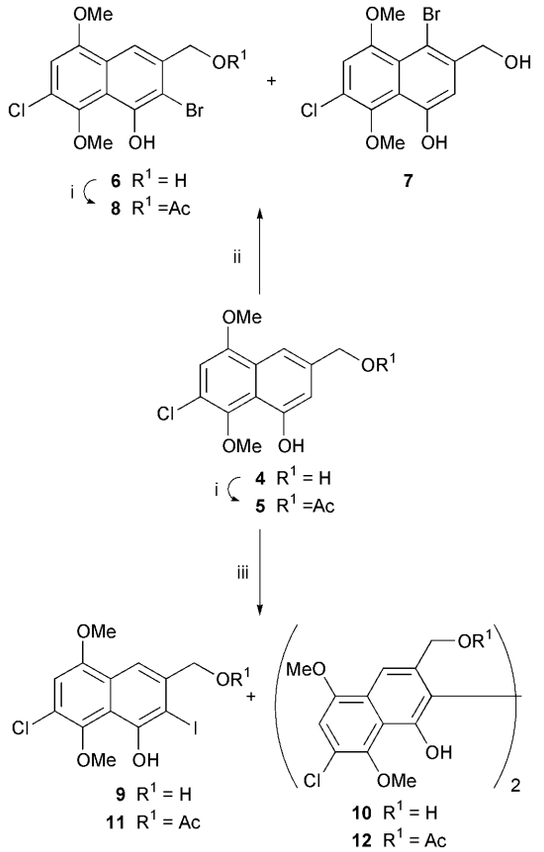


Scheme 2 Retro-synthesis of espicufolin.

Halogenation of naphthols

As attempts to introduce an acetyl group at the 2-position of **4** by the Friedel–Crafts reaction and the Fries rearrangement both failed, we thought to introduce the acyl groups by the reaction of a lithio derivative from **4** with acylating reagents. Since the starting **4** has a chlorine atom, the directed ortho-lithiation method[12] of alkyllithiums utilizing the neighbouring hydroxy group as a methoxymethoxy group cannnot be applied. We decided to generate the lithio compound by the halogen–lithium exchange reaction. Thus, we examined the regioselective halogenation of the naphthols **4** and **5**, the latter of which can be quantitatively obtained by selective acetylation with Ac_2O in the presence of a catalytic amount of $HClO_4$ (Scheme 3).

Treatment of the naphthol **4** with 1.2 equiv. of *N*-bromosuccinimodide (NBS) in CH_2Cl_2 gave a regioisomeric mixture of 2-bromonaphthol **6** and 4-bromonaphthol **7** in respective yields of 24% and 14% (run 1). The regiochemistry of **6** and **7** was unambiguously determined by differential nuclear Overhauser effect (NOE) experiments. Regioselective bromination giving the 2-bromonaphthols **6** (92%) and **8** (98%) was achieved using NBS in dimethylformamide (DMF).[13] This preference for the 2-bromo derivatives over 4-bromo derivatives was quite different from the result obtained in the bromination of 1-hydroxy-9,10-anthraquinones, where the bromination preferentially occurred at the 4-position.[14] This difference could be due to the steric effect of the peripheral methoxy substituent in the naphthols **4** and **5**. When 1.0 or 1.2 equiv. (0.5 or 0.6 mol per the naphthol) of 1,3-dibromo-5,5-dimethylhydantoin (DBH) was used as the brominating reagent,[15] the target bromide **6** was obtained in good yields (88–90%) irrespective of the solvent (DMF or CH_2Cl_2). This high regioselectivity of DBH would be attributed to the bulkiness of DBH compared to NBS. The advantage of using DBH should be emphasized because both the bromine atoms were available for this bromination. Reaction of **5** with I_2 and *N*-methylmorpholine (NMM) gave mainly dimeric compounds such as **12** in 66% yield in addition to 2-iodonaphthol **11** (31%).[16] No formation of a 4-iodo derivative was observed. One of the dimers was isolated in 36% yield by recrystallization and the structure was determined as the 2,2′-dimer **12** by ^{1}H NMR analysis. Structures of other dimeric compounds in the mother liquor were assumed to be 2,4′- and 4,4′-dimers and their partially iodinated compounds by ^{1}H NMR analysis, though the precise assignment could not be done. In order to suppress the formation of dimers, the reaction was carried out at a lower concentration. When the reaction was conducted at a 0.05 M concentration, yield of the iodide **11** was remarkably improved to 77%. Slight electronic and steric changes from **5** to **4** hampered the iodination. The iodination of **4** under similar conditions resulted in considerable formation of dimers such as **10** (32%) in addition to **9** (43%). 2,2′-Dimer **10** was isolated in 24% yield by recrystallization of the dimeric mixture.

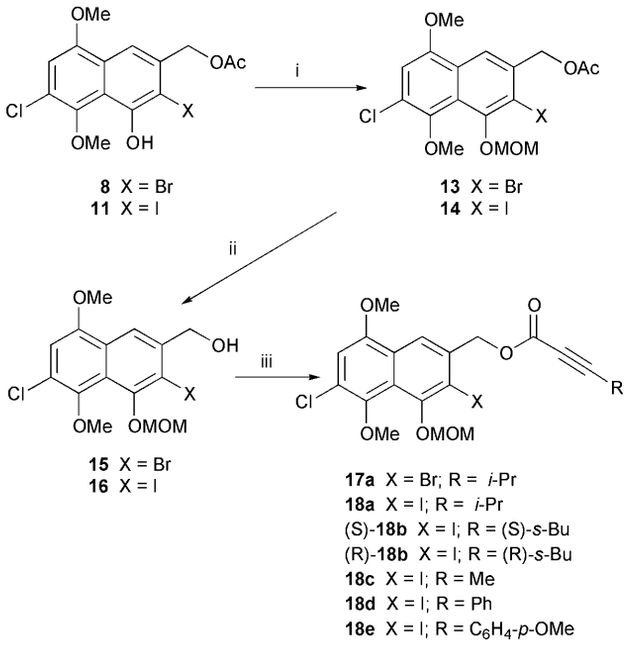


Scheme 3 *Reagents and conditions*: i) Ac_2O, $HClO_4$, rt; ii) NBS or DBH; iii) I_2, NMM, rt.

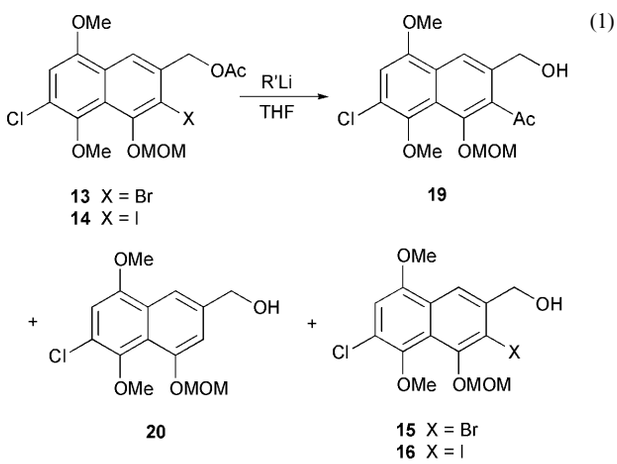
Intramolecular acyl-transfer reaction

As debromination and deacetylation of **8** to **4** were observed upon treatment of **8** with *n*-BuLi, the 2-bromo- and 2-iodonaphthols **8** and **11** were first converted into methoxymethyl ethers **13** and **14**, in 96% and 89% yield, respectively (Scheme 4). The acetyl group of **13** and **14** was then hydrolyzed to give alcohols **15** and **16** in respective yields of 92% and 93%. Then, intermolecular acylation of the alcohol **15** at the 2-position was attempted. When the alcohol **15** was treated with 2 equiv. of *n*-BuLi at −78 °C followed by methyl 4-methylpent-2-ynoate, none of the acylated compound was formed and the simply debrominated compound **20** was obtained in quantitative yield. This fact may indicate that the bromine–lithium exchange is followed by rapid quenching of the carbanion by the intramolecular hydroxy group or that the carbanion at the 2-position is severely hindered by the adjacent substituents. Therefore, we decided to utilize the 3-hydroxymethyl group as an acyl group carrier. The 3-hydroxymethyl group of **15** and **16** was acylated with a variety of alkynoic acids[17] to give alkynoyl esters **17a** and **18a**–**18e** in good yields (60–94%).[18]

An intramolecular acyl-transfer reaction was examined by generation of an anion at the 2-position of the naphthalenes under various conditions. First, a halogen–lithium exchange reaction of **13** and **14** was carried out [reaction (1)]. The reaction of **13** with an equal equivalent of *n*-BuLi at −78 °C gave almost the same amount of the aimed for product **19** (33%) and a simply deacylated alcohol **15** (28%). From the NMR analysis, the 2-acetyl compound **19** was proved to exist as a *ca.* 1:7

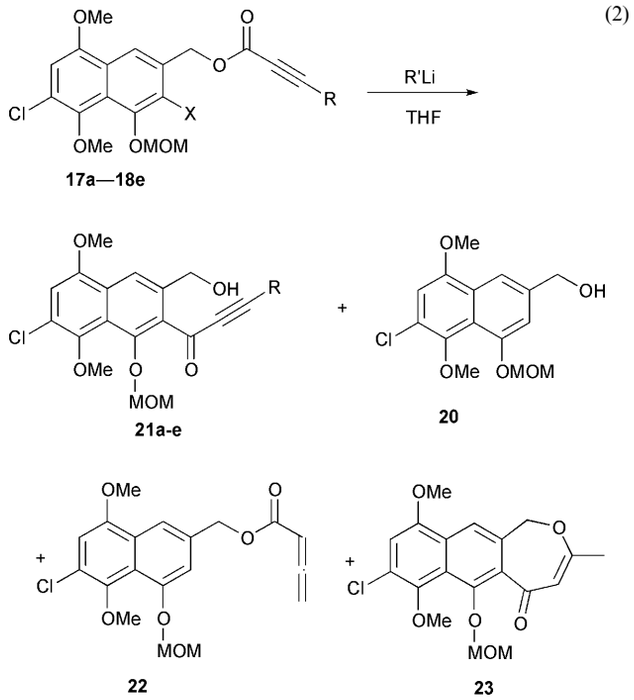


Scheme 4 *Reagents and conditions*: i) MOMCl, Et_3N, CH_2Cl_2, rt; ii) NaOH, THF–MeOH, rt; iii) alk-2-ynoic acid, BOPCl, Et_3N, CH_2Cl_2, rt.



mixture of keto and hemiacetal forms in $CDCl_3$ at ambient temperature. When 2.1 equivalents of *tert*-BuLi were employed instead of *n*-BuLi, the yield of 2-acetyl compound **19** was greatly improved to 75%, and compound **20** was formed as a by-product in 8% yield. In the reaction of the iodo derivative **14** with *n*-BuLi at −78 °C, the aimed for product **19** was formed as a sole product in 88% yield.

Next, the alkynoyl-transfer reaction was examined [reaction (2)]. The reaction of **17a** with *tert*-BuLi at −78 °C was hampered by the nucleophilic attack to give a considerable amount of **20** (52%) as well as **21a** (40%), probably due to the sterically less hindered nature of the alkynoyl ester moiety. The side reaction giving **20** could not be suppressed by reduction of the reaction temperature to −100 °C, and a mixture of **20** (41%) and **21a** (59%) was obtained. On the other hand, highly reactive iodo compound **18a** underwent smooth alkynoyl-transfer reaction even on treatment with *n*-BuLi at −78 °C to give the desired compound **21a** in 80% yield as well as a small amount of **20** (5%). Transformation of other alkynoyloxy derivatives (*S*)-**18b**, (*R*)-**18b**, **18c**, **18d** and **18e** was also achieved in respective yields of 95, 95, 65, 73 and 95%. In the case of 3-(but-2-ynoyloxymethyl)naphthalene **18c** with *n*-BuLi, the yield of **21c** was slightly low (65%). From NMR and IR analyses of the by-products, buta-2,3-dienoyloxy and oxepin derivatives **22** and **23** were formed in respective yields of 3 and 4%. The buta-

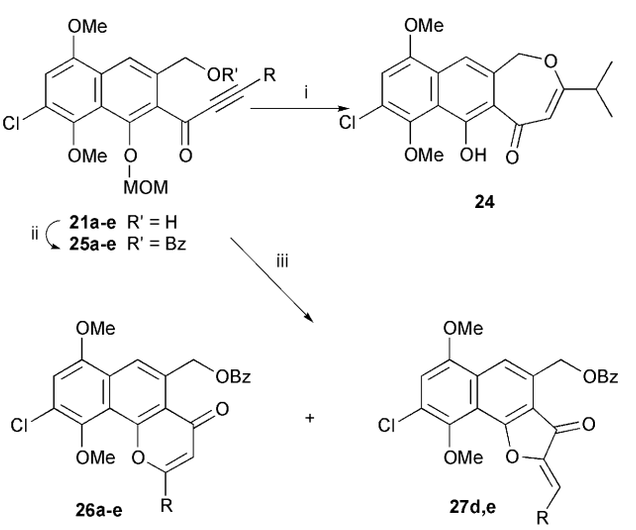


2,3-dienoyloxy compound **22** would be generated by proton abstraction from the acidic butynoyl moiety followed by protonation to the α-position upon quenching. As an allenic sp carbon is more susceptible toward nucleophilic attack than is an acetylenic sp carbon, mainly due to stability of the resulting intermediates (allylic *vs*. vinylic), the oxepin formation giving **23** would proceed *via* the acetylene–allene tautomerization of **21c** followed by an intramolecular ring closure.

Intramolecular cyclization of *o*-alkynoylnaphthols

At first, we attempted to remove the methoxymethyl group of 2-alkynoylnaphthalenes **21** under acidic conditions prior to the intramolecular cyclization. Treatment of the 2-alkynoyl compound **21a** with HCl in aq. tetrahydrofuran (THF)–Pr^{i}OH, however, gave undesired oxepine derivative **24** as the main product in 62% yield. Formation of **24** was the formal 7-*endo*-*digonal* ring closure which was reported as a favourable process.[19] Thus, the 3-hydroxymethyl group of **21a**–**21e** was protected as the benzoate esters **25a**–**25e** (Scheme 5).

The compound **25a** was refluxed in a THF–Pr^{i}OH–HCl (3 M) solution under argon to give the target pyrone **26a** in 85%

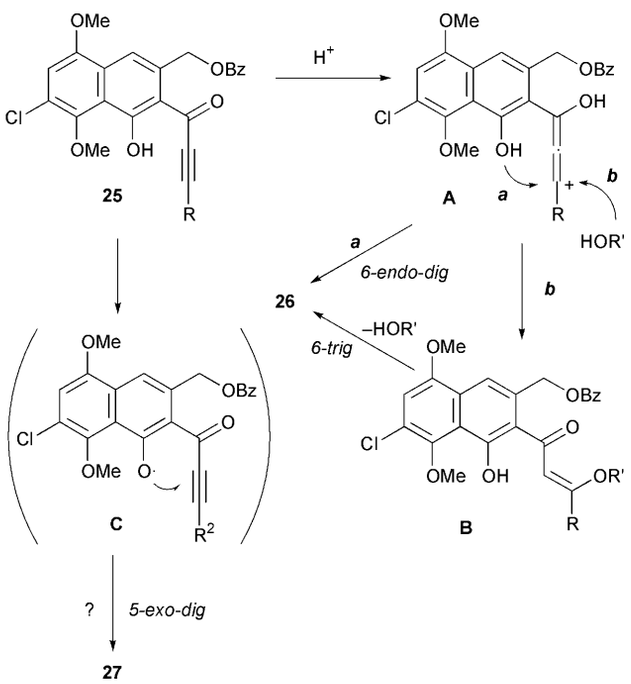


Scheme 5 *Reagents and conditions*: i) **21a**, HCl, aq. THF–Pr^{i}OH, reflux; ii) BzCl, pyridine, rt; iii) **25a**–**25e**, HCl, aq. THF–Pr^{i}OH, reflux.

yield. When the reaction was carried out under air, however, an intractable mixture was obtained. In this mixture, considerable amounts of dimeric compounds were identified by ^{1}H NMR and MS analyses, though the structures could not be assigned. In the cases of aliphatic alkynoyl derivatives (*S*)-**25b**, (*R*)-**25b** and **25c**, yields of the pyrones (*S*)-**26b**, (*R*)-**26b** and **26c** were good (77, 77 and 65%, respectively). On the other hand, a similar reaction of aralkynoyl compound **25d** gave a mixture of pyrone **26d** (41%) and furanone **27d** (41%). A similar result was obtained in the reaction of **25e**; a mixture of **26e** (48%) and **27e** (46%) was formed. In order to suppress the undesired 5-membered-ring formation, we examined the cyclization of enaminones derived from addition of diethylamine to the triple bond.[20] The aralkynoyl compounds **25d** and **25e** were treated with diethylamine and then the crude enaminones were refluxed under acidic conditions to afford only pyrones **26d** and **26e** in excellent yields (87 and 92%, respectively).

Mechanistic considerations of the cyclization

Possible reaction pathways to the observed products are illustrated in Scheme 6.[7] Since the oxidative dimerization was

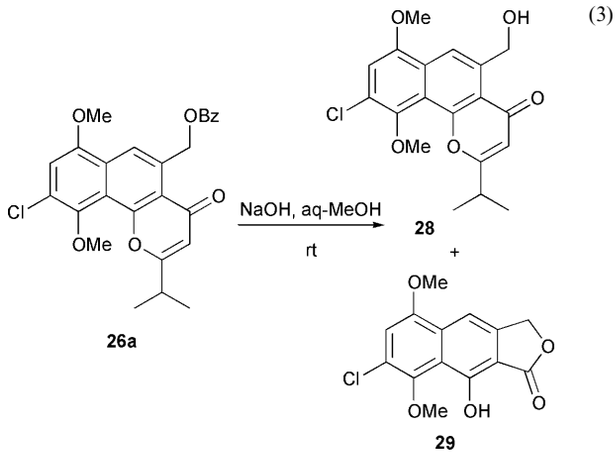


Scheme 6 Proposed reaction pathways.

observed in the presence of oxygen and the furanone formation was observed only in the reactions of the aralkynoyl derivatives **25d** and **25e**, we have suspected the participation of a radical intermediate such as **C** which then leads to the undesired furanones **27** in the 5-*exo-digonal* fashion.[21] It is very difficult to confirm the participation of the naphthoxyl radical intermediate, because naphthoxyl radicals are far more stable than phenoxyl radicals and are readily formed under various conditions.[22] Indeed, even in the presence of tocopherol as a radical scavenger or azoisobutyronitrile (AIBN) as a radical promoter, the ratio of **26**:**27** was unchanged. In spite of all of our efforts, participation of the radical intermediate could not be confirmed. Although formation of the furanones **27** is not clear at this moment, the main reaction pathways leading to **26** are as follows. Under acidic conditions, protonation of the ynone carbonyl would occur to give an allenyl cationic intermediate **A**. The intermediate would be attacked at the β-position either by an intramolecular hydroxy group (6-*endo-digonal* mode; route ***a***)[23] or by water or Pr^{i}OH (route ***b***, ***via* B**) followed by 6-*exo-trigonal* or 6-*endo-trigonal* ring closure[21] to give **26**.

Preparation of espicufolin

The obtained naphtho[1,2-*b*]pyran-4-one **26b** was transformed into espicufolin **1**. First, deprotection of the benzoyl group was tested by using **26a** as a substrate [reaction (3)]. When **26a** was



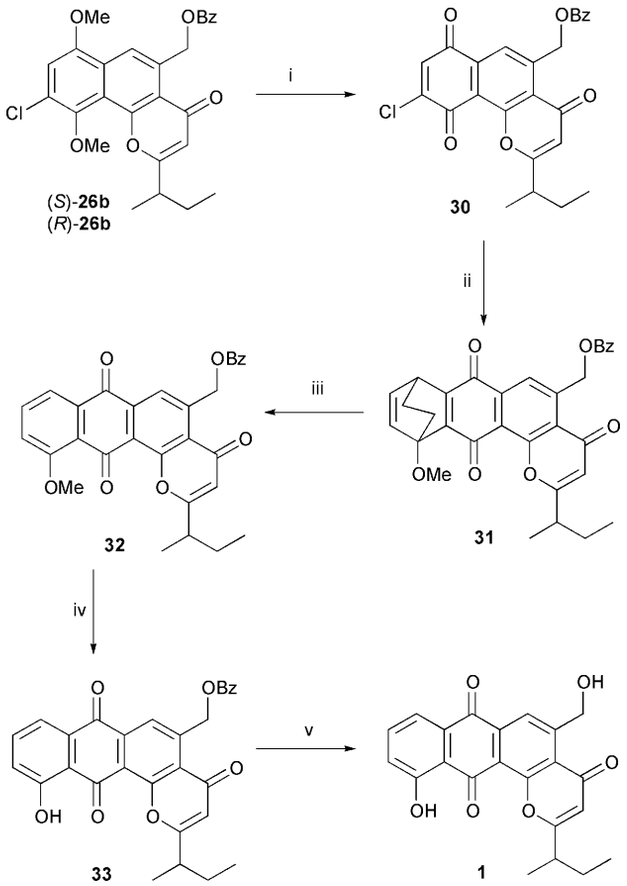
(3)

treated with NaOH in aq. THF–MeOH at room temperature for 1 h, the target compound **28** and γ-lactone **29** were obtained in 33 and 37% yield, respectively. The by-product **29** would be derived from the hydrolysis of the γ-pyrone ring of **28** to a β-diketo derivative, which would decompose by the intramolecular nucleophilic attack of the adjacent hydroxymethyl group. In fact, shortening the reaction time increased the yield of **28** to 70% and lowering the reaction temperature to 0 °C brought about almost quantitative formation of **28**. As oxidation of **28** with cerium(IV) ammonium nitrate (CAN), however, gave a complex mixture probably due to the highly electron-rich nature of the substrate, we decided to deprotect the benzoyl group at the final step.

Conversion of the γ-pyrone-fused naphthalene derivative (*S*)-**26b** to the target γ-pyrone-fused anthraquinone was achieved by the reported protocol.[11] Oxidation of (*S*)-**26b** with CAN gave naphthoquinone (*S*)-**30** in 75% yield (Scheme 7). One-pot conversion[11] of naphthoquinone **30** to the anthraquinone resulted in intractable mixture formation, from which the target anthraquinone **32** was obtained in an only trace amount. As hydrogen chloride developed during the aromatization would destroy the γ-pyrone moiety at the elevated temperature employed, we employed the two-step method. The Diels–Alder reaction of (*S*)-**30** with 1-methoxycyclohexa-1,3-diene followed by elimination of hydrogen chloride with pyridine gave (*S*)-**31** as a mixture of diastereomers (≈1:1) in 69% yield. The target anthraquinone (*S*)-**32** was obtained in 74% yield by heating neat (*S*)-**31** at 150 °C. Cleavage of the methyl ether (to afford **33**) followed by saponification of the benzoyl group at 0 °C provided (*S*)-espicufolin [(*S*)-**1**] in 50% yield. Similarly, (*R*)-espicufolin [(*R*)-**1**] was also prepared. The analytical data of the synthesized (*R*)-espicufolin were identical with the reported data for natural espicufolin in all respects including the $[\alpha]_D$-value [(*R*)-**1**: +8.5 ($CHCl_3$, *c* 0.02); (*S*)-**1**: −11.3 ($CHCl_3$, *c* 0.02); natural espicufolin: +9.4 ($CHCl_3$, *c* 0.02)]. Therefore, the unknown chiral center of C-14 of natural espicufolin was determined to be *R*.

in vitro Examination of espicufolin

To examine if espicufolin can promote neuronal survival, an *in vitro* study was conducted with the use of rat cerebrocortical neurons. Rat cerebrocortical neurons were separated from brains of 17-day embryos.[24] The neurons were seeded on poly-L-lysine-coated 24-well plates at a density of ≈500 000 cells cm^{-2} and cultured for 16 h in Dulbecco's modified Eagle's medium (DMEM, Sigma) with 10% fetal calf serum. Thereafter the medium was replaced with a serum-free DMEM



Scheme 7 *Reagents and conditions*: i) CAN, MeCN; ii) 1-methoxycyclohexa-1,3-diene, CH_2Cl_2, pyridine; iii) 150 °C; iv) BBr_3, CH_2Cl_2; v) NaOH, THF–MeOH, 0 °C.

containing calf serum albumin, insulin, transferrin, sodium selenite and 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES) (pH 7.3). After the neurons were cultured for 4 or 5 days, they were exposed to glutamate (300 μM) or sodium nitroprusside (SNP; 300 μM) to induce neuronal death. 12 h before neurons were exposed to the cytotoxic agents, 100 fg ml^{-1}, 10 pg ml^{-1}, 1 ng ml^{-1}, 100 ng ml^{-1} and 10 μg ml^{-1} of (±)- and (*S*)-espicufolins were added into the culture medium. By incubation of the neurons with 300 μM L-glutamic acid for 4 or 8 h, 30 and 45% of the neurons degenerated in the absence of espicufolin, respectively. The viability was estimated by the use of a redox indicator Alarmar Blue as described.[25] Espicufolin did not significantly improve the viability of the neurons which were exposed to glutamate. On the contrary, all neurons degenerated when they were incubated with 10 μg ml^{-1} of (±)- and (*S*)-espicufolin. SNP, a nitric oxide donor, is known to induce apoptotic neuronal death.[25] Espicufolins at any concentration did not rescue the neurons from SNP-induced apoptotic neuronal death. Taken together, we concluded that espicufolin is not able to promote survival of rat neurons against the toxicity of L-glutamic acid and nitric oxide.

Conclusions

We developed an efficient preparation of naphtho[1,2-*b*]pyran-4-ones with a combination of alkynoyl transfer and intramolecular cyclization. The target naphtho[1,2-*b*]pyran-4-ones with various kinds of substituents were prepared from the corresponding 2-alkynoyl-1-naphthols by proper choice of the reaction conditions. Espicufolin was prepared by this route. This methodology would be applicable for the preparation of other members of the pyranoanthraquinone family such as indomycinones,[4] premithramycinones[6] and AH-1763 IIa.[26] Regretfully, our *in vitro* study showed (*S*)- and (±)-espicufolin had no protective activity but weak cytotoxicity against rat embryonic neuronal cells.

Experimental

Mps were measured on a Yanagimoto micromelting apparatus and are uncorrected. Unless otherwise specified, NMR spectra were obtained with a JEOL GSX-270 or EX-400 spectrometer at ambient temperature by using $CDCl_3$ as solvent, and tetramethylsilane as internal standard for ^1H and ^{13}C. Mass spectra were measured with a Hitachi M80B spectrometer under the EI (electron impact, 20 eV) ionizing conditions. $[\alpha]_D$-Values were measured with a JASCO DIP-1000 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. THF was distilled from sodium benzophenone ketyl, and dichloromethane was distilled from CaH_2 prior to use. DMF was distilled under reduced pressure and then stored over molecular sieves (MS) 4 Å. Pyridine was distilled from CaH_2 and stored over MS 4 Å.

3-Acetoxymethyl-7-chloro-5,8-dimethoxy-1-naphthol 5

To a stirred suspension of **4** (7.550 g, 28.1 mmol) and acetic anhydride (3.17 ml, 33.7 mmol) in dry CH_2Cl_2 (100 ml) was added one drop of conc. perchloric acid at room temperature. The suspension became a clear solution. After the mixture had been stirred for 2 h, aq. $NaHCO_3$ (50 ml) was added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 ml). The combined organic phase was washed with brine (50 ml), dried over Na_2SO_4, filtered through a short column of silica gel, and concentrated to give 8.67 g (99%) of **5**. Recrystallization from CH_2Cl_2–hexane gave 7.826 g (90%) of **5** as *colorless needles* (Found: C, 57.80; H, 4.84. $C_{15}H_{15}ClO_5$ requires C, 57.98; H, 4.87%), mp 100–102 °C; R_f (30% EtOAc–hexane) 0.3; δ_H 2.13 (3H, s), 3.96 (3H, s), 4.03 (3H, s), 5.18 (2H, s), 6.72 (1H, s, H^6), 6.96 (1H, d, *J* 1.2, H^2), 7.68 (1H, d, *J* 1.2, H^4) and 9.44 (1H, s, OH); δ_C 21.0, 55.9, 62.3, 66.2, 106.2 (C-6), 111.9 (C-2 or -4), 112.8 (C-4 or C-2), 117.7, 121.7, 126.8, 135.3, 144.8 (C-8), 152.7 (C-1 or -5), 153.5 (C-5 or C-1) and 170.8 (C=O); *m/z* (rel. intensity) 312 [M^+(^{37}Cl), 34], 310 [M^+(^{35}Cl), 100], 297 (22), 295 (64), 255 (18) and 253 (53); ν_{max} (KBr)/cm^{-1} 3379, 1738, 1367, 1253 and 1055.

Halogenation of naphthols 4 and 5

NBS Method in CH_2Cl_2. To a stirred solution of **4** (269 mg, 1 mmol) in CH_2Cl_2 (10 ml) was added NBS (214 mg, 1.2 mmol) at room temperature. After 2 h, the reaction was quenched by addition of 5 ml of 1 M $NaHSO_3$. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 ml). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered through a short column of silica gel, and concentrated. The residue was chromatographed on silica gel (20–50% EtOAc–hexane).

NBS Method in DMF. To a stirred solution of a naphthol (24 mmol) in 48 ml of dry DMF was transferred a solution of NBS (3.560 g, 20 mmol) in dry DMF (20 + 10 ml) by a cannula. The mixture was stirred overnight and then water (300 ml) was added. The precipitates were filtered off, washed with water (3 × 50 ml), and dried to give the crude bromonaphthol. Recrystallization from CH_2Cl_2–hexane gave the pure material.

DBH Method. The reaction was carried in the same manner as above except for the use of DBH.

Iodination. To a stirred solution of a naphthol (9 mmol) and I_2 (18 mmol) in dry CH_2Cl_2 was added NMM (aq. 1.19 ml, 10.8 mmol) at room temperature. After 3 h, a mixture of aq. $NaHSO_3$ (1 M; 20 ml) and water (50 ml) was added. The mixture was extracted with $CHCl_3$ (3 × 50 ml). The organic extract was washed with brine, dried over Na_2SO_4, and concentrated.

The residue was recrystallized from CH_2Cl_2–hexane and/or chromatographed on silica gel (20–50% EtOAc–hexane).

2-Bromo-7-chloro-3-hydroxymethyl-5,8-dimethoxy-1-naphthol ***6***. *Colorless needles* (Found: C, 44.85; H, 3.47. $C_{13}H_{12}BrClO_4$ requires C, 44.92; H, 3.48%), mp 184–186 °C; R_f (30% EtOAc–hexane) 0.35; δ_H 2.17 (1H, br, OH), 3.96 (3H, s), 4.04 (3H, s), 4.86 (2H, br), 6.73 (1H, s, H^6), 7.80 (1H, s, H^4) and 10.20 (1H, s, OH); δ_C 56.0, 62.6, 65.6 (Ar*C*H_2O), 106.5 (C-6), 107.2, 112.6 (C-4), 117.6, 122.3, 125.2, 138.7, 143.9 (C-8), 149.5 and 152.7 (C-1 and -5); *m*/*z* (rel. intensity) 350 [M^+($^{37}Cl^{81}Br$), 20], 348 [M^+($^{35}Cl^{81}Br$ + $^{37}Cl^{79}Br$), 76], 346 [M^+($^{35}Cl^{79}Br$), 59], 335 (24), 333 (100) and 331 (77); ν_{max} (KBr)/cm^{-1} 3241, 1600, 1490, 1388, 1345 and 1050.

4-Bromo-7-chloro-3-hydroxymethyl-5,8-dimethoxy-1-naphthol ***7***. δ_H 2.04 (1H, br, OH), 3.91 (3H, s), 3.99 (3H, s), 4.83 (2H, br), 6.82 (1H, s, H^6), 7.15 (1H, s, H^2) and 9.82 (1H, s, OH). This compound could not be isolated.

3-Acetoxymethyl-2-bromo-7-chloro-5,8-dimethoxy-1-naphthol ***8***. *Colorless crystals* (Found: C, 45.89; H, 3.59. $C_{15}H_{14}BrClO_5$ requires C, 46.24; H, 3.62%), mp 183–185 °C; R_f (30% EtOAc–hexane) 0.65; δ_H 2.17 (3H, s), 3.96 (3H, s), 4.04 (3H, s), 5.30 (2H, s, CH_2O), 6.73 (1H, s, H^6), 7.74 (1H, s, H^4) and 10.23 (1H, s, OH); δ_C 20.9, 56.0, 62.5, 66.3 (ArCH_2O), 106.5 (C-6), 107.8, 114.1 (C-4), 117.8, 122.7, 124.8, 133.9, 143.8 (C-8), 149.7 (C-1 or -5), 152.6 (C-5 or C-1) and 170.5 (C=O); *m*/*z* (rel. intensity) 392 [M^+($^{37}Cl^{81}Br$), 26], 390 [M^+($^{35}Cl^{81}Br$ + $^{37}Cl^{79}Br$), 100], 388 [M^+($^{37}Cl^{79}Br$), 77], 375 (28), 373 (22), 331 (12), 267 (35), 251 (98) and 223 (53); ν_{max} (KBr)/cm^{-1} 3211, 1736, 1367, 1348, 1250, 1240 and 1045.

7-Chloro-3-hydroxymethyl-2-iodo-5,8-dimethoxy-1-naphthol ***9***. *Colorless crystals* (Found: C, 39.60; H, 3.25. $C_{13}H_{12}ClIO_4$ requires C, 39.57; H, 3.07%), mp 162–163 °C; R_f (40% EtOAc–hexane) 0.6; δ_H 2.14 (1H, t, *J* 6.4, OH), 3.97 (3H, s), 4.05 (3H, s), 4.82 (2H, d, *J* 6.4, ArCH_2O), 6.78 (1H, s, H^6), 7.82 (1H, s, H^4) and 10.53 (1H, s, OH); δ_C 56.0, 62.6, 69.7 (Ar*C*H_2O), 84.3 (C-2), 106.8 (C-6), 112.7, 116.8, 122.0, 126.2, 141.0, 143.8, 152.0 and 152.7; *m*/*z* (rel. intensity) 396 [M^+(^{37}Cl), 34], 394 [M^+(^{35}Cl), 100], 381 (31), 379 (92) and 219 (10); ν_{max} (KBr)/cm^{-1} 3293, 1598, 1481, 1386, 1374, 1343, 1047 and 953.

7,7′-Dichloro-1,1′-dihydroxy-3,3′-bis(hydroxymethyl)-5,5′, 8,8′-tetramethoxy-2,2′-binaphthyl ***10***. *Colorless crystals* (Found: C, 52.32; H, 4.47. $C_{26}H_{24}Cl_2O_8 \cdot CH_2Cl_2$ requires C, 52.28; H, 4.47%), mp 257–259 °C; R_f (40% EtOAc–hexane) 0.2; δ_H 2.78 (2H, br, OH), 3.99 (6H, s), 4.00 (6H, s), 4.48 (2H, d, *J* 13.2, CH_2O), 4.50 (2H, d, *J* 13.2, CH_2O), 6.75 (2H, s, H^6 and $H^{6'}$), 7.96 (2H, s, H^4 and $H^{4'}$) and 9.81 (2H, s, OH); δ_C 56.0, 62.5, 64.2 (Ar*C*H_2O), 106.2 (C-6), 114.1 (C-4), 117.5, 119.0, 121.9, 126.6, 139.5, 144.7, 149.7 and 152.9; *m*/*z* (rel. intensity) 536 [M^+($^{37}Cl^{35}Cl$), 38], 534 [M^+($^{35}Cl^{35}Cl$), 60], 516 (20), 500 (70), 498 (100), 485 (46), 483 (62), 468 (23) and 453 (33); ν_{max} (KBr)/cm^{-1} 3392, 3226, 1599, 1488, 1339 and 1051.

3-Acetoxymethyl-7-chloro-2-iodo-5,8-dimethoxy-1-naphthol 11. *Colorless crystals* (Found: C, 41.10; H, 3.23. $C_{15}H_{14}ClIO_5$ requires C, 41.26; H, 3.23%), mp 164–166 °C; R_f (30% EtOAc–hexane) 0.5; δ_H 2.18 (3H, s), 3.97 (3H, s), 4.05 (3H, s), 5.27 (2H, s, ArCH_2O), 6.76 (1H, s, H^6), 7.75 (1H, s, H^4) and 10.6 (1H, s, OH); δ_C 20.9, 55.9, 62.5, 70.3 (Ar*C*H_2O), 84.7 (C-2), 106.6 (C-6), 106.6 (C-4), 113.9, 122.3, 125.6, 136.2, 143.4 (C-8), 152.1 (C-1 or -5), 152.4 (C-5 or C-1) and 170.4 (C=O); *m*/*z* (rel. intensity) 436 (M^+, 100), 310 (59), 252 (97) and 223 (10); ν_{max} (KBr)/cm^{-1} 3286, 1737, 1369, 1346, 1242 and 1047.

3,3′-Bis(acetoxymethyl)-7,7′-dichloro-1,1′-dihydroxy-5,5′, 8,8′-tetramethoxy-2,2′-binaphthyl ***12***. *Colorless crystals*, mp 225–226 °C (Found: C, 57.40; H, 4.56. $C_{30}H_{28}Cl_2O_{10} \cdot \frac{1}{2}H_2O$ requires C, 57.34; H, 4.65%); R_f (30% EtOAc–hexane) 0.3; δ_H 1.99 (6H, s), 3.99 (6H, s), 4.02 (6H, s), 5.05 (2H, d, *J* 13.2, CH_2O), 5.08 (2H, d, *J* 13.2, CH_2O), 6.77 (2H, s, H^6 and $H^{6'}$), 7.91 (2H, s, H^4 and $H^{4'}$) and 9.78 (2H, s, OH); δ_C 20.8, 56.0, 62.5, 64.9 (Ar*C*H_2O), 106.4 (C-6 and -6′), 113.0 (C-4 and -4′), 117.7, 118.3, 122.0, 126.4, 134.9, 144.9, 149.9, 152.8 and 170.5; *m*/*z* (rel. intensity) 620 [M^+($^{37}Cl^{35}Cl$), 25], 618 [M^+($^{35}Cl_2$), 36], 500 (71), 498 (100), 485 (29) and 483 (40); ν_{max} (KBr)/cm^{-1} 3296, 1734, 1344, 1246, 1234 and 1047.

3,3′-Bis(acetoxymethyl)-7,7′-dichloro-1,1′-dihydroxy-5,5′, 8,8′-tetramethoxy-2,4′-binaphthyl. R_f (30% EtOAc–hexane) 0.25; δ_H 1.98 (3H, s), 2.18 (3H, s), 3.97 (3H, s), 4.00 (3H, s), 4.01 (3H, s), 4.05 (3H, s), 5.03 (1H, d, *J* 13.2, CH_2O), 5.04 (1H, d, *J* 13.2, CH_2O), 5.27 (2H, s, CH_2O), 6.76 (2H, s, H^6 and $H^{6'}$), 7.75 (1H, s, $H^{2'}$), 7.88 (1H, s, H^4), 9.76 (1H, s, OH) and 10.58 (1H, s, OH).

3-Acetoxymethyl-7-chloro-2-iodo-5,8-dimethoxy-1-(methoxymethoxy)naphthalene 14. The naphthol **11** (5.796 g, 13.27 mmol) and NaH (60% dispersion; 0.53 g, 13.3 mmol) were placed in a flask and dry DMF (55 ml) was added under Ar. The mixture was cooled in an ice-bath and then MOMCl (1.21 ml, 15.9 mmol) was added by a syringe. After the mixture had been stirred for 6 h, water (500 ml) was added. The precipitates were filtered, washed with water (100 ml), and dried. The precipitates were dissolved in warm $CHCl_3$ (100 ml) and the solution was filtered through a column of $MgSO_4$ and silica gel, which was washed with $CHCl_3$ (3 × 50 ml). Concentration of the filtrate gave 6.26 g (98%) of **14** as an amber-white solid. Recrystallization from CH_2Cl_2–diethyl ether–hexane gave 5.623 g (88%) of **14** as *colorless crystals* (Found: C, 42.48; H, 3.77. $C_{17}H_{18}ClIO_6$ requires C, 42.29; H, 3.68%), mp 155–157 °C; R_f (20% EtOAc–hexane) 0.45; δ_H 2.19 (3H, s), 3.76 (3H, s), 3.82 (3H, s), 3.97 (3H, s), 5.13 (2H, s, OCH_2O), 5.29 (2H, s, ArCH_2O), 6.84 (1H, s, H^6) and 8.06 (1H, s, H^4); δ_C 20.9, 55.9, 56.0, 59.1, 70.7 (Ar*C*H_2O), 97.8 (C-2), 101.7 (OCH_2O), 107.1 (C-6), 119.5 (C-4), 122.8, 126.4, 126.9, 135.7, 143.4, 151.6, 152.1 and 170.5 (C=O); *m*/*z* (rel. intensity) 480 (M^+, 33), 436 (13), 376 (53), 293 (100) and 266 (21); ν_{max} (KBr)/cm^{-1} 1743, 1583, 1321, 1228 and 1049.

7-Chloro-3-hydroxymethyl-2-iodo-5,8-dimethoxy-1-(methoxymethoxy)naphthalene 16. The acetate **14** (2.20 g, 4.58 mmol) was dissolved in freshly distilled THF (100 ml) and MeOH (35 ml). To the stirred solution was added aq. NaOH (1.0 M; 15 ml) at room temperature. After 1 h, brine (100 ml) was added. The suspension was extracted with EtOAc (3 × 50 ml). The organic phase was washed with brine (50 ml), dried over $MgSO_4$, and concentrated to give a crude product. Chromatography on silica gel (20–30% EtOAc–hexane) gave 2.08 g of **16** as *colorless crystals* (Found: C, 41.04; H, 3.66. $C_{15}H_{16}ClIO_5$ requires C, 41.07; H, 3.68%), mp 134–135 °C; R_f (40% EtOAc–hexane) 0.55; δ_H 2.75 (1H, t, *J* 7.4, OH), 3.77 (3H, s), 3.79 (3H, s), 3.91 (3H, s), 4.75 (2H, d, *J* 7.4, CH_2OH), 5.15 (2H, s, OCH_2O), 6.74 (1H, s, H^6) and 7.95 (1H, s, H^4); δ_C 55.9, 59.0, 61.7, 69.9 (Ar*C*H_2O), 96.6 (C-2), 101.8 (OCH_2O), 106.7 (C-6), 117.4 (C-4), 122.2 (C-8a), 125.3 (C-7 or -4a), 127.1 (C-4a or -8), 140.2 (C-3), 143.2 (C-8), 151.2 (C-1) and 151.8 (C-5); *m*/*z* (rel. intensity) 438 (M^+, 77), 375 (66), 311 (17), 279 (43) and 251 (100); ν_{max} (KBr)/cm^{-1} 3434, 1585, 1477, 1455, 1411, 1330, 1311, 1247, 1211 and 1187.

General procedure for condensation of 3-(hydroxymethyl)-naphthalenes 15 and 16 with alkynoic acid

To a solution of a 3-(hydroxymethyl)naphthalene (1.5 mmol), alkynoic acid (1.8 mmol) and Et_3N (0.50 ml, 3.6 mmol) in dry CH_2Cl_2 (2 ml) was added *N*,*N*-bis(2-oxooxazolidin-3-yl)-phosphorodiamidic chloride (BOPCl) (458 mg, 1.8 mmol) at room temperature under argon. After 20 h, the reaction mixture was quenched by addition of saturated aq. $NaHCO_3$ (10 ml). The organic phase was separated and the aqueous phase was extracted with $CHCl_3$ (3 × 20 ml). The combined organic phases were washed with brine (50 ml), dried over $MgSO_4$, and concentrated to give a crude product, which was purified by recrystallization or column chromatography on silica gel.

7-Chloro-2-iodo-5,8-dimethoxy-1-methoxymethoxy-3-[(4-methylpent-2-ynoyloxy)methyl]naphthalene 18a. 87% Yield; *colorless crystals* (Found: C, 47.08; H, 4.15. $C_{21}H_{22}ClIO_6$ requires C, 47.34; H, 4.16%), mp 161–163 °C; R_f (30% EtOAc–hexane) 0.7; δ_H 1.24 (6H, d, *J* 6.8), 2.71 (1H, sept, *J* 6.8), 3.76 (3H, s), 3.81 (3H, s), 3.97 (3H, s), 5.12 (2H, s, OCH_2O), 5.38 (2H, s, $ArCH_2O$), 6.84 (1H, s, H^6) and 8.09 (1H, s, H^4); δ_C 20.6 ($CHMe_2$), 21.7 ($CHMe_2$), 56.1, 59.1, 61.8, 71.9 ($ArCH_2O$), 72.0 ($COC\equiv$), 95.1 ($\equiv CPr^i$), 97.9 (C-2), 101.8 (OCH_2O), 107.2 (C-6), 120.2 (C-4), 123.0, 126.3, 127.0, 134.8, 143.4, 151.7, 152.2 and 153.5; *m*/*z* (rel. intensity) 534 [M^+(^{37}Cl), 8], 532 [M^+(^{35}Cl), 10], 376 (81), 293 (33), 129 (100) and 112 (45); ν_{max} (KBr)/cm^{-1} 2235, 1714, 1587, 1251 and 1165.

(*S*)-7-Chloro-2-iodo-5,8-dimethoxy-1-methoxymethoxy-3-[(4-methylhex-2-ynoyloxy)methyl]naphthalene (*S*)-18b. 90% Yield; *colorless crystals* (Found: C, 48.65; H, 4.46. $C_{22}H_{24}ClIO_6$ requires C, 48.33; H, 4.42%), mp 144–146 °C; $[\alpha]_D^{27}$ −5.06 (*c* 1.00, $CHCl_3$); R_f (30% EtOAc–hexane) 0.7; δ_H 1.03 (3H, t, *J* 7.3), 1.23 (3H, d, *J* 6.8), 1.57 (2H, m), 2.53 (1H, m), 3.76 (3H, s), 3.82 (3H, s), 3.97 (3H, s), 5.13 (2H, s, OCH_2O), 5.38 (2H, s, $ArCH_2O$), 6.84 (1H, s, H^6) and 7.26 (1H, s, H^4); δ_C 11.6 (CH_2CH_3), 19.4 ($CHCH_3$), 27.6 (CH_2CH_3), 28.9 ($CHCH_3$), 56.1, 59.1, 61.8, 71.8 ($ArCH_2O$), 73.1 ($COC\equiv$), 94.3 ($\equiv CBu^s$), 97.8 (C-2), 101.8 (OCH_2O), 107.2 (C-6), 120.1 (C-4), 123.0, 126.3, 127.0, 134.9, 143.4, 151.7, 152.5 and 153.5; *m*/*z* (rel. intensity) 548 [M^+(^{37}Cl), 1], 546 [M^+(^{35}Cl), 3], 376 (100), 293 (31), 249 (12) and 109 (3); ν_{max} (KBr)/cm^{-1} 1714, 1585, 1332, 1321, 1247 and 1054.

(*R*)-**18b**: 90% yield; $[\alpha]_D^{27}$ +14.5 (*c* 1.07, $CHCl_3$).

General procedure for nucleophilic acyl-transfer reaction

To a stirred solution of an ester **13**, **14**, **17** or **18** (1 mmol) in THF (20 ml) was slowly added a solution of BuLi (1.2 mmol) at the indicated temperature in the text under argon. After 1 h, water (20 ml) was added and then the mixture was warmed to room temperature. The mixture was extracted with EtOAc (3 × 20 ml). The extract was washed with brine (50 ml), dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (20–50% EtOAc–hexane) to give 2-acylnaphthalene **19** or **21**, which was recrystallized from CH_2Cl_2–diethyl ether–hexane if necessary.

2-Acetyl-7-chloro-3-hydroxymethyl-5,8-dimethoxy-1-(methoxymethoxy)naphthalene 19. *Colorless crystals* (Found: C, 57.17; H, 5.35. $C_{17}H_{19}ClO_6$ requires C, 57.55; H, 5.40%), mp 125–128 °C; R_f (20% EtOAc–hexane) 0.3; **19** exists as a 1:7 mixture of keto and hemiketal forms. Keto form: δ_H 2.74 (3H, s, Ac), 2.90 (1H, t, *J* 5.9, OH), 3.46 (3H, s), 3.85 (3H, s), 3.96 (3H, s), 4.63 (2H, d, *J* 5.9, CH_2OH), 5.07 (2H, s, OCH_2O), 6.84 (1H, s, H^6) and 8.04 (1H, s, H^4); δ_C (typical signals) 32.9, 55.9, 58.1, 61.7, 63.9 ($ArCH_2O$), 102.3 (OCH_2O), 107.5 (C-6), 119.6 and 206.0 (Ac).

Hemiketal form: δ_H 2.01 (3H, s, Me), 3.54 (3H, s), 3.85 (3H, s), 3.96 (3H, s), 4.66 (1H, s, OH), 5.03 (1H, d, *J* 5.9, OCH_2O), 5.10 (1H, d, *J* 13.2, CH_2OH), 5.22 (1H, d, *J* 5.9, OCH_2O), 5.30 (1H, d, *J* 13.2, CH_2OH), 6.81 (1H, s, H^6) and 7.90 (1H, s, H^4); δ_C 27.3, 56.0, 57.5, 61.5, 70.5 ($ArCH_2O$), 101.5 (OCH_2O), 106.5, 106.5 (C-1 and C-6), 111.4 (C-4), 122.6, 124.8, 129.1, 135.6, 138.8, 144.7 (C-8), 146.7 (C-1) and 152.1 (C-5); *m*/*z* (rel. intensity) 356 [M^+(^{37}Cl), 38], 354 [M^+(^{35}Cl), 100], 250 (55) and 249 (53); ν_{max} (KBr)/cm^{-1} 3444, 1643, 1599, 1508, 1344 and 1052.

2-Chloro-6-hydroxymethyl-1,4-dimethoxy-8-(methoxymethoxy)naphthalene 20. *Colorless needles* (Found: C, 57.37; H, 5.39. $C_{15}H_{17}ClO_5$ requires C, 57.61; H, 5.48%), mp 108–109 °C; R_f (20% EtOAc–hexane) 0.25; δ_H 2.32 (1H, br, OH), 3.59 (3H, s), 3.86 (3H, s), 3.92 (3H, s), 4.76 (2H, br, $ArCH_2OH$), 5.29 (2H, s, OCH_2O), 6.76 (1H, s, H^3), 7.16 (1H, d, *J* 1.0, H^7) and 7.82 (1H, d, *J* 1.0, H^5); δ_C 55.8 ($ArCH_2O$), 56.5 (MeO), 61.5 (MeO), 65.1 (MeO), 96.3 (OCH_2O), 106.5 (C-3), 112.6, 114.0, 121.1, 124.5, 127.5, 138.8, 145.1 (C-1), 151.7 and 152.9; *m*/*z* (rel. intensity) 314 [M^+(^{37}Cl), 36], 312 [M^+(^{35}Cl), 100], 282 (12), 267 (23), 250 (22), 249 (16) and 237 (12); ν_{max} (KBr)/cm^{-1} 3487, 1591, 1342, 1263, 1145, 1055 and 970.

7-Chloro-3-hydroxymethyl-5,8-dimethoxy-1-(methoxymethoxy)-2-(4-methylpent-2-ynoyl)naphthalene 21a. *Pale yellow crystals* (Found: C, 61.77; H, 5.78. $C_{21}H_{23}ClO_6$ requires C, 61.99; H, 5.70%), mp 128–130 °C; R_f (30% EtOAc–hexane) 0.35; **21a** exists as a 5:1 mixture of keto and hemiketal forms. Keto form: δ_H 1.18 (6H, d, *J* 6.8), 2.73 (1H, sept, *J* 6.8), 3.27 (1H, br, OH), 3.54 (3H, s), 3.78 (3H, s), 3.84 (3H, s), 4.66 (2H, s, CH_2OH), 5.06 (2H, s, OCH_2O), 6.70 (1H, s, H^6) and 7.90 (1H, s, H^4); δ_C 20.9 ($CHMe_2$), 21.6 ($CHMe_2$), 55.7, 57.9, 61.5, 62.8 ($ArCH_2O$), 82.0 (C-2′), 101.8 (OCH_2O), 101.9 (C-3′), 107.4, 118.1, 122.0, 125.5, 127.7, 133.3, 136.1, 144.4, 150.8, 151.7 and 181.6 (C-1′).

Hemiketal form: δ_H 1.13 (3H, d, *J* 6.8), 1.15 (3H, d, *J* 6.8), 2.60 (1H, sept, *J* 6.8), 3.68 (3H, s), 3.80 (3H, s), 3.87 (3H, s), 5.02 (1H, d, *J* 6.7, OCH_2O), 5.13 (1H, d, *J* 13.2, $ArCH_2O$), 5.19 (1H, d, *J* 6.7, OCH_2O), 5.24 (1H, d, *J* 13.2, $ArCH_2O$), 5.42 (1H, br, OH), 6.71 (1H, s, H^6) and 7.77 (1H, s, H^4); δ_C (typical signals) 71.0 (CH_2O), 78.5, 90.3, 98.4 (hemiketal C), 102.0 (OCH_2O), 123.0, 124.7, 129.0, 133.3, 134.8, 137.6, 144.7, 146.8 150.8 and 151.0; *m*/*z* (rel. intensity) 408 [M^+(^{37}Cl), 8], 406 [M^+(^{35}Cl), 23], 346 (100), 331 (81), 329 (64), 308 (45), 276 (53) and 265 (85); ν_{max} (KBr)/cm^{-1} 3508, 3332, 2214, 1655, 1635, 1587, 1333, 1215 and 1047.

(*S*)-7-Chloro-3-hydroxymethyl-5,8-dimethoxy-1-(methoxymethoxy)-2-(4-methylhex-2-ynoyl)naphthalene (*S*)-21b. *Pale yellow crystals* (Found: C, 62.40; H, 5.83. $C_{22}H_{25}ClO_6$ requires C, 62.78; H, 5.99%), mp 92–93 °C; $[\alpha]_D^{31}$ +11.6 (*c* 0.65, $CHCl_3$); R_f (30% EtOAc–hexane) 0.45; **21b** exists as a 6:1 mixture of keto and hemiketal forms. Keto form: δ_H 1.03 (3H, t, *J* 7.3, $H^{6'}$), 1.24 (3H, d, *J* 7.3, 4′-Me), 1.56 (2H, m, $H^{5'}$), 2.63 (1H, m, $H^{4'}$), 3.04 (1H, br t, *J* 6.4, OH), 3.58 (3H, s), 3.84 (3H, s), 3.95 (3H, s), 4.71 (2H, d, *J* 6.4, $ArCH_2O$), 5.10 (2H, s, OCH_2O), 6.83 (1H, s, H^6) and 8.04 (1H, s, H^4); δ_C 11.5 (C-6′), 19.4 (4′-Me), 28.1 (C-5′), 29.0 (C-4′), 56.0, 58.1, 61.6, 63.6 (CH_2OH), 83.3 (C-2′), 101.3 (C-3′), 102.2 (OCH_2O), 107.8, 119.0, 122.3, 125.9, 128.0, 133.9, 136.2, 144.7, 151.4, 152.0 and 181.8 (C-1′).

Hemiketal form (1:1 diastereomeric mixture): δ_H 1.02 (3H both, t, *J* 7.3, $H^{5'}$), 1.18 (3H of one diastereomer, d, *J* 7.3, 4′-Me), 1.19 (3H of another diastereomer, d, *J* 7.3, 4′-Me), 1.53 (2H, m, $H^{4'}$), 2.49 (1H, m, $H^{3'}$), 3.71 (3H of one diastereomer, s), 3.72 (3H of another diastereomer, s), 3.85 (3H both, s), 3.96 (3H both, s), 5.0–5.4 (5H, m, CH_2O, OH and OCH_2OMe), 6.81 (1H both, br s, H^6) and 7.89 (1H both, br s, H^4); δ_C 14.0 (C-6′), 15.2 (C-6′), 20.2 (4′-Me), 20.2 (4′-Me), 27.5 (C-5′), 27.5 (C-5′), 29.5 (C-4′), 29.6 (C-4′), 57.9, 61.5, 65.8, 71.2 (C-3), 71.2 (C-3), 79.8 (C-1′), 89.3, 98.5, 101.4, 101.4, 102.2, 106.6, 111.3, 123.0, 124.8, 129.2, 135.1, 137.8, 137.8, 144.9 and 147.0; *m*/*z* (rel. intensity) 420 (M^+, 27), 360 (100), 343 (75), 330 (60), 294 (72), 265 (97) and 248 (58); ν_{max} (KBr)/cm^{-1} 3456, 2200, 1650, 1334 and 1068.

(*R*)-**21b**: $[\alpha]_D^{27}$ −10.7 (*c* 0.65, $CHCl_3$).

6-(Buta-2,3-dienoyloxymethyl)-2-chloro-1,4-dimethoxy-8-(methoxymethoxy)naphthalene 22. White solid, R_f (30% EtOAc–hexane) 0.55; δ_H 3.60 (3H, s, MeO), 3.87 (3H, s, MeO), 3.96 (3H, s, MeO), 5.25 (2H, m, $=CH_2$), 5.28 (2H, s), 5.31 (2H, s), 5.71 (1H, t, *J* 6.4, COCH=), 6.81 (1H, s, H^3), 7.19 (1H, s, H^7) and 7.92 (1H, s, H^5); δ_C 55.9 (MeO), 56.5 (MeO), 61.6 (MeO), 66.6 ($ArCH_2O$), 79.4 ($=CH_2$), 87.8 ($COCH=$), 96.5 (OCH_2O), 106.7, 113.5, 116.0, 121.6, 125.1, 127.4, 133.5, 145.2, 151.8, 153.0, 165.7 (C=O) and 216.1 (=C=); *m*/*z* (rel. intensity) 380 [M^+(^{37}Cl), 33], 378 [M^+(^{35}Cl), 100], 316 (15), 301 (18), 250 (76)

and 249 (49); ν_{max} (KBr)/cm^{-1} 1968, 1938, 1720, 1590, 1342, 1159 and 1053.

8-Chloro-7,10-dimethoxy-6-(methoxymethoxy)-3-methylnaphtho[2,3-*c*]oxepin-5(1*H*)-one 23. *Pale yellow crystals* (Found: C, 60.14; H, 5.09. $C_{19}H_{19}ClO_6$ requires C, 60.24; H, 5.06%), mp 175–177 °C; R_f (30% EtOAc–hexane) 0.4; δ_H 2.00 (3H, s, 3-Me), 3.53 (3H, s, MeO), 3.86 (3H, s, MeO), 3.98 (3H, s, MeO), 5.07 (2H, s, OCH_2O), 5.22 (2H, s, H^1), 5.54 (1H, s, H^4), 6.88 (1H, s, H^9) and 7.99 (1H, s, H^{11}); δ_C 22.2 (3-Me), 56.1 (MeO), 57.7 (MeO), 61.9 (MeO), 74.9 (C-1), 102.2 (OCH_2O), 107.9, 108.4, 118.9, 124.0, 126.7, 127.8, 130.5, 135.3, 145.5, 150.2, 152.0, 168.5 (C-3) and 190.5 (C-5); *m*/*z* (rel. intensity) 380 [M$^+$(^{37}Cl), 42], 378 [M$^+$(^{35}Cl), 100], 316 (17), 301 (19), 251 (37), 250 (88) and 249 (59); ν_{max} (KBr)/cm^{-1} 1652, 1616, 1592, 1456, 1331, 1155 and 1045.

General procedure for benzoylation of alcohols 21a–e

To a stirred solution of an alcohol **21a**–**e** (1 mmol) in dry pyridine (5 ml) was slowly added freshly distilled benzoyl chloride (1.1 mmol) at 0 °C under argon. After 3 h, water (20 ml) was added and the mixture was warmed to room temperature. The mixture was extracted with $CHCl_3$ (3 × 20 ml). The combined extract was washed successively with cool aq. HCl (3 M; 3 × 20 ml), saturated aq. $NaHCO_3$ (50 ml) and brine (50 ml), dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography to give the corresponding benzoyl ester **25a**–**e**, which was recrystallized from CH_2Cl_2–diethyl ether–hexane if necessary.

3-Benzoyloxymethyl-7-chloro-5,8-dimethoxy-1-(methoxymethoxy)-2-(4-methylpent-2-ynoyl)naphthalene 25a. 69% Yield; *yellow crystals* (Found: C, 65.68; H, 5.42. $C_{28}H_{27}ClO_7$ requires C, 65.82; H, 5.33%), mp 135–137 °C; R_f (30% EtOAc–hexane) 0.55; δ_H 1.16 (6H, d, *J* 6.8), 2.68 (1H, sept, *J* 6.8), 3.59 (3H, s), 3.86 (3H, s), 3.95 (3H, s), 5.11 (2H, s, OCH_2O), 5.60 (2H, s, C*H*$_2$OBz), 6.87 (1H, s, H^6), 7.41 (2H, m, Bz), 7.53 (1H, m, Bz), 8.07 (2H, m, Bz) and 8.15 (1H, s, H^4); δ_C 20.9 (*C*HMe$_2$), 21.6 (CH*Me*$_2$), 56.0 (MeO), 57.9 (MeO), 61.7 (MeO), 64.7 (*C*H$_2$Bz), 81.9 (C-2′), 101.2 (C-3′), 102.1 (OCH_2O), 107.8, 120.1, 123.0, 126.4, 127.4, 128.2, 128.2, 129.8, 130.5, 132.9, 133.9, 144.7, 150.5, 152.0, 166.0 and 180.3 (C-1′); *m*/*z* (rel. intensity) 510 [M$^+$(^{35}Cl), 3], 450 (10), 405 (5), 373 (13), 344 (21) and 105 (100); ν_{max} (KBr)/cm^{-1} 2203, 1714, 1663, 1335, 1267, 1036, 917 and 714.

(*S*)-3-Benzoyloxymethyl-7-chloro-5,8-dimethoxy-1-(methoxymethoxy)-2-(4-methylhex-2-ynoyl)naphthalene (*S*)-25b. 87% Yield; *yellow crystals* (Found: C, 66.20; H, 5.54. $C_{29}H_{29}ClO_7$ requires C, 66.35; H, 5.57%), mp 97–99 °C; $[\alpha]_D^{31}$ +10.7 (*c* 0.98, $CHCl_3$); R_f (30% EtOAc–hexane) 0.6; δ_H 0.95 (3H, t, *J* 7.3, H$^{6'}$), 1.14 (3H, d, *J* 6.8, 4′-Me), 1.47 (2H, m, H$^{5'}$), 2.50 (1H, m, H$^{4'}$), 3.58 (3H, s, MeO), 3.85 (3H, s, MeO), 3.97 (3H, s, MeO), 5.10 (2H, s, OC*H*$_2$OMe), 5.59 (2H, s, C*H*$_2$OBz), 6.87 (1H, s, H^6), 7.41 (2H, m, Bz), 7.54 (1H, m, Bz), 8.06 (2H, m, Bz) and 8.16 (1H, s, H^4); δ_C 11.5 (C-6′), 19.3 (4′-Me), 28.0 (C-5′), 29.0 (C-4′), 56.0 (MeO), 58.0 (MeO), 61.7 (MeO), 64.7 (*C*H$_2$OBz), 83.1 (C-2′), 100.5 (C-3′), 102.2 (O*C*H$_2$OMe), 107.8, 120.2, 123.0, 126.4, 127.5, 128.2, 129.9, 130.6, 133.0, 133.9, 134.1, 144.8, 150.7, 152.1, 166.1 (*C*OPh) and 180.4 (C-1′); *m*/*z* (rel. intensity) 526 [M$^+$(^{37}Cl), 1], 524 [M$^+$(^{35}Cl), 3], 464 (10), 419 (5), 387 (8), 343 (10) and 105 (100); ν_{max} (KBr)/cm^{-1} 2204, 1716, 1648 and 1590.

(*R*)-**25b**: $[\alpha]_D^{28}$ −9.72 (*c* 0.99, $CHCl_3$).

General procedure for intramolecular reaction of alkynones 25a–e

A solution of an alkynone **25a**–**e** (1 mmol) in a mixture of THF (10 ml), propan-2-ol (5 ml) and aq. HCl (3 M; 3 ml) was refluxed for 24 h. The mixture was cooled to room temperature and then quenched with saturated aq. $NaHCO_3$ (≈30 ml). The reaction mixture was extracted with $CHCl_3$ (3 × 20 ml). The combined extract was washed with brine (50 ml), dried over $MgSO_4$, and concentrated. The residue was purified by silica gel or activated alumina column chromatography.

Prior treatment with Et$_2$NH. To a stirred solution of an alkynone **25** (1 mmol) in a mixture of THF (10 ml) and propan-2-ol (5 ml) was added diethylamine (0.2 ml, 2 mmol) at room temperature under argon. After the consumption of **25** was checked by TLC (*ca*. 24 h), aq. HCl (3 M, 2 ml) was added and the mixture was refluxed for 16 h. The mixture was cooled to room temperature and then quenched with saturated aq. $NaHCO_3$ (≈30 ml). The mixture was extracted with $CHCl_3$ (3 × 20 ml). The combined extract was washed with brine (50 ml), dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography.

8-Chloro-6-hydroxy-7,10-dimethoxy-3-(1-methylethyl)naphtho[2,3-*c*]oxepin-5(1*H*)-one 24. *Pale yellow crystals* (Found: C, 62.52; H, 5.32. $C_{19}H_{19}ClO_5$ requires C, 62.90; H, 5.28%), mp 207–209 °C; R_f (30% EtOAc–hexane) 0.25; δ_H 1.20 (6H, d, *J* 6.8), 2.93 (1H, sept, *J* 6.8), 3.96 (3H, s), 4.09 (3H, s), 5.58 (2H, s, H^1), 6.57 (1H, s, H^4), 6.77 (1H, s, H^9), 7.61 (1H, s, H^{11}) and 10.62 (1H, s); δ_C 19.1, 41.0, 56.1, 62.6, 75.6 (C-1), 99.6 (C-4), 105.2, 107.6, 116.8, 117.5, 121.8, 128.6, 140.0, 145.8, 151.4, 152.3, 164.9 (C-3) and 203.5 (C-5); *m*/*z* (rel. intensity) 364 [M$^+$(^{37}Cl), 12], 362 [M$^+$(^{35}Cl), 32], 321 (36), 319 (100), 304 (16), 294 (20) and 289 (16); ν_{max} (KBr)/cm^{-1} 1599, 1507, 1358, 1209 and 1029.

5-Benzoyloxymethyl-9-chloro-7,10-dimethoxy-2-(1-methylethyl)naphtho[1,2-*b*]pyran-4-one 26a. *Pale yellow crystals* (Found: C, 65.58; H, 4.42. $C_{24}H_{19}ClO_6$ requires C, 65.68; H, 4.36%), mp 169–171 °C; R_f (30% EtOAc–hexane) 0.45; δ_H 2.53 (3H, s), 3.95 (3H, s), 3.97 (3H, s), 6.15 (2H, C*H*$_2$OBz), 6.34 (1H, s, H^3), 7.01 (1H, s, H^8), 7.47 (2H, m, Bz), 7.57 (1H, m, Bz), 8.17 (2H, m, Bz) and 8.27 (1H, s, H^6); δ_C 20.0, 56.2, 61.3, 65.8 (*C*H$_2$OBz), 109.8 (C-3), 112.9 (C-11), 117.4 (C-6), 119.2 (C-10a), 119.9 (C-4b), 127.0 (C-9), 127.1 (C-6a), 128.3, 129.8, 130.5, 132.9, 133.0, 145.4, 151.6, 154.5, 164.3, 166.2 (C=O) and 179.1 (C=O); *m*/*z* (rel. intensity) 440 [M$^+$(^{37}Cl), 1], 438 [M$^+$(^{35}Cl), 3], 335 (35), 333 (100), 305 (8), 303 (23) and 105 (5); ν_{max} (KBr)/cm^{-1} 1718, 1654, 1619, 1335, 1273 and 1068.

(*S*)-5-Benzoyloxymethyl-9-chloro-7,10-dimethoxy-2-(1-methylpropyl)naphtho[1,2-*b*]pyran-4-one (*S*)-26b. *Pale yellow crystals* (Found: C, 67.29; H, 5.21. $C_{27}H_{25}ClO_6$ requires C, 67.43; H, 5.24%), mp 141–142 °C; $[\alpha]_D^{29}$ −2.64 (*c* 1.00, $CHCl_3$); R_f (30% EtOAc–hexane) 0.5; δ_H 1.01 (3H, t, *J* 7.3, H$^{3'}$), 1.40 (3H, d, *J* 6.8, 1′-Me), 1.74 (1H, m, H$^{2'}$), 1.94 (1H, m, H$^{2'}$), 2.76 (1H, m, H$^{1'}$), 3.91 (3H, s), 3.93 (3H, s), 6.12 (2H, C*H*$_2$OBz), 6.32 (1H, s, H^3), 6.95 (1H, s, H^8), 7.45 (2H, m, Bz), 7.56 (1H, m, Bz), 8.15 (2H, m, Bz) and 8.21 (1H, s, H^6); δ_C 11.5 (C-3′), 17.5 (1′-Me), 27.2 (C-2′), 39.9 (C-1′), 56.0, 61.4, 65.6 (*C*H$_2$OBz), 109.6 (C-3), 110.8 (C-11), 116.9 (C-5), 119.0, 119.9, 126.7, 126.9, 128.2, 129.6, 130.3, 132.7, 132.8, 145.5, 151.3, 154.5, 166.0, 171.8 (C=O) and 179.2 (C=O); *m*/*z* (rel. intensity) 482 [M$^+$(^{37}Cl), 1], 480 [M$^+$(^{35}Cl), 3], 377 (36), 375 (100) and 345 (11); ν_{max} (KBr)/cm^{-1} 1716, 1651, 1626, 1489, 1336, 1273 and 710.

(*R*)-**26b**: $[\alpha]_D^{28}$ +1.98 (*c* 1.02, $CHCl_3$).

5-Benzoyloxymethyl-9-chloro-7,10-dimethoxy-2-phenylnaphtho[1,2-*b*]pyran-4-one 26d. *Pale yellow crystals* (Found: C, 68.58; H, 4.33. $C_{29}H_{21}ClO_6 \cdot \frac{1}{2}H_2O$ requires C, 68.31; H, 4.35%), mp 236–240 °C; R_f (33% EtOAc–hexane) 0.4; δ_H 3.85 (3H, s), 3.96 (3H, s), 6.18 (2H, s, ArC*H*$_2$O), 6.95 (1H, s, H^3), 7.03 (1H, s, H^8), 7.47 (2H, m), 7.57 (4H, m), 8.17 (4H, m) and 8.31 (1H, s, H^6); δ_C 56.3, 61.7, 65.8 (*C*H$_2$OBz), 109.7 (C-3), 110.0 (C-11), 117.8 (C-5), 119.3, 120.5, 126.5, 127.1, 127.4,

128.4, 129.2, 129.8, 130.5, 131.5, 131.7, 132.9, 133.1, 145.8, 151.7, 154.4, 162.8, 166.3 (*C*OPh) and 179.3 (C-4); *m/z* (rel. intensity) 502 [M^+(^{37}Cl), 1], 500 [M^+(^{35}Cl), 3], 397 (36), 395 (100), 367 (10) and 365 (26); ν_{max} (KBr)/cm^{-1} 1716, 1641, 1622, 1390, 1279 and 713.

4-Benzoyloxymethyl-2-benzylidene-8-chloro-6,9-dimethoxynaphtho[1,2-*b*]furan-3(2*H*)-one 27d. *Yellow crystals* (Found: C, 68.07; H, 4.24. $C_{29}H_{21}ClO_6 \cdot \frac{1}{2}H_2O$ requires C, 68.31; H, 4.35%), mp 232–233 °C; R_f (33% EtOAc–hexane) 0.6; δ_H 3.98 (3H, s), 4.06 (3H, s), 5.90 (2H, s, ArCH_2O), 6.98 (1H, s, H^7 or =C*H*Ph), 6.99 (1H, s, =C*H*Ph or H^7), 7.4–7.6 (6H, m), 8.03 (1H, s, H^5) and 8.11 (4H, m); δ_C 56.2, 62.4, 62.6 (*C*H_2OBz), 110.6, 114.0, 116.9, 117.0, 117.0, 125.9, 128.4, 129.0, 129.6, 129.8, 130.1, 130.3, 130.9, 131.7, 132.2, 133.0, 145.2, 146.8, 152.3, 164.4 (C-2), 166.2 (COPh) and 183.8 (C-3); *m/z* (rel. intensity) 502 [M^+(^{37}Cl), 7], 500 [M^+(^{35}Cl), 17], 397 (36), 395 (100), 367 (8), 365 (21) and 105 (29); ν_{max} (KBr)/cm^{-1} 1718, 1693, 1647, 1618, 1581, 1522, 1277 and 714.

(*S*)-5-Benzoyloxymethyl-9-chloro-2-(1-methylpropyl)naphtho-[1,2-*b*]pyran-4,7,10-trione (*S*)-30

The naphthol (*S*)-**26b** (84 mg, 0.17 mmol) was dissolved in acetonitrile (15 mL) and then aq. cerium(IV) ammonium nitrate (CAN) (0.25 g, 0.46 mmol in 1.4 mL) was added. During the addition, the starting yellow colour turned dark brown and then reddish orange. After 30 min, the mixture was poured into a 100 ml separating funnel and CH_2Cl_2 (20 ml) and water (20 ml) were added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic phase was washed with brine (50 ml), dried over $MgSO_4$, filtered through a short silica-gel column which was washed with diethyl ether (50 ml) and concentrated in the dark by a rotary evaporator. Recrystallization from CH_2Cl_2–diethyl ether–hexane gave 58 mg (75%) of the *title compound* (*S*)-**30** as orange crystals (Found: C, 66.48; H, 4.30. $C_{25}H_{19}ClO_6$ requires C, 66.60; H, 4.25%), mp 196–198 °C; $[\alpha]_D^{31}$ −7.84 (*c* 1.0, $CHCl_3$); R_f (30% EtOAc–hexane) 0.6; δ_H 0.98 (3H, t, *J* 7.5, H$^{3'}$), 1.43 (3H, d, *J* 6.7, 1′-Me), 1.80 (1H, m, H$^{2'}$), 1.96 (1H, m, H$^{2'}$), 2.74 (1H, m, H$^{1'}$), 6.16 (2H, s, CH_2O), 6.31 (1H, s, H^3), 7.26 (1H, s, H^8), 7.53 (2H, m), 7.64 (1H, m), 8.19 (2H, m) and 8.25 (1H, s, H^6); δ_C 11.7 (C-3′), 17.9 (1′-Me), 27.3 (C-2′), 40.5 (C-1′), 65.3 (CH_2OBz), 111.1 (C-3), 118.9 (C-6), 125.1 (C-4a or -10a), 128.6, 129.6, 133.4, 134.0, 134.6, 147.9, 155.8, 166.0 (CO), 173.6 (C-2), 174.9 (C-4), 178.7 (C-10), 181.5 (C-7), and one carbon (C-4a or -10a) could not be found; *m/z* 450 (M^+, 2), 345 (100), 249 (12) and 105 (68); ν_{max} (KBr)/cm^{-1} 1716, 1680, 651, 1267, 883 and 711.

(*R*)-**30**: 77% yield; $[\alpha]_D^{28}$ +7.22 (*c* 1.0, $CHCl_3$).

(*S*)-5-Benzoyloxymethyl-11-methoxy-2-(1-methylpropyl)-8,11-dihydro-8,11-ethanoanthra[1,2-*b*]pyran-4,7,12-trione (*S*)-31

The quinone **30** (45 mg, 0.1 mmol) and 1-methoxycyclohexa-1,3-diene (0.018 ml, 0.15 mmol) in CH_2Cl_2 (1 ml) were stirred at room temperature for 24 h. The reaction mixture was concentrated to give a dark brown oil, which was dissolved in pyridine (0.2 ml). After 24 h, 5% aq. HCl (10 ml) was added and the mixture was extracted with $CHCl_3$ (20 ml × 3). The combined extract was washed successively with 5% aq. HCl (20 ml × 3), saturated aq. $NaHCO_3$ (30 ml), and brine (30 ml), dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography followed by recrystallization from CH_2Cl_2–diethyl ether–hexane to give 36 mg (69%) of a diastereomeric mixture of (*S*)-**31** as yellow crystals, mp 150 °C (decomp.); $[\alpha]_D^{23}$ −20.3 (*c* 0.93, $CHCl_3$); R_f 0.45 (30% EtOAc–hexane); δ_H 0.97 (3H, m, H$^{3'}$), 1.40 (3H, d, *J* 7.0, 1′-Me), 1.75 (1H, m, H$^{2'}$), 1.83 (1H, m, H$^{2'}$), 1.90 (2H, m, CH_2CH_2), 2.00 (2H, m, CH_2CH_2), 2.72 (1H, m, H$^{1'}$), 3.67 (3H, s, OMe), 4.41 (1H, m, H^8), 6.13 (2H, m, CH_2O), 6.25 (1H, s, H^3), 6.41 (1H, m, H^9 or H^{10}), 6.60 (1H, d, *J* 7.6, H^{10} or H^9), 7.51 (2H, m), 7.62 (1H, m) and 8.19 (3H, m, H^6 and ArH); δ_C (most signals of the diastereomers appeared as pairs in identical positions; numerals in brackets are signals due to the other isomer) 11.6 [11.7] (C-3′), 17.8 (1′-Me), 25.4 (C-2′), 27.3 [27.3], 31.4, 33.5, 40.4 [40.4], 55.6 (OMe), 65.3 (*C*H_2OBz), 85.6 (C-11), 110.7, 118.4, 120.1, 125.0, 128.5, 129.8, 131.5, 133.3, 134.5, 135.2, 135.2, 144.9, 148.5, 151.0, 155.2, 166.0 (CO), 173.4 [173.5] (C-2), 179.0 (C-10), 179.5 (C-4), 179.5 (C-7) and 180.1 (C-12); *m/z* 524 (M^+, 0.07), 496 (2.3), 391 (100), 362 (4) and 105 (12); ν_{max} (KBr)/cm^{-1} 2869, 1724, 1664, 1652, 1587, 1560 and 1465.

(*R*)-**31**: 54% yield; $[\alpha]_D^{25}$ +22.2 (*c* 1.0, $CHCl_3$).

(*S*)-5-Benzoyloxymethyl-11-methoxy-2-(1-methylpropyl)-anthra[1,2-*b*]pyran-4,7,12-trione (*S*)-32

The Diels–Alder adduct (*S*)-**31** (10 mg, 0.019 mmol) was heated to 150 °C on a melting-point apparatus. After 30 min, the residue was recrystallized from MeOH to give 7 mg (74%) of (*S*)-**32** as *yellow crystals* (Found: M^+, 496.1516. $C_{30}H_{24}O_7$ requires *M*, 496.1522), mp 277–279 °C; $[\alpha]_D^{20}$ −25.3 (*c* 0.50, $CHCl_3$); R_f (30% EtOAc–hexane) 0.1; δ_H (espicufolin numbering) 1.00 (3H, d, *J* 7.6, H^{16}), 1.44 (3H, d, *J* 7.0, H^{17}), 1.79 (1H, m, H^{15}), 1.98 (1H, m, H^{15}), 2.80 (1H, m, H^{14}), 4.06 (3H, s, OMe), 6.17 (2H, s, H^{13}), 6.33 (1H, s, H^3) , 7.37 (1H, d, *J* 7.0, H^{10}), 7.53 (2H, m), 7.62 (1H, m), 7.67 (1H, dd, *J* 7.0 and 7.6, H^8), 7.78 (1H, d, *J* 7.6, H^9), 8.22 (2H, m) and 8.47 (1H, s, H^6); δ_C 11.6 (C-16), 17.9 (C-17), 27.3 (C-15), 40.2 (C-14), 56.2 (OMe), 65.4 (C-13), 110.6 (C-3), 118.3 (C-11a), 118.6 (C-8), 118.7 (C-6), 119.3 (C-12a), 123.3 (C-4a), 123.6 (C-10), 125.3, 129.8, 129.9, 131.5, 133.3 (C-7a), 134.5 (C-6a), 144.6 (C-9), 155.3 (C-5), 155.7 (C-12b), 159.7 (C-11), 166.1 (*C*OPh), 173.8 (C-2), 179.0 (C-4), 180.3 (C-7) and 182.8 (C-12); *m/z* 496 (M^+, 1.5), 391 (100), 359 (6) and 105 (13); ν_{max} (KBr)/cm^{-1} 1716, 1680, 1645, 1585, 1558, 1463, 1444, 1419, 1392, 1369 and 1344.

(*R*)-**32**: 83% yield; $[\alpha]_D^{24}$ +27.0 (*c* 0.30, $CHCl_3$).

(*S*)-5-Benzoyloxymethyl-11-hydroxy-2-(1-methylpropyl)anthra-[1,2-*b*]pyran-4,7,12-trione (*S*)-33

To a solution of compound (*S*)-**32** (11 mg, 0.022 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise 1.0 M BBr_3 in CH_2Cl_2 (0.05 ml, 0.05 mmol) at −78 °C. After 30 min, the reaction mixture was quenched with saturated aq. $NaHCO_3$ (10 ml) and then warmed to room temperature. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (10 ml × 2). The combined organic phases were washed successively with saturated aq. $NaHCO_3$ (20 ml) and brine (20 ml), dried over $MgSO_4$, filtered and concentrated. The residue was recrystallized from CH_2Cl_2–diethyl ether–hexane to give 8 mg (75%) of (*S*)-**33** as *yellow crystals* (Found: M^+, 482.1357. $C_{29}H_{22}O_7$ requires *M*, 482.1366), mp 227–229 °C; $[\alpha]_D^{20}$ −19.7 (*c* 0.30, $CHCl_3$); R_f (30% EtOAc–hexane) 0.5; δ_H 1.00 (3H, d, *J* 7.3, H^{16}), 1.45 (3H, d, *J* 6.7, H^{17}), 1.80 (1H, m, H^{15}), 1.99 (1H, m, H^{15}), 2.76 (1H, m, H^{14}), 6.19 (2H, s, H^{13}), 6.33 (1H, s, H^3), 7.37 (1H, dd, *J* 8.2 and 1.2, H^{10}), 7.52 (2H, m), 7.63 (1H, m), 7.70 (1H, dd, *J* 8.2 and 7.6, H^8), 7.85 (1H, d, *J* 7.6 and 1.2, H^9), 8.22 (2H, m), 8.47 (1H, s, H^6) and 12.84 (1H, s, OH); δ_C 11.7 (C-16), 17.9 (C-17), 27.4 (C-15), 40.5 (C-14), 65.4 (C-13), 111.1 (C-3), 116.8 (C-11a), 119.4 (C-8), 119.5 (C-6), 120.8 (C-12a), 125.3 (C-4a), 125.4 (C-10), 128.6, 129.8, 129.9, 132.2, 133.4 (C-7a), 136.5 (C-6a), 136.6 (C-9), 147.0 (C-5), 156.4 (C-12b), 162.6 (C-11), 166.0 (*C*OPh), 173.6 (C-2), 178.9 (C-4), 181.6 (C-7), 187 (C-12); *m/z* 482 (M^+, 1.2), 440 (31), 362 (100), 281 (33) and 122 (83); ν_{max} (KBr)/cm^{-1} 3438, 1718, 1654, 1637, 1587, 1461, 1267 and 1220.

(*R*)-**33**: 52% yield; $[\alpha]_D^{23}$ +23.3 (*c* 0.30, $CHCl_3$).

(*S*)-Espicufolin (*S*)-1

The benzoate (*S*)-**33** (13 mg, 0.027 mmol) in dry THF (5 mL) was dissolved in MeOH (0.43 ml) and 1 M NaOH (0.11 ml) at

0 °C. The mixture was stirred for 40 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl (10 ml) and the mixture was concentrated by a rotary evaporator. The residual syrup was extracted with EtOAc and the extract was washed successively with saturated aq. $NaHCO_3$ (20 ml) and brine (20 ml), dried over $MgSO_4$, filtered, and concentrated by a rotary evaporator to give a crude product, which was recrystallized from CH_2Cl_2–diethyl ether–hexane to give 7 mg (69%) of (*S*)-**1** as *yellow crystals* (Found: M^+, 378.1104. $C_{22}H_{18}O_6$ requires *M*, 378.1103), mp 185–187 °C; $[\alpha]_D^{23}$ −11.28 (*c* 0.02, $CHCl_3$); R_f (30% EtOAc–hexane) 0.25; δ_H (DMSO-d_6) 0.93 (3H, d, *J* 7.3, H^{16}), 1.38 (3H, d, *J* 6.8, H^{17}), 1.75 (1H, m, H^{15}), 1.92 (1H, m, H^{15}), 2.78 (1H, m, H^{14}), 5.16 (2H, d, *J* 4.8, H^{13}), 5.56 (1H, t, *J* 4.8, 13-OH), 6.34 (1H, s, H^3), 7.38 (1H, d, *J* 8.3, H^{10}), 7.68 (1H, d, *J* 7.3, H^8), 7.77 (1H, dd, *J* 8.3 and 7.3, H^9), 8.51 (1H, s, H^6) and 12.65 (1H, s, -11–OH); δ_C (DMSO-d_6) 11.17 (C-16), 17.30 (C-17), 26.56 (C-15), 39.19 (C-14), 62.07 (C-13), 110.3 (C-3), 116.6 (C-11a), 118.5 (C-8), 118.7 (C-6), 119.6 (C-12a), 123.9 (C-4a), 124.4 (C-10), 132.0 (C-7a), 135.9 (C-6a), 136.4 (C-9), 153.1 (C-5), 155.5 (C-12b), 161.2 (C-11), 172.4 (C-2), 178.1 (C-4), 181.4 (C-7), and 186.8 (C-12); ν_{max} (KBr)/cm^{-1} 3473, 1676, 1647, 1583, 1460, 1272 and 1220; *m*/*z* 378 (M^+, 11), 267 (21), 320 (9), 349 (18) and 378 (100).

(*R*)-**1**: 63% yield, mp 186–187 °C (lit.,[3] 184–186 °C); $[\alpha]_D^{25}$ +8.50 (*c* 0.02, $CHCl_3$) {natural espicufolin: $[\alpha]_D^{23}$ +9.44 (*c* 0.02, $CHCl_3$)}.

(±)-**1**, mp 189–192 °C.

Acknowledgements

We thank Professor Haruo Seto for the gift of natural (*R*)-espicufolin. This work was partly supported by a Grant-in-Aid for Scientific Research (No. 12640521) from the Ministry of Education, Science, Sports and Culture.

References

1 N. Kotoda, K. Shin-ya, K. Furihata, Y. Hayakawa and H. Seto, *J. Antibiot.*, 1997, **50**, 770 and references cited therein.
2 D. W. Choi, *J. Neurosci.*, 1990, **10**, 2493; A. J. Grau, E. Berger, K.-L. Paul Sung and G. W. Schmid-Schönbein, *Stroke*, 1992, **23**, 33; K. Baker, C. B. Marcus, K. Huffman, H. Kruk, B. Malfroy and S. R. Doctrow, *J. Pharmacol. Exp. Ther.*, 1998, **284**, 215.
3 J.-S. Kim, K. Shin-ya, J. Eishima, K. Furihata and H. Seto, *J. Antibiot.*, 1996, **49**, 947.
4 R. H. Thomson, *Naturally Occurring Quinones III*, Chapman and Hall, London, 1987; R. H. Thomson, *Naturally Occurring Quinones: Recent Advances*, Blackie Academic & Professional, London, 4th edn., 1997.
5 H. Inouye and E. Leistner, *The Chemistry of Quinonoid Compounds*, ed. S. Patai and Z. Rappoport, John Wiley and Sons, London, 1988, vol. 2, ch. 22.
6 F. Lombó, E. Künzel, L. Prado, A. F. Braña, K. U. Bindseil, J. Frevert, D. Bearden, C. Méndez, J. A. Salas and J. Rohr, *Angew. Chem., Int. Ed.*, 2000, **39**, 796.
7 K. Sakamoto, E. Honda, N. Ono and H. Uno, *Tetrahedron Lett.*, 2000, **41**, 1819.
8 H. Uno, K. Sakamoto, E. Honda and N. Ono, *Chem. Commun.*, 1999, 1005.
9 Y. Naruta and K. Maruyama, *The Chemistry of Quinonoid Compounds*, ed. S. Patai and Z. Rappoport, John Wiley and Sons, London, 1988, vol. 2, ch. 8.
10 K. Nakatani, A. Okamoto, T. Matsuno and I. Saito, *J. Am. Chem. Soc.*, 1998, **120**, 11219.
11 J. L. Bloomer, K. W. Stagliano and J. A. Gazzillo, *J. Org. Chem.*, 1993, **58**, 7906.
12 R. E. Gawley and K. Rein, *Comprehensive Organic Chemistry*, series ed. B. M. Trost and I. Fleming, volume ed. S. L. Schreiber, Pergamon Press, Oxford, vol. 1 ch. 2.1.
13 R. H. Mitchell, Y.-H. Lai and R. V. Williams, *J. Org. Chem.*, 1979, **44**, 4733.
14 J. Alexander, A. V. Bhatia, L. A. Mitscher, S. Omoto and T. Suzuki, *J. Org. Chem.*, 1980, **45**, 20.
15 J. Auerbach, S. A. Weissman, T. J. Blacklock, M. R. Angeles and K. Hoogsteen, *Tetrahedron Lett.*, 1993, **34**, 931.
16 C. A. Giza and R. L. Hinman, *J. Org. Chem.*, 1964, **29**, 1453.
17 E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 1972, 3769.
18 J. Diago-Mesequer, A. L. Palomo-Coll, J. R. Fernández-Lizarbe and A. Zugaza-Bilbao, *Synthesis*, 1980, 547.
19 A. T. Bottini, F. P. Corson and E. F. Böttner, *J. Org. Chem.*, 1965, **30**, 2988.
20 S. Torii, H. Okumoto, L. H. Hu, M. Sadakane, M. V. Shostakovsky, A. B. Ponomaryov and V. N. Kalinin, *Tetrahedron*, 1993, **49**, 6773.
21 J. E. Baldwin, R. C. Thomas, L. I. Kruse and L. Silberman, *J. Org. Chem.*, 1977, **42**, 3846; J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734; S. A. Kandil and R. E. Dessy, *J. Am. Chem. Soc.*, 1966, **88**, 3027.
22 K. Mukai, K. Okabe and H. Hosose, *J. Org. Chem.*, 1989, **54**, 557.
23 K. Nakatani, A. Okamoto, M. Yamanuki and I. Saito, *J. Org. Chem.*, 1994, **59**, 4360; H. Garcia, S. Iborra, J. Primo and M. A. Miranda, *J. Org. Chem.*, 1986, **51**, 4432.
24 J. Tanaka, K. Toku, B. Zhang, K. Ishihara, M. Sakanaka and N. Maeda, *Glia*, 1999, **28**, 85.
25 K. Toku, J. Tanaka, H. Yano, J. Desaki, B. Zhang, L. Yang, K. Ishihara, M. Sakanaka and N. Maeda, *J. Neurosci. Res.*, 1998, **53**, 415.
26 M. Uyeda, K. Yokomizo, A. Ito, K. Nakayama, H. Watanabe and Y. Kida, *J. Antibiot.*, 1997, **50**, 828.