Total Synthesis of Spiromamakone A and Structure Revision of Spiropreussione A

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Total Synthesis of Spiromamakone A and Structure Revision of Spiropreussione A

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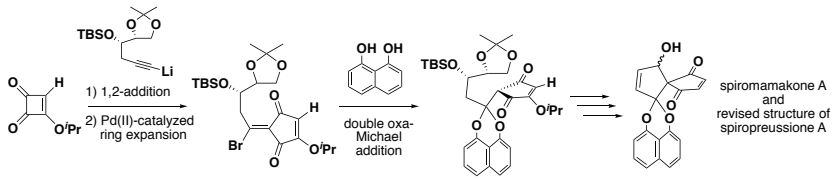


ABSTRACT

Spiromamakone A is a racemic natural product having a naphthyl acetal group on a spiro[4,4]nonadiene skeleton. Its total synthesis was achieved by double oxa-Michael addition of 1,8-dihydroxynaphthalene to 2-(1-bromoalkylidene)-4-isopropoxy-4-cyclopentene-1,3-dione, which was prepared by palladium(II)-catalyzed ring expansion of 4-(1-alkynyl)-4-hydroxy-3-isopropoxy-2-cyclobuten-1-one, and subsequent intramolecular aldol reaction. The synthesis using optically active intermediates enabled to identify the racemization step of spiromamakone A and revealed that spiromamakone A and spiropreussione A are identical; the latter has been reported as a constitutional isomer of the other.

Spiromamakone A (**1**)[1] and spiropreussione A (**2**)[2] were isolated from endophytic fungi by the groups of Munro and Guo, respectively. These natural products belong to the spirobisnaphthalene class of compounds, characterized by two naphthalene-derived C10 units bridged by a spiroacetal linkage[3]; however, they have a unique spiro[4,4]nonadiene skeleton resulting from the loss of one carbon atom and the intramolecular aldol reaction during biosynthesis.[4, 5] These compounds have a single stereogenic center on the A-rings, but they are isolated as a racemic mixture because of their aldol-adduct structure, which can undergo a reversible retro-aldol reaction. They exhibit cytotoxicity against cancer cell lines; in particular, spiromamakone A has an IC_{50} of 0.33 μM against the murine leukemia cell line P388, and spiropreussione A shows IC_{50} of 2.4 and 3.0 μM against the human ovarian carcinoma cell line A2780 and the liver carcinoma cell line BEL-704, respectively. As part of our ongoing research to find more potent anticancer agents,[6] we recently achieved the syntheses of the proposed structure for spiropreussione A (**2**) as well as spiromamakone A benzo-analog **3** (Figure 1).[7, 8] The syntheses showed that analog **3** was as cytotoxic as spiromamakone A (**1**), and the proposed structure of **2** was incorrect. Here we report a total synthesis of spiromamakone A (**1**) based on the double oxa-Michael addition of 1,8-dihydroxynaphthalene (DHN) to 2-(1-bromoalkylidene)-4-isopropoxy-4-cyclopentene-1,3-dione and the intramolecular aldol reaction. The study determined what makes **1** racemic, and the results allowed us to revise the structure of spiropreussione A (**2**), which turned out to be identical to spiromamakone A (**1**).

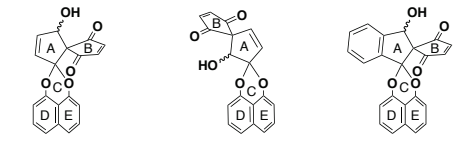


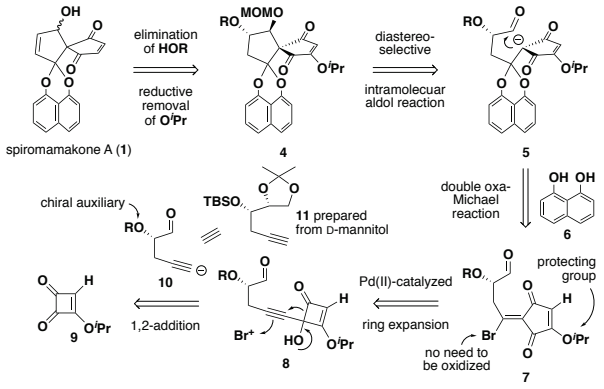
Figure 1. Structures of spiromamakone A (**1**), spiropreussione A (**2**),[7, 8] and spiromamakone A benzo-analog **3**.

The synthesis of spiromamakone A benzo-analog **3** was based on successive substitutions of the methylthio groups in α,α′-dioxoketene dithioacetal derived from 1,3-cyclopentanedione by arylmagnesium bromide and DHN.[7] Therefore, to construct an A-ring with a double bond instead of a benzene ring via a substitution reaction, Grignard reagents other than arylmagnesium bromide

were tested.[9] Although neither alkenyl- nor alkynylmagnesium bromides provided the desired products, the alkylmagnesium one underwent the substitution as effectively as the aryl one did. However, the following double oxa-Michael addition[10] of DHN to the resulting sulfide or sulfoxide was unsuccessful because of either the low reactivity of the sulfide or the instability of the sulfoxide. Moreover, it would be difficult to investigate a racemization process of **1** in the synthetic route using a chiral auxiliary, i.e., a heteroatom at the β- or α-position of the alkylmetal species, because of its susceptibility to β-elimination or epimerization, respectively.

We assumed that the stability of the Michael acceptor would be improved by substituting 4-cyclopentene-1,3-dione for cyclopentane-1,3-dione owing to an increase in the strain of the transient dienolate generated by the nucleophilic addition prior to the elimination, although a protecting group is necessary to prevent undesired nucleophilic addition to the *endo*-olefin. Hence, we chose **7** as the Michael acceptor, in which the *endo* olefin is protected by an isopropoxy group and the leaving group, i.e., bromide, does not need to be oxidized (Scheme 1). The Michael acceptor can be synthesized by palladium(II)-catalyzed ring expansion[11, 12] of propargyl alcohol **8** prepared by regioselective 1,2-addition of acetylide **10** to 3-isopropoxy-3-cyclobutene-1,2-dione **9**.[13] The use of optically active acetylide **10** would induce the diastereoselective intramolecular aldol reaction for **5** after double oxa-Michael addition of DHN to **7**. As an equivalent to aldehyde **10**, we selected isopropylidene acetal **11**,[14] in which the terminal acetal can be transformed into aldehyde through successive hydrolysis and oxidative cleavage in the presence of periodic acid.[15] The protection of the resulting aldol hydroxyl group and the following introduction of a double bond in the A-ring and reductive removal of the isopropoxy group from the B-ring can provide an optically active protected spiromamakone A. The synthetic route enabled us to identify the racemization step during or after the deprotection.

Scheme 1. Retrosynthesis of Spiromamakone A (1).

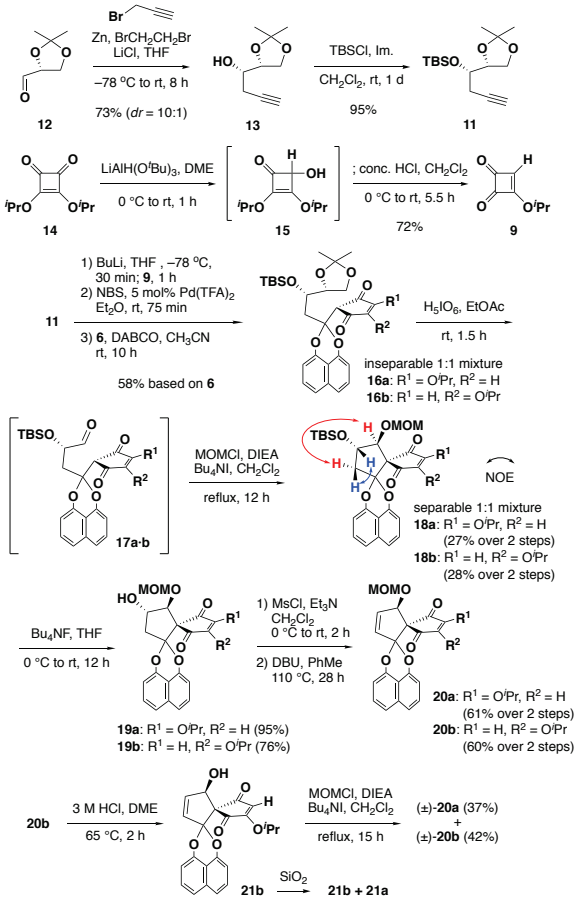


The synthesis of spiromamakone A (**1**) began with the preparation of terminal alkyne **11**[14] and 3-isopropoxy-3-cyclobutene-1,2-dione **9**.[13] Protected D-glyceraldehyde **12** (Scheme 2) was prepared from D-mannitol according to the well-known procedure[16] and treated with propargylzinc bromide. Despite the several reports on the selective conversion of **12** into homopropargylic alcohol **13** using a propargylzinc reagent generated in situ,[17–19] all of the reported reactions were not reproducible and formed both its diastereomer and isomeric allene in considerable amounts. We screened different conditions to determine the optimal combination to generate the organozinc reagent; the addition of a stoichiometric amount of lithium chloride and a catalytic amount of 1,2-dibromoethane and a reaction temperature of −78 °C were the most effective conditions for the highly diastereoselective propargylation of aldehyde **12** without formation of allene.[20] Alcohol **13** was protected by a TBS group and used for the successive ethynylation of **9**,[13] which was obtained via a modified one-pot sequence consisting of the reduction of diisopropyl squarate **14**[13] with lithium tri-*tert*-butoxyaluminum hydride and acid hydrolysis.

Regioselective 1,2-addition of the lithium salt of **11** to 1,2-diketone **9** was followed by palladium(II)-catalyzed ring expansion[11, 12] reaction after aqueous work-up. Although the ring expansion of the monosubstituted cyclobutene was much less clean than that of the 3,4-disubstituted one, a DABCO-promoted double oxa-Michael addition with excess of crude bromide in relation to DHN **6** resulted in naphthyl acetals **16a** and **16b** as an inseparable 1:1 diastereomeric mixture in moderate yield. Interestingly, successive hydrolysis and oxidative cleavage of terminal isopropylidene acetal **16a–b**[15] led to the formation of crude aldehydes **17a–b** instead of aldol

products, which were successfully converted into methoxymethyl-protected aldols **18a–b** as a separable 1:1 diastereomeric mixture under the general conditions for the protection of a hydroxyl group with a methoxymethyl group. NOESY spectra of diastereomers **18a** and **18b** suggested that *trans*-1,2-diols were formed during the intramolecular aldol reaction and that the diastereomers derived from spiro carbon C-5. Removal of TBS protecting groups from **18a** and **18b** resulted in the formation of alcohols **19a** and **19b**. The structure of **19a** was determined by X-ray crystallography (Figure 2) to support the above prediction.[21] Then, a double bond between C-2 and C-3 was introduced by *anti*-elimination through mesylation of the alcohol and subsequent DBU-promoted elimination.

Scheme 2. Synthesis of the Isopropoxy Analog of Spiromamakone A.



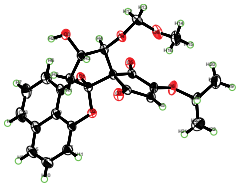


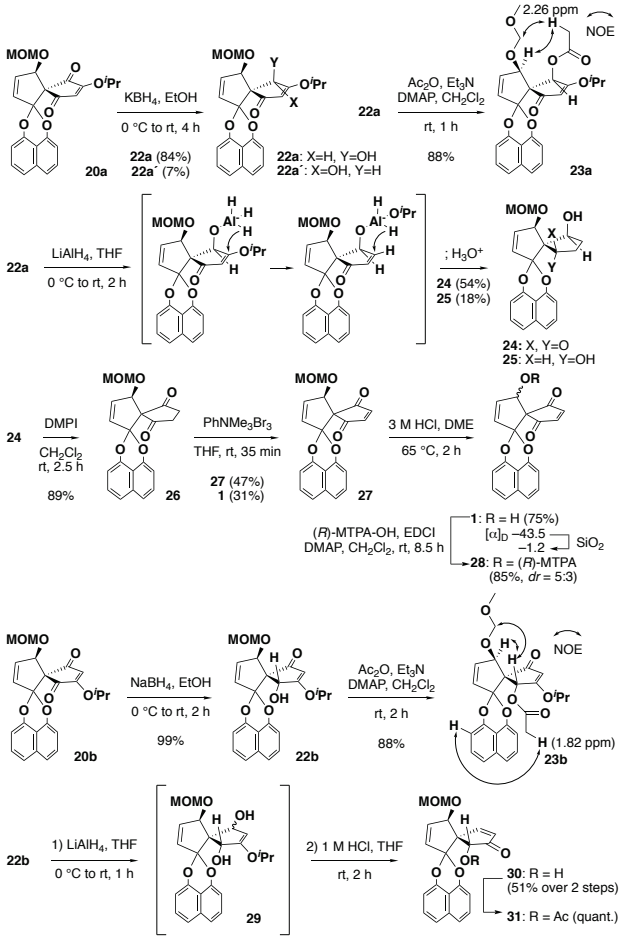
Figure 2. X-ray crystal structure of alcohol **19a** (ellipsoid contour at the 50% probability level).

To get insights into the racemization of **1**, the methoxymethyl group was removed from isopropoxy analog **20b**. Although aldol **21b** was obtained as a single diastereomer in the crude product, the purification on a silica gel formed an inseparable 1:1 diastereomeric mixture of **21b** and **21a** (diastereomerically pure **21a** was also obtained by acid hydrolysis of **20a**; see Experimental Section). Moreover, diastereomerically pure **21b** was reprotected by a methoxymethyl group to give a separable 1:1 diastereomeric mixture of **20a** and **20b**, both of which were racemic according to their specific rotation values. The results showed that the aldol/retro-aldol reaction took place during the treatment with silica gel and the methoxymethyl protection. On the basis of this observation, we assumed that parent natural product **1** would behave similarly.

The final step was the reductive removal of the isopropoxy group from **20a–b**. Lithium aluminum hydride can reduce 4-hydroxy or acetoxy-3-alkoxy-2-cyclopenten-1-one to 4-hydroxy-1-cylopentanone,[22, 23] which is transformed into 4-cyclopentene-1,3-dione by two-step oxidation through 1,3-cyclopentanedione. The reduction proceeds through formation of aluminate at C-4, intramolecular 1,4-addition of hydride, elimination of alkoxy group from C-3, and second 1,4-reduction to give 4-hydroxycyclopentanone after hydrolytic work-up. To conduct such conversion, 4-hydroxy-3-isopropoxy-2-cyclopenten-1-one **22a** was prepared by regio- and stereoselective 1,2-reduction of ketone **20a** with potassium borohydride, and the stereochemistry of **22a** was determined by NOESY spectra of its acetate **23a** (Scheme 3). As expected, the treatment of **22a** with lithium aluminum hydride in THF provided 3-hydroxy-cyclopentanone **24** in 54% yield along with 1,3-cyclopentanediol **25**. Dess–Martin oxidation of **24** and **25** gave 1,3-cyclopentanedione **26** in 89% and 93% yield, respectively (see also Scheme 4). Further oxidation of **26** with trimethylphenylammonium tribromide[24] formed 4-cyclopentene-1,3-dione **27** along with spiromamakone A (**1**), and the latter could be obtained by cleavage of the methoxymethyl group

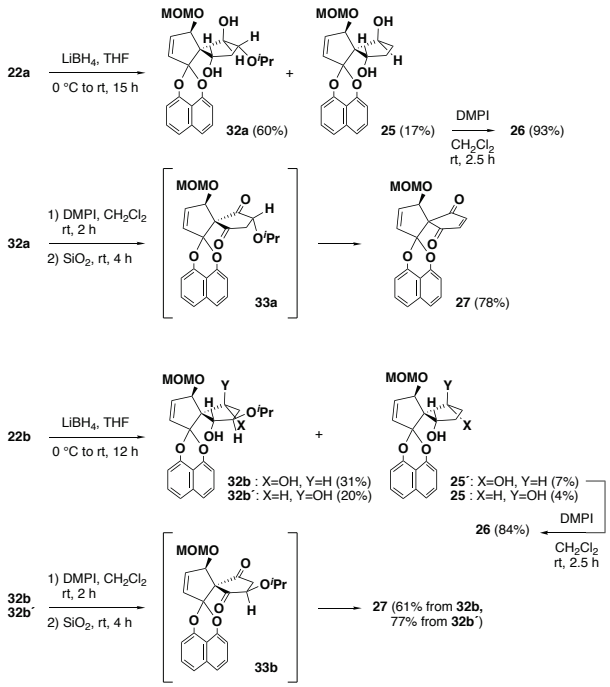
with in situ generated hydrogen bromide. Removal of the methoxymethyl group from **27** in acidic conditions successfully provided **1** in high yield. NMR spectral data of synthetic **1** in methanol-d_4 were in full agreement with those of natural spiromamakone A reported by Munro.[1] As observed in **21b** (Scheme 2), the specific rotation value of crude **1** was lowered by purification with silica gel chromatography. In addition, the NMR spectra of the synthesized spiromamakone A in chloroform-*d* were completely identical to those recorded for spiropreussione A, whose proposed structure was proved incorrect by our previous study.[8] Therefore, the revised structure of spiropreussione A should be spiromamakone A itself. Unfortunately, 3-hydroxy-4-cyclopenten-1-one **22b** obtained by reduction of diastereomer **20b** with sodium borohydride underwent not 1,4-reduction but 1,2-reduction to give 2-hydroxy-4-cyclopenten-1-one **30** after acid hydrolysis.

Scheme 3. Transformation of 20a into Spiromamakone A.



Although **20b** can be reused after its conversion into a mixture of **20a** and **20b** through the above-mentioned sequence, reducing agents other than lithium aluminum hydride were screened to transform both diastereomers **22a** and **22b** into the natural product (Scheme 4). Among the tested reagents, lithium borohydride in THF reduced **22a** and **22b** and gave 4-isopropoxy-1,3-cyclopentanediol **32a** and a diastereomeric mixture of **32b** and **32b′** along with their analogs **25** and **25′** without isopropoxy groups, and the latter can be converted to common 1,3-cyclopentanedione **26** by Dess–Martin oxidation. Unlike lithium aluminum hydride, the reduction with lithium borohydride involves protonation of an enolate generated in situ by 1,4-reduction and 1,2-reduction prior to the elimination of isopropoxide, although it is unclear what could be the proton source in the aprotic solvent THF.[25] Dess–Martin oxidation of diols **32a**, **32b**, and **32b′** and exposure of crude cyclopentane-1,3-diones **33a** and **33b** on silica gel for 4 h led to the formation of common 4-cyclopentene-1,3-dione **27** in good yield through β-elimination of isopropanol. Thus, the reaction sequence using lithium borohydride can convert both diastereomers **22a** and **22b** to methoxymethyl-protected spiromamakone A without the oxidation of cyclopentane-1,3-dione.

Scheme 4. Transformation of 22a–b into MOM-Protected Spiromamakone A 27.



In summary, we achieved a total synthesis of spiromamakone A (**1**), in which the key naphthyl acetal was obtained by double oxa-Michael addition of 1,8-dihydroxynaphthalene to 2-(1-bromoalkylidene)-4-isopropoxy-4-cyclopentene-1,3-dione. The reductive removal of the 4-isopropoxy group in 4-cyclopentene-1,3-diones **20a–b** was given by silica gel-promoted elimination of isopropanol from the saturated cyclopentane-1,3-diones **33a–b** obtained by a reaction sequence involving regio- and stereoselective 1,2-reduction, successive lithium borohydride-promoted 1,4- and 1,2-reductions, and oxidation of cyclopentane-1,3-diols **32a–b**. The optically active protected spiromamakone A readily underwent racemization during not the deprotection but the purification step on silica gel. In addition, we revealed that spiropreussione A, considered an isomer of spiromamakone A, was identical to spiromamakone A itself. A structure–activity relation study of the synthesized compounds and their derivatives is underway.

EXPERIMENTAL SECTION

General Techniques. All commercially available reagents and anhydrous solvents including dichloromethane, 1,2-dimethoxyethane, ethyl acetate, and tetrahydrofuran (THF) were purchased and used without further purification. Anhydrous acetonitrile was obtained by distillation from calcium hydride. Anhydrous diethyl ether was obtained by drying over molecular sieves 4A. Anhydrous toluene was obtained by distillation from sodium. All reactions were monitored by thin layer chromatography (TLC) performed on 0.25 mm silica gel glass plates (60 F_{254}) using UV light and ethanolic *p*-anisaldehyde-sulfuric acid, ethanolic molybdatophosphoric acid, aqueous cerium sulfate-hexaammonium heptamolybdate-sulfuric acid, or aqueous potassium permanganate-potassium carbonate-sodium hydroxide solutions as visualizing agents. Flash column chromatography was carried out with silica gel (spherical, neutral, 63–210 μm grade). Preparative TLC was performed on 0.75 mm silica gel glass plates. Preparative HPLC was carried out by using UV detection at 254 nm. Yields refer to chromatographically and spectroscopically homogenous materials. Melting points were measured on a melting point apparatus and were uncorrected. Specific rotations ($[\alpha]_D$) were measured at 589 nm. Only the strongest and/or structurally important

absorptions of infrared (IR) spectra are reported in reciprocal centimeters (cm^{-1}). ^{1}H NMR spectra (400 MHz) and $^{13}C\{^{1}H\}$NMR spectra (100 MHz) were recorded in the indicated solvent. Chemical shifts are reported in delta (δ) units, parts per million (ppm). Chemical shifts for ^{1}H NMR spectra are given relative to signals for internal tetramethylsilane (0 ppm) or residual nondeuterated solvents, i.e., chloroform (7.26 ppm) and methanol (3.30 ppm). Chemical shifts for ^{13}C NMR spectra are given relative to the signal for chloroform-*d* (77.0 ppm) and methanol-d_4 (49.0 ppm). Multiplicities are reported by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Coupling constants (*J*) are represented in hertz (Hz). ^{1}H and ^{13}C NMR chemical shifts were assigned using a combination of COSY, NOESY, HMQC, and HMBC. Low and high-resolution mass spectra were measured on TOF-MS with EI, FAB, or ESI probe.

(*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-yn-1-ol (13)[17–19]**:** Lithium chloride (8.48 g, 200 mmol) was placed in a 300 mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, a septum rubber, and a reflux condenser with a three-way stopcock connected to a balloon filled with argon. The flask was heated at 140 °C under reduced pressure (1 mmHg) for 4 h, during which time Zn powder (30 g, 0.46 g-atom) was activated by stirring with 1 M aqueous HCl (200 mL) for 15 min twice, before being washed with H_2O (4 x 100 mL), EtOH (2 x 100 mL), and Et_2O (100 mL) and dried at 80 °C for 2 h under reduced pressure (1 mmHg). Then the flask was cooled to room temperature before successive addition of activated Zn powder (19.6 g, 300 mg-atom), anhydrous THF (100 mL), and 1,2-dibromoethane (0.86 mL, 10 mmol). To the stirred suspension was slowly added propargyl bromide (7.5 mL, 100 mmol) at room temperature while keeping the exothermic reaction gentle reflux. The resulting mixture was stirred at room temperature for 1.5 h and cooled to –78 °C before addition of a solution of freshly prepared and distilled **12**[16] (10.8 g, 83.0 mmol) in anhydrous THF (40 mL). The reaction mixture was allowed to warm to room temperature over 8 h and treated with saturated aqueous NH_4Cl (80 mL). The immiscible mixture was filtered through a Celite pad, which was thoroughly rinsed with EtOAc. The filtrate was separated and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The

residue was purified by silica gel column chromatography (20% EtOAc/hexane) to give **13** (10.3 g, 73%) as a white solid. The spectroscopic data of **13** were in good agreement with those reported in the literature.[17–19]

***tert*-Butyl(((*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-yn-1-yl)oxy)dimethylsilane (11)[14]:** To a stirred solution of alcohol **13** (17.0 g, 100 mmol) and imidazole (13.6 g, 200 mmol) in anhydrous CH_2Cl_2 (100 mL) was added *tert*-butyldimethylchlorosilane (19.6 g, 130 mmol) at room temperature. After being stirred at the same temperature for 26 h, the reaction mixture was treated with saturated aqueous NH_4Cl (100 mL). The immiscible mixture was extracted with Et_2O, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (3% EtOAc/hexane) to give **11** (27.0 g, 95%) as a pale yellow oil. The spectroscopic data of **11** were in good agreement with those reported in the literature.[14]

3-Isopropoxycyclobut-3-ene-1,2-dione (9)[13]: To a stirred suspension of lithium aluminum hydride (3.98 g, 105 mmol) in anhydrous DME (52 mL) was added a solution of *t*-BuOH (31 mL, 0.32 mol) in anhydrous DME (52 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min before addition of **14**[13] (14.9 g, 75.2 mmol). The reaction mixture was allowed to warm to room temperature over 1 h, cooled to 0 °C again, diluted with CH_2Cl_2 (675 mL), and treated with conc. HCl (44 mL). After being allowed to warm to room temperature over 4.5 h, the resulting mixture was treated with another conc. HCl (6 mL). The mixture was stirred at room temperature for 1 h, diluted with H_2O (250 mL), extracted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (25–30% EtOAc/hexane) to give **9** (7.54 g, 72%) as a pale yellow oil. The spectroscopic data of **9** were in good agreement with those reported in the literature.[13]

(*S*)- and (*R*)-2-(2-((*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)–naphtho[1,8-*de*][1,3]dioxin-2-yl)-4-isopropoxycyclopent-4-ene-1,3-diones (16a·b): To a stirred solution of alkyne **11** (7.11 g, 25.0 mmol) in anhydrous THF (50 mL) was slowly added 2.65 M BuLi solution (9.9 mL, 26 mmol) in hexane at –78 °C. The resulting mixture was stirred at the same temperature for 30 min before slow addition of a solution of diketone **9** (3.51 g, 25.0

mmol) in anhydrous THF (25 mL) at –78 °C. After being stirred at the same temperature for further 1 h, the reaction mixture was treated with saturated aqueous NH_4Cl (50 mL) and H_2O (10 mL) at –78 °C. The immiscible mixture was allowed to warm to room temperature, stirred for another 15 min, extracted with Et_2O, washed with brine, dried over $MgSO_4$, and concentrated to give a crude alcohol (11.7 g), which was used for the next reaction without further purification.

To a stirred solution of the crude alcohol (11.7 g) in anhydrous Et_2O (100 mL) were successively added NBS (5.34 g, 30.0 mmol, recrystallized from H_2O) and $Pd(TFA)_2$ (416 mg, 1.25 mmol) at room temperature. After being stirred at the same temperature for 75 min, the reaction mixture was treated with saturated aqueous $NaHCO_3$ (25 mL) and 20% aqueous $Na_2S_2O_3 \cdot 5H_2O$ (25 mL). The immiscible mixture was extracted with Et_2O, washed with H_2O and brine successively, dried over $MgSO_4$, and concentrated to give a crude bromide (12.2 g, 97%), which was used for the next reaction without further purification.

To a stirred solution of the crude bromide (12.2 g) and 1,8-dihydroxynaphthalene (**6**) (1.94 g, 12.1 mmol) in anhydrous CH_3CN (48 mL) was added DABCO (2.04 g, 18.2 mmol) at room temperature. After being stirred at the same temperature for 10 h, the reaction mixture was concentrated. The residue was diluted with Et_2O (50 mL) and filtered through a Celite pad, which was thoroughly rinsed with Et_2O. The filtrate was washed with aqueous NH_4Cl and brine successively, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (13% EtOAc/hexane) to give **16a·b** (as a 1:1 diastereomeric mixture, 4.06 g, 58% based on **6**) as a brown amorphous mass. Analytical sample of **16a·b** (pure 58.2 mg along with impure 11.6 mg) was obtained by further purification of the above material (100 mg) with preparative thin layer chromatography (17% EtOAc/toluene).

R_f 0.44 (33% EtOAc/hexane). $[\alpha]_D^{23.9}$ –1.08 (*c* 1.00, $CHCl_3$). IR (compression cell, cm^{-1}): 2933, 1699, 1601, 1379, 1272, 1216, 1103, 1071, 836 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.47–7.38 (m, 4H), 7.02–6.93 (m, 2H), 6.24 (s, 0.5H), 6.23 (0.5H), 4.47–4.36 (m, 2H), 4.30–4.24 (m, 1H), 3.97–3.89 (m, 1H), 3.86–3.80 (m, 1H), 3.56 (s, 0.5H), 3.55 (s, 0.5H), 2.26–2.15 (m, 2H), 1.41–1.36 (m, 9H), 1.30 (s, 3H), 0.86 (s, 4.5H), 0.85 (s, 4.5H), 0.08 (s, 1.5H), 0.06 (s, 1.5H), 0.03 (s, 1.5H), 0.02 (s,

1.5H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 193.6, 193.4, 192.7, 192.6, 170.99, 170.98, 146.50, 146.49, 146.45, 134.0, 127.59, 127.54, 127.53, 127.47, 120.75, 120.72, 120.70, 120.66, 119.84, 119.78, 113.19, 113.16, 109.9, 109.78, 109.75, 109.71, 108.93, 108.89, 100.9, 100.8, 78.7, 78.6, 76.51, 76.48, 67.1, 67.0, 64.60, 64.57, 54.0, 53.9, 40.3, 40.2, 26.4, 26.3, 25.92, 25.90, 25.35, 25.32, 21.15, 21.13, 21.04, 21.02, 18.08, 18.06, -4.48, -4.51, -4.52, -4.60. LRMS (EI) *m/z* (relative intensity): 582 $[M]^+$ (0.9), 567 (5), 525 (23), 467 (33), 323 (100), 313 (54), 281 (64), 211 (33), 149 (32). HRMS (EI, $[M]^+$): calcd for $C_{32}H_{42}O_8Si$, 582.2649; found 582.2640.

(1*S*,3'*S*,4'*S*)- and (1*R*,3'*S*,4'*S*)-4'-((*tert*-Butyldimethylsilyl)oxy)-3-isopropoxy-3'-(methoxymethoxy)dispiro–[cyclopentane-1,2'-cyclopentane-1',2''-naphtho[1,8-*de*][1,3]dioxin]-3-ene-2,5-diones (18a and 18b): To a stirred solution of **11** (3.91 g, 6.71 mmol) in anhydrous EtOAc (34 mL) was added orthoperiodic acid (2.29 g, 10.0 mmol) at room temperature. After being stirred at the same temperature for 1.5 h, the reaction mixture was diluted with Et_2O (34 mL) and filtered through a Celite pad, which was thoroughly rinsed with Et_2O. The filtrate was concentrated to give a crude aldehyde **17a·b** (3.71 g), which was used for the next reaction without further purification.

To a stirred solution of the crude aldehyde **17a·b** (3.70 g) and a catalytic amount of tetrabutylammonium iodide in anhydrous CH_2Cl_2 (13 mL) were successively added *N*,*N*-diisopropylethylamine (11.5 mL, 68 mmol) and chloromethyl methyl ether (2.6 mL, 34 mmol) at room temperature. After being refluxed for 12 h, the reaction mixture was cooled to room temperature. The reaction mixture was treated with H_2O. The immiscible mixture was extracted with Et_2O twice. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (5–6% Et_2O/toluene) to give **18a** (1.00 g, 27% from **11** over 2 steps) and **18b** (1.05 g, 28% from **11** over 2 steps) as a faster- and slower-moving component, respectively.

18a as a yellow amorphous mass: R_f 0.47 (13% EtOAc/toluene). $[\alpha]_D^{24.7}$ –151 (*c* 1.01, $CHCl_3$). IR ν (compression cell, cm^{-1}): 2930, 1701, 1604, 1244, 1085, 837. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.40 (m, 3H), 7.34 (dd, *J* = 7.5, 8.3 Hz, 1H), 7.00 (dd, 1H, *J* = 2.7, 5.8 Hz), 6.79 (dd, *J* = 0.8, 7.5 Hz

1H), 6.13 (s, 1H), 4.89–4.84 (m, 1H), 4.68 (d, *J* = 7.0 Hz, 1H), 4.66 (d, *J* = 6.5 Hz, 1H), 4.54 (d, *J* = 6.5 Hz, 1H), 4.26 (qq, *J* = 6.1, 6.1 Hz, 1H), 3.11 (s, 3H), 2.72 (dd, *J* = 9.5, 14.3 Hz, 1H), 2.11 (dd, *J* = 5.7, 14.3 Hz, 1H), 1.30 (d, *J* = 6.1 Hz, 3H), 1.21 (d, *J* = 6.1 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 192.7, 171.6, 147.1, 146.9, 134.1, 127.7, 127.0, 120.9, 120.6, 118.8, 113.3, 110.6, 109.4, 105.8, 97.6, 87.2, 76.2, 73.5, 66.5, 55.5, 44.1, 25.7, 21.1, 20.9, 17.8, -4.8, -4.9. LRMS (EI) *m/z* (relative intensity): 554 $[M]^+$ (9), 497 (72), 423 (60), 361 (70), 319 (100), 241 (72). HRMS (EI, $[M]^+$): calcd for $C_{30}H_{38}O_8Si$, 554.2336; found 554.2295.

18b as an orange amorphous mass: R_f 0.39 (13% EtOAc/toluene). $[\alpha]_D^{25.0}$ –71.8 (*c* 1.01, $CHCl_3$). IR ν (compression cell, cm^{-1}): 2955, 2932, 1702, 1600, 1260, 1103, 1044, 837. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.38 (m, 3H), 7.33 (dd, *J* = 7.5, 8.3 Hz, 1H), 6.98 (dd, *J* = 1.7, 6.7 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 6.01 (s, 1H), 4.85–4.79 (m, 1H), 4.71 (d, *J* = 7.2 Hz, 1H), 4.67 (d, *J* = 6.5 Hz, 1H), 4.52 (d, *J* = 6.5 Hz, 1H), 4.26 (qq, *J* = 6.1, 6.1 Hz, 1H), 3.13 (s, 3H), 2.64 (dd, *J* = 9.0, 14.2 Hz 1H), 2.12 (dd, *J* = 6.6, 14.2 Hz, 1H), 1.34 (d, *J* = 6.1 Hz, 3H), 1.27 (d, *J* = 6.4 Hz, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 192.6, 170.3, 146.92, 146.91, 133.9, 127.6, 127.1, 121.0, 120.6, 119.8, 113.5, 110.6, 109.5, 105.8, 97.4, 85.7, 76.2, 73.2, 66.4, 55.8, 43.7, 25.7, 21.1, 21.0, 17.8, -4.7, -4.9. LRMS (EI) *m/z* (relative intensity): 554 $[M]^+$ (5), 467 (84), 361 (40), 221 (51), 178 (45), 149 (100). HRMS (EI, $[M]^+$): calcd for $C_{30}H_{38}O_8Si$, 554.2336; found 554.2332.

(1*S*,3'*S*,4'*S*)-4'-Hydroxy-3-isopropoxy-3'-(methoxymethoxy)dispiro[cyclopentane-1,2'-cyclo–pentane-1',2''-naphtho[1,8-*de*][1,3]dioxin]-3-ene-2,5-dione (19a): To a stirred solution of **18a** (891 mg, 1.61 mmol) in anhydrous THF (3.2 mL) was added 1.0 M tetrabutylammonium fluoride solution in THF (2.4 mL, 2.4 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature over 1.5 h and stirred for another 10.5 h at room temperature. The resulting mixture was treated with saturated aqueous NH_4Cl (6 mL), extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (50–60% ethyl acetate/hexane) to give **19a** (672mg, 95%) as a pale yellow solid. R_f 0.22 (25% EtOAc/toluene). Mp. 215–220 °C. $[\alpha]_D^{22.0}$ –172 (*c* 1.01, $CHCl_3$). IR ν (neat, cm^{-1}): 3464, 2982, 2935, 1698, 1599, 1272, 1237, 1101, 1044, 757. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.31 (m, 3H), 7.33

(dd, *J* = 7.5, 8.3 Hz, 1H), 6.99 (dd, *J* = 3.1, 5.3 Hz, 1H), 6.79 (dd, *J* = 0.8, 7.8 Hz, 1H), 6.09 (s, 1H), 4.87–4.81 (m, 1H), 4.67 (d, *J* = 7.0 Hz, 1H), 4.59 (d, *J* = 7.0 Hz, 1H), 4.53 (d, *J* = 7.1 Hz, 1H), 4.19 (qq, *J* = 6.1, 6.1 Hz, 1H), 3.55 (br-s, 1H), 3.38 (s, 3H), 2.89 (dd, *J* = 10.1, 14.7 Hz, 1H), 2.30 (dd, *J* = 6.0, 14.7 Hz, 1H), 1.27 (d, *J* = 6.1 Hz, 3H), 1.14 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.1, 192.5, 171.4, 147.0, 146.8, 134.1, 127.8, 127.0, 121.0, 120.7, 119.2, 113.1, 110.5, 109.4, 105.3, 97.7, 89.0, 76.3, 71.9, 67.3, 56.0, 43.3, 21.0. HRMS (ESI, $[M+Na]^+$): calcd for $C_{24}H_{24}O_8Na$, 463.1369; found: 463.1362.

(1*R*,3'*S*,4'*S*)-4'-Hydroxy-3-isopropoxy-3'-(methoxymethoxy)dispiro[cyclopentane-1,2'-cyclopentane-1',2''-naphtho[1,8-*de*][1,3]dioxin]-3-ene-2,5-dione (19b): Following the procedure described above for **19a**, the desilylation of **18b** (982 mg, 1.77 mmol) and flash column chromatography (50–60% ethyl acetate/hexane) afforded **19b** (589 mg, 76%) as a pale brown amorphous mass. R_f 0.17 (25% EtOAc/toluene). $[\alpha]_D^{25.1}$ –87.3 (*c* 1.01, $CHCl_3$). IR ν (neat, cm^{-1}): 3449, 2929, 1699, 1599, 1412, 1379, 1272, 1237, 1103, 1045, 758. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.39 (m, 3H), 7.32 (dd, *J* = 7.5, 8.2 Hz, 1H), 6.99 (dd, *J* = 2.1, 6.3 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 5.94 (s, 1H), 4.84‑4.78 (m, 1H), 4.67 (d, *J* = 7.0 Hz, 1H), 4.58 (d, *J* = 7.0 Hz, 1H), 4.53 (d, *J* = 7.3 Hz, 1H), 4.22 (qq, *J* = 6.1, 6.1 Hz, 1H), 3.63 (br-s, 1H), 3.39 (s, 3H), 2.83 (dd, *J* = 9.7, 14.6 Hz, 1H), 2.29 (dd, *J* = 6.8, 14.6 Hz, 1H), 1.35 (d, *J* = 6.1 Hz, 3H), 1.25 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 192.3, 170.3, 146.9, 146.8, 133.9, 127.7, 127.0, 121.1, 120.7, 119.9, 113.4, 110.5, 109.4, 105.5, 97.5, 88.2, 76.4, 71.6, 67.1, 56.0, 43.0, 21.1, 20.9. HRMS (ESI, $[M+Na]^+$): calcd for $C_{24}H_{24}O_8Na$, 463.1369; found: 463.1362.

(1*S*,5'*R*)-3-Isopropoxy-5'-(methoxymethoxy)dispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-3,3'-diene-2,5-dione (20a): To a stirred solution of alcohol **19a** (494 mg, 1.12 mmol) in anhydrous CH_2Cl_2 (5.6 mL) were successively added triethylamine (0.47 mL, 3.4 mmol) and methanesulfonyl chloride (0.13 mL, 1.7 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature over 2 h and treated with *N*,*N*-dimethyl-1,3-propanediamine (143 μL, 1.15 mmol). The resulting mixture was stirred for another 30 min, diluted with EtOAc,

washed with 1 M aqueous HCl, H_2O, saturated aqueous $NaHCO_3$, and brine successively, dried over $MgSO_4$, and concentrated to give a crude mesylate (604 mg) as a pale yellow amorphous mass.

Mesylate of 19a: R_f 0.33 (25% EtOAc/toluene). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.42 (m, 3H), 7.34 (dd, *J* = 7.5, 8.3 Hz, 1H), 7.03 (dd, *J* = 1.5, 6.9 Hz, 1H), 6.79 (dd, *J* = 0.8, 7.5 Hz, 1H), 6.27 (s, 1H), 5.61–5.56 (m, 1H), 4.96 (d, *J* = 6.4 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.58 (d, *J* = 6.8 Hz, 1H), 4.35 (qq, *J* = 6.1, 6.1 Hz, 1H), 3.19 (s, 3H), 3.04 (s, 3H), 3.02 (dd, *J* = 10.1, 15.2 Hz, 1H), 2.46 (dd, *J* = 3.9, 15.2 Hz, 1H), 1.33 (d, *J* = 6.1 Hz, 3H), 1.26 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.8, 191.2, 172.1, 146.6, 146.2, 134.1, 127.8, 127.1, 121.3, 121.0, 119.0, 113.0, 110.5, 109.4, 105.2, 97.5, 83.6, 80.9, 76.6, 66.1, 55.9, 41.7, 38.0, 21.1, 20.9. LRMS (EI) *m/z* (relative intensity): 518 $[M]^+$ (100), 422 (72), 335 (52). HRMS (EI, $[M]^+$): calcd for $C_{25}H_{26}O_{10}S$, 518.1247; found 518.1205.

To a stirred solution of the crude mesylate (604 mg) in anhydrous toluene (5.6 mL) was added DBU (0.50 mL, 3.4 mmol) at room temperature. After being refluxed for 28 h, the reaction mixture was cooled to room temperature and concentrated. The residue was purified by silica gel chromatography (40% EtOAc/hexane) to give pure **20a** (268 mg, 57% from **19a** over 2 steps) as a colorless solid and impure **20a** (34 mg). The latter was further purified by preparative thin layer chromatography (50% EtOAc/hexane, developed 3 times) to give another pure **20a** (18 mg, 4% from **19a** over 2 step).

20a: R_f 0.33 (50% EtOAc/hexane). Mp. 151–154 °C. $[\alpha]_D^{27.5}$ –288 (*c* 1.18, $CHCl_3$). IR ν (neat, cm^{-1}): 2987, 2935, 1700, 1600, 1413, 1379, 1275, 1233, 1103, 1040, 757. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.38 (m, 3H), 7.35 (dd, *J* = 7.5, 8.3 Hz, 1H), 6.89 (dd, *J* = 1.8, 6.6 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.50 (dd, *J* = 1.6, 5.9 Hz, 1H), 6.09 (s, 1H), 6.00 (dd, *J* = 2.1, 5.9 Hz, 1H), 5.30 (dd, *J* = 1.6, 2.1 Hz, 1H), 4.60 (d, *J* = 6.8 Hz, 1H), 4.58 (d, *J* = 6.8 Hz, 1H), 4.14 (qq, *J* = 6.1, 6.2 Hz, 1H), 3.21 (s, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.12 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2, 191.4, 170.7, 147.6, 147.4, 139.4, 134.2, 129.0, 127.8, 127.2, 120.8, 120.5, 119.5, 113.0, 109.9, 109.25, 109.23, 97.7, 83.9, 76.2, 68.3, 55.7, 21.0, 20.9. HRMS (ESI, $[M+Na]^+$): calcd for $C_{24}H_{22}O_7Na$, 445.1263; found: 445.1256.

(1*R*,5'*R*)-3-Isopropoxy-5'-(methoxymethoxy)dispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-3,3'-diene-2,5-dione (20b): Following the procedure described above for **20a**, the dehydration of **19b** (505 mg, 1.15 mmol) and flash column chromatography (33% EtOAc/hexane) afforded **20b** (290 mg, 60%) as a pale yellow amorphous mass.

Mesylate of 19b: R_f 0.29 (25% EtOAc/toluene). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.41 (m, 3H), 7.33 (dd, *J* = 7.5, 8.2 Hz, 1H), 7.02 (d, *J* = 7.1 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 6.14 (s, 1H), 5.57–5.52 (m, 1H), 5.01 (d, *J* = 6.4 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.58 (d, *J* = 6.8 Hz, 1H), 4.37 (qq, *J* = 6.1, 6.1 Hz, 1H), 3.22 (s, 1H), 3.04 (s, 3H), 2.97 (dd, *J* = 9.8, 15.2 Hz, 1H), 2.46 (dd, *J* = 4.3, 15.2 Hz, 1H), 1.40 (d, *J* = 6.1 Hz, 3H), 1.36 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.0, 191.9, 170.5, 146.5, 146.2, 134.0, 127.7, 127.0, 121.4, 121.1, 120.6, 113.1, 110.5, 109.3, 105.3, 97.3, 82.4, 80.5, 76.6, 66.0, 56.1, 41.4, 38.1, 21.1, 21.0. LRMS (EI) *m/z* (relative intensity): 518 $[M]^+$ (100), 422 (52), 335 (49). HRMS (EI, $[M]^+$): calcd for $C_{25}H_{26}O_{10}S$, 518.1247; found 518.1198.

20b: R_f 0.43 (50% EtOAc/hexane). $[\alpha]_D^{28.6}$ −243 (*c* 0.985, $CHCl_3$). IR ν (neat, cm^{-1}): 2982, 2929, 1704, 1601, 1413, 1379, 1276, 1234, 1104, 1046, 756. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.37 (m, 3H), 7.33 (dd, *J* = 7.5, 8.4 Hz, 1H), 6.90 (dd, *J* = 1.3, 7.8 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.48 (dd, *J* = 1.7, 5.9 Hz, 1H), 5.99 (dd, *J* = 2.0, 5.9 Hz, 1H), 5.94 (s, 1H), 5.34 (dd, *J* = 1.7, 2.0 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 4.57 (d, *J* = 6.9 Hz, 1H), 4.22 (qq, *J* = 6.1, 6.2 Hz, 1H), 3.22 (s, 3H), 1.35 (d, *J* = 6.1 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 190.2, 170.9, 147.5, 147.2, 139.4, 134.0, 129.1, 127.6, 127.1, 121.0, 120.5, 119.1, 113.4, 109.88, 109.86, 109.2, 97.6, 83.1, 76.3, 67.9, 55.9, 21.1, 21.0. HRMS (ESI, $[M+Na]^+$): calcd for $C_{24}H_{22}O_7Na$, 445.1263; found: 445.1256.

(1*S*,5'*R*)-5'-Hydroxy-3-isopropoxydispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-3,3'-diene-2,5-dione (21a): To a solution of **20a** (10.0 mg, 0.0237 mmol) in DME (0.2 mL) was added 3 M aqueous HCl (0.1 mL) at room temperature. The resulting mixture was stirred at 65 °C for 2 h, cooled to room temperature, and diluted with EtOAc. The immiscible mixture was washed with saturated aqueous $NaHCO_3$ and brine successively, dried over $MgSO_4$,

and concentrated to give crude **21a** (10.4 mg) as a pale yellow amorphous. R_f 0.18 (25% EtOAc/toluene). $[\alpha]_D^{23.3}$ –145 (*c* 0.520, $CHCl_3$). IR ν (compression cell, cm^{-1}): 3477, 2982, 2926, 1695, 1597, 1274, 1232, 1079, 757. ^1H NMR (400 MHz, $CDCl_3$): δ 7.46–7.41 (m, 3H), 7.38 (dd, *J* = 7.5, 8.3 Hz, 1H), 6.89–6.87 (m, 2H), 6.44 (dd, *J* = 1.8, 5.8 Hz, 1H), 6.05 (dd, *J* = 1.7, 5.8 Hz, 1H), 6.00 (s, 1H), 5.37 (d, *J* = 12.3 Hz, 1H), 4.09 (qq, *J* = 6.1, 6.2 Hz, 1H), 2.79 (d, *J* = 12.3 Hz, 1H), 1.26 (d, *J* = 6.1 Hz, 3H), 1.12 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.8, 192.9, 171.4, 147.3, 147.1, 141.4, 134.1, 130.0, 127.9, 127.3, 120.9, 120.7, 119.3, 113.1, 110.3, 109.9, 109.5, 78.3, 76.8, 68.0, 20.92, 20.90. LRMS (EI) *m/z* (relative intensity): 378 $[M]^+$ (85), 267 (100). HRMS (EI, $[M]^+$): calcd for $C_{22}H_{18}O_6$, 378.1103; found 378.1095.

(1*R*,5'*R*)-5'-Hydroxy-3-isopropoxydispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-3,3'-diene-2,5-dione (21b): Following the procedure described above for **21a**, the acid hydrolysis of **20b** (10.2 mg, 0.0241 mmol) gave crude **21b** (10.0 mg) as a pale yellow amorphous mass. R_f 0.18 (25% EtOAc/toluene). $[\alpha]_D^{22.0}$ –93.7 (*c* 0.500, $CHCl_3$). IR ν (compression cell, cm^{-1}): 3446, 2983, 2930, 1695, 1598, 1273, 1232, 1094, 757. ^1H NMR (400 MHz, $CDCl_3$): δ 7.46–7.34 (m, 4H), 6.90 (d, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.43 (dd, *J* = 1.9, 5.8 Hz, 1H), 6.04 (dd, *J* = 1.6, 5.8 Hz, 1H), 5.96 (s, 1H), 5.40 (d, *J* = 12.0 Hz, 1H), 4.17 (qq, *J* = 6.1, 6.2 Hz, 1H), 2.55 (d, *J* = 12.0 Hz, 1H), 1.32 (d, *J* = 6.2 Hz, 3H), 1.20 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.61, 193.56, 170.7, 147.3, 146.9, 140.8, 133.9, 130.2, 127.6, 127.3, 121.1, 120.7, 120.0, 113.4, 110.3, 110.1, 109.6, 77.6, 67.5, 21.03, 20.98. LRMS (EI) *m/z* (relative intensity): 378 $[M]^+$ (85), 267 (100). HRMS (EI, $[M]^+$): calcd for $C_{22}H_{18}O_6$, 378.1103; found 378.1089.

Purification of the crude **21b** with preparative thin layer chromatography (33% EtOAc/toluene) resulted in the formation of a 1:1 mixture of **21a** and **21b**.

(1*S,5'*R**)- and (1*R**,5'*R**)-3-Isopropoxy-5'-(methoxymethoxy)dispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-3,3'-diene-2,5-dione ((±)-20a and (±)-20b):** To a stirred solution of the crude aldol **21b** (18.7 mg, obtained from **20b** (21.0 mg, 0.0497 mmol)) and a catalytic amount of tetrabutylammonium iodide in anhydrous CH_2Cl_2 (0.4 mL) were successively added *N*,*N*-diisopropylethylamine (87 μL, 0.50 mmol) and chloromethyl methyl ether (19 μL, 0.25

mmol) at room temperature. After being refluxed for 15 h, the reaction mixture was cooled to room temperature, diluted with Et_2O, washed with saturated aqueous NH_4Cl and brine successively, dried over $MgSO_4$, and concentrated. The residue was purified by preparative thin layer chromatography (20% EtOAc/toluene, developed 6 times) to give (±)-**20a** (7.7 mg, 37% from **20b** over 2 steps) and (±)-**20b** (8.8 mg, 42% from **20b** over 2 steps) as a slower- and faster-moving component, respectively.

(±)-**20a**: R_f 0.26 (25% EtOAc/toluene). $[\alpha]_D^{25.5}$ −1.8 (*c* 0.39, $CHCl_3$).

(±)-**20b**: R_f 0.33 (25% EtOAc/toluene). $[\alpha]_D^{23.7}$ −1.8 (*c* 0.44, $CHCl_3$).

(1*S*,2*R*,5'*R*)- and (1*S*,2*S*,5'*R*)-2-Hydroxy-3-isopropoxy-5'-(methoxymethoxy)dispiro[cyclo–pentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-3,3'-dien-5-ones (22a and 22a'): To a stirred suspension of enone **20a** (170 mg, 0.401 mmol) in EtOH (4 mL) was portionwise added potassium borohydride (65.7 mg, 1.22 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature over 4 h and treated with saturated aqueous NH_4Cl (4 mL). The resulting mixture was stirred for another 1 h, extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by preparative thin layer chromatography (50% EtOAc/toluene, developed 2 times) to give pure **22a** (144 mg, 84%) and impure **22a'** (20.4 mg) as a slower- and faster-moving component, respectively. The latter was further purified by preparative thin layer chromatography (30% acetone/hexane, developed 2 times) to give pure **22a'** (12.0 mg, 7%).

22a as a white amorphous mass: R_f 0.25 (40% EtOAc/toluene). $[\alpha]_D^{23.4}$ –299 (*c* 1.39, $CHCl_3$). IR ν (neat, cm^{-1}): 3397, 2982, 2929, 1072, 1602, 1411, 1379, 1274, 1130, 1104, 1053, 1041, 755. ^1H NMR (400 MHz, $CDCl_3$): δ. 7.47–7.44 (m, 2H), 7.40–7.35 (m, 2H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 7.5 Hz 1H), 6.32 (dd, *J* = 1.6, 6.1 Hz, 1H), 5.95 (dd, *J* = 2.2, 6.1 Hz, 1H), 5.46 (s, 1H), 5.36–5.33 (m, 2H), 4.84 (d, *J* = 7.1 Hz, 1H), 4.76 (d, *J* = 7.1 Hz, 1H), 4.50 (qq, *J* = 6.1, 6.2 Hz, 1H), 3.85 (d, *J* = 9.1 Hz, 1H), 3.38 (s, 3H), 1.42 (d, *J* = 6.1 Hz, 3H), 1.40 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 184.8, 147.88, 147.87, 139.1, 134.2, 127.8, 127.3, 127.2, 120.7, 120.5, 113.8,

109.8, 109.5, 108.9, 105.7, 97.9, 82.5, 75.8, 71.2, 70.3, 55.8, 21.5, 21.3. HRMS (ESI, $[M+Na]^+$): calcd for $C_{24}H_{24}O_7Na$, 447.1420; found: 447.1411.

22a' as a white amorphous mass: R_f 0.35 (40% EtOAc/toluene). $[\alpha]_D^{19.7}$ –318 (*c* 0.770, $CHCl_3$). IR ν (compression cell, cm^{-1}): 3533, 2933, 1709, 1605, 1273, 1107, 1042, 757. ^1H NMR (400 MHz, $CDCl_3$): δ. 7.52–7.48 (m, 2H), 7.43–7.36 (m, 2H), 7.01 (dd, *J* = 0.8, 7.6 Hz, 1H), 6.87 (d, *J* = 6.9 Hz 1H), 6.36 (dd, *J* = 1.4, 6.2 Hz, 1H), 6.05 (dd, *J* = 2.0, 6.2 Hz, 1H), 5.52 (s, 1H), 5.16 (d, *J* = 1.8 Hz, 1H), 5.14 (dd, *J* = 1.4, 2.0 Hz, 1H), 4.72 (d, *J* = 7.0 Hz, 1H), 4.65 (d, *J* = 7.0 Hz, 1H), 4.52 (qq, *J* = 6.1, 6.2 Hz, 1H), 4.21 (d, *J* = 1.8 Hz, 1H), 3.35 (s, 3H), 1.45 (d, *J* = 6.2 Hz, 3H), 1.41 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 184.3, 147.4, 146.8, 138.8, 134.2, 129.6, 127.6, 126.9, 121.5, 120.9, 113.9, 110.8, 110.7, 109.4, 106.5, 96.3, 84.2, 75.8, 75.7, 67.3, 55.6, 21.4, 21.2. LRMS (EI) *m/z* (relative intensity): 424 $[M]^+$ (86), 362 (45), 265 (43), 223 (100). HRMS (EI, $[M]^+$): calcd for $C_{24}H_{24}O_7$, 424.1522; found 424.1509.

(1*R*,2*R*,5'*R*)-2-Hydroxy-3-isopropoxy-5'-(methoxymethoxy)dispiro[cyclopentane-1,1'-cyclo–pentane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-3,3'-dien-5-one (22b): To a stirred suspension of enone **20b** (168 mg, 0.398mmol) in EtOH (4 mL) was portionwise added sodium borohydride (45.0 mg, 1.19 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature over 2 h and treated with saturated aqueous NH_4Cl (5 mL). The resulting mixture was stirred for another 1 h, extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by preparative thin layer chromatography (50% EtOAc/hexane) to give **22b** (167 mg, 99%) as a white amorphous mass. R_f 0.34 (40% EtOAc/toluene). $[\alpha]_D^{23.4}$ −97.8 (*c* 1.01, $CHCl_3$). IR ν (neat, cm^{-1}): 3559, 2982, 2935, 1699, 1606, 1586, 1413, 1379, 1273, 1105, 1033, 757. ^1H NMR (400 MHz, $CDCl_3$): δ 7.52–7.45 (m, 2H), 7.42–7.36 (m, 2H), 6.94 (dd, *J* = 1.0, 7.5 Hz 1H), 6.90 (dd, *J* = 0.8, 7.5 Hz, 1H), 6.43 (dd, 1H, *J* = 1.9, 6.0 Hz), 5.94 (dd. 1H, *J* = 1.7, 6.0 Hz), 5.32 (dd, *J* = 0.8, 10.1 Hz, 1H), 5.27 (dd, *J* = 1.7, 1.9 Hz, 1H), 5.18 (br-s, 1H), 4.77 (d, *J* = 6.6 Hz, 1H), 4.75 (d, *J* = 6.6 Hz, 1H), 4.39 (qq, *J* = 6.1, 6.1 Hz, 1H), 3.82 (d, *J* = 10.1 Hz, 1H), 3.38 (s, 3H), 1.40 (d, *J* = 6.1 Hz, 3H), 1.38 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 185.3, 147.3, 146.8, 139.9, 134.1, 128.9,

127.8, 126.8, 121.5, 120.6, 113.5, 110.9, 110.2, 108.7, 102.6, 97.0, 80.1, 75.9, 71.6, 70.3, 55.6, 21.32, 21.26. HRMS (ESI, $[M+Na]^+$): calcd for $C_{24}H_{24}O_7Na$, 447.1420; found: 447.1412.

(1*R*,5*R*,5'*R*)-4-Isopropoxy-5'-(methoxymethoxy)-2-oxodispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-3,3'-dien-5-yl acetate (23a): To a stirred solution of alcohol **22a** (10.9 mg, 0.0257 mmol) and a catalytic amount of DMAP in anhydrous CH_2Cl_2 (0.5 mL) were successively added triethylamine (17 μL, 0.12 mmol) and acetic anhydride (7 μL, 0.074 mmol) at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was treated with *N*,*N*-dimethyl-1,3-propanediamine (10 μL, 0.080 mmol). The resulting mixture was stirred for another 30 min, diluted with EtOAc, washed with 1 M aqueous HCl, H_2O, saturated aqueous $NaHCO_3$, and brine successively, dried over $MgSO_4$, and concentrated. The residue was purified by preparative thin layer chromatography (33% EtOAc/toluene) to give **23a** (10.6 mg, 88%) as a white amorphous mass. R_f 0.38 (40% EtOAc/toluene). $[\alpha]_D^{23.1}$ –262 (*c* 0.530, $CHCl_3$). IR ν (neat, cm^{-1}): 2935, 1756, 1717, 1607, 1379, 1368, 1273, 1227, 1104, 756. ^1H NMR (400 MHz, $CDCl_3$): δ. 7.45–7.43 (m, 2H), 7.39–7.33 (m, 2H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.73 (s, 1H), 6.32 (dd, *J* = 1.4, 6.2 Hz, 1H), 5.99 (dd, *J* = 2.0, 6.2 Hz, 1H), 5.48 (s, 1H), 5.23 (br-s, 1H), 4.82 (d, *J* = 6.8 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.44 (septet, *J* = 6.1 Hz, 1H), 3.42 (s, 3H), 2.26 (s, 3H), 1.35 (d, *J* = 6.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 181.8, 168.8, 147.7, 147.6, 138.7, 134.2, 128.2, 127.3, 127.2, 120.7, 120.5, 113.7, 109.8, 108.9, 108.7, 106.7, 96.1, 79.8, 76.0, 69.8, 69.1, 55.5, 21.3, 21.2, 20.9. HRMS (ESI, $[M+Na]^+$): calcd for $C_{26}H_{26}O_8Na$, 489.1525; found: 489.1516.

(1*R*,5*S*,5'*R*)-4-Isopropoxy-5'-(methoxymethoxy)-2-oxodispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-3,3'-dien-5-yl acetate (23a'): Following the procedure described above for **23a**, the acetylation of **22a'** (11.4 mg, 0.0269 mmol) and preparative thin layer chromatography (33% EtOAc/toluene) afforded **23a'** (11.1 mg, 89%) as a white amorphous mass. R_f 0.44 (40% EtOAc/toluene). $[\alpha]_D^{18.1}$ –330 (*c* 0.555, $CHCl_3$). IR ν (neat, cm^{-1}): 2935, 1748, 1716, 1609, 1379, 1274, 1236, 1105, 1043. ^1H NMR (400 MHz, $CDCl_3$): δ. 7.47–7.33 (m, 4H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 6.9 Hz, 1H), 6.42 (s, 1H), 6.32 (dd, *J* = 1.3, 6.2 Hz, 1H), 6.04 (dd, *J* = 2.0, 6.2

Hz, 1H), 5.59 (s, 1H), 5.23 (br-s, 1H), 4.75 (d, *J* = 7.0 Hz, 1H), 4.72 (d, *J* = 7.0 Hz, 1H), 4.49 (septet, *J* = 6.1 Hz, 1H), 3.37 (s, 3H), 1.78 (s, 3H), 1.38 (d, *J* = 6.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 181.7, 170.5, 147.6, 147.3, 137.9, 134.2, 130.1, 127.4, 127.2, 120.6, 120.3, 113.3, 109.9, 109.0, 108.5, 107.9, 96.8, 85.0, 75.9, 73.1, 66.5, 55.6, 21.4, 21.2, 20.6. LRMS (EI) *m/z* (relative intensity): 466 $[M]^+$ (100), 320 (68), 223 (66). HRMS (EI, $[M]^+$): calcd for $C_{26}H_{26}O_8$, 466.1628; found 466.1603.

(1*S*,5*R*,5'*R*)-4-Isopropoxy-5'-(methoxymethoxy)-2-oxodispiro[cyclopentane-1,1'-cyclopent–ane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-3,3'-dien-5-yl acetate (23b): Following the procedure described above for **23a**, the acetylation of **22b** (10.8 mg, 0.0254 mmol) and preparative thin layer chromatography (33% EtOAc/toluene) afforded **23b** (10.5 mg, 88%) as a white amorphous mass. R_f 0.44 (40% EtOAc/toluene). $[\alpha]_D^{22.8}$ +118 (*c* 0.525, $CHCl_3$). IR ν (neat, cm^{-1}): 2982, 2939, 1752, 1711, 1608, 1413, 1380, 1276, 1238, 1103, 1037, 756. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.34 (m, 4H), 6.95 (dd, *J* = 0.9, 7.8 Hz, 1H), 6.86 (d, *J* = 6.8 Hz, 1H), 6.65 (s, 1H), 6.31 (dd, *J* = 2.5, 6.1 Hz, 1H), 6.12 (d. *J* = 6.1 Hz, 1H), 5.33 (s, 1H), 4.82 (d, *J* = 6.9 Hz, 1H), 4.75 (d, *J* = 6.9 Hz, 1H), 4.67 (d, *J* = 2.5 Hz, 1H), 4.42 (qq, *J* = 6.2, 6.2 Hz, 1H), 3.40 (s, 3H), 1.82 (s, 3H), 1.38 (d, *J* = 6.2 Hz, 3H), 1.36 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 182.3, 170.0, 147.9, 147.4, 136.7, 134.1, 132.5, 127.4, 127.2, 120.4, 120.3, 113.5, 110.0, 109.7, 108.5, 104.2, 96.5, 82.5, 76.1, 70.6, 66.4, 55.7, 21.3, 21.2, 20.8. HRMS (ESI, $[M+Na]^+$): calcd for $C_{26}H_{26}O_8Na$, 489.1525; found: 489.1516.

(1*S*,2*S*,5'*R*)-2-Hydroxy-5'-(methoxymethoxy)dispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxin]-3'-en-5-one (24) and (2*S*,5*S*,5'*R*)-5'-(methoxymethoxy)dispiro–[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxin]-3'-ene-2,5-diol (25): To a stirred solution of alcohol **22a** (8.3 mg, 0.020 mmol) in anhydrous THF (0.4 mL) was added 1.0 M lithium aluminum hydride solution in THF (0.06 mL, 0.06 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature over 2 h, cooled to 0 °C again, and treated with saturated aqueous $Na_2SO_4 \cdot 10H_2O$ (13 μL). The resulting mixture was stirred at room temperature for 1 h, dried over $MgSO_4$, diluted with EtOAc, and filtered through a Celite pad, which was thoroughly

rinsed with EtOAc. The filtrate was concentrated. The residue was purified by preparative thin layer chromatography (50% EtOAc/hexane) to give impure hydroxy-ketone **24** (4.3 mg) and diol **25** (1.6 mg) as a faster- and slower-moving component, respectively. The former and latter were further purified by preparative thin layer chromatography (40% EtOAc/toluene and 20% acetone/toluene, respectively) to give pure **24** (3.9 mg, 54%) as a white solid and **25** (1.3 mg, 18%) as a white amorphous mass.

24: R_f 0.44 (60% EtOAc/hexane), 0.21 (30% acetone/hexane), 0.43 (40% EtOAc/toluene) and 0.45 (20% acetone/toluene). Mp. 182–186 °C. $[\alpha]_D^{20.6}$ –310 (*c* 1.02, $CHCl_3$). IR ν (neat, cm^{-1}): 3591, 3491, 3016, 2951, 1752, 1607, 1412, 1275, 1098, 1043, 757. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.47 (m, 2H), 7.43–7.36 (m, 2H), 6.94 (dd, *J* = 0.8, 7.5 Hz, 1H), 6.81 (dd, *J* = 0.7, 7.5 Hz, 1H), 6.37 (dd, *J* = 1.4, 6.1 Hz, 1H), 5.94 (dd, *J* = 1.9, 6.1 Hz, 1H), 5.40 (dd, *J* = 1.4, 1.9 Hz, 1H), 5.01–4.96 (m, 1H), 4.87 (d, *J* = 6.9 Hz, 1H), 4.71 (d, *J* = 6.9 Hz, 1H), 3.41 (s, 3H), 2.87–2.85 (m, 1H), 2.60−2.52 (m, 1H), 2.44−2.32 (m, 2H), 2.06−1.98 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.9, 147.6, 147.4, 139.6, 134.2, 128.3, 127.5, 127.1, 121.0, 120.9, 113.7, 110.2, 110.0, 108.9, 96.8, 80.1, 71.6, 69.7, 55.8, 38.0, 27.3. HRMS (ESI, $[M+Na]^+$): calcd for $C_{21}H_{20}O_6Na$, 391.1158; found: 391.1151.

25: R_f 0.43 (60% EtOAc/hexane), 0.18 (30% acetone/hexane), 0.23 (40% EtOAc/toluene) and 0.26 (20% acetone/toluene). $[\alpha]_D^{17.8}$ +56 (*c* 0.37, $CHCl_3$). IR ν (compression cell, cm^{-1}): 3578, 3432, 2951, 1607, 1275, 1095, 1033, 756. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.50 (m, 2H), 7.44–7.40 (m, 2H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.35 (dd, *J* = 2.6, 6.0 Hz, 1H), 5.99 (d, *J* = 6.0 Hz, 1H), 5.36–5.32 (m, 1H), 4.78–4.74 (m, 3H), 4.70 (d, *J* = 2.6 Hz, 1H), 3.39 (s, 3H), 2.85 (br-s, 1H), 2.46–2.37 (m, 1H), 2.18–2.10 (m, 1H), 1.85–1.66 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 147.5, 139.7, 134.3, 130.6, 127.4, 127.3, 121.1, 120.9, 114.0, 112.0, 109.8, 109.5, 97.0, 81.3, 74.2, 73.5, 63.3, 55.6, 28.7, 28.2. LRMS (EI) *m/z* (relative intensity): 370 $[M]^+$ (5), 352 (100), 291 (36), 160 (72). HRMS (EI, $[M]^+$): calcd for $C_{21}H_{22}O_6$, 370.1416; found 370.1419.

(*R*)-5'-(Methoxymethoxy)dispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]–dioxin]-3'-ene-2,5-dione (26): To a stirred solution of hydroxy-ketone **24** (13.4 mg, 0.0364 mmol) in anhydrous CH_2Cl_2 (0.4 mL) was added Dess-Martin periodinane (31.3 mg, 0.0738 mmol) at room

temperature. After being stirred at the same temperature for 2.5 h, the reaction mixture was treated with saturated aqueous $NaHCO_3$ (2 mL), 20% aqueous $Na_2S_2O_3 \cdot 5H_2O$ (2 mL), and Et_2O (4 mL). The immiscible mixture was stirred for 2.5 h, extracted with Et_2O, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by preparative thin layer chromatography (20% EtOAc/toluene) to give **26** (11.9 mg, 89%) as a white amorphous mass. R_f 0.61 (40% EtOAc/toluene). $[\alpha]_D^{20.0}$ –195 (*c* 0.595, $CHCl_3$). IR ν (neat, cm^{-1}): 3019, 2929, 1736, 1608, 1412, 1379, 1274, 1096, 1039, 758. ^1H NMR (400 MHz, $CDCl_3$): δ 7.52–7.47 (m, 2H), 7.43–7.38 (m, 2H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.43 (dd, *J* = 1.7, 5.9 Hz, 1H), 5.82 (dd, *J* = 2.2, 5.9 Hz, 1H), 5.26 (dd, *J* = 1.7, 2.2 Hz, 1H), 4.63 (d, *J* = 6.5 Hz, 1H), 4.60 (d, *J* = 6.5 Hz, 1H), 3.22 (s, 3H), 2.92–2.80 (m, 1H), 2.67–2.44 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.7, 204.1, 147.1, 146.9, 139.5, 134.0, 127.6, 127.3, 126.7, 121.4, 120.9, 113.5, 110.7, 109.9, 109.7, 98.4, 83.7, 71.8, 55.8, 37.2, 36.1. HRMS (ESI, $[M+Na]^+$): calcd for $C_{21}H_{18}O_6Na$, 389.1001; found: 389.0994.

Following the procedure described above for **26**, the oxidation of diol **25** (7.4 mg, 0.020 mmol) with Dess-Martin periodinane (34.4 mg, 0.081 mmol) and preparative thin layer chromatography (20% EtOAc/toluene) afforded **26** (6.8 mg, 93%).

Following the procedure described above for **26**, the oxidation of diol **25'** (8.8 mg, 0.024 mmol) with Dess-Martin periodinane (40.8 mg, 0.096 mmol) and preparative thin layer chromatography (20% EtOAc/toluene) afforded **26** (7.3 mg, 84%).

(*R*)-5'-(Methoxymethoxy)dispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]–dioxine]-3,3'-diene-2,5-dione (27): To a stirred solution of cyclopentane-1,3-dione **26** (19.5 mg, 0.0532 mmol) in anhydrous THF (0.5 mL) was added trimethylphenylammonium tribromide (22.1 mg, 0.0588 mmol) at 0 °C. The reaction mixture was warmed to room temperature, stirred at the same temperature for 35 min, and treated with saturated aqueous $NaHCO_3$ (2 mL) and 20% aqueous $Na_2S_2O_3 \cdot 5H_2O$ (2 mL). The immiscible mixture was extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by preparative thin layer chromatography (20% EtOAc/toluene) to give **27** (9.2 mg, 47%) as a pale yellow amorphous mass along with **1** (5.3 mg, 31%) as a pale yellow amorphous mass. R_f 0.55 (33% Et_2O/toluene). $[\alpha]_D^{23.3}$ –

296 (*c* 0.46, $CHCl_3$). IR ν (neat, cm^{-1}): 2929, 1710, 1608, 1412, 1379, 1274, 1108, 1041, 757. ^1H NMR (400 MHz, $CDCl_3$): δ 7.46–7.33 (m, 4H), 7.23 (d, *J* = 6.1 Hz, 1H), 7.09 (d, *J* = 6.1 Hz, 1H), 6.90 (d, *J* = 7.3 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 6.47 (dd, *J* = 1.6, 5.9 Hz, 1H), 5.97 (dd, *J* = 2.1, 5.9 Hz, 1H), 5.30 (dd, *J* = 1.6, 2.1 Hz, 1H), 4.59 (d, *J* = 6.8 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 1H), 3.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 195.5, 150.1, 149.7, 147.5, 147.2, 139.4, 134.2, 128.7, 127.6, 127.3, 121.2, 120.8, 113.3, 109.8, 109.7, 109.5, 97.7, 83.6, 67.1, 55.8. HRMS (EI, $[M]^+$): calcd for $C_{21}H_{16}O_6$, 364.0947; found: 364.0952.

Following the procedure described above for **26**, the oxidation of diol **32a** (8.0 mg, 0.019 mmol) with Dess-Martin periodinane (32.3 mg, 0.076 mmol) gave crude diketone **33a**. After analysis of **33a**, the crude was purified by preparative thin layer chromatography (20% EtOAc/toluene, left on a silica gel plate for 4 h after development) to give **27** (5.3 mg, 78%).

33a as a pale yellow oil: R_f 0.67 (40% EtOAc/toluene). $[\alpha]_D^{22.0}$ –159 (*c* 0.48, $CHCl_3$). IR ν (compression cell, cm^{-1}): 2972, 2929, 1737, 1608, 1380, 1276, 1103, 1041, 758. ^1H NMR (400 MHz, $CDCl_3$): δ 7.48–7.45 (m, 2H), 7.42–7.35 (m, 2H), 6.94 (dd, *J* = 0.9, 7.5 Hz, 1H), 6.88 (dd, *J* = 0.9, 7.5 Hz, 1H), 6.37 (dd, *J* = 1.7, 5.9 Hz, 1H), 5.83 (dd, *J* = 2.2, 5.9 Hz, 1H), 5.22 (dd, *J* = 1.7, 2.2 Hz, 1H), 4.63 (d, *J* = 6.6 Hz, 1H), 4.58 (d, *J* = 6.6 Hz, 1H), 4.15 (dd, *J* = 4.1, 7.5 Hz, 1H), 3.83 (qq, *J* = 6.0, 6.2 Hz, 1H), 3.24 (s, 3H), 2.91 (dd, *J* = 7.5, 19.0 Hz, 1H), 2.82 (dd, *J* = 4.1, 19.0 Hz, 1H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.68 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.7, 202.3, 147.03, 147.00, 138.6, 134.1, 127.6, 127.33, 127.30, 120.9, 120.8, 113.2, 110.6, 109.6, 109.3, 98.3, 85.2, 75.0, 70.6, 70.4, 55.8, 46.3, 22.1, 20.7. LRMS (EI) *m/z* (relative intensity): 424 $[M]^+$ (100), 363 (39), 249 (33). HRMS (EI, $[M]^+$): calcd for $C_{24}H_{24}O_7$, 424.1522; found 424.1512.

Following the procedure described above for **26**, the oxidation of diol **32b** (7.2 mg, 0.017 mmol) with Dess-Martin periodinane (30.0 mg, 0.071 mmol) gave crude diketone **33b**. After analysis of **33b**, the crude was purified by preparative thin layer chromatography (20% EtOAc/toluene, left on a silica gel plate for 4 h after development) to give **27** (3.7 mg, 61%).

33b as a pale yellow oil: R_f 0.71 (40% EtOAc/toluene). $[\alpha]_D^{23.0}$ –149 (*c* 0.42, $CHCl_3$). IR ν (compression cell, cm^{-1}): 2928, 1738, 1609, 1379, 1274, 1101, 1047, 759. ^1H NMR (400 MHz,

$CDCl_3$): δ 7.53–7.48 (m, 2H), 7.43–7.38 (m, 2H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.41 (dd, *J* = 1.7, 5.9 Hz, 1H), 5.77 (dd, *J* = 2.2, 5.9 Hz, 1H), 5.35 (dd, *J* = 1.7, 2.2 Hz, 1H), 4.63 (d, *J* = 7.0 Hz, 1H), 4.61 (d, *J* = 7.0 Hz, 1H), 4.45 (dd, *J* = 5.7, 9.7 Hz, 1H), 4.04 (qq, *J* = 6.1, 6.2 Hz, 1H), 3.30 (s, 3H), 2.92 (dd, *J* = 9.7, 18.7 Hz, 1H), 2.57 (dd, *J* = 5.7, 18.7 Hz, 1H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.18 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.3, 202.4, 147.0, 146.9, 139.9, 134.1, 127.6, 127.2, 126.3, 121.5, 121.0, 113.4, 110.5, 110.0, 109.6, 97.9, 82.4, 72.5, 72.2, 56.7, 44.8, 22.5, 21.6. LRMS (EI) *m/z* (relative intensity): 424 $[M]^+$ (46), 364 (100), 280 (76), 149 (61). HRMS (EI, $[M]^+$): calcd for $C_{24}H_{24}O_7$, 424.1522; found 424.1510.

Following the procedure described above for **26**, the oxidation of diol **32b'** (7.5 mg, 0.018 mmol) with Dess-Martin periodinane (30.6 mg, 0.071 mmol) gave crude diketone **33b**. After analysis of **33b**, the crude was purified by preparative thin layer chromatography (20% EtOAc/toluene, left on a silica gel plate for 4 h after development) to give **27** (4.9 mg, 77%).

5'-Hydroxydispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-3,3'-diene-2,5-dione (Spiromamakone A, 1): Following the procedure described above for **21a**, the acid hydrolysis of **27** (8.6 mg, 0.024 mmol) gave crude spiromamakone A (**1**). After measurement of the specific rotation of **1**, the crude was purified by preparative thin layer chromatography (25% EtOAc/toluene) to give **1** (5.7 mg, 75%) as a pale yellow amorphous mass. R_f 0.32 (25% EtOAc/toluene). $[\alpha]_D^{27.3}$ –43.5 (*c* 0.38, $CHCl_3$) and $[\alpha]_D^{25.2}$ –1.2 (*c* 0.29, $CHCl_3$) before and after preparative thin layer chromatography, respectively. IR ν (neat, cm^{-1}): 3444, 2923, 2852, 1705, 1608, 1412, 1273, 1105, 1076, 757. HRMS (EI, $[M]^+$): calcd for $C_{19}H_{12}O_5$, 320.0685; found 320.0698.

^{1}H NMR (400 MHz, CD_3OD): δ 7.37 (d, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.30 (dd, *J* = 7.6, 7.7 Hz, 1H), 7.26 (dd, *J* = 7.6, 7.7 Hz, 1H), 7.12 (d, *J* = 6.1 Hz, 1H), 6.99 (d, *J* = 6.1 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.30 (dd, *J* = 1.7, 5.8 Hz, 1H), 5.83 (dd, *J* = 2.0, 5.8 Hz, 1H), 5.20 (dd, *J* = 1.7, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 200.8, 198.3, 151.9, 151.6, 149.1, 148.5, 142.4, 135.7, 129.7, 128.7, 128.4, 122.2, 121.7, 114.5, 111.4, 110.7, 110.3, 78.9, 68.6.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.39 (dd, *J* = 7.6, 8.4 Hz, 1H), 7.37 (dd, *J* = 7.6, 8.4 Hz, 1H), 7.19 (d, *J* = 6.1 Hz, 1H), 7.13 (d, *J* = 6.1 Hz, 1H), 6.88 (d, 1H, *J* = 7.6 Hz), 6.85 (d, 1H, *J* = 7.6 Hz), 6.41 (dd, *J* = 1.9, 5.8 Hz, 1H), 6.00 (dd, *J* = 1.6, 5.8 Hz, 1H), 5.37 (d, *J* = 11.6 Hz, 1H), 2.66 (d, *J* = 11.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.5, 197.6, 150.8, 150.2, 147.2, 146.9, 140.8, 134.1, 129.6, 127.6, 127.3, 121.2, 120.9, 113.3, 110.1, 110.0, 109.6, 77.8, 66.8.

(*R*)- and (*S*)- 2,5-Dioxodispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]–dioxine]-3,3'-dien-5'-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (28a and 28b): To a stirred solution of alcohol **1** (9.1 mg, 0.028 mmol) and (*R*)-MTPA-OH (10.7 mg, 0.046 mmol) in anhydrous CH_2Cl_2 (0.3 mL) were successively added EDCI (10.9 mg, 0.057 mmol) and DMAP (1.2 mg, 9.8 μmmol) at room temperature. After being stirred at the same temperature for 1.5 h, the reaction mixture was treated with (*R*)-MTPA-OH (4.5 mg, 0.019 mmol) and EDCI (5.6 mg, 0.029 mmol) and stirred for another 2 h. Again, (*R*)-MTPA-OH (6.4 mg, 0.027 mmol) was added to the mixture. The mixture was stirred for another 2 h and treated with additional small amounts of (*R*)-MTPA-OH, EDCI, and DMAP to complete the consumption of **1**. After being stirred for another 3 h, the resulting mixture was diluted with Et_2O, washed with 1 M aqueous HCl, H_2O, saturated aqueous $NaHCO_3$, and brine successively, dried over $MgSO_4$, and concentrated. The residue was purified by preparative thin layer chromatography (toluene only, developed 10 times) to give (*R*)-2,5-dioxodispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-3,3'-dien-5'-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **28a** (8.0 mg, 53%) and (*S*)-2,5-dioxodispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-3,3'-dien-5'-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **28b** (4.8 mg, 32%) as a faster- and slower-moving component, respectively.

(*R*)-2,5-Dioxodispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-3,3'-dien-5'-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**28a**, upper and major component) as a yellow waxy solid: R_f 0.73 (25% EtOAc/toluene). $[\alpha]_D^{25.4}$ –148 (*c* 0.090, $CHCl_3$). IR ν (compression cell, cm^{-1}): 2927, 1748, 1714, 1269, 1195, 1037, 758. ^{1}H NMR (400 MHz, $CDCl_3$): δ

7.48–7.35 (m, 8H), 7.16 (d, *J* = 6.1 Hz, 1H), 7.11 (d, *J* = 6.1 Hz, 1H), 6.91 (dd, *J* = 0.9, 7.5 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.39 (dd, *J* = 1.9, 5.9 Hz, 1H), 6.15 (dd, *J* = 1.7, 5.9 Hz, 1H), 6.07 (dd, *J* = 1.7, 1.9 Hz, 1H), 3.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 194.1, 166.9, 149.54, 149,49, 146.9, 146.7, 135.6, 134.1, 132.2, 131.4, 129.8, 128.5, 127.6, 127.35, 127.32 (q, *J* = 1.2 Hz), 122.9 (q, *J* = 289 Hz), 121.3, 121.1, 113.2, 110.0, 109.9, 109.8, 84.3 (q, *J* = 27.8 Hz), 80.4, 64.8, 55.7 (q, *J* = 1.4 Hz). LRMS (EI) *m/z* (relative intensity): 536 $[M]^+$ (68), 303 (30), 189 (100). HRMS (EI, $[M]^+$): calcd for $C_{29}H_{19}F_3O_7$, 536.1083; found 536.1081.

(*S*)-2,5-Dioxodispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-3,3'-dien-5'-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**28b**, lower and minor component) as a yellow waxy solid: R_f 0.73 (25% EtOAc/toluene). $[\alpha]_D^{24.3}$ +196 (*c* 0.24, $CHCl_3$). IR ν (compression cell, cm^{-1}): 2926, 1749, 1714, 1273, 1195, 1056, 758. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.33 (m, 8H), 7.08 (d, *J* = 6.1 Hz, 1H), 7.05 (d, *J* = 6.1 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.49 (dd, *J* = 1.8, 5.9 Hz, 1H), 6.24 (dd, *J* = 1.8, 1.8 Hz, 1H), 6.16 (dd, *J* = 1.8, 5.9 Hz, 1H), 3.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 193.8, 166.3, 149.6, 149.5, 147.0, 146.7, 135.6, 134.1, 132.2, 131.4, 129.7, 128.5, 127.7, 127.30, 127.28, 122.9 (q, *J* = 288 Hz), 121.5, 121.4, 121.1, 113.1, 110.0, 109.7, 109.5, 84.4 (q, *J* = 27.8 Hz), 79.7, 64.8, 55.5 (q, *J* = 1.3 Hz). LRMS (EI) *m/z* (relative intensity): 536 $[M]^+$ (59), 303 (30), 189 (100), 149 (36). HRMS (EI, $[M]^+$): calcd for $C_{29}H_{19}F_3O_7$, 536.1083; found 536.1035.

(1*R*,5*R*,5'*R*)-5-Hydroxy-5'-(methoxymethoxy)dispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-2,3'-dien-4-one (30): To a stirred suspension of lithium aluminum hydride (30.1 mg, 0.793 mmol) in anhydrous THF (0.4 mL) was added a solution of allyl alcohol **22b** (170 mg, 0.401 mmol) in anhydrous THF (4 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature over 1 h, cooled to 0 °C again, and treated with saturated aqueous $Na_2SO_4{\cdot}10H_2O$ (151 μL). The resulting mixture was stirred at room temperature for 1 h, dried over $MgSO_4$, diluted with EtOAc, and filtered through a Celite pad, which was thoroughly rinsed with EtOAc. The filtrate was concentrated to give a crude alcohol **29** (154 mg, 90%), which was used for the next reaction without further purification.

To a stirred solution of the crude alcohol **29** (154 mg) in anhydrous THF (3.6 mL) was added 1 M aqueous HCl (1.2 mL, 1.2 mmol) at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was basified with saturated aqueous $NaHCO_3$ (4 mL). The resulting mixture was extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by preparative thin layer chromatography (33% EtOAc/toluene) and then HPLC (column size: 8ø x 300 mm, eluent: 20% *i*-PrOH/hexane, flow rate: 1 mL/min, RT: 23–25 min) to give **30** (75.0 mg, 51% from **22b** over 2 steps) as a white solid. R_f 0.19 (25% EtOAc/toluene). Mp. 151–153 °C. $[\alpha]_D^{17.2}$ –341 (*c* 0.670, $CHCl_3$). IR ν (compression cell, cm^{-1}): 3570, 2946, 1731, 1611, 1414, 1271, 1146, 1116, 959, 813. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 6.4 Hz, 1H), 7.51–7.46 (m, 2H), 7.41–7.36 (m, 2H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.43 (d, *J* = 6.4 Hz, 1H), 6.40 (dd, *J* = 1.5, 6.2 Hz, 1H), 6.03 (dd, *J* = 2.3, 6.2 Hz, 1H), 5.21 (dd, *J* = 1.5, 2.3 Hz, 1H), 4.86 (d, *J* = 11.1 Hz, 1H), 4.84 (d, *J* = 6.9 Hz, 1H), 4.76 (d, *J* = 6.9 Hz, 1H), 3.39 (s, 3H), 3.09 (d, *J* = 11.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.9, 158.0, 147.2, 146.6, 139.7, 134.2, 133.8, 129.3, 127.33, 127.28, 121.5, 120.9, 113.5, 111.3, 109.6, 109.1, 96.7, 81.8, 75.9, 66.0, 55.8. LRMS (EI) *m/z* (relative intensity): 366 $[M]^+$ (81), 304 (100), 275 (52), 133 (58). HRMS (EI, $[M]^+$): calcd for $C_{21}H_{18}O_6$, 366.1103; found 366.1082.

(1*S*,5*R*,5'*R*)-5'-(Methoxymethoxy)-4-oxodispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxine]-2,3'-dien-5-yl acetate (31): Following the procedure described above for **23a**, the acetylation of **30** (11.2 mg, 0.0306 mmol) and preparative thin layer chromatography (20% EtOAc/toluene) afforded **31** (12.8 mg, quant.) as a white amorphous mass. R_f 0.55 (40% EtOAc/toluene). $[\alpha]_D^{21.0}$ –322 (*c* 0.640, $CHCl_3$). IR ν (compression cell, cm^{-1}): 2934, 1752, 1735, 1608, 1379, 1230, 1115, 1056, 759. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 6.4 Hz, 1H), 7.48–7.44 (m, 2H), 7.42–7.35 (m, 2H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.4 Hz, 1H), 6.38 (d, *J* = 6.4 Hz, 1H), 6.24 (dd, *J* = 1.4, 6.2 Hz, 1H), 6.14 (s, 1H), 6.01 (dd, *J* = 2.3, 6.2 Hz, 1H), 5.21 (dd, *J* = 1.4, 2.3 Hz, 1H), 4.83 (d, *J* = 6.9 Hz, 1H), 4.77 (d, *J* = 6.9 Hz, 1H), 3.39 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.9, 169.8, 158.4, 147.8, 147.5, 138.5, 134.2, 130.3, 127.5, 127.2, 120.9, 120.7, 113.9, 109.7, 109.6, 108.7, 96.9, 81.6, 72.7, 66.2, 55.9, 21.0. LRMS (EI) *m/z* (relative

intensity): 408 $[M]^+$ (62), 304 (100), 275 (38), 247 (37), 225 (31). HRMS (EI, $[M]^+$): calcd for $C_{23}H_{20}O_7$, 408.1209; found 408.1190.

(1*S*,2*R*,5*S*,5'*R*)-3-Isopropoxy-5'-(methoxymethoxy)dispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxin]-3'-ene-2,5-diol (32a) and (2*S*,5*S*,5'*R*)-5'-(methoxymethoxy)dispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxin]-3'-ene-2,5-diol (25): To a stirred solution of alcohol **22a** (10.4 mg, 0.0245 mmol) in anhydrous THF (0.5 mL) was added 2.0 M lithium borohydride solution in THF (0.075 mL, 0.15 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature over 15 h and treated with saturated aqueous NH_4Cl (3 mL). The immiscible mixture was stirred for another 1 h, extracted with EtOAc, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by preparative thin layer chromatography (50% EtOAc/hexane) to give pure **32a** (6.3 mg, 60%) and impure **25** (1.6 mg) as a faster- and slower-moving component, respectively. The latter was further purified by preparative thin layer chromatography (20% acetone/toluene) to give pure **25** (1.5 mg, 17%).

32a as a white amorphous mass: R_f 0.48 (60% EtOAc/hexane), 0.25 (30% acetone/hexane), 0.39 (40% EtOAc/toluene) and 0.40 (20% acetone/toluene). $[\alpha]_D^{21.0}$ +7.7 (*c* 1.30, $CHCl_3$). IR ν (compression cell, cm^{-1}): 3569, 3450, 2970, 1608, 1380, 1275, 1148, 1037, 758. ^1H NMR (400 MHz, $CDCl_3$): δ 7.52–7.49 (m, 2H), 7.43–7.39 (m, 2H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 6.33 (dd, *J* = 2.5, 6.1 Hz, 1H), 5.98 (d, *J* = 6.1 Hz, 1H), 5.16 (dd, *J* = 3.8, 6.8 Hz, 1H), 4.77–4.72 (m, 3H), 4.67 (d, *J* = 2.5 Hz, 1H), 4.02–3.97 (m, 1H), 3.82 (qq, *J* = 6.1, 6.2 Hz, 1H), 3.40 (s, 3H), 2.91 (br-s, 1H), 2.48–2.41 (m, 1H), 2.00–1.98 (m, 1H), 1.83 (dd, *J* = 2.8, 14.5 Hz, 1H), 1.25 (d, *J* = 6.1 Hz, 3H), 1.23 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 147.4, 139.3, 134.3, 130.7, 127.4, 127.2, 121.2, 120.9, 113.9, 111.7, 109.7, 109.5, 96.7, 81.5, 79.8, 78.8, 71.5, 70.8, 62.0, 55.7, 37.0, 23.0, 22.3. LRMS (EI) *m/z* (relative intensity): 428 $[M]^+$ (6), 410 (65), 251 (100), 149 (37). HRMS (EI, $[M]^+$): calcd for $C_{24}H_{28}O_7$, 428.1835; found 428.1852.

(1*R*,2*R*,5*S*,5'*R*)-3-Isopropoxy-5'-(methoxymethoxy)dispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxin]-3'-en-2,5-diyl diacetate (Diacetate of 32a): Following the procedure described above for **23a**, the acetylation of **32a** (2.6 mg, 0.0061 mmol) with triethylamine

(9+4 μL, 0.094 mmol) and acetic anhydride (4+2 μL, 0.063 mmol) and preparative thin layer chromatography (33% EtOAc/toluene) afforded diacetate of **32a** (2.8 mg, 90%) as a white amorphous mass. R_f 0.57 (40% EtOAc/toluene). $[\alpha]_D^{17.6}$ +66 (*c* 0.37, $CHCl_3$). IR ν (neat, cm^{-1}): 2971, 2930, 1739, 1608, 1380, 1236, 1150, 1041, 758. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.34 (m, 4H), 6.88 (d, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 7.4 Hz, 1H), 6.38 (d, *J* = 6.2 Hz, 1H), 6.26 (dd, *J* = 2.8, 6.1 Hz, 1H), 5.95 (d, *J* = 6.1 Hz, 1H), 5.77 (d, *J* = 5.0 Hz, 1H), 4.81 (d, *J* = 7.0 Hz, 1H), 4.75 (d, *J* = 7.0 Hz, 1H), 4.60 (d, *J* = 2.8 Hz, 1H), 4.12–4.08 (m, 1H), 3.63 (qq, *J* = 6.1, 6.1 Hz, 1H), 3.41 (s, 3H), 2.60–2.52 (m, 1H), 2.02 (s, 3H), 1.82 (dd, *J* = 3.3, 15.4 Hz, 1H), 1.71 (s, 3H), 1.16 (d, *J* = 6.1 Hz, 3H), 1.15 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 168.6, 148.0, 147.7, 136.5, 134.1, 132.4, 127.34, 127.33, 120.3, 120.0, 113.3, 109.2, 109.1, 108.8, 96.3, 81.4, 79.55, 79.51, 73.1, 71.1, 61.4, 55.8, 36.6, 22.39, 22.37, 21.61, 21.13. LRMS (EI) *m/z* (relative intensity): 512 $[M]^+$ (100), 306 (56), 305 (62). HRMS (EI, $[M]^+$): calcd for $C_{28}H_{32}O_9$, 512.2046; found 512.2020.

(1*R*,2*R*,5*R*,5'*R*)- and (1*R*,2*R*,5*S*,5'*R*)-3-Isopropoxy-5'-(methoxymethoxy)dispiro[cyclopent–ane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxin]-3'-ene-2,5-diols (32b and 32b') and (2*S*,5*S*,5'*R*)- and (1*s*,2*R*,5*S*,5'*R*)-5'-(methoxymethoxy)dispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxin]-3'-ene-2,5-diol (25, 25'): Following the procedure described above for **32a** and **25**, the reduction of **22b** (100 mg, 0.236 mmol) gave a mixture containing **32b**, **32b'**, **25**, and **25'**. The products were purified by preparative thin layer chromatography (17% EtOAc/toluene, developed 4 times) to give two mixtures of **32b**+**25'** and **32b'**+**25** as a faster- and slower-moving component, respectively. Further purification of the former mixture with preparative thin layer chromatography (30% acetone/hexane, developed 2 times) afforded pure **32b** (31.6 mg, 31%) and impure **25'** (9.6 mg) as a faster- and slower-moving component, respectively. Pure **25'** (3.9 mg, 7%) was obtained by further purification with preparative thin layer chromatography (60% EtOAc/hexane, developed 3 times). Further purification of the latter mixture with preparative thin layer chromatography (30% acetone/hexane, developed 2 times) afforded pure **32b'** (19.9 mg, 20%) and impure **25** (5.6 mg) as a faster- and slower-moving component, respectively. Pure **25** (3.9 mg,

4%) was obtained by further purification with preparative thin layer chromatography (60% EtOAc/hexane, developed 3 times).

32b as a white amorphous mass: 0.33 (40% EtOAc/toluene). $[\alpha]_D^{20.3}$ –137 (*c* 0.650, $CHCl_3$). IR ν (compression cell, cm^{-1}): 3563, 2970, 1608, 1413, 1380, 1273, 1038. ^1H NMR (400 MHz, $CDCl_3$): δ 7.57–7.54 (m, 2H), 7.48–7.41 (m, 2H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.40 (dd, *J* = 1.8, 6.2 Hz, 1H), 5.88 (dd, *J* = 1.4, 6.2 Hz, 1H), 4.94 (br-s, 1H), 4.85 (d, *J* = 7.1 Hz, 1H), 4.83 (d, *J* = 7.1 Hz, 1H), 4.43 (dd, *J* = 5.5, 10.2 Hz, 1H), 4.33–4.26 (m, 2H), 3.95 (d, *J* = 9.8 Hz, 1H), 3.84 (qq, *J* = 6.1, 6.1 Hz, 1H), 3.44 (s, 3H), 2.87 (d, *J* = 10.2 Hz, 1H), 2.39 (ddd, *J* = 9.7, 9.7, 13.5 Hz, 1H), 2.07 (ddd, *J* = 2.7, 7.0, 13.5 Hz, 1H), 1.22 (d, *J* = 6.1 Hz, 3H), 1.20 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 146.6, 140.9, 134.3, 128.5, 127.39, 127.37, 121.5, 121.4, 113.9, 113.8, 109.8, 109.7, 97.3, 81.4, 81.1, 79.4, 73.4, 70.5, 63.0, 55.7, 39.1, 22.7, 22.4. LRMS (EI) *m/z* (relative intensity): 428 $[M]^+$ (14), 410 (100), 251 (65). HRMS (EI, $[M]^+$): calcd for $C_{24}H_{28}O_7$, 428.1835; found 428.1836.

32b' as a white amorphous mass: 0.30 (40% EtOAc/toluene). $[\alpha]_D^{20.5}$ –9.5 (*c* 0.37, CH_3OH). IR ν (compression cell, cm^{-1}): 3573, 3438, 2969, 1607, 1380, 1274, 1096, 1038. ^1H NMR (400 MHz, $CDCl_3$): δ 7.54–7.50 (m, 2H), 7.45–7.40 (m, 2H), 6.99 (d, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 7.0 Hz, 1H), 6.35 (dd, *J* = 2.4, 6.0 Hz, 1H), 5.92 (d, *J* = 6.0 Hz, 1H), 5.00 (dd, *J* = 7.6, 12.0 Hz, 1H), 4.94 (d, *J* = 6.9 Hz, 1H), 4.83 (d, *J* = 2.4 Hz, 1H), 4.80 (dd, *J* = 2.8, 5.5 Hz, 1H), 4.74 (d, *J* = 6.9 Hz, 1H), 4.03–3.99 (m, 1H), 3.83 (qq, *J* = 6.1, 6.2 Hz, 1H), 3.41 (s, 3H), 2.93 (d, *J* = 5.5 Hz, 1H), 2.65 (ddd, *J* = 7.3, 7.6, 13.7 Hz, 1H), 1.94 (br-s, 1H), 1.73 (ddd, *J* = 5.5, 8.2, 13.7 Hz, 1H), 1.21 (d, *J* = 6.2 Hz, 3H), 1.19 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 147.3, 140.9, 134.3, 129.2, 127.4, 127.3, 121.3, 120.9, 114.0, 111.9, 109.65, 109.57, 97.5, 81.6, 80.5, 78.7, 72.2, 70.2, 63.7, 55.6, 38.0, 22.9, 22.1. LRMS (EI) *m/z* (relative intensity): 428 $[M]^+$ (20), 410 (100), 251 (36). HRMS (EI, $[M]^+$): calcd for $C_{24}H_{28}O_7$, 428.1835; found 428.1846.

25' as a white amorphous mass: 0.27 (30% acetone/hexane) and 0.30 (40% EtOAc/toluene). $[\alpha]_D^{19.3}$ –61 (*c* 0.44, $CHCl_3$). IR ν (compression cell, cm^{-1}): 3548, 2948, 1608, 1413, 1381, 1276, 1041, 758. ^1H NMR (400 MHz, $CDCl_3$): δ 7.54–7.51 (m, 2H), 7.45–7.40 (m, 2H), 6.99 (dd, *J* = 0.8,

7.5 Hz, 1H), 6.92 (dd, *J* = 0.7, 7.5 Hz, 1H), 6.31 (dd, *J* = 2.3, 6.1 Hz, 1H), 6.01 (dd, *J* = 0.7, 6.1 Hz, 1H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.74–4.70 (m, 1H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.35 (dd, *J* = 0.7, 2.3 Hz, 1H), 4.27–4.22 (m, 2H), 3.40 (s, 3H), 3.37 (d, *J* = 9.1 Hz, 1H), 2.26–2.12 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 147.0, 138.5, 134.3, 130.7, 127.4, 127.2, 121.3, 121.0, 114.0, 113.6, 109.8, 109.5, 96.8, 83.3, 77.9, 74.2, 63.3, 55.7, 31.5, 31.4. LRMS (EI) *m/z* (relative intensity): 370 $[M]^+$ (12), 352 (100), 291 (25), 160 (37). HRMS (EI, $[M]^+$): calcd for $C_{21}H_{22}O_6$, 370.1416; found 370.1413.

(1*S*,2*R*,5*R*,5'*R*)-3-Isopropoxy-5'-(methoxymethoxy)dispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxin]-3'-en-2,5-diyl diacetate (Diacetate of 32b): Following the procedure described above for **23a**, the acetylation of **32b** (6.2 mg, 0.014 mmol) with triethylamine (20 μL, 0.14 mmol) and acetic anhydride (8 μL, 0.085 mmol) and preparative thin layer chromatography (25% EtOAc/toluene) afforded diacetate of **32b** (6.4 mg, 86%) as a white solid. R_f 0.67 (40% EtOAc/toluene). Mp. 169–171 °C. $[\alpha]_D^{24.7}$ –18 (*c* 0.32, $CHCl_3$). IR ν (compression cell, cm^{-1}): 2969, 1733, 1381, 1236, 1034, 994. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.44 (m, 2H), 7.42–7.36 (m, 2H), 6.91 (d, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 7.4 Hz, 1H), 6.19 (dd, *J* = 1.2, 6.1 Hz, 1H), 5.98 (d, *J* = 3.3 Hz, 1H), 5.90 (d, *J* = 6.1 Hz, 1H), 5.60 (d, *J* = 2.9 Hz, 1H), 4.85 (d, *J* = 7.0 Hz, 1H), 4.78 (d, *J* = 7.0 Hz, 1H), 4.49 (br-s, 1H), 4.37–4.33 (m, 1H), 3.87 (qq, *J* = 6.0, 6.1 Hz, 1H), 3.38 (s, 3H), 2.37–2.31 (m, 1H), 2.11–2.07 (m, 1H), 2.05 (s, 3H), 1.86 (s, 3H), 1.19 (d, *J* = 6.1 Hz, 3H), 1.15 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 169.8, 148.1, 147.9, 137.3, 134.3, 131.7, 127.4, 127.3, 120.34, 120.26, 113.8, 110.3, 108.9, 108.7, 97.2, 84.4, 81.0, 75.2, 70.7, 63.4, 55.5, 38.3, 22.9, 21.7, 21.5, 21.3. LRMS (EI) *m/z* (relative intensity): 512 $[M]^+$ (100), 306 (79), 160 (51). HRMS (EI, $[M]^+$): calcd for $C_{28}H_{32}O_9$, 512.2046; found 512.2036.

(1*S*,2*R*,5*S*,5'*R*)-3-Isopropoxy-5'-(methoxymethoxy)dispiro[cyclopentane-1,1'-cyclopentane-2',2''-naphtho[1,8-*de*][1,3]dioxin]-3'-en-2,5-diyl diacetate (Diacetate of 32b'): Following the procedure described above for **23a**, the acetylation of **32b'** (6.0 mg, 0.014 mmol) with triethylamine (20 μL, 0.14 mmol) and acetic anhydride (8 μL, 0.085 mmol) and preparative thin layer chromatography (25% EtOAc/toluene) afforded diacetate of **32b'** (7.0 mg, 97%) as a white

amorphous mass. R_f 0.73 (40% EtOAc/toluene). $[\alpha]_D^{21.4}$ +96 (*c* 0.35, $CHCl_3$). IR ν (compression cell, cm^{-1}): 2971, 2930, 1743, 1608, 1381, 1231, 1037, 758. ^1H NMR (400 MHz, $CDCl_3$): δ 7.47–7.43 (m, 2H), 7.40–7.36 (m, 2H), 6.89 (d, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.27 (dd, *J* = 2.7, 6.1 Hz, 1H), 6.06 (dd, *J* = 8.3, 8.5 Hz, 1H), 5.93 (br-s, 1H), 5.87 (d, *J* = 6.1 Hz, 1H), 4.92 (d, *J* = 6.9 Hz, 1H), 4.74 (d, *J* = 6.9 Hz, 1H), 4.65 (d, *J* = 2.7 Hz, 1H), 3.90–3.83 (m, 2H), 3.66 (s, 3H), 2.89 (ddd, *J* = 8.2, 8.3, 14.3 Hz, 1H), 2.01 (s, 3H), 1.74–1.67 (m, 1H), 1.70 (s, 3H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.13 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 169.8, 148.1, 147.9, 138.8, 134.2, 130.4, 127.4, 127.3, 120.4, 120.1, 113.5, 111.0, 109.0, 108.9, 97.6, 82.0, 78.8, 76.9, 73.2, 70.7, 61.6, 55.4, 36.7, 22.8, 21.7, 21.1, 20.9. LRMS (EI) *m/z* (relative intensity): 512 $[M]^+$ (100), 408 (41), 306 (66), 160 (41). HRMS (EI, $[M]^+$): calcd for $C_{28}H_{32}O_9$, 512.2046; found 512.2020.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI:.

X-ray crystal structure of **19a** and ^1H, ^{13}C, and 2D NMR spectra for synthetic compounds (PDF). Crystallographic data for compound **19a** (CIF).

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