Studies of the Asymmetric Total Synthesis of Clavilactone D by the 'Lariat' Cyclization Strategy

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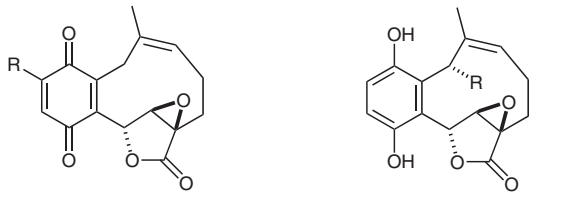
Abstract: A route to the core structure of clavilactone D, a new member of the tyrosine kinase inhibitors, is reported. The route employs sequential cyclization initiated by iodo etherification followed by Friedel–Crafts cyclization to furnish a polycyclic lactone fused with an aromatic ring, which is readily transformed into the proposed clavilactone scaffold.

Key words: total synthesis, natural products, cyclizations, asymmetric synthesis, alkylations

Clavilactone D (**1**), a new member of the tyrosine kinase inhibitors, has attracted considerable attention owing to the prospect that it would serve as a potent molecularly targeted anticancer agent.[1,2] This naturally occurring molecule belongs to the clavilactone family that includes the various congeners A (**3**), B (**2**), C (**4**), and E (**5**), all of which possess a unique constrained ten-membered ring system attached to a 2,3-epoxy-γ-lactone and a benzoquinone or a hydroquinone ring (Figure 1).[3]



clavilactone D R = OH (**1**)
clavilactone B R = H (**2**)

clavilactone A R = H (**3**)
clavilactone C R = OH (**4**)
clavilactone E R = OMe (**5**)

Figure 1 Clavilactone D and its congeners (revised absolute structure, see ref. 4)

This intriguing structure and the biological significance make this family an attractive target for synthesis. Barrett and co-workers have recently established a concise route to clavilactone B (**2**) through a highly convergent three-component benzyne coupling strategy and confirmed the absolute stereochemistry of the natural compound.[4,5] We are interested in clavilactone D (**1**), one of the most bioactive congeners, because it exerts a significant inhibitory effect on tyrosine kinase and has yet to be chemically produced. Its structure has been elucidated by an extensive NMR study and its absolute stereochemistry was correlated with that of clavilactone B (**2**) (Figure 1). Therefore, with a view to confirming the proposed structure, which would enable us to undertake structure–activity relationship studies and to devise powerful candidates for potent anticancer agents, we initiated a research program directed at the enantioselective total synthesis of clavilactone D (**1**). In the present paper, we report the asymmetric construction of the clavilactone ring system through the 'lariat' strategy, which is initiated by iodo etherification and followed by Friedel–Crafts-type cyclization.

The key transformations for producing the clavilactone core are shown in Scheme 1. Iodo etherification of alkenyl alcohol **10a** led to tetrahydrofuran derivative **i**, whose chiral menthyloxy auxiliary was extruded by reaction with the resultant hydroiodic acid in situ, to afford oxocarbenium intermediate **ii**. Intermediate **ii** was then captured by the electron-rich aromatic ring to deliver polycyclic compound **9**. Highly fused-ring system **9** was then subjected to reductive regeneration of *Z*-olefin, furnishing clavilactone skeleton **8**. Several chemical manipulations were applied to **8** to finally yield the clavilactone D skeleton **6**.

Substrate **10** was prepared by the aldol reaction of known chiral lactone **11**[6] with aldehyde **12**[7] (Scheme 2). The aldol reaction took place in good yield (92%), although the diastereoselectivity of this process was found to be only moderate (**10a/10b/10c** = 3:1:2).[8] We then investigated the 'lariat' cyclization of alcohol **10a** (Table 1). Cyclization of alkenyl alcohol **10a** with three equivalents of iodine was found to provide highly fused polycyclic compound **9a** in moderate yield along with diastereomeric non-macrocyclic compounds **13a** and **14a** (entry 1). It was revealed that neither reagent amount nor temperature had any significant effect on the product yields and ratios (entries 2–4). This reaction was considered to take place through the initial generation of an iodonium intermediate (shown in brackets) that underwent tetrahydrofuran formation. The tetrahydrofuran-tethered system served as a good molecular scaffold that increased the proximity of the aromatic ring to the oxocarbenium center generated at the lactone acetal, both being suitably positioned for their connection. The importance of the tetrahydrofuran-tethered system for successful cyclization was suggested by the fact that the *O*-acetyl derivative of **10a** gave no detectable macrocycles. It should also be emphasized that not only alkenyl alcohol **10a**, but also **10b** and **10c** similarly underwent the cyclization irrespective of their relative ste-

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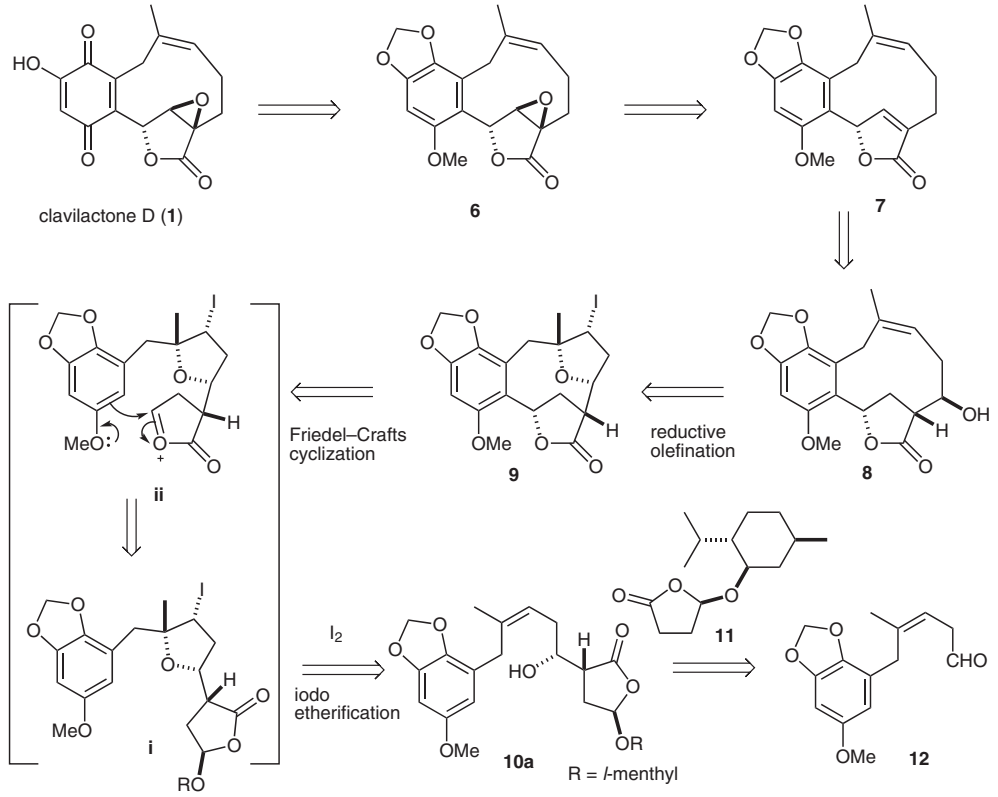
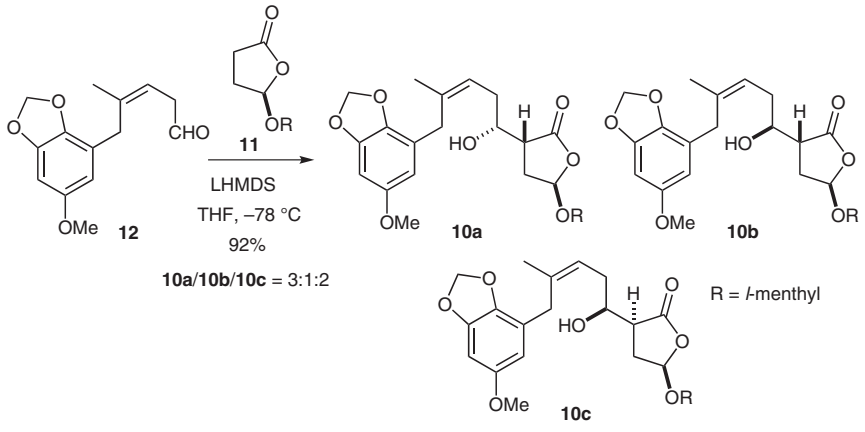


Scheme 1 Retrosynthesis of clavilactone D

reochemistry, giving rise to corresponding polycyclic lactones **9b** (from **10b**) and *ent*-**9a** (from **10c**).

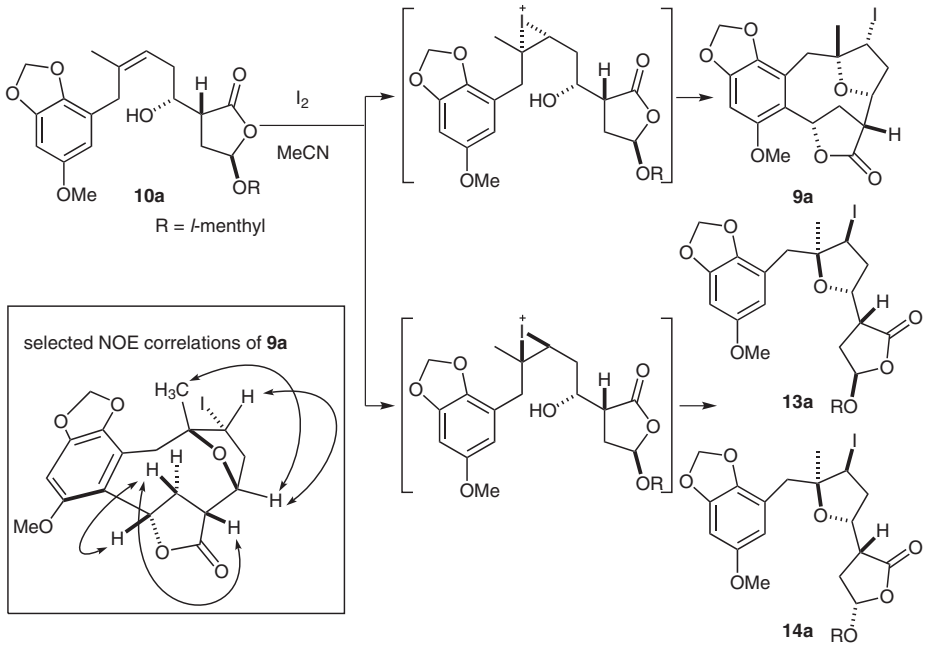
Iodo ether **9a** was then subjected to reductive olefination in the presence of a metal reagent (Scheme 3). Although initial attempts to regenerate the olefin functionality by use of zinc metal led to low selectivity (*Z*/*E* = ca. 1:1), we eventually found that indium metal afforded a high degree of *Z* selectivity (*Z*/*E* = ca. 10:1).[9] The origin of the good selectivity in the latter case is still unclear, although it may be attributed to the steric effect of the large organoindium intermediate that could maintain stereospecificity during the removal of the iodo ether functionality.

The next task was to convert alcohol **8** into butenolide **7** (Scheme 3). We envisaged that it would be readily achieved by β-elimination of the hydroxyl group followed by an olefin isomerization to provide butenolide **7**. However, such attempts were unsuccessful. Therefore, compound **8** was first converted into thionocarbonate **15**,[10] which, by radical reduction with tributyltin hydride, provided lactone **16** in good yield. Enolization of lactone **16** with lithium hexamethyldisilazide, followed by the capture of the resultant enolate with diphenyl disulfide, gave α-thiophenylated lactone **17**. Lactone **17** was then oxidized with sodium periodate to give a sulfoxide, which immediately underwent elimination of thiophenol under gentle heating to afford butenolide **7** quantitatively. The epoxide moiety of the clavilactone core was installed by the reaction of butenolide **7** with *tert*-butyl hydroperoxide



Scheme 2 Synthesis of alkenyl alcohol **10**

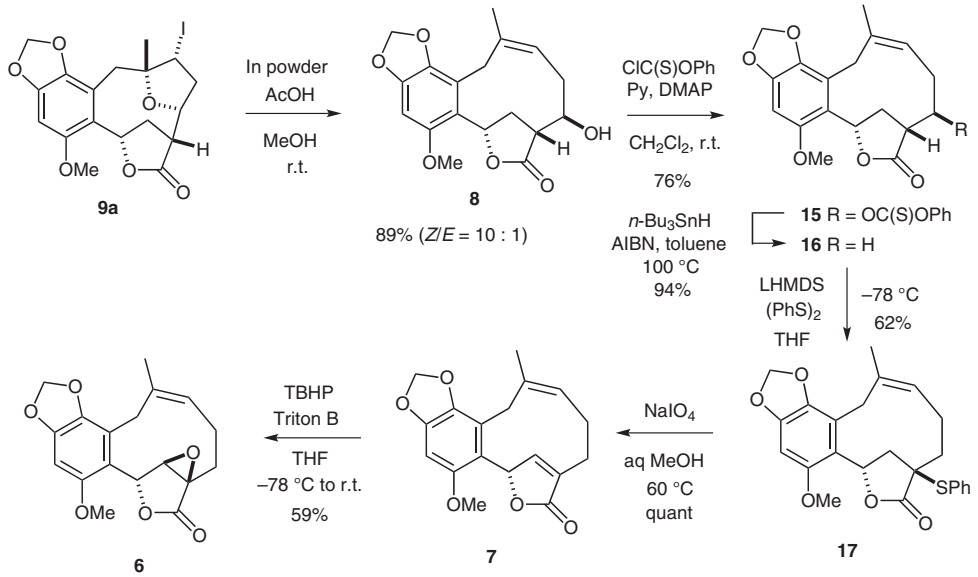
Table 1 'Lariat' Cyclization of Alkenyl Alcohol **10a**



Entry	I_2 (equiv)	Temp	Time (h)	Products (yield, %)
1	3.0	r.t.	1	**9a** (27), **13a** (13), **14a** (8)
2	10.0	r.t.	2.5	**9a** (28), **13a** (12), **14a** (8)
3	3.0	0 °C to r.t.	1.5	**9a** (28), **13a** (11), **14a** (6)
4	1.5	0 °C to r.t.	1.5	**9a** (25), **13a** (10), **14a** (8)

in the presence of Triton B. The epoxidation took place smoothly to furnish compound **6**, a lactone fused with an aromatic ring, which constituted the proposed clavilactone scaffold (Scheme 3).

It was revealed that during the epoxidation reaction under basic conditions, epimerization at the γ-position of the butenolide occurred, which led to a slight decrease in the optical purity of product **6** (ca. 82% ee). However, fortunately, the rigidity of the macrocyclic architecture of butenolide **7** prevented the system from undergoing considerable racemization. Furthermore, the recrystallization of product **6** allowed us to obtain an enantiomerically pure epoxide **6** (100% ee as determined by HPLC analysis). The relative structure of **6** was also confirmed by X-ray



Scheme 3 Synthesis of the clavilactone D core

crystallographic analysis of its racemic crystals,[11] indicating that the epoxidation took place from the β-face, as expected, to furnish the desired relative stereochemistry that matches that proposed for the natural product (Figure 2).[12]

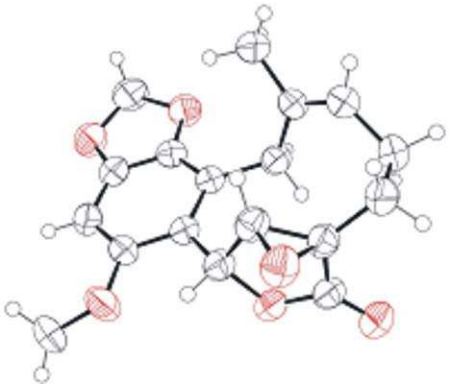


Figure 2 X-ray crystal structure of *rac*-**6**; thermal ellipsoids are shown at the 50% probability level

In conclusion, we have established an asymmetric approach to the clavilactone core. Our route to the core utilized the 'lariat' cyclization of alkenyl alcohol triggered by iodo etherification followed by a Friedel–Crafts-type cyclization. The present versatile route exemplifies a novel concept applicable not only to clavilactones, but also to highly fused macrocyclic natural compounds. Further studies are in progress to accomplish the total synthesis of natural clavilactone D (**1**) and the results will be reported in due course.

Melting points are uncorrected. Chemicals were used as received from commercial suppliers unless otherwise noted. ^{1}H NMR spectra (500, 300, or 270 MHz) and ^{13}C NMR spectra (125, 75, or 67.5 MHz) were measured of samples dissolved in $CDCl_3$ unless otherwise stated. Chemical shifts are reported relative to the internal solvent signal: $CDCl_3$ (δ = 7.26) for ^{1}H NMR and $CDCl_3$ (δ = 77.0) for ^{13}C NMR. The proton signal of TMS (δ = 0.00) was also used in some cases as the internal standard for ^{1}H NMR spectra. FT-IR spectra were recorded for samples loaded on NaCl or KBr. Mass spectra were obtained according to the specified technique. Analytical TLC was performed on Kieselgel 60 F_{254}, and compounds were visualized with UV light, anisaldehyde soln, phosphomolybdic acid in EtOH, I_2, or $KMnO_4$ soln.

(3*R*,5*R*)-3-[(1*R*,3*Z*)-1-Hydroxy-5-(6-methoxy-2*H*-1,3-benzodioxol-4-yl)-4-methylpent-3-en-1-yl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}dihydrofuran-2(3*H*)-one (10a), (3*R*,5*R*)-3-[(1*S*,3*Z*)-1-Hydroxy-5-(6-methoxy-2*H*-1,3-benzodioxol-4-yl)-4-methylpent-3-en-1-yl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}dihydrofuran-2(3*H*)-one (10b), and (3*S*,5*R*)-3-[(1*S*,3*Z*)-1-Hydroxy-5-(6-methoxy-2*H*-1,3-benzodioxol-4-yl)-4-methylpent-3-en-1-yl]-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}dihydrofuran-2(3*H*)-one (10c)

A 1.1 M soln of LHMDS in THF (1.62 mL, 1.78 mmol) was added to a stirred soln of lactone **11** (428 mg, 1.78 mmol) in THF (8 mL) at –78 °C. After 30 min, a soln of aldehyde **12** (442 mg, 1.78 mmol) in THF (8 mL) was added over 20 min, and the mixture was stirred for an additional 40 min. The reaction was quenched with sat. NH_4Cl (50 mL), and the mixture was poured into a separatory funnel where it was partitioned between Et_2O (2 × 20 mL) and brine (10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, E_2O–*n*-hexane, 1:2 to 2:1) to give alcohols **10a**, **10b**, and **10c**, all as colorless oils.

10a

Yield: 390 mg (45%); colorless oil; $[\alpha]_D^{27}$ –69.7 (*c* 3.00, $CHCl_3$).

IR (neat): 3503, 2955, 2924, 1771 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.34 (d, *J* = 2.5 Hz, 1 H), 6.16 (d, *J* = 2.5 Hz, 1 H), 5.87 (s, 2 H), 5.65 (d, *J* = 4.9 Hz, 1 H), 5.39 (t, *J* = 7.3 Hz, 1 H), 3.79 (dt, *J* = 7.7, 4.3 Hz, 1 H), 3.70 (s, 3 H), 3.49 (dt, *J* = 10.7, 4.3 Hz, 1 H), 3.33 (d, *J* = 14.7 Hz, 1 H), 3.24 (d, *J* = 14.7 Hz, 1 H), 2.87 (ddd, *J* = 10.7, 8.9, 7.7 Hz, 1 H), 2.50–2.36 (m, 2 H), 2.19 (dd, *J* = 12.8, 8.9 Hz, 1 H), 2.16–1.98 (m, 3 H), 1.69 (s, 3 H), 1.69–1.60 (m, 2 H), 1.36 (m, 1 H), 1.21 (m, 1 H), 0.93–0.84 (m, 3 H), 0.92 (d, *J* = 6.7 Hz, 3 H), 0.87 (d, *J* = 7.0 Hz, 3 H), 0.75 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.8, 154.9, 147.6, 139.7, 136.0, 121.5, 120.7, 106.0, 100.7, 98.7, 95.1, 77.2, 71.7, 55.9, 47.6, 43.0, 39.7, 34.2, 33.3, 32.8, 31.7, 31.3, 25.4, 23.5, 22.9, 22.2, 20.8, 15.4.

MS (FAB): *m*/*z* (%) = 511 $[M + Na]^+$, 83 (100).

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{40}O_7Na$: 511.2672; found: 511.2678.

10b

Yield: 129 mg (15%); colorless oil; $[\alpha]_D^{27}$ –80.4 (*c* 3.00, $CHCl_3$).

IR (neat): 3495, 2955, 2922, 1771 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.36 (d, *J* = 2.4 Hz, 1 H), 6.14 (d, *J* = 2.4 Hz, 1 H), 5.89 (s, 2 H), 5.67 (d, *J* = 5.7 Hz, 1 H), 5.31 (t, *J* = 7.3 Hz, 1 H), 4.27 (m, 1 H), 3.72 (s, 3 H), 3.51 (dt, *J* = 10.4, 4.0 Hz, 1 H), 3.34 (d, *J* = 14.8 Hz, 1 H), 3.25 (d, *J* = 14.8 Hz, 1 H), 2.91 (ddd, *J* = 10.4, 8.8, 2.8 Hz, 1 H), 2.50 (ddd, *J* = 13.0, 10.4, 5.7 Hz, 1 H), 2.42–1.95 (m, 5 H), 1.72–1.59 (m, 2 H), 1.69 (s, 3 H), 1.41–1.15 (m, 2 H), 1.04–0.78 (m, 3 H), 0.93 (d, *J* = 6.7 Hz, 3 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 0.77 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.9, 154.9, 147.7, 139.6, 136.5, 121.5, 120.5, 106.1, 100.8, 99.1, 95.1, 76.4, 69.0, 55.8, 47.7, 44.2, 39.8, 34.2, 33.9, 31.9, 31.3, 28.7, 25.3, 23.4, 22.9, 22.2, 20.9, 15.5.

MS (FAB): *m*/*z* (%) = 511 $[M + Na]^+$, 83 (100).

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{40}O_7Na$: 511.2672; found: 511.2687.

10c

Yield: 282 mg (32%); colorless oil; $[\alpha]_D^{27}$ –72.2 (*c* 3.50, $CHCl_3$).

IR (neat): 3501, 2953, 2924, 1768 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.35 (d, *J* = 2.4 Hz, 1 H), 6.17 (d, *J* = 2.4 Hz, 1 H), 5.89 (s, 2 H), 5.68 (t, *J* = 5.5 Hz, 1 H), 5.39 (t, *J* = 7.3 Hz, 1 H), 3.93 (m, 1 H), 3.73 (s, 1 H), 3.71 (s, 3 H), 3.55 (dt, *J* = 10.6, 4.2 Hz, 1 H), 3.32 (d, *J* = 14.6 Hz, 1 H), 3.27 (d, *J* = 14.6 Hz, 1 H), 2.72 (dt, *J* = 9.9, 8.9 Hz, 1 H), 2.49 (ddd, *J* = 13.5, 9.9, 5.5 Hz, 1 H), 2.49–2.33 (m, 2 H), 2.17–2.02 (m, 2 H), 1.86 (ddd, *J* = 13.5, 8.9, 5.5 Hz, 1 H), 1.72–1.58 (m, 2 H), 1.70 (s, 3 H), 1.44–1.18 (m, 2 H), 0.94–0.85 (m, 3 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.79 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.2, 154.9, 147.6, 139.7, 135.9, 121.4, 120.7, 105.9, 100.8, 100.0, 95.0, 78.4, 71.7, 55.9, 47.6, 44.8, 39.9, 34.1, 33.0, 32.4, 31.6, 31.3, 25.2, 23.5, 22.6, 22.2, 20.9, 15.5.

MS (FAB): *m*/*z* (%) = 511 $[M + Na]^+$, 83 (100).

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{40}O_7Na$: 511.2672; found: 511.2678.

(2*R*,5*S*,16*R*,17*R*)-17-Iodo-7-methoxy-16-methyl-4,10,12,19-tetraoxapentacyclo[14.2.1.1^{2,5}.0^{6,14}.0^{9,13}]icosa-6,8,13-trien-3-one (9a), (3*R*,5*R*)-3-{(4*S*)-4-Iodo-5-[(6-methoxy-2*H*-1,3-benzodioxol-4-yl)methyl]-5-methyltetrahydrofuran-2-yl}-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}dihydrofuran-2(3*H*)-one (13a) and (3*R*,5*S*)-3-{(4*S*)-4-Iodo-5-[(6-methoxy-2*H*-1,3-benzodioxol-4-yl)methyl]-5-methyltetrahydrofuran-2-yl}-5-{[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}dihydrofuran-2(3*H*)-one (14a); Typical Procedure for Iodine-Mediated 'Lariat' Cyclization (Table 1, entry 3)

I_2 (156 mg, 0.614 mmol) was added to a stirred soln of alcohol **10a** (98.2 mg, 0.201 mmol) in MeCN (1 mL) at 0 °C. After 15 min, the mixture was allowed to warm to r.t. and the stirring was continued for 1 h further. The mixture was poured into a separatory funnel where it was partitioned between Et_2O (20 mL) and a mixture of sat. $NaHCO_3$ and sat. Na_2SO_3 (1:1, 20 mL). The organic extracts were combined, washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, acetone–*n*-hexane, 1:20) to give iodo ether **13a** as a colorless oil and iodo ether **14a** as a colorless oil. Further elution (acetone–*n*-hexane, 1:5) gave iodo ether **9a** as a colorless solid.

9a

Yield: 25.4 mg (28%); colorless needles; mp 203–204 °C (dec) (EtOAc–*n*-hexane); $[\alpha]_D^{25}$ +7.3 (*c* 3.53, $CHCl_3$).

IR (KBr): 2939, 1755 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.49 (s, 1 H), 6.28 (d, *J* = 8.6 Hz, 1 H), 5.91 (d, *J* = 1.2 Hz, 1 H), 5.84 (d, *J* = 1.2 Hz, 1 H), 4.37 (dd, *J* = 15.0, 6.9 Hz, 1 H), 3.99 (dd, *J* = 11.0, 9.2 Hz, 1 H), 3.78 (s, 3 H), 3.21 (d, *J* = 14.5 Hz, 1 H), 3.08 (ddd, *J* = 14.3, 11.0, 7.1 Hz, 1 H), 2.88–2.71 (m, 3 H), 2.59 (d, *J* = 14.5 Hz, 1 H), 2.51 (m, 1 H), 1.15 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.8, 152.3, 146.1, 141.6, 120.4, 119.5, 100.4, 93.1, 82.7, 76.8, 75.3, 56.6, 44.9, 37.3, 34.9, 31.1, 27.6, 22.5.

MS (FAB): *m*/*z* (%) = 459 [M + H]$^+$, 154 (100).

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}O_6I$: 459.0305; found: 459.0298.

13a

Yield: 14.0 mg (11%); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.36 (d, *J* = 2.6 Hz, 1 H), 6.29 (d, *J* = 2.6 Hz, 1 H), 5.87 (s, 1 H), 5.86 (s, 1 H), 5.62 (dd, *J* = 6.0, 2.0 Hz, 1 H), 4.21 (dd, *J* = 11.0, 6.6 Hz, 1 H), 4.15 (ddd, *J* = 11.0, 5.8, 4.0 Hz, 1 H), 3.75 (s, 3 H), 3.51 (dt, *J* = 10.6, 4.4 Hz, 1 H), 3.10 (m, 1 H), 3.08 (d, *J* = 13.5 Hz, 1 H), 2.84 (dt, *J* = 12.2, 11.0 Hz, 1 H), 2.67 (d, *J* = 13.5 Hz, 1 H), 2.51 (ddd, *J* = 12.2, 6.6, 5.8 Hz, 1 H), 2.39 (ddd, *J* = 13.0, 9.2, 6.0 Hz, 1 H), 2.22 (ddd, *J* = 13.0, 9.2, 2.0 Hz, 1 H), 2.16–1.91 (m, 2 H), 1.71–1.57 (m, 3 H), 1.40 (m, 1 H), 1.23 (s, 3 H), 1.01–0.74 (m, 12 H).

14a

Yield: 7.0 mg (6%); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.38 (s, 2 H), 5.874 (s, 1 H), 5.870 (s, 1 H), 5.55 (t, *J* = 5.7 Hz, 1 H), 4.28 (dt, *J* = 9.7, 5.7 Hz, 1 H), 4.25 (dd, *J* = 9.7, 7.1 Hz, 1 H), 3.75 (s, 3 H), 3.41 (dt, *J* = 10.6, 4.2 Hz, 1 H), 3.10 (d, *J* = 13.7 Hz, 1 H), 3.04 (ddd, *J* = 9.4, 8.4, 5.7 Hz, 1 H), 2.73 (d, *J* = 13.7 Hz, 1 H), 2.60 (dt, *J* = 13.0, 9.7 Hz, 1 H), 2.54 (ddd, *J* = 13.7, 9.4, 5.7 Hz, 1 H), 2.22–1.98 (m, 2 H), 2.17 (ddd, *J* = 13.7, 8.4, 5.7 Hz, 1 H), 2.06 (ddd, *J* = 13.0, 7.1, 5.7 Hz, 1 H), 1.68–1.55 (m, 3 H), 1.36 (m, 1 H), 1.22, (s, 3 H), 1.08–0.75 (m, 3 H), 0.92 (d, *J* = 7.0 Hz, 3 H), 0.91 (d, *J* = 6.4 Hz, 3 H), 0.78 (d, *J* = 7.0 Hz, 3 H).

Compounds *ent*-9a and 9b from 10c and 10b

The same protocol was applied to alkenyl alcohols **10b** and **10c**, similarly affording the corresponding polycycles. The spectroscopic data are given below.

(2*S*,5*R*,16*S*,17*S*)-17-Iodo-7-methoxy-16-methyl-4,10,12,19-tetraoxapentacyclo[14.2.1.1^{2,5}.0^{6,14}.0^{9,13}]icosa-6,8,13-trien-3-one (*ent*-9a)

Treatment of **10c** (97.6 mg, 0.200 mmol) by the protocol described above for **10a** afforded iodo ether *ent*-**9a** as a colorless solid.

Yield: 24.3 mg (27%); colorless needles; mp 203–204 °C (dec.) (EtOAc–*n*-hexane); $[\alpha]_D^{22}$ –7.3 (*c* 0.85, $CHCl_3$). The other spectral data of this material were identical with those of lactone **9a**.

(2*R*,5*S*,16*S*,17*S*)-17-Iodo-7-methoxy-16-methyl-4,10,12,19-tetraoxapentacyclo[14.2.1.1^{2,5}.0^{6,14}.0^{9,13}]icosa-6,8,13-trien-3-one (9b) from 10b

Compound **10b** (307 mg, 0.628 mmol) was also transformed into the corresponding iodo ether **9b** by the protocol described above for **10a**.

Yield: 67.8 mg (24%); colorless amorphous; $[\alpha]_D^{26}$ +55.9 (*c* 2.10, $CHCl_3$).

IR (neat): 2934, 1759 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.54 (s, 1 H), 6.33 (d, *J* = 9.8 Hz, 1 H), 5.89 (s, 1 H), 5.87 (s, 1 H), 4.62 (dd, *J* = 9.2, 7.4 Hz, 1 H), 4.06 (dt, *J* = 12.5, 7.2 Hz, 1 H), 3.81 (s, 3 H), 3.28 (d, *J* = 14.7 Hz, 1 H), 2.97 (m, 1 H), 2.89 (d, *J* = 14.7 Hz, 1 H), 2.74 (dt, *J* = 12.5, 7.4 Hz, 1 H), 2.72–2.62 (m, 2 H), 2.35 (dt, *J* = 12.5, 9.2 Hz, 1 H), 1.22 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.2, 156.1, 146.8, 141.3, 118.6, 117.9, 100.4, 94.2, 82.9, 77.7, 77.2, 57.1, 45.7, 39.7, 36.4, 27.9, 23.9, 22.2.

MS (FAB): *m*/*z* (%) = 459 [M + H]$^+$, 154 (100).

HRMS–FAB: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}O_6I$: 459.0305; found: 459.0299.

(1*S*,12*Z*,15*R*,16*R*)-15-Hydroxy-3-methoxy-12-methyl-6,8,18-trioxatetracyclo[14.2.1.0^{2,10}.0^{5,9}]nonadeca-2,4,9,12-tetraen-17-one [(*Z*)-8] and (1*S*,12*E*,15*R*,16*R*)-15-Hydroxy-3-methoxy-12-methyl-6,8,18-trioxatetracyclo[14.2.1.0^{2,10}.0^{5,9}]nonadeca-2,4,9,12-tetraen-17-one [(*E*)-8]

AcOH (3 mL) and In metal (956 mg, 8.34 mmol) were added to a stirred soln of iodo ether **9a** (190 mg, 0.415 mmol) in MeOH (50 mL) at r.t. After 3 h of vigorous stirring of the mixture, sat. $NaHCO_3$ (50 mL) was added and the mixture was filtered through a Celite pad. After concentration of the filtrate under reduced pressure, the residue was extracted with Et_2O (2 × 20 mL) and washed with brine (10 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, EtOAc–*n*-hexane, 1:1) to give *E*-alcohol **8** (9%) as a colorless oil and *Z*-alcohol **8** (89%) as a colorless amorphous.

Alcohol (*Z*)-8

Yield: 123 mg (89%); colorless amorphous; $[\alpha]_D^{23}$ +14.9 (*c* 2.61, $CHCl_3$).

IR (neat): 3420, 2969, 2913, 1744 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, including rotamer): δ = 6.45 (s, 0.6 H), 6.43 (s, 0.4 H), 6.33 (t, *J* = 9.8 Hz, 0.6 H), 6.22, (t, *J* = 9.2 Hz, 0.4 H), 5.92 (s, 1.2 H), 5.90 (s, 0.8 H), 5.48 (t, *J* = 8.0 Hz, 0.4 H), 5.05 (br d, *J* = 8.5 Hz, 0.6 H), 4.57 (m, 0.6 H), 4.41 (t, *J* = 5.5 Hz, 0.4 H), 3.93 (d, *J* = 15.9 Hz, 0.6 H), 3.80 (d, *J* = 14.0 Hz, 0.4 H), 3.73 (s, 1.8 H), 3.72 (s, 1.2 H), 3.40–3.31 (m, 0.4 H), 3.38 (d, *J* = 15.9 Hz, 0.6 H), 3.18 (d, *J* = 14.0 Hz, 0.4 H), 3.08 (ddd, *J* = 9.2, 8.6, 2.4 Hz,

0.6 H), 2.81 (ddd, *J* = 14.1, 9.8, 9.2 Hz, 0.6 H), 2.76–2.63 (m, 1.4 H), 2.45–2.32 (m, 2 H), 1.61 (s, 1.2 H), 1.44 (s, 1.8 H).

^{13}C NMR (125 MHz, $CDCl_3$, rotamer *): δ = 178.2*, 177.3, 154.9, 153.1*, 147.4, 147.2*, 142.4, 142.2*, 138.8*, 137.0, 121.1, 120.8*, 120.6*, 119.8, 118,8*, 116.4, 100.6 (overlapped), 93.9, 93.3*, 74.6*, 72.8, 72.3, 67.9*, 57.3, 57.0*, 47.9*, 46.9, 32.5, 30.4*, 29.7, 28.4*, 27.3*, 22.7, 22.23*, 22.15.

MS (FAB): *m*/*z* (%) = 355 $[M + Na]^+$, 176 (100).

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{20}O_6Na$: 355.1158; found: 355.1159.

Alcohol (*E*)-8

Yield: 11.8 mg (9%); colorless oil; $[\alpha]_D^{26}$ +81.5 (*c* 0.28, $CHCl_3$).

IR (neat): 3428, 3009, 2924, 1748 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.45 (s, 1 H), 6.08 (t, *J* = 9.2 Hz, 1 H), 5.95 (d, *J* = 1.5 Hz, 1 H), 5.88 (d, *J* = 1.5 Hz, 1 H), 5.23 (br d, *J* = 11.6 Hz, 1 H), 4.74 (dt, *J* = 8.8, 2.8 Hz, 1 H), 3.75 (s, 3 H), 3.64 (d, *J* = 13.7 Hz, 1 H), 3.37 (d, *J* = 13.7 Hz, 1 H), 3.04 (ddd, *J* = 10.8, 9.2, 2.8 Hz, 1 H), 2.74 (m, 1 H), 2.46 (ddd, *J* = 13.2, 10.8, 9.2 Hz, 1 H), 2.22 (dt, *J* = 13.0, 8.8 Hz, 1 H), 1.85 (dt, *J* = 13.2, 9.2 Hz, 1 H), 1.37 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.9, 152.9, 146.6, 141.6, 136.8, 121.9, 121.0, 117.3, 100.6, 93.0, 75.0, 70.5, 56.8, 47.7, 36.4, 33.6, 26.2, 15.9.

MS (FAB): *m*/*z* (%) = 333 $[M + H]^+$, 69 (100).

HRMS–FAB: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{21}O_6$: 333.1338; found: 333.1325.

(1*S*,12*Z*,15*R*,16*R*)-3-Methoxy-12-methyl-15-[(phenoxycarbonothioyl)oxy]-6,8,18-trioxatetracyclo[14.2.1.0^{2,10}.0^{5,9}]nonadeca-2(10),3,5(9),12-tetraen-17-one (15)

ClC(S)OPh (102 μL, 0.741 mmol), py (120 μL, 1.48 mmol), and DMAP (90 mg, 0.741 mmol) were added to a stirred soln of alcohol **8** (121 mg, 0.364 mmol) in CH_2Cl_2 (10 mL) at r.t. After 18 h, the mixture was poured into a separatory funnel where it was partitioned between Et_2O (2 × 40 mL) and H_2O (200 mL). The organic extract was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, E_2O–*n*-hexane, 1:2).

Yield: 130 mg (76%); colorless amorphous; $[\alpha]_D^{23}$ +17.7 (*c* 2.14, $CHCl_3$).

IR (neat): 2969, 2940, 1755 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, including rotamer): δ = 7.45–7.10 (m, 5 H), 6.50 (s, 0.6 H), 6.47 (s, 0.4 H), 6.38 (t, *J* = 9.3 Hz, 0.6 H), 6.29 (t, *J* = 9.3 Hz, 0.4 H), 6.02 (m, 0.6 H), 5.95 (s, 1.2 H), 5.91 (s, 0.8 H), 5.81 (br t, *J* = 5.5 Hz, 0.4 H), 5.39 (t, *J* = 8.6 Hz, 0.4 H), 5.13 (br d, *J* = 11.0 Hz, 0.6 H), 4.01 (d, *J* = 15.8 Hz, 0.6 H), 3.90 (m, 0.4 H), 3.85 (d, *J* = 14.6 Hz, 0.4 H), 3.78 (s, 1.8 H), 3.75 (s, 1.2 H), 3.48 (m, 0.6 H), 3.49 (d, *J* = 15.8 Hz, 0.6 H), 3.34 (dt, *J* = 14.1, 9.3 Hz, 0.4 H), 3.26 (d, *J* = 14.6 Hz, 0.4 H), 2.99 (dt, *J* = 14.1, 9.3 Hz, 0.6 H), 2.99–2.71 (m, 2 H), 2.60–2.38 (m, 1 H), 1.65 (s, 1.2 H), 1.52 (s, 1.8 H).

^{13}C NMR (75 MHz, $CDCl_3$, rotamer *): δ = 193.5, 193.4*, 176.5*, 175.1, 155.1 (overlapped), 153.2 (overlapped), 147.6, 147.4*, 142.5, 142.3*, 139.2*, 138.8, 129.5 (overlapped), 126.6 (overlapped), 121.8, 121.7*, 120.8, 120.4*, 120.2*, 118.7*, 118.1, 116.2, 100.7 (overlapped), 94.1, 93.4*, 83.7, 79.6*, 74.4*, 72.5, 57.4, 57.1*, 44.1*, 43.5, 29.9, 28.6*, 28.4, 27.5*, 27.3*, 23.2, 22.3, 22.2*.

MS (FAB): *m*/*z* (%) = 491 $[M + Na]^+$, 176 (100).

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{24}O_7SNa$: 491.1140; found: 491.1145.

(1*S*,12*Z*,16*S*)-3-Methoxy-12-methyl-6,8,18-trioxatetracyclo[14.2.1.0^{2,10}.0^{5,9}]nonadeca-2(10),3,5(9),12-tetraen-17-one (16)

n-Bu_3SnH (131 μL, 0.496 mmol) and AIBN (81.4 mg, 0.496 mmol) were added to a stirred soln of thionoester **15** (75.4 mg, 0.161 mmol) in toluene (5 mL) at r.t. After being heated at 100 °C for 1 h, the mixture was cooled to r.t. and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, acetone–*n*-hexane, 1:10 to 1:3).

Yield: 47.8 mg (94%); colorless amorphous; $[\alpha]_D^{25}$ +74.4 (*c* 0.90, $CHCl_3$).

IR (neat): 2965, 2922, 1759 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, including rotamer): δ = 6.44 (s, 0.3 H), 6.43 (s, 0.7 H), 6.27 (m, 0.3 H), 6.14 (t, *J* = 9.2 Hz, 0.7 H), 5.91 (s, 1.4 H), 5.87 (s, 0.6 H), 5.35 (br s, 0.7 H), 5.13 (br d, *J* = 7.9 Hz, 0.3 H), 3.91 (m, 0.3 H), 3.90 (d, *J* = 14.6 Hz, 0.7 H), 3.74 (s, 0.9 H), 3.72 (s, 2.1 H), 3.40 (d, *J* = 15.9 Hz, 0.3 H), 3.20–2.00 (m, 7 H), 3.15 (d, *J* = 14.6 Hz, 0.7 H), 1.57 (s, 2.1 H), 1.47 (s, 0.9 H).

^{13}C NMR 125 MHz, $CDCl_3$): δ = 180.6*, 180.3, 154.9*, 153.1, 147.2*, 147.0, 142.4*, 142.2, 136.0, 135.4*,126.3, 124.0*, 121.4*, 120.9, 119.3, 117.0*, 100.6 (overlapped), 93.9*, 93.2, 74.0, 71.9*, 57.5*, 57.0, 41.3, 38.7*, 30.9, 29.7*, 28.4*, 28.1, 25.8, 24.6*, 24.3, 23.2*, 21.9, 19.3*.

MS (FAB): *m*/*z* (%) = 339 $[M + Na]^+$, 339 (100).

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{20}O_5Na$: 339.1208; found: 339.1209.

(1*S*,12*Z*,16*R*)-3-Methoxy-12-methyl-16-(phenylsulfanyl)-6,8,18-trioxatetracyclo[14.2.1.0^{2,10}.0^{5,9}]nonadeca-2(10),3,5(9),12-tetraen-17-one (17)

A 1.1 M soln of LiHMDS in THF (316 μL, 0.348 mmol) was added to a stirred soln of lactone **16** (99.1 mg, 0.313 mmol) in THF (3 mL) at –78 °C. After 30 min, a soln of $(PhS)_2$ (75.9 mg, 0.348 mmol) in THF (3 mL) was added over 15 min, and the mixture was stirred at the same temperature for a further 45 min. The reaction was quenched with sat. NH_4Cl (30 mL), and the mixture was poured into a separatory funnel where it was extracted with Et_2O (2 × 20 mL). The organic extract was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, E_2O–*n*-hexane, 1:3 to 1:1).

Yield: 82.5 mg (62%); colorless amorphous; $[\alpha]_D^{25}$ +131.4 (*c* 0.81, $CHCl_3$).

IR (neat): 3007, 2940, 1757 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65–7.37 (m, 5 H), 6.37 (s, 1 H), 5.90 (s, 1 H), 5.86 (s, 1 H), 5.41 (t, *J* = 9.2 Hz, 1 H), 5.33 (t, *J* = 7.3 Hz, 1 H), 3.75 (d, *J* = 14.7 Hz, 1 H), 3.65–3.60 (m, 1 H), 3.61 (s, 3 H), 3.11 (d, *J* = 14.7 Hz, 1 H), 2.52 (br dd, *J* = 14.0, 12.8 Hz, 1 H), 2.33 (dd, *J* = 15.3, 9.2 Hz, 1 H), 2.15 (m, 1 H), 2.11 (ddd, *J* = 14.0, 7.3, 6.7 Hz, 1 H), 1.76 (t, *J* = 12.8 Hz, 1 H), 1.58 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.6, 153.3, 147.2, 142.3, 137.52, 137.45, 130.0, 129.9, 129.0, 125.2, 120.9, 118.5, 100.7, 93.6, 72.4, 57.2, 57.0, 37.8, 32.3, 28.2, 25.0, 22.0.

MS (FAB): *m*/*z* (%) = 447 $[M + Na]^+$, 154 (100).

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{24}O_5SNa$: 447.1242; found: 447.1240.

(1*S*,12*Z*)-3-Methoxy-12-methyl-6,8,18-trioxatetracyclo[14.2.1.0^{2,10}.0^{5,9}]nonadeca-2(10),3,5(9),12,16(19)-pentaen-17-one (7)

A soln of $NaIO_4$ (20.4 mg, 0.0954 mmol) in H_2O (0.5 mL) was added to a stirred soln of sulfide **17** (13.8 mg, 0.0325 mmol) in MeOH (5 mL) at r.t. Then the mixture was heated at 60 °C for 17 h. After concentration of the mixture under reduced pressure, the residue

was extracted with Et_2O (2 × 20 mL), the mixture was washed with H_2O (70 mL) and brine (10 mL), and the Et_2O fraction was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, EtOAc–*n*-hexane, 1:5). The HPLC analysis of **7** revealed that during this oxidation process no racemization had occurred.

Yield: 10.2 mg (quant); colorless amorphous; $[\alpha]_D^{25}$ +61.5 (*c* 0.18, $CHCl_3$).

IR (neat): 2963, 2938, 1749 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.75 (s, 1 H), 6.74 (s, 1 H), 6.50 (s, 1 H), 5.93 (d, *J* = 1.4 Hz, 1 H), 5.88 (d, *J* = 1.4 Hz, 1 H), 5.14 (dd, *J* = 9.8, 7.2 Hz, 1 H), 3.82 (s, 3 H), 3.02 (d, *J* = 14.7 Hz, 1 H), 2.82 (m, 1 H), 2.71 (d, *J* = 14.7 Hz, 1 H), 2.24 (ddt, *J* = 12.8, 7.2, 3.2 Hz, 1 H), 1.97 (ddt, *J* = 12.8, 9.8, 2.6 Hz, 1 H), 1.86 (ddd, *J* = 12.8, 12.0, 3.2 Hz, 1 H), 1.59 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9, 154.4, 149.7, 147.9, 142.3, 138.7, 129.1, 121.6, 121.4, 111.2, 100.8, 93.9, 76.2, 57.4, 28.2, 25.1, 24.7, 22.1.

MS (FAB): *m*/*z* (%) = 337 $[M + Na]^+$, 314 (100).

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{18}O_5Na$: 337.1052; found: 337.1064.

(1*R*,4*Z*,16*R*,17*R*)-14-Methoxy-5-methyl-9,11,18,20-tetraoxapentacyclo[14.2.2.2.0^{1,17}.0^{7,15}.0^{8,12}]icosa-4,7(15),8(12),13-tetraen-19-one (6)

A 5.5 M aq soln of TBHP (43 μL, 0.239 mmol) followed by a 40% soln of Triton B in MeOH (50 μL, 0.119 mmol) were added to a stirred soln of butenolide **7** (24.1 mg, 0.767 mmol) in THF (2 mL) at –78 °C. Then the mixture was allowed to warm to r.t. over 1 h, and the stirring was continued for an additional 2 h. Sat. NH_4Cl (10 mL) and sat. Na_2SO_3 (10 mL) were added and the mixture was extracted with Et_2O (2 × 10 mL). The organic extract was washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2–*n*-hexane, 3:1); this gave epoxide **6** as a colorless solid; recrystallization (CH_2Cl_2–Et_2O) gave colorless plates.

Yield (colorless solid): 15.0 mg (59%); mp (colorless plates) 167–168 °C (CH_2Cl_2–Et_2O); $[\alpha]_D^{24}$ +87.2 (*c* 0.46, $CHCl_3$).

IR (neat): 2963, 2922, 1770 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.50 (s, 1 H), 6.28 (s, 1 H), 5.98 (s, 1 H), 5.91 (s, 1 H), 5.29 (t, *J* = 8.3 Hz, 1 H), 3.92 (s, 1 H), 3.79 (s, 3 H), 3.30 (d, *J* = 15.3 Hz, 1 H), 3.19 (d, *J* = 15.3 Hz, 1 H), 2.72 (dd, *J* = 13.4, 2.1 Hz, 1 H), 2.46 (dddd, *J* = 14.2, 12.8, 8.3, 2.1 Hz, 1 H), 2.19 (m, 1 H), 1.56 (s, 3 H), 1.25 (ddd, *J* = 14.2, 13.4, 2.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.2, 154.7, 148.3, 142.0, 136.6, 122.7, 121.7, 133.2, 101.0, 93.6, 74.9, 63.7, 61.5, 57.1, 28.6, 25.1, 22.6, 21.7.

MS (FAB): *m*/*z* (%) = 353 $[M + Na]^+$, 176 (100).

HRMS–FAB: *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{18}O_6Na$: 353.1001; found: 353.1008.

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