Syntheses of naturally occurring cytotoxic [7.7]paracyclophanes, (−)-cylindrocyclophane A and its enantiomer, and implications for biological activity†

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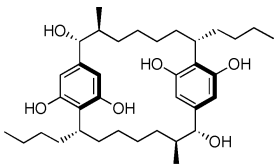
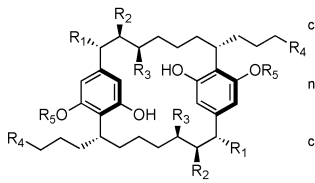
The total syntheses of (−)-cylindrocyclophane A (**1**), a naturally occurring, cytotoxic [7.7]paracyclophane, and its enantiomer have been achieved in an enantiodivergent manner starting from a chiral propargyl alcohol building block using Smith's cross metathesis/ring-closing metathesis protocol as the key step. The biological evaluation of both enantiomers of cylindrocyclophane A (**1** and ***ent*-1**) and its analogues indicated that the chirality of **1** is irrelevant to its cytotoxicity, which is attributed to the resorcinol motifs embedded in the robust [7.7]paracyclophane framework.

Introduction

Since their introduction by Cram and Steinberg in 1951[1], the bridged class of aromatic compounds, widely referred to as cyclophanes, have been inspiring chemists to imagine advanced molecules with novel functions.[2] In the 1990s, the first naturally occurring [m.n]paracyclophanes, namely, cylindrocyclophanes[3] and nostocyclophanes[4], were isolated from extracts of terrestrial blue-green algae, belonging to *Cylindrospermum licheniforme* Kützing and *Nostoc linckia* Roth (Bornet), respectively (Fig. 1). Their unprecedented 22-membered, C_2-symmetric [7.7]paracyclophane structures were unambiguously elucidated on the basis of extensive NMR studies in conjunction with CD spectroscopy and X-ray crystallography.[5] In addition to their novel structures, cylindrocyclophanes and nostocyclophanes were found to exhibit cytotoxicity against the KB and LoVo tumor cell lines at IC_{50} values of 2–10 μg/mL.[3,4]



(−)-cylindrocyclophane A (**1**)



cylindrocyclophanes : R_1 = OH or OAc or H; R_2 = Me R_3 = H; R_4 = Me R_5 = H

nostocyclophanes : R_1 = OH or OMe; R_2 = H R_3 = Cl; R_4 = Me R_5 = H or Glu

carbamidocyclophane[9] : R_1 = $OCONH_2$; R_2 = Me R_3 = H; R_4 = Me or CH_2Cl or $CHCl_2$; R_5 = H

Fig. 1 Naturally occurring [7.7]paracyclophanes.

Their unique architectures have necessarily attracted considerable attention from the synthetic community and spurred intense studies on the construction of chirally modified, C_2-symmetric cyclophanes that have culminated in several elegant total syntheses.[6] Meanwhile, little is known about the molecular basis of the cytotoxicity of these naturally occurring [7.7]paracyclophanes.

We took an interest in these natural products in view of them being structural hybrids of [7.7]paracyclophane and 2,5-dialkylresorcinol; the latter motif has attracted attention owing to its wide range of biological activities, including fungicidal, bacteriocidal, and cytotoxic activities.[7,8] To gain insight into the cytotoxic origin of these chirally modified [7.7]paracyclophanes, we envisioned a preliminary SAR study of cylindrocyclophane A based on its enantiocontrolled total synthesis.

We describe herein the expedient, enantiocontrolled total syntheses of both enantiomers of cylindrocyclophane A (**1** and ***ent*-1**) starting from a tartrate-derived, chiral propargyl alcohol building block, and the evaluations of cytotoxicity thereof.

Synthesis plan and SAR panel of cylindrocyclophane A

Considering the synthetic reliability and design of the SAR panel, we decided to follow Smith's protocol employing a tandem cross metathesis/ring-closing metathesis (CM/RCM) of the diolefin **4** for the construction of the [7.7]paracyclophane framework (Scheme 1).[6b–d] Thus, it was envisioned that biological evaluations of a set of synthetic samples, including natural and unnatural cylindrocyclophane A, the half-sized analogue **2**, and tetramethylate **3**, would lead us to identify toxicophore structures.

To acquire both enantiomers of Smith's diolefin **4**, we intended to use **5** as the common chiral intermediate, which is a logical product of the Johnson–Claisen rearrangement of **6**. The bottom-arm portions of **4** would be prepared in an enantiodivergent manner *via* two conventional sets of manipulations. Thus, the conversion of the ethoxycarbonylmethyl moiety of **5** to either a

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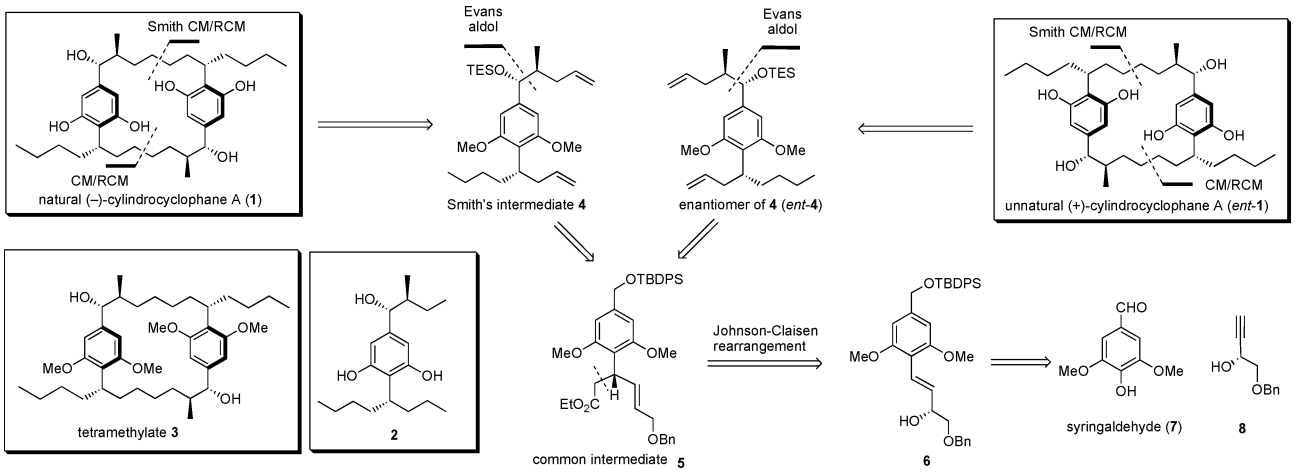
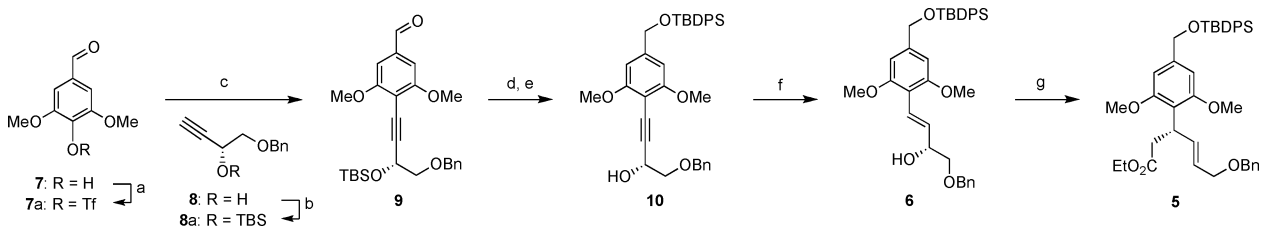
† Electronic supplementary information (ESI) available: Synthetic methods and compound data; ^{1}H- and ^{13}C-NMR spectra. See DOI: 10.1039/b909646a



Scheme 1 Retrosynthetic analysis and intended SAR items.



Scheme 2 Synthesis of the common intermediate **5**. *Reagents and conditions*: a) Tf_2O, pyridine, CH_2Cl_2, 92%; b) TBSCl, imidazole, DMF, 96%; c) $PdCl_2(PPh_3)_2$, CuI, PPh_3, K_2CO_3, Bu_4NI, THP, 70 °C, 78%; d) (i) $NaBH_4$, MeOH; (ii) TBAF, AcOH, THF, 96%; e) TBDPSCl, NEt_3, DMAP, CH_2Cl_2, 77%; f) LAH, THF, 86%; g) $CH_3C(OEt)_3$, cat. *o*-NO_2PhOH, 140 °C, 72%.

butyl or allyl group, and of the allyl ether moiety to either an allyl or butyl group, will establish enantiodivergent routes to the 4-(oct-1-enyl) appendant of **4**. As for the upper-arm portions of **4**, we assigned the Evans asymmetric aldolization as a pivotal reaction for the enantiodivergent installation of contiguous hydroxy and methyl groups. The intermediate **6** could be synthesized from syringaldehyde (**7**) and chiral acetylene **8** *via* the Sonogashira coupling reaction[10] followed by stereoselective reduction of the alkyne moiety (Scheme 1).

Results and discussion

Synthesis of common intermediate 7

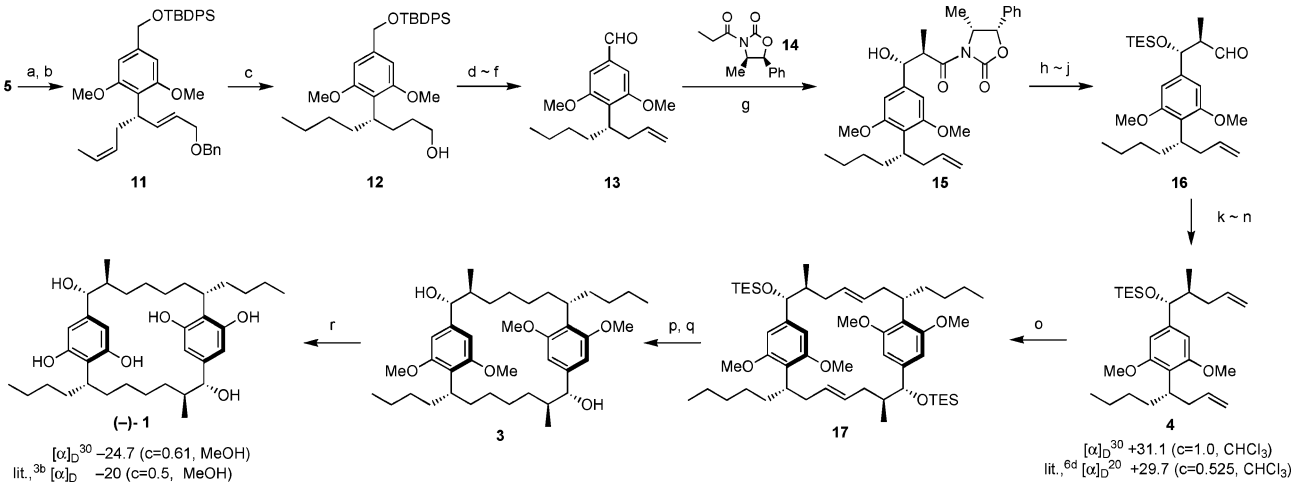
The synthesis of the common chiral platform **5** began by triflating commercially available **7** to give the triflate **7a** (Scheme 2). The propargyl alcohol **8**, which was prepared from L-diethyl tartrate in accordance with the literature,[11] was equipped with a TBS group. The resulting **8a** was subjected to Sonogashira coupling[10] with **7a** using cat. $PdCl_2(PPh_3)_2$ and CuI in the presence of PPh_3, K_2CO_3, and Bu_4NI in boiling tetrahydropyran (THP)[12] to give the aldehyde **9** in 78% yield[12,13] with an enantiomeric excess >99% ee. To set the stage for the projected Johnson–Claisen rearrangement, **9** was sequentially subjected to $NaBH_4$ reduction, desilylation, and selective TBDPS protection of the primary hydroxy group to give **10** in 74% yield. **10** was then reduced in a diastereocontrolled manner using $LiAlH_4$ in THF to furnish *E*-alkene **6** in 86% yield. Upon heating in triethyl orthoacetate in the presence of a catalytic amount of *o*-nitrophenol,[14] **6** furnished the γ,δ-unsaturated ester **5** in 72% yield with a high enantiomeric excess (>99% ee), which was determined by HPLC (Scheme 2). It is worth commenting that when pivalic acid was used as a promoter, pivalate was produced as the by-product, supporting the advantageous use of *o*-nitrophenol as the catalyst.

Synthesis of natural (–)-cylindrocyclophane A

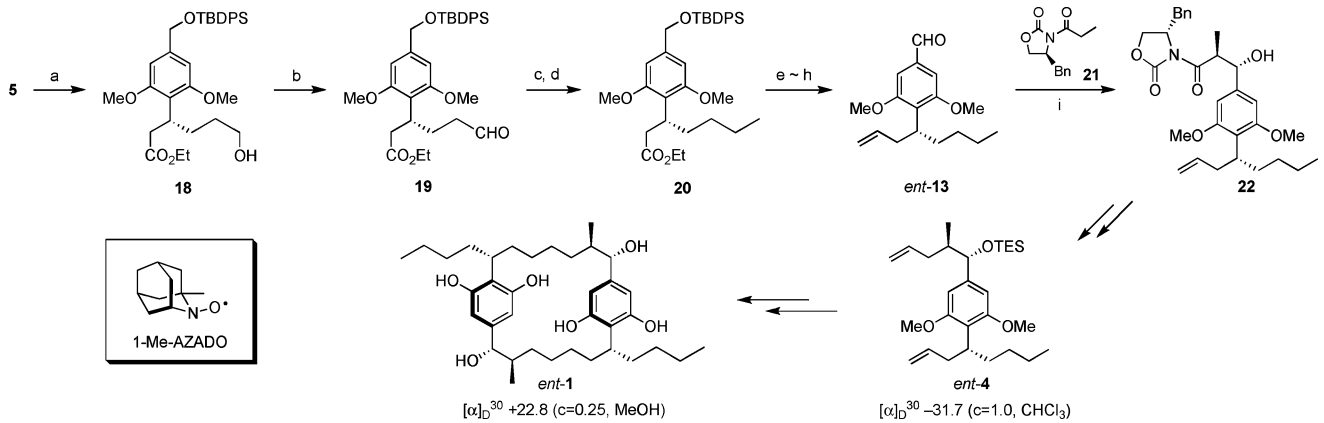
Having secured the chiral building block **5**, our focus moved to tailoring the alkyl terminus as in Smith's intermediate (+)-**4** (Scheme 3). To this end, the ester **5** was partially reduced with DIBAL, and the aldehyde generated was subjected to the Wittig reaction using ethylidenetriphenylphosphorane to give **11** in 97% yield.

After considerable experimentation, a stepwise hydrogenation of the olefins with catalytic Pd/C and hydrogenolysis[15] of the benzyl ether with catalytic $Pd(OH)_2$ was confirmed to be essential for procuring the alcohol **12**: all the attempted one-step reductions were thwarted by the production of a considerable amount of unidentifiable compounds.

The dehydration of the alcohol **12** employing the method of Grieco *et al.*[16] was followed by desilylation and MnO_2-mediated oxidation to afford **13**, the projected substrate for the Evans aldol reaction. The diastereoselective aldol reaction[17] between the enol borinate of the oxazolidinone **14** and **13** afforded the desired **15** in 97% yield and >99% de. The TES protection of the secondary hydroxy group, the formation of the Weinreb amide, and the following treatment with DIBAL liberated the aldehyde **16**. Upon successive Horner–Wadsworth–Emmons reaction, the 1,4-reduction of the α,β-unsaturated ester, LAH reduction, and Grieco dehydration,[16] **16** furnished the known diolefin **4**.[6b–d]



Scheme 3 Total synthesis of (–)-cylindrocyclophane A (**1**). *Reagents and conditions*: a) DIBAL, toluene, –78 °C, 86%; b) $Ph_3P^+EtI^-$, KHMDS, THF, 97%; c) H_2, Pd/C, THP; $Pd(OH)_2$, 94%; d) *o*-NO_2PhSeCN, PBu_3, THF; H_2O_2, THF, 94%; e) TBAF, THF, 99%; f) MnO_2, CH_2Cl_2, 97%; g) NEt_3, Bu_2BOTf, CH_2Cl_2, –78 °C, 97%; h) HN(OMe)Me·HCl, Me_3Al, THF, –15 °C, 91%; i) TESCl, imidazole, DMF, 99%; j) DIBAL, toluene, –78 °C, 96%; k) $EtO_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C, 94%; l) Mg, MeOH, 0 °C, 98%; m) LAH, THF, 0 °C, 91%; n) *o*-NO_2PhSeCN, PBu_3, THF; H_2O_2, THF (93%); o) Grubbs 2nd, DCE, 80 °C, 40%; p) TBAF, THF, 74%; q) H_2, PtO_2, EtOH, 99%; r) PhSH, K_2CO_3, NMP, sealed tube, 215 °C, 85%.



Scheme 4 Total synthesis of (+)-cylindrocyclophane A (***ent*-1**). *Reagents and conditions*: a) H_2, Pd/C, $Pd(OH)_2$, THP, 99%; b) 1-Me-AZADO, BAIB, CH_2Cl_2, 87%; c) $Ph_3P^+MeBr^-$, KHMDS, THF, 84%; d) H_2, Pd/C, AcOEt, 98%; e) DIBAL, toluene, 99%; f) $Ph_3P^+MeBr^-$, KHMDS, THF, 84%; g) TBAF, THF, 99%; h) MnO_2, CH_2Cl_2, 97%; i) NEt_3, Bu_2BOTf, CH_2Cl_2, –78 °C, 83%.

The crucial CM/RCM reaction constructing the [7.7]paracyclophane framework was experimented on by following Smith *et al.*'s procedures.[6b–d] The dimerization of **5** proceeded best using Grubbs 2nd-generation catalyst in boiling dichloroethane to give **17** in 40% yield. The deprotection of the TES ether with TBAF, followed by hydrogenation with PtO_2 afforded the tetramethylate **3**. Finally, the treatment of **3** with PhSH and K_2CO_3 in NMP at 215 °C gave clean demethylation to furnish (–)-cylindrocyclophane A (**1**). The ^{1}H- and ^{13}C-NMR spectral data of synthetic **1** were identical to those reported by Smith *et al.*[6b–d] and Hoye *et al.*[6e]

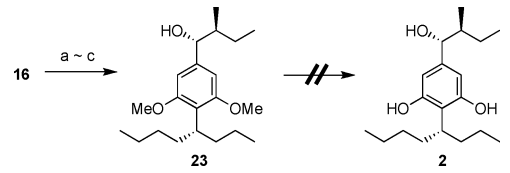
Synthesis of unnatural (+)-cylindrocyclophane A

The synthesis of unnatural (+)-cylindrocyclophane A (***ent*-1**) began with the transformation of the allyl ether moiety of **5** into a butyl group (Scheme 4). Thus, **5** was subjected to a sequential hydrogenation/hydrogenolysis to give the alcohol **18**. Upon treatment with a catalytic amount of 1-Me-AZADO[18] in the presence of 1.1 equivalent of $PhI(OAc)_2$ in CH_2Cl_2, **18** was cleanly oxidized to give the corresponding aldehyde in 87% yield. The subjection of **19** to Wittig methylenation followed by hydrogenation gave the ester **20**. Next, the ethoxycarbonylmethyl appendage was transformed into an allyl group in a conventional two-step operation entailing the partial reduction of **20** with DIBAL and the following Wittig reaction. Desilylation and MnO_2-mediated oxidation furnished ***ent*-13**, on which the same set of operations, except the use of the oxazolidinone **21** in the aldolization, was performed as described for the synthesis of **1**, and furnished (+)-cylindrocyclophane A (***ent*-1**). All the spectral data of ***ent*-1** were identical to those of **1** and the absolute value of optical rotation was identical but in an opposite sense to that of (–)-cylindrocyclophane A (**1**).

Synthesis of a half-sized analogue

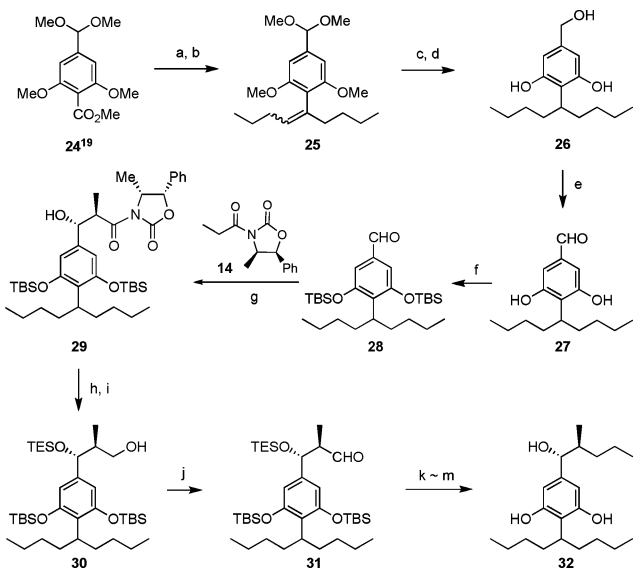
The acquisition of the projected half-sized analogue **2** from the intermediate **16** was unexpectedly hampered by the methyl groups that had been charged with protecting the resorcinol moiety: all

attempts, including the use of Smith's conditions that enabled the acquisition of **1** from **3**, resulted in an intractable decomposition of **2** (Scheme 5).



Scheme 5 Attempted synthesis of the half-sized analogue **2**. *Reagents and conditions*: a) $Ph_3P^+MeBr^-$, KHMDS, THF, 99%; b) H_2, PtO_2, EtOH, 99%; c) TBAF, THF, 88%.

Revisions, therefore, were made to the synthesis plan: (a) switching the protective groups; (b) removing the stereogenic center by adding an extra carbon to **2** to save synthetic steps, thereby revealing the new target **32** (Scheme 6). To this end, the ester **24**[19] was converted to **25** *via* double alkylation using butyllithium followed by dehydration. A straightforward sequence entailing hydrogenation, the hydrolytic deprotection of the dimethyl acetal, $LiAlH_4$ reduction, and BBr_3-mediated demethylation allowed us to transform **25** into **26** in 26% yield.[20] The oxidation of the benzyl alcohol **26** to the corresponding aldehyde failed owing to damage of the resorcinol portions. However, it was found that $TEMPO^+ \cdot Cl^-$ allowed the transformation in 69% yield,[21] where MnO_2 oxidation resulted in 27% yield. Upon bis-TBS protection, and Evans aldolization using **14**, **28** afforded **29** in 97% yield. After the protection of the secondary hydroxy group with the TES group, the chiral auxiliary was detached reductively using



Scheme 6 Synthesis of the half-sized analogue **32**. *Reagents and conditions*: a) BuLi, THF, −78 °C, 66%; b) $CH(OMe)_3$, *c.* HCl, MeOH, −78 °C, *E*:*Z* = 2.2:1; c) (i) H_2, Pd/C, AcOEt; (ii) AcOH, H_2O, reflux; (iii) LAH, THF, 0 °C, 52%; d) BBr_3, CH_2Cl_2, −78 °C; 10% aq. NaOH, 51%; e) $TEMPO^+Cl^-$, CH_2Cl_2, 69%; f) TBSCl, imidazole, CH_2Cl_2, 80%; g) NEt_3, Bu_2BOTf, CH_2Cl_2, −78 °C, 97%; h) TESCl, imidazole, DMF, 99%; i) $LiBH_4$, THF, 88%; j) 1-Me-AZADO, BAIB, CH_2Cl_2, 70%; k) $Ph_3P^+EtI^-$, *n*-BuLi, THF, −78 °C, 72%; l) H_2, Pd/C, AcOEt, 94%; m) TBAF, THF, 84%.

Table 1 Cell growth inhibitions against HCT116

compound	GI_{50} (μM)
(−) cylindrocyclophane A (**1**)	2
(+) cylindrocyclophane A (***ent*-1**)	2
tetramethylate **3**	> 50
half-sized **32**	20

$LiBH_4$ to give the alcohol **30**.[22] 1-Me-AZADO[18] catalyzed oxidation, Wittig reaction with ethylidenetriphenylphosphorane, and hydrogenation of the resulting alkene, followed by global deprotection completed the construction of the half-sized analogue **32** (Scheme 6).

Evaluation of biological activities

Both enantiomers of cylindrocyclophane A, tetramethylate **3**, and the half-sized analogue **32** were evaluated for tumor cell growth inhibitory activity against the human colon cancer cell line HCT-116 (Table 1).[23] From the cell growth inhibition assay, (i) synthetic (−)-cylindrocyclophane A (**1**) exhibited activity (GI_{50} = 2 μM) comparable to the reported cytotoxicity of natural **1** against KB and LoVo tumor cell lines[3]; (ii) (+)-cylindrocyclophane A (***ent*-1**) exhibited cell growth inhibition at almost the same level as that of (−)-cylindrocyclophane A (**1**); (iii) the half-sized analogue **32** which has the 2,5-dialkylresorcinol motif of **1**, showed a decreased cell growth inhibition level; (iv) the cylindrocyclophane A tetramethylate **3** showed no cell growth inhibition. Taken together, these results indicated that: (a) 2,5-dialkylresorcinol functionality is essential for eliciting the cytotoxicity; (b) the [7.7]paracyclophane framework enhances the potency of the resorcinol toxicophore; (c) chirality is irrelevant to the cytotoxicity, implying that cylindrocyclophane A elicits its toxicity through actions in biological spaces where chirality plays no dominant roles.

Conclusions

We have demonstrated an enantiodivergent synthesis of natural and unnatural cylindrocyclophane A's, by adopting Smith's CM/RCM protocol. Both enantiomers of Smith's diolefin **4** were accessed from a common intermediate, which was readily synthesized from the commercially available L-diethyl tartrate and syringaldehyde.

The cytotoxic activities of both enantiomers of cylindrocyclophane A and its analogues **3** and **32** indicated that the toxicophore of cylindrocyclophane A is attributed to the resorcinol portion and that the paracyclophane structure is auxiliary. This information would be helpful for future development of [m.n]paracyclophane-based molecular tools in biological systems.

Experimental

General

All reactions were carried out under an atmosphere of argon unless otherwise specified. Anhydrous solvents were transferred *via* syringe to flame-dried glassware, which had been cooled under

a stream of dry nitrogen. Ethereal solvents and dichloromethane (anhydrous; Kanto Chemical Co., Inc) were used as received. All other solvents were dried and distilled by standard procedures. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials unless otherwise stated. Reagents were purchased at highest commercial quality and used without further purification unless otherwise stated.

Reaction were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as visualizing agent and *p*-anisaldehyde in ethanol/aqueous H_2SO_4/CH_3CO_2H for staining. Column chromatography was performed using silica gel 60 particle size 0.063–0.210 mm. The eluents employed are reported as volume/volume.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using JEOL JMN-AL400 (400 MHz), and JEOL JNM-ECP-500 (500 MHz) spectrometers. Chemical shift (δ) is reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS). Coupling constants (J) are reported in Hz. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using JEOL JMN-AL400 (100 MHz) and JEOL JNM-ECP-500 (125 MHz) spectrometers. Chemical shift is reported in ppm relative to the center of $CDCl_3$ or CD_3OD.

Melting point were determined using Yazawa BY-2 melting point apparatus and are reported uncorrected. Infrared spectra were obtained on a JASCO *FT/IR*-410 Fourier Transform Infrared Spectrophotometer at 4.0 cm^{-1} resolution and are reported in wavenumbers. Low and high resolution mass spectra were recorded on a JEOL JMS-DX303 or a JMS-700 using electron impact (EI). FAB mass spectra were recorded on a JEOL-JMS700 spectrometer using 3-nitrobenzyl alcohol as a matrix. Optical rotations were measured on a JASCO DIP-370 Digital Polarimeter using the sodium D line.

Synthesis of (–)-cylindrocyclophane A

(*R*)-4-(4-Benzyloxy-3-*tert*-butyldimethylsilyloxybut-1-ynyl)-3,5-dimethoxybenzaldehyde 9. The triflate **7a** (500 mg, 1.6 mmol), $(PPh_3)_2PdCl_2$ (111 mg, 0.16 mmol), PPh_3 (125 mg, 0.48 mmol), Bu_4NI (1.2 g, 3.2 mmol), K_2CO_3 (660 mg, 4.8 mmol) and CuI (91 mg, 0.48 mmol) were charged in a 2-necked, round-bottomed 50 mL flask equipped with a rubber septum and a condenser. To the flask was introduced a degassed solution of the propargyl ether **8a** (600 mg, 2.1 mmol) in tetrahydropyran (16 mL). The mixture was heated at 70 °C for 18 h. After cooling to room temperature, the mixture was filtered through a pad of Celite and the Celite layer was washed with Et_2O. The combined filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 1/4) to give **9** (565 mg, 78% yield) as a red oil; $[\alpha]_D^{30}$ –35.0 (*c* 1.13, $CHCl_3$); FT-IR (neat) ν 1698, 1574, 1462, 1230, 1130 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.91 (1H, s), 7.39–7.25 (5H, m), 7.01 (2H, s), 4.91 (1H, dd, J = 7.0, 5.0 Hz), 4.70 (2H, s), 3.89 (6H, s), 3.75 (1H, dd, J = 10.2, 5.0 Hz), 3.70 (1H, ddd, J = 10.2, 7.0, 2.8 Hz), 0.96 (9H, s), 0.22 (3H, s), 0.19 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 191.2, 138.4, 136.6, 128.2, 127.5, 127.4, 107.5, 104.3, 100.7, 76.7, 74.5, 73.4, 63.9, 56.1, 25.9, 18.4, –4.6, –4.9; MS (FAB) m/z 453 [(M-H)$^+$], 91 (100%); HRMS (FAB) m/z calcd for $C_{36}H_{33}O_5Si$ [(M-H)$^+$]: 453.6229, found: 453.2029.

(*R*)-1-Benzyloxy-4-(4-hydroxymethyl-2,6-dimethoxyphenyl)-but-3-yn-2-ol. To a solution of **9** (200 mg, 0.44 mmol) in MeOH (2.2 mL) was added $NaBH_4$ (10 mg, 0.26 mmol) at 0 °C and the mixture was stirred for 1 h. The reaction mixture was quenched with 1% aqueous HCl (2.2 mL) and MeOH was evaporated under reduced pressure. The residue was extracted AcOEt and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in THF (2.2 mL) and then, acetic acid (0.05 mL, 0.88 mol) and TBAF (1M in THF, 0.88 mL, 0.88 mmol) were added at 0 °C. The reaction mixture was stirred for 30 h at room temperature and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 4/1) to give the diol (146 mg, 96% yield) as a yellow oil; $[\alpha]_D^{33}$ +5.7 (*c* 0.96, $CHCl_3$); FT-IR (neat) ν 3376, 1574, 1459, 1416, 1126 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39–7.26 (5H, m), 6.48 (2H, s), 4.87 (1H, dd, J = 7.0, 3.9 Hz), 4.70 (1H, d, J = 12.1 Hz), 4.65 (1H, d, J = 12.1 Hz), 4.64 (2H, s), 3.80 (6H, s), 3.79 (1H, ddd, J = 10.0, 3.9, 1.0 Hz), 3.72 (1H, ddd, J = 10.0, 7.0, 0.9 Hz), 3.01 (1H, brs), 2.30 (1H, brs); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.5, 143.6, 137.9, 128.4, 127.7, 127.6, 101.7, 995, 95.3, 76.7, 73.8, 73.4, 65.2, 62.6, 55.9; MS (EI) m/z 342 (M$^+$), 221 (100%); HRMS (EI) m/z calcd for $C_{20}H_{22}O_5$ (M$^+$): 342.1467, found: 342.1477.

(*R*)-1-Benzyloxy-4-(4-*tert*-butyldiphenylsilyloxymethyl-2,6-dimethoxyphenyl) but-3-yn-2-ol 10. To a solution of the diol (108 mg, 0.31 mmol) in CH_2Cl_2 (1.6 mL) was added TBDPSCl (0.081 mL, 0.31 mmol), followed by Et_3N (0.087 mL, 0.63 mmol) and DMAP (7 mg, 0.063 mmol) at 0 °C. The mixture was stirred for 1 h and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 1/2) to give **10** (140 mg, 77% yield) as a colorless amorphous solid; $[\alpha]_D^{29}$ +4.9 (*c* 1.02, $CHCl_3$); FT-IR (neat) ν 3452, 1574, 1461, 1416, 1230, 1128 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.68–7.66 (4H, m), 7.45–7.27 (11H, m), 6.50 (2H, s), 4.89 (1H, dd, J = 7.3, 3.7 Hz), 4.87 (2H, s), 4.72 (1H, d, J = 12.1 Hz), 4.66 (1H, d, J = 12.1 Hz), 3.82 (1H, dd, J = 9.9, 3.7 Hz), 3.79 (6H, s), 3.74 (1H, dd, J = 9.9, 7.3 Hz), 2.66 (1H, brs), 1.10 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.5, 143.5, 138.0, 135.5, 133.3, 129.8, 128.4, 127.8, 127.7, 127.6, 100.9, 98.9, 94.8, 76.7, 73.9, 73.4, 65.5, 62.7, 55.9, 26.8, 19.3; MS (EI) m/z 580 (M$^+$), 523 (100%); HRMS (EI) m/z calcd for $C_{36}H_{40}O_5Si$ (M$^+$): 580.2645, found: 580.2631.

(*R*,*E*)-1-Benzyloxy-4-(4-*tert*-butyldiphenylsilyloxymethyl-2,6-dimethoxyphenyl) but-3-en-2-ol 6. To a solution of **10** (130 mg, 0.22 mmol) in THF (1.1 mL) was added LAH (10 mg, 0.27 mmol) at 0 °C. After stirring for 3 h at room temperature, another portion of LAH (10 mg, 0.27 mmol) was added at 0 °C. The reaction mixture was stirred for 3 h at room temperature and quenched by addition of H_2O. The mixture was filtered through a pad of Celite and the Celite layer was washed with AcOEt. The combined filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography

(AcOEt/Hexane = 2/3) to give **6** (112 mg, 86% yield) as a colorless oil. The chiral HPLC analysis showed the product to have >99% ee.; $[\alpha]_D^{31}$ −0.5 (*c* 1.11, $CHCl_3$); FT-IR (neat) *ν* 3450, 1607, 1577, 1455, 1420, 1111 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 7.70–7.68 (4H, m), 7.45–7.26 (11H, m), 6.98 (1H, d, *J* = 16.2 Hz), 6.60 (1H, dd, *J* = 16.2, 6.7 Hz), 6.54 (2H, s), 4.75 (2H, s), 4.61 (2H, s), 4.51 (1H, m), 3.79 (6H, s), 3.63 (1H, dd, *J* = 9.6, 3.3 Hz), 3.49 (1H, dd, *J* = 9.6, 8.3 Hz), 2.47 (1H, brs), 1.10 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 158.2, 141.5, 137.9, 135.3, 133.1, 130.8, 129.5, 128.1, 127.7, 127.5, 127.4, 122.1, 112.0, 101.2, 74.4, 73.1, 72.9, 65.6, 55.4, 26.7, 19.2; MS (EI) *m/z* 582 (M^+), 461 (100%); HRMS (EI) *m/z* calcd for $C_{36}H_{42}O_5Si$ (M^+): 582.2802, found: 582.2755.

(*S*,*E*)-Ethyl 6-benzyloxy-3-(4-*tert*-butyldiphenylsilyloxy-methyl-2,6-dimethoxyphenyl)hex-4-enoate 5. A mixture of **6** (130 mg, 0.22 mmol) and *o*-NO_2PhOH (1.2 mg, 0.17 mmol) in triethyl orthoacetate (1.2 mL) was heated for 2 h at 140 °C. The mixture was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and aqueous layer extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 1/4) to give **5** (86 mg, 72% yield) as a yellowish oil. The chiral HPLC analysis showed the product to have >99% ee; $[\alpha]_D^{31}$ +1.9 (*c* 0.99, $CHCl_3$); FT-IR (neat) *ν* 1731, 1672, 1609, 1585, 1455, 1426, 1367, 1116 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 7.70–7.68 (4H, m), 7.42–7.19 (11H, m), 6.53 (2H, s), 6.08 (1H, dd, *J* = 15.4, 7.7 Hz), 5.63 (1H, dt, *J* = 15.4, 6.4 Hz), 4.74 (2H, s), 4.59 (1H, m), 4.44 (2H, s), 4.04 (2H, q, *J* = 7.1 Hz), 3.96 (2H, d, *J* = 6.4 Hz), 3.75 (6H, s), 2.97 (1H, dd, *J* = 15.0, 8.7 Hz), 2.78 (1H, dd, *J* = 15.0, 6.8 Hz), 1.15 (3H, t, *J* = 7.1 Hz), 1.11 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 172.6, 157.9, 141.0, 138.4, 135.4, 135.2, 129.6, 128.1, 127.6, 127.5, 127.3, 126.1, 116.9, 101.8, 71.3, 70.7, 65.5, 59.9, 55.6, 38.2, 34.6, 26.8, 19.3, 14.2; MS (EI) *m/z* 652 (M^+), 595 (100%); HRMS (EI) *m/z* calcd for $C_{40}H_{48}O_6Si$ (M^+): 652.3220, found: 652.3200.

(*S*,*E*)-6-Benzyloxy-3-(4-*tert*-butyldiphenylsilyloxymethyl-2,6-dimethoxyphenyl) hex-4-enal. To a solution of **5** (172 mg, 0.26 mmol) in toluene (3.6 mL) was added DIBAL (1.01 M in toluene, 0.21 mL, 0.32 mmol) at −78 °C, and stirred for 20 min at the same temperature. The mixture was quenched by addition of 0.5 N aqueous HCl and allowed to warm up to room temperature. The mixture was diluted with AcOEt and H_2O. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 1/4) to give the aldehyde (138 mg, 86% yield) as a yellowish oil; $[\alpha]_D^{25}$ +0.6 (*c* 1.00, $CHCl_3$); FT-IR (neat) *ν* 1724, 1585, 1455, 1426, 1112 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 9.63 (1H, t, *J* = 2.4 Hz), 7.69–7.67 (4H, m), 7.43–7.24 (11H, m), 6.53 (2H, s), 6.08 (1H, dd, *J* = 15.4, 7.6 Hz), 5.64 (1H, dt, *J* = 15.4, 6.2 Hz), 4.73 (2H, s), 4.64 (1H, m), 4.47 (1H, d, *J* = 11.8 Hz), 4.43 (1H, d, *J* = 11.8 Hz), 3.97 (2H, d, *J* = 6.2 Hz), 3.75 (6H, s), 2.92 (1H, ddd, *J* = 16.3, 7.3, 2.4 Hz), 2.86 (1H, ddd, *J* = 16.3, 7.6, 2.4 Hz), 1.11 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 203.1, 157.8, 141.4, 138.3, 135.4, 135.0, 133.3, 129.6, 128.2, 127.7, 127.6, 127.4, 126.3, 116.2, 101.8, 71.7, 65.5, 55.6, 47.0, 32.6, 26.9, 19.4; MS (EI) *m/z* 608 (M^+), 551 (100%); HRMS (EI) *m/z* calcd for $C_{38}H_{44}O_5Si$ (M^+): 608.2958, found: 608.2973.

4{[(*S*,2*E*,6*Z*)-1-Benzyloxyocta-2,6-dien-4-yl]-3,5-dimethoxy-benzyloxy}-*tert*-butyldiphenylsilane 11. To a solution of ethyltriphenylphosphonium iodide (303 mg, 0.73 mmol) in THF (4.0 mL) was added KHMDS (0.7 M in toluene, 0.90 mL, 0.68 mmol) at −78 °C. After stirring for 20 min, a solution of the aldehyde (138 mg, 0.23 mmol) in THF (1.5 mL) was added dropwise *via* cannula. After stirring for 1 h at −78 °C, the reaction mixture was brought to 0 °C and quenched with saturated aqueous NH_4Cl and diluted with Et_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 1/9) to give **11** (136 mg, 97% yield) as a colorless oil; $[\alpha]_D^{25}$ +6.6 (*c* 0.96, $CHCl_3$); FT-IR (neat) *ν* 1608, 1585, 1455, 1426, 1111 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 7.70–7.67 (4H, m), 7.43–7.24 (11H, m), 6.52 (2H, s), 6.15 (1H, dd, *J* = 15.4, 8.0 Hz), 5.58 (1H, dt, *J* = 15.4, 6.4 Hz), 5.39–5.33 (2H, m), 4.73 (2H, s), 4.49 (1H, d, *J* = 11.7 Hz), 4.45 (1H, d, *J* = 11.7 Hz), 4.06 (1H, m), 3.97 (2H, m), 3.74 (6H, s), 2.57 (2H, m), 1.55 (3H, d, *J* = 5.9), 1.10 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 158.0, 140.4, 138.5, 137.3, 135.5, 133.4, 129.6, 129.5, 128.2, 127.8, 127.6, 127.3, 125.4, 124.0, 118.4, 101.9, 71.3, 71.0, 65.5, 55.7, 38.3, 30.5, 26.9, 19.4, 13.0; MS (EI) *m/z* 620 (M^+), 565 (100%); HRMS (EI) *m/z* calcd for $C_{40}H_{48}O_4Si$ (M^+): 620.3322, found: 620.3311.

(*S*)-4-(4-*tert*-Butyldiphenylsilyloxymethyl-2,6-dimethoxy-phenyl)octan-1-ol 12. A solution of **11** (297 mg, 0.48 mmol) in THP (4.8 mL) was hydrogenated in the presence of Pd/C (30 mg) under atmospheric pressure of H_2 for 3 h. To the reaction mixture was added $Pd(OH)_2$ (45 mg) thrice at 3 h intervals. After stirring for 1 d, the reaction mixture was filtered through a pad of Celite and the Celite layer was washed with Et_2O. The combined filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 1/4) to give **12** (243 mg, 95% yield) as a colorless oil; $[\alpha]_D^{26}$ −0.5 (*c* 1.16, $CHCl_3$); FT-IR (neat) *ν* 3357, 1608, 1584, 1461, 1425, 1370, 1112 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 7.70–7.68 (4H, m), 7.43–7.35 (6H, m), 6.51 (2H, s), 4.74 (2H, s), 3.72 (6H, s), 3.57 (2H, t, *J* = 6.6 Hz), 3.28 (1H, m), 1.89–1.78 (2H, m), 1.66–1.55 (2H, m), 1.47–1.32 (2H, m), 1.27–1.05 (5H, m), 1.11 (9H, s), 0.83 (3H, t, *J* = 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 139.9, 135.5, 133.5, 129.6, 127.6, 119.4, 65.8, 65.6, 63.5, 34.8, 33.5, 31.6, 30.5, 29.7, 26.9, 22.9, 19.4, 15.3, 14.3, 14.2; MS (EI) *m/z* 534 (M^+), 379 (100%); HRMS (EI) *m/z* calcd for $C_{33}H_{46}O_4Si$ (M^+): 534.3165, found: 534.3167.

(*S*)-*tert*-Butyl[3,5-dimethoxy-4-(oct-1-en-4-yl)benzyloxy]-diphenylsilane. To a solution of **12** (120 mg, 0.22 mmol) in THF (1.2 mL) was added *o*-NO_2PhSeCN (153 mg, 0.67 mmol) and PBu_3 (0.17 mL, 0.67 mmol). After stirring for 3 h, to the mixture was added 30% aqueous H_2O_2 (0.17 mL, 1.5 mmol) over 10 min at 0 °C. The reaction mixture was stirred for 8 h and diluted with Et_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 1/9) to give the

alkene (109 mg, 94% yield) as a colorless oil; $[\alpha]_D^{26}$ +0.8 (*c* 0.96, $CHCl_3$); FT-IR (neat) *ν* 1609, 1584, 1461, 1426, 1369, 1213, 1112 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 7.70–7.68 (4H, m), 7.43–7.33 (6H, m), 6.51 (2H, s), 5.70 (1H, m), 4.92 (1H, dd, J = 17.1, 2.4 Hz), 4.82 (1H, dt, J = 10.2, 1.2 Hz), 4.75 (2H, s), 3.72 (6H, s), 3.36 (1H, m), 2.53 (1H, m), 2.43 (1H, m), 1.80 (1H, m), 1.60 (1H, m), 1.30–1.04 (4H, m), 1.11 (9H, s), 0.83 (3H, t, J = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 139.9, 139.0, 135.5, 133.5, 129.6, 127.7, 127.6, 119.5, 114.1, 102.0, 65.9, 65.7, 38.3, 35.1, 32.9, 30.5, 26.9, 22.9, 19.4, 14.2; MS (EI) *m/z* 516 (M^+), 475 (100%); HRMS (EI) *m/z* calcd for $C_{33}H_{44}O_3Si$ (M^+): 516.3060, found: 516.3047.

(*S*)-3,5-Dimethoxy-4-(oct-1-en-4-yl)methanol. To a solution of the silane (109 mg, 0.21 mmol) in THF (1.1 mL) was added TBAF (1.0 M in THF, 0.32 mL, 0.32 mmol) at room temperature. After stirring for 3 h, H_2O and AcOEt were added to the mixture. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 3/7) to give the alcohol (58 mg, 99% yield) as a colorless solid; mp 39–41 °C; $[\alpha]_D^{24}$ –0.5 (*c* 0.98, $CHCl_3$); FT-IR (neat) *ν* 3323, 1583, 1455, 1421, 1213, 1135 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 6.52 (2H, s), 5.67 (1H, m), 4.90 (1H, d, J = 17.1 Hz), 4.80 (1H, d, J = 10.1 Hz), 4.61 (2H, s), 3.77 (6H, s), 3.37 (1H, m), 2.53 (1H, m), 2.41 (1H, m), 1.89 (1H, brs), 1.80 (1H, m), 1.59 (1H, m), 1.29–1.01 (4H, m), 0.81 (3H, t, J = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 139.6, 138.8, 120.4, 114.2, 102.9, 65.6, 55.7, 55.6, 38.1, 35.0, 32.8, 30.4, 22.9, 14.1; MS (EI) *m/z* 278 (M^+), 181 (100%); HRMS (EI) *m/z* calcd for $C_{17}H_{26}O_3$ (M^+): 278.1882, found: 278.1878.

(*S*)-3,5-Dimethoxy-4-(oct-1-en-4-yl)benzaldehyde 13. A mixture of the alcohol (58 mg, 0.21 mmol) and MnO_2 (180 mg, 2.1 mmol) in CH_2Cl_2 (4.2 mL) was stirred for 2 h at room temperature. The mixture was diluted with Et_2O, and filtered through a pad of Celite and the Celite layer was washed with Et_2O. The combined filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 3/7) to give **13** (55 mg, 97% yield) as a colorless oil; $[\alpha]_D^{24}$ –5.3 (*c* 0.93, $CHCl_3$); FT-IR (neat) *ν* 1695, 1582, 1455, 1421, 1381, 1308, 1213, 1145 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 9.88 (1H, s), 7.04 (2H, s), 5.65 (1H, m), 4.89 (1H, d, J = 17.1 Hz), 4.80 (1H, d, J = 10.1 Hz), 3.85 (6H, s), 3.49 (1H, m), 2.57 (1H, m), 2.43 (1H, m), 1.85 (1H, m), 1.63 (1H, m), 1.29–0.99 (4H, m), 0.81 (3H, t, J = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 191.5, 138.1, 135.2, 128.7, 114.6, 105.1, 55.7, 55.5, 37.7, 35.6, 32.4, 30.3, 22.7, 14.0; MS (EI) *m/z* 276 (M^+), 179 (100%); HRMS (EI) *m/z* calcd for $C_{17}H_{24}O_3$ (M^+): 276.1725, found: 276.1745.

(4*R*,5*S*)-3-{(2*R*,3*R*)-3-[3,5-Dimethoxy-4-((*S*)-oct-1-en-4-yl)-phenyl]-3-hydroxy-2-methylpropionyl}-4-methyl-5-phenyl-oxazolidin-2-one 15. To a solution of **14** (59 mg, 0.22 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added Et_3N (0.09 mL, 0.65 mmol) and dibutylboron triflate (1.1 M in toluene, 0.51 mL, 0.56 mmol). After stirring for 1 h at 0 °C, the mixture was cooled to –78 °C. Then, a solution of **13** (59 mg, 0.22 mmol) in CH_2Cl_2 (0.70 mL) was added and the mixture was stirred for 1 h at –78 °C and for 2.5 h at 0 °C. The mixture was quenched by addition of pH 7.0 phosphate buffer (1.8 mL) and MeOH (1.0 mL) at 0 °C, and then a mixture of MeOH (0.75 mL) and 30% aqueous H_2O_2 (1.0 mL) at 0 °C. The resultant mixture was stirred for 1 h and the volatile material was evaporated under reduced pressure. The residue was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (AcOEt/Hexane = 1/4) to give **15** (106 mg, 97% yield) as a colorless solid; mp 53–54 °C; $[\alpha]_D^{24}$ –6.2 (*c* 0.93, $CHCl_3$); FT-IR (neat) *ν* 3498, 1780, 1696, 1638, 1582, 1455, 1367, 1195 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 7.40–7.22 (5H, m), 6.58 (2H, s), 5.64 (1H, m), 5.32 (1H, d, J = 7.1 Hz), 4.91–4.85 (2H, m), 4.73 (1H, dd, J = 11.2, 1.0 Hz), 4.55 (1H, m), 4.21 (1H, m), 3.78 (6H, s), 3.36 (1H, m), 3.20 (1H, brs), 2.50 (1H, m), 2.41 (1H, m), 1.75 (1H, m), 1.60 (1H, m), 1.28 (3H, d, J = 6.8 Hz), 1.26–0.94 (4H, m), 0.85 (3H, d, J = 6.6 Hz), 0.77 (3H, t, J = 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 175.7, 152.4, 140.3, 138.6, 132.8, 128.6, 128.5, 125.3, 120.4, 114.1, 102.2, 78.8, 75.1, 60.3, 55.0, 44.8, 37.9, 35.0, 32.8, 30.3, 22.7, 14.3, 14.1, 14.0, 11.7; MS (EI) *m/z* 509 (M^+), 468 (100%); HRMS (EI) *m/z* calcd for $C_{30}H_{39}NO_6$ (M^+): 509.2777, found: 509.2811.

(2*R*,3*R*)-3-{3,5-Dimethoxy-4-[(*S*)-oct-1-en-4-yl]phenyl}-3-hydroxy-*N*-methoxy-*N*,2-dimethylpropionamide. To a suspension of HN(OMe)Me·HCl (41 mg, 0.42 mmol) in THF (0.47 mL) was added Me_3Al (1.03 M in hexane, 0.42 mL, 0.42 mmol) at 0 °C, and the mixture was stirred for 30 min. To this mixture was added **15** (72 mg, 0.14 mmol) in THF (0.47 mL) *via* cannula at –15 °C. The mixture was stirred for 15 min at –15 °C and then warmed to 0 °C. After stirring for 3 h at room temperature, the mixture was added dropwise *via* cannula into a stirred mixture of CH_2Cl_2 and 0.5 N aqueous HCl at 0 °C. The resulting two-phase mixture was stirred for 1 h at 0 °C. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 3/7) to give the amide (51 mg, 91% yield) as a colorless solid; mp 77–80 °C; $[\alpha]_D^{25}$ –7.1 (*c* 0.84, $CHCl_3$); FT-IR (neat) *ν* 3421, 1638, 1582, 1456, 1421, 1134, 1114 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 6.54 (2H, s), 5.65 (1H, m), 4.98 (1H, d, J = 3.6 Hz), 4.89 (1H, ddd, J = 17.1, 2.4, 1.2 Hz), 4.78 (1H, dt, J = 10.0, 1.2 Hz), 4.04 (1H, s), 3.77 (6H, s), 3.61 (3H, s), 3.35 (1H, m), 3.17 (3H, s), 3.14 (1H, brs), 2.53 (1H, m), 2.44 (1H, m), 1.79 (1H, m), 1.59 (1H, m), 1.29–1.00 (4H, m), 1.14 (3H, d, J = 7.1 Hz), 0.81 (3H, t, J = 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 177.5, 140.6, 138.9, 120.0, 114.1, 102.3, 77.2, 73.8, 61.5, 55.8, 41.5, 38.2, 35.0, 32.8, 31.9, 30.4, 22.8, 14.2, 11.0; MS (EI) *m/z* 393 (M^+), 352 (100%); HRMS (EI) *m/z* calcd for $C_{22}H_{35}NO_5$ (M^+): 393.2515, found: 393.2522.

(2*R*,3*R*)-3-{3,5-Dimethoxy-4-[(*S*)-oct-1-en-4-yl]phenyl}-*N*-methoxy-*N*,2-dimethyl-3-triethylsilyloxypropionamide. To a suspension of the amide (62 mg, 0.16 mmol) in CH_2Cl_2 (3.2 mL) was added 2,6-lutidine (0.12 mL, 1.00 mmol), followed TESOTf (0.090 mL, 0.39 mmol) at 0 °C After stirring for 1.5 h, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 1/4) to give the silane (79 mg, 99% yield) as

a colorless oil; $[\alpha]_D^{26}$ −2.3 (*c* 1.06, $CHCl_3$); FT-IR (neat) *ν* 1657, 1607, 1583, 1456, 1421, 1098 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 6.53 (2H, s), 5.60 (1H, m), 4.83 (1H, dd, *J* = 17.1, 2.4 Hz), 4.74 -4.69 (2H, m), 3.73 (6H, s), 3.34 (1H, m), 3.20 (1H, brs), 3.16 (3H, s), 2.95 (3H, s), 2.51 (1H, m), 2.36 (1H, m), 1.80 (1H, m), 1.55 (1H, m), 1.31–0.92 (4H, m), 1.30 (3H, d, *J* = 6.6 Hz), 0.88 (9H, t, *J* = 7.8 Hz), 0.78 (3H, t, *J* = 7.3 Hz), 0.54 (6H, q, *J* = 7.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 175.3, 142.8, 138.8, 119.7, 113.9, 102.9, 76.8, 61.0, 55.8, 45.0, 38.2, 34.9, 32.7, 31.5, 30.3, 22.8, 15.2, 14.2, 6.8, 4.8; MS (EI) *m/z* 507 (M^+), 466 (100%); HRMS (EI) *m/z* calcd for $C_{28}H_{49}NO_5Si$ (M^+): 507.3380, found: 507.3396.

(2*R*,3*R*)-3-{3,5-Dimethoxy-4-[(*S*)-oct-1-en-4-yl]phenyl}-2-methyl-3-triethylsilyloxypropanal 16. To a stirred solution of the amide (79 mg, 0.16 mmol) in THF (0.79 mL) was added slowly DIBAL (1.01 M in toluene, 0.31 mL, 0.32 mmol) at −78 °C. After stirring for 3 h at the same temperature, the mixture was quenched with 0.5 N aqueous HCl and then warmed to room temperature and diluted with Et_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 1/9) to give **16** (67 mg, 96% yield) as a colorless oil; $[\alpha]_D^{26}$ +32.0 (*c* 0.93, $CHCl_3$); FT-IR (neat) *ν* 1726, 1639, 1606, 1584, 1455, 1419, 1213, 1100 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 9.72 (1H, d, *J* = 1.2 Hz), 6.46 (2H, s), 5.66 (1H, m), 5.03 (1H, d, *J* = 4.9 Hz), 4.88 (1H, ddd, *J* = 17.0, 2.4, 1.2 Hz), 4.79 (1H, ddd, *J* = 10.0, 2.3, 1.2 Hz), 3.76 (6H, s), 3.36 (1H, m), 2.63 (1H, m), 2.51 (1H, m), 2.41 (1H, m), 1.81 (1H, m), 1.60 (1H, m), 1.29–1.02 (4H, m), 1.09 (3H, d, *J* = 6.8 Hz), 0.86 (9H, t, *J* = 7.8 Hz), 0.81 (3H, t, *J* = 7.2 Hz), 0.53 (6H, q, *J* = 7.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 204.5, 141.2, 138.8, 120.2, 114.1, 102.4, 74.6, 54.7, 38.2, 35.1, 32.7, 30.4, 30.3, 22.8, 14.2, 8.6, 6.8, 6.7, 4.8; MS (EI) *m/z* 448 (M^+), 407 (100%); HRMS (EI) *m/z* calcd for $C_{26}H_{44}O_4Si$ (M^+): 448.3009, found: 448.3033.

(4*S*,5*R*,*E*)-Ethyl 5-{3,5-dimethoxy-4-[(*S*)-oct-1-en-4-yl]phenyl}-4-methyl-5-triethylsilyloxypent-2-enoate. To a solution of triethyl phosphonoacetate (0.12 mL, 0.56 mmol) in THF (1.0 mL) was added NaH (60% in mineral oil, 21 mg, 0.52 mmol) at 0 °C. After stirring for 10 min, a solution of the aldehyde (167 mg, 0.37 mmol) in THF (0.90 mL) was added dropwise *via* cannula. After stirring for 30 min, H_2O was added to the mixture and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 1/99) to give the enoate (181 mg, 94% yield) as a colorless oil; $[\alpha]_D^{25}$ +3.6 (*c* 1.33, $CHCl_3$); FT-IR (neat) *ν* 1722, 1653, 1606 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 6.93 (1H, dd, *J* = 15.6, 7.7 Hz), 6.40 (2H, s), 5.69 (1H, d, *J* = 15.6 Hz), 5.65 (1H, m), 4.86 (1H, dd, *J* = 17.1, 1.7 Hz), 4.77 (1H, d, *J* = 10.3 Hz), 4.49 (1H, d, *J* = 5.6 Hz), 4.15 (2H, qd, *J* = 7.1, 1.5 Hz), 3.74 (6H, s), 3.33 (1H, m), 2.59 (1H, m), 2.51 (1H, m), 2.38 (1H, m), 1.80 (1H, m), 1.59 (1H, m), 1.26 (3H, t, *J* = 7.1 Hz), 1.05 (3H, d, *J* = 6.6 Hz), 1.31–0.96 (4H, m), 0.87 (9H, t, *J* = 7.9 Hz), 0.80 (3H, t, *J* = 7.2 Hz), 0.52 (6H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 166.5, 151.4, 141.8, 138.9, 120.8, 120.0, 114.0, 102.9, 78.2, 60.1, 45.1, 38.2, 35.1, 32.7, 30.4, 22.8, 14.4, 14.3, 14.2, 6.9, 6.8, 4.9, 4.8; MS (EI) *m/z* 518 (M^+), 391 (100%); HRMS (EI) *m/z* calcd for $C_{30}H_{50}O_5Si$ (M^+): 518.3428, found: 518.3409.

(4*S*,5*R*)-Methyl 5-{3,5-dimethoxy-4-[(*S*)-oct-1-en-4-yl]phenyl}-4-methyl-5-triethylsilyloxypentanoate. A mixture of the enoate (42 mg, 0.080 mmol) and magnesium turnings (20 mg, 0.8 mmol) in MeOH (0.40 mL) was stirred at 0 °C for 10 h. The mixture was diluted with hexane and Et_2O, and filtered through a pad of Celite. The filtrate was washed consecutively with 0.5 N aqueous HCl, saturated aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 1/99) to give the ester (41 mg, 98% yield) as a colorless oil; $[\alpha]_D^{26}$ +25.0 (*c* 1.26, $CHCl_3$); FT-IR (neat) *ν* 1741, 1639, 1607, 1583, 1455, 1420, 1135 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 6.43 (2H, s), 5.67 (1H, m), 4.88 (1H, d, *J* = 17.0 Hz), 4.78 (1H, d, *J* = 10.0 Hz), 4.35 (1H, d, *J* = 5.6 Hz), 3.58 (6H, s), 3.64 (3H, s), 3.33 (1H, m), 2.52 (1H, m), 2.38 (1H, m), 2.32 (1H, m), 2.23 (1H, m), 1.80 (1H, m), 1.78–1.56 (3H, m), 1.40 (1H, m), 1.38–1.02 (4H, m), 0.93 (3H, d, *J* = 6.6 Hz), 0.88 (9H, t, *J* = 7.9 Hz), 0.82 (3H, t, *J* = 7.2 Hz), 0.51 (6H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 174.2, 142.9, 138.9, 119.7, 114.0, 103.1, 79.2, 51.5, 41.0, 38.3, 35.1, 32.7, 32.3, 30.4, 28.6, 22.9, 14.8, 14.2, 6.9, 4.9; MS (EI) *m/z* 506 (M^+), 391 (100%); HRMS (EI) *m/z* calcd for $C_{29}H_{50}O_5Si$ (M^+): 506.3428, found: 506.3413.

(1*R*,2*S*)-5-{3,5-Dimethoxy-4-[(*S*)-oct-1-en-4-yl]phenyl}-4-methyl-5-triethylsilyloxypentan-1-ol. To a solution of the ester (243 mg, 0.48 mmol) in THF (3.2 mL) was added LAH (22 mg, 0.58 mmol) at 0 °C. After stirring for 1.5 h at 0 °C, the mixture was quenched with 28% aqueous NH_3 and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 1/4) to give the alcohol (208 mg, 91% yield) as a colorless oil; $[\alpha]_D^{27}$ +27.9 (*c* 1.00, $CHCl_3$); FT-IR (neat) *ν* 3335, 1639, 1607, 1583, 1455, 1419, 1135, 1099 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* 6.43 (2H, s), 5.66 (1H, m), 4.88 (1H, d, *J* = 17.0 Hz), 4.78 (1H, d, *J* = 10.0 Hz), 4.32 (1H, d, *J* = 5.9 Hz), 3.75 (6H, s), 3.56 (2H, m), 3.33 (1H, m), 2.52 (1H, m), 2.40 (1H, m), 1.88–1.55 (4H, m), 1.48–1.01 (8H, m), 0.94 (3H, d, *J* = 6.6 Hz), 0.86 (9H, t, *J* = 7.9 Hz), 0.80 (3H, t, *J* = 7.2 Hz), 0.49 (6H, q, *J* = 7.9 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ* 143.2, 138.9, 119.6, 114.0, 103.1, 79.5, 63.2, 41.2, 38.3, 35.1, 32.7, 30.6, 30.4, 29.2, 22.8, 15.2, 14.2, 6.9, 4.9; MS (EI) *m/z* 478 (M^+), 391 (100%); HRMS (EI) *m/z* calcd for $C_{28}H_{50}O_4Si$ (M^+): 478.3478, found: 478.3480.

{(1*R*,2*S*)-1-[3,5-Dimethoxy-4-((*S*)-oct-1-en-4-yl)phenyl]-2-methylpent-4-enyloxy}triethylsilane 4. To a solution of the alcohol (49 mg, 0.10 mmol) in THF (0.52 mL) was added *o*-NO_2PhSeCN (47 mg, 0.21 mmol) and PBu_3 (0.050 mL, 0.21 mmol) at 0 °C. After stirring for 3 h, the mixture was added 30% aqueous H_2O_2 (0.080 mL, 0.67 mmol) over 10 min at 0 °C. The mixture was stirred for 8 h and diluted with Et_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/Hexane = 1/24) to give **4** (44 mg, 93% yield) as a colorless oil; $[\alpha]_D^{30}$ +31.9 (*c* 1.00, $CHCl_3$); FT-IR (neat) *ν* 1639, 1606, 1583,

1455, 1419, 1134 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.23 (2H, s), 5.81–5.60 (2H, m), 4.96 (2H, m), 4.87 (1H, d, $J = 17.1$ Hz), 4.78 (1H, d, $J = 10.3$ Hz), 4.35 (1H, d, $J = 5.4$), 3.75 (6H, s), 3.33 (1H, m), 2.54 (1H, m), 2.40 (1H, m), 2.12 (1H, m), 1.88–1.71 (3H, m), 1.60 (1H, m), 1.31–0.95 (4H, m), 0.91 (3H, d, $J = 6.1$ Hz), 0.86 (9H, t, $J = 8.0$ Hz), 0.80 (3H, t, $J = 7.2$ Hz), 0.50 (6H, q, $J = 8.0$ Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 143.2, 139.0, 137.7, 119.6, 115.5, 114.0, 103.2, 79.1, 41.4, 38.3, 37.9, 35.1, 32.8, 30.4, 22.9, 14.8, 14.2, 6.9, 5.0; MS (EI) *m/z* 460 (M^+), 419 (100%); HRMS (EI) *m/z* calcd for $C_{28}H_{48}O_3Si$ (M^+): 460.3373, found: 460.3364.

(+)-Cyclophane 17, (–)-Diol, (–)-Tetra-*O*-methylcylindrocyclophane A 3. See ESI.†

(–)-Cylindrocyclophane A 1. To a solution of **3** (15 mg, 0.024 mmol) in 1-methyl-2-pyrrolidinone (3.0 mL) was added K_2CO_3 (20 mg, 0.14 mmol) followed by thiophenol (0.73 mL, 7.1 mmol). The reaction vessel was sealed and heated to 215 °C for 6 h, at which time it was diluted with AcOEt (30 mL) and pH 4 buffer (15 mL). The layers were separated and the aqueous layer was saturated with NaCl and extracted with AcOEt followed by 5% MeOH in CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (AcOEt/Hexane = 1/4) to give **4** (12 mg, 85% yield) as a white solid; mp 276–278 °C {lit.[6d] mp 276–278 °C}; $[\alpha]_D^{30}$ –24.7 (*c* 0.61, MeOH) {lit.[6d] $[\alpha]_D^{20}$ –20.7 (*c* 0.14, MeOH); FT-IR (neat) ν 3398, 1654, 1260, 1024 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3OD) δ 6.23 (2H, s), 6.05 (2H, s), 3.73 (2H, d, $J = 9.4$ Hz), 3.14 (2H, m), 2.03 (2H, m), 1.94 (2H, m), 1.53 (2H, m), 1.40–1.10 (12H, m), 1.07 (6H, d, $J = 6.4$ Hz), 1.15–0.79 (4H, m), 0.78 (6H, t, $J = 7.1$ Hz), 0.79–0.60 (8H, m); ^{13}C-NMR (125 MHz, CD_3OD) δ 158.9, 157.0, 143.9, 117.8, 109.0, 105.1, 81.6, 42.1, 36.9, 35.5, 35.3, 34.9, 31.7, 30.7, 29.9, 23.9, 17.0, 14.5; MS (FAB) *m/z* 607 [$(M + Na)^+$], 419 (100%); HRMS (FAB) *m/z* calcd for $C_{36}H_{56}O_6Na$ [$(M + Na)^+$]: 607.3935, found: 607.4001.

Synthesis of (+)-Cylindrocyclophane A (*ent*-1) and the half-sized analogue 32. See ESI.†

Cell growth suppression analysis

HCT116 was obtained from the Cell Resource Center for Biomedical Research (Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan). Growth suppressive effects of the compounds were measured for 48 hours. Cell viability was assayed by quantitation of the uptake and digestion of 2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2*H*-tetrazolium monosodium salt according to the manufacturer's instructions (Dojindo Laboratories, Kumamoto, Japan) by 96-well plate reader, MPR-4Ai (Tosoh Corp., Tokyo, Japan). The percentage cell growth of the control, which was treated with 1% DMSO alone, was calculated and plotted, and then the mean growth inhibitory concentration (GI_{50}) value was determined.

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