Total Synthesis

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Synthesis and Determination of the Absolute Configuration of Cavicularin by a Symmetrization/Asymmetrization Approach**

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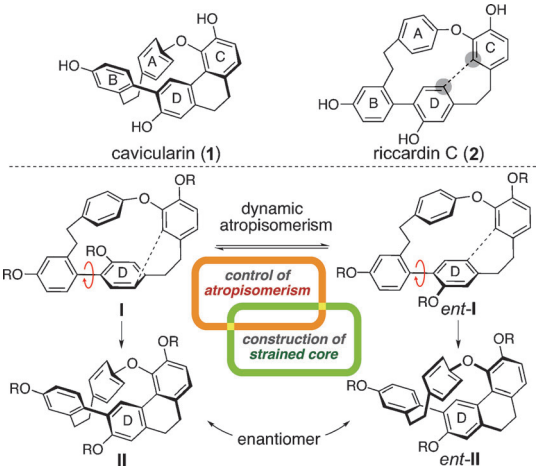
Dedicated to Professor Yoshinori Asakawa

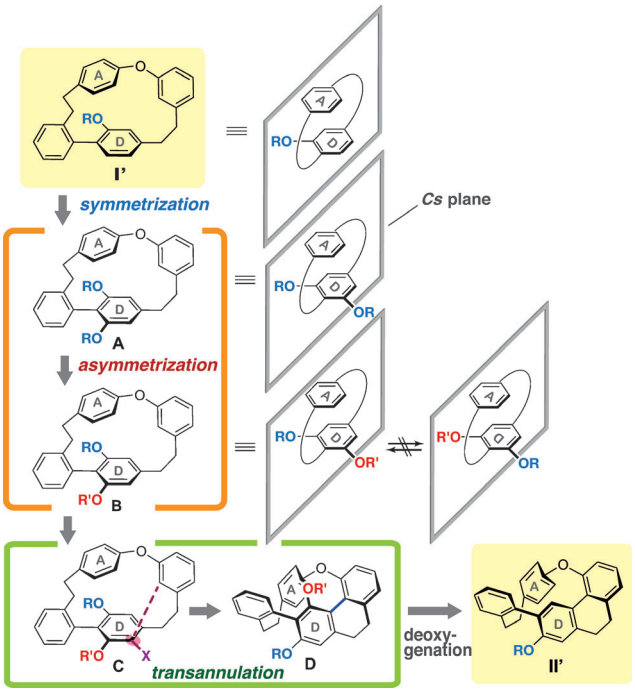
Cavicularin (**1**), isolated from a rare liverwort species, *Cavicularia densa* Steph. (Blasiaceae) by Asakawa and co-workers,[1] showcases several unusual structural features. Firstly, the polycyclophane ring system is highly strained, which manifests itself in the bent *para*-substituted benzene ring (A ring) identified by X-ray analysis. Two synthetic approaches have so far been developed for this intriguing strained scaffold, whereby Harrowven et al. exploited a radical cyclization[2] while Zhao and Beaudry used a pyrone Diels–Alder reaction.[3] Secondly, **1** is the first natural compound that displays optical activity solely derived from the atropisomerism, and where the absolute configuration has remained unassigned.[1,4]

As a result of our synthetic interest in cyclophanes,[5] we recently reported a concise synthesis of riccardin C (**2**),[5c] a typical member of the liverwort-derived family of bis-(bibenzyl) natural products,[6] and a putative biosynthetic precursor to **1** through an oxidative transannulation (dotted line in **2**; Scheme 1). We identified two related problems with the asymmetric synthesis of **1** by a transannulation: 1) the large increase in the strain energy on transannulation of **I** into **II** in a regioselective manner, and 2) rapid interconversion of atrop-enantiomer **I** into *ent*-**I** by rotation of the D ring, thus making access to the correct atropisomer **II** difficult.



Scheme 1. Two issues in the biomimetic approach.

We developed a symmetrization/asymmetrization strategy (Scheme 2) to solve these problems.[7] The key is the strategic addition of an extra oxy function onto riccardin C (abbreviated as **I′**, Scheme 2), thereby generating the key symmetrized intermediate **A**. Two attributes reside in **A** for a stereocontrolled synthesis, 1) it is *Cs* symmetric, and 2) the rotation of the D ring would be suppressed, which would allow a stepwise pathway leading to **1**. The first step of this pathway, **A**→**B**, is asymmetrization by discriminating between two RO functions, thereby inducing the planar chirality. In the second step, **B**→**C**, the X group is installed as a handle to control the regioselectivity in the key transannulation that leads to construction of the strained core, **C**→**D**. Finally, removal of the extra oxy function would give the target structure **II′**.



Scheme 2. Symmetrization/asymmetrization strategy (**I′**→**II′**).

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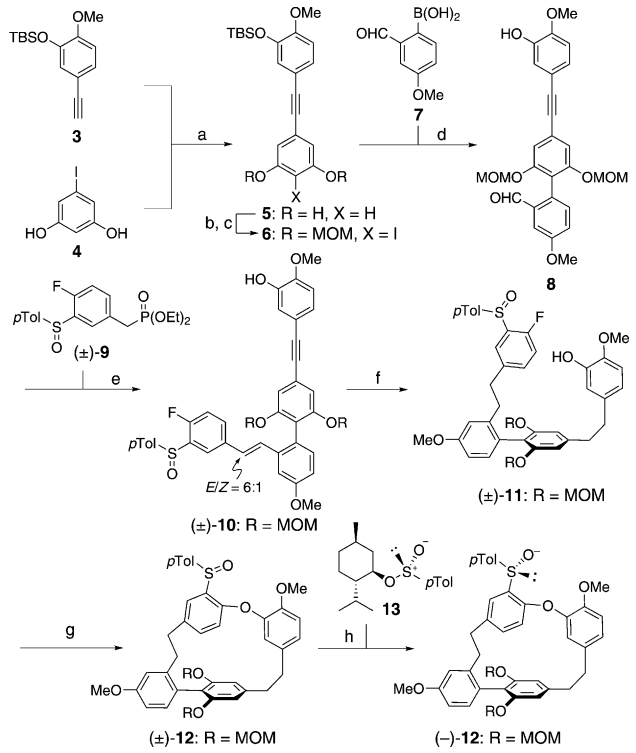
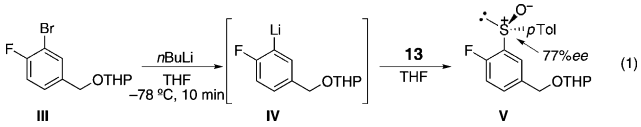


Scheme 3. Synthesis of (−)-**12**: a) $[Pd(PPh_3)_4]$ (10 mol%), CuI, NEt_3, THF, RT, 10 min. b) I_2, $NaHCO_3$, THF, H_2O, 0°C, 10 min. c) MOMCl, iPr_2NEt, CH_2Cl_2, RT, 1 h, d) **7**, $[Pd(PPh_3)_4]$ (10 mol%), K_3PO_4, 1,2-dimethoxyethane, H_2O, 85°C, 5 h (4 steps, 54%). e) **9**, NaH, DMF, −20°C, 2 h (92%). f) $TsNHNH_2$, $NaHCO_3$, 2-ethoxyethanol, 110°C, 1 h (96%). g) CsF, $CaCO_3$, 3 Å M.S., DMF (5×10^{-3} M), 150°C, 4 h (92%). h) *t*BuLi, THF, −78°C, 10 min; **13**, THF, −78°C, 10 min (73%). TBS = *tert*-butyldimethylsilyl, MOM = methoxymethyl, DMF = *N*,*N*-dimethylformamide, Ts = *p*-toluenesulfonyl.

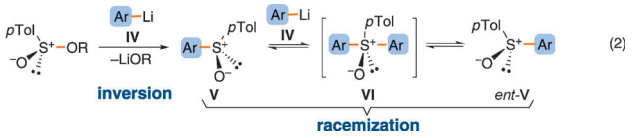
Herein, we report the success of this scenario, and achieve the first asymmetric synthesis of **1** and the assignment of its absolute configuration as shown in Scheme 1.

Scheme 3 shows the preparation of the key intermediate (−)-**12**. The synthesis was carried out by using the same procedure as for our previous synthesis of **2**,[5c] except that the D-ring unit **4** was equipped with an extra oxy function to realize the above-stated strategy. A Sonogashira reaction of alkyne **3**[8] with iodide **4**[9] gave alkyne **5**, which was regioselectively iodinated, and the two phenol groups protected as MOM ethers to give iodobenzene **6**. Suzuki–Miyaura coupling of **6** with boronic acid **7**[10] gave aldehyde **8**, which was subjected to a Horner–Emmons reaction with phosphonate (±)-**9**.[5c] Reduction of the resulting enyne (±)-**10** with diimide yielded the cyclization precursor (±)-**11**, which was subjected to an intramolecular S_NAr reaction [CsF, 3 Å molecular sieves, DMF (5×10^{-3} M)][11] to give the cyclized product (±)-**12** in 92% yield.

At this stage, the racemic sulfinyl group in (±)-**12** was replaced by an enantiomerically enriched counterpart to give (−)-**12**. This seemingly peculiar transformation was a countermeasure to two racemization issues of chiral sulfoxides. We initially attempted the installation of a chiral, nonracemic sulfinyl group at an earlier stage [Eq. (1); THP = tetrahydropyran, Tol = tolyl] by using the Andersen sulfinate [(1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate (**13**)],[12] but



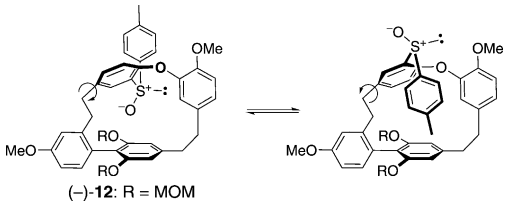
this gave sulfoxide **V** with considerable racemization (77% *ee*). This unexpected outcome can be ascribed to ligand exchange via an ate complex [Eq. (2)]. If aryl lithium



IV attacked the product **V**, a symmetrical ate complex **VI** would form, thereby leading to racemization because of the good leaving ability of aryl lithium **IV**, which was stabilized by an adjacent fluorine atom. An additional risk was the configurational instability of diaryl sulfoxides under light, a long-known, but less-noted racemization process.[13]

Thus, we chose to install the chiral, nonracemic sulfoxide at the stage stated above, namely (±)-**12**→(−)-**12** (see Scheme 3). Here, careful control of the reaction conditions was also needed to minimize the racemization: sulfoxide (±)-**12** was treated with *t*BuLi (1.2 equiv, −78°C, 10 min) to generate the corresponding lithio species,[14] into which was cannulated a precooled solution of **13** (1.5 equiv, −78°C, THF, 10 min), thereby leading to enantiomerically enriched chiral sulfoxide (−)-**12** (73% yield).

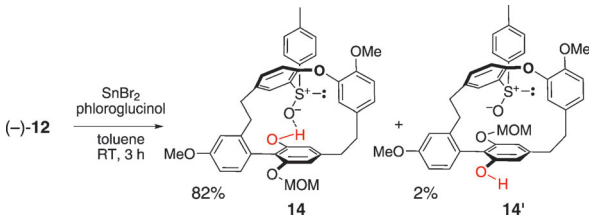
The enantiomeric purity of (−)-**12** could not be assessed at this stage, because of atropisomerism (Scheme 4).[15] However, it is well over 95% based on a back calculation from the



Scheme 4. Atropisomerization of (−)-**12**.

ee value of the advanced intermediate **15** (95–99.6% *ee*, see below).[16] A small fluctuation may originate from the two racemization processes stated above, that is, at the stage of (±)-**12**→(−)-**12** and/or during the subsequent conversion into **14**.

The next stage was the discrimination of two oxy functions on the D ring, which was nicely achieved by selective acetal cleavage (Scheme 5). Treatment of bis-MOM ether (−)-**12** with $SnBr_2$ (3.0 equiv)[5a,17] in the presence of phloroglucinol (3.0 equiv, toluene, RT, 3 h)[18] allowed the highly group-selective cleavage of one of the MOM groups, thus yielding



Scheme 5. Group-selective acetal cleavage of (−)-**12**.

the major diastereomer **14** (82%; Figure 1) in large preference over the minor diastereomer **14′** (2%). Notably, chromatographic separation of the diastereomers **14** and **14′** was easy because of the marked difference in their mobilities on silica gel (**14**: $R_f = 0.41$ and **14′**: $R_f = 0.21$, SiO_2, Et_2O/hexane = 4:1).

The distinct behaviors of **14** and **14′** on the silica gel plate can be ascribed to the presence/absence of a hydrogen bond. The presence of a hydrogen bond in the major isomer **14** was suggested by the downfield resonance of the phenol proton ($\delta = 7.7$ ppm) in the ^{1}H NMR spectrum. The internal hydrogen bond in **14** was consistent with its lower affinity to the SiO_2 surface. In contrast, the phenol signal of the minor isomer **14′** appeared at a normal position ($\delta = 5.2$ ppm), thus suggesting the absence of a hydrogen bond, which was consistent with the smaller R_f value (see above).

Gratifyingly, recrystallization of **14** gave single crystals suitable for X-ray analysis (Figure 1),[19] which allowed the rigorous structural assignment of **14**. Also, the cavernous

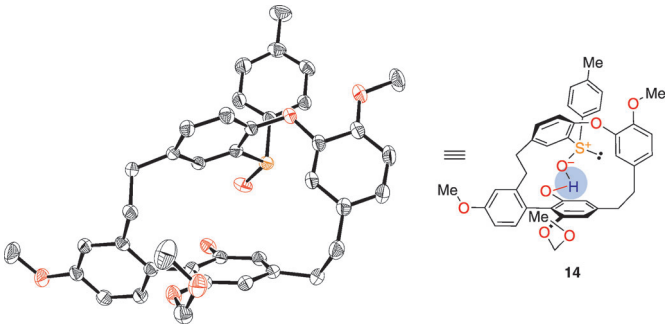


Figure 1. Single-crystal X-ray analysis of **14.** Hydrogen atoms are omitted for clarity.

molecular shape strongly suggested the presence of a hydrogen bond in **14** (blue circle).

The group-selective cleavage of the acetal could be explained by the following model (Figure 2): Let us compare two conformers **A** and **A′**, in which the sulfinyl group disposes the lone pair of electrons on the sulfur atom coplanar to the oxygen atom on ring A.[5a,17,20] In conformer **A**, chelation would be available, which would assist the cleavage of one of the MOM groups (colored in red). In contrast, such an effect is absent in **A′**. Thus, the role of the sulfinyl oxygen atom in **A** is to increase the effective concentration of the Lewis acid at one of the acetals by coordinating to the Sn^{II} species. It is interesting to compare the Sn^{II}-chelated structure **A**[5a,17,21]

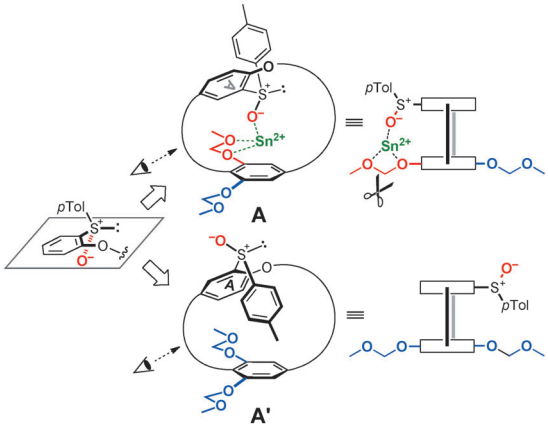
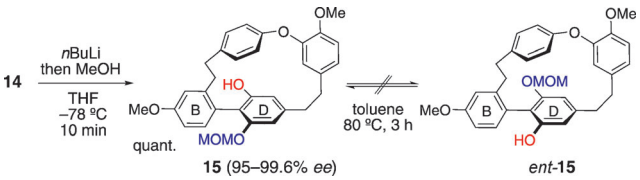


Figure 2. Rationale for the group-selective acetal cleavage.

with the X-ray structure of **14** containing a hydrogen bond (see Figure 1).

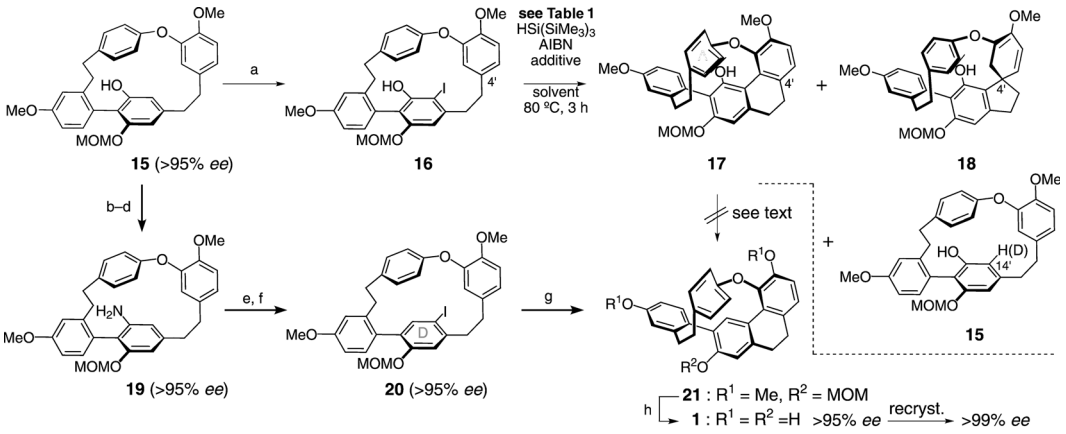
Having played a key role as an excellent chiral auxiliary for the asymmetrization, the chiral, nonracemic sulfinyl group in **14** was now removed by sulfinyl–lithium exchange (*n*BuLi, THF, −78 °C, 10 min) followed by protonolysis (MeOH, −78 °C, 10 min; Scheme 6). The cyclophane **15** thus obtained



Scheme 6. Stereochemical stability after desulfurization.

was devoid of stereogenic centers, but proved to be a stable atrop-enantiomer: the presence of the extra oxy group in the D ring should restrict the rotation around the biaryl bond between the B and D rings [see riccardin C (**2**), Scheme 1]. The enantiomeric excess of **15** was excellent, in the range of 95–99.6% (HPLC analysis on a chiral stationary phase).[22] This planar stereochemistry of **15** proved fairly stable; no racemization was detected even after heating at 80 °C (toluene, 3 h), while partial racemization (95→78% *ee*) was observed on heating at 110 °C (toluene, 3 h).

Scheme 7 shows the attempts at converting **15** into the target structure **1**. Preparing for the key transannulation stage, an iodine atom was regioselectively installed at the *ortho* position to the free phenol group in **15** to give iodide **16**. The key radical reaction[23] of **16**, which was based on the strategy of Harrowven et al.[2] required optimization (Table 1). Treatment of **16** with $HSi(SiMe_3)_3$ (2.2 equiv)[24] and a stoichiometric amount of AIBN[23a] (1.0 equiv, toluene, 80 °C, 3 h) gave the desired product **17** in 25% yield (entry 1). Noting that the poor material balance was due to the partial removal of the MOM group caused by the tris(trimethylsilyl)silyl iodide generated by the reaction, the next reaction was attempted in the presence of Na_2HPO_4 as an acid



Scheme 7. Unsuccessful/successful routes toward **1**. a) *N*-iodosuccinimide, MeCN, RT, 10 min (84%). b) K_2CO_3, $PhNTf_2$, acetone, RT, 4 h (98%). c) Benzophenone imine, $Pd(OAc)_2$, binap, Cs_2CO_3, toluene, reflux, 3 h. d) 2 M HCl, THF, 0°C→RT, 20 min (2 steps, 86%). e) $BnNMe_3ICl_2$, CH_2Cl_2, MeOH, 0°C, 20 min (88%). f) $NaNO_2$, AcOH, $Na_2S_2O_3$, THF, H_2O, RT, 2 h (42%). g) $HSi(SiMe_3)_3$, AIBN, Na_2HPO_4, benzene, 80°C, 3 h (82%). h) BBr_3, CH_2Cl_2, RT, 5 h (85%). Tf = trifluoromethanesulfonyl, binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, AIBN = 2,2′-azobisisobutyronitrile.

Table 1: Radical transannulation of **16**.[a]

Entry	Additive	Solvent	**17** [%]	**15** [%]	**18** [%]
1	none	toluene	25	50	none
2	Na_2HPO_4	toluene	32	45	15
3	Na_2HPO_4	[D_8]toluene	35	40[b]	19
4	Na_2HPO_4	benzene	50	5	33

[a] Reaction conditions: $HSi(SiMe_3)_3$ (2.2 equiv), AIBN (1.0 equiv), 80°C, 3 h. [b] 77% deuterium incorporation at the 14′-position.

scavenger, which resulted in a slightly improved yield of **17** (entry 2). Another side product was **15**, a simple deiodination product. We surmized that the hydrogen source is not only the silane, but also the solvent, toluene. Indeed, the reaction conducted in [D_8]toluene gave **15** which was deuterated at the 14′-position (77% D, entry 3). When benzene was used as the solvent, the yield of **17** improved to 50% (entry 4). A substantial amount of the spiro compound **18** was also produced by radical attack at the 4′-position. Extensive studies on changing various reaction parameters (initiators, hydrogen donors, etc.) failed to give any further improvement in the yield of **17**, and thus, we proceeded to the final stage of the synthesis.

However, we were unable to remove the extra oxy function. For example, the triflate, derived from **17** in 78% yield ($PhNTf_2$, K_2CO_3, acetone, reflux, 2 h), proved completely resistant toward attempted hydrogenolysis in the presence of various Pd- and Ni-based catalysts. Extreme steric hindrance around the triflate seemed to be the problem, and the attempted high-pressure hydrogenolysis using Pd/C or Raney-Ni led to saturation of the twisted A ring.

At this juncture, we chose to conduct the deoxygenation prior to the transannulation reaction. For this purpose, phenol **15** (>95% *ee*) was converted in three steps into aniline **19** in 86% yield: 1) conversion to the corresponding triflate, 2) coupling with benzophenone imine,[25] and 3) hydrolysis. Regioselective iodination of **19** followed by deamination ($Na_2S_2O_3$, AcOH)[26] gave iodide **20**.

Although the stereochemical purity of iodide **20** was confirmed (>95% *ee*), our concern was that removal of the amino group might reduce the stereochemical stability associated with rotation of the D ring. Fortunately, however, no racemization occurred even after heating of **20** at 110°C for 3 h (toluene), which suggests that the iodine atom is also able to stabilize the planar chirality in **20**.

Now the stage was reset for the key radical transannulation, and, pleasingly, iodide **20** underwent a smooth reaction under the above-stated conditions [$HSi(SiMe_3)_3$ (2.2 equiv), AIBN (1.0 equiv), Na_2HPO_4, benzene, 80°C, 3 h], cleanly giving product **21** in 82% yield. At this stage, a small amount of the de-iodinated product could not be separated. However, final removal of the MOM and methyl protecting groups with BBr_3 (CH_2Cl_2, RT, 5 h) allowed clean production and isolation of the target **1** in 85% yield.

The synthetic material **1** was identical in all respects with the reported data for the natural product (^1H, ^{13}C NMR, IR, HRMS). The enantiomeric excess of **1** exceeded 95%, thus proving that no racemization occurred during the transannulation. Recrystallization (*n*-hexane, ethyl acetate) raised the *ee* value, thereby giving enantiopure **1** (>99% *ee*, colorless needles, m.p. 213–214°C, lit.[1] m.p. 244–246°C). Importantly, the synthetic material **1** was antipodal to the natural product, as evident from the sign of the optical rotation: $[\alpha]_D^{20} = -1.9 \times 10^2$ ($c = 0.14$, MeOH) [lit.[1] $[\alpha]_D^{21} = +1.7 \times 10^2$ ($c = 0.25$, MeOH)].

Single-crystal X-ray analysis reconfirmed the unusual strained ring system of **1**, with the twisted benzene ring (Figure 3); the measured value of the dihedral angles between C2-C3-C5-C6 and C1-C2-C6, C3-C4-C5 were 6.2° and 9.5°, respectively.[27]

In summary, the first asymmetric total synthesis of (−)-cavicularin has been achieved, thereby establishing its absolute configuration. Noteworthy features of the synthesis

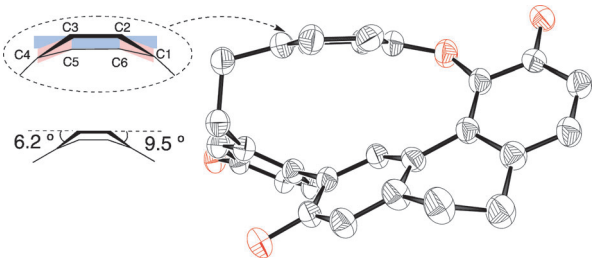


Figure 3. Single-crystal X-ray analysis of **1**. Hydrogen atoms are omitted for clarity.

are 1) the group-selective acetal cleavage to induce the planar chirality and 2) the radical transannulation to effect the construction of the highly strained ring system in an enantiospecific manner.

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[22] DAICEL CHIRALPAKIA (0.46 × 25 cm, hexane/EtOAc = 7:3, flow rate = 1.0 mL min^{-1}, 20 °C, 254 nm, t_R = 6.7 min for **15**, 7.9 min for *ent*-**15**; for details, see the Supporting Information.
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[27] CCDC 931676 (**1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.