# Notes

## Synthesis of Optically Pure (2*R*,2'*R*,5*R*,5'*R*)-5,5'-Bisiodomethyl-octahydro-[2,2']-bifuran from Diethyl D-tartrate: Iodoetherification of (5*R*,6*R*)-5,6-Dihydroxy-1,9-decadiene

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The annonaceous acetogenins, which were isolated from several species of *Annonaceae*, have received a great deal of attention during the last decade because they showed the highly potent antitumor and pesticidal activities.[1] They usually contain 35 or 37 carbon atoms, one or two tetrahydrofuran rings, and a γ-lactone with five to eight carbinol asymmetric centers. Among these compounds with adjacent bistetrahydrofuran (bis-THF) ring (Fig. 1), uvaricin, for example, is a prototype of the compounds in this class and has a stereochemically *trans-threo-trans* fragment in the bis-THF ring. The mechanism for the action of acetogenins is suggested that bis-THF fragment might be an essential part for cell growth inhibitory effect through involvement in a metal cation binding.[2] Therefore, stereoselective synthesis of bis-THF ring has been an attractive target to synthetic chemists for the development of new derivatives of acetogenins.

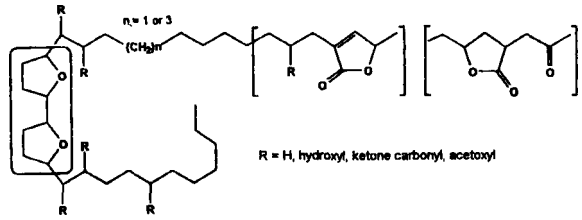
Recently, the construction of 2,5-disubstituted bis-THF ring was reviewed[3] and the following general reactions were utlized for the ring construction: 1) intramolecular epoxide opening reactions, 2) epoxide-cyclization cascade and bi-directional reactions, and 3) intramolecular Williamson reactions. Since controlling the stereochemistry of bis-THF ring is a crucial step for the syntheses of various bis-THF acetogenins, we have investigated stereoselective synthetic methods to construct the bis-THF ring by using electrophile-mediated double cyclization reactions. Here, we report our results of double cyclization of (5*R*,6*R*)-5,6-dihydroxy-1,9-decadiene (**5**), and the stereoselective synthetic method of (2*R*,2'*R*,5*R*,5'*R*)-5,5'-bisiodomethyl-octahydro-[2,2']-bifuran (**8**) as a key intermediate of bis-THF acetogenin derivatives.

### Experimental Section

**General procedure.** All commercially chemicals were used without further purification. Requiring dry solvents, tetrahydrofuran, was distilled from sodium/benzophenone. Methylene chloride was distilled over calcium hydride. $^1$H and $^{13}$C NMR spectra were obtained at 200 and 50 MHz, respectively, using tetramethylsilane (TMS) as an internal standard. Infrared (IR) spectra were recorded on a Perkin-Elmer 1130 Grating Diffraction IR-spectrometer as neat. High resolution mass spectra were obtained at the Korea Basic Science Institute Mass Spectrometry Facility. Low resolution mass spectra were recorded on a HP590 GC/MS 5792 MSD. Optical rotations were recorded on JASCO DIP-370 polarimeter. Column chromatography was performed with E. Merck 230-400 mesh silica gel. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 plates.

**Diethyl-2,3-O-isopropylidene-D-tartrate (2).** To a solution of (-)-diethyl D-tartrate (**1**) (5.0 g, 24.2 mmol) and 2,2-dimethoxypropane (3.04 g, 29 mmol) in 12 mL of benzene, *p*-TsOH (12 mg, 0.063 mmol) was added. The mixture was then heated and distilled to remove benzene-methanol azeotrope (bp 58 °C). The mixture was then cooled to room temperature and shaken with 10% aq. -$K_2CO_3$ solution. The aqueous layer was extracted with diethyl ether, the combined organic layer was dried over $K_2CO_3$ and the solvent was evaporated. The light yellow liquid obtained was simply distilled under vaccum to yield 5.6 g (94%) of **2**. $R_f$=0.6 (*n*-Hex : EA=2 : 1); IR(neat, cm$^{-1}$): 2960, 1745, 1465, 1320; $^1$H NMR ($CDCl_3$, 200 MHz) δ 1.3 (t, 6H, two methyl), 1.5 (s, 3H, $CH_3$), 1.55 (s, 3H, $CH_3$), 4.33 (q, 4H, $CH_2$), 4.8 (m, 2H, CH); MS (m/e) 247 ($M^+$+1), 232, 231, 173, 161, 155, 115, 89, 87, 85, 83, 71, 59.

**(4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol (3).** Under $N_2$ and cooling with ice, 2 mL of anhydrous tetrahydrofuran was added to 60 mg of $LiAlH_4$ without temperature rising above 10 °C. Then, 330 mg (1.34 mmol) of **2** in 2 mL of anhydrous THF was slowly added




| | |
|---|---|
| Uvaricin | : *trans-threo-trans* |
| Rollinicin | : *trans-threo-trans* |
| Asimicin | : *trans-threo-trans* |
| Rolliniastatin | : *trans-threo-trans* |
| Bullatacin | : *cis-threo-cis* |
| Bullatacinone | : *trans-threo-trans* |

**Figure 1.** Structure of bifuran ring in annonaceae.

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with stirring and keeping the temperature below 25 °C. Then 2 mL of satd. -$Na_2SO_4$ was added slowly. After stirring for 1 h at room temperature, the mixture was filtered through glass filter and the residue was washed 3 times with 3 mL of $CH_2Cl_2$-MeOH (4 : 1). The combined filtrates was dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography (Hex : EA=1 : 1) to give 210 mg (97%) of **3** as an oil.

IR (cm $^{-1}$): 3400, 2950, 1450, 1375, 1365; $^1$H NMR ($CDCl_3$, 200 MHz): δ 1.44 (s, 6H, $CH_3$), 2.15 (br, 2H), 3.71-3.89 (m, 4H, $CH_2$), 4.08 (m, 2H, CH).

**(4*R*,5*R*)-4,5-Di(3-buten-1-yl)-1,3-dioxolane (4).** To a solution of 3 (300 mg, 1.88 mmol) and $Et_3N$ (1.1 mL) in 10 mL of $CH_2Cl_2$ at − 15 °C was added triflic anhydride (1.15 g, 4.1 mmol) in 4 mL of $CH_2Cl_2$. The reaction mixture was stirred for 30 minutes. After dilution with $CH_2Cl_2$, the organic layer was washed with water, saturated $NaHCO_3$, and brine solution. The extract was dried over $MgSO_4$ and filtered through silica gel plug to remove any polar impurity. After solvent removal, the crude triflate was used for the next reaction.

To a solution of CuBr (54 mg, 0.38 mmol) in 10 mL ether at 0 °C was added the allylmagnesium bromide solution [which was obtained from the reaction of allyl bromide (1.2 mL, 14 mmol) with magnesium (~1 g) in 15 mL ether] followed by the above triflate in 5 mL ether, and the reaction mixture was stirred for 12 hours. After being quenched with water, the organic layer was washed with water, saturated $NaHCO_3$, and brine solution. Following solvent removal, the crude product was purified by column chromatography to give 213 mg (55%) of **4** as an oil.

IR (cm $^{-1}$): 3080, 2960, 1650, 1460, 1370; $^1$H NMR ($CDCl_3$, 200 MHz): d 1.4 (s, 6H, $CH_3$), 1.65 (m, 4H, $CH_2$), 2.06-2.4 (m, 4H, $CH_2$), 3.65 (m, 2H, CH), 4.95-5.13 (m, 4H, $CH_2$), 5.74-5.95 (m, 2H, CH); $^{13}$C NMR: δ 138.04, 114.82, 107.97, 80.19, 32.14, 30.14, 27.30.

**(5*R*,6*R*)-5,6-Dihydroxy-1,9-decadiene (5).** To a solution of **4** (720 mg, 3.42 mmol) in 20 mL EtOH-$H_2O$ (4 : 1) was added 10N-HCl (3 mL). After being stirred for 3 hours at room temperature, the reaction mixture was partitioned between water (15 mL) and ether (4 times 10 mL). The combined extracts were dried over $MgSO_4$ and purified by column chromatography to give 553 mg (95%) of compound **5**.

$[\alpha]^2D^0$=+22.1° (c=0.0038, $CHCl_3$); IR (cm $^{-1}$): 3450, 3080, 2960, 1650; $^1$H NMR ($CDCl_3$, 200 MHz): δ 1.60 (m, 4H, $CH_2$), 1.7 (br, 2H, HO), 2.1-2.3 (m, 4H, $CH_2$), 3.45 (m, 2H, CH), 4.9-5.15 (m, 4H, $CH_2$), 5.75-5.95 (m, 2H, CH); $^{13}$C NMR: δ 138.44, 115.23, 77.84, 32.93, 30.11.

**(5*R*,6*R*)-Dibenzyloxy-1,9-decadiene (6).** To a mixture of **5** (20 mg, 0.12 mmol) and 60% dispersion NaH in oil (84 mg, 0.35 mmol) in 2 mL of THF was added benzyl chloride (44 mg, 0.35 mmol). Then 0.12 g of tert-butyl ammonium chloride was added. The reaction mixture was stirred for 27 hours. After dilution with ethyl ether, the organic layer was washed with water. The extract was dried over $MgSO_4$ and purified by column chromatography to give 41 mg (97%) of compound **6**.

FT-IR(neat, cm $^{-1}$): 3072.0, 3039.1, 2933.8, 2868.0, 1104.2, 1071.3; $^1$H NMR($CDCl_3$): δ 1.52-1.89(m, 4H, $C_{4,4'}$H), 2.01-2.39(m, 4H, $C_{3,3'}$H), 3.48-3.66(m, 2H, $C_{5,5'}$H), 4.49-4.73(q, 4H, $C_{6,6'}$H), 4.92-5.15(m, 4H, $C_{1,1'}$H), 5.71-5.99(m, 2H, $C_{2,2'}$H), 7.29-7.58(m, 10H); $^{13}$C NMR($CDCl_3$): δ 139.12, 138.99, 128.68, 128.28, 128.11, 127.94, 115.04, 79.47, 72.94, 30.47, 29.41.

**(5*R*,6*R*)-Di-(dichlorobenzyloxy)-1,9-decadiene (7).** To a solution of NaH in oil (68 mg of 60% dispersion, 1.13 mmol) in 2 mL DMF was added compound **5** (60 mg, 0.353 mmol) in 1 mL DMF. Then 2,6-dichlorobenzyl chloride (0.21 g, 1.06 mmol) was added. After being stirred for 3.5 hours at room temperature, the reaction mixture was partitioned between water (15 mL) and ether (3 times 10 mL). The combined extracts were dried over $MgSO_4$ and purified by column chromatography to give 139 mg (81%) of compound **7**.

mp 59-60 °C

FT-IR(cm $^{-1}$, neat): 3078.6, 2953.6, 2920.7, 1446.6, 1097.6; $^1$H NMR($CDCl_3$): δ 1.39-1.86(m, 4H, $C_{4,4'}$H), 1.91-2.39(m, 4H, $C_{3,3'}$H), 3.59-3.77(m, 2H, $C_{5,5'}$H), 4.73-4.90(q, 4H, $C_{6,6'}$H), 4.88-5.01(m, 4H, $C_{1,1'}$H), 5.64-5.94(m, 2H, $C_{2,2'}$H), 7.10-7.43(m, 6H, DCB); $^{13}$C NMR($CDCl_3$): d 138.72, 136.92, 133.72, 129.90, 128.42, 114.64($C_{1,1'}$), 78.18, 66.49, 30.29, 28.07.

**Iodocyclization of 5 and 7 to 8tt, 8ct, 8cc.** To a solution of **5** (30 mg, 0.18 mmol) and $NaHCO_3$ (89 mg, 1.1 mmol) in 3 mL of THF was added $I_2$ (450 mg, 1.8 mmol). The reaction mixture was stirred for 5 hours. Then sat-$Na_2S_2O_3$ solution was added until the reaction mixture was decolorized. The reaction mixture was partitioned between water (15 mL) and ethyl acetate (3 × 10 mL). The combined extracts were dried over $MgSO_4$ and purified by column chromatography to give 50.7 mg and 17.8 mg of two diastereomers **8tt** and **8ct**, respectively (chemical yield 92%).

A mixture of **5** (30 mg, 0.18 mmol) and $NaHCO_3$ (89 mg, 1.1 mmol) in 3 mL of THF was stirred at − 78 °C. Then $I_2$ (450 mg, 1.8 mmol) was added. The reaction mixture was stirred for 2 hours at − 78 °C and allowed to warm to room temperature. Then sat-$Na_2S_2O_3$ solution was added until the reaction mixture was decolorized. The reaction mixture was partitioned between water (15 mL) and ethyl acetate (3 times 10 mL). The combined extracts were dried over $MgSO_4$ and purified by column chromatography to give 68 mg of mixture **8tt** and **8ct** (92%).

A solution of **7** (60 mg, 0.12 mmol) in 2 mL of $CH_3CN$ was stirred at 0 °C. Then $I_2$ (94 mg, 0.37 mmol) was added. The reaction mixture was stirred for 3 hours at 0 °C. Then sat-$Na_2S_2O_3$ solution was added until the reaction mixture was decolorized. The reaction mixture was partitioned between water (15 mL) and ethyl acetate (3 times 10 mL). The combined extracts were dried over $MgSO_4$ and purified by column chromatography to give 42.2 mg of diastereomeric mixture (89%). The major product was **8cc** and the minor was **8ct**, which were not ease to separate, and the ratio of these diastereomers determined by $^{13}$C NMR peak height (**8cc : 8ct**=~90 : 10).

Compound **8tt**: $[\alpha]^2D^0$=+68.7°(c=0.0018, $CHCl_3$); Rf 0.69 (*n*-Hex : EA=2 : 1); $^1$H NMR($CDCl_3$, 200 MHz): δ 1.5-2.3 (m, 8H, $CH_2$), 3.1-3.36 (m, 4H, $CH_2I$), 3.83-4.22 (m, 4H, 2CHO); $^{13}$C NMR: δ 82.72, 78.97, 32.61, 28.59, 10.57; MS (m/e) 422($M^+$), 295, 237, 211, 210, 183, 141, 83, 55; HRMS: calcd for $C_{10}H_{16}I_2O_2$ 422.9240, found 421.9244, base peak 210.9620.

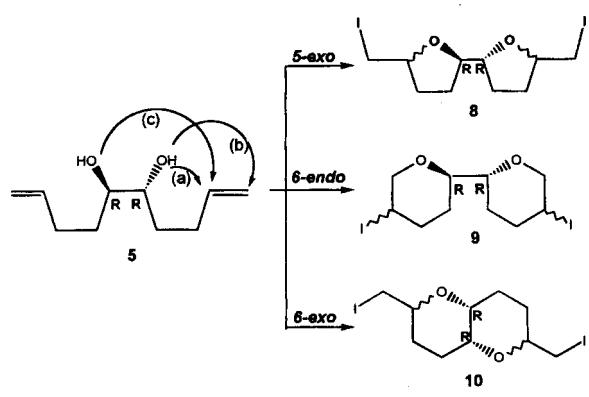
Compound **8ct**: Rf 0.65 (*n*-Hex : EA=2 : 1); $^1$H NMR ($CDCl_3$, 200 MHz): δ 1.66-1.82 (m, 4H, $CH_2$), 1.9-2.33 (md, 4H, $CH_2$), 3.1-3.36 (md, 4H, $CH_2I$), 3.9-4.16 (m, 4H, 2 CHO); $^{13}$C NMR: δ 83.10, 82.15, 79.22, 32.60, 32.40, 28.74, 27.54, 10.50; MS (m/e) 422($M^+$), 295, 237, 211, 210, 183, 113, 83, 55; HRMS: calcd for $C_{10}H_{16}I_2O_2$ 421.9240, found 421.9241, base peak 210.9620.

Compound **8cc** (data from the mixture of **8cc : 8ct**=~90 : 10): $^1$H NMR($CDCl_3$, 200 MHz): δ 1.46-2.35(m, 8H), 2.99-3.40(m, 4H), 3.77-4.23(m, 4H); $^{13}$C NMR: δ 82.73, 78.98, 31.33, 27.59, 10.49.

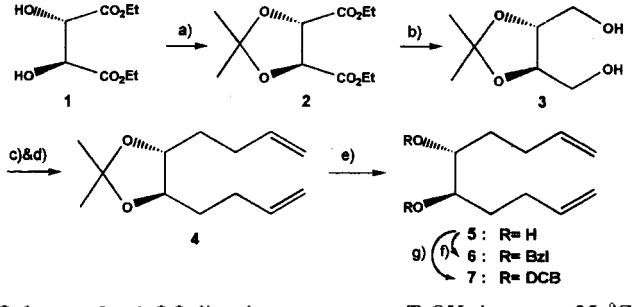
## Results and Discussion

**Synthesis of (5*R*,6*R*)-5,6-Dihydroxy-1,9-decadiene (5) and its Derivatives (6 and 7).** The synthesis started from commercially available (-)-diethyl D-tartrate (Scheme 1). The hydroxyl groups of diethyl tartrate were first protected by forming ketal **2** (94%) in 2,2-dimethoxypropane/p-TsOH/benzene, and resulting diester **2** was transformed to diol **3** (97%) by reduction using $LiAlH_4$ in THF.[4] The diol **3** was converted into the corresponding ditriflate in $Tf_2O/Et_3N/CH_2Cl_2$, and subsequent carbon-chain elongation with allylmagnesium bromide in ether at 0°C gave compound **4** (55%).[5] The protecting group of **4**, isopropylidene, was removed (95%) using 10N HCl in EtOH/$H_2O$ (4 : 1) at room temperature. The overall yield of five steps from (-)-diethyl tartrate to the bisolefinic diol **5** was 47%. The benzyloxy derivatives **6** and **7** were obtained from **5** in 97% and 81% yield, respectively.[6]

**Regioselectivity in the iodocyclization of (5*R*,6*R*)-5,6-dihydroxy-1,9-decadiene (5).** The electrophile-mediated cyclization of oxygen to yield cyclic ethers has provided a versatile and useful methodology for organic synthesis.[7] As an example, the iodocyclization of γ-hydroxyalkenes is a well known synthetic procedure to form a tetrahydrofuran ring.[8] In general, it is known that the regiochemistry of these types of reactions is controlled by a combination of electronic, steric and entropic factors. The ring-size selectivity could arise from one-step cyclization of γ,γ'-dihydroxydiene **5** as well as the *trans/cis* diastereoselectivity. As shown in Scheme 2, the cyclization of dihydroxydiene **5** could follow three different pathways: a) *5-exo* cyclization to form a THF-dimer **8**; b) *6-endo* cyclization to form a THP-dimer **9**; c) *6-exo* cyclization to form a fused THP-dimer **10**. According to the literature,[7-9] we can predict the preference for *5-exo* cyclization over *6-endo* and *6-exo* cyclizations, then THF-dimer **8** would be the major product among these. As predicted above, the iodocyclization of **5** gave only bifuran isomer **8** without producing other isomers (**9** and **10**). Our experimental results demonstrated another remarkable example for five-membered ring-selectivity in double cyclization.[10]



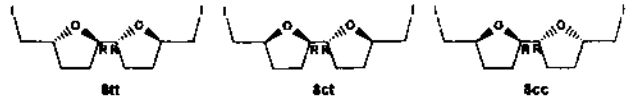

**Scheme 2.**




**Scheme 1.** a) 2,2-dimethoxypropane, *p*-TsOH, benzene, 25 °C, 94%. b) $LiAlH_4$, THF, 97%. c) $(CF_3SO_2)_2O$, $Et_3N$, $CH_2Cl_2$, −15 °C. d) allylmagnesium bromide, CuBr, ether, 0 °C, 55% from **3**. e) 10N HCl, EtOH-$H_2O$ (4 : 1), 25 °C, 3 hr, 95%. f) NaH, benzyl chloride, THF, 25 °C, 1 day, 97%. g) NaH, 2,6-dichlorobenzyl chloride, DMF, 25 °C, 3.5 hr, 81%.

***Cis/trans* selectivities in double cyclization of compound 5 and its derivatives.** In general, high stereocontrol for constructing 2,5-disubstituted tetrahydrofuran ring, in which two chiral centers are in a 1,3-relationship, is not very successful using conventional synthetic method. As an example, Rychnovsky and Bartlett have reported that the iodocyclization of 2-methyl-hept-6-en-3-ol under usual conditions ($I_2$, $NaHCO_3$, THF, 25 °C) showed 80/20 ratio of *trans/cis* 2,5-disubstituted tetrahydrofurans, where the *trans* isomer is slightly more stable than *cis* isomer thermodynamically.[8] As depicted in Fig. 2, three diastereomers **8tt, 8ct, 8cc** (**tt, ct, cc** designate *trans-trans, cis-trans*, and *cic-cis*, respectively) could be formed from double cyclization of compound **5**. Being applied to the double cyclization system upon the basis of *trans/cis* ratio of mono-THF ring formation, the iodocyclization of **5** could show about 64/32/4 ratio[11] of bifuran **8tt/8ct/8cc.**

In our experimental results, iodocyclization of **5** under the common reaction conditions ($I_2$, $NaHCO_3$, THF, 25 °C) gave bifurans **8tt**(68%) and **8ct**(24%). These two isomers were separable by silica gel column chromatography. Although these were analysized using $^1$H NMR, $^{13}$C NMR, and mass spectra, it was still not able to make a conclusion that the major product is *trans-trans* isomer **8tt**.[12] To check the possibility for the major product being a *cis-cis* isomer, we prepared **8cc** using a known method and compared its $^{13}$C NMR spectra with those of above two bifurans. In this way, we came to the indirect conclusion that **8cc** was not produced in the iodocyclization of **5**. Here, the compound **8cc**, which was not obtained in pure form, was prepared us-




(**tt, ct, cc** designate *trans-trans, cis-trans*, and *cic-cis*, respectively)

**Figure 2.** Stereoisomers of bifuran **8**.

**Table 1.** Diastereoselectivity of iodocyclization to bifuran

| Entry | Reaction conditions | Reactant | Yield | 8tt | 8ct | 8cc |
|---|---|---|---|---|---|---|
| 1 | $I_2$, $NaHCO_3$, THF, RT | 5 | 92% | 74 | 26 | - |
| 2 | $I_2$, $NaHCO_3$, THF, -78°-25 °C | 5 | 92% | 88 | 12 | - |
| 3 | NaI, MCPBA, THF | 5 | 74% | 74 | 26 | - |
| 4 | NIS, THF, RT | 5 | 91% | 75 | 25 | - |
| 5 | NIS, THF, -78°-25 °C | 5 | 95% | 77 | 23 | - |
| 6 | $ICH_2CH_2I$, $NaHCO_3$, THF, RT | 5 | 91% | 74 | 26 | - |
| 7 | $ICH_2CH_2I$, $NaHCO_3$, THF, -78°-25 °C | 5 | 87% | 77 | 23 | - |
| 8 | $I(collidine)_2ClO_4$, $CH_2Cl_2$, RT | 5 | 80% | 52 | 48 | - |
| 9 | $I_2$, $NaHCO_3$, $CH_3CN$, 0 °C | 6 | 52% | 30 | 35 | 35 |
| 10 | $I_2$, $NaHCO_3$, $CH_3CN$, 0 °C | 7 | 89% | | 10 | 90 |

The ratio of **8tt** & **8ct** are determined by HPLC (entry 1-8). The ratios in entry 9 & 10 are roughly estimate by the peak height on $^{13}C$ NMR of reaction mixture.

ing Bartlett's conditions ($I_2$, $NaHCO_3$, $CH_3CN$, 0 °C with compound **6** and **7**).[8] Since the *trans-trans* stereochemistry usually occurs in natural bis-THF acetogenins (Fig. 1), our initial study has been focused on investigating diastereoselectivity for **8tt** under various iodocyclization conditions. The experimental results are summarized in Table 1. Reaction of **5** with iodine at room temperature gave **8tt** and **8ct** in ratio of 74 : 26 (entry 1). When the reaction was started at -78 °C and warmed to 25 °C during the reaction, the stereoselectivity increased to some extent (entry 2; **8tt : 8ct**= 88 : 12). Similar stereoselectivity was observed with NaI-MCPBA (entry 3; **8tt : 8ct**=74 : 26), NIS (entry 4; **8tt : 8ct**= 75 : 25), and 1,2-diiodoethane (entry 6; **8tt : 8ct**=74 : 26), but the stereoselectivity was not improved in low temperature reaction (entry 5 & 7). On the other hand, the reaction of **5** with bis(symcollidine)iodine(I) perchlorate[13] did not show any stereoselectivity (entry 8; **8tt : 8ct**=52 : 48). The iodocyclization of **6** gave three isomers (entry 9; **8tt : 8ct : 8cc**=30 : 35 : 35), that of **7** gave two isomers (entry 10; **8ct : 8cc**=10 : 90). In our experiments, the best stereoselectivity for *trans-trans* isomer **8tt** was observed in reaction with iodine at -78°-25 °C (entry 2). As described above, the double cyclization, which has reasonably high diastereoselectivity (88 : 12) and chemical yield (92%), is one-step reaction to form two new chiral centers.[14] It could be a useful synthetic route to construct bifuran ring with the same stereochemistry as that of commonly occurring natural annonacea.

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11. The bis-THF ratio being expected can be calculated from $(\Phi_{trans})^2$: $2(\Phi_{trans} \times \Phi_{cis})$: $(\Phi_{cis})^2$, where the value of $\Phi_{trans}$ and $\Phi_{cis}$ are 0.8 and 0.2 respectively. The value of $\Phi_{trans}$ and $\Phi_{cis}$ are derived from the *trans/cis* product ratio in the iodocyclization of 5-hydroxy-6-methyl-1-heptene (see, ref. 8).
12. The conclusive structural determination of **8tt** was not able to be accomplished from NOESY and COSY.
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14. Another two chiral centers are derived from starting material (-)-diethyl D-tartrate.