

Article

## Observations on an Iodocarbonate Route to Certain 1,3-Diols Related to the C22-34 Subunit of FK-506

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A iodolactonização do carbonato alílico **2.8**, obtido pela adição da allenilestanana **2.4** ao enal **2.3**, promovida por  $\text{BF}_3$ , produziu o iodocarbonato **2.9** com inversão do estereocentro alílico. O estereoisômero esperado **2.11** foi formado em menor proporção. Essa inversão deve ter ocorrido através de um caminho dissociativo envolvendo o carbocátion alílico **5.2**.

Iodolactonization of the allylic carbonate **2.8**, secured through  $\text{BF}_3$ -promoted addition of allenylstannane **2.4** to enal **2.3**, afforded iodocarbonate **2.9** with inversion of the allylic stereocenter. The expected stereoisomer **2.11** was formed as a minor product. The inversion is thought to proceed by a dissociative pathway involving the allylic carbocation **5.2**.

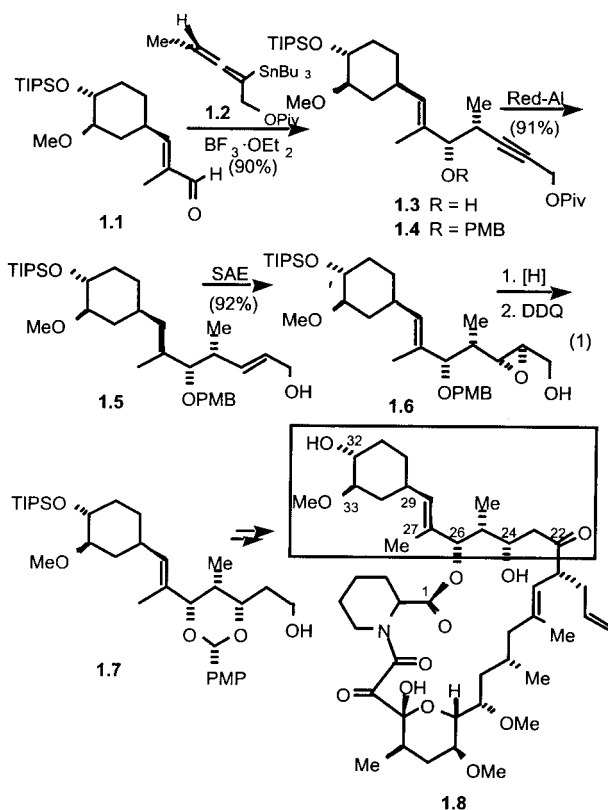
**Keywords:** iodolactonization, allylic carbonate, cyclic carbonate

### Introduction

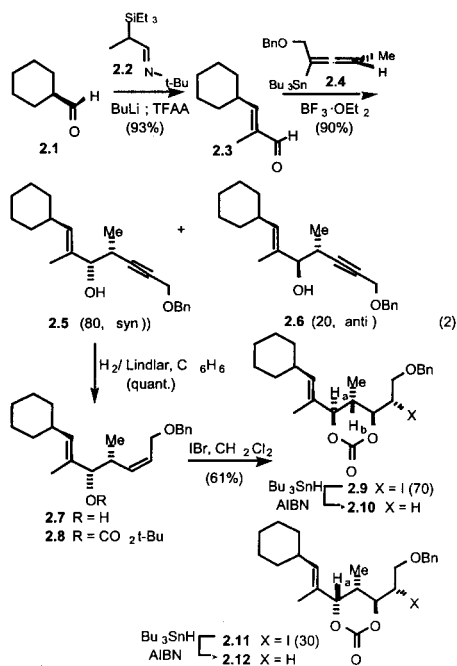
We recently described an efficient route to the C22-34 subunit **1.7** of the immunosuppressant FK-506 (**1.8**)<sup>1</sup>. A key feature of this synthesis was the homologation of enal **1.1** with the enantioenriched allenic stannane **1.2**<sup>2</sup> to yield the *syn* adduct **1.3**. Elaboration of this adduct was effected though reduction of the PMB derivative **1.4** to allylic alcohol **1.5** which could be epoxidized efficiently by Sharpless methodology. Subsequent reduction of epoxide **1.6** with DIBAL-H and oxidation afforded the dioxolane **1.7**, an intermediate in Danishefsky's synthesis of FK-506<sup>3</sup>.

In some related exploratory studies on alternative methodology for the conversion of homopropargylic alcohols, such as **1.3**, to 1,3-diols, we examined an iodocarbonate route. Although, for reasons that will become apparent, the sequence was not applicable to the FK-506 project, our findings provide some useful insights on potential applications of this methodology to similar intermediates.

The model system employed in these studies was the racemic aldehyde **2.3**, prepared by Peterson olefination of cyclohexanecarboxaldehyde with the imine **2.2** and subsequent hydrolysis<sup>4</sup>. Addition of the racemic allenylstannane **2.4**, in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  afforded an 80:20 mixture of separable *syn* and *anti* adducts **2.5** and **2.6**<sup>1,2</sup>. Hydrogenation of the former over Lindlar's catalyst<sup>5</sup> gave

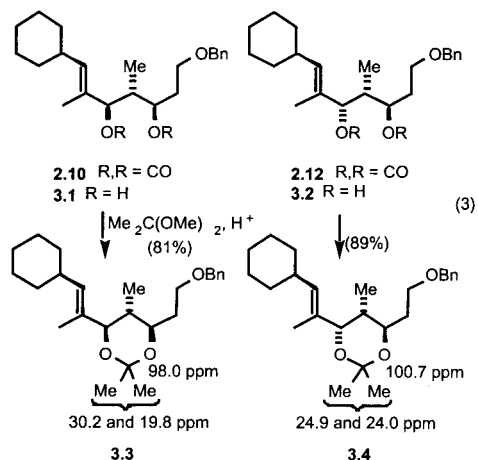


the (*Z*)-allylic alcohol **2.7** which, without purification, was converted to the *t*-butyl carbonate **2.8**. Upon treatment with IBr in CH<sub>2</sub>Cl<sub>2</sub> **2.8** gave rise to a 70:30 mixture of isomeric iodo carbonates **2.9** and **2.11**<sup>6</sup>.



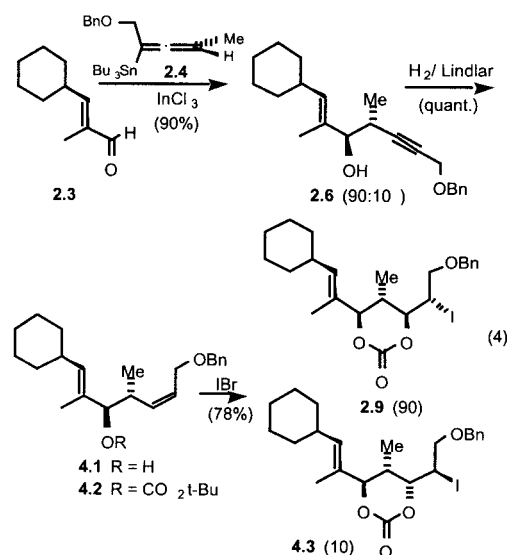
To our surprise the major iodo carbonate **2.9** displayed a doublet for the allylic carbonyl proton H<sub>a</sub> at 4.41 ppm with a coupling constant, *J* = 10.7 Hz, indicative of an *anti* (diaxial) relationship with H<sub>b</sub>. In the minor iodo carbonate this proton appeared at 4.76 ppm with *J* = 5.2 Hz. It can therefore be surmized that either a) our assignments of stereochemistry to alcohols **2.5** and **2.6** should be reversed or b) epimerization of the allylic carbonyl center has occurred *en route* to carbonates **2.9** and **2.11**.

As further proof for the structures of these iodo carbonates we effected their hydrogenolysis to **2.10** and **2.12** which were saponified to diols **3.1** and **3.2**. The <sup>13</sup>C-NMR

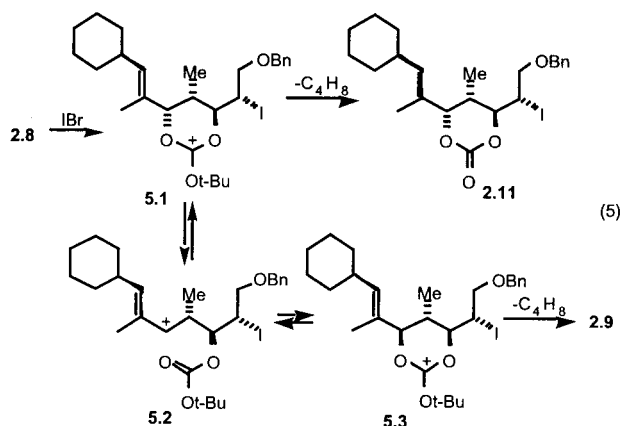


spectra of the derived acetonides **3.3** and **3.4** were in accord with the assigned structures as *anti,anti* and *syn,anti*.<sup>7</sup>

To confirm the stereochemical assignments of alcohols **2.5** and **2.6**, the addition of allenic stannane **2.4** to enal **2.3** was effected in the presence of InCl<sub>3</sub>, conditions previously shown to favor *anti* adducts.<sup>8</sup> This led to a 90:10 mixture of the alcohols produced in the BF<sub>3</sub> reaction, but now favoring **2.6**. Following the previous sequence, we prepared the (*Z*)-allylic carbonate **4.2**. Upon treatment with IBr, carbonate **4.2** afforded a 90:10 mixture of iodo carbonates **2.9** and, presumably, **4.3**.

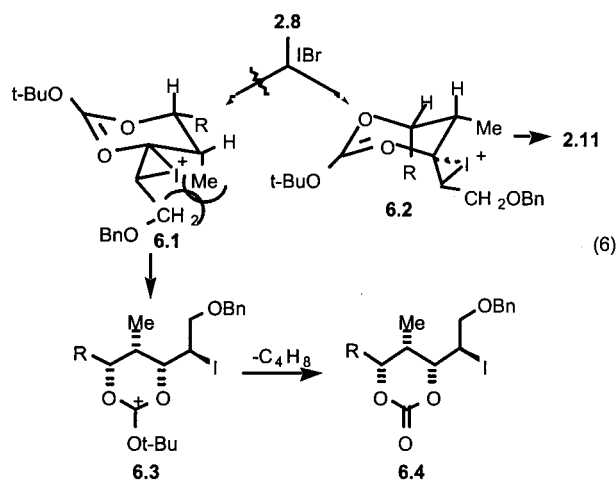


It can therefore be surmized that iodolactonization of the *syn* carbonate **2.8** proceeds with predominant inversion of the allylic carbonyl center. A plausible sequence of events is outlined in eq 5. Accordingly, attack of the carbonyl oxygen on the iodonium species derived from **2.8** would afford the intermediate oxo cation **5.1**. Loss of isobutylene would yield iodo carbonate **2.11**, one of the expected products<sup>6</sup>. However, a second low energy pathway could transform the strained oxo cation **5.1** to the



allylic cation **5.2**. This could then cyclize to the unstrained oxo cation **5.3** *en route* to the major product **2.9**.

It should be noted that the *syn,syn* cyclic carbonate **6.4** was not observed as a significant cyclization product of the *syn* carbonate **2.8**. Tirando and Prieto reported analogous findings for iodocarboxylation of a related *syn*, (*Z*)-homoallylic alcohol with CO<sub>2</sub>, I<sub>2</sub> and BuLi.<sup>9</sup> It is presumed that steric interactions in the transition state **6.1** disfavor this mode of cyclization. The *syn,syn* carbonate (diastereomeric with **6.4** at the iodo center) would expectedly be favored if the above sequence were effected on the (*E*)-isomer of carbonate **2.8**. However, this option was not pursued because a more satisfactory route to the *syn,syn* dioxolane **1.2** was developed as outlined in Eq. 1<sup>2</sup>.



The present findings reveal potential pitfalls in the use of the iodocarbonate sequence for introduction of oxygen stereocenters to homoallylic alcohols. In the present case, the complications stem from a combination of unfavorable steric interactions and a low energy dissociation pathway for the oxocation intermediate **5.1**.

## Experimental<sup>10</sup>

### (*E*)-3-Cyclohexyl-2-methyl-2-propenal (**2.3**)

To a solution of 7.38 g (32.5 mmol) of the *N*-*t*-butylimine of 2-(triethylsilyl)propanal<sup>4</sup> in 80 mL of THF was added 13.0 mL (32.5 mmol) of 2.5 M *n*-BuLi (in hexanes) dropwise at -78 °C. The reaction mixture was gradually warmed to -40 °C over 1.5 h and then recooled to -78 °C. To the yellow solution was added 2.80 g (25.0 mmol) of cyclohexanecarboxaldehyde dropwise. After being gradually warmed to -40 °C over 1.5 h, the mixture was treated with 6.73 mL (87.4 mmol) of trifluoroacetic acid, then warmed to 0 °C and stirred for 1 h, followed by addition of 14 mL of water. After being stirred at 0 °C for an additional 12 h (overnight), the mixture was diluted with water and extracted three times with Et<sub>2</sub>O. The combined

organic extracts were successively washed with saturated NaHCO<sub>3</sub> and brine, dried over anhydrous MgSO<sub>4</sub> and concentrated under reduced pressure. The brown residue was chromatographed on silica gel (10% Et<sub>2</sub>O-hexanes) to yield 3.53 g (93%) of aldehyde **2.3** as a yellow liquid: <sup>1</sup>H-NMR (400 MHz) δ 1.12-1.37 (m, 6 H), 1.66-1.77 (m, 4 H), 1.73 (d, *J* = 1.3 Hz, 3 H), 2.47 (m, 1 H), 6.28 (d, *J* = 9.5 Hz, 1 H), 9.35 (s, 1 H).

### (±)-(*E*, 3*S*, 4*R*)- and (*E*, 3*R*, 4*R*)-7-Benzoyloxy-1-cyclohexyl-2,4-dimethyl-1-hepten-5-yn-3-ol (**2.5** and **2.6**)

A solution of 637 mg (2.88 mmol) of InCl<sub>3</sub> in 5 mL of acetone was cooled to 0 °C, followed by addition of 438 mg (2.88 mmol) of aldehyde **2.3** in 0.5 mL of acetone. The solution was cooled to -40 °C; then 1.60 g (3.45 mmol) of stannane **2.4** was added in 1 mL of acetone. After being warmed to -30 °C, the mixture was stirred for 20 h, and then quenched with water. Acetone was mostly removed under reduced pressure and the resultant residue was diluted with water and extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous MgSO<sub>4</sub> and concentrated under reduced pressure to yield a yellow residue, which was chromatographed on silica gel (30% Et<sub>2</sub>O-hexanes) to provide 701 mg (76%) of more polar *anti* product **2.6** and 150 mg (16%) of a 1:1 mixture of **2.5** and **2.6** (*syn:anti*). This brought the total *syn/anti* ratio to 9:91.

**2.5** (*syn*) IR (film) 3444, 2230 cm<sup>-1</sup>; <sup>1</sup>H-NMR δ 0.98-1.31 (m, 6 H), 1.17 (d, *J* = 6.9 Hz, 3 H), 1.56-1.71 (m, 4 H), 1.64 (d, *J* = 1.3 Hz, 3 H), 1.70 (d, *J* = 4.6 Hz, 1 H), 2.17 (m, 1 H), 2.69 (m, 1 H), 3.91 (dd, *J* = 6.8, 3.4 Hz, 1 H), 4.13 (d, *J* = 2.0 Hz, 2 H), 4.55 (s, 2 H), 5.30 (d, *J* = 9.2 Hz, 1 H), 7.27-7.34 (m, 5 H); <sup>13</sup>C-NMR δ 137.6, 134.3, 132.6, 128.4, 128.0, 127.8, 88.8, 80.0, 77.8, 71.3, 57.6, 36.6, 33.0, 30.8, 26.1, 25.9, 16.3, 12.1.

**2.6** (*anti*) <sup>1</sup>H-NMR δ 0.98-1.29 (m, 6 H), 1.06 (d, *J* = 7.0 Hz, 3 H), 1.59-1.72 (m, 4 H), 1.59 (d, *J* = 1.2 Hz, 3 H), 2.12 (d, *J* = 3.3 Hz, 1 H), 2.18 (m, 1 H), 2.68 (m, 1 H), 3.75 (dd, *J* = 8.1, 3.1 Hz, 1 H), 4.17 (d, *J* = 1.9 Hz, 2 H), 4.57 (s, 2 H), 5.24 (d, *J* = 9.0 Hz, 1 H), 7.28-7.35 (m, 5 H); <sup>13</sup>C-NMR δ 137.5, 135.6, 131.8, 128.4, 128.1, 127.8, 88.4, 81.2, 78.4, 71.4, 57.6, 36.7, 33.0, 31.4, 26.1, 25.9, 17.6, 11.0.

Compounds **2.5** and **2.6** were also prepared by BF<sub>3</sub>•Et<sub>2</sub>O promoted addition of stannane **2.4** to aldehyde **2.3**.<sup>2</sup> In that case, the *syn* product **2.5** was favored over the *anti* product **2.6** by 80:20.

### (±)-(*1E*, 5*Z*, 3*S*, 4*R*,-)-7-Benzoyloxy-1-cyclohexyl-2,4-dimethyl-1,5-heptadien-3-ol (**2.7**)

A mixture of 200 mg (0.612 mmol) of alkynyl alcohol **2.5** and 20 mg of Lindlar's catalyst (10 wt% Pd) in 3 mL of benzene was stirred at rt under hydrogen (supplied and maintained from a balloon) for 5 h. The reaction mixture

was filtered through a short pad of Celite and washed with two portions of Et<sub>2</sub>O. The combined filtrate and washings were concentrated under reduced pressure to yield 201 mg (quantitative) of (*Z*)-olefin **2.7** which was used for the next step without further purification: <sup>1</sup>H-NMR δ 0.99 (d, J = 6.7 Hz, 3 H), 1.10-1.31 (m, 6 H), 1.45-1.70 (m, 5 H), 1.51 (d, J = 1.2 Hz, 3 H), 2.09-2.18 (m, 1 H), 2.51-2.64 (m, 1 H), 3.72 (d, J = 7.5, 3.1 Hz), 4.03 (d, J = 6.6 Hz, 2 H), 4.50 (ABq, J<sub>AB</sub> = 10.0 Hz, Δv = 11.4 Hz, 2 H), 5.15 (d, J = 9.1 Hz, 1 H), 5.36 (t, J = 10.0 Hz, 1 H), 5.53 (dt, J = 10.0, 6.6 Hz, 1 H), 7.25-7.34 (m, 5 H).

(±)-(1*E*, 5*Z*, 3*S*, 4*R*)-7-Benzoyloxy-1-cyclohexyl-2,4-dimethyl-1,5-heptadien-3-yl tert-Butyl Carbonate (**2.8**)

Two portions of dry hexane were used to wash 105 mg (0.913 mmol) of 35 wt% potassium hydride (oil dispersion). The washed potassium hydride was suspended in 0.6 mL of DMPU and 3 mL of THF at 0 °C, followed by addition of 201 mg (0.612 mmol) of alcohol **2.7**. The mixture was stirred for 1 h and 199 mg (0.913 mmol) of di-*t*-butyl dicarbonate was added in one portion. After being stirred at 0 °C for 3 h, the mixture was poured into saturated NaHCO<sub>3</sub> and extracted with Et<sub>2</sub>O. The combined organic extracts were washed with brine, dried over anhydrous MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 10% Et<sub>2</sub>O-hexane afforded 264 mg of *t*-butyl carbonate **2.8** as a colorless liquid (contaminated with a small amount of di-*t*-butyl dicarbonate): IR (film) 2980, 2924, 1739 cm<sup>-1</sup>; <sup>1</sup>H-NMR δ 0.97 (d, J = 6.7 Hz, 3 H), 1.00-1.30 (m, 6 H), 1.43 (s, 9 H), 1.45-1.70 (m, 4 H), 1.51 (s, 3 H), 2.05-2.18 (m, 1 H), 2.74-2.81 (m, 1 H), 4.01 (m, 2 H), 4.46 (ABq, J<sub>AB</sub> = 8.2 Hz, Δv = 5.7 Hz, 2 H), 4.60 (d, J = 8.5 Hz, 1 H), 5.20 (d, J = 9.2 Hz, 1 H), 5.30 (t, J = 10.1 Hz, 1 H), 5.55 (dt, J = 10.1, 6.3 Hz, 1 H), 7.25-7.34 (m, 5 H).

Cyclic Carbonates of (±)-(*E*, 3*R*, 4*S*, 5*S*, 6*S*)-7-Benzoyloxy-1-cyclohexyl-2,4-dimethyl-6-iodo-1-heptene-3,5-diol (**2.9**) and (±)-(*E*, 3*S*, 4*S*, 5*S*, 6*S*)-7-(Benzyl)oxy-1-cyclohexyl-2,4-dimethyl-6-iodo-1-heptene-3,5-diol (**2.11**)

#### A. Iodolactonization of *t*-Butyl Carbonate **2.8**

A solution of 264 mg (ca 0.612 mmol with di-*t*-butyl dicarbonate impurity) of *t*-butyl carbonate **2.8** in 6 mL of CH<sub>2</sub>Cl<sub>2</sub> was cooled to -78 °C, followed by addition of 1.40 mL (1.40 mmol) of iodine monobromide (1 M in CH<sub>2</sub>Cl<sub>2</sub>). The reaction was complete in less than 30 min. The reaction mixture was poured into water and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were successively washed with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and brine, dried over anhydrous MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 10% Et<sub>2</sub>O-hexanes afforded 131 mg (43% from **2.7**) of iodocar-

bonate **2.9** and 55.0 mg (18% from **2.7**) of iodocarbonate **2.11**, both as liquids.

**2.9** IR (film) 2923, 2846, 1754 cm<sup>-1</sup>; <sup>1</sup>H-NMR δ 0.76 (d, J = 6.7 Hz, 3 H), 0.95-1.35 (m, 6 H), 1.58-1.70 (m, 5 H), 1.64 (d, J = 1.2 Hz, 3 H), 2.10-2.20 (m, 2 H), 3.72 (dd, J = 10.1, 1.0 Hz, 1 H), 3.85 (t, J = 9.8 Hz, 1 H), 4.00 (dd, J = 9.8, 5.6 Hz, 1 H), 4.26 (ddd, J = 6.9, 3.5, 1.2 Hz, 1 H), 4.41 (d, J = 10.7 Hz, 1 H), 4.56 (ABq, J<sub>AB</sub> = 11.8 Hz, Δv = 22.7 Hz, 2 H), 5.30 (d, J = 10.2 Hz, 1 H), 7.29-7.38 (m, 5 H); <sup>13</sup>C-NMR δ 148.9, 140.2, 140.1, 137.5, 128.6, 128.1, 127.9, 127.8, 127.4, 89.5, 79.3, 73.5, 71.8, 36.8, 35.1, 32.8, 32.4, 31.3, 25.9, 25.7, 11.5, 10.6.

**2.11** IR (film) 2924, 2850, 1756 cm<sup>-1</sup>; <sup>1</sup>H-NMR δ 0.83 (d, J = 7.0 Hz, 3 H), 0.92-1.28 (m, 6 H), 1.45-1.75 (m, 5 H), 1.61 (d, J = 1.0 Hz, 3 H), 2.12-2.22 (m, 1 H), 2.35-2.43 (m, 1 H), 3.80-3.92 (m, 3 H), 4.19 (m, 1 H), 4.53 (ABq, J<sub>AB</sub> = 11.7 Hz, Δv = 23.0 Hz, 2 H), 4.76 (d, J = 5.2 Hz, 1 H), 5.25 (d, J = 9.2 Hz, 1 H), 7.24-7.35 (m, 5 H).

#### B. Iodolactonization of *t*-Butyl Carbonate **4.2**

The above procedure was applied to 228 mg (ca. 0.383 mmol with di-*t*-butyl dicarbonate impurity) of *t*-butyl carbonate **4.2** and 0.77 mL of iodine monobromide (1 M in CH<sub>2</sub>Cl<sub>2</sub>) in 4 mL of CH<sub>2</sub>Cl<sub>2</sub> at -78 °C for 15 min to yield a crude product as a brown liquid. The <sup>1</sup>H-NMR spectrum showed two products in the ratio of 90:10 by integration. The crude product was chromatographed on silica gel (10% Et<sub>2</sub>O-hexanes) to yield 133 mg (70% from **4.1**) of iodocarbonate **2.9** and 15.2 mg (8% from **4.1**) of the minor product. The spectral data (IR, <sup>1</sup>H and <sup>13</sup>C-NMR) of the major product were identical to those obtained from part A. However, the minor product consisted of a new compound, presumed to be **4.3**, not seen in the <sup>1</sup>H-NMR spectrum of the above minor product.

Cyclic Carbonate of (±)-(*E*, 3*R*, 4*R*, 5*R*)-7-Benzoyloxy-1-cyclohexyl-2,4-dimethyl-1-heptene-3,5-diol (**2.10**)

To a solution of 70 mg (0.140 mmol) of iodocarbonate **2.9** in 2 mL of benzene was added 56 μL (0.21 mmol) of *n*-Bu<sub>3</sub>SnH and 7 mg (0.042 mmol) of AIBN. The mixture was stirred at reflux for 6 h, cooled to rt and benzene was removed under reduced pressure. The residue was diluted with Et<sub>2</sub>O, treated with saturated KF and stirred for 15 min. The resultant suspension (*n*-Bu<sub>3</sub>SnF) was filtered and washed with two portions of Et<sub>2</sub>O. The combined filtrate and washings were diluted with water and extracted with Et<sub>2</sub>O. The combined organic extracts were washed with brine, dried over anhydrous MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 50% Et<sub>2</sub>O-hexanes afforded 41.9 mg (80%) of carbonate **2.10** as a liquid: IR (film) 2924, 2851, 1749 cm<sup>-1</sup>; <sup>1</sup>H-NMR δ 0.82 (d, J = 6.7 Hz, 3 H), 1.00-1.35 (m, 6 H), 1.50-1.90 (m, 6 H), 1.59 (d, J = 1.2 Hz,

3 H), 2.04-2.15 (m, 1 H), 2.15-2.30 (m, 1 H), 3.62-3.75 (m, 2 H), 4.26 (dt,  $J = 8.9, 2.4$  Hz, 1 H), 4.28 (d,  $J = 10.7$  Hz, 1 H), 4.50 (ABq,  $J_{AB} = 11.7$  Hz,  $\Delta\nu = 16.2$  Hz, 2 H), 5.30 (d,  $J = 9.2$  Hz, 1 H), 7.24-7.35 (m, 5 H);  $^{13}\text{C-NMR}$   $\delta$  149.6, 139.8, 138.2, 128.4, 127.7, 127.6, 90.6, 80.6, 73.3, 65.2, 36.8, 33.2, 32.8, 32.4, 26.1, 25.9, 25.8, 25.7, 12.2, 10.5.

*Cyclic Carbonate of ( $\pm$ )-(E, 3S, 4R, 5R)-7-Benzyloxy-1-cyclohexyl-2,4-dimethyl-1-heptene-3,5-diol (2.12)*

The dehalogenation procedure for carbonate **2.10** was applied to 27.0 mg (0.0541 mmol) of iodocarbonate **2.11**, 22  $\mu\text{L}$  (0.081 mmol) of *n*-Bu<sub>3</sub>SnH and 2.7 mg (0.016 mmol) of AIBN in 2 mL of benzene at reflux for 6 h to provide, after chromatography on silica gel (50% Et<sub>2</sub>O-hexanes), 18.8 mg (93%) of carbonate **2.12** as a liquid: IR (film) 2924, 2850, 1750  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz)  $\delta$  0.91 (d,  $J = 7.2$  Hz, 3 H), 1.02-1.30 (m, 6 H), 1.53-1.70 (m, 4 H), 1.55 (d,  $J = 1.9$  Hz, 3 H), 1.92-1.99 (m, 2 H), 2.03-2.24 (m, 2 H), 3.60-3.70 (m, 2 H), 4.43 (m, 1 H), 4.50 (ABq,  $J_{AB} = 11.8$  Hz,  $\Delta\nu = 16.4$  Hz, 2 H), 4.77 (d,  $J = 3.2$  Hz, 1 H), 5.27 (d,  $J = 9.1$  Hz, 1 H), 7.24-7.35 (m, 5 H);  $^{13}\text{C-NMR}$   $\delta$  149.0, 138.0, 134.4, 128.4, 127.8, 127.7, 126.3, 80.9, 80.7, 73.4, 65.8, 65.6, 36.8, 34.6, 32.8, 32.7, 32.3, 25.9, 15.3, 13.6, 11.8.

*( $\pm$ )-(E, 3R, 4R, 5R)-7-Benzyloxy-1-cyclohexyl-2,4-dimethyl-1-heptene-3,5-diol (3.1)*

A mixture of 40.0 mg (0.107 mmol) of carbonate **2.10** and 44.0 mg (0.322 mmol) of anhydrous K<sub>2</sub>CO<sub>3</sub> in 1.5 mL of methanol was stirred at rt for 5 h. The mixture was diluted with water and extracted with Et<sub>2</sub>O. The combined organic extracts were washed with brine, dried over anhydrous MgSO<sub>4</sub> and concentrated under reduced pressure to give 32.5 mg (87%) of *syn* 1,3-diol **3.1**: IR (film) 3394, 2926, 1449  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz)  $\delta$  0.60 (d,  $J = 6.9$  Hz, 3 H), 0.95-1.30 (m, 6 H), 1.50-1.70 (m, 6 H), 1.59 (d,  $J = 1.2$  Hz, 3 H), 1.85-1.95 (m, 1 H), 2.15-2.20 (m, 1 H), 3.61-3.80 (m, 3 H), 3.83 (d,  $J = 9.3$  Hz, 1 H), 3.94 (br s, 1 H), 4.27 (br s, 1 H), 4.51 (s, 2 H), 5.15 (d,  $J = 9.0$  Hz, 1 H), 7.24-7.35 (m, 5 H);  $^{13}\text{C-NMR}$   $\delta$  137.8, 135.2, 133.8, 128.5, 128.4, 127.8, 127.7, 86.0, 73.5, 69.1, 40.6, 36.5, 34.2, 33.0, 32.9, 26.1, 26.0, 13.5, 10.7.

*( $\pm$ )-(E, 3S, 4R, 5R)-7-Benzyloxy-1-cyclohexyl-2,4-dimethyl-1-heptene-3,5-diol (3.2)*

The procedure for diol **3.1** was applied to 18.0 mg (0.0483 mmol) of *anti* 1,3-diol carbonate **2.12** and 20.0 mg (0.145 mmol) of anhydrous K<sub>2</sub>CO<sub>3</sub> in 1.5 mL of methanol at rt for 5 h to give 15.7 mg (94%) of *anti* 1,3-diol **3.2**: IR (film) 3415, 2915, 1446  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$   $\delta$  0.85 (d,  $J = 7.1$  Hz, 3 H), 1.00-1.30 (m, 6 H), 1.53 (s, 3 H), 1.54-1.80 (m, 6 H), 1.89-1.99 (m, 1 H), 2.15-2.23 (m, 1 H), 2.80 (br s, 1

H), 3.56-3.76 (m, 3 H), 3.84 (m, 1 H), 4.28 (br s, 1 H), 4.51 (s, 2 H), 5.27 (d,  $J = 9.1$  Hz, 1 H), 7.24-7.35 (m, 5 H);  $^{13}\text{C-NMR}$   $\delta$  137.8, 133.2, 131.0, 128.5, 127.8, 127.7, 75.4, 75.3, 73.5, 69.7, 40.2, 36.7, 34.4, 33.2, 33.1, 26.1, 13.8, 10.3.

*3,5-Acetonide Derivative of ( $\pm$ )-(E, 3R, 4R, 5R)-7-Benzyloxy-1-cyclohexyl-2,4-dimethyl-1-heptene-3,5-diol (3.3)*

A mixture of 32.5 mg (0.0937 mmol) of *syn* 1,3-diol **3.1** and 1.8 mg of *p*-TsOH (monohydrate) in 2 mL of 2,2-dimethylpropane was stirred at rt for 6 h. The reaction mixture was concentrated under reduced pressure to give a residue which was chromatographed on silica gel. Elution with 10% Et<sub>2</sub>O-hexane yielded 29.3 mg (81%) of *syn* 1,3-diol acetonide **3.3**: IR (film) 2923, 2854, 1453  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz)  $\delta$  0.66 (d,  $J = 6.7$  Hz, 3 H), 0.97-1.76 (m, 12 H), 1.37, 1.43 (s, 6 H), 1.61 (s, 3 H), 1.99 (m, 1 H), 2.17-2.25 (m, 1 H), 3.59 (m, overlapped, 2 H), 3.66 (dt,  $J = 9.7, 2.3$  Hz, 1 H), 3.77 (d,  $J = 10.3$  Hz, 1 H), 4.50 (ABq,  $J_{AB} = 12.0$  Hz,  $\Delta\nu = 24.8$  Hz, 2 H), 5.24 (d,  $J = 8.8$  Hz, 1 H), 7.25-7.35 (m, 5 H);  $^{13}\text{C-NMR}$   $\delta$  138.7, 136.4, 131.2, 128.3, 127.6, 127.5, 98.0, 82.2, 73.0, 71.3, 66.6, 36.7, 35.8, 33.7, 33.0, 32.7, 30.2, 26.1, 26.0, 25.9, 19.8, 12.2, 11.0.

*3,5-Acetonide Derivative of ( $\pm$ )-(E, 3S, 4R, 5R)-7-Benzyloxy-1-cyclohexyl-2,4-dimethyl-1-heptene-3,5-diol (3.4)*

The procedure for acetonide **3.3** was applied to 15.7 mg (0.0453 mmol) of *anti* 1,3-diol **3.2** and 0.8 mg of *p*-TsOH (monohydrate) in 2 mL of 2,2-dimethylpropane at rt for 6 h to give, after chromatography on silica gel (10% Et<sub>2</sub>O-hexane), 15.5 mg (89%) of *anti* 1,3-diol acetonide **3.4**

IR (film) 2915, 2846, 1446  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz)  $\delta$  0.66 (d,  $J = 6.8$  Hz, 3 H), 1.05-1.28 (m, 6 H), 1.31, 1.51 (s, 6 H), 1.51 (s, 3 H), 1.56-1.79 (m, 6 H), 1.87 (m, 1 H), 2.14-2.22 (m, 1 H), 3.40 (m, 1 H), 3.56 (m, 2 H), 4.18 (d,  $J = 5.0$  Hz, 1 H), 4.49 (ABq,  $J_{AB} = 12.0$  Hz,  $\Delta\nu = 18.7$  Hz, 2 H), 5.23 (d,  $J = 9.1$  Hz, 1 H), 7.25-7.35 (m, 5 H);  $^{13}\text{C-NMR}$   $\delta$  138.6, 130.2, 130.0, 128.3, 127.6, 127.5, 100.7, 73.1, 71.8, 71.7, 67.2, 39.6, 36.6, 35.0, 33.4, 33.2, 26.2, 26.1, 24.9, 24.0, 14.1, 12.0.

*( $\pm$ )-(1E, 5Z, 3R, 4R)-7-Benzyloxy-1-cyclohexyl-2,4-dimethyl-1,5-heptadien-3-ol (4.1)*

The procedure for diene **2.7** was applied to 125 mg (0.383 mmol) of alkynyl alcohol **2.6** and 12.5 mg of Lindlar's catalyst (10 wt% Pd) under hydrogen in 3 mL of benzene at rt for 5 h to yield 128 mg (quantitative) of crude (*Z*)-olefin **4.1** which was used for the next step without further purification:  $^1\text{H-NMR}$   $\delta$  0.78 (d,  $J = 6.8$  Hz, 3 H), 1.02-1.38 (m, 6 H), 1.50-1.79 (m, 4 H), 1.56 (d,  $J = 1.3$  Hz, 3 H), 2.09-2.20 (m, 1 H), 2.27 (d,  $J = 2.6$  Hz, 1 H), 2.50-2.58 (m, 1 H), 3.53 (dd,  $J = 7.5, 2.6$  Hz, 1 H), 4.05 (dd of ABq,

$J_{dd} = 7.1, 2.5$  Hz,  $J_{AB} = 11.5$  Hz,  $\Delta\nu = 32$  Hz, 2 H), 4.53 (s, 2 H), 5.18 (d,  $J = 9.1$  Hz, 1 H), 5.47 (t,  $J = 10.0$  Hz, 1 H), 5.79 (dt,  $J = 10.0, 6.6$  Hz, 1 H), 7.25-7.34 (m, 5 H).

(±)-(1E, 5Z, 3R, 4R, )-7-Benzoyloxy-1-cyclohexyl-2,4-dimethyl-1,5-heptadien-3-yl tert-Butyl Carbonate (**4.2**)

The procedure for *t*-butyl carbonate **2.8** was applied to 128 mg (ca. 0.383 mmol) of alcohol **4.2**, 65.8 mg (0.574 mmol) of 35 wt% potassium hydride (oil dispersion) and 126 mg (0.0574 mmol) of di-*t*-butyl dicarbonate in 0.5 mL of DMPU and 2 mL of THF at 0 °C for 3 h to give, after chromatography on silica gel (10% Et<sub>2</sub>O-hexanes), 228 mg of *t*-butyl carbonate **4.2** as a colorless liquid (contaminated with a small amount of di-*t*-butyl dicarbonate): <sup>1</sup>H-NMR δ 0.84 (d,  $J = 6.8$  Hz, 3 H), 0.90-1.30 (m, 4 H), 1.39 (s, 9 H), 1.42-1.75 (m, 6 H), 1.57 (d,  $J = 1.2$  Hz, 3 H), 2.10-2.19 (m, 1 H), 2.65-2.75 (m, 1 H), 4.09 (dd of ABq,  $J_{dd} = 5.7, 1.5$  Hz,  $J_{AB} = 12.5$  Hz,  $\Delta\nu = 38.9$  Hz, 2 H), 4.50 (s, 2 H), 4.63 (d,  $J = 8.9$  Hz, 1 H), 5.26 (d,  $J = 9.0$  Hz, 1 H), 5.41 (t,  $J = 10.1$  Hz, 1 H), 5.61 (dt,  $J = 10.1, 6.2$  Hz, 1 H), 7.24-7.34 (m, 5 H).

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