A Method for *Syn*-Dihydroxylation of Double Bonds *Cis* to a Hydroxymethyl Substituent

Rasmus P. Clausen and Mikael Bols*

Department of Chemistry, Aarhus University, Aarhus DK-8000 C, Denmark

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Introduction

Syn dihydroxylation of olefins is an extremely useful synthetic transformation in organic chemistry. It is usually carried out with OsO_4 or $KMnO_4$ giving normally preferential addition to the double bond from the least-hindered side of the molecule.[1] Even though examples of preferential addition of the diol from the more-hindered side do exist,[2] they appear to be exceptional cases. Substrate-directed addition, which is successful for many other reactions, does not work well for osmylations,[3] and therefore control of the diastereoselectivity of the transformation seems to be a problem.

Nevertheless, addition of the diol from the more-hindered face could be very useful. In a research program where carbohydrate mimetics with a galactose type stereochemistry was needed (carbocyclic or heterocyclic six-ring systems with an overall *syn cis* 2,3-dihydroxy-1-hydroxymethyl substitution, Figure 1), it was obvious that a potentially very convient way of obtaining these compounds would be by a dihydroxylation of the corresponding homoallylic alcohol from the hydroxymethyl face. Osmium tetraoxide-catalyzed dihydroxylation cannot be applied to obtain this stereochemistry: Kishi has shown that dihydroxylation of 3-methylcyclohexene with OsO_4 gives exclusively addition from the *anti* face,[4] while similar dihydroxylation of *N*-methyl-3-hydroxymethylpiperid-4-ene gives a 5:1 ratio of *anti* over *syn* addition.[5]

In contrast to dihydroxylation, intramolecular addition of nucleophiles to an olefin activated by electrophiles occurs from the *syn* face with high stereoselectivity.[6] The arch-type reaction of this kind is the well-known halolactonization;[7] this procedure has been further developed to tethered versions involving cyclic carbonates[8] and ureas[9] as well as haloetherifications[10] and halosiloxylations.[11] These reactions add an oxygen nucleophile from the *syn* face and a leaving group from the *anti* face. Thus nucleophilic substitution of the leaving group with an oxygen nucleophile should lead to the desired *syn syn* diol. The halocarbonate reactions have been used to epoxidize the *syn* face, but there are to our knowledge no examples of a transformation that results in a *syn* dihydroxylation of the hydroxymethyl face of a ring.[12]

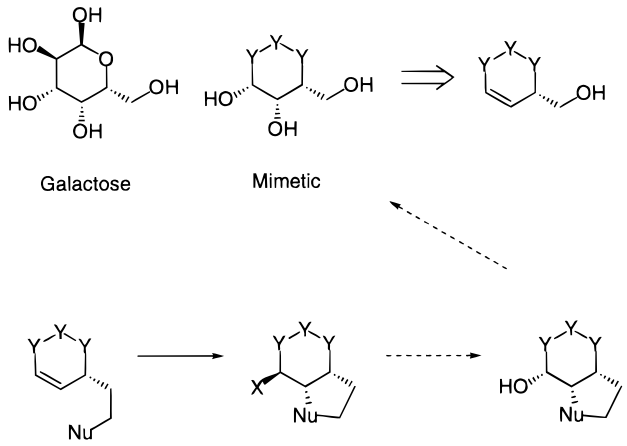

Figure 1.

In this paper we present an indirect procedure based on halolactonization that allows diastereoselective *cis*/*cis* dihydroxylation of a homoallylic double bond. We also present a new haloacetalization reaction.

Results and Discussion

To use a halolactonization type reaction for hydroxyl-directed dihydroxylation a tethered reaction was required in which the tether could be connected to a hydroxy-group and contained an O-nucleophile. Two solutions were found to this problem: A method based on the halolactonization reactions of Rousseau[7b] and a haloacetalization reaction using the 2-trimethylsilylethoxymethyl (SEM) group. In the first case an acetate residue is connected to the hydroxyl group and this is used to direct attack in a halolactonization. Later the acetate is removed by α-bromination and hydrolysis. In the second case an allylic or homoallylic alcohol is protected as a SEM group, which then with halonium ions undergo reaction to form a methylene acetal.

All the halonium-promoted reactions reported in this paper were attempted with NIS, iodonium dicollidine perchlorate (IDCP), ICl, and I_2/KI as well as iodonium dicollidine hexafluorophosphate (IDCH) and bromonium dicollidine hexafluorophosphate (BrDCH), but similarly to Rousseau[7b,c] we found that IDCH and BrDCH gave the best results. Since no proper literature procedure for synthesis of these reagents have been reported, we describe their synthesis in the Experimental Section.

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(12) For an example where the *cis-cis*-2,3-dihydroxy-1-hydroxymethyl substructure was obtained in another way, see ref 1a.

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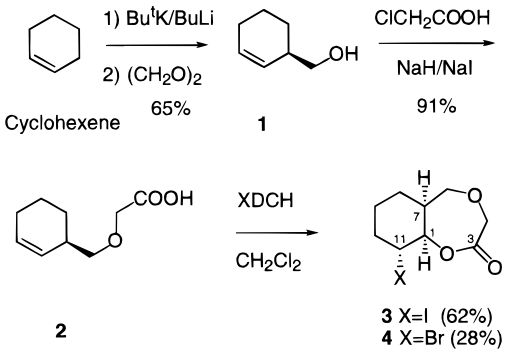
Scheme 1

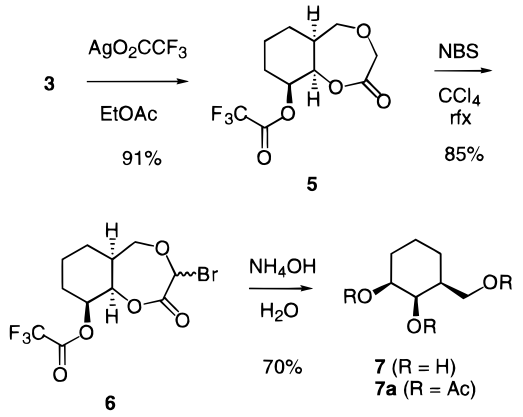


The study was carried out on cyclohex-2-enemethanol (**1**), which was synthesized from cyclohexene by deprotonation with Schlossers base[13] (BuLi/Bu^{t}K) and alkylation with paraformaldehyde (Scheme 1). This gave **1** in 65% yield.[12]

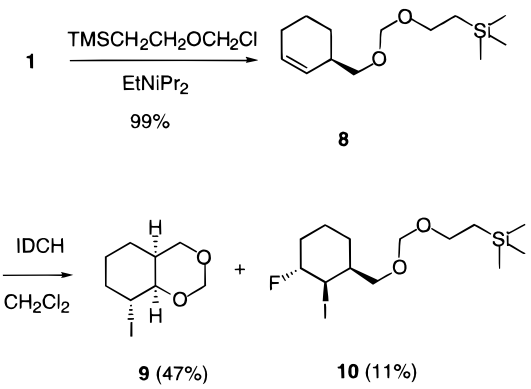
Halolactonization Strategy. The homoallyl alcohol **1** was reacted with chloroacetate in the presence of NaH and NaI (nucleophilic catalyst) in THF to give the corresponding carboxymethylated alcohol **2** in 91% yield (Scheme 1). Treatment of **2** in CH_2Cl_2 with IDCH, formed in situ from the silver salt and I_2, gave the iodolactone **3** as a single product in 62% yield. Rousseau has carried out the same type of reaction on acyclic systems, forming seven-membered lactones in good yield.[7b] However, the fact that this bicyclic version of his reaction is stereoselective is remarkable, because the lactone is so large that a *trans*-fused system could easily be formed. The structure of **3** was therefore critically analyzed by ^{1}H NMR. The most downfield proton H-1 (δ 4.95) only has small couplings. This is inconsistent with *trans*-fused rings, because such a stereochemical relationship would force H-1 and H-7 to be axial giving a large $J_{1,7}$. The substitution at C-1 and C-7 must therefore be *cis* as depicted. The very downfield chemical shift of H-1 also show that it is equatorial. Furthermore, H-11 (δ 4.63) has relatively small couplings as well ($J \leq 6$ Hz) showing that this proton is equatorial, and the iodine axial. This means that the substituents at C-1 and C-11 have a *trans* relationship. Stereoselectivity is probably caused by stringent geometrical requirements to the position of the nucleophile in order to be able to open the iodonium ion. The carboxylate has to attack from an almost axial position, and it is difficult to meet these requirements on the anti face. The reaction was also attempted with BrDCH, giving the corresponding bromolactone **4** in 28% yield.

The iodide **3** was now substituted with trifluoroacetate by reaction with AgO_2CF_3 in EtOAc at 0 °C (Scheme 2). This gave the trifluoroacetate **5** with inversion of configuration in a remarkable yield of 91%. In a case such as this, where the reagent is a silver salt, the configurational assignment should be carried out with caution, as both inversion or retention of configuration could be anticipated. Indeed, literature examples of both stereochemical behaviors, as well as rearrangements, can be found for iodide substitution with AgO_2CF_3.[15] However, as with the iodide **3**, ^{1}H NMR clearly shows the relative stereochemistry of **5**. The H-1 proton (δ 4.78) only has

Scheme 2



Scheme 3



small couplings, while H-11 (δ 3.85) has one large coupling ($J = 9.5$ Hz). This shows that H-11 is axial and has one diaxial coupling, but not to H-1. Therefore, H-1 must be equatorial, and the C-1/C-11 substituents must consequently have a *cis* stereochemistry.

The acetate tether was removed using the following sequence: Lactone **5** was subjected to radical bromination conditions using NBS in CCl_4 at reflux[16] in the presence of radical initiator lauryl peroxide. This reaction gave the bromide **6** in 85% yield as one compound but with unknown stereochemistry at C-4. The bromoether **6** was subjected to hydrolysis using aqueous ammonia at 0 °C, which removed both bromoacetate and trifluoroacetate to give the triol **7**. This compound was characterized as the triacetate **7a**, which was obtained in 70% yield from **6**. The stereochemistry could also be confirmed from the NMR spectra of **7a**. The low field chemical shift of H-2 (δ 5.32) shows that it is an equatorial proton. The H-3 proton (δ 4.69) has a large coupling ($J = 9$ Hz) to another proton, which shows that it is axial. Their large coupling is not to H-2, however, which again shows that H-2 is equatorial. Thus the acetylated diol has *cis* stereochemistry.

Haloacetalization Strategy. Reaction of **1** with SEM chloride and Hünigs base in CH_2Cl_2 gave the SEM ether **8** in 99% yield. This compound was reacted with IDCH, generated in situ, in CH_2Cl_2. This gave the iodoacetal **9**

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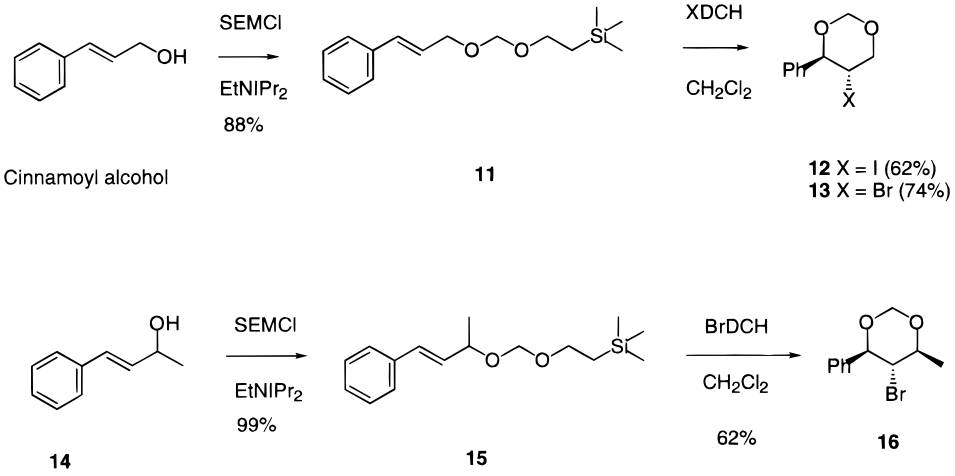
Scheme 4



as the main product in 47% yield. The fluorinated derivative **10** was isolated as a byproduct in 11% yield. The regio- and stereochemistry of the two products were determined from one- and two-dimensional NMR spectra. In **9** the iodide carbon is again easily assigned in HETCOR as the upfield ^{13}C (32.7 ppm) correlating to a downfield ^{1}H (4.52 ppm). In COSY this proton couples to a proton below 2.0, which is from a CH_2 rather than a CH, meaning that iodide has substituted at C-10, coupling to a proton on C-1 (δ 3.98). As in **3** and **5** the arguments of *cis* relationship between C-1 and C-6 holds in bicyclic iodide **9**, too. The H-1 only has small couplings and must be equatorial. This is the case with the H-10 also, and the configuration of **9** must therefore be as shown in Scheme 3. In compound **10** the fluorine-substituted carbon exhibits excessive coupling in ^{13}C NMR. Only three carbons showed C−F couplings: A peak at 91.7 ppm shows one-bond coupling, while two signals at 37.2 and 25.4 ppm showed two-bond couplings. This leads to the conclusion that the fluoride is substituted at C-3; otherwise it would not couple with the C-4 (25.4 ppm). The HETCOR of **10** also reveals the C-2 (37.2 ppm) and H-2 (δ 4.7) to be the iodo-substituted site, and this carbon couples with fluorine as expected. The H-3 (δ 5.02) only has small couplings and must therefore be equatorial. The H-2 signal has a relatively low chemical shift of δ 4.7, which also fits an equatorial proton as compared with H-10 in **9** or H-11 in **3**. Thus, the two halogen atoms must be *trans*. Assuming a chair conformation with two *trans* axial substituents, it is fair to conclude that the C-1 SEM,oxymethyl-substituent is equatorial since if it was axial the compound would be expected to shift to the all-equatorial chair confomation. It is therefore concluded that the stereochemistry of **10** is as shown in Scheme 3.

The formation of stereoisomer **9** is expected to give the stereoselectivity of the reaction **2** to **3** since in this case the new ring is smaller. The formation of the fluoride **10** is more surprising. The stereochemistry of **10** suggests that it is formed from the *cis* iodonium ion that cannot lead directly to **9**. In any case the lesser efficiency of this reaction compared to the halolactonization makes this strategy less attractive.

We also tried this new haloacetalization reaction on allyl alcohols. The SEM-protected alcohol **11** was synthesized by reaction of cinnamoyl alcohol with SEM chloride and Hünigs base (Scheme 4). Reaction of **11** with IDCH in CH_2Cl_2 gave the iodo acetal **12** in 62% yield as the only product. The structure including stereochemistry is easily seen from the observations obtained by ^{1}H NMR and HETCOR that the proton (H-5) of the iodo-substituted carbon has three couplings of which two are large. This is only possible in the isomer shown (Scheme 4).

Reaction of **11** with bromonium dicollidine hexafluorophosphate (BrDCH) was an even faster and more-efficient reaction, giving the corresponding bromide **13** in 74%. The reaction occurred with rapid evolution of a colorless gas presumably ethylene. Gas evolution was also observed in the formation of **12** and **9** but at a much slower pace. The structure of **13** was determined similarly to **12** from the couplings of H-5 (δ 4.14).

The reaction also worked on the methyl analogue **15** (obtained by SEM protection of **14** in 99% yield). Treatment with of **15** with BrDCH gave the dioxane **16** in 62% yield as the only product. The different regioselectivity on the reations of cinnamoyl derivatives, as compared with the cyclohexene system, leading to endo and not exo opening of the halonium ions, is undoubtedly caused by the stabilizing effect of the phenyl group toward carbocations. The results show that the haloacetalization reaction of a SEM group is an interesting reaction but less effective for solving the problem at hand.

The present work has shown that carboxymethylation of a homoallylic alcohol with chloroacetic acid followed by IDCH-promoted iodolactonization and substitution of the iodide with silver trifluoroacetate can be used for diastereoselective *syn-syn* dihydroxylation of the double bond. The method works on a cyclic alkene. It is likely that the method can be extended to cyclic allylic alcohols as well since the basic principles governing the stereoselectivity should be the same.

Experimental Section

General. ^{13}C NMR and ^{1}H NMR spectra were recorded on a Varian Gemini 2000 instrument using DHO (^{1}H NMR: δ 4.7 ppm) or acetone (^{1}H NMR: δ 2.05 ppm; ^{13}C NMR: δ 29.8 ppm) as reference. EI mass spectra were obtained using a VG TRIO-2 spectrometer. Concentrations were carried out on a rotary evaporator at temperatures below 40 °C. TLC was performed on Kieselgel 60 F_{254} glass-backed plates (Merck) with detection by soaking in 1% cerium sulfate and 1.5% molybdic acid in 10% aqueous H_2SO_4 followed by heating to 200 °C for 60 s. The pyridine was dried over KOH.

Silver Dicollidine Hexafluorophosphate. $AgNO_3$ (9.00 g, 53.0 mmol) and $NaPF_6$ (11.0 g, 65.5 mmol) were dissolved in H_2O (100 mL), and 2,4,6-collidine (20.0 mL) was added. After

stirring for 30 min. the precipitate was filtered on a sintered glass funnel and washed with H_2O (4×, EtOH (1×), and Et_2O (2×). The white material was dried in a desiccator in vacuo over silica, giving the title compound (25.9 g, 52.3 mmol, 99%).

Bromonium Dicollidine Hexafluorophosphate (BrDCH). To silver dicollidine hexafluorophosphate (9.90 g, 20.0 mmol) in CH_2Cl_2 (100 mL) was added Br_2 (~1.00 mL, ~3.20 g, 20.0 mmol) dropwise. Addition was continued until the solution became colored. The solution was filtered through Celite, leaving the precipitated AgBr on the filter. Upon evaporation, Et_2O was added to the residue. The precipitate was filtered, washed with pentane, and dried in vacuo, giving bromonium dicollidine hexafluorophosphate (7.84 g, 16.8 mmol, 84%) as off-white crystals.

Iodonium Dicollidine Hexafluorophosphate (IDCH). To silver dicollidine hexafluorophosphate (13.8 g, 27.9 mmol) in CH_2Cl_2 (150 mL) was added finely ground I_2 (7.00 g). Pale yellow AgI precipitated and after 30 min the solution was filtered through Celite. The solution was evaporated to ~20 mL, and Et_2O (50 mL) was added. Filtration, washing with pentane, and drying in vacuo gave the title compound as off-white crystals (12.1 g, 23.5 mmol, 85%).

Cyclohex-2-enemethanol (1). Potasium *tert*-butoxide (17.0 g, 0.152 mol) was suspended in distilled cyclohexene (110 mL) degassed with N_2. BuLi (100 mL, 1.6 M, 0.16 mol) was added dropwise over 2 h, keeping the temperature under 40 °C. The reaction was left stirring overnight leaving a brownish yellow suspension. The mixture was heated to 60 °C. Paraformaldehyde (5.2 g, 0.172 mol) (dried over silica) was carefully added portionwise causing an exothermic reaction upon every addition. At the end of addition a clear light green solution evolves which was left stirring for 1 h. The solution was cooled and poured into NH_4Cl (aq) at 0 °C. The organic phase was separated and the aqueous phase extracted with 3 × 150 mL of CH_2Cl_2. The collected organic phases were washed with 3 × 100 mL H_2O/NaCl(aq)/H_2O, dried ($MgSO_4$), and evaporated. Distillation gave 11.0 g of **1** (0.098 mol, 65%).[14] ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.6−5.5 (dm, 1H), 5.45−5.35 (dm, 1H), 3.45 (s, 1H), 3.25 (d, 2H), 2.15−2.0 (m, 1H), 1.85−1.75 (m, 2H), 1.65−1.5 (m, 2H), 1.45−1.3 (m, 1H), 1.25−1.1 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 128.7, 127.8, 66.4, 37.9, 25.3, 25.1, 20.7.

Cyclohex-2-enylmethoxyacetic Acid (2). To 2.24 g (20.0 mmol) of **1**, 2.1 g (22 mmol) of chloroacetic acid, and a catalytic amount of NaI in 50 mL of THF was added 2.4 g (80 mmol) NaH (80% dispersion in mineral oil). The mixture was refluxed overnight and poured on 100 mL H_2O (0 °C). The aqueous basic solution was washed with 100 mL of Et_2O, acidified (H_2SO_4), and extracted with 3 × 100 mL of CH_2Cl_2. The collected organic phases were dried ($MgSO_4$) and evaporated. Column chromatography (SiO_2, 2% AcOH in EtOAc) gave 3.10 g (18 mmol, 91%) of **2**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.1 (s, 1H) 5.6−5.5 (dm, 1H), 5.45−5.35 (dm, 1H), 3.95 (s, 2H), 3.25 (d, 2H), 2.25−2.15 (m, 1H), 1.8−1.7 (m, 2H), 1.7−1.05 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 175.7, 128.9, 127.4, 75.9, 67.7, 35.4, 25.6, 25.1, 20.6.

(1*RS*,7*SR*,11*RS*)-2,5-Dioxa-11-iodo-3-oxobicyclo[5.4.0]-undecane (3). To 9.90 g (20.0 mmol) of silver dicollidine hexafluorophosphate dissolved in 150 mL of CH_2Cl_2 was added 5.10 g (20.0 mol) finely grounded I_2. The solution was filtered through oven-dried Celite and added to 2.0 g (11.8 mmol) of **2**. The mixture was refluxed for 4 h. The resulting solution was washed with 5% $Na_2S_2O_3$ (aq) and evaporated. Column chromatography (SiO_2/CH_2Cl_2) gave 2.15 g (7.30 mmol, 62%) of **3**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.95 (bs, 1H, H-1), 4.63 (dd, 1H, J = 6 and 3 Hz, H-11), 4.41 (d, 1H, J = 16 Hz, H-4a), 4.26 (d, 1H, J = 16 Hz, H-4b), 3.89 (dd, 1H, J = 5.5 and 12.5 Hz, H-6a), 3.49 (dd, 1H J = 5.5 and 12.5 Hz, H-6b), 2.85−2.71 (m, 1H, H-7), 2.04−1.93 (m, 1H, H-10a), 1.87−1.40 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.7 (C-3), 78.4 (C-1), 74.8 (C-6), 71.9 (C-4), 35.9 (C-7), 29.4 (C-11), 29.2, 23.7, 21.1. (Assignments based on COSY and HETCOR spectra). MS (EI): m/z 297($M^+ + 1$).

(1*RS*,7*SR*,11*RS*)-11-Bromo-2,5-dioxa-3-oxobicyclo[5.4.0]-undecane (4). To 170 mg (1.00 mmol) of **2** in 15.0 mL of CH_2Cl_2 was added 1.00 g (2.14 mmol) of bromonium dicollidine hexafluorophosphate. The mixture was refluxed for 4 h. Evaporation and column chromatography (SiO_2, EtOAc/pentane (1:1)) gave 70 mg of the bromide **4** (0.28 mmol, 28%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.92 (bs, 1H, H-1), 4.50 (m, 1H, H-11) 4.47 (d, 1H, J = 17 Hz, H-4a), 4.28 (d, 1H, J = 17 Hz, H-4b), 3.93 (dd, 1H, J = 5.5 and 12.5 Hz, H-6a), 3.43 (dd, 1H, J = 5.5 and 12.5 Hz, H-6b), 2.73−2.59 (m, 1H, H-7), 2.33−2.14 (m, 1H, H-10a), 1.97−1.43 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.1, 76.5, 74.1, 70.9, 48.7, 34.6, 26.9, 22.4, 18.5. (Assignments based on COSY spectra).

(1*RS*,7*SR*,11*SR*)-2,5-Dioxa-11-trifluoroacetoxy-3-oxobicyclo[5.4.0]undecane (5). To 1.10 g (3.7 mmol) of **3** in 10 mL of EtOAc was added 1.00 g (4.3 mmol) AgO_2CCF_3 at 0 °C, and the mixture was left stirring for 4 h at room temperature. Then 10.0 mL of pentane was added, and the suspension was filtered through a pad of SiO_2 (1:1 EtOAc/pentane). Evaporation gave 0.95 g (3.40 mmol, 91%) of **5**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.78 (t, 1H, J = 3 Hz, H-1), 4.41 (d, 1H, J = 2 Hz, H-6a), 4.37 (s, 1H, H-6b), 4.33 (s, 1H, H-4a), 4.32 (s, 1H, H-4b), 3.85 (ddd, 1H, J = 3, 6.5 and 9.5 Hz, H-11), 2.25−2.05 (m, 1H, H-7), 1.95−1.62 (m, 3H) 1.59−1.27 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.4 (C-3), 157.1 (q, J = 43 Hz, CF_3CO), 114.1 (q, J = 285 Hz, CF_3), 75.3 (C-1), 70.1 (C-11), 66.7 (C-6), 61.1 (C-4), 38.9 (C-7), 23.7 (C-10), 21.8 (C-9), 21.5 (C-8). (Assignments based on COSY and HETCOR spectra). MS (EI): m/z 282 (M^+).

(1*RS*,7*SR*,11*SR*)-4-Bromo-2,5-dioxa-11-trifluoroacetoxy-3-oxobicyclo[5.4.0]undecane (6). To 1.20 g (4.25 mmol) of **5** in 25.0 mL of CCl_4 was added 0.85 g (4.78 mmol) *N*-bromosuccinimide and a spatula point of lauryl peroxide. The solution was refluxed for 30 min. Filtration and evaporation gave 1.30 g (3.60 mmol, 85%) of crude **6**. Due to instability the product was not further purified. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.41 (s, 1H, H-4), 5.53 (t, 1H, J < 2 Hz, H-1), 4.41 (d, 1H, J = 2 Hz, H-6a), 4.37 (s, 1H, H-6b), 4.23−4.12 (m, 1H, H-11), 2.20−2.07 (m, 1H, H-7), 1.89−1.78 (m, 2H), 1.63−1.30 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 161.6 (C-3), 157.0 (q, J = 42 Hz, CF_3CO), 114.3 (q, J = 286 Hz, CF_3), 73.9 (C-4), 73.0 (C-11), 71.5 (C-1), 66.5 (C-6), 38.0 (C-7), 27.0, 21.5, 21.4. (Assignments based on COSY and HETCOR spectra). MS (EI): m/z 363($M^+ + 3$), 361($M^+ + 1$).

(1*SR*,2*RS*,3*SR*)-2,3-Diacetoxycyclohexanemethanyl Acetate (7a). 6 (1.30 g, 3.60 mmol) was treated with NH_3 (aq, 25%, 25 mL) at 0 °C. Cooling was removed, and the mixture was left stirring at 25 °C until finished (TLC, 10% MeOH in EtOAc). The solution was evaporated, and the residue was suspended in MeOH. The suspension was filtered through a pad of SiO_2 (10% MeOH in EtOAc) and evaporated, giving 610 mg of crude triol **7**. (^{1}H NMR (300 MHz, D_2O): δ 3.86 (bs, 1H, H-2), 3.52 (dd, 1H, J = 11, 7.5 Hz, H-1′a), 3.49 (ddd, 1H, J = 11, 4.5 and 2.5 Hz, H-3), 3.39 (dd, 1H, J = 11, 6.5 Hz, H-1′b), 1.70−0.97 (m, 7H). ^{13}C NMR (75 MHz, D_2O): δ 72.4 (C-3, 70.1 (C-2), 63.8 (C-1′), 42.8 (C-1), 27.7, 23.0, 21.7 (Assignments based on COSY and HETCOR spectra). MS (EI): m/z 146 (M^+). Peak match:146.0943 (calcd:146.0943).) This sample was treated with pyridine and acetic anhydride. The solution was evaporated and water was added. Extraction (CH_2Cl_2), evaporation, and column chromatography gave 680 mg (2.50 mmol, 70% from **6**) of **7a** as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.32 (t, 1H, J = 2.5 Hz, H-2), 4.69 (ddd, 1H, J = 9, 7 and 2.5 Hz, H-3), 3.85 (dd, 1H, J = 11 and 9 Hz, H-1′a), 3.76 (dd, 1H, J = 11 and 6.5 Hz, H-1′b), 2.00 (s, 3H, Ac), 1.93 (s, 3H, Ac), 1.89 (s, 3H, Ac), 1.90−1.16 (m, 7H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.7 (Ac), 170.1 (Ac), 170.0 (Ac), 72.2 (C-3), 67.9 (C-2), 63.7 (C-1′), 38.5 (C-1), 25.4, 22.5, 22.3, 20.8 (Ac), 20.64 (Ac), 20.61 (Ac). (Assignments based on COSY and HETCOR spectra). MS (EI): m/z 272 (M^+).

Cyclohex-2-enylmethoxy(2-trimethylsilylethoxy)-methane (8). To 1.12 g (10.0 mmol) of **1** in 10.0 mL CH_2Cl_2 were added 1.85 g of SEM-Cl (11.1 mmol) and 2 mL of DIPEA (11.5 mmol). When the reaction was complete (TLC, CH_2Cl_2, 1 h), the solvent was evaporated. Column chromatography (SiO_2/CH_2Cl_2) gave 2.39 g (10.0 mmol, 99%) of **8**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.74 (ddd, 1H, J = 3.5, 6.0 and 10.0 Hz), 5.57 (ddd, 1H, J = 1.8, 4.2 and 10.0 Hz) 4.65 (s, 2H) 3.60 (t, 2H, J = 8.4 Hz), 3.98 (d, 2H, J = 6.4 Hz), 2.43−2.22 (m, 1H), 2.02−1.93 (m, 2H) 1.84−1.12 (m, 4H), 0.92 (t, 2H, J = 8.4 Hz), 0.00 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 128.6, 128.2, 94.8, 71.8, 64.8, 35.8, 26.0, 25.2, 20.9, 18.0, −1.4.

(2*RS*,4*SR*,10*RS*)-2,4-Dioxa-10-iodobicyclo[4.4.0]decane (9) and (1*SR*,2*RS*,3*RS*)-3-Fluoro-2-iodocyclohexanylmethoxy-(2-trimethylsilylethoxy)methane (10). To 2.00 g (4.04 mmol) of silver dicollidine hexafluorophosphate dissolved in 40.0 mL of CH_2Cl_2 was added 1.03 g (4.06 mmol) of finely grounded I_2.

The solution was filtered through oven-dried Celite and added to 485 mg (2.00 mmol) of **8** and left stirring overnight. The solution was washed with $Na_2S_2O_3$ (5% aq) and evaporated. Column chromatography gave 250 mg (0.93 mmol, 47%) of **9** and 85 mg of a faster running compound which was identified to be **10** (11%). **9:** ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.97 (d, 1H, J = 6.5 Hz, H-3a), 4.64 (d, 1H, J = 6.5 Hz, H-3b), 4.52 (dd, 1H, J = 5 and < 2 Hz, H-10), 3.98 (d, 1H, J < 2 Hz, H-1), 3.78 (d, 2H, J < 2 Hz, H-5′), 2.12−1.40 (m, 7H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 93.9 (C-3), 78.5 (C-1), 72.1 (C-5), 32.7 (C-10), 31.1 (C-6), 29.6, 23.9, 21.5. (Assignments based on COSY and HETCOR spectra). MS (EI): m/z 268 (M^+). **10:** ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.02 (d, 1H, J = 48.2 Hz, H-3), 4.7 (m, 3H, H-2, OCH_2O), 3.59 (t, 2H, J = 8 Hz), 3.44−3.23 (m, 2H, H-1′a, H-1′b), 2.54−2.12 (dm, 1H, J = 45 Hz), 2.0−1.15 (m, 6H), 0.93 (t, 2H, J = 8 Hz), 0.00 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 95.0 (OCH_2O), 91.7 (d, J = 176 Hz, C-3), 73.0 (C-1′), 65.2, 37.2 (d, J = 23 Hz, C-2), 36.1, 25.4 (d, J = 21 Hz, C-4), 24.2, 19.6, 18.1, −1.4. (Assignments based on COSY and HETCOR spectra). MS (EI): m/z 387 (M^+ − H, vw).

1-*O*-[(2-Trimethylsilylethoxy)methyl]cinnamyl Alcohol (11). To 1.34 g (10 mmol) cinnamyl alcohol in 10.0 mL of CH_2Cl_2 were added 2.00 mL of DIPEA and 2 mL (1.88 g, 11.3 mmol) of SEMCl. After 4 h the solution was evaporated, and column chromatography (SiO_2, Et_2O/pentane, 1:4) gave 2.32 g (8.8 mmol, 88%) of **11**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.43−7.18 (m, 5H), 6.63 (d, 1H, J = 16 Hz), 6.31 (dt, 1H, J = 16, 6 Hz), 4.76 (s, 2H), 4.26 (d, 2H, J = 6 Hz), 3.68 (t, 2H, J = 8 Hz), 0.95 (t, 2H, J = 8 Hz), 0.00 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.6, 132.4, 128.5, 127.6, 126.4, 125.6, 92.9, 67.8, 65.1, 18.0, −1.4.

(4,5-*trans*)-5-Iodo-4-phenyl-1,3-dioxane (12). To 265 mg (1.00 mmol) of **11** in 5.00 mL of CH_2Cl_2 was added 1.0 g (1.90 mmol) IDCH, and the mixture was left stirring for 4 h at 25 °C. Washing with $Na_2S_2O_3$ (5% aq) followed by column chromatography (SiO_2, CH_2Cl_2) gave 180 mg (0.62 mmol, 62%) of **12**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36−7.32 (m, 5H, Ph), 5.27 (dd*, 1H, J = 6.5 Hz, H-2eq), 4.90 (d, 1H, J = 6.5 Hz, H-2ax), 4.58 (d, 1H, J = 10 Hz, H-4), 4.39 (ddd*, 1H, J = 11, 4.5 Hz, H-6eq), 4.25 (ddd, 1H, J = 11, 10 and 4.5 Hz, H-5), 3.92 (t, 1H, J = 11 Hz, H-6ax). * very small long-range coupling due to w-configuration can be observed. ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.1, 128.9, 128.3, 127.6, 94.6 (C-2), 85.3 (C-4), 74.0 (C-6), 28.4 (C-5). (Assignments based on COSY and HETCOR spectra). MS (EI): m/z 290 (M^+). Peak match 289.9805 (calcd 289.9804).

(4,5-*trans*)-5-Bromo-4-phenyl-1,3-dioxane (13). To 500 mg (1.10 mmol) of BrDCH in 2 mL of CH_2Cl_2 was added 264 mg (1.00 mmol) of **11**. Gas evolved and after 10 min, the solution was concentrated and subjected to column chromatography (SiO_2, CH_2Cl_2), which gave 180 mg (0.74 mmol, 74%) of **13**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36−7.32 (m, 5H, Ph), 5.26 (dd*, 1H, J = 6.5 Hz, H-2eq), 4.91 (d, 1H, J = 6.5 Hz, H-2ax), 4.56 (d, 1H, J = 10 Hz, H-4), 4.43 (ddd*, 1H, J = 11 and 4.5 Hz, H-6ax), 4.14 (ddd, 1H, J = 10, 11 and 4.5 Hz, H-5), 3.87 (t, 1H, J = 11 Hz, H-6eq) * very small long-range coupling due to w-configuration can be observed. ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.4, 128.9, 128.3, 127.5, 94.3 (C-2), 84.5 (C-4), 72.1 (C-6), 46.8 (C-5). (Assignments based on COSY and HETCOR spectra).

(±)-1-Phenylbut-1-en-3-ol (14). (*E*)-4-Phenylbut-3-en-2-one (2.92 g, 0.02 mol) was dissolved in 100 mL of MeOH, and 4.4 g (0.04 mol) of anhydrous $CaCl_2$ was added. After stirring 30 min, the solution was cooled to 0 °C, and 1.14 g (0.03 mol) $NaBH_4$ was added portionwise. The solution was left stirring 1 h at 25 °C and poured onto 150 mL of brine. This was extracted twice with Et_2O, dried ($MgSO_4$), and evaporated giving 2.0 g (13.5 mmol; 67%) of **14**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.27−7.13 (m, 5H), 6.42 (d, 1H, J = 16 Hz), 6.12 (dd, 1H, J = 16, 6.2 Hz), 4.34 (dp, 1H, J = 1.1, 6.2 Hz), 2.46 (s, 1H), 1.24 (d, 3H, J = 6.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.6, 133.5, 129.1, 128.4, 127.4, 126.3, 68.6, 23.3.

(±)-1-*O*-[(2-Trimethylsilylethoxy)methyl]-1-phenylbut-1-en-3-ol (15). To 740 mg (5.00 mmol) of **14** in 5.00 mL of CH_2Cl_2 was added 1.00 mL of DIPEA and 1.00 mL (0.94 g, 5.60 mmol) of SEM-Cl. The solution was left stirring until finished (TLC, EtOAc:pentane 1:4, 4 h). Evaporation and column chromatography (SiO_2, EtOAc/pentane (1:4)) gave 1.38 g (4.95 mmol, 99%) of **15**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.37−7.18 (m, 5H), 6.52 (d, 1H, J = 16 Hz), 6.06 (dd, 1H, J = 16, 8 Hz), 4.74 (d, 1H, 7 Hz), 4.66 (d, 1H, J = 7 Hz), 4.34 (p, 1H, J = 8 Hz), 3.73 (dt, 1H, J = 8, 9 Hz), 3.56 (dt, 1H, J = 8, 9 Hz), 1.34 (d, 3H, J = 8 Hz), 0.93 (t, 2H, J = 8 Hz), 0.00 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.5, 131.3, 130.9, 128.5, 127.5, 126.4, 92.0, 72.4, 64.9, 21.5, 18.1, −1.5.

(4,5-*trans*-5,6-*trans*)-5-Bromo-6-methyl-4-phenyl-1,3-dioxane (16). To **15** (278 mg, 1.00 mmol) in CH_2Cl_2 (5.00 mL) was added BrDCH (0.60 g, 1.32 mmol), and the mixture was left stirring for 30 min. Evaporation followed by chromatography (SiO_2/CH_2Cl_2) gave **16** (180 mg, 0.70 mmol, 62%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.38−7.32 (m, 5H), 5.18 (d, 1H, J = 7 Hz), 4.88 (d, 1H, J = 7 Hz), 4.53 (d, 1H, J 10 Hz), 3.83 (dd, 1H, J = 11 and 7 Hz), 3.73 (dd, 1H, J = 10 and 11 Hz), 1.24 (d, 3H, J = 7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.8, 128.8, 128.3, 127.7, 93.8, 84.3, 78.3, 54.6, 19.7.

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Supporting Information Available: Copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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