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Facile One-Step Synthesis of β-Alkoxy Lactone via Sequential Lactonization and 1,4-Addition of Alkoxide Group: Total Synthesis of All Stereoisomers of Dihydrokawain-5-ol†

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Received January 25, 2004

We describe here a divergent total synthesis of all of the four stereoisomers of dihydrokawain-5-ol starting from α-D-glucose. The approach involves the use of Ando's modification of Horner−Wadsworth−Emmons homologation to give a α,β-unsaturated ester. Subsequently, lactonization and 1,4-addition of OMe group in one step provided a δ-lactone, which was converted into the target compounds in two steps.

Introduction

(+)-Dihydrokawain-5-ol **1a**, a unique 6-alkyl-5-hydroxy-5,6-dihydropyran-2-one, was isolated from the methanol extracts of the kava plant (*Piper mythisticum*), a Polynesian shrub of the Pepper family.[1] The extract of roots and stem of these plants are utilized in folk medicine and in the preparation of a traditional ceremonial beverage.[2] The dihydropyran moiety is a frequently encountered substructure in natural products (Figure 1).[3] This and other kava constituents having an α-pyrone or dihydropyrone skeleton such as (+)-kawain **2**, methisticin **3**, yangonin **4**, and dihydrokawain **5** have attracted considerable interest from the pharmaceutical industry because of their sedative, anxiolytic, and analgesic properties.[4]

The absolute configuration (5*R*,6*S*) in (+)-dihydrokawain-5-ol **1a** was suggested by its synthesis through SeO_2 allylic oxidation of (+)-dihydrokawain **5**, derived from kawain **2**.[5] The interesting structural properties, especially the presence of oxygen substituents at both the C5 and C6 positions on the pyranone scaffold and the *syn* relationship between the oxygens at C5/C6, make dihydrokawain-5-ol an attractive and challenging synthetic target.[6] The C5 hydroxyl group in **1a** makes the molecule susceptible to rearrangement to furanone under basic condition.[7] It is surprising to note that so far only one asymmetric synthesis of (+)-dihydrokawain-5-ol **1a** has been reported[8] in the literature, and there is no report for the synthesis of its other stereoisomers.[9] As a part of our continuing interest in the synthesis of natural products having δ-lactone rings,[10] we were interested in the synthesis of all stereoisomers of dihydrokawain-5-ol. In this article, we delineate our efforts on their total synthesis from α-D-glucose, which is available in abundance.[11]

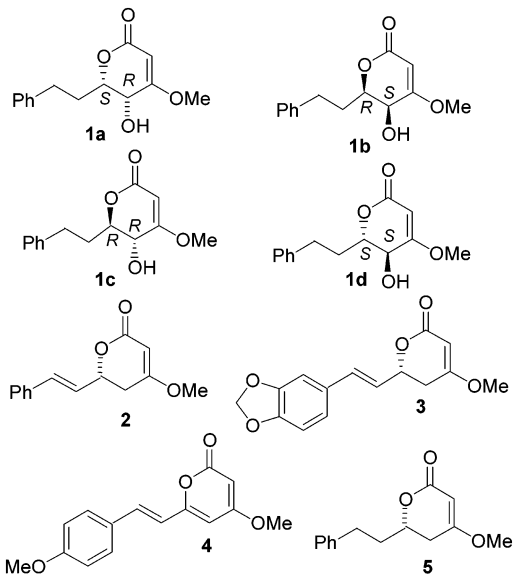

FIGURE 1.

† This paper is dedicated with respect to Professor H. Ila on her 60th birthday.

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10.1021/jo049858n CCC: $27.50
Published on Web 04/20/2004

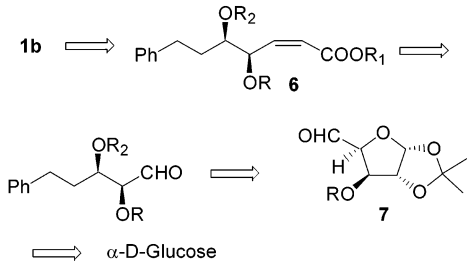


FIGURE 2.

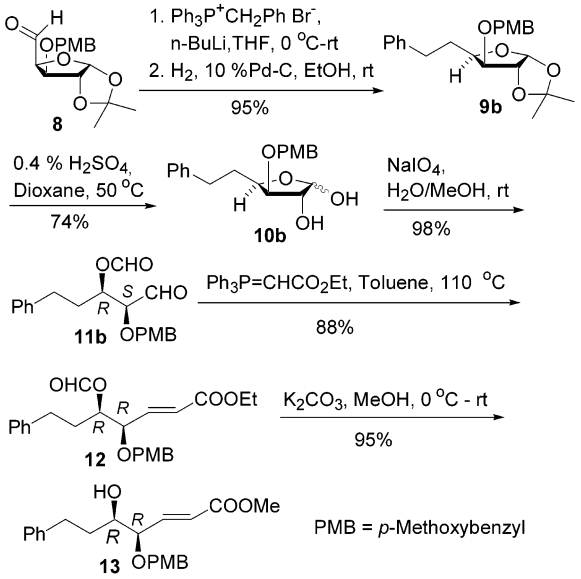
Results and Discussion

The retrosynthetic analysis of **1b** is outlined in Figure 2. It was conceived that a *β*-methoxy *δ*-lactone type of system could be built up from the 1,4-addition of methoxy group on the unsaturated *δ*-hydroxy ester derivative **6**. Structural mapping of this subtarget was done with the α-D-glucose derivative **7**, keeping in mind the following transformations: an addition of the side chain through Wittig chemistry and the conversion of the acetonide to an aldehyde for Horner−Emmons olefination reaction. The above strategy was validated and executed successfully (vide infra).

The synthesis of (−)-dihydrokawainol **1b** involved α-D-pentodialdose **8**, which was easily synthesized from D-glucose using literature procedures.[12] The aldehyde **8** was converted into **9b** by performing Wittig olefination with a ylid ($Ph_3P{=}CHPh$) followed by hydrogenation of the double bond. The acetonide of **9b** was deprotected with dilute sulfuric acid in dioxane to provide a hemiacetal **10b**. Oxidative cleavage of the hemiacetal **10b** with $NaIO_4$ led to an aldehyde **11b** that was directly subjected to Wittig olefination reaction with a stabilized ylid ($Ph_3P{=}CHCO_2Et$). This gave an α,*β*-unsaturated ester **12** exclusively in the *E*-isomer (Scheme 1).

Now, what was left was to convert **12** into a *δ*-lactone **15b**. At the outset, it appeared that it could be done in one step by using K_2CO_3 in MeOH. This was based on a proposition that under this condition methanol will add to an α,*β*-unsaturated ester in a 1,4-fashion concomitant with the formation of *δ*-lactone after hydrolysis of the formate ester. There are some close precedents in the literature where MeOH adds to alkynyl ester in a 1,4-fashion.[13,14] However, it was observed that the reaction of **12** with K_2CO_3 in MeOH failed to give **15b**. Instead, transesterification of ethyl ester with MeOH along with cleavage of the formyl ester to a hydroxy group took place to give **13** in quantitative yield (Scheme 1). It was expected that this *trans*-hydroxy ester **13** would not

SCHEME 1



lactonize because of geometrical constraint. Now, it became logical to synthesize the (*Z*)-α,*β*-unsaturated ester as *cis*-geometry would favor lactonization and then 1,4-addition of MeOH to the α,*β*-unsaturated lactone is more likely to happen. Thus, α,*β*-unsaturated ester **14b** was synthesized from the aldehyde **11b** using Hornor−Wadsworth−Emmons reaction under Ando's condition.[15] It was gratifying to note that a treatment of the *Z*-ester **14b** with K_2CO_3 in MeOH gave the desired *δ*-lactone **15b** in quantitative yield. It was also observed that EtOH can be added in this reaction if desired. However, other higher alkoxides did not add on that pattern. On the basis of the above results, it was postulated that 1,4-addition of MeOH or EtOH took place after the lactonization.

The double bond in the lactonic ring of **15b** was introduced by doing phenylselenation[16] with sodium hexamethyldisilazide (NaHMDS) and trimethyl silyl chloride (TMSCl) followed by oxidative *syn* elimantion. The **16b** thus obtained was treated with DDQ under buffer condition[17] to deprotect the *p*-methoxybenzyl (PMB) ether group. This provided (−)-(5*S*,6*R*)-dihydrokawainol **1b** in 91% yield (Scheme 2).

Once the total synthesis of **1b** was achieved, we realized that by manipulating the stereochemistry of some of the sugar intermediates other stereoisomers of dihydrokawainol could be synthesized. By looking at our next target **1c**, we realized that this could be done by using the above strategy provided we can invert the stereochemistry of OPMB ether in **9b**. Thus, compound **17** was chosen as a suitable precursor for this purpose. Hydrogenolysis of the benzyl ether in **17** gave alcohol **18**, which without any purification was oxidized under Swern condition to give ketone **19**. The reduction of ketone **19** with sodium borohydride, in which hydride will attack

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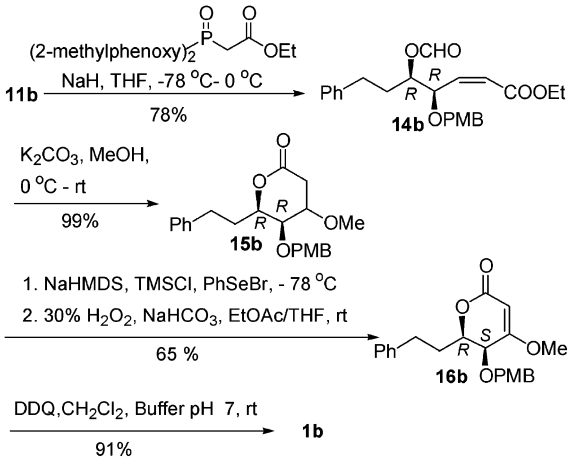
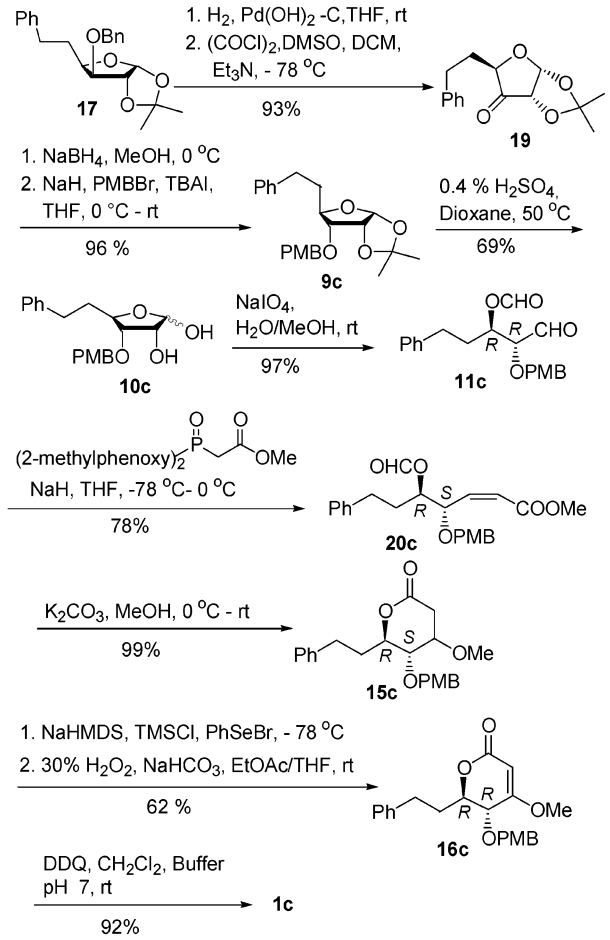
SCHEME 2

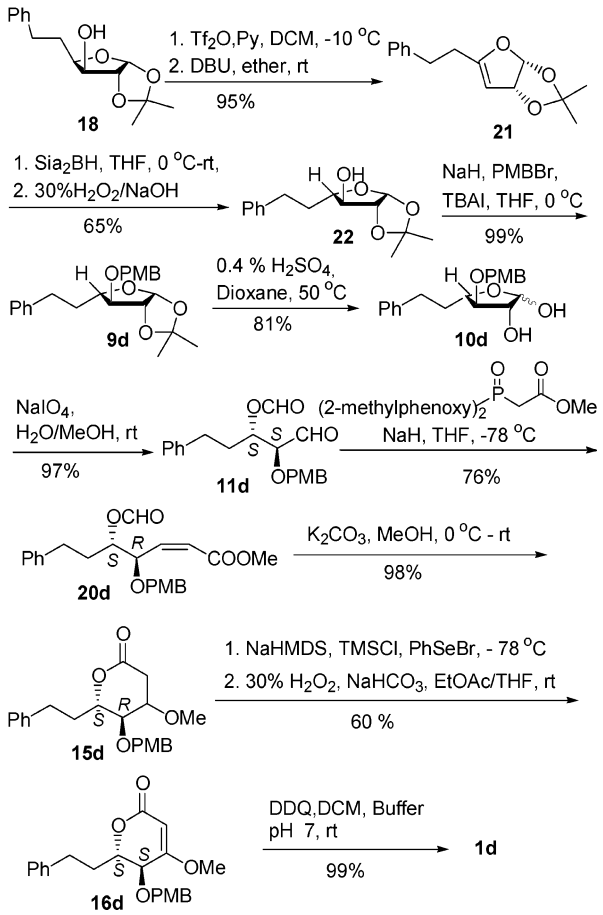


SCHEME 3



the ketone from the top face, provided an alcohol as a sole product, which was protected as PMB ether. Thus **9c** was obtained in high yield in which the stereochemistry of the OPMB ether was opposite to that of **9b**. Now, using a similar sequence of reactions as described above, we were able to synthesize **1c** in an efficient manner (Scheme 3). By looking at the stereochemistry of **1d**, it was obvious that this could be synthesized if the orientation of the alkyl side chain in **9b** was changed. This was done nicely by taking the alcohol **18** as a precursor. It was converted into olefin **21** by elimination of the

SCHEME 4



corresponding triflate. The reaction of the olefin with a hindered boron reagent such as disiamylborane (Sia_2BH) followed by oxidation with basic hydrogen peroxide gave alcohol **22** as an exclusive product. As expected, the hydroboration took place from the top face of the olefin.[18,19] The hydroxyl group in **22** was protected as a PMB ether to give **9d** in which stereochemistry of the alkyl side chain is opposite to that of **9b**. Following the similar sequence of reactions, synthesis of **1d** was completed (Scheme 3).

After successful synthesis of all the unnatural stereoisomers, we decided to complete the synthesis of natural dihydrokawainol **1a** by inverting the stereochemistry of hydroxyl group in **22**. This was achieved by reducing the corresponding ketone **19a** with sodium borohydride where the hydride approached the ketone exclusively from the top face. The alcohol, without any purification, was converted into PMB ether **9a**. Once **9a** was in hand, it was transformed into the natural **1a** using the similar sequence of reactions (Scheme 5).

In conclusion, we have completed total synthesis of all stereoisomers of dihydrokawainol from α-D-glucose in an efficient manner. The synthetic strategy focused on lactonization followed by 1,4-addition of OMe group in one step. The simplicity of the reactions with good yields provided elegance to the synthesis.

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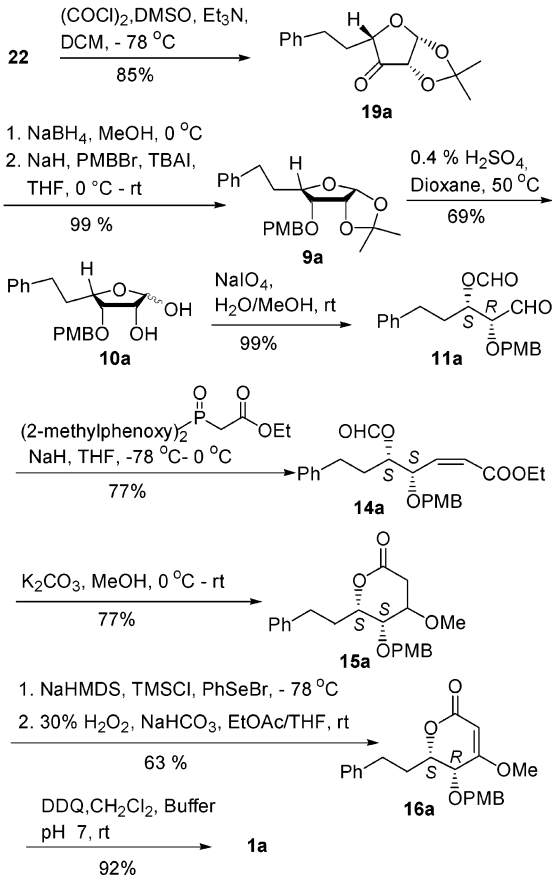
SCHEME 5



Experimental Section

5,6-Dideoxy-1,2-*O*-isopropylidene-3-*O*-(4-methoxybenzyl)-6-*C*-(phenyl)-α-D-glucofuranose (9b). *n*-BuLi (1.5 M solution in *n*-hexane, 40 mL) was added dropwise to a solution of triphenylphosphonium benzyl bromide (23.9 g, 55 mmol) in anhydrous THF (200 mL) at 0 °C and allowed to stir for 15 min. Then, a solution of the aldehyde **8** (13.8 g, 50 mmol) in anhydrous THF (50 mL) was added, and the mixture was stirred at room temperature for 6 h. The reaction mixture was quenched with water and filtered through Celite. The filtrate was concentrated by evaporation and taken into ethyl acetate. It was washed with water and brine and dried over Na_2SO_4. After concentration on a rotary evaporator, the crude reaction mixture was purified over silica gel to provide pure alkene (18 g), which was hydrogenated (10% Pd/C, 500 mg) in EtOH at 1 atm pressure for 6 h. It was filtered through Celite, and the filtrate was concentrated to give pure saturated furanose **9b** (17.9 g, 95% yield) as an oil: $[\alpha]^{25}_D$ −37.2 (*c* 4.53, $CHCl_3$); IR (thin film, cm^{-1}) 2934, 2890, 1173; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (s, 3H), 1.37 (s, 3H,), 1.77−1.86 (m, 1H), 1.98−2.06 (m, 1H), 2.45−2.52 (m, 1H), 2.59−2.66 (m, 1H) 3.66 (d, J = 3.16 Hz, 1H), 3.71 (s, 3H), 4.02−4.07 (m, 1H), 4.41 (ABq, J = 11.68 Hz, $\Delta\nu$ = 97.4 Hz, 2H) 4.53 (d, J = 3.92 Hz, 1H), 5.84 (d, J = 3.92 Hz, 1H), 6.77−6.83 (m, 2H), 7.08−7.13 (m, 3H), 7.16−7.21 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.3, 26.6, 29.5, 32.3, 55.3, 71.3, 79.5, 81.4, 82.3, 104.6, 111.2, 113.8, 125.8, 128.3, 128.4, 129.4, 129.6, 141.7, 159.4; MS (FAB) 385 (M^+ + 1). Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.79; H, 7.29. Found: C, 71.75; H, 7.36.

5,6-Dideoxy-1,2-*O*-dihydroxy3-*O*-(4-methoxybenzyl)-6-*C*-(phenyl)-α-D-glucofuranose (10b). A solution of the acetonide **9b** (1.54 g, 4.0 mmol) in dioxane (10 mL) was treated with 0.4% H_2SO_4 (13 mL) at 50 °C for 2 h. The reaction mixture was neutralized with solid Na_2CO_3 and then concentrated to a residue, which was taken into EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The crude reaction mixture was chromatographed over silica gel to give 0.95 g (74% yield based on recovered **9b**) of hemiacetal **10b** as a white solid: mp 72 °C; $[\alpha]^{25}_D$ +12 (*c* 0.50, $CHCl_3$); IR (KBr, cm^{-1}) 3550, 2990, 1100; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.85−2.03 (m, 2H), 2.53−2.80 (m, 3H), 3.59 (m, 1H), 3.79 (s, 3H), 3.81−3.83 (m, 1H) 4.21−4.26 (m, 2H) 4.52 (ABq, J = 11.48 Hz, $\Delta\nu$ = 73.48 Hz, 2H) 5.51 (m, 1H), 6.85−6.90 (m, 2H), 7.15−7.19 (m, 3H), 7.22−7.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.6, 32.2, 55.3, 71.4, 75.7, 78.4, 83.3, 95.6, 113.8, 114.0, 125.8, 128.3, 128.4, 128.4, 129.4, 129.7, 141.8, 159.4; MS (FAB) 345 (M^+ + 1). Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 6.99. Found: C, 69.89; H, 6.92.

(2*S*,3*R*)-2-(4-Methoxybenzyloxy)-3-formyloxy-5-phenyl-1-pentanal (11b). A solution of **10b** (0.69 g, 2 mmol) in MeOH (40 mL) was treated with 0.6 N $NaIO_4$ aqueous solution (51 mL). The reaction mixture was stirred at room temperature for 1 h and then concentrated on rotary evaparator. After the reaction mixture was diluted with H_2O (10 mL), it was extracted with CH_2Cl_2 (few times). The organic layers were combined, washed with brine, and dried with Na_2SO_4. The solvent was removed in vacuo, and the residue was chromatographed over silica gel to give aldehyde **11b** as a yellow liquid (0.68 g, 98% yield): $[\alpha]^{25-20}_D$ (*c* 0.65, $CHCl_3$); IR (thin film, cm^{-1}) 3059, 2934, 2837,1723, 1174; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.97−2.10 (m, 2H), 2.44−2.52 (m, 1H), 2.58−2.66 (m, 1H), 3.67−3.86 (m, 4H), 4.60 (ABq, J = 11.72 Hz, $\Delta\nu$ = 75.32 Hz, 2H), 5.21−5.30 (m, 1H), 6.83−6.90 (m, 2H), 7.10−7.30 (m, 7H), 8.05 (s, 1H), 9.60 (d, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.4, 31.6, 55.2, 71.9, 73.0, 82.3, 114.0, 126.2, 128.3, 128.4, 128.4, 128.5, 130.1, 140.3, 160.2, 201.0; MS (FAB) 343 (M^+ + 1). Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.43. Found: C, 69.98; H, 6.56.

(4*R*,5*R*)-Ethyl,4-(4-methoxybenzyloxy)-5-(formidohydroxy)-7-phenyl-(2*E*)-heptenoate (12). A solution of the aldehyde **11b** (342 mg, 1 mmol) and a stabilized Wittig reagent (696 mg, 2 mmol) in anhydrous toluene (5 mL) was refluxed for 6 h. The reaction mixture was diluted with water and extracted with EtOAc. It was washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed over silica gel to give 0.36 g (88% yield) of an oily α,β-unsaturated *E*-ester **12**: $[\alpha]^{25}_D$ −32.3 (*c* 1.88, $CHCl_3$); IR (thin film, cm^{-1}) 2934, 2359, 1723, 1175; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (t, J = 7.08 Hz, 3H), 1.84−2.00 (m, 2H), 2.48−2.55 (m, 1H), 2.60−2.68 (m, 1H), 3.80 (s, 3H), 4.05−4.08 (m, 1H), 4.21 (q, J = 7.08 Hz, 2H), 4.44 (ABq, J = 11.72 Hz, $\Delta\nu$ = 94.34 Hz, 2H), 5.07 (quintet, J = 4.4 Hz, 1H), 6.08 (dd, J = 15.88, 1.24 Hz, 1H), 6.78−6.88 (m, 3H), 7.11−7.29 (m, 7H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 31.3, 31.5, 55.2, 60.7, 71.3, 73.8, 77.3, 113.9, 124.5, 126.1, 128.3, 128.4, 129.2, 129.6, 140.7, 143.1, 159.4, 160.6, 165.7; MS (FAB) 413 (M^+ + 1). Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.90; H, 6.79; Found: C, 69.98; H, 6.81.

(4*R*,5*R*)-Methyl,4-(4-methoxybenzyloxy)-5-(hydroxy)-7-phenyl-(2*E*)-heptenoate (13). A solution of compound **12** (121 mg, 0.29 mmol) in MeOH (2 mL) was treated with K_2CO_3 (50 mg, 0.35 mmol) at 0 °C for 1 h. The reaction mixture was quenched with 2 N HCl (3 mL) and concentrated on a rotary evaporator. The crude residue was taken into EtOAc, washed with water and brine, and dried with Na_2SO_4. The solvent was removed in vacuo, and the crude reaction mixture was chromatographed over silica gel to give 101 mg (yield 95%) of α,β-unsaturated δ-hydroxy *E*-ester **13** as an oil: $[\alpha]^{25}_D$ −32.3 (*c* 1.88, $CHCl_3$); IR (thin film, cm^{-1}) 3488, 2947, 1722, 1513, 1249; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.53 (bs, 1H), 1.62−1.68 (m, 2H), 2.52−2.59 (m, 1H), 2.72−2.79 (m, 1H), 3.49 (q, J = 6.36 Hz, 1H), 3.69 (s, 3H), 3.70−3.72 (m, 1H), 3.73 (s, 3H), 4.35 (ABq, J = 11.00 Hz, $\Delta\nu$ = 115.08 Hz, 2H), 5.98 (d, J = 15.88 Hz, 1H), 6.74 (dd, J = 15.88, 7.08 Hz, 1H), 6.80−6.82 (m, 2H), 7.08−7.21 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.7, 34.4, 51.8, 55.3, 71.1, 72.5, 81.5, 113.9, 124.3, 125.8, 128.3, 128.5, 129.3, 129.7, 141.7, 144.6, 159.5, 166.1; MS (FAB) 371

($M^+ + 1$). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.35; H, 7.03. Found: C, 71.38; H, 7.00.

(*4R*,*5R*)-Ethyl,4-(4-methoxybenzyloxy)-5-(formidohydroxy)-7-phenyl-(2*Z*)-heptenoate (14b). To a suspension of NaH (65 mg, 60% dispersion in oil, 2.7 mmol) in anhydrous THF (4.5 mL) was slowly added a solution of phosphonoacetate (480 mg, 1 mmol) in anhydrous THF (1.5 mL) at −78 °C under an argon atmosphere. The reaction mixture was stirred for 15 min at the same temperature. Then, a solution of the aldehyde **11b** (492 mg, 1.44 mmol) in THF (1.5 mL) was slowly added, and the reaction mixture was stirred at −78 °C for 40 min. It was then brought to −35 °C and quenched with aqueous NH_4Cl solution. The reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine. It was dried over Na_2SO_4 and concentrated. The crude residue was chromatographed over silica gel to give α,*β*-unsaturated *Z*-ester **14b** as an oil (420 mg, 78% yield based on recovered starting material): $[\alpha]^{25}_D$ −10.9 (*c* 0.66, $CHCl_3$); IR (thin film, cm^{-1}) 2934, 2865, 1721, 1649; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, $J = 7.08$ Hz, 3H), 1.95−2.03 (m, 2H), 2.46−2.53 (m, 1H), 2.60−2.68 (m, 1H), 3.77 (s, 3H), 4.15 (q, $J = 7.08$ Hz, 2H), 4.43 (ABq, $J = 11.48$ Hz, $\Delta\nu = 90.08$ Hz, 2H), 5.12−5.16 (m, 1H), 5.23 (dd, $J = 9.6$, 4.12 Hz, 1H), 5.97 (d, $J = 11.96$ Hz, 1H), 6.14 (m, 1H), 6.84 (d, $J = 8.04$ Hz, 2H), 7.10−7.27 (m, 7H), 8.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 14.1, 31.4, 31.8, 55.1, 60.4, 71.2, 73.6, 75.0, 113.7, 123.5, 125.9, 128.3, 128.3, 129.6, 129.7, 141.0, 146.1, 159.3, 160.7, 165.4; MS (FAB) 413 ($M^+ + 1$). Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.79; H, 6.79; Found: C, 69.74; H, 6.86.

(*5R*,*6R*)-4-Methoxy-5-(4-methoxybenzyloxy)-6-(1-phenylethyl)-3,4,5,6-tetrahydro-4*H*-pyran-2-one (15b). A solution of **14b** (20 mg, 0.05 mmol) in MeOH (1 mL) was treated with K_2CO_3 (8 mg, 0.06 mmol) at 0 °C for 1 h. The reaction mixture was quenched with 2 N HCl (500 μL) and concentrated on a rotary evaporator. The crude residue was taken into EtOAc and washed with water brine, and dried with Na_2SO_4. The solvent was removed in vacuo, and the crude reaction mixture was chromatographed over silica gel to give 17.6 mg (99% yield) of an oily lactone **15b**: $[\alpha]^{25}_D$ +30.3 (*c* 1.60, $CHCl_3$); IR (thin film, cm^{-1}) 2921, 1725, 1510, 1245; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.78−1.87 (m, 1H), 2.18−2.27 (m, 1H), 2.57−2.65 (m, 2H), 2.78−2.87 (m, 2H), 3.31 (s, 3H), 3.50−3.52 (m, 1H), 3.68−3.71 (m, 1H), 3.80 (s, 3H), 4.45−4,50 (m, 1H), 4.57 (ABq, $J = 11.48$ Hz, $\Delta\nu = 40.76$ Hz, 2H), 6.87 (d, $J = 8.28$ Hz, 2H), 7.15−7.30 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.3, 31.9, 32.3, 55.3, 56.7, 72.0, 72.6, 73.8, 113.9, 126.0, 128.4, 129.2, 129.5, 141.1, 159.4, 169.6; MS (FAB) 371 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.35; H, 7.02; Found: C, 71.49; H, 6.96.

(5*S*,6*R*)-4-Methoxy-5-(4-methoxybenzyloxy)-6-(1-phenylethyl)-5,6-dihydro-2*H*-pyran-2-one (16b). NaHMDS (1.2 mL of 2 M solution in THF, 2.23 mmol) was slowly added to a solution of the compound **15b** (687 mg, 1.86 mmol) in THF (10 mL) at −78 °C over 30 min, and stirring was continued for 30 min at the same temperature. TMSCl (0.47 mL, 3.71 mmol) was then added over a period of 15 min, and the reaction mixture was stirred for the next 1 h. PhSeBr (prepared from 2 mmol of PhSeSePh and Br_2) was slowly added under an argon atmosphere, and the whole mixture was stirred for 1.5 h. It was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with water and brine and dried. Solvent removal and quick filtration over silica gel provided 670 mg of α-selenyl lactone, which was taken in THF/EtOAc (1:1, 10 mL). This was treated with $NaHCO_3$ (312 mg, 3.9 mmol) followed by slow addition of 30% H_2O_2 (730 μL, 3.12 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h, diluted with some water, and extracted with Et_2O. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator, and the crude mixture was chromatographed over silica gel to give 432 mg (65% yield) of lactone **16b** as an oil: $[\alpha]^{25}_D$ −140.9 (*c* 3.27, $CHCl_3$); IR (thin film, cm^{-1}) 1707, 1635; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.83−1.92 (m, 1H), 2.27−2.36 (m, 1H), 2.62−2.69 (m, 1H), 2.74−2.81 (m, 1H), 3.69 (dd, $J = 1.72$, 0.72 Hz, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 4.16−4.20 (m, 1H), 4.56 (Abq, $J = 11.44$ Hz, $\Delta\nu = 75.7$ Hz, 2H), 5.20 (s, 1H), 6.85−6.88 (m, 2H), 7.14−7.29 (m, 7H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 30.8, 31.2, 55.2, 56.0, 70.7, 72.0, 78.0, 92.3, 113.7, 126.0, 128.5, 129.2, 129.7, 140.8, 159.4, 166.1, 171.8; MS (FAB) 369 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.74; H, 6.52. Found: C, 71.66; H, 6.67.

(−)-(5*S*,6*R*)-Dihydrokawain-5-ol (1b). A solution of **16b** (64.2 mg, 0.17 mmol) was treated with DDQ (59.4 mg, 0.26 mmol) in CH_2Cl_2−phosphate buffer (10:1, 8 mL) at room temperature. The reaction mixture was stirred vigorously for 4 h and quenched with an aqueous saturated sodium hydrogen carbonate (15 mL). The aqueous layer was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator, and the crude mixture was chromatographed over silica gel to give 39.2 mg (91% yield) of lactone **1b** as a yellow liquid: $[\alpha]^{25}_D$ −66.3 (*c* 1.02, $CHCl_3$); IR (thin film, cm^{-1}) 3387, 2943, 1696, 1633, 1230; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.95−2.02 (m, 1H), 2.20−2.29 (m, 1H), 2.68−2.84 (m, 2H), 3.12 (bs, 1H), 3.68 (s, 3H), 3.86 (s, 1H), 4.12−4.15 (m, 1H), 5.07 (s, 1H) 7.10−7.23 (m, 5H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 30.8, 31.0, 56.3, 66.0, 78.2, 91.3, 126.1, 128.5, 128.5, 140.7, 166.6, 172.6; MS (FAB) 249 ($M^+ + 1$). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.45. Found: C, 67.98; H, 6.40.

5,6-Dideoxy-1,2-*O*-isopropylidene-5-*C*-(benzyl)-α-D-glucofuranose (18). A solution of benzyl-protected glucofuranose (384 mg, 1 mmol) was hydrogenated in the presence of $Pd(OH)_2$/C (150 mg, 0.1 mmol) in anhydrous THF (5 mL) at 1 atm pressure for 12 h. The reaction mixture was filtered through Celite and concentrated to give 277 mg (99% yield) of **18** as a white solid: mp 93−94 °C; $[\alpha]^{25}_D$ −2.9 (*c* 0.93, $CHCl_3$); IR (thin film, cm^{-1}) 3557, 2988, 1453, 1265; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.33 (s, 3H), 1.53 (s, 3H), 1.89−1.98 (m, 2H), 2.09−2.18 (m, 1H), 2.66−2.73 (m, 1H), 2.82−2.89 (m, 1H), 3.91−3.96 (m, 1H), 4.10 (s, 1H), 4.52 (d $J = 4.16$ Hz, 1H), 5.92 (d, $J = 3.88$ Hz, 1H), 7.16−7.30 (m, 5H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 26.2, 26.5, 29.4, 32.2, 75.4, 79.5, 85.3, 104.1, 111.5, 126.1, 128.4, 128.4, 141.4; MS (FAB) 265 ($M^+ + 1$). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.18; H, 7.57. Found: C, 68.11; H, 7.71.

5,6-Dideoxy-1,2-*O*-isopropylidene-3-carbonyl-5-*C*-(benzyl)-α-D-allofuranose (19). A solution of oxalyl chloride (0.26 mL, 3.0 mmol) was cautiously treated with DMSO (0.43 mL, 6 mmol) in CH_2Cl_2 (20 mL) at −78 °C under a nitrogen atmosphere. To this solution was added a solution of the alcohol **18** (556 mg, 2 mmol) in CH_2Cl_2 (10 mL). After the reaction mixture was stirred for 2 h at −78 °C, Et_3N (500 μL) was added, and the resulting reaction mixture was allowed to come to 0 °C. The reaction mixture was diluted with phosphate buffer (30 mL) and then extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The crude mixture was chromatographed over silica gel to give 512 mg (93% yield) of ketofuranose **19** as a yellow solid: mp 60−61 °C; $[\alpha]^{25}_D$ +120.9 (*c* 1.21, $CHCl_3$); IR (thin film, cm^{-1}) 3055, 2987, 2254, 1771, 1265; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (s, 3H), 1.47 (s, 3H), 1.87−1.96 (m, 1H), 2.04−2.13 (m, 1H), 2.75 (t, $J = 7.56$ Hz, 2H), 4.26 (d, $J = 4.4$ Hz, 1H), 4.34 (dd, $J = 7.32$, 4.4 Hz, 1H), 6.05 (d, $J = 4.64$ Hz, 1H), 7.18−7.21 (m, 3H), 7.26−7.30 (m, 2H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 27.0, 27.1, 31.0, 32.2, 76.0, 76.8, 102.4, 113.8, 126.2, 128.4, 128.6, 140.5, 210.1; MS (FAB) 263 ($M^+ + 1$). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.78; H, 6.87. Found: C, 68.71; H, 6.84.

5,6-Dideoxy-1,2-*O*-isopropylidene-3-*O*-(4-methoxybenzyloxy)-5-*C*-(benzyl)-α-D-allofuranose (9c). A solution of **19** (442 mg, 1.6 mmol) in MeOH (180 mL) was treated with $NaBH_4$ (303 mg, 8 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. After the evaporation of methanol, the crude material was diluted with water (60 mL) and then extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was chro-

matographed over silica gel to give 440 mg of an alcohol, which was added to a suspension of NaH (60 mg) in THF at 0 °C. Then, *p*-methoxybenzylbromide (400 mg) and a catalytic amount of *tetra*-butylammonium iodide was added and the reaction mixture was stirred for 4 h (0 °C to rt) and quenched with water. It was extracted with EtOAc, washed with water and brine, and dried. Solvent removal and purification over silica gel gave **9c** as an oil in 528 mg (yield 96%).

3,5,6-Trideoxy-1,2-*O*-isopropylidene-α-D-erythro-2-phenyleth-3-enofuranose (21). A solution of **18** (1.4 gm, 5 mmol) in CH_2Cl_2 (70 mL) was treated with pyridine (1.5 mL) and trifluoromethanesulfonic anhydride (1.65 mL, 10 mmol) at −10 °C. The reaction mixture was stirred at the same temperature for 1 h and then diluted with ether (70 mL) to give a white precipitate. It was filtered, and the filtrate was successively washed with H_2O, 5% HCl, aqueous $NaHCO_3$ solution, and saturated NH_4Cl solution. The organic layer was dried over Na_2SO_4, filtered, and concentrated to give 2.1 g of triflate, which was taken in 50 mL of ether and then treated with DBU (3.2 g, 21 mmol) at room temperature for 24 h. It was then washed with water and brine and dried. The solvent was removed, and the crude was chromatographed over silica gel to give 1.16 g (95% yield) of **21** as a slightly yellow oil: $[\alpha]^{25}_D$ −25.7 (*c* 7.0, $CHCl_3$); IR (thin film, cm^{-1}) 2929, 2254, 1454, 1245, 909; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 6H), 2.43−2.50 (m, 2H), 2.79−2.87 (m, 2H), 4.91−4.92 (m, 1H), 5.22−5.24 (m, 1H), 6.01 (d, J = 5.12 Hz, 1H), 7.16−7.28 (m, 5H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ 27.7, 28.0, 30.0, 32.0, 83.8, 97.6, 105.7, 111.7, 126.0, 128.3, 140.7, 161.7; MS (FAB) 247 (M^+ + 1). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.17; H, 7.31; Found: C, 73.01; H, 7.40.

5,6-Dideoxy-1,2-*O*-isopropylidene-5-*C*-(benzyl)-α-D-galactofuranose (22). To a solution of BH_3·DMS (925 μL, 12.2 mmol) in anhydrous THF (12 mL) was added 2-methyl-2-butene (1.7 gm, 24.4 mmol) in anhydrous THF (10 mL) under a nitrogen atmosphere at 0 °C. After the mixture was stirred for 2 h at the same temperature, a solution of **21** (1.35 gm, 5.2 mmol) in THF (30 mL) was added dropwise. The reaction mixture was stirred for 24 h again at room temperature. The flask was cooled to 0 °C, and 3 N NaOH (2.6 mL) was added to the reaction mixture. This was followed by a slow addition of 30% H_2O_2 (3 mL). The reaction mixture was stirred for 1 h at room temperature and filtered. The organic layer was separated. The aqueous layer was extracted with ether. The organic layers were mixed and dried (Na_2SO_4). Solvent removal and chromatographic separation gave 0.63 g (65% yield based on recovered SM) of **22** as a white solid: mp 81−82 °C; $[\alpha]^{25}_D$ −42.8 (*c* 3.7, $CHCl_3$); IR (thin film, cm^{-1}) 3412, 2925, 1377; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (s, 3H), 1.55 (s, 3H), 1.92−2.01 (m, 1H), 2.11−2.21 (m, 1H), 2.68−2.76 (m, 1H), 2.84−2.92 (m, 1H), 3.94−3.98 (m, 1H), 4.12 (d, J = 1.48 Hz, 1H), 4.54 (d, J = 4.16 Hz, 1H), 5.94 (d, J = 3.92 Hz, 1H), 7.19−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.1, 26.8, 32.2, 35.4, 78.8, 86.9, 87.2, 105.5, 112.5, 125.9, 128.4, 128.5, 141.4; MS (FAB) 265 (M^+ + 1). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.18; H, 7.57. Found: C, 68.41; H, 7.68.

Acknowledgment. We thank CSIR for a research grant and senior research fellowship to R.P.S.

Supporting Information Available: General methods and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049858N