Simple Synthesis of (*R*)-(+)-4-Hexanolide, the Pheromone of *Trogoderma glabrum*; an application of Furanoid Glycal

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ABSTRACT:

Furanoid glycals have been shown to possess great potential, as they have been used as key intermediates for the synthesis of structurally diverse molecules including natural products and natural product like molecules with various biological activities. In this research work, one of the pre-synthesized furanoid glycals has been identified as a building block to achieve the synthesis of (*R*)-(+)-4-hexanolide, a sexual pheromone secreted by the female of the dermestid beetle *Trogoderma glabrum*.

Introduction

Carbohydrates represent one of the most privileged classes of naturally occurring versatile building blocks in synthetic organic chemistry due to their wealth of unique functional, conformational, and stereochemical information. This "chiron" approach[1] is also very cost effective as starting material is derived from inexpensive carbohydrate or amino acid. Cyclic enol ether frameworks, especially stereochemically pure furanoid and pyranoid glycals are well known highly functionalized chiral building blocks. Furanoid Glycals are very important and well known highly functionalized CBBs and find their huge applications in 'chiron' approach synthesis.[2] They are highly reactive due to their enol ether geometry (a double bond between the carbon atoms 1 and 2 of the ring). They have been shown to possess great potential, as they have been used as key intermediates for the synthesis of structurally diverse molecules including natural products with various biological activities since their discovery in 1963 by Ness and Fletcher. [3a-h] Shaw's group had been working toward the synthesis of enantiomerically pure sugar derived building blocks and their utilization to accomplish the total synthesis of target biologically relevant natural products,[4b,d,g,h] and natural product like molecules.[4a,c,e,f,i]

Pal *et al* have already disclosed the synthesis of four stereochemically different enantiomerically pure furanoid glycal building blocks **1a-d** (Figure 1)[5] and also showed their synthetic utility to obtain few natural products such as aggregation pheromones Brevicomins (**2a-d**) and styryllactones (+)-Cardiobutanolide **3a**, (−)-Cardiobutanolide **3b** and (+)-Goniofufurone **4a** (Figure 2).[4h] Pal and Shaw also reported synthesis of six 2'-deoxynucleoside analogue building blocks (**5a-f**) from the stereochemically different furanoid glycals **1a-d** (Figure 3).[4i] Recently Pal and Shaw have compiled various syntheses and versatile applications of furanoid glycals since the inception to date in the form of a review.[6]
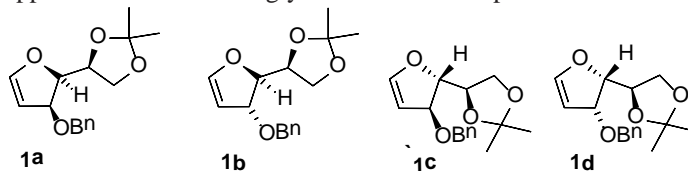

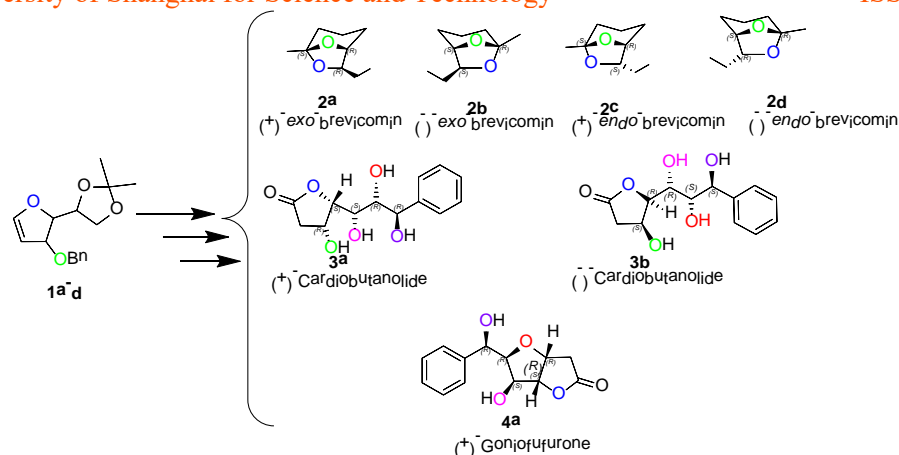**Figure 1**. Structures of furanoid glycals **1a**–**d**.

Figure 2. Structures of Brevicomins (**2a–d**), (+)-Cardiobutanolide (**3a**), (–)-Cardiobutanolide (**3b**) and (+)-Goniofufurone (**4a**).
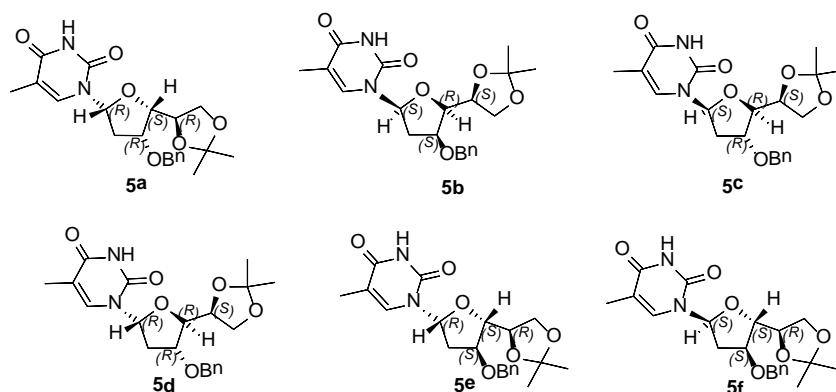

Figure 3. Structures of 2'-deoxynucleoside analogues **5a**-**f**.

Once again to show the application of one of the furanoid glycals, furanoid glycal **1c** has been identified as a building block to achieve the synthesis of (*R*)-(+)-4-hexanolide **13**, a sexual pheromone secreted by the female of the dermestid beetle *Trogoderma glabrum*. The beetle has been reported to respond only to the (*R*)-isomer not to its antipode or racemic mixture.[7] The synthesis of optically active lactone **13** has received global interest for last three decades. Among the several methods reported for its synthesis some of them are categorized in following methods: (i) stereoselective synthesis from optically active starting materials such as Glutamic acid,[8a] δ-D-(+)-gluconolactone,[8b] D-(+)-ribonolactone,[8c] (*R*)-(+)-pulegone,[8d] D-mannitol,[8e] (ii) Baker's yeast[9a-b,d] or chiral reducing agent[9c,e-f] mediated asymmetric reduction of prochiral ketone; (iii) enzyme catalyzed hydrolysis of γ-hydroxy esters,[10a] microbial hydrolysis of γ-hydroxy nitriles,[10b] and γ-hydroxy amides;[10c] (iv) some chiral methods involving Sharpless asymmetric epoxidation as key step and also from chiral synthons.[11] In the year of 2007, this optically active hexanolide **14** was synthesized by L-proline catalyzed sequential α-aminolysis-HWE olefination[12] of n-butyraldehyde. In 2008, Veselovsky *etal.* prepared (±)-4-alkanolides from pent-4-enoic acid.[13]

Results and Discussion

Synthesis of (*R*)-(+)-4-Hexanolide

The synthetic strategy to obtain (*R*)-(+)-4-hexanolide from furanoid glycal **1c** is shown in Scheme 1. The glycal **1c** was converted into compound **6** by oxymercuration-demercuration,[14] 4h sequence in 98% yield. The anomeric hydroxyl group was then oxidized with PDC in dry DCM at refluxing temperature for 2 h to obtain lactone **7** as yellow syrup in 77% yield. The deprotection of the isopropylidene group of compound **7** was carried out smoothly with 60% aqueous acetic acid at room temperature for 18-20 h to give compound **8** as a white solid. The diol **8,** without further purification**,** was mesylated with methanesulfonyl chloride in pyridine at 0 °C for 3 h to afford column pure dimesyl derivative **9** as a white solid in 65% yield (for two steps). The diester **9** was then subjected to undergo reductive elimination[15] with NaI in 2-butanone at reflux temperature for 12 h to give vinylbutyrolactone derivative **10** in 92% yield. The deprotection of the C-4 benzyloxy group and reduction of the unsaturation of the side chain were performed in a single step with H$_2$ in presence of 10% Pd-C for 5 h to obtain compound **11** which was without purification, treated with methanesulfonyl chloride-triethyl amine at -15 °C-0 °C in dry DCM for 4 h followed by elimination[16] of MsOH under basic condition to produce the unsaturated lactone derivative **12** in 46% yield for two steps. The compound **12** was hydrogenated with H$_2$ in presence of 10% Pd-C to obtain 4-hexanoilde **13** in 39% yield.[8c, 8e]
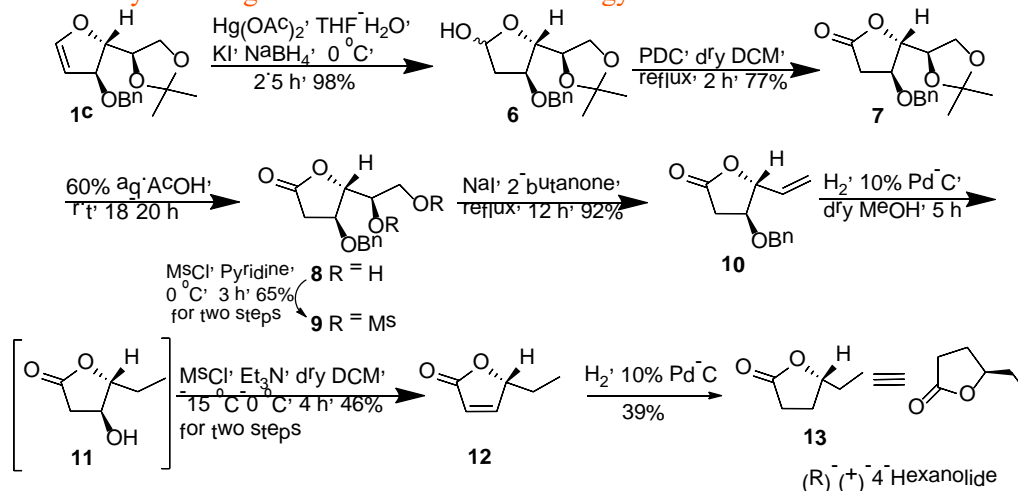
Scheme 1. Synthesis of (*R*)-(+)-4-Hexanolide

Conclusion

In summary, by utilizing inexpensive and easily available reagents one of the furanoid glycals **1c** can be converted to naturally occurring (*R*)-(+)-4-hexanolide, sexual pheromone of *Trogoderma glabrum*. The selection of furanoid glycals (**1a–d**) in the present work was done on the basis of the stereochemistry of the chiral centre of the above-mentioned target molecule. Here the importance of the work lies in the fact that the strategies employed for the synthesis of the title compound **13** can be followed to access same from furanoid glycal **1d**. In addition to that it is worth mentioning that compounds **6-10** will find wide applications to serve as versatile chiral building blocks toward the synthesis of various natural products, their analogues and molecules of biological importance as well.

Experimental Section

Compound 12. A catalytic amount of 10% Pd-C (~ 20 mg) was added to a solution of **10** (160 mg, 0.733 mmol) in dry methanol (5 mL). A vacuum was created in a round bottom flask containing the above reaction mixture with the help of pump and the mixture was stirred under H_2 atmosphere at room temperature for 5 h. After completion of the reaction (TLC control) catalyst was removed by filtration through Celite, washed with methanol twice and the solvent was evaporated in vacuum to obtain crude light yellowish compound **11** (110 mg) which was directly used for next step without further purification.

To a stirred solution of **11** (110 mg, 0.85 mmol) dissolved in dry DCM (5 mL) was added Et_3N (0.35 mL, 2.53 mmol) dropwise at -15 °C and left the reaction mixture for stirring for 10 min. The methanesulfonyl chloride (0.08 mL, 1.02 mmol) was added dropwise to this reaction mixture at the same temperature and stirring was continued for another 15 min. The temperature of the reaction was raised to 0 °C and stirring was further continued for additional 4 h. The reaction mixture was diluted with water, organic layer was separated and the aqueous layer was extracted with DCM (2 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to obtain the crude product which on column chromatographic purification (60-120 mesh silica gel) gave pure **12** (38 mg, 46%, for two steps) as a light yellow oil. Eluent for column chromatography: EtOAc/hexane (2/23, v/v); $[\alpha]^{28}_D$ = -58.2 (*c* 0.33, CHCl$_3$), {lit.[21c] $[\alpha]^{20}_D$=-97.6 (*c* 2.08, CH$_2$Cl$_2$), lit.[22e] $[\alpha]^{20}_D$=-94 (*c* 1.05, CH$_2$Cl$_2$), lit.[28] $[\alpha]^{23}_D$ = -95 (liq. longitude=1 dm)}; R_f = 0.61 (3/7 EtOAc/hexane); IR (neat, cm^{-1}): 761, 1261, 1603, 1752, 2361, 2934, 2975, 3021; ^1H NMR (300 MHz, CDCl$_3$): δ 0.92 (t, *J* = 7.9 Hz, 3H, H-2'), 1.60-1.80 (m, 2H, H-1'), 4.92-4.96 (m, 1H, H-5), 6.05 (dd, *J* = 1.9, 5.7 Hz, 1H, H-3), 7.38 (dd, 1H, *J* = 1.4, 5.7 Hz, H-4); ^{13}C NMR (75 MHz, CDCl$_3$): δ 9.0 (CH$_3$), 26.3 (CH$_2$), 84.3 (CH), 121.8 (CH), 155.9 (CH), 173.1 (C=O); mass (ESI-MS) *m/z* 112, found 151 [M+K]$^+$.

Compound 13.

To a degassed solution of **12** (50 mg, 0.45 mmol) in MeOH (5 mL) was added 10% Pd/C (70-80 mg). The resulting mixture was placed under a hydrogen atmosphere and stirred overnight. After filtration through Celite and removal of the solvent, the residue was purified by silica gel chromatography to afford **13** as a colorless oil (20 mg, 39%).EtOAc/hexane (2/23, v/v); $[\alpha]^{28}_D$ = +50.8 (*c* 1.5, MeOH), {lit.[9a] $[\alpha]^{25}_D$=+53.1 (*c* 1.0, MeOH), lit.[12] $[\alpha]^{25}_D$=+51.7 (*c* 1.0, MeOH)}; IR (neat, cm^{-1}): 754, 970, 1176, 1353, 1458, 1600, 1766, 2360, 2990; ^1H NMR (300 MHz, CDCl$_3$): δ: 1.00 (t, *J*=7.3 Hz, 3H), 1.56–1.95 (m, 3H), 2.23–2.36 (m, 1H), 2.49–2.57 (m, 2H), 4.36–4.50 (m, 1H).
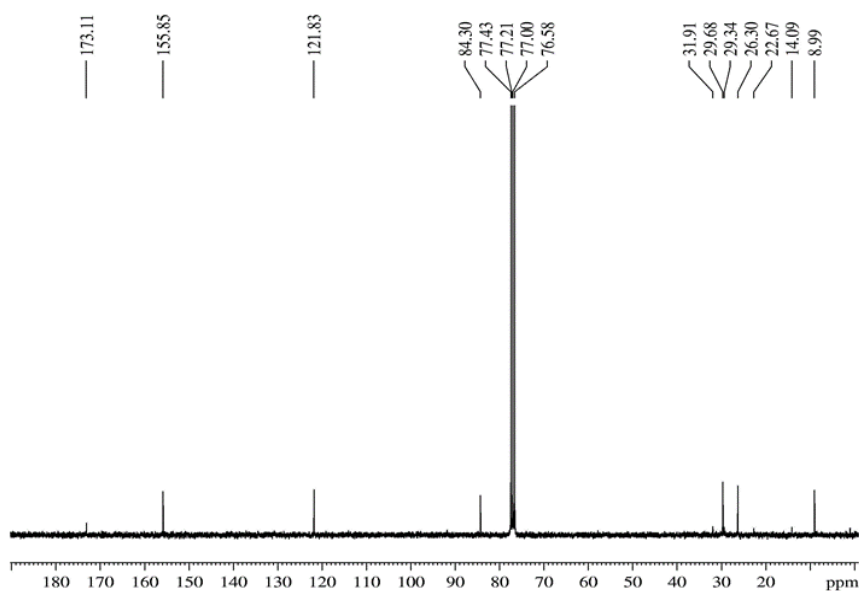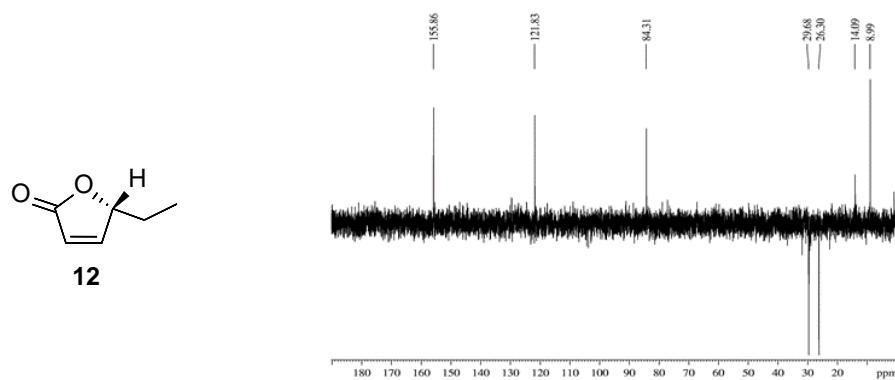
Supporting Information

General experimental details, full characterization and copies of ^{1}HNMR and ^{13}CNMR spectra of compounds **12** and **13** are provided.

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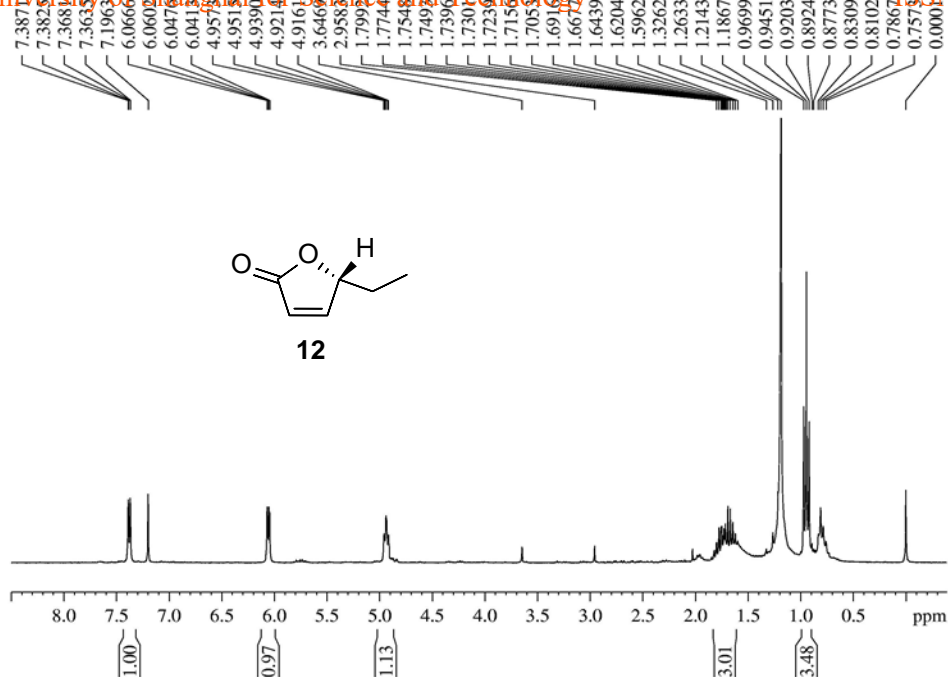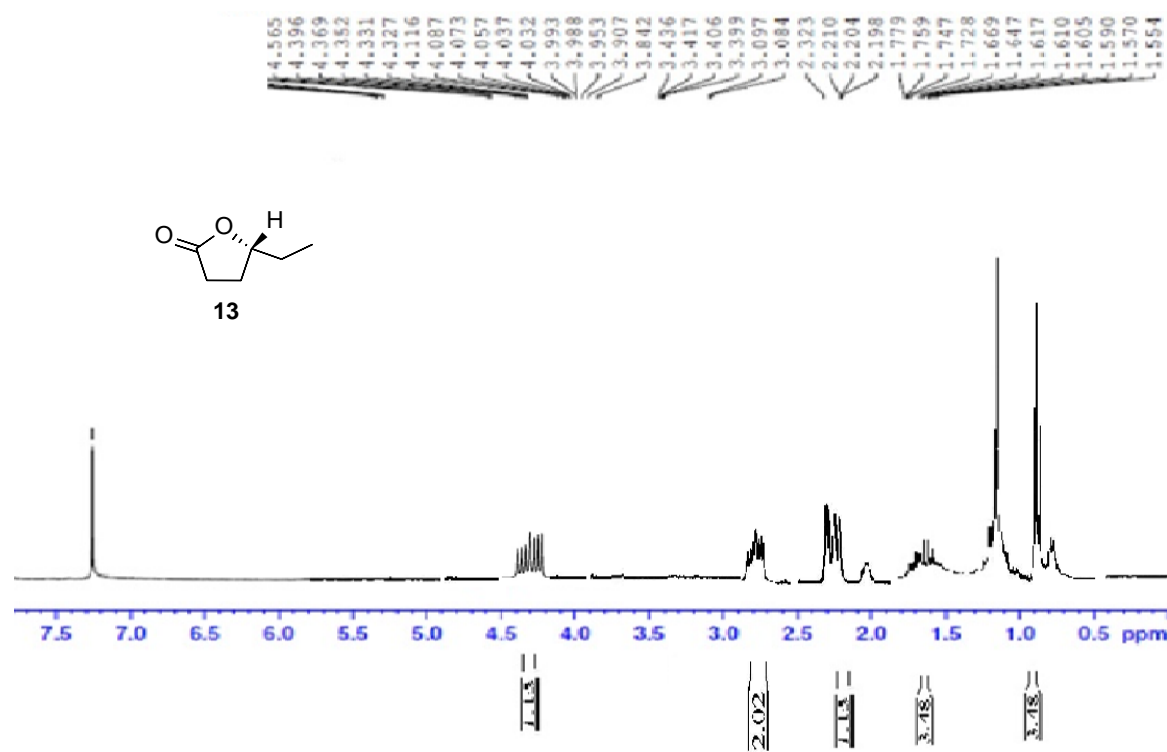
Fig. 1: ^{1}H NMR spectrum of compound **12**

Fig. 2: ^{13}C NMR and DEPT 135 spectra of compound **12**

Fig. 3: ^{1}H NMR spectrum of compound 13