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HIGHLY STEREOSELECTIVE COUPLINGS OF CARBOHYDRATE LACTONES WITH TERPENE KETONES PROMOTED BY SmI_2

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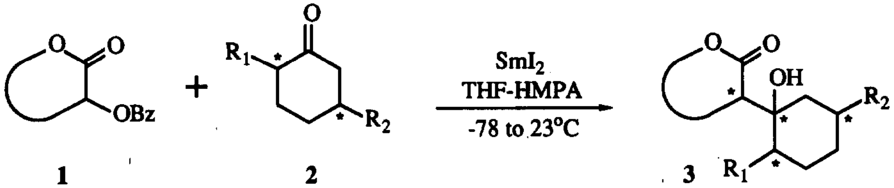
Key Words: ketyl, SmI_2, carbohydrate lactone, (+)-dihydrocarvone, (-)-menthone

Abstract: Lactone 3-deoxycarbohydrates were reacted with samarium diiodide (SmI_2) in THF/HMPA and the terpene ketones, (-)-menthone or (+)-dihydrocarvone; a serial reductive deoxygenation and an attendant carbonyl addition reaction afforded C_2 branched sugars with high diastereoselectivities (up to 99:1).

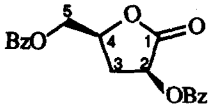
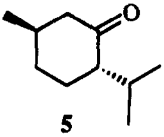
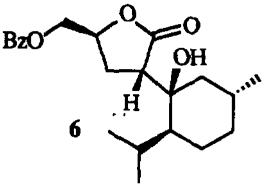
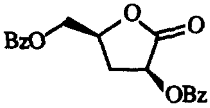
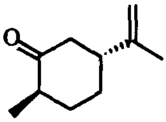
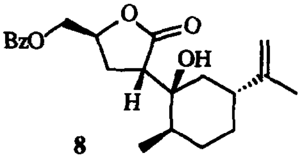
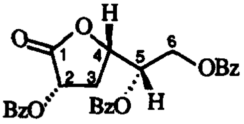
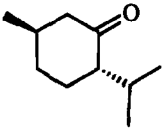
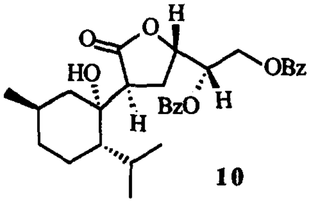
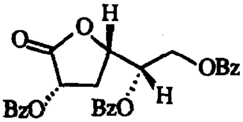
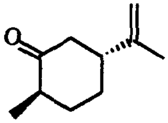
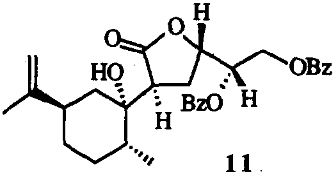
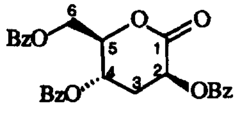
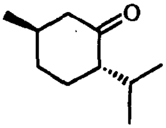
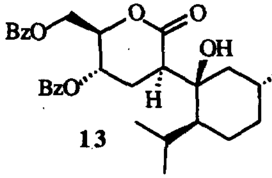
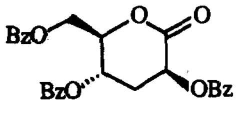
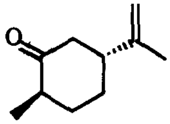
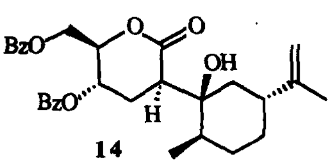
Substantial efforts by organic chemists to explore the various transformations of samarium diiodide (SmI_2) have been well-documented in the last ten years.[1] Various applications of SmI_2 in total synthesis and methodology easily serve to demonstrate the versatility of this one-electron transfer agent.[2] The utilization of SmI_2 in transformations of complex, optically active compounds such as carbohydrates and terpenes is in direct contrast to nearly all current technology, which primarily involves simple achiral substrates as synthetic vehicles.[2(g,i,m)] Herein we would like to describe a novel carbonyl addition reaction of these two precursors to prepare a C_2-branched sugar which occurs in a serial reaction with concomitant deoxygenation of the carbohydrate lactone ring.



The uncommon synthetic approach we studied was to afford a terpene and carbohydrate coupling. A general solution to this synthetic strategy can provide access to several naturally occuring compounds which contain hydroxylated tetrahydropyran or furan moieties coupled to isoprenoid-type segments in a wide array of acyclic and annulated forms.[3] These include the loganins,[4(a)] goldinodox,[4(b-c)] ambruticin,[4(d-e)] pseudomonic acids,[4(f-h)] and tirandimycin[4(i-k)] to name a few.

In the reaction we examined, lactone 3-deoxycarbohydrates[5] were reacted with the terpene ketones (-)-menthone or (+)-dihydrocarvone with SmI_2 and HMPA.[6] It is important to note that the ketone must be present at the onset of the reaction or the carbohydrate lactone decomposes and substantially reduced yields were observed.[2(l)] No other currently available method will both induce a similar deoxygenation[7] and carbonyl addition in a single serial reaction, moreover, the stereochemical control aspect of this reaction provides an additional attractive element.

Table I. SmI_2-Promoted Coupling of Lactone Carbohydrates to Ketone Terpenes

Entry	Carbohydrate	Ketone	Product[a]	Yield	Ratio
1	 4	 5	 6	46%	35 : 1
2	 4	 7	 8	58%	50 : 1
3	 9	 5	 10	53%	14 : 1
4	 9	 7	 11	59%	99 : 1
5	 12	 5	 13	45%	35 : 1
6	 12	 7	 14	57%	30 : 1

[a]Conditions: SmI_2 (4 equiv), THF-HMPA, -78 to 23°C, 1-6 hr.[6]

We were pleased to observe high diastereoselectivities in the products, shown in Table I, with both new carbon centers formed in the reaction with excellent stereocontrol. The ratios were as high as 99:1, as determined by capillary GC, for compound **11** in entry 4 and all were 30:1 or higher except entry 3. We also examined simple ketones such as cyclohexanone, however, only modest (3:1) ratios were observed in these cases. The use of chiral ketones supports an earlier observation with acyclic achiral esters and (-)-menthone, where it appears that the inherent stereochemistry of the ketone has a greater effect on the diastereoselectivity of the reaction than the ester/lactone component.[2(l)]

During the first stages of the reductive coupling, chelation of the SmI_2 with the carbohydrate C_1 lactone carbonyl and the carbonyl of the C_2 benzoate ester likely initiates the one-electron transfer process.[7(a),2(l)] After expulsion of the C_2 benzoate, a second one-electron reduction forms a samarium(III) enolate[8] which subsequently undergoes a carbonyl addition reaction with the terpene ketone.[2(l)]

The stereochemistry of the new C_2 stereocenter on the carbohydrate lactone was confirmed by difference NOE studies and x-ray crystallography.[9] In entries 1-4, the least hindered face of the lactone ring of the sugar was favored in the carbonyl addition reaction. The δ-lactones in entries 5 and 6 appear to have a preference for attack on the β-face of the carbohydrate ring which is a stereoelectronic result of preferred axial approach of the ketone to the samarium(III) enolate.[10] The stereochemistry of the terpene alcohol center in products **6**, **10**, and **13** from (-)-menthone (**5**) was a result of a known preference for addition to the π-face of the cyclohexanone carbonyl opposite the isopropyl group.[11] Compounds **8**, **11**, and **14**, resulting from addition to (+)-dihydrocarvone (**7**), have the terpene alcohol center drawn as shown because attack occurs in a manner analogous to (-)-menthone, in this case opposite the methyl substituent. Single crystal x-ray studies of compounds **10** and **11** readily confirmed the preference for addition of the precursors on the least hindered face of each ring.

To summarize, a useful and novel coupling of terpene ketones with lactone 3-deoxycarbohydrates with SmI_2 has been achieved with high levels of diastereoselectivity. After ejection of the C_2-benzoate, the approach of the ketone to the lactone in the major product is controlled by the steric and stereoelectronic effects. The overall synthetic technology shown herein allows the construction of C_2-branched sugars with a net coupling of two chiral carbonyl components.

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(6) In a typical deoxygenation/condensation procedure to prepare the coupled products: samarium metal (2.5 mmol) was stirred with THF (0.1 M in carbohydrate) under Ar atmosphere. Diiodomethane (2.0 mmol) and HMPA (300 μL) were added and the color of the reaction mixture turned blue-purple. After 1.5 h, the solution was cooled to -78 °C and the lactone 3-deoxycarbohydrate (0.5 mmol) and the terpene ketone (1.0 mmol) were added in THF (ca. 1 mL), via syringe, and the reaction warmed to room temperature. When the carbohydrate was consumed by TLC analysis, several drops of $NaHCO_3$ (aq. sat.) and ethyl acetate (15 mL) were added and stirring continued for 0.5 h to extract the product. After suction filtration through celite and evaporation of the solvents, the product was isolated by flash column chromatography.

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