Photochemically Induced Addition of 2-Propanol to Hex-2-enono-δ-lactones Followed by Radical Cyclization: A Novel Entry to Branched Cyclohexanes and Cyclopentanes from Carbohydrates

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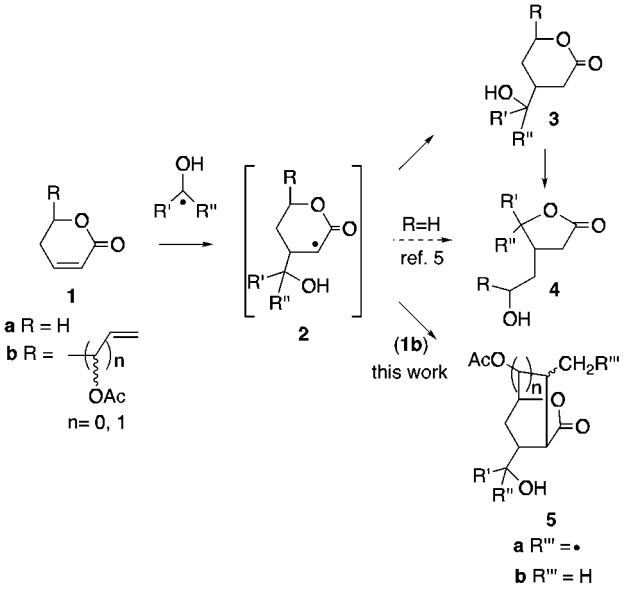
Received May 5, 1997[⊗]

Photochemically induced conjugated addition of 2-propanol to carbohydrate-derived hex-2-enono-δ-lactones **7**−**10**, substituted at C-6 or C-7 to give electron rich unsaturation, takes place at C-3 generating a radical at C-2 (carbohydrate numbering) which then undergoes efficient radical cyclization onto the pendant olefin to give the corresponding carbocycle. The reaction allows a rapid access to highly functionalized cyclohexanes and cyclopentanes from simple carbohydrate precursors and takes place in a highly stereocontrolled manner. Only one isomer is obtained on the cyclization of lactones from the *gluco* series, **7**−**9**, where three new stereogenic centers are created. On the other hand, galactose-derived lactone **10**, furnished upon application of the protocol a ≈4:1 mixture of two epimers at C-7.

Introduction

The photoinduced addition of alcohols to unsaturated carbonyl compounds has proved to be an excellent method for carbon-carbon bond formation.[1] In this context, Fraser-Reid and co-workers have reported on the addition of alcohols to carbohydrate derived α-enones for the stereocontrolled access to branched chain sugars.[2] This methodology, however, could not be extended to α,β-unsaturated δ-lactones **1** to prepare the corresponding C-3 branched derivatives (e.g., **3**), because a spontaneous translactonization process (e.g., **3** → **4**) would take place to yield exclusively butyrolactones **4**.[3] More recently Mann *et al.* [4] have extended this methodology to the use of unsaturated 1,4-lactones where translactonization does not take place.[5] From a mechanistic standpoint it is generally accepted[2c] that the reaction takes place through conjugate addition of a hydroxyalkyl radical to the olefin **1**, which is followed by hydrogen atom transfer to the resulting α-carbonyl radical **2**, to produce the adduct **3** (see Scheme 1). In the context of our continuing interest in the preparation of optically active carbocycles from carbohydrates[6,7] we hypothesized that the α-carbonyl radical **2b** could experience radical addition onto a suitably located olefin (e.g., **2b** → **5a**) faster than hydrogen transfer from 2-propanol (e.g., **2** → **3**), therefore allowing direct access to carbocycles and therefore avoiding the formation of butyrolactones (e.g., **2** → **4**). Here we report our success in incorporating the α-carbonyl radical **2** in a 5-*exo*- or 6-*exo*-*trig* radical cyclization process leading to homochiral cyclohexanes and cyclopentanes **5b**.[8]

Scheme 1



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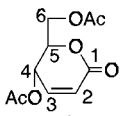
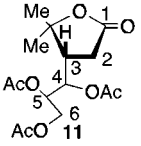
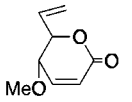
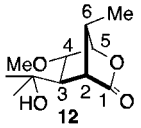
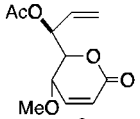
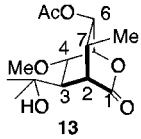
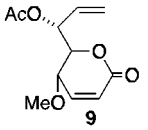
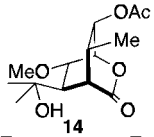
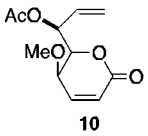
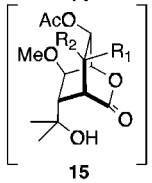
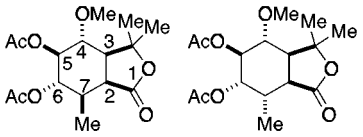
S0022-3263(97)00793-7 CCC: $14.00

Table 1. Preparation of Carbocycles by Irradiation of Pyranolactones in 2-Propanol with (or without) Benzophenone as Sensitizer

Entry	Substrate	Concentration (mol/L)	Sensitizer	Reaction time (h)	Product	Yield (%)
1	 **6**	$5.8\ 10^{-3}$	Ph_2CO	2	 **11**	59[a]
2	**6**	$1.5\ 10^{-3}$	---	2	**11**	79
3	 **7**	$2.0\ 10^{-3}$	Ph_2CO	1	 **12**	50
4	 **8**	$2.0\ 10^{-3}$	Ph_2CO	1	 **13**	80
5	**8**	$1.5\ 10^{-3}$	---	1	**13**	77
6	**8**	$1.5\ 10^{-2}$	---	4	**13**	72
7	 **9**	$1.1\ 10^{-3}$	---	1	 **14**	71
8	 **10**	$1.0\ 10^{-3}$	---	1	 **15** (4:1) **a** R_1= Me, R_2= H; **b** R_1= H, R_2= Me	72[b]

[a] Isolated after acetylation (Ac_2O/Pyridine) of the crude reaction mixture. [b] Isolated after acetylation (Ac_2O/Pyridine) of the crude reaction mixture as a mixture of translactonized products **16a,b** on a ≈ 4:1 ratio (^1H NMR, 300 MHz).



16a (4 : 1) **16b**

Results and Discussion

We have applied this protocol to known lactone **6**[9] and to dienic lactones **7**−**10**, syntheses of which have been reported by us,[7,10] and the results are shown in Table 1. Irradiation of lactone **6**[9] in 2-propanol as solvent (entries 1 and 2) led to butyrolactone **11**, which results from translactonization of the initially formed photoadduct. Glucose derived lactones **7**−**9** reacted to give single isomeric bicyclic compounds **12**−**14**, respectively (entries 4−6). Galactose derivative **10** furnished, upon irradiation, a (≈ 4:1) mixture of cyclohexane lactones **16a**,**b** resulting from translactonization of the initially formed adducts **15a**,**b** (entry 8).

From the results outlined in the Table 1 some conclusions can be drawn: (a) the reaction can be carried out in the absence of benzophenone[3c] without any considerable change either in reaction rate or stereoselectivity (compare entries 1, 2, and 4, 5); (b) the stereochemistry of the C-3 branch (entries 1−8) is the result of a preferred *anti* approach of the incoming radical with respect to the methoxy substituent at C-4, in keeping with literature precedents;[11] (c) the stereochemical outcome observed in the radical cyclizations for the *gluco*-type substrates (entries 3−7) seems to be governed by the release in steric repulsion from the bulky propyl substituent with the pendant olefin (B, Figure 1) rather than by the most favorable conformation for the chain in the transition state which would minimize 1,3 allylic strain (A, Figure 1);[7,12] (d) in the *galacto* case (entry 8), where interaction in the transition state between the isopropyl branch and the pendant olefin is not possible, a (≈4:1) mixture of products is obtained in which release of the 1,3 allylic strain is responsible for the observed ratio;[7,12] (e) finally, translactonization leading to butyrolactones[3] is a very favored process also in the carbohydrate series and takes place on simple δ-pyrones (entries 1 and 2) and on bicyclic compounds whenever the new hydroxy group has the correct orientation (see entry 8, compare with entries 3−7).

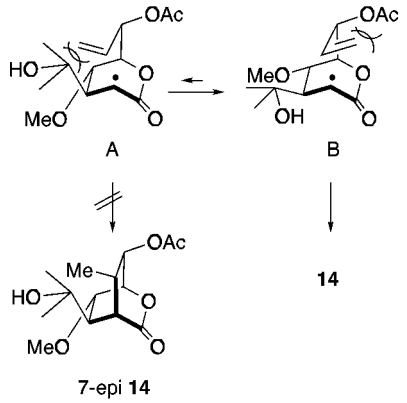


Figure 1.

The configuration at C-3 and at C-6 or C-7 in all the stereostructures has been rigorously assigned on the basis of diagnostic nuclear Overhauser effects (NOE) obtained in the corresponding bicyclic products.

Besides its synthetic value, the process described herein also has some implications on the possible reaction course. Interestingly, radical cyclization of lactone radicals, e.g., **2b**, has to be faster than hydrogen atom transfer from 2-propanol. In the cases where the reaction takes place without sensitizer, it is likely that it proceeds *via* a radical chain mechanism, as suggested by Mann *et al.*,[4d] although with the insertion of one additional chain-transfer step.[13] Conjugate addition of the hydroxypropyl radicals to lactone **1b** (Scheme 1) results in generation of lactone radical **2**, cyclization of which (5-*exo*- or 6-*exo*-*trig*)[13] onto the pendant olefin generates a new radical, **5a**. Finally hydrogen atom transfer to **5a** from 2-propanol would result in the production of hydroxypropyl

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radical, which could add to lactone **1b** then carrying the chain. The cyclization process is also, as expected, faster than the translactonization step.

The protocol disclosed here rapidly gives fairly complex products from simple precursors. It allows a ready and efficient entry into cycloalkanes from carbohydrates which takes place with very good stereocontrol in the formation of the three new stereocenters. This method also complements a protocol, recently reported by some of us, for the preparation of branched cyclohexanes from pyranosides in which the first radical addition at C-3 was carried out intramolecularly rather than intermolecularly.[14]

Experimental Section

General. Melting points were determined in capillary tubes and are uncorrected. Optical rotations were determined at the sodium D line and measured in chloroform. $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. High-field NMR spectra were recorded at 200, 300, or 500 MHz in $CDCl_3$; chemical shifts (δ) are relative to $CHCl_3$ as internal reference. TLC was conducted in precoated Kieselgel 60 F_{254}. Detection was first by UV (254 nm) and then charring with a solution of ammonium molybdate(VI) tetrahydrate (12.5 g) and cerium(IV) sulfate tetrahydrate (5.0 g) in 10% aqueous sulfuric acid (500 mL). Column chromatography was carried out on Kieselgel (230−400 mesh) and mixtures of hexane−ethyl acetate (Hexane−EtOAc) as eluant. All reactions were conducted under an atmosphere of argon. Anhydrous $MgSO_4$ or Na_2SO_4 was used to dry the organic solutions during workup, and the removal of the solvents was done under vacuum on a Rotovapor. Unless otherwise noted, materials were obtained from commercially available sources and used without further purification. Solvents were dried and purified using standard methods.

General Procedure for the Photochemical Reaction. Method A. The corresponding lactone, with benzophenone (0.5 molar equiv), was dissolved in 2-propanol (150 mL), and the reaction was irradiated in a water-cooled Pyrex immersion-well reactor with the light from a medium pressure mercury lamp (125 W). Argon was continuously bubbled before (20 min) and during the irradiation. At the end of the reaction the solvent was removed under reduced pressure and the residue purified by flash chromatography.

Method B *(without sensitizer).* The corresponding lactone was dissolved in 2-propanol (150 mL) and was irradiated in a water-cooled Pyrex immersion-well reactor with the light from a medium pressure mercury lamp (125 W). Argon was continuously bubbled before (20 min) and during the irradiation. At the end of the reaction the solvent was removed under reduced pressure and the residue purified by flash chromatography.

(3*R*)-3(1′*S*, 2′*R*)-3′-(1,2,3-Triacetoxypropyl)-4,4-dimethylbutan-4-olide (11). The irradiation of 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enono-1,5-lactone,[6] **9**, according to either method A (200 mg, 0.87 mmol) or method B (50 mg, 0.22 mmol) led after acetylation (excess Ac_2O, pyridine) of the crude reaction mixtures and flash chromatography (40% EtOAc in hexane) to **11** (169 mg, 59%; 57 mg, 79%, respectively) as a pale oil: $[\alpha]^{21}_D$ +36.5° (*c* 0.75); ^{1}H NMR (300 MHz) δ 1.24 (s, 3H), 1.46 (s, 3H), 2.05 (s, 3H), 2.07 (s, 3H), 2.10 (s, 3H), 2.64 (m, 3H), 4.07 (dd, J = 12.1, 7.7 Hz, 1H), 4.40 (dd, J = 12.1, 3.7 Hz, 1H), 4.94 (m, 1H), 5.32 (m, 1H); ^{13}C NMR (50.3 MHz) δ 20.7, 20.8, 21.8, 28.9, 32.1, 45.6, 61.1, 71.5, 72.2, 85.8, 169.5, 170.4, 170.6, 173.1. Anal. Calcd for $C_{15}H_{22}O_8$: C, 54.42; H, 6.72. Found: C, 54.21; H, 6.43.

(1*R*,4*S*,5*R*,6*S*,7*R*)-5-(1-Hydroxy-1-methylethyl)-6-methoxy-7-methyl-2-oxabyciclo[2.2.1]heptan-3-one (12). This compound was prepared by the general method A from lactone **7**[7] (40 mg, 0.30 mmol) followed by chromatography (40% EtOAc in hexane) to give **12** (32 mg, 50%) as a pale oil that crystallized on standing: mp 57−59 °C; $[\alpha]^{21}_D$ −99.3° (*c* 0.70); ^{1}H NMR (300 MHz) δ 1.08 (dd, J = 6.8, 0.7 Hz, 3H), 1.30 (s, 3H), 1.32 (s, 3H), 1.62 (d, J = 4.4 Hz, 1H), 2.64 (bs, 1H), 2.73 (m, 1H), 3.40 (s, 3H), 3.99 (d, J = 4.4 Hz, 1H), 4.68 (s, 1H); ^{13}C NMR (50.3 MHz) δ 11.4, 28.9, 29.3, 41.8, 50.4, 54.1, 56.9, 71.0, 82.2, 83.2, 178.2. Anal. Calcd for $C_{11}H_{20}O_5$: C, 61.65; H, 8.47. Found: C, 61.38; H, 8.43.

(1*S*, 4*S*, 5*R*, 6*S*, 7*S*, 8*R*)-5-(1-Hydroxy-1-methylethyl)-6-methoxy-7-acetoxy-8-methyl-2-oxabyciclo[2.2.2]octan-3-one (13). Lactone **8**[7] was subjected to the standard photochemical reaction conditions according the method A (70 mg, 0.31 mmol) or method B (50 mg, 0.22 mmol). Flash chromatography (40% EtOAc in hexane) of the crude reaction mixtures afforded **13** (71 mg, 80% and 47 mg, 77%, respectively) as a white solid: mp 68−70 °C; $[\alpha]^{21}_D$ +11.3° (*c* 0.98), ^{1}H NMR (500 MHz) δ 1.12 (dd, J = 7.3, 0.7 Hz, 3H), 1.31 (s, 6H), 1.73 (m, 2H), 2.08 (s, 3H), 2.65 (t, J = 1.8, 1H), 2.80 (m, 1H), 3.35 (s, 3H), 3.93 (d, J = 5.8, 1H), 4.63 (t, J = 4.4 Hz, 1H), 4.76 (d, J = 4.4 Hz, 1H); ^{13}C NMR (125 MHz) δ 19.6, 20.8, 29.0, 30.4, 30.6, 44.9, 50.7, 56.0, 72.0, 73.7, 73.9, 74.9, 170.0, 173.4. Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.71; H, 7.75. Found: C, 59.18: H, 8.03.

(1*S*, 4*S*, 5*R*, 6*S*, 7*R*, 8*R*)-5-(1-Hydroxy-1-methylethyl)-6-methoxy-7-acetoxy-8-methyl-2-oxabicyclo[2.2.2]octan-3-one (14). This compound was prepared according to the general method B from lactone **9**[7] (39 mg, 0.17 mmol) followed by chromatography (40% EtOAc in hexane) to give the title compound **14** (29 mg, 71%) as a single stereoisomer: $[\alpha]^{21}_D$ +28.2° (*c* 0.70), ^{1}H NMR (300 MHz) δ 0.94 (d, J = 7.6 Hz, 3H), 1.31 (s, 6H), 1.65 (s, 1H), 1.71 (m, 1H), 2.11 (s, 3H), 2.72 (t, J = 2.4, 1H), 3.19 (m, 1H), 3.40 (s, 3H), 3.75 (dd, J = 4.0, 1.4, 1H), 4.82 (d, J = 1.1 Hz, 1H), 5.01 (dd, J = 9.5, 1.1 Hz, 1H); ^{13}C-NMR (50 MHz) δ 14.2, 20.7, 28.6, 29.1, 45.3, 50.5, 56.1, 68.9, 71.5, 76.7, 77.6, 78.1, 170.7, 173.5. Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.71; H, 7.75. Found: C, 59.06, H, 8.12.

(1*S*, 5*S*, 6*R*, 7*S*, 8*S*)-4-Dimethyl-6-methoxy-7,8-diacetoxy-9-methyl-3-oxabicyclo[4.3.0]nonan-2-one (16). Lactone **10**[7] was subjected to the standard photochemical reaction conditions according to method B (50 mg, 0.22 mmol). Flash chromatography (40% EtOAc in hexane) and acetylation of the crude reaction mixture afforded **16** as an inseparable mixture (4:1) of two diastereomers (51 mg, 72%): ^{1}H NMR (500 MHz, major isomer) δ 1.32 (d, J = 6.9 Hz, 3H), 2.04 (s, 3H), 2.07 (s, 3H), 2.14 (m, 1H), 2.24 (dd, J = 9.6, 7.4 Hz, 1H), 3.12 (dd, J = 7.4, 5.7 Hz, 1H), 3.39 (m, 1H), 3.42 (s, 3H), 4.86 (t, J = 9.6 Hz, 1H), 5.02 (t, J = 9.6 Hz, 1H); ^{13}C NMR (50.3 MHz) δ 13.1, 20.5, 21.0, 24.3, 27.0, 33.6, 42.8, 49.7, 58.6, 72.6, 77.3, 78.0, 83.1, 169.8, 170.0, 173.4; ^{1}H NMR (500 MHz, minor isomer, selected data) δ 1.18 (d, J = 7.2 Hz, 3H), 2.39 (dd, J = 10.4, 8.4 Hz, 1H), 2.56−2.77 (m, 1H), 2.89 (dd, J = 8.4, 4.3 Hz, 1H), 5.16 (t, J = 8.3 Hz, 1H). Anal. Calcd for $C_{16}H_{24}O_7$: C, 58.51; H. 7.37. Found: C, 58.78, H, 7.75.

Acknowledgment. This research was supported with funds from the Dirección General de Investigación Científica y Técnica (Grants: PB96-0822 and PB94-0104). We are deeply indebted to our colleague Dr. Francisco Amat-Guerri for his sustained interest, his help in the photochemical experiments, and useful discussions. A.M.G. thanks the Consejo Superior de Investigaciones Científicas for financial support.

JO970793G

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