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Regio- and stereoselective Baeyer–Villiger oxidation on (*R*)-(+)-camphor adducts

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Abstract—New chiral lactones were prepared regio- and stereoselectively from (*R*)-(+)-camphor adducts in 72% yield via Baeyer–Villiger oxidation with sodium perborate in acetic acid.

1. Introduction

The Baeyer–Villiger oxidation is a useful reaction in synthetic organic chemistry. Ketones are converted to either an ester or a lactone.[1–4] Of particular interest in this reaction is that the migration occurs with the retention of configuration; the stereochemistry of the original carbon–oxygen bond is also retained.[5] Steric factors play an important role in allowing or restricting the formation of the Criegge intermediate.[6,7]

2. Results and discussion

Herein, we report the preparation of lactones **4** and **5** in approximately 72% overall yield each from a mixture of *exo*/*endo* isomers **2** and **3**, obtained by the reaction of the lithium enolate of (*R*)-(+)-camphor with 2-methylpropanal[8] and decanal,[9] and its subsequent oxidation to lactone. The Baeyer–Villiger reaction with (*R*)-(+)-camphor **1** has been reported to produce two lactones in a ratio that depends on the electronic and steric factors as well as on the solvent.[10] We also report the preparation of *exo* lactones **4** and **5** when the Baeyer–Villiger oxidation with sodium perborate in acetic acid was applied to a mixture of *exo*/*endo* adducts **2** and **3**, previously obtained in 67% yield from (*R*)-(+)-camphor in a 3/1 ratio, according to the reaction sequence. *endo* Isomer **3** was recovered unreacted from this mixture. The reaction sequence is outlined in Scheme 1.

Identification and quantification of *exo* **2** and *endo* **3** isomers of (*R*)-(+)-camphor were performed using ^{1}H NMR based on bicyclo[2.2.1]heptane systems. The ^{1}H NMR spectrum of this mixture indicated the prevalence of *exo*-adduct **2** with a 3/1 ratio. In a separate experiment, isomers **2** and **3** were best isolated, purified and characterised as acetates **6** and **7**. In these systems, an *exo*-oriented substituent on C3 presents an H4–H3 coupling constant below 1 Hz. In contrast, an *endo*-orientation indicates a coupling constant of approximately 4.0 Hz.[11] The stereochemistry for carbinol **2** obtained in the aldol reaction was assigned on the basis of the value of the H3–H3′ coupling constant (Scheme 1) and the chemical shift values of both carbon atoms. A value for the coupling constant $J_{H3H3'} \approx 7$–12 Hz was assigned to the *threo* isomer due to the *anti*-orientation of both hydrogens. A coupling constant of 0.0-4.0 Hz arising from the *gauche* relationship of these hydrogens was assigned to the *erythro* isomer **3**.[12]

The alcohol mixture **2** and **3** was treated with sodium perborate as an oxidising agent in glacial acetic acid at 60 °C slowly producing peroxyacetic acid in situ.[13] Preliminary studies of the regioselectivity of the Baeyer–Villiger reaction with sodium perborate in acetic acid were studied with (*R*)-(+)-camphor, affording two lactones in a 6/4 ratio, favouring the lactone in which the migration of the C1–C2 bond had occurred (Fig. 1a). The lactone ratio was determined by the study of the corresponding ^{1}H and ^{13}C chemical shifts.[14] Surprisingly, when the oxidation was

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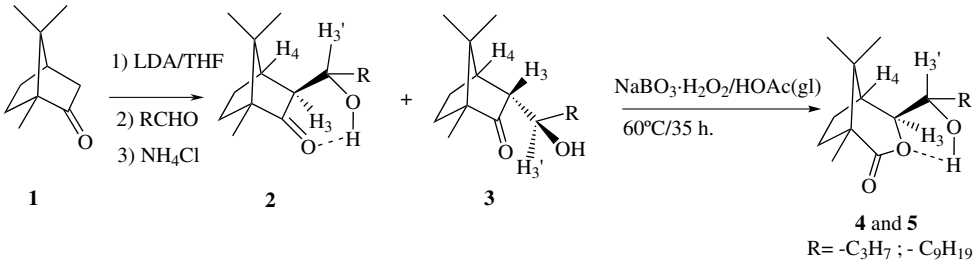

Scheme 1.

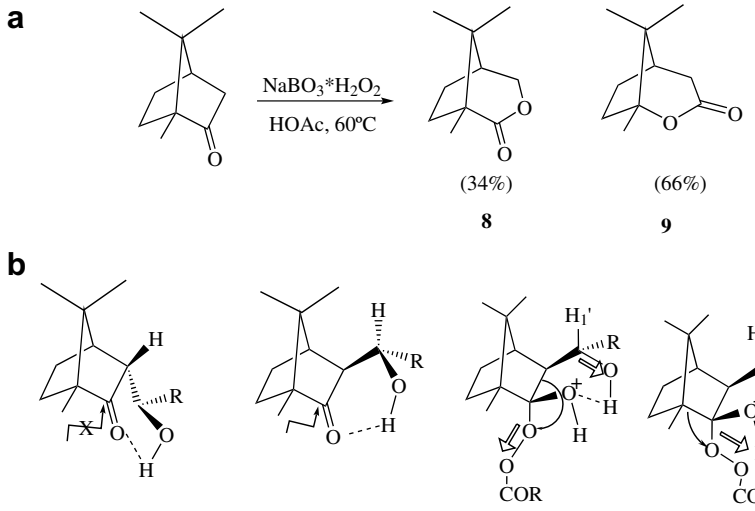

Figure 1.

carried out with a mixture of (*R*)-(+)-camphor adducts, only the lactone arising from the oxidation of the *exo*-isomer was produced. Lactones **4** and **5** were completely characterised by ^{1}H and ^{13}C NMR analysis. The configuration at C3 (the numbering of camphor is retained) was assigned as (*S*) from the study of the H3–H4 coupling constant ($J_{H3H4} = 0$ Hz). The stereochemistry of the carbon in the camphor adducts was similarly assigned.[15] A coupling constant $J_{H3H3'} = 10$ Hz, suggesting an *anti*-orientation of both hydrogens, indicated an (*S*)-configuration for C3′ in the lateral chain. ^{1}H NMR and the correlation experiments corroborated that the *endo* adduct had been recovered unreacted from the reaction mixture. The value of the coupling constant $J_{H3H4} = 4.9$ Hz indicated a *syn*-orientation for both hydrogens in this adduct thus supporting its structure.

A possible explanation for these results can be found in the analysis of the model given in Figure 1b. In this model, it is possible to observe that the *endo* orientation of the substituent containing the carbinol carbon in C3 hinders the approach of the oxidising agent at the α-face. In contrast, the isomer with this substituent in the *exo*-orientation does not present this steric factor. A structure such as the one shown in the model is capable of orienting the oxidising agent's leaving group antiperiplanar to the C2–C3 bond, favouring this bond's migration. The formation of an intramolecular hydrogen bond between the hydroxyl hydrogen and the carbonyl group in this *exo* adduct favours the formation of the Criegge intermediate.

The exclusive formation of only one lactone from the mixture of β-ketoalcohols of (*R*)-(+)-camphor adducts opens up an interesting synthetic route for chiral compounds in asymmetric syntheses.

3. Experimental

The solvents used were distilled from sodium under a nitrogen atmosphere. The products were isolated by liquid column chromatography on Silica Gel 60 G (particle size 230 mesh, Merck). ^{1}H NMR (250 MHz) and ^{13}C NMR (62.4 MHz) spectra were measured on a Bruker instrument in $CDCl_3$ as a solvent using TMS as a internal standard. Chemical shifts are expressed as δ ppm. Coupling constants are in Hertz. FTIR spectra (cm^{-1}) were measured on a Nicolet 550 spectrophotometer.

3.1. Aldolisation procedure

Lithium diisopropylamide (LDA) was prepared by the reaction of diisopropylamine (12.4 mL, 92.1 mmol) with *n*-butyllithium (51.4) mL of a 1.6 M solution in hexane, (82.24 mmol) in 30.0 mL of dry THF at −78 °C. The solution was stirred for 30 min and then a solution of camphor

(12.0 g, 78.9 mmol) in dry THF (52.0 mL) was added dropwise. After the addition, the solution was stirred for 2.5 h, and treated with freshly distilled aldehyde (79.0 mmol) and stirred for an additional 20 min. The reaction was quenched at −78 °C with a saturated aqueous NH_4Cl solution (20 mL). The reaction mixture was extracted with ethyl ether (3 × 30 mL). The combined organic layers were washed with an aqueous NaCl solution, dried over Na_2SO_4 and concentrated in vacuum to afford the adduct mixture. Products were purified by liquid column chromatography and the adduct ratio obtained was quantified by ^1H NMR spectroscopy.

3.2. Camphor adducts with 2-methylpropanal[4]

3.2.1. 3-*exo*-(1′-Acetoxy-2′-methylpropyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 6. ^1H NMR: 5.3 (1H, dd, $J = 10.3$, 2.2), 2.0 (3H, s), 1.97 (1H, m, $J = 2.0$), 1.1–1.84 (3H, m), 1.5 (1H, m), 1.35 (2H, m), 0.90 (3H, s), 0.88 (3H, s), 0.84 (6H, d, $J = 2.0$), 0.82 (3H, s). ^{13}C NMR: 218.3, 170.2, 76.7, 57.9, 54.9, 46.0, 45.2, 29.9, 29.6, 29.0, 21.0, 20.7, 20.3, 19.0, 15.0, 9.0. Anal. Calcd for $C_{16}H_{26}O_3$: C, 74.95; H, 10.78. Found: C, 74.93; H, 10.80.

3.2.2. 3-*endo*-(1′-Acetoxy-2′-methylpropyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 7. ^1H NMR: 5.1 (1H, dd, $J = 10$, 2), 2.40 (1H, dd, $J = 10.0$, 4.0), 2.04 (3H, s), 1.96 (1H, t, $J = 4.0$), 1.75 (2H, m), 1.58 (1H, m), 1.40 (2H, m), 0.91 (3H, s), 0.83 (6H, m), 0.80 (3H, s), 0.78 (3H, s). ^{13}C NMR: 217.2, 171.0, 74.0, 58.2, 54.9, 49.0, 46.0, 44.7, 30.0, 29.5, 21.0, 19.8, 19.3, 18.8, 14.8, 9.3.

3.3. Camphor adducts with decanal[5]

3.3.1. 3-*exo*-(1-Hydroxydecyl)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one. ^1H NMR: 4.15 (1H, s), 3.90 (1H, m), 2.04 (1H, dd, $J = 10.2$, 2), 1.97–1.91 (2H, br), 1.76–1.26 (19H, br), 0.94 (3H, s), 0.91 (3H, s), 0.88 (3H, s), 0.85 (3H, s). ^{13}C NMR: 223.6, 73.30, 59.56, 57.84, 46.90, 46.01, 36.17, 31.90, 29.61, 29.70–29.31 ($5CH_2$), 24.76, 22.67, 21.67, 20.44, 14.05, 9.04. Anal. Calcd for $C_{20}H_{36}O_2$: C, 77.92; H, 11.69. Found: C, 77.93; H, 11.79.

3.3.2. 3-*endo*-(1-Hydroxydecyl)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one. ^1H NMR: 3.92 (1H, s), 3.74 (1H, m), 2.34 (1H, dd, $J = 9.4$, 4.5), 2.10 (1H, s), 1.77–1.69 (2H, m), 1.47–1.39 (4H, m), 1.27 (14H, br), 0.98 (3H, s), 0.92 (3H), 0.88 (3H, s), 0.85 (3H, s). ^{13}C NMR: 223.7, 73.2, 59.6, 57.8, 46.84, 46.0, 36.05, 31.52, 29.56, 29.24 ($5CH_2$), 24.67, 20.81, 19.54, 18.53, 15.20, 9.24.

3.4. General procedures for lactone syntheses

To (3.0 g, 19.7 mL) the targeted adducts in 25 mL of pure ethanoic acid, 12.2 g (78.8 mmol) of sodium perborate was added and the mixture stirred at 60 °C for 35 h. The reaction mixture was extracted with dichloromethane (3 × 30 mL). The organic layer was washed with aqueous $NaHCO_3$ (3 × 20 mL) and dried over Na_2SO_4. The removal of solvent at a reduced pressure gave a mixture of products. The products were isolated by liquid column chromatography (72% yield).

3.4.1. 4-(1-Hydroxy-2-methylpropyl)-1,8,8-trimethyl-3-oxabicyclo[3.2.1] octan-2-one 4. Oil, $[\alpha]_D = +53.5$ (*c* 2.2, EtOH); ^1H NMR: 4.10 (1H, d, $J = 9.6$), 3.80 (1H, ddd, $J = 9.6$, 2.3, 2.3), 2.6 (1H, dd, $J = 2.3$, 1.2), 2.00 (H_5, d, $J = 5.9$), 2.22 (1H, m), 1.60 (1H, m), 2.12 (1H, m), 1.85 (1H, m), 1.80 (1H, m), 1.60 (3H, d, $J = 6.79$), 0.87 (3H, d, $J = 6.79$), 1.17 (3H, s), 1.08 (3H, s), 0.96 (3H, s).^{13}C NMR: 176.27, 90.11, 75.75, 52.89, 44.34, 42.50, 34.52, 29.35, 23.76, 21.46, 20.20, 15.64, 14.20. FTIR (cm^{-1}): 3472, 2966, 1730, 1463, 1371, 1322, 1224, 1158, 1011, 1001, 948. Anal. Calcd for $C_{14}H_{24}O_3$: C, 74.24; H, 10.54. Found: C, 74.27; H, 10.53

3.4.2. 4-(1-Hydroxydecyl)-1,8,8-trimethyl-3-oxabicyclo[3.2.1]-octan-2-one 5. Oil, $[\alpha]_D = +17.5$ (*c* 1.9, EtOH); ^1H NMR: 3.94 (1H, d, $J = 10$); 3.92 (1H, ddd, $J = 10$, 9.7, 9.2); 2.82 (1H, br s); 2.23 (2H, m); 2.13 (1H, d, $J = 5.7$); 1.80 (1H, m); 1.26 (17H, br s); 1.17 (3H, s); 1.08 (3H, s); 0.96 (3H, s), 0.88 (3H, t, $J = 6.84$); ^{13}C NMR: 176.0, 91.58, 72.26, 52.91, 44.48, 42.60, 34.56, 32.58, 31.87, 30.93, 29.55,29.40, 29.30, 29.0, 25.04, 23.77, 22.66, 21.62, 14.70, 14.09. Anal. Calcd for $C_{20}H_{36}O_3$: C, 74.0; H, 11.11. Found: C, 74.54; H, 11.60.

3.4.3. 1,8,8-Trimethyl-3-oxabicyclo[3.2.1]octan-2-one 8. ^1H NMR: 4.47 (1H, ddd, $J = 10.7$, 2.9, 1.7), 4.10 (1H, d, $J = 10.7$), 2.20 (1H, m), 2.0 (2H, m), 1.7 (2H, m), 1.17 (3H, s), 1.09 (3H, s), 0.97 (3H, s). ^{13}C NMR: 171.78, 73.97, 53.71, 44.67, 43.40, 36.14, 26.97, 22.39, 19.89, 14.25.

3.4.4. 1,8,8-Trimethyl-2-oxabicyclo[3.2.1]octan-3-one 9. ^1H NMR: 2.81 (1H, ddd, $J = 18.7$, 4.97, 2.47), 2.41 (1H, dd, $J = 18.7$, 1.25), 2.15 (2H, m), 2.0 (1H, m), 1.56 (2H, m), 0.96 (3H, s), 0.91 (3H, s), 0.86 (3H, s). ^{13}C NMR: 171.7, 92.9, 42.5, 38.5, 37.0, 27.8, 26.9, 23.8, 18.3, 17.4.

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