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Reduction of 2-Alkyl-2-carbomethoxy-cyclopentanone Derivatives with Sodium Borohydride. II. The Elucidation of the Diastereoselective Control

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REDUCTION OF 2-ALKYL-2-CARBOMETHOXY-CYCLOPENTANONE DERIVATIVES WITH SODIUM BOROHYDRIDE . PART 2. THE ELUCIDATION OF THE DIASTEREOSELECTIVE CONTROL [a)]

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Abstract: The synthesis and reduction of four new 2-substituted β-keto-ester derivatives (6-9), employing inexpensive sodium borohydride, were achieved to evaluate the diastereoselectivity of the reduction process of 2-allyl-2-carbomethoxy cyclopentanone derivative (1a) in the same conditions. These results indicating that the diastereoselective control in this process depend on blockage of the re-face of (1a) by a proposed carbonyl-π-stacking type interaction.

The preparation of β-hydroxy-ester derivatives exploring the chemo- and diastereoselective reduction of functionalized β-keto-esters consist in an efficient and useful strategy to access new synthetic building blocks[1].

In a previous paper[2] we described an efficient method to obtain, diastereoselectively, 2-allyl-2-alkoxycarbonyl-cyclopentanol derivatives (2a-c) and

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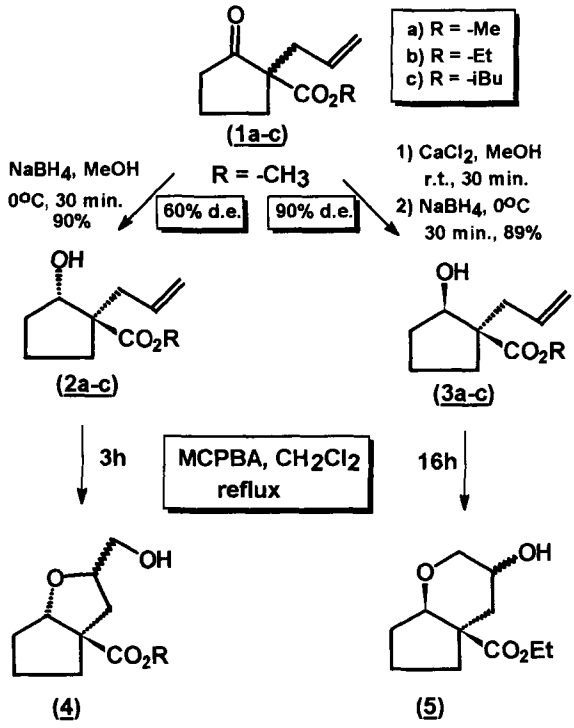
[a)] This work represents the contribution # 19 from LASSBio, UFRJ.

(3a-c), exploring the reduction of the corresponding β-ketoester derivative (1a-c) with sodium borohydride. Applying the diastereoselective cationic oxidative cyclization process[3], the cyclopentanol derivatives (2) and (3) would be converted in the bicyclic synthons (4) and (5), respectively, which are useful key intermediate in synthesis of new bioactive compounds[4,5] (Scheme 1).

Scheme 1

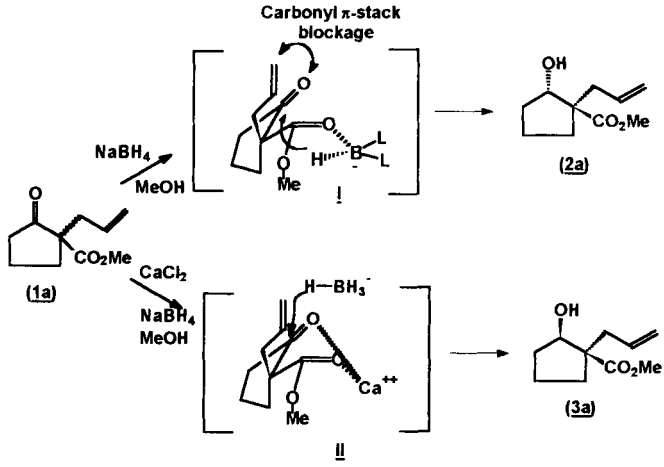


In those initial studies, varying the volume of the ester group, we joined evidences that suggests that the mechanism of the diastereoselective reduction of cyclopentanone (2a) with sodium borohydride, in presence or absence of calcium chloride, is major dependent of chelating factors, in detriment of steric ones, as

indicated by molecular modeling of transition states that conduces to corresponding cyclopentanol derivatives (2a) and (3a)[6].

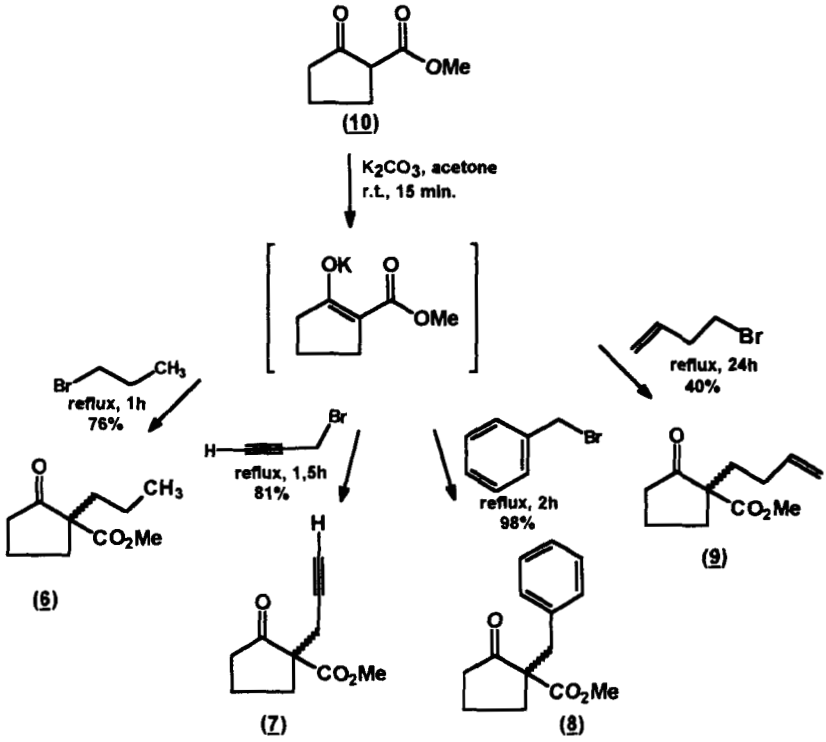
In order to identify the principal groups involved in the chelation control, we designed four new β-ketoesters, i.e. 2-propyl-2-carbomethoxy-cyclopentanone (6), 2-propargyl-2-carbomethoxy-cyclopentanone (7), 2-benzyl-2-carbomethoxy-cyclopentanone (8) and 2-(1-butenyl)-2-carbomethoxy-cyclopentanone (9) to submit at reductive conditions with sodium borohydride in polar protic media. The compounds (6-9) were also planned in order to evaluate the possible contribution of an carbonyl-π-stacking type interaction[7] presenting in species I or a Lewis acid-dicarbonyl-complex represented by species II in control of the diastereoselectivity of the process (Scheme 2).

Scheme 2



The C-2 alkylated ß-keto-esters (6), (7), (8) and (9) were prepared, in very good yield, from 2-carbomethoxy-cyclopentanone[8,9] (10) by a regioselective C-alkylation reaction with an excess of corresponding alkyl halide using Barco's conditions[10], as described previously[2] (Scheme 3).

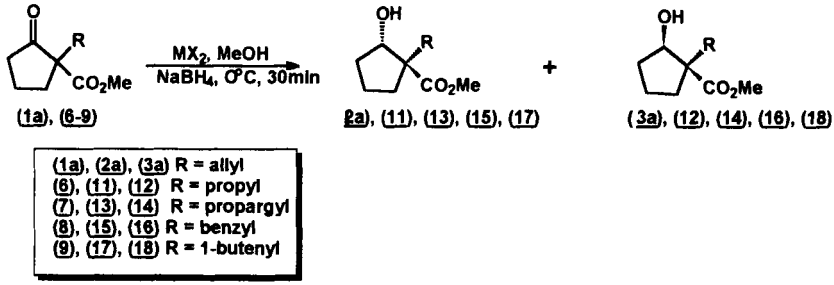
Scheme 3



Compounds (6-9) were full spectroscopic characterized and then submitted to two different reduction conditions, employing $NaBH_4$ and $NaBH_4$-$CaCl_2$[11] in MeOH at 0°C by 30 minutes, referred as conditions A and B, respectively, as shown in table 1.

These data are striking in several regards. First, submitting the 2-propyl-2-carbomethoxycyclopentanone derivative (6) to reduction conditions A (entry 3) and B (entry 4) not implicate in inversion of the diastereoselectivity, as described to reduction of the allyl derivative (1a)[2]. In spite of this, the reduction of (6) with sodium borohydride-calcium chloride showed a high diastereoselective profile (entry 4) contributing with the hypothesis of reduction of allyl derivative (1a) with

TABLE 1: Reduction of 2-alkyl-2-carbomethoxy-cyclopentanone derivatives (6-8), employing sodium borohydride.



(1a), (6-9) (2a), (11), (13), (15), (17) (3a), (12), (14), (16), (18)

(1a), (2a), (3a) R = allyl
(6), (11), (12) R = propyl
(7), (13), (14) R = propargyl
(8), (15), (16) R = benzyl
(9), (17), (18) R = 1-butenyl

Compound	Entry	Lewis Acid[b]	Products[c,d]	Yield (%)	Relative proportion[c,d]
1a[a]	1	-----	2a-3[a]	90	4 : 1
1a[a]	2	$CaCl_2$	2a-3[a]	89	1 : 19
6	3	-----	11-12	30	1 : 1.9
6	4	$CaCl_2$	11-12	30	1 : 99
7	5	-----	13-14	86	1.4 : 1
7	6	$CaCl_2$	13-14	78	1 : 7.7
8	7	-----	15-16	72	1 : 2
8	8	$CaCl_2$	15-16	78	1 : 11.9
9	9	-----	17-18	78	1 : 2.3
9	10	$CaCl_2$	17-18	30	1 : 7.1

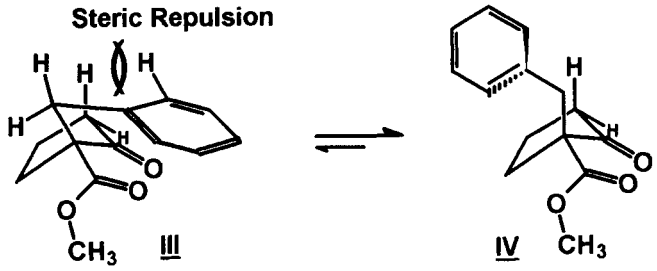
[a] As described in reference 2.
[b] Were employed 1.2 eq. de $NaBH_4$ e 2 eq. de MX_2 ($CaCl_2$ or $ZnBr_2$).
[c] The relative diastereomeric ratio was determined by HRGC in a column HP-1 at 150-250°C/15°C/min.
[d] The qualitative determination of diastereoisomeric alcohols was made by analysis of ^1H NMR at 200 or 300 MHz, in presence of $Eu(thd)_3$.

$NaBH_4$ (entry 1) is carbonyl-π-stacking controlled. In fact, this result suggest that carbonyl-π-stacking type interaction contribute to blockage the re-face of 2-allyl-2-carbomethoxy-cyclopentanone (1a), so that the hydride is major transferred by si-face, as represented by species I (Scheme 2), affording predominantly the *anti* cyclopentanol derivative (2a). Second, the reduction of allyl-homologous derivative (9) (entry's 9 and 10) showed a similar profile to that described for propyl derivative (6), indicating that the 1-butenyl group not present the ideal distance[7] to carbonyl-π-stacking type interaction. However, the diastereoselectivity of the reduction process with $CaCl_2$ (entry 10) was decreased, *i.e.* 98% d.e. versus 75% d.e., possibly due to steric effects or to fragile carbonyl-π-stacking type interactions.

Additionally, the reduction of benzyl derivative (8) (entry's 7 and 8) also displayed the same pattern to that described for reduction of (6) and (9), indicating that the conformation of (8) that would permit a classical carbonyl-π-stacking interaction is energetically disfavorable possibly due to strong steric 1,3-diaxial interactions between hydrogen atom at Ar-2' and it at C-5, so that the phenyl group could assume a conformational orientation perpendicular to carbonyl group (Scheme 4). Therefore, in the calcium mediated process (entry 8), the access of the hydride by re-face in the conformer IV (Scheme 4) is more favorable, resulting in an increase of the diastereomeric excess, *i.e.* 85% (entry 8) when compared with the reduction of 1-butenyl derivative (9) in the same conditions (entry 10).

Interestingly, the comportment of the propargyl derivative (7) followed the profile of the reduction of the allyl derivative (1a), with inversion of the diastereoselectivity in function of the employment of the calcium chloride (entry 6). In this case, the poor observed distereoselectivity using only sodium

Scheme 4



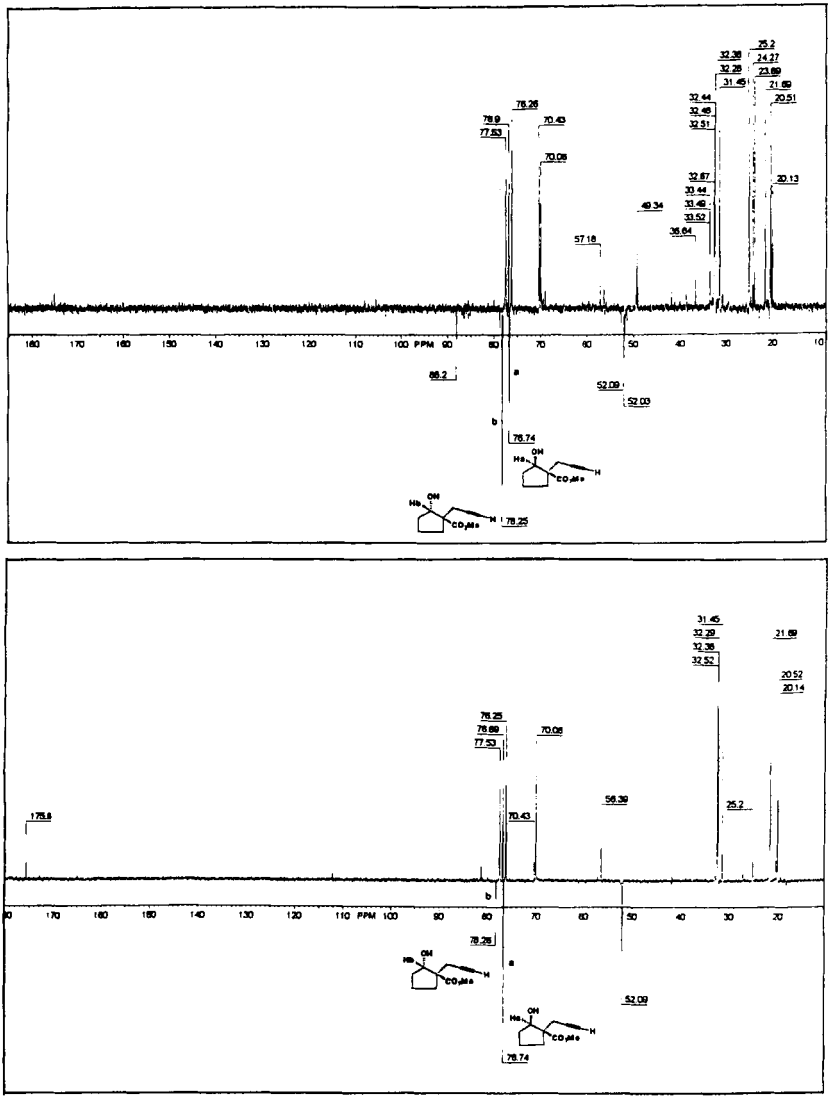
borohydride (entry 5) suggest the possibility of a powerless carbonyl-π-stacking type interaction decurrent of linear geometry of the sp-carbons of the propargyl group.

The diastereoselectivity inversion that characterized the reduction of the propargyl derivative employing the conditions A and B (Table 1), was well identified by comparison of the relative integration in ^{13}C NMR spectra of the signal referent to hydroxyl linked methyne group (signals a and b) in the diastereomeric mixture of the respective cyclopentanol derivatives (13) and (14) (Figure 1).

Finally, these studies indicated to us that the diastereoselectivity of the reduction of the 2-allyl-2-carbomethoxy cyclopentanone derivative (1a) is effectively dependent of the carbonyl-π-stacking type interaction (Scheme 2), which is function of the distance and the relative geometry between the carbonyl and the double bond groups. These results would be confirmed by careful measurement of the theoretical carbonyl-double bond distance of the all ketone derivatives (2a, 6-9), however preliminary results[12] employing the PC-MODEL program suggesting that only the allyl-double bond/carbonyl interaction presented a distance inside in the range of that described in the literature[7] for this kind of process, *i.e.* ~3-3.5 A.

Figure 1

^{13}C NMR (200 MHZ) spectra (APT experiment) of distereomeric mixture of 2-propargyl-2-carbomethoxy cyclopentanols (13) and (14) obtained from sodium borohydride reduction (**upper**) and sodium borohydride-$CaCl_2$ reduction (**below**).



Experimental Section.

^{1}H- and ^{13}C NMR spectra were determined in deuterochloroform containing c.a. 1% tetramethylsilane as an internal standard with Brucker AC200 and Varian VxR 300 spectrometers. Splitting patterns were as follows: s, singlet; d, doublet; t, triplet; td, deformed triplet; qt, quintet; dd, double doublet; m, multiplet. Infrared spectra (IR) spectra were obtained with a Perkin-Elmer 1600 spectrophotometer as neat films on sodium chloride plates. The mass spectra (MS) were obtained on a GC/VG Micromass 12 at 70 eV. Gas chromatography (HRGC) were recorded in a Hewlett Packard model 5987-A using injection in the splitness mode. The HRGC analysis was performed in a HP-1 (Crosslinked Methyl Silicone Gum) capillary column (50 m X 0.2 mm X 0.33 μm) by *on column* injection of 0.4 μl of the diastereomeric misture of cyclopentanols at 40°C/3°C/min/150°C.

The progress of all reactions was monitored by tlc which was performed on 2.0 cm X 6.0 cm aluminum sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were visualized with molybdatophosphoric acid in ethanol. For column chromatography Merck silica gel (70-230 mesh) was used. Solvents used in the reactions were generally redistilled prior use. The "usual workup" means that the organic extracts prior to concentration, under reduced pressure (80 mmHg), were treated with a saturated aqueous sodium chloride solution, referred to as brine, dried over anhydrous sodium sulfate and filtered.

General procedure for the C-alkylation of the ß-keto-ester (10)[2,10].

To a suspension of anhydrous potassium carbonate (10.6 g; 28.2 mmol) in anhydrous acetone (18 ml) was added a solution of 2-carbomethoxycyclopentanone[8] (10) (1 g; 0.87 ml; 7 mmol) in anhydrous acetone (9 ml). The reaction mixture displays a characteristic yellow color[2] after stirring at room temperature for 15 min.. Then, respective alkyl bromide (14 mmol) was added slowly and the mixture was refluxed for 1-2h (monitored by tlc). The formed suspension was filtered, the filtrate concentrated at reduced pressure (80

mmHg) and the residue diluted with ether (50 ml). The "usual workup" give the respective 2-alkyl-2-carbomethoxy cyclopentanone (6-8).

2-Propyl-2-carbomethoxy-cyclopentanone (6).

From alkylation of (9) with propyl bromide (1.7 g; 1.27 ml), this compound was obtained in 76% yield as an colorless oil; I.R. (film): ν C-H 2950, ν C=O 1740 and 1720, ν C-O 1210 cm^{-1}; ^1H NMR (300 MHz): 0.94 (t, 3, CH_2-CH_2-$\underline{CH_3}$, J = 7 Hz), 1.10-1.65 (m, 3, C3-H *syn* to propyl group and -$\underline{CH_2}$-CH_2-CH_3), 1.85-2.05 (m, 4, C4-$\underline{H_2}$ in cyclopentane ring and -CH_2-$\underline{CH_2}$-CH_3), 2.13-2.60 (m, 3, C5-$\underline{H_2}$ in cyclopentane ring and C3-H *anti* to propyl group), 3.69 (s, 3, O-$\underline{CH_3}$); ^{13}C NMR (75 MHz): 214.5 ($\underline{C}$=O in cyclopentane ring), 171.5 (H_3CO-$\underline{C}$=O), 60.5 (C-2), 52.2 ($\underline{H_3C}$O-C=O), 37.8 (C-5), 36.1 ($\underline{C}H_2$-CH_2-CH_3), 32.7 (C-3), 19.4 (C-4), 18.1 (CH_2-$\underline{C}H_2$-CH_3) 14.2 (CH_2-CH_2-$\underline{C}H_3$); MS (70 eV) m/z (relative abundance): 184 (M^+, 10%), 125 (M^+- O=C-O-Me, 28%), 115 (CH_3-CH(CO_2Me)C≡O+, 100%), 97 (H_2C=C(nPr)-C≡O+, 39%), 55 (+H_2C-CH=C=O, 80%).

Anal. Calcd. for $C_{10}H_{16}O_3$: C 65.19; H 8.74. Found: C 65.21; H 8.75.

2-Propargyl-2-carbomethoxy-cyclopentanone (7).

From alkylation of (9) with propargyl bromide (1.66 g; 1.3 ml), this compound was obtained in 81% yield as an colorless oil; I.R. (film): ν -C≡C-H 3280, ν C-H 2960, ν C=O 1750 and 1722, ν C-O 1155 cm^{-1}; ^1H NMR (200 MHz): 1.98 (t, 1, -C≡$\underline{C}$-$\underline{H}$, J = 3 Hz), 2.00-2.15 (m, 2, C4-$\underline{H_2}$ in cyclopentane ring), 2.20-2.38 (m, 2, C3-$\underline{H_2}$ in cyclopentane ring), 2.40-2.60 (m, 2, C5-$\underline{H_2}$ in cyclopentane ring), 2.71 (dd, 2, -$\underline{H_2C}$-C≡C-H, J_{AX} = 2.6 and J_{BX} = 1.2 Hz), 3.72 (s, 3, O-$\underline{CH_3}$); ^{13}C NMR (50 MHz): 213.4 ($\underline{C}$=O in cyclopentane ring), 170.7 (H_3CO-$\underline{C}$=O), 79.6 (-$\underline{C}$≡C-H), 70.6 (-C≡$\underline{C}$-H), 58.6 (C-2), 52.6 ($\underline{H_3C}$O-C=O), 38.1 (C-5), 32.3 (C-3), 23.0 ($\underline{C}H_2$-C≡CH), 19.5 (C-4); MS (70 eV) m/z (relative abundance): 180 (M^+, 16%), 165 (M^+-CH_3, 5%), 152 (M^+- C≡O, 81%), 124

(CH_3-CH(CO_2Me)C≡O+, 100%), 93 (H_2C=C(CH_2C≡CH)-C≡O+, 91%), 53 (H_2C=CH-C≡O+, 32%).

Anal. Calcd. for $C_{10}H_{12}O_3$: C 66.64; H 6.70. Found: C 66.60; H 6.71.

2-Benzyl-2-carbomethoxy-cyclopentanone (8).

From alkylation of (9) with benzyl bromide (2.4 g; 2.25 ml), this compound was obtained in 98% yield as an colorless oil; I.R. (film): ν -C=C-H 3120, ν C-H 2960, ν C=O 1745 and 1724, ν C-O 1155 cm^{-1}; ^1H NMR (300 MHz): 1.50-1.73 (m, 1, C3-H *syn* to benzyl group), 1.78-2.15 (m, 3, C3-H *anti* to benzyl group and C4-H_2 in cyclopentane ring), 2.30-2.50 (m, 2, C5-H_2 in cyclopentane ring), 3.16 (dd, 2, -CH_2-Ph, J_{AX} = 22.9 Hz and J_{BX} = 13.5 Hz), 3.72 (s, 3, O-CH_3), 7.05-7.15 (m, 2, *meta*Ar-H), 7,20-7.45 (m, 3, *ortho*Ar-H and *para*Ar-H); ^{13}C NMR (75 MHz): 214.6 (C=O in cyclopentane ring), 171.3 (H_3CO-C=O), 136.4 (*ipso*Ar), 130.0 (*ortho*Ar) , 128.3 (*meta*Ar), 126.8 (*para*Ar), 61.4 (C-2), 52.5 (H_3CO-C=O), 39.0 (-CH_2Ph), 38.2 (C-5), 31.6 (C-3), 19.3 (C-4); MS (70 eV) m/z (relative abundance): 232 ($M^{+\cdot}$, 3%), 217 ($M^{+\cdot}$-CH_3, 10%), 173 ($M^{+\cdot}$- CO_2CH_3, 18%), 155 ($M^{+\cdot}$-Ph, 9%), 91 (Tropilium+, 100%), 65 (Tropilium - HC≡CH, 18%).

Anal. Calcd. for $C_{14}H_{16}O_3$: C 72.39; H 6.94. Found: C 72.36; H 6.95.

2-(1-Butenyl)-2-carbomethoxy-cyclopentanone (9).

From alkylation of (10) with 4-bromo-1-butene (1.89 g; 1.42 ml), this compound was obtained in 40% yield after chromatographyc separation of the corresponding O-alkylation derivative, as an colorless oil; I.R. (film): ν -C=C-H 3118, ν C-H 2960, ν C=O 1740 and 1720, ν C-O 1160 cm^{-1}; ^1H NMR (200 MHz): 1.60-2.60 (m, 10, CH_2 in cyclopentane ring and -CH_2CH_2CH=CH_2), 3.72 (s, 3, O-CH_3), 4.90-5.1 (m, 2, -CH_2CH_2CH=CH_2), 5.68-5.90 (m, 1, -CH_2CH_2CH=CH_2); ^{13}C NMR (50 MHz): 214.5 (C=O in cyclopentane ring), 171.2 (H_3CO-C=O), 137.4 (-CH_2CH_2CH=CH_2), 115.0 (-CH_2CH_2CH=CH_2), 60.1 (C-2), 52.4 (H_3CO-C=O), 37.8 (C-5), 32.9 (C-3), 32.6 (-CH_2CH_2CH=CH_2), 29.0

(-$CH_2\underline{C}H_2CH{=}CH_2$), 19.4 (C-4); MS (70 eV) m/z (relative abundance): 196 ($M^{+\cdot}$, 1%), 165 ($M^{+\cdot}$-OCH_3, 8%), 142 ($M^{+\cdot}$- $H_2C{=}CH\text{-}CH{=}CH_2$, 100%), 110 ($M^{+\cdot}$-$H_2C{=}CH\text{-}CH{=}CH_2$ -HOMe, 68%), 55 (+$H_2C\text{-}CH{=}C{=}O$, 17%).

Anal. Calcd. for $C_{11}H_{16}O_3$: C 67.32; H 8.21. Found: C 67.30; H 8.20.

General Procedure for reduction of 2-alkyl-2-carbomethoxy-cyclopentanone derivatives (6-8) with sodium borohydride (REDUCTION CONDITION A)[2,11].

To a solution of β-ketoester derivative (6-9) (1.53 mmol) in methanol (9 ml) , at 0°C, was added 0.07 g (1.83 mmol) of sodium borohydride. The reaction mixture was stirred for 30 min., at 0°C, then the methanol was concentrated at reduced pressure (80 mmHg). The white doughy residue was diluted with methylene chloride (20 ml) and saturated aqueous ammonium chloride solution (20 ml). The organic layer was separated and after the "usual workup" afforded the mixture of diastereomeric alcohols as described in table 1.

Diastereomeric mixture of (11) and (12).

Prepared from reduction of (6); I.R. (film): ν O-H 3480, ν C-H 3070 and 2940, ν C=O 1719, ν C-O 1215 cm^{-1}; ^1H NMR (300 MHz): δ 0.91 (t, 3, $CH_2\text{-}CH_2\text{-}\underline{CH_3}$, J = 7 Hz); 1.15-2.5 (m, 10, $\underline{CH_2}$ in cyclopentane ring and $\underline{CH_2}\text{-}\underline{CH_2}\text{-}CH_3$), 3.65 and 3.71 (two singlets, 3, O-$\underline{CH_3}$), 3.95-4.13 and 4.23-4.36 (two multiplets, 1, $\underline{CH}$ in cyclopentane ring); ^{13}C NMR (75 MHz): δ 177.2 and 176.6 ($H_3CO\text{-}\underline{C}{=}O$), 79.3 and 77.1 ($\underline{CH}$-OH in cyclopentane ring), 58.7 and 57.6 (C-2) 51.6 ($\underline{H_3C}O\text{-}C{=}O$), 38.7 (C-5), 34.0 and 32.2 ($\underline{CH_2}\text{-}CH_2\text{-}CH_3$), 32.1 and 31.1 (C-3) , 20.4 and 19.8 ($CH_2\text{-}\underline{CH_2}\text{-}CH_3$), 18.7 and 18.4 (C-4), 14.5 and 14.3 ($CH_2\text{-}CH_2\text{-}\underline{CH_3}$); MS (70 eV) m/z (relative abundance): 186 ($M^{+\cdot}$, 3%), 185 ($M^{+\cdot}$-1, 4%), 157 ($M^{+\cdot}$- $H_2C{=}CH_2$, 28%), 149 ($M^{+\cdot}$- $H_2C{=}CH_2$ -H_2O, 100%), 115 ($CH_3\text{-}CH(CO_2Me)C{\equiv}O^+$, 83%), 97 ($H_2C{=}C(nPr)\text{-}C{\equiv}O^+$, 32%), 55 (+$H_2C\text{-}CH{=}C{=}O$, 48%).

Anal. Calcd. for $C_{10}H_{18}O_3$: C 64.48; H 9.73. Found: C 64.50; H 9.76.

Diastereomeric mixture of (13) and (14).

Prepared from reduction of (7); I.R. (film): ν O-H 3460, ν -C≡C-H 3280, ν C-H 2950, ν C=O 1725, ν C-O 1210 cm^{-1}; ^1H NMR (200MHz): δ 2.02 (t, 1, -C≡C-H, J = 3 Hz), 2.02-2.35 (m, 4, C4-H_2 and C3-H_2 in cyclopentane ring), 2.45-2.55 (m, 2, C5-H_2 in cyclopentane ring), 2.60 (dd, 2, -H_2C-C≡C-H, J_{AX} = 2.5 and J_{BX} = 1.2 Hz), 3.74 and 3.76 (two singlets, 3, O-CH_3), 4.21 and 4.42 (two deformed triplets, 1, CH-OH in cyclopentane ring, J = 7 Hz); ^{13}C NMR (50 MHz): 175.8 and 175.1 (H_3CO-C=O), 88.2 (-C≡C-H), 78.2 and 76.7 (CH-OH), 70.4 and 70.0 (-C≡C-H), 57.1 and 56.5 (C-2), 52.0 (H_3CO-C=O), 32.5 and 32.4 (C-5), 25.2 (C-3), 21.6 (CH_2-C≡CH), 20.5 and 20.1 (C-4); MS (70 eV) m/z (relative abundance): 182 ($M^{+\cdot}$, 3%), 123 ($M^{+\cdot}$-CO_2Me , 25%), 94 ($H_3C(CH_2C{\equiv}CH)C{=}C{=}O^+$, 30%), 79 cyclopropene$^+$-$CH_2CH{\equiv}CH$, 100%), 59 ($O{=}C{=}O^+$-$CH_3$, 98%), 53 ($H_2C{=}CH{-}C{\equiv}O$+, 79%).

Anal. Calcd. for $C_{10}H_{14}O_3$: C 65.91; H 7.74. Found: C 65.94; H 7.75.

Diastereomeric mixture of (15) and (16).

Prepared from reduction of (8); I.R. (film): ν -C=C-H 3120, ν C-H 2960, ν C=O 1723, ν C-O 1155 cm^{-1}; ^1H NMR (200 MHz): 1.55-2.15 (m, 6, CH_2 in cyclopentane ring), 2.84 (dd, 1, -CH_2-Ph, J_{AX} = 62.2 Hz and J_{BX} = 14.2 Hz), 3.00 (dd, 1, -CH_2-Ph, J_{AX} = 97.4 Hz and J_{BX} = 14.2 Hz), 3.59 and 3.66 (two singlets, 3, O-CH_3), 4.04-4.12 and 4.28-4.37 (two multiplets, 1, CH-OH in cyclopentane ring), 7.00-7.15 (m, 2, *meta*Ar-H), 7,17-7.38 (m, 3, *ortho*Ar-H and *para*Ar-H); ^{13}C NMR (50 MHz): 176.4 and 176.05 (H_3CO-C=O), 138.3 and 137.22 (*ipso*Ar), 129.6 and 129.4 (*ortho*Ar) , 128.1 (*meta*Ar), 126.6 and 126.3 (*para*Ar), 78.4 and 77.1 (CH-OH), 59.9 and 59.1 (C-2), 51.5 (H_3CO-C=O), 41.2 and 37.3 (-CH_2Ph), 31.9 and 31.7 (C-5), 30.5 and 30.1 (C-3), 20.1 and 19.5 (C-4); MS (70 eV) m/z (relative abundance): 234 ($M^{+\cdot}$, 8%), 216 ($M^{+\cdot}$-H_2O, 8%), 184 ($M^{+\cdot}$- OCH_3, -OH, 34%), 174 ($M^{+\cdot}$- CO_2CH_3, -H, 19%), 143 ($M^{+\cdot}$- CH_2Ph, 41%), 91 (Tropilium+, 100%), 65 (Tropilium - HC≡CH, 32%).

Anal. Calcd. for $C_{14}H_{18}O_3$: C 71.77; H 7.74. Found: C 71.74; H 7.72.

Diastereomeric mixture of (17) and (18).

From reduction of (9); I.R. (film): ν 3480 O-H, ν -C=C-H 3118, ν C-H 2960, ν C=O 1740 and 1720, ν C-O 1162 cm^{-1}; ^1H NMR (200 MHz): 1.45-2.30 (m, 10, $\underline{CH_2}$ in cyclopentane ring and $-\underline{CH_2}\underline{CH_2}CH=CH_2$), 3.72 and 3.75 (two singlets, 3, O-$\underline{CH_3}$), 4.00-4.12 and 4.26-4.40 (m, 1, $\underline{CH}$-OH in cyclopentane ring), 4.86-5.05 (m, 2, $-CH_2CH_2CH=\underline{CH_2}$), 5.65-5.90 (m, 1, $-CH_2CH_2\underline{CH}=CH_2$); ^{13}C NMR (50 MHz): 176.9 and 176.4 ($H_3CO-\underline{C}=O$), 138.1 and 137.8 ($-CH_2CH_2\underline{C}H=CH_2$), 114.7 and 114.5 ($-CH_2CH_2CH=\underline{C}H_2$), 79.1 ($\underline{C}H_2$-OH), 58.1 and 57.0 (C-2), 51.7 and 51.6 ($\underline{H_3C}O-C=O$), 32.0 (C-5), 31.1 (C-3), 30.8 and 30.7 ($-\underline{C}H_2CH_2CH=CH_2$), 29.9 and 29.5 ($-CH_2\underline{C}H_2CH=CH_2$), 20.2 and 19.6 (C-4); MS (70 eV) m/z (relative abundance): 166 ($M^{+\cdot}$-$HOCH_3$, 7%), 157 ($M^{+\cdot}$- H_2C-$CH=CH_2$, 57%), 125 ($M^{+\cdot}$- $H_2C=CH-CH=CH_2$, $-H_2O$, 100%), 109 ($M^{+\cdot}$-$H_2C=CH-CH=CH_2$, $-H_2O$, C≡O, 29%), 55 ($+H_2C-CH=C=O$, 69%).

Anal. Calcd. for $C_{11}H_{18}O_3$: C 66.63; H 9.14. Found: C 66.60; H 9.12.

General Procedure for reduction of 2-alkyl-2-carbomethoxy-cyclopentanone (6-9) with sodium borohydride/$CaCl_2$[2,11].

To a solution of β-ketoester (6-9) (0.433 g; 2.38 mmol) in methanol (24 ml), was added anhydrous calcium chloride (0.53 g; 4.76 mmol) and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0°C, and 0.108 g of sodium borohydride (2.85 mmol) was slowly added. A clear solution was obtained, which was stirred for 30 min. The solvent was concentrated at reduced pressure (80 mmHg) affording a doughy residue that was diluted with methylene chloride (15 ml) and saturated aqueous ammonium chloride solution (15 ml). The separated organic layer was submitted to the "usual workup" to furnish the corresponding diastereomeric mixture of alcohols as showed in table 1.

Diastereomeric mixture of (11) and (12).

Prepared from reduction of (6); I.R. (film): ν O-H 3480, ν C-H 3070 and 2940, ν C=O 1717, ν C-O 1215 cm^{-1}; ^1H NMR (200 MHz): δ 0.95 (t, 3, CH_2-

CH_2-CH_3, J = 7.2 Hz); 1.50-1.90 (m, 8, C3-H_2, C4-H_2 in cyclopentane ring and CH_2-CH_2-CH_3), 2.09 (qt, 1, C5-H *anti* to hydroxyl group on C-1, J = 7.0 Hz), 2.28-2.42 (m, 1, C5-H *syn* to hydroxyl group on C-1, J = 7.0 Hz) 3.66 and 3.70 (two singlets, O-CH_3), 4.48-4.53 (m, 1, CH_2-OH in cyclopentane ring); ^{13}C NMR (50 MHz): δ 177.2 (H_3CO-C=O), 79.3 (CH-OH in cyclopentane ring), 58.7 (C-2), 51.6 (H_3CO-C=O), 38.7 (C-5), 34.0 (CH_2-CH_2-CH_3), 32.1 (C-3) , 20.4 (CH_2-CH_2-CH_3), 18.7 (C-4), 14.5 (CH_2-CH_2-CH_3).

Anal. Calcd. for $C_{10}H_{18}O_3$: C 64.48; H 9.73. Found: C 64.47; H 9.77.

Diastereomeric mixture of (13) and (14).

Prepared from reduction of (7); I.R. (film): ν O-H 3460, ν -C≡C-H 3280, ν C-H 2950, ν C=O 1725, ν C-O 1210 cm^{-1}; ^{1}H NMR (200MHz): δ 1.60-1.95 (m, 4, C4-H_2 and C3-H_2 in cyclopentane ring), 2.02 (t, 1, -C≡C-H, J = 3 Hz), 2.05-2.25 (m, 2, C5-H_2 in cyclopentane ring), 2.60 (dd, 2, -H_2C-C≡C-H, J_{AX} = 2.5 and J_{BX} = 1.2 Hz), 3.73 and 3.75 (two singlets, 3, O-CH_3), 4.43 (td, 1, CH-OH in cyclopentane ring, J = 7 Hz); ^{13}C NMR (50 MHz): 175.8 and 175.1 (H_3CO-C=O), 81.2 and 80.0 (-C≡C-H), 78.2 and 76.6 (CH-OH), 70.3 and 69.9 (-C≡C-H), 57.1 and 56.3 (C-2), 52.0 (H_3CO-C=O), 32.4 and 32.3 (C-5), 25.1 (C-3), 21.6 (CH_2-C≡CH), 20.4 and 20.1 (C-4).

Anal. Calcd. for $C_{10}H_{14}O_3$: C 65.91; H 7.74. Found: C 65.92; H 7.74.

Diastereomeric mixture of (15) and (16).

Prepared from reduction of (8); I.R. (film): ν O-H 3470, ν -C=C-H 3120, ν C-H 2960, ν C=O 1724, ν C-O 1155 cm^{-1}; ^{1}H NMR (200 MHz): 1.55-2.15 (m, 6, CH_2 in cyclopentane ring), 3.00 (dd, 1, -CH_2-Ph, J_{AX} = 97.4 Hz and J_{BX} = 14.2 Hz), 3.58 and 3.66 (two singlets, 3, O-CH_3), 4.33 (td, 1, CH-OH in cyclopentane ring, J = 7.1 Hz), 7.00-7.15 (m, 2, *meta*Ar-H), 7.17-7.38 (m, 3, *ortho*Ar-H and *para*Ar-H); ^{13}C NMR (50 MHz): 176.4 (H_3CO-C=O), 138.3 (*ipso*Ar), 129.6 (*ortho*Ar) , 128.1 (*meta*Ar), 126.6 (*para*Ar), 78.4 (CH-OH), 59.9 (C-2), 51.5 (H_3CO-C=O), 41.2 (-CH_2Ph), 31.9 (C-5), 30.5 (C-3), 20.1 (C-4).

Anal. Calcd. for $C_{14}H_{18}O_3$: C 71.77; H 7.74. Found: C 71.72; H 7.73.

Diastereomeric mixture of (17) and (18).

From reduction of (9); I.R. (film): ν 34700 O-H, ν -C=C-H 3115, ν C-H 2960, ν C=O 1742 and 1720, ν C-O 1162 cm^{-1}; ^1H NMR (200 MHz): 1.50-2.40 (m, 10, $\underline{CH_2}$ in cyclopentane ring and $-\underline{CH_2}\underline{CH_2}CH=CH_2$), 3.72 and 3.68 (two singlets, 3, O-$\underline{CH_3}$), 4.25-4.35 (m, 1, $\underline{CH}$-OH in cyclopentane ring), 4.90-5.10 (m, 2, $-CH_2CH_2CH=\underline{CH_2}$), 5.65-5.90 (m, 1, $-CH_2CH_2\underline{CH}=CH_2$); ^{13}C NMR (50 MHz): 176.9 and 176.4 ($H_3CO-\underline{C}=O$), 138.1 and 137.8 ($-CH_2CH_2\underline{C}H=CH_2$), 114.7 ($-CH_2CH_2CH=\underline{C}H_2$), 79.1 ($\underline{C}H_2$-OH), 58.1 (C-2), 51.7 ($\underline{H_3C}O-C=O$), 32.0 (C-5), 31.1 (C-3), 30.8 ($-\underline{C}H_2CH_2CH=CH_2$), 29.9 ($-CH_2\underline{C}H_2CH=CH_2$), 20.2 (C-4).

Anal. Calcd. for $C_{11}H_{18}O_3$: C 66.63; H 9.14. Found: C 66.61; H 9.15.

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