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STUDIES TOWARD THE DIASTEREOSELECTIVE REDUCTION OF 2-ALKOXYCARBONYL-2-ALLYL-CYCLOPENTANONE DERIVATIVES WITH BORON HYDRIDES.[a)]

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Abstract: The reduction of 2-alkoxycarbonyl-2-allyl-cyclopentanone derivatives with inexpensive boron hydrides were studied showing that this process depend on chelation factors instead steric ones, affording the isomeric alcohols 2a and 3a with high diastereomeric excess.

As part of a research program aiming at the synthesis of new bioactive modified prostanoid derivatives[1] an efficient method to obtain functionalized 2-oxabicyclo-[3.3.0]-octane compounds[2] (1) was developed. Compounds 1 are a attractive synthons to a new series of prostacyclin analogues[3], and allow to explore the stereochemistry of the cationic oxidative-cyclization process of *cis-*,*trans-*

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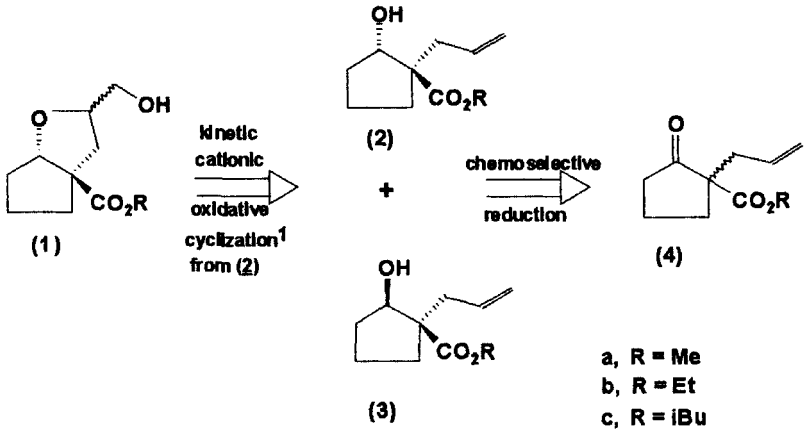
a) This work represents the contribution # 02 from LASSBio, UFRJ

2-alkoxycarbonyl-2-allyl-cyclopentanol[4]. Further studies showed that under kinetic conditions the only bicyclo derivative obtained is derived from *trans*-2-alkoxycarbonyl-2-allyl-cyclopentanol derivative (2)[5]. In order to obtain selectively the desired *trans*-alcohol (2) we studied the chemoselective reduction[6] of the corresponding precursor carbonyl compound (4)[7] (Scheme 1).

Scheme 1



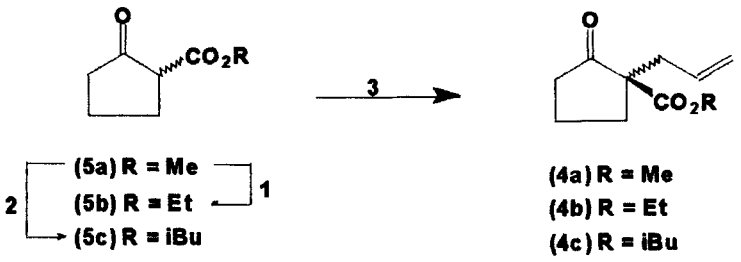
In this paper we describe the highly diastereoselective reduction of the keto group of 2-alkoxycarbonyl-2-allyl-cyclopentanone derivatives (4) using inexpensive and accessible boron hydrides. Our initial efforts lead us to the observation that the sodium borohydride reduction of the derivative (4b) resulted in a mixture of 2-allyl-2-carbethoxy-cyclopentanol derivatives (2b) and (3b) (^{1}H NMR).

In order to elucidate the importance of the steric versus the chelation factors we synthesized a series of 2-alkoxycarbonyl-2-allyl-cyclopentanone derivatives (4a-4c), different in the size of ester moiety, and investigated their chemical reactivity upon reduction with sodium borohydride[8] and the bulky lithium tri-sec-butyl-borohydride[9].

The ß-keto-esters (5b, 5c) were prepared in very good yield from 2-carbomethoxy-cyclopentanone[10] (5a) by a classical transesterification reaction, catalyzed by TsOH[11].

Compounds 5 were then submitted to a regioselective C-allylation reaction with a slight excess of allyl bromide using Barco's conditions[12], as described previously[1], to afford compounds 4 in very high yield (Scheme 2).

Scheme 2[a]



a) 1- EtOH, TsOH (cat.), reflux (92%); 2- tBuOH, TsOH (cat.), reflux (88%) 3- K_2CO_3, acetone, 30 min., r.t., then $BrCH_2CHCH_2$, reflux, 1h.

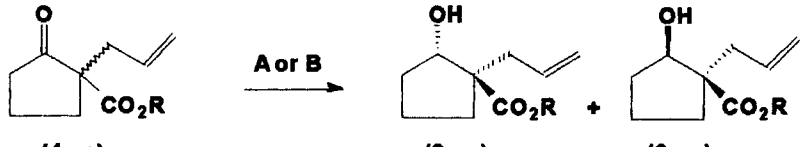
When 2-allyl-ß-ketoesters 4 were submitted to the two different reduction conditions A and B, many interesting features emerge from the analysis of this data, as shown in table 1. First, in both procedures, the diastereoselectivity of this reductive process is inversely dependent on the size of the alkyl group of the ester moiety. For the same 2-allyl-ß-ketoesters (4), the diastereoselectivity was practically unaffected by the reduction conditions, i.e. A e B.

These evidences can be rationalized by formation of a boron coordinated species I which could be driving the diastereoselection of this process, affording the *trans* isomer (2a-2c) preferentially (Scheme 3).

Preliminary results of molecular modeling of the probable transition states[16] of the reduction of (4a) by sodium borohydride, affording the diastereomeric

Table 1

Reduction of the 2-alcoxycarbonyl-2-allyl-cyclopentanone derivatives (4a-c).



(4a-c) (2a-c) (3a-c)

a R = Me
b R = Et
c R = iBu

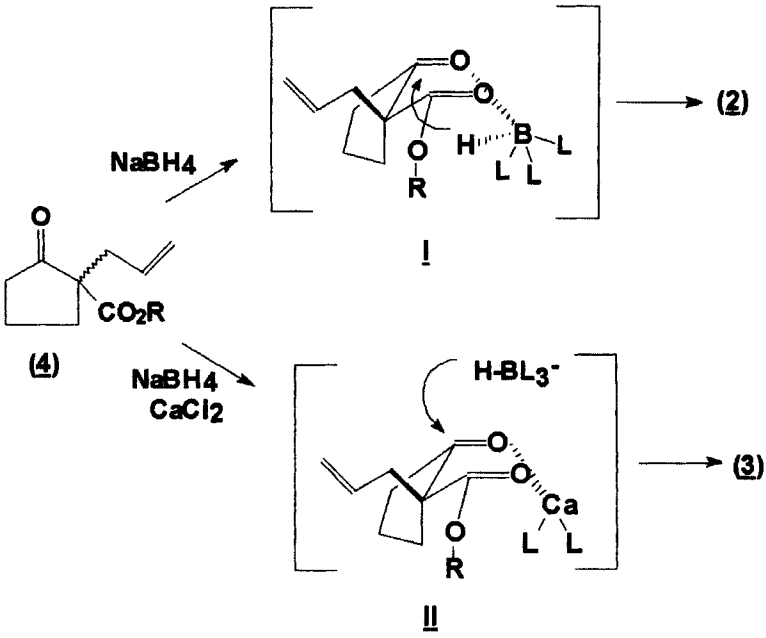
2-allyl-ß-keto-ester	reduction conditions[a]	additive	product	yield (%)	ratio 2 : 3 [b,c]
4a	A	---	2a:3a	90	4 : 1
4a	B	---	2a:3a	74	3 : 1
4a	A	$CaCl_2$	2a:3a	89	1 : 19
4b	A	---	2b:3b	92	1.8 : 1
4b	B	---	2b:3b	83	1.9 : 1
4c	A	---	2c:3c	87	1.6 : 1
4c	B	---	2c:3c	80	1.6 : 1

[a] Reductant condition A: $NaBH_4$ (1.2 eq), MeOH, 0°C, 30 min.[2]; reductant condition B: L-selectride (1.5 eq.), THF, -78°C, 30 min.[9].

[b] The relative proportion of this diastereomeric mixture was determined by GC[13].

[c] The assignment of the diastereomeric alcohols was made by ^1H NMR in presence of $Eu(thd)_3$[14] and confirmed by chemical evidence[15].

Scheme 3



products (2a) and (3a) using the AM1 program insert in MOPAC 6.00 system indicated that transition structure leading to *trans* alcohol (2a) is energetically favorable by 8 Kcal/mol[17].

In order to verify the possible anticipated coordination effect, we submitted the derivative (4a) to the reduction condition A (Table 1), adding 2 equiv. of $CaCl_2$ as complexating agent, under careful experimental conditions (see Experimental Section) in order to assure that the major reducing species in this process is the sodium borohydride. An strong experimental evidence for that was the same kinetic behavior observed in the reduction of (4a) at the same temperature, in the presence and in the absence of the complexating agent[7,18].

In fact, using these experimental conditions we were able to obtain the *cis* alcohol (3a) in as high as 90% d.e.. These results only could be rationalized by an

effective participation of calcium-coordinated species II, as showed in scheme 3, similar to that observed by Fujii et al. in related reductions of α,β-epoxy-ketones[18].

Finally, these results allowed us to optimize the preparation of the respective methyl ester of the 2-oxabicyclic derivative (1)[15], employing the 2-allyl-ß-ketoester (4a) as a useful precursor to *cis-* or *trans-* 2-allyl-2-carbomethoxy-cyclopentanol derivative (2a) or (3a), respectively, and inexpensive sodium borohydride as the diastereoselective reducing agent.

Experimental Section.

^{1}H NMR spectra are determined in deuterochloroform containing c.a. 1% tetramethylsilane as an internal standard with a Varian T-60 spectrometer at 60 MHz. Infrared spectra (IR) spectra were obtained with a Perkin-Elmer 257 spectrophotometer. Gas chromatography were recorded in a Hewlett Packard model 5987-A using injection in the splitness mode.

The progress of all reactions was monitored by tlc which was performed on 2.0 cm X 6.0 cm aluminium 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 synthesis of ß-keto-esters (5b and 5c) by transesterification of (5a)[11].

To a solution of 5a (1 g, 7 mmol) in 20 ml of the respective alcohol was

added a catalytic amount of p-toluenesulfonic acid (0.01 g) and the reaction mixture was refluxed to 24 h. The excess alcohol was removed by distillation at normal pressure affording an oily residue that was submitted to careful molecular distillation at reduced pressure (20 mmHg).

2-Carboethoxy-cyclopentanone (5b).

This compound (b.p. 100°C, lit.[19] 83-88°C/ 5 mmHg) was obtained in 92% yield as a colorless oil; I.R. (film): ν C-H 2970, ν C=O 1740 and 1720, ν C-O 1225 cm^{-1}; ^1H NMR: δ 1.25 (t, 3, O-CH_2-CH_3, J = 7 Hz), 1.7-2.6 (m, 6, CH_2 in cyclopentane ring), 3.1 (t, 1, CH in cyclopentane ring, J = 8 Hz), 4.15 (q, 2, O-CH_2-CH_3).

2-Carboisobutoxy-cyclopentanone (5c).

This compound (b.p. 110°C) was obtained in 88% yield as a colorless oil; I.R. (film): ν C-H 3080, ν C=O 1740 and 1718, ν C-O 1223 cm^{-1}; ^1H NMR: δ 0.96 (d, 6, -CH-(CH_3)$_2$, J = 8 Hz), 1.36 (m, 1, -CH-(CH_3)$_2$), 1.8-2.8 (m, 6, CH_2 in cyclopentane ring), 3.15 (t,1, CH in cyclopentane ring, J = 8 Hz), 4.15 (q, 2, O-CH_2-CH(CH_3)$_2$, J = 7 Hz).

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75; O, 26.05. Found: C, 65.18; H, 8.78; O, 26.08.

General procedure for the C-alkylation of the ß-keto-esters (5a-5c)[12].

To a suspension of anhydrous potassium carbonate (10.6 g; 77 mmol) in anhydrous acetone (48 ml) was added a solution of ß-keto-ester (5a-5c) (19.2 mmol) in anhydrous acetone (24 ml). The reaction mixture displays a characteristic yellow color[2] after stirring at room temperature for 15 min.. Then, allyl bromide (3.4 ml ; 39 mmol) was added slowly and the mixture was refluxed for 1 h. 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-alkoxycarbonyl-2-allyl-cyclopentanone derivative (4a-4c).

2-Allyl-2-carbomethoxy-cyclopentanone (4a).

From the ß-ketoester (6a) this compound was obtained in 84% yield as an colorless oil; I.R. (film): ν C-H 3075 and 2950, ν C=O 1740 and 1720, ν C-O 1220 cm^{-1}; ^1H NMR: 1.9-3.0 (m, 8, $\underline{CH_2}$ in cyclopentane ring and $\underline{CH_2}$-$CH=CH_2$), 3.65 (s, 3, O-$\underline{CH_3}$), 4.8-6.0 (m, 3, CH_2-$\underline{CH}$=$\underline{CH_2}$).

2-Allyl-2-carboethoxy-cyclopentanone (4b).

From the ß-ketoester (6b) this compound was obtained in 91% yield as an colorless oil; I.R. (film): ν C-H 3080 and 2980, ν C=O 1740 and 1720, ν C-O 1222 cm^{-1}; ^1H NMR: δ 1.2 (t, 3, O-CH_2-$\underline{CH_3}$, J = 7 Hz), 1.8-2.9 (m, 8, $\underline{CH_2}$ in ciclopentane ring and $\underline{CH_2}$-$CH=CH_2$), 4.08 q, 2, O-$\underline{CH_2}$-CH_3, J = 7 Hz), 4.8-6.2 (m, 3, CH_2-$\underline{CH}$=$\underline{CH_2}$).

2-Allyl-2-carboisobutoxy-cyclopentanone (4c).

From the ß-ketoester (6c) this compound was obtained in 81% yield as an light yellow oil; I.R. (film): ν C-H 3080 and 2970, ν C=O 1740 and 1720, ν C-O 1230 cm^{-1}; ^{1} H NMR: δ 0.9 (d, 6, -CH-($\underline{CH_3}$)$_2$, J = 7 Hz), 1.25-1.55 (m, 1, -$\underline{CH}$-$(CH_3)_2$), 1.8-2.8 (m, 8, $\underline{CH_2}$ in cyclopentane ring and $\underline{CH_2}$-$CH=CH_2$), 3.8 (d, 2, O-$\underline{CH_2}$-CH-$(CH_3)_2$, J = 7 Hz), 4.7-5.8 (m, 3, CH_2-$\underline{CH}$=$\underline{CH_2}$).

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99; O, 21.4. Found: C, 69.68; H, 9.02; O, 21.2.

General Procedure for reduction of 2-allyl-ß-ketoesters (3a-3b) with sodium borohydride (REDUCTION CONDITION A)[2].

To a solution of 2-allyl-2-alkoxycarbonyl-cyclopentanone derivative 4 (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 (2 and 3) as described in table 1.

Diastereomeric mixture of (2a) and (3a).

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: δ 1.6-2.8 (m, 8, CH_2 cyclopentane ring and CH_2-CH=CH_2), 3.6-3.65 (two singlets, 3, O-CH_3), 4.0-4.3 (m, 1, CH in cyclopentane ring), 4.9-6.0 (m, 3, CH_2-CH=CH_2).

Diastereomeric mixture of (2b) and (3b).

I.R. (film): ν O-H 3475, ν C-H 3080 and 2960, ν C=O 1723, ν C-O 1215 cm^{-1}; ^1H NMR: δ 1.05-1.35 (two triplets, 3, O-CH_2-CH_3), 1.5-2.6 (m, 8, CH_2 in cyclopentane ring and CH_2-CH=CH_2), 3.0 (br., 1, -OH), 3.62 (t, 1, CH in cyclopentane ring, J = 3 Hz), 3.85-4.3 (two quartets, 2, -O-CH_2-CH_3), 4.75-6.0 (m, 3, CH_2-CH=CH_2).

Diastereomeric mixture of (2c) and (3c).

I.R. (film): ν O-H 3450, ν C-H 3080 and 2980, ν C=O 1718, ν C-O 1220 cm^{-1}; ^1H NMR: δ 0.8-1.0 (two doublets, 6, -CH-(CH_3)$_2$), 1.2-1.4 (m, 1, CH_2-CH-(CH_3)$_2$), 1.6-2.6 (m, 8, CH_2 in cyclopentane ring and CH_2-CH=CH_2), 3.3-3.6 (two triplets, 1, CH in cyclopentane ring), 3.8-3.95 (two doublets, 2, O-CH_2-CH-(CH_3)$_2$), 4.8-6.0 (m, 3, CH_2-CH=CH_2).

General Procedure for reduction of 2-allyl-ß-ketoesters (4a-4b) with lithium tri-sec-butyl-borohydride (REDUCTION CONDITION B)[9].

To a solution of 2-allyl-2-alkoxycarbonyl-cyclopentanone derivative 4 (5.48mmol) in anhydrous THF (12 ml), under nitrogen atmosphere, at -78°C, was added 8.2 ml (8.2 mmol) of 1M solution of the lithium-tri-sec-butyl-borohydride

(L-Selectride) in anhydrous THF. The reaction mixture was stirred at -78°C for 30 min. and then for 15 min. at 0°C and 28 ml of 1M solution of H_2O_2 and 44 ml of the 0.2 N NaOH was added. After 15 min., the system was diluted with ether (20 ml) and the separated organic layer washed with a saturated solution of sodium bisulfite (20 ml) and submitted to the "usual workup" to afford the diastereomeric mixture of alcohols (2 and 3) as described in table 1. This mixture showed, respectively, the same spectroscopic pattern as described under reduction condition A.

Procedure for reduction of 2-allyl-2-carbomethoxy-cyclopentanone (4a) with sodium borohydride/$CaCl_2$[7,18].

To a solution of 4a (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 diastereomeric mixture of alcohols (2a and 3a) as showed in table 1.

Diastereomeric mixture of (2a) and (3a).

I.R. (film): ν O-H 3480, ν C-H 3080 and 2960, ν C=O 1720, ν C-O 1220 cm^{-1}; ^1H NMR: δ 1.6-2.6 (m, 8, $\underline{CH_2}$ in cyclopentane ring and $\underline{CH_2}$-CH=CH_2), 3.6 (s, 3, O-$\underline{CH_3}$), 4.2-4.4 (m, 1, $\underline{CH}$ in cyclopentane ring), 4.8-6.0 (m, 3, CH_2-$\underline{CH}$=$\underline{CH_2}$).

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