STUDIES ON DIASTEREOSELECTIVE SYNTHESIS OF 3-VINYL-5-CARBOMETHOXY-2-OXABICYCLO[3.3.0]OCTANE DERIVATIVES EMPLOYING PALLADIUM(II) OXIDATIVE CYCLIZATION

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Abstract-3-α,β-Vinyl-5-carbomethoxy-2-oxabicyclo[3.3.0]octane derivatives (**7a,b**) were synthesized through heterocyclization of alcohols *trans*- and *cis*-2-[(*E*)-buten-2-yl-1]-2-carbomethoxycyclopentanols (**5a,b**) employing a palladium acetate / cupric acetate catalytic system. This cyclization process was diastereoselective, favoring the formation of 3β-vinyl (*exo*) diastereomer (**7b**). In addition, the employ of adequate solvent system, *i.e.* isopropanol/water, could prevent a ketalization side reaction verified in methanol/water.

In a research program aiming at the development of new antithrombotic compounds, we have described previously the use of 2-oxabicyclo[3.3.0]octane 5-carboxylate derivatives (**1a,b**), as key intermediates in the synthesis of bioactive compounds as the bicyclic platelet activating factor antagonist (**2**)[1] and the 8ω-prostacyclin analogue (**3**).[2] The bicyclic alcohols (**1a,b**) were obtained as a 1:1 diastereomeric mixture of 3α-*endo* (**1a**) and 3β-*exo* (**1b**) by *m*CBPA mediated oxidative cationic cyclization of cyclopentanol derivatives (**4a,b**)[3] (Figure 1).

Since the synthesis of the bioactive compounds requires the employment of the 2-oxabicyclo[3.3.0]octane system *in the diastereomerically pure form and the chromatographic* separation of derivatives (**1a,b**) represents a very hard task, we decided to investigate the diastereoselective construction of the 2-oxabicyclo[3.3.0]octane ring through palladium(II)

catalyzed heterocyclization.[4-6] Once this reaction incorporates an oxidative β-hydride elimination step,[7] the alcohol (**5a**) was identified as key intermediates. This β-hydride elimination on cyclization intermediates (**6a,b**) would lead to the desired 3-vinyl derivatives (**7a,b**), as an attractive synthon to new bioactive compounds of this bicyclic class (Scheme 1).

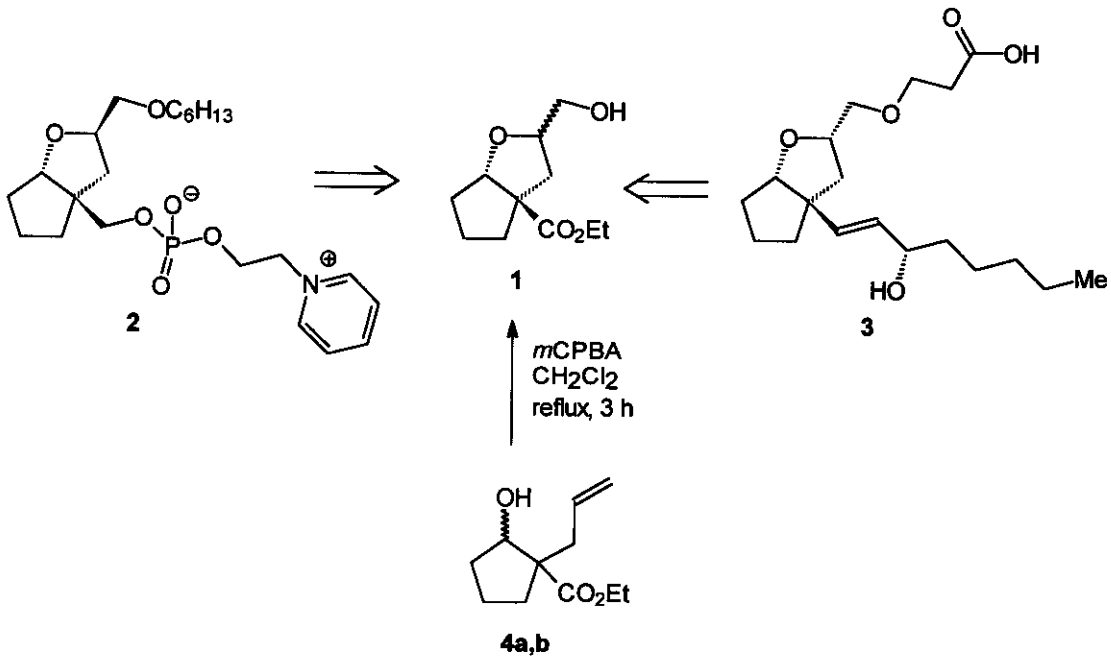
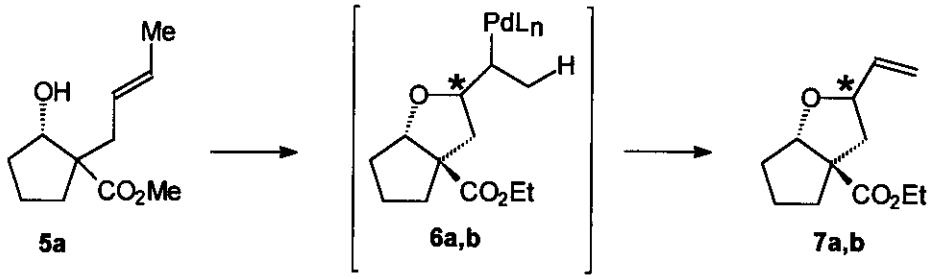


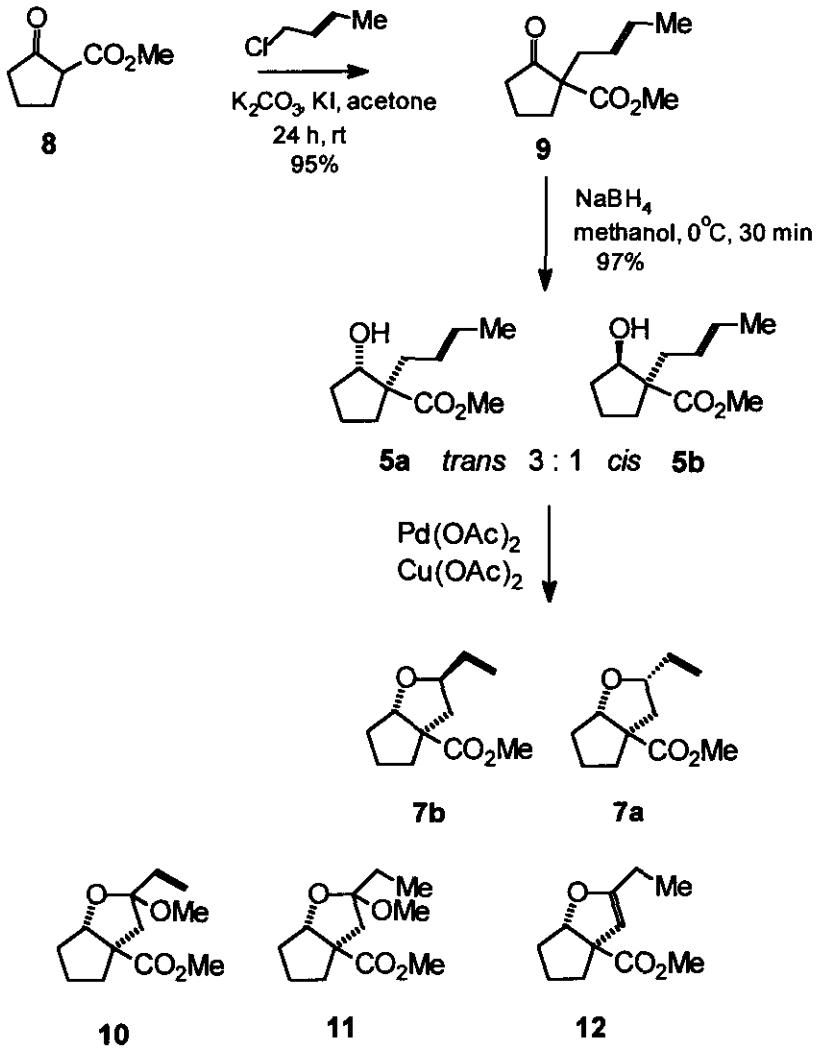
Figure 1



Scheme 1

The key intermediate (**5a**) was produced in good yield, in two steps from methyl 2-oxocyclopentanecarboxylate (**8**). Initially, the regioselective *C*-alkylation was performed with 1-chloro-2-butene, applying Barco's procedure, *i.e.* potassium carbonate in acetone,[8] to furnish the derivative (**9**) in 95% yield (Scheme 2). Thus, compound (**9**) was next submitted to treatment

with sodium borohydride in methanol at 0°C for 30 min[9,10] producing an inseparable mixture of the corresponding alcohols *trans*-**5a** and *cis*-**5b** in the combined chemical yield of 97%, with a diastereomeric ratio of 3 : 1, favoring the desirable *trans*-**5a** isomer.



Scheme 2

The palladium catalyzed cyclization of **5a,b**, under the described experimental conditions, was performed employing palladium acetate (10% mol), cupric acetate (100% mol) in methanol : water (100:8) at room temperature.[11]

In this process we were able to detect a time dependent profile. After 4 h at room temperature we obtained a mixture of 3α- and 3β-vinyl bicyclic derivatives (**7a**) and (**7b**) in 1 : 3 diastereomeric ratio. The overall yield of bicyclic products was 57% and the unexpected cyclic

ketal (**10**) was obtained as by-product in *ca.* 5%. When the reaction time was extended to 8 h, twice amount of the ketal (**10**) could be obtained. Curiously, under these experimental conditions the process was less diastereoselective, as shown in Table 1. In a 24 h reaction, we obtained a mixture of bicyclic compounds in 48% yield consisting of 3-vinyl bicyclic derivative (**7a**), in only 3% yield, the cyclic ketal (**10**), its saturated analogue (**11**) and the enol ether (**12**) in 8 % yield (Table 1).

Table 1. Behavior of time dependent palladium acetate catalyzed cyclization of (**5a,b**).

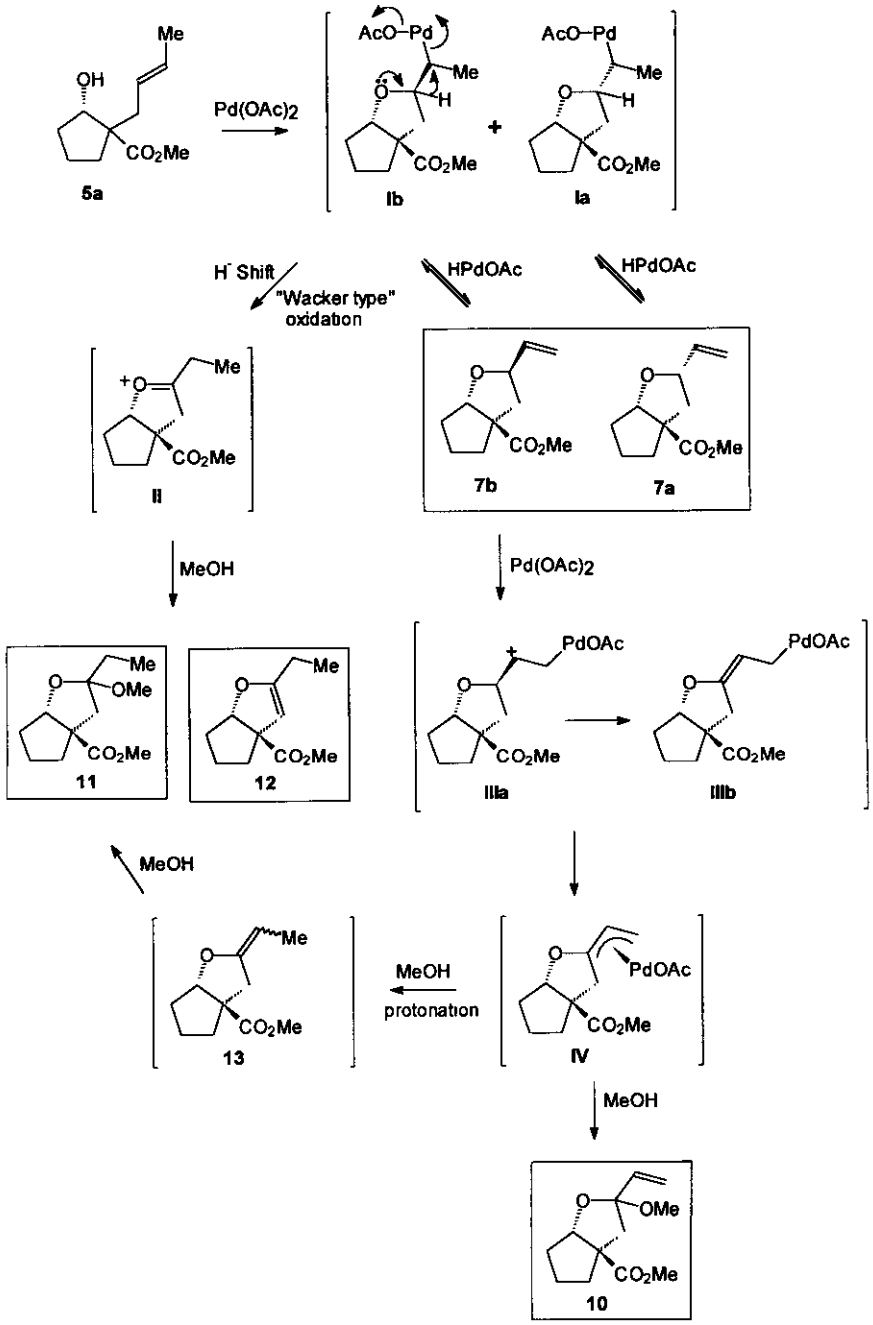
Compound	Solvent			
	Methanol			Isopropanol 24 h
	4 h	8 h	24 h	
12	10%	8%	8%	7%
7a	11%	10%	3%	10%
7b	31%	21%	-	42%
10	5%	10%	24%	-
11	-	-	13%	-

None bicyclic products derived from alcohol (**5b**) were detected, instead, it led to formation of more polar products, which were separated by flash chromatography.

In order to avoid the observed ketalization side reaction, we decided to investigate the solvent effect by using isopropanol and adjusting the water proportion to *ca.* 20%, in order to preserve the solubility profile of the reagents. After a 24 h reaction at room temperature, using this solvent, we were able to improve the yield of the desired bicyclic compounds (**7a,b**) at 52%, without any ketalization product. The diastereomeric ratio verified to **7a**, **7b** was 1 : 4 and only 7% yield of the enol ether (**12**) was produced. In fact, employing isopropanol as solvent, the presence of ketalization products was detected only in reactions longer than 72 h.

The conversion of the 3-vinyl derivatives (**7a**) and (**7b**) to ketal (**10**), suggested by data described in Table 1, could be confirmed by submitting **7a** and **7b** mixture (1:4 ratio), to the same palladium catalyzed cyclization procedure, in methanol for 24 h at room temperature. Under this reaction condition a mixture of **7a**, **10** and **11**, in 1 : 6 : 1 ratio, was obtained in 78% yield. Since only small amounts of derivative (**11**) could be detected in this experiment, the formation of this compound during the cyclization step from **5a** was rationalized by probable formation of Wacker type oxidation intermediate (**II**),[12] followed by ketalization with solvent. The

probable reaction course is described in Scheme 3. Compound (**10**) could be possibly formed by nucleophilic solvent displacement over π-allylpalladium intermediate (**IV**), while compounds (**11**) and (**12**) could be formed from **7a,b**, respectively, after solvolysis and double bound isomerization of enol ether (**13**), transiently produced from protonation of **IV**.[13]



Scheme 3

The full structural characterization of the products was achieved by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopies and bidimensional techniques H-H COSY and HETCOR. Compounds (**10**) and (**11**) were obtained in diastereomerically pure form, however the unambiguous configuration assignment was not possible. The indication of the relative configuration in the bicyclic compounds (**7a,b**) and its precursor cyclopentanol derivatives (**5a,b**) is in agreement with previous related papers.[1,3,9,10] The assignment of isomers ratios was performed by ^{1}H-NMR spectroscopy, after flash chromatography of the reaction products. An isolated GC-MS experiment[14] from a crude reaction product was performed in order to validate the ^{1}H-NMR obtained ratios.

In summary, the results herein described indicated that the palladium(II) catalyzed heterocyclization of derivatives (**5a,b**) represents a new efficient diastereoselective entry to useful functionalized 2-oxabicyclo[3.3.0]octane system of **7a,b** in which, the 3β-vinyl (*exo*) isomer could be obtained as the major product in good yields.

EXPERIMENTAL

^{1}H-NMR spectra were determined in deuterated chloroform containing *ca.* 1% tetramethylsilane as an internal standard, with Brucker AC 200 or Varian GEMINI 200 at 200 MHz or Brucker DRX 300 at 300 MHz. ^{13}C-NMR spectra were determined in the same spectrometers described above at 50 or 75 MHz respectively, employing the same solvents. IR spectra were obtained with Phillips PYE UNICAM SP3-100 and Nicolet 505 Magna spectrophotometers by using sodium chloride cell. Microanalysis data was obtained with Perkin Elmer 240 analyzer, using Perkin Elmer AD-4 balance.

The progress of all reactions was monitored by TLC, which was performed on aluminum sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were viewed under UV light or iodine revelation. For column chromatography Merck silica gel (70-230 mesh) was used. Solvents used in the reactions were redistilled prior to use and stored over 3-4 Å molecular sieves. The usual work-up means that the organic extracts prior to concentration under reduced pressure, were treated with a saturated aqueous sodium chloride solution, referred as to brine, dried over anhydrous sodium sulfate and filtered.

2-[(*E*)-Buten-2-yl-1]-2-carbomethoxycyclopentanone (9). 1-Chloro-2-butene (1.80 g, 30 mmol), was added over a solution of methyl 2-oxocyclopentanecarboxylate (**8**) (1.42 g, 10 mmol), K_2CO_3 (4.14 g, 30 mmol) and KI (0.07 g, 0.5 mmol) in 10 mL of acetone. The reaction mixture was stirred at rt for 24 h, then 10 mL of hexane was added and the solution was filtered and concentrated under vacuum. The residue was dissolved in ether (30 mL) and extracted with

10% NaOH (2 X 15 mL). After usual work-up the organic layer furnished pure **9** (1.85 g, 95%) as an yellow oil (R_f=0.49, 30% AcOEt/hexane). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.49 (m, 1H, -C<u>H</u>=CHCH$_3$), 5.24 (m, 1H, -CH=C<u>H</u>CH$_3$), 3.67 (s, 3H, COOC<u>H</u>$_3$); 2.56-1.91 (m, -C<u>H</u>$_2$CH=CH- , H-C3, H-C4, H-C5), 1.60 (m, 3H, -CH=CHC<u>H</u>$_3$) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): δ 214. 88 (C1), 171.60 (COO), 129.98 (-<u>C</u>H=CHCH$_3$), 125.33 (-CH=<u>C</u>HCH$_3$), 60.34 (C2), 52.60 (COO<u>C</u>H$_3$), 38.36 (-<u>C</u>H$_2$CH=CH-), 32.40 (C5), 30.92 (C3), 19.60 (C4), 18.07 (-CH=CH<u>C</u>H$_3$) ppm; IR (cm^{-1}): 3010 (υ C-H olefinic), 1750, 1730 (υ C=O), 1450 (δ CH$_2$), 1240 (δ C-O-C), 970 (δ C=C). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.11; H, 8.14

***cis*- and *trans*-2-[(*E*)-Buten-2-yl-1]-2-carbomethoxycyclopentanols (5a,b).** Sodium borohydride (0.057 g, 1.3 mmol) was added to a solution of **9** (0.196 g, 1 mmol) in 14 mL of methanol at 0°C and the mixture was stirred at this temperature for 30 min. The solution was concentrated under vacuum and the residue was dissolved in dichloromethane (30 mL) and washed with saturated ammonium chloride solution (3 x 15 mL). After usual work-up the organic layer furnished pure **5a,b** (0.192 g, 97%) as an yellow oil (R_f=0.38, 30% AcOEt/hexane). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.51 (m, 1H, -C<u>H</u>=CHCH$_3$), 5.38 (m, 1H, -CH=C<u>H</u>CH$_3$), 4.36 (q, 0.75H, *J*=5.27 Hz, H-C1 *trans*), 4.12 (m, 0.25H, H-C1 *cis*), 3.71(s, 3H, COOC<u>H</u>$_3$), 2.59-2.04 (m, 6H, H-C3, H-C5, -C<u>H</u>$_2$CH=CH-), 1.77-1.64 (m, 5H, H-C4, -CH=CHC<u>H</u>$_3$) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 177.14 (COO), 128.77 (-<u>C</u>H=CHCH$_3$), 126.12 (-CH=<u>C</u>HCH$_3$), 77.23 (C1), 57.41 (C2), 51.90 (COO<u>C</u>H$_3$), 35.10 (-<u>C</u>H$_2$CH=CH-), 32.32 (C5), 29.09 (C3), 19.87 (C4),18.10 (CH=CH<u>C</u>H$_3$) ppm; ; IR (cm^{-1}): 3450 (υ O-H) , 3010 (υ C-H olefinic), 1730 (υ C=O), 1450 (δ CH$_2$), 1200 (δ C-O-H), 970 (δ C=C-CH$_3$). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.60; H, 9.15. Found: C, 66.71; H 9.18.

General procedure for palladium catalyzed cyclization (Condition A)

Palladium acetate (0.224 g, 1 mmol, 10% mol) and cupric acetate monohydrate (1.810 g, 10 mmol) were added to a solution of compounds (**5a,b**) (1.980 g, 10 mmol) in 25 mL of methanol and 2 mL of water. The solution was stirred at rt (reaction time described in Table 1). The solution was filtered after Celite *ca.* 1.0 g addition, diluted in 100 mL of water and extracted with ether (3 x 30 mL) and submitted to usual work-up and subsequent SiO_2 flash chromatography purification.

Compound (10) ^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.82 (dd, *J*=10.7 and 17.4 Hz, 1H, -C<u>H</u>=CH$_2$), 5.45 (dd, *J*=1.8 and 17.4 Hz, 1H, CH=C<u>H</u>$_2$-*cis*), 5.25 (dd, *J*=1.8 and 10.7 Hz, 1H, CH=C<u>H</u>$_2$-*trans*), 4.78 (d, *J*= 4.5 Hz, 1H, H-C1), 3.73 (s, 3H, COOC<u>H</u>$_3$), 3.11 (s, 3H, -OC<u>H</u>$_3$), 2.88 (d, *J*=

13.0 Hz, 1H, Hβ-C4), 1.95-1.54 (m, 7H, Hα-C4, H-C6, H-C7, H-C8) ppm; ^{13}C-NMR (50 MHz, $CDCl_3$): δ 176.68 (COO), 135.55 (CH=CH_2), 117.31 (CH=CH_2), 107.84 (C3), 86.55 (C1), 59.58 (C5), 52.24 (COOCH_3), 49.15 (-OCH_3), 43.91 (C6) 39.54 (C4), 34.67 (C8), 24.45 (C7). IR (cm^{-1}): 3010 (υ C-H olefinic), 1730 (υ C=O), 1450 (υ CH_2), 1280 (δ C-O-C), 1240 (δ C-O-C), 1000 (δ C=C-H), 920. (δ C=C-H). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.74; H, 8.09

Compound (11) ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.69 (d, *J*= 4.5 Hz, 1H, H-C1), 3.68 (s, 3H, COOCH_3), 3.06 (s, 3H, -OCH_3), 2.73 (d, *J*= 13.1 Hz, 1H, Hβ-C4), 1.92-1.42 (m, 9H, -CH_2CH_3, Hα-C4, H-C6, H-C7, H-C8), 0.85 (t, *J*= 7.3 Hz) ppm; ^{13}C-NMR (50 MHz, $CDCl_3$): δ 176.47 (COO), 110.15 (C3), 86.36 (C1), 59.43 (C5), 52.24 (COOCH_3), 48.64 (-OCH_3), 43.91 (C6), 39.32 (C4), 34.67 (C8), 33.52 (CH_2CH_3), 25.41 (C7), 8.80 (CH_2CH_3) . IR (cm^{-1}): 1730 (υ C=O), 1450 (υ CH_2), 1280 (δ C-O-C), 1240 (δ C-O-C). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.26; H, 8.89.

General procedure for palladium catalyzed cyclization (Condition B)

Palladium acetate (0.224 g, 1 mmol, 10% mol) and cupric acetate monohydrate (1.810 g, 10 mmol) were added to a solution of compounds (**5a,b**) (1.980 g, 10 mmol) in 20 mL of isopropanol and 5 mL of water. The solution was stirred at rt for 24 h and filtered after celite *ca.* 1.0 g addition, diluted in ether (50 mL) and washed with brine (6 x 30 mL). After usual workup and SiO_2 flash chromatography purification, compound (**12**) (R_f=0.68, 10% AcOEt/hexane) (0.138 g, 7%) and compound (**7a,b**) (R_f=0.65, 10% AcOEt/hexane) (1.02 g, 52%) were obtained.

3α-Vinyl-5-carbomethoxy-2-oxabicyclo[3.3.0]octane (7a) and 3β-vinyl-5-carbomethoxy-2-oxabicyclo[3.3.0]octane (7b). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.84 (m, 1H, -CH=CH_2), 5.20 (m, 2H, -CH=CH_2), 4.75 (m, 0.8H, H-C1 *exo*), 4.48 (m, 1H, H-C3 *exo*, H-C1 *endo*), 4.21 (m, 0.2H, H-C3 *endo*), 3.72 (s, 0.6H, COOCH_3 *endo*), 3.70 (s, 2.4H, COOCH_3 *exo*), 2.68 (dd, 0.2H, *J*=10.4 and 12.6 Hz, Hβ-C4 *endo*), 2.36 (dd, 0.8H, *J*=8.1 and 12.7 Hz, Hβ-C4 *exo*), 2.16 (m, 1H, Hβ-C6), 2.01 (dd, 0.8H, *J*=5.8 and 12.6Hz, Hβ-C4 *exo*), 1.96-1.20 (m, 5.2H, Hα-C4 *endo*, Hα-C6, H-C7, H-C8) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): δ 176.75 (COO *endo*), 176.46 (COO *exo*), 137.88 (CH=CH_2 *exo*), 136.98 (CH=CH_2 *endo*), 116.98 (CH=CH_2 *endo*), 116.10 (CH=CH_2 *exo*), 88.59 (C1 *endo*), 88.08 (C1 *exo*), 80.73 (C3 *endo*), 80.46 (C3 *exo*), 60.40 (C5), 52.24 (COOCH_3), 43.91 (C6) 37.87 (C4 *exo*), 37.40 (C4 *endo*), 34.66 (C8), 25.42 (C7 exo), 24.15 (C7 *endo*). IR (cm^{-1}): 3010 (υ C-H olefinic), 1730 (υ C=O), 1450 (υ CH_2), 1280 (δ C-O-C), 1240 (δ C-

O-C), 1000 (δ C=C-H), 920. (δ C=C-H). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.24; H, 8.17

Compound (12) ^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.18 (d, *J*= 4.2 Hz, 1H, H-C1), 4.50 (d, *J*= 1.1Hz, 1H, H-C4) 3.72 (s, 3H, $COOC\underline{H}_3$), 2.10 (dq, J=1.1 and 7.4 Hz, 2H, $-C\underline{H}_2CH_3$), 1.92-1.42 (m, 6H, H-C6, H-C7, H-C8), 1.05 (t, *J*= 7.5 Hz) ppm. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.43; H, 8.26.

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14. GC-MS was performed in a HP-5972A Gas-chromatography-mass-spectrometer provided with a HP-5ms capillary column (30 m x 250 μm x 0.25 μm, 70 - 10°C/min - 290°C).

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