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Syntheses of *rac*- and Optically Active 2-alkyl- γ-Butyrolactones and 2 –alkyl-Cyclobutanones

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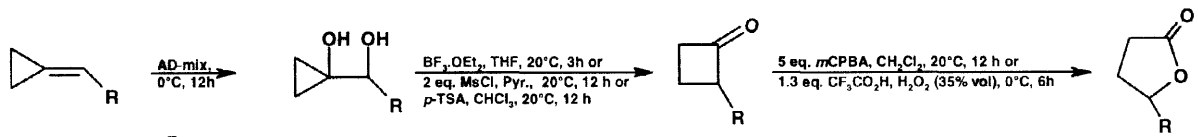
Abstract: γ-Butyrolactones have been produced in good yield from alkylidene cyclopropanes, as racemates or as an enantiomerically enriched mixture of stereoisomers (e.e.>60%) depending upon the method used. Optically active cyclobutanones which are intermediate in the process have been in some cases isolated. We show the limitations of a competitive method previously described and point out its weak step. © 1998 Published by Elsevier Science Ltd. All rights reserved.

We recently described[1] that optically active cyclobutanones **3** and the γ-butyrolactones **4** can be prepared in average 50-70% enantiomeric excess using as key steps (i) the enantioselective Sharpless catalytic asymmetric dihydroxylation (AD)[2] of alkylidenecyclopropane **1** promoted by AD-mix reagents (1.5 g/mmol., *t*-BuOH-H_2O, NH_2SO_2Me, 0°C, 4h-5h) and (ii) the facile rearrangement of the resulting hydroxycyclopropylcarbinols **2** to cyclobutanones on reaction with boron trifluoride etherate or mesyl chloride (Scheme 1).

We became aware, when we decided to publish the results of our work, of a series of papers by Fukumoto[3] which in fact described almost the same transformation (**1**->**2**->**3**) using thionyl chloride instead of boron trifluoride etherate or mesyl chloride, as the promoter of the rearrangeent of the diol to cyclobutanone.[1] Both overall yields were similar but the enantiomeric excesses they described for **3** (**3a** e.e. = 5%, **3b** e.e. = 3%)[3b] were dramatically lower than the results we obtained (**3b** e.e. = 62%).[1] In order to understand the discrepancies between the two sets of results, we decided to repeat them on nonanal and octanal. We report here the results of that study.

Scheme 1



	R			
1a	Hept	2a	3a	4a
1b	Oct	2b	3b	4b

Entry	Product	R	Conditions	**3** (yield %) (ee %)
a	**2a**	C_7H_{15}	(i) 0.1 eq. *p*TSA , $CHCl_3$, RT, 12h	82 (58)
b	**2b**	C_8H_{17}	(i) 0.1 eq. *p*TSA , $CHCl_3$, RT, 12h	71 (64)

+This work is dedicated to the memory of Sir Derek Barton. His inspiration, passion and devotion to Organic Chemistry and his encouragements will never be forgotten.

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We confirm our results on the osmium tetroxide oxidation reaction. Reactions involving **1a** and **1b** went both to completion after 12h at 0°C and do not require a week as suggested by Fukumoto in his "General Procedure for Asymmetric dihydroxylation of Cyclopropylidene Derivatives".[3b,4] These reactions produce the diols **2** possessing specific rotations (**2a** ($[\alpha]_D^{20}$ = +10 (c 1.20 $CHCl_3$) and **2b** ($[\alpha]_D^{20}$ = +14 (c 1.12 $CHCl_3$)) closely related to those reported by Fukumoto.[3b,5] The yields are good and the enantioselectivity ranges from 50 to 60 % as checked on the corresponding lactone prepared as described in Scheme 1.[1]

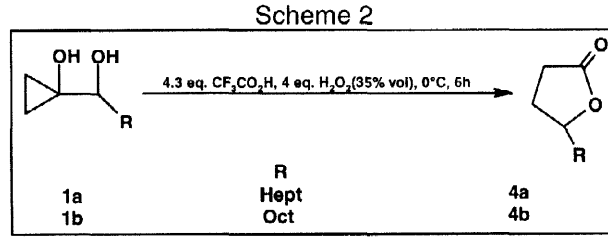
It became soon apparent that the differences between our results and those of Fukumoto were due to the second step of the process. It was in fact found that the reaction of the diols **2** with thionyl chloride does not proceed, in our hands, as described by Fukumoto.[3] Only a trace amount of cyclobutanone is produced under the conditions reported by this author but the reaction delivers instead a mixture of two compounds whose structures are compatible with that of cyclic sulfinates (as a mixture of stereoisomers). We have not been able to purify them since they both decompose, on standing (very slow decomposition at 20°C) or on TLC plate, to provide the cyclobutanone **3**. Formation of **3** has been more conveniently achieved on heating the intermediates in toluene (110°C, 0.3 h). Although the yields were constantly in the 45-68% range, the e.e.'s values were erratic although often as low as the one's described by Fukumoto (for example **3a** $[\alpha]_D^{20}$ = 0 (c 1.08 $CHCl_3$) and **3b** $[\alpha]_D^{20}$ = 0 (c 1.08 $CHCl_3$) or -14 (c 0.53 $CHCl_3$)).[6] We therefore suspect that the ring enlargement reaction is not always stereoselective or that epimerisation takes place just after the rearrangement on the cyclobutanone **3**.

We did not pursue experiments in that direction since mesyl chloride,[1] boron trifluoride etherate[1] or *p*-toluenesulfonic acid proved to be by far superior to thionyl chloride, for the transformation of **2** to **3** : they all deliver directly, at room temperature, the cyclobutanones in high yields (71-82%) and with complete stereocontrol. For example *p*-toluenesulfonic acid reacts at room temperature with the diols **2** and provides the cyclobutanones **3** (**3a** 71% yield, e.e = 58%,[6] $[\alpha]_D^{20}$ = -30 (c 1.10 $CHCl_3$) and **3b** 82% yield, e.e = 64%[1] $[\alpha]_D^{20}$ = -32 (c 0.56 $CHCl_3$)).

Furthermore, the method used by Fukumoto to determine the e.e. of the products is based on reduction of the optically active cyclobutanones by $NaBH_4$ followed by ^1H NMR analysis of their Mosher's esters.[3] He has not proved that the reduction of 2-alkyl-cyclobutanones is diastereoselective and therefore the results are ambiguous. In our case, we have determined the stereoisomeric ratio of 2-alkyl-cyclobutanones by performing chromatographic analysis using chiral column, on the corresponding γ-butyrolactones **4** readily available by Bayer-Villiger reaction from **3**.[1,6]

The synthesis of optically active γ-butyrolactones **4** has been also directly achieved optically active diols **2** on reaction with trifluoroperacetic acid in the presence of trifluoroacetic acid Scheme 2. The later initiates the rearrangement of **2** to **3** and the peracid present in the medium oxidize it on the spot to **4**. The yields are comparable to those obtained by the stepwise route disclosed in Scheme 1 but the e.e were slightly lower (compare Scheme 2, entry a to Scheme 1, entry a).

Scheme 2



Entry	Product	R	Conditions	**4** (yield %), (ee %)
a	**2a**	C_7H_{15}	4.3 eq. TFAA, 4 eq. H_2O_2, CH_2Cl_2, 0° to 20°C, 6-12h	85 (54)
c	**2b**	C_8H_{17}	4.3 eq. TFAA, 4 eq. H_2O_2, CH_2Cl_2, 0° to 20°C, 6-12h	70 (56)

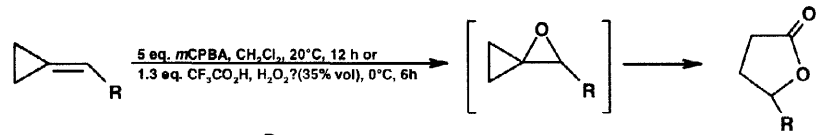
We took advantage of these results to propose efficient one pot transformations of alkylidenecyclopropanes **1** to *rac*-butyrolactones **4**. These have in fact been used for as models for the chiral GC analysis reported above.

Trifluoroperacetic acid proved to be the choice reagent since it is able to achieve cleanly, under mild conditions, each of the single steps required (< 20°C, Scheme 3, entries a, c).[7] Interestingly, the acid catalyst needed for the rearrangement of the oxaspiropentane is generated *in situ* as the by-product of the epoxidation reaction. *m*CPBA was also able to perform the same transformation but it required the concomitant use of a catalytic amount of trifluoroacetic acid (Scheme 3, entries b, d).

Benzene perseleninic acid[8] performs the Bayer-Villiger reaction, even when used in catalytic amounts, proved to be largely inferior for that purpose (Scheme 3, entry e).

Although the transformation described above has been often carried out stepwise even with we are not aware of an expeditious process related to the one we just describe.

Scheme 3



	R		
1a	Hept	5a	4a
1b	Oct	5b	4b

Entry	Product	R	Conditions	**4** (yield %)
a	**1a**	C_7H_{15}	4.3 eq. TFAA, 4 eq. H_2O_2, CH_2C_2, 0° to 20°C, 6-12h	68
b	**1a**	C_7H_{15}	4 eq. *m*CPBA, TFA cat., CH_2Cl_2, 0° to 20°C, 12h	72
c	**1b**	C_8H_{17}	4.3 eq. TFAA, 4 eq. H_2O_2, CH_2Cl_2, 0° to 20°C, 6-12h	64
d	**1b**	C_8H_{17}	4 eq. *m*CPBA, TFA cat., CH_2Cl_2, 0° to 20°C, 12h	59
e	**1b**	C_8H_{17}	0.1 eq. $PhSeO_2H$, 3 eq. H_2O_2, CH_2Cl_2, 0° to 20°C, 6-12h	37

In conclusion we have shown that the method we described[1] for the synthesis of γ-butyrolactones from alkylidenecyclopropanes, is reasonably good and far superior to the one previously described by Fukumoto.[3] The enantiomeric excesses are not as good as we expected to achieve but we know that it is due to the Sharpless AD reaction.[2] This reaction usually leads to much higher enantioselectivities with other olefins. We are trying to find a better catalyst or better experimental conditions.

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EXPERIMENTAL SECTION

The solvents have been distilled, prior to be used as described in the following. Tetrahydrofurane (THF) and diethylether (Et_2O), from sodium-benzophenone and dichloromethane (CH_2Cl_2) from P_2O_5. ^1H NMR (400 MHz), ^{13}C NMR (100 MHz) spectra were recorded on a Jeol JNM EX-400. Specific rotation were measured on a Perkin Elmer 241C polarimeter with sodium lamp (589 nm) at 20°C. All reactions were monitored by thin-layer chromatography (Macherey-Nagel Alugram Sil G/UV 254). Preparative chromatography (PLC) was performed with Merck Silicagel 60 (70-230 mesh ASTM). Spectroscopic (^1H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatographically homogeneous samples. Microanalysis have been performed in Paris (University Pierre et Marie Curie, centre de microanalyse). Chiral [GC],[1,10] Magerey-Nagel, Lipodex D, 0.2 mm, 0.25 mm x 25 m, isotherm 100°C for 10 min. then 2°C/min. till 200°C then 200°C. Chiral HPLC : Chiracel OD-H, $\phi = 0.46$ cm; l= 25 cm, hexane-*i*-PrOH, $\lambda = 254$ nm.

General procedure for the synthesis of Alkylidenecyclopropanes 1 :

The preparation of **nonylidenecyclopropane 1b** is described as a typical example.
To the ylide (prepared from the cyclopropyltriphenylphosphonium bromide (20.78g; 54.27 mmol) and LDA (50.61 mmol) in THF (15 ml) at -78°C, under argon atmosphere) in THF (80 ml), at -78°C, is added the aldehyde in THF (5 ml). The mixture is allowed to warm slowly to room temperature. After hydrolysis and extraction with diethylether, the organic phases are dried ($MgSO_4$) and concentrated under reduced pressure. Nonylidenecyclopropane **1b** is isolated, in 65% yield, after purification by PLC (pentane) as a colorless oil (4.55g).
IR (neat) 3052, 2059, 2927, 2856, 1465, 932. ^{1}H NMR (400 MHz, $CDCl_3$, δ, PPM): 5.77 (1H, H_3, br d d, 7.2Hz), 1.50-1.40 (2H, H_4, m), 1.35-1.25 (10H, $H_{5\text{-}9}$, m), 1.10 (4H, H_1 and $H_{1'}$, m), 0.90 (3H, H_{10}, t, 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 120.8 (C_2), 119.6 (C_3), 31.9 (C_4), 31.8-29.5-29.4-29.3-22.7-(C_5-C_9), 14.1(C_{10}), 2.1-1.8 (C_1 and $C_{1'}$)
MS (EI) m/z : 166 ($M^{+\cdot}$), 151 (M-Me), 137 (M-Et), 123 (M-Pr), 109 (M-Bu), 95 (M-Pent)

Octylidenecyclopropane 1a is produced in 28% yield using the above disclosed procedure.
IR (neat): 2930, 2857, 1460, 1095, 909, 735. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 5.72 (1H, H_3, m), 2.16 (2H, H_4, m), 1.60-0.80 (17H, $H_{5\text{-}10}$, H_1, $H_{1'}$, m). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 120.8 (C_2), 118.5 (C_3), 31.9 , 29.4, 29.3, 29.2, 22.7 (C_4-C_9), 14.1(C_{10}), 2.1-1.8 (C_1 and $C_{1'}$)
MS (EI) m/z: 152 ($M^{+\cdot}$), 137 (M-Me), 109 (M-Pr), 95 (M-Bu)
Anal. Calcd for $C_{11}H_{20}$: calculated C 86.76, H 13.24. Found C 85.11, H 13.05

General procedure for the preparation of 1-(1-hydroxy)-cyclopropyl carbinol 2[1,3] :

(2*R*)-1-Cyclopropyl-1,2-dihydroxy-decane 2b
AD-mix β (10.12 g) and methanesulfonamide (647mg) in *t*-butanol (34 ml) and water (34 ml) are stirred for 30 min. at 0°C. To the mixture was added nonylidenecyclopropane **1b** (1.13g; 6.8 mmol). The reaction mixture is stirred at 0°C for 12h, then treated with sodium sulfite (10.21g), allowed to stirred to raise slowly room temperature (1h), and extracted with CH_2Cl_2. The organic phases are washed with 2N NaOH, dried over $MgSO_4$ and concentrated under reduced pressure. The residue is purified by PLC (Pentane/diethyl ether: 40/60; Rf = 0.3) to give the diol **2b** as a white solid (1.17 g; 86%yield).
mp 77-79°C, $[\alpha]_D$ = + 13 (c 1.27, $CHCl_3$)
HPLC : hexane/*i*-PrOH (83/17), p = 50 bar, flow rate1 ml / min., rt.β 8 min., rt.α 10 min.
IR (neat): 3387, 3281, 2977, 2922, 2853, 1466, 1417, 1384, 1229, 1124. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.10 (1H, H_2, br t, 5.0 Hz), 1.90-1.05 (14H, $H_{3\text{-}9}$, m), 1.00-0.50 (7H, H_{10}, $(C\underline{H}_2)_2C$, m). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 76.7 (C_2), 58.8 (C_1), 33.5, 32.2, 30.0, 29.9, 29.6, 26.4, 22.9 (C_3-C_9), 14.4 (C_{10}), 11.8 and 11.5 ($(C\underline{H}_2)_2C$)
MS (EI) m/z: 141 ($C_9H_{17}O$), 125 (C_9H_{17}), 111 (C_8H_{15}), 97 (C_7H_{13}), 57 (C_3H_5O).
Anal. Calcd for $C_{12}H_{24}O_2$: calculated C 71.95, H 12.07. Found C 71.92, H 12.13

(2*R*)-1-Cyclopropyl-1,2-dihydroxy-nonane 2a
Has been prepared according to the above described procedure in 59% yield.
mp 76-78°C, $[\alpha]_D$ = + 10 (c 1.20, $CHCl_3$)
IR (neat): 3386, 3278, 2922, 2855, 1611, 1406, 1124, 912, 742. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.16 (1H, H_2, t, 5.3 Hz), 1.90-1.10 (12H, $H_{3\text{-}8}$, m), 1.05-0.50 (7H, H_9, $(C\underline{H}_2)_2C$, m). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 71.1 (C_2), 58.4 (C_1), 33.1, 31.8, 29.6, 29.2, 26.0, 22.6 (C_3- C_8), 14.1 (C_9), 12.5 and 11.3 ($(C\underline{H}_2)_2C$)
MS (EI) m/z: 127 ($C_8H_{15}O$), 98 (C_7H_{14}), 57 (C_3H_5O).
Anal. Calcd for $C_{11}H_{22}O_2$: calculated C 70.92, H 11.90. Found C 70.90, H 11.86

Rearrangement of (2*R*)-1-cyclopropyl-1,2-dihydroxy-alcane 2 into 2-alkyl-cyclobutanones 3 : general procedure
Method A:
$BF_3.Et_2O$ (10% mol) is added to a solution of the diol **2** in dry THF stirred at 20°C under an argon atmosphere. The mixture is stirred for 4h at that temperature then hydrolysed, extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated under reduced pressure. The crude material is purified by PLC (Pentane/diethyl ether: 98/02; Rf = 0.3) to give the corresponding 2-alkyl-cyclobutanone **3**.

Method B:
methanesulfonic/*p*-toluenesulfonic chloride (2 eq.) is added to a solution of the diol **2** stirred in dry pyridine at 0°C, under argon atmosphere. The mixture is stirred at RT for 4h, then hydrolysed with a saturated aqueous solution of $CuSO_4$ and extracted with CH_2Cl_2. The organic phases are dried over $MgSO_4$, concentrated under reduced pressure and the crude material purified by PLC (Pentane/diethyl ether: 98/02; Rf = 0.3) to give corresponding 2-alkyl-cyclobutanone **3**.

Method C:
p-toluenesulfonic acid (10%mol) is added at 20°C to a stirred solution of diol **2** in $CHCl_3$. The mixture is stirred for 12h then concentrated under reduced pressure. The crude material is purified by PLC (Pentane/diethyl ether: 98/02; Rf = 0.3) to give corresponding 2-alkyl-cyclobutanone **3**.

(2*R*)-2-Heptyl-cyclobutanone 3a[2]
Yield : 94%
$[\alpha]_D$ = -30 (c 1.10, $CHCl_3$)
IR (neat): 2927, 2865, 1782, 1466, 1093, 722. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.32-3.20 (1H, H_2, m), 3.07-2.85 (2H, H_4, m), 2.22-2.10 (1H, H_{3a}, m), 1.75-1.18 (13H, H_{3b}, $H_{1'-6'}$, m), 0.86 (3H, $H_{7'}$, t, 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) :212.5 (C_1), 60.6 (C_2), 44.3 (C_4), 31.7, 29.4, 29.3, 29.0, 26.9, 22.6, 22.7, 16.89 ($C_3C_{1'-6'}$), 14.0 ($C_{7'}$).
MS (EI) m/z : 98 (C_7H_{14}), 84 (C_6H_{12}), 69 (C_4H_5O), 57 (C_3H_5O).

(2*R*)-2-Octyl-cyclobutanone 3b[2]
$[\alpha]_D$= -32 (c 0.56, $CHCl_3$)
IR (neat): 3437, 2927, 2856, 1782, 1464, 1093. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.32-3.20 (1H, H_2, m), 3.10-2.85 (2H, H_4, m), 2.30-2.10 (1H, H_{3a}, m), 1.72-1.15 (15H, H_{3b}, $H_{1'-7'}$, m), 0.86 (3H, $H_{8'}$, t, 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm):212.6 (C_1), 60.6 (C_2), 44.3 (C_4), 31.8, 29.5, 29.4, 29.3, 27.0, 22.6, 22.7, 16.9 ($C_3C_{1'-7'}$), 14.1 ($C_{8'}$).
MS (EI) m/z : 182 ($M^{+\cdot}$), 167 (M-Me), 153 (M-Et), 139 (M-Pr),113 (C_8H_{17}), 69 (C_4H_5O), 57 (C_3H_5O).

Chiral 4-alkyl-γ-butyrolactones 4 : general procedure
A. From 2-alkyl-cyclobutanones **3**:
To a solution of 2-alkyl-cyclobutanone **3** in CH_2Cl_2, at 0°C, is added *m*-CPBA (1.2 eq.) or trifluoroperacetic acid (TFAA/H_2O_2) (1.2 eq.). After 6-12h, the reaction is quenched with a solution of $NaHCO_3$, then extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated under reduced pressure. The crude material is purified by PLC (Pentane/diethyl ether: 80/20; R f= 0.3) to give the corresponding 4-alkyl-γ-butyrolactone **4**.
The major isomer of γ-butyrolactone **4b** proved to be (*R*) by comparison of its retention time to the one described in the literature[10] (chiral [GC][2] isotherm 100°C for 10 min. then 2°C/min. till 200°C then 200°C, **4a** rt.β 39.3 min.., rt.α 39.8 min.. , **4b** rt.β 44.1min., rt.α 44.5 min.).

B. From diols **2**:
A solution of diol **2** in CH_2Cl_2 is added to a solution of trifluoroperacetic acid (4eq.) (TFAA/ H_2O_2) in CH_2Cl_2 at 0°C. The mixture is stirred for 6h, then quenched with a solution of $NaHCO_3$, extracted (CH_2Cl_2) and dried ($MgSO_4$). After concentration under reduced pressure, the crude oil is purified by PLC (Pentane/diethyl ether: 80/20; Rf = 0.3) to give the corresponding 4-alkyl-γ-butyrolactone **4**.

γ-Butyrolactones 4 from alkylidene cyclopropanes 1 : general procedure
A solution of alkylidene cyclopropane **1** in CH_2Cl_2 is added to a solution of trifluoroperacetic acid (4eq.) (from trifluoroacetic and hydrogen peroxide) in CH_2Cl_2 at 0°C. The mixture is stirred for 6h, then quenched with a solution of $NaHCO_3$, extracted (CH_2Cl_2) and dried ($MgSO_4$). After extraction (CH_2Cl_2), concentration under reduced pressure, the crude oil is purified by PLC (Pentane/diethyl ether: 80/20; Rf = 0.3) the corresponding 4-alkyl-γ-butyrolactone **4**.

4-Heptyl-γ-butyrolactone 4a
Yield : 87%

IR (neat): 3058, 2931, 2859, 1772, 1462, 1267, 1183, 911, 739. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.55-4.45 (1H, H_4, m), 2.62-2.50 (2H, H_2, m), 2.40-2.30 (1H, H_{3a}, m), 1.97-1.70 (2H, H_{3b}, $H_{1'a}$, m), 1.65-1.20 (11H, $H_{1'b}$, $H_{2'-6'}$, m), 0.88 (3H, $H_{7'}$, t, 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 177.1 (C_1), 81.0 (C_4), 35.6 (C_2), 31.7, 30.3, 29.0, 28.8, 27.9, 25.2, 22.6 (C_3,$C_{1'-6'}$), 14.0 ($C_{7'}$).

4-Octyl-γ-butyrolactone 4b
Yield: 84%
IR (neat): 2928, 2858, 1777, 1461, 1180. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.55-4.45 (1H, H_4, m), 2.60-2.48 (2H, H_2, m), 2.38-2.25 (1H, H_{3a}, m), 1.90-1.65 (2H, H_{3b}, $H_{1'a}$, m), 1.60-1.20 (13H, $H_{1'b}$, $H_{2'-7'}$, m), 0.85 (3H, $H_{8'}$, t, 6.7 Hz).^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 177.3 (C_1), 81.1 (C_4), 35.5 (C_2), 31.7, 29.4, 29.3, 28.8, 27.9, 25.1, 22.6 (C_3,$C_{1'-7'}$), 14.3 ($C_{8'}$).
MS (EI) m/z : 198 ($M^{+\cdot}$), 183 (M-Me), 169 (M-Et), 155 (M-Pr),113 (C_8H_{17}), 57 (C_3H_5O).

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4. See ref. 3b page 5517.
5. **2b** ($[\alpha]_D^{20}$ = +14.89 (c 0.79 $CHCl_3$)[3b] and **2a** ($[\alpha]_D^{20}$ = +15.6 (c 0.9 $CHCl_3$).[3b]
6. **3b** ($[\alpha]_D^{20}$ = -8.71 (c 0.94 $CHCl_3$)) [3b] and **3a** ($[\alpha]_D^{20}$ = -7.97 (c 0.3 $CHCl_3$)).[3b]
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