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TETRAHEDRON: *ASYMMETRY*

Enzymatic acylation of cyclobutene and cyclobutane *meso*-diols at low temperature

Christophe Pichon, Cécile Hubert, Christian Alexandre* and François Huet*

Laboratoire de Synthèse Organique, UPRES A CNRS 6011, Faculté des Sciences, Université du Maine, Avenue Olivier Messiaen, F-72085 Le Mans Cedex 9, France

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Abstract

Acylation of cyclobutane and cyclobutene diols **5** and **8** in the presence of *Pseudomonas fluorescens* lipase below room temperature led to monoacetates (+)-**6** and (–)-**9**, respectively. The chemical yields and enantiomeric excesses were nearly quantitative.

1. Introduction

Enzymatic asymmetrization is a useful way to synthesize numerous chiral building blocks.[1] It has given good results in numerous cases, for instance starting from several cyclobutane compounds and especially for the enzymatic hydrolysis of cyclobutane diester **1** mediated by pig liver esterase,[2] acylation of diol **5** in the presence of SAM-II lipase,[3] and hydrolysis of diacetate **7** using the same lipase[3] or the pancreatic porcine lipase (PPL).[4] Enantiomerically enriched hemiester **2** or monoacetates (+)-**6** and (–)-**6** thus became easily available (Scheme 1). Cyclobutene diester **3**,[5] diol **8**[6] and diacetate **11**[5a] also led to satisfying results. The resulting products were used in the synthesis of a nucleoside analogue[5b] and of both enantiomers of lactone **10**.[6] One of these lactones was also obtained in high enantiomeric excess by selective oxidation of diol **8** in the presence of horse liver alcohol dehydrogenase (HLAD) as the catalyst.[7] This lactone, in the racemic form, proved to be a useful starting material in the synthesis of the first cyclobutene nucleosides unsubstituted at the vinylic position.[8]

In the course of our research program on cyclobutene compounds, we were interested in obtaining (–)-**9** and we first used *Pseudomonas fluorescens* lipase (PFL) under the experimental conditions previously described.[6] In our hands, the result was either nearly equivalent or less satisfactory, depending on the exact experimental conditions. Moreover we encountered some difficulties in the accurate measurement of the enantiomeric excess in the presence of $Eu(hfc)_3$,[6]

* Corresponding authors. Fax: (33) 2 43 83 33 66; e-mail: fhuet@aviion.univ-lemans.fr

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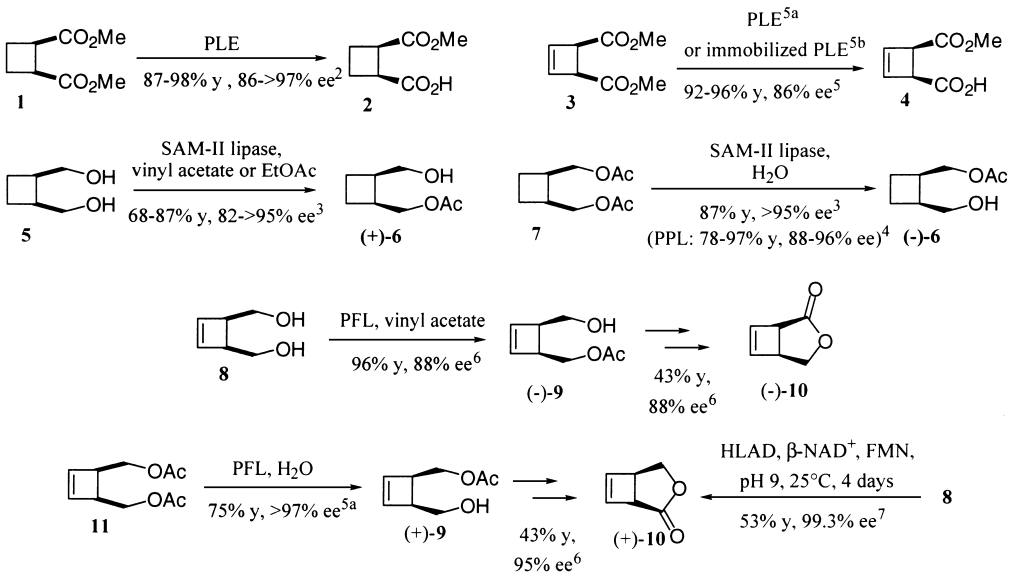


Scheme 1.

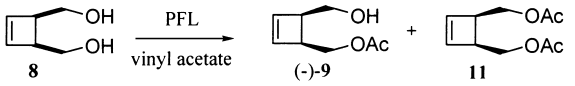
especially when this excess was high, and therefore we envisaged trying to obtain a higher enantiomeric excess in a reproducible manner.

2. Results and discussion

To measure more accurately the enantiomeric excess of (–)-**9**, we planned to use chiral gas phase chromatography. However, since cyclobutenes have a low thermal stability, we examined the possibility of reducing them and to analyze the corresponding cyclobutane compounds. Hydrogenation in the presence of 10% Pd/C was quite successful and quickly yielded (+)-**6** in 3 h. This reaction led to a quantitative yield, and moreover, as isomerization is improbable in this case, the enantiomeric excess of **6** should precisely reflect the one of **9**. The subsequent analysis by chiral gas phase chromatography equally gave excellent results.

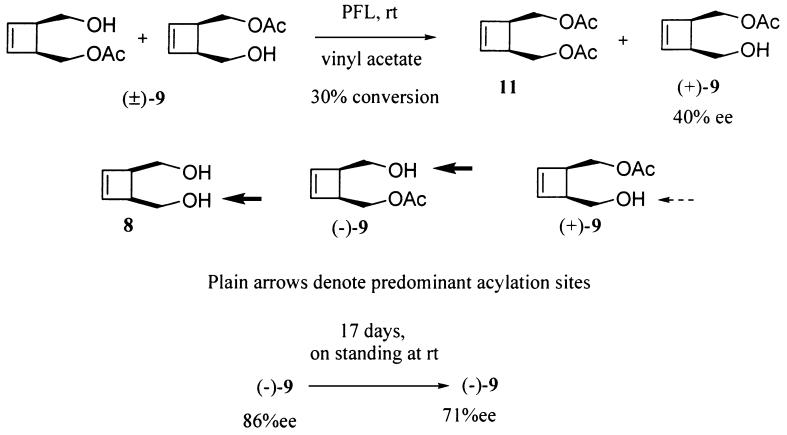
We then carried out various experiments to analyze the reasons why there were variations in the enantiomeric excesses. We observed that one of the important parameters was the conversion percent. Precisely, in an experiment at room temperature, when the reaction was stopped just before obtaining the diacetate **11** (Table 1, entry 1), an 86% ee of (–)-**9** was measured. In contrast when the experiment was run until total disappearance of **8**, which led to a certain amount of **11** being obtained, the ee of (–)-**9** dropped down significantly (entry 2). It thus seemed that, in the course of diacylation, isomer (–)-**9** was a better substrate for the enzyme than (+)-**9**. This hypothesis was clearly verified by the result of a reaction with racemic **9**. Indeed, in this case, the reaction led to a moderate ee in favor of (+)-**9** (Scheme 2). It then appears that the selectivity of acylation is reversed for **9** with respect to **8**. One of the reasons why there were variations in the results according to the experimental conditions is thus explained. However, we noticed that another parameter also had an influence. When a sample of (–)-**9** of 86% ee was kept for 17 days at room temperature, the ee dropped to 71% showing that a slow transesterification between the functional groups can occur.

Table 1



Entry	Temp (°C)	Reaction time	**8/9/11** ratio	Yield[a] of **9** (%)	Ee of **9** (%)
1	20	1 h 45 min	1.0/12.0/0.0	71	86[b]
2	20	2 h 15 min	1.0/17.0/1.7	79	78[b]
3	4	3h	1.0/19.0/0.2	85	92[c]
4	0	9h	1.6/97.7/0.7	97	97.9[c]
5	-15	19h	0.6/99.1/0.3	97	98.5[c]
6	-25	20 h 30 min	0.5/99.3/0.1	97	98.6[c]

(a) yield of isolated product; (b) ee measured by ^{1}H NMR in the presence of Eu(hfc)$_3$; (b) ee measured by chiral GPC



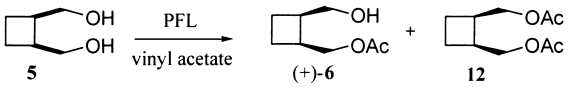
Scheme 2.

As we had obtained improvements in another case with the same enzyme, by operating at a lower temperature,[9] we tried to do the same in the case of **8**. Cooling effectively led to appreciable increases, not only of the enantiomeric excess but also of the yield, due to the possibility, under these experimental conditions, of obtaining a very high conversion without obtaining diacetate **11**. The results were already very good at 0°C and excellent at –25°C. Moreover the reaction time stayed within reasonable limits (entries 4–6).

We then envisaged examining the acylation of the cyclobutane compound **5**. We first noticed that the results were already good at room temperature (Table 2, entry 1), showing that PFL leads to the same predominant isomer as SAM-II lipase, with nearly equivalent yield and enantiomeric excess.[3] Obviously, in this case, the effect of cooling was less spectacular than from **8**, however it also led to a noticeable improvement (entry 2).

Finally, in both cases, chemical yields and enantiomeric excesses were significantly increased when the enzymatic acylations were run below room temperature, with the reaction times not

Table 2



5 (+)-6 12

Entry	Temp (°C)	Reaction time	**5/6/12** ratio	Yield of **6** (%)	Ee of **6** (%)
1	20	6h 30 min	2.0/97.0/1.0	91	96.9[a]
2	-2°C	13 h 45 min	0.1/99.9/0.0	99.9	>99.9[a]

(a) ee measured by by chiral GPC

being increased too much. The only inconvenience of the method is that this enzyme is somewhat expensive. However it may be recycled and we could carry out five successive preparations of (+)-**6** with the same catalyst without any deterioration in the results.

3. Experimental

3.1. General

NMR spectra were recorded in $CDCl_3$ solutions at 400 MHz (^1H) or 100.6 MHz (^{13}C) on a Bruker AC-400 instrument. Chemical shifts are reported in ppm downfield from TMS which was used as an internal reference. Infrared spectra were scanned on a Nicolet 5DX spectrometer and peaks are reported in cm^{-1}. Optical rotation values were obtained from a Perkin–Elmer 241 polarimeter. Chromatographic analyses were performed with a Varian 3300 apparatus equipped with an SE 30 column (megabore DB1, 30 m×0.53 mm) or with a Hewlett–Packard HP 6890 Series GC apparatus equipped with a column Restek-β Dex Sm (25 m×0.25 mm) column ($T_{inlet} = T_{detector} = 200°C$, oven: 90°C for 5 min then 1°C/min until 130°C; (–)-**9**: $t_R = 42.8$ min, (+)-**9**: $t_R = 43.1$ min; R = 1.7). *Pseudomonas fluorescens* lipase was purchased from Aldrich. Vinyl acetate was stirred with K_2CO_3 then distilled over $MgSO_4$.

3.2. [(1S,4R)-4-(Hydroxymethyl)-2-cyclobutenyl]methyl acetate (–)-9

Pseudomonas fluorescens lipase (10 mg, 470 units) was added at –25°C and under nitrogen to a stirred solution of (4-hydroxymethyl-2-cyclobutenyl)methanol **8** (120 mg, 1.05 mmol) in vinyl acetate (2.1 mL). The progress of the reaction was monitored by TLC (CH_2Cl_2:Et_2O = 7:3). When a trace of diacetate ($R_f = 0.83$) was detected (20 h 30 min), the solution was diluted with Et_2O and filtered. The solid was washed with Et_2O (3×4 mL) and the combined filtrate and washings were evaporated under reduced pressure thus leaving (–)-**9** as an oil (163 mg, 1.05 mmol, quantitative). The practically pure product (>98% purity by ^1H NMR) could be purified by column chromatography on silica gel (CH_2Cl_2:Et_2O = 7:3, $R_f = 0.49$), (159 mg, 1.02 mmol, 97% yield, 98.6% ee). IR (neat) 3455, 2957, 1735, 1440, 1282; ^1H NMR δ 6.15 (d, 1H, $J = 3.1$ Hz), 6.12 (d, 1H, $J = 3.0$ Hz), 4.35 (dd, 1H, $J = 11.3$, 6.1 Hz), 4.18 (dd, 1H, $J = 11.3$, 8.6 Hz), 3.76 (d, 2H, $J = 6.9$ Hz), 3.24 (m, 1H), 3.19 (m, 1H), 2.33 (br s, 1H), 2.08 (s, 3H); ^{13}C NMR 170.8, 138.2, 137.4, 64.1, 62.01, 47.8, 44.2, 20.9; $[\alpha]_D^{22}$ –8.9 ($c = 2$, $CHCl_3$). Lit.[6] $[\alpha]_D^{20}$ –7.2 ($c = 2$, $CHCl_3$) for an 88% ee sample.

3.3. (±)-4-(Hydroxymethyl)-2-cyclobutenylmethyl acetate **9** and (±)-4-(acetoxymethyl)-2-cyclobutenylmethyl acetate **11**

A mixture of diol **8** (1.35 g, 11.85 mmol), acetic anhydride (1.12 mL, 11.82 mmol) and pyridine (965 μL, 11.85 mmol) was stirred at room temperature for 3 h. Saturated aqueous $NaHCO_3$ (40 mL) was then added. Extraction with AcOEt (4×40 mL), successive washings of the combined organic layers with 10% aqueous HCl (30 mL) and brine (40 mL), then evaporation, yielded a mixture of **8**, **9**, and **11** in a 1:1.3:0.9 ratio, respectively. Column chromatography on silica gel (CH_2Cl_2:Et_2O = 95:5 to 60:40) provided successively **11** [oil, 657 mg, 3.32 mmol, 27%; R_f = 0.87 (CH_2Cl_2:Et_2O = 7:3)], **9** (oil, 666 mg, 4.27 mmol, 36%) then **8** [oil, 372 mg, 3.10 mmol; R_f = 0.21 (CH_2Cl_2:Et_2O = 7:3)]. Data for **11**: IR (neat) 3050, 2956, 1735, 1451, 1385, 1366, 1236; ^{1}H NMR δ 6.02 (s, 2H), 4.09–4.13 (m, 4H), 3.12–3.18 (m, 2H), 1.95 (s, 6H); ^{13}C NMR 170.9, 137.9, 63.9, 44.3, 21.0.

3.4. Typical procedure for hydrogenation of (–)-**9** into (+)-**6**

Compound (–)-**9** (30 mg, 0.19 mmol) in AcOEt (30 mL) was hydrogenated under 50 psi in the presence of 10% Pd/C (50 mg) at 20°C for 3 h. Filtration and evaporation left (+)-**6** as an oil (30 mg, 0.19 mmol, quantitative). It was used without further purification for the analysis by chiral GPC.

3.5. [(1S,2R)-2-(Hydroxymethyl)cyclobutyl]methyl acetate (+)-**6**

Pseudomonas fluorescens lipase (10 mg, 470 units) was added at –2°C and under nitrogen to a stirred solution of (2-hydroxymethyl-cyclobutyl)-methanol **5** (122 mg, 1.05 mmol) in vinyl acetate (2.1 mL). The progress of the reaction was monitored by TLC (CH_2Cl_2:Et_2O = 7:3). When a trace of diacetate (R_f = 0.83) was detected (13 h 45 min), the solution was diluted with Et_2O and filtered. The solid was washed with Et_2O (3×4 mL) and the combined filtrate and washings were evaporated under reduced pressure thus leaving (+)-**6** as an oil (> 99% purity by GPC), (163 mg, 1.05 mmol, quantitative, > 99.9% ee). IR (neat) 3411, 2943, 2868, 1735, 1367, 1248; ^{1}H NMR δ 4.23 (dd, 1H, J = 17.3, 3.1 Hz), 4.20 (dd, 1H J = 17.3, 6.4 Hz), 3.77 (dd, 1H, J = 11.3, 8.5 Hz), 2.64–2.80 (2m, 2H), 2.06 (s, 3H), 2.01–2.17 (m, 2H), 1.63–1.76 (m, 3H); ^{13}C NMR 170.9, 64.7, 37.9, 34.5, 21.1, 21.0, 20.7; $[\alpha]_D^{22}$ +2.1 (c = 4.1, $CHCl_3$). Lit[4a] $[\alpha]_D^{20}$ –1.5 (c = 4.23, $CHCl_3$) for an 88% ee sample of (–)-**6**.

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