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Article

Evaluation of Lipases in the Desymmetrization of *meso-exo*-3,5-Dihydroxymethylenetricyclo[5.2.1.$0^{2,6}$]decane and the Synthesis of Chiral Derivatives

Valentim E. U. Costa*, Adriana R. Pohlmann and Marli L. T. de Sordi

Instituto de Química, Universidade Federal do Rio Grande do Sul, Av.Bento Gonçalves, 9500,
91501-970 Porto Alegre-RS, Brazil

A dessimetrização mais eficiente do composto *meso*-*exo*-3,5-dihidroximetilenotriciclo[5.2.1.$0^{2,6}$]decano foi com a lipase da *Pseudomonas cepacia* (PS–C 'Amano' II) em acetato de vinila, quando obteve-se alto rendimento químico (93%) e excelente excesso enantiomérico (*ee* ≥ 99%), determinado por cromatografia gasosa em coluna quiral. Desse sistema quiral, foram preparados derivados enantiopuros com potenciais aplicações como intermediários sintéticos.

meso-*exo*-3,5-dihydroxymethylenetricyclo[5.2.1.$0^{2,6}$]decane was efficiently desymmetrized by the lipase from *Pseudomonas cepacia* (PS–C 'Amano' II) in vinyl acetate in high yields (93%) and with excellent enantiomeric excesses (*ee* ≥ 99% by chiral GC). Chiral synthons for asymmetric synthesis were synthesized from this enantiopure compound.

Keywords: lipases, enzymatic catalysis, desymmetrization, chiral compounds

Introduction

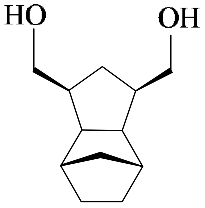
Bicyclic amino alcohol derivatives are stereochemically constrained compounds and are interesting systems used as chiral auxiliaries,[1-5] as well as synthetic intermediates and chiral ligands for asymmetric synthesis.[1,6-8] Optically active amino alcohols are constituents of many biologically and pharmacologically important compounds such as adrenaline, β-adrenergic receptor blockers and local anaesthetics.[9] The abundance and crystallinity of (+)-camphor have attracted considerable interest to the synthesis of enantiomerically pure derivatives including 3-*endo*-amino-2-*endo*-bornanol,[10] *exo*,*exo*-amino alcohol,[11] *anti*-(+)-camphorquinone-3-oxime[12] and bridgehead-substituted 2-norbornanones and 2-norbonanoximes.[13]

The desymmetrization of an *meso* compound by reaction with a suitable enantiomerically pure reagent provides a versatile approach to the preparation chiral synthons for asymmetric synthesis.[14] Desymmetrization of *meso*-compounds or prochiral diols and diacetates in the presence of lipase has become a practical approach for the preparation of chiral compounds due to its high specificity and reproducibility.[9]

Optically active aminooxy alcohols would appear to be very interesting building blocks in the search for novel biologically active compounds and the synthesis of such optically active derivatives by using a lipase-catalyzed acetylation has been described.[9]

The goal of our research group over the last few years has been the study and application of constrained polycyclic compounds, from both a conformational and stereochemical viewpoint,[15] as well as in terms of their reactivity and enantiomeric resolution.[16]

In this work we report the evaluation of various lipases for the desymmetrization of *meso*-*exo*-3,5-dihydroxymethylenetricyclo[5.2.1.$0^{2,6}$]decane in vinyl acetate and the preparation of derivatives as chiral building blocks, carrying functional groups in flexible chains on appropriate positions of the tricyclic framework.



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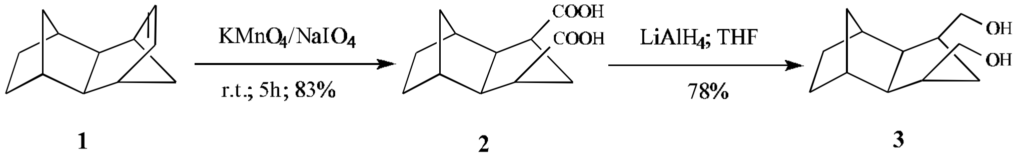
* e-mail: valentim@iq.ufrgs.br



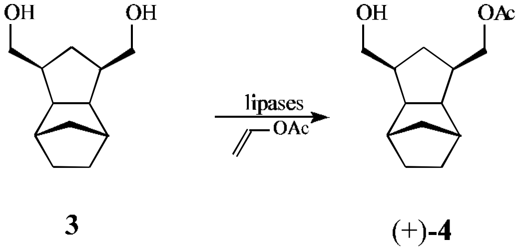
Scheme 1. Synthesis of *meso*-3,5-dihydroxymethylene-*exo*-tricyclo[5.2.1.$0^{2,6}$]decane, (**3**).

Results and Discussion

The symmetric starting material *endo,exo*-tetracyclo[6.2.1.$1^{3,6}$.$0^{2,7}$]dodec-4-ene, (**1**), was prepared easily by the Diels-Alder reaction between norbornene and dicyclopentadiene according to known procedure.[17]

The treatment of the resulting adduct **1** with $KMnO_4$ and $NaIO_4$ at room temperature over 5 h gave the respective dicarboxylic acid **2** in 83% yield,[18] while the use of $RuCl_3.3H_2O$ (cat.), $NaIO_4$, CCl_4-CH_3CN-H_2O provided yields around 85%.[19] This *meso* diacid was then reduced with lithium aluminium hydride in tetrahydrofuran to give the *meso*-diol **3** in 78% yield (Scheme 1).

The lipase-catalysed transesterification reaction with vinyl acetate at 23-26°C was used to afford the kinetic desymmetrization of *meso*-diol **3** (Scheme 2).



Scheme 2. Lipase-catalysed acetylation of *meso*-*exo*-3,5-dihydroxymethylenetricyclo[5.2.1.$0^{2,6}$]decane, (**3**).

Catalytic desymmetrization reaction of *meso*-diol **3** mediated by lipase from *Pseudomonas cepacia* supplied in three different preparations were evaluated: powder (Lipase PS “Amano”), immobilized on ceramic particles chemically modified with methacrylic groups (Lipase PS–C “Amano” II) and immobilized on diatomaceous earth (Lipase PS–D “Amano” I). The same reaction mediated by lipase from *Candida rugosa* (AY Amano 30) and lipase from *Porcine pancreatic* (PPL) supplied as a powder were also evaluated.

The AY Amano 30 lipase (from *Candida rugosa* supplied as a powder) gave only the racemic monoacetate (±)–**4** while all the other lipases produced exclusively monoacetate (+)–**4** with high enantiomeric excesses (*ee* ≥ 99%). However, the Amano PS – C II lipase was found to be the best catalyst, giving the highest yields (93%) and the most favorable reaction time (Table 1).

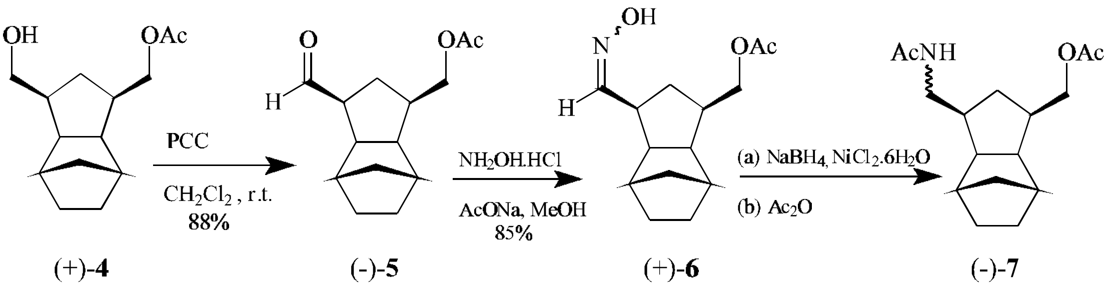
After reaction, the acetoxy alcohol (+)–**4** was purified by filtration over Celite with ethyl acetate. The enantiomeric excess (*ee*%) of the separated acetate was determined by gas chromatography on a Beta-Dex™ 120 chiral column.

The oxidation of the acetoxy alcohol (+)–**4** with pyridinium chlorotrioxochromate (PCC) gave the respective enantiomerically pure acetoxy aldehyde (-)-**5** in 88% yield with an $[\alpha]_D^{20} = -16$ (c =2, CH_2Cl_2); as this aldehyde is unstable we prepared directly its oxime derivative and, consequently, the elemental analysis was made of its oxime. The acetoxy oxime derivative (+)-**6** was obtained from the reaction of the aldehyde (-)-**5** with hydroxylamine chloride/sodium acetate in a 65-85% yield. The acetoxy oxime (+)-**6** is a conformer mixture determined by ^1H NMR (60:40) and it had a specific rotation of $[\alpha]_D^{20} = +24$ (2, CH_2Cl_2).

In order to obtain the protected amino alcohol **7** the oxime (+)-**6** was reduced with nickel chloride hexahydrate and sodium borohydride in methanol. However, direct extraction and purification of the chiral amino-alcohol afforded poor yields, and to overcome this, *in situ* acetylation of the reaction product was carried out, producing the protected amino alcohol (-)-**7** in a 77% yield

Table 1. Results of the lipase-catalysed transesterification reactions of *meso*-*exo*-3,5-dihydroxymethylenetricyclo[5.2.1.$0^{2,6}$]decane, (**3**)

Lipase	Reaction time (h)	Chemical conversion (%)	Enantiomeric excess: *ee* (%)	$[\alpha]_D^{20}$ (c = 2; CH_2Cl_2)
AY “Amano” 30	20	48	0	0
Porcine pancreatic (PPL)	96	78	≥ 99	+ 1
PS-C “Amano” II	1.5	93	≥ 99	+ 1
PS-D “Amano” I	7	80	≥ 99	+ 1
PS “Amano”	48	80	≥ 99	+ 1



Scheme 3. Synthesis of chiral derivatives from 3-hydroxymethylene-5-aceto-methylenetricyclo[5.2.1.0^{2,6}]decane, [(+)-**4**].

($[\alpha]_D^{20}$ = - 10 (1, CH_2Cl_2)). The acetyl group of the amide function has two preferential conformers because it is possible to observe in ^{13}C-NMR double signals for the methyl and carbonyl groups.

Conclusion

The Amano PS – C II lipase was found to be the best catalyst, giving highest yields and the best reaction rate in the desymmetrization reaction of *meso*-*exo*-3,5-dihydroxymethylenetricyclo[5.2.1.0^{2,6}]decane, (**3**) in vinyl acetate. Chiral derivatives, in non-racemic form, have been prepared, carrying functional groups on flexible chains in appropriate positions of this tricyclic framework. This constitutes an effective and convenient synthetic approach for the preparation of new chiral auxiliaries, synthons and building blocks.

Experimental

General

Melting points were determined on an Electrothermal IA9000 apparatus and are presented without correction. Infrared spectra were recorded using a Mattson 3020 FTIR spectrometer. Mass spectra were acquired on an HP 5988A spectrometer. NMR spectra were recorded on a Varian VXR-200 spectrometer at a magnetic field of 4.7 T at 22 °C. Chemical shifts are expressed as δ (ppm) relative to TMS as internal standard and the J values are given in Hz. Elemental analyses were recorded on a Perkin – Elmer 2400 CHN elemental analyzer. The products were analyzed by GC on a Shimadzu GC – 17A Gas Chromatograph equipped with an FID detector. Optical rotations were recorded on a Perkin – Elmer 341 polarimeter using the sodium D line or mercury 365 nm line with a 0.1 dm cell at a temperature of 20 °C. Lipase PS "Amano" (Lot. LPSAX10508), PS – C "Amano" I (Lot. IPSAX08531K), PS – C "Amano" II (Lot. ILPSAX01520K), PS – D "Amano" I (Lot. ILPSAX02520K), AK "Amano" 20 (Lot. LAKX09510) from Pseudomonas and lipase AY Amano 30 (Lot. LAYY0450102S), were kindly provided by Amano Enzyme U.S.A. Co. Vinyl acetate was distilled from hydroquinone just before use. All enzymatic resolutions were carried out at 20 °C under anhydrous conditions on a Mistral Multi-Mixer apparatus. *GC parameters for achiral analysis.* injector 250 °C; detector 300 °C; oven 100 °C for 5 min then 10 °C min^{-1} until 300 °C; column pressure 15 kPa; column flow 9.5 mL min^{-1}; linear velocity 84.7 cm s^{-1}; total flow 200 mL; split ratio 1:20; column DB1 15 m x 0.53 mm (internal diameter).

GC parameters for chiral analysis. injector 250 °C; detector 300 °C; oven 150 °C for 10 min then 5 °C min^{-1} until 200 °C; column pressure 138 kPa; column flow 2.7 mL min^{-1}; linear velocity 75.5 cm s^{-1}; total flow 35 mL; split ratio 1:10; column b- cyclodextrin 30 m x 0.25 mm (internal diameter).

exo-Tricyclo[5.2.1.0^{2,6}]decan-3,5-dioic acid, (2)

To a solution of **1** (2.0 g, 4.5 mmol) in *t*-butanol (50 mL) was added an aqueous solution (150 mL) of $NaIO_4$ (10.0 g, 46.7 mmol), $KMnO_4$ (5.2 g, 32.9 mmol), and K_2CO_3 (10.0 g, 72.4 mmol). The medium was adjusted to pH 8 by the addition of a 3 mol L^{-1} NaOH aqueous solution and the reaction underwent magnetic stirring at room temperature. After 5 h, the medium was acidified with concentrated HCl to pH 1 and sodium bisulfite was added. The mixture was extracted with ethyl acetate (3 x 40 mL), and the combined organic layers were extracted with 3 mol L^{-1} NaOH aqueous solution (3 x 40 mL). Then, the dicarboxylate aqueous solution was acidified (concentrated HCl) to pH 3-4 and extracted with ethyl acetate (3 x 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure, giving 2.3 g of diacid **2** (82% yield). Elemental analysis: Found: C, 64.17; H, 7.18%; Calcd. for $C_{12}H_{16}O_4$: C, 64.28; H, 7.14%; mp 224° C; IR (KBr) ν_{max}/ cm^{-1}: 3000, 1711; ^{1}H NMR (CD_3OD, 300 MHz): δ 1.0-1.5 (m, 6H, tricyclic moiety), 1.8 (m, 1H, tricyclic moiety), 2.2-2.6 (m, 5H, tricyclic moiety), 3.1 (m, 2H, CH-3 and CH-5), 9.9 (s, 2H, COOH);

^{13}C NMR (CD_3OD, 75 MHz): δ 30.0 (CH_2), 33.0 (CH_2), 36.5 (CH_2), 41.0 (CH), 49.0 (CH), 51.8 (CH), 177.0 (COOH).

*meso-endo,exo-3,5-dihydroxymethylene-tricyclo[5.2.1.0^{2,6}]decane, (**3**)*

To a suspension of $LiAlH_4$ (1.0 g, 27.2 mmol) in dry THF (50 mL) under argon was added a solution of diacid **2** (1.0 g, 4.46 mmol) in dry THF (10 mL). The reaction was carried out during 6 h with magnetic stirring at room temperature. Then, the mixture was added of distilled water (3 mL) and 30% (m/V) NaOH aqueous solution (10 mL). The precipitate was removed by filtration, and the filtrate was dried over anhydrous $NaSO_4$, filtered and evaporated under reduce pressure. The pure diol **3** (0.680 g, 3.5 mmol) was obtained in 78% of yield. Elemental analysis: Found: C, 72.02; H, 10.82%; Calcd. for $C_{12}H_{20}O_2$: C, 72.36; H, 10.20%; IR (KBr) ν_{max}/ cm^{-1}: 3280, 1021; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.8-2.5 and 0.9-1.4 (m, 14H, tricyclic moiety and 2 H, OH), 3.7 (dd, *J* 13.0 Hz and *J* 7.6 Hz, 4H, 2 x CH_2-OH); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz): δ 30.0 (CH2), 36.8 (CH2), 37.8 (CH2), 38.2 (CH), 47.0 (CH), 51.4 (CH), 64.0 (CH2O).

*3-Hydroxymethylene-5-acetomethylene-tricyclo[5.2.1.0^{2,6}]decane, [(±)-**4**]*

The racemic standard (±)-**4** was prepared to carry out the chiral chromatographic analyses. The *meso*-diol **3** (0.140 g, 0.71 mmol) and 0.550 g of silica gel (60, 70-230 mesh) were shaken. To this mixture sufficient acetic anhydride was added to cover the solid. After 2 h, the reaction was quenched by the addition of distilled water (20 mL). The mixture was neutralised with an aqueous solution of $NaHCO_3$ and extracted with ethyl acetate (3 x 40 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduce pressure. The GC analysis of crude product showed 3 peaks: A, 27%; B, 56% and C, 17%. The peaks A and B were the *meso*-diol **3** and the monoacetate (±)-**4** respectively. Column chromatography (silica gel 60, 70-230 mesh; cyclohexane/ ethyl acetate 3:1) of crude product gave the monoacetate (±)-**4** in 47% yield. Elemental analysis: Found: C,70.07; H,9.31%; Calcd. for $C_{14}H_{22}O_3$: C,70.58; H,9.24%; IR (neat) ν_{max}/ cm^{-1}: 3460, 1740, 1243, 1033; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.1 (m, 2H, CH_2-OAc), 3.7 (m, 2H, CH_2-OH), 3.3 (bs, 2H, CH-3 and CH-5), 2.2 (m, 2H, tricyclic moiety), 2.1 (s, 3H, CH_3), 1.7-1.9 (m, 2H, tricyclic moiety), 1.4 (m, 3H, tricyclic moiety), 0.9-1.3 (m, 5H, tricyclic moiety, and 1 H, OH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.9 (CH_3), 29.5 (2 CH_2), 35.2 (CH_2), 36.5 (CH_2), 36.7 (CH), 36.8 (CH), 41.4 (CH), 45.2 (CH), 49.6 (CH), 49.8 (CH), 65.2 (CH_2-OH), 66.2 (CH_2-OAc), 171.3 (CO).

*3-Hydroxymethylene-5-acetomethylene-tricyclo[5.2.1.0^{2,6}]decane, [(+)-**4**]*

The general procedure for enzyme catalytic reactions (Table 1) was carried out as described for PS-C "Amano" II: to a solution of diol **3** (0.250 g, 1.27 mmol) in vinyl acetate (20 mL) was added the lipase (0.050 g). The reaction was stirred during 1.5 h at room temperature. The mixture was filtered over Celite, using ethyl acetate (30 mL). Then, the filtrate was evaporated under reduce pressure to give the product (+)-**4** (0.265 g; 1.11 mmol, 88%). $[\alpha]_D^{20}$ +1 (*c* = 2, CH_2Cl_2); the physical data are described above to racemic compound.

*5-Acetomethylenetricyclo[5.2.1.0^{2,7}]decane-3-carbaldehyde, [(-)-**5**]*

To a solution of product (+)-**4** (0.100 g, 0.42 mmol) in CH_2Cl_2 (15 mL) was added pyridinium chlorotrioxochromate (PCC, 0.250 g, 1.16 mmol). After 4 h under magnetic stirring at room temperature, ethyl ether (10 mL) was added and a black precipitate was formed, which was filtered off with a small column fitted with silica gel 60 (70-230 mesh), and eluted with ethyl ether. The filtrate was evaporated under reduce pressure to give a colourless oil corresponding to aldehyde (-)-**5** (0.087 g; 0.36 mmol, 88%), which was used immediately to avoided oxidation. $[\alpha]_D^{20}$ -16 (*c* = 2, CH_2Cl_2); Elemental analysis: data were obtained from its stable oxime derivative; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.0 – 2.8 (m, 13H, tricyclic moiety), 2.1 (s, 3H, CH_3), 3.0 (ddd, *J* 9.77 Hz, *J* 9.44 Hz, *J* 1.52 Hz, 1H, CH-CHO), 4.2 (dd, *J* 7.47 Hz and *J* 4.80 Hz, 2H, CH2-OAc), 9.8 (d, *J* 1.53 Hz, 1H), ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.9 (CH_3), 29.1 (CH_2),), 29.5 (CH_2), 29.6 (CH_2), 31.1 (CH_2), 36.6 (CH), 38.4 (CH), 41.4 (CH), 49.8 (CH), 49.8 (CH), 55.3 (CH), 65.1 (CH_2O), 171.2 (AcCO), 202.9 (CHO).

*3-acetomethylene-5-oximemethylene-tricyclo[5.2.1.0^{2,6}]decane, [(+)-**6**]*

To a solution of acetoaldehyde (-)-**5** (0.450 g, 1.89 mmol) in methanol was added sodium acetate (0.200 g; 2.0 mmol) and $NH_2OH.HCl$ (0.138 g; 2.0 mmol). The mixture was stirred at room temperature for 18h, water was added (20 cm^3) and then extracted with ethyl acetate (3 x 20 cm^3). The organic layer was washed with $NaHCO_3$ solution (10%; m/ v), dried over $MgSO_4$, filtered and *evaporated* in vacuo, affording the oxime (+)-**6** (0.405 g; 0.123 mmol) with 85%

of yield. $[\alpha]_D^{20}$ + 24 (*c* = 2, CH_2Cl_2); Elemental analysis: Found: C, 68.20; H, 8.64; N, 5.26%; Calcd. for $C_{14}H_{21}NO_3$: C, 68.18; H, 8.33; N, 5.30%; IR ($CHCl_3$ film) $\nu_{max.}$/cm^{-1}: 3388 (N-OH), 1739 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.9 – 3.0 (m, 14H), 2.1 (s) and 2.2 (s) (3H), 4.2 (m, 2H), 6.8 (d, *J* 6.4Hz, 1H) and 7.52 (d, *J* 7.0Hz) (1H), 8.7 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9 (CH_3), 29.2 (CH_2), 29.6 (CH_2), 35.2 (CH_2), 36.1 (CH_2), 36.9 (CH_2), 38.0 (CH), 41.9 (CH), 42.8 (CH), 49.5 and 50.0 (CH), 51.2 and 51.8 (CH), 65.2 and 65.3 (CH_2), 153 (C=N), 171.2 and 171.3 (C=O).

*3-acetomethylene-5-acetoamidomethylene-tricyclo[5.2.1.0^{2,6}]decane, [(-)-**7**]*

To a solution of hydroxy oxime (+)-**6** (0.310 g; 1.11mmol) in methanol (10mL), nickel (II) chloride hexahydrate (0.47 g; 1.96 mmol) was added under magnetic stirring. After nickel dissolution, the solution was cooled to –78 °C. Powdered sodium borohydride (0.390 g; 10.2 mmol) was added in small portions under efficient stirring. The solution turned blue, and was stirred for an additional 12 h when the colour changed to black. The methanol was removed and acetic anhydride (10 mL) was added and the solution refluxed for 90 min. The excess anhydride was removed by distillation. The residue was neutralized with a solution of saturated potassium carbonate until pH 9–10 and extracted three times with chloroform, yielding, after solvent evaporation, a yellow oil corresponding to the compound (-)-**7** (238 mg; 0.85 mmol, 77%). $[\alpha]_D^{20}$ - 10 (*c* = 1, CH_2Cl_2); Elemental analysis: Found: C, 66.85; H, 8.85; N, 4.65%; Calcd. for $C_{16}H_{25}NO_4$.1/2H_2O: C, 66.67; H, 9.02; N, 4.86%; IR ($CHCl_3$ film) $\nu_{max.}$/cm^{-1} 3297 (N-H), 1739 (C=O; ester), 1650 (C=O; amide); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.02 (m, tricyclic moiety, 4H), 1.22 (m, tricyclic moiety, 1H), 1.42 (m, tricyclic moiety, 2H), 1.78 (m, tricyclic moiety, 1H), 1.90 – 2.40 (m, tricyclic moiety, 6H), 1.98 and 2.03 (2s, 3H, CH_3 amide), 2.05 (s, 3H, CH_3 ester), 3.26 – 3.34 (m, 2H, CH_2-NH), 4.06 – 4.15 (m, 2H, CH_2O), 5.8 (bs, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.70 and 20.85 (CH3 amide), 22.93 (CH3 ester), 29.30 (CH2), 29.39 (CH2), 36.11 (CH2), 36.42 (CH2), 36.68 (CH), 36.76 (CH), 40.85 (CH2), 41.25 (CH), 42.21 (CH), 49.78 (CH), 49.81 (CH), 65.20 (CH2), 170.66 (CO, ester), 171.24 and 175.60 (CO, amide).

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