Electronic Supplementary Material (ESI) for Green Chemistry.

New renewably-sourced polyesters from limonene-derived monomers

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Supplementary Information

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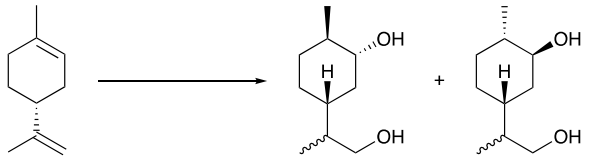
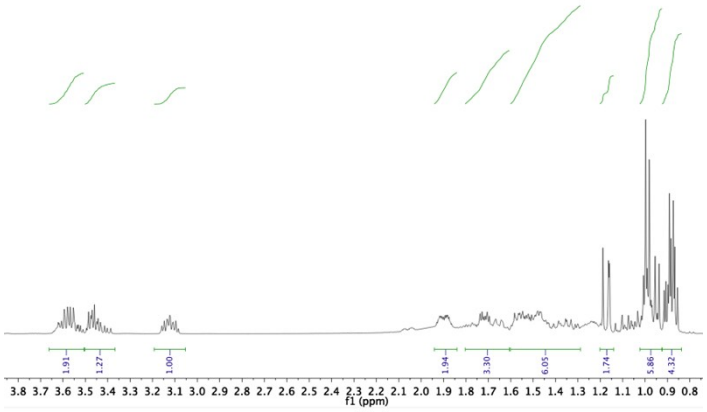
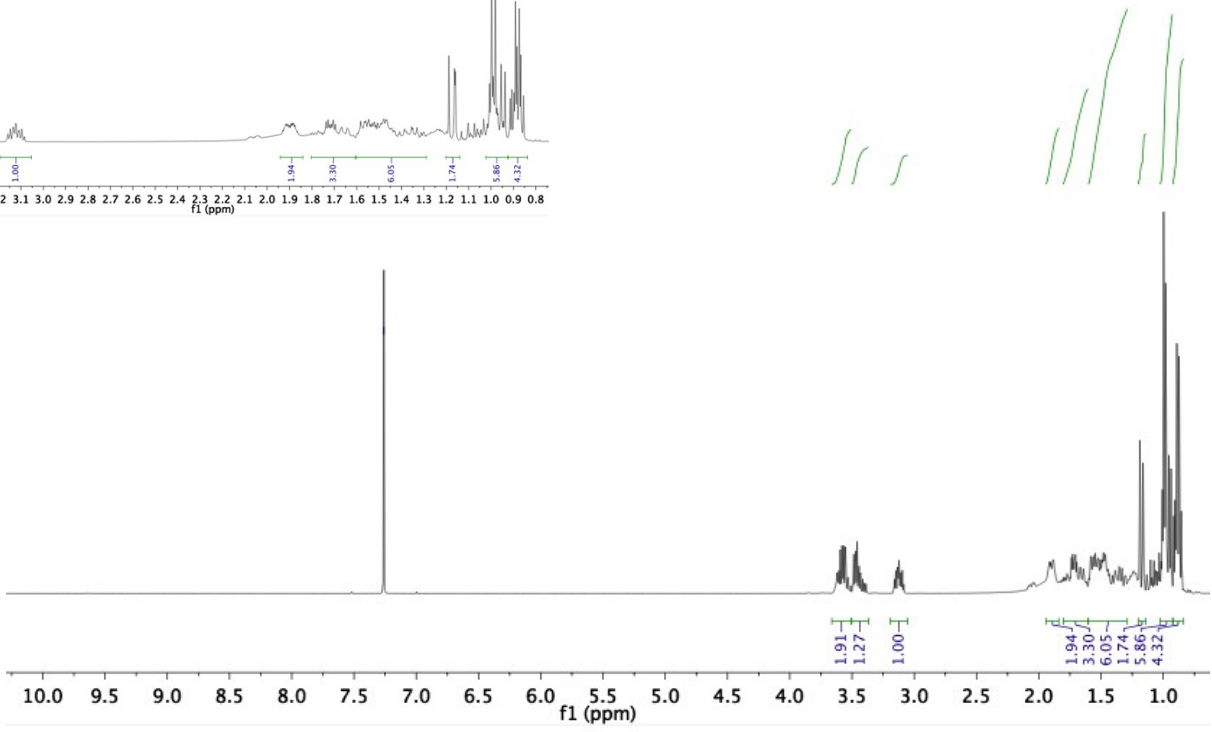
1. Experimental Procedures

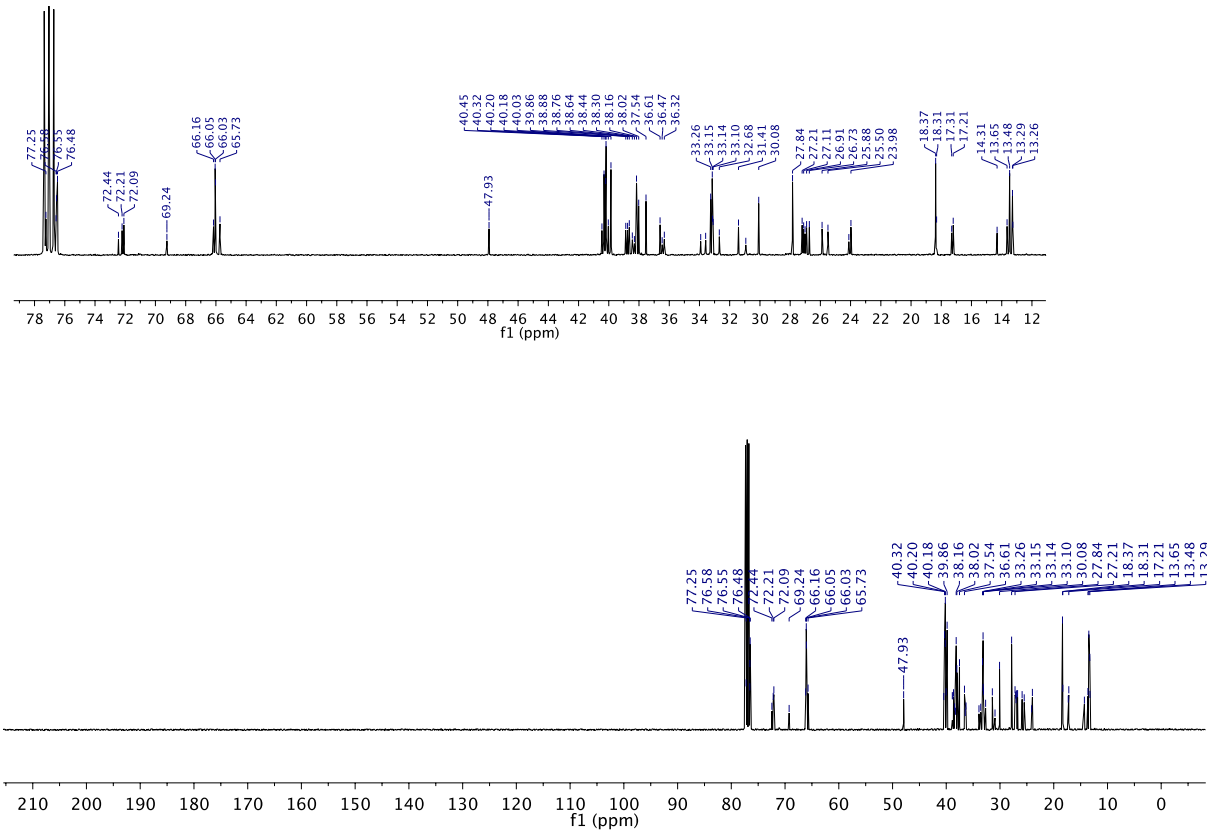
Synthesis of 2a and 2b



1 2a 2b



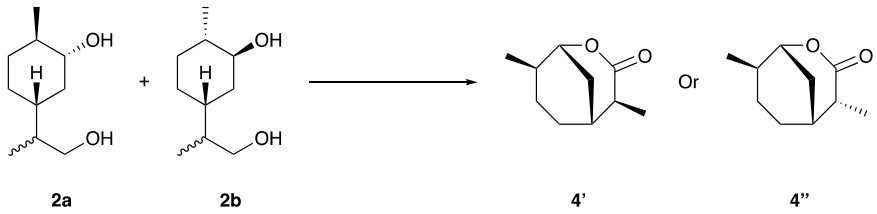




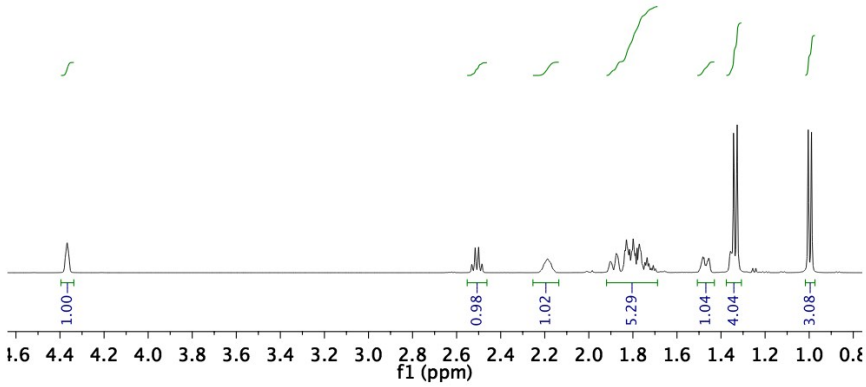
FTIR (ATR) ν_{max} 3604, 3449, 2940, 2867, 1653, 1183; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.67 – 3.54 (m), 3.53 – 3.37 (m), 3.19 – 3.07 (m), 1.96 – 1.85 (m), 1.81 – 1.62 (m), 1.61 – 1.29 (m), 1.20 – 1.15 (m), 1.03 – 0.93 (m), 0.93 – 0.85 (m); **HRMS** (ESI) *m/z* calculated for $C_{10}H_{20}NaO_2$ $[M + Na]^+$ 195.1361 found 195.1366.

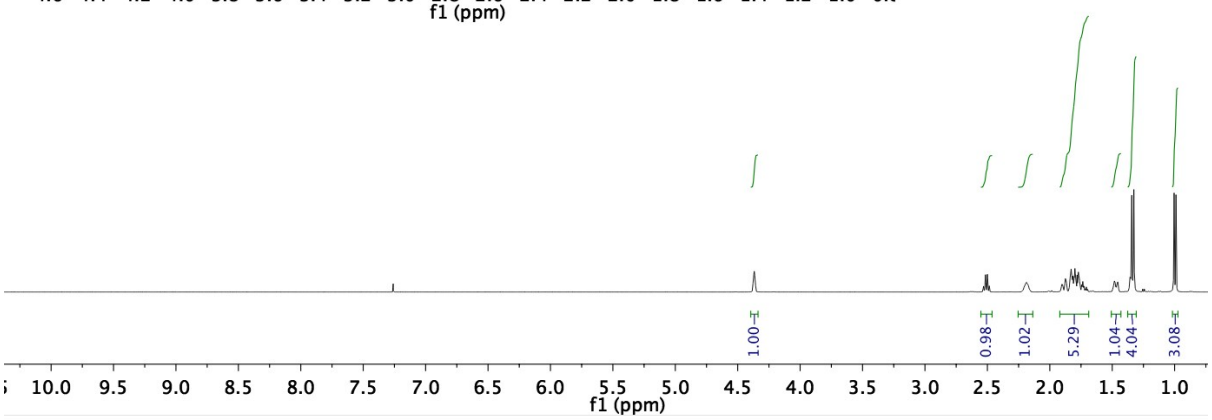
Synthesis of 4

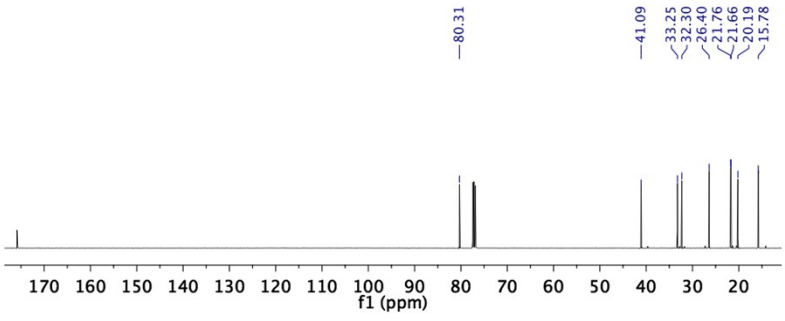
(1*R*,5*R*,8*R*)-4,8-dimethyl-2-oxabicyclo[3.3.1]nonan-3-one (4)

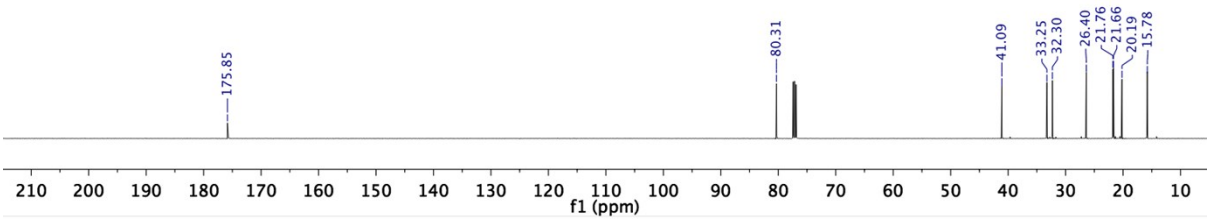


2a **2b** **4'** **4''**







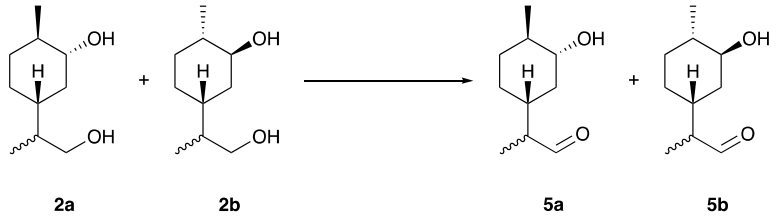


A small sample of the epimers **4'** and **4''** was cooled to -20 °C to induce precipitation of **4'** or **4''** (unconfirmed) as a single diastereomer for analytical purposes (reported).

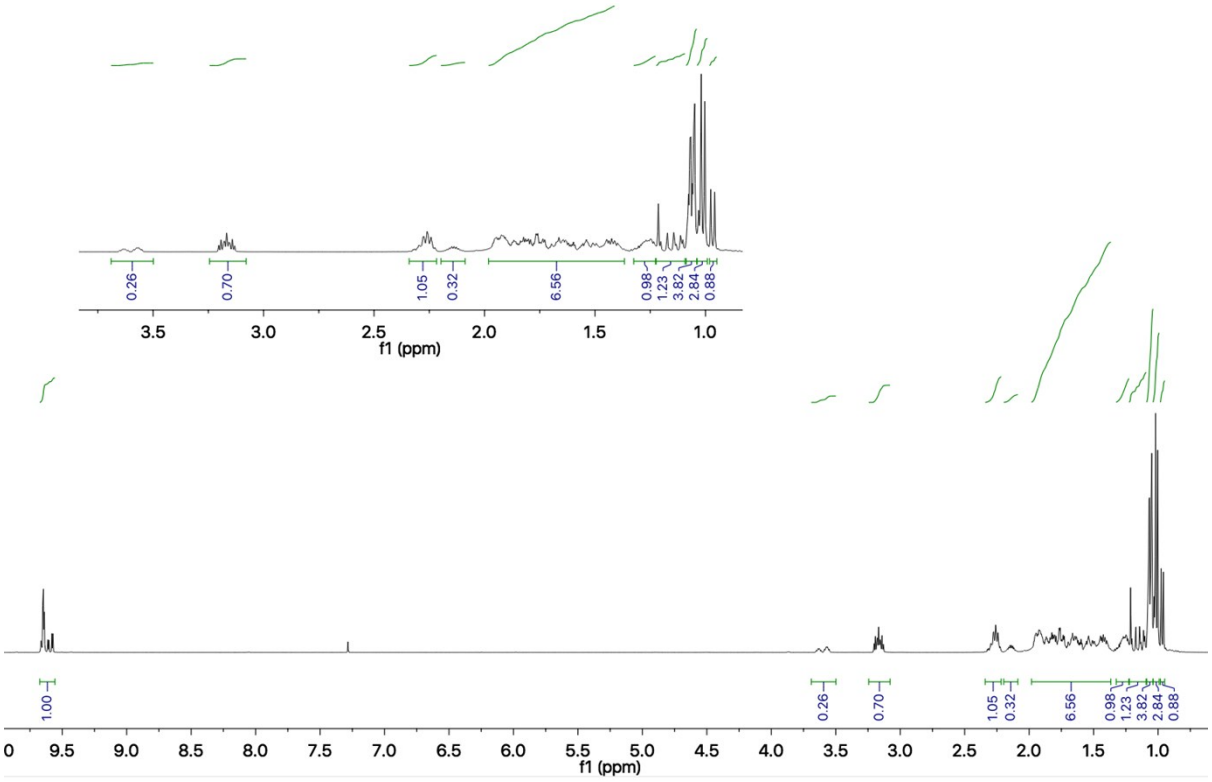
FTIR (ATR) ν_{max} 3248, 2970, 2924, 2865, 2846, 1698; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 4.50 – 4.19 (m, 1H), 2.51 (qd, *J* = 7.7, 0.7 Hz, 1H), 2.24 – 2.10 (m, 1H), 1.93 – 1.85 (m, 1H), 1.85 – 1.69 (m, 4H), 1.52 – 1.43 (m, 1H), 1.37 – 1.31 (m, 1H), 1.34 (dd, *J* = 7.7, 1.0 Hz, 3H), 1.00 (d, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 175.7, 80.2, 41.0, 33.2, 32.2, 26.3, 21.7, 21.6, 20.1, 15.7. **HRMS** (ESI) *m/z* calculated for $C_{10}H_{16}NaO_2$ $[M + Na]^+$ 191.1048 found 191.1042.

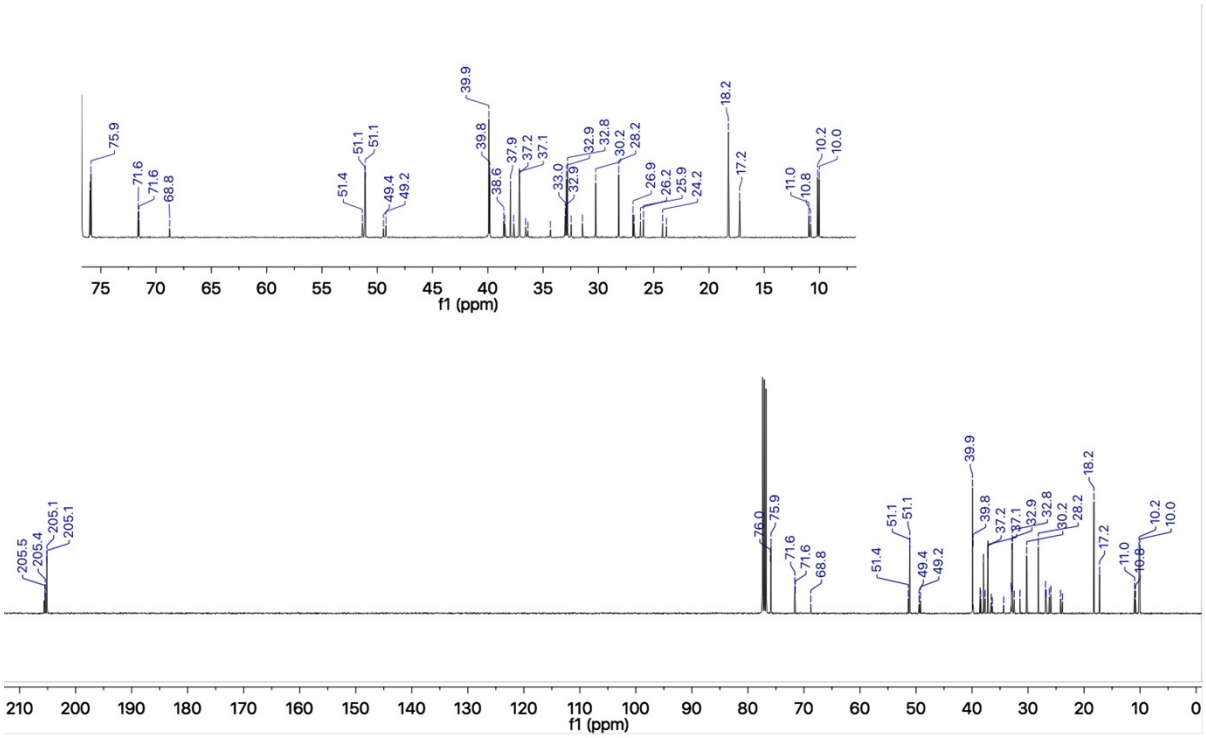
Synthesis of 5a and 5b

2-((1*R*,3*R*,4*R*)-3-hydroxy-4-methylcyclohexyl)propanal (5a) and 2-((1*R*,3*S*,4*S*)-3-hydroxy-4-methylcyclohexyl)propanal (5b)



2a **2b** **5a** **5b**

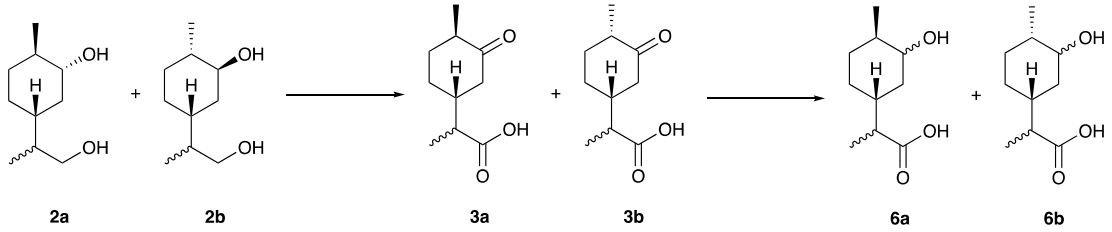




FTIR (ATR) ν_{max} 3320, 2953, 2922, 2871, 1714; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.69 – 9.55 (m), 3.70 – 3.49 (m), 3.23 – 3.11 (m), 2.34 – 2.20 (m), 1.99 – 1.69 (m), 1.70 – 1.36 (m), 1.33 – 1.19 (m), 1.17 – 1.10 (m), 1.09 – 1.04 (m), 1.03 – 0.99 (m), 0.97 (d, *J* = 7.0 Hz); ^{13}C NMR data are reported for the major diastereomer **5a ^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 205.2, 76.0, 51.2, 40.0, 39.9, 37.2, 32.9, 28.3, 18.3, 10.2; **HRMS** (ESI) *m/z* calculated for $C_{10}H_{18}NaO_2$ $[M + Na]^+$ 193.1204 found 193.1201

Synthesis of 6

Method 1 – Global oxidation/ketone reduction



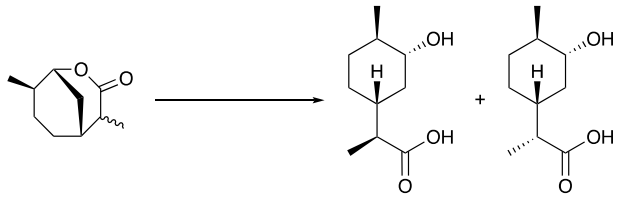
2a **2b** **3a** **3b** **6a** **6b**

CrO_3 (10 g, 100 mmol) was dissolved in H_2SO_4 (10 mL), the resulting solution was carefully added to H_2O (30 mL) cooled to 0 ^oC. This solution (3.83 mL, 9.57 mmol) was added dropwise to a solution of **2a** and **2b** (500 mg, 2.9 mmol) in acetone (30 mL) at 0 ^oC and the resulting red solution was stirred (20 min). The reaction mixture was cooled to 0 ^oC and quenched with 2-propanol until the red colour disappeared and a green colour persisted. The reaction mixture was filtered and the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (15 mL) and washed with water (3 x 10 mL), $NaCl_{(aq)}$ (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to yield the diastereomers **3a** and **3b** as a pale yellow oil (530 mg, 2.9 mmol, quantatative) that was used without further purification.

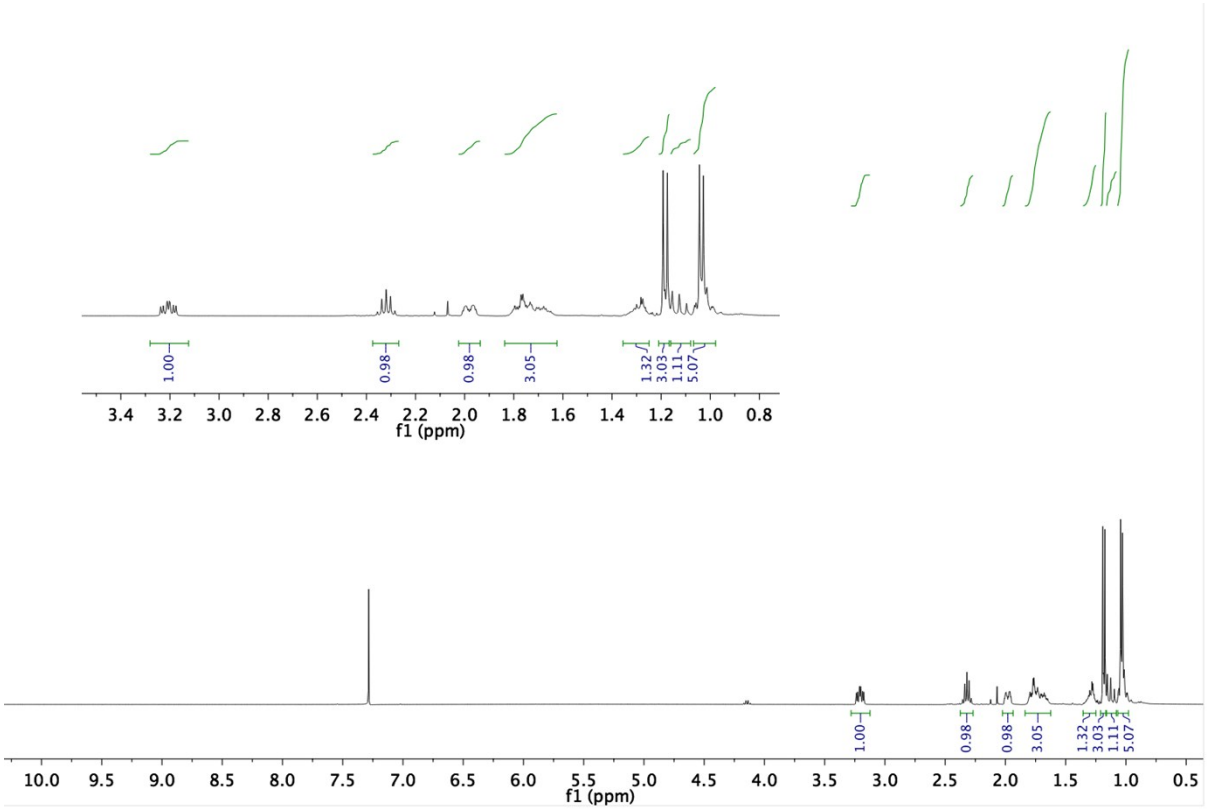
MeOH (30 mL) was cooled to 0 ^oC and $NaBH_4$ (462 mg, 12.23 mmol) was added in portions. A solution of **3a** and **3b** (530 mg, 2.9 mmol) in MeOH (5 mL) was added dropwise and the resulting mixture was stirred (30 min). The reaction was quenched with water (10 mL) and the MeOH removed under reduced pressure. CH_2Cl_2 (20 mL) was added to the residue, then the aqueous was neutralised with $HCl_{(aq)}$ (2 M) and extracted into CH_2Cl_2 (2 x 20 mL). The organic extracts were combined and washed with $NaCl_{(aq)}$ (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to yield **6** as a mixture of diastereomers as a pale yellow oil (202 mg, 1.10 mmol, 38%).

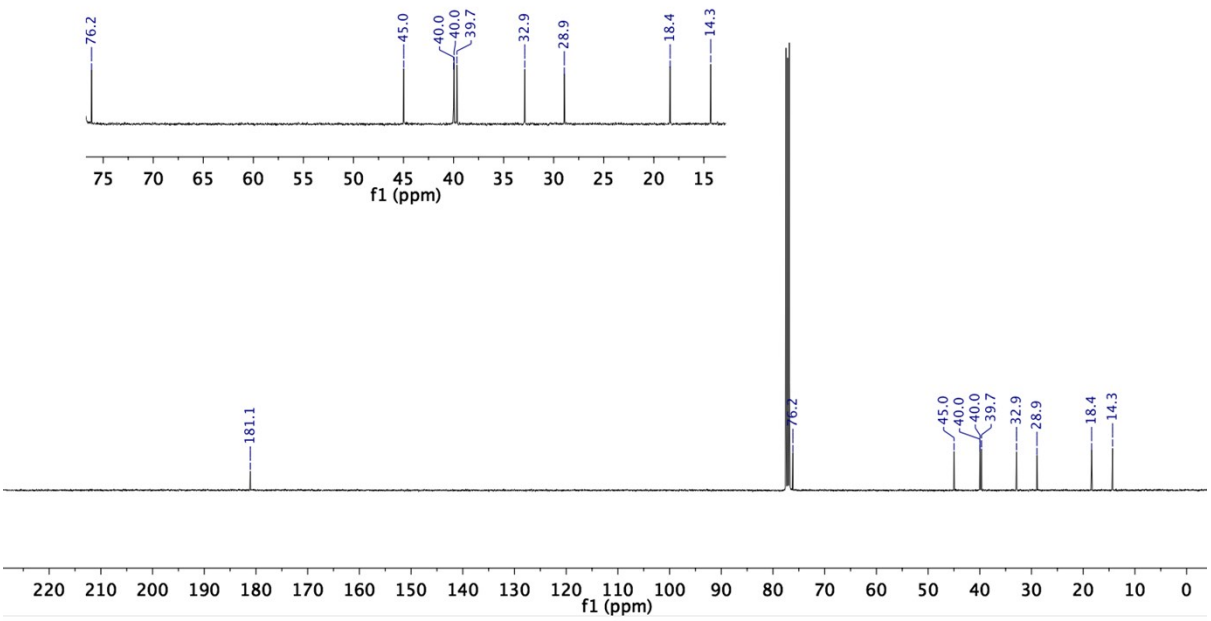
Method 2 – Hydrolysis of the lactone 4

(*S*)-2-((1*R*,3*R*,4*R*)-3-hydroxy-4-methylcyclohexyl)propanoic acid (6a') and (*R*)-2-((1*R*,3*R*,4*R*)-3-hydroxy-4-methylcyclohexyl)propanoic acid (6a'')



4 6a' 6a''



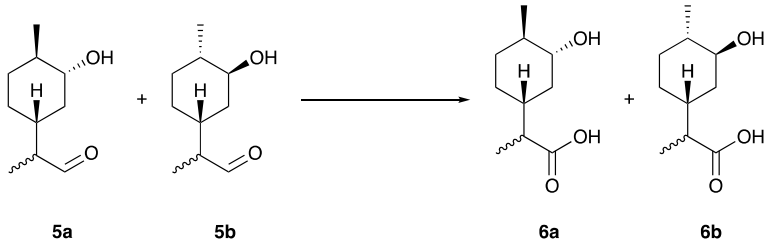


To a solution of **4** (927 mg, 5.52 mmol) in THF (80 mL) was added $NaOH_{(aq)}$ (79.8 mL, 79.8 mmol, 1 M), the reaction mixture was heated to reflux and stirred (18 h). The THF was removed under reduced pressure then the aqueous solution was acidified with $HCl_{(aq)}$ (2 M) and extracted into EtOAc (3 x 30 mL). The organic extracts were combined, washed with $NaCl_{(aq)}$ (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure to yield a mixture of epimers **6a'** and **6a''** as a brown oil (1.01 g, 5.43 mmol, 98%). Recrystallisation from hot EtOAc to yield a single diastereomer **6a'** or **6a''** as a pale brown solid (reported)

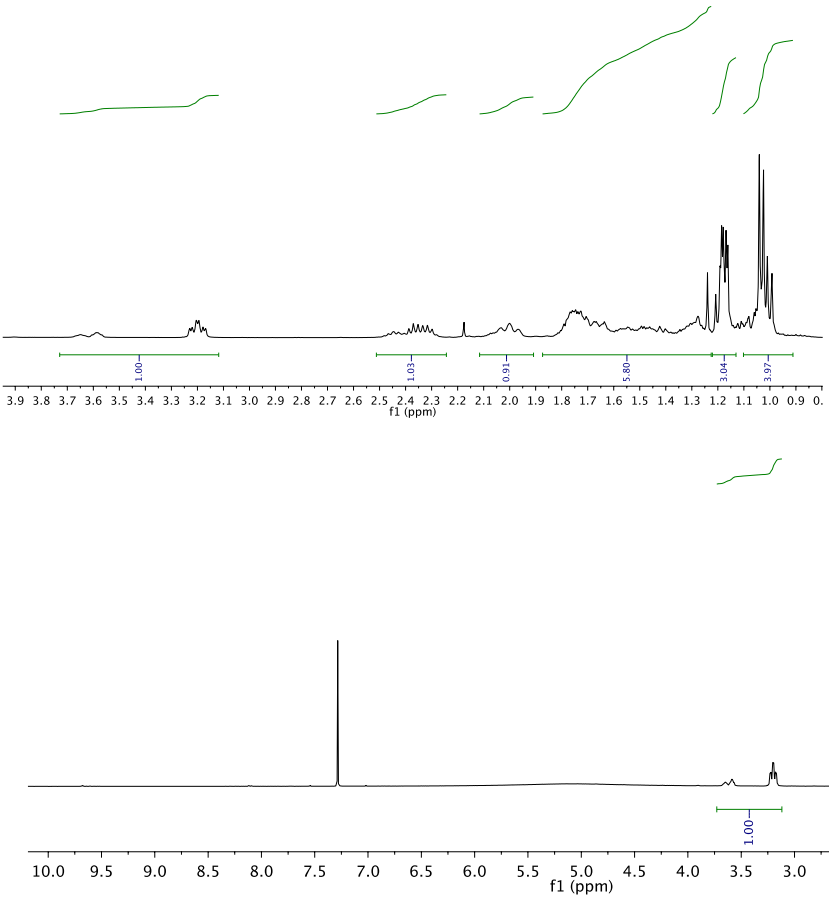
m.p 125 ^{o}C; **FTIR** (ATR) ν_{max} 3239, 2991, 2934, 2538, 1677, 1262 ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.21 (app ddd, *J* = 10.9, 9.7, 4.2 Hz, 1H), 2.32 (app p, *J* = 7.1 Hz, 1H), 2.03 – 1.93 (m, 1H), 1.84 – 1.71 (m, 2H), 1.71 – 1.63 (m, 1H), 1.35 – 1.23 (m, 1H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.16 – 1.08 (m, 1H), 1.07 – 0.98 (m, 5H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 181.0, 76.1, 45.0, 40.0, 39.9, 39.7, 32.8, 29.0, 18.4, 14.3. **HRMS** (ESI) *m/z* calculated for $C_{10}H_{18}NaO_3$ $[M + Na]^+$ 209.1154 found 209.1146.

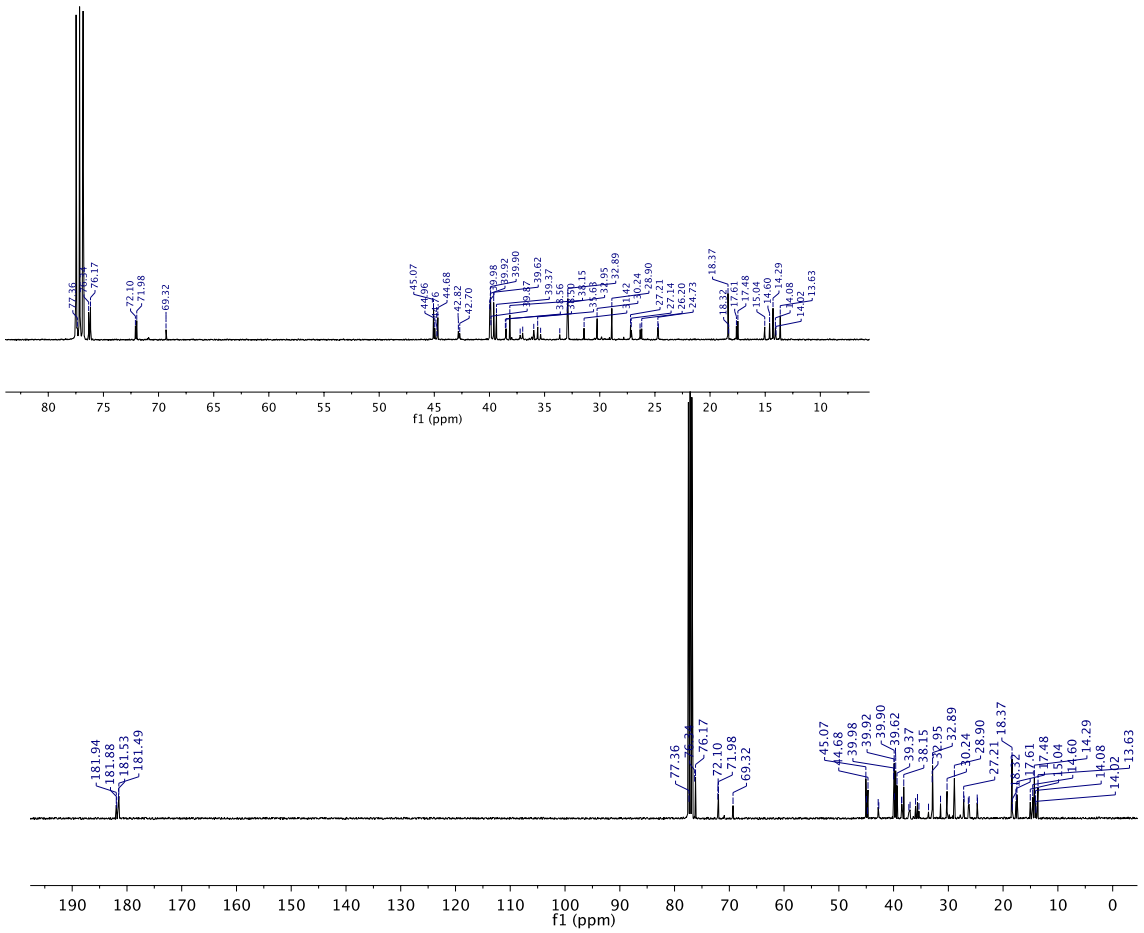
Method 3 – Pinnick oxidation of the aldehyde 5

2-((1*R*,3*R*,4*R*)-3-hydroxy-4-methylcyclohexyl)propanoic acid (6a) and
2-((1*R*,3*S*,4*S*)-3-hydroxy-4-methylcyclohexyl)propanoic acid (6b)



5a **5b** **6a** **6b**

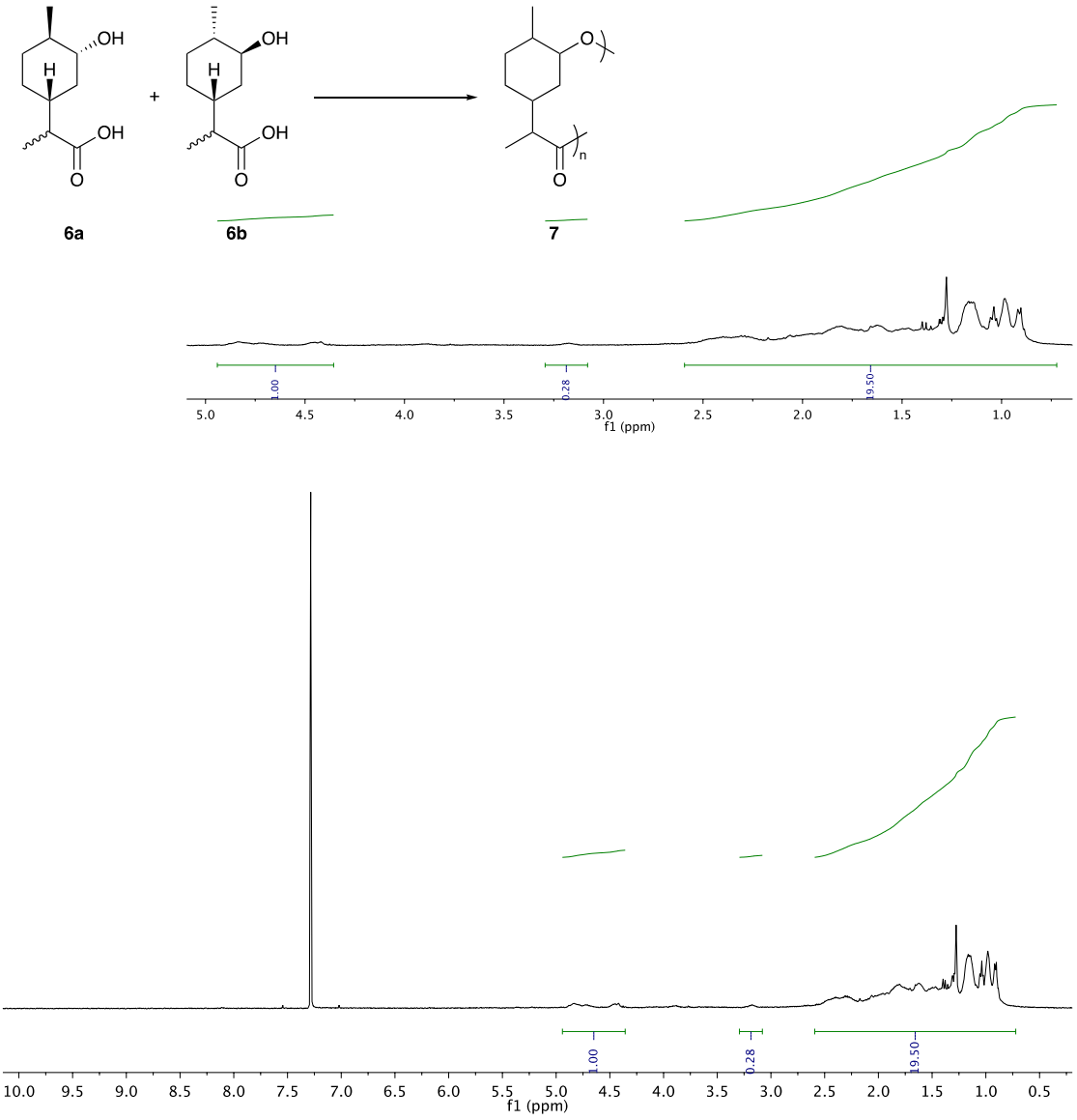




To a solution of **5a** and **5b** (3:1) (3 g, 17.5 mmol) in ^{t}BuOH/H_2O (2:1, 80 mL) was added NaH_2PO_4 (8.19 g, 52.5 mmol) and the resulting solution was cooled to 0 ^{o}C. H_2O_2 (6.83 mL, 87.5 mmol, 30% w/v in H_2O) was added, followed by $NaClO_2$ (11.87 g, 105 mmol, purity assumed to be 80%) in portions over 45 min. The reaction was allowed to stir at 0 ^{o}C (30 min) and then extracted into EtOAc (80 mL). The organic extract was washed with H_2O (5 x 50 mL), $NaCl_{(aq)}$ (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to yield the the four diastereomers **6a** and **6b** as a white semi-solid. (2.2 g, 11.82 mmol, 68%).

FTIR (ATR) ν_{max} 3437, 2935, 2873, 2567, 1702, 1238; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.23 (br s), 3.74 – 3.45 (m), 3.17 (app td, *J* = 10.4, 4.2 Hz), 2.48 – 2.22 (m), 2.03 – 1.90 (m), 1.80 – 1.60 (m), 1.32 – 1.19 (m), 1.20 – 1.11 (m), 1.06 – 0.93 (m); **HRMS** (ESI) *m/z* calculated for $C_{10}H_{18}NaO_3$ $[M + Na]^+$ 209.1154 found 209.1146.

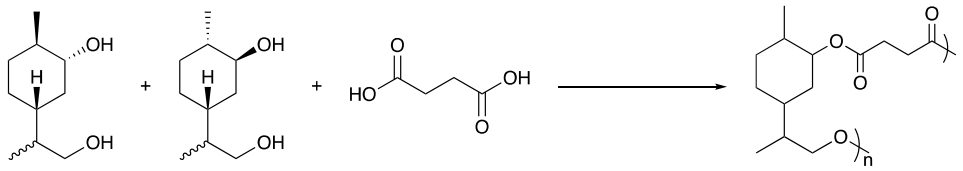
Synthesis of 7



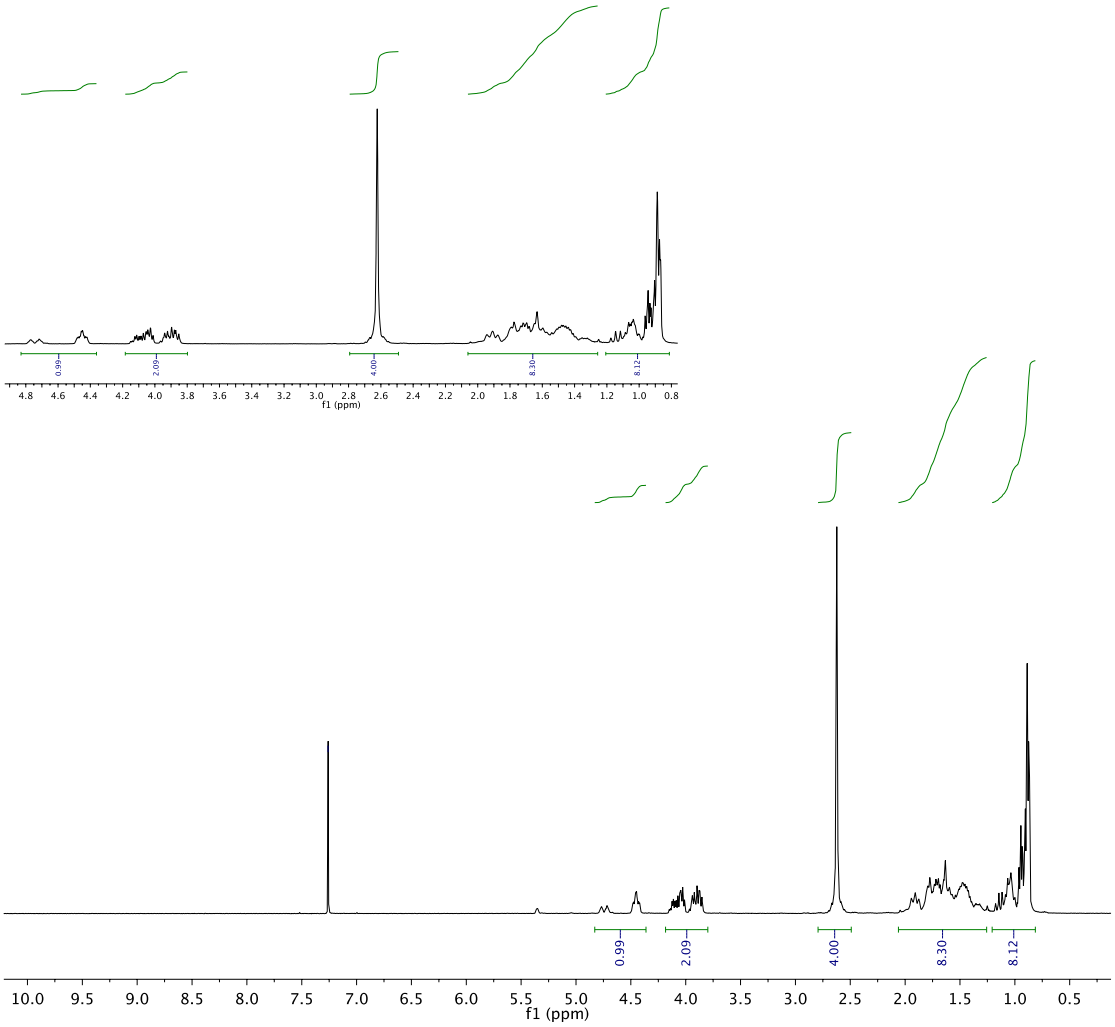
6a and **6b** (3:1) (500 mg, 2.68 mmol) and $Sn(oct)_2$ (8.5 µL, 1 mol%) were added to a flame dried flask under a flow of N_2, which was heated to either 120 or 180 ^oC and stirred for the required time period. The temperature was then set to 180 ^oC and the system put under vacuum for 24 h. The polymerisation was stopped by cooling to -5 ^oC and the resulting polymer dried under vacuum for 24 h.

FTIR (ATR) ν_{max} 3459, 2932, 1772, 1722, 1457, 1168; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.92-4.32 (m), 3.24-3.08 (m), 2.55-0.75 (m).

Synthesis of 10



2a **2b** **9** **10**



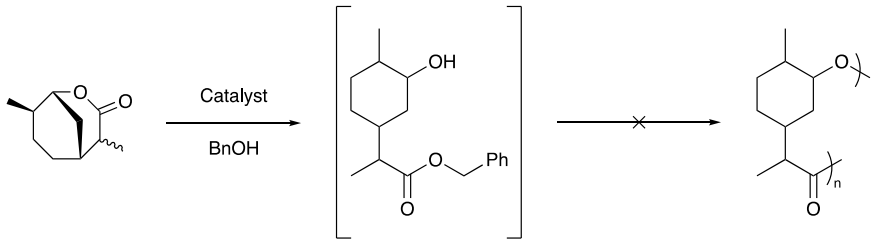
FTIR (ATR) ν_{max} 3430, 2932, 2878, 1728, 1454, 1187; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.81-4.40 (m, 1H), 4.16-3.84 (m, 2H), 2.62 (s, 4H), 1.96-1.26 (m, 8H), 1.20-0.84 (m, 8H).

Attempted degradation of 10 in buffered solutions

For hydrolytic degradation studies **10** (30 mg) was weighed into a vial and solubilised in CH_2Cl_2 the sample was then dried under vacuum at 40 ^oC to a constant weight to create a thin film of **10**. Buffered solutions (3 mL) of the appropriate pH were added. Parallel experiments were carried out with samples immersed in citric acid buffer (pH 2.5), sodium phosphate buffer (pH 7) and sodium carbonate buffer (pH 10) at a temperature of 60 ^oC. Vials were sealed to avoid partial evaporation, and after the fixed period of time the samples were rinsed and dried to constant weight.

2. Investigations into the ROP of lactone 4

Table S1: *Investigations into the ROP of lactone* ***4****.*



4 **8** **7**

Entry	Catalyst	Cat / mol%	BnOH / mol%	Concentration	Time	Temp / ºC	Result
1	$HCl.Et_2O$	1.80	0.6	0.4 M	4 days	25	No reaction
2	$HCl.Et_2O$	1.80	0.6	0.4 M	7 days	100	No reaction
3	$Sn(oct)_2$	0.20	2	Neat	7 days	100	No reaction
4	$Sn(oct)_2$	1	2	Neat	1 month	120	No reaction
5	$Sn(OTf)_2$	0.04	1.2	Neat	6 days	25	No reaction
6	$Sc(OTf)_3$	0.04	1.2	Neat	6 days	25	No reaction
7	$Sc(OTf)_3$	10	1	0.9 M	6 months	25	**8**
8	TBD	10	1	Neat	6 months	25	**8**
9	TBD	10	1	Neat	7 days	0	**8**
10	TBD	10	1	Neat	7 days	120	**8**
11	TBD	100	1	Neat	6 months	25	**8**
12	DABCO	10	N/A	Neat	4 days	25	No reaction
13	DABCO	10	N/A	Neat	4 days	100	No reaction

Initially, Brønsted acid catalysis was investigated under conditions reported by Lou *et al.*[1] (Entries 1 and 2); ^{1}H NMR analysis indicated that the lactone **4** remained intact. Next, $Sn(oct)_2$ was employed using conditions reported by Cooper *et al*.[2] (Entry 3); after 7 days, the lactone **4** remained intact. The reaction was subsequently repeated at a higher temperature however no change could be observed, even after 1 month (Entry 4). $Sn(OTf)_2$ and $Sc(OTf)_3$ were also investigated at 25 ^{o}C (Entries 3-7); the lactone **4** remained intact in each case except for when $Sc(OTf)_3$ was employed at 10 mol% as a solution in toluene (Entry 7). In the latter entry, ^{1}H NMR analysis indicated formation of **8** however after 6 months reaction time no evidence of propagation could be obtained. TBD was also investigated at a variety of temperatures and times however only initiation could be observed (Entries 8-11). When DABCO was employed at 25 and 100 ^{o}C (Entries 12 and 13) the lactone **4** again remained intact.

3. DFT Studies

DFT computational details

All calculations were performed using the Gaussian09 suite of codes (revision D.01).[1] Geometries were fully optimised without any symmetry or geometry constraints. The nature of all the stationary points as minima was verified by calculations of the vibrational frequency spectrum, and characterised by no imaginary mode. Only the intermediates of lowest free enthalpy found are reported here. Free enthalpies were calculated within the harmonic approximation for vibrational frequencies.

Geometries optimisations were carried out using the M06-2X functional developed by Trulhar and coworkers for applications involving main-group thermochemistry and noncovalent interactions (relevant to the growth of macromolecules), and parametrised only for non-metals.[2] The calculations were all carried out using the 6-311++g(2d,p) basis set, and a temperature of either 298.15 or 453.15 K (to model respectively the hypothetical ring-opening of lactone **4** at 25 °C, and the polycondensation of **6a** and **6b** at 180 °C). Self-consistent reaction-cavity continuum

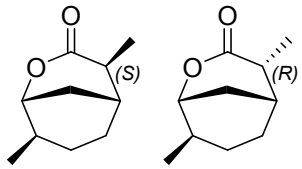
solvation model (cpcm) was used with ethylacetate as the solvent to model solvation in monomers and in the resulting polyester.[3]

Full coordinates for all the stationary points, together with computed Gibbs free energy and vibrational frequency data, are available *via* the corresponding Gaussian 09 output files, stored in the digital repository: DOI: 10.6084/m9.figshare.6957368 (private link for review purposes: https://figshare.com/s/50a0aa5abec69022fd1a).

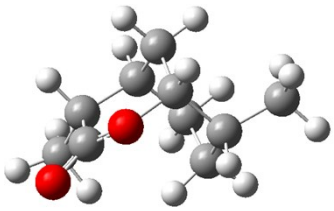
DFT calculations related to the formation and to the ring-opening of lactone 4

Lowest energy conformation of lactone 4

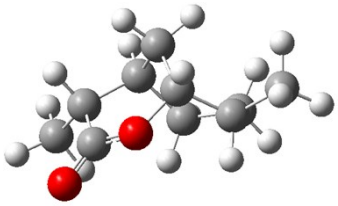
Table S2. Computed free Gibbs energies at the rM06-2X/6-311++g(2d,p)/cpcm=ethylethanoate/298K level of theory, for various conformers of lactone **4**



Possible stereochemistry of **4**



Structure **4-1**
(*R*-Chair configuration)



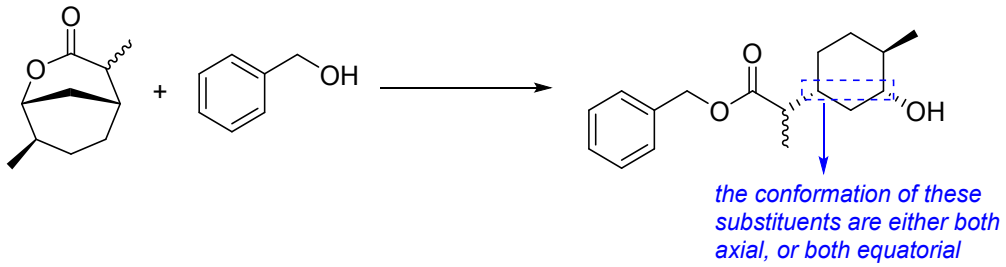
Structure **4-2**
(*R*-Boat configuration)

Structure	***Stereochemistry* (α to C(=O))**	***Hydrocarbon ring conformation***	***G (Hartree)***	***ΔG (kcal mol^{-1})***
4-1	*R*	Chair	-540.89703	+0.0 (reference)
4-2	*R*	Boat	-540.889565	+4.7
4-3	*S*	Chair	-540.896484	+0.3
4-4	*S*	Boat	-540.889649	+4.6

Ring-opening reaction of lactone 4

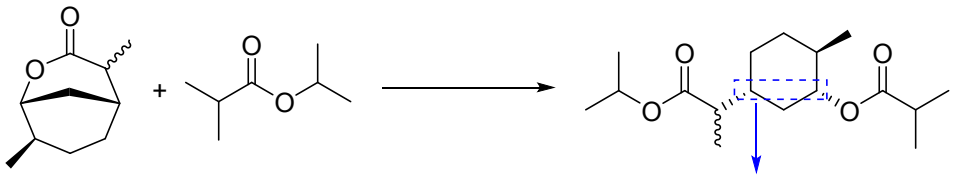
The structures of **4** were taken as the lowest calculated in Table 3 (structures 4-1 and 4-3 for stereoisomer *R* and *S*, respectively).

Table S3. Computed free Gibbs energies at the rM06-2X/6-311++g(2d,p)/cpcm=ethylethanoate/298.15K level of theory, for the ring-opening of lactone **4** by benzyl alcohol.



Structure	***Conformation of ring substituents***	***G (Hartree)***	***ΔG (kcal mol^{-1})***
Benzyl alcohol	-	-346.632287	
(*R*)-**4** (4-1)	-	-540.89703	
(*S*)-**4** (4-3)	-	-540.896484	
Reference for (R)-4	-	-887.529317	*+0.0*
Benzyl ester of ring-opened (*R*)-4	axial	-887.521039	+5.2
Benzyl ester of ring-opened (*R*)-4	equatorial	-887.527113	+1.4
Reference for (S)-4	-	-887.528771	*+0.0*
Benzyl ester of ring-opened (S)-4	axial	-887.519581	+5.8
Benzyl ester of ring-opened (*S*)-4	equatorial	-887.525055	+2.3

Table S4. Computed enthalpies at the rM06-2X/6-311++g(2d,p)/cpcm=ethylethanoate/298.15K level of theory, for the isodesmic reactions between isopropylisopropanoate and lactone **4**.



based on previous calculations, geometries were optimised with these substituents in equatorial or axial position

Structure	***Ring substituents position***	***H (Hartree)***	***G (Hartree)***	***ΔH (kcal mol^{-1})***	***ΔG (kcal mol^{-1})***
Isopropyl-isopropanoate		-425.378255	-425.426797		
(*R*)-**4** (4-1)		-540.849962	-540.89703		
(*S*)-**4** (4-3)		-540.848921	-540.896484		
Reference for (R)-4		-966.228217	-966.323827	*+0.0*	*+0.0*
Diester from (*R*)-4	Equatorial	-966.2409	-966.319751	-8.0	+2.6
Diester from (*R*)-4	Axial	-966.235765	-966.31443	-4.7	+5.9
Reference for (S)-4		-966.227176	-966.323281	*+0.0*	*+0.0*
Diester from (*S*)-4	Equatorial	-966.239354	-966.318842	-7.6	+2.8
Diester from (*S*)-4	Axial	-966.236292	-966.314569	-5.7	+5.5

Reaction of lactonisation of 6a into 4

For simplicity, calculations were only carried out on the stereoisomers with an (*R*)-configuration α to the carbonyl groups (i.e. **6a'** or **4'**).

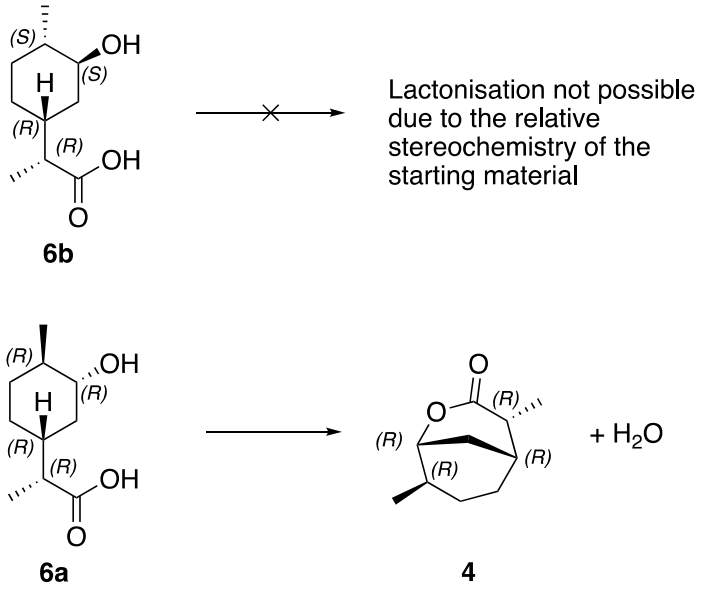


Table S5. Computed free Gibbs energies at the rM06-2X/6-311++g(2d,p)/cpcm=ethylethanoate/453.15K level of theory, for the lactonisation of **6a** into **4**.

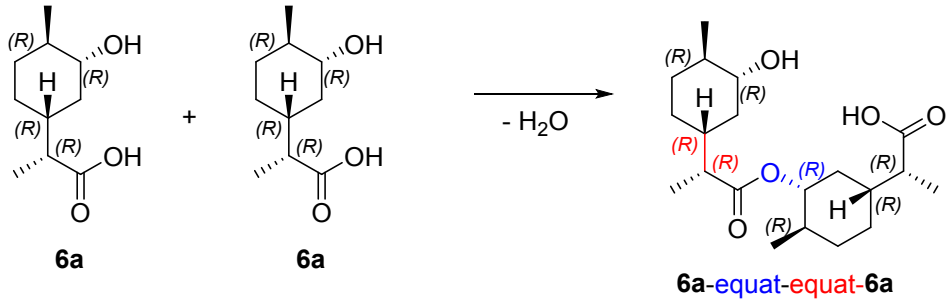
Structure	***Conformation of ring substituents***	***G (Hartree)***	***ΔG (kcal mol^{-1})***
(2-*R*)-**6a**	All equatorial (chair conformation)	-617.349972	+0.0
(2-*R*)-**6a**	All axial (chair conformation)	-617.345053	+3.1
(2-*R*)-**6a**	All axial (boat conformation)	-617.337729	+7.7
H_2O	-	-76.436954	
Reference (2-*R*)-6a – H_2O	-	-540.913018	*+0.0*
(*R*)-**4** (4-1 from Table S2)	-	-540.926242	*-8.3*

Reaction of condensation of 6a and 6b

For simplicity, calculations were only carried out on the stereoisomers with an (*R*)-configuration α to the carboxylic acid groups i.e. (**6a'** or **6b'**)

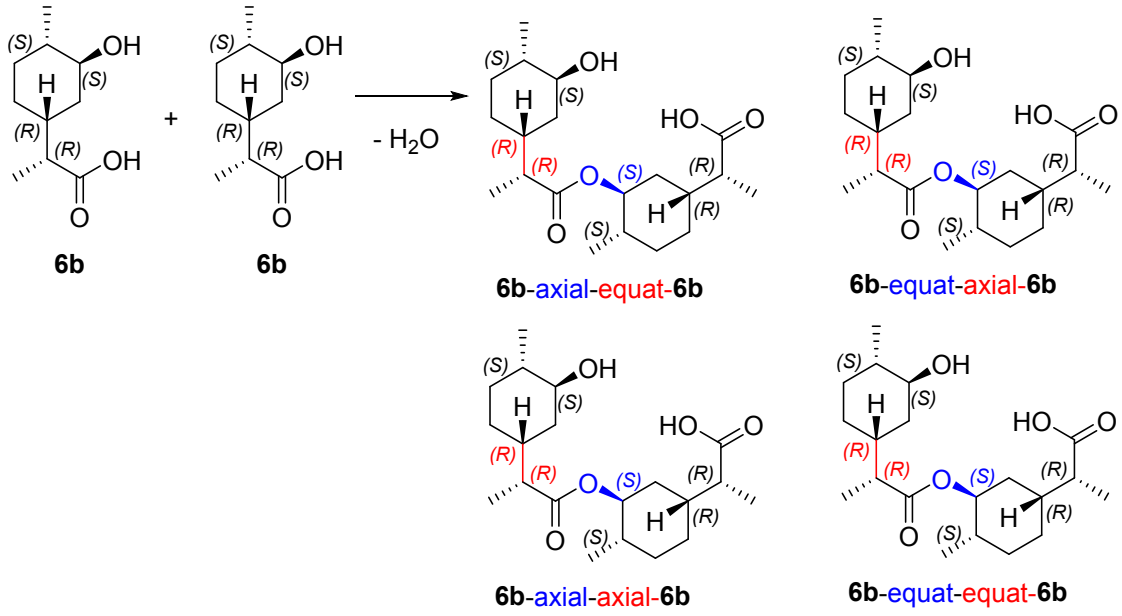
For nomenclature purposes, the polymer chains are considered to grow from the alcohol moiety (i.e. in the direction OH→COOH), and polymers (here dimers) are named Monomer 1-configuration of the acid group of Monomer 1(equatorial/axial)-configuration of the alcohol group of Monomer 2(equatorial/axial)-Monomer 2 (for example **6a-equat-equat-6a**, see below for graphical representation).

*Homopolymerisation of **6a***



The dimer **6a-axial-axial-6a** was not calculated based on steric and energetic considerations (**6a** in boat form, with acid and alcohol groups in axial is not favoured, see Table S5).

*Homopolymerisation of **6b***



*Copolymerisation of **6a** and **6b***

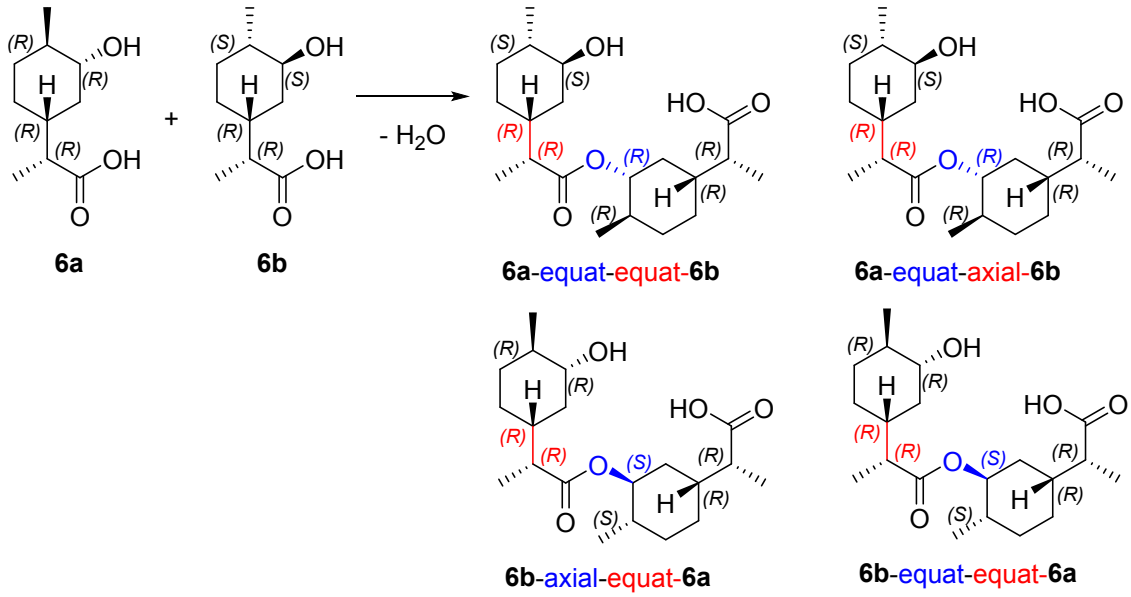


Table S6. Computed free Gibbs energies at the rM06-2X/6-311++g(2d,p)/cpcm=ethylethanoate/453.15K level of theory, for the copolymerisation of **6a** and **6b**

Structure	***G (Hartree)***	***ΔG (kcal mol^{-1})***
(2-*R*)-**6a** (all substituents in equatorial)	-617.349972	+0.0 (Ref)
(2-*R*)-**6a** (all substituents in axial)	-617.345053	+3.1
(2-*R*)-**6b** (alcohol in axial, acid group in equatorial)	-617.348092	+1.2
(2-*R*)-**6b** (alcohol in equatorial, acid group in axial)	-617.346959	+1.9
H_2O	-76.436954	
Reference homopolymerisation of (2-*R*)-**6a** (2 × (2-*R*)-**6a** – H_2O)	-1158.26299	*+0.0*
6a-equat-equat-6a	-1158.264488	-0.9
Reference homopolymerisation of (2-*R*)-**6b** (2 × (2-*R*)-**6b** – H_2O)	-1158.25923	*+0.0*
6b-axial-equat-6b	-1158.259696	-0.3
Reference homopolymerisation of (2-*R*)-**6b** (2 × (2-*R*)-**6b** – H_2O)	-1158.256964	*+0.0*
6b-equat-axial-6b	-1158.258235	-0.8
Reference homopolymerisation of (2-*R*)-**6b** ((2-*R*)-**6b**+(2-*R*)-**6b** – H_2O)	-1158.258097	*+0.0*
6b-axial-axial-6b	-1158.26093	-1.8
6b-equat-equat-6b	-1158.261062	-1.9
Reference copolymerisation of (2-*R*)-**6b** and(2-*R*)-**6a** ((2-*R*)-**6a**+(2-*R*)-**6b** – H_2O)	-1158.26111	*+0.0*
6a-equat-equat-6b	-1158.262504	-0.9
6b-axial-equat-6a	-1158.262652	-1.0
Reference copolymerisation of (2-*R*)-**6b** and(2-*R*)-**6a** ((2-*R*)-**6a**+(2-*R*)-**6b** – H_2O)	-1158.259977	*+0.0*
6a-equat-axial-6b	-1158.261065	-0.7
6b-equat-equat-6a	-1158.266156	-3.9

References

1 X. Lou, C. Detrembleur and R. Jérôme, *Macromolecules*, 2002, **35**, 1190–1195.

2 B. M. Cooper, D. Chan-Seng, D. Samanta, X. Zhang, S. Parelkar and T. Emrick, *Chem. Commun.*, 2009, 815–817.

3 M. J. Frisch, G. W. Frucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. Montgomery, J. A.;, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford CT, 2009.

4 Y. Zhao and D. G. Truhlar, *Theoretical Chemistry Accounts*, 2008, **120**, 215-241.

5 (a) G. Scalmani and M. J. Frisch, *The Journal of Chemical Physics*, 2010, **132**, 114110; (b) D. M. York and M. Karplus, *The Journal of Physical Chemistry A*, 1999, **103**, 11060-11079.