SUPPORTING INFORMATION

For

Making mixtures to solve structures: Structural elucidation via combinatorial synthesis

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See the main manuscript for general details.

2-Iodohexane (16) was prepared using a procedure adapted from previous work.[1] PPh_3 (98.8 g, 0.38 mol), imidazole (25.1 g, 0.37 mol) and 2-hexanol (25.2 g, 0.25 mol) were dissolved in CH_2Cl_2 (500 mL) and cooled in an ice-bath. I_2 (94.1 g, 0.37 mol) was added in portions over 1 h. The mixture was stirred for a further 2 h before being poured into pentane (1.5 L), causing formation of copious amounts of precipitate that was removed by filtration though a pad of Celite. The volume of the filtrate was reduced to 500 mL and filtered though a pad of neutral alumina. The residual solvent was removed and the crude product was distilled under reduced pressure (59–61 °C @ ~10 mmHg, [lit.[2] 50.5–51.5 °C @ 12 mmHg]) to give **16** as a colorless liquid (37.4 g, 70%). The product was stored at –10 °C to minimize decomposition. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ (ppm) 0.90 (t, *J* = 6.6 Hz, 3H, H6), 1.23–1.88 (m, 6H, H3–H5), 1.91 (d, *J* = 6.9 Hz, 3H, H1), 4.18 (m, 1H, H2); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ (ppm) 14.09 (CH_3), 21.99 (CH_2), 29.06 (CH_3), 30.85 (CH), 31.98 (CH_2), 42.77 (CH_2); GC–MS: 8.14 min - *m/z* 43 (100%), 55, 57, 85, 127, 141, 155, 169, 183, 212 ($M^{\bullet+}$, 0.08%). The data are consistent with those reported.[3]

Methyl 2,4-dimethyloctanoate (19).[4] $Ni(OAc)_2.4H_2O$ (4.72 g, 19.0 mmol) was added to stirred suspension of BER (56.05 g, 190.6 mmol) in MeOH (600 mL) at 0 °C under argon until H_2 evolution subsided and the solution became black. Freshly distilled methyl methacrylate (193.6 g, 1.92 mol) and 2-iodohexane (20.01 g, 94.3 mmol) were added quickly and the mixture was stirred at 0 °C for 3 h. The reaction mixture was filtered and the resin was thoroughly washed with MeOH. The solvent was removed under reduced pressure and the viscous oily residue was distilled under reduced pressure, giving **19** as a colorless oil (14.4 g, 82%), bp 59–61 °C @ 1.4 mmHg. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.81–0.89 (m, 6H, H8 & C4(CH_3)), 1.02–1.51 (m, 9H, H3/H5–H7 & C2(CH_3), 1.65–1.72 (m, 1H, 4H), 2.46–2.58 (m, 1H, 2H), 3.64 (s, 3H, OCH_3). The ^{1}H NMR data were somewhat different to those reported at 200 MHz[4]; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ (ppm) 14.22 (CH_3), 14.24 (CH_3), 17.2 (CH_3), 18.1 (CH_3), 19.5 (CH_3), 19.7 (CH_3), 23.05 (CH_2), 23.06 (CH_2), 29.16 (CH_2), 29.22 (CH_2), 30.6 (CH), 30.9 (CH), 36.8 (CH_2), 36.9 (CH_2), 37.3 (CH), 37.5 (CH), 41.2 (CH_2), 41.7 (CH_2), 51.5 (CH_3, OMe), 51.6 (CH_3, OMe), 177.7 (C=O), 177.9 (C=O); GC–MS: 15.70 min - *m/z* 43, 55, 57, 69, 73, 88 (100%), 101, 115, 129, 143, 155, 171, 186 ($M^{\bullet+}$, 0.15%); 15.85 min - *m/z* 43, 55, 57, 69, 85, 88 (100%), 101, 115, 129, 143, 155, 171, 186 ($M^{\bullet+}$, 0.26%); HR-EI^+-MS: $C_{11}H_{22}O_2$ requires 186.1620, found 186.1616; IR (thin film): ν (cm^{-1}) 1740 (C=O).

Examination of the distillation residue using GC–MS revealed the presence of the diester dimethyl 2,4-dimethyl-2-(2-methylhexyl)pentanedioate **20** but it was not isolated in pure form, or further characterised: GC–MS: 21.49 min - *m/z* 43, 55, 57, 59, 69, 83, 88, 101, 109, 111, 128 (100%), 139, 156 (98%), 167, 169, 178, 188, 195, 199, 212, 227, 255 ($[M–OMe]^{\bullet+}$, 2.87%); 21.58 min - *m/z* 43, 55, 57, 59, 69, 83, 88, 101, 109, 111, 128 (99%), 139, 156 (100%), 167, 169, 178, 188, 195, 199, 212, 227, 255 ($[M–OMe]^+$, 3.42%).

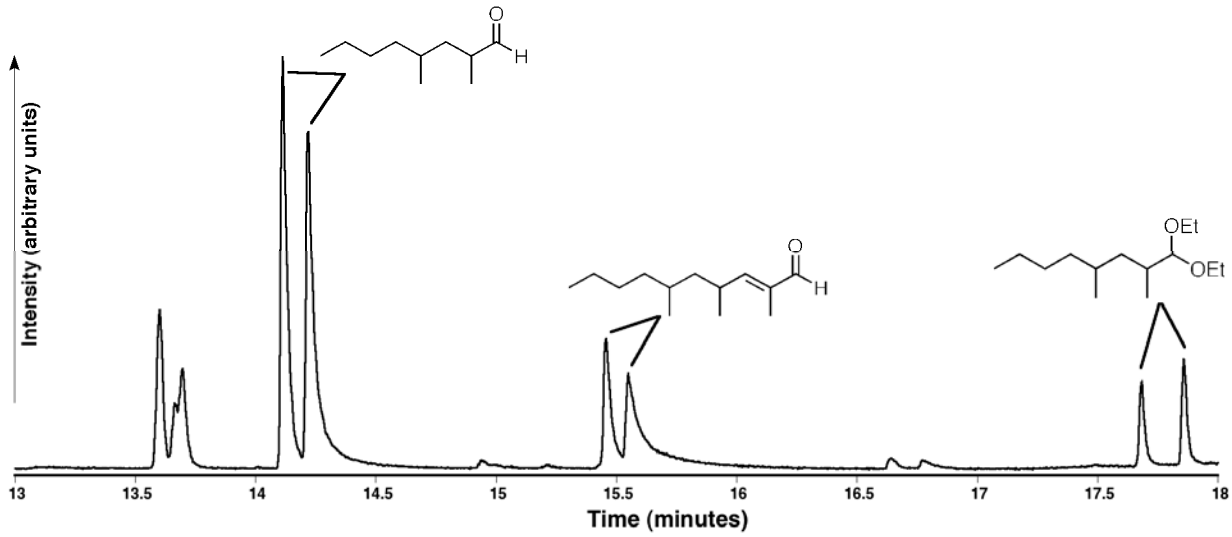
General Conditions for Reaction of 21 with 9. Phosphorane **9** was dried under vacuum for 30 min before being dissolved in the specified solvent (Table S1, ~ 5 mL). Aldehyde **21** was added and the mixture was heated at the indicated temperature for the time shown in table S1. Reactions were monitored by removal of 20 μL and analysis by GC–MS.

Table S1: Conditions investigated for Wittig olefination of 9 with 21 including general results

Entry	9 (g)	21 (g)	solvent	temp (°C)	time	result
1	1.01	0.48	THF	80[(a)]	7 d	no reaction
2	2.00	0.50	THF/H_2O (9:1)	80[(a)]	4 d	trace, (b)
3	0.99	0.46	EtOH	reflux	5 d	minor, (c)
4	0.74	0.31	^{t}BuOH	100	7 d	no reaction
5	0.75	0.23	DMA	100	7 d	no reaction
6	1.02	0.45	toluene	100	6 d	no reaction

(a) reaction performed in a sealed tube (b) Trace acid formation, (c) acetal formation,

Figure S1. Partial GC–MS trace of reaction of **21** with **9** in EtOH (entry 3 in Table S1)



(2-Ethoxy-2-oxoethyl)triphenyl phosphonium bromide (23a) was prepared as previously described,[5] except acetone was used as the solvent in place of ethyl acetate. A solution of PPh_3 (20.13 g, 76.8 mmol) and ethyl bromoacetate (14.03 g, 84.01 mol) in acetone (150 mL) was heated under reflux overnight, resulting in the formation of a white precipitate. The precipitate was filtered, washed with cold acetone and dried under reduced

pressure giving **23a** as a white solid (30.12 g, 91%). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ (ppm) 0.98 (t, *J* = 7.1 Hz, 3H, OEt CH_3), 3.94 (q, *J* = 7.1 Hz, OEt CH_2), 5.35 (d, *J* = 13.9 Hz, 2H, H1) 7.58–7.63 (cm, 6H, ArH), 7.70–7.75 (cm, 3H, ArH), 7.78–7.83 (cm, 6H, ArH); ^{31}P{^{1}H} NMR (242.9 MHz, $CDCl_3$): δ (ppm) 21.23. The ^{1}H-NMR data are slightly different from those reported.[5]

(2-Ethoxy-1-methyl-2-oxoethyl)triphenyl phosphonium bromide (24a) was prepared in a similar manner to that previously described.[6] A solution of PPh_3 (25.0 g, 95.3 mmol) and ethyl 2-bromopropionate (21.0 g, 116 mmol) in acetone (200 mL) was heated under reflux overnight. The solvent was evaporated and the oily residue was dissolved in CH_2Cl_2 and poured into rapidly stirring Et_2O. The resulting precipitate was filtered, washed with cold Et_2O and dried under reduced pressure, giving **24a** as a white solid (39.7 g, 94%). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ (ppm) 0.89 (t, *J* = 7.1 Hz, OEt CH_3), 1.59 (dd, J_1 = 18.4 Hz, J_2 = 7.2 Hz, C1(CH_3)), 3.84–3.96 (cm, 2H, OEt CH_2), 6.45 (cm, 1H, H1), 7.58–7.65 (cm, 6H, ArH), 7.68–7.73 (cm, 3H, ArH), 7.81–7.85 (cm, 6H, ArH); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ (ppm) 12.95 (d, $J_{C\text{-}P}$ = 2.9 Hz, CH_3), 13.52 (CH_3), 36.60 (d, $J_{C\text{-}P}$ = 50.3 Hz, CH), 62.82 (CH_2), 117.53 (d, $J_{C\text{-}P}$ = 86.3 Hz, C_q), 130.20 (d, $J_{C\text{-}P}$ = 12.7 Hz, CH), 134.15 (d, $J_{C\text{-}P}$ = 10.0 Hz, CH), 134.96 (d, $J_{C\text{-}P}$ = 2.4 Hz, CH), 167.76 (d, $J_{C\text{-}P}$ = 1.5 Hz, C_q); ^{31}P{^{1}H} NMR (242.9 MHz, $CDCl_3$): δ (ppm) 28.50 (s).

Diethyl-(2-oxopropyl)phosphonate (12) was prepared[7] and purified[8] as previously described. Freshly distilled chloroacetone (138 g, 1.5 mol), MeCN (500 mL) and acetone (500 mL) were added to a 2 L round-bottomed flask fitted with a 250 mL dropping funnel, argon inlet and mechanical stirrer. The solution was cooled in an ice-bath before addition of KI (248 g, 1.5 mol). The solution was stirred at 0 °C for 15 min before the rapid dropwise addition of freshly distilled triethylphosphite (250 g, 1.5 mol). The mixture was stirred for a further 3 days at room temperature. H_2O (1 L) was added to dissolve the potassium salts and the Me_2CO and MeCN were evaporated. The aqueous solution was transferred to a conical flask and solid Li_2CO_3 was added until the solution pH was 10. The solution was then extracted with CH_2Cl_2/n-hexanes (5:95, 3 x 300 mL). The extract was dried ($MgSO_4$), filtered and the evaporated, giving a colourless liquid (16.3 g), which was shown by GC–MS analysis to be a mixture of $P(OEt)_3$ (8%), $OP(OEt)_3$ (15%), enol phosphonate (65%), phosphonate (2%) and various siloxanes. A second extract from the aqueous solution with CH_2Cl_2 (3 x 300 mL) was treated in the same manner giving a viscous yellow oil (260 g). GC–MS analysis of this fraction revealed the major product to be the desired phosphonate, with traces of the enol phosphate and oligomeric phosphates comprising the major impurities. Careful fraction distillation of the mixture under reduced pressure (92–96 ^{O}C @ 0.5 mmHg, [lit.[9] 83-84 °C @ 0.4mmHg]) gave **12** as a colorless liquid (182 g, 62%), with purity of 95% based on GC–MS and ^{1}H-NMR . ^{1}H NMR (600.1 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.0 Hz, 6H, OEt CH_3), 2.24 (s, 3H, H3), 3.00 (d, *J* = 22.9

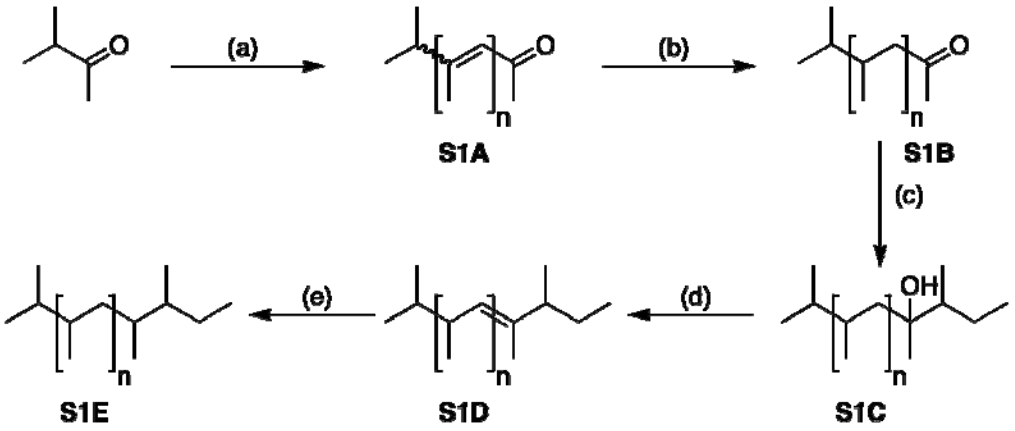
Hz, 2H, H1), 4.02–4.11 (cm, 4H, OEt CH_2); $^{31}P\{^1H\}$ NMR (242.9 MHz, $CDCl_3$): δ 20.11 (s); GC–MS: 16.86 min - *m/z* 43 (84.1%), 58 (32.0%), 65, 78, 79, 80, 81, 91, 96, 97 (81%), 108, 109 (38%), 121, 123, 125 (100%), 137, 139, 149, 151, 152 (53%), 167 (16%), 179 (17%), 194 ($M^{\bullet+}$, 11.7%); HREI-MS: $C_7H_{15}O_4P$ requires 194.0708 found 194.0713; IR (thin film): ν (cm^{-1}) 3479 (br, s), 2985 (s), 2920 (s), 2913 (s), 1716 (vs), 1655 (br, w), 1479 (w), 1445 (m), 1425 (m) 1394 (s), 1362 (s) 1255 (br, vs), 1163 (s), 1124 (sh, m), 1098 (s), 1051 (vs), 1027 (vs) 981 (vs), 963 (vs), 854 (m), 821 (s), 791 (m), 698 (m). The data are consistent with those reported.[8]

Note on Compound Designations

The mixtures produced at each step are designated a code based on the series they belong to, i.e., S1 for series 1, followed by the relevant step, i.e., step A giving S1A, and the oligomers present identified in brackets, i.e., for a mixture containing n = 1–4 oligomers, the designations would be S1A{1-4}.

Details for Series 1 Compounds

Scheme S1: Synthetic Route to Series 1 mixed HBA's



(a) $(OEt)_2P(O)(CH_2C(O)CH_3)$, NaH, PhMe, 100 °C, 6 d (b) Pd/C-H_2, MeOH, O/N (c) (i) *sec*-BuMgBr (5 equ), THF, reflux, O/N (ii) H_3O^+ (d) $BF_3.Et_2O$, CH_2Cl_2, –10°C (e) Pd/C-H_2 (50 atm), MeOH/CH_2Cl_2 (1:1), O/N, r.t.

Figure S2: Partial GC chromatogram of S1A{1-2}

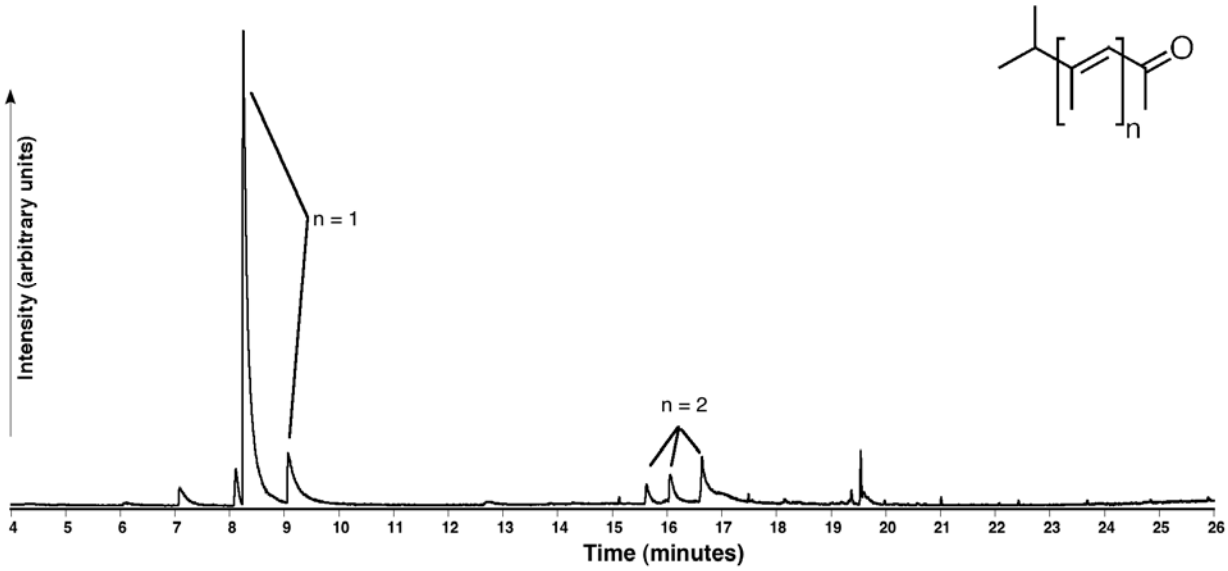


Figure S3: Partial GC chromatogram of S1B{1-3}

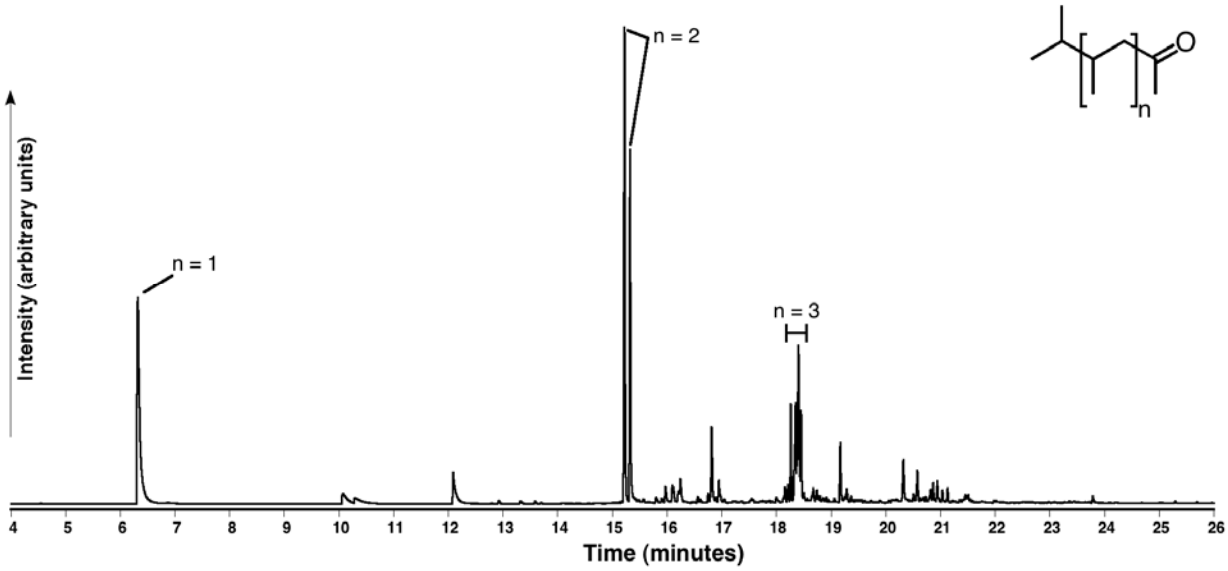


Figure S4: Partial GC chromatogram of S1C{1-2}

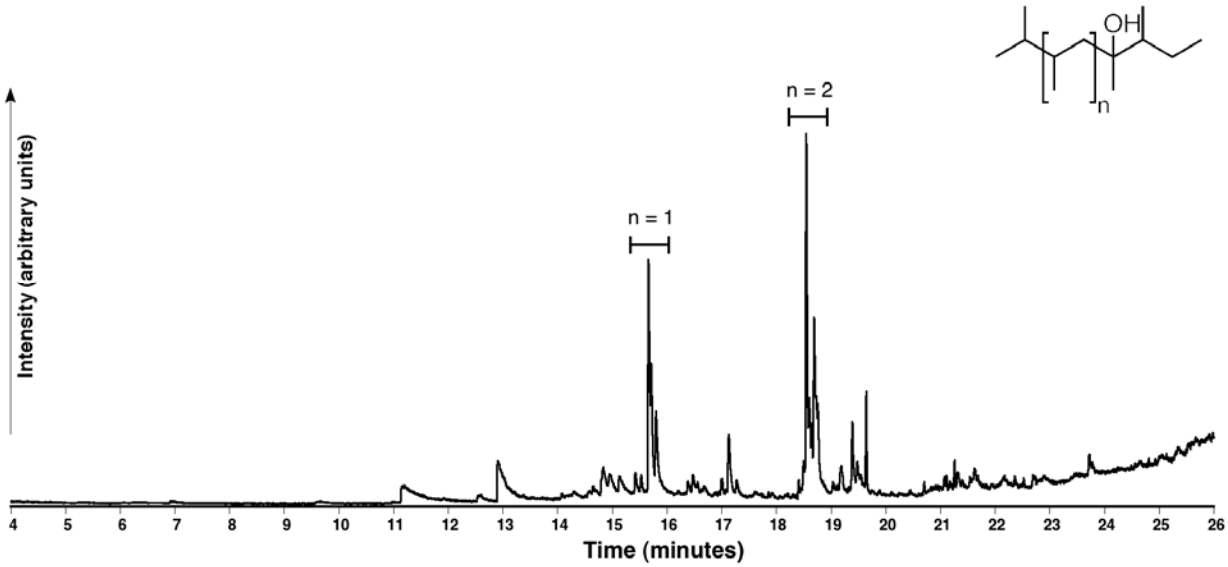


Figure S5: Partial GC chromatogram of S1D{2-4}

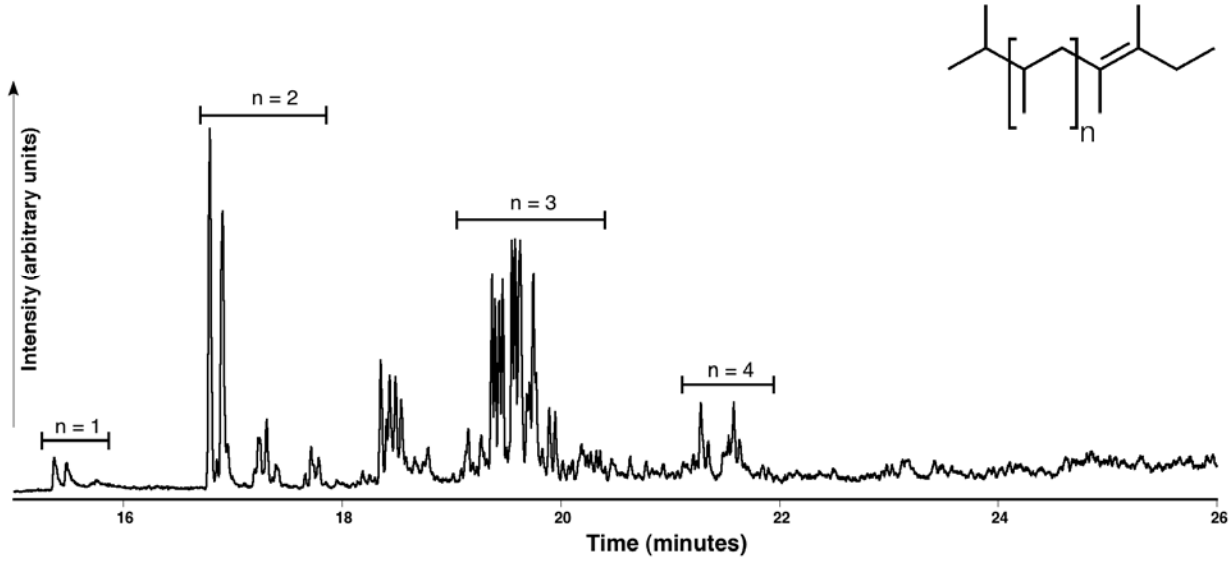


Figure S6: Partial GC chromatogram of S1E{2-4}

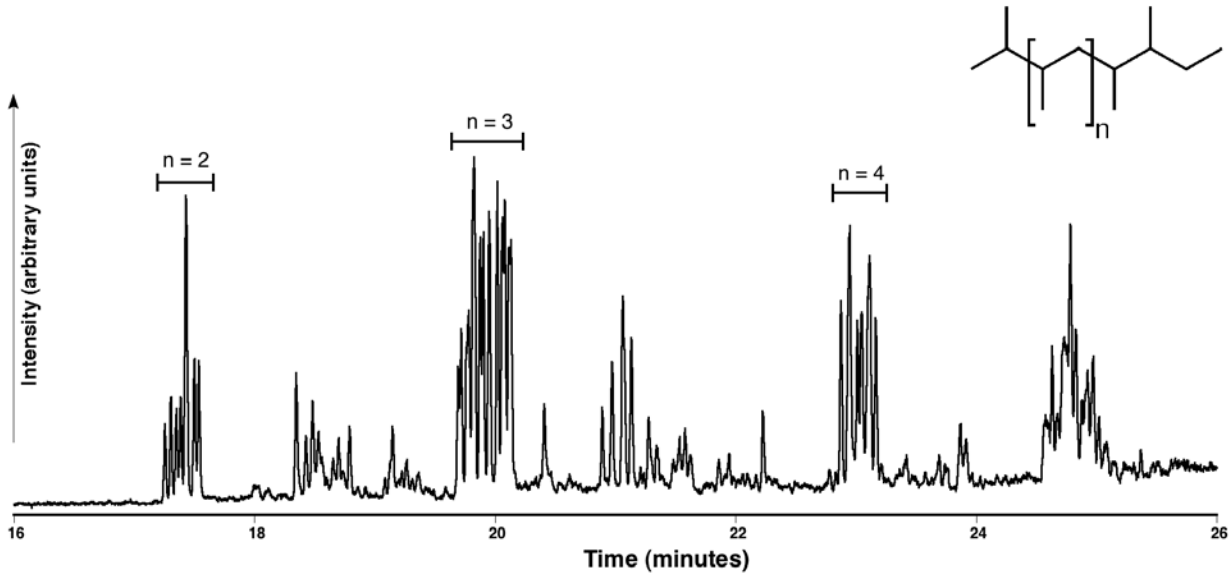


Figure S7: Mass spectrum of S1E{2}

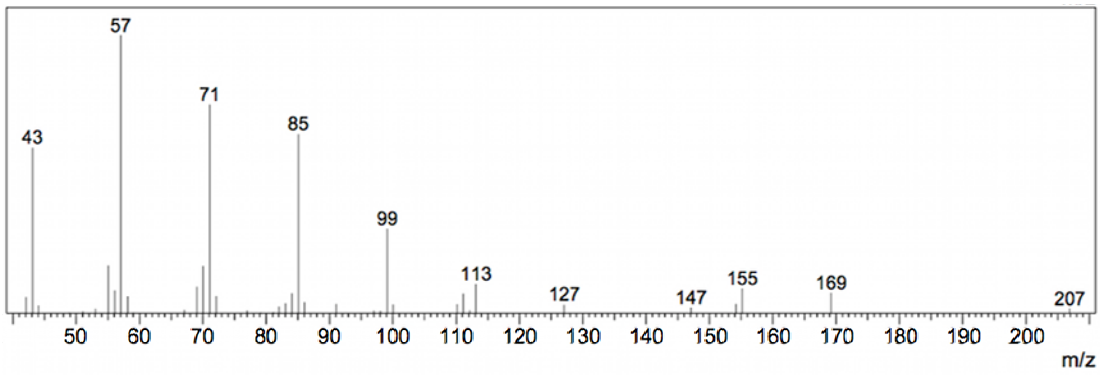


Figure S8: Mass spectrum of S1E{3}

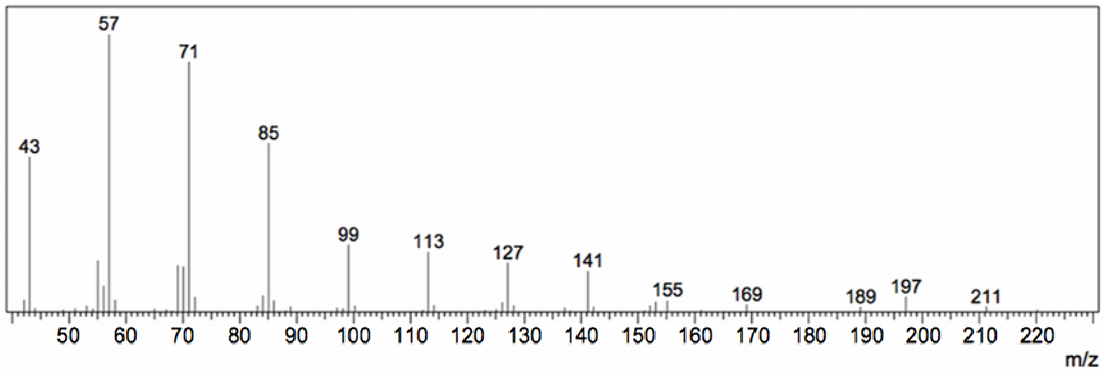
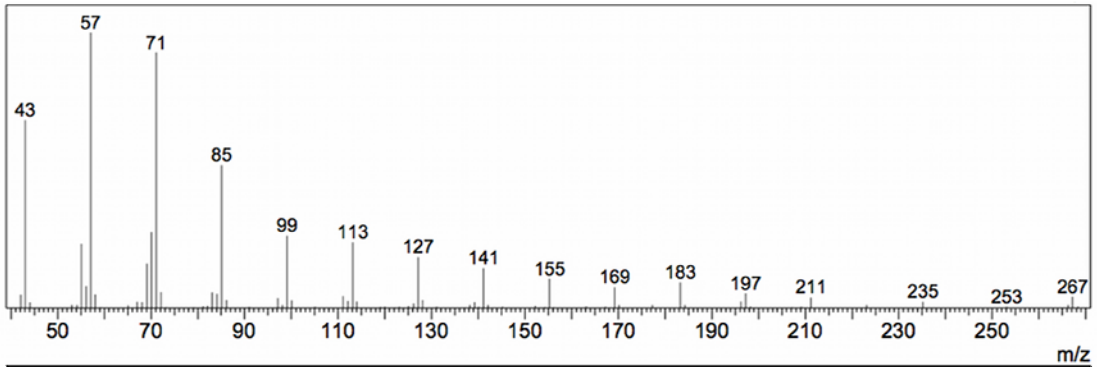
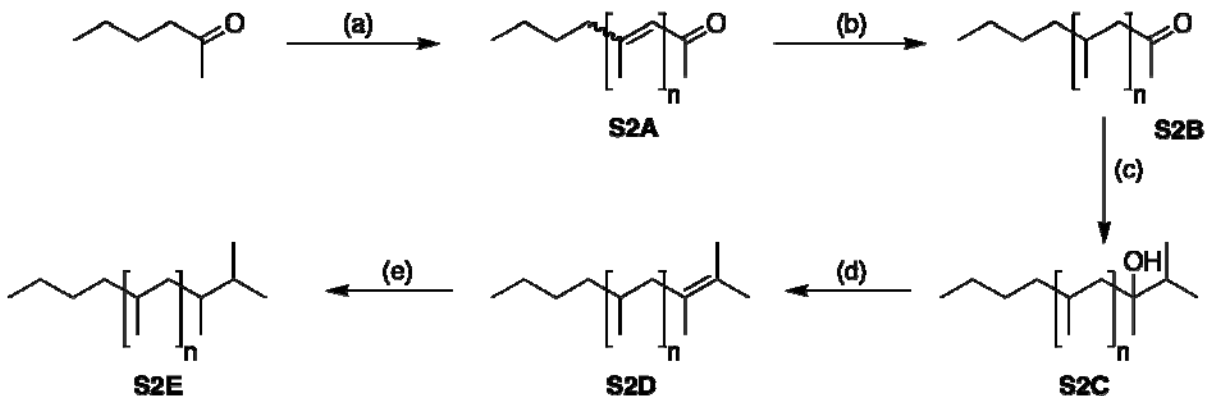


Figure S9: Mass spectrum of S1E{4}



Details for Series 2 Compounds

Scheme S2: Synthetic Route to Series 2 mixed HBA's



(a) $(OEt)_2P(O)(CH_2C(O)CH_3)$, NaH, PhMe, 100 °C, 8 d (b) Pd/C-H_2, MeOH, O/N (c) (i) *i*-PrMgBr (5 equ), THF, r.t., O/N (ii) H_3O^+ (d) $BF_3.Et_2O$, CH_2Cl_2 , –10°C (e) Pd/C-H_2 (50 atm), MeOH/CH_2Cl_2 (1:1), O/N, r.t.

Figure S10: Partial GC–MS chromatogram of S2A{2-3}

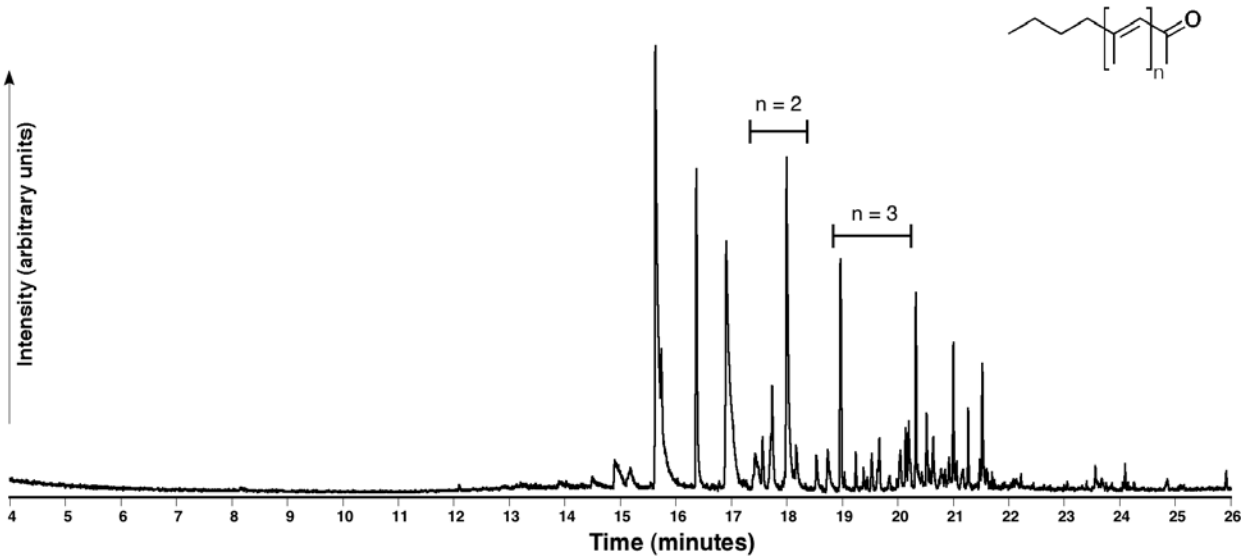


Figure S11: Partial GC–MS chromatogram of S2B{1-3}

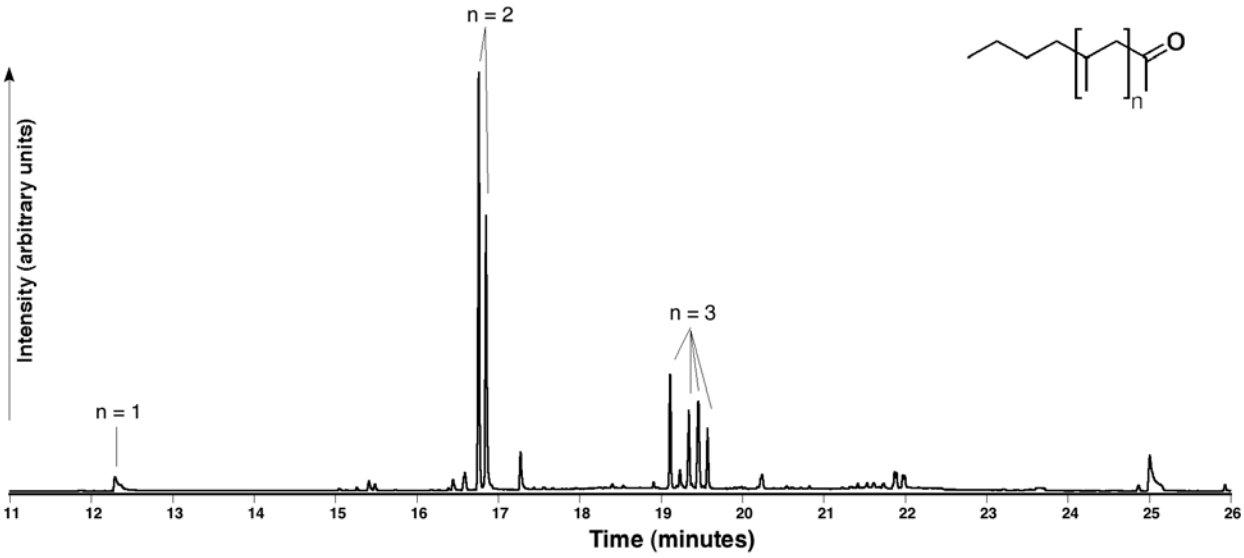


Figure S12: Partial GC–MS chromatogram of S2C{1-3}

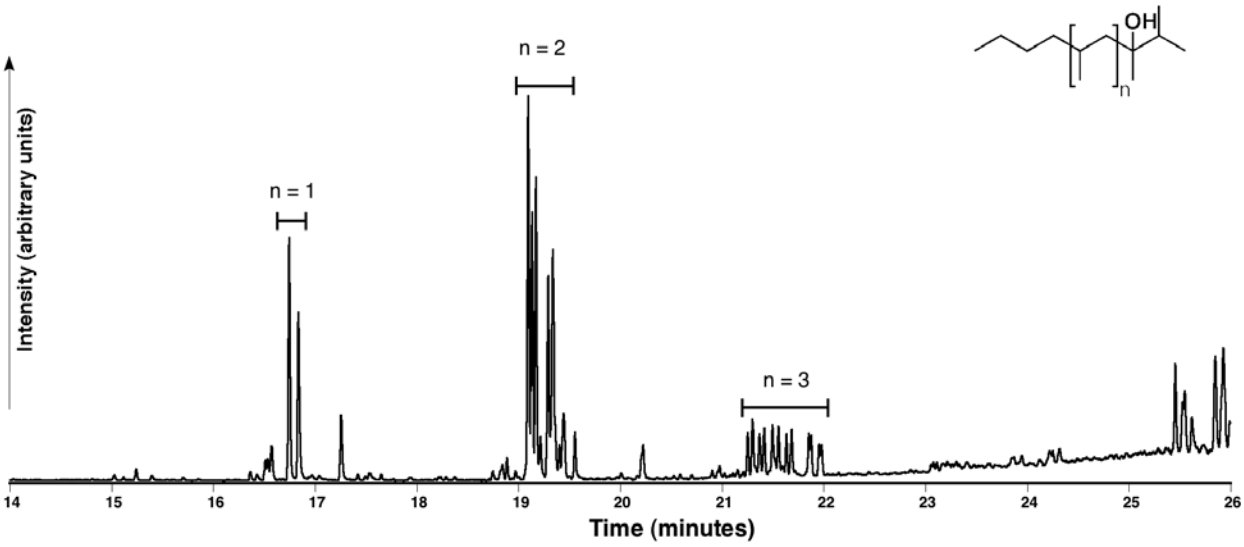


Figure S13: Partial GC–MS chromatogram of S2D{1-4}

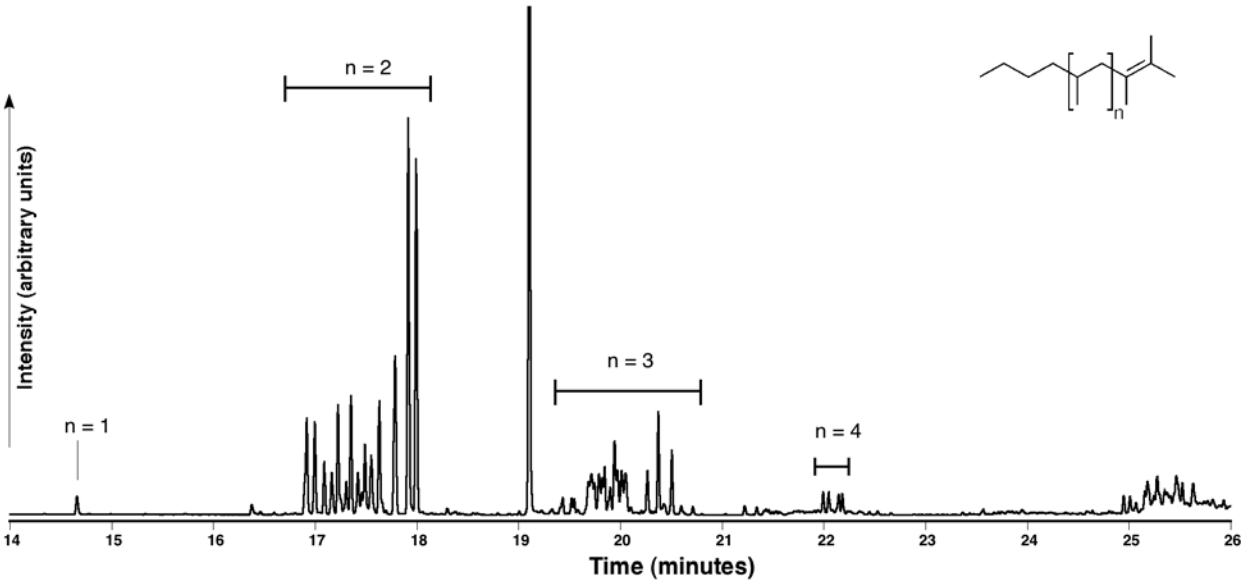


Figure S14: Partial GC–MS chromatogram of S2E{2-4}

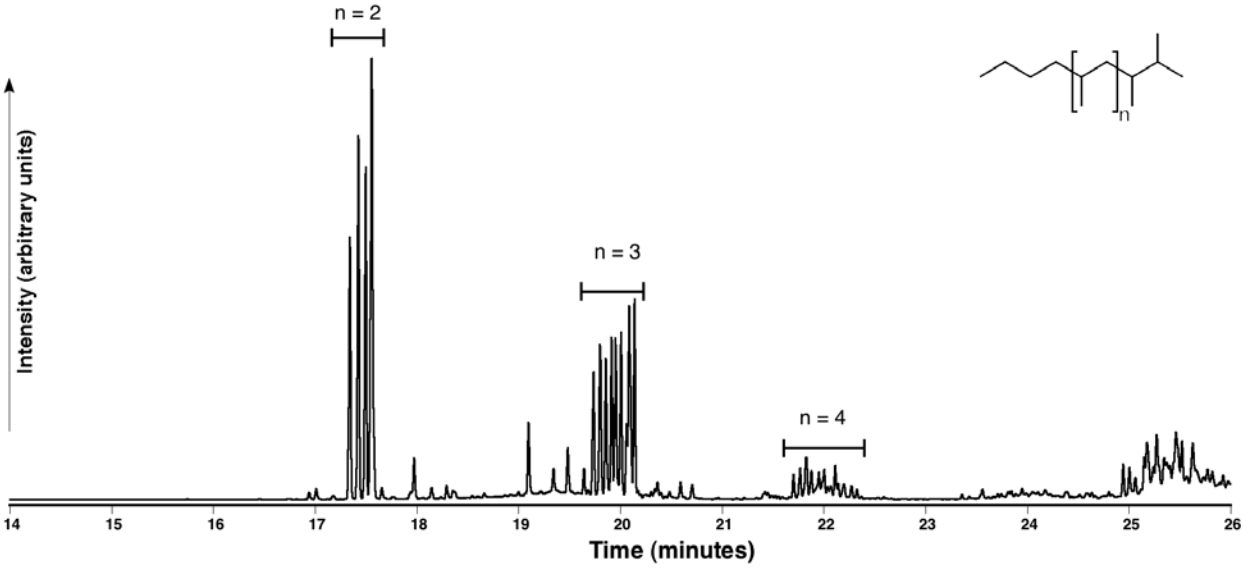


Figure S15: Mass spectrum of S2E{2}

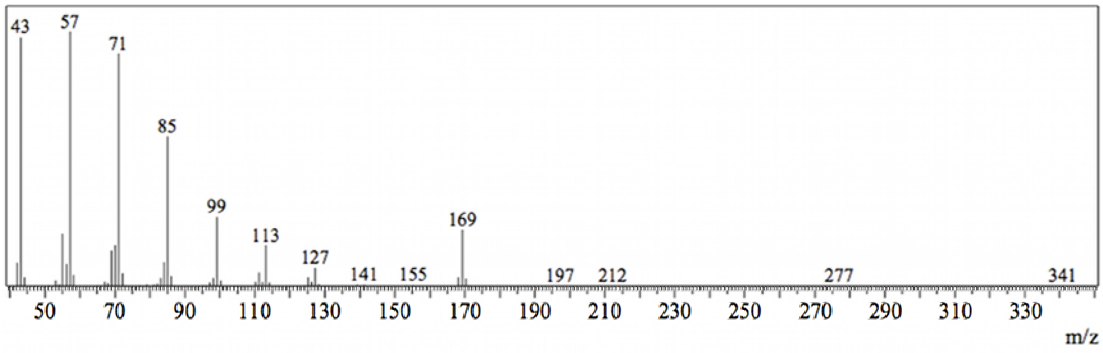


Figure S16: Mass spectrum of S2E{3}

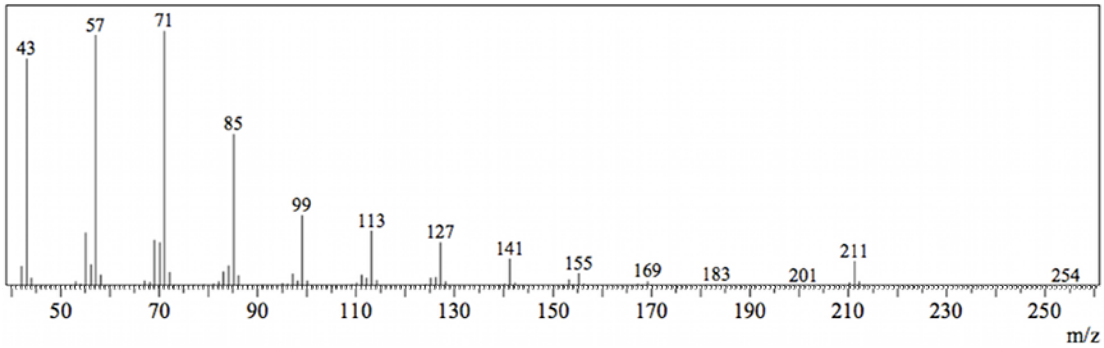
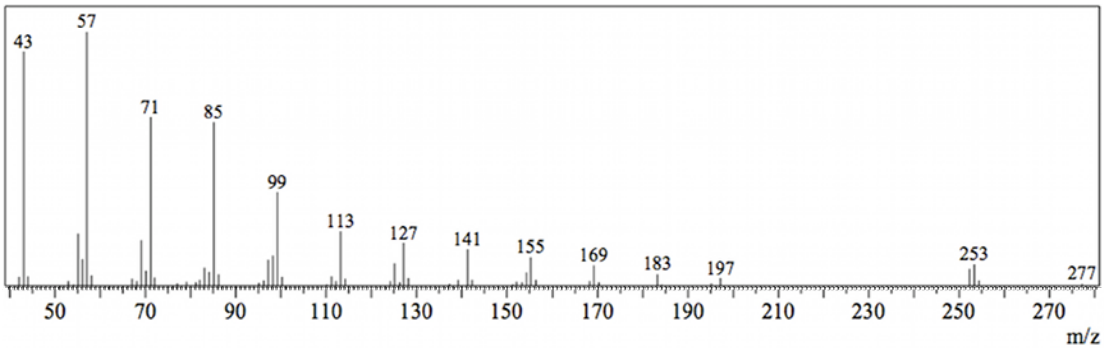
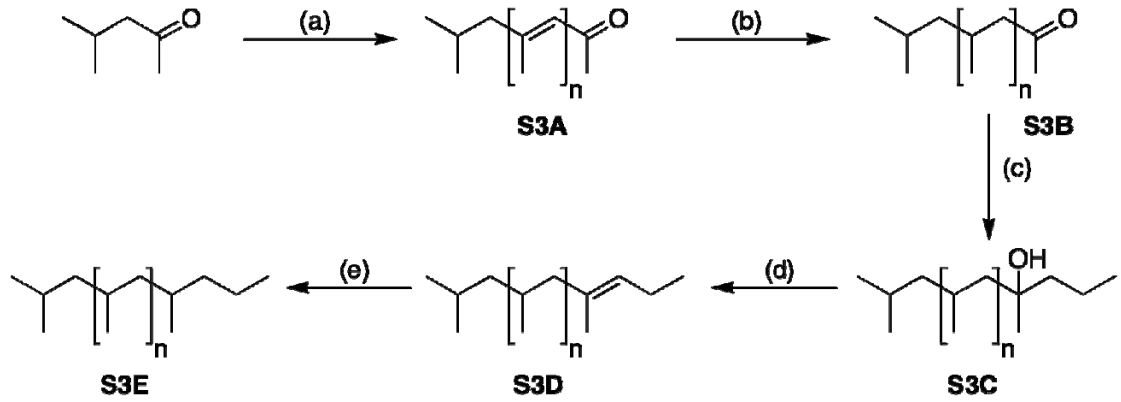


Figure S17: Mass spectrum of S2E{4}



Details for Series 3 Compounds

Scheme S3. Synthetic Route to Series 3 mixed HBA's



(a) $(OEt)_2P(O)(CH_2C(O)CH_3)$, NaH, PhMe, 100 °C, 8 d (b) Pd/C-H_2, MeOH, O/N (c) (i) *n*-PrMgBr (5 equ), THF, r.t., O/N (ii) H_3O^+ (d) $BF_3.Et_2O$, CH_2Cl_2 , –10°C (e) Pd/C-H_2 (50 atm), MeOH/CH_2Cl_2 (1:1), O/N, r.t.

Figure S18: Partial GC–MS chromatogram of S3A{1-4}

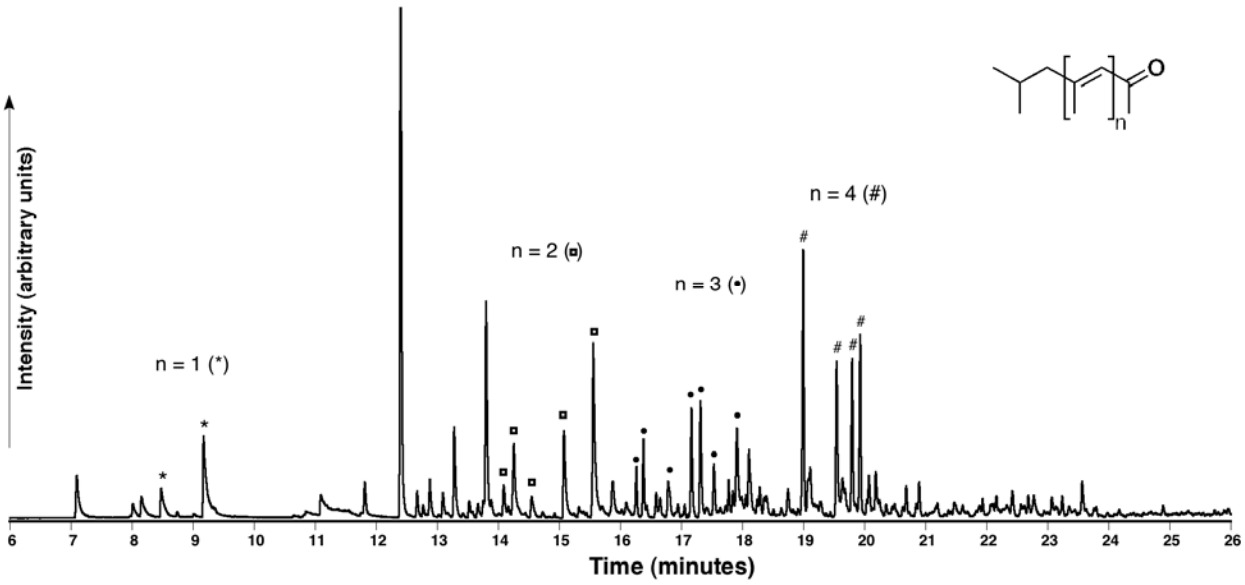


Figure S19: Partial GC–MS chromatogram of S3B{2-4}

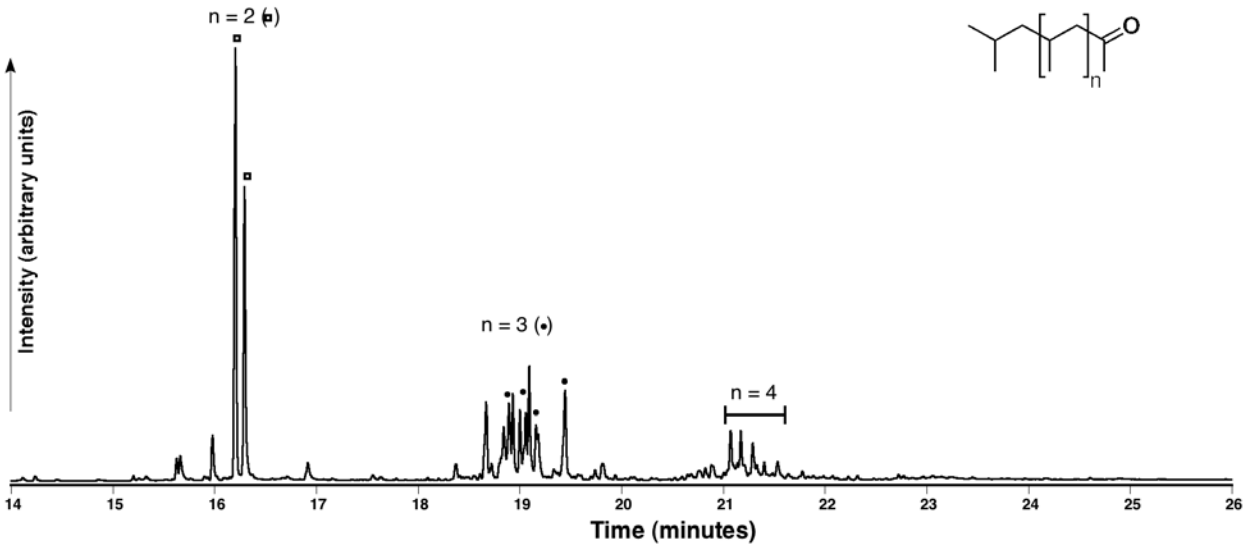


Figure S20: Partial GC–MS chromatogram of S3C{2-4}

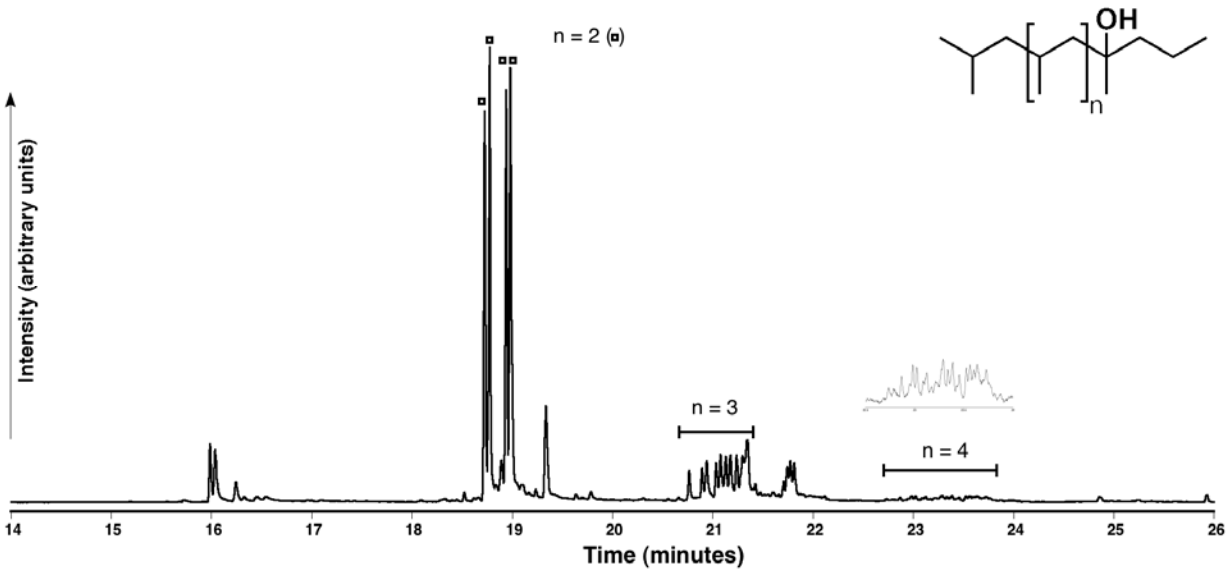


Figure S21: Partial GC–MS chromatogram of S3D{2-4}

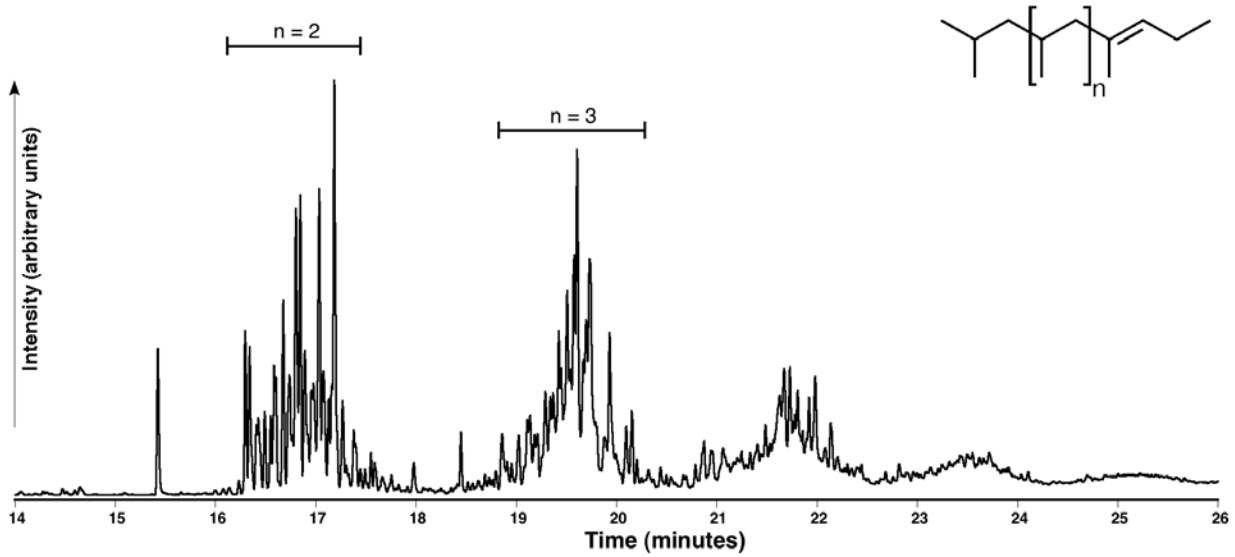


Figure S22: Partial GC–MS chromatogram of S3E{2-4}

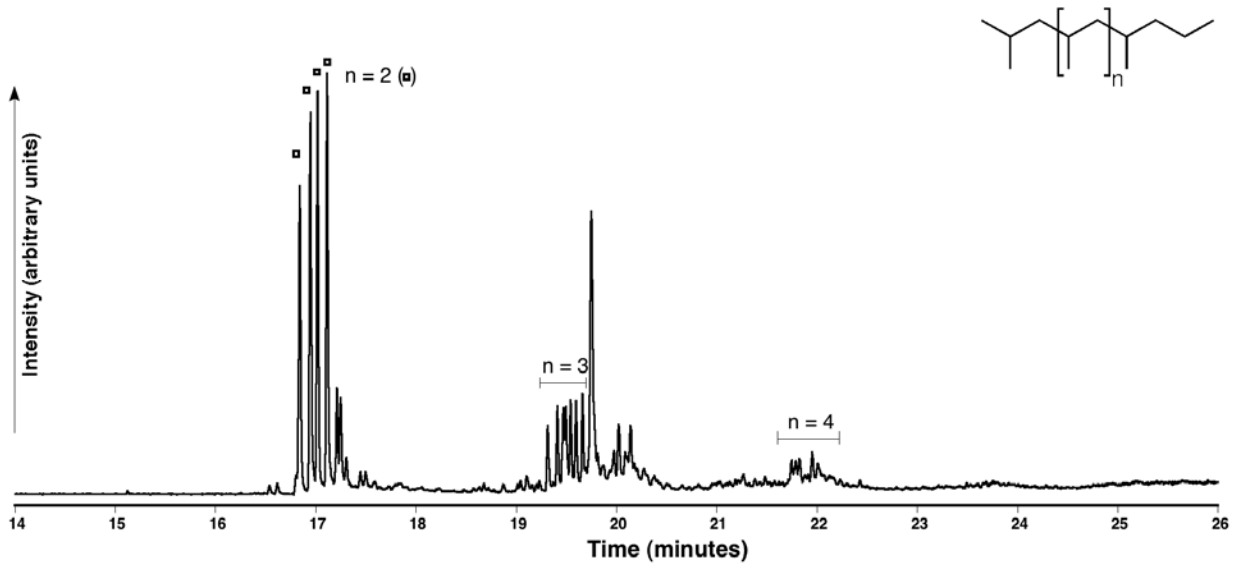


Figure S23: Mass spectrum of S3E{2}

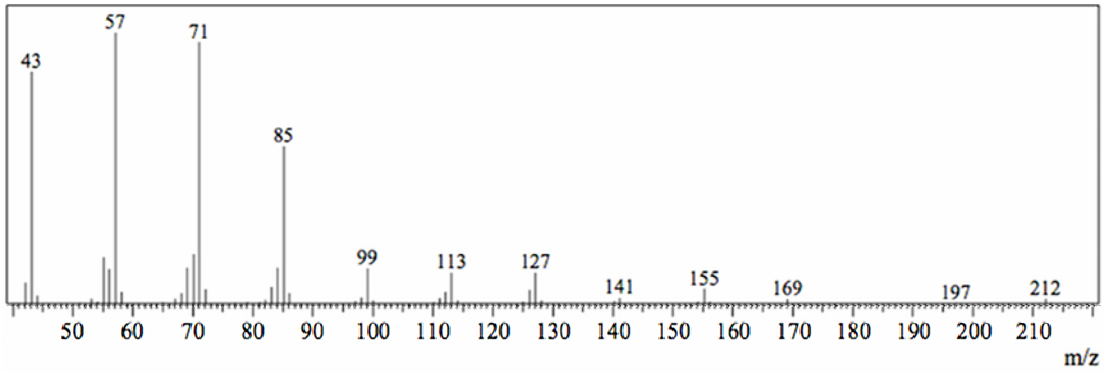


Figure S24: Mass spectrum of S3E{3}

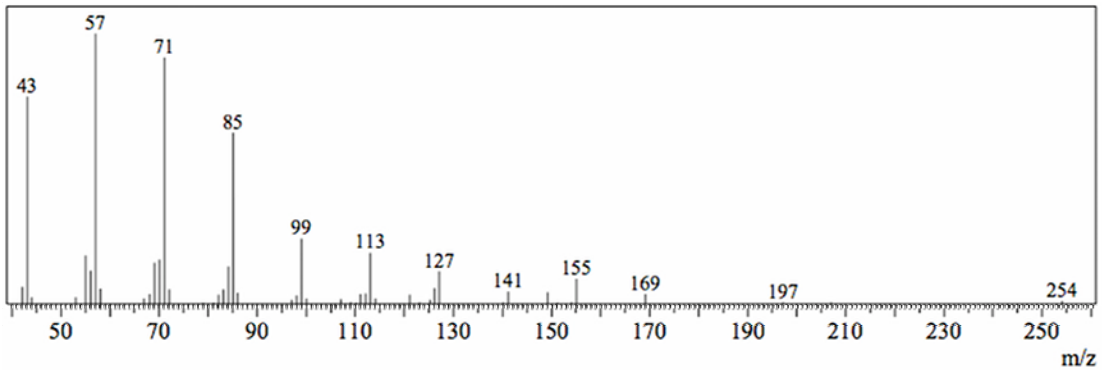
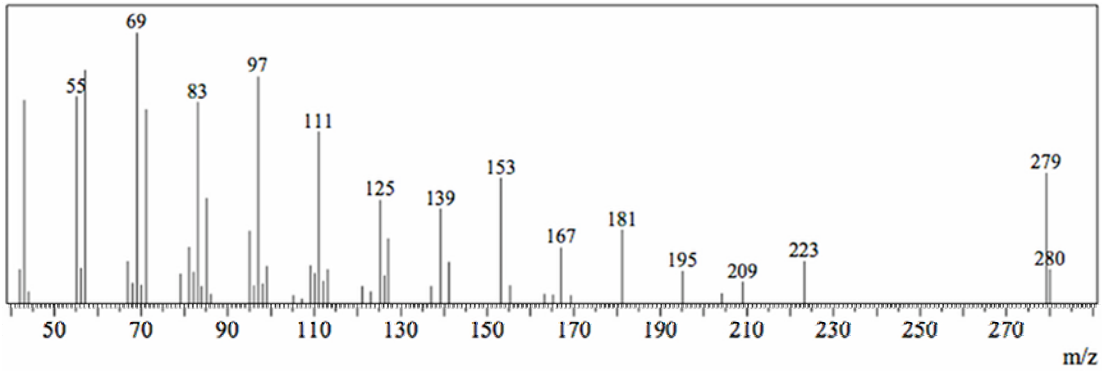
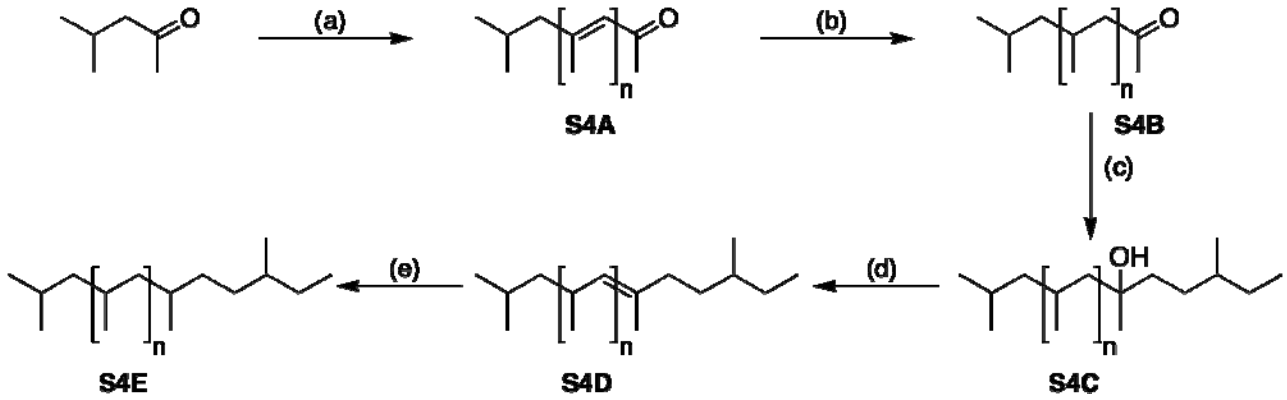


Figure S25: Mass spectrum of S3E{4}



Details for Series 4 Compounds

Scheme S4: Synthetic Route to Series 4 mixed HBA's



(a) $(OEt)_2P(O)(CH_2C(O)CH_3)$, NaH, PhMe, 100 °C, 7 d (b) Pd/C-H_2, MeOH, O/N (c) (i) $(CH_3CH_2CH(CH_3)CH_2CH_2)MgBr$, THF, r.t., O/N (ii) H_3O^+ (d) $BF_3.Et_2O$, CH_2Cl_2, –10°C (e) Pd/C-H_2 (50 atm), MeOH/CH_2Cl_2 (1:1), O/N, r.t.

Figure S26: Partial GC–MS Chomatogram of S4A{1-4}

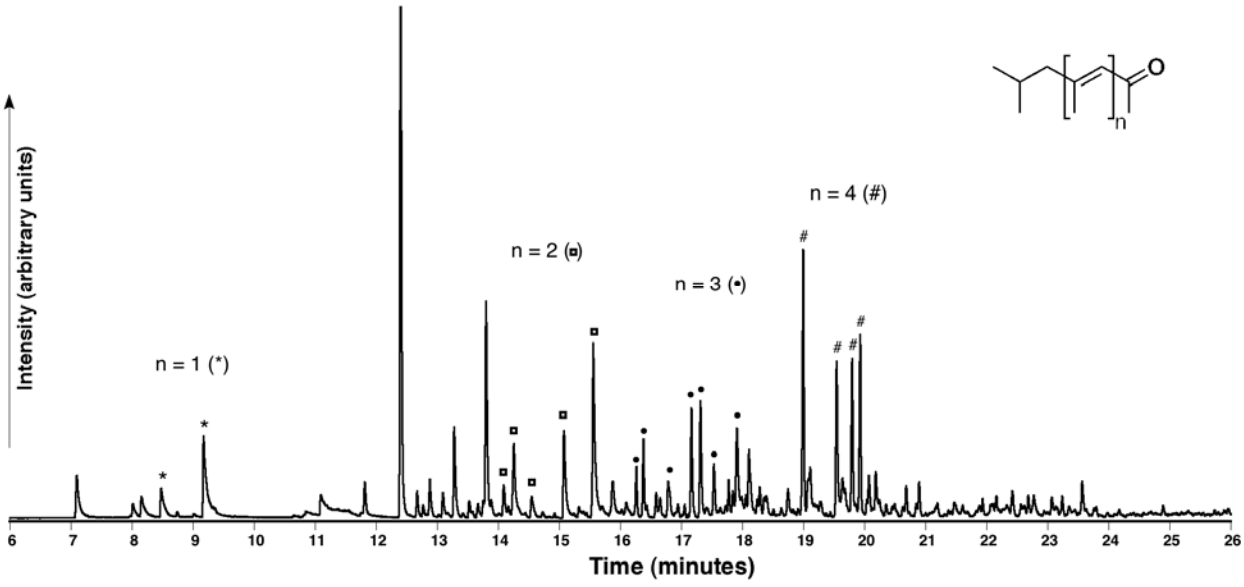


Figure S27: Partial GC–MS Chomatogram of S4B{2-4}

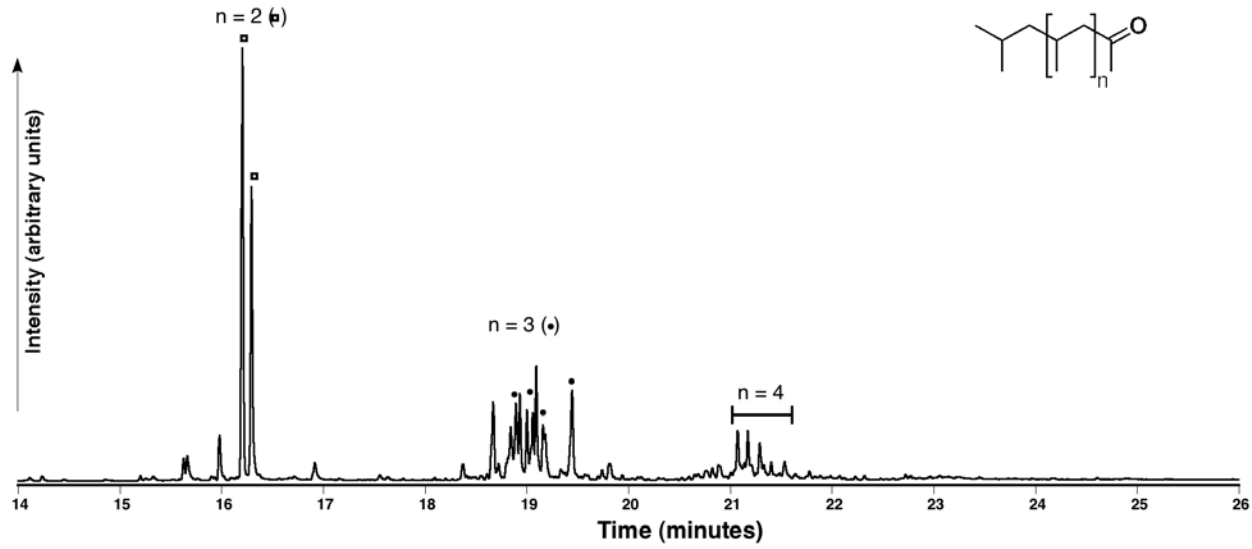


Figure S28: Partial GC–MS chromatogram of S4C{1-3}

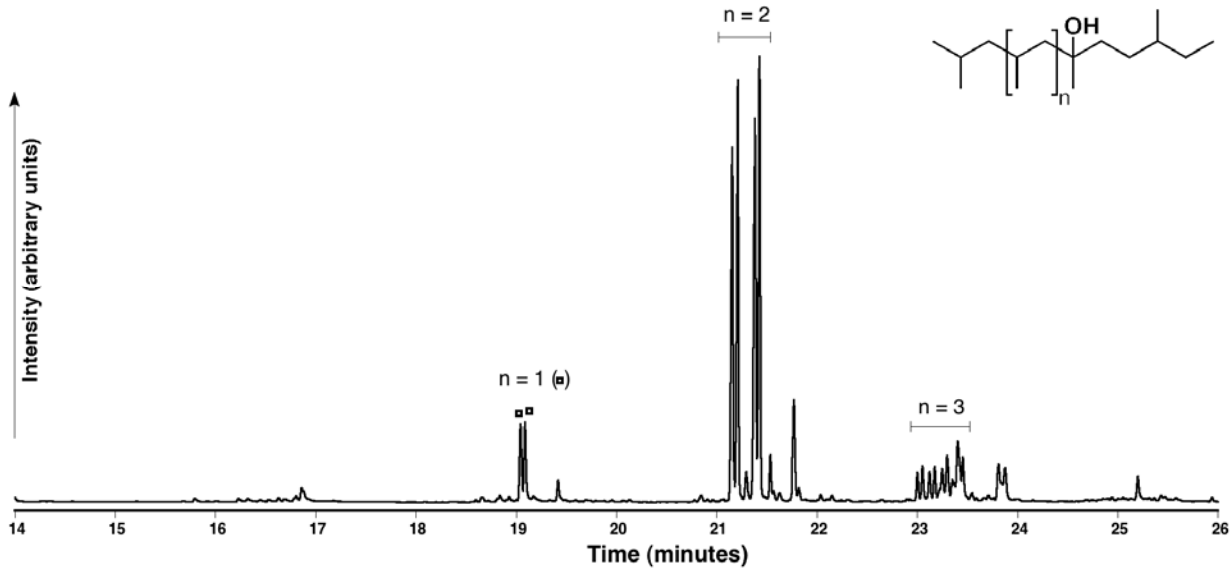


Figure S29: Partial GC–MS chromatogram of S4D{1-3}

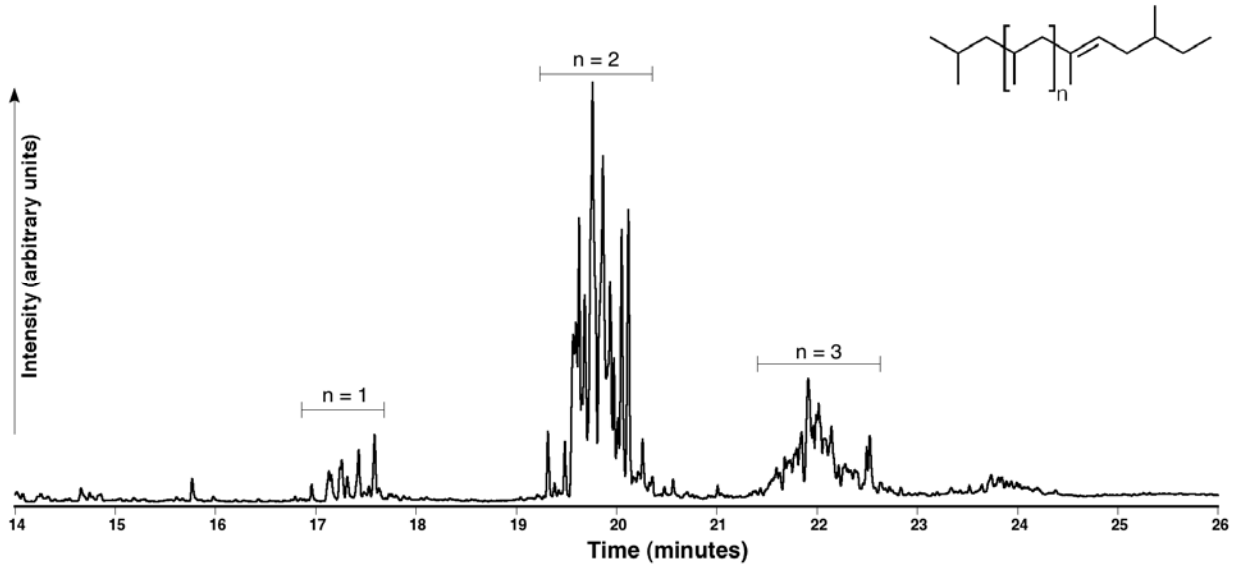


Figure S30: Partial GC–MS chromatogram of S4E{1-3}

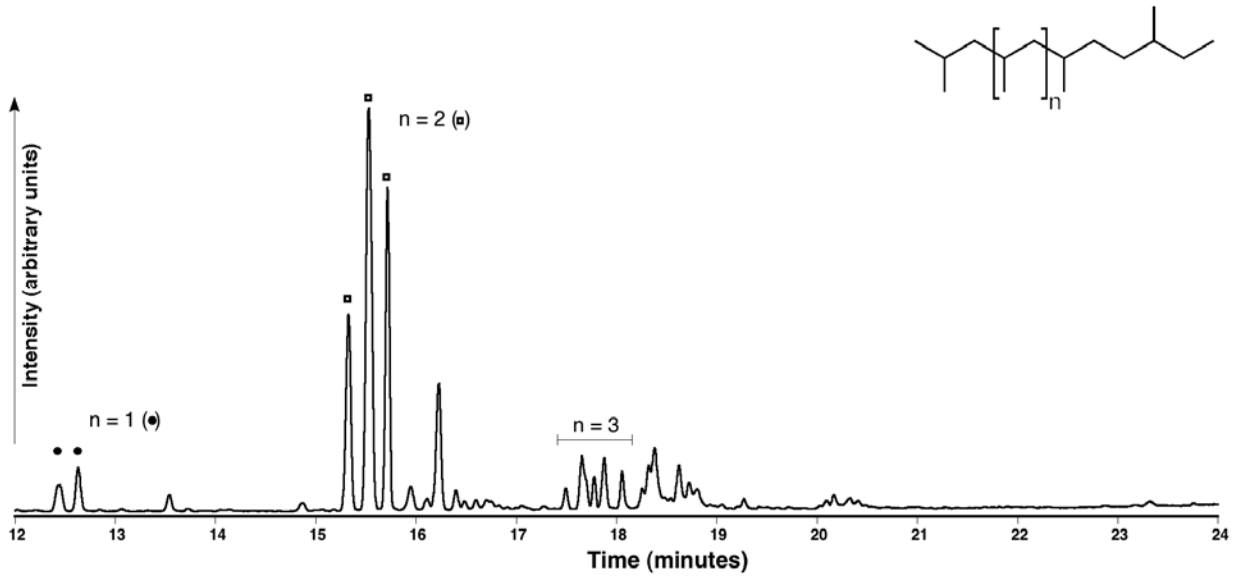


Figure S31: Mass spectrum of S4E{1}

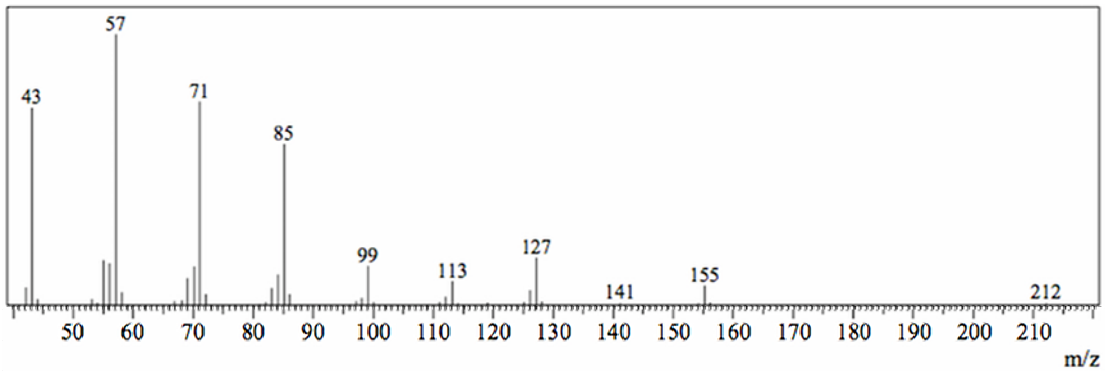


Figure S32: Mass spectrum of S4E{2}

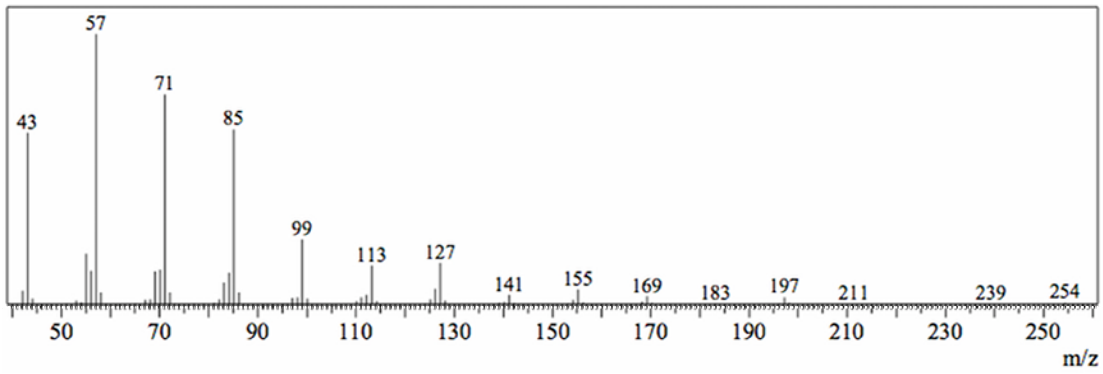
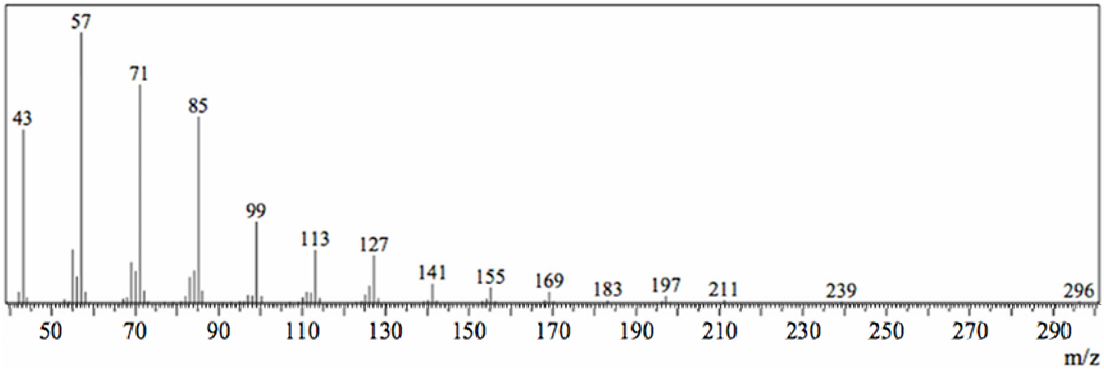
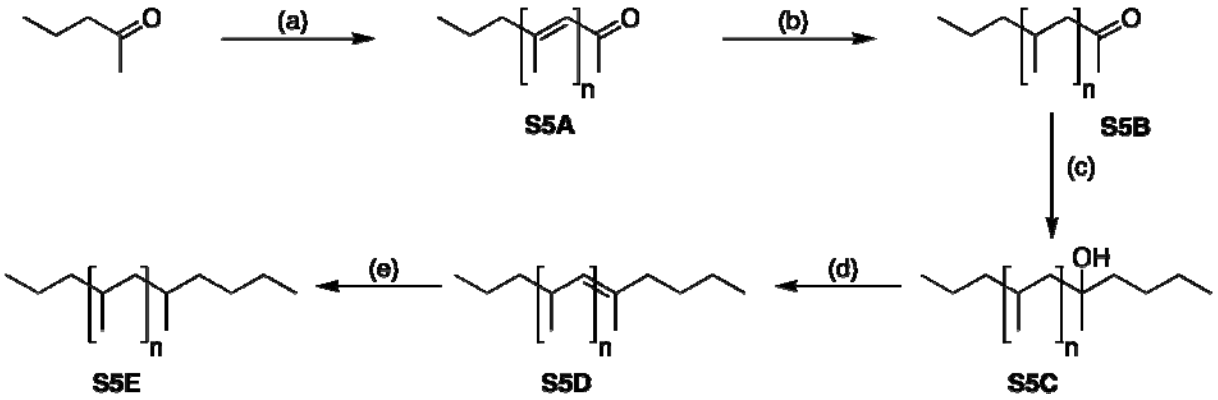


Figure S33: Mass spectrum of S4E{3}



Details for Series 5 Compounds

Scheme S5: Synthetic Route to Series 5 mixed HBA's



(a) $(OEt)_2P(O)(CH_2C(O)CH_3)$, NaH, PhMe, 100 °C, 6 d (b) Pd/C-H_2, MeOH, O/N (c) (i) ^{n}BuMgBr, THF, r.t., O/N (ii) H_3O^+ (d) $BF_3.Et_2O$, CH_2Cl_2 , –10°C (e) Pd/C-H_2 (50 atm), MeOH/CH_2Cl_2 (1:1), O/N, r.t.

Figure S34: Partial GC–MS chromatogram of S5A{1-2}

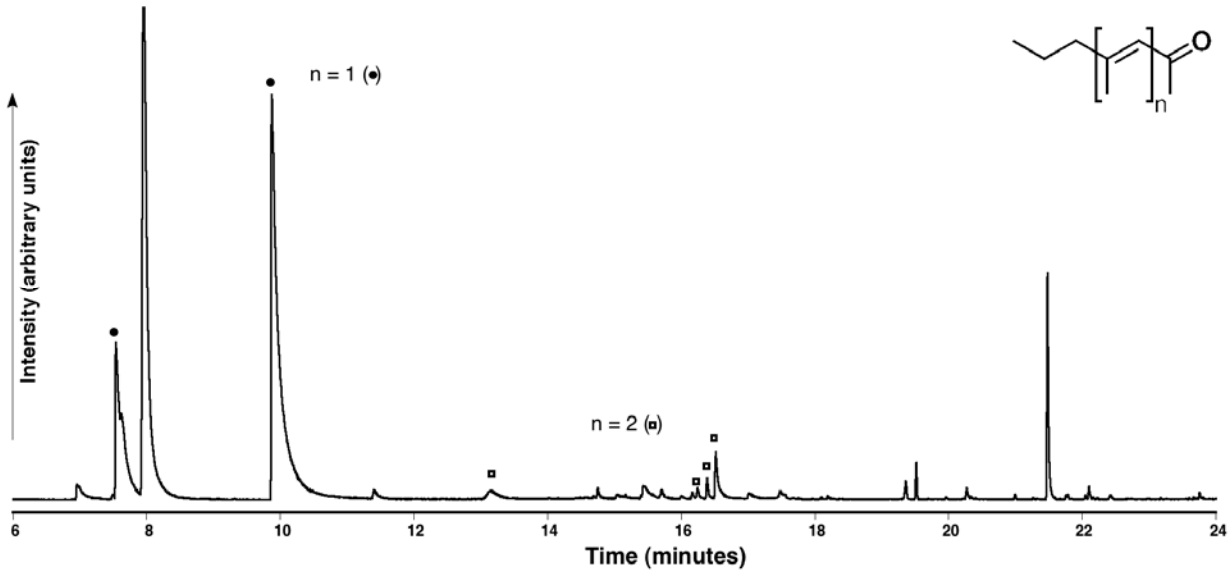


Figure S35: Partial GC–MS chromatogram of S5B{1-2}

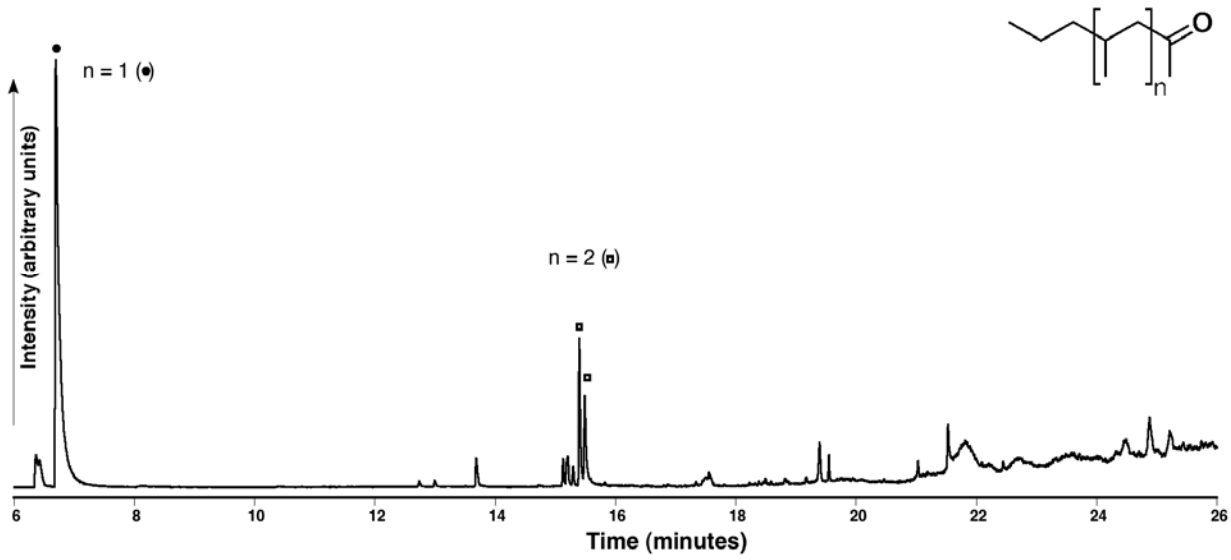


Figure S36: Partial GC–MS chromatogram of S5C{1-2}

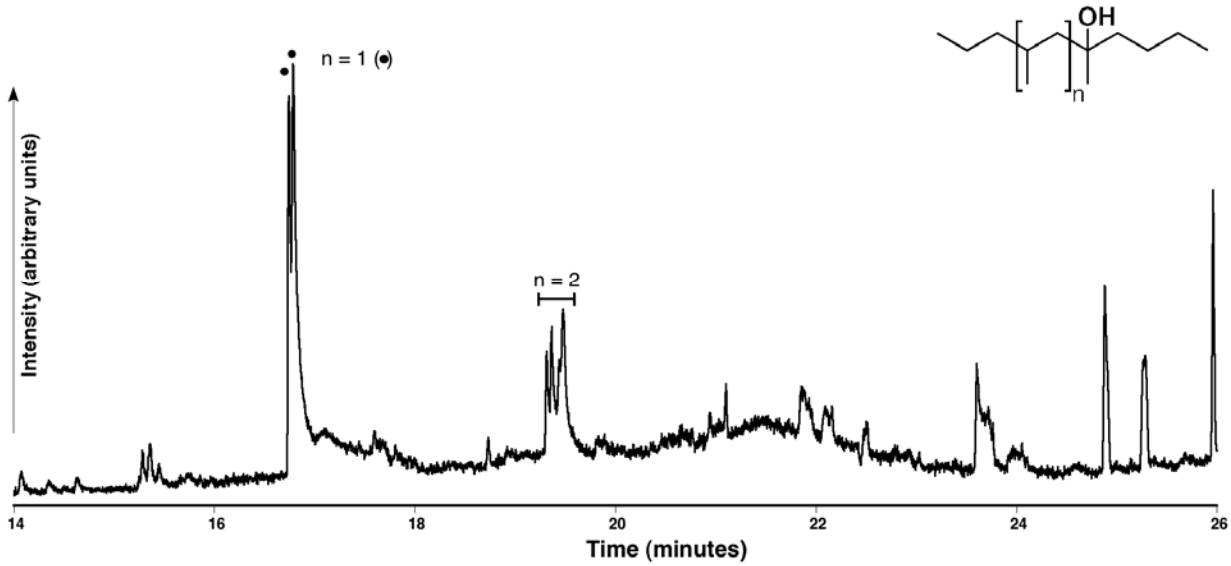


Figure S37: Partial GC–MS chromatogram of S5D{1-3}

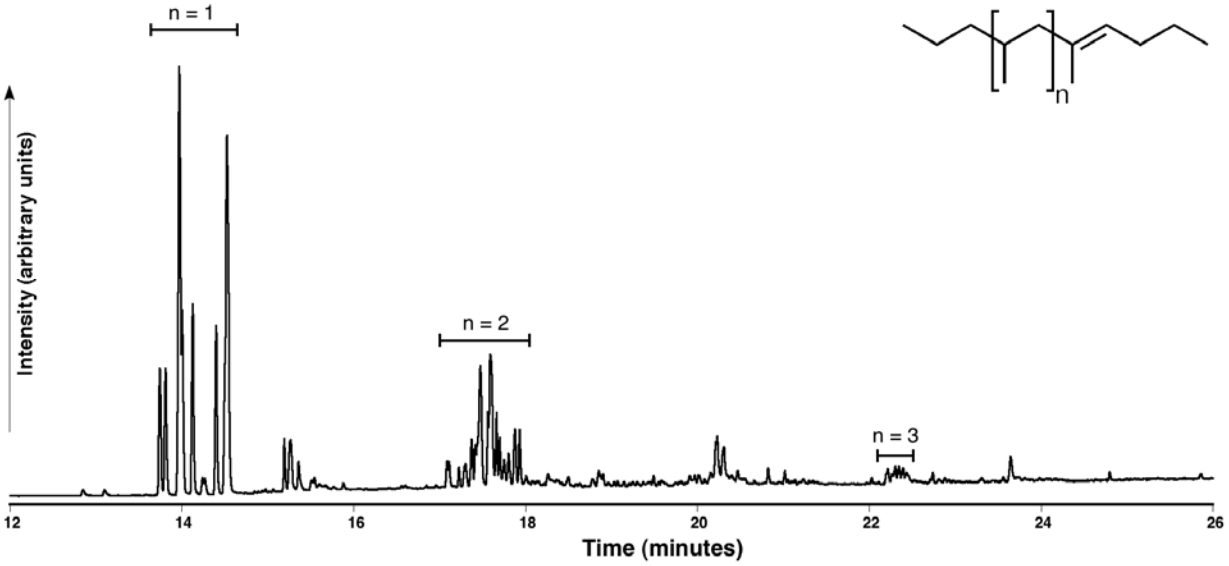


Figure S38: Partial GC–MS chromatogram of S5E{1-3}

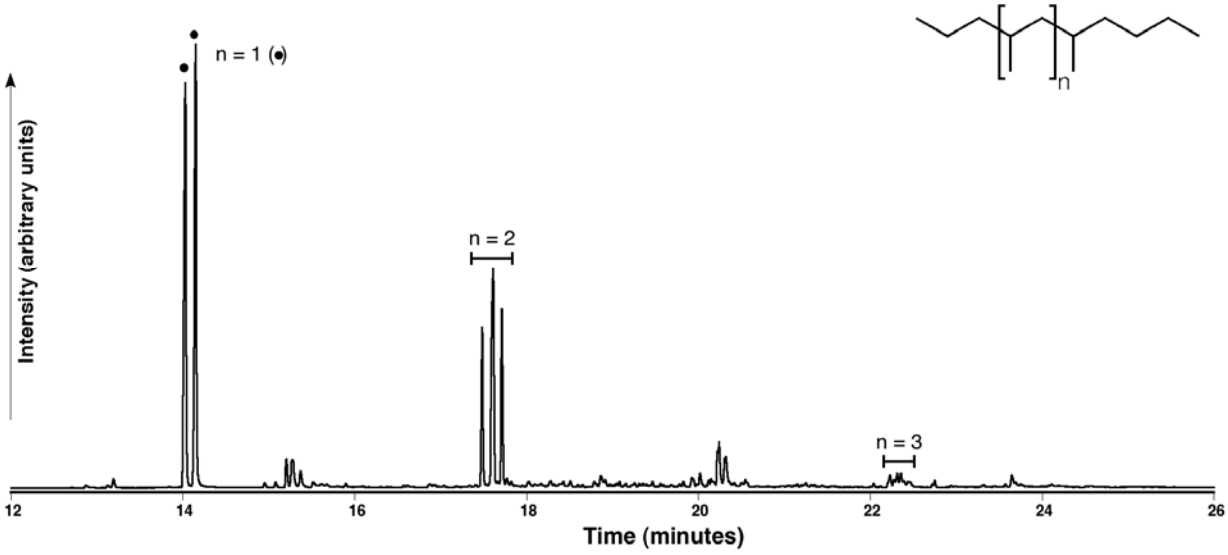


Figure S39: Mass spectrum of S5E{1}

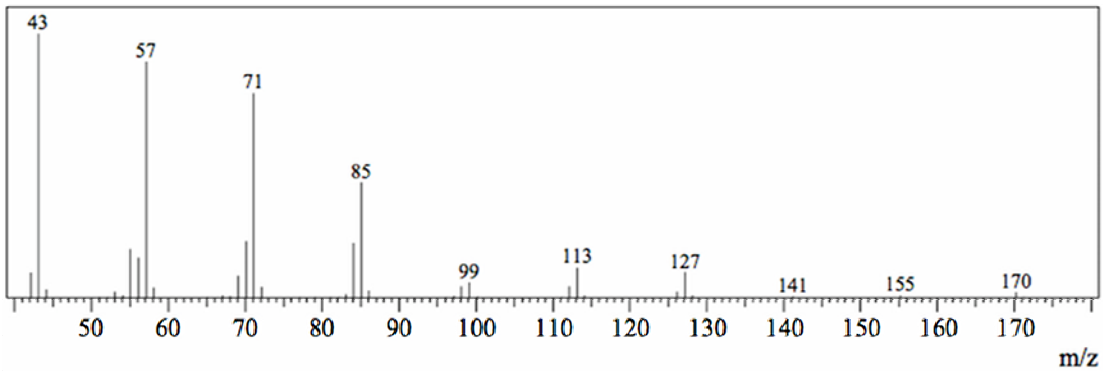


Figure S40: Mass spectrum of S5E{2}

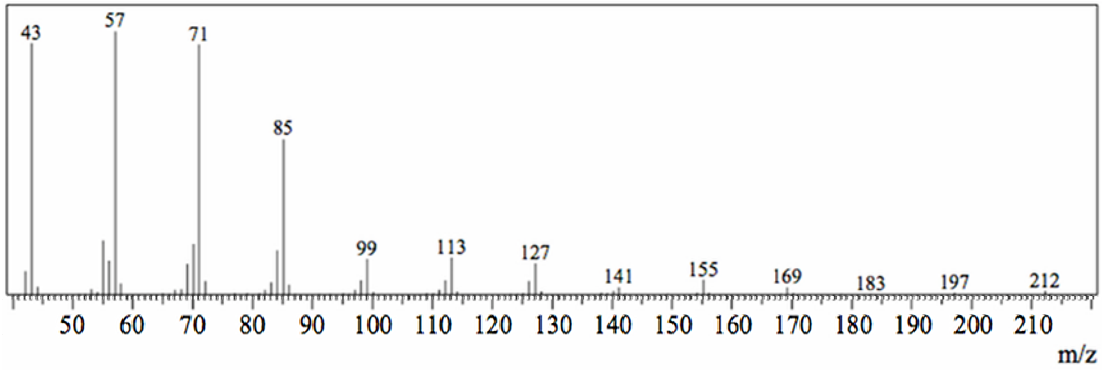
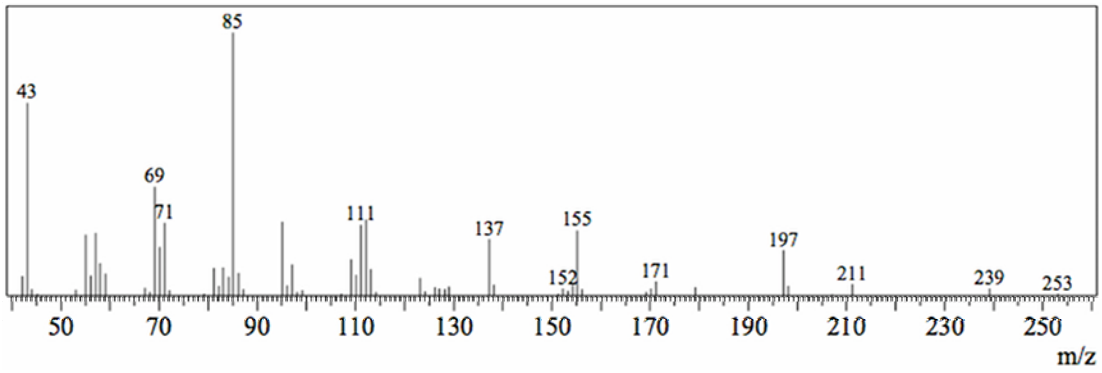
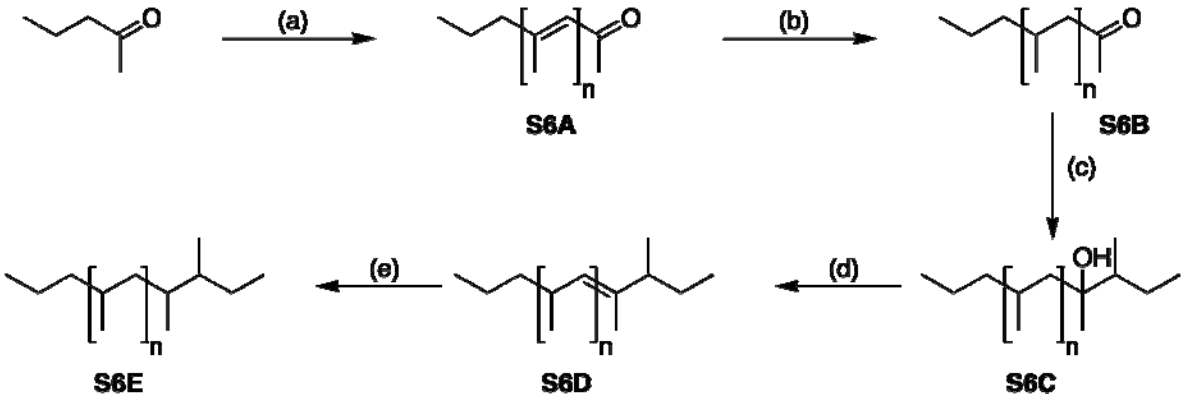


Figure S41: Mass spectrum of S5E{3}



Details for Series 6 Compounds

Scheme S6: Synthetic Route to Series 6 mixed HBA's



(a) $(OEt)_2P(O)(CH_2C(O)CH_3)$, NaH, PhMe, 100 °C, 7 d (b) Pd/C-H_2, MeOH, O/N (c) (i) *sec*-BuMgBr, THF, r.t., O/N (ii) H_3O^+ (d) $BF_3.Et_2O$, CH_2Cl_2 , –10°C (e) Pd/C-H_2 (50 atm), MeOH/CH_2Cl_2 (1:1), O/N, r.t.

Figure S42: Partial GC–MS chromatogram of S6A{1-4}

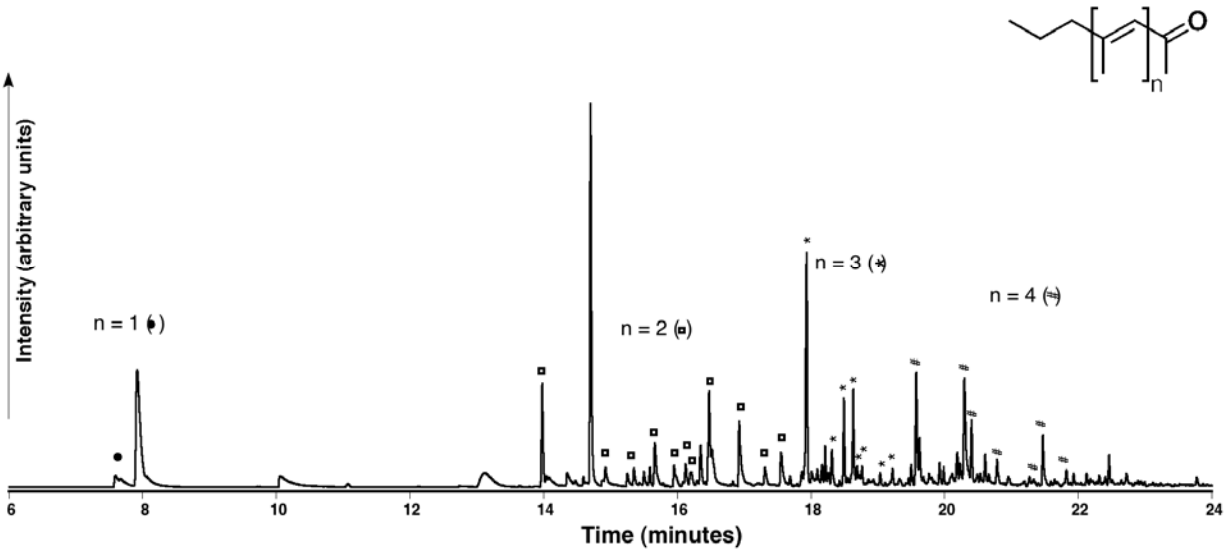


Figure S43: Partial GC–MS chromatogram of S6B{2-4}

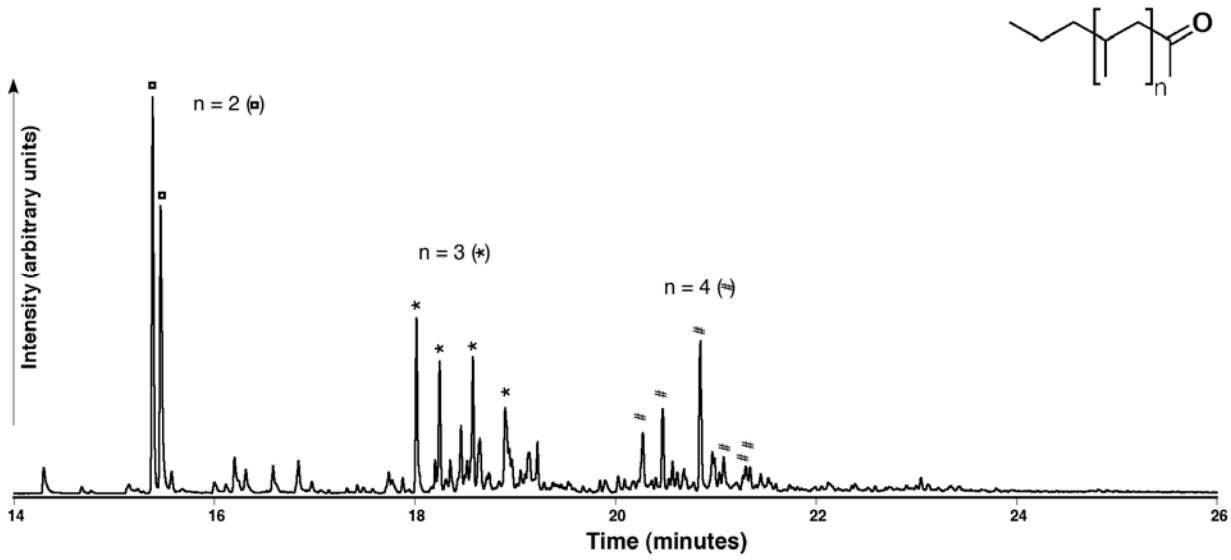


Figure S44: Partial GC–MS chromatogram of S6C{2-4}

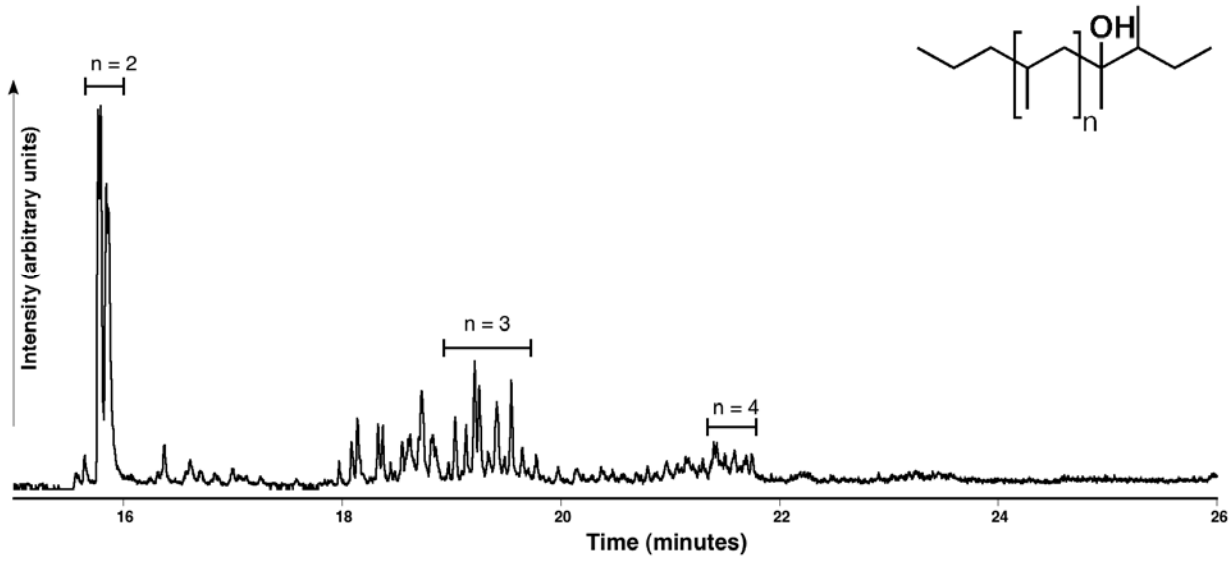


Figure S45: Partial GC–MS chromatogram of S6A{2-4}

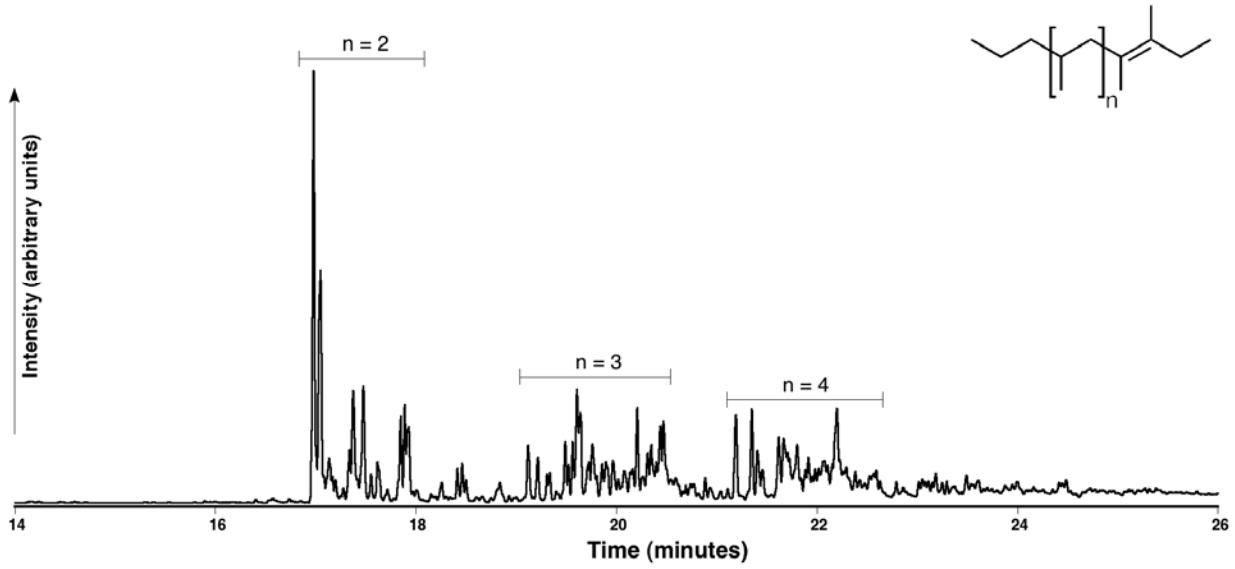


Figure S46: Partial GC–MS (total ion) chromatogram of S6E{1-3}

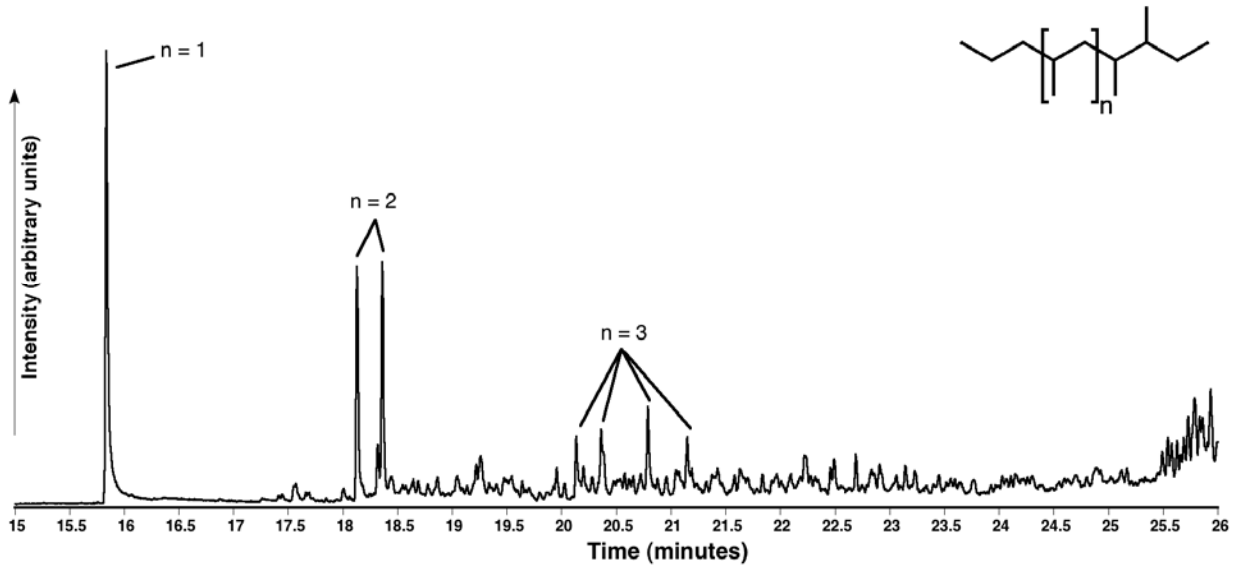


Figure S47: Mass spectrum of S6E{1}

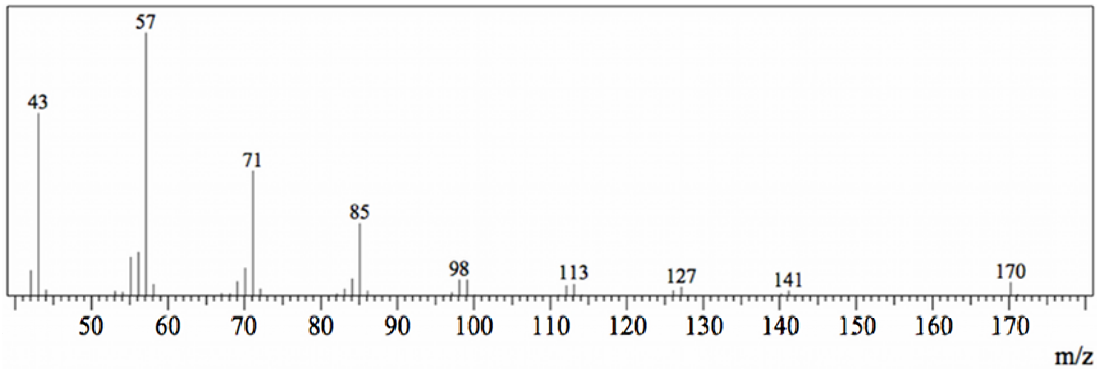


Figure S48: Mass spectrum of S6E{2}

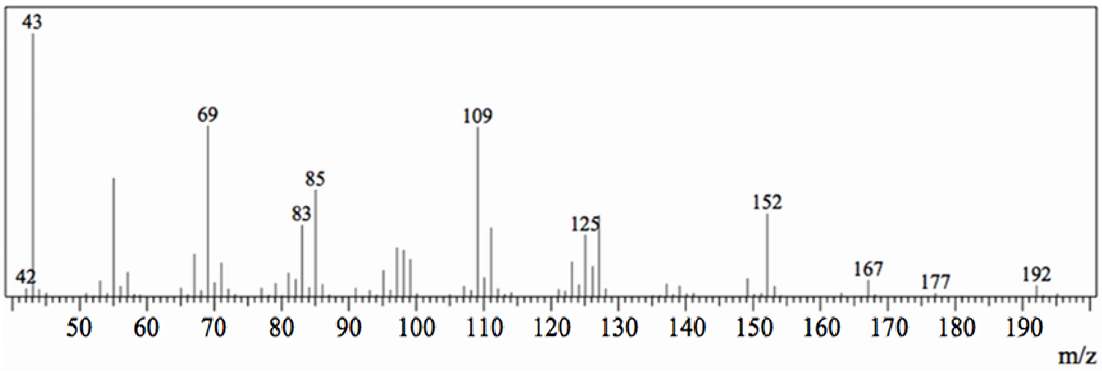
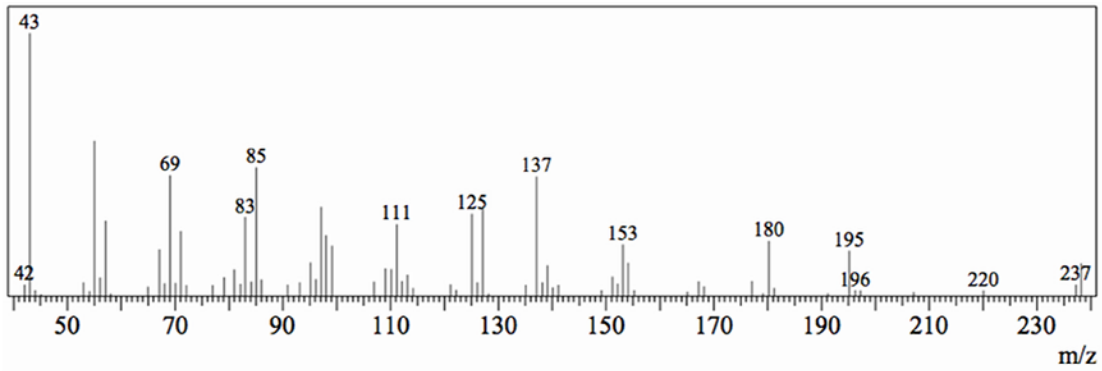
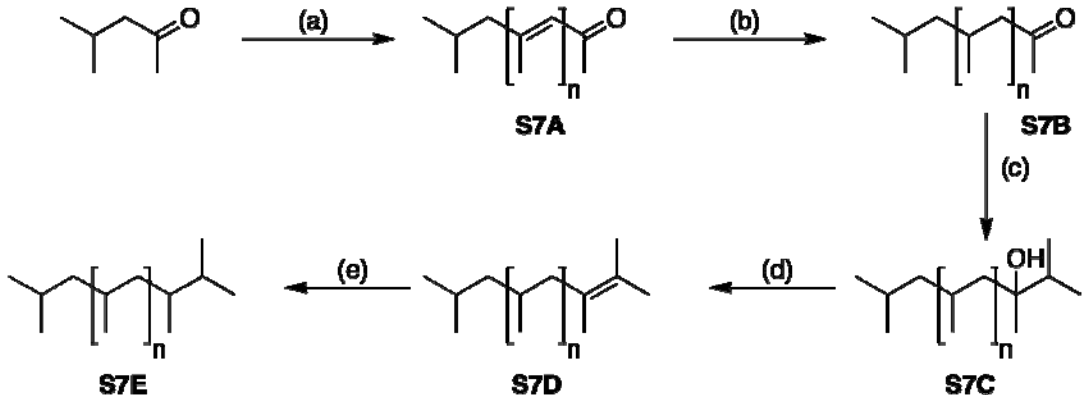


Figure S49: Mass spectrum of S6E{3}



Details for Series 7 Compounds

Scheme S7: Synthetic Route to Series 7 mixed HBA's



(a) $(OEt)_2P(O)(CH_2C(O)CH_3)$, NaH, PhMe, 100 °C, 5d (b) Pd/C-H_2, MeOH, O/N (c) (i) ^{i}BuMgBr, THF, r.t., O/N (ii) H_3O^+ (d) $BF_3.Et_2O$, CH_2Cl_2 , –10°C (e) Pd/C-H_2 (50 atm), MeOH/CH_2Cl_2 (1:1), O/N, r.t.

Figure S50: Partial GC–MS chromatogram of S7A{1-4}

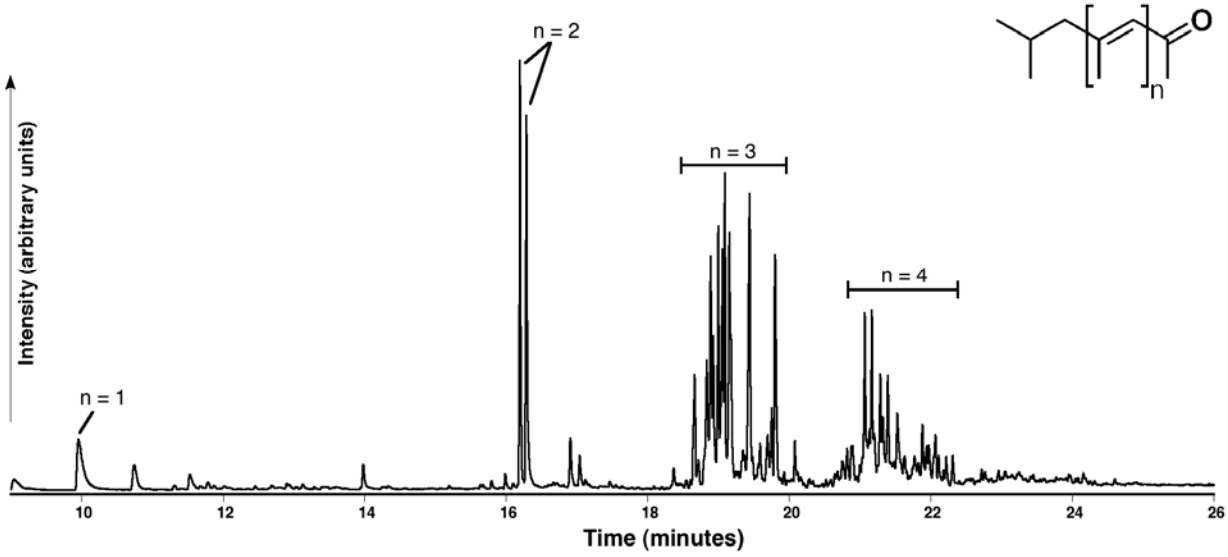


Figure S51: Partial GC–MS chromatogram of S7B{1-4}

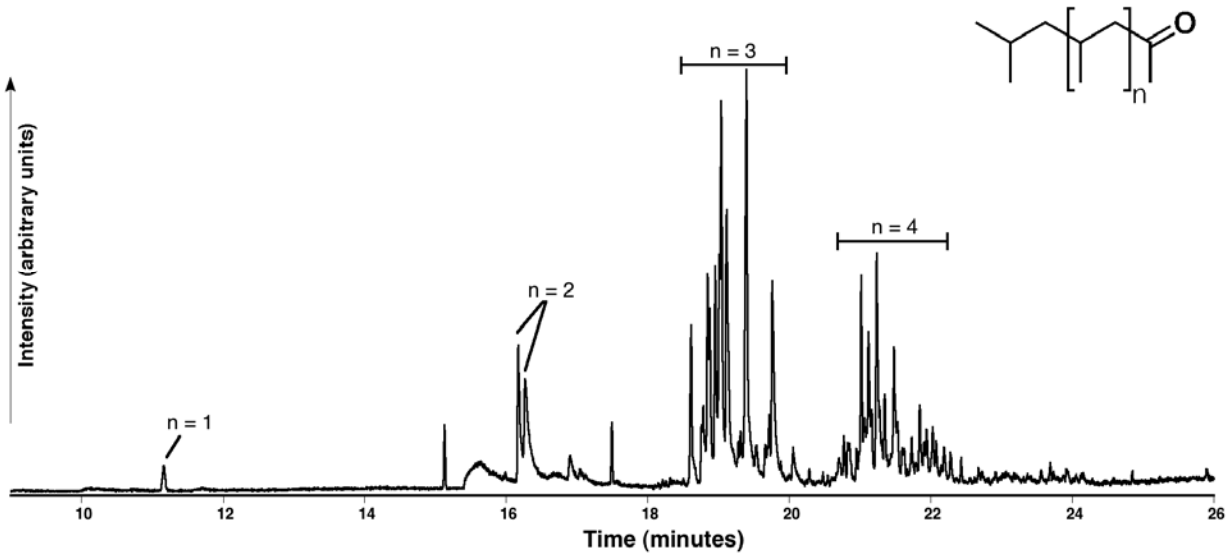


Figure S52: Partial GC–MS chromatogram of S7C{1-3}

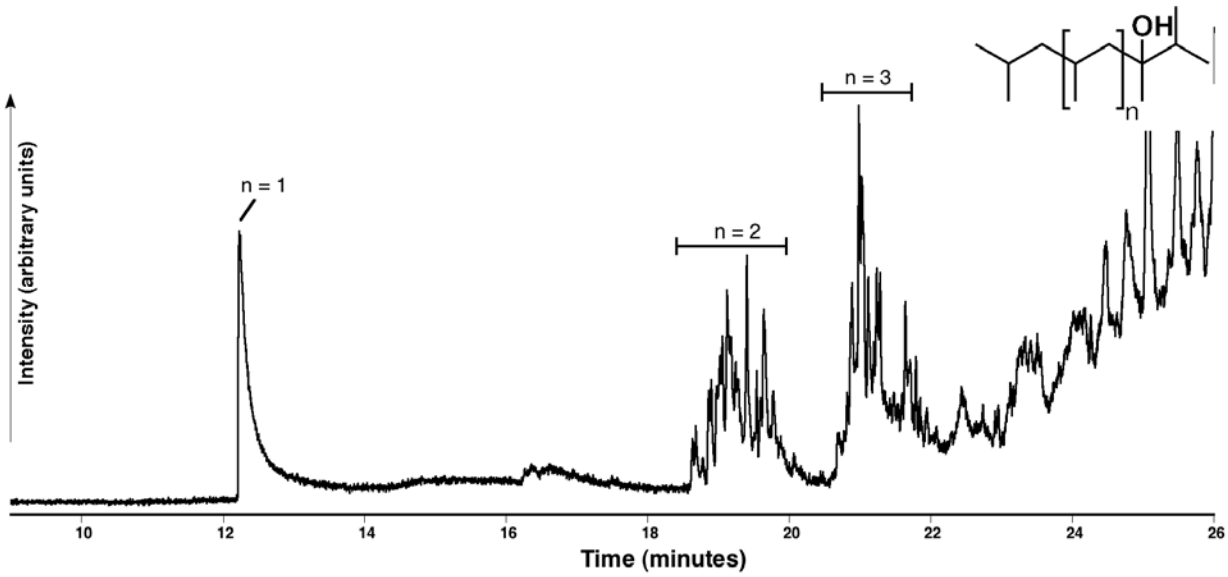


Figure S53: Partial GC–MS chromatogram of S7D{1-4}

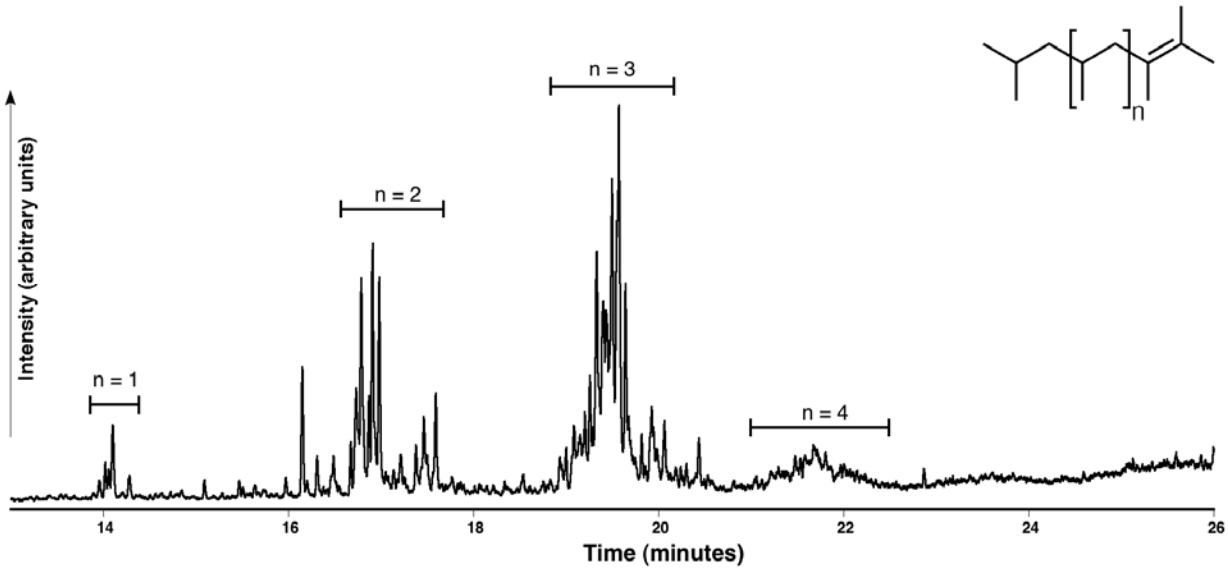


Figure S54: Partial GC–MS chromatogram of S7E{1-2}

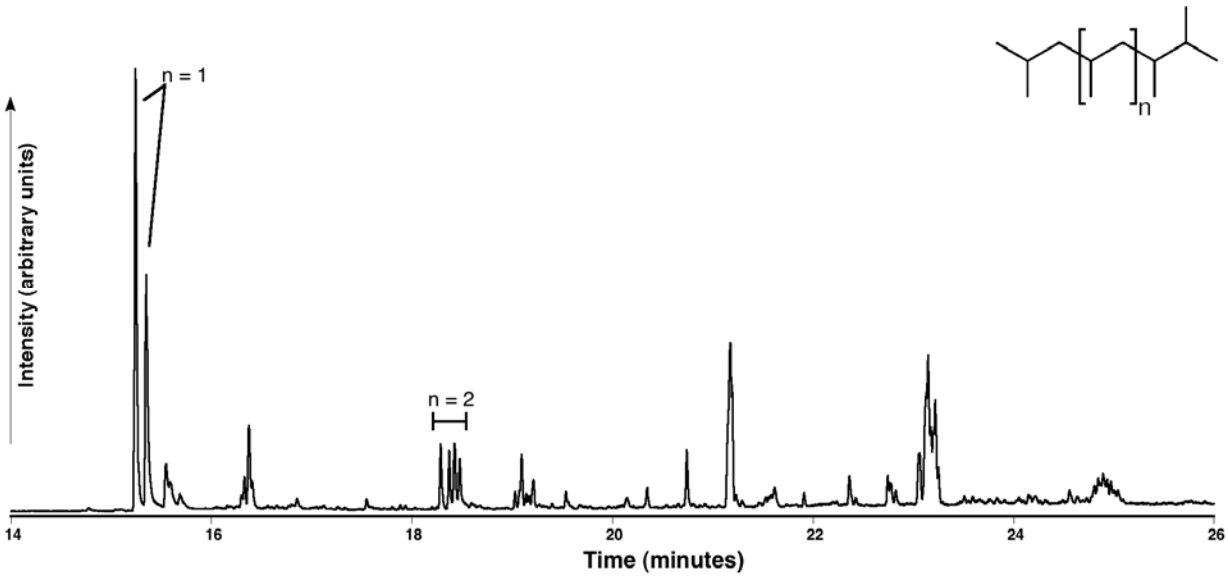


Figure S55: Mass spectrum of S7E{1}

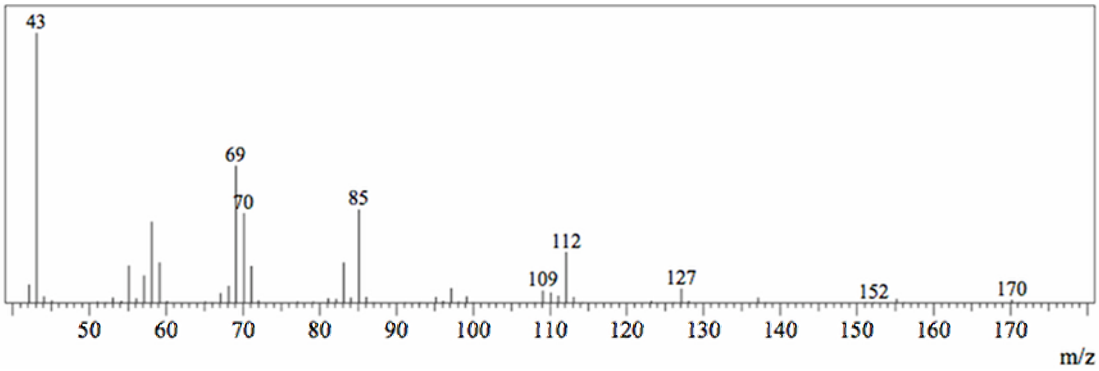
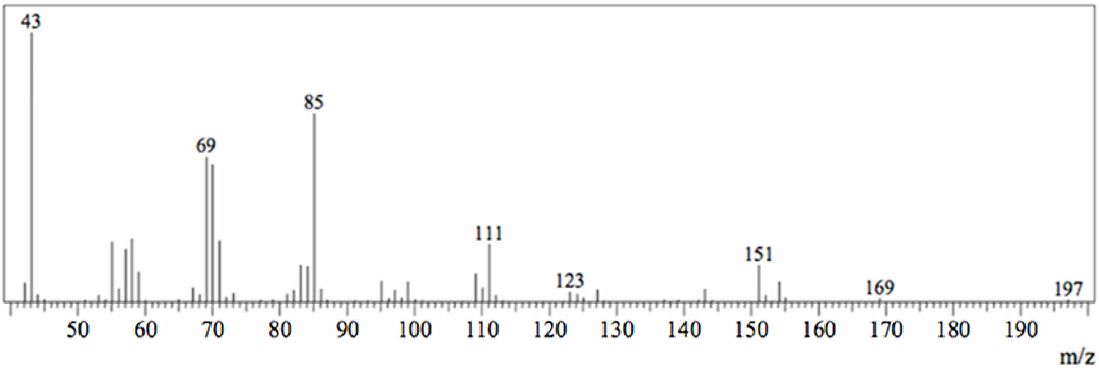


Figure S56: Mass spectrum of S7E{2}



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