Making Mixtures to Solve Structures: Structural Elucidation via Combinatorial Synthesis

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A domino Horner−Wadsworth−Emmons olefination strategy has been used to prepare homologous series of (polyen)ones, and through combinatorial elaboration, corresponding families of highly branched hydrocarbons. Gas chromatography−mass spectrometry of the mixtures has enabled the rapid and unambiguous identification of several highly branched alkanes of geochemical importance. This is the first example of the use of combinatorial synthesis for the elucidation of structural connectivity.

Introduction

Unambiguous synthesis has always provided the ultimate proof of molecular structure, most notably of natural products. The traditional one starting material, one (major) product approach to synthesis has confirmed the structure of myriad natural products, which have been the main inspiration and proving ground driving the development of novel, sophisticated synthetic organic chemistry over the last century.[1–6] In many other cases, synthesis has refuted the putative structure of a natural product,[7–9] even where an X-ray crystal structure had been determined.[10]

Structural elucidation of the components of compound libraries is generally considered to be a *problem* associated with combinatorial diversity-oriented synthesis.[11,12] However, Curran has elegantly and extensively demonstrated the power of a combinatorial split and mix approach using fluorous tagging for the elucidation of stereochemical configuration of various natural products.[13–23] Herein, we report the rapid, combinatorial synthesis of seven homologous series of highly branched alkanes (HBAs), which were used to unambiguously identify several hydrocarbons detected in environmental samples. To the best of our knowledge, this is the first time combinatorial synthesis has been used as a tool for elucidating structural connectivity.

The hydrocarbons of interest are unusual $(C_3)_n$ ($n = 4-10$) series of HBAs, which have been detected in the extracts of several ancient sediments,[24–30] and in the surface and groundwater of a South Australian winery.[26,31] An anthropogenic origin was supported by their GC-MS correlation with components of extracts of a commercially available polypropylene (PP);[15] however, fluctuation in the abundance of the HBAs through several sedimentary profiles was not consistent with a common plastic source. Furthermore, the sedimentary occurrence of these compounds has been closely correlated with several distinctive lithological features,[24,25,27,30] raising the possibility of a novel biological source.

Although several structural features have been inferred from their GC-MS characteristics, and four candidate series (**1**−**4**) were proposed (Figure 1),[26] unequivocal structural assignment requires correlation with authentic compounds.[32–34] Accordingly, we developed a synthetic route to the four candidate HBA series previously proposed, along with three other closely related families (**5**−**7**) (Figure 1).

Synthetic Strategy. The total or partial synthesis of polypropylene oligomers[35,36] and natural products[37–42] containing C_3 repeat units like those in the target molecules has been reported previously. While natural products might be suitable precursors to series **3**, **5**, and **6**, they are not readily amenable to the synthesis of the other target compounds; accordingly we opted for total synthesis.

Initially we were attracted by two similar, linear approaches in which the core C_3 units were derived from a

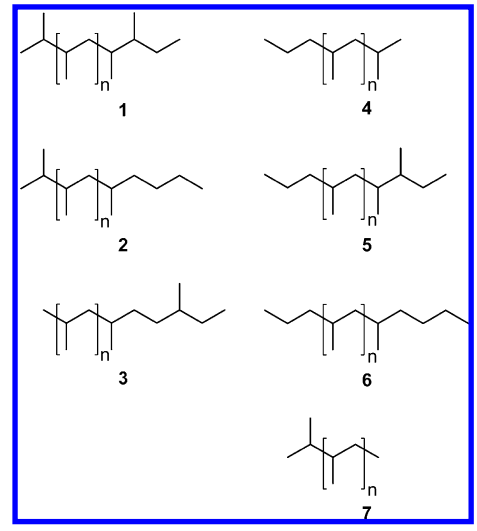

Figure 1. Target HBA series, $n = 1-3$.

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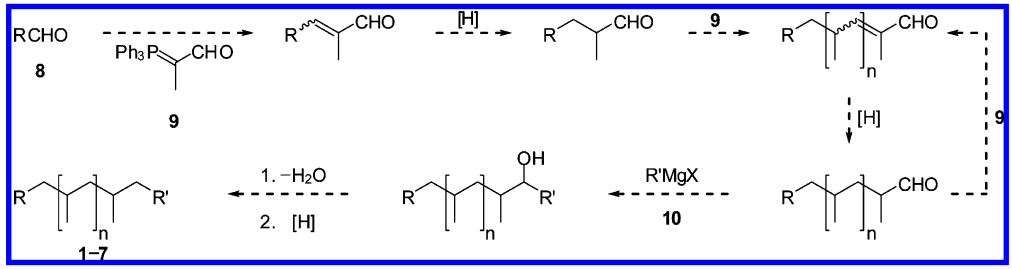
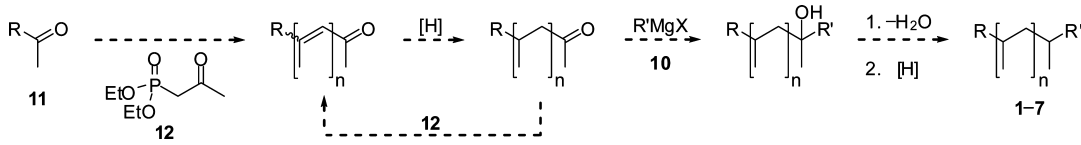
Scheme 1. Proposed Synthetic Route to HBAs ($n = 1-3$) Employing Iterative Wittig Olefination



Scheme 2. Proposed Synthetic Route to HBAs ($n = 1-3$) Employing Iterative HWE Olefination



single precursor, namely, the phosphorane **9** (Scheme 1) or phosphonate **12** (Scheme 2), making use of iterative Wittig or Horner−Wadsworth−Emmons (HWE) reactions, respectively. In each case, the homologous series are differentiated by the choice of starting aldehyde **8** (Scheme 1) or ketone **11** (Scheme 2), and Grignard reagent **10**, which define the terminal alkyl substituents.

We envisaged that complications associated with the production of mixtures of *E*/*Z* isomers would be overcome by immediate reduction of the olefins. Mixtures of regioisomeric alkenes formed after dehydration of the penultimate alcohols would be treated similarly. Obviously, we expected these approaches to provide mixtures of all the possible diastereomers; indeed they were required for comparison with the naturally occurring hydrocarbons. We anticipated that the diastereomers might be separable using gas chromatography, a prediction that was ultimately substantiated.

Although the approaches in Scheme 1 and 2 appear straightforward, it rapidly became apparent that traditional synthesis of all target compounds would be prohibitively laborious. Each series required approximately 15 linear steps to make the $n = 1-3$ homologues, amounting to well over 100 synthetic operations in total. Consequently, we opted for a much more efficient combinatorial strategy that would provide structurally well-defined mixtures, which could be resolved and analyzed by GC-MS.

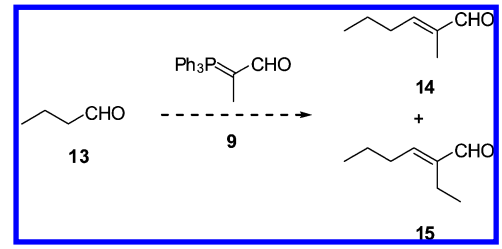
Results and Discussion

Wittig Approach. Initial investigations focused on a Wittig reaction of butyraldehyde (**13**) (Scheme 3), which could ultimately give rise to the series **2** and **6** hydrocarbons. No reaction between **13** and the phosphorane **9** was observed in DCM at room temperature, and at higher temperatures in a variety of different solvents the major product was **15**, resulting from aldol condensation of the butyraldehyde (**13**). Only the use of H_2O/THF (1/9) as solvent avoided significant aldol coupling, but the conversion to the desired olefin (**14**) was low. This was improved with a large excess of the phosphorane **9**, but its expense made such methodology uneconomical.

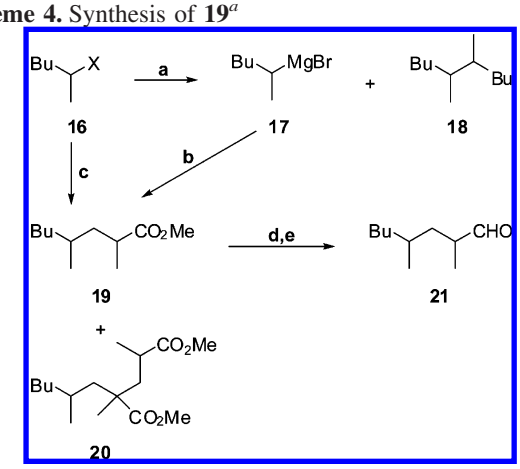
To circumvent the problems associated with volatile starting materials, we chose to prepare 2,4-dimethyloctanal (**21**), a more advanced precursor to the series **2** and **6** hydrocarbons, by an alternative route, and test the Wittig methodology on this substrate. An initial attempt at the synthesis of **21** began with the conjugate addition of the cuprate derived from 2-hexylmagnesium bromide (**17**) with methyl methacrylate (Scheme 4). Preparation of the Grignard was complicated by formation of the homocoupled product **18** unless highly activated magnesium was used at 0 °C or lower. The organocuprate, formed by treatment of **17** with CuBr-LiCl, underwent Michael addition with methyl methacrylate, but the desired product **19** was contaminated by the diester **20**, arising from a second Michael addition of the intermediate enolate to another molecule of methyl methacrylate.

A more efficient and simple synthesis of **19** was achieved using Ni_2B-BER-catalyzed (BER = borohydride exchange

Scheme 3. Reaction of Butyraldehyde with the Phosphorane **9**

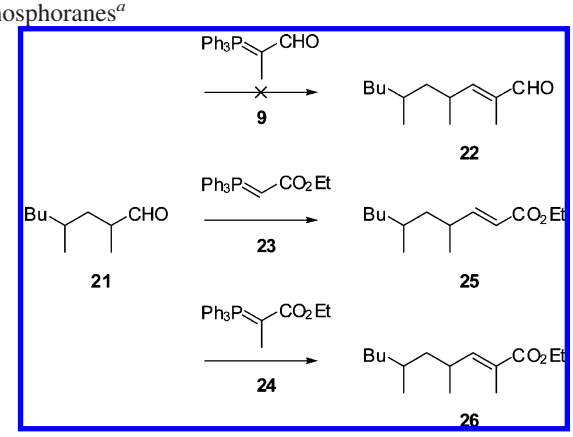


Scheme 4. Synthesis of **19**[a]



[a] Reagents and conditions: (a) Mg, THF, 0 °C; (b) (i) CuBr-LiCl, −78 °C, (ii) methyl methacrylate, 26% over 3 steps; (c) Dowex 1X2 (BH_4^- form), $Ni(OAc)_2$, MeOH, methyl methacrylate, X = Br, 42%, X = I, 84%; (d) $LiAlH_4$, THF, Δ, 3 d, 92%; (e) PCC, DCM, 0 °C, 2 h, 89%.

Scheme 5. Reactions of **19** with Different Stabilized Phosphoranes[a]



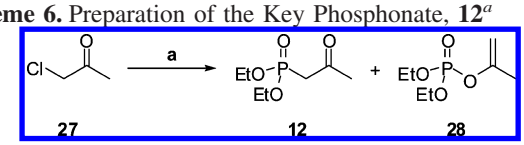
[a] Esters **25** and **26** gave rise (separately) to just two peaks with equivalent mass spectra in the GC-MS, indicating only a single alkene configuration, presumably *E*, but a mixture of diastereomers because of the two stereocenters.

resin, BH_4^- form Dowex 1X2 100−200 mesh) radical addition of 2-halohexanes **16** to methyl methacrylate (Scheme 4).[43] The reaction was particularly effective in the case of the iodide, giving **19** in 84% yield after distillation. Reduction of **19** to the corresponding alcohol,[44] followed by PCC oxidation, afforded the required aldehyde **21**, which was annoyingly prone to spontaneous oxidation.

Surprisingly, the Wittig reaction of **21** with the phosphorane **9** gave only trace quantities of the desired enal **22** by GC-MS, despite much experimentation and precedent with similar reactants.[45] It was unclear if the lack of reaction was due to the aldehyde **21** or the phosphorane **9**; thus, the reactivity of the former was explored with two electronically similar phosphoranes, **23** and **24** (Scheme 5). There was a marked difference in the reactivity of the two phosphoranes with **21**; the olefination with **23** was complete within 1 h, giving the α,β-unsaturated ester **25**, whereas the reaction with **24** required nearly 24 h for consumption of the aldehyde. The dramatic reduction in the reactivity of **24** would be mirrored in **9**, which presumably is also more susceptible to auto-condensation, accounting for the poor conversion to **22**. These setbacks prompted us to progress to the second strategy using the more reactive phosphonate **12**.

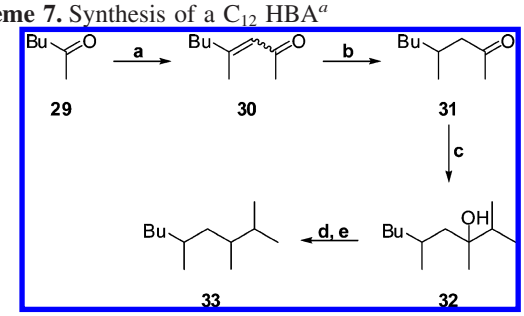
HWE Approach. Although the phosphonate **12** required for the HWE reactions is commercially available, it is quite expensive, and as large amounts were required, we opted for synthesis. The literature preparations of **12**[46–49] are either low yielding or poorly described. The reaction of a trialkyl phosphite with an α-haloketone can produce both Michaelis−Arbuzov (β-ketophosphonate) and Perkow (enol phosphate) products, α-iodoketones giving the former, and α-bromo and α-chloroketones giving predominately the latter. Employing an in situ Finkelstein reaction[46] of chloroacetone (**27**), the Michaelis−Arbuzov reaction with triethyl phosphite predominated, with separation of minor amounts of the enol phosphate **28** achieved by treatment with aqueous lithium carbonate,[47] giving **12** in 70% yield after distillation. Careful purification of the starting materials, in particular freeing triethyl phosphite of contaminating triethyl phosphate, was crucial in obtaining

Scheme 6. Preparation of the Key Phosphonate, **12**[a]



[a] Reagents and conditions: (a) KI, Me_2CO/MeCN, 0 °C, 12 h, 62% (**12** only).

Scheme 7. Synthesis of a C_{12} HBA[a]



[a] Reagents and conditions: (a) **12**, NaH, PhMe, 100 °C, 3 d, 82%; (b) Pd/C, H_2, MeOH, 12 h, 82%; (c) (i) *i*-PrMgBr, Et_2O, 0 °C, (ii) H_3O^+, 57%; (d) $BF_3.Et_2O$, Et_2O, 0 °C (e) Pd/C, H_2, DCM/MeOH, 12 h, 71% (2 steps).

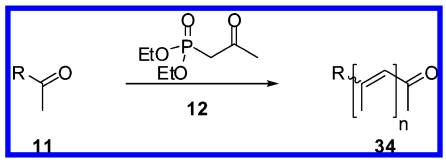
phosphonate **12** of good purity, which in turn was critical to the success of its HWE reactions.

To validate the HWE approach, the C_{12} HBA **33** (Figure 1, Series 2, $n = 1$) was chosen as a target (Scheme 7). The HWE reaction of 2-hexanone (**29**) with phosphonate **12** gave a 17:3 mixture of the known[50] *E* and *Z*-enones **30**, although reaction times were lengthy (1−3 days). Catalytic hydrogenation of the mixture gave the known[51] saturated ketone **31**, which upon treatment with excess isopropylmagnesium bromide afforded tertiary alcohol **32**, as a mixture of diastereomers, as shown by GC-MS. Dehydration of **32** with boron trifluoride diethyl etherate[52] gave a mixture of isomeric alkenes (again shown by GC-MS), which simplified to the diastereomeric mixture of alkanes **33** upon catalytic hydrogenation.

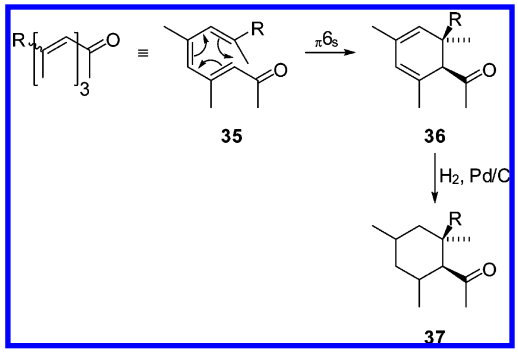
Attempts to improve the yield of the HWE reaction by increasing the excess of phosphonate **12** resulted in near complete consumption of ketone but produced a large number of other products. Analysis of the GC-MS of these mixtures revealed the other products to be (polyen)ones arising from domino HWE reactions. To the best of our knowledge, domino HWE (or Wittig) reactions have not been used synthetically, presumably because mixtures of homologues are formed. In our case the formation of a series of homologous (polyen)ones was advantageous, and so we sought to exploit this methodology for the combinatorial synthesis of the target HBAs.

Optimization of the Domino HWE Reaction. Progress of the HWE reactions was monitored using GC-MS. The choice of solvent and reaction temperature had a significant effect on the product distribution; reactions performed under reflux in tetrahydrofuran (THF) gave primarily the (monoen)one **34** ($n = 1$), irrespective of the excess of phosphonate used (up to 8 fold), or reaction time. Reactions in toluene resulted in formation of the (monoen)one within the first 24 h, followed by slow conversion to the (polyen)ones **34** ($n > 1$) (Scheme 8), as expected given the reduced reactivity of the

Scheme 8. Domino HWE Synthesis of (Polyen)ones **34**



Scheme 9. Proposed Electrocyclization of *E,Z,E*-Triene **35**, Followed by Hydrogenation to Give Four Diastereomeric Cyclohexanes **37**



conjugated ketones. Reaction times of 1 week or more were required to produce detectable amounts of the higher order (polyen)ones **32** ($n = 2-4$).

After prolonged reaction times, the number of peaks observed in the gas chromatograms of the (polyen)ones **34** was greater than the total number of possible *E/Z* isomers expected when $n \geq 3$. These minor byproducts were clearly isomeric, given their equivalent *m/z* and similar mass spectra, but their structure was not obvious until the mixtures of (polyen)ones were subjected to exhaustive catalytic hydrogenation, which revealed peaks in the GC-MS with [*m/z*−2] relative to the desired saturated ketones, indicating monocyclic structures. We propose that the byproducts arise from electrocyclization, as exemplified in Scheme 9 for the triene **35**.

As can be seen in Figure 2, only four of the possible eight diastereomeric cyclohexanes are observed in the gas chromatogram of the hydrogenation product **37**. It would seem most likely that these arise via suprafacial electrocyclization of the *E,Z,E*-triene **35** (the configuration of the central double bond must be *Z* to allow electrocyclization to occur), to give the cyclohexadiene **36** with a *cis*-relationship of the *iso*-butyl and acetyl groups, hydrogenation of which results in four diastereomeric cyclohexanes **37**. Presumably, the other diasteroisomeric *E,Z,Z* and *Z,Z,E* trienes and the corresponding cyclohexadienes/cyclohexanes with a *trans*-relationship of the *iso*-butyl and acetyl groups are formed in smaller quantities.

The formation of the cyclohexadiene byproducts was favored at higher temperatures, thus the optimal reaction temperature, balancing (polyen)one formation with minimal electrocyclization, was typically 90−100 °C. The cyclohexadienes were difficult to preparatively separate from the acyclic ketones and so were carried though the remaining steps in the synthesis. However, they and their "progeny" were in general easily separated from the desired products with GC, and so did not interfere with the analysis of the mixtures.

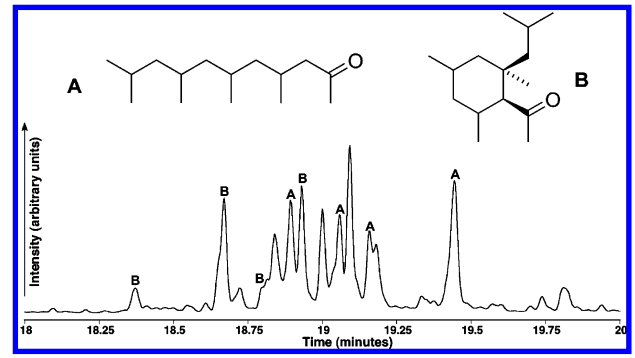


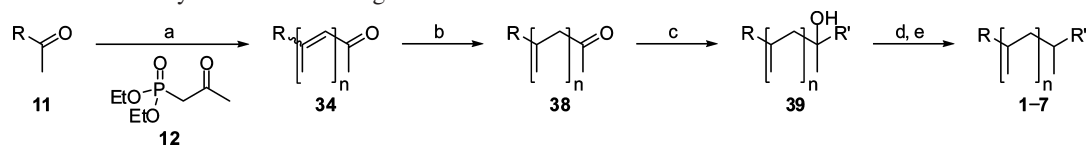
Figure 2. Section of the gas chromatogram from the crude mixture of products derived from a domino HWE reaction that was left for an extended period to maximize the formation of electrocyclization byproducts, followed by catalytic hydrogenation. **A** = four diastereomeric C_{15} acyclic saturated ketones (*m/z* = 226); **B** = the four diastereomeric cyclohexanes (*m/z* = 224) (and their enantiomers). Unlabeled peaks are due to unidentified byproducts. It should be noted that under the optimized domino HWE conditions, all byproducts were much less prevalent.

Aside from these electrocyclization products, some other minor peaks were observed by GC-MS, most of which could not be identified. The few that were, comprised a family of $(C_3)_n$ hydrocarbons resistant to catalytic hydrogenation, suggesting that they were aromatic. The mass spectrum of the first peak in the series ($n = 4$) was consistent with mesitylene, with the higher order members presumably being mesitylene derivatives bearing additional C_3 units. Presumably these are formed by homo-oligomerization of the phosphonate. Again these were well separated by GC from the desired HBAs of interest, and thus did not interfere with subsequent analyses.

Combinatorial Synthesis of the Target Hydrocarbons. Having established the synthesis of **33** (Scheme 7) starting from a single ketone, the methodology was now applied to the combinatorial synthesis of the target hydrocarbon series, by elaboration of each mixture of (polyen)ones **34** (Scheme 10). The starting ketones (**11**) and Grignard reagents used for the synthesis of each target series are listed in Table 1.

All reactions were monitored, and products characterized, by GC-MS; given the complex mixtures of homologues and diastereomers formed, spectroscopic characterization was of very limited value. By way of example, gas chromatograms of the series **2** intermediates and final products are shown in Figure 3. The corresponding gas chromatograms for the other series are included in the Supporting Information. In most cases the gas chromatograms of the target HBAs **1**−**7** displayed peaks corresponding to the expected number of diastereomers for each cluster ($n = 1$, 2, etc.), which is testament to the remarkable resolving power of analytical gas chromatography. Some of the low molecular weight homologues (usually $n = 1$) were lost during the syntheses because of their volatility. However, this was inconsequential as only the higher homologues were required; the lower homologues are not present in the environmental samples, presumably because of evaporation.

Scheme 10. Combinatorial Synthesis of the Target HBAs[a]



[a] Reagents and conditions: (a) **12**, NaH, PhMe, 100 °C, 3−7 d; (b) Pd/C, H_2, MeOH, O/N; (c) (i) RMgBr, Et_2O (ii) H_3O^+; (d) $BF_3.Et_2O$, Et_2O, −10 °C, 2−4 h (e) Pd/C, H_2, DCM/MeOH, O/N.

Table 1. Starting Ketones **11** and Grignard Reagents Used in the Synthesis of the Target HBA Series (Figure 1)

target HBAs	ketone **11**, R =	R′MgBr, R′ =
1	*i*-Pr	*sec*-Bu
2	Bu	*i*-Pr
3	*i*-Bu	Pr
4	*i*-Bu	3-methylpentyl
5	Pr	Bu
6	Pr	*sec*-Bu
7	*i*-Bu	*i*-Pr

Correlation with $(C_3)_n$ HBAs from Polypropylene and Environmental Extracts. The GC-MS data derived from the synthetic HBAs were compared with those from a polypropylene extract that had previously been shown to contain the same $(C_3)_n$ HBAs detected in environmental samples. The C_{15} and C_{18} congeners of what have been designated series E and F,[27] correlate precisely with the first eluting C_{15} and C_{18} diastereomers of HBA series **4** and **6**, respectively, both in retention time (Figure 4) and mass spectra (detailed elsewhere[53]), allowing their structural connectivity to be assigned unambiguously. In support of these conclusions, series **4** and **6** compounds have been identified as products of the hydro-oligomerization of propylene using a zirconium metallocene complex.[54]

In all cases, a single diastereomer predominates in the PP extract, reflecting diastereoselective industrial synthesis,[23] although it is clear that some of the other diastereomers are also present in smaller amounts. It has been demonstrated with the use of pyrolysis GC-MS that the fragments derived from isotactic PP elute before those of syndiotactic or atactic PP.[55,56] Accordingly, it is most likely that the major correlating peaks from the PP extracts and the series **4** and **6** hydrocarbons are the meso^n diastereomers in both cases.

A comprehensive comparison of the GC and MS data of the series **E** and **F** $(C_3)_n$ HBAs and the authentic materials prepared in this study has been reported.[53]

Conclusions

We have developed an expedient and unambiguous synthesis of seven homologous series of HBAs using domino HWE reactions to prepare the initial mixtures of (polyen)ones for subsequent combinatorial elaboration. In conjunction with GC-MS, this strategy enabled the rapid identification of the structures of some HBAs detected in environmental samples, and has confirmed that they are not biomarkers, but actually polypropylene oligomer contaminants from plastic sampling containers. The combinatorial approach described herein may prove useful for the preparation of other series of volatile oligomeric

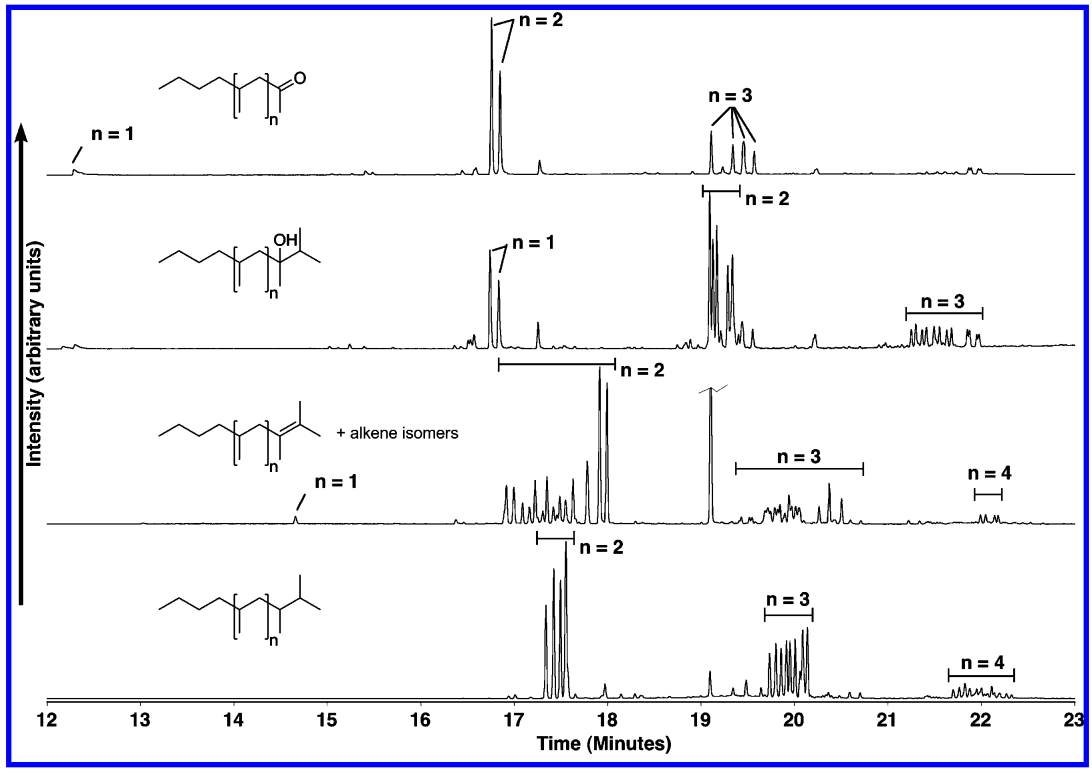


Figure 3. Gas chromatograms of Series **2** intermediates and targets.

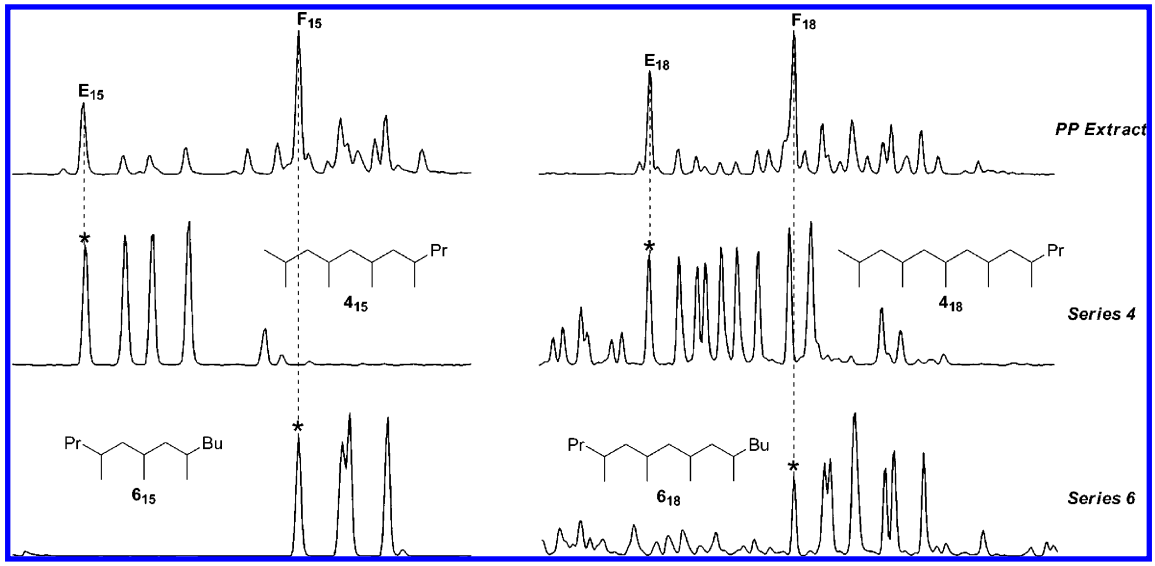


Figure 4. Partial *m*/*z* 85 chromatograms of a PP extract, series **4**, and series **6**, showing retention time correlations. The relative abundance of each chromatogram has been separately normalized. $E_{15/18}$ and $F_{15/18}$ are the $C_{15/18}$ members of $(C_3)_n$ HBA series previously called E and F.[27]

compounds, where the primary goal is rapid structural elucidation of components of complex mixtures.

Experimental Section

Dry THF, toluene, and diethyl ether were distilled from sodium benzophenone ketyl radical under argon. Boron trifluoride etherate complex ($BF_3.Et_2O$), 1-bromobutane, 2-bromobutane, 2-bromopropane, ethyl bromoacetate, ethyl 2-bromopropionate, 2-hexanol, 2-hexanone, 2-pentanone, 3-methyl-2-butanone, 3-methyl-1-pentanol, 4-methyl-2-pentanone, pyridinium chlorochromate (PCC), and triphenylphosphine were used as received. Methyl methacrylate and triethylphosphite were distilled under reduced pressure just prior to use. Chloroacetone was freshly distilled under reduced pressure with the aid of an air-leak tube (fitted to an argon filled balloon) and a 10 cm Vigreux column to avoid carryover from bumping. 1-Bromo-3-methylpentane was prepared from 3-methyl-1-pentanol as previously described.[57] Grignard reagents were prepared by reaction of alkyl halides with a 5-fold excess of mechanically activated[58] magnesium in anhydrous Et_2O. Grignard reagents were standardized immediately after preparation by titration against ~1 M HCl, and were typically between 0.5 and 2.0 M. Borohydride (BH_4^-) - form Dowex 1X2 (100 − 200 mesh) anion exchange resin (BER) was prepared by treatment of a stirring slurry of the commercially available chloride (Cl^-) - form in water with excess $NaBH_4$ for 30 min before being filtered, washed with H_2O and EtOH, and dried under vacuum. The BH_4^- content was determined by measurement of the volume of H_2 produced on treatment with HCl. AR acetone, diethyl ether, and MeCN were used as received. Solvents for general use, DCM, and hexanes were distilled prior to use.

NMR spectra were acquired on either a Bruker AV500 (^1H at 500.1 MHz and ^{13}C at 125.4 HMz) or a Bruker AV600 (^1H at 600.1 MHz and ^{13}C at 150.9 HMz) spectrometer. Infrared spectra were collected using a Perkin-Elmer Spectrum One Spectrometer at 2 cm^{-1} resolution; liquids were acquired as thin films between NaCl plates and solids were acquired as KBr discs. Routine GC-MS was carried out on a Shimadzu QP2010 GC-MS using a Restek 5MS column (30 m × 0.25 mm ID). UHP Helium was used as the carrier gas at a flow rate of 0.94 mL/min at 44.7 KPa. Injections of 1:1 DCM/MeOH solutions of the mixtures were performed using a split injection mode at an injection port temperature of 250 °C. The oven was held at 40 °C for 10 min before being heated to 250 at 12 °C/min. Full scan (*m*/*z* 25−350) mass spectra were acquired with an electron energy of 70 eV and source temperature of 200 °C. Comparison GC-MS data were acquired on an Agilent 6890/5975b GC-MS using a Phenomenex ZB-5 column (30 m × 0.25 mm × 0.25 μm). The GC was used in pulsed splitless mode, and the oven was temperature programmed from an initial 40 °C held isothermal for 2 min then increased at a rate of 4 °C/min 300 °C and held isothermal for 25 min. Helium carrier gas was maintained at a constant flow of 1.1 mL/min. Full scan (*m*/*z* 25−400) and selected ion (*m*/*z* 85, 141, 155, 169, 212, 254) mass spectral data were both acquired with an electron energy of 70 eV, source temperature of 230 °C, and transfer line temperature of 300 °C.

2,4-Dimethyl-1-octanol (1:0.61 Ratio of Diastereomers). Methyl 2,4-dimethyloctanoate (**19**) (10 g, 54 mmol) was added to a suspension of $LiAlH_4$ (15.54 g, 409 mmol) in THF (350 mL) under argon, and the mixture was heated under reflux for 2 d. The flask was cooled in an ice bath, and MeOH was cautiously added until gas evolution ceased, followed by H_2O (10 mL). The mixture was diluted further with H_2O (100 mL), then acidified to pH 5 with 1 M HCl. The resulting solution was extracted with DCM (3 × 100 mL). The organic extract was dried ($MgSO_4$) and evaporated giving the title alcohol as a colorless viscous oil (7.83 g, 92%). ^1H NMR (600.1 MHz, C_6D_6): δ (ppm) 0.83−0.93 (m, 9H, all CH_3), 0.97−1.37 (m, 8H, H3 and H5−H7), 1.40−1.49 (m, 1H, H4), 1.57−1.66 (m, 1H, H2), 3.18−3.35 (m, 2H, H1). The ^1H NMR data were somewhat different to those reported at 200 MHz;[44] ^{13}C NMR (125.8 MHz, C_6D_6): δ (ppm) 14.4 (CH_3), 16.6, 17.6 (CH_3), 19.7 (CH_3), 20.6 (CH_3),

23.47 (CH_2), 23.49 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 30.3 (CH), 30.4 (CH), 33.5 (CH), 33.6 (CH), 36.8 (CH_2), 38.1 (CH_2), 41.1 (CH_2), 41.5 (CH_2), 68.1 (CH_2O), 68.9 (CH_2O); GC-MS: 15.45 min - *m/z* 43 (100%), 55, 56, 57, 69, 70, 71, 83, 84, 85, 98, 112, 127, 140, 157; 15.54 min - *m/z* 43 (100%), 55, 56, 57, 69, 70, 71, 83, 84, 85, 98, 112, 127, 140; GC−CI$^+$-HRMS: $C_{10}H_{21}O$ requires 157.1592 found 156.9950; IR (thin film): ν (cm^{-1}) 3338 (OH).

2,4-Dimethyloctanal (21) (1:0.73 Ratio of Diastereomers). 2,4-Dimethyloctanol (1.00 g, 6.32 mmol) was dissolved in DCM (50 mL), and the solution was sparged with argon for 5 min while being cooled in an ice-bath. PCC (4.07 g, 18.9 mmol) was added in portions over 10 min with vigorous stirring. The mixture was stirred at room temperature overnight, after which time Florosil (2 g) was added. After stirring for 30 min the suspension was vacuum-filtered through a column of Florosil (30 g). The column was washed with DCM, and the filtrate was evaporated to give **21** as a colorless oil (0.88 g, 89%). The compound was used immediately because of its rapid aerial oxidation. ^{1}H NMR (600.1 MHz, $CDCl_3$): δ (ppm) 0.84−0.89 (m, 6H), 1.06 (m, 3H), 1.08−1.32 (m, 6H), 1.43−1.72 (m, 2H), 2.35−2.46 (m, 1H, H2), 9.56 (d, J = 2.5 Hz, 1H, CHO), 9.59 (d, J = 2.1 Hz, 1H, CHO); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ (ppm) 13.5 (CH_3, C8), 14.2 (CH_3), 14.3 (CH_3), 19.4, 20.0, 23.04 (CH_2, C7), 23.06 (CH_2, C7), 29.1 (CH_2, C6), 29.3 (CH_2, C6), 30.3, 30.5, 36.6 (CH_2, C5), 37.2 (CH_2, C5), 37.8 (CH_2, C3), 38.4 (CH_2, C3), 44.3, (CH, C2), 44.4 (CH, C2), 196.2 (CH, CHO); GC-MS: 14.13 min - *m/z* 43, 55, 56, 57 (100%), 58, 69, 71, 85, 98, 99, 113; 14.24 min - *m/z* 43, 55, 56, 57 (100%), 58, 69, 71, 85, 98, 99, 113; HREI-MS: $C_{10}H_{20}O$ requires 156.1514 found 156.1512; IR (thin film): ν (cm^{-1}) 1727 (C═O). This compound has been reported but not characterized.[59]

(E)-Ethyl 4,6-Dimethyldec-2-enoate (25) (1:0.73 Ratio of Diastereomers). (2-Ethoxy-2-oxoethyl)triphenyl phosphonium bromide (2.05 g, 4.78 mmol) was dried under vacuum for 30 min. Dry THF (20 mL), Et_3N (2 mL) and **21** (487 mg, 3.12 mmol) were added, and the mixture was heated under reflux overnight. The mixture was poured into H_2O (250 mL) and extracted with Et_2O (3 × 40 mL). The extract was dried ($MgSO_4$) and evaporated. The crude product was subjected to flash chromatography. Elution with Et_2O/hexane (2:98) gave **25** as a pale yellow oil (81 mg, 12%). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ (ppm) 0.81−0.85 (m, 3H, C6(CH_3)), 0.85−0.90 (m, 3H, H10), 0.99−1.04 (m, 3H, C4(CH_3)), 1.05−1.48 (m, 12H, H5−H9 and OEt(CH_3)), 4.18 (q, J = 7.2 Hz, 2H, OCH_2), 5.74− 5.79 (m, 1H, H2), 6.77−6.89 (m, 1H, H3); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ (ppm) 14.3 (CH_3), 14.4 (CH_3), 19.4, 19.6, 19.9, 23.1 (CH_2), 23.2 (CH_2), 29.15 (CH_2), 29.20 (CH_2), 30.3 (CH), 30.5 (CH), 34.14 (CH), 34.41 (CH), 36.7 (CH_2), 37.2 (CH_2), 43.7 (CH_2), 44.0 (CH_2), 60.3 (CH_2), 119.3 (C2H), 119.8 (C2H), 154.9 (C3H), 155.3 (C3H), 167.1 (C═O), 167.2 (C═O); GC-MS: 19.52 min - *m/z* 43, 53, 55, 57, 67, 68, 69 (100%), 81, 82, 83, 84, 95, 96, 97, 98, 99, 100, 101, 109, 113, 213, 125, 128, 129, 138, 141, 142, 143, 169, 181, 184, 197, 211, 226 ($M^{\bullet+}$, 0.66%); 19.64 min - *m/z* 43, 53, 55, 57, 67, 68, 69 (100%), 81, 82, 83, 84, 95, 96, 97, 98, 99, 100, 101, 109, 113, 213, 125, 128, 129, 138, 141, 142, 143, 169, 181, 184, 197, 211, 226 ($M^{\bullet+}$, 0.59%); EI-HRMS: $C_{14}H_{26}O_2$ requires 226.1933 found 226.1928; IR (thin film): ν (cm^{-1}) 1721 (C═O), 1651 (C═C).

(E)-Ethyl 2,4,6-Trimethyldec-2-enoate (26) (1:0.76 Ratio of Diastereomers). (2-Ethoxy-1-methyl-2-oxoethyl)triphenyl phosphonium bromide (2.18 g, 4.92 mmol) was dried under vacuum for 30 min. Dry THF (20 mL), Et_3N (2 mL) and **21** (490 mg, 3.14 mmol) were added, and the mixture was heated under reflux overnight. The mixture was poured into H_2O (250 mL) and extracted with Et_2O (3 × 40 mL). The extract was dried ($MgSO_4$) and evaporated. The crude product was subjected to flash chromatography. Elution with Et_2O/hexane (2:98) gave **26** as a colorless oil (156 mg, 21%). ^{1}H NMR (600.1 MHz, $CDCl_3$): δ 0.78−0.90 (m, 6H), 0.96 (t, J = 6.7 Hz, 3H), 0.99−1.63 (m, 12H, H5−H9 and OEt(CH_3)), 1.80−1.86 (m, 3H, C2(CH_3)), 2.52−2.65 (m, 1H, H4), 4.17 (q, J = 7.1 Hz, OEt(CH_2), 6.45−6.56 (m, 1H, H3); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ (ppm) 13.97 (CH_3), 14.13 (CH_3), 19.45, 19.65, 19.81, 20.93, 22.52 (CH_2), 22.86 (CH_2), 28.93 (CH_2), 30.29, 30.56, 30.64, 30.75, 31.46 (CH_2), 36.37 (CH_2), 37.12 (CH_2), 44.15 (CH_2), 44.43 (CH_2), 60.23 (CH_2), 125.62 (=C), 126.00 (=C), 148.13 (=CH), 148.36 (=CH), 168.24 (C═O), 168.39 (C═O); GC-MS: 19.82 min - *m/z* 43, 55, 57, 67, 69, 83, 87, 95, 102, 109, 113, 115 (100%), 126, 127, 139, 142, 155, 156, 179, 183, 195, 211, 225, 240 ($M^{\bullet+}$, 2.82%); 19.95 min - *m/z* 43, 55, 57, 67, 69, 83, 87, 95, 102, 109, 113, 115 (100%), 126, 127, 139, 142, 155, 156, 179, 183, 195, 211, 225, 240 ($M^{\bullet+}$, 3.68%); EI-HRMS: $C_{15}H_{28}O_2$ requires 240.2089 found 240.2096.

4-Methyloct-3-en-2-one (30)[50] (17:3 Mixture of E/Z Isomers). A suspension of NaH 60% dispersion in mineral oil (2.71 g, 67.8 mmol) in anhydrous toluene (100 mL) was vigorously stirred for 30 min to dissolve the mineral oil. The stirring was stopped, and the toluene was removed using a filter-tip cannula. The NaH was resuspended in toluene (100 mL), the suspension was cooled in an ice bath, and a solution of diethyl 2-oxopropylphosphonate (**12**) (12.2 g, 62.8 mmol) in toluene (50 mL) was added dropwise over 30 min, resulting in effervescence because of production of H_2. The solution was allowed to stir for 1 h before the addition of 2-hexanone (6.22 g, 61.9 mmol) in one portion. The viscous mixture was heated under reflux overnight, whereupon it darkened considerably. Upon cooling to room temperature, a viscous orange oil separated. The mixture was poured into H_2O (300 mL), and washed in with Et_2O. 1 M HCl was added until the water layer was neutral and the organic layer was collected. The aqueous layer was extracted with Et_2O (2 × 100 mL), and the combined extract was dried ($MgSO_4$) and evaporated. The residue was fractionally distilled to give **30** as a colorless oil (7.14 g, 82%), bp = 30−40 °C at 0.7 mmHg. ^{1}H NMR (500.1 MHz, $CDCl_3$) *E*-isomer: δ (ppm) 0.92 (t, J = 7.2 Hz, 3H, H8), 1.28−1.48 (m, 4H, H6 and H7), 2.10−2.13 (m, 5H, H1 and H5), 2.17 (s, 3H, C4(CH_3)), 6.07 (s, 1H, H3); GC-MS: 13.73 min - *m/z* 43 (90%), 55 (75.9%), 69 (43%), 83 (100%), 98 (91%), 111, 125 (34%), 140 ($M^{\bullet+}$, 0.7%). These data are consistent with those published.[50] The minor *Z*-isomer[50] eluted at 12.93 min - *m/z* 43 (100%), 55 (56%), 69, 82, 97, 111, 125 140 ($M^{\bullet+}$, 5%).

4-Methyloctan-2-one (31). A solution of **30** (5.02 g, 35.8 mmol) in MeOH (50 mL) was stirred with 10% Pd/C (~ 200 mg) under 10 atm of H_2 in an autoclave overnight. The suspension was filtered though a pad of Celite and washed with MeOH. The solvent was evaporated to give **31** as a colorless liquid, (4.46 g, 82%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ (ppm) 0.881 (t, $J = 7.1$ Hz, 3H, H8), 0.885 (d, $J = 6.7$ Hz, 3H, C4(CH_3)), 1.21−1.30 (m, 6H, H5−H7), 1.95−2.00 (m, 1H, H4), 2.12 (s, 3H, H1), 2.19−2.23 (AA′B, 2H, H3); GC-MS: 12.26 min - *m*/*z* 43 (100%), 57, 58 (82%), 69, 71, 85 (36%), 99, 113, 127, 142 ($M^{\bullet+}$, 3.8%). These data are consistent with those published.[51]

2,3,5-Trimethylnonan-3-ol (32). A solution of **31** (1.32 g, 9.28 mmol) in dry Et_2O (200 mL) was cooled in an ice bath and a 0.62 M solution of *i*-PrMgBr in Et_2O (20 mL, 12.3 mmol) was added dropwise via syringe. After stirring at 0 °C for 2 h, the mixture was allowed to warm to room temperature and stirring was continued overnight. The reaction was quenched by the cautious addition of saturated aqueous NH_4Cl (10 mL) followed by H_2O (50 mL). The Et_2O fraction was collected, and the aqueous fraction was extracted with Et_2O (2 × 100 mL). The combined organic fraction was dried ($MgSO_4$) and evaporated, giving a pale yellow oil (1.37 g) which was subjected to careful Kugelrohr distillation. At 0.1 mmHg and ~50 °C, unreacted **31** (162 mg) distilled, and at 75−100 °C, **32** distilled as a colorless oil (675 mg). GC-MS analysis of the 2,3,5-trimethylnonan-3-ol fraction revealed it was ~90% pure. The viscous yellow distillation residue (537 mg) was subjected to RSF. Elution with Et_2O/ hexane (1:19), followed by Et_2O/ hexane (1:4) gave **32** as a colorless oil (312 mg, 18%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ (ppm) 0.85−0.92 (m, 9H, H1/C2(CH_3)/ H9), 0.95 (t, $J = 6.6$ Hz, 3H, H9), 1.08 (d, $J = 4.0$ Hz, 3H, H5), 1.10−1.48 (m, 7H, H2/H6/H7/H8), 1.56−1.72 (m, 2H, H4), 4.09 (m, 1H, OH); ^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) 14.3 (CH_3), 17.16 (CH_3), 17.24 (CH_3), 17.7 (CH_3), 17.9 (CH_3), 22.1 (CH_3), 22.2 (CH_3), 23.1 (CH_2, C8), 23.5 (CH, C2), 23.6 (CH, C2), 28.5 (CH_3), 28.7 (CH_3), 29.47 (CH_2, C7), 29.51 (CH_2, C7), 37.6 (CH, C5), 38.3 (CH, C5), 38.9 (CH_2, C6), 39.0 (CH_2, C6), 46.1 (CH_2, C4), 46.6 (CH_2, C4), 75.55 (COH), 75.57 (COH); GC-MS: 16.55 min - *m*/*z* 43, 57, 59, 69, 85, 87 (100%), 99, 125, 143, 154, 171; 16.58 min - *m*/*z* 43, 57, 59, 69, 85, 87 (100%), 99, 125, 143, 154, 171; CI-HRMS: $C_{12}H_{26}O$ requires 186.1984, found 169.1359 ($[C_{12}H_{25}]^+$); IR (thin film): ν (cm^{-1}) 3467 (OH).

2,3,5-Trimethylnonane (33) (1:0.74 Ratio of Diastereomers). A solution of **32** (0.300 g, 1.61 mmol) in dry DCM (10 mL) under argon was cooled in an ice-salt bath, then treated with $BF_3.Et_2O$ (0.250 mL, 1.99 mmol), whereupon the mixture immediately became cloudy. After 15 min a clear solution had formed and GC-MS revealed that the starting material had been consumed. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (2 mL) followed by H_2O (3 mL). The DCM layer was collected, and the aqueous layer was extracted with DCM (2 × 5 mL). The combined organic phase was dried ($MgSO_4$) and evaporated. The residue was dissolved in pentane, filtered though a short plug of SiO_2, and the filtrate was evaporated yielding a colorless liquid (209 mg, 77%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ (ppm) [NB: integrals meaningless in this case because of mixture of diastereomers] 0.80−1.05 (m), 1.18−1.41 (m), 1.55−1.71 (m), 1.86−2.02 (m), 2.10−2.36 (m), 4.66−5.21 (m, =CH); ^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) major isomer (2,3-ene) 14.3 (CH_3), 18.8, 19.6, 20.72, 20.78, 23.2 (CH_2), 29.7 (CH_2), 32.3, 37.0 (CH_2), 42.2 (CH_2), 124.9 (C=), 127.2 (C=); minor component (3,4-ene) 13.6 (CH_3), 21.5, 21.7, 21.8, 23.1 (CH_2), 29.9 (CH_2), 32.1, 37.0, 37.8, 129.3 (=CH), 139.2 (C=); GC-MS: 13.05 min - *m*/*z* 42, 55, 69 (100%), 83, 111, 125, 153, 168 ($M^{\bullet+}$, 10.2%); 13.63 min - *m*/*z* 43, 55, 69 (100%), 84, 111, 125 168 ($M^{\bullet+}$, 12.0%): 14.69 min - *m*/*z* 43, 55, 69, 83 (100%), 111, 125, 152, 168 ($M^{\bullet+}$, 25.2%); GC-EI-HRMS: $C_{12}H_{24}$ requires 168.1878 found 168.1881.

The mixture of isomeric alkenes was dissolved in DCM (20 mL), and the solution was stirred with 10% Pd/C (22 mg) under a balloon of H_2. After 5 h, GC-MS indicated that the reaction was complete. The suspension was vacuum-filtered though a pad of Celite, and washed through with DCM. The filtrate was evaporated giving **33** as a colorless liquid (211 mg, 92%). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ (ppm) 0.82−1.03 (m, 15H), 1.17−1.44 (m, 8H), 1.58−1.69 (m, 3H); GC-MS: 13.77 min - *m*/*z* 43, 57, 71 (100%), 85, 98, 113, 127, 141, 155, 170 ($M^{\bullet+}$, 0.46%): 13.90 min - *m*/*z* 43 (100%), 57, 71, 85, 98, 113, 127, 141, 155, 170 ($M^{\bullet+}$, 0.54%) GC-EI-HRMS: $C_{12}H_{26}$ requires 170.2035 found 170.2035.

General Procedures for the Synthesis of the HBA Series. Domino HWE Reactions. Diethyl 2-oxopropylphosphonate (**12**) (8 equiv) was added dropwise to a suspension of oil-free NaH (9 equiv) in dry toluene (5 mL per mmol) at 0 °C. After the vigorous evolution of H_2 had subsided, the mixture was allowed to warm to room temperature, whereupon a precipitate formed. The resulting slurry was treated with the appropriate ketone (1 equiv) and then heated at 100 °C, causing dissolution of the precipitate. During the course of the reaction, diethyl phosphoric acid separated as a viscous, dark-orange layer. When GC-MS indicated adequate conversion, the reaction mixture was cooled to room temperature, and the toluene phase was diluted with H_2O (200 mL) and then extracted with Et_2O (3 × 250 mL). The extract was dried ($MgSO_4$), and the solvent was evaporated to give a yellow oil, which was dissolved in Et_2O and vacuum-filtered through a short plug of silica gel. Evaporation of the filtrate afforded the mixture of (polyen)ones **34**.

Catalytic Hydrogenation. A solution of **34** in MeOH was stirred with 10% Pd/C under an atmosphere of H_2 until GC-MS showed the hydrogenation to be complete. The reaction mixture was vacuum-filtered though a plug of Celite, the solvent was carefully evaporated, and the residue was subjected to RSF. Elution with hexane then 1:4 hexane-Et_2O gave the saturated ketones **38**.

Grignard Addition. A solution of the appropriate Grignard reagent (2 equiv based on $n = 2$) was added to a stirred solution of the ketones **38** in Et_2O (50 mL) at 0 °C under argon. The mixture was stirred overnight at room temperature before being quenched by cautious addition of saturated aqueous NH_4Cl (10 mL) and H_2O (100 mL). The organic

layer was collected, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic phase was dried ($MgSO_4$) and evaporated, and the residue was subjected to RSF. Elution with 1:1 hexane-Et_2O gave the tertiary alcohols **39**.

Dehydration/Reduction. $BF_3.Et_2O$ (2 equiv based on $n = 2$) was added dropwise to a stirred solution of the alcohols in dry DCM (25 mL) at −10 °C under argon.[52] After 3 h, EtOH (2 mL) was added, and the volatiles were evaporated. The residue was dissolved in pentane and vacuum-filtered through a plug of silica gel then evaporated. The residue was hydrogenated as described above, except that 1:1 DCM-MeOH was used as solvent. Vacuum filtration of a pentane solution of the reduced products through a plug of silica gel gave the target hydrocarbons **1**−**7**, ready for GC-MS analysis.

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Supporting Information Available. The ESI includes full experimental procedures and details, gas chromatograms of the products of each step for the combinatorial HBA synthesis, and mass spectra of the final HBA samples for each series. This material is available free of charge via the Internet at http://pubs.acs.org.

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