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An indium mediated 2-oxonia Cope rearrangement of 1,4-dienols to 1,3-dienols

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ABSTRACT

An indium-mediated isomerization of 1,4-dienols to 1,3-dienols is described. This procedure consists of the addition of pentadienyliindium, in a protic solvent, to aldehydes giving the kinetic γ-allylation product in high yields. The subsequent conversion of this γ-allylation product to its thermodynamic 1,3-dienol α-isomer can be achieved by its exposure to indium triflate in the presence of a sub-stoichiometric amount of aldehyde at room temperature. This transformation exhibited moderate to good substrate scope and has been shown to proceed by a 2-oxonia Cope rearrangement.
INTRODUCTION

1,4-Dienol motifs (1) are a valuable and sought after precursors in organic synthesis due to their unique functional connectivity. 1,4-Dienols 1 can undergo elimination reactions to give trienes such as 2 that have been shown to be excellent Diels-Alder platforms (scheme 1), therefore enabling significant molecular complexity to be built up quickly in very few synthetic transformations.

The connectivity of 1,4-dienols (1) has been harnessed in ruthenium catalyzed RCM transformation delivering unique cyclic and polycyclic structures. Furthermore, 1,4-dienol 1 can undergo facile isomerization to the thermodynamically favored α-allylic alcohol product 3 (1,3-dienol) that is central to numerous natural products of biological importance as well as useful synthetic intermediates (Scheme 1).

Scheme 1. Synthetic utility of 1,4-dienols and their conversion to 1,3-dienols.

The resolvin D- and E-series (Scheme 2, e.g. resolving D1 and resolving E1) are a class of metabolites derived from the ω-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). They have been implicated in the regulation of human diseases linked to chronic inflammation such as cardiovascular disease, asthma and rheumatoid arthritis. In a project looking at the biological importance of these fatty acids metabolites we required access to a range of racemic 1,3-dienols with aryl, alkenyl and alkynyl substitution that mirrored that within the resolvin D1 and E1 structures (scheme 2, 4-6). We envisaged that 1,3-dienols of this type could be accessed via a 2-oxonia Cope rearrangement of a 1,4-dienol, which in turn could be accessed from an appropriate aldehyde (9) and a pentadienyl equivalent (scheme 2). This approach was based on two benchmarks (a) the ability to easily synthesize the 1,4-dienol precursors; and (b) literature precedent for the thermodynamic rearrangement to the required 1,3-dienols.
Scheme 2. Targeted 1,3-dienols using a 2-oxonia Cope rearrangement.

Firstly, within the literature there are several robust synthetic methods for the synthesis of the 1,4-dienol precursors (10), all of which are based on the addition of a pentadienyl equivalent to a carbonyl substrate 9 (scheme 2). These include the Lewis acid mediated addition of 2,4-pentadienyltrimethylsilane,\(^5\)\(^-\)\(^7\) and pentadienyltrimethylstannane\(^2\)\(^d\),\(^8\) to an aldehyde. Pentadienylzincates\(^9\) and penta-2,4-dienyltitanium complexes\(^10\) have also been successfully added to carbonyls; and the direct addition of a 1,4-pentadienyl equivalent via treatment with strong base,\(^11\) has also been successfully employed. An alternate and more environmentally applicable approach has been the addition of pentadienylindium, generated from indium metal and pentadienylbromide, to the requisite carbonyl. Indium has become an important metal in a range Barbier type additions to carbonyls due to its functional group tolerance and low toxicity.\(^12\),\(^13\) Secondly, the 2-oxonia Cope rearrangements are not unprecedented when performed on 1,4-dienols (scheme 2); Nokami\(^3\)\(^a\) and co-workers demonstrated that 1,4-dienol 7 undergoes a diastereoselective, acid catalyzed, 2-oxonia Cope rearrangement to give its α-product 8, in high enantiomeric excess; however, this report was limited to only three aliphatic examples. Therefore,
we would like to disclose our results on using this 2-oxonia Cope rearrangement to synthesise 1,3-dienols with aryl, alkenyl and alkynyl substitutions.

RESULTS AND DISCUSSION

The target compounds for our study necessitated the selection of aldehyde 12 as the starting point. Previous reports had already indicated that DMF, THF and DMSO would be ideal solvents for the addition of bromide 13, as they all gave the required γ-addition product. However, in a desire to use more environmentally benign solvents, H$_2$O was selected as the starting point, previously used only by Fallis within the context of bromide 13 and a small subset of aldehydes and ketones.$^{1f,3b}$ Consequently, when aldehyde 12 was exposed to 13, indium (1.5 equiv.) and H$_2$O, it was gratifying to isolate the desired γ-addition product 14 in 51% isolated yield (scheme 3). This modest yield and significant amount of unreacted starting material in the crude $^1$H NMR led us to question the solubility of starting material 12 in H$_2$O as solvent. To address this a 3:1 mixture of ethanol$^{14}$ and water was trialed leading to a welcomed increase isolated yield of 67% confirming our speculation. Finally, further increase in isolated yield to 81% was obtained when absolute ethanol was used.

Scheme 3. Indium mediated addition of bromide 13 to aldehyde 12 in H$_2$O, ethanol and mixtures thereof.

With optimized conditions in hand, we then examined these conditions on range of aryl, alkenyl and alkynyl aldehydes that were appropriate for our study (scheme 4).
Scheme 4. Synthesis of 1,4-dienols.

Benzaldehyde and 2-, 3-, and 4-bromobenzaldehyde gave the expected 1,4-dieneol products (15-18) in good to excellent yields of 71-92%; however, p-anisaldehyde yielded its addition product 19 in a very poor isolated yield of only 5%, due likely to the deactivation of the electrophile by the methoxy group. An increase in steric bulk was accommodated as indicated by the successful conversion of α-naphthaldehyde giving its addition product 20 in 86% isolated yield. Acetophenone also underwent smooth addition to give the γ-addition product 21a in 76%; however, within the crude $^1$H NMR, a small trace amount of the α-addition product 22b could be identified, possibly due to the increase in steric bulk of the electrophile. Cinnamaldehyde gave
its addition product 22 in 60% isolated yield, and both linear and branched aliphatic aldehydes gave the desired 1,4-dienols in good to high yields giving 23 and 24 in 76% and 69% yields, respectively. The alkylnl aldehyde 12, crucial to our own work,\textsuperscript{4d} could also be scaled up to 12 mmol, giving the addition product 14 in an isolated yield of 80%. We also found that glycoaldehyde dimer 26 could be utilized in this process giving access to the diol 25 in 72% isolated yield.

The isomerization of the 1,4-dienols to the desired 1,3-dienols was optimized using substrate 15 (scheme 5 and table 1).

**Scheme 5 and table 1.** Optimization experiments for the conversion of 1,4-dienol 15 to its respective conjugated species 27.\textsuperscript{a}

\[
\begin{array}{ccc}
\text{entry} & \text{Lewis Acid}\textsuperscript{b} & \text{Benzaldehyde (mol%)} & \text{Temp. (°C)} & \text{Yield 27 [%]}\textsuperscript{c} \\
1 & - & - & \text{rt} & - \\
2 & - & - & 40 & - \\
3 & \text{In(O Tf)}_3 & - & \text{rt} & 23 \\
4 & \text{AlCl}_3 & - & \text{rt} & 22 \\
5 & \text{Sn(O Tf)}_2 & - & \text{rt} & 23 \\
6 & \text{In(O Tf)}_3 & 10 & \text{rt} & 67 \\
7 & \text{In(O Tf)}_3 & 20 & \text{rt} & 65 \\
8 & \text{In(O Tf)}_3 & 50 & \text{rt} & 67 \\
9 & \text{In(O Tf)}_3 & 100 & \text{rt} & 67 \\
10 & - & 10 & \text{rt} & - \\
11 & \text{In(O Tf)}_3 & 10 & 40 & 63 \\
12 & \text{In(O Tf)}_3 & - & 40 & 19 \\
13\textsuperscript{d} & \text{In(O Tf)}_3 & 10 & \text{rt} & 66 \\
\end{array}
\]

\textsuperscript{a}Reactions were performed in CH\textsubscript{2}Cl\textsubscript{2} under N\textsubscript{2} atmosphere at 0.5M for 24h unless otherwise stated. \textsuperscript{b}10 mol% of Lewis acid. \textsuperscript{c}Isolated yields in all cases. \textsuperscript{d}48h reaction time.
Initially, we found that simple heating of 15 did not yield the desired 1,3-dienol but simply returned starting material (entries 1 and 2). We then investigated the use of a Lewis acid catalyst to effect the rearrangement of 15 to 27 and found that In(OTf)$_3$, Sn(OTf)$_2$, and AlCl$_3$, all at room temperature, achieved the rearrangement, but in poor isolated yields (entries 3-5). It must be noted that 27 was isolated in a $E:Z$ ratio of approx. 9:1, in favor of the $E$-stereoisomer, in each case. With these promising results in hand, we next examined the addition of benzaldehyde in an effort to promote the 2-oxonia Cope rearrangement. Accordingly, upon the addition of 10 mol% of benzaldehyde, in the presence of In(OTf)$_3$ we isolated the desired 1,3-diene-ol 27 in a dramatically improved yield of 67% (entry 6). A screen in the amount of benzaldehyde was then examined but no discernible increase in isolated yields was observed (entries 7-9). A control experiment in the absence of Lewis acid, but in the presence of 10 mol% of benzaldehyde, confirmed the crucial role of the Lewis acid in this rearrangement (entry 10). An increase in reaction temperature had no significant effect on the isolated product yield of 27 (entry 11); and when this elevated temperature attempt was performed in the absence of benzaldehyde (entry 12) the result mirrored that in entry 3. Finally, extending the reaction time had no noticeable effect in the isolated yield of 27 (entry 13).

With conditions for the 2-oxonia Cope rearrangement of 1,4-dienol 15 to 27 now identified, the scope of this reaction process was examined using the 1,4-dienols from scheme 4 (scheme 6).
Scheme 6. Synthesis of 1,3-dienols.

This process was met with moderate success. The 2-, 3-, and 4-bromoaryl analogues were all rearranged to the target 1,3-diene-ol in good isolated yields giving 28, 29 and 30, respectively. The α-naphthyl analogue participated in the rearrangement giving the thermodynamic product 32 in good yield, and the rearrangement was tolerant of alkyl substitution as exemplified by the cyclohexyl 34 and isovaleryl 35 examples. The aryl 1,4-diene 15 could be rearranged at an increased scale of 5 mmol giving the 1,3-diene 27 in comparable chemical yield. Finally, the TMS protected alkynyl-1,4-diene 14 was converted to its 1,3-diene isomer 36 in a good yield, and pleasingly this gave a valuable building block that could be potentially used in further work towards the synthesis of the resolvins and other marine derived fatty acids. Unfortunately, the 4-methoxyaryl (22), pent-4-en-2-ol (21a), cinnamyl (22) and 1,2-diol 25 precursors, gave little or none of the desired
products (31, 33, 21b and 37, respectively), as well as yielding complex mixtures of products as identified by NMR in each case. With regard to the E/Z stereoisomer ratio, the majority of the aryl derivatives were obtained in a ratio in-line with the parent phenyl analogue, i.e. E/Z ratio of approx. 9:1. However, the 2-bromophenyl derivative, 30, was obtained as the E-isomer exclusively, with none of its Z-isomer observed in the 1H NMR spectra. In contrast, the cyclohexyl (30) and isovaleryl (31) analogues were obtained in E/Z ratios of 3:2 and 3:1, respectively.

The 1,3-dienol 37 derived from 1,2-diol 25 would have contained a useful synthetic handle; however, its failure to participate in the rearrangement could be mitigated as shown below in scheme 7. Treatment of 15 with ethyl propiolate gave the enol ester 38, that when treated with TFA gave the thermodynamic diene 39 in 82% in an E/Z ratio of 94:6, and with a 1,3-diene with a useful synthetic handle for further manipulation.

Scheme 7. Acid catalyzed rearrangement of 1,2-diol 38.

Mechanistically the 2-oxonia Cope rearrangement follows the reports previously published (scheme 5).3,15 Firstly, Lewis acid activation of benzaldehyde promotes formation of the oxocarbenium ion 41 via 40. This oxocarbenium ion 41 then undergoes a 2-oxonia Cope rearrangement to deliver the thermodynamic product 42, with none of the Prins cyclisation product 43 being detected or isolated. It is assumed15,17 that the 2-oxonia Cope rearrangement goes via the corresponding chair transition states. The dominant stereoisomer in each rearrangement was of E-stereochemistry, however in some cases a small amount of the Z-stereoisomer could be detected by 1H NMR spectroscopy, and this presumably occurs via bond rotation between C2-C3 within 41 as shown by 41a and 41aa (scheme 7).
CONCLUSIONS

In summary, we have reported a two-step process for the synthesis of 1,3-dienols. A 2-oxonia Cope rearrangement was utilized to rearrange 1,4-dienols to their thermodynamic 1,3-dienol products, and this was facilitated by Lewis acid catalysis with a sub-stoichiometric amount of the requisite aldehyde. This process has modest substrate scope, but unfortunately failed with cinnamyl-substituted systems. However, it was demonstrated to be tolerant of alkynes, which in the context of our research programme should provide a suitable synthetic building for synthesizing fatty acid analogues.

EXPERIMENTAL PROCEDURES

General procedure for indium addition with (E)-5-bromopenta-1,3-diene.
Aldehyde or ketone (1.00 mmol) and (E)-5-bromopenta-1,3-diene 13 (1.20 mmol) were added to absolute ethanol (6 mL) and allowed to stir at room temperature. Indium powder (1.50 mmol) was added slowly, so as not to increase the temperature of the reaction mixture, and then allowed to stir at room temperature for 72 h. The reaction mixture was diluted with diethyl ether and then filtered through a plug of silica. The solvent was then removed by evaporation under reduced pressure and the crude product purified by column chromatography.
The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, \( R_f = 0.4 \)) yielding a colorless liquid (157 mg, 0.90 mmol, 92%): \(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) 7.41 - 7.28 (m, 5H), 5.88 (dd, \( J = 17.2, 10.4, 8.2 \) Hz, 1H), 5.71 (dd, \( J = 17.2, 10.4, 7.2 \) Hz, 1H), 5.26 (dt, \( J = 9.6, 0.8 \) Hz, 1H), 5.22 (dt, \( J = 16.0, 1.2 \) Hz, 1H), 5.07 (dt, \( J = 10.4, 1.2 \) Hz, 1H), 5.04 (dt, \( J = 17.2, 1.2 \) Hz, 1H), 4.61 (dd, \( J = 6.8, 2.0 \) Hz, 1H), 3.13 (dq, \( J = 7.2, 0.8 \) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 100MHz): \(\delta\) 140.8, 135.8, 135.7, 127.1, 126.9, 125.7, 117.4, 116.1, 75.2, 55.2; IR (NaCl): 3079, 3066, 1634, 1603 cm\(^{-1}\); HRMS (ESI): \(m/z [M+H]^+\) calcd for C\(_{12}\)H\(_{14}\)O: 175.1123, found: 175.1126.

The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, \( R_f = 0.4 \)) yielding a colorless liquid (225 mg, 0.89 mmol, 89%): \(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) 7.50 (dd, \( J = 8.0, 1.2 \) Hz, 1H), 7.46 (d, \( J = 7.6 \) Hz, 1H), 7.31 (t, \( J = 15.2 \) Hz, 1H), 7.11 (dt, \( J = 7.6, 2.0 \) Hz, 1H), 5.95 - 5.83 (m, 2H), 5.21 - 5.01 (m, 5H), 3.20 (q, \( J = 6.8 \) Hz, 1H), 2.25 (s, 1H); \(^{13}\)C NMR (CDCl\(_3\), 100MHz): \(\delta\) 141.1, 137.1, 135.6, 132.7, 128.9, 129.6, 127.7, 122.6, 118.6, 117.0, 74.5, 54.5; IR (NaCl): 3427, 3077, 1636, 619 cm\(^{-1}\); HRMS (ESI): \(m/z [M+H]^+\) calcd for C\(_{12}\)H\(_{12}\)O\(_79\)Br: 251.0066, found: 251.0068.

The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, \( R_f = 0.4 \)) yielding a colorless liquid (180 mg, 0.71 mmol, 71%): \(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) 7.44 (d, \( J = 8.0 \) Hz, 2H), 7.17 (d, \( J = 8.4 \) Hz, 2H), 5.80 (dd, \( J = 18.0, 10.8, 8.4 \) Hz, 1H), 5.64 (ddd, \( J = 17.2, 10.8, 7.2 \) Hz, 1H), 5.25 - 5.13 (m, 2H), 5.07 - 4.97 (m, 2H), 4.54 (dd, \( J = 8.0, 2.0 \) Hz, 1H), 5.04 (dt, \( J = 17.2, 1.2 \) Hz, 1H), 4.61 (dd, \( J = 6.8, 2.0 \) Hz, 1H), 3.13 (dq, \( J = 7.2, 0.8 \) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 100MHz): \(\delta\) 144.2, 136.3, 136.2, 130.7, 129.9, 129.7, 125.6, 118.8, 117.6, 122.3, 75.5, 56.2; IR (NaCl): 3400, 3084, 1637, 739 cm\(^{-1}\); HRMS (ESI): \(m/z [M+H]^+\) calcd for C\(_{12}\)H\(_{12}\)O\(_79\)Br: 251.0066, found: 251.0058.
= 7.2, 3.2 Hz, 1H), 3.03 (q, J = 7.6 Hz, 1H), 2.24 (d, J = 3.2 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100MHz) δ 140.8, 136.4, 136.3, 131.2, 128.6, 121.5, 118.8, 117.8, 75.5, 56.3; IR (NaCl): 3420, 3079, 1635, 623 cm$^{-1}$; HRMS (ESI): m/z [M+H]$^+$ calcd for C$_{12}$H$_{12}$O$_7$Br: 251.0066, found: 251.0068.

1-(4-Methoxyphenyl)-2-vinylbut-3-en-1-ol (19).$^{9b}$ The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, R$_f$ = 0.3) yielding a dark yellow liquid (11 mg, 0.05 mmol, 5%): $^1$H NMR (CDCl$_3$, 400MHz) δ 7.22 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 7.6 Hz, 2H), 5.84 (dt, J = 16.8, 9.2 Hz, 1H), 5.64 (dt, J = 16.8, 8.0 Hz, 1H), 5.21 (dd, J = 16.4, 10.0 Hz, 2H), 5.01 (t, J = 10.4 Hz, 2H), 4.52 (d, J = 7.2 Hz, 1H), 3.79 (s, 3H), 3.07 (q, J = 7.6 Hz, 1H), 2.16 (bs, 1H); $^{13}$C NMR (CDCl$_3$, 100MHz) δ 159.1, 137.1, 136.8, 134.0, 128.1, 118.3, 117.0, 113.6 (x2), 75.8, 56.3, 55.3; IR (NaCl): 3419 (br), 1634, 1219 cm$^{-1}$; HRMS (ESI): m/z [M+Na]$^+$ calcd for C$_{13}$H$_{16}$O: 227.1048, found: 227.1037.

1(1-Naphthyl)-2-vinylbut-3-en-1-ol (20). The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, R$_f$ = 0.4) yielding a colorless liquid (192 mg, 0.86 mmol, 86%): $^1$H NMR (CDCl$_3$, 400MHz) δ 8.08 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.53 - 7.45 (m, 4H), 5.96 - 5.81 (m, 2H), 5.45 (dd, J = 6.0, 3.6 Hz, 1H), 5.22 (dd, J = 10.4, 0.8 Hz, 1H), 5.12 - 5.03 (m, 3H), 3.41 - 3.38 (m, 1H), 2.22 (d, J = 3.6 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100MHz) δ 137.8, 137.6, 136.3, 133.9, 130.7, 129.1, 128.2, 126.1, 125.5, 125.3, 124.5, 123.3, 118.6, 116.8, 72.9, 54.8; IR (NaCl): 3583, 3084, 1677, 1421, 1265 cm$^{-1}$; HRMS (ESI): m/z [M+Na]$^+$ calcd for C$_{16}$H$_{16}$O: 247.1099, found: 247.1083.

2-Phenylpent-4-en-2-ol (21a).$^{8d}$ The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, R$_f$ = 0.4) yielding a colorless liquid (142 mg, 0.76 mmol, 76%): $^1$H NMR (CDCl$_3$, 400MHz) δ 7.44 - 7.41 (m, 2H), 7.38 - 7.33 (m, 2H), 7.28 - 7.24 (m, 1H), 5.81 (ddd, J = 17.2, 10.4, 8.8 Hz, 1H), 5.74 (ddd, J = 17.6, 10.4, 7.2 Hz, 1H), 5.20 (ddd, J = 10.4, 1.6, 0.4 Hz, 1H), 5.16 - 5.13 (m, 1H), 5.14 - 5.09 (m, 2H), 3.15 (t, J = 7.6 Hz, 1H), 2.17 (s, 1H), 1.57 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100MHz) δ 146.4, 136.8, 136.3, 127.9, 126.7, 125.5, 118.1, 75.3, 29.8, 27.6; HRMS (ESI): m/z [M+Na]$^+$ calcd for C$_{13}$H$_{16}$O: 211.1099, found: 211.1087.
1-(Cinnamyl)-2-vinylbut-3-en-1-ol (22). The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, \( R_f = 0.3 \)) yielding a dark yellow liquid (120 mg, 0.60 mmol, 60%): \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.46 – 7.41 (m, 2H), 7.38 – 7.34 (m, 2H), 7.31 – 7.26 (m, 1H), 6.65 (dd, \( J = 16.0, 0.8 \) Hz, 1H), 6.27 (dd, \( J = 16.0, 6.4 \) Hz, 1H), 5.97 - 5.88 (m, 1H), 5.92 – 5.86 (m, 1H), 5.29 - 5.19 (m, 4H), 4.30 (t, \( J = 6.0 \) Hz, 1H), 3.08 - 3.02 (tq, \( J = 7.2, 1.2 \) Hz, 1H), 2.12 (bs, 1H); \(^13\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 136.8, 136.6, 131.6, 129.7, 128.6, 127.7, 126.6, 118.0, 117.7, 76.8, 55.0; IR (NaCl): 3400, 3061, 1636 cm\(^{-1}\); HRMS (ESI): \( m/z \) [M+H]\(^+\) calcd for C\(_{14}\)H\(_{16}\)O: 201.1279, found: 201.1273.

1-Cyclohexyl-2-vinylbut-3-en-1-ol (23). The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, \( R_f = 0.5 \)) yielding a colorless liquid (137 mg, 0.76 mmol, 76%): \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 5.85 (ddd, \( J = 16.4, 10.0, 8.0 \) Hz, 1H), 5.81 (ddd, \( J = 12.8, 7.6, 4.4 \) Hz, 1H), 5.17 (dd, \( J = 10.0, 1.6 \) Hz, 1H), 5.12 (ddd, \( J = 10.8, 2.0, 1.2 \) Hz, 1H), 5.12 – 5.10 (m, 1H), 5.09 – 5.07 (m, 1H), 3.29 - 3.25 (m, 1H), 2.95 (q, \( J = 7.2 \) Hz, 1H), 1.88 - 1.79 (m, 1H), 1.78 - 1.69 (m, 2H), 1.68 - 1.57 (m, 2H), 1.48 - 1.37 (m, 1H), 1.29 - 1.00 (m, 5H), \(^13\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 136.5, 135.3, 115.4, 114.2, 75.3, 49.7, 38.4, 27.9, 24.9, 24.5, 24.4, 24.2; IR (NaCl): 3435 (br), 3077, 1633 cm\(^{-1}\); HRMS (ESI): \( m/z \) [M+Na]\(^+\) calcd for C\(_{12}\)H\(_{20}\)O: 203.1412, found: 203.1406.

6-Methyl-3-vinylhept-1-en-4-ol (24). The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, \( R_f = 0.4 \)) yielding a colorless liquid (106 mg, 0.69 mmol, 69%): \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 5.86 (ddd, \( J = 16.0, 8.0, 4.8 \) Hz, 1H), 5.81 (ddd, \( J = 12.8, 7.6, 4.4 \) Hz, 1H), 5.21 (dd, \( J = 10.4, 1.2 \) Hz, 1H), 5.18 – 5.15 (m, 1H), 5.16 – 5.14 (m, 1H), 5.13 (ddd, \( J = 5.6, 2.4, 0.8 \) Hz, 1H), 3.65 (dt, \( J = 9.6, 4.4 \) Hz, 1H), 2.79 (q, \( J = 7.6 \) Hz, 1H), 1.89 - 1.79 (m, 1H), 1.65 (d, \( J = 4.4 \) Hz, 1H), 1.36 - 1.29 (m, 2H), 0.95 (d, \( J = 6.8 \) Hz, 3H), 0.92 (d, \( J = 6.4 \) Hz, 3H), \(^13\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 137.6, 136.9, 117.6, 116.9, 71.2, 55.4, 43.4, 24.6, 23.8, 21.7; IR (NaCl): 3368 (br), 3079, 1635 cm\(^{-1}\); HRMS (ESI): \( m/z \) [M+H]\(^+\) calcd for C\(_{10}\)H\(_{18}\)O: 155.1436, found: 155.1429.

3-Vinylpent-4-ene-1,2-diol (25). The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, \( R_f = 0.2 \)) yielding a colorless oil (92 mg, 0.72 mmol, 72%): \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 5.86 (ddd, \( J = 16.8, 10.8, 8.0 \) Hz, 1H), 5.82 (ddd, \( J = 16.8, 10.8, 8.0 \) Hz, 1H), 5.12 (dd, \( J = 10.4, 2.4 \) Hz, 1H), 5.04 (dd, \( J = 10.0, 5.8 \) Hz, 1H), 3.91 (ddd, \( J = 16.8, 10.8, 8.0 \) Hz, 1H), 2.57 (dd, \( J = 10.4, 2.4 \) Hz, 1H), 1.87 - 1.79 (m, 1H), 1.66 (d, \( J = 4.8 \) Hz, 1H), 1.36 - 1.29 (m, 2H), 0.95 (d, \( J = 6.8 \) Hz, 3H), 0.92 (d, \( J = 6.4 \) Hz, 3H), \(^13\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 137.6, 136.9, 117.6, 116.9, 71.2, 55.4, 43.4, 24.6, 23.8, 21.7; IR (NaCl): 3368 (br), 3079, 1635 cm\(^{-1}\); HRMS (ESI): \( m/z \) [M+H]\(^+\) calcd for C\(_{10}\)H\(_{18}\)O: 155.1436, found: 155.1429.
Hz, 1H), 5.77 (ddd, J = 16.8, 10.8, 8.0 Hz, 1H), 5.21 - 5.16 (m, 2H), 5.15 – 5.11 (m, 2H), 3.71 - 3.62 (m, 2H), 3.55 - 3.47 (m, 1H), 3.23 (bs, 1H), 3.15 (m, 1H), 2.88 (q, J = 8.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100MHz) δ 136.8, 136.7, 117.5, 117.1, 73.6, 64.6, 51.7; IR (NaCl): 3365 (br), 3003, 1637 cm$^{-1}$; HRMS (ESI): m/z [M+Na]$^+$ calcd for C$_7$H$_{12}$O$_2$: 151.0735, found: 151.0729.

1-(Trimethylsilyl)-4-vinylhex-5-en-1-yn-3-ol (14). Aldehyde 12 (1.51 g, 12.00 mmol) and (E)-5-bromopenta-1,3-diene 13 (2.12 g, 14.40 mmol) were added to absolute ethanol (20 mL) and allowed to stir at room temperature. Indium powder (2.05 g, 18.00 mmol) was added in portions, so as not to increase the temperature of the reaction mixture, and then allowed to stir at room temperature for 72 h. The reaction mixture was diluted with diethyl ether and then filtered through a plug of silica. The solvent was then removed by evaporation under reduced pressure and the crude product purified by column chromatography. The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, R$_f$ = 0.6) yielding a pale yellow oil (1.87 g, 9.60 mmol, 80%): $^1$H NMR (CDCl$_3$, 400MHz) δ 5.91 (ddd, J = 17.2, 10.4, 8.0 Hz, 2H), 5.28 - 5.18 (m, 4H), 4.33 (dd, J = 7.2, 5.6 Hz, 1H), 3.07 - 3.02 (m, 1H), 2.10 (d, J = 7.2 Hz, 1H), 0.19 (s, 9H); $^{13}$C NMR (CDCl$_3$, 100MHz) δ 136.1, 135.7, 118.7, 118.2, 104.6, 91.2, 65.3, 54.7, 0.01; IR (NaCl): 3429 (br), 3008, 2173, 1638 cm$^{-1}$; HRMS (ESI): m/z [M+Na]$^+$ calcd for C$_{11}$H$_{18}$OSi: 217.1019, found: 217.1020.

**General procedure for the rearrangement from branched to straight chain diene**

Branched chain diene (1.0 mmol) in dichloromethane (2.0 mL / mmol) was added to indium trifluoromethanesulfonate (10 mol %) and the aldehyde (10 mol %) and allowed to stir at room temperature for 24 h. The reaction mixture was then transferred to a separating funnel, diluted with further dichloromethane and washed with distilled water. The organic extracts were retained, dried (Na$_2$SO$_4$), filtered and the solvent removed by evaporation under reduced pressure. The title compound was isolated by column chromatography. The following compounds were synthesized using this method.
(E)-1-Phenylhexa-3,5-dien-1-ol (27). The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, Rf = 0.3) yielding a colorless liquid (116 mg, 0.67 mmol, 67%): 1H NMR (400MHz, CDCl3) δ 7.42 - 7.29 (m, 5H), 6.35 (td, J = 16.8, 10.0 Hz, 1H), 6.22 (dd, J = 15.2, 10.4 Hz, 1H), 5.71 (dt, J = 15.2, 7.2 Hz, 1H), 5.18 (d, J = 16.4 Hz, 1H), 5.06 (d, J = 10.0 Hz, 1H), 4.80 - 4.74 (m, 1H), 2.60 - 2.56 (m, 2H), 2.13 (d, J = 3.2 Hz, 1H); 13C NMR (100MHz, CDCl3) δ 143.9, 136.8, 134.4, 130.1, 128.5, 127.7, 125.8, 116.3, 73.7, 42.6; IR (NaCl): 3411, 3080, 3030, 1634, 1603 cm⁻¹; HRMS (ESI): m/z [M-H]⁺ calcd for C₁₂H₁₃O: 173.0966, found: 173.0961.

(E)-1-(2-Bromophenyl)hexa-3,5-dien-1-ol (28). The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, Rf = 0.3) yielding a colorless liquid 182 mg, 0.72 mmol, 71%): 1H NMR (400MHz, CDCl3) δ 7.82 (d, J = 7.6 Hz, 1H), 7.64 (dd, J = 8.0, 1.2 Hz, 1H), 7.18 - 7.08 (m, 2H), 6.07 (d, J = 1.2 Hz, 1H), 5.95 - 5.84 (m, 1H), 5.71 (dd, J = 16.0, 5.6 Hz, 1H), 5.29 (dd, J = 5.6, 2.4 Hz, 1H), 4.58 (dd, J = 10.8, 5.6 Hz, 1H), 2.64 - 2.53 (m, 1H), 2.39 - 2.28 (m, 1H); 13C NMR (100MHz, CDCl3) δ 142.7, 133.1, 132.7, 132.6, 130.5, 128.5, 121.2, 100.6, 78.0, 77.2, 72.1, 40.6; IR (NaCl) 3428, 3077, 1636, 704 cm⁻¹; HRMS (ESI): m/z [M-H⁺] calcd for C₁₂H₁₂O⁻Br: 251.0072, found: 251.0065.

(E)-1-(3-Bromophenyl)hexa-3,5-dien-1-ol (29). The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, Rf = 0.3) yielding a colorless liquid (175 mg, 0.69 mmol, 69%): 1H NMR (400MHz, CDCl3) δ 7.57 - 7.54 (m, 1H), 7.45 - 7.41 (m, 1H), 7.31 - 7.22 (m, 2H), 6.34 (td, J = 16.8, 10.0 Hz, 1H), 6.20 (dd, J = 15.2, 10.4 Hz, 1H), 5.68 (dt, J = 15.2, 7.6 Hz, 1H), 5.19 (d, J = 16.8 Hz, 1H), 5.08 (d, J = 10.0 Hz, 1H), 4.75 - 4.71 (m, 1H), 2.59 - 2.46 (m, 2H), 2.11 (d, J = 3.2 Hz, 1H); 13C NMR (100MHz, CDCl3) δ 146.2, 133.1, 132.7, 132.6, 130.5, 128.5, 121.2, 100.6, 78.0, 77.2, 72.1, 40.6; IR (NaCl) 3391, 3084, 1637, 704 cm⁻¹; HRMS (ESI): m/z [M-H⁺] calcd for C₁₂H₁₂O⁻Br: 251.0072, found: 251.0059.

(E)-1-(4-Bromophenyl)hexa-3,5-dien-1-ol (30). The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, Rf = 0.3) yielding a colorless liquid (180 mg, 0.71 mmol, 72%): 1H NMR (400MHz, CDCl3) δ 7.46 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.30 (td, J = 16.8, 10.8 Hz, 1H), 6.15 (dd, J = 15.6, 10.4 Hz, 1H), 5.63 (dt, J = 14.4, 8.0 Hz, 1H), 5.15 (dd, J = 16.8, 7.6 Hz, 1H),
5.07 - 5.01 (m, 1H), 4.74 - 4.66 (m, 1H), 2.55 - 2.43 (m, 2H), 2.00 (d, J = 3.2 Hz, 1H); 
$^{13}$C NMR (100MHz, CDCl$_3$) δ 142.8, 136.6, 134.9, 131.6, 129.4, 127.6 (x2), 121.4, 116.6, 70.0, 42.7; IR (NaCl) 3419, 3079, 1635, 623 cm$^{-1}$; HRMS (ESI) m/z [M-H$^-$] calcd for C$_{12}$H$_{12}$O$^{79}$Br: 251.0072, found: 251.0066.

**(E)-1-(1-Naphthyl)hexa-3,5-dien-1-ol (14) (32).** The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, R$_f$ = 0.3) yielding a colorless liquid (152 mg, 0.68 mmol, 72%): $^1$H NMR (400MHz, CDCl$_3$) δ 8.06 (d, J = 8.8 Hz, 1H), 7.88 - 7.86 (m, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.65 - 7.46 (m, 3H), 6.34 (dt, J = 16.8, 10.4 Hz, 1H), 6.22 (dd, J = 14.8, 10.4 Hz, 1H), 5.81 (pent, J = 7.6 Hz, 1H), 5.52 (dd, J = 8.4, 3.2 Hz, 1H), 5.19 - 5.16 (m, 1H), 5.08 - 5.04 (m, 1H), 2.84 - 2.75 (m, 1H), 2.66 - 2.59 (m, 1H), 2.13 (bs, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 139.5, 136.8, 134.4, 133.9, 130.5, 130.3, 129.1, 128.1, 126.2, 125.6, 125.6, 123.0, 122.9, 116.4, 70.5, 41.8; HRMS (ESI) m/z [M+Na$^+$] calcd for C$_{16}$H$_{16}$O: 247.1099, found: 247.1083.

**(E)-1-Cyclohexylhexa-3,5-dien-1-ol (34).** The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, R$_f$ = 0.4) yielding a colorless liquid (108 mg, 0.60 mmol, 60%): $^1$H NMR (400MHz, CDCl$_3$) δ 6.31 (td, J = 17.2, 10.4 Hz, 1H), 6.18 - 6.08 (m, 1H), 5.70 (q, J = 8.0 Hz, 1H), 5.11 (d, J = 16.4 Hz, 2H), 3.42 - 3.34 (m, 1H), 2.38 - 2.29 (m, 2H), 2.22 - 2.13 (m, 1H), 1.40 - 0.98 (m, 10H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 136.9, 134.0, 131.3, 115.8, 75.3, 41.4, 29.9, 29.7, 26.6, 26.4, 26.3, 22.7; IR (NaCl) 3457, 3088, 2928, 1650 cm$^{-1}$; HRMS (ESI) m/z [M+Na$^+$] calcd for C$_{16}$H$_{16}$O: 247.1099, found: 247.1083.

**(E)-1-Isovalerylhexa-3,5-dien-1-ol (35).** The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, R$_f$ = 0.4) yielding a colorless liquid (97 mg, 0.63 mmol, 63%): $^1$H NMR (400MHz, CDCl$_3$) δ 6.31 (td, J = 16.8, 10.4 Hz, 1H), 6.12 (dd, J = 15.2, 10.8 Hz, 1H), 5.70 (pent, J = 7.6 Hz, 1H), 5.13 (d, J = 12.4 Hz, 1H), 5.00 (dd, J = 8.8, 1.2 Hz, 1H), 3.72 - 3.68 (m, 1H), 2.36 - 2.25 (m, 1H), 2.19 - 2.11 (m, 1H), 1.86 - 1.72 (m, 1H), 1.49 (bs, 1H), 1.42 - 1.36 (m, 1H), 1.27 - 1.19 (m, 1H), 0.91 - 0.88 (m, 6H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 136.9, 134.3, 130.7, 116.0, 69.2, 46.2, 41.3, 24.7, 26.5, 22.1; IR (NaCl) 3584, 3086, 2927, 1651, 1467, 1367, 1004 cm$^{-1}$; HRMS (ESI) m/z [M+Na$^+$] calcd for C$_{10}$H$_{18}$O: 177.1255, found: 177.1241.
(E)-1-(Trimethylsilyl)octa-5,7-dien-1-yn-3-ol (36). The title compound was isolated by column chromatography (4:1, light petroleum: ethyl acetate, Rf = 0.5) yielding a pale yellow liquid (110 mg, 0.53 mmol, 53%): \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 6.37 (td, \(J = 16.8, 10.8\) Hz, 1H), 6.26 - 6.19 (m, 1H), 5.77 (td, \(J = 14.8, 7.6\) Hz, 1H), 5.19 (dd, \(J = 16.8, 0.8\) Hz, 1H), 5.09 (dd, \(J = 10.4, 1.2\) Hz, 1H), 4.43 (q, \(J = 6.0\) Hz, 1H), 2.52 (t, \(J = 6.4\) Hz, 2H), 0.18 (s, 9H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 137.0, 135.0, 128.5, 116.5, 105.9, 90.0, 62.2, 40.9, 0.1; IR (NaCl) 3400, 2999, 2152, 1618 cm\(^{-1}\); HRMS (ESI) \(m/z\) [M+H\(^{+}\)] calcd for C\(_{11}\)H\(_{18}\)OSi: 195.1205, found: 195.1200.

Ethyl (E)-3-[[1-phenyl-2-vinylbut-3-en-1-yl]oxy]acrylate (38)

To a solution of diene 15 (192 mg, 1.10 mmol) THF (3.00 mL) was added DABCO (12 mg, 0.10 mmol) and the resulting solution stirred under N\(_2\) and cooled to 0°C. To this was added ethyl propiolate (0.10 mL, 1.00 mmol) drop wise over 5 min. and the reaction mixture then allowed to warm to room temperature and stirred for overnight. The reaction mixture was then concentrated in vacuo and the resultant oil purified by column chromatography (4:1, light petroleum: ethyl acetate, Rf = 0.8) yielding a colourless liquid (284 mg, 0.95 mmol, 95%): \(^1\)H NMR (CDCl\(_3\), 400MHz) \(\delta\) 7.48 (d, \(J = 12.8\) Hz, 1H), 7.35 - 7.25 (m, 3H), 7.22 - 7.18 (m, 2H), 5.80 (ddd, \(J = 17.2, 10.4, 7.6\) Hz, 1H), 5.69 (ddd, \(J = 17.2, 10.0, 7.2\) Hz, 1H), 5.18 (d, \(J = 12.4\) Hz, 1H), 5.15 - 5.04 (m, 2H), 5.05 - 4.98 (m, 2H), 4.83 (d, \(J = 6.0\) Hz, 1H), 4.14 - 4.09 (m, 2H), 3.24 - 3.18 (m, 1H), 1.20 (t, \(J = 6.8\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100MHz) \(\delta\) 167.8, 161.5, 137.6, 136.0, 135.6, 128.4, 128.3, 127.0, 118.0, 117.7, 98.7, 86.4, 59.8, 54.2, 14.4; IR (NaCl): 3584, 2981, 1731, 1651, 1373 cm\(^{-1}\); HRMS (ESI): \(m/z\) [M+Na]\(^{+}\] calcd for C\(_{17}\)H\(_{20}\)O\(_3\): 295.1310, found: 295.1293.

Ethyl (E)-3-hydroxyocta-5,7-dienoate (39). To a solution of 38 (100 mg, 0.37 mmol) in CH\(_2\)Cl\(_2\) (2.00 mL) under a N\(_2\) atmosphere at 0°C was added TFA (0.03 mL, 0.41 mmol) and the resultant reaction mixture allowed to warm to room temperature and stirred overnight. After this period NaHCO\(_3\) (2 mL) was added to the reaction mixture, the reaction mixture was then transferred to a separating funnel with additional CH\(_2\)Cl\(_2\) (20 mL) and water (20 mL), the layers separated, and the aqueous layer extracted with a further portion of CH\(_2\)Cl\(_2\) (20 mL). The combined organic extracts were then dried (Na\(_2\)SO\(_4\)), filtered and the solvent removed under vacuum and the crude oil purified by column chromatography (4:1, light petroleum: ethyl
acetate, \( R_f = 0.3 \) yielding a colourless liquid (56 mg, 0.30 mmol, 82%): \(^1\)H NMR (CDCl\textsubscript{3}, 400MHz) \( \delta \) 6.30 (dt, \( J = 16.8, 10.4 \, \text{Hz}, \, 1\text{H} \)), 6.12 (dd, \( J = 15.2, 10.8 \, \text{Hz}, \, 1\text{H} \)), 5.69 (pent, \( J = 7.2 \, \text{Hz}, \, 1\text{H} \)), 5.12 (d, \( J = 16.8 \, \text{Hz}, \, 1\text{H} \)), 5.00 (d, \( J = 9.6 \, \text{Hz}, \, 1\text{H} \)), 4.15 (q, \( J = 7.6 \, \text{Hz}, \, 1\text{H} \)), 4.11 - 4.04 (m, 1H), 2.98 (d, \( J = 3.6 \, \text{Hz}, \, 1\text{H} \)), 2.50 (dd, \( J = 16.8, 4.0 \, \text{Hz}, \, 1\text{H} \)), 2.40 (dd, \( J = 16.4, 8.8 \, \text{Hz}, \, 1\text{H} \)), 2.36 - 2.23 (m, 2H), 1.25 (t, \( J = 7.2 \, \text{Hz}, \, 3\text{H} \)); \(^{13}\)C NMR (CDCl\textsubscript{3}, 100MHz) \( \delta \) 171.9, 136.8, 134.3, 129.7, 116.3, 67.7, 60.8, 40.7, 39.7, 14.3; IR (NaCl): 3583, 2983, 2253, 1719, 1374 cm\(^{-1}\); HRMS (ESI): \( m/z \) [M+Na]\(^+\) calcd for C\textsubscript{10}H\textsubscript{16}O\textsubscript{3}: 207.0997, found: 207.0983.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publications website at

Copies of \(^1\)H and \(^{13}\)C spectra of all products (PDF).

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Notes
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