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Synthesis of (+)- and (–)-Gossonorol and Cyclisation to Boivinianin B

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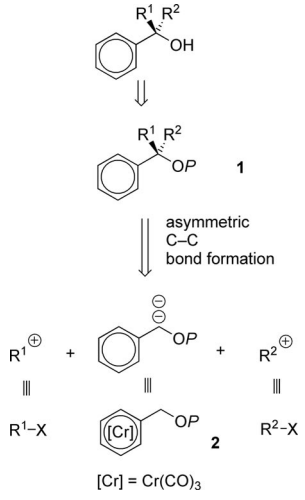
The first enantioselective synthesis of gossonorol has been achieved in good overall yield and excellent enantioselectivity, demonstrating the utility of a novel approach to enantiopure tertiary benzylic alcohols. Epoxidation of enantiopure gossonorol followed by acid-catalysed cyclisation gave a diastereoisomeric mixture of boivinianin B, typical of the diastereoisomeric mixtures of this compound found in nature. Separation of the diastereoisomers and determination of their enantiopurity revealed that the stereochemical integrity of the benzylic alcohol of gossonorol had been preserved during the epoxidation/cyclisation reaction.

Introduction

The synthesis of enantiopure tertiary alcohols is more difficult than the synthesis of enantiopure secondary alcohols. This may be attributed in part to the challenges associated with developing conditions for the selective addition of nucleophiles to ketones compared to aldehydes i.e. lower reactivity of ketones, smaller steric and electronic differences between the two substituents on the prochiral carbon, and also to the steric demands of tertiary alcohols and their derivatives, which have rendered them a challenge to enantiomer separation methods such as those based on enzymatic kinetic resolutions. Contemporary responses to these challenges include the use of carefully chosen combinations of metal catalyst, enantiopure chiral ligand, ketone and nucleophile,[1–2] such as the use of zinc-based nucleophiles in the presence of titanium tetraisopropoxide and C_2-symmetric bis(camphorsulfonamide) ligands,[3–6] the use of mutated forms of esterases to hydrolyse acetates of tertiary alcohols,[7] a diastereoselective S_N2' allylic substitution on pentafluorobenzoates of enantiopure trisubstituted allylic alcohols followed by oxidation and a Baeyer–Villiger reaction,[8] and the conversion of enantiopure secondary alcohols into enantiopure tertiary alcohols via a lithiation–borylation–oxidation sequence.[9]

We recently reported a new approach to the synthesis of enantiopure benzylic alcohols that is based on tricarbonylchromium(0) complexes of protected benzyl ethers.[10] Whilst most of the alcohols we synthesized during the course of this methodology study were secondary alcohols, a single attempt to make a tertiary alcohol proved successful. A retrosynthetic analysis of this new route to enantiopure tertiary benzylic alcohols is presented in Scheme 1. The key disconnection involves the breaking of two carbon–carbon bonds in **1** and requires the benzylic carbon to twice react as a nucleophile with electrophilic sources of R^1 and R^2.



Scheme 1. A retrosynthetic analysis of enantiopure tertiary benzylic alcohols.

In order to start to define the scope and limitations of this methodology in synthesis, we decided to use it to carry out the first enantioselective synthesis of 6-methyl-2-*p*-tolylhept-5-en-2-ol or gossonorol. Gossonorol (structure **3** in Figure 1) was first isolated from a natural source, the cotton plant, in 1984 as part of a study of into chemical communication between the cotton plant (genus: *Gossypium*) and the parasitoid *Campoletis sonorensis*.[11] It was described as having a heavy, slightly floral scent, somewhat reminiscent of commercial air-freshner.[11] Gossonorol has since been found in many other species, such as *Artemisia sieberi*, an odiferous plant that grows in the region around Tehran,[12]

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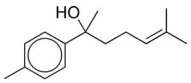
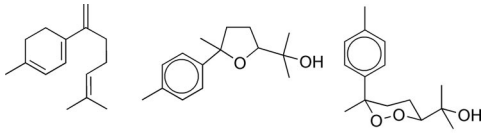
Chamomilla recutita, a medicinal plant rich in oils known for their beneficial effects,[13] and *Laurencia tristicha*, a red alga found in Chinese waters.[14]



3 gossonorol

Figure 1. (6-Methyl-2-*p*-tolylhept-5-en-2-ol), isolated from the cotton plant in 1984.

Gossonorol has been used in the synthesis of many target compounds[15–23] including dehydro-α-curcumene **4**,[16] boivinianin B **5**,[18] and yingzhaosu C **6**[23] (Figure 2). The latter is the active constituent of extracts from the roots of yingzhao (*Artabotrys uncinatus*), a rare vine that grows on the island of Heinan and in coastal regions of Guangdong, which have been used in China for many centuries as a remedy for malaria.[23]



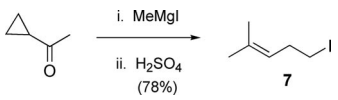
4 dehydro-α-curcumene **5** boivinianin B **6** yingzhaosu C

Figure 2. The structures of typical compounds synthesized from racemic gossonorol.

Despite its widespread occurrence in nature, its interesting biological properties and its frequent use in synthetic work, gossonorol has always been reported as a racemic compound. No enantioselective synthesis has been reported and, to the best of our knowledge, its optical rotation has not been recorded. We report herein the first enantioselective synthesis of gossonorol, and its cyclisation to give enantiopure samples of the two diastereomers of boivinianin B (**5**).

Results and Discussion

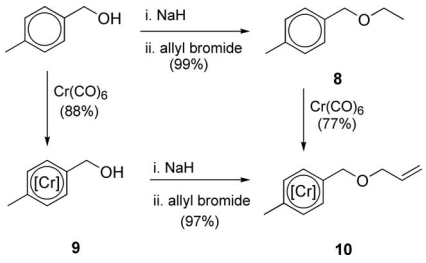
The benzylic position of gossonorol is substituted by a methyl group and an unsaturated hydrocarbon chain. Adhering to the synthetic strategy depicted in Scheme 1, it was planned to introduce the methyl group using iodomethane, and the unsaturated hydrocarbon substituent using 5-iodo-2-methylpent-2-ene **7**. The latter was synthesised according to a slightly modified literature procedure (Scheme 2).[24,25]



7

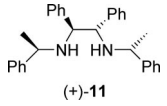
Scheme 2. Preparation of the electrophile **7**.

The substrate required for elaboration by two deprotonation/electrophilic quench sequences, allyl benzyl ether chromium complex **10**, was synthesized from commercially available 4-methylbenzyl alcohol using two different routes (Scheme 3). Deprotonation of 4-methylbenzyl alcohol followed by the addition of allyl bromide gave ether **8**.[26] Ether **8** was then heated with hexacarbonylchromium(0) to give the novel complex **10** as an orange oil. By reversing the allylation and complexation steps and proceeding via 4-methylbenzyl alcohol complex **9**,[27] the overall yield for the formation of **10** from 4-methylbenzyl alcohol was improved from 76% to 86%.



Scheme 3. Activation/protection of 4-methylbenzyl alcohol.

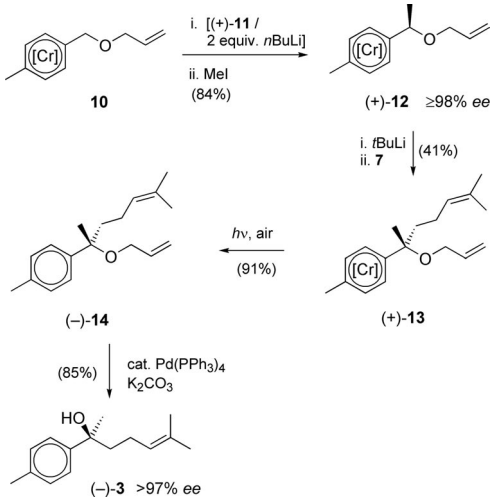
With electrophile **7** and chromium complex **10** in hand, the only remaining reagents that were required for our proposed synthesis of enantiopure gossonorol were the chiral diamines (+)- and (–)-**11** (Figure 3). These were prepared according to a literature procedure that involved the condensation of α-methylbenzylamine with glyoxal followed by the addition of phenylmagnesium chloride.[28]



(+)-**11**

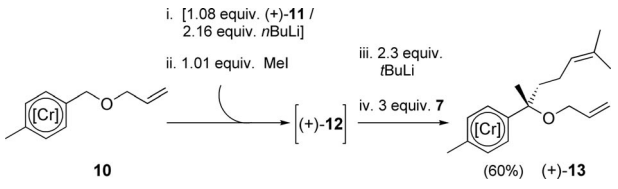
Figure 3. Structure of the chiral base (+)-**11**.

As preliminary studies had revealed that the second deprotonation/alkylation was more efficient with a relatively small benzylic substituent in place, it was decided to first introduce the methyl substituent. Deprotonation of complex **10** with the chiral bases derived from (+)- and (–)-**11** at –78 °C followed by the addition of iodomethane and work-up gave the methyl-substituted complexes (+)- and (–)-**12** respectively [Scheme 4; synthesis of (–)-enantiomer not depicted]. Analysis of both products by chiral HPLC revealed that they had both been formed in ≥ 98% *ee*. The absolute configuration of (+)- and (–)-**12** was assigned by comparison of these experiments with deprotonations performed on a range of closely related complexes, the outcome of which was supported either by correlation with known compounds[29,30] or by *X*-ray crystallographic analysis.[31–33] Deprotonation of (+)- and (–)-**12** with *t*BuLi followed by quenching with freshly distilled 5-iodo-2-methylpent-2-ene **7** gave the disubstituted ethers (+)- and (–)-**13** in moderate yield (41 and 60% yield, respectively). It was deduced that (+)- and (–)-**13** were formed with overall retention of configuration by comparison of the *t*BuLi deprotonation/alkylation reactions that led to their formation with a *t*BuLi deprotonation/benzylation reaction on a complex closely related to (+)-**12**, the result of which was verified by X-ray crystallography.[34]



Scheme 4. Synthesis of the (–)-enantiomer of gossonorol.

There is precedent in the literature for a one-pot chiral base/*t*BuLi double deprotonation/electrophilic quench sequence,[35] and so it was decided at this point to determine whether or not a one-pot approach would lead to a more efficient conversion of substrate **10** to dialkylated product **13**. To 1.08 equiv. of deprotonated (+)-**11** in THF at –78 °C was added 1.01 equiv. of iodomethane (Scheme 5). To this solution was added complex **10** over a 10 min period after which the resulting mixture was stirred for 45 min at –78 °C. Subsequent addition of 2.3 equiv. of *t*BuLi at –78 °C and stirring for 50 min were followed by the addition of 3 equiv. of electrophile **7**. Finally stirring for a further 2.5 h, quenching with methanol and work-up gave (+)-**13** in 60% yield, a significantly greater yield than the combined yield of the two separate steps (Scheme 4). Interestingly, isolation of (+)-**13** from this protocol revealed that deprotonated (+)-**11** acted predominantly as a base rather than as a nucleophile under the reaction conditions employed.



Scheme 5. A one-pot double deprotonation/alkylation conversion of **10** to (+)-**13**.

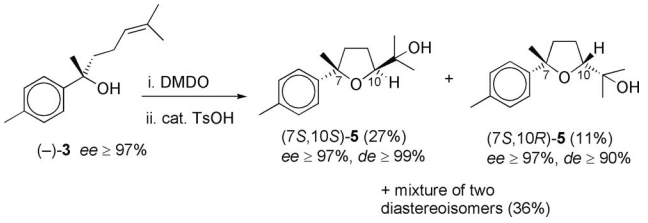
To complete the synthesis of the two enantiomers of gossonorol it was necessary to remove the tricarbonylchromium(0) unit and the allyl protecting group. The former was readily achieved by air/light oxidation and gave ethers (–)- and (+)-**14** in 91 and 95% yield respectively (Scheme 4). The ethers were successfully deprotected using 5 mol-% $Pd(PPh_3)_4$ and potassium carbonate.[10] After careful neutralization with 1 M HCl and work-up, the two alcohols (–)- and (+)-**3** were obtained as colourless oils with a floral scent in 85% and 78% respectively. The analytical data obtained for the two enantiomers of **3** correlated well with the literature values available for gossonorol, and analysis of both products by chiral HPLC revealed that (–)-gossonorol had been formed in ≥ 97% *ee* and (+)-gossonorol had been formed in >99% *ee*.

Access to enantiopure gossonorol has the potential to provide direct routes to further enantiopure compounds such as boivinianin B, **5**, and yingzhaosu C **6**. In the latter case, radical cyclisation of the hydroperoxide derived from racemic gossonorol has been shown to give **6**.[23] The fate of the enantiopure tertiary benzylic alcohol of gossonorol in further reactions, however, was open to question, and so we decided to examine the conversion of gossonorol into boivinianin B in order to determine whether or not the absolute stereochemistry that had been created in our synthesis of gossonorol would be maintained or destroyed.

The two diastereoisomers of the sesquiterpene **5**, were first isolated from a natural source in 2005 when they were found alongside gossonorol in the red alga *Laurencia tristicha*.[14] A year later, the two diastereoisomers of **5** were isolated from the plant *Cipadessa boiviniana* and the diastereoisomeric mixture was named boivinianin B.[36] Before it was isolated from natural sources, compound **5** had been synthesised twice,[18,21] on both occasions by the epoxidation and cyclisation of racemic gossonorol which lead in both cases to a mixture of diastereoisomers. Although a diastereoselective synthesis of racemic *cis*-boivinianin B, based on a rhodium-catalysed reaction of alkynyl oxiranes with arylboronic acids that produces *syn*-configured α-allenols with high diastereoselectivity,[37] and an enantioselective synthesis of *cis*-(7*R*,10*S*)-boivinianin B, based on a Sharpless dihydroxylation of dehydro-α-curcumene **4** followed by a moderately diastereoselective iodoetherification of the resulting diol,[38] have been reported very recently, the possibility of accessing enantiopure boivinianin B by the epoxidation and cyclisation of enantiopure gossonorol has not been considered to date.

In order to maintain neutral conditions during the epoxidation of gossonorol, it was decided to use dimethyldioxirane (DMDO) for the oxidation. DMDO was thus added to a sample of (–)-gossonorol in acetone and the mixture was stirred at room temperature for 15 min. After changing the solvent to chloroform, a catalytic amount of acid was added and stirring was continued for a further 15 min (Scheme 6). Work-up and column chromatography yielded a sample of the *trans* isomer of **5** (27%), a sample of the *cis* isomer of **5** (11%), and a sample that contained both isomers (36%). The cis and *trans* isomers of **5** were assigned by correlation with literature NMR spectroscopic data.[36] In particular, H-10 in the *trans* isomer of **5** resonates at δ = 3.79 whilst H-10 in the *cis* isomer resonates at δ = 3.98 ppm. (The numbering used for boivinianin B herein is based on the system defined in reference 36.) Chiral HPLC of the two diastereoisomers revealed that the *trans* and *cis* isomers of **5** had both been formed in the same enantiopurity as the gossonorol starting material (*ee* ≥ 97%). The diastereopurity of the samples was assessed from their ^{1}H NMR spectra

and their HPLC analyses: no trace of the *cis* isomer was found in the *trans* sample but the *cis* sample was contaminated with a small amount (≤ 5%) of the *trans* isomer.



Scheme 6. Synthesis of (7*S*,10*S*)- and (7*S*,10*R*)-boivinianin B.

The enantiopurity of the boivinianin B diastereoisomers suggests that the stereochemical integrity of gossonorol has been maintained during their formation. This is consistent with epoxide formation followed by an acid-catalysed ring-opening of the epoxide by the benzylic alcohol, in which either stereochemically uncontrolled formation of the epoxide and/or the formation of a partial carbocation during ring-opening result in poor control over the formation of the new stereocentre at C-10. On the basis of this model, the two diastereoisomers were assigned as (7*S*,10*S*)- and (7*S*,10*R*)-boivinianin B.

Conclusions

The first enantioselective synthesis of both enantiomers of the naturally occurring sesquiterpene gossonorol has been achieved in good overall yield and excellent enantioselectivity, demonstrating the utility of our novel approach to enantiopure tertiary benzylic alcohols. A similar approach could be adopted for the synthesis of 7-hydroxynuciferol, a benzylic tertiary alcohol isolatd from sandalwood.[39] Epoxidation of enantiopure gossonorol followed by acid-catalysed cyclisation led to the production of a diastereoisomeric mixture of boivinianin B, typical of the diastereoisomeric mixtures of this compound found in nature. Separation of samples of the diastereoisomers and measurement of their enantiopurity revealed that the stereochemical integrity of the benzylic alcohol of gossonorol had been preserved during the epoxidation/cyclisation reaction.

Experimental Section

General: Syntheses were carried out under an atmosphere of nitrogen in oven-dried glassware using standard Schlenk techniques. Reactions involving the use of arene tricarbonylchromium(0) complexes were protected from light. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl and used immediately. Dichloromethane was distilled from calcium hydride. The concentration of *n*BuLi was determined by titration against diphenylacetic acid in tetrahydrofuran.[40] The diamines (+)- and (–)-**11**,[28] and the dimethyldioxirane solution in acetone[41] were prepared according to literature procedures. All other reagents are commercially available and were used as received. Melting points were recorded on a Sanyo Gallenkamp melting point apparatus in open capillaries and are uncorrected. Optical rotations were recorded on an AA 10 polarimeter from Index Instruments or on a Perkin–Elmer 241 polarimeter using a 1 dm path length; concentrations are given as g/100 mL. IR spectra were recorded on Perkin–Elmer Spectrum RX and 100 FT-IR spectrometers. NMR spectra were recorded at room temperature on a Bruker AV 400 instrument in $CDCl_3$ at 400 MHz (^1H) and 100 MHz (^{13}C). Mass spectra were recorded on Micromass Platfrom II and Micromass AutoSpec-Q instruments by the mass spectrometry service at Imperial College London. Elemental analyses were performed by the London Metropolitan University microanalytical service.

5-Iodo-2-methylpent-2-ene (7):[24,25] To a stirred solution of methylmagnesium iodide in diethyl ether (25.0 mL, 3 M in diethyl ether, 75.0 mmol) was added dropwise a solution of cyclopropyl methyl ketone (5 mL, 50.5 mmol) in dry diethyl ether (25 mL). The reaction mixture was heated under reflux for 2 h then slowly added to a stirred and cooled (0 °C) solution of concentrated sulfuric acid (7.5 mL) in water (15 mL) at a rate to maintain the temperature below 10 °C. After the addition was complete, stirring was continued for 30 min. The ethereal layer was separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined ethereal phases were decolorised by the addition of 5% aqueous $NaHSO_3$ (150 mL), neutralised with 5% aqueous $NaHCO_3$ (150 mL), washed with brine (150 mL) and dried with $MgSO_4$. The solvent was removed in vacuo and the residue distilled in vacuo to give **7** (8.22 g, 78%) as a colourless liquid; b.p. 44–46 °C, 3 Torr (ref.[24] 65 °C, 10 Torr). IR (neat): $\tilde{\nu}$ = 1670 (w, C=C), 600 cm^{-1} (s, C–I). ^1H NMR: δ = 1.61 (s, 3 H, CH_3), 1.70 (s, 3 H, CH_3), 2.57 [apparent q, ^3J(H,H) = 7.5 Hz, 2 H, CH_2CH$_2$I], 3.11 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, CH$_2$CH_2I), 5.09 ppm (t, $^3J_{H,H}$ = 7 Hz, 1 H, *C*H=C). ^{13}C NMR: δ = 6.1 (CH_2I), 18.0 (CH_3), 25.7 (CH_3), 32.5 (*C*H$_2$CH$_2$I), 123.1 (*C*H=C), 134.5 ppm (CH=*C*). MS (CI): *m*/*z* (%): 228 (11) $[M + NH_4]^+$, 211 (26) $[M + H]^+$, 100 (100) $[M – HI + NH_4]^+$.

1-Allyloxymethyl-4-methylbenzene (8):[26] 4-Methylbenzyl alcohol (4.00 g, 32.8 mmol) was added to a suspension of sodium hydride (1.56 g, 60% dispersion in mineral oil, 39.3 mmol, previously washed with hexane) in THF (100 mL) and the mixture was stirred for 1 h at 0 °C before allyl bromide (5.6 mL, 64.7 mmol) was added in one portion. After stirring for 16 h at room temperature, methanol (2 mL) was added and the solvent was removed in vacuo. The crude product was filtered through a long silica gel column in hexane and then hexane/diethyl ether, 90:10 to yield ether **8** (5.26 g, 99%) as a slightly yellow oil. IR (neat): $\tilde{\nu}$ = 1650 cm^{-1} (w, C=C), 1081 cm^{-1} (s, C–O). ^1H NMR: δ = 2.37 (s, 3 H, CH_3), 4.04 (d, $^3J_{H,H}$ = 5.5 Hz, 2 H, OCH_2CH=CH$_2$), 4.52 (s, 2 H, OCH$_2$Ar), 5.23 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, CH=CH$H_{(E)}$), 5.33 (d, $^3J_{H,H}$ = 17 Hz, 1 H, CH=CH$H_{(Z)}$), 5.98 (ddt, $^3J_{H,H}$ = 17, 10.5, 5.5 Hz, 1 H, C*H*=CH$_2$), 7.19 (d, $^3J_{H,H}$ = 8 Hz, 2 H, $C_{Ar}H \times 2$), 7.27 ppm (d, $^3J_{H,H}$ = 8 Hz, 2 H, $C_{Ar}H \times 2$). ^{13}C NMR: δ = 20.8 (CH_3), 71.0 (O*C*H$_2$CH=CH$_2$), 72.0 (O*C*H$_2$C$_{Ar}$), 116.7 (CH=*C*H$_2$), 125.9, 129.1 ($C_{Ar}H \times 4$), 134.9 (*C*H=CH$_2$), 135.3 (C_{Ar}CH$_2$), 137.3 ppm (C_{Ar}CH$_3$). MS (CI): *m*/*z* (%): 180 (100) $[M + NH_4]^+$, 162 (4) $[M]^+$, 122 (30) $[M – (CH_2=CH–CH_2)]^+$, 105 (9) $[M – (CH_2=CH–CH_2–O)]^+$.

(4-Methylbenzyl alcohol)tricarbonylchromium(0) (9):[27] Dry di-*n*-butyl ether (230 mL) and THF (23 mL) were added to 4-methylbenzyl alcohol (5.00 g, 40.9 mmol) and hexacarbonylchromium(0) (10.80 g, 49.1 mmol) and the mixture was saturated with nitrogen and shielded from ambient light. The reaction mixture was heated under reflux for 39 h and then cooled to room temperature. The mixture was filtered through a pad of Celite® and rinsed with dichloromethane. The solvent was removed in vacuo and the crude

mixture was purified by column chromatography (SiO_2; dichloromethane) to yield complex **9** (9.27 g, 88%) as a yellow powder; m.p. 80–81 °C (ref.[27] 80–82 °C). IR (neat): $\tilde{\nu}$ = 3309 cm^{-1} (br., OH), 1942 (s, CO), 1844 cm^{-1} (s, CO). ^1H NMR: δ = 1.82 (t, $^3J_{H,H}$ = 6 Hz, 1 H, OH), 2.19 (s, 3 H, CH_3), 4.38 (d, $^3J_{H,H}$ = 6 Hz, 2 H, CH_2OH), 5.22 (d, $^3J_{H,H}$ = 6 Hz, 2 H, $C_{Cr}H \times 2$), 5.50 ppm (d, $^3J_{H,H}$ = 6 Hz, 2 H, $C_{Cr}H \times 2$). ^{13}C NMR: δ = 20.5 (CH_3), 63.1 (CH_2OH), 92.8, 92.9 ($C_{Cr}H \times 4$), 108.6, 109.1 ($C_{Cr}C \times 2$), 233.1 ppm (CO × 3). MS (CI): *m*/*z* (%): 276 (99) $[M + NH_4]^+$, 259 (94) $[M + H]^+$, 258 (28) $[M]^+$, 241 (100) $[M – OH]^+$, 174 (3) $[M – 3CO]^+$, 122 (17) $[M – Cr(CO)_3]^+$. $C_{11}H_{10}CrO_4$ (258.19): calcd. C 51.17, H 3.90; found C 51.26, H 3.92.

(1-Allyloxymethyl-4-methylbenzene)tricarbonylchromium(0) (10): i) From **8**: Allyl ether **8** (5.03 g, 31.0 mmol) and hexacarbonylchromium(0) (8.18 g, 37.2 mmol) were added to dry di-*n*-butyl ether (175 mL) and THF (17 mL) and the mixture was saturated with nitrogen and shielded from ambient light. The reaction mixture was heated under reflux for 44 h and then cooled to room temperature. The solvents were removed under reduced pressure and the crude mixture was purified by column chromatography (SiO_2; hexane/diethyl ether, 100:0–80:20) to yield complex **10** (7.08 g, 77%) as an orange oil.

ii) From **9**: Alcohol **9** (8.00 g, 31.0 mmol) was added under nitrogen to a suspension of sodium hydride (1.48 g, 60% dispersion in mineral oil, 37.2 mmol, previously washed with hexane) in THF (100 mL) and the mixture was stirred for 1 h at 0 °C before allyl bromide (5.4 mL, 62.4 mmol) was added in one portion. After stirring for a further 19 h at room temperature, methanol (2 mL) was added and the solvent was removed in vacuo. The resulting crude product was purified by column chromatography (SiO_2; hexane/diethyl ether, 95:5–90:10) to yield complex **10** (8.98 g, 97%) as an orange oil.

R_f = 0.24 (SiO_2; hexane/diethyl ether, 90:10). IR (neat): $\tilde{\nu}$ = 1950 cm^{-1} (s, CO), 1856 cm^{-1} (s, CO). ^1H NMR: δ = 2.17 (s, 3 H, CH_3), 4.08 (d, $^3J_{H,H}$ = 5.5 Hz, 2 H, OCH_2CH=CH_2), 4.15 (s, 2 H, OCH_2Ar), 5.19 (d, $^3J_{H,H}$ = 6.5 Hz, 2 H, $C_{Cr}H \times 2$), 5.25 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, CH=CH$H_{(E)}$), 5.32 (d, $^3J_{H,H}$ = 17 Hz, 1 H, CH=CH$H_{(Z)}$), 5.46 (d, $^3J_{H,H}$ = 6.5 Hz, 2 H, $C_{Cr}H \times 2$), 5.92 ppm (ddt, $^3J_{H,H}$ = 17, 10.5, 5.5 Hz, 1 H, C*H*=CH_2). ^{13}C NMR: δ = 20.5 (CH_3), 70.1 (O*C*H_2CH=CH_2), 71.9 (O*C*H_2C_{Cr}), 92.7, 94.1 ($C_{Cr}H \times 4$), 104.6 ($C_{Cr}CH_3$), 108.7 ($C_{Cr}CH_2$), 117.9 (CH=*C*H_2), 134.0 (*C*H=CH_2), 233.0 ppm (CO × 3). MS (CI): *m*/*z* (%): 316 (61) $[M + NH_4]^+$, 299 (34) $[M + H]^+$, 242 (38) $[M – 2CO]^+$, 241 (100) $[M – (CH_2=CH–CH_2–O)]^+$. $C_{14}H_{14}CrO_4$ (298.03): calcd. C 56.38, H 4.73; found C 56.38, H 4.75.

(+)-(*R*)-[1-(1-Allyloxyethyl)-4-methylbenzene]tricarbonylchromium(0) [(+)-12]: *n*-Butyllithium (6.25 mL, 1.6 M in hexanes, 10.0 mmol) was added to a solution of diamine (+)-**11** (2.10 g, 5.00 mmol) in THF (50 mL) at –78 °C. The solution was warmed to room temperature over a period of 30 min. The deep red solution was cooled to –78 °C. A solution of heat gun-dried lithium chloride (210 mg, 5.00 mmol) dissolved in THF (25 mL) was added and the reaction mixture was stirred for a further 5 min before a solution of complex **10** (1.49 g, 5.00 mmol) in THF (12.5 mL) was added. After stirring for 30 min at –78 °C, iodomethane (1.0 mL, 15.0 mmol) was added. Stirring was continued for a further 30 min after which the reaction was quenched with methanol (1.5 mL). The solvent was removed in vacuo, the crude residue dissolved in diethyl ether and the chiral base was extracted with 1 M HCl (3 × 75 mL). The organic layer was washed with brine (75 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2; hexane/diethyl ether, 90:10) afforded complex (+)-**12** (1.31 g, 84%) as a yellow oil. R_f = 0.33 (SiO_2; hexane/diethyl ether, 90:10); enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min, UV 330 nm); (*S*)-enantiomer t_r = 11.7 min (minor); (*R*)-enantiomer t_r = 12.4 min (major): ≥ 98% *ee*. $[\alpha]_D^{20}$ = +39 (*c* = 0.97, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1953 cm^{-1} (s, CO), 1853 cm^{-1} (s, CO). ^1H NMR: δ = 1.43 (d, $^3J_{H,H}$ = 6.5 Hz, 3 H, CHCH_3), 2.19 (s, 3 H, CH_3Ar), 4.03–4.16 (m, 3 H, C*H*CH_3 + OCH_2CH=CH_2), 5.12 (apparent t, $^3J_{H,H}$ = 5.5 Hz, 2 H, $C_{Cr}H \times 2$), 5.21 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, CH=CH$H_{(E)}$), 5.32 (d, $^3J_{H,H}$ = 17.5 Hz, 1 H, CH=CH$H_{(Z)}$), 5.45 (d, $^3J_{H,H}$ = 6 Hz, 1 H, $C_{Cr}H$), 5.61 (d, $^3J_{H,H}$ = 6 Hz, 1 H, $C_{Cr}H$), 5.93 ppm (ddt, $^3J_{H,H}$ = 17.5, 10.5, 5.5 Hz, 1 H, C*H*=CH_2). ^{13}C NMR: δ = 20.5 (CH_3Ar), 23.3 (CH*C*H_3), 70.4 (O*C*H_2CH=CH_2), 74.4 (*C*HCH_3), 91.4, 91.8, 92.8, 93.5 ($C_{Cr}H \times 4$), 109.9 ($C_{Cr}CH_3$), 110.4 ($C_{Cr}CH$), 117.5 (CH=*C*H_2), 134.4 (*C*H=CH_2), 233.3 ppm (CO × 3). MS (CI): *m*/*z* (%): 330 (6) $[M + NH_4]^+$, 312 (2) $[M]^+$, 256 (39) $[M – 2CO]^+$, 255 (100) $[M – (OCH_2CH=CH_2)]^+$. $C_{15}H_{16}CrO_4$ (312.05): calcd. C 57.69, H 5.16; found C 57.63, H 5.11.

(–)-(*S*)-[1-(1-Allyloxyethyl)-4-methylbenzene]tricarbonylchromium(0) [(–)-12]: Complex (–)-**12** was prepared from **10** (1.19 g, 4.00 mmol) and diamine (–)-**11** (1.68 g, 4.00 mmol) following the procedure described for (+)-**11**. 87% yield, yellow oil; *ee* ≥ 98%. $[\alpha]_D^{20}$ = –41 (*c* = 1.01, $CHCl_3$); all other analytical data were identical to those obtained for (+)-**12**.

(+)-(*S*)-[1-(2-Allyloxy-6-methylhept-5-en-2-yl)-4-methylbenzene]tricarbonylchromium(0) [(+)-13]: i) From (+)-**12**: *tert*-Butyllithium (3.12 mL, 1.6 M in pentane, 5.00 mmol) was added to a solution of complex (+)-**12** (1.20 g, 3.85 mmol) in THF (38 mL) at –78 °C. After stirring for 45 min at –78 °C, iodide **7** (2.42 g, 11.5 mmol) was added. Stirring was continued for a further 3 h after which the reaction was quenched with methanol (1.5 mL). After removal of the solvent in vacuo, purification by column chromatography (SiO_2; hexane/diethyl ether, 100:0–98:2) yielded (+)-**13** (619 mg, 41%) as yellow crystals.

ii) One-pot synthesis from **10**: *n*-Butyllithium (0.86 mL, 2.5 M in hexanes, 2.16 mmol) was added to a solution of diamine (+)-**11** (454 mg, 1.08 mmol) in THF (10 mL) at –78 °C. The solution was warmed to room temperature over a period of 30 min. The deep red solution was cooled to –78 °C. A solution of heat gun-dried lithium chloride (45 mg, 1.08 mmol) dissolved in THF (5 mL) was added and the reaction mixture was stirred for a further 5 min before iodomethane (143 mg, 1.01 mmol) was added. Then a solution of complex **10** (298 g, 1.00 mmol) in THF (3.5 mL) was added via a cannula over 10 min. Stirring was continued for a further 45 min after which time *tert*-butyllithium (1.44 mL, 1.6 M in pentane, 2.30 mmol) was added and the reaction mixture was stirred for a further 50 min before **7** (630 mg, 3.00 mmol) was added. Stirring was continued for a further 2.5 h after which the reaction was quenched with methanol (1 mL). The solvent was removed in vacuo. The crude residue was dissolved in diethyl ether and the chiral base was extracted with 1 M HCl (3 × 50 mL). The organic layer was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2; hexane/diethyl ether, 100:0–98:2) afforded complex (+)-**13** (238 mg, 60%) as yellow crystals.

R_f = 0.47 (SiO_2; hexane/diethyl ether, 95:5); m.p. 32–34 °C. $[\alpha]_D^{20}$ = +17 (*c* = 1.05, $CHCl_3$). IR (neat): 1947 (s, CO), 1873 (s, CO), 1849 cm^{-1} (s, CO). ^1H NMR: δ = 1.48–2.08 [m, 13 H, CH_2CH_2CH=C$(CH_3)_2$ + CH_2CH_2CH=C$(CH_3)_2$ + CH_2CH_2CH=C$(CH_3)_2$ + OCCH_3], 2.20 (s, 3 H, CH_3Ar), 3.95 (dd, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 5 Hz, 1 H, OC*H*HCH=CH_2), 4.10 (dd, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 5 Hz, 1 H, OCH*H*CH=CH_2), 4.97–5.09 [m, 3 H,

CH_2CH_2CH=$C(CH_3)_2$ + $C_{Cr}H \times 2$], 5.16 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, OCH_2CH=$CH_{(E)}$), 5.36 (d, $^3J_{H,H}$ = 17 Hz, 1 H, OCH_2CH=$CH_{(Z)}$), 5.42 (d, $^3J_{H,H}$ = 6.5 Hz, 1 H, $C_{Cr}H$), 5.87–6.00 ppm (m, 2 H, OCH_2CH=CH_2 + $C_{Cr}H$). ^{13}C NMR: δ = 17.6 [CH=$C(CH_3)_2 \times 1$], 20.4 (CH_3Ar), 22.3 [CH_2CH_2CH=$C(CH_3)_2$], 24.6 (CH=$C(CH_3)_2 \times 1$), 25.7 (CCH_3), 42.8 [CH_2CH_2CH=$C(CH_3)_2$], 63.2 (OCH_2CH=CH_2), 76.7 ($OCCH_3$), 90.5, 90.7, 93.1, 94.1 ($C_{Cr}H \times 4$), 110.3 (CH_3C_{Cr}), 114.5 ($C_{Cr}C$), 115.6 (CH=CH_2), 123.6 [CH=$C(CH_3)_2$], 132.0 [CH=$C(CH_3)_2$], 135.1 (CH=CH_2), 233.6 ppm (CO × 3). MS (CI): *m*/*z* (%): 412 (2) [M + NH_4]$^+$, 337 (100) [M – (CH_2=CH–CH_2–O)]$^+$, 336 (30) [M – 2CO]$^+$. $C_{21}H_{26}CrO_4$ (394.12): calcd. C 63.95, H 6.64; found C 63.95, H 6.68.

(–)-(*R*)-[1-(2-Allyloxy-6-methylhept-5-en-2-yl)-4-methylbenzene]tricarbonylchromium(0) [(–)-13]: Complex (–)-**13** was prepared from (–)-**12** (598 mg, 1.91 mmol) following the procedure described for (+)-**13**. 60% yield, yellow crystals. $[\alpha]_D^{20}$ = –17 (*c* = 1.06, $CHCl_3$); all other analytical data were identical to those obtained for (+)-**13**.

(–)-(*S*)-1-[2-(Allyloxy)-6-methylhept-5-en-2-yl]-4-methylbenzene [(–)-14]: Complex (+)-**13** (595 mg, 1.51 mmol) in diethyl ether (600 mL) was exposed to air and light for 24 h. The reaction mixture was filtered through a pad of Celite® and rinsed with diethyl ether. The solvent was removed in vacuo and the crude mixture was purified by column chromatography (SiO_2; hexane/diethyl ether, 100:0–98:2) to afford (–)-**14** (355 mg, 91%) as a colourless oil. (The chromium-contaminated Celite was packaged for disposal in a secure landfill.) $[\alpha]_D^{20}$ = –1 (*c* = 1.00, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1649 cm^{-1} (w, C=C). ^{1}H NMR: δ = 1.53 [s, 3 H, $C(CH_3)_2$], 1.55 [s, 3 H, $C(CH_3)_2$], 1.65 (s, 3 H, $OCCH_3$), 1.77–1.85 [m, 2 H, CH_2CH_2CH=$C(CH_3)_2$], 1.86–1.98 [m; 2 H, CH_2CH_2CH=$C(CH_3)_2$], 2.35 (s, 3 H, CH_3Ar), 3.68 (dd, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 5 Hz, 1 H, $OCHHCH$=CH_2), 3.78 (dd, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 5 Hz, 1 H, $OCHHCH$=CH_2), 5.06 [t, $^3J_{H,H}$ = 7 Hz, 1 H, CH_2CH_2CH=$C(CH_3)_2$], 5.13 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, OCH_2CH=$CH_{(E)}$), 5.32 (d, $^3J_{H,H}$ = 17 Hz, 1 H, OCH_2CH=$CH_{(Z)}$), 5.92 (ddt, $^3J_{H,H}$ = 17, 10.5, 5 Hz, 1 H, OCH_2CH=CH_2), 7.15 (d, $^3J_{H,H}$ = 8 Hz, 2 H, $C_{Ar}H \times 2$), 7.28 ppm (d, $^3J_{H,H}$ = 8 Hz, 2 H, $C_{Ar}H \times 2$). ^{13}C NMR: δ = 17.6 [CH=C-$(CH_3)_2 \times 1$], 21.0 (CH_3Ar), 22.7 [CH_2CH_2CH=$C(CH_3)_2$], 23.9 [CH=$C(CH_3)_2 \times 1$], 25.7 (CCH_3), 42.6 [CH_2CH_2CH=$C(CH_3)_2$], 63.6 (OCH_2CH=CH_2), 78.9 ($OCCH_3$), 115.4 (CH=CH_2), 124.4 [CH=$C(CH_3)_2$], 126.0, 128.8 ($C_{Ar}H \times 4$), 131.3 [CH=$C(CH_3)_2$], 135.8 (CH=CH_2), 136.2, 142.5 ppm ($C_{Ar} \times 2$). MS (CI): *m*/*z* (%): 276 (1) [M + NH_4]$^+$, 218 (60) [M – (CH_2CH=CH_2) + H]$^+$, 201 (100) [M – (OCH_2CH=CH_2)]$^+$. $C_{18}H_{26}O$ (258.20): calcd. C 83.67, H 10.14; found C 83.62, H 10.17.

(+)-(*R*)-1-[2-(Allyloxy)-6-methylhept-5-en-2-yl]-4-methylbenzene [(+)-14]: Ether (+)-**14** was prepared from (–)-**19** (425 mg, 1.08 mmol) following the procedure described for (–)-**14**. 95% yield, colourless oil. $[\alpha]_D^{20}$ = +1 (*c* = 1.01, $CHCl_3$); all other analytical data were identical to those obtained for (–)-**14**.

(–)-(*S*)-6-Methyl-2-*p*-tolylhept-5-en-2-ol [(–)-Gossonorol] [(–)-3]: Ether (–)-**14** (347 mg, 1.34 mmol) was dissolved in anhydrous methanol (14 mL) and placed under a nitrogen atmosphere. $Pd(PPh_3)_4$ (77.7 mg, 0.067 mmol) was added and the resulting yellow solution was stirred for 5 min before K_2CO_3 (558 mg, 4.03 mmol) was added. The mixture was heated under reflux for 72 h. After cooling to room temperature, the mixture was carefully neutralised with 1 M HCl and extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried with $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (SiO_2; hexane/diethyl ether, 90:10) afforded (–)-**3** (249 mg, 85%) as a colourless oil. Enantiomeric excess was determined by HPLC analysis (Chiralcel OB, *n*-hexane/*i*PrOH, 98:2, 0.5 mL/min, UV 220 nm); (*R*)-enantiomer t_r = 14.9 min (minor); (*S*)-enantiomer t_r = 24.1 min (major): ≥ 97% *ee*. $[\alpha]_D^{20}$ = –18 (*c* = 1.00, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3430 cm^{-1} (br., OH). ^{1}H NMR: δ = 1.49 [s, 3 H, $C(CH_3)_2$], 1.52 [s, 3 H, $C(CH_3)_2$], 1.65 (s, 3 H, CCH_3), 1.76–2.03 [m, 5 H, CH_2CH_2CH=$C(CH_3)_2$ + CH_2CH_2CH=C-$(CH_3)_2$ + OH], 2.34 (s, 3 H, CH_3Ar), 5.09 [t, $^3J_{H,H}$ = 6.5 Hz, 1 H, CH_2CH_2CH=$C(CH_3)_2$], 7.15 (d, $^3J_{H,H}$ = 8 Hz, 2 H, $C_{Ar}H \times 2$), 7.31 ppm (d, $^3J_{H,H}$ = 8 Hz, 2 H, $C_{Ar}H \times 2$). ^{13}C NMR: δ = 17.6 [CH=$C(CH_3)_2 \times 1$], 20.9 (CH_3Ar), 23.0 [CH_2CH_2CH=$C(CH_3)_2$], 25.7 (CCH_3), 30.7 [CH=$C(CH_3)_2 \times 1$], 43.7 [CH_2CH_2CH=C-$(CH_3)_2$], 74.9 ($OCCH_3$), 124.2 [CH=$C(CH_3)_2$], 124.7, 128.8 ($C_{Ar}H \times 4$), 132.1 [CH=$C(CH_3)_2$], 136.0, 144.9 ppm ($C_{Ar} \times 2$). MS (CI): *m*/*z* (%): 236 (1) [M + NH_4]$^+$, 219 (7) [M + H]$^+$, 218 (39) [M]$^+$, 201 (100) [M – OH]$^+$. $C_{15}H_{22}O$ (218.17): calcd. C 82.52, H 10.16; found C 82.62, H 10.19.

(+)-(*R*)-6-Methyl-2-*p*-tolylhept-5-en-2-ol [(+)-Gossonorol] [(+)-3]: Alcohol (+)-**3** was prepared from (+)-**14** (100 mg, 0.39 mmol) following the procedure described for (–)-**3**. 78% yield, colourless oil; *ee* > 99%. $[\alpha]_D^{20}$ = +15 (*c* = 1.00, $CHCl_3$); all other analytical data were identical to those obtained for (–)-**3**.

(7*S*,10*S*)- and (7*S*,10*R*)-Boivinianin B 5: Dimethyldioxirane solution in acetone (8.0 mL, 0.072 M, 0.58 mmol) was added to a solution of (–)-gossonorol (–)-**3** (111 mg, 0.51 mmol) in acetone (2.5 mL) and the mixture was stirred at room temperature for 15 min. After removal of the acetone in vacuo, the paste remaining was dissolved in dichloromethane (2 mL), and reduced to dryness in vacuo twice and then dried under high vacuum. The crude mixture was dissolved in $CDCl_3$ (2.5 mL) and a catalytic amount of *p*-toluenesulfonic acid monohydrate (1.4 mg, 0.007 mmol) was added. The mixture was stirred for 15 min and then the solvent was removed in vacuo. The mixture was dissolved in diethyl ether and filtered through a short pad of alumina. After removal of the solvent in vacuo, purification by column chromatography [SiO_2; hexane/diethyl ether, 100:0–90:10 (very slow gradient), then 90:10–70:30] afforded (7*S*,10*S*)-**5** (32 mg, 27%), (7*S*,10*R*)-**5** (13 mg, 11%) and a mixture of both (43 mg, 36%) as colourless oils. IR (neat): $\tilde{\nu}$ = 3445 (br., OH), 1099(s, C–O), 1078 cm^{-1} (s, C–O). MS (CI): *m*/*z* (%): 486 (6) [2M + NH_4]$^+$, 252 (100) [M + NH_4]$^+$, 235 (4) [M + H]$^+$, 217 (90) [M – OH]$^+$. $C_{15}H_{22}O_2$ (234.16): calcd. C 76.88, H 9.46; found C 76.78, H 9.35. (7*S*,10*S*)-**5**: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H, *n*-hexane/*i*PrOH, 98:2, 0.3 mL/min, UV 220 nm); (7*R*,10*S*)-enantiomer t_r = 18.5 min (minor); (7*S*,10*S*)-enantiomer t_r = 21.3 min (major): ≥ 97% *ee*, ≥ 99% *de*. $[\alpha]_D^{20}$ = –10 (*c* = 1.01, $CHCl_3$). ^{1}H NMR: δ = 1.17 [s, 3 H, $C(CH_3)_2$], 1.29 [s, 3 H, $C(CH_3)_2$], 1.50 (s, 3 H, CCH_3), 1.62 (br. s, 1 H, OH), 1.70–1.79 (m, 1 H, $CCH_2CHHCHO$), 1.84–1.94 (m, 1 H, $CCH_2CHHCHO$), 2.00–2.07 (m, 1 H, $CCHHCH_2CHO$), 2.19–2.27 (m, 1 H, $CCHHCH_2CHO$), 2.33 (s, 3 H, CH_3Ar), 3.80 (apparent t, $^3J_{H,H}$ = 7.5 Hz, 1 H, CH_2CH_2CHO), 7.14 (d, $^3J_{H,H}$ = 8 Hz, 2 H, $C_{Ar}H \times 2$), 7.28 ppm (d, $^3J_{H,H}$ = 8 Hz, 2 H, $C_{Ar}H \times 2$). ^{13}C NMR: δ = 21.0 (CH_3Ar), 24.2 [$C(CH_3)_2$], 26.5 (CCH_2CH_2CHO), 27.3 [$C(CH_3)_2$], 30.6 (CCH_3), 39.6 (CCH_2CH_2CHO), 71.1 (COH), 84.6 (CCH_3), 85.4 (CHO), 124.6, 128.9 ($C_{Ar}H \times 4$), 136.0 ($C_{Ar}CH_3$), 145.3 ppm ($C_{Ar}CO$). (7*S*,10*R*)-**5**: Enantiomeric excess was determined by HPLC analysis (Chiralcel OD-H, *n*-hexane/*i*PrOH, 98:2, 0.3 mL/min, UV 220 nm); (7*R*,10*R*)-enantiomer t_r = 20.0 min (minor); (7*S*,10*R*)-enantiomer t_r = 20.7 min (major), (7*S*,10*S*)-diastereomer t_r = 21.3 min: ≥ 97% *ee*, ≥ 90% *de*. $[\alpha]_{365}^{20}$ = +5.1, $[\alpha]_{436}^{20}$ = +1.6, $[\alpha]_{546}^{20}$ = +0.7, $[\alpha]_{578}^{20}$ = +0.2 (*c* = 1.04, $CHCl_3$). ^{1}H NMR: δ = 1.12 [s, 3 H, $C(CH_3)_2$], 1.29 [s, 3 H, $C(CH_3)_2$], 1.48

(s, 3 H, CCH_3), 1.59 (br. s, 1 H, OH), 1.82–1.91 (m, 1 H, $CCH_2CHHCHO$), 1.93–2.02 (m, 1 H, $CCH_2CHHCHO$), 2.07–2.14 (m, 1 H, $CCHHCH_2CHO$), 2.16–2.23 (m, 1 H, $CCHHCH_2CHO$), 2.33 (s, 3 H, CH_3Ar), 3.98 (apparent t, $^3J_{H,H}$ = 7.5 Hz, 1 H, CH_2CH_2CHO), 7.14 (d, $^3J_{H,H}$ = 8 Hz, 2 H, $C_{Ar}H \times 2$), 7.32 ppm (d, $^3J_{H,H}$ = 8 Hz, 2 H, $C_{Ar}H \times 2$). ^{13}C NMR: δ = 21.0 (CH_3Ar), 24.5 [$C(CH_3)_2$], 26.3 (CCH_2CH_2CHO), 27.4 [$C(CH_3)_2$], 29.5 (CCH_3), 38.9 (CCH_2CH_2CHO), 71.5 (COH), 84.5 (CCH_3), 85.2 (CHO), 124.5, 129.0 ($C_{Ar}H \times 4$), 136.1 ($C_{Ar}CH_3$), 145.4 ppm ($C_{Ar}CO$).

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