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Reactions of Myrtenylzinc Bromide with Carbonyl Compounds. Regio- and Diastereo-selectivity

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Dedicated to Professor Lennart Eberson on the occasion of his 65th birthday

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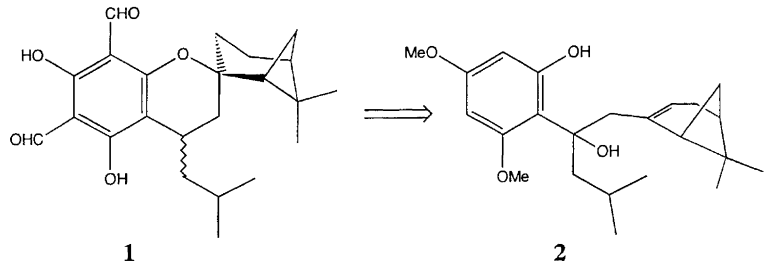
The organozinc reagent obtained from (−)-myrtenyl bromide and zinc powder in THF, under ultrasonic conditions, reacts rapidly with ketones and aldehydes furnishing homoallylic alcohols in high yields. The reactions were carried out both with preformed allylzinc compound and under Barbier conditions. Significant regio- and diastero-selectivity was observed; aldehydes gave preferentially products from a diastereoselective reaction at the most substituted carbon (γ-allylation) of the allylzinc reagent, while ketones reacted at the least substituted carbon (α-allylation) and generally with less stereoselectivity. The absolute configuration of one of the alcohols was determined based on X-ray diffraction.

Robustadial A and B (**1**) are naturally occurring diastereomeric chroman derivatives from *Eucalyptus robusta*, that have been reported to exhibit antimalarial properties.[1] As part of a strategy towards their synthesis[2] we needed the homoallylic alcohol **2**, which we planned to obtain by reacting 2-hydroxy-4,6-dimethoxyisovalerophenone with myrtenylzinc bromide. The regioisomer with an endocyclic double bond would be needed for the subsequent acid-catalysed cyclisation to the spiro-annulated chromene, which by catalytic hydrogenation should afford the cyclic framework of robustadial. The above combination of reactions applied to other 2-hydroxyphenacyl derivatives had previously proved a convenient method for the preparation of chromenes,[3] and we therefore had reason to believe that this protocol would succeed.

Homoallylic alcohols are formed from reactions of allylic organometallic compounds and aldehydes or ketones.[4] The reactions have been carried out by two principally different methods: (i) the use of preformed organometallic reagent or (ii) reaction of the metal with the allylic halide in the presence of the carbonyl compound (Barbier conditions).[5] Either method may be highly regio- and stereo-selective, but the selectivity is strongly dependent on the metal employed and the reaction conditions generally. In the case of zinc, recent evidence indicates that the reaction under Barbier conditions also involves the allylzinc derivative as an intermediate.[6] Our synthetic strategy towards robustadial required bond formation between the carbonyl carbon of the isovalerophenone derivative and the least substituted allylic carbon of myrtenylzinc bromide (α-allylation). Unfortunately, this appears to be the least favoured site of reaction of allylmetal derivatives; reac-



1 **2**

Scheme 1.

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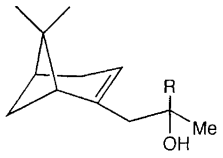
tions with aldehydes and ketones occur preferentially at the most substituted carbon (γ-allylation).[4] However, several examples of α-allylation with zinc reagents are known, particularly with hindered ketones.[7]

When the present work was initiated, reactions of myrtenylzinc bromide had not yet been described in the literature. However, Hoffmann and coworkers reported recently the stereoselective formation of homoallylic alcohols in moderate yields from zinc-promoted reactions of (−)-myrtenyl bromide and aldehydes.[8] They reacted the bromide and aldehyde with zinc in saturated aqueous ammonium chloride–THF, conditions first reported by Petrier and Luche.[9] Dimerization of the organozinc reagent (Wurtz coupling) was an important side reaction. Under their Barbier-type reactions ketones were unreactive, in sharp contrast with independent results from our laboratory on similar reactions with myrtenylzinc bromide. However, our allylzinc reagent was prepared and employed under other reaction conditions and, since its reactivity was significantly different from that observed by Hoffmann, we undertook an investigation in order to compare the two methods. The present paper contains our results from reactions of preformed myrtenylzinc bromide in THF with some aldehydes and ketones and also some reactions under Barbier conditions, but with THF as solvent and the use of ultrasound.

Results and discussion

Reaction of (−)-myrtenyl bromide with zinc powder in THF under ultrasonic conditions provided a solution of the corresponding organozinc reagent. The reaction was carried out without cooling and was complete in a few minutes. Acetophenone and 2-hydroxyacetophenone were chosen as model ketones. The former reacted with the allylzinc compound at room temperature to give a 2:1 mixture of the diastereomeric homoallylic alcohols **3a**, which were not separated. The homoallylic alcohols resulting from α- and γ-allylation contain endo- and exocyclic double bonds, respectively, and were easily characterized by NMR spectroscopy. The single proton of the endocyclic double bond appeared in the δ 5.20–5.45 region while the exocyclic methylene protons gave rise to signals at δ 4.75–5.00. Similar chemical shift differences were observed in the carbon spectra which also distinguished between the diastereisomers. Hence, the presence in compound **3a** of a one proton signal at δ 5.35, as the sole absorption in this region of the ^{1}H NMR spectrum, indicated that α-allylation had taken place exclusively. This looked promising, but the reaction of 2-hydroxyacetophenone turned out to be more complicated giving rise to a mixture of three isomeric homoallylic alcohols in 79% combined yield. They were only partially separated by chromatography, and according to the NMR spectra the mixture consisted of the regioisomeric alcohols **3b** and **4a** in practically equal amounts; the latter consisted of a 1:1 mixture of diastereoisomers with an exocyclic double bond, as a result of γ-allylation, while the isomeric alcohol **3b** was formed stereoselectively and shown to contain an endocyclic double bond. For comparison the reaction was also carried out under Barbier-type conditions in THF as solvent, furnishing the alcohol **3b** as the sole product in 83% yield. When this alcohol was treated with *p*-toluenesulfonic acid (PTSA) in toluene the chroman **5** was formed in 36% yield as a 9:1 mixture of stereoisomers, together with some β-pinene. Despite the poor yield of the cyclisation reaction, the overall results encouraged us to react 2-hydroxy-4,6-dimethoxyisovalerophenone, having methoxy groups at the same positions in the molecule as the hydroxy groups of robustadial. Using preformed allylzinc reagent the crystalline alcohol **2** was obtained in 85% yield as a single diastereomer. The presence of only one olefinic proton signal at δ 5.38 in the NMR spectrum showed that the alcohol contained the desired endocyclic double bond. The alcohol proved to be unstable in solution; after some weeks at 5 °C it had partially reverted to the starting ketone. Besides which, all attempts to convert the alcohol **2** into the corresponding chromene were futile; the acid conditions that had successfully transformed **3b** into **5** caused rearrangement of the terpene framework resulting in a mixture of isomeric chromenes. Hence, we abandoned this synthetic approach to robustadial. However, the high degree of regio- and stereo-selectivity observed with formation of the alcohols **2** and **3b** combined with the appearance of the paper by Hoffmann *et al.* prompted us to carry out some additional allylations of aldehydes and ketones under our conditions. For comparison we included the same aldehydes as those used by Hoffmann *et al.*

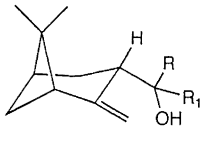


3 a: R = Ph

b: R = 2-HO-Ph

c: R = 2-MeO-Ph

d: R = Et

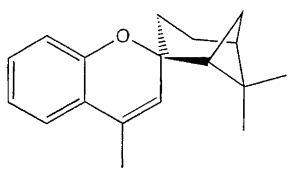


4 a: R = Me; R_1 = 2-HO-Ph

b: R = H; R_1 = Me

c: R = H; R_1 = Ph

d: R = H; R_1 = 2-HO-Ph



5

Scheme 2.

The reactions with preformed allylzinc reagent were carried out in the same way as that used for aceto-

phenone, and the Barbier reactions were performed under ultrasonic conditions. Both type of reaction were complete in less than 30 min. The yields of the homoallylic alcohols **3** and **4** were consistently above 75% and are based on isolated product. Wurtz coupling or other side reactions were not observed. With respect to the reactions of the aldehydes, the results of Hoffmann *et al.* were confirmed; reactions of acetaldehyde and of benzaldehyde took place at the most substituted carbon (γ-allylation) furnishing the alcohols **4b** and **4c**, respectively, as sole products as far as our analytical procedure (NMR) could detect. Since the absolute configuration of the terpene moiety was known, X-ray diffraction of the *p*-nitrobenzoate derived from **4b** (Tables 1 and 2) established the absolute configuration as that depicted in Fig. 1. Hence, the reaction took place from the least hindered side of the organozinc compound yielding the *endo* product. Salicylaldehyde also exhibited the same kind of regioselectivity in its reaction with preformed zinc reagent, but only with limited stereoselectivity; however, under Barbier conditions the diastereoselectivity was improved to 6:1. It thus appears that aldehydes have a pronounced tendency to undergo highly stereoselective γ-allylation with myrtenylzinc bromide, while ketones seem strongly to prefer α-allylation, albeit with limited stereoselectivity in most cases; hence, the exclusive formation of alcohol **2** seemed fortuitous at first.

A six-membered cyclic transition state is suggested for the γ-allylation which in the present case gives rise to formation of two new stereogenic centres. With the reasonable assumption that bond formation with the carbonyl carbon takes place from the least hindered side of the allylzinc reagent, it is readily seen from models that even with this aproach there may be severe steric hindrance. Steric restrictions are certainly less with aldehydes than with ketones, and it is not surprising that they react by γ-allylation, the generally preferred mode of reaction of allyl metal derivatives. Hence, the high stereoselectivity observed for the γ-allylations must be ascribed to steric effects in the cyclic transition state. The absolute configuration of **4b** provides support for a cyclic transition state in which the methyl group originating from the aldehyde attains a pseudoequitorial position, the least sterically crowded arrangement, as depicted in Fig. 2. The same argument applies to the stereoselective formation of **4c**, for which we assume the *S*-configuration around the exocyclic stereogenic centre. However, the low stereoselectivity obtained in the reaction of preformed allylzinc reagent and salicylaldehyde is not easily explained, particularly since Barbier conditions resulted in considerably higher diastereoselectivity. Comparison with benzaldehyde suggests that the *ortho*-hydroxy group must play a part by complexing with the allylzinc reagent. Regarding reactions of the ketones, the additional steric demand from the second substituent on the carbonyl carbon, a methyl group in most cases, seems sufficient for α-allylation to become competitive. This mode proceeds through an acyclic transition state, generating only one new stereogenic centre. The degree of diastereoselectivity must be governed by steric interactions encountered on the approach of the allylzinc reagent to the ketone.

Table 1. Crystal data and structure refinement of the *p*-nitrobenzoate of **46**.

Empirical formula	$C_{19}H_{23}NO_4$
Formula weight	329.38
Temperature	138(2) K
Wavelength	0.7093 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	$a=7.002(1)$ Å $b=6.637(2)$ Å $c=19.154(2)$ Å $\beta=95.42(2)°$
Volume, Z	886.2(3) Å^3, 2
Density (calculated)	1.234 Mg m^{-3}
Absorption coefficient	0.086 mm^{-1}
$F(000)$	352
Crystal size	0.5 × 0.3 × 0.1 mm
Theta range for data collection	2.13–32.48°
Limiting indices	$0\leqslant k\leqslant 10$, $0\leqslant k\leqslant 10$, $-28\leqslant l\leqslant 28$
Reflections collected	3445
Independent reflections	3445
Refinement method	Full-matrix least-squares on F^2
Data/restraint/parameters	3445/1/309
Goodness-of-fit on F^2	0.938
Final R indices [$I>2\sigma(I)$]	$R1=0.0649$, $wR2=0.1441$
R indices (all data)	$R1=0.1508$, $wR2=0.1762$
Largest diff. peak and hole	0.252 and −0.213 e Å^{-3}

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (10^3 Å^2) for the *p*-nitrobenzoate of **4b**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	x	y	z	U(eq)
O(13)	6499(3)	1887(5)	3340(1)	42(1)
O(23)	13 108(3)	1718(5)	6209(1)	50(1)
O(24)	10 853(3)	2054(6)	6890(1)	58(1)
N(22)	11 419(4)	1863(5)	6307(1)	39(1)
C(1)	5649(7)	3389(8)	868(2)	57(1)
C(2)	4902(5)	3913(7)	1548(2)	50(1)
C(3)	6218(5)	3345(6)	2199(2)	39(1)
C(4)	8157(5)	2412(7)	2037(2)	42(1)
C(5)	8343(7)	2241(7)	1248(2)	50(1)
C(6)	6511(8)	1267(8)	897(2)	62(1)
C(7)	7733(6)	4197(7)	847(2)	49(1)
C(8)	8170(8)	6258(7)	1170(3)	59(1)
C(9)	8364(9)	4236(11)	99(2)	71(1)
C(10)	3261(7)	4824(10)	1579(3)	76(2)
C(11)	5133(5)	2060(7)	2713(2)	43(1)
C(12)	4493(9)	14(9)	2483(3)	65(1)
C(14)	5761(4)	1848(6)	3958(1)	37(1)
C(16)	7301(4)	1784(6)	4558(1)	32(1)
C(17)	6723(4)	1759(7)	5237(2)	43(1)
C(18)	8063(4)	1782(7)	5813(2)	40(1)
C(19)	9985(4)	1812(6)	5696(1)	32(1)
C(20)	10 601(4)	1809(5)	5027(1)	29(1)
C(21)	9236(4)	1807(6)	4462(1)	32(1)
O(15)	4073(3)	1851(6)	4032(1)	51(1)

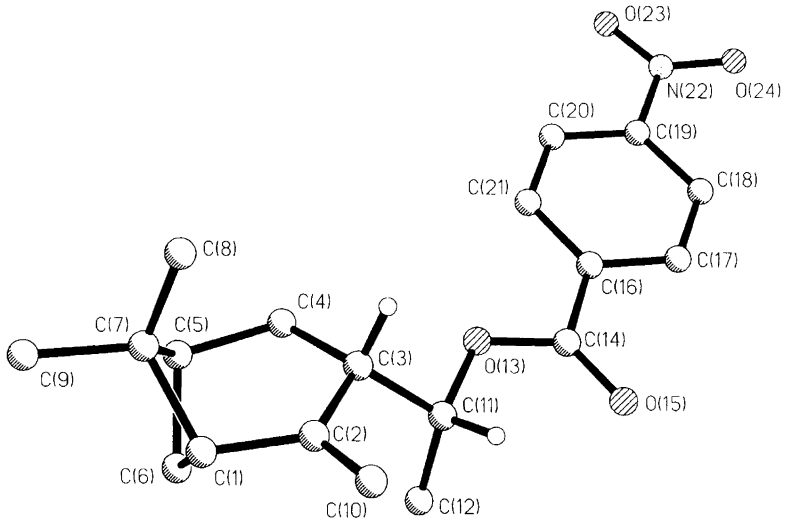


Fig. 1.

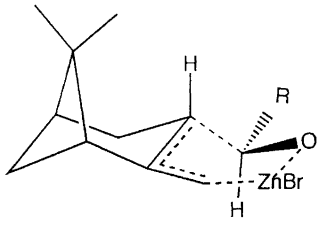


Fig. 2.

Under Barbier-type conditions the reaction of 2-hydroxyacetophenone resulted in a clean stereoselective α-allylation, which is particularly interesting since it has been claimed that the allylzinc reagent is initially formed under these conditions as well.[6] There is obviously a mechanistic difference between these two methods.

Comparing the results from the reactions of preformed allylzinc reagent with 2-hydroxyacetophenone and the corresponding isovalerophenone derivative, it is not difficult to accept that the size of the isobutyl group suppresses γ-allylation, but the high diastereoselectivity observed is not evident from model studies. The high diastereoselectivity is quite unusual for allylzinc reactions, and must be attributed to the bulkiness of the pinene skeleton. We did try to establish the configuration of compound **2**, which is crystalline. Crystals of sufficient size for X-ray diffraction studies were obtained; however, disorder occurred in the pinene moiety even at low temperature, thereby rendering the diffraction data useless. Attempts to circumvent this problem by chemically manipulating the molecule were unsuccessful.

In conclusion we have shown that the organozinc reagent derived from (−)-myrtenyl bromide in THF reacts with both aldehydes and ketones to afford good yields of the corresponding homoallylic alcohols. Some reactions exhibited a high degree of diastereoselectivity as well.

Experimental

General. GLC analyses were performed on a 30 m capillary column of SP2100, and for analyses of optical purity a 25 m Chirasil-L-Val column was used. IR spectra were recorded on a Perkin Elmer 1310 instrument. NMR spectra were obtained on Varian XL-300 and 200 instruments. MS data were recorded on a Fisons Instruments ProSpec-Q mass spectrometer. Optical rotations were measured on a Perkin Elmer 241 polarimeter. Capillary melting points were taken on a Büchi SMP-20 apparatus and are uncorrected.

Reagents. Myrtenyl bromide was prepared in 96% yield from commercially available (−)-myrtenol according to the literature,[10] $[\alpha]_D^{20}$ −31.5° (*c* 0.025, $CHCl_3$); (lit.[8] $[\alpha]_D^{20}$ −29.2° (*c* 0.0159, $CHCl_3$).

Reaction with acetophenone. Method A. General procedure. A solution of (−)-myrtenyl bromide (3.22 g, 14.9 mmol) in THF (20 ml) was added dropwise to a suspension of activated zinc powder (3.75 g, 30.6 mmol) in THF (40 ml) at room temperature under ultrasonic conditions. After 10 min freshly distilled acetophenone (1.50 g, 12.5 mmol) in THF (10 ml) was added dropwise. After 30 min at room temperature water (25 ml) was added. The organic phase was separated and the aqueous phase extracted with ether (50 ml). The ether phase was washed with aqueous 10% $NaHCO_3$ (2 × 50 ml) and water (50 ml), and dried ($MgSO_4$). The residue was purified by flash chromatography on silica gel (hexane–EtOAc 95:5) and afforded the homoallylic alcohol **3a** (1.08 g, 78%) as a 2:1 mixture of diastereomers. Diastereomer I: ^1H NMR (200 MHz, $CDCl_3$): δ 0.76 (s, 3 H), 1.12 (d, 1 H), 1.13 (s, 3 H), 1.50 (s, 3 H), 1.85 (m, 1 H), 2.05 (m, 2 H), 2.21–2.70 (m, 5 H), 5.35 (m, 1 H), 7.20–7.50 (m, 5 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.95, 27.67, 31.99, 33.10, 33.39, 38.94, 41.48, 48.61, 52.76, 74.51, 123.21, 125.26, 126.72, 128.19, 128.43,

145.00, 148.17. Diastereomer II: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.81 (s, 3 H), 0.91 (d, 1 H), 1.13 (s, 3 H), 1.54 (s, 3 H), 1.85 (m, 1 H), 2.05 (m, 1 H), 2.21–2.65 (m, 6 H), 5.35 (m, 1 H), 7.20–7.50 (m, 5 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.82, 27.75, 31.84, 33.10, 33.39, 38.94, 41.48, 48.20, 53.36, 74.45, 123.14, 125.19, 126.67, 128.13, 145.12, 148.17.

Method B. Barbier conditions. General procedure. A mixture of (−)-myrtenyl bromide (3.22 g, 14.9 mmol), acetophenone (1.50 g, 12.5 mmol) and zinc powder (3.75 g, 35.7 mmol) in dry THF (70 ml) was stirred under the influence of ultrasound at room temperature for 30 min. The mixture was worked up with water as described under method A. Flash-chromatography (silica gel, hexane–EtOAc 95:5) gave **3a** (74%) as a 2:1 mixture of diastereomers.

Reactions with 2-hydroxyacetophenone. Method A. The reaction of myrtenylzinc bromide with 2-hydroxyacetophenone according to the general procedure gave the liquid homoallylic alcohols **3b** and **4a** (79%) as a 6:4 mixture. Moreover, the alcohol **4a** was formed as a 1:1 mixture of diastereomers. Diastereomer I: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.74 (s, 3 H), 1.24 (s, 3 H), 1.32 (d, 1 H), 1.78 (s, 3 H), 1.88 (m, 2 H), 2.15–2.52 (m, 4 H), 3.22 (m, 1 H), 4.62 (m, 1 H), 4.82 (m, 1 H), 6.80–7.60 (m, 4 H), 9.40 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.50, 26.54, 27.91, 29.25, 30.70, 41.12, 41.88, 44.64, 54.19, 82.53, 113.91, 118.16, 119.65, 128.05, 129.98, 130.20, 150.52, 156.26. Diastereomer II: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.78 (s, 3 H), 1.26 (s, 3 H), 1.68 (s, 3 H), 1.90 (m, 2 H), 2.20–2.50 (m, 4 H), 3.35 (m, 2 H), 4.82 (m, 1 H), 5.04 (m, 1 H), 6.80–7.60 (m, 4 H), 9.15 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.65, 26.09, 26.78, 29.00, 38.44, 41.26, 41.32, 42.87, 54.65, 81.37, 112.43, 118.13, 119.60, 127.81, 129.16, 130.43, 152.10, 156.26.

Method B. The reaction of (−)-myrtenyl bromide, 2-hydroxyacetophenone and zinc powder according to the general procedure gave **3b** (83%) as a liquid, $[\alpha]_D^{20} = -40.55°$ (*c* 0.018, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78 (s, 3 H), 1.15 (d, *J* 8.4 Hz, 1 H), 1.20 (s, 3 H), 1.56 (s, 3 H), 1.99 (q, 1 H), 2.08 (m, 1 H), 2.28 (m, 2 H), 2.36 (m, 2 H), 2.71 (d, *J* 13.8 Hz, 1 H), 3.11 (s, 1 H), 5.45 (m, 1 H), 6.82 (m, 2 H), 7.20 (d, *J* 1.8 Hz, 1 H), 7.05 (t, 1 H), 9.31 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.01, 26.00, 28.93, 31.54, 31.88, 37.53, 39.91, 47.73, 49.69, 76.89, 117.45, 119.11, 123.59, 125.98, 128.61, 129.53, 144.51, 155.47.

*4,6′,6′-Trimethyl{spiro-3,4-dihydro-2*H*-1-benzopyran-2,2′-bicyclo[3.1.1] heptane}* (**5**). The alcohol **3b** (1.00 g, 3.7 mmol) was dissolved in benzene (50 ml) with a catalytic amount of PTSA, and the solution heated under reflux for 75 min. Isolation in the usual way gave β-pinene, identified by comparison with an authentic sample, and the chroman **5** (0.33 g, 36%) as a 9:1 mixture of stereoisomers. The major isomer was isolated by flash chromatography on silica gel and tentatively assigned the *endo* configuration. IR (film): 3040 (m), 1640 (m), 1600 (m), 1270 (s), 1120 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 3 H), 1.25 (s, 3 H), 1.74 (d, 1 H), 1.85–2.34 (m, 7 H), 2.06 (d, *J* 1.5 Hz, 3 H), 5.69 (d, *J* 1.5 Hz, 1 H) 6.85 (d, 1 H), 6.91 (t, 1 H), 7.16 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.25, 23.68, 24.58, 25.72, 27.26, 30.81, 37.77, 40.40, 50.31, 81.66, 116.52, 120.40, 123.13, 123.94, 127.80, 128.69, 129.51, 153.01.

Reaction with 2-hydroxy-4,6-dimethoxyisovalerophenone. The reaction of myrtenylzinc bromide with 2-hydroxy-4,6-dimethoxyisovalerophenone[11] according to the general procedure gave the homoallylic alcohol **2** (85%) as a single diastereomer, m.p. 88 °C (from hexane), $[\alpha]_D^{20}$ +8.69° (*c* 0.013, MeOH). Found: $[M-H_2O]^+$ 254.167 527. Calc. for $C_{18}H_{22}O$: 254.167 066). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.70 (d, *J* 6.7 Hz, 3 H), 0.77 (s, 3 H), 0.92 (d, *J* 6.7 Hz, 3 H), 1.13 (s, 3 H), 1.28 (m, 3 H), 1.62 (m, 1 H), 1.92 (m, 1 H), 2.05 (m, 1 H), 2.24 (m, 1 H), 2.33 (m, 1 H), 2.52 (d, *J* 13.9 Hz, 1 H), 2.96 (d, *J* 13.9 Hz, 1 H), 3.29 (m, 1 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 5.38 (m, 1 H), 5.94 (d, *J* 2.6 Hz, 1 H), 6.00 (d, *J* 2.6 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.60, 25.52, 26.62, 32.17, 32.30, 37.95, 40.48, 47.62, 49.60, 50.77, 55.54, 55.60, 81.97, 91.47, 95.07, 108.31, 124.03, 146.19, 158.19, 159.42, 160.24.

Reaction with 2-methoxyacetophenone. The reaction of myrtenylzinc bromide with 2-methoxyacetophenone according to the general procedure gave the liquid homoallylic alcohols **3c** (85%) as a 5:4 mixture of diastereomers. Diastereomer I: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.73 (s, 3 H), 0.99 (d, 1 H), 1.07 (s, 3 H), 1.56 (s, 3 H), 1.61 (m, 1 H), 1.90–2.21 (m, 4 H), 2.58 (d, 1 H), 2.79 (m, 1 H), 3.56 (s, 1 H), 3.88 (s, 3 H), 5.28 (m, 1 H), 6.90 (m, 2 H), 7.22 (m, 1 H), 7.39 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.14, 27.04, 28.20, 32.37, 38.28, 40.95, 49.89, 55.85, 74.77, 111.33, 121.06, 122.13, 127.48, 128.43, 135.52, 145.66, 156.84. Diastereomer II: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.79 (s, 3 H), 0.89 (d, 1 H), 1.11 (s, 3 H), 1.58 (s, 3 H), 1.61 (m,1 H), 1.90–2.21 (m, 4 H), 2.52 (d, 1 H), 2.85 (m, 1 H), 3.57 (s, 1 H), 3.88 (s, 3 H), 5.21 (m, 1 H), 6.90 (m, 2 H), 7.22 (m, 1 H), 7.39 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.00, 27.04, 28.02, 32.50, 32.64, 38.17, 47.72, 55.85, 74.35, 111.33, 121.03, 122.04, 127.31, 128.43, 135.62, 146.00, 156.75.

Reaction with 2-butanone. The reaction of myrtenylzinc bromide with 2-butanone according to the general procedure gave the liquid homoallylic alcohols **3d** (75%) as a 3:2 mixture of diastereomers. Found: $[M-H_2O]^+$ 190.174 511. Calc. for $C_{14}H_{22}$ 190.172 151. Diastereomer I: ^{1}H NMR (200 MHz, $CDCl_3$) : δ 0.86 (s, 3 H), 0.90 (t, 3 H), 1.08 (s, 3 H), 1.16 (d, 1 H, *J* 10.0 Hz), 1.26 (s, 3 H), 1.44 (q, 2 H), 1.70 (s, 1 H), 2.11(m, 4 H), 2.25

(m, 2 H), 2.39 (m, 1 H), 5.32 (br s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.84, 21.80, 26.82, 32.06, 32.46, 35.29, 40.80, 48.38, 49.20, 72.89, 122.18, 145.76. Diastereomer II: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.86 (s, 3 H), 0.90 (t, 3 H), 1.10 (s, 3 H), 1.18 (d, 1 H, *J* 10.0 Hz), 1.26 (s, 3 H), 1.44 (q, 2 H), 1.70 (s, 1 H), 2.11 (m, 4 H), 2.25 (m, 2 H), 2.39 (m, 1 H), 5.32 (br s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.93, 26.69, 26.93, 32.06, 32.46, 35.15, 38.15, 48.17, 49.33, 73.13, 122.18, 145.65.

Reaction with acetaldehyde. The reaction of myrtenylzinc bromide with acetaldehyde according to the general procedure afforded the homoallylic alcohol **4b** (86%) as a single diastereomer, m.p. 20 °C (from pentane), $[\alpha]_D^{20}$ +27.2° (*c* 0.15, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.70 (s, 3 H), 1.20 (obscured d, 3 H), 1.21 (s, 3 H), 1.23 (d, 1 H), 1.52 (m, 1 H), 1.92–2.05 (m, 2 H), 2.25 (m, 2 H), 2.42 (t, 1 H), 2.58 (br s, 1 H), 3.52 (dq, 1 H), 4.76 (s, 1 H) 4.80 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.48, 21.39, 25.61, 26.40, 27.22, 40.47, 40.90, 43.45, 52.06, 71.32, 110.83, 152.13. The *p*-nitrobenzoate derivative was prepared in the usual way, m.p. 92–95 °C (from hexane).

Reaction with benzaldehyde. The reaction of myrtenylzinc bromide with benzaldehyde according to the general procedure afforded the liquid homoallylic alcohol **4c** (77%) as a single diastereomer, $[\alpha]_D^{20}$ +18.75° (*c* 1.5, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.73 (s, 3 H), 1.26 (s, 3 H), 1.27 (d, *J* 9.2 Hz, 1 H),1.55 (m, 1 H), 1.75 (m, 1 H), 2.93 (m, 1 H), 2.30 (m, 1 H), 2.55 (t, 1 H), 2.81 (br t, 1 H), 3.08 (s, 1 H), 4.43 (d, *J* 9.2 Hz, 1 H), 4.96 (br s, 1 H), 5.02 (br s, 1 H), 7.40 (m, 5 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.46, 26.65, 27.33, 27.71, 41.30, 42.14, 43.66, 53.09, 79.26, 112.13, 128.15, 128.42, 128.74, 142.88, 152.65.

Reaction with salicylaldehyde. Method A. The reaction of myrtenylzinc bromide with salicylaldehyde according to the general procedure afforded the liquid homoallylic alcohols **4d** (79%) as a 2:1 mixture of diastereomers. Diastereomer I: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.70 (s, 3 H), 1.27 (s, 3 H), 1.37 (d, *J* 10.5 Hz, 1 H), 1.60 −1.85 (m, 2 H), 1.98 (m, 1 H), 2.32 (m, 1 H), 2.58 (t, 1 H), 2.89 (t, 1 H), 4.49(d, *J* 10.2 Hz, 1 H), 5.00 (s, 1 H), 6.80–6.92 (m, 2 H), 7.90–7.25 (m, 2 H) 7.90 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.33, 25.55, 26.14, 26.60, 40.43, 40.93, 41.47, 52.13, 79.05, 112.30, 117.45, 119.22, 125.06, 129.03, 129.53, 152.24, 155.74. Diastereomer II: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.78 (s, 3 H), 1.25 (s, 3 H), 1.36 (m, 1 H), 1.69 −1.77 (m, 1 H), 1.98 (m, 1 H), 2.17 (s, 1 H), 2.35 (m, 1 H), 2.50 (t, 1 H), 3.04 (m, 1 H), 4.76 (s, 1 H), 4.86 (s, 1 H), 5.32 (m, 1 H), 6.80–7.60 (m, 4 H), 8.61 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.64, 25.90, 25.94, 28.99, 31.45, 40.36, 41.33, 52.43, 77.33, 109.08, 117.18, 119.28, 124.53, 127.40, 128.35, 152.24, 155.90.

Method B. The reaction of (−)-myrtenyl bromide, salicylaldehyde and zinc powder according to the general procedure gave **4d** (76%) as a 6:1 mixture of diastereomers.

X-Ray crystallography

X-Ray data for unit cell determination and intensity data were collected using a Nicolet *P3/F* four-circle diffractometer and graphite crystal monochromated Mo*K*α radiation. Crystal and experimental data, and structure refinement details are given in Table 1. The structure was determined and refined by the use of the program assembly SHELXTL Version 5.[12] The non-hydrogen atoms were refined with anisotropic thermal parameters; the hydrogen positions were calculated and refined isotropically. Final figures of merit are included in Table 1. Positional parameters and equivalent isotropic thermal parameters for the non-hydrogen atoms are given in Table 2. A full list of parameters, bond lengths and angles (e.s.d.s of 0.003–0.007 Å and 0.2–0.4°), and structure factors may be obtained from C. R. upon request. A PLUTO plot of the molecule is presented in Fig. 1.

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