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Natural Products

Total Synthesis and Absolute Configuration Assignment of MRSA Active Garcinol and Isogarcinol

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Abstract: A short total synthesis of (±)-garcinol and (±)-isogarcinol, two *endo*-type B PPAPs with reported activity against methiciline resistant *Staphylococcus aureus* (MRSA), is presented. The separation of framework-constructing from framework-decorating steps and the application of two highly regio- and stereoselective Pd-catalysed allylations, that is, the Pd-catalysed decarboxylative Tsuji–Trost allylation and the diastereoselective Pd-catalysed allyl–allyl cross-coupling, are key elements that allowed the total synthesis to be accomplished within 13 steps starting from acetylacetone. After separation of the enantiomers the absolute configurations of the four natural products (i.e., (−)-garcinol, (+)-guttiferone E (i.e., *ent*-garcinol), (−)-isogarcinol, and (+)-isoxanthochymol (i.e., *ent*-isogarcinol)) were assigned based on ECD spectroscopy.

Introduction

The PPAPs (polyprenylated polycyclic acylphloroglucinols) are a growing family of natural products that consists of more than 200 members.[1] The majority of PPAPs possess a characteristic perprenylated bicyclo[3.3.1]nonatrione core and interesting biological activities that alter depending on the nature of the side-chain or position of the exocyclic acyl group within the core. Within recent years a number of sophisticated synthetic approaches toward type A and type B PPAPs have been reported by the groups of Simpkins, Marazano, Shibasaki, Danishefsky, Shair, Coltart, Porco, and most recently Barriault.[1,2] In 2009 our group reported a general strategy toward *endo*-type B PPAPs in which the separation of framework-constructing from framework-decorating steps allowed the access of various PPAPs without altering the overall synthetic strategy.[3] Based on this platform we were subsequently able to elaborate methods that allowed either a site-selective oxidation of one out of three different prenyl-type side-chains or to introduce another quarternary stereocentre at C7 within the bicyclic framework.[4] Amongst the plethora of PPAPs reported to date a significant number possess isogeranyl side-chains. Some examples worth mentioning, besides garcinol, are guttiferone F, 14-deoxygarcinol and 7-*epi*-isogarcinol (Figure 1). Guttiferone F, an epimer of garcinol at C-30, shows antiprotozal activity against *Leishmania donovani* with an IC_{50} lower than miltefosine, used as reference.[5] The other two mentioned natural products are also closely related to garcinol and display antiplasmodial effects against *Plasmodium falciparum* (Figure 1).[6]

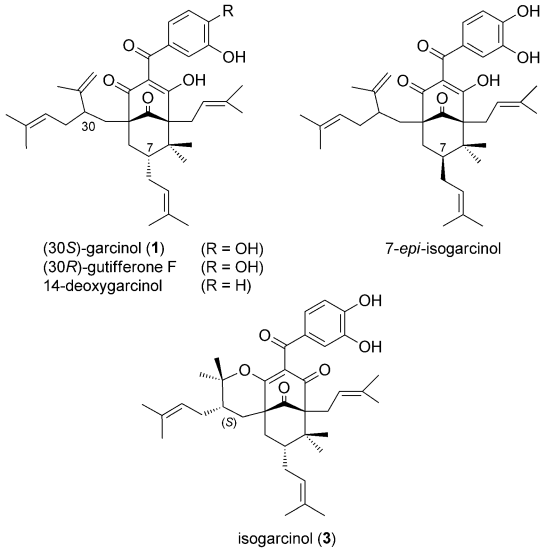

Figure 1. Bioactive natural products structurally related to garcinol.

Both garcinol (**1**) and isogarcinol (**3**) show interesting biological activities. Garcinol suppresses colonic aberrant crypt foci (ACF) formation, acts as a histone acetyltransferase (HATs) inhibitor,[7] and induces apoptosis through cytochrome c release and activation of caspase in human leukemia HL-60 cells.[8] More recently, they were shown to have anti-inflammatory and anticarcinogenic properties.[9,10] These compounds are reported to inhibit the NF-κB activation and COX-2 expression, and to decrease iNOS expression and NO release from LPS-stimulated macrophages by inhibition of the signal transducer and activator of transcription-1 (STAT-1).[10,11] Further biological studies indicated both compounds to have interesting antiulcer and in

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particular antibiotic activities against methiciline-resistant *Staphylococcus aureus* (MRSA).[12,13] Interestingly, the reported activities are comparable to that of vancomycine, which serves as a second-defense-line antibiotic.[14] The growing problem of MRSA, the reported mode of action of garcinol in cancer therapy and, from a chemical point of view, the interesting question on how to create an all-carbon stereocentre in an exocyclic isogeranyl side-chain as it is found in many PPAPs, spurred our interest in developing a short total synthetic approach toward garcinol.

Herein we report the successful realisation of this synthetic venture by employing two consecutive substrate controlled, highly diastereo- and regioselective Pd-catalysed allyl-transfer reactions at a late stage of the synthesis, that is, a decarboxylative Tsuji–Trost allylation to generate a quarternary stereocentre and a allyl–allyl cross-coupling to establish the isogarcinol-type side-chain (Figure 2). The regioselective cyclization of garcinol into isogarcinol, the separation of the enantiomers and the assignment of the absolute configuration of the natural products by ECD spectroscopy are also reported herein.

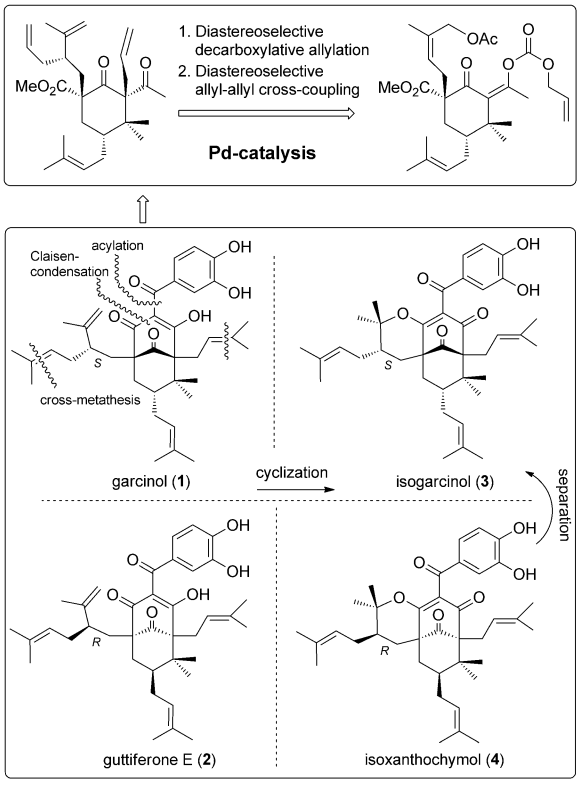
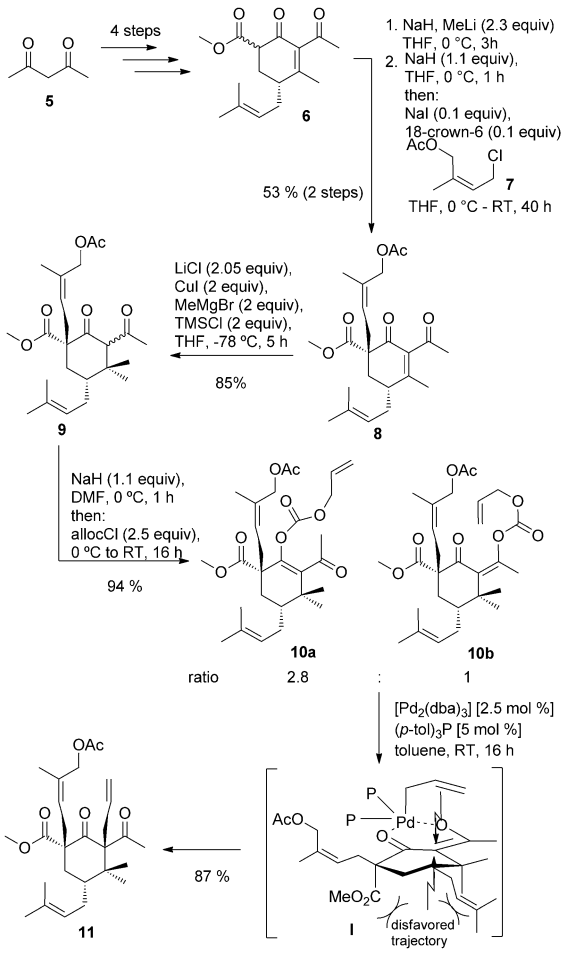


Figure 2. Pd-catalysed allyl transfer reactions as key steps in the synthesis of garcinol.

Results and Discussion

Total synthesis of garcinol and isogarcinol

Our synthesis started from acetylacetone **5**. Following the literature reported sequence of isoprenylation, decarboxylative aldol-condensation, domino Michael-addition-Dieckmann condensation, and 1,2-addition afforded cyclohexenone **6** in good overall yield (Scheme 1).



Scheme 1. Diastereoselective synthesis of the allyl–allyl cross coupling precursor **11**.

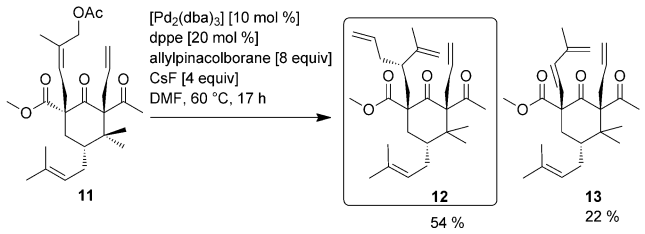
Since preliminary studies aiming to introduce the isogeranyl side-chain by α-alkylation of **6** with lavandulyl bromide met with failure we envisioned a Pd-catalysed allyl–allyl cross-coupling to be a promising strategy to build up the isogeranyl motif on a late stage of the total synthesis. This cross-coupling reaction has been investigated by the groups of Echavarren and more recently by Morken, amongst others.[14,15] However, it has not been applied within a complex natural product synthesis. Apart from the question of whether the catalytic conditions for this particular type of cross-coupling reaction are compatible with a densely functionalized core structure, the allyl–allyl cross-coupling precursor needed to be stable against an 1,4-addition with organocopper reagents and unreactive under the conditions of a Pd-catalysed decarboxylative Tsuji–Trost allylation. We decided to introduce an acetoxylated prenyl-type side-chain due to the comparably low leaving group tendency of this functional group under various substitution conditions.

Fortunately, the introduction of 4-acetoxylated prenylchloride **7** led to the allylation product **8** in good yield and high *trans*-diastereoselectivity. Subsequent 1,4-addition of MeCu furnished cyclohexanone **9**. A competing S_N-type reaction be-

tween the exocyclic allylacetate and the organocopper species was not observed. Finally, cyclohexanone **9** was transferred into a mixture of two regioisomeric allyl vinyl carbonates **10a** and **10b** in order to set the stage for the decarboxlative Tsuji–Trost allylation (Scheme 1). Both regioisomers were subsequently subjected to a decarboxylative Tsuji–Trost allylation using catalytic amounts of $[Pd_2dba_3]/(p\text{-tol})_3P$.[4] The desired C-allylated cyclohexenone **11** was obtained in good yields and excellent diastereoselectivity. No attack of the Pd-catalyst at the exocyclic allylic acetate was observed. The diastereoselective course of the C–C bond formation is most likely directed by steric repulsion between the allyl-Pd moiety and an axially oriented methyl group on the one side and the carboxylate moiety on the other side (Scheme 1).

With key intermediate **11** in hand, we set out to develop the allyl–allyl cross-coupling (Table 1).

Table 1. Development of the diastereoselective Pd-catalysed allyl–allyl cross-coupling.



Entry[a]	Ligand	Solvent	*T* [°C]	Stoichiometry (borane/CsF) [equiv]	Yield **12**/**13** [%][b]
2	dppm	THF	60	4:3	0:58
3	dppe	THF	60	4:3	50:34
4	dppp	THF	60	4:3	6:40
5	dpp-benzene	THF	60	4:3	34:23
6	dppe	heptane	60	4:3	25:28
7	dppe	toluene	60	4:3	33:41
8	dppe	CH_3CN	60	4:3	26:18
9	dppe	DMF	60	4:3	30:8
10	dppe	DMF	80	4:3	10:34
11	dppe	DMF	60	8:3	19:32
12	**dppe**	**DMF**	**60**	**8:4**	**54:22**
13[c]	dppe	DMF	60	4:2	45:22

[a] All reactions were performed on a 0.1 mmol scale in the appropriate solvent (0.3 mL) under a N_2 atmosphere. [b] Isolated yields. [c] $Pd(OAc)_2$ (10 mol%) was used as the catalyst under otherwise identical reaction conditions.

Attempts to introduce an allyl side-chain by using organocopper chemistry met with failure. However, the Pd-catalysed cross-coupling using allyl boronate was successful. Depending on the nature of the Pd-precatalyst, solvent, and in particular the ligand, significant amounts of diene **13** were formed probably by a competing β-hydride elimination pathway (Table 1). Whereas variation of the stoichiometries and the solvent led to a slight improvement, the ligand bite angle proved to be the key parameter. The use of bis-diphenylphosphinoethane (dppe) as a ligand and addition of CsF as activator led to a clean formation of **12** with full control of regio- and stereoselectivity (entry 12, Table 1). We did not observe the formation of another diastereoisomer in either of the catalytic cross-couplings. The C–C bond was formed with exclusive stereoselectivity. We were pleased to obtain a crystal structure of **12**, which allowed us to confirm unambiguously the correct relative configuration of the newly formed exocyclic stereocentre (Figure 3).[16] The stereochemical course can be explained by transition state **II** (Figure 3), in which the Pd-catalyst is coordinated to the carbonyl group with formation of a rigid allyl–Pd complex. The subsequent metal-to-ligand allyl transfer sets the observed configuration of the exocyclic stereocentre.

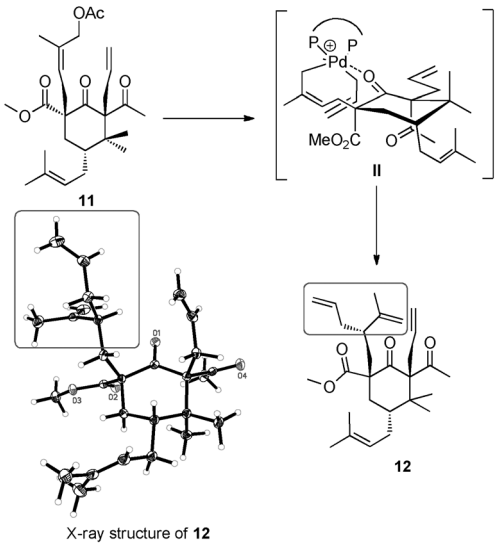
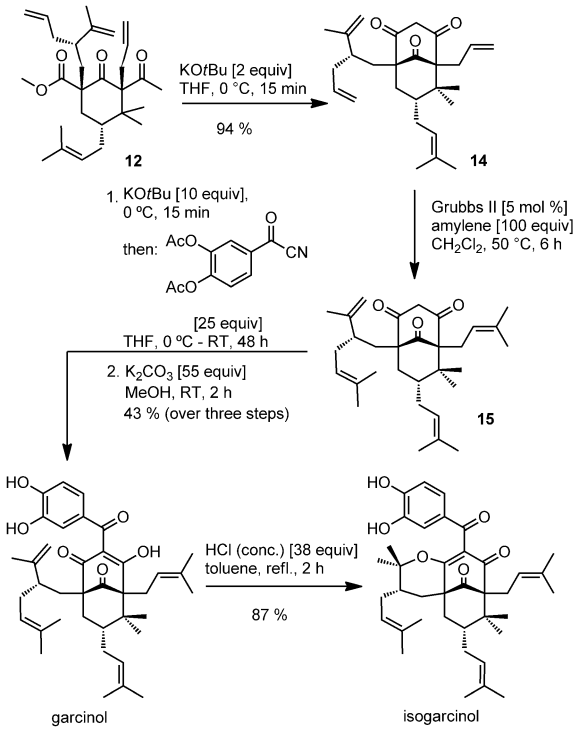


Figure 3. Stereochemical model for the Pd-catalysed allyl–allyl cross-coupling; X-ray structure of **12**.

With this piece of information in hand, the stereoselective course of the cross-coupling might be rationalized by assuming that the trajectory of the incoming Pd-catalysts is directed through coordination of the carbonyl oxygen atoms within the cyclohexanone core. Through ionization π-allyl–Pd complex **II** is formed which undergoes a transmetallation with the fluoride-activated allylboronate. C–C bond formation under S_N2'-type conditions via metal-to-ligand transfer furnishes the desired product in a highly diastereoselective manner (Figure 3).

Compound **12** allowed for the completion of the total synthesis of (±)-garcinol through a base-mediated intramolecular Claisen cyclization to construct the bicyclo[3.3.1]nonatrione core **14** followed by cross-metathesis to install the prenyl side-chains and acylation to give, after deprotection, the desired natural product (Scheme 2).

In total we were able to synthesize (±)-garcinol in 13 steps starting from acetylacetone in an overall yield of 4%. This natural product was subsequently treated with conc. HCl solution to furnish the tricyclic natural product (±)-isogarcinol in 87% yield as a single regioisomer (Scheme 2).



Scheme 2. Final steps in the total synthesis of (±)-garcinol and (±)-isogarcinol.

Assignment of absolute configuration

Both enantiomeric forms of garcinol and isogarcinol were isolated from natural sources and were given different names: (−)-garcinol (or camboginol); (+)-garcinol (which was named guttiferone E); (+)-isogarcinol (which was named isoxanthochymol); and (−)-isogarcinol (or cambogin). The various names for the same natural product plus the discrepancies in the optical rotation between two enantiomers encouraged us to assign the absolute configuration of the respective natural products by means of ECD spectroscopy and quantum mechanical calculations. Both enantiomers of racemic isogarcinol were separated by means of preparative chiral HPLC to give the respective enantiomerically pure natural products (−)-isogarcinol and (+)-isoxanthochymol. Optical rotations were measured and compared to that of (−)-isogarcinol prepared from commercial (−)-garcinol by acid-catalysed cyclization (Scheme 2). The absolute configuration of these two synthetic natural products was unambiguously assigned by CD spectroscopy in combination with a computational method.

In the lowest energy conformer of isogarcinol the aromatic ring lies perpendicular to the diketone system, as was previously observed in an X-ray crystallographic analysis of this compound (Figure 4).[16] The tetrahydropyran ring has a twist-boat-like conformation to allow the bulky isoprenyl substituent to be equatorial, whereas the cyclohexanone lies in a chair-like conformation. The structure of the lowest energy conformer of each enantiomer was used as a starting point for a geometry optimization in methanol solution at the PBE0/def2-SVPD level of theory, using TURBOMOLE 6.5[17] in combination with the

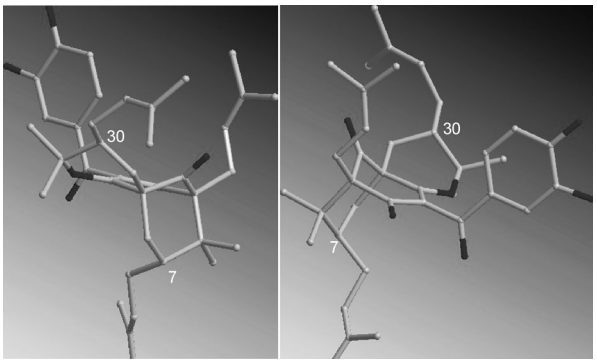


Figure 4. Lowest energy conformer of isogarcinol optimized at PBE0/def2-SVPD.

graphical interface TmoleX 3.4.[18] Solvent effects were considered through the conductor-like screening model (COSMO), a continuum solvation model.

Time dependent density functional theory (TD-DFT) was used to calculate the excitation energies and rotatory strengths of the 40 lowest spin allowed excited states, with the same combination of method and basis set at the optimized geometries. Conversion of these data into simulated electronic circular dichroism spectra gave theoretical curves that were compared with those derived experimentally for both synthetic natural products (isogarcinol and isoxanthochymol). The calculated spectrum of the enantiomer with *S* configuration at C-30 showed diagnostic positive and negative Cotton effects around 220 and 265 nm, respectively. This simulated CD spectrum was in good agreement with that experimentally derived for synthetic isogarcinol (Figure 5), indicating this enantiomer represented the actual structure of the natural product.[16] The theoretical ECD spectrum of the enantiomer with *R* configuration at C-30 showed opposite sign bands when compared with that of isogarcinol. This simulated spectrum was in good agreement with the experimental CD spectrum of isoxanthochymol. Hence, based on these theoretical and experimental data, the absolute configurations of **1**–**4** were unambiguously assigned as depicted (Figure 2).

Conclusions

Herein we report a short concise total synthesis of (±)-garcinol and (±)-isogarcinol within 13 and 14 steps, respectively, starting from acetylacetone. Two consecutive highly diastereoselective Pd-catalysed allyl transfer reaction, that is, a decarboxylative Tsuji–Trost allylation and an allyl–allyl cross-coupling, were used in order to build up the correct relative configurations. Whereas the appropriate choice of leaving groups set the stage for the high chemoselectivity, the diastereoselectivity is orchestrated by the set of chiral centres present in the respective substrate. Acid treatment of garcinol led to the regioselective tetrahydropyrane formation in isogarcinol which was separated in its enantiomers by means of chiral HPLC. The absolute configuration was unambiguously assigned by combining in silico and experimental ECD spectroscopy and comparing the

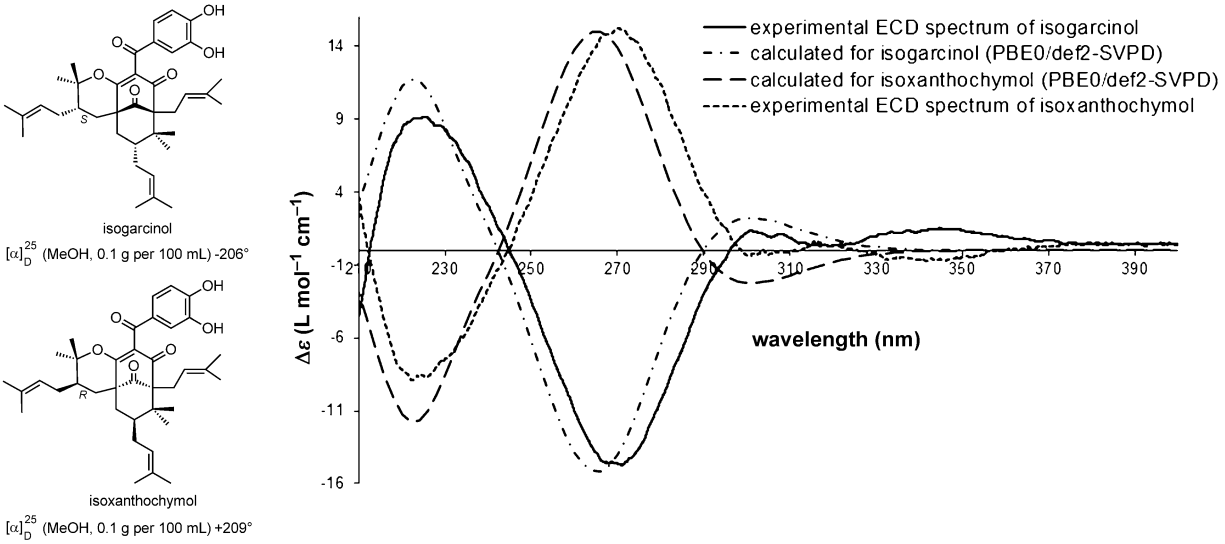


Figure 5. Comparison of calculated and experimental ECD spectra in MeOH for both enantiomers of isogarcinol.

results to those of an authentic sample. By these means, the absolute configurations of garcinol and its enantiomer guttiferone E, as well as those of isogarcinol and its enantiomer isoxanthochymol were unambiguously assigned for the first time.

Experimental Section

General remarks

All reactions and manipulation of substances which are sensitive to air or moisture were performed under dry nitrogen by using standard Schlenk techniques. Solvents were purified prior to use. Chemicals were purchased from Acros Organics, Sigma Aldrich, Alfa Aesar or Enzo Life Sciences. Reactions were monitored by thin layer chromatography on 0.20 mm Macherey–Nagel Alugram Xtra Sil silica gel plates. Purification by semipreparative HPLC was carried out on a Knauer System, pump K-501 and RI detector K-2400, using a Nucleodur 100-5 Si or a Chiralpak AD CPS column (250 mm × 20 mm i.d.). NMR spectra were recorded at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR) on a Burker Avance 300 spectrometer or at 500 MHz (^{1}H NMR) and 125.6 MHz (^{13}C NMR) on a Bruker Avance 500 spectrometer. ^{1}H chemical shifts are expressed in ppm, using a residual solvent signal as reference ($CDCl_3$, $\delta = 7.26$ ppm; [D_6]acetone, $\delta = 2.05$ ppm, [D_5]pyridine, $\delta = 7.62$ ppm), with multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet) and coupling constants (J) in Hz. ^{13}C chemical shifts are reported as chemical shifts (δ) with residual chloroform ($\delta =$ 77.16 ppm) as internal reference. IR spectra were recorded on a FT-IR spectrometer, Vektor 22 from Bruker, in an ATR mode. Mass spectra were measured using electrospray ionization (ESI) or electron impact (EI) on a Bruker Micro-TOF-Q or a Finnigan MAT 95 spectrometer, respectively. ECD spectra were registered on a JASCO J-815 spectropolarimeter, using MeOH as solvent.

General procedure for allyl–allyl cross coupling (GP-I)[15]

The solvent (0.3 mL) was freeze dried and then the Pd catalyst (10 mol%) and the ligand (20 mol%) were added. The resulting slurry was stirred for 90 min at RT. Then, the substrate (46 mg, 0.1 mmol, 1 equiv), allylpinacolborane (67 mg, 0.4 mmol, 4 equiv) and CsF (45.6 mg, 0.3 mmol, 3 equiv) were added successively. The reaction mixture was stirred at 60 °C, overnight, diluted with Et_2O and transferred to a separation funnel. The mixture was washed with $NaHCO_3$ (sat.) and brine and dried with Na_2SO_4. The solvent was removed and the desired product was purified by column chromatography and HPLC (petroleum ether/EtOAc, 7:1).

General procedure for the acid catalysed cyclization (GP-II)

To a solution of garcinol (10 mg, 0.3 mmol, 1 equiv) in toluene (10 mL), HCl (37% solution, 50 μL) was added under N_2. The mixture was refluxed for 2 h and then transferred to a separation funnel. The water phase was removed and the organic layer was washed twice with water, once with brine and dried with Na_2SO_4. The solvent was removed at reduced pressure. The residue was processed by column chromatography over silica gel (petroleum ether/EtOAc, 1:1).

Cyclohexenone 8

Diester **6**[3] (2.94 g, 10 mmol, 1 equiv) was dissolved in THF (30 mL) and cooled to 0 °C. Then, NaH (60% in mineral oil, 440 mg, 11 mmol, 1.1 equiv) was added portion wise. After stirring for 1 h at this temperature, methyllithium (1.6 M in THF, 14.4 mL, 23 mmol, 2.3 equiv) was added dropwise and the mixture was further stirred for 3 h at 0 °C. The solution was hydrolysed with sat. NH_4Cl (3 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated at reduced pressure. The crude product was used without further purification. The crude product (10 mmol, 1 equiv) was dissolved in THF (30 mL). The solution was cooled to 0 °C and NaH (60% in mineral oil, 440 mg, 11 mmol, 1.1 equiv) was added portion wise followed by 18-crown-6 (264 mg, 1 mmol, 0.1 equiv). After being stirred at this temperature for 1 h, **7** (53%, 6.1 g, 20 mmol, 2 equiv) and NaI (150 mg, 1 mmol, 0.1 equiv) were added successively. The reaction mixture was allowed to warm to room temperature and was further stirred for 48 h. Then, the reaction was quenched by adding NH_4Cl (sat.) and was extracted three times with EtOAc. The combined organic layers were washed with

brine, dried with Na_2SO_4, and the solvent was removed at reduced pressure. The resulting orange oil was purified by column chromatography over silica gel using petroleum ether/EtOAc (7:1→3:1). The desired product was further purified via HPLC (petroleum ether/EtOAc, 3:1) to yield 2.14 g of a yellow oil (53% yield after two steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.34 (brt, J = 7.2 Hz, 1H), 5.05 (brt, J = 7.0 Hz, 1H), 4.61 (d, J = 12.2 Hz, 1H), 4.54 (d, J = 12.2 Hz, 1H), 3.72 (s, 3H), 2.66 (dd, J = 14.8, 7.2 Hz, 1H), 2.56 (dd, J = 14.8, 7.5, Hz, 1H), 2.44–2.36 (overlapping signals, 2H), 2.27 (dd, J = 13.8, 7.4 Hz, 1H), 2.28 (s, 3H), 2.08–2.02 (overlapping signals, 2H), 2.05 (s, 3H), 1.93 (s, 3H), 1.74 (brs, 3H), 1.72 (brs, 3H), 1.61 ppm (brs, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.0, 194.4, 172.7, 171.1, 160.8, 139.0, 135.0, 133.7, 124.7, 120.6, 63.0. 56.1, 52.7, 38.5, 33.3, 31.41, 31.39, 30.5, 26.0, 21.8, 21.0, 19.6, 18.1 ppm; IR (film): $\tilde{\nu}$ = 1733 (s), 1704 (m), 1659 (m), 1377 (w), 1356 (w), 1225 cm^{-1} (s); ESI-HR-MS calcd for $[C_{23}H_{32}O_6Na]^+$: 427.2104, found: 427.2097.

Cyclohexanones 9a/9b

LiCl (416 mg, 9.8 mmol, 2.05 equiv) was heated at 80 °C for 3 h under vacuo (1 mbar). THF (40 mL) and CuI (1.82 g, 9.54 mmol, 2 equiv) were added at room temperature. After being stirred for 5 min at this temperature the suspension was cooled to −78 °C and methylmagnesium bromide (3 M in THF, 3.2 mL, 9.54 mmol, 2 equiv), TMSCl (1.2 mL, 9.54 mmol, 2 equiv) and a solution of **8** (1.93 g, 4.77 mmol, 1 equiv) in THF (30 mL) were successively added. The resulting mixture was stirred at −78 °C for 5 h. The reaction was hydrolysed with NH_4Cl/2N HCl (1:1, 100 mL) and extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with NH_4Cl/NH_3 (1:1, until the organic layer was colourless) and brine, and then dried over Na_2SO_4 filtered and concentrated in vacuo. The crude product was purified by flash chromatography to yield 1.71 g of a slightly yellow oil as a mixture of diastereomers (85% yield, **a**/**b**, 1:3).

Diastereomer 9a: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.29 (t, J = 7.4 Hz, 1H), 5.11 (t, J = 6.6 Hz, 1H), 4.58 (d, J = 12.3 Hz, 1H), 4.51 (d, J = 12.3 Hz, 1H), 3.71 (s, 1H), 3.70 (s, 3H), 2.48 (td, J = 14.6, 7.8 Hz, 1H), 2.47 (td, J = 14.6, 7.0, Hz, 1H), 2.26 (brdd, J = 13.8, 4.6 Hz, 1H), 2.20 (dd, J = 14.4, 7.6 Hz, 1H), 2.14 (s, 3H), 2.04 (s, 3H), 1.87 (dd, J = 14.4, 4.4 Hz, 1H), 1.83–1.76 (m, 1H), 1.75–1.67 (overlapping signal, 1H), 1.70 (brs, 6H), 1.57 (brs, 3H), 1.06 (s, 3H), 0.99 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.7, 204.0, 173.1, 171.1, 133.7, 133.2, 124.6, 122.9, 70.9, 63.0, 60.2, 52.6, 42.0, 41.1, 34.0, 32.6, 32.3, 26.8, 25.9, 24.9, 24.4, 21.6, 21.0, 18.0 ppm; IR (film): $\tilde{\nu}$ = 1722 (s), 1688 (m), 1387 (w), 1355 (w), 1225 cm^{-1} (s); EI-HR-MS calcd for $[C_{24}H_{36}O_6]^+$: 420.2512, found: 420.2505.

Diastereomer 9b: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.30 (t, J = 6.8 Hz, 1H), 5.02 (brt, J = 7.4 Hz, 1H), 4.82 (d, J = 12.2 Hz, 1H), 4.42 (d, J = 12.2 Hz, 1H), 3.72 (s, 3H), 3.56 (s, 1H), 2.85 (dd, J = 15.1, 8.0 Hz, 1H), 2.67 (dd, J = 15.1, 5.8, Hz, 1H), 2.22 (dd, J = 13.6, 5.0 Hz, 1H), 2.07 (t, J = 13.2 Hz, 1H), 2.04 (s, 3H), 1.99 (s, 3H), 1.87 (dd, J = 14.5, 3.6 Hz, 1H), 1.75–1.61 (overlapping signals, 2H), 1.72 (brs, 3H), 1.68 (brs, 3H), 1.57 (brs, 3H), 1.08 (s, 3H), 1.07 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.6, 204.7, 172.2, 171.0, 133.6, 133.4, 124.6, 122.7, 69.4, 62.8, 61.6, 52.5, 43.9, 43.0, 35.2, 32.7, 31.9, 27.1, 26.2, 25.9. 21.6, 21.0, 18.0, 16.0 ppm; IR (film): $\tilde{\nu}$ = 1723 (s), 1700 (m), 1387 (w), 1355 (w), 1229 cm^{-1} (s); EI-HR-MS calcd for $[C_{24}H_{36}O_6]^+$: 420.2512, found: 420.2509.

Allylvinylcarbonates 10a/10b

To a solution of the starting material (4.18 g, 9.94 mmol, 1 equiv) in DMF at 0 °C, NaH (60% in mineral oil, 398 mg, 10.9 mmol, 1.1 equiv) was added portion-wise. The mixture was stirred for 1 h at this temperature and then, allylchloroformiate (2.6 mL, 24.9 mmol, 2.5 equiv) was added dropwise. The mixture was allowed to warm to room temperature and was further stirred, overnight. The reaction was hydrolysed with NH_4Cl (sat.) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The product was purified by flash chromatography to afford a colourless oil (4.7 g, 94% yield) as a mixture of regioisomers (**a**/**b**, 1:2.8).

Regioisomer 10a: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.87 (tdd, J = 17.0, 10.2, 5.8 Hz, 1H), 5.33 (dd, J = 17.0, 1.0 Hz, 1H), 5.26 (brd, J = 10.2, 1.2 Hz, 1H), 5.25 (t, J = ND, 1H), 4.99 (brt, J = 7.1 Hz, 1H), 4.61–4.51 (overlapping signals, 4H), 3.63 (s, 3H), 2.86 (dd, J = 14.8, 6.7 Hz, 1H), 2.46 (dd, J = 14.8, 8.5, Hz, 1H), 2.27 (s, 3H), 2.12 (brd, J = 13.8 Hz, 1H), 2.05 (s, 3H), 2.03 (t, J = 13.4 Hz, 1H), 1.76 (dd, J = ND, 2.8 Hz, 1H), 1.74 (brs, 3H), 1.73–1.64 (overlapping signal, 1H), 1.69 (brs, 3H), 1.58 (brs, 3H), 1.40 (ddt, J = 13.0, 10.8, 2.4 Hz, 1H), 1.15 (s, 3H), 1.07 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.8, 172.9, 171.1, 152.5, 143.8, 140.8, 133.46, 133.36, 131.1, 125.2, 122.9, 119.5, 69.4, 63.2, 52.8, 50.4, 40.9, 38.1, 33.5, 32.4, 30.5, 27.7, 26.0, 25.2, 21.8, 21.1, 21.0, 18.0 ppm; IR (film): $\tilde{\nu}$ = 1767 (m), 1735 (s), 1698 (m), 1386 (w), 1367 (w), 1223 (s), 1171 cm^{-1} (m); ESI-HR-MS calcd for $[C_{28}H_{40}O_8Na]^+$: 527.2621, found: 527.2624. ND: not determined due to overlapping signals.

Regioisomer 10b: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.94 (tdd, J = 17.0, 10.3, 5.8 Hz, 1H), 5.39 (dd, J = 17.0, 1.2 Hz, 1H), 5.30 (dd, J = 10.3, 1.2 Hz, 1H), 5.29 (t, J = 7.6 Hz, 1H), 4.99 (brt, J = 7.0 Hz, 1H), 4.67 (d, J = 6.0 Hz, 2H), 4.60 (d, J = 12.4 Hz, 1H), 4.57 (d, J = 12.4 Hz, 1H), 3.59 (s, 3H), 2.66 (dd, J = 14.5, 7.6 Hz, 1H), 2.59 (dd, J = 14.5, 7.6, Hz, 1H), 2.36 (dd, J = 14.2, 13.4 Hz, 1H), 2.10 (brd, J = 14.2 Hz, 1H), 2.05 (s, 3H), 1.96 (s, 3H), 1.78 (dd, J = 14.5, 3.2 Hz, 1H), 1.74 (brs, 3H), 1.72–1.65 (overlapping signal, 1H), 1.69 (brs, 3H), 1.58 (brs, 3H),1.21–1.14 (overlapping signal, 1H) 1.19 (s, 3H), 1.14 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.3, 171.9, 171.1, 151.9, 150.5, 135.2, 133.9, 133.4, 131.2, 124.4, 122.8, 119.7, 69.2, 63.0, 60.1, 52.7, 44.2, 41.8, 32.9, 32.6, 27.5, 26.6, 26.0, 21.8, 21.0, 19.1, 18.5, 18.0 ppm; IR (film in CH_2Cl_2): $\tilde{\nu}$ = 1763 (m), 1738 (s), 1701 (m), 1384 (w), 1367 (w), 1230 (s), 1172 cm^{-1} (m); ESI-HR-MS calcd for $[C_{28}H_{40}O_8Na]^+$: 527.2621, found: 527.2614.

Cyclohexanone 11

Tris(dibenzylideneacetone)dipalladium(0) (108 mg, 0.12 mmol, 0.025 equiv) and tri(*p*-tolyl)phosphine (86 mg, 0.28 mmol, 0.06 equiv) were dissolved in toluene (60 mL) and stirred for 30 min at RT. Then, a solution of the substrate (2.37 g, 4.7 mmol, 1 equiv) in toluene (25 mL) was added slowly. The resulting mixture was stirred at 60 °C, overnight, and then filtered through a plug of silica gel using petroleum ether/ethyl acetate (7:1). The desired product was purified by HPLC (petroleum ether/EtOAc, 7:1) to yield 1.88 g of a white solid (87% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.42 (brt, J = 7.2 Hz, 1H), 5.31 (dddd, J = 17.8, 12.5, 8.9, 5.2 Hz, 1H), 5.01 (brt, J = 7.8 Hz, 1H), 4.94 (d, J = 4.2 Hz, 1H), 4.91 (s, 1H), 4.60 (d, J = 12.3 Hz, 1H), 4.56 (d, J = 12.3, Hz, 1H), 3.18 (brdd, J = 14.2, 5.1 Hz, 1H), 3.75 (s, 3H), 2.59–2.47 (m, 2H), 2.27 (dd, J = 14.5, 9.0 Hz, 1H), 2.21–2.14 (m, 1H), 2.12 (s, 3H), 2.08–2.00 (overlapping signals, 2H), 2.06 (s, 3H), 1.93 (dd, J = 14.5, 2.6 Hz, 1H), 1.82–1.70 (overlapping signal, 1H), 1.78 (s, 3H), 1.71 (s, 3H), 1.60 (s, 3H), 1.06 (s, 3H), 0.99 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.0, 206.3, 173.0, 171.0, 134.0, 133.7, 133.6, 125.6, 122.8, 117.6, 73.7, 63.0, 59.8, 52.7, 40.6, 37.8, 37.4, 32.9, 32.4, 31.7, 27.5, 26.0, 22.2, 21.9, 21.8, 21.0, 18.1 ppm; IR (film): $\tilde{\nu}$ = 1736 (s),

1701 (m), 1686 (s), 1372 (w), 1354 (w), 1220 (s), 1165 cm^{-1} (m); ESI-HR-MS calcd for $[C_{27}H_{40}O_6Na]^+$: 483.2723, found: 483.2729.

Cyclohexanone 12[15]

DMF (0.3 mL) was freeze dried and then tris(dibenzylideneacetone)-dipalladium(0) (9.2 mg, 10 mol%) and 1,2-bis(diphenylphosphino)-ethane (8 mg, 20 mol%) were added. The resulting solution was stirred for 90 min at RT. Then, the substrate (46 mg, 0.1 mmol, 1 equiv), pinacol allylboronate (134 mg, 0.8 mmol, 8 equiv) and CsF (61 mg, 0.4 mmol, 4 equiv) were added successively. The reaction mixture was stirred at 60 °C for 17 h. After cooling the mixture to room temperature, the mixture was diluted with Et_2O and transferred to a separation funnel. It was then washed with $NaHCO_3$ (sat.) and brine. The organic layer was dried with Na_2SO_4 and the solvent was removed at reduced pressure. The desired product was purified by HPLC (petroleum ether/EtOAc, 7:1) to yield 24 mg of the cross coupling product **12** (54% yield) and 9 mg of the elimination product **13** (22% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.64 (ddt, J = 16.8, 10.4, 7.1 Hz, 1H), 5.32 (dddd, J = 17.2, 10.0, 8.9, 5.1 Hz, 1H), 5.10 (brt, J = 7.0 Hz, 1H), 4.96 (d, J = 17.2 Hz, 1H), 4.94 (d, J = 10.0 Hz, 1H), 4.92 (d, J = 10.4 Hz, 1H), 4.88 (d, J = 16.8, Hz, 1H), 4.80 (brs, 1H), 4.75 (s, 1H), 3.75 (s, 3H), 3.17 (brdd, J = 14.5, 5.0 Hz, 1H), 2.31 (m, 1H), 2.25–2.16 (overlapping signals, 2H), 2.10 (s, 3H), 2.16–2.02 (overlapping signals, 4H), 1.85–1.76 (overlapping signals, 4H), 1.72 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.04 (s, 3H), 0.96 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.9, 206.5, 173.3, 147.3, 136.7, 134.1, 133.1, 122.9, 117.4, 115.9, 112.4, 73.9, 60.7, 52.5, 43.7, 40.5, 39.3, 37.9, 37.5, 36.4, 33.0, 31.0, 28.1, 26.2, 22.3, 21.8, 20.0, 18.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3075 (w), 1748 (s), 1726 (m), 1699 (s), 1688 (s), 1641 (w), 1375 (w), 1220 (s), 1168 (s), 1109 (s), 911 cm^{-1} (m); ESI-HR-MS calcd for $[C_{28}H_{42}O_4Na]^+$: 465.2975, found: 465.2978.

13: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.29 (d, J = 16.2 Hz, 1H), 5.56 (d, J = 16.2 Hz, 1H), 5.34–5.18 (overlapping signals, 2H), 5.06 (brs, 1H), 4.97 (brs, 1H), 4.88 (dt, J = 10.1, 1.7 Hz, 1H), 4.74 (brd, J = 16.7 Hz, 1H), 3.76 (s, 3H), 3.03 (ddt, J = 14.0, 4.9, 1.6 Hz, 1H), 2.37 (dd, J = 14.6, 3.4 Hz, 1H), 2.39–2.19 (overlapping signals, 2H), 2.17 (s, 3H), 2.06 (dd, J = 14.1, 8.8 Hz, 1H), 1.96 (tt, J = 10.9, 2.7 Hz, 1H), 1.89–1.76 (overlapping signal, 1H), 1.83 (brs, 3H), 1.78 (brs, 3H), 1.66 (brs, 3H), 1.09 (s, 3H), 0.97 ppm (s, 3H); IR ($CHCl_3$): $\tilde{\nu}$ = 1734 (s), 1694 (s), 1375 (m), 1355 (m), 1241 (s), 1223 cm^{-1} (s); ESI-HR-MS calcd for $[C_{25}H_{36}O_4Na]^+$: 423.2511, found: 423.2508.

Bicyclo[2.2.1]nonatrione 14[3,4]

The starting material (71.6 mg, 0.16 mmol, 1 equiv) was dissolved in dry THF (4.5 mL) and cooled to 0 °C. Then, KO*t*Bu (36.3 mg, 0.32 mmol, 2 equiv) was added under N_2. After stirring for 15 min at this temperature, the reaction was quenched by adding NH_4Cl (sat.). The mixture was poured into a separation funnel and was extracted three times with EtOAc. The combined organic layers were washed with brine and dried with Na_2SO_4. The solvent was then removed at reduced pressure. The product was purified by column chromatography (petroleum ether/EtOAc, 7:1) to afford 63 mg of a white solid (94% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.71 (ddt, J = 17.2, 10.0, 7.0 Hz, 1H), 5.64 (dddd, J = 16.5, 10.0, 9.0, 5.5 Hz, 1H), 5.09 (d, J = 17.2 Hz, 1H), 5.04 (dd, J = 10.0, 2.0 Hz, 1H), 5.03 (dd, J = 17.0, 2.0 Hz, 1H), 4.98 (dd, J = 10.0, 2.0 Hz, 1H), 4.83 (brt, J = 6.5 Hz, 1H), 4.53 (s, 2H), 3.57 (d, J = 17.0 Hz, 1H), 2.94 (m, 1H), 2.76 (dd, J = 12.5, 6.0 Hz, 1H), 2.47 (dd, J = 12.5, 9.0 Hz, 1H), 2.31 (dd, J = 13.5, 1.0 Hz, 1H), 2.14 (brd, J = 15.5 Hz, 1H), 2.09–2.02 (overlapping signals, 3H), 1.98 (dd, J = 14.0, 6.0 Hz, 1H), 1.72 (dd, J = 14.0, 3.0 Hz, 1H), 1.66 (s, 3H), 1.51 (s, 3H), 1.47 (s, 3H), 1.39 (dd, J = 14.5, 7.5 Hz, 1H), 1.35–1.23 (overlapping signals, 2H), 1.22 (s, 3H), 0.98 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.7, 202.6, 202.5, 148.8, 136.8, 133.9, 132.5, 122.5, 120.5, 115.9,114.2, 71.6, 64.0, 63.0, 52.5, 46.8, 44.7, 43.3, 39.0, 37.6, 32.2, 29.1, 26.5, 25.9, 23.4, 18.1, 16.9 ppm; IR (solid): $\tilde{\nu}$ = 3076 (w), 2663 (br), 2609 (br), 2532 (br), 1722 (m), 1641 (w), 1605 (m), 1586 (m), 1520 (s), 1231 (s), 911 (m), 890 cm^{-1} (m); ESI-HR-MS calcd for $[C_{27}H_{38}O_3Na]^+$: 433.2719, found: 433.2696.

Bicyclo[2.2.1]nonatrione 15[4]

To a solution of the starting material (63 mg, 0.15 mmol, 1 equiv) in CH_2Cl_2 (1.6 mL), the catalyst (6.4 mg, 5 mol%) and amylene (1.6 mL, 15 mmol, 100 equiv) were added successively under N_2. The Schlenk was capped and heated to 50 °C for 6 h. The reaction mixture was filtered through a plug of silica gel and processed by normal phase HPLC (petroleum ether/EtOAc, 7:1) to yield an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.03 (brt, J = 6.7 Hz, 1H), 4.92 (brt, J = 7.3 Hz, 1H), 4.82 (brt, J = 6.1 Hz, 1H), 4.53 (s, 2H), 3.55 (d, J = 17.1 Hz, 1H), 3.47 (d, J = 17.1 Hz, 1H), 2.92 (m,1H), 2.56 (d, J = 7.3 Hz, 2H), 2.28 (dd, J = 13.8, 0.9 Hz, 1H), 2.14 (brd, J = ND, 1H), 2.07–1.80 (overlapping signals, 4H), 1.73 (dd, J = 14.0, 3.7 Hz, 1H), 1.68 (brs, 3H), 1.65 (s, 3H), 1.63 (s, 3H), 1.61 (s, 6H), 1.50 (s, 3H), 1.46 (s, 3H), 1.37 (dd, J = 13.9, 7.0 Hz, 1H), 1.30 (m, 1H), 1.24 (s, 3H), 0.97 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.0, 203.2, 202.9, 149.4, 136.2, 133.8, 132.3, 122.7, 122.5, 118.0, 113.9, 71.1, 63.8, 63.0, 52.4, 46.8, 44.9, 43.6, 38.0, 33.0, 29.1, 27.0, 26.6, 26.1, 25.9(2C), 23.5, 18.1 (2C), 18.0, 17.0 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3048 (w), 1705 (s), 1599 (m), 1394 (w), 1375 cm^{-1} (m); EI-HR-MS calcd for $[C_{31}H_{46}O_3]^+$: 466.3447, found: 466.3443. ND: not determined due to overlapping signals.

(±)-Garcinol[3,4]

The crude product **15** (0.15 mmol, 1 equiv) was dissolved in dry THF (4.5 mL) and the solution was cooled to 0 °C. KO*t*Bu (168 mg, 1.5 mmol, 10 equiv) was added. The mixture was stirred at this temperature for 45 min and then cyanide (927 mg, 3.75 mmol, 25 equiv) was added portion wise. The reaction mixture was allowed to warm to room temperature and was further stirred for 48 h and then MeOH (4.5 mL) and K_2CO_3 (1.14 g, 55 equiv) were added. After being stirred for 2.5 h, the reaction was quenched with NH_4Cl (sat.) and extracted three times with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4 and the solvent was removed. The residue was processed by column chromatography and the product was purified by HPLC (petroleum ether/EtOAc, 1:1) to afford 39.1 mg of a yellow oil (43% yield after 3 steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.98–6.96 (overlapping signals, 2H), 6.72 (d, J = 9.0 Hz, 1H), 5.10 (brs, 1H), 5.04 (brt, J = 6.5 Hz, 1H), 4.92 (brt, J = 7.0 Hz, 1H), 4.42 (s, 1H), 4.37 (s, 1H), 2.80–2.72 (overlapping signals, 2H), 2.58 (brd, J = 13.5 Hz, 1H), 2.36 (d, J = 14.0 Hz, 1H), 2.22–1.40 (overlapping signals, 6H), 2.14 (dd, J = 13.5, 10.0 Hz, 1H), 1.90 (dd, J = 13.5, 3.8 Hz, 1H), 1.80 (s, 3H), 1.75 (s, 3H), 1.69 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.54 (s, 6H), 1.17 (s, 3H), 1.02 ppm (s, 3H); ^{1}H NMR (500 MHz, [D_5]pyridine): δ = 7.93 (d, J = 2.0 Hz, 1H), 7.64 (dd, J = 8.3, 2.0 Hz, 1H), 7.24 (d, J = ND, 1H), 5.61 (brt, J = 6.0 Hz, 1H), 5.31 (brt, J = 6.6 Hz, 1H), 5.08 (brt, J = 6.9 Hz, 1H), 4.94 (d, J = 2.4 Hz, 1H), 4.80 (brs, 1H), 3.16 (m, 1H), 3.04 (dd, J = 13.2, 8.5 Hz, 1H), 2.92 (dd, J = 13.4, 4.8 Hz, 1H), 2.70 (m, 1H), 2.51 (d, J = 13.9 Hz, 1H), 2.50–2.37 (overlapping signals, 2H), 2.32 (dd, J = 13.8, 8.3 Hz, 1H), 2.33–2.21 (overlapping signals, 2H), 2.20 (dd, J = 14.3, 7.1 Hz, 1H), 1.87 (s, 3H), 1.85 (s, 3H), 1.80 (s, 3H), 1.71 (s, 3H), 1.69 (s, 3H), 1.68 (s, 3H), 1.66 (s, 3H), 1.59 (m, 1H), 1.40 (s, 3H), 1.26 (m, 1H), 1.14 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.2, 199.0, 195.4, 194.0, 149.8, 148.2, 143.8,

135.4, 133.1, 132.2, 128.0, 124.2, 124.0, 122.7, 120.2, 116.6, 116.0, 114.7, 112.9, 69.9, 58.0, 49.8, 46.9, 43.7, 42.7, 36.3, 32.8, 29.0, 27.2, 26.2, 26.0, 25.9, 22.9,18.3, 18.1, 18.0, 17.8 ppm; IR (in $CHCl_3$): $\tilde{\nu}$ = 3363 (broad), 3074 (w), 1728 (m), 1644 (m), 1596 (s), 1374 (s), 1290 cm^{-1} (s); ESI-HR-MS calcd for $[C_{38}H_{50}O_6Na]^+$: 625.3607, found: 625.3493. ND: not determined due to overlapping signals.

Preparation of racemic isogarcinol

According to **GP-II** racemic garcinol (12 mg, 0.02 mmol, 1 equiv) in toluene (12 mL) was treated with HCl (37% solution, 60 μL) to afford 10 mg of a yellow solid. Enantiomers were separated by chiral HPLC (Chiralpak AD CPS column, *n*-heptane/isopropanol, 9:1) to afford isogarcinol **3** (3.5 mg, t_R = 16 min) and isoxanthochymol **4** (3.2 mg, t_R = 41 min).

Isogarcinol 3: $[\alpha]_D = -206$ (MeOH, 25 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 1.8 Hz, 1H), 7.03 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 5.11 (brt, *J* = 6.3 Hz, 1H), 4.92 (brt, *J* = 7.2 Hz, 1H), 4.87 (brt, *J* = 6.2 Hz, 1H), 3.05 (dd, *J* = 14.3, 3.7 Hz, 1H), 2.71–2–59 (overlapping signals, 2H), 2.46 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.29 (d, *J* = 14.4 Hz, 1H), 2.20 (brd, *J* = 14.1 Hz, 1H), 2.05–1.94 (overlapping signals, 2H), 1.77 (m, 1H), 1.71 (s, 3H), 1.67 (s, 3H), 1.64 (s, 3H), 1.58 (s, 9H), 1.49–1.36 (overlapping signals, 3H), 1.24 (s, 3H), 1.16 (s, 3H), 0.99 (s, 3H), 0.92 ppm (s, 3H); ^{1}H NMR (500 MHz, [D_6]acetone): δ = 8.62 (br s, 1H), 8.40 (br s, 1H), 7.36 (d, *J* = 2.0 Hz, 1H),7.12 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 5.20 (brt, *J* = 6.3 Hz, 1H), 4.95 (br s, 2H), 3.02 (dd, *J* = 14.1, 3.6 Hz, 1H), 2.76 (ddd, *J* = 14.3, 11.2, 9.0 Hz, 1H), 2.63 (dd, *J* = 13.5, 8.4 Hz, 1H), 2.41 (dd, *J* = 13.6, 5.0 Hz, 1H), 2.29 (d, *J* = 14.6 Hz, 1H), 2.15–2.07 (overlapping signals, 2H), 2.04 (dd, *J* = 14.6, 7.7 Hz, 1H), 1.86 (m, 1H), 1.76 (s, 3H), 1.69 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H), 1.55 (s, 3H), 1.54 (s, 3H), 1.54–1.49 (overlapping signal, 1H), 1.44 (ddt, *J* = 13.2, 10.0, 3.6 Hz, 1H), 1.27 (s, 3H), 1.14 (s, 3H), 1.07 (t, *J* = 13.4 Hz, 1H), 0.98 (s, 3H), 0.93 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$/CD_3OD, 5:1): δ = 207.2, 194.6, 193.2, 171.7, 150.6, 144.7, 134.6, 133.6, 133.0, 129.8, 125.1, 124.8, 123.8, 121.3, 119.6, 114.4, 114.3, 86.7, 68.2, 51.2, 46.2, 46.1, 42.8, 39.3, 29.5, 29.2, 28.5, 28.2, 26.6, 25.9, 25.7, 25.6, 25.4, 22.3, 21.1, 17.9, 17.82, 17.80 ppm; IR (solid): $\tilde{\nu}$ = 3463 (w), 3359 (broad), 1718 (m), 1678 (m), 1638 (m), 1602 (s), 1364 (s), 1350 (s), 1296 cm^{-1} (s); ESI-HR-MS calcd for $[C_{38}H_{50}O_6Na]^+$: 625.3505, found: 625.3480.

Isoxanthochymol 4: $[\alpha]_D = +209$ (MeOH, 24.5 °C); ^{1}H NMR (500 MHz, $CDCl_3$) identical to that of compound **3**; ^{13}C NMR (125 MHz, $CDCl_3$/CD_3OD, 5:1): identical to that of compound **3**; IR (film): identical to that of **3**; ESI-HR-MS calcd for $[C_{38}H_{50}O_6Na]^+$: 625.3505, found: 625.3492.

Preparation of enantiomerically pure isogarcinol

According to **GP-II** natural garcinol (10 mg, 0.016 mmol, 1 equiv) in toluene (10 mL) was treated with HCl (37% solution, 50 μL) to afford 8.7 mg of a yellow solid (87% yield). The spectroscopic data of this compound were identical to those of **3**.

Isogarcinol 3: $[\alpha]_D = -206$ (MeOH, 24.5 °C); ESI-HR-MS: calcd for $[C_{38}H_{50}O_6Na]^+$: 625.3505, found: 625.3481.

Computational details

Electronic circular dichroism spectra were simulated from calculated transition energies and rotatory strengths by applying the following equations:

$$\Delta\varepsilon = \frac{\lambda_n R_n}{22.94\sqrt{\pi}\Delta\lambda} \times 10^{40}$$

where $\Delta\varepsilon_n$ is the peak intensity of the *n*th transition in $L\,mol^{-1}\,cm^{-1}$, λ_n is the wavelength of this transition in cm, R_n is the rotatory strength, and $\Delta\lambda_n$ is the width at 1/e of the peak maximum.

$$\Delta\lambda_n = {\lambda_n}^2\Delta\nu,$$

$\Delta\nu$ was considered equal to 2500 cm^{-1} in this particular case:

$$\Delta\varepsilon(\lambda) = \sum_n \Delta\varepsilon \exp\left[-\left(\frac{\lambda-\lambda_n}{\Delta\lambda_n}\right)^2\right]$$

A scale factor (0.2) was used to fit the calculated molar circular dichroism to the experimental CD spectra.

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FULL PAPER

Natural Products

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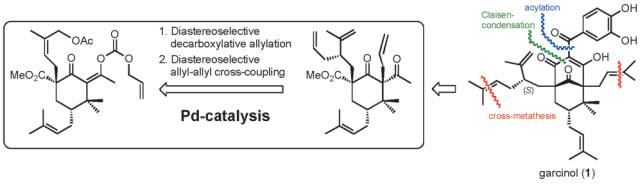
Total Synthesis and Absolute Configuration Assignment of MRSA Active Garcinol and Isogarcinol



A quick fix: A short total synthesis of (±)-garcinol and (±)-isogarcinol, two *endo*-type B PPAPs with reported activity against methiciline resistant Staphylococcus aureus (MRSA), is presented. The stereo- and regioselective Pd-catalysed decarboxylative Tsuji–Trost allylation/allyl–allyl cross-coupling are key elements that allowed the total synthesis to be accomplished within 13 steps starting from acetylacetone (see scheme).