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A divergent and stereoselective approach to phenolic 1,7-dihydroxy-bisabolane sesquiterpenes: asymmetric total synthesis of (+)-curcutetraol, (+)-sydonol, (+)-sydonic acid, and (+)-7-*O*-methylsydonic acid

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ABSTRACT

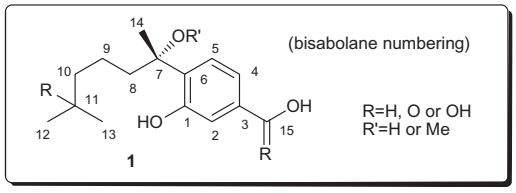
The combined use of the Sharpless asymmetric epoxidation, a number of stereospecific chemical transformations, and the 3,5-hexadienoic acid benzannulation protocol allowed us to devise a new, divergent, and stereoselective approach to terpenes with a chiral tertiary hydroxyl group at the *ortho*-position of a phenol functional group. Accordingly, the natural occurring enantiomeric forms of the bisabolane sesquiterpenes (+)-curcutetraol, (+)-sydonol, (+)-sydonic acid, and (+)-7-*O*-methylsydonic acid were synthesized with high enantiomeric purity starting from geraniol. The latter two acids were prepared in enantioenriched form for the first time.

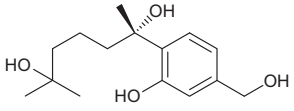
1. Introduction

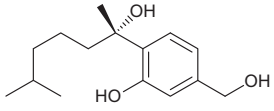
Phenolic sesquiterpenes belonging to the bisabolane family often possess specific biological activities, which are strictly related to their stereochemical structures. As a consequence, much effort has been spent for their chemical characterization and for their stereoselective synthesis. In spite of this fact, only a few investigations have concerned the bisabolane sesquiterpenes with the general framework **1**[1–13] (Fig. 1). Moreover, the main part of these studies deals with their characterization and isolation from natural sources without providing any suitable approach for their synthesis. This is due to the general difficulties related to the selective construction of the benzylic stereocentre, which become more demanding when a potentially unstable quaternary carbinol has to be synthesized. Therefore, these issues have hampered the development of a reliable and general synthetic approach to compounds of type **1**.

Some relevant examples of phenolic sesquiterpenes of this kind concern benzylic alcohols curcutetraol **1a** and sydonol **1b**, which were both isolated from microbial cultures. More specifically tetrol (+)-**1a** was extracted[4] from the marine bacterium CNH-741 and fungus CNC-979 whereas triol **1b** was isolated from a different strain of *Aspergillus* sp. either as (+)-(*S*)-[2,11] or (−)-(*R*)-[10] isomeric forms.

It is noteworthy that the stereochemistry of these compounds considerably affects their biological activity. Compound (+)-**1b** exhibited antifungal activity against *Cochliobolus lunata*[2] (IFO 6299) whereas (−)-**1b** revealed[10] selective antibacterial properties. Another interesting instance concerns acid **1c**[1,6–8,12] and **1d**,[9] which have chemical structures very close to those of **1a** and **1b**




(+)-curcutetraol **1a**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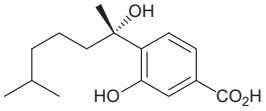
(+)-sydonic acid **1c**

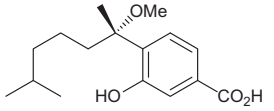
(+)-7-*O*-methylsydonic acid **1d**

Figure 1. General structure of the 1,7-dihydroxy-bisabolane framework and structures of some relevant sesquiterpenes having the same skeleton.

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and both were also isolated from microorganisms but display only modest biological activities.

To the best of our knowledge, only one[5] specific synthetic method allows for the enantioselective preparation of (+)-curcutetraol and (+)-sydonol. In addition, the synthesis of sydonic acid was accomplished[13] merely for a racemic material, whereas the preparation of 7-*O*-methyl-sydonic acid is still lacking.

As an extension of our program on the enantioselective synthesis of phenolic sesquiterpenes,[14–16] we devised a new and general synthetic approach to compounds of type **1**. The existing method[5] bases the construction of the benzylic stereocentre on the diastereoselective addition of an aryl Grignard reagent on a chiral methoxycarbonyl aminal. We envisaged that an alternative approach could be the construction of the substituted phenol ring starting from an aliphatic precursor bearing an existing quaternary stereocentre. The latter method can overcome some of the above described issues, as demonstrated previously[17,18] through the synthesis of different phenolic sesquiterpenes.

Herein we report the result of our studies, comprising of the stereoselective synthesis of four compounds **1a**–**d** as well as the development of a general and reliable process for the preparation of the components of this class of natural products.

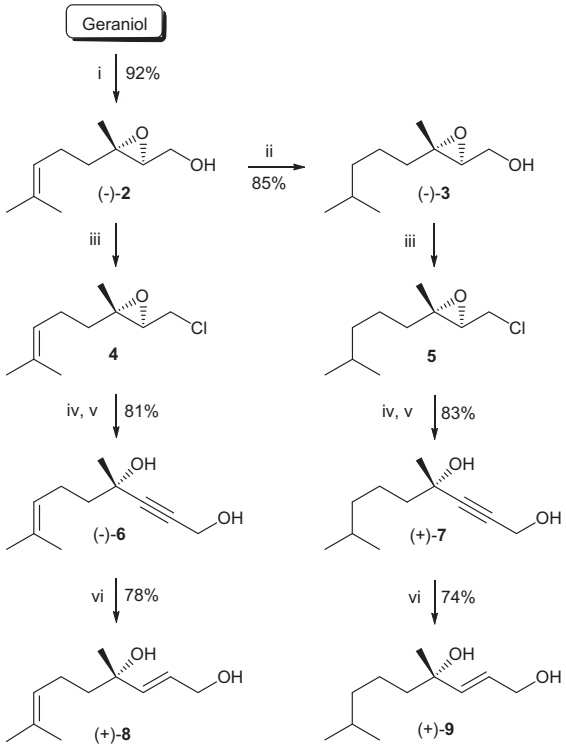
2. Results and discussion

2.1. Preparation of the chiral synthons (*S*)-(*E*)-4,8-dimethylnona-2,7-diene-1,4-diol and (*S*)-(*E*)-4,8-dimethylnon-2-ene-1,4-diol

We based our retrosynthetic plan on the benzannulation reaction[19] of a chiral aliphatic precursor. According to our expertise, we looked for the preparation of a substituted 3,5-hexadienoic acid that had a suitable quaternary stereocentre at the 7-position. The cyclization of this can give the phenolic derivative with a chiral tertiary hydroxyl group at the *ortho*-position of the phenol functional group. Finally, functional group transformations can afford the whole 1,7-dihydroxy-bisabolane framework and thus the target compounds.

We have previously established[17,18] a synthetic path that allows for the preparation of this type of dienic acid starting from allylic alcohols with a stereocentre at the γ-position. For this reason, we selected ((2*S*,3*S*)-3-methyl-3-(4-methylpent-3-enyl)oxiran-2-yl) methanol **2** (Scheme 1), as a chiral building block for the synthesis of all of our target compounds. Both enantiomeric forms of the epoxy-alcohol can be prepared[20] with high enantiomeric purity (95% ee) by Sharpless asymmetric epoxidation of geraniol. Furthermore, (−)-**2** can be easily converted into (*S*)-dehydrolinalool,[20,21] which could give access to propargylic alcohol derivatives of type **6** through exploitation of the acetylenic group.

Accordingly, we synthesized epoxy-alcohol (−)-**2** starting from geraniol and epoxy-alcohol (−)-**3** by means of atmospheric pressure hydrogenation of (−)-**2**, using Pd/C as the catalyst. The following transformation of the hydroxyl functional group into the corresponding chloride group was performed by refluxing the epoxy-alcohols (−)-**2** and (−)-**3** with triphenylphosphine in carbon tetrachloride to afford epoxy-chloride **4** and **5**, respectively. The latter compounds were then treated with at least 3 equiv of BuLi at low temperature. Under these conditions, the epoxy-chloride moiety undergoes a base-mediated rearrangement to give the corresponding 1-propyn-3-ol dilithium salt derivative. These intermediates were treated in situ with formaldehyde (solid), which reacts at room temperature to form a new hydroxy-methylenic group. As a result, we converted epoxy-alcohols (−)-**2** and (−)-**3** into diols (−)-**6** and (+)-**7**, respectively, in 81% and 83% overall yields.



Scheme 1. Synthesis of the (*S*)-(*E*)-4,8-dimethylnona-2,7-diene-1,4-diol and of the (*S*)-(*E*)-4,8-dimethylnon-2-ene-1,4-diol from geraniol. Reagents and conditions: (i) (+)-DIPT, Ti(O*i*Pr)$_4$, TBHP, molecular sieves, CH_2Cl_2, −25 °C, 8 h; (ii) H_2, 10% Pd/C cat., EtOAc, atm. pressure; (iii) Ph_3P, CCl_4, reflux 5 h; (iv) BuLi, THF, −78 °C, 30 min then rt; (v) CH_2O, rt 2 h; (vi) $NaAlH_2(OCH_2CH_2OMe)_2$, Et_2O, 0 °C, 30 min then 1 h at rt.

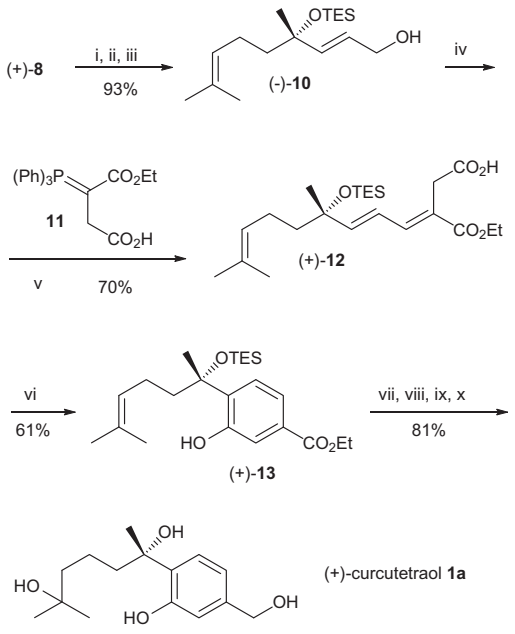
We previously demonstrated that the Denmark reduction protocol[22] can be successfully applied to 4-alkoxy-propyn-1-ol derivatives[18,23] to give the corresponding (*E*)-4-alkoxy-propen-1-ol derivatives. Therefore, we tried to adapt this synthetic method to the reduction of our propargylic diols. Accordingly, diols (−)-**6** and (+)-**7** were treated with at least 2 equiv of sodium bis(methoxyethoxy)aluminum hydride in dry diethyl ether to give diols (+)-**8** and (+)-**9**, respectively, in 78% and 74% yields.

Thus, the latter chiral building blocks have been exploited in the synthesis of the target bisabolane sesquiterpenes. We used (+)-**8** or (+)-**9** as the starting material, depending on whether the carbon at the 11-position had to be functionalized with a hydroxyl group or not.

2.2. Synthesis of (*S*)-(+)-curcutetraol

(*S*)-(*E*)-4,8-Dimethylnona-2,7-diene-1,4-diol (+)-**8** was chosen as the starting material for the synthesis of (+)-curcutetraol **1a**. As demonstrated by some preliminary experiments, the tertiary hydroxyl group must be protected before the homologation step. Hence, we looked for a suitable protecting group which could be easily introduced/removed from this sterically hindered position. After some disappointing results with acetyl and trimethylsilyl groups, we finally selected triethylsilylchloride as a reagent of choice for this step. Accordingly, the primary hydroxyl group of (+)-**8** was selectively acetylated using acetic anhydride and pyridine and the crude monoacetate was treated with triethylsilylchloride and imidazole in the presence of a catalytic amount of DMAP (Scheme 2).

The following reaction with methanolic NaOH allowed for the cleavage of the ester functionality, leaving the silyl ether



Scheme 2. Synthesis of (+)-curcutetraol starting from (*S*)-(*E*)-4,8-dimethylnona-2,7-diene-1,4-diol. Reagents and conditions: (i) Ac_2O, Py; (ii) Et_3SiCl, THF, imidazole, DMAP cat., 60 °C, 3 h; (iii) NaOH, MeOH, 30 min rt; (iv) MnO_2, CH_2Cl_2, reflux 4 h; (v) **11**, toluene, 80 °C, 3 h; (vi) $(CF_3CO)_2O$, Et_3N, THF, 0 °C, then rt 1 h; (vii) Ac_2O, Py, DMAP cat.; (viii) MCPBA, CH_2Cl_2, 0 °C; (ix) $LiAlH_4$, THF, reflux 1 h; (x) HCl aq.

unaffected. The allylic alcohol (−)-**10** obtained was oxidized with an excess of MnO_2 in refluxing CH_2Cl_2 and the resulting aldehyde was treated with ylide **11**[24] to give acid (+)-**12** in good yield. It is noteworthy that the latter Wittig reaction proceeded with very high stereoselectivity and we were able to detect only the (3*E*,5*E*)-isomeric form of the trienic acid in the crude reaction mixture.

The benzannulation of acid (+)-**12** using trifluoroacetic anhydride as an activating agent and triethylamine as a base provided isomerically pure phenol (+)-**13** in satisfactory yield. We found that the best reaction conditions consisted of adding 1.5–2 equiv of anhydride to a cooled (0 °C) solution of the acid and of the triethylamine (at least 4 equiv) in THF. Higher amounts of anhydride or higher temperatures increased the formation of side products, such as the trifluoroacetate of the phenol or unidentified degradation derivatives. The use of only 1 equiv of activating agent or performing the reaction at a lower temperature (−20 °C or below) significantly decreased the yield.

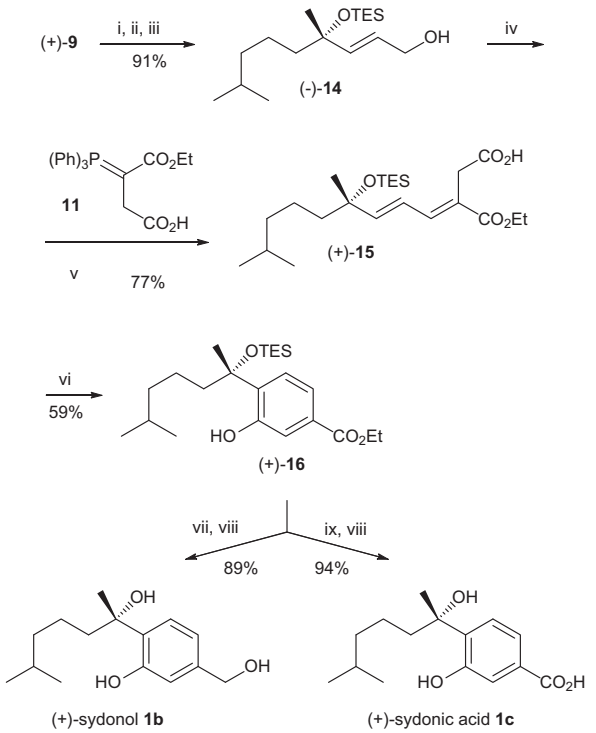
Starting from (+)-**13**, only a few high yielding functional group interconversions allowed us to prepare curcutetraol without isolation of the intermediates. Accordingly, phenol **13** was acetylated by acetic anhydride and pyridine in the presence of a catalytic amount of DMAP. The ester was then treated with MCPBA in CH_2Cl_2 in order to epoxidize the C(10)–C(11) double bond. The crude epoxide was dropped into a refluxing suspension of $LiAlH_4$ in THF to allow the simultaneous reduction of the benzoate ester, the cleavage of the phenol acetate, and regioselective epoxide reduction. Careful quenching of the reaction mixture with dilute hydrochloric acid triggered the hydrolysis of the silyl ether. After work-up and chromatographic purification, (+)-curcutetraol **1a** was isolated in very good yield and its spectroscopic data were in good agreement with those previously reported. Moreover, we recorded a specific rotation value of +6.3 (*c* 2.2, MeOH), which corroborated both the absolute configuration and the occurrence in enantioenriched form of the natural product, which showed $[\alpha]_D^{20} = +5.2$ (*c* 0.74, MeOH).[4]

2.3. Synthesis of (+)-sydonol and (+)-sydonic acid

The above experimental procedure can be easily adapted to the synthesis of sydonol and sydonic acid. Diol (+)-**9** was acetylated using acetic anhydride and pyridine. The crude monoacetate was treated with triethylsilylchloride and imidazole in the presence of a catalytic amount of DMAP followed by reaction with methanolic NaOH (Scheme 3). The obtained allylic alcohol (−)-**14** was oxidized with an excess of MnO_2 in refluxing CH_2Cl_2 and the resulting aldehyde was treated with ylide **11** to give acid (+)-**15** in good yield. As described earlier, the benzannulation reaction was performed in THF, using 1.9 equiv of trifluoroacetic anhydride and an excess of triethylamine as the base. The obtained phenol (+)-**16** is the direct precursor of both target compounds **1b** and **1c**. Treatment of the latter phenol with $LiAlH_4$ in refluxing THF allowed the reduction of the benzoate ester functional group to a benzylic alcohol. Quenching the reaction mixture with dilute hydrochloric acid hydrolyzed the triethylsilyl protecting group to afford (+)-sydonol **1b** in very good yield.

In the same way, treatment of phenol (+)-**16** with an excess of sodium hydroxide in methanol followed by quenching with dilute hydrochloric acid affected hydrolysis of both the ethyl ester and of the triethylsilyl protecting group to afford (+)-sydonic acid **1c** in nearly quantitative yield.

The spectroscopic data and specific rotation value that we recorded for both (+)-**1b** and (+)-**1c** were in good agreement with those previously reported. However, we observed a discrepancy concerning the melting points of sydonic acid (+)-**1c**. For this compound we measured a value of 66–68 °C whereas for an enantioenriched sample[6] and for a racemic sample,[1] melting points of 85–86 and of 158–159 °C, respectively, were recorded. This case is noteworthy as it demonstrates how a variation of the enantiomeric



Scheme 3. Synthesis of (+)-sydonol and (+)-sydonic acid starting from (*S*)-(*E*)-4,8-dimethylnon-2-ene-1,4-diol. Reagents and conditions: (i) Ac_2O, Py; (ii) Et_3SiCl, THF, imidazole, DMAP cat., 60 °C, 3 h; (iii) NaOH, MeOH, 30 min rt; (iv) MnO_2, CH_2Cl_2, reflux 4 h; (v) **11**, toluene, 80 °C, 3 h; (vi) $(CF_3CO)_2O$, Et_3N, THF, 0 °C, then rt 1 h; (vii) $LiAlH_4$, THF, reflux 30 min; (viii) HCl aq; (ix) NaOH, MeOH, reflux 30 min.

composition of a given compound can markedly affect not only the biological activity but also physical data.

2.4. Synthesis of (+)-7-*O*-methylsydonic acid

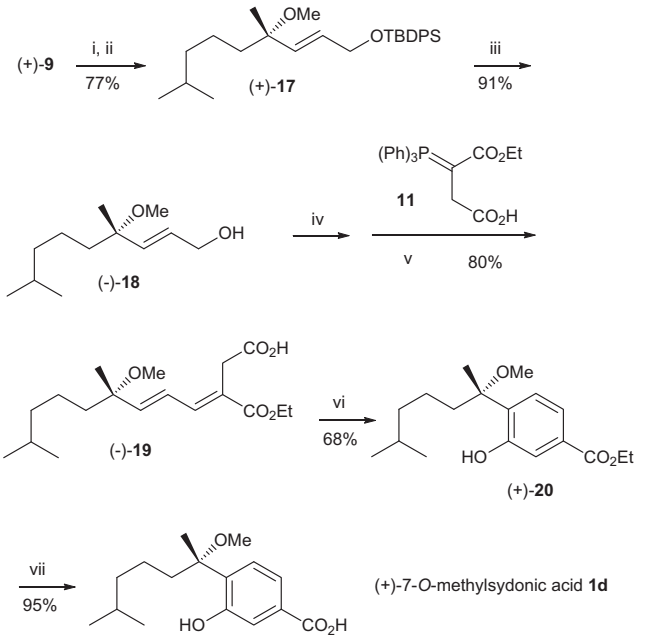
The stereoselective preparation of the 7-*O*-methylsydonic acid is strictly related to that of sydonic acid, although it exhibits a further synthetic issue. The methylation of the tertiary hydroxyl group has to be performed under harsh experimental conditions, which require functionalization of the primary hydroxyl group with a very stable and yet easily removable protecting group. Therefore, we treated diol (+)-**9** with *tert*-butylchlorodiphenyl silane, imidazole, and catalytic DMAP in DMF, at rt (Scheme 4). Under these experimental conditions, the tertiary hydroxyl group was unaffected and the crude product obtained consisted of a single silyl ether derivative (by NMR analysis).

The latter material was thus used without further purification in the next step. Treatment with BuLi in THF at low temperature gave the corresponding lithium alkoxide, which reacted smoothly at rt with MeI in the presence of DMPU as co-solvent. Although the reaction needed a long reaction time (48 h), the methyl ether derivative (+)-**17** was obtained in good yield. The following deprotection of the primary hydroxyl group was performed using TBAF in THF to give (−)-**18** in nearly quantitative yield.

From this point onward, the synthetic steps were the same of those described for the preparation of sydonic acid.

Allylic alcohol (−)-**18** was oxidized with an excess of MnO_2 in refluxing CH_2Cl_2 and the resulting aldehyde was treated with ylide **11** to give acid (−)-**19** in good yield. The benzannulation reaction was performed using the experimental conditions described before to give phenol (+)-**20** in satisfactory yield. Treatment of the latter phenol with an excess of sodium hydroxide in methanol followed by quenching with dilute hydrochloric acid afforded (+)-7-*O*-methylsydonic acid **1d** in nearly quantitative yield.

The spectroscopic data recorded for **1d** were in good agreement with those reported for extractive (+)-7-*O*-methylsydonic acid. Therefore, we can confirm both the chemical structure and the absolute configuration of the natural product. Moreover, we measured a specific rotation value of +3.9 (*c* 1.9, MeOH) for our synthetic material whereas a value of +2 (*c* 1.9, MeOH) was reported[9] for natural **1d**. Due to the low magnitude of the specific rotation and the resulting low accuracy in the measurement, we can assert that the natural product is enantioenriched although we have to leave some extent of uncertainty concerning its enantiomeric purity.



Scheme 4. Synthesis of (+)-7-*O*-methylsydonic acid starting from (*S*)-(*E*)-4,8-dimethylnon-2-ene-1,4-diol. Reagents and conditions: (i) TBDPSCl, DMF, imidazole, DMAP cat., rt 3 h; (ii) BuLi, THF, −78 °C, 20 min then MeI and DMPU, rt 48 h; (iii) TBAF, THF, rt 1 h; (iv) MnO_2, CH_2Cl_2, reflux 4 h; (v) **11**, toluene, 80 °C 3 h; (vi) $(CF_3CO)_2O$, Et_3N, THF, 0 °C, then rt 1 h; (vii) NaOH, MeOH, reflux 30 min.

3. Conclusion

Herein we have reported on a new stereoselective approach to the phenolic 1,7-dihydroxy-bisabolane sesquiterpenes. The synthetic method is divergent since all of the obtained compounds were prepared starting from geraniol. The key synthetic steps comprise of a Sharpless asymmetric epoxidation, transformation of ((2*S*,3*S*)-3-methyl-3-(4-methylpent-3-enyl)oxiran-2-yl)methanol (−)-**2** into allylic diols (+)-**8** and (+)-**9,** and benzannulation of the 3,5-hexadienoic acids (+)-**12**, (+)-**15,** and (−)-**19**. Overall, different outcomes were achieved. We proposed an alternative approach that allows the construction of substituted phenol rings with a chiral tertiary hydroxyl group at the *ortho* position of the phenol functional group starting from an aliphatic precursor bearing an existing quaternary stereocentre. Since all of the described chemical transformations do not involve racemization, both the intermediates and the natural occurring enantiomeric forms of the bisabolane sesquiterpenes (+)-curcutetraol **1a**, (+)-sydonol **1b**, (+)-sydonic acid **1c,** and (+)-7-*O*-methylsydonic acid **1d** were synthesized with high enantiomeric purity (ee 95%) and in good overall yields. Our approach compares favorably to the previous asymmetric syntheses of (+)-**1a** and (+)-**1b** in terms of reliability and general applicability. In addition, the acids (+)-**1c** and (+)-**1d** were prepared in enantioenriched form for the first time. It is worth noting that the Sharpless asymmetric epoxidation can afford either (*S*)- or (*R*)-enantiomers with the same selectivity. The present study also represents a formal enantioselective synthesis of (−)-**1a**, (−)-**1b**, (−)-**1c,** and (−)-**1d**.

4. Experimental

4.1. General

All moisture-sensitive reactions were carried out under a static atmosphere of nitrogen. All solvents and reagents were of commercial quality. TLC: *Merk* silica gel *60* F_{254} plates. Column chromatography (CC): silica gel. GC–MS analyses: *HP-6890* gas chromatograph equipped with a 5973 mass detector, using a *HP-5MS* column (30 m × 0.25 mm, 0.25 μm film thickness; *Hewlett Packard*) with the following temp. program: 60° (1 min)–6°/min–150° (1 min)–12°/min–280° (5 min); carrier gas, He; constant flow 1 mL/min; split ratio, 1/30; t_R given in min: t_R(**2**) 14.45, t_R(**3**) 13.87, t_R(**10**) 22.92, t_R(**14**) 23.20, t_R(**17**) 29.50, t_R(**18**) 16.71. Mass spectrum of compounds (−)-**6**, (+)-**7**, (+)-**8**, (+)-**9**, (+)-**12**, (+)-**13**, (+)-**1a**, (+)-**15**, (+)-**16**, (+)-**1b**, (+)-**1c**, (−)-**19**, (+)-**20** and (+)-**1d** were recorded on a Bruker ESQUIRE 3000 PLUS spectrometer (ESI detector). Optical rotations: *Jasco-DIP-181* digital polarimeter. ^1H and ^{13}C Spectra and DEPT experiments: $CDCl_3$ solutions at rt using a *Bruker-AC-400* spectrometer at 400, 100, and 100 MHz, respectively; chemical shifts in ppm rel to internal $SiMe_4$ (=0 ppm), *J* values in Hz. Melting points were measured on a Reichert apparatus, equipped with a Reichert microscope, and are uncorrected.

4.2. Preparation of the epoxy-alcohols (−)-2 and (−)-3

((2*S*,3*S*)-3-Methyl-3-(4-methylpent-3-enyl)oxiran-2-yl)methanol (−)-**2** (ee 95%, 94% chemical purity by GC, 92% yield) was prepared

by Sharpless asymmetric epoxidation of geraniol according to a previously reported[20] experimental procedure.

A solution of ((2*S*,3*S*)-3-methyl-3-(4-methylpent-3-enyl)oxiran-2-yl)methanol (−)-**2** (17 g, 0.1 mol) in ethyl acetate (60 mL) was hydrogenated at atmospheric pressure using Pd/C (10% w/w) as the catalyst. After adsorbing 1.05 equiv of hydrogen, the catalyst was removed by filtration, the solvent was evaporated under reduced pressure, and the residue was purified by chromatography eluting with hexane/acetate (9:1–7:3) as eluent to afford pure ((2*S*,3*S*)-3-methyl-3-(4-methylpentyl)oxiran-2-yl)methanol (−)-**3** (14.6 g, 85% yield) as a colorless oil. $[\alpha]_D^{20} = -6.6$ (*c* 3, $CHCl_3$), 94% of chemical purity by GC. Lit.[25] $[\alpha]_D^{20} = -7.1$ (*c* 0.0195, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.6 Hz, 6H), 1.14–1.22 (m, 2H), 1.28 (s, 3H), 1.33–1.48 (m, 3H), 1.48–1.65 (m, 2H), 2.77 (br t, *J* = 5.4 Hz, 1H), 2.96 (dd, *J* = 6.7, 4.4 Hz, 1H), 3.62–3.72 (m, 1H), 3.76–3.86 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 22.4, 22.4, 22.7, 27.8, 38.6, 38.8, 61.2, 61.2, 63.0. GC–MS *m*/*z* (rel intensity) 172 (M^+, <1), 157 (2), 129 (17), 115 (50), 111 (27), 95 (23), 85 (11), 71 (100), 69 (91), 55 (46), 43 (62).

4.3. Preparation of the propargylic diols (−)-6 and (+)-7

A mixture of ((2*S*,3*S*)-3-methyl-3-(4-methylpent-3-enyl)oxiran-2-yl)methanol (−)-**2** (10 g, 58.8 mmol), Ph_3P (16 g, 61 mmol), $NaHCO_3$ (1 g, 11.9 mmol), and CCl_4 (100 mL) was heated at reflux with stirring. When the starting alcohol could no longer be detected by TLC analysis (8 h) the reaction was cooled to 0 °C and the precipitated phosphine oxide was removed by filtration. The solution was concentrated under reduced pressure and the residue was purified by chromatography eluting with hexane/ether (95:5–8:2) as the eluent. The oil obtained consisted of 3-(chloromethyl)-2-methyl-2-(4-methylpent-3-enyl)oxirane impure with some residual Ph_3P. The whole aforementioned material was dissolved in dry THF (80 mL) and cooled to −78 °C. Next, BuLi (78 mL of a 2.5 M solution in hexane, 195 mmol) was added dropwise under a static atmosphere of nitrogen and the mixture was stirred at this temperature for one additional hour. The reaction was allowed to reach rt and then a slurry of paraformaldehyde (9 g, 0.3 mol) in dry THF (20 mL) was added in a few portions. After the exothermic reaction settled down, stirring was prolonged for a further 2 h and then the obtained jelly mixture was poured into a saturated solution of NH_4Cl (100 mL). The reaction was extracted with diethyl ether (3 × 100 mL) and the combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/EtOAc (9:1–6:4) as eluent to afford pure (*S*)-4,8-dimethylnon-7-en-2-yne-1,4-diol (−)-**6** (8.7 g, 81% yield) as a colorless oil. $[\alpha]_D^{20} = -11.9$ (*c* 1.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 3H), 1.64 (s, 3H), 1.69 (s, 3H), 1.59–1.76 (m, 2H), 2.09–2.32 (m, 2H), 2.52 (br s, 2H), 4.29 (s, 2H), 5.15 (br t, *J* = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 23.6, 25.6, 29.7, 43.3, 50.9, 68.3, 81.7, 89.4, 123.7, 132.3. MS (ESI): 205.3 (M^++Na).

The above described procedure was repeated starting from ((2*S*,3*S*)-3-methyl-3-(4-methylpentyl)oxiran-2-yl)methanol (−)-**3** (10 g, 58.1 mmol) to give pure (*S*)-4,8-dimethylnon-2-yne-1,4-diol (+)-**7** (8.9 g, 83% yield). $[\alpha]_D^{20} = +2.6$ (*c* 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.7 Hz, 6H), 1.20 (q, *J* = 7.5 Hz, 2H), 1.39–1.71 (m, 5H), 1.48 (s, 3H), 2.89 (bs s, 1H), 2.92 (br s, 1H), 4.28 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 22.5, 22.5, 27.8, 29.5, 38.9, 43.7, 50.7, 68.1, 81.4, 89.5. MS (ESI): 207.4 (M^++Na).

4.4. Preparation of allylic diols (+)-8 and (+)-9

A solution of (*S*)-4,8-dimethylnon-7-en-2-yne-1,4-diol (−)-**6** (5.5 g, 30.2 mmol) in dry diethyl ether (30 mL) was added dropwise to a cooled and stirred solution of sodium bis(methoxyethoxy)aluminum hydride (26 mL of a 3.46 M solution in toluene) in dry diethyl ether (50 mL). After the addition was complete, the reaction was allowed to reach rt and then stirred at this temperature for 1 h. The mixture was then cooled to 0 °C and quenched by the dropwise addition of a saturated solution of potassium sodium tartrate (60 mL) and water (90 mL). The organic layer was separated and the aqueous phase was extracted with further ethyl acetate (100 mL). The combined organic phases were washed with brine (100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by chromatography eluting with hexane/EtOAc (9:1–6:4) as eluent to afford pure (*S*)-(*E*)-4,8-dimethylnona-2,7-diene-1,4-diol (+)-**8** (4.35 g, 78% yield). $[\alpha]_D^{20} = +4.4$ (*c* 2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.51–1.66 (m, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 1.71 (br s, 1H), 1.93–2.12 (m, 2H), 4.17 (br s, 2H), 5.11 (br t, *J* = 7.3 Hz, 1H), 5.77 (d, *J* = 15.9 Hz, 1H), 5.84 (dt, *J* = 15.9, 4.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 22.8, 25.6, 27.9, 42.3, 63.1, 72.8, 124.3, 126.7, 131.9, 138.4. MS (ESI): 207.3 (M^++Na).

The above described procedure was repeated starting from (*S*)-4,8-dimethylnon-2-yne-1,4-diol (+)-**7** (7 g, 38 mmol) to give pure (*S*)-(*E*)-4,8-dimethylnon-2-ene-1,4-diol (+)-**9** (5.2 g, 74% yield). $[\alpha]_D^{20} = +6.8$ (*c* 4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.6 Hz, 6H), 1.10–1.23 (m, 2H), 1.24–1.38 (m, 2H), 1.28 (s, 3H), 1.44–1.62 (m, 3H), 1.74 (br s, 1H), 1.92 (br s, 1H), 4.15 (br s, 2H), 5.74–5.86 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 22.5, 22.5, 27.8, 27.9, 39.4, 42.9, 63.1, 72.7, 126.5, 138.7. MS (ESI): 209.4 (M^++Na).

4.5. Synthesis of (+)-curcutetraol 1a

Acetic anhydride (10 mL) was added to a solution of (*S*)-(*E*)-4,8-dimethylnona-2,7-diene-1,4-diol (+)-**8** (5 g, 27.2 mmol) in pyridine (10 mL). After 2 h at rt, the starting diol was completely acetylated (TLC analysis) and both pyridine and acetic anhydride were removed under reduced pressure. The residue was dissolved in dry THF (40 mL) and treated with imidazole (2.9 g, 42.6 mmol), DMAP (0.1 g, 0.8 mmol), and chlorotriethylsilane (6.2 g, 41.1 mmol). The reaction mixture was heated at 60 °C under nitrogen for 3 h, then was cooled to rt, diluted with water (100 mL), and extracted with diethyl ether (2 × 100 mL). The combined organic phases were washed with a saturated solution of $NaHCO_3$ (60 mL) and were concentrated in vacuo. The residue was treated with a solution of NaOH (4 g, 0.1 mol) in MeOH (30 mL) while stirring at rt until the starting acetate was no longer detectable by TLC analysis (30 min). The reaction was then diluted with water (100 mL) and extracted with diethyl ether (2 × 100 mL). The combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by chromatography eluting with hexane–diethyl ether (95:5–8:2) as eluent to afford pure (*S*,*E*)-4,8-dimethyl-4-(triethylsilyloxy)nona-2,7-dien-1-ol (−)-**10** (7.55 g, 93% yield) as a colorless oil. $[\alpha]_D^{20} = -1.5$ (*c* 2.1, $CHCl_3$), 95% of chemical purity by GC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.58 (q, *J* = 8.0 Hz, 6H), 0.95 (t, *J* = 8.0 Hz, 9H), 1.30 (br s, 1H), 1.31 (s, 3H), 1.46–1.53 (m, 2H), 1.59 (s, 3H), 1.67 (s, 3H), 1.88–2.09 (m, 2H), 4.15 (br s, 2H), 5.04–5.12 (m, 1H), 5.71 (d, *J* = 15.6 Hz, 1H), 5.77 (dt, *J* = 15.6, 5.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.8, 7.1, 17.6, 22.8, 25.6, 27.8, 44.0, 63.4, 74.7, 124.7, 126.3, 131.1, 139.3. GC–MS *m*/*z* (rel intensity) 280 (M^+-H_2O, 1), 267 (6), 215 (100), 199 (3), 185 (10), 166 (6), 159 (5), 149 (6), 135 (34), 115 (60), 103 (54), 87 (33), 75 (54), 69 (52), 59 (13).

A mixture of alcohol (−)-**10** (3.4 g, 11.4 mmol), CH_2Cl_2 (40 mL), and MnO_2 (15 g, 173 mmol) was stirred at reflux until complete oxidation to the aldehyde (4 h, TLC analysis). The reaction was then filtered and the organic phase was concentrated under reduced

pressure. The residue was dissolved in toluene (25 mL) and treated with BHA (50 mg, 0.28 mmol) and ylide **11** (6.8 g, 16.7 mmol). The heterogeneous mixture obtained was stirred under nitrogen at 80 °C until the starting aldehyde could not be detected by TLC analysis (3 h). The solvent was removed under reduced pressure and the residue was purified by chromatography eluting with hexane-ethyl acetate (9:1–7:3) as eluent to afford pure (*S*,3*E*,5*E*)-3-(ethoxycarbonyl)-7,11-dimethyl-7-(triethylsilyloxy)dodeca-3,5,10-trienoic acid (+)-**12** (3.4 g, 70% yield) as a pale yellow oil. $[\alpha]_D^{20} = +5.4$ (*c* 2.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.60 (q, *J* = 8.0 Hz, 6H), 0.96 (t, *J* = 8.0 Hz, 9H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.35 (s, 3H), 1.45–1.62 (m, 2H), 1.57 (s, 3H), 1.66 (s, 3H), 1.85–2.11 (m, 2H), 3.48 (s, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 5.06 (br t, *J* = 7.0 Hz, 1H), 6.17 (d, *J* = 15.0 Hz, 1H), 6.46 (dd, *J* = 15.0, 11.6 Hz, 1H), 7.36 (d, *J* = 11.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.9, 7.0, 14.2, 17.6, 22.9, 25.6, 28.0, 32.4, 43.8, 61.0, 75.5, 121.9, 122.9, 124.4, 131.4, 141.1, 151.6, 167.5, 175.7. MS (ESI): 447.6 (M^++Na).

At first, $(CF_3CO)_2O$ (1.4 mL, 10 mmol) was added dropwise at 0 °C to a stirred solution of acid (+)-**12** (2.2 g, 5.2 mmol) and Et_3N (4 mL, 28.7 mmol) in dry THF (20 mL). The mixture was stirred at room temperature for 1 h then water (50 mL) was added, and the reaction was extracted with diethyl ether (2 × 60 mL). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane–diethyl ether (95:5–8:2) as eluent to afford pure (*S*)-ethyl 3-hydroxy-4-(6-methyl-2-(triethylsilyloxy)hept-5-en-2-yl)benzoate (+)-**13** (1.29 g, 61% yield). $[\alpha]_D^{20} = +15.4$ (*c* 1.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (q, *J* = 8.0 Hz, 6H), 0.95 (t, *J* = 8.0 Hz, 9H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.49 (s, 3H), 1.62 (s, 3H), 1.75 (s, 3H), 1.80–1.97 (m, 4H), 4.34 (q, *J* = 7.2 Hz, 2H), 4.95–5.02 (m, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 7.47 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.49 (d, *J* = 1.6 Hz, 1H), 9.19 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.4, 6.7, 14.3, 17.5, 23.1, 25.5, 27.6, 44.2, 60.8, 81.6, 118.4, 120.2, 123.4, 125.7, 130.9, 131.9, 135.1, 156.3, 166.3. MS (ESI): 429.5 (M^++Na).

Acetic anhydride (5 mL) and DMAP (0.1 g, 0.8 mmol) were added to a solution of compound (+)-**13** (1.1 g, 2.7 mmol) in pyridine (5 mL). After 3 h at rt, the starting phenol was completely acetylated (TLC analysis) and both pyridine and the acetic anhydride were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (15 mL) and a solution of MCPBA (0.6 g, 3.48 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C with stirring. As soon as the epoxidation was complete, the reaction was diluted with CH_2Cl_2 (80 mL) and quenched by the addition of a 5% aq solution of Na_2SO_3 (50 mL). The organic phase was separated and then washed in turn with a saturated solution of $NaHCO_3$ (50 mL) and with brine. After drying (Na_2SO_4), the solvent was removed under reduced pressure and the residue was dissolved in dry THF (5 mL) and added dropwise to a stirred suspension of $LiAlH_4$ (0.3 g, 7.9 mmol) in refluxing THF (20 mL). After 1 h the reaction was cooled (0 °C) and quenched by the dropwise addition of dilute HCl (60 mL). The resulting mixture was extracted with ethyl acetate (3 × 60 mL) and the combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by chromatography eluting with hexane–ethyl acetate (9:1–1:1) as eluent to afford pure (+)-**1a** (0.59 g, 81% yield), as a thick oil. $[\alpha]_D^{20} = +6.3$ (*c* 2.2, MeOH), lit.[4] $[\alpha]_D^{20} = +5.2$ (*c* 0.74, MeOH), lit.[5] $[\alpha]_D^{20} = +5.9$ (*c* 0.74, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.17 (s, 3H), 1.36–1.51 (m, 5H), 1.63 (s, 3H), 1.76–1.88 (m, 1H), 1.88–2.00 (m, 2H), 3.24 (s, 1H), 4.58 (s, 2H), 6.80 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.82 (d, *J* = 1.6 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 9.35 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 29.3, 29.3, 29.4, 43.1, 43.5, 64.8, 71.2, 78.6, 116.0, 117.9, 126.3, 129.0, 141.7, 156.2. MS (ESI): 291.4 (M^++Na) and 267.3 (M^-).

4.6. Synthesis of (+)-sydonol 1b and (+)-sydonic acid 1c

According to the procedure described for the synthesis of (−)-**10**, diol (+)-**9** (8 g, 43 mmol) was transformed into triethylsilyl derivative (−)-**14** (11.7 g, 91% yield). $[\alpha]_D^{20} = -3.1$ (*c* 2.6, $CHCl_3$), 95% of chemical purity by GC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (q, *J* = 8.0 Hz, 6H), 0.86 (d, *J* = 6.7 Hz, 6H), 0.95 (t, *J* = 8.0 Hz, 9H), 1.08–1.18 (m, 2H), 1.20–1.41 (m, 3H), 1.29 (s, 3H), 1.42–1.60 (m, 3H), 4.11–4.17 (m, 2H), 5.68–5.79 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.9, 7.0, 21.8, 22.6, 22.6, 27.8, 27.9, 39.5, 44.3, 63.5, 74.9, 126.2, 139.6. GC–MS *m*/*z* (rel intensity) 285 (M^+−Me, 4), 271 (14), 253 (2), 243 (2), 215 (100), 187 (5), 159 (5), 115 (34), 103 (51), 95 (16), 87 (24), 75 (33).

According to the procedure described for the synthesis of (+)-**12**, triethylsilyl derivative (−)-**14** (6 g, 20 mmol) was transformed into dienic acid (+)-**15** (6.6 g, 77% yield). $[\alpha]_D^{20} = +6.5$ (*c* 2.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59 (q, *J* = 8.0 Hz, 6H), 0.85 (d, *J* = 6.7 Hz, 6H), 0.95 (t, *J* = 8.0 Hz, 9H), 1.07–1.17 (m, 2H), 1.18–1.40 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.33 (s, 3H), 1.43–1.58 (m, 3H), 3.48 (s, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 6.17 (d, *J* = 15.0 Hz, 1H), 6.45 (dd, *J* = 15.0, 11.6 Hz, 1H), 7.36 (d, *J* = 11.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.8, 7.0, 14.2, 21.8, 22.5, 22.6, 27.9, 27.9, 32.4, 39.4, 44.1, 61.0, 75.6, 121.7, 122.8, 141.2, 151.9, 167.4, 176.0. MS (ESI): 449.6 (M^++Na) and 427.6 (M+H^+).

According to the procedure described for the synthesis of (+)-**13**, dienic acid (+)-**15** (3.5 g, 8.2 mmol) was transformed into phenol (+)-**16** (1.97 g, 59% yield). $[\alpha]_D^{20} = +3.9$ (*c* 2.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (q, *J* = 8.0 Hz, 6H), 0.79 (d, *J* = 6.7 Hz, 6H), 0.94 (t, *J* = 8.0 Hz, 9H), 1.02–1.31 (m, 4H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.39–1.52 (m, 1H), 1.73 (s, 3H), 1.76–1.85 (m, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 7.02 (d, *J* = 8.1 Hz, 1H), 7.46 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.49 (d, *J* = 1.7 Hz, 1H), 9.16 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.5, 6.7, 14.3, 22.0, 22.4, 22.5, 27.6, 27.7, 39.0, 44.4, 60.8, 81.8, 118.4, 120.2, 125.7, 130.9, 135.4, 156.3, 166.3. MS (ESI): 431.5 (M^++Na).

Phenol (+)-**16** (0.9 g, 2.21 mmol) was dissolved in dry THF (5 mL) and added dropwise to a stirred suspension of $LiAlH_4$ (0.2 g, 5.3 mmol) in refluxing THF (20 mL). After 30 min, the reaction was cooled (0 °C) and quenched by the dropwise addition of dilute HCl (50 mL). The resulting mixture was extracted with ethyl acetate (3 × 40 mL) and the combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by chromatography eluting with hexane–ethyl acetate (9:1–6:4) as eluent to afford pure (+)-**1b** (0.50 g, 89% yield), as a thick oil. $[\alpha]_D^{20} = +5.8$ (*c* 2.0, MeOH), lit.[11] $[\alpha]_D^{20} = +6.1$ (*c* 0.53, $CHCl_3$), lit.[6] $[\alpha]_D^{20} = +8.6$ (*c* 1, MeOH), lit.[5] $[\alpha]_D^{20} = +9.0$ (*c* 1, MeOH), lit.[2] $[\alpha]_D^{20} = +7.2$ (*c* 1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, *J* = 6.6 Hz, 6H), 1.10–1.21 (m, 2H), 1.23–1.38 (m, 2H), 1.43–1.56 (m, 1H), 1.62 (s, 3H), 1.73–1.83 (m, 1H), 1.83–1.94 (m, 2H), 2.67 (s, 1H), 4.58 (s, 2H), 6.79 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.80 (d, *J* = 1.7 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 9.20 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 22.5, 22.5, 27.8, 29.0, 39.1, 43.0, 64.8, 78.7, 116.0, 117.9, 126.4, 129.1, 141.7, 156.2. MS (ESI): 275.4 (M^++Na), 527.2 ($2M^+$+Na) and 251.2 (M^-).

At first, NaOH (1 g, 25 mmol) in methanol (10 mL) was added to a solution of phenol (+)-**16** (0.7 g, 1.72 mmol) in methanol (5 mL). The obtained mixture was stirred at reflux until the starting ester was no longer detected by TCL analysis (approximately 30 min). The reaction was then cooled to 0 °C, quenched with dilute HCl aq (50 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane–ethyl acetate (9:1–6:4) as eluent to afford pure (+)-**1c** (0.43 g, 94% yield), as a white solid. mp 66–68 °C, lit.[6] mp 85–86 °C, lit.[1] mp 158–159 °C (for the racemic acid) $[\alpha]_D^{20} = +1.5$ (*c* 1.4, MeOH), lit.[9] $[\alpha]_D^{20} = +2.0$

(*c* 2, MeOH), lit.[6] $[\alpha]_D^{20} = +2.73$ (*c* 2.3, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 0.82 (d, *J* = 6.6 Hz, 6H), 1.08–1.17 (m, 2H), 1.17–1.26 (m, 1H), 1.26–1.41 (m, 3H), 1.42–1.55 (m, 1H), 1.60 (s, 3H), 1.79 (ddd, *J* = 13.8, 11.6, 4.7 Hz, 1H), 1.94 (ddd, *J* = 13.8, 11.9, 4.6 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 1.7 Hz, 1H), 7.44 (dd, *J* = 8.1, 1.7 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 22.9, 22.9, 23.0, 28.9, 29.0, 40.5, 43.8, 78.1, 118.7, 121.6, 127.8, 131.7, 138.0, 157.0, 169.9. MS (ESI): 555.2 ($2M^+$+Na) and 265.2 (M^-).

4.7. Synthesis of (+)-7-*O*-methylsydonic acid 1d

A solution of diol (+)-**9** (5 g, 26.9 mmol), imidazole (3.5 g, 51.4 mmol), and DMAP (0.1 g, 0.8 mmol) in dry DMF (15 mL) was treated with *tert*-butylchlorodiphenyl silane (8.1 g, 29.5 mmol) with stirring at rt for 3 h. The reaction was then quenched by the addition of a saturated solution of $NaHCO_3$ (100 mL) and extracted with diethyl ether (2 × 100 mL). The combined organic phases were dried and concentrated under reduced pressure. The residue was dissolved in dry THF (50 mL), cooled at −78 °C, and treated under nitrogen with BuLi (12 mL of a 2.5 M solution in hexane). The reaction was kept at this temperature for 20 min., then MeI (2.5 mL, 40.2 mmol) and DMPU (10 mL) were added, the temperature was allowed to reach rt and stirring was prolonged for 48 h. Quenching was performed by the addition of a saturated solution of NH_4Cl (100 mL) followed by extraction with diethyl ether (2 × 100 mL). The combined organic phases were dried, concentrated under reduced pressure, and the residue was purified by chromatography eluting with hexane–diethyl ether (95:5–9:1) as eluent to afford pure (+)-**17** (9.1 g, 77% yield), as a colorless oil. $[\alpha]_D^{20} = +2.5$ (*c* 0.6, $CHCl_3$), 93% of chemical purity by GC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.6 Hz, 6H), 1.06 (s, 9H), 1.11–1.22 (m, 2H), 1.20 (s, 3H), 1.23–1.35 (m, 2H), 1.42–1.60 (m, 3H), 3.11 (s, 3H), 4.25 (br s, 2H), 5.65 (br s, 2H), 7.32-7.44 (m, 6H), 7.65–7.71 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 21.5, 22.0, 22.6, 22.6, 26.9, 28.0, 39.6, 40.3, 49.9, 64.3, 76.8, 127.6, 129.2, 129.6, 133.9, 134.9, 135.6. GC–MS *m*/*z* (rel intensity) 423 (M^+−Me, <1), 406 (2), 381 (9), 349 (17), 261 (9), 213 (100), 199 (64), 183 (23), 153 (40), 135 (20), 95 (18), 81 (7), 69 (8).

At first, TBAF (6.4 g of the trihydrate salt, 20.3 mmol) was added portionwise at rt to a stirred solution of ether (+)-**17** (8.5 g, 19.4 mmol) in dry THF (40 mL). When the silyl ether was completely cleaved (1 h), the reaction was diluted with diethyl ether (100 mL) and quenched with water (100 mL). The aqueous phase was then extracted with ether (100 mL) and the combined organic phases were washed with brine, dried, and concentrated in vacuo. The residue was purified by chromatography eluting with hexane–diethyl ether (95:5–8:2) as eluent to afford pure (−)-**18** (3.55 g, 91% yield), as a colorless oil. $[\alpha]_D^{20} = -11.6$ (*c* 2, $CHCl_3$), 97% of chemical purity by GC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.6 Hz, 6H), 1.11–1.19 (m, 2H), 1.22–1.33 (m, 2H), 1.23 (s, 3H), 1.45–1.59 (m, 3H), 1.92 (br s, 1H), 3.14 (s, 3H), 4.16 (d, *J* = 5.4 Hz, 2H), 5.63 (dt, *J* = 16.0, 1.3 Hz, 1H), 5.74 (dt, *J* = 16.0, 5.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 22.0, 22.5, 22.5, 27.8, 39.4, 40.0, 49.8, 63.2, 76.7, 129.3, 136.2. GC–MS *m*/*z* (rel intensity) 185 (M^+−Me, 3), 169 (5), 143 (2), 135 (1), 115 (100), 109 (4), 97 (19), 83 (44), 73 (43), 55 (44), 43 (13).

According to the procedure described for the synthesis of (+)-**12**, allylic alcohol (−)-**18** (3.1 g, 15.5 mmol) was transformed into dienic acid (−)-**19** (4.05 g, 80% yield). $[\alpha]_D^{20} = -7.6$ (*c* 2.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, *J* = 6.6 Hz, 6H), 1.10–1.20 (m, 2H), 1.22–1.34 (m, 2H), 1.27 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.45–1.61 (m, 3H), 3.16 (s, 3H), 3.50 (s, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 6.10 (d, *J* = 15.4 Hz, 1H), 6.39 (dd, *J* = 15.4, 11.4 Hz, 1H), 7.37 (d, *J* = 11.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.3, 22.2, 22.5, 22.5, 27.9, 32.5, 39.4, 39.8, 50.2, 61.0, 77.4, 123.5, 123.9, 140.9, 149.1, 167.3, 175.8. MS (ESI): 349.5 (M^++Na).

According to the procedure described for the synthesis of (+)-**13**, dienic acid (−)-**19** (2.5 g, 7.7 mmol) was transformed into phenol (+)-**20** (1.60 g, 68% yield). $[\alpha]_D^{20} = +15.7$ (*c* 2.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.6 Hz, 6H), 1.06–1.22 (m, 3H), 1.25–1.41 (m, 1H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.42–1.56 (m, 1H), 1.60 (s, 3H), 1.76–1.90 (m, 2H), 3.22 (s, 3H), 4.35 (q, *J* = 7.1 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 1H), 7.50 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.51 (d, *J* = 1.7 Hz, 1H), 8.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.5, 22.2, 22.4, 22.5, 27.7, 39.1, 39.9, 50.5, 60.8, 83.0, 118.0, 120.5, 127.3, 131.4, 132.8, 156.0, 166.3. MS (ESI): 331.5 (M^++Na) and 639.1 ($2M^+$+Na).

According to the procedure described for the synthesis of (+)-**1c**, phenol derivative (+)-**20** (0.8 g, 2.6 mmol) was transformed into acid (+)-**1d** (0.69 g, 95% yield) as a colorless gum. $[\alpha]_D^{20} = +3.9$ (*c* 1.9, MeOH), lit.[9] $[\alpha]_D^{20} = +2$ (*c* 1.9, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, *J* = 6.6 Hz, 6H), 1.06–1.22 (m, 3H), 1.23–1.41 (m, 1H), 1.42–1.56 (m, 1H), 1.62 (s, 3H), 1.76–1.92 (m, 2H), 3.24 (s, 3H), 7.10 (d, *J* = 8.5 Hz, 1H), 7.57 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.58 (d, *J* = 1.7 Hz, 1H), 9.00 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 22.2, 22.4, 22.5, 27.7, 39.1, 39.8, 50.5, 83.1, 118.7, 121.2, 127.4, 130.1, 133.9, 156.1, 171.6. MS (ESI): 303.4 (M^++Na) and 279.2 (M^-).

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