Synthesis of (−)-Vulcanolide by Enantioselective Protonation

Charles Fehr,* Nathalie Chaptal-Gradoz, and José Galindo[a]

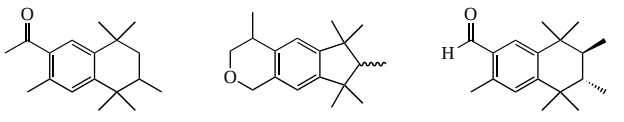
Abstract: Two efficient enantioselective syntheses of the more active (*S*,*S*)-enantiomer of the powerful musk odorant Vulcanolide are described. In both syntheses, the key step is an enantioselective protonation of a ketone enolate. A third enantioselective protonation, of a thiol ester enolate, was applied for the determination of the absolute configuration of Vulcanolide by comparison with a known compound.

Keywords: asymmetric synthesis · enantioselectivity · lithium enolate · natural products · protonation

Introduction

The outstanding place of musk odorants in perfumery derives from their characteristic odor which is referred to as warm, sensual, animal, natural, and to the fact that they are long-lasting and tenacious. Interestingly, the musk odor is found in a large variety of structural classes, among which the benzenoid musks Tonalid (Polak's Frutal Works) (or Fixolide (Givaudan)) (**1**) and Galaxolide (**2**) (International Flavors and Fragrances Inc.), although showing some bioaccumulation problems, still represent the highest tonnage products (several thousands of tons per year), due to an excellent price/performance ratio.[1, 2]

In 1989, we reported that incorporation of supplementary methyl groups into the basic skeleton of benzenoid musks gave excellent new musk odorants, possessing highly crowded structures of enhanced lipophilicity but of similar global shape.[3] This allowed the discovery of Vulcanolide (**3**) which turned out to be 10 to 20 times stronger than Tonalid, previously considered as the strongest musk odorant among hundreds of structurally related analogues (Figure 1).



Tonalid **1** (= Fixolide) | Galaxolide **2** | Vulcanolide **3** (*rac.*) (*S*,*S*)-(-)-Vulcanolide (-)-**3**

Figure 1.

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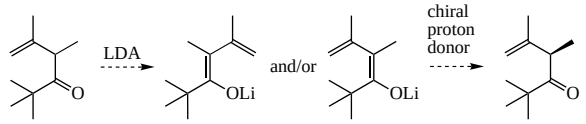
Subsequently, the two enantiomers of **3** were synthesized by a multi-step sequence including a classical resolution step, thus allowing the evaluation of the fragrances of (*R*,*R*)-(+)- and (*S*,*S*)-(−)-**3**.[4] In view of its superiority, it was decided to elaborate an enantioselective synthesis of (*S*,*S*)-(−)-Vulcanolide. This would allow the use of even smaller amounts of Vulcanolide without change in perception, and a diminished environmental problem.

Results and Discussion

Upon investigating the known enantioselective reactions, it becomes evident that only few are suited to the construction of sterically crowded chiral centers, and enantioselective protonation is often the method of choice.[5] Our plan was to prepare ketone (*R*)-**4** by enantioselective protonation of either the (*Z*)- or (*E*)-enolate [(*Z*)-**5** or (*E*)-**5**)] (Scheme 1), and to follow the efficient synthetic route described previously for the synthesis of racemic Vulcanolide (Scheme 2).



(±)-**4** (*Z*)-**5** (*E*)-**5** (*R*)-**4**

Scheme 1. Enantioselective protonation to yield (*Z*)-**5** and (*E*)-**5**.

In spite of the risk of racemization via carbocationic species, both in the Friedel – Crafts alkylation with (*R*)-**4** and, even more importantly, during acid-catalyzed cyclization of **7**, this approach[6] was considered the most interesting in view of its simplicity and similarity to the established route.

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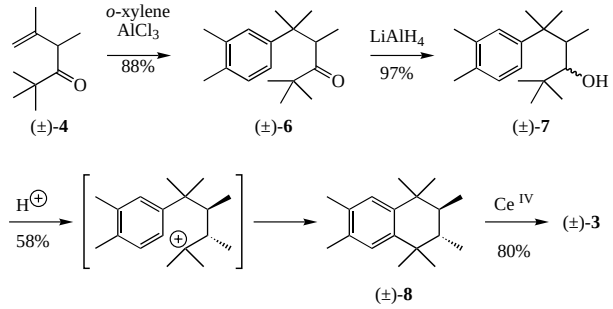
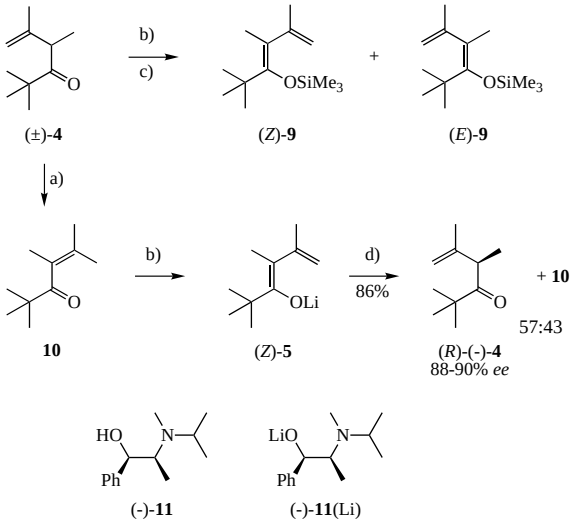


Scheme 2. Synthesis of racemic Vulcanolide previously described.

Deprotonation of **4** was best effected with 3 equiv LDA in THF at $-45\,^{\circ}C$. Silylation with excess TMSCl showed that the deprotonation exhibited a 9:1 selectivity in favor of (*Z*)-**9** (Scheme 3). Lower temperatures or the use of less LDA gave incomplete conversion. Another indication for the successful deprotonation is the appearance of conjugated enone **10** upon quenching the enolate with 5% HCl. The ratio **4**:**10** is approximately 1:1, and, although strongly dependent on the reaction conditions, is helpful for following the course of deprotonation.

We next examined the deprotonation of enone **10**, which is readily available by acid-catalyzed isomerization of **4**. A deprotonation/enantioselective protonation sequence starting from **10** has the advantage that incomplete deprotonation of the ketone has no effect on the observed *ee* of **4**. Two equivalents of LDA and a temperature of $-45\,^{\circ}C$ (or 1.05 equivalents of LDA and a final temperature of $20\,^{\circ}C$), guarantee full conversion and the exclusive formation of the *Z*-enolate as verified by trapping the enolate as TMS-ether (*Z*)-**9**; its configuration was determined by NMR (NOESY). The excellent selectivity in favor of enolate (*Z*)-**5** is probably due to chelation control and creates the most favorable conditions for an efficient enantioselective protonation, keeping in mind that *E*- and *Z*-isomeric enolates generally exhibit different (but not necessarily opposite) enantioselectivites with a given chiral proton donor. Quenching the enolate with 5% HCl gave **10** and **4** in a ratio of $\approx$1:1.



Scheme 3. a) *p*TsOH·H_2O (cat.), toluene, reflux; b) LDA, THF/hexane; c) TMSCl; d) see Table 1, entry 3.

All protonation experiments were performed with (−)-*N*-isopropylephedrine [(−)-**11**], because **11** had already been used with success in various other enolate protonations.[5] In addition, both enantiomeric forms are readily available and readily recovered by an acid/base workup.

In a first experiment, the 9:1-enolate mixture (*Z*)-**9**/(*E*)-**9**, obtained by deprotonation of (±)-**4** using 3 equivalents of LDA, was protonated with 3.5 equivalents of (−)-**11**. After stirring at $-100\,^{\circ}C$ for 30 min, chiral GC analysis of a hydrolyzed sample indicated a 20% *ee* in favor of (*S*)-(−)-**4** (for the assignment of the (*S*)-configuration, see below). The temperature was then allowed to reach $-10\,^{\circ}C$ over a period of 1 h. This gave rise to an *ee* of 55%, which remained unchanged after prolonged reaction time. This result shows that protonation does not go to completion at $-100\,^{\circ}C$; the ratio **4**:**10** was 50:50 (Table 1, entry 1).

Table 1. Protonation conditions.

Entry	Substrate	Reaction conditions (equiv, $T\,^{\circ}C$ (t [min]))[a]	**4**:**10**	(*R*)-**4** [% *ee*]	Yield [%]
1	(±)-**4**	LDA (3.0, −45 (180)) (−)-**11** (3.5, −100 → −10 (90))	50:50	55	
2	**10**	LDA (3.0, −45 (120)) (−)-**11** (3.9, −100 → −10 (90))	55:45	91	
3		LDA (2.0, −45 (60)) (−)-**11** (2.6, −45 (60) → −10 (25))[b]	57:43	88–90	49%
4		LDA (1.05, −45 → 25 (60)) (−)-**11** (1.15, −45 (60)	25:75	84	
5		LDA (1.05, −45 → 25 (60)) added to (−)-**11**(Li)(3.0)/(−)-**11**(1.5)(-45 (60))	62:38	86	
6		LDA (2.0, −20(20))[c] (−)-**11**(2.6, −20(30))	73:27	83	

[a] THF, hexane (from BuLi), except where stated otherwise. [b] 100 mmol scale (see Experimental Section). [c] 13 mmol scale: THF (25 mL), toluene (60 mL), BuLi/hexane (17 mL).

Application of the protonation conditions mentioned above to protonation of the pure (*Z*)-enolate (*Z*)-**5**, obtained by deprotonation of **10**, afforded an excellent enantioselectivity of 91% *ee* and a **4**:**10** ratio of 55:45 (Table 1, entry 2). Lowering the amount of reagents by one third has little effect (88–90% *ee*; entry 3). Using only 1.05 equivalents LDA, followed by 1.15 equivalents (−)-**11** gave (*R*)-**4** with 84% *ee*, but as the minor product (**4**:**10** = 25:75) (entry 4).

In these experiments, excess LDA deprotonates (−)-**11**; the generated lithium alkoxide (−)-**11**(Li) most probably forms a mixed aggregate with the enolate, which then displays a modified reactivity. Moreover, diisopropylamine and excess LDA also alter the structure of the enolate. We have also observed that the **4**:**10** ratio generally increases during protonation with progressive formation of the lithium alkoxide (−)-**11**(Li); its beneficial participation was also recognized when the protonating reaction mixture consisted of a 2:1 mixture of (−)-**11**(Li) and (−)-**11** (**4**:**10** = 62:38; (*R*)-**4**: 86% *ee*) (entry 5), or when the enolate was treated with (−)-**11**(Li) prior to protonation with (−)-**11**.

We have also briefly studied solvent effects and noticed that apolar solvents at a higher temperature favor the desired α-protonation. Repeating the conditions of entry 3 (2 equiv

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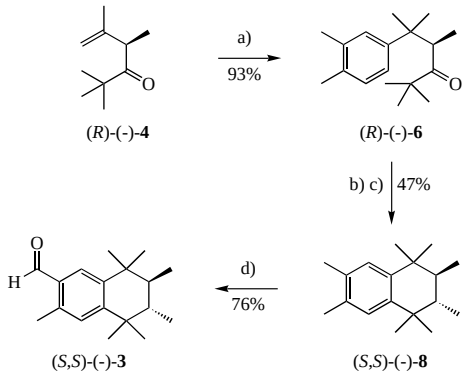
LDA and 2.6 equiv (−)-**11**) in toluene (containing some THF and hexane) at −20 °C afforded predominantly (*R*)-**4** (83 % *ee*) (**4**:**10** = 73:27) (entry 6).

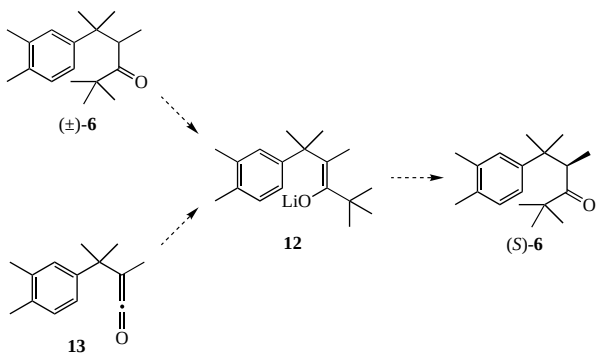
Of course, TMS-ether (*Z*)-**9** can also be transformed into the lithium enolate (*Z*)-**5** and protonated enantioselectively after appropriate complexation, but these conditions offered no real advantage and are therefore not described in this work.[7]

For the synthesis of (−)-Vulcanolide, it was not necessary to separate **4** from **10**, as enone **10** proved to be inert to the subsequent Friedel–Crafts reaction conditions. Thus, treatment of the **4**/**10** mixture with *o*-xylene and $AlCl_3$, gave the aromatic ketone (*R*)-**6** and unreacted **10**, which was recovered by distillation (Scheme 4). As shown by Eu shift NMR and by chiral GC, the enantiomeric purity of of the alkylation product was 88 %. Alcohol **7**, obtained by $LiAlH_4$ reduction (see Scheme 2), was cyclized almost without affecting the previously built chiral center, and afforded *trans*-hydrocarbon (*S*,*S*)-(−)-**8** with 83 % *ee*. After crystallization (to remove the minor *cis* diastereomer), one of the two homotopic methyl groups of (−)-**8** was oxidized with CAN to furnish (−)-Vulcanolide (83 % *ee*) (Scheme 4). An organoleptic evaluation clearly confirmed the superiority of this quality over that of the racemate.

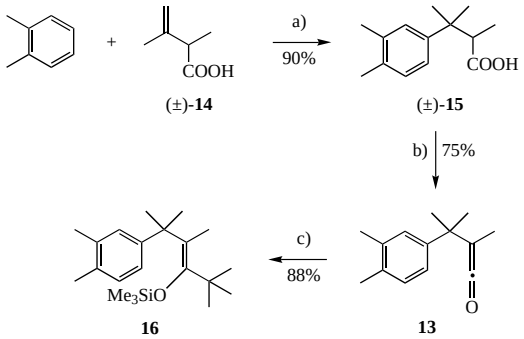


Scheme 4. a) $AlCl_3$, *o*-xylene, −5 → 12 °C; $LiAlH_4$, Et_2O, rt; c) H_2SO_4, cyclohexane, −10 → 10 °C; d) $[Ce(NH_4)_2(NO_3)_6]$, MeOH, 50 °C.

As an alternative, we also considered the enantioselective protonation of enolate **12**, derived from ketone **6** (Scheme 5). The advantage of enolate **12** over enolate (*Z*)-**5** is that only α-protonation can take place. Unfortunately, this sterically hindered ketone could not be deprotonated under a variety of reaction conditions. We therefore devised a new route to enolate **12**, based on the addition of *t*BuLi to ketene **13**, which was expected to take place from the less hindered side (Scheme 5). Indeed, sterically hindered ketenes are relatively stable; they dimerize only very slowly, and are thus ideal precursors for enolates of defined configuration.[5] This direct access to enolates, followed by enantioselective protonations, has already been successfully applied in our laboratory[8] and by another group.[9] Accordingly, Friedel–Crafts alkylation of *o*-xylene with the readily accessible acid (±)-**14**[10] gave acid (±)-**15** in 92 % yield (Scheme 6). This was converted into the acid chloride, which, after prolonged heating in refluxing toluene and triethylamine, afforded ketene **13** in 75 % yield.



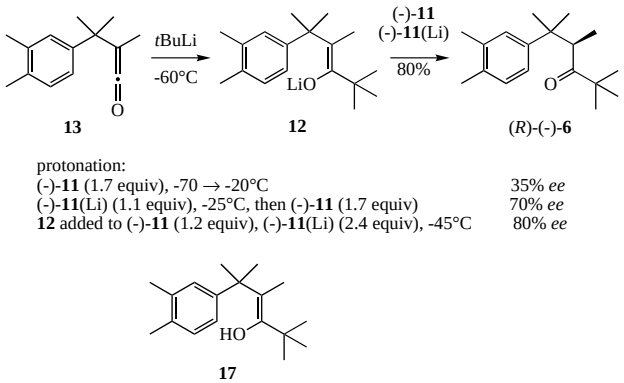
Scheme 5. Possible generation and enantioselective protonation of **12**.



Scheme 6. a) $AlCl_3$, 18 → 23 °C; b) $(COCl)_2$, DMF (cat.), CH_2Cl_2, then NEt_3, reflux; c) *t*BuLi, −78 → 25 °C, then TMSCl.

Addition of *t*BuLi at low temperature, followed by silylation, confirmed the formation of **16** as a single isomer.

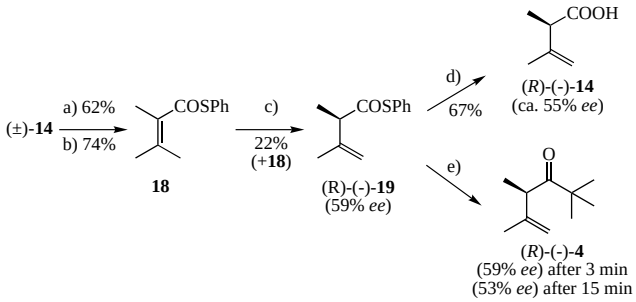
After the enolate **12** which formed in situ was treated with (−)-*N*-isopropylephedrine [(−)-**11**] at −70 °C, GC injections indicated the presence of a transient species which, upon warming the mixture to −20 °C, slowly vanished in favor of ketone **6**. This species most probably represents enol **17**, which is formed reversibly, and which slowly undergoes tautomerization to ketone **6** via deprotonation and irreversible C-protonation. After disappearance of the enol, (*R*)-(−)-**6** was isolated with 35 % *ee* (Scheme 7). This low enantioselectivity is ascribed to the temporary accumulation of enol **17**, which can act as achiral proton source for the C-protonation of the surrounding enolate. A more rapid and more enantioselective tautomerization of enol **17** could be realized by adding one



Scheme 7. Optimizing reaction conditions for the enantioselective protonation by minimizing the temporary accumulation of achiral **17**.

equivalent of lithium ephedrate (−)-**11**(Li) to the enolate, and by slowly adding (−)-**11** at the higher temperature of −25 °C (70% *ee*). Next, to minimize the amount of enolate in the reaction medium, the enolate was added to a 2:1 mixture of (−)-**11**(Li) and (−)-**11** at −45 °C. Under these conditions, only trace amounts of enol were detected by GC, and protonation took place with an improved enantiomeric excess of 80%. Ketone (*R*)-**12** was finally transformed into (−)-Vulcanolide [(−)-**3**] of 75% *ee* as shown above (Scheme 4).

As the absolute configurations of the enantiomers of acid **14** are known,[10b, 11] we prepared the corresponding enantiomerically enriched thiol ester **19** by enantioselective protonation and compared it with **14** (Scheme 8). In the presence of *t*BuLi, (*R*)-(−)-**19** (59% *ee*) afforded ketone (−)-**4** with an unchanged *ee* (after short reaction times), as proven by chiral GC. Thus, the levorotatory enantiomer (peak 2 on chiral GC; see Experimental Section) is (*R*)-**4**.



Scheme 8. a) *p*TsOH·H_2O (cat.), toluene, reflux; b) $(COCl)_2$, CH_2Cl_2, 5→20 °C, then PhSLi, 0→20 °C; c) LDA, THF, hexane, then (−)-**11**; d) 35% H_2O_2, LiOH·H_2O, EtOH, H_2O, 45 °C; e) *t*BuLi, THF, 0 °C.

Based on results from our earlier work, in which *ee* values of 96 to over 99% were obtained, thiol ester **19** of high *ee* was expected to be a promising target for enantioselective protonation.[12] The lower *ee* of 59% observed herein is probably due to the ease of elimination of phenylthiolate, giving rise to the ketene (deep yellow color of the reaction solution and distinctive smell of thiophenol). Re-addition of thiolate to this hypothetical ketene species then would account for the formation of a mixture of *E*- and *Z*-enolates and thus for the modest *ee*. Another possibility is partial racemization of **19** under the protonation conditions containing amine and in situ generated (−)-**11**(Li). Indeed, a deterioration of the *ee* could be observed in the subsequent reaction of **19** with *t*BuLi, where addition and deprotonation are in competition. Racemization was also observed during saponification of **19**. For example, KOH in MeOH (15 min at 0 °C)[11] gave rise to almost complete racemization. However, the use of LiOOH in EtOH/H_2O[12] proved to be an efficient solution to this problem (<5% racemization).

Conclusion

The work presented herein describes two efficient syntheses of (*S*,*S*)-(−)-Vulcanolide (−)-**3**, both of which are based on enantioselective protonations. A third enantioselective protonation was applied for the assignment of the absolute configuration. These examples largely extend the scope of enantioselective protonation, using (+)- or (−)-isopropylephedrine (**11**) as the chiral proton donor.

Experimental Section

General: TLC: silica gel F-254 glass plates (Merck); detection with EtOH/anisaldehyde/H_2SO_4 18:1:1. Column chromatography: silica gel 60 (Merck, 0.063–0.2 mm, 70–230 mesh, ASTM). GC: Varian instrument, model 3500; cap. columns: DB1 30W (15 m × 0.319 mm), DB-WAX 15W (15 m × 0.32 mm); chiral cap. column: Megadex 5 (16 m × 0.25 mm) (Megadex Capillary Columns Laboratory, Via Plinio 29, 20025 Legnano, Italy) or CP-Chirasil-DEX CB (25 m × 0.25 mm) (Chrompack), carrier gas He at 0.63 bar. Optical rotations: 1 mL cell, Perkin–Elmer 241 polarimeter. ^1H and ^{13}C NMR: Bruker WH 360. MS: Finnigan 1020 automated GC/MS instrument, electron energy 70 eV.

2,2,4,5-Tetramethylhex-4-en-3-one (10): Racemic **4**[3] (30.8 g, 200 mmol) and *p*TsOH·H_2O (3.08 g) were heated in toluene (100 mL) at 100 °C. After 24 h, the mixture containing 75% of **10** and 25% of **4** was cooled and extracted with Et_2O. The organic phase was washed successively with saturated $NaHCO_3$, H_2O, saturated NaCl, dried (Na_2SO_4), evaporated and fractionally distilled. The first distillation fractions contained recovered **4** (4.2 g, 14%; b.p. 50 °C/10 Torr), followed by mixed fractions (5.6 g, 18%). Pure ketone **10** (19.8 g, 64%) was finally obtained by distillation at 60 °C/8 Torr. ^1H NMR: $\delta = 1.18$ (s, 9H), 1.57 (s, 3H), 1.66 (s, 3H), 1.77 (s, 3H); ^{13}C NMR: $\delta = 218.3$ (s); 131.6 (s); 128.4 (s); 44.0 (s); 27.5 (q); 22.5 (q); 19.1 (q); 16.4 (q); MS: *m*/*z*: 154 (3) $[M]^+$, 97 (100), 69 (62), 41 (65), 39 (20).

(−)-(*R*)-2,2,4,5-Tetramethylhex-5-en-3-one [(*R*)-(−)-4]: A solution of **10** (15.40 g, 100 mmol) in THF (80 mL) was added dropwise at −45 °C to a mechanically stirred solution of LDA (200 mmol; prepared from BuLi (1.51N in hexane; 133 mL) and diisopropylamine (22.22 g, 220 mmol)) in THF (200 mL). After 45 min a solution of freshly distilled (−)-**11** (53.80 g, 260 mmol) in THF (250 mL) was added at −45 °C to the enolate (*Z*)-**5**. After addition (60 min) the cooling bath was removed and the temperature was allowed to reach −10 °C (25 min). The reaction mixture was poured into a well-stirred solution of 15% aqueous HCl and extracted twice with Et_2O. The organic layers were washed (H_2O, saturated $NaHCO_3$ and saturated NaCl), dried (Na_2SO_4) and evaporated. Bulb-to-bulb distillation (70–100 °C (bath temperature)/4 Torr) afforded a mixture of (−)-**4** and **10** (13.24 g, (−)-**4**:**10** = 57:43 (86%); yield (−)-**4** (in mixture): 49%; 88% *ee* (in another experiment 90% *ee*), as determined by chiral GC (Megadex 5; major enantiomer: peak 2)). $[\alpha]_D^{20}$ (purified (−)-**4**) = −235 (*c* = 2.2 in $CHCl_3$).

(−)-(*R*)-5-(3,4-Dimethylphenyl-2,2,4,5-tetramethylhexan-3-one [(*R*)-(−)-6]: A solution of (−)-**4** and **10** [(−)-**4**:**10** 57:43, 12.95 g, 84.1 mmol; (−)-**4**: 47.9 mmol] in *o*-xylene (18 mL) was added dropwise (15 min.) at −5 °C to a mechanically stirred suspension of $AlCl_3$ (12.91 g, 96.7 mmol) in *o*-xylene (150 mL). At the end of the addition the cooling bath was removed and the temperature was allowed to reach 12 °C. The reaction mixture was then cooled at −15 °C, and hydrolyzed with H_2O (125 mL) at such a rate that the temperature did not exceed 30 °C. The reaction mixture was extracted (Et_2O) and the organic phase washed (5% aqueous NaOH, H_2O and saturated NaCl), dried (Na_2SO_4) and evaporated. The mixture of **10** and *o*-xylene was distilled (60–100 °C/25–4 Torr; on a larger scale, the distillative separation of **10** from the *o*-xylene is facile) and the residue bulb-to-bulb distilled (80 °C (bath temperature)/0.01 Torr) to afford pure (−)-**6** (11.63 g, 93%, 88% *ee*). The *ee* was determined by chiral GC (CP-Chirasil-DEX CB; (−)-**6**: peak 1). $[\alpha]_D^{20} = -115$ (*c* = 1.14 in $CHCl_3$). The spectroscopic data are identical with those reported for racemic **6**.[3]

(−)-(2*S*,3*S*)-1,2,3,4-Tetrahydro-1,1,2,3,4,4,6,7-octamethylnaphthalene [(−)-8]: A solution of (−)-**6** (88% *ee*, 8.64 g, 33.2 mmol) in Et_2O (30 mL) was added (1 h) at 20 °C (cooling bath) to a mechanically stirred solution of $LiAlH_4$ (0.728 g, 19.2 mmol) in Et_2O (100 mL). After 1 h, the cooled (0 °C) reaction mixture was carefully hydrolyzed with H_2O (0.728 mL), then 5% aqueous NaOH solution (0.728 mL) and H_2O (2.2 mL), filtered on Celite and evaporated. Bulb-to-bulb distillation (100 °C/0.01 Torr) afforded **7** (8.65 g, 100% yield, 85% *de*, 88% *ee*). The *ee* was determined by chiral GC

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(CP-Chirasil-DEX CB; major enantiomer (of either diastereomer): peak 1). A solution of **7** (4.00 g, 15.3 mmol) in cyclohexane (30 mL) was slowly added under stirring at −10 °C to H_2SO_4 (4.00 g, 40.8 mmol). At the end of the addition, the cooling bath was removed and the temperature was allowed to reach 10 °C.The brown reaction mixture was poured into cold water and extracted three times with Et_2O. The organic layers were washed (5% aqueous NaOH, H_2O and saturated. NaCl), dried (Na_2SO_4) and evaporated. Bulb-to-bulb distillation (100–150 °C (bath temperature)/ 2 Torr) afforded 3.36 g of a mixture of (−)-**8** (53% by GC) and its diastereomer (12% by GC). Crystallization furnished pure (−)-**8** (1.51 g, 40%). $[\alpha]_D^{20} = -39$ ($c = 0.22$ in $CHCl_3$), 83% *ee* (CP-Chirasil-DEX CB; (−)-**8**: peak 2)) and an oil (1.80 g, 14% pure). Yield of (−)-**8** from (−)-**6**: 47%. The spectroscopic data are identical with those reported for racemic **8**.[3]

(−)-(6*S*,7*S*)-5,6,7,8-Tetrahydro-3,5,5,6,7,8,8-heptamethyl 2-naphthalene carbaldehyde [(−)-(*S*,*S*)-Vulcanolide (−)-(3)]: Following the procedure for the racemic sequence,[3] (−)-**8** (1.41 g, 5.78 mmol) afforded (−)-(**3**) (1.13 g, 76%). The *ee* (83%) was determined by conversion into two diastereomeric non-racemic aminals (using (*S*,*S*)-(−)-DMPEDA) and measurement of the ^{1}H NMR NMe signals[13] as done before.[4] $[\alpha]_D^{20} = -42$ ($c = 1.08$ in $CHCl_3$). All other analytical data were identical with those reported for (±)-**7**.[3]

(±)-2,3-Dimethyl-3-butenoic acid [(±)-14]:[10] A 250 mL three neck Schlenk flask fitted with a sintered glass introduction pipe was treated with Et_2O (20 mL), cooled at −30 °C and saturated with CO_2. Then an Et_2O solution of 2-methyl-2-butenyl magnesium bromide (1.5 N, 56.0 mL, 84.0 mmol; prepared from isoprene[3, 10]) was added (30 min) so that the temperature did not exceed −22 °C. At the end of the introduction, more CO_2 was bubbled through for 5 min. The thick reaction mixture was then poured into a cold 10% HCl solution and the neutral parts extracted twice with Et_2O. The acid **14** was isolated by standard acid/base extraction, followed by bulb-to-bulb distillation (50–70 °C (bath temperature)/ 0.01 Torr). Yield of (±)-**14**: 8.27 g, 86%.

(±)-2,3-Dimethyl-3-(3,4-dimethylphenyl)-butanoic acid [(±)-15]: A solution of (±)-**14** (5.56 g, 48.8 mmol) in *o*-xylene (12 mL) was added dropwise (40 min) between 18 and 23 °C to a mechanically stirred suspension of $AlCl_3$ (16.90 g, 0.127 mol) in *o*-xylene (30 mL). After stirring for 15 min, the reaction mixture was poured into cold H_2O and extracted twice with Et_2O. The title compound was isolated as a white solid by standard acid/ base extraction (9.91 g, 97% pure, 90%). ^{1}H NMR: $\delta = 0.96$ (d, $J = 7$ Hz, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 2.22 (s, 3H), 2.26 (s, 3H), 2.79 (q, $J = 7$ Hz, 1H), 7.04–7.14 (m, 3H), 10.5–11.5 (m, 1H); ^{13}C NMR: $\delta = 182.0$ (s), 145.2 (s), 136.0 (s), 134.2 (s), 129.4 (d), 127.4 (d), 123.5 (d), 50.2 (d), 39.4 (s), 28.1 (q), 22.9 (q), 20.1 (q), 19.2 (q), 13.0 (q); MS: *m*/*z*: 220 (5) $[M]^+$, 147 (100), 119 (20), 107 (10), 91 (8).

3-(3,4-Dimethylphenyl)-2,3-dimethyl-1-buten-1-one (13): In a 250 mL three necked flask fitted with an efficient stirrer, a solution of (±)-**15** (9.00 g, 40.9 mmol) and DMF (0.8 mL) in CH_2Cl_2 (40 mL) was heated at reflux and treated dropwise with oxalyl chloride (8.30 g, 5.61 mL, 65.4 mmol). After stirring for 15 min, the solvent was distilled under N_2 at atmospheric pressure. Bulb-to-bulb distillation (100–130 °C (bath temperature)/0.01 Torr) of the residue gave pure acid chloride (9.46 g, 97%). A solution of this chloride (7.00 g, 29.4 mmol), triethylamine (8.90 g, 88.2 mmol) and toluene (120 mL) was heated at reflux for 22 h. Then the cooled (25 °C) reaction mixture was filtered under N_2 on Celite. The filtrate was concentrated at reduced pressure (under N_2) and the residue bulb-to-bulb distilled (100–140 °C (bath temperature)/0.01 Torr) to afford **13** (4.68 g, 95% pure, 75%). The ketene was diluted in pentane and stored under argon in the freezer. ^{1}H NMR: $\delta = 1.42$ (s, 3H), 1.45 (s, 6H), 2.23 (s, 3H), 2.26 (s, 3H), 7.05–7.15 (m, 3H); ^{13}C NMR: $\delta = 204.4$ (s), 145.0 (s), 136.3 (s), 134.4 (s), 129.5 (d), 127.5 (d), 123.6 (d), 37.2 (s), 36.7 (s), 29.0 (2q), 20.0 (q), 19.3 (q), 8.0 (q); MS: *m*/*z*: 202 (15) $[M]^+$, 187 (100), 159 (68), 148 (25), 144 (28), 129 (20), 128 (20), 119 (20), 115 (14), 105 (10), 91 (13).

(*Z*)-{[1-*tert*-Butyl-3-(3,4-dimethylphenyl)-2,3-dimethyl-1-butenyl]oxy}-trimethylsilane (16): A pentane solution of *t*BuLi (1.50 N, 3.06 mL, 4.59 mmol) was added to a solution of **13** (0.808 g, 4.00 mmol) in THF (15 mL) between −78 and −55 °C. After addition, the cooling bath was removed, and the temperature allowed to warm up to 25 °C. The reaction mixture containing the enolate was cooled at −45 °C and treated at once with TMSCl (0.564 g, 5.19 mmol). After 1 h at 25 °C, the reaction mixture was poured into a cold well-stirred mixture of saturated $NaHCO_3$ and pentane. The organic phase was washed (H_2O and saturated NaCl), dried (Na_2SO_4), filtered and evaporated. Bulb-to-bulb distillation (100–150 °C (bath temperature)/0.01 Torr) afforded **16** (1.20 g, 97% pure, 88%). ^{1}H NMR: $\delta = 0.01$ (s, 9H), 1.25 (s, 9H), 1.44 (s, 6H), 1.66 (s, 3H), 2.23 (s, 3H), 2.25 (s, 3H), 7.02 (2s, 2H), 7.04 (br s, 1H); ^{13}C NMR: $\delta = 153.3$ (s), 149.2 (s), 135.4 (s), 132.8 (s), 129.2 (d), 127.6 (d), 123.6 (d), 119.3 (s), 43.6 (s), 37.7 (s), 30.8 (3q), 30.3 (2q), 20.1 (q), 19.3 (q), 18.3 (q), 2.4 (3q); MS: *m*/*z*: 232 (19) $[M]^+$, 317 (9), 275 (26), 261 (18), 227 (15), 212 (16), 185 (19), 147 (33), 119 (14), 101 (17), 73 (100), 57 (25).

(−)-(*R*)-5-(3,4-Dimethylphenyl-2,2,4,5-tetramethylhexan-3-one [(*R*)-(−)-6]: In a first setup, BuLi (1.44 N in hexane, 1.34 mL, 1.93 mmol) was added between 25 and 40 °C to a stirred solution of (−)-**11** (0.600 g, 2.90 mmol) in THF (5 mL). In a second setup, *t*BuLi (1.50 N in pentane, 0.613 mL, 0.92 mmol) was added at −78 °C to a solution of **13** (161.6 mg, 0.80 mmol) in THF (7 mL). After addition, the cooling bath was removed, and the temperature was allowed to warm up to 25°. The reaction mixture containing the enolate was then cooled again at −45 °C and added in 45 min to the reaction mixture of setup 1 (containing a 2:1 mixture of (−)-**11**(Li)/(−)-**11**). At the end of the addition, the temperature was slowly allowed to reach −20 °C. Then TMSCl (0.378 g, 3.5 mmol) was added to trap possible non-protonated enolate (a sample quenched on saturated $NaHCO_3$/pentane did not show any trace of **16**). Once the reaction mixture had attained rt, it was poured into cold 5% HCl and extracted with Et_2O. The organic phase was washed (H_2O, saturated $NaHCO_3$ and saturated NaCl), dried (Na_2SO_4) and evaporated. Bulb-to-bulb distillation (100–150 °C (bath temperature)/0.01 Torr) gave (−)-**6** (0.182 g, 91% pure, 80%, 80% *ee*). A pure sample was obtained by chromatography (silica gel, cyclohexane/AcOEt 95:5). $[\alpha]_D^{20} = -97$ ($c = 0.16$ in $CHCl_3$). The *ee* was determined by chiral GC (CP-Chirasil-DEX CB; (−)-**6**: peak 1) and by Eu(hfbc)$_3$ ^{1}H NMR.

S-Phenyl 2,3-dimethyl 2-butenethioate (18): Oxalyl chloride (4.50 g, 3.04 mL, 35.4 mmol) was added at 5 °C to a solution of 2,3-dimethyl-2-butenoic acid[14] (2.53 g, 22.2 mmol) in CH_2Cl_2 (25 mL). The temperature was allowed to attain 20 °C and the mixture was then concentrated in vacuo. In another flask, a solution of thiophenol (2.32 g, 2.15 mL, 21.1 mmol) in THF (20 mL) was deprotonated at 0 °C by addition of of *n*BuLi (1.5 N in hexanes, 14.0 mL, 21 mmol). After 10 min at 20 °C, the thiophenate solution was added dropwise at 0–5 °C to the solution of crude acid chloride dissolved in THF (20 mL). After 15 min at 0 °C, the solution was poured into cold 5% NaOH and extracted twice with Et_2O. The organic layer was washed (H_2O, saturated NaCl), dried (Na_2SO_4) and concentrated. The residue was bulb-to-bulb distilled (115 °C (bath temperature)/ 0.01 Torr) to give thiol ester **18** (3.20 g, 74% based on thiophenol) as a pale yellow liquid. ^{1}H NMR: $\delta = 1.80$ (s, 3H), 1.96 (s, 3H), 2.00 (s, 3H), 7.30–7.53 (m, 5H); ^{13}C NMR: $\delta = 194.3$ (s), 140.0 (s), 134.8 (d), 129.2 (d + s), 129.1 (d), 128.5 (s), 22.8 (q), 22.0 (q), 16.0 (q); MS: *m*/*z*: 206 (1) $[M]^+$, 109 (10), 97 (100), 69 (26), 41 (16).

(−)-(*R*)-S-Phenyl 2,3-dimethyl-3-butenethioate [(−)-19]: A solution of thiol ester **18** (948 mg, 4.60 mmol) in THF (5 mL) was added at −100 °C to a solution of LDA (9.20 mmol) in THF (15 mL). After 45 min at −100 °C, a solution of (−)-isopropylephedrine ((−)-**11**) (2.48 g, 12.0 mmol) in THF (10 mL) was added dropwise over 20 min. Stirring was continued at −100 °C for 1 h and at −78 °C for 90 min. The mixture was then allowed to reach −10 °C, poured into 5% NaOH (removal of thiophenol) and extracted (Et_2O). The organic layer was washed (H_2O, 5% HCl, H_2O, saturated NaCl), dried (Na_2SO_4) and concentrated (**19**:**18** = 35:65[15]). Pure (−)-**19** (210 mg, 22%, 59% *ee*) and recovered **18** (436 mg, 46%),were obtained by chromatography (silica gel, pentane/ether 99:1). Almost quantitative recovery of (−)-**11** was achieved by basification of the acidic aqueous phase and extraction (Et_2O). $[\alpha]_D^{20} = -113$ ($c = 1.48$ in $CHCl_3$). The *ee* was determined by Eu(hfbc)$_3$ ^{1}H NMR spectra. ^{1}H NMR: $\delta = 1.35$ (d, $J = 7$ Hz, 3H), 1.81 (s, 3H), 3.47 (q, $J = 7$ Hz, 1H), 5.00 (split s, 1H), 5.03 (s, 1H), 7.39 ("s", 5H); ^{13}C NMR: $\delta = 198.9$ (s), 143.4 (s), 134.5 (d), 129.2 (d), 129.1 (d), 128.0 (s), 114.6 (t), 55.7 (d), 20.1 (q), 15.9 (q); MS: *m*/*z*: 206 (6) $[M]^+$, 178 (24), 110 (46), 109 (34), 97 (27), 69 (100), 41 (28).

(−)-(*R*)-2,3-Dimethyl-3-butenoic acid [(*R*)-(−)-14]:[11] A mixture of (−)-**19** (244 mg, 1.18 mmol, 59% *ee*) in EtOH (7 mL) and $LiOH \cdot H_2O$ (150 mg, 3.57 mmol) in H_2O (3 mL) was treated in four portions at 45 °C with 35% H_2O_2 (0.4 mL, 3.9 mmol). After complete introduction (20 min), stirring was continued for 30 min. The mixture was cooled to 20 °C, poured into a

5% NaOH solution and shaken with Et_2O. The aqueous layer was acidified with 5% HCl and extracted (Et_2O). The organic extracts were washed (H_2O, 5% $NaHSO_3$, saturated NaCl), dried (Na_2SO_4) and concentrated to give crude (−)-**14** (95 mg, 94% pure by GC, 67%, ca. 55% *ee*). $[\alpha]_D^{20} = -19.4$ ($c = 1.12$ in $CHCl_3$). The *ee* and absolute configuration were determined by comparison with the literature value ((−)-**14** (71% *ee*) $[\alpha]_D^{20} = -27$).[11]

(−)-(*R*)-2,2,4,5-Tetramethylhex-5-en-3-one [(*R*)-(−)-4]: A solution of (−)-**19** (100 mg, 0.48 mmol) in THF (5 mL) was treated at 0 °C with *t*BuLi (1.40 N in pentane, 208 μL, 0.29 mmol, 0.6 equiv (to minimize racemization). After 3 min, an aliquot was analyzed by chiral GC (Megadex 5) and shown to possess an *ee* of 59%. After a reaction time of 15 min, a test sample showed 53% *ee*. The major enantiomer was peak 2 on GC; thus (−)-**4** obtained in the protonation experiments possesses the (*R*)-configuration (see above). This clean, but incomplete reaction, was not purified.

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[7] Treatment of (*Z*)-**9** with MeLi (1.77 equiv), followed by protonation with (−)-**11** (1.94 equiv) at −45 °C afforded a 79:21 mixture of **10** and (*R*)-**4** (78% *ee*). Addition of the above amine-free enolate (*Z*)-**5** at −45 °C to a THF solution of (−)-**11**(Li) (2.5 equiv) and (−)-**11** (1.25 equiv), followed by silylation of unreacted enolate (TMSCl, 1.2 equiv), gave **10** and (*R*)-**4** (84% *ee*) in a 58:42 ratio and 6% of (*Z*)-**9**. When enolate (*Z*)-**5** was treated with diisopropylamine (1.0 equiv) prior to protonation with (−)-**11** (2.8 equiv) at −45 °C, **10** and (*R*)-**4** (85% *ee*) were obtained in a 64:36 ratio.

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