42. Syntheses of the Enantiomers of γ-Cyclogeranic Acid, γ-Cyclocitral, and γ-Damascone: Enantioselective Protonation of Enolates

by **Charles Fehr*** and **José Galindo**

Firmenich SA, Research Laboratories, P.O.B. 239, CH-1211 Geneva 8

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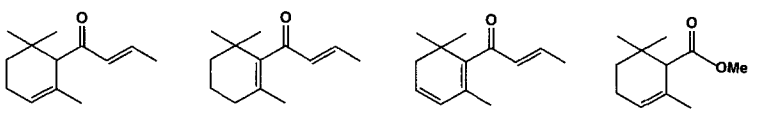
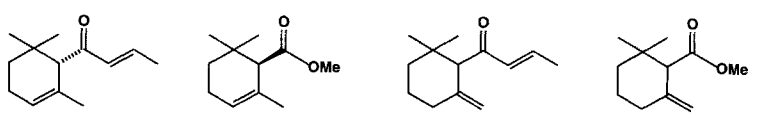
(*R*)- and (*S*)-γ-cyclogeranic acid ((*R*)- and (*S*)-**9**, resp.) were obtained by resolution of the racemate, and their absolute configurations determined by chemical correlation. The γ-acids (*R*)- and (*S*)-**9** were converted into (*R*)- and (*S*)-methyl γ-cyclogeranate ((*R*)- and (*S*)-**6**, resp.), and (*R*)- and (*S*)-γ-damascone ((*R*)- and (*S*)-**5**, resp.). A more direct entry to (*R*)- and (*S*)-**9** consisted in the enantioselective protonation of a thiol ester enolate with (−)- or (+)-*N*-isopropylephedrine ((−)- or (+)-**20**) and subsequent hydrolysis of the (*R*)- and (*S*)-*S*-phenyl γ-thiocyclogeranate ((*R*)- and (*S*)-**24**, resp.; 97% ee). The esters (*R*)- and (*S*)-**24** were also used as precursors of (*R*)- and (*S*)-γ-damascone ((*R*)- and (*S*)-**5**, resp.). Alternatively, (*S*)-**5** (75% ee) was obtained by enantioselective protonation of ketone enolate **29** with (−)-*N*-isopropylephedrine ((−)-**20**). Organoleptic evaluation demonstrated that the (*S*)-enantiomers of methyl γ-cyclogeranate and γ-damascone are markedly superior to their (*R*)-enantiomers.

Introduction. – Recently, γ-damascone (**5**) [1] and methyl γ-cyclogeranate (**6**) [1b] [2] have been recognized as original fragrance materials which can favorably complement the widely used α-damascone (**1**), β-damascone (**2**), β-damascenone (**3**), and methyl α-cyclogeranate (**4**) [3]. In addition, (*S*)-α-damascone ((*S*)-**1**) and (*R*)-methyl α-cyclogeranate ((*R*)-**4**) have been shown to possess far superior odor qualities than their enantiomers [3a] [4] [5]. We, therefore, became interested in the synthesis and olfactive evaluation of the enantiomers of both **5** and **6**, together with related esters.

The first part of this work describes the preparation of enantiomerically pure (*R*)- and (*S*)-γ-cyclogeranic acid ((*R*)- and (*S*)-**9**, resp.) by application of classical resolution techniques, the determination of the absolute configuration by chemical correlation, as well as the preparation and organoleptic evalution of the target molecules.



1 **2** **3** **4**

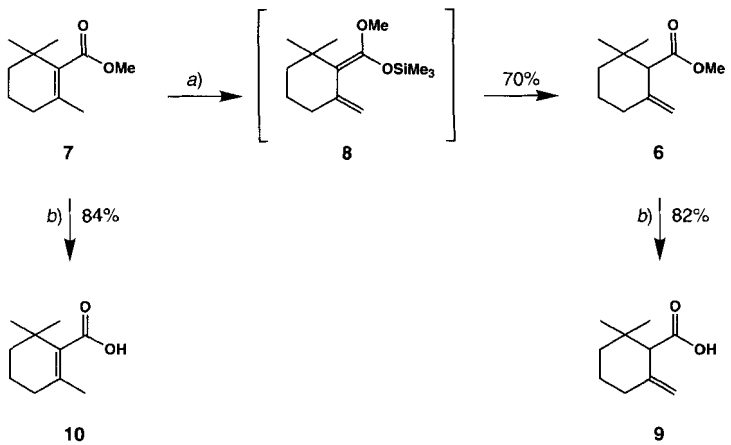


(*S*)-1 **(*R*)-4** **5** **6**

In the second part, the application of enantioselective protonation to directly synthesize the organoleptically preferred enantiomer of either γ-cyclogeranic acid (**9**) or γ-damascone (**5**) is reported.

Results. – *(R)- and (S)-γ-Cyclogeranic Acid* ((*R*)- and (*S*)-**9**, resp.) *by Resolution.* The racemic acid (*RS*)-**9**, previously obtained as a mixture of regioisomers [2b], was prepared in two steps starting from easily accessible methyl β-cyclogeranate (**7**) [6] (*Scheme 1*). Deprotonation of ester **7** with LDA (3 equiv.) followed by hydrolysis (aq. HCl), afforded mixtures of γ- and β-ester (**6**/**7** 72:28), which could easily be separated by fractional distillation. However, we found that deprotonation of **7** with BuLi and trapping of the enolate with Me_3SiCl, followed by hydrolytic desilylation of ketene acetal **8** [1a] with aq. HCl afforded pure **6** (70%) devoid of any β-isomer.

Scheme 1



a) BuLi (1.40 equiv.), THF, −10 → 15°; then Me_3SiCl (3.0 equiv.), −30 → 20°. *b*) PhSH (1.05 equiv.), KOH (1.05 equiv.), DMF, 100°.

As the saponification of cyclogeranates or 5-Me homologous esters requires very harsh reaction conditions (excess KOH, EtOH, sealed tube, 170°), under which extensive double-bond isomerization takes place [7], we sought a Me–O bond-cleavage reaction which could be performed under neutral conditions and found that KSPh in DMF at 100° smoothly effected the desired transformation of ester **6** to isomerically pure γ-acid **9** in excellent yield[1]). This mild and simple procedure (KSPh is prepared *in situ* from PhSH and KOH and the neutral by-product thioanisol is removed by extraction) was also successfully applied to the preparation of β-acid **10** from ester **7**[2]).

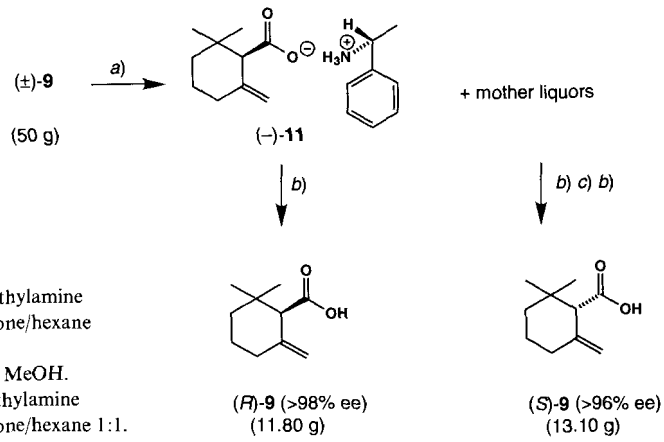
For the resolution of (±)-**9**, (*R*)- and (*S*)-1-phenylethylamine were used[3]). When (±)-**9** was treated with (+)-(*R*)-1-phenylethylamine in acetone/hexane 1:1, pure carboxylate

[1]) Similar conditions had been applied to the cleavage of phenacyl esters, but these conditions failed with methyl esters (see [8]).

[2]) For a further application of this reaction, see [9].

[3]) These amines were shown earlier to be efficient for the resolution of α-cyclogeranic acid (**14**, see [10]).

Scheme 2

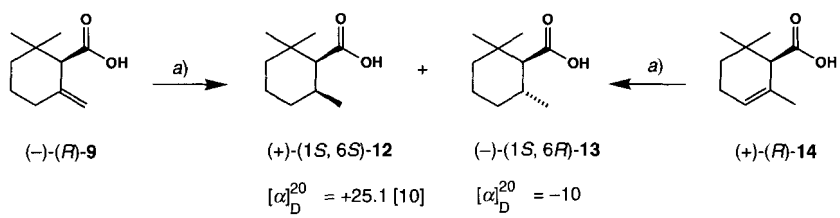


a) (+)-(*R*)-1-Phenylethylamine (0.75 equiv.), acetone/hexane 1:1, 25°.
b) 5% aq. HCl soln., MeOH.
c) (–)-(*S*)-1-Phenylethylamine (1.00 equiv.), acetone/hexane 1:1.

(+)-**11** could be obtained after three recrystallizations, and enantiomerically pure (*R*)-**9** was liberated by acid treatment (*Scheme 2*). Likewise, the mother liquors were acidified, and the recovered acid (*S*)-**9** (~ 30% ee) was treated with (–)-(*S*)-1-phenylethylamine to afford (*S*)-**9** of high enantiomeric purity (> 96% ee).

*Determination of the Absolute Configuration of (+)- and (–)-***9**. The assignment of the (*R*)-absolute configuration to (–)-**9** is based on its hydrogenation to the saturated acids (+)-(1*S*,6*S*)-**12** and (–)-(1*S*,6*R*)-**13** (*Scheme 3*). The absolute configuration of (+)-(1*S*,6*S*)-**12** had already been established by hydrogenation of (+)-(*R*)-α-cyclogeranic acid ((*R*)-**14**) [11]. The two independently prepared samples of (+)-**12** were shown to be identical by comparison of their optical rotation and their retention times on chiral GC[4]).

Scheme 3

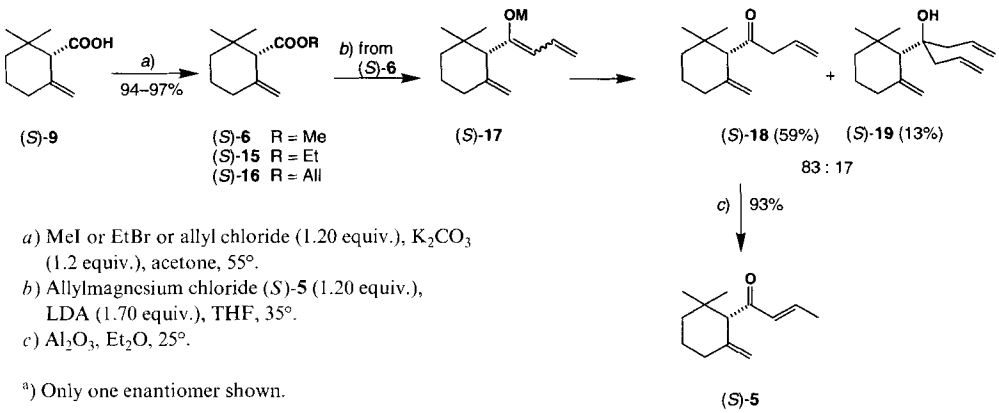


a) H_2, PtO_2, AcOH.

Preparation and Olfactive Evaluation of Enantiomers of γ-Cyclogeranates **6**, **15**, **16**, *and of γ-Damascone* (**5**). Using standard conditions, (*R*)- and (*S*)-**9** were converted into the methyl esters (*R*)- and (*S*)-**6**[4]), respectively, the ethyl esters (*R*)- and (*S*)-**15**[4]), respectively, and the allyl esters (*R*)- and (*S*)-**16**[4]), respectively (*Scheme 4*). The esters (*R*)- and (*S*)-**6**

[4]) Chiral GC: *Megadex 5* column (*Megadex Capillary Columns Laboratory*, Via Plinio 29, I-20025 Legnano, Italy).

Scheme 4[a])



a) MeI or EtBr or allyl chloride (1.20 equiv.), K_2CO_3 (1.2 equiv.), acetone, 55°.
b) Allylmagnesium chloride (*S*)-**5** (1.20 equiv.), LDA (1.70 equiv.), THF, 35°.
c) Al_2O_3, Et_2O, 25°.

[a]) Only one enantiomer shown.

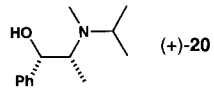
were also converted by mono-*Grignard* reaction [3] into the enantiomers of γ-damascone ((*R*)- and (*S*)-**5**)[4]), respectively, without racemization. Thus, using allylmagnesium chloride/LDA the incipient propenyl ketone (*S*)-**18** was rapidly regioselectively deprotonated to enolate (*S*)-**17** to largely suppress the nucleophilic attack of a second allylic species. After hydrolysis, ketone (*S*)-**18**[4]) and diadduct (*S*)-**19** were isolated in 59 and 13%, respectively. Treatment of propenyl ketone (*S*)-**18** (Al_2O_3, Et_2O) then afforded (*S*)-γ-damascone ((*S*)-**5**)[4]) in almost quantitative yield.

The organoleptic evaluation of the enantiomeric esters **6**, **15**, **16**, and of γ-damascone (**5**) revealed that the (*S*)-series possesses excellent fruity-floral, aromatic odor qualities, whereas the (*R*)-series shows a more common odor profile containing undesired notes (*Table 1*).

Table 1. *Organoleptic Evaluation of the Enantiomeric Esters* **6**, **15**, **16**, *and γ-Damascone* (**5**)

(*S*)-**6**	aromatic, damascone-like, thujone, fruity	(*R*)-**6**	more common than (*S*)-**6**, camphoraceous, corky, cellar
(*S*)-**15**	aromatic, fruity, damascone-like	(*R*)-**15**	less fruity, aromatic, rosmary, less powerful than (*S*)-**15**
(*S*)-**16**	green, floral, blackcurrant, aromatic, fruity, pleasant	(*R*)-**16**	more green, less blackcurrant, less floral, weaker than (*S*)-**16**
(*S*)-**5**	nice damascone character, camphoraceous	(*R*)-**5**	liquorice, damascone-like, camphoraceous, inferior to (*S*)-**5**

Syntheses of Enantiomers of γ-Cyclogeranic Acid (6) and of γ-Damascone (5) by Enantioselective Protonation of Enolates. – The remarkable odor qualities of esters (*S*)-**6**, (*S*)-**15**, and (*S*)-**16** compared to their enantiomers, together with the superiority of (*S*)-γ-damascone ((*S*)-**6** with respect to (*R*)-**6**), prompted us to consider a direct access to the desired enantiomers, based on the enantioselective protonation of enolates [4] [5] [12–14]. This reaction had already been employed as the key step in our syntheses of enantiomerically pure (*R*)- and (*S*)-α-damascone ((*R*)- and (*S*)-**1**, resp.) [4] and (*R*)- and (*S*)-α-cyclogeranic acid ((*R*)- and (*S*)-**14**, resp.) [5] [12], where the readily accessible (+)- or (−)-*N*-isopropylephedrine ((+)- or (−)-**20**, resp.) was used as the chiral proton

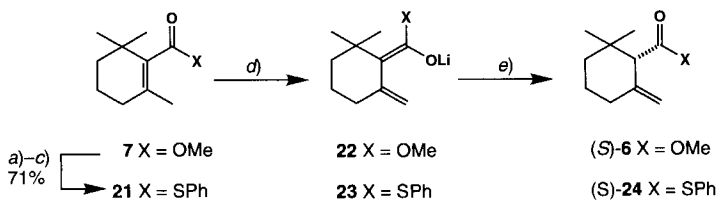


(+)-20

source[5]). The most recent development of this transformation involves a catalytic version in which 0.2 mol-equiv. of (+)- or (−)-**20** are used, together with an achiral protonating agent [14].

Enantioselective Protonation of Ester Enolate **22** *and Thioester Enolate* **23** (*Scheme 5*). Undoubtedly, the most direct access to (*S*)-**6** would be the enantioselective protonation of the corresponding enolate **22**. Therefore, this protonation was examined first, although we knew from a related study that insufficient structural differentiation of the

Scheme 5



a) See *Scheme 1*. *b*) $(COCl)_2$ (1.60 equiv.), CH_2Cl_2, 0 → 20°. *c*) PhSH (1.93 equiv.), BuLi (0.96 equiv.), THF, 0 → 15°. *d*) LDA (3.0 equiv.), THF, −78°. *e*) (+)-**20** (4.0 equiv.), THF, −100 → −10°.

Table 2. *Enantioselective Protonation of Enolates* **22** *and* **23**

Entry	Sub-strate	Reaction conditions (equiv.; °C (min))	**6**/**7** or **24**/**21**	% ee **6** or **24**	Yield [%] **24** + **21**	**24**
1	**7**	*1*) BuLi (1.5, −78 (165)) *2*) (−)-**20** (2.0; −100 (80) → −10 (30))	22:78	36 (*R*)	–	
2		*1*) LDA (3.0; −78 (180)) *2*) (+)-**20** (3.3; −100 (100) → −10 (30))	33:67	50 (*S*)[a])	–	
3		*1*) LDA (3.0; −78 (180)) *2*) aq. HCl (excess; −78 (180) (quenching))	72:28	–		
4	**21**	*1*) BuLi (2.0; −78(180)) *2*) (−)-**20** (2.7; −100 (80) → −10 (30))	43:57	96 (*R*)	81[b])	
5		*1*) LDA (3.0; −78 (165)) *2*) (−)-**20** (4.0; −100 (60) → −10 (30))	56:44	97 (*R*)[c])	84[d])	34[d])
6		*1*) LDA (3.0; −78 (165) *2*) (+)-**20** (4.0; −100 (60) → −10 (30))	53:47	96 (*S*)	86[b])	37[d])
7		*1*) LDA (1.5; −78 (210)) *2*) (+)-**20** (2.0; −100 (60) → −10 (30))	55:45	94 (*S*)	76[b])	–
8		*1*) LDA (1.5; −78 (210)) *2*) (+)-**20** (0.5; −100 (60)) *3*) $PhCH_2COCH_3$ (1.5; −100 (60) → −10 (30))	45:55	88 (*S*)	80[b])	–

[a]) Protonation at −50° gave 17% ee.
[b]) Bulb-to-bulb distillation (oven temp. 150°/0.01 Torr).
[c]) Use of enantiomerically impure (−)-**20** (50% ee) gave (*R*)-**24** with only 33% ee.
[d]) Column chromatography.

[5]) For very recent successes in this area, see [13].

enolate substituents in a methyl ester enolate (OLi *vs.* OMe) could appear to be responsible for low enantiodiscriminations [5] [12]. Indeed, deprotonation of ester **7** with BuLi and protonation of the resulting (*E*)-enolate **22** ((*E*)/(*Z*) 19:1) [1a] with (−)-**20** at −100° afforded γ-ester (*R*)-**6** with 36% ee (*Scheme 1* and *Table 2, Entry 1*). This protonation protocol not only exhibits a low enantioselectivity, but also a disappointingly low site selectivity (**6**/**7** 22:78). Using excess LDA as base, both the site selectivity (**6**/**7** 33:67) and the enantioselectivity (50% ee) of the enolate protonation could be slightly improved (*Entry 2*). In contrast, protonation of **22** with aqueous HCl afforded predominantly racemic ester **6** (**6**/**7** 72:28; *Entry 3*). In view of these disappointing, but not unexpected results, we next examined the protonation of **23**. Based on our previous work [5], we hoped that an optimal structural differentiation of the enolate substituents on C(1) (OLi *vs.* SPh) would ensure efficient enantiotopic recognition. In addition, the lower pK_a value of aromatic thioesters was expected to allow a slower and more selective protonation.

Accordingly, thioester **21** was prepared from β-cyclogeranic acid (**10**; *Scheme 1*) *via* the *in situ* formed acid chloride (*Scheme 5*). The deprotonation of **21** was effected with BuLi (*Entry 4*) or LDA (*Entry 5*) at −78°. Re-protonation of (*E*)-enolate **23** ((*E*)/(*Z*) ≥ 19:1)[6]) with excess (−)-**20** (−100 → −10°) gave (*R*)-**24** with excellent enantioselectivity (97% ee)[7]), regardless of the base used (BuLi or LDA). However, a better site selectivity (**24**/**21** *ca.* 55:45) was achieved with LDA, thus demonstrating that either $(i\text{-Pr})_2NH$ or excess LDA also participates in the protonation step. Likewise, the (*S*)-thioester (*S*)-**24** was obtained with 96% ee[7]) and 37% yield (*Entry 6*). Using only 1.5 equiv. of LDA, the deprotonation was slower, and the final yield slightly lower, possibly due to the relative instability of enolate **23**, but the protonation with (+)-**20** (2 equiv.) occurred with almost identical selectivity (94% ee; *Entry 7*). Finally, we have tested the protonation, using only 0.5 equiv. of (+)-**20**, followed by 1.5 equiv. of 1-phenylpropan-2-one [14] and were pleased to attain 88% ee (*Entry 8*).

*Thioesters (*R*)-***24*** and (*S*)-***24*** as Chiral Building Blocks.* Hydrolysis of (*R*)- and (*S*)-**24** to acids (*R*)- and (*S*)-**9** (95% ee), respectively, with less than 2% racemization could be achieved with LiOOH in aqueous EtOH (*Scheme 6*). This protocol is particularly useful for sterically hindered thioesters [5], where the application of more vigorous conditions leads to extensive racemization. $LiAlH_4$ reduction of (*R*)- and (*S*)-**24** afforded alcohols (*R*)- and (*S*)-**25**[8]), respectively (96–97% ee), and the hitherto unknown enantiomers of γ-cyclocitral ((*R*)- and (*S*)-**26**, respectively; 95–96% ee[4])[9])) were obtained by *Swern* oxidation. The direct conversion of (*R*)- and (*S*)-**24** into (*R*)- and (*S*)-**18**, respectively, and finally (*R*)- and (*S*)-γ-damascone ((*R*)- and (*S*)-**5**, resp.; 96–97% ee) parallels the aforementioned mono-*Grignard* reaction on methyl ester (*R*)- and (*S*)-**6**, respectively (*Scheme 4*). It is noteworthy that, even under these basic conditions, no racemization was detected.

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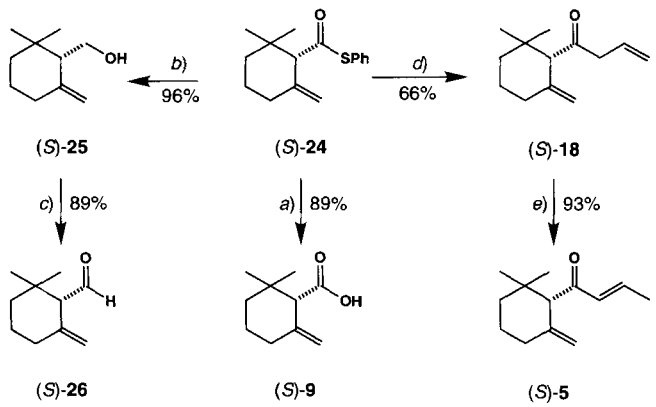
[6]) Quenching of enolate **23** with Me_3SiOTf (3 equiv.) at −78° gives essentially (*E*)-ketene thiol acetal (*ca.* 19:1). After distillation, the (*E*)/(*Z*) ratio is *ca.* 5:1 (GC and NOE experiments). Trapping of **23** with the less reactive Me_3SiCl gives an (*E*)/(*Z*) ratio of 5:1 (2:1 after distillation); ketene-acetal isomerizations have been recently reported [15]. As the enolate itself may undergo (*E*)/(*Z*)-isomerization [16], we recommend the use of the highly reactive Me_3SiOTf for a more accurate determination of the enolate geometry.

[7]) Determined by conversion into (*R*)- and (*S*)-**18**, respectively; see *Scheme 6*.

[8]) Also obtained by reduction of (*R*)- and (*S*)-**9**, respectively, with excess $LiAlH_4$. For *rac*-**25**, see [17] [26].

[9]) For *rac*-**26**, see [18].

Scheme 6[a])

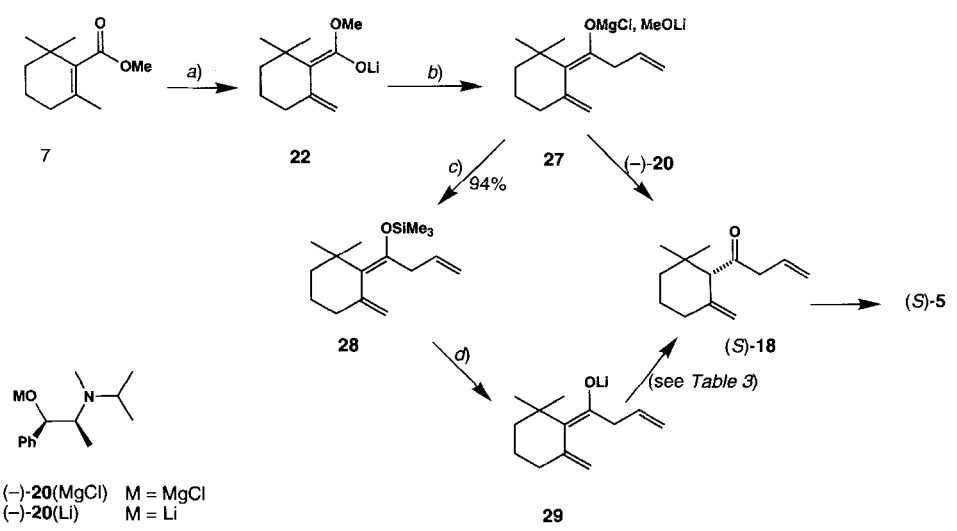


a) $LiOH \cdot H_2O$ (3.0 equiv.), H_2O_2 (3.30 equiv.), EtOH, H_2O, 45–50°. *b*) $LiAlH_4$ (1.05 equiv.), Et_2O, 25°. *c*) $(COCl)_2$ (1.50 equiv.), DMSO (2.16 equiv.), NEt_3 (4.50 equiv.), CH_2Cl_2, $-70° \rightarrow 0°$. *d*) Allylmagnesium chloride (1.20 equiv.), LDA (1.70 equiv.), THF, 35°. *e*) See *Scheme 4*.

[a]) Only (*S*)-enantiomers shown.

(R)- and (S)-γ-Damascone ((*R*)- and (*S*)-**5**, resp.) *by Enantioselective Protonation of Enolates* **27** *and* **29**. In 1988, we reported an unprecedentedly short synthesis of γ-damascone (**5**) [1a]. Methyl β-cyclogeranate (**7**) was deprotonated with BuLi, and the resultant enolate **22** was treated with allylmagnesium chloride to afford enolate **27** (*Scheme 7*).

Scheme 7



a) BuLi (1.20 equiv.), THF, $-78° \rightarrow 0°$. *b*) Allylmagnesium chloride (1.05 equiv.), THF, 35–45°. *c*) Me_3SiCl (3.0 equiv.), THF, $-50 \rightarrow 20°$. *d*) MeLi (0.90 equiv.), THF, 40°.

This enolate was trapped with Me_3SiCl to afford (*E*)-silyl enol ether **28** or hydrolyzed (→ **18**) and isomerized to **5**.

We have now studied the enantioselective protonation of enolates **27** and **29**, using (−)-**20** as chiral proton donor. When *in situ* formed enolate **27** was cooled at −78° and protonated with (−)-**20** (*Table 3, Entry 1*), (*S*)-**18** of low enantiomeric enrichment (25% ee) was obtained. As indicated by GC[4]), this reaction was slow and unselective at low temperature. We, therefore, next tested the protonation of **27** at 0°. To minimize the risk of double-bond isomerization and racemization, enolate **27** was added to excess (−)-**20** (*Entry 2*), thus minimizing side reactions between enolate and product ketone (*S*)-**18**. Under these conditions, (*S*)-**18** was favored over (*R*)-**18** in a 3:1 ratio, but base-catalyzed double-bond isomerization and racemization (due to the presence of (−)-**20**(MgCl)) could not be completely avoided.

Table 3. *Enantioselective Protonation of Enolates* **27** *and* **29**

Entry	Enolate	Equiv. (−)-**20**	Equiv. (−)-**20** (Li)	Add. mode	THF+ cosolvent	*T* [°C]	*t* [min]	% ee (*S*)-**18**[a]) after 25	50	75	100% addition	Yield [%]
1	**27**	2.0	0.4[b])	norm.	hexane	−78 → 0	60				25	
2		2.5	0.2[b])	inv.	hexane	0	60	–	51	–	49[c]) (44)[d])	
3	**29**	1.05	0.15	norm.	Et_2O/hexane	−50	60	8	39	63	62	
4		1.05	0.15	inv.	Et_2O/hexane	−50	60	26	35	43	49	
5		1.0	1.0	inv.	Et_2O/hexane	−50	60	–	65	–	68[e])[f])	
6		1.0	2.0	inv.	Et_2O/hexane	−50	60	–	69	–	70[g])	
7		1.0	2.0	inv.	–	−50	60	–	75	–	75[h])[i])[j])	87

[a]) Contains minor amounts of isomeric ketones. [b]) Contains small amounts of (−)-**20**(MgCl), due to excess allylmagnesium chloride. [c]) At −30°: 37% ee. [d]) 30 min after complete addition. [e]) At −72°: 44% ee. [f]) Same result in THF as only solvent. [g]) Use of enantiomerically impure chiral reagent (50% ee) gave (*S*)-**18** with 50% ee. [h]) At −30°: 73% ee. [i]) Approximately same result, when 1:1 enolate-alkoxide complex **29**/(−)-**20**(Li) was added to (−)-**20** or (−)-**20**/(−)-**20**(*Li*) 1:1, but formation of *β*-damascone (**2**) in trace amounts (*ca.* 5%). [j]) Use of enantiomerically impure chiral reagent (30% ee) gave (*S*)-**18** with 32% ee.

To test the reactivity of Mg-free lithium enolate **29**, the configurationally pure (*E*)-silyl enol ether **28** was treated with MeLi (1.15 equiv.) in Et_2O/THF at 40° for 10 min, the solution was then cooled at −50° and protonated by continuous addition of freshly distilled (−)-**20**[10]) (1.2 equiv.) in THF during 1 h (*Entry 3*). After *ca.* 25, 50, 75, and 100% addition of amino alcohol (−)-**20**, samples of the reaction were hydrolyzed (aq. HCl) and the ee's of (*S*)-**18** determined by GC[4]) (8, 39, 63, and 62% ee, resp.). Interestingly, protonation had barely started after 25% addition (possibly due to excess MeLi) and was complete after 75% addition of (−)-**20**. Presumably, protonated (*S*)-**18** makes available another proton (in the side chain) – formally for reprotonation of (−)-**20**(Li) – thus rendering the process sub-stoichiometric in (−)-**20** [14].

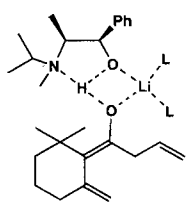
Addition of enolate **29** to a THF soln. of (−)-**20** at −50° (*Entry 4*) was also very instructive, as the measured ee's constantly increased during the introduction of the

[10]) In this case, we observed that consistently lower ee's were attained with aged samples of (−)-**20**, although they were shown to be pure by GC (presence of H_2O or O_2?).

enolate (25, 50, 75, 100% addition: 26, 35, 43, 49% ee, resp.). It should be specified that, prior to sampling, the addition was interrupted for 3 min to avoid eventual accumulation of enolate. Therefore, it can be calculated that the second 50% of added enolate was protonated with *ca.* 63% ee. This remarkable result seems to indicate that the lithium alkoxide (−)-**20**(Li) formed during the proton transfer also participates in the process. Indeed, when the protonation was performed with a 1:1 or 1:2 mixture of (−)-**20** and (−)-**20**(Li), enantioselectivities of 68 and 70% ee, respectively, were observed, values which only slightly fluctuated during enolate introduction (*Entries 5* and *6*). Finally, when THF was used as the sole solvent, a maximum of 75% ee[11]) was attained (*Entry 7*).

Discussion. – Whereas the highly enantioselective protonation of thioester enolate **23** (97% ee) parallels our recently published results on structurally related thioester enolates [5], the protonations of ketone enolates **27** and **29** differ from the α-damascone case [4] [14] in that they are much more sensitive to variation of reaction parameters such as mode of addition, stoichiometry of lithium alkoxide (−)-**20**(Li), reaction temperature, and choice of solvent. In addition, the enantiofacial discrimination of 7:1, although appreciable, is markedly inferior to the 95% ee obtained in the enantioselective synthesis of (*S*)-α-damascone ((*S*)-**1**). To verify if enolate **29** undergoes (*E*)/(*Z*)-isomerization under the reaction conditions, we silylated (Me_3SiOTf) the enolate after partial protonation. Unchanged (*E*)-enol ether **28** was recovered, thus indicating the configurational stability of enolate **29**.

So far, no case of enantioselective protonation of (*E*)/(*Z*)-isomeric enolates is known, but interestingly, protonation of thioester enolate **23** and ketone enolate **29**, which possess opposite enolate geometries, give rise to inverse asymmetric induction. A correlation between enolate configuration and enantiotopicity can be extended to the α-damascone [4] [14] and α-cyclogeranate [5] [12] series.



30

As discussed earlier [3a] [5] [12] [14], we suggest that a chiral complex of type **30** between lithium enolate **29** (or **23**) and chiral amino alcohol (−)-**20** is formed, and that the N-atom of (−)-**20** participates in the stereoinducing proton transfer. In view of the nonlinear relationship between the enantiomeric purity of chiral reagent and the enantiomeric excess of the reaction product [19] (*Table 2, Footnote d; Table 3, Footnotes g* and *j*), complex **30** is probably further aggregated with chiral ligands.

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[11]) Use of excess MeLi had a deleterious effect on enantioselectivities. When excess MeLi was quenched with Me_3SiCl prior to protonation, the ee could be improved to 80%. It remains to be clarified, whether the *in situ* formed LiCl influences the protonation.

We are presently extending our methodology to other, structurally diverse enolates, which we hope will enable us to give a rationale for the observed enantiofacial discrimination.

We thank Dr. *P.-A. Blanc, Firmenich SA,* for the organoleptic evaluation and Mr. *W. Thommen* and Mr. *R. Brauchli, Firmenich SA,* for the NOE experiments.

Experimental Part

General. TLC: silica-gel *F-254* plates (*Merck*; when not otherwise stated); 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 × 0.319 mm), *DB-WAX 15W* (15 m × 0.32 mm); chiral cap. column (16 m × 0.25 mm): *Megadex 5* column (*Megadex Capillary Columns Laboratory*, Via Plinio 29, I–20025 Legnano, Italy), carrier gas He at 0.63 bar. Optical rotations: 1-ml cell, *Perkin-Elmer-241* polarimeter. ^{1}H- and ^{13}C-NMR: *Bruker WH 360* (360 MHz). MS: *Finnigan 1020* automated GC/MS instrument, electron energy 70 eV.

(RS)-Methyl γ-Cyclogeranate (= *(RS)-Methyl 2,2-Dimethyl-6-methylidenecyclohexane-1-carboxylate*; **6**). A mechanically stirred soln. of *methyl 2,6,6-trimethylcyclohex-1-ene-1-carboxylate* (**7**) (80.0 g, 0.440 mol) in THF (640 ml) was treated under cooling (−10–0°) with 1.5M BuLi in hexane (411 ml, 0.617 mol). After addition (30 min), the soln. was stirred at 15–17° for 10 min, cooled to −30°, and Me_3SiCl (143.4 g, 1.32 mol) was introduced at such a rate that the temp. did not exceed 10° (*ca.* 30 min). The soln. was warmed at 20° (10 min) and poured into 5% aq. HCl soln. (1 l). After stirring for 10 min, the mixture was extracted (Et_2O), the org. phase washed with sat. aq. $NaHCO_3$ soln. and sat. aq. NaCl soln., evaporated, and distilled (50°/0.05 Torr) to afford a first fraction of pure **6** (51.04 g, 64%) and a second, less pure fraction of **6** (5.86 g, 88% pure by GC, 6%)[12]).

(RS)-γ-Cyclogeranic Acid (= *(RS)-2,2-Dimethyl-6-methylidenecyclohexane-1-carboxylic Acid*; **9**). A mechanically stirred suspension of **6** (50.0 g, 0.275 mol), PhSH (31.63 g, 0.288 mol), and KOH (16.42 g, 0.288 mol) in DMF (200 ml) was heated at 100° and the resulting soln. stirred for 8 h. The cooled mixture was poured into 5% aq. NaOH soln. and extracted twice with Et_2O. After washing the org. extracts with H_2O, the combined basic aq. phases were acidified with conc. HCl, extracted twice with Et_2O, washed with H_2O and sat. aq. NaCl soln., dried (Na_2SO_4), and concentrated. The residue was heated at 100°/10 Torr for 4 h to remove the excess PhSH[13]) and distilled (100°/0.05 Torr) to afford **9** (37.93 g, 82%).

β-Cyclogeranic Acid (= *2,6,6-Trimethylcyclohexane-1-carboxylic Acid*; **10**). Proceeding as above (see **9**), the reaction of **7** (100.0 g, 0.549 mol), PhSH (63.35 g, 0.576 mol), KOH (32.30, 0.576 mol), and DMF (400 ml) afforded **10** (77.47 g, 84%).

(R)-γ-Cyclogeranic Acid ((*R*)-**9**) *by Resolution.* In a 500-ml 3-necked flask containing a soln. of (±)-**9** (50.0 g, 0.297 mol) in acetone/hexane 1:1 (320 ml) was added dropwise, under slow mechanical stirring, (+)-(*R*)-1-phenylethylamine (*Fluka*; $[\alpha]_D^{20} = +30\pm2$; 27.0 g, 0.224 mol) at 25–30° (*ca.* 45 min). The mixture was stirred for 30 min and the white cake filtered to give (−)-**11** (56.8 g, *ca.* 30% ee). Two crystallizations of this ammonium salt with acetone/toluene 1:1 (*ca.* 640 ml) afforded pure (−)-**11** (22.6 g). M.p. 159–160°. $[\alpha]_D^{20} = -64.2$ (MeOH, $c = 0.013$). The combined mother liquors were concentrated and used for the preparation of (*S*)-**9** (see below).

A soln. of (−)-**11** (22.0 g, 0.076 mol) in MeOH (240 ml) was acidified with a 5% aq. HCl soln. (*ca.* 67 ml). After 30 min, the MeOH was evaporated at 10 Torr and the residue dissolved in Et_2O. The org. phase was washed with H_2O and sat. aq. NaCl soln., dried (Na_2SO_4), and concentrated to give (*R*)-**9** (11.80 g, > 98% ee; 47% from (±)-**9**). M.p. 62–63°. $[\alpha]_D^{20} = -125$ ($CHCl_3$, $c = 0.037$).

The mother liquors (see above) were treated accordingly to afford (*S*)-**9** (36.6 g, ~ 30% ee) as a brown solid. For further purification, the solid was dissolved in Et_2O, shaken with 5% aq. NaOH soln., and the aq. phase acidified with conc. HCl and extracted (Et_2O) in the usual manner to afford white crystals of (*S*)-**9** (36.0 g, 0.214 mol, *ca.* 30% ee).

(S)-γ-Cyclogeranic Acid ((*S*)-**9**) *by Resolution.* Proceeding as above (see (*R*)-**9**), the reaction of (*S*)-**9** (36.0 g, 0.214 mol, *ca.* 30% ee) and (−)-(*S*)-1-phenylethylamine (*Fluka*, $[\alpha]_D^{20} = -40\pm5$; 25.90 g, 0.214 mol) afforded after two crystallizations (+)-**11** (22.90 g). M.p. 159–160°. $[\alpha]_D^{20} = +62.5$ (MeOH, $c = 0.014$). Acidic treatment of (+)-**11** gave (*S*)-**9** (13.1 g, > 96% ee; 52% from (±)-**9**). M.p. 61–62°. $[\alpha]_D^{20} = +122$ ($CHCl_3$, $c = 0.034$).

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[12]) For anal. data, see [1b] [2].

[13]) Alternatively, crude **6** can be directly purified by column chromatography.

(+)-(1S,6S)-2,2,6-Trimethylcyclohexane-1-carboxylic Acid ((+)-(1*S*,6*S*)-**12**) *and (−)-(1S,6R)-2,2,6-Trimethylcyclohexane-1-carboxylic Acid* ((−)-(1*S*,6*R*)-**13**). A soln. of (*R*)-**9** (0.20 g, 1.2 mmol) in AcOH (10 ml) was hydrogenated using PtO_2 (0.10 g). After uptake of 30 ml of H_2 (1 h), the mixture was filtered (*Hyflo*) and extracted (H_2O/pentane). The org. phase was washed twice with water and sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated, giving (+)-**12** and (−)-**13** (*ca.* 55:45; 0.173 g, 87%). Chromatography (SiO_2, cyclohexane/AcOEt 95:5) afforded pure (+)-**12** (42 mg, > 98% ee[4])), $[\alpha]_D^{20} = +25.1$ ($CHCl_3$, $c = 0.021$; [11]: +25.1) and (−)-**13** (18 mg), $[\alpha]_D^{20} = -10$ ($CHCl_3$, $c = 0.009$)[14]).

(R)-Methyl γ-Cyclogeranate ((*R*)-**6**). A soln. of (*R*)-**9** (1.20 g, 7.1 mmol) and MeI (1.22 g, 8.6 mmol) in acetone (35 ml) was heated at reflux on K_2CO_3 (1.18 g, 8.6 mmol) for 90 min. The mixture was filtered and the solvent evaporated. After extraction of the oil (Et_2O/H_2O), the org. extracts were washed with 1% aq. NaOH soln., H_2O and sat. aq. NaCl soln., dried (Na_2SO_4), evaporated, and purified by bulb-to-bulb distillation (50°/0.05 Torr) to afford (−)-**6** (1.23 g, 95%; > 98% ee). $[\alpha]_D^{20} = -104$ ($CHCl_3$, $c = 0.045$).

(S)-Methyl γ-Cyclogeranate ((*S*)-**6**) was obtained accordingly from (*S*)-**9**. > 96% ee. $[\alpha]_D^{20} = +104$ ($CHCl_3$, $c = 0.036$).

(R)-Ethyl γ-Cyclogeranate (= *(R)-Ethyl 2,2-Dimethyl-6-methylidenecyclohexane-1-carboxylate*; (*R*)-**15**). Proceeding as above (see (*R*)-**6**), the reaction of (*R*)-**9** (0.50 g, 3.0 mmol), EtBr (0.392 g, 3.6 mmol), K_2CO_3 (0.497 g, 3.6 mmol), and acetone (25 ml) gave, after refluxing for 3 h and bulb-to-bulb distillation, (*R*)-**15** (0.553 g, 94%; > 98% ee). $[\alpha]_D^{20} = -93$ ($CHCl_3$, $c = 0.026$)[15]).

(S)-Ethyl γ-Cyclogeranate ((*S*)-**15**) was obtained accordingly from (*S*)-**9**. > 96% ee. $[\alpha]_D^{20} = +90$ ($CHCl_3$, $c = 0.039$).

(R)-Allyl γ-Cyclogeranate (= *(R)-Allyl 2,2-Dimethyl-6-methylidenecyclohexane-1-carboxylate*; (*R*)-**16**). Proceeding as above (see (*R*)-**6**), the reaction of (*R*)-**9** (0.50 g, 3.0 mmol), allyl bromide (0.432 g, 3.6 mmol), K_2CO_3 (0.492 g, 3.6 mmol), and acetone (20 ml) gave, after refluxing for 2 h and bulb-to-bulb distillation, (*R*)-**16** (0.608 g, 97%; > 98% ee). $[\alpha]_D^{20} = -92$ ($CHCl_3$, $c = 0.041$).

(S)-Allyl γ-Cyclogeranate ((*S*)-**16**) was obtained accordingly from (*S*)-**9**. > 96% ee. $[\alpha]_D^{20} = +87$ ($CHCl_3$, $c = 0.043$).

(S)-γ-Damascone (= *(E)-1-[(S)-2,2-Dimethyl-6-methylidenecyclohexyl]but-2-en-1-one* (*S*)-**5**). A soln. of 1.9M allylmagnesium chloride in THF (6.40 ml, 12.2 mmol) was rapidly added to a cold soln. of LDA (18.7 mmol; prepared from 2.4M BuLi in hexane and $(i\text{-}Pr)_2NH$) in THF (25 ml). The mixture was immediately heated at 35°, and a soln. of (*S*)-**6** (2.0 g, 11.0 mmol) in THF (5 ml) was added (5 min), the temp. being maintained at 35–40°. After stirring for 45 min at 35°, the mixture was poured into a vigorously stirred 5% aq. HCl soln. and extracted twice with Et_2O. The org. extracts (containing (*S*)-**5**, (*S*)-**18**, and (*S*)-**19** (**5** + **18**/**19** 83:17)) were washed with H_2O, sat. aq. $NaHCO_3$ soln. and sat. aq. NaCl soln., dried (Na_2SO_4), evaporated, and purified by bulb-to-bulb distillation (100°/4.5 Torr) to afford (*S*)-**5** + (*S*)-**18** (1.34 g, 93% pure by GC, 59%), and (*S*)-**19** (0.42 g, 83% pure by GC). The ketone fraction (*S*)-**5** + (*S*)-**18** was dissolved in Et_2O (50 ml) and isomerized by stirring 1 h at 25° over neutral Al_2O_3 (5.0 g). The mixture was filtered, evaporated, and purified by bulb-to-bulb distillation (100°/4.5 Torr) to give (*S*)-**5** (1.15 g containing *ca.* 7% of (*Z*)-isomer; 55%; > 96% ee). (*Z*)-Isomer-free (*S*)-**5** (> 96% ee), $[\alpha]_D^{20} = +259$, was obtained by FC (SiO_2, cyclohexane/AcOEt 98:2).

(R)-γ-Damascone ((*R*)-**5**) was obtained accordingly from (*R*)-**6**. > 98% ee. $[\alpha]_D^{20} = -267$ ($CHCl_3$, $c = 0.020$).

Phenyl β-Cyclothiogeranate (= *S-Phenyl 2,6,6-Trimethylcyclohex-1-ene-1-carbothioate* (**21**)). Oxalyl chloride (8.45 g, 66.5 mmol) was added (20 min), under N_2, to an ice-cooled soln. of **10** (7.00 g, 41.7 mmol) in CH_2Cl_2 (70 ml). The temp. was allowed to attain 20° and the mixture concentrated under vacuum (*ca.* 10 Torr[16])). In a second flask, a soln. of PhSH (8.87 g, 80.7 mmol) in THF (40 ml) was treated at 0–10° with 1.4M BuLi in hexane (28.6 ml, 40.0 mmol). After 10 min at 25°, this soln. was added dropwise (30 min) at 0–5° to the soln. of the crude acyl chloride in THF (100 ml). After complete addition, the mixture was stirred at 15° for 10 min, and then poured into a cold 5% aq. NaOH soln. and extracted twice with Et_2O. The org. extracts were washed with H_2O and sat. aq. NaCl soln., dried (Na_2SO_4), evaporated, and purified by bulb-to-bulb distillation (120–160°/0.01 Torr) to afford **21** as a pale yellow oil (9.50 g, 84%[17]); ≥ 96% pure by GC). ^{1}H-NMR: 1.18 (*s*, 6H); 1.49 (*m*, 2H); 1.68 (*m*, 2H); 1.83 (*s*, 3H); 2.04 (*t*, *J* = 6.5, 2H); 7.43 (*m*, 5H). ^{13}C-NMR (360 MHz): 195.7 (*s*); 141.4 (*s*); 134.3 (2*d*); 133.7 (*s*); 129.2

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[14]) For (±)-**13**, see [11].

[15]) For (±)-**15**, see [2a].

[16]) Water should be rigorously excluded. Overheating (without vacuum) leads to substantial amounts of isomeric α-thioester.

[17]) Contains traces of Ph_2S_2 (*ca.* 2%).

(3*d*); 128.8 (*s*); 38.7 (*t*); 33.4 (*s*); 31.5 (*t*); 28.8 (2*q*); 21.4 (*q*); 18.7 (*t*). MS: 152 (12), 151 (100), 123 (28), 109 (12), 81 (43), 79 (12), 41 (12).

(S)-Phenyl γ-Cyclothiogeranate (= *(S)*-S-*Phenyl 2,2-Dimethyl-6-methylidenecyclohexane-1-carbothioate*; (*S*)-**24**). A soln. of **21** (8.00 g, 30.8 mmol) in THF (15 ml) was added dropwise (30 min) at −78° to a mechanically stirred soln. of LDA (94.2 mmol; prepared from 1.4M BuLi in hexane and (i-Pr)$_2$NH) in THF (200 ml). After stirring at −78° for 165 min, the mixture was treated dropwise (45 min) below −100° (Et_2O/N_2 bath) with a soln. of (+)-**20** (25.40 g, 122.9 mmol) in THF (25 ml). The temp. was maintained between −105 and −100° for 1 h, and then allowed slowly (20 min) to warm up to −80°. Finally, the temp. was allowed to warm up to −10°, and the mixture was poured into cold 5% aq. NaOH soln. and extracted with Et_2O. The org. phase was washed with H_2O, 5% aq. HCl soln., H_2O, sat. aq. $NaHCO_3$ soln., and sat. aq. NaCl soln., dried (Na_2SO_4), evaporated, and purified by bulb-to-bulb distillation (oven temp. 150°/0.01 Torr) furnishing a 53:47 mixture of (*S*)-**24** and **21** (7.14 g; GC: 96% pure; 86%). FC (SiO_2, 40–60 μ, 300 g; cyclohexane/AcOEt 98:2) afforded (*S*)-**24** (2.96 g, 37%; ≥ 96% ee[7]). $[\alpha]_D^{20} = +261$ ($CHCl_3$, $c = 0.035$) and a mixture of (*S*)-**24**/**21** (19:81; 3.89 g).

The combined acidic aq. phase was basified (10% aq. KOH soln.), extracted (Et_2O), and distilled to afford recovered (+)-**20** (24.90 g, 98%).

(R)-Phenyl γ-cyclothiogeranate ((*R*)-**24**) was obtained accordingly when (−)-**20** was used. (≥ 97% ee[7]). $[\alpha]_D^{20} = -264$ ($CHCl_3$, $c = 0.030$). ^{1}H-NMR (360 MHz): 0.96 (*s*, 3 H); 1.08 (*s*, 3 H); 1.23 (*dt*, $J = 13, 4, 1$ H); 1.52 (*m*, 1 H); 1.62 (*m*, 1 H); 1.87 (*d*, dist. *t*, $J \approx 4, 12, 1$ H); 2.16 (*dt*, $J = 14, 4, 1$ H); 2.33 (*m*, 1 H); 3.15 (*s*, 1 H); 4.87 (*s*, 1 H); 4.94 (*s*, 1 H); 7.38 (*s*, 5 H). ^{13}C-NMR (360 MHz): 196.5 (*s*); 144.0 (*s*); 139.4 (2*d*); 129.2 (*d*); 129.1 (2*d*); 128.6 (*s*); 112.8 (*t*); 68.4 (*d*); 35.8 (*s*); 35.5 (*t*); 31.8 (*t*); 27.3 (*q*); 27.2 (*q*); 22.6 (*t*). MS: 260 (1, $M^{+\cdot}$); 232 (5), 151 (16), 123 (100), 109 (22), 81 (47), 67 (15), 41 (16).

(S)-γ-Cyclogeranic Acid ((*S*)-**9**) *from (S)*-**24**. A mechanically stirred mixture of (*S*)-**24** (1.50 g, 5.8 mmol) in EtOH (36 ml) and LiOH · H_2O (0.727 g, 17.3 mmol) in H_2O (14.1 ml) was treated at 45–50° with 30% aq. H_2O_2 soln. (1.95 ml, *ca.* 19.0 mmol) as follows: the reaction was initiated by adding 0.3 ml, and after 10 min the remainder was added portionwise (11 × 0.150 ml) in 5-min intervals. The mixture was then cooled, poured into 5% aq. NaOH soln. and extracted with Et_2O. After washing the org. extracts with H_2O, the combined basic aq. phases were acidified with conc. HCl and extracted twice with Et_2O. These org. extracts were washed with 5% aq. $NaHSO_3$ soln., H_2O, and sat. aq. NaCl soln., dried (Na_2SO_4), evaporated, and purified by bulb-to-bulb distillation (100–150°/0.01 Torr) to afford (*S*)-**9** (0.884 g, 98% pure by GC[18]), 89%; ≥ 94% ee).

(R)-γ-Cyclogeranic acid ((*R*)-**9**; ≥ 95% ee) was obtained accordingly from (*R*)-**24** (≥ 97% ee).

(S)-γ-Cyclogeraniol (= *(S)-2,2-Dimethyl-6-methylidenecyclohexane-1-methanol*; (*S*)-**25**). A soln. of (*S*)-**24**[19]) (0.770 g, 3.00 mmol) in Et_2O (5 ml) was added dropwise at 25° to a stirred suspension of $LiAlH_4$ (0.120 g, 3.16 mmol) in Et_2O (25 ml). After stirring for 1 h, the mixture was cooled at 0°, and then carefully hydrolyzed successively with H_2O (0.12 ml), 5% aq. NaOH soln. (0.240 ml), and H_2O (0.360 ml). After filtration of the white cake, the org. phase was washed with 5% aq. NaOH soln., H_2O, and sat. aq. NaCl soln., dried (Na_2SO_4), evaporated, and purified by bulb-to-bulb distillation (100–120°/*ca.* 4 Torr) to afford (*S*)-**25** (0.444 g, 96%, ≥ 96% ee[20]). $[\alpha]_D^{20} = +24.5$ ($CHCl_3$, $c = 0.030$).

(R)-γ-Cyclogeraniol ((*R*)-**25**) was obtained accordingly. ≥ 97% ee. $[\alpha]_D^{20} = -25.0$ ($CHCl_3$, $c = 0.017$).

(S)-γ-Cyclocitral (= *(S)-2,2-Dimethyl-6-methylidenecyclohexane-1-carbaldehyde*; (*S*)-**26**). To a soln. of oxalyl chloride (0.953 g, 7.50 mmol) in CH_2Cl_2 (15 ml) was added at −78° a soln. of DMSO (0.839 g, 10.80 mmol) in CH_2Cl_2 (3 ml). After stirring for 10 min, a soln. of (*S*)-**25** (0.770 g, 5.00 mmol) in CH_2Cl_2 (3 ml) was introduced at such a rate that the temp. did not exceed −65°. After complete addition, the white suspension was stirred during 15 min, and then treated dropwise with NEt_3 (2.27 g, 22.5 mmol). The temp. was then allowed to warm up at 0°, and the mixture poured into H_2O and extracted with pentane. The org. phase was washed with sat. aq. NaCl soln., dried (Na_2SO_4), and concentrated. The crude product was dissolved in Et_2O (*ca.* 30 ml) and vigorously stirred over sat. aq. $NaHCO_3$ soln. (*ca.* 40 ml) for 15 h. The org. phase was then washed with sat. aq. NaCl soln., dried (Na_2SO_4), and concentrated. Bulb-to-bulb distillation (100°/4 Torr) afforded (*S*)-**26** (0.676 g, 89%; > 96% ee[4])).

(R)-γ-Cyclocitral ((*R*)-**26**) was obtained accordingly from (*R*)-**25**. > 97% ee[4]). $[\alpha]_D^{20} = -165$ ($CHCl_3$, $c = 0.036$).

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[18]) Contains 1–2% of **10**.

[19]) We have now found that (*S*)-**24** is reduced much faster than **21**. This allows to use the product mixture (*S*)-**24**/**21**.

[20]) Determined by conversion into (*S*)- and (*R*)-**26**, resp.

(S)-1-(2,2-Dimethyl-6-methylidenecyclohexyl)but-3-en-1-one ((*S*)-**18**). A soln. of (*S*)-**24** (0.390 g, 150 mmol) in THF (2 ml) was added to a heated (35°) mixture of 1.9M allylmagnesium chloride in THF (0.95 ml, 1.80 mmol) and a soln. of LDA (2.50 mmol) in THF (10 ml) as described above for (*S*)-**5**. After 45 min, the mixture was poured into a vigorously stirred 5% aq. HCl soln. and extracted twice with Et_2O. The org. extracts containing (*S*)-**18** as a mixture of double-bond isomers and **19**, ((*S*)-**18**/**19** 84:16) were washed with H_2O, 2% aq. NaOH soln., H_2O, and sat. aq. NaCl soln., dried (Na_2SO_4), and purified by bulb-to-bulb distillation (100°/4.5 Torr) to give (*S*)-**18** (0.202 g, 94% pure by GC, 66%, > 96% ee[4]))[21]).

(R)-**18** of ≥ 97% ee[4]) was obtained accordingly from (*R*)-**24**. (*S*)- and (*R*)-**18** were isomerized into (*S*)-(*R*)-**5**, resp., as described above.

1,1-Dimethyl-3-methylidene-2-[(E)-1-(trimethylsilyloxy)but-3-enylidene]cyclohexane (**28**). A mechanically stirred soln. of **7** (12.00 g, 0.066 mol) in THF (150 ml) was deprotonated at −78° by slow addition of 1.4M BuLi in hexane (56.5 ml, 0.079 mol). After 30 min, the cooling bath was removed and, once the temp. had reached 0°, the mixture was heated with a water bath (bath temp. 40°) and immediately treated with 1.9M allylmagnesium chloride in THF (36.5 ml, 0.069 mol). When the temp. attained 30°, the heating bath was removed and after stirring between 35 and 45° for 10 min the mixture was cooled at −50° and rapidly treated with Me_3SiCl (21.50 g, 0.198 mol). The mixture was stirred at r.t. for 30 min, cooled to −10°, and then poured into a vigorously stirred mixture of sat. aq. $NaHCO_3$ soln. and pentane. The org. phase was washed with 10% aq. $NaHCO_3$ soln. and sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated. A rapid bulb-to-bulb distillation (100–130°/0.01 Torr) gave **28** (16.35 g, 94%). ^{1}H-NMR (360 MHz): 0.21 (*s*, 9H); 1.18 (*s*, 6H); 1.35 (br. *t*, $J \approx 6.5$, 2H); 1.63 (br. *quint.*, $J \approx 6.5$, 2H); 2.17 (*t*, $J = 6.5$, 2H); 3.05 (br. *d*, $J = 5.5$, 2H); 4.63 (*d*, $J = 3$, 1H); 4.82 (br. 1H); 5.03 (br. *d*, $J = 10.5$, 1H); 5.05 (br. *d*, $J = 17$, 1H); 5.84 (*ddt*, $J = 17$, 10.5, 5.5, 1H). *NOE Experiments*: Irradiation at 0.21 gave pos. NOE at 1.18, 3.05, 5.03, 5.05, 5.84; irradiation at 4.63 gave pos. NOE at 3.05, 4.82. ^{13}C-NMR (360 MHz): 148.4 (*s*); 142.6 (*s*); 136.9 (*d*); 128.3 (*s*); 115.5 (*t*); 111.8 (*t*); 41.7 (*t*); 38.9 (*t*); 37.1 (*s*); 35.3 (*t*); 28.2 (2*q*); 28.1 (*t*); 1.2 (3*q*). MS: 264 (9, $M^{+\cdot}$), 249 (35), 236 (16), 221 (36), 207 (12), 193 (12), 179 (52), 105 (10), 91 (15), 73 (100), 45 (28), 41 (27).

(S)-γ-Damascone ((*S*)-**5**) *by Enantioselective Protonation*. A soln. of 1.6M MeLi in Et_2O (280 ml, 4.50 mmol) was concentrated (vacuum/N_2, *Firestone* valve) and the resulting white powder treated with a soln. of **28** (1.31 g, 5.0 mmol) in THF (25 ml). After heating at 40° for 15 min, the enolate soln. was ready for protonation. In another flask, neat MeLi (10 mmol, from 6.25 ml) was treated at −70° with a soln. of freshly distilled (−)-**20** (3.10 g, 15.0 mmol) in THF (15 ml) and the reaction mixture heated at 40° for 5 min. Next, the enolate soln. was transferred with a syringe (under N_2) into a dropping funnel of the flask containing (−)-**20**/(−)-**20**(Li). The mechanically stirred soln. was cooled to −50° and the enolate **29** in THF added dropwise (1 h) to this soln. After complete addition, stirring was continued for 5 min, the mixture was then cooled at −78° and quenched with sat. aq. NH_4Cl soln. (10 ml), followed by immediate addition of Et_2O (50 ml) and 5% aq. HCl soln. (25 ml). The neutral parts were extracted twice with Et_2O and the org. extract washed with H_2O, sat. aq. $NaHCO_3$ soln., and sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated. FC (SiO_2, 40–60 μ, 40 g; cyclohexane/AcOEt 98:2) of (*S*)-**18**/**28** (85:15) afforded **28** (140 mg, 11%) and (*S*)-**18** (833 mg, 87%, 75% ee[4]). (*S*)-**18** was isomerized into (*S*)-**5** (75% ee) as described above and (−)-**20** recovered in the usual way (see (*S*)-**24**).

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