

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

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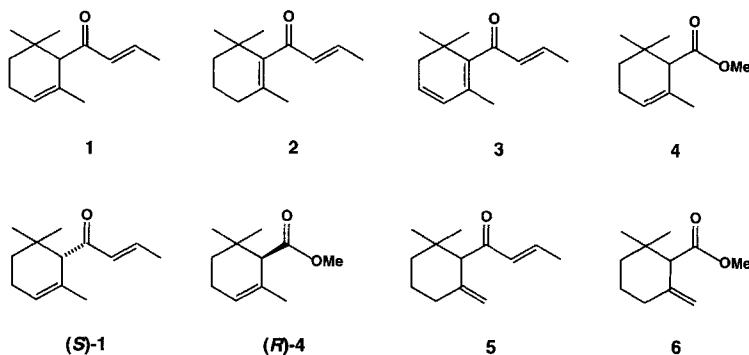
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(19.I.95)

(*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 -thio-cyclogeranate ((*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.

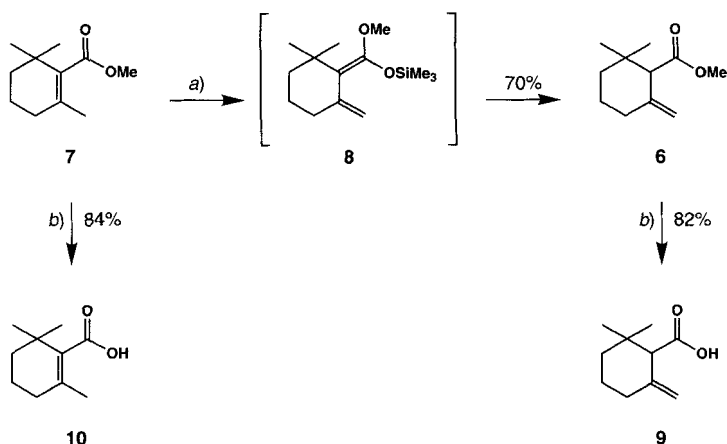
The first part of this work describes the preparation of enantiomerically pure (*R*)- and (*S*)- γ -cyclogeranic acid ((*R*)- and (*S*)-**9**, resp.) by application of classical resolution techniques, the determination of the absolute configuration by chemical correlation, as well as the preparation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



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 Me₃SiCl, 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, $-10 \rightarrow 15^\circ$; then Me₃SiCl (3.0 equiv.), $-30 \rightarrow 20^\circ$. 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 yield¹⁾. This mild and simple procedure (KSPH is prepared *in situ* from PhSH and KOH and the neutral by-product thioanisole is removed by extraction) was also successfully applied to the preparation of β -acid **10** from ester **7**²⁾.

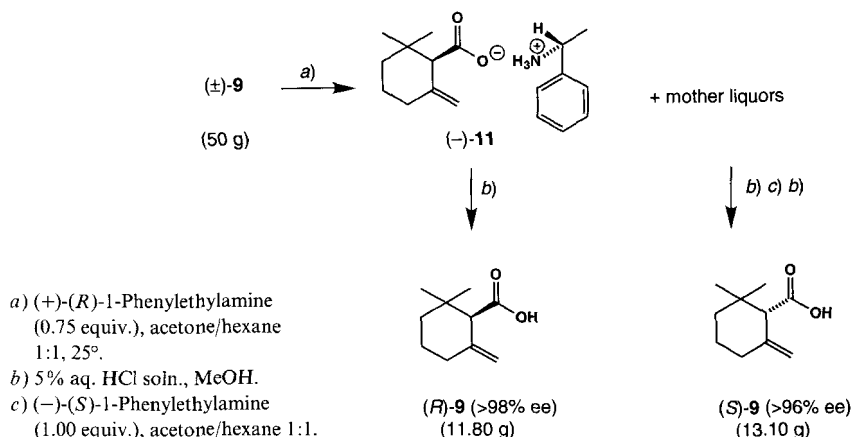
For the resolution of ($\pm$)-**9**, (*R*)- and (*S*)-1-phenylethylamine were used³⁾. When ($\pm$)-**9** was treated with (+)-(*R*)-1-phenylethylamine in acetone/hexane 1:1, pure carboxylate

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]).

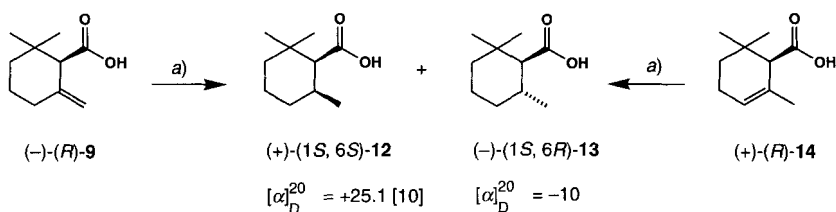
Scheme 2



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

Determination of the Absolute Configuration of $(+)\text{-}$ and $(-)\text{-9}$. The assignment of the (R) -absolute configuration to $(-)\text{-9}$ is based on its hydrogenation to the saturated acids $(+)\text{-}(1S,6S)\text{-12}$ and $(-)\text{-}(1S,6R)\text{-13}$ (Scheme 3). The absolute configuration of $(+)\text{-}(1S,6S)\text{-12}$ had already been established by hydrogenation of $(+)\text{-}(R)\text{-}\alpha$ -cyclogeranic acid ($(R)\text{-14}$) [11]. The two independently prepared samples of $(+)\text{-12}$ were shown to be identical by comparison of their optical rotation and their retention times on chiral GC⁴).

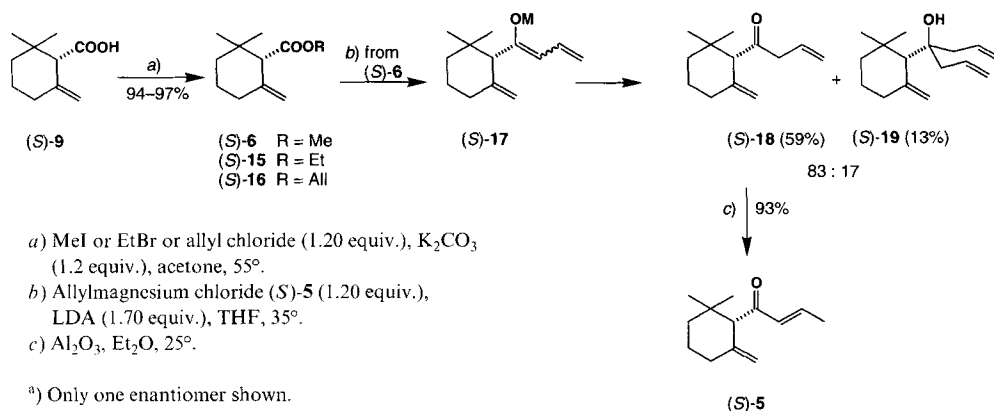
Scheme 3



a) H_2 , PtO_2 , AcOH .

Preparation and Olfactive Evaluation of Enantiomers of γ -Cyclogerانات 6, 15, 16, and of γ -Damascone (5). Using standard conditions, $(R)\text{-}$ and $(S)\text{-9}$ were converted into the methyl esters $(R)\text{-}$ and $(S)\text{-6}^4$, respectively, the ethyl esters $(R)\text{-}$ and $(S)\text{-15}^4$, respectively, and the allyl esters $(R)\text{-}$ and $(S)\text{-16}^4$, respectively (Scheme 4). The esters $(R)\text{-}$ and $(S)\text{-6}$

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

Scheme 4^{a)}

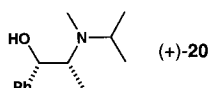
were also converted by mono-*Grignard* reaction [3] into the enantiomers of γ -damascone ((*R*)- and (*S*)-5⁴), respectively, without racemization. Thus, using allylmagnesium chloride/LDA the incipient propenyl ketone (*S*)-18 was rapidly regioselectively deprotonated to enolate (*S*)-17 to largely suppress the nucleophilic attack of a second allylic species. After hydrolysis, ketone (*S*)-18⁴ 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*)-5⁴) 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)

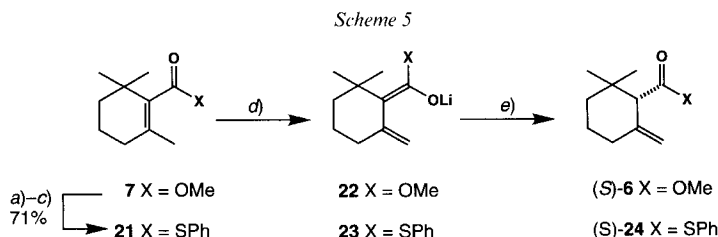
(<i>S</i>)-6	aromatic, damascone-like, thujone, fruity	(<i>R</i>)-6	more common than (<i>S</i>)-6, camphoraceous, corky, cellar
(<i>S</i>)-15	aromatic, fruity, damascone-like	(<i>R</i>)-15	less fruity, aromatic, rosmari, less powerful than (<i>S</i>)-15
(<i>S</i>)-16	green, floral, blackcurrant, aromatic,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



source⁵). 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



a) See Scheme 1. b) (COCl)₂ (1.60 equiv.), CH₂Cl₂, 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	Substrate	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))	22:78	36 (<i>R</i>)	–	
2		2) (–)- 20 (2.0; –100 (80) → –10 (30))				
3	21	1) LDA (3.0; –78 (180))	33:67	50 (<i>S</i>) ^{a)}	–	
4		2) (+)- 20 (3.3; –100 (100) → –10 (30))				
5	21	1) LDA (3.0; –78 (180))	72:28	–	–	
6		2) aq. HCl (excess; –78 (180) (quenching))				
7	21	1) BuLi (2.0; –78 (180))	43:57	96 (<i>R</i>)	81 ^{b)}	
8		2) (–)- 20 (2.7; –100 (80) → –10 (30))				
9	21	1) LDA (3.0; –78 (165))	56:44	97 (<i>R</i>) ^{c)}	84 ^{d)}	
10		2) (–)- 20 (4.0; –100 (60) → –10 (30))				
11	21	1) LDA (3.0; –78 (165))	53:47	96 (<i>S</i>)	86 ^{b)}	
12		2) (+)- 20 (4.0; –100 (60) → –10 (30))				
13	21	1) LDA (1.5; –78 (210))	55:45	94 (<i>S</i>)	76 ^{b)}	
14		2) (+)- 20 (2.0; –100 (60) → –10 (30))				
15	21	1) LDA (1.5; –78 (210))	45:55	88 (<i>S</i>)	80 ^{b)}	
16		2) (+)- 20 (0.5; –100 (60))				
17	21	3) PhCH ₂ COCH ₃ (1.5; –100 (60) → –10 (30))			–	

^{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*) $\geq$ 19:1⁶) with excess (–)-**20** (–100 $\rightarrow$ –10°) gave (*R*)-**24** with excellent enantioselectivity (97% ee⁷), 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-Pr)₂NH or excess LDA also participates in the protonation step. Likewise, the (*S*)-thioester (*S*)-**24** was obtained with 96% ee⁷ 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*).

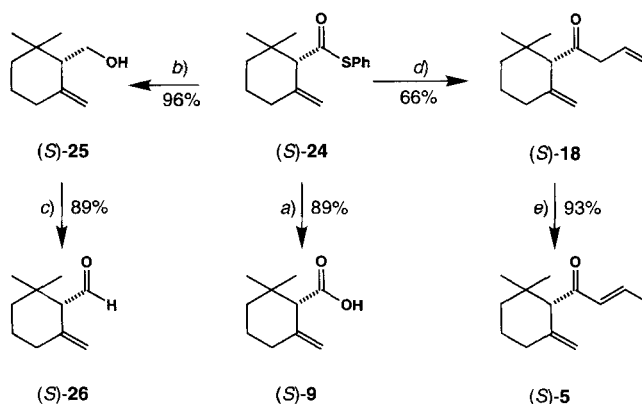
Thioesters (R)-24 and (S)-24 as Chiral Building Blocks. Hydrolysis of (*R*)- and (*S*)-**24** to acids (*R*)- and (*S*)-**9** (95% ee), respectively, with less than 2% racemization could be achieved with LiOOH in aqueous EtOH (*Scheme 6*). This protocol is particularly useful for sterically hindered thioesters [5], where the application of more vigorous conditions leads to extensive racemization. LiAlH₄ 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.

⁶) Quenching of enolate **23** with Me₃SiOTf (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 Me₃SiCl 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 Me₃SiOTf 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 LiAlH₄. For *rac*-**25**, see [17] [26].

⁹) For *rac*-**26**, see [18].

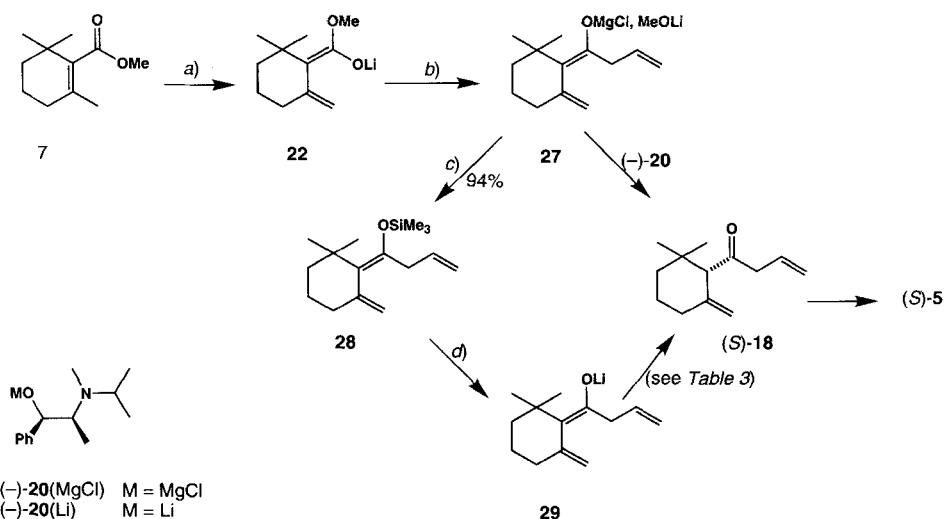
Scheme 6^{a)}


a) LiOH·H₂O (3.0 equiv.), H₂O₂ (3.30 equiv.), EtOH, H₂O, 45–50°. b) LiAlH₄ (1.05 equiv.), Et₂O, 25°. c) (COCl)₂ (1.50 equiv.), DMSO (2.16 equiv.), NEt₃ (4.50 equiv.), CH₂Cl₂, –70° → 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° → 0°. b) Allylmagnesium chloride (1.05 equiv.), THF, 35–45°. c) Me₃SiCl (3.0 equiv.), THF, –50 → 20°. d) MeLi (0.90 equiv.), THF, 40°.

This enolate was trapped with Me_3SiCl to afford (*E*)-silyl enol ether **28** or hydrolyzed ($\rightarrow$ **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 GC⁴), 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.		Add. mode	THF+ cosolvent	<i>T</i> [°C]	<i>t</i> [min]	% ee (<i>S</i>)- 18 ^{a)} after				Yield [%]
		(–)- 20	(–)- 20 (Li)					25	50	75	100% addition	
1	27	2.0	0.4 ^{b)}	norm.	hexane	$-78 \rightarrow 0$	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)	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 GC⁴) (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].

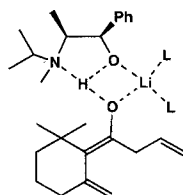
Addition of enolate **29** to a THF soln. of (–)-**20** at -50° (Entry 4) was also very instructive, as the measured ee's constantly increased during the introduction of the

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% ee¹¹⁾ 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 (Me₃SiOTf) 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.

¹¹⁾ Use of excess MeLi had a deleterious effect on enantioselectivities. When excess MeLi was quenched with Me₃SiCl 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 $\times$ 0.319 mm), *DB-WAX 15W* (15 m $\times$ 0.32 mm); chiral cap. column (16 m $\times$ 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. ^1H - 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 $100^\circ/10$ Torr for 4 h to remove the excess PhSH¹³ 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 ($\pm$)-**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*; $[\alpha]_{\text{D}}^{20} = +30 \pm 2$; 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° . $[\alpha]_{\text{D}}^{20} = -64.2$ (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 ($\pm$)-**9**). M.p. 62 – 63° . $[\alpha]_{\text{D}}^{20} = -125$ (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*, $[\alpha]_{\text{D}}^{20} = -40 \pm 5$; 25.90 g, 0.214 mol) afforded after two crystallizations (+)-**11** (22.90 g). M.p. 159 – 160° . $[\alpha]_{\text{D}}^{20} = +62.5$ (MeOH, $c = 0.014$). Acidic treatment of (+)-**11** gave (*S*)-**9** (13.1 g, > 96% ee; 52% from ($\pm$)-**9**). M.p. 61 – 62° . $[\alpha]_{\text{D}}^{20} = +122$ (CHCl_3 , $c = 0.034$).

¹²) For anal. data, see [1b] [2].

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

(+)-(1*S*,6*S*)-2,2,6-Trimethylcyclohexane-1-carboxylic Acid ((+)-(1*S*,6*S*)-**12**) and (–)-(1*S*,6*R*)-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 PtO₂ (0.10 g). After uptake of 30 ml of H₂ (1 h), the mixture was filtered (*Hyflo*) and extracted (H₂O/pentane). The org. phase was washed twice with water and sat. aq. NaCl soln., dried (Na₂SO₄), and evaporated, giving (+)-**12** and (–)-**13** (ca. 55:45; 0.173 g, 87%). Chromatography (SiO₂, cyclohexane/AcOEt 95:5) afforded pure (+)-**12** (42 mg, > 98% ee¹⁴), [α]_D²⁰ = +25.1 (CHCl₃, *c* = 0.021; [11]: +25.1) and (–)-**13** (18 mg, [α]_D²⁰ = –10 (CHCl₃, *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 K₂CO₃ (1.18 g, 8.6 mmol) for 90 min. The mixture was filtered and the solvent evaporated. After extraction of the oil (Et₂O/H₂O), the org. extracts were washed with 1% aq. NaOH soln., H₂O and sat. aq. NaCl soln., dried (Na₂SO₄), evaporated, and purified by bulb-to-bulb distillation (50°/0.05 Torr) to afford (–)-**6** (1.23 g, 95%; > 98% ee). [α]_D²⁰ = –104 (CHCl₃, *c* = 0.045).

(*S*)-Methyl γ -Cyclogeranate ((*S*)-**6**) was obtained accordingly from (*S*)-**9**. > 96% ee. [α]_D²⁰ = +104 (CHCl₃, *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), K₂CO₃ (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). [α]_D²⁰ = –93 (CHCl₃, *c* = 0.026)¹⁵.

(*S*)-Ethyl γ -Cyclogeranate ((*S*)-**15**) was obtained accordingly from (*S*)-**9**. > 96% ee. [α]_D²⁰ = +90 (CHCl₃, *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), K₂CO₃ (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). [α]_D²⁰ = –92 (CHCl₃, *c* = 0.041).

(*S*)-Allyl γ -Cyclogeranate ((*S*)-**16**) was obtained accordingly from (*S*)-**9**. > 96% ee. [α]_D²⁰ = +87 (CHCl₃, *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*-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 Et₂O. The org. extracts (containing (*S*)-**5**, (*S*)-**18**, and (*S*)-**19** (**5** + **18**/**19** 83:17)) were washed with H₂O, sat. aq. NaHCO₃ soln. and sat. aq. NaCl soln., dried (Na₂SO₄), 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 Et₂O (50 ml) and isomerized by stirring 1 h at 25° over neutral Al₂O₃ (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), [α]_D²⁰ = +259, was obtained by FC (SiO₂, cyclohexane/AcOEt 98:2).

(*R*)- γ -Damascone ((*R*)-**5**) was obtained accordingly from (*R*)-**6**. > 98% ee. [α]_D²⁰ = –267 (CHCl₃, *c* = 0.020).

Phenyl β -Cycliotheranate (= *S*-Phenyl 2,6,6-Trimethylcyclohex-1-ene-1-carbothioate (**21**)). Oxalyl chloride (8.45 g, 66.5 mmol) was added (20 min), under N₂, to an ice-cooled soln. of **10** (7.00 g, 41.7 mmol) in CH₂Cl₂ (70 ml). The temp. was allowed to attain 20° and the mixture concentrated under vacuum (ca. 10 Torr¹⁶). 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 Et₂O. The org. extracts were washed with H₂O and sat. aq. NaCl soln., dried (Na₂SO₄), 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); $\geq$ 96% pure by GC). ¹H-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). ¹³C-NMR (360 MHz): 195.7 (s); 141.4 (s); 134.3 (2d); 133.7 (s); 129.2

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 Ph₂S₂ (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 -Cyclothiogermanate (= (*S*)-*S*-Phenyl 2,2-Dimethyl-6-methylenecyclohexane-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 1.4*M* BuLi in hexane and (*i*-Pr)₂NH) in THF (200 ml). After stirring at -78° for 165 min, the mixture was treated dropwise (45 min) below -100° (Et₂O/N₂ 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 Et₂O. The org. phase was washed with H₂O, 5% aq. HCl soln., H₂O, sat. aq. NaHCO₃ soln., and sat. aq. NaCl soln., dried (Na₂SO₄), 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 (SiO₂, 40–60 μ , 300 g; cyclohexane/AcOEt 98:2) afforded (*S*)-**24** (2.96 g, 37%; $\geq 96\%$ ee⁷). [α]_D²⁰ = +261 (CHCl₃, *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 (Et₂O), and distilled to afford recovered (+)-**20** (24.90 g, 98%).

(*R*)-Phenyl γ -cyclothiogermanate ((*R*)-**24**) was obtained accordingly when (–)-**20** was used. ($\geq 97\%$ ee⁷). [α]_D²⁰ = –264 (CHCl₃, *c* = 0.030). ¹H-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). ¹³C-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 (*r*); 68.4 (*d*); 35.8 (*s*); 35.5 (*r*); 31.8 (*t*); 27.3 (*q*); 27.2 (*q*); 22.6 (*t*). MS: 260 (1, *M*⁺); 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·H₂O (0.727 g, 17.3 mmol) in H₂O (14.1 ml) was treated at 45–50° with 30% aq. H₂O₂ 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 $\times$ 0.150 ml) in 5-min intervals. The mixture was then cooled, poured into 5% aq. NaOH soln. and extracted with Et₂O. After washing the org. extracts with H₂O, the combined basic aq. phases were acidified with conc. HCl and extracted twice with Et₂O. These org. extracts were washed with 5% aq. NaHSO₃ soln., H₂O, and sat. aq. NaCl soln., dried (Na₂SO₄), evaporated, and purified by bulb-to-bulb distillation (100–150°/0.01 Torr) to afford (*S*)-**9** (0.884 g, 98% pure by GC¹⁸), 89%; $\geq 94\%$ ee).

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

(*S*)- γ -Cyclogeraniol (= (*S*)-2,2-Dimethyl-6-methylenecyclohexane-1-methanol; (*S*)-**25**). A soln. of (*S*)-**24**¹⁹ (0.770 g, 3.00 mmol) in Et₂O (5 ml) was added dropwise at 25° to a stirred suspension of LiAlH₄ (0.120 g, 3.16 mmol) in Et₂O (25 ml). After stirring for 1 h, the mixture was cooled at 0°, and then carefully hydrolyzed successively with H₂O (0.12 ml), 5% aq. NaOH soln. (0.240 ml), and H₂O (0.360 ml). After filtration of the white cake, the org. phase was washed with 5% aq. NaOH soln., H₂O, and sat. aq. NaCl soln., dried (Na₂SO₄), evaporated, and purified by bulb-to-bulb distillation (100–120°/ca. 4 Torr) to afford (*S*)-**25** (0.444 g, 96%, $\geq 96\%$ ee²⁰). [α]_D²⁰ = +24.5 (CHCl₃, *c* = 0.030).

(*R*)- γ -Cyclogeraniol ((*R*)-**25**) was obtained accordingly. $\geq 97\%$ ee. [α]_D²⁰ = –25.0 (CHCl₃, *c* = 0.017).

(*S*)- γ -Cyclocitral (= (*S*)-2,2-Dimethyl-6-methylenecyclohexane-1-carbaldehyde; (*S*)-**26**). To a soln. of oxalyl chloride (0.953 g, 7.50 mmol) in CH₂Cl₂ (15 ml) was added at -78° a soln. of DMSO (0.839 g, 10.80 mmol) in CH₂Cl₂ (3 ml). After stirring for 10 min, a soln. of (*S*)-**25** (0.770 g, 5.00 mmol) in CH₂Cl₂ (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 NEt₃ (2.27 g, 22.5 mmol). The temp. was then allowed to warm up at 0°, and the mixture poured into H₂O and extracted with pentane. The org. phase was washed with sat. aq. NaCl soln., dried (Na₂SO₄), and concentrated. The crude product was dissolved in Et₂O (ca. 30 ml) and vigorously stirred over sat. aq. NaHCO₃ soln. (ca. 40 ml) for 15 h. The org. phase was then washed with sat. aq. NaCl soln., dried (Na₂SO₄), and concentrated. Bulb-to-bulb distillation (100°/4 Torr) afforded (*S*)-**26** (0.676 g, 89%; $> 96\%$ ee⁴).

(*R*)- γ -Cyclocitral ((*R*)-**26**) was obtained accordingly from (*R*)-**25**. $> 97\%$ ee⁴. [α]_D²⁰ = –165 (CHCl₃, *c* = 0.036).

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-methylenecyclohexyl)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 Et₂O. The org. extracts containing (*S*)-**18** as a mixture of double-bond isomers and **19**, ((*S*)-**18**/**19** 84:16) were washed with H₂O, 2% aq. NaOH soln., H₂O, and sat. aq. NaCl soln., dried (Na₂SO₄), and purified by bulb-to-bulb distillation (100°/4.5 Torr) to give (*S*)-**18** (0.202 g, 94% pure by GC, 66%, > 96% ee²¹).

(*R*)-**18** of ≥ 97% ee⁴) 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 Me₃SiCl (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. NaHCO₃ soln. and pentane. The org. phase was washed with 10% aq. NaHCO₃ soln. and sat. aq. NaCl soln., dried (Na₂SO₄), and evaporated. A rapid bulb-to-bulb distillation (100–130°/0.01 Torr) gave **28** (16.35 g, 94%). ¹H-NMR (360 MHz): 0.21 (s, 9H); 1.18 (s, 6H); 1.35 (br. t, *J* ≈ 6.5, 2H); 1.63 (br. quint., *J* ≈ 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. ¹³C-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 (2q); 28.1 (t); 1.2 (3q). MS: 264 (9, *M*⁺), 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 Et₂O (280 ml, 4.50 mmol) was concentrated (vacuum/N₂, 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 N₂) 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. NH₄Cl soln. (10 ml), followed by immediate addition of Et₂O (50 ml) and 5% aq. HCl soln. (25 ml). The neutral parts were extracted twice with Et₂O and the org. extract washed with H₂O, sat. aq. NaHCO₃ soln., and sat. aq. NaCl soln., dried (Na₂SO₄), and evaporated. FC (SiO₂, 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% ee⁴). (*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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²¹) For (±)-**18**, see [1b].

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