# Electrophilic Cyclization of 1,6-Dienes Containing an Allylsilane Moiety − Enantioselective Synthesis of *cis*- and *trans*-γ-Irone

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In this paper, we report the first examples of Lewis acid and mercuric trifluoroacetate promoted cyclizations of 1,6-dienes containing an allylsilane moiety. Mercuric trifluoroacetate has been proved to be the reagent of choice leading to methylenecyclohexane derivatives in good yields and with complete regioselectivity albeit with poor diastereoselectivity. Using this methodology a stereodivergent synthesis of enantiomerically pure (−)-(2*S*,6*R*)-*cis*-γ-irone and (−)-(2*S*,6*S*)-*trans*-γ-irone, two precious aroma constituents, has been accomplished. This represents an innovative approach with respect to previous syntheses of γ-irones.



## Introduction

Irones are $C_{14}$ norterpenoid ketones, responsible for the powerful and pleasant violet-like scent of the essential oil of *Iris* rhizomes and precious constituents of expensive aromas, perfumes, and other cosmetics.[1] Most *Iris* oils contain the three α-, β-, and γ-double-bond isomers **1**−**3** in different proportions.[2] In the natural oils *cis*-α-irone and *cis*-γ-irone are the major components, but *trans*-α-irone is also found and, on one occasion, traces of (−)-*trans*-γ-irone have been detected.[2b][2f] In addition, enantiomeric irones can be isolated from *Iris* plants of different geographical origin. The olfactory properties of the three regioisomers are remarkably different and even for the single regioisomer, intensity and characters of the *Iris*-like notes are dramatically dependent on the relative and absolute stereochemistry.[2g]

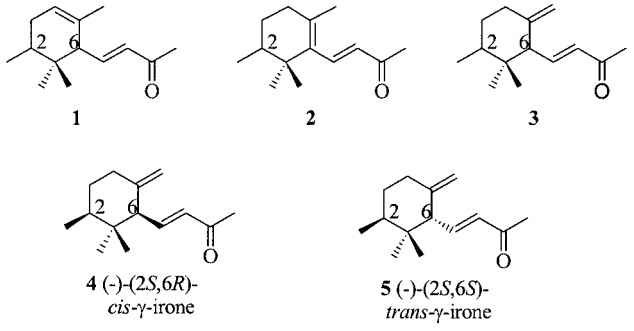
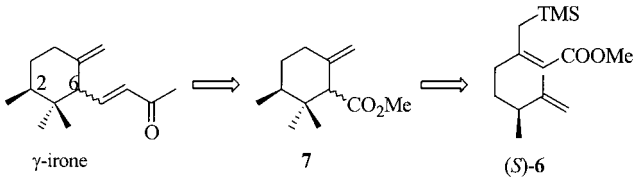



Figure 1. Components of *Iris* oil

In the γ-series, (−)-(2*S*,6*R*)-*cis*-irone (**4**) is considered to have the strongest and finest aroma of the four isomers,[3,4l] whereas the threshold value of (−)-(2*S*,6*S*)-*trans*-irone (**5**) is four times higher than that of the (+)-enantiomer.[2f]

Chemists have struggled with the synthesis of γ-irones for a long time,[4] the first syntheses of the single enantiomers having appeared in the literature only recently.[2f,3,4d,4l,4m] On the other hand, even the synthesis of each diastereomer turns out to be troublesome; indeed, literature data reveal that *cis*-γ-irone is the more difficult to achieve due to the severe 1,3-allylic interaction[5] between the exocyclic double bond and the nearby side chain.

We envisioned that an innovative approach for the enantioselective synthesis of γ-irone diastereomers, namely (−)-(2*S*,6*R*)-*cis*-γ-irone (**4**) and (−)-(2*S*,6*S*)-*trans*-γ-irone (**5**), could be based on an intramolecular electrophilic cyclization[6] of the chiral allylsilane **6** (Scheme 1). In fact, we expected that the allylsilyl moiety would allow the regioselective formation of the exocyclic double bond[7] of γ-irones, whereas the absolute configuration of the allylsilane **6**, derived from the chiral pool (vide infra), would dictate the absolute stereochemistry of the cyclized product. Two crucial issues of the reaction remained, however, to be explored, namely the preference of the electrophilic species for the distal double bond with respect to the trisubstituted one and the role of different factors affecting the cyclization diastereoselectivity. Indeed, it must be stressed that, in contrast




Scheme 1. Retrosynthesis of γ-irone

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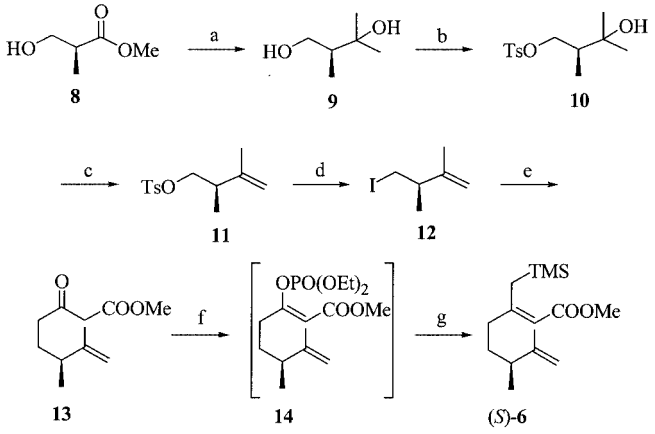
with the intramolecular electrophilic cyclizations of simple 1,5- and 1,6-dienes,[6,8] annulations of 1,6-dienes containing an allylsilane moiety of type **6** were unknown at the onset of our work.

## Results and Discussion

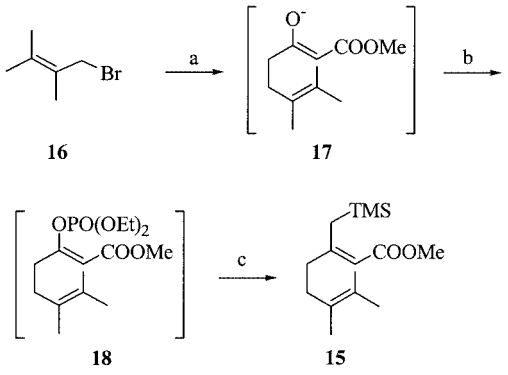
### Cyclization Studies

The required allylsilane **6** was synthesized (Scheme 2) starting from the commercially available chiral building block methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (**8**) (*ee* > 99%), which already contained the C-2 stereogenic center of irones. Reaction of **8** with methylmagnesium bromide furnished diol **9**, which was selectively protected as its primary *p*-toluenesulfonate **10**.[9] Regioselective elimination of the tertiary hydroxy group was then easily accomplished[10] by exposure of **10** to mesyl chloride followed by in situ elimination of the corresponding tertiary methanesulfonate group with excess $Et_3N$ to give the terminal olefin **11**[11] in 66% overall yield (3 steps), without traces of the internal $\Delta^2$-olefin ($^1$H NMR spectrum). Exchange of the tosylate group with LiI furnished the more reactive iodide **12**, which was readily alkylated with the Na/Li methyl acetoacetate dianion[12] to give the γ-alkylated β-oxo ester **13** in 40% unoptimized overall yield (2 steps). The allylsilyl moiety was then introduced with a tandem reaction[7c] via the intermediate enol phosphate **14** to give the required allylsilane **6** in 70% overall yield over 2 steps. The (*Z*)/(*E*) stereoselectivity was estimated from the $^1$H and $^{13}$C NMR spectra of ester **6** to be greater than 50:1.




Scheme 2. a) MeMgBr, $Et_2O$, 0 °C, 1.5 h; b) TsCl, pyridine, 0 °C, 15 h; c) $CH_3SO_2Cl$, $Et_3N$, $Et_2O$, 0 °C to room temp., 15 h, 66% yield (3 steps); d) LiI, THF, reflux, 2 h; e) Na/Li methyl acetoacetate dianion, THF, 0 °C to room temp., 1.5 h, 40% yield (2 steps, unoptimized); f) NaH, THF, 0 °C, 15 min, then $ClP(O)(OEt)_2$, 0 °C to room temp., 1.5 h; g) $Me_3SiCH_2MgCl$ (1 M in THF), cat. $Ni(acac)_2$, 0 °C, 1 h, 69% yield (2 steps)

The corresponding racemic reference series was prepared from the achiral allylic silane **15** which, by analogy with **6**, was synthesized from methyl acetoacetate and the readily accessible bromide **16**[13] via β-oxo ester **17** and enol phosphate **18** (Scheme 3). Our recently discovered one-pot procedure[14] for the synthesis of terpenoid allylsilanes secured compound **15** with (*Z*)/(*E*) stereoselectivity > 50:1, in 42% overall yield over 3 steps.

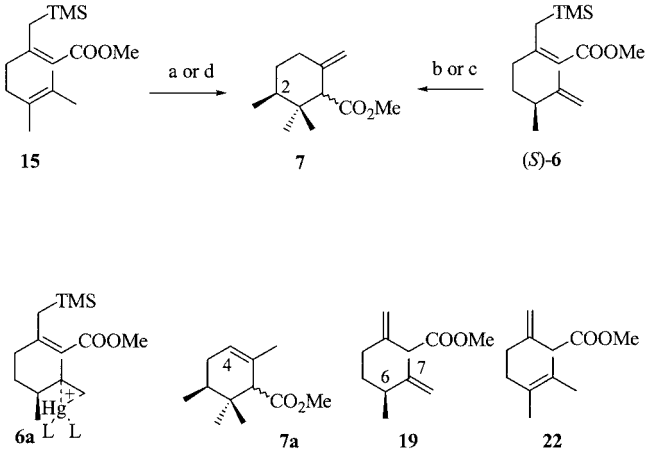



Scheme 3. a) Na/Li methyl acetoacetate dianion, THF, 0 °C to room temp., 1 h; b) $ClP(O)(OEt)_2$, 0 °C to room temp., 1.5 h; c) $Me_3SiCH_2MgCl$, cat. $Ni(acac)_2$, THF, 0 °C, 1 h, 42% yield (3 steps)

With dienes **6** and **15** in hand, we reasoned that the electronic properties of their two double bonds were similar to those of previously investigated allylic 1,5-dienylsilanes which require a strong Lewis acid or a species able to generate a bridged cation, to promote the electrophilic cyclization.[7b][7c]

At first, different Lewis acids and a number of reaction conditions were tested for the cyclization of achiral allylic dienylsilane **15** in order to avoid protodesilylation and shift of the double bond in the cyclized product **7**, resulting in an unfruitful mixture of regioisomeric olefins.

Eventually, cyclization of **15** with $SnCl_4$ (4 equiv.) in wet $CH_2Cl_2$ at −30/−20 °C readily afforded the desired *exo*-olefin **7**,[15] albeit as a 1:1.5 mixture of chromatographically inseparable *cis*-/*trans*-**7** stereoisomers,[16] in 85% yield (Scheme 4, route a). Noteworthy, this ratio was quite different from the thermodynamic equilibrium ratio, which PM3




Scheme 4. a) $SnCl_4$, wet $CH_2Cl_2$, −30 to −20 °C, 2 h, 85% yield; b) $SnCl_4$, wet $CH_2Cl_2$, −30 to −20 °C, 1 h, 92% yield or $TiCl_4$, dry $CH_2Cl_2$, −30 to −20 °C, 1 h, 87% yield; c) $Hg(OCOCF_3)_2$, $CH_3CN$, 0 °C, 45 min; then satd. aq. NaCl, 0 °C, 30 min; then $NaBH_4$, NaOH 15%, 0 °C, 30 min, 82% yield; d) $Hg(OCOCF_3)_2$, $CH_3CN$, −40 °C, 45 min; then satd. aq. NaCl, 0 °C, 30 min; then $NaBH_4$, NaOH 15%, 0 °C, 30 min, 57% yield

Table 1. Electrophilic cyclizations of diene (*S*)-**6**; composition of the reaction mixtures

| Compound | % after 30 min[a] | % after 30 min[b] | % after 60 min[a] | % after 60 min[b] | *ee* after 60 min[a] | *ee* after 60 min[b] |
|---|---|---|---|---|---|---|
| *cis*-**7** | 25.6 | 47.5 | 58.5 | 57.2 | 40 | 45 |
| *trans*-**7** | 17.3 | 23.7 | 34.2 | 29.5 | [c] | [c] |
| (*S*)-**6** | 49.7 | 28.8 | 3.2 | 2.2 | | |
| **15** | 7.4 | < 5 | 2.5 | 1.0 | | |

[a] $SnCl_4$ was used as Lewis acid. [b] $TiCl_4$ was used as Lewis acid. [c] No GC base separation was observed for the *trans* enantiomers.

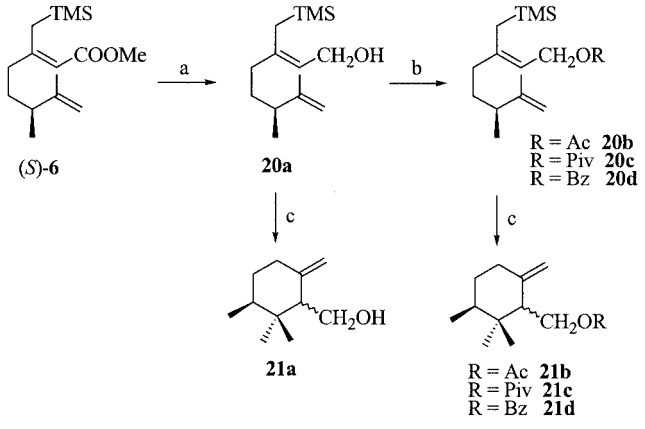
methods estimated to be about 1:9, thus indicating that the main factor controlling the cyclization diastereoselectivity was the comparable activation energy of competing transition states.

Cyclization of optically active diene **6** (Scheme 4, route b) under the above condition proved, however, to be unfeasible. Actually, besides a disappointingly low *cis*/*trans* diastereoselectivity, we noticed a severe loss of stereochemical integrity for the C-2 stereogenic center in product **7**. The same result was observed with $TiCl_4$ (2 equiv.) in dry $CH_2Cl_2$ at −30/−15 °C. In fact, the enantiomeric excess of *cis*-**7**, estimated by enantioselective GC analysis, was only 40 and 45%, respectively. It was interesting to compare the composition of the reaction mixtures after 30 and 60 min (see Table 1). After 60 min, cyclization yields (GC) reached 92% with $SnCl_4$ and 86.7% with $TiCl_4$, favoring the *cis*-**7** isomer in both cases (*cis*/*trans* = 1.7:1 with $SnCl_4$ and 1.9:1 with $TiCl_4$).

Moreover, the ratio of the two diastereomers did not change significantly with time, a clear indication that it was kinetically controlled with both Lewis acids. To account for the dramatic erosion of the enantiomeric purity of compound **7** with respect to **6**, the presence of compound **15** in the reaction mixtures proved that, before cyclization, the terminal 1,1-disubstituted double bond of diene **6** underwent a significant isomerization to the more stable tetrasubstituted olefin, probably by a rapid [1,2]-H shift between the C-6 and C-7 carbocationic centers, so that the actual cyclizing substrate was a mixture of the chiral allylsilane **6** and the achiral allylsilane **15**. The same kind of racemization was observed to occur in the Lewis acid promoted cyclization of simple 1,6-dienes.[8a] Thus, it appeared that though the allylic silane moiety should furnish a more nucleophilic double bond with respect to trimethylsilyl-unsubstituted 1,6-dienes, cyclization of compound **6** was still a relatively slow process and likely proceeded through a non-concerted mechanism.

These results strongly suggested to perform cyclization of diene **6** via an intermediate "*onio*" species in order to avoid a shift of the distal double bond.[17] To this aim mercury salts appear to be unique in maintaining the stereochemical integrity of double bonds and, among them, as an additional benefit, mercury trifluoroacetate proved to be an efficient initiator of electrophilic olefin cyclizations though, to the best of our knowledge, 1,6-dienes appear to have never been used before as substrates.[6a][7b,18]

As expected, on exposure to $Hg(OCOCF_3)_2$ (1.05 equiv.) in deoxygenated acetonitrile at 0 °C, followed by reductive demercuration of mercurial products, diene **6** readily produced the exocyclic product **7**, without traces of the endocyclic olefin **7a**, in 82% isolated yield and > 99% GC purity (Scheme 4, route c). A small amount (4.5%) of the open-chain product **19**, resulting from mercury desilylation of the allylsilane moiety, was also isolated. A GC analysis showed that, once again, the diastereoselectivity of the cyclization was disappointingly low (*cis*-**7**/*trans*-**7** ≈ 1:1), similar to the stereoselectivity of acid-mediated cyclizations of trimethylsilyl-unsubstituted 1,6-dienes;[8a,8b] however, each diastereomer **7** was enantiomerically pure, confirming the crucial role of the bridged mercurinium ion **6a** in preventing erosion of the stereochemistry of diene **6**. It was not immediately apparent what the controlling factors were in the competing transition states leading to *cis*- and *trans*-**7**, though we expected that the allylic strain[5] between the methoxycarbonyl group and the developing exocyclic double bond could play an important role. In order to test this hypothesis and a possible influence of electronic factors on the cyclization diastereoselectivity, we prepared other dienes (**20a**−**d**, Scheme 5) and investigated their reactions with $Hg(OCOCF_3)_2$ in propionitrile at −78 °C.




Scheme 5. a) DIBALH, $Et_2O$, 0 °C, 1 h, 85% yield; b) RCOCl, pyridine, cat. DMAP, $CH_2Cl_2$, 1 h, 85% (**20b**), 98% (**20c**), 99% (**20d**); c) $Hg(OCOCF_3)_2$, $CH_3CH_2CN$, −78 °C, 45 min; then satd. aq. NaCl, 0 °C, 30 min; then $NaBH_4$, NaOH 15%, 0 °C, 30 min

The cyclizations still proceeded readily leading to the expected products **21a**−**d**, but without any appreciable improvement of the diastereoselectivity (Table 2).

It was interesting to compare the $Hg(OCOCF_3)_2$-promoted cyclizations of 1,6-dienes **6** and **20a**−**d** with the reaction of 1,5-diene **15**. Indeed, when the reaction of compound **15** was performed at −18 °C, the cyclized compound

Table 2. Results of the $Hg(OCOCF_3)_2$-promoted cyclizations of dienes (*S*)-**6**, **15**, and **20a**−**d**

| Substrate | Product (% isolated yield) | Product purity (%, GC) | *cis*/*trans* ratio of cyclized product (GC) |
|---|---|---|---|
| (*S*)-**6** | **7** (82) | > 99 | 1:1 |
| **15**[a] | **7** (57) | 92[a] | 7:1[a] |
| **20a** | **21a** (61) | 90 | 1:1 |
| **20b** | **21b** (74) | 82 | 1:1 |
| **20c** | **21c** (87) | 96 | 1:1 |
| **20d** | **21d** (76) | 81 | 1:1.25 |

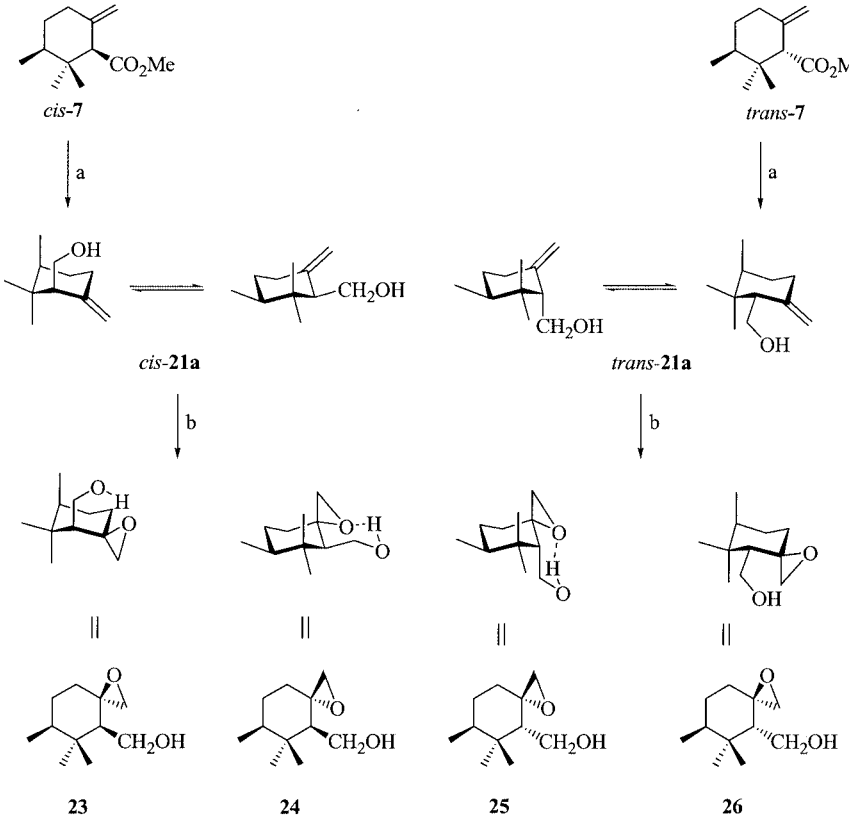
[a] The reaction was run at −40 °C.

**7** accounted for only 55% of the product mixture; the diastereoselectivity was, however, significantly higher than for 1,6-dienes, corresponding to a ratio of *cis*-**7**/*trans*-**7** = 5:1, which improved to 7:1 at −40 °C (Scheme 4, route d). By contrast, the desilylated product **22** accounted for about 17% of the reaction mixture, significantly more than the corresponding desilylated product **19** produced in the reaction of olefin (*S*)-**6**.

This result indicated that, with respect to **6**, the higher steric hindrance near the distal tetrasubstituted double bond of diene **15** forced the large $Hg^{II}$ species to add, at least in part, to the internal allylsilane moiety. Moreover, it appears that, with respect to 1,5-dienes, the additional $sp^3$-carbon atom between the two double bonds of the 1,6-dienes confers a higher flexibility to the acyclic chain, resulting in a deterioration of the cyclization diastereoselectivity.

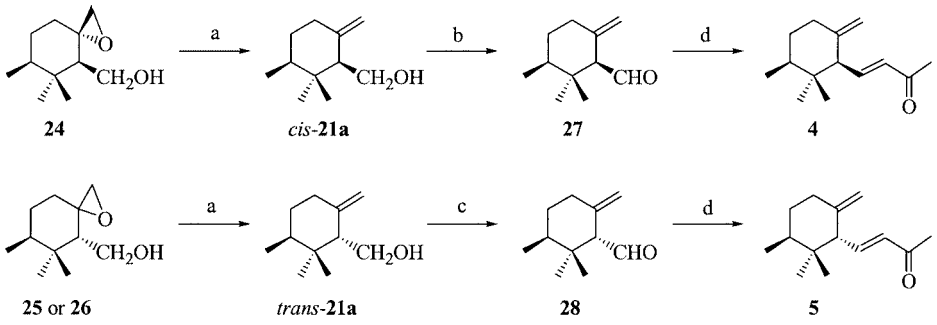
### Synthesis of (−)-(2*S*,6*R*)-*cis*-γ-Irone (4) and (−)-(2*S*,6*S*)-*trans*-γ-Irone (5)

Compounds *cis*- and *trans*-**7** are key intermediates[4] in the synthesis of *cis*- and *trans*-γ-irone, respectively; therefore, given the easy accessibility to these two diastereomers in enantiomerically pure form, we considered it worthy of interest to pursue a divergent synthesis of both irones if esters **7** or derivatives could be readily separated. To this aim, the above 1:1 mixture of isomers **7** was reduced with DIBALH[19] to give a 48:52 mixture of the corresponding *cis*- and *trans*-alcohol **21a** in 92% yield.




Scheme 6. a) DIBALH, $Et_2O$, 0 °C, 45 min, 92% yield; b) *t*BuOOH, $VO(acac)_2$, $CH_2Cl_2$, −20 °C, 22 h; 85% isolated yield of compounds **24**−**26** in a ratio of 56:38:6, < 2% (GC) of compound **23**




Scheme 7. a) $[Bu_3SnAlMe_3]Li$, $CH_2Cl_2$, 0 °C, 2 h, 70% yield; b) Swern oxidation, 86% yield; c) Dess−Martin periodinane reagent,[23] $CH_2Cl_2$, room temp., 2 h, 96% yield; d) $(EtO)_2POCH_2COCH_3$, $Ba(OH)_2{\cdot}8H_2O$, THF/$H_2O$ = 40:1, room temp., 18 h; **4** 70% yield, **5** 72% yield

It is reported in the literature that these diastereomeric alcohols can be separated only by preparative GC.[4b] In search of a more practical method of separation, we first attempted the kinetic separation of alcohols **21a** through a Sharpless asymmetric epoxidation.[20] In the event, at 53% conversion after 22 h at −20 °C, (+)-DIPT afforded a 47% yield of a *trans*/*cis* = 4.4:1 mixture of unchanged alcohols **21a**, while, under similar conditions, (−)-DIPT afforded, at 56% conversion, 44% yield of a *trans*/*cis* = 10:1 mixture of starting material.

Although (−)-DIPT proved to be more selective, diastereomerically pure *trans*-**21a** could be obtained only by forcing the epoxidation up to a conversion of 65−70%.

Eventually, we succeeded in the separation of the two series by resorting to a $VO(acac)_2$-catalyzed epoxidation[21] (Scheme 6) of the mixture of homoallylic alcohols **21a**.

In the event, reaction of **21a** with *t*BuOOH (1.5 equiv.) and 5% $VO(acac)_2$ produced the expected four epoxides **23**−**26**, with compound **23** occurring only in traces (GC). The *cis*/*trans* relationship between the C-2 and C-6 substituents of each epoxide was unambiguously determined by its conversion into the original olefin (vide infra), while the relative stereochemistry of the epoxy ring was determined by NOE experiments. Since the mechanism of the epoxidation required assistance of the alcoholic group,[21] it resulted that epoxide **24** derived from the diequatorial conformer of *cis*-**21a**, while epoxides **25** and **26** were likely formed from the more and less stable conformations of *trans*-**21a**, respectively. The three epoxides **24**−**26** were isolated in 85% overall yield, in a ratio of 56:38:6.

The conversion of each epoxide into *cis*- and *trans*-γ-irone is outlined in Scheme 7. At first, they were reconverted into the corresponding olefin according to the Oshima−Nozaki protocol,[22] thus avoiding the protection of the alcoholic function. Thus, on treatment with 4 equiv. of $[Bu_3SnAlMe_3]Li$, each epoxide furnished the parent olefin in ca. 70% yield. Oxidation of *cis*-**21a** was then performed with the Swern protocol using DIPEA instead of TEA,[4m] yielding the desired aldehyde **27** in 86% yield and 98% *de* (GC). Alcohol *trans*-**21a** was instead oxidized with the Dess−Martin periodinane reagent[23] to aldehyde **28** in 96% yield and 98% *de* (GC).

Finally, each of the two highly epimerizable, base-sensitive aldehydes **27** and **28** was submitted to the barium hydroxide promoted Horner−Wadsworth−Emmons (HWE) reaction, according to the procedure previously reported by Monti,[4m] to give enantiomerically pure γ-irones **4** and **5**, respectively.

Our sample of (−)-*cis*-γ-irone (**4**) showed *de* = 93% (GC), *ee* = 100% (chiral GC), and $[\alpha]_D^{20} = -6.4$ (*c* = 1.06, $CH_2Cl_2$),[24] whereas our sample of (−)-*trans*-γ-irone (**5**) showed *de* = 97% (GC), *ee* = 100% (chiral HPLC), and $[\alpha]_D^{20} = -58.4$ (*c* = 0.37, $CH_2Cl_2$).[25]

## Conclusion

In conclusion, we explored the Lewis acid and mercuric trifluoroacetate promoted intramolecular cyclization of acyclic 1,6-dienes containing an allylsilane moiety as a novel synthetic method for the construction of 1,3-disubstituted 4-methylenecyclohexanes. Mercuric trifluoroacetate proved to be superior, preventing extensive racemization of stereogenic centers caused by an undesired double-bond isomerization in the starting chiral dienes, which instead was observed when Lewis acids were used. Due to the flexibility of the acyclic substrate, the cyclization likely proceeds through competitive transition states of a similar energy, thus affording a low *cis*/*trans* product diastereoselectivity. However, a mechanistic discussion of the reaction seems to be premature at this stage, in absence of other precedents in the literature on the $Hg^{II}$-initiated cyclizations of 1,6-dienes and more experimental results.

An effective strategy for the ready separation of the *cis* and *trans* products has been developed, thanks to which a stereodivergent synthesis of enantiopure and diastereomerically enriched (−)-(2*S*,6*R*)-*cis*-γ-irone (**4**) and (−)-(2*S*,6*S*)-*trans*-γ-irone (**5**) was accomplished from the same enantiopure starting material.

## Experimental Section

**General Remarks:** THF and $Et_2O$ were dried by distillation under argon from potassium benzophenone ketyl; pyridine and $CH_2Cl_2$

were distilled from $CaH_2$. All other solvents were distilled under argon. MeCN was deoxygenated by bubbling argon for at least 1 h through it and used without any drying being applied. Commercially available reagents were used as supplied, without further purification, except MsCl and $Et_3N$, that were distilled from $CaH_2$ under argon immediately prior to use. All reactions were performed under a slightly positive static pressure of argon in oven-dried (140 °C for at least 3 h) glassware. Routine monitoring of reactions was performed by using silica gel (0.20 mm thickness) aluminum-supported TLC plates. Compounds were visualized by UV irradiation at a wavelength of 254 nm, or stained by exposure to a 0.5% vanillin solution in $H_2SO_4$/EtOH (4:1), followed by heating. Preparative liquid chromatography was accomplished with 60 Kieselgel (40−63 μm). Optical rotation values ($10^{-1}$ deg cm$^2$ g$^{-1}$) were measured at 589 nm (D line) in the solvent and at the temperatures indicated. Melting points were determined with a hot-stage apparatus and are uncorrected. GCMS data were recorded using the electron impact ionization technique (70 eV, 0.5 mA). $^1$H NMR (300 MHz) and $^{13}$C NMR (75.47 MHz) spectra were obtained in $CDCl_3$ solution at 22 °C. Chemical shifts are reported in δ units relative to $CHCl_3$ [$\delta_H$ = 7.26 ppm; $\delta_C$ (central line of t) = 77.0 ppm]; the multiplicity (in parentheses) of each carbon signal was determined by DEPT experiments. IR spectra were obtained as liquid films. Compounds **1**−**5**, **7**, **21**, **23**−**26**, **27**, and **28** have been numbered according to carotenoid numbering.[4b]

**(*S*)-Diol 9:** A solution of methyl (*S*)-(+)-3-hydroxy-2-methylpropionate [10.7 g, 90.2 mmol, *ee* = 99% (GC)] in dry $Et_2O$ (50 mL) was added dropwise over 30 min to a freshly prepared solution of MeMgBr (300 mmol, 3.3 equiv.) in dry $Et_2O$ (300 mL) at room temperature. After complete addition, stirring was continued for further 90 min at room temperature. The reaction mixture was then cautiously poured into a mixture of 1 M HCl and $Et_2O$ at 0 °C under vigorous stirring. The aqueous phase was extracted with $Et_2O$ and the combined organic layers were washed with satd. aq. $NaHCO_3$ and brine. The acidic aqueous phase was then neutralized and extracted in continuum with $CH_2Cl_2$ for 48 h. The $Et_2O$ and $CH_2Cl_2$ solutions were combined, dried ($MgSO_4$), and the solvents evaporated to give diol **9**[9] (10.5 g, 99% yield) as a viscous colorless oil. An analytical sample was prepared by column chromatography ($SiO_2$; EtOAc/hexanes, 3:1). $[\alpha]_D^{20}$ = −10.9 (*c* = 0.23, EtOH). IR $\tilde{\nu}$ = 3356, 2974, 2936, 2886, 1705, 1664, 1472, 1385, 1368, 1176, 1159, 1097, 1057, 1027, 947, 905, 858 cm$^{-1}$. $^1$H NMR: δ = 0.86 (d, *J* = 7.3 Hz, 3 H, C*H*$_3$CH), 1.20 (s, 3 H, C*H*$_3$), 1.28 (s, 3 H, C*H*$_3$), 1.78−1.85 (m, 1 H, C*H*CH$_3$), 2.54 and 2.88 (2 br. s, 2 × 1 H, exchangeable with $D_2O$, 2 O*H*), 3.67−3.76 (m, 2 H, C$H_2$O) ppm. $^{13}$C NMR: δ = 12.8 (3), 23.8 (3), 29.5 (3), 43.7 (1), 65.9 (2), 74.5 (0) ppm. GCMS: *m*/*z* (%) = 103 (5) [M − 15]$^+$, 85 (11), 69 (2), 59 (100), 55 (10), 45 (8), 43 (74), 42 (20), 41 (32). $C_6H_{14}O_2$ (118.17): calcd. C 60.98, H 11.94; found C 61.13, H 11.83. $^1$H and $^{13}$C NMR spectra are consistent with the literature data.[9]

**(*S*)-3-Hydroxy-2,3-dimethylbutyl 4-Toluenesulfonate (10):** 4-Toluenesulfonyl chloride (17.2 g, 90.2 mmol) was added to a solution of crude diol **9** (10.64 g, 90.2 mmol) in dry pyridine (80 mL) at 0 °C and the resulting solution was stirred at 0 °C for 15 h. The mixture was then poured into iced water, extracted with $Et_2O$, and the organic phase was washed with satd. aq. $KHSO_4$, satd. aq. $NaHCO_3$, brine, dried ($MgSO_4$), and the solvents were evaporated. The crude product was used for the following reaction. An analytical sample was prepared by column chromatography ($SiO_2$; EtOAc/hexanes, 1:1). IR $\tilde{\nu}$ = 3342, 3418, 2976, 1598, 1494, 1466, 1357, 1307, 1293, 1211, 1189, 1174, 1121, 1097, 1035, 1019, 963, 840, 815, 736, 685, 666 cm$^{-1}$. $^1$H NMR: δ = 0.96 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CH), 1.12 (s, 3 H, C*H*$_3$), 1.19 (s, 3 H, C*H*$_3$), 1.81−1.91 (m, 1 H, C*H*CH$_3$), 2.45 (s, 3 H, C*H*$_3$Ar), 3.90−3.95 (m, 1 H, C*H*HO), 4.37 (dd, *J* = 9.2, 4.6 Hz, 1 H, CH*H*O), 7.34−7.81 (AA′BB′ system, 4 H, Ar*H*) ppm. $^{13}$C NMR: δ = 12.4 (3), 21.4 (3), 25.8 (3), 28.4 (3), 43.2 (1), 71.8 (0), 72.5 (2), 127.7 (2 × 1), 129.7 (2 × 1), 132.7 (0), 144.6 (0) ppm. $C_{13}H_{20}O_4S$ (272.36): calcd. C 57.33, H 7.40; found C 57.45, H 7.33. The $^{13}$C NMR spectrum is consistent with the literature data.[9]

**(*R*)-2,3-Dimethyl-3-butenyl 4-Toluenesulfonate (11):** Mesyl chloride (22.7 g, 198.4 mmol) was added dropwise to a solution of crude **10** (24.5 g, 90.2 mmol) in dry $Et_2O$ (800 mL), then the mixture was cooled to 0 °C and $Et_3N$ (137 g, 1.35 mol) was added in 1 h; after complete addition the solution was stirred for 15 h while warming to room temperature. The reaction mixture was then poured into a mixture of 1 M HCl and $Et_2O$ at 0 °C under vigorous stirring; the aqueous phase was extracted with $Et_2O$ and the combined organic layers were sequentially washed with 1 M HCl, satd. aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and the solvents evaporated. The crude product was purified by chromatography ($SiO_2$; hexanes/ethyl acetate = 7:3) to give 14.8 g of product **11**[11] as a colorless oil (65% overall yield over 3 steps). $[\alpha]_D^{20}$ = −6.9 (*c* = 1.2, $CHCl_3$). IR $\tilde{\nu}$ = 3074, 2973, 1649, 1599, 1504, 1457, 1359, 1189, 1177, 1097, 969, 898, 839, 814, 769, 666 cm$^{-1}$. $^1$H NMR: δ = 1.02 (d, *J* = 6.7 Hz, 3 H, C*H*$_3$CH), 1.62 (s, 3 H, C*H*$_3$C=), 1.81−1.91 (m, 1 H, CH$_3$C*H*), 2.45 (s, 3 H, C*H*$_3$Ar), 3.86 (dd, *J* = 9.4, 7.4 Hz, 1 H, C*H*HO), 3.98 (dd, *J* = 9.4, 6.6 Hz, 1 H, CH*H*O), 4.69 (br. s, 1 H, =C*H*H), 4.78 (br. s, 1 H, =CH*H*), 7.33−7.80 (AA′BB′ system, 4 H, Ar*H*) ppm. $^{13}$C NMR: δ = 17.2 (3), 21.4 (3), 22.9 (3), 41.4 (1), 74.4 (2), 113.3 (2), 129.2 (2 × 1), 131.1 (2 × 1), 134.4 (0), 146.0 (0), 146.2 (0) ppm. GCMS: *m*/*z* (%) = 173 (5), 155 (41), 122 (3), 91 (87), 83 (27), 82 (100), 69 (27), 67 (88), 65 (48), 53 (10), 51 (9), 41 (59) ppm. $C_{13}H_{18}O_3S$ (254.35): calcd. C 61.39, H 7.13; found C 61.47, H 7.25. The spectroscopic data are consistent with the literature data.[11]

**(*R*)-Iodide 12:** LiI (8.6 g, 64 mmol) was added in one portion to a solution of toluenesulfonate **11** (14.8 g, 58.2 mmol) in THF (120 mL) and the mixture was heated at reflux for 2 h. The mixture was then filtered and the residue washed exhaustively with. $Et_2O$. The organic phase was then washed with satd. aq. $NH_4Cl$ and brine, dried ($MgSO_4$), and concentrated at room pressure to ca. 100 mL. This solution was directly used in the following reaction. A small portion was concentrated and the residue chromatographed ($SiO_2$; hexanes/EtOAc, 95:5) to give an analytical sample. IR: $\tilde{\nu}$ = 3075, 2965, 2925, 2870, 1645, 1455, 1375, 1277, 1186, 1165, 1102, 894 cm$^{-1}$. $^1$H NMR: δ = 1.16 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$CH), 1.71 (s, 3 H, C*H*$_3$C=), 2.35−2.46 (m, 1 H, CH$_3$C*H*), 3.16−3.29 (m, 2 H, C$H_2$I) 4.77 (br. s, 1 H, =C*H*H), 4.84 (br. s, 1 H, =CH*H*) ppm. $^{13}$C NMR: δ = 13.0 (2), 19.3 (3), 19.4 (3), 43.0 (1), 111.2 (2), 146.9 (0) ppm. GCMS: *m*/*z* (%) = 210 (3) [M$^+$], 169 (12), 155 (2), 127 (16), 119 (8), 83 (72), 79 (13), 77 (38), 69 (8), 67 (8), 55 (54), 41 (100). HRMS: calcd. for $C_6H_{11}I$ [M]$^+$ 209.9905; found 209.9910.

**(*S*)-Oxo Ester 13:** A solution of methyl acetoacetate (14.8 g, 127.6 mmol) in dry THF (80 mL) was added dropwise to NaH (60% dispersion in mineral oil, 5.7 g, 142 mmol) in THF (80 mL) at 0 °C and the mixture was stirred for 15 min at the same temperature. BuLi (2.5 M solution in hexanes, 56.8 mL, 142 mmol) was then added dropwise and the mixture was stirred at 0 °C for an additional 15 min. To the resulting orange mixture the previously prepared solution of iodide **12** (see above) (ca. 58 mmol), diluted with THF (100 mL), was added and stirring was maintained for 90 min

while warming to room temperature. The reaction mixture was then poured into a mixture of 1 M HCl and $Et_2O$ at 0 °C; the aqueous phase was extracted with $Et_2O$ and the combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was chromatographed ($SiO_2$; hexanes/EtOAc, 95:5 → 90:10) to give 4.57 g of product **13** as a colorless oil (40% yield over 2 steps, not optimized). $[\alpha]_D^{20} = -0.62$ ($c = 0.90$, $CH_2Cl_2$). IR: $\tilde{\nu}$ = 3072, 2960, 2875, 1751, 1718, 1646, 1449, 1438, 1407, 1376, 1322, 1241, 1196, 1153, 1066, 1006 $cm^{-1}$. $^1H$ NMR: δ = 1.04 (d, $J$ = 6.8 Hz, 3 H, C$H_3$CH), 1.65 (br. s, 3 H, C$H_3$C=), 1.61−1.71 (m, 2 H, 5-$H_2$), 2.11−2.25 (m, 1 H, 6-H), 2.49 (t, $J$ = 7.5 Hz, 2 H, 4-$H_2$), 3.46 (s, 2 H, 2-$H_2$), 3.76 (s, 3 H, OC$H_3$), 4.70 (s, 1 H, =C$H$H), 4.74 (s, 1 H, =CH$H$) ppm. $^{13}C$ NMR: δ = 18.4 (3), 19.5 (3), 27.9 (2), 40.3 (1), 40.8 (2), 49.0 (2), 51.2 (3), 110.3 (2), 148.6 (0), 167.5 (0), 202.6 (0) ppm. GCMS: $m/z$ (%) = 198 (4) [$M^+$], 181 (42), 180 (25), 167 (9), 149 (9), 139 (2), 129 (16), 125 (14), 124 (15), 121 (18), 120 (23), 116 (12), 109 (22), 107 (25), 102 (17), 101 (18), 97 (20), 95 (15), 83 (24), 82 (28), 81 (38), 74 (55), 69 (67), 67 (100), 59 (14), 55 (65), 43 (90), 41 (55) ppm. $C_{11}H_{18}O_3$ (198.26): calcd. C 66.64, H 9.15; found C 66.79, H 9.27.

**(*S*,*Z*)-Ester 6:** A solution of β-oxo ester **13** (2.85 g, 14.4 mmol) in THF (10 mL) was added dropwise to NaH (60% dispersion in mineral oil, 633 mg, 15.8 mmol) in THF (20 mL) at 0 °C and the mixture was stirred at 0 °C for 15 min. Diethyl chlorophosphate (2.61 g, 15.1 mmol) was then added dropwise and the resulting mixture was stirred for 1.5 h while warming to room temperature, followed by a slow transfer via cannula to a mixture of $Me_3Si$-$CH_2MgCl$ and $Ni(acac)_2$, prepared meanwhile from Mg (648 mg, 26.6 mmol) and $Me_3SiCH_2Cl$ (3.2 g, 25.9 mmol) in dry THF (30 mL), to which the Ni catalyst (260 mg, 1 mmol) was added 15 min before the addition of the enol phosphate. The reaction mixture was then stirred at 0 °C for 1 h, poured into a mixture of 1 M HCl and *tert*-butyl methyl ether (MTBE) at 0 °C, and extracted with MTBE; the combined organic layers were washed with satd. aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and the solvents evaporated. The residue was chromatographed ($SiO_2$; hexanes/EtOAc, 100:0 → 98:2) to give 2.67 g of product (*S*)-**6** as a pale yellow oil (69% yield). $[\alpha]_D^{20} = -11.5$ ($c = 0.97$, $CH_2Cl_2$). IR: $\tilde{\nu}$ = 3072, 2955, 2906, 1715, 1625, 1458, 1435, 1373, 1249, 1235, 1189, 1159, 1060, 1031, 925, 877, 846, 769, 695, 635 $cm^{-1}$. $^1H$ NMR: δ = 0.07 [s, 9 H, Si(C$H_3$)$_3$], 1.05 (d, $J$ = 6.9 Hz, 3 H, C$H_3$CH), 1.47−1.59 (m, 2 H, C$H_2$TMS), 1.68 (br. s, 3 H, C$H_3$C=), 2.03 (br. t, $J$ = 7.5 Hz, 2 H, 5-$H_2$), 2.15−2.21 (m, 1 H, 6-H), 2.40−2.48 (m, 2 H, 4-$H_2$), 3.69 (s, 3 H, OC$H_3$), 4.73 (br. s, 1 H, =C$H$H), 4.76 (br. s, 1 H, =CH$H$), 5.57 (s, 1 H, 2-H) ppm. $^{13}C$ NMR: δ = −0.9 (3 × 3), 18.7 (3), 19.6 (3), 26.5(2), 33.1(2), 38.4 (2), 40.8 (1), 50.4 (3), 110.0 (2), 110.8 (1), 149.1 (0), 165.0 (0), 167.6 (0) ppm. GCMS: $m/z$ (%) = 268 (1) [$M^+$], 253 (18), 240 (12), 237 (4), 225 (3), 211 (2), 195 (12), 183 (25), 171 (13), 164 (7), 149 (6), 137 (12), 136 (28), 121 (23), 107 (11), 95 (11), 89 (13), 82 (100), 73 (69), 67 (14), 59 (10), 55 (9), 45 (13), 41 (19) ppm. $C_{15}H_{28}O_2Si$ (268.47): calcd. C 67.11, H 10.51; found C 67.26, H 10.38.

**Methyl (2*S*,6*RS*)-2-Methyl-γ-cyclogeraniate [(2*S*,6*RS*)-7]:** A solution of $Hg(OCOCF_3)_2$ (2.14 g, 5 mmol) in deoxygenated $CH_3CN$ (20 mL) was added dropwise via cannula to a solution of diene (*S*)-**6** (1.28 g, 4.78 mmol) in deoxygenated (Ar bubbling for 30 min) $CH_3CN$ (25 mL) at 0 °C and the mixture was stirred at the same temperature for 45 min. Deoxygenated brine (15 mL) was added and the mixture was stirred for 30 min at 0 °C. Finally, a deoxygenated solution of $NaBH_4$ (360 mg, 9.56 mmol) in 15% aq. NaOH (15 mL) was added and the mixture was stirred for further 30 min, then transferred into a separating funnel, diluted with abundant water, and the aqueous phase was extracted with hexanes. The combined organic layers were washed with brine, dried ($Na_2SO_4$), and the solvents evaporated. Chromatographic purification of the residue ($SiO_2$; hexanes/EtOAc, 98:2 → 95:5) and concentration of the fractions at room pressure, afforded 41.6 mg (4.5% yield) of diene **19** [$^1H$ NMR: δ = 1.02 (d, $J$ = 6.9 Hz, 3 H), 1.25−1.75 (m, 3 H), 1.65 (s, 3 H), 2.0−2.25 (m, 2 H), 3.05 (s, 2 H), 3.74 (s, 3 H), 4.70 (br. s, 2 H), 4.87 (s, 1 H), 4.90 (s, 1 H) ppm] and 765 mg of product **7** as a colorless oil with a pleasant fragrance (82% yield, GC purity > 99%, *cis*/*trans*, 49:51). $[\alpha]_D^{20} = -42.2$ ($c = 1.27$, $CH_2Cl_2$). IR: $\tilde{\nu}$ = 3074, 2960, 2882, 2861, 1736, 1648, 1458, 1436, 1391, 1377, 1367, 1337, 1287, 1254, 1231, 1190, 1152, 1137, 1089, 1045, 1025, 952, 895, 865, 772, 743, 685, 645 $cm^{-1}$. $C_{12}H_{20}O_2$ (196.29): calcd. C 73.43, H 10.27; found C 73.40, H 10.31. ***cis* Isomer:** $^1H$ NMR: δ = 0.86 (d, $J$ = 6.4 Hz, 3 H, 2-C$H_3$), 0.92 (s, 3 H, 1-C$H_3$), 0.98 (s, 3 H, 1-C$H_3$), 1.27−1.72 (m, 2 H), 2.04−2.23 (m, 2 H), 2.34 (ddd, $J$ = 13.4, 4.4, and 2.2 Hz, 1 H), 2.92 (s, 1 H, 6-H), 3.69 (s, 3 H, OC$H_3$), 4.67 (br. s, 1 H, =C$H$H), 4.85 (s, 1 H, =CH$H$) ppm. $^{13}C$ NMR: δ = 14.3 (3), 16.0 (3), 27.3 (3), 32.2 (2), 36.4 (2), 38.9 (0), 42.6 (1), 51.4 (3), 61.3 (1), 108.8 (2), 144.5 (0), 172.9 (0) ppm. GCMS: $m/z$ (%) = 196 (11) [$M^+$], 181 (59), 168 (6), 153 (24), 149 (38), 139 (35), 137 (54), 136 (52), 127 (25), 125 (51), 123 (13), 121 (62), 114 (28), 112 (31), 111 (15), 107 (33), 105 (16), 99 (11), 95 (59), 93 (56), 91 (42), 83 (100), 82 (47), 81 (62), 79 (76), 77 (48), 70 (14), 69 (22), 67 (58), 65 (25), 59 (17), 55 (94), 52 (27), 43 (16), 41 (81). ***trans* Isomer:** $^1H$ NMR: δ = 0.83 (d, $J$ = 7.0 Hz, 3 H, 2-C$H_3$), 0.79 (s, 3 H, 1-C$H_3$), 0.98 (s, 3 H, 1-C$H_3$), 1.20−1.64 (m, 2 H), 2.04−2.23 (m, 2 H), 2.62 (tdt, $J$ = 13.4, 5.5, and 2.0 Hz, 1 H), 2.92 (s, 1 H, 6-H), 3.65 (s, 3 H, OC$H_3$), 4.76 (br. s, 1 H, =C$H$H), 4.85 (br. s, 1 H, =CH$H$) ppm. $^{13}C$ NMR: δ = 16.0 (3), 20.7 (3), 26.7 (3), 31.6 (2), 32.0 (2), 34.6 (1), 37.4 (0), 51.6 (3), 61.9 (1), 112.6 (2), 145.2 (0), 173.5 (0) ppm. GCMS: $m/z$ (%) = 196 (1) [$M^+$], 181 (1), 164 (1), 153 (13), 149 (11), 139 (13), 137 (48), 136 (63), 127 (38), 125 (48), 121 (74), 114 (25), 111 (12), 107 (28), 105 (13), 99 (10), 95 (68), 93 (46), 91 (32), 83 (93), 82 (40), 81 (54), 79 (55), 77 (37), 67 (60), 65 (18), 59 (17), 55 (100), 43 (12), 41 (46). *ee* > 99% for the *cis* isomer {determined on an enantioselective DMePeBETACDX column (25 m, 0.25 mm i.d., 0.25 μm f.t.); carrier gas = He, 1 mL/min; split 1:50; detector: FID; temperature program: 70 °C (0 min) → 2°C/min → 140 °C (5 min); (2*R*,6*S*)-*cis*-**7**, $t_R$ = 28.7 min; (2*S*,6*R*)-*cis*-**7**, $t_R$ = 29.3 min; no base separation was obtained for the *trans* enantiomers.

**(2*S*,6*RS*)-2-Methyl-γ-cyclogeraniol [(2*S*,6*RS*)-21a]:** A solution of esters **7** (153 mg, 0.78 mmol) in $Et_2O$ (8 mL) at 0 °C was added dropwise via cannula to a solution of DIBALH (1 M in hexanes, 1.7 mL, 1.7 mmol) and the mixture was stirred at 0 °C for 45 min. The reaction was quenched with a 1:1 mixture of satd. aq. $NH_4Cl$ and satd. aq. sodium potassium tartrate and the mixture was stirred at room temperature until clearness (ca. 30 min). After dilution with $Et_2O$, the mixture was washed with 1 M HCl and the aqueous phase was extracted with $Et_2O$. The combined organic layers were washed with satd. aq. $NaHCO_3$, followed by brine, dried ($Na_2SO_4$), and the solvents evaporated. Chromatography of the residue ($SiO_2$; pentane/diethyl ether, 8:2) gave 121 mg of alcohol **21a** as a colorless oil (92% yield, GC purity > 99%, *cis*/*trans*, 48:52). $[\alpha]_D^{20} = -34.1$ ($c = 0.79$, $CH_2Cl_2$). IR: $\tilde{\nu}$ = 3385, 3070, 2961, 2931, 2880, 1649, 1451, 1389, 1365, 1246, 1195, 1170, 1067, 1046, 1019, 956, 932, 889 $cm^{-1}$. The NMR and MS data of each stereoisomer are reported below.

**Epoxides 24−26:** Vanadyl acetylacetonate (26.8 mg, 0.1 mmol) and *tert*-BuOOH (5.5 M in nonane, 0.48 mL, 2.62 mmol) were added to a solution of alcohol **21a** (*cis*/*trans*, 48:52, 340 mg, 2.02 mmol) in

dry $CH_2Cl_2$ (20 mL) at 0 °C. After stirring at 0 °C for 24 h, the reaction was quenched by addition of satd. aq. $Na_2SO_3$; the mixture was stirred at room temp. for 15 min, then satd. aq. $NaHCO_3$ was added. After separation of the two phases, the aqueous one was extracted with $CH_2Cl_2$ and the combined organic layers were washed with brine, dried ($Na_2SO_4$), and the solvents evaporated. Three successive chromatographic purifications ($SiO_2$; hexanes/EtOAc, 90:10 → 70:30) of the mixture of epoxides afforded 162 mg of **24** (91% yield with respect to *cis*-**21a**), 137 mg of **25** (71% yield with respect to *trans*-**21a**), and 20 mg of **26** (10% yield with respect to *trans*-**21a**) in 85% overall yield. **Epoxide 24:** Colorless oil, $[\alpha]_D^{20}$ = +13.7 (*c* = 1.0, $CH_2Cl_2$). IR: $\tilde{\nu}$ = 3490, 2969, 2932, 2877, 2864, 1475, 1452, 1423, 1391, 1368, 1339, 1196, 1152, 1102, 1045, 1014, 961, 863, 833, 801, 710 $cm^{-1}$. $^1H$ NMR: δ = 0.67 (s, 3 H, 1-C*H*$_3$), 0.88 (d, *J* = 6.3 Hz, 3 H, 2-C*H*$_3$), 1.05 (s, 3 H, 1-C*H*$_3$), 1.28−1.36 (m, 1 H), 1.38−1.50 (m, 2 H), 1.65−1.73 (m, 1 H), 1.97 (dd, *J* = 10 and 2.9 Hz, 1 H), 1.97−2.09 (m, 1 H), 2.71 (d, *J* = 3.7 Hz, 1 H), 3.17 (br., 1 H, O*H*), 3.22 (br. s, 1 H), 3.46 (t, *J* = 11.2 Hz, 1 H, C*H*HOH), 3.71 (dd, *J* = 11.2, 2.8 Hz, 1 H, CH*H*OH) ppm. $^{13}C$ NMR: δ = 14.7 (3), 15.0 (3), 26.3 (3), 29.9 (2), 35.3 (2), 37.8 (0), 41.3 (1), 50.7 (2), 51.2 (1), 59.3 (2), 61.5 (0) ppm. GCMS: *m*/*z* (%) = 184 (2) [$M^+$], 169 (9), 167 (14), 166 (9), 151 (25), 137 (12), 135 (8), 123 (42), 121 (16), 113 (91), 111 (14), 109 (28), 107 (19), 97 (22), 96 (36), 95 (55), 93 (29), 91 (27), 83 (68), 82 (37), 81 (99), 79 (49), 77 (25), 70 (23), 69 (51), 67 (54), 55 (69), 53 (28), 43 (44), 42 (20), 41 (100). $C_{11}H_{20}O_2$ (184.28): calcd. C 71.70, H 10.94; found C 71.88, H 11.13. **Epoxide 25:** Colorless oil, $[\alpha]_D^{20}$ = −12.4 (*c* = 1.2, $CH_2Cl_2$). IR: $\tilde{\nu}$ = 3443, 2964, 2929, 2877, 1463, 1449, 1390, 1367, 1294, 1199, 1150, 1104, 1074, 1046, 1022, 998, 966, 938, 888, 844, 816, 752 $cm^{-1}$. $^1H$ NMR: δ = 0.85 (d, *J* = 6.4 Hz, 3 H, 2-C*H*$_3$), 0.95 (s, 3 H, 1-C*H*$_3$), 1.00 (s, 3 H, 1-C*H*$_3$), 1.18−1.30 (m, 2 H), 1.40−1.54 (m, 2 H), 1.62−1.70 (m, 1 H), 2.10−2.24 (m, 1 H), 2.64−2.74 (m, 3 H), 3.79−3.90 (m, 1 H, C*H*HOH), 4.09 (br. t, *J* = 10.2 Hz, 1 H, CH*H*OH) ppm. $^{13}C$ NMR: δ = 15.7 (3), 21.9 (3), 27.5 (3), 29.9 (2), 30.3 (2), 36.1 (1), 37.9 (0), 54.7 (1), 55.6 (2) 61.0 (0), 61.9 (2) ppm. GCMS: *m*/*z* (%) = 184 (2) [$M^+$], 169 (25), 167 (21), 151 (38), 139 (10), 137 (27), 123 (72), 121 (31), 113 (82), 111 (18), 109 (26), 107 (25), 97 (22), 96 (30), 95 (52), 93 (45), 91 (36), 83 (55), 82 (20), 81 (100), 79 (73), 77 (33), 70 (25), 69 (54), 67 (56), 65 (21), 55 (66), 53 (26), 43 (42), 42 (20), 41 (96). $C_{11}H_{20}O_2$ (184.28): calcd. C 71.70, H 10.94; found C 71.88, H 11.23. **Epoxide 26:** Colorless oil, $[\alpha]_D^{20}$ = −3.8 (*c* = 1.0, $CH_2Cl_2$). IR: $\tilde{\nu}$ = 3417, 2960, 2930, 2875, 1462, 1433, 1390, 1373, 1366, 1287, 1276, 1206, 1126, 1071, 1048, 1021, 998, 959, 922, 902, 836, 813, 740 $cm^{-1}$. $^1H$ NMR: δ = 0.95 (s, 3 H, 1-C*H*$_3$), 0.99 (d, *J* = 6.7 Hz, 3 H, 2-C*H*$_3$), 1.02 (s, 3 H, 1-C*H*$_3$), 1.47−1.83 (m, 6 H, 2-H, 3-H, 4-H, OH), 2.25 (m, 1 H, 6-H), 2.63 (d, *J* = 4.2 Hz, 1 H, epoxide-H), 2.99 (d, *J* = 4.2 Hz, 1 H, epoxide-H′), 3.65 (t, *J* = 11.4 Hz, 1 H, C*H*HOH), 3.74 (dd, *J* = 11.4, 4.3 Hz, 1 H, CH*H*OH) ppm. $^{13}C$ NMR: δ = 15.5 (3), 25.1 (3), 26.0 (3), 28.8 (2), 30.6 (2), 37.6 (0), 38.5 (1), 49.9 (1), 52.0 (2), 61.3 (2), 63.8 (0) ppm. GCMS: *m*/*z* (%) = 184 (2) [$M^+$], 169 (25), 152 (11), 151 (39), 137 (12), 127 (9), 123 (34), 121 (18), 113 (90), 111 (12), 109 (24), 107 (19), 105 (11), 97 (20), 96 (35), 95 (48), 93 (30), 91 (30), 83 (58), 82 (22), 81 (91), 79 (49), 77 (28), 71 (20), 70 (25), 69 (52), 67 (53), 65 (19), 55 (70), 53 (28), 43 (43), 42 (20), 41 (100). $C_{11}H_{20}O_2$ (184.28): calcd. C 71.70, H 10.94; found C 71.60, H 11.17.

**(2*S*,6*R*)-*cis*-2-Methyl-γ-cyclogeraniol (*cis*-21a):** BuLi (1.6 M solution in hexanes, 1.33 mL, 2.13 mmol) was added dropwise to a solution of bis(tributyltin) (1.23 g, 2.13 mmol) in dry THF (1.5 mL) at 0 °C. The resulting yellow solution was stirred at 0 °C for 15 min, then $AlMe_3$ (2 M solution in toluene, 1.06 mL, 2.12 mmol) was added dropwise. Stirring was maintained at 0 °C for 15 min, then a solution of epoxide **24** (97.1 mg, 0.53 mmol) in dry THF (1 mL) was added dropwise via cannula. After complete addition, stirring was continued at room temperature for 4 h. The reaction was then quenched by dilution with $Et_2O$ and careful addition of satd. aq. $NH_4Cl$ at 0 °C. 1 M HCl was then added until two clear phases were obtained. After separation of the two phases, the aqueous phase was extracted with $Et_2O$ and the combined organic layers were washed with satd. aq. $NaHCO_3$ and brine, dried ($Na_2SO_4$), and the solvents evaporated at atmospheric pressure. The crude product was adsorbed onto a flash silica gel column for 4 h in order to allow complete decomposition of the intermediate β-oxystannane, then it was eluted (hexanes/EtOAc, 95:5 → 90:10) to give 62.3 mg (70% yield) of *cis*-**21a** as a dense colorless oil, $[\alpha]_D^{20}$ = −15.2 (*c* = 1.0, $CH_2Cl_2$) {ref.[4b] $[\alpha]_D^{20}$ = −28.5 (*c* = 1.0, $CHCl_3$)}. IR: $\tilde{\nu}$ = 3661, 2993, 2944, 2876, 1643, 1463, 1385, 1197, 1048, 906 $cm^{-1}$. $^1H$ NMR: δ = 0.58 (s, 3 H, 1-$CH_3$), 0.84 (d, *J* = 7.0 Hz, 3 H, 2-$CH_3$), 1.04 (s, 3 H, 1-$CH_3$), 1.19−1.34 (m, 2 H), 1.40−1.53 (m, 1 H), 1.56−1.66 (m, 1 H), 1.99−2.12 (m, 2 H), 2.33 (ddd, *J* = 12.8, 4.3, and 3.1 Hz, 1 H), 3.78−3.94 (m, 2 H, C$H_2$OH), 4.68 (br. s, 1 H, =C*H*H), 4.97 (br. s, 1 H, =CH*H*) ppm. $^{13}C$ NMR: δ = 14.8 (3), 15.7 (3), 26.4 (3), 32.9 (2), 36.9 (2), 38.1 (0), 42.0 (1), 56.4 (1), 59.5 (2), 106.5 (2), 148.0 (0) ppm. GCMS: *m*/*z* (%) = 169 (10) [M +1$^+$], 151 (100), 150 (42), 149 (11), 137 (20), 135 (49), 125 (12), 123 (33), 122 (14), 121 (18), 111 (19), 109 (48), 107 (51), 97 (15), 95 (89), 94 (26), 93 (31), 91 (21), 83 (72), 81 (69), 79 (39), 70 (18), 69 (23), 67 (45), 65 (16), 57 (15), 55 (66), 53 (20). The spectroscopic data are consistent with the literature data.[4b]

**(2*S*,6*S*)-*trans*-2-Methyl-γ-cyclogeraniol (*trans*-21a):** *trans*-**21a** was prepared from epoxides **25** and **26**, separately, by using the same procedure described above for *cis*-**21a**. Compound **25** (120 mg, 0.65 mmol) gave 76.7 mg (70% yield) of *trans*-**21a**, whereas **26** (19 mg, mmol) afforded 12 mg (69% yield) of the same product; white solid, m.p. 30−33 °C (ref.[4b] m.p. 34−38 °C). $[\alpha]_D^{20}$ = −42.9 (*c* = 0.87, $CH_2Cl_2$) {ref.[4b] $[\alpha]_D^{20}$ = −34.0 (*c* = 0.95, $CHCl_3$)}. IR (KBr): $\tilde{\nu}$ = 3663, 3075, 2992, 2941, 1644, 1467, 1389, 1049, 903 $cm^{-1}$. $^1H$ NMR: δ = 0.81 (s, 3 H, 1-C*H*$_3$), 0.82 (d, *J* = 7.0 Hz, 3 H, 2-C*H*$_3$), 0.95 (s, 3 H, 1-C*H*$_3$), 1.25−1.38 (m, 2 H), 1.50−1.63 (m, 2 H), 2.03 (dd, *J* = 10.0, 6.1 Hz, 1 H), 2.20 (dd, *J* = 8.6, 3.3 Hz, 2 H), 3.62−3.70 (m, 2 H, C$H_2$OH), 4.76 (s, 1 H, =C*H*H), 4.93 (s, 1 H, =CH*H*) ppm. GCMS: *m*/*z* (%) = 169 (15) [M + 1$^+$], 152 (12), 151 (100), 150 (21), 137 (34), 135 (37), 125 (12), 123 (22), 122 (13), 121 (15), 109 (36), 107 (40), 95 (96), 94 (21), 93 (28), 91 (18), 83 (47), 81 (68), 79 (38), 70 (17), 69 (22), 67 (40), 57 (15), 55 (42), 53 (18). The spectroscopic data are consistent with the literature data.[4b]

**(2*S*,6*R*)-*cis*-2-Methyl-γ-cyclocitral (27):** A solution of dry DMSO (70 mg, 0.9 mmol) in dry $CH_2Cl_2$ (2 mL) was added dropwise to a solution of freshly distilled $(COCl)_2$ (68.5 mg, 0.54 mmol) in dry $CH_2Cl_2$ (5 mL) at −78 °C. The mixture was stirred at −78 °C for 15 min, then a solution of alcohol *cis*-**21a** (60.0 mg, 0.36 mmol) in dry $CH_2Cl_2$ (3 mL) was added dropwise. The solution was stirred at −78 °C for further 30 min, then freshly distilled DIPEA (209 mg, 1.62 mmol) was added and stirring was maintained for 2 h while warming to −20 °C. The reaction was quenched by addition of water; after extraction with $CH_2Cl_2$, the combined organic layers were washed with brine, dried ($Na_2SO_4$), and the solvents evaporated at 300 Torr. The crude product was purified by flash silica gel column chromatography (pentane/$Et_2O$, 95:5) to give aldehyde **27** (51.6 mg, 86.3% yield) as a colorless oil, $[\alpha]_D^{20}$ = +54 (*c* = 1.00, $CH_2Cl_2$) {ref.[4b] $[\alpha]_D^{20}$ = +24.8 (*c* = 1.15, $CCl_4$) for a sample of 76% *ee*}. IR: $\tilde{\nu}$ = 3110, 2964, 2755, 1732, 1658, 1465, 1398, 1377, 904 $cm^{-1}$. $^1H$ NMR: δ = 0.86 (d, *J* = 7.0 Hz, 3 H, 2-C*H*$_3$), 0.98

(s, 3 H, 1-C$H_3$), 1.00 (s, 3 H, 1-C$H_3$), 1.17−1.45 (m, 2 H), 1.54−1.62 (m, 1 H), 2.10 (br. t, $J$ = 13.1 Hz, 1 H, 4-H), 2.34 (dt, $J$ = 13.1, 3.1 Hz, 1 H, 4-H′), 2.55 (br. d, $J$ = 4.8 Hz, 1 H, 6-H), 4.52 (s, 1 H, =C$H$H), 4.93 (s, 1 H, =CH$H$), 9.92 (d, $J$ = 4.8 Hz, 1 H, *CHO*) ppm. $^{13}$C NMR: δ = 14.9 (3), 15.2 (3), 27.1 (3), 31.5 (2), 36.0 (2), 37.9 (0), 41.6 (1), 65.2 (1), 109.4 (2), 145.1 (0), 205.3 (1) ppm. GCMS: *m*/*z* (%) = 166 (2) [M$^+$], 151 (28), 137 (17), 135 (16), 133 (12), 123 (32), 122 (20), 109 (43), 108 (23), 107 (22), 96 (20), 95 (100), 93 (24), 91 (26), 84 (25), 83 (42), 82 (45), 81 (64), 79 (44), 77 (26), 69 (23), 67 (55), 65 (20), 55 (81), 53 (38), 51 (17), 41 (92). The spectroscopic data are consistent with the literature data.[4b]

**(2*S*,6*S*)-*trans*--2-Methyl-γ-cyclocitral (28):** Dess−Martin periodinane reagent[23] (44.8 mg, 0.10 mmol) was added to a solution of alcohol *trans*-**21a** (14.8 mg, 0.088 mmol) in dry $CH_2Cl_2$ (2 mL) and the solution was stirred at room temperature for 2 h. The reaction mixture was then diluted with $Et_2O$ and filtered through a pad of silica gel and Celite washing thoroughly with a mixture of pentane/$Et_2O$ in a ratio of 8:2. The solution was concentrated at 300 Torr and the residue was purified by flash silica gel column chromatography (pentane/$Et_2O$, 9:11 → 8:2) to give aldehyde **28** (14.0 mg, 96% yield, GC purity > 99%, *de* = 98%) as a colorless oil. $[\alpha]_D^{20}$ = −127 ($c$ = 0.7, $CH_2Cl_2$) {ref.[4b] $[\alpha]_D^{20}$ = −82.6 ($c$ = 1.1, $CCl_4$) for a sample of 76% *ee*}. IR: ṽ = 3109, 2962, 2753, 1734, 1656, 1465, 1400, 1375, 901 cm$^{-1}$. $^1$H NMR: δ = 0.83 (s, 3 H, 1-C$H_3$), 0.88 (d, $J$ = 7.0 Hz, 3 H, 2-C$H_3$), 1.11 (s, 3 H, 1-C$H_3$), 1.24−1.43 (m, 1 H), 1.59−1.70 (m, 1 H), 1.80−1.94 (m, 1 H), 2.26−2.37 (m, 2 H, 4-$H_2$), 2.75 (d, $J$ = 3.4 Hz, 1 H, 6-H), 4.77 (s, 1 H, =C$H$H), 4.95 (s, 1 H, =CH$H$), 9.89 (d, $J$ = 3.5 Hz, 1 H, C$H$O) ppm. $^{13}$C NMR: δ = 15.5 (3), 20.9 (3), 26.4 (3), 31.2 (2), 32.6 (2), 37.0 (1), 37.6 (0), 69.2 (1), 113.3 (2), 142.9 (0), 202.6 (1) ppm. GCMS: *m*/*z* (%) = 166 (4) [M$^+$], 151 (8), 137 (23), 135 (28), 133 (10), 123 (20), 121 (7), 109 (31), 108 (28), 107 (15), 96 (20), 95 (100), 93 (19), 91 (22), 83 (34), 82 (16), 81 (55), 79 (43), 77 (32), 69 (13), 67 (47), 65 (14), 55 (53), 53 (23), 51 (15), 43 (12), 41 (65). The spectroscopic data are consistent with the literature data.[4b]

**(−)-(2*S*,6*R*)-*cis*-γ-Irone (4) and (−)-(2*S*,6*S*)-*trans*-γ-Irone (5):** Aldehydes **27** (50 mg, 0.30 mmol) and **28** (14 mg, 0.08 mmol) were separately submitted to Monti's procedure[4m] to afford *cis*-γ-irone (**4**) (43.3 mg, 70% yield) and *trans*-γ-irone (**5**) (11.9 mg, 72% yield), respectively. The *cis*-isomer **4** [*de* = 94% (GC), *ee* > 99% (GC)] was obtained as a colorless oil with an intense and distinctive *Iris* fragrance. $[\alpha]_D^{20}$ = −6.4 ($c$ = 1.06, $CH_2Cl_2$).[24] IR: ṽ = 2993, 2940, 2866, 1678, 1655, 1629, 1365, 1253, 997, 896 cm$^{-1}$. $^1$H NMR: δ = 0.74 (s, 3 H, 1-C$H_3$), 0.88 (d, $J$ = 6.5 Hz, 3 H, 2-C$H_3$), 0.89 (s, 3 H, 1-C$H_3$), 1.26−1.62 (m, 3 H), 2.07 (br. td, $J$ = 13.4, 5.2 Hz, 1 H, 4-H), 2.30 (s, 3 H, 10-$H_3$), 2.35 (ddd, $J$ = 13.4, 4.3, 2.5 Hz, 1 H, 4-H′), 2.57 (d, $J$ = 10.4 Hz, 1 H, 6-H), 4.45 (br. s, 1 H, =C$H$H), 4.81 (br. s, 1 H, =CH$H$), 6.11 (d, $J$ = 15.8 Hz, 1 H, 8-H), 6.95 (dd, $J$ = 15.8, 10.4 Hz, 1 H, 7-H) ppm. $^{13}$C NMR: δ = 14.3 (3), 15.8 (3), 27.2 (3), 27.6 (3), 31.9 (2), 36.2 (2), 38.8 (0), 42.0 (1), 57.8 (1), 108.7 (2), 133.6 (1), 147.1 (1), 148.8 (0), 198.0 (0) ppm. GCMS: *m*/*z* (%) = 206 (3) [M$^+$], 191 (5), 173 (5), 163 (22), 149 (33), 145 (8), 135 (7), 133 (8), 121 (82), 109 (24), 107 (25), 105 (12), 95 (9), 93 (18), 92 (10), 91 (28), 83 (19), 81 (35), 79 (27), 77 (22), 65 (15), 55 (39), 43 (100), 41 (44). The spectroscopic data are consistent with the literature data.[4b] The *trans* isomer **5** [*de* = 97% (GC), *ee* > 99% (HPLC)] was obtained as a colorless oil with a very weak fragrance. $[\alpha]_D^{20}$ = −61.4 ($c$ = 0.37, $CH_2Cl_2$).[25] IR ṽ = 2961, 2940, 1683, 1622, 1365, 1256, 987, 895 cm$^{-1}$. $^1$H NMR: δ = 0.83 (s, 3 H, 1-C$H_3$), 0.88 (d, $J$ = 6.6 Hz, 3 H, 2-C$H_3$), 0.90 (s, 3 H, 1-C$H_3$), 1.23−1.40 (m, 1 H), 1.55−1.73 (m, 2 H), 2.21−2.27 (m, 2 H, 4-$H_2$), 2.25 (s, 3 H, 10-$H_3$), 2.65 (d, $J$ = 9.1 Hz, 1 H, 6-H), 4.66 (br. s, 1 H, =C$H$H), 4.75 (br. s, 1 H, =CH$H$), 6.11 (d, $J$ = 15.7 Hz, 1 H, 8-H), 7.09 (dd, $J$ = 15.7, 9.1 Hz, 1 H, 7-H) ppm. $^{13}$C NMR: δ = 15.5 (3), 21.4 (3), 27.0 (3), 27.3 (3), 31.4 (2 × 2), 36.2 (1), 37.6 (0), 59.5 (1), 110.4 (2), 131.8 (1), 147.4 (1), 147.9 (0), 198.3 (0) ppm. GCMS: *m*/*z* (%) = 206 (2) [M$^+$], 191 (4), 178 (8), 163 (29), 149 (21), 145 (9), 135 (10), 133 (6), 121 (58), 109 (28), 107 (24), 105 (12), 95 (9), 93 (18), 91 (26), 83 (17), 81 (38), 79 (28), 77 (23), 65 (15), 55 (39), 43 (100), 41 (42). The spectroscopic data are consistent with the literature data.[4b] The *ee* of *cis*-γ-irone (**4**) was estimated by enantioselective GC analysis with a DMePeBETACDX column (25 m, 0.25 mm i.d., 0.25 μm f.t.); carrier gas = He, split 1:50, flow = 1 mL/min; detector: FID; temperature program: 80 °C (0 min), then 2°C/min to 160 °C (5 min); (2*R*,6*S*)-*cis*-**4**, $t_R$ = 39.6 min; (2*S*,6*R*)-*cis*-**4**, $t_R$ = 40.0 min. The *ee* of *trans*-γ-irone **5** was estimated by enantioselective HPLC analysis with a Chiralcel® OD column (4.6 × 250 mm). UV detector (254 nm); hexane/*i*PrOH = 99:1, 0.6 mL/min; (2*R*,6*R*)-*trans*-**5**, $t_R$ = 23.6 min; (2*S*,6*S*)-*trans*-**5**, $t_R$ = 26.6 min.

**Methyl (*Z*)-Ester 15:** A solution of methyl acetoacetate (6.3 g, 54.0 mmol) in dry THF (50 mL) was added dropwise to NaH (60% dispersion in mineral oil, 2.38 g, 59.4 mmol) in THF (100 mL) at 0 °C and the mixture was stirred for 15 min at the same temperature. BuLi (2.5 M solution in hexanes, 22.7 mL, 56.7 mmol) was then added dropwise and the mixture was stirred at 0 °C for an additional 15 min. To the resulting orange solution freshly prepared bromide **16**[13] (8.8 g, 54.0 mmol) was added dropwise and the mixture was stirred for 1 h while warming to room temperature, then it was cooled to 0 °C and diethyl chlorophosphate (9.8 g, 56.7 mmol) was added dropwise. The resulting mixture was stirred for an additional 1.5 h while warming to room temperature, then it was slowly added via cannula to a mixture of $Me_3SiCH_2MgCl$ and $Ni(acac)_2$ at 0 °C, prepared meanwhile from Mg (2.23 g, 91.8 mmol) and $Me_3SiCH_2Cl$ (11.3 g, 91.8 mmol) in dry $Et_2O$ (90 mL), to which the Ni catalyst (971 mg, 3.78 mmol) was added 15 min before the addition of the enol phosphate. After complete addition (30 min), the mixture was stirred at 0 °C for 1 h and eventually poured into a mixture of 1 M aq. HCl and $Et_2O$ at 0 °C under vigorous stirring; the separated organic phase was washed with a further portion of 1 M HCl, and the aqueous phase was extracted with $Et_2O$. The combined organic layers were washed with brine, dried ($Na_2SO_4$), and the solvents evaporated. Separation of the crude product by flash silica gel column chromatography (hexanes/EtOAc, 100:0 → 98:2) gave 6.04 g of ester **15** as a pale yellow oil (42% yield). IR: ṽ = 2952, 2863, 1716, 1625, 1504, 1435, 1371, 1249, 1235, 1190, 1158, 1035, 926, 844, 695, 630 cm$^{-1}$. $^1$H NMR: δ = 0.05 [s, 3 × 3 H, Si(C$H_3$)$_3$], 1.62 [s, 3 × 3 H, C$H_3$C=C(C$H_3$)$_2$], 2.02−2.21 (m, 4 H, C$H_2$C$H_2$), 2.42 (s, 2 H, C$H_2$Si), 3.63 (s, 3 H, OC$H_3$), 5.53 (s, 1 H, =C$H$) ppm. $^{13}$C NMR: δ = −1.0 (3 × 3), 18.3 (3), 19.9 (3), 20.5 (3), 26.1 (2), 33.4 (2), 39.1 (2), 50.3 (3), 110.8 (1), 125.0 (0), 126.3 (0), 164.8 (0), 167.6 (0) ppm. GCMS: *m*/*z* (%) = 268 (2) [M$^+$], 253 (19), 237 (5), 194 (8), 186 (11), 171 (22), 164 (12), 149 (26), 136 (15), 122 (16), 121 (60), 120 (14), 107 (17), 93 (18), 89 (21), 83 (46), 82 (76), 73 (100), 67 (12), 59 (11), 55 (44), 45 (24), 43 (13), 41 (25). $C_{15}H_{28}O_2Si$ (268.47): calcd. C 67.11, H 10.51; found C 67.22, H 10.43.

**Methyl (±)-(2*RS*,6*RS*)-2-Methyl-γ-cyclogeraniate [(±)-*cis*-7 and (±)-*trans*-7]. (a) Procedure A:** $SnCl_4$ (1 M in $CH_2Cl_2$, 26.9 mL, 26.9 mmol) was added to a solution of diene **15** (1.80 g, 6.70 mmol) in $CH_2Cl_2$ (70 mL), saturated with $H_2O$ at −30 °C. The mixture was stirred between −30 °C and −20 °C for 2 h, then quenched with satd. aq. $NaHCO_3$, and stirred at room temperature for

further 15 min. The mixture was transferred into a separating funnel, diluted with $CH_2Cl_2$ and washed with 1 M HCl until two clear phases were obtained. The phases were separated, the organic phase was washed with a further portion of 1 M HCl and the aqueous phase was extracted with $CH_2Cl_2$; the combined organic layers were washed with satd. aq. $NaHCO_3$, followed by brine, dried ($Na_2SO_4$), and the solvents evaporated at atmospheric pressure. Purification of the crude product by flash silica gel column chromatography (hexanes/EtOAc, 98:2 → 96:4) gave product (±)-**7** as a pale yellow oil (1.12 g, 85% yield; *trans*/*cis* = 1.5:1). Spectroscopic data match those of enantiomerically pure diastereomers reported above. **(b) Procedure B:** Diene ester **15** (1.2 g, 4.5 mmol) was exposed to a solution of $Hg(OCOCF_3)_2$ in deoxygenated $CH_3CN$ at −40 °C according to the procedure described for the cyclization of ester (*S*)-**6** (see above). Workup of the reaction mixture and chromatographic separation of the crude mixture afforded, in the order, compound (±)-**7** (0.50 g, 57% yield; *trans*/*cis* = 1:7) and the desilylated ester **22** (154.3 mg, 17.5% yield), as a colorless oil. $^1$H NMR: δ = 1.68 [s, 3 × 3 H, $CH_3C{=}C(CH_3)_2$], 2.10−2.25 (m, 4 H, $CH_2CH_2$), 3.12 (s, 2 H, $CH_2COOCH_3$), 3.75 (s, 3 H, $OCH_3$), 4.90 (s, 1 H, =C*H*H), 4.95 (s, 1 H, =CH*H*) ppm. GCMS: *m*/*z* (%) = 196 (2) [$M^+$], 140 (18), 136 (24), 123 (13), 121 (13), 107 (13), 83 (89), 81 (29), 67 (22), 55 (100), 41 (36).

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[1] [1a] A. Tschirsch, "Rizoma Iridis", in *Handbuch der Pharmakognosie*, C. H. Tachnitz Verlag, Leipzig, **1917**, p. 1143. [1b] G. Ohloff, in *Scent and Fragrancies*, Springer-Verlag, Berlin-Heidelberg, **1994**; p. 164. [1c]L. Jaenicke, F. J. Marner, *Pure Appl. Chem.* **1990**, *62*, 1365−1368.

[2] [2a] W. Krick, F. J. Marner, L. Jaenicke, *Helv. Chim. Acta* **1984**, *67*, 318−323. [2b] V. Rautenstrauch, B. Willhalm, W. Thommen, G. Ohloff, *Helv. Chim. Acta* **1984**, *67*, 325−331. [2c] F. J. Marner, L. Jaenicke, *Helv. Chim. Acta* **1989**, *72*, 287−294. [2d] F. J. Marner, T. Runge, W. A. König, *Helv. Chim. Acta* **1990**, *73*, 2165−2170. [2e] A. Galfré, P. Martin, M. Petrizlka, *J. Essent. Oil Res.* **1993**, *5*, 265−277. [2f] E. Brenna, C. Fuganti, S. Ronzani, S. Serra, *Helv. Chim. Acta* **2001**, *84*, 3650−3666. [2g] E. Brenna, C. Fuganti, S. Serra, *Tetrahedron: Asymmetry* **2003**, *14*, 1−42.

[3] E. Brenna, M. Delmonte, C. Fuganti, S. Serra, *Helv. Chim. Acta* **2001**, *84*, 69−86.

[4] (−)-*trans*-γ-Irone + (+)-*trans*-α-irone: [4a] D. Helmlinger, G. Fràter, *Helv. Chim. A*cta **1989**, *72*, 1515−1521. (−)-*trans*-γ-Irone + (−)-*cis*-γ-irone (separated by prep. GC): [4b]C. Chapuis, R. Brauchli, *Helv. Chim. Acta* **1993**, *76*, 2070−2088. (−)-*trans*-γ-Irone: ref.[2f] (+)-*trans*-γ-Irone [(*Z*)/(*E*) mixture]: [4c] M. Miyashita, N. Makino, M. Singh, A. Yoshikoshi, *J. Chem. Soc., Perkin Trans. 1* **1982**, 1303−1309. (+)-*trans*-γ-Irone: [4d] H. Monti, G. Audran, J.-P. Monti, G. Leandri, *J. Org. Chem.* **1996**, *61*, 6021−6023; ref.[2f] (±)-*trans*-γ-Irone + (±)-*cis*-γ-irone: [4e] T. Kitahara, K. Tanida, K. Mori, *Agric. Biol. Chem.* **1983**, *47*, 581−586. [4f] F. Leyendecker, M.-T. Comte, *Tetrahedron* **1987**, *43*, 85−92. [4g] P. Gosselin, A. Perrotin, S. Mille, *Tetrahedron* **2001**, *57*, 733−738. (±)-*trans*-γ-Irone: [4h] H. Favre, H. Schinz, *Helv. Chim. Acta* **1958**, *41*, 1368−1376. [4i] J. Garnero, D. Joulain, *Bull. Soc. Chim. Fr.* **1979**, II-15−II-16. [4j]O. Takazawa, K. Kogami, K. Hayashi, *Bull. Chem. Soc., Jpn.* **1985**, *58*, 389−390. [4k] T. Kawanobe, M. Iwamoto, K. Kogami, M. Matsui, *Agric. Biol. Chem.* **1987**, *51*, 791−796; ref.[2f] (−)-*cis*-γ-Irone: [4l] T. Inoue, H. Kiyota, T. Oritani, *Tetrahedron: Asymmetry* **2000**, *11*, 3807−3818; ref.[3] (+)-*cis*-γ-Irone: ref.[4l] [4m] G. Laval, G. Audran, J-M. Galano, H. Monti, *J. Org. Chem.* **2000**, *65*, 3551−3554; ref.[3]; (±)-*cis*-γ-Irone: ref.[4k] [4n] C. Nussbaumer, G. Fráter, *Helv. Chim. Acta* **1988**, *71*, 619−623. [4o] H. Monti, G. Laval, M. Féraud, *Eur. J. Org. Chem.* **1999**, 1825−1829.

[5] R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841−1860.

[6] [6a] J. K. Sutherland, "Polyene cyclizations" in *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming) Pergamon Press, Oxford, New York, Seoul, Tokyo, **1991**, vol. 3, p. 341−377. [6b]E. Langkopf, D. Schinzer, *Chem. Rev.* **1995**, *95*, 1375−1408.

[7] [7a] I. Fleming, A. Pearce, R. L. Snowden, *J. Chem. Soc., Chem. Commun.* **1976**, 182−183. [7b] R. J. Armstrong, F. L. Harris, L. Weiler, *Can. J. Chem.* **1982**, *60*, 673−675. [7c] R. J. Armstrong, L. Weiler, *Can. J. Chem.* **1983**, *61*, 2530−2539. [7d] G. Vidari, G. Lanfranchi, F. Masciaga, J-D. Meriggi, *Tetrahedron: Asymmetry* **1996**, *7*, 3009−3020.

[8] For electrophilic cyclizations of dienes in irone synthesis, see: [8a] C. Chapuis, K. H. Schulte-Elte, *Helv. Chim. Acta* **1995**, *78*, 165−176. [8b] K. H. Schulte-Elte, H. Pamingle, A. P. Uijttewal, R. L. Snowden, *Helv. Chim. Acta* **1992**, *75*, 759−765 and references cited therein. [8c] S. Torii, K. Uneyama, S. J. Matsunami, *J. Org. Chem.* **1980**, *45*, 16−20.

[9] J. C. Hanekamp, R. B. Rookhulzen, H. J. T. Bos, L. Brandsma, *Tetrahedron* **1992**, *48*, 5151−5162.

[10] T. Suga, S. Ohta, T. Ohmoto, *J. Chem. Soc., Perkin Trans. 1* **1987**, 2845−2848.

[11] J. D. White, G. N. Reddy, G. O. Spessard, *J. Chem. Soc., Perkin Trans. 1* **1993**, 759−767.

[12] [12a] S. N. Huckin, L. Weiler, *J. Am. Chem. Soc.* **1974**, *96*, 1082−1087. [12b] F. W. Sum, L. Weiler, *Tetrahedron* **1981**, *37, Supplement I*, 303−317.

[13] E. L. Clennan, X. Chen, *J. Am. Chem. Soc.* **1989**, *111*, 5787−5792.

[14] S. Beszant, E. Giannini, G. Zanoni, G. Vidari, *Tetrahedron: Asymmetry* **2002**, *13*, 1245−1255.

[15] The $^1$H NMR spectrum ($\delta_{4\text{-H}}$ = 5.55 ppm; $\delta_{5\text{-Me}}$ = 1.68 ppm) revealed also the presence (ca.15%) of the endocyclic olefin **7a**.

[16] The relative stereochemistry of compound **7** and derivatives can easily be assigned on the basis of the chemical shift values of the vinyl protons, see: [16a] J.-P. Pillot, G. Déléris, J. Dunoguès, R. Calas, *J. Org. Chem.* **1979**, *44*, 3397−3400. [16b] M. G. Organ, D. D. Winkle, J. Huffmann, *J. Org. Chem.* **1997**, *62*, 5254−5266). In *cis*-**7** these two proton signals are separated farther than in *trans*-**7** (δ = 4.67 and 4.85 ppm vs. δ = 4.76 and 4.85 ppm, respectively).

[17] To this purpose, cyclizations promoted by "onio" species resemble those initiated by protonation of the terminal epoxide of a polyolefin; see: ref.[6a] and: [17a] R. J. Armstrong, L. Weiler, *Can. J. Chem.* **1986**, *64*, 584−596 and references cited therein.

[18] [18a] M. Kurbanov, A. V. Semenovsky, W. A. Smit, L. V. Shmelev, V. F. Kucherov, *Tetrahedron Lett.* **1972**, 2175−2178. [18b] E. J. Corey, M. A. Tius, J. Das, *J. Am. Chem. Soc.* **1980**, *102*, 7612−7613. [18c] T. R. Hoye, A. J. Caruso, M. J. Kurth, *J. Org. Chem.* **1981**, *46*, 3550−3552. [18d] M. Nishizawa, H. Takenaka, H. Nishide, Y. Hayashi, *Tetrahedron Lett.* **1983**, *24*, 2581−2584. [18e] M. Nishizawa, H. Takenaka, Y. Hayashi, *J. Org. Chem.* **1986**, *51*, 806−813. [18f] M. Nishizawa, H. Takenaka, T. Kohno, H. Takao, H. Yamada, *Chem. Pharm. Bull.* **1993**, *41*, 791−792.

[19] Interestingly, reduction of a *cis*/*trans* = 1:2 mixture of compound **7** with $LiAlH_4$ returned a *cis*/*trans* = 1:5 mixture of compound **21a**.

  

[20] [20a] Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. KO, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780. [20b] V. S. Martin, S. S. Woodard, T. Kabuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc.* **1981**, *103*, 6237−6240.
[21] K. B. Sharpless, T. R. Verhoeven, *Aldrichim. Acta* **1979**, *12*, 63−74.
[22] S. Matsubara, T. Nonaka, Y. Okuda, S. Kanemoto, K. Oshima, H. Nozaki, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1480−1483.
[23] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.
[24] Available reference data: $[\alpha]_D^{20} = -5.4$ ($c = 1.66$, $CH_2Cl_2$), *ee* = 76%.[4b] $[\alpha]_D < -2$, *ee* = 99%.[4l] $[\alpha]_D^{20} = -6.3$ ($c = 1.05$, $CH_2Cl_2$), *ee* = 97%.[3]
[25] Available reference data: $[\alpha]_D^{20} = -43.3$ ($c = 0.8$, $CH_2Cl_2$), *ee* = 70%;[4a] $[\alpha]_D^{20} = -53.4$ ($c = 2.34$, $CHCl_3$), *ee* = 76%;[4b] $[\alpha]_D^{20} = -81$ ($c = 1.0$, $CH_2Cl_2$), *ee* > 99%[2e].

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