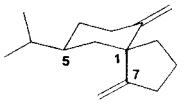
# Synthesis of (−)-Erythrodiene and (+)-7-Epispirojatamol *via* Intramolecular Pd-Catalyzed Allylzincation[1])

by **Wolfgang Oppolzer**[2]) and **Felix Flachsmann**[3])*

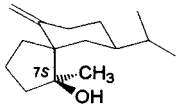
Département de Chimie Organique, Université de Genève, CH-1211 Genève 4

Two spirobicyclic sesquiterpenoids, (−)-erythrodiene (**1**) and (+)-7-epispirojatamol (**30**), were synthesized in enantiomerically pure form *via* an intramolecular allylzincation process. The allylzinc species were formed in the presence of $Et_2Zn$ *via* transmetallation of a catalytically generated allylpalladium intermediate. Several Pd catalysts were tested for this transformation, and $[Pd(OAc)_2]/Bu_3P$ (1 equiv.) was found to be, by far, the most effective. Whereas the preparation of **1** involved allylzincation of a tethered terminal olefin, **30** was formed *via* a novel intramolecular allyl zincation of a methyl ketone. Both reactions showed the same stereochemical preference, yielding the spirobicyclic products in 95:5 and 4:1 diastereoisomer ratios, respectively.

**1. Introduction.** – (−)-Erythrodiene (**1**) and (+)-spirojatamol (**2**) are two structurally closely related sesquiterpenes that have been isolated from widely diverse organisms. (+)-Spirojatamol (**2**) was found to be a constituent of the roots and rhizomes of the Indian plant *Nardostachys jatamansi*, which is used in traditional Indian medicine for the treatment of a variety of diseases, including epilepsy and mental disorders [1]. Its structure, including the absolute and relative configuration, was reported in 1989 by *Bagchi et al.* [1]. (−)-Erythrodiene ((−)-**1**) was isolated from the Caribbean soft coral *Erythropodium caribaeorum* by *Fenical* and co-workers, and the (1*S*,5*S*)-configuration[4]) was tentatively assigned based on its similarity with spirojatamol [2].




**1** (-)-erythrodiene
(trivial numbering)




**2** (+)-spirojatamol

Efforts directed at the synthesis of these two unusual spirobicyclic natural products have resulted in one total synthesis of optically pure (−)-erythrodiene (**1**) and (−)-spirojatamol (*ent*-**2**) by *Huang et al.*, as well as two independent approaches to the racemic compounds [3–5]. All the employed strategies feature a key C(1)–C(7) cyclization step. With the exception of a moderate 7:3 *anti*-selectivity obtained in an

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[1]) Parts of this work have been published in preliminary form [7].

[2]) Deceased March 15, 1996.

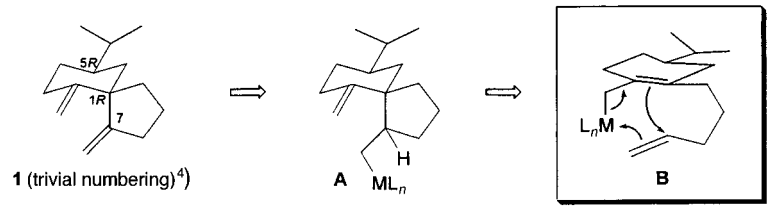
[3]) Current address: *Givaudan S.A.*, Überlandstrasse, CH-8400 Dübendorf (phone 01-824 22 65; fax 01-824 29 26; e-mail: felix.flachsmann@givaudan.com).

[4]) Trivial numbering in **1**, **2**, **4**, **12**, **13**, **24**, **25**, and **30**; for systematic names, see *Exper. Part.*

intramolecular carbomercuration reaction [3][4], no diastereocontrol was observed in the formation of spiro center C(1).

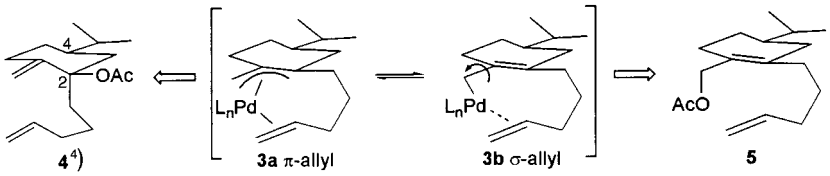
As part of our long-standing interest in the application of intramolecular allyl metalations ('metallo-ene reactions' [6]) to the synthesis of natural products, we identified (−)-erythrodiene (**1**) as a potential target molecule for an unprecedented intramolecular metallo-ene spirocyclization **A** → **B** (*Scheme 1*) [7].

*Scheme 1*




With Pd as the metal of choice, the ene process would be followed by a $\beta$-hydride elimination from **A** (M = Pd$^{II}$), yielding directly the target compound. Systematic studies from our laboratory as well as many applications of the palladium-ene reaction to the synthesis of complex polycyclic natural products over the past 10 years have shown that pre-existing stereogenic centers strongly influence the stereochemical outcome of this reaction [8]. We reasoned that the conformational mobility of the $\sigma$-allylpalladium intermediate **3b** (*Scheme 2*) would result in a preferred cyclization from the ring side opposite the isopropyl substituent at C(4)[4]). Nonbonding interactions would be minimized, and the reaction would lead to the correct configuration at the spiro center.

*Scheme 2*

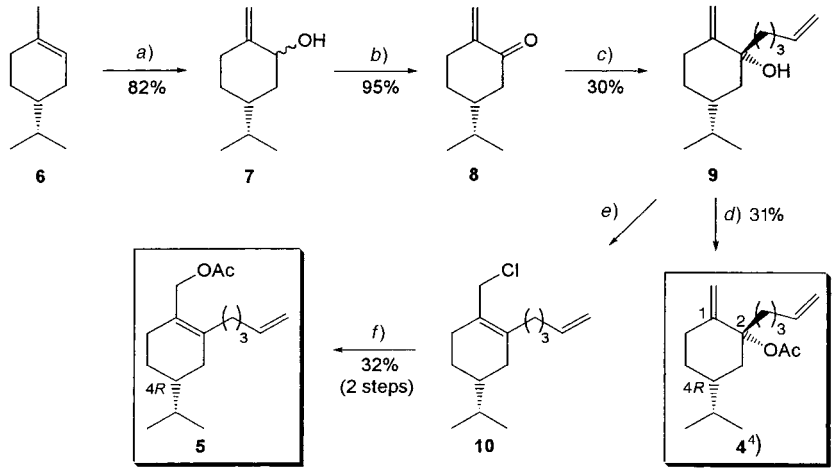



Allylpalladium precursor **3** can be generated *via* oxidative addition of either tertiary or primary allyl acetate **4** or **5** to Pd$^0$ (*Scheme 2*). Tertiary acetate **4** seemed preferable as $\gamma$-disubstitution kinetically disfavors oxidative addition of allyl acetates to Pd$^0$ [9]. Furthermore, the stereoselectivity of the overall reaction might be improved by chirality transfer from C(2) in the matched (2*R*)-acetate **4**[4]) (oxidative additions of allyl acetates to Pd$^0$ complexes occur with inversion of configuration [10]).

**2. Results and Discussion.** – Our initial synthesis of acetates **4** and **5** is outlined in *Scheme 3*. According to a procedure of *Pietra* and co-workers, epoxidation with 3-chloroperbenzoic acid (*m*CPBA) and base-induced rearrangement of commercial (−)-*p*-menthene (**6**) yielded a 1:1 mixture of diastereoisomeric allyl alcohols **7** [11]. The oxidation of this mixture led to $\alpha$-santolinenone (**8**), a product that had been

erroneously described as a natural product [11][12]. The product was obtained by *Pietra* and co-workers in only 25% yield with $Ag_2O$ as the oxidant [11]. To improve this step, we applied alternative oxidation protocols and found a gradual improvement from the *Swern* oxidation over tetrapropylammonium perruthenate (TPAP) to the *Dess-Martin* periodinane [13]. The latter led to a clean and quantitative oxidation of both diastereoisomeric alcohols. This optimization was crucial to the preparation of useful quantities of $\alpha$-santolinenone (**8**). Unfortunately, **8** dimerized rapidly *via* a hetero-*Diels-Alder* reaction (also observed by *Pietra* and co-workers [11]). This side reaction complicated the addition of the pentenyl side chain *via* the corresponding lithium or *Grignard* reagent. Moreover, the latter yielded substantial amounts of 1,4-addition product. Precomplexation of ketone **8** with anhydrous $CeCl_3$ followed by addition of the *Grignard* reagent, as described by *Dimitrov et al.*, was found to be the only practicable way to prepare the tertiary alcohol **9** [14]. The sterically hindered OH function of **9** proved to be inert in a variety of acetylation protocols, including on use of very active $Me_3SiOTf$ and scandium(II) catalysts [15][16]. The problem was finally overcome by deprotonating the alcohol with PhLi followed by reaction with $Ac_2O$. This afforded the desired (+)-acetate **4** in 31% yield along with 30% of unreacted starting material **9**. The primary (+)-acetate **5** was then obtained *via* reaction of **9** with thionyl chloride ($\rightarrow$ **10**) and subsequent nucleophilic substitution with potassium acetate in DMPU (*N*,*N*′-dimethylpropyleneurea = 3,4,5,6-tetrahydro-1,3-dimethylpyrimidin-2(1*H*)-one) [17].

*Scheme 3*




*a*) 1. *m*CPBA; 2. lithium diisopropylamide. *b*) *Dess-Martin* periodinane. *c*) $CeCl_3$, then $H_2C{=}CH(CH_2)_2CH_2MgBr$. *d*) PhLi, then $Ac_2O$. *e*) $SOCl_2$. *f*) KOAc, DMPU.

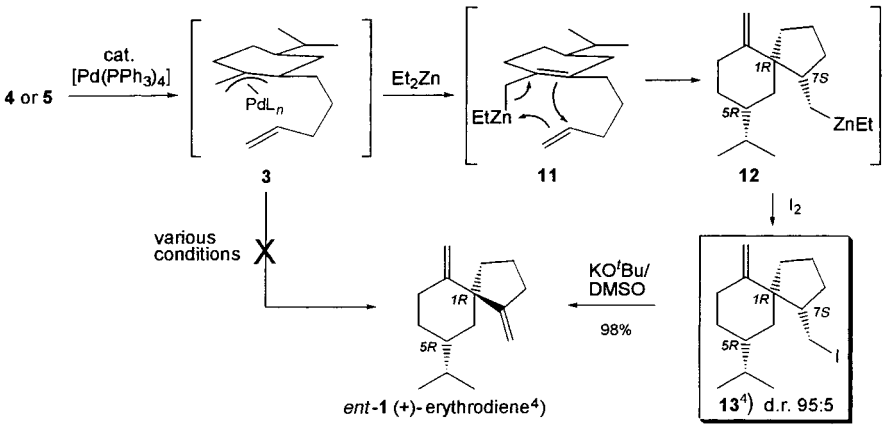
After exposing precursor **4** to the standard conditions for palladium-ene reactions, *i.e.* 5% of $[Pd(PPh_3)_4]$ in degassed AcOH at 80° for 2–20 h, mixtures of starting material, rearranged acetate **5**, and trienes were isolated. However, not even traces of a spirobicyclic product could be detected. The situation improved neither upon raising the temperature to 120° and prolonging the reaction time nor by more acidic conditions

(4 equiv. of $H_2SO_4$ in THF) [18]. Similar observations were made with primary acetate **5** as the starting material.

In view of these disappointing results, we turned to a Pd → Zn transmetallation protocol for the intermediate allylpalladium complex. The *in situ* generation of allylzinc species from catalytically formed allylpalladium complexes in the presence of an excess of diethylzinc and a ketone or ester was introduced by *Tamaru* and co-workers [19]. The allylzinc intermediate smoothly added to the carbonyl compound, resulting in an efficient overall preparation of homoallyl alcohols and ketones from allyl benzoates. In our laboratory, a convenient and highly stereoselective intramolecular allyl-zincation reaction was developed based on the Pd → Zn transmetallation [20]. This Pd-catalyzed zinc-ene reaction requires milder conditions than the palladium-ene reaction (Pd: AcOH, 80°; Zn: $Et_2O$, 35°). Its obvious advantage is the simplified access to the allylzinc intermediate compared to previous protocols for intramolecular allyl zincations[5]) [21].

Applying this protocol to tertiary acetate **4** resulted in a smooth spirocyclization. Quenching with $I_2$ provided iodo intermediate **13**, which was isolated in excellent 95 : 5 diastereoselectivity over two newly formed stereogenic centers (*Scheme 4*). The same stereochemical outcome and comparable yield were observed with primary acetate **5** as the starting material. This finding is in accordance with a 'zinc-ene' cyclization pathway to **12** *via* the 'flat' allylzinc intermediate **11** as depicted in *Scheme 4*.

*Scheme 4*




Base-induced dehydroiodination in virtually quantitative yield from iodide **13** afforded a diene *ent*-**1**, which showed spectroscopical data identical to those of (−)-erythrodiene (**1**), but with a positive sign of optical rotation. Therefore, (−)-erythrodiene must have the (1*S*,5*S*)-configuration[4]), a finding confirmed by *Forsyth* and *Huang* [3].

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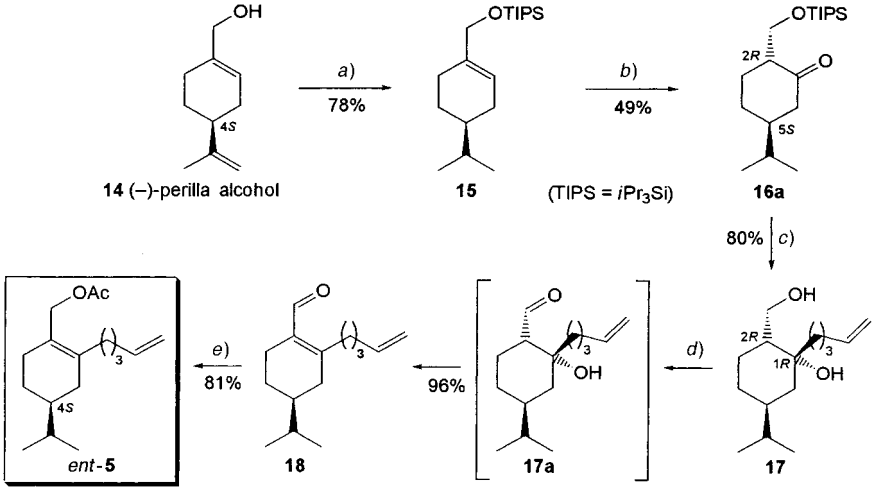
[5]) An alternative access to allylzinc species by fragmentation of homoallylzinc alkoxides has recently been introduced by *Millot* and *Knochel* [21b].

To address the target compound as its natural enantiomer and with regard to the difficulties encountered during the preparation of acetates **4** and **5** (*Scheme 3*), an improved synthesis for primary acetate *ent*-**5** was designed and carried out as depicted in *Scheme 5*. After selective hydrogenation of the exocyclic C=C bond of commercial (−)-perilla alcohol (**14**), the allyl alcohol was protected as its silyl ether **15**. Regioselective hydroboration/oxidation was followed by oxidation of the crude alcohol to yield a 1:1 mixture of diastereoisomeric ketones **16a**/**16b**. Base-induced equilibration afforded the pure *trans*-diastereoisomer **16a** (49% yield from **15**). The relative configurations *trans* and *cis* of **16a** and **16b**, respectively, were assigned based on the comparison of their relative $^{13}$C-NMR shifts with those of the known *trans*- and *cis*-5-(*tert*-butyl) analoga [22]. Addition of 4-pentenylmagnesium bromide to ketone **16a** and subsequent desilylation furnished diol **17**. Not surprisingly, $H_2O$ elimination from **17** under a variety of conditions yielded inseparable mixtures of double-bond isomers. To form regioselectively the desired 1,2-double bond, we decided to oxidize the primary OH function intermittently to the aldehyde. After some experimentation, conditions for a one-pot oxidation-elimination sequence were established by employing the *Parikh-Doering* oxidation protocol (DMSO, pyridine·$SO_3$, $Et_3N$) [23]. Simple addition of a wet basic MeOH solution after complete oxidation of the primary OH group led to the clean, quantitative formation of the desired $\alpha,\beta$-unsaturated aldehyde **18**. This process probably involved two steps: formation of a dimethyl sulfide adduct of the tertiary alcohol group in **17a**, followed by elimination of DMSO *via* the aldehyde enolate. The synthesis was completed by diisobutylaluminium hydride (DIBAH) reduction of aldehyde **18** and acetylation of the resulting allyl alcohol, which yielded the desired cyclization precursor *ent*-**5** in 27% yield over 9 steps with only three products to be purified.

*Scheme 5*




*a*) 1. $H_2$, $PtO_2$; 2. $^i$Pr$_3$SiCl, 1*H*-imidazole. *b*) 1. $BH_3\cdot Me_2S$, $H_2O_2$; 2. tetrapropylammonium perruthenate ($(Pr_4N)RuO_4$; TPAP), 4 Å molecular sieves, 4-methylmorpholine 4-oxide, (NMO); 3. $K_2CO_3$, MeOH. *c*) 1. $H_2C{=}CH(CH_2)_2CH_2MgBr$; 2. $Bu_4NF$. *d*) Py·$SO_3$, DMSO, $Et_3N$; then KOH/MeOH. *e*) 1. DIBAH 2. $Ac_2O$, DMAP.

Thus, having at our disposal an efficient access to the precursor *ent*-**5**, efforts to optimize the cyclization step could be undertaken. The moderate 51% yield of iodide **13** (*Scheme 6*) obtained with $[Pd(PPh_3)_4]$ as the catalyst (*Table*, *Entry 1*) was due to the incomplete conversion of the starting material and the formation of the reduced by-product **19**. To find a more effective Pd catalyst than $[Pd(PPh_3)_4]$, the influence of the ligand was studied. Surprisingly, with the more electron-rich tri(furan-2-yl)phosphine ($P(fur)_3$), diene **19** was the major product (*Table*, *Entry 2*). This observation indicates that a double reductive elimination on palladium as depicted in *Scheme 7* competed with the desired transmetalation. Generation of a hydridopalladium species such as **21** *via* ligand transfer from organozinc reagents ($\rightarrow$ **20**) and subsequent $\beta$-H-elimination is amply described in the literature [24].

On the other hand, cyclization in the presence of the 'naked' $Pd^0$ species obtained upon *in situ* reduction of $[Pd(OAc)_2]$ with 1 equiv. of $PBu_3$ led not only to a virtually complete conversion but also suppressed the undesired reduction pathway (*Table*, *Entry 3*) [25]. Finally, the yield of the cyclization step was substantially improved by increasing the amount of $Et_2Zn$ (*Table*, *Entry 4*). In view of these findings, a catalytic cycle for Pd involving **22** and **23** as presented in *Scheme 8* is proposed [19a][26].

*Scheme 6*

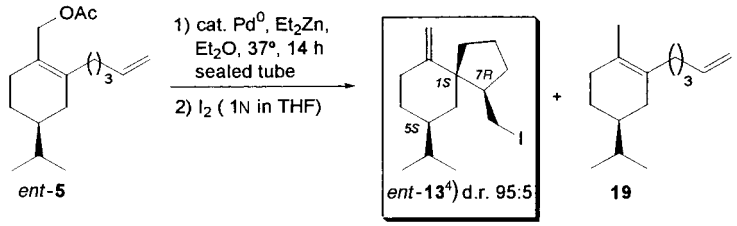


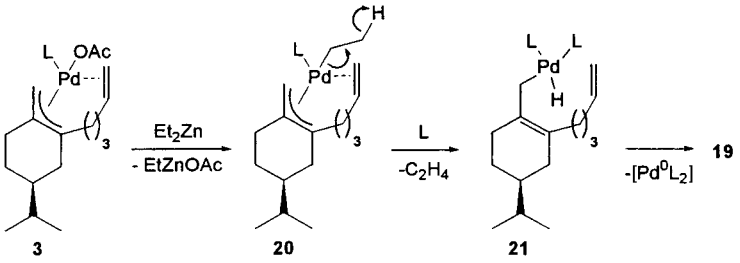

Table. *Cyclization of* ent-**5** *to the Spiro Compound* **13**: *Conditions and Yields*[a])

| *Entry* | Catalyst[b]) | $Et_2Zn$ [equiv.] | *ent*-**5** [%] | **19** [%] | *ent*-**13** [%] |
|---|---|---|---|---|---|
| *1* | 5% $[Pd(PPh_3)_4]$ | 10 | 10–15 | 15 | 51 |
| *2* | 5% $[Pd_2(dba)_3]$, 4 equiv. $P(fur)_3$ | 10 | 0 | (61)[a]) | (26)[a]) |
| *3* | 5% $[Pd(OAc)_2]$, 1 equiv. $P(Bu)_3$ | 10 | 0 | (3)[a]) | 72 |
| *4* | 5% $[Pd(OAc)_2]$, 1 equiv. $P(Bu)_3$ | 20 | 0 | 0 | 90 |

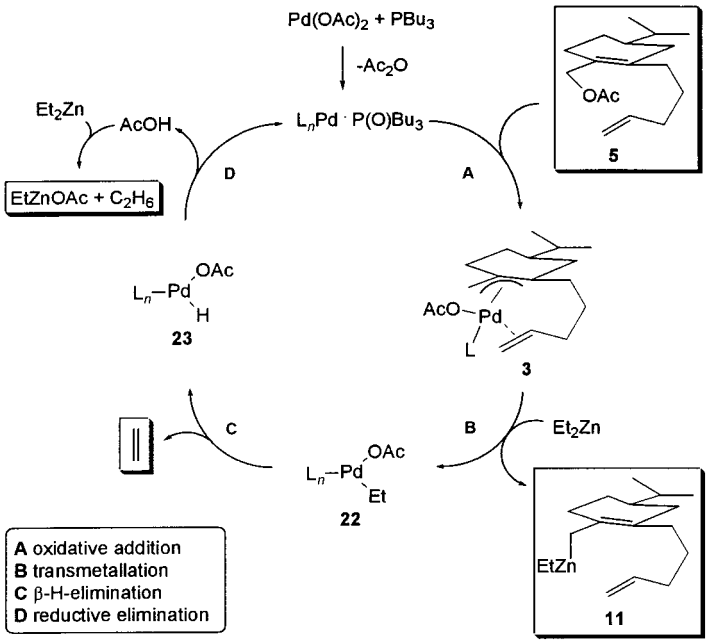
[a]) Yields of isolated material; yields in parentheses are GC yields. [b]) dba = Dibenzylideneacetone = 1,5-diphenylpenta-1,4-dien-3-one; fur = furan-2-yl.

After dehydroiodination (*Scheme 4*) and destruction of chiral center C(7)[4]), (−)-erythrodiene (**1**) was obtained from *ent*-**13** in the same 95:5 diastereoisomer ratio as observed for *ent*-**1** from iodide **13**. It follows that the two diastereoisomers obtained for iodide **13** are epimers at C(1)[4]). Therefore, chiral center C(7) must have been generated in a completely diastereoselective way on cyclization, which may be regarded as the consequence of a stereospecific concerted ene process. The minor isomer could be separated by column chromatography on $AgNO_3$-impregnated silica gel. Synthetic (−)-erythrodiene (**1**) thus obtained corresponded in all physical and spectroscopical data to those reported for the natural product (see *Exper. Part*).

*Scheme 7*



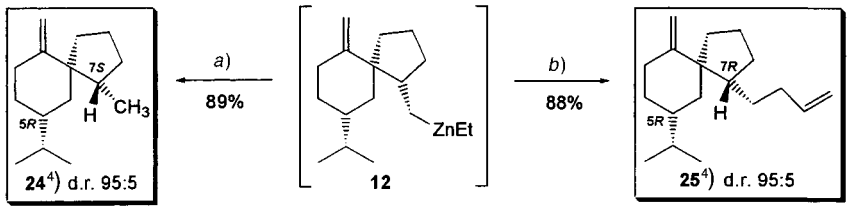

*Scheme 8*




To demonstrate the flexibility of the zinc-ene approach, the intermediate alkylzinc species **12** (prepared from the enantiomeric primary acetate **5**, see *Scheme 4*) was also subjected to protonation and $Cu^{I}$-promoted allylation (*Scheme 9*) [27]. Thereupon, the erythrodiene analogues **24** and **25**, respectively, could be isolated in high yields and the same diastereoselectivity as iodide **13**.

As a part of our initial project, the possibility of synthesizing (+)-spirojatamol (**2**) *via* intramolecular allyl metalation of a methyl ketone in the tethered chain was examined. *Tamaru* and co-workers reported allyl benzoates to give better yields than acetates in this type of reaction [19a]. Accordingly, the required ketone precursor **28** was readily assembled from the common intermediate *ent*-**16a** and the *Grignard* reagent **26** (*Scheme 10*). The relative *cis* configuration of the substituents at C(1) and C(2) in intermediate diol **27** was confirmed by a smooth intramolecular transketalization reaction in the presence of pyridinium *p*-toluenesulfonate (PPTS) to yield the

*Scheme 9*

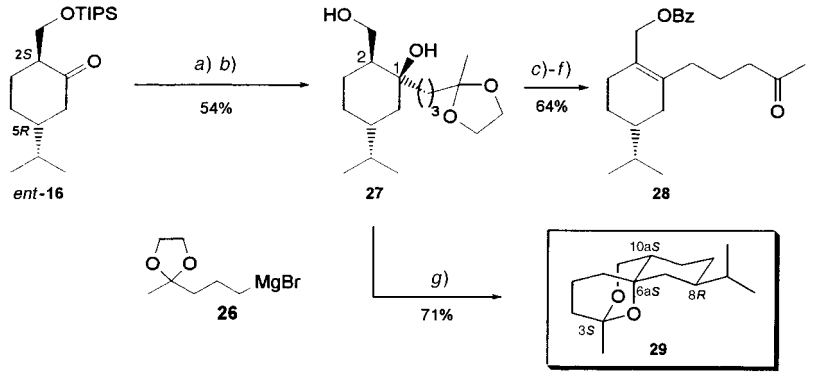



*a*) aq. $NH_4Cl$ soln. *b*) 1. $CuCN \cdot 2LiCl$; 2. allyl bromide

tricyclic 1,3-dioxane **29**. To the best of our knowledge, tricycle **29** belongs to an as yet undescribed skeleton class.

Initial attempts to effect the crucial intramolecular allylzincation on methyl ketone **28** under *Tamaru*'s conditions (5% $[Pd(PPh_3)_4]$, 2.5 equiv. of $Et_2Zn$ in THF) gave a poor 27% yield of bicyclic product **30** (*Scheme 12*). This result was improved again by employing the catalyst system $[Pd(OAc)_2]/Bu_3P$ 1:1 (5%) in the presence of 3.8 equiv. of $Et_2Zn$; thus, 42% of spirobicyclic alcohol **30** was isolated as a not readily separable 82:18 mixture of two diastereoisomers. Based on the relative position of the $^{13}$C-NMR signals of the spiro center of **30**, the (2*S*)-configuration was first assigned to the major isomer (53.1 *vs.* 55.4 ppm). However, the remaining $^{13}$C-NMR spectrum of this compound did not match the published data for (+)-spirojatamol (**2**). Careful NOE studies revealed that product **30** was the C(7)[4]) epimer of (+)-spirojatamol (**2**). This stereochemical outcome indicates that the cyclization occurs *via* a similar transition-state geometry as in the above zinc-ene reaction (*Scheme 11*).

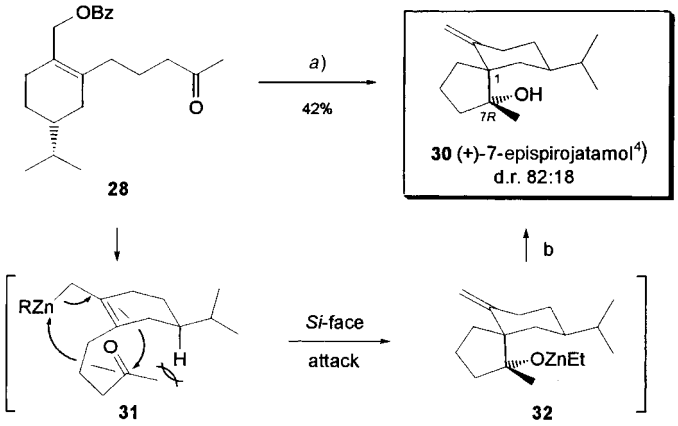
*Scheme 10*




*a*) **26**. *b*) $Bu_4NF$. *c*) 1. $Py \cdot SO_3$, DMSO, $Et_3N$; 2. KOH, $MeOH/H_2O$. *d*) DIBAH. *e*) PhCOCl, pyridine. *f*) pyridinium *p*-toluenesulfonate (PPTS), acetone/$H_2O$, reflux. *g*) PPTS, $C_6H_6$, reflux, 1 h.

**3. Conclusions.** – In summary, this work features a highly diastereoselective intramolecular Pd-catalyzed zinc-ene reaction as the key step in the total synthesis of (−)-erythrodiene (**1**). The choice of the palladium catalyst was shown to be crucial for the efficiency of the process. By far the best results were obtained with the $[Pd(OAc)_2]$/

*Scheme 11*




*a*) $Et_2Zn$ (3.8 equiv.), 5% $[Pd(OAc)_2]/Bu_3P$, THF, 20°, 24 h. *b*) aq. $NH_4Cl$ soln.

$Bu_3P$ catalyst. We demonstrated that the pivotal spirobicyclic zinc intermediate **12** was amenable to various derivatizations, including further C–C bond formation. Finally, the chemical feasability of an intramolecular allyl zincation of a methyl ketone moiety was demonstrated with the synthesis of (+)-7-epi-spirojatamol (**30**). The similar stereochemical outcome of the two reactions reflects their conceptual analogy. Future possibilites in this field include allyl zincations of 1,2-disubstituted C=C bonds to create chiral centers directly bound to Zn, as the configurational stability of chiral dialkylzinc compounds has recently been established [28]. Furthermore, the reuse of the palladium catalyst for subsequent coupling reactions of the alkylzinc intermediates (*e.g.* with acid chlorides [29]) might be envisaged.

The author thanks Dr. *Chantal Wiaux-Zamar*, Professor *Ernst Peter Kündig*, and Dr. *Rita Cannas* for critical reading of the manuscript. Financial support of this work by the *Swiss National Science Foundation* is gratefully acknowledged. The author wishes to thank the *Stipendienfonds der Basler Chemischen Gesellschaft* for a PhD scholarship.

## Experimental Part

*General*. All reactions were carried out with magnetical stirring and, if $O_2$- or moisture-sensitive, under Ar. Solvents were dried by distillation from drying agents as follows: $Et_2O$ and THF (Na/benzophenone), toluene (Na), $CH_2Cl_2$, and $Et_3N$ ($CaH_2$). Workup denotes extraction with an org. solvent, washing with $H_2O$ and brine, drying of the org. layer ($MgSO_4$), and evaporation. M.p.: *Kofler* hot stage; uncorrected. Optical rotation ($[\alpha]_D$): *Perkin-Elmer 241* polarimeter at 20° ± 1°; concentration (*c*) in g/100 ml. IR Spectra: *Perkin-Elmer 1600 FTIR*; solids in KBr pellets, liquids as thin films; in $cm^{-1}$. $^1$H-NMR Spectra: unless otherwise stated, at 400 MHz in $CDCl_3$; chemical shifts $\delta$ in ppm rel. to $SiMe_4$ at 0 ppm, *J* in Hz. $^{13}$C-NMR Spectra: unless otherwise stated, at 100.6 MHz in $CDCl_3$. MS: *Varian CH-4* or *Finnigan 4023*; *m/z* (rel. %).

*1-Bromo-3-(2-methyl-1,3-dioxolan-2-yl)propane* was prepared from 1-bromo-pent-4-ene by *Wacker* oxidation [30] and subsequent ketalization with ethylene glycol [31]. Spectroscopic data: in accordance with [32].

*(5*R*)-2-Methylidene-5-isopropylcyclohexanone* (= *α-Santolinenone*; **8**). The diastereomer mixture of allyl alcohols **7** (2.03 g, 13.2 mmol) in dry $CH_2Cl_2$ (40 ml) was added to the slightly cloudy solution of *Dess-Martin* periodinane (8.08 g, 19.7 mmol, 1.5 equiv.) in $CH_2Cl_2$ (80 ml). After stirring at 25° for 3.5 h with air contact, $Et_2O$ (120 ml) was added and the resulting white suspension treated with 1N aq. NaOH (100 ml). After 15 min, a

clear biphasic mixture had formed. The org. layer was washed with 1N aq. NaOH (100 ml), then $H_2O$, and brine, dried ($MgSO_4$), and evaporated in the cold: crude **8** (*ca.* 2.1 g, *ca.* 100%). The clear colorless oil was immediately redissolved in THF for the subsequent reaction. A sample of **8** was isolated and quickly submitted to $^1$H-NMR and IR analysis. Strong minty smell, reminiscent of carvone. $[\alpha]_{578} = +37.7$, $[\alpha]_{546} = +44.2$, $[\alpha]_{436} = +99.0$, $[\alpha]_{365} = +320.0$ (EtOH, $c = 0.9$). IR: 2963*s*, 2838*s*, 1725*s*, 1694v*s*, 1600*m*, 1388*m*, 1363*m*, 1294*m*, 1163*m*, 944*m*. $^1$H-NMR: 5.82 (*t*, $J = 22$, 1 H); 5.13 (*m*, 1 H); 2.78–2.30 (*m*, 3 H); 2.09 (*dd*, $J = 16.6, 11.8$, 1 H); 1.95–1.81 (*m*, 1 H); 1.77–1.25 (*m*, 3 H); 0.90 (*d*, $J = 6.7$, 3 H); 0.89 (*d*, $J = 6.6$, 3 H).

*(1*R*,5*R*)-5-Isopropyl-2-methylidene-1-(pent-4-enyl)cyclohexanol* (**9**). $CeCl_3 \cdot 7\,H_2O$ (270 mg, 1.1 mmol, 1.2 equiv.) was dried by heating it slowly to 135° at 0.1 Torr and keeping it at 135°/0.1 Torr for 20 h. After cooling to 25°, THF (1 ml) was added, yielding a white paste to which the freshly prepared **8** was added (140 mg, 0.92 mmol) as a soln. in THF (1 ml). After 1.5 h, the mixture became a white, shiny gel. Then 0.8M *Grignard* reagent (1.5 ml, 1.20 mmol, 1.3 equiv.), freshly prepared from 1-bromopent-4-ene in THF, was added *via* cannula within 7 min at 25°. The gel cleared to yield a yellowish thin emulsion. After further 30 min stirring at 25°, 10% aq. AcOH (10 ml) was added and the mixture worked up as usual. Purification by FC (hexane/$Et_2O$ 9:1) yielded diastereoisomerically pure (by NMR) **9** (62 mg, 30%). IR: 3448*m*, 3070*w*, 2933*s*, 2860*m*, 1665*w*, 1640*m*, 1450*m*, 1447*m*, 1369*w*, 1367*w*, 995*w*, 907*s*. $^1$H-NMR: 5.80 (*ddt*, $J = 16.9, 10.2, 6.6$, 1 H); 5.00 (br. *d*, $J = 16.9$, 1 H); 4.95 (br. *d*, $J = 10.3$, 1 H); 4.92 (*s*, 1 H); 4.78 (*s*, 1 H); 2.34 (*ddd*, $J = 13.8, 4.0, 2.6$, 1 H); 2.08–1.99 (*m*, 3 H); 1.89 (*dt*, $J = 12.5$, *ca.* 3, 1 H); 1.81–1.64 (*m*, 3 H); 1.52–1.22 (*m*, 5 H); 1.09 (*t*, $J = 12.8$, 1 H); 1.02 (*qd*, $J = 12.8, 3.5$, 1 H); 0.84 (*d*, $J = 6.4$, 3 H); 0.83 (*d*, $J = 6.4$, 3 H). $^{13}$C-NMR: 153.65 (*s*); 138.88 (*d*); 114.51 (*t*); 105.84 (*t*); 75.67 (*s*); 45.25 (*t*); 41.66 (*d*); 37.07 (*t*); 33.96 (*t*); 33.42 (*t*); 32.47 (*d*); 31.02 (*t*); 22.34 (*t*); 19.83 (*q*); 19.75 (*q*). MS (formation of a self-condensation product): 426 (4, ($[2M^+ - H_2O]^+$), 374 (5), 329 (13), 305 (7), 222 (5, $M^+$), 192 (18), 153 (39), 140 (35), 135 (21), 121 (22), 109 (49), 81 (67), 69 (93), 55 (100). HR-MS: 222.19980 ($C_{15}H_{26}O^+$; calc. 222.19836).

*(1*R*,5*R*)-5-Isopropyl-2-methylidene-1-(pent-4-enyl)cyclohexyl Acetate* (**4**). To a soln. of **9** (260 mg, 1.17 mmol) in $Et_2O$ (5 ml), 1.8M PhLi in cyclohexane/$Et_2O$ 7:3 (1 ml, 1.80 mmol, 1.5 equiv.) was added. The yellow soln. was stirred for 1 h at 25°, then freshly distilled $Ac_2O$ (194 mg, 1.90 mmol, 1.6 equiv.) was introduced dropwise. During the addition, a precipitate was formed. The soln. was stirred for 30 min more, then the reaction was quenched with $H_2O$. Usual workup and FC (pentane/$Et_2O$ 25:1 → 1:1) yielded 95 mg (31%) of **4** and 120 mg (46%) of starting material. $[\alpha]_D = +66$, $[\alpha]_{578} = +70$, $[\alpha]_{546} = +79$, $[\alpha]_{436} = +135$, $[\alpha]_{365} = +215$ ($CHCl_3$, $c = 0.8$). IR: 3077*w*, 2957v*s*, 2857v*s*, 1736v*s*, 1643*m*, 1457*m*, 1386*w*, 1367*s*, 1245v*s*, 1016*m*, 906*s*. $^1$H-NMR: 5.77 (*ddt*, $J = 17.1, 10.0, 6.6$, 1 H); 4.99 (br. *d*, $J = 17.1$, 1 H); 4.95 (br. *d*, $J = 10.3$, 1 H); 4.91 (*s*, 1 H); 4.84 (*s*, 1 H); 2.58 (br. *d*, $J = 11.8$, 1 H); 2.35–2.24 (*m*, 2 H); 2.12–1.39 (*m*, 2 H); 2.03 (*s*, 3 H); 1.83–1.72 (*m*, 2 H); 1.54–1.39 (*m*, 4 H); 1.26 (*quint.*, $J = 7.7$, 2 H); 1.09 (*qd*, $J = 12.6, 4.0$, 1 H); 0.87 (*d*, $J = 0.66$, 3 H); 0.86 (*d*, $J = 6.6$, 3 H). $^{13}$C-NMR: 169.61 (*s*); 147.90 (*s*); 138.73 (*d*); 114.56 (*t*); 107.84 (*t*); 86.89 (*s*); 40.98 (*d*); 40.39 (*t*); 33.59 (*t*); 33.13 (*t*); 33.07 (*t*); 32.45 (*d*); 30.24 (*t*); 22.34 (*t* + *q*); 19.96 (*q*); 19.46 (*q*). MS. 264 ($M^+$), 204 (16), 189 (13), 161 (100), 133 (24), 107 (54), 91 (60), 79 (44), 67 (28), 55 (24). HR-MS: 264.20816 ($C_{17}H_{28}O_2^+$; calc. 264.20892).

*Triisopropyl {[(4*S*)-4-isopropylcyclohex-1-enyl]methoxy}silane* (**15**). To the soln. of (−)-perilla alcohol (4.80 g, 31.5 mmol) in MeOH (30 ml), $PtO_2$ (15 mg, 0.07 mmol, 0.2%) was added. The flask was purged with $H_2$ and then left at 25° under 1 atm of $H_2$ with intense stirring. After 2 h (TLC: only traces of starting material), the mixture was filtered over a $SiO_2$ pad (25 cm) (rinsing with $Et_2O$. After concentration and bulb-to-bulb distillation at 100°/10 Torr, dihydroperilla alcohol (4.66 g, 96%) was obtained as a colorless oil with a strong, pleasant smell, with spectroscopic data identical to [2]. This alcohol (4.18 g, 27.1 mmol) and 1*H*-imidazole (3.64 g, 54.2 mmol, 2.0 equiv.) in dry DMF (20 ml) were treated dropwise with neat $^i$Pr$_3$SiCl (5.74 g, 29.8 mmol, 1.1 equiv.) at 0°. After removal of the cooling bath, the soln. was stirred for a further 20 min at 25°, then poured into $H_2O$ and extracted with hexane. After the usual workup, the crude oil was heated to 70° *in vacuo* (0.5 Torr) for 1 h to remove silanol by-products: 7.68 g (91%) of **15**. Clear colorless oil. $^1$H-NMR: 5.68 (br. *s*, 1 H); 4.09 (br. *s*, 2 H); 2.12–1.91 (*m*, 3 H); 1.82–1.69 (*m*, 2 H); 1.47 (*sext.*, $J = 6.4$, 1 H); 1.34–1.18 (*m*, 2 H); 1.08, 1.06 (2*s*, 21 H); 0.89 (*d*, $J = 6.6$, 3 H); 0.88 (*d*, $J = 6.6$, 3 H). $^{13}$C-NMR: 137.12 (*s*); 120.67 (*d*); 67.17 (*t*); 40.38 (*d*); 32.31 (*d*); 28.54 (*t*); 26.14 (*t*); 26.07 (*t*); 19.95 (*q*); 19.66 (*q*); 18.03 (*q*); 12.05 (*q*). MS: 310 (0.4, $M^+$), 267 (100, $[M^+ - C_3H_7]^+$), 225 (8), 181 (3), 131 (53), 103 (35), 75 (57).

*(2*R*,5*S*)- and (2*S*,5*S*)-5-Isopropyl-2-{[(triisopropylsilyl)oxy]methyl}cyclohexanone* (**16a** and **16b**). To a soln. of $BH_3 \cdot DMS$ (1.62 g, 21.1 mmol, 1.1 equiv.) in THF (20 ml), 0.5N **15** (6.01 g, 19.3 mmol) in THF was added dropwise within 20 min. After stirring for 2 h at 25°, 3N aq. NaOH (20 ml) was added, followed by 30% aq. $H_2O_2$ soln. (20 ml), both dropwise. The soln. was warmed to 50–60° and left at this temp. for 30 min. After 2 h, usual workup yielded 6.60 g of product as a clear colorless oil (1:1 diastereoisomer mixture, by GC and $^1$H-NMR). To the crude in $CH_2Cl_2$ (35 ml), 4-methylmorpholine 4-oxide (3.80 g, 32.4 mmol, 1.5 equiv.) was added, followed by

powdered, activated 4-Å molecular sieves (8.0 g). During the subsequent portionwise addition of TPAP (290 mg, 0.83 mmol, 5 mol-%), the soln. was warmed to reflux. After 1.5 h, the soln. was filtered through $SiO_2$ rinsing with $CH_2Cl_2$) and evaporated: 6.55 g (*ca.* 100%) of crude oil as a 1:1 diastereomer mixture. This product was equilibrated at 25° in half-sat. $K_2CO_3$ soln. in MeOH (80 ml), yielding a 9:2 diastereomer mixture within 30 min (by GC). The soln. was neutralized with 1N aq. HCl (*ca.* 15 ml). After usual workup and careful FC (4% $Et_2O$/hexane), 3.12 g (49%) of **16a** and 720 mg (11%) of isomer **16b** were obtained, besides some mixed fractions.

*Data of* **16a**: $[\alpha]_D = +7$, $[\alpha]_{578} = +7$, $[\alpha]_{546} = +9$, $[\alpha]_{436} = +12$, $[\alpha]_{365} = -2$ ($CHCl_3$, $c = 0.3$). IR: 2944vs, 2867vs, 1709*s*, 1465*m*, 1388*m*, 1368*w*, 1122*m*, 1087*m*, 883*m*. $^1$H-NMR: 4.07, 3.63 (2 × 2 lines, *AB* of *ABX*, $J_{gem} =$ 10.2, 2 H); 2.49–2.41 (*m*, 2 H); 2.36 (*ddd*, $J = 13.6, 3.5, 3.1$, 1 H); 2.06 (*t*, $J = 12.8$, 1 H); 1.93 (*dm*, $J = 12.4$, 1 H); 1.61–1.25 (series of *m*, 4 H); 1.06, 1.04 (2*s*, 21 H); 0.91 (*d*, $J = -6.6$, 3 H); 0.89 (*d*, $J = 6.6$, 3 H). $^{13}$C-NMR: 212.4 (*s*); 62.5 (*t*); 52.7 (*d*); 46.6 (*d*); 45.7 (*t*); 32.7 (*d*); 30.1 (*t*); 28.4 (*t*); 19.6 (*q*); 18.0 (*q*); 12.0 (*d*). MS: 283 (16, [*M* – $^i$Pr]$^+$), 253 (2), 241 (94), 225 (3), 213 (2), 211 (2), 197 (5), 75 (100, $C_2H_7OSi^+$). Anal. calc. for $C_{19}H_{38}O_2Si$: C 69.80, H 11.73; found: C 69.67, H 11.80.

*Data of* **16b**: $^1$H-NMR: $[\alpha]_D = -35$, $[\alpha]_{578} = -36$, $[\alpha]_{546} = -43$, $[\alpha]_{436} = -88$, $[\alpha]_{365} = -203$ ($CHCl_3$, $c = 1$). 3.94, 3.81 (2 × 4 lines, *AB* of *ABX*, $J_{gem} = 9.7$, 2 H); 2.53 ('*quint.*', 1 H); 2.37 (*dd*, $J = 14.0, 4.4$, 1 H); 2.26 (*dd*, $J =$ 14.0, 9.5, 1 H); 1.91 (*q*, $J = 6.6$, 2 H); 1.73–1.60 (*m*, 3 H); 1.52 (*sext.*, $J = 6.6$, 1 H); 1.05, 1.04 (2*s*, 21 H); 0.9 (*d*, $J = 6.6$, 6 H). $^{13}$C-NMR (50 MHz): 214.6 (*s*); 53.6 (*t*); 52.2 (*d*); 44.4 (*d*); 44.3 (*t*); 31.2 (*d*); 26.6 (*t*); 25.2 (*t*); 19.8 (*q*); 18.0 (*q*); 11.9 (*d*).

*(1*R*,2*R*,5*S*)-2-(Hydroxymethyl)-5-isopropyl-1-(pent-4-enyl)cyclohexanol* (= *((1*R*,2*R*,4*S*)-2-Hydroxy-4-isopropyl-2-(pent-4-enyl)cyclohexanemethanol*; **17**). A soln. of **16a** (2.51 g, 7.69 mmol) in THF (5 ml) was added dropwise within 30 min (syringe pump) to 0.5N pent-4-enylmagnesium bromide in THF (34.0 ml, 17.0 mmol, 2.2 equiv.). After stirring at 25° overnight, the mixture was poured onto a sat. aq. $NH_4Cl$ soln. and worked up as usual. The crude oil (3.10 g) was dissolved in 10 ml of THF and treated with 1N $Bu_4NF$ in THF (10 ml, 10 mmol, 1.3 equiv.). After 1 h at 25°, $H_2O$ (7 ml) was added and the product worked up as usual. FC (hexane/$Et_2O$ 1:1) yielded pure **17** (1.48 g, 80%). White solid. M.p. 71–73°. $[\alpha]_D = -23$, $[\alpha]_{578} = -25$, $[\alpha]_{546} = -28$, $[\alpha]_{436} = -50$, $[\alpha]_{365} = -82$ ($CHCl_3$, $c = 1.2$). $^1$H-NMR: 5.82 (*ddt*, $J = 17.2, 10.2, 6.6$, 1 H); 5.03 (br. *d*, $J = 17.2$, 1 H); 4.97 (*d*, $J =$ 10.2, 1 H); 4.12 (*dt*, $J = 11.1, 2.8$, 1 H); 3.58 (*ddd*, $J = 11.0, 6.5, 2.7$, 1 H); 2.53 (br. *dd*, OH); 2.37 (br. *s*, OH); 2.08 (sym. *m*, 2 H); 1.91 (*qd*, $J = 13.1, 3.7$, 1 H); 1.80 (*quint. d*, $J = 12.7, 2.9$, 1 H); 1.72–1.35 (series of *m*, 8 H); 1.30 (*dq*, $J = 12.8, 3.1$, 1 H); 1.09 (*t*, $J = 12.6$, 1 H); 0.96 (*qd*, $J = 12.8, 3.8$, 1 H); 0.87 (*d*, $J = 6.6$, 3 H); 0.86 (*d*, $J = 6.6$, 3 H). $^{13}$C-NMR: 138.6 (*d*); 114.8 (*t*); 75.2 (*s*); 64.6 (*t*); 43.61 (*d*); 41.2 (*t*); 40.5 (*t*); 38.7 (*d*); 34.3 (*t*); 32.6 (*d*); 28.9 (*t*); 25.4 (*t*); 23.3 (*t*); 19.9 (*q*); 19.4 (*q*). MS: 240 (< 1, $M^+$), 222 (1), 197 (12), 179 (14), 172 (12), 171 (100, [*M* – $C_5H_9$]$^+$), 135 (11), 112 (12), 111 (15), 110 (21), 109 (20), 97 (32), 69 (79), 67 (24), 55 (43). HR-MS: 240.21094 ($C_{15}H_{28}O_2^+$; calc. 240.20892). Anal. calc. for $C_{15}H_{28}O_2$: C 74.95, H 11.74; found: C 74.86, H 11.81.

*(4*S*)-4-Isopropyl-2-(pent-4-enyl)cyclohex-1-en-1-carboxaldehyde* (**18**). The soln. of pyridine · $SO_3$ (2.40 g, 15.1 mmol, 2.7 equiv.) in DMSO (24 ml) was added within 10 min *via* syringe pump to the soln. of **17** (1.32 g, 5.49 mmol) and $Et_3N$ (5.25 g, 52 mmol, 10 equiv.) in DMSO (24 ml). After 30 min stirring at 25°, 0.9N KOH in MeOH/$H_2O$ 1:1 (50 ml, *ca.* 45 mmol, 8 equiv.) was added dropwise (temp. raise to 50°). After 1 h, the yellow suspension was acidified to pH 2 with 1N aq. HCl and worked up as usual: 1.16 g (96%) of anal. pure **18**. The aldehyde is not very stable and was immediately submitted to the following reduction. $[\alpha]_D = -132.8$, $[\alpha]_{578} =$ $-138.5$, $[\alpha]_{546} = -161.1$, $[\alpha]_{436} = -308.3$ ($CHCl_3$, $c = 1.09$). IR: 2956*s*, 2929*s*, 2870*s*, 1667vs, 1631*m*, 1466*m*, 1366*m*, 1244*m*, 993*m*, 912*m*, 751*m*. $^1$H-NMR: 10.10 (*s*, 1 H); 5.79 (*ddt*, $J = 16.2, 10.2, 6.6$, 1 H); 5.06 (br. *d*, $J = 16$, 1 H); 5.02 (br. *d*, $J = 10$, 1 H); 2.57–2.46 (*m*, 3 H); 2.14 (*dm*, $J = 16$, 1 H); 2.11 (*q*, $J = 7.1$, 1 H); 2.05–1.98 (*m*, 3 H); 1.84 (br. *d*, $J = 12$, 1 H); 1.63 (*quint.*, $J = 7.4$, 2 H); 1.50 (*sept.*, $J = 6.6$, 1 H); 1.36–1.22 (*m*, 1 H); 1.09 (*qd*, $J = 11.9, 5.3$, 1 H); 0.92, 0.91 (2*d*, $J = 6.6$, each 3 H). $^{13}$C-NMR: 190.7 (*d*); 159.9 (*s*); 138.0 (*d*); 133.8 (*s*); 115.4 (*t*); 39.8 (*d*); 36.1 (*t*); 33.5 (*t*); 31.99 (*d*); 31.6 (*t*); 27.2 (*t*); 25.1 (*t*); 22.9 (*t*); 19.7 (*q*); 19.6 (*q*). MS: 220 (6, $M^+$), 191 (3), 177 (100, [$M - C_3H_7$]$^+$), 161 (53), 119 (35), 95 (47), 91 (49), 81 (56), 79 (55), 55 (66). HR-MS: 220.18271 ($C_{15}H_{24}O^+$; calc. 220.18288).

*(4*S*)-4-Isopropyl-2-(pent-4-enyl)cyclohex-1-en-1-yl)methyl Acetate* ((−)-**5**). To a cooled (−78°) soln. of **18** (1.16 g, 5.25 mmol) in dry toluene (50 ml), neat DIBAH (838 mg, 5.89 mmol, 1.1 equiv.) was added dropwise. After 15 min further stirring, MeOH (20 ml) was added and the soln. warmed to 0° and then acidified to pH 2 with 1N aq. HCl. After standard extraction and drying, 1.16 g (98%) of anal. pure product was obtained as a yellow oil, which was dissolved in $CH_2Cl_2$ (5 ml), together with $Ac_2O$ (1.12 g, 11.0 mmol, 2.1 equiv.), pyridine (870 mg, 11.0 mmol, 2.1 equiv.) and *N*,*N*-dimethylpyridin-4-amine (DMAP; 20 mg). After stirring at 25° for 2 h, MeOH (0.5 ml) was added, the soln. evaporated, and the residue subjected to FC (5% $Et_2O$/hexane): *ent*-**5** (1.15 g, 83%). $[\alpha]_D = -71.4$, $[\alpha]_{578} = -74.3$, $[\alpha]_{546} = -84.8$, $[\alpha]_{436} = -149.7$, $[\alpha]_{365} = -248.8$ ($CHCl_3$, $c = 0.88$).

IR: 3076*w*, 2929*s*, 2871*s*, 1740v*s*, 1640*w*, 1464*w*, 1437*w*, 1369*m*, 1237v*s*, 1021*m*, 958*w*, 910*w*. $^1$H-NMR: 5.80 (*ddt*, $J$ = 17.3, 1.2, 6.6, 1 H); 5.01 (br. *d*, $J$ = 17.3, 1 H); 4.96 (br. *d*, $J$ = 10.2, 1 H); 4.55 (*AB*, $J_{AB}$ = 11.9, 2 H); 2.17–1.96 (*m*, 7 H); 2.05 (*s*, 3 H); 1.85–1.73 (*m*, 2 H); 1.52–1.41 (*m*, 3 H); 1.34–1.23 (*m*, 1 H); 1.16 (*qd*, $J$ = 11.9, 5.8, 1 H); 0.90 (*d*, $J$ = 6.6, 6 H). $^{13}$C-NMR: 171.4 (*s*); 138.6 (*d*); 137.6 (*s*); 125.3 (*s*); 114.6 (*t*); 64.4 (*t*); 40.3 (*d*); 33.7 (*t*); 33.6 (*t*); 32.8 (*t*); 32.2 (*d*); 28.5 (*t*); 28.1 (*t*); 26.1 (*t*); 21.1 (*q*); 19.8 (*q*); 19.7 (*q*). MS: 264 (0.5, $M^+$), 204 (13), 189 (9), 175 (6), 161 (86), 149 (11), 135 (2), 119 (47), 107 (74), 91 (100), 79 (86), 67 (65), 55 (75). Anal. calc. for $C_{17}H_{28}O_2$: C 77.21, H 10.68; found: C 77.21, H 10.80.

*(1*R*,5*S*,9*S*)-1-(Iodomethyl)-9-isopropyl-6-methylidenespiro[4.5]decane* (*ent*-**13**). [Pd(OAc)$_2$] (21 mg, 0.09 mmol) and $PBu_3$ (20.5 mg, 0.10 mmol, 1.1 equiv.) were dissolved in degassed $Et_2O$ (5 ml) to yield a pale yellow 0.02N catalyst soln. A *Carius* tube was carefully dried and put under Ar, then the catalyst soln. (0.50 ml, 0.009 mmol, 5 mol-%) was introduced and diluted with degassed $Et_2O$ (1 ml). The substrate *ent*-**5** (54 mg, 0.20 mmol) in $Et_2O$ (0.5 ml) was added and additional $Et_2O$ (1.5 ml) introduced to concentrate all the product in the bottom phase. After the dropwise addition of $Et_2Zn$ (492 mg, 4.00 mmol, 20 equiv.), the soln. turned black. The tube was closed, left under stirring at 37° for 14 h, and then cooled to 25°. A 1N $I_2$ soln. in THF (*ca.* 5 ml, 5 mmol, *ca.* 2 equiv. rel. to $Et_2Zn$) was added dropwise. During the addition, the nearly black soln. cleared to pale yellow. After 30 min of further stirring, the mixture was diluted with pentane, the soln. washed with sodium thiosulfite soln., $H_2O$, and brine and evaporated, and the residue adsorbed on $SiO_2$ and purified by FC (pentane): 60 mg (90%) of *ent*-**13** as a 95:5 diastereoisomer mixture (by GC and $^1$H-NMR). $[\alpha]_D$ = +7.3, $[\alpha]_{578}$ = +7.3, $[\alpha]_{546}$ = +7.4, $[\alpha]_{436}$ = +4.6, $[\alpha]_{365}$ = −9.2 ($CHCl_3$, $c$ = 0.98). $^1$H-NMR: 4.78 (br. *s*, 1 H); 4.63 (br. *s*, 1 H); 3.15 (*d*, $^3J$ = 9.4, 2.7, 1.5, 1 H); 2.68 (*dd*, $^3J$ = 12.6, 9.6, 1 H); 2.52–2.47 (*m*, 1 H); 2.32 (*dt*, $J$ = 13.0, 3.3, 1 H); 2.04–1.93 (*m*, 3 H); 1.88–1.70 (*m*, 4 H); 1.48–1.37 (*m*, 3 H); 1.27–1.22 (*m*, 1 H); 1.04 ('*qd*', $^3J$ = 12.5, 3.8, 1 H); 0.86, 0.85 (2*d*, $^3J$ = 6.4, each 3 H); 0.80 (*t*, $^3J$ = 12.6, 1 H). $^{13}$C-NMR: 152.1 (*s*); 107.8 (*t*); 53.7 (*s*); 46.0 (*d*); 41.7 (*t*); 39.6 (*d*); 35.2 (*t*); 35.5 (*t*); 32.4 (*d*); 31.5 (*t*); 29.4 (*t*); 20.1 (*q*); 19.6 (*q*); 19.6 (*t*); 14.0 (*t*). MS: 332 (4, $M^+$), 206 (11), 205 (68), 163 (10), 149 (83), 135 (151), 123 (68), 121 (35), 109 (98), 95 (98), 81 (100), 79 (50), 67 (82), 55 (54). HR-MS: 332.10005 ($C_{15}H_{25}I^+$; calc. 332.10010). Anal. calc. for $C_{15}H_{25}I$: C 54.22, H 7.58; found: C 54.50, H 7.71.

*(1*S*,5*R*,9*R*)-9-Isopropyl-1-methyl-6-methylidenespiro[4.5]decane* (**24**). As described for *ent*-**13**, with **5** (33 mg, 0.12 mmol), 0.02N Pd catalyst (0.30 ml, 0.006 mmol, 5 mol-%), and $Et_2Zn$ (0.250 ml, 301 mg, 2.45 mmol, 20 equiv.) in $Et_2O$ (3 ml) (14 h). The soln. was cooled to 0°, and aq. $NH_4Cl$ soln. (*ca.* 3 ml) was added dropwise. Usual workup (volatility of the product required extraction with pentane and evaporation in the cold) and FC (pentane) yielded 22 mg (89%) of **24**, d.r. 95:5 ($^1$H-NMR). Intense smelling volatile oil. $[\alpha]_D$ = +26.7, $[\alpha]_{578}$ = +27.8, $[\alpha]_{546}$ = +31.4, $[\alpha]_{436}$ = +53.5, $[\alpha]_{365}$ = +84.9 ($CHCl_3$, $c$ = 1.0). $^1$H-NMR: 4.70 (br. *s*, 1 H); 4.60 (br. *s*, 1 H); 2.26 (*ddd*, $J$ = 12.2, 3.4, 3.2, 1 H); 2.16 (*q*, $J$ = 7.1, 1 H); 2.06–1.92 (*m*, 4 H); 1.84–1.75 (*m*, 3 H); 1.72–1.60 (*m*, 3 H); 1.50–1.26 (*m*, 3 H); 1.20–1.13 (sym. *m*, 1 H); 1.03 (*qd*, $J$ = 11.8, 3.9, 1 H); 0.87 (*d*, $J$ = 6.5, 3 H); 0.86 (*d*, $J$ = 6.4, 3 H); 0.78 (*t*, $J$ = 12.3, 1 H). $^{13}$C-NMR: 154.1 (*s*); 106.0 (*t*); 52.3 (*s*); 41.3 (*t*); 39.6 (*d*); 35.2 (*t*); 33.5 (*t*); 32.6 (*d*); 31.8 (*t*); 31.0 (*t*); 20.1 (*t*); 19.7 (2*q*); 18.1 (*q*). MS: 206 (3, $M^+$), 86 (18), 81 (11), 69 (10), 57 (100). HR-MS: 206.20416 ($C_{16}H_{26}^+$; calc. 206.20345).

*(1*R*,5*R*,9*R*)-1-(But-3-enyl)-9-isopropyl-6-methylidenspiro[4.5]decane* (**25**). As described for *ent*-**13**, with **5** (166 mg, 0.63 mmol), 0.02N Pd catalyst (1.60 ml, 0.032 mmol, 5 mol-%), and $Et_2Zn$ (1.20 ml, 1.45 g, 11.8 mmol, 19 equiv.) (12 h). The soln. was cooled to 0°, and vacuum was applied carefully. After 20 min, the residue was dissolved in THF (5 ml) and the soln. cooled to −78°, upon which 1N CuCN · 2 LiCl soln.[6]) in THF (1.00 ml, 1.00 mmol, 1.6 equiv.) was added slowly. After shortly warming to 0°, allyl bromide (1.29 g, 10.6 equiv.) in THF (5 ml) was added dropwise at −78°. The soln. was warmed to 25° overnight, aq. $NH_4Cl$ soln. added, and workup effected as usual (extraction with pentane). FC (pentane) yielded **25** (147 mg, GC purity of 93%, 88% yield) as a 94.6 diastereomer mixture (GC). $[\alpha]_D$ = +25.5, $[\alpha]_{578}$ = +26.5, $[\alpha]_{546}$ = +29.8, $[\alpha]_{436}$ = +47.3, $[\alpha]_{365}$ = +67.1 ($CHCl_3$, $c$ = 0.9). $^1$H-NMR: 5.79 (*ddt*, $J$ = 17.0, 10.3, 6.4, 1 H); 4.99 (*dq*, $J$ = 7.1, 1.4, 1 H); 4.93 (br. *d*, $J$ = 11, 1 H); 4.72 (*t*, $J$ = 2.0, 1 H); 4.58 (*d*, $J$ = 1.5, 1 H); 2.26 (*ddd*, $J$ = 12.8, 3.9, 3.6, 1 H); 2.17–2.06 (*m*, 1 H); 2.01–1.62 (*m*, 8 H); 1.54–1.34 (*m*, 4 H); 1.24–1.13 (*m*, 3 H); 1.03 (*qd*, $J$ = 11.3, 3.9, 1 H); 0.87 (*d*, $J$ = 6.4, 3 H); 0.86 (*d*, $J$ = 6.4, 3 H); 0.76 (*t*, $J$ = 12.5, 1 H). $^{13}$C-NMR: 153.9 (*s*); 139.3 (*d*); 114.2 (*t*); 106.5 (*t*); 52.6 (*s*); 41.5 (*d*); 41.4 (*t*); 39.5 (*d*); 35.3 (*t*); 34.1 (*t*); 32.7 (*t*); 32.6 (*d*); 31.8 (*t*); 30.4 (*t*); 27.1 (*t*); 20.2 (*t*); 20.1 (*q*); 19.7 (*q*). Anal. calc. for $C_{18}H_{30}$: C 87.72, H 12.28; found: C 87.58, H 12.10.

*(5*S*,9*S*)-9-Isopropyl-1,6-bis(methylidene)spiro[4.5]decane* (*=(−)-Erythrodiene*; **1**). Iodide *ent*-**13** (96 mg, 0.29 mmol) was treated with freshly prepared 1N KO$^t$Bu in dry DMSO (1.50 ml, 1.50 mmol, 5.2 equiv.). Then

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[6]) For the preparation, see [26] and refs. cit. therein.

$Et_2O$ (0.5 ml) was added to yield a homogeneous yellow soln. After 30 min stirring at 25°, the reaction was quenched by addition of sat. aq. $NH_4Cl$ soln. Standard pentane extraction and evaporation in the cold yielded **1** (58 mg, 98%) as a 95:5 diastereomer mixture. The crude product was further purified by careful FC ($AgNO_3$-treated $SiO_2$, pentane/$Et_2O$ 95:5): 46 mg of 94% pure and 7 mg of > 98% pure **1** (single diastereoisomer). $[\alpha]_D = -111.9$, $[\alpha]_{578} = -117.1$, $[\alpha]_{546} = -135.7$, $[\alpha]_{436} = -256.0$, $[\alpha]_{365} = -462.6$ ($CHCl_3$, $c = 0.5$) [3]: $[\alpha]_D^{25} = 121 \pm 11$ ($CHCl_3$, $c = 0.3$). $^1$H-NMR: 4.97 (*s*, 1 H); 4.86 (*s*, 1 H); 4.76 (*s*, 1 H); 4.74 (*s*, 1 H); 2.45–2.33 (*m*, 3 H); 2.28 (*dt*, *J* = 13.0, 4.0, 1 H); 2.10 (*dt*, *J* = 12.4, 7.0, 1 H); 1.83–1.74 (*m*, 2 H); 1.69 ('*quint.*', *J* = 7.2, 2 H); 1.65–1.52 (*m*, 3 H); 1.48 (*dt*, *J* = 12.4, 7.5, 1 H); 1.09 (*m*, 1 H); 0.87 (*d*, *J* = 6.4, 3 H); 0.85 (*d*, *J* = 6.4, 3 H). $^{13}$C-NMR: 158.1 (*s*); 153.0 (*s*); 106.7 (*t*); 105.8 (*t*); 51.3 (*s*); 41.1 (*t*); 39.7 (*d*); 39.7 (*t*); 35.5 (*d*); 33.8 (*t*); 33.1 (*t*); 31.1 (*d*); 20.8 (*t*); 20.1 (*q*); 19.7 (*q*). MS: 204 (1; $M^+$), 176 (2), 161 (100, $[M - C_3H_7]^+$), 133 (97), 122 (25), 121 (49), 120 (65), 119 (54), 117 (13), 109 (25), 108 (34), 105 (63), 91 (95), 67 (41), 55 (30). HR-MS: 204.18758 ($C_{15}H_{24}^+$; calc. 204.18781).

*(1*S*,2*S*,5*R*)-2-(Hydroxymethyl)-5-isopropyl-1-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]cyclohexanol* (= *(1*S*,2*S*,4*R*)-2-Hydroxy-4-isopropyl-2-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]cyclohexanemethanol*; **27**). A soln. of *ent*-**16a**[7]) (2.10 g, 6.43 mmol) in THF (3 ml) was added dropwise at 25° to the *Grignard* reagent **26** prepared from 1-bromo-3-(2-methyl-1,3-dioxolan-2-yl)propane (1.92 g, 9.18 mmol, 1.43 equiv.) and Mg (220 mg, 9.05 mmol, 1.41 equiv.) in THF (18 ml, $c = 0.5$M). After stirring the soln. overnight, aq. $NH_4Cl$ soln. was added and the product worked up as usual. The crude (*ca.* 2.5 g) was dissolved in THF (10 ml) and treated with 1N $Bu_4NF$ in THF (6.00 ml, 6.00 mmol, 0.93 equiv.). After 1 h, $Et_2O$ was added and the org. layer washed with $H_2O$. The usual workup and FC ($Et_2O$) yielded 1.05 g (54%) of solid **27**. M.p. 93–94°. $[\alpha]_D = +21.5$, $[\alpha]_{578} = +22.5$, $[\alpha]_{546} = +25.6$, $[\alpha]_{436} = +43.9$, $[\alpha]_{365} = +68.9$ ($CHCl_3$, $c = 1.2$). IR: 3298v*s*, 2948v*s*, 2923v*s*, 2862*m*, 1374*m*, 1159*m*, 1032*m*, 948*m*, 746*w*. $^1$H-NMR: 4.12 (br. *d*, *J* = 8, 1 H); 3.97–3.93 (*m*, 1 H); 3.62–3.51 (*m*, 1 H); 2.59 (br. *s*, 1 H); 2.46 (*s*, 1 H); 1.90 (*qd*, *J* = 12.1, 4.3, 3 H); 1.82–1.80 (*m*, 1 H); 1.61–1.28 (*m*, 11 H); 1.41 (*s*, 3 H); 1.08 (*t*, *J* = 10.1, 1 H); 0.92 (2*d*, *J* = 6.4, 6 H). $^{13}$C-NMR: 110.0 (*s*); 75.1 (*s*); 64.6 (2 *t*); 43.6 (*d*); 41.8 (*t*); 40.4 (*t*); 39.7 (*t*); 38.6 (*d*); 28.9 (*t*); 32.8 (*t*); 25.4 (*t*); 23.8 (*q*); 20.0 (*q*); 19.5 (*q*); 18.3 (*t*). MS: 267 (1, $[M - 33]^+$), 239 (6), 221 (3), 195 (12), 171 (20), 153 (5), 135 (11), 102 (38), 87 (100), 69 (41), 59 (83), 45 (22). Anal. calc. for $C_{17}H_{28}O_2$: C 67.82, H 10.67; found: C 67.96, H 10.74.

*(3*S*,6a*S*,8*R*,10a*S*)-1,3,4,5,6,7,8,9,10,10a-Decahydro-8-isopropyl-3-methyl-3,6a-epoxy-6a*H*-2-benzoxocin* (= *(1*S*,3*R*,6*S*,9*S*)-9-Methyl-3-isopropyl-8,13-dioxatricyclo[7.3.1.1$^{6}$]tridecane*; **29**). To a soln. of **27** (19 mg, 0.06 mmol) in benzene (2.5 ml), PPTS (4 mg, 0.02 mmol, 0.3 equiv.) was added. After heating the soln. to reflux for 2 h, it was cooled to 25° and the product extracted with pentane. FC (2% $Et_2O$/pentane) yielded **29** (11.5 mg, 70%). $[\alpha]_D = +40.0$, $[\alpha]_{578} = +42.0$, $[\alpha]_{546} = +47.2$, $[\alpha]_{436} = +79.6$, $[\alpha]_{365} = +124$ ($c = 0.5$, $CHCl_3$). IR ($CHCl_3$): 2998*m*, 2935v*s*, 1603*w*, 1461*w*, 1381*m*, 1224*m*, 1126*s*, 967*w*. $^1$H-NMR: 4.63 (*dd*, *J* = 11.6, 3.7, 1 H); 3.47 (*d*, *J* = 11.8, 1 H); 2.12–2.01 (*m*, 3 H); 1.90–1.83 (*m*, 1 H); 1.75–1.44 (*m*, 8 H); 1.40 (*sext.*, *J* = 6.5, 1 H); 1.33 (*s*, 3 H); 1.20 (*dt*, *J* = 12.3, 3.9, 1 H); 1.02 (*t*, *J* = 12.8, 1 H); 0.89 (*d*, *J* = 6.9, 3 H); 0.85 (*d*, *J* = 6.9, 3 H). $^{13}$C-NMR: 96.4 (*s*); 70.5 (*s*); 66.7 (*t*); 44.4 (*t*); 39.0 (*d*); 37.3 (*d*); 35.2 (*t*); 33.1 (*t*); 32.4 (*d*); 29.8 (*q*); 27.8 (*t*); 27.6 (*t*); 20.0 (*q*); 19.9 (*t*); 19.0 (*q*). MS: 238 (2, $M^+$), 195 (13), 178 (88), 135 (97), 121 (17), 107 (100), 93 (42), 79 (33), 69 (26), 55 (21). HR-MS: 238.19419 ($C_{15}H_{26}O_2^+$; calc. 238.19328).

*[(4*R*)-4-Isopropyl-2-(4-oxobutyl)cyclohex-1-en-1-yl]methyl Benzoate* (**28**). To a soln. of **27** (938 mg, 3.12 mmol) in DMSO (15 ml), $Et_3N$ (2.90 g, 28.7 mmol, 9.2 equiv.) was added, followed by the soln. of pyridine · $SO_3$ (1.43 g, 8.98 mmol, 2.9 equiv.) in DMSO (15 ml). After 1 h, oxidation was complete, and 0.9N KOH in MeOH/$H_2O$ 1:1 (30 ml, 27 mmol, 9 equiv.) was added dropwise, upon which the temp. raised gently to 40°. After 30 min, the soln. was neutralized with 1N aq. HCl, and usual workup yielded 820 mg of colorless oil, which was dissolved in toluene (30 ml). This soln. was cooled to −78°. DIBAH (471 mg, 3.31 mmol, 1.1 equiv.) was added dropwise *via* syringe. After 20 min, MeOH (10 ml) was added and the soln. warmed to 25°. After usual workup, 683 mg (78%) of allyl alcohol was obtained. To a part of this product (420 mg, 1.49 mmol) in $CH_2Cl_2$ (5 ml), pyridine (245 mg, 3.1 mmol, 2.1 equiv.) was added, followed by DMAP (10 mg) and benzoyl chloride (363 mg, 2.58 mmol, 1.7 equiv.). After 1 h, MeOH (0.5 ml) was added and the soln. evaporated. The residue was dissolved in acetone (15 ml) and $H_2O$ (4 ml). PPTS (100 mg, 0.40 mmol, 0.3 equiv.) was added and the soln. heated under reflux for 2 h. Standard workup and FC (hexanes/$Et_2O$ 9:1 → 4:1) yielded 420 mg (82%) of **28**. Viscous oil. $[\alpha]_D = +60.1$, $[\alpha]_{578} = +62.8$, $[\alpha]_{546} = +71.9$, $[\alpha]_{436} = +128$, $[\alpha]_{365} = +215$ ($CHCl_3$, $c = 0.5$). IR: 2955*m*, 2948v*s*, 2871*m*, 1716v*s*, 1602*w*, 1584*w*, 1451*m*, 1366*m*, 1314*w*, 1270*s*, 1175*w*, 1181*w*, 1100*m*, 1069*m*, 1026*w*, 944*w*, 924*w*, 712*s*. $^1$H-NMR: 8.26 (br. *d*, *J* = 8.1, 2 H); 7.18–7.07 (*m*, 3 H); 5.03, 4.89 (*AB*, *J* = 11.8, 2 H); 2.27

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[7]) $[\alpha]_D = -8$ ($CHCl_3$, $c = 1.0$), prepared from (+)-perilla alcohol.

(br. *d*, *J* = 20, 1 H); 2.21–2.11 (*m*, 1 H); 2.07 (*dd*, *J* = 8.4, 5.9, 2 H); 1.98 (*t*, *J* = 7.1, 2 H); 2.01–1.94 (*m*, 1 H); 1.82–1.76 (*m*, 1 H); 1.75–1.63 (sym. *m*, 6 H); 1.42 (*sext.*, *J* = 6.6, 1 H); 1.30–1.19 (*m*, 1 H); 1.13 (*ddd*, *J* = 23.0, 12.0, 5.4, 1 H); 0.90, 0.89 (2*t*, *J* = 6.9, 6 H). $^{13}$C-NMR: 208.5 (*s*); 166.6 (*s*); 136.8 (*s*); 132.7 (*d*); 130.5 (*s*); 129.5 (*d*); 128.3 (*d*); 126.2 (*s*); 64.8 (*t*); 43.2 (*t*); 40.3 (*d*); 33.5 (*t*); 32.6 (*t*); 32.1 (*d*); 29.8 (*q*); 28.6 (*t*); 26.1 (*t*); 22.7 (*t*); 19.72 (*q*); 19.65 (*q*). MS: 220 (50, [*M* – benzoate]$^+$), 106 (43), 114 (39), 105 (100), 83 (38), 77 (43). HR-MS: 220.18276 ($C_{15}H_{24}O^+$; calc. 220.18271).

*(1*R*,5*S*,9*R*)-9-Isopropyl-1-methyl-6-methylidenspiro[4.5]decan-1-ol* (**30**). To **28** (0.13 mmol) in a conical flask, 0.02N [$Pd(OAc)_2$]/$Bu_3P$ in THF (0.40 ml, 0.008 mmol; 6%) was added to yield a yellow soln. Upon dropwise addition of $Et_2Zn$ (0.05 mmol, 60 mg, 0.49 mmol, 3.8 equiv.), the soln. became nearly colorless. After 24 h, aq. $NH_4Cl$ soln. was added and workup effected as usual. FC (hexanes/$Et_2O$ 9:1) yielded 12 mg (42%) of **30**. Colorless oil, 82:18 diastereomer mixture ($^1$H-NMR). $[\alpha]_D = +32.0$, $[\alpha]_{578} = +33.5$, $[\alpha]_{546} = +38.0$, $[\alpha]_{436} = +67.3$, $[\alpha]_{365} = +110$ (*c* = 0.4, $CHCl_3$). IR ($CHCl_3$): 3529 (br.), 3019*s*, 2959v*s*, 1625*w*, 1451*w*, 1365*m*, 1274*w*, 1229*w*, 1112*m*, 907*w*, 836*w*, 739*s*, 667*w*. $^1$H-NMR: major isomer: 5.05 (br. *s*, 1 H); 4.90 (br. *s*, 1 H); 2.38 (*dd*, *J* = 5.4, 5.2, 2 H); 2.32–2.25 (sym. *m*, 1 H); 2.23–2.12 (sym. *m*, 1 H); 1.95–1.74 (*m*, 4 H); 1.70–1.52 (*m*, 3 H); 1.45–1.19 (*m*, 3 H); 1.34 (*s*, 3 H); 1.05–0.96 (*t*, *J* = 13.0, 1 H); 0.89 (*d*, *J* = 6.4, 3 H); 0.88 (*d*, *J* = 6.4, 3 H); minor isomer (selected lines): 4.97 (br. *s*); 4.94 (br. *s*); 1.30 (*s*, 3 H); determination of d.r. from the integration of the $CH_2$=C(6) signals at 5.05 and 4.90 (major, 82%) and 4.97 and 4.94 (minor, 18%). $^{13}$C-NMR: major isomer: 151.7 (*s*); 111.2 (*t*); 81.1 (*s*); 53.1 (*s*); 40.3 (*d*); 40.1 (*t*); 39.4 (*t*), 38.8 (*d*); 36.1 (*t*); 33.0 (*d*); 30.8 (*t*); 25.9 (*q*); 19.7 (*q*); 19.6 (*q*); 18.9 (*t*); minor isomer: 152.2 (*s*); 108.8 (*t*); 81.9 (*s*); 55.4 (*s*); 39.0 (*t*); 38.5 (*d*); 35.6 (*t*); 34.5 (*t*); 33.6 (*t*); 32.5 (*d*); 29.6 (*t*); 22.3 (*q*); 20.1 (*q*); 19.5 (*q*); 18.5 (*t*). MS: 222 (17, $M^+$), 204 (11, [$M - H_2O$]$^+$), 149 (8), 137 (15), 135 (13), 122 (23), 122 (23), 121 (100), 119 (12), 109 (64), 108 (14), 107 (25), 105 (49), 95 (44), 94 (13), 93 (95), 91 (27), 82 (22), 81 (40), 79 (40), 77 (15), 71 (43), 69 (20), 67 (25), 55 (28). HR-MS: 220.19837 ($C_{15}H_{26}O^+$; calc. 222.19836).

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*Received September 21, 2000*