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Synthesis of (−)-Cubebol by Face-Selective Platinum-, Gold-, or Copper-Catalyzed Cycloisomerization: Evidence of Chirality Transfer and Mechanistic Insights

Charles Fehr,* Beat Winter, and Iris Magpantay[a]

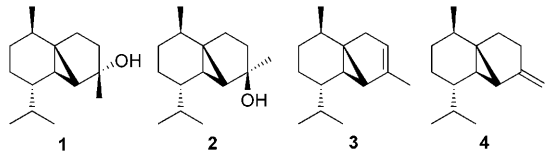
Abstract: We describe in detail a direct, stereoselective synthesis of (−)-cubebol based on a Pt-, Au-, or Cu-catalyzed cycloisomerization in which control of the configuration of the propargylic center is essential for the facial selectivity. In addition, we show that cycloisomerization reactions of enantioenriched propargyl pivalates occur with substantial chirality transfer. We confirm a mechanism by means of cyclization followed by an [1,2]-acyl migration for the Pt- and the Au-catalyzed cycloisomerization. So far, no evidence supports that the Cu-catalyzed cycloisomerization follows the same reaction course.

Keywords: cycloisomerization · cyclopropanes · diastereoselectivity · homogeneous catalysis · natural products

Introduction

Recently,[1] we reported a direct, stereoselective synthesis of (−)-cubebol (**1**)[2] based on a Pt-, Au-, or Cu-catalyzed enyne cycloisomerization.

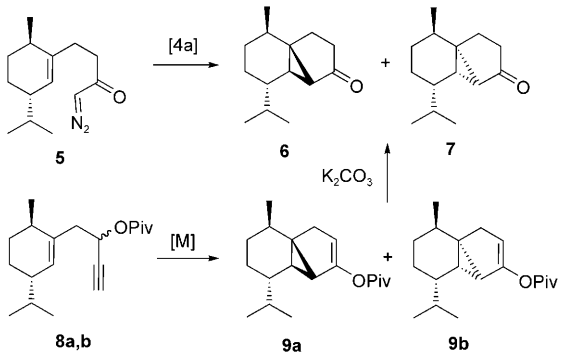
(−)-Cubebol (**1**), (−)-4-epicubebol (**2**), and (−)-α- and β-cubebene (**3** and **4**) are naturally occurring sesquiterpenes isolated from the berries of *Piper cubeba* (Scheme 1).[1]



Scheme 1. Constituents of *Piper cubeba*.

The dried berries containing approximately 2% of cubebol or the cubeb oil are appreciated food additives in Indonesia and other Asian countries. Whereas **2** has a very bitter taste, the almost odorless **1** has a pronounced cooling effect that develops in the mouth after a delay of approximately 1 to 2 min and lasts for approximately 30 min. It lends itself to diverse flavor applications, as demonstrated by our colleagues at Firmenich.[3]

Shortly after the discovery of this new skeleton, syntheses of **3** and **4**, and **1**–**4** were reported by the groups of Piers and Yoshikoshi, respectively.[4] Both syntheses are based on a cyclopropanation of diazoketone **5** (or the analogous isopropenyl compound; Scheme 2). Unfortunately, this route is not diastereoface-selective, and affords the desired ketone **6** as the minor stereoisomer in only moderate yield. After a long period without any new developments, Fürstner and Hannen published a new stereoselective synthesis of (−)-cubebol in 2006[5] that is closely related to ours.[1]



Scheme 2. Classical and new synthetic approaches towards **6**.

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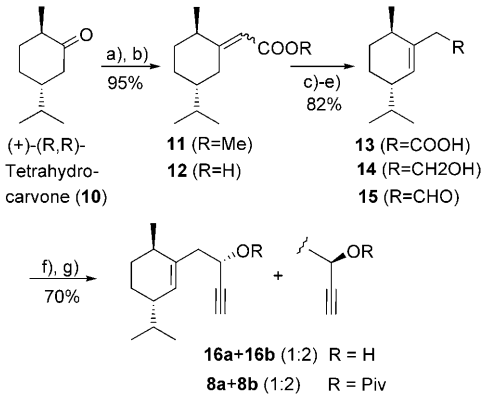
We realized that the application of the Pt-,[6,7] Au-,[8] or Cu-catalyzed[9] cycloisomerization of enynol esters **8a**,**b** to **9a**,**b**[10] would represent a direct and efficient access to cubebol (Scheme 2). The major concern was the uncertainty about the stereocontrol.

Results and Discussion

The key precursors **8a** and **8b** (1:2 diastereomeric mixture) were readily prepared from (+)-(*R*,*R*)-tetrahydrocarvone (**10**) in an overall yield of 55% (Scheme 3). A Wittig–



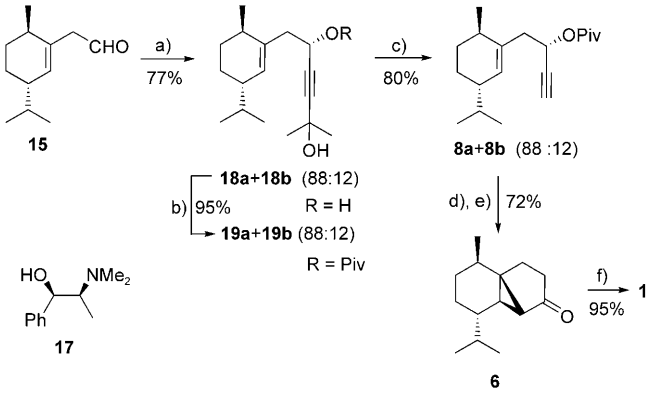
Scheme 3. Reagents and conditions: a) trimethyl phosphonoacetate (1.5 equiv), NaH (1.4 equiv), THF, reflux, 15 h; b) KOH (1.7 equiv), EtOH, H_2O, 60 °C, 24 h; c) BuLi (3.0 equiv), TMP (3.15 equiv), THF, −5 °C, 30 min, then **12**, −25 °C to RT, 16 h; then 5% HCl; d) $LiAlH_4$ (2 mol equiv), Et_2O, reflux, 45 min; e) $(COCl)_2$ (1.5 equiv), DMSO (2.15 equiv), CH_2Cl_2, −70 °C, then $EtN(iPr)_2$ (6 equiv); f) HCCMgBr (1.2 equiv), THF, 25–28 °C, 45 min; g) PivCl (1.1 equiv), NEt_3 (1.2 equiv), DMAP (0.12 equiv), CH_2Cl_2, 0 °C, 2 h.

Horner reaction and saponification afforded the acid **12**. Whereas base-catalyzed deconjugation of ester **11** was unselective, deprotonation of **12** using excess LiTMP (TMP = 2,2,6,6-tetramethylpiperidine), followed by protonation of the dianion with 5% HCl, selectively furnished β,γ-unsaturated **13**. $LiAlH_4$ reduction and Swern oxidation then afforded the β,γ-unsaturated aldehyde **15**. Addition of ethynylMgBr and esterification with pivaloyl (Piv) chloride produced **8a** and **8b** as a 1:2 diastereomeric mixture.

Chromatographic purification of the alcohols **16a**,**b** and esterification of the fractions enriched in **16a** or **16b** gave access to the pivalates **8a**,**b**, enriched in **8a** and **8b**, respectively. These were then submitted separately to the Pt- or Au-catalyzed cycloisomerization reaction (Table 1, entries 1–3). When a mixture of **8a** and **8b** (10:90) was treated with 2 mol% of $PtCl_2$, the expected tricyclic enol pivalates **9a** and **9b** (60:40) were formed in 80% yield (entry 1); the Au-catalyzed reaction gave, in a less clean reaction, a 47:53 mixture of **9a** and **9b** (entry 2). In contrast, the reaction of **8a** and **8b** (70:30) with $PtCl_2$ afforded mainly the desired **9a** (**9a**/**9b** 86:14; entry 3).

From the results shown in entries 1 and 3, it was anticipated that pure **8a** would afford **9a** with excellent facial selectivity.

A diastereoselective synthesis of **8a** was accomplished by a reagent-controlled diastereoselective addition (88:12) of 2-methyl-3-butyn-2-ol to aldehyde **15** using the Zn reagent obtained from (−)-*N*-methylephedrine (**17**) and $Zn(OTf)_2$, followed by esterification of **18a** and **18b** and base-catalyzed cleavage of the carbinol fragment of **19a** and **19b**, as reported by Carreira and co-workers (Scheme 4).[11,12] The *S* configuration of the newly formed stereogenic center is in agreement with the above-cited work of Carreira and coworkers. A mixture of pivalates **8a** and **8b** (88:12) was used for the cycloisomerization step.



Scheme 4. Reagents and conditions: a) $Zn(OTf)_2$ (2.0 equiv), **17** (2.1 equiv), NEt_3, toluene, RT, 2 h; then 2-methyl-3-butyn-2-ol (2.1 equiv), RT, 15 min; then slow addition of **15** in toluene at RT (15+9 h after addition); b) PivCl (2.2 equiv), NEt_3 (1.1 equiv), DMAP (0.12 equiv), 0 °C to RT, 15 h; c) K_2CO_3 (1.2 equiv), [18]crown-6 (0.4+0.4 equiv), toluene, reflux, 19+5 h; d) see Table 1; e) K_2CO_3 (1.2 equiv), MeOH, RT, 90 min; f) $CeCl_3$ (2.0 equiv), MeLi (2.0 equiv), THF, −78 °C, 1 h; then **6**, −78 °C to RT, 2 h.

Table 1. Cycloisomerization of **8a** and **8b**.

Entry	**8a**/**8b**	Conditions[a]	**9a**/**9b**	Yield [%]
1	10:90	$PtCl_2$ (2 mol%), DCE, 70 °C, 9 h	60:40	80
2	10:90	$AgSbF_6$/[AuCl(PPh_3)] (2 mol%), CH_2Cl_2, 20 °C, 40 min	47:53	65
3	70:30	$PtCl_2$ (2 mol%), DCE, 70 °C, 9 h	86:14	–
4	88:12	$PtCl_2$ (2 mol%), DCE, 70 °C, 9 h	94:6	81
5	98:2	$PtCl_2$ (2 mol%), DCE, 70 °C, 9 h	99:1	–
6	98:2	$[Cu(CH_3CN)_4]BF_4$ (2 mol%), toluene, 60 °C, 9 h	99:1	77[b]

[a] DCE = 1,2-dichloroethane. [b] 90% conversion.

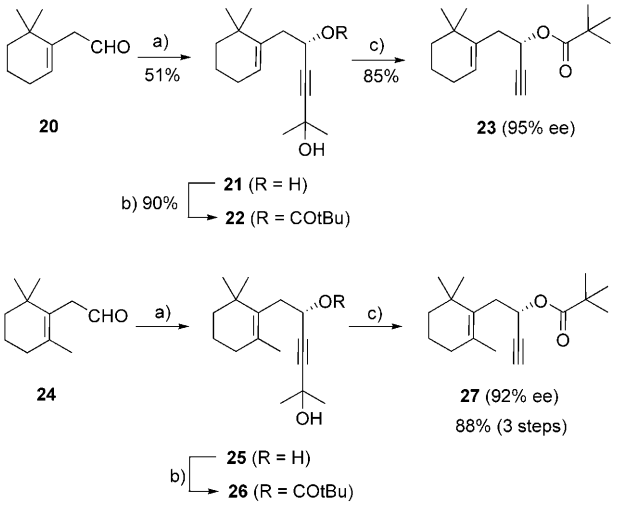
Indeed, $PtCl_2$-catalyzed cycloisomerization of **8a** and **8b** (88:12) afforded **9a** and **9b** with a 94:6 selectivity (Table 1, entry 4), and chromatographically enriched **8a** (98% stereochemical purity) afforded **9a** with excellent facial selectivity (99:1; entry 5). Interestingly, inexpensive $[Cu(CH_3CN)_4]BF_4$ (2 mol%) also efficiently catalyzed the cycloisomerization (99:1; 77% isolated yield after 90% conversion).[9] Prolonged reaction times or higher temperatures (70°C) favored the formation of byproducts.

Hydrolysis of **9a** afforded the known ketone **6**, and diastereoselective (97:3) addition of MeLi/$CeCl_3$ furnished (−)-cubebol (**1**) in 95% yield, identical in all respects with an authentic sample isolated at Firmenich.[3]

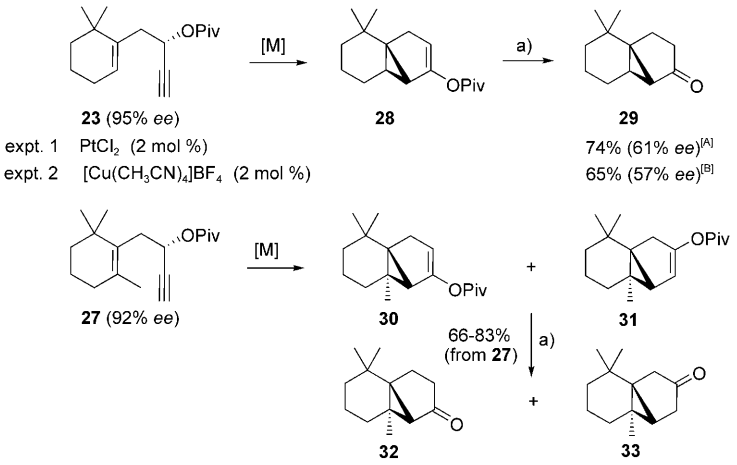
The choice of the pivaloyl group in **8a** was based on the reasoning that this bulky group would preferably occupy the least hindered position, thus bringing the acetylene moiety in closer contact with the cyclohexene unit. Propargylic pivalates had also been used by Toste and co-workers in the Rautenstrauch rearrangement.[13] However, the choice of the ester group does not appear to be crucial, as the $PtCl_2$-catalyzed cycloisomerization of the corresponding acetate, reported by Fürstner and Hannan,[5] proceeded with equal efficiency and stereoselectivity.

The different diastereoface selectivities observed for the cycloisomerizations of **8a** and **8b** prompted us to examine the chirality transfer of the enantioenriched propargyl pivalates **23** and **27**, readily accessible from aldehydes **20**[14] and **24**[15] (Scheme 5). Pt- or Cu-catalyzed rearrangement of **23** (95% *ee*) afforded **28**, which gave, after hydrolysis, ketone **29** with 57–61% *ee* (Scheme 6, expt 1 and 2).[16] The *ee* values of **23** and **27** remained unaltered throughout the course of the reaction, as shown by measurements taken after 50% conversion.

Surprisingly, Pt-catalyzed cycloisomerization of **27** (92% *ee*) afforded, in addition to the expected rearranged



Scheme 5. Reagents and conditions: for a) to c) see Scheme 4a) to c).

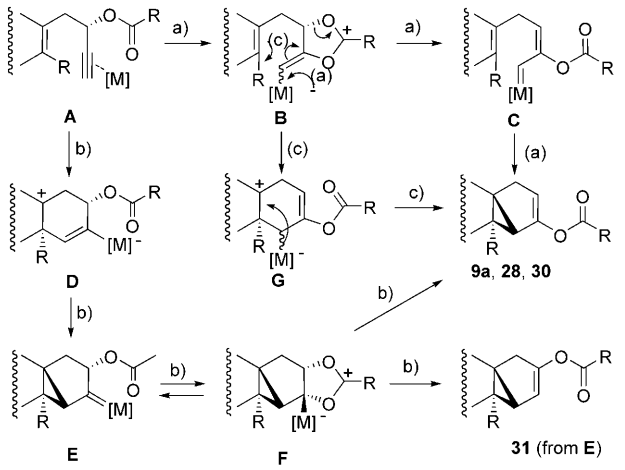


Scheme 6. Reagents and conditions: a) K_2CO_3 (1.2 equiv), MeOH, RT, 90 min. Percentages of **32** and **33** refer to relative amounts (GC analysis); [A] DCE, 70°C, 8 h; [B] toluene, 70°C, 8 h, [C] toluene, 50°C, 4 h, 50% conversion starting from **27** (69% *ee*); [D] DCE, 50°C, 90 min; [E] DCE, 70°C, 90 min; 66% yield.

enol pivalate **30** (−21 to 13% *ee*), variable amounts of the isomeric non-rearranged enol pivalate **31** (79–88% *ee*; expt 3–6), as shown by conversion of **30** and **31** into the ketones **32** and **33**, respectively. The different *ee* values and ratios of products may be due to the variable quality of $PtCl_2$. Indeed, in experiments 5 and 6 we had to add more catalyst to achieve full conversion. Using $[Cu(CH_3CN)_4]BF_4$ (2 mol%), the expected acyl transposition product **30** was highly favored over **31** (expt 7 and 8). A much higher reactivity and better chirality transfer was noticed in 1,2-dichloroethane (DCE) compared with toluene. The Au-catalyzed reaction also afforded a mixture of **30** and **31** (expt 9). The absolute configurations of **32** and **33** were determined by chemical correlation (see below).

Mechanism: Prior to our work[1] and that of Fürstner and co-workers,[5] the Pt- or Au-catalyzed cycloisomerizations of secondary enynol esters were generally believed to proceed by an initial [1,2]-acyl shift of the metal-complexed acetylene **A** and subsequent cyclopropanation of the achiral transient vinyl carbene **C** (pathway (a); Scheme 7).[6] This pathway is certainly operative when the cyclization is slow enough to allow the [1,2]-acyl shift to occur. This is the case in intermolecular reactions[17] and medium-sized ring closures.[6e] The proof for such a reaction course was recently established by the enantioselective cycloisomerization of chiral, racemic propargylic esters.[8b]

However, on the basis of the highly stereoselective cycloisomerization of pivalate **8a** to **9a** in the cubebol synthesis,



Scheme 7. [1,2]-Acyl versus [1,2]-H shift: different mechanistic pathways for the cycloisomerization of enynol esters.

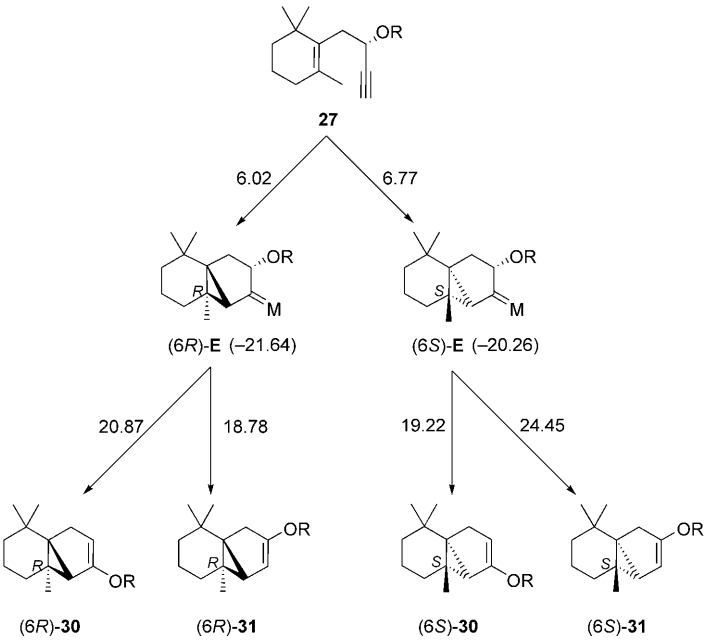
and the unselective reaction of **8b**, pathway (a) can be dismissed. In support of this, a substantial chirality transfer was observed in the cycloisomerization of **23** (95% *ee*) to **28** (57–61% *ee*). The loss in *ee* certainly reflects an imperfect stereocontrol and not a racemization, as the *ee* values of **23** and **28** both remained constant during the reaction. A competing reaction through a vinyl carbene **C** (pathway (a)) cannot be excluded. The behavior of pivalate **27** is more complex, as two reaction pathways are followed, giving the regioisomeric enol pivalates **30** and **31** in variable proportions and *ee* values, depending on the reaction conditions (see below).

The obtained results again show that cyclopropanation of the electron-rich olefin with the metal-complexed acetylene **A** has to (mostly) take place prior to the loss of the propargylic stereogenic center. The most plausible pathway is cycloisomerization of **A** to **E**, followed by [1,2]-acyl migration (pathway (b)). This mechanism has also been proposed by Soriano et al.[7] on the basis of a DFT computational study, and is consistent with the mechanism of the related cycloisomerization of 5-en-1-yn-3-ols[6a,c,8,9] as shown by us[9] and reported by Soriano et al.[7b] Another possibility that was proposed in our preliminary account[1] is a cyclopropanation of a vinyl metal species **B** whose ester function is "half-transposed" but still contains the chiral information (pathway (c)).

As mentioned already, Cu-catalyzed cycloisomerization of **27** leads almost exclusively to the expected product **30**, whereas Pt- or Au-catalyzed cycloisomerization gives the regioisomeric enol pivalates **30** and **31** in variable proportions and *ee* values. The proposition that pathway (b) leads to the formation of **31** and pathway (c) to the formation of **30** would be consistent with the different *ee* values measured. Incidentally, pathway (c) is closely related to the mechanism proposed for the Rautenstrauch rearrangement.[13] Interestingly, Malacria and co-workers recently described other examples in which the [1,2]-H shift competes with the [1,2]-acyl shift.[6d] They also proposed pathway (c) for the acyl shift. In one case, intermediate **G** (Scheme 7) allows the rationalization of the predominant formation of a cyclohexadiene.

However, Soriano and Marco-Contelles[18] have studied our system computationally (with R = acetyl (Ac)) and propose that pathway (b) is operative for both the acyl transposition and the H shift. Indeed, as the chirality transfer is not perfect (loss of *ee*) in the cycloisomerization of **27** to **30** and **31**, two diastereomeric intermediates of type **E** are formed that exhibit different activation barriers for both the acyl shift (leading to **30**) and the H shift (leading to **31**). Since our preliminary report,[1] we have determined the absolute configurations of **30** and **31** (see below). Therefore it makes sense to verify how the amounts of (6*R*)-**30**, (6*S*)-**30**, (6*R*)-**31**, and (6*S*)-**31** agree with the work of Soriano and Marco-Contelles.[18] However, it should be kept in mind that R equals $COC(CH_3)_3$ in the experiments, whereas R is $COCH_3$ in the calculations.[19]

The calculations of Soriano and Marco-Contelles show that the Pt-catalyzed cycloisomerization of **27** is favored from the "top-face", thereby leading preferentially to intermediate (6*R*)-**E** (Scheme 8). The difference in activation



Scheme 8. [1,2]-Acyl versus [1,2]-H shift. The numbers on the arrows represent activation barriers (in kcal mol^{-1}); the numbers in parentheses represent free-energy differences in solution (DCE; in kcal mol^{-1}) relative to $PtCl_2$-complexed **27**.

energy of 0.75 kcal mol^{-1} at a reaction temperature of 70°C should favor (6*R*)-**E** over (6*S*)-**E** in a proportion of approximately 67:33. Intermediate (6*R*)-**E** then preferentially undergoes a [1,2]-H shift (18.78 vs. 20.87 kcal mol^{-1} for the acyl shift). Indeed, the free-energy difference of 2.04 kcal mol^{-1}

is expected to induce a ratio of 19:1 for (6*R*)-**31**/(6*R*)-**30**. In contrast, (6*S*)-**E** exclusively undergoes the acyl shift to afford (6*S*)-**30**. With a free-energy difference of 5.23 kcal mol^{-1}, the alternative [1,2]-H shift can be neglected.

Table 2, entry 1 shows the expected product distribution based on a starting material **27** of 100% *ee*. Entries 2 to 5 show our experimental results using $PtCl_2$ (also extrapolated to **27** of 100% *ee*). Unexpectedly, larger amounts of catalyst had to be used for attaining full conversion in two experiments (3% of $PtCl_2$ in entry 4; 5% in entry 5). These data are in agreement with the proposed mechanism and the product distribution reported in entries 2 and 3 are close to the calculated values. The product distribution in entries 4 and 5 is slightly different from the calculations, but, interestingly, this can again be traced back to almost the same ratio for intermediates (6*R*)-**E** and (6*S*)-**E** (ca. 3:1). This is also true for the Au-catalyzed cycloisomerization (entry 8).

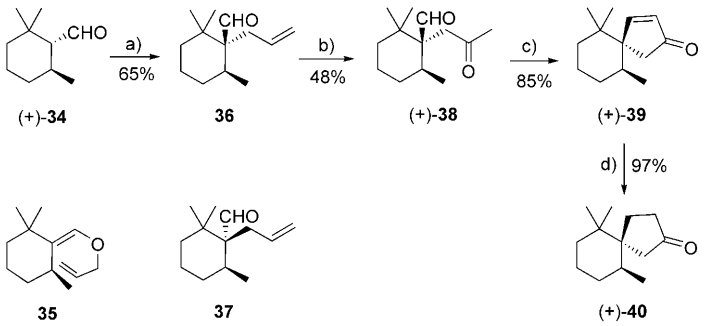
Table 2. Calculated (entry 1) and experimental (entries 2–8) isomer distributions for **30** and **31**.

Entry	(6*R*)-**30**	(6*R*)-**31**	(6*R*)-**E**	(6*S*)-**E**	(6*S*)-**30**	(6*S*)-**31**
1 (ref. [18])	3	64	67	33	33	0
2 (Pt)	11.5	66.5	78	22	18.5	3.5
3 (Pt)	14	62	76	24	19	5
4 (Pt)	24.5	48	72.5	27.5	25.5	2
5 (Pt)	33	41	74	26	25	1
6 (Cu)	37	trace	37	63	63	trace
7 (Cu)	21	trace	21	79	79	trace
8 (Au)	36	34	70	30	29	1

Conversely, the Cu-catalyzed cycloisomerization of **27** shows a completely different reaction profile. If the same reaction pathway is followed, (6*S*)-**E** is favored with respect to (6*R*)-**E**, and both (6*R*)-**E** and (6*S*)-**E** undergo almost exclusively the acyl shift (entries 6 and 7). It is important to note that in the cycloisomerizations of **8a** and **23**, the same face selectivity is favored, regardless of the metal used (Cu, Pt, or Au catalysis). The calculations of Soriano and Marco-Contelles[18] show that the observed face selectivities are dictated by steric factors and, for **8a**, **8b**, and **23**, by the positive interaction between the vinylic hydrogen and the ether oxygen of the ester group.

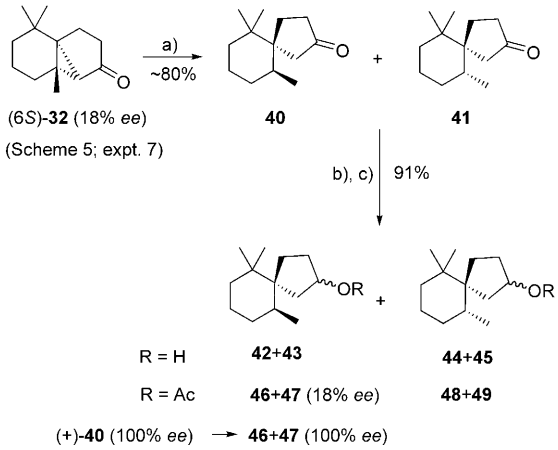
In conclusion, the detailed results strongly support pathway (b) for the Pt- or Au-catalyzed cycloisomerization of **8a**, **8b**, **23**, and **27**, but are inconclusive for the Cu-catalyzed reaction. Nevertheless, it should be kept in mind that the acyl transposition (pathway (a)) and in particular step **A** to **B** (pathway (a) or (c)) possess a low activation energy and therefore the followed pathway and the outcome of the cycloisomerizations may depend on a multitude of factors, such as the substrate and the nature of the catalyst.[20]

Determination of the absolute configurations of 32 and 33: In an independent study, one of us (B.W.) has synthesized enantiopure spiro ketone **40** from (+)-(1*R*,6*S*)-**34**[21] (Scheme 9). The allylation of (+)-(1*R*,6*S*)-**34** by means of Claisen rearrangement of the allyl enol ether **35** afforded **36** with high diastereoselectivity, together with minor amounts of **37** (**36**/**37** 90:10). The *trans* relationship between the allyl and the methyl group in **36** was unambiguously established by NOE. Wacker oxidation of **36** afforded the crystalline keto aldehyde **38**, which underwent smooth intramolecular aldolization/dehydration. Finally, the resulting enone **39** was hydrogenated to generate spiro ketone **40**.



Scheme 9. Reagents and conditions: a) $HC(OMe)_3$ (1.14 equiv), cat. HCl, MeOH, −7°C to RT, 2 h; then cat. NaOAc, allyl alcohol (2 equiv), cat. CF_3CO_2H, 80–150°C, 16 h; b) $PdCl_2$ (10 mol%), $CuCl_2$ (10 mol%), 1,2-dimethoxyethane, H_2O, O_2, RT, 56 h; c) KOH (2.2 equiv), MeOH, RT, 15 h; d) H_2, Pd/C EtOH, RT, 5 h.

Hydrogenation of (6*S*)-**32** (Scheme 6, entry 5; 18% *ee* by chiral GC; the absolute configuration was determined from this study), afforded two diastereomeric spiro ketones, **40** and **41** (Scheme 10). At this stage, correlation with enantiomerically pure **40** (Scheme 9) was not possible, as only three peaks were visible by chiral GC. Fortunately, without the need of a separation, ketones **40** and **41** could be transformed by reduction and acetylation into a mixture of four



Scheme 10. Reagents and conditions: a) H_2, Pd/C, AcOH, RT, 24 h; b) $LiAlH_4$ (1.1 equiv), Et_2O, RT, 1 h; c) Ac_2O, pyridine, RT, 4 h.

diastereomeric acetates (**46**–**49**) that separated on chiral GC. The resolved 8 enantiomers and their superimposition on the racemic compound mixture and with the enantiomerically pure **46**/**47** mixture are shown in Figure 1. It can be

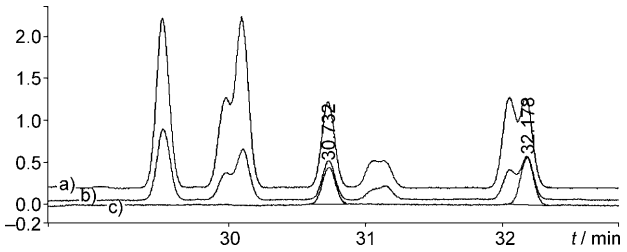


Figure 1. Chiral GC (chiral cap. column: CP-Chirasil-DEX CB (25 m × 0.25 mm) (Chrompack)) of acetates **46**–**49**: a) % racemic mixture of **46**–**49**, b) **46**–**49** (18 % *ee*), c) **46** and **47** (100 % *ee*) from (+)-**40** (100 % *ee*).

seen that our major enantiomers **46** and **47** (18 % *ee*) correspond to the enantiopure enantiomers **46** and **47** derived from enantiomerically pure (+)-**40**.

For the determination of the absolute configuration of **33**, both (6*R*)-**32** (13 % *ee*) and (6*R*)-**33** (88 % *ee*) (Scheme 6; expt 6) were converted into the same hydrocarbon **51** by Shapiro reaction of the corresponding hydrazones (6*R*)-**50** and (6*R*)-**52** (Scheme 11). The sequence was at first tested with racemic substrates. Thus, (±)-**32** was converted into recrystallized hydrazone (±)-**50** and submitted to a Shapiro reaction. The obtained hydrocarbon (±)-**51** readily separated on chiral GC (Figure 2). Likewise, (±)-**33** afforded recrystallized hydrazone (±)-**52** that, upon treatment with BuLi, afforded a mixture of hydrocarbons (±)-**51**/(±)-**53** (40:60). When we repeated these reactions with (6*R*)-**32** (13 % *ee*), we obtained (6*R*)-**51** (9 % *ee*) from recrystallized (6*R*)-**50** (21 % *ee* from the mother liquor of (6*R*)-**50**). In the

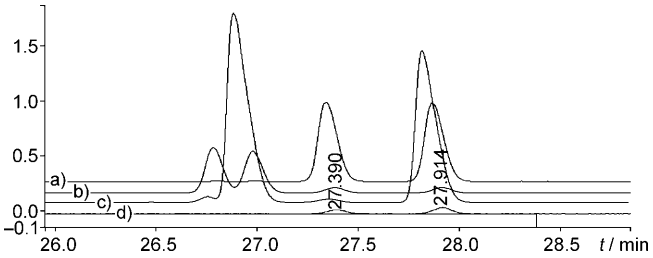


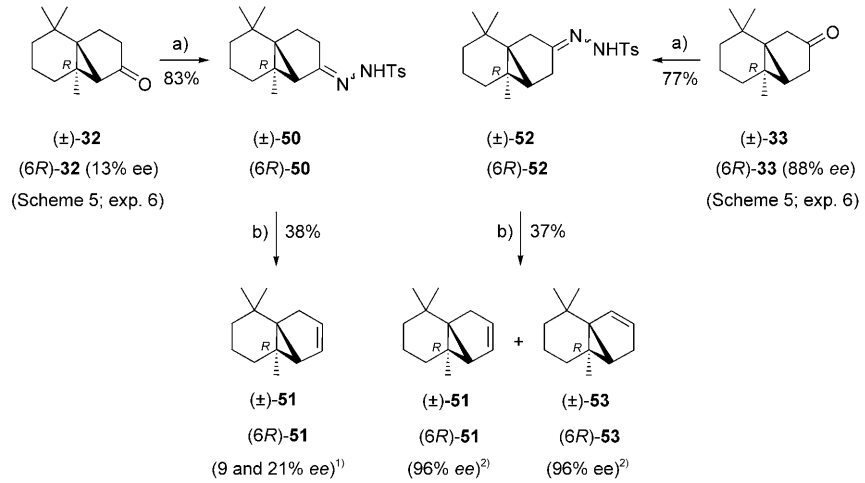
Figure 2. Chiral GC (chiral cap. column: CP-Chirasil-DEX CB (25 m × 0.25 mm) (Chrompack)) of **51** and **53**. a) (±)-**51**, b) (±)-**53**/(±)-**51** 88:12, c) (6*R*)-**53** (96 % *ee*)/(6*R*)-**51** (96 % *ee*) 60:40, d) (6*R*)-**51** (21 % *ee*). From left to right: peak 1) (6*S*)-**53**; peak 2) (6*R*)-**53**; peak 3) (6*S*)-**51**; peak 4) (6*R*)-**51**.

sequence starting from (6*R*)-**33** (88 % *ee*) we used the mother liquor of (6*R*)-**52** and obtained (6*R*)-**51** and (6*R*)-**53** (12:88; 96 % *ee*). As shown in Figure 2, by superimposition of the chiral chromatograms, the major enantiomer of hydrocarbon **51** obtained from **33** (Scheme 6, expt 6) is identical to (6*R*)-**51** derived from (6*R*)-**32**.

Conclusion

In conclusion, we have succeeded in a direct, stereoselective synthesis of (−)-cubebol (**1**) based on a Pt-, Au-, or Cu-catalyzed cycloisomerization in which control of the configuration of the propargylic center is essential for the facial selectivity. In addition, complementary cycloisomerization reactions of enantioenriched propargyl pivalates occur with substantial chirality transfer. A proposed mechanism by means of cyclization followed by an [1,2]-acyl migration is consistent with the calculations of Soriano and Marco-Contelles for the Pt- and the Au-catalyzed cycloisomerization.[18] Conversely, the Cu-catalyzed cycloisomerization may follow a different reaction course. Special calculations would be needed for more accurate mechanistic predictions.

Note added in proof: After submission of this manuscript, a new stereoselective synthesis of (−)-cubebol was published.[22]



Scheme 11. Reagents and conditions: a) NH_2NHTs (1.1 equiv; Ts = tosyl), MeOH, cat. AcOH, reflux, 2 h; b) BuLi (4.0 equiv), TMEDA, −78 °C (or −50 °C) to RT, 80 min; [A] 9 % *ee* from crystallized (6*R*)-**50**; 21 % *ee* from mother liquor of (6*R*)-**50**; [B] from mother liquor of (6*R*)-**52**.

Experimental Section

General: For bulb-to-bulb distillation, a Büchi GKR-51 glass oven was used, with boiling point corresponding to the oven temperature. For TLC, silica gel F-254 plates (Merck) were used; detection with EtOH/anisaldehyde/H_2SO_4 18:1:1. For column chromatography, silica gel 60 (Merck; 0.063–0.2 mm, 70–230 mesh, ASTM)

was used. A Varian instrument model 3500 was used for GC; cap. columns: DB1 30 W (15 m × 0.319 mm), DB-WAX 15 W (15 m × 0.32 mm); chiral cap. column: CP-Chirasil-DEX CB (25 m × 0.25 mm) (Chrompack), carrier gas He at 0.63 bar. Optical rotations were measured using a Perkin–Elmer 241 polarimeter (1 mL cell); c in g 100 mL^{-1} solution. A Bruker WH 400 (400 MHz) spectrometer was used for ^{1}H and ^{13}C NMR spectroscopy. For MS, a Hewlett Packard MSD 5972 automated GC–MS instrument was used (electron energy 70 eV).

(+)-Tetrahydrocarvone ((+)-10): A solution of (+)-**10** (*cis*/*trans* 4:1; 203.0 g, 1.32 mol; flavor ingredient from Firmenich SA) in NaOMe/MeOH (prepared from 20 mL of MeOH and 0.753 g of NaOMe (= 13.24 mmol)) was stirred for 2 h at RT. The clear brown *cis*-enriched product mixture ((+)-**10**; *cis*/*trans* 9:1) was extracted (Et_2O/H_2O), washed (H_2O, then aqueous NaCl, then saturated aqueous NaCl), dried (Na_2SO_4), and concentrated (204.5 g).

An aliquot of the extracted product (+)-**10** (*cis*/*trans* 9:1; 98.1 g, 637 mmol) was added under vigorous stirring to a suspension of sodium trimethylphosphonoacetate (obtained from trimethylphosphonoacetate (25.7 g, 141 mmol; 0.22 equiv) and NaH (5.55 g; 55% in oil; washed 3× with pentane; 127 mmol; 0.2 equiv) in THF (70 mL)) and heated at reflux for 90 min. After cooling and quenching (5% HCl) the product mixture was extracted (2× pentane), washed (H_2O, then saturated aqueous $NaHCO_3$, then saturated aqueous NaCl), dried (Na_2SO_4), and concentrated (102.4 g).

The remaining (+)-**10** was separated from the diastereomeric mixture of **11** by Vigreux distillation. This afforded a main fraction of (+)-**10** (73.7 g; 95% pure, *cis*/*trans* 98:2; b.p. 80–83 °C; 5 mbar).

[(2*R*,5*R*)-5-Isopropyl-2-methylcyclohexylidene]acetic acid (12) (*E*/*Z* 88:12): (+)-**10** (*cis*/*trans* 98:2; 35.0 g; 95% pure; 227 mmol) was added under vigorous stirring to a suspension of sodium trimethylphosphonoacetate (obtained from trimethylphosphonoacetate (62.05 g, 341 mmol) and NaH (13.9 g; 55% in oil; washed 3× with pentane; 318 mmol) in THF (950 mL)) and heated at reflux for 15 h. After cooling and quenching (5% HCl), the product mixture was extracted (2× Et_2O), washed (H_2O, then saturated aqueous $NaHCO_3$, then saturated aqueous NaCl), dried (Na_2SO_4), and concentrated.

The crude ester **11** (48.1 g) was dissolved in EtOH (335 mL), treated with an aqueous solution of KOH (from KOH (15.2 g, 272 mmol) and H_2O (95 mL)), and heated at 60 °C for 15 h. As the saponification was incomplete (due to concomitant formation of the corresponding ethyl ester (20%)), more aqueous KOH was added (from KOH (4.80 g, 85.7 mmol) and H_2O (30 mL)), and heating continued for 5 h (90% conversion). Again, more aqueous KOH was added (from KOH (2.00 g, 35.7 mmol) and H_2O (12 mL)) and heating continued for 5 h (98% conversion). The cooled reaction mixture was concentrated at the rotavapor and the neutral parts (3.5 g) were separated by extraction (Et_2O/H_2O). The aqueous phase was acidified with concentrated HCl (39.4 mL, 472 mmol) and the acid **12** extracted (2× Et_2O), washed (H_2O, then saturated aqueous NaCl), dried (Na_2SO_4), and concentrated. Bulb-to-bulb distillation (oven temp. 150 °C/0.01 mbar) afforded pure **12** (*E*/*Z* 88:12; 42.2 g; 95% yield from (+)-**10**). ^{1}H NMR ($CDCl_3$): $\delta = 0.89$ (d, $J = 6.7$ Hz, 3H), 0.91 (d, $J = 6.7$ Hz, 3H), 1.06 (d, $J = 6.6$ Hz, 3H), 1.13 (m, 1H), 1.28 (m, 2H), 1.47–1.60 (m, 2H), 1.75 (m, 1H), 1.96 (m, 1H), 2.15 (m, 1H), 3.93 (br d, $J = 12.6$ Hz, 1H), 5.58 (s, 1H), 11.9–12.3 ppm (br, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 17.9$ (q), 19.5 (q), 19.8 (q), 29.2 (t), 32.8 (d), 34.3 (t), 37.2 (t), 40.3 (d), 46.8 (d), 109.7 (d), 170.5 (s), 173.1 ppm (s).

(+)-2-[(3*S*,6*R*)-3-Isopropyl-6-methyl-1-cyclohexen-1-yl]acetic acid ((+)-13): A solution of BuLi (1.40 N in hexane; 64.3 mL; 90.0 mmol) was added at −10–0 °C to a solution of 2,2,6,6-tetramethylpiperidine (13.32 g, 16.02 mL, 94.5 mmol) in THF (90 mL). After 30 min the solution was cooled to −25 °C and treated dropwise (in 10 min) with a solution of **12** (5.88 g, 30.0 mmol). During addition, the temperature rose to −10 °C. After complete addition, the cooling bath was removed and stirring continued at RT for 16 h. The reaction mixture was poured into a vigorously stirred ice-cold solution of aqueous HCl (from concentrated HCl (11 mL) and H_2O (300 mL)) and extracted (2× Et_2O/H_2O). The organic phases were basified with aqueous NaOH (from NaOH (1.44 g, 36.0 mmol) and H_2O (15 mL)) and the neutral parts were extracted (2× Et_2O). The aqueous phase was acidified with concentrated HCl (3.6 mL, 43.2 mmol) and acid **13** was extracted (2× Et_2O), washed (H_2O, then saturated aqueous NaCl), dried (Na_2SO_4), and concentrated. Bulb-to-bulb distillation (oven temp. 130 °C/0.01 mbar) afforded approximately 97% pure **13** (5.40 g, 92% yield). ^{1}H NMR ($CDCl_3$): $\delta = 0.86$ (d, $J = 6.8$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H), 1.01 (d, $J = 7.0$ Hz, 3H), 1.17–1.31 (m, 2H), 1.59 (m, 1H), 1.67 (m, 1H), 1.85 (m, 1H), 1.95 (m, 1H), 2.25 (m, 1H), 2.96 (d, $J = 15.2$ Hz, 1H), 3.16 (br d, $J = 15.2$ Hz, 1H), 5.48 (s, 1H), 10.3–11.8 ppm (br, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 19.3$ (q), 19.6 (q), 19.8 (q), 24.4 (t), 32.1 (t), 32.2 (d), 32.6 (d), 40.8 (t), 42.3 (d), 131.2 (d), 135.0 (s), 178.8 ppm (s); MS: m/z (%): 196 (11) $[M]^+$, 153 (20), 136 (37), 107 (18), 93 (100), 91 (20), 79 (15).

(+)-2-[(3*S*,6*R*)-3-Isopropyl-6-methyl-1-cyclohexen-1-yl]ethanol (14): A solution of **13** (5.38 g, 27.5 mmol) in Et_2O (50 mL) was added dropwise (in 5 min) to a suspension of $LiAlH_4$ (2.09 g, 55.0 mmol). During addition, the reaction mixture warmed up to reflux. Refluxing was maintained for 45 min, after which the cooled (20 °C) reaction mixture was successively treated dropwise with H_2O (2.1 mL), 5% aqueous NaOH (2.1 mL), and H_2O (6.3 mL). The slurry was stirred for 40 min and filtered through Celite. Concentration and bulb-to-bulb distillation (oven temp. 100–125 °C/0.01 mbar) afforded approximately 97% pure **14** (4.80 g, 96%). $[\alpha]_D^{20} = +34$ ($c = 2.20$ in $CHCl_3$) (lit. [5]: $[\alpha]_D^{20} = +39.3$ (CH_2Cl_2)). The ^{1}H NMR, ^{13}C NMR, and MS spectra are in perfect agreement with those reported.[5]

(+)-2-[(3*S*,6*R*)-3-Isopropyl-6-methyl-1-cyclohexen-1-yl]acetaldehyde (15): Oxalyl chloride (4.88 g (3.31 mL), 38.5 mmol) was added at −78 °C to a solution of DMSO (4.29 g (3.91 mL), 55.0 mmol) in CH_2Cl_2 (105 mL). After 15 min, a solution of **14** (4.66 g, 25.6 mmol) in CH_2Cl_2 (30 mL) was added dropwise (in 20 min) at −70 °C. After 15 min, the white suspension was treated with *N*-ethyldiisopropylamine (19.8 g (26.8 mL), 154 mmol). After addition, the reaction mixture was allowed to warm up to 0 °C. After 5 min the reaction mixture was poured into water, extracted (2× Et_2O), and washed (saturated aqueous $NaHCO_3$, then saturated aqueous NaCl). As GC indicated 3% of remaining **14** (incomplete deprotonation of the Swern intermediate), the organic phase was treated with saturated aqueous $NaHCO_3$ (150 mL) and vigorously stirred under N_2 for 2 h. The phases were separated, and the organic phase was washed (saturated aqueous NaCl), dried (Na_2SO_4), and concentrated. Bulb-to-bulb distillation (oven temp. 80 °C/0.01 mbar) afforded approximately 97% pure **15** (4.29 g, 93% yield), which was stored in the refrigerator. A sample was purified by column chromatography (silica gel; cyclohexane/AcOEt 95:5). $[\alpha]_D^{20} = +110$ ($c = 1.30$ in $CHCl_3$) (lit. [5]: $[\alpha]_D^{20} = +99.4$ (CH_2Cl_2)). The ^{1}H NMR, ^{13}C NMR, and MS spectra are in perfect agreement with those reported.[5]

(−)-(2*S*)-1-[(3*S*,6*R*)-3-Isopropyl-6-methyl-1-cyclohexen-1-yl]5-methyl-3-hexyne-2,5-diol (18a): A mechanically stirred mixture of $Zn(OTf)_2$ (9.80 g, 28.4 mmol) and (−)-*N*-methylephedrine ((−)-**17**; 5.08 g, 27.0 mmol) was treated successively with toluene (19.5 mL) and triethylamine (2.86 g (3.97 mL), 28.4 mmol). After 2 h, 2-methyl-3-butyn-2-ol (2.39 g (2.75 mL), 28.4 mmol) was added. After 15 min a solution of **15** (2.43 g, 12.8 mmol) in toluene (18 mL) was added in 15 h by syringe pump. As the conversion was incomplete (85%), stirring was continued for 8 h (97% conversion). The reaction mixture was poured into a vigorously stirred ice-cold solution of 5% aqueous HCl and extracted (2× Et_2O/H_2O). The organic phases were washed (H_2O, then saturated aqueous $NaHCO_3$, then saturated aqueous NaCl), dried (Na_2SO_4), and concentrated (3.70 g). Flash chromatography, using silica gel (150 g) and cyclohexane/AcOEt 4:1 afforded 96% pure **18a**/**18b** (2.73 g, 88:12; 77%). Pure **18a** (**18a**/**18b** > 98:2) was obtained after subjecting the sample to chromatography a second time. $[\alpha]_D^{20} = -12.4$ ($c = 1.09$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 0.86$ (d, $J = 6.9$ Hz, 3H), 0.89 (d, $J = 6.7$ Hz, 3H), 1.01 (d, $J = 7.1$ Hz, 3H), 1.22 (m, 2H), 1.51 (s, 6H),1.57 (m, 1H), 1.66 (m, 1H), 1.85 (m, 1H), 1.94 (br, 1H), 2.07 (br, OH), 2.14 (br, 1H), 2.20 (br, OH), 2.26 (dd, $J = 13.9$, 9.3 Hz, 1H), 2.61 (m, 1H), 4.39 (dd, $J = 9.1$, 4.5 Hz, 1H), 5.47 ppm (br s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 19.4$ (q), 19.7 (q), 19.9 (q), 24.5 (t), 31.4 (2q), 31.7 (d), 31.9 (t), 32.2 (d), 42.3 (d), 43.8 (t), 60.0 (d), 65.1 (s), 82.9 (s), 89.2 (s), 130.9 (d), 137.4 ppm (s); MS: m/z

(%): 231 (6), 213 (6), 203 (11), 185 (11), 161 (10), 151 (33), 109 (100), 95 (84), 67 (39), 43 (72).

(−)-(1*S*)-4-Hydroxy-1-{[(3*S*,6*R*)-3-Isopropyl-6-methyl-1-cyclohexen-1-yl]-methyl}-4-methyl-2-pentynylpivalate (19a): A solution of **18a/18b** (88:12; 96% pure; 2.73 g, 9.92 mmol) and DMAP (160 mg) in CH_2Cl_2 (25 mL) was treated with NEt_3 (1.15 g (1.60 mL), 11.4 mmol). The stirred, cooled (0°C) solution was treated with pivaloyl chloride (1.31 g (1.33 mL), 10.9 mmol) and stirred at RT for 15 h. The reaction mixture was poured into 5% aqueous HCl and extracted ($2\times Et_2O/H_2O$). The organic phases were washed (H_2O, then saturated aqueous $NaHCO_3$, then saturated aqueous NaCl), dried (Na_2SO_4), and concentrated at partial and finally at high vacuum (0.01 mbar) to remove traces of pivaloyl chloride. The oil **19a/19b** (88:12; 92% pure; 3.54 g, 95%) was used without further purification.

Likewise, pure **19a** was obtained from pure **18a**. $[\alpha]_D^{20}=-25.2$ ($c=0.86$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=0.86$ (d, $J=6.9$ Hz, 3H), 0.90 (d, $J=6.6$ Hz, 3H); 1.01 (d, $J=7.0$ Hz, 3H), 1.19 (s, 9H), 1.19 (m, 2H), 1.49 (s, 6H), 1.49 (m, 1H), 1.66 (m, 1H), 1.83 (m, 2H), 2.05 (brs, OH), 2.15 (m, 1H), 2.40 (dd, $J=14.4$, 8.5 Hz, 1H), 2.57 (m, 1H), 5.44 ppm (m, 2H);^{13}C NMR ($CDCl_3$): $\delta=19.7$ (q), 19.9 (q), 20.0 (q), 24.6 (t), 27.0 (q), 31.2 (q), 31.3 (q), 31.9 (d), 32.0 (t), 32.4 (d), 38.7 (s), 40.4 (t), 42.4 (d), 62.4 (d), 65.0 (s), 80.2 (s), 89.4 (s), 129.7 (d), 136.6 (s), 177.5 ppm (s); MS: *m/z* (%): 213 (12), 203 (18), 185 (15), 173 (8), 145 (19), 131 (13), 105 (13), 91 (20), 79 (18), 57 (100), 43 (44).

(−)-(1*S*)-1-{[(3*S*,6*R*)-3-Isopropyl-6-methyl-1-cyclohexen-1-yl]methyl}-2-propynylpivalate (8a): Powdered K_2CO_3 (1.38 g, 10.0 mmol) was added to a solution of **19a/19b** (88:12; 92% pure; 3.54 g, 9.37 mmol) and [18]crown-6 (1.06 g, 4.00 mmol) in toluene (25 mL). After heating at reflux for 15 h (90% conversion), more K_2CO_3 (0.69 g, 5.0 mmol) and [18]crown-6 (0.53 g, 2.00 mmol) was added and heating continued for 2 h (full conversion). The cooled reaction mixture was poured into H_2O and extracted ($2\times Et_2O/H_2O$). The organic phases were washed (H_2O, then saturated aqueous NaCl), dried (Na_2SO_4), and concentrated. Flash chromatography using silica gel (140 g) and cyclohexane/AcOEt 95:5 afforded **8a/8b** (88:12; 2.18 g, 80%).

Likewise, pure **8a** was obtained from pure **19a**. $[\alpha]_D^{20}=-14.2$ ($c=1.2$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=0.86$ (d, $J=6.8$ Hz, 3H), 0.90 (d, $J=6.8$ Hz, 3H), 1.01 (d, $J=7.0$ Hz, 3H), 1.19 (s, 9H), 1.19 (m, 2H), 1.51 (m, 1H), 1.66 (m, 1H), 1.84 (m, 2H), 2.15 (m, 1H), 2.40 (d, $J=2.0$ Hz, 1H), 2.43 (dd, $J=14.2$, 8.4 Hz, 1H), 2.63 (m, 1H), 5.42 (m, 1H), 5.46 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$): $\delta=19.7$ (q), 19.9 (q), 20.0 (q), 24.6 (t), 27.0 (q), 31.8 (d), 32.1 (t), 32.4 (d), 38.7 (s), 40.3 (t), 42.5 (d), 62.2 (d), 73.0 (d), 81.8 (s), 129.9 (d), 136.4 (s), 177.5 ppm (s); MS: *m/z* (%): 188 (9), 173 (19), 145 (75), 117 (35), 105 (25), 91 (34), 57 (100), 41 (53).

(−)-(1*R*,5*R*,6*R*,7*S*,10*R*)-7-Isopropyl-10-methyltricyclo[4.4.0.0^{1,5}]decan-4-one ((−)-6): A solution of **8a** and **8b** (**8a/8b** 88:12; 1.98 g, 6.83 mmol) in 1,2-dichloroethane (30 mL) was treated with $PtCl_2$ (36 mg, 0.136 mmol) and heated for 9 h at 70°C. The solution was cooled and poured in saturated aqueous $NaHCO_3$. Extraction (Et_2O), washing (H_2O, then saturated aqueous NaCl), drying (Na_2SO_4), concentration and bulb-to-bulb distillation (100–120°C/0.01 mbar) afforded **9a** and **9b** (**9a/9b** 94:6; 1.60 g, 81%). A solution of **9a** and **9b** (**9a/9b** 94:6; 1.50 g, 5.17 mmol) in MeOH (25 mL) was treated with K_2CO_3 (861 mg, 6.24 mmol) and stirred for 90 min at RT. After partial concentration, the product was extracted (Et_2O/H_2O), washed (H_2O, then saturated aqueous NaCl), dried (Na_2SO_4), concentrated, and bulb-to-bulb distilled (100–125°C/0.01 mbar) to afford 86% pure **6** (1.13 g, 91%). Purification by chromatography using silica gel (150 g) and cyclohexane/AcOEt 7:3, followed by crystallization in pentane at −78°C, afforded pure **6** (680 mg). M.p. 60–60.5°C (lit. [4b]: 58.5–59.5°C; lit. [5]: 57–58°C); $[\alpha]_D^{20}=-20.1$ ($c=1.30$ in $CHCl_3$) (lit. [4b]: $[\alpha]_D^{20}=-23.9$ (isooctane); lit. [5]: $[\alpha]_D^{20}=-21.8$ (CH_2Cl_2)); ^{1}H NMR ($CDCl_3$): $\delta=0.59$ (m, 1H), 0.90–1.00 (m, 1H), 0.91 (d, $J=7.0$ Hz, 3H), 0.95 (d, $J=6.5$ Hz, 3H), 0.99 (d, $J=6.0$ Hz, 3H), 1.19 (m, 1H), 1.27 (t, $J=2.5$ Hz, 1H), 1.45–1.52 (m, 2H), 1.58–1.70 (m, 2H), 1.78–1.90 (m, 2H), 1.98–2.21 ppm (m, 3H); ^{13}C NMR ($CDCl_3$): $\delta=18.9$ (q), 19.4 (q), 19.9 (q), 26.0 (t), 26.6 (t), 30.8 (t), 31.3 (d), 32.5 (d), 33.2 (d), 33.3 (t), 39.7 (d), 40.3 (s), 43.4 (d), 214.6 ppm (s); MS: *m/z* (%): 206 (65) $[M]^+$, 191 (24), 164 (88), 149 (45), 135 (35), 122 (100), 107 (55), 93 (64), 91 (65), 79 (75), 69 (40), 55 (41), 41 (46).

(−)-(1*R*,4*S*,5*R*,6*R*,7*S*,10*R*)-7-Isopropyl-4,10-dimethyltricyclo[4.4.0.0^{1,5}]-decan-4-ol ((−)-1): Dried anhydrous $CeCl_3$ (468 mg, 1.90 mmol) was suspended in THF (3 mL) and stirred for 1 h at RT. The milky suspension was cooled to −78°C and treated dropwise with MeLi (1.55 N in Et_2O; 1.19 mL, 1.84 mmol). After stirring for 1 h, a solution of **6** (189 mg, 0.92 mmol) in THF (1.5 mL) was added. After 15 min the temperature was allowed to reach 0°C in 30 min. The reaction mixture was poured into saturated aqueous NH_4Cl and the product was extracted (Et_2O), washed (H_2O, then saturated aqueous NaCl), dried (Na_2SO_4), concentrated, and bulb-to-bulb distilled (100–125°C/0.01 mbar) on $CaCO_3$ to afford **1** (200 mg, 98%) containing 3% of the epimeric alcohol. Crystallization in acetonitrile afforded highly pure (−)-cubebol (**1**). M.p. 61–62°C (lit. [4b]: 61–62°C; lit. [5]: 59–60.4°C); $[\alpha]_D^{20}=-56.5$ ($c=0.48$ in $CHCl_3$) (lit. [4b]: $[\alpha]_D^{20}=-48.3$ ($CHCl_3$); lit. [5]: $[\alpha]_D^{20}=-51$ ($CHCl_3$)); ^{1}H NMR spectra are in perfect agreement with those reported.[5] ^{13}C NMR and MS spectra show very minor differences: ^{13}C NMR ($CDCl_3$): $\delta=18.8$ (q), 19.7 (q), 20.1 (q), 22.6 (d), 26.5 (t), 27.9 (q), 29.6 (t), 30.9 (d), 31.7 (t), 33.5 (s), 33.7 (d), 36.4 (t), 39.1 (d), 44.2 (d), 80.4 ppm (s); MS: *m/z* (%): 222 (2) $[M]^+$, 207 (46), 204 (31), 161 (100), 119 (38), 105 (48), 93 (24), 91 (31), 81 (22), 43 (25). Our data are in all respects identical with an authentic sample isolated at Firmenich.[3]

(6,6-Dimethyl-1-cyclohexen-1-yl)acetaldehyde (20): Aldehyde **20** was prepared in four steps starting from 6,6-dimethylcyclohexanone (50.0 g, 391 mmol). The Wittig–Horner reaction was performed as described above for **11** and afforded ethyl (2*E*)-(2,2-dimethylcyclohexylidene)acetate (76.6 g, 100%). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.3$ (q), 22.2 (t), 25.8 (t), 27.8 (q), 28.1 (t), 38.2 (s), 42.0 (t), 59.5 (t), 111.2 (d), 167.5 (s), 169.6 ppm (s).

A solution of the above ester (20.0 g, 102 mmol) in THF (30 mL) was added at −25 to −16°C to a solution of lithium diisopropylamide (LDA) in THF (300 mL) (prepared from BuLi (1.48 N in hexane; 73.0 mL, 108 mmol) and diisopropylamine (11.5 g (16.0 mL), 114 mmol)). The temperature was allowed to reach 16°C and the reaction mixture was poured into vigorously stirred 5% aqueous HCl. Usual workup afforded ethyl (6,6-dimethyl-1-cyclohexen-1yl)acetate (16.8 g, 84%). ^{13}C NMR ($CDCl_3$): $\delta=14.2$ (q), 19.1 (t), 26.0 (t), 27.8 (2q), 34.2 (s), 38.3 (t), 39.3 (t), 60.4 (t), 125.7 (d), 138.1 (s), 173.0 ppm (s).

A solution of the above ester (11.8 g, 60.1 mmol) in Et_2O (40 mL) was added dropwise (5 min) into a suspension of $LiAlH_4$ (3.42 g, 90.2 mmol). During addition, the reaction mixture was warmed up to reflux. After 5 min the formed (6,6-dimethyl-1-cyclohexen-1-yl)ethanol was isolated in the usual manner and bulb-to-bulb distilled (see **14**) (8.90 g; 92% pure; 93%). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=19.2$ (t), 26.0 (t), 28.1 (2q), 34.1 (s), 34.2 (t), 39.5 (t), 62.0 (t), 122.6 (d), 141.0 ppm (s).

The oxidation of the above alcohol (4.70 g, 30.7 mmol) to **20** (4.15 g, 89%) was performed as described for **15**. ^{1}H NMR ($CDCl_3$): $\delta=0.98$ (s, 6H), 1.51 (m, 2H), 1.62 (m, 2H), 2.04 (m, 2H), 2.98 (m, 2H), 5.47 (brt, $J=3.9$ Hz, 1H), 9.55 ppm (t, $J=3.0$ Hz, 1H);^{13}C NMR ($CDCl_3$): $\delta=19.1$ (t), 26.2 (t), 27.7 (2q), 34.1 (s), 39.1 (t), 47.3 (t), 127.5 (d), 136.4 (s), 201.7 ppm (d); MS: *m/z* (%): 152 (21) $[M]^+$, 137 (20), 123 (24), 109 (61), 93 (100), 81 (76), 67 (76), 55 (33), 41 (50).

(−)-(2*S*)-1-(6,6-Dimethyl-1-cyclohexen-1-yl)-5-methyl-3-hexyne-2,5-diol (21): Procedure as described for **18a**. Starting from **20** (3.13 g, 20.6 mmol), pure **21** (2.50 g, 51%; 95% *ee* (see **23**)) was obtained. $[\alpha]_D^{20}=-16.8$ ($c=1.01$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=1.02$ (s, 6H), 1.46 (m, 2H), 1.52 (s, 6H), 1.60 (m, 2H); 2.01 (m, 2H), 2.37 (m, 2H), 2.47 (s, OH), 4.52 (m, 1H), 5.51 ppm (brt, $J=3.9$ Hz, 1H);^{13}C NMR ($CDCl_3$): $\delta=19.1$ (t), 26.0 (t), 28.1 (2q), 31.4 (2q), 34.1 (s), 39.5 (t), 40.0 (t), 61.5 (d), 65.1 (s), 83.2 (s), 89.5 (s), 124.5 (d), 140.0 ppm (s); MS: *m/z* (%): 203 (40) $[M]^+$, 185 (16), 175 (24), 147 (21), 133 (20), 123 (28), 109 (100), 95 (41), 81 (73), 67 (49), 43 (64).

(−)-(1*S*)-1-[(6,6-Dimethyl-1-cyclohexen-1-yl)methyl]-4-hydroxy-4-methyl-2-pentynyl pivalate (22): Procedure as described for **19a**. Starting from **21** (2.36 g, 10.0 mmol), **22** (2.90 g, 91%; 95% *ee* (see **23**)) was obtained after concentration at 80°C/0.1 mbar. $[\alpha]_D^{20}=-61.8$ ($c=0.76$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=1.02$ (s, 6H), 1.20 (s, 9H), 1.44 (m, 2H),

1.49 (s, 6H), 1.57 (m, 2H), 1.96 (m, 2H), 2.16 (s, OH), 2.37 (m, 1H), 2.44 (m, 1H), 5.44 (br t, J=3.8 Hz, 1H), 5.50 ppm (dd, J=8.3, 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=19.1 (t), 26.0 (t), 27.0 (3q), 28.0 (2q), 31.3 (2q), 34.0 (s), 36.8 (t), 38.7 (s), 39.5 (t), 63.2 (d), 65.0 (s), 80.2 (s), 89.7 (s), 124.5 (d), 138.8 (s), 177.4 ppm (s); MS: m/z (%): 218 (7) $[M]^+$, 217 (7), 203 (29), 185 (10), 175 (13), 149 (15), 133 (16), 105 (10), 85 (12), 57 (100), 41 (19).

(−)-(1*S*)-1-[(2,6,6-Dimethyl-1-cyclohexen-1-yl)methyl]-2-propynyl pivalate (23): Procedure as described for **8a**. Starting from **22** (2.78 g, 8.69 mmol), 95% pure **23** (2.05 g, 85%; 95% *ee* (see **23**)) was obtained. $[\alpha]_D^{20}$=−51.0 (c=0.79 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=1.02 (s, 3H), 1.03 (s, 3H), 1.20 (s, 9H), 1.45 (m, 2H), 1.57 (m, 2H), 1.96 (m, 2H), 2.41 (d, J=2.1 Hz, 1H), 2.46 (m, 2H), 5.45 (m, 1H), 5.47 ppm (m, 1H); ^{13}C NMR ($CDCl_3$): δ=19.1 (t), 25.9 (t), 27.0 (3q), 28.0 (2q), 34.0 (s), 36.6 (t), 38.7 (s), 39.5 (t), 62.9 (d), 73.0 (d), 81.9 (s), 124.4 (d), 138.6 (s), 177.4 ppm (s); MS: m/z (%): 262 (2) $[M]^+$, 178 (13), 163 (7), 160 (9), 145 (74), 117 (15), 108 (22), 91 (19), 57 (100), 41 (26).

(2*S*)-5-Methyl-1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-5-methyl-3-hexyne-2,5-diol (25): Procedure as described for **18a**. Starting from **24** (8.73 g, 52.6 mmol), nonpurified **25** (14.22 g, max. 52.6 mmol; 92% *ee* (see **27**)) was obtained. ^{1}H NMR ($CDCl_3$) (characteristic signals): δ=1.03 (s, 6H), 1.52 (s, 6H), 1.70 (s, 3H), 4.56 ppm (dd, J=8.3, 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ=19.3 (t), 21.2 (q), 28.8 (q), 29.0 (q), 31.4 (2q), 33.1 (t), 34.8 (s), 36.9 (t), 39.9 (t), 62.4 (d), 65.1 (s), 83.4 (s), 89.4 (s), 132.0 (s), 132.5 ppm (s); MS: m/z (%): 232 (5) $[M]^+$, 217 (8), 189 (10), 137 (100), 123 (51), 95 (93), 81 (55).

(1*S*)-4-Hydroxy-4-methyl-1-[(2,6,6-trimethyl-1-cyclohexen-1-yl)methyl]-2-pentynyl pivalate (26): Procedure as described for **19a**. Starting from **25** (14.22 g, max. 52.6 mmol), nonpurified **26** (17.4 g, max. 52.1 mmol; 92% *ee* (see **27**)) was obtained after concentration at 80°C/0.1 mbar. ^{1}H NMR ($CDCl_3$): δ=1.02 (2s, 6H), 1.20 (s, 9H), 1.42 (m, 2H), 1.48 (s, 6H), 1.59 (m, 2H), 1.70 (s, 3H), 1.94 (br t, J=6.5 Hz, 2H), 2.53 (dd, J=14.5, 7.3 Hz, 1H), 2.59 (dd, J=14.5, 8.0 Hz, 1H), 5.53 ppm (t, J=7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.3 (t), 21.2 (q), 27.0 (3q), 28.9 (2q), 31.2 (2q), 33.0 (t), 33.5 (t), 34.6 (s), 38.6 (s), 39.9 (t), 64.2 (d), 65.0 (s), 80.5 (s), 89.6 (s), 131.4 (s), 132.0 (s), 177.6 ppm (s); MS: m/z (%): 316 (1) $[M]^+$, 232 (8), 217 (28), 199 (8), 189 (15), 163 (13), 147 (16), 137 (22), 95 (24), 85 (20), 57 (100).

(1*S*)-1-[(2,6,6-Trimethyl-1-cyclohexen-1-yl)methyl]-2-propynyl pivalate (27): Procedure as described for **8a**. Starting from **26** (17.4 g, max. 52.1 mmol), pure bulb-to-bulb distilled **23** (12.76 g, 88% from **24**; 92% *ee*) was obtained. A separation of the enantiomers was possible by chiral GC, but a better separation that gave more accurate values was obtained by injection of the corresponding alcohol (most easily produced by diisobutylaluminium hydride (DIBAH) reduction in THF). $[\alpha]_D^{20}$=−49.2 (c=0.99 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=1.02 (s, 3H), 1.03 (s, 3H), 1.21 (s, 9H), 1.42 (m, 2H), 1.59 (m, 2H), 1.71 (s, 3H), 1.95 (br t, J=6.0 Hz, 2H), 2.40 (d, J=2.3 Hz, 1H), 2.58 (dd, J=14.7, 6.6 Hz, 1H), 2.65 (dd, J=14.7, 8.4 Hz, 1H), 5.49 ppm (m, 1H); ^{13}C NMR ($CDCl_3$): δ=19.3 (t), 21.2 (q), 27.0 (3q), 28.9 (2q), 28.9 (q), 33.0 (t), 33.5 (t), 34.6 (s), 38.7 (s), 39.9 (t), 63.9 (d), 73.1 (d), 82.2 (s), 131.7 (s), 177.5 ppm (s); MS: m/z (%): 276 (1) $[M]^+$, 192 (5), 174 (13), 159 (100), 137 (32), 95 (33), 57 (67), 41 (23).

(−)-(1*R*,5*R*,6*R*)-10-Dimethyl-tricyclo[4.4.0.0^{1,5}]decan-4-one ((−)-29): A solution of **23** (1.69 g, 6.45 mmol) in 1,2-dichloroethane (26 mL) was treated with $PtCl_2$ (35 mg, 0.132 mmol) and heated for 8 h at 70°C. The solution was cooled and poured in saturated aqueous $NaHCO_3$. Extraction (Et_2O), washing (H_2O, then saturated aqueous NaCl), drying (Na_2SO_4), concentration, and bulb-to-bulb distillation (100–120°C/0.01 mbar) afforded **28** (1.49 g) containing 5% of **29**. It was dissolved in MeOH (25 mL) and treated with K_2CO_3 (1.08 g, 7.83 mmol) and stirred for 165 min at RT. After partial concentration, the product was extracted (Et_2O/H_2O), washed (H_2O, then saturated aqueous NaCl), dried (Na_2SO_4), concentrated, and bulb-to-bulb distilled (100–125°C/0.01 mbar) to afford **29** (853 mg, 74%; 61% *ee*). $[\alpha]_D^{20}$=+24.8 (c=0.56 in $CHCl_3$) (61% *ee* by chiral GC (major enantiomer: first peak)); ^{1}H NMR ($CDCl_3$): δ=0.92–1.02 (m, 1H); 0.96 (s, 3H), 1.09 (s, 3H), 1.20–1.30 (m, 2H), 1.35–1.55 (m, 2H), 1.51 (d, J=2.5 Hz, 1H), 1.59 (ddd, J=8.0, 2.5, 2.1 Hz, 1H), 1.80–1.90 (m, 1H), 1.95–2.12 ppm (m, 4H); ^{13}C NMR ($CDCl_3$): δ=18.0 (t), 23.3 (t), 24.6 (t), 24.9 (q), 27.9 (q), 28.4 (d), 29.9 (s), 33.2 (t), 37.3 (t), 41.1 (d), 43.2 (s), 214.8 ppm (s); MS: m/z (%): 178 (26) $[M]^+$, 163 (9), 136 (16), 135 (16), 121 (30), 110 (100), 107 (25), 93 (28), 91 (22), 79 (33), 69 (40).

Alternatively, a solution of **23** (50 mg, 0.191 mmol) in toluene (1 mL) was treated with $[Cu(CH_3CN)_4]BF_4$ (1.2 mg, 0.0038 mmol) and heated for 8 h at 70°C. Proceeding as above afforded (−)-**29** (22.0 mg, 65%; 57% *ee* by chiral GC (major enantiomer: first peak)).

(1*S*,5*S*,6*S*)-6,10,10-Trimethyltricyclo[4.4.0.0^{1,5}]decan-4-one (*ent*-32) (Scheme 6, expt 8): A solution of **27** (224 mg, 92% pure; 0.746 mmol; 92% *ee*) in 1,2-dichloroethane (8 mL) was treated with $[Cu(CH_3CN)_4]BF_4$ (5.0 mg, 0.0159 mmol) and heated for 90 min at 50°C. Filtration through silica, washing with CH_2Cl_2, and evaporation afforded *ent*-**30** (198 mg, 87% by GC). It was dissolved in MeOH (3 mL), treated with K_2CO_3 (103 mg, 0.75 mmol), and stirred for 15 h at RT. The product was extracted (2×pentane/saturated aqueous NaCl), dried (Na_2SO_4), concentrated, and bulb-to-bulb distilled (100°C/0.04 mbar) to afford of *ent*-**32** (117 mg; GC: 88%; 72%; 53% *ee* by chiral GC (major enantiomer: first peak)).

Starting from **27** (46% *ee*), the cycloisomerization catalyzed by $[Cu(CH_3CN)_4]BF_4$ (Scheme 6, expt 8) afforded *ent*-**32** (26% *ee*). $[\alpha]_D^{20}$=−4.03 (c=1.02 in $CHCl_3$) (26% *ee* by chiral GC (major enantiomer: first peak)).

In another experiment, (±)-**27** (3.00 g, 93% pure; 10.1 mmol) afforded (±)-**32** (1.78 g, 91% by GC; 83%); ^{1}H NMR ($CDCl_3$): δ=0.90 (s, 3H), 0.99 (s, 3H),1.00 (s, 3H), 1.07–1.30 (m, 4H), 1.34–1.48 (m, 1H), 1.60–1.70 (m, 2H), 2.15 (d, J=19.5 Hz, 1H), 2.24 (d, J=19.5 Hz, 1H), 2.51 (d, J=19.5 Hz, 1H), 2.52 ppm (m, 1H); ^{13}C NMR ($CDCl_3$): δ=17.1 (q), 18.1 (t), 24.4 (s), 25.6 (d), 27.6 (2q), 30.2 (s), 33.8 (t), 36.8 (s), 37.5 (t), 39.5 (t), 40.5 (t), 220.2 ppm (s); MS: m/z (%): 192 (51) $[M]^+$, 177 (57), 149 (63), 136 (64), 107 (73), 93 (100), 79 (97), 69 (71), 67 (38), 55 (39), 41 (48).

(1*R*,5*R*,6*R*)-6,10,10-Trimethyltricyclo[4.4.0.0^{1,5}]decan-3-one (33) (Scheme 6, expt 6): A solution of **27** (3.52 g, 12.76 mmol; 92% *ee*) in 1,2-dichloroethane (40 mL) was treated with $PtCl_2$ (5.0 mg, 0.256 mmol) and heated for 2 h at 70°C (14% conversion). Another portion of $PtCl_2$ was added (102 mg, 0.383 mmol) and heating continued for 6 h. Filtration through silica, washing with CH_2Cl_2, and evaporation afforded 3.38 g of **30** (53% by GC) and **31** (39% by GC). It was dissolved in MeOH (40 mL), treated with K_2CO_3 (1.85 g, 13.4 mmol), and stirred for 2 h at RT. After partial concentration, the products **32** and **33** were extracted (2×pentane/saturated aqueous NaCl), dried (Na_2SO_4), concentrated (2.28 g), and separated by chromatography (silica gel; cyclohexane/AcOEt 95:5) to afford successively **33** (744 mg, 34%; 88% *ee* by chiral GC (major enantiomer: first peak)) and **32** (1.09 g, 44%; 13% *ee* by chiral GC (major enantiomer: second peak)).

*Compound **33** (from a previous experiment)*: $[\alpha]_D^{20}$=−29.9 ($CHCl_3$; c=1.07) (62% *ee* by chiral GC (major enantiomer: first peak)); ^{1}H NMR ($CDCl_3$): δ=0.95 (s, 3H), 1.05–1.10 (m, 1H), 1.06 (s, 3H), 1.15–1.25 (m, 2H), 1.19 (s, 3H), 1.42 (m, 1H), 1.65 (s, 1H), 1.65–1.87 (m, 3H), 1.96–2.04 (m, 1H), 2.15–2.28 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ=18.0 (t), 18.8 (q), 21.9 (t), 26.2 (q), 27.6 (2q), 30.9 (s), 31.8 (s), 34.2 (t), 37.8 (2t), 44.5 (d), 49.3 (s), 215.9 ppm (s); MS: m/z (%): 192 (43) $[M]^+$, 177 (27), 150 (58), 136 (71), 135 (100), 123 (60), 121 (55), 107 (64), 93 (59), 79 (57), 69 (38), 55 (30), 41 (38).

(1*S*,6*S*)- and (1*R*,6*S*)-1-Allyl-2,2,6-trimethylcyclohexanecarbaldehyde (36 and 37): Concentrated HCl (1 mL, 10 mmol) was added to a stirred solution of (+)-**34** (100 g; purity 89% (containing 7% of *cis* diastereomer); 0.63 mol) and trimethyl orthoformate (Fluka purum; 77.5 g (80.0 mL), 0.72 mol) in MeOH (70 mL) at −7°C, and the mixture was stirred at RT over 2 h. NaOAc (1.7 g, 20 mmol) was added, followed by allyl alcohol (Fluka purum; 76.6 g (90 mL), 1.23 mol) and trifluoroacetic acid (Fluka purum; 0.34 g, 3 mmol), and the mixture was slowly heated to 80°C (bath temp.), while the volatiles were distilled through a 20 cm Vigreux column over 2 h. The temperature of the bath was then raised to 150°C and heating continued for 16 h. The cooled mixture was diluted with Et_2O and H_2O and extracted. The organic phase was washed (10% aqueous HCl, then H_2O, then saturated aqueous $NaHCO_3$, then brine), dried (Na_2SO_4),

and concentrated (113 g). Distillation (20 cm Vigreux column) under vacuum gave a first fraction containing 88% pure product (13.1 g) and a second fraction (b.p. 59°C/0.3 mbar) containing 99% pure product (82.6 g; total yield 76%). Subsequently, ^{1}H and ^{13}C NMR spectroscopic analysis showed that fraction 2 consisted of an approximately 9:1 mixture of **36** and **37**. Data for **36**: ^{1}H NMR ($CDCl_3$): $\delta=0.84$ (d, $J=7$ Hz, 3H), 0.92 (s, 3H), 1.07 (s, 3H), 1.28–1.35 (m, 4H), 1.50–1.71 (m, 4H), 1.85–1.95 (m, 2H), 2.41 (dd, $J=16$, 9 Hz, 1H), 2.50 (dd, $J=16$, 9 Hz, 1H), 4.98 (dd, $J=10$, 1 Hz, 1H), 5.07 (dd, $J=17$, 1 Hz, 1H), 5.85–5.97 (m, 1H), 10.07 ppm (s, 1H; NOE with the two equatorial Me groups, but not with the axial Me group); ^{13}C NMR ($CDCl_3$): $\delta=17.3$ (q), 22.0 (t), 24.6 (q), 27.2 (q), 32.2 (t), 34.2 (d), 34.3 (t), 36.9 (s), 39.0 (t), 56.4 (s), 116.4 (t), 137.1 (d), 208.6 ppm (d); MS: *m*/*z* (%): 194 (4) $[M]^+$, 179 (12), 152 (23), 137 (43), 125 (51), 109 (100), 95 (89), 81 (82), 69 (77), 67 (60). 55 (91), 41 (84).

(1*R*,6*S*)-1-Allyl-2,2,6-trimethylcyclohexanecarbaldehyde (37): Characteristic signals: ^{1}H NMR ($CDCl_3$): $\delta=0.90$ (d, $J=7$ Hz, 3H), 0.98 (s, 3H), 1.03 (s, 3H), 9.68 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta=19.0$ (q), 24.0 (q), 26.9 (q), 116.1 (t), 137.4 (d), 208.5 ppm (d).

(+)-(1*S*,6*S*)-2,2,6-Trimethyl-1-(2-oxopropyl)cyclohexanecarbaldehyde ((+)-38): $PdCl_2$ (4.0 g, 22 mmol) and $CuCl_2$ (3.0 g, 22 mmol) were added to a solution of **36** and **37** (9:1) (43.7 g, 223 mmol) in 1,2-dimethoxyethane (360 mL) and H_2O (40 mL) at RT, and the mixture was stirred under O_2 at RT over 56 h. The mixture was diluted with diethyl ether and H_2O and then extracted. The organic phase was washed (H_2O, then brine), dried (Na_2SO_4), and concentrated (48 g). Distillation (Widmer column) under vacuum gave **38** (b.p. 89°C/0.14 mbar) as a yellowish liquid (25 g) which solidified on standing. Crystallization from pentane at −30°C afforded 99% pure (+)-**38** (22.7 g, 48%) as colorless crystals. M.p. = 53–55°C; $[\alpha]_D^{20}=+52.7$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=$ 0.82 (d, $J=7$ Hz, 3H), 0.92 (s, 3H), 0.98 (s, 3H), 1.27–1.35 (m, 1H), 1.50–1.58 (m, 1H), 1.60–1.84 (m, 4H), 2.20 (s, 3H), 2.20–2.31 (m, 1H), 2.67 (d, $J=18$ Hz, 1H), 2.91 ppm (d, $J=18$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=18.2$ (q), 21.8 (t), 24.7 (q), 26.8 (q), 31.6 (t), 31.6 (q), 34.3 (d), 36.9 (s), 37.9 (t), 43.5 (t), 56.6 (s), 206.0 (d), 207.8 ppm (s); MS: *m*/*z* (%): 195 (1), 167 (1), 153 (12), 137 (15), 123 (20), 109 (44), 81 (22), 67 (20), 55 (28), 43 (100), 41 (55), 39 (25), 29 (22), 27 (15).

(+)-(5*R*,10*S*)-6,6,10-Trimethylspiro[4.5]dec-3-en-2-one ((+)-39): A solution of (+)-**38** (14.3 g, 67.1 mmol) in 1 M methanolic KOH (150 mL) was stirred at RT over 15 h. The mixture was diluted with diethyl ether and H_2O, and extracted. The organic phase was washed (saturated aqueous $NaHCO_3$, then H_2O), dried (Na_2SO_4), and concentrated to a solid (12.8 g). Crystallization from pentane at −30°C afforded 99% pure (+)-**39** (11.0 g, 85%) as colorless crystals. M.p. 67–68°C; $[\alpha]_D^{20}=+66.9$ ($c=$ 2.00 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=0.64$ (d, $J=7$ Hz, 3H), 0.73 (s, 3H), 1.03 (s, 3H), 1.18–1.28 (m, 1H), 1.35–1.39 (m, 1H), 1.57–1.68 (m, 4H), 1.92–2.02 (m, 1H), 2.05 (d, $J=18$ Hz, 1H), 2.33 (d, $J=18$ Hz, 1H), 6.21 (d, $J=6$ Hz, 1H), 7.71 ppm (d, $J=6$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=17.2$ (q), 21.8 (t), 23.7 (q), 27.1 (q), 32.2 (t), 35.1 (d), 35.7 (s), 37.1 (t), 43.1 (t), 55.7 (s), 134.6 (d), 167.9 (d), 209.8 ppm (s); MS: *m*/*z* (%): 192 (15) $[M]^+$, 177 (11), 149 (16), 135 (9), 122 (37), 108 (81), 91 (52), 79 (100), 77 (63), 69 (27), 55 (46), 53 (37), 41 (87), 39 (49), 29 (27), 27 (25).

(+)-(5*R*,10*S*)-6,6,10-Trimethylspiro[4.5]decan-2-one ((+)-40): Pd/C (10%, 200 mg) was added to a solution of (+)-**39** (4.00 g, 20.8 mmol) in EtOH (40 mL) at RT, and the mixture was shaken under H_2 (1 atm) over 5 h. The catalyst was filtered off through Celite and the filtrate concentrated (4.10 g). Bulb-to-bulb distillation (oven temp. 100–150°C/0.15 mbar) afforded >99% pure (+)-**40** (3.94 g, 97%). Crystallization from pentane at −30°C gave colorless crystals (3.56 g). M.p. 53–54°C; $[\alpha]_D^{20}=+60.3$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=0.77$ (d, $J=7$ Hz, 3H), 0.90 (s, 3H), 0.94 (s, 3H), 1.15 (m, 2H), 1.38–1.59 (m, 4H), 1.80–1.95 (m, 3H), 1.99 (d, $J=18$ Hz, 1H), 2.18–2.36 (m, 2H), 2.39 ppm (d, $J=18$ Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta=17.4$ (q), 21.6 (t), 21.7 (t), 23.0 (q), 26.4 (q), 30.9 (t), 36.4 (d), 36.4 (t), 36.9 (s), 39.2 (t), 45.9 (t), 48.1 (s), 221.1 ppm (s); MS: *m*/*z* (%): 194 (57) $[M]^+$, 123 (72), 110 (58), 95 (23), 83 (100), 69 (43), 67 (37), 55 (49), 41 (45), 39 (17).

(+)-(5*R*,10*S*)-6,6,10-Trimethylspiro[4.5]decane-2-ol (42 and 43): A solution of (+)-**40** (1.74 g, 9.00 mmol) in Et_2O (20 mL) was added dropwise to a suspension of $LiAlH_4$ (0.34 g, 9.5 mmol) in diethyl ether (10 mL) at RT, and the mixture was stirred at RT over 1 h. The mixture was cooled to 4°C, acetone (1 mL) was added dropwise, followed by 4% aqueous NaOH (2 mL), and the mixture was stirred at RT over 30 min. Na_2SO_4 was added, the solids were filtered off, and the filtrate was concentrated to afford a mixture of **42** and **43** (1.83 g). Crystallization from pentane at −30°C afforded a >99% pure mixture of **42** and **43** (1.68 g, ratio ≈ 1:1; 96%) as colorless crystals. M.p. 60–62°C; ^{1}H NMR ($CDCl_3$, data for characteristic signals): $\delta=0.77$ (d, $J=5$ Hz, 1.5H), 0.78 (d, $J=5$ Hz, 1.5H), 0.87 (s, 1.5H), 0.89 (s, 1.5H), 0.90 (s, 1.5H), 0.91 (s, 1.5H), 4.09–4.18 (m, 0.5H), 4.19–4.27 ppm (m, 0.5H); ^{13}C NMR ($CDCl_3$): $\delta=18.0$ and 18.3 (q); 21.8 and 22.2 (t); 21.8 and 22.8 (q); 23.9 and 24.6 (t); 26.5 and 27.2 (q); 31.1 and 32.0 (t); 35.2 and 36.4 (d); 36.6 and 36.9 (t); 37.0 and 37.1 (s); 37.1 and 37.3 (t); 41.0 and 42.6 (t); 49.6 and 50.8 (s); 74.0 and 74.5 ppm (d); MS: *m*/*z* (%): 196 (8) $[M]^+$, 178 (22), 163 (18), 135 (23). 121 (21), 112 (27), 109 (37), 107 (78), 94 (81), 83 (100), 79 (37), 69 (43), 67 (47), 55 (57), 41 (47), 39 (13).

(5*R*,10*S*)-6,6,10-Trimethylspiro[4.5]decalyl-2-acetate (46 and 47): Ac_2O (4 mL) was added to a solution of **42** and **43** (ca. 1:1, 0.85 g, 4.3 mmol) in pyridine (4 mL), and the mixture was stirred at RT over 4 h. The mixture was concentrated to afford a colorless oil (1.06 g). Bulb-to-bulb distillation (oven temp. 112°C/0.3 mbar) afforded a >99% pure mixture of **46** and **47** (0.98 g, ratio ≈ 1:1; 95%). ^{1}H NMR ($CDCl_3$, data for characteristic signals): $\delta=0.79$ (s, 1.5H), 0.81 (d, $J=7$ Hz, 1.5H), 0.85 (d, $J=7$ Hz, 1.5H), 0.88 (s, 1.5H), 0.89 (s, 1.5H), 0.91 (s, 1.5H), 2.00 (s, 1.5H), 2.02 (s, 1.5H), 4.88–4.98 (m, 0.5H), 5.02–5.09 ppm (m, 0.5H). ^{13}C NMR ($CDCl_3$): $\delta=17.9$ and 18.0 (q); 21.3 and 21.4 (q); 21.9 and 22.1 (t); 21.9 and 22.5 (q); 23.5 and 24.9 (t); 26.4 and 27.0 (q); 31.1 and 32.1 (t); 32.8 and 33.9 (t); 35.3 and 36.4 (d); 36.9 and 37.1 (s); 37.2 and 37.3 (t); 38.1 and 38.8 (t); 49.3 and 50.9 (s); 76.2 and 77.4 ppm (d); MS: *m*/*z* (%): 178 (87), 163 (12), 135 (20), 122 (18), 107 (100), 94 (88), 82 (37), 79 (20), 69 (25), 67 (32), 55 (27), 43 (43), 41 (26).

Compounds 46–49: A suspension of (*S*)-**32** (60 mg, 0.313 mmol; 18% *ee* (from Scheme 6; expt 7), AcOH (0.5 mL), and 10% Pd/C (20 mg) was stirred under H_2. After 24 h, the suspension was filtered over Celite, and the filter cake was washed with Et_2O. The filtrate was washed (H_2O, then saturated aqueous $NaHCO_3$, then saturated aqueous NaCl), dried (Na_2SO_4), and concentrated. The product mixture of **40** and **41** (containing 20% of unreacted (*S*)-**32**) was reduced, and the alcohol diastereomers **42**–**45** were converted into the acetates **46**–**49** as described above. Superimposition with the enantiomerically pure mixture of **46** and **47** on the chiral GC allowed the determination of the absolute configuration of (*S*)-**32** (see Figure 1).

(1*RS*,5*RS*,6*RS*)-6,10,10-Trimethyltricyclo[4.4.0.0^{1,5}]decan-4-toluenesulfonylhydrazone ((±)-50): A solution of (±)-**32** (1.78 g, 8.42 mmol; 91% pure), tosylhydrazide (1.72 g, 9.26 mmol), and AcOH (3 drops) in MeOH (12 mL) was heated at reflux for 3 h. The reaction mixture was half-concentrated and stored in the refrigerator for 2 d. The formed crystals were isolated by filtration and washed with cold MeOH. Yield: 2.52 g (83%). A sample was recrystallized for analytical purposes. Characteristic signals (*E*/*Z* or *Z*/*E* 60:40): ^{1}H NMR ($CDCl_3$): $\delta=0.89$ (0.85) (s, 3H), 0.87 (s, 3H), 0.97 (s, 3H), 2.42 (2.41) (s, 3H), 7.29 (m, 2H), 7.84 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): $\delta=17.9$ (t), 18.1 (t), 18.6 (q), 19.0 (q), 21.6 (q), 23.1 (t), 24.3 (t), 26.5 (q), 26.6 (q), 27.5 (q), 27.6 (q), 29.6 (t), 30.7 (s), 30.9 (s), 33.4 (t), 33.8 (t), 34.0 (t), 37.5 (t), 37.9 (t), 39.2 (d), 127.9 (2d), 129.6 (2d), 135.4 (s), 135.6 (s), 143.8 (s), 143.9 (s), 171.2 ppm (br s).

(1*RS*,5*RS*,6*RS*)-6,10,10-Trimethyltricyclo[4.4.0.0^{1,5}]dec-3-ene ((±)-51): A solution of (±)-**50** (500 mg, 1.39 mmol) in *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethane (TMEDA; 7 mL) was cooled to −78°C and treated dropwise with BuLi (1.41 M; 3.94 mL, 5.56 mmol). The temperature was maintained below −65°C. The red solution was stirred at −70°C for 5 min and allowed to reach RT (30 min). Stirring was continued for 80 min. The solution was then poured into 5% HCl/ice, and the product was extracted (2 × pentane/H_2O), washed (4 × H_2O), dried (Na_2SO_4), concentrated, and filtered (silica gel; heptanes) to afford (±)-**51** (93 mg, 38%). ^{1}H NMR ($CDCl_3$): $\delta=0.78$ (s, 3H), 0.86 (s, 3H), 0.97 (s, 1H), 1.04 (m, 1H), 1.18 (m, 1H), 1.22 (m, 1H), 1.37 (m, 1H), 1.49 (t, $J=2.5$ Hz, 1H), 1.62 (m, 1H), 1.81 (m, 1H), 1.98 (dq, $J=18.0$, 2.4 Hz, 1H), 2.46 (d, $J=18.0$ Hz,

1H), 5.49 (m, 1H), 5.64 ppm (m, 1H); ^{13}C NMR ($CDCl_3$): δ=15.8 (q), 18.7 (t), 24.7 (s), 26.4 (q), 27.9 (q), 30.6 (s), 33.7 (t), 34.9 (t), 38.5 (t), 38.6 (d), 42.3 (s), 129.6 (d), 130.8 ppm (d); MS: *m*/*z* (%): 176 (42) $[M]^+$, 161 (26), 133 (22), 119 (25), 105 (100), 91 (93), 79 (19), 77 (17).

(1*R*,5*R*,6*R*)-6,10,10-Trimethyltricyclo[4.4.0.0^{1,5}]dec-3-ene ((6*R*)-51) from (6*R*)-32 (13% *ee*): Starting from (6*R*)-**32** (1.09 g, 5.68 mmol; 13% *ee*; Scheme 6, expt 6), 1.60 g (78%) of crystalline (6*R*)-**50** (9% *ee*; see below) and 485 mg of mother liquor containing (6*R*)-**50** (21% *ee*; see below) were obtained. The crystals and the mother liquor were separately converted into (6*R*)-**51** of 9% *ee* (98 mg, 30%) and 21% *ee*, respectively (chiral GC: second peak major in both cases).

(1*RS*,5*RS*,6*RS*)-6,10,10-Trimethyltricyclo[4.4.0.0^{1,5}]decan-3-toluenesulfonylhydrazone (±)-52: A solution of (±)-**33** (1.00 g, 5.21 mmol), tosylhydrazide (1.07 g, 5.73 mmol) and AcOH (3 drops) in MeOH (10 mL) was heated at reflux for 2 h. The reaction mixture was cooled to RT and stored in the freezer for 15 h. The formed crystals were isolated by filtration and washed with cold MeOH. Yield: 1.44 g (77%). A sample was recrystallized for analytical purposes. Characteristic signals (*E*/*Z* or *Z*/*E* 60:40): ^{1}H NMR ($CDCl_3$): δ=0.68 (0.69) (s, 3H), 0.87 (0.88) (s, 3H), 0.93 (0.94) (s, 3H), 2.42 (s, 3H), 7.30 (m, 2H), 7.83 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ=16.4 (q), 16.5 (q),18.1 (t), 21.6 (q), 23.9 (s), 24.0 (s), 27.5 (q), 27.5 (d), 27.6 (d), 29.2 (t), 30.1 (t), 30.6 (s), 33.8 (t), 34.0 (t), 35.0 (t), 37.9 (t), 38.0 (t), 38.5 (s), 39.4 (s), 127.9 (2d), 129.6 (2d), 135.6 (s), 143.9 (s), 168.6 (s), 168.8 ppm (s).

(1*RS*,5*RS*,6*RS*)-6,10,10-Trimethyltricyclo[4.4.0.0^{1,5}]dec-3-ene ((±)-51) and (1*RS*,5*RS*,6*RS*)-6,10,10-trimethyl-tricyclo[4.4.0.0^{1,5}]dec-2-ene ((±)-53): Procedure as described for (±)-**51**. Starting from (±)-**52** (500 mg, 1.39 mmol), (±)-**51**/**53** (12:88; 76 mg, 31%) was isolated. Analytical data of **53**: ^{1}H NMR ($CDCl_3$): δ=0.81 (s, 3H), 0.87 (s, 3H), 1.13 (s, 1H), 1.05–1.25 (m, 3H), 1.30–1.45 (m, 2H), 1.62 (m, 1H), 1.72 (m, 1H), 2.07 (d, *J*= 18.0 Hz, 1H), 2.47 (m, 1H), 5.51 (m, 1H), 5.64 ppm (m, 1H); ^{13}C NMR ($CDCl_3$): δ=16.0 (q), 18.4 (t), 25.6 (s), 28.6 (q), 28.9 (q), 29.5 (d), 29.8 (s), 33.3 (t), 33.7 (t), 38.7 (t), 50.7 (s), 130.1 (d), 132.5 ppm (d); MS: *m*/*z* (%): 176 (36) $[M]^+$, 161 (50), 133 (34), 119 (42), 105 (100), 91 (90), 79 (22), 77 (19).

(1*R*,5*R*,6*R*)-6,10,10-Trimethyltricyclo[4.4.0.0^{1,5}]dec-3-ene ((6*R*)-51) and (1*R*,5*R*,6*R*)-6,10,10-trimethyltricyclo[4.4.0.0^{1,5}]dec-2-ene ((6*R*)-53) from (6*R*)-33 (88% *ee*): Starting from (*R*)-**33** (744 mg, 3.87 mmol; 88% *ee*; Scheme 6, expt 6), 101 mg (7%) of crystalline **52** (probably racemic; see below) and 1.34 g of mother liquor containing (*R*)-**52** (max. 93% yield; 96% *ee*; see below) were obtained. Proceeding as described for (±)-**51**, but at a temperature of −40 to −50 °C instead of −78 °C, the mother liquor (600 mg, max. 1.61 mmol) was converted into a mixture of (6*R*)-**51** and (6*R*)-**53** (40:60) of 96% *ee* (129 mg, 82% pure; 37% over 2 steps) (chiral GC: second peaks major) (see Figure 2).

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[14] Synthesis of **20**: see the Experimental Section.

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[19] A referee asked for an explanation why this study was done with the pivalate and not the acetate. Originally, we supposed that a crowded ester group would favor the desired reactive conformer (placing the carbonyl group in the vicinity of the alkynyl group) and

had used the pivalates prior to the study by Soriano and Marco-Contelles (see ref. [18]). As can be seen from the work of Fürstner and Hannen (see ref. [5]), the cycloisomerizations of the acetates corresponding to the pivalates **8a** and **8b** exhibit the same selectivities. Nevertheless, we prepared the acetate corresponding to **27** (92% *ee*) and submitted it to the conditions of Scheme 5, expt 5. The results are in line with those of the pivalate: **32**: 37% (1% *ee*); **33**: 63% (87% *ee*). This gives the following values for Table 2: (6*R*)-**30**: 18.5; (6*R*)-**31**: 59; (6*R*)-**E**: 77.5; (6*S*)-**E**: 22.5; (6*S*)-**30**: 18.5; (6*S*)-**31**: 4.

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