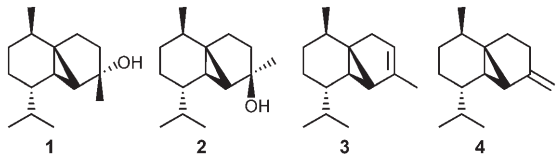
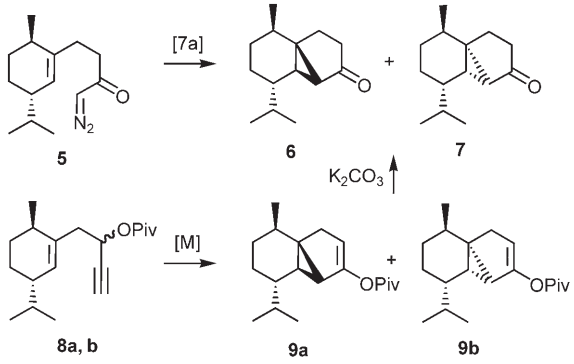


Scheme 1. Constituants of *Piper cubeba*.

Shortly after the discovery of this new skeleton, a synthesis of the racemic cubebenes **3** and **4** was reported by Piers et al., and a synthesis of **1**–**4** was reported by Yoshikoshi and coworkers.[7] Both syntheses are based on a cyclopropanation of diazoketone **5** (or the analogous isopropenyl compound, Scheme 2). Unfortunately, this route is not diastereoface-



Scheme 2. Reported and planned synthesis of **6**.

Synthetic Methods

DOI: 10.1002/anie.200504543

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

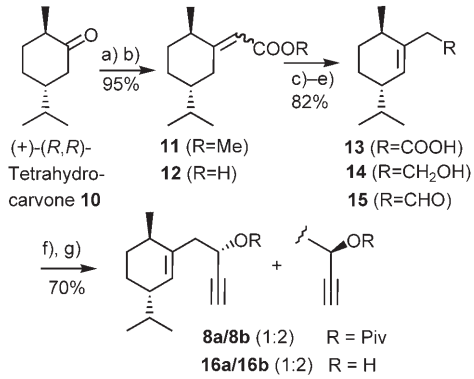
Charles Fehr and José Galindo*

Herein we describe a direct, stereoselective synthesis of (−)-cubebol,[1] based on Pt-,[2,3] Au-,[4] and Cu-catalyzed[5] enyne cycloisomerizations.

(−)-Cubebol (**1**), 4-epicubebol (**2**), and α- and β-cubebenes **3** and **4**, respectively, are naturally occurring sesquiterpenes, isolated from the berries of *Piper cubeba* (Scheme 1).[1] Whereas **2** has a very bitter taste, the almost odorless (−)-cubebol (**1**) has a pronounced cooling effect and lends itself to diverse applications in the field of flavors.[6]

selective and affords the desired ketone **6** as the minor isomer in only moderate yield. We realized that a Pt-[2,3] or Au-catalyzed[4] cycloisomerization of enynol esters[8] would represent a direct and efficient access to cubebol.

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–



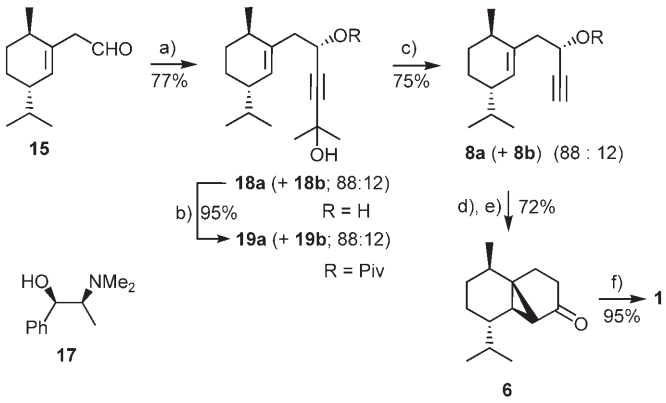
Scheme 3. Reagents and conditions: a) trimethyl phosphonoacetate (1.2 equiv), NaH (1.1 equiv), THF, reflux, 15 h; b) KOH (1.7 equiv), EtOH, 60 °C, 24 h; c) BuLi (3.0 equiv), 2,2,6,6-tetramethylpiperidine (TMP, 3.15 equiv), THF, −5 °C, 30 min, then **11**, −25 °C to RT, 16 h; then 5% HCl; d) $LiAlH_4$ (2 mol equiv), Et_2O, reflux, 45 min; e) Swern oxidation; 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. Piv = pivaloyl, DMAP = *N*,*N*-dimethylaminopyridine.

[*] Dr. C. Fehr, J. Galindo
Firmenich SA
Corporate R&D Division
P.O. Box 239, CH-1211 Genève 8 (Switzerland)
Fax: (+41) 22-780-3334
E-mail: charles.fehr@firmenich.com

[**] We thank Dr. Jean-Yves de Saint Laumer, Firmenich SA, Geneva, for the energy calculations.

Horner reaction and saponification afforded the acid **12**. Whereas base-catalyzed deconjugation of the ester **11** proved to be unselective, and afforded (*Z*)-**11** and substantial amounts of the isomeric ester with a tetrasubstituted double bond, deprotonation of **12** using excess Li-TMP, followed by protonation of the dianion with 5% HCl, readily furnished **13**. $LiAlH_4$ reduction and Swern oxidation afforded the β,γ-unsaturated aldehyde **15**. Addition of ethynyl-MgBr and esterification with pivaloyl 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** (1:9) was treated with 2 mol% of $PtCl_2$, the expected tricyclic enol pivalates **9a** and **9b** were formed in a ratio of 3:2 in 80% yield (entry 1), and 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 a mixture of **8a** and **8b** (7:3) with $PtCl_2$ afforded mainly the desired **9a** (**9a**/**9b** = 86:14; entry 3).



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 h + 9 h after introduction); 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 h + 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	**9a**/**9b**	Yield [%]
1	10:90	$PtCl_2$ (2 mol%), DCE[a], 70°C, 9 h	60:40	80
2	10:90	$AgSbF_6/Ph_3PAuCl$ (2 mol%), CH_2Cl_2, 20°C, 40 min	47:53	65
3	70:30	$PtCl_2$ (2 mol%), DCE[a], 70°C, 9 h	86:14	–
4	88:12	$PtCl_2$ (2 mol%), DCE[a], 70°C, 9 h	94:6	81
5	98:2	$PtCl_2$ (2 mol%), DCE[a], 70°C, 9 h	99:1	–
6	98:2	$[Cu(CH_3CN)_4](BF_4)$ (2 mol%), DCE[a], 60°C, 9 h	99:1	77[b]

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

From the results shown in entries 1 and 3 it was anticipated that **8a** would afford **9a** with an excellent facial selectivity. We therefore addressed the question of a diastereoselective synthesis of **8a**, which 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 a mixture of **18a** and **18b** and base-catalyzed cleavage of the carbinol fragment of **19a** and **19b**, according to the procedure of Carreira and co-workers (Scheme 4).[9,10] The *S* configuration of the newly formed stereogenic center is in accord with the above-cited work of Carreira and co-workers. A mixture of pivalates **8a** and **8b** (88:12) was used for the cycloisomerization step.

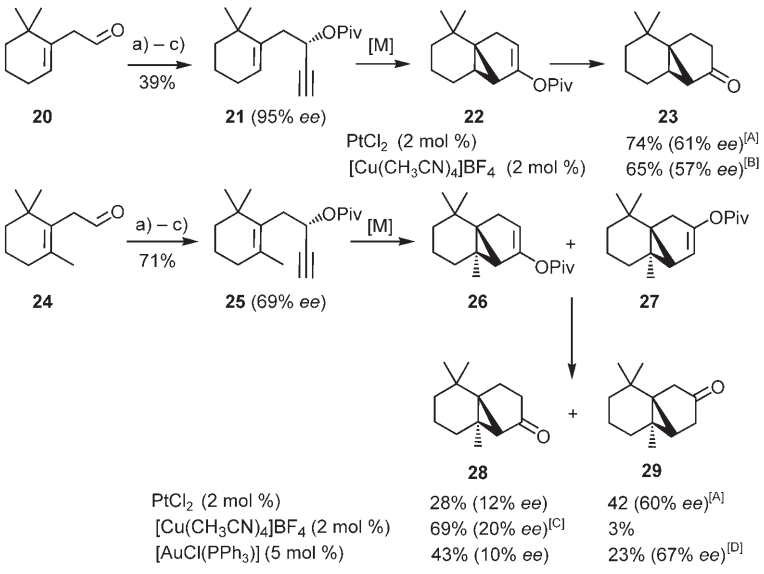
Indeed, $PtCl_2$-catalyzed cycloisomerization of a mixture of **8a** and **8b** (88:12) afforded **9a** with a 94:6 selectivity (Table 1, entry 4), and chromatographically enriched **8a** (**8a**/**8b** 98:2) afforded **9a** with excellent facial selectivity (99:1; entry 5). Interestingly, inexpensive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

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

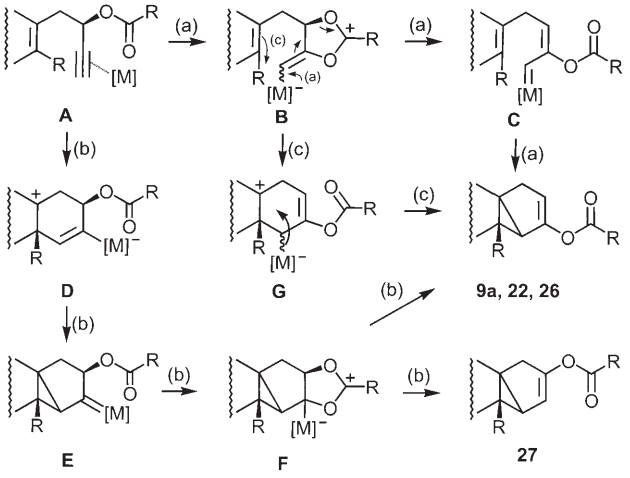
The different diastereoface selectivities observed for the cycloisomerizations of **8a** and **8b** prompted us to examine the chirality transfer from the enantioenriched propargyl pivalates **21** and **25**, which are readily accessible from the aldehydes **20** and **24**.[11] Pt- or Cu-catalyzed rearrangement of **21** (95% *ee*) afforded **22**, which gave, after hydrolysis, ketone **23** with 57–61% *ee* (Scheme 5).[12] The *ee* value of **21** and **22** remained unaltered throughout the course of the reaction, as shown by measurements taken after 50% conversion.

Surprisingly, Pt-catalyzed cycloisomerization of **25** (69% *ee*) afforded, in addition to the expected rearranged enol pivalate **26** (10–20% *ee*, unknown absolute configuration), the isomeric non-rearranged enol pivalate **27** (60–67% *ee*, unknown absolute configuration), as evidenced by conversion of **26** and **27** into the ketones **28** and **29**, respectively.

The Pt- or Au-catalyzed cycloisomerizations of secondary enynol esters are believed to proceed by an initial [1,2] O shift of the metal-complexed acetylene **A** and subsequent cyclopropanation of the achiral transient vinyl carbene **C** (pathway (a); Scheme 6).[2] On the basis of the chirality transfer we observed, pathway (a) can be dismissed.[13] Alternatively, cyclopropanation of the electron-rich olefin with the metal-complexed acetylene **A**, followed by [1,2]-O-migration of **E** (pathway (b)),[14] the presumed reaction course for the formation of the non-rearranged enol pivalate **27** by a [1,2] H shift of **E** or **F**,[15] is also not operative for **26**, as the rearranged and non-rearranged cycloisomerization products **26** and **27** exhibit different enantiomeric excess values. This leads us to propose a new mechanism for the cycloisomerization with [1,2]-acyl shift (pathway (c)). Intramolecular addition of the ester carbonyl to the metal-complexed acetylene **A**



Scheme 5. Reagents and conditions: a)–c) see Scheme 3 a)–c); [A] DCE, 70 °C, 8 h; [B] toluene, 50 °C, 9 h, 73% conversion; [C] toluene, 50 °C, 4 h, 50% conversion; [D] DCE, 70 °C, 90 min; GC yields.



Scheme 6. Proposed mechanism for the cycloisomerizations.

leads to the vinyl metal species **B**, followed by nucleophilic attack of the C–C double bond to the oxy-allyl system and cyclopropane ring closure in **G**.[16,17]

In conclusion, we have succeeded in 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, complementary cycloisomerization studies of enantioenriched propargyl pivalates suggests that the cyclization occurs on a "half-rearranged" species **B** (Scheme 6).

Experimental Section

(−)-**6**: A solution of **8a** and **8b** (**8a**/**8b** = 88:12; 1.98 g; 6.80 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 into 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 1.60 g of **9a** and **9b** (**9a**/**9b** = 94:6; 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 1.13 g of **6** (86% pure, 91%). Purification by chromatography on SiO_2 (150 g) with an eluent of cyclohexane/AcOEt (7:3), followed by crystallization in pentane at −78 °C afforded 680 mg of pure **6**. M.p. 60–60.5 °C (lit. 58.5–59.5 °C[7b]),$[\alpha]_D^{20}$ ($CHCl_3$; $c = 1.30$) −20.1 (lit. $[\alpha]_D^{20} = -23.9$ (isooctane)[7b]); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.59$ (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 (100 MHz, $CDCl_3$): δ = 214.6 (s), 43.4 (d), 40.3 (s), 39.7 (d), 33.3 (t), 33.2 (d), 32.5 (d), 31.3 (d), 30.8 (t), 26.6 (t), 26.0 (t), 19.9 (q), 19.4 (q), 18.9 ppm (q); MS: m/z (%): 206 [M^+] (65), 191 (24), 164 (88), 149 (45), 135 (35), 122 (100), 107 (55), 93 (64), 91 (65), 79 (75), 69 (40), 55 (41), 41 (46).

23: $[\alpha]_D^{20}$ ($CHCl_3$; $c = 0.56$) + 24.8 (61% *ee* by chiral GC[18] (major enantiomer: first peak)); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.92$–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 (100 MHz, $CDCl_3$): $\delta = 214.8$ (s), 43.2 (s), 41.1 (d), 37.3 (t), 33.2 (t), 29.9 (s), 28.4 (d), 27.9 (q), 24.9 (q), 24.6 (t), 23.3 (t), 18.0 ppm (t); MS: m/z (%): 178 [M^+] (26), 163 (9), 136 (16), 135 (16), 121 (30), 110 (100), 107 (25), 93 (28), 91 (22), 79 (33), 69 (40).

28: 12% *ee* by chiral GC[18] (major enantiomer: first peak); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$ (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 (100 MHz, $CDCl_3$): $\delta = 220.2$ (s), 40.5 (t), 39.5 (t), 37.5 (t), 36.8 (s), 33.8 (t), 30.2 (s), 27.6 (2q), 25.6 (d), 24.4 (s), 18.1 (t); 17.1 ppm (q); MS: m/z (%): 192 [M^+] (51), 177 (57), 149 (63), 136 (64), 107 (73), 93 (100), 79 (97), 69 (71), 67 (38), 55 (39), 41 (48).

29: 60% *ee* by chiral GC[18] (major enantiomer: first peak); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.95$ (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 (100 MHz, $CDCl_3$): $\delta = 215.9$ (s), 49.3 (s), 44.5 (d), 37.8 (2t), 34.2 (t), 31.8 (s), 30.9 (s), 27.6 (q), 26.2 (q), 21.9 (t), 18.8 (q); 18.0 ppm (t); MS: m/z (%): 192 [M^+] (43), 177 (27), 150 (58), 136 (71), 135 (100), 123 (60), 121 (55), 107 (64), 93 (59), 79 (57), 69 (38), 55 (30), 41 (38).

Received: December 21, 2005
Published online: March 23, 2006

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

[1] F. Vanasek, V. Herout, F. Sorm, *Collect. Czech. Chem. Commun.* **1960**, *56*, 919; Y. Ohta, K. Ohara, Y. Hirose, *Tetrahedron Lett.* **1968**, *9*, 4181, and references therein.

[2] Pt catalysis: a) Y. Harrak, C. Blaszykowski, M. Bernard, K. Cariou, E. Mainetti, V. Mouriès, A.-L. Dhimane, L. Fensterbank,

M. Malacria, *J. Am. Chem. Soc.* **2004**, *126*, 8656; C. Blaszykowski, Y. Harrak, M.-H. Gonçalves, J.-M. Cloarec, A.-L. Dhimane, L. Fensterbank, M. Malacria, *Org. Lett.* **2004**, *6*, 3771; b) S. Anjum, J. Marco-Contelles, *Tetrahedron* **2005**, *61*, 4793; c) V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126*, 8654.

[3] a) E. Soriano, P. Ballesteros, J. Marco-Contelles, *Organometallics* **2005**, *24*, 3182; b) E. Soriano, J. Marco-Contelles, *J. Org. Chem.* **2005**, *70*, 9345.

[4] Au catalysis: A. Fürstner, P. Hannen, *Chem. Commun.* **2004**, 2546; F. Gagosz, *Org. Lett.* **2005**, *7*, 4129 and Ref. [2c].

[5] $[Cu(CH_3CN)_4](BF_4)$ efficiently catalyzes the cycloisomerization of certain unsaturated tertiary propargylic alcohols: C. Fehr, I. Farris, H. Sommer.

[6] M. I. Velazco, L. Wuensche, P. Deladoey (Firmenich SA), US 6214788 (prior. 31.03.1999), **1999**; [*Chem. Abstr.* **2000**, *133*, 265959].

[7] a) E. Piers, R. W. Britton, W. de Waal, *Tetrahedron Lett.* **1969**, *10*, 1251; E. Piers, R. W. Britton, W. de Waal, *Can. J. Chem.* **1971**, *49*, 12; b) A. Tanaka, R. Tanaka, H. Uda, A. Yoshikoshi, *J. Chem. Soc. Perkin 1* **1972**, 1721; A. Tanaka, H. Uda, A. Yoshikoshi, *Chem. Commun.* **1969**, 308; c) see also: S. Torii, T. Okamoto, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 771.

[8] Reviews: S. Ma, S. Yu, Z. Gu, *Angew. Chem.* **2006**, *118*, 261; *Angew. Chem. Int. Ed.* **2006**, *45*, 200; C. Bruneau, *Angew. Chem.* **2005**, *117*, 2380; *Angew. Chem. Int. Ed.* **2005**, *44*, 2328; A. M. Echavarren, C. Nevado, *Chem. Soc. Rev.* **2004**, *33*, 431; M. Méndez, V. Mamane, A. Fürstner, *Chemtracts: Org. Chem.* **2003**, *16*, 397; C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813.

[9] D. Boyall, F. Lopez, H. Sasaki, D. Frantz, E. M. Carreira, *Org. Lett.* **2000**, *2*, 4233; J. W. Bode, E. M. Carreira, *J. Org. Chem.* **2001**, *66*, 6410.

[10] Despite the slow addition of **15**, it accumulates during the reaction. Diminishing the amount of reagents leads to a slower reaction and to the formation of by-products.

[11] Synthesis of **20**: a) 2,2-dimethylcyclohexanone, triethyl phosphonoacetate (1.2 equiv), NaOEt (1.1 equiv), pentane, reflux, 24 h (100%); b) lithium diisopropylamide (LDA, 1.05 equiv), THF, −25°C to RT, 30 min (80%); c) $LiAlH_4$ (1.50 mol equiv), Et_2O, reflux, 45 min (93%); d) Swern oxidation (92%); for the synthesis of **21**, see: O. Isler, M. Montavon, R. Rüegg, P. Zeller, *Helv. Chim. Acta* **1956**, *39*, 259; G. L. Olson, H.-C. Cheung, K. D. Morgan, R. Borer, G. Saucy, *Helv. Chim. Acta* **1976**, *59*, 567.

[12] The indicated absolute configuration of **23** is based on the stereoselectivity observed in the cycloisomerization of **8a** (cubebol synthesis).

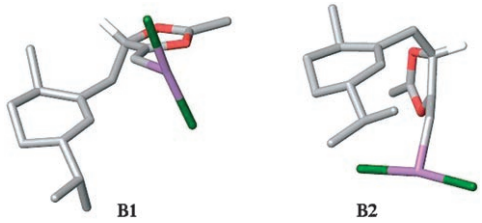
[13] The lower *ee* values of the rearrangement products when compared to the substrates reflect an imperfect stereocontrol and not a racemization, as the *ee* values of **21** and **22** remained constant during the reaction.

[14] This mechanism has recently been proposed on the basis of a DFT computational study: see Ref. [3].

[15] For the related cycloisomerization of propargylic alcohols or ethers, see E. Soriano, P. Ballesteros, J. Marco-Contelles, *Organometallics* **2005**, *24*, 3172 and Refs. [2a, 2c, 3b, 4, and 5].

[16] Incidentally, this mechanism is closely related to the mechanism proposed for the Rautenstrauch rearrangement: X. Shi, D. J. Gorin, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 5802; we cannot exclude that, depending on the substrate, the reaction pathways (a) or (b) compete with pathway (c).

[17] A referee pointed out that the vinyl metal species **B** would most likely possess the *E* configuration. However, the formation of the *Z* isomer by anchimeric assistance[3b] is also plausible and would allow the cyclization **B**→**G** to occur with minimal steric interactions. The stereoselectivity of the cycloisomerization **8a**→**9a** can be rationalized by invoking minimal steric interactions. Placing the side chain above the cyclohexene ring orients the dioxolane and $PtCl_2$ (in (*Z*)-**B**, Scheme 6) away from the cyclohexene and the isopropyl groups. A preliminary calculation of the two possible reactive conformers (with OAc instead of OPiv) with an imposed distance of 3 Å shows that **B1** is more stable than **B2** by ca. 2.9 kcal mol^{-1}. Calculations were performed at the DFT level (B3LYP/LACVP**), using Jaguar 5.5; Schrödinger, Inc., Portland, OR, 1991–2005. Most probably the same diastereoface selectivity is observed in the cyclization **21**→**22**. The lower selectivity is certainly caused by the missing



isopropyl group. Surprisingly, the cycloisomerization **25**→**26** is much less selective. This may be due to steric interactions between the methyl group and the metal. The cyclization **25**→**27** is highly selective. Probably the reaction conformer **A** (Scheme 6) in which the acetylene group is above the cyclohexene ring minimizes the steric interactions between the pivalate and the cyclohexene ring.

[18] Chiral capillary column: CP-Chirasil-DEX CB (25 m × 0.25 mm) (Chrompack).

