CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200501299

Platinum- and Gold-Catalyzed Rearrangement Reactions of Propargyl Acetates: Total Syntheses of (−)-α-Cubebene, (−)-Cubebol, Sesquicarene and Related Terpenes

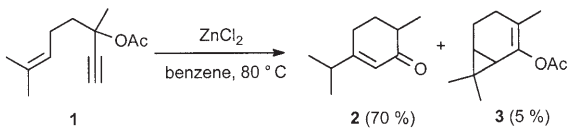
Alois Fürstner* and Peter Hannen[a]

Abstract: Propargyl acetates, in the presence of catalytic amounts of late transition-metal salts such as $PtCl_2$ or $AuCl_3$, represent synthetic equivalents of α-diazoketones. This notion is corroborated by a concise approach to various sesquiterpene natural products starting from readily available substrates. Specifically, (+)-carvomenthone (**17**) is converted into propargyl acetate (*S*)-**26** by a sequence involving Stille cross-coupling of its kinetic enol triflate **18**, regioselective hydroboration/oxidation of the resulting 1,3-diene **19**, and addition of an alkynyl cerium reagent to aldehyde **21** thus obtained. Since the latter step was found to be unselective, the configuration of the reacting propargyl acetate was unambiguously set by oxidation followed by diastereoselective transfer hydrogenation by using Noyori's catalyst **25**. Compound (*S*)-**26**, on treatment with $PtCl_2$ in toluene, converted exclusively to the tricyclic enol acetate **27**, which was saponified to give norcubebone **11** in excellent overall yield. The conversion of this compound into the sesquiterpene alcohol (−)-cubebol (**6**) was best achieved with $MeCeCl_2$ as the nucleophile, whereas the formation of the parent hydrocarbon (−)-α-cubebene (**4**) was effected in excellent yield by recourse to iron-catalyzed cross coupling methodology developed in this laboratory. Since norketone **11** has previously been transformed into (−)-β-cubebene (**5**) as well as (−)-4-epicubebol **8**, our approach constitutes formal total syntheses of these additional natural products as well. Along similar lines, the readily available propargyl acetates **1**, **33** and **47** were shown to give access to 2-carene **44**, sesquicarene **39**, and epi-sesquicarene **51** in excellent overall yields. In this series, however, the cycloisomerization reaction was best achieved with catalytic amounts of $AuCl_3$ in 1,2-dichloroethane as the solvent. In addition to these preparative results, our data provide some insight into the mechanism of these remarkable skeletal rearrangement reactions. Transformations of this type are likely triggered by initial coordination of the alkyne unit of the substrate to the carbophilic transition-metal cation. Formal attack of the alkene moiety onto the resulting π-complex engenders the formation of an electrophilic cyclopropyl carbene species which subsequently reacts with the adjacent acetate unit to give the final product. The alternative phasing of events, implying initial attack of the acetate (rather than the alkene moiety) onto the metal–alkyne complex, is inconsistent with the stereochemical data obtained during this total synthesis campaign.

Keywords: carbenes · gold · natural products · platinum · terpene

Introduction

In 1976, Ohloff et al. reported the serendipitous discovery that treatment of propargyl acetate **1** with $ZnCl_2$ in benzene at 80 °C afforded small amounts (ca. 5%) of 2-acetoxy-2-carene (**3**) in addition to carvenone (**2**) formed as the major product under these conditions (Scheme 1).[1] Although the authors proposed a possible mechanism for this unusual transformation,[2] the reaction remained unoptimized and its scope unexplored, even when Rautenstrauch rediscovered this type of cycloisomerization during studies on $PdCl_2$-cata-



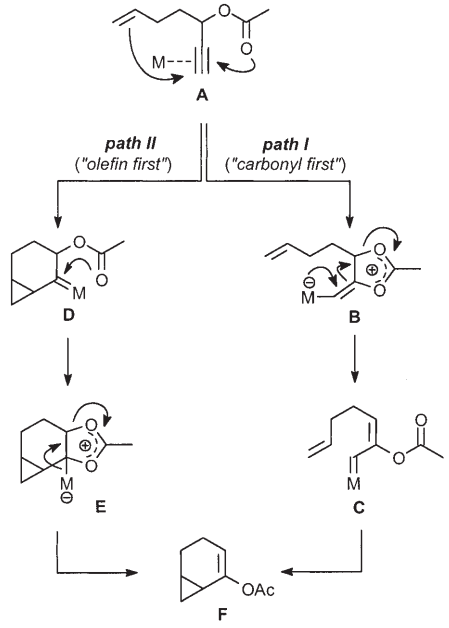
Scheme 1. Ohloff's original discovery of a transition metal catalyzed cycloisomerization with concomitant 1,2-acetyl shift.

[a] Prof. A. Fürstner, Dipl.-Chem. P. Hannen
Max-Planck-Institut für Kohlenforschung
45470 Mülheim/Ruhr (Germany)
Fax: (+49) 208-306-2994
E-mail: fuerstner@mpi-muelheim.mpg.de

lyzed Nazarov-type reactions of certain acetoxylated enynes.[3]

Only very recently has the preparative potential of this particular skeletal reorganization been appreciated, which is accompanied by a characteristic 1,2-acyl shift.[4–6] This development came alongside the increasing understanding for the activation of unsaturated substrates by late transition metals which act as efficient "carbophilic" Lewis acids in a variety of cases.[7] Specifically, complexation to soft noble metal cations such as Pt^{II}, Au^{I}, or Au^{III} renders alkynes susceptible to attack by (tethered) nucleophiles including alkenes, arenes, ethers or carbonyl groups. The cyclopropyl–carbene complexes primarily formed as reactive intermediates evolve along different pathways that are best rationalized if these species are seen as latent "non-classical" carbocations complexed to a transition-metal template.[8] This rationale readily explains the highly diverse set of product structures accessible by this user-friendly methodology. From the preparative point of view it is noteworthy that such skeletal reorganizations engender a significant increase in molecular complexity, while being operationally simple, safe and convenient to perform.[4–13]

This global picture allows to rationalize the outcome of the "Ohloff–Rautenstrauch" rearrangement without difficulties; at a closer look, however, two slightly different scenarios must be considered (Scheme 2). Path I assumes that the tethered acetyl group initially attacks the electrophilic η^2-metal–alkyne complex **A** with formation of a polarized oxacycle **B**; the latter evolves into a vinyl–carbene species **C** effecting the cyclopropanation of the lateral alkene moiety to give the observed bicyclic product **F**. Alternatively, it is conceivable that the olefin acts as the primary nucleophile, furnishing a cyclopropyl–carbene complex **D** by a well established *endo*-cyclization process (path II). Subsequent attack of the adjacent acetyl group onto the electrophilic carbene center affords **F** via oxatricyle **E**. Computational studies suggest that both reaction coordinates are feasible and similar in energy, with path II being only slightly favored in the gas phase,[14] thus making an unambiguous decision impossible as to which mode is operative in solution.

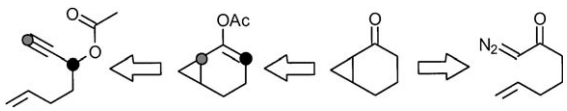


Scheme 2. Two conceivable mechanisms of the "Ohloff–Rautenstrauch" rearrangement proceeding via electrophilic metal carbene intermediates.

Outlined below we describe what are believed to be the first applications of noble metal-catalyzed propargyl acetate rearrangements to natural-product synthesis.[15] Moreover, the preparative data allow us to distinguish between the two mechanistic scenarios outlined above and provide strong evidence for path II playing the major role under the chosen reaction conditions.

Results and Discussion

Total synthesis of cubebene and cubebol: Hydrolysis of the enol ester initially formed by noble metal-catalyzed propargyl acetate cycloisomerizations delivers a cyclopropyl carbonyl derivative (Scheme 3). Since compounds of this type are usually prepared by intramolecular cyclopropanation of unsaturated α-diazoketones, one may conclude that the "Ohloff–Rautenstrauch" rearrangement represents an attractive and less hazardous synthetic equivalent to classical diazocarbonyl chemistry.[16,17]

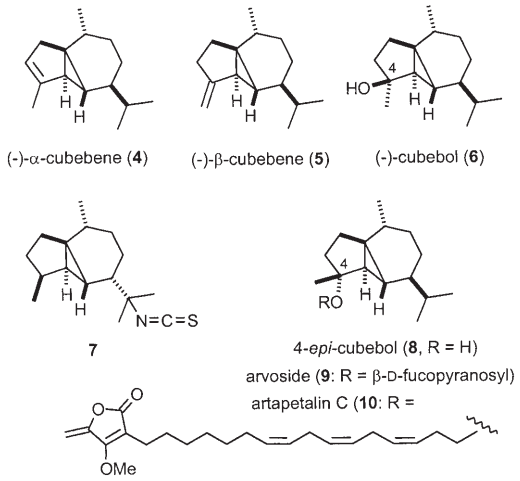


Scheme 3. Synthetic equivalence of classical α-diazoketone methodology and noble metal catalyzed propargyl acetate rearrangements. The labels visualize the positioning of the propargylic atoms in the product.

A total synthesis of cubebene and related cadinane sesquiterpenes was planned to scrutinize this aspect (Scheme 4). The isomeric alkenes (−)-α-cubebene (**4**) and (−)-β-cubebene (**5**) together with the tertiary alcohol (−)-cubebol (**6**)[18] are important components of the essential oil of *Piper cubeba* L. from which they were originally isolated.[19] Interestingly enough, the same compounds were later found in taxonomically unrelated organisms as different as brown algae, gorgonians and liverworts.[20]

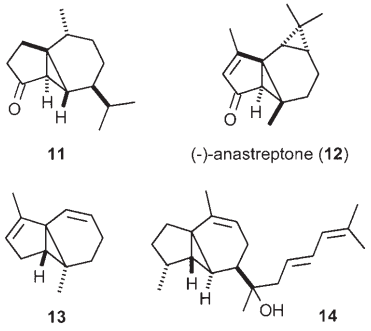
Furthermore it is noteworthy that compound **8**, featuring an epimeric configuration of the tertiary alcohol center at C-4, and even the enantiomeric terpene (+)-α-cubebene (*ent*-**4**) have also been isolated from natural sources.[21] In addition to these parent sesquiterpenes, a variety of derivatives is known, amongst which the glycoside **9**, the ether derivative **10** and compound **7** bearing a rare isothiocyanate motif are most remarkable.[22]

The cubebane family shares a common tricyclo[4.4.0.$0^{1,5}$]decane skeleton with a variety of other bioactive natural products, some of which are depicted in



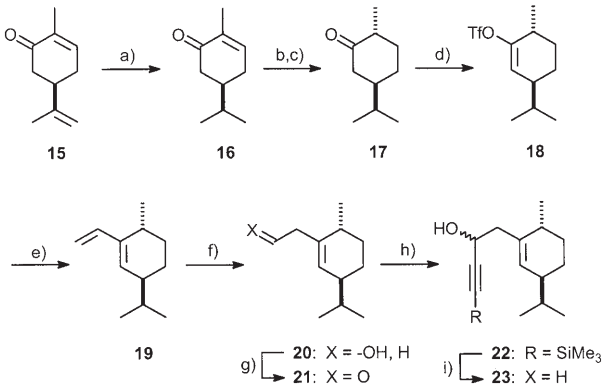
Scheme 4. Representative members of the cubebane family of tricyclic sesquiterpenes.

Scheme 5.[23] This highly condensed carbocyclic framework invites construction by cyclopropanation techniques; in fact, all known syntheses of the cubebenes rely on intramolecular α-diazoketone cyclization reactions in the presence of suitable metal catalysts.[24] However, these transformations invariably afforded mixtures of the required norketone **11** and isomers thereof; moreover, all published routes require separation of isomeric compounds by preparative GC at some stage of the synthesis.[24] In view of these obvious shortcomings, it seemed appropriate to target cubebene and cubebol by the envisaged cycloisomerization route in order to assess its preparative potential.



Scheme 5. Norketone skeleton of the cubeban family (**11**) and other natural products with a tricyclo[4.4.0.0^{1,5}]decane skeleton.

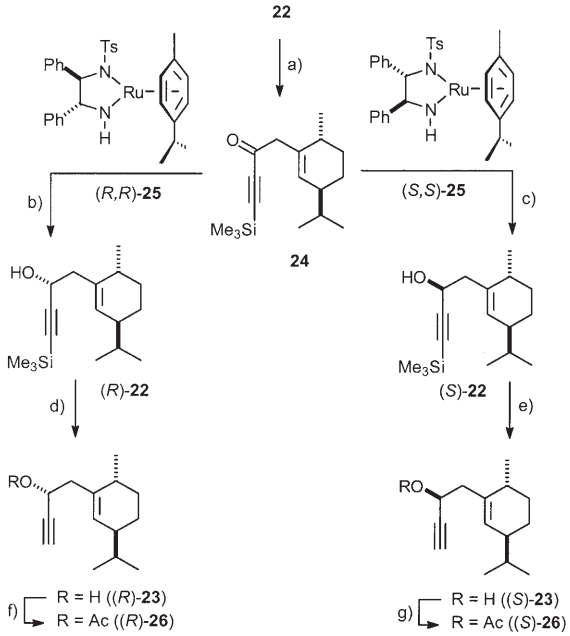
Our synthesis started from (*R*)-(−)-carvone **15** which was converted to carvomenthone **17** by a two-step reduction protocol followed by isomerization of the α-methyl group (Scheme 6).[25] This procedure minimizes double-bond transposition and concomitant racemization and ensures that **17** is obtained with high diastereoselectivity (*dr* 90:10), superior to that obtained by alternative methods.[26] Enolization of ketone **17** also required careful optimization. With the aid of lithio 2,2,6,6-tetramethylpiperidinide as base and Comins reagent[27] as electrophile it was possible to obtain the kinetic enol triflate **18** in high yield and purity. Sterically less encumbered bases (LDA, cyclohexyl(isopropyl)NLi, LiHMDS) gave inferior results. Stille cross-coupling of **18** with commercial vinylstannane provided diene **19** in high yield, the terminal alkene of which was regioselectively hydroborated with 9-BBN to give alcohol **20** after oxidative work-up.[28] Exposure to Dess–Martin periodinane[29] cleanly afforded the corresponding aldehyde **21** which reacted with the alkynylcerium reagent $Me_3SiC{\equiv}CCeCl_2$[30,31] to give a mixture of both possible propargyl alcohols **22** in a 65:35 diastereomeric ratio. Cleavage of the silyl group followed by acetylation of the alcohol **23** under standard conditions gave propargyl acetate **26**, thus setting the stage for the envisaged cycloisomerization.



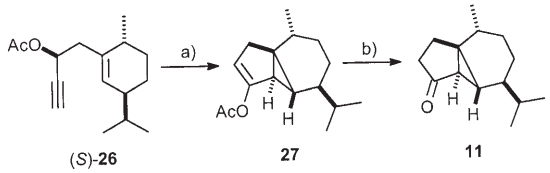
Scheme 6. a) [$(PPh_3)_3RhCl$] cat., H_2 (3 atm), benzene, 98%; b) Pd/C (10% w/w), H_2 (1 atm), MeOH, *dr* 1:1; c) NaOMe, MeOH, 90%, *dr* 9:1; d) lithium 2,2,6,6-tetramethylpiperidinide, THF, −78°C, then *N*-(5-chloro-2-pyridyl)bistrifluoromethanesulfonimide (Comins reagent), −78°C → 0°C, 87%; e) $H_2C{=}CHSn\text{-}Bu_3$, [$Pd(PPh_3)_4$] cat., LiCl, THF, reflux, 85%; f) 9-BBN, THF, then aq. H_2O_2, aq. NaOH, 87%; g) Dess–Martin periodinane, CH_2Cl_2, 86%; h) $Me_3SiC{\equiv}CH$, BuLi, then $CeCl_3$, THF, −78°C, 93%, *dr* 65:35; i) TBAF, THF.

Although a rapid conversion took place on exposure of this substrate to $PtCl_2$ in toluene at 80°C, a product mixture containing an isomeric compound in addition to the desired enol ester **27** was obtained, which turned out to be difficult to separate by routine measures. For the sake of practicality it was therefore necessary to find a more selective entry into the tricyclic cubebene skeleton.

Monitoring of the course of the $PtCl_2$-catalyzed cycloisomerization reaction indicated that the diastereomeric propargyl acetates **26** react with different rates and likely different selectivities; therefore it was decided to investigate the behavior of the individual isomers separately (Scheme 7). To this end, oxidation of alcohol **22** to the corresponding ketone **24** followed by chemo- and stereoselective transfer hydrogenation[32] gave access to (*S*)-**26** and (*R*)-**26**, both of which could be obtained in highly enriched form (*dr* 95:5).[33] Gratifyingly, (*S*)-**26** derived thereof underwent a remarkably clean cycloisomerization in the presence of catalytic amounts of $PtCl_2$ in toluene, forming enol acetate **27** exclusively, which was isolated in 92% yield as a diastereomerically pure compound (Scheme 8). Subsequent ester cleavage afforded the known norketone **11**, the spectroscop-



Scheme 7. a) Dess–Martin periodinane, CH_2Cl_2, 94%; b) (*R*,*R*)-**25** (5 mol%), isopropanol, 93% (*dr* 85:15); c) (*S*,*S*)-**25** (5 mol%), isopropanol, 94% (*dr* 86:14); d) TBAF, THF, 88%; e) TBAF, THF, 89%; f) Ac_2O, Et_3N, DMAP cat., CH_2Cl_2, 81%; g) Ac_2O, Et_3N, DMAP cat., CH_2Cl_2, 93%.

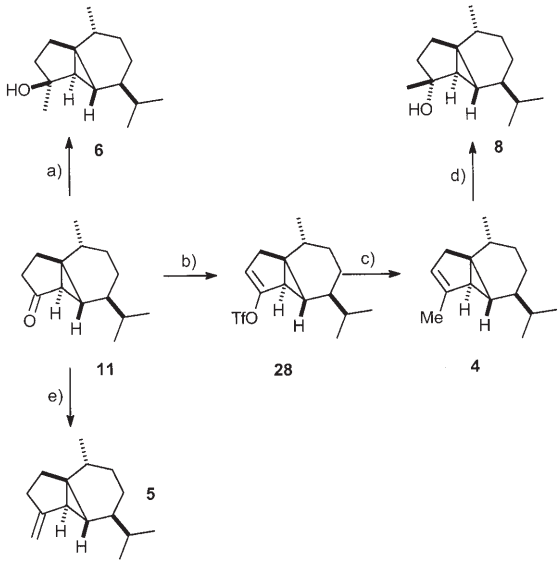


Scheme 8. a) $PtCl_2$ (2 mol%), toluene, 80°C, 92%; b) K_2CO_3, MeOH, 76%.

ic data of which were identical to those previously reported in the literature.[24,34]

While the conversion of ketone **11** into (−)-β-cubebene **5** is known to be high yielding, requiring a routine Wittig methylenation only,[24] the literature procedures for its conversion into (−)-cubebol **6** and (−)-α-cubebene **4** are hardly satisfactory. Addition of either MeLi of MeMgBr to **11** is reported to give the desired alcohol **6** in 47–49% only.[24d,e] Assuming that competing enolization might be responsible for this rather low yield, MeLi was first transmetallated with $CeCl_3$ before ketone **11** was added to the mixture (Scheme 9).[30b,31] In fact, the less basic $MeCeCl_2$ thus formed behaved exceptionally well, affording (−)-cubebol **6** as a single diastereomer in 91% isolated yield. NOESY spectra confirmed that the attack of the methyl donor onto the carbonyl group occurred exclusively from the face opposite to the adjacent cyclopropane ring.

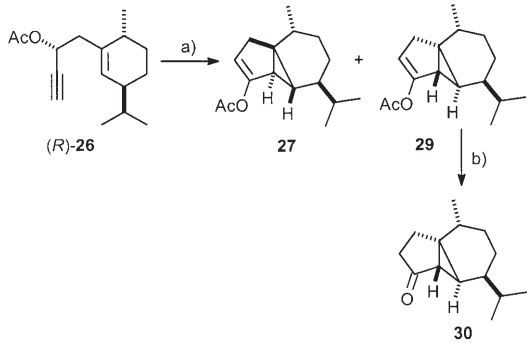
Likewise, the formation of (−)-α-cubebene from norketone **11** could also be significantly improved over prior art. Specifically, deprotonation of **11** with LDA at low temperature followed by quenching of the resulting enolate with



Scheme 9. a) MeLi, $CeCl_3$, THF, −78°C, 91%; b) LDA, THF, −78°C, then *N*-(5-chloro-2-pyridyl)bistrifluoromethanesulfonimide (Comins reagent), −78°C → RT, 91%; c) MeMgBr, $[Fe(acac)_3]$ (10 mol%), THF/NMP, −30°C, 90%; d) ref. [24d]; e) $Ph_3P{=}CH_2$, DMSO, 99%, ref. [24b].

Comins reagent[27] gave triflate **28** which was alkylated with MeMgBr in the presence of $[Fe(acac)_3]$ as the precatalyst of choice.[35] (−)-α-Cubebene **4** was thus obtained in 90% isolated yield, thus corroborating the notion that iron-based cross coupling reactions hold considerable promise as efficient, cheap and benign alternatives to established methodology.[36–38]

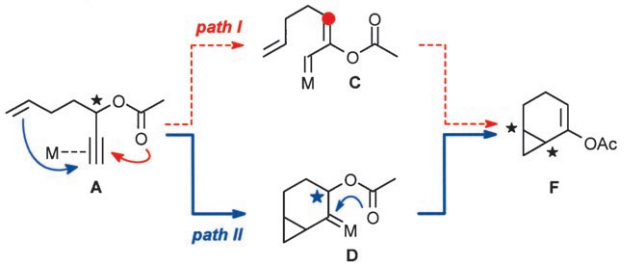
Mechanistic implications: While the diastereoselective platinum-catalyzed cycloisomerization of (*S*)-**26** paved an efficient way to the cubebane sesquiterpenes as outlined above, the corresponding reaction of its (*R*)-configured isomer provided valuable mechanistic information. Under the same conditions, (*R*)-**26** afforded a mixture of **27** and a diastereomeric compound **29** in a ~1:1 ratio (GC) (Scheme 10). The structure of the latter was unambiguously established after hydrolytic cleavage of its enol ester moiety with K_2CO_3 in MeOH. Careful analysis of the NMR spectra (400 MHz) of



Scheme 10. a) $PtCl_2$ (2 mol%), toluene, 80°C, 79%; b) K_2CO_3, MeOH, 80%.

the resulting ketone **30** shows the presence of the tricyclo[4.4.0.0^{1,5}]decane skeleton,[39] which must be isomeric to that found in **11** with regard to the stereochemistry of the ring junction.

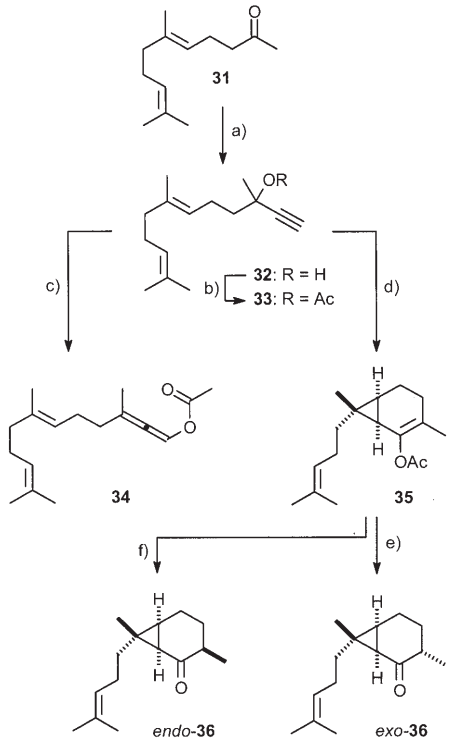
The striking difference between the stereoselective cycloisomerization of (*S*)-**26** on the one hand and the unselective transformation of (*R*)-**26** on the other hand shows that the configuration of the stereogenic center carrying the acetate unit translates into the stereochemistry of the product. Hence, this position *cannot* be planarized before cyclopropanation has occurred. According to our present understanding of such reactions (Schemes 2 and 11), path I involves a *vinyl* carbene intermediate **C** prior to cyclization and hence implies that both isomers lead to the same product distribution, whereas path II is consistent with the observed stereodivergent behavior. We are therefore inclined to believe that path II, which was slightly favored in previous computational studies in the gas phase,[14] is in fact operative under the chosen experimental conditions.[40,41]



Scheme 11. Path II of the proposed cyclization mechanism is consistent with the observed *stereodivergent* behavior of (*R*)- and (*S*)-**26**, whereas path I assuming a vinyl carbene intermediate would imply a *stereoconvergent* course (the stereogenic center of the substrate marked * is planarized before the chiral centers of the cyclopropane unit are generated, cf. red label).

2-Sesquicarene: This successful implementation of the noble metal catalyzed rearrangement spurred our efforts to improve Ohloff's original access to the carane skeleton[1] upon replacement of $ZnCl_2$ by a more appropriate catalyst.[15,42]

The results summarized in Schemes 12 and 13 are consistent with this conjecture. Sesquicarene **39**, a component of the essential oil of the fruit *Schisandra chinensis*,[43] was chosen as our initial target because this compound allows one to address additional questions concerning the regioselectivity of the skeletal rearrangement reaction.[44,45] The required propargyl acetate **33** was prepared by two routine operations from commercial geranylacetone **31**. Although exposure of this substrate to catalytic amounts of $PtCl_2$ in various solvents resulted in the formation of the desired bicyclo[4.1.0]heptane skeleton **35** in decent yield [GC: 62% (toluene), 86% (DME), 75% (1,2-dichloroethane), 48% (MeCN)], allenyl acetate **34** formed by a competing [3,3]-sigmatropic rearrangement[46] of the substrate was invariably formed as a byproduct. Since **34** is difficult to separate from



Scheme 12. a) HC≡CMgBr, THF, 0°C → RT, 96%; b) Ac_2O, DMAP, Et_3N, 98%; c) $AgBF_4$, DME, 76%; d) $AuCl_3$ (5 mol%), 1,2-dichloroethane; e) K_2CO_3, MeOH, *dr* 6.7:1, 74% (over two steps); f) $LiAlH_4$, THF, 0°C → RT, 60% (over two steps).

the desired compound **35** by any of the conventional methods, we chose to optimize this catalytic system further.

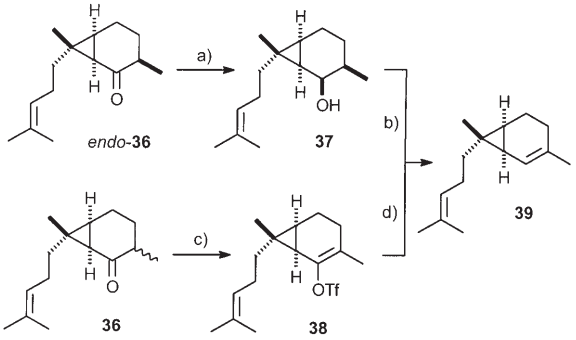
Amongst the host of metal salts screened,[47] $AgBF_4$ led to the exclusive formation of allene **34** which could be isolated in 76% yield,[48,49] whereas the use of $AuCl_3$ (5 mol%)[11] in 1,2-dichloroethane at ambient temperature showed by far the best selectivity in favor of the desired carene framework. Under these conditions, enol ester **35** was formed in excellent yield and purity (ca. 95%), with only marginal amounts of allenyl acetate **34** being detectable in the crude reaction mixture. No cyclopropanation of the distal double bond of **33** was observed, thus showing that the cyclization of the conceivable 10-membered ring does not compete with the kinetically and thermodynamically more favorable formation of the sesquicarane skeleton during the $AuCl_3$-catalyzed process.

Since compound **35** is rather labile, it was immediately hydrolysed with K_2CO_3 in MeOH to give sesquicarone **36** as a mixture of diastereomers (74%, > 96% pure by GC). It is interesting to note that a reductive rather than hydrolytic cleavage of the ester bond in **35** with $LiAlH_4$ in THF afforded the *endo* isomer of **36** exclusively, although in lower yield (60% over cycloisomerization/reduction). The assignment of the stereochemistry at the quarternary center of this compound is based on the observed NOE data.

Even though the conversion of ketone **36** into sesquicarene **39** seems trivial, this step had been a major hurdle in

previous syntheses of this target. It is reported in the literature that a variety of approaches is plagued by concomitant cleavage of the cyclopropane ring even under seemingly mild conditions. The "best" method turned out to be the pyrolysis of the tosylhydrazone salts derived from ketone **36** which furnished a complex mixture from which the desired product **39** could be obtained in only 15–22% yield by preparative GC.[44a,b]

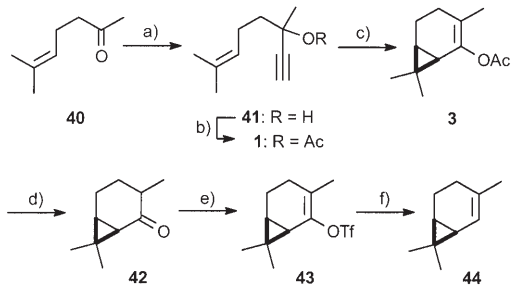
This unacceptable solution prompted us to reinvestigate the transformation (Scheme 13). Two different approaches were pursued: First, *endo*-**36** was reduced with L-Selectride



Scheme 13. a) L-Selectride, THF, −78°C → RT, 93%; b) PPh_3, DEAD, THF, 70%; c) LDA, THF, −78°C, then *N*-(2-pyridyl)bistriflimide, −78°C → RT; d) $[Pd(PPh_3)_4]$ cat., LiCl, Et_3SiH, THF, 60°C, 74%.

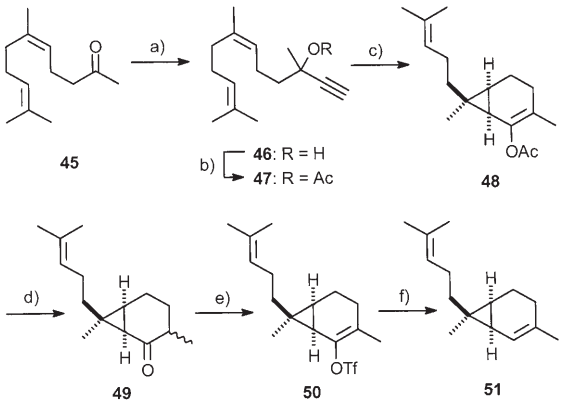
to alcohol **37**, which reacted with PPh_3 and DEAD at ambient temperature to give sesquicarene **39** as the major product (70%).[50] Although this method constitutes an improvement over prior art, the isolation of this hydrocarbon product in analytically pure form still required prep-GC. Gratifyingly, however, this cumbersome purification method could be avoided upon conversion of sesquicarone **36** into enol triflate **38** followed by palladium catalyzed reduction using Et_3SiH as the optimal hydride donor.[51,52] Under these conditions, sesquicarene **39** was obtained in 74% yield in pure form after routine flash chromatography of the crude reaction mixture. Therefore it remains to conclude that the overall efficiency as well as the practicality of our new route to 2-sesquicarene **39** is far superior to that of the α-diazoketone based approaches previously reported in the literature.[44]

2-Carene and episesquicarene: In view of the foregoing, it comes as no surprise that the truncated substrate **1** cyclized equally effectively in the presence of $AuCl_3$ (5 mol%), affording carenyl acetate **3** in almost quantitative yield (Scheme 14). This exemplifies that the change of the catalyst from $ZnCl_2$ originally used by Ohloff[1] to the soft and carbophilic Au^{III} cation upgrades the cycloisomerization process from a minor side reaction to an exquisitely productive yet user-friendly method. Conversion of enol acetate **3** to 2-carene **44** essentially followed the sequence outlined above. The fact that the final palladium-catalyzed reduction of enol triflate **43** gave only 45% isolated yield is mainly due to the volatility of the resulting hydrocarbon.



Scheme 14. a) HC≡CMgBr, THF, 0°C → RT, 87%; b) Ac_2O, DMAP, Et_3N, 97%; c) $AuCl_3$ (5 mol%), 1,2-dichloroethane, 98%; d) K_2CO_3, MeOH, 60% (*dr* 5:1); e) LDA, THF, −78°C, then *N*-(5-chloro-2-pyridyl)bistrifluoromethanesulfonimide (Comins reagent), −78°C → RT; f) $[Pd(PPh_3)_4]$ cat., LiCl, Bu_3SnH, THF, 60°C, 45% (over two steps) (see text).

Finally, the effect of the geometry of the reacting double bond on the outcome of the intramolecular cyclopropanation was investigated (Scheme 15). For this purpose, neryl-

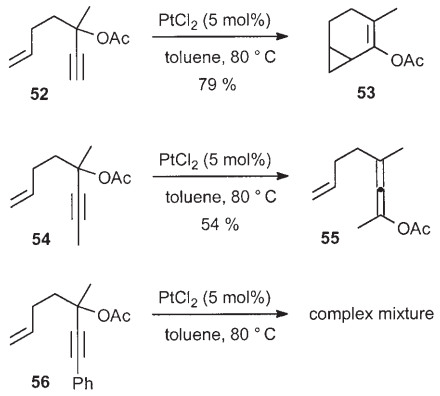


Scheme 15. a) HC≡CMgBr, THF, 0°C → RT, 96%; b) Ac_2O, DMAP, Et_3N, 92%; c) $AuCl_3$ (5 mol%), 1,2-dichloroethane; d) K_2CO_3, MeOH, *dr* 4.5:1, 65% (over two steps); e) LDA, THF, −78°C, then *N*-(5-chloro-2-pyridyl)bistriflimide, −78°C → RT; f) $[Pd(PPh_3)_4]$ cat., LiCl, Et_3SiH, THF, RT, 75% (over both steps).

acetone **45** was converted to propargyl acetate **47** on reaction with ethynylmagnesium bromide followed by acetylation under standard conditions.[53] Treatment of compound **47** containing a (*Z*)-configured double bond in its backbone with catalytic amounts of $AuCl_3$ in 1,2-dichloroethane at ambient temperature afforded enol ester **48**, which is isomeric at C-7 to product **35** derived from the geranyl series (Scheme 12). Therefore it must be concluded that the Au-catalyzed skeletal rearrangement proceeds *stereospecifically*, translating the configuration of the reacting alkene into the stereochemistry of the emerging cyclopropane unit. Compound **48** could then be converted into episesquicarene **51** by the established route via ketone **49** and the enol triflate **50** derived thereof.[54]

Conclusion

The results outlined above highlight the remarkable catalytic reactivity of late transition metal cations such as Pt^{II} or Au^{III} for fully atom economical and complexity-inducing cycloisomerization reactions that can be applied with confidence in natural product synthesis. Although some empirical optimization of the catalyst system is mandatory, propargyl acetates in general can be viewed as synthetic equivalents of α-diazoketones for intramolecular cyclopropanation processes; thereby, the reacting olefin can be mono-, di- or even trisubstituted. Comparison of the cyclization of the geranyl derived substrate **33** with the analogous compound **47** belonging to the neryl series reveals that the cycloisomerization proceeds stereospecifically, translating the geometry of the reacting double bond to the configuration of the resulting cyclopropane derivative. At the same time, these examples show that proximal alkenes react selectively in the presence of distal alkenes with the same degree of substitution. In contrast to this flexibility with respect to the reacting olefin, the methodology is presently limited to propargylic substrates of *terminal* alkynes. This is evident from the examples compiled in Scheme 16, amongst which the terminal acetylene derivative **52** is the only substrate to convert to the corresponding bicyclo[4.1.0]heptane **53**[4b] under the chosen reaction conditions.



Scheme 16. Present limitations of $PtCl_2$-catalyzed cycloisomerizations: Effect of the substituent on the alkyne moiety.

The preparative data obtained during this total synthesis campaign, which led to 2-carene, sesquicarene, episesquicarene, cubebol, α-cubebene, β-cubebene and 4-epicubebol, also shed light onto the mechanism of noble metal catalyzed cycloisomerizations in general. Not only do they confirm previous mechanistic assumptions implying electrophilic carbenes as key intermediates, but also provide more detailed information concerning the individual steps by which such reactive species might form and evolve. This growing mechanistic understanding guides our ongoing investigations on the use of noble metal salts as selective "π-acidic" catalysts for a host of skeletal rearrangement reactions.[5,8,10]

Experimental Section

General: All reactions were carried out under Ar in flame-dried glassware. The solvents used were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg/anthracene), CH_2Cl_2, 1,2-dichloroethane (P_4O_{10}), MeCN, Et_3N, NMP (CaH_2), MeOH, *i*PrOH (Mg), hexane, benzene, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR: Spectra were recorded on a Bruker DPX 300 or AV 400 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: $\delta_C \equiv 77.0$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv 7.24$ ppm; CD_2Cl_2: $\delta_C \equiv 53.8$ ppm; residual CH_2Cl_2 in CD_2Cl_2: $\delta_H \equiv 5.32$ ppm). Where indicated, the signal assignments are unambiguous; the numbering scheme is arbitrary and is shown in the inserts. The assignments are based upon 1D and 2D spectra recorded using the following pulse sequences from the Bruker standard pulse program library: DEPT; COSY (cosygs and cosydqtp); HSQC (invietgssi) optimized for $^1J(C,H) = 145$ Hz; HMBC (inv4gslplrnd) for correlations via $^nJ(C,H)$; HSQC-TOCSY (invietgsml) using an MLEV17 mixing time of 120 ms. IR: Nicolet FT-7199 spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: Finnigan MAT 95, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet). Melting points: Büchi melting point apparatus B-540 (corrected). Elemental analyses: H. Kolbe, Mülheim/Ruhr. All commercially available compounds (Fluka, Lancaster, Aldrich) were used as received.

Cubebene series

(+)-(2*R*,5*R*)-5-Isopropyl-2-methylcyclohexanone [(+)-carvomenthone, 17]: An autoclave was charged with a solution of (−)-(*R*)-carvone (**15**) (4.0 g, 26.6 mmol) and $[Rh(PPh_3)_3Cl]$ (246 mg, 0.266 mmol) in benzene (25 mL) and the resulting solution was stirred for 40 h at 25 °C under an atmosphere of H_2 (3 atm). After venting the autoclave, the solvent was evaporated and the residue was purified by flash chromatography (hexanes/ethyl acetate 10:1) to give product **16** as a colorless liquid (3.95 g, 98 %). To a solution of this product in MeOH (40 mL) was added Pd/C (195 mg, 5 %) and the resulting suspension was stirred for 6 h under H_2 (1 atm). Filtration over a pad of silica gel and evaporation of the filtrate yielded product **17** as a 1:1 mixture of diastereomers (3.81 g, 96 %). Equilibration was effected by stirring a solution of this mixture in MeOH (15 mL) in the presence of NaOMe (267 mg, 4.94 mmol) for 30 min, furnishing the desired *trans*-isomer as a colorless liquid after standard work up (3.42 g, 90 %, $dr \geq 90{:}10$). $[\alpha]_D^{23} = +13.4°$ ($c = 3$, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.39$ (ddd, $J = 2.3$, 3.4, 13.0 Hz, 1H), 2.31 (dddd, $J = 1.2$, 6.4, 13.1, 13.1 Hz, 1H), 2.06 (m, 2H), 1.85 (dddd, $J = 2.8$, 2.8, 5.4, 12.4 Hz, 1H), 1.55 (m, 2H), 1.42 (m, 1H), 1.29 (ddd, $J = 3.3$, 12.8, 15.6 Hz, 1H), 1.01 (d, $J = 6.5$ Hz, 3H), 0.90 (d, $J = 4.2$ Hz, 3H), 0.88 (d, $J = 4.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.7$, 45.7, 44.5, 44.1, 34.3, 31.9, 28.1, 18.7, 18.5, 13.5; IR (KAP): $\tilde{\nu} = 2960$, 2931, 2871, 1710, 1455, 1428, 1387, 1368, 1315, 1240, 1220, 1197, 1127 cm^{-1}.

(3*S*,6*R*)-3-Isopropyl-6-methylcyclohex-1-enyl-trifluoromethanesulfonate (18): *n*BuLi (1.55 M in hexanes, 5.02 mL, 7.78 mmol) was added dropwise to 2,2,6,6-tetramethylpiperidine (1.42 mL, 8.43 mmol) in THF (15 mL) at 0 °C and the resulting solution was stirred for 30 min before it was cooled to −78 °C and a solution of carvomenthone **17** (1.0 g, 6.48 mmol) in THF (7 mL) was added dropwise with a syringe pump. After stirring for 2 h at −78 °C, a chilled solution of *N*-(5-chloro-2-pyridyl)bistriflimide (3.05 g, 7.78 mmol) in THF (15 mL) was introduced and the resulting mixture was allowed to reach ambient temperature over the course of 2 h. For work up, the solvent was evaporated and the residue purified by flash chromatography (pentane) yielding product **18** as a colorless liquid (1.61 g, 87 %). $[\alpha]_D^{20} = +41°$ ($c = 1.2$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.64$ (s, 1H), 2.51 (m, 1H), 2.15 (m, 1H), 2.01 (td, $J = 5.5$, 10.6 Hz, 1H), 1.68 (m, 2H), 1.32 (m, 2H), 1.12 (d, $J = 6.9$ Hz, 3H), 0.90 (d, $J = 6.8$ Hz, 3H), 0.898 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 153.6$, 122.0, 118.7 (q, $J_{CF} = 318$ Hz), 42.3, 33.2, 32.1, 32.0, 24.1, 19.5, 19.4, 18.0; IR (KAP): $\tilde{\nu} = 2963$, 2940, 2876, 1677, 1415, 1246, 1201, 1141, 1048, 1027, 1008, 938, 894, 875, 861, 828 cm^{-1}; MS (EI): m/z (%): 286 (10) [M^+], 243 (64), 153 (7), 113 (16), 93 (100), 69 (36), 55 (22),

41 (36); elemental analysis calcd (%) for $C_{11}H_{17}F_3O_3S$ (286.31): C 46.14, H 5.98; found: C 46.08, H 6.04.

(3*S*,6*R*)-3-Isopropyl-6-methyl-1-vinylcyclohex-1-ene (19): A suspension of $[Pd(PPh_3)_4]$ (307 mg, 0.265 mmol) and LiCl (675 mg, 15.93 mmol) in THF (12 mL) was stirred for 10 min before a solution of triflate **18** (1.52 g, 5.31 mmol) and tributyl(vinyl)stannane (1.55 mL, 5.31 mmol) in THF (4 mL) was added. The mixture was refluxed for 4 h, diluted with pentane and poured onto sat. aq. NH_4Cl and 10% aq. NH_3. After stirring for 30 min, the organic phase was washed with water and brine before being dried over Na_2SO_4. The solvent was evaporated and the residue purified by flash chromatography (hexanes) to yield the desired product as a colorless liquid (737 mg, 85%). $[\alpha]_D^{20} = +172.3°$ ($c=2$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.25$ (ddd, $J=0.4$, 10.9, 17.7 Hz, 1H), 5.69 (d, $J=3.4$ Hz, 1H), 5.11 (d, $J=17.7$ Hz, 1H), 4.94 (d, $J=11.0$ Hz, 1H), 2.50 (m, 1H), 1.93 (m, 1H), 1.81 (m, 1H), 1.71 (m, 1H), 1.61 (dddd, $J=6.7$, 6.7, 6.7, 13.4 Hz, 1H), 1.35 (m, 2H), 1.08 (d, $J=7.0$ Hz, 1H), 0.93 (d, $J=6.8$ Hz, 1H), 0.89 (d, $J=6.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=141.6$, 139.5, 132.5, 110.8, 41.7, 32.7, 29.7, 28.7, 22.3, 20.5, 20.37, 20.35; IR (KAP): $\tilde{\nu}=2957$, 2927, 2871, 1635, 1600, 1462, 1384, 1367, 1164, 1113, 989, 892 cm^{-1}; MS (EI): *m*/*z* (%): 164 (29) [M^+], 121 (100), 93 (69), 79 (43), 55 (26), 41 (22); elemental analysis calcd (%) for $C_{12}H_{20}$ (164.29): C 87.73, H 12.27; found: C 87.64, H 12.22.

2-((3*S*,6*R*)-3-Isopropyl-6-methylcyclohex-1-enyl)ethanol (20): A solution of diene **19** (765 mg, 4.66 mol) in THF (12 mL) was added to a solution of 9-BBN (568 mg, 2.33 mmol) in THF (30 mL) and the resulting mixture stirred for 2 h at ambient temperature. The reaction was quenched at 0°C by successive addition of aq. NaOH (3 M, 1.9 mL) and aq. H_2O_2 (30%, 1.6 mL) and the resulting mixture was stirred for 12 h before it was diluted with *tert*-butyl methyl ether and water. Upon acidification with 10% aq. HCl, the precipitate dissolved and the water phase was extracted with *tert*-butyl methyl ether. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent followed by purification of the crude product by flash chromatography (hexanes/ethyl acetate gradient, max. 35% ethyl acetate) gave compound **20** as a colorless oil (737 mg, 87%). $[\alpha]_D^{20} = +39.3°$ ($c=1$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.39$ (s, 1H), 3.63 (m, 2H), 2.42 (m, 1H), 2.17 (ddd, $J=4.1$, 7.8, 15.0 Hz, 1H), 2.10 (m, 1H), 1.92 (m, 1H), 1.84 (ddd, $J=5.5$, 5.5, 10.8 Hz, 1H), 1.65 (m, 1H), 1.55 (m, 2H), 1.21 (m, 2H), 0.99 (d, $J=6.9$ Hz, 3H), 0.88 (d, $J=6.8$ Hz, 3H), 0.85 (d, $J=6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=138.4$, 128.9, 60.6, 42.4, 38.2, 32.4, 32.2, 32.17, 24.8, 20.0, 19.5, 19.1; IR (KAP): $\tilde{\nu}=$ 3336, 2955, 2928, 2871, 1462, 1444, 1384, 1367, 1039, 1015, 848 cm^{-1}; MS (EI): *m*/*z* (%): 182 (35) [M^+], 139 (71), 121 (90), 93 (100), 79 (58), 67 (24), 55 (26), 41 (39); elemental analysis calcd (%) for $C_{12}H_{22}O$ (182.30): C 79.06, H 12.16; found: C 79.13, H 12.07.

2-((3*S*,6*R*)-3-Isopropyl-6-methylcyclohex-1-enyl)acetaldehyde (21): A solution of alcohol **20** (722 mg, 3.96 mmol) in CH_2Cl_2 (10 mL) was added to a solution of Dess–Martin periodinane (1.85 g, 4.36 mmol) in CH_2Cl_2 (20 mL). After stirring for 1.5 h, the mixture was diluted with pentane before it was filtered through a plug of silica gel (pentane/*tert*-butyl methyl ether 4:1). The filtrate was evaporated and the residue purified by flash chromatography (hexanes/ethyl acetate 20:1) to give product **21** as a colorless liquid (611 mg, 86%). $[\alpha]_D^{20} = +99.4°$ ($c=1$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=9.58$ (t, $J=2.7$ Hz, 1H), 5.45 (d, $J=$ 0.7 Hz, 1H), 3.10 (m, 1H), 2.96 (ddd, $J=0.9$, 2.4, 15.6 Hz, 1H), 2.10 (m, 1H), 2.00 (m, 1H), 1.86 (m, 1H), 1.67 (m, 1H), 1.58 (ddd, $J=6.8$, 12.5, 13.5 Hz, 1H), 1.24 (m, 2H), 0.96 (d, $J=7.0$ Hz, 3H), 0.89 (d, $J=6.8$ Hz, 3H), 0.86 (d, $J=6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=201.1$, 133.8, 132.0, 50.2, 42.6, 33.5, 32.3, 32.1, 24.6, 19.8, 19.7, 19.5; IR (KAP): $\tilde{\nu}=$ 2956, 2929, 2872, 1724, 1461, 1385, 1368, 1043 cm^{-1}; MS (EI): *m*/*z* (%): 180 (8) [M^+], 136 (23), 95 (16), 93 (100), 81 (10), 67 (13), 55 (9), 41 (19); elemental analysis calcd (%) for $C_{12}H_{20}O$ (180.29): C 79.94, H 11.18; found: C 79.86, H 11.09.

1-((3*S*,6*R*)-3-Isopropyl-6-methylcyclohex-1-enyl)-4-(trimethyl-silyl)but-3-yn-2-ol (22): A suspension of dry $CeCl_3$ (1.61 g, 6.54 mmol) in THF (15 mL) was stirred at ambient temperature for 16 h. In another Schlenk flask, a solution of *n*BuLi (1.7 M in hexanes, 3.12 mL, 5.30 mmol) was added to a solution of trimethylsilylacetylene (0.793 mL, 5.61 mmol) in THF (15 mL) at −78°C. After stirring for 30 min, the resulting solution of 2-trimethylsilylethynyllithium was transferred via cannula to the $CeCl_3$ suspension, which was previously cooled to −78°C. The resulting mixture was stirred for 30 min before a solution of aldehyde **21** (562 mg, 3.12 mmol) in THF (20 mL) was added dropwise. After stirring for 2.5 h at that temperature, excess alkynylcerium dichloride was quenched by addition of sat. aq. NH_4Cl. The mixture was warmed to ambient temperature and the precipitate dissolved by addition of aq. HCl (1 M). Standard extractive work up followed by purification of the crude product by flash chromatography (hexanes/ethyl acetate gradient, max. 15% ethyl acetate) gave compound **22** as a colorless oil (803 mg, 93%, *dr* 65:35). See below for a compilation of the physical data of the individual isomers.

1-((3*S*,6*R*)-3-Isopropyl-6-methylcyclohex-1-enyl)-4-(trimethyl-silyl)but-3-yn-2-one (24): Dess–Martin periodinane (1.36 g, 3.2 mmol) was added in portions at 0°C to a solution of alcohol **22** (810 mg, 2.90 mmol) in CH_2Cl_2 (30 mL) and the resulting mixture was stirred at ambient temperature for 1 h. For work up, the mixture was diluted with pentane, the precipitates were filtered through a pad of silica gel (pentane/*tert*-butyl methyl ether 4:1), the filtrate was evaporated and the residue purified by flash chromatography (hexanes/ethyl acetate gradient, max. 10% ethyl acetate), yielding ketone **24** as a yellow liquid (753 mg, 94%). $[\alpha]_D^{20} = +105.5°$ ($c=1$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.50$ (s, 1H), 3.29 (ddd, $J=1.2$, 1.2, 14.8 Hz, 1H), 3.11 (dd, $J=0.5$, 14.8 Hz, 1H), 2.18 (m, 1H), 1.97 (m, 1H), 1.84 (m, 1H), 1.64 (m, 2H), 1.25 (m, 2H), 0.97 (d, $J=7.0$ Hz, 3H), 0.91 (d, $J=6.8$ Hz, 3H), 0.88 (d, $J=6.8$ Hz, 3H), 0.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=186.6$, 134.9, 132.5, 102.2, 98.0, 51.8, 42.6, 32.9, 32.5, 32.2, 24.4, 20.0, 19.7, 19.6, −0.6; IR (KAP): $\tilde{\nu}=$ 2957, 2929, 2872, 1674, 1462, 1368, 1251, 1220, 1110, 1089, 842, 760 cm^{-1}; MS (EI): *m*/*z* (%): 276 (5) [M^+], 261 (36), 234 (31), 191 (27), 136 (22), 125 (100), 97 (34), 95 (45), 93 (45), 73 (63); elemental analysis calcd (%) for $C_{17}H_{28}OSi$ (276.49): C 73.85, H 10.21; found: C 73.89, H 10.15.

(*S*)-1-((3*S*,6*R*)-3-Isopropyl-6-methylcyclohex-1-enyl)-4-(trimethylsilyl)-but-3-yn-2-ol [(*S*)-22]: A degassed solution of ketone **24** (200 mg, 0.723 mmol) in *i*PrOH (3 mL) was added to a degassed solution of [(1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylene-diamine-Ru-η^6-*p*-cymene] [(*S*,*S*)-**25**] (22 mg, 0.036 mmol)[32] in *i*PrOH (4 mL) and the resulting mixture was stirred for 4 h. Evaporation of the solvent followed by flash chromatography (hexane/ethyl acetate 20:1) of the crude product afforded alcohol (*S*)-**22** as a yellow oil (189 mg, 94%, *dr* 82:18). Careful chromatography provided a sample of diastereomerically pure product in about 60% yield. $[\alpha]_D^{20} = -5.3°$ ($c=1$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.48$ (s, 1H), 4.37 (dd, $J=4.8$, 9.3 Hz, 1H), 2.64 (m, 1H), 2.27 (dd, $J=9.3$, 14.0 Hz, 1H), 2.13 (m, 1H), 1.94 (m, 2H), 1.84 (m, 1H), 1.66 (m, 1H), 1.57 (dddd, $J=6.8$, 12.4, 12.4, 12.4 Hz, 1H), 1.21 (m, 2H), 1.01 (d, $J=7.0$ Hz, 3H), 0.88 (d, $J=6.8$ Hz, 3H), 0.86 (d, $J=6.8$ Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=137.5$, 131.0, 106.7, 89.1, 60.6, 43.8, 42.4, 32.4, 32.1, 31.9, 24.6, 20.0, 19.8, 19.6, 0.0; IR (KAP): $\tilde{\nu}=$ 3349, 2956, 2928, 2871, 1462, 1443, 1385, 1367, 1249, 1054, 1031, 1012, 894, 838, 759, 735, 698 cm^{-1}; MS (EI): *m*/*z* (%): 278 (1) [M^+], 173 (13), 145 (12), 109 (100), 99 (22), 95 (59), 81 (19), 73 (43), 43 (14); elemental analysis calcd (%) for $C_{17}H_{30}OSi$ (278.51): C 73.31, H 10.86; found: C 73.46, H 10.77.

(*R*)-1-((3*S*,6*R*)-3-Isopropyl-6-methylcyclohex-1-enyl)-4-(trimethylsilyl)-but-3-yn-2-ol [(*R*)-22]: Prepared analogously using the enantiomeric catalyst (*R*,*R*)-**25**. Pale yellow oil (18.6 mg, 93%, *dr* 85:15). An analytically pure sample (*dr* > 95:5) was obtained by careful chromatography. $[\alpha]_D^{20} = +56.2°$ ($c=0.93$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.46$ (s, 1H), 4.44 (dd, $J=5.3$, 7.4 Hz, 1H), 2.62 (m, 1H), 2.27 (dd, $J=7.4$, 13.7 Hz, 1H), 2.25 (m, 1H), 1.94 (m, 2H), 1.84 (m, 1H), 1.67 (m, 1H), 1.57 (dddd, $J=6.8$, 12.4, 12.4, 12.4 Hz, 1H), 1.22 (m, 2H), 1.02 (d, $J=$ 7.0 Hz, 3H), 0.90 (d, $J=6.8$ Hz, 3H), 0.87 (d, $J=6.8$ Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=137.4$, 130.7, 106.9, 89.4, 61.5, 43.0, 42.5, 32.9, 32.5, 32.3, 24.7, 20.1, 20.0, 19.7, −0.03; IR (KAP): $\tilde{\nu}=$ 3310, 2956, 2927, 2872, 1460, 1444, 1382, 1367, 1249, 1040, 1013, 894, 839, 759, 734, 698 cm^{-1}; MS (EI): *m*/*z* (%): 278 (1) [M^+], 217 (12), 173 (10), 145 (11), 136 (11), 109 (100), 99 (22), 95 (58), 73 (43), 43 (19); elemental analysis calcd (%) for $C_{17}H_{30}OSi$ (278.51): C 73.31, H 10.86; found: C 73.26, H 10.81.

(*S*)-1-((3*S*,6*R*)-3-Isopropyl-6-methylcyclohex-1-enyl)but-3-yn-2-ol [(*S*)-23]: TBAF (1 M in THF, 0.66 mL, 0.66 mmol) was added at 0 °C to a solution of (*S*)-**22** (154 mg, 0.55 mmol) in THF (4 mL) and the resulting mixture was stirred for 1 h. After dilution with *tert*-butyl methyl ether, the organic phase was washed with water and brine before it was dried over Na_2SO_4. Evaporation of the solvent followed by flash chromatography (hexanes/ethyl acetate 10:1) gave the title compound as a yellow liquid (102 mg, 89 %). $[\alpha]_D^{20} = -13.1°$ ($c = 1.05$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.49$ (s, 1H), 4.38 (ddd, $J = 2.1$, 4.4, 9.5 Hz, 1H), 2.67 (m, 1H), 2.44 (d, $J = 2.1$ Hz, 1H), 2.28 (dd, $J = 9.6$, 14.1 Hz, 1H), 1.23 (m, 1H), 1.95 (m, 1H), 1.85 (m, 2H), 1.66 (m, 1H), 1.58 (dddd, $J = 6.8$, 12.3, 12.2, 12.2 Hz, 1H), 1.23 (m, 2H), 1.01 (d, $J = 7.0$ Hz, 3H), 0.88 (d, $J = 6.8$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 137.2, 131.2, 84.9, 72.7, 59.8, 43.8, 42.5, 32.3, 32.1, 31.8, 24.6, 20.0, 19.8, 19.5; IR (KAP): $\tilde{\nu} =$ 3411, 3311, 2955, 2927, 2871, 1462, 1443, 1385, 1367, 1297, 1255, 1029, 836 cm^{-1}; MS (EI): *m*/*z* (%): 206 (15) [M^+], 163 (52), 135 (52), 107 (43), 93 (100), 79 (97), 67 (50), 55 (62), 41 (68).

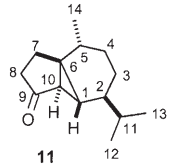
(*R*)-1-((3*S*,6*R*)-3-Isopropyl-6-methylcyclohex-1-enyl)but-3-yn-2-ol [(*R*)-23]: Prepared analogously from (*R*)-**22** as a pale yellow oil (89 mg, 88 %). $[\alpha]_D^{20} = +65.6°$ (c = 1.05, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.46$ (s, 1H), 4.47 (ddd, $J = 2.1$, 5.7, 7.7 Hz, 1H), 2.64 (m, 1H), 2.42 (d, $J =$ 2.0 Hz, 1H), 2.29 (dd, $J = 7.4$, 13.6 Hz, 1H), 2.19 (m, 1H), 1.93 (m, 2H), 1.84 (m, 1H), 1.65 (m, 1H), 1.59 (ddd, $J = 4.9$, 10.2, 13.5 Hz, 1H), 1.22 (m, 2H), 1.02 (d, $J = 7.0$ Hz, 3H), 0.89 (d, $J = 6.9$ Hz, 3H), 0.87 (d, $J =$ 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 137.2$, 130.7, 84.9, 73.2, 61.1, 43.2, 42.4, 32.8, 32.4, 32.3, 24.5, 20.0, 19.8, 19.5; IR (KAP): $\tilde{\nu} =$ 3362, 3311, 2955, 2927, 2871, 1462, 1443, 1385, 1367, 1260, 1037, 1014 cm^{-1}; MS (EI): *m*/*z* (%): 206 (12) [M^+], 191 (12), 173 (13), 163 (21), 145 (44), 109 (46), 95 (100), 81 (36), 67 (37), 55 (49), 41 (45); elemental analysis calcd (%) for $C_{14}H_{22}O$ (206.32): C 81.50, H 10.75; found: C 81.37, H 10.65.

(*S*)-1-((3*S*,6*R*)-3-Isopropyl-6-methylcyclohex-1-enyl)but-3-yn-2-yl acetate [(*S*)-26]: DMAP (127 mg, 1.04 mmol), acetic anhydride (0.295 mL, 3.13 mmol) and Et_3N (0.439 mL, 3.13 mmol) were successively added to a solution of (*S*)-**23** (215 mg, 1.04 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 40 min before it was diluted with *tert*-butyl methyl ether and poured onto ice water. The aqueous phase was repeatedly extracted with *tert*-butyl methyl ether, the combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated. Purification of the residue by flash chromatography (hexanes/ethyl acetate 20:1) yielded product (*S*)-**26** as a colorless liquid (241 mg, 93 %). $[\alpha]_D^{20} = -25.2°$ ($c = 1$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.47$ (ddd, $J =$ 2.2, 4.8, 9.1 Hz, 1H), 5.41 (s, 1H), 2.63 (m, 1H), 2.43 (d, $J = 2.1$ Hz, 1H), 2.38 (m, 1H), 2.14 (m, 1H), 2.04 (s, 3H), 1.91 (m, 1H), 1.82 (ddd, $J = 5.7$, 5.7, 9.9 Hz, 1H), 1.57 (m, 2H), 1.18 (m, 2H), 0.99 (d, $J = 6.9$ Hz, 3H), 0.87 (d, $J = 6.8$ Hz, 3H), 0.85 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.0$, 136.4, 130.5, 81.8, 73.4, 62.0, 42.4, 40.9, 32.4, 32.1, 31.8, 24.4, 21.1, 20.0, 19.8, 19.4; IR (KAP): $\tilde{\nu} =$ 3302, 3288, 2956, 2929, 2871, 1741, 1462, 1444, 1431, 1368, 1227, 1024 cm^{-1}; MS (EI): *m*/*z* (%): 248 (0.5) [M^+], 188 (22), 173 (21), 145 (100), 117 (25), 105 (20), 95 (26), 43 (88); elemental analysis calcd (%) for $C_{16}H_{24}O_2$ (248.36): C 77.38, H 9.74; found: C 77.45, H 9.71.

(*R*)-1-((3*S*,6*R*)-3-Isopropyl-6-methylcyclohex-1-enyl)but-3-yn-2-yl-acetate [(*R*)-26]: Prepared analogously from (*R*)-**23** as a colorless oil (63 mg, 81 %). $[\alpha]_D^{20} = +78°$ ($c = 1$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 5.45 (dd, $J = 2.4$, 6 Hz, 1H), 5.43 (dd, $J = 2.4$, 6 Hz, 1H), 2.63 (ddt, $J = 1.2$, 6.0, 13.6 Hz, 1H), 2.41 (d, $J = 2$ Hz, 1H), 2.32 (dd, $J = 8.9$, 13.4 Hz, 1H), 2.12 (m, 1H), 2.07 (s, 3H), 1.92 (m, 1H), 1.84 (m, 1H), 1.61 (m, 1H), 1.58 (m, 1H), 1.20 (m, 2H), 1.02 (d, $J = 7.0$ Hz, 3H), 0.88 (d, $J = 6.8$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.0$, 136.4, 130.4, 81.3, 63.2, 42.4, 40.5, 32.4, 32.3, 24.4, 21.2, 19.9, 19.8, 19.4; IR (KAP): $\tilde{\nu} =$ 3312, 2956, 2928, 2872, 1740, 1463, 1443, 1370, 1227, 1021, 960 cm^{-1}; MS (EI): *m*/*z* (%): 248 (0.7) [M^+], 188 (21), 173 (21), 145 (100), 117 (26), 105 (21), 95 (28), 43 (80); HRMS (ESI): *m*/*z*: calcd for $C_{16}H_{24}O_2$+Na: 271.1666, found 271.1668 [M^++Na].

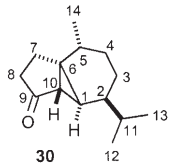
(−)-(1*R*,5*R*,6*R*,7*S*,10*R*)-7-Isopropyl-10-methyl-tricyclo[4.4.0.0^{1,5}]dec-3,4-en-4-yl-acetate (27): A solution of (*S*)-**26** (100 mg, 0.403 mmol) in toluene (3 mL) was added to a suspension of $PtCl_2$ (2.1 mg, 0.0081 mmol) in toluene (1 mL) and the resulting mixture was stirred at 80 °C for 3 h. For work up, the solvent was evaporated and the residue purified by flash chromatography (hexanes/ethyl acetate 20:1) to give product **27** as a yellow oil (92 mg, 92 %). $[\alpha]_D^{20} = -2.8°$ ($c = 0.74$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.98$ (t, $J = 2.2$ Hz, 1H), 2.53 (dd, $J = 2.1$, 17.0 Hz, 1H), 2.20 (td, $J = 2.7$, 17.0 Hz, 1H), 2.14 (s, 3H), 1.79 (sept, $J = 2$ Hz, 1H), 1.62 (m, 1H), 1.60 (m, 1H), 1.40 (ddd, $J = 2.5$, 4.8, 5.1 Hz, 1H), 1.36 (dd, $J = 2.6$, 5.7 Hz, 1H), 1.10 (m, 1H), 0.96 (d, $J = 6.2$ Hz, 3H), 0.95 (d, $J = 6.5$ Hz, 3H), 0.91 (d, $J = 6.7$ Hz, 3H), 0.85 (m, 1H), 0.61 (t, $J = 2.8$ Hz, 1H), 0.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.6$, 154.9, 108.1, 43.8, 36.0, 34.3, 33.5, 32.6, 31.4, 31.2, 30.4, 26.3, 21.2, 20.0, 19.7, 19.6; IR (KAP): $\tilde{\nu} =$ 2956, 2926, 2870, 2852, 1763, 1649, 1458, 1368, 1202, 1161, 1141 cm^{-1}; MS (EI): *m*/*z* (%): 248 (16) [M^+], 206 (86), 163 (100), 152 (18), 121 (57), 107 (39), 93 (17), 55 (33), 43 (45); HRMS (ESI): *m*/*z*: calcd for $C_{16}H_{24}O_2$+Na: 271.1666, found 271.1668 [M^++Na].

(−)-(1*R*,5*R*,6*R*,7*S*,10*R*)-7-Isopropyl-10-methyl-tricyclo[4.4.0.0^{1,5}]decane-4-one (11): K_2CO_3 (60 mg, 0.43 mmol) was added to a solution of enol ester **27** (214 mg, 0.86 mmol) in MeOH (4 mL). After stirring for 45 min, the mixture was diluted with *tert*-butyl methyl ether and water. Standard extractive work up followed by flash chromatography (hexanes/ethyl acetate 20:1) gave ketone **11** as a yellow oil which slowly crystallized upon standing (135 mg, 76 %). M.p. 58.5–60 °C (ref.:[24c] 57–58 °C); $[\alpha]_D^{20} = -21.8°$ ($c = 0.72$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.12$ (m, 1H, H-8a), 2.10 (m, 1H, H-7a), 2.00 (m, 1H, H-8b), 1.797 (d(qi), $J = 6.0$, 12.0 Hz, 1H, H-5), 1.796 (m, 1H, H-7b), 1.63 (dddd, $J = 2.4$, 4.8, 5.2, 13.6 Hz, 1H, H-4a), 1.61 (oct, $J = 6.6$ Hz, 1H, H-11), 1.455 (d, $J = 2.7$ Hz, 1H, H-10), 1.45 (ddt, $J = 2.4$, 4.7, 4.7, 12.8 Hz, 1H, H-3a), 1.23 (t, $J = 2.6$ Hz, 1H, H-1), 1.15 (dddd, $J = 2.6$, 4.8, 6.0, 12.8 Hz, 1H, H-2), 0.95 (d, $J = 6.6$ Hz, 3H, H-14), 0.92 (ddt, $J = 2.4$, 12.8, 12.8, 13.2 Hz, 1H, H-3b), 0.91 (d, $J = 6.8$ Hz, 3H, H-12), 0.88 (d, $J =$ 6.8 Hz, 3H, H-13), 0.55 (ddt, $J = 2.4$, 11.4, 13.2, 13.2 Hz, 1H, H-4b); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 214.4$ (C-9), 43.3 (C-2), 40.3 (C-6), 39.7 (C-10), 33.3 (C-8), 33.2 (C-11), 32.5 (C-1), 31.3 (C-5), 30.8 (C-4), 26.6 (C-7), 26.0 (C-3), 19.9 (C-12), 19.4 (C-13), 18.9 (C-14); IR (KAP): $\tilde{\nu} =$ 2947, 2926, 2889, 2859, 1707, 1455, 1249, 1185, 912 cm^{-1}; MS (EI): *m*/*z* (%): 206 (97) [M^+], 191 (20), 164 (99), 149 (36), 135 (23), 122 (100), 110 (46), 93 (61), 79 (69), 69 (30), 55 (62), 41 (68); HRMS (ESI): *m*/*z*: calcd for $C_{14}H_{22}O$+Na: 229.1563, found 229.1563 [M^++Na].



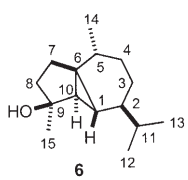
11

(1*S*,5*S*,6*S*,7*S*,10*R*)-7-Isopropyl-10-methyl-tricyclo[4.4.0.0^{1,5}]decane-4-one (30): Prepared analogously; the pure compound was isolated from the mixture of isomeric products by preparative HPLC. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.10$ (m, 1H, H-7a), 2.06 (m, 1H, H-8a), 2.01 (m, 1H, H-7b), 1.98 (m, 1H, H-8b), 1.93 (d(dq), $J =$ 6.2, 6.8, 10.2 Hz, 1H, H-5), 1.59 (m, 1H, H-4), 1.57 (dt, $J = 3.2$, 3.6 Hz, 1H, H-1), 1.565 (m, 1H, H-3), 1.555 (t, $J =$ 3.2 Hz, 1H, H-10), 1.545 (m, 1H, H-2), 1.40 (m, 1H, H-11), 1.09 (d, $J =$ 7.1 Hz, 3H, H-14), 0.95 (m, 1H, H-4), 0.92 (d, $J = 6.6$ Hz, 3H, H-12), 0.89 (d, $J = 6.6$ Hz, 3H, H-13), 0.72 (m, 1H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 215.2$ (C-9), 40.5 (C-2), 37.6 (C-6), 37.5 (C-10), 33.0 (C-8), 32.8 (C-11), 32.2 (C-1), 32.1 (C-4), 30.7 (C-5), 26.8 (C-7), 23.1 (C-3), 20.7 (C-12), 20.5 (C-13), 18.7 (C-14).



30

(−)-(1*R*,4*S*,5*R*,6*R*,7*S*,10*R*)-7-Isopropyl-4,10-dimethyl-tricyclo[4.4.0.0^{1,5}]decane-4-ol [(−)-cubebol, 6]: A suspension of $CeCl_3$ (50 mg, 0.204 mmol) in THF (1 mL) was stirred for 16 h at ambient temperature before MeLi (1.6 M in Et_2O, 0.118 mL, 0.189 mmol) was added at −78 °C. After 30 min, a solution of ketone **11** (30 mg, 0.145 mmol) in THF (1 mL) was added dropwise. Stirring was continued for 45 min before the reaction



6

was quenched by addition of aq. sat. NH_4Cl and warmed to room temperature. Standard extractive work up followed by purification of the crude product by flash chromatography yielded cubebol **6** as a colorless solid (29.2 mg, 91%). M.p. 59–60.4°C (ref.:[24c] 61–62°C); $[\alpha]_D^{20} = -51°$ ($c=1$, $CHCl_3$) [$[\alpha]_D^{20} = -48.3°$ ($c=3.52$, $CHCl_3$)];[24c] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.82$ (ddd, $J=8.6$, 11.6, 12.6 Hz, 1H, H-7a), 1.63 (d(quint.), $J=6.2$, 11.4 Hz, 1H, H-5), 1.60 (oct., $J=6.8$ Hz, 1H, H-11), 1.57 (dddd, $J=2.2$, 4.6, 5.2, 13.6 Hz, 1H, H-4a), 1.51 (ddt, $J=0.8$, 8.8, 13.2 Hz, 1H, H-8a), 1.50 (ddd, $J=0.8$, 8.6, 12.6 Hz, 1H, H-7b), 1.42 (s, 1H, H-16), 1.36 (ddt, $J=2.3$, 4.4, 12.4 Hz, 1H, H-3a), 1.33 (dddd, $J=1.0$, 8.6, 11.6, 13.2 Hz, 1H, H-8b), 1.26 (d, $J=0.9$ Hz, 3H, H-15), 0.97 (dddd, $J=3.2$, 4.4, 6.2, 12.4 Hz, 1H, H-2), 0.94 (d, $J=6.7$ Hz, 3H, H-12), 0.91 (d, $J=6.4$ Hz, 3H, H-14), 0.90 (d, $J=6.7$ Hz, 3H, H-13), 0.84 (d, $J=3.2$ Hz, 1H, H-10), 0.80 (t, $J=3.2$ Hz, 1H, H-1), 0.79 (d(dt), $J=2.2$, 12.6, 13.6 Hz, 1H, H-3b), 0.49 (dddd, $J=2.0$, 11.1, 13.2, 13.6 Hz, 1H, H-4b); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=80.9$ (C-9), 44.2 (C-2), 39.1 (C-10), 36.4 (C-8), 33.7 (C-11), 33.5 (C-6), 31.7 (C-4), 31.0 (C-5), 29.6 (C-7), 28.0 (C-15), 26.5 (C-3), 22.6 (C-1), 20.1 (C-12), 19.7 (C-13), 18.8 (C-14); IR (KAP): $\tilde{\nu}$ = 3279, 2952, 2925, 2865, 1462, 1451, 1384, 1369, 1300, 1184, 1133, 1099, 1032, 929 cm^{-1}; MS (EI): m/z (%): 222 (12) [M^+], 207 (100), 161 (82), 121 (34), 105 (35), 93 (26), 81 (26), 55 (26), 43 (78); HRMS (EI): m/z: calcd for $C_{15}H_{26}O$: 222.1987, found 222.1984 [M^+].

(−)-(1*R*,5*R*,6*R*,7*S*,10*R*)-7-Isopropyl-10-methyl-tricyclo[4.4.0.0^{1,5}]dec-3,4-en-4-trifluoromethanesufonate (28): *n*BuLi (1.55 M in hexanes, 0.176 mL, 0.273 mmol) was added dropwise to a solution of $(i\text{Pr})_2NH$ (0.042 mL, 0.296 mmol) in THF (2 mL) at 0°C and the resulting mixture was stirred for 30 min before it was cooled to −78°C. At that temperature, a solution of ketone **11** (47 mg, 0.228 mmol) in THF (1 mL) was introduced and stirring continued for 2 h before *N*-(5-chloro-2-pyridyl)bistriflimide (107 mg, 0.273 mmol) in THF (2 mL) was added and the reaction allowed to reach ambient temperature. The solvent was evaporated and the residue was purified by flash chromatography (pentane) to yield product **28** as a colorless liquid (70 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.20$ (t, $J=$ 2.2 Hz, 1H), 2.56 (dd, $J=2.3$, 17.5 Hz, 1H), 2.27 (td, $J=2.8$ Hz, 17.5 Hz, 1H), 1.80 (sept, 1H), 1.64 (m, 1H), 1.62 (ddd, $J=6.5$, 13.4, 13.5 Hz, 1H), 1.47 (t, $J=2.9$ Hz, 1H), 1.42 (m, 1H), 1.15 (m, 1H), 0.96 (d, $J=6.5$ Hz, 3H), 0.94 (d, $J=6.8$ Hz, 3H), 0.92 (m, 1H), 0.91 (d, $J=6.8$ Hz, 3H), 0.70 (t, $J=2.7$ Hz, 1H), 0.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=153.1$, 117.2 (q, $J_{CF}=318$ Hz), 113.0, 43.4, 35.4, 34.4, 33.6, 33.4, 31.4, 30.9, 29.3, 26.3, 19.8, 19.77, 19.5; IR (KAP): $\tilde{\nu}$= 2959, 2930, 2857, 1643, 1421, 1245, 1203, 1140, 1113, 1098, 905, 855, 821 cm^{-1}; MS (EI): m/z (%): 338 (54) [M^+], 295 (83), 253 (100), 239 (46), 145 (43), 105 (27), 91 (53), 77 (31), 69 (63), 55 (88), 41 (56); HRMS (EI): m/z: calcd for $C_{15}H_{21}F_3O_3S$: 338.1165, found 338.1164 [M^+].

(−)-(1*R*,5*R*,6*R*,7*S*,10*R*)-7-Isopropyl-10,4-dimethyl-tricyclo[4.4.0.0^{1,5}]dec-3,4-ene [(−)-α-cubebene, 4]: A solution of triflate **28** (54 mg, 0.16 mmol) in THF (2 mL) was added to a solution of $[Fe(acac)_3]$ (5.6 mg, 0.016 mmol) and 1-methyl-2-pyrrolidinone (NMP, 0.147 mL) in THF (1 mL). The mixture was cooled to −30°C before a solution of MeMgBr (3 M in Et_2O, 0.106 mL, 0.318 mmol) was added dropwise. The resulting mixture was stirred for 40 min before the reaction was quenched with aq. sat. NH_4Cl. A standard extractive work up followed by purification of the crude product by flash chromatography (pentane) furnished α-cubebene **4** as a colorless oil (29.2 mg, 90%). $[\alpha]_D^{20} = -18.4°$ ($c=0.7$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.89$ (d, $J=1.2$ Hz, 1H), 2.52 (td, $J=2$, 16.8 Hz, 1H), 2.15 (ddd, $J=2.2$, 4.5, 17.1 Hz, 1H), 1.82 (sep, $J=6$ Hz, 1H), 1.76 (dd, $J=2.0$, 3.8 Hz, 3H), 1.60 (ddd, $J=5.7$, 5.7, 13.1 Hz, 1H), 1.60 (ddd, $J=6.7$, 14.4, 14.5 Hz, 1H), 1.38 (m, 1H), 1.15 (t, $J=2.6$ Hz, 1H), 1.08 (m, 1H), 0.93 (d, $J=6.6$ Hz, 6H), 0.91 (m, 1H), 0.89 (d, $J=$ 6.8 Hz, 3H), 0.52 (dddd, $J=2.3$, 13.4, 13.3, 13.3 Hz, 1H), 0.22 (t, $J=$ 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=145.9$, 120.3, 44.8, 40.6, 36.3, 34.9, 34.5, 33.6, 31.6, 31.3, 26.7, 20.0, 19.8, 19.78, 16.8; IR (KAP): $\tilde{\nu}$= 2955, 2927, 2909, 2870, 2852, 1457, 1444, 1385, 1369, 1319, 1165, 1032, 931, 825, 776 cm^{-1}; MS (EI): m/z (%): 204 (33) [M^+], 161 (100), 119 (69), 105 (67), 91 (25), 81 (18), 41 (21); HRMS (EI): m/z: calcd for $C_{15}H_{24}$: 204.1881, found 204.1878 [M^+].

Carene series

3,7-Dimethyloct-6-en-1-yn-3-ol (41): A solution of ethynylmagnesium bromide (0.5 M in THF, 10 mL, 5 mmol) was added to a solution of 6-methyl-5-hepten-2-one (**40**) (428 mg, 3.39 mmol) in THF (10 mL) at −78°C. The resulting mixture was allowed to reach ambient temperature and was stirred for 1 h. After quenching with aq. sat $KHSO_4$, the aqueous phase was repeatedly extracted with *tert*-butyl methyl ether, the combined organic layers were washed with brine and dried over Na_2SO_4 before being concentrated. Purification of the residue by flash chromatography (pentane/diethyl ether 6:1) gave product **41** as a yellow liquid (447 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.17$ (ddd, $J=1.4$, 2.8, 8.1 Hz, 1H), 2.46 (s, 1H), 2.27 (ddd, $J=7.8$, 14.7, 21.5 Hz, 1H), 2.19 (ddd, $J=7.3$, 13.8, 21.9 Hz, 1H), 2.07 (s, 1H), 1.70 (t, $J=7.6$ Hz, 1H), 1.69 (t, $J=10.8$ Hz, 1H), 1.69 (s, 3H), 1.66 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=132.7$, 123.8, 87.7, 71.6, 68.4, 43.3, 30.0, 25.8, 23.7, 17.9; IR (KAP): $\tilde{\nu}$= 3400, 3307, 2972, 2938, 2856, 1740, 1449, 1375, 1119, 1083, 907 cm^{-1}; MS (EI): m/z (%): 137 (41), 119 (84), 109 (18), 91 (36), 69 (99), 55 (74), 41 (100); HRMS (CI): m/z: calcd for $C_{10}H_{16}O$: 153.1279; found: 153.1281 [M^++H].

(*E*)-3,7,11-Trimethyldodeca-6,10-dien-1-yn-3-ol (32): Prepared analogously from geranyl acetone **31** as a yellow oil (2.16 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.18$ (ddd, $J=1.2$, 6.8, 7.8 Hz, 1H), 5.08 (ddd, $J=$ 1.4, 5.4, 6.9 Hz, 1H), 2.46 (s, 1H), 2.28 (m, 1H), 2.20 (m, 1H), 2.15–1.96 (m, 5H), 1.72 (m, 2H), 1.68 (d, $J=1.2$ Hz, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=136.4$, 131.7, 124.3, 123.7, 87.8, 71.6, 68.4, 43.3, 39.8, 30.0, 26.8, 25.8, 23.6, 17.8, 16.2; IR (KAP): $\tilde{\nu}$= 3358, 3308, 2969, 2917, 1447, 1375, 1109, 907, 838 cm^{-1}; MS (EI): m/z (%): 220 (0.1) [M^+], 205 (10), 187 (13), 159 (14), 136 (15), 123 (13), 105 (38), 93 (35), 81 (19), 69 (100), 55 (18), 41 (83); HRMS (ESI): m/z: calcd for $C_{15}H_{24}O$+Na: 243.1725; found: 243.1722 [M^++Na].

(*Z*)-3,7,11-Trimethyldodeca-6,10-dien-1-yn-3-ol (46):[53] Prepared analogously from neryl acetone **45** as a yellow liquid (2.19 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.17$ (dt, $J=1.2$, 7.5 Hz, 1H), 5.12 (m, 1H), 2.45 (m, 1H), 2.24 (m, 2H), 2.08 (m, 5H), 1.69 (m, 2H), 1.69 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=136.4$, 131.8, 124.5, 124.4, 87.7, 71.6, 68.4, 43.6, 32.1, 29.9, 26.7, 25.9, 23.6, 23.5, 17.8; IR (KAP): $\tilde{\nu}$= 3350, 3308, 2966, 2928, 2857, 1448, 1375, 1146, 1112, 1024, 907, 833 cm^{-1}; MS (EI): m/z (%): 220 (1) [M^+], 205 (8), 187 (9), 159 (10), 133 (9), 119 (11), 105 (22), 93 (25), 81 (15), 69 (100), 55 (14), 41 (74).

3,7-Dimethyl-oct-6-en-1-yn-3-yl acetate (1): DMAP (160 mg, 1.3 mmol) and acetic anhydride (0.62 mL, 6.57 mmol) were added to a solution of alcohol **41** (200 mg, 1.3 mmol) in Et_3N (10 mL). After stirring for 3 h at ambient temperature, the mixture was poured onto water, the aqueous phase was extracted with *tert*-butyl methyl ether, the combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated. Flash chromatography (hexanes/ethyl acetate 5:1) of the residue gave the desired product **1** as a colorless liquid (248 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.11$ (tddd, $J=1.3$, 2.7, 5.6, 8.5 Hz, 1H), 2.55 (s, 1H), 2.16 (m, 2H), 2.02 (s, 3H), 1.94 (m, 1H), 1.81 (ddd, $J=6.6$, 10.2, 13.5 Hz, 1H), 1.68 (s, 6H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=169.5$, 132.4, 123.3, 83.9, 74.9, 73.4, 41.5, 26.5, 25.8, 23.0, 22.0, 17.8; IR (KAP): $\tilde{\nu}$= 3287, 2971, 2921, 2860, 1743, 1444, 1367, 1230, 1167, 1080, 1014, 940, 830 cm^{-1}; MS (EI): m/z (%): 152 (36), 137 (23), 119 (95), 109 (18), 91 (37), 79 (10), 69 (35), 55 (19), 43 (100); HRMS (CI): m/z: calcd for $C_{12}H_{18}O_2$: 195.1385; found: 195.1382 [M^++H].

(*E*)-3,7,11-Trimethyldodeca-6,10-dien-1-yne-3-yl acetate (33): Prepared analogously from alcohol **32** as a pale yellow oil (581 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.13$ (dt, $J=1.2$, 7.1 Hz, 1H), 5.08 (ddd, $J=1.4$, 2.8, 7.0 Hz, 1H), 2.56 (s, 1H), 2.20 (m, 2H), 2.07 (m, 2H), 2.03 (s, 3H), 2.02–1.92 (m, 3H), 1.82 (ddd, $J=6.7$, 10.2, 13.5 Hz, 1H), 1.69 (s, 3H), 1.68 (d, $J=1.2$ Hz, 3H), 1.62 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=169.4$, 135.9, 131.4, 124.3, 123.0, 83.8, 74.7, 73.3, 41.3, 39.7, 26.7, 26.4, 25.7, 22.8, 21.9, 17.7, 16.0; IR (KAP): $\tilde{\nu}$= 3296, 2967, 2916, 1745, 1444, 1367, 1230, 1167, 1085, 1013, 940, 836 cm^{-1}; MS (EI): m/z (%): 262 (0.3) [M^+], 220 (30), 159 (18), 133 (37), 119 (17), 105 (59), 91 (31), 81 (18), 69 (100), 55 (16), 43 (69); HRMS (ESI): m/z: calcd for $C_{17}H_{26}O_2$: 285.1830; found: 285.1830 [M^++Na].

(*Z*)-3,7,11-Trimethyldodeca-6,10-dien-1-yne-3-yl acetate (47): Prepared analogously from alcohol **46** as a colorless liquid (2.23 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.13 (t, J = 7.2 Hz, 1H), 5.12 (t, J = 7.0 Hz, 1H), 2.55 (s, 1H), 2.18 (dd, J = 7.9, 16.4 Hz, 1H), 2.18 (dd, J = 8.0, 15.5 Hz, 1H), 2.06 (m, 1H), 2.05 (s, 3H), 2.03 (s, 3H), 1.94 (m, 1H), 1.80 (ddd, J = 6.9, 10.0, 13.5 Hz, 1H), 1.69 (m, 3H), 1.687 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5, 136.2, 131.8, 124.4, 124.0, 83.9, 74.8, 73.4, 41.8, 32.1, 26.7, 26.5, 25.9, 23.5, 22.8, 22.0, 17.8; IR (KAP): $\tilde{\nu}$ = 3308, 2966, 2919, 2858, 1745, 1445, 1367, 1231, 1170, 1085, 1014, 940, 830 cm^{-1}; MS (EI): m/z (%): 220 (21) [M^+−AcOH], 187 (11), 159 (12), 136 (28), 119 (15), 105 (32), 93 (22), 81 (16), 69 (100), 55 (13), 43 (77); HRMS (ESI): m/z: calcd for $C_{17}H_{26}O_2$+Na: 285.1830; found: 285.1829 [M^++Na].

3,7,7-Trimethylbicyclo[4.1.0]hept-2-en-2-yl acetate (3): A flame dried 25 mL two-necked flask was charged with $AuCl_3$ (16 mg, 0.052 mmol). After a solution of acetate **1** (200 mg, 1.03 mmol) in 1,2-dichloroethane (10 mL) had been added, the mixture was stirred under argon for 12 h. During the course of the reaction a characteristic color change from yellow to orange and finally brownish grey occurred. The mixture was filtered through a pad of Celite (hexanes/ethyl acetate 3:1) and the filtrate was evaporated yielding product **3** as a yellow liquid (197 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.24 (dd, J = 7.6, 15.7 Hz, 1H), 2.16 (s, 3H), 1.83 (m, 1H), 1.78 (m, 1H), 1.64 (m, 1H), 1.53 (s, 3H), 1.09 (m, 2H), 1.06 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 140.5, 118.1, 29.8, 28.1, 25.0, 24.7, 24.0, 21.1, 17.7, 16.2, 15.8; IR (KAP): $\tilde{\nu}$ = 2918, 2865, 1753, 1698, 1449, 1367, 1208, 1165, 1097, 1044, 1009, 922, 889 cm^{-1}; MS (EI): m/z (%): 194 (16) [M^+], 152 (100), 137 (58), 119 (5), 109 (46), 95 (17), 81 (7), 67 (12), 55 (9), 43 (42); HRMS (EI): m/z: calcd for $C_{12}H_{18}O_2$: 194.1307; found: 194.1304 [M^+].

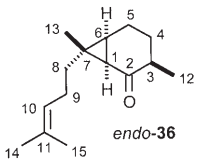
3,7,7-Trimethylbicyclo[4.1.0]heptan-2-one (42): K_2CO_3 (17 mg, 0.12 mmol) was added to a solution of enol acetate **3** (100 mg, 0.51 mmol) in MeOH (5 mL). After stirring for 16 h at ambient temperature, the mixture was diluted with water and the aqueous phase was repeatedly extracted with *tert*-butyl methyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated and the residue was purified by flash chromatography (hexanes/ethyl acetate 20:1) to give ketone **42** as a yellow liquid (47 mg, 60% over two steps, *dr* 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (ddd, J = 5.9, 12.2, 18.1 Hz, 1H), 2.03 (ddd, J = 4.4, 6.0, 14.7 Hz, 1H), 2.03 (dd, J = 5.5, 14.7 Hz, 1H), 1.83 (dtd, J = 2.7, 6.6, 9.3 Hz, 1H), 1.44 (d, J = 7.6 Hz, 1H), 1.43 (ddd, J = 6.0, 12.1, 16.2 Hz, 1H), 1.23 (t, J = 6.8 Hz, 1H), 1.11 (s, 3H), 1.10 (s, 3H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.3, 42.8, 34.3, 30.0, 28.6, 25.8, 23.7, 19.4, 17.8, 14.3; IR (KAP): $\tilde{\nu}$ = 2931, 2865, 1693, 1455, 1375, 1329, 1217, 1178, 1119, 1072, 1024, 986, 955, 935, 885, 786 cm^{-1}; MS (EI): m/z (%): 152 (27) [M^+], 110 (26), 95 (26), 82 (100), 67 (59), 41 (35); HRMS (EI): m/z: calcd for $C_{10}H_{16}O$: 152.1201; found: 152.1200 [M^+].

3,7,7-Trimethylbicyclo[4.1.0]hept-2-ene (2-Carene, 44): *n*BuLi (1.6 M in hexanes, 0.484 mL, 0.77 mmol) was added dropwise to a solution of (iPr)$_2$NH (0.108 mL, 0.77 mmol) in THF (3 mL) at 0 °C and the resulting mixture was stirred for 30 min before it was cooled to −78 °C. A solution of ketone **42** (107 mg, 0.7 mmol) in THF (2 mL) was slowly introduced at that temperature and stirring continued for 16 h before a solution of *N*-(5-chloro-2-pyridyl)bistriflimide (276 mg, 0.7 mmol) in THF (3 mL) was added and the reaction allowed to reach ambient temperature. The mixture was diluted with *tert*-butyl methyl ether and the organic layer was successively washed with water, aq. sat. Na_2CO_3 and brine. Evaporation of the solvent gave triflate **43** as a yellow oil which was directly used in the next step.

A solution of this crude triflate (200 mg, 0.7 mmol) in THF (3 mL) was added to a suspension of [Pd(PPh$_3$)$_4$] (16 mg, 0.014 mmol) and LiCl (89 mg, 2.11 mmol) in THF (4 mL) followed by addition of Bu_3SnH (0.223 mL, 0.84 mmol). The mixture was stirred at 60 °C for 16 h before it was diluted with pentane and repeatedly washed with aq. NH_3. The organic phase was washed with brine, dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 20:1) to give 2-carene **44** as a colorless liquid (43 mg, 45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.54 (m, 1H), 1.92 (ddd, J = 2.2, 6.5, 7.3 Hz, 1H), 1.83 (dd, J = 6.2, 13.4 Hz, 1H), 1.70 (m, 1H), 1.66 (s, 3H), 1.64 (m, 1H), 1.06 (s, 3H), 0.95 (dd, J = 4.4, 8.7 Hz, 1H), 0.85 (s, 3H), 0.81 (ddd, J = 3.0, 8.1, 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.7, 119.6, 28.7, 27.6, 24.2, 24.0, 23.0, 21.2, 17.9, 15.6; IR (KAP): $\tilde{\nu}$ = 2956, 2924, 2860, 1689, 1450, 1374, 1260, 1213, 1098, 1022, 826, 804 cm^{-1}; MS (EI): m/z (%): 136 (36) [M^+], 121 (79), 105 (21), 93 (100), 79 (43), 65 (9), 53 (11), 41 (28).

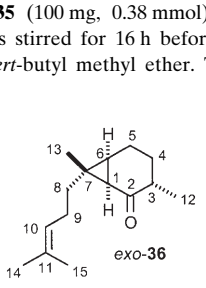
(1*R,6*S**,7*R**)-3,7-Dimethyl-7-(4-methylpent-3-enyl)bicyclo[4.1.0]hept-2-en-2-yl acetate (35)**: A flame dried 100 mL two-necked flask was charged with $AuCl_3$ (57 mg, 0.19 mmol). After adding a solution of acetate **33** (1.0 g, 3.81 mmol) in 1,2-dichloroethane (40 mL) the resulting mixture was stirred under argon for 4 h during which a characteristic color change from orange to purple and finally blue was observed. The reaction mixture was filtered through a pad of Celite (hexanes/ethyl acetate 3:1) and the filtrate was evaporated yielding the crude product **35** (~1 g) which was used without further purification. Characteristic data: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.08 (m, 1H), 2.24 (dd, J = 7.9, 16.2 Hz, 1H), 2.15 (s, 3H), 2.08–1.95 (m, 3H), 1.82 (m, 1H), 1.78 (m, 1H), 1.67 (s, 3H), 1.65 (m, 1H), 1.60 (s, 3H), 1.54 (s, 3H), 1.23 (m, 1H), 1.21 (ddd, J = 6.7, 9.3, 13.7 Hz, 1H), 1.10 (m, 1H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 140.3, 130.2, 123.7, 118.3, 41.3, 28.8, 28.1, 24.8, 24.6, 23.2, 22.4, 20.0, 16.7, 16.65, 15.2, 12.1; IR (KAP): $\tilde{\nu}$ = 2966, 2916, 2852, 1753, 1447, 1367, 1209, 1096 cm^{-1}; MS (EI): m/z (%): 262 (24) [M^+], 220 (75), 151 (46), 135 (100), 109 (34), 69 (42), 43 (76); HRMS (EI): m/z: calcd for $C_{17}H_{26}O_2$: 262.1933; found: 262.1930 [M^+].

(1*R,6*S**,7*R**)-3,7-Dimethyl-7-(4-methylpent-3-enyl)-bicyclo-[4.1.0]heptan-2-one (*endo*-36)**: A solution of the crude acetate **35** (1.0 g, 3.81 mmol) in THF (5 mL) was added dropwise at −78 °C to a suspension of $LiAlH_4$ (217 mg, 5.72 mmol) in THF (15 mL). The reaction mixture was allowed to reach ambient temperature overnight before it was quenched by careful addition of aq. sat. Na_2SO_4 at 0 °C. After filtration over Celite and extensive rinsing of the filter cake with *tert*-butyl methyl ether, the combined filtrates were washed with brine, dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 20:1) to give *endo*-**36** as a yellow liquid (470 mg, 60% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.04 (t(sept), J = 1.4, 7.2 Hz, 1H, H-10), 2.13 (d(qi), J = 6.4, 12.4 Hz, 1H, H-3), 2.10 (dddd, J = 6.2, 7.0, 12.2, 14.8 Hz, 1H, H-5a), 2.01 (m, 2H, H-9a,b), 1.98 (dddd, J = 1.8, 2.6, 6.0, 14.8 Hz, 1H, H-5b), 1.80 (dddd, J = 2.6, 6.2, 7.2, 14.6 Hz, 1H, H-4a), 1.65 (d, J = 1.2 Hz, 3H, H-15), 1.58 (d, J = 1.2 Hz, 3H, H-14), 1.40 (d, J = 7.6 Hz, 1H, H-1), 1.39 (dddd, J = 6.0, 12.0, 12.4, 14.6 Hz, 1H, H-4b), 1.38 (ddd, J = 5.8, 9.6, 13.6 Hz, 1H, H-8a), 1.20 (ddd, J = 1.6, 6.1, 7.8 Hz, 1H, H-6), 1.05 (s, 3H, H-13), 1.04 (m, 1H, H-8b), 1.00 (d, J = 6.6 Hz, 3H, H-12); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.2 (C-2), 131.6 (C-11), 124.0 (C-10), 43.8 (C-8), 42.8 (C-3), 33.6 (C-1), 28.6 (C-4), 27.2, 25.7 (C-15), 25.0 (C-6), 24.9, 19.4, 17.6 (C-14), 15.2 (C-13), 14.2 (C-12); IR (KAP): $\tilde{\nu}$ = 2963, 2915, 1695, 1450, 1375, 1317, 1250, 1213, 1178, 1099, 1077, 886, 829 cm^{-1}; MS (EI): m/z (%): 220 (14) [M^+], 151 (37), 138 (22), 123 (31), 107 (25), 93 (26), 81 (100), 69 (94), 55 (27), 41 (94); HRMS (EI): m/z: calcd for $C_{15}H_{24}O_2$: 220.1827; found: 220.1825 [M^+].



endo-**36**

Solvolytic cleavage of the enol acetate: K_2CO_3 (35 mg, 0.25 mmol) was added to a solution of the crude acetate **35** (100 mg, 0.38 mmol) in MeOH (4 mL) and the resulting mixture was stirred for 16 h before it was diluted with water and extracted with *tert*-butyl methyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated. Purification of the residue by flash chromatography (hexanes/ethyl acetate 20:1) furnished product **36** as a yellow liquid in a diastereomeric ratio of 6.7:1 in favor of the *exo*-isomer (62 mg, 74% over two steps).



exo-**36**

^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 5.07$ (t(sept), $J = 1.4$, 7.2 Hz, 1H, H-10), 2.06 (m, 2H, H-9a,b), 2.03 (m, 1H, H-5a), 1.95 (m, 1H, H-3), 1.81 (m, 1H, H-4a), 1.67 (d, $J = 1.4$ Hz, 3H, H-15), 1.60 (s, 3H, H-14), 1.62–1.50 (m, 3H, H-4b, H-5b, H-6), 1.38 (d, $J = 7.6$ Hz, 1H, H-1), 1.31 (m, 1H, H-8a), 1.24 (m, 1H, H-8b), 1.17 (s, 3H, H-13), 0.99 (d, $J = 6.6$ Hz, 3H, H-12); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 211.2$ (C-2), 131.9 (C-11), 124.3 (C-10), 43.8 (C-3), 43.7 (C-8), 35.9 (C-4), 34.9 (C-1), 31.49, 31.47 (C-6), 25.7 (C-15), 25.5, 19.2 (C-5), 17.7 (C-14), 15.8 (C-12), 14.1 (C-13).

(1*R,6*S**,7*R**)-3,7-Dimethyl-7-(4-methylpent-3-enyl)bicyclo[4.1.0]hept-2-ene (2-sesquicarene, 39)**: *n*BuLi (1.6 M in hexanes, 0.195 mL, 0.31 mmol) was added dropwise to a solution of $(i\text{Pr})_2$NH (0.048 mL, 0.34 mmol) in THF (1 mL) at 0 °C and the resulting mixture was stirred for 30 min at that temperature before it was cooled to −78 °C. A solution of ketone **36** (63 mg, 0.28 mmol) in THF (2 mL) was slowly added and the mixture stirred for 16 h at that temperature before a solution of *N*-(2-pyridyl)bis-triflimide (102 mg, 0.28 mmol) in THF (2 mL) was introduced and the reaction allowed to reach ambient temperature. The mixture was diluted with *tert*-butyl methyl ether and successively washed with water and brine. The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated to give enol triflate **38** which was used without further purification in the following step.

A solution of crude **38** (100 mg, 0.28 mmol) and Et_3SiH (0.063 mL, 0.4 mmol) in THF (1 mL) was added to a suspension of $[Pd(PPh_3)_4]$ (6.6 mg, 0.0057 mmol) and LiCl (36 mg, 0.85 mmol) in THF (2 mL). The mixture was stirred at 60 °C for 1.5 h before it was diluted with pentane and washed with aq. $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography (pentane) to give sesquicarene **39** as a colorless liquid (43 mg, 74% over two steps). ^{1}H NMR (400 MHz, C_6D_6): $\delta = 5.36$ (m, 1H), 4.93 (tddd, $J = 1.3$, 2.7, 5.5, 8.5 Hz, 1H), 1.87 (dd, $J = 7.5$, 15.1 Hz, 2H), 1.60 (m, 1H), 1.53 (m, 1H), 1.40 (d, $J = 0.9$ Hz, 3H), 1.36 (ddd, $J =$ 2.9, 5.7, 13.7 Hz, 1H), 1.35 (s, 3H), 1.29 (s, 3H), 1.25 (m, 1H), 1.10 (m, 1H), 0.95 (ddd, $J = 7.2$, 9.0, 13.4 Hz, 1H), 0.78 (dd, $J = 4.3$, 8.4 Hz, 1H), 0.67 (s, 3H), 0.55 (ddd, $J = 2.9$, 5.0, 10.7 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 132.3$, 129.3, 124.0, 118.6, 41.9, 27.1, 26.4, 24.7, 24.5, 22.6, 21.4, 19.4, 16.9, 16.3, 11.5; IR (KAP): $\tilde{\nu} =$ 2964, 2912, 2853, 1448, 1377, 1209, 1098, 1066, 993, 983, 968, 953, 825 cm^{-1}; MS (EI): *m*/*z* (%): 204 (40) [M^+], 189 (4), 161 (15), 147 (9), 134 (21), 119 (100), 107 (36), 93 (78), 79 (36), 69 (31), 55 (37), 41 (68), 29 (15); elemental analysis calcd (%) for $C_{15}H_{24}$ (204.35): C 88.16, H 11.84; found: C 88.26, H 11.78.

(1*R,6*S**,7*S**)-3,7-Dimethyl-7-(4-methylpent-3-enyl)bicyclo[4.1.0]hept-2-en-2-yl acetate (48)**: A flame dried 25 mL two-necked flask was charged with $AuCl_3$ (15 mg, 0.05 mmol). After a solution of acetate **47** (262 mg, 1 mmol) in 1,2-dichloroethane (10 mL) had been added, the resulting mixture was stirred under argon for 4 h during which a characteristic color change from orange to purple and finally to blue was observed. The mixture was filtered through a pad of Celite (hexanes/ethyl acetate 3:1) and the filtrate was evaporated yielding crude **48** (258 mg) which was pure enough for further use without purification. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.14$ (m, 1H), 2.26 (m, 1H), 2.16 (s, 3H), 2.11–1.94 (m, 2H), 1.82 (m, 2H), 1.69 (s, 3H), 1.65 (m, 1H), 1.61 (s, 3H), 1.53 (s, 3H), 1.35 (m, 1H), 1.31 (ddd, $J = 5.7$, 10.6, 10.8 Hz, 1H), 1.12 (m, 2H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.6$, 141.2, 131.2, 125.2, 119.8, 30.2, 30.0, 28.8, 25.9, 25.4, 25.3, 25.2, 24.2, 21.1, 18.1, 17.6, 16.2; IR (KAP): $\tilde{\nu} =$ 2923, 2857, 1753, 1728, 1448, 1368, 1227, 1210, 1095, 1009, 889 cm^{-1}; MS (EI): *m*/*z* (%): 262 (24) [M^+], 220 (74), 202 (20), 177 (12), 164 (11), 151 (53), 135 (100), 121 (20), 109 (37), 91 (17), 79 (13), 69 (37), 55 (22), 43 (81); HRMS (EI): *m*/*z*: calcd for $C_{17}H_{26}O_2$: 262.1933; found: 262.1934 [M^+].

(1*R,3*R**,6*S**,7*S**)-3,7-Dimethyl-7-(4-methylpent-3-enyl)bicyclo-[4.1.0]heptan-2-one (49)**: K_2CO_3 (17 mg, 0.12 mmol) was added to a solution of crude enol acetate **48** (131 mg, 0.5 mmol) in MeOH (5 mL) and the resulting mixture was stirred for 16 h before it was diluted with water and extracted with *tert*-butyl methyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (hexanes/ethyl acetate 40:1) to give ketone **49** as a yellow liquid in a diastereomeric ratio of 4.5:1 in favor of the *exo*-diastereomer (62 mg, 65% over two steps). Characteristic data of the *exo*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.07$ (m, 1H), 2.15–1.89 (m, 5H), 1.80 (m, 1H), 1.65 (s, 3H), 1.59 (m, 3H), 1.55 (s, 3H), 1.49 (dd, $J = 5.4$, 11.1 Hz, 1H), 1.44 (d, $J = 7.6$ Hz, 1H), 1.12 (s, 3H), 1.02 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 211.8$, 132.1, 124.0, 43.6, 35.9, 35.8, 33.1, 32.0, 30.9, 26.7, 25.8, 25.1, 19.1, 17.6, 15.7. Characteristic data of the *endo*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.07$ (m, 1H), 2.19–2.08 (m, 4H), 2.03 (m, 1H), 1.85 (m, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.53 (ddd, $J = 5.2$, 11.2, 14.4 Hz, 1H), 1.46 (d, $J = 7.6$ Hz, 1H), 1.42 (m, 1H), 1.26 (m, 1H), 1.25 (m, 1H), 1.11 (s, 3H), 1.04 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 210.3$, 130.8, 123.3, 41.9, 34.1, 32.4, 27.9, 27.4, 26.2, 25.6, 24.8, 24.3, 19.0, 16.7, 13.5; IR (KAP): $\tilde{\nu} =$ 2962, 2928, 2868, 1692, 1452, 1376, 1327, 1181, 1083, 1071, 1000, 889 cm^{-1}; MS (EI): *m*/*z* (%): 220 (3) [M^+], 151 (25), 138 (100), 111 (23), 93 (13), 81 (52), 69 (56), 55 (16), 41 (60); HRMS (EI): *m*/*z*: calcd for $C_{15}H_{24}O$: 220.1827; found: 220.1828 [M^+].

(1*R,6*S**,7*S**)-3,7-Dimethyl-7-(4-methylpent-3-enyl)bicyclo[4.1.0]hept-2-ene (episesquicarene, 51)**: *n*BuLi (1.5 M in hexanes, 0.4 mL, 0.6 mmol) was added dropwise to a solution of $(i\text{Pr})_2$NH (0.091 mL, 0.65 mmol) in THF (2 mL) at 0 °C and the resulting mixture was stirred for 30 min before it was cooled to −78 °C. A solution of ketone **49** (120 mg, 0.54 mmol) in THF (1.4 mL) was slowly added and stirring continued for 16 h before a solution of *N*-(5-chloro-2-pyridyl)bistriflimide (235 mg, 0.60 mmol) in THF (2 mL) was introduced and the reaction was allowed reach ambient temperature. The mixture was diluted with *tert*-butyl methyl ether and successively washed with water and brine. The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated to give enol triflate **50** as a pale brown oil which was used without further purification in the following step.

A solution of this crude triflate (150 mg, 0.43 mmol) and Et_3SiH (0.680 mL, 4.26 mmol) in THF (1 mL) was added to a suspension of $[Pd(PPh_3)_4]$ (9.8 mg, 0.0085 mmol) and LiCl (54 mg, 1.28 mmol) in THF (3 mL). The reaction was stirred at ambient temperature for 5 h before it was diluted with pentane and washed with aq. $NaHCO_3$ and brine. The combined organic layers were dried over Na_2SO_4 and evaporated, and the residue was purified by flash chromatography (pentane) to furnish episesquicarene **51** as a colorless liquid (83 mg, 75% over two steps). ^{1}H NMR (400 MHz, C_6D_6): $\delta = 5.66$ (m, 1H), 5.26 (m, 1H), 2.13 (dd, $J =$ 7.4, 15.8 Hz, 2H), 1.91 (m, 1H), 1.84 (ddd, $J = 5.9$, 11.1, 15.0 Hz, 1H), 1.71 (m, 1H), 1.66 (d, $J = 0.8$ Hz, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.39–1.34 (m, 3H), 1.04 (s, 3H), 1.02 (m, 1H), 0.81 (ddd, $J = 3.4$, 8.0, 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 133.9$, 130.7, 125.8, 119.9, 30.4, 28.1, 27.9, 26.2, 25.9, 25.8, 24.0, 23.9, 22.1, 18.6, 17.6; IR (KAP): $\tilde{\nu} =$ 2956, 2912, 2858, 1448, 1376, 1078, 1025, 990, 969, 827 cm^{-1}; MS (EI): *m*/*z* (%): 204 (41) [M^+], 161 (16), 147 (9), 134 (20), 119 (100), 107 (36), 93 (79), 79 (39), 69 (29), 55 (36), 41 (66), 29 (15); elemental analysis calcd (%) for $C_{15}H_{24}$ (204.35): C 88.16, H 11.84; found: C 88.24, H 11.73.

Acknowledgements

We thank Dr. R. Mynott and P. Philipps for their invaluable help with numerous NMR analyses. Generous financial support by the Max-Planck-Society, the Fonds der Chemischen Industrie, and the Merck Research Council is gratefully acknowledged. Moreover, we thank Umicore AG & Co KG, Hanau, for a gift of noble metal salts.

[1] H. Stickler, J. B. Davis, G. Ohloff, *Helv. Chim. Acta* **1976**, *59*, 1328–1332.
[2] Ohloff et al. assumed that the rearrangement is triggered by coordination of the zinc cation to the double bond, whereas all experimental and computational evidence presently available suggests that noble metal catalysts initiate the transformation by complexation of the triple bond.
[3] V. Rautenstrauch, *J. Org. Chem.* **1984**, *49*, 950–952.
[4] a) E. Mainetti, V. Mouriès, L. Fensterbank, M. Malacria, J. Marco-Contelles, *Angew. Chem.* **2002**, *114*, 2236–2239; *Angew. Chem. Int.*

Ed. **2002**, *41*, 2132–2135; b) S. Anjum, J. Marco-Contelles, *Tetrahedron* **2005**, *61*, 4793–4803; c) C. Blaszykowski, Y. Harrak, M.-H. Goncalves, J.-M. Cloarec, A.-L. Dhimane, L. Fensterbank, M. Malacria, *Org. Lett.* **2004**, *6*, 3771–3774; d) 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*, 8656–8657; e) X. Shi, D. J. Gorin, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 5802–5803; f) B. A. B. Prasad, F. K. Yoshimoto, R. Sarpong, *J. Am. Chem. Soc.* **2005**, *127*, 12468–12469; g) K. Kato, Y. Yamamoto, H. Akita, *Tetrahedron Lett.* **2002**, *43*, 6587–6590.

[5] V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655.

[6] For an intermolecular version see: a) K. Miki, K. Ohe, S. Uemura, *J. Org. Chem.* **2003**, *68*, 8505–8513; b) K. Miki, K. Ohe, S. Uemura, *Tetrahedron Lett.* **2003**, *44*, 2019–2022.

[7] Reviews: a) M. Méndez, A. M. Echavarren, *Eur. J. Org. Chem.* **2002**, 15–28; b) G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1*, 215–236; c) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813–834; d) M. Méndez, V. Mamane, A. Fürstner, *Chemtracts* **2003**, *16*, 397–425; e) C. Bruneau, *Angew. Chem.* **2005**, *117*, 2380–2386; *Angew. Chem. Int. Ed.* **2005**, *44*, 2328–2334.

[8] A. Fürstner, H. Szillat, B. Gabor, R. Mynott, *J. Am. Chem. Soc.* **1998**, *120*, 8305–8314.

[9] For leading references on related cycloisomerization reactions of enynes catalyzed by platinum species see: a) N. Chatani, N. Furukawa, H. Sakurai, S. Murai, *Organometallics* **1996**, *15*, 901–903; b) J. Blum, H. Beer-Kraft, Y. Badrieh, *J. Org. Chem.* **1995**, *60*, 5567–5569; c) M. Méndez, M. P. Muñoz, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2001**, *123*, 10511–10520; d) B. Martín-Matute, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2003**, *125*, 5757–5766; e) C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Chem. Eur. J.* **2003**, *9*, 2627–2635; f) S. Oi, I. Tsukamoto, S. Miyano, Y. Inoue, *Organometallics* **2001**, *20*, 3704–3709; g) L. Charruault, V. Michelet, R. Taras, S. Gladiali, J.-P. Genêt, *Chem. Commun.* **2004**, 850–851; h) F. Marion, J. Coulomb, C. Courillon, L. Fensterbank, M. Malacria, *Org. Lett.* **2004**, *6*, 1509–1511.

[10] a) A. Fürstner, H. Szillat, F. Stelzer, *J. Am. Chem. Soc.* **2000**, *122*, 6785–6786; b) A. Fürstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869; c) A. Fürstner, V. Mamane, *J. Org. Chem.* **2002**, *67*, 6264–6267; d) A. Fürstner, V. Mamane, *Chem. Commun.* **2003**, 2112–2213; e) V. Mamane, P. Hannen, A. Fürstner, *Chem. Eur. J.* **2004**, *10*, 4556–4575; f) A. Fürstner, P. W. Davies, T. Gress, *J. Am. Chem. Soc.* **2005**, *127*, 8244–8245; g) A. Fürstner, P. W. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025.

[11] Short reviews on gold-catalyzed reactions: a) A. S. K. Hashmi, *Gold Bull.* **2004**, *37*, 51–65; b) A. Hoffmann-Röder, N. Krause, *Org. Biomol. Chem.* **2005**, *3*, 387–391; c) G. Dyker, *Angew. Chem.* **2000**, *112*, 4407–4409; *Angew. Chem. Int. Ed.* **2000**, *39*, 4237–4239.

[12] For leading references on gold-catalyzed cycloisomerizations of enynes see: a) C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem.* **2004**, *116*, 2456–2460; *Angew. Chem. Int. Ed.* **2004**, *43*, 2402–2406; b) A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem.* **2000**, *112*, 2382–2385; *Angew. Chem. Int. Ed.* **2000**, *39*, 2285–2288; c) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554; d) J. Zhu, A. R. Germain, J. A. Porco, Jr., *Angew. Chem.* **2004**, *116*, 1259–1263; *Angew. Chem. Int. Ed.* **2004**, *43*, 1239–1243; e) M. Georgy, V. Boucard, J.-M. Campagne, *J. Am. Chem. Soc.* **2005**, *127*, 14180–14181; f) F. Gagosz, *Org. Lett.* **2005**, *7*, 4129–4132; g) N. Mézailles, L. Richard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133–4136; h) T. Yao, X. Zhang, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 7679–7685; i) M. H. Suhre, M. Reif, S. F. Kirsch, *Org. Lett.* **2005**, *7*, 3925–3927; j) D. J. Gorin, N. R. Davis, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 11260–11261; k) J. P. Markham, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 9708–9709; l) C. Nieto-Oberhuber, S. Lopez, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179; m) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2005**, *127*, 6962–6963; n) B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978–15979; o) M. R. Luzung, J. P. Markham, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 10858–10859; p) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 11806–11807.

[13] For leading references on related cycloisomerizations of enynes catalyzed by other transition-metal cations see: a) B. M. Trost, M. K. Trost, *J. Am. Chem. Soc.* **1991**, *113*, 1850–1852; b) N. Chatani, T. Morimoto, T. Muto, S. Murai, *J. Am. Chem. Soc.* **1994**, *116*, 6049–6050; c) N. Chatani, H. Inoue, T. Morimoto, T. Muto, S. Murai, *J. Org. Chem.* **2001**, *66*, 4433–4436; d) N. Asao, T. Nogami, S. Lee, Y. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 10921–10925; e) N. Chatani, H. Inoue, T. Kotsuma, S. Murai, *J. Am. Chem. Soc.* **2002**, *124*, 10294–10295; f) T. Shibata, Y. Kobayashi, S. Maekawa, N. Toshida, K. Takagi, *Tetrahedron* **2005**, *61*, 9018–9024; g) Y. Chen, D. M. Ho, C. Lee, *J. Am. Chem. Soc.* **2005**, *127*, 12184–12185; h) M. Eckert, F. Monnier, G. T. Shchetnikov, I. D. Titanyuk, S. N. Osipov, L. Toupet, S. Dérien, P. H. Dixneuf, *Org. Lett.* **2005**, *7*, 3741–3743 and references therein.

[14] The transition state for the rate-determining step of path II was calculated to be about 2 kcal mol^{-1} lower in energy in the gas phase, compare: E. Soriano, P. Ballesteros, J. Marco-Contelles, *Organometallics* **2005**, *24*, 3182–3191.

[15] Parts of this study have been published in preliminary form, see: A. Fürstner, P. Hannen, *Chem. Commun.* **2004**, 2546–2547.

[16] α-Diazoketone cyclizations were pioneered by: G. Stork, J. Ficini, *J. Am. Chem. Soc.* **1961**, *83*, 4678.

[17] a) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1998**; b) H. M. L. Davies, in *Comprehensive Organic Synthesis, Vol. 4* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 1031–1067; c) A. Padwa, K. E. Krumpe, *Tetrahedron* **1992**, *48*, 5385–5453.

[18] Cubebol is also called cubebanol in the older literature.

[19] a) F. Vonasek, V. Herout, F. Sorm, *Collect. Czech. Chem. Commun.* **1960**, *25*, 919–925; b) Y. Ohta, T. Sakai, Y. Hirose, *Tetrahedron Lett.* **1966**, 6365–6370; c) Y. Ohta, K. Ohara, Y. Hirose, *Tetrahedron Lett.* **1968**, 4181–4184.

[20] a) X. H. Chen, S.-S. Kim, T. Kashiwagi, S.-I. Tebayashi, M. Horiike, *Biosci. Biotechnol. Biochem.* **2001**, *65*, 1434–1437; b) S. de Rosa, A. de Guilio, C. Iodice, N. Zavodink, *Phytochemistry* **1994**, *37*, 1327–1330; c) C. Tringali, M. Piattelli, C. Spatafora, *Phytochemistry* **1995**, *40*, 827–831.

[21] a) M. Suzuki, N. Kowata, E. Kurosawa, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2366–2368; b) J. D. Connolly, W. R. Phillips, S. Huneck, *Phytochemistry* **1982**, *21*, 233–234; c) K. L. McPhail, M. T. Davies-Coleman, J. Starmer, *J. Nat. Prod.* **2001**, *64*, 1183–1190.

[22] a) F. Bohlmann, J. Jakupovic, W. Vogel, *Phytochemistry* **1982**, *21*, 1153–1154; b) H. He, J. Salva, R. F. Catalos, D. J. Faulkner, *J. Org. Chem.* **1992**, *57*, 3191–3194; c) H.-F. Wong, G. D. Brown, *Phytochemistry* **2002**, *59*, 99–104; d) C. Pizza, N. de Tommasi, *J. Nat. Prod.* **1987**, *50*, 784–789.

[23] a) K. Kurata, K. Shiraishi, T. Takato, K. Taniguchi, M. Suzuki, *Chem. Lett.* **1988**, 1629–1632; b) R. Takeda, K. Katoh, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1265–1266; c) M. Kobayashi, B. W. Son, Y. Kyogoku, I. Kitagawa, *Chem. Pharm. Bull.* **1984**, *32*, 1667–1670; d) S. H. Kang, W. J. Kim, Y. B. Chae, *Tetrahedron Lett.* **1988**, *29*, 5169–5172.

[24] a) E. Piers, R. W. Britton, W. de Waal, *Tetrahedron Lett.* **1969**, 1251–1253; b) E. Piers, R. W. Britton, W. de Waal, *Can. J. Chem.* **1971**, *49*, 12–19; c) A. Tanaka, H. Uda, A. Yoshikoshi, *J. Chem. Soc. D* **1969**, 308; d) A. Tanaka, R. Tanaka, H. Uda, A. Yoshikoshi, *J. Chem. Soc. Perkin Trans. 1* **1972**, 1721–1727; e) S. Torii, T. Okamoto, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 771–774; f) for a study towards cubebene using different methodology see: H. Hagiwara, F. Abe, H. Uda, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2651–2655.

[25] E. J. Corey, D. Y. Gin, *Tetrahedron Lett.* **1996**, *37*, 7163–7166.

[26] The following literature procedures were tested which led in our hands to the diastereomeric ratios (*dr*) indicated: a) M. Yamashita, Y. Kato, R. Suemitsu, *Chem. Lett.* **1980**, 847–848 (*dr* 73:27); b) J. H. Tatlock, V. J. Kahlish, H. E. Parge, D. R. Knighton, R. E. Showalter, C. T. Lewis, J. V. French, J. E. Villafranca, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2489–2494 (*dr* 80:20); c) J. M. Fortunato, B. Ganem, *J. Org. Chem.* **1976**, *41*, 2194–2200 (*dr* 83:17).

[27] D. L. Comins, A. Dehghani, *Tetrahedron Lett.* **1992**, *33*, 6299–6302.
[28] Other methods for the introduction of the side chain have been briefly explored but remained largely unsuccessful. This includes attempted alkylation of the vinyllithium species derived from the sulfonyl hydrazone of carvomenthone **17**, with or without prior transmetalation to a vinylcopper species.
[29] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156; b) R. K. Boeckman, P. Shao, J. J. Mullins, *Org. Synth.* **2000**, *77*, 141–152.
[30] a) M. Suzuki, Y. Kimura, S. Terashima, *Chem. Pharm. Bull.* **1986**, *34*, 1531–1539; b) recent review: H.-J. Liu, K.-S. Shia, X. Shang, B.-Y. Zhu, *Tetrahedron* **1999**, *55*, 3803–3830.
[31] For previous applications of organocerium reagents from our laboratory see: a) A. Fürstner, K. Langemann, *J. Org. Chem.* **1996**, *61*, 8746–8749; b) A. Fürstner, H. Weintritt, *J. Am. Chem. Soc.* **1998**, *120*, 2817–2825.
[32] a) K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem.* **1997**, *109*, 297–300; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285–288; b) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97–102.
[33] Although the diastereoselectivity of the transfer hydrogenation was only ~85:15 in both cases, pure samples of the individual isomers can be obtained by careful flash chromatography at this stage. The absolute stereochemistry of the newly formed chiral center was confirmed by the analysis of the corresponding Mosher esters and is in line with the predictions of Noyori's model.
[34] W. E. Thiessen, *Acta Crystallogr. Sect. B* **1977**, *33*, 3838–3842.
[35] a) B. Scheiper, M. Bonnekessel, H. Krause, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3943–3949; b) for a mechanistic study of this transformation see: A. Fürstner, H. Krause, C. W. Lehmann, *Angew. Chem.* **2006**, *118*, 454–458; *Angew. Chem. Int. Ed.* **2006**, *45*, 440–444.
[36] A. Fürstner, R. Martin, *Chem. Lett.* **2005**, 624–629.
[37] Methodology development from our group: a) A. Fürstner, A. Leitner, *Angew. Chem.* **2002**, *114*, 632–635; *Angew. Chem. Int. Ed.* **2002**, *41*, 609–612; b) A. Fürstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856–13863; c) A. Fürstner, M. Méndez, *Angew. Chem.* **2003**, *115*, 5513–5515; *Angew. Chem. Int. Ed.* **2003**, *42*, 5355–5357; d) R. Martin, A. Fürstner, *Angew. Chem.* **2004**, *116*, 4045–4047; *Angew. Chem. Int. Ed.* **2004**, *43*, 3955–3957; e) A. Fürstner, R. Martin, K. Majima, *J. Am. Chem. Soc.* **2005**, *127*, 12236–12237; f) A. Fürstner, A. Leitner, G. Seidel, *Org. Synth.* **2005**, *81*, 33–42.
[38] Applications: a) A. Fürstner, A. Leitner, *Angew. Chem.* **2003**, *115*, 320–323; *Angew. Chem. Int. Ed.* **2003**, *42*, 308–311; b) A. Fürstner, D. De Souza, L. Parra-Rapado, J. T. Jensen, *Angew. Chem.* **2003**, *115*, 5516–5518; *Angew. Chem. Int. Ed.* **2003**, *42*, 5358–5360; c) G. Seidel, D. Laurich, A. Fürstner, *J. Org. Chem.* **2004**, *69*, 3950–3952; d) B. Scheiper, F. Glorius, A. Leitner, A. Fürstner, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11960–11965; e) O. Lepage, E. Kattnig, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126*, 15970–15971; f) A. Fürstner, L. Turet, *Angew. Chem.* **2005**, *117*, 3528–3532; *Angew. Chem. Int. Ed.* **2005**, *44*, 3462–3466; g) A. Fürstner, D. Kirk, M. D. B. Fenster, C. Aïssa, D. De Souza, O. Müller, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 8103–8108.
[39] As such, compound **30** constitutes the *nor*-ketone of 6-*epi*-cubebene, a natural product that was isolated only recently from the essential oils of *Solidago canadensis*, see: A. A. Kasali, O. Ekundayo, C. Paul, W. A. König, *Phytochemistry* **2002**, *59*, 805–810.
[40] It should be noted, however, that these data do not allow us to conclude that it is the *only* pathway that is operative; at least theoretically, the possibility remains that both pathways are populated to some extent.
[41] For an example of a gold-catalyzed skeletal rearrangement in which the stereochemistry of the substrate affects the outcome of the reaction see ref. [12f].
[42] A related approach to the carene family has been published after our preliminary communication (ref. [15]) although the natural products per se have not been prepared, see ref. [4b].
[43] Y. Ohta, Y. Hirose, *Tetrahedron Lett.* **1968**, 1251–1254.
[44] For previous entries into the carane family by α-diazoketone cyclizations see: a) R. M. Coates, R. M. Freidinger, *Tetrahedron* **1970**, *26*, 3487–3493; b) K. Mori, M. Matsui, *Tetrahedron* **1970**, *26*, 2801–2814; c) E. J. Corey, K. Achiwa, *Tetrahedron Lett.* **1969**, 1837; d) E. J. Corey, K. Achiwa, *Tetrahedron Lett.* **1969**, 3257–3258; e) G. Büchi, J. D. White, *J. Am. Chem. Soc.* **1964**, *86*, 2884–2887; f) F. Medina, A. Manjarrez, *Tetrahedron* **1964**, *20*, 1807–1810; g) see also: E. J. Corey, K. Achiwa, J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **1969**, *91*, 4318–4320; h) J. J. Plattner, U. T. Bhalerao, H. Rapoport, *J. Am. Chem. Soc.* **1969**, *91*, 4933–4934.
[45] For syntheses of carene terpenoids employing other methods see the following for representative examples: a) C. R. Johnson, J. F. Kadow *J. Org. Chem.* **1987**, *52*, 1493–1500; b) W. B. Motherwell, L. R. Roberts, *Tetrahedron Lett.* **1995**, *36*, 1121–1124; c) T. Uyehara, K. Ogata, J. Yamada, T. Kato, *J. Chem. Soc. Chem. Commun.* **1983**, 17–18; d) K. Kitatani, T. Hiyama, H. Nozaki, *J. Am. Chem. Soc.* **1976**, *98*, 2362–2364; e) M. Franck-Neumann, P. Geoffroy, M. Miesch, F. Zaragoza-Dörwald, *Tetrahedron Lett.* **1990**, *31*, 4121–4124 and references therein.
[46] Although two consecutive acetyl migrations via intermediates such as **B** and **C** could also explain the formation of the allenyl acetate **34**, previous literature reports generally assume a [3,3]-sigmatropic pathway for reactions of this type, see ref. [48].
[47] The catalytic activity of the following metal salts and complexes in 6 different solvent systems (toluene, CH_2Cl_2, 1,2-dichloroethane, DME, THF, MeCN) has been screened: $PtCl_2$, $PtCl_4$, $[Pt(acac)_2]$, $[(cod)PtCl_2]$, $PtBr_2$, PtI_2, $Pt(CN)_2$, $[(PhCN)_2PtCl_2]$, $AgBF_4$, AgOTf, $PdCl_2$, InCl, $InCl_3$, $RuCl_3{\cdot}nH_2O$, $FeCl_3$, ZnI_2, $CoBr_2{\cdot}nH_2O$, $IrCl_3$, $NiCl_2$, $[(cod)RhCl]_2$, $[(CO)_3RuCl_2]_2$, $[(Ph_3P)AuCl]/AgSbF_6$.
[48] For precedence see: a) U. Koch-Pomeranz, H.-J. Hansen, H. Schmid, *Helv. Chim. Acta* **1973**, *56*, 2981–3004; b) K. Cariou, E. Mainetti, L. Fensterbank, M. Malacria, *Tetrahedron* **2004**, *60*, 9745–9755 and references therein.
[49] K. M. Saplay, R. Sahni, N. P. Damodaran, S. Dev, *Tetrahedron* **1980**, *36*, 1455–1461.
[50] Other conceivable methods for the dehydration of alcohol **37** gave much more complex product mixtures.
[51] W. J. Scott, J. K. Stille, *J. Am. Chem. Soc.* **1986**, *108*, 3033–3040.
[52] The use of Bu_3SnH or $HCOOH/Et_3N$ as hydride sources led to somewhat lower yields in this particular transformation (60 and 41%, respectively).
[53] A. G. Myers, K. R. Condroski, *J. Am. Chem. Soc.* **1995**, *117*, 3057–3083.
[54] It is worth mentioning that isosequicarene, a natural product isolated from *Haplopappus tenuisectus*, shows this particular configuration at C-7 but has a 3-carene rather than a 2-carene core, see: T. Uyehara, J. Yamada, T. Kato, F. Bohlmann, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 861–867.

Received: October 20, 2005
Published online: February 3, 2006

