Planar-Chiral (2*E*,7*Z*)- and (2*Z*,7*E*)-Cyclonona-2,7-dien-1-yl Carbamates by Asymmetric, Bis-Allylic α,α'-Cycloalkylation—Studies on Their Conformational Stability

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Dedicated to Professor Hans J. Schäfer on the occasion of his 65th birthday

Abstract: Enantiomerically enriched (>80% *ee*) (*M*,1*R*,2*Z*,7*E*)- and (*M*,1*R*,2*E*,7*Z*)-cyclonona-2,7-dienyl carbamates have been synthesized by an intramolecular cycloalkylation of the corresponding 1-lithio-9-chlorononа-2,7-dienyl carbamates. The enantioenriched precursors were generated by asymmetric deprotonation of the dienyl carbamates by means of *n*-BuLi/(−)-sparteine. The primarily obtained cyclononadienes, each bearing one element of planar and centre chirality, were formed by an α,α' coupling of both allylic moieties. These are the thermodynamically less favoured epimers, which arise from those allyllithiums bearing the carbamoyloxy residue in a 1-*endo* position. Both (*M*,*R*)-cyclononadienes epimerize slowly ($t_{1/2}$ = 209 min and 328 min at 308 K) with inversion of the planar chirality to the corresponding, more stable (*P*)-epimers (ratios 3:97 and 30:70). The kinetics were measured by ^{1}H NMR spectroscopy, the activation energies E_A were found to be 26.4 and 27.5 kcal mol^{-1}. From quantum-chemical calculations with the B3LYP density functional, the epimerization process was shown to consist of two coupled major conformational changes with high energy barriers. The calculated values match well with the observed ones.

Keywords: computer chemistry · cyclization · lithiation · planar chirality · sparteine

Introduction

Planar-chiral molecules are of considerable interest due to their unusual shape, their interesting properties and their difficult enantioselective synthesis.[1] An important class of planar-chiral compounds, which were first synthesized in the pioneering work of Cope, are *trans*-cycloalkenes.[2] *trans*-Cyclooctene, the best-known representative, is configurationally stable at room temperature ($t_{1/2} = 10^5$ s at 30 °C).[3] This configurational stability decreases dramatically with increasing ring size. Hence, *trans*-cyclononene is configurationally labile ($t_{1/2} = 6$ s at 30 °C) and *trans*-cyclodecene could not be isolated in an enantioenriched form ($t_{1/2} = 10^{-4}$ s at 30 °C).[4] A triple-substituted double bond[5] or the introduction of a second double bond[6] leads to a higher configurational stability. The previously described enantioenriched *trans*-cycloalkenes were obtained by resolutions of racemates or by enantioselective syntheses starting from already chiral precursors.

Since we had developed a novel intramolecular coupling reaction of allyllithium species,[7] which leads to enantioenriched cyclononadienes,[8] we applied this methodology to the synthesis of planar-chiral (2*E*,7*Z*)- and (2*Z*,7*E*)-cyclononadienes.[9] To the best of our knowledge, these are the first syntheses of enantioenriched *trans*-cycloalkenes by an enantioselective ring-closing reaction;[10] the chiral induction derives from the external ligand (−)-sparteine.[11] Due to the fact that both types of chirality, planar and centre, exist in these molecules, we also investigated a subsequent epimerization of the cyclization products.[12] Through ^{1}H NMR measurements and ab initio calculations it was possible to gain deeper insight into the epimerization mechanism.

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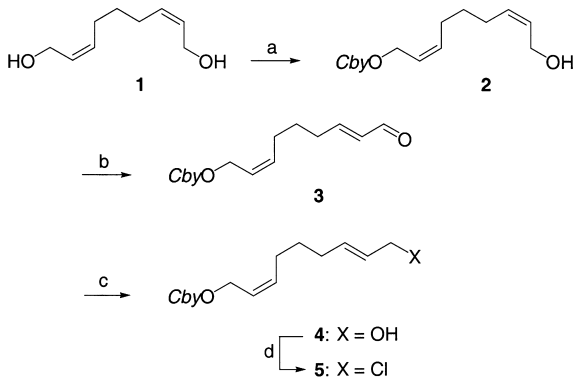
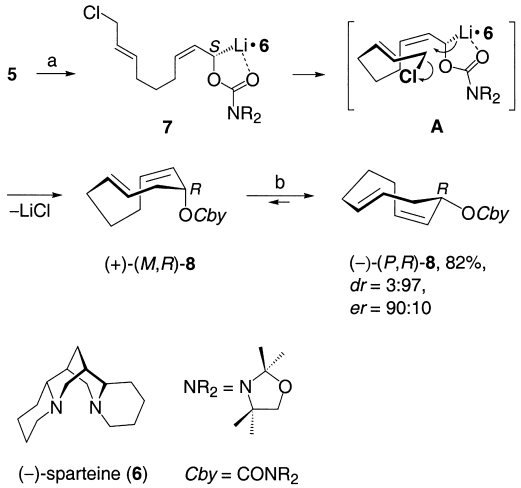
Results and Discussion

(2*Z*,7*E*)-Cyclononadiene: The synthesis of the cyclization precursor (2*Z*,7*E*)-**2** could be achieved starting from known (2*Z*,7*Z*)-nona-2,7-dien-1,9-diol (**1**).[13] Monocarbamoylation with 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyl chloride (*Cby*Cl)[14] furnished the carbamate **2**, whose 7-double bond was inverted by employing North's procedure.[15] The (*E*)-geometry of the 7-double bond of **3** was determined by the large olefinic coupling constant of 15.5 Hz in the ^{1}H NMR spectrum. 1,2-Reduction of the crude product and subsequent chlorination[16] of the allylic alcohol **4** furnished the cyclization precursor **5** (Scheme 1).



Scheme 1. Synthesis of the cyclization precursor **5**. Reagents: a) NaH, *Cby*Cl, THF, 85%; b) PCC, CH_2Cl_2; c) DIBAH, THF, $-78\,^\circ$C, 96%; d) *n*BuLi, CH_3SO_2Cl, LiCl, THF, 75%. The yield was calculated on the amount of CbyCl.

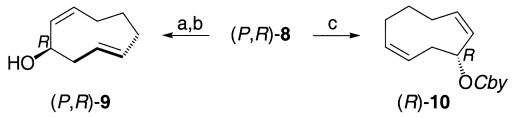
The enantioselective cyclization of (2*Z*,7*E*)-**5** was carried out by addition of *n*-BuLi to a solution of **5** and (−)-sparteine (**6**) in toluene at $-88\,^\circ$C. After stirring the reaction mixture for 2 h, a standard work-up procedure (during which the crude product was kept at room temperature) and flash chromatography furnished the pure diastereomeric cyclization products (+)-(*M*,*R*)-**8** and (−)-(*P*,*R*)-**8** in 82% yield and in a ratio of 7:3 (Scheme 2).[17] In the ^{1}H NMR spectrum of (*P*,*R*)-**8**, the typical



Scheme 2. Cyclization of **5** and subsequent epimerization. Reagents: a) *n*BuLi, **6**, toluene, $-88\,^\circ$C, 2 h; b) epimerization at 20–45 °C. The initial ratio of (*M*,*R*):(*P*,*R*) after flash chromatography was found to be approximately 7:3. It depends on the individual workup procedure due to slow epimerization.

olefinic coupling constants of a (*Z*)- and an (*E*)-double bond are visible (11.4 and 15.0 Hz). This cyclization reaction is initiated by an enantioselective, (−)-sparteine-mediated deprotonation of **5**. The allyllithium species (1*S*)-**7** is generated by abstraction of the 1-*pro*-*S* proton[18] and reacts, via conformation **A**, with inversion of configuration[19] at the lithium-bearing carbon atom and elimination of lithium chloride, to give the (2*Z*,7*E*)-cyclononadiene (+)-(*M*,*R*)-**8**. Since in **7**, and in **A**, the allyllithium moiety favours an *endo*-conformation,[20] the cyclization product (+)-(*M*,*R*)-**8** arises with the O*Cby*-group in a pseudo-axial position. Thus, (+)-(*M*,*R*)-**8** has a strong 1,3-allylic strain[21] between the axial O*Cby*-group and the methylene unit adjacent to the (*Z*)-double bond. Hence, a nearly complete epimerization towards the thermodynamically favoured (−)-(*P*,*R*)-**8** takes place; this puts the carbamate group in an equatorial position and minimizes the 1,3-allylic strain.

The enantiomeric ratio of (−)-(*P*,*R*)-**8** to (+)-(*M*,*R*)-**8** was determined to be 90:10, after cleavage of the carbamate group[22] and GLC of the obtained alcohol **9** on a chiral stationary phase. The configuration of the stereogenic carbon centre was identified by conversion of **8** into the known (1*R*,2*Z*,7*Z*)-cyclononadiene **10**[8] by an iodine-catalyzed inversion of the (*E*)-double bond (Scheme 3). The rela-



Scheme 3. Removal of the *Cby*-group and isomerization of the *E* double bond. Reagents: a) CH_3SO_3H, CH_3OH, reflux; b) KOH, CH_3OH, reflux, 87%, *er* = 90:10; c) I_2, hexane, 10 d, 10%.

tive configuration of **8** could be assigned to (*P*,*R*) by X-ray crystal-structure analysis.[23, 24] In addition, this structure clearly shows the thermodynamically favoured cross-conformation,[25] the pseudo-equatorial position of the O*Cby*-group and the torsional angle of the (*E*)-double bond of 147°.

The synthesis of a racemic sample of **8** was achieved in 81% yield by employing the achiral base *n*BuLi/TMEDA (*N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethanediaminein ether) at $-78\,^\circ$C.

One question arising from these observations was how to gain deeper insights into the epimerization mechanism? Fortunately, the 600 MHz ^{1}H NMR spectra of (*M*,*R*)-**8** and (*P*,*R*)-**8** show two separated sets of signals for the olefinic protons at $\delta = 4.99 - 5.13$ and at $\delta = 5.42 - 5.51$ (Figure 1). This allowed us to determine the *dr* at any time and at several temperatures. After establishment of the equilibrium of the epimerization we found a *dr* of 97:3 at 298 K. The resulting equilibrium constant of $K = 32.3$ has the highest value ever reported for an epimerization of a monosubstituted *trans*-cycloalkene. From this equilibrium constant for (*M*,*R*)-**8**/(*P*,*R*)-**8**, a value of $\Delta G = 2.1$ kcal mol^{-1} was calculated for the difference of the free enthalpies at 298 K.

The epimerization was also carried out at higher temperatures, while measuring the concentrations by ^{1}H NMR spectroscopy after suitable intervals. Plotting ln[(*M*,*R*)-**8**] versus time furnished straight lines; by employing a linear

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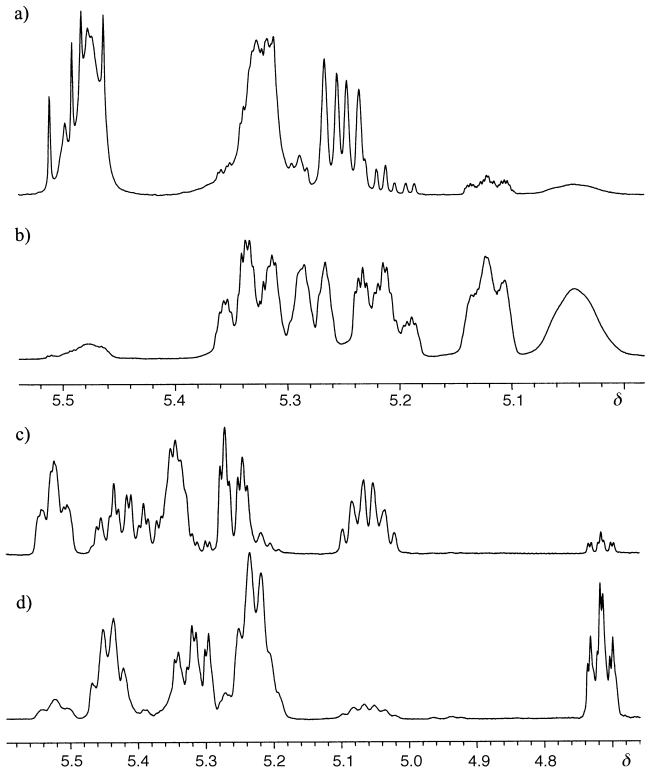


Figure 1. NMR spectra of a) (*M*,*R*)-**8** (0 min, 323 K); b) (*P*,*R*)-**8** (150 min, 323 K); c) (*M*,*R*)-**19** (0 min, 303 K); d) (*P*,*R*)-**19** (2500 min, 303 K).

regression,[26] the corresponding rate constants, k, and half-lives, $t_{1/2}$, of the transformation of the unstable diastereomer (*M*,*R*)-**8** were obtained (Table 1).[27] At 308 K, the half-life of the inversion of the plane of chirality is 208 min, which is a much higher value than reported for *trans*-cyclononene ($t_{1/2}$ = 6 s at 308 K). Analysis of these rate constants by an Arrhenius plot and a further linear regression enabled us to calculate the activation energy for the epimerization as $E_A = (26.36 \pm 0.15)$ kcal mol^{-1} (Figure 2).

This detailed information about the epimerization led us to the question: which conformational motions are responsible for the observed transformation of (*M*,*R*)-**8** into (*P*,*R*)-**8**?

In an attempt to elucidate this, we carried out ab initio density functional theory calculations. We chose Becke's three-parameter hybrid functional in the Gaussian program[28] because of its successful application to a number of conformational problems. The 6–31G* basis set seemed to be sufficiently large for optimization of medium-sized organic molecules.[29] For the optimized structures, a normal coordinate

Table 1. Kinetic measurements of the epimerization of **8**.

	T [K]	k [10^{-5} s^{-1}]	$t_{1/2}$ [min]
1	298	1.2853	899
2	308	5.5299	209
3	318	21.135	55
4	323	35.701	32

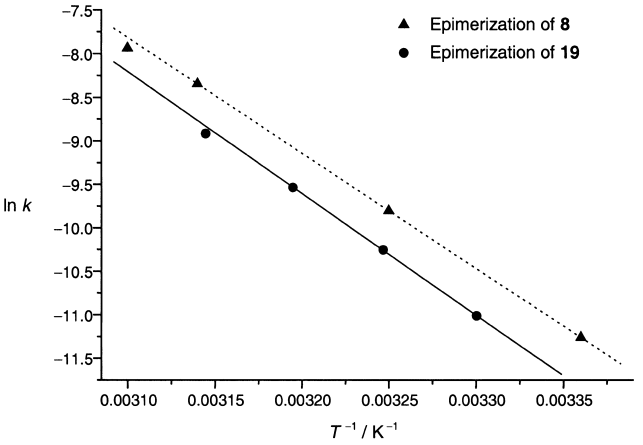


Figure 2. Arrhenius plots of the epimerization of **8** and **19**.

analysis was carried out to verify the nature of the ground and the transition structures (TS) and to obtain thermodynamic corrections at 298 K from the molecular partition functions. All calculated energies and the relative energies for the respective conformers are given in Table 2.

First, we looked at the unsubstituted ring: two conformational interconversions are possible in (1*E*,5*Z*)-cyclonona-1,5-diene (**11**). It is notable that in the minimum structure (*M*)-**11A** the torsional angle (C-C=C-C) of the carbon atoms of the (*E*)-double bond (150.0°) indicates a huge amount of ring strain, probably due to the presence of the (*Z*)-double bond. Figure 3 gives the stationary points for the two independent

Table 2. Energies (B3LYP/6–31G(d)) of conformers and corresponding transition structures of **11**, **8′**, and **19′**.

Conformer	E_{rel} [a.u.][a]	E_{therm} (298 K) [a.u.][a]	E_{rel} (0 K) [kcal mol^{-1}]	ΔH_{rel} (298 K) [kcal mol^{-1}][b]	ΔG_{rel} (298 K) [kcal mol^{-1}][c]
(*M*)-**11A** = *ent*-(*P*)-**11B**	−351.341472	0.219136	0.0	0.0	0.0
(*P*)-**11A** = *ent*-(*M*)-**11A**	−351.332678	0.219263	+5.5	+5.6	+5.3
(*M*-*P*)-**TS11A** = *ent*-(*M*-*P*)-**TS11A**	−351.299729	0.218658	+26.2	+25.9	+26.5
(*P*)-**TS11A-B** = *ent*-(*M*)-**TS11A-B**	−351.316324	0.218375	+15.8	+15.3	+15.6
$(P,R)_{eq}$-**8′**	−673.889634	0.314812	0.0	0.0	0.0
$(P,R)_{ax}$-**8′**	−673.876669	0.314896	+8.1	+8.2	+8.2
$(M,R)_{ax}$-**8′**	−673.8864096	0.314899	+2.0	+2.1	+2.1
$(M,R)_{eq}$-**8′**	−673.8811558	0.314691	+5.3	+5.2	+4.4
$(P,R)_{ax\text{-}eq}$-**TS8′**	−673.864507	0.314042	+15.8	+15.3	+15.7
$(M\text{-}P,R)_{ax}$-**TS8′**	−673.842131	0.314225	+29.8	+29.4	+30.1
$(M,R)_{ax\text{-}eq}$-**TS8′**	−673.861961	0.314120	+17.4	+16.9	+17.0
$(M\text{-}P,R)_{eq}$-**TS8′**	−673.845929	0.314108	+27.4	+27.0	+26.8
$(P,R)_{eq}$-**19′**	−673.890137	0.314854	0.0	0.0	0.0
$(P,R)_{ax}$-**19′**	−673.880032	0.314751	+6.3	+6.3	+5.9
$(M,R)_{ax}$-**19′**	−673.887479	0.314867	+1.7	+1.7	+1.9
$(M,R)_{eq}$-**19′**	−673.879620	0.315010	+6.6	+6.7	+6.5
$(P,R)_{ax\text{-}eq}$-**TS19′**	−673.865613	0.314106	+15.4	+14.9	+15.2
$(M\text{-}P,R)_{ax}$-**TS19′**	−673.847857	0.314347	+26.5	+26.2	+26.7
$(M,R)_{ax\text{-}eq}$-**TS19′**	−673.862603	0.314006	+17.3	+16.7	+17.4
$(M\text{-}P,R)_{eq}$-**TS19′**	−673.848302	0.314306	+26.3	+25.9	+26.4

[a] 1 a.u. = 627.51 kcal mol^{-1}. [b] Thermal correction for the enthalpy at 298 K. [c] Including thermal correction for ΔG at 298 K.

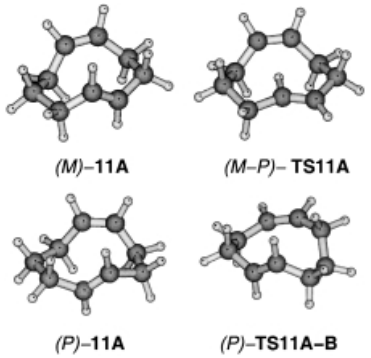


Figure 3. Optimized structures of the conformers and TS of (*Z*,*E*)-cyclonona-1,5-diene **11** (B3LYP/6–31G(d)).

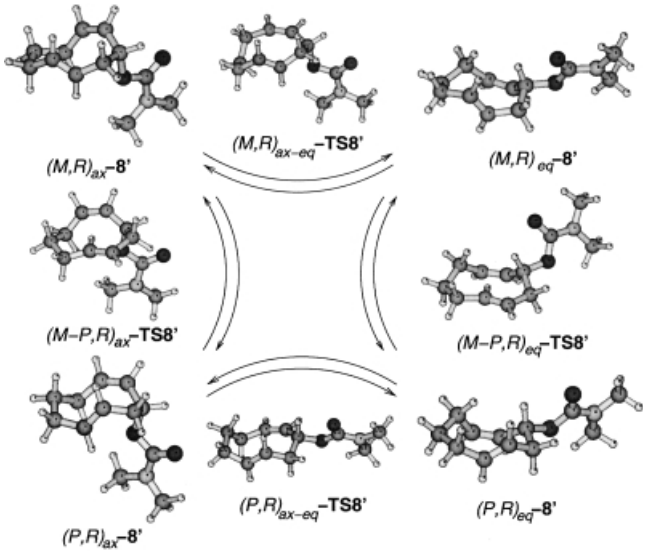
conformational processes: rotation of the (*E*)-double bond of (*M*)-**11A** around the two σ-bonds is responsible for the racemization of the chiral ring and proceeds with only minor conformational changes. In the preferred transition structure (*M*-*P*)-**TS11A**, the hydrogen atom at C1 is pointing towards the (*Z*)-double bond. This path has a barrier of $\Delta H^{\neq}(298\ \mathrm{K}) = 25.9\ \mathrm{kcal\,mol^{-1}}$. The alternative path—hydrogen atom at C2 pointing inwards, the structure is not given here—is disfavoured by $1.7\ \mathrm{kcal\,mol^{-1}}$.

The resulting conformer (*P*)-**11A** is higher ($5.6\ \mathrm{kcal\,mol^{-1}}$) in energy but is not the mirror image of (*M*)-**11A**. It relaxes to the ground structure of the enantiomer (*P*)-**11B** (= *ent*-(*M*)-**11A**) in another conformational process. Starting from (*P*)-**11A**, the TS ((*P*)-**TS11A-B**) lies lower in energy than (*M*-*P*)-**TS11A**. The motion of the (Z)-double bond through the plane of the ring requires a simultaneous disrotatory motion of the σ-bonds; this affords a much larger reorganization of the ring conformation. Following the reaction path on the semiempirical AM1 level showed that the two flexible "hinges" of the molecule move in a concerted, although asynchronous, mechanism.

For calculations of the "real system", which started from the conformation found in the X-ray structure analysis of (*P*,*R*)-**8**, *N*,*N*-dimethylcarbamoyl (**8′**) was chosen to be the substituent instead of *Cby*. For the (1*R*)-diastereomers of **8′**, two epimeric pairs of conformers, (*P*,*R*)-**8′** and (*M*,*R*)-**8′**, were found, which were interconverted by the two conformational processes discussed above. The four conformers and the TS interconnecting them are given in Scheme 4 and the corresponding energies in Table 2.

The relative energies are very similar to the energies in the unsubstituted system **11**, if the position of the substituent is not changed. The carbamate group does not substantially change the barrier of the conformational relaxation process. However the two resulting conformations, derived from **11A** and **11B**, have a larger energy separation, due to the position—either axial or equatorial—of the substituent.

$(M,R)_{ax}$-**8′** is the conformer supposed to result from the intramolecular allylation reaction. The two sequential steps occurring to furnish the solid state conformer $(P,R)_{eq}$-**8′** are the rotation of the (*E*)-double bond ((*M*-*P*,*R*)-**TS8′**) and the flipping of the (*Z*)-double bond through the ring plane ($(P,R)_{ax\text{-}eq}$-**TS8′**); this brings the substituent into an equatorial position.



Scheme 4. Optimized structures of the conformers and TS of (1*R*,2*Z*,7*E*)-cyclononadiene **8′** (B3LYP/6–31G(d)).

The motion of the C5–C6 bridge is less constrained, thus the rotation of the C1–C9 bond through the plane of the *Z* double bond represents the point of highest energy in the process (cf. the structure of $(M,R)_{ax\text{-}eq}$-**TS8′**). Starting with the *E* double bond rotation is the disfavoured way for $(M,R)_{ax}$-**8′** to epimerize ($(M\text{-}P,R)_{ax}$-**TS8′**, $\Delta H_{rel} = 29.4\ \mathrm{kcal\,mol^{-1}}$). Instead, the carbamate substituent is first moved into the equatorial position via $(M,R)_{ax\text{-}eq}$-**TS8′** ($\Delta H_{rel} = 16.9\ \mathrm{kcal\ mol^{-1}}$). This process is endothermic ($+5.1\ \mathrm{kcal\,mol^{-1}}$) but not rate determining. The second step ($(M\text{-}P,R)_{eq}$-**TS8′**) requires $\Delta H^{\neq} = 22.6\ \mathrm{kcal\,mol^{-1}}$ and leads to the global minimum $(P,R)_{eq}$-**8′**—in accordance with the X-ray structure. Remarkably, the enthalpy difference of the experiment is exactly reproduced with the modest basis set we have chosen ($\Delta H = 2.1\ \mathrm{kcal\,mol^{-1}}$).[30] The overall activation energy is estimated to be ($E_A = \Delta H^{\neq} + RT$, $\Delta H^{\neq} = 24.9\ \mathrm{kcal\,mol^{-1}}$) $27.4\ \mathrm{kcal\,mol^{-1}}$ at 298 K, very close to the experimental result of $26.4\ \mathrm{kcal\,mol^{-1}}$. The alternative reaction path—starting with the (*M*-*P*)-epimerization—would proceed over a higher barrier ($\Delta H^{\neq} = 27.3\ \mathrm{kcal\,mol^{-1}}$) and is therefore expected to be much slower than the aforementioned sequence.

(2*E*,7*Z*)-Cyclononadiene: After obtaining such detailed information about the (2*Z*,7*E*)-cyclononadiene **8**, we also wanted to investigate its (2*E*,7*Z*)-isomer. The synthesis of the (2*E*,7*Z*)-cyclization precursor is depicted in Scheme 5. Again starting from the known compound **1**, a *tert*-butyldimethylsilyl (TBDMS) protection[31] of one hydroxy group furnished **12** in 72% yield. To invert the double bond geometry of the allylic alcohol moiety, North's procedure was used again:[15] a pyridinium chlorochromate (PCC) oxidation turned (*Z*,*Z*)-**12** into the enal (*Z*,*E*)-**13** (93% yield); the *E* geometry of the 7-double bond was confirmed by the large olefinic coupling constant ($^3J = 15.6$ Hz) in the ^{1}H NMR spectrum. The allylic alcohol **14** was obtained in 87% yield after reduction of **13** with diisobutylaluminium hydride (DIBAH) at $-78\,^{\circ}$C. Carbamoylation with *Cby*Cl furnished the carbamate **15** in 88% yield. The synthesis of

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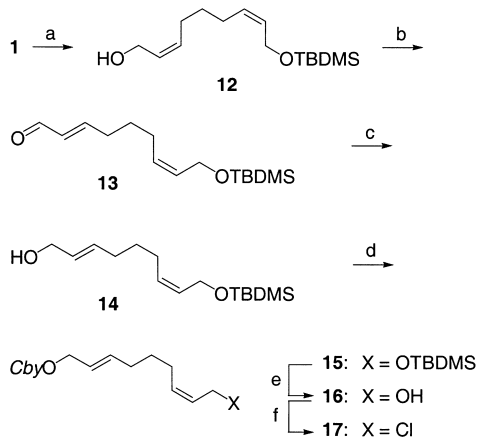
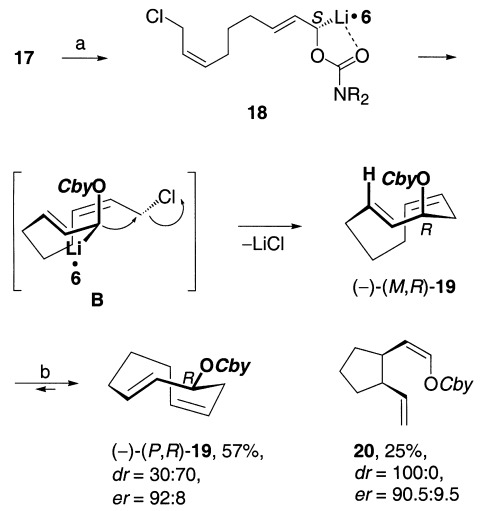


Scheme 5. Synthesis of the cyclization precursor **17**. a) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 72%; b) PCC, CH_2Cl_2, 93%; c) DIBAH, toluene, THF, 87%; d) NaH, *Cby*Cl, THF, Δ, 88%; e) TBAF, Et_2O, 99%; f) *n*BuLi, MsCl, LiCl, THF, 76%.

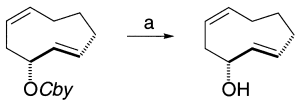
(*Z*,*E*)-**17** was completed by a quantitative desilylation[32] to yield the alcohol **16** (99% yield), which was converted into the cyclization precursor (*Z*,*E*)-**17** in 76% yield.

As before, the cyclization of **17** was carried out in toluene at −88 °C with of the chiral base *n*BuLi/(−)-sparteine. Here, formation of the (*S*)-configured lithium species **18** can be assumed, too. The coupling reaction proceeds via the *endo*-conformation **B**, leading initially to (−)-(*M*,*R*)-**19** with the O*Cby*-group in a pseudo-axial position (Scheme 6). After a



Scheme 6. Cyclization of **17** and subsequent epimerization. a) *n*BuLi, **6**, toluene, −88 °C, 2 h; b) epimerization at 25–40 °C. The initial ratio of (*M*,*R*):(*P*,*R*) after flash-chromatography was found to be approximately 86:14. It depends on the individual workup procedure due to slow epimerization. In **B**, the chelate of the lithium cation and the *Cby*-group is omitted for the sake of clearness.

workup procedure at room temperature and subsequent flash chromatography, the separated diastereomers (−)-(*M*,*R*)-**19** and (−)-(*P*,*R*)-**19** were obtained with 57% yield and in a diastereomeric ratio of 86:14. The epimerization of (*M*,*R*)-**19** to (*P*,*R*)-**19** seemed to be slower than those of **8**: a value of 30:70 was obtained as the final diastereomeric ratio. Additionally, the cyclization reaction furnished the already known divinylcyclopentane (*R*,*R*)-**20** in 25% yield.[33] It was diastereomerically pure and in an enantiomeric excess of 81% (*er* = 90.5:9.5). After removal of the *Cby*-group with DIBAH (Scheme 7)[34] and GLC of the alcohol **21** on a chiral sta-



Scheme 7. Removal of the *Cby*-group. a) DIBAH, toluene, RT, 87%.

tionary phase, the enantiomeric excess of (*P*,*R*)-**19** was determined to be 84% *ee* (*er* = 92:8). When the achiral diamine TMEDA was employed instead of (−)-sparteine, *rac*-**19** (63%, *dr* = 86:14) and *rac*-**20** (13%, *dr* = 100:0) were obtained.

In analogy to the previously reported cyclizations, the *R* configuration was assigned to the stereogenic carbon atom in **19**. The relative configuration of (*P*,*R*)-**19** was determined by X-ray crystal-structure analysis, which also indicated the pseudo-equatorial position of the O*Cby*-group (Figure 4).[35]

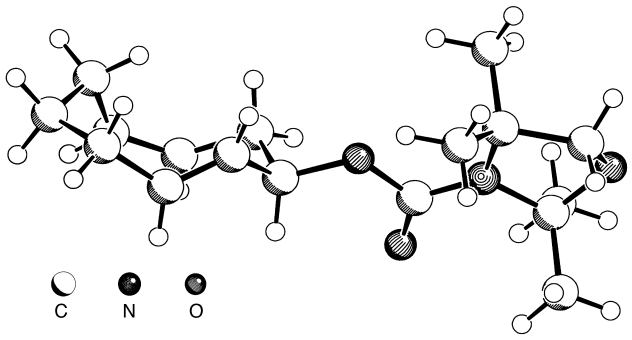


Figure 4. Crystal structure analysis of (*P*,*R*)-**19**.

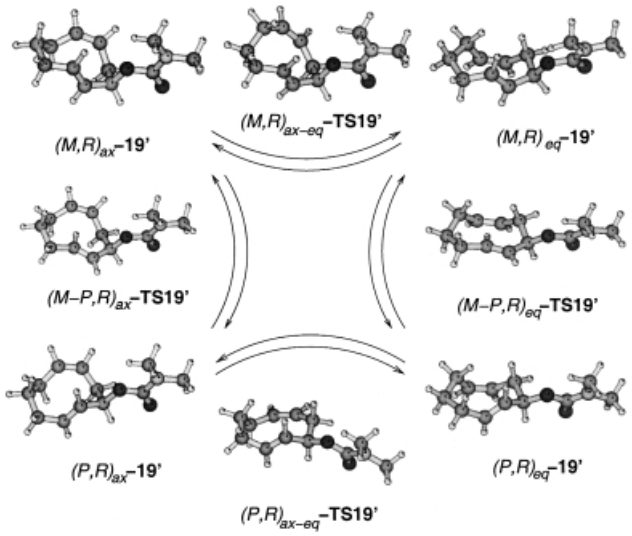
Again, the ^{1}H NMR spectra of (*M*,*R*)-**19** and (*P*,*R*)-**19** showed different chemical shifts of the olefinic protons (Figure 1); this enabled us to perform kinetic measurements. Because of the poorly developed equilibrium state (*dr* = 30:70), we could separate the diastereomers and watched the epimerization of both, starting from (*M*,*R*)-**19** and starting from (*P*,*R*)-**19**. For a better comparison with the (2*Z*,7*E*)-cyclononadiene **8**, the NMR measurements were carried out for the transformation of (*M*,*R*)-**19** to (*P*,*R*)-**19**. Here, plotting ln[(*M*,*R*)-**19**] against time, only furnished a straight line in the initial period, because the formation of (*P*,*R*)-**19** leads to the appearance of the reverse reaction (*P*,*R*)-**19** → (*M*,*R*)-**19**. Therefore, the linear regression was only employed for this initial period (initial-rate method);[36] the rate constants and half-lives obtained are depicted in Table 3. An Arrhenius plot of the ln *k* values at 303 K, 308 K and 313 K produced an excellent straight line and an activation energy of the epimerization of $E_A = (27.50 \pm 0.03)$ kcal mol^{-1} (Figure 2). The free-enthalpy difference of $\Delta G = 0.50$ kcal mol^{-1} for (*M*,*R*)-**19** and (*P*,*R*)-**19** was calculated from the low equilibrium constant of $K = 2.33$. The slower epimerization of

Table 3. Kinetic measurements of the epimerization of **19**.

	T [K]	k [10^{-5} s^{-1}]	$t_{1/2}$ [min]
1	303	1.6780	688
2	308	3.5273	328
3	313	7.2216	160
4	318	13.422	86

(*M*,*R*)-**19**, its slightly higher activation energy and the smaller enthalpy difference of the diastereomers compared with (*M*,*R*)-**8** may be explained by a less strained geometry of (*M*,*R*)-**19**. In (*M*,*R*)-**19**, a comparatively low 1,3-allylic strain exists between the O*Cby*-group and the H atom, whereas in (*M*,*R*)-**8** a sterically more demanding methylene group occupies the allylic *endo*-position. To verify this interpretation and to see whether the epimerization mechanism of (*M*,*R*)-**19** is the same as for (*M*,*R*)-**8** or not, we performed some ab initio calculations again.

In **19′**, the carbamate substituent (*N*,*N*-dimethylcarbamoyloxy instead of *Cby*O) is not connected to one of the allylic carbon atoms of the (7*Z*)-double bond (Scheme 8). Therefore, the motion of the *Z* double bond changes the position of the



Scheme 8. Optimized structures of the conformers and TS of (1*R*,2*E*,7*Z*)-cyclononadiene **19′** (B3LYP/6–31G(d)).

carbamate group less than in **8′**. The two alternative pathways are now kinetically less separated than before. Starting from the initial low energy conformer $(M,R)_{ax}$-**19′**, motion of the *Z* double bond, followed by epimerization through rotation of the *E* double bond is only just preferred—the energy barrier is only 0.3 kcal mol^{-1} smaller. A comparison of the two transition structures $(M\text{-}P,R)_{ax}$-**TS** and $(M\text{-}P,R)_{eq}$-**TS** of **8′** and **19′** (Schemes 4 and 8) shows that for **8′** the position of the substituent is responsible for more steric interactions, especially in $(M\text{-}P,R)_{ax}$-**TS8′**. This is in contrast to **19′**, for which the steric hindrance is rather similar for both axial and equatorial TS.

As for **8′**, the *E*-double-bond motion is rate determining for **19′**, but the barrier is 1.1 kcal mol^{-1} lower. This contradicts the experimental findings. For $(M,R)_{ax}$-**19′** E_A ($= \Delta H^{\neq} + RT$, $\Delta H^{\neq} = 24.2$ kcal mol^{-1}) is 26.7 kcal mol^{-1}, 0.6 kcal mol^{-1} lower than for the conformational equilibration of (*M*,*R*)-**8′**. However, in the experiment, (−)-(*P*,*R*)-**19** is formed more slowly than (*P*,*R*)-**8** from its diastereomeric precursor. The barrier is predicted to within 0.8 kcal mol^{-1}, which is still a good result. The enthalpy difference of the two diastereomers (*P*,*R*)-**19′** and (*M*,*R*)-**19′**, is found to be smaller in experiment ($\Delta G =$ 0.5 kcal mol^{-1}) than calculated ($\Delta G = 1.9$ kcal mol^{-1}, $\Delta H =$ 1.7 kcal mol^{-1}), although this difference is lower than the error margin one would assume for this level of calculation.

Conclusion

Herein, we reported the first example of a ring-closing reaction leading to enantioenriched (*E*,*Z*)-cyclononadienes. The synthesis of nearly diastereomerically pure (*P*,1*R*,2*Z*,7*E*)-**8** (*dr* = 97:3 after equilibration, 80% *ee*) was achieved in 82% yield. (*P*,1*R*,2*E*,7*Z*)-**19** was synthesized in 57% yield (*dr* = 70:30, 84% *ee*). The strategy, consisting of the asymmetric deprotonation of a 9-chloro-substituted alka-2,7-dienyl carbamate and its stereospecific intramolecular cycloalkylation, is expected to be applicable to the synthesis of many substituted nine-membered carbocycles. Both major diastereomers are the thermodynamically favoured ones, as a result of a preceding slow epimerization of the corresponding kinetically preferred (*M*)-epimers **8** and **19**. This epimerization was kinetically investigated by ^{1}H NMR measurements. The experimentally observed structural parameters in the crystal structure analyses of the stable diastereomers were used as a basis for ab initio DFT calculations of the epimerizations. The racemization of (*Z*,*E*)-cyclonona-1,5-diene was computationally investigated with the B3LYP density functional for the first time. Two steps are necessary for the interconversion of the enantiomers: the rotation of the *E* double bond moiety has a barrier of 26 kcal mol^{-1}, it follows the conformational motion of the *Z* double bond through the ring plane, which has a lower barrier of 15 kcal mol^{-1}. The barrier is significantly higher than for cyclononene, most likely due to the additional strain introduced by the plane of the *Z* double bond. The attachment of a carbamoyloxy group to the cyclononadiene ring at the 3 or 4 position does not alter the barriers at large. The relative stability of the resulting diastereomers is predicted correctly. This underlines the usefulness of the B3LYP functional with double-zeta basis sets when it is applied to ground state structures of organic molecules.

Experimental Section

General methods: The NMR spectra were measured at 25 °C, and the chemical shifts are expressed in ppm downfield from tetramethylsilane. The doubling of some signals in the NMR spectra occurs as a result of the *E*/*Z* isomerism of the carbamate group; these signals are separated by slashes. (−)-Sparteine (**6**) is commercially available (Aldrich) and was stored under argon; TMEDA was distilled from CaH_2 and kept under argon. *n*BuLi was received as a 1.6 M solution in hexane from Acros. Reactions with air- and moisture-sensitive reagents were done in dried glassware with dry solvents,

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freshly distilled before use. Flash chromatography was performed with an excess pressure of 1 bar on silica gel (Merck, mesh 40–63 μm).[37] GLC was performed on a 25 m HP1 column at an oven temperature of 50 °C for 1 min, the temperature was increased by 10 °C min^{-1} to 290 °C, then kept there for 10 min. Alternatively, a 25 m HP 1701 column was used at an oven temperature of 50 °C for 1 min, the temperature was increased by 10 °C min^{-1} to 260 °C and kept there for 10 min. For GLC on a chiral stationary phase, a 30 m BetaDex 120 column (Supelco) was used in an isothermic fashion; the main enantiomer is marked by an asterisk.

(2*Z*,7*Z*)-9-Hydroxynona-2,7-dienyl 2,2,4,4-tetramethyl-1,3-oxazolidin-3-carboxylate (2): NaH (420 mg, 10.5 mmol, 0.3 equiv, 60% suspension in mineral oil) was added to a stirred solution of **1** (5.47 g, 35.0 mmol, 1.0 equiv) in THF (30 mL), and stirring was continued for further 60 min. Then, *Cby*Cl (2.01 g, 10.5 mmol, 0.3 equiv) was added, and the reaction mixture was heated at 60 °C overnight. The reaction was quenched by addition of water (15 mL), the layers were separated, and the aqueous phase was extracted with Et_2O (4 × 50 mL). The combined organic phases were dried ($MgSO_4$), the solvents were removed in vacuo, and the crude product was purified by flash chromatography on silica gel (ether). The carbamate **2** (5.80 g, 88% yield, calculated on the amount of *Cby*Cl) was obtained as a colourless liquid. Furthermore, starting material **1** (3.62 g, 66%, calculated on the amount of **1**) was reisolated. t_R = 19.12 min (HP 1); R_f = 0.42 (ether); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.32/1.39 (s, 6H; CH_3), 1.43 (m, 2H; CH_2), 1.48/1.52 (s, 6H; CH_3), 1.84 (br s, 1H; OH), 2.03–2.12 (m, 4H; CH_2), 3.69 (s, 2H; CH_2), 4.14 (dd, ^4J(H,H) = 0.9 Hz, ^3J(H,H) = 5.1 Hz, 2H; CH_2), 4.60 (m, 2H; CH_2), 5.43–5.63 (m, 4H; CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.1/25.2/26.4, 26.7, 26.9, 28.7, 58.4, 60.3, 63.5/65.7, 76.1/76.3, 94.9/95.8, 124.6, 129.3, 131.9, 133.9, 151.9/152.7; IR (neat): $\tilde{\nu}$ = 3440 (br, OH), 1697 cm^{-1} (C=O); MS (70 eV, EI): *m/z* (%): 311 (1) [M^+], 296 (12) [M^+-CH_3]; elemental analysis calcd (%) for $C_{17}H_{29}NO_4$ (311.42): C 65.57, H 9.39, N 4.50; found C 65.27, H 9.72, N 4.85.

(2*Z*,7*E*)-9-Oxonona-2,7-dienyl 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate (3): The allylic alcohol **2** (670 mg, 2.15 mmol, 1.0 equiv) was introduced at room temperature to a suspension of pyridinium chlorochromate (PCC; 557 mg, 2.58 mmol, 1.2 equiv) in CH_2Cl_2 (15 mL) and stirred for 3 h. After filtration through a small column of silica gel and evaporation of the solvent in vacuo, the crude product, checked by measuring a ^{1}H and a ^{13}C NMR spectrum, was used in the next step without further purification. t_R = 19.05 min (HP 1); R_f = 0.35 (ether/pentane 1:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.33/1.39 (s, 6H; CH_3), 1.49/1.53 (s, 6H; CH_3), 1.59 (quin, ^3J(H,H) = 10.2 Hz, 2H; CH_2), 2.13–2.20 (m, 2H; CH_2), 2.32 (ddt, ^3J(H,H) = 10.2 Hz, ^3J(H,H) = 7.4 Hz, ^4J(H,H) = 1.3 Hz, 2H; CH_2), 3.69 (s, 2H; CH_2), 4.61 (d, ^3J(H,H) = 5.4 Hz, 2H; CH_2), 5.56–5.59 (m, 2H; CH), 6.09 (ddt, ^3J(H,H) = 15.5 Hz, ^3J(H,H) = 7.8 Hz, ^3J(H,H) = 1.3 Hz, 1H; CH); 6.80 (dt, ^3J(H,H) = 7.4 Hz, ^3J(H,H) = 1.3 Hz, ^3J(H,H) = 15.5 Hz, 1H; CH), 9.48 (d, ^3J(H,H) = 7.8 Hz, 1H; CH); ^{13}C NMR (90 MHz, $CDCl_3$, 25 °C): δ = 24.1/25.2/26.4, 26.9, 27.5, 32.0, 59.7/60.6, 60.0 76.1/76.5, 94.8/95.8, 125.1, 133.1, 133.2, 152.4, 157.9, 198.8.

(2*Z*,7*E*)-9-Hydroxynona-2,7-dienyl 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate (4): The crude product (645 mg, 2.08 mmol, 1.0 equiv) of the previous step was dissolved in THF (5 mL) and cooled to −78 °C. After injection of DIBAH (2.7 mL, 2.71 mmol, 1.3 equiv, 1M solution in heptane) within 10 min, the reaction mixture was stirred for further 40 min. Then, methanol (2 mL) and water (0.5 mL) were added, and the reaction mixture was allowed to warm up to room temperature. After drying ($MgSO_4$), filtration and evaporation of the solvent, the crude product was purified by flash chromatography on silica gel (ether). The product **4** (620 mg) was obtained in 93% yield (over the last two steps) as a colourless liquid. t_R = 23.64 min (HP 1701); R_f = 0.47 (ether); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.33/1.39 (s, 6H; CH_3), 1.46 (m, 2H; CH_2), 1.48/1.53 (s, 6H; CH_3), 1.81 (br s, 1H; OH), 2.00–2.14 (m, 4H; CH_2), 3.69 (s, 2H; CH_2), 4.14 (m, 2H; CH_2), 4.60 (d, ^3J(H,H) = 5.1 Hz, 2H; CH_2), 5.50–5.65 (m, 4H; CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.1/25.2/26.5, 26.7, 28.6, 29.2/31.3, 59.7, 60.3, 63.6, 76.1/76.3, 94.9/95.8, 124.4, 129.9, 132.3, 134.1, 153.5; IR (neat): $\tilde{\nu}$ = 3451 (br), 1697 cm^{-1} (C=O); MS (70 eV, EI): *m/z* (%): 311 (1) [M^+], 296 (7) [M^+-CH_3]; elemental analysis calcd (%) for $C_{17}H_{29}NO_4$ (311.42): C 65.57, H 9.39, N 4.50; found C 65.92, H 9.72, N 4.67.

(2*Z*,7*E*)-9-Chloronona-2,7-dienyl 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate (5): The carbamate **4** (550 mg, 1.78 mmol, 1.0 equiv) and dry LiCl (75 mg, 1.78 mmol, 1.0 equiv) were stirred in THF (5 mL) at −78 °C. After injection of *n*BuLi (1.2 mL, 1.96 mmol, 1.1 equiv, 1.6M solution in hexane) and additional stirring for 15 min, CH_3SO_2Cl (245 mg, 2.14 mmol, 1.2 equiv) was added, and the reaction mixture was allowed to warm up to room temperature over 48 h. After addition of water (0.7 mL) and Et_2O (50 mL), the mixture was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (ether/pentane 1:5) furnishing the allyl chloride **5** (411 mg, 70% yield) as colourless liquid. t_R = 19.17 min (HP 1); R_f = 0.47 (ether/pentane 2:5); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.34/1.40 (s, 6H; CH_3), 1.44–1.59 (m, 8H; CH_2, CH_3), 2.03–2.15 (m, 4H; CH_2), 3.70 (s, 2H; CH_2), 4.00 (dd, ^4J(H,H) = 0.9, ^3J(H,H) = 6.9 Hz, 2H; CH_2), 4.61 (d, ^3J(H,H) = 5.1 Hz, 2H; CH_2), 5.52–5.64 (m, 2H; CH), 5.69–5.80 (m, 2H; CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.1/25.3/26.5, 26.9, 28.5, 31.4, 45.2, 59.7/60.6, 60.2, 76.5/76.6, 95.8, 124.6, 126.4, 133.9, 135.3, 153.9; IR (neat): $\tilde{\nu}$ = 1697 cm^{-1} (C=O); MS (70 eV, EI): *m/z* (%): 329 (0.3) [M^+], 314 (7) [$M^+ - CH_3$]$^+$, 294 (61) [M^+ − Cl]; elemental analysis calcd (%) for $C_{17}H_{28}ClNO_3$ (329.86): C 61.90, H 8.56, N 4.25; found C 62.08, H 8.79, N 4.41.

(*M*,1*R*,2*Z*,7*E*)- and (*P*,1*R*,2*Z*,7*E*)-Cyclonona-2,7-dien-1-yl 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate (8): The allyl chloride **5** (150 mg, 0.45 mmol, 1.0 equiv) and (−)-sparteine (213 mg, 0.91 mmol, 2.0 equiv) were dissolved in toluene (5 mL) and cooled to −88 °C. After dropwise injection of *n*BuLi (0.57 mL, 0.91 mmol, 2.0 equiv, 1.6M in hexane), the reaction mixture was stirred for 2 h. The reaction was quenched by addition of CH_3OH (0.4 mL), sat. NH_4Cl(aq) (0.2 mL) and Et_2O (35 mL). The reaction mixture was warmed up to room temperature, dried with $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography of the crude product on silica gel (ether/pentane 1:5) furnished the slowly interconverting cyclononadienes (*M*,*R*)-**8** and (*P*,*R*)-**8** (109 mg, 82%) in a ratio of 7:3. (*M*,*R*)-**8**: Colourless oil; R_f = 0.38 (ether/pentane 2:5); $[\alpha]_D^{20}$ = +15.0 (*c* = 1.200, $CHCl_3$, 80% *ee*); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.36–1.43 (m, 6H; CH_3), 1.48–1.60 (m, 7H; CH_3, CH_2), 1.74–1.82 (m, 1H; CH_2), 1.83–1.92 (m, 1H; CH_2), 1.92–2.00 (m, 3H; CH_2), 2.40–2.43 (m, 1H; CH_2), 2.61–2.64 (m, 1H; CH_2), 3.71/3.72 (s, 2H; CH_2), 5.24–5.28 (m, 1H; CH), 5.29–5.36 (m, 2H; CH), 5.44–5.53 (m, 2H; CH); ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ = 24.1/25.2/25.3/25.5/26.6/26.7, 28.3, 32.1, 34.1, 34.6, 74.9/75.0, 76.0/76.6, 123.4, 124.2, 136.9, 137.8, 151.7; (*P*,*R*)-**8**: White solid; m.p. 81 °C; R_f = 0.43 (ether/pentane 2:5); $[\alpha]_D^{20}$ = −58.2 (*c* = 0.555, $CHCl_3$, 80% *ee*); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.37–1.47 (m, 7H; CH_3, CH_2), 1.52/1.54/1.55 (s, 6H; CH_3), 1.61–1.68 (m, 1H; CH_2), 1.75–1.90 (m, 2H; CH_2), 1.91–1.98 (m, 2H; CH_2), 2.35–2.40 (m, 1H; CH_2), 2.57–2.62 (m, 1H; CH_2), 3.70/3.71 (s, 2H; CH_2), 5.00–5.06 (m, 1H; CH), 5.08–5.12 (m, 1H; CH), 5.21 (ddd, ^3J(H,H) = 15.0 Hz, ^3J(H,H) = 10.8 Hz, ^3J(H,H) = 4.8 Hz, 1H; CH), 5.25–5.31 (m, 1H; CH), 5.34 (ddd, ^3J(H,H) = 11.4 Hz, ^3J(H,H) = 3.7 Hz, 1H; CH); ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ = 24.1/24.2/25.3/25.4/25.5/25.6, 27.4, 30.4, 34.1, 37.4, 59.7/60.6, 73.0, 76.0/76.3, 124.7/124.8, 125.2, 134.1/134.2, 137.0, 151.5/152.2; IR (KBr): $\tilde{\nu}$ = 1692 cm^{-1} (C=O); MS (70 eV, EI): *m/z* (%): 293 (3) [M^+]; elemental analysis calcd (%) for $C_{17}H_{27}NO_3$ (293.40): C 69.59, H 9.28, N 4.77; found C 69.35, H 9.42, N 4.39.

(*P*,1*R*,2*Z*,7*E*)-Cyclonona-2,7-diene-1-ol (9): The carbamate (*P*,*R*)-**8** (100 mg, 0.24 mmol, 1.0 equiv) was dissolved in CH_3OH (4 mL), treated with CH_3SO_3H (65 mg, 0.68 mmol, 2.0 equiv) and the reaction mixture was heated under reflux for 3 h. Then, KOH (76 mg, 1.36 mmol, 4.0 equiv) was added, and, after additional refluxing for 3 h, the solvent was removed in vacuo. The residue was suspended in Et_2O (5 mL) and filtered, and the filtrate was concentrated in vacuo. Flash chromatography of the crude product on silica gel (ether/pentane 1:1) furnished the alcohol **9** (41 mg, 87%) as a colourless liquid. t_R = 9.77 min (HP 1701); t_R = 64.6 min* 69.3 min (BetaDex 120, 110 °C isotherm); R_f = 0.33 (ether/pentane 1:1); $[\alpha]_D^{20}$ = −79.19 (*c* = 1.73, $CHCl_3$, 80% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.44 (ddt, ^3J(H,H) = 5.7 Hz, ^3J(H,H) = 11.6 Hz, ^3J(H,H) = 16.5 Hz, 1H; CH_2), 1.58 (q, ^3J(H,H) = 11.6 Hz, 1H; CH_2), 1.71–1.97 (m, 4H; CH_2), 2.33–2.40 (m, 1H; CH_2), 2.47 (dt, ^3J(H,H) = 3.6 Hz, ^3J(H,H) = 10.8 Hz, 1H; CH_2), 4.14–4.22 (m, 1H; CH), 5.00 (dd, ^3J(H,H) = 6.8 Hz, ^3J(H,H) = 11.7 Hz, 1H; CH), 5.12–5.19 (m, 1H; CH), 5.20–5.26 (m, 1H; CH), 5.28–5.34 (m, 1H; CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 27.3, 30.5, 34.1, 40.5, 71.1, 126.4, 129.0, 133.4. 136.2; IR (neat): $\tilde{\nu}$ = 3340 cm^{-1} (br, OH); MS (70 eV, EI): *m/z* (%): 138 (1), [M^+], 120 (19) [$M^+ - H_2O$]; HRMS calcd for $C_9H_{14}O$ (138.21): 120.09390 [$M^+ - H_2O$]; found 120.09326 [$M^+ - H_2O$].

(1*R*,2*Z*,7*Z*)-Cyclonona-2,7-dienyl 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate (10): The (*E*,*Z*)-cyclononadiene **8** (20 mg, 0.07 mmol, 1.00 equiv) and I_2 (0.9 mg, 3.5 μmol, 0.05 equiv) were dissolved in *n*-hexane (2 mL) and stirred at room temperature for 10 d. After purification by flash-chromatography on silica gel (ether/pentane 1:5), the known (*Z*,*Z*)-cyclononadiene **10** (3 mg, 15 %) was obtained. By GLC on a chiral stationary phase (BetaDex 120) and comparison with a known sample,[33] **10** could be assigned the (1*R*)-configuration. $t_R = 215.9$ min*, 222.6 min (BetaDex 120, 140 °C).

(2*Z*,7*Z*)-9-*tert*-Butyldimethylsilyloxynona-2,7-diene-1-ol (12): (2*Z*,7*Z*)-Nona-2,7-diene-1,9-diol (**1**) (10.0 g, 64.0 mmol, 3.2 equiv) was dissolved in CH_2Cl_2 (25 mL). After addition of Et_3N (3.84 g, 38.0 mmol, 1.9 equiv), TBDMSCl (3.01 g, 20.0 mmol, 1.0 equiv) and 4-(dimethylamino)pyridine (DMAP; 50 mg), the reaction mixture was stirred at room temperature overnight. Water (20 mL) was added, the layers were separated, and the aqueous phase was extracted with Et_2O (5 × 60 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (ether/pentane 1:2 → ether), furnishing the starting material **1** (4.56 g, 45 %) and the desired product **12** (3.87 g, 72 %, calculated on the amount of TBDMSCl) as a colourless liquid. $t_R = 19.04$ min (HP 1701); $R_f = 0.49$ (ether); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.05$ (s, 6H; CH_3), 0.89 (s, 9H; CH_3), 1.43 (quin, $^3J(H,H) = 7.3$ Hz, 2H; CH_2), 1.77 (br s, 1H; OH), 2.05 (quin, $^3J(H,H) = 7.9$ Hz, $^3J(H,H) = 7.3$ Hz, 4H; CH_2), 4.14 (m, 2H; CH_2), 4.19 (dd, $^3J(H,H) = 6.4$ Hz, $^4J(H,H) = 0.9$ Hz, 2H; CH_2), 5.33 – 5.64 (m, 4H; CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = -5.1$, 18.4, 25.6, 25.9, 26.7, 29.2, 58.5, 59.4, 129.3, 130.0, 130.4, 132.6; IR (neat): $\tilde{\nu} = 3351$ cm^{-1} (br, OH); MS (70 eV, EI): *m/z* (%): 213 (9) [$M^+ - t$Bu]; elemental analysis calcd (%) for $C_{15}H_{30}O_2Si$ (270.48): C 66.61, H 11.18; found C 66.52, H 11.14.

(2*E*,7*Z*)-9-*tert*-Butyldimethylsilyloxynona-2,7-diene-1-al (13): Allylic alcohol **12** (5.80 g, 21.4 mmol, 1.2 equiv) was treated with PCC (5.50 g, 25.7 mmol, 1.2 equiv) as described for the preparation of **3**. Compound **13** was obtained as a colourless oil. Yield: 5.30 g (93 %); $t_R = 19.37$ min (HP 1701); $R_f = 0.63$ (ether); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.04$ (s, 6H; CH_3), 0.87 (s, 9H; CH_3), 1.56 (quin, $^3J(H,H) = 7.4$ Hz, 2H; CH_2), 2.08 (dt, $^3J(H,H) = 7.4$ Hz, $^3J(H,H) = 7.5$ Hz, 2H; CH_2), 2.32 (ddd, $^4J(H,H) = 1.5$ Hz, $^3J(H,H) = 6.8$ Hz, $^3J(H,H) = 7.4$ Hz, 2H; CH_2), 4.17 (d, $^3J(H,H) = 6.3$ Hz, 2H; CH_2), 5.33 – 5.43 (m, 1H; CH), 5.50 – 5.59 (m, 1H; CH), 6.09 (ddt, $^3J(H,H) = 7.8$ Hz, $^3J(H,H) = 15.6$ Hz, $^4J(H,H) = 1.5$ Hz, 1H; CH), 6.80 (dt, $^3J(H,H) = 15.6$ Hz, $^3J(H,H) = 6.8$ Hz, 1H; CH), 9.47 (d, $^3J(H,H) = 7.8$ Hz, 1H; CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = -5.2$, 18.3, 25.9, 26.9, 27.7, 32.0, 59.2, 129.5, 130.6, 133.1, 157.9, 193.9.

(2*E*,7*Z*)-9-*tert*-Butyldimethylsilyloxynona-2,7-diene-1-ol (14): The crude aldehyde **13** (5.30 g, 19.7 mmol) in THF (40 mL) and DIBAH (1 M, 25.7 mL, 25.7 mmol, 1.3 equiv) were treated as described for **4**, yielding 4.65 g (87 %) of **14** as a colourless oil. $t_R = 19.04$ min (HP 1701); $R_f = 0.59$ (ether); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.05$ (s, 6H; CH_3), 0.83 (s, 9H; CH_3), 1.38 (quin, $^3J(H,H) = 7.4$ Hz, 2H; CH_2), 1.50 (br s, 1H; OH), 1.94 – 2.04 (m, 4H; CH_2), 4.00 (m, 2H; CH_2), 4.13 (dd, $^3J(H,H) = 6.3$ Hz, $^4J(H,H) = 1.2$ Hz, 2H; CH_2), 5.28 – 5.56 (m, 2H; CH); 5.57 – 5.65 (m, 2H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = -5.1$, 18.3, 25.9, 26.6, 28.9, 31.7, 59.4, 63.7, 129.2, 129.9, 130.5, 132.7; IR (neat): $\tilde{\nu} = 3362$ cm^{-1} (br, OH); MS (70 eV, EI): *m/z* (%): 269 (1), [$M^+ - CH_3$], 227 (5) [$M^+ - t$Bu]; elemental analysis calcd (%) for $C_{15}H_{30}O_2Si$ (270.48): C 66.61, H 11.18; found C 66.40, H 11.13.

(2*E*,7*Z*)-9-*tert*-Butyldimethylsilyloxynona-2,7-dienyl 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate (15): The alcohol **14** (4.21 g, 15.6 mmol, 1.0 equiv) and NaH (779 mg, 19.5 mmol, 1.3 equiv, 60 % suspension in mineral oil) were stirred in THF (50 mL) for 1 h. Then, *Cby*Cl (3.60 g, 18.7 mmol, 1.2 equiv) was added, and the reaction mixture was heated to 60 °C overnight. The reaction was quenched by addition of water (20 mL), the layers were separated, and the aqueous phase was extracted with Et_2O (4 × 50 mL). The combined organic phases were dried ($MgSO_4$), the solvents were removed in vacuo, and the crude product was purified by flash chromatography on silica gel (ether/pentane 1:4). The carbamate **15** was obtained as a colourless oil in 88 % yield (5.80 g). $t_R = 26.88$ min (HP 1701); $R_f = 0.69$ (ether/pentane 1:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 0.04$ (s, 6H; CH_3); 0.83 (s, 9H; CH_3), 1.29 – 1.52 (m, 14H; CH_3, CH_2), 1.99 (q, $^3J(H,H) = 7.3$ Hz, 4H; CH_2), 3.71 (s, 2H; CH_2), 4.13 (dd, $^4J(H,H) = 0.9$ Hz, $^3J(H,H) = 6.0$ Hz, 2H; CH_2), 4.45 (d, $^3J(H,H) = 6.3$ Hz, 2H; CH_2), 5.30 – 5.72 (m, 4H; CH); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = -5.3$, 18.1, 23.1/25.1/25.6/26.8, 25.7, 26.9, 28.6, 31.5, 59.1, 59.4/62.3, 64.8, 75.9/76.4, 94.6/95.5, 124.7, 129.7, 130.0, 134.8, 152.4; IR (neat): $\tilde{\nu} = 1700$ cm^{-1} (C=O); MS (70 eV, EI): *m/z* (%): 425 (1) [M^+], 410 (2) [$M^+ - CH_3$], 368 (4) [$M^+ - t$Bu]; elemental analysis calcd (%) for $C_{23}H_{43}NO_4Si$ (425.68): C 64.90, H 10.18, N 3.29; found C 64.86, H 10.57, N 3.40.

(2*E*,7*Z*)-9-Hydroxynona-2,7-dienyl 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate (16): The desilylation was carried out with **15** (5.80 g, 13.63 mmol, 1.0 equiv) in Et_2O (50 mL) by addition of tetrabutyl ammonium fluoride (TBAF; 41 mL, 40.9 mmol, 3.0 equiv, 1 M solution in THF). After the mixture had been stirred at room temperature for 2 h, water (20 mL) was added, the layers were separated, and the aqueous phase was extracted with Et_2O (4 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo. Subsequent flash chromatography on silica gel (ether/pentane 1:1) furnished **16** (4.20 g, 99 %) as a colourless liquid. $t_R = 23.96$ min (HP 1); $R_f = 0.49$ (ether); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.37/1.43$ (s, 6H; CH_3), 1.45 – 1.59 (m, 8H; CH_3, CH_2), 1.75 (br s, 1H; OH), 2.05 – 2.15 (m, 4H; CH_2), 3.73 (s, 2H; CH_2), 4.18 (d, $^3J(H,H) = 6.9$ Hz, 2H; CH_2), 4.53 (d, $^3J(H,H) = 5.7$ Hz, 2H; CH_2), 5.46 – 5.67 (m, 3H; CH), 5.74 (dt, $^3J(H,H) = 15.3$ Hz, $^3J(H,H) = 6.9$ Hz, 1H; CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 24.1/25.2/26.5$, 26.7, 28.7, 31.5, 58.4, 59.7/60.5, 65.0, 76.1/76.3, 94.9/95.8, 124.5, 129.0, 132.0, 134.9, 151.9; IR (neat): 3449 (br, OH), 1698 cm^{-1} (C=O); MS (70 eV, EI): *m/z* (%): 311 (1) [M^+], 296 (6) [$M^+ - CH_3$]; elemental analysis calcd (%) for $C_{17}H_{29}NO_4$ (311.42): C 65.57, H 9.39, N 4.50; found C 65.40, H 9.20, N 4.59.

(2*E*,7*Z*)-9-Chlorononona-2,7-dienyl-2,2,4,4-tetramethyl 1,3-oxazolidine-3-carboxylate (17): The carbamate **16** (4.30 g, 13.8 mmol, 1.0 equiv) and dry LiCl (585 mg, 13.8 mmol, 1.0 equiv) were treated with *n*BuLi (9.5 mL, 15.2 mmol, 1.1 equiv, 1.6 M solution in hexane) and CH_3SO_2Cl (2.06 g, 17.9 mmol, 1.3 equiv) as described for the synthesis of **5**. The chloride **17** (3.45 g, 76 %) was obtained as a colourless liquid. $t_R = 23.42$ min (HP 1701); $R_f = 0.56$ (ether/pentane 1:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 1.37/1.42$ (s, 6H; CH_3), 1.45 – 1.60 (m, 8H; CH_3, CH_2), 2.06 – 2.17 (m, 4H; CH_2), 3.72 (s, 2H; CH_2), 4.07 (d, $^3J(H,H) = 6.6$ Hz, 2H; CH_2), 4.53 (d, $^3J(H,H) = 6.0$ Hz, 2H; CH_2), 5.56 – 5.79 (m, 4H; CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 24.0/25.2/26.2/26.4$, 28.3, 31.1, 31.4, 39.2, 59.6/60.4, 64.9, 76.0/76.3, 95.7, 125.1, 125.5, 134.6; IR (neat): $\tilde{\nu} = 1698$ cm^{-1} (C=O); MS (70 eV, EI): *m/z* (%): 329 (1) [M^+], 314 (6) [$M^+ - CH_3$], 294 (56) [$M^+ - Cl$]; elemental analysis calcd (%) for $C_{17}H_{28}ClNO_3$ (329.86): C 61.90, H 8.57, N 4.25; found C 61.71, H 8.86, N 4.34.

(*M*,1*R*,2*Z*,7*E*)- and (*P*,1*R*,2*Z*,7*E*)-Cyclonona-2,7-dienyl 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carboxylate [(*M*,1*R*,2*Z*,7*E*)-19 and (*P*,1*R*,2*Z*,7*E*)-19]: The carbamate **17** (1.20 g, 3.64 mmol, 1.0 equiv) and (−)-sparteine (1.71 g, 7.28 mmol, 2.0 equiv) were dissolved in toluene (50 mL), and the solution was cooled to −88 °C. *n*BuLi (4.55 mL, 7.28 mmol, 2.0 equiv, 1.6 M solution in hexane) was added slowly, and the reaction mixture was stirred at this temperature for 2 h. Methanol (5 mL) and water (5 mL) were then injected, the reaction mixture was warmed up to room temperature, the layers were separated, and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$. The solvent was removed in vacuo while keeping the product at room temperature. Subsequent flash chromatography on silica gel (ether/pentane 1:10) yielded 595 mg (57 %) of (*M*,*R*)-**19** and (*P*,*R*)-**19** in a ratio of 86:14 and the known cyclopentane **20** (262 mg, 25 %, 81 % *ee*). An identical reaction with TMEDA, instead of (−)-sparteine, in Et_2O at −78 °C furnished *rac*-(*M*,*R*)-**19** and *rac*-(*P*,*R*)-**19** (86:14) in 63 % yield and *rac*-**20** in 13 % yield. (*M*,*R*)-**19**: colourless oil; $R_f = 0.27$ (ether/pentane 1:4); $[\alpha]_D^{20} = -26.6$ ($c = 2.64$, $CHCl_3$, 84 % *ee*); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): $\delta = 1.32/1.36/1.38$ (s, 6H; CH_3), 1.48/1.50/1.52 (s, 6H; CH_3), 1.48 – 1.56 (m, 1H; CH_2), 1.65 (dq, $^3J(H,H) = 12.6$ Hz, $^3J(H,H) = 5.4$ Hz, 1H; CH_2), 1.82 – 1.92 (m, 2H; CH_2), 1.96 – 2.04 (m, 2H; CH_2), 2.38 – 2.44 (m, 1H; CH_2), 2.52 – 2.57 (m, 1H; CH_2), 3.67/3.68 (s, 2H; CH_2), 5.04 (q, $^3J(H,H) = 9.5$ Hz, 1H; CH), 5.20 – 5.29 (m, 1H; CH), 5.31 – 5.35 (m, 1H; CH), 5.36 – 5.44 (m, 1H; CH), 5.49 – 5.53 (m, 1H; CH); ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): $\delta = 24.1/25.0/25.1/25.3$, 26.4, 32.1, 32.3, 34.0, 59.5/60.5, 71.1, 76.0/76.4, 94.7/95.8, 118.6/118.8, 128.7, 131.4/131.5, 137.9, 151.0/151.7. (*P*,*R*)-**19**: white solid; m.p. 53 °C; $R_f = 0.35$ (ether/pentane 1:4); $[\alpha]_D^{20} = -20.3$ ($c = 2.17$, $CHCl_3$, 84 % *ee*); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): $\delta = 1.38/1.40$ (s, 6H; CH_3), 1.48 – 1.54 (m, 7H; CH_3, CH_2), 1.81 – 1.92 (m, 3H; CH_2), 2.09 – 2.17 (m, 1H; CH_2), 2.33 – 2.39 (m, 1H; CH_2), 2.40 – 2.44 (m, 1H; CH_2), 3.70/3.71 (s, 2H; CH_2), 4.71 (ddd, $^3J(H,H) = 9.0$ Hz, $^3J(H,H) = 9.0$ Hz, $^3J(H,H) = 3.0$ Hz, 1H; CH), 5.19 – 5.23

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(m, 2H; CH), 5.32 (ddd, ^3J(H,H) = 4.2 Hz, ^3J(H,H) = 10.8 Hz, ^3J(H,H) = 10.8 Hz, 1H; CH), 5.44 (dd, ^3J(H,H) = 16.8 Hz, ^3J(H,H) = 10.2Hz, 1H; CH); ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ = 24.1/24.2/25.3725.4/26.5/26.6, 26.1/26.8, 31.2, 34.5, 34.8, 59.7/60.5, 75.6, 76.0/76.3, 92.8/95.8, 121.3, 128.5/128.6, 131.4/131.5, 137.9/138.0, 151.5/152.2; IR (neat): $\tilde{\nu}$ = 1699 cm^{-1} (C=O); MS (70 eV, EI): *m/z* (%): 293 (6) [M^+]; elemental analysis calcd (%) for $C_{17}H_{27}NO_3$ (293.40): C 69.59, H 9.28, N 4.77; found C 69.62, H 9.42, N 4.73.

Determination of the enantiomeric ratio: (*P*,1*R*,2*Z*,7*E*)-Cyclonona-2,7-diene-1-ol (21): (*P*,*R*)-19 (13 mg, 0.04 mmol, 1.0 equiv) was dissolved in toluene (3 mL) and treated with DIBAH (0.44 mL, 0.44 mmol, 10.0 equiv, 1M solution in toluene). After being stirred at room temperature overnight, the reaction mixture was poured into Et_2O (15 mL). H_2O (0.4 mL) was added, and the suspension was stirred for 15 min. Drying over $MgSO_4$, filtration, concentration on a rotary evaporator and flash chromatography of the crude product on silica (ether/pentane 1:4) yielded **21** (5 mg, 82%), which was dissolved in pentane (2 mL). GLC of this sample on a chiral stationary phase (BetaDex 120) indicated an enantiomeric ratio *er* = 92:8 (84% *ee*). t_R = 9.79 min (HP 1701); t_R = 167.1 min*, 174.8 min (BetaDex 120, 95 °C isothermic); R_f = 0.59 (ether); MS (70 eV, EI): *m/z* (%): 138 (1) [M^+].

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[20] a) Review: M. Schlosser, O. Desponds, R. Lehmann, E. Moret, G. Rauchschwalbe, *Tetrahedron* **1993**, *49*, 10175–10203; b) see also: D. Hoppe, *Angew. Chem.* **1984**, *96*, 930–946; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 932–948; c) X-ray crystal structure analysis of a lithiated allylic carbamate: M. Marsch, K. Harms, O. Zschage, D. Hoppe, G. Boche, *Angew. Chem.* **1991**, *103*, 338–339; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 321–322.
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[23] Crystals suitable for X-ray diffraction analysis were grown by vapour diffusion of pentane into an ethereal solution of (*P*,*R*)-**8**.
[24] X-ray crystal structure analysis of (*P*,*R*)-**8**: formula $C_{17}H_{27}NO_3$, M = 293.40, colourless crystal 0.30 × 0.15 × 0.05 mm, a = 7.295(2), b = 10.900(2), c = 11.366(2) Å, α = 76.21(2), β = 88.53(2), γ = 76.68(2)°, V = 853.7(3) Å^3, ρ_{calc} = 1.141 g cm^{-3}, μ = 6.16 cm^{-1}, empirical absorption correction from ψ scan data ($0.837 \le T \le 0.970$), Z = 2, triclinic, space group $P\bar{1}$ (No. 2), λ = 1.54178 Å, T = 223 K, $\omega/2\theta$ scans, 3752 reflections collected ($-h, \pm k, \pm l$), [(sinθ)/λ] = 0.62 Å^{-1}, 3466 independent (R_{int} = 0.023) and 1642 observed reflections [$I \ge 2\sigma(I)$], 225 refined parameters, R = 0.063, wR^2 = 0.162, max. residual electron density 0.22 (−0.20) e Å^{-3}, disorder in the nine-membered ring, refined with split positions, the oxygen atom in the five-membered ring could not be unambiguously defined, hydrogens calculated and refined as riding atoms.
Data sets were collected with Nonius CAD4 and Kappa CCD diffractometers, the later equipped with a rotating anode generator Nonius FR591. Programs used: data collection EXPRESS (Nonius B.V., 1994) and COLLECT (Nonius B.V., 1998), data reduction MolEN (K. Fair, Enraf-Nonius B.V., 1990) and Denzo-SMN (Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307–326), absorption correction for CCD data SORTAV (R. H. Blessing, *Acta Crystallogr.* **1995**, *A51*, 33–37; R. H. Blessing, *J. Appl. Crystallogr.* **1997**, *30*, 421–426), structure solution SHELXS-97 (G. M. Sheldrick, *Acta Crystallogr.* **1990**, *A46*, 467–473), structure refinement SHELXL-97 (G. M. Sheldrick, Universität Göttingen, **1997**), graphics DIAMOND (K. Brandenburg, Universität Bonn, **1997**). See also ref. [35b].
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[28] All structures were fully optimized (B3LYP/6–31G(d)) starting from AM1 stationary points. The nature of the stationary point was verified in every case by a frequency calculation (number of imaginary frequencies = 0 for minima and 1 for TS). The zero point vibrational and thermodynamic corrections were taken from the thermochemistry calculation at 298.15 K and 1 atm. (*Gaussian 98* (Revision A.7), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi,

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[29] For some stationary points of **16**, single point energy calculations were carried out with the B3LYP functional by using the program TURBOMOLE. With the large TZVPP basis set, only small changes in relative energies of the conformers discussed were observed. Barriers were about 0.3 – 0.7 kcal mol^{-1} lower.

[30] As the two epimers (*M*,*R*)-**5** and (*P*,*R*)-**5** (or (*M*,*R*)-**16** and (*P*,*R*)-**16**) mostly differ in their conformation, the entropic term in ΔG was disregarded, this leads to the measurement of ΔH.

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