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Asymmetric Synthesis of a (2*Z*,7*E*)-Cyclononadiene by an Intramolecular Cycloalkylation and Insight to Its Conformational Properties

Alexander Deiters, Christian Mück-Lichtenfeld,[†] Roland Fröhlich,[‡] and Dieter Hoppe*[,§]

*Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster,
Corrensstrasse 40, D-48149 Münster, Germany*

dhoppe@uni-muenster.de

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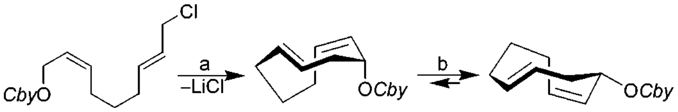
ABSTRACT



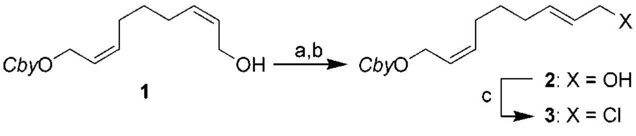
a. *n*BuLi, (–)-sparteine, toluene, –88°C. b. Epimerization.

Here, we report a novel synthesis of a monosubstituted, enantio- and diastereomerically enriched *trans*-cyclononadienol. The reaction consists of an enantioselective (–)-sparteine-mediated allylic lithiation of an achiral 7-chlorononadienyl carbamate and a subsequent stereospecific intramolecular allyllithium–allyl chloride coupling. The stereochemical course of the cyclization has been determined, and the high configurative stability of the chiral nine-membered carbocycle has been investigated by kinetic measurements and rationalized by computational calculations.

trans-Cycloalkenes are chiral, but rings larger than (*E*)-cyclooctene suffer from low configurative stability.[1] Due to this, substituted *trans*-cyclononenes are existing in two diastereomeric forms, showing the effect of epimerization, but mostly with a poorly pronounced equilibrium state.[2]

We became interested into this field of planar chirality[3] because of a new method for the enantioselective synthesis of nine-membered carbocycles developed in our laboratory.[4] Therefore, we applied our cyclization protocol to the (2*Z*,7*E*)-cyclization precursor **3**, which has been synthesized by inverting the 7,8-double bond in **1**[4] by North's procedure[5] to **2** and a subsequent chlorination (Scheme 1).

Scheme 1



a. PCC, CH_2Cl_2. b. DIBAH, THF, –78°C, 96%. c. *n*BuLi, CH_3SO_2Cl, LiCl, THF, 75%.

The treatment of **3** with *n*BuLi/(−)-sparteine in toluene at −88 °C for 2 h afforded the nine-membered *trans*-configured carbocycle **5** in a suprisingly high yield. We detected two products which could be easily separated by

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[†] X-ray analysis.

[$] Calculations.

[§] Fax: +251-83-39772.

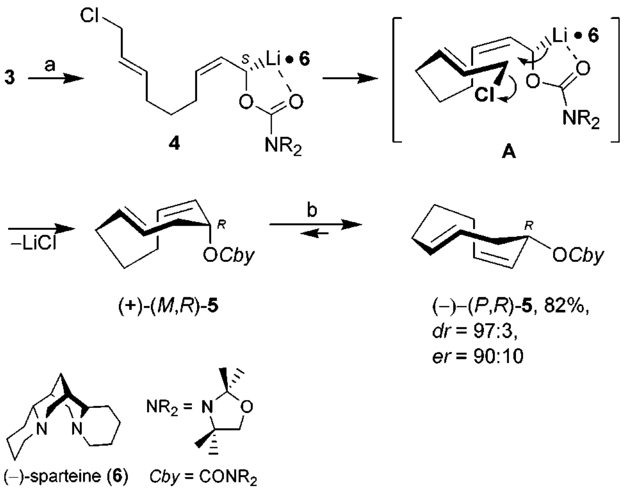
(1) (a) (*E*)-Cyclooctene is the only unsubstituted *trans*-cycloalkene which is configuratively stable at rt ($t_{1/2} = 10^5$ y at 30 °C): Cope, A. C.; Pawson, B. A. *J. Am. Chem. Soc.* **1965**, *87*, 3649−3651. (b) The next homologue, (*E*)-cyclononene, racemizes much faster ($t_{1/2} = 6$ s at 30 °C): Cope, A. C.; Ganellin, C. R.; Johnson, H. W., Jr.; Van Auken, T. V.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1965**, *87*, 3644−3649. See also refs 3 and 11.

(2) For analysis of the diastereoisomerism of substituted racemic *trans*-cyclononenes, see: Reese, C. B.; Shaw, A. *Chem. Commun.* **1970**, 1367−1368. Reese, C. B.; Shaw, A. *J. Chem. Soc., Perkin Trans. I* **1975**, 2422−2429. Further observations of diastereomeric *trans*-cyclononenes: Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159−169. Loozen, H. J. J.; de Haan, J. W.; Buck, H. M.; *J. Org. Chem.* **1977**, *42*, 418−422. Loozen, H. J. J.; Robben, W. M. M.; Richter, T. L.; Buck, H. M. *J. Org. Chem.* **1976**, *41*, 384−385. For a synthetic application of this effect in nine-membered heterocycles, see: Sudau, A.; Münch, W.; Nubbemeyer, U. *J. Org. Chem.* **2000**, *65*, 1710−1720.

10.1021/ol005998h CCC: $19.00

chromatography and were identified as the slowly interconverting diastereomers (*M*,*R*)-**5** and (*P*,*R*)-**5** (Scheme 2).

Scheme 2



a. *n*BuLi, (−)-sparteine (**6**), toluene, −88°C, 2 h. b. Epimerization at 20 - 45°C. The initial ratio of (+)-(*M*,*R*) : (−)-(*P*,*R*) after flash chromatography was found to be approx. 7:3. It depends on the individual workup procedure due to slow epimerization.

The reaction sequence starts with an enantioselective allylic lithiation of **3** by means of the chiral base *n*BuLi/(−)-sparteine,[6] furnishing the *S*-configured lithium species **4**.[7] **4** reacts via conformation **A** under inversion[8] of the configuration at the metal-bearing carbon atom to the *R*-configured coupling product **5**, which could be isolated in 82% yield and with an er of 90:10.[9] In **4**, and hence in **A**, the O*Cby* group favors an *endo*-position[10] which leads to a pseudoaxial position in (*M*,*R*)-**5**.[11] The relatively strained geometry in (*M*,*R*)-**5** causes a nearly complete epimerization of the *trans*-cyclononadiene ring which results in the more stable product (*P*,*R*)-**5** with the O*Cby* group in a pseudoequatorial position, minimizing the 1,3-allylic strain.[12] The X-ray crystal structure analysis[13] of (*P*,*R*)-**5** clearly shows the relative configuration and the thermodynamically favored cross-conformation[14] of the cyclononadiene ring (Figure 1).[15]

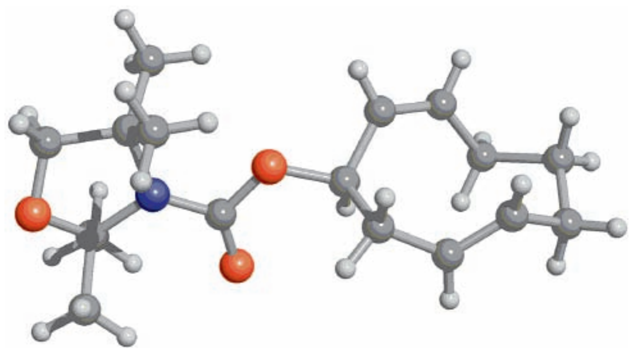
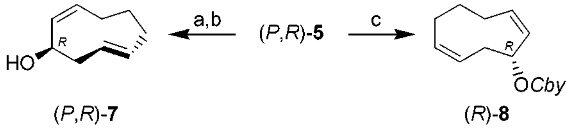


Figure 1. Crystal structure analysis of (*P*,*R*)-**5**.

The er of **5** was determined by GLC after cleavage[16] of the carbamate group to the alcohol (*P*,*R*)-**7**.[17] The absolute configuration of (*P*,*R*)-**5** could be assigned by conversion to the known (1*R*,2*Z*,7*Z*)-cyclonona-2,7-dienyl carbamate[4] (*R*)-**8** by an iodine-catalyzed isomerization of the *E* double bond (Scheme 3).

Scheme 3



a. CH_3SO_3H, CH_3OH, reflux; b. KOH, CH_3OH, reflux, 87%, *er* = 90:10; c. I_2, hexane, 10 d, 10%.

After establishment of the equilibrium we found a dr of 97:3,[18] from which an equilibrium constant of $K = 32.3$[19]

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(3) *trans*-Cycloalkenes are classified as planar chiral compounds: Schlögl, K. *Top. Curr. Chem.* **1984**, *125*, 27−62. Nakazaki, M.; Yamamoto, K.; Naemura, K. *Top. Curr. Chem.* **1984**, *125*, 1−25.

(4) Deiters, A.; Fröhlich, R.; Hoppe, D. *Angew. Chem., Int. Ed.* In press.

(5) Buck, J. C.; Ellis, F.; North, P. C. *Tetrahedron Lett.* **1982**, *23*, 4161−4162.

(6) Reviews: Hoppe, D.; Hense, T. *Angew. Chem.* **1997**, *109*, 2376−2410; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282−2316. Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552−560.

(7) In all known examples, deprotonation of *O*-allylic carbamates with *n*BuLi/(−)-sparteine led to the *S*-configurated organolithium compound. For example: (a) Deiters, A.; Hoppe, D. *Angew. Chem.* **1999**, *111*, 529−532; *Angew. Chem., Int. Ed.* **1999**, *38*, 546−548. (b) Behrens, K.; Fröhlich R.; Meyer O.; Hoppe D. *Eur. J. Org. Chem.* **1999**, 2397−2403. See also ref 4.

(8) This represents the typical stereochemical course in substitution reactions of allyllithium compounds. See ref 7b and Weisenburger, G. A.; Faibish, N. C.; Pippel, D. A.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 9522−9530 and references therein.

(9) When the reaction was carried out with *n*BuLi/TMEDA in ether at −78 °C, *rac*-**5** was obtained in 81% yield.

(10) (a) Hoppe, D. *Angew. Chem.* **1984**, *96*, 930−946; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932−948. (b) For X-ray crystal structure analysis of a lithiated allylic carbamate, see: Marsch, M.; Harms, K.; Zschage O.; Hoppe D.; Boche, G. *Angew. Chem.* **1991**, *103*, 338−339; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 321−322.

(11) The stereochemical terminology is that of Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; J. Wiley: New York, 1994; pp 1172−1175.

(12) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

(13) Crystals suitable for X-ray diffraction analysis were grown by vapor diffusion of pentane into an ethereal solution of (*P*,*R*)-**5**.

(14) A similar structure has been also investigated for *trans*-cyclononene derivatives: Manor, P. C.; Shoemaker, D. P.; Parkes, A. S. *J. Am. Chem. Soc.* **1970**, *92*, 5260−5262; Gavin, R. M., Jr.; Wang, Z. F. *J. Am. Chem. Soc.* **1973**, *95*, 1425−1429.

(15) One of the referees pointed out that the structure of the initial cyclization product (+)-(*M*,*R*)-**5** has not been rigorously assigned. The configuration of (+)-(*M*,*R*)-**5** could not determined directly by NMR methods due to line broadening, caused by dynamic processes. However, the (2*Z*,7*E*)-configuration of (+)-(*M*,*R*)-**5** results inevitably from the open-chain precursor (2*Z*,7*E*)-**3**. Thus, both cyclic species cannot differ in double bond geometry. When considering possible reversible interconversions which can be affiliated to the observed energetic barrier and the enthalpy difference, we were unable to determine processes other than epimerization of the *E* double bond.

(16) Hintze, F.; Hoppe, D. *Synthesis* **1992**, 1216−1218.

(17) The enantiomeric ratio of **7** was determined by GLC on a chiral stationary phase (Beta-Dex 120, Supelco, USA).

and an enthalpy difference for (M,R)-**5** and (P,R)-**5** of $\Delta H = 2.1$ kcal mol^{-1} follows.

Running the epimerization at four different temperatures while measuring the dr afforded the rate constants and the half-times of the unstable diastereomer (M,R)-**5**, as depicted in Table 1.[20]

Table 1. Kinetic Measurements of the Epimerization

entry	T/K	k/10^{-5} s^{-1}	$t_{1/2}$/min
1	298	1.2308	939
2	308	5.5614	208
3	318	21.713	53
4	323	38.178	30

Using these datas for an Arrhenius plot and employing a linear regression leads to an activation energy for epimerization of $E_A = 26.4$ kcal mol^{-1} (Figure 2). The half-time $t_{1/2}$ of the inversion of the plane of chirality in diene **5** at 30 °C is 208 min, much higher than that reported for (E)-cyclononene (6 s).[2b]

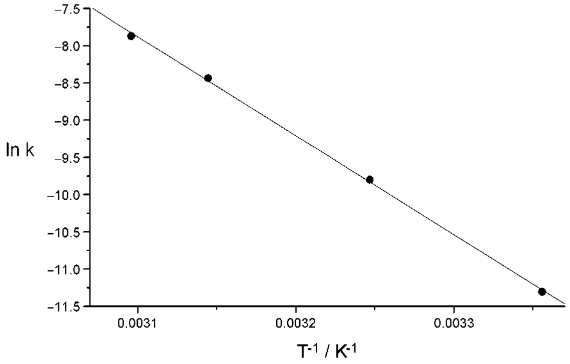

Figure 2. Arrhenius plot of the epimerization of (M,R)-**5**.

In an attempt to decide which conformational motions are responsible for the observed equilibration barrier, we carried out ab initio DFT calculations.[21] For convenience, the substituent in **5′** was chosen to be N,N-dimethylcarbamoyl instead of *Cby*; starting from the conformation found in the X-ray structure analysis of (P,R)-**5**. Looking only at the (1R)-diastereomers of **5**, two epimeric pairs of conformers, (P,R)-**5′** and (M,R)-**5′**, are found which are interconverted by conformational changes only. The four conformers and the transition structures (TS) interconnecting them are given in Figure 3 and the corresponding energies in Table 2.

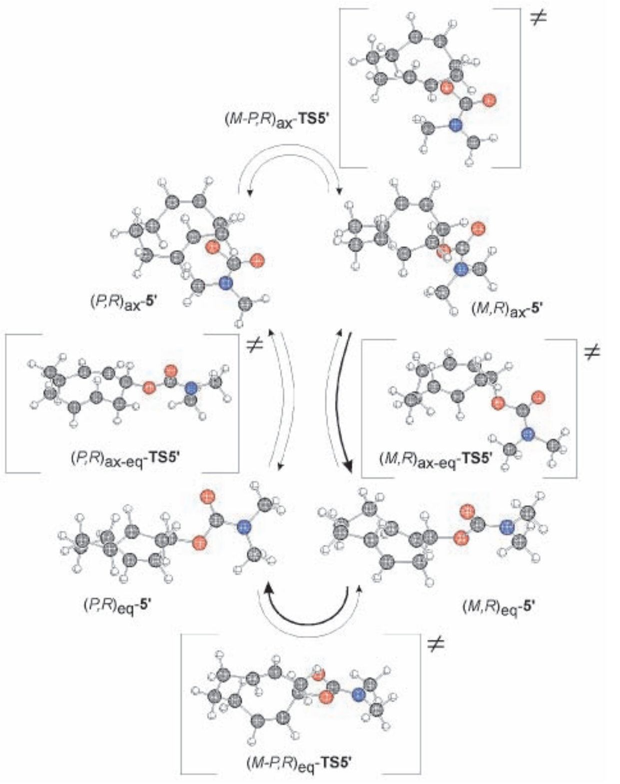

Figure 3. Conformational motion of (R)-**5′** (B3LYP/6-31G(d)).

Table 2. Relative Energies (B3LYP/6-31G(d)) of Conformers and Corresponding Transition Structures of **5′** (kcal mol^{-1})

conformer	E_{rel} (0 K)	ΔH_{rel} (298 K)
$(P,R)_{\mathrm{eq}}-\mathbf{5'}$	0.0	0.0
$(P,R)_{\mathrm{ax}}-\mathbf{5'}$	+8.1	+8.2
$(M,R)_{\mathrm{ax}}-\mathbf{5'}$	+2.1	+2.1
$(M,R)_{\mathrm{eq}}-\mathbf{5'}$	+5.0	+5.2
$(P,R)_{\mathrm{ax-eq}}-\mathbf{TS5'}$	+15.6	+15.3
$(M-P,R)_{\mathrm{ax}}-\mathbf{TS5'}$	+29.8	+29.4
$(M,R)_{\mathrm{ax-eq}}-\mathbf{TS5'}$	+17.2	+16.9
$(M-P,R)_{\mathrm{eq}}-\mathbf{TS5'}$	+27.2	+27.0

$(M,R)_{\mathrm{ax}}$-**5′** is the conformer that is predicted to result from the intramolecular nucleophilic substitution reaction. As has been discussed for *trans*-cyclooctene before,[11] two steps are required for inverting the cyclononadiene ring to furnish the conformer found in the solid state, $(P,R)_{\mathrm{eq}}$-**5′**: (i) a rotation of the E double bond moiety around the axis of the sp^3 carbon atoms (($M-P$)-**TS**) and (ii) flipping of the Z double bond array through the ring plane, which brings the substituent in an equatorial position (ax-eq-**TS**).

The geometry of the TS for the motion of the Z double bond was found by calculating the reaction coordinate for

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(18) The 600 MHz ^{1}H NMR spectra of (M,R)-**5** and (P,R)-**5** in CDCl$_3$ show two sets of signals for the olefinic protons at 4.99−5.13 and 5.42−5.51 ppm, which allowed us to perform kinetic measurements by ^{1}H NMR.

(19) To the best of our knowledge, this seems to be the highest equilibrium constant K reported for the epimerization of a monosubstituted *trans*-cycloalkene.

(20) The reaction constants were obtained by measuring the concentration of (M,R)-**5** by ^{1}H NMR after suitable time intervals and calculating an exponential regression of the decay (first-order process) by the use of Microcal Origin (Microcal Software, USA) running under MS Windows NT.

rotation of the C1−C9 bond on the semiempirical AM1 level of theory. It turned out that the two flexible "hinges" of the molecule flip in a concerted, although asynchronous mechanism. The motion of the C5−C6 bridge is less constrained; thus 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 $(M,R)_{\mathrm{ax-eq}}$-**TS5′**). When starting with the *E* double bond, rotation is not the preferred method for $(M,R)_{\mathrm{ax}}$-**5′** to epimerize ($(M-P,R)_{\mathrm{ax}}$-**TS5′**, $\Delta H_{\mathrm{rel}} = 29.4$ kcal mol^{-1}).

Instead, the carbamate substituent is moved into the equatorial position first via $(M,R)_{\mathrm{ax-eq}}$-**TS5′** ($\Delta H_{\mathrm{rel}} = 16.9$ kcal mol^{-1}). This process is endothermic (+3.1 kcal mol^{-1}) but not rate determining. The second step ($(M-P,R)_{\mathrm{eq}}$-**TS5′**) requires $\Delta H^{\ddagger} = 21.8$ kcal mol^{-1} and leads to the global minimum $(P,R)_{\mathrm{eq}}$-**5′**—in accordance with the X-ray structure.[22] Remarkably, the enthalpy difference of the experiment is exactly reproduced with the modest basis set we have chosen ($\Delta H = 2.1$ kcal mol^{-1}). The overall activation energy is estimated to be ($E_{\mathrm{A}} = \Delta H^{\ddagger} + RT$) 25.5 kcal mol^{-1} at 298 K, very close to the experimental result of 26.4 kcal mol^{-1}. The alternative reaction path—beginning with the $(M-P)$-epimerization—has a higher barrier ($\Delta H^{\ddagger} = 27.3$ kcal mol^{-1}) and is therefore expected to be much slower than the aforementioned sequence.

In conclusion, the method outlined here provides an easy access to optically active, medium-sized (*E*,*Z*)-cycloalkadienes by an enantioselective ring closing reaction, which includes the induction of planar chirality by a chiral center generated by our (−)-sparteine method. Moreover, due to the conformational stability of the initial product (*M*,*R*)-**5**, experimental evidence is seen for the first time for the broadly accepted assumption that α-alkylations of 1-oxy-substituted allyllithium compounds proceed from the 1-*endo*-confomers[10,23] as γ-alkylations and carbonyl addition reactions do.[10a] The stereochemical properties of the cyclization product have been extensively studied by kinetic measurements and computational calculations.

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Supporting Information Available: Detailed experimental procedures with spectroscopic data for the compounds **2**, **3**, (*M*,*R*)-**5**, and (*P*,*R*)-**5**, crystal data for compound (*P*,*R*)-**5**, and the data of the ab initio DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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[21] 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. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 1998.)

[22] In an alternative transition structure, the *E* double bond is rotated in the opposite direction, putting the C8−H in the endocyclic position. This process requires a higher activation barrier.

[23] Review: Schlosser, M.; Desponds, O.; Lehmann, R.; Moret, E.; Rauchschwalbe, G. *Tetrahedron* **1993**, *49*, 10175−10203.