Enantioselective Synthesis of Functionalized 1,5-Cyclononadienes by Intramolecular Cycloalkylation under α,α'-Diallyl Coupling**

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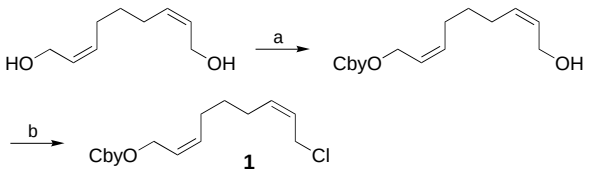
In spite of the biological importance of medium-size carbocycles, only a few ring-closing reactions are known for the synthesis of nine-membered monocarbocyclic rings.[1] Classic examples are the acyloin condensation of nonanedioic acid dimethyl esters[2a] and the McMurry reaction[2b]; however, for reasonable yields, a high dilution of the substrate and a long reaction time are always necessary.[2c]

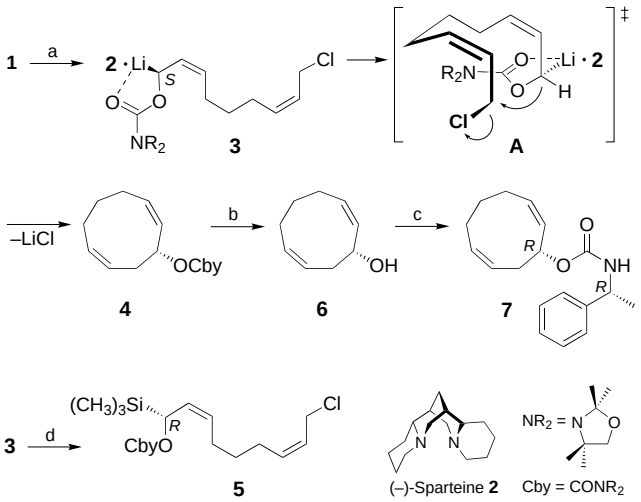
When we applied our protocol for an intramolecular lithium–ene reaction[3] on the (2*Z*,7*Z*)-9-chloro-2,7-nonadienyl carbamate **1**, we found a suprisingly efficient synthesis of a nine-membered carbocycle. The reaction proceeds to completion without any by-products within 2 h, even in 0.15 M solution. On the other hand, the (2*E*,7*E*)-isomer furnishes the expected *cis*-1,2-dialkenylcyclopentane **14**, as we recently reported (see Scheme 5).[3] Compound **1** was synthesized from the known compound *cis*,*cis*-nona-2,7-diene-1,9-diol (Scheme 1).[4]



Scheme 1. Synthesis of the dienyl carbamate **1**. a) 0.3 equiv NaH, 0.3 equiv CbyCl, THF, Δ, 85 %; b) 1.0 equiv *n*BuLi, 1.3 equiv MsCl, 1.0 equiv LiCl, THF, −78 °C→RT, 73 %.[23] Cby = 2,2,4,4-tetramethyl-1,3-oxazolidin-3-ylcarbonyl, Ms = methanesulfonyl.

Treatment of **1** with *n*-butyllithium/(−)-sparteine (**2**)[5] in toluene at −88 °C provided the (1*R*,2*Z*,7*Z*)-2,7-cyclononadienyl carbamate **4** in 73 % yield and with an *ee* value of 88 % (e.r. = 94:6; Scheme 2).[6, 7] The *S* configuration of the intermediate lithium complex **3** was confirmed by conversion into the silane (*R*)-**5** (87 % *ee*).[8, 9] Thus, the α,α'-coupling[10] of the allyl moieties in **3** proceeds under inversion of configuration at the metal-bearing carbon atom and, therefore, presumably passes through the transition state **A**.[11]

The cleavage[12] of the carbamate group led to the (*R*)-cyclononadienol **6** and addition of this to (*R*)-1-phenylethyl



Scheme 2. Cycloalkylation of the dienyl carbamate **1** and synthesis of the silane **5**. a) 2.0 equiv *n*BuLi, 2.0 equiv **2**, toluene, −88 °C, 73 %, e.r. = 94:6 (88 % *ee*.); b) 1.) 2.0 equiv CH_3SO_3H, CH_3OH, Δ; 2.) 4.0 equiv KOH, CH_3OH, Δ, 96 %; c) 3.0 equiv (*R*)-(+)-1-phenylethyl isocyanate, CH_2Cl_2, Δ, 63 %; d) 1.5 equiv *n*BuLi, 1.5 equiv (−)-sparteine, 2.7 equiv $(CH_3)_3SiCl$, toluene, −78 °C, 61 %, 87 % *ee*.[23]

isocyanate furnished the carbamate **7**. The X-ray analysis[13] of **7** (Figure 1) clearly shows the relative configuration *l* and hence the *R* configuration for (+)-**6** and (+)-**4**.

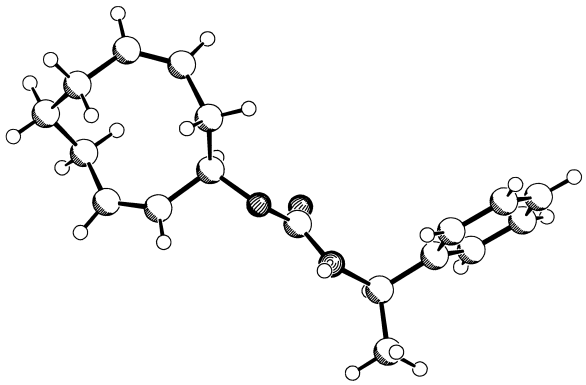


Figure 1. X-ray crystal structure analysis of **7**.[13]

The analogous TBDPS-oxydienyl carbamate (*R*)-**8** has been synthesized starting from (*S*)-epichlorohydrin (Scheme 3). Cyclization of (*R*)-**8** (100 % *ee*) by means of *n*BuLi/**2** furnished the enantiomericaly pure cyclononadiendiol derivatives (1*R*,5*S*)-**9** and (1*S*,5*S*)-**9**, in a diastereomeric ratio of 94:6, which are easily separated by chromatography.[15] The stereogenic center at C-5 affects neither the deprotonation nor the cyclization step; by use of the achiral base *n*BuLi/TMEDA, (1*R*,5*S*)-**9** and (1*S*,5*S*)-**9** were obtained in the ratio 53:47. Corresponding to this, *rac*-**8** furnished, after treatment with *n*BuLi/**2**, the epimers (1*R*,5*S*)-**9** and (1*R*,5*R*)-**9** in 74 % yield with a diastereomeric ratio of 55:45 and each with an *ee* value of 92 % (Scheme 4). After deprotection to the alcohol (1*R*,5*R*)-**10** and X-ray analysis, the relative configuration *l* was confirmed (Figure 2).[16]

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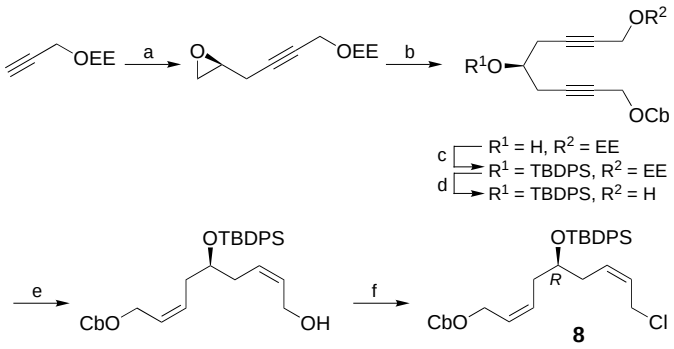
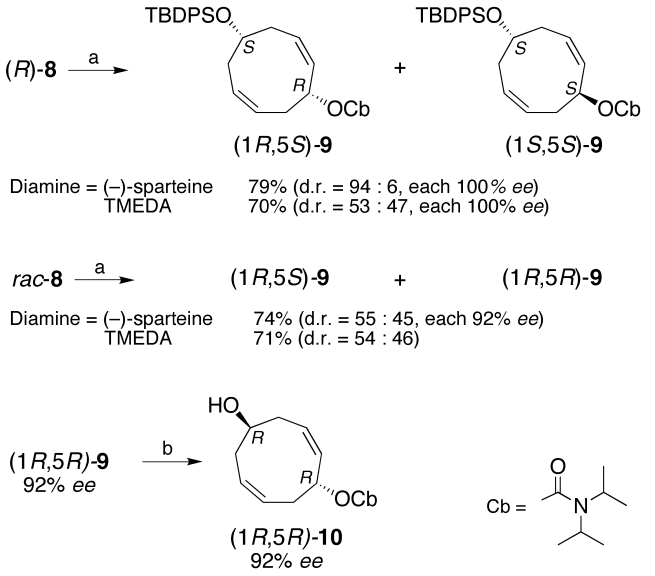


Scheme 3. Synthesis of the enantiomericaly pure dienyl carbamate **8**. a) 1.) 1.0 equiv *n*BuLi, 0.5 equiv (*S*)-(+)-epichlorohydrin, 1.0 equiv $BF_3 \cdot OEt_2$, THF, $-78\,^{\circ}C \rightarrow RT$; 2.) 1.0 equiv NaH, THF, $-10\,^{\circ}C$, 89%; b) 2.0 equiv $HCCCH_2OCb$,[14a] 2.0 equiv *n*BuLi, 2.0 equiv $BF_3 \cdot OEt_2$, THF, $-78\,^{\circ}C \rightarrow RT$, 98%;[14b] c) 1.2 equiv TBDPSCl, 2.5 equiv imidazole, DMF, 83%; d) 0.07 mass% amberlyst 15, MeOH, 40 °C, 95%; e) H_2, 5.0 mass% Lindlar catalyst, 0.15 equiv quinoline, MeOH, 96%; f) 1.0 equiv *n*BuLi, 1.2 equiv MsCl, 1.0 equiv LiCl, THF, $-78\,^{\circ}C \rightarrow RT$, 76%.[23] Cb = diisopropylaminocarbonyl, EE = ethoxyethyl, TBDPS = *tert*-butyldiphenylsilyl.



Scheme 4. Cycloalkylation of the dienyl carbamate **8** and deprotection of the product **9**. a) 2.0 equiv *n*BuLi, 2.0 equiv diamine, toluene, $-88\,^{\circ}C$, 2 h; b) 3.0 equiv tetrabutylammonium fluoride, THF, 74%.[23] TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

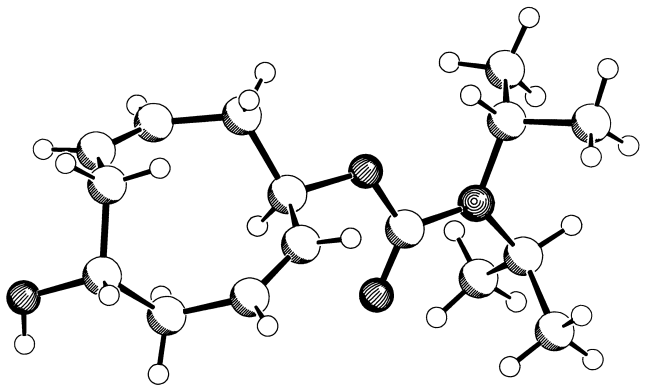
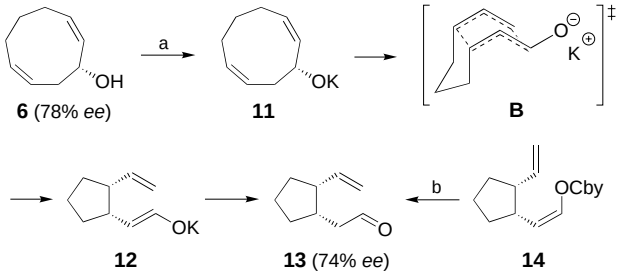


Figure 2. X-ray crystal structure analysis of (1*R*,5*R*)-**10**.[16]

The (*Z*,*Z*)-cyclonona-1,5-diene structure is destined for Cope rearrangements which pass through boatlike transition states:[17] After conversion of **6** into the potassium alcoholate **11** an anionic oxy-Cope rearrangement[18a] takes place at room temperature. The aldehyde (+)-**13**, obtained after protonation of the potassium enolate **12**, shows 95% stereoselectivity for the rearrangement.[18b] This seems to be the highest grade of chiral transmission in anionic oxy-Cope rearrangements of dienols which only contain a stereogenic center at the oxygen-bearing carbon atom.[19] The absolute configuration of **13** was determined by its synthesis from **14**[3] through deprotection of the enol.[20] Together with the *R* configuration of **6**, a reaction pathway via the transition state **B** with an equatorial oxido group[19c] takes place (Scheme 5).



Scheme 5. Enantioselective anionic oxy-Cope rearrangement. a) 1.3 equiv $KN(Si(CH_3)_3)_2$, THF, RT, 75%; b) 15 equiv $Al\textit{i}Bu_2H$, toluene, RT, 65%.

The method reported herein provides simple, flexible, and also enantioselective access to highly functionalized nine-membered carbocycles. The application of the homoenolate chemistry[5a, 21] on the configuratively stable secondary lithium species generated by deprotonation of **4** bears additional possibilities in the synthesis of nine-membered ring compounds.[22]

Experimental Section

Under argon, compounds **1** (500 mg, 1.52 mmol) and **2** (713 mg, 3.04 mmol) were dissolved in toluene (10 mL). After cooling to $-88\,^{\circ}C$, a 1.6 M solution of *n*-butyllithium in hexane (1.90 mL, 3.04 mmol) was slowly injected and the solution was stirred at this temperature for 2 h. Subsequently, CH_3OH (1 mL) and saturated aqueous NH_4Cl (1 mL) were added and the reaction mixture was allowed to warm to room temperature. Standard work up and purification by flash column chromatography over silica gel (Et_2O:pentane = 2:5) furnished **4** (324 mg, 73%, 88% *ee*) as a colorless solid (m.p. 72 °C).

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[1] The synthesis of nine-membered rings is particularly strongly disfavored because of the adverse entropic term, the Baeyer strain, and the Pitzer strain, as well as the transannular interactions: E. L. Eliel, S. H. Wilen in *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, pp. 675–685.

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[4] P. Lennon, M. Rosenblum, *J. Am. Chem. Soc.* **1983**, *105*, 1233 – 1241.

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

[6] If the reaction is carried out at $-78\,^{\circ}C$, **4** is obtained in 66% yield and 86% *ee*. By using the achiral base *n*BuLi/TMEDA in Et_2O at $-78\,^{\circ}C$, *rac*-**4** is yielded in 76%.

[7] Compound **4**: Mp 72 °C; $[\alpha]_D^{20} = +14.8$ ($c = 0.59$, $CHCl_3$; 88% *ee*); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.34 - 1.56$ (m, 14H, CH_2, CH_3(Cby)), 1.85 – 2.03 (m, 4H, CH_2), 2.22 and 2.43 (both m, each with 1H, CH_2), 3.70 and 3.71 (s, 2H, CH_2(Cby)), 5.10 (dd, 1H, CHO, $^3J = 7.8$, 7.8 Hz), 5.38 (dt, 1H, CH, $^3J = 9.6$, 9.6 Hz), 5.47 (dt, 1H, CH, $^3J = 5.8$, 10.1 Hz), 5.62 (m, 1H, CH), 5.79 (dt, 1H, CH, $^3J = 10.1$, 8.5 Hz). The enantiomeric ratio of **4** was determined by gas chromatography on a chiral stationary phase (Beta-Dex 120, Supelco, USA).

[8] Compound **5**: $[\alpha]_D^{20} = +10.3$ ($c = 1.27$, $CHCl_3$; 87% *ee*); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.05$ (s, 9H, $Si(CH_3)_3$), 1.30 – 1.51 (m, 14H, CH_2, CH_3(Cby)), 1.96 – 2.30 (m, 4H, CH_2), 3.69 (s, 2H, CH_2(Cby)), 4.07 (dd, 2H, CH_2Cl, $^4J = 1.8$, $^3J = 5.1$ Hz), 5.35 – 5.42 (m, 3H, CH, CHSi), 5.58 – 5.62 (m, 2H, CH). The enantiomeric ratio of the silane **5** was determined by ^1H NMR shift experiments in the presence of $[Eu(hfc)_3]$ (hfc = 3-(heptafluoropropylhydroxymethylene)-D-camphorate). After hydrogenation of the double bonds and hydrogenolytic cleavage of the chlorine atom, the corresponding 1-trimethylsilylnonyl carbamate was obtained.[3] Its enantiomer was synthesized by the *s*BuLi/(−)-sparteine method.[5a] A correlation of the optical rotations assigned the *R* configuration for (+)-**5**.

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[10] a) H. Yamamoto et al. reported intermolecular α,α'-allyl couplings by the use of allylbarium reagents.[10b] However, an intramolecular coupling reaction was unknown: A. Yanagisawa, K. Yasue, H. Yamamoto, *Synlett* **1996**, 842 – 844; A. Yanagisawa, H. Hibino, S. Habaue, Y. Hisada, H. Yamamoto, *J. Org. Chem.* **1992**, *57*, 6386 – 6387; b) A. Yanagisawa, H. Yamamoto in *Active Metals* (Ed.: A. Fürstner), VCH, Weinheim, **1995**, pp. 61 – 84.

[11] Presumably, the topology of the transition state **A** is influenced by $\pi - \pi^*$ interactions of the allylic moieties by precoordination and, therefore, favor the entropic term of the cyclization. In principle a γ,γ'-coupling between C-3 and C-7 is also possible and would lead to the *cis* configured five-membered ring. However, this would cause an increase of transannular and diaxial interactions of the side chains with the ring system; for this reason, the formation of a nine-membered ring takes place.

[12] F. Hintze, D. Hoppe, *Synthesis* **1992**, 1216 – 1218.

[13] X-ray crystal structure analysis of **7**: $C_{18}H_{23}NO_2$, $M_r = 285.37$, light yellow crystal, $0.20 \times 0.10 \times 0.05$ mm, $a = 23.258(1)$, $c = 5.106(1)$ Å, $\gamma = 120^{\circ}$, $V = 2392.0(5)$ Å^3, $\rho_{calcd} = 1.189$ g cm^{-3}, $\mu = 0.77$ cm^{-1}, absorption correction with SORTAV ($0.985 \le T \le 0.996$), $Z = 6$, trigonal, space group $P3_1$ (No. 144), $\lambda = 0.71073$ Å, $T = 198$ K, ω and φ scans, 20958 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.65$ Å^{-1}, 7097 independent ($R_{int} = 0.056$) and 4457 observed reflections [$I \ge 2\sigma(I)$], 387 refined parameters, $R = 0.066$, $wR^2 = 0.131$, max./min. residual electron density 0.42/ − 0.25 e Å^{-3}, Flack parameter − 0.1(14), the asymmetric unit contains two independent, nearly identical molecules, hydrogens were calculated and refined as riding atoms.[16b]

[14] a) For 2-alkynyl carbamates, see: S. Dreller, M. Dyrbusch, D. Hoppe, *Synlett* **1991**, 397 – 400; b) For a similar reaction sequence, see: S. Hatakeyama, H. Irie, T. Shintani, Y. Noguchi, H. Yamada, M. Nishizawa, *Tetrahedron* **1994**, *50*, 13369 – 13376.

[15] Compound (1*R*,5*S*)-**9**: $[\alpha]_D^{20} = -37.7$ ($c = 0.43$, $CHCl_3$, 100% *ee*); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.07$ (s, 9H, *t*Bu), 1.22 (d, 12H, CH_3(Cb), $^3J = 6.9$ Hz), 1.93 – 2.00 (m, 1H, CH_2), 2.11 (dd, 2H, CH_2, $^3J = 6.9$, 3.6 Hz), 2.19 – 2.38 (m, 2H, CH_2, CH_2), 2.53 (ddd, 1H, CH_2, $^3J = 8.7$, 9.0, $^2J = 12.9$ Hz), 3.80 – 4.03 (m, 3H, CH(Cb), CHOSi), 5.03 (dd, 1H, CHOCb, $^3J = 6.0$, 6.9 Hz), 5.35 (dt, 1H, CH, $^3J = 10.6$, 5.7 Hz), 5.67 – 5.81 (m, 3H, CH, CH, CH), 7.32 – 7.70 (m, 10H, CH(phenyl)). After cleavage of the TBDPS group, the enantiomeric ratio of (1*R*,5*S*)-**10** was determined as described in reference [7].

[16] a) X-ray crystal structure analysis of (1*R*,5*R*)-**10**: $C_{16}H_{27}NO_3$, $M_r = 281.39$, colorless crystal, $0.40 \times 0.25 \times 0.15$ mm, $a = 26.159(5)$, $b = 10.884(2)$, $c = 12.918(3)$ Å, $\beta = 113.71(2)^{\circ}$, $V = 3367.5(12)$ Å^3, $\rho_{calcd} = 1.110$ g cm^{-3}, $\mu = 6.04$ cm^{-1}, absorption correction with ψ-scan data ($0.794 \le T \le 0.915$), $Z = 8$, monoclinic, space group $C2$ (No. 5), $\lambda = 1.54178$ Å, $T = 223$ K, $\omega/2\theta$ scans, 3697 reflections collected ($\pm h$, $+k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.62$ Å^{-1}, 3611 independent ($R_{int} = 0.077$) and 3159 observed reflections [$I \ge 2\sigma(I)$], 372 refined parameters, $R = 0.044$, $wR^2 = 0.119$, max./min. residual electron density 0.24/ − 0.17 e Å^{-3}, Flack Parameter 0.3(2), the asymmetric unit contains two independent, nearly identical molecules, hydrogens were calculated and refined as riding atoms; b) The data sets were collected with Nonius CAD4 and Nonius KappaCCD diffractometers equipped with a Nonius FR590 sealed tube generator or a Nonius FR591 rotating anode generator. The following programs were used: For data collection, EXPRESS (Nonius B.V., **1994**) and COLLECT (Nonius B.V., **1998**); for data reduction, MolEN (K. Fair, Enraf – Nonius B.V., **1990**) and Denzo-SMN (Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307 – 326); for absorption corrections for CCD data, SORTAV (R. H. Blessing, *Acta Crystallogr. Sect. A* **1995**, *51*, 33 – 37; R. H. Blessing, *J. Appl. Crystallogr.* **1997**, *30*, 421 – 426); for structure solution, SHELXS-97 (G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467 – 473); for structure refinement, SHELXL-97 (G. M. Sheldrick, University of Göttingen, **1997**); for graphics, SCHAKAL (E. Keller, University of Freiburg, **1997**). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-139019 and -139020. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[17] By heating **4** up to 220 °C, a stereospecific Cope rearrangement takes place;[22] Cope rearrangement of (*Z*,*Z*)-cyclonona-1,5-diene: E. Vogel, W. Grimme, E. Dinné, *Angew. Chem.* **1963**, *75*, 1103.

[18] a) Review of anionic oxy-Cope rearrangements: L. A. Paquette, *Tetrahedron* **1997**, *53*, 13971 – 14020; b) anionic oxy-Cope rearrangement of *rac*-**6**: L. A. Paquette, G. D. Crouse, A. K. Sharma, *J. Am. Chem. Soc.* **1982**, *104*, 4411 – 4423. The enantiomeric ratio of **13** was determined as described in reference [7].

[19] a) S.-Y. Wei, K. Tomooka, T. Nakai, *Tetrahedron* **1993**, *49*, 1025 – 1042; b) L. A. Paquette, G. D. Maynard, *Angew. Chem.* **1991**, *103*, 1392 – 1394; *Angew. Chem. Int. Ed. Eng.* **1991**, *30*, 1368 – 1370; c) in anionic oxy-Cope rearrangements the oxido group prefers an equatorial position: L. A. Paquette, G. Maynard, *J. Am. Chem. Soc.* **1992**, *114*, 5018 – 5027.

[20] K. Tomooka, N. Komine, T. Sasaki, H. Shimizu, T. Nakai, *Tetrahedron Lett.* **1998**, *39*, 9715 – 9718.

[21] Review of homoenolate chemistry: D. Hoppe, *Angew. Chem.* **1984**, *96*, 930 – 946; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 932 – 948.

[22] A. Deiters, D. Hoppe, unpublished results.

[23] All new compounds were analytically pure (error in C,H,N elemental analyses ±0.4).

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