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Synthesis of an Ethynyl Carbamate and Application for Enantioselective Cyclocarbolithiation

Gabriele Gralla, Birgit Wibbeling,[‡] and Dieter Hoppe*,[†]

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

dhoppe@uni-muenster.de

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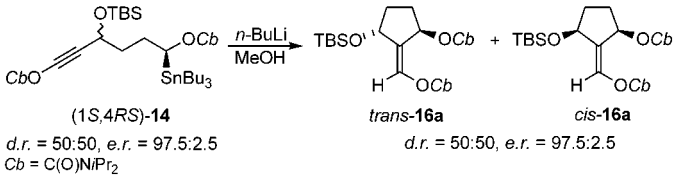
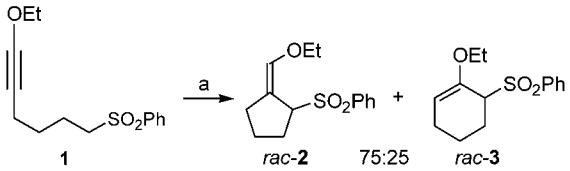
ABSTRACT



The intramolecular *trans*-cyclocarbolithiation of the α-lithiated 4-substituted 5-hexynyl carbamate (1*S*,4*RS*)-14 employing lithiodestannylation is presented. The 5-*exo*-*dig* cyclization products *cis*-/*trans*-16a were formed exclusively. The highly enantioenriched organotin precursor (*S*)-11 was synthesized via an asymmetric deprotonation of the corresponding alkyl carbamate 10 by the chiral complex *sec*-butyllithium/(−)-sparteine and subsequent substitution with tributyltin chloride.

Enantioenriched 2-alkylidene-cyclopentanols have been prepared by asymmetric deprotonation[1] of 5-alkynyl carbamates and subsequent 5-*exo*-*dig* ring closure[2] of the intermediate chiral lithium compound.[3,4] Funk et al. reported on the intramolecular carbolithiation reaction of the racemic lithium compound derived from the 6-ethoxy-5-hexynyl sulfone **1** (Scheme 1).[5] Here the cyclization proceeds with only low regioselectivity to the racemic *exo*-/*endo*-adducts **2** and **3**. We expected that by application of ω-carbamoyloxy-5-hexynyl higher regioselectivities in favor of the five-membered ring should be achieved (as a result of the complexation of the lithium cation by the carbamoyloxy group). Further synthetic options are possible by substitution via the intermediate lithiovinyl carbamate.[6] In addition, we expected that the carbon chain of precursor (1*S*,4*RS*)-**14** can

Scheme 1[a]



[a] Reagents: (a) BuLi, HMPA, THF, −78 °C to rt, 53%.

[†] Fax: (+49)251/8336531.

[‡] To whom correspondence regarding X-ray analysis should be addressed.

(1) (a) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem.* **1990**, *102*, 1457−1459; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422−1423. (b) Review: Hoppe, D.; Hense, T. *Angew. Chem.* **1997**, *109*, 2376−2410; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282−2316. (c) Beak, P.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552−560.

(2) Reviews: (a) Marek, I.; Normant, J. F. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 271−337. (b) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 4, pp 865−911. (c) Review: Marek, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 535−544. (d) Bailey, W. F.; Carson, M. W. *J. Org. Chem.* **1998**, *2*, 361−365. (e) Bailey, W. F.; Mealy, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 6787−6788.

(3) For the 5-*exo*-*trig* ring closure, see: (a) Woltering, M. J.; Fröhlich, R.; Hoppe, D. *Angew. Chem.* **1997**, *109*, 1804−1805; *Angew. Chem., Int. Ed. Engl.* **1997**, *29*, 1764−1766. (b) Woltering, M. J.; Fröhlich, R.; Wibbeling, B.; Hoppe, D. *Synlett* **1998**, 797. (c) Hoppe, D., Woltering, M. J.; Oestreich, M.; Fröhlich, R. *Helv. Chim. Acta* **1999**, *82*, 1860.

(4) For the 5-*exo*-*dig* ring closure, see: (a) Oestreich, M.; Fröhlich, R.; Hoppe, D. *Tetrahedron Lett.* **1998**, *39*, 1745−1748. (b) Oestreich, M.; Fröhlich, R.; Hoppe, D. *Tetrahedron Lett.* **1999**, *40*, 1881−1884. (c) Oestreich, M.; Fröhlich, R.; Hoppe, D. *J. Org. Chem.* **1999**, *64*, 8616−8626.

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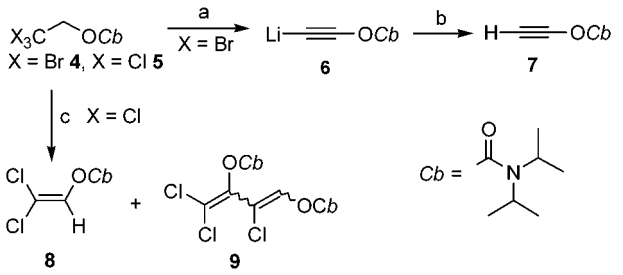
be easily constructed via the substitution of the highly acidic proton in an ethynyl carbamate.[7]

3-Alkene-1-ynyl carbamates[8] have been reported, but ethynyl carbamates are still unknown. The ethynyl carbamate **7** was synthesized via the corresponding lithium acetylide **6** by treatment of 2,2,2-tribromoethyl carbamate **4** with 4.5 equiv of lithium *N*,*N*-diisopropylamide (LDA) at −78 °C in THF, presumably involving two elimination steps and one reductive lithiation (Scheme 2).[9] Interestingly, under similar

Scheme 2[a]

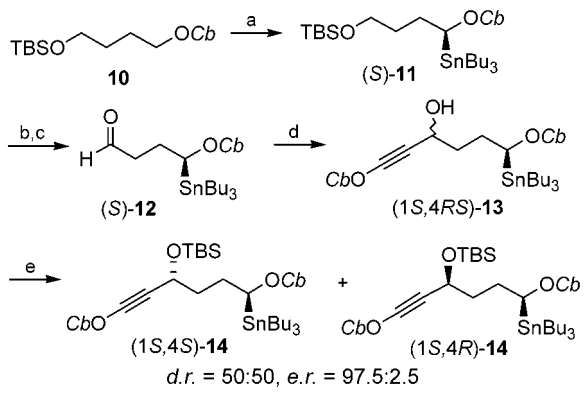


[a] Reagents: (a) 4.5 equiv of LDA, THF, −78 °C. (b) MeOH, 72%. (c) (i) 3.5 equiv of LDA, THF, −78 °C; (ii) MeOH, 13% (**8**), 70% (**9**) or (i) 3.1 equiv of LDA, Et_2O, −78 °C; (ii) MeOH, 90% (**8**), 0% (**9**).

conditions the transformation of the analogous 2,2,2-trichloroethyl carbamate **5** in THF furnished the diene **9** as a single isomer of unknown configuration in 70% yield, whereas when diethyl ether was used as the solvent, the 2,2-dichlorovinyl carbamate[10] **8** was isolated in 90% yield.

The aldehyde (*S*)-**12** (≥95% ee) was synthesized from 1,4-butanediol via (−)-sparteine-mediated lithiation[1] and subsequent substitution by tributyltin chloride.[11] The addition of the aldehyde (*S*)-**12** onto the lithium acetylide **6** in the presence of LiCl in THF furnished the desired alcohols (1*S*,4*RS*)-**13** with a ratio of 50:50 in 92% yield. The protection of (1*S*,4*RS*)-**13** with TBSOTf led to the optically active key intermediate (1*S*,4*RS*)-**14** in good yield (Scheme 3).

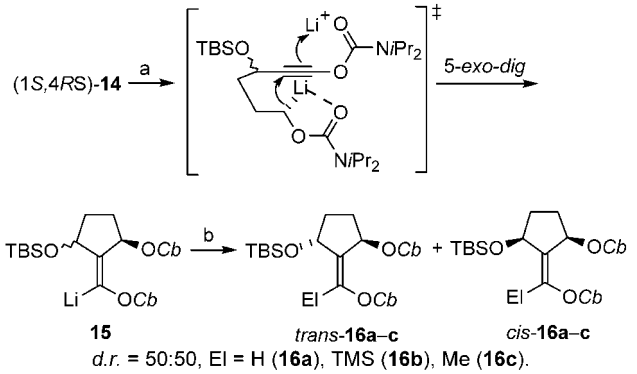
Scheme 3[a]



[a] Reagents: (a) (i) *s*-BuLi, (−)-sparteine, −78 °C, Et_2O; (ii) Bu_3SnCl, 88%. (b) TBAF, Et_2O, 100%. (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 95%. (d) **7**, LDA, LiCl then (*S*)-**12**, −78 to −20 °C, 92%. (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 86%.

The lithiodestannylation[11,12] of (1*S*,4*RS*)-**14** with 1.5−2.5 equiv of *n*-butyllithium in diethyl ether or THF at −78 °C for 4 h resulting in an asymmetric 5-*exo*-*dig* ring closure provided the cyclization products *cis*-**16a**−**c** and *trans*-**16a**−**c** in a ratio of 50:50 after substitution with different electrophiles (Scheme 4). All products *cis*-/*trans*-**16a**−**c** were

Scheme 4[a]



[a] Reagents: (a) Method A: 1.5 equiv of *n*-BuLi, −78 °C, THF. Method B: 2.5 equiv of *n*-BuLi, −78 °C, Et_2O. Method C: 1.5 equiv of *n*-BuLi, 3.0 equiv of LiCl, −78 °C, Et_2O. (b) ElX = HOMe, TMSCl, or MeI.

isolated in high enantiomeric excess (Table 1). The diastereomers *cis*-/*trans*-**16a**−**c** were readily separated by flash column chromatography. The double bond geometries of *cis*/*trans*-**16a**−**c** were determined by NOE experiments. When

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(6) (a) Kocienski, P.; Dixon, N. J. *Synlett* **1989**, 52. (b) Sengupta, S.; Snieckus, V. *J. Org. Chem.* **1990**, *55*, 5680−5683. (c) Peschke, B. Dissertation, Universität Kiel, 1991.

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(9) The reaction of **4** with 3.5 equiv of LDA afforded **7** in 56% yield.

(10) For the preparation of 2,2-difluorovinyl carbamates, see: (a) Howarth, J. A.; Owton, W. M.; Percy, J. M.; Rock, M. H. *Tetrahedron* **1995**, *51*, 10289−10302. (b) Howarth, J. A.; Owton, W. M.; Percy, J. M.; Rock, M. H. *Tetrahedron Lett.* **1996**, *37*, 5975−5978. (c) Balnaves, A. S.; Palmer, M. J.; Percy, J. M.; Rock, M. H. *Chem. Commun.* **1999**, 2183-2184.

(11) Christoph, G.; Hoppe, D. *Org. Lett.* **2002**, *4*, 2189−2192.

(12) Further examples: (a) Tomooka, K.; Komine, N.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 8939−8942. (b) Coldham, I.; Hufton, R.; Snowden, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5322−5323. (c) Coldham, I.; Fernandez, J. C.; Price, K. N. *J. Org. Chem.* **2000**, *65*, 3788−3795. (d) Coldham, I.; Hufton, R.; Price, K. N.; Rathmell, R. E.; Snowden, D. J.; Vennall, G. P. *Synthesis* **2001**, 1523−1531. (e) Serino, C.; Stehle, N.; Park, Y. S.; Florio, S.; Beak, P. *J. Org. Chem.* **1999**, *64*, 1160−1165.

Table 1. Cyclization of (1*S*,4*RS*)-**14**

entry	method[a]	solvent	ElX	product dr 50:50	yield (%)	er[b]
1[c]	**A**	Et_2O	MeOH	**16a**	35	97.5:2.5
2	**B**	Et_2O	MeOH	**16a**	59	97.5:2.5
3	**C**	Et_2O	MeOH	**16a**	63	97.5:2.5
4	**A**	THF	MeOH	**16a**	92	97.0:3.0
5	**B**	Et_2O	TMSCl	**16b**	61	97.5:2.5
6	**A**	THF	TMSCl	**16b**	91	97.0:3.0
7	**A**	THF	MeI	**16c**	90	97.0:3.0

[a] Method A: 1.5 equiv of *n*-BuLi. Method B: 2.5 equiv of *n*-BuLi. Method C: 1.5 equiv of *n*-BuLi, 3.0 equiv of LiCl. [b] The er ratio was determined for *cis*- and *trans*-diastereomers **16a**−**c**. [c] 46% of the starting material (1*S*,4*RS*)-**14** was recovered.

the cyclization precursors (1*S*,4*RS*)-**14** were treated with 1.5 equiv of *n*-butyllithium in diethyl ether the desired cyclocarbolithiation was incomplete. After quenching with MeOH the product *cis*-/*trans*-**16a** was obtained in 35% yield and further 46% of the starting material (1*S*,4*RS*)-**14** was recovered (Table 1, entry 1). Employing a substantial excess of *n*-butyllithium (2.5 equiv) leads to a marked improvement in the yield (59%) (Table 1, entry 2). We examined the addition of lithium chloride to the reaction mixture in order to enhance the reactivity of the intermediate lithium species. However, the isolated yield of the cyclization products *cis*-/*trans*-**16a** shows a slight increase (Table 1, entry 3). By changing the solvent from diethyl ether to THF, the cyclocarbolithiation proceeds smoothly to *cis*-/*trans*-**16a**, isolated in high yield (Table 1, entry 4). Other electrophiles such as trimethylsilyl chloride and methyl iodide were employed in this reaction sequence leading to optically active cyclization products *cis*-/*trans*-**16b**−**c** in excellent yields (Table 1, entries 6 and 7). The reaction with trimethylsilyl chloride in diethyl ether yields *cis*-/*trans*-**16b** in 62%.

From these results, it can be concluded that a lithium cation might complex the carbonyl oxygen atom of carbamate groups of (1*S*,4*RS*)-**14** and facilitate the addition step.

The er values of the cyclization products *cis*-**16a**−**c** and *trans*-**16a**−**c** were determined by HPLC. Running the cyclization reactions of (1*S*,4*RS*)-**14** in THF leads to a slight loss of ee (94% ee) (Table 1, entries 4, 6, and 7), whereas in diethyl ether we obtained 95% ee. The absolute and relative configuration of the diastereomer *cis*-**16a** was elucidated by the X-ray crystal structure analysis of its urethane *cis*-**17** (Figure 1), which shows the geometry of the double bond[13] and the (*R*)-configuration in the 1-position. The (1*R*,2*Z*)-configuration of *cis*-**16a** implies the usual retention at the stereogenic carbon atom and an *anti*-addition onto the triple bond to form the vinyllithium intermediate **15**. These cyclization reactions usually proceed as a *syn* process.[4] The compound *rac*-**2**[5] in a formal sense arises from an *anti*-addition, too. It is possible that isomerization of the

(13) Crystals suitable for X-ray diffraction analysis were grown by vapor diffusion of pentane into an ethereal solution of *cis*-**17**.

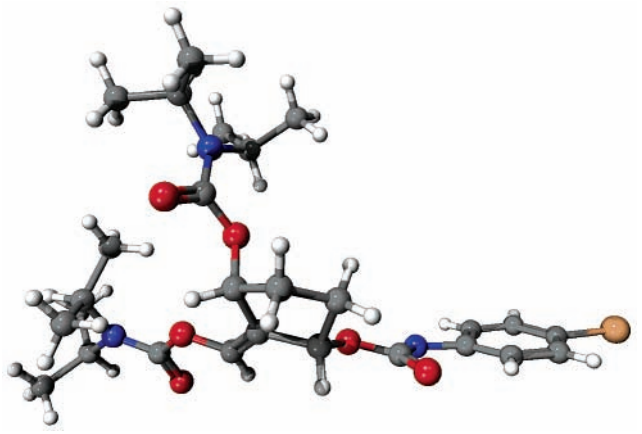
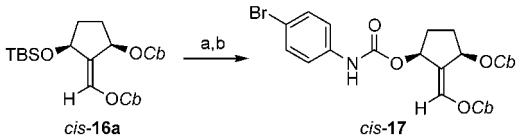


Figure 1. Crystal structure of carbamate *cis*-**17**.

highly acidic allyl sulfone takes place by torsion in the allylic anion. However, a subsequent isomerization of the double bond in the vinyllithium **15** cannot be excluded completely at the present stage of investigations.

The tricarbamate *cis*-**17** was prepared from *cis*-**16a** via cleavage of the silyl ether followed by addition onto *p*-bromophenyl isocyanate in a satisfactory yield of 74% (Scheme 5).

Scheme 5[a]



cis-**16a** *cis*-**17**

[a] Reagents: (a) TBAF, Et_2O, 100%. (b) *p*BrPhNCO, CH_2Cl_2, reflux, 74%.

In summary, we have reported the highly *trans*-selective cyclocarbolithiation of a *ω*-lithiated alkynyl carbamate utilizing lithiodestannylation to highly enantioenriched protected 2-alkylidene cyclopentane-1,3-diols, bearing a masked carbonyl group. The ring closure of the α-lithiated 4-substituted 5-hexynyl carbamate proceeds with complete regioselectivity (5-*exo*-*dig* exclusively), avoiding the prior use of the toxic reagent HMPA.

Acknowledgment. G.G. thanks Mrs. U. Janz for technical assistance.

Supporting Information Available: Detailed experimental procedures with spectroscopic data for all new compounds and crystal analysis data of *cis*-**17** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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