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Synthesis of 2-alkylidene-cycloalkane-1,3-diols via enantioselective intramolecular carbolithiation

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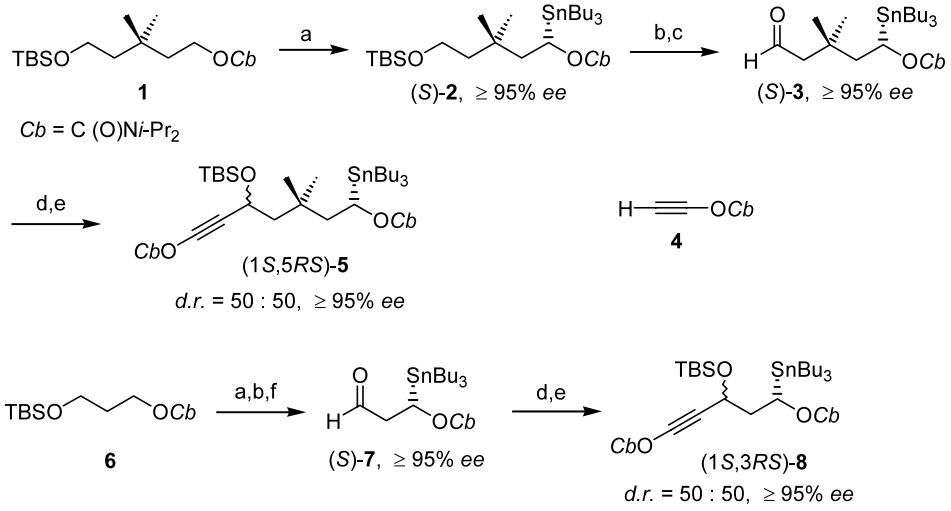
Abstract—The lithiodestannylation and intramolecular *anti*-selective carbolithiation of α-lithiated ω-carbamoyloxy-1-alkynyl carbamates have been used to synthesize highly enantioenriched protected 2-alkylidene-cycloalkane-1,3-diols.

The intramolecular carbolithiation of lithium carbanions onto multiple bonds is an efficient method for the construction of carbocycles.[1,2] These reactions usually proceed rapidly only for the formation of five-membered rings.[3,4] In this context, we have recently reported the first example of an asymmetric intramolecular *anti*-selective 5-*exo*-*dig*[5] cyclocarbolithiation of an α-lithiated ω-carbamoyloxy-5-hexynyl carbamate generated by lithiodestannylation.[6] The ring closure proceeds with complete regioselectivity to highly enantioenriched protected 2-alkylidene-cyclopentane-1,3-diols in good yields. In contrast to the above-mentioned cyclocarbolithiations, an *anti*-addition onto the triple bond took place. During our further studies, we extended this application to the synthesis of chiral 2-alkylidene-cyclohexane and -cyclobutane derivatives.



Scheme 1. *Reagents and conditions*: (a) i) *sec*-BuLi, (–)-sparteine, Et_2O, −78°C, 6 h; ii) Bu_3SnCl, −78°C→rt, 14 h, 66–73%; (b) TBAF, Et_2O, rt, 97%; (c) i) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, 60 min; ii) Et_3N, −78°C→rt, 89%; (d) i) **4**, LDA, LiCl, THF, −40°C, 30 min; ii) (*S*)-**3** or (*S*)-**7**, −40°C→−20°C, 16 h, 51–76%; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 30 min, quantitative; (f) PDC, molecular sieves 4 Å, CH_2Cl_2, rt, 2 h.

Keywords: asymmetric deprotonation; (–)-sparteine; lithiodestannylation; intramolecular carbolithiation; chiral alkylidene-cyclobutanes and -cyclohexane.

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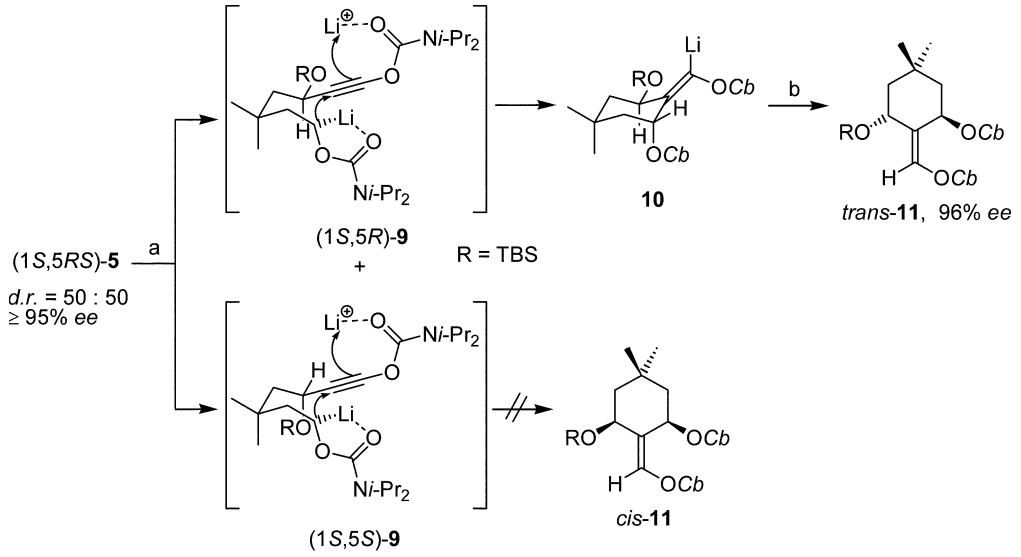


Scheme 2. *Reagents and conditions*: (a) *n*-BuLi, LiCl, THF, −100°C, 20 min; (b) MeOH, −100°C→rt, 37%.

The requisite ω-carbamoyloxy-1-alkynyl carbamates were prepared following the reaction sequence summarized in Scheme 1. The optically active key intermediates (1*S*,5*RS*)-**5** and (1*S*,3*RS*)-**8** were synthesized starting from 3,3-dimethyl-1,5-pentanediol[7] and 1,3-propanediol. These were transformed into alkyl carbamates and then subjected to an asymmetric deprotonation[8] by the chiral complex *sec*-butyllithium/(−)-sparteine followed by subsequent substitution with tributyltin chloride. After deprotection, a Swern oxidation or a PDC oxidation[9] of the primary alcohols provided the corresponding aldehydes (*S*)-**3** and (*S*)-**7**, which were alkynylated with lithiated ethynyl carbamate[6] **4** in the presence of LiCl. The protection of the secondary alcohols with TBSOTf furnished the cyclization precursors (1*S*,5*RS*)-**5** and (1*S*,3*RS*)-**8** in a diastereomeric ratio of 50:50 and in quantitative yields.

Tin–lithium exchange of (1*S*,5*RS*)-**5** with *n*-butyllithium in THF at −100°C in the presence of LiCl for 20 min resulted in an asymmetric *anti*-selective 6-*exo*-*dig* carbolithiation providing the cyclization product **10**. After quenching with MeOH a single diastereomer *trans*-**11** was obtained in 37% yield with an enantiomeric excess of 96% (Scheme 2).[10] Formation of the other diastereomer *cis*-**11** was not observed, but decomposition of the α-lithiated precursor (1*S*,5*S*)-**9** took place. Presumably, the 1,3,5-triaxial interaction between the TBSO-, the CbO-group and one methyl group prevents the formation of transition state (1*S*,5*S*)-**9**.

The absolute configuration and the double bond geometry of *trans*-**11** were determined on the basis of X-ray crystal structure analysis (Fig. 1).[11] The (1*R*)-configuration at the former lithium-bearing carbon atom indicates the generation of the lithium carbanions by lithiodestannylation with the usual retention of configuration. The double bond geometry of *trans*-**11** coincides with our presumption that the cyclization reaction proceeds as an *anti* process. Usually the intramolecular addition reaction of lithium carbanions onto trimethylsilyl- or phenyl-substituted multiple bonds occurs with complete *syn*-selectivity.[3,4f]

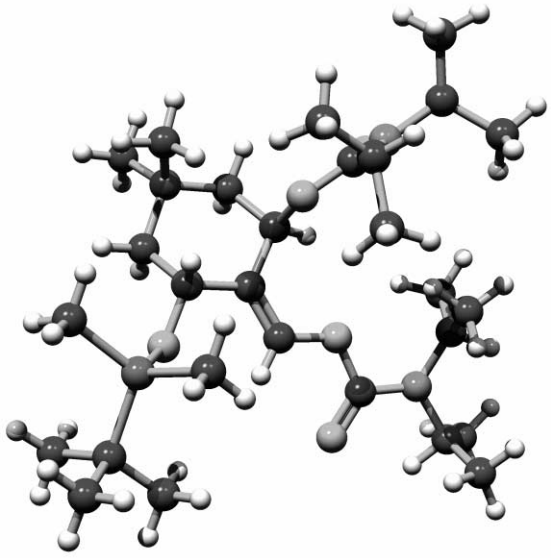
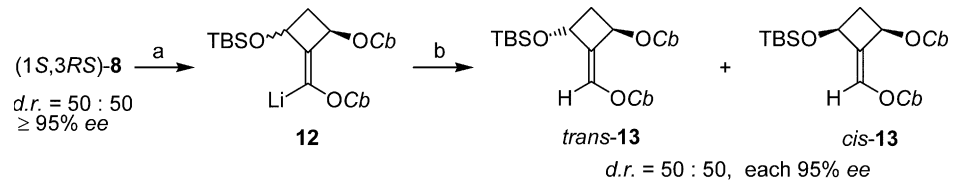


Figure 1. Crystal structure of the compound *trans*-**11**.

Analogously we examined the carbolithiation of the diastereomeric mixture (1*S*,3*R*)-**8** and (1*S*,3*S*)-**8**, which was treated with *n*-butyllithium in THF at −40°C in the presence of LiCl. Subsequent protonation of the intermediate lithium species **12** with HOAc furnished the diastereomers *cis*- and *trans*-**13** in a ratio of 50:50 in 50% yield with an enantiomeric excess for each of 95%. The diastereomer mixture *cis*- and *trans*-**13** was readily separated by flash column chromatography. Changing the temperature from −40°C to −78°C led to incomplete carbolithiation in which exclusively *trans*-**13** was formed in low yield (13%) (Scheme 3).



entry	method	*trans*-**13** (%)	*cis*-**13** (%)	*ee* (%)
1	A	25	25	95
2	B	13	–	95

Scheme 3. Method A: (a) *n*-BuLi, THF, LiCl, –40°C, 3 h; (b) HOAc, –40°C→rt. Method B: (a) *n*-BuLi, THF, LiCl, –78°C, 3 h; (b) HOAc, –78°C→rt.

In summary, we have reported stereoselective intramolecular 4- and 6-*exo*-*dig* carbolithiations, which occur highly regio- and diastereoselectively with respect to the double bond geometry to form enantioenriched protected 2-alkylidene-cyclohexane- and -cyclobutane-1,3-diols. The addition of the lithium carbanion pair onto the triple bond proceeds *anti*-selectively, presumably due to the precomplexation of the lithium cation by the carbonyl oxygen atom of the carbamate.

Acknowledgements

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9. The chiral aldehyde (*S*)-**7** is very unstable, therefore it was not purified. Synthesis of (*S*)-**7**: To a suspension of pyridinium dichromate (PDC) (0.573 g, 1.52 mmol, 1.5 equiv.) and molecular sieves 4 Å (0.573 g) in CH_2Cl_2 (4 mL) under an argon atmosphere was added the stannylated primary alcohol (0.500 g, 1.02 mmol, 1.0 equiv.) at room temperature. The suspension was stirred for 2 h

and subsequently filtered by flash column chromatography on silica gel (2×26 cm) with diethyl ether.

10. A solution of (1*S*,5*RS*)-**5** or (1*S*,3*RS*)-**8** (1.0 equiv.) in dry THF under an argon atmosphere was cooled to −100°C (for (1*S*,5*RS*)-**5**) or −40°C (for (1*S*,3*RS*)-**8**). After dropwise injection of *n*-BuLi (1.6 M in *n*-hexane, 1.5 equiv.) the reaction mixture was stirred for 20 min (for (1*S*,5*RS*)-**5**) or 3 h (for (1*S*,3*RS*)-**8**). Addition of MeOH at −100°C (for (1*S*,5*RS*)-**5**) or HOAc (1 M in toluene, at −40°C for (1*S*,3*RS*)-**8**) stopped the reaction. *Work-up for trans*-**11**: After addition of sat. aqueous NH_4Cl; the organic layer was separated and the aqueous layer was extracted with diethyl ether several times. Drying ($MgSO_4$), concentration in vacuo, and purification of the crude product by flash column chromatography on silica gel (pentane/ether = 10:1) provided *trans*-**11**. The ee value was determined by HPLC (column: ChiraGrom 2 (2×250 mm, *i*-PrOH/*n*-hexane = 1:1000). *trans*-**11**: $[\alpha]_D^{20} = -72.0$ (*c* 0.49, $CHCl_3$, 96% ee). *Work-up for cis-/trans*-**13**: After addition of HOAc (1 M in toluene) the reaction mixture was brought to ambient temperature. The organic solution was neutralized ($NaHCO_3$) and dried ($MgSO_4$). The purification of the residue by flash column chromatography on silica gel (pentane/ether = 10:1) afforded *cis-/trans*-**13**. The ee values were determined by HPLC (*trans*-**13**: column: ChiraGrom 2 (2×250 mm, *i*-PrOH/*n*-hexane = 1:1200; *cis*-**13**: column: ChiraGrom 2 (2×250 mm, *i*-PrOH/*n*-hexane = 1:1500). *trans*-**13**: $[\alpha]_D^{20} = -122$ (*c* 0.40, $CHCl_3$, 95% ee); ^{1}H NMR (600 MHz, CD_3OD) δ: 0.03 (s, 6H); 0.85 (s, 9H); 1.15 (m, 24H); 2.29 (m, 2H); 3.83, 4.10 (2×b s, 4H); 5.06 (m, 1H); 5.62 (m, 1H); 7.08 (s, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ: −4.3, 19.2, 20.8, 22.2, 26.5, 41.9, 48.1, 48.6, 68.3, 68.9, 126.8, 134.8, 154.4, 156.8. *cis*-**13**: $[\alpha]_D^{20} = -72.2$ (*c* 0.54, $CHCl_3$, 95% ee); ^{1}H NMR (600 MHz, CD_3OD) δ: 0.03, 0.05 (s, 6H); 0.85 (s, 9H); 1.15 (m, 24H); 1.87 (ddd, J = 6.1 Hz, 6.8 Hz, 12.1 Hz, 1H); 2.77 (ddd, J = 6.0 Hz, 6.8 Hz, 12.1 Hz, 1H); 3.86, 3.92 (2×b s, 4H); 4.55 (m, 1H); 5.34 (m, 1H); 7.07 (s, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ: −4.2, 19.2, 20.9, 22.1, 26.6, 42.0, 47.2, 48.2, 65.3, 66.1, 127.6, 134.6, 153.9, 156.6.

11. Crystal structure data of *trans*-**11**: Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC 215997).
X-Ray crystal structure analysis of *trans*-**11**: formula $C_{29}H_{56}N_2O_5Si$, M = 540.85, colourless crystal 0.40×0.10×0.10 mm, a = 9.926(1), b = 13.635(1), c = 24.745(1) Å, V = 3349.0(8) Å^3, ρ_{calcd} = 1.073 g cm^{-3}, μ = 8.93 cm^{-1}, empirical absorption correction via ψ scan data ($0.716 \leq T \leq 0.916$), Z = 4, orthorhombic, space group $P2_12_12_1$ (No. 19), λ = 1.54178 Å, T = 223 K, $\omega/2\theta$ scans, 3840 reflections collected ($+h$, $-k$, $+l$), $[(\sin\theta)/\lambda] = 0.62$ Å^{-1}, 3840 independent and 2858 observed reflections [$I \geq 2\sigma(I)$], 349 refined parameters, R = 0.042, wR^2 = 0.101, max. residual electron density 0.18 (−0.24) e Å^{-3}, Flack parameter 0.07(4), hydrogens calculated and refined as riding atoms. Data set was collected with an Enraf Nonius CAD4 diffractometer. Programs used: data collection EXPRESS (Nonius BV, 1994), data reduction MolEN (Fair, K. Enraf-Nonius BV, 1990), structure solution SHELXS-97 (Sheldrick, G. M. *Acta Crystallogr*. **1990**, *A46*, 467–473), structure refinement SHELXL-97 (Sheldrick, G. M. Universität Göttingen, 1997), graphics MOPICT 3.2 (Brüggemann, M. Universität Münster, 2001).