ORGANIC LETTERS

2002
Vol. 4, No. 13
2189−2192

Asymmetric Synthesis of 2-Alkenyl-1-cyclopentanols via Tin–Lithium Exchange and Intramolecular Cycloalkylation

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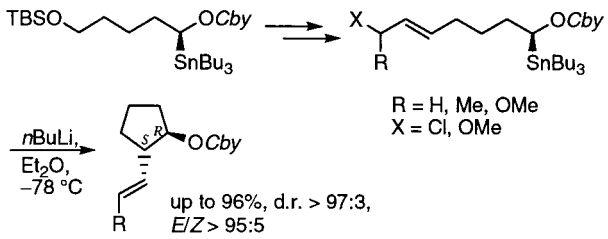
Received April 23, 2002

ABSTRACT

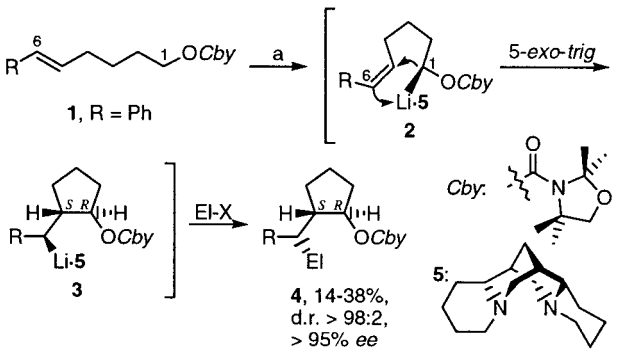


We report a method for the synthesis of chiral cyclopentanes using tin–lithium exchange and cycloalkylation reactions. The *sec*-butyllithium/(–)-sparteine-mediated deprotonation of an alkyl carbamate and subsequent substitution furnishes a highly enantioenriched stannane as a stable carbanion equivalent. It was transformed into suitable cyclization precursors, which underwent tin–lithium exchange and stereoselective cycloalkylation when reacted with *n*-butyllithium, giving highly enantioenriched cyclopentanes in very good yields. A kinetic resolution was observed with a higher substituted stannane.

The asymmetric deprotonation[1] of achiral 5-alkenyl carbamates of type **1** by *sec*-butyllithium/(−)-sparteine **5** followed by a 5-*exo*-*trig* cyclization[2] was found to be a powerful route to 2-substituted cyclopentanols **4** (Scheme 1).[3]

The cyclocarbolithiation[4] proceeds with strict stereoretention at C-1 and a high diastereofacial selection at the double bond, which leads to a mesomerically stabilized benzyl anion. Noteworthy, the strong directing power of the carbamate group overrides the inherent acidity of the C-4 protons in **1**.

Scheme 1. Cyclocarbolithiation of **1**[a]



[a] (a) (i) 1.5 equiv of *s*BuLi/(−)-sparteine **5**, Et_2O, −78 °C, 20−30 h; (ii) El-X, −78 °C to rt.

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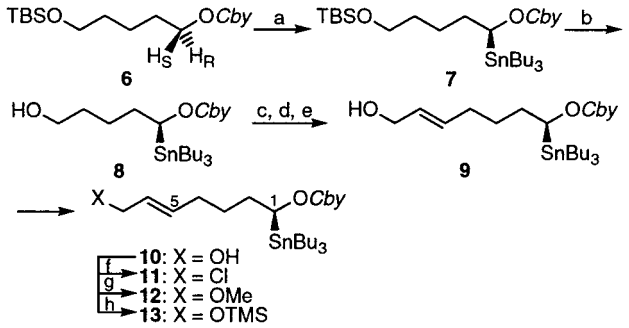
10.1021/ol026068w CCC: $22.00
Published on Web 05/25/2002

The concept could be extended to a number of substituted alkenyl-, alkynyl-, and alkadienyl carbamates.[5] The reaction requires a carbanion-stabilizing substituent in the 6-position. Intramolecular allylic substitution extends the scope, but it is only applicable to allylic carbamates.[6] Allylic chlorine in compound **1** (R = CH_2Cl) does not survive the conditions of α-deprotonation.

As a result, we introduced a tributylstannyl group at an early stage as a chiral carbanion equivalent,[7] which could be carried through the synthesis and converted stereospecifically to lithium in the presence of sensitive functionality. The use of enantioenriched α-oxy-stannanes and α-stannylated *N*-heterocycles for stereoselective cyclizations has been described in the literature.[8]

Deprotonation of the 5-TBSO-pentyl carbamate **6** by *sec*-butyllithium/(−)-sparteine and subsequent quench with tributyltin chloride afforded the enantiopure stannane (*S*)-**7** with 85% yield (Scheme 2). The (*S*)-configuration of **7** is a consequence of the high pro-*S*-selectivity in the deprotonation and the retention in the substitution step of alkyl carbamates, which was stated in numerous examples.[1b] Compound **7** was converted into the allyl chloride **11** by standard steps.

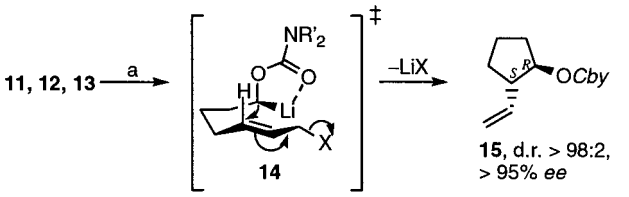
Scheme 2. Synthesis of Cyclization Precursors **11**−**13**[a]



[a] (a) (i) 1.4 equivof *s*BuLi, 1.5 equiv of (−)-sparteine **5**, −78 °C, Et_2O; (ii) 1.7 equiv of Bu_3SnCl, −78 °C to rt, 85%; (b) TBAF, Et_2O, rt, quant; (c) Swern oxidation, 93%; (d) $(EtO)_2P(O)CH_2CO_2Et$, DBU, LiCl, CH_3CN, rt, 94%, *E*/*Z* > 97:3; (e) DIBAL, THF, −78 °C, 98%; (f) KHMDS, MsCl, LiCl, THF, −78 °C to rt, 93%; (g) LiHMDS, MeOTf, THF, −78 °C to rt, 78%; (h) LiHMDS, TMSCl, −78 °C to rt, THF, 75%.

The treatment of **11** in ethereal solution with 1.5 equiv of *n*-butyllithium at −78 °C led to a rapid tin−lithium exchange under retention of configuration, followed by a highly stereoselective cyclization. The formed *trans*-configured product **15** was isolated in essentially quantitative yield as a single diastereomer and enantiomer (Scheme 3).[9,10]

Scheme 3. Cyclization to the 2-Vinylcyclopentanol **15**

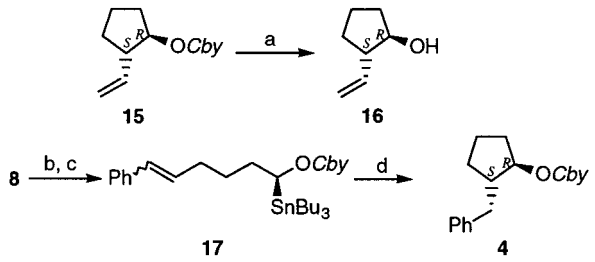


[a] (a) 1.5 equiv of *n*BuLi, Et_2O, −78 °C, 96% (X = Cl), 82% (X = OMe), 44% (X = OTMS), $[\alpha]^{20}_D = -50.2$ (*c* 0.99, CH_2Cl_2).

Similar results, albeit in lower yields, were obtained when the methyl ether **12** or the silyl ether **13** were employed (Scheme 3). These reactions can be rationalized as intramolecular S_N2' substitutions of the allylic leaving groups by a lithium carbanion nucleophile.

The structure elucidation and the determination of the enantiomeric excess were accomplished, as outlined in Scheme 4, by the conversion of **15** to the vinylcyclopentanol **16**. Comparison of the ^1H NMR spectra of **16** and of the known racemate[11] confirmed the *trans* configuration. The

Scheme 4. Structure Elucidation of Cyclization Product **15**[a]



[a] (a) (i) $MeSO_3H$, MeOH, reflux; (ii) K_2CO_3, reflux, 81%; (b) Swern, 93%; (c) $PhCH_2PPh_3Br$, KO*t*Bu, Et_2O, −40 °C to rt, 93%, *E*/*Z* = 72:28; (d) 1.5 equiv of *n*BuLi, Et_2O, −78 °C, 56%, $[\alpha]^{20}_D = -21.9$ (*c* 1.11, CH_2Cl_2) (lit.[3] $[\alpha]^{20}_D = -20.9$ (*c* 0.98, CH_2Cl_2)).

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(9) **Representative Cyclization Procedure.** A solution of the allyl chloride **11** (169 mg, 0.285 mmol) in dry Et_2O (3 mL) under an atmosphere of argon in a flame-dried flask, sealed with a rubber septum, was cooled to −78 °C. *n*-Butyllithium (0.27 mL, 0.43 mmol, 1.5 equiv; 1.6 M in hexanes) was added dropwise, and the mixture was stirred for 2 h. After quenching with MeOH (0.2 mL) and H_2O (0.1 mL) at −78 °C, the mixture was allowed to warm to rt, dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (silica gel, petroleum ether to Et_2O/petroleum ether = 1:4) afforded the product **15** as a colorless oil (73 mg, 0.273 mmol, 96%; $[\alpha]^{20}_D = -50.2$ (*c* 0.99, CH_2Cl_2)).

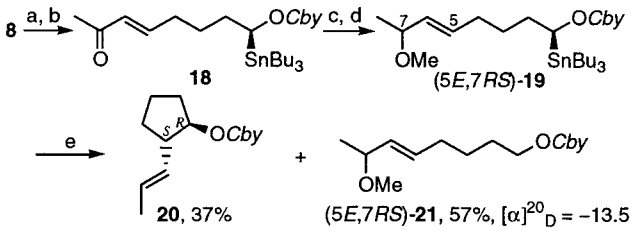
(10) All new compounds were characterized by ^1H NMR, ^{13}C NMR, IR, MS, and elemental analysis.

ee was determined to be >95% by chiral GC. The application of the tin−lithium exchange/asymmetric cyclization protocol to the 6-phenyl-5-hexenyl stannane **17** afforded the known cyclopentane **4** (El = H), which is identical in all respects with a sample from the direct deprotonation/cyclocarbolithiation. Therefore, the retention of configuration at C-1 in the course of the tin−lithium exchange is confirmed.

These encouraging results led us to the question what influence the exchange of a hydrogen by a methyl group at the carbon bearing the leaving group would have concerning the configuration of the product, either to the *cis*/*trans*-geometry in the ring and/or to the *E*/*Z*-geometry of the newly built double bond.

The methyl ether **19** was prepared in a similar fashion as compound **12**. Application of the standard cyclization conditions (−78 °C, 2 h) to **19** gave exclusively the (*E*)-configured cyclization product **20** as a single diastereomer (1,2-*trans*) but in a poor yield (Scheme 5). In addition, the

Scheme 5. Synthesis and Cyclization of Methyl Ether **19**[a]



[a] (a) Swern oxidation, 93%; (b) $(EtO)_2P(O)CH_2C(O)CH_3$, DBU, LiCl, CH_3CN, rt, 58%, *E*/*Z* > 97:3; (c) DIBAL, THF, −78 °C, 88%; (d) KHMDS, MeOTf, Et_2O, −78 °C to rt, 78%; (e) 1.5 equiv of *n*BuLi, Et_2O, −78 °C. **20**: $[\alpha]^{20}_D = -62.6$ (*c* 0.38, CH_2Cl_2).

destannylated compound **21** showed a considerable optical activity, which led us to the assumption of a kinetic resolution in the cyclization step.[12]

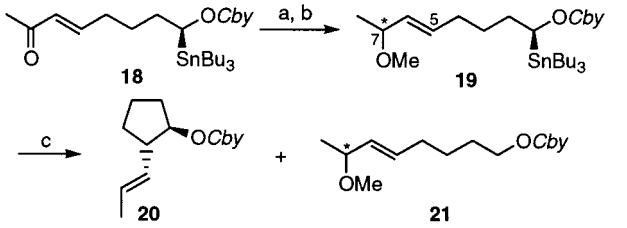
Thus, with the intention of proving this hypothesis, the methyl ethers (7*R*)- and (7*S*)-**19** were prepared by an enantioselective CBS-reduction[13] as the key step and submitted to the standard cyclization conditions, i.e., 1.5 equiv of *n*-butyllithium at −78 °C for 2 h (Table 1). These experiments furnished the cyclization product **20** in 74% yield from (*R*)-**19**. In comparison with that, the reaction of (*S*)-**19** afforded only traces of **20**. The different ability of the pure diastereomers **19** to undergo the cyclization (Scheme 6, entries 2 and 3) gives strong support for an efficient kinetic diastereomer resolution.

(11) Hoffmann, R. W.; Niel, G. *Liebigs Ann. Chem.* **1991**, 1195−1201.

(12) (a) For a kinetic resolution in the cyclization step of an enantioselective carbolithiation, see ref 5d. (b) A cyclization onto a trisubstituted methyl allyl ether without kinetic resolution is described by Broka et al. There, primary stannanes were used, and the reaction mixture was allowed to warm from −78 to 0 °C: Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1338−1340.

(13) Review: Corey, E. J.; Helal, C. *Angew. Chem.* **1998**, *110*, 2092−2118; *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012. Usually, the (*R*)-CBS-oxazaborolidine furnishes the (*S*)-alcohol, and the (*S*)-CBS-oxazaborolidine gives the (*R*)-alcohol. According to the published closely related examples, the de is assumed to be >95%.

Table 1. Cyclization of Pure C-7 Epimers (7*R*)- and (7*S*)-**19**

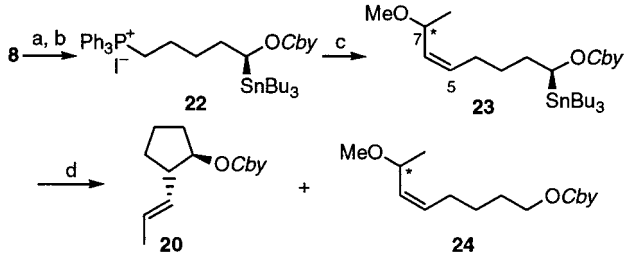


entry	config **19**[a]	yield **19**[b]	yield **20**	yield **21**	α_D **21**
1	7*RS*	69%[c]	37%[d]	57%	−13.5
2	7*R*	96%	74%[d,e]	25%	+21.4
3	7*S*	86%	6%[d]	13%[f]	−25.3

[a] Configuration at C-7. [b] Over two steps (reduction/methylation). [c] The reduction was carried out with DIBAL; see Scheme 5. [d] *E*/*Z* > 97:3. [e] $[\alpha]^{20}_D = -61.4$ (*c* 1.515, CH_2Cl_2). [f] Most of the starting material decomposed under the reaction conditions.

Analogously, we examined the influence of the double bond geometry in the cyclization precursor **19**. However, the reaction of both C-7 epimers of **23** that are derived from the alcohol **8** via the phosphonium salt **22** afforded at −78 °C only the destannylated compound **24**; no cyclization product was detected (Table 2). Ring closure to **20** occurred

Table 2. Cyclization of (*Z*)-Methyl Ethers (7*R*)- and (7*S*)-**23**



entry	config **23**[a]	yield **23**	*T* (°C)	yield **20**	yield **24**	α_D **24**
1	7*S*	77%[b]	−78	0%	96%	−6.3
2	7*S*		−40	35%[c]	14%	*e*
3	7*R*	66%[b]	−78	0%	32%	+0.8[f]
4	7*R*		−40	37%[d]	26%	*e*

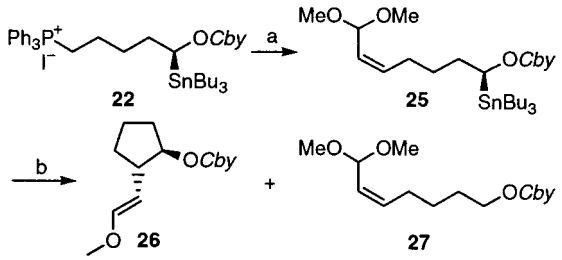
[a] Configuration at C-7. [b] *E*/*Z* < 3:97. [c] *E*/*Z* > 97:3, $[\alpha]^{20}_D = -58.6$ (*c* 0.145, CH_2Cl_2). [d] *E*/*Z* > 97:3, dr = 95:5, $[\alpha]^{20}_D = -51.1$ (*c* 0.73, CH_2Cl_2). [e] Not determined. [f] Partial racemization occurred in the course of the synthesis of (*R*)-2-methoxypropanal.[15]

when the temperature was raised to −40 °C.[14] Again, **20** was isolated as a single stereoisomer (1,2-*trans*, 2(1*E*)), but with rather poor yield.

In summary the configuration at C-7, as well as the double bond geometry, in the cyclization precursors **19** and **23** have no effect on the stereochemistry of the product **20**. Both influence only the cyclization rate of the compounds **19** and **23**.

(14) Higher temperatures have not been applied, as the configurational and thermal stability of the intermediate α-oxy lithium compound is certain only below −40 °C.[7]

Table 3. Synthesis and Cyclization of Acetal **25**



entry	*E*/*Z* **25**	*T* (°C)	yield **26**	*E*/*Z* **26**	yield **27**
1	< 3:97	−78	14%[b]	>97:3	81%
2	< 3:97	−40	82%[c]	95:5	11%

[a] Isomers are separatable. [b] $[\alpha]^{20}_{D} = -66.2$ (*c* 1.07, CH_2Cl_2). [c] dr = 95:5.

Similar results as for **23** were obtained in the cyclization of the acetal **25** (Table 3). No cyclization was observed when employing the standard cyclization conditions (2 h, −78 °C), as outlined in Table 3. Cyclization occurred when the reaction was accomplished at −40 °C, affording the (*E*)-configured enol ether **26** in good yield.

In summary, we have shown that tin−lithium exchange followed by intramolecular cycloalkylation proceeds with very high stereoselection to furnish new enantioenriched cyclopentanols. The chiral precursors are easily prepared by the *sec*-butyllithium/(−)-sparteine deprotonation method and subsequent stannylation; the stannane unit, as a chiral carbanion equivalent, was maintained during the construction of the alkyllithium-sensitive internal allylic moiety. Another application is reported in the following paper.[16] Expanding the scope of this asymmetric cyclization method to further carbo- and heterocycles is in progress and will be published in due course.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (Sonderforschungs-bereich 424). We thank Mrs. C. Weitkamp for her skillful experimental assistance.

Supporting Information Available: Detailed experimental procedures for the cyclizations and spectroscopic data for the compounds **4**, **7**, **15**, **16**, **20**, **21**, **24**, **26**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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