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Asymmetric Synthesis of 4,5,6- and 3,4,5,6-Substituted Azepanes by a Highly Diastereoselective and Enantioselective Lithiation−Conjugate Addition Sequence

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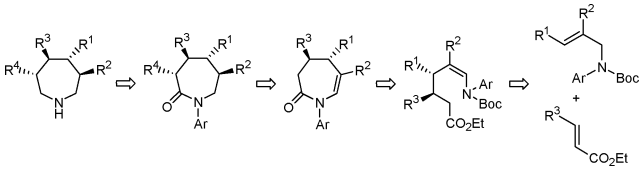
Azepane rings are present in a number of biologically interesting molecules and are homologues of the five- and six-membered nitrogen heterocycles which have been extensively developed as core pharmacophores. Methodology for the asymmetric synthesis of polysubstituted azepanes has not been developed. Syntheses of enantioenriched azepane rings have been reported coincident to the preparations of specific compounds of biological interest, but general approaches, particularly for substitutions nonadjacent to the nitrogen atom, have not been available.[1−3]

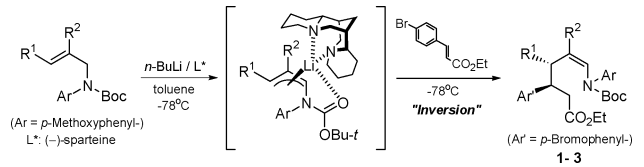
We now wish to report lithiation−addition methodology for the asymmetric synthesis of both enantiomers of 4,5,6 and 3,4,5,6 carbon-substituted azepanes. The key step in our approach is a highly diastereoselective and enantioselective conjugate addition of a lithiated *N*-Boc-2,3-substituted allylamine to a *β*-aryl α,*β*-unsaturated ester, which is shown as the first step in the retrosynthetic analysis of Scheme 1.

Scheme 1



(−)-Sparteine-mediated asymmetric lithiation of *N*-Boc-*N*-(*p*-methoxyphenyl)-2,3-substituted allylamines with *n*-BuLi at −78 °C followed by conjugate additions to ethyl *trans*-*p*-bromocinnamate provides the highly diastereo- and enantioenriched enecarbamates **1**−**3** in the yields shown in Table 1. The absolute configuration of **3**, determined by X-ray crystallography, indicates that the stereochemical course of the conjugate addition is inversion of configuration.[4]

Table 1. (−)-Sparteine-Mediated Asymmetric Lithiation−Substitution Sequences



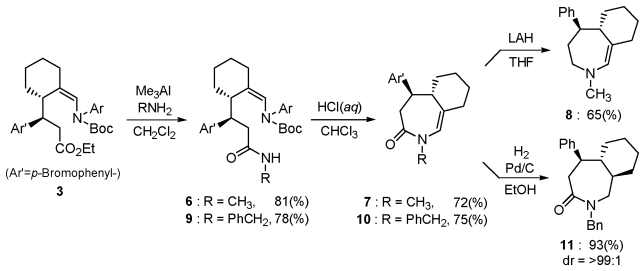
1- 3

R^1	R^2	product	yield (%)	dr[a]	er
CH_3	CH_3	(*Z*,*S*,*R*)-**1**	92	95:5	>95:5[b]
Ph	CH_3	(*Z*,*S*,*R*)-**2**	86	93:7	>97:3[b]
$(CH_2)_2$−	$(CH_2)_2$−	(*Z*,*S*,*R*)-**3**	75	96:4	99:1[c]

[a] Diastereomeric ratios (dr) were determined by ^{1}H NMR analysis. [b] Enantiomeric ratios (er) were assessed to be >95:5 and >97:3 after aminolysis of **1** and **2** with (*S*)-(−)-α-methylbenzylamine, respectively.[5] [c] The enantiomeric ratio of **3** was determined by CSP−HPLC analysis.

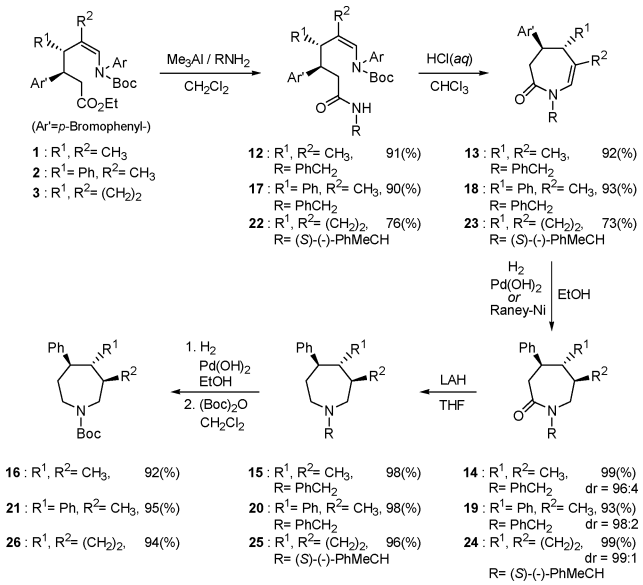
Conversion of ester **3** to the amides **6** and **9**[6a] followed by acid hydrolysis of the enamide to the aldehyde and subsequent cyclization provided the corresponding *N*-alkyl lactams **7** and **10**, as shown in Scheme 2.[7] Reductive conversions of **7** and **10** to **8** and **11** were accompanied by debrominations of the aromatic ring.[6b]

Scheme 2



Efficient syntheses of 4,5,6-substituted azepanes are shown in Scheme 3. Enantioenriched **1**, **2**, and **3** were converted to the corresponding 4,5,6-substituted *N*-Boc azepanes **16**, **21**, and **26** in high yields via aminolysis, hydrolysis, reduction, debenzylation, and addition of the Boc group. The stereochemistry at the C-6 positions of **14**, **19**, and **24** generated by hydrogenation was identified as *trans* geometry by X-ray crystallography as well as by ^{1}H NMR analysis.[7,8]

Scheme 3



Enolization and substitution of the lactam **29** provides a route to 3,4,5,6-substituted azepanes, as shown in Scheme 4.[9] Aminolysis of **1** with *p*-anisidine to **27** followed by hydrolysis and hydrogena-

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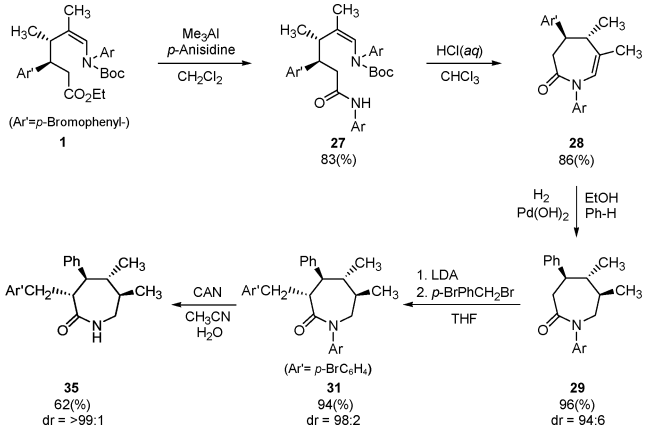
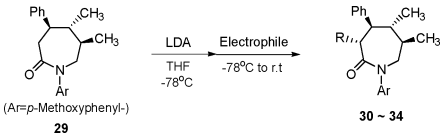
Scheme 4. Asymmetric Synthesis of 3,4,5,6-Substituted Azepanes



tion provided **29**.[8] Substitutions of **29** by selected electrophiles using LDA as the base provided (*R*,*S*,*R*,*S*)-**30**−**33** and (*S*,*S*,*R*,*S*)-**34** in good yields with high diastereoselectivities (Table 2). In all cases, the C-3 and C-4 stereochemistry is assigned as *trans* by ^{1}H NMR analysis.[8] Dearylation of **31** by CAN[6c] proceeds smoothly to give (*R*,*S*,*R*,*S*)-**35** in good yield with diastereomeric and enantiomeric purities greater than 98:2.

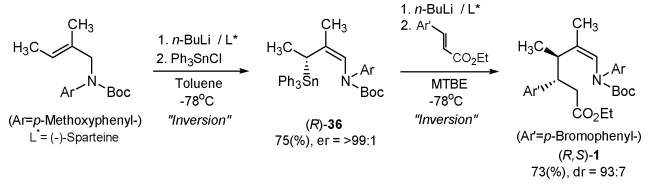
Table 2. Substitutions of **29**



electrophile	product	yield (%)	dr
CH_3I	(*R*,*S*,*R*,*S*)-**30**	96	98:2
p-BrPhCH_2Br	(*R*,*S*,*R*,*S*)-**31**	94	98:2
CH_2═$CHCH_2$Br	(*R*,*S*,*R*,*S*)-**32**	73	99:1
PhOC(═O)Cl	(*R*,*S*,*R*,*S*)-**33**	71	99:1
p-BrPhC(═O)Cl	(*S*,*S*,*R*,*S*)-**34**	82	95:5

To provide a route to the enantiomeric azepanes, we have taken advantage of the lithiation−stannylation−lithiation sequence, which provides the epimeric *N*-Boc-substituted allyllithium intermediate.[4] The sequence leading to (*R*,*S*)-**1** is shown in Scheme 5.[10] The enantiomeric ratio of (*R*,*S*)-**1** was assessed to be 99:1 by determination of the diastereomeric ratio of (*R*,*S*,*S*)-**4** after aminolysis of (*R*,*S*)-**1** with (*S*)-(−)-α-methylbenzylamine.[7,11] Use of the sequences in Schemes 3 and 4 with (*R*,*S*)-**1** would provide the enantiomeric azepanes.

Scheme 5. Enantioselective Synthesis of Enantiomer (*R*,*S*)-**1**



In summary, enantioselective synthesis of both enantiomers 4,5,6- and 3,4,5,6-substituted azepanes can be achieved from the highly diastereoenriched and enantioenriched enecarbamates **1**−**3** generated by (−)-sparteine-mediated asymmetric deprotonative lithiations−conjugate additions of *N*-Boc-*N*-(*p*-methoxyphenyl)-2,3-substituted allylamines. Opening the ring of the lactam intermediates and/or further substitutions at positions adjacent to nitrogen in the intact ring are available for further development.

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Supporting Information Available: All experimental procedures and spectroscopic data for new compounds, and crystallographic data of **7**, **24**, **36**, and (*R*,*S*,*S*)-**4** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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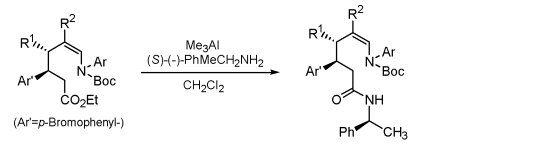
(5) The diastereomeric ratios of (*S*,*R*,*S*)-**4** and (*S*,*R*,*S*)-**5** were determined to be 96:4 and 98:2 by ^{1}H NMR analysis, respectively.



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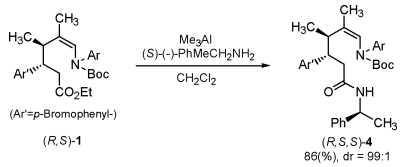
(7) The absolute configurations of **7**, **24**, **36**, and (*R*,*S*,*S*)-**4** were established by X-ray crystallography structures. Crystallographic data for structures **7**, **24**, **36**, and (*R*,*S*,*S*)-**4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary CCDC numbers 286543, 286544, 286545, and 286546, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(8) Coupling constants between H_5 on C-5 and H_6 on C-6 for **14**, **19**, **24**, and **29**, and between H_3 on C-3 and H_4 on C-4 for **30**−**34** are the typical *trans*-coupling constants (J_H−J_H = 10.4 Hz). See Supporting Information.

(9) Attempted enolization−substitution of **24** resulted in substitution at benzylic carbon due to benzylic metalation. See: Meyers, A. I.; Kunnen, K. B.; Still, W. C. *J. Am. Chem. Soc*. **1987**, *109*, 4405−4407.

(10) The enantiomeric ratio (er = >99:1) of (*R*)-**36** was directly determined by CSP−HPLC, after crystallization.

(11) The diastereomeric ratio of (*R*,*S*,*S*)-**4** was determined to be 99:1 by ^{1}H NMR analysis.



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