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STEREOSELECTIVE SYNTHESIS OF γ- AND δ-SULTAMS BY INTRAMOLECULAR DIELS-ALDER REACTION OF VINYLSULFONAMIDES POSSESSING AN ACYCLIC OR CARBOCYCLIC 1,3-DIENE MOIETY

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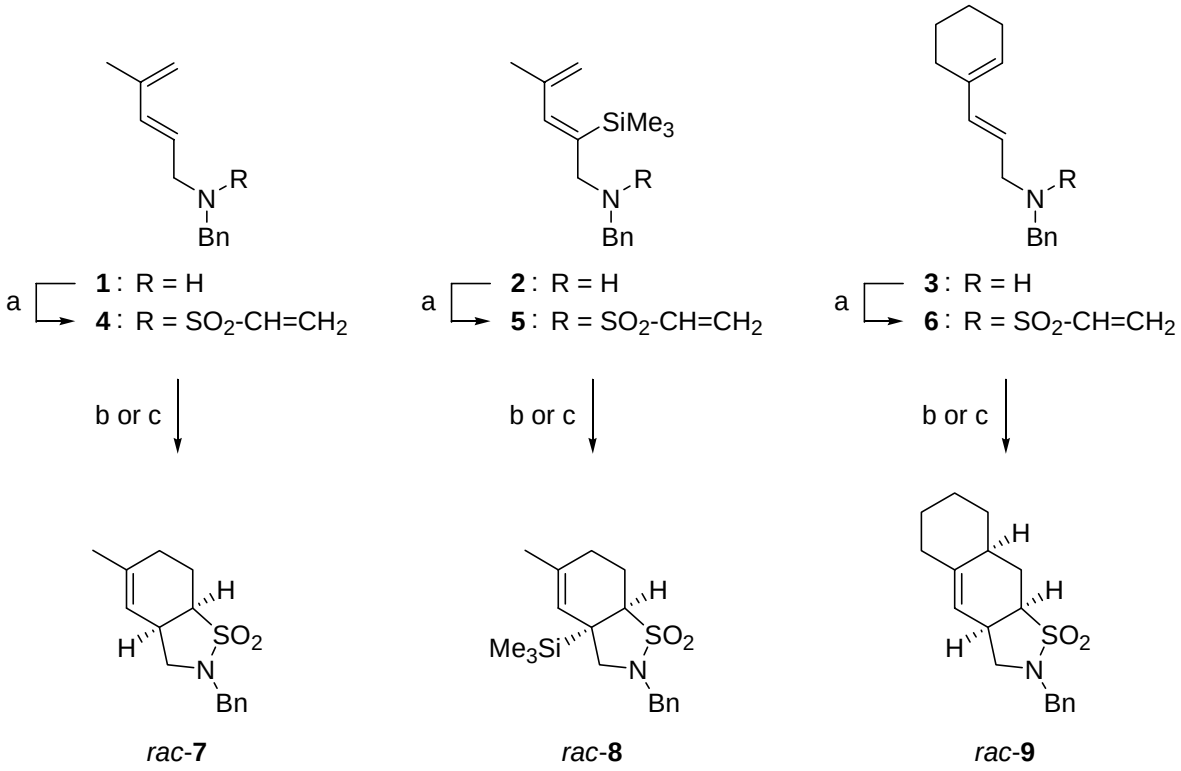
Abstract – A range of novel γ- and enantiopure δ-sultams was prepared by intramolecular [4+2] cycloaddition of vinylsulfonamides with purely thermal activation and under high pressure.

INTRODUCTION

Sultams[1] are useful heterocycles for asymmetric synthesis[2] and medicinal chemistry.[3] Recently developed powerful methodologies for the generation of these cyclic sulfonamides include the intramolecular Diels-Alder reaction,[4] sulfonamide dianion alkylation,[5] radical cyclization,[6] ring closing metathesis,[7] and intramolecular Heck cyclization.[8] In a previous communication,[4a] we reported the preparation of five- and six-membered sultams *via* thermal and high pressure intramolecular [4+2] cycloadditions of furan-containing vinylsulfonamides. Here we communicate an extension of these studies to the synthesis of γ- and enantiomerically pure δ-sultams by intramolecular Diels-Alder reaction of vinylsulfonamides possessing an acyclic or carbocyclic 1,3-diene moiety.

RESULTS AND DISCUSSION

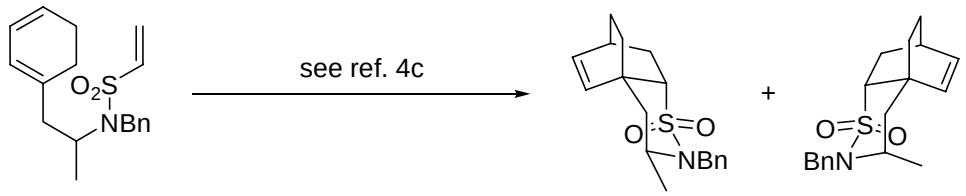
Vinylsulfonamides (**4-6**) incorporating a three atom tether connecting diene and dienophile were readily available by treatment of *N*-benzyldienylamines (**1-3**)[9] with vinylsulfonyl chloride[10] (Scheme 1). Upon refluxing a solution of **4-6** in toluene,[11] γ-sultams (*rac*-**7**), (*rac*-**8**), and (*rac*-**9**) were formed in good yields as single diastereomers, respectively. Subjecting a solution of **4-6** in dichloromethane to a pressure of 13 kbar at room temperature[11] proved to be even more efficient. The relative configuration of the γ-sultams was elucidated by 2D NOESY experiments and additionally by X-Ray diffraction analysis in case of sultam (*rac*-**9**).[12]



Reagents and conditions: (a) CH_2=$CHSO_2Cl$, Et_3N, CH_2Cl_2, 0°C, 1-2 h, 92% **4**, 95% **5**, 96% **6**; (b) toluene, reflux, 1 bar, 70% *rac*-**7** (22 h), 79% *rac*-**8** (8 h), 71% *rac*-**9** (16 h); (c) CH_2Cl_2, rt, 13 kbar, 71% *rac*-**7** (29 h), 93% *rac*-**8** (10 h), 90% *rac*-**9** (12 h).

Scheme 1.

An earlier investigation revealed a high diastereoselectivity in the cyclization of vinylsulfonamide (*rac*-**10**) featuring a 1,3-cyclohexadienyl unit to give the *endo* δ-sultams (*rac*-**11**) and (*rac*-**12**) under purely thermal activation or high pressure conditions (Scheme 2).[4c] Following our studies on furan-containing substrates bearing an external chiral auxiliary attached to the nitrogen atom,[4a] we examined a similar approach toward enantiopure δ-sultams derived from a carbocyclic 1,3-diene moiety.

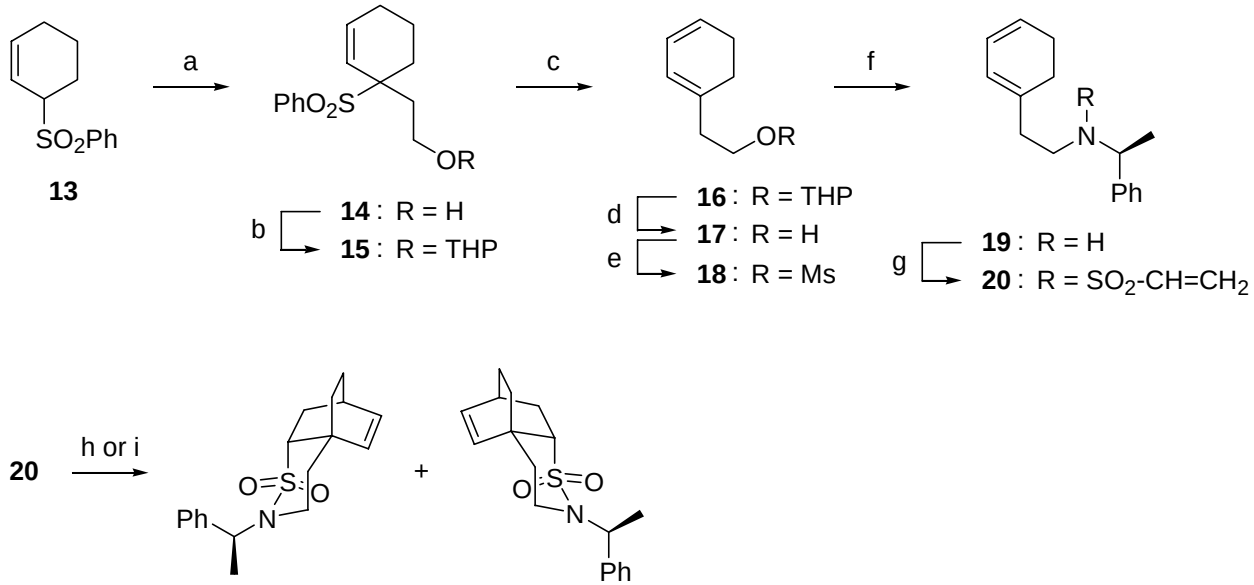


rac-**10** *rac*-**11** *rac*-**12**

toluene, reflux, 1 bar (3 h)	90	:	10	(77%)
CH_2Cl_2, rt, 13 kbar (12 h)	97	:	3	(93%)

Scheme 2.

Primary alcohol (**17**) was synthesized from sulfone (**13**) according to a known methodology[13,14] (Scheme 3). Nucleophilic substitution of mesylate (**18**) derived from **17** with (*S*)-(–)-1-phenylethylamine and subsequent treatment of the resultant amine (**19**)[15] with vinylsulfonyl chloride gave rise to vinylsulfonamide (**20**)[15] carrying a nitrogen-bound (*S*)-(–)-1-phenylethyl unit. Both the thermal and the high pressure cycloaddition[11] led to a roughly 1:1 ratio of *endo* product diastereomers.[16,17] Nevertheless, δ-sultams (**21**) and (**22**) could be readily isolated in pure form after separation by flash chromatography followed by recrystallization (methanol), and their configuration was unambiguously established by X-Ray diffraction analysis of **22**.[12,15]

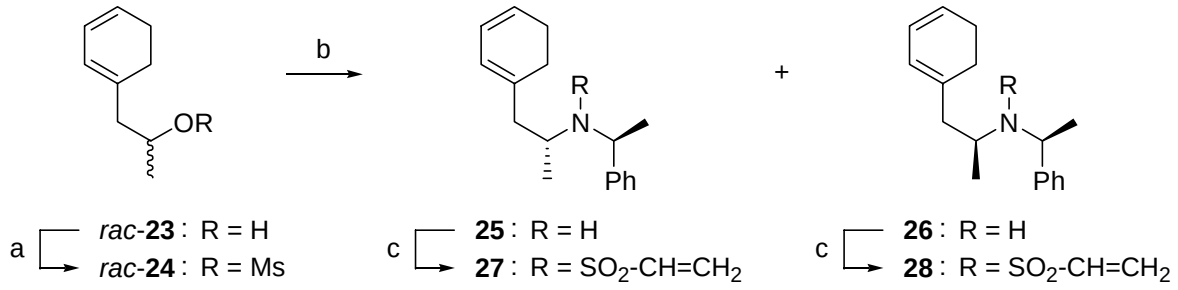


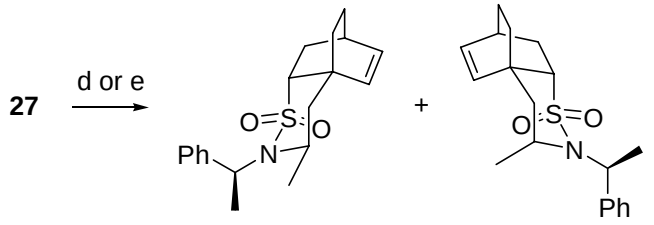
	21		**22**
h:	53	:	47
i:	45	:	55

Reagents and conditions: (a) BuLi, THF, –30°C, 1.5 h, then ethylene oxide, –30°C (1 h) to rt, 98%; (b) 3,4-dihydro-2*H*-pyrane, PPTS, CH_2Cl_2, 0°C, 24 h, 100%; (c) *t*-BuOK, *t*-BuOH, reflux, 1.5 h, 57%; (d) EtOH, PPTS, 60°C, 24 h, 63%; (e) MsCl, Et_3N, CH_2Cl_2, 0°C, 1 h, 93%; (f) (*S*)-(–)-1-phenylethylamine, 80°C, 12 h, 79%; (g) CH_2=$CHSO_2Cl$, Et_3N, CH_2Cl_2, 0°C, 1 h, 77%; (h) toluene, reflux, 1 bar, 17 h, 60%; (i) CH_2Cl_2, rt, 13 kbar, 23 h, 75%.

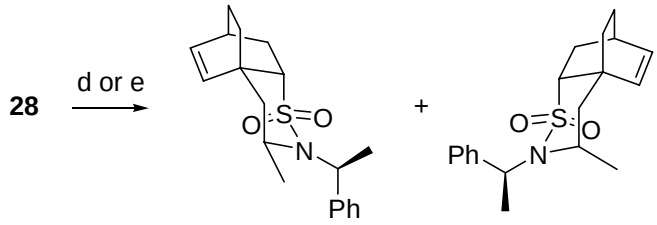
Scheme 3.

In a further series of experiments, the double stereodifferentiation brought about by the simultaneous presence of a stereogenic center within the tether (see Scheme 2) and a chiral auxiliary on nitrogen (see Scheme 3) was investigated (Scheme 4).





	29	:	30
d:	70	:	30
e:	94	:	6



	31	:	32
d:	73	:	27
e:	96	:	4

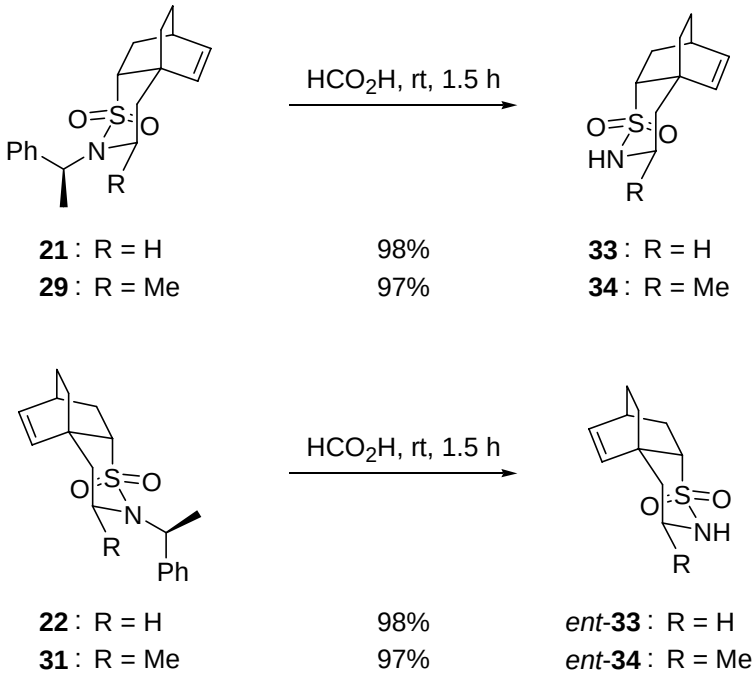
Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0°C, 1 h, 96%; (b) (*S*)-(–)-1-phenylethylamine, 80°C, 12 h, 31% **25** + **26**; (c) CH_2=$CHSO_2Cl$, Et_3N, CH_2Cl_2, 0°C, 3 h, 76% **27**, 79% **28**; (d) toluene, reflux, 1 bar, 24 h, 44% **29** + **30**, 36% **31** + **32**; (e) CH_2Cl_2, rt, 13 kbar, 82 h, 68% **29** + **30**, 66% **31** + **32**.

Scheme 4.

To this end, alcohol (*rac*-**23**)[13] was converted by mesylation and nucleophilic substitution with (*S*)-(–)-1-phenylethylamine to give a 1:1 mixture of the diastereomeric amines (**25**) and (**26**),[15] which were separated by flash chromatography. *N*-Sulfonation of **25** and **26** with vinylsulfonyl chloride delivered the vinylsulfonamides (**27**) and (**28**),[15] respectively, as pure stereoisomers. Due to the additional methyl substituent present in **27** and **28** as compared to **20** or *rac*-**10**, a considerably lower reactivity for cycloaddition was noted for these sterically more encumbered substrates. As listed in Scheme 4, the 13

kbar activation was associated with a significantly higher asymmetric induction than the reflux/ambient pressure process for both **27** and **28**.[11,16] Clearly, a preferential equatorial orientation of the methyl substituent on a chair-like folded tether controlled the stereochemical outcome of these reactions. Interestingly, and in contrast to the situation with furan substrates,[4a] the diastereoselectivities noted for the thermal reactions of **27** and **28** at ambient pressure were likewise not affected to a great extent by the (*S*)-(–)-1-phenylethyl unit. Separation of the two resulting sultam mixtures (**29**/**30**) and (**31**/**32**), respectively, by flash chromatography was not possible. However, pure isomers (**29**) and (**31**) could be obtained by recrystallization (methanol) of the product mixtures from the high pressure reactions instead, and their configuration was unequivocally determined by X-Ray diffraction analysis.[12,15]

Application of our optimized conditions for reductive debenzylation of *N*-1-phenylethyl-δ-sultams[4a,18] smoothly effected cleavage of the chiral auxiliary from the sultams (**21**), (**29**), (**22**), and (**31**) in nearly quantitative yield (Scheme 5). Similar to the furan cases studied before,[4a] X-Ray diffraction analysis of the debenzylated sultams (**33**), (**34**) [and (*ent*-**34**)] unveiled an sp^3 hybridized nitrogen atom (sum of angles around N = 333.8° - 335.9°) with axial orientation of N-H on a chair δ-sultam,[12,15] whereas the crystal structures of *N*-1-phenylethyl-δ-sultams (**22**) and (**31**) feature an sp^2 hybridized nitrogen atom (sum of angles around N = 355.0° for **22** and 355.2° for **31**), and the *N*-1-phenylethyl substituent in **29** (sum of angles around N = 340.8°) is oriented nearly equatorially on a chair δ-sultam in the solid state.[12]



21 : R = H 98% **33** : R = H
29 : R = Me 97% **34** : R = Me

22 : R = H 98% *ent*-**33** : R = H
31 : R = Me 97% *ent*-**34** : R = Me

Scheme 5.

In conclusion, a range of novel γ- and enantiomerically pure δ-sultams was efficiently prepared by intramolecular Diels-Alder reaction of vinylsulfonamides possessing an acyclic or carbocyclic 1,3-diene moiety. Further synthetic elaboration of these heterocycles will be reported in due course.

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REFERENCES AND NOTES

1. A. J. Buglass and J. G. Tillett, 'The Chemistry of Sulphonic Acids, Esters and their Derivatives', ed. by S. Patai and Z. Rappoport, Wiley, New York, 1991, pp. 789-878.
2. For applications of chiral sultam auxiliaries in asymmetric synthesis, see: H.-K. Zhang, W.-H. Chan, A. W. M. Lee, W.-Y. Wong, and P.-F. Xia, *Tetrahedron: Asymmetry*, 2005, **16**, 761 and references cited therein.
3. (a) S. Hanessian, H. Sailes, and E. Therrien, *Tetrahedron*, 2003, **59**, 7047. (b) L. Zhuang, J. S. Wai, M. W. Embrey, T. E. Fisher, M. S. Egbertson, L. S. Payne, J. P. Guare, Jr., J. P. Vacca, D. J. Hazuda, P. J. Felock, A. L. Wolfe, K. A. Stillmock, M. V. Witmer, G. Moyer, W. A. Schleif, L. J. Gabryelski, Y. M. Leonard, J. J. Lynch, Jr., S. R. Michelson, and S. D. Young, *J. Med. Chem.*, 2003, **46**, 453. (c) M. Inagaki, T. Tsuri, H. Jyoyama, T. Ono, K. Yamada, M. Kobayashi, Y. Hori, A. Arimura, K. Yasui, K. Ohno, S. Kakudo, K. Koizumi, R. Suzuki, M. Kato, S. Kawai, and S. Matsumoto, *J. Med. Chem.*, 2000, **43**, 2040. (d) R. A. Miller, G. R. Humphrey, D. R. Lieberman, S. S. Ceglia, D. J. Kennedy, E. J. J. Grabowski, and P. J. Reider, *J. Org. Chem.*, 2000, **65**, 1399.
4. (a) V. O. Rogatchov, H. Bernsmann, P. Schwab, R. Fröhlich, B. Wibbeling, and P. Metz, *Tetrahedron Lett.*, 2002, **43**, 4753. (b) I. R. Greig, M. J. Tozer, and P. T. Wright, *Org. Lett.*, 2001, **3**, 369. (c) B. Plietker, D. Seng, R. Fröhlich, and P. Metz, *Tetrahedron*, 2000, **56**, 873. (d) A. D. Brosius, L. E. Overman, and L. Schwink, *J. Am. Chem. Soc.*, 1999, **121**, 700. (e) P. Metz, D. Seng, R. Fröhlich, and B. Wibbeling, *Synlett*, 1996, 741.
5. J. Lee, Y.-L. Zhong, R. A. Reamer, and D. Askin, *Org. Lett.*, 2003, **5**, 4175.
6. M. Ueda, H. Miyabe, A. Nishimura, O. Miyata, Y. Takemoto, and T. Naito, *Org. Lett.*, 2003, **5**, 3835.
7. (a) For a review, see: M. D. McReynolds, J. M. Dougherty, and P. R. Hanson, *Chem. Rev.*, 2004, **104**, 2239. (b) S. Karsch, D. Freitag, P. Schwab, and P. Metz, *Synthesis*, 2004, 1696. (c) D. Freitag, P. Schwab, and P. Metz, *Tetrahedron Lett.*, 2004, **45**, 3589.
8. S. Merten, R. Fröhlich, O. Kataeva, and P. Metz, *Adv. Synth. Catal.*, 2005, **347**, 754.

9. S. Rehn, A. R. Ofial, and H. Mayr, *Synthesis*, 2003, 1790.
10. C. S. Rondestvedt Jr., *J. Am. Chem. Soc.*, 1954, **76**, 1926.
11. Substrate concentration 0.025 M for all thermal and high pressure cycloadditions reported in this study.
12. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC 283208 (*rac*-**9**), CCDC 283211 (**22**), CCDC 283209 (**29**), CCDC 283210 (**31**), CCDC 283212 (**33**), CCDC 283213 (**34**), CCDC 283214 (*ent*-**34**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) +44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].
13. (a) P. Metz, M. Fleischer, and R. Fröhlich, *Tetrahedron*, 1995, **51**, 711. (b) P. Metz, M. Fleischer, and R. Fröhlich, *Synlett*, 1992, 985.
14. (a) M. Sellén, J.-E. Bäckvall, and P. Helquist, *J. Org. Chem.*, 1991, **56**, 835. (b) J.-E. Bäckvall and P. G. Andersson, *J. Org. Chem.*, 1991, **56**, 2274.
15. **19**: $[\alpha]^{20}_D$ = –50.4° (*c* 1.0, CH_2Cl_2); **20**: $[\alpha]^{20}_D$ = –14.2° (*c* 1.0, CH_2Cl_2); **21**: $[\alpha]^{20}_D$ = –39.0° (*c* 1.0, CH_2Cl_2); **22**: $[\alpha]^{20}_D$ = –29.0° (*c* 1.0, CH_2Cl_2); **25**: $[\alpha]^{20}_D$ = –94.5° (*c* 1.0, CH_2Cl_2); **26**: $[\alpha]^{20}_D$ = –35.4° (*c* 1.0, CH_2Cl_2); **27**: $[\alpha]^{20}_D$ = +29.4° (*c* 1.0, CH_2Cl_2); **28**: $[\alpha]^{20}_D$ = –10.0° (*c* 1.0, CH_2Cl_2); **29**: $[\alpha]^{20}_D$ = +0.4° (*c* 1.0, CH_2Cl_2); **31**: $[\alpha]^{20}_D$ = –2.3° (*c* 1.0, CH_2Cl_2); **33**: $[\alpha]^{20}_D$ = +10.4° (*c* 1.0, CH_2Cl_2); *ent*-**33**: $[\alpha]^{20}_D$ = –10.4° (*c* 1.0, CH_2Cl_2); **34**: $[\alpha]^{20}_D$ = +10.1° (*c* 1.0, CH_2Cl_2); *ent*-**34**: $[\alpha]^{20}_D$ = –10.1° (*c* 1.0, CH_2Cl_2).
16. Diastereomeric ratios were determined by ^{1}H NMR spectral integration of the crude product mixture. Only *endo* sultams were formed.
17. For recent publications on the effect of high pressure on the diastereoselectivity of intra- and intermolecular Diels-Alder reactions, see references 4a and 4c and: (a) F.-G. Klärner and F. Wurche, *J. Prakt. Chem.*, 2000, **342**, 609. (b) L. F. Tietze, M. Henrich, A. Niklaus, and M. Buback, *Chem. Eur. J.*, 1999, **5**, 297.
18. For a similar reductive debenzylation of *N*-1-phenylethyl-γ-sultams, see: (a) K. F. Ho, D. C. W. Fung, W. Y. Wong, W. H. Chan, and A. W. M. Lee, *Tetrahedron Lett.*, 2001, **42**, 3121. (b) W. H. Chan, A. W. M. Lee, L. S. Jiang, and T. C. W. Mak, *Tetrahedron: Asymmetry*, 1997, **8**, 2501.