Exchange of the *tert*-butyloxycarbonyl carbamate of **31** for the acetamide (3.0 M HCl/EtOAc, 25 °C, 2 h; $(CH_3CO)_2O$, $NaHCO_3$, THF, 25 °C, 2 h, 89% overall) followed by hydrolysis of the C-9 methyl ester ($LiOH \cdot H_2O$, THF/MeOH/H_2O, 25 °C, 4 h, 93%) provided K-13 ($[\alpha]^{22}_D$ −5.6° (*c* 0.53, methanol) natural $[\alpha]^{19}_D$ −3.4° (*c* 0.6, methanol)[2]), identical in all additional comparable respects with the naturally occurring material.[17]

Acknowledgment. This work was assisted by the financial support of the National Institutes of Health (Grant CA41101), the Alfred P. Sloan Foundation, and a Purdue University Cancer Center fellowship (D.Y.). We thank Professor D. A. Evans for providing us with details of their efforts in advance of publication (ref 7) and Dr. Sano for copies of spectra of naturally occurring K-13 (ref 16).

Supplementary Material Available: Experimental details and full spectroscopic and physical characterization of **1**, **17–20**, **23–32**, and the cyclic amides **37–39** and **46–48** are provided (15 pages). Ordering information is given on any current masthead page.

Highly Selective Formation of Cis-Substituted Hydroxylactams via Auxiliary-Controlled Reduction of Imides

Scott A. Miller and A. Richard Chamberlin*

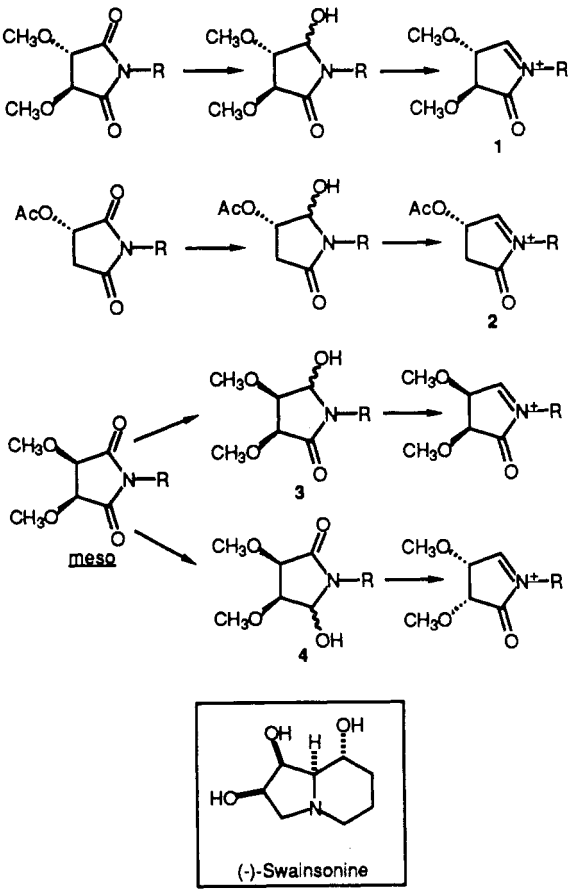
Department of Chemistry, University of California, Irvine, California 92717

Received March 8, 1989

Summary: A protected *cis*-dihydroxytartarimide with an appended chiral auxiliary undergoes highly selective reduction of either carbonyl group, affording acyliminium ion precursors that are not readily available by conventional imide reduction techniques.

Sir: Nucleophilic addition to acyliminium ions is a valuable method for the preparation of nitrogen-containing natural products.[1] One reason for the popularity of this reaction is that acyliminium ions are very convenient to prepare, via simple hydride reduction of cyclic imides[2] followed by elimination. While this reaction sequence has most often been carried out on simple achiral imides, enantiomerically pure chiral acyliminium ions such as **1** (Scheme I) can be generated from imides with C_{2v} symmetry (in which the carbonyl groups are chemically equivalent),[3] while monosubstituted derivatives such as **2** (Scheme I) have been prepared by regioselective reduction of unsymmetrical imides derived from malic acid.[4] This straightforward methodology is not applicable, however, to the enantioselective preparation of cis-substituted hydroxy lactams such as **3** or **4** because the corresponding starting material is a meso imide and thus would give racemic product. We have investigated several potential solutions to this interesting dilemma, which presents itself in iminium ion cyclization routes to glycosidase inhibitors such as swainsonine,[5] and in this communication we report our initial results on reductions directed by a stereogenic center attached at nitrogen.

Scheme I



For the initial studies, a chiral auxiliary was chosen so that several reduction modes could be examined: (a) intramolecular delivery of hydride, (b) chelation-controlled reduction (i.e., selective activation of one carbonyl group by auxiliary/metal/carbonyl chelation), and (c) sterically controlled reduction. The auxiliary selected based on these criteria was commercially available D-(−)-α-phenylglycinol,[6]

(1) (a) Chamberlin, A. R.; Chung, J. Y. L. *J. Org. Chem.* **1985**, *50*, 4425 and references therein. (b) Hart, D. J.; Yang, T.-K. *J. Org. Chem.* **1985**, *50*, 235. (c) Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron Lett.* **1975**, 3963. (d) For a review of acyliminium cyclizations in alkaloid synthesis, see: Speckamp, W. N. *Recueil* **1981**, *100*, 345.

(2) (a) $NaBH_4$/ethanol/acid: Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437. (b) $NaBH_4$/MeOH: Chamberlin, A. R.; Nguyen, H. D.; Chung, J. Y. L. *J. Org. Chem.* **1984**, *49*, 1682. (c) Diisobutylaluminum hydride: Hart, D. J.; Kanai, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 1255.

(3) For examples, see: Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1980**, 1987 and ref 1d.

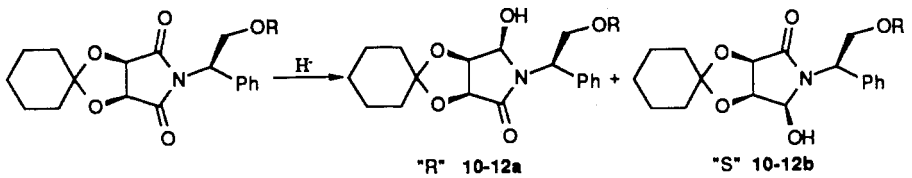
(4) (a) Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653. (b) Hart, D. J.; Yang, T.-K. *J. Chem. Soc., Chem. Commun.* **1983**, 135.

(5) For a recent synthesis of (−)-swainsonine and references to previous syntheses, see: Dener, J. M.; Hart, D. J.; Ramesh, S. *J. Org. Chem.* **1988**, *53*, 6022.

(6) This compound serves as chiral auxiliary for a related transformation leading to lactones: Mukaiyama, T.; Yamashita, H.; Asami, M. *Chem. Lett.* **1983**, 385.

0022-3263/89/1954-2502$01.50/0

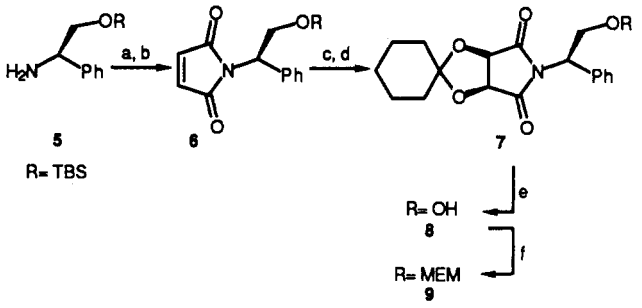
Table I. Reduction Studies of Chiral Imides 7, 8, and 9



entry	R	H^-	reaction conditions	% yield[a]	ratio of *S*:*R*	%de
1	H	$LiAlH_4$	Et_2O, −109 °C, 5.5 h	75	39:61	22
2	H	Red-Al	1.5 THF/Et_2O, −109 °C, 2 h	80	18:82	64
3	**H**	**$Me_4NHB(OAc)_3$**	**MeCOMe/AcOH, 25 °C, 5 days**	**87**	**4:96**	**92**
4	**H**	**$Me_4NHB(OAc)_3$**	**CH_3CN/AcOH, 25 °C, 14 days**	**63, 76[c]**	**<1:99**	**>98**
5	H	L-Selectride[b]	1.5 THF/Et_2O, −109 °C, 5 h	69	84:16	68
6	MEM	$LiAlH_4$	Et_2O, −109 °C, 6 h	78	54:45[d]	8
7	MEM	L-Selectride[b]	Et_2O, −109 °C, 7 h	83	91:9[d]	82
8	TBS	$LiAlH_4$	Et_2O, −109 °C, 6 h	91	54:46	8
9	TBS	Red-Al	1.5 THF/Et_2O, −109 °C, 6 h	91	50:50	0
10	**TBS**	**L-Selectride[b]**	**Et_2O, −109 °C, 5.5 h**	**98**	**>99:1**	**>98**
11	TBS	$Me_4NHB(OAc)_3$	CH_3CN/AcOH, 25 °C, 3 days	N.R.		

[a] Yield after purification. [b] In all cases K-Selectride was less selective than L-Selectride. [c] Yield based on recovered starting material. [d] Absolute configuration was not determined.

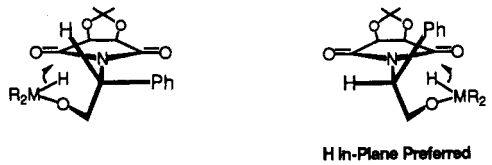
Scheme II[a]



[a] (a) Maleic anhydride, Et_2O; (b) sodium acetate, acetic anhydride, 37%; (c) OsO_4, NMO, acetone/H_2O, 86%; (d) 1-methoxycyclohexene, mesitylenesulfonic acid, C_6H_6, 77%; (e) HF, CH_3CN, 93%; (f) MEM-Cl, CH_2Cl_2, ethyldiisopropylamine, 88%.

which was first treated with benzyl chloroformate and sodium bicarbonate, followed by protection of the alcohol with *tert*-butyldimethylsilyl chloride (TBS-Cl). Deprotection of the amine using 10% Pd/C and hydrogen (40 psi) gave the TBS-protected phenylglycinol **5** (Scheme II) in 92% yield. All attempts to convert this amine directly into the desired tartarimide **7** by reaction with meso tartaric acid derivatives failed. Instead, **5** was treated with maleic anhydride followed by sodium acetate in acetic anhydride to give the maleimide **6**, which was catalytically osmylated and then protected (1-methoxycyclohexene, mesitylenesulfonic acid) to give the TBS-protected chiral imide **7**. Removal of the silyl group with hydrofluoric acid in acetonitrile[7] gave the alcohol **8**, which was treated with MEM-Cl and ethyldiisopropylamine to give **9**. This trio of derivatives (**7**, **8**, and **9**, Scheme II) allowed all three modes of reduction to be tested.

Initial attempts at selective reduction[8] of one of the diastereotopic carbonyl groups relied upon the intramolecular reaction of an alkoxide/metal hydride species[9] formed from the alcohol **8**. The conformation required for such a reaction places either phenyl or H approximately in-plane with the other carbonyl group, and the latter arrangement should be more favorable[10] (eq 1). Initially the selectivities were disappointing: lithium aluminum hydride gave a diastereomeric excess (de)[11] of only 22%

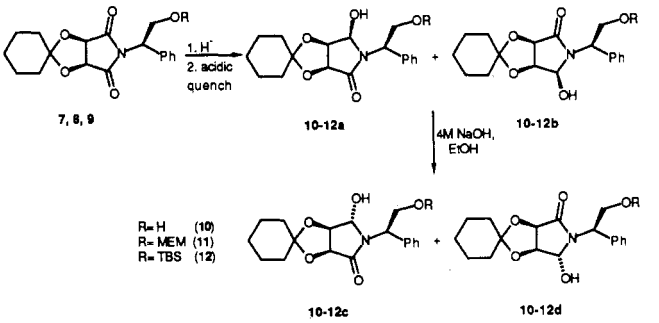


(1)

(entry 1, Table I), while the use of Red-Al resulted in a somewhat better 64% de. However, with tetramethylammonium triacetoxyborohydride the stereoselectivity improved dramatically (entry 4, Table I), to levels exceeding 98% de. This reducing agent has been reported to reduce β-hydroxy ketones intramolecularly[9] but is unreactive in intermolecular reductions. The fact that reduction of the protected alcohol **7** (entry 11, Table I) gave no hydroxy lactam is consistent with that reactivity pattern

(7) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

(8) Reductions were carried out as indicated (Table I), and product ratios were determined by proton NMR integration. The analysis of product ratios is complicated by the possibility that the two reduction "regio-isomers" (which are of course really diastereomers) can themselves consist of diastereomeric pairs (α- or β-OH); in all cases, however, no more than two diastereomers are produced, each of which is cleanly converted under basic conditions to a more stable diastereomer that is identical with an authentic hydroxy lactam prepared independently. (Authentic samples were prepared from D-(−)-lyxose and D-(−)-ribonolactone and compared with the α epimers of the reduction products. Synthesis details will appear in the full paper.) This behavior is consistent with kinetically controlled formation of the β-hydroxy lactams in the reduction, indicating that delivery of hydride occurs in all cases from the convex face of the heterobicyclo[3.3.0] ring system, as expected.



(9) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560 and references cited therein.

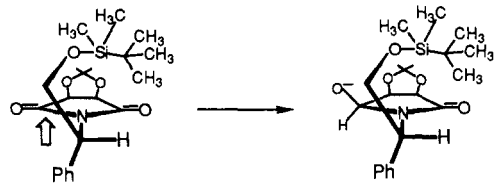
(10) Since the N–C bond has substantial π character, the H in-plane conformer should be favored by analogy with related sp^3-sp^2 preferences in alkenes. See: Karabatsos, G. J.; Fenoglio, D. J. *Top. Stereochem.* **1970**, *5*, 167.

(11) Diastereomer ratios are reported as % de in order to reflect the enantiomeric excesses expected if the chiral auxiliary were to be removed.

and provides evidence that the highly selective reduction of 8 is indeed intramolecular. Furthermore, the stereochemistry of the major product is that expected for reduction in the H in-plane conformer proposed above. Presumably, the lower selectivity of Red-Al and lithium aluminum hydride are due to competitive intermolecular reduction; note that L-Selectride (entry 5, Table I), which is unlikely to deliver hydride intramolecularly, favors reduction of the opposite carbonyl group.

In contrast to the predictable selectivity of the intramolecular reductions, it was much less clear what result to expect when the alcohol group is capable of chelation. Nonetheless, several reductions of the MEM ether **9**, which can chelate metal ions and thereby (in principle) activate one of the carbonyl groups toward nucleophilic hydride attack, were attempted. Some representative examples are included in the table, but in general only poor selectivity was noted (e.g., entry 6). Although a better ratio (82% de) was observed with L-Selectride, this probably is not due to chelation but instead is consistent with steric control (see below).

For derivatives incapable of intramolecular hydride delivery or chelation, it is even more treacherous to predict which carbonyl group should be reduced because there are a number of conformations available to the chiral auxiliary, none of which is strongly preferred by inspection of models or by molecular mechanics calculations. We therefore were not surprised to discover that the reduction of **7** with $LiAlH_4$ or Red-Al (Aldrich) gave virtually no selectivity. *In direct contrast, however, reaction with L-Selectride gave a nearly quantitative yield of a single diastereomer (>98% de).* This unanticipated yet remarkable result is consistent with reduction of the alternative H in-plane conformer[12] (eq 2) compared with that postulated for the



intramolecular reduction. The selectivity may be attributable to impeded approach of the hydride reagent by the pendant phenyl group, analogous to Speckamp's observation that unsymmetrically substituted imides are reduced preferentially at the more highly α-substituted carbonyl group,[13] or to an unfavorable nonbonding interaction in a late transition state between the developing alkoxide and the *tert*-butyl group positioned above the less reactive carbonyl group.[12,14] Regardless of the reason for the high diastereoselectivity, this result complements the intramolecular reaction and allows the highly selective reduction of either carbonyl group of the imide via a single chiral auxiliary. Analogous reductions of other, more highly substituted imide derivatives are currently being investigated.

Acknowledgment. Funding for this project from the National Institutes of Health (NS-25401) is gratefully acknowledged. We wish to thank Dr. J. Ziller for the X-ray crystal structure determination of **7**.

Supplementary Material Available: Full experimental and spectral data of the numbered compounds, spectral data for authentic samples, and X-ray crystallographic coordinates for **7** (15 pages). Ordering information is given on any current masthead page.

(12) We have obtained a single-crystal X-ray structure of imide **7** that shows two different conformers in the unit cell, each with the H approximately in plane, phenyl anti to the protected diol, and TBS siloxy methyl syn (see supplementary material for structures).

(13) Wijnberg, J. B. P. A.; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 179.

(14) Unfortunately, attempts to shed any light on the solution conformation of this compound by difference NOE studies have thus far been unsuccessful.