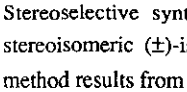
STEREOSELECTIVE SYNTHESIS OF 3-HYDROXY-2,6-DIALKYLPIPERIDINES[1]

Kenn E. Harding* and Michael W. Jones

Department of Chemistry, Texas A&M University
College Station, TX 77843, USA

Abstract - A new method for stereoselective synthesis of 3-hydroxy-2,6-dialkylpiperidine alkaloids is reported. The key trans-oxazolidine intermediate **8** was generated by mercuric ion-initiated cyclofunctionalization of an N-acylaminomethyl ether derivative of allylic alcohol **5** (**6** --> **7**). Racemic deoxocassine (**3**) was synthesized by addition of a C_{11} chain (**8** --> **9**), cleavage of the oxazolidine ring under basic conditions (**9** --> **17**), and reductive amination to generate the piperidine ring (**17** --> **3**). It was found that attempts to cleave the cyclohexyl carbamate group of oxazolidine **9** under acidic conditions resulted in rapid rearrangement to oxazolidinone **10** with inversion of stereochemistry at the O-substituted carbon. This oxazolidinone was converted to racemic isodeoxycassine (**4**) by ring cleavage (**10** --> **14**) and reductive amination. Treatment of oxazolidine **9** under strongly acidic conditions led to isolation of the 3-acetoxy-2,5-dialkylpiperidine **11**, the product of an intramolecular Mannich reaction.

The members of one major sub-group of the naturally occurring piperidine alkaloids incorporate a 3-hydroxy-2,6-dialkyl substitution pattern (**1**).[2] Although several stereochemical relationships are found in this class of alkaloids, most of the alkaloids with a C-2 methyl substituent possess an "all-cis" (2α,3α,6α) stereochemistry (representative examples are given by structures **2a-d**). Several synthetic approaches to alkaloids with structure **2** have been reported,[3-10] but many of these syntheses suffer from lack of stereochemical control at C-3 or require correction of stereochemistry at this center.[11] We have developed a new method that contains sufficient flexibility to allow for stereoselective synthesis of alkaloids **1** with a variety of structural and stereochemical relationships. Stereoselective syntheses of (±)-deoxocassine (**3**),[12] a simple analog of the natural alkaloids **2**, and of the stereoisomeric (±)-isodeoxocassine (**4**) are reported in this paper. The stereodivergent nature of the synthetic method results from a novel, stereospecific rearrangement of a key synthetic intermediate.

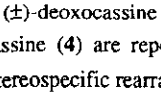


1

R_1 = H or acyl

R_2 = substituted alkyl

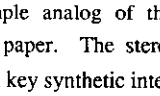
Y = H or OH



[2R,3R,6S]

2a) R = $(CH_2)_{10}COCH_3$, (-)-cassine

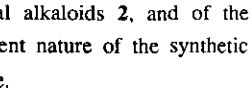
2b) R = $(CH_2)_9COCH_2CH_3$, (-)-prosafrinine



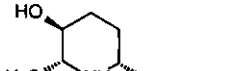
[2S,3S,6R]

2c) R = $(CH_2)_5CO_2H$, (+)-azimic acid

2d) R = $(CH_2)_7CO_2H$, (+)-carpamic acid



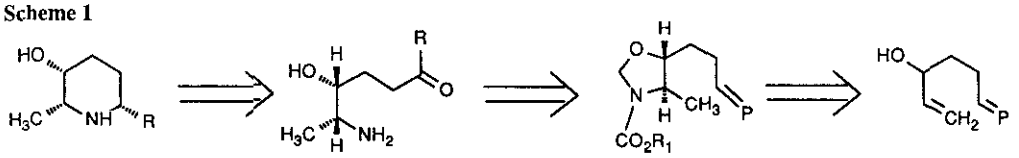
3 deoxocassine



4 isodeoxocassine

A retrosynthetic analysis for the all-cis 3-hydroxy-2-methyl-6-alkylpiperidines is shown in Scheme 1. Stereoselective reductive amination of δ-amino ketones to *cis*-2,6-dialkylpiperidines has been used in a variety of syntheses.[3-5,7,13-15] Thus, a key structure in our synthetic approach is the γ-hydroxy-δ-amino ketone II. The major consideration then becomes control of the relative stereochemistry of the β-amino alcohol functionality in structure II. Our earlier studies[16] on intramolecular amidomercuration of N-acylaminomethyl derivatives of allylic alcohols (Scheme 2) led us to consider the oxazolidine structure III as an appropriate precursor to II. The oxazolidine also

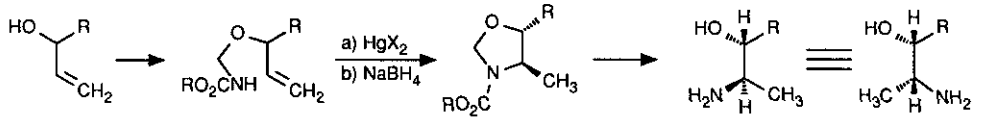
Scheme 1



I II III IV

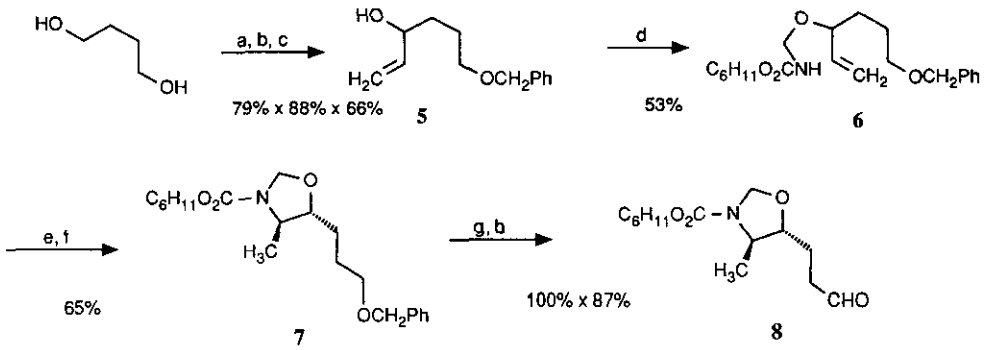
serves as a protecting group for the amino alcohol functionality during the steps necessary to introduce varying R groups late in the synthesis. This analysis leads to selection of a suitably protected allylic alcohol (IV) as the starting material for these syntheses.

Scheme 2



The synthesis of the protected allylic alcohol **5** and its conversion to the key oxazolidine intermediate **8** is shown in Scheme 3. Allylic alcohol **5** was prepared from butane-1,4-diol by monoprotection with benzyl bromide,[17] oxidation to the aldehyde with PCC, and treatment with vinylmagnesium bromide. This alcohol was converted to an N-acylaminomethyl derivative by treatment with an N-(hydroxymethyl)carbamate and *p*-toluenesulfonic acid as catalyst. Although benzyl carbamates were used extensively in our earlier studies,[16,18-20] the use of the benzyl ether protecting group for the primary alcohol required a different carbamate. Methyl and isobutyl carbamates were examined, but the cyclohexyl carbamate proved most useful for facile preparation of the requisite N-acylaminomethyl ether derivative **6**.[21] Cyclohexyl N-(hydroxymethyl)carbamate was prepared by condensation of cyclohexyl carbamate with formalin (1.5 eq) and sodium carbonate (0.5 eq). A mixture of alcohol **5**, cyclohexyl N-(hydroxymethyl)carbamate (1.1 eq), and a catalytic amount of *p*-TsOH in ether was heated at reflux with a Dean-Stark trap for 40 min. The ether derivative **6** was isolated in 53% yield after preparative HPLC purification. Recovered alcohol **5** could be recycled to improve the conversion to **6**. Compound **6** was converted to oxazolidine **7** by treatment with mercuric acetate in acetonitrile followed by reductive demercuration. The reductive demercuration was effected by removal of acetonitrile under vacuum, dilution of the organomercurial with CH_2Cl_2, anion exchange with KOH and a phase-transfer catalyst, and reduction with basic sodium borohydride.[22] This cyclization provided trans oxazolidine **7** and the cis diastereomer in a ratio of 4.4:1. The pure trans isomer **7** was obtained in 65% yield after purification by preparative HPLC. This cyclofunctionalization reaction not only

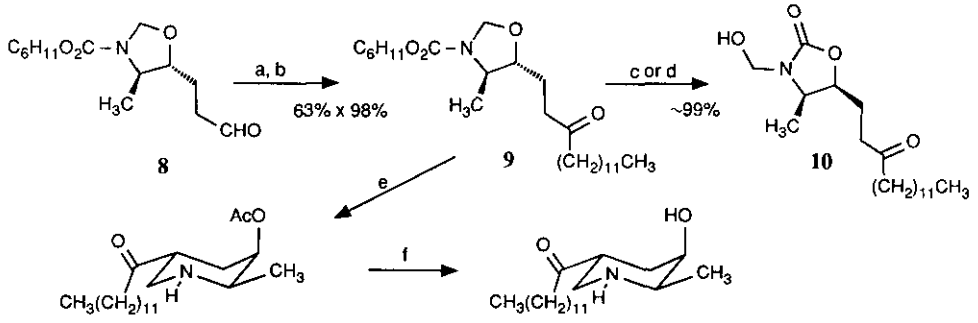
Scheme 3



a) $PhCH_2Br$, KOH; b) PCC, CH_2Cl_2, c) H_2C=CH-MgBr, THF, d) $C_6H_{11}O_2CNHCH_2OH$, p-TsOH, Et_2O;
e) $Hg(OAc)_2$, CH_3CN; f) $NaBH_4$, KOH; g) H_2, 10% Pd/C, EtOH

generates the correct stereochemical relationship for the β-amino alcohol functionality, but also provides suitable protection for further elaboration of the appropriate side chain. The benzyl ether protecting group was cleaved by hydrogenolysis, and the alcohol was oxidized with PCC to give oxazolidine aldehyde **8** (87% crude yield). Although this aldehyde could be isolated and chromatographed, higher yields in the next reaction were obtained by use of the crude aldehyde directly (see below) Aldehyde **8** can be considered a suitable precursor for synthesis of any of the 2α-methyl-3α-hydroxypiperidine alkaloids through addition of varying groups to generate the appropriate 6-substituent.

Although initial studies were directed toward synthesis of azimic acid (**2c**), attempts to cleave the oxazolidine ring after addition of the side chain gave results which were difficult to interpret.[21] We therefore directed our attention to synthesis of deoxocassine (**3**) with a non-functionalized side-chain in order to simplify the spectra of the intermediates. Oxazolidine **8** was converted to oxazolidine **9** by reaction with dodecyllithium followed by oxidation. The cleavage of cyclohexyl carbamates with HBr in nitromethane[23] has been reported, and other studies



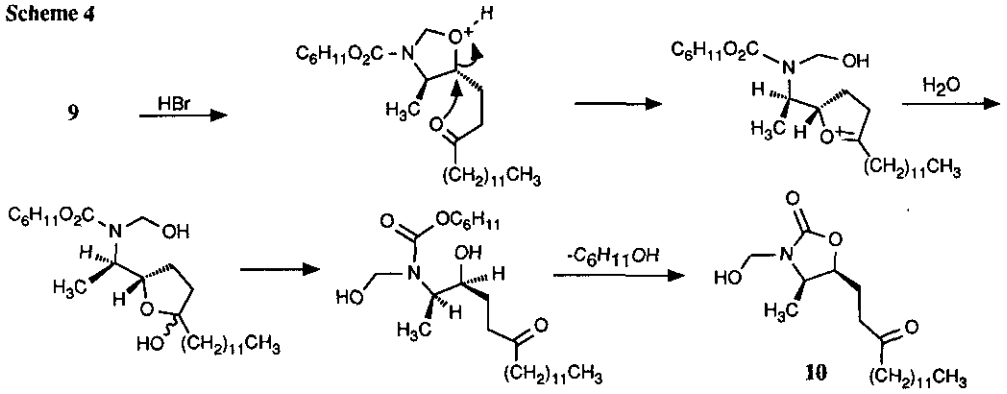
a) $CH_3(CH_2)_{11}$-Li; b) Jones' reagent, c) HBr/CH_3NO_2, rt, d) HBr/AcOH, rt; e) HBr/AcOH, 64 °C, f) NaOH, H_2O/EtOH

from these laboratories[24] used HBr in acetic acid at 64 °C for this purpose. The carbamate functionality in oxazolidine **9** was cleaved much more readily than cyclohexyl carbamates in other systems. It was found that reaction with HBr/CH_3NO_2 at room temperature led to complete loss of the cyclohexyl group within 10 min. The resulting product, however, was not the simple unprotected oxazolidine or products resulting from further hydrolysis to the amino alcohol. Careful analysis of the nmr spectra of the product established that it was the rearranged *cis*-oxazolidinone **10**![25] The structure and stereochemistry of **10** was further confirmed by elaboration into (±)-isodeoxocassine (**4**) (see below). Cleavage of the cyclohexyl carbamate of oxazolidine **9** with HBr/HOAc at 64 °C resulted in an even more complex rearrangement from which acetate **11** was isolated. After hydrolysis of the acetate and chromatographic purification, amino alcohol **12** was isolated in 22% yield.[26] The structure of alcohol **12** was deduced from analysis of the 400 MHz ^1H nmr spectrum in conjunction with a 2-D COSY spectrum.[27] It was shown, however, that reaction of **9** with HBr/HOAc at room temperature for 30 min[28] also gave the oxazolidinone **10**.

The facile reaction of carbamate **9** with acid and the inverted stereochemistry observed in the resulting product **10** can be rationalized by the mechanism shown in Scheme 4. In this mechanism, the side-chain carbonyl serves as an intramolecular nucleophile to cleave the C-O bond cleavage with inversion of configuration.[30] The cyclohexyl group is then lost by intramolecular ring closure to form the oxazolidinone structure **10.** Further rearrangement of oxazolidinone **10** to piperidine **11** must involve ring opening of the oxazolidinone, again with inversion or racemization at the oxygen-substituted carbon,[26] followed by an intramolecular Mannich reaction.

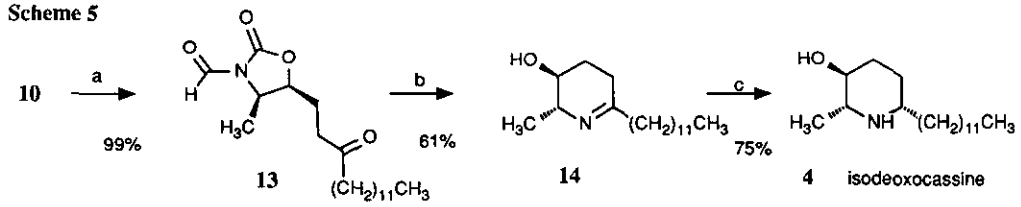
Decoupling experiments with oxazolidinone **10** at 400 MHz showed that the coupling constant between the protons at C-4 and C-5 was 8 MHz, consistent only with the cis stereochemistry.[31] This oxazolidinone was converted into (±)-isodeoxocassine as shown in Scheme 5. Oxidation of **10** with Jones' reagent gave the N-formyl oxazolidinone

Scheme 4



13. Hydrolysis with base then cleaved the N-formyl group and the oxazolidinone ring. The resulting tetrahydropyridine **14** was hydrogenated over palladium on carbon to give (±)-isodeoxocassine.[32]

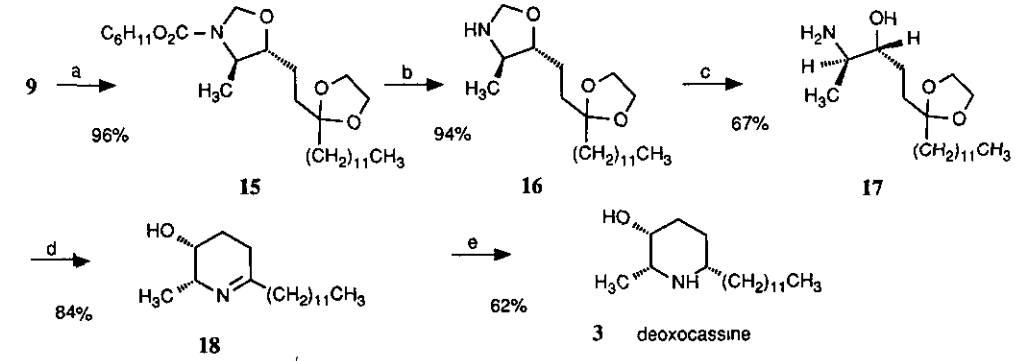
Scheme 5



a) Jones' reagent, b) 2N NaOH, EtOH/H_2O, reflux; c) H_2, Pd/C

Since acidic cleavage of the carbamate in oxazolidine **9** resulted in inversion of stereochemistry at a critical chiral center, hydrolysis under basic conditions seemed the only alternative. The ketone functionality was first protected as a ketal to avoid problems with aldol condensation. Treatment under a variety of strongly basic conditions failed to cleave the cyclohexyl carbamate.[21] We finally found that treatment with sodium methoxide in methanol at 120 °C (sealed ampoule)[33] resulted in clean conversion to unprotected oxazolidine **16** (Scheme 6). Because of concerns over Mannich reaction, the oxazolidine was cleaved under conditions which retained the ketal protecting group. Thus, *treatment with malonic acid and pyridine*[34] *in ethanol gave the threo amino alcohol* **17**. This compound was converted into (±)-deoxocassine (**3**) by acid hydrolysis of the ketal group and hydrogenation.[32]

Scheme 6



a) $HOCH_2CH_2OH$, p-TsOH, PhH, reflux; b) 2N NaOMe, MeOH, 120 °C, 12 h; c) $HO_2CCH_2CO_2H$, Py/EtOH, reflux, d) 0.25 N H_2SO_4, H_2O, THF; e) H_2, Pd/C, EtOH

The results described above demonstrate that a single oxazolidine precursor such as **9** can serve as a starting material for synthesis of hydroxypiperidine alkaloids with either 2α,3α or 2α,3β stereochemistry. Previous studies[35] have shown that tetrahydropyridines related to **14** and **18** can be converted to *trans*-2,6-substituted piperidines (2α,6β stereochemistry) by reduction with triethylaluminum followed by diisobutyl aluminum hydride. Earlier studies from our laboratories[20,24] on the oxidative demercuration of organomercurials resulting from intramolecular amidomercuration of N-acylaminomethyl ethers suggest that cyclofunctionalization of intermediate **6** could be used to synthesize the dihydroxypiperidine alkaloids (**1**, Y = OH). Thus, the method reported in this paper could be extended to provide a unified methodology that could be applied to the stereoselective synthesis of any of the 2,6-disubstituted 3-hydroxypiperidine alkaloids (**1**) from a single intermediate, the cyclofunctionalization substrate **6**.

ACKNOWLEDGEMENTS

We thank the Robert A. Welch Foundation and the National Institutes of Health for support of this research.

REFERENCES AND NOTES

1. This paper is dedicated to Professor D. H. R. Barton, a most vigorous and stimulating colleague, on the occasion of his 70th birthday.
2. G. M. Strunz and J. A. Findlay In *The Alkaloids*; A. Brossi, Ed.; Academic Press: Orlando, FL, 1985: Vol. 26, pp 89-183.
3. E. Brown and A. Bourgouin, *Tetrahedron*, **1975**, *31*, 1047.
4. E. Brown and R. Dhal, *J. Chem. Soc., Perkin Trans 1*, **1976**, 2190.
5. E. Brown and A. Bonte, *Tetrahedron Lett.*, **1975**, 2881.
6. M. Paterne and E. Brown, *J. Chem. Res., Synop.*, **1985**, 278.
7. S. Hanessian and R. Frenette, *Tetrahedron Lett.*, **1979**, 3391.
8. M. Natsume and M. Ogawa, *Heterocycles*, **1980**, *14*, 169.
9. M. Natsume and M. Ogawa, *Heterocycles*, **1980**, *14*, 615.
10. A. B. Holmes, C. Swithenbank, and S. F. Williams, *J. Chem. Soc., Chem. Commun.*, **1986**, 265.
11. Only the syntheses reported by Hanessian and coworkers[7] and by Holmes and coworkers[10] avoid this problem.
12. K. Kurihara, T. Sugimoto, T, Saitoh, Y. Igarashi, H. Hirota, Y. Moriyama, T. Tsuyuki, T. Takahashi, and Q. Khuong-Huu, *Bull. Chem Soc. Jpn.*, **1985**, *58*, 3337.
13. (a) E. Brown, J. Lavoue, and R. Dhal, *Tetrahedron*, **1973**, *29*, 455. (b) E. Brown and R. Dhal, *Bull. Soc. Chem. Fr.*, **1972**, 4292.
14. R. K. Hill and T. Yuri, *Tetrahedron*, **1977**, *33*, 1569.
15. A. Astier and M. M. Plat, *Tetrahedron Lett*, **1978**, 2051.
16. K. E. Harding, R. Stephens, and D. R. Hollingsworth, *Tetrahedron Lett.*, **1984**, *25*, 4631.
17. M. Kanao, T. Hashizume, Y. Ichikawa, K. Irie, and S. Isoda, *J. Med. Chem.*, **1982**, *25*, 1358.
18. K. E. Harding, T. H. Marman, and D.-H. Nam, *Tetrahedron Lett.*, **1988**, *29*, 1627.
19. K. E. Harding and D. R. Hollingsworth, *Tetrahedron Lett.*, **1988**, *29*, 3789.
20. K. E. Harding, T. H. Marman, and D.-H. Nam, *Tetrahedron*, **1988**, *44*, 5605.
21. M. W. Jones, Ph.D. Dissertation, Texas A&M University, 1988.
22. K. E. Harding and T. H. Marman, *J. Org. Chem*, **1984**, *49*, 2838. These conditions were necessary to obtain reproducible results in the reductive demercuration.
23. F. C. McKay and N. F. Albertson, *J. Am. Chem Soc.*, **1957**, *79*, 4686.
24. K. E. Harding and D.-H. Nam, *Tetrahedron Lett.*, **1988**, *29*, 3793.
25. Spectral data for oxazolidinone **10**: ^{1}H Nmr (200 MHz, $CDCl_3$) δ 0.88 (bt, J=6 Hz, 3 H, terminal CH_3), 1.26 (br, 19 H, methylenes, CH_3 of oxazolidinone), 1.5-2.03 (m, 6 H, CH_2), 2.42 (t, J = 7.4 Hz, 2 H,

$CH_2C=O$), 2.5-2.75 (m, 2 H, $CH_2C=O$), 3.7 (very br s, 1 H, OH), 4.12 (dq with similar J values of ca 7.8 and 7.4 Hz, 1 H, CH-N), 4.50 (ddd, J = 10.8, 7.8, and 3.1 Hz, 1 H, CH-O), 4.65 (d, J = 11.5 Hz, 1 H, NCH_aH_bOH), 4.94 (d, J = 11.5 Hz, 1 H, NCH_aH_bOH); ^{13}C Nmr (50 MHz, $CDCl_3$) δ 13.4 (CH_3 of oxazolidinone), 14.1 (terminal CH_3), 22.7, 23.1, 23.9, 29.2, 29.3, 29.4, 29.6, 31.9 (CH_2), 38.0, 43.0 ($CH_2C=O$), 52.8 (CH-N), 66.6 (NCH_2O), 77.1 (CH-O), 157.6 (N-C=O), 209.9 (C=O).

26. The absence of stereoisomers of structures **11** and **12** has not been demonstrated conclusively.
27. Spectral data for alcohol **12**: ^1H Nmr (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.5 Hz, 3 H, terminal CH_3), 1.11 (d, J = 6.5 Hz, 3 H, ring CH_3), 1.27 (br, 18 H, CH_2), 1.49-1.63 (m including a ddd at 1.59, J = 13.5, 13.5, and 2.5 Hz, 3 H, CH_2 and C4-H_{ax}), 2.12 (dddd, J = 13.5, 4, 4, and 2 Hz, 1 H, C4-H_{eq}), 2.32 (br, 2H, NH, OH), 2.42 (td, J = 7.5 and 1.5 Hz, 2 H, CH_2-C=O), 2.69 (dd, J = 12 and 12 Hz, 1 H, C6-H_{ax}), 2.71 (qd, J = 6.5 and 1.5 Hz, 1 H, C2-H_{ax}), 2.91 (ddddt, J = 13.5, 12, 4, 4, and 1.5 Hz, 1 H, C5-H_{ax}), 3.16 (ddd, J = 12, 4, and 2 Hz, 1 H, C6-H_{eq}), 3.68 (br, only small J values, 1 H, C3-H_{eq}); ^{13}C Nmr (50 MHz, $CDCl_3$) δ 14.1 (terminal CH_3), 18.3 (ring CH_3), 22.7, 23.6, 29.27, 29.35, 29.4, 29.5, 29.6, 31 9, 34.7, 41.4 ($CH_2C=O$), 43.9 (C-5), 48.3 (C-6), 55.1 (C-2), 67.5 (C-3), 212.7 (C=O).
28. Cyclohexyl carbamates of simple secondary amines are not cleaved under these conditions.[29]
29. D.-H. Nam, Ph.D. Dissertation, Texas A&M University, 1987.
30. The carbamate functionality of N-(cyclohexyloxycarbonyl)-protected oxazolidines lacking the side-chain carbonyl has been cleaved without inversion of configuration.[24,29]
31. Considerable literature precedent exists for use of the coupling constant between the protons at C-4 and C-5 of oxazolidinone rings to assign stereochemistry. See *inter alia:* (a) S. Futagawa, T. Inui, and T. Shiba, *Bull Chem. Soc. Jpn.*, **1973**, *46*, 3308. (b) D. H. Rich and E. T. O. Sun, *J. Med. Chem.*, **1980**, *23*, 27. (b) J. R. Luly, J. F. Dellaria, J. J. Plattner, J. L. Soderquist, and N. Yi, *J. Org. Chem.*, **1987**, *52*, 1487. (c) G. Cardillo, M. Orena, S. Sandri, and C. Tomasini, *Tetrahedron*, **1985**, *41*, 163. (d) M.-N. Dufour, P. Jouin, J. Poncet, A. Pantaloni, and B. Castro, *J. Chem. Soc., Perkin Trans. I*, **1986**, 1895. (e) D. J. Kempf, *J. Org. Chem.*, **1986**, *51*, 3921. (f) H. L. Sham, C. A. Rempel, H. Stein, and J. Cohen, *J. Chem. Soc., Chem. Commun.*, **1987**, 683. (g) B. D. Harris, K. L. Bhat, and M. M. Joullie, *Tetrahedron Lett.*, **1987**, *28*, 2837.
32. The structure and stereochemistry of **3** and **4** were confirmed by comparison of ^1H nmr and ^{13}C nmr spectral data with literature values.
33. For an example of hydrolysis in methanol at 120 °C using sealed ampoules, see: E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Am Chem. Soc.*, **1968**, *90*, 3245. E. J. Corey, N. H. Andersen, and K. E. Harding, unpublished results, Harvard University, 1969.
34. S. Nagarajan and B. Ganem, *J. Org. Chem.*, **1985**, *50*, 5735.
35. K. Maruoka, T. Miyazaki, M. Ando, Y. Matsumura, S. Sakane, K. Hattori, and H. Yamamoto, *J. Am. Chem. Soc.*, **1983**, *105*, 2831.

Received, 6th September, 1988