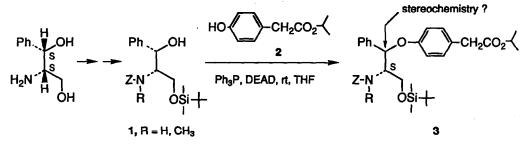
Tetrahedron Letters, Vol.31, No.37, pp 5253-5256, 1990 Printed in Great Britain

THE STEREOCHEMICAL OUTCOME FROM MITSUNOBU COUPLINGS OF VICINAL, N-PROTECTED ACYCLIC AMINO ALCOHOLS

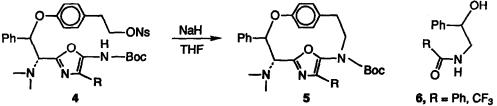
Bruce H. Lipshutz^{*} and Todd A. Miller Department of Chemistry University of California, Santa Barbara, CA 93106

Summary: Contrary to results expected in Mitsunobu reactions of amides derived from acyclic vic-amino alcohols (i.e., double inversion and hence, retention), urethane derivatives afford products solely of *inversion*.

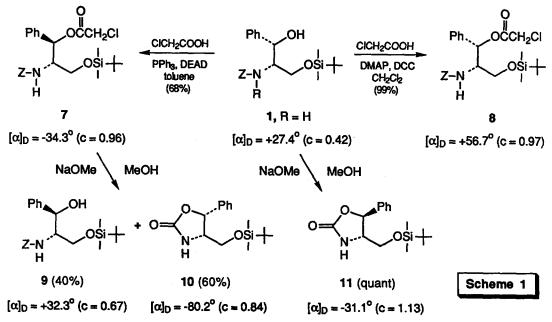
During the course of our synthetic studies¹ on the specific ion sequestering cyclopeptide alkaloids,² our strategy called for a key Mitsunobu coupling³ of chiral, non-racemic urethane 1 with phenolic ester 2.



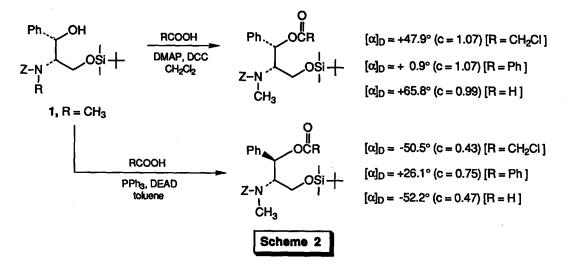
Although initially our goal was to establish the viability of macrocycle (5) formation via 5-aminooxazole intermediates (4) irrespective of the absolute stereochemical assignment at C-9, 4 we anticipated that net retention would be observed (for $1 + 2 \rightarrow 3$) based on participation of the carbonyl group as noted previously with amides 6.⁵ Surprisingly, there does not appear to be a single example of an intermolecular Mitsunobu reaction involving a vicinally disposed acyclic amino alcohol where nitrogen is derivatized as a secondary or tertiary urethane.⁶ Given the current interest in controlling stereochemical relationships in amino alcohols,⁷ together with the extensive utilization of the Mitsunobu protocol,³ we investigated this process, the details of which are described herein.



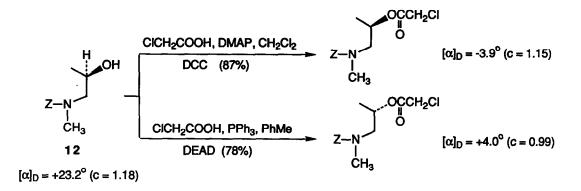
Exposure of 1 (R = H) in the presence of RCOOH to standard Mitsunobu conditions³ afforded a single product, ester 7. That clean *inversion* had occurred was readily discerned by comparison of 7 with the product (8) of DCC coupling of 1 (R = H) with the same acid (Scheme 1). In addition, transesterification of 7 led to two new materials, compounds 9 and 10, the former being a diastereomer of 1, while the oxazolidone is a diastereomer of 11 formed by ring closure directly from 1.



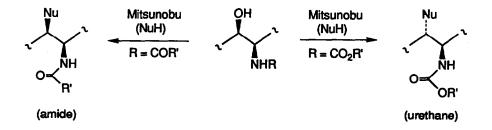
Tertiary carbamate 1 ($R = CH_s$) was tested in a likewise manner using three different acids (Scheme 2). In all cases, the same conclusions were drawn (i.e., that a single inversion had taken place) and hence, both secondary and tertiary carbamates give the same stereochemical results.



To insure the generality of these observations, given the benzylic nature of alcohol 1 and the presence of a heteroatom at the β -site (however unlikely its involvement), educt 12^a was subjected to the identical series of reactions. As expected, the product of net inversion was realized.



In conclusion, it has been unequivocally established that both secondary and tertiary carbamates bearing a vicinal relationship to a hydroxyl function undergo Mitsunobu couplings with clean inversion at carbon.⁹ Unlike secondary amides, which readily form oxazolines and would be expected to lead to net retention, urethanes in general do not participate in such intramolecular closures. This presumably reflects the greater buildup of negative charge on oxygen due to amide resonance as compared with that for carbamates. *The ability to predetermine the stereochemical consequences of Mitsunobu reactions on vic*-amino alcohols by simply chosing an appropriate nitrogen protecting group represents, therefore, a valuable tool for controlling acyclic stereochemistry.



Acknowledgement. Financial support provided by the National Institutes of Health (GM 28128), the Sloan & Dreyfus Foundations, and UCSB is gratefully acknowledged.

References and Notes

- 1. Lipshutz, B.H., Huff, B.E., McCarthy, K.E., Mukkaram, S.M.J., Siahaan, T.J., Vaccaro, W.D., Webb, H., Falick, A.M., submitted.
- (a) For excellent reviews, see (a) Bhat, K.L., Joullie, M.M., J. Chem. Ed., 1988, 64, 21; (b) Joullie, M.M., Nutt, R.F., in "Alkaloids: Chemical and Biological Perspectives," Pelletier, S.W., Ed., Wiley, N.Y., 1985, vol. 3, pp 113-168; (c) Schmidt, U., Haslinger, E., in "The Alkaloids," Brossi, A., Ed., Academic Press, N.Y., 1985, vol. 26, chpt. 6, pp 299-327; (d) Tschesche, R., <u>Heterocycles</u>, 1976, 4, 107; (e) Tschesche, R., Kaussmann, E.U., in "The Alkaloids," Manski, R.H.F., Ed., Academic Press, N.Y., 1975, vol. 15, chpt. 4, pp 165-205; (f) Ogihara, Y., Ann. Rep. Fac. Pharm. Sci. Nagoya City Univ., 1974, 22, 1; (g) Pais, M., Jarreau, F.-X., in "Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins, "Weinstein, B., Ed., Dekker, N.Y., 1971, vol. 1, chpt. 5, pp 127-157; (h) Warnhoff, E.W., Fortschr. Chem. Org. Naturst., 1970, 28, 162.
- (a) Mitsunobu, O., <u>Synthesis</u>, 1981, 1; (b) Hughes, D.L., Reamer, R.A., Bergan, J.J., Grabowski, E.J.J., J. <u>Am. Chem. Soc.</u>, 1988, <u>110</u>, 6487; (c) Varasi, M., Walker, K.A.M., Maddox, M.L., <u>J. Org. Chem.</u>, 1987, <u>52</u>, 4235; (d) Camp, D., Jenkins, I.D., <u>ibid.</u>, 1989, <u>54</u>, 3045; (e) <u>ibid.</u>, 1989, <u>54</u>, 3049.
- Lipshutz, B.H., Hungate, R.W., McCarthy, K.E., J. Am. Chem. Soc., 1983, 105, 7703; Tetrahedron Lett., 1983, 24, 5155.
- 5. Roush, D.M., Patel, M.M., Syn. Comm., 1985, 15, 675
- For a cyclic case, see Heffner, R.J., Joullie, M.M., <u>Tetrahedron Lett.</u>, in press; For intramolecular processes, see e.g., Bose, A.K., Manhas, M.S., Sahu, D.P., Hedge, V.R., <u>Can. J.</u> Chem., <u>1984</u>, 62, <u>2498</u>; Miller, M.J., Mattingly, P.G., Morrrison, M.A., Kerwin, J.F., <u>J. Am. Chem. Soc.</u>, 1980, <u>102</u>, 7026. Review on Mitsunobu reactions: Hughes, D.L., Grabowski, E.J.J., <u>Org. React.</u>, submitted.
- For some very recent representative examples, see Kamimura, A., Ono, N., <u>Tetrahedron Lett.</u>, 1989, 30, 731; Roemmele, R.C., Rapoport, H., <u>J. Org. Chem.</u>, 1989, <u>54</u>, 1866; Dai, L., Lou, B., Zhang, Y., <u>J.</u> <u>Am. Chem. Soc.</u>, 1988, <u>110</u>, 5195; Roskamp, E.J., Pedersen, S.F., <u>ibid.</u>, 1987, <u>109</u>, 6551; Trost, B.M., Sudhaker, A.R., <u>ibid.</u>, 1987, <u>109</u>, 3792.
- Alcohol 12 was prepared from commercially available (Aldrich Chemical Co.) S-(+)-1-amino-2propanol.
- 9. All new compounds were fully characterized by IR, NMR, MS, and HRMS analyses. Optical rotations were obtained in EtOH at ambient temperatures (ca. 23°).