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CARBONYL PARTICIPATION IN THE REACTION OF N-ACYL-2-ISOPROPENYLPYRROLIDINES WITH HALOGEN ELECTROPHILES. STEREOCONTROLLED PREPARATION OF ENANTIOMERICALLY PURE SYNTHONS FOR THE SYNTHESIS OF PUMILIOTOXIN A ALKALOIDS.

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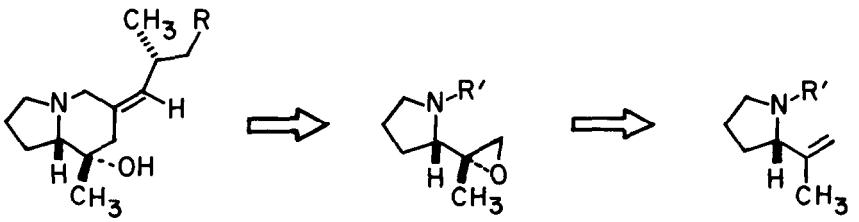
Summary: Allylic carbamate 4 and allylic benzamide 12 react with halogen electrophiles with high 1,2-relative asymmetric induction via carbonyl participation.

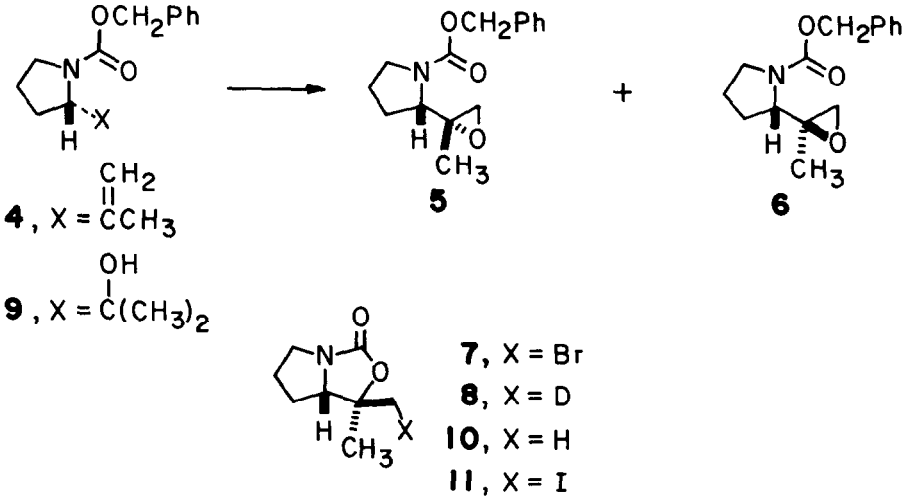
The control of acyclic 1,2-stereochemical relationships by relative asymmetric induction in the reaction of allylically substituted alkenes with electrophiles is of considerable importance in organic synthesis.[1,2] Although acyclic allylic alcohols have been widely studied,[1] and impressive selectivities recorded,[1,3] stereocontrol in related reactions of allylic amines and derivatives with electrophiles remains largely unexplored.[4] We had occasion to investigate this issue during our current synthetic efforts[5,6] directed at members of the pumiliotoxin A alkaloid class (1). For these studies we required enantio-



1 2 3

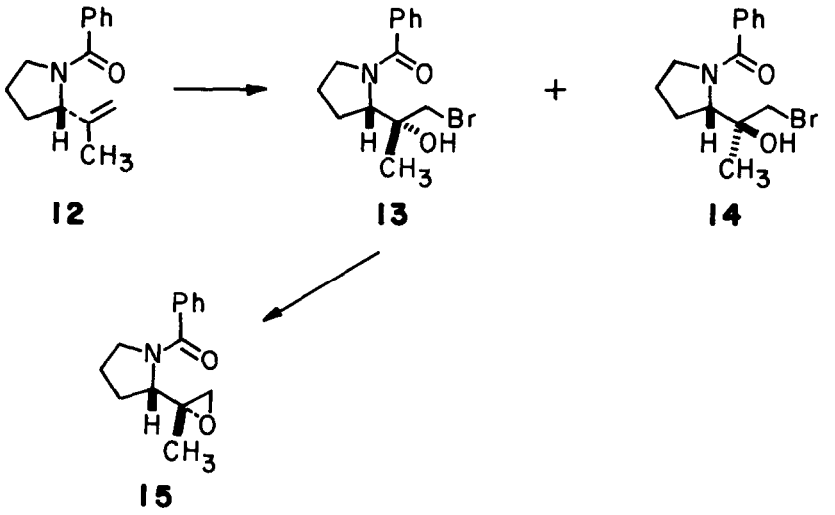
merically pure synthons 2, which should be available from L-proline. In this Letter we report that, although peracid epoxidations of N-acyl-2-isopropenylpyrrolidines (3, R'=COR) occur with little asymmetric induction,[5] halocyclization reactions[7] proceed with good selectivity and provide a stereocontrolled route for the synthesis of enantiomerically pure epoxides 2.

Asymmetric induction in the epoxidation of carbamate 4[5] with m-chloroperbenzoic acid was somewhat solvent dependent,[8] although at best (25°C in hexane) only a 2:1 ratio of epoxides 5[5] and 6[5] was realized. Similar low stereoselec-



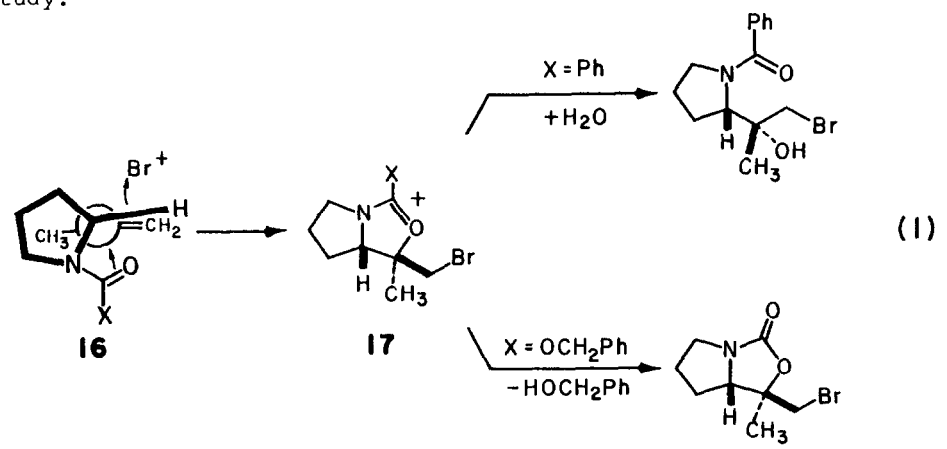
tivity was observed in the bis-hydroxylation of 4 with OsO_4. In marked contrast, 4 reacted with N-bromosuccinimide (NBS) in DMSO-H_2O (50:1, 25°C)[9] to give a single[10] bicyclic bromocarbamate 7[11] (mp 75-76°C; ^1H NMR δ 1.54, s, Me, 3.52 ABq, CH_2Br) which was isolated in 83% yield. That 7 had the same absolute configuration at the quarternary carbon as the desired synthons 2 was determined by conversion of 7 to deuterocarbamate 8[11] (mp 56-58°C, 82%) upon reaction with Bu_3SnD (PhH, 50°C). The ^1H decoupled ^{13}C NMR spectrum of 8 showed a singlet for the CH_3 group at 23.0 ppm, and a characteristic triplet for the CH_2D group at 28.6 ppm. The stereochemical assignment follows from our previous experience[5] that groups on the α-face of this rigid bicyclic ring system experience upfield ^{13}C NMR shifts. That the carbamate group of 4 was directly participating in the bromination step was established by treatment of a 1·1 mixture of 4 and alcohol 9 (a model for the bromohydrin of 4) with NBS in DMSO-H_2O to give bromocarbamate 7 and recovered alcohol 9 (carbamate 10 could not be detected by ^1H NMR, GLC, or TLC analysis). Similar selectivity was observed when 4 was treated with iodine (25°C, CH_3CN) to give a single[10] iodocarbamate 11[11] (mp 83-84°C; ^1H NMR δ 1.47 s, Me, 3.44 ABq, CH_2I) in 84% yield.[12]

Similar, although considerably reduced, selectivity was observed in bromohydrin formation from benzamide 12.[13,14] Thus, treatment of 12 with NBS in DMSO-H_2O (25°C, 50:1) afforded a 7:3 mixture of bromohydrins 13 (^1H NMR δ 1.31, s, Me) and 14 (^1H NMR δ 1.25, s, Me) in 83% yield. The selectivity was increased to 9 1 when the reaction was conducted at -10°C in THF-H_2O (50·1), and the major isomer 13[11] (mp 104-104.5°C) could be isolated in 50% yield after chromatography



on silica gel. The stereochemistry of 13 was established by correlation[15] with 8. The desired epoxide 15[11] (an oil; ^{1}H NMR δ 1.44, s, Me, 2.80 ABq, CH_2O, 4.59, t, J = 7.4, CHN) was obtained from 13 in 75% yield by reaction for 2h at room temperature with 0.3 M NaOH (5:2 THF-H_2O) followed by rapid chromatography on silica gel.

The high stereoselectivity observed in the reaction of allylic carbamate 4 and allylic benzamide 12 with NBS and H_2O can be rationalized as illustrated in eq 1.[16,17] Preferential reaction of conformer 16 is consistent with the "eclipsed alkene" model[1,3,18] of reactions of this type, as well as a recent computational study.[2]



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References and Notes

1. For a recent review, see Bartlett, P.A. Tetrahedron 1980, 36, 2-72.

2. For a recent theoretical analysis, see Caramella, P.; Rondan, N.G.; Paddon-Row, M.N.; Houk, K.N. J. Am. Chem. Soc. 1981, 103, 2438-2440.

3. Cf. Sharpless, K.B.; Verhoeven, T.R. Aldrichimica Acta 1979, 12, 63. Kishi, Y. Aldrichimica Acta 1980, 13, 23-30.

4. (a) For a recent example in a cyclic system, see Georges, M.; Fraser-Reid, B. Tetrahedron Lett. 1981, 22, 4635-4638; (b) For an independent investigation of the halocyclization of acyclic allylic carbamates, see Parker, K.A.; O'Fee, P.P. manuscript submitted for publication.

5. For the total synthesis of enantiomerically pure toxin 251 D (1, R=n-C_3H_7) see Overman, L.E.; Bell, K.L. J. Am. Chem. Soc. 1981, 103, 1851-1853.

6. For current efforts directed at pumiliotoxin B (1, R=CH=C(Me)CH(OH)CH(OH)Me), see Overman, L.E.; McCready, R.J. Tetrahedron Lett. 1982, 23, 2355-2358.

7. For a review of halolactonization, see Dowle, M.D.; Davies, D.I. Chem. Soc. Rev. 1979, 171-197.

8. Ratios of 5:6 as determined by HPLC analysis of epoxidation reactions conducted at 25°C were: 52:48 (CH_2Cl_2 or CH_3CN), 58:42 (EtOAc), 59:41 (THF), 65:35 (hexane).

9. Cf. Dalton, D.R.; Dutta, V.P.; Jones, D.C. J. Am. Chem. Soc. 1968, 90, 5498-5501.

10. The ratio of the two possible diastereomers was greater than 20:1 (^1H NMR).

11. All new compounds showed IR, 250 MHz ^1H NMR ($CDCl_3$), 63 MHz ^{13}C NMR ($CDCl_3$), and mass spectra which were fully in accord with their assigned structures.

12. This reaction was first conducted by Dr. Kenward Vaughan.

13. $Mp_{5,11}$ 101-102°C; prepared from N-benzoyl L-proline in a fashion similar to 4.

14. Direct epoxidation of 12 with m-chloroperbenzoic acid was nonstereoselective.

15. Accomplished in 25% overall yield by the following sequence: (a) Bu_3SnD, PhH, 50°C; (b) DIBAL-H, 25°C, PhMe; H_2, Pd-C; (c) $PhCH_2OCOCl$, Et_3N, 25°C; BuLi, THF, 25°C.

16. The lower stereoselectivity observed with 12 may reflect competing bromohydrin formation by a nonstereoselective reaction which does not involve carbonyl participation.

17. The somewhat related formation of halolactones from the reaction of 3-butenylcarboxamides with I_2 and H_2O has been reported: Takano, S.; Hirama, M.; Ogasawara, K. J. Org. Chem. 1980, 45,3729-3730.

18. For a recent example, see Collum, D.B.; McDonald, III, J.H.; Still, W.C. J. Am. Chem. Soc. 1980, 102, 2118-2120.

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