Tetrahedron Letters No. 15, pp 1141 - 1144, 1976. Pergamon Press. Printed in Great Brita

# AN APPLICATION OF STERIC ACCESSIBILITY CONTROL IN HYDROBORATION TO THE SYNTHESIS OF EPIMERIC ALCOHOLS

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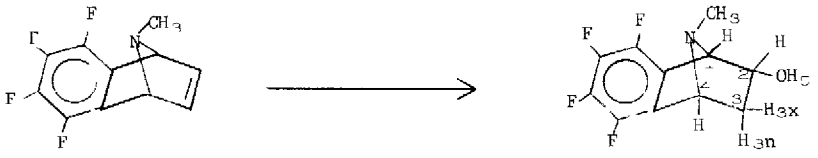
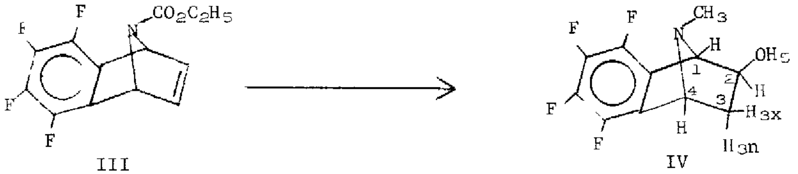
(Received in USA 21 January 1976; received in UK for publication 5 March 1976)

It is well established that hydroboration stereochemistry in bicyclic olefins is controlled by the extent of steric accessibility to the two faces of the double bond [1] Set forth below is a novel application of this principle in which a nitrogen atom proximate to an olefinic linkage is used to control the steric course of hydroboration such that the same reagent, borane in tetrahydrofuran (THF BH$_3$), can be used for the highly stereoselective synthesis of either endo (II) or exo (IV) 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydronaphthalen-1,4-imine-2-ol This is accomplished by changing the N-substituent in the olefin from methyl (I)[2] to carboethoxy (III) [3] Thus, treatment of 5,6,7,8-tetrafluoro-9-methyl-1,4-dihydronaphthalen-1,4-imine (I) with excess THF BH$_3$ followed by oxidation with hydrogen peroxide effected a preferential conversion of I to the endo alcohol II, while similar treatment of the N-carboethoxy olefin III produced predominately the exo epimer IV

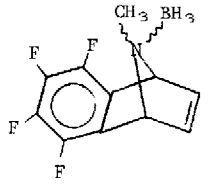


I II

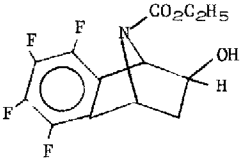


III IV

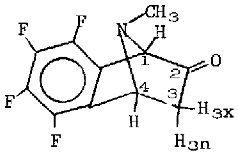
The reasonable explanation for these results is that I, but not III, rapidly forms an amine-borane on contact with THF BH$_3$ Thus, the conversion of the tercovalent nitrogen in I to a quadricovalent state in V provides sufficient steric hindrance to the exo face of the olefin to make the endo face relatively more accessible to borane and/or other organoborane species As would be anticipated, evaporation of the THF solution obtained by titration of I with one molecular equivalent of 0 93 molar THF $BH_3$ in THF, even after 48 hours, produced only the amine-borane V as evidenced by its ir and proton nmr spectra $\nu_{max}^{Nujol}$ 2360 and 2320 $cm^{-1}$, $\delta_{ppm}^{TMS}$ ($CDCl_3$) 2 9 (N-$CH_3$, s), 5 1 (bridgehead H, m), 7 0 (vinyl H, m) The presence of the vinyl proton signal clearly indicated that hydroboration had not occurred. The infrared spectrum[4] of V and the downfield shift of the N-$CH_3$ group relative to I (δ 2 0) in its proton nmr spectrum[5] are in accord with the amine-borane structure, however, these data do not reveal the stereochemistry of V [6] Addition of a second molecular equivalent of THF $BH_3$ to V, followed by the usual oxidative treatment with basic hydrogen peroxide afforded an 85% yield of a mixture of II (97%) and IV (3%) [7] Epimer II, m p 189-191°, was readily separated from the mixture in 75% yield on washing with ether followed by sublimation of the ether insoluble material



V



VI



VII

In contrast to the hydroboration of I, titration of III with one molecular equivalent of THF $BH_3$ followed by peroxide oxidation and separation of the neutral and basic products by extraction gave IV (21%) and the urethane VI[8] (53%) Similar treatment of III with excess THF $BH_3$ and peroxide anion gave IV, m p 138-139°, in 70% isolated yield along with VI (2%) and II (4%) Clearly, a normal hydroboration of III occurred with the initially added THF $BH_3$ Thus, hydroboration occurred preferentially from the less hindered exo face of the double bond as it does with benzonorbornadiene [9] The appearance of IV as the minor product under the former conditions and the major product with excess THF $BH_3$ was surprising in view of the usual resistance of urethanes to reduction with this reagent Since the N-carboethoxy group in VI and 5,6,7,8-tetrafluoro-9-carboethoxy-1,2,3,4-tetrahydronaphthalen-1,4-imine was not reduced with excess THF $BH_3$, further experiments have been designed and are in progress to clarify the nature of this reduction

The epimeric relationship between II and IV was indicated by the oxidation [$(CH_3)_3N$ $SO_3$ in DMSO][10] of II and IV to the same ketone VII, m p 101-103°, $\nu_{max}^{Nujol}$ 1760 $cm^{-1}$, $\delta_{ppm}^{TMS}$ ($CDCl_3$) 2 0 ($H_{3n}$, d, J = 16Hz), 2 3 (N-$CH_3$, s), 2 7 ($H_{3x}$, dd, $J_{3x,3n}$ = 16Hz, $J_{3x,4}$ = 4Hz), 4 5 ($H_1$, m), 4 8 ($H_4$, m), m/e 245 ($M^+$), m/e 217 ($M^+$-CO), m/e 203 ($M^+$-$C_2H_2O$) Furthermore, lithium aluminum hydride (LAH) reduction of VII gave II (97%) and IV (3%) as did THF $BH_3$ (92% II and 8% IV), aluminum isopropoxide in isopropanol (90% II and 10% IV) and sodium borohydride (64% II and 36% IV) [7] The high stereoselectivity observed with LAH and THF $BH_3$ may be mediated by an organometallic species formed by covalent interaction of the reducing agent with the basic nitrogen of *VII* thus allowing intramolecular hydride transfer from the metal to the carbonyl carbon. In this case, N-complex formation would facilitate attack at C-2 from the *exo* side. Such an intramolecular mechanism has recently been proposed by Marchand for the LAH reduction of the olefinic linkage in 9-methyl-1,4-dihydronaphthalen-1,4-imine.[11]

The configurational assignments of the *endo* hydroxy group to *II* and the *exo* to *IV* followed from comparison of the respective nmr spectra.[12] *II* $\delta^{TMS}_{ppm}$ ($CDCl_3$) 1.0 ($H_{3n}$, dd, $J_{3n,2}$ = 2.8Hz, $J_{3n,3x}$ = 12.3Hz), 1.5 (OH, d, $J_{2,5}$ = 6.5Hz, exchanged by $D_2O$), 2.05 (N-$CH_3$, s), 2.55 ($H_{3x}$, ddd, $J_{3x,2}$ = 8.4Hz, $J_{3x,3n}$ = 12.3Hz, $J_{3x,4}$ = 4.8Hz), 4.35 ($H_4$, m), 4.5 ($H_1$, m), 4.7 ($H_2$, m). *IV* $\delta^{TMS}_{ppm}$ ($CDCl_3$) 1.85 ($H_{3x}$ and $H_{3n}$, m, J = 4Hz), 2.15 (N-$CH_3$, s), 2.35 (OH, d, J = 10Hz, exchanged by $D_2O$), 3.85 ($H_2$, dt, $J_{2,5}$ = 10Hz, $J_{2,3x3n}$ = 4Hz, becomes t, J = 4Hz on exchange with $D_2O$), 4.3 ($H_1$, m), 4.35 ($H_4$, m). The coupling constants were obtained by extensive decoupling and $D_2O$ exchange studies. These studies also identified $H_1$ and $H_2$ the signals of which were complicated by fluorine coupling. Shielding by the aromatic ring placed the carbinyl proton $H_2$ at higher field in *IV* than in *II*. The coupling between $H_2$ and $H_{3x}$ (J = 8.4Hz) and $H_2$ and $H_{3n}$ (J = 2.8Hz) in *II* and the fact that $H_2$ is coupled to $H_1$ (J = 4Hz) in *II* but not in *IV* ($J \sim 0$) further supported the view that $H_2$ must be *exo* in *II* and thus *II* is the *endo* alcohol.[13] The downfield shift of $H_{3n}$ in *IV* relative to *II* was apparently a consequence of intramolecular hydrogen bonding (OH N). The ir spectrum of *IV* in dilute carbon tetrachloride exhibited intense absorptions at 3550 and 3400 $cm^{-1}$, while that of *II* showed only free OH at 3620 $cm^{-1}$.

It is of some interest that the chromatographic behavior of *II* and *IV* was also in accord with the above structural assignments. Thus *IV*, the epimer with intense intramolecular hydrogen bonding, had a shorter glc retention time (504 sec.) than *II* (720 sec.).[7] A thin layer chromatogram on silica gel (3% methanol in chloroform) showed *IV* to have a larger $R_f$ (0.38) than *II* (0.20) consistent with the known tendency of molecules which have intramolecular hydrogen bonding to have lower adsorption affinity for silica gel than isomeric substances which do not have this type of bonding.[14] These data as well as solubility data are indicative that *IV* is less polar than *II* due to intramolecular OH N hydrogen bonding.

The epimeric alcohols *II* and *IV* were not distinguishable by mass spectrometry. In each case a very weak molecular ion (m/e 247) and a somewhat more intense $M^+$-1 ion (m/e 246) were observed. The most abundant ion (m/e 203) resulted from fragmentation to 2-methyl-4,5,6,7-tetrafluoroisoindole. This apparent reverse Diels-Alder fragmentation to an isoindole was found to be the dominant fragmentation pathway for all of the dihydro and tetrahydronaphthalen-1,4-imines described here.[16]

Other applications of the amine-borane *V* to directing synthesis at the olefinic linkage are being examined. The addition of dipolar reagents and dienes to the double bond of *I* occurs readily and exclusively from the *exo* face of the olefin.[15] Experiments in progress will determine if additions of this type to the amine-borane *V* occur on the *endo* face of the double bond.

## Acknowledgment

I am indebted to Professor Gordon Gribble for several valuable discussions and to Dr Byron Arison and Mr Riley McGaughran for assistance in obtaining and interpreting the ir and nmr spectra

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7. All relative percentages reported in this communication were obtained by glc on a 6' ¼" o d 5% OV 17 on 60-80 mesh chromosorb W column operated at 170°C with a helium flow rate of 32 ml/min
8. VI M.P 93-95°, $\nu^{Nujol}_{max}$ 3360 and 1685 $cm^{-1}$, $\delta^{TMS}_{ppm}$ ($CDCl_3$) 1 25 ($CH_3$, t, J = 6 3Hz), 1 90 ($CH_2$, m), 2 9 (OH, d, J = 9 5Hz), 4.1 ($O-CH_2$, q, J = 6 3Hz), 4.2 (carbinyl, m, converted to t on exchange with $D_2O$), 5 3 (bridgehead H, m), 5 45 (bridgehead H, m), m/e 305 ($M^+$), m/e 261 ($M^+-C_2H_4O$), m/e 189 (isoindole)
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11. A P Marchand and R W Allen, Tetrahedron Letters, 67 (1975).
12. Compare the spectrum of IV with that shown by Marchand (ref 11) for N-methyl-7-aza-2,3-benzo-exo-5-deuterionorbornene The lithium aluminum deutride reduction of VII to yield exo-2-deuterio II, $\delta^{TMS}_{ppm}$ ($CDCl_3$) 1 0 ($H_{3n}$, d, $J_{3n,3x}$ = 12 3Hz) 2 55 ($H_{3x}$, dd, $J_{3x,3n}$ = 12 3Hz, $J_{3x,4}$ = 4 8Hz), also supported these assignments. The exo proton $H_{3x}$ is coupled to the bridgehead proton $H_4$, while the endo proton $H_{3n}$ is not.
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