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ALKYLATION STEREOCHEMISTRY OF CAMPHOR DERIVATIVES OF GLYCINATES. DOUBLE CHIRAL INDUCTION WITH SECONDARY HALIDES.

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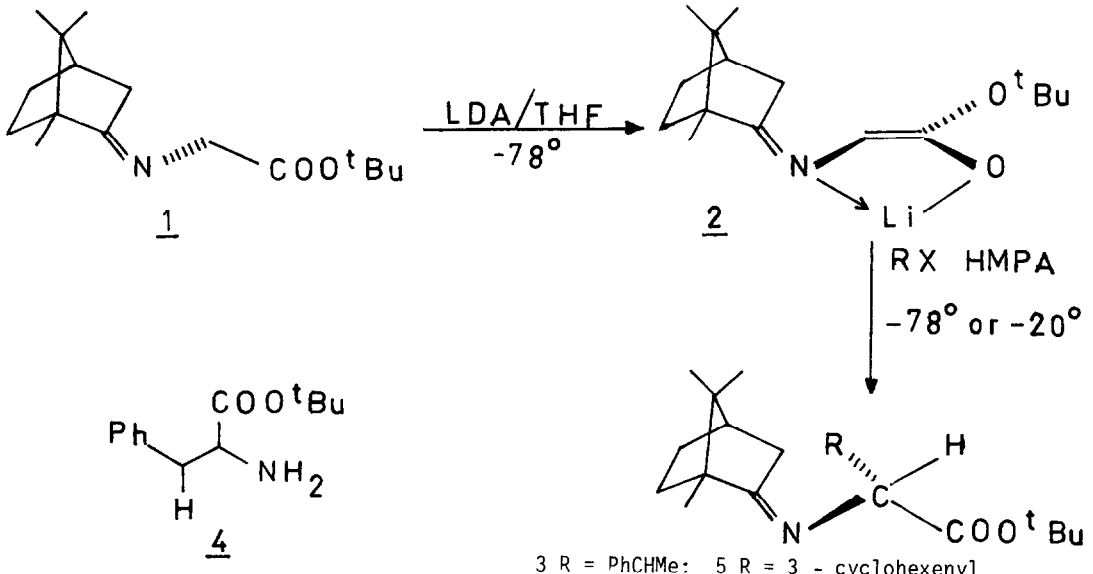
Abstract: Alkylation of the D-camphor imine of tert-butyl glycinate with secondary allylic and benzylic halides affords products which have high stereochemical purity, particularly at the halogen displacement site.

We have recently reported[1] that alkylation of anions derived from the D-camphor imine of tert-butyl glycinate (1) with primary allylic or benzylic halides gives significantly higher diastereomeric excesses (de's) (75→98%) than do aliphatic analogs (0-60%) and a model was proposed to rationalize these results. We now report the results using some racemic secondary halides as the alkylating agent.

When the anion 2[2] was allowed to react with one equivalent of racemic 1-phenethyl bromide for 1 h at -78° in the presence of one equivalent of HMPA[3], a 50% yield of alkylated product was obtained (99% based on unreacted starting material). A priori this could consist of a mixture of up to four diastereomers (assuming that the configuration of the imine double bond is E[1]). Although the ^{13}Cnmr (75 MHz.) showed only the twenty peaks expected for one diastereomer, the 300 MHz. ^{1}Hnmr showed two one-proton doublets at δ 3.97 and 3.93 (J=7.9 Hz) in a ratio of 9:1. In analogy with the previous report, these signals are assigned to the methine protons adjacent to nitrogen in two diastereomers of 3. A clean one-proton five-line pattern centered at δ 3.50 (J=7.6 Hz) is assigned to the benzylic proton coupled equally to the adjacent methyl and methine protons. While no indication of separation of diastereomers could be obtained from capillary g.c., it appears that the diastereoselectivity of the reaction

is at least 80% at one center and, within the limits of detection, 100% at the second center. The data do not allow a decision as to which of the two chiral centers is stereochemically homogeneous. However, on the basis of results obtained using 3-bromocyclohexene (see below) as the alkylating agent, we tentatively conclude that it is the benzylic position which is stereochemically pure. The configuration at the newly created chiral site on 2 is assigned the R-configuration (alkylation from the Re face of 2) in accordance with previous work.[1] The combination of a 50% chemical yield and the formation of a product of high de suggested that one enantiomer of 1-phenethyl



3 R = PhCHMe: 5 R = 3 - cyclohexenyl
6 R = cyclohexyl: 9 R = 2-butyl: 10 R = iPr

bromide might be reacting preferentially. Indeed, the recovered alkylating agent showed strong optical activity ($[\alpha]_D^{25}$ -63° (c 2.1, EtOH). The sign of rotation indicates that the recovered bromide possesses the S-configuration[4], which implies that the configuration at the benzylic position of 3 should also be S assuming inversion during alkylation. Transamination of 3 with hydroxylamine acetate[5] led to the recovery of 4. The nmr spectra of 4 were completely consistent with a 9:1 mixture of diastereomers. The complete stereochemistry of the major diastereomer of 4 can be tentatively assigned

as (2R,3S). When the reaction was repeated with two equivalents of alkylating agent, the yield of 3 using the same reaction times and conditions increased to 60%. Diastereomerically pure 3 could be obtained after one recrystallization from hexane. The ^{1}Hnmr was unchanged.

As noted above, the question of which of the two newly created chiral centers is being formed in a stereospecific manner is not easily answered in this system. To address this point, alkylation with 3-bromocyclohexene was examined. In this case, a 60% yield of 5 was obtained. Nmr analysis showed that only two diastereomers (ratio 5.6:1, de=69%) were present. Again, this requires that one of the newly created chiral centers must be homogeneous within the limits of detection. Hydrogenation of 5 gave a quantitative yield of 6 whose nmr showed the same two doublets for C2 (amino acid numbering) as in 5. This result demands that the stereochemically homogeneous center in 5 be the carbocyclic one. When the reaction was repeated with two equivalents of electrophile, the chemical yield of 5 increased to 67% and the de increased to 89%. One recrystallization of 5 (hexane) was sufficient to raise the de to 100%. An X-ray crystal structure is in progress to determine the absolute configuration of this material.

That these stereochemical results are unique to allylic and benzylic halides is indicated by the results obtained used 2 equivalents of 2-iodobutane (7) and isopropyl iodide (8) as the electrophiles. With 7 a 40% chemical yield of 9 which contained all four possible diastereomers was produced. A reaction temperature of -20^o was required in this case. When 8 reacted with 2, compound 10 (86%, de=68%) was obtained.

Previous work[1] has indicated that the presence of a carbon pi-system adjacent to the center undergoing alkylation in primary alkyl halides significantly increased the diastereoselectivity of the reaction with 2. The results reported herein confirm these findings and show that not only the stereochemistry at the anionic center, but also at the electrophilic center is significantly affected by this structural feature. The examples cited provide an excellent example of double asymmetric induction[6] wherein high diastereofacial and enantiofacial selectivity is conferred on the reaction by the

presence of the Π-bond. The results also suggest that, in such cases, the stereochemical demands are most stringent on the centre undergoing halide displacement. Work is in progress to further test this unexpected result and refine the proposed alkylation model.

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References and Notes:

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2. The camphor used possessed the 1-(R) configuration.
3. These represent the alkylation conditions used in all experiments unless otherwise noted.
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