SYNTHESIS AND CHARACTERIZATION OF CIS AND TRANS-4-d_1-1-TETRALOL

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SUMMARY

Trans-4-d_1-tetrahydronaphthalen-1-ol (trans-4-d_1-1-tetralol)[1] was synthesized from 1,4-epoxy-1,2,3,4-tetrahydronaphthalene using lithium tri-tert-butoxyaluminodeuteride. Cis-4-d_1-1-tetralol was made by epimerizing the trans- compound. Both compounds were characterized by high field 360 MHz NMR spectroscopy.

Key Words: tetralol, lithium tri-tert-butoxyaluminodeuteride, epimerization, NMR, mass spectrometry

The mass spectrometry of 1,2,3,4-tetrahydronaphthalen-1-ol (1-tetralol) has been under investigation in this laboratory since 1976 (1,2,3). The title compounds were synthesized to further the understanding of the stereochemistry of water loss (a 1,4-elimination). The results of these investigations will be published elsewhere. The strategy followed in this work was based on the reductive ring cleavage of 1,4-epoxy-1,2,3,4-tetrahydronaphthalene, 2, which resulted in only trans-4-d_1-1-tetralol, 3. The trans- compound was then epimerized to yield the cis-4-d_1-1-tetralol, 5 (see Scheme).

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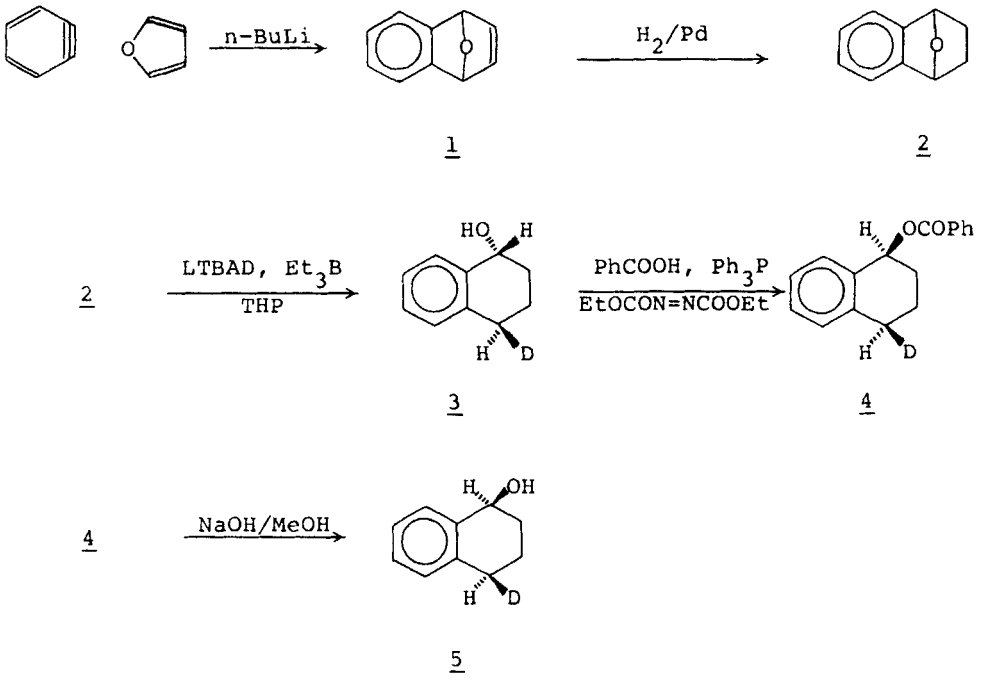
SCHEME



1,4-Epoxy-1,4-dihydronaphthalene, 1, was obtained from the Diels-Alder reaction of furan and benzyne generated at -70°C from ortho-dibromobenzene and n-butyl lithium (4). The product was hydrogenated using a palladium catalyst (5) to yield 1,4-epoxy-1,2,3,4-tetrahydronaphthalene, 2. The ether linkage in this compound was cleaved in an S_N2 fashion using lithium tri-tert-butoxyaluminodeuteride and triethyl borane (6). The product was characterized using high field NMR and mass spectrometry.

1-Tetralol proved difficult to epimerize since many derivatives commonly used for epimerization spontaneously eliminated upon formation. In fact, the methane sulfonyl ester decomposed explosively. Epimerization was achieved by reacting trans-4-d_1-1-tetralol, 3, with benzoic acid, diethyl azodicarboxylate and triphenyl phosphine (7), which yielded cis-4-d_1-1-benzoyloxytetrahydronaphthalene, 4. Base hydrolysis yielded the cis-4-d_1-1-tetralol, 5, which was characterized by high field NMR (Fig. 1) and mass spectrometry. Some of the benzoate formed via an alternate mechanism, and, as a result, the cis-4-d_1-1-tetralol, 5, formed is only about 87% cis- as determined by NMR (see below).

The NMR spectra taken at high field are characteristic for the two isomers. The unlabelled compound gives rise to a multiplet centered at 2.76 ppm which is assigned to the hydrogens in the 4-position. It appears as an AB pattern that is complicated by vicinal couplings. For the trans-d- compound, the signal is simplified and is observed as a broadened singlet at 2.78 ppm. In the spectrum of the epimerized product, this singlet is now observed at 2.68 ppm accompanied by some residual signal at 2.78 ppm (see Fig. 1). This smaller signal is attributed to the presence of unepimerized trans-4-d_1-1-tetralol, 3.

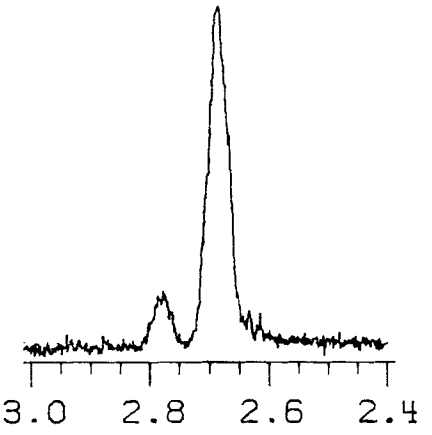


Fig. 1. Partial 360 MHz NMR spectra of epimerized tetralol. Broad singlets at 2.68 and 2.78 ppm correspond to cis- (87%) and trans-4-d_1-1-tetralol (13%), respectively.

These spectral preferences can be understood by assuming that the saturated ring of tetralol prefers the half chair conformation and that the hydroxyl group prefers the pseudo-axial conformation. Then the hydrogen on the 4-carbon is fixed in a pseudo-equatorial conformation in the trans-4-d_1-1-tetralol, 3, and in a pseudo-axial conformation in the cis-4-d_1-1-tetralol, 5. The hydroxyl conformation has been verified by infrared spectroscopy studies (8,9), and the assumption concerning the ring conformation is not unreasonable since an analogous compound, cyclohexene, also prefers the half chair conformation (10). The consequence of these conformation preferences in NMR spectroscopy is that the diamagnetic anisotropy of the aromatic ring deshields the pseudo-equatorial proton of the trans- compound and shields the pseudo-axial proton of the cis-. Although the cis- and trans-compounds gave nearly identical 90 MHz NMR spectra, their structures were easily established by the 360 MHz NMR spectra.

EXPERIMENTAL

Trans-4-d_1-1-tetralol:

1,4-Epoxy-1,4-dihydronaphthalene (4), 1, and 1,4-epoxy-1,2,3,4-tetrahydronaphthalene (5), 2, were synthesized according to the literature. 1,4-Epoxy-1,2,3,4-tetrahydronaphthalene, 2, was converted to trans-4-d_1-1-tetralol, 3, as follows. To an oven dried, nitrogen flushed, 3-neck flask equipped with a pressure equalizing dropping funnel and a magnetic stirrer were added 7 g (25.5 mmoles) of lithium tri-tert-butoxyaluminodeuteride (Alpha Ventron Corporation, Danvers, MA) and 10 ml dry tetrahydropyran (Aldrich Chemical Company, Milwaukee, WI). A solution of 1 g (6.8 mmoles) 1,4-epoxy-1,2,3,4-tetrahydronaphthalene, 2, and 1.5 ml dry tetrahydropyran was slowly added to the stirring solution via the dropping funnel. When the addition was complete, 27.4 ml (27.4 mmoles) of 1 F triethyl borane in tetrahydropyran (Aldrich Chemical Company, Milwaukee, WI) were slowly added via a syringe. The reaction was allowed to stir for 12 hr.

The reaction was worked up using hydrogen peroxide according to the procedure of Brown, Krishnamurthy, Hubbard, and Coleman (11). The reaction mixture was quenched by adding 24 ml of 3 F NaOH. Then 24 ml of 30% H_2O_2 was cautiously added as an exothermic reaction took place. To this was added 60 g K_2CO_3, and the mixture allowed to stand for 1 hr. The organic supernatant was separated and dried over anhydrous K_2CO_3. Filtration and concentration yielded an oil. To estimate percent yield, gas chromatography was performed on a 5% DEGS-PS on 100/120 mesh

Supelcoport column (Supelco Inc., Bellefonte, PA) operated at 144°C with a flow rate of 80 ml/min. The yield was estimated from peak areas to be 78% for the reductive cleavage.

The crude product was purified using flash chromatography (12), with a 5% ethyl acetate/petroleum ether eluant. Mass spectrometry established the isotopic purity at 96.6% $-d_1$ and 3.4% d_0. The molecular ion of the acetoxy derivative of trans-4-d_1-1-tetralol, 3, was used for this determination rather than that of the alcohol since the acetate does not have an M-H interference.

Cis-4-d_1-1-tetralol:

A solution of 0.96 g (6.5 mmoles) trans-4-d_1-1-tetralol, 3, and 20 ml tetrahydrofuran was added to a 100 ml flask equipped with a magnetic stirrer. 2.5 g (9.5 mmoles) of triphenyl phosphine (Aldrich Chemical Company, Milwaukee, WI) and 1.2 g (9.8 mmoles) benzoic acid were then added. To the resultant solution was added a solution of 1.7 g (9.8 mmoles) diethyl azodicarboxylate (Aldrich Chemical Company, Milwaukee WI) and 13 ml THF. The reaction was stirred for 100 hr. After solvent removal, cis-4-d_1-1-benzoyloxytetrahydronaphthalene, 4, was purified on consecutive flash columns (12) using eluants of 7.5% and then 4.0% ethyl acetate/petroleum ether. The yield was 0.4 g of the pure benzoate (25% of theoretical).

To a solution of 0.4 g cis-4-d_1-1-benzoyloxytetrahydronaphthalene, 4, and 5 ml diethyl ether was added 25 ml of a 5% NaOH/methanol solution. After stirring for 22 hr., the product was extracted into diethyl ether, neutralized and dried over

anhydrous Na_2CO_3. The product showed one spot on silica TLC using 5% ethyl acetate/petroleum ether as the eluting solvent. The solvent was removed to yield cis-4-d_1-1-tetralol, 5.

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