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ENANTIOSELECTION VIA BIRCH REDUCTION-ALKYLATION OF A CHIRAL ANTHRANILIC ACID DERIVATIVE. SYNTHESIS OF ENANTIOMERICALLY PURE AMINOCYCLOHEXANES

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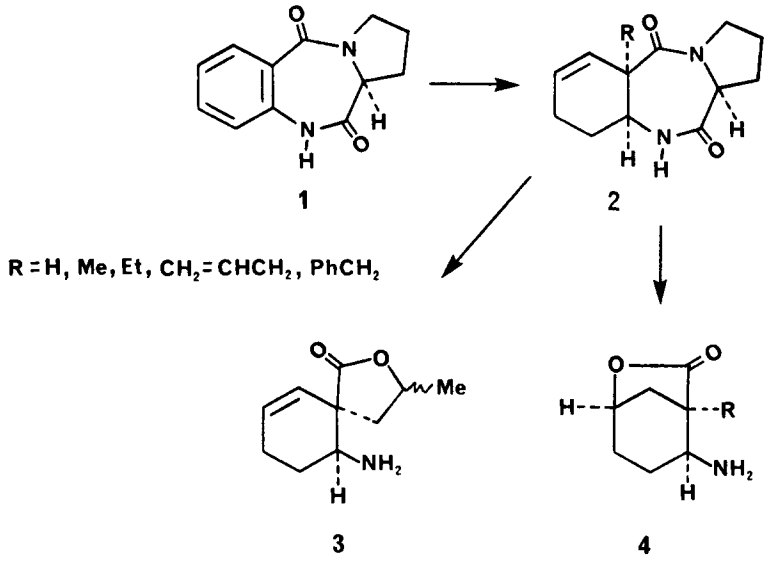
Summary: The first method for preparation of enantiomerically pure aminocyclohexanes by Birch reduction-alkylation of a chiral anthranilic acid derivative is described; stereochemistry of alkylation is demonstrated by X-ray structural studies with 2b.

Herein we report the first method for preparation of enantiomerically pure aminocyclohexanes by Birch reduction-alkylation of a chiral anthranilic acid derivative; e.g., 1 → 2 → 4. This two step adaptation of the chiral auxiliary technique[2] features inexpensive reagents and a simple solvent extraction procedure for isolation of the aminocyclohexane.



1 2 3 4

Heterocycle 1 is prepared by reaction of isatoic anhydride with L-proline.[3] Birch reduction of 1 is performed with potassium (4.4 equiv) in NH_3-THF solution in the presence of tert-butanol (2 equiv). After cooling to -78°C, the characteristic blue color is

dissipated by addition of pentadiene, after which the alkylation reagent is added (2-3 equiv); upon warming to refluxing ammonia temperature the reaction mixture is stirred for 1.5 h. Conventional reaction work-up and recrystallization provides analytically pure 2b-2e in yields ranging from good to excellent (Table I)[4]. Protonation of Birch reduced 1 with NH_4Cl gives β,γ-unsaturated amide 2a. The stereochemistry of 2a-2e follows from a single crystal X-ray structure determination of 2b and ^1H NMR spectral comparisons within the series.

Table I. Stereoselective Birch Reduction-Alkylation of 1

protonation or alkylation reagent	isolated yields of 2a-2e, %[a]	mp,°C
NH_4Cl	2a:73	185-6
MeI	2b:54	245.5-7.0
EtI	2c:68	220.5-1.5
C_3H_5Br	2d:62(88)[b]	176-7
$PhCH_2Br$	2e:68	170-1

[a]Yields are for analytically pure products and are based on 1. [b]The allyl derivative, 2d, also is obtained by alkylation with 1,3-dibromopropane.

Suitable crystals of 2b for X-ray diffraction studies formed as large needles from an ethyl acetate solution. The space group symmetry was $P2_1$ with a = 9.654(2) A, b = 9.426(4) A, c = 13.541(4) A and β = 96.88(2)° for Z = 4. Of the 1772 reflections measured with an automatic four circle diffractometer equipped with Cu radiation, 1423 were observed ($I \geq 3\sigma I$). The structure was solved with a multi-solution tangent formula approach and difference Fourier analysis and refined using full-matrix least-squares techniques.[5] Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $\Sigma\omega(|F_o|-|F_c|)^2$ with $\omega = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.049. The temperature parameters for C3 and C3′ were abnormally large indicating a certain amount of disorder in their positions. As a consequence the bond distances and angles involving C3 and C3′ have significant deviations from generally accepted values. Hydrogens attached to C3 and C3′ were kept in calculated positions because they refine poorly. The two independent molecules have virtually the same conformation shown in Figure 1.

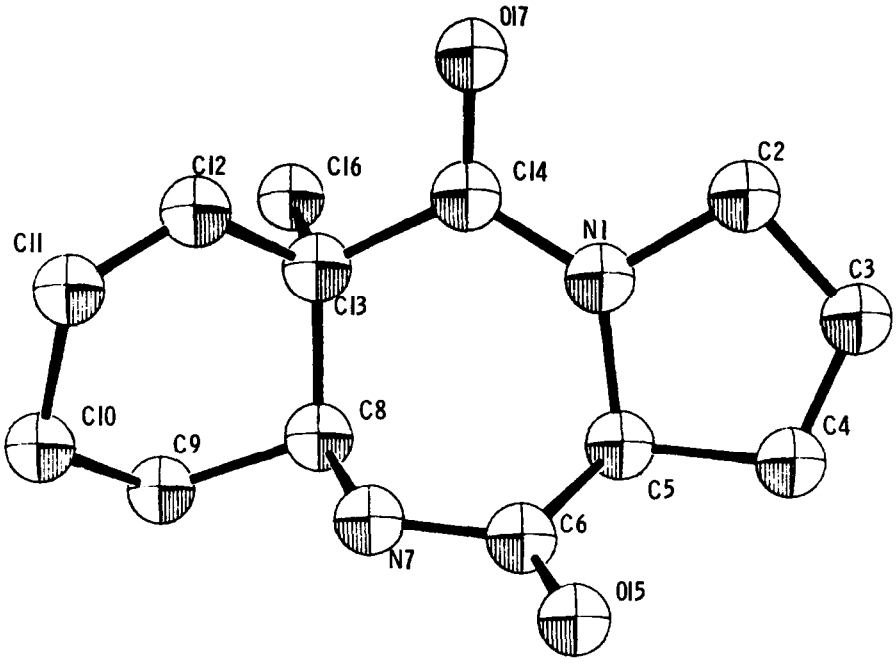


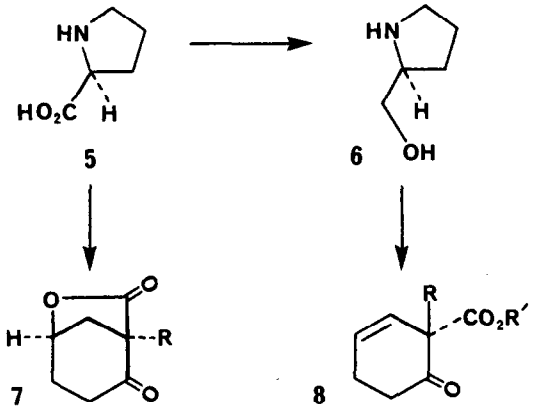
Figure 1. A perspective drawing of 2b derived from the X-ray coordinates with hydrogens omitted for clarity.

Removal of the chiral auxiliary is accomplished by treatment of 2a-e with 50% aqueous sulfuric acid at 100°C for ~6 h. Pure amino lactones 4 are obtained after partitioning reaction components between chloroform and aqueous sodium bicarbonate solutions (Table II). We presume that protiolactonization occurs after hydrolysis of the amide bonds in 2. With the allyl derivative 2d, protiolactonization occurs at the side chain to give spirolactone 3 as a mixture of diastereoisomers. Remarkably, the unsubstituted amino lactone 4a is obtained by this procedure, albeit in an unoptimized 34% yield.

Table II. Removal of Chiral Auxiliary from 2

compound	isolated yields of aminolactones, %
2a(R=H)	4a:34
2b(R=Me)	4b:62
2c(R=Et)	4c:82
2d(R=CH_2=$CHCH_2$)	3:82
2e(R=$PhCH_2$)	4e:83

Amino lactones 4 are converted to keto lactones 7 by biomimetic oxidative deamination.[6] For example 7(R=Et) is obtained in 82% isolated yield (mp 54-55°C) by sequential treatment of 4c with 4-formyl-1-methylpyridinium benzenesulfonate and 1,5-diazabicyclo[4.3.0]non-5-5-ene (DBN). This experiment demonstrates that 2-alkylated cyclohexanone derivatives, 7, may be obtained from anthranilic acid by use of L-proline (5) as the chiral auxiliary, whereas, we have previously shown that 2-alkylated cyclohexanone derivatives of opposite absolute configuration (e.g., 8) are available from salicylic acid by use of the chiral auxiliary L-prolinol (6).[7] L-Prolinol is prepared from L-proline by lithium aluminum hydride reduction;[8] thus, both enantiomeric series 7 and 8 are obtained from the same natural chiral auxiliary source.[9]



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References and Notes

1. Author to whom inquiries regarding X-ray crystallographic analysis should be directed.
2. "Asymmetric Synthesis - A Multivolume Treatise"; Morrison, J. D., Ed., Academic Press: New York, 1984.
3. (a) Carabateas, P. M.; Harris, L. S. J. Med. Chem. 1966, 9, 6. (b) Kim, D. H. J. Het. Chem. 1975, 12, 1323.
4. Less than 4 equiv of potassium in the Birch reduction step currently results in synthetically unacceptable mixtures of dihydro- (both α- and γ-enolate alkylation observed) and tetrahydro-derivatives. Details of this study and mechanistic considerations are reserved for the full account of this work.
5. The following library of crystallographic programs was used: MULTAN 80, University of York, York, England (1980); Structure Determination Package Plus V1.1, Enraf-Nonius Corporation, Delft, Holland (1983); ORTEP-II, Oak Ridge National Laboratory, Oak Ridge, Tennessee (1970).
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8. Enders, D.; Eichenauer, H. Angew. Chem. Int. Ed. Engl. 1976, 15, 549.
9. Compounds 2a, 2b, 2c, 2d, 2e, 4a, 4b, 4c, 4e, and 7(R=Et) gave satisfactory combustion analyses.

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