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# Absolute Configuration of Optically Active Tricyclo[2.2.1.$0^{2,6}$]heptan-3-ol (Nortricyclanol). An Enhancement of Enantiomeric Purity of a Chiral Alcohol by Repeating Enzymatic Kinetic Resolution

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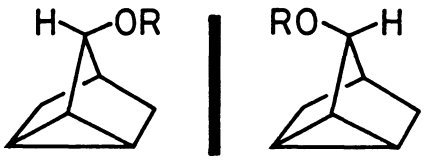
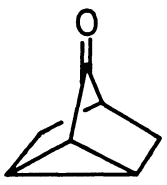
Tricyclo[2.2.1.$0^{2,6}$]hept-3-yl acetate (1b) was resolved by repeated enantioselective hydrolysis catalyzed by Candida cylindracea lipase, to give (+)-1b and (-)-nortricyclanol (1a) in high enantiomeric excess. By the chemical correlation with the known exo-2-norbornanol, the absolute configuration of (-)-1a was assigned to be (1R,3S,6S).

Use of enzymatic system in practical organic synthesis is currently of particular interest.[1] Applications of the method to the stereospecific transformations of the compounds with rigid conformation have been reported from this laboratory.[2] In the course of our investigation, it was found that various cage-shaped ketones showed wide variety of reaction rate in the horse liver alcohol dehydrogenase (HLADH)-catalyzed reduction to the corresponding alcohols, in spite of the presence of the common bicyclo[2.2.1]heptan-7-one structure incorporated in their carbon frameworks. In this context, we investigated the absolute configuration of tricyclo[2.2.1.$0^{2,6}$]heptan-3-ol (nortricyclanol, 1a[3]) which can be derived by the reduction of nortricyclanone (2), a cage-shaped meso-ketone whose carbonyl face is coincident with the plane of symmetry in contrast to the ordinary meso-ketones, e.g., cis-2,6-dimethylcyclohexanone, in which the carbonyl face is perpendicular to the plane of symmetry. This structural feature of 2 causes the generation of chirality in 1a.




(1R,3S,6S)-1 (1R,3R,6S)-1

1a: R= H
1b: R= $COCH_3$
1c: R= $COCH_2CH_2CH_3$




2

($C_s$-symmetry)

Microbial or enzyme-catalyzed asymmetric reduction of 2 was first attempted for the preparation of optically active 1a.[4] Biocatalysts used for the purpose

were HLADH,[6] pig liver alcohol dehydrogenase (PLADH),[6] Rhodotorula rubra, Curvularia lunata and bakers' yeast. In each case, being monitored by GLC, incubation was terminated when the bulk of the substrate had been consumed. After extraction with pentane, the crude extract was purified by preparative TLC [silica gel; pentane: ether (5:1) as eluent] followed by sublimation in vacuo to give the fairly volatile 1a in a moderate yield. The results are summarized in Table 1.

The HLADH-catalyzed reduction yielded (-)-1a, $[\alpha]_D$ -13.9° ($Et_2O$) or -22.3° ($CHCl_3$), which was found to be 54.7% e.e. by an HPLC analysis of its phenylcarbamate derivative [column; amylose tris(3,5-dimethylphenylcarbamate) on silica gel; hexane: i-PrOH (99:1) as eluent].[8] Absolute rotation value of 1a, therefore, can be estimated to be 25.4° in ether or 40.8° in $CHCl_3$, respectively. Reduction with R. rubra and C. lunata gave (+)-enantiomer preferentially in contrast to the reduction with HLADH, which is similar to the cases of the racemic cage-shaped ketones with $C_2$-symmetry.[2]

Table 1. Asymmetric reduction of nortricyclanone (2)[a]

| Enzyme Microbe | Substrate (mg)[b] | Time h | 1a yield/% | 1a $[\alpha]_D$/°($Et_2O$) | 1a % e.e. |
|---|---|---|---|---|---|
| HLADH[c] | 50 | 290 | 73 | -13.9 | 54.7 |
| PLADH[d] | 120 | 72 | 78 | +12.3 | 48.4 |
| R. rubra[e] | 33 | 330 | 66 | + 4.9 | 19.4 |
| C. lunata[e] | 60 | 170 | 69 | +17.2 | 67.6 |
| Bakers' yeast | 160 | 85 | 59 | - 2.8 | 11.0 |

a) Performed at r.t. b) Per 100 mL medium. c) In 1/15 M-Sørensen's buffer (pH 7.0) added $NAD^+$ and EtOH (1 M= 1 mol/$dm^3$). d) In 1/10 M-phosphate buffer (pH 7.4) added $NADP^+$, G-6-P-DH and G-6-P. e) In $H_2O$ (resting cells).

For the preparation of both enantiomers of 1a more efficiently than the above, next we examined the kinetic resolution, i.e., enantioselective hydrolysis, of racemic esters 1b and 1c catalyzed by Candida cylindracea lipase (CCL)[9] and resting cells of Trichoderma koningii and Bacillus subtilis var. niger. After incubation was continued until the stage of 50% conversion of the substrate to 1a with GLC monitoring, the alcohol and the substrate were isolated from the crude pentane extract by preparative TLC followed by sublimation (Table 2). Although pig liver esterase (PLE) and porcine pancreas lipase (PPL) were also examined as the catalyst, it was found to be difficult to terminate the reaction at the stage of 50% conversion because of the unusually high reaction rate in the case of PLE or the steep acceleration of the reaction after about 40% conversion in the case of PPL. Substitution of the acetyl group to the butyryl group in the substrate resulted in a considerable improvement in reaction time as well as the optical purity of the products except the case with CCL (Table 2, Entries 4, 5,and 6).

In the case of kinetic resolution, a repeated reaction using the substrate partially resolved by the first reaction is expected to result in the enhancement of the optical purity of the product if the reaction is terminated at an appro-

Table 2. Enantioselective hydrolysis of the esters 1b and 1c[10),a)]

| Entry | Microbe Enzyme | Substrate | (mg)[b)] | Time h | Conversion % | 1a $[\alpha]_D$/°($Et_2O$) | 1a % e.e. |
|---|---|---|---|---|---|---|---|
| 1 | T. koningii | (±)-1b | 27 | 20 | 51 | + 3.1 | 12.2 |
| 2 | B. subtilis | (±)-1b | 15 | 74 | 50 | - 0.4 | 1.5 |
| 3 | CCL | (±)-1b | 24 | 52 | 52 | -16.9 | 66.5 |
| 4 | T. koningii | (±)-1c | 50 | 4 | 50 | - 8.2 | 32.2 |
| 5 | B. subtilis | (±)-1c | 40 | 16 | 50 | - 6.8 | 26.6 |
| 6 | CCL | (±)-1c | 144 | 4 | 45 | - 9.5 | 37.4 |

a) Performed at r.t. in $H_2O$ (resting cells) for the microbes or in 0.1 M-phosphate buffer (pH 7.4) for CCL, respectively. b) Per cultures grown fully in one 25 mL-volume medium for the microbes or per crude CCL 10 mg.

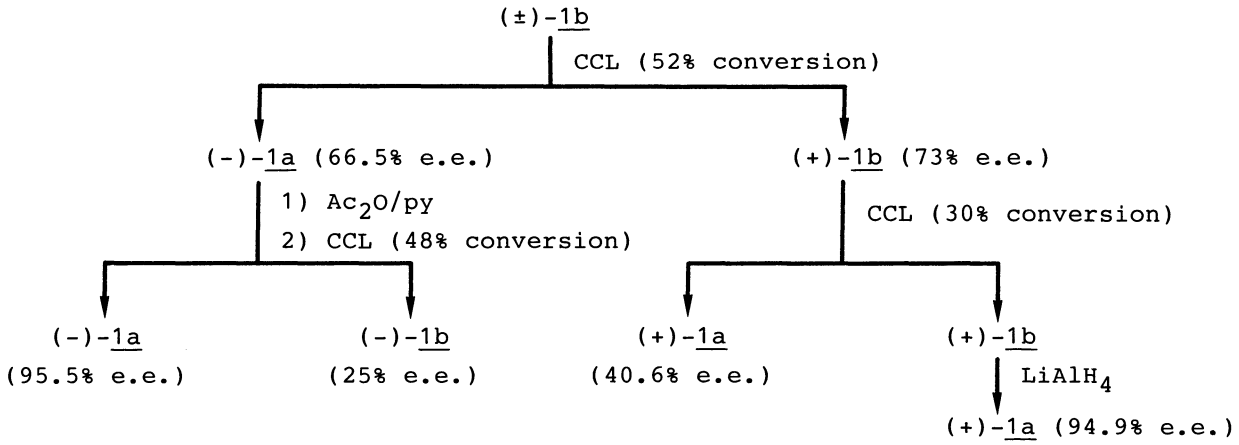
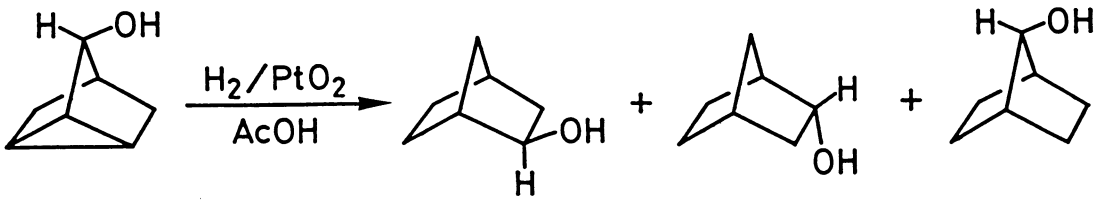



Fig. 1. Repeated enantioselective hydrolysis of the acetate 1b with CCL.

priate stage. Thus, (-)-1a, 66.5% e.e., derived by the first CCL-catalyzed hydrolysis of (±)-1b (Table 2, Entry 3), was again acetylated with acetic anhydride and pyridine and submitted to the second CCL-catalyzed enantioselective hydrolysis[11)] to give (-)-1a with high optical purity ($[\alpha]_D$ -24.3° ($Et_2O$), 95.5% e.e.). On the other hand, (+)-enantiomer of 1a with high optical purity ($[\alpha]_D$ +24.1° ($Et_2O$), 94.9% e.e.) was obtained by $LiAlH_4$ reduction of (+)-1b, $[\alpha]_D$ +45.0° ($Et_2O$), recovered from the second CCL-catalyzed enantioselective hydrolysis[11)] of the partially resolved (+)-1b, $[\alpha]_D$ +36.3° ($Et_2O$), which had been recovered from the first CCL-catalyzed reaction listed in Table 2, Entry 3 (Fig. 1).

Hydrogenolysis[12)] of (-)-1a, 95.5% e.e., in acetic acid in the presence of platinum oxide as catalyst (r.t., 1 atom) yielded a mixture of three alcohols. All of these showed m/z 112 ($M^+$) on GC-MS and their retention times on GLC[13)] were in accord with those of authentic samples of 3 (39 min), 4 (42.5 min) and 5 (45.5 min), respectively (3:4:5=47:18:35). Among those, the major product, $[\alpha]_D$ +2.5° ($CHCl_3$), was isolated by preparative GLC and was found to be identical with (+)-(1R,2R,4S)-3, $[\alpha]_D$ +2.8° ($CHCl_3$), prepared according to the known procedure.[14)] Absolute configuration of (-)-1a, therefore, can be concluded to be (1R,3S,6S).




(-)-1a (+)-(1R,2R,4S)-3 4 5

The cyclopropylmethanol derivatives have been noted as a potent latent inhibitor of HLADH, recently.[15] Experiments for the evaluation of the kinetic parameters involving that for latent inhibition in the HLADH-catalyzed oxidoreduction of (+)- and (-)-1a are being continued in this laboratory.

References

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4) HLADH-catalyzed reduction of 2 has been reported previously without describing the stereochemistry of the product 1a.[5]

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6) HLADH was purchased from Boehringer (Mannheim). PLADH was extracted from pig liver and purified by the known procedure.[7]

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9) The crude enzyme was purchased from Sigma (Type VII) and used without further purification.

10) In all the cases, 1a and the recovered 1b or 1c were obtained in the range of 64 to 80% of the values expected from the conversion.

11) The second enzymatic reactions were performed at r.t. under the following conditions; (-)-1b 19 mg per CCL 10 mg (7 h): (+)-1b 40 mg per CCL 10 mg (30 h).

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