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ENZYMIC OPTICAL RESOLUTION AND ABSOLUTE CONFIGURATION OF TRICYCLO[5.2.1.$0^{2,6}$]DECADIENONES

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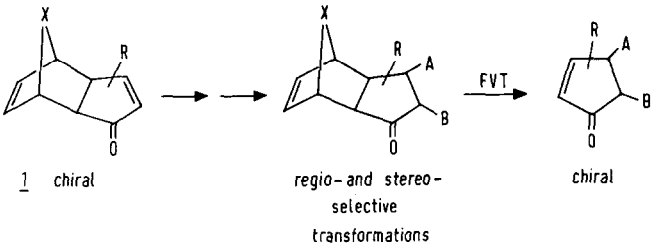
Abstract: Access to optically active *endo*-tricyclodecadienones 1 (X=CH_2) has been realized by (i) classical resolution of the diastereomeric ephedrine salts of 3 and (ii) pig liver esterase catalyzed kinetic resolution of 2.

The tricyclodecadienone system 1 (X=CH_2, O) can be considered a cyclopentadienone in which one of the double bonds is masked in a crossed Diels-Alder adduct with either cyclopentadiene or furan. Chemical transformation of the remaining enone moiety in 1 followed by a demasking reaction using *flash vacuum thermolysis*, produces a functionalized cyclopentenone (Scheme I). This strategy has successfully been aplied by us for the stereoselective synthesis of cyclopentenoid natural products such as (±)terrein[1] and (±)pentenomycin[2].

Scheme I



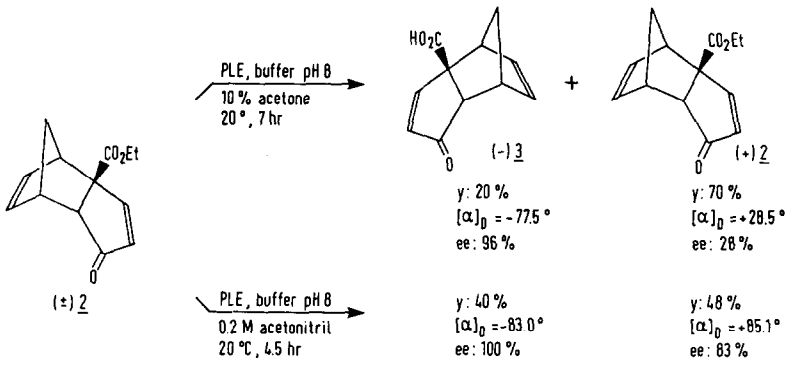
The great potential of 1 as a synthon for cyclopentenoids lies undoubtedly in its tricyclic structure which enforces chemical transformations to occur in a stereospecific manner, ultimately leading to cyclopentenones with a defined stereochemistry. As these tricyclodecadienones 1 also possess intrinsic chirality, our strategy offers in principle interesting prospects for the synthesis of optically active cyclopentenones, provided that the starting tricyclic dienones can be readily obtained in optically pure form. In this communication, we describe an efficient route to both enantiomers of *endo*-tricyclodecadienone 1 (X=CH_2), using enzymatic kinetic resolution of tricyclic ester 2.

Among the conceivable ways to obtain optically active tricyclodecadienones, we considered resolution as the most realistic one. Two approaches were investigated, *viz* (i) the classical separation of an appropriate diastereomeric mixture[3,4] and (ii) kinetic resolution using enzymes[4,5]. A suitable substrate to examine these resolution techniques is ester 2 which is readily available from cyclopentadiene and benzoquinone on multigram scale[6]. The classical resolution was carried out with the corresponding acid 3, that was converted into a mixture of diastereomeric am-

monium salts by treatment with either α-methyl benzyl amine or ephedrine as the optically active amines[7]. Although in both cases a crystalline material separated from the ether solution, an effective resolution was only achieved in case of the ephedrine salts. With l-ephedrine, a single diastereomer was obtained after just one crystallization from acetone (m.p. 162-164 °C, $[\alpha]_D^{23.4}$ = -179°), however in a moderate yield (14%). Subsequent hydrolysis with 3% HCl aq. afforded (-)-carboxylic acid 3, $[\alpha]_D^{24.8}$ = -77°, in quantitative yield. Its (+)-antipode, $[\alpha]_D^{24.8}$ = +78°, was obtained in the same yield (14%) from the enriched diastereomeric mother liquor by repeating the resolution procedure with d-ephedrine. The sharp melting points of both ephedrine salts, the observed coincidence of the rotations of the enantiomers of carboxylic acid 3 and the correspondence with the independent results of the enzymatic resolution procedure (*vide infra*), proved that the resolved carboxylic acids 3 were of high optical quality (ee> 93%). Notwithstanding these encouraging results, we did not try to improve the efficiency of this classical resolution as the enzymatic approach turned out to be superior.

Although kinetic resolution of racemic substrates using enzymes and microorganisms is increasingly encountered in the literature[4,5], the synthetic application of this method is still in its infancy. Initiated by the elegant work of Ohno *et al*, who reported among others the highly efficient enantioselective hydrolysis of bicyclic *meso*-diesters using pig liver esterase (PLE)[8], we attempted the kinetic resolution of ester 2 applying this hydrolase[9] (Scheme II).

Scheme II



Tricyclic ethyl ester 2 was treated with pig liver esterase at 30 °C for 4 hrs in 0.1M phosphate buffer (pH 8.0) containing acetone (10% by volume) as a co-solvent. Under these conditions, 2 was slowly hydrolyzed to give carboxylic acid 3 in moderate yield but with a high optical purity (ee 90%). Both the chemical and optical yield of this PLE catalyzed hydrolysis could be improved by lowering the reaction temperature to 20 °C and extending the reaction time to 7 hrs. Under these optimum conditions, (-) 3 was isolated in 20% yield (calculated on the total amount of racemic ester 2) and with an optical rotation of -77.5°. This latter rotation agrees very well with that observed for (-) 3 obtained by the aforementioned classical resolution.

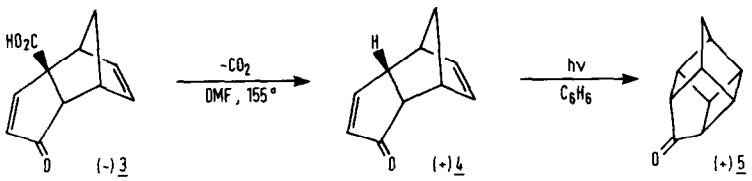
A spectacular improvement was attained by replacing acetone by acetonitril as the co-solvent. A suspension of ester 2 (17.3 g) in 0.1M Na/K phosphate buffer (1100 ml) containing 0.2 Mol. CH_3CN was incubated until half of the starting ester had been hydrolyzed (after 4.5 hrs). (-)-Carboxylic acid 3 was now isolated as a white crystalline solid (m.p. 125-130 °C) with

$[\alpha]_D^{23} = -83°$ (c = 0.66, MeOH) in 40% yield. The high enantioselectivity of this hydrolysis reaction is convincingly demonstrated by the optical purity of the remaining ester (8.3 g) which amounts to 83% ee. Enantiomerically pure ester 2 (8.0 g, $[\alpha]_D^{23} = +106.3°$ (c = 1.02, MeOH) can be simply obtained by repeating the enzymatic hydrolysis procedure with this enriched ester mixture and crystallizing the residual ester from petroleum ether (60-80°). Alkaline hydrolysis of the obtained (+)-ester 2 furnished optically pure (+)-carboxylic acid 3, $[\alpha]_D^{22} = +84°$, indicating that both antipodes of 3 can be readily obtained as optically pure compounds, and that this enzymatic resolution can be performed on multigram scale.

The favourable effect of acetonitrile on the outcome of the PLE catalyzed hydrolysis of 2 is very impressive. It is therefore surprising that, although Junge and Heymann[10], reported on the accelerating effect of acetonitrile on the PLE catalyzed hydrolysis of 4-nitrofenyl acetate already in 1979, no other studies have appeared dealing with such effects of acetonitrile on PLE catalyzed enantioselective transformations[11].

The consistency in rotations of both enantiomers of acid 3 *viz* $[\alpha]_D^{23} = -83°$ for the acid obtained directly from racemic ester 2 and $[\alpha]_D^{22} = +84°$ for the acid obtained from chemical hydrolysis of the residual enriched ester mixture, allows the assumption that these acids are optically pure substances. However, we wanted a more quantitative assessment. Attempts to establish the enantioselectivity of the PLE hydrolysis of 2 by ^{1}HNMR spectroscopic examination using optical shift reagents failed both for acid 3 and its ethyl and methyl ester. Therefore, we sought to correlate our tricyclic structure 3 with a known optically active compound. Such a structure appeared to be 1,3-bishomocubanone 5 (Scheme III).

Scheme III



Nazaki and Naemura[12] prepared 5 in optically pure form, $[\alpha]_D^{15} = +11.0°$, and determined its absolute configuration using CD spectroscopy. Hence, chemical transformation of 3 into 5 would provide an excellent method to establish not only the optical purity of 3 but also its absolute configuration. The conversion of (-) 3 into cage ketone (+) 5 has been realized as depicted in Scheme III. Being a vinologeous β-ketoester, (-) 3 ($[\alpha]_D^{23} = -83°$) is readily decarboxylated by heating in DMF (155 °C) to afford the parent tricyclodecadienone 4, $[\alpha]_D^{23} = +141.6°$, in 83% yield. Intramolecular photochemical cyclization of (+) 4 afforded (+) 1,3-bishomocubanone 5 in quantitative yield. Its optical rotation, $[\alpha]_D^{23} = +11°$, appeared to be the same as that reported by Nakazaki *et al*[12], indicating that the optically purity of (-)-acid 3 obtained in the PLE catalyzed hydrolysis of 2 in the presence of acetonitrile as co-solvent, is 100% ee[13]. Based on the observed positive rotation of 5, the absolute configuration of (-) acid 3 is consequently as 1R,2S,6R,7S (the correct structure is pictured in Scheme III).

In conclusion, pig liver esterase shows a very high enantioselectivity towards racemic ethyl tricyclic ester 2[14]. *Both* enantiomers are obtained in excellent chemical and optical yield. The attainment of a practical route to optically active tricyclodecadienones now allows the preparation of enantiomerically pure cyclopentenones, which may be of importance for the synthesis of biological interesting compounds. The synthesis of some representative cyclopentenones wil be presented in a forthcoming paper[15].

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11. Preliminary studies carried out by us on the PLE catalyzed hydrolyses of some bicyclic esters show that this effect of acetonitrile is highly substrate dependent.
12. M. Nakazaki and K. Naemura, J. Org. Chem. 42, 2985 (1977).
13. This conclusion was confirmed at a later stage of this project using Mosher's ester of an appropriate derivative of carboxylic acid 3[15].
14. We also studied the PLE hydrolysis of the corresponding methyl ester. Here, both the chemical and the optical yield is somewhat lower than with the ethyl ester 2.
15. A.J.H. Klunder, W.B. Huizinga, P.J.M. Sessink and B. Zwanenburg, forthcoming paper.

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