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# ENZYMIC OPTICAL RESOLUTION AND FLASH VACUUM THERMOLYSIS IN CONCERT FOR THE SYNTHESIS OF OPTICALLY ACTIVE CYCLOPENTENONES

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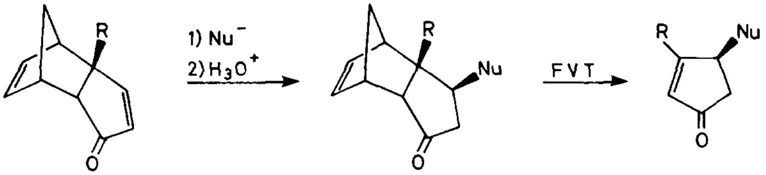
*Abstract: A practical synthesis of enantiomerically pure cyclopentenones with a predeterminated absolute configuration has been realized, starting from optically active tricyclo[5.2.1.$0^{2,6}$]decadienones.*

Functionalized cyclopentenones are essential synthetic intermediates in many routes to important natural products containing five membered rings[1]. The majority of these syntheses starts from a racemic cyclopentenone, with an optical resolution at some stage of the synthesis to ultimately obtain the enantiomerically pure natural product. In most cases, the availability of an appropriately functionalized, optically pure cyclopentenone would considerably improve the efficiency of such a synthesis[2]. In a preceding paper[3] we reported on an efficient enzymatic resolution of the tricyclodecadienone **1a** using pig's liver esterase (PLE) and the preparation of the parent compound **1b** through the decarboxylation of the corresponding carboxylic acid. We will now demonstrate the use of these tricyclodecadienones **1** for the synthesis of enantiomerically pure cyclopentenones and derivatives. The concept of our approach is outlined in Scheme I.

Scheme I



1a R = $CO_2R'$
b R = H

2

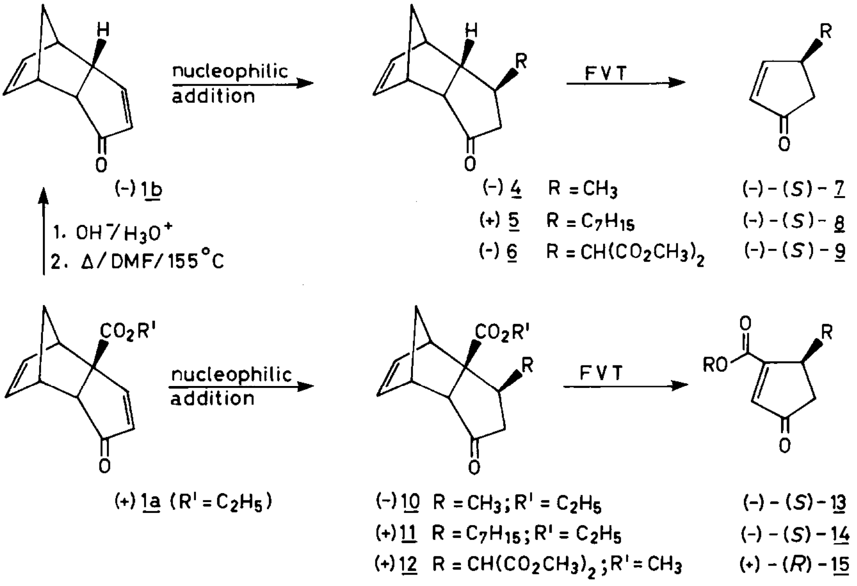
3

Chemical modification of the enone moiety in **1** *e.g.* by nucleophilic addition leads stereospecifically to **2** which on *flash vacuum thermolysis* produces cyclopentenones **3** in a thermal cycloreversion proces. The rigid *endo* configuration of **1** causes strict stereochemical control of the nucleophilic addition to **1** as its concave face is entirely blocked. Consequently, thermal cycloreversion will lead to cyclopentenones with a well defined stereochemistry[4].

The synthesis of optically active cyclopentenones **7**, **8** and **9**, that have a relatively simple substitution pattern, has been realized as depicted in Scheme II. None of these cyclopentenones has been obtained optically active before[5]. Starting material[3] in this approach is (+)tricyclic ethyl ester **1a** ($R'=C_2H_5$; m.p. 35-37 °C, $[\alpha]_D$= 106.3°, MeOH) which is readily transformed into the parent (-)tricyclodecadienone **1b** ($[\alpha]_D$= -139.4°, MeOH). Nucleophilic addition of either methylmagnesium iodide or n-heptylmagnesium bromide in the presence of cuprous chloride led stereospecifically to β-substituted tricyclic ketones **4** ($[\alpha]_D$= -177°, MeOH) and **5** ($[\alpha]_D$= -74°, MeOH), respectively in yields of 85-90%. The corresponding malonate **6** ($[\alpha]_D$= -82.0°, MeOH) was obtained in the same high yield by treatment of **1b** with dimethyl sodiomalonate in MeOH. Flash vacuum thermolysis (500°C, $10^{-2}$ torr) of these tricyclic ketones led to the respective cyclopentenones **7** ($[\alpha]_D$= -188°, MeOH)[6], **8** ($[\alpha]_D$= -137°, MeOH) and **9** ($[\alpha]_D$= -123°, MeOH) in high yields (80 to 100%)[7].

Based on the absolute configuration of the starting tricyclodecenones[3,8], these cyclopentenones have the (S)-configuration. An unambigeous prove of the correctness of this assessment and of the optical integrity of the produced cyclopentenones was obtained from correlation of **7** with the known optical active (R)-3-methylcyclopentanone ($[\alpha]_D$= +154°, MeOH)[9]. Hydrogenation (Pd/C, EtOH) of **7** ($[\alpha]_D$= -188°) gave the expected (R)-3-methylcyclopentanone[6]with $[\alpha]_D$= +147°, EtOH).

Scheme II



(-) 1b

(-) 4 R = $CH_3$ (-)-(S)-7
(+) 5 R = $C_7H_{15}$ (-)-(S)-8
(-) 6 R = $CH(CO_2CH_3)_2$ (-)-(S)-9

(+) 1a ($R' = C_2H_5$)

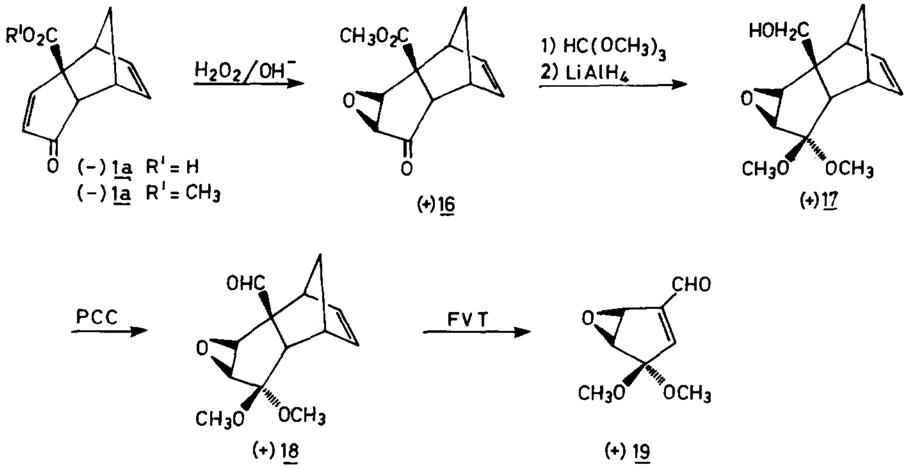
(-) 10 R = $CH_3$; $R' = C_2H_5$ (-)-(S)-13
(+) 11 R = $C_7H_{15}$; $R' = C_2H_5$ (-)-(S)-14
(+) 12 R = $CH(CO_2CH_3)_2$; $R' = CH_3$ (+)-(R)-15

Tricyclic ester **1a** ($R'= C_2H_5$) was also subjected to nucleophilic addition. Whereas addition of methylmagnesium iodide and n-heptylmagnesium bromide proceeded again smoothly to afford β-alkyl ketones **10** ($[\alpha]_D$= -24.3°, MeOH) and **11** ($[\alpha]_D$= = +16.2°, MeOH) in yields of 80%-90%, the addition of dimethyl sodiomalonate (MeOH) occurred only very sluggishly to give tricyclic malonate **12** ($[\alpha]_D$= = +4.3°, MeOH) in a relative low yield of 54%. In this reaction the transesterified methyl ester **1a** ($R'= CH_3$) was recovered in 33% yield. Apparently, the *exo* approach of the incoming nucleophile is hampered through the *exo* ester function. However, no reaction from the sterically totally shielded *endo* face of the enone moiety was observed[10].

Flash vacuum thermolysis (500°, $10^{-2}$ torr) of **10**, **11** and **12** smoothly led to enantiomerically pure cyclopentenone esters **13** ($[\alpha]_D$= -35.9°, MeOH), **14** ($[\alpha]_D$= -41.0°, MeOH) and **15** ($[\alpha]_D$= +50.8°, MeOH) respectively, almost quantitatively[7].

In our route to terrein[11], cyclopentadienone dimethyl acetal epoxide **19** constitutes a key intermediate (Scheme III). Therefore, as an illustration of the potential of our strategy, we sought to prepare this masked multifunctional cyclopentenone derivative in optically active form. Optically pure carboxylic acid[3] **1a** (R'= H, $[\alpha]_D$= -83°, MeOH) was esterified with $CH_2N_2$/ether to give methyl ester **1a** (R'= $CH_3$, m.p. 67-68 °C, $[\alpha]_D$= -94.3°, MeOH). Stereospecific epoxidation ($NaOH/H_2O_2$) afforded *exo* epoxide **16** (m.p. 102-103 °C, $[\alpha]_D$= +42°, MeOH) in an overall yield of 78%. Protection of the ketone function as a dimethyl acetal followed by reduction with $LiAlH_4$ gave epoxy alcohol **17** (m.p. 81-82.5 °C, $[\alpha]_D$= +38°, MeOH) in 80% yield. This compound is a single enantiomer as was shown by F-NMR analysis of the Mosher ester[12] of **17**. Oxidation of alcohol **17** with PCC afforded the corresponding tricyclic epoxy aldehyde **18** (m.p. 130.5-132 °C, $[\alpha]_D$= +31°, MeOH) in a yield of 70%.

Scheme III



This optically pure tricyclic aldehyde **18** was subjected to flash vacuum thermolysis (18 cm quartz tube, 475 °C, $10^{-2}$ torr) to give aldehyde **19** as an enantiomerically pure compound in 77% yield[7]. It shows a very high optical rotation, *viz.* +278.5° ($CH_2Cl_2$), which seems to be characteristic for this class of compounds[13]. Again, based on the absolute configuration of the starting tricyclic carboxylic acid **1a** (R'= H), (+)aldehyde **19** has the (4S,5S)-configuration as shown in Scheme III.

In conclusion, the efficient access to some interesting optically active cyclopentenones has been accomplished from enantiomerically pure tricyclodecadienones. These starting substrates are readily available in both enantiomeric forms by enzymatic resolution using PLE, hence giving access to cyclopentenones with a predeterminated absolute configuration. Further elaboration of the use of the concept outlined here is in progress.

## References and Notes

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4. Michael additions to racemic **1b**, followed by thermal cycloreversion have been described: J.L. Ripoll, A. Rouessac and F. Rouessac, Tetrahedron **1978**, 19.
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6. Due to the volatility of **7** and its hydrogenation product ( *vide infra* ), the error in the observed rotation is estimated to be ca. 5%.
7. In all cases, the isolated cyclopentenones were pure compounds as shown by capillary GLC analysis.
8. The correct absolute structures of (+) **1a** and (-) **1b** are depicted in Scheme II.
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