The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/27916

Please be advised that this information was generated on 2019-10-25 and may be subject to change.
Asymmetric Desymmetrization of a Pseudo-meso endo-Tricyclo[5.2.1.0^2,6]deca-4,8-dien-3-one by Chiral Amines

Frank J.A.D. Bakkeren, Namakkal G. Ramesh, Debby de Groot, Antonius J.H. Klunder and Binne Zwanenburg*

Department of Organic Chemistry, NSR Center for Molecular Structure, Design and Synthesis, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

Abstract: A novel route to the enantiopure endo-tricyclodecadienone system has been realized starting from the readily accessible pseudo-meso-5-hydroxy-endo-tricyclo[5.2.1.0^2,6]deca-4,8-dien-3-one 4. Dynamic kinetic resolution of (±)-4 using (S)-prolinol or its methyl ether leads to the corresponding enamiones \(^{6b,c}\) in high yields and with a de of 50%. Complete separation of the diastereomers of \(^{6b}\) is conveniently accomplished via their acetates. The absolute stereochemistry of the major diastereomer was shown to be \(\text{ent-}^{6b}\). Reductive elimination of the chiral auxiliary in \(\text{ent-}^{6b}\) with lithium aluminum hydride affords optically pure parent tricyclodecadienone \((\pm)-1\) \((X=H)\) in good overall yield.

In recent years, the endo-tricyclo[5.2.1.0^2,6]deca-4,8-dien-3-one system 1 has proven to be an extremely useful synthon for a wide range of naturally occurring cyclopentanoids and other pharmacologically important structures\(^1,2,3\). In addition, this system is an indispensable precursor for cubane-type polycyclic cage compounds\(^3\).

For the synthesis of enantiopure tricyclodecadienone 1 \((X=H)\), two practical methods have been reported which are essentially based on the enzymatic resolution of suitable tricyclodecenyl compounds \(\text{viz.}\) carboxylic ester 2\(^4\) and allylic alcohol 3 or its acetate\(^5,6\). Although these resolutions occur with optimal optical efficiency, chemical yields are obviously limited to 50%. For this reason, we studied alternative enantioselective routes to the tricyclodecadienone system based on either asymmetric synthesis or asymmetric transformation of an appropriate tricyclodecadienone derivative. In a recent paper, we discussed the asymmetric Diels-Alder
approach, in this report we disclose the desymmetrization of a pseudo-meso tricyclodecadienone, viz. 5-hydroxy-endo-tricyclo[5.2.1.0²,6]decadienone 4, employing chiral amines.

A most convenient and direct route to the endo-tricyclodecadienone system 1 constitutes the Diels-Alder reaction of cyclopentene-1,3-dione with cyclopentadiene (Scheme 1). Interestingly, the adduct 5 is completely enolized and actually consists of a racemic and rapidly equilibrating mixture of antipodes 4 and ent-4. This fast enantioenomerization of tricyclic enols 4 in principle allows a dynamic kinetic resolution, possibly leading to the high yield formation of a single enantiomer or diastereomer. For 4 such a process could also be denoted as an asymmetric desymmetrization of a pseudo-meso compound.

Our first attempts to achieve a desymmetrization of 4 involved an enzyme catalyzed kinetic resolution. Enantioselective acylation of one antipode of 4 along with concomitant fast equilibration of the substrate should in principle constitute a route to an enantiopure enol ester of 4. However, the use of several lipases e.g. Porc Pancreatic Lipase (PPL, from Sigma) or lipases AY, A and PS (from Amano), in a variety of organic solvents and with methyl acetate or vinyl acetate as the acyl donors, did not lead to significant amounts of the corresponding enol acetates, even after reaction times of several weeks. Most likely the main reason for this failure is the poor solubility of 4 in the solvents suitable for this enzymatic transesterification.

An important new lead for the desired desymmetrization was the finding that enols 4 can readily be aminated in a highly effective manner by an experimentally convenient process for a wide range of amines. By simply mixing 4 and a small excess (1.1 equiv.) of amine in toluene and heating this mixture under reflux for 17-48 h enaminones 6 were obtained in almost quantitative yields (Scheme 2). It is of interest to note that, although the tricyclodecadienone 4 is virtually insoluble in toluene, addition of the amine followed by heating almost immediately leads to a clear solution indicating the initial formation of the ammonium salt of 4.

For the purpose of a dynamic kinetic resolution of 4 first (R)-(+)-α-phenylethylamine was attempted as the chiral amine. The corresponding enaminone 6a was obtained in 80% yield but, disappointingly, without any
diastereoselectivity (Scheme 3). Fortunately, both diastereomers could be readily, and completely, separated by column chromatography on silica gel. Thus, the first optical resolution of 5-hydroxy-endo-tricyclodecadienone 4 was therefore accomplished. Both the structure and the absolute configuration of one of the diastereomers, \textit{viz.} ent-6a, were established by single crystal X-ray diffraction analysis\textsuperscript{12}.

A more rewarding result was obtained when L-prolinol was used as the chiral amine. Enaminone 6b was obtained in an overall yield of 91% but now with a diastereomeric excess of 50\%. The predominant diastereomer ent-6b could be obtained by repeated fractional crystallization; its absolute configuration was established by single crystal X-ray diffraction analysis\textsuperscript{12} (Scheme 4). Complete separation of the diastereomers of 6b could not be achieved in a direct manner, however, an indirect method involving conversion into the corresponding acetates was more successful. Thus, reacting the mixture of diastereomers 6b with acetic

\[
(\pm)-4 \xrightarrow{\text{R}_1\text{R}_2\text{NH}} \text{toluene, } \Delta \xrightarrow{-\text{H}_2\text{O}} \text{6b}
\]

\[
\text{HNR}_1\text{R}_2: \quad \text{ratio of diastereomers} \quad \text{overall isolated yield}
\begin{align*}
\text{(R)-(+)\-\alpha-phenylethylamine} & \quad 6\text{a} & 1 : 1 & \text{ent-6a} & 80\% \\
\text{(S)-(+)\-prolinol} & \quad 6\text{b} & 1 : 3 & \text{ent-6b} & 91\% \\
\text{(S)-(+)\-prolinol methyl ether} & \quad 6\text{c} & 1 : 3 & \text{ent-6c} & 79\% \\
\text{(S)-(+)\-methyl prolinate} & \quad 6\text{d} & 1 : 1.8 & \text{ent-6d} & 94\%
\end{align*}
\]

Scheme 3: Asymmetric desymmetry yielding tricyclic enaminoes

anhydride and triethylamine in the presence of a catalytic amount of dimethylaminopyridine afforded quantitatively the respective acetates, which were then readily separated by column chromatography on silica gel by elution with a mixture of ethyl acetate and methanol.

The hydroxyl group in prolinol is not essential for the desymmetry process as the use of prolinol methyl ether instead of prolinol did not significantly change the optical yield (Scheme 3). The use of methyl prolinate, however, led to a considerably lower diastereomeric ratio (Scheme 3).

\[
(+)-1 \text{ (ee > 98\%)} \quad [\alpha]_{24}^\text{D} = +137 \text{ (c=1.05, MeOH)}
\]

Scheme 4: X-ray structure and reduction of tricyclic enaminone ent-6b to unsubstituted enone (+)-1.
In order to complete this novel enantioselective route to the tricyclodecadienone system, it is essential to remove the chiral auxiliary in an efficient and convenient way without loss of optical integrity. We found that enaminone \textit{ent-6b} is readily converted into the parent tricyclodecadienone (+)-1 by lithium aluminum hydride reduction and subsequent basic work-up (Scheme 4). Enantiopure (+)-1 was isolated in 71% yield after column chromatography on silica. Its specific rotation $\{[\alpha]^2_{D} = +137 (c=1.05, \text{MeOH})\}$ was in good agreement with the literature values $\{[\alpha]^2_{D} = +139 (c=0.95, \text{MeOH})\}$, indicating an enantiomeric purity of more than 98%.

This high optical yield and the observation that the absolute stereochemistry of the thus obtained tricyclodecadienone (+)-1 is the same as that of \textit{ent-6b} proves that the lithium aluminum hydride reduction of \textit{ent-6b} proceeds entirely through a 1,4-addition process (1,2-hydride reduction followed by hydrolysis of the resulting imine would have led to inversion of the absolute configuration).

In conclusion, we have shown that 5-hydroxytricyclodecadienone 4 undergoes a dynamic kinetic resolution to enaminones 6 applying prolinol or its methyl ether as chiral mediator. This approach which constitutes an asymmetric desymmetrization of Diels–Alder adduct 5, is a novel and attractive alternative for the existing enzymatic methodology to obtain enantiopure tricyclodecadienones. In addition, the tricyclic enaminones 6 are interesting structures as they may possess pharmacological activity and furthermore they act as conceivable synths for aminocyclopentenoids and aza-cubanes.

Acknowledgment. This investigation was supported by the Netherlands Foundation of Chemical Research (SON) with financial aid from the Netherlands Organization for Scientific Research (NWO).

REFERENCES AND NOTES

6. In addition a stereoselective enzymatic esterification of a meso-tricyclodecadiene-1,3-diol has been reported. However, this approach seems less practical than the resolution of alcohol 3 as it involves two more steps starting from 3 and allows the formation of only one of the possible antipodes of 1.

(Received in UK 26 June 1996; accepted 13 September 1996)