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Asymmetric Desymmetrization of a *Pseudo-meso* *endo*-Tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one by Chiral Amines

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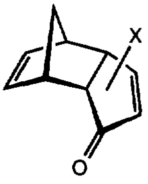
Abstract: A novel route to the enantiopure *endo*-tricyclodecadienone system has been realized starting from the readily accessible *pseudo-meso*-5-hydroxy-*endo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one **4**. Dynamic kinetic resolution of (±)-**4** using (S)-prolinol or its methyl ether leads to the corresponding enaminones **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 *ent*-**6b**. Reductive elimination of the chiral auxiliary in *ent*-**6b** with lithium aluminum hydride affords optically pure parent tricyclodecadienone (+)-**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]. 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 *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



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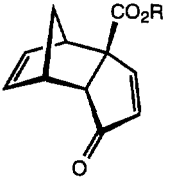

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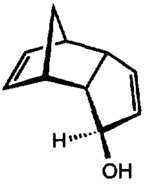

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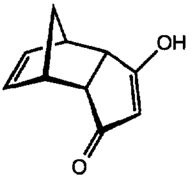
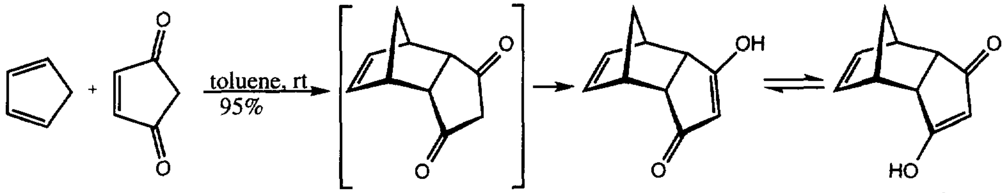


(±)-**4**

approach[8], in this report we disclose the desymmetrization of a *pseudo-meso* tricyclodecadienone, *viz.* 5-hydroxy-*endo*-tricyclo[5.2.1.0^{2,6}]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[9] (Scheme 1). Interestingly, the adduct **5** is completely



5 **4** *ent*-**4**

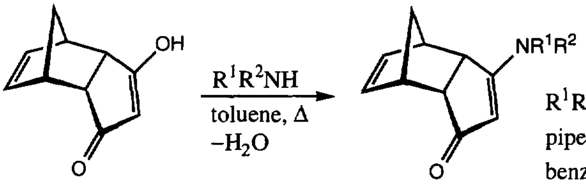
Scheme 1: Synthesis of racemic 5-hydroxytricyclodecadienone, **4** and *ent*-**4**

enolized and actually consists of a racemic and rapidly equilibrating mixture of antipodes **4** and *ent*-**4**. This fast enantiomerization of tricyclic enols **4** in principle allows a dynamic kinetic resolution[10], 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[11]. 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

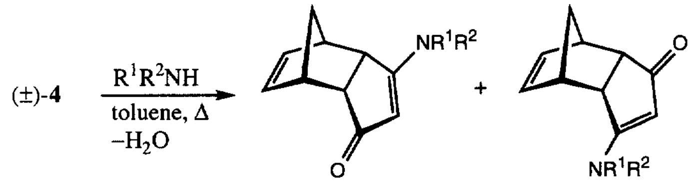


R^1R^2NH: morpholine (94%), pyrrolidine (93%), piperidine (92%), n-pentylamine (92%), benzylamine (94%), cyclohexylamine (98%)

(±)-**6**

Scheme 2: Synthesis of racemic tricyclic enaminones 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, *viz. ent*-**6a**, were established by single crystal X-ray diffraction analysis[12].

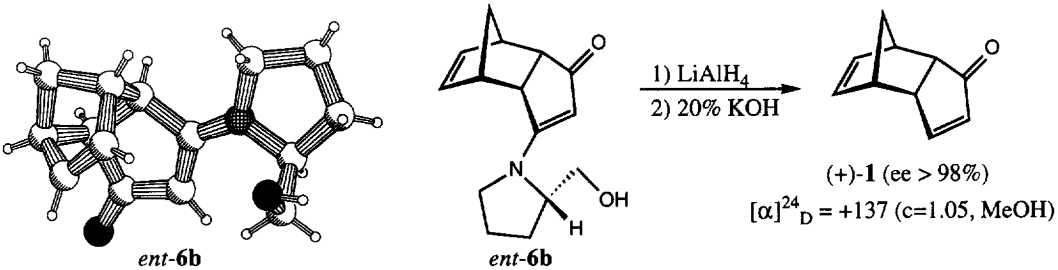
A more rewarding result was obtained when L-prolinol was used as the chiral amine. Enaminone **6b** was obtained in an overall yield of 91% but now with a diastereomeric excess of 50%. The predominant diastereomer *ent*-**6b** could be obtained by repeated fractional crystallization; its absolute configuration was established by single crystal X-ray diffraction analysis[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 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.



HNR^1R^2:	ratio of diastereomers					overall isolated yield
(R)-(+)-α-phenylethylamine	**6a**	1	:	1	*ent*-**6a**	80%
(S)-(+)-prolinol	**6b**	1	:	3	*ent*-**6b**	91%
(S)-(+)-prolinol methyl ether	**6c**	1	:	3	*ent*-**6c**	79%
(S)-(-)-methyl prolinate	**6d**	1	:	1.8	*ent*-**6d**	94%

Scheme 3: Asymmetric desymmetrization yielding tricyclic enaminones

The hydroxyl group in prolinol is not essential for the desymmetrization 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).



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 *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 {$[\alpha]^{24}_{D}$ = +137 (c=1.05, MeOH)}was in good agreement with the literature values {$[\alpha]^{20}_{D}$ = +139 (c=0.95, MeOH)}[1], 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 of *ent*-**6b** proves that the lithium aluminum hydride reduction of *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[13] and furthermore they act as conceivable synthons for aminocyclopentenoids and aza-cubanes.

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