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Asymmetric desymmetrization of pseudo-*meso* 5-hydroxy-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ones

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Abstract—A novel route to the enantiopure *endo*-tricyclodecadienone system has been accomplished starting from readily accessible pseudo-*meso*-5-hydroxy-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one. Desymmetrization using (*S*)-prolinol or its methyl ether leads to the corresponding enaminones in high yields and with a de of 50%. Complete separation of the diastereomers has been conveniently achieved via their acetates. The absolute stereochemistry of the major diastereomer was determined by single-crystal X-ray diffraction analysis. Reductive elimination of the chiral auxiliary with lithium aluminum hydride affords optically pure parent tricyclodecadienone in good overall yield.

1. Introduction

The *endo*-tricyclodecadienone system **1** has been the pivotal intermediate in the synthesis of a large variety of naturally occurring cyclopentanoids[1,2] and other compounds of pharmacological interest.[3] In addition, this system is an indispensable precursor for cubane-type polycyclic compounds.[4,5] The practical synthesis of enantiopure tricyclodecadienones **1** so far relied mostly on the enzymatic hydrolysis of carboxylic esters **2**[6] and **4**[6,7] or esterification of the allylic alcohol **3**[7] (Fig. 1).

Although these enzyme mediated kinetic resolutions can be accomplished with good optical efficiency, chemical yields are obviously limited to 50% of one enantiomer. Interconversion of both enantiomers of **1** (R=H) can be achieved using Wharton's methodology to effect a 1,3-ketone transposition, but the overall yield of this conversion is generally moderate.[8] For this reason alternative enantioselective routes to the tricyclodecadienone system based on either asymmetric synthesis or asymmetric transformation are much in demand. Our earlier reports on the synthesis of tricyclodecadienone **13** relied on the asymmetric Diels–Alder approach of enantiopure 4-substituted cyclopentenones **11** with cyclopentadiene (Scheme 1).[9] The key step in the preparation of the starting cyclopentenones was the enantioselective hydrolysis of the *meso*-diacetate **9**. As a result of low π-facial selectivity during the Diels–Alder addition with cyclopentadiene, the ees of the tricyclic compounds **12** and **13** were only moderate (61%).[9]

Ogasawara et al.[10] described a kinetic desymmetrization of the *meso*-diol **5** for the enantioselective preparation of the *endo*-tricyclodecadienone **13**. This methodology is closely related to the approach depicted in Scheme 1. Feringa and coworkers have reported the synthesis of enantiopure **13** starting from the Diels–Alder adduct **6** of cyclopentadiene and enantiopure 5*R*-(*l*-menthyloxy)-2(5*H*)furanone.[11]

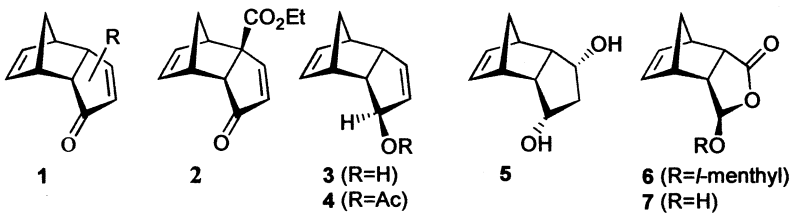

Figure 1.

Keywords: dynamic kinetic resolution; pseudo-*meso*; asymmetric desymmetrization; tricyclodecadienone.
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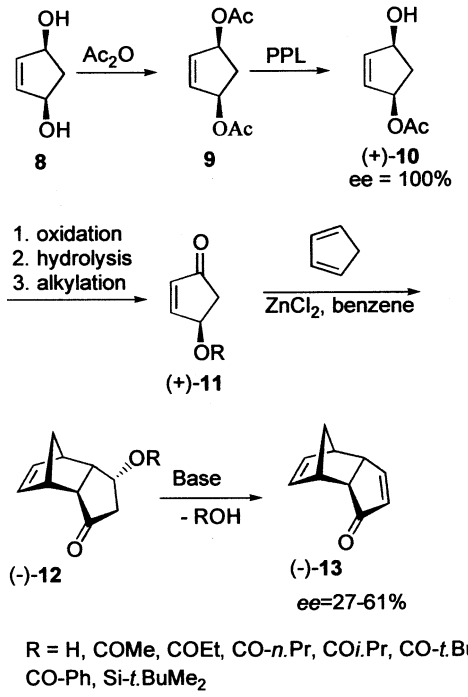
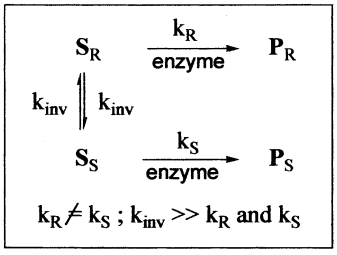


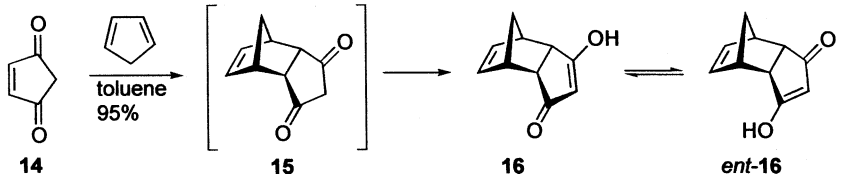
Scheme 1.

is expressed by the equation Kk_R/k_S, wherein k_R and k_S are the respective rate constants of the reaction of *R* and *S* enantiomers. For an enantioselective reaction with, e.g. an enzyme, one of the enantiomers will predominate or be obtained exclusively in an ideal case. A chiral reagent will lead to a mixture of diastereomeric products, of which one may be formed preferentially depending on the ratio of k_R/k_S (Scheme 3). For **16** such a process can also be denoted as an asymmetric desymmetrization of a pseudo-*meso* compound.

The objective of this study is to utilize the enolic nature of compound **16** and perform a desymmetrization either enzymatically or chemically in order to obtain optically pure tricyclodecadienone system **1**.



Scheme 3.



Scheme 2.

We have recently communicated a novel and non enzymatic route for the synthesis of optically active tricyclodecadienone[12] via an asymmetric desymmetrization of β-hydroxy-α,β-unsaturated ketone **16** using chiral amines. In this article we report a full account of our findings including our attempted enzymatic approach to achieve the target.

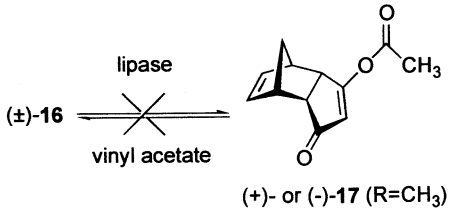
2. Results and discussion

The Diels–Alder reaction of cyclopentadiene with cyclopenten-1,4-dione **14**[13] offers a convenient and direct route to substituted *endo*-3-oxo-dicyclopentadiene system **1** (Scheme 2). Interestingly, cycloadduct **15** does not exist in its *meso*-symmetric form but is completely enolized as is evident from its ^{1}H NMR spectrum. The adduct actually consists of a racemic and rapidly equilibrating mixture of antipodes **16** and *ent*-**16**. These adducts **16** have no C_s-symmetry but as a result of the very fast tautomeric equilibrium they behave like *meso*-compounds. For this reason the term pseudo-*meso* has been assigned to the equilibrating compounds.[14]

The fast enantiomerization of tricyclic enols **16** in principle allows a dynamic kinetic resolution,[15] with the possible formation of a single enantiomer or diastereomer. Assuming a fast interconversion of both enantiomers, the product ratio

2.1. Enzymatic resolution

Preliminary attempts were made to carry out the asymmetric desymmetrization of the tricyclic alcohol **16** in an enzymatic fashion with a lipase under non aqueous conditions using vinyl acetate as acyl donor under a variety of conditions (Scheme 4). Disappointingly, under the conditions applied no esterification was observed, not even after stirring the reaction mixture for several weeks. In all the cases, the starting material was recovered quantitatively. This result is rather unexpected as a closely related compound **7** is known to give excellent results.[11,16] Further efforts to transesterify compound **16** using different enzymes such as porcine pancreatic lipase (PPL), candida cylindracea lipase (CCL)) and other acyl donors (i.e. methyl acetate, trichloroethyl ester of butanoic acid) also met with little success.

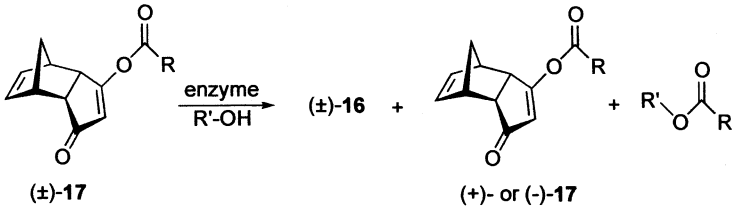


Scheme 4.

Table 1. Reaction conditions for enzymatic hydrolysis of **17** (R=CH_3)

Entry	Enzyme	R′–OH[a]	Time (h)	$[\alpha]_D^{20b}$ (°)	ee (%)
1	Lipase PS	*n*-BuOH	3	+5.8	~3–4
2	Lipase AY	*n*-BuOH	4	+4.2	~2
3	Lipase R	*n*-BuOH	2.5	+2.0	~1
4	Lipase N conc	*n*-BuOH	5	0	
5	Lipase PS	*n*-OctOH	5.5	0	
6[c]	Lipase PS	*n*-BuOH	2.2	0	
7[c]	Lipase R	*n*-BuOH	2	0	
8[d]	Lipase PS	*n*-BuOH	4	+1.2	<1

All reactions were terminated at 50% conversion.
[a] A 25% solution of the alcohol R′–OH in *n*-hexane was applied.
[b] (*c*=0.5, MeOH).
[c] 4 equiv. of triethylamine was added.
[d] 0.5 equiv. of pyridine was added.



Scheme 5.

As the 5-hydroxytricyclodecadienone **16** can be considered as a vinylogous acid, reaction with an alcohol could, in principle, lead to vinylogous ester (i.e. an enol ether). However attempts to perform such an esterification (etherification) in presence of lipase and various alcohols (methanol, 1-butanol, 1-octanol) was not successful.

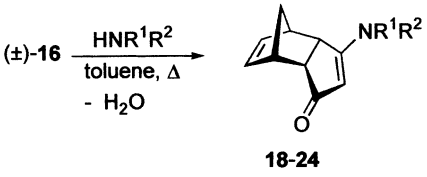
An alternative approach to obtain an enantiopure 5-substituted tricyclodecadienone involves the enzymatic resolution of 5-alkylcarbonyloxy compounds **17**. Initial attempts using PLE in an aqueous phosphate buffer did not lead the desired result, instead a spontaneous non enzymatic hydrolysis of **17** (R=CH_3, *n*-C_3H_7, *i*-C_3H_7, *n*-C_7H_{15}) was observed. Such a hydrolysis even took place in demineralized water without any addenda. Enzymatic alcoholysis of **17** was considered next. No optically enriched product was obtained using butyrate **17** (R=C_3H_7) or acetate **17** (R=CH_3) and ethanol in the presence of PPL, in fact no reaction took place at all. Transesterification of acetoxy derivative **17** (R=CH_3) using Amano lipases and *n*-butanol led to some enrichment with an estimated ee of 3–4% (measured with ^{1}H NMR using Eu(hfc)$_3$ as the chiral shift reagent) (Table 1). The lack of enantioselectivity may be attributable to the flat nature of the enone unit and the remote position of the stereogenic center in the substrate (Scheme 5).

In view of the disappointing results with enzymatic resolutions, attention was focused on chemical approaches.

2.2. Chemical resolution

2.2.1. Preparation of tricyclic enaminones. An important lead to a chemical desymmetrization of **16** was that these enols can be efficiently aminated to the corresponding enaminones **18**–**24** using the common method[17] of heating **16** to reflux in toluene in the presence of a small excess of amine (Scheme 6). The enaminones were obtained in excellent yields except in one case (Table 2). Azeotropic removal of water was not necessary. Attempts to perform this reaction in lower boiling solvents, such as benzene, *n*-hexane or THF resulted in incomplete conversions and formation of a substantial amount of the corresponding ammonium salt. Such salt formation is a well known phenomenon for this type of reaction.[18] Hence, it has been inferred that after the initial salt formation, the elimination of water leads to the desired enaminone only when the reaction is carried out for a sufficiently long time and at a high temperature of at least 111°C in the present case. Attempts to accomplish the amination of enol **16** at lower temperatures either by acid- or base-catalysis or at high pressure were not successful. Reaction of the tosylate of **16** with ammonia led to a quantitative reformation of **16** and *p*-toluenesulfonamide. Mitsunobu condition or use of dicyclohexylcarbodiimide (DCC) as a coupling reagent for the amination of **16** resulted only in the formation of the corresponding ammonium salts.

2.2.2. Dynamic kinetic resolution utilizing chiral amines. Next the synthesis of enaminones using optically active amines was investigated in order to perform an asymmetric desymmetrization of **16**. First, (*R*)-(+)-α-phenylethylamine was used as the chiral amine. The corresponding enaminone **25** was obtained in an excellent yield of 91%, but no diastereoselectivity was observed (Scheme 7, Table 3, entry 1). Fortunately, both diastereomers **25a** and **25b** could be readily separated by crystallization from ethyl acetate and subsequent column chromatography on silica gel. Thus, the

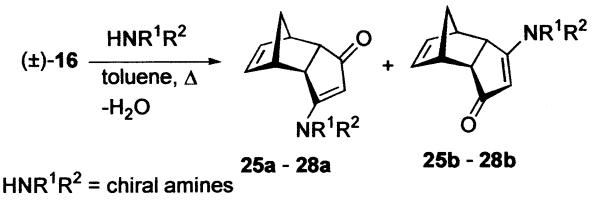


Scheme 6.

Table 2. Synthesis of tricyclic enaminones **18**–**24**

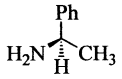
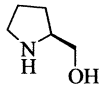
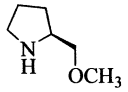
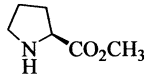
Entry	HNR^1R^2	Product	Time (h)	Yield (%)
1	Cyclohexylamine	**18**	24	95
2	*n*-Pentylamine	**19**	48	89
3	Benzylamine	**20**	23	94
4	Pyrrolidine	**21**	23	93
5	Piperidine	**22**	24	92
6	Morpholine	**23**	24	94
7	Di-*n*-butylamine	**24**	120	9

All reactions were performed in refluxing toluene.



Scheme 7.

Table 3. Asymmetric desymmetrization of **16** using chiral amines

Entry	HNR^1R^2	Product	Time (h)	Yield (%)	Ratio (**a/b**)
1		**25**	60	91	1:1
2		**26**	48	91	3:1
3		**27**	42	79	3:1
4		**28**	24	94	1.8:1

first optical resolution of 5-hydroxy-3-oxo-dicyclopentadiene **16** was accomplished. The absolute configuration of one of the two diastereomers ($[\alpha]_D^{20}=+178$ ($c=1$, $CHCl_3$), mp 222–224°C) was established to be **25a** by single-crystal X-ray diffraction (Fig. 2).[19] In this case of α-phenylethylamine the reaction rate for the formation of the diastereomeric enaminone was practically the same (see Scheme 3).

When *S*-(+)-prolinol[20] was used as the chiral amine, enaminone **26** was obtained in an overall yield of 91% and with a de of 50% as established by ^1H NMR analysis (Table 3, entry 2). The major diastereomer ($[\alpha]_D^{20}=-20.8$ ($c=1.14$, $CHCl_3$), mp 182°C) was separated by repeated crystallization from ethyl acetate and its absolute configuration was established to be as shown in **26a** by single-crystal X-ray diffraction analysis (Fig. 2).[21] Complete separation of the diastereomers of **26** was not possible directly, but could be accomplished via their acetates. Under standard acylating conditions the respective acetates **29a** and **29b** were obtained in almost quantitative yield from **26** which could then be easily separated by column chromatography (Scheme 8).

The NMR analyses of the prolinol-derived enaminones were not quite as trivial as may be anticipated. This is due to the appearance of an extra set of signals because of the occurrence of rotamers as was clearly evident from the ^1H NMR spectrum wherein the signal due to H_4, the enaminone α-proton, appeared as two singlets. Both the ^1H and ^{13}C NMR spectra indicated that at room temperature both diastereomeric products **26** exist as two rotamers in a ratio of about 4:1. These rotamers are the result of hindered rotation around the C_5–N bond which is nicely supported by the crystallographic analysis, revealing a significantly shorter C_5–N bond (1.33 Å) as compared to a regular, non conjugated C–N bond (1.40 Å).

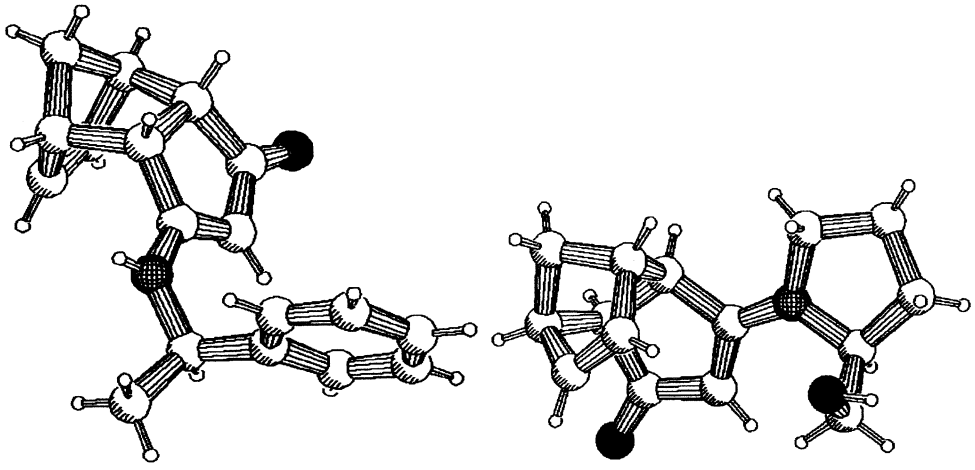
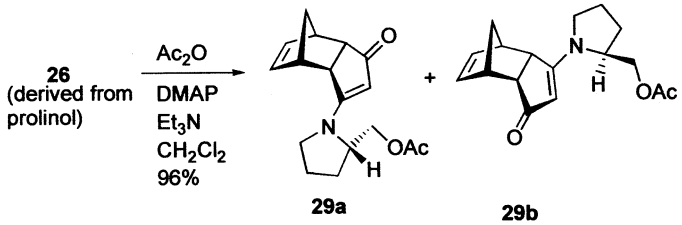
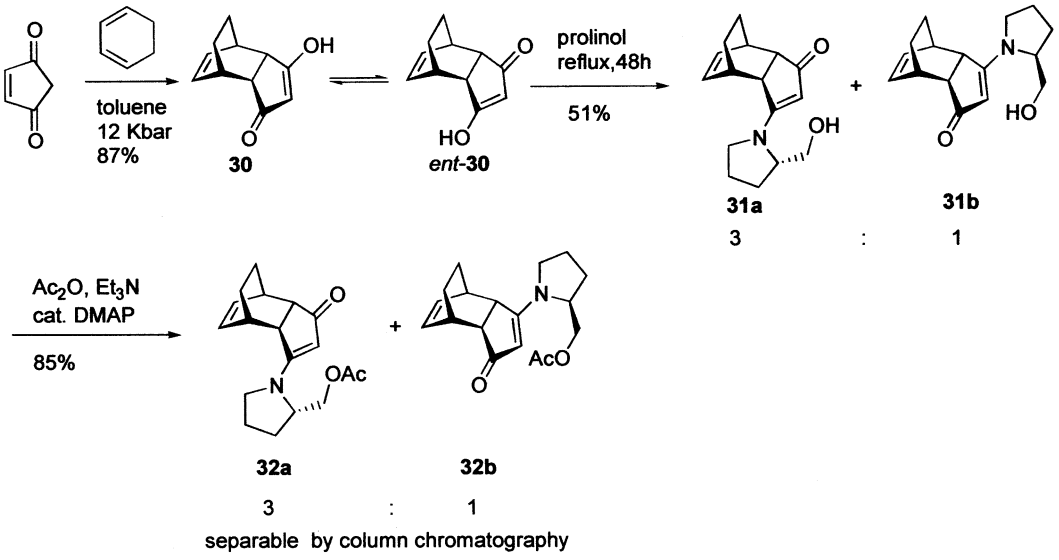


Figure 2.



Scheme 8.



Scheme 9.

Rotamers were also observed for the acetates **29**. The minor acetate **29b** has a rotamer ratio of 3:1 at room temperature, as was indicated by its ^{1}H NMR (400 MHz). Variable temperature NMR studies using a 90 MHz NMR instrument reveal that H_4 signal starts to coalesce at 300 K. At 315 K a single sharp signal was obtained. Similar results were obtained for the acetate **29a** with the signals starting to coalesce at 317 K (90 MHz) and finally merge to give a sharp signal at 330 K.

The same optical yield was obtained for the desymmetrization process using (*S*)-(+)-prolinol methyl ether[20] instead of prolinol (Table 3, entry 3). GC-analysis of the mixture of diastereomers **27** showed a 3:1 ratio. This mixture itself could not be separated as crystallization failed and no difference in R_f on TLC was observed. The absolute configuration of the major enaminone **27a** was the same as that of **26a**. Simple methylation of **26a** yielded **27a** which, according to GC analysis, was identical to the most abundant diastereomer in the mixture of **26a** and **26b**. Tricyclic enaminone **27a** also consisted of two rotamers in a ratio of 5:2 at room temperature.

An efficient desymmetrization of *meso*-anhydrides derived from norbornene using (*S*)-(−)-methyl prolinate, reported by Albers et al.[22] prompted the investigation of proline methyl ester in the present case. However, contrary to the expectation, the use of methyl prolinate instead of prolinol rather resulted in a considerable reduction of the diastereoselectivity. The diastereomers were obtained in a ratio of 1.8:1 as was determined by GC analysis (Table 3, entry 4). In analogy with the results described earlier it is assumed that the major diastereomer has absolute configuration **28a**.

Proline itself showed a deviating behavior. For the completion of its reaction with the tricyclic enol (±)-**16** 4 days of heating at reflux was necessary. This resulted in a considerable decomposition of the starting material and/or product and hence a moderate yield of product (ca. 60%) was obtained. According to the ^{1}H NMR (400 MHz) spectrum a mixture of diastereomers was obtained. The ratio could not be determined precisely due to the presence of rotamers. However a rough estimate indicates a ratio of ca. 10:1. Coalescence could not be achieved as the temperature necessary to enforce coalescence at 400 MHz could not be reached.

This prolinol mediated desymmetrization reaction was also successful for the hydroxytricycloundecadienone **30** derived from cyclohexadiene and cyclopentendione (Scheme 9). Compound **30** was prepared under high pressure,[23] and heated at reflux with prolinol in toluene to obtain the optically active tricyclic enaminone **31** in 51% yield with a de of 50%. However, the diastereomers could not be separated directly but only through their acetates **32a** and **32b**. The obsolute configuration was assigned to the diastereomers of **31** by analogy. Interestingly, the major diastereomer **32a** exists as a single rotomer at room temperature whereas the minor diastereomer **32b** had a rotomer ratio of 85:15.

The diastereoselectivity in the reaction of the proline derivatives with the pseudo-*meso* tricyclic enol can be explained in analogy with that of Albers et al.[22] for the desymmetrization of norbornene derived anhydrides where steric effects between the anhydride and the proline reactants are held responsible. Hence it is assumed that the proline reacts exclusively with the keto–enol moiety from the less hindered *exo*-face of the tricyclic system

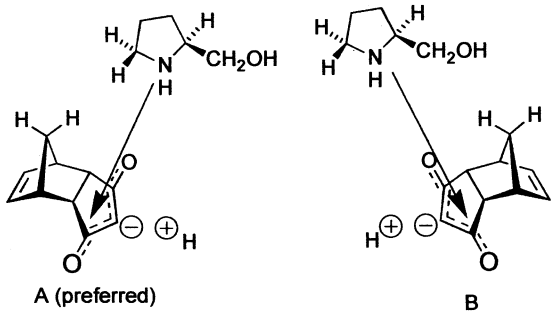


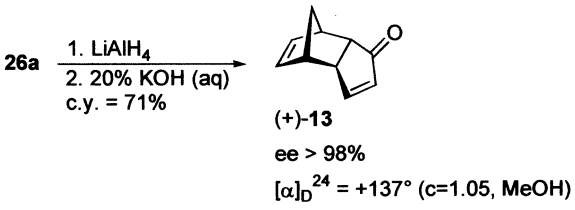
Figure 3.

thereby approaching the flat keto–enol system along a trajectory of 109° as shown in Fig. 3, and whereby the CH_2OH-group will be positioned as remote as possible. The steric hindrance exerted by the methylene bridge hydrogen H_{10a} on the incoming proline-derivative, therefore, determines the stereochemistry of the product. This steric approach control results in a preference for pathway A in which the hindrance between the methylene bridge and prolinol is the least. The observed stereochemistry is in agreement with this explanation.

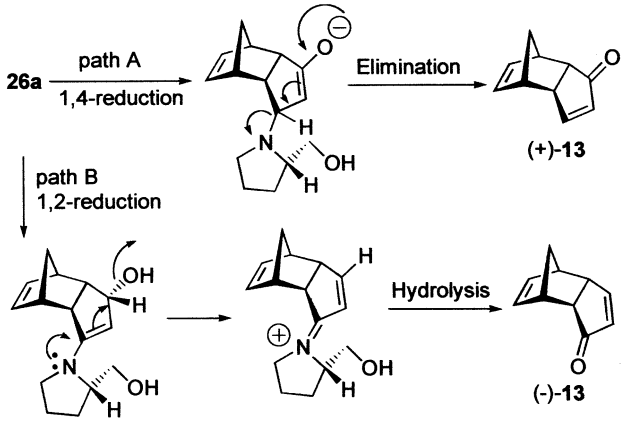
A series of other chiral amines, namely L-2′-diphenylprolinol, (2*S*)-hydroxymethylpiperidine, (1*R*,2*S*)-(−)-ephedrine, (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propandiol, (+)-dehydroabiethylamine, (4*R*,5*S*)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione, were also tried in this desymmetrization reaction. None of them was effective. Thus, prolinol is a unique chiral auxiliary for this desymmetrization.

2.2.3. Reduction of tricyclic enaminones. In order to obtain optically pure tricyclodecadienone **13**, it is essential to remove the chiral auxiliary in an efficient and convenient way. This was achieved by the reduction of tricyclic enaminone **26a** with $LiAlH_4$ whereby parent tricyclodecadienone (+)-**13** was obtained in 71% yield with an enantiomeric purity of more than 98% (Scheme 10).

Two different mechanistic pathways can be envisaged for the reduction of **26a**, as depicted in Scheme 11. As the absolute configuration of the obtained tricyclodecadienone (+)-**13** is the same as that of **26a**, reduction proceeds exclusively by a 1,4-addition process (pathway A). Initial 1,2-hydride reduction followed by hydrolysis would have caused an inversion of the absolute configuration (pathway B).



Scheme 10.



Scheme 11.

The reaction conditions for the reduction in order to achieve selective formation of parent tricyclodecadienone **13** are critical. The best result was obtained when only 0.7 equiv. of $LiAlH_4$, was added as a 1.0 M solution in THF to the neat substrate.

3. Conclusions

It was established that pseudo-*meso* 5-hydroxytricyclodecadienone **16** undergoes an asymmetric desymmetrization to enaminones applying prolinol or its methyl ether as chiral mediator. The diastereoselectivity of this asymmetric desymmetrization amounts to a de of 50%. Both diastereomers derived from prolinol could conveniently be separated via their acetates. When α-phenylethylamine is used as a chiral amine the diastereomeric enaminones were obtained in equal amounts, but separation by crystallization and subsequent chromatography could be readily achieved. Attempts to accomplish an enzymatic desymmetrization were not successful, which underlines the importance of chemical methods via chiral enaminones. Reduction of the enaminone **26a** with $LiAlH_4$ under carefully chosen conditions allows the preparation of enantiopure parent tricyclodecadienone **13** in good yield.

4. Experimental

4.1. General

Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were recorded on a Perkin Elmer 298 infrared spectrophotometer. FT-IR spectra were taken on a Biorad WIN-IR FTS-25 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-400, a Bruker AC-300 and a Bruker AC-100 at rt unless stated otherwise. Chemical shifts are reported in ppm relative to TMS. For mass spectra a double focussing VG 7070E mass spectrometer was used. GC–MS spectra were run on a Varian Saturn 2 benchtop GC–MS ion-trap system. Elemental analyses were performed on a Carlo Erba Instruments CHNS-O 1108 Elemental Analyzer. Optical rotations were measured with a Perkin Elmer 241 Polarimeter. GC analyses were conducted with a Hewlett–Packard HP5890II instrument. Flash chromatography was carried out using Merck Kieselgel 60H and column chromatography at atmospheric pressure was performed using Merck Kieselgel 60. Thin layer chromatography (TLC) was carried out on Merck precoated silicagel 60 F254 plates (0.25 mm) and spots were visualized with UV, iodine or a molybdate spray. Solvents used were of analytical grade and wherever necessary, were dried using the standard methods.

4.1.1. 5-Hydroxy-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (16). The Diels–Alder reaction of cyclopentadiene and cyclopenten-1,4-dione **14**[13c] using the procedure of DePuy et al.[13a] gave **16** in 96% yield. Recrystallization from 2-propanol gave analytically pure samples. Mp 170°C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.80 (brs, 1H, exchangeable with D_2O), 5.87 (s, 2H), 4.82 (s, 1H), 2.96 (s, 4H), 1.57 (d, J=8.2 Hz, 1H), 1.47 (d, J=8.2 Hz, 1H); ^{13}C

NMR (100 MHz, DMSO-d_6) δ 200.6, 133.6, 108.6, 52.8, 49.2, 43.9; IR (KBr, cm^{-1}) ν 3055, 1615 and 1495; MS (EI, *m/z*): 162 (M^+), 134, 97, 91, 66.

4.1.2. General procedure for the attempted lipase-catalyzed acylation of 5-hydroxy-*endo*-tricyclo[5.2.1.0^{2,6}]-deca-4,8-dien-3-one (16). Following the procedure of Klunder et al.,[4e] the lipase (200 mg) and powdered molecular sieves (4 Å, 100 mg) were added under argon to a stirred suspension of **16** (100 mg, 0.62 mmol) and vinyl acetate (6 mL, 65 mmol) in 3 mL of the solvent. The reaction was monitored by GC and TLC (eluent=chloroform/methanol=7:1).

4.1.3. General procedure for the attempted lipase-catalyzed transesterification of 5-acetoxy-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (17) (R=CH_3). The lipase (100 mg) was added to a stirred solution of **17** (R=CH_3) (200 mg, 1.0 mmol) and biphenyl (60 mg) in a 3:1 mixture of *n*-hexane and the alcohol mentioned in Table 1 (32 mL). The suspension was stirred at room temperature for the time indicated in Table 1. The reaction was monitored by GC-analysis. At 50% conversion the reaction was terminated by filtering the suspension over a celite pad. The mixture was then concentrated in vacuo; the alcohol used was removed azeotropically by adding cyclohexane. Pure **17** (R=CH_3) was obtained by flash chromatography (diethyl ether/*n*-hexane=3:1) in yield varying between 35 and 45%.

4.1.4. General procedure for the reaction of 5-hydroxy-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (16) with amines. Synthesis of enaminones. To a suspension of the compound **16** in toluene was added the desired amine and the reaction mixture was heated at reflux. During this treatment the reaction mixture became clear and then turned yellow. In some cases, within a few hours the product started to precipitate. After refluxing for the required time, the reaction mixture was cooled to rt and the product was obtained by filtration followed by extensive washing with diethyl ether. In some cases, yellow oil was obtained. Recrystallization of the crude product from 2-propanol and/or purification by column chromatography provided analytically pure enaminones as white or yellow crystals.

4.1.5. 5-Cyclohexylamino-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (18). Enaminone **18** was obtained in 95% yield (7.27 g) as white crystals by refluxing cyclohexylamine (3.45 g, 34.8 mmol) with **16** (5.11 g, 31.5 mmol) in toluene (100 mL) for 24 h. Mp 249°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (dd, *J*=5.4, 2.8 Hz, 1H), 5.81 (dd, *J*=5.4, 2.6 Hz, 1H), 4.82 (s, 2H), 3.17 (brs, 1H), 3.13 (m, 2H), 2.97 (brs, 1H), 2.90 (t, *J*=5.4 Hz, 1H), 1.94 (brt, 2H), 1.78 (brt, 4H), 1.73 (d, *J*=8.3 Hz, 1H), 1.50 (d, *J*=8.3 Hz, 1H), 1.40–1.10 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 174.5, 134.8, 130.9, 101.9, 53.5, 51.6, 50.6, 46.3, 43.6, 43.3, 32.4, 25.4, 24.6 24.5; IR (KBr, cm^{-1}) ν 3220, 3190, 1640, 1590–1520, 1450; MS (EI, *m/z*): 243 (M^+), 215, 177, 161, 146, 133, 118, 96, 82, 66, 28; HRMS/EI: *m/z* calcd for $C_{16}H_{21}NO$: 243.1623 (M^+) Found: 243.1625; Anal. calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76 (%). Found: C, 78.72, H, 8.81, N, 5.76 (%).

4.1.6. 5-*n*-Pentylamino-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (19). Enaminone **19** was obtained in 89% yield (3.22 g) as white crystals by refluxing *n*-pentylamine (1.49 g, 17.1 mmol) with **16** (2.52 g, 15.6 mmol) in toluene (50 mL) for 48 h. Mp 119°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (dd, *J*=5.4, 2.9 Hz, 1H), 5.82 (dd, *J*=5.4, 2.7 Hz, 1H), 5.22 (brs, 1H), 4.81 (s, 1H), 3.15 (brs, 1H), 3.14 (t, *J*=5.9 Hz, 1H), 3.05 (q, *J*=6.5 Hz, 2H), 3.00 (brs, 1H), 2.91 (t, *J*=5.5 Hz, 1H), 1.74 (d, *J*=8.3 Hz, 1H), 1.56 (t, *J*=7.0 Hz, 2H), 1.51 (d, *J*=8.3 Hz, 1H), 1.32 (m, 4H), 0.91 (t, *J*=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 176.0, 134.7, 131.1, 101.6, 51.7, 50.8, 46.1, 44.8, 43.6, 43.3, 29.0, 28.4, 22.3, 13.9; IR (KBr, cm^{-1}) ν 3210, 1640, 1550 (broad), 1475; MS(EI, *m/z*): 231 (M^+), 216, 203,188, 174, 165, 160, 150, 146, 137, 122, 109, 66, 43, 28; HRMS/EI: *m/z* calcd for $C_{15}H_{21}NO$: 231.1623 (M^+) Found: 231.16233 (M^+); Anal. calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05 (%). Found: C, 77.82; H, 9.16; N, 6.10 (%).

4.1.7. 5-Benzylamino-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (20). Enaminone **20** was obtained in 94% yield (3.66 g) as white crystals by refluxing benzylamine (1.88 g, 17.6 mmol) with **16** (2.52 g, 15.6 mmol) in toluene (50 mL) for 23 h. Mp 157°C; ^{1}H NMR (400 MHz, $CDCl_3$, *T*=310 K) δ 7.30 (m, 5H), 6.12 (brs, 1H), 6.03 (dd, *J*=5.5, 2.8 Hz, 1H), 5.82 (dd, *J*=5.5, 2.8 Hz, 1H), 4.82 (s, 1H), 4.19 (d, *J*=3.3 Hz, 2H), 3.18 (t, *J*=5.2 Hz, 1H), 3.10 (brs, 1H), 3.03 (brs, 1H), 2.85 (t, *J*=5.6 Hz, 1H), 1.71 (d, *J*=8.3 Hz, 1H), 1.48 (d, *J*=8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, *T*=310 K) δ 204.5, 176.3, 137.0, 134.5, 131.3, 128.7, 127.8, 127.5, 102.1, 51.8, 50.9, 46.1, 43.7, 43.3, 48.9; IR (KBr, cm^{-1}) ν 3184, 3060, 1638, 1572–1533 (broad), 1454; MS (EI, *m/z*): 251 (M^+), 223, 185, 160, 146,132, 104, 91, 77, 66, 28; Anal. calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57 (%). Found: C, 81.23; 6.82; N, 5.58 (%).

4.1.8. 5-Pyrrolidino-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (21). Enaminone **21** was obtained in 93% yield (0.242 g) as yellow crystals by refluxing pyrrolidine (0.097 g, 1.37 mmol)) with **16** (0.196 g, 1.21 mmol) in toluene (30 mL) for 23 h. Mp 165–167°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (dd, *J*=5.6, 2.9 Hz, 1H), 5.81 (dd, *J*=5.6, 2.9 Hz, 1H), 4.70 (s, 1H), 3.65 (m, 1H), 3.53 (m, 1H), 3.26 (dd, *J*=6.1, 4.3 Hz, 1H), 3.20 (m, 1H), 3.18 (s, 2H), 3.07 (brs, 1H), 2.96 (dd, *J*=6.1, 4.6 Hz, 1H), 2.00 (m, 4H), 1.75 (d, *J*=8.4 Hz, 1H), 1.55 (d, *J*=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 174.3, 134.6, 130.6, 102.8, 51.8, 51.4, 49.1, 48.2, 45.9, 44.1, 43.8, 25.6, 24.7; IR (KBr, cm^{-1}) ν 1643, 1576 (broad); MS(EI, *m/z*): 215 (M^+), 187, 149, 121, 70, 66, 28. Anal. calcd for $C_{14}H_{17}NO$: C, 78.11; H, 7.95; N, 6.51 (%). Found: C, 77.26; H, 7.92; N, 6.52 (%).

4.1.9. 5-Piperidino-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (22). Enaminone **22** was obtained in 92% yield (2.59 g) as yellow crystals by refluxing piperidine (1.15 g, 13.6 mmol) with **16** (2.00 g, 12.3 mmol) in toluene (30 mL) for 24 h. Mp 135–137°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (dd, *J*=5.6, 2.9 Hz, 1H), 5.83 (dd, *J*=5.6, 2.9 Hz, 1H), 4.85 (s, 1H), 3.60 (brs, 1H), 3.40 (brs, 1H), 3.30 (brs, 1H), 3.25 (dd, *J*=6.3, 4.0 Hz, 1H), 3.20 (brs, 1H), 3.19 (brs, 1H), 3.02 (brs, 1H), 2.95 (dd, *J*=6.3, 4.6 Hz, 1H), 1.65 (m, 6H),

1.73 (d, J=8.4 Hz, 1H), 1.54 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, T=260 K) δ 203.6, 175.6, 134.9, 130.8, 101.7, 51.6, 51.1, 49.0, 48.7, 45.1, 44.6, 43.5, 26.3, 25.1, 23.9; IR (KBr, cm^{-1}) ν 1643, 1560 (broad); MS (EI, m/z): 229 (M^+), 201, 163, 135, 117, 84, 79, 66, 28. Anal. calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11 (%). Found: C, 78.45; H, 8.32; N, 6.18 (%).

4.1.10. 5-Morpholino-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (23). Enaminone **23** was obtained in 94% yield (1.34 g) as yellow crystals by refluxing morpholine (0.59 g, 6.78 mmol) with (1.00 g, 6.17 mmol) in toluene (30 mL) for 24 h. Mp 113°C; ^{1}H NMR (400 MHz, $CDCl_3$, T=330 K, ppm) δ 6.11 (dd, J=5.5, 2.8 Hz, 1H), 5.82 (dd, J=5.5, 2.8 Hz, 1H), 4.86 (s, 1H), 3.73 (t, J=5.0 Hz, 4H), 3.36 (m, 4H), 3.25 (dd, J=6.4, 4.0 Hz, 1H), 3.20 (brs, 1H), 2.97 (brs, 1H), 2.95 (dd, J=6.4, 4.5 Hz, 1H), 1.75 (d, J=8.4 Hz, 1H), 1.64 (brs, H_2O), 1.55 (d, J=8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 203.8, 176.0, 135.1, 130.5, 103.5, 66.4, 51.8, 51.4, 47.6, 45.1, 44.8, 43.8; IR (KBr, cm^{-1}) ν 3470, 1630, 1550 (broad), 1455; MS (EI, m/z): 231 (M^+), 203, 165, 145, 137, 117, 79, 66, 51, 28; HRMS/EI: m/z calcd for $C_{14}H_{17}NO_2$: 231.1259 (M^+). Found: 231.12584 (M^+); Anal. calcd for $C_{14}H_{17}NO_2 \cdot 0.5H_2O$: C, 69.98; H, 7.55; N, 5.83 (%). Found: C, 69.94; H, 7.56; N, 5.87 (%).

4.1.11. 5-Di-*n*-butylamino-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (24). Di-*n*-butylamine (0.878 g, 6.79 mmol) was added to a suspension of **16** (1.00 g, 6.17 mmol) in toluene (30 mL). The reaction mixture was heated at reflux for 120 h. During this treatment the reaction mixture turned into a yellow suspension. After cooling, the precipitated salt was filtered off and the filtrate was concentrated in vacuo. The residue was dissolved in dichloromethane, extracted with 1 M HCl (aq.), 1 M KOH (aq.) and brine and subsequently dried over $MgSO_4$. Purification by flash chromatograpy (ethyl acetate/methanol=10:1) yielded pure **24** (0.15 g, 9%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (dd, J=5.6, 2.9 Hz, 1H), 5.77 (dd, J=5.6, 2.8 Hz, 1H), 4.78 (s, 1H), 3.38 (m, 2H), 3.25 (m, 1H), 3.19 (brs, 1H), 3.07 (m, 2H), 3.00 (brs, 1H), 2.95 (m, 1H), 1.75–1.25 (m, 10H), 0.99 (t, J=7.3 Hz, 3H), 0.92 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 175.8, 135.0, 130.5, 102.9, 51.6, 51.4, 50.5, 50.2, 45.4, 45.0, 43.7, 31.1, 28.1, 20.1, 20.0, 13.8, 13.7; IR (CH_2Cl_2, cm^{-1}) ν 1640, 1555 (broad), 1460; MS (EI, m/z): 273 (M^+), 245, 230, 216, 188, 164, 150, 137, 123, 109; HRMS/EI: m/z calcd for $C_{18}H_{27}NO$: 273.20926 (M^+). Found: 273.20923 (M^+).

4.1.12. 5-((*R*)-1′-Phenylethylamino)-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (25). (*R*)-(+)-α-phenylethylamine (2.11 g, 17.4 mmol) was added to a suspension of **16** (2.55 g, 15.7 mmol) in toluene (50 mL). The reaction mixture was heated at reflux for 60 h after which it was cooled and concentrated in vacuo. The diastereomers were separated by flash chromatography (ethyl acetate/methanol=10:1), affording **25a** (1.89 g) and **25b** (1.89 g) in an overall yield of 91%. Analytically pure samples of **25a** and **25b** were obtained as white crystals by crystallization from 2-propanol and ethyl acetate, respectively.

(1R,2S,6R,7S,1′R)-5-(1′-Phenylethylamino)-endo-tricyclo-[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**25a**). Mp 222–224°C; $[\alpha]_D^{20}$=+178 (c=1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5H), 6.09 (dd, J=4.8, 2.6 Hz, 1H), 5.89 (brs, 1H), 5.47 (brd, J=5.0 Hz, 1H), 4.73 (s, 1H), 4.35 (quin, J=6.6 Hz, 1H), 3.14 (brs, 2H), 3.03 (brs, 1H), 2.84 (t, J=5.4 Hz, 1H), 1.74 (d, J=8.3 Hz, 1H), 1.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.5, 174.6, 142.2, 134.7, 131.1, 128.8, 127.7, 125.9, 103.4, 54.6, 51.8, 50.7, 46.3, 43.6, 43.3, 22.5; IR (KBr, cm^{-1}) ν 3199, 1640, 1550 (broad), 1493, 1447; MS (EI, m/z): 265 (M^+), 237, 222, 199, 184, 171, 160, 132, 105, 77, 66, 28; Anal. calcd for $C_{18}H_{19}NO$: C, 81.48; H, 7.22; N, 5.28 (%). Found: C, 81.49; H, 7.19; N, 5.39 (%).

(1S,2R,6S,7R,1′R)-5-(1′-Phenylethylamino)-endo-tricyclo-[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**25b**). Mp 208–209°C; $[\alpha]_D^{20}$=+117 (c=0.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, T=320 K, ppm) δ 7.3 (m, 5H), 5.96 (dd, J=5.5, 2.9 Hz, 1H), 5.68 (brs, 1H), 5.21 (brs, 1H), 4.72 (s, 1H), 4.37 (brs, 1H), 3.13 (t, J=6.5 Hz, 1H), 3.12 (brs, 1H), 2.99 (brs, 1H), 2.86 (dd, J=6.3, 4.6 Hz, 1H), 1.71 (d, J=8.4 Hz, 1H), 1.48 (d, J=8.4 Hz, 1H), 1.51 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, T=320 K, ppm) δ 204.3, 174.5, 142.6, 134.7, 130.9, 128.8, 127.7, 125.8, 103.6, 54.7, 51.8, 50.8, 46.4, 43.9, 43.4, 22.8; IR (KBr, cm^{-1}) ν 3202, 1638, 1550 (broad), 1493, 1448; MS (EI, m/z): 265 (M^+), 237, 222, 199, 184, 171, 160, 132, 105, 77, 66; Anal. calcd for $C_{18}H_{19}NO$: C, 81.48; H, 7.22; N, 5.28 (%). Found: C, 81.40; H, 7.19; N, 5.36 (%).

4.1.13. 5-((*S*)-2′-Hydroxymethylpyrrolidin-1′-yl)-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (26). (*S*)-(+)-prolinol[20] (0.97 g, 9.6 mmol) was added to a suspension of **16** (1.30 g, 8.0 mmol) in toluene (30 mL). The reaction mixture was heated at reflux for 48 h after which it was cooled and concentrated in vacuo. Purification by column chromatography (ethyl acetate/methanol=6:1) afforded a 3:1 diastereomeric mixture of **26** in 91% (1.79 g) yield. When the reaction was performed on larger scale (40 mmol) **26a** was obtained in pure form in 42% yield (4.13 g) as colorless crystals from the diastereomeric mixture by repeated crystallization from ethyl acetate.

(1R,2S,6R,7S,2′R)-5-(2′-Hydroxymethylpyrrolidin-1′-yl)-endo-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**26a**). Mp 182°C; $[\alpha]_D^{20}$=−20.8 (c=1.14, $CHCl_3$); The NMR spectral data of the major rotomer of **26a** are given below. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.01 (dd, J=5.5, 2.8 Hz, 1H); 5.83 (dd, J=5.5, 2.8 Hz, 1H); 4.84 (s, 1H), 3.63 (m, 4H), 3.42 (m, 1H), 3.26 (m, 1H), 3.15 (m, 2H), 3.07 (brs, 1H), 2.92 (m, 1H), 2.04 (m, 4H), 1.73 (d, J=8.3 Hz, 1H), 1.54 (d, J=8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 203.7, 175.3, 134.3, 130.9, 102.6, 62.0, 60.5, 51.6, 50.9, 49.0, 46.2, 44.0, 43.9, 27.4, 23.5; IR ($CHCl_3$, cm^{-1}) ν 3300, 1635, 1545; MS (EI, m/z): 245 (M^+), 217, 180, 148; HRMS/EI: m/z calcd for $C_{15}H_{19}NO_2$: 245.1416 (M^+). Found 245.14164 (M^+).

4.1.14. 5-((*S*)-2′-Methoxymethylpyrrolidin-1′-yl)-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (27). (*S*)-(+)-prolinol methyl ether[20] (0.28 g, 2.4 mmol) was added to a suspension of **16** (0.32 g, 2.0 mmol) in toluene (20 mL).

The reaction mixture was heated at reflux for 42 h. During this treatment the reaction mixture became clear and then turned yellow. After cooling, the reaction mixture was concentrated in vacuo. The 3:1 diastereomeric mixture of **27a** and **27b** was purified by column chromatography (ethyl acetate/methanol=4:1) but the isomers could not be separated. The overall yield of the reaction was 79% (0.49 g).

(1R,2S,6R,7S,2′R)-5-(2′-Methoxymethylpyrrolidin-1′-yl)-endo-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**27a**). The major diastereomer **27a** could be obtained in pure form by alkylating **26a**. Sodium hydride (0.36 g of a 50% suspension in mineral oil, 7.5 mmol) was added to a solution of **26a** (1.23 g, 5.0 mmol) in DMF (12 mL), under argon at room temperature. After 15 min of stirring, methyl iodide (1.07 g, 7.5 mmol) was added through a syringe. The reaction mixture was stirred for 1 h at room temperature. After quenching with water the reaction mixture was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude reaction product was purified by flash chromatography (ethyl acetate/methanol=6:1), yielding **27a** as a yellowish oil (1.18 g, 91%). The NMR spectral data of the major rotomer of **27a** are given below. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (dd, J=5.4, 2.8 Hz, 1H); 5.77 (dd, J=5.4, 2.8 Hz, 1H); 4.77 (s, 1H), 3.73–2.91 (m, 6H), 3.32 (s, 3H), 3.21 (brs, 1H), 3.05 (brs, 1H), 2.93 (m, 1H), 2.03 (m, 4H), 1.74 (d, J=8.3 Hz, 1H), 1.55 (d, J=8.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 174.2, 134.5, 130.6, 102.8, 70.8, 59.6, 58.9, 51.5, 50.9, 48.9, 46.3, 44.0, 43.9, 27.8, 23.7; IR ($CHCl_3$, cm^{-1}) ν 1640, 1550 (broad); MS (EI, *m/z*): 259 (M^+), 231, 214, 193, 186, 148; HRMS/EI: *m/z* calcd for $C_{16}H_{21}NO_2$: 259.1572 (M^+). Found: 259.15705 (M^+).

4.1.15. 5-((*S*)-2′-Carbomethoxypyrrolidin-1′-yl)-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (28). L-proline methyl ester (0.39 g, 3.0 mmol) was added to a suspension of **16** (0.32 g, 2.0 mmol) in toluene (20 mL). The reaction mixture was heated at reflux for 24 h after which it was cooled and concentrated in vacuo. The 1.8:1 diastereomeric mixture of **28a** and **28b** was purified by column chromatography (ethyl acetate/methanol=6:1) but the isomers could not be separated. The overall yield is 94% (0.55 g). IR ($CHCl_3$, cm^{-1}) ν 1735, 1655, 1555; MS (EI, *m/z*): 273 (M^+), 245, 214, 207, 186, 148, 70; HRMS/EI: *m/z* calcd for $C_{16}H_{19}NO_3$: 273.1365 (M^+). Found: 273.1365 (M^+). The NMR spectra were very complex due to the mixture of both the diastereomers and the presence of rotamers for each diastereomer.

4.1.16. Acetylation of enaminone (26). A 3:1 mixture of **26a** and **26b** (261 mg, 1.07 mmol) was dissolved in dichloromethane (5 mL) together with triethylamine (222 mg, 2.2 mmol) and DMAP (12 mg, 0.1 mmol). After the addition of acetic anhydride (123 mg, 1.2 mmol) the reaction mixture was stirred for 25 min at room temperature. The reaction was terminated by concentration in vacuo. The crude reaction mixture was purified by flash chromatography (ethyl acetate/methanol=4:1). Both the diastereomers **29a** (212 mg) and **29b** (73 mg) were obtained separately as yellowish oil in an overall yield of 96%.

(1R,2S,6R,7S,2′S)-5-(-2′-Acetoxymethylpyrrolidin-1′-yl)-endo-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**29a**). The NMR spectral data of the major rotomer of **29a** are given below. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.08 (dd, J=5.4, 2.9 Hz, 1H), 5.78 (dd, J=5.4, 2.8 Hz, 1H), 4.86 (s, 1H), 4.10 (dd, J=11.1, 5.1 Hz, 1H), 3.93 (dd, J=11.1, 6.3 Hz, 1H), 3.83 (m, 1H), 3.65 (m, 2H), 3.28 (dd, J=6.0, 4.2 Hz, 1H), 3.19 (brs, 1H), 3.06 (brs, 1H), 2.92 (dd, J=5.8, 4.8 Hz, 1H), 2.04 (m, 4H), 2.00 (s, 3H), 1.74 (d, J=8.3 Hz, 1H), 1.55 (d, J=8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 174.5, 134.4, 130.5, 103.5, 62.8, 58.6, 51.5, 50.9, 48.4, 46.1, 43.9, 43.8, 27.5, 23.4, 20.7; IR ($CHCl_3$, cm^{-1}) ν 1735 (C=O, acetate), 1640, 1545 (broad); MS (EI, *m/z*): 287 (M^+), 259, 222, 162, 148; HRMS/EI; *m/z* calcd for $C_{17}H_{21}NO_3$: 287.1521 (M^+). Found: 287.1522 (M^+).

(1S,2R,6S,7R,2′S)-5-(-2′-Acetoxymethylpyrrolidin-1′-yl)-endo-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**29b**). The NMR spectral data of the major rotomer of **29b** are given below ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (brs, 1H), 5.82 (brs, 1H), 4.88 (s, 1H), 4.15 (dd, J=11.1, 3.7 Hz, 1H), 3.94 (dd, J=11.1, 7.8 Hz, 1H), 3.80 (brs, 1H), 3.70 (m, 1H), 3.56 (m, 1H), 3.28 (dd, J=5.8, 4.3 Hz, 1H), 3.20 (brs, 1H), 3.09 (brs, 1H), 2.97 (m, 1H), 2.15–1.85 (m, 4H), 2.05 (s, 3H), 1.75 (d, J=8.3 Hz, 1H), 1.56 (d, J=8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 173.9, 134.8, 130.3, 104.5, 62.1, 58.6, 52.0, 51.4, 48.6, 46.4, 44.2, 44.1, 28.2, 23.2, 20.7; IR ($CHCl_3$, cm^{-1}) ν 1730, 1640, 1545 (broad); MS (EI, *m/z*): 287 (M^+), 259, 222, 162, 148; HRMS/EI: *m/z* calcd for $C_{17}H_{21}NO_3$: 287.1521 (M^+). Found: 287.1522 (M^+).

4.1.17. Synthesis of *endo*-tricyclo[5.2.2.0^{2,6}]undeca-4,8-dien-3-one (30). Compound **30** was prepared as per literature procedure.[23] A solution containing cyclopentadienone (1.55 g, 16.2 mmol), cyclohexadiene (3.37 g, 42.1 mmol) and few crystals of hydroquinone in benzene/toluene (1:9) solvent mixture taken in a Teflon tube fitted with a metal screw cap, was subjected to 12 kbar pressure at room temperature overnight after which the precipitate formed was filtered, washed with acetone followed by hexane and dried to afford the enol **30** in 87% yield (2.40 g) as a white solid. The ^{1}H NMR spectrum of this compound was found to be identical with that of the literature reported one.[23] ^{1}H NMR (100 MHz, DMSO-d_6,) δ 6.03 (t, J=4.2 Hz, 2H), 5.05 (s, 1H), 3.50 (broad, OH), 2.85 (bs, 2H), 2.57 (m, 2H), 1.57 (m, 2H), 1.30 (m, 2H).

4.1.18. 5-((*S*)-2′-Hydroxymethylpyrrolidin-1′-yl)-*endo*-tricyclo[5.2.2.0^{2,6}]undeca-4,8-dien-3-one (31). (*S*)-(+)-Prolinol (303 mg, 3 mmol) was added to a suspension of the enol **30** (372 mg, 2 mmol) in toluene (10 mL). The reaction mixture was heated under reflux for 48 h after which it was cooled, concentrated and purified by column chromatography (EtOAc/MeOH 6:1) to afford an inseparable diastereomeric mixture of the enaminones **31** in 51% yield. The diastereomeric ratio was found to be 3:1.

(1R,2S,6R,7S,2′R)-5-(2′-Hydroxymethylpyrrolidin-1′-yl)-endo-tricyclo[5.2.2.0^{2,6}]undeca-4,8-dien-3-one (**31a**). Spectral data for the major diastereomer **31a** from the mixture of **31a** and **31b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (m, 1H), 5.91 (m, 1H), 5.03 (s, 1H), 3.85–3.30 (m, 5H), 3.00–2.85

(m, 3H), 2.49 (dd, *J*=6.4, 3.2 Hz, 1H), 2.30–1.80 (m, 5H), 1.70–1.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.2, 204.6, 176.7, 132.8, 128.9, 103.2, 62.1, 61.2, 50.0, 49.6, 45.3, 32.5, 27.6, 25.1, 24.2, 23.5; MS (EI, *m/z*): 259 (M^+), 228, 200, 148; HRMS/EI: *m/z* calcd for $C_{16}H_{21}NO_2$: 259.15723 (M^+). Found: 259.15730 (M^+).

4.1.19. Acetylation of enaminone (31). A 3:1 mixture of the prolinol enaminone **31** (207 mg, 0.8 mmol) was dissolved in 10 mL of CH_2Cl_2 and cooled to 0°C. 0.22 mL of Et_3N (1.6 mmol) was added followed by 5 mg of DMAP. The reaction mixture was stirred for 10 min and 0.11 mL (1 mmol) of Ac_2O was added. After stirring the reaction mixture for 0.5 h at 0°C, when TLC indicated the absence of starting material the reaction was stopped and CH_2Cl_2 was concentrated. Separation of the two diastereomers was achieved by column chromatography (EtOAc/MeOH 6:1) to afford **32a** (155 mg) and **32b** (50 mg) as colorless oil in an overall yield of 85% (205 mg).

(1R,2S,6R,7S,2′S)-5-(2′-Acetoxymethylpyrrolidin-1′-yl)-endo-tricyclo[5.2.2.0^{2,6}]undeca-4,8-dien-3-one (**32a**). The major diastereomer was found to exist in only one rotomeric form at room temperature when the spectrum was recorded in a 300 MHz NMR instrument. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (t, *J*=7.2 Hz, 1H), 5.94 (m, 1H), 5.03 (s, 1H), 4.18 (m, 1H), 3.95 (m, 1H), 3.60 (bs, 1H), 3.13–2.82 (m, 4H), 2.51 (dd, *J*=6.4, 3.1 Hz, 1H), 2.25–1.88 (m, 8H), 1.65–1.25 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 174.6, 170.4, 133.0, 128.6, 104.5, 61.5, 59.0, 49.9, 48.1, 45.3, 32.3, 31.5, 27.9, 25.3, 23.2, 20.7; MS (EI, *m/z*) 301 (M^+), 273, 228, 200, 148, 43; HRMS/EI: calcd for $C_{18}H_{23}NO_3$: 301.1678 (M^+). Found: 301.1677 (M^+).

(1S,2R,6S,7R,2′S)-5-(2′-Acetoxymethylpyrrolidin-1′-yl)-endo-tricyclo[5.2.2.0^{2,6}]undeca-4,8-dien-3-one (**32b**). The minor diastereomer was found to exist in a rotomeric ratio of 85:15. NMR spectral data of major rotomer of **32b** are given below. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (t, *J*=7.0 Hz, 1H), 5.89 (t, *J*=7.0 Hz, 1H), 5.04 (s, 1H), 4.16 (dd, *J*=10.8, 5.1 Hz, 1H), 3.90 (m, 2H), 3.60 (m, 2H), 3.01 (bs, 1H), 2.82 (m, 2H), 2.48 (m, 1H), 2.20–1.80 (m, 7H), 1.70–1.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.2, 176.1, 170.4, 132.7, 132.6, 128.8, 103.8, 63.3, 58.8, 49.5, 48.3, 45.1, 32.3, 32.2, 27.5, 25.1, 23.8, 23.4, 20.7; MS (EI, *m/z*) 301 (M^+), 228, 200, 148, 43; HRMS/EI: calcd for $C_{18}H_{23}NO_3$: 301.1678 (M^+). Found 301.1677 (M^+).

4.1.20. (+)-(1*R*,2*S*,6*R*,7*S*)-*endo*-Tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one ((+)-13). A 1.0 M solution (0.70 mL, 0.7 mmol) of $LiAlH_4$ in THF was added to neat compound **26a** (245 mg, 1 mmol) through a syringe, under argon at room temperature. The reaction mixture became homogeneous after 30 min Stirring was continued for an additional hour. The reaction mixture was quenched with water (0.5 mL) and stirred for 5 min Subsequently a 20% aqueous solution of KOH (1 mL) was added and stirring continued for another 45 min. The reaction mixture was diluted with water (10 mL), neutralized with a dilute aqueous solution of HCl and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude reaction product was purified by flash chromatography (*n*-hexane/ethyl acetate=2:1), to give colorless crystalline optically pure (+)-**13** (104 mg, 71%). $[\alpha]_D^{24}$=+137 (*c*=1.05, MeOH) [lit. $[\alpha]_D^{20}$=+139 (*c*=0.95, MeOH)].[1j,6a]

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