Tetrahedron Vol 46, No 12, pp 4283–4294, 1990
Printed in Great Britain

0040–4020/90 $3.00+ 00

MENTHOL MEDIATED OPTICAL RESOLUTION OF 10-OXATRICYCLODECADIENONES. APPLICATION IN THE ENANTIOSELECTIVE SYNTHESIS OF CYCLOPENTENOIDS.

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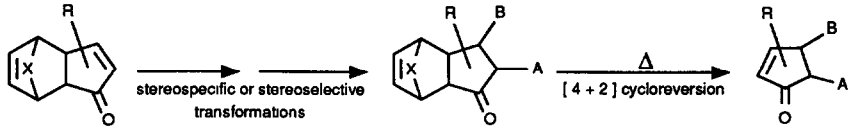
(*Received in UK* 29 *March* 1990)

Abstract: *The efficient conversion of 5-ethoxy-4-*p*-tolylsulphonylmethyl-*exo*-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one* **6** *into a diastereomeric mixture of the (-)menthyl ethers,* **9a** *and* **9b**, *is described. Separation of these ethers, followed by reduction with DIBAL and trans-etherification with NaOMe affords the enantiomerically pure methoxymethyl substituted 10-oxatricyclodecadienones* (+)**14** and (-)**14**. *These tricyclodecadienones are enantiospecifically converted into the cyclopentadienone epoxides* (-)**16** *and* (+)**16**, *respectively, by successive alkaline epoxidation and Flash Vacuum Thermolysis. The absolute configurations of all compounds, from* **9a**, **9b** *up to* (-)**16**, (+)**16** *were established by means of X-Ray diffraction analyses.*

Introduction

Tricyclodecadienones **1** (X = CH_2, O) can be employed as versatile substrates for the synthesis of functionalized cyclopentenones. Conjugate addition to their enone moiety, followed by electrophilic substitution and appropriate functional group transformations, allows the introduction of various functional groups. The resulting tricyclodecenones **2** (X = CH_2, O) can subsequently be converted into the desired cyclopentenones **3** by a thermal [4+2] cycloreversion[1,2]. This reaction sequence, which is summarized in Scheme 1, constitutes a

Scheme 1

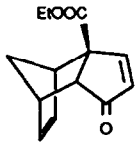


1 **2** **3**

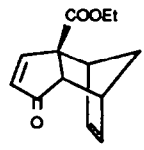
stereoselective synthetic method for the preparation of cyclopentenoids **3**, since both the formation of **2** from **1** and the thermal cycloreversion to **3** proceed in a stereocontrolled manner. Control of stereochemistry during the formation of **2** is associated with the tricyclic structure of the substrate, which enforces reactants to enter exclusively from the least hindered *exo*-face of the molecule[1,2]. The stereospecifity of the cycloreversion is

inherent to the mechanism of the retro-Diels-Alder reaction. The effectiveness of the sequence is demonstrated by our syntheses of the naturally occurring cyclopentenoids: terrein, pentenomycin, *epi*-pentenomycins and sarkomycins[2].

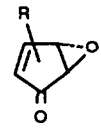
In order to extend the scope of this method to *enantioselective syntheses*, several ways to obtain enantiomerically pure tricyclodecadienones **1** were investigated. We previously reported[3] the efficient separation of the tricyclic ester **4** by enantioselective enzymatic hydrolysis using pig liver esterase. Both enantiomers, (+)**4** and (-)**4**, were obtained in high optical and chemical yield and various optically pure cyclopentenones have since



(+) **4**



(-) **4**



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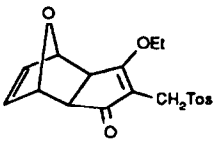
been prepared[4] from these esters, using the strategy given in Scheme 1. In this paper the attention is focused on the optical resolution of furan derived tricyclodecadienones **1** (X = O). As has recently been reported [5,6], these 10-oxatricyclodecadienones are excellent precursors for cyclopentadienone epoxides **5**, which are of interest for the preparation of highly oxygenated cyclopentenoid natural products[2b,2c,6]. In our synthesis of functionalized cylopentadienone epoxides an essential role is played by sulphone **6**. This sulphone, which is readily available from the Diels Alder adduct of furan and cyclopentene-1,4-dione, owes its versatility as synthon primarily to its special behaviour towards nucleophilic reagents[5,7]. On treatment with sodium alcoholates it undergoes a facile displacement of the tosyl group resulting in the formation of tricyclic ethers **7**[5]. These ethers, in turn, can



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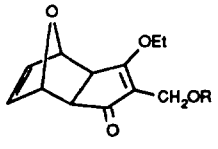

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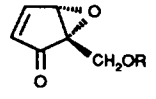

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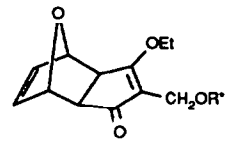


9a,b $R^* =$ (-) menthyl

efficiently be transformed into alkoxymethyl substituted cyclopentadienone epoxides **8**, successively by a metal hydride reduction[5], an alkaline epoxidation and a thermal cycloreversion[6].

The displacement of the tosyl group in **6** by alkoxides offers an interesting possibility to achieve the desired optical resolution of the 10-oxatricyclodecadienone system. If in this displacement reaction optically pure alcoholates are employed, a mixture of diastereomeric ethers will be obtained. Separation of the diastereomers and subsequent removal of the chiral auxiliary should then eventually lead to enantiomerically pure cyclopentadienone epoxides.

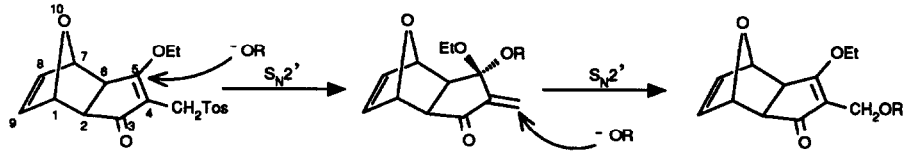
The preparation and separation of a diastereomeric mixture of menthyl ethers **9a,b** and the subsequent transformation into enantiomerically pure products is presented in this report. The enantioselective synthesis of functionalized cyclopentenoids will be illustrated by the preparation of enantiomerically pure **8** (R = Me). Furthermore, the absolute configuration of the diastereomers **9a** and **9b** and their respective derivatives will be elucidated.

Results and Discussion

Synthesis and separation of the menthyl ethers **9a** *and* **9b**.

The formation of the tricyclic ethers **7** from sulphone **6** on treatment with sodium alcoholate, proceeds via two consecutive S_N2' reactions[5]. The first one involves the substitution of the allylic tosyl group by attack of the alcoholate at C-5 of sulphone **6**. This leads to a reactive intermediate **10**, which then reacts with a second alcoholate molecule at the exo-cyclic methylene carbon in an S_N2' fashion to give compound **7** (Scheme 2).

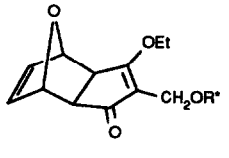
Scheme 2



6 **10** **7**

The experimental procedure for the preparation of **9a,b** involving reaction of sulphone **6** with *ca.* 1.5 equiv. of sodium (-)mentholate, at ambient temperature in a solution in DMF to which an extra equivalent of (-)menthol was added, resulted in a smooth conversion in the menthyl ethers **9a,b** in 85-90% yield. The extra amount of (-)menthol was essential (if omitted, considerable degradation and low and irreproducable yields, ~15-40%, were obtained), probably because interfering deprotonation reactions either at C-2 or C-6 of substrate and products, which may lead to β-elimination of the 10-oxa bridge[8,9], are suppressed.

After some experimentation, it was found that one of the diastereomers, **9a** (mp 127-128°C), could be obtained in pure form by one single crystallization from hexaneethyl acetate (5:1). The efficiency of this crystallization averaged around 50-55%, implying an absolute yield of *ca.* 27%. The mother liquor gave, on careful chromatography, the other diastereomer, **9b** (mp 94.5-96.5°C), in *ca.* 15% absolute yield (*ca.* 30% efficiency). No further efforts were made to separate the residual mixture of diastereomers.

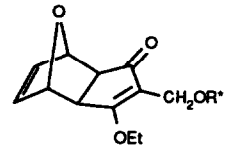


9a

mp 127-128°C

$[\alpha]_D^{rt}$ = -71.5° (c = 0.6; $CHCl_3$)

R* = (-) menthyl



9b

mp 94.5-96.5°C

$[\alpha]_D^{rt}$ = -72.8° (c = 0.6; $CHCl_3$)

The structures of both diastereomers were secured by IR, ^{1}H-NMR and mass spectra. The IR and mass spectra of **9a** and **9b** are nearly identical. The same holds for the majority of their ^{1}H-NMR resonances. Only the resonance pattern of the $\underline{CH_2}O$-(-)menthyl protons differs distinctly. These protons appear as an AB quartet at $\delta \sim 4.17$ ppm. The size and shape of these quartets are characteristic for the particular diastereomer and can be used for a rapid identification.

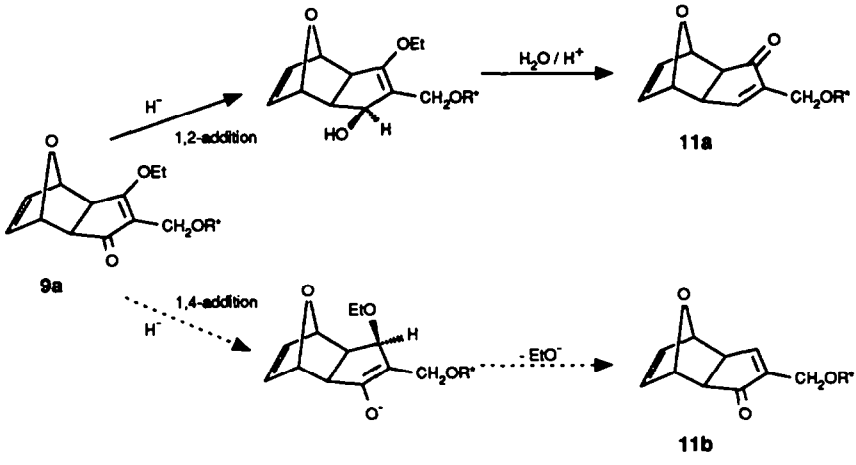
An attempt to establish the absolute configuration of **9a** by means of an X-Ray analysis failed as no suitable single crystal could be obtained. Fortunately, X-Ray analyses of derivatives of diastereomer **9b** could be made (*vide infra*). These revealed the absolute configuration of **9b** and indirectly also that of **9a**.

Removal of the menthyl group. Conversion of the menthyl ethers **9a** *and* **9b** *into enantiomerically pure methyl ethers* (+)**14** and (-)**14**.

In connection with the enantioselective synthesis of *epi*-pentenomycins[2d,6], the removal of the chiral auxiliary using a displacement of the menthyl group by a methyl group was considered. Previous observations[5] that alkoxide exchange reactions of the tricyclic ethers **7** (R = Me, Et) were accompanied by substantial deterioration (yields ≤ 5%), suggest that the menthyl ethers **9a,9b** may not be suitable substrates for such a displacement reaction. It was therefore decided to subject the menthyl ethers **9a**, **9b** first to a reduction and subsequent hydrolysis and then to attempt the trans-etherification reaction.

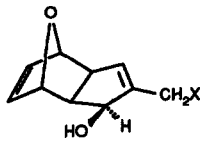
Reduction of **9a** and **9b** with DIBAL, followed by acidic work-up, afforded the ethers **11a** and **11b**, respectively, in quantitative yield. The applied procedure was identical to that of the DIBAL reductions of the analogous compounds **7** (R = Me, Et, iPr)[5]. The DIBAL reduction of **9a,b** proceeds via a highly selective (1,2) hydride addition to the enone moiety and subsequent acid hydrolysis of the resulting γ-hydroxy-enolether. The (1,2) selectivity of the reduction step is absolutely essential for the conservation of chiral integrity, since (1,4) hydride addition followed by elimination of the ethoxy group will lead to the other diastereomer (Scheme 3) and,

Scheme 3



in consequence, will produce the opposite enantiomer after displacement of the menthyl group. If both routes would take place, racemisation would occur. Although DIBAL is known to reduce α,β-unsaturated enones preferentially in a (1,2) fashion[10,11], it is not trivial that this DIBAL reduction of **9a** and **9b** proceeds with complete regiocontrol. Our work[5] and that of others[12] reveals that β-alkoxy-enones sometimes also undergo (1,4) reduction on treatment with DIBAL. For example, when excess of DIBAL was applied in the reduction of sulphone **6**, a by-product **12** (X = Tos) was obtained, which is indicative of a (1,4) reduction. The formation of this product also shows that enone **13**, if initially formed as a result of (1,4) reduction, will be converted *in situ* into **12** (X = Tos) by a selective (1,2) reduction (compare ref 12). Since similar by-products, **12** (X = OAlkyl),

were neither observed in the DIBAL reductions of **7** (R = Me, Et, iPr), nor in that of **9a** and **9b**, we may conclude that during the conversion of **9** into **11** the chiral integrity is not endangered by the reduction with DIBAL. The (1,4) DIBAL reduction is apparently restricted to sulphone **6**.



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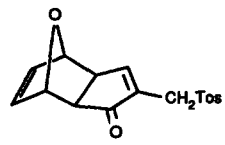

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The menthyl ethers **11a** and **11b** display nearly identical ^{1}H-NMR and IR spectra, which are entirely consistent with their structures. The individual diastereomers could not be separated by chromatographic techniques. Attempts to separate them by crystallization also failed, blocking resolution of the 10-oxatricyclodecadienone system in this stage. The pure diastereomers **11a** and **11b**, obtained from the respective diastereomers **9a** and **9b**, differ considerably in their crystallizability. Whereas diastereomer **11a**, derived from **9a** (mp 127-128°C), is isolated as a solid (mp 111-113°C), the other one, **11b**, is obtained as a viscous oil, which partially crystallizes on standing in the refrigerator. Their diastereomeric purity was confirmed by their conversion into optically pure (+)**14** and (-)**14** (*vide infra*). The absolute configurations of **11a** and **11b**, as given in Scheme 3, was established by X-Ray diffraction analyses of derivatives of **11b** (*vide infra*).

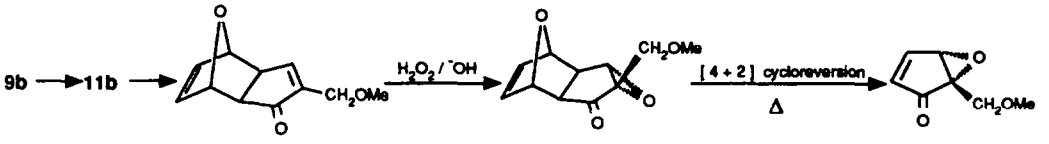
The trans-etherification of **11a** and **11b** was first tested on the diastereomeric mixture **11a,b**. Heating of this mixture under reflux in methanol with *ca.* 3 equiv. of sodium methanolate gave **14** in only 23% yield. Application of a smaller amount (1.4 equiv) of methanolate led to a substantial improvement in yield (53%). The ^{1}H-NMR analysis of **14** using optical shift reagent Eu(hfc)$_3$[13] revealed a downfield shift for all the resonances and a prominent 1:1 splitting of the methyl singlet of the methoxymethyl group, which was suitable for a fast and accurate determination of the optical purity. Treatment of diastereomerically pure **11a** with sodium methoxide under the above optimal conditions afforded enantiomerically pure (+)**14**. No trace of the other enantiomer was observed in the ^{1}H-NMR spectrum of the crude product upon analysis with Eu(hfc)$_3$. This confirmed the enantiomeric purity of the product and also the diastereomeric purity of the substrate. The antipode, (-)**14**, was similarly prepared from **11b**. It was, however, also possible and in fact much easier, to obtain (-)**14** by methanolysis of partially resolved **11**, enriched in **11b**. Such a sample was obtained by DIBAL reduction of the mother liquor, that had been retained from the first resolving crystallization of **9a,b** (*vide supra*). Methanolysis of this partially resolved **11** resulted in an enantiomeric mixture enriched in (-)**14**. ^{1}H-NMR analysis of this mixture with Eu(hfc)$_3$ revealed an enantiomeric ratio (-)**14**:(+)**14** = 3:1. Crystallization of this material from hexane gave enantiomerically pure (-)**14**. This finding demonstrates that maximum diasteromeric purity of the key menthyl ethers, **9a** and **9b**, is not an absolute prerequisite to obtain the methyl ethers **14** in an enantiomerically pure state[14]. Crystals of (-)**14** were subjected to an X-Ray diffraction analysis to establish the absolute structure of this compound (*vide infra*).

Preparation of (+)-4,5-epoxy-5-(methoxymethyl)-cyclopentenone.

The next step in the sequence aiming at optically pure *epi*-pentenomycins involves the conversion of both antipodes of **14** into optically pure 4,5-epoxy-5-(methoxymethyl)-cyclopentenone **8** (R = Me). This transformation requires an alkaline epoxidation and a subsequent thermal cycloreversion, as shown in Scheme 4 for (-)**14**.

Both reactions have recently[6] been described for racemic **14**. Therefore, the discussion will here be confined to the optical purity of the respective products.

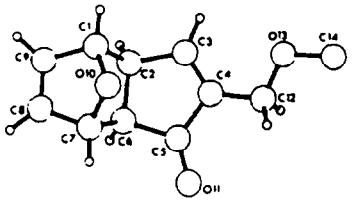
Scheme 4



(-)14	(-)15	(+)16
mp 104-106.5°C	mp 56-59°C	oil
$[\alpha]_D^{22}$ = -78.4° (c = 0.55; $CHCl_3$)	$[\alpha]_D^{22}$ = -234° (c = 0.53; $CHCl_3$)	$[\alpha]_D^{22}$ = +330° (c = 0.7; $CHCl_3$)

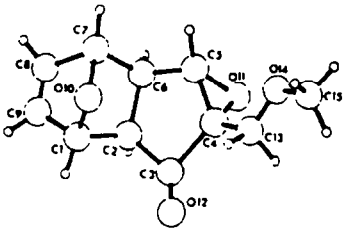
The alkaline epoxidation of **(-)14** afforded **(-)15** as a white solid in nearly quantitative yield. No trace of the antipode **(+)15** was detected in the ^{1}H-NMR spectrum of the crude product. Crystallization from hexane-ethyl acetate provided analytically pure **(-)15** as fine needles, which were subjected to an X-Ray diffraction analysis. This structure determination confirmed the general structure of **(-)15**, in particular, the position of the epoxide ring at the least hindered *exo*-face of the molecule, *anti* to the oxa-bridge[6]. The absolute configuration of **(-)15** could be established to a very high confidence level. Nevertheless, because of the rather poor quality of the crystals it was not sure that the assumption of a Gaussian error distribution was correct. Therefore, also crystals of its precursor **(-)14** were subjected to an X-Ray diffraction analysis. Although this X-ray analysis was also hampered by decomposition of the crystals during the measurements, the quality of the data was now sufficient to allow the determination of the absolute configuration with a very high confidence level. The result for **(-)14** confirms the result for **(-)15**. The definite assignments of the absolute structures of **(-)14** and **(-)15** are shown in the Figures 1 and 2, respectively. The absolute structures of the preceding menthyl ethers **9b** and **11b** and, in

Figure 1



(-)14

Figure 2



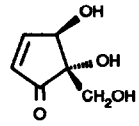
(-)15

consequence, also those of the corresponding diastereomers **9a** and **11a** can now readily be derived. They are incorporated in the respective structures given in the above Schemes.

The thermal cycloreversion of **(-)15**, which was carried out under Flash Vacuum conditions, afforded **(+)16**, as an oil, in 68% yield. Again no trace of the antipode **(-)16** was observed in the ^{1}H-NMR spectrum of this product. This confirms the stereochemical integrity of the thermal cycloreversion. The absolute configuration of **(+)16**, as shown in Scheme 4, follows from the absolute structure of its precursor **(-)15**.

Conversion of (+)**16** *into an enantiomericallly pure* epi-*pentenomycin.*

As stated in the introduction, cyclopentadienone epoxides may be useful synthons for the preparation of highly oxygenated cyclopentenoids, *e.g. epi*-pentenomycin, **17**. The trans-diol moiety of **17** can retro-synthetically be regarded as an epoxide ring and accordingly cyclopentadienone epoxide **16** may be a suitable precursor for this compound, provided that its epoxide ring can be hydrolyzed in trans-fashion. As has been



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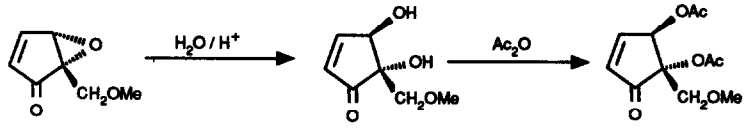
demonstrated[6] previously, this trans-opening of the epoxide ring can be achieved by an acid catalyzed hydrolysis and the resulting *epi*-pentenomycin analogue **18** can conveniently be characterized as its diacetate **19** (Scheme 5). When homochiral (+)**16** was subjected to this acid hydrolysis and subsequent acylation, optically

Scheme 5



(+)**16** (+ or -)**18** (+)**19**

active **19** was obtained. ^{1}H-NMR analysis of this product with Eu(hfc)$_3$ unequivocally established its enantiomeric purity. Similar to racemic **19**, a downfield shift for all the resonances was found, however, in contrast to racemic **19** here no splitting of the singlets of the methyl groups of the acetate moieties and the methylene protons of the methoxymethyl group was observed. This implies that the acid catalyzed epoxide ring opening of **16** to give **18** is a stereo- as well as a regio-specific process and, that under the conditions of the acylation neither epimerization nor racemization takes place. Despite repeated chromatography the preparation of an analytically pure sample failed. The actual specific rotation of (+)**19** will probably be *ca.* 5° higher than the measured optical rotation of the material obtained: +55° (c=0.32; chloroform) (see experimental section). A conclusion about the precise site of the epoxide ring opening, being either C-4 or C-5, can in this stage not be drawn. Evidence, obtained later, indicating that the epoxide ring of **16** under acidic conditions opens regiospecifically at C-4, is presented in a separate paper[15]. The implication of this regiochemistry for the absolute structure of (+)**19** is included in Scheme 5.

Concluding remarks

The results presented in this paper demonstrate that the conversion of sulphone **6** into the menthyl ethers **9a,9b** gives access to homochiral 10-oxatricyclodecadienones, which enantioselectively can be transformed into enantiomerically pure cyclopentenoids.

Experimental section

General remarks

Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were taken on a Perkin Elmer 298 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-390 or a Bruker WH-90 spectrometer, using TMS as internal standard. For mass spectra a Varian SM-1B or a double focussing VG 7070E mass spectrometer was used. Flash column chromatography was carried out at a pressure of *ca* 1.5 bar, a column length of *ca* 15 cm and a column diameter of 1-4 cm, using Merck Kieselgel 60 H or Merck Aluminium Oxid 150 neutral (Typ T). For preparative TLC precoated Kieselgel plates Merck 60-F254 were used. All solvents used were dried and distilled by standard procedures. The data for the X-ray crystal structure analyses were collected for **(-)15** on a Picker-four circle diffractometer with Mo-Kα radiation and for **(-)11** on an Enraf-Nonius CAD4 diffractometer with Cu-Kα radiation. Standard experimental details and methods for structure solution and refinement are given elsewhere[16]. The structures were solved by the MULTAN direct method.

5-ethoxy-4-(-)menthyloxymethyl-exo-10-oxatricyclo[5.2.1.0^{2,6}]deca -4,8-dien-3-one (**9a,b**).

A solution of sodium (-)mentholate in DMF[17] (4.5 ml; *ca.* 2M) was added to a solution of sulphone **6**[5] (1.8 g; 5.0 mmol) and (-)menthol (801 mg; 5.1 mmol) in dichloromethane (70 ml). The resulting mixture was stirred for 1 hr at room temperature. Then sat NH_4Claq was added (50 ml) and stirring was continued for a few min. The mixture was filtered and the organic phase was washed with water (1x50 ml). The combined aqueous layers were extracted with dichloromethane (4x50 ml). The organic extracts were dried ($MgSO_4$), filtered and evaporated. The residue (4.2 g) was purified by flash chromatography (SiO_2/hexane-ethyl acetate mixtures ranging from 3:1 to 1:1) affording 1.6 g (88%) of **9a,b** as a pale tinted solid. Subsequent crystallization from hexane-ethyl acetate (5:1; *ca.* 15 ml) gave 480 mg (26% absolute yield; 53% efficiency) of analytically and diastereomerically pure *(2R,6S)-5-ethoxy-4-(-)menthyloxymethyl-10-oxatricyclo[5.2.1.0^{2,6}] deca-4,8-dien-3-one* (**9a**), white platelets, mp: 127-128°C. $[\alpha]_D^{rt}$= -71.5° (c=0.6; chloroform). IR(KBr) ν_{max}: 2955, 2920, 2870, 1685 (C=O), 1618(C=COEt), 1382, 1352, 1328, 1085, 1015 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.71(3H,d,J=7Hz;CH_3), 0.86 (3H,d,J=7Hz;CH_3), 0.91(3H,d,J=6Hz;CH_3), 0.69-1.07(3H,m)/1.07-1.79(4H,m), 1.42(3H,t,J=7Hz;OCH_2CH_3), 2.00-2.38(2H,m), 2.53(1H,d,$J_{2,6}$=6Hz;H_2), 2.77(1H,d,$J_{6,2}$=6Hz;H_6), 3.10(1H,dt,J=4Hz,J=10Hz), 3.98/4.12/ 4.25/4.38(2H,AB_q,J_{AB}=11Hz;CH_2O(-)menthyl), 4.58(2H,q,J=7Hz;OCH_2CH_3), 4.94(1H,s)/5.04(1H,s)(H_1,H_7), 6.45(2H,s;H_8,H_9). MS(EI) m/e(%): 360(10;M$^+$), 292(32;-furan), 204(23;-menthol), 176(16;-menthol,-CO), 156 (88;menthol$^+$), 155(23), 154(52), 138(100), 137(86), 125(17), 110(21), 109(85), 83(15), 81(14), 69(15), 68(14; furan$^+$). (Found: C 72.96, H 8.91. Calc. for $C_{22}H_{32}O_4$: C 73.30, H 8.95%.)

Careful flash chromatography of the mother liquor (SiO_2/hexane-ethyl acetate (3:1)), followed by crystallization of the first fraction from hexane-ethyl acetate (5:1) afforded in *ca.* 15% absolute yield (30% efficiency) *(2S,6R)-5-ethoxy-4-(-)menthyloxymethyl-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-di en-3-one* (**9b**), glittering white needlets, mp: 94.5-96.5°C. $[\alpha]_D^{rt}$= -72.8° (c=0.6; chloroform). IR(KBr) ν_{max}: 2980, 2925, 1690(C=O), 1618(C=COEt), 1378, 1328, 1045, 1018, 872, 722, 705 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.70(3H,d,J=7Hz; CH_3), 0.89(3H,d,J=7Hz;CH_3), 0.90(3H,d,J=6Hz;CH_3), 0.64-1.09(3H,m)/1.09-1.80(4H,m), 1.40(3H,t,J=7Hz; OCH_2CH_3), 1.96-2.33(2H,m), 2.52(1H,d,$J_{2,6}$=6Hz;H_2), 2.75(1H,d,$J_{6,2}$=6Hz;H_6), 3.05(1H,dt,J=4Hz,J=10Hz), 4.02/4.14/4.17/4.31(2H,AB_q,J_{AB}=12Hz;CH_2O(-)menthyl), 4.39-4.73(2H,ABX_3 multiplet,J_{AB}=10Hz, J_{AX}=J_{BX}=7Hz;OCH_2CH_3), 4.92(1H,s)/5.00(1H,s)(H_1,H_7), 6.43(2H,s;H_8,H_9). MS(EI) m/e(%): same fragmentation pattern as **9a**. (Found: C 73.02, H 9.00. Calc. for $C_{22}H_{32}O_4$: C 73.30, H 8.95%.)

4-(-)menthyloxymethyl-exo-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**11a,b**).

A solution of Di-iso-Butyl Aluminium Hydride (DIBAL) in hexane (*ca.* 3 ml; 1 M) was added to a solution of **9a,b** (509 mg; 1.4 mmol) in dry benzene (25 ml), under nitrogen and cooled on ice. The resulting mixture was stirred for 30 min at 0°C and was then allowed to warm up to room temperature. Stirring was continued for 1 hr. Ether (40 ml) and 3% HCl (20 ml) were added and the resulting two phase system was stirred vigorously for 1 hr. The aqueous layer was separated and extracted with ether (3x40 ml). The combined organic layers were washed with water (3x20 ml), dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography (SiO_2/hexane-ethyl acetate (3:1)) to afford 460 mg (100%) of **11a,b**, as a thick white oil. In the ^{1}H-NMR spectrum of **11a,b** no distinct resonance pattern, indicative of a mixture of diastereomers, was observed. The diastereomers could neither be differentiated on TLC or capillary GC. The ^{1}H-NMR and IR spectra of **11a,b** were identical to those of **11a** and **11b** (*vide infra*).

(2S,6R)-4-(-)menthyloxymethyl-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**11a**).

The reduction of **9a** (853 mg; 2.4 mmol) with DIBAL (3 mmol) was carried out as described for **9a,b** (see **11a,b**). This afforded 743 mg of crude **11a** as a white solid (*ca.* 100% yield). An analytically pure sample

was obtained by flash chromatography (SiO_2/hexane-ethyl acetate (3:2)) and subsequent crystallization from pet. ether$^{40-60}$/ether (3:1) and recrystallization from hexane. mp: 111-113°C. IR(KBr) ν_{max}: 3000, 2960/2920/2870, 1690(broad;C=O), (1620(w;conj C=C)), 1125/1115, 1082, 1052, 1010, 955, 908/902, 870, 708 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.74(3H,d,J=6.4Hz;CH_3), 0.86(3H,d,J=6.6Hz;CH_3), 0.89(3H,d,J=6.6Hz;CH_3), 1.02-1.71 (7H,m), 1.98-2.36(2H,m), 2.44(1H,d,$J_{2,6}$=4.4Hz;H_2), 2.91(1H,m,$J_{6,5}$=2.6Hz,$J_{6,2}$=4.4Hz;H_6), 3.11(1H,dt,J=4Hz, J=10Hz), 3.91(t)/4.05(t)/4.22(t)/4.38(t)(2H,AB system,J_{AB}=14Hz,$J_{A,6}$=2Hz,$J_{B,6}$=1.4Hz;CH_2O(-)menthyl), 4.69(1H,br s)/4.97(1H,br s)(H_1,H_7), 6.39(1H,dd,J=1.7Hz,J=4.8Hz)/6.52(1H,dd,J=1.7Hz,J=4.8Hz)(H_8,H_9), 7.45 (1H,m,$J_{5,6}$=2.6Hz;H_5). MS(EI) m/e(%): 316(0.12;M^+), 248(1.09;-furan), 1.78(72;-menthene), 160(87;-menthol), 132(55;-menthol,-CO), 110(24;-menthene,-furan), 94(40), 83(100), 68(17;furan$^+$). (Found: C 75.53, H 8.96. Calc. for $C_{20}H_{28}O_3$: C 75.91, H 8.92%.)

(2R,6S)-4-(-)menthyloxymethyl-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**11b**).

The reduction of **9b** (352 mg; 0.98 mmol) with 1.5 mmol of DIBAL, was carried out as described for **9a,b** (see **11a,b**). After flash chromatography (SiO_2/hexane-ethyl acetate (3:2)), 307 mg (99%) of **11b** was obtained, as a colourless oil, which on standing for months in the freezer slowly crystallized. The diasteromeric purity of this product was confirmed by its subsequent conversion into enantiomerically pure (-)**14**. IR(CCl_4) ν_{max}: 2960/2925/2870, 1705(C=O), 1118, 1090, 1050, 950, 912, 875, 700/690 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: identical to the ^{1}H-NMR spectrum of **11a**. MS(CI) m/e(%): 317(24;M+1$^+$), 179(100;-menthene), 161(31; -menthol), 139(70;menthyl$^+$), 137(46;menthene-1$^+$), 111(66;-furan,-menthene), 83(50), 81(29), 69(36;furan+1$^+$). HRMS(CI) m/e: 317.2101 (calc. for $C_{20}H_{29}O_3$ (M+1): 317.2117).

Preparation of racemic **14** *by trans-etherification of* **11a,b**.

A solution of **11a,b** (405 mg; 1.3 mmol) in methanol (30 ml) was heated under reflux with 1.8 ml of a 1 M solution of sodium methanolate in methanol. After one hour an extra amount (1.8 mmol) of sodium methanolate was added and reflux was continued overnight. The reaction mixture was cooled to room temperature and concentrated in vacuo. Work-up was carried out as usual[5]. This afforded 375 mg of a dark coloured oil, containing a mixture of (-)menthol and **14** (^{1}H-NMR data). Flash chromatography (SiO_2/hexane ethyl acetate (1:1)) gave as the first fraction 182 mg of (-)menthol (*ca.* 92%). The second fraction left 58 mg (23%) of pure **14**. The spectral data of this material were in full accord with those reported previously[5]. ^{1}H-NMR analysis of this material with the optical shift reagent Eu(hfc)$_3$[13] revealed a downfield shift for all the resonances and a prominent 1:1 splitting of the methyl signal of the methoxymethyl group.

Preparation of (+)**14** *from* **11a**.

A solution of sodium methanolate in methanol (2 ml; *ca.* 1.7 M) was added to a solution of **11a** (634 mg; 2 mmol) in methanol (25 ml). The resulting mixture was heated under reflux for 20 hrs and then worked-up as described for racemic **14**. The crude product was purified by flash chromatography (SiO_2/hexane-ethyl acetate (1:1)). The resulting, not entirely pure (TLC and ^{1}H-NMR data) (+)**14** (yield not determined) was subsequently subjected to preparative TLC (SiO_2/ethyl acetate). This provided 78 mg (20%) of enantiomerically pure (+)**14**, which after two crystallizations (hexane-ether) afforded fine needlets, mp: 104-106.5°C[18], $[\alpha]_D^{24}$= +77.5°(c=0.6; chloroform). (Found: C 68.39, H 6.03. Calc. for $C_{11}H_{12}O_3$: C 68.74, H 6.29%.)

Preparation of (-)**14** *from partially resolved* **11**.

A mixture of **11b** and **11a** (467 mg; 1.4 mmol of substrate, obtained by DIBAL reduction of the mother liquor retained after crystallization of **9a,b**; main constituent **11b**) was dissolved in 20 ml of methanol. After the addition of 0.5 ml of a 4 M solution of sodium methanolate in methanol the solution was heated under reflux for 17.5 hrs. Subsequent work-up was carried out as described for racemic **14**. Flash chromatography (SiO_2/hexane-ethyl acetate (1:1)) of the crude product afforded 141 mg (52%) of a mixture of (-)**14** and (+)**14**. Part of this mixture was crystallized from hexane. The rest was subjected to ^{1}H-NMR analysis to determine the enantiomeric ratio. Treatment of this sample with Eu(hfc)$_3$ revealed a ratio of 3:1 ± 10%. The crystallized material gave optically and analytically pure (-)**14**, mp: 104-106,2°C[18], $[\alpha]_D^{22}$= -78.4°(c=0.55; chloroform). (Found: C 68.51, H 6.28. Calc. for $C_{11}H_{12}O_3$: C 68.74, H 6.29%.)

(-)-exo-*4,5-epoxy*-endo-*4-methoxymethyl*-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-8- en-3-one*, (-)**15**.

The epoxidation of (-)**14** (109 mg; 0.57 mmol) was carried out with 35% H_2O_2 (0.2 ml) and 0.2 N NaOH (0.2 ml) in a mixture of dichloromethane (1.5 ml) and methanol (1.5 mml) as described previously[6]. This afforded 120 mg (*ca.* 100% yield) of crude (-)**15** as a white solid. Subsequent crystallization from hexane-ethyl acetate gave crystalline (-)**15**, as fine needlets, mp 56-59°C[19], $[\alpha]_D^{22}$= -234°(c=0.53; chloroform). Its spectral data were entirely identical to those of racemic **15**, reported previously[6].

(+)-4,5-epoxy-5-methoxymethyl-2-cyclopentenone, (+)**16**.

Flash vacuum thermolysis[6,20] (16 cm quartz tube/0.14 mbar/preheating temp 75°C/oven temp 360°C) of (-)**15** (103 mg; 0.5 mmol) and subsequent flash chromatography (SiO_2/hexane-ethyl acetate (2:1)) of the crude pyrolysate gave 48 mg (68%) of (+)**16**. The ^{1}H-NMR spectrum of this material showed, in contrast to racemic **16**, no splitting of the methyl singlet of the methoxy methyl group on treatment with Eu(hfc)$_3$. Since its capillary GC output revealed small impurities, it once again was subjected to flash chromatography (SiO_2/hexane-ethyl acetate (3:2)). This afforded *ca.* 40 mg (*ca.* 57%) of analytically (capillary GC data) pure (+)**16**, $[\alpha]_D^{22} = +330°$ (c=0.7; chloroform)[21]. Its spectral data were entirely identical to those of racemic **16**, reported previously[6].

(+)-(trans-4,5-diacetoxy)-5-methoxymethyl-2-cyclopentenone, (+)**19**.

The hydrolysis of (+)**16** (*ca.* 40 mg; 0.28 mmol) and subsequent acylation of the resulting diol was carried out as described previously[6]. Column chromatography (SiO_2/ethyl acetate) of the crude product afforded 44 mg (*ca.* 65% overall yield) of (+)**19**. ^{1}H-NMR analysis with Eu(hfc)$_3$ established the optical purity of this product. Its chemical purity however was insufficient for a reliable determination of optical rotation. A second chromatography (SiO_2/hexane-ethyl acetate (1:1)) left only 19 mg of (+)**19**, that still contained a persistent contamination (*ca.* 15%; capillary GC data). This impurity was presumably an achiral compound, since it revealed only a shift but no splitting of its ^{1}H-NMR signals on treatment with Eu(hfc)$_3$. The twice purified material displayed a specific rotation of +55° (c=0.32; chloroform). Further purification was not attempted. The spectral data, belonging to (+)**19**, were identical to those of racemic **19**, reported previously[6].

X-Ray analysis of (-)**14**.

The crystals are monoclinic, space group $P2_1$ with unit cell $a = 10.266(2)$, $b = 5.093(1)$, $c = 10.419(2)$, $\beta = 118.02(2)°$ with $Z = 2$. Because of the decomposition of the crystal only the first part (intensity decrease down to 70%) of the measurements has been used for the structure analysis and the refinement of the atomic parameters. The intensity data of 1834 reflections were used (up to $\theta = 70°$), with 1023 unique reflections of which 669 were 'observed' with $I > 3\ \sigma(I)$, $R_{merge} = 0.09$ and 0.07 for the 'observed' reflections only. During the refinement of the atomic parameters the hydrogen atoms, except those of the CH_2 group, were located from a difference Fourier map and kept at fixed positions. The conventional agreement factor was $R = 0.046$ for 680 'observed' reflections and 139 variables. Another set of intensities on another crystal was measured to collect data of Friedel pairs for the determination of the absolute configuration. The intensity data of 5634 reflections (intensity decrease down to 75 %) were used (up to $\theta = 70°$), with 1809 unique reflections of which 786 were 'observed' with $I > 3\ \sigma(I)$, $R_{merge} = 0.11$ and 0.08 for the 'observed' reflections only. The Bijvoet coefficient for 55 Friedel pairs was $B = 0.39(13)$, which established the absolute configuration. Atomic parameters are given in Table 1. The molecular configuration and the crystallographic numbering scheme are presented in Figure 1 (see: Results and Discussion).

Table 1.

Atomic positional and vibrational parameters (with esd's) of (-)**14**.

Atom	x	y	z	100 U_{eq}(Å^2)
C1	0.9473(5)	0.2085(9)	0.6145(5)	7.98(24)
C2	1.1040(5)	0.1126(8)	0.7261(5)	7.50(22)
C6	1.1228(5)	0.2620(9)	0.8630(4)	7.49(22)
C7	0.9768(5)	0.4104(10)	0.8050(5)	7.96(24)
C8	0.8572(5)	0.2097(11)	0.7753(5)	8.73(25)
C9	0.8398(6)	0.0867(10)	0.6584(6)	8.60(25)
O10	0.9516(3)	0.4762(6)	0.6608(3)	7.62(14)
C3	1.2277(5)	0.2181(10)	0.6997(5)	8.11(24)
C4	1.3069(5)	0.4055(9)	0.7948(5)	7.37(22)
C5	1.2537(5)	0.4440(10)	0.9001(5)	7.99(23)
O11	1.2974(4)	0.6065(8)	0.9977(4)	10.84(19)
C12	1.4309(6)	0.5569(11)	0.8020(5)	8.8(3)
O13	1.4373(4)	0.5402(10)	0.6740(4)	13.22(26)
C14	1.5458(7)	0.7111(15)	0.6678(7)	13.6(4)

X-Ray analysis of (-)**15**.

The crystals are orthorhombic, space group $P2_1\,2_1\,2_1$ with unit cell $a = 5.685(1)$, $b = 9.780(3)$, $c = 18.157(5)$ Å and $Z = 4$. The intensity data of 1643 reflections were measured (half a sphere up to $\theta = 25°$), with 834 unique reflections of which 486 were observed with $I > 3\,\sigma(I)$, $R_{merge} = 0.08$ for all reflections and 0.02 for the 'observed' reflections only. Because of the small number of data the refinement of the atomic parameters was partly with isotropic and partly with anisotropic temperature factors. The conventional agreement factor was $R = 0.096$ for 486 'observed' reflections and 111 variables. The Bijvoet coefficient for 100 Friedel pairs was $B = 0.38(7)$, which established the absolute configuration. Atomic parameters are given in Table 2. The molecular configuration and the crystallographic numbering scheme are shown in Figure 2 (see: Results and Discussion).

Table 2.

Fractional positional and thermal parameters (with esd's) of (-)**15**.

Atom	x	y	z	$100\,U_{eq}(Å^2)$
C1	-0.764(4)	-0.0959(17)	-0.6505(10)	5.9(8)
C2	-0.630(3)	-0.2124(20)	-0.6802(11)	6.1(7)*
C3	-0.796(4)	-0.3305(22)	-0.7097(12)	6.5(7)*
C4	-0.738(3)	-0.4566(18)	-0.6516(11)	5.0(8)
C5	-0.542(3)	-0.4059(18)	-0.6043(11)	4.8(5)*
C6	-0.473(3)	-0.2624(18)	-0.6195(9)	4.0(5)*
C7	-0.561(3)	-0.1622(20)	-0.5555(13)	7.1(9)
C8	-0.482(6)	-0.0169(22)	-0.5897(13)	8.6(12)
C9	-0.590(4)	0.0138(27)	-0.6377(14)	8.0(11)
O10	-0.8084(27)	-0.1512(15)	-0.5837(8)	7.3(5)*
O11	-0.4925(27)	-0.4940(17)	-0.6632(8)	8.8(7)
O12	-0.963(3)	-0.3305(17)	-0.7420(8)	10.0(7)
C13	-0.910(3)	-0.5575(16)	-0.6399(10)	4.3(7)
O14	-0.859(3)	-0.6422(16)	-0.5902(8)	10.2(8)
C15	-1.023(5)	-0.7475(25)	-0.5723(21)	15.5(16)

* Isotropic temperature factors.

Acknowledgements: We are grateful to the Institute of Crystallography of the University Karlsruhe, Germany, for collecting part of the X-Ray data and to Mr. Mattern for his support and to Dr. H. Behm and Mr. J. M. M. Smits for valuable assistance.

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13. Tris[3-(heptafluoropropyl-hydroxymethylene)-d-camphorato]europium^{III}.
14. The observation that it is often possible to obtain the pure enantiomer by one crystallization of a partially resolved mixture is discussed in Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates and Resolutions*; Wiley & Sons: New York, 1981; p 423.
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17. The sodium mentholate solution can best be prepared shortly before the reaction. This preparation involves stirring of NaH (80% suspension in oil) in dried DMF under a nitrogen atmosphere with a slight excess of (-)menthol, until a glassy, grey/green solution is obtained (*ca.* 2 hrs).
18. This melting point is about 25°C higher than that of racemic **14**. The racemate displays a rather broad melting traject between 76-81°C, which is indicative of a racemic crystal structure (see: Kagan,H.B. *Organische Stereochemie*; Thieme: Stuttgart, 1977; p 92.).
19. Racemic **15** is a thick white oil at room temperature.
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21. A similar high rotation was found for a structurally related compound, *viz.* (+)-4,5-epoxy-3,3-dimethoxy-1-cyclopenten-1-carbaldehyde, see ref 4.