Synthesis of (*R*)- and (*S*)-*O*-Methylcannabispirenone by Desymmetrization of *O*-Methylcannabispirone

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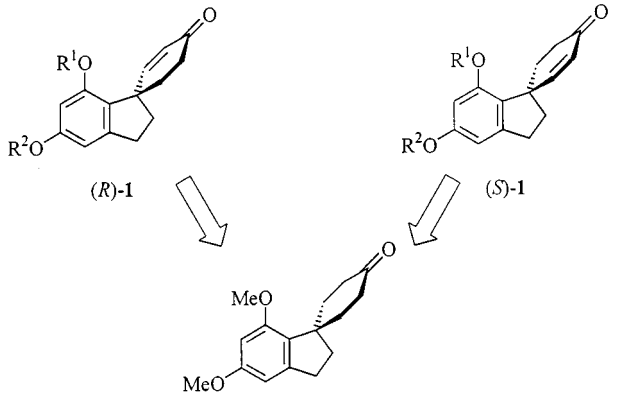
O-Methylcannabispirenone (**1c**) is available by a one-pot protocol that involves enantioselective deprotonation of the ketone **2**, conversion of the lithium enolate thus formed into the β-keto selenide, oxidation and spontaneous elimination. When the C_2-symmetric lithium base **5b** is used for enolate formation, (*S*)-**1c** is obtained in 45–54% *ee* In contrast, the lithium amide **6b**, derived from the diamine **6a**, gives the enantiomeric enolate predominantly, thus leading to (*R*)-**1c**. The norephedrine-derived base **6b**, hitherto not applied for enantioselective deprotonations of *meso*-ketones, provides a higher enantioselectivity in the formation of the spirenone **1c** (84% *ee*) than the amide base **5b**. According to known procedures, the dimethyl ether **1c** can be converted into the nonhallucinogenic natural products cannabispirenone A (**1a**) and B (**1b**). The enantiomeric excess of (*R*)- and (*S*)-**1c** was determined by treatment with (*R*,*R*)-diol **8**, leading to the diastereomeric acetals **9** and **10**.

Introduction

Cannabispirenones A (**1a**) and B (**1b**) belong to a group of spirocyclic, nonhallucinogenic natural products that can be isolated from *Cannabis sativa*.[1] They are considered to be interesting compounds because of their various biological activities. Thus, they have been reported to exert antiproliferative effects on HEp-2 cells,[2] to influence the plasmid transfer in *Escherichia coli*,[3] and to lower the intraocular pressure.[4] Within the family of naturally occurring cannabispiranes, the enones **1a** and **1b** are the only chiral ones. Several studies have led to syntheses of the racemic compounds **1**,[5] as well as to an enantioselective route that provided (+)-**1a** in approximately 50% enantiomeric excess.[6]

It turns out that the opposite enantiomers of cannabispirenone A (**1a**) occur in different plants and that the optical purities differ considerably depending on the natural sources that provide the samples. Thus, cannabispirenone A (**1a**) isolated from Indian *Cannabis* displays a positive optical rotation ($[\alpha]_D^{20} = +34$) whereas the compound found in Thai *Cannabis* shows a an $[\alpha]_D^{27}$ value of −231, both data having been recorded in methanol. The (*R*)-(+) and the (*S*)-(−) configurations were assigned to cannabispirenone A (**1a**) based on ORD spectroscopy.[6,7] However, the optical rotation did not prove itself to be a reliable method for the determination of the optical purity of natural or synthetic samples of cannabispirenone A (**1a**) and *O*-methylcannabispirenone (**1c**).[6,7] In this article, we report an enantioselective route to (*S*)-(−)- and (*R*)-(+)-*O*-methylcannabispirenone (**1c**) using as the key step the desymmetrization of the spirone **2** with chiral lithium amide bases (Scheme 1). A one-pot protocol has been developed, based on deprotonation, selenation of the enolate, oxidation, and elimination, so that a direct enantioselective conversion of a *meso*-ketone into a chiral enone is feasible. Furthermore, the specific rotation of both enantiomers of *O*-methylcannabispirenone, whose conversion into the natural product **1a** and **1b** is known,[5b,6] is correlated with the enantiomeric excess.



1	R^1	R^2
a	H	Me
b	Me	H
c	Me	Me

Scheme 1

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Results and Discussion

The achiral cannabispirone **2** is available from indanone **3**[8] in four steps by following known procedures. For this purpose, the aldehyde **4**, prepared from indanone **3**, was submitted to a Robinson annulation[5c,5d] followed by a catalytic hydrogenation[5b] of the spirenone **1c** formed thereby.

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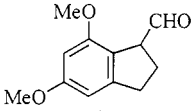

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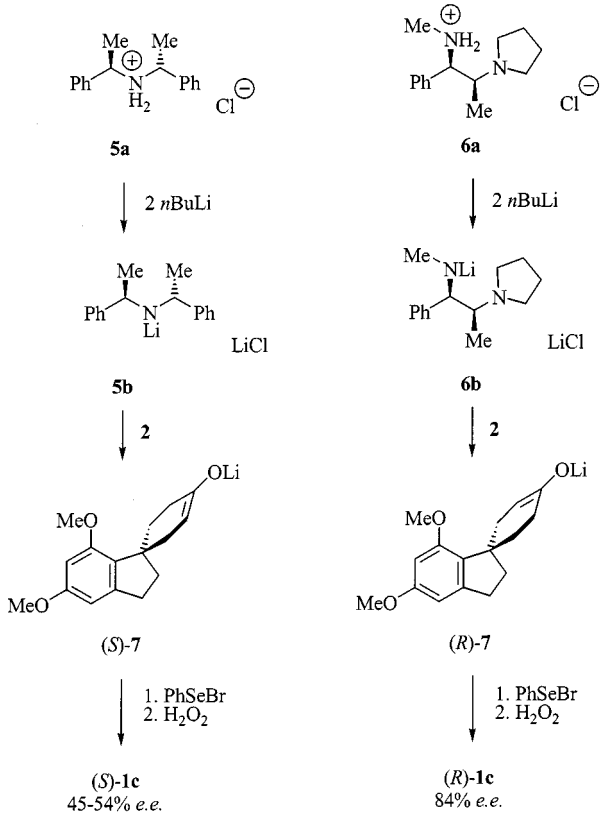
When ketone **2** is deprotonated, the quaternary carbon atom becomes a stereogenic center, and enantiomeric enolates (*R*)-**7** and (*S*)-**7** result. As the deprotonation of carbonyl compounds by lithium amide bases is known to be an irreversible process,[9] no interconversion of the enantiomeric enolates (*R*)- and (*S*)-**7** is expected.

As shown by Simpkins[10] and Koga,[11] asymmetric deprotonation of prochiral cyclic ketones is feasible by means of chiral lithium amide bases, and a series of these reagents have been developed in recent years.[12] Here, the C_2 symmetric lithium amide **5b**[13] and the norephedrine-derived base **6b**[14] have been applied for a first enantioselective deprotonation of cannabispirone **2**. Both lithium amides **5b** and **6b** were generated from the corresponding hydrochlorides **5a** and **6a** (Scheme 2), so that equimolar amounts of lithium chloride were present during the deprotonation of the ketone **2**.[15] Hitherto, the lithiated diamine **6b** has not been used for the enantioselective formation of lithium enolates.[16]

First, the (*R*,*R*)-configured lithium amide **5b** was chosen for the deprotonation of the spirone **2**. The lithium enolate **7** thus formed was treated in situ with phenyl selenyl bromide or chloride. Neither the β-keto selenide thus formed nor the corresponding selenoxide (generated by means of hydrogen peroxide) had to be isolated,[17] so that spirenone **1c** could be prepared in a one-pot reaction from the ketone **2**.[18] The optical rotation ($[\alpha]_D^{20}$ = −80 to −95) revealed that the (*S*)-enantiomer of *O*-methylcannabispirenone **1c** had formed.

When, on the other hand, the lithium amide **6b**, generated from (1*R*,2*S*)-*N*-methyl-1-phenyl-2-(1-pyrrolidinyl)-1-propylamine (**6a**) was used, the enantiomeric lithium enolate (*R*)-**7** obviously formed in excess. Thus, application of the elimination protocol outlined above gave (*R*)-*O*-methylcannabispirenone (**1c**) with a specific rotation of +142. A remarkably higher enantioselectivity of 82−84% *ee* was reached with the lithium base **6b**, whereas the C_2 symmetric base **5b** gave the opposite enantiomer of **1c** in 45−54% *ee*.

Assuming that the benzyl substituent at the quaternary carbon center of the spirone **2** occupies the equatorial position,[19] the (*R*,*R*)-lithium amide **5b** obviously abstracts the axial proton at the pro-*S* carbon atom in the α-position of

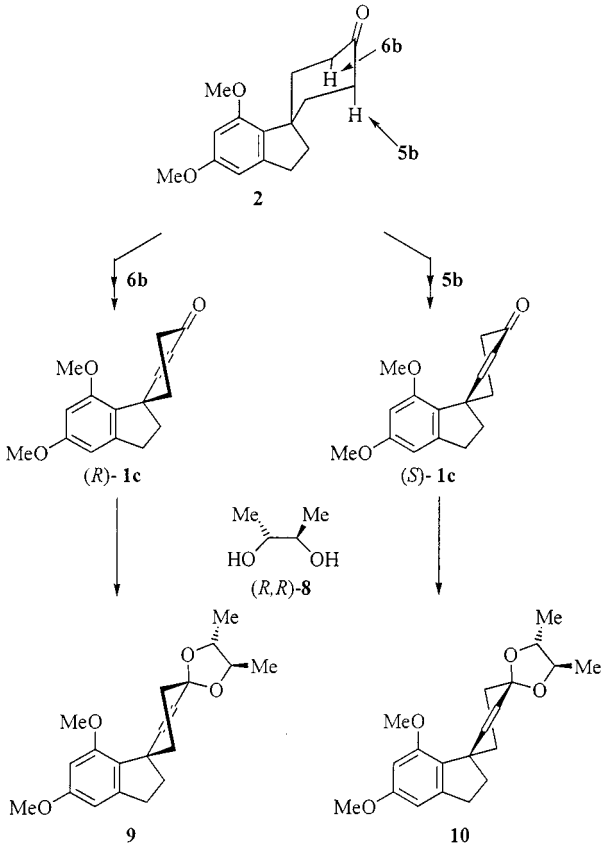


Scheme 2

the keto group. This is in accordance with the outcome of the deprotonation of 4-*tert*-butylcyclohexanone by (*R*,*R*)-**5b**.[12b,13] However, the axial proton in the pro-*R* α-keto position of the spirone **2** seems to be attacked by the (1*R*,2*S*)-enantiomer of the lithium base **6b**. The isolated chemical yield of purified (*R*)- or (*S*)-*O*-methylcannabispirenone (**1c**) amounted to 35 to 42.6% (65 to 76%, based on converted ketone **2**).

In view of the fact that the optical rotations reported for the natural products **1a** and **1b**, as well as synthetic and semisynthetic **1c**, differ considerably depending on the source of the sample, the specific rotation cannot be considered to be a reliable measure of the enantiomeric excess. Thus it was felt that the enantiomeric ratio in the samples of **1c** obtained above should be determined unambiguously. First, racemic **1c** and (*R*)- and (*S*)-**1c** were investigated by ^{1}H NMR spectroscopy in the presence of the chiral shift reagent Eu(hfc)$_3$.[20] The enantiomers of **1c** revealed a shift difference of 0.021 ppm [molar ratio of **1c**:Eu(hfc)$_3$ = 1:4.6] in the signal of the vinylic proton in the 2-position. The doublet of the (*S*)-enantiomer of **1c** appeared at higher, and that of the (*R*)-enantiomer at lower, field. Nevertheless, the determination of the enantiomeric ratio in nonracemic samples of **1c** turned out to be difficult as a base-line separation of the peaks could not be reached. A line shape analysis, performed with the program "Microcal Origin"[21] revealed an enantiomeric ratio of (*R*)-**1c**:(*S*)-**1c** of about 90:10 in a sample that was obtained from the deprotonation of **2** with the norephedrine-derived base **6b**.

Because of the uncertainty connected with the europium shift-reagent measurements, an unambiguous method for the determination of the enantiomeric excess in samples of (*R*)- and (*S*)-**1c** was necessary. For this purpose, (*R*)-spirenone **1c** was converted into the acetal by reaction with the C_2 symmetric (*R*,*R*)-butanediol **8** (Scheme 3). The diastereomeric acetals **9** and **10** clearly differ in their ^{1}H NMR spectra. Characteristic chemical shift differences were displayed by the vinylic protons of the two diastereomers (see Exp. Sect.). A ratio of 92:8 was detected for the diastereomers **9/10** prepared from the above mentioned sample of (*R*)-**1c**. Thus the result obtained by the europium shift reagent could be confirmed. From the 92:8 diastereomeric ratio of the acetals **9/10**, an enantiomeric excess of 84% can be deduced for the sample of (*R*)-**1c**, originating from enantioselective deprotonation by the lithium amide **6b**. When, on the other hand, samples of (*S*)-**1c**, generated by means of the base **5b**, were acetalized with (*R*,*R*)-diol **8**, the diastereomer **10** formed predominantly, as expected. Based on the ^{1}H NMR spectra of the mixture **9/10**, the diastereomeric ratio could be determined and the enantiomeric excess of (*S*)-**1c** could be deduced. Depending on the temperature that had been used during the deprotonation of the ketone **2**, the enantiomeric excesses of (*S*)-**1c** ranged from 45 to 54%.



Scheme 3

Conclusion

The protocol described above offers a simple route to nonracemic *O*-methylcannabispirenone **1c** by desymmetrization of the *meso*-compound **2**. For this purpose, a one-pot procedure for the enantioselective introduction of a conjugated double bond into the spirone **2** has been elaborated. As the dimethyl ether **1c** can be converted selectively into either cannabispirone A (**1a**) or B (**1b**),[5b,6] a simple route to these chiral natural products is opened. The key step, the enantioselective enolate formation, is most effectively accomplished by the norephedrine-derived lithium amide **6b**, a reagent that, hitherto, has not been used for the enantioselective deprotonation of *meso*-ketones. It permits to obtain the (*R*)-cannabispirenones **1** in 84% *ee* The enantiomeric compounds (*S*)-**1a,b**, naturally occurring substances as well, are available from (*S*)-**1c** by using the lithium amide **5b**. Furthermore, they will be accessible by the same protocol, when the corresponding lithium base *ent*-**6b** is applied, which is derived from (1*S*,2*R*)-norephedrine.

Experimental Section

Melting points (uncorrected): Büchi 540. NMR: Varian VXR 300, Bruker AM 200 SY and DRX 500. The spectra were recorded with TMS as internal standard, except for the spectra that were measured in D_2O (external standard). MS: Varian MAT 311 A and Finnigan INCOS 50. Specific rotations: Perkin−Elmer 314. TLC: DC-Alufolien Sil-60G/UV254 (Merck). CC: Kieselgel 60, mesh size 0.04−0.063 mm (Merck).

Solvents and Reagents: The generation and reactions of the lithium enolates were carried out under an atmosphere of dry nitrogen. Tetrahydrofuran (THF) and diethyl ether were predried with KOH and distilled under N_2 from sodium/benzophenone. They were taken from the reaction flask, which was closed by a septum, with syringes or cannulas. *n*-Butyllithium was purchased as a solution in *n*-hexane. Reactions at temperatures below −20 °C were monitored by a thermocouple connected to a resistance thermometer (Ebro). General remarks concerning the handling of lithium enolates and other organolithium compounds are given in ref.[22]

***rac*-2′,3′-Dihydro-5′,7′-dimethoxyspiro{2-cyclohexene-1,1′-[1*H*]-inden}-4-one (*O*-Methylcannabispirenone) (1c)** was prepared from aldehyde **4** according to refs.[5c,5d]

2′,3′-Dihydro-5′,7′-dimethoxyspiro{cyclohexane-1,1′-[1*H*]inden}-4-one (*O*-Methylcannabispirone) (2): A mixture of *rac*-**1c** (0.170 g, 0.66 mmol), THF (4 mL), and palladium on charcoal (10 mg) was hydrogenated in a 25-mL flask at atmospheric pressure. When the uptake of hydrogen had ceased, the mixture was filtered and the filtrate was concentrated in a rotary evaporator. The oily residue was submitted to column chromatography (*n*-hexane/ethyl acetate, 3:1) to give 0.168 g (97%) of yellowish solid **2**; R_f = 0.55; m.p. 125 °C {ref.[5e] m.p. 123−124 °C}.

(*R*,*R*)-*N*-(1′-Phenylethyl)-1-phenylethylamine Hydrochloride (5a) was prepared according to ref.[23]

(1*R*,2*S*)-*N*-Methyl-1-phenyl-2-(1-pyrrolidinyl)-1-propanamine Hydrochloride (6a): A 250-mL two-necked flask, equipped with a reflux condenser and an inlet tube, was charged with 100 mL of dry diethyl ether and (1*R*,2*S*)-*N*-methyl-1-phenyl-2-(1-pyrrolidinyl)-1-

propanamine (2.62 g, 12.06 mmol), which had been prepared according to ref.[14] {$[\alpha]_D^{20} = -22.6$ (c = 1.0 in chloroform)}. A stream of hydrogen chloride gas was passed through the solution for 1 h. The white precipitate formed thereby was filtered and dried under an oil pump vacuum to give 3.09 g (99%) of colorless, crystalline **5a**; m.p. 223 °C. $[\alpha]_D^{20} = +14.5$ (c = 1.0 in water). ^{1}H NMR (D_2O, 500 MHz): δ = 1.50 (d, J = 6.6 Hz, 3 H, CH_3CH_2), 1.70−1.95 [m, 4 H, $N(CH_2CH_2)_2$], 2.28 (s, 3 H, NCH_3), 3.14−3.31 [m, 4 H, $N(CH_2CH_3)_2$], 4.20 (m, 1 H, 2-H), 4.39 (d, J = 10.0 Hz, 1 H, 1-H), 7.41−7.55 (m, 5 H, aromatic H). ^{13}C NMR (D_2O, 75 MHz): δ = 11.4 (C-3), 24.9 ($N-CH_2-CH_2$), 32.8 (NCH_3), 52.9 ($N-CH_2-CH_2$), 62.3 (C-1 or C-2), 65.1 (C-2 or C-1), 129.0, 129.6, 131.1, 132.2 (aromatic C).

General Procedure for the Conversion of *O*-Methylcannabispirone (2) into (*R*)- or (*S*)-1c: A 50-mL two-necked flask was equipped with a magnetic stirrer, connected to the combined nitrogen/vacuum line, charged with 2.0 mmol of the corresponding hydrochloride **5a** or **6a**, and closed with a septum. The air in the flask was replaced by nitrogen, and dry THF (10 mL) was injected through the septum with a syringe. The suspension thus formed was cooled to −78 °C, and a 1.6 M solution of *n*-butyllithium in *n*-hexane (2.5 mL, 4.0 mmol) was added to the vigorously stirred suspension with a syringe. Stirring was continued for 1 h at −78 °C and for 10 min at 0 °C. Then, the mixture was cooled to −110 °C. In a second flask, ketone **2** (0.26 g, 1.0 mmol) was dissolved in 2 mL of dry THF. A slight nitrogen overpressure was maintained in this flask while the solution of **2** was transferred by cannula into the two-necked flask within 10 min. During the course of this transfer the latter flask was evacuated slightly. Stirring was continued for 3 h at −110 °C. A solution of phenyl selenyl bromide (0.283 g, 1.20 mmol) in THF (2 mL), again prepared under nitrogen, was added by syringe. The mixture was allowed to reach 0 °C, and then treated with water (1.5 mL) and acetic acid (0.45 mL). Thereafter a 30% aqueous solution of hydrogen peroxide (0.69 mL, 6 mmol) was added by syringe. After the mixture had been stirred for 1 h at 0 °C and for 3 h at room temperature, a 1:1 mixture of diethyl ether and *n*-hexane (30 mL) was added. The mixture was transferred into a separating funnel, washed with water (50 mL), 3% hydrochloric acid (20 mL), water (50 mL) and brine (50 mL) and dried with $MgSO_4$. The solvent was removed in a rotary evaporator, and the residue was submitted to column chromatography (*n*-hexane/ethyl acetate, 5:1). Unchanged spiranone **2** was removed (R_f = 0.55), and spirenone **1c** was isolated and dried under an oil pump vacuum. Following this procedure we obtained:

(*R*)-2′,3′-Dihydro-5′,7′-dimethoxyspiro{2-cyclohexene-1,1′-[1*H*]-inden}-4-one (*O*-Methylcannabispirenone) (1c): Prepared by deprotonation of **2** (0.260 g, 1.0 mmol) with the lithium amide **6b** generated from **6a** (0.51 g, 2.0 mmol). Column chromatography gave **1c** (0.086 g, 33%) and recovered **2** (0.128 g, 49%). The yield of **1c** was 65%, based on converted **2**. $[\alpha]_D^{20} = +142$ (c = 1 in ethanol), {ref.[1d] (*S*)-**1c**, prepared from naturally occurring (*S*)-**1a**: $[\alpha]_D^{23} = -135$ (c = 0.034 in ethyl acetate)} {ref.[6] synthetic (*R*)-**1c**: $[\alpha]_D = +148$ (c = 1.01 in ethanol)}, m.p. 104−106 °C; [ref.[1d] m.p. 110−112 °C]. The ^{1}H NMR spectroscopic data are in accordance with those of a sample of **1c** that was obtained from methylation of natural cannibispirenone A.[1d] The ^{13}C NMR spectroscopic data correspond to those of synthetic **1c**.[5b]

(*S*)-2′,3′-Dihydro-5′,7′-dimethoxyspiro{2-cyclohexene-1,1′-[1*H*]-inden}-4-one (*O*-Methylcannabispirenone) (1c): Prepared by deprotonation of **2** (0.523 g, 2.0 mmol) at −110 °C with the lithium amide **5b** generated from **5a** (1.05 g, 4.0 mmol). Column chromatography gave **1c** (0.182 g, 35%) and recovered **2** (0.225 g, 43%). The yield of **1c** was 61.4%, based on converted **2**; 0.182 g (35%). $[\alpha]_D^{25} = -95.2$ (c = 1 in ethanol). Deprotonation of **2** (0.260 g, 0.98 mmol) at −78 °C led to (*S*)-**1c** in 42.6% yield (0.110 g) and recovered **2** (0.115 g, 44%). The yield of **1c** was 76%, based on converted **2**. $[\alpha]_D^{20} = -81.7$ (c = 1 in ethanol).

(4*R*,5*R*,4′*R*)- and **(4*R*,5*R*,4′*S*)-2′′,3′′-Dihydro-5′′,7′′-dimethoxydispiro{1,3-dioxolane-2,1′-(2-cyclohexene)-4′,1′′-[1*H*]-indene} (9 and 10):** A 100-mL one-necked flask was charged with **1c** (0.129 g, 0.50 mmol), (*R*,*R*)-**8** (0.055 mL, 0.6 mmol) and 70 mL of benzene. *p*-Toluenesulfonic acid (5 mg) was added, and the flask was equipped with a magnetic stirrer and a Soxhlet extractor and filled with molecular sieves (4 Å). The mixture was refluxed for three days under nitrogen. When the solution had cooled to room temperature, it was washed with an aqueous solution of Na_2CO_3 and with water. The organic layer was dried with Na_2CO_3, and the solvent was removed in a rotary evaporator. The residue was exposed to oil pump vacuum for several hours to give oily **9/10** in quantitative yield. $[\alpha]_D^{20} = -62.6$ (c = 1.2 in ethanol) for a sample that contained **9** and **10** in a ratio of 1:3.2.

9: ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.75−2.30 (m, 6 H, 2′′, 5′, 6′-H), 1.2 (m, 6 H, $OCHCH_3$), 2.65−2.90 (m, 2 H, 3′′-H), 3.50−3.75 (m, 2 H, 4-H, 5-H), 3.67 and 3.70 (2s, 3H each, OCH_3), 5.46 (dd, J = 10.0, J = 1.1 Hz, 1 H, 3′-H), 5.76 (dd, J = 10.0, J = 1.1 Hz, 1 H, 2′-H), 6.18−6.20 (m, 1 H, aromatic H), 6.26−6.29 (m, 1 H, aromatic H). ^{13}C NMR (125 MHz): δ = 16.6, 16.8, 30.0, 31.2, 33.2, 36.9, 48.2, 55.3, 55.4, 77.8, 78.1, 97.2, 100.6, 104.6, 125.7, 129.0, 140.2, 146.1, 157.4, 160.7.

10: The ^{1}H NMR spectrum differs from that of **9** in: δ = 5.53 (dd, J = 10.0, J = 0.9 Hz, 1 H, 3′-H), 5.75 (dd, J = 10.0, J = 1.1 Hz, 1 H, 2′H). ^{13}C NMR (125 MHz): δ = 17.2, 17.3, 30.5, 31.1, 33.7, 38.3, 48.2, 55.3, 55.4, 78.2, 78.6, 97.2, 100.7, 104.8, 126.2, 128.7, 140.1, 146.3, 157.5, 160.6. MS (70 eV, EI): m/z (%) = 330 (19) [M^+], 302 (41) [$M^+ - CO$], 216 (23), 187 (29), 149 (24), 135 (27), 57 (100).

Acknowledgments

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[18] The isolation (cf.: ref.[13]) of the silyl enol ether **7** (Me_3Si instead of Li) prior to the selenation is not necessary; it neither enhances the chemical yield nor the enantioselectivity.
[19] This assumption is based on a crystal structure analysis of cannabispiran, see: ref.[1b]
[20] $Eu(hfc)_3$ = tris[3-(2,2,3,3,4,4,4-heptafluoro-1-hydroxybutylidene)-*d*-camphorato]europium (Aldrich).
[21] Origin Version 6; www.originlab.com.
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