Enantioselective Synthesis of (+)-Royleanone from Sulfinyl Quinones

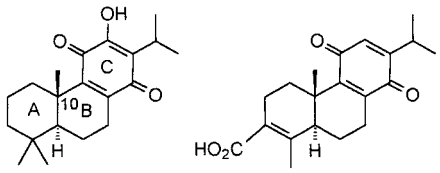
M. Carmen Carreño,* José L. García Ruano,* and Miguel A. Toledo[a]

Abstract: A convergent enantioselective synthesis of (+)-royleanone (**1**) is described starting from enantiomerically pure (*S*)-3-hydroxy-2-isopropyl-5-*tert*-butylsulfinyl-*p*-benzoquinone, which is readily available from 3-isopropyl-1,2,4-trimethoxybenzene and 1,3,3-trimethyl-2-vinylcyclohexene. The key step is a tandem asymmetric Diels–Alder reaction/pyrolytic sulfoxide elimination process.

Keywords: asymmetric synthesis · cycloadditions · natural products · quinones · royleanone · sulfoxides

Introduction

Among the components of the abietane diterpenoid family, tricyclic quinones such as (+)-royleanone (**1**) and (+)-triptoquinone A are of special interest because of their biological properties.[1] For instance, royleanone was used in



the Himalaya region as an insecticide and disinfectant, and shows modest antitumor activity against several types of cancer, and triptoquinone A is being used in the treatment of arthritis.[2] These compounds share the common features of a tricyclic perhydrophenanthrene skeleton and an isopropyl substituent at the C ring as well as an angular methyl group at the A/B ring junction.[3] Some of them have additional oxygenated functions or olefin moieties at various positions.

Royleanone (**1**), which was first isolated by Edwards et al.[4] in 1962 from the root of *Inula Royleana* D.C., was also found in other plants.[2, 5] The asymmetric syntheses of **1** reported up to date rely on the transformation of abietic acid derivatives.[6] Racemic **1** has been the subject of several total syntheses. The main strategies used for the construction of the tricyclic framework are based on Robinson annulation,[7] and Friedel–Crafts intramolecular acylation.[5c, 8] The Dötz reaction of a vinyl chromium carbene complex[9] has also been successfully used for this goal. More recently, a photochemical aromatic annulation has been applied to the synthesis of several diterpenoid quinones.[10] One of the more convergent approaches reported up to date relies on a Diels–Alder reaction between an adequately substituted benzoquinone and 1,3,3-trimethyl-2-vinylcyclohexene as a key step.[11]

In connection with our research devoted to asymmetric Diels–Alder reactions with enantiomerically pure sulfinyl quinones,[12] we focused on these diterpenoid quinones bearing the angularly fused tricyclic skeleton with the aim of finding a general approach to efficiently create the C-10 asymmetric center. The protocol takes advantage of the tandem Diels–Alder reaction/pyrolytic sulfoxide elimination which occurs when such sulfinyl quinones are allowed to react as dienophiles with acyclic dienes, and has been already applied to the efficient construction of other polycyclic quinones.[13] Herein we report an enantioselective and convergent synthesis of the natural isomer of royleanone (**1**) using a stereocontrolled Diels–Alder reaction between an enantiomerically pure sulfinyl quinone **4** and 1,3,3-trimethyl-2-vinylcyclohexene (**2**)[14] as the key step.

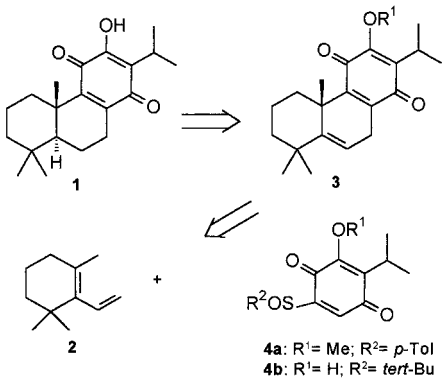
Results and Discussion

As shown in the retrosynthetic scheme (Scheme 1), the tricyclic derivative **3**, an immediate precursor of the natural product, can be synthesized through the stereoselective Diels–Alder reaction of an enantiomerically pure sulfinyl quinone **4**.

We initially attempted to use (*S*)-3-methoxy-2-isopropyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (**4a**)[15] as the dienophile; however, cycloaddition of **4a** with vinylcyclohexene **2** did not occur in refluxing toluene nor in other solvents (CH_2Cl_2, mixtures THF:H_2O, H_2O). The presence of Lewis acids promoted the formation of 3-methoxy-2-isopropyl-5-(*p*-tolyl-

[*] Prof. M. C. Carreño, Prof. J. L. García Ruano, Dr. M. A. Toledo
Departamento de Química Orgánica C-I
Universidad Autónoma
E-28049 Madrid (Spain)
Fax: (+34) 913973966
E-mail: carmen.carrenno@uam.es

0947-6539/00/0602-0288 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 2

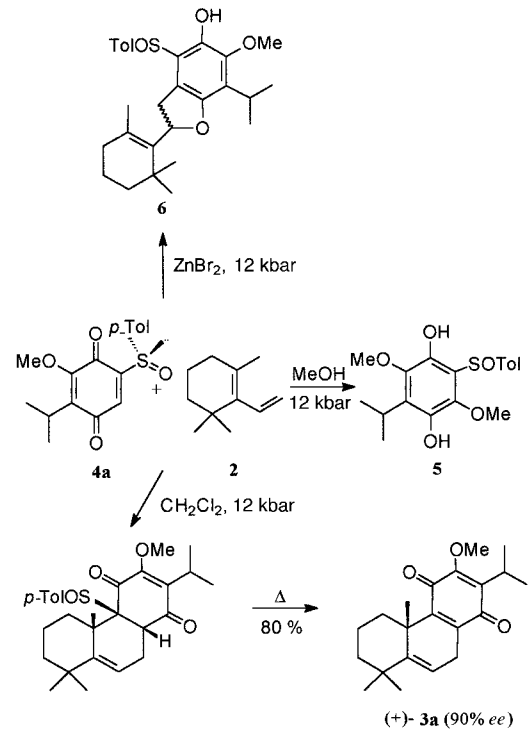


Scheme 1. Retrosynthetic scheme for the synthesis of **1**.

sulfinyl)-1,4-hydroquinone ($BF_3 \cdot OEt_2$) and/or the polymerization of the diene and decomposition to uncharacterized products [$Sc(OTf)_3$, $SnCl_4$] after long reaction times. The Diels–Alder adduct was only detected under high-pressure conditions (CH_2Cl_2, 12 kbar, 2 days). Under these conditions, a mixture of the initial adduct and the tricyclic derivative **3a**, resulting from the pyrolytic elimination of the sulfoxide, were obtained. Finally, the desired quinone **3a** was obtained in pure form after heating the resulting reaction mixture to complete the pyrolysis of the initially formed adduct (Scheme 2). Compound **3a** was thus isolated in 80% yield and was demonstrated to be enantiomerically enriched (90% *ee*).[16]

We further tried to improve the 90% enantiomeric excess by effecting the reaction between **4a** and **2** in other solvents (diethyl ether, CH_3CN, H_2O, 12 kbar), but the resulting compound **3a** showed always a similar 90% *ee*. With MeOH (12 kbar) as solvent, 1,4-dihydroxy-2-isopropyl-3,6-dimethoxy-5-(*p*-tolylsulfinyl)benzene (**5**) was formed, and working in the presence of $ZnBr_2$ (CH_2Cl_2, 12 kbar) led to a complex reaction mixture, which contained, among other products, a benzofuran derivative **6**, which has not been fully characterized. A similar structure resulting from an initial Michael-type addition of the vinyl moiety of **2** to C-6 of a benzoquinone derivative, followed by enolization of the intermediate and further cyclicization had been already reported by Engler et al.[11]

In accordance with our previous results,[12, 13] the diastereoselectivity of Diels–Alder reactions with 2-*p*-tolylsulfinyl quinone **4a** must be explained on steric grounds under the assumption that the major reaction involves a conformation of the sulfinyl quinone in which the sulfinyl oxygen atom is placed *s-cis* with respect to the dienophilic double bond (see Scheme 2). The favored approach of the diene from the face

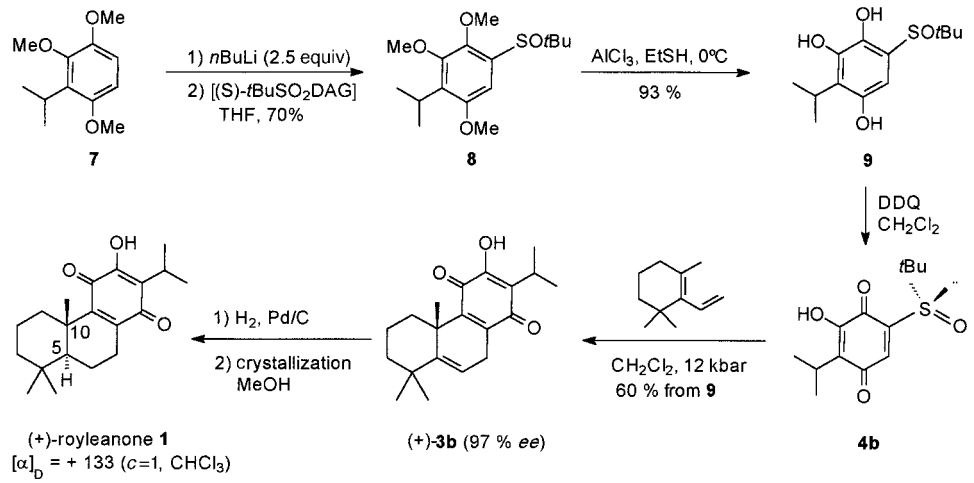


Scheme 2.

bearing the lone pair of electrons at sulfur explains the formation of (*S*)-**3a** as the major product. Based on this mechanistic assumption, we reasoned that the enantiomeric excess of the final tricyclic quinone could be improved by using a new chiral quinone **4b** bearing the bulkier *tert*-butyl sulfoxide. Compound **4b** was synthesized by using 2-isopropyl-1,3,4-trimethoxybenzene (**7**) according to the sequence given in Scheme 3. The orthometalation/sulfinylation process with (*S*)-diacetone glucose *tert*-butylsulfinate [(*S*)-*tert*-$BuSO_2$-DAG][17] afforded a 85:15 mixture of **8** and its regioisomer from which sulfoxide **8** was isolated in 70% yield. Direct oxidative demethylation was attempted with cerium ammonium nitrate (CAN), AgO, and $Pb(OAc)_4$; however, the desired 3-methoxy-2-isopropyl-5-*tert*-butylsulfinyl-*p*-benzoquinone was not formed. We finally synthesized the hydroxy-substituted (*S*)-*tert*-butyl sulfinyl-*p*-benzoquinone **4b**, after complete demethylation of **8** with $AlCl_3$ in EtSH followed by oxidation[18] of the intermediate hydroquinone **9** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Purification of **4b** by chromatography on silica gel produced different degradation products. Therefore, **4b** was employed in the subsequent Diels–Alder reaction without further purification.

Reaction of (*S*)-3-hydroxy-2-isopropyl-5-*tert*-butylsulfinyl-1,4-benzoquinone (**4b**) with diene **2** in CH_2Cl_2 at 12 kbar gave the tricyclic derivative **3b** in 60% overall yield (from **9**) and >97% *ee*.[19] The *tert*-butyl sulfoxide group present in dienophile **4b** proved to be more efficient in the asymmetric cycloaddition than the analogous *p*-tolyl sulfoxide group, corroborating the role of steric effects in the control of the diene approach occurring from the less hindered face of the sulfinylquinone, which reacts in its *s-cis* conformation.[12]

Abstract in Spanish: *La síntesis enantioselectiva de la (+)-Royleanona **1** se ha logrado de forma convergente a partir de la (S)-3-hidroxi-2-isopropil-5-terc-butilsulfinil-p-benzoquinona enantioméricamente pura (obtenida a partir de 3-isopropil-1,2,4-trimetoxibenceno) y 1,3,3-trimetil-2-vinilciclohexeno. La etapa clave corresponde a una reacción de Diels-Alder asimétrica seguida de la eliminación pirolítica del sulfóxido que tiene lugar de forma espontánea.*



Scheme 3. Synthesis of **1** from **7** via the key intermediate **4b**.

Having the tricyclic quinone **3b** in hand, the reduction of the double bond was the only step to complete the total synthesis of **1**. The formation of the *trans*-fused natural compound from tricyclic analogues of **3b** in the hydrogenation step was known to be difficult.[7b, 20] Therefore, we carried out the catalytic hydrogenation by using various catalysts (Pd/C, PtO_2 or [Ir(cod)py(PCy_3)]PF_6 (Crabtree catalyst[21]); cod = cyclooctadiene, py = pyridine) and solvents (AcOEt, AcOEt mixed with EtOH and H_2O or amines, AcOH). In all cases, we obtained mixtures of royleanone (**1**) and its C-5 epimer; the best result was achieved working with H_2 at atmospheric pressure in the presence of Pd/C and in a 1:1 mixture of AcOEt:AcOH. Under these conditions a 60:40 mixture of royleanone (**1**) and the *cis*-fused isomer was formed from which the former could be isolated in pure form after crystallization from MeOH. The resulting royleanone (+)-**1** was thus isolated in 35% yield and was shown to have all the characteristics described in the literature for the natural product.[1] That the natural enantiomer was obtained confirmed the 10*S* absolute configuration for all the precursors, including compounds **3a** and **3b** which resulted from the asymmetric Diels–Alder reaction.

In summary, we have reported a convergent asymmetric total synthesis of the terpene quinone royleanone (**1**) from readily available 3-isopropyl-1,2,4-trimethoxybenzene and 1,3,3-trimethyl-2-vinylcyclohexene in five steps and 13% overall yield. The key step is the construction of the tricyclic framework in a one-pot, tandem asymmetric Diels–Alder reaction of enantiomerically pure sulfinyl benzoquinone **4b**/pyrolytic sulfoxide elimination process.

Experimental Section

(*S*)-1,4-Dihydroxy-2-isopropyl-3,6-dimethoxy-5-(*p*-tolylsulfinyl)benzene (5): A solution of (*S*)-2-isopropyl-3,6-dimethoxy-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (**4a**) (60 mg, 0.19 mmol) and 1,3,3-trimethyl-2-vinylcyclohexene (**2**) (0.08 mL) in MeOH (2 mL) was submitted to a pressure of 13 kbar for three days. The crude mixture was concentrated in vacuo and purified by chromatography (hexane:AcOEt 4:1): $[\alpha]_D^{20} = 9.9$ ($c = 1.7$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta = 10.52$ (br. s, 1H; OH), 7.68 and 7.28 (4H, ^3J(H,H) = 9 Hz, 2H; *p*-Tol), 5.06 (br. s, 1H; OH), 3.86 (s, 3H; OCH_3), 3.79 (s, 3H), 3.46 (sept, 1H, J = 7.1 Hz), 2.37 (s, 3H), 1.29 (t, 6H, J = 7.1 Hz); ^{13}C NMR: $\delta = 146.6$, 144.1, 142.3, 140.6, 139.7, 138.3, 133.7, 130.1 (2C), 125.2 (2C), 114.1, 61.9, 60.9, 25.8, 21.4, 20.8, 20.5.

(*S*)-12-Methoxy-11,14-dioxoabieta-5,8,12-triene (3a): A solution of (*S*)-2-isopropyl-3,6-dimethoxy-5-(*p*-tolylsulfinyl)-1,4-benzoquinone **4a** (475 mg, 1.49 mmol) and 1,3,3-trimethyl-2-vinylcyclohexene (**2**) (0.7 mL) in CH_2Cl_2 (2 mL) was submitted to a pressure of 13 kbar for three days. The crude mixture was refluxed for 3 h to complete the pyrolytic elimination of *p*-toluenesulfenic acid. The resulting solution was concentrated in vacuo and purified by chromatography (hexane to separate the excess of diene followed by hexane:AcOEt 100:1). Compound **3a** was obtained as a yellow solid (80% yield, 90% *ee*): m.p.: 81–82 °C (methanol), ref.[11] 78.5–79 °C $[\alpha]_D^{20} = -274$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR: $\delta = 5.70$ (dd, 1H, $J = 5.3$ and 2.4 Hz), 3.87 (s, 3H), 3.20 (dd, 1H, $J = 24.2$ and 5.3 Hz), 3.18 (sept, 1H, J = 7.0 Hz), 2.84 (dd, 1H, $J = 24.2$ and 2.3 Hz), 2.78 (dtd, 1H, J = 13.1, 3.7, and 1.7 Hz), 1.97–1.76 (m, 1H), 1.62–1.42 and 1.39–1.20 (2m, 4H), 1.49 (s, 3H), 1.20 (s, 3H), 1.20 (d, 3H, $J = 7.1$ Hz), 1.18 (d, 3H, J = 7.1 Hz), 1.13 (s, 3H); ^{13}C NMR: $\delta = 187.7$, 183.8 (2C), 156.9, 148.5, 146.3, 139.9, 135.2, 115.6, 60.7, 40.5, 39.2, 36.4, 36.3, 33.0, 30.7, 26.1, 24.8, 24.3, 20.6, 20.4, 18. 7.

(*S*)-1-(*tert*-Butylsulfinyl)-4-isopropyl-2,3,5-trimethoxybenzene (8): A solution of *n*BuLi (12.42 mL, 28.57 mmol of 2.3 M solution in hexane) in THF (15 mL) was added by cannula to a solution of 2-isopropyl-1,3,4-trimethoxy benzene (**7**) (2.50 g, 11.9 mmol) in THF (25 mL) at room temperature. After the mixture had been stirred for 1 h, it was cooled at −78 °C and a solution of (−)-(*S*)-diacetone glucose *tert*-butyl sulfinate[16] (4.77 g, 13.09 mmol) in THF (40 mL) was then added and the evolution was monitored by TLC. The hydrolytic treatment (saturated solution of NH_4Cl) was effected at −78 °C. The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and the solvent evaporated. The residue was a 85:15 mixture of **8** and its regioisomer (*S*)-1-(*tert*-butylsulfinyl)-3-isopropyl-2,4,5-trimethoxybenzene. Both isomers were separated by chromatography (hexane:isopropyl alcohol 30:1). Compound **8**: white solid (70% yield): m.p. 114–115 °C; $[\alpha]_D^{20} = -101.7$ ($c = 1$, $CHCl_3$); ^{1}H NMR: $\delta = 6.93$ (s, 1H), 3.81 (s, 3H), 3.80 (2s, 6H), 3.51 (sept, 1H, J = 7.0 Hz), 1.30 and 1.28 (2d, 6H, J = 7.0 Hz), 1.21 (s, 9H); ^{13}C NMR: $\delta = 155.0$, 151.4, 145.0, 133.8, 131.0, 103.3, 60.8, 60.5, 57.5, 55.8, 25.3, 22.9, 20.9, 20. 7; elemental analysis calcd (%) for $C_{16}H_{26}O_4S$: C 61.12, H 8.33, S 10.20; found: C 61.09, H 8.31, S 10.72.

(*S*)-1-(*tert*-Butylsulfinyl)-3-isopropyl-2,4,5-trimethoxybenzene: White solid; 13% yield; m.p.: 109.5–110.5 °C; $[\alpha]_D^{20} = -195.4$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR: $\delta = 7.15$ (s, 1H), 3.89, 3.88 and 3.74 (3s, 9H), 3.36 (sept, 1H, J = 7.1 Hz), 1.37 and 1.30 (2d, 6H, $J = 7.1$ Hz), 1.18 (s, 9H); ^{13}C NMR: $\delta = 151.3$, 150.2, 149.7, 135.2, 127.7, 107.2, 62.3, 60.8, 57.9, 56.0, 25.7, 22.9, 21.8 and 21. 4; elemental analysis calcd. (%) for $C_{16}H_{26}O_4S$: C 61.12, H 8.33, S 10.20; found: C 60.97, H 8.42, S 10.66.

(*S*)-1-(*tert*-Butylsulfinyl)-2,3,5-trihydroxy-4-isopropylbenzene (9): A solution of (*S*)-1-(*tert*-butylsulfinyl)-4-isopropyl-2,3,5-trimethoxybenzene (**8**) (1.28 g, 4.07 mmol) in EtSH (25 mL) was added to a mixture of $AlCl_3$ (5.43 g, 40.72 mmol) and EtSH (25 mL) at 0 °C by cannula. After the mixture had been stirred for 10 min, it was poured into cool water (0–4 °C), extracted with CH_2Cl_2, dried over $MgSO_4$, and the solvent was evaporated. Compound **9** was obtained as a white solid in 90% yield: m.p.: 166–167 °C (decomp) (CH_2Cl_2); $[\alpha]_D^{20} = -146$ ($c = 0.5$, acetone); ^{1}H NMR: $\delta = 10.52$ (s, 1H), 5.94 (s, 1H), 5.89 (s, 1H), 5.47 (s, 1H), 3.46 (sept, 1H, $J = 7$ Hz), 1.35 (d, 6H, $J = 7.0$ Hz), 1.31 (s, 9H); ^{13}C NMR: $\delta = 149.0$, 145.1, 138.5, 125.2, 120.9, 102.9, 57.1, 24.6, 22.7 (3C), 20.5 (2C, $CH(CH_3)_2$); elemental analysis calcd. (%) for $C_{13}H_{20}O_4S$: C 57.33, H 7.40, S 11.77; found: C 57.01, H 7.33, S 12.14.

0947-6539/00/0602-0290 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 2

(*S*)-5-(*tert*-Butylsulfinyl)-3-hydroxy-2-isopropyl-1,4-benzoquinone (4b): A solution of 2,3-diciano-5,6-dichloro-1,4-benzoquinone (DDQ) (0.5 g, 2.22 mmol) in CH_2Cl_2 (50 mL) was added to (*S*)-1-(*tert*-butylsulfinyl)-2,3,5-trihydroxy-4-isopropylbenzene (**9**) (0.5 g, 1.84 mmol) dissolved in CH_2Cl_2 (100 mL) at room temperature. After 10 min, the mixture was washed with H_2O (5 × 50 mL) and the organic layer was dried over $MgSO_4$ and the solvent evaporated at reduced pressure. The product **4b** (82% yield) was purified by chromatography (silica gel from SDS was essential to reach the indicated yield, hexane:AcOEt 3:1) or used in the next step without further purification. Orange solid: m.p. 102–104 °C (decomp); $[\alpha]_D^{20} = +90.2$ ($c = 0.06$, $CHCl_3$); ^{1}H NMR: $\delta = 7.16$ (s, 1H), 3.23 (sept, 1H, $J = 7.0$ Hz), 1.27 (s, 9H), 1.21 (2d, 6H, $J = 7.0$ Hz); ^{13}C NMR: $\delta = 184.4$ and 180.5 (2C), 151.0, 146.6, 139.4, 127.1, 58.5, 24.1, 23.1 (3C), 19.5 (2C).

(*S*)-12-Hydroxy-11,14-dioxoabieta-5,8,12-triene (3b): The solid resulting in the oxidation of (*S*)-1-(*tert*-butylsulfinyl)-2,3,5-trihydroxy-4-isopropylbenzene (**9**) (25 mg) with DDQ was mixed with 1,3,3-trimethyl-2-vivnylcyclohexene (**2**) (0.05 mL) and CH_2Cl_2 (2 mL) and the solution was submitted to a pressure of 13 kbar for 24 h. The resulting mixture was concentrated in vacuo and purified by chromatography (hexane to separate the excess of diene followed by hexane:AcOEt 125:1). Compound **3b** was obtained as a yellow solid (60% overall yield from **9**, >97% *ee*): m.p.: 151–152 °C (hexane); $[\alpha]_D^{20} = -118$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR: $\delta = 7.30$ (br, s, 1H), 5.66 (dd, 1H, $J = 5.1$ and 2.5 Hz), 3.29 (dd, 1H, $J = 25.2$ and 5.0 Hz), 3.15 (sept, 1H, $J = 7.0$ Hz), 2.88 (dd, 1H, $J = 25.2$ and 2.4 Hz), 2.82 (dtd, 1H, $J = 13.1$, 3.7, and 1.5 Hz), 1.84 (tt, 1H, $J = 13.0$ and 3.6 Hz), 1.62–1.20 (m, 4H), 1.46 (s, 3H), 1.20 (2d, 6H, $J = 7.0$ Hz), 1.19 (s, 3H), 1.12 (s, 3H); ^{13}C NMR: $\delta =$ 186.7, 183.4 (2C), 150.7, 147.7, 143.1, 142.6, 123.4, 115.1, 40.6, 39.1, 36.4 (2C), 33.1, 30.4, 26.0, 25.4, 24.0, 19.9, 19.8, 18.8; elemental analysis calcd (%) for $C_{20}H_{26}O_3$: C 76.40, H 8.33; found: C 76.16, H 8.48.

(+)-Royleanone (1): A mixture of Pd/C (10%) (100 mg) and a solution of (*S*)-12-hydroxy-11,14-dioxoabieta-5,8,12-triene (**3b**) (150 mg, 0.47 mmol) in a 1:1 mixture of acetic acid and AcOEt (15 mL) was maintained in an atmosphere of hydrogen at atmospheric pressure for 24 h. The resulting mixture was filtered over celite and washed with a saturated solution of $NaHCO_3$. The organic phase was dried over $MgSO_4$ and the solvent eliminated at reduced pressure. The crude product (90% yield) contained a 60:40 ratio of *trans*-fused (+)-(5*S*,10*S*)-Royleanone (**1**) and its *cis*-fused (5*R*,10*S*)-epimer. After three successive crystallizations (methanol), the natural epimer (+)-**1** was isolated in 35% yield as a yellow solid: m.p.: 180–181 °C (ref.[1]: 179–181 °C); $[\alpha]_D^{20} = +133$ ($c = 1$, $CHCl_3$); ref. $[\alpha]_D$[1]: 134 ($c = 1$, $CHCl_3$); ^{1}H NMR: $\delta = 7.23$ (s, 1H), 3.15 (sept, 1H, $J = 6.5$ Hz), 2.71 (m, 2H), 2.30 (ddd, 1H, $J = 21$, 12 and 7 Hz), 1.90–0.98 (m, 6H), 0.94–0.80 (m, 2H), 1.25 (s, 3H), 1.20 and 1.19 (2d, 6H, $J = 6.5$ Hz), 0.93 and 0.90 (2s, 6H); ^{13}C NMR: $\delta = 187.5$, 183.4, 150.6, 146.5, 146.0, 123.7, 51.7, 41.3, 38.4, 36.2, 33.5, 33.4, 26.7, 24.1, 21.8, 20.1, 20.0, 19.9, 18.9, 17.4.

Acknowledgment

We thank the DGICYT (Grants PB95–0174 and PB96–0035) for financial support.

[1] a) S. M. Kupchan, A. Karim, C. Marks, *J. Am. Chem. Soc*. **1968**, *90*, 5923–5924; b) S, M. Kupchan, A. Karim, C. Marks, *J. Org. Chem*. **1969**, *34*, 3912–3918.

[2] K. Shishido, K. Goto, S. Miyoshi, Y. Takaishi, M. J. Shibuya, *J. Org. Chem*. **1994**, *59*, 406–414.

[3] K. Nakanishi, T. Goto, S. Ito, S. Natori, S. Nozol, *Natural Products Chemistry*, *Vol. 1*, Academic Press, London, **1974**, Chapter 4.

[4] O. E. Edwards, G. Feniak, M. Los, *Can. J. Chem*. **1962**, *40*, 1540–1546.

[5] a) J. H. Gough, M. D. Sutherland, *Aust. J. Chem*. **1966**, *19*, 329–330; b) C. H. Brieskorn, L. Buchberger, *Planta Med*. **1973**, *24*, 190–195; c) F. Yoshizaki, P. Rüedi, C. H. Eugster, *Helv. Chim. Acta* **1979**, *62*, 2754–2762; d) A. S. Romanova, A. V. Patudin, A. M. Makmedov, L. N. Pervykh. *Khim. Priv. Soedin*. **1980**, 564; e) J. A. Hueso-Rodríguez, M. L. Jimeno, B. Rodríguez, G. Savona, M. Bruno, *Phytochemistry* **1983**, *22*, 2005–2009; f) A. Michavila. F. Fernández-Gadea, B. Rodríguez, *Phytochemistry* **1986**, *25*, 266–268; g) F. Simoes, A. Michavila, B. Rodríguez, M. C. García Alvarez, M. Hasan, *Phytochemistry*, **1986**, *25*, 755–756.

[6] a) T. Matsumoto, Y. Oshuga, S. Harada, K. Fukui. *Bull. Chem. Soc. Jpn*. **1977**, *50*, 266–272; b) Y. Ohtsuka, A. Tahara. *Chem. Pharm. Bull*. **1978**, *26*, 2007–13.

[7] a) T. Matsumoto, Y. Tachibana, K. Fukui, *Chem. Lett*. **1972**, 321–324; b) Y. Tachibana, *Bull. Chem. Soc. Jpn*. **1975**, *48*, 298–301; c) T. Matsui, *J. Sci. Hirosima Univ. Ser. A* **1976**, *40*, 129–141.

[8] L. S. Liebskind, R. Chidabaram, S. Nimkar, D. Liotta. *Tetrahedron Lett*. **1990**, *31*, 3723–3726.

[9] J. King, P. Quayle, J. F. Malone, *Tetrahedron Lett*. **1990**, *31*, 5221–5224.

[10] R. K.Danheeiser, D. S. Casebier, F. Firooznia, *J. Org. Chem*. **1995**, *60*, 8341–8350.

[11] T. A.Engler, U. Sampath, S. Naganathan, D. Vander Velde, F. Takusagawa, D. Yohannes, *J. Org. Chem*. **1989**, *54*, 5712–5727 and references therein.

[12] For recent references see: a) M. C. Carreño, A. Urbano, C. Di Vitta, *J. Org. Chem*. **1998**, *63*, 8320–8330; b) M. C. Carreño, S. García Cerrada, A. Urbano, C. Di Vitta, *Tetrahedron: Asymmetry* **1998**, *9*, 2965–2969; c) M. C. Carreño, J. L. García Ruano, A. Urbano, M. I. López-Solera, *J. Org. Chem*. **1997**, *62*, 976–981; d) M. C. Carreño, J. L. García Ruano, M. A. Hoyos, A. Urbano, *J. Org. Chem*. **1996**, *61*, 2980–2985; e) M. C. Carreño, J. L. García Ruano, M. A. Toledo, A. Urbano, C. Z.Remor, V. Stefani, *J. Org. Chem*. **1996**, *61*, 503–509.

[13] a) M. C. Carreño, A. Urbano, J. Fischer, *Angew. Chem. 109*, 1695–1697; *Angew. Chem. Int. Ed. Engl*. **1997**, 36, 1621–1623; b) M. C. Carreño, J. L. García Ruano, C. Z. Remor, A. Urbano, *Tetrahedron Lett.* **1997**, 38, 9077–9080.

[14] D. M. Hollinshead, S. C. Howell, S. V. Sey, M. Mahon, N. M. Ratcliffe, P. A. Worthington, *J. Chem. Soc. Perkin Trans. 1* **1983**, 1579–1589.

[15] M. C. Carreño, J. L. García Ruano, M. A. Toledo, A. Urbano, *Tetrahedron: Asymmetry* **1997**, 8, 913–921.

[16] Optical purity was determined by ^{1}H NMR spectroscopy [Pr(hfc)$_3$] (hfc = 3-(heptafluoropropylhydroxymethylene)-D-camphorate). Racemic **3a** necessary for such determination was obtained from racemic **4a**.

[17] a) I. Fernández. N. Khiar, J. M. Llera, F. Alcudia, *J. Org. Chem*. **1992**, *57*, 6789–6796; b) N. Khiar, I. Fernández, F. Alcudia, *Tetrahedron Lett.* **1994**, *35*, 5719–5722.

[18] Y. Oikawa, T. Yoshida, O. Yonemitsu. *Tetrahedron Lett*. **1982**, *23*, 885–888.

[19] Optical purity of **3b** was determined by ^{1}H NMR [Pr(hfc)$_3$] after its transformation into **3a** (1. $Na_2S_2O_4$, diethyl ether; 2. K_2CO_3, Me_2SO_4, acetone, reflux).

[20] See for instance: a) F. Marletti, F. Delle Monache, G. B. Marini-Bettolo, M. D. C. M. De Araujo, M. D. S. B. Caralcanti, J. L. D'Alburquerque, O. G. De Lima, *Gazz. Chim. Ital*. **1976**, *106*, 119–126; b) S. P. Tanis, K. Nakanishi, *J. Am. Chem. Soc*. **1979**, *101*, 4398–4400.

[21] J. W. Suggs, S. D. Cox, R. H. Crabtree, J. M. Quirk. *Tetrahedron Lett*. **1981**, *22*, 303–306.

Received: June 10, 1999 [F1843]