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Enantioselective Syntheses and Resolution of the Key White Intermediate for the Synthesis of Trisporic Acids

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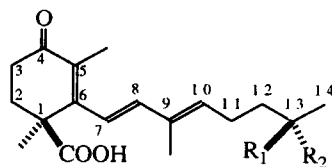
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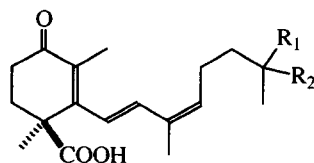
Abstract: Two asymmetric syntheses of the alkylated cyclohexenone carboxylic acid moiety, the key White intermediate (**4a**), of trisporic acids A, B and C are described. The syntheses feature a Michael addition in tandem with an aldol condensation as the central step. The resolution of this readily available intermediate is also described.

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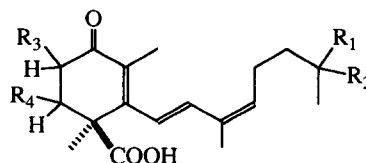
The trisporic acids constitute a family of naturally occurring fungal pheromones derived from β -carotene that included (9E)-trisporic acid A (**1a**), B (**1b**) and C (**1c**), their 9Z isomers **2a**, **2b** and **2c**, and the corresponding methyl esters.¹ Recently, trisporic acids E (3R)-(**3a**), E (3S)-(**3b**) and D (2S)-(**3c**), carrying a hydroxyl group on the cyclohexenone moiety, were isolated and characterized.² The absolute configuration at C-1 of trisporic acid C (**1c**) was shown to be *S* on the basis of a CD study of the acetate of its tetrahydroderivative as methyl ester,³ whereas the configuration at C-13 was established as *R* by chemical correlation with a known compound.⁴ As a consequence of these studies, the same configuration was assigned to all members of the family at these stereocenters.



1a, $R_1=R_2=H$
1b, $R_1, R_2=O$
1c, $R_1=OH, R_2=H$



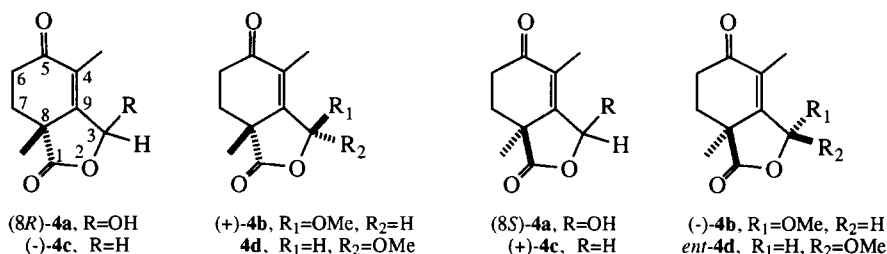
2a, $R_1=R_2=H$
2b, $R_1, R_2=O$
2c, $R_1=OH, R_2=H$



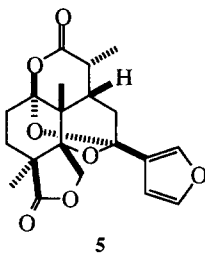
3a, $R_1=H, R_2=OH, R_3=OH, R_4=H$
3b, $R_1=H, R_2=OH, R_3=OH, R_4=H$
3c, $R_1, R_2=O, R_3=H, R_4=OH$

Several synthetic routes directed to specific members of this group of natural products have been reported.⁵⁻⁷ More recently, however, White *et al.*⁸ described a general convergent approach to the synthesis of trisporic acids A, B and several related products, *via* a Wittig reaction of lactol **4a** with an appropriate phosphorane.

In view of our interest in the application of the Michael addition-aldol condensation sequence for the preparation of key intermediates towards the synthesis of natural products,⁹ we decided to study the enantioselective synthesis of **4a** by reaction of a suitable Michael donor and ethyl vinyl ketone.¹⁰ The availability of both enantiomers of **4a** would eventually allow the preparation of trisporic acids A and/or B in optically active form in order to elucidate the role of the configuration at C-1 in their biological activities.



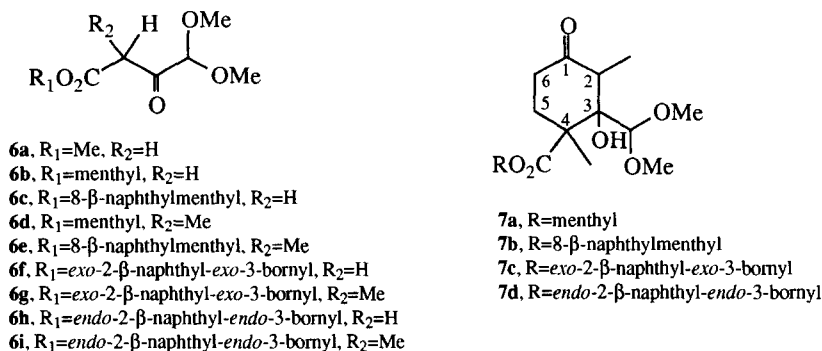
Our interest in the development of simple sequences to **4a** is also due to the fact that the related lactone **4c**,⁸ easily prepared from **4a**, as shown below, has recently been used as starting material in an approach to the synthesis of the naturally occurring hypoglycemic agent saudine (**5**).¹¹



For the preparation of the Michael donor we started with the known β -keto ester **6a**,⁷ which was first transformed into the corresponding menthyl ester **6b**, by a 4-(dimethylamino)pyridine-catalyzed ester exchange in the presence of molecular sieves,¹² first reported by Taber,¹³ and then, into the monoalkylated ester **6d** by treatment with methyl iodide and thallium (I) ethoxide.¹⁴ Attempted monoalkylation of **6b** under other reported conditions was unsuccessful; **6b** reacted slowly and tended to give a dialkylated product.¹⁵⁻¹⁷

With the ester **6d** in hand we decided to study the Michael addition-aldol condensation sequence, in order to find the best reaction conditions. After considerable experimentation we found that the treatment of **6d** with ethyl vinyl ketone using potassium carbonate as a base, in methanol at -20°C, afforded directly a mixture of stereoisomeric aldols (**7a**). However, the ¹H NMR spectrum of the crude reaction product showed that the reactions had occurred with very low diastereoselectivity. Better results were obtained by using 8-phenylmenthol¹⁸ and 8- β -naphthylmenthol¹⁹ as chiral auxiliaries. In particular, when 8- β -naphthylmenthol was used for the preparation of the Michael donor (**6e**), an aldol product (**7b**) was predominantly obtained. Although

the actual configuration of the major product was not determined at this point, the mixture of aldols was submitted to a dehydration reaction by treatment with copper (II) sulfate adsorbed on silica gel in refluxing toluene.²⁰ Under these conditions the dehydration occurred smoothly with elimination of the chiral auxiliary as a mixture of alkenes and simultaneous formation of **4b**. Compound (+)-**4b**²¹ was isolated by direct crystallization from the reaction mixture in approximately 20% overall yield from **6c** (**6c**→**6e**→**7b**→**4b**), without purification of intermediates, and in more than 95% enantiomeric excess. However, the purification of the mother liquors by column chromatography allowed us to isolate a minor stereoisomeric product related to (+)-**4b**.



A careful ¹H NMR analysis of these compounds, including a series of nuclear Overhauser enhancement (NOE) experiments, clearly indicated that major and minor products, (+)-**4b** and **4d** respectively, differ only in the configuration of the acetal group at C-3 (Fig. 1).²² This was confirmed by acid-catalyzed isomerization of **4d** which gave (+)-**4b**, as the major component of the mixture. Energy minimisation of the possible conformers of both diastereoisomers using semi-empirical calculations (PM3),²³ gave an energy difference of 2.35 kcal/mol in favor of (+)-**4b**, in agreement with the equilibration experiment.

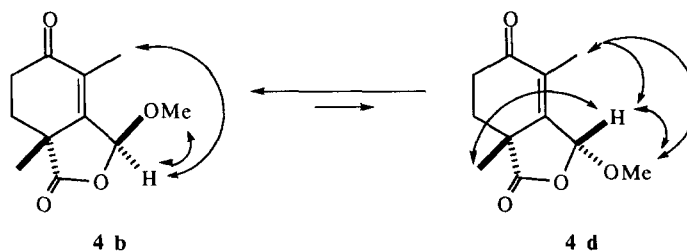


Figure 1. Relative stereochemistry of compounds **4b** and **4d** and proton-proton through-space interactions, obtained by NOE difference experiments.

Acidic hydrolysis of (+)-**4b** afforded quantitatively **4a**, showing a ¹H NMR spectrum coincident with that previously described for the racemic modification.⁸

For the determination of the absolute configuration of (+)-**4b** and consequently that at C-8 of **4a**, we transformed this lactol into the bicyclic lactone (-)-**4c** by a sequence of reactions involving reduction with sodium borohydride in the presence of cerium (III) chloride followed by Jones oxidation. The ¹H NMR spectrum of (-)-**4c** was coincident with the spectral data previously reported for (±)-**4c**⁸ and also for (+)-**4c**.²⁴ Since the absolute configuration at C-8 of (+)-**4c** has been established as *S*, we concluded that the absolute

configuration at the same carbon of (-)-**4c** and consequently of **4a** must be *R*. This correlation establishes the absolute configuration of (+)-**4b** and **4d** as 3*S*, 8*R* and 3*R*, 8*R*, respectively.

Although the key intermediate **4a**, with the required configuration for the synthesis of natural trisporic acids, could be obtained simply by using the enantiomer of 8- β -naphthylmenthol for the preparation of the β -keto ester, we decided to study the ability of other chiral auxiliaries, particularly those derived from β -naphthylborneol, to control the stereochemistry of the sequence. We selected these derivatives instead of the well known *exo*-3- α -naphthylborneol,²⁵ hoping that the β -naphthyl moiety could increase the facial selectivity in the Michael step.

We have found that when using *exo*-2- β -naphthyl-*exo*-3-borneol as chiral auxiliary and following the sequence described above (**6a**→**6f**→**6g**→**7c**→**4b**) compound (+)-**4b** was obtained in comparable chemical yield, however, in only 48% ee. On the other hand, when using *endo*-2- β -naphthyl-*endo*-3-borneol as chiral auxiliary, the pure aldol product **7d** was obtained by direct crystallization of the crude reaction mixture in approximately 20% overall yield from **6h** (**6h**→**6i**→**7d**). An X-ray analysis of **7d** clearly showed that the absolute configuration of the three chiral centers generated in this two-step sequence are 2*S*, 3*R* and 4*S*, relative to the known stereocenters of the borneol moiety, indicating that the Michael addition step had occurred, in this case, with reversal of stereoselectivity (Fig. 2). The reversal of stereoselectivity observed between the *exo* and *endo* isomers of the chiral auxiliary is in agreement with previous reports for related transformations.^{26,27}

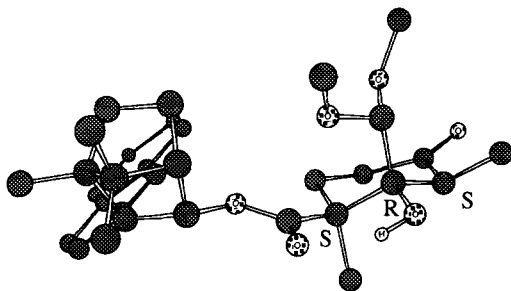


Figure 2. X-ray crystal structure of compound **7d**.

The ¹³C NMR spectrum of the major aldol **7b**, in which the absolute configuration at C-4 must be *R*, showed the cyclohexanone moiety carbon shifts in good agreement with those of comparable sites of **7d** (Table 1), thereby suggesting that the stereocenters of both aldols should have the same relative but opposite absolute configurations.

Table 1. Carbon shifts of the cyclohexenone ring of compound **7d** and the major product **7b**.

Carbon	C-1	C-2	C-3	C-4	C-5	C-6	4-Me	2-Me	$\underline{\text{CH}}(\text{OMe})_2$	$\underline{\text{COOR}}$
7d	206.89	48.04	80.54	45.03	35.86	26.58	19.73	7.04	111.28	178.26
7b	207.24	48.07	80.33	44.67	35.02	26.62	19.29	7.01	111.80	178.25

This observation allowed us to propose two "pseudo enantiomeric" transition states for the formation of **7b** and **7d**. As shown in Figure 3 and accepting the well known conformation of the β -keto ester enolates (A

and A'),²⁸ a π stacking effect²⁹ induced by the β -naphthyl moiety could be invoked to explain the stereochemistry at the quaternary carbon atom of both Michael addition products (B and B'). The "pseudo enantiomeric" chair-like transition states in which the steric interactions between the dimethylacetal and the methyl groups are avoided (C and C'), would lead then to both aldols **7b** and **7d** with the observed stereochemistry. It is worthwhile mentioning that **7d** does not suffer isomerization by treatment with potassium carbonate in methanol at -20°C , even after ten days under these conditions.

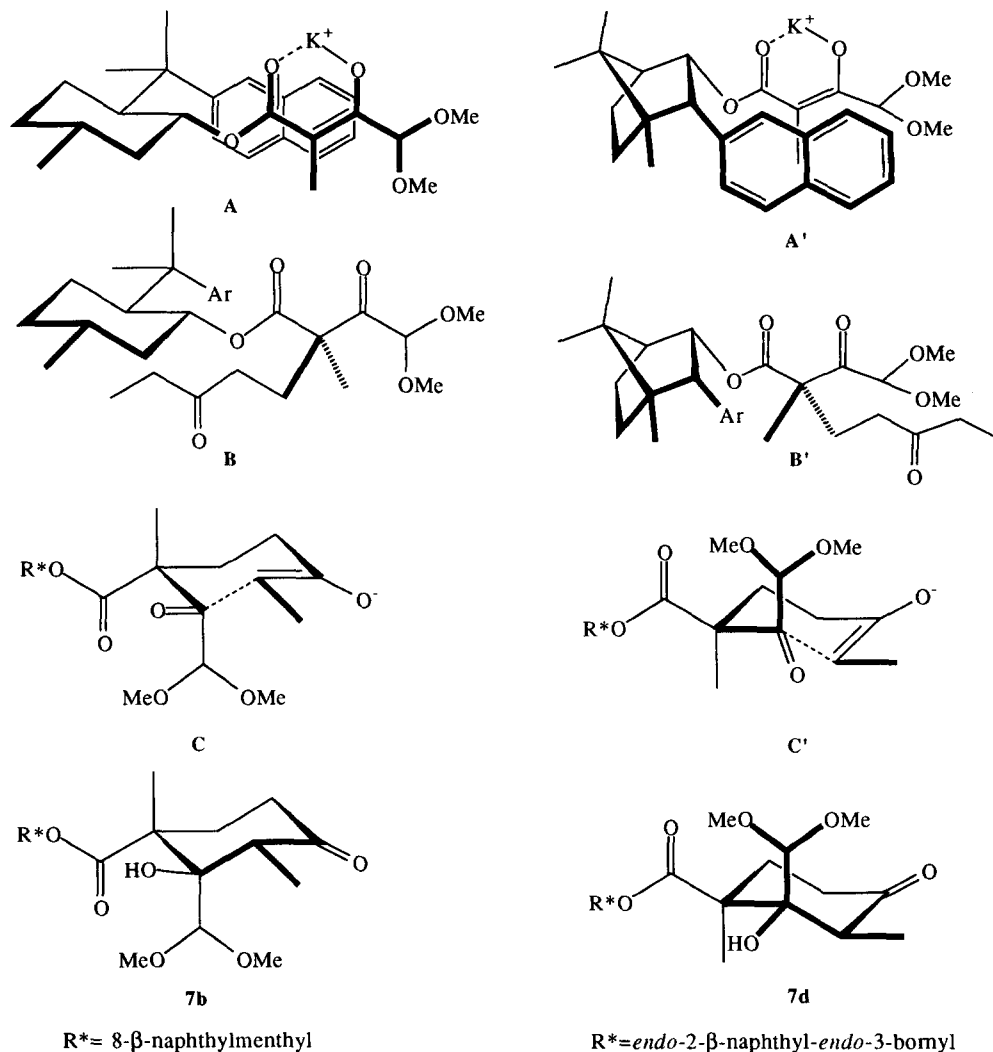
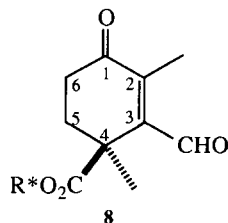


Figure 3. Proposed preferred conformations of the β -ketoesters enolates showing the π stacking effect of the naphthyl moiety and chair-like transition states for the aldol condensation step leading to **7b** and **7d**.

With access to compound **7d** in pure form, we carried out a careful analysis of the reaction induced by copper (II) sulfate adsorbed on silica gel in refluxing toluene.²⁰ Based on the absolute configuration determined

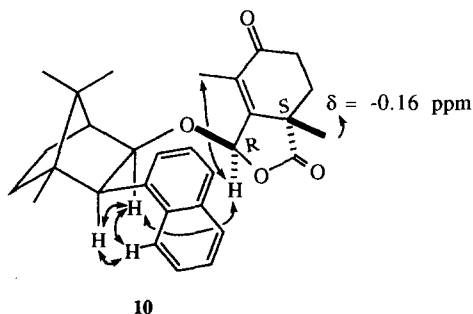
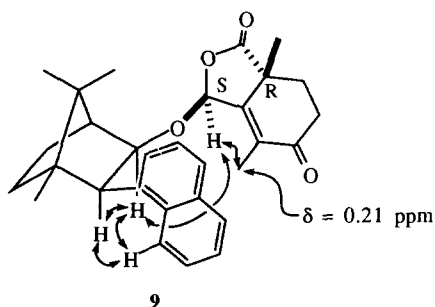
above for (+)-**4b** and on the X-ray analysis, we expected the formation of (-)-**4b** from **7d**. In fact, when **7d** was submitted to the dehydration reaction (3*R*,8*S*)-(-)-**4b** and the minor diastereoisomer (3*S*,8*S*)-*ent*-**4d** were obtained in 48% and 14% yield, respectively. Furthermore, the formation of the aldehyde **8** in 34% yield, together with a mixture of alkenes arising from the elimination of the chiral auxiliary, was also detected. No aldehydes were detected by ¹H NMR spectroscopy in the crude reaction product from the dehydration reaction of **7b**.



R*=*endo*-2-β-naphthyl-*endo*-3-bornyl

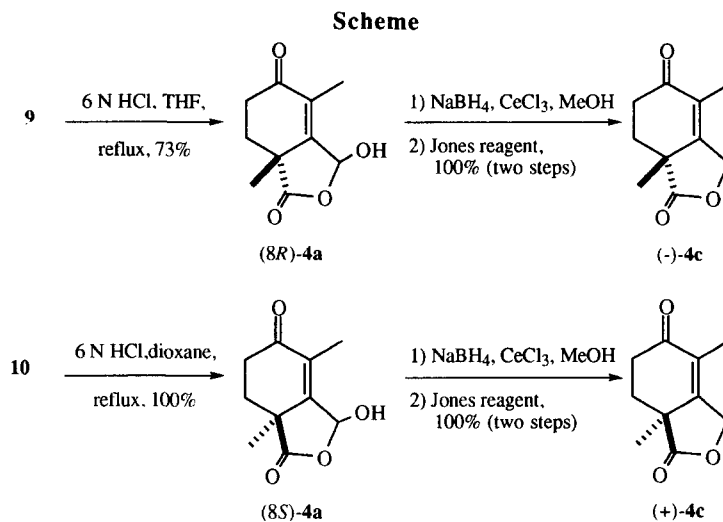
In order to have a more direct access to both enantiomers of **4a**, we also evaluated the resolution of its readily available racemic modification⁸ through the preparation of diastereoisomeric acetals by reaction of (±)-**4a** with a chiral alcohol. We expected, based on our experience with compounds [(+)-**4b** and **4d**], that working under equilibrium-controlled conditions two diastereoisomers should predominantly be obtained.

After several attempts, we found that the treatment of (±)-**4a** with *exo*-2-α-naphthyl-*exo*-3-borneol²⁵ in the presence of a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene afforded only two acetals (TLC).³⁰ These acetals were then separated by column chromatography on silica gel and exhaustively analyzed by ¹H NMR spectroscopy. The most interesting feature in the ¹H NMR spectrum of the less polar diastereoisomer is the unusual high field signal attributed to the vinylic methyl group at δ 0.21, indicating a preferred conformation in which the methyl group suffers a shielding effect induced by the naphthalene moiety. This information together with a series of NOE experiments suggested that the absolute configuration at the acetal moiety is 3*S* and 8*R* as shown in structure **9**. In the ¹H NMR spectrum of the more polar diastereoisomer, the signal attributed to the C-8 methyl group, appearing at δ -0.16, again indicated a preferred conformation that, together with the information obtained by NOE experiments suggested that the absolute configuration is, in this case, 3*R* and 8*S* (**10**).



That the absolute configuration at C-8 in **9** and **10** is *R* and *S* respectively, was unequivocally determined by chemical correlation with the already known bicyclic lactones (-)-**4c** and (+)-**4c**, respectively. As shown in the Scheme, the first step in this correlation is precisely the acid catalyzed hydrolysis of **9** and **10**, affording our

target enantiomers (8*R*)-**4a** and (8*S*)-**4a** in 73% and 100% yield, respectively, with simultaneous recovering of the resolving agent. In turn, the enantiomeric lactols were easily converted into both enantiomers of **4c** in very good yield.



The absolute configuration suggested for C-3 of **9** and **10** as *S* and *R* respectively, on the basis of the spectral analysis discussed above, is in agreement with the results obtained by molecular mechanics calculations (MM+).³¹

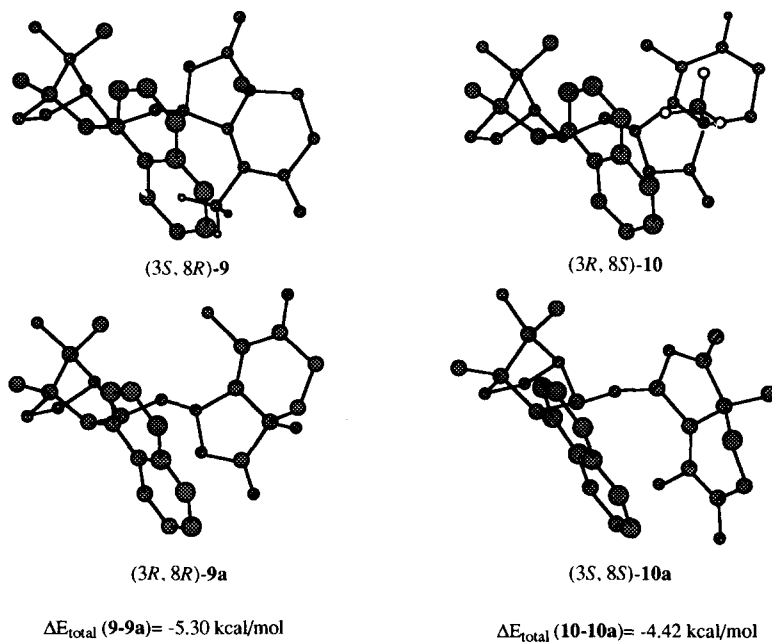


Figure 4. Projections of the lowest-energy conformations of compounds **9**, **9a**, **10** and **10a** predicted on the basis of molecular mechanics calculations.

As shown in Fig. 4, the minimum energy conformation of (3*S*,8*R*)-**9** is favored to the one with 3*R*,8*R* configuration (**9a**) by 5.3 kcal/mol. Similarly, for the more polar diastereoisomer **10**, the difference in energy between the preferred conformations is 4.42 kcal/mol in favor of that having the 3*R*,8*S* configuration. Finally, the X-ray analysis of **10** unequivocally confirms the configurational assignment discussed above. As shown in Fig. 5 the absolute configuration of **10** is 3*R* and 8*S*, relative to the known configuration of the chiral auxiliary.

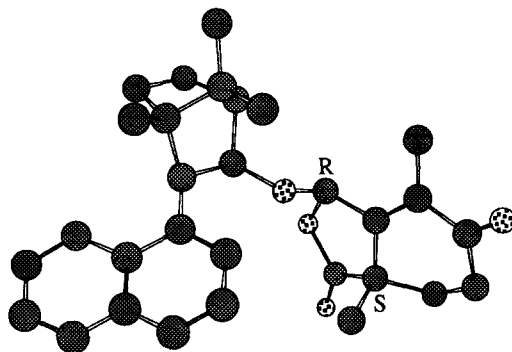


Figure 5. X-ray crystal structure of compound **10**.

In conclusion, we have developed two enantioselective sequences toward both enantiomers of the key intermediate **4a**, in excellent enantiomeric excess and from readily available starting materials, furthermore, we have also developed a simple resolution of (\pm)-**4a**, making of these enantiomers and related optically active products, such as (-)-**4c** and (+)-**4c**, attractive intermediates for the synthesis of complex natural products.

Experimental Section

All melting points were determined in a hot-stage microscope, and are uncorrected. IR spectra were measured in a Bruker FT-IFS25 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 spectrometer for CDCl_3 solutions with Me_4Si as internal standard. For the 2D, COSY and NOE experiments Bruker standard software was employed. Column chromatography was performed on silica gel 60 H, slurry packed, run under low pressure of nitrogen and employing increasing amounts of EtOAc in hexane as solvent. Analytical TLC was carried out using Kieselgel Merck F254 with thickness 0.20 mm. The homogeneity of all intermediates prior to the high resolution mass spectral determination was carefully verified by TLC. Reactions were routinely run under a dry nitrogen atmosphere with magnetic stirring. All chemicals were used as purchased or purified according to standard procedures. All calculations were performed using the routines available in the HyperChem 3.0 software package. The enantiomeric purities (% ee, $\pm 5\%$) were established *via* ^1H NMR analysis employing the shift reagent *tris*(3-[heptafluoropropyl-hydroxymethylene]-*d*-camphorato) europium (III) derivative $[\text{Eu}(\text{hfc})_3]$. The X-Ray crystal measurements were made on a Stoe STADI-4 diffractometer with $\text{MoK}\alpha$ ($\lambda=0.71069 \text{ \AA}$) radiation. The structure was solved by direct methods (SHELXS, SHELXS76) and refined through full-matrix least-squares on F^2 calculations. Full details have been deposited at the Cambridge Crystallographic Data Centre.

The numbering sequence used for reporting NMR parameters for compounds **4a-d**, **6a-i** and **7a-d** are indicated in the corresponding formulae. The chiral auxiliary moieties are numbered in the usual manner.

Preparation of 7a (6a→6b→6d→7a)

A suspension of (-)-menthol (885 mg, 5.66 mmol), methyl 4,4-dimethoxy-3-oxobutanoate (**6a**),⁷ (1.50 g, 8.50 mmol), DMAP (128 mg, 1.05 mmol) and molecular sieves 4 Å (1.5 g) in toluene (18 mL) was heated at reflux until TLC spot for menthol had disappeared (6 h). The suspension was allowed to cool and then filtered through a short pad of silica gel with copious washings with benzene. The filtrate was concentrated and the excess of **6a** eliminated by a short-path distillation (100°C, 1 Torr). The residue was chromatographed, yielding **6b** as an oil, which showed to be a 2:1 mixture of the keto and enol forms by ¹H NMR spectroscopy. Yield: 1.53 g, 90%; IR (film) 1748, 1728, 1660 cm⁻¹; ¹H NMR δ 4.81-4.66 (1H, m, H-1'), 4.62 (1H, s, H-4), 3.58 (3H, s, OMe), 3.43 (3H, s, OMe), 2.10-0.96 (m), 0.92 (6H, d, J=6.4 Hz, 8'-Me), 0.78 (3H, d, J=6.9 Hz, 5'-Me). The following signals of the enol form were also detected: δ 12.01 (1H, s, OH), 5.41 (1H, s, H-2), 4.84 (1H, s, H-4), 3.41 (3H, s, OMe), 3.39 (3H, s, OMe), 0.90 (6H, d, J=7.0 Hz, 8'-Me), 0.77 (3H, d, J=7.0 Hz, 5'-Me); ¹³C NMR δ 197.93 (C-3), 170.22 (C-1), 103.13 (C-4), 75.02 (C-1'), 54.41 (OMe), 54.34 (OMe), 46.62 (C-2'), 44.57 (C-2), 40.44 (C-6'), 33.91 (C-4'), 31.09 (C-5'), 25.75 (C-8'), 23.05 (C-3'), 21.69 (5'-Me), 20.43 (8'-Me), 15.89 (8'-Me). The following signals of the enol form were also detected: δ 171.88 (C-3), 166.25 (C-1), 99.40 (C-4), 90.66 (C-2), 74.06 (C-1'), 53.19 (OMe), 52.91 (OMe), 46.72 (C-2'), 40.62 (C-6'), 25.94 (C-8'), 23.21 (C-3'), 16.07 (8'-Me).

To a solution of **6b** (1.53 g, 5.1 mmol) in anhydrous hexane (5 mL), thallium (I) ethoxide (1.152 g, 327 μL, 4.63 mmol) was added dropwise. The resulting light-orange solution was stirred for 30 min at RT, concentrated and dried (RT, 1 Torr). The thallium enolate was dissolved in methyl iodide (15.96 g, 7 mL, 112 mmol), and the solution was heated at reflux for 4 h, the excess of methyl iodide was then distilled. The residue was allowed to cool, diluted with EtOAc, filtered through silica gel and the filtrate concentrated. This residue may be used in the next step without further purification. A small sample was chromatographed affording **6d** as an unseparable 1:1 mixture of diastereoisomers at C-2. Yield: 1.536 g, 96%; IR (film) 1744, 1724 cm⁻¹; ¹H NMR δ 4.69 (2H, dt, J=4.6 and 10.4 Hz, H-1'), 4.68 (2H, s, H-4), 3.81 (2H, q, J=7.2 Hz, H-2), 3.40 (3H, s, OMe), 3.39 (3H, s, OMe), 3.38 (3H, s, OMe), 3.36 (3H, s, OMe), 2.05-1.40 (m), 1.33 (6H, d, J=7.2 Hz, 2-Me), 0.90 (6H, d, J=6.5 Hz, 8'-Me), 0.88 (6H, d, J=7.0 Hz, 8'-Me), 0.76 (3H, d, J=6.9 Hz, 5'-Me), 0.75 (3H, d, J=6.9 Hz, 5'-Me); ¹³C NMR δ 200.83 (C-3), 169.76 (C-1), 102.73 (C-4), 74.93 (C-1'), 54.47 (OMe), 53.92 (OMe), 48.19 (C-2), 46.69 (C-2'), 40.40 (C-6'), 40.31 (C-6'), 33.93 (C-4'), 31.09 (C-5'), 25.85 (C-8'), 25.68 (C-8'), 23.02 (C-3'), 21.74 (5'-Me), 20.51 (8'-Me), 15.85 (8'-Me), 12.35 (2-Me). To a solution of crude **6d** (1.50 g, 4.78 mmol) in MeOH (9.5 mL), anhydrous K₂CO₃ (940 mg, 6.81 mmol) was added. After 1 h at RT the suspension was cooled to -20°C and ethyl vinyl ketone (724 mg, 856 μL, 8.6 mmol) was added. After 21 h at this temperature, the mixture was filtered through a bed of Celite with copious washings with EtOAc. The filtrate was evaporated to give a mixture of four diastereoisomeric aldols **7a** (3:2:2:1), on the basis of its ¹H NMR spectrum. ¹H NMR δ 6.02 (1H, d, J=1.4 Hz, OH), 5.89 (1H, d, J=1.5 Hz, OH), 5.47 (1H, s, OH), 5.18 (1H, s, OH), 4.75-4.56 (4H, m, H-1'), 4.34 (1H, d, J=2.1 Hz, H-4), 4.25 (1H, s, H-4), 4.23 (1H, s, H-4), 4.21 (1H, d, J=1.3 Hz, H-4), 3.48 (3H, s, OMe), 3.44 (3H, s, OMe), 3.43 (3H, s, OMe), 3.40 (3H, s, OMe), 3.34 (3H, s, OMe), 3.32 (3H, s, OMe), 3.31 (3H, s, OMe), 3.30 (3H, s, OMe), 2.55-1.60 (m), 1.51 (3H, s), 1.42 (3H, s, 4-Me), 1.12 (3H, d, J=6.6 Hz), 1.06 (3H, d, J=7.2 Hz), 1.03 (3H, d, J=7.0 Hz), 0.93-0.88 (m), 0.80-0.70 (m).

Preparation of 7b (6a→6c→6e→7b)

Compound **7b** was prepared following the procedure described for the preparation of **7a**, using 8-β-

naphthylmentol as chiral alcohol. This chiral auxiliary was prepared from (*R*)-(+)-pulegone following the procedure reported by Potin *et al.*¹⁹

Compound 6c: Colorless oil. Yield: 96%; IR (film) 1748, 1718 cm^{-1} ; ^1H NMR δ 7.85-7.35 (m, Ar), 4.88 (2H, dt, $J=4.4$ and 10.7 Hz, H-1'), 4.29 (2H, s, H-4), 3.27 (3H, s, OMe), 3.25 (3H, s, OMe), 2.67 (2H, dd, $J=16.7$ and 30.6 Hz, H-2), 1.43 (3H, s, 8'-Me), 1.31 (3H, s, 8'-Me), 0.88 (1H, d, $J=6.4$ Hz, H-5'), The following signals of the enol form were also detected: δ 11.78 (1H, s, OH), 4.46 (1H, s, H-2), 4.43 (1H, s, H-4), 3.20 (3H, s, OMe) 3.17 (3H, s, OMe), 1.33 (3H, s, 8'-Me); ^{13}C NMR δ 198.06 (C-3), 166.21 (C-1), 149.01 (Ar), 131.34 (Ar), 127.76 (Ar), 127.19 (Ar), 127.12 (Ar), 125.74 (Ar), 125.06 (Ar), 124.92 (Ar), 122.64 (Ar), 102.70 (C-4), 75.21 (C-1'), 54.26 (OMe x 2), 49.87 (C-2'), 44.31 (C-2), 41.22 (C-6'), 39.70 (C-8'), 34.38 (C-4'), 31.17 (C-5'), 27.80 (8'-Me), 26.41 (C-3'), 24.37 (8'-Me), 21.63 (5'-Me). The following signals of the enol form were also detected: δ 169.68 (C-1), 148.53 (Ar), 133.21 (Ar), 98.96 (C-4), 91.07 (C-2) 74.27 (C-1'), 53.34 (OMe), 52.61 (OMe), 50.04 (C-2'), 41.63 (C-6'), 39.80 (C-8'), 27.31 (8'-Me).

Compound 6e: ^1H NMR δ 7.81-7.40 (m, Ar), 5.00-4.80 (m, H-1'), 4.68 (1H, s, H-4), 4.35 (1H, s, H-4), 3.41 (3H, s, OMe), 3.38 (3H, s, OMe), 3.25 (3H, s, OMe), 3.23 (3H, s, OMe), 2.71-2.60 (m, H-2), 1.45 (3H, s, 8'-Me), 1.43 (3H, s, 8'-Me), 1.36 (3H, s, 8'-Me), 1.30 (3H, s, 8'-Me), 1.02 (3H, d, $J=7.3$ Hz, 2-Me), 0.93 (3H, d, $J=7.1$ Hz, 2-Me), 0.89 (3H, d, $J=6.2$ Hz, 5'-Me), 0.86 (3H, d, $J=6.4$ Hz, 5'-Me).

Compound 7b. Signals of the major isomer: IR (film) 3418, 1708, 1684 cm^{-1} ; ^1H NMR δ 7.85-7.30 (7H, m, Ar), 5.46 (1H, s, OH, disappears upon addition of D_2O), 4.83 (1H, dt, $J=4.2$ and 10.7 Hz, H-1'), 4.14 (1H, s, $\text{CH}(\text{OMe})_2$), 3.38 (3H, s, OMe), 3.23 (3H, s, OMe), 2.45-2.25 (4H, m), 2.20-2.05 (2H, m), 1.85-1.60 (4H, m), 1.55-1.45 (1H, m), 1.43 (3H, s, Me), 1.26 (3H, s, Me), 1.13 (3H, s, Me), 1.01 (3H, d, $J=6.6$, 2-Me), 0.91 (3H, d, $J=6.4$ Hz, 5'-Me); ^{13}C NMR δ 207.24 (C-1), 178.25 (COOR), 149.21 (Ar), 133.20 (Ar), 131.39 (Ar), 127.55 (Ar x 2), 127.06 (Ar), 125.72 (Ar), 125.10 (Ar), 124.65 (Ar), 122.58 (Ar), 111.80 ($\text{CH}(\text{OMe})_2$), 80.33 (C-3), 75.87 (C-1'), 58.92 (OMe), 57.50 (OMe), 48.77 (C-5'), 48.07 (C-2), 44.67 (C-4), 40.34 (C-6'), 39.50 (C-8'), 35.02 (C-6), 34.30 (C-4'), 30.94 (C-2'), 28.75 (8'-Me), 26.62 (C-5), 24.50 (8'-Me), 24.02 (C-3'), 21.67 (5'-Me), 19.29 (4-Me), 7.01 (2-Me).

Preparation of (+)-4b

To a solution of the mixture of aldols **7b** (141.0 mg, 0.269 mmol) in dry toluene (9.3 mL) was added copper (II) sulfate on silica gel²⁰ (251.3 mg, 0.276 mmol). The vigorously stirred pale blue suspension was heated to reflux until the TLC spot for the starting material had disappeared (1 h). The mixture was filtered through a bed of Celite with copious washings with Et_2O . Evaporation of the filtrate afforded a residue which was recrystallized from diisopropyl ether to yield pure acetal (+)-**4b**²¹ (24 mg, 23% from **6c**): mp 140-142°C; $[\alpha]_D^{20} +17.14$ ($c=0.7$, CHCl_3); IR (KBr) 1790, 1664 cm^{-1} ; ^1H NMR δ 5.82 (1H, s, H-3), 3.64 (3H, s, OMe), 2.78-2.42 (2H, m, H-6), 2.28-1.92 (2H, m, H-7), 1.81 (3H, s, 4-Me), 1.57 (3H, s, 8-Me); ^{13}C NMR δ 197.26 (C-5), 177.62 (C-1), 151.72 (C-9), 130.89 (C-4), 101.86 (C-3), 57.50 (OMe), 40.39 (C-8), 32.43 (C-6), 30.17 (C-7), 21.90 (8-Me), 10.26 (4-Me). Chromatography of the mother liquors yielded pure **4d** (5.2 mg, 4.9% from **6c**): mp 89-90.5 °C (diisopropyl ether); IR (KBr) 1775, 1670 cm^{-1} ; ^1H NMR δ 6.14 (1H, dd, $J=1.29$ and 1.33 Hz, H-3), 3.62 (3H, s, OMe), 2.64-2.56 (2H, m, H-6), 2.20-2.12 (2H, m, H-7), 1.86 (3H, d, $J=1.29$ Hz, 4-Me), 1.47 (3H, s, 8-Me); ^{13}C NMR δ 197.15 (C-5), 176.35 (C-1), 152.49 (C-9), 132.44 (C-4), 102.57 (C-3), 56.77 (OMe), 43.10 (C-8), 32.14 (C-6), 26.64 (C-7), 23.17 (8-Me), 11.27 (4-Me).

Equilibration of **4d**

To a solution of **4d** (16 mg, 0.08 mmol) in dry benzene (2 mL) was added a crystal of p-TsOH. After 20 h of stirring at room temperature the solvent was evaporated, the residue taken up with Et₂O (20 mL) and poured into brine (20 mL). The aqueous layer was extracted with Et₂O (3x10 mL), the organic extracts were dried (Na₂SO₄) and evaporated to give a 8:1 mixture of epimers **4b** and **4d**, on the basis of its ¹H NMR spectrum. The residue was crystallized from diisopropyl ether to give pure (+)-**4b**, its melting point and spectral data were coincident with those reported above. Anal. Calcd. for C₁₁H₁₄O₄: C, 62.83; H, 6.72. Found: C, 62.49; H, 6.72.

Preparation of (8*R*)-**4a**

To a solution of (+)-**4b** (57.0 mg, 0.27 mmol) in THF (6.3 mL) was added 3N aqueous HCl (1.5 mL). The resulting solution was heated at 60°C for 1 h. The reaction mixture was poured into brine (5 mL) and extracted with Et₂O (2x15 mL) and EtOAc (2x15 mL). The combined organic extracts were washed with saturated NaHCO₃ solution and brine, dried (Na₂SO₄), and evaporated. The residue (53.5 mg, 100%) that crystallized on standing was washed with Et₂O, affording pure **4a**: ¹H NMR (acetone-d₆) δ 7.23 (1H, br s, disappears upon addition of D₂O), 6.55 (1H, br s), 1.78 (3H, s), 1.53 (3H, s). The ¹H NMR spectrum is coincident with that reported by White *et al.*⁸ for (±)-**4a**. Melting point determinations gave non reproducible values due to extensive decomposition.

Transformation of **4a** into (-)-**4c**

To a solution of **4a** (25.2 mg, mmol), in MeOH (1 mL), CeCl₃·7H₂O (25 mg, 0.65 mmol) and NaBH₄ (8 mg, 0.21 mmol) were added. After 20 min the reaction was completed (TLC). Upon acidification with 6N aqueous HCl (pH 1), the mixture was poured into brine (10 mL) and extracted with Et₂O (3 x 10 mL) and EtOAc (3 x 10 mL). The organic phases were dried (Na₂SO₄) and evaporated. The residue was dissolved in acetone and oxidized at 0°C with Jones reagent. After stirring the mixture at RT for 20 min, Celite and 2-propanol were added. The resulting slurry was filtered through a short pad of silica gel, washed copiously with EtOAc and the filtrate evaporated to yield crystalline (-)-**4c** (26 mg, 100% from **4a**), mp 95.5-96.5°C; [α]_D²⁰ -226 (c=0.35, CHCl₃), ee>95%. [lit⁸ mp 58-60°C for the racemic compound]. The ¹H NMR spectrum is coincident with that reported by White *et al.*⁸ Compound (-)-**4c** ¹H NMR δ 4.98 (2H, bs, H-3), 2.64-2.56 (2H, m), 2.24-2.00 (2H, m), 1.74 (3H, bs, 4-Me), 1.50 (3H, s, 8-Me).

Preparation of **7c** (6f→6g→7c)

Compound **7c** was prepared following the procedure described for the preparation of **7a**, using *exo*-3-hydroxy-*exo*-2-(β-naphthyl)bornane as chiral alcohol. This chiral auxiliary was prepared as described below.

Compound 6f: Colorless oil. Yield: 68%; ¹H NMR δ 7.80-7.63 (4H, m, Ar), 7.45-7.30 (3H, m, Ar), 5.32 (1H, d, J= 8.6 Hz, H-3'), 4.13 (1H, s, H-4), 3.52 (1H, bd, J= 8.6 Hz, H-2'), 3.14 (3H, s, OMe), 3.10 (3H, s, OMe), 3.06 (2H, dd, H-2), 2.10-1.60 (5H, m), 1.33 (3H, s, Me), 1.04 (3H, s, Me), 0.97 (3H, s, Me). The following signals of the enol form were also detected: δ 11.66 (1H, s, OH), 5.39 (1H, d, J=8.6, H-3'), 4.92 (1H, s, H-2), 4.60 (1H, s, H-4), 3.21 (3H, s, OMe), 2.98 (3H, s, OMe), 1.40 (3H, s, Me), 1.00 (3H, s, Me). ¹³C NMR δ 197.24 (C-3), 165.62 (C-1), 136.07 (Ar), 132.68 (Ar), 131.31 (Ar), 129.78 (Ar), 129.04 (Ar), 127.60 (Ar), 126.89 (Ar), 126.34 (Ar), 125.33 (Ar), 125.19 (Ar), 102.45 (C-4), 80.46 (C-3'), 60.27 (C-2'), 54.03 (OMe), 53.90 (OMe), 50.18 (C-4'), 49.34 (C-1'), 47.60 (C-7'), 43.91 (C-2), 40.70 (C-6'), 23.46 (C-5'), 22.72 (C-9'), 21.34 (C-8'), 13.67 (C-10'). The following signals of the enol form were also detected: δ 171.16 (C-3), 169.69 (C-1), 135.87 (Ar), 129.90 (Ar), 129.27 (Ar), 127.92 (Ar), 126.80 (Ar), 126.22 (Ar),

125.10 (Ar), 124.97 (Ar), 98.67 (C-4), 90.47 (C-2), 79.57 (C-3'), 60.70 (C-2'), 52.89 (OMe), 51.71 (OMe), 50.09 (C-4'), 49.42 (C-1'), 47.72 (C-7'), 23.57 (C-5'), 21.46 (C-8'), 14.92 (C-10').

Compound 6g: Colorless oil. Yield: 100%; ^1H NMR δ 7.80-7.68 (8H, m, Ar), 7.45-7.30 (6H, m, Ar), 5.31 (1H, d, J = 8.7 Hz, H-3'), 5.29 (1H, d, J = 8.7 Hz, H-3'), 4.23 (1H, s, H-4), 4.05 (1H, s, H-4), 3.53 (2H, d, J = 8.7 Hz, H-2'), 3.38 (1H, q, J = 7.2 Hz, H-2), 3.30 (1H, q, J = 7.2 Hz, H-2), 3.15 (3H, s, OMe), 3.13 (3H, s, OMe), 3.12 (3H, s, OMe), 3.11 (3H, s, OMe), 2.00-1.30 (10H, m), 1.35 (3H, s, Me), 1.07 (3H, s, Me), 0.97 (3H, s, Me), 0.75 (3H, d, J = 7.2 Hz, C-2-Me), 0.67 (3H, d, J = 7.2 Hz, C-2-Me).

Compound 7c: Colorless oil; ^1H NMR δ 7.80-7.65 (4H, m, Ar), 7.45-7.30 (3H, m, Ar), 5.27 (1H, d, J = 7.7 Hz, H-3'), 4.99 (1H, s, OH), 4.07 (1H, s, $\text{CH}(\text{OMe})_2$), 3.58 (1H, d, J = 7.7 Hz, H-2'), 3.40 (3H, s, OMe), 3.22 (3H, s, OMe), 2.35-1.20 (10H, m), 1.40 (3H, s, 4-Me), 1.14 (3H, s), 1.00 (3H, s, Me), 0.97 (3H, d, J = 6.7 Hz, C-2-Me), 0.62 (3H, s, H-10').

Preparation of 7d (6a→6h→6i→7d)

Compound **7d** was prepared following the procedure described for the preparation of **7a**, using *endo*-3-hydroxy-*endo*-2-(β -naphthyl)bomane as chiral alcohol. This chiral auxiliary was prepared as described below.

Compound 6h: Colorless oil. Yield: 87%, IR (film) 1748, 1729, 1659, 1633 cm^{-1} ; ^1H NMR δ 7.87-7.60 (4H, m, Ar), 7.45-7.30 (3H, m, Ar), 5.61-5.51 (1H, m, H-3'), 4.38 (1H, s, H-4), 3.52-3.30 (3H, om, H-2 + H-2'), 3.28 (3H, s, OMe), 3.20 (3H, s, OMe), 2.20-1.80 (2H, m), 1.75-1.50 (2H, m), 1.25-1.00 (1H, m), 1.15 (3H, s, Me), 1.02 (3H, s, Me), 0.70 (3H, s, Me). The following signals of the enol form were also detected: δ 11.52 (1H, s, OH), 5.61-5.51 (1H, om, H-3'), 5.41 (1H, s, H-2), 4.68 (1H, s, H-4), 3.30 (3H, s, OMe), 3.10 (3H, s, OMe), 1.17 (3H, s, Me), 1.03 (3H, s, Me), 0.71 (3H, s, Me); ^{13}C NMR δ 197.63 (C-3), 165.92 (C-1), 134.39 (Ar), 132.88 (Ar), 131.82 (Ar), 130.08 (Ar), 129.98 (Ar), 127.66 (Ar), 127.05 (Ar), 126.39 (Ar), 125.20 (Ar), 125.08 (Ar), 102.97 (C-4), 75.29 (C-3'), 54.38 (2 x OMe), 52.32 (C-4'), 50.68 (C-1'), 48.97 (C-2'), 46.90 (C-7'), 44.38 (C-2), 27.58 (C-6'), 19.33 (C-9'), 19.14 (C-5'), 18.48 (C-8'), 14.46 (C-10'). The following signals of the enol form were also detected: δ 171.66 (C-3), 169.90 (C-1), 98.87 (C-4), 90.72 (C-2), 74.47 (C-3'), 53.13 (OMe), 52.52 (OMe), 52.08 (C-4').

Compound 6i: Colorless oil. Yield: 100%; ^1H NMR δ 7.85-7.60 (8H, m, Ar), 7.48-7.30 (6H, m, Ar), 5.54 (2H, dd, J = 5.3, 10.1 Hz, H-3'), 4.41 (1H, s, H-4), 4.38 (1H, s, H-4), 3.70 (1H, q, J = 7.3 Hz, H-2), 3.60-3.30 (2H, m, H-2'), 3.26 (3H, s, OMe), 3.25 (3H, s, OMe), 3.18 (3H, s, OMe), 3.09 (3H, s, OMe), 2.10-1.10 (10H, m), 1.21 (3H, d, J = 7.3 Hz, C-2-Me), 1.15 (3H, s, Me), 1.09 (3H, d, J = 7.3 Hz, C-2-Me), 1.01 (3H, s, Me), 0.69 (3H, s, H-10').

Compound 7d: Yield: 22%; mp 205.2-206.6°C (EtOH); $[\alpha]_{\text{D}}^{20}$ -5.35 (c = 0.99, CHCl_3); IR (KBr) 3451, 1705, 1692 cm^{-1} ; ^1H NMR δ 7.85-7.70 (4H, m, Ar), 7.50-7.35 (3H, m, Ar), 5.51 (1H, ddd, J = 1.7, 4.3, 10.4 Hz, H-3'), 4.99 (1H, s, OH), 4.17 (1H, s, $\text{CH}(\text{OMe})_2$), 3.49 (1H, dd, J = 1.6, 10.4 Hz, H-2'), 3.41 (3H, s, OMe), 3.32 (3H, s, OMe), 2.70 (1H, dt, J = 5.5, 13.2 Hz, H-6), 2.43 (2H, m, H-2+H-5), 2.14 (3H, m, H-4'+H-5+H-5'), 1.77 (3H, m, H-6+H-5'+H-6'), 1.30 (1H, m, H-6'), 1.18 (3H, s, H-8'), 1.05 (3H, d, J = 6.7 Hz, C-2-Me), 1.04 (3H, s, H-9'), 1.00 (3H, s, C-4-Me), 0.71 (3H, s, H-10'); ^{13}C NMR δ 206.89 (C-1), 178.26 (COOR), 134.12 (Ar), 132.67 (Ar), 131.82 (Ar), 130.27 (Ar), 130.21 (Ar), 127.43 (Ar), 127.15 (Ar), 126.33 (Ar), 125.49 (Ar), 125.17 (Ar), 111.28 ($\text{CH}(\text{OMe})_2$), 80.54 (C-3), 74.86 (C-3'), 59.29 (OMe), 56.89 (OMe), 52.27 (C-2'), 50.81 (C-1'), 49.21 (C-4'), 48.04 (C-2), 46.81 (C-7'), 45.03 (C-4), 35.87 (C-5), 27.66 (C-6'), 26.58 (C-6), 19.73 (C-4-Me), 19.37 (C-9'), 19.21 (C-5'), 18.52 (C-8'), 14.44 (C-10'), 7.04 (C-2-Me); HRMS: Found for M^+ 522.2987, Calc. for $\text{C}_{32}\text{H}_{42}\text{O}_6$: 522.2982.

Crystal Data: Empirical formula, C₃₂H₄₂O₆, M= 522.30, T= 293(2) °K, orthorhombic, a= 9.2930(10) Å, b= 13.376(2) Å, c= 22.730(2) Å, α= 90°, β= 90°, γ= 90°; V= 2825.4(6) Å³, space group P2₁2₁2₁, Z= 4, d calc. 1.223 g/cm³, F(000)= 1064.

Data collection θ range for 1.77 to 26.00°, reflections collected: 6300, independent reflections: 5562 (R_{int}, 0.0170), goodness-of-fit on F²: 1.015. Final R indices [I>2σ(I)], R1= 0.0402, wR2= 0.0984, R indices (all data), R1= 0.0915, wR2= 0.1136.

Preparation of 4b

From 7c: Following the same procedure described for the preparation of (+)-**4b** from **7b**, **7c** gave (+)-**4b** (24% from **6f**), ee=48%.

From 7d: Following the same procedure described for the preparation of (+)-**4b** from **7b**, pure **7d** (191mg, 0.37 mmol) gave, after column chromatography, (-)-**4b**, *ent*-**4d**, **8** and a mixture of alkenes derived from the chiral auxiliary. Compound (-)-**4b** (36.8 mg, 48%), mp 141-143°C (diisopropyl ether); [α]_D²⁰ -18.94 (c=0.47, CHCl₃), ee>95%, with spectral data coincident with those of (+)-**4b**. The enantiomer of **4d** (11.1 mg, 14%), showed mp, IR and ¹H NMR identical with **4d**. Acid catalyzed equilibration of *ent*-**4d** gave (-)-**4b**. Compound **8** (56.7 mg, 34%) is a colorless oil; IR (film) 1742, 1675 cm⁻¹; ¹H NMR δ 10.33 (1H, s, CHO), 7.82-7.21 (7H, m, Ar), 5.62 (1H, dd, J= 4.4, 6.5 Hz, H-3'), 3.43 (1H, dd, J= 2.1, 10.4 Hz, H-2'), 2.50-2.10 (3H, m), 2.32 (3H, s, Me), 2.05-1.20 (6H, m), 1.37 (3H, s, Me), 1.15 (3H, s, Me), 0.99 (3H, s, Me), 0.69 (3H, s, Me); ¹³C NMR δ 199.30 (C-1), 192.70 (CHO), 174.29 (COOR), 147.98 (C-3), 143.21 (C-2), 134.17 (Ar), 132.63 (Ar), 131.79 (Ar), 130.46 (Ar), 130.30 (Ar), 127.34 (Ar), 127.23 (Ar), 126.10 (Ar), 125.63 (Ar), 125.35 (Ar), 74.57 (C-3'), 52.28 (C-2'), 50.83 (C-4), 48.96 (C-4'), 47.02 (C-1'), 43.79 (C-7'), 33.18 (C-6), 32.46 (C-6'*), 27.74 (C-5), 20.83 (4-Me), 19.34 (C-9' + C-5'*), 18.57 (C-8'), 14.49 (C-10'), 9.92 (2 Me). The assignments for signals marked with (*) may be reversed.

Resolution of (±)-4a

To a suspension of (±)-**4a** (170 mg, 0.87 mmol), prepared according to the sequence described by White *et al.*,⁸ in dry benzene (8 mL), was added a solution of α-naphthylborneol²⁵ (275 mg, 0.98 mmol) in benzene (8 mL) and a crystal of *p*-TsOH at RT. After 9 h of heating at reflux the solvent was evaporated, the residue taken in Et₂O, poured into brine, and the aqueous phase extracted with Et₂O (4 x 25 mL) and EtOAc (3 x 25 mL). The combined organic extracts were washed with saturated aqueous NaHCO₃ solution (50 mL), dried (Na₂SO₄) and evaporated to give a residue which was chromatographed to yield the less polar acetal **9** (88.1 mg, 22%), a 2:1 mixture of **9** and **10** (100.3 mg, 25%) and the more polar acetal **10** (116.8 mg, 30%).

Acetal 9: mp 225-227°C; [α]_D²⁰ -156 (c=2.0, CHCl₃); IR (KBr) 1786, 1670 cm⁻¹; ¹H NMR δ 8.17 (1H, d, J=8.5 Hz, H-8''), 7.82 (1H, dd, J=1.4, 8.0 Hz, Ar), 7.68-7.32 (5H, m, Ar), 5.44 (1H, s, H-3), 4.46 (1H, d, J=8.5 Hz, H-3'), 4.13 (1H, d, J=8.5 Hz, H-2'), 2.40-2.32 (2H, m), 2.18 (1H, d, J=5.1 Hz), 2.05-1.68 (4H, m), 1.58-1.38 (2H, m), 1.33 (3H, s, Me), 1.29 (3H, s, Me), 1.19 (3H, s, Me), 1.01 (3H, s, Me), 0.21 (3H, s, 4-Me); ¹³C NMR δ 197.94 (C-5), 177.91 (C-1), 151.02 (C-9), 135.08 (Ar), 133.75 (Ar), 133.34 (Ar), 130.45 (C-4), 129.35 (Ar), 127.53 (Ar), 126.48 (Ar), 126.06 (Ar), 124.99 (Ar), 124.70 (Ar), 122.83 (Ar), 101.27 (C-3), 88.47 (C-3'), 56.24 (C-2'), 52.44 (C-4'), 49.20 (C-1'*), 48.22 (C-7'*), 42.31 (C-6'), 40.24 (C-8), 32.17 (C-6), 30.07 (C-7), 24.29 (C-8'**), 23.85 (C-5'), 21.44 (C-9'**), 21.08 (8-Me**), 14.41 (C-10'), 8.22 (4-Me). The assignments for signals marked with (*) and (**) may be reversed; HRMS: Found for M⁺ 458.24086, Calc. for C₃₀H₃₄O₄: 458.2448.

Acetal 10: mp 198–199.5°C; $[\alpha]_D^{20}$ -299 ($c=2.0$, CHCl_3); IR (KBr) 1780, 1670 cm^{-1} ; ^1H NMR δ 8.12 (1H, d, $J=8.6$ Hz, H-8''), 7.75 (1H, dd, $J=1.2, 8.0$ Hz, Ar), 7.62–7.27 (5H, m, Ar), 5.90 (1H, s, H-3), 4.69 (1H, d, $J=8.9$ Hz, H-3'), 4.11 (1H, d, $J=8.9$ Hz, H-2'), 2.32–2.25 (2H, m), 2.17 (1H, d, $J=5.0$ Hz), 2.10–1.90 (1H, m), 1.89–1.68 (3H, m), 1.66 (3H, s, 4-Me), 1.43–1.35 (2H, m), 1.31 (3H, s, Me), 1.27 (3H, s, Me), 1.05 (3H, s, Me), -0.16 (3H, s, 8-Me); ^{13}C NMR δ 197.31 (C-5), 176.83 (C-1), 151.96 (C-9), 135.35 (Ar), 133.40 (Ar), 133.25 (Ar), 129.38 (C-4), 128.32 (Ar), 126.95 (Ar), 126.12 (2 x Ar), 125.12 (Ar), 124.11 (Ar), 123.53 (Ar), 97.54 (C-3), 84.50 (C-3'), 55.49 (C-2'), 49.02 (C-1'*), 48.53 (C-4'), 48.11 (C-7'*), 42.51 (C-6'), 39.83 (C-8), 32.13 (C-6), 29.77 (C-7), 23.92 (C-8'**), 23.68 (C-5'), 21.57 (C-9'**), 18.70 (8-Me**), 14.70 (C-10'), 10.08 (4-Me). The assignments for signals marked with (*) and (**) may be reversed; HRMS: Found for M^+ 458.24686, Calc. for $\text{C}_{30}\text{H}_{34}\text{O}_4$: 458.2448.

Crystal Data: Empirical formula, $\text{C}_{30}\text{H}_{34}\text{O}_4$, $M=458.25$, $T=293(2)$ °K; orthorhombic, $a=7.0491(5)$ Å, $b=7.9369(5)$ Å, $c=43.357(5)$ Å, $\alpha=90.000(8)^\circ$, $\beta=90.000(8)^\circ$, $\gamma=90.000(6)^\circ$, $V=2425.7(4)$ Å³, space group $\text{P}2_12_12_1$, $Z=4$, $d_{\text{calc}}=1.255$ g/cm³, $F(000)=988$

Data collection θ range for data collection, 1.88 to 26.08°, reflections collected: 4134, independent reflections: 3597 ($R_{\text{int}}=0.0149$), goodness-of-fit on F^2 : 1.052. Final R indices [$I>2\sigma(I)$], $R_1=0.0486$, $wR_2=0.1316$; R indices (all data), $R_1=0.1108$, $wR_2=0.2710$.

Hydrolysis of **9** (**9**→(**8R**)-**4a**→(-)-**4c**)

To a solution of **9** (198 mg, 0.43 mmol) in THF (40 mL), 6N aqueous HCl (5 mL), was added. The solution was heated at reflux for 6 h, until the TLC spot for the starting material had disappeared. The mixture was cooled at RT, made alkaline with 2.5 M aqueous NaOH to pH 11 and poured into H₂O (50 mL). The aqueous phase was extracted with Et₂O (4x50 mL) and the combined ethereal extracts, containing the resolving agent, were dried (Na_2SO_4) and evaporated (120 mg, 100%). The aqueous phase was acidified with 6N aqueous HCl to pH 1 and extracted with Et₂O (3 x 100 mL) and EtOAc (3 x 100 mL). The organic phases were washed with brine (100 mL), dried (Na_2SO_4) and evaporated to yield **4a** (62 mg, 73%).

To a magnetically stirred solution of crude **4a** (50.4 mg), in MeOH (2 mL), $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (50 mg, 0.13 mmol) and NaBH_4 (16 mg, 0.42 mmol) were added. After 20 min the reaction was completed (TLC). Upon acidification with 6N aqueous HCl (pH 1), the mixture was poured into brine (20 mL) and extracted with Et₂O (3 x 10 mL) and EtOAc (3 x 10 mL). The organic phases were dried (Na_2SO_4) and evaporated. The residue was dissolved in acetone and oxidized at 0°C with Jones reagent. After stirring the mixture at RT for 20 min, Celite and 2-propanol were added. The resulting slurry was filtered through a short pad of silica gel, washed copiously with EtOAc and the filtrate evaporated to yield crystalline (-)-**4c** (46 mg, 100% from **4a**), mp 95.5–96.5°C; $[\alpha]_D^{20}$ -226 ($c=0.35$, CHCl_3), $ee>95\%$. [lit.⁸ mp 58–60°C for the racemic compound]. The ^1H NMR spectrum is coincident with that reported by White *et al.*⁸ Compound (-)-**4c** ^1H NMR δ 4.98 (2H, bs, H-3), 2.64–2.56 (2H, m), 2.24–2.00 (2H, m), 1.74 (3H, bs, 4-Me), 1.50 (3H, s, 8-Me).

Hydrolysis of **10** (**10**→(**8S**)-**4a**→(+)-**4c**)

To a solution of **10** (40.0 mg, 0.087 mmol) in dioxane (6 mL), 6N aqueous HCl (0.6 mL), was added. The solution was heated at reflux for 6.5 h until the TLC spot for the starting material had disappeared. The mixture was worked up as described for the hydrolysis of **9**, to give crude **4a** (17.1 mg, 100%). Following the same sequence as mentioned above, crystalline (+)-**4c** was obtained (100%), mp 95.0–96.0°C; $[\alpha]_D^{20} +220$ ($c=0.35$, CHCl_3), $ee>95\%$. [lit.²⁴ $[\alpha]_D^{20} +181$ ($c=6.1$, CHCl_3), $ee=94\%$]; ^1H NMR δ 4.99 (2H, dd, $J=20.2, 21.4$ Hz,

H-3), 2.64-2.56 (2H, m), 2.25-2.00 (2H, m), 1.73 (3H, bs, 4-Me), 1.50 (3H, s, 8-Me); ^{13}C NMR δ 196.43 (C-5), 178.16 (C-1), 154.44 (C-9), 128.73 (C-4), 67.14 (C-3), 49.19 (C-8), 32.33 (C-6), 29.40 (C-7), 21.12 (8-Me), 10.62 (4-Me).

Preparation of *exo*-3-hydroxy-2-*exo*-(β -naphthyl)bornane

This chiral auxiliary was prepared from (+)-camphor following the sequence reported by Taber et al. for the preparation of the corresponding α -naphthyl derivative,²⁵ consequently, only the spectral data of the intermediates are described.

2-hydroxy-2-(β -naphthyl)bornanes: ^1H NMR δ 8.00-7.40 (14H, m, Ar), 2.50-1.20 (14H, m), 1.31 (3H, s, Me), 0.98 (3H, s, Me), 0.95 (3H, s, Me), 0.93 (3H, s, Me), 0.90 (3H, s, Me) and 0.83 (3H, s, Me).

2-(β -naphthyl)born-2-ene: mp 50-53.4°C; IR (KBr) 1742, 1628, 1605 cm^{-1} ; ^1H NMR δ 7.85-7.30 (7H, m, Ar), 6.10 (1H, d, J = 3.5 Hz, H-3), 2.43 (1H, t, J = 3.5 Hz, H-4), 2.05-1.30 (4H, m, H-5+H-6), 1.17 (3H, s, Me), 0.94 (3H, s, Me), 0.85 (3H, s, Me); ^{13}C NMR δ 149.69 (C-2), 135.96 (Ar), 133.36 (Ar), 132.28 (C-3), 132.16 (Ar), 127.71 (Ar), 127.45 (Ar), 127.39 (Ar), 125.80 (Ar), 125.54 (Ar), 125.16 (Ar), 124.48 (Ar), 57.05 (C-1), 54.98 (C-7), 51.66 (C-4), 31.92 (C-6), 25.69 (C-5), 19.65 (C-8 + C-9), 12.70 (C-10).

3-hydroxy-2-(β -naphthyl)bornanes: The 1:1 mixture of diastereomeric alcohols was separated by column chromatography to yield *exo*-3-hydroxy-*endo*-2-(β -naphthyl)bornane: IR (film) 3441 cm^{-1} , ^1H NMR δ 7.85-7.60 (4H, m, Ar), 7.45-7.26 (3H, m, Ar), 4.32 (1H, d, J = 4.4 Hz, H-3), 3.27 (1H, dt, J = 1.8, 4.4 Hz, H-2), 2.40-1.40 (5H, m), 1.31 (3H, s, Me), 0.94 (3H, s, Me), 0.80 (3H, s, Me); ^{13}C NMR δ 137.84 (Ar), 133.24 (Ar), 132.20 (Ar), 128.30 (Ar), 127.66 (Ar), 127.49 (Ar), 127.43 (Ar), 127.09 (Ar), 125.78 (Ar), 125.24 (Ar), 80.29 (C-3), 61.54 (C-2), 52.28 (C-4), 51.16 (C-1*), 49.49 (C-7*), 27.10 (C-6), 25.14 (C-5), 20.60 (C-9), 20.07 (C-8), 13.95 (C-10), and *endo*-3-hydroxy-*exo*-2-(β -naphthyl)bornane: IR (film) 3415 cm^{-1} , ^1H NMR δ 7.82-7.73 (4H, m, Ar), 7.49-7.34 (3H, m, Ar), 5.11 (1H, dt, J = 1.2, 6.5 Hz, H-3), 2.75 (1H, d, J = 6.5 Hz, H-2), 2.10-1.50 (5H, m), 0.97 (3H, s, Me), 0.90 (3H, s, Me), 0.76 (3H, s, Me); ^{13}C NMR δ 138.61 (Ar), 133.12 (Ar), 131.79 (Ar), 129.07 (Ar), 127.63 (Ar), 127.17 (Ar), 126.82 (Ar), 125.79 (Ar), 125.60 (Ar), 125.16 (Ar), 74.46 (C-3), 61.66 (C-2), 51.07 (C-1), 50.96 (C-4), 47.80 (C-7), 40.73 (C-6), 21.33 (C-9), 19.78 (C-8), 18.28 (C-5), 14.47 (C-10).

***exo*-2-(β -naphthyl)bornan-3-one:** Obtained from *endo*-3-hydroxy-*exo*-2-(β -naphthyl)bornane. Mp 140-160.5°C (dec.); IR (KBr) 1736 cm^{-1} ; ^1H NMR δ 7.80-7.72 (3H, m, Ar), 7.46-7.34 (4H, m, Ar), 3.54 (1H, bs: $w_{1/2}$ = 2.9 Hz, H-2), 2.36 (1H, d, J = 4.1 Hz, H-4), 2.20-1.90 (2H, m), 1.75-1.68 (2H, m), 1.05 (3H, s, Me), 1.01 (3H, s, Me), 0.96 (3H, s, Me); ^{13}C NMR δ 217.39 (C-3), 134.33 (Ar), 132.95 (Ar), 131.77 (Ar), 128.78 (Ar), 128.57 (Ar), 127.80 (Ar), 127.15 (Ar), 126.91 (Ar), 125.61 (Ar), 125.52 (Ar), 62.47 (C-2*), 59.73 (C-4*), 50.78 (C-1), 47.76 (C-7), 38.65 (C-6), 21.72 (C-5), 20.70 (C-9), 19.65 (C-8), 14.06 (C-10); MS m/z 279 (M+1), 278 (M⁺), 168 (100).

***exo*-3-hydroxy-*exo*-2-(β -naphthyl)bornane:** mp 60-62°C; IR (KBr) 3564 cm^{-1} ; ^1H NMR δ 7.87-7.75 (4H, m, Ar), 7.48-7.40 (3H, m, Ar), 4.24 (1H, d, J = 8.0 Hz, H-3), 3.43 (1H, d, J = 8.0 Hz, H-2), 1.98 (1H, d, J = 5.0 Hz, H-4), 1.95-1.63 (2H, m), 1.45 (3H, s, Me), 1.39-1.20 (2H, m), 1.08 (3H, s, Me), 0.97 (3H, s, Me); ^{13}C NMR δ 136.48 (Ar), 132.93 (Ar), 131.40 (Ar), 129.94 (Ar), 129.66 (Ar), 127.60 (Ar), 126.99 (Ar), 126.72 (Ar), 125.46 (Ar), 125.12 (Ar), 78.68 (C-3), 62.41 (C-2), 51.52 (C-4), 49.14 (C-1), 47.40 (C-7), 40.99 (C-6), 23.66 (C-5), 23.20 (C-9), 21.81 (C-8), 13.84 (C-10); MS m/z 281 (M+1), 280 (M⁺), 170 (100).

Preparation of *endo*-3-hydroxy-*endo*-2-(β -naphthyl)bornane

Preparation of 2-(β -naphthyl)bornan-3-ones

Jones reagent (214 μ L, 1.71 mmol) was added dropwise to a stirred solution of the 1:1 diastereoisomeric mixture of 3-hydroxy-2-(β -naphthyl)bornanes (469.1 mg, 1.675 mmol) in acetone (10 mL) at 0°C. After complete addition, the mixture was allowed to reach RT and stirred until the reaction reached completion by the absence of starting material by TLC. The reaction was then quenched by the addition of 2-propanol (1 mL) and Celite (200 mg). The suspension was filtered through silica gel with copious washings (acetone). The filtrate was concentrated to yield the crude ketones as an oil (448.3 mg, 96%). ^1H NMR δ 7.85-7.70 (6H, m, Ar), 7.45-7.30 (6H, m, Ar), 7.32 (1H, dd, J = 1.3, 8.4 Hz, Ar), 7.13 (1H, dd, J = 1.8, 8.5, Ar), 3.66 (1H, bs, H-2), 3.54 (1H, bs, H-2), 2.45-1.30 (10H, m), 1.13 (3H, s, Me), 1.07 (3H, s, Me), 1.05 (6H, s, 2 x Me), 1.01 (3H, s, Me), 0.96 (3H, s, Me).

Preparation of *endo*-2-(β -naphthyl)bornan-3-one

To a solution of the crude mixture of bornanones (854 mg, 3.07 mmol) in EtOH (15 mL), KOH (877 mg, 15.6 mmol) and water (2 mL) were added. The resulting clear solution was heated at reflux for 6 h. The cooled solution was saturated with solid NaCl, and extracted exhaustively with CH_2Cl_2 . The combined organic extracts were dried (MgSO_4) and evaporated to give *endo*-2-(β -naphthyl)bornan-3-one (854 mg, 100%), as large colorless crystals, mp 152.6-153.5°C; IR (KBr) 1735 cm^{-1} ; ^1H NMR δ 7.85-7.75 (3H, m, Ar), 7.48-7.42 (3H, m, Ar), 7.13 (1H, dd, J = 1.8, 8.5 Hz, Ar), 3.66 (1H, bs, H-2), 2.41 (1H, d, J = 5.1 Hz, H-4), 2.21-2.03 (1H, m, H-5 exo), 1.75-1.55 (1H, m, H-5 endo), 1.50-1.37 (2H, m, H-6), 1.13 (3H, s, H-9), 1.07 (3H, s, H-8), 1.05 (3H, s, H-10); ^{13}C NMR δ 217.18 (C-3), 133.58 (Ar), 133.01 (Ar), 132.08 (Ar), 128.20 (Ar), 127.47 (3 x Ar), 127.20 (Ar), 125.65 (Ar), 125.39 (Ar), 61.53 (C-2), 60.44 (C-4), 51.13 (C-1), 45.84 (C-7), 27.32 (C-6), 22.16 (C-5), 18.79 (C-9), 17.81 (C-8), 13.81 (C-10); MS m/z 279 ($M+1$), 278 (M^+); HRMS: Found for M^+ 278.1671, Calc. for $\text{C}_{20}\text{H}_{22}\text{O}$: 278.1670.

Preparation of *endo*-3-hydroxy-*endo*-2-(β -naphthyl)bornane

The reduction of *endo*-2-(β -naphthyl)bornan-3-one with lithium aluminum hydride was carried out following the procedure of Taber *et al.*²⁵ to afford *endo*-3-hydroxy-*endo*-2-(β -naphthyl)bornane, as colorless needles (306 mg, 100%); mp 109-111°C (EtOH); $[\alpha]_{\text{D}}^{20}$ -5.86 (c = 1.11, CHCl_3); IR (KBr) 3406 cm^{-1} ; ^1H NMR δ 7.85-7.75 (4H, m, Ar), 7.50-7.38 (3H, m, Ar), 4.68 (1H, bdd (simplifies when irradiating OH signal), J = 3.3, 9.4 Hz, H-3), 3.28 (1H, dd, J = 2.3, 9.4 Hz, H-2), 2.25-1.20 (5H, m, H-4+H-5+H-6), 1.50 (1H, bs, OH), 1.10 (3H, s, H-8), 1.01 (3H, s, H-9), 0.69 (3H, s, H-10); ^{13}C NMR δ 135.11 (Ar), 132.85 (Ar), 131.77 (Ar), 130.74 (Ar), 130.63 (Ar), 127.66 (Ar), 127.09 (Ar), 126.14 (Ar), 125.28 (Ar), 125.06 (Ar), 70.80 (C-3), 53.41 (C-2), 50.77 (C-4), 50.70 (C-1), 46.33 (C-7), 27.83 (C-6), 19.53 (C-9), 18.38 (C-8), 18.06 (C-5), 14.89 (C-10); MS m/z 281 ($M+1$), 280 (M^+); HRMS: Found for M^+ 280.18319, Calc. for $\text{C}_{20}\text{H}_{24}\text{O}$: 280.18271.

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