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An Efficient Chemo-Enzymatic Approach to (+)-Meroquinene

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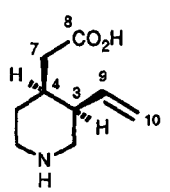
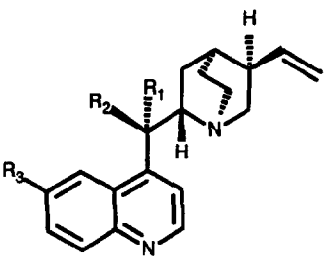
Abstract : Meroquinene (+)-1 was prepared in an efficient and stereocontrolled fashion from (1*R*-2*S*)-4-cyclohexene dimethanol monoacetate (-)-**8**. Key steps are the enzyme-catalyzed hydrolysis of the available diacetate **5** to (-)-**8** and of the intermediate diester **17** to hemiester **18**, which allow the stereo- and regiocontrolled elaboration of the vicinal vinyl and carboxymethyl groups.

Meroquinene (+)-**1** [(3*R*,4*S*)-3-vinyl-4-piperidine acetic acid], firstly obtained by degradation of cinchonine **2**,[1,2] has attracted wide interest in the last years because it represents a key-intermediate in the synthesis of some medicinally valuable *Cinchona* alkaloids such as quinine **3** and cinchonamine **4**.[3] This remarkable importance, coupled with its relatively straightforward structure, makes meroquinene (+)-**1** a challenging target for synthetic works. Many reports concerned with the racemic synthesis of **1** have appeared in the literature.[4] In one case[5] a resolution step of a racemic intermediate allowed to obtain both (+)-**1** and non natural (-)-**1**. An enantioconservative approach to (+)-**1** was designed by Brown[6] starting from secologanine which embodies the entire carbon skeleton of (+)-**1** with the correct chirality at the stereogenic centers. Very recently Hanessian[7] described an enantioselective synthesis of (+)-**1** by the "chiron approach" in which the two vicinal vinyl and carboxymethyl groups are efficiently introduced utilizing a chiral template derived from D-glucose.

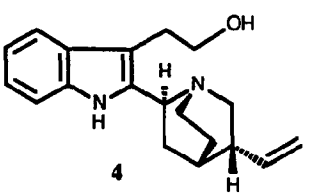


(+)-**1**



2 R_1 = OH, R_2 = R_3 = H

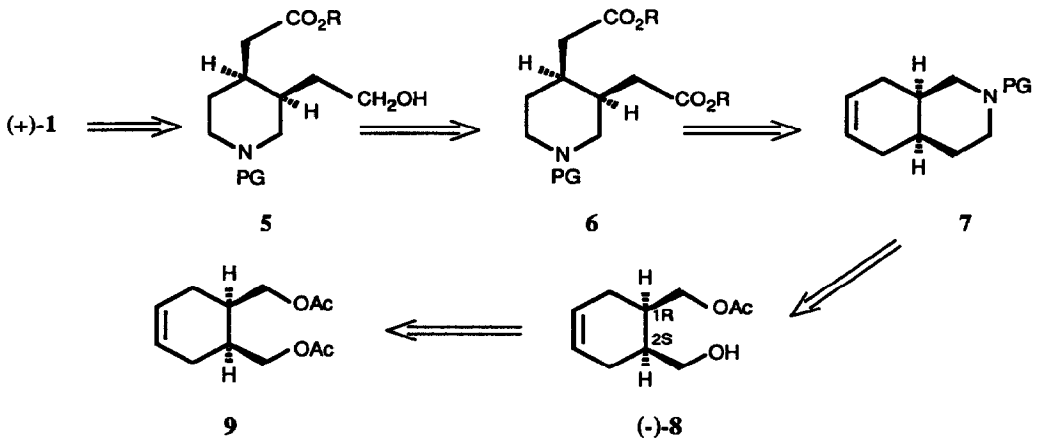
3 R_1 = H, R_2 = OH, R_3 = OMe



4

These significant advances not withstanding, we were nevertheless intrigued by the prospect of design an efficient entry to optically pure (+)-**1**.[8] This paper describes the full details of our approach based upon an

extensive use of hydrolytic enzymes in key steps involving a high degree of enantio- and regio-control.



Scheme

Recognition of (+)-**1** as a functional equivalent of alcohol **5** (Scheme) suggested the (3*R*,4*S*) diester **6** as a pivotal intermediate, which in turn would be produced upon oxidative cleavage of the *cis*-octahydroisoquinoline **7**. The synthetic precursor of **7** can be seen to be the (1*R*,2*S*)-4-cyclohexene dimethanol monoacetate (-)-**8** which is available by the *pro*(*S*) porcine pancreatic lipase (PPL)-catalyzed hydrolysis[9] of the *meso* diacetate **9**.

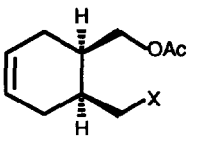
In order to realize the retrosynthetic approach outlined above, we initially undertook the synthesis of dimethyl ester **17** starting from the optically pure [>99% e.e.] (-)-**8** obtained by us in 95% yield from **9**.

Addition of carbon tetrabromide to a solution of (-)-**8** in dichloromethane at 0°C, followed by treatment with triphenylphosphine, cleanly afforded the bromo derivative **10**,[10] which produced the nitrile **11** in good yield on treatment with potassium cyanide in dimethyl sulfoxide at 60°C. Once in hand, the nitrile **11** was converted into the *cis*-octahydroisoquinoline **15** *via* a straightforward four step-sequence: carefully controlled hydrolysis of acetate **11** with KOH in aqueous methanol furnished the alcohol **12** which was converted into the mesylate **13** by successive reaction with MsCl in dichloromethane at 0°C in the presence of pyridine. Reduction of this mesylate **13** with lithium aluminum hydride in the presence of $AlCl_3$[11] gave the *cis*-octahydroisoquinoline **14** which, without isolation, was converted into the carbobenzyloxy derivative **15** in 84% yield, in order to protect the amino group from the subsequent oxidation.

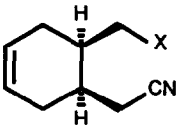
Following the procedure of Gais[12] ($KMnO_4$, H_2O/dichloromethane, Aliquat®336, 0°C), **15** was transformed into the dicarboxylic acid **16** in almost quantitative yield, which was then reacted with ethereal diazomethane to form the desired diester **17** in 44% overall yield from (-)-**8**.

Completion of the total synthesis of (+)-**1**, required the regioselective elaboration of the C(3) acetic acid appendage of **17** into the requisite vinyl side chain. The key to the implementation of this approach was the effective differentiation of the two carbomethoxy groups. After several futile attempts to prepare regioselectively the hemiester **18** or **19** or the quinuclidone **20** by chemical methods, we turned our attention to enzyme-mediated transformations. In fact, hydrolytic enzymes have been used for regioselective acyl-exchange of sugars,[13] glycols,[14] and for the regio- and enantioselective hydrolysis of some racemic

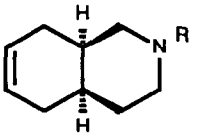
diesters[15] and unsymmetrical anhydrides.[16] We envisaged that this biocatalytic method for the conversion of **17** into **18** or **19** could be attractive if the enzyme possesses a high degree of stereochemical preference. Pig liver esterase (PLE) which not only shows high reaction selectivity, but also accepts a broad range of structurally different substrates therefore seemed a suitable reagent for the above transformation.



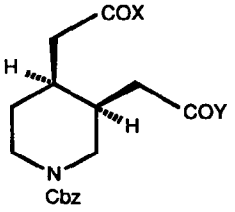
10 X = Br
11 X = CN



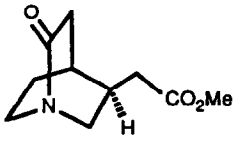
12 X = OH
13 X = OMs



14 R = H
15 R = Cbz



16 X = Y = OH
17 X = Y = OMe
18 X = OMe, Y = OH
19 X = OH, Y = OMe



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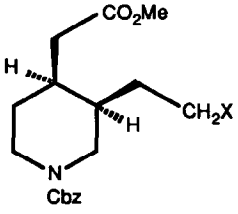
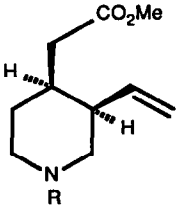


21 X = OH
22 X = Se(C_6H_4)-2-NO_2



23 R = Cbz
24 R = CO_2Et

We found that treatment of **17** with PLE according to a modification of Schneider procedure[17] resulted in the regioselective hydrolysis of the carbomethoxy group β at the 3(R) chiral center, affording the required **18** as the sole product in 93% yield.

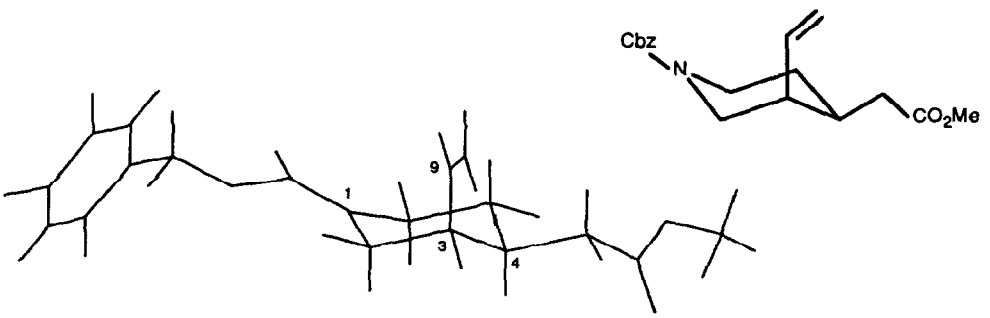
It should be noted that we did not know whether we had **18** or its regioisomer **19**, in that the spectroscopic data accumulated for this ihemiester did not allow unambiguous assignment. However, the regiochemistry of **18** formation was disclosed, *ex post facto*, by its conversion to the N-carbobenzyloxy meroquinene methyl ester **23**. Selective reduction of **18** with borane-dimethyl sulphide complex in THF at -78°C gave alcohol **21** in 86% yield The conversion of **21** to **23** was accomplished by treatment with o-nitrophenyl selenocyanate/*n*-Bu_3P,[18] followed by oxidative elimination with sodium metaperiodate in aqueous methanol at 0°C (53% yield) or, more efficiently (65%) with sodium perborate under phase-transfer catalysis (PTC) conditions.[19]

The structure and the stereochemistry of **23** was verified by inspection of ^1H NMR and homo J-decoupled spectra in conjunction with molecular mechanics analysis. Furthermore, the ^1H and ^{13}C NMR spectra of this compound exhibit spectral patterns which are in good agreement with those reported by Hanessian[7] for the closely related intermediate **24**. Especially characteristic was the signal for H-3_{eq} which appeared at δ 2.38 as a multiplet coupled to the vinyl methine H-9 (δ 5.75) through a large vicinal constant (9.0 Hz), and to the resonances at δ 4.02 (J = 3.0 Hz) and δ 3.11 (J = 2.8 Hz) whose chemical shift clearly supports assignment

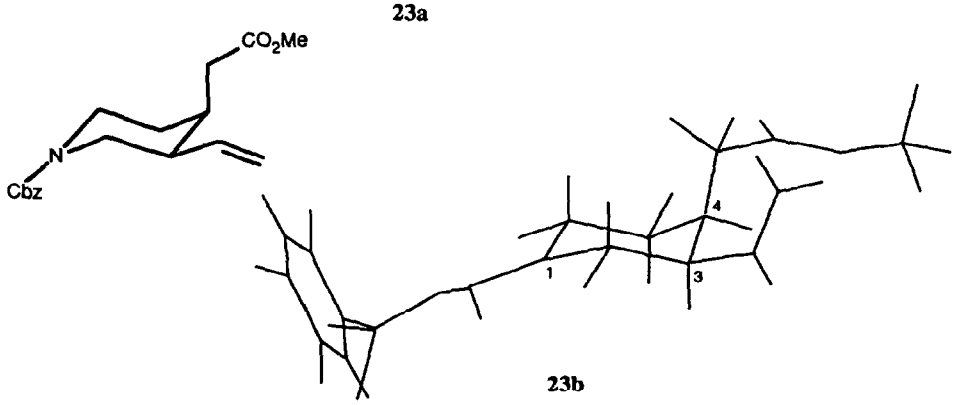
to the diasterotopic aminomethylene protons H-2_{eq} and H-2_{ax},respectively.

These and other features of ^{1}H NMR of **23** (see Experimental) suggested a single conformation **23a** with the C-3 vinyl group axial oriented and C-4 equatorial CH_2CO_2Me moiety.

Molecular Dreiding models suggest two different possible conformations for **23**, namely **23a** and **23b**, involving chair-shaped piperidine ring. By starting with conformations that were close to each of the two structures under consideration, we were able to determine minimum energies using an empirical force field study (Figure).[20] Consistently with the aforementioned NMR data, the result of calculation indicate that, in $CHCl_3$ (ϵ = 4.8), **23b** is a local minimum with **23a** representing the global minimum. In fact the energy difference (1.64 kcal mol^{-1}) is such that **23b** is not expected to make a significant contribution. It must be noted that the value of 177.9° calculated for the H_9-C_9-C_3-H_3 torsion angle in **23a** is consistent with the large value observed for $J_{9,3}$.



23a



23b

Figure

Finally, **23** could be transformed (88% yield) into meroquinene hydrochloride (+)-**1** HCl by the action of 6M hydrochloric acid at reflux. (+)-**1** HCl thus obtained, mp 146-148°C, $[\alpha]_D^{25}$ +27.5 (*c* 0.60, MeOH); [lit[5]: mp 147-149°C; $[\alpha]_D^{25}$ +30.97 (*c* 1.02, MeOH)]; [lit[7]: $[\alpha]_D^{25}$ +27 (*c* 0.61, MeOH)] gave spectra (IR, 300

MHz ^{1}H NMR, ^{13}C NMR, MS) identical with those reported in literature.[7]

Acknowledgments
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Experimental Section

Melting points are uncorrected and were determined in open-ended capillaries. IR spectra were obtained on a Perkin Elmer 681 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WP-80 (80 MHz and 20.12 MHz, respectively) in $CDCl_3$, unless otherwise stated. Chemical shifts are expressed in part per million (δ)downfield from internal Me_4Si and coupling costants (*J*) are given in Hz. Mass spectra (EI and positive FAB) were recorded on a VG 70-70 EQ instrument equipped with standard sources. Optical rotations were measured on a Perkin Elmer 241 polarimeter. Flash chromatography (FC) was carried out using Merck Kieselgel 60, 230-400 mesh. Porcine pancreatic lipase (PPL) and pig liver esterase (PLE) were purchased from Sigma Chemical Co. and had a specific activity of 16 and 200 units/mg of protein, respectively. PPL was in form of powder containing approx. 25% of protein, PLE was used as a suspension in 3.2 M ammonium sulphate solution.

(1*R*,2*S*)-4-Cyclohexene dimethanol monoacetate (-)-8. According to the procedure described by Schneider[9], to a suspension of **5** (14 g, 61.9 mmol) in phosphate buffer solution (pH 7.0, 150 mL) was added crude PPL (1.24 g). The resulting mixture was stirred at room temperature while the pH was maintained to 7.2 using a pH stat with 1M NaOH solution. After the addition of 63 mL of the NaOH solution (22 h), the reaction was stopped by filtration on celite, and the filtrate was evaporated. The residue was distilled under reduced pressure to give (-)-**6** (10.8 g, 95%) as an oil; bp 135-140°C/0.6 mmHg; $[\alpha]_D^{25}$ -18.98 (*c* 4.04, $CHCl_3$), [lit[9]: -19.4 ($CHCl_3$)]; IR (neat) 3630 and 1735 cm^{-1}; ^{1}H NMR δ 2.06 (s, 3H, CH_3CO), 3.70 (m, 2H, CH_2-OH), 4.21 (m, 2H,CH_2-OAc), 5.65 (m, 2H, H-4 + H-5); MS (EI) *m/z* 184 ($M^{+\cdot}$, 8%), 166 (35), 106 (100). The enantiomeric excess of (-)-**8** was estimated >99% by ^{19}F NMR spectroscopy (188.22 MHz) of the *R*-MTPA ester.

(1*S*,2*R*)-1-Bromomethyl-2-methanol-4-cyclohexene acetate 10. To a solution of (-)-**6** (5 g, 27.2 mmol) and carbon tetrabromide (11.34 g, 34.4 mmol) in anhydrous dichloromethane (150 mL) under nitrogen, was slowly added tri-phenylphosphine (8.97 g, 34.1 mmol) at 0°C. After 1.5 h the resulting mixture was allowed to warm up to room temperature and was concentrated (< 30°C) to give a yellow oil. The residue was triturated in *n*-hexane (100 mL) and the resulting mixture was stirred for 1 h. The solution was filtered, the solids washed with *n*-hexane (2 x 20 mL) and the combined organic solutions was evaporated. The residue was distilled under reduced pressure to give **10** (6.18 g, 92%) as an oil; bp 125-130°C/0.3 mmHg; $[\alpha]_D^{25}$ -6.6 (*c* 5.0, $CHCl_3$); IR (neat) 1734 cm^{-1}; ^{1}H NMR δ 2.70 (s, 3H, CH_3CO), 3.31 (dd, 1H, *J* = 11.0, 7.7 Hz, CH-Br), 3.49 (dd, 1H, *J* = 11.0, 6.4 Hz, CH-Br), 4.02 (br d, 2H, *J* = 6.8 Hz, CH_2-OAc), 5.63 (m, 2H, H-4 + H-5); MS (EI) *m/z* 248 [$M^{+\cdot}$(^{81}Br), 12%], 246 [$M^{+\cdot}$(^{79}Br), 10].

(1*R*,2*R*)-1-Methanol-2-acetonitrile-4-cyclohexene acetate 11. A solution of **10** (3.71 g, 15 mmol) in dry

dimethylsulfoxide (10 mL) was added dropwise over 10 min to a stirred mixture of KCN (6.24 g, 96 mmol) in dimethylsulfoxide (38 mL) at 60°C under nitrogen. After 1.5 h saturated aqueous NH_4Cl solution (600 mL) was introduced, and the mixture extracted with Et_2O (4 x 50 mL). The extracts were combined, dried and concentrated to give an oil. FC of the crude oil (Et_2O/*n*-hexane 1:1) gave pure **11** (2.44 g, 84%); $[\alpha]_D^{25}$ -8.46 (*c* 5.05, $CHCl_3$); IR (neat) 2245, 1735 and 1640 cm^{-1}; ^1H NMR δ 2.08 (s, 3H, CH_3CO), 4.01 (d, 2H, *J* = 6.7 Hz, CH_2-OAc), 5.66 (m, 2H, H-4 + H-5); MS (EI) *m/z* 193 ($M^{+\cdot}$, 5%), 133 (55), 93 (100).

(1*R*,2*R*)-1-Methanol-2-acetonitrile-4-cyclohexene 12. To a solution of **11** (10.5 g, 54.4 mmol) in 90% aqueous methanol (70 mL) was added anhydrous KOH (3.79 g, 67.6 mmol). After being stirred for 2 h, the reaction mixture was diluted with water and washed with Et_2O. The aqueous layer was acidified with 10% hydrochloric acid and extracted with Et_2O. The extracts were combined, dried and concentrated to give an oil. The residue was distilled under reduced pressure to give **12** (6.75 g, 82%) as a clear oil; bp 140°C/2.2 mmHg; $[\alpha]_D^{25}$ -10.4 (*c* 4.06, $CHCl_3$); IR (neat) 3620, 2240 and 1650 cm^{-1}; ^1H NMR δ 1.92 (s, 1H, OH), 3.56 (d, 2H, *J* = 6.7 Hz, $C\underline{H}_2$-OH), 5.63 (m, 2H, H-4 + H-5); MS (EI) *m/z* 151 ($M^{+\cdot}$, 32%), 134 (99), 133 (100).

(1*R*,2*R*)-1-Methanol-2-acetonitrile-4-cyclohexene mesylate 13. Hydroxy nitrile **12** (4.5 g, 29.8 mmol) and dry pyridine (4.0 mL, 49.6 mmol) were dissolved in dichloromethane (50 mL) and cooled to 0°C. Mesyl chloride (4.8 mL) in dichloromethane (20 mL) was then added dropwise, and the resulting solution stirred overnight at room temperature. The reaction mixture was washed twice with 1N HCl, twice with 5% $NaHCO_3$, and twice with brine. The organic layer was dried and concentrated *in vacuo* to give chromatographically pure **13** (6.41 g, 94%) as a clear oil; IR (neat) 2240 and 1640 cm^{-1}; ^1H NMR δ 3.02 (s, 3H, CH_3-SO_3), 4.18 (d, 2H, *J* = 6.5 Hz, CH_2-OMs), 5.66 (m, 2H, H-4 + H-5); MS (EI) *m/z* 229 ($M^{+\cdot}$, 3%), 133 (43), 93 (100).

***cis*-(4a*R*,8a*R*)-2-Benzyloxycarbonyl-1,2,3,4,4a,5,8,8a-octahydroisoquinoline 15.** To a suspension of $LiAlH_4$ (496 mg, 13.1 mmol) in dry Et_2O (20 mL) was added $AlCl_3$ (2.67 g, 20 mmol) in portions with ice cooling followed by mesylate **13** (2 g, 8.73 mmol) in dry THF (20 mL). After addition, the reaction mixture was stirred for 3 h at room temperature. After cooling to 0°C, saturated aqueous NH_4Cl solution (1 mL) was introduced followed by anhydrous Na_2SO_4 (2 g) and the resulting mixture was stirred overnight. The resulting mixture was filtered and the solids washed with THF (20 mL). To the combined THF solutions was added aqueous 2N NaOH (18 mL) and benzyl chloroformate (3.3 g, 19.6 mmoL). After stirring 10 h, biphasic system was separated and the aqueous phase was extracted with ethyl acetate. Evaporation of the solvent gave an oil which was distilled under reduced pressure to give **15** (2.0 g, 84%) as an oil; bp 195°C/2 mmHg; $[\alpha]_D^{25}$ +49.3 (*c* 4.20, $CHCl_3$); IR (neat) 1685 cm^{-1}; ^1H NMR δ 2.80-3.15 (m, 2H, H_{ax}-1 + H_{ax}-3), 3.60-4.15 (m, 2H, H_{eq}-1 + H_{eq}-3), 5.10 (br s, 2H, CH_2-Ph), 5.53 (s, 2H, H-6 + H-7), 7.31 (br s, 5H, Ar-H); MS (FAB^+) *m/z* 272 (MH^+).

(3*R*,4*S*)-1-Benzyloxycarbonyl-3,4-piperidine diacetic acid 16. To a stirred solution of octahydro isoquinoline **15** (1 g, 3.7 mmol) in dichloromethane (10 mL) at 0°C was added a solution of $KMnO_4$ (1.75 g, 11.1 mmol) and Aliquat®336 (36 mg) in H_2O (15 mL) in one portion. The resulting brown suspension was stirred efficiently for 3 h at room temperature and then ethanol (1 mL) was added. After 30 min the mixture

was filtered through celite. The manganese dioxide was washed well with H_2O and the washings were combined with the initial filtrate. The aqueous phase was acidified with 6N HCl and extracted with a mixture of THF/ethyl acetate 1:1 (3 x 30 mL). Drying and evaporation of the solvent furnished crude **16** (1.19 g, 96%). A portion was purified by TLC(*i*-PrOH/HCO_2H/H_2O 90:7:3) and the remaining material was used directly in the next step. **16**: clear oil; IR (neat) 3450,1715 and 1685 cm^{-1}; ^1H NMR δ 5.03 (s, 2H, CH_2-Ph), 7.35 (s, 5H, Ar-H); MS (EI) *m/z* 335 ($M^{+\cdot}$, 6%), 318 (3.5), 244 (45), 200 (58), 91 (100).

(3*R*,4*S*)-1-Benzyloxycarbonyl-3,4-piperidine diacetic acid dimethyl ester 17. A solution of the diacid **16** (880 mg, 2.62 mmol) in dichloromethane (5 mL) at 0°C was treated with ethereal CH_2N_2 until a yellow color persisted. Acetic acid was added dropwise to consume excess CH_2N_2, and then the mixture was concentrated *in vacuo* to give a clear oil. Purification of the residue by FC (ethyl acetate/ *n*-hexane 1:1) gave pure **17** (866 mg, 91%) as an oil; $[\alpha]_D^{25}$ +47.7 (*c* 3.5, MeOH); IR (neat) 1735 and 1690 cm^{-1}; ^1H NMR δ 3.58 (s, 3H, CH_3O), 3.65 (s, 3H, CH_3O), 5.07 (br s, 2H, CH_2-Ph), 7.30 (br s, 5H, Ar-H); ^{13}C NMR δ 47.7 (C-2), 35.2 (C-3), 34.0 (C-4), 27.2 (C-5), 43.3 (C-6), 36.9 (C-7), 172.7 (C-8), 30.3 (C-9), 172.4 (C-10), 51.6 (2 OMe), 155.5 (NCO), 67.0 (Ar-CH_2); MS (EI) *m/z* 363 ($M^{+\cdot}$, 5%), 317 (14), 287 (21).

Enzymatic conversion of 17 into hemiester 18. A solution of **17** (726 mg, 2 mmol) in dimethylsulfoxide (20 mL) was added to a stirred phosphate buffer solution (pH 7.0, 160 mL) followed by the addition of 250 μL of PLE (suspension). The resulting mixture was stirred at 25°C while the pH was maintained to 7.2 using a pH stat with 0.1 M NaOH solution. After the addition of 21 mL of the NaOH solution (20 h), the reaction was acidified with 6N HCl and extracted with Et_2O (5 x 10 mL). After removal of the solvent, the residue was purified by FC (ethyl acetate) to give pure **18** as a wax (650 mg, 93%); $[\alpha]_D^{25}$ +49.8 (*c* 3.0, MeOH); IR ($CHCl_3$) 3445, 1734, 1705 and 1680 cm^{-1}; ^1H NMR δ 3.60 (s, 3H, CH_3O), 5.05 (s, 2H, CH_2-Ph), 5.63 (s, 1H, OH), 7.25 (br s, 5H, Ar-H); MS (FAB^+) *m/z* 350 (MH^+).

Reduction of 18 to 21. A solution of **18** (1 g, 2.86 mmol) in anhydrous THF (10 mL) was cooled to -78°C under a nitrogen atmosphere. 2N Borane-methyl sulphide complex solution in THF (2 mL, 4 mmol) was injected with stirring over a 15 min period. After 18 h the resulting mixture was allowed to warm up to -20°C and then 0.1 M K_2HPO_4 solution (6 mL) was added. After being stirred for another 30 min, the resulting mixture was extracted with Et_2O. Usual work up and purification of the residue by FC (ethyl acetate/ *n*-hexane 9:1) gave the alcohol **21** as an oil (823 mg, 86%); IR ($CHCl_3$) 3620, 1735 and 1685 cm^{-1}; ^1H NMR δ 2.57 (s, 1H, OH), 3.65 (s, 3H, CH_3O), 5.10 (s, 2H, CH_2-Ph), 7.33 (br s, 5H, Ar-H); MS (EI) *m/z* 335 ($M^{+\cdot}$, 11%), 244 (13), 200 (59).

Seleno derivative 22. To a solution of **21** (515 mg, 1.54 mmol) and sublimed *o*-nitrophenyl selenocyanate (383 mg, 1.70 mmol) in THF/pyridine 1:1 (10 mL) was added tributylphosphine (417 μL, 1.70 mmol) at ambient temperature. After stirring for 45 min under nitrogen, the solvent was evaporated off and the selenide **22** (656 mg, 82%) was isolated after FC (Et_2O/*n*-hexane 7:3) as a yellow foam; ^1H NMR δ 2.50-3.18 (m, 4H, H_{ax}-2 + H_{ax}-6 + CH_2-SeAr), 3.63 (s, 3H, CH_3O), 3.80-4.20 (m, 2H, H_{eq}-2 + H_{eq}-6), 5.10 (br s, 2H, CH_2-Ph), 7.30-7.35 (m, 8H, Ar-H), 8.25 (m, 1H, Ar-H).

N-Benzyloxycarbonyl meroquinene methyl ester 23. To an ice-cooled stirred solution of the selenide **22**

(600 mg, 1.15 mmol) in dichloromethane/acetic acid 19:1 (50 mL) under nitrogen, were added tetrabutylammonium hydrogen sulphate (41 mg, 0.13 mmol) and then, portionwise, sodium perborate tetrahydrate (195 mg, 1.26 mmol). After being stirred for 1 h at 0°C, the solution was poured into ice. The resulting organic phase was washed with saturated $NaHCO_3$ solution and dried. Concentration *in vacuo*, followed by FC (dichloromethane), gave pure **23** (289 mg, 79%) as an oil; $[\alpha]_D^{25}$ +45.6 (*c* 0.98, MeOH); IR ($CHCl_3$) 1735 and 1685 cm^{-1}; ^1H NMR (Bruker AC-300, 300 MHz) δ 1.38-1.60 (m, 2H, 2H-5), 2.20 (m, 2H, 2H-7), 2.28 (m, 1H, H-4), 2.38 (m, 1H, H-3), 2.95 (m, 1H, H_{ax}-6), 3.11 (dd, 1H, *J* = 13.0, 2.8 Hz, H_{ax}-2), 3,66 (s, 3H, CH_3O), 4.02 (ddd, 1H, *J* = 13.0, 3.0, 1.2 Hz, H_{eq}-2), 4.09 (m, 1H, H_{eq}-6), 5.07 and 5.15 (AB system, 2H, *J* = 12.5 Hz, N-CH_2-CO), 5.08 (br d, 1H, *J* = 17.0 Hz, H-10 *trans*), 5.11 (br d, 1H, *J* = 10.7 Hz, H-10 *cis*), 5.75 (ddd, 1H, *J* = 17.0, 10.7, 9.0 Hz, H-9), 7.35 (m, 5H, Ar-H); ^{13}C NMR δ 48.5 (C-2), 42.4 (C-3), 35.4 (C-4), 27.3 (C-5), 43.7 (C-6), 37.5 (C-7), 173.0 (C-8), 134.9 (C-9), 117.8 (C-10), 51.5 (OMe), 155.5 (NCO), 67.0 (Ar-CH_2); MS (EI) *m/z* 317 ($M^{+\cdot}$, 5%), 242 (16), 226 (18), 182(100).

Meroquinene hydrochloride (+)-1 HCl. A suspension of compound **23** (200 mg, 0.63 mmol) in 6M HCl (25 mL) was heated at reflux 4 h. The reaction was then partially concentrated *in vacuo*, cooled, washed twice with Et_2O and then the solvent was removed under reduced pressure to give pure meroquinene hydrochloride (+)-**1** HCl (123 mg, 95%); mp 146-148°C (ethanol), $[\alpha]_D^{25}$ +27.5 (*c* 0.60, MeOH), [lit[5]: mp 147-149°C, $[\alpha]_D^{25}$ +30.97 (*c* 1.02, MeOH); lit[7]: $[\alpha]_D^{25}$ +27 (*c* 0.61, MeOH)];

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