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Enantioselective Synthesis of (-)-Meroquinene Through Tandem Michael Reaction Methodology.

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Abstract: An enantioselective approach to the synthesis of non natural (-)-meroquinene **1** based on sequential inter- and intramolecular Michael reaction between (L)-menthyl N-benzyl-5-amino-2E-pentenoate **3** and 1-acetyloxy-4-methoxymethyloxy-2-nitrobutane **10b**, acting as surrogate of 2-nitro-1,3-butadiene **4**, is described. The heterocyclization process led to the formation of the piperidine ring system **12**, obtained as an unseparable 80:20 mixture of diastereomers at the newly created chiral centres at C-3 and C-4, which became easily separable by column chromatography after transformation of the nitrogen protective benzyl group into the corresponding carbamates **14** and **15**. Both compounds, after elaboration of the chain geminal to the nitro group into a vinyl appendage, underwent regio- and stereo-selective removal of the nitro group by palladium-catalyzed displacement with hydride generated by formate to give the precursor **19**, easily converted by treatment with hydrochloric acid to **1**, isolated as hydrochloride.

A tandem reaction is usually defined as a sequence involving two or more consecutive reactions in which the functionalities created by bond formation in the initial step allow further reactions. Although by no means new, the field of tandem reaction has witnessed a striking progress over the last years. In fact, the variety of elegant and convenient synthetic applications based on this strategy have been recently reviewed[1] and a useful classification of the different sequences has been suggested.

Accordingly, the tandem Michael reaction methodology, which we have developed for employment in a program directed at the synthesis of biologically active compounds with a pyrrolidine ring system as the salient structural feature, is an anionic-anionic process; the primary step being the intermolecular addition of a nitrogen nucleophile to an electrophilic olefin to form a new anionic functionality which is subsequently captured by a built-in electrophile acceptor.

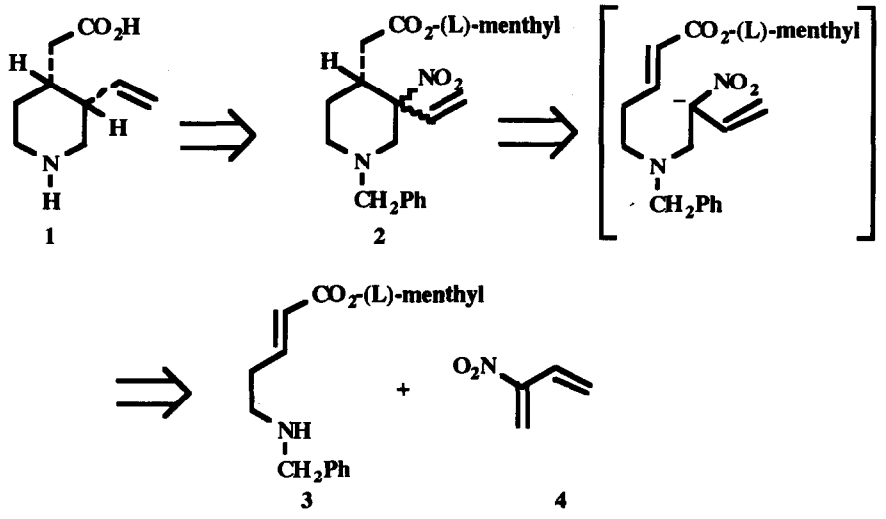
Recent applications of this strategy from our laboratories have resulted in concise enantioselective syntheses of (+)- and (-)-α-allokainic,[2] (-)-α-kainic acid[2] and acromelic acid A.[3]

One of the most attractive features of this approach consists in its inherent flexibility. It allows 2,3,4-trisubstituted pyrrolidine ring systems to be obtained with a C-2, C-3-trans, C-3, C-4-trans-arrangement of the side chains resident on the heterocyclic ring and is also easily adaptable for the construction of pyrrolidines possessing a C-2, C-3 trans C-3, C-4-cis stereochemical orientation of the substituents, simply by using an electrophilic alkene bearing an electronwithdrawing group (e.g., nitro group), removable at a later stage.
Moreover, we envisaged control of the configuration of the developing centers C(3) and C(4) by means of a preexisting center C(2). Given our success in the pyrrolidine area, the potential for extending the protocol to the preparation of substituted piperidine ring systems clearly exists. We anticipated that a simple one-carbon

elongation of the tether joining the nitrogen nucleophile and the built-in α,β-unsaturated acceptor could afford the donor-acceptor fragment suitable for the reaction with an electrophilic olefin. In addition, we were particularly interested in evaluating the enantioselectivity of the heterocyclization process introducing a chiral auxiliary in the aminoester subunit.

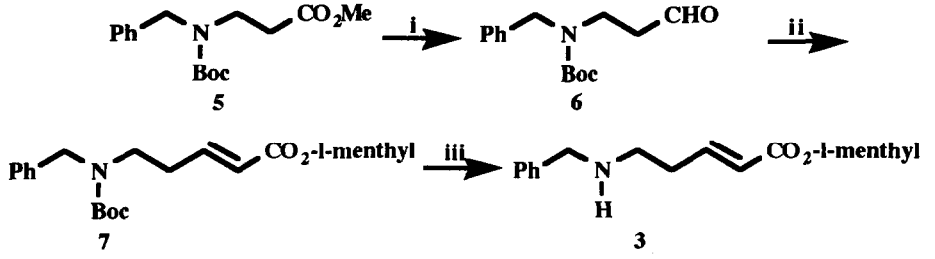
We were intrigued by the possibility of using this protocol in the formulation of a novel entry to (+)-meroquinene, a degradation product of quinine, extensively used as key synthetic precursor to a number of medicinally important alkaloids such as quinine itself and cinchonamine,[4-6] or to the natural antipode (-)-**1**. To this end, we planned a synthetic approach to the target **1** along the lines retrosynthetically depicted in Scheme 1.

SCHEME 1



Having established the essential features of the synthetic approach, preparation of the requisite starting materials **3** and **4** was undertaken. The preparation of the segment **3** containing both the nitrogen nucleophile and the suitably placed α,β-unsaturated Michael acceptor was easily achieved by a straighforward sequence of reactions (Scheme 2) using the readily available compound **5**, obtained through nitrogen protection as t-butyloxycarbonyl (Boc) of the 1,4-addition product of benzylamine to methyl acrylate.[7]

SCHEME 2



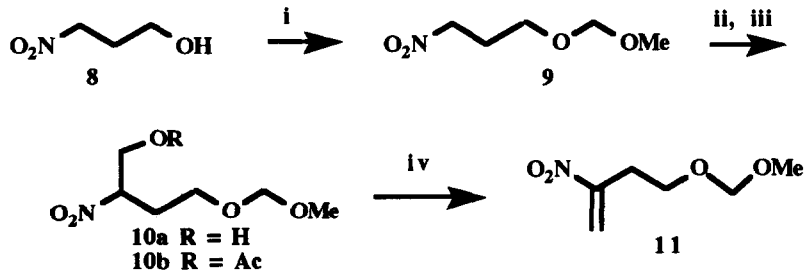
Reagents: i, DIBAH; ii, $Ph_3\overset{+}{P}\text{-}\overset{-}{C}H\text{-}CO_2$-l-menthyl; iii, CF_3CO_2H

DIBAH reduction of the ester moiety produced the corresponding aldehyde **6**, which underwent Wittig-Horner reaction with (L)-menthyl (triphenylphosphoranylidene)acetate[8] to afford the required subunit **3**.

Unfortunately, the utilization of 2-nitro-1,3-butadiene **4** as counterpart in the key heterocyclization was precluded by its propensity to anionic polymerization. Therefore, we were forced to search for a suitable device to overcome this serious problem. A tactical solution was eventually found by utilizing the nitro derivative **10b**, featuring two differently protected primary alcohol functionalities to serve as suitable precursors for introducing the diene unit in a stepwise manner rather then as single entity.

Thus, the readily available 3-nitropropanol **8**,[9] after being protected as its methoxymethyl ether (MOM) **9** by treatment with methylal in the presence of P_2O_5, was subjected to base-catalyzed hydroxymethylation with formaldehyde to afford **10a**. Acetylation of the latter with acetyl chloride/pyridine provided the corresponding acetyl derivative **10b**, a convenient source for the *in situ* generation of the the required nitro alkene **11**. (Scheme 3).

SCHEME 3

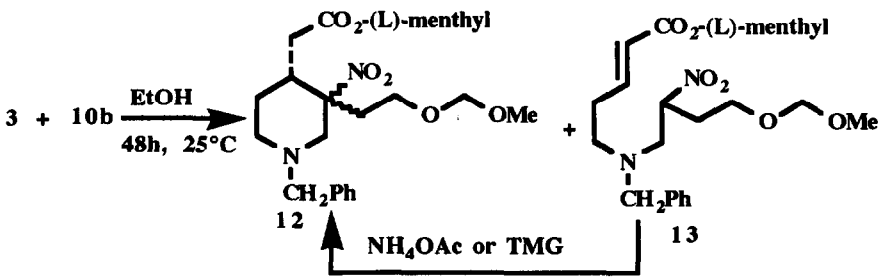


Reagents: i, $CH_2(OMe)_2$; P_2O_5; ii, MeONa, CH_2O; iii, AcCl, C_5H_5N; iv, base

Having in hand the two subunits the stage was set for the crucial coupling which was performed simply by mixing equimolecular amounts of **3** and **10b** in ethanol solution at room temperature. Preliminary experiments have shown that the reaction period for completion of the heterocyclization process leading to the formation of six-membered ring systems was longer than that for forming the five-membered rings.[2,3]

Thus, after 48h, we observed the disappereance of the starting materials and the formation of three products., These were easily separated by chromatography and identified as the cyclized product **12**, consisting of an unseparable 80:20 mixture of diastereomers on the basis of the integration of signals due to methoxyl groups in the ^1H NMR , and the acyclic intermolecular adduct **13**. (Scheme 4).

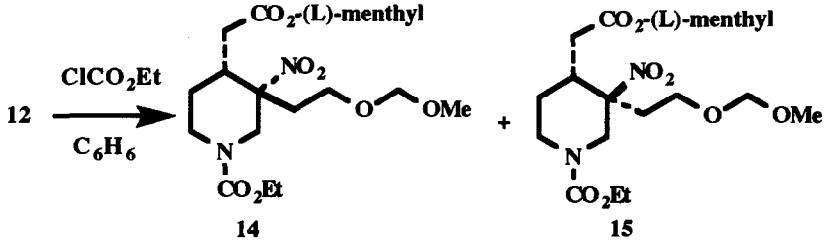
SCHEME 4



Interestingly, when the latter was subjected to cyclization in the presence of different catalysts, namely ammonium acetate and tetramethylguanidine (TMG), the original diastereomeric ratio of cyclized products was obtained in the presence of ammonium acetate, while a 1:3 mixture of diastereomers resulted under more basic conditions, which probably favour the equilibration of the first formed diastereomer through a retro-Michael-Michael reaction.

The stereochemical outcome of the heterocyclization was not predictable. Gratifyingly, only two of the four possible diastereomers are formed which could be easily separated by column chromatography after quantitative conversion into the two corresponding carbamates **14** and **15** by treatment of the mixture with ethyl chloroformate in anhydrous boiling benzene. (Scheme 5). Being confident that the nitro group could offer sufficient stereoelectronic interactions in the transition state leading to cyclization, we were hopeful that the two compounds were diastereomeric at C(3), the predominant diastereomer having a trans relationship between the acetic chain and the nitro group. The modest diastereoselectivity observed in the formation of **12** does not represent any inconvenience from the synthetic standpoint because this stereocenter could be easily adjusted at a later stage. Even more interestingly, the chiral ester auxiliary was effective for the diastereoselectivity of the process permitting selective chiral induction at C-4.

SCHEME 5

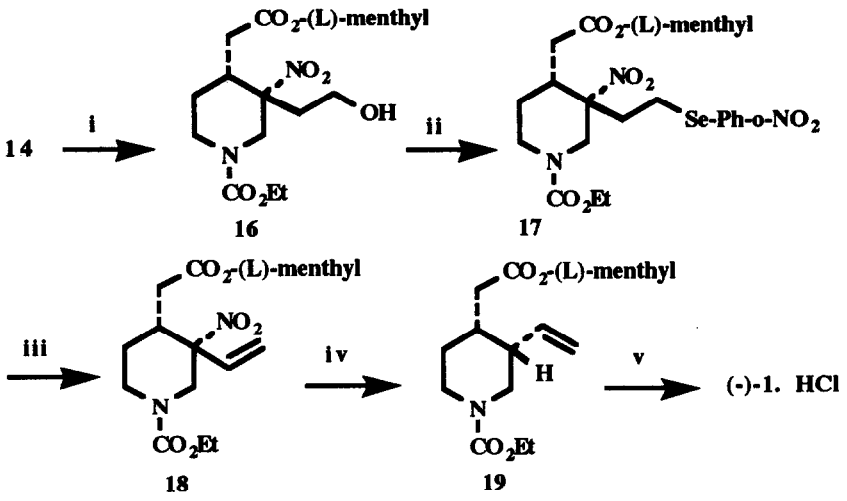


In order to remove the nitro group regio- and stereoselectively, its allylic nature had to be restored, requiring the elaboration of the C(3) chain to the requisite vinyl appendage. This task was accomplished on both compounds through the sequence outlined in Scheme 6 for the isomer **14**. This involved removal of the hydroxyl protective group by aqueous hydrochloric acid treatment to produce **16**, followed by transformation into the corresponding selenyl derivative **17** by reaction with o-nitrophenylselenyl cyanide in the presence of triphenylphosphine and final oxidative elimination by action of sodium perborate to yield **18**.

The stage was now set for submitting separately both the allylic nitro compound **18** and its C-3 epimer to palladium-catalyzed displacement reaction with hydride generated from formate as a nucleophile,[10] which not unexpectedly gave rise in both cases to the formation of the same compound **19**. As suggested by Tsuji[11], this result can be accounted for by the rearrangement of the initially formed η^3-allyl complex to a η^1-allyl complex, the hydride transfer proceeding from the side opposite to the acetic chain in order to minimize steric interactions.

The structure and stereochemistry of **18** was determined by the observation of a NOE effect between the methylene hydrogens of the acetic chain and the vinyl protons in the 2D NMR spectra of the corresponding methyl esters, obtained by sodium methoxide promoted transesterification, while no corresponding NOE was observed in the corresponding epimer. The treatment of the denitrated product **19** with 10% hydrochloric acid at reflux produced the crystalline hydrochloride of (-)-**1**, which gave spectra (IR, ^{1}H NMR, ^{13}C NMR, MS) identical with those reported in the literature for (+)-meroquinene hydrochloride, but with opposite value of $[\alpha]^{20}_D$ = -23 (c 0.60, MeOH), the non-natural enantiomer being obtained. The preparation of (+)-meroquinene would require the employment of the more expensive (+)-menthol as chiral template.

SCHEME 6



Reagents: i, H^+, Me_2CO : H_2O; ii, o-NO_2-Ph-SeCN, (n-But)$_3$P; iii, $NaBO_3.4H_2O$; iv, $Pd^0(PPh_3)_4$, Ph_3P, HCO_2NH_4, THF, 80°C; v, 10% HCl, reflux, 6h.

In summary, this result highlights once more the preparative utility of the tandem Michael reaction methodology for the construction of substituted nitrogen heterocycle ring systems, further enhanced by the chiral induction observed in the key cyclization step.

EXPERIMENTAL

General remarks. Melting points were determined with a Büchi-Tottoli apparatus and are uncorrected. Reactions and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel coated plates F_{254} (Merck) and visualized with iodine, aqueous potassium permanganate or methanolic ninhydrin. IR spectra were measured with a Perkin-Elmer Model 297 instrument. ^1H NMR spectra were recorded on a Bruker AC-200 spectrometer for solutions in $CDCl_3$ unless otherwise noted and peak positions are given in ppm downfield from tetramethylsilane as an internal standard. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Organic solutions were dried over anhydrous magnesium sulphate and evaporated with a rotary evaporator. Light petroleum refers to the fractions boiling in the range 40-60°C and ether to diethyl ether. Flash-chromatography was carried out with Merck silica gel (230-400 mesh). All reactions were carried out under a N_2 atmosphere unless otherwise stated. Elemental analyses were performed by the microanalytical laboratory of Dipartimento di Chimica, Università di Ferrara.

3-[N-Benzyl-N-(t-butyloxycarbonyl)-aminopropanal 6.

Diisobutylaluminum hydride (1.5M in toluene, 27ml) was added into a stirred and cooled (-78°C) solution of **5** (7g, 3.6mmol) in toluene (100ml). Stirring at -78°C was continued for 2h, saturated ammonium chloride (5ml) was added, the cold bath was removed, and the reaction mixture was left for 1h to warm at 25°C. The organic phase was separated, the aqueous phase extracted with EtOAc (2x25ml), the organic extracts washed with brine, dried and evaporated to yield **6** (5.41g, 57%) as an oil. IR (neat): 1720, 1680, 1600, 1580 cm^{-1}; ^1H NMR: δ 1.47 (s, 9H), 2.63 (t, 2H, J=8), 3.50 (t, 2H, J=8), 4.45 (s, 2H), 7.30 (m, 5H), 9.73 (s, 1H).

(L)-Menthyl N-benzyl-N-(t-butyloxycarbonyl)-5-amino-2E-pentenoate 7.

To a solution of (L)-carbomenthyloxymethyl triphenylphosphonium bromide[8] (7.5g, 14mmol) in 1:1 benzene:dioxane solution (35ml) was added potassium t-butoxide (1.75g, 15.2 mmol) and the mixture stirred for 30min at 25°C. A solution of the aldehyde **6** (3.16g, 14mmol) in benzene (15ml) was then added and the mixture stirred for 2h and evaporated. A 1:2 mixture of ether / light petroleum was added to the residue and the mixture filtered and concentrated. The residue was purified by flash chromatography (ether / light petroleum 1:2) to give **7** (3.5g, 57.6%) as an oil, $[\alpha]^{20}_D$ -41.75 (c 1.14, $CHCl_3$). IR (neat): 1700, 1680, 1650 cm^{-1}; ^1H NMR: δ 0.75 (d, 3H, J=7), 0.85 (d, 3H, J=7), 0.87 (d, 3H, J=7), 1.5 (s, 9H), 1.7 (m, 2H), 1.85 (m, 1H), 2.03 (m, 1H), 2.38 (m, 2H), 3.29 (m, 2H), 4.44 (m, 2H), 4.73 (dt, 1H, J=9.5, J=4.6), 5.8 (d, 1H, J=15.6), 6.88 (dt, 1H,J=15.6, J=8.1), 7.28 (m, 5H).

(L)-Menthyl N-benzyl-5-amino-2E-pentenoate 3.

Trifluoroacetic acid (12.5ml, 16.3mmol) in CH_2Cl_2 (5ml) was added dropwise to an ice-cooled solution of **7** (3.41g, 7.7mmol) in CH_2Cl_2 (14ml) and the mixture stirred until completion of the reaction. The solvent was evaporated and the residue dissolved in EtOAc (15ml), washed with saturated $NaHCO_3$ (10ml), dried and evaporated. The residue was purified by flash chromatography (AcOEt / MeOH 95:5) to give as a solid **3** (2.31g, 87.3%), mp 107-109°C, $[\alpha]^{20}_D$ -46.4 (c 0.66, $CHCl_3$). IR (nujol): 3400, 1710, 1650 cm^{-1}; ^1H NMR: δ 0.75 (d, 3H, J=7), 0.88 (d, 3H, J=7), 0.90 (d, 3H, J=7), 2.39 (m, 2H), 2.85 (m, 2H), 3.9 (s, 2H), 4.75 (dt, 1H, J=9.5, J=4.6), 5.81 (d, 1H, J=15.6), 6.75 (dt, 1H, J=15.6, J=8.1), 7.2 (bs,1H), 7.35 (m, 5H). (Found: C, 76.88; H, 9.61; N, 3.98. $C_{22}H_{33}O_2N$ requires C, 76.92; H, 9.68; N, 4.08).

3-Methoxymethyloxy-1-nitropropane 9.

A solution of **4** (1g, 9.5 mmol) in $CHCl_3$ (10 ml) was added to an ice-cooled suspension of P_2O_5 (15g, 105.6 mmol) in dry $CHCl_3$ (20ml) containing methylal (9.34g, 122.89 mmol). The mixture was left at 25°C until completion (4h), then poured into an ice-cooled sodium carbonate solution. The remaining oil in the reaction flask was washed out with Na_2CO_3 solution and the combined mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried and evaporated. The residue was purified by flash chromatography (ether / light petroleum 4:1) to afford **9** (0.7g, 49.5%) as an oil. IR (neat): 1560, 1120 cm^{-1}; ^1H NMR: δ 2.29 (q, 2H, J=6Hz), 3.35 (s, 3H), 3.62 (t, 2H, J=6), 4.53 (t, 2H, J=6), 4.6 (s, 2H).

4-Methoxymethyloxy-2-nitrobutan-1-ol 10a.

A solution of **9** (0.59g, 3.9mmol) and paraformaldehyde (0.12g, 1.33mmol) in MeOH (3ml) was added to a cooled (0°C) solution of MeONa (from 0.09g of Na) in MeOH (5ml) and stirred for 18h at the same temperature. The solid sodium nitronate was filtered, suspended in ether (25ml) containing acetic acid (0.14ml) and stirred for 1h at 25°C and for 2h at 40°C. After filtration, the organic layer was concentrated and the residue was purified by flash chromatography (ether / light petroleum 2:1) to afford **10a** (0.53g, 76%) as an oil; IR (neat): 3420, 1540, 1100 cm^{-1}; ^1H NMR: δ 2.05 (m, 1H), 2.2 (m, 1H), 3.35 (s, 3H), 3.4 (brs, 1H), 3.59 (m, 2H), 3.97 (m, 2H), 4.59 (s, 2H), 4.85 (m, 1H).

1-Acetyloxy-4-methoxymethyloxy-2-nitrobutane 10b.

Acetyl chloride (0.5ml, 5.6mmol) was added to an ice-cooled solution of **10a** (1g, 5.6mmol) in CH_2Cl_2 (5ml) containing pyridine (0.45ml, 5.6mmol) and the mixture stirred until completion of the reaction (10min). Water (10ml) was added, the organic layer separated, washed with saturated aqueous $NaHCO_3$ and dried. The solvent was evaporated to give a residue which was purified by column chromatography (ether / light petroleum 1:1) to yield **10b** (1.05g, 79.3%) as an oil. IR (neat): 1740, 1540, 1100 cm^{-1}; ^1H NMR: δ 2.07 (s, 3H), 2.1 (m, 1H), 2.3 (m, 1H), 3.35 (s, 3H), 3.57 (m, 2H), 4.48 (m, 2H), 4.59 (s, 2H), 4.94 (m, 1H). (Found: C, 43.39; H, 6.70; N, 6.27. $C_8H_{15}O_6N$ requires C, 43.44; H, 6.83; N, 6.33).

(L)-Menthyl N-benzyl-3-[2-methoxymethyl]ethyl]-3-nitro-4-piperidine acetate 12 and (L)-Menthyl N-benzyl-N-[3-[[2-methoxymethyl]ethyl]-3-nitro]-5-amino-2E-pentenoate 13.

A solution of **3** (2.26g, 6.6mmol) and **10b** (1.89g, 8mmol) in absolute EtOH (15ml) was stirred at 25°C for 48h. Solid K_2CO_3 (0.1g) was then added and stirring was continued for further 60h. The mixture was concentrated in vacuo, diluted with water (15ml) and extracted with EtOAc (3x25ml). Evaporation of the dried extracts and flash chromatography of the the residue (ether / light petroleum 1:1) furnished, in order of elution, **12** (1.7g, 51.1%) as an unseparable mixture of diastereomers in a 80:20 approximate ratio: IR (neat): 1720,1530 cm^{-1}; ^1H NMR: δ 0.7 (d, 3H, J=7), 0.87 (d, 3H, J= 7), 0.89 (d, 3H, J=7), 3.4 (s, 3H), 3.4-3.55 (m, 6H), 4.46 (m, 2H), 4.65 (m, 1H),7.28 (m, 5H); and **13** (1.2g, 36%) IR (neat): 1700, 1640, 1540 cm^{-1}; ^1H NMR: δ 0.8 (d, 3H, J=7), 0.9 (d, 3H, J= 7), 0.91 (d, 3H, J=7), 3.34 (s, 3H), 3-3.9 (m, 6H), 4.57 (s, 2H), 4.9 (m, 1H), 5.78 (d, 1H, J=15.5), 6.85 (dt, 1H, J=15.5, J=7), 7.28 (m, 5H).

A solution of **13** (1.2g, 2.38mmol) in absolute EtOH (10ml) was stirred at 25°C in the presence of ammonium acetate (0.1g) for 60h to give after usual work-up the cyclized product **12** (1.02g, 85%). (Found: C, 66.53; H, 8.71; N, 5.48. $C_{28}H_{44}O_6N_2$ requires C, 66.64; H, 8.79; N, 5.55).

(L)-Menthyl 1-carboethoxy-3-[2-methoxymethyloxy]ethyl]-3-nitro-4-piperidine acetates 14 and 15.

Ethyl chloroformate (3ml) were added to a solution of **12** (0.77g, 1.53mmol) in benzene (5ml) and the mixture refluxed for 24h. Ether (10ml) and water (10ml) were added, the organic phase washed with saturated $NaHCO_3$, dried and evaporated. The crude residue was purified by flash-chromatography (ether / light petroleum 1:1) to give, in order of elution, **14** (0.52g, 72%), $[\alpha]^{20}_D$ -30.39 (c 1.26, $CHCl_3$) ; IR (neat): 1720, 1680, 1530 cm^{-1}; ^1H NMR: δ 0.74 (d, 3H, J=7), 0.89 (d, 3H, J= 7), 0.90 (d, 3H, J=7), 1.27 (t, 3H, J=7), 2.3 (m, 2H), 2.67 (m, 1H), 2.8 (m, 1H), 3.2 (m, 1H), 3.34 (s, 3H), 3.6 (m, 2H), 3.85 (m, 2H), 4.2 (q, 2H, J=7), 4.55 (s, 2H), 4.65 (m, 1H); and **15** (0.13g, 18%), $[\alpha]^{20}_D$ -32.1 (c 1.05, $CHCl_3$); IR (neat): 1720, 1680, 1530 cm^{-1}; ^1H NMR: δ 0.74 (d, 3H, J=7), 0.89 (d, 3H, J= 7), 0.90 (d, 3H, J=7), 1.27 (t, 3H, J=7), 2.2 (m, 1H), 2.5 (m, 3H), 3.2 (m, 1H), 3.36 (s, 3H), 3.65 (m, 2H), 3.8 (m, 1H), 4.15 (q, 2H, J=7), 4.55 (s, 2H), 4.4 (m, 1H), 4.56 (s, 2H), 4.65 (dt, 1H, J=12, J=5.8). (Found: C, 59.18; H, 8.61; N, 5.68. $C_{24}H_{42}O_8N_2$ requires C, 59.24; H, 8.70; N, 5.76).

(L)-Menthyl 1-carboethoxy-3-(2-hydroxyethyl)-3-nitro-4-piperidine acetate 16.

A solution of **14** (0.75g, 15.7mmol) in acetone (20ml) containing diluted HCl (10ml) was stirred at 25°C for 18h and then concentrated. The residue was treated with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (4x25ml). The dried organic extracts were evaporated to leave **16** (0.44g, 40%) as an oil; $[\alpha]^{20}_D$ = -43.33 (c 0.18, $CHCl_3$); IR (neat): 3450, 1730, 1680, 1530 cm^{-1}; ^1H NMR: δ 0.73 (d, 3H, J=7), 0.88 (d, 3H, J=7), 0.90 (d, 3H, J=6.9), 1.27 (t, 3H, J=7.1), 3.76 (bs, 3H), 3.9 (m, 1H), 4.16 (q, 2H, J=7.1), 4.2-4.4 (m, 2H), 4.69 (m, 1H). (Found: C, 59.63; H, 8.57; N, 6.27. $C_{22}H_{38}O_7N_2$ requires C, 59.71; H, 8.65; N, 6.33).

(L)-Menthyl-1-carboethoxy-3-[2-(2-nitrophenylseleno)ethyl]-3-nitro-4-piperidine acetate 17.

To a solution of **16** (0.35g, 0.81mmol) and o-nitrophenyl selenocyanate (0.22g, 0.97mmol) in THF (10ml) was added tributylphosphine (0.25g, 1.2mmol) at 25°C. After stirring for 2h under argon, the solvent was evaporated off and the residue purified by column chromatography (ether / light petroleum 1:1) to give **17** (0.42g, 84.2%) as an oil. IR (neat): 1730, 1685, 1540, 1520, 1450 cm^{-1}; ^1H NMR: δ 0.7 (d, 3H, J=7), 0.9 (d, 3H, J=6.9), 0.91 (d, 3H, J=7), 1.3 (t, 3H, J=7), 3.5 (m, 2H), 4.0 (m, 2H), 4.2 (q, 2H, J=7), 4.65 (m, 1H), 7.5 (m, 2H), 7.9 (m, 1H), 8.3 (m, 1H).

(L)-Menthyl 1-carboethoxy-3-nitro-3-vinyl-4-piperidine acetate 18.

To an ice-cooled and stirred solution of **17** (0.42g, 0.68mmol) in CH_2Cl_2/$MeCO_2H$ 19/1 (30ml) were added tetrabutylammonium hydrogen sulphate (20mg, 0.06mmol) and sodium perborate tetrahydrate (0.4g). After being stirred at 25°C for 7h, the solution was poured into ice. The resulting organic phase was washed with saturated $NaHCO_3$, dried and concentrated in vacuo. Flash chromatography of the residue (ether / light petroleum 1:2) gave pure **18** (0.22g, 80%) as an oil; $[\alpha]^{20}_D$ = -36 (c 0.28, $CHCl_3$); IR (neat): 1720, 1690, 1535 cm^{-1}; ^1H NMR: δ 0.65 (d, 3H, J=7), 0.82 (d, 3H, J=7), 0.83 (d, 3H, J=7), 0.9-1.1 (m, 3H), 1.2 (t, 3H, J=7), 1.2-1.5 (m, 3H), 1.5-2 (m, 6H), 2.15 (dd, 1H, J=14, J=5) 3.0 (m, 1H), 3.2 (m, 1H), 3.65 (m, 1H), 3.85 (m, 1H), 4.07 (q, 2H, J=7), 4.65 (m, 1H), 5.5 (m, 2H), 5.85 (dd, 1H, J=17.5, J= 12). (Found: C, 62.19; H, 8.51; N, 6.54. $C_{22}H_{36}O_6N_2$ requires C, 62.24; H, 8.55; N, 6.60).

(L)-Menthyl 1-carboethoxy-3-vinyl-4-piperidine acetate 19.

A solution of **18** (0.73g, 1.81mmol), ammonium formate (0.378g, 6mmol), Ph_3P (0.131g, 5mmol) and $Pd(PPh_3)_4$ (0.29g, 0.25mmol) in THF (30ml) was heated at reflux for 48h and then concentrated. The residue was flash chromatographed (ether / light petroleum 1:2) to give **19** (0.2, 64%) as an oil, $[\alpha]^{20}_D$ -35.5 (c 0.89, $CHCl_3$); IR (neat): 3050, 1720, 1690 cm^{-1}; ^1H NMR: δ 0.65 (d, 3 H, J= 7), 0.85 (d,3H, J=7), 0.9 (d, 3H, J=7), 0.9 (m, 2H), 1.22 (t, 3H, J=7), 1.2-1.5 (m, 3H), 1.5-2.0 (m, 6H), 2.3 (m, 4H), 3.0-3.2 (m, 1H), 3.4-3.7 (m, 1H), 3.9 (m, 2H), 4.2 (q, 2H, J=7), 4.6 (m, 1H), 5.1 (m, 2H), 5.75 (ddd, 1H, J=15, J=8, J=10). (Found: C, 69.53; H, 9.80; N, 3.57. $C_{22}H_{37}O_4N$ requires C, 69.62; H, 9.83; N, 3.69).

(-)-Meroquinene 1 hydrochloride.

A suspension of **19** (70mg, 19mmol) in 10% hydrochloric acid (7.5ml) was refluxed for 6h, cooled and partially concentrated in vacuo, extracted with CH_2Cl_2 (2x10ml) and then concentrated to leave (-)-meroquinene **1** as hydrochloride (56mg, 70%), mp 147-148°C (EtOH), $[\alpha]^{20}_D$ -23 (c 0.60, MeOH), [lit[4]: mp 147-149°C, $[\alpha]^{25}_D$ +27.5 (c 0.60, MeOH) for the hydrochloride of the natural enantiomer.

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