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TOTAL SYNTHESIS OF (+)-MEROQUINENE

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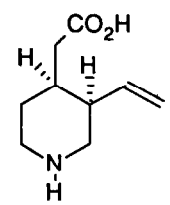
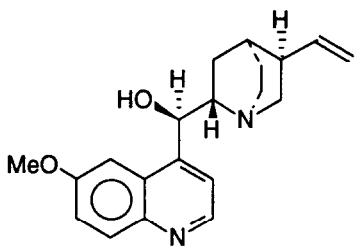
Summary - A synthesis of (+)-meroquinene is described in which two vicinal vinyl and carboxymethyl groups are efficiently introduced utilizing a carbon framework derived from D-glucose.

Meroquinene **1** is a key synthetic precursor to a number of medicinally important alkaloids such as quinine **2** and cinchonamine **3**[1] (Figure 1). Meroquinene and the corresponding homomeroquinene, (3R)-vinyl-(4S)-piperidine propionic acid, are also degradation products of cinchonine.[2,3] While the original elegant syntheses of these *Cinchona* alkaloids utilized homomeroquinene,[4] the more recent syntheses utilize meroquinene itself in enantiomerically pure or racemic form.[5]

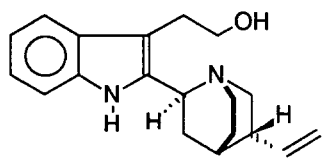
Figure 1



(+)-Meroquinene
1



Quinine
2



Cinchonamine
3

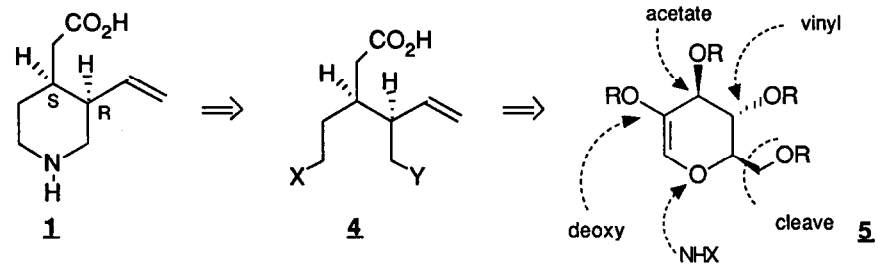
A number of syntheses of meroquinene from achiral precursors have been reported.[6] In some instances, an advanced intermediate was resolved to lead ultimately to (+)- and (-)-meroquinene.[6a] Another synthesis of precursors to (+)-meroquinene was reported starting with secologanin.[7]

Examination of the structure of this target reveals the presence of two vicinal, functionalized chains with a (3R), (4S)-*syn* orientation. Clearly, the placement of this type of substitution pattern on an appropriate template with the correct sense of chirality would seem to be the main challenge in the synthesis of (+)-meroquinene. We reasoned that a conformationally biased cyclic molecule could serve as a template for the regio- and stereocontrolled introduction of the vinyl and carboxymethyl substituents. The glucal derivative **5**, which is readily available from D-glucose[8] was chosen as the starting material. The overall synthetic plan is shown in Figure 2.

Thus, if a suitable anchoring group were introduced in a D-glucal derivative, the conditions for conformational bias would be fulfilled, and the question of further carbon functionalization can be addressed provided that the resident groups were amenable to manipulation. Treatment of 2-acetoxy D-glucal triacetate **6**[9]

(Figure 3) with t-butyl alcohol in the presence of boron trifluoride etherate [10] gave the crystalline *t*-butyl enoside derivative **7** [11] in 78% yield. Previously, we had reported[11] that **7** underwent smooth 1,4-conjugate addition with lithium dimethylcuprate to give a stereochemically defined 4-C-methyl derivative. [12] Alternatively, sequential treatment of **7** with the anion of trimethylphosphonoacetate and the cuprate had led to the same product in somewhat higher yield.[11] Based on this precedent, we prepared the enone derivative **8** from **7** in 63% yield.

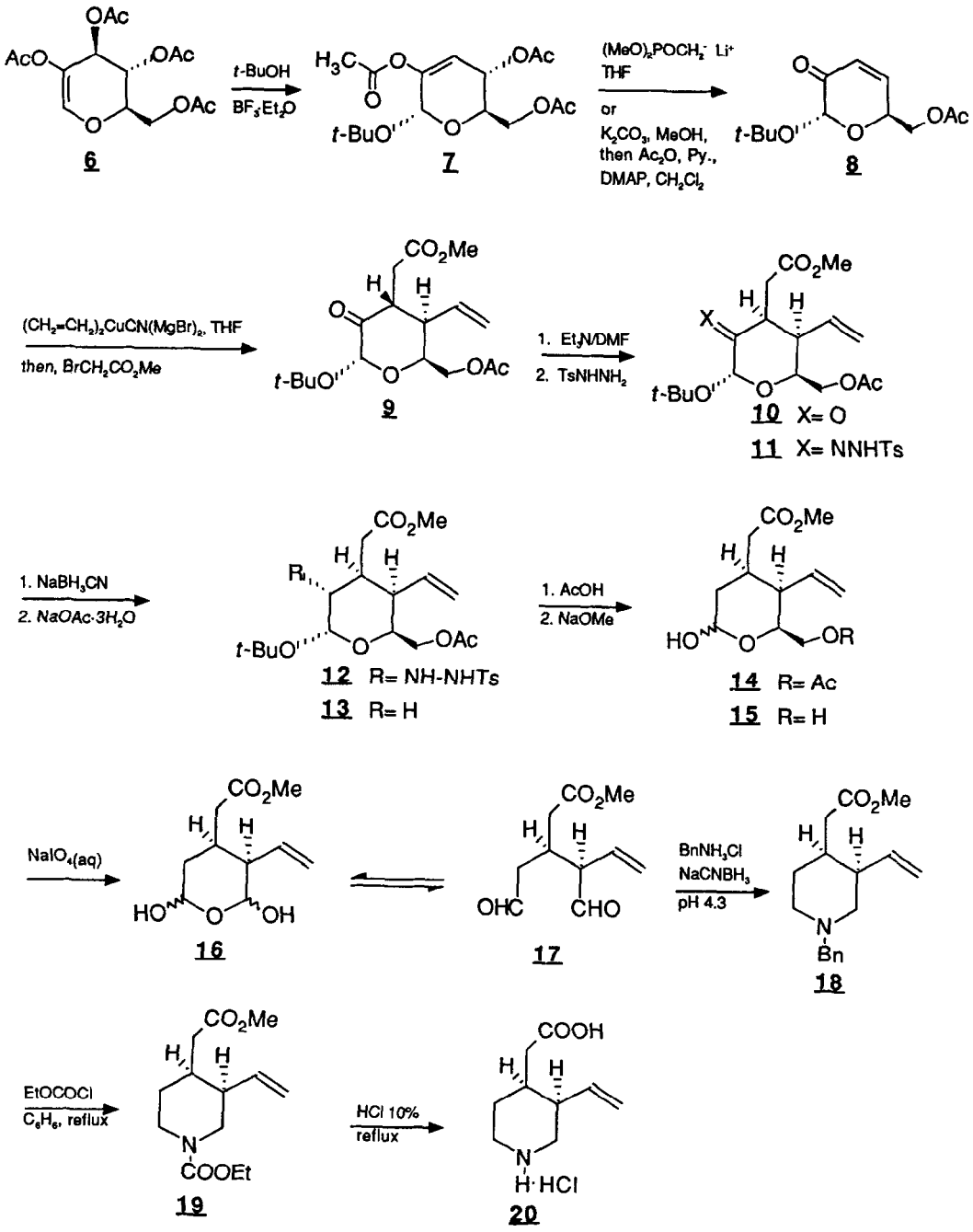
Figure 2



A minor product (4%) was found to be the corresponding diene, presumably arising from β-elimination. We envisage the attack of an anionic specie derived from the reagent on the carbonyl group of the 2-acetoxy group in **7**, triggering a cascade event with the ejection of the 4-acetoxy group and the ultimate formation of the enone **8**. In the case where the reaction is done with the cuprate directly, further 1,4-addition takes place to give the 4-C-methyl derivative.[11] Evidently, no such addition takes place with the phosphonoacetate anion since the reaction cleanly affords the enone **8** itself which is inert to the reagent. A simpler and more reproducible approach to **8** involved treatment of **7** with potassium carbonate in methanol followed by acetylation (70%). We next addressed the question of site- and stereoselective functionalization of the enone system in order to introduce appropriate carbon appendages. Thus, treatment of **8** with the mixed bromomagnesium cyano divinylcuprate[13] derived from vinylmagnesium bromide and cuprous cyanide, followed by addition of methyl bromoacetate to the resulting enolate led, in a one-pot operation to the disubstituted glycoside **9** in good overall yield. The introduction of the methoxycarbonylmethyl group was expected to afford a mixture of the desired *cis*, and undesired *trans* additions products. N.m.r. investigation revealed that the product was almost exclusively the *trans* isomer **9**. Treatment of **9** with triethylamine effected complete epimerization to the desired *cis* isomer **10** in good overall yield. With the critical vicinal functionality conveniently introduced with virtually complete regio- and stereoselectivity, we turned our attention to the task of converting **10** into our intended target **1**. To this end, it would be necessary to deoxygenate at C-2, excise C-6 and construct the piperidine ring.

Reduction of **10** with a variety of borohydrides ranging from sodium borohydride, to 9-borabicyclo-[3.3.1]nonane or L-selectride led to mixtures of epimeric alcohols. Unfortunately the *syn*-alcohol underwent ready intramolecular transesterification to afford the corresponding lactone, thus making this approach impractical. We then turned our attention to the prospects of deoxygenating the carbonyl group via its N-tosylhydrazone derivative,[14] by adapting the conditions developed for other carbohydrate ketones[15] to our substrate. Thus, **10** was transformed into the corresponding N-tosylhydrazone **11** under strict temperature control. Reduction to the corresponding N-tosylhydrazine **12** derivative and treatment of an ethanolic solution of the latter compound with sodium acetate trihydrate at 72°C led to a smooth conversion to **13** in good overall yield. The structure and

Figure 3


OAc
AcO
OAc
OAc
O
6
t-BuOH
BF3Et2O
H3C
O
O
OAc
OAc
t-BuO
O
7
(MeO)2POCH2- Li+
THF
or
K2CO3, MeOH,
then Ac2O, Py.,
DMAP, CH2Cl2
O
t-BuO
O
OAc
8
(CH2=CH2)2CuCN(MgBr)2, THF
then, BrCH2CO2Me
CO2Me
H
H
O
t-BuO
O
OAc
9
1. Et3N/DMF
2. TsNHNH2
CO2Me
H
H
X
t-BuO
O
OAc
10 X= O
11 X= NNHTs
1. NaBH3CN
2. NaOAc·3H2O
CO2Me
H
H
R
t-BuO
O
OAc
12 R= NH-NHTs
13 R= H
1. AcOH
2. NaOMe
CO2Me
H
H
HO
O
OR
14 R= Ac
15 R= H
NaIO4(aq)
CO2Me
H
H
HO
O
OH
16
CO2Me
H
H
OHC
CHO
17
BnNH3Cl
NaCNBH3
pH 4.3
CO2Me
H
H
N
Bn
18
EtOCOCl
C6H6, reflux
CO2Me
H
H
N
COOEt
19
HCl 10%
reflux
COOH
H
H
N
H·HCl
20

stereochemistry of the chiron **13** in which the critical side-chains of meroquinene were introduced by sequential conjugate addition, enolate trapping and epimerization, were ascertained by an X-ray analysis of the corresponding lactol derivative **15**.[16]

The final task in our synthesis of enantiomerically pure (+)-meroquinene consisted of excising the terminal hydroxymethyl group and insertion of an amino group to form the piperidine ring. Considering the structure of **13**, a number of options were available, culminating in a reductive amination of a transient ω-amino aldehyde as in our synthesis of (+)-azimic and (+)-carpamic acid.[17] An alternative shorter route, that would not require manipulation of each extremity in **14** independently, was envisaged via a Borch-type amination[18] of the dialdehyde **16-17**. Although this type of reductive amination has been extensively utilized,[18] there are few examples involving the formation of cyclic amines from a dicarbonyl compound and an amine or its equivalent.[19,20] The issue in our case would be further complicated by the presence of internal hemiacetals hence the equilibrium between **16** and **17**.

In the event, oxidation of **15** with sodium periodate in aqueous acetone followed by treatment with ammonium sulfate[18] in the presence of sodium cyanoborohydride led to the expected meroquinene methyl ester, albeit in poor yield (~10-15%). An alternative approach consisted in treating the dialdehyde product **16** with benzylamine hydrochloride under reductive amination conditions. This process afforded N-benzyl meroquinene methyl ester **18** in 34% overall yield (from **14**) identical in all respects with authentic sample prepared by mono-N-benzylation of meroquinene *t*-butylester followed by transesterification in acidic methanol.

Finally, N-debenzylation of **18** was accomplished by treatment with ethyl chloroformate,[20] followed by acid hydrolysis of the resultant N-ethoxycarbonyl derivative **19**. Meroquinene hydrochloride thus obtained was found to be identical in all respects with authentic material prepared from the hydrolysis of the meroquinene t-butyl ester tartrate.[21] The ^{13}C n.m.r. data for meroquinene and several of its derivatives and precursors are listed in Tables 1 and 2.

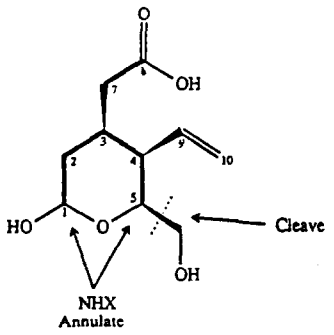
Computer-Assisted Synthesis Planning

One of the attributes of the Chiron approach in organic synthesis [22] is the utilization of chiral templates derived from natural sources such as amino acids, carbohydrates, hydroxy acids and terpenes. Consequently, the prospects of producing optically pure target molecules are excellent, provided no racemization takes place en route. Since a number of chiral templates can be envisaged for meroquinene, it was of interest to run a Computer Assisted Precursor Selection (CAPS) search using the Chiron program.[23] Version 4.0 of the program comprises about 1500 chiral non-racemic, chiral racemic and achiral precursors in its data base. Figure 4 illustrates some of the acyclic precursors that were found, which includes D-glucose, a branched chain derivative, and (S,S)-tartaric acid. Since the timing of transformations is most critical in a synthesis, the presently depicted format of chemical events that relate keywords to reaction types accentuates our chemical reflexes and creates a fertile ground for discussions.

From Figure 4A, it is clear that all of the stereocenters in D-glucose must be sacrificed, and that inherent functionality must be used to introduce the necessary branches en route to the intended target. While the combination of "annulate" and "NHX" may lead us to think of a reductive amination sequence via a dialdehyde, it is less clear how two vicinal stereocontrolled C-C bond forming reactions can be effected. Consequently the program gives a very low score to D-glucose as a precursor. In this regard the finding of an appropriate branched-chain carbohydrate as a chiron may be more practical. This is clear from Figure 4B, where the precursor found by Chiron is the same as the one conceived visually and as a result of past experience by the chemist.

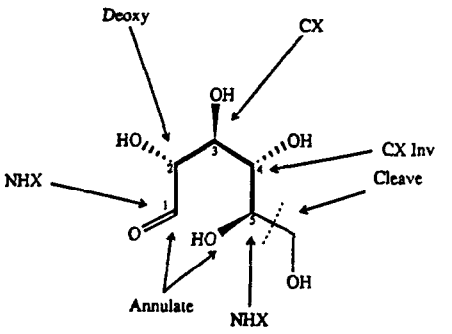
Figure 4

Computer Assisted Precursor Selection



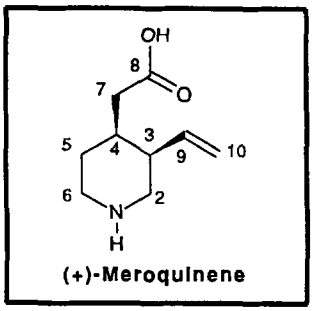
2,3,4-Trideoxy-4-C-vinyl-3-(methoxycarbonylmethyl)-D-lyxopyranose
89% # 1, P-M : 1-2/10-12 (Cleaved and reshaped)

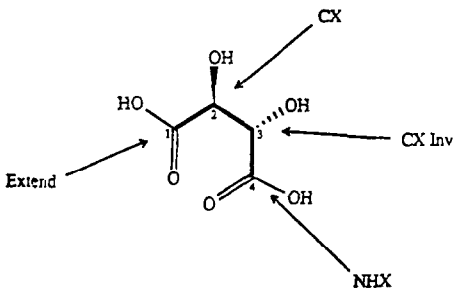
A



D-Glucose
Comm., F=ACYCLIC-6
6% # 11, P-M : 1-6/5-2 (Cleaved and reshaped)

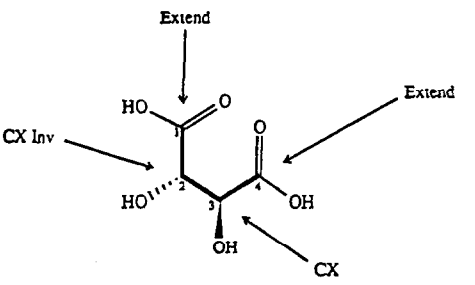
B





(S,S)-Tartaric acid
Comm., F=ACYCLIC-3-4
11% # 87, P-M : 1-5/4-2

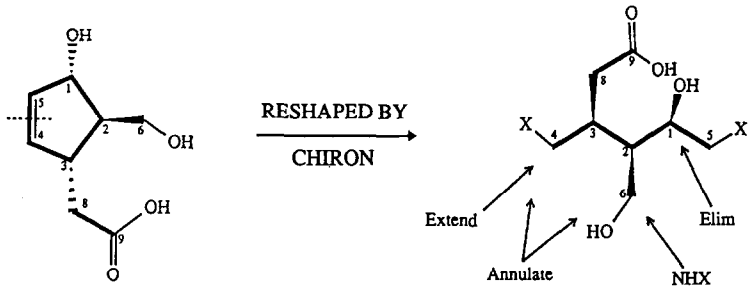
A



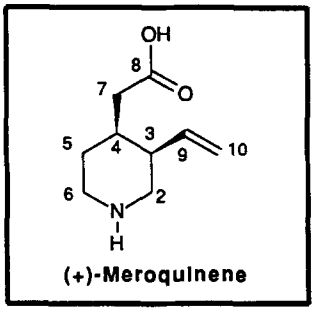
(S,S)-Tartaric acid
Comm., F=ACYCLIC-3-4
12% # 87, P-M : 1-7/4-9

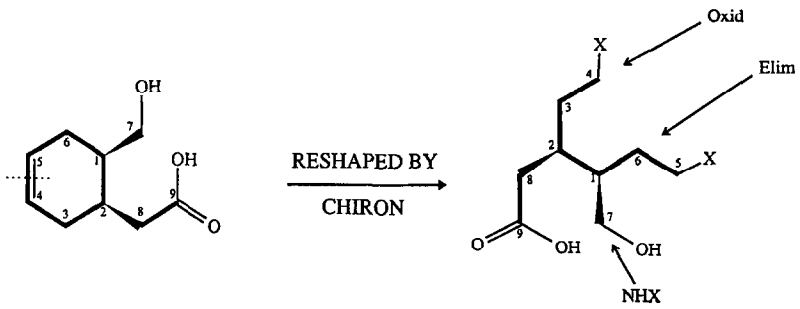
B

Figure 5



(1S,2R,3R)-1-Hydroxy-2-hydroxymethyl-4-cyclopentene-3-acetic acid [R]
E.J. Corey et al, JACS, 95, 6832 (1973), F=CARBOCYCLIC-BRANCHED
75% # 42, P-M : 4-5/9-8 (Cleaved and reshaped)





(1R,2R)-2-Carboxymethyl-1-hydroxymethyl-4-cyclohexene [M]
J.B. Jones et al, JACS, 104, 4659 (1982), F=CARBOCYCLIC-BRANCHED
65% # 24, P-M : 4-8/9-6 (Cleaved and reshaped)

Since only two stereocenters are involved in the construction of the target, the "right" tartaric acid could, in principle, be a suitable precursor, provided the desired functionality can be introduced in a site-selective manner. Chiron gives the user the choice of two perspectives depending on how the precursor and target frameworks overlap. Both perspectives have a low score because of the difficulties associated with site-selective vicinal C-branching of S,S-tartaric acid.

The Chiron Program has the capability of reshaping molecules after cleavage at strategic sites (ex. double bonds, diols and ketones via a Baeyer-Villiger reaction). Figure 5 illustrates the results of two such "cleave and reshape" options which represents a new dimension in heuristic analysis and perception . Clearly, the two cyclic olefins can be excellent precursors to meroquinene since the streochemistry of the two cis-vicinal centers is present initially, albeit, disguised in a form that is difficult to decode in a visual manner. These considerations are also evident in the respective scores for each precursor.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H n.m.r. spectra were recorded on Brucker 250 MHz, 300 MHz and 400 MHz. Spectrometers infrared spectra were obtained as neat films from syrups or films obtained by gentle melting the solids on sodium chloride pellet on a Perkin Elmer model 781 spectrometer. Optical rotations were measured at room temperature with a Perkin Elmer model 141 polarimeter. Mass spectra were obtained on a VG-1212 low resolution and Kratos-50 high resolution spectrometers by the chemical ionization technique.

t-Butyl 2,4,6-tri-O-acetyl-3-deoxy-α-D-erythro-hex-2-enopyranoside **7**. To a solution of **6**[9] (5.3g) in 60 mL of toluene, was added *t*-butanol (5.3 mL) followed by boron trifluoride etherate (dropwise, 2 mL) under argon. The progress of the reaction was followed by t.l.c. (EtOAc-hexanes, 3:7). After completion, 10 mL of water was added to the amber-colored solution, and it was further treated with saturated sodium bicarbonate (20 mL). The organic phase was separated, washed with water and processed in the usual manner to give a yellow syrup that crystallized from a mixture of ether and petroleum ether (b.p. 30-60°). Filtration and chromatography of the mother liquors (EtOAc-hexanes 3:17) on silica, gave 4.3 g (combined yield 78%) of the title compound, mp 63° (reported,[11] mp 63°); $[\alpha]_D$ + 83.7° (c 1.2, $CHCl_3$).

t-Butyl-6-O-acetyl-3,4-dideoxy-α-D-hex-3-eno-pyran-2-uloside **8**. - Method A. - A solution of *n*-butyl lithium (78 mL, 1.2 mmol, 1.6 M in THF) was added to 2.5 equiv. of trimethylphosphonoacetate (15.1 mL, 140 mmoles) in THF (200 mL), dropwise and with stirring at -12°. The suspension was stirred at this temperature for 30 min, then it was added dropwise (double-tip needle), to the solution of **7** (17.2g, 50 mmol) in 75 mL of THF. The resulting mixture was stirred at room temperature for 3h, whereupon t.l.c. analysis (EtOAc-hexanes, 3:7) indicated the presence of the desired product and some starting material. The reaction mixture was cooled down to -12° and another 2.5 equiv. of trimethylphosphonoacetate anion was added. After stirring for 45 min. at room temperature, the reaction mixture was diluted sequentially with dichloromethane (750 mL), and 5% hydrochloric acid (200 mL). Extraction, and processing the organic layer in the usual manner gave a pale yellow syrup. Purification by flash column chromatography (EtOAc-hexanes, 3:17) or by preparative HPLC (15% EtOAc in hexanes), gave the diene (360 mg, 4%), and the desired product **8** as a colorless syrup (7.62g, 63%); $[\alpha]_D$+4.4° (c 1.4, $CHCl_3$)[11]; ^{1}H n.m.r. (250 MHz, $CDCl_3$, δ ppm) 1.3 (s, 9H, t-Bu), 2.09 (s, 3H, Ac), 4.20 (dd, 1H, J=11.2, 4.5 Hz, H-6), 4.37 (dd, 1H, J=11.2, 5.6 Hz, H-6), 4.83 (m, 1H, H-5) 5.01 (s, 1H, H-1), 6.17 (dd, 1H, J=10.8, 3.4 Hz, H-4), 6.94 (dd, 1H, J=10.8, 2 Hz, H-3); ^{1}H n.m.r. (250 MHz, acetone, δ ppm) 1.28 (S, 9H, t-Bu), 2.01 (s, 3H, Ac), 4.22 (dd, 1H, J=11.2, 4.5 Hz, H-6), 4.31 (dd, 1H, J=11.2, 5.6 Hz, H-6), 4.88 (m, 1H, H-5), 5.10 (s, 1H, H-1), 6.10 (dd, 1H, J=11.2, 3.4 Hz, H-4), 7.16 (dd, 1H, J=11.2, 2 Hz, H-3).

Method B - A solution of the substrate **7** (10.2 g, 29.7 mmol) in methanol (120 mL, spectro grade) was flushed with argon and cooled in a carbon tetrachloride - dry ice bath. One equivalent of potassium carbonate (4,09 g) was added at once to the solution and stirring was maintained for one hour or until no starting material remained by t.l.c. Then the reaction mixture was quenched with Dowex -50 (H^+), allowed to warm up to room temperature and filtered. After evaporation of the methanol, the crude residue was dissolved in ether,washed with a saturated aqueous sodium bicarbonate solution, then brine, dried over magnesium sulfate filtered and evaporated. The crude product was acetylated with acetic anhydride (2 mL) and DMAP (catalytic) in dichloromethane (20 mL) and pyridine (2 mL) for 30 minutes. After an aqueous work-up and purification by flash chromatography (hexanes-EtOAc, 9:1), 5.0 g of the desired product (70%) was obtained.

t-Butyl-6-O-acetyl-3,4-dideoxy-4-C-vinyl-3-C-(methoxycarbonylmethyl)-α-D-lyxo-hexopyran-2-uloside **10**. - Vinyl magnesium bromide (1,0 M/THF, Aldrich) was added dropwise to a stirred suspension of cuprous cyanide (4.02 g, 44.9 mmole, 1.1 equiv) in THF (160 mL) at -78°C. The suspension was then stirred for 5 to 9 min. at 0°C during which time a color change from pale greeen to brown was observed (reaction time was dependent on the scale of the reaction). The brown suspension was cooled to -78° and stirred efficiently (caution - slurry formation during large scale operations). A solution of the enone **8** (9.88 g, 40.88 mmol) in THF (75 mL) was added dropwise with a double tip needle to the suspension of the cuprate at -78°C. The reaction mixture was stirred at this temperature for 30 min, whereupon, t.l.c. analysis (EtOAc-hexanes, 3:7) indicated disappearance of starting material. Methyl bromoacetate (22 mL) was added dropwise and the temperature allowed to reach 25°C. After stirring for 8 h, the orange-colored suspension was diluted with ether (800 mL), and washed with 10% ammonium hydroxide in saturated ammonium chloride (3 x 150 mL). The organic layer was processed in the usual manner to give a yellow oil (**9**) which was dissolved in DMF (55 mL) and triethylamine (30 mL) at 0°C. The solution was stirred at room temperature overnight after which time epimerization was complete (t.l.c.). The solution was diluted with ether, washed with 5% aq. hydrochloric acid, then water. Drying and evaporation afforded a dark-brown oil which was purified by flash chromatography (EtOAc-hexanes, 1:9) or by preparative HPLC (same solvent) to give 8.43 g (60.7%) of the title compound **10**; $[\alpha]_D$ + 137.9° (c 1, $CHCl_3$); ^1H n.m.r. (250 MHz, $CDCl_3$, δ ppm) 1.31 (s, 9H, t-Bu), 2.07 (s, 3H, Ac), 2.22 (dd, 1H, J=18.3, 7.5 Hz, C<u>H</u>COOCH$_3$), 2.76 (dd, 1H, J=18.3, 5.6 Hz, C<u>H</u>COOCH$_3$), 2.91 (ddd, 1H, J=11.2, 5.6, 2 Hz, H-4) 3,65 (td, 1H, J_t=7,5, J_d=5.6 Hz, H-3), 3.70 (s, 3H, OCH$_3$), 4.04 (d, 2H, J=5.6 Hz, 2H-6) 4.81 (td, 1H, J_t=5.6, J_d=2 Hz, H-5), 4.99 (s, 1H, H-1), 5.10 (dd, 1H, J=17, 2 Hz, H vin.*trans*), 5.27 (dd, 1H, J=11, 2 Hz, H vin.*cis*), 5.55 (td, 1H, J_t=17, J_d=11 Hz, RC<u>H</u>=CH$_2$).

<u>Preparation of the N-tosylhydrazone **11** from **10**</u> - N-Tosylhydrazine (2.34 g, 13.67 mmol) was added to a solution of (4.25 g, 12.43 mmol) in ethanol (60 mL). This mixture was heated at 72-74°C (external) for 1.5 hours. Evaporation of the solvent gave a yellow viscous oil. Purification by flash chromatography (hexanes - EtOAc, 17:3) afforded the desired hydrazone derivative **11** as a syrup (5.13 g, 81%) along with recovery of starting material (364 mg, 9%), $[\alpha]_D$ + 139,4° (c 1, $CHCl_3$); I.r. (film) 3220 (NH), 1740 (sh. 1720, C=O), 1640 (C=C alkene) and 1600 cm^{-1} (C=Car.); m.s. (DCI, isobutane, m/e) 513 (12%, (M+H)$^+$), 512 (39%, (M+H)-1), 511 (100%, (M+H)-2); ^1H n.m.r. (300 MHz, $CDCl_3$, δ ppm) 1.30 (s, 9H, *t*-Bu), 2.00 (s, 3H, Ac), 2.14 (dd, 1H, J=17, 8 Hz, C<u>H</u>COOCH$_3$) 2.43 (s, 3H, CH$_3$ ar.), 2.57 (ddd, 1H, J=4.4, 1.4, 0.5 Hz, H-4), 2.69 (dd, 1H, J=17, 5 Hz, C<u>H</u>COOCH$_3$), 3.32 (td, 1H, J_t=5, J_d=8 Hz, H-3), 3.64 (s, 3H, OCH$_3$), 3.92 (d, 2H, J=6 Hz, 2H-6), 4.42 (td, 1H, J_t=6, J_d=0.6 Hz, H-5), 4.49 (dd, 1H, J=17, 1 Hz, H vin.*trans*), 5.10 (dd, 1H, J=10, 1 Hz, H vin.*cis*), 5.30 (td, 1H, J_t=10, J_d=17 Hz, RC<u>H</u>=CH$_2$), 5.71 (s, 1H, H-1), 7.31 (d, 2H, J=8 Hz, 2H ar.), 7.46 (s, 1H, NH), 7.78 (d, 2H, J=8 Hz, 2H ar.); ^{13}C n.m.r. (see Table I).

<u>*t*-Butyl-6-O-acetyl-2,3,4-trideoxy-4-C-vinyl-3-C-(methoxycarbonylmethyl)-2-N-tosylhydrazino-α-D-lyxo-hexopyranoside-2-**12**</u> - To a solution of the tosylhydrazone **11** (5.13 g, 10.06 mmol) in THF-methanol (1:1) (150 mL) was added a small amount of methyl orange.[15] Aliquots of sodium cyanoborohydride (~50 mg) were added every 10 minutes and the pH of the solution maintained at the end point (~3.8) by adding drops of a solution of concentrated hydrochloric acid in methanol (1 mL/10 mL). On completion of the reaction (t.l.c., 1,5 hours) saturated aqueous sodium bicarbonate (~100 mL) was added and stirring was continued for 15 minutes. Work-up consisted in extracting the resulting solution with dichloromethane, drying and evaporation of the organic phase to give the title compound, as a colorless oil (5.0g, 97%). I.r. (film) 3470 (NH), 3240 (NH), 3080, (C=H alkene), 1740 (sh. 1720, C=O), 1640 (C=C alkene) and 1600 cm^{-1} (C=C ar.); M.S. (DCI, isobutane, m/e) 255 (32%, (m+H) -260), 117 (100% (M+H) -398), 99 (77% (M+H) -416); ^1H n.m.r. (250 MHz, $CDCl_3$, δ ppm) 1.20 (s, 9H, t-Bu), 2.00 (s, 3H, Ac), 2.24 (dd, 1H, J=17, 5.5 Hz, C<u>H</u>-COOCH$_3$), 2.40 (dd, 1H, J=17, 9 Hz, C<u>H</u>COOCH$_3$), 2.44 (s, 3H, CH$_3$ ar.) 2.64 (m, 1H, J=4.5 Hz, H-3), 2.71 (dd, 1H, J=4, 1 Hz, H-4), 3.55 (dd, 1H, J=5.7, 3.8 Hz, N<u>H</u>-NHTs), 3.69 (s, 3H, CH$_3$O), 3.75 (m, 1H, H-2), 3.84 (dd, 1H, J=11, 3.8 Hz, H-6), 3.96 (dd, 1H, J=11, 8 Hz, H-6), 4.32 (td, 1H, J_t=3.8, J_d=8 Hz, H-5), 4.94 (dd, 1H, J=17, 2 Hz, H vin.*trans*), 5.04 (s, 1H, H-1), 5.09 (dd, 1H, J=10, 2 Hz, H vin.*cis*), 5.61 (td, 1H, J_t=10, J_d=17 Hz, RC<u>H</u>=CH$_2$), 6.10 (d, 1H, J=3.8 Hz, NH-N<u>H</u>TS), 7.37 (d, 2H, J=8 Hz, 2Har), 7.79 (d, 2H, J=8 Hz, 2H ar.); ^{13}C n.m.r. (see Table I).

<u>*t*-Butyl-6-O-acetyl-2,3,4-trideoxy-4-C-vinyl-3-C-(methoxycarbonylmethyl)-α-D-lyxo-hexopyranoside **13**</u> - Trihydrated sodium acetate (4.932 g) was added to a solution of the tosylhydrazine **12** (930 mg, 1,813 mmol) in absolute ethanol (26 mL).[24] This heterogenous mixture was stirred at 72±1°C (external). Evolution of nitrogen was observed after a few minutes. On completion of the reaction (1.5 hours, t.l.c.), the reaction mixture was diluted with water, extracted with dichloromethane, dried and evaporated to yield a colorless oil (602 mg). Purification by flash chromatography (hexanes-EtOAc, 9:1) afforded the desired product **13** (429 mg, 72%) as a

colorless oil; I.r. (film) 1735 (C=O) and 1630 cm^{-1} (C=C alkene); M.S. (DCI, isobutane, m/e), 255 (100%, (M+H) - 74 (*t*-BuOH)), 195 (40% (M+H)-134); precise mass calc. for $C_{13}H_{19}O_5$ (M-(O-*t*-Bu)): 255.1233, found: 255.1175. ^1H n.m.r. (400 MHz, $CDCl_3$, δ ppm), 1.25 (s, 9H, t-Bu), 1.41 (dd, 1H, J=13, 4 Hz, H-2), 1.58 (td, 1H, J_t=13, J_d=4 Hz, H-2), 2.02 (s, 3H, Ac), 2.08 (dd, 1H, J=15.8, 6 Hz, C<u>H</u>COOCH$_3$), 2.23 (dd, 1H, J=15.8, 8.8 Hz, C<u>H</u>COOCH$_3$) 2,32 (dl, 1H, J=10.3 Hz, H-3), 2.67 (oc.d, 1H, J_o=4, J_d=5.6 Hz, H-4), 3.67 (s, 3H, CH_3O), 3.96 (m, 2H, 2H-6), 4.34 (ddd, 1H, J=2.3, 5.5, 7.3 Hz, H-5), 5.06 (dd, 1H, J=17, 2 Hz, H vin.*trans*), 5.21 (d, 1H, J=4 Hz, H-1), 5.21 (dd, 1H, J=10, 2 Hz, H vin.*cis*) 5,86 (td, J_t=10, J_d=17 Hz, RC<u>H</u>=CH$_2$); ^{13}C n.m.r. (see Table I).

<u>6-O-Acetyl-2,3,4-trideoxy-4-C-vinyl-3-C-(methoxycarbonylmethyl)-α,β-D-lyxopyranose 14</u> - Four drops of 10% aqueous hydrochloric acid were added to a solution of **12** (487 mg, 1.485 mmol) in a (1:2:3) mixture of THF (6 mL), water (12 mL) and acetic acid (18 mL). The resulting solution was stirred at 35°C for 24 hours. On completion of the reaction (t.l.c.), the reaction mixture was diluted with dichloromethane and neutralized by washing with small portions of saturated aqueous sodium bicarbonate, dried and evaporated. The desired compound **14** was obtained as a colorless oil (360 mg, 89%); I.r. (film) 3450 (OH), 1740 (C=O) and 1640 cm^{-1} (C=C alkene); M.S. (DCI, isobutane, m/e) 255 (100%, (M+H)-18) 256 (14%, (M+H)-18+1), 257 (6%, (M+H)-18+2); precise mass calc. for $C_{13}H_{19}O_5$: 255.1233, found: 255.1255. ^1H n.m.r. (300 MHz, $CDCl_3$, δ ppm) 1.3 (m, H-2), 1.6 (m, H-2), 1.82 (td, J_t=2, J_d=13 Hz, H-3), 2.08 (s, Ac), 2.1-2.4 (m, C<u>H</u>$_2$COOCH$_3$, H-4, H-3, OH), 2.7 (m, H-4), 3.670, 3.674 (2S, OCH_3), 3.84 (m, H-5), 4.00 (m, 2H-6), 4.40 (m, H-5), 4.89 (dd, J=8, 2 Hz, H-1), 5.09 (2dd, J=17, 2 Hz, H vin.*trans*), 5.26 (dd, J=10, 2 Hz, H vin.*cis*), 5.41 (d, J=3 Hz, H-1), 5.86 (m, RC<u>H</u>=CH$_2$), ^{13}C n.m.r. (see Table 1).

<u>2,3,4-Trideoxy-4-vinyl-3-(methoxycarbonylmethyl)-α,β-D-lyxopyranose 15 from 14</u> - Two drops of sodium methoxide (25%, w/w, in methanol) were added to a solution of the substrate **14** (105 mg, 0.386 mmol) in methanol (10 mL, commercial spectrograde). The resulting solution was stirred until the hydrolysis was complete (t.l.c., 1.5 hours). Neutralization was accomplished with Dowex-50 (H^+). Filtration and evaporation to dryness afforded the desired compound **15** as a colorless oil (89 mg, quantitative); I.r. (film) 3400 (OH), 1725 (C=O) and 1625 cm^{-1} (C=C); M.S. (DCI, isobutane, m/e) 213 (100%, (M+H)-18), 129 (53%, (M+H)-102); ^1H n.m.r. (250 MHz, $CDCl_3$, δ ppm) 1.31 (m, H-2), 1.58 (m, H-2), 1.66 (dt, J=13 Hz, H-2), 2.25 (m, C<u>H</u>$_2$COOCH$_3$, H-3, OH), 2.65 (m, H-4), 3.24 (dl, J=20 Hz, H-4), 3.48 (m, 2H-6), 3.65 (s, OCH_3), 4.28 (td, J_t=3, J_d=8 Hz, H-5), 4.44 (s, H-1), 4.88 (dd, J=9 Hz, H-5), 5.01 (2dd, J=17, 2 Hz, H vin.*trans*), 5.19 (dd, J=10, 2 Hz, H vin.*cis*), 5.39 (sl, H-1), 6.82 (2td, J_t=17, J_d=10 Hz, RC<u>H</u>=CH$_2$).

<u>Oxidative cleavage of diol 15</u> - Sodium periodate (828 mg, 3.87 mmol) was added to a solution of **15** (89 mg, 0.387 mmol) in water-acetone (1:1, 10mL) with stirring. After one day, a second portion of the oxidant was added and stirring continued for one more day to achieve complete oxidation (t.l.c.). Work up was accomplished by filtration of the salts, dilution with water, extraction with dichloromethane, drying and evaporation of the solvent. The product (60 mg) was obtained as a colorless oil; I.r. (film) 3450 (OH), 1740 (C=O) and 1640 cm^{-1} (C=C alkene); M.S. (DCI, isobutane, m/e) 213 (100% $(M+H)^+$ or $(M+H)-H_2O$). The mixture was used in the next step without further purification.

<u>N-Benzyl meroquinene methyl ester 18</u> - The crude dialdehyde mixture (60 mg) was dissolved in a 1:1 mixture of acetonitrile and aqueous sodium phosphate (0,5 M, pH 4.3) (15 mL) and stirred in the presence of sodium cyanoborohydride (132 mg, 2.1 mmol) and benzylamine hydrochloride (151 mg, 1.065 mmol) for 24 hours. Dilution with saturated aqueous sodium bicarbonate, extraction with dichloromethane, drying and evaporation afforded a colorless oil. Purification by flash chromatography (hexanes-EtOAc, 9:1) gave the desired product **18** (36 mg, 34%, 2 steps) as a colorless oil; $[\alpha]_D$+49.0 (c 0.45, CH_3OH); I.r. (film) 1730 (C=O), 1630 (C=C alkene) and 1600 cm^{-1} (C=C ar.); m.s. (DCI, isobutane) 274 (100%, $(M+H)^+$); precise mass calc. for $C_{17}H_{23}NO_2$: 273.1729, found: 273.1714; ^1H n.m.r. (300 MHz, C_6D_6, δ ppm) 1.36 (m, 2H, J=3.7 Hz, 2H-5), 1.86 (td, 1H, J_t=10.8, J_d=3.7 Hz, H-4), 2.03 (d, 2H, J=10.8 Hz, C<u>H</u>$_2$COOCH$_3$), 2.08 (t, 1H, J=3 Hz, <u>H</u>-6) 2.18 (t, 1H, J=9 Hz, H-3), 2.27 (dd, 1H, J=9, 3 Hz, H-6) 2.64 (dd, 2H, J=10, 3 Hz, 2H-2), 3.237, 3.246 (2s, 2H, NCH$_2$Ar), 3.34 (s, 3H, CH_3O), 4.97 (dd, 1H, J=17, 2.3 Hz, H vin.*trans*), 5.04 (dd, 1H, J=10, 2.3 Hz, H vin.*cis*), 6.23 (td,. 1H, J_t=10, J_d=17, RC<u>H</u>=CH$_2$), 7.09 (tt, 1H, J_o=7, J_m=2 Hz, H para), 7.20 (td, 2H, J_t=2, J_d=7 Hz, H meta), 7.29 (td, 2H, J_t=2, J_d=7 Hz, H ortho); ^{13}C n.m.r. (see Table 2).

<u>N-Carboethoxymeroquinene methyl ester 19</u> - To a solution of N-benzylmeroquinene methyl ester **18** (83 mg, 0.304 mmol) in dry benzene (10 mL) was added freshly distilled ethyl chloroformate (322 µL, 3.365 mmol, 11 eq.) with a microsyringe. The resulting mixture was heated to 75-80°C (external) under argon until completion of the reaction (6 hours, t.l.c.). Evaporation gave a light brown oil which was purified by flash chromatography (dichloromethane to ethyl acetate, rapid gradient) to afford the desired ethylcarbamate derivative **19** (63 mg, 81%)

as a colorless oil.; $[\alpha]_D$ + 45.9° (c 0.850, CH_3OH); 1740 (C=O), 1700 (C=O) and 1640 cm^{-1} (C=C); M.S. (E.I., m/e) 255 (26%, M^+), 256 (6%, M+1), 257 (1%, M+2) and 182 (79%, M-73 (COOEt)); precise mass calc. for $C_{13}H_{21}NO_4$ 255.1471, found 255.1451; n.m.r. ^1H n.m.r. (300 MHz, $CDCl_3$, δ ppm) 1.24 (t, 3H, J=7.15 Hz, NCOOEt), 1.38-1.55 (m, 2H, 2H-5), 1.60 (sl, 1H, H-6), 2.10-2.25 (m, 2H, $C\underline{H}_2COOCH_3$), 2.29 (t, 1H, J=9 Hz, H-4), 2.35-2.40 (m, 1H, H-3), 2.85-3.00 (sl, 1H, H-6), 3.09 (dd, 1H, J=13.25, 3.11 Hz, H-2), 3.67 (s, 3H, OCH_3), 3.98 (dl, 1H, J=13.3 Hz, H-2), 4.12 (2q, 2H, J=7.15 Hz, NCOOEt), 5.09 (ddd, 1H, J=17.1, 1.9, 0.9 Hz, H vin.*trans*), 5.14 (ddd, 1H, J=10.5, 1.9, 0.5 Hz, H vin.*cis*), 5.78 (ddd, 1H, J=17.1, 10.5, 9.0 Hz, $RC\underline{H}=CH_2$); ^{13}C n.m.r. (see Table 2).

Meroquinene hydrochloride **20** - The previous compound **19** (62 mg, 0.243 mmole) was dissolved in aqueous hydrochloric acid (10%, 10 mL) and the resulting mixture heated under reflux for 3 hours. Drying and evaporation afforded 50 mg of crude material which was purified by redissolving in aqueous hydrochloric acid (10%) and washing with dichloromethane. The resulting aqueous solution was reevaporated to give 46 mg (93%) of chromatographically pure meroquinene hydrochloride identical in all respects with material prepared from the hydrolysis of authentic *t*-butyl ester; $[\alpha]_D$ +23.3 (c 0.785, CH_3OH); precise mass calc. for $C_9H_{15}NO_2$ (m-HCl) 169,1103, found 169.1099; ^{13}C n.m.r. (see Table 1).^1H n.m.r. (300 MHz, D_2O, δ ppm) 1.65-1.80 (m, 1H, H-5 axial), 1.80-1.90 (m, 1H, H-5 equatorial), 2.25-2.45 (m, 3H, H-4, $C\underline{H}_2COOH$), 2.77 (six, 1H, J=4 Hz, H-3), 3.11 (ddd, 1H, J=14, 10, 4 Hz, H-6 axial), 3.31 (d, 2H, J=4.28, 2H-2), 3.33 (td, 1H, J_t=14, J_d=4.6 Hz, H-6 equatorial), 5.22 (td, 1H, J_t=1.3; J_d=17.12 Hz, H vin.*trans*), 5.30 (td, 1H, J_t=1.3, J_d=10.5 Hz, H vin.*cis*), 5.91 (ddd, 1H, J=17.12, 10.5, 8.28 Hz, $RC\underline{H}=CH_2$); ^1H n.m.r. (300 MHz, CD_3OD, δ ppm, $C\underline{H}D_2OD$ at 3.30 ppm) 1.65-1.79 (m, 1H, H-5 axial), 1.81-1.91 (m, 1H, H-5 equatorial), 2.20-2.40 (m, 3H, H-4, $C\underline{H}_2COOH$) 2.77 (six, 1H, J=4.2 Hz, H-3), 3.05-3.15 (m, 3H, 2H-5, H-6 axial), 3.17-3.27 (m, 3H, 2H-5, H-6), 5.23 (td, 1H, J_t=1.5, J_d=17.1 Hz, H vin.*trans*), 5.30 (td, 1H, J_t=1.1, J_d=10.5 Hz, H vin.*cis*), 5.96 (ddd, 1H, J=17.1, 10.5, 8.5 Hz, $RC\underline{H}=CH_2$).

N-benzoylmeroquinene methyl ester was prepared in the usual manner (CH_2N_2, then BzCl, Et_3N, CH_2Cl_2), $[\alpha]_D$ +42.3° (c 0.65, CH_3OH); lit,[6] $[\alpha]_D$ + 49.7° (c 0.99, CH_3OH), precise mass calc. for $C_{17}H_{21}NO_3$: 287.1521; found 287.1524.

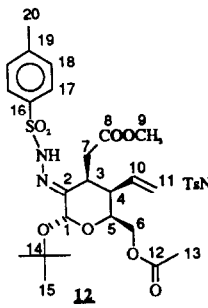
N-Benzyl meroquinene *t*-butyl ester - Meroquinene *t*-butyl ester free base was obtained from a solution of the tartrate salt (115 mg) [21] in ethyl acetate by washing with a saturated aqueous sodium bicarbonate solution, drying and evaporating the solvent to give a pale yellow oil (64mg): $[\alpha]_D$ + 42.6° (c 0.9, CH_3OH); I.r. (film) 3430, 3360, 3280 (NH), 2860, 2810, 2740 (characteristic triple peak), 1730 (C=O) and 1640 (C=C); ^1H n.m.r. (300 MHz, $CDCl_3$, δ ppm) 1.22 (q, 1H, J=6.3 Hz, H-5), 1.44 (s, 9H, *t*-Bu), 1.45 (m, 1H, H-5), 1.90 (sl, 1H, NH), 2.10 (m, 1H, H-4), 2.18 (d, 2H, J=11 Hz, $C\underline{H}_2COO$*t*-Bu), 2.30 (dd, 1H, J=9, 3 Hz, H-3), 2.92 (m, 4H, $2C\underline{H}_2N$), 5.06 (ddd, 1H, J=17.2, 2.1, 1 Hz, H vin.*trans*), 5.13 (ddd, 1H, J=10.4, 2.1, 0.6 Hz, H vin.*cis*), 6.06 (ddd, 1H, J=17.2, 10.4, 9 Hz, $RC\underline{H}=CH_2$); ^{13}C n.m.r. (see Table 1).
Meroquinene *t*-butyl ester was N-benzylated by treatment of a THF solution with NaH (1.5 eq.) followed by addition of benzyl bromide (1.7 eq.).Neutralization with Dowex -50 (H^+), filtration, evaporation and flash chromatography (hexane-EtOAc, 9:1) afforded N-benzyl meroquinene *t*-butyl ester; $[\alpha]_D$ + 22.9° (c 0.95, $CHCl_3$), $[\alpha]_D$ + 27.3 (c 0.2, CH_3OH); ^1H n.m.r. (300 MHz, C_6D_6, δ ppm) 0.9-1.1 (m, 2H, 2H-5), 1.38 (s, 9H, *t*-Bu), 1.88 (td, 1H, J_t=10.8, J_d=3.7 Hz, H-4), 2.0-2.15 (m, 3H, $C\underline{H}_2COO$ *t*-Bu, H-6), 2.18 (t, 1H, J=9 Hz, H-6), 2.27 (dd, 1H, J=9, 3 Hz, H-6), 2.65 (dl, 2H, J=10.3 Hz, 2H-2), 5.01 (dd, 1H, J=17, 2.3 Hz, H vin.*trans*), 5.06 (dd, 1H, J=10.4, 2.3 Hz, H vin.*cis*), 6.26 (td, 1H, J_t=10.4, J_d=17 Hz, $RC\underline{H}=CH_2$), 7.08 (tt, 1H, J_o=7, J_m=2 Hz, H para), 7.20 (td, 2H, J_t=2, J_d=7.2 Hz, H meta) 7.29 (td, 2H, J_t=2, J_d=7 Hz, 2H ortho); ^{13}C n.m.r. (see Table 2).

N-Benzylmeroquinene methyl ester **18** from N-benzylmeroquinene *t*-butyl ester - N-benzyl meroquinene *t*-butyl ester was transesterified to the methyl ester by stirring in a 6% methanolic hydrogen chloride solution for 18 hr. Evaporation of the reaction mixture followed by addition of ethyl acetate, washing with saturated aqueous sodium bicarbonate and conventional processing gave an oil which was purified by flash chromatography (hexanes-EtOAc, 4:1) to yield N-benzyl meroquinene methyl ester; $[\alpha]_D$ + 47.4° (C 0.645, CH_3OH). ^1H n.m.r. and ^{13}C n.m.r. (see Table 2) data were identical with those of the synthetic sample.

Meroquinene hydrochloride from meroquinene *t*-butyl ester - A solution of meroquinene *t*-butyl ester (20.0 mg, 0.0885 mmol) in aqueous hydrochloric acid (10%, 4mL) was vigorously refluxed under argon for 4 hours. The reaction mixture was evaporated to dryness to give 20 mg of chromatographically pure meroquinene hydrochloride as a colorless oil; $[\alpha]_D$ + 27° (0.61, CH_3OH); ^{13}C n.m.r. (see Table 2).

TABLE 1

^{13}C n.m.r. DATA



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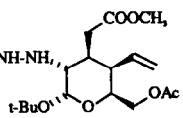
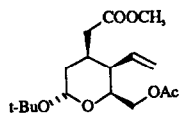


13



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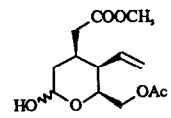
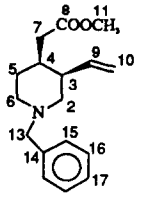


15

#C	$CDCl_3$	$CDCl_3$	DEPT[a]	$CDCl_3$	DEPT	$CDCl_3$		DEPT
1	85.697	91.888	+	91.389	+	96.046;	91.419	+
2	155.87	62.863	+	29.724	-	34.319;	31.435	-
3	38.311	20.613	+	20.868	+	20.702		+
4	46.720	43.101	+	44.361	+	44.338;	43.839	+
5	69.152	67.398	+	68.044	+	75.216;	68.560	+
6	64.864	65.366	-	66.033	-	65.910;	65.447	-
7	31.996	34.021	-	37.928	-	37.752;	37.499	-
8	172.86	172.716	o	172.791	o	172.434		o
9	51.445	51.463	+	51.471	+	51.413;	51.345	+
10	131.128	133.491	+	131.812	+	131.363;		
	131.012	+						
11	120.663	119.614	-	120.074	-	120.331		-
12	170.48	170.593	o	170.785	o	170.709		o
13	31.063	32.332	+	33.235	+	34.053;	29.115	+
14	in solvent	75.273	o	74.348	o			
15	28.721	28.358	+	28.698	+			
16	144.76	143.952	o					
17	129.390	129.440	+					
18	128.055	128.127	+					
19	135.71	134.944	o					
20	21.457	21.419	+					

a) DEPT: CH_3, CH= +, CH_2= -, quaternary C=0

TABLE 2
^{13}C n.m.r. DATA



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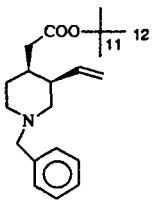

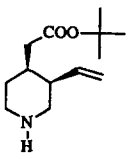

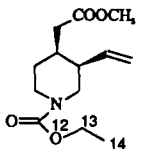

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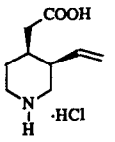

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#C	C_6D_6	DEPT[a]	C_6D_6[b]	DEPT	$CDCl_3$[b]	DEPT	$CDCl_3$	DEPT	CD_4OD	DEPT
2	58.700	-	58.812	-	51.193	-	47.951	-	48.554	-
3	43.684	+	43.674	+	42.839	+	42.192	+	41.007	+
4	35.735	+	35.933	+	35.570	+	35.440	+	33.903	+
5	28.527	-	28.517	-	28.738	-	27.277	-	25.889	-
6	53.615	-	53.705	-	45.935	-	43.382	-	43.894	-
7	37.884	-	39.373	-	39.243	-	37.357	+	36.431	-
8	172.70	o	171.849	o	172.112	o	172.954	o	175.355	o
9	138.496	+	138.630	+	137.034	+	134.957	+	134.875	+
10	116.349	+	116.232	-	116.481	-	117.594	-	119.977	-
11	50.845	+	79.413	o	79.912	o	51.396	+		
12			28.178	+	27.965	+	155.772	o		
13	63.439	-	63.462	-			61.158	-		
14	139.496	o	139.543	o			14.572	+		
15	129.020	+	129.023	+						
16	128.49	+	128.349	+						
17	127.161	+	127.129	+						

a) DEPT: CH_3, CH= +, CH_2= -, quaternary C=0
b) From authentic material.

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24. A concentration of 190 mg of sodium acetate trihydrate per milliliter of ethanol (99%) appeared to be critical. More dilute solutions gave a mixture of unidentified compounds..