Tetrahedron. Vol. 28, pp. 611 to 621. Pergamon Press 1972. Printed in Great Britain

SYNTHESIS OF MARRUBIIN

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(*Received in the UK* 18 *August* 1971; *Accepted for publication* 15 *September* 1971)

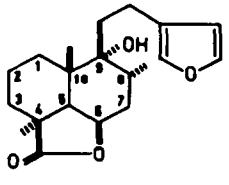
Abstract—The synthesis of marrubiin has been achieved starting from the keto lactone (II) which was prepared stereoselectively from the known keto ester (XI).

THE structure of marrubiin, the diterpene lactone of *Marrubium vulgare**, has long been established.[2–4] More recently the stereochemical details included in the formula (I) have been clarified.[5–12] In connection with our research in this field, this paper describes results which are referred to in two preliminary communications.[13, 14]

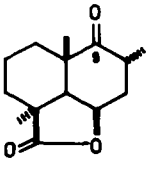
Some of our previous results[12] suggested that the keto lactone (II), easily obtained by degradation of marrubiin,[2–4, 12] could be an intermediate for the projected synthesis, since in II most of the structural features of marrubiin are present as well as a keto group at the 9-position, which could be used to introduce the side-chain bearing the furane ring.

The reaction of II with a suitable organometallic compound was conditioned by the considerable steric hindrance of the keto group, especially by the side of the molecule bearing both the angular methyl and the γ-lactone ring. Consequently, the preferential formation of a compound with the wrong configuration at C_9 (oxygen β-oriented) could be expected. On the other hand, owing to the poor reactivity of the CO group, the keto lactone (II) failed to react even with triphenyl-methylene-phosphorane. This observation precluded the use of the Wittig reaction in order to obtain an olefin derivative, from which one might have expected the formation of an intermediate with the correct configuration at C_9 by attack of a suitable reagent (e.g. a peracid) from the less hindered α-side.

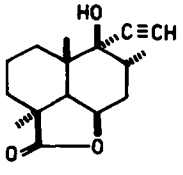
Therefore another route was devised which involves the destruction of the chiral centre initially formed at C_9 thus making the direction of the attack on the CO group unimportant. Owing to the availability of the optically active keto lactone (II), we also decided to start with the keto lactone (II) of natural origin and to postpone the problem of its synthesis to a later stage of our research.



(I)

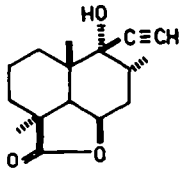


(II)

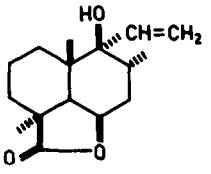


(III)

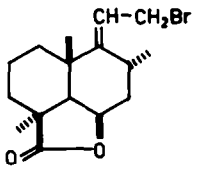
* It has been recently reported[1] that marrubiin may not be originally present in the plant.



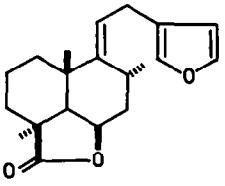
(IV)



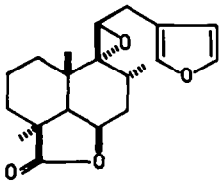
(V)



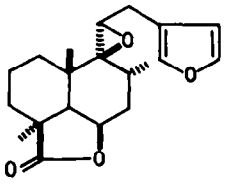
(VI)



(VII)



(VIII)



(IX)

Treatment of II with lithium acetylide-ethylenediamine adduct[15, 16] in dioxan gave the two crystalline ethynyl carbinols (III; 75%) and (IV; 15%).

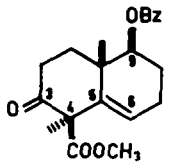
Catalytic hydrogenation of III quantitatively led to the corresponding ethylene alcohol (V), from which the primary crystalline allylic bromide (VI) was obtained by treatment with phosphorus tribromide in pyridine.[17] However, the bromide (VI) could be more easily obtained by hydrogenation of the mixture of epimers (III and IV) and subsequent reaction of the resulting product with phosphorous tribromide in pyridine.

Introduction of the furane ring was carried out by reaction of the bromide (VI) with β-furil-lithium.[18] The product was identical with the known anhydromarrubiin (VII)[6, 19] in all respects. The transformation of the latter into marrubiin, though formally a hydration of a trisubstituted double bond according to Markovnikov, could only be accomplished indirectly.

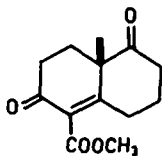
After a number of unsuccessful attempts, including oxymercuration-demercuration,[20] the epoxide (VIII) was used as an intermediate. Owing to the presence of furane ring, it was found that the best yields were obtained by reaction of VII with perphthalic acid for a very short time at room temperature. Although a large amount of unreacted VII was recovered, the crystalline α-epoxide (VIII) accompanied by very small quantities of its isomer (IX), could be easily obtained. Reduction of the α-epoxide with lithium ethylamine finally gave a compound identical in all respects with the natural marrubiin.

In order to synthetize the keto lactone (II), the keto ester (X), used for the synthesis of the andrographolide lactone,[21] was chosen since it has the carbomethoxyl group correctly oriented with respect to the angular methyl and in addition an oxygenated function at C_9 and the 5,6 double bond suitably placed for the introduction of the other oxygenated function at C_6.

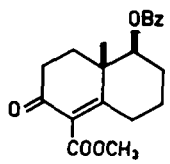
The keto ester (X) was stereospecifically prepared from the ester (XI), according to the method of Pelletier,[21] although a few modifications were made. The most important of these is the use of potassium t-amylate[22, 23] in the reaction of methylation



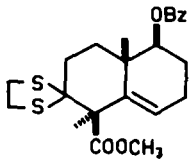
(X)



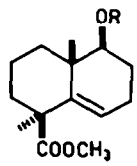
(XI)



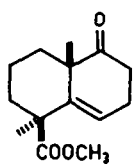
(XII)



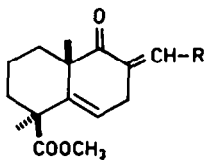
(XIII)



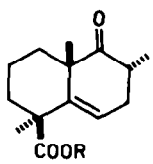
(XIV a) R = Bz
(XIV b) R = H



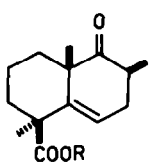
(XV)



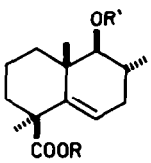
(XVI a) R = OH
(XVI b) R = S-C₄H₉-n



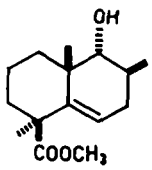
(XVII a) R = CH₃
(XVII b) R = H



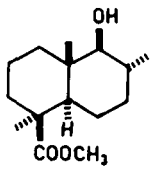
(XVIII a) R = CH₃
(XVIII b) R = H



(XIX a) R = CH₃ ; R' = H
(XIX b) R = H ; R' = H
(XIX c) R = CH₃ ; R' = Ac



(XX)



(XXI)

of the benzoate (XII). Besides a considerable improvement in the yield the keto ester (X) was obtained in the crystalline form. Elimination of the carbonyl at C_3 was achieved by conventional methods: treatment of X with ethanedithiol and boron trifluoride provided the crystalline thioketal (XIII), and desulfurization of this with Raney Ni yielded the desired ester (XIVa).

Introduction of the 8-methyl was achieved through the hydroxymethylene derivative (XVIa). Hydrolysis of XIVa with methanolic KOH gave the monoester (XIVb) which by chromic oxidation gave the corresponding crystalline keto ester (XV). Treatment of XV with ethyl formate and sodium hydride then gave crystalline

hydroxymethylene derivative (XVIa), which was transformed into the corresponding butylthioenol ether (XVIb). Desulfurization of the latter was carried out by brief treatment with very active Raney Ni, since it had been found that a longer reaction time caused the contemporary reduction of the double bond and of the carbonyl group.

In this way a mixture of the two epimeric 8-methyl-ketones (XVIIa and XVIIIa) was obtained in variable ratios depending upon the time of the reaction and upon the alkalinity of the catalyst. They were both isolated in crystalline form and were shown to be actually epimers at the 8 position by the fact that by equilibration with sodium methoxide they both provide a mixture formed from 70% of XVIIa and 30% of XVIIIa.

Because of the strong interaction which should be present between the 8β methyl and the angular methyl in a 'half-chair' conformation, the comparable stability of XVIIa and XVIIIa can be rationalized only by assuming that in the 8β-methyl epimer ring B is in a flexible conformation.[12,24,25] This situation obviously does not allow the unequivocal attribution of structure XVIIa (8-methyl α-equatorial) to the epimer which is more abundant at equilibrium. Nevertheless that this has actually the structure XVIIa was shown by its reduction with sodium borohydride. The reaction stereospecifically afforded a crystalline hydroxy ester, which by oxidation with Jones' reagent quantitatively gave back the starting keto ester, showing that no variation of the stereochemistry at C_8 takes place during the reduction. In the NMR spectrum of the hydroxy ester, the hydrogen at C_9 appears as a doublet at δ 2·94, with a coupling constant (10 c/s) only compatible with the stereostructure (XIXa) in which the protons at C_8 and at C_9 are *trans*-diaxial.

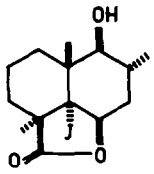
However the high value of J could also be justified by the stereostructure (XX) provided that the ring B is in a flexible conformation, owing to the trigonal carbons of the 5,6 double bond. This ambiguity was eliminated, since catalytic hydrogenation of XIXa quantitatively led to the *trans*-fused* ester (XXI) (certainly in double chair conformation) which still shows the 9H NMR signal as a doublet with a coupling constant of 10 c/s.

The next objective was the introduction of the oxygen into 6-position and the concomitant formation of the required *trans*-decalinic junction.

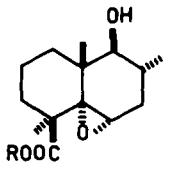
The classic anti-Markovnikov hydration by hydroboration-oxidation was not considered owing to the possible reduction of the carbomethoxl group by diborane. In addition (see catalytic hydrogenation of XIXa), the cis-addition from the less hindered α-side would have yielded an intermediate with the desired *trans*-decalinic junction but with the wrong configuration at C_6.

For this reason, attention was given to alternative routes which however gave discouraging results. They include (i) the iodolactonization[30] of XIXb to the iodolactone (XXII); (ii) the reduction of the epoxy acid (XXIIIb) and the BF_3-treatment[31,32] of the ester (XXIIIa), both available from XIXb; (iii) the acidic treatment[33] of the diol (XXIV), obtained by OsO_4-hydroxylation of the acetate (XIXc).

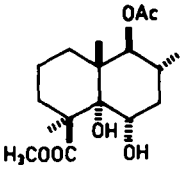
* The presence at δ 0·63 of a Me signal in the NMR spectrum of (XXI) strongly supports the cis-1,3-diaxial relationship of the carbomethoxyl and the angular methyl groups[26] and confirms that hydrogenation occurs from the less hindered α-side, for which there are ample precedents.[27–29]



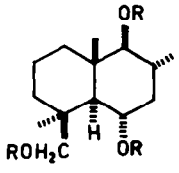
XXII



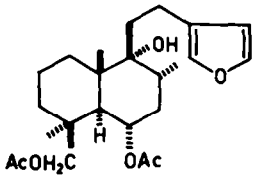
(XXIII a) R = CH_3
(XXIII b) R = H



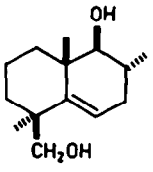
(XXIV)



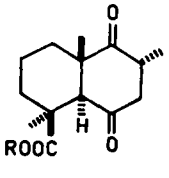
(XXV a) R = H
(XXV b) R = Ac



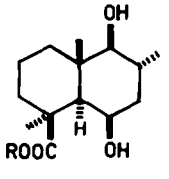
(XXVI)



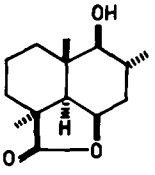
(XXVII)



(XXVIII a) R = H
(XXVIII b) R = CH_3



(XXIX a) R = H
(XXIX b) R = CH_3



(XXX)

Finally the hydroboration-oxidation of the 5,6-double bond was reconsidered but in order to avoid reduction of the carbomethoxyl group, the hydroxy ester (XIXa) was initially submitted to hydroboration with 9-bora-bicyclo [3.3.1.]-nonane.[34] Unfortunately, this reagent was completely inert and when the more reactive diborane was used it caused almost total reduction of the ester group with formation as main product of the crystalline triol (XXVa). The stereostructure (XXVa) assigned to this triol was based on *cis*-addition from the side opposite to the angular methyl, and strongly supported by the NMR spectrum of the corresponding triacetate (XXVb) from which clearly results the equatorial nature of the acetate at C_6. The signal due to the proton in this position appears as a multiplet with the half-height width of 26 c/s and that due to the protons of the 4-methylene as a singlet, in close analogy with the report for the protons placed in similar positions of XXVI.[8]

Once established that the introduction of the hydroxyl into 6-position necessarily brought the contemporary reduction of the carbomethoxyl group, it was found that the triol (XXVa) could more conveniently be prepared by hydroboration-oxidation of the diol (XXVII) easily available by LAH reduction of the keto ester (XVIIa) or of the hydroxy ester (XIXa) (yield XVIIa → XXVa 90%).

With the triol (XXVa) in our hands, apart from the restoration of the carboxyl function, the inversion of the hydroxyl at the 6 position became the key point of our synthetic scheme.

The triol XXVa was oxidized to the crystalline diketo acid (XXVIIIa). This compound and its methyl ester (XXVIIIb) have IR and NMR spectra identical to those of the optically active compounds obtained by degratation of marrubiin,[3] so providing the first correlation with a natural product of known structure and stereochemistry. The reduction of XXVIIIa provided[8,35] the dihydroxy acid (XXIXa) in which both the chiral centres at C_5 and C_6 both finally possess the desired configuration. In fact, the NMR signal due to the 6-proton of the methyl ester (XXIXb), which appears at δ 4·33 as a multiplet with half-height width of 7 c/s, definitively shows the axial nature of the OH in such a position.[8,36,37]

The lactonization of XXIXa[12] easily gave the crystalline hydroxy lactone (XXX), the IR and NMR spectra of which are identical with those of the optically active lactone recently obtained from marrubiin.[10] Finally, the oxidation of XXX gave a quantitative yield of the keto lactone (II), which possesses IR and NMR spectra identical with those of the optically active keto lactone. In consideration of the transformation of the latter into marrubiin, the synthesis of II represents the total synthesis of marrubiin.

EXPERIMENTAL

M.ps are uncorrected. IR spectra were determined on a Perkin–Elmer mod. 137 Infracord spectrophotometer. NMR spectra were recorded on a Varian A-60A or a Perkin–Elmer R12A spectrometers with TMS as an internal standard. Rotations were taken for $CHCl_3$ solns at r.t. with a Perkin–Elmer mod. 141 polarimeter. TLC were performed on silica gel F_{254} (Merck). Silica gel 0·05–0·20 mm (Merck) or alumina (Woelm) was used for column chromatography. VPC was run on a 6′ × ¼″ glass column with chromosorb G (80–100 mesh) as the column support and SE-30 (3%) as the stationary phase using a Perkin–Elmer 881 chromatograph.

Ethynyl carbinol (III) *and ethynyl carbinol* (IV). To anhydrous dioxan (50 ml) saturated with acetylene was added with stirring lithium acetylide-ethylenediamine complex (7 g), followed by a soln of II (1·28 g) in anhydrous dioxan (50 ml) over a period of 20 min. During the addition and for 60 min thereafter, a stream of acetylene was bubbled through the mixture. NH_4Cl aq was added slowly, the layers were separated and the aqueous layer was extracted several times with ether. The organic phases were combined, dried (Na_2SO_4) and concentrated to give a solid (1·275 g) which was chromatographed on silica gel (65 g). Elution with 8:2 hexane-ether afforded 73 mg of IV, then 200 mg of a 1:1 mixture of III and IV and finally 804 mg of III.

The ethynyl carbinol (IV) had m.p. 209·5–210° (from benzene–hexane): (Found: C 72·88; H 8·36. $C_{16}H_{22}O_3$ requires: C 73·25; H 8·45%); $[\alpha]_D$ + 43·5° (c = 0·6); ν_{max} ($CHCl_3$) 3560, 3290, 1760 cm^{-1}: δ ($CDCl_3$) 1·07 (3H, d, J = 6 c/s, $CHC\underline{H}_3$), 1·20 (3H, s, CCH_3), 1·28 (3H, s, CCH_3), 2·44 (1H, s, —C≡CH), 4·66 (1H,m,—CH—OCO—).

The ethynyl carbinol (III) had m.p. 206° (from benzene-hexane): (Found: C 72·88; H 8·34. $C_{16}H_{22}O_3$ requires: C 73·25; H 8·45%); $[\alpha]_D$ + 16·6° (c = 1); ν_{max}($CHCl_3$) 3550, 3270, 1760 cm^{-1}; δ ($CDCl_3$) 1·05 (3H,d,J = 5 c/s, $CHC\underline{H}_3$), 1·14 (3H,s,CCH_3), 1·28 (3H,s,CCH_3), 2·60 (1H,s,—C≡CH), 4·63 (1H,m,—CH—OCO—).

Ethenyl carbinol (V). Compound III (600 mg) in 5 ml 0·1N methanolic KOH was hydrogenated at room temp and atm pressure over 120 mg 10% Pd on $BaSO_4$. The theoretical amount of H_2 (53 ml) was absorbed, the catalyst was filtered off and the solvent evaporated. The residue was dissolved in chloroform and washed with water. The evaporation of the solvent gave 593 mg of V, m.p. 161–162° (from benzene-hexane): (Found: C 72·86; H 9·39, $C_{16}H_{24}O_3$ requires: C 72·69; H 9·15%); $[\alpha]_D$ + 26° (c = 1,1); ν_{max}

($CHCl_3$) 3550, 1760, 990, 925 cm^{-1}; δ ($CDCl_3$) 0·80 (3H, d, J = 6 c/s, $CHC\underline{H}_3$), 1·23 (3H,s,CCH_3), 1·28 (3H,s, CCH_3), 4·72 (1H,m,—CH—OCO) 5·15–6·22 (3H,ABXpattern,—CH = CH_2).

Bromide (VI). Compound V (500 mg) dissolved in dry chloroform (0·9 ml) and cooled at −15° was treated with a soln of pyridine (0·1 ml) and PBr_3 (0·1 ml) in chloroform (2·5 ml). The mixture was stirred at −15° for 2 hr and then left at room temp overnight. The soln was washed with $NaHCO_3$ aq, 2N HCl and water. Removal of the solvent, after drying, gave a solid (545 mg) which was chromatographed on silica gel (16 g). Elution with 95:5 benzene-ether afforded 305 mg of VI, m.p. 143, 5–145° (from hexane): (Found: C 59·06; H 7·14. $C_{16}H_{23}O_2Br$ requires: C 58·71; H 7·03%); $[\alpha]_D$ + 70° (c = 1·2); ν_{max} ($CHCl_3$) 1760, 1640 cm^{-1}; δ ($CDCl_3$) 1·08 (3H,s,CCH_3), 1·18 (3H,d,J = 7 c/s, $CHC\underline{H}_3$), 1·28 (3H,s,CCH_3), 4·00 (2H,d,J = 8·5 c/s, $—CH_2Br$), 5·00 (1H, double t, $J_{H_6,H_5} = J_{H_6,H_{7\alpha}}$ = 5 c/s, $J_{H_6,H_{7\beta}}$ = 8·5 c/s —CH—OCO—), 5·51 (1H,t,J = 8·5 c/s, —C = CH—). A comparable yield of VI was also obtained by the above sequence of reactions without separating the epimeric mixture of III and IV.

Anhydromarrubiin (VII). To THF (0·8 ml) was added, with stirring and under N_2, n-BuLi (0·4 ml of a 12·5% soln in hexane) and, after cooling to −70°, 3-iodofuran (140 mg). After 10 min, VI (60 mg) in THF (2 ml) was added. The mixture was stirred at −70° for 4 hr. Wet ether (10 ml) was added and the mixture was allowed to come to room temp. The ether soln was washed with water, dried (Na_2SO_4) and evaporated to give an oil (74 mg) which was chromatographed on neutral alumina BIV (2·5 g). Elution with hexane gave VII (40 mg), m.p. 94–96° (from MeOH), identical in all respects (TLC,VPC,IR,NMR, rotation, mixed m.p.) with an authentic sample of anhydromarrubiin.

α-Epoxide (VIII) *and β-epoxide* (IX). Monoperphtalic acid (134 ml of a 4% ether soln) was added with stirring to anhydromarrubiin (1·85 g) in benzene (12 ml). The mixture was allowed to stand at room temp for 5 min, then usual work up gave an oil (1·8 g) which was chromatographed on neutral alumina B III (180 g). Elution with 95:5 hexane-ether gave unreacted VII (1475 mg); further elution with 9:1 hexane-ether gave VIII (244 mg) first, and then IX (39 mg).

The α-epoxide VIII had m.p. 106–107° (from hexane): (Found: C 72·66; H 8·10. $C_{20}H_{26}O_4$ requires: C 72·40; H 7·93%); $[\alpha]_D$ + 5·0° (c = 1,1); ν_{max} ($CHCl_3$) 1760 cm^{-1}; δ ($CDCl_3$), 1·05 (3H,s,CCH_3), 1·08 (3H,d,J = 7 c/s, $CHC\underline{H}_3$), 1·28 (3H,s,CCH_3), 5·00 (1H,m,—CH—OCO.—).

The β-epoxide IX had m.p. 169–171° (from hexane): (Found: C 72·61; H 7·90. $C_{20}H_{26}O_4$ requires: C 72·40; H 7·93%); $[\alpha]_D$ − 67·4° (c = 0·8); ν_{max} ($CHCl_3$) 1760 cm^{-1}; δ ($CDCl_3$) 1·08 (3H,s,CCH_3), 1·18 (3H,d,J = 7 c/s, $CHC\underline{H}_3$), 1·30 (3H,s,CCH_3), 4·93 (1H,m, —CH—OCO—).

Marrubiin (I). The α-epoxide VIII (80 mg) was dissolved in anhydrous ethylamine (10 ml) and Li cut in thin slices (10 mg) was added. The mixture was stirred 5 min longer than required for the disappearance of the initial blue colour. Solid NH_4Cl was added until the mixture remained clear. Solvent was allowed to evaporate and water was added to the residue. Extraction with chloroform gave a solid (86 mg) which was chromatographed on silica gel (5g). Elution with 9:1 benzene-ether afforded I (42 mg), m.p. 159–160° (from EtOH): (Found: C 72·41; H 8·53. $C_{20}H_{28}O_4$ requires: C 72·26; H 8·49%), identical in all respects (TLC,IR,NMR, rotation, mixed m.p.) with an authentical sample of marrubiin.

Keto ester (X). K (2,6 g) was dissolved in refluxing t-BuOH (7·2 ml) and dry benzene (200 ml) and XII (16·86 g) was added to the cooled soln. After stirring and heating at 50–60° for 20 min solid material began to separate. The mixture was cooled, MeI (12·2 ml) was added and the mixture was heated under reflux for 3 hr. After cooling, water (5 ml) was added carefully and the benzene soln was washed with water until washings were neutral, dried (Na_2SO_4) and concentrated *in vacuo* to give an oil (18·1 g) which was chromatographed on silica gel (400 g). Elution with 85:15 hexane-ether afforded 12·1 g of X, m.p. 112·5° (from benzene); ν_{max} ($CHCl_3$) 1735, 1725, 1715, 1645, 1600, 1585, 1310, 1270, 1110 cm^{-1}; δ ($CDCl_3$) 1·33 (3H,s,CCH_3), 1·50 (3H,s,CCH_3), 3·69 (3H,s,$COOCH_3$), 5·00 (1H,m, $—C\underline{H}OCOC_6H_5$), 5·60 (1H,m, —C = CH—).

Thioketal (XIII). The benzoate X (15 g) in chloroform (75 ml) was treated with 1,2-ethanedithiol (15 ml) and BF_3-etherate (15 ml). The soln was stirred at room temp overnight, then washed with water, dried (Na_2SO_4) and evaporated to give a solid which on crystallization from 10:1 hexane-benzene furnished

15 g of XIII, m.p. 143·5–145°: (Found: C 63·92; H 6·58. $C_{23}H_{28}O_4S_2$ requires: C 63·88; H 6·53%); ν_{max}(CHCl$_3$) 1725, 1720, 1600, 1310, 1270, 1110 cm^{-1}; δ (CDCl$_3$) 1·16 (3H,s,CCH$_3$), 1·73 (3H,s,CCH$_3$), 3·15 (4H,m,—SCH$_2$CH$_2$S—), 3·65 (3H,s,COOCH$_3$), 4·95 (1H,m,—CH—OCOC$_6$H$_5$), 5·84 (1H,m, —C=CH—).

Benzoate (XIVa). The thioketal XIII (11·6 g) dissolved in dioxan (220 ml) was treated while stirring with W-4 Raney Ni (80 g) at 90–100° for 3 hr. The catalyst was filtered off and the solvent was evaporated to give 9 g of XIVa, m.p. 96·5–98° (from hexane): (Found: C 73·62; H 7·68. $C_{21}H_{26}O_4$ requires: C 73·66; H 7·66%); ν_{max}(CHCl$_3$) 1725, 1715, 1600, 1310, 1270, 1110 cm^{-1}; δ (CDCl$_3$) 1·11 (3H,s,CCH$_3$), 1·30 (3H,s,CCH$_3$), 3·66 (3H,s,COOCH$_3$), 4·98 (1H,m,—CHOCOC$_6$H$_5$), 5·72 (1H,m,—C=CH—).

Hydroxy ester (XIVb). The benzoate XIVa (9 g) dissolved in 10% methanolic KOH (270 ml) was refluxed for 3 hr. After removal of MeOH *in vacuo*, the residue was treated with water and extracted with ether. The combined ether extracts were washed with water, dried (Na$_2$SO$_4$) and evaporated to give XIVb (6·2 g), m.p. 96–98° (from hexane): (Found: C 70·59; H 9·32. $C_{14}H_{22}O_3$ requires: C 70·55; H 9·31%); ν_{max}(CCl$_4$) 3570, 3450, 1730, 1245, 1230, 1150, 1060 cm^{-1}; δ (CCl$_4$) 0·80 (3H,s,CCH$_3$), 1·20 (3H,s,CCH$_3$), 3·30 (1H,m, —CH—OH), 3·55 (3H,s,COOCH$_3$), 5·50 (1H,m,—C=CH—).

Keto ester (XV). The ester XIVb (6·2 g) was dissolved in acetone (20 ml) and oxidized with the Jones. reagent at 0–5°. Usual work up gave XV (6·05 g), m.p. 44–46° (from hexane): ν_{max}(CCl$_4$) 1725, 1720, 1245, 1145 cm^{-1}; δ (CCl$_4$) 1·10 (3H,s,CCH$_3$), 1·33 (3H,s,CCH$_3$), 3·67 (3H,s,COOCH$_3$), 5·79 (1H,m,—C=CH—).

Hydroxymethylene derivative (XVIa). To a stirred soln of XV (8·86 g) in ethyl formate (95 ml; dried over K$_2$CO$_3$), cooled at −10°, under N$_2$, was added NaH (3·84 g of a 50% dispersion) and then 0·1 ml of abs MeOH. The mixture was stirred in the cold until the ppt became so thick that stirring was impeded, whereupon anhydrous ether (250 ml) was added and the mixture was stirred at room temp overnight. Ice was added and the aqueous layer was extracted with ether. The combined ether layers were extracted with 2% NaOHaq, and the extract combined with the original aqueous layer. Acidification (12N H$_2$SO$_4$) of this soln and extraction with ether afforded XVIa (9·2 g), which gave a deep purple colour with FeCl$_3$ soln, m.p. 134·5–136° (from hexane): (Found: C 67·84; H 7·79. $C_{15}H_{20}O_4$ requires; C 68·16; H 7·63%); ν_{max}(CCl$_4$) 1725, 1665, 1640 cm^{-1}; δ(CCl$_4$) 1·18 (3H,s,CCH$_3$), 1·31 (3H,s,CCH$_3$), 3·10 (2H,m,C=C—CH$_2$—C=C), 3·60 (3H,s,COOCH$_3$), 5·80 (1H,t,—C=CH—), 8·85 (1H,s,=CH—OH), 14·55 (1H,broad, =CH—OH).

Keto ester (XVIIa) *and keto ester* (XVIIIa). A soln of XVIa (9 g) in benzene (80 ml) containing n-butyl mercaptan (20 ml) and *p*-toluenesulfonic acid (10 mg) was refluxed under a Dean–Stark water separator for 30 min. The mixture was cooled, washed with NaHCO$_3$aq water, dried (Na$_2$SO$_4$) and evaporated to give 11 g of XVIb as an oil: ν_{max} (film) 1725, 1665, 1550, 1235 cm^{-1}.

To a suspension of 100 g of W-2 Raney Ni in 200 ml EtOH was added 10 g of XVIb. The mixture was stirred at room temp for 10 min and then the catalyst was filtered off. Removal of the solvent afforded an oil (6·8 g) which was chromatographed on silica gel (68 g). Elution with benzene gave a mixture (4·4 g) of XVIIa and XVIIIa in the ratio of 15:85 as estimated on the basis of the NMR spectrum by careful integration of the signals of the olefinic protons and of the ester methyls (ratios even very different from 15:85 were obtained when other batches of W-2 Raney nickel were used). Subsequent elution with 7:3 benzene-ether gave 2·2 g of hydroxylated material (IR spectrum).

On crystallization of the mixture of the epimeric keto esters from hexane, pure XVIIIa was obtained (3·1 g), m.p. 71–73°: (Found: C 71·82; H 8·92. $C_{15}H_{22}O_3$ requires: C 71·97; H 8·86%); ν_{max}(CCl$_4$) 1730, 1720, 1245, 1150 cm^{-1}; δ (CCl$_4$) 1·02 (3H,s,CCH$_3$), 1·05 (3H, d, J = 5 c/s, CHCH$_3$), 1·30 (3H,s,CCH$_3$), 3·58 (3H,s,COOCH$_3$), 5·90 (1H,double d,—C=CH—).

The 15:85 mixture (2 g from another experiment) dissolved in abs MeOH (200 ml) containing NaOMe (from 2 g Na) was left at room temp for 2 hr. After removal of MeOH *in vacuo*, the residue was treated with water and extracted with ether. The combined ether extracts were washed with water, dried (Na$_2$SO$_4$) and evaporated to give a mixture (2 g) of XVIIa and XVIIIa in the ratio of 70:30 (estimated as above). On crystallization of this mixture from hexane, pure XVIIa was obtained (1·2 g), m.p. 65–67°: (Found:

C 71·80; H 8·93. $C_{15}H_{22}O_3$ requires: C 71·97; H 8·86%); ν_{max}(CCl_4) 1730, 1720, 1245, 1150 cm^{-1}, δ (CCl_4) 1·02 (3H,d,J = 5 c/s, $CHC\underline{H}_3$), 1·07 (3H,s,CCH_3), 1·29 (3H,s,CCH_3), 3·62 (3H,s,$COOCH_3$), 5·70 (1H, double d,—C=C<u>H</u>—).

Both XVIIa and XVIIIa, when separately treated with NaOMe in MeOH as described, gave the same 70% XVIIa: 30% XVIIIa mixture.

Hydrolysis of a 15:85 mixture of XVIIa and XVIIIa in ethylene glycol with KOH (1 hr; bath temp: 200°) afforded a 70:30 mixture of the corresponding acids XVIIb and XVIIIb.

Hydroxy ester (XIXa). The ester XVIIa (0·7 g) dissolved in MeOH (20 ml) was treated with $NaBH_4$ (70 mg) and stirred at room temp for 30 min. Water (30 ml) was added, the soln was acidified (12N H_2SO_4) and extracted with ether. The ether layers were washed with water and dried (Na_2SO_4) to give XIXa (0·68 g) m.p. 71–73° (from hexane): (Found: C 71·15; H 9·47. $C_{15}H_{24}O_3$ requires: C 71·39; H 9·59%; ν_{max} (CCl_4) 3570, 1730, 1245, 1155, 1050, 990 cm^{-1}; δ (CCl_4) 0·81 (3H,s,CCH_3), 0·98 (3H,d,J = 5 c/s, $CHC\underline{H}_3$), 1·22 (3H,s,CCH_3), 2·94 (1H,d,J = 10 c/s,—C<u>H</u>OH), 3·54 (3H,s,$COOCH_3$), 5·48 (1H,m,—C=C<u>H</u>—).

Oxidation of XIXa. The ester XIXa (50 mg) was dissolved in acetone (4 ml) and oxidized with the Jones' reagent at 0–5°. Usual work up gave a solid (47 mg), identical in all respects (IR,NMR,TLC,mixed m.p.) with XVIIa.

Hydroxy ester (XXI). The ester XIXa (60 mg) in glacial AcOH (5 ml) was hydrogenated over PtO_2 (60 mg). Removal of catalyst and solvent afforded XXI (60 mg), m.p. 75–77° (from hexane): ν_{max} (CCl_4) 3560, 1725 cm^{-1}; δ (CCl_4) 0·63 (3H,s,CCH_3), 0·90 (3H,d,J = 6 c/s, $CHC\underline{H}_3$), 1·12 (3H,s,CCH_3), 2·52 (1H,d,J = 10 c/s, —C<u>H</u>—OH), 3·58 (3H,s,$COOCH_3$).

Hydroxy acid (XIXb). The XIXa (425 mg) dissolved in ethylene glycol (10 ml) and water (1 ml) containing KOH (600 mg) was heated in an oil-bath at 200° for 1 hr. At the end of this period the soln was cooled, water (20 ml) was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water, dried (Na_2SO_4) and evaporated to give XIXb (392 mg), m.p. 180–182° (from EtOAc): (Found: C 70·64; H 9·35. $C_{14}H_{22}O_3$ requires: C 70·55: H 9·31%); ν_{max} ($CHCl_3$) 3400, 3200–2600, 1700 cm^{-1}.

Epoxy acid (XXIIIb) *and epoxy ester* (XXIIIa). The acid XIXb (420 mg) was treated with monoperphtalic acid (17 ml of a 15% soln in ether). The mixture was left at room temp overnight, washed with water and evaporated. The residue was extracted thrice with 10 ml hot benzene. Evaporation of the benzene extracts gave a solid (430 mg) which was chromatographed on silica gel (12 g). Elution with 9:1 benzene-ether gave XXIIIb (413 mg), m.p. 193–194° from EtOAc.

The methyl ester XXIIIa, obtained by reaction with diazomethane of XXIIIb, had m.p. 100–101° (from hexane): ν_{max} (CCl_4) 3450, 1725 cm^{-1}; δ (CCl_4) 0·83 (3H,s,CCH_3), 0·91 (3H,s,CCH_3), 0·93 (3H,d,J = 5 c/s, $CHC\underline{H}_3$), 3·10–3·30 (2H,H at C_9 and H at C_6), 3·65 (3H,s,$COOCH_3$).

Acetate (XIXc). The ester XIXa (80 mg) in pyridine (2 ml) and Ac_2O (0·4 ml) was allowed to stand at room temp overnight. Usual work up gave a solid (91 mg) which was chromatographed on neutral alumina B III (2·5 g). Elution with 97:3 hexane-ether afforded XIXc (75 mg), m.p. 101–102° (from hexane), ν_{max} ($CHCl_3$) 1740, 1725, 1250 cm^{-1}; δ (CCl_4) 0·85 (3H, d, J = 4 c/s, $CHC\underline{H}_3$), 0·88 (3H, s, CCH_3), 1·25 (3H,s,CCH_3), 2·00 (3H,s,$OCOCH_3$), 3·58 (3H,s,$COOCH_3$), 4·58 (1H,d,J = 10 c/s, —CHOAc), 5·57 (1H,m,—C=CH).

Diol (XXIV). The acetate XIXc (65 mg) was dissolved in pyridine (1·8 ml) and treated with OsO_4 (63 mg) and allowed to stand in the dark for 4 days. Pyridine (1 ml), water (2·5 ml) and $NaHSO_3$ aq (1·5 ml, 28 β-é) was added; the mixture was stirred for 30 min and then extracted with CH_2Cl_2, which was washed with water, 2N HCl, 2N Na_2CO_3, water, dried (Na_2SO_4) and evaporated to give XXIV (70 mg), m.p. 162·5–164° (from 1:1 hexane-benzene); ν_{max} ($CHCl_3$) 3600, 1740, 1725 cm^{-1}; δ ($CDCl_3$) 0·83 (3H,s,CCH_3), 0·85 (3H,δ,J = 5 c/s, $CHC\underline{H}_3$), 1·33 (3H,s,CCH_3), 2·03 (3H,s,$OCOCH_3$), 3·71 (3H,s,$COOCH_3$), 4·68 (1H,m,—C<u>H</u>—OH), 5·00 (1H,d,J = 10 c/s, —C<u>H</u>—OAc).

Diol (XXVII)

(a) *From the hydroxy ester* (XIXa). The ester XIXa (65 mg) was reduced in ether with LAH. The resultant

XXVII (58 mg) was an oil, ν_{max} (CCl_4) 3560, 3450, 1060, 1030 cm^{-1}, δ ($CDCl_3$) 1·03 (3H,d,J = 6 c/s,$CHC\underline{H}_3$), 1·08 (3H, s, CCH_3), 1·09 (3H, s, CCH_3), 3·05 (1H, d, J = 9·5 c/s, $-C\underline{H}-OH$), 3·44 (2H, AB q, $J_{A,B}$ = 10 c/s, $\delta_A - \delta_B$ 26 c/s, $-C\underline{H}_2-OH$), 5·45 (1H, m, $-C=CH-$).

The 3,5-dinitrobenzoate, made by use of 3,5-dinitrobenzoylchloride and dry pyridine at room temp for 2 days, crystallized from benzene, m.p. 97–98°; ν_{max} ($CHCl_3$) 3030, 1725, 1630, 1545, 1275, 1160 cm^{-1}, δ ($CDCl_3$) 0·96 (3H,d,J = 5 c/s, $CHC\underline{H}_3$), 1·28 (3H,s,CCH_3), 1·34 (3H,s,CCH_3), 4·36 (2H,s,$-CH_2-O-$), 5·02 (1H,d,J = 10 c/s, $-CH-O-$), 5·74 (1H,m,$-C=CH-$).

(b) *From the keto ester* (XVIIa). The ester XVIIa (46 mg) was reduced as above to XXVII (35 mg), identical in all respects (TLC,IR,NMR) with the diol obtained from XIXa.

Triol (XXVa) *and triacetate* (XXVb). The idol XXVII (545 mg) dissolved in dry THF (24 ml) was treated in the cold with a 0·75 M soln (24 ml) of diborane in THF and then left at room temp overnight. Water was added to consume the excess of diborane, followed by 2N NaOH (10 ml) and 30% H_2O_2 (10 ml). The mixture was stirred at 50–60° for 2 hr, cooled, diluted with EtOAc (50 ml), washed with NaCl sat, dried (Na_2SO_4) and evaporated to give a solid (560 mg) which was chromatographed on silica gel (9 g). Elution with 7:3 benzene-ether gave XXVa (550 mg), m.p. 148·5–149·5° (from benzene): (Found: C 69·09; H 10·84. $C_{14}H_{26}O_3$ requires: C 69·38; H 10·81%); ν_{max} ($CHCl_3$) 3570, 3330, 1110, 1040 cm^{-1}.

The triacetate XXVb, made by use of Ac_2O and dry pyridine at room temp for 24 hr, crystallized from hexane, m.p. 120–122°, ν_{max} (CCl_4) 1740, 1240, 1030 cm^{-1}, δ (CCl_4) 0·81 (3H,d,J = 6 c/s, $CHC\underline{H}_3$), 1·05 (3H,s,CCH_3), 1·08 (3H,s,CCH_3), 1·97 (3H,s,$OCOCH_3$), 1·98 (3H,s,$OCOCH_3$), 2·05 (3H,s,$OCOC\underline{H}_3$), 4·05 (2H,s,$-CH_2-OAc$), 4·26 (1H,d,J = 10 c/s, $-CH-OAc$ at C_9), 5·05 (1H,m,$W_{1/2}$ 26 c/s, $-CH-OAc$ at C_6).

Diketo acid (XXVIIIa). The triol XXVa 76 mg) dissolved in acetone (2 ml) was treated with the Jones' reagent and allowed to stand at room temp overnight. EtOAc (5 ml) was added and the mixture was washed with water, dried and evaporated to give a solid (77 mg) which was chromatographed on silica gel (2·5 g). Elution with benzene afforded XXVIIIa (50 mg), m.p. 132–134° from benzene: (Found: C 66·33; H 8·01. $C_{14}H_{20}O_4$ requires: C 66·64; H 7·99%); ν_{max} ($CHCl_3$) 3200–2700, 1740, 1720, 1700, 1130, 995 cm^{-1}. A sample was esterified with diazomethane to XXVIIIb, m.p. 103–105° (from hexane); ν_{max} (CCl_4) 1740, 1720, 1710, 1225, 1140 cm^{-1}; δ (CCl_4) 1·10 (3H,d,J = 6 c/s, $CHC\underline{H}_3$), 1·20 (3H,s,CCH_3), 1·26 (3H,s,CCH_3), 3·68 (3H,s,$COOCH_3$). This ester has IR and NMR spectra identical with those of the optically active compound, m.p. 88–89·5°, obtained with CH_2N_2 from the known corresponding acid.[2]

Dihydroxy acid (XXIXa). The acid XXVIIIa (64 mg) dissolved in 2N Na_2CO_3 (2 ml) was treated with $NaBH_4$ (50 mg) at room temp for 2 hr. The mixture was acidified (12N H_2SO_4) and extracted with EtOAc. Removal of the solvent after drying gave a solid (61 mg) which was chromatographed on silica gel (0·6 g). Elution with 1:1 benzene-ether gave XXIXa (46 mg), m.p. 230° (from benzene); ν_{max} ($CHCl_3$) 3500–2700, 1725 cm^{-1}. A sample was esterified with diazomethane to XXIXb, m.p. 140–142° (from benzene); ν_{max} (CCl_4) 3550, 3425, 1715, 1250, 1225, 1170, 1060, 1040 cm^{-1}; δ ($CDCl_3$) 0·99 (3H,d,J = 6 c/s, $CHC\underline{H}_3$), 1·00 (3H,s,CCH_3), 1·31 (3H,s,CCH_3), 2·75 (1H,d,J = 10 c/s, $-C\underline{H}OH$ at C_9), 3·79 (3H,s,$COOCH_3$), 4·33 (1H,m,$W_{1/2}$ 7 c/s $-CHOH$ at C_6).

Hydroxy lactone (XXX). The acid XXIXa (150 mg), triethylamine (0·5 ml), ethyl chloroformate (0·12 ml) and dry chloroform (5 ml) were stirred at 0–5° for 30 min. After this period, the soln was washed with 2N HCl, 2N Na_2CO_3, water, dried (Na_2SO_4) and evaporated to give an oil (155 mg) which was chromatographed on silica gel (4 g). Elution with 7:3 benzene-ether gave XXX (82 mg), m.p. 113–115° (from 1:2 benzene-hexane); ν_{max} (CCl_4) 3545, 3470, 1750 cm^{-1}; δ (CCl_4) 1·05 (3H,d,J = 5 c/s, $CHC\underline{H}_3$), 1·06 (3H,s,CCH_3), 1·31 (3H,s,CCH_3), 2·93 (1H,d,J = 9 c/s, $-C\underline{H}OH$), 4·67 (1H,m,$-CH-OCO-$).

Keto lactone (II). The lactone XXX (50 mg) was dissolved in acetone (5 ml) and oxidized with the Jones' reagent at 0–5°. Usual work up gave II (46 mg), m.p. 192–193° (from 1:2 benzene-hexane); the Ir and NMR spectra were identical with those of the optically active II obtained from marrubiin.

Acknowledgement—This work was supported by the C.N.R. The authors thank Mr. I. Giudicianni for technical assistance.

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