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SYNTHESIS OF DITERPENOID ACIDS—VII[1a]

THE STEREOCHEMISTRY OF MARRUBIIN

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Abstract—Reduction of dehydrotetrahydromarrubic acid (**2b**) with $NaBH_4$ or Li in liquid ammonia gave tetrahydromarrubic acid (**4b**). Treatment of dehydromarrubic acid (**2a**) with $NaBH_4$ led to marrubic acid (**4a**); use of Li in liquid ammonia produced a mixture of **4a** and its C_6 epimer **3a**.

Reduction of methyl dehydro marrubate (**2c**) with LAH gave marrubenol (**5a**) which was converted to its diacetate **5b**: treatment of **2c** with Li in liquid ammonia formed the isomeric triol **6a** isolated as its diacetate **6b**. The IR and NMR spectra of these compounds support the stereochemistry shown in **1** for the lactone ring of marrubiin. The production of axial alcohols in the Li–ammonia reductions of **2a** and **2b** is discussed.

An α configuration is proposed for the Me group at C_8. Our results and those of others lead to the stereochemistry of marrubiin shown in **1a**. The stereochemistry proposed for the isoambreinolide **9** has been modified to **10**.

THE structure of marrubiin (**1a**) proposed in 1953[2] has been confirmed by later work.[3–6] At present several attempts are being made to synthesize this compound.[7–10] The stereochemistry shown in **1a** with the opposite configuration at C_9, was proposed by Cocker.[11] Later, Burn and Rigby[4] strongly criticized Cocker's arguments claiming

[1] [a] Part VI A. Lickei, A. C. Rieke and D. M. S. Wheeler, *J. Org. Chem.* in press, 1967.

[1] [b] This work was started at the University of South Carolina, Columbia, South Carolina.

[1] [c] National Science Foundation Undergraduate Research Participant Summer 1960. W. H. C. thanks the NSF for this support.

[2] W. Cocker, B. E. Cross, S. R. Duff, J. T. Edward, and T. F. Holley, *J. Chem. Soc.* 2540 (1953).

[3] D. G. Hardy, W. Rigby, and D. P. Moody, *J. Chem. Soc.* 2955 (1957).

[4] D. Burn, and W. Rigby, *J. Chem. Soc.* 2964 (1957).

[5] D. P. Moody, *Chem. & Ind.* 75 (1960).

[6] W. H. Castine, D. M. S. Wheeler, and M. M. Wheeler, *Abstracts of Communications, 2nd International Symposium on the Chemistry of Natural Products.* 99 (1962).

[7] S. L. Mukherjee and P. C. Dutta, *J. Chem. Soc.* 3554 (1964).

[8] D. P. Moody, *Chem. & Ind.* 85 (1965).

[9] S. K. Roy and D. M. S. Wheeler, *Abstracts of Papers at A.C.S. Meeting Denver*, 41C (1964).

[10] A. C. Ghosh, S. K. Roy, K. Mori, A. C. Rieke, and D. M. S. Wheeler, *J. Org. Chem.* **32**, 722 (1967).

[11] W. Cocker, J. T. Edward and T. F. Holley, *Chem. & Ind.* 772 (1955) (cf., W. Cocker, J. T. Edward and T. F. Holley, *Ibid.* 1564 (1954).

they established nothing. Rigby's own work[4, 12] showed that the absolute stereochemistry of the angular Me group is as indicated in **1**, and also suggested that the ring junction is *trans*; this latter point was confirmed by ORD studies.[13]

Cocker's assignment[11] of the diaxial arrangement of the lactone ring appears[14] to have been based on two considerations:

(a) the application of Klynes modification of Hudson's isolactone rule suggests that the oxygen attached at the 6 position[15] is β; (b) if the oxygen at 6 is β oriented, the carbonyl at 4 must also have a β arrangement as otherwise the lactone would be impossibly strained.

Burn and Rigby[4] claimed both these points are unsound. On the basis of some preliminary reduction studies we[17] proposed that the lactone is fused α, α. Later work[6] showed that this suggestion was wrong and that the C_6 oxygen is β. Recently Fulke and McCrindle[18] reported evidence from NMR spectra which supported Cocker's original proposal for positions 4, 6 and 8. We have independently reached the same conclusion on the basis of better evidence and now report our results, which have also enabled us to deduce the stereochemistry of some synthetic compounds.[10]

Reduction studies. Originally we wanted to reduce the keto acid **2b** stereospecifically to the corresponding equatorial (**3b**) and axial (**4b**) alcohols. One of these should be tetrahydromarrubic acid and this would establish the configuration at C_6. Studies of the ease of lactonization of tetrahydromarrubic acid and its C_6 epimer would then establish the arrangement at C_4. In our early work[17] we reduced the keto acid **2b**[3, 19] with sodium borohydride, from which we expected[20] to obtain the axial alcohol **4b**. We also reduced **2b** with lithium in liquid ammonia in the presence of methanol in the hope[20, 21] of obtaining the equatorial alcohol **3b**. In both reductions the same product, tetrahydromarrubic acid, was obtained: thus one of the reductions had taken place in an unexpected fashion. From other work[22] we suspected that the anomaly arose in the borohydride reductions and was caused by the carboxyl group in **2b**. To check this point we decided to study the reduction of the methyl ester of **2b**. However, we were not able to crystallize this compound and so turned from the tetrahydro to the marrubiin series.

Before examining the ester **2c** we studied the reductions of the acid **2a**. With sodium borohydride **2a** gave marrubic acid (**4a**) in excellent yield. In the early experiments with lithium in liquid ammonia we only isolated **4a**, but never in good yield. More recently (after we had established the stereochemistry of the lactone) we reinvestigated

[12] D. Burn and W. Rigby, *Chem. & Ind.* 386 (1955).

[13] C. Djerassi and W. Klyne, *J. Chem. Soc.* 4929 (1962).

[14] The original paper published in 1954[11] contained an error in the interpretation of the optical rotation data; the later paper corrected this without stating explicitly the argument for the new assignment.

[15] We use the numbering system recommended by McCrindle and Overton.[16]

[16] R. McCrindle and K. H. Overton, *Advances in Organic Chemistry, Methods and Results*, (Edited by R. A. Raphael, E. C. Taylor and H. Wynberg) Vol. 5; pp. 50 and 53. Interscience, New York (1965).

[17] W. H. Castine, D. M. S. Wheeler, and M. Wheeler, *Chem. & Ind.* 1832 (1961).

[18] J. W. B. Fulke and R. McCrindle, *Chem. & Ind.* 647 (1965).

[19] Some improvements in the preparation of some of the previously known derivatives of marrubiin are mentioned briefly in the Experimental section.

[20] D. H. R. Barton, *J. Chem. Soc.* 1027 (1953).

[21] G. Ourisson and A. Rassat, *Tetrahedron Letters* No. 21, 16 (1960).

[22] D. M. S. Wheeler and M. M. Wheeler, *J. Org. Chem.* 27, 3796 (1962).

the lithium ammonia reduction of **2a**. TLC of the crude product suggested there were at least two products, but the R_f values were not sufficiently different for separation of the compounds. The crude products were converted to their methyl esters which were then separated by preparative TLC, into three components: methyl marrubate (**4c**); about 20% of crude methylated material), its C_6 epimer (**3c**; 30%), and product (30%) which did not crystallize and which no longer contained the furan ring (absence of IR absorption at 875 cm^{-1}).

The best way of preparing the ketoester **2c** is by oxidizing methyl marrubate (**4c**). However, we had some difficulty in preparing the ketoesters, and some of our other preparative work in this area is described in the Experimental. Attempts to reduce **2c** with sodium borohydride at room temperature were unsuccessful, and the starting material was recovered. When the reaction was tried under reflux in isopropyl alcohol, the starting ester, marrubic acid, and perhaps a trace of triol were obtained. Clearly the reduction had been accompanied by a cleavage of the ester (presumably an alkyl oxygen fission) induced by the borohydride. Wenkert[23] observed similar cleavage of esters of podocarpic acid during treatment with lithium in liquid ammonia. Our cleavage appears to be without precedent in hydride reductions. However, as we did not know whether the cleavage preceded or followed the reduction of the ketone in **2c**, the result did not help us in our study.

We therefore used lithium aluminum hydride to reduce keto ester **2c**. As lithium aluminum hydride is more covalent in character than sodium borohydride, it tends in reducing asymmetric cyclohexanones to give more of the equatorial isomer. However, the differences in the composition of epimers formed by these two reagents is not great.[24] Reduction of **2c** with lithium aluminum hydride gave marrubenol (**5a**) which is also obtained by direct reduction of marrubiin by lithium aluminum hydride.[2] Reduction of the ester **2c** in methanol with lithium in liquid ammonia gave an oil, whose IR spectrum showed strong OH absorption and little carbonyl absorption. We were not able to crystallize the oil. On acetylation it gave a diacetate. A comparison of the IR and (particularly) the NMR spectra of this diacetate with the spectra of the diacetate of marrubenol (**5b**) leaves no doubt that the oil is the C_6 epimer of marrubenol. As the hydride reductions gave the same results with both the acid and the ester while the lithium ammonia reductions gave different results, we conclude that the anomalous reductions of the keto acids were those in which lithium in liquid ammonia was used.

IR spectra. Bory and Fetizon[25] examined the IR spectra of the methyl esters of a large number of di- and triterpenes which contain a *gem*-Me carboxyl at position 4. They found that when the carbomethoxy group is equatorial the spectrum contains a single intense band at 1245 ± 4 cm^{-1}. By contrast compounds with axial carbomethoxy groups show little absorption at 1245 cm^{-1}, but have an intense peak (with some shoulders) at 1145 ± 5 which is accompanied by a less intense peak at 1190 ± 5 and a very weak one at 1230 ± 5 cm^{-1}. Examination of the spectra (taken under the same conditions as described by Bory and Fetizon[25]) of methyl marrubate (**4c**), methyl epimarrubate (**3c**), and methyl dehydromarrubate (**2c**) show patterns which

[23] E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.* **80**, 217 (1958).
[24] O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.* **27**, 3803 (1962).
[25] S. Bory and M. Fetizon, *Bull. Soc. chim. Fr*, 570 (1964).

conform to the axial arrangement of the carbomethoxy group. Although the compounds studied by Bory and Fetizon[25] did not contain substituents at C_6, we feel justified in using their criteria since we observed the axial pattern for the carbomethoxy group at C_4 in compounds in which C_6 was a ketone, or had an axial, or equatorial OH attached to it.

The IR spectrum of methyl marrubate (**4c**) shows the carbonyl ester band at 1697 cm^{-1}, with a small shoulder at 1726 and an intense OH peak at 3430 cm^{-1}, with a much smaller band at 3620 cm^{-1}. The C_6 epimer of methyl marrubate (**3c**) shows a carbonyl peak at 1704 which has a shoulder of almost equal intensity at 1725 and a broad OH peak at 3630 which has a shoulder at 3550 cm^{-1}. Clearly hydrogen bonding occurs in both compounds and is stronger in **4c** than in **3c**. It follows that the C_6 OH in **4c** is *cis* to the axial carbomethoxy group and therefore β. This conclusion is supported by Tahara *et al.*'s[26] study of the IR spectra of two epimeric esters, which are enantiomorphous with the podocarpic acid series; a 4-axial carbomethoxy, 6-equatorial hydroxy compound and its C_6 epimer. They reported hydrogen bonding with both epimers with the stronger bonding being observed for the axial-axial isomer. Similarly, the diols marrubenol and epimarrubenol both show evidence of strong hydrogen bonding, stronger in the former than the latter.

The keto acids **2a** and **2b** show two strong bands in the carbonyl region; one at 1735 cm^{-1} and the other at 1665 cm^{-1}. There are also strong bands at 2940 and 2740 cm^{-1}. We attribute the bands at 2740 and 1665 to intramolecular hydrogen bonding between the acidic hydrogen and the ketone group. The intensity of the ketone peak in the UV spectrum is greater than is usual for a ketone and greater than in the keto acid **7**. The IR spectrum of **7** shows no indication of strong intramolecular hydrogen bonding. We suggest that the differences between the keto acids (**2a** and **2b**), and **7** result from the steric interactions between the angular Me group and the axial carboxyl group in **2a** and **2b**, which force the carboxyl to take up the conformation most favorable for intramolecular hydrogen bonding with the ketone group.

NMR studies. The NMR spectrum of marrubiin is in complete accord with the accepted structure (**1a**). In particular, the presence of a β-substituted furan is confirmed.[5,6] In marrubiin and those derivatives which contain the lactone ring, the proton at C_6 gives a signal at $\delta = 4{\cdot}80$ ppm with width at half height of 13 c/s and the width at the base of the peak is 16 c/s. We have examined the corresponding peak in a series of simple lactones from hydrogenated 8-hydroxynaphthoic acids.[27] Using our results from these studies and given that the ring junction in marrubiin is *trans*, we conclude that the shape of the peak in the marrubiin series is consistent with a β arrangement of oxygen at C_6. This evidence, like that of Fulke and McCrindle,[18] is not conclusive because it is based on examination of only one epimer. However, it is in accord with the evidence of optical rotations[11] and the course of our reductions of the keto ester **2c**.

The conclusive evidence for the stereochemistry at C_4 and C_6 comes from a study of the NMR spectra of the esters **3c** and **4c** and the acetates **5b** and **6b**. The signals for the C_6 proton in the spectra of methyl marrubate and methyl 6-epimarrubate are at $\delta = 4{\cdot}40$ ($W_{\frac{1}{2}} = 6$ c/s) and $\delta = 4{\cdot}08$ ($W_{\frac{1}{2}} = 35$ c/s), respectively. Similarly, the C_6

[26] A. Tahara, K. Hirao, and Y. Hamazaki, *Tetrahedron* **21**, 2133 (1965).

[27] G. A. Gallup, S. K. Roy, and D. M. S. Wheeler, unpublished work.

proton appears at $\delta = 5{\cdot}4$ ($W_{\frac{1}{2}} = 6$ c/s) in the spectrum of **5b**, and at $\delta = 5{\cdot}1$ ($W_{\frac{1}{2}} = 25$ c s) in the spectrum of **6b**. It is well-known,[28] that with both the hydroxy and acetoxy pairs of epimers the signal for the C_6 proton should be narrower and occur at lower field for the compound with the proton equatorial (oxygenated substituent axial, **4c** and **5b**) than for the compound with the proton axial (oxygenated substituent equatorial, **3c** and **6b**).

A study of the NMR spectra of the acetates **5b** and **6b** also leads us to assign the stereochemistry at C_4. In the spectrum of **5b**, the protons of the methylene group attached to the acetoxy group appear as an AB quartet with shifts of $\delta = 4{\cdot}57$ and 4·45 and $J = 12$ c/s. In the epi acetate, the protons on the methylene group attached to acetoxy appear as a single (broadened) peak at 4·1. The appearance of this signal at lower field in **5b** than **6b** can be accounted for if the acetoxy Me group is axial in both compounds. In the marrubenol derivative, the protons in this group are more deshielded by the axial acetoxy group at 6 than the corresponding protons in the epi compound are deshielded by the equatorial acetoxy group. In both **5b** and **6b** the protons of the methylene group are magnetically non equivalent (regardless of the conformational populations); the effect is more marked in **5b**. Our evidence complements the results of Fulke and McCrindle[18] who also observed that the methylene group in the monoacetate of marrubenol is deshielded as compared with the C_6 desoxy compound. However, their evidence was ambiguous because there was a possibility that the deshielding could have been due to the action of an axial OH on an equatorial acetoxy Me group. In marrubenol and epimarrubenol, the quartet from the hydroxymethyl group overlaps with the signal from the C_6 proton. This complicates the analysis of these spectra. However, here again the C_6 proton appears to occur at lower field and has a sharper signal in marrubenol.

The shifts in the positions of the signals for the Me groups with changes in structure (Table 1) also support the stereochemistry we propose. We consider the tertiary methyls first. As expected, the peaks for these groups appear in almost the same positions in the spectra of **1a**, **1b**, **8** and **4c**. In going from **4c** to **3c** the C_6 OH goes from β to α, which leads to the observed shielding of the C_{10}-Me and a deshielding of the C_4 Me.

The change of the OH group at C_6 to a ketone (**2a**, **2b**, and **2c**) should lead to an upfield shift of the C_{10}-Me peak.[29] This change is observed in the acids **2a** and **2b**, but in the ester **2c** there is a slight downfield shift. The ester **2c** differs from the other compounds we studied in that there is no hydrogen bonding between the C_4 and C_6 substituents. Thus in **2a** and **2b** the carbonyl of the acid will be in the same plane as, but point away from, C_6; while in the ester **4c** the ester carbonyl is in the same plane but pointing towards C_6.[30] With **2c**, however, dipole-dipole repulsion between the carbonyl groups may cause the carbomethoxy group to twist to a new conformation which would affect the shielding of the angular methyl group, thus accounting for the anomalous shift.

[28] N. S. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry* pp. 78 and 79. Holden Day, San Francisco (1964).

[29] Ref. 28, pp. 19 and 20.

[30] Work[16] in the podocarpic acid series suggests that even in the absence of a substituent at C_6, an axial carbomethoxy group at C_4 will orient itself with the carbonyl group in plane with and pointing in the direction of C_6.

TABLE 1. POSITIONS OF C-ME PEAKS IN NMR SPECTRA OF MARRUBIIN AND ITS DERIVATIVES. ($CDCl_3$ SOLUTIONS)[a]

Compound	C_4 Me	C_{10} Me	C_8 Me[b]
1a	78	64	58
1b	77	63	55
8	77	65	66[c]
4c	78	63	59
3c	88	46	57
2a	76	52	66
2b	72	58	63[d]
2c	74	67	62
5a	63	79	58
5b	61	76	56
6a	75	62	58
6b	68	61	55

[a] Shifts (obtained on a Varian A-60 instrument) given in c/s downfield from TMS.

[b] Except where indicated, this signal appears as a doublet with a coupling constant $J = 6$ c/s.

[c] $J = 8$ c/s.

[d] Only one half of doublet visible.

The shift values of the C_4 and the C_{10}-Me peaks in the spectra of **5a** and **5b** are assigned in the reverse order to those in the spectra of the other compounds. The change from carbomethoxy to hydroxymethyl in going from **4c** to **5a** should shield the C_4-Me by 13 c/s and deshield the C_{10} by 9 c/s.[31] The shifts shown in our compounds are somewhat larger. As expected, changing the OH from 6β- to 6α- (going from **5a** to **6a**) deshields the C_4-Me and shields the C_{10}-Me. The shifts shown by the acetates (**5b** and **6b**) parallel those shown by the corresponding hydroxy compounds. Tahara *et al.*[26, 32] reported the NMR spectra of a series of compounds which were enantiomorphous with the podocarpic acid series, and which had substitution patterns at C_4 and C_6 corresponding to **3c**, **4c**, **5a**, and **6a**. The positions of the C_4-Me in these compounds correspond almost exactly with those in ours, while their peaks for the C_{10} methyls are shifted downfield from the corresponding positions in our spectra by 15–20 c/s, presumably through the influence of the aromatic ring C.

Examination of the position of the peaks for the C_8-Me shows that the changes of its position with structure do not parallel those shown by the C_{10}; for example, the exocyclic bond in 8 has a paramagnetic effect (**1b** → **8**) on the C_8 and practically no effect on the C_{10}-Me; again, in going from **4a** to **2a** the peaks for C_8-and C_{10} move in opposite directions. It seems safe to conclude that the C_8-Me is equatorial. Fulke and McCrindle[18] on the basis of similar but more limited studies reached the

[31] E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.* **30**, 713 (1965).

[32] A. Tahara and K. Hirao, *Chem. Pharm. Bull.* **12**, 1121 (1964).

same conclusion. It is possible that C_8-Me could be equatorial and β with ring B in a nonchair form. In marrubiin itself and its derivatives in which the C_4-C_6 lactone is closed, ring B is probably in a twist form. This is indicated by ORD evidence[13] of ring distortion in the C_{14} ozonolysis product from **8**. In addition, we have evidence[27] that ring B in some simple model lactones is a twist. However, in compounds with the C_4-C_6 lactone open, the general pattern of the shifts in peak positions over the compounds studied suggests that the rings are in or close to the chair form. We thus support the view that the C_8-Me is α.[17, 18]

This assignment of stereochemistry is contrary to that suggested by Mangoni and Belardini.[33] They reported a partial synthesis of the isoambreinolide, obtained from marrubiin.[4] They claim that their synthesis establishes the stereochemistry of this compound as shown in **9**, which would then assign β configurations to the alkyl groups at positions 8 and 9 in marrubiin. However, the assignment they suggest for C_8 is ambiguous:[34] and so we think that the C_8-Me has an α configuration **10**. Such a configuration can be accounted for mechanistically. Ambreinolide (**11**) has the same configuration at C_9 as the isoambreinolide (**10**). This suggests that the formation of **10** from **11** is not a concerted reaction, which is supported by the observation[35] that this reaction is accompanied by formation of the corresponding $\Delta^{8,9}$ unsaturated acid. If this acid is an intermediate, then lactone closure to **10** should take place to give the C_8-Me group in an α configuration.

The arguments that Mangoni and Belardini[33] advance to support their stereochemistry at C_9 are clearly sound and so establish a similar stereochemistry in marrubiin (**1a**). However, this leaves the problem of explaining why **1b** gives on dehydration a poor yield (less than 40%) of **8** and apparently no product from endocyclic dehydration. This apparent anomaly is accounted for by the idea that as the lactone ring in **8** is closed ring B is in a twist form: thus the hydrogen at C_8 and the OH at C_9 are no longer *trans* and diaxial, and endocyclic dehydration is not particularly favored.

Discussion of reductions. The work described in previous paragraphs together with the results of others [4, 13, 18, 33] establishes the stereochemistry shown in **1a**, which conforms to Cocker's original proposal at all centers except C_9. However, the results of our reduction studies deserve some further comment. Firstly, the keto ester **2c** was reduced to the corresponding axial and equatorial alcohols by using the appropriate reagents. This type of reagent specificity only occurs when the axial approach of hydride to the ketone is hindered. The 11-keto steroids still represent the best-known example of this type of behavior. With unhindered ketones changing the reagents makes little difference in the epimeric composition of the products.[20, 24]

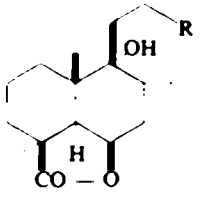
A second point concerns the lithium ammonia reductions of the acids **2a** and **2b**. The latter compound gave mainly the axial product; with the former, both epimers were obtained with the equatorial apparently in greater amount. While the reason for the difference in behavior between these compounds is not clear, the surprising

[33] L. Mangoni and M. Belardini, *Gazz. Ital.* **93**, 465 (1963).

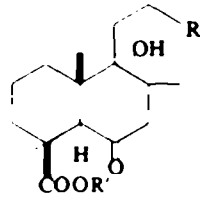
[34] Their assignment was based on the result that catalytic reduction of the $\Delta^{7,8}$ derivative of **10** gave the isoambreinolide as the major and its C_8 epicompound as the minor product. Whatever the validity of such evidence, on its own might be, it is considerably weakened by their observation that hydrogenation of the C_8 methylene derivative of **10** gave the C_8 epicompound as the major product.

[35] C. Collin-Asselineau, E. Lederer, D. Mercier, and J. Polonsky, *Bull. Soc. chim. Fr*, 720 (1950).

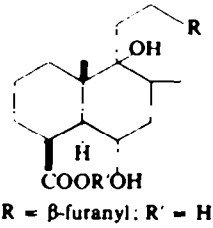
point is that even with **2a** such a large proportion of axial alcohol was formed. In general, lithium-ammonia reductions lead to a clear predominance of the more stable alcohol,[20] even with those compounds in which the use of other alkali metals gives mainly the less stable alcohol.[21] Recently Huffman *et al.*[36] observed that the lithium–ammonia reduction of 12-ketocholanic acids produced the 12-axial alcohol as the major product. Huffman attributed this to shielding of the ketone by the C_{21}-Me group, which both slows down formation of the dianion and inhibits protonation to give the more stable product. However, this explanation does not account for the behavior of **2a** because the corresponding ester (**2c** in which steric hindrance should be as great as in the acid) gave on reduction mainly the equatorial alcohol. Huffman also reported an example closer to ours: he found that the reduction of 3α-hydroxy-12-oxoetianic acid gave more of the 12 axial alcohol than expected. He explained this result by pointing out that during the reduction electrostatic repulsions between the carboxylic anion and the C-O dianion will be minimized if the 12-oxygen takes up the axial position. Huffman's idea predicts a greater predominance of equatorial alcohol in the reduction of **2a** than in the reduction of **2c**, unless ring A in these compounds is in a twist conformation in which the carboxyl anion is closer to the 6-equatorial than the 6-axial substituent. In marrubiin derivatives in which the lactone is open, ring A is close to the chair form. Another possible explanation is that during the reduction the carboxylate anion is bound to lithium which can also coordinate with an axial but not an equatorial alkoxide ion (see **12**). This would facilitate formation of the axial alcohol. This theory explains why in earlier work[22] we observed exclusive formation of the equatorial alcohol from lithium-ammonia reduction of **7**. If electrostatic repulsions had been an important factor in this reduction, they would have favored formation of the axial epimer. As lithium has more covalent character than sodium, our theory also explains why the reduction of **7** with lithium–ammonia gave a better yield of the equatorial alcohol than reduction with sodium and propanol.



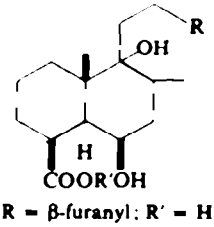
1a R = β-furanyl
1b R = β-tetrahydrofuranyl



2a R = β-furanyl; R' = H
2b R = β-tetrahydrofuranyl; R' = H
2c R = β-furanyl; R' = Me

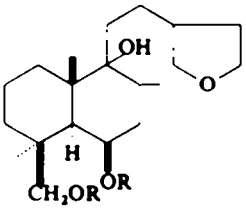


3a R = β-furanyl; R' = H
3b R = β-tetrahydrofuranyl; R' = H
3c R = β-furanyl; R' = Me



4a R = β-furanyl; R' = H
4b R = β-tetrahydrofuranyl; R' = H
4c R = β-furanyl; R' = Me

[36] J. W. Huffman, D. M. Alabran, T. W. Bethea, and A. C. Ruggles, *J. Org. Chem.* **29**, 2963 (1964).



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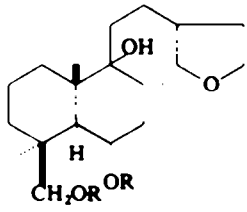
5b R = Ac



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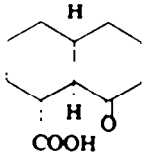

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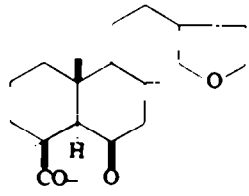

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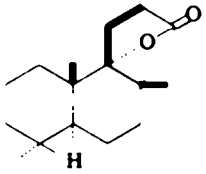

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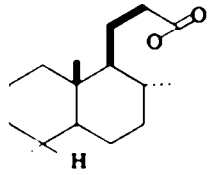

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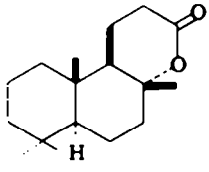

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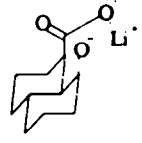

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EXPERIMENTAL[37]

Marrubiin (1a). Marrubiin obtained from a crude acetone extract of horehound by chromatography on alumina had m.p. 162–163°, after crystallization from EtOH, and NMR peaks at: 58 (3H doublet J = 6 c s), 64 (3H singlet), 78 (3H singlet), 90–170 (15 H complex), 288 (1 H complex, $W_{at\ base}$ = 16, $W_{\frac{1}{2}}$ = 13 c s), 381 (1H singlet), and 439 (2H doublet with further splitting) c s.

Dehydromarrubic acid (2a). A soln of CrO_3 in H_2SO_4aq[38] was added to a stirred soln of 4a[39] (3 g) in acetone (50 ml, distilled from permanganate) at 0° in a N_2 atm. The stirring was continued for 5 min. The reaction mixture was poured into ice and water (150 ml) and the product was extracted in $CHCl_3$. The $CHCl_3$ soln was washed with sat NaClaq and water and was dried (Na_2SO_4). On evaporation of the

[37] M.ps. are uncorrected. Unless otherwise specified, IR spectra were determined for CH_2Cl_2 solns, UV spectra for 95% EtOH solns and NMR spectra for $CDCl_3$ solns (approximately 10%). The NMR data (obtained on a Varian A-60 spectrometer) are given in c/s relative to TMS.

[38] C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.* **21**, 1547 (1956).

[39] A. Lawson and E. D. Eustice, *J. Chem. Soc.* 587 (1939).

$CHCl_3$, the product was obtained as oily crystals, (3·1 g) which were chromatographed on Florisil. Dehydromarrubic acid (**2a**, 1·6 g) was eluted in benzene–AcOEt (1:1). The acid crystallized from AcOEt light petroleum in rhombs, m.p. 147–148° (800 mg). (Found: C, 68·85; H, 7·99; O, 23·04. $C_{20}H_{28}O_5$ requires: C, 68·94; H, 8·10; O, 22·96%) and m.p. 152·5–154° (274 mg). The m.p. of the latter material was raised to 156–157°. (Found: C, 69·01; H, 8·18; O, 22·88%) on further crystallization from AcOEt–light petroleum. The compounds were identical from analysis, IR spectra in soln and NMR spectra: ν_{max} 3590, 2940, 2740, 1732, 1663, 1500, 1462, 1410, 1230, 1190, 1150, 1060, 1023, and 872 cm^{-1}; NMR peaks at 52 (3H singlet), 66 (3H, doublet J = 6 c s), 76 (3H, singlet), 85–186 (14H, complex), 201 (1H, singlet), 337 (1H, singlet), 438 (2H, doublet with further splitting), and 779 (1H, broad singlet) c s; λ_{max} 281 mμ (ε 42).

Reduction of dehydromarrubic acid

(a) *Sodium borohydride.* A soln of $NaBH_4$ (80 mg) in water (5 ml) was added to a soln of **2a** (200 mg) in $NaHCO_3$ aq (50 mg in 5 ml water) at 0°. The soln was kept at 0° overnight and was then acidified (Congo Red) with 20% H_2SO_4. The ppt was washed with water, and on drying had m.p. 188–191° (198 mg). Crystallization from AcOEt gave **4a** m.p. 198–201° (131 mg) identified by mixed m.p. and IR spectrum.

(b) *Lithium and liquid ammonia.*[40] Li metal (200 mg) was added over 30 min to a stirred soln of dehydromarrubic acid (304 mg) in MeOH (10 ml) and liquid ammonia (250 ml). NH_4Cl (6 g) was then added. After the NH_3 had evaporated, water was added and neutral material (11 mg) was extracted with $CHCl_3$. The aqueous soln was acidified (pH1) and extracted with $CHCl_3$, and the $CHCl_3$ soln was dried (Na_2SO_4). Removal of the solvent gave crude product m.p. 135–185° (289 mg). TLC on silicic acid (using various grades of absorbent and various solvent systems) indicated the presence of marrubic acid and a second product which could not be separated completely on the plates. The crude acidic material (283 mg) in MeOH (10 ml) and ether (10 ml) was treated with an excess of diazomethane in ether, and the solvent was removed next day. Examination of the crude oil (308 mg) by TLC on Mallinckrodt Silicar 7GF using CCl_4 (65%), AcOEt (35%), showed two main spots—one with R_f 0·59 (corresponding to methyl marrubate) and the other with R_f 0·37 (corresponding to methyl 6-epimarrubate). Preparative TLC separated the product into four fractions: two with material (78 mg) which did not contain the furan ring; methyl marrubate (54 mg) identified by IR spectra and TLC behavior; and methyl 6-epimarrubate (total yield of material homogeneous by TLC and IR spectrum 83 mg) which on crystallization from AcOEt–pentane had m.p. 119–121° (30 mg). (Found: C, 69·20; H, 8·79; O, 21·93. $C_{21}H_{32}O_5$ requires: C, 69·20; H, 8·85; O, 21·95%.) ν_{max} 3630, 3550 (sh.), 2960, 2900 (sh.), 1725, 1704, 1507, 1467, 1395, 1380, 1305, 1238, 1200 (sh.), 1160, 1092, 1043, 1026, 979, 875 and 782 cm^{-1}. NMR peaks at: 46 (3H singlet), 58 (3H doublet J = 6 c s), 88 (3H singlet), 91–170 (16H complex), 245 (1H singlet, $W_{\frac{1}{2}}$ = 35 c s), 377 (1H singlet), 439 (2H doublet with further splitting) c s.

Methyl marrubate (**4c**). A soln of the crude potassium salt from **4a** (6·12 g) in acetone (100 ml) was refluxed for 5 hr with MeI (10 ml). The cooled mixture was evaporated almost to dryness. Water was added to the residue, and the aqueous soln was extracted with $CHCl_3$. The $CHCl_3$ soln was washed with 10% $NaHCO_3$ aq, water and was dried (Na_2SO_4). Evaporation of the solvent gave the crystalline **4c** (6·5 g) which on recrystallization from AcOEt–pentane had m.p. 85–86·5° (5·7 g), (lit.[41] 84–85°). ν_{max} 3620, 3430, 2960, 1726, 1697, 1505, 1465, 1378, 1343, 1230, 1194, 1160, 1091, 1059, 1025, 981, 915, and 874 cm^{-1}; NMR peaks at: 59 (3H, doublet, J = 6 c s), 63 (3H, singlet), 78 (3H, singlet), 83 (1H, singlet, disappears on addition of D_2O), 95–167 (14H, complex), 225 (3H, singlet), 264 (1H, singlet, $W_{\frac{1}{2}}$ = 6 c s), 342 (1H, singlet, disappears on addition of D_2O), 377 (1H, singlet), and 438 (2H, doublet with further splitting, J = 7 c/s) c/s.

The ester (mixed m.p. and IR comparison) may also be prepared in good yield by treating a soln of marrubic acid in ether and a little EtOH with an excess of ethereal diazomethane (cf.[2]).

Methyl dehydromarrubate (**2c**)

(a) *Oxidation of methyl marrubate.* A soln of chromic acid in dil H_2SO_4 aq (3·7 ml)[38] was added slowly to a cooled stirred soln of **4c** (3·6 g) in acetone (30 ml, distilled over $KMnO_4$) in a N_2 atm. When the mixture had been stirred for 5 min, ice and water (100 ml) were added, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water and sat NaCl aq and was dried (Na_2SO_4). Evaporation of the

[40] In early experiments, the reduction of **2a** with Li and liquid ammonia led to a 50% yield of a material with m.p. 194–197° (marrubic acid 203°), IR spectrum identical with marrubic acid.

[41] F. Hollis, J. H. Richards, and A. Robertson, *Nature, Lond.* **143**, 604 (1939).

solvent gave crude product (3·7 g). This product in benzene was chromatographed on alumina. Elution with benzene–AcOEt (1:1) gave the methyl ester **2c** (2·3 g) which on recrystallization from AcOEt–pentane had m.p. 122–124° (1·6 g). The ketoester, crystallized twice from AcOEt–pentane for analysis, had m.p. 123 124·5°. (Found: C, 69·40; H, 8·16; O, 22·07. $C_{21}H_{30}O_5$ requires: C, 69·58; H, 8·34; O, 22·07%.) ν_{max} 3600, 2930, 1713, 1580, 1510, 1470, 1446, 1374, 1305, 1225, 1194, 1152, 1065, 1028, 975, and 875 cm^{-1}; NMR peaks at: 62 (3H, doublet J = 6 c/s), 67 (3H, singlet), 74 (3H, singlet), 90–167 (12H complex, peak at 112 disappears on addition of D_2O), 194 (1H, singlet), 220 (3H, singlet), 379 (1H, singlet), 440 (2H doublet with further splitting) c/s; and in benzene the Me peaks were at 45 (doublet J = 5 c/s), 70 and 85; and the peak at 194 had shifted to 212 c/s; λ_{max} 271 mμ (ε 64).

(b) *From dehydromarrubic acid.* A soln of **2a** (1 g) in ether and MeOH was treated with an ethereal soln of diazomethane. Next day the remaining solvent was blown off with N_2. Methylene chloride was added to the resultant semi-crystalline solid, and the soln was filtered through Celite and evaporated to dryness. The IR spectrum of the product (1·05 g) showed a small trace of acid. The product was chromatographed on alumina, and the benzene–AcOEt (1:1) eluate yielded **2c** (893 mg) which on recrystallization from AcOEt pentane had m.p. 125–127° (431 mg) and 123–125° (348 mg). The ester was identical with the product prepared by oxidation of methyl marrubate (IR spectrum, NMR spectrum and mixed m.p.)

Reduction of methyl dehydromarrubate

(a) *Lithium in liquid ammonia.* Li metal (155 mg) was added in small pieces over 20 min to a soln of **2c** (348 mg) in MeOH (10 ml), ether (20 ml) and liquid ammonia (250 ml). NH_4Cl (6 g) was then added. After the ammonia had evaporated, ice water and AcOEt were added to the residue, and the AcOEt layer was washed with water, sat NaCl aq and was dried (Na_2SO_4). Removal of the solvent gave an oily product (281 mg) presumably mainly 6-epimarrubenol (ν_{max} 3580, 3450, 2900, 1503, 1465, 1375, 1135, 1097, 1045, 1026, 971, and 875 cm^{-1}; NMR peaks at: 58 (3H, doublet, J = 6 c/s), 62 (3H, singlet), 75 (3H, singlet), 78 161 (16H, complex), 194·255 (4H, complex, which includes AB quartet at 194, 205, 244, and 255, J = 11 c/s), 377 (1H, singlet), and 439 (2H doublet with further splitting) c/s. The aqueous layer after acidification and extraction with AcOEt gave acidic material (5 mg) which was discarded.

A soln of the crude epimarrubenol (274 mg) in pyridine (2 ml) and Ac_2O (2 ml) was kept overnight at room temp. The mixture was poured into cold dil HCl aq which was extracted with AcOEt. The AcOEt extract was washed with water and dried (Na_2SO_4). Removal of the solvent gave the crude diacetate (333 mg) which was chromatographed on Florisil. The fractions (260 mg) eluted in benzene and benzene–3% AcOEt were almost pure diacetate (IR spectrum), which after crystallization from AcOEt light petroleum (b.p. 30–60°) had m.p. 135–138° (126 mg) and 133-136° (61 mg). For analysis the diacetate had m.p. 138 139°. (Found: C, 68·49; H, 8·68; O, 23·04. $C_{24}H_{36}O_6$ requires: C, 68·54; H, 8·63; O, 22·83%.) ν_{max} 3590, 2930, 1729, 1470, 1376, 1242, 1025, 966 and 873 cm^{-1}; NMR peaks at: 55 (3H, doublet, J = 6 c/s), 61 (3H, singlet), 68 (3H, singlet), 78 178 (21H, complex with strong peak at 123), 248 (2H, singlet), 306 (1H, singlet, $W_{\frac{1}{2}}$ = 25 c/s), 376 (1H, singlet), 437 (2H, doublet with further splitting) c/s.

(b) *Sodium borohydride in 2-propanol.* Compound **2c** (658 mg) in 2-propanol (10 ml) was added to $NaBH_4$ (657 mg) in 2-propanol (about 300 ml) and the mixture was refluxed for 24 hr, cooled and evaporated to dryness. Water (50 ml) was added and the mixture was acidified and extracted 4 times with $CHCl_3$. The combined $CHCl_3$ solns were washed with water, and then extracted 3 times with 10% $NaHCO_3$ aq. The $CHCl_3$ soln was washed with water and dried (Na_2SO_4). Evaporation of solvent gave a crude product (299 mg). The IR spectrum indicated that this was mainly marrubiin with possibly a trace of triol.

The $NaHCO_3$ soln on acidification and extraction with $CHCl_3$ yielded crude product, m.p. 166–172° (280 mg), which was identified as marrubic acid by its IR spectrum.

On recrystallization, marrubic acid, m.p. 173 175° (172 mg) (lit. m.p.[39,42] 173-174°, and 205°) was obtained.

(c) *Lithium aluminum hydride.* Methyl dehydromarrubate (202 mg) in a Soxhlet thimble was refluxed for 19 hr with LAH (200 mg) in ether (50 ml), and the soln was kept for 2 days. AcOEt, followed by water and finally 10% HCl aq were added slowly to the mixture. The layers were separated and the aqueous layer extracted with AcOEt. The combined AcOEt ether layers were washed with water and sat NaCl aq and dried (Na_2SO_4). On evaporation of the solvent, an oil (178 mg) was obtained. The IR spectrum of the crude product showed weak carbonyl absorption but was very similar to the spectrum of marrubenol. In particular, the spectrum in the 3600 3300 cm^{-1} and in the 1000 cm^{-1} regions was different from that of epimarrubenol.

[42] H. M. Gordin, *J. Am. Chem. Soc.* **30**, 265 (1908).

After treatment with charcoal, the product (142 mg) was chromatographed on neutral alumina and the pet. ether–benzene (1:1) eluate gave marrubenol (53 mg) which crystallized and was identified by IR spectrum. The remaining fractions were mainly marrubenol contaminated with ketone.

Marrubenol diacetate (**5b**). A soln of **5a** (207 mg) in Ac_2O (1 ml) and pyridine (1 ml) was kept at room temp for 36 hr and was then heated on a steam-bath for 8 hr. Examination of a sample of the reaction mixture by TLC showed that the diacetylation was complete. Most of the solvents were removed *in vacuo* at room temp and dil HCl aq followed by AcOEt was added to the residue. The aqueous layer was further extracted with AcOEt and the combined AcOEt layers were washed with water, sat $NaHCO_3$ aq and dried (Na_2SO_4). Evaporation of the solvent yielded an oil (215 mg) which crystallized on trituration with light petroleum, to give crude **5b** m.p. 96–100° (181 mg). Further crystallization from ether–light petroleum gave the diacetate in needles, m.p. 102–103° (92 mg). (Found: C, 68·41; H, 8·54; O, 23·02. $C_{24}H_{36}O_6$ requires: C, 68·54; H, 8·63; O, 22·83%.) ν_{max} 3590, 2930, 1730, 1503, 1468, 1375, 1275, 1240, 1155, 1025, 980, 955, and 873 cm^{-1}; NMR peaks at: 56 (3H, doublet, J = 6 c/s), 61 (3H, singlet), 76 (3H, singlet), 80–165 (21H, complex with strong peaks at 122 and 125), 232–277 (2H, AB quartet, J = 12 c/s), 323 (1H, singlet, $W_{\frac{1}{2}}$ = 6 c/s), 377 (1H, singlet), 437 (2H doublet with further splitting) c/s.

Tetrahydromarrubiin (**1b**). Tetrahydromarrubiin (m.p. 122–124°) is best prepared by hydrogenation of marrubiin in the presence of rhodium on charcoal.[43] We did not separate the product into the epimers at C_{13} which have been reported by Boyle.[44] Presumably our compounds in the tetrahydro series were mixtures of epimers at C_{13}. While this may have been responsible for the difficulty we had in crystallizing some compounds (not reported in this paper), it probably does not affect the validity of our reduction studies. The NMR spectrum of tetrahydromarrubiin had peaks at: 55 (3H, doublet J = 6 c/s), 63 (3H, singlet), 77 (3H, singlet), 82–140 (18H, complex), 190–243 (4H, complex), 285 (1H complex triplet, $W_{at\ base}$ = 16, $W_{\frac{1}{2}}$ = 13) c/s.

Dehydrotetrahydromarrubic acid (**2b**). Compound **4b**[41] (2 g) was oxidized by the procedure used for marrubic acid. The crude **2b** (1·84 g) on recrystallization from AcOEt had m.p. 155–157° (1·52 g). Further recrystallization raised the m.p. to 159–161° (lit.[3] 159°). ν_{max} 3625, 2945, 2735, 1737, 1667, 1470, 1417, 1288, 1236, 1200, 1130, 1047, 960 and 907 cm^{-1}; λ_{max}^{EtOH} 277 mμ (ε 51); NMR peaks at 58 (3H singlet), 63 (3H doublet, J = 6 c/s), 72 (3H singlet), 80–240 (complex), and 776 (broad peak) c/s.

Reduction of dehydrotetrahydromarrubic acid

(a) *Sodium borohydride*. A soln of $NaBH_4$ (80 mg) in water (2 ml) was added to a refluxing mixture of **2b** (202 mg) suspended in water (5 ml) and $NaHCO_3$ aq (58 mg in 5 ml water). The refluxing was continued for 1 hr and the cooled mixture was acidified with 20% H_2SO_4. The white ppt was washed with water and dried (148 mg, m.p. 173–176°, mixed melt with tetrahydromarrubic acid 178–180°).

The filtrate was extracted with AcOEt and the combined AcOEt fractions were washed with sat NaCl aq and dried (Na_2SO_4). On evaporation further crude tetrahydromarrubic acid (45 mg) was obtained.

The combined products (193 mg) crystallized from an AcOEt–hexane mixture to give tetrahydromarrubic acid m.p. 180–182° (156 mg), raised to 182–184° on addition of authentic tetrahydromarrubic acid.

The IR spectra of the product and that of authentic tetrahydromarrubic acid (m.p. 180–181°) were identical.

(b) *Lithium in liquid ammonia*. A soln of **2b** (217 mg) in MeOH (15 ml) was added, with stirring, to liquid ammonia (300 ml). Li metal (800 mg) was added in portions, over a period of 30 min, waiting after each addition until the blue color had disappeared before adding more Li. When all the Li had been added, NH_4Cl (15 g) was slowly added to the mixture, which was then left stirring until all the NH_3 had evaporated. Ice water was added to the residue and the soln was acidified with HCl. The acidified soln was extracted with AcOEt, and the combined AcOEt fractions were washed with sat NaCl aq and dried (Na_2SO_4). Evaporation of the AcOEt gave crude product (211 mg) which on recrystallization from AcOEt gave **4b** (162 mg), identified by m.p. 179–181°, mixed m.p. 179–181°, and IR spectrum.

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[43] This experiment was first carried out by Miss Marsha J. Grant whom we thank.

[44] P. H. Boyle, *Chem. & Ind.* 33 (1966).

Chemical Society. Grateful acknowledgement is made to the donors of these funds. We also thank Professor W. Cocker for supplying some of the crude horehound extract used in this work, Dr. B. L. Shapiro for running and interpreting NMR spectra in early phases of the work, Dr. A. Tahara for copies of some of his NMR spectra,[26, 32] and Dr. J. T. Edward for a stimulating discussion.