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A BIOGENETICALLY-PATTERNED SYNTHESIS OF OPTICALLY ACTIVE TETRONIC ACIDS VIA ACYLATION. (R)-CAROLIC ACID AND ANALOGUES.

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A number of α-acyl derivatives of R-γ-methyltetronic acid (MTA) 1a are of interest both as biosynthetic and synthetic precursors of the natural tetronic acids produced by moulds, many of which contain the R-γ-methyl functionality.[1,2] Our interest in acylation as a synthetic route to tetronic acids is due to the observation of Boll[2] that ethyl-S-lactate may be converted to 2 and thence to 1b by previously reported conditions[3,4] in good optical purity, as well as our own recent observation[5] that R-MTA 1 is incorporated into R-carolic acid 3 in good yield by Penicillium charlesii. Since the only other published work on the synthesis of mould tetronic acids, viz. carolic 3 and carolinic 4 acids[6,7] gave racemic materials, use of R- or S- MTA as synthons represented a potential biogenetically-patterned synthesis of optically active tetronic acids.

For initial studies, we prepared RS-MTA.[2,3,4,8] Synthesis of this material could be improved by use of an alternate route to 5, previously prepared from the α-haloacid chloride and sodio diethyl malonate.[8] In the general synthetic scheme, RCH_2COCl (where R=H, Me, Ph or EtO_2CCH_2) is treated with ethoxymagnesio diethyl malonate to give esters 6-9, which, like acetoacetic ester,[1] gave rearranged products upon bromination, e.g., 7 via 10 gave 5. This was cyclised to 13 which could be easily hydrolysed and decarboxylated to 14. We converted 6 to 15 and 16 similarly, and 8 to 17 and 18. The corresponding synthesis with 9 failed due to elimination, only maleic acid being isolated.

Earlier attempts to acylate γ-alkyl-substituted tetronic acids with MeCOCl and metal chlorides failed[9] although 19 could be prepared from 18 in isolable yield, and the method was good for γ,γ-disubstituted tetronic acids 20. A slight amount of acylation of MTA was, however, detected chromatographically.

Direct C-acylation of MTA with RCO_2H and PPA or HF failed. The thallium enolate of MTA was obtained quantitatively with TlOEt in benzene/ethanol and converted with RCOCl to the O-acyl derivatives in ca. 90% yields. Subsequent Fries rearrangement gave only yields of ca. 30% for the C-acyl compounds 21-23. Optimum conditions were $TiCl_4$ in $PhNO_2$. Far the best synthetic method was treatment of MTA directly with RCOCl and $TiCl_4$ in $PhNO_2$. Thus, Pr^nCOCl gave a 71% yield of 22, and $BrCH_2CH_2CH_2COCl$ gave 23, which was not isolated as such, but treated with HO^- to give a 74% overall yield of RS-3 (isolated in its cyclic[5] form).

Application to 1a was straightforward, and 3 was obtained which was identical to the natural carolic acid in all respects, and 97% optically pure. The enantiomer of 3 has been prepared independently from 1b by Boll[10] as well as 21-23 above and the unnatural analogues 24-26. Homolog 27 was very recently reported [11]

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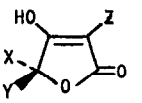
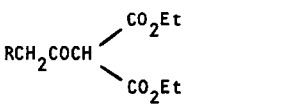
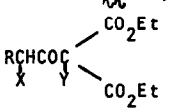


1a X=Me, Y=Z=H
1b X=Z=H Y=Me
2 X=H Y=Me Z=Ac
3 X=Me Y=H $Z=COCH_2CH_2CH_2OH$
4 X=Me Y=H $Z=COCH_2CH_2CO_2H$
13 X,Y=Me,H $Z=CO_2Et$
14 X,Y=Me,H Z=H
15 X=Y=H $Z=CO_2Et$
16 X=Y=Z=H
17 X,Y=Ph,H $Z=CO_2Et$
18 X,Y=Ph,H Z=H
19 X,Y=Ph,H Z=Ac
20 X=Y=Alkyl Z=Ac
21 X,Y=Me,H Z=Ac
22 X,Y=Me,H $Z=COPr^n$
23 X,Y=Me,H $Z=COCH_2CH_2CH_2Br$
24 X,Y=H,Me Z=COEt
25 X,Y=H,Me $Z=COPr^i$
26 X,Y=H,Me $Z=COCH_2Ph$
27 X,Y=Et,H Z=Ac



6 R=H 8 R=Ph
7 R=Me 9 $R=EtO_2CCH_2-$



5 R=Me X=Br Y=H
10 R=Me X=H Y=Br

References

1. Reviewed by L. J. Haynes and J. R. Plimmer, Quart. Rev. 1960, 14, 292.
2. P. M. Boll, E. Sorensen, and E. Balieu, Acta Chem. Scand. 1968, 22, 3251.
3. R. N. Lacey, J. Chem. Soc. 1954, 832.
4. P.W.Clutterbuck, H.Raistrick, and F. Reuter, Biochem. J. 1935, 29, 300,871, 1300.
5. J.L.Bloomer, F.E.Kappler, and G.N. Pandey, J.C.S.Chem. Comm. 1972, 243.
6. R. Sudo, A. Kaneda, and N. Itoh, J. Org. Chem., 1966, 32, 1844.
7. L. J. Haynes, J. R. Plimmer, and A. H. Stanners, J. Chem. Soc. 1956, 4661.
8. E. Benary, Ber. 1907, 40, 1079. See also R. Anschutz and W. Bertram, Ber. 1903, 36, 468. R. Anschutz and R. Bocker, Ann. 1909, 368, 53.
9. L. J. Haynes and J. W. M. Jamieson, J. Chem. Soc. 1958, 4132
10. P. M. Boll, Personal communication.
11. T.P.C.Mulholland, R.Foster, and D.B.Haydock, J.C.S.Perkin I 1972, 1225.