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Analogues of the Quararibea metabolite chiral enolic-γ-lactone from (2*S*,3*S*)- and (2*S*,3*R*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acids

Chithra Gopinath,[a] Salini Thomas,[a] Mangalam S. Nair[b] and Ibrahim Ibnusaud[a,*]

[a]*School of Chemical Sciences, Mahatma Gandhi University, P. D. Hills P. O, Kottayam, Kerala 686 560, India*
[b]*Organic Chemistry Division, Regional Research Laboratory (CSIR), Thiruvananthapuram 695 019, Kerala, India*

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Abstract—Reaction of dialkyl (2*S*,3*S*)- or (2*S*,3*R*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylates with $POCl_3$ in pyridine followed by diazomethane resulted in the isolation of dialkyl 2*S*-4-methoxy-5-oxo-2,5-dihydro-2,3-furandicarboxylates, which are analogues of the Quararibea metabolite chiral enolic-γ-lactone (3-hydroxy-4,5-(*R*)-dimethyl-2(5*H*)-furanone). An unusual α-hydroxylation of γ-butyrolactone takes place involving $POCl_3$ in pyridine. When the dehydration was facilitated with methanesulfonyl chloride in triethylamine, instead of $POCl_3$, aromatic dialkyl 5-[(methylsulfonyl)oxy]-2,3-furandicarboxylates were obtained.

It is estimated that chiral butenolide sub-structures form building blocks for the synthesis of about 13,000 natural products including molecules bearing 2(5*H*)-furanone subunits.[1] These structural motifs include pheromones, the antibiotic strobilin, pencillianic acid, pulvinones, and several secondary metabolites of fungal and marine origin as well as sesquiterpenoid lactones.[2] Often, chiral butenolides have been obtained either from carbohydrates, γ-keto acids, glutamic acid or from acyclic systems such as acetylenic compounds, pyruvic acid derivatives, and cyanohydrins of conjugated aldehydes, mostly involving multi-step procedures.[3,4]

During a project devoted to the synthesis of chiral γ-butyrolactone based molecules, we recently identified (2*S*,3*S*)- and (2*S*,3*R*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acids **1** and **2**, which can be obtained in large amounts from the chiral pool, as ideal starting materials for the synthesis of several interesting chiral γ-butyrolactone based molecules (Fig. 1).[5]

Minor functional group modification of **1** and **2** can give isocitric acid **3**, the quararibea metabolite the chiral enolic-γ-lactone **4**, (+)-avenaciolide **5**, (+)-canadensolide **6**,

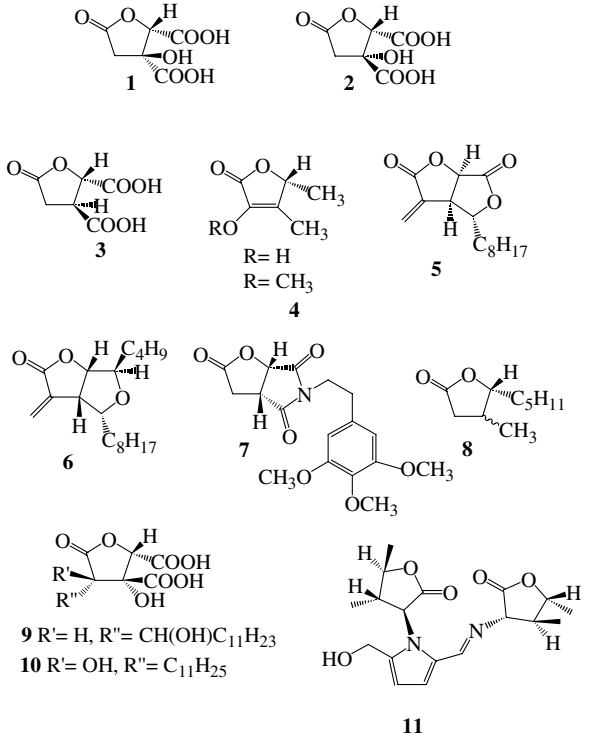

Figure 1.

Keywords: Garcinia acid; Hibiscus acid; Chiral butenolide.
* Corresponding author. Tel.: +91 481 2731036; fax: +91 481 2731002/1009; e-mail: i_ibnu@yahoo.co.in

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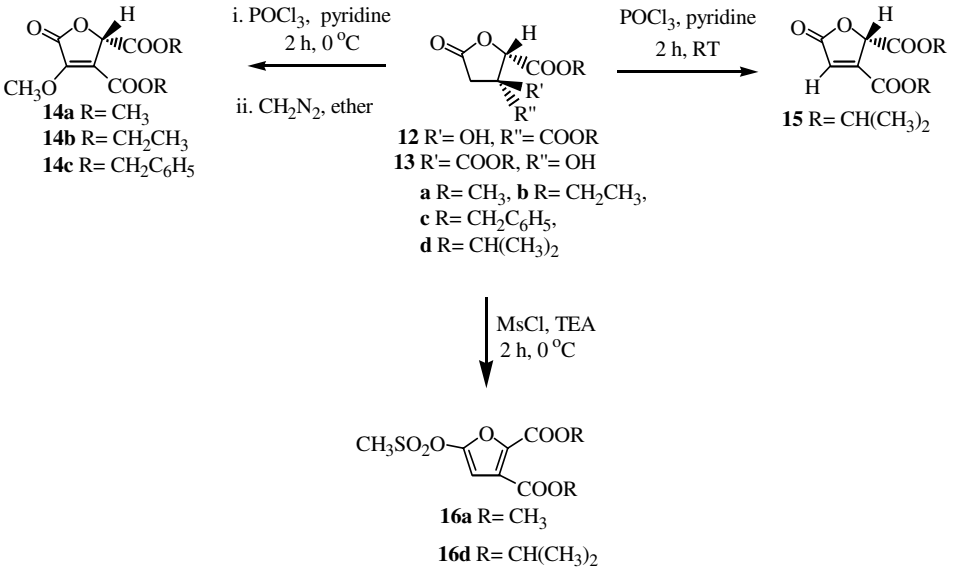


Scheme 1.

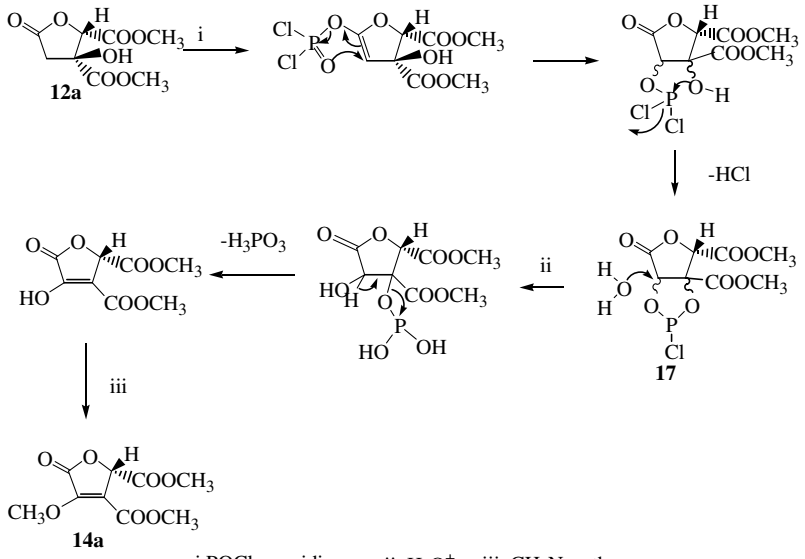
mescaline isocitrimide lactone **7**, cis and trans whisky lactones **8**, cinatrin C_2 **9** and C_3 **10** and (−)-funebrine **11**.[6–14] Among these, the syntheses or partial syntheses of **3**, **5**, **6**, and **7** from **1** or **2** have been carried out.[15]

Treatment of ester derived from **1** and **2**, that is, **12a–c** and **13a–c**[5] with $POCl_3$ in pyridine followed by work-up with aqueous HCl furnished a polar intermediate which on treatment with diazomethane in ether gave the unexpected methyl ethers of the chiral enolic-γ-lactones **14a–c** instead of the anticipated dehydration product **15** (R = CH_3, CH_2CH_3, $CH_2C_6H_5$) (Scheme 1).[16] α-Hydroxylation of γ-butyrolactones **12** and **13** occurs involving $POCl_3$ in pyridine.

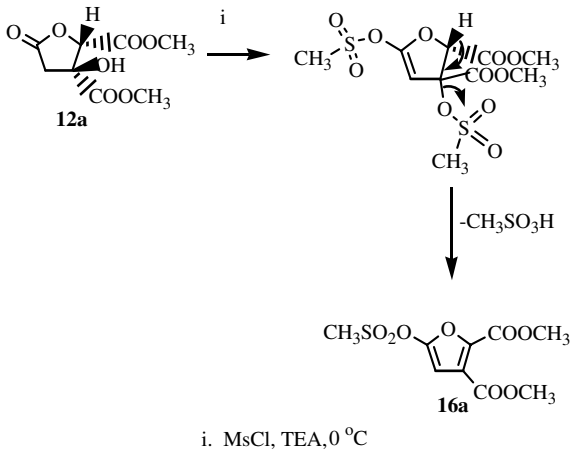
The formation of compounds **14a–c** was confirmed by IR, ^1H and ^{13}C NMR, and mass spectroscopy.[17,18] For example, the IR spectrum of **14a** shows a peak at 1740 cm^{-1} indicative of the presence of a lactone moiety, the ^1H NMR spectrum shows the presence of an $-OCH_3$ group at 3.95 ppm whilst the ^{13}C NMR spectrum shows the presence of olefinic carbons at δ 133.4 and 126.7 ppm. In addition, DEPT experiments clearly indicated the absence of CH_2 protons and the presence of three CH_3 and one CH moieties. The HMBC spectrum confirmed the position of the olefinic bond at C3–C4.[19]

However, when the reaction was repeated with the isopropyl esters **12d** or **13d**, the simple dehydration product **15** was obtained (Scheme 1).[20,21]

In order to gain a clear understanding of the above observation, the dehydrations of **12a**, **12d**, **13a**, and **13d** were effected using methanesulfonyl chloride in



Scheme 2.



Scheme 3.

triethylamine.[22] Interestingly, instead of **14** or **15** ($R = CH_3$, $CH(CH_3)_2$), aromatic dialkyl-5-[(methyl-sulfonyl)oxy]-2,3-furandicarboxylates **16a** and **16d** were isolated irrespective of the substitution in **12** and **13**. The formation of **16** was confirmed by IR, ^1H, and ^{13}C NMR and mass spectroscopy.[23,24]

The formation of compounds **14a–c** can be explained on the basis of an intramolecular rearrangement mechanism involving cyclic intermediate **17** (Scheme 2).

Enolisation of the lactone carbonyl in **12** and **13** occurs with both $POCl_3$ and methanesulfonyl chloride, however, these acid chlorides react differently with **12** and **13**. Cyclic intermediates **17** are not involved in the reaction with methanesulfonyl chloride (Scheme 3).

The syntheses of several γ-butyrolactone based natural products are underway starting from furandicarboxylic acids **1** and **2**.

Acknowledgements

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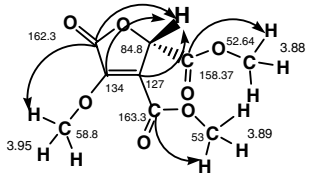
17. General procedure for the preparation of **14**. To a solution of diester **12** or **13** (4 mmol, **12a–c** or **13a–c**) in pyridine 5 mL, $POCl_3$ (4 mmol) was added at 0 °C and the reaction was stirred for 2 h. The reaction mixture was quenched with aqueous HCl (2 N), extracted with $CHCl_3$ and concentrated. The oily residue obtained was dissolved in methanol, followed by the addition of diazomethane in ether. After completion of the reaction (monitored by TLC), excess diazomethane was removed along with solvent by concentration. The residue obtained was purified by column chromatography (silica gel, hexane–chloroform, 8:2).
18. Spectral data for dimethyl 3-methoxy-2(5*H*)-furanone-4,5 dicarboxylate (**14a**): Yield 0.4 g (43%), mp: 71 °C, $[\alpha]_D^{27}$ −31 (*c* 1.0, $CHCl_3$); IR (KBr): 2954, 1740, 1716, 1608, 1558, 1442, 1400 cm^{-1}; UV ($CHCl_3$) λ_{max} 295 nm; δ_H (300 MHz, $CDCl_3$): 5.60 (s, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H); δ_C (75 MHz, $CDCl_3$): 162.7, 161.9, 157.7, 133.5, 126.7, 84.4, 58.2, 52.4, 52.0 ppm; *m*/*z* (EIMS): 230

(M^+, 7.1%), 217 (2.5%), 216 (13.6%), 15 (100%), 185 (3.4%), 184 (26%), 172 (21.7%), 56 (15.1%), 141 (4.1%), 127 (8.7%). Anal. Calcd for $C_9H_{10}O_7$: C, 46.99; H, 4.38. Found: C, 47.01; H, 4.37.

19. Correlation diagram of **14a**:



20. General procedure for the preparation of **15**. To a solution of diester **12d** or **13d** (4 mmol) in pyridine 5 mL, $POCl_3$ (4 mmol) was added at 0 °C and the reaction was stirred for 2 h at 25 °C. The reaction mixture was quenched with aqueous HCl (2 N), extracted with $CHCl_3$ and concentrated. The residue obtained was purified by column chromatography (silica gel, hexane–chloroform, 8.5:1.5).
21. Spectral data for diisopropyl 2*S*-5-oxo-2,5-dihydro-2,3-furandicarboxylate (**15**): Yield: 0.465 g (45%); $[\alpha]_D^{27}$ −14 (*c* 1.0, $CHCl_3$); IR (liquid film): 2981, 1728, 1654, 1554, 1450, 1276, 1107 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 6.80 (s, 1H), 5.21–4.90 (m, 2H), 3.90 (s, 1H), 1.22–1.33 (m, 12 × H); δ_C (100 MHz, $CDCl_3$): 169.4, 165.6, 164.91, 140.2, 129.18, 69.4, 68.5, 68.3, 21.7 ppm; *m*/*z* (EIMS): 256 (M^+, 25.4%), 214 (25.4%), 198 (65.0%), 156 (82.5%), 43 (100%).
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23. General procedure for the preparation of **16**. To a solution of **12a**, **12d**, **13a** or **13b** (4 mmol), triethylamine (2 mL) in 20 mL of dichloromethane, methanesulfonyl chloride (4 mmol) was added at 0 °C and the reaction stirred for 2 h. The reaction mixture was quenched with 2 N hydrochloric acid followed by a brine wash. The aqueous layer was extracted with $CHCl_3$. The residue obtained after concentration was purified by column chromatography (silica gel, hexane–chloroform, 8.5:1.5).
24. Spectral data for dimethyl 5-[(methylsulfonyl)oxy]2,3-furandicarboxylate (**16a**): Yield: 0.779 g (70%); IR (liquid film): 2956, 1733, 1548, 1442, 1386, 1278, 1185, 1065 cm^{-1}; UV ($CHCl_3$) λ_{max} 242 nm; δ_H (300 MHz, $CDCl_3$): 6.40 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.40 (s, 3H); δ_C (75 MHz, $CDCl_3$): 161.4, 157.1, 149.0, 137.9, 125.2, 81.6, 52.59, 52.56, 39.07 ppm; HRMS (EI): *m*/*z* calcd for $C_9H_{10}S_1O_8$ [M^+]: 278.236. Found: 278.0036.