Pergamon

Tetrahedron 58 (2002) 4887–4892

TETRAHEDRON

Chiral γ-butyrolactones related to optically active 2-hydroxycitric acids

Ibrahim Ibnusaud,[a,*] Puthiaparambil Tom Thomas,[a] Rajasekharan Nair Rani,[a] Paleapadam Vavan Sasi,[a] Thomas Beena[a] and Abdulkhader Hisham[b,*]

[a]*School of Chemical Sciences, Mahatma Gandhi University, P.D. Hills P.O., Kottayam, Kerala 686560, India*
[b]*Department of Chemistry, College of Science, P.O. Box 36, Sultan Qaboos University, 123, Oman*

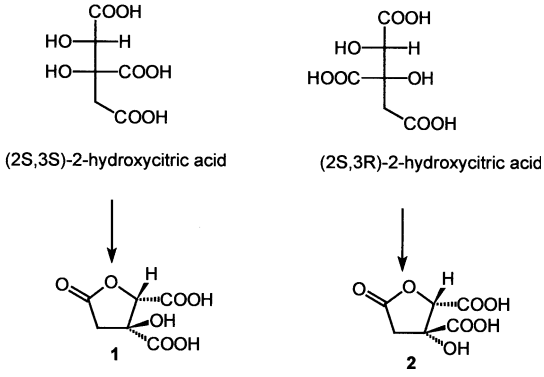
Received 15 January 2002; accepted 18 April 2002

Abstract—The complete spectroscopic data and other physical constants of two naturally occuring, diastereomeric, optically active γ-lactones derived from inexpensive 2-hydroxycitric acids, namely garcinia acid [(2*S*,3*S*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid] and hibiscus acid [(2*S*,3*R*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid] and related derivatives have been described for the first time. © 2002 Published by Elsevier Science Ltd.

Strategies in enantioselective synthesis involve the use of molecules from the chiral pool as chiral building blocks, chiral auxiliaries, chiral ligands—catalytically or stoichiometrically, or chiral molecules as starting points.[1] The search for inexpensive chiral molecules possessing various functional groups and stereocenters from the chiral pool, for employing them in enantioselective synthesis is of current interest. The chiral pool approach relies on one or other inexpensive and naturally occurring chiral entities namely terpenes, amino acids, carbohydrates, hydroxy acids etc. Hydroxy acids present an attractive starting point for the preparation of a range of chiral synthons, ligands for catalysts and auxiliaries.[2,3] Hence, naturally occurring hydroxy acids namely ascorbic acid, lactic acid, malic acid and tartaric acid are frequently encountered in the broad area of asymmetric synthesis.

Optically active diastereomers of 2-hydroxycitric acid, (2*S*,3*S*) and (2*S*,3*R*)-2-hydroxycitric acid are extensively distributed in nature and are present in plant species *Garcinia cambogia*, *Hibiscus sabdariffa* or *Hibiscus furcatus*, respectively.[4,5] While *Garcinia Cambogia* is extensively distributed across southern parts of India, and the dried rind of the fruit is traditionally used for curing fish materials is cheap and readily available in several markets in many Asian countries, other plant species are widely distributed in the hotter parts of India and tropics of the globe.[6] The isolation of these compounds as tricarboxylic acids, i.e. in its natural form, is extremely difficult because of their spontaneous lactonisation during their isolation process due to the presence of a γ-hydroxyl group. Hence the (2*S*,3*S*) isomer lactonises to give (2*S*,3*S*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid (garcinia acid, **1**), whereas (2*S*,3*R*) isomer gives (2*S*,3*R*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid (hibiscus acid, **2**) during isolation. There is only one route for this lactonisation which results in single isomer. Several reports pertaining to the pharmaceutical applications of garcinia acid are available, especially in fat metabolism and also as an anti-obesity agent (Scheme 1).[7a–j]

Though Boll et al.[8] reported the absolute configuration of **1** and **2** to be (2*S*,3*S*) and (2*S*,3*R*) respectively, it is rather surprising to note that these compounds have evaded the attention of organic chemists. The chemistry of garcinia acid and hibiscus acid still remains unexplored irrespective of the fact that these compounds can be easily made available from cheap natural sources.

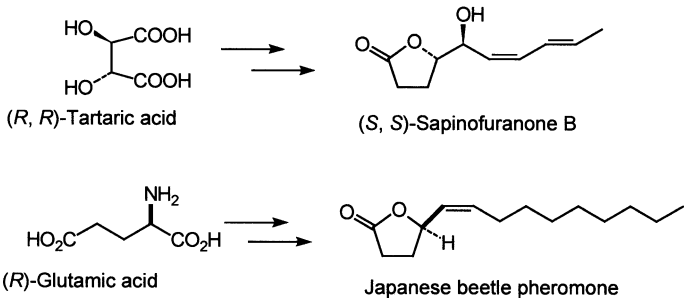


Scheme 1.

Keywords: γ-lactones; Hibiscus acid; diesters; Garcinia acid.

* Corresponding authors. Tel.: +91-481-731036; fax: +91-481-731009; e-mail: i_ibnu@yahoo.co.in

0040–4020/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4020(02)00431-3



Scheme 2.

Usually chiral γ-butyrolactones, very common structural units in several biologically active molecules, have been made available either from glutamic acid or tartaric acid (Scheme 2).[9a,b] The unique γ-butyrolactone structure and the absolute configuration of compounds **1** and **2** match with fragments of several biologically active molecules[9a–k] and hence indicate their potential use in the enantioselective synthesis of such compounds. The limiting factor for the synthetic scope of these molecules can be attributed to the non-availability of title compounds at the disposal of synthetic organic chemists due to the lack of convenient methods for the large scale isolation of these compounds from complex plant extracts. In order to overcome this hurdle, our laboratory has recently developed efficient, practical and economic procedures for the large-scale isolation of both compounds from plant sources with maximum purity.[10,11] Further, very little is known about the spectroscopy of these molecules except the preliminary low resolution ^{1}H NMR data.[4,5] Therefore it has become inevitable to investigate the spectroscopy of these molecules in detail to differentiate them spectroscopically and also to reconfirm their structures. The present study describes the spectroscopic details of garcinia acid and hibiscus acid for the first time and the preparation of several potential derivatives of these molecules.

Pure samples of garcinia acid (**1**) and hibiscus acid (**2**) were isolated in large amounts from plant materials using our recently developed isolation methods and both compounds were analyzed for the formulae $C_6H_6O_7$ and showed different R_f values, mp's and $[\alpha]_D$'s indicating their diastereoisomeric nature. The IR spectrum of both compounds showed characteristic bands for the hydroxyl, carboxyl and γ-lactone groups. The $[\alpha]_D$'s of **1** and **2** match the reported values, which assures the optical purity of the isolated compounds.

A comparison of our newly obtained ^{1}H and ^{13}C NMR chemical shift data for **1** and **2** showed a marked distinction which differentiates them spectroscopically. The differences in the chemical shifts between both isomers were much more pronounced in the ^{13}C NMR spectrum.

Exact assignments of the carbonyl carbon shifts in both compounds were difficult from the 1D NMR spectrum. Even though tentative assignments of carbonyl carbon shifts in both compounds can be made by comparison of the ^{13}C NMR shifts of the underivatized materials (**1** and **2**) with those in their corresponding derivatives such as dimethyl esters (**1b** and **2b**) and methylthiomethyl esters (**1c** and **2c**), direct assignments were made on the basis of the ^{1}H–^{13}C long-range correlations observed in the 2D HMBC spectrum as represented in Fig. 1. The carbonyl carbon signal at δ 174.9 in **1** showed three-bond correlations with H-4 and H-2 protons whereas carbonyl carbon at δ 169.2 showed correlation with only the H-2 proton, which suggested the chemical shift of C-3 acid carbonyl group as 174.9 and that of C-2 acid carbonyl group as 169.2. The remaining carbonyl carbon signal at δ 172.0 in **1** can be assigned to the lactone carbonyl as evidenced from its correlation with H-4 protons. Similar correlations observed in the HMBC spectrum of **2** leading to the shift assignment of C-3 acid carbonyl as 172.9, C-2 acid carbonyl as 167.8 and C-5 lactone carbonyl as δ 174.0.

Scheme 3 depicts the preparation of various derivatives of **1** and **2** retaining the chiral lactone moiety.

The attempted preparation of dimethyl esters following the procedure reported by Lewis et al.[5] resulted in a mixture of cyclic dimethyl ester and acyclic trimethyl ester—formed by opening the lactone ring. By adopting mild esterification methods, involving diazomethane or diacid chloride

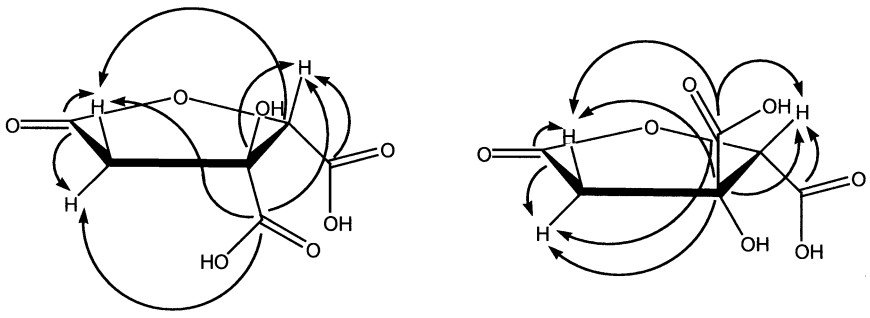
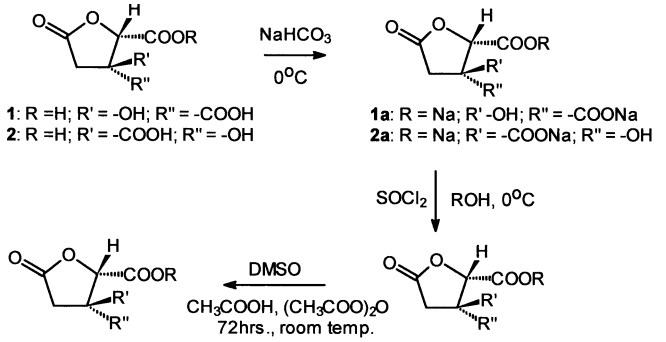


Figure 1. ^{1}H–^{13}C long-range correlations in the 2D HMBC spectrum of **1** and **2**.



1: R =H; R' = -OH; R'' = -COOH
2: R =H; R' = -COOH; R'' = -OH

1a: R = Na; R' -OH; R'' = -COONa
2a: R = Na; R' = -COONa; R'' = -OH

1c: R = CH_3; R' = $-OCH_2SCH_3$; R'' = $-COOCH_3$
2c: R = CH_3; R' = $-COOCH_3$; R'' = $-OCH_2SCH_3$

1b: R = CH_3; R' = -OH; R'' = $-COOCH_3$
1d: R = CH_2CH_3; R' = -OH; R'' = $-COOCH_2CH_3$
1e: R = $CH(CH_3)_2$; R' = -OH; R'' = $-COOCH(CH_3)_2$
1f: R = CH_2Ph; R' = -OH; R'' = $-COOCH_2Ph$
2b: R = CH_3; R' = $-COOCH_3$; R'' = -OH
2d: R = CH_2CH_3; R' = $-COOCH_2CH_3$; R'' = -OH
2e: R = $CH(CH_3)_2$; R' = $-COOCH(CH_3)_2$; R'' = -OH
2f: R = CH_2Ph; R' = $-COOCH_2Ph$; R'' = -OH

Scheme 3.

intermediate, exclusively diesters were formed. Even direct use of thionyl chloride for the preparation of acid chloride resulted in the opening of the lactone ring. This was avoided by preparing disodium salts (**1a** and **2a**) from **1** and **2** and which were subsequently converted to diacid chlorides. There are no reports of **1a** and **2a** which are formed instantaneously by reacting **1** and **2** with aqueous sodium bicarbonate. Unlike trisodium salts, disodium salts are stable and not hygroscopic and can be stored for long periods.

Diesters **1b**–**1f** and **2b**–**2f** have been effectively used for the preparation of optically pure butenolides, cyclic imides, triesters and polyols[12–17] in this laboratory recently.

1. Conclusion

Inexpensive, naturally occuring, liberally functionalised, optically active (2*S*,3*S*)-tetrahydro-3-hydroxy-5-oxo-2,3-furan dicarboxylic acid (garcinia acid) and (2*S*,3*R*)-tetrahydro-3-hydroxy-5-oxo-2,3-furan dicarboxylic acid (hibiscus acid) have been isolated and characterised with complete spectroscopic data and physical constants. From these molecules several derivatives, retaining optically active γ-butyrolactones, have been directly obtained.

2. Experimental

2.1. General

All commercial solvents were distilled prior to use. Dry solvents and reagents were prepared by following the procedures described in *Purification of Laboratory Chemicals* by Perrin, D. D. and Armarego, W. L. F. (3rd ed., Pergamon Press, 1988). Dry THF was used as such received from Aldrich. All reactions, which require anhydrous conditions, were carried out under a positive flow of dry nitrogen. Anhydrous sodium sulphate was used to dry organic extracts. Melting points are uncorrected. IR spectra were recorded using a 'Shimadzu' IR 470 spectrophotometer as KBr pellets (solids) or thin films (liquids). ^{1}H NMR spectra were recorded on a Brucker WM 300 MHz or Brucker Avance 300 or Jeol GSX 400 MHz or Brucker AMX 400 MHz NMR system and chemical shift values are reported in parts per million (ppm) relative to tetramethylsilane as internal standard (0.00 ppm). ^{13}C NMR were recorded on a Brucker WM 300 (75.5 MHz) or Jeol GSX 400 (100.6 MHz) or Brucker AMX 400 (100.6 MHz) NMR system and chemical shift values are reported in parts per million (ppm) relative to tetramethylsilane (0.00 ppm). HMBC spectrum was recorded on Brucker DRX 500 NMR system. Electron impact mass spectra were recorded on a Finnigan MAT MS 8230 or Jeol D-300 or Jeol SX-102 and LC-MSD-Trap 00148 mass spectrometer. Specific rotations were recorded using Jasco DIP 370 or Jasco DIP 1000 digital polarimeter. The optical purity of isolated garcinia and hibiscus acids were verified by comparing the $[\alpha]_D$'s with the reported $[\alpha]_D$'s of the optically pure samples. Elemental analyses were carried out on a Heraeus Carlo Erba 1108 instrument. The plant materials for the isolation of garcinia acid and hibiscus acid were collected random from Quilon and Kottayam districts of Kerala State, India.

2.1.1. Isolation of (2*S*,3*S*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid (*Garcinia acid*, 1).[10] The water extract (2.0 L) of dried fruit rinds of *Garcinia cambogia* (2.0 kg) was concentrated (500 mL) and a sufficient quantity of methanol (ca 5.0 L) was added to precipitate pectin. The pectin free filtrate was further concentrated to a syrup, which was made alkaline by adding a sufficient quantity of aqueous sodium hydroxide (10%) followed by the addition of methanol (ca 2.0 L) till two layers separated. The separated trisodium salt of **1** (lower layer) was washed several times with aqueous methanol (60%, 3×1.0 L). The pure sodium salt was dissolved in sufficient quantity of 2N hydrochloric acid (ca 2.0 L) to regenerate the free acid and

which was concentrated and extracted with acetone. Evaporation followed by recrystallisation (acetone-chloroform) gave the *title compound* **1** (135.0 g, 6.75%) as a colourless crystalline solid, mp 178°C, lit.[5] mp 178°C; [Found: C, 37.73; H, 3.15. $C_6H_6O_7$ requires C, 37.89; H, 3.16%]; $[\alpha]_D^{26}=+102.2$ (*c* 1.0, H_2O), lit.[5] $[\alpha]_D^{20}=+100.0$ (*c* 1.0, H_2O); ν_{max} (KBr) 3400, 1790, 1740 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 4.80 (1H, S, C*H*–COOH); 3.07 (1H, d, *J*=17.4 Hz, CH_aH$_b$COHCOOH); 2.60 (1H, d, *J*=17.4 Hz, CH$_a$$H_b$COHCOOH); δ_C (400 MHz, DMSO-d_6) 174.9, 172.0, 169.2, 84.8, 79.0, 39.7; *m/z* (EIMS). 191 (2, M+1), 173 (1), 162 (6), 145 (3), 127 (10), 116 (48), 99 (70), 88, (100), 60 (40), 55 (20%).

2.1.2. Disodium (2*S*,3*S*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylate (1a). To an aqueous solution of **1** (2.0 g, 10.5 mmol, in 10 mL water), saturated aqueous sodium bicarbonate was added till the pH of the reaction mixture became neutral (ca 15 mL). The residue obtained after evaporation of the reaction mixture under reduced pressure, was triturated and washed with dry acetone (5×20 mL). The product was finally dried under vacuum to give a colourless solid. Yield 2.0 g (82%); [Found: C, 30.68; H, 1.70. $C_6H_4O_7Na_2$ requires C, 30.76; H, 1.71%]; $[\alpha]_D^{29}=+81.8$ (*c* 1.63, H_2O); ν_{max} (KBr) 3400, 1800, 1600 cm^{-1}; δ_H (400 MHz, D_2O) 4.84 (1H, s, C*H*–COONa); 3.19 (1H, d, *J*=17.8 Hz, CH_aH$_b$COHCOONa); 2.83 (1H, d, *J*=17.8 Hz, CH$_a$$H_b$COHCOONa); 2.27 (1H, s, C*OH*COONa); δ_C (400 MHz, D_2O) 179.4, 177.4, 174.69, 89.1, 81.5, 42.7; *m/z* (ESI) 257 (100, M+23), 240 (58), 195 (35.5), 155 (20.9).

2.1.3. Dimethyl (2*S*,3*S*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylate (1b). A solution of **1** (2.0 g, 10.5 mmol in 50 mL ether) was treated with excess diazomethane in ether. The reaction mixture upon concentration gave the *title compound* **1b** (2.2 g, 96%) as yellow oil. [Found: C, 44.12; H, 4.57. $C_8H_{10}O_7$ requires C, 44.04; H, 4.59%]; $[\alpha]_D^{19}=+93.1$ (*c* 0.43, MeOH), lit.[8] $[\alpha]_D^{25}=+92.1$ (*c* 0.30, MeOH); ν_{max} (liquid film) 3450, 1795, 1740 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.96 (1H, s, C*H*–COOMe); 3.82 (3H, s, CH–COO*Me*); 3.78 (3H, s, COH–COO*Me*); 3.20 (1H, d, *J*=19.0 Hz, CH_aH$_b$COHCOOMe); 2.82 (1H, d, *J*=19.0 Hz, CH$_a$$H_b$COHCOOMe); δ_C (400 MHz, $CDCl_3$) 172.5, 170.2, 166.9, 84.2, 79.2, 53.7, 52.9, 39.7; *m/z* (EIMS) 219 (1, M+1), 191 (3), 159 (26), 141 (6), 131 (25), 99 (100), 59 (93%).

2.1.4. Dimethyl (2*S*,3*S*)-tetrahydro-3-oxo-[(methylthio) methoxy]-5-oxo-2,3-furandicarboxylate (1c). To a solution of **1b** (2 g, 9.2 mmol) in DMSO (28 mL), acetic acid (3.5 mL) in acetic anhydride (20 mL) was added. The mixture was allowed to stand for three days. The reaction mixture was added to saturated aqueous solution of sodium bicarbonate (400 mL) and stirred for 1 h. It was extracted with chloroform (3×125 mL) and the combined chloroform extract was washed with saturated sodium bicarbonate solution (100 mL) followed by water (2×50 mL) and which was dried (sodium sulphate) and evaporated to give the crude product which was purified by column chromatography (17% hexane/chloroform) to give the *title compound* **1c** (0.75 g, 29%) as a yellow oil. [Found: C, 43.25; H, 4.95. $C_{10}H_{14}O_7S$ requires C, 43.32; H, 5.05%]; $[\alpha]_D^{23}=+47.3$ (*c* 2.3, $CHCl_3$); ν_{max} (liquid film) 1800, 1745 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.13 (1H, s, C*H*–COOMe); 4.74 (2H, s, SCH_2); 3.80 (3H, s, CH–COO*Me*); 3.79 (3H, s, C COO*Me*); 3.29 (1H, d, *J*=16.3 Hz, CH_aH$_b$C COOMe); 3.01 (1H, d, *J*=16.3 Hz, CH$_a$$H_b$C COOMe); 2.22 (3H, s, S*Me*); δ_C (400 MHz, $CDCl_3$) 172.0, 168.0, 167.0, 85, 81.7, 71.4, 53.4, 53.2, 36.6, 14.5; *m/z* (EIMS) 278 (4, M+1), 262 (3), 231 (66), 219 (38), 201 (18), 173 (7), 141 (33), 113 (50), 61 (100), 46 (40%).

2.1.5. Diethyl (2*S*,3*S*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylate (1d). To a precooled (−5–0°C) suspension of **1a** (1.0 g, 4.4 mmol) in dry ethanol (10 mL), thionyl chloride (0.7 mL, 10 mmol) was added. The mixture was then stirred for 48 h at room temperature. After filtration of the reaction mixture, pH of the filtrate was adjusted to 7.0, by adding saturated aqueous sodium bicarbonate and was extracted with chloroform (3×10 mL). The combined extract upon drying and evaporation gave the *title compound* **1d** (0.9 g, 77%) as a pale yellow liquid. [Found: C, 48.74; H, 5.69. $C_{10}H_{14}O_7$ requires C, 48.98; H, 5.71%]; $[\alpha]_D^{27}=-81.0$ (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 3500, 1800, 1740 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.90 (1H, s, C*H*–COOEt); 4.30 (4H, m, O$CH_2$$CH_3$×2); 3.10 (1H, d, *J*=16.7 Hz, CH_aH$_b$COHCOOEt); 2.8 (1H, d, *J*=16.7 Hz, CH$_a$$H_b$COHCOOEt); 1.18–1.32 (6H, m, $CH_2$$CH_3$×2); δ_C (400 MHz, $CDCl_3$) 172.0, 170.5, 170.0, 84.0, 75.0, 62.5, 62.0, 40.0, 15.0; *m/z* (EIMS) 246 (5.5, M+1), 218 (29.8), 200 (5.96), 188 (41.7), 172 (99.8), 156 (17.9), 144 (87.9), 127 (5.9), 114 (67.05), 104 (90.9), 99 (95.4), 88 (20.8), 76 (70), 59 (5.9), 42 (65.6%).

2.1.6. Diisopropyl (2*S*,3*S*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylate (1e). The procedure adopted for **1d** was followed with **1a** (1.0 g, 4.4 mmol), isopropyl alcohol (10 mL) and thionyl chloride (0.7 mL, 10 mmol). After work-up, gave the *title compound* **1e** (0.5 g, 41%) as a yellow oil. [Found: C, 52.32; H, 6.59. $C_{12}H_{18}O_7$ requires C, 52.55; H, 6.57%]; $[\alpha]_D^{27}=+32.0$ (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 3500, 1800, 1740 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.10–5.18 (1H, m, CH–COOC*H*Me_2); 3.96 (1H, s, C*H*–COOCHMe_2); 2.98 (1H, d, *J*=16.3 Hz, CH_aH$_b$COH-COOCHMe_2); 2.93 (1H, d, *J*=16.3 Hz, CH$_a$$H_b$COH-COOCH$Me_2$); 1.18–1.32 (12H, m, $CH(CH_3)_2$×2); δ_C (400 MHz, $CDCl_3$) 171.5, 170.1, 169.2, 83.9, 74.6, 71.7, 69.8, 40.0, 21.6, 21.5; *m/z* (EIMS) 274 (7.4, M+), 246 (60.3), 232 (34.2), 216 (21.8), 204 (37.1), 190 (15.8), 174 (23), 162 (52.3), 144 (58.7), 132 (43.6), 117 (12), 98 (15), 76 (52), 42 (100%).

2.1.7. Dibenzyl (2*S*,3*S*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylate (1f). To a suspension of **1** (4.0 g, 20.8 mmol) in dry benzyl alcohol (6.4 mL), *p*-toluene sulphonic acid monohydrate (50.0 mg, 0.26 mmol) and toluene (42.4 mL) were added. The mixture was then refluxed for 13 h at about 130°C. The mixture was allowed to cool, diluted with chloroform and poured into saturated aqueous sodium bicarbonate. The organic layer was seperated and the aqueous layer was extracted with chloroform (2×20 mL). The combined organic phase upon drying, evaporation and recrystallisation from chloroform–hexane gave the *title compound* **1f** (7.0 g, 90%, mp 81–83°C) as colourless crystals. [Found: C, 64.55; H, 4.87. $C_{20}H_{18}O_7$

requires C, 64.86; H, 4.89%]; $[\alpha]_D^{27}=+34.7$ (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 3500, 3100, 1820, 1700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25–7.34 (10H, m, CH_2Ar); 5.09–4.92 (4H, m, CH_2Ar); 4.87 (1H, s, C*H*–$COOCH_2Ar$); 3.07 (1H, d, *J*=13.5 Hz, $CH_aH_bCOHCOOCH_2Ar$); 2.80 (1H, d, *J*=13.5 Hz, $CH_aH_bCOHCOOCH_2Ar$); δ_C (400 MHz, $CDCl_3$) 171.8, 170, 166.2, 134.3, 133.8, 129.1, 128.8, 128.7, 128.6, 84.1, 78.9, 69.0, 67.9, 39.7; *m/z* (EIMS) 370 (7.0, M+), 280 (6.6), 251 (3.9), 180 (9.4), 107 (86.4), 91 (100), 65 (20.8), 43 (4.4%).

2.1.8. Isolation of (2*S*,3*R*)-tetrahydro-3-hydroxy-5-oxo-2,3,furandicarboxylic acid (Hibiscus acid, 2).[11] A: To the hexane washed, concentrated water extract (250 mL) of fresh leaves of *Hibiscus furcatus*/*Hibiscus sabdariffa* (1 kg), acetone (1 L) was added to precipitate insoluble materials. After evaporating the acetone, sufficient NaOH solution (8 M) was added to adjust the pH to 12.0. Addition of alcohol (ca 1 L) resulted in the precipitation of trisodium salt of **2**. The pH was readjusted to 2.0 by the addition of HCl (2 M) and which was concentrated to a syrup followed by extraction with acetone (2×250 mL). The crude acid (**2**) resulted, upon concentration, was recrystallised (ether–chloroform) to yield 10 g of **2** (1%) as colourless crystals.

B: Fresh calyxes (1 kg) of *Hibiscus sabdariffa* were extracted following the procedure described above yielding 16 g of **2** (1.6%). Mp 182°C requires[8] 182–183°C; [Found: C, 37.72; H, 3.15. $C_6H_6O_7$ requires C, 37.89; H, 3.16%]; $[\alpha]_D^{27}=+111$ (*c* 1.0, H_2O), lit.[8] $[\alpha]_D^{25}=+110$ (*c* 1.37, H_2O); ν_{max} (KBr) 3400, 1790, 1735 cm^{-1}; δ_H (400 MHz, acetone-d_6) 5.38 (1H, s, C*H*–COOH); 3.30 (1H, d, *J*=17.1 Hz, $CH_aH_bCOHCOOH$); 2.80 (1H, d, *J*=17.1 Hz, $CH_aH_bCOHCOOH$); δ_C (400 MHz, acetone-d_6) 173.2, 172.3, 167.1, 82.9, 78.4, 42.2; *m/z* (EIMS) 191 (2, M+1), 172 (1), 162 (5), 145 (60), 127 (12), 116 (38), 99 (84), 88 (100), 60 (48), 55 (28%).

2.1.9. Disodium(2*S*,3*R*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylate (2a). The procedure adopted for **1a** was followed with **2** and obtained as a colourless solid (2.0 g, 82%); [Found: C, 30.74; H, 1.70. $C_6H_4O_7Na_2$ requires C, 30.76; H, 1.71%]; $[\alpha]_D^{29}=+56.5$ (*c* 1.02, H_2O); ν_{max} (KBr) 3400, 1800, 1600 cm^{-1}; δ_H (400 MHz, D_2O) 5.17 (1H, s, C*H*–COONa), 3.21 (1H, d, *J*=17.8 Hz, $CH_aH_bCOHCOONa$); 2.24 (1H, d, *J*=17.8 Hz, $CH_aH_bCOHCOONa$); 2.27 (1H, s, C*OH*COONa); δ_C (400 MHz, D_2O) 179.9, 178.1, 173.9, 88.5, 80.5, 43.7; *m/z* (ESI) 257 (100, M+23), 238 (41.23), 195 (43.59), 168 (39.9), 142.1 (15.96%).

2.1.10. Dimethyl (2*S*,3*R*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylate (2b). A solution of **2** (1.0 g, 5.25 mmol in 25 mL ether) was treated with excess diazomethane in ether. The reaction mixture on concentration gave the *title compound* **2b** (1.13 g; 98%) as colourless crystals. Mp 128–129°C; [Found: C, 44.07; H, 4.61. $C_8H_{10}O_7$ requires C, 44.04; H, 4.59%]; $[\alpha]_D^{22}=+116$ (*c* 0.49, MeOH), lit.[8] $[\alpha]_D^{25}=+112$ (*c* 0.49, MeOH); ν_{max} (KBr) 3500, 1795, 1745 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.31 (1H, s, C*H*–COOMe); 3.95 (3H, s, CH–COO*Me*); 3.84 (3H, s, COH–COO*Me*); 3.10 (1H, d, *J*=20.3 Hz, $CH_aH_bCOHCOOMe$); 2.87 (1H, d, *J*=20.3 Hz, $CH_aH_bCOHCOOMe$); δ_C (400 MHz, DMSO-d_6) 172.7, 170.8, 166.1, 81.96, 77.90, 53.12, 53.03, 40.14; FABMS *m/z* 219 (66, M+1), 191 (2), 159 (100), 141 (10), 130 (38), 99 (100), 74 (25%).

2.1.11. Dimethyl (2*S*,3*R*)-tetrahydro-3-oxo-[(methylthio)methoxy]-5-oxo-2,3-furandicarboxylate (2c). The procedure adopted for **1c** was followed using acetic acid (1.5 mL), acetic anhydride (10 mL), **2b** (1 g, 4.6 mmol) and anhydrous DMSO (14 mL). After work-up and purification of the crude product by column chromatography (18% hexne/chloroform), gave the *title compound* **2c** 0.50 g 19.3% as a yellow oil. [Found: C, 42.43; H, 5.04. $C_{10}H_{14}O_7S$ requires C, 43.32; H, 5.05%]; $[\alpha]_D^{19}=-147.7$ (*c* 0.98, $CHCl_3$); ν_{max} (liquid film) 1800, 1745 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.10 (1H, s, C*H*–COOMe); 4.74 (2H, s, SCH_2); 3.77 (3H, s, CH–COO*Me*); 3.76 (3H, s, $COCH_2S$ CH_3COOMe); 3.23 (1H, d, *J*=1.9 Hz, $CH_aH_bCOCH_2SCH_3$-COOMe); 2.97 (1H, d, *J*=17.9 Hz, $CH_aH_bCOCH_2SCH_3$-COOMe); 2.14 (3H, s, S*Me*); δ_C (400 MHz, $CDCl_3$) 172.0, 168.0, 167.1, 85.0, 81.7, 71.4, 53.3, 53.1, 40.1, 14.5; *m/z* (EIMS) 278 (11.6, M+), 262 (13.3), 259 (24.3), 220 (8.7), 219 (64.9), 191 (29.9), 159 (100), 141 (14.6), 131 (11.9), 113 (5.2), 99 (40.3), 90 (4.5), 69 (2.98), 59 (17.1), 44 (25.3%).

2.1.12. Diethyl (2*S*,3*R*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylate (2d). The procedure adopted for **1d** was followed with **2a** (1.0 g, 4.4 mmol), ethanol (10 mL) and thionyl chloride (0.7 mL, 10 mmol). After work-up and purification gave the *title compound* **2d** (0.8 g, 68%) as a pale yellow liquid; [Found: C, 48.65; H, 5.70. $C_{10}H_{14}O_7$ requires C, 48.98; H, 5.71%]; $[\alpha]_D^{27}=+51.4$ (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 3450, 1800, 1740 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.10 (1H, s, C*H*–COOEt); 4.20 (4H, m, OCH_2CH_3×2); 3.90 (1H, d, *J*=19.6 Hz, CH_aH_bCOH-COOEt); 3.10 (1H, d, *J*=19.6 Hz, $CH_aH_bCOHCOOEt$); 1.18–1.32 (6H, m, CH_2CH_3×2); δ_C (400 MHz, $CDCl_3$) 173.0, 170.5, 170.0, 82.0, 74.0, 62.5, 62.0, 44.0, 15.0; *m/z* (EIMS) 246 (14.7 M+1), 218 (30.80), 188 (27.9), 144 (100), 114 (27.9), 103 (28), 98. (57.3), 82 (52.9), 75 (55.8) 57 (5.88), 46 (26.4), 42 (44.1%).

2.1.13. Diisopropyl (2*S*,3*R*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylate (2e). The procedure adopted for **1e** was followed with **2a** (1.0 g, 4.4 mmol), isopropyl alcohol (10 mL) and thionyl chloride (0.7 mL, 10 mmol). **2e** was isolated as a pale yellow oil (0.5 g, 41%); [Found: C, 52.47; H, 6.58, $C_{12}H_{18}O_7$ requires C, 52.55; H, 6.57%]; $[\alpha]_D^{27}=+41.2$ (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 3500, 1800, 1740 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.10 (1H, m, CH–COOC*H*Me_2); 4.90 (1H, m, COH–COOC*H*Me_2); 4.27 (1H, s, C*H*–$COOCHMe_2$); 3.10 (1H, d, *J*=17.3 Hz, $CH_aH_bCOHCOOCHMe_2$); 2.80 (1H, d, *J*=17.3 Hz, CH_aH_b-$COHCOOCHMe_2$); 1.10–1.30 (12H, m, $CH(CH_3)_2$×2); δ_C (400 MHz, $CDCl_3$) 171.7, 170.21, 169.5, 82.0, 74.6, 70.0, 68.4, 40.6, 21.5, 20.6; *m/z* (EIMS) 274 (2.9, M+), 246 (5.9), 232 (4.9), 216 (5.9), 204 (13.4), 190 (11.9), 174 (20.8), 162 (35.8), 144 (52.2), 132 (47.7), 117 (10.4), 98 (14.9), 86 (4.4), 76 (41.7), 42 (100%).

2.1.14. Dibenzyl (2*S*,3*R*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylate (2f). The procedure adopted for **1f** was followed with **2** (4.0 g, 20.8 mmol), benzyl alcohol (6.4 mL), *p*-toluene sulphonic acid monohydrate (50.0 mg,

0.26 mmol) and toluene (42.4 mL). After work-up and recrystallisation **2f** was isolated as colourless crystals (7.5 g, 90.9%); mp 90°C; [Found: C, 64.7; H, 4.9. $C_{20}H_{18}O_7$ requires C, 64.86; H, 4.89%]; $[\alpha]_D^{27}=+26.9$ (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 3495, 3100, 1820, 1790, 1750 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.26–7.38 (10H, m, CH_2Ar); 5.17–5.35 (4H, m, CH_2Ar); 5.10 (1H, s, CH–$COOCH_2Ar$); 3.03 (1H, d, J=7.47 Hz, $CH_aH_bCOHCOO$-CH_2Ar); 2.83 (1H, d, J=7.47 Hz, $CH_aH_bCOHCOOCH_2Ar$); δ_C (400 MHz, $CDCl_3$) 171.3, 170.8, 165.2, 134.6, 133.9, 129.2, 128.9, 128.8, 128.7, 85.6, 81.9, 69.5, 67.9, 40.3; *m*/*z* (EIMS) 370 (0.4, M+), 368 (0.7), 278 (10.3), 179 (9.7), 145 (2.5) 107 (78.52), 91 (100), 77 (11.1), 65 (34.07), 51 (5.93), 40 (7.41%).

Acknowledgements

This work was financially supported by the Department of Science and Technology vide project no: SP/S1/G-07/95/PRU. The authors thank Professor S. Chandrasekaran, IISc. Bangalore for valuable suggestions, SIF, IISc, Bangalore and RSIC, Madras for recording the NMR spectra, CDRI, Lucknow for obtaining the Mass spectra and elemental analysis data, IIT Madras and RRL, Trivandrum for measuring the optical rotation values.

References

1. Morrison, J. D., Ed.; *Asymmetric Synthesis*, Academic: New York, 1983–1985; Vols. 1–5, p 23.
2. Coppola, G. M.; Schuster, H. F. α-*Hydroxy Acids in Enantioselective Syntheses*; VCH: Weinheim, 1997.
3. Ghosh, A. K.; Koltun, E. S.; Bileer, G. *Synthesis* **2001** (9), 1281.
4. Lewis, Y. S.; Neelakantan, S.; Anjanamurthy, C. *Curr. Sci.* **1964**, *3*, 82–83.
5. Lewis, Y. S.; Neelakantan, S. *Phytochemistry* **1965**, *4*, 619–625.
6. (a) *The Useful Plants of India*; Amasta, S. P., Ed.; Publication and Interpretation Directorate, Council of Scientific and Industrial Research: New Delhi, 1986; pp 229–232. (b) Kirtikar, K. R.; Basu, B. D. *Indian Medicinal Plants*; Vol. 1, p 326 and 329.
7. (a) Guthrie, W. R.; Kierstead; Wightman, R. US Patent No. 4005086. (b) Guthrie, W. R.; Kierstead, Wightman, R. US Patent No. 4006166. (c) Guthrie, W. R.; Kierstead; Wightman, R. US Patent No. 4007208. (d) Moffett, S. A.; Bhandari, A. K.; Ravindranath, B. US Patent No. 5536516. (e) Moffett, S. A.; Bhandari, A. K.; Ravindranath, B. US Patent No. WO 9605741 A1 960229. (f) Majeed, M.; Badmaev, V.; Ranjendran, R. US Patent No. WO 9636585 A1 961121. (g) Triscari, J.; Sullivan, A. C. *Chem. Abstr.* **1977**, *86*, 186629r. (h) Brunengraber, H.; Lowenstein, J. M. *Chem. Abstr.* **1976**, *85*, 41531x. (i) Szutowicz, A.; Lysiak, W.; Angielski, S. *Chem. Abstr.* **1977**, *87*, 195626k. (j) Lowenstein, J. M.; Brunengraber, H. *Chem. Abstr.* **1982**, *96*, 30421n.
8. Boll, P. M.; Sorensen, E.; Balieu, E. *Acta Chem. Scand.* **1969**, *23*, 286–293.
9. (a) Mori, K. *Tetrahedron* **1975**, *31*, 3011–3012. (b) Ghosh, A. K.; Koltun, E. S.; Bilcer, G. *Synthesis* **2001**, 1281–1283. (c) Moret, E.; Sclosser, M. *Tetrahedron Lett.* **1984**, *25*, 4491–4494. (d) Cardellach, J.; Estopu, C.; Font, J.; Moreo-Manas, M.; Ortuno, R. M.; Sanchez-Ferrando, F.; Valle, S.; Vilamjo, L. *Tetrahedron* **1982**, *38*, 2377–2384. (e) Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449–1452. (f) Drioli, S.; Felluga, F.; Forzato, C. *J. Org. Chem.* **1998**, *63*, 2385–2388. (g) Herrman, J. L.; Schlessingr, R. H. *J. Chem. Soc., Chem. Commun.* **1973**, 711–712. (h) CananKoch, S. S.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725–2729. (i) Kunesch, G.; Zagatti, P. *Tetrahedron Lett.* **1981**, *22*, 5271–5274. (j) Vigneron, J. P.; Merie, R. *Tetrahedron Lett.* **1982**, *23*, 5051–5054. (k) Doolittle, R. E.; Heath, R. R. *J. Org. Chem.* **1984**, *49*, 5041–5045.
10. Ibnusaud, I.; Thomas, P. T.; Thomas, B. US Patent No.: 6,147,228; Indian Patent Appl. No.: 2248/Del/98, 1998.
11. Ibnusaud, I.; Nair, R. R.; Philip, T.; Thomas, S. US Patent No.: 6,127,553; Indian Patent Appl. No.: 2249/Del/98, 1998.
12. Ibnusaud, I.; Gopinath, C.; Thomas, B. Indian Patent Appl. No. 884/Del/2000.
13. Ibnusaud, I.; Thomas, G.; Sasi, P. V. Indian Patent Appl. No. 885/Del/2000.
14. Ibnusaud, I.; Nair, R. R. Indian Patent Appl. No. 886/Del/2000.
15. Ibnusaud, I.; Thomas, P. T. Indian Patent Appl. No. 887/Del/2000.
16. Thomas, P. T. Ph.D. Thesis, Mahatma Gandhi University, Kerala, India, 2000.
17. Rani. R. N. Ph.D. Thesis, Mahatma Gandhi University, Kerala, India, 2001.