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Tetrahedron Letters 44 (2003) 1247–1249

TETRAHEDRON
LETTERS

Biologically interesting chiral 3,4-disubstituted pyrrolidines from optically active hydroxycitric acid lactones

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Received 24 October 2002; revised 29 November 2002; accepted 6 December 2002

Abstract—Starting with (2*S*,3*S*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid (garcinia acid), isolated from the chiral pool, and alkyl amines, 3,4-disubstituted pyrrolidinediones, analogues of naturally occurring mescaline isocitrimidelactone, have been obtained in one-pot. These imides were subsequently converted into optically active pyrrolidines. © 2003 Elsevier Science Ltd. All rights reserved.

Chiral pyrrolidines are common structural subunits found in a variety of natural and unnatural bioactive products.¹ Depending on the substitution pattern and functionality, pyrrolidines have been shown to be effective antibacterials, neuroexcitatory agents, potent venoms, glycosidase inhibitors and fungicides.² Numerous biological compounds possess pyrrolidine rings as their framework and some of them are pharmaceutically important. In addition, enantiomerically pure pyrrolidines are also useful chiral auxiliaries.³ Hence, preparation of enantiopure polysubstituted pyrrolidine derivatives is quite a challenging subject. A number of stereoselective methods for the synthesis of 2,5-disubstituted pyrrolidines have been reported during the last decade.⁴ These include cyclisation of bis-allylic amines, 1,3-dipolar cycloaddition, reduction–cyclisation of γ -aza derivatives of ketones, synthesis from aza heterocycles etc. Nonetheless, general and effective methods for the selective synthesis of 3,4-polysubstituted pyrrolidines are noticeably rare.⁵ Since a number of natural products containing pyrrolidines with this specific substitution pattern are of particular interest, a search for improved methods for their preparation is warranted. This communication reports a simple synthesis of chiral 3,4-disubstituted pyrrolidines from optically active hydroxycitric acid lactones.

Chiral hydroxy acids such as malic acid and tartaric acid have been extensively employed for the construction of nitrogen heterocycles like pyrrolidines, pyrrolizidine alkaloids etc.⁶ Though optically active hydroxy acids namely Garcinia acid **1** and its diastereomer Hibiscus acid **2** have been known since the

1960s, and can be easily isolated from natural sources following our recently reported methods,⁷ no efforts have been made to explore them as potential synthons in organic synthesis (Fig. 1).

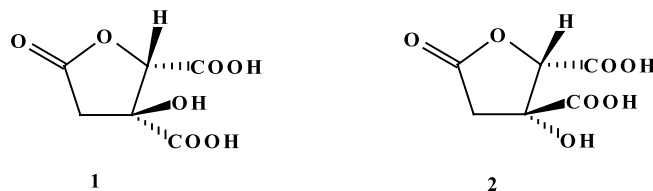
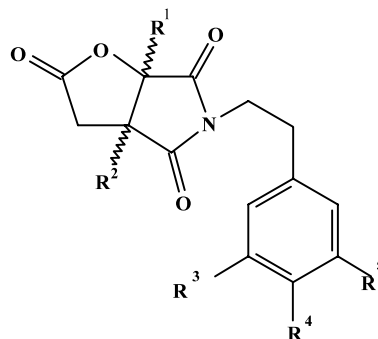


Figure 1.

When **1** is successively treated with acetyl chloride, appropriate amines and acetyl chloride, cyclic imides **4a–d** are obtained in good yields. From Garcinia acid dimethylester **3**, imides **4a'–d'** were obtained by refluxing with appropriate amines in toluene (Scheme 1). The

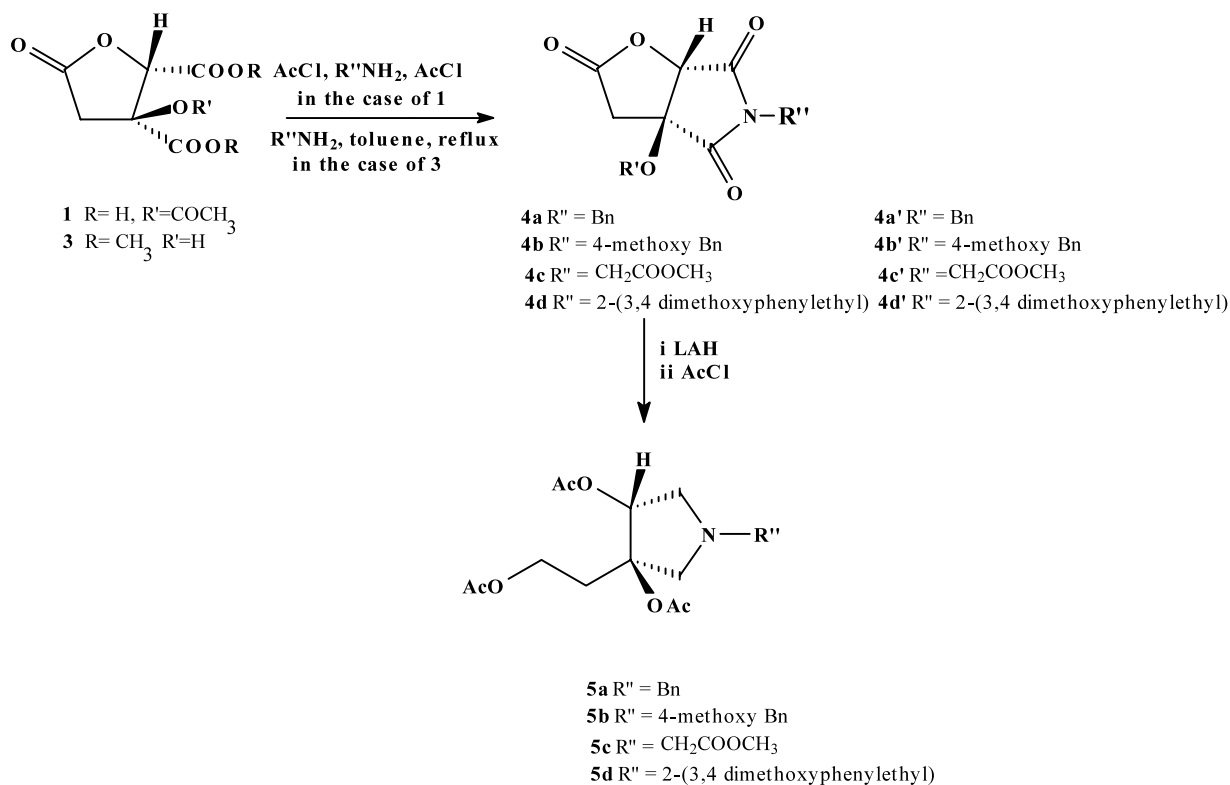


9 $R^1 = R^2 = H, R^3 = R^4 = R^5 = OCH_3$

4d $R^1 = H, R^2 = OCOCH_3, R^3 = H, R^4 = R^5 = OCH_3$

Figure 2.

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Scheme 1.

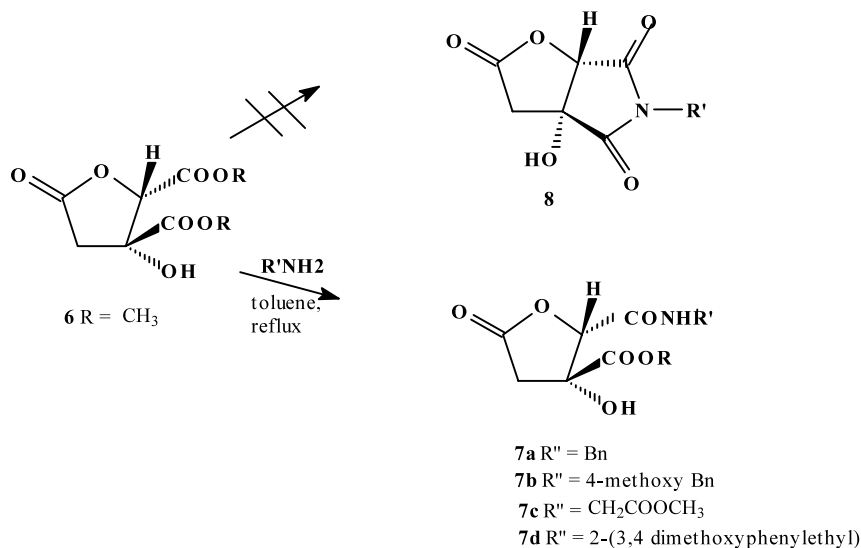
IR, ^1H and ^{13}C NMR spectra clearly indicate the presence of γ -butyrolactone and cyclic imide moieties.⁹ The imides were further reduced with LAH followed by refluxing with acetyl chloride to give 3,4-disubstituted pyrrolidines **5a–d**.

It is interesting to note that cyclic imides **4d** and **4d'** are analogues of the less well known mescaline isocitrimide lactone **9**, a psychotic bioprinciple obtained from mes-cal (*Lophophora williamsii*) a rare and very slow growing solitary cactus, which is also classified as an

endangered species with very low active principle content⁸ (Fig. 2).

When the experiment is repeated with hibiscus acid **2**, or its ester **6** and alkyl amines, no cyclic imide is formed as the expected product **8** would be *trans* fused. Instead, mono amides **7a** to **7d** were isolated in good yields (Scheme 2).

Further use of **4**, **5** and **7** for the synthesis of biologically interesting molecules is underway.



Scheme 2.

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 SIF, I.I.Sc., Bangalore for recording the NMR spectra CDRI, Lucknow for obtaining the mass spectra and elemental analysis data, RRL, Trivandrum for measuring the optical rotation values.

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- General procedure for the synthesis of a representative example (**4a**) and its spectral data.
A suspension of Garcinia acid **1** (1 g, 5 mmol) in 4 ml of acetyl chloride was refluxed for 2 h. The resulting mixture was concentrated in vacuo to give a white solid, which was dissolved in 5 ml of THF. Benzylamine (0.52 g, 5 mmol) was added, the mixture was stirred at rt for 4 h and thoroughly concentrated in vacuo. Acetyl chloride (5 ml) was added and the mixture was further refluxed for 18 h. After concentration in vacuo, recrystallisation (EtOH) afforded **4a** as white crystals (0.8 g, 52%), mp 165°C; $[\alpha]_D^{27} = +136.24$ (c 1.0, CHCl₃); ν_{\max} (KBr) 1790; 1740; 1250; 1030; 750 cm⁻¹; δ_H (400 MHz, CDCl₃): 7.45–7.25 (m, 5 arom H); 5.31 (1H); 4.8–4.65 (q, 2H $J=7$ Hz); 3.9 (d, 1H, $J=9.8$ Hz); 3.2 (d, 1H, $J=9.8$ Hz); 2.2 (s, 3H) ppm. δ_C (400 MHz, CDCl₃) 170.6, 170.4, 170.1, 167.3, 134, 128.9, 128.8, 128.5, 128.4, 79.7, 79.8, 43.3, 35.9, 20.1; m/z (EIMS) 303 (M⁺, 5.9), 243 (41.72), 199 (16.39), 132 (28), 111 (90), 91 (62.58), 83 (14.9), 77 (5.9), 57 (41.7), 43 (100%); (b) satisfactory elemental analytical data have been obtained for all new compounds.