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Synthesis of enantiopure concave (+)-avenaciolide and (−)-canadensolide skeletons

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Abstract—Simultaneous regio- and chemoselective reduction of the carboxyl group of (2*S*,3*S*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid (garcinia acid), isolated from plant sources in large amounts, has been carried out to reach the core concave bislactone structures of fungal metabolites (+)-avenaciolide and (−)-canadensolide in one and two steps, respectively.

Natural and synthetic optically active γ-butyrolactones and related bislactones have attracted much attention due to their biological and functional properties.[1] Also, these molecules play key roles as building blocks for the syntheses of many types of natural product and potential drugs.[2] The favourable cis/trans orientation of adjacent C2 and C3 carboxyl groups, the matching absolute configurations and appropriate number of carbon atoms make **1** and **2** synthetically under utilised naturally occurring lactones, which can be isolated in large amounts from cheap plant sources[3] (Fig. 1). They could be precursors for the synthesis of γ-butyrolactone-based natural products.

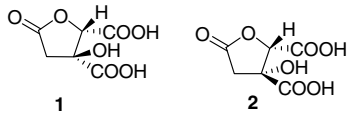

Figure 1.

Among these, bislactones (+)-avenaciolide (**3**), (+)-isoavenaciolide (**4**), ethisolide (**5**), (−)-canadensolide (**6**), xylobovide (**7**), sporothriolide (**8**) and (+)-dihydrocanadensolide (**9**) are challenging and fascinating targets due to their concave structure, with all cis stereochemistry of the adjacent methine protons.[4] Almost all the known methods for the construction of the concave skeleton are tedious, time consuming and often result in racemic products.[5]

A retrosynthetic analysis of **3** and **6** from **1** depicts the involvement of **12** and **14** to be obtained by the selective reduction of C3 and C2 carboxyls independently. The Swern oxidation of **12** and **14** followed by the nucleophilic addition of alkyl donor synthons, subsequent deoxygenation, followed by the introduction of an α-methylene group would be expected to give **3** and **6**, respectively (Scheme 1).

Taking advantage of the presence of the tertiary hydroxyl group at C3 of **1**, a regioselective reduction was successfully carried out.[6] Treatment of dimethyl (2*S*,3*S*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylate (**16**) with borane dimethyl sulfide (BMS) in tetrahydrofuran and catalytic $NaBH_4$ resulted in the formation of only **12**, methyl (2*S*,3*R*)-tetrahydro-3-hydroxy-3-(hydroxymethyl)-5-oxo-2 furancarboxylate. Attempted chromatographic purification of **12** over silica gel afforded **10**, (3a*R*,6a*S*)-3a-hydroxytetrahydrofuro[3,4-*b*]furan-2,6-dione, the (+)-avenaciolide skeleton as a sharp melting solid (mp, 136–138 °C) in 81% yield, $[\alpha]_D^{20}$ +20.64, (*c* 0.28, H_2O) (Scheme 2). Acetylation of crude **12** afforded **17**.

On the other hand selective reduction[7] of the C2 carboxyl of **1** was carried out after protection of the C3 geminal carboxylate and hydroxyl using

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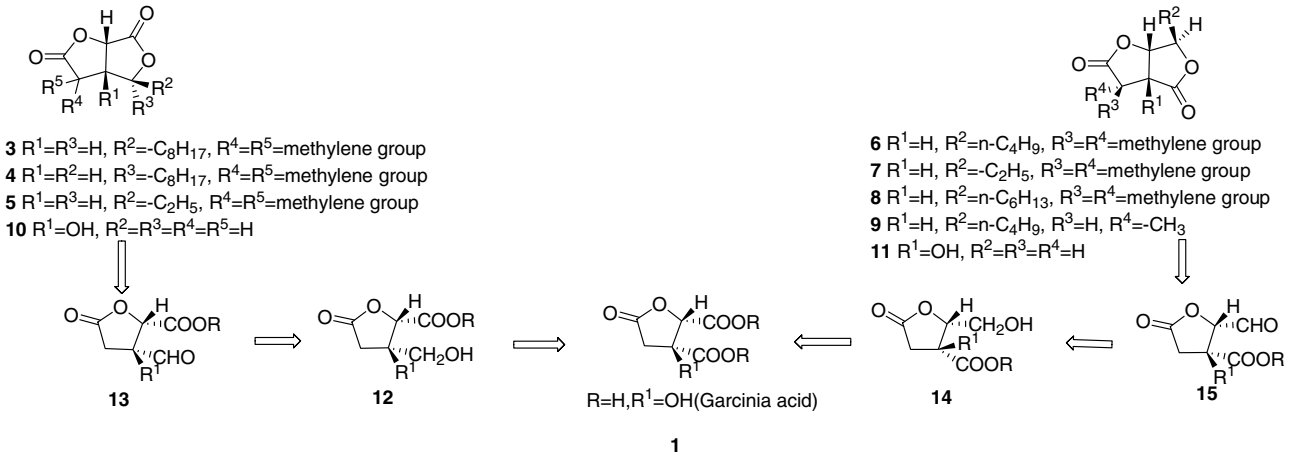
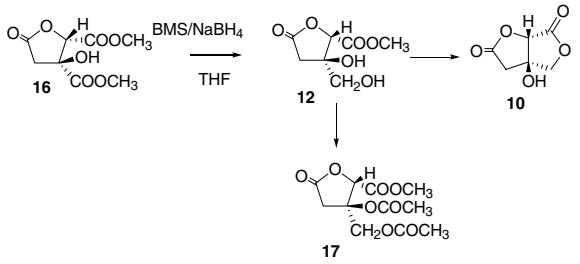
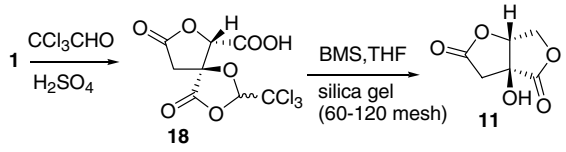


Scheme 1.



Scheme 2.

trichloroacetaldehyde.[8] Reduction of **18** (5*S*,6*S*)-4,8 dioxo-2-(trichloromethyl)-1,3,7-trioxaspiro[4,4]nonane-6-carboxylic acid using BMS/THF followed by purification over silica gel directly resulted in the isolation of **11** (3a*S*,6a*S*)-3-hydroxytetrahydrofuro[3,4-*b*]furan-2,4-dione, the canadensolide skeleton as a crystalline solid (mp 143–145 °C, 72% yield), $[\alpha]_D^{20}$ −89.067 (*c* 0.1, H_2O) (Scheme 3).



Scheme 3.

Structures **10** and **11** were confirmed on the basis of their IR, ^1H, ^{13}C NMR and mass spectra. The ^1H NMR spectra of **10** showed two double doublets at 2.95 δ and 4.35 δ corresponding to the methylene protons at C3 and C4, a singlet at 5.05 δ corresponding to the C6a methine proton, whereas **11** showed a double doublet at 3.1 δ, a multiplet at 4.6 δ and a doublet of doublets at 5.03 δ corresponding to protons at C3, C6, C6a, respectively.

A single crystal X-ray analysis confirmed the concave nature and absolute configuration of **10** and **11** (Figs. 2 and 3).

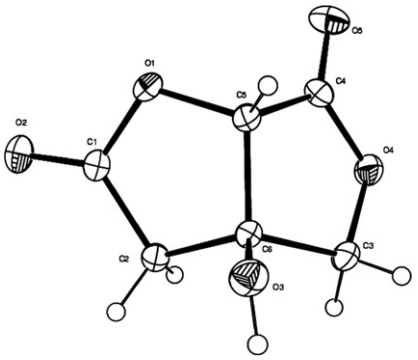


Figure 2. The ORTEP diagram of **10**.

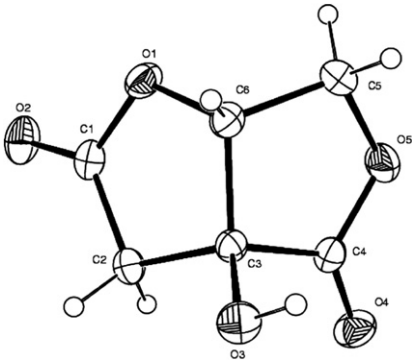
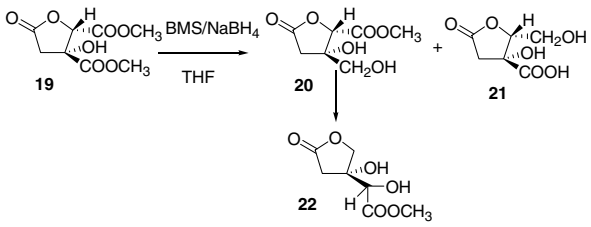


Figure 3. The ORTEP diagram of **11**.

Reduction of **19**, a diastereomer of **16**, using BMS/$NaBH_4$ showed no preference for either of the carboxyl groups, but gave an inseparable mixture of **20** and **21** in equal amounts. Attempted separation of **20** and **21** using column chromatography resulted in the isolation of **22** methyl (2*R*)-2-hydroxy-2-[(3*S*)-3-hydroxy-5-oxotetrahydro-3-furanyl] ethanonate.

Structure **22** was confirmed on the basis of IR, ^1H, ^{13}C NMR and mass spectra, {$[\alpha]_D^{20}$ +21.516 (*c* 0.1, $CHCl_3$)} (Scheme 4).



Scheme 4.

The poor selectivity observed in the case of **19**, where the C2–C3 carboxylic groups are trans to each other, provides an explanation for the site selectivity reported earlier.[6]

Thus we suggest that the site selectivity in the case of **16** over **19** could be explained by an activation energy difference between the two possible intermediates **23** and **24**, where the boron atom intramolecularly coordinates the carbonyl oxygens to form the five-membered or the six-membered intermediates **23** and **24** (Fig. 4).

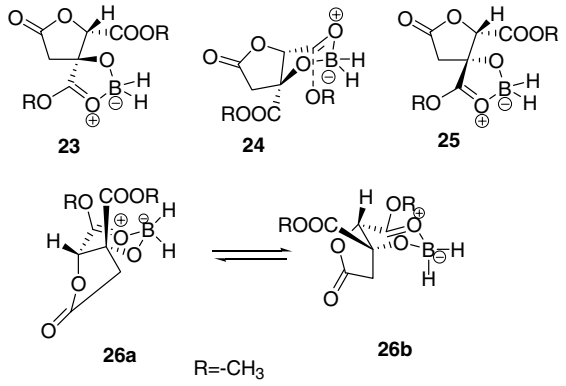


Figure 4.

Intermediate **24** would experience severe 1,3-diaxial interaction between the OCH_3 and the hydrogen on the boron atom. Also the steric interaction of C3 ester group with the OCH_3 group as well as with the hydrogen on the boron atom is much more severe. This is because of the short boron–oxygen bond length.[7]

In the case of **19**, the possibility of forming five- and six-membered intermediates exists (**25** and **26**). However, **26** is conformationally mobile and conformer **26b** would be preferred as there are three diaxial interactions in **26a** and only two in **26b** (Fig. 4). It is evident that there are only two 1,3-diaxial interactions in the case of **26** and three in **24** clearly favouring the formation of **26**.

In conclusion, an expeditious semisynthetic route for the construction of concave molecules **10** and **11** has been developed from abundantly available **1**. An extended mechanistic explanation for the selective reduction of **1** and **2** using BMS/$NaBH_4$ is provided. Synthesis of **3**, **6** and several chiral γ-butyrolactones based molecules with matching stereochemistry to that in **1** and **2** is underway.

Acknowledgements

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Supplementary data

Experimental procedures and full spectroscopic data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.081.

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