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Isolation and Synthesis of 3,4-Bis(indol-3-yl)pyrrole-2,5-dicarboxylic Acid Derivatives from the Slime Mould *Lycogala epidendrum*

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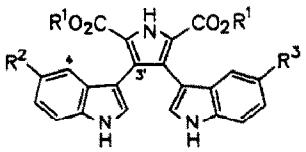
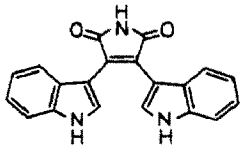
Abstract: Fruit bodies of the myxomycete *Lycogala epidendrum* contain the title compounds **1a-c** and **2**, staurosporinone (**3**) and traces of bisindolylmaleimides. Lycogalic acid A dimethyl ester (**1a**) has been synthesized from methyl 3-(indol-3-yl)pyruvate in a one-pot reaction.

Lycogala epidendrum (L.) Fries is a common slime mould with ubiquitous distribution. Recently, *Asakawa et al.*[1] isolated three novel metabolites from fruit bodies (aethalia) of this species and determined their structures as **1a**, **1b** and **1c**. In the case of **1c** the unusual 5,5'-substitution pattern was unambiguously established by X-ray analysis of the permethyl derivative. In continuation of our work on secondary metabolites from myxomycetes[2] we have independently investigated *L. epidendrum*. Gel chromatography of its methanolic extract followed by preparative HPLC of the crude fractions, which were first monitored by analytical HPLC with diode-array detection,[3] yielded three main components which were named lycogalic acid dimethyl esters A, B and C.[4] From their spectral data the structures **1a-1c**[5] were deduced, in agreement with lit.[1] In addition, we were able to isolate lycogalic acid A (**2**)[6] and staurosporinone (**4**)[7,8] together with traces of arcyriarubin A (**3**) and arcyriaflavin A (**5**).[9]



	1a	1b	1c	2
R^1	Me	Me	Me	H
R^2	H	OH	OH	H
R^3	H	H	OH	H



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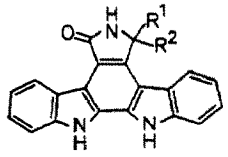
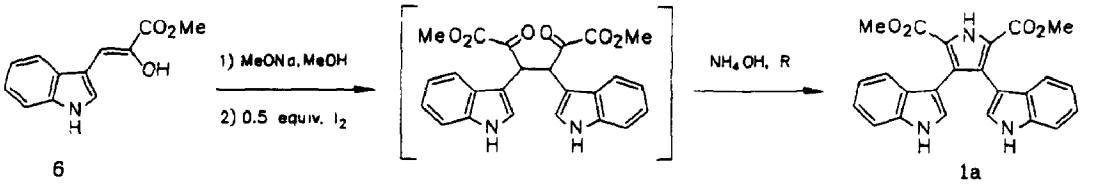


	4	5
R^1	H	} O
R^2	H	

The lycogalic acids are an interesting addition to the bisindolylmaleimide group of myxomycete metabolites,[2,10] and their co-occurrence with arcyriarubin A (**3**) in *L. epidendrum* points to a close biosynthetic relationship. Recently, it was shown that in cultures of *Chromobacterium violaceum* lycogalic acid A ('chromopyrrolic acid') is derived from tryptophan.[6] It is tempting to assume that lycogalic acid A is formed

by oxidative dimerization of 3-(indol-3-yl)pyruvic acid followed by reaction of the resulting 1,4-dicarbonyl intermediate with an equivalent of ammonia. We have used this idea for a simple one-pot synthesis of **1a** from methyl 3-(indol-3-yl)pyruvate (**6**). For this purpose, a methanolic solution of **6** is treated with NaOMe, and the resulting enolate oxidized with 0.5 equiv. of iodine. After addition of aqueous NH_4OH the mixture is refluxed for one hour. Usual work-up afforded **1a** in 42% yield, in every respect identical with the natural product.



6 1a

This reaction can also be applied to other arylpyruvates. Thus, methyl 3-(4-hydroxyphenyl)pyruvate and methyl 3-phenylpyruvate gave the corresponding dimethyl 3,4-diarylpyrrol-2,5-dicarboxylates in 52 and 60% yield, respectively, after treating the crude reaction products with diazomethane.

References and Notes

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2. M. Gill, W. Steglich, *Progr. Chem. Org. Nat. Prod.* **1987**, *51*, pp. 216-226; W. Steglich, *Pure & Appl. Chem.* **1989**, *61*, 281.
3. HPLC: a) LiChrosorb RP 18, 7 µm (Merck), 250 x 4 mm, linear gradient: 0 min: MeOH/H_2O 1:9, 40 min MeOH, flow rate 1 ml/min, retention times: **1a** 32.8, **1b** 27.2, **1c** 22.2, **4** 36.8, **5** 39.8 min.
   b) Nucleosil C18, 5 µm (Macherey & Nagel, Düren), 250 x 4 mm, linear gradient: 0 min: MeCN/H_2O 1:9 + 0.5 % TFA, 30 min: MeCN; flow rate 1 ml/min, retention times: **2** 18.3, **3** 20.5 min.
4. Prof. Asakawa has kindly agreed to use the names lycogalic acid A, B, C for **1a-1c**, respectively, instead of lycogarubin C, B, A proposed in his earlier publications [lit. 1]. We thank Prof. Asakawa (Tokushima) for kindly providing us with a preprint of his recent publication.
5. Selected spectroscopic data: **1c**: UV (MeOH): λ_{max} (lg ε) = 224 (4.70), 268 (4.53), 298 sh (4.20), 332 nm sh (3.63); ^{13}C-NMR ([D_6]acetone, 100.6 MHz): δ = 126.3 (Dd, *J* = 182.0/4.0 Hz, C-2), 108.5 (m, C-3), 131.6 (m, C-3a), 112.1 (D, *J* = 158.0 Hz, C-4), 111.7 (Dd, *J* = 157.6/4.6 Hz, C-5), 151.4 (d, *J* = 9.0 Hz, C-6), 104.8 (Dd, *J* = 158.0/4.0 Hz, C-7), 129.9 (ddd, *J* = 6.6/6.2/4.8 Hz, C-7a), 123.6 (d, 2.0 Hz, C-2'), 126.2 (d, br, 7.6 Hz, C-3'), 161.5 (dq, *J* = 3.8/2.0 Hz, COOMe), 51.5 (Q, J = 147.0 Hz, .COOMe).
   2: UV (MeOH): λ_{max} (lg ε) = 226 (4.65), 264 (4.35), 290 sh (4.23), 332 nm sh (3.66); ^{1}H-NMR ([D_4]MeOH): δ = 6.89 (s, 2-H), 7.19 (d, *J* = 7.2 Hz, 4-H), 6.81 (dd, *J*= 7.2/7.0 Hz, 5-H), 6.98 (dd, *J* = 8.0/7.0 Hz, 6-H), 7.24 (d, *J* = 8.0 Hz, 7-H); ^{13}C-NMR ([D_4]MeOH, 100.6 MHz): δ = 125.8 (D, *J* = 182 Hz, C-2), 110.1 (dd, *J* = 7.0/3 0 Hz, C-3), 129.3 (dd, *J* = 7.8/6.2 Hz, C-3a), 120.7 (Dd, *J* = 158.0/8.0 Hz, C-4), 119.2 (Dd, *J* = 158.0/8.0 Hz, C-5), 121.4 (Dd, *J* = 158.0/8.0 Hz, C-6), 111.7 (Dd, *J* = 158.0/7.8 Hz, C-7), 137 4 (dd, *J* = 8 6/8.0 Hz, C-7a), 125.0 (s, br, C-2'), 126.1 (s, br, C-3'), 165.1 (s, COOH).
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