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SYNTHETIC STRATEGIES BASED ON AROMATIC METALATION - CROSS COUPLING LINKS. REGIOSPECIFIC SYNTHESIS OF THE PHENANTHRENE NATURAL PRODUCT GYMNOPUSIN

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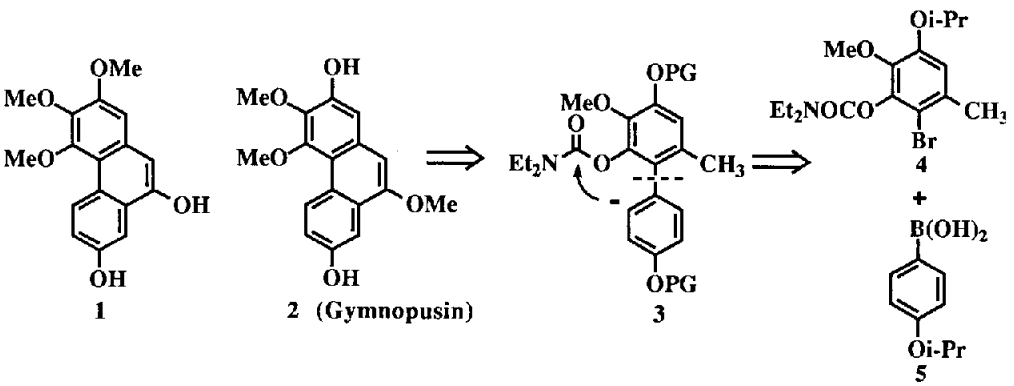
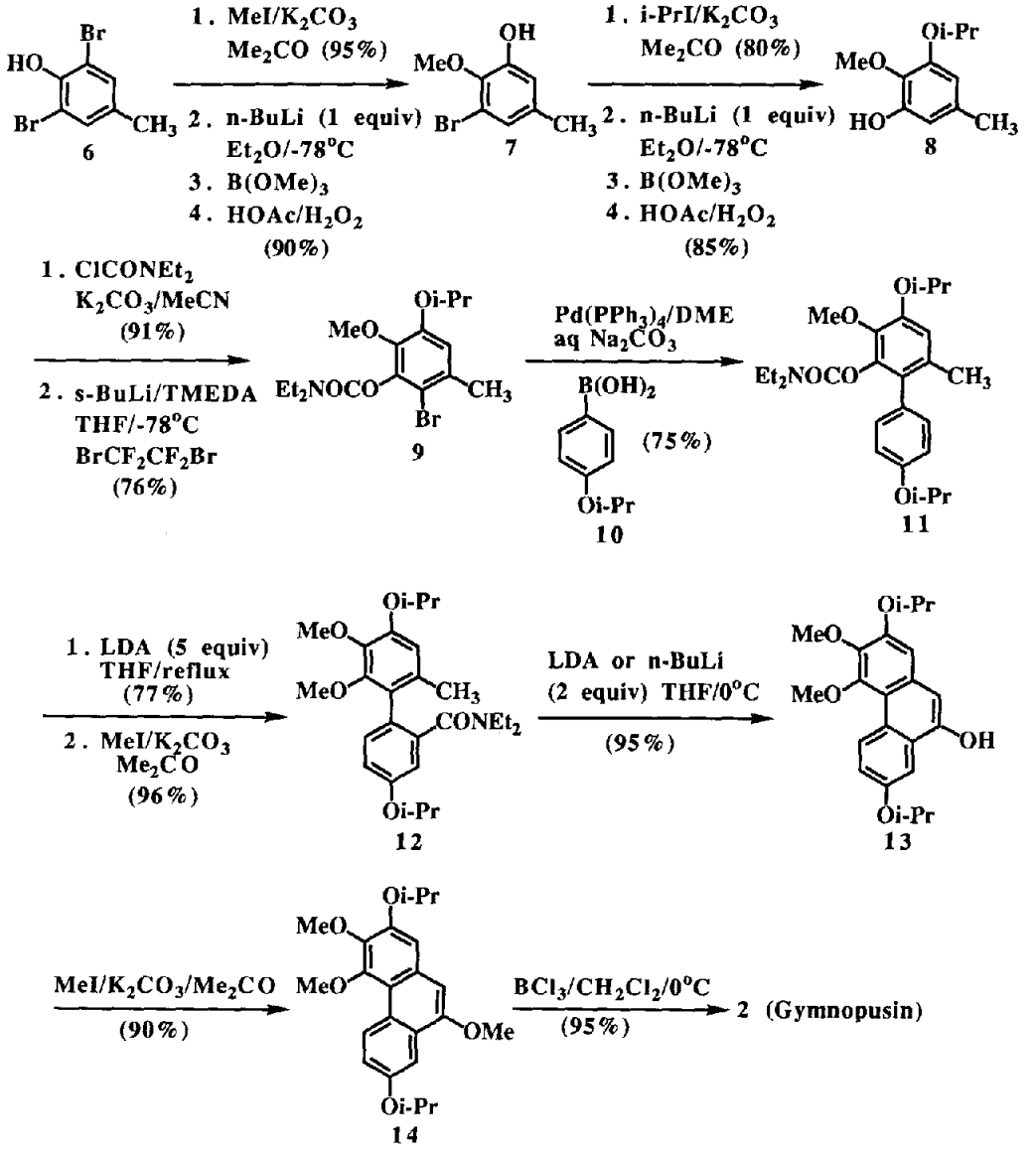
Summary: An efficient synthesis of gymnopusin (**2**) using ortho metalation, Suzuki cross coupling, and new anionic Fries rearrangement (**3**) steps has been achieved.

Gymnopusin, an unusual C-9(-10)-oxygenated phenanthrene isolated from *Bulbophyllum gymnopus* (Orchidaceae) was originally assigned structure **1**,[1] but was reassigned structure **2** on the basis of reinterpretation of spectral data[2,3] and synthesis of both **1** and **2**.[3] As part of efforts aimed to develop combinational directed ortho metalation - cross coupling strategies,[4] we also synthesized[5] **1** by application of our new general route to 9-phenanthrols[6] and established its nonidentity with the natural product. Herein we report a total synthesis of gymnopusin which illustrates the versatility of the aromatic metalation[7] - cross coupling[8] connection (**Scheme 1, 4 + 5 → 3**) and incorporates a new remote anionic Fries rearrangement[9] (**3**).



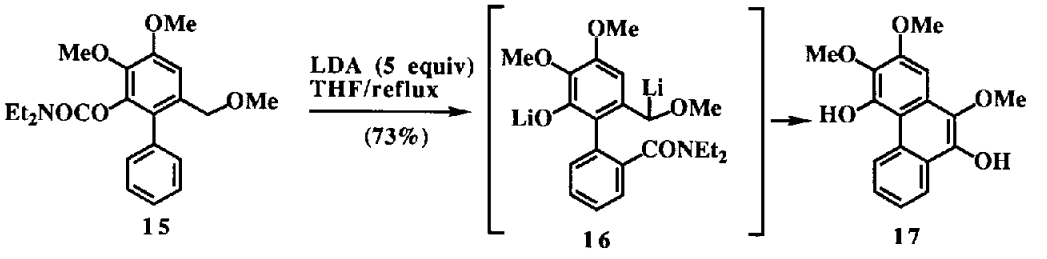
Scheme 1


1. MeI/K2CO3
Me2CO (95%)
2. n-BuLi (1 equiv)
Et2O/-78°C
3. B(OMe)3
4. HOAc/H2O2
(90%)
1. i-PrI/K2CO3
Me2CO (80%)
2. n-BuLi (1 equiv)
Et2O/-78°C
3. B(OMe)3
4. HOAc/H2O2
(85%)
1. ClCONEt2
K2CO3/MeCN
(91%)
2. s-BuLi/TMEDA
THF/-78°C
BrCF2CF2Br
(76%)
Pd(PPh3)4/DME
aq Na2CO3
(75%)
1. LDA (5 equiv)
THF/reflux
(77%)
2. MeI/K2CO3
Me2CO
(96%)
LDA or n-BuLi
(2 equiv) THF/0°C
(95%)
MeI/K2CO3/Me2CO
(90%)
BCl3/CH2Cl2/0°C
(95%)
2 (Gymnopusin)
6
7
8
9
10
11
12
13
14

Scheme 2

To initiate the synthesis (**Scheme 2**), commercially available 2,6-dibromo-4-methylphenol **6** was methylated and the resulting methyl ether was subjected to mono metal-halogen exchange[10] followed by the trimethyl borate - hydrogen peroxide oxidation protocol[11] to afford **7**. Isopropylation followed by a second metal-halogen exchange - $B(OMe)_3/H_2O_2$ sequence furnished **8** in which the three contiguous oxygen functionalities are differentiated. Phenol **8**, equipped with the powerful carbamate ortho metalation director,[7] was subjected to regiospecific metalation - bromination with $BrCF_2CF_2Br$, a modification of a previously reported procedure,[12] to give the aryl bromide **9**. Cross coupling of **9** with the aryl boronic acid **10**[13] under modified Suzuki conditions[14] led to the biaryl **11** in good yield. The key remote anionic ring to ring carbamoyl transfer[9] proceeded smoothly using excess LDA in refluxing THF; subsequent methylation provided the biaryl amide **12**. As precedented,[6] treatment with LDA (or n-BuLi) resulted in a vinylogous ortho-tolyl metalation - cyclization to give the known[3] phenanthrol **13**. Methylation delivered the highly unstable methyl ether **14** which was immediately treated with BCl_3 to afford gymnopusin (**2**)[15] in excellent yield.

The implied driving force of aromatization in the overall conversion of **11** to **13** raises the question why, under the excess LDA conditions, the reaction proceeds only to the biaryl amide stage (**12**). This question is given immediacy by the observation that exposure of the related biaryl **15** (**Scheme 3**) to identical conditions leads to the phenanthrol **17** in good yield as the sole isolable product. The acidifying and coordination effects of the benzylic methoxy group, the major structural difference between the probable intermediate **16** and that derived from **11**, appear to be responsible for inducing cyclization. Efforts to understand structure-reactivity relationships in these multi-anionic transformations are in progress.



Scheme 3

The present synthesis of gymnopusin (**2**), achieved in 12 steps and 18% oveall yield,[16] follows a directed ortho metalation - cross coupling theme and is highlighted by a remote anionic Fries rearrangement. Broader application of these tactics to the synthesis of polycondensed aromatics and heteroaromatics, including alkaloids, may be anticipated.

References and Footnotes:

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11. Iwao, M.; Mahalanabis, K.K.; Wantanabe, M.; de Silva, S.O.; Snieckus, V. *Tetrahedron* **1983**, *39*, 1955.

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13. Prepared from 4-isopropoxybromobenzene by sequential treatment with n-BuLi (1 equiv, THF/-78 °C/10 min) and $B(OMe)_3$ (2 equiv) followed by acidic work up, and used without purification.

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15. Mp 194-196 °C, lit[1] mp 192 °C, lit[3] mp 202-204 °C; diacetate mp 125-126 °C, lit[1] mp 113 °C, lit[3] mp 126.5-127 °C, mixture mp 124-126 °C, identical IR, ^1H NMR, MS spectra with those reported.[1-3]

16. Comparable (13 steps, 19.9% overall yield) to the synthesis of Hughes and Sargent.[3]

17. All new compounds show analytical and spectral (IR, NMR, MS) data consistent with the indicated structures.

18. We heartily thank Dr. J.-m. Fu for providing the foundation for this work by a synthesis of unnatural gymnopusin (**1**) and Professor P.L. Majumder for a comparison sample of gymnopusin diacetate and encouragement. We acknowledge with gratitude NSERC Canada for sustaining financial support.

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