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Directed *ortho* Metalation-Cross Coupling Route to Indolo- 4,5-quinodimethanes. Synthesis of Benz[*e*]indoles

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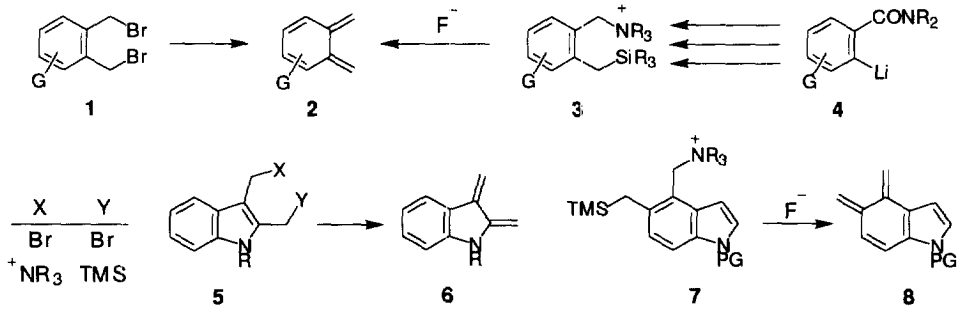
Abstract: The first generation of the indolo-4,5-quinodimethane **8** by *O*-carbamate Directed *ortho* Metalation - cross coupling tactics and its reaction with dienophiles to afford products **14-20** is reported.

ortho-Quinodimethane (*o*QDM) species **2** (Scheme 1), first observed by Cava[2] constitutes significant chapters in mechanistic,[3] synthetic organic,[4] and biological[5] chemistry which is manifested mainly in cycloaddition and nucleophilic reactions. The classical methods for the generation of **2**, e.g., from **1** have been superceded by the mild Saegusa-Ito procedure based on fragmentation of **3** induced by fluoride.[6] These classical and recent methods have been adapted for the generation of indolo-2,3-quinodimethanes **5** → **6**.[7, 8] In order to provide new scope for the generation of diversely substituted *o*QDM, we have previously established a link between Directed *ortho* Metalation (D*o*M) **4** and the Saegusa-Ito intermediate **3**.[9] Herein we report the first generation of indolo-4,5-quinodimethane species by the Saegusa-Ito procedure, **7** → **8** and its trapping with a variety of dienophiles to afford annelated products **14-20** (Table 1). The achievement of these results has been permitted by the expedient preparation of the precursor **13** using indole *O*-carbamate D*o*M[10] and nickel-catalyzed Grignard-*O*-carbamate cross coupling[11] reactions recently reported from our laboratories.



Scheme 1

The preparation of *o*QDM precursor **13** (Scheme 2) began by highly regioselective metalation- carboxamidation of the readily available *O*-carbamate **9**[10] to give **10**, which upon subjection to cross coupling with $TMSCH_2MgCl$ under Ni-catalyzed conditions, led to benzyl silane **11**. DIBAL reduction followed by treatment with MeI afforded quaternary salt **12**. The inability to effect selective formation of the *o*QDM species from **12** without *N*-desilyation[12]

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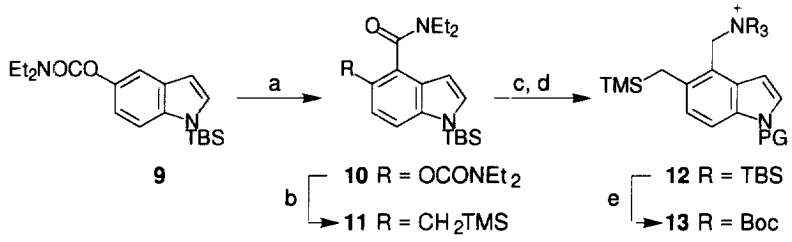
forced a protecting group switch. To this end, **12** was treated with CsF and $(Boc)_2O$ and gave the *N*-Boc derivative **13**, a convenient and mild one-pot procedure which may have broader synthetic utility in indole chemistry. The entire sequence **9** → **13** was carried out on several gram scale and required minimal chromatography.



a) i) *s*-BuLi, TMEDA, THF, -78 °C; ii) Et_2COCl; 80%. b) $TMSCH_2MgCl$, $Ni(acac)_2$, THF, 50 °C, 4 h; 59%. c) i) DIBAL, THF, 0 °C → rt; ii) Rochelle Salt; >95%. d) MeI, MeCN, rt, 12 h; 89%. e) $(Boc)_2O$, CsF, MeCN, rt, 12 h; 69-75%.

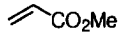
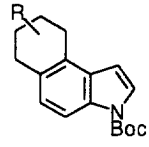
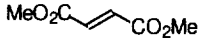
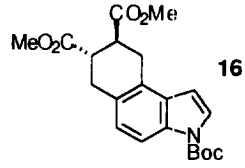
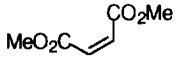
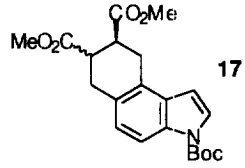
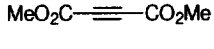
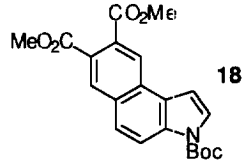
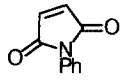
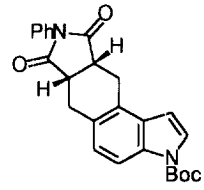
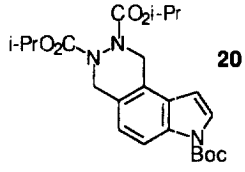
Scheme 2

Cycloaddition reaction of **13** with a number of dienophiles (large excess) in the presence of CsF or TBAF at ambient temperature are presented in Table 1. With one exception (entry 6), excellent yields of cycloadducts were obtained. Reactions of methyl acrylate (entry 1) and acrylonitrile (entry 2) afforded inseparable regioisomeric mixtures of adducts **14** and **15**, both in 3:2 ratios.[13] DDQ oxidation (PhH/reflux/2 h) provided the corresponding 3*H*-benz[*e*]indoles. This constitutes a new approach to this ring system, tetrahydro derivatives of which exhibit potent serotonergic activity.[14] Efficient trapping was also observed with dimethyl fumarate (entry 3) and dimethyl maleate (entry 4) to give **16** and **17** respectively; while the former gave the *trans*-adduct **16** exclusively, the latter afforded a 3:1 *cis:trans* mixture. The structure of the major isomer was secured by X-ray crystallographic analysis.[15,16] Reaction of dimethyl acetylene dicarboxylate furnished a mixture of double bond isomers which was treated with DDQ (PhH/reflux/2 h) to give the benz[*e*]indole **18** (entry 5) in 65% overall yield. Trapping with *N*-phenylmaleimide and diisopropyl azodicarboxylate afforded the new ring systems **19** (entry 6) and **20** (entry 7) in modest and excellent yields respectively.[17]

In summary, the first generation of the indolo-4,5-quinodimethane **8** species has been demonstrated. The overall route illustrates a new connection between *Do*M and cross coupling chemistry, which by virtue of the regioselectivity of the *Do*M process, may find advantageous application in synthetic aromatic and heteroaromatic chemistry.[18]

Acknowledgments. We are grateful to NSERC and Allelix Biopharmaceuticals Inc. for support under the NSERC CRD program. We thank Dr. Suman Rakhit for valuable discussion, Dr. David Roe for experimental guidance, Dr. Nick Taylor and Brian Chapell for the determination of the X-ray crystal structure of the adduct **17**, and Jan Venne for assistance with NMR spectroscopic determinations.

Table. Synthesis of 4,5-fused Indoles **14-20.**[a]

Entry	Dienophile	Product		Yld, %
1[b]			**14** R = CO_2Me	>95[c]
2			**15** R = CN	>95[c]
3			**16**	88
4			**17**	69[d]
5			**18**	68[e]
6			**19**	40[f]
7			**20**	92

[a]Conditions: 20 equiv dienophile, 4 equiv CsF, MeCN, rt, 12 h [b]Alternate conditions: 20 equiv dienophile, slow addition of 1.1 equiv TBAF, MeCN, rt [c]Combined yield of 3:2 mixture of regioisomers (^{1}H NMR analysis) [d]Combined yield of 3:1 mixture of *cis:trans* isomers (^{1}H NMR analysis). [e]Yield over two steps (see text). [f]Assumed to be *cis* addition product, 30% spiro dimers also isolated.

References and Footnotes

1. (a) Brantford Chemicals Inc., Station Main P.O. Box 1979, Brantford, Ontario, N3T 5W5 CANADA (b) Department of Chemistry, Queen's University, Kingston, Ontario, K7L 3N6 CANADA; email: baderadm@chem.queensu.ca
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12. For example, reaction of **12** with methyl acrylate under CsF or TBAF conditions described for **13** gave, in addition to the expected cycloadducts **14**. indole-*N* Michael addition products. Kinsman, A. C. M.Sc. Thesis, University of Waterloo, 1997.
13. ^{1}H NMR spectroscopic and ^{1}H, ^{13}C COSY experiments on these mixtures suggested that the C-8 ester is the major isomer.
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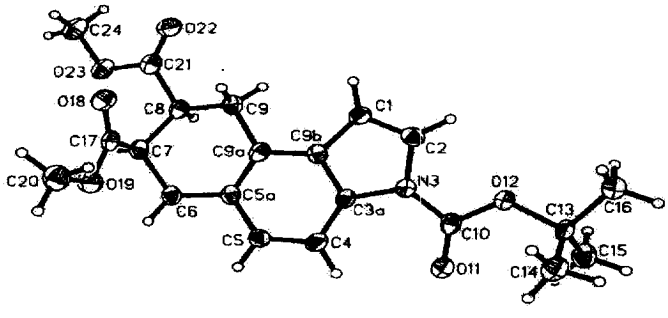
15. X-ray structure of **17**.



16. Control experiments indicated that this product distribution was the result of isomerization of dimethyl maleate under the reaction conditions coupled with the relatively rapid cycloaddition rate of dimethyl fumarate.
17. In the absence of dienophile, formation of dimeric products (M+ 486, quantitative yield, 2:1 mixture by ^{1}H NMR). Inability to separate the isomers or to obtain crystalline materials has precluded structural elucidation. See reference 12. For analogous dimers in the benzene series, see Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 7609.
18. All new compounds were characterized by ^{1}H and ^{13}C NMR, IR, LRMS and either elemental analysis or HRMS.