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Synthesis of Tetrahydrofurocarbazolones *via* Intramolecular Diels-Alder Reactions

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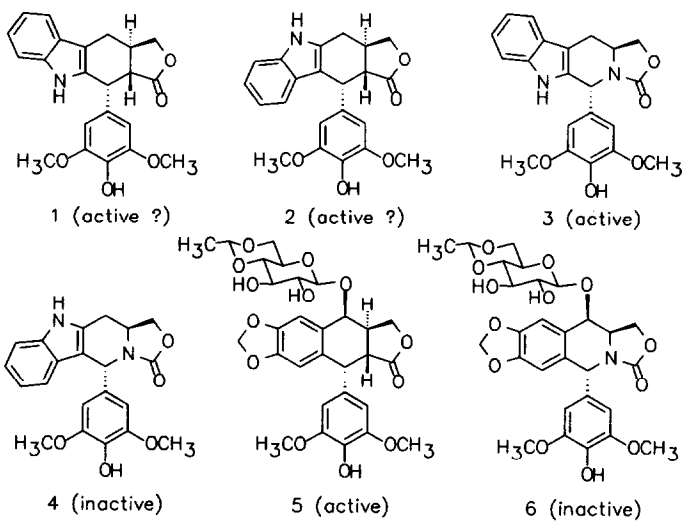
SUMMARY: 10-Aryl-3a,4,10,10a-tetrahydrofuro[3,4-b]carbazol-1-ones were synthesized by an intramolecular Diels-Alder reaction. *Exo*/*endo* product ratios were found to be sensitive to both solvent and temperature. The synthesis of *iso*elliptitoxin **2**, a hybrid molecule of ellipticine and 4'-demethylpodophyllotoxin, is presented.

As part of our program aimed at the development of novel DNA topoisomerase II (topo II) inhibitors,[1] the syntheses of a series of tetrahydrofurocarbazolones, illustrated by elliptitoxin **1** and *iso*elliptitoxin **2**, were desired. We have previously reported that *aza*-elliptitoxin **3** possesses activity in the *in vitro* formation of topo II-associated DNA strand breaks comparable to the clinically important antitumor agent, etoposide **5**, and that *aza*-isoelliptitoxin **4** is inactive in this assay.[2] Concurrent with our studies, a report by the Pearce group demonstrated that 2-*aza*-etoposide **6** was devoid of topo II activity.[3] Since both classes of topo II-directed agents exhibit non-intercalative behavior with DNA and are thought to effect topo II-mediated cleavage activity by an analogous mechanism, at issue was whether conversion of the *aza*-elliptitoxin analogs, **3** and **4**, into their *carbocyclic* counterparts, **1** and **2**, would increase biological potency.



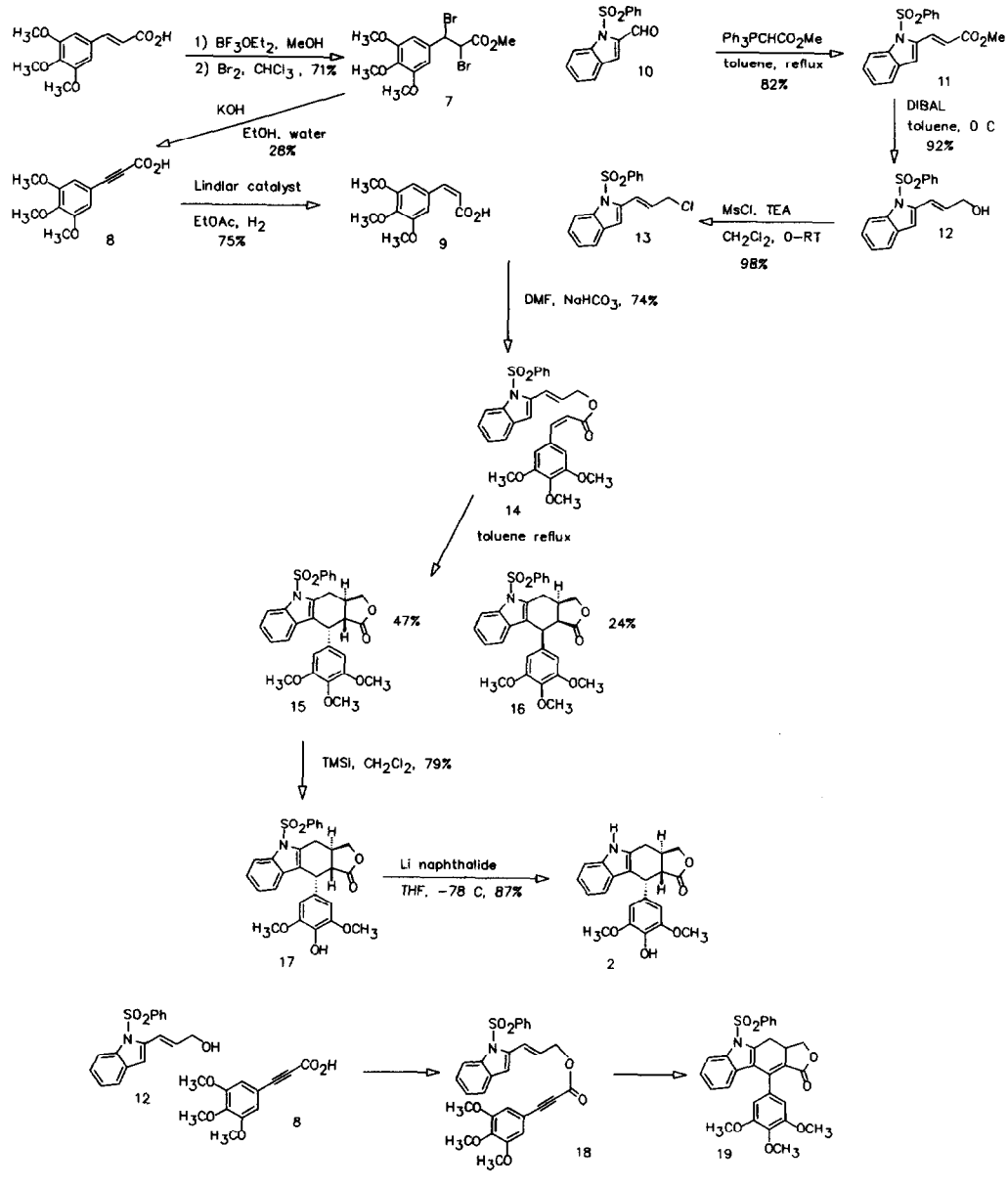
Our approach to the podophyllotoxin-like framework of *iso*elliptitoxin is illustrated in Scheme 1. The key step involved an intramolecular Diels-Alder reaction of **14**. Although *intra*molecular Diels-Alder approaches related to that outlined in Scheme 1 are well precedented in syntheses of the lignin lactone family, illustrated by the podophyllotoxin skeleton,[4] the cycloaddition reactions produce the incorrect, *syn-syn* relative stereochemistry, rather than the desired, *syn-anti* stereochemistry of the substituted cyclohexene ring. We reasoned that since *cis*-cinnamic esters are not planar due to the repulsive interaction between the C2 hydrogen on the aromatic ring and the ester carbonyl, the minimum energy cinnamate conformation would engender considerable steric hindrance in the *endo* transition state. In addition, the dienophile would be anticipated to be more reactive in the non-planar staggered conformation.

The synthesis of the dienophilic substructure was accomplished through modifications of literature procedures. Treatment of 3,4,5-trimethoxycinnamic acid with BF_3OEt in refluxing methanol, followed by bromination with Br_2 in $CHCl_3$, gave the dibromoester **7** (71% for both steps).[4] Dehydrohalogenation of **7** was accomplished with KOH in refluxing $EtOH/H_2O$ (28%).[4] Hydrogenation over Lindlar catalyst of the propiolic acid **8** smoothly afforded the *cis*-cinnamic acid **9** (75%).[4] The dienic component of the molecule was synthesized by a facile 3 step procedure. Treatment of benzenesulfonyl indole-2-carboxaldehyde[5] with the methyl triphenylphosphoranylideneacetate in refluxing toluene provided the conjugated ester **11** (82%).[6] Reduction of **11** was accomplished with 2.5 equivalents of DIBAL in toluene at 0° to smoothly afford the allylic alcohol **12** (92%).[7] The coupling of the allylic alcohol **12** with the *cis*-cinnamic acid **9** by standard esterification methodology proved challenging, due either to the unreactivity of the hindered *cis*-carboxylic acid or to formation of the *trans*-ester. As an alternative, the alcohol **12** was converted to the allylic chloride **13** with MsCl and TEA in CH_2Cl_2 (98% crude yield).[8,9] Esterification was then accomplished with $NaHCO_3$ (2.0 eq), the allyl chloride **13** (1.5 eq) and *cis*-cinnamic acid **9** (1.0 eq) in DMF at RT for 48 hrs (74%).[10]

The *exo-endo* ratio of the *intra*molecular cycloaddition reaction was both solvent and temperature dependent (Table 1); the yields of isolated products was >75% under all conditions studied. In a representative set of conditions, the ester **14** in degassed toluene was warmed to reflux (111°C) for 6 hrs to yield the desired, *exo*-transition state derived product, N-benzenesulfonyl-4'-methyl *iso*elliptitoxin **15** (47%). The isomeric product **16** arising from the *endo* transition state (24%) and the isomerized, *trans*-

Table 1. The *Exo/Endo* Product Ratios for the Cycloaddition of **14**

Solvent	Temperature (°C)	*Exo/Endo* Ratio (15/16)
acetonitrile	82	0.34
acetonitrile	106	0.45
cyclohexane	81	0.63
toluene	111	1.9
p-xylene	88	1.1
p-xylene	118	1.75
p-xylene	140	1.0



Scheme 1. Approach to the syntheses of tetrahydrofurocarbazolone **2** and dihydrofurocarbazolone **19**.

cinnamyl ester (6%) were also isolated. The optimal ratio for *exo*/*endo* product formation (**15**/**16**) occurred in aromatic solvents (*p*-xylene and toluene) and at ≈110°C. Interestingly, the temperature dependence of the *exo*/*endo* product ratio in *p*-xylene was biphasic.

Desulfonylation of **15** utilizing a variety of methods [buffered Na/Hg amalgam, sodium naphthalide, lithium naphthalide, lithium 2,6-di-*tert*-butylnaphthalide] led to concomitant epimerization at C-10a. To circumvent this problem, the selective demethylation of the 4'-methylether was accomplished with TMSI in CH_2Cl_2 (79%) and the resultant product was subjected to lithium naphthalide at -78°C in THF to provide *iso*elliptitoxin **2** (84%).[11,12,13] Studies of the biological activity of **2** will be reported elsewhere.

Attempts at utilizing this strategy for the synthesis of elliptitoxin **1** proved unsuccessful, due to the failure of the *intra*molecular Diels-Alder reaction under all conditions examined. The only characterizable product in all studies was derived from alkene isomerization to the *trans*-cinnamate. The *trans*-cinnamyl ester precursors to either the elliptitoxin **1** or *iso*elliptitoxin **2** skeleton were resistant to cycloaddition under the conditions investigated. The propiolyl ester **18**, derived from the corresponding acid **8** and alcohol **12**, underwent cycloaddition to the dihydrofurocarbazolone nucleus **19** *in situ* utilizing either a literature procedure for related coupling reactions [$SOCl_2$/pyridine/benzene; reflux] or the Mukayiama reagent [CH_2Cl_2; reflux] (> 60%) (Scheme 1). Attempts to effect reduction of the conjugated alkene in **19** by a variety of methods to the desired *syn-anti* stereochemistry observed in the elliptitoxin and *iso*elliptitoxin nuclei were unsuccessful and resulted in the *syn-syn* or *anti-anti* relative stereochemical relationship.

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