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# A DIRECT SYNTHESIS OF TRANS 2-ARYLBENZOCYCLOBUTENOL, A POTENTIAL INTERMEDIATE FOR PODOPHYLLOTOXIN SYNTHESIS: USE OF LDA FOR BENZYNE FORMATION AND TRAPPING

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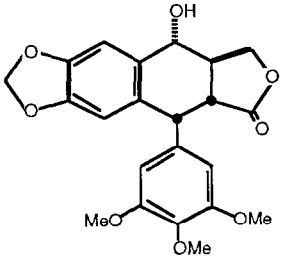
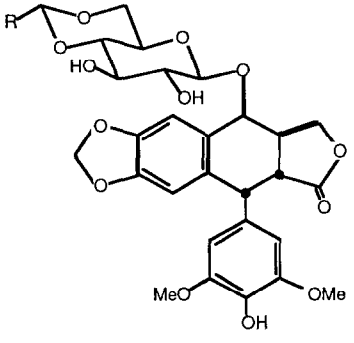
**Abstract**: Treatment of m-alkoxyaryl bromides with LDA in THF produces the corresponding aryne which can be trapped intramolecularly by an anion α to a nitrile to produce a substituted benzocyclobutenyl nitrile, the precursor of a trans arylbenzocyclobutenol potentially useful for podophyllotoxin synthesis.

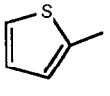
Recently we published an account of our work[2] on a proposed synthesis of the active principle of podophyllin, podophyllotoxin **1**, derivatives of which have shown great promise as cancer chemotherapeutic agents, such as Etoposide and Teniposide.[3] Our proposed approach to **1** involved an intramolecular Diels-Alder cycloaddition of the mixed carbonate **2** (or some other similar derivative) via the ortho-quinodimethane **3** to produce the tetralin **4** as the major regio- and stereochemical product. In order to substantiate this hypothesis, we carried out the cycloaddition of the very similar lower homologue of **4**, the ester **5** which gave an approximate 2:1 mixture of the trans and cis products **6a** and **6b**, in which the trans compound predominated. Since one would expect the 6-membered analogue of this 5-membered case to give even more of the desired trans compound, we decided to redouble our efforts to prepare the required mixed carbonate **2**. This necessitated a new approach to the trans 2-arylbenzocyclobutenol **7**. We describe herein the successful synthesis of **7** in only 8 steps from bromopiperonal **8** by a route which uses LDA to generate a benzyne in the key constructive step.[4]

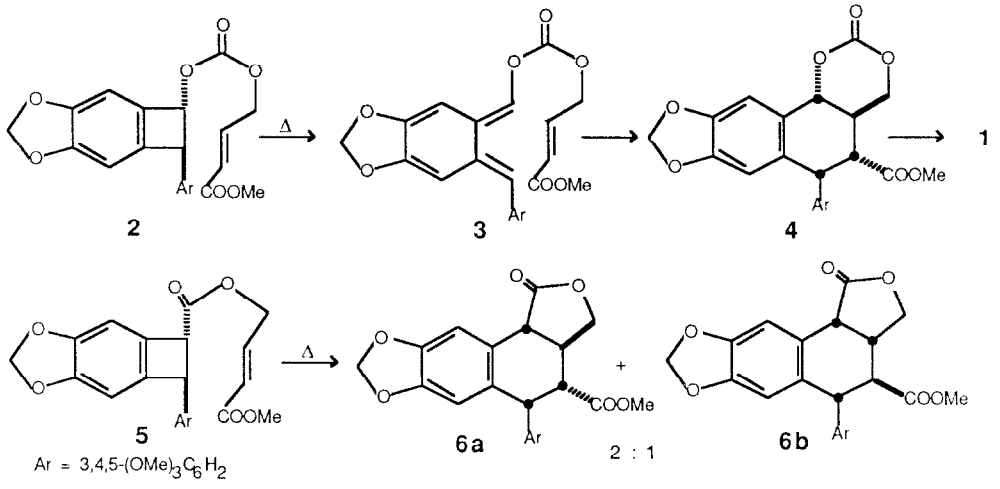



**1**

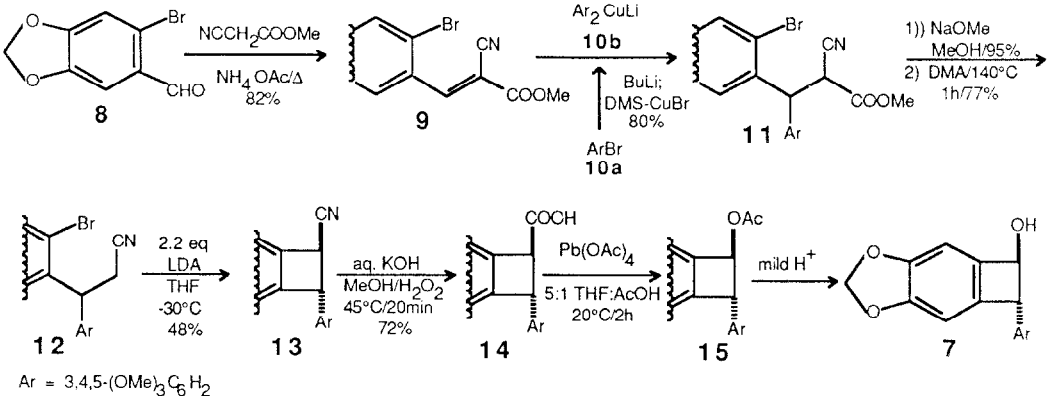



Etoposide R = Me

Teniposide R = 

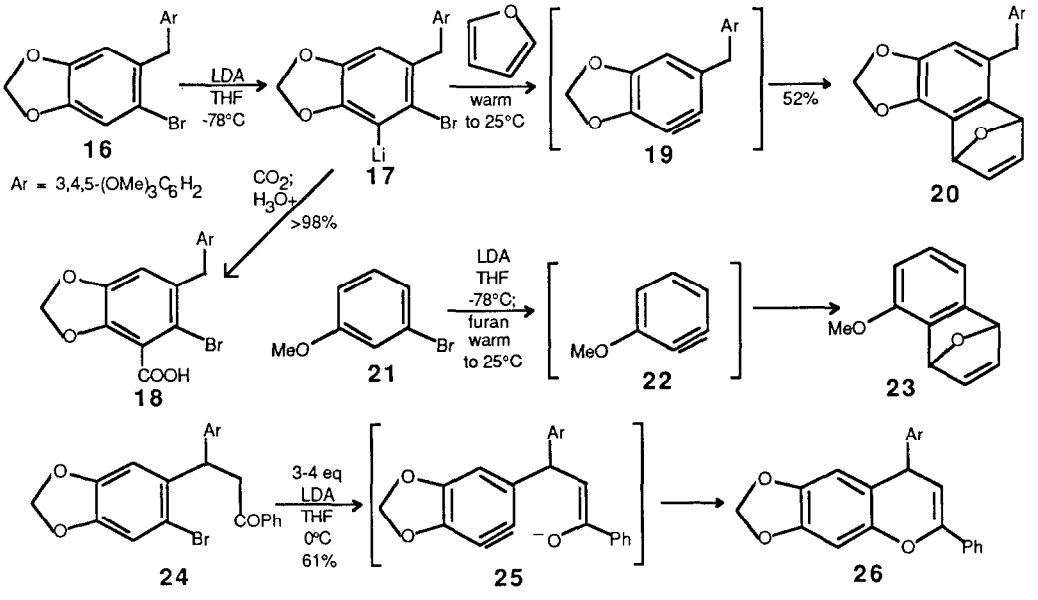



Treatment of bromopiperonal **8** with methyl cyanoacetate and ammonium acetate afforded the Knoevenagel product **9** as a mixture of stereoisomers in 82% yield. Lithium-halogen exchange of 3,4,5-trimethoxyphenyl bromide **10a** with n-butyllithium, followed by reaction with DMS-CuBr gave the lithium diarylcuprate **10b** which was added to the cyano ester **9** to furnish the coupled product **11** in 80% yield. Saponification (95% yield) and thermal decarboxylation (77% yield) produced the ß-aryl nitrile **12**. The key constructive step in this approach was the formation of the benzocyclobutene by intramolecular trapping of a benzyne intermediate by the anion α to the nitrile. This transformation is generally effected with amide bases in liquid ammonia but we found it preferable to utilize LDA in THF, a new procedure for benzyne formation-trapping. Thus treatment of **12** with 4 eq of LDA at -30°C afforded the desired nitrile in 48% unoptimized yield.[6] Hydrolysis of the nitrile proved troublesome but could be easily accomplished with 10% aqueous KOH and hydrogen peroxide in methanol at 45°C for 20 min to give **14** in 72% yield. This acid was identical to the one we had already prepared earlier by a different route[2] and which had been shown to have the trans stereochemistry. The final transformation - oxidative decarboxylation - was effected by treatment of the pure acid **14** with lead tetraacetate in 5:1 THF:acetic acid to produce the acetate **15**



in good yield. This compound could be hydrolyzed under mild acidic conditions[5] to give the desired benzocyclobutenol **7**, thus completing an 8-step synthesis from **8** in fair overall yield.

We also carried out a brief investigation of the utility of LDA as a base for deprotonation of aryl bromides. While Snieckus and others[7] have amply demonstrated the usefulness of alkyllithium for deprotonation of aryl systems, LDA is not generally useful for this process and often deprotonates preferentially at a benzylic site rather than an aromatic one. We now report that m-alkoxyaryl bromides are readily deprotonated by LDA on the aromatic nucleus and the resultant anion can be trapped at -78°C or allowed to warm to generate the corresponding benzyne. Thus treatment of **16** with LDA in THF at -78°C afforded the anion **17** which could be trapped with $CO_2$ to give the acid **18** in >98% yield.[8] Alternatively addition of furan to the THF solution at -78°C and warming to 25°C produced the benzyne **19** which was trapped as the Diels-Alder adduct **20** in 52% yield. Likewise 3-bromoanisole **21** produced the adduct **23** via the benzyne **22** under analogous treatment. The bromoketone **24** produced the enol ether **26** in 61% yield on treatment with 3-4 eq of LDA in THF, thus implying that a ketone enolate prefers to trap the benzyne **25** via oxygen to give the 6-membered ring rather than via carbon to give the benzocyclobutenyl ketone.[9] Finally the necessity for the m-alkoxy group was underscored when both 2-bromo and 4-bromoanisole failed to react with LDA under identical conditions.




Thus we have developed a new approach for benzyne formation and used it in a short approach to the useful podophyllotoxin intermediate **7**.

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## References and Notes


1. UCLA Gold Shield Faculty Awardee, 1986-8.
2. Jung, M. E.; Lam, P. Y.-S.; Mansuri, M. M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087.
3. Jardin, I. *J. Med. Chem.* **1980**, *16*, 319.
4. While our work was in progress, an excellent synthesis of **7** along very similar lines was accomplished by Macdonald and Durst.[5] We thank them for informing us of their results before publication and for helpful discussions.
5. Macdonald, D. I.; Durst, T. *Tetrahedron Lett.* **1986**, *27*, 2235.
6. All new compounds exhibited spectroscopic data (high field $^{1}H$ and $^{13}C$ NMR, IR, high resolution MS and/or elemental analysis) in full accord with their assigned structures.
7. a) Beak, P.; Snieckus, V. *Acct. Chem. Res.* **1982**, *15*, 306. b) Snieckus, V.; *et. al. J. Am. Chem. Soc.* **1985**, *107*, 6312; *Tetrahedron Lett.* **1985**, *26*, 1145, 1149. c) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837.
8. This result is in contrast to the corresponding ester (COOR in place of COPh) which gives the cyclobutane in good yield.[5]


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