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A SYNTHESIS OF TRANS-2-ARYLBENZOCYCLOBUTEN-1-OLS

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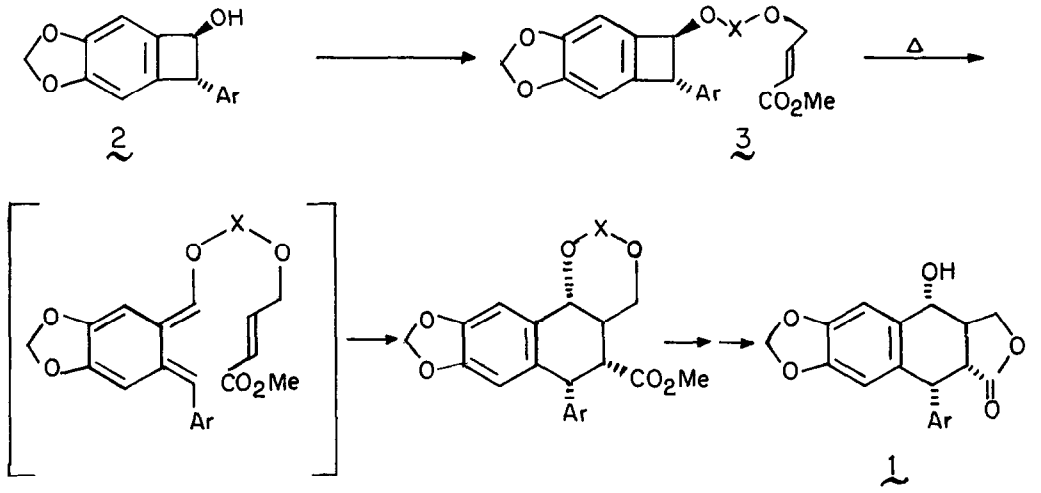
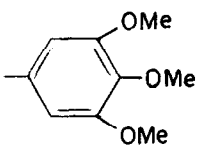
Abstract: trans-2-Arylbenzocyclobuten-1-ols have been prepared by $Pb(OAc)_4$ decarboxylation of 2-arylbenzocyclobutene-1-carboxylic acids followed by careful hydrolysis of the acetoxy group. The benzocyclobutene ring was formed via intramolecular nucleophilic addition to a benzyne intermediate.

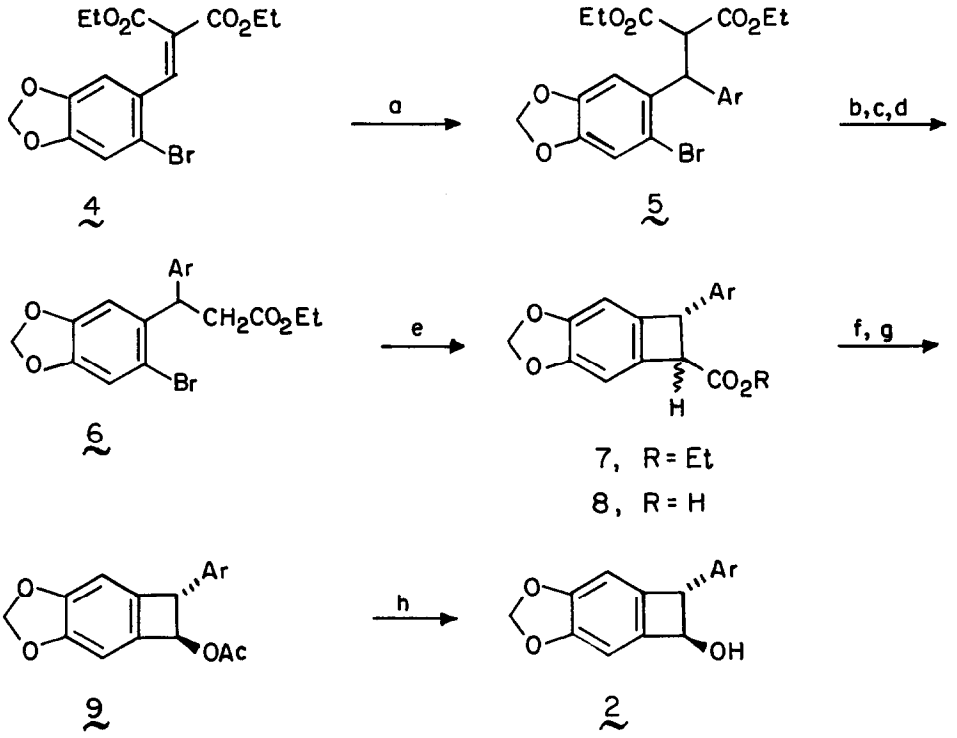
Although a number of syntheses of benzocyclobutenols are known[1], no examples of such compounds bearing a 2-aryl substituent have been described.[2] Jung and coworkers[1] have studied a number of plausible approaches to such compounds since they considered these derivatives to be key intermediates in their proposed synthesis of lignan lactones, in particular, podophyllotoxin 1, the aglycone of the anti-cancer drugs, Etoposide[3] and Teniposide.[3] (Scheme 1).



Scheme 1: Ar = 

, X = C=O

We too had recognized the potential of the intramolecular Diels-Alder reaction in an expected stereospecific synthesis of podophyllotoxin[4] and would like to present a viable synthesis of 2 which has sufficient versatility to allow for the preparation of other derivatives of 2 modified in either of the two aromatic rings. (Scheme 2).



Scheme 2

Ar = 3,4,5-trimethoxyphenyl. In series 5a, 6a etc., Ar = Ph. Reagents: a) ArMgBr or Ar(CN)CuLi[5]; b) $\bar{O}H$; c) H^+/Δ; d) $EtOH/H^+$; e) $^-NH_2/NH_3$, -78^o; f) $NaOH/H_2O/DMSO$; g) $Pb(OAc)_4$; h) $H^+/MeOH/\ 0^o$.

Thus the diester 4, prepared in 91% yield from 6-bromopiperonal and diethyl malonate in refluxing toluene using piperidinium benzoate as catalyst, reacted with the trimethoxyphenyllithium cuprous cyanide complex[5] or phenylmagnesium bromide to afford the Michael adducts 5[6] and 5a[6] in 42 and 82% yield, respectively. These compounds were converted into the monoesters 6 (55%) and 6a (54%) via saponification, decarboxylation and re-esterification. Reaction of 6

and 6a with 4 equiv. of $NaNH_2$ in NH_3 at -78° for 5 min. gave, via a benzyne intermediate[7], cis-trans mixtures of the desired benzocyclobutene carboxylic esters 7 (58%) and 7a (87%). Hydrolysis of these esters in a 1:1 mixture of 50% aqueous KOH and DMSO for 1.5 hr. at 25° was accompanied by isomerization and afforded the trans acids 8 and 8a. The trans stereochemistry in 8 was assigned on the basis of the 1.9 Hz coupling constant between the hydrogens at C_1(δ=3.93) and C_2(δ=4.67)[1,8]. The acids were converted into the corresponding acetoxy derivatives 9[9] and 9a[9] by treatment with $Pb(OAc)_4$ in 5:1 THF-acetic acid at r.t. for 2h. Careful hydrolysis of the acetates 9 and 9a using a 5:1 mixture of methanol-acetyl chloride at 0° for 1-2 hr. gave the desired trans-2-arylbenzocyclobuten-1-ols. The overall yield of 2 and 2a from 4, in eight steps, was 5% and 10% respectively. The key aspects of the proton nmr spectra for 2[10] are: 4.17 (s, CHAr) and 4.77 (broad singlet, 2H, CHOH and OH). The corresponding signals for 2a were found at 4.25 (s, CHAr), 4.79 (d, J=7.6 H, CHOH) and 2.29 (d, J=7.6 Hz, CHOH).

The trans-2-arylbenzocyclobuten-1-ols are exceptionally labile and are rapidly converted to o-benzylbenzaldehydes under even very mildly basic conditions. They are thus unlikely to be convertable into the mixed carbonate 3(X=CO) envisaged by Jung.[1] If the hydrolysis of the acetates 9 is carried out above 0°, considerable amounts the above aldehydes are formed in addition to the benzocyclobutenols. Any attachment of 2 or 2a to a hydroxycrotonate side chain or variations thereof in order to set up an intramolecular Diels-Alder as shown in Scheme 1 will probably need to be carried out under very mild, essentially neutral conditions. We are presently investigating such possibilities in order to complete a stereoselective synthesis of podophyllotoxin from 2.

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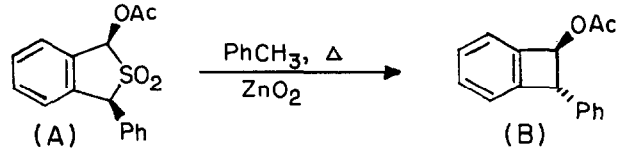
References and Footnotes

1. M.E. Jung, P.Y.-S. Lam, M.M. Mansuri and L.M. Speltz, J. Org. Chem., 1985, 50, 1087, and references therein.

2. Charlton and Alauddin have shown that thermolysis of the cis acetate (A) in refluxing toluene afforded trans-2-phenyl-1-acetoxy-benzocyclobutene (B) in about 50% isolated yield (76% corrected) for recovered (A). J.L. Charlton and M.M. Alauddin, private

communication.



3. I. Jardin, Med. Chem. (Wiley), 1980, 16, 319.

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5. J.P. Gorlier, L. Hamon, J. Levisalles and J. Wagnon, J. Chem. Soc. Chem. Commun., 1973, 88.

6. All new compounds were characterized by nmr, ir, m.s. and/or analytical data.

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8. The proton nmr of acid 8 matched within experimental error that described by Jung et al. Acid 8a: 3.93(d, J=2.6 Hz, 1H), 4.75(d, J=2.6 Hz, 1H), 5.90(d, J=1.6 Hz, 1H), 5.93(d, J=1.6 Hz, 1H), 6.73(s, 1H), 6.78(s, 1H), 7.15-7.35(m, 5H).

9. Nmr for 9: 2.12(s, 3H), 3.81(s, 6H), 3.82(s, 3H), 4.38(d, J=1.8 Hz, 1H), 5.45(d, J=1.8 Hz, 1H), 5.93(d, J=2.0 Hz, 1H), 5.96(d, J=2.0 Hz, 1H), 6.45(s, 2H), 6.70(s, 1H), 6.83(s, 1H); for 9a: 2.12(s, 3H), 4.46(s, 1H), 5.45(s, 1H), 5.94(s, 2H), 6.69(s, 1H), 6.83(s, 1H), 7.2-7.35(m, 5H).

10. Nmr for 2: 3.80(s, 6H), 3.82(s, 3H), 4.17(s, 1H), 4.77(bs, 2H), 5.93(d, J=2 Hz, 1H), 5.96(d, J=2 Hz, 1H), 6.40(s, 2H), 6.71(s, 1H), 6.84(s, 1H); for 2a: 2.29(d, J=7.6 Hz, OH), 4.25(s, 1H), 4.79(d, J=7.6 Hz, 1H), 5.93(s, 2H), 6.70(s, 1H), 6.83(s, 1H), 7.2-7.4(m, 5H).

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