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A Novel Double Friedel-Crafts Reaction: A New Entry into Bicyclo[3.2.2]nonane system.

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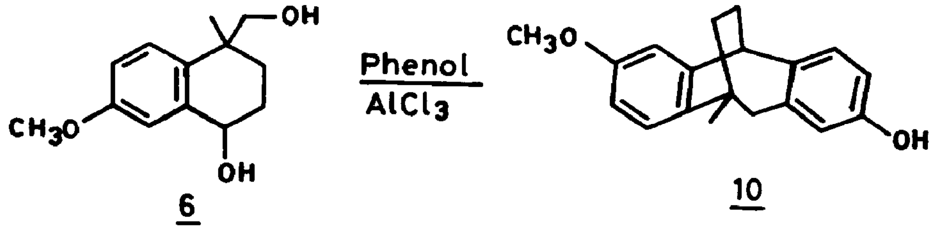
***Abstract:** A novel synthesis of dibenzobicyclo[3.2.2]nonane systems is described through a double Friedel-Crafts reaction.*

Recently we reported[1] a single step synthesis of 1-aryltetralins from 1-tetralols and phenol by the Friedel-Crafts reaction. During the preparation of a potential intermediate 7 required for building the A-ring aromatic steroids[2] from the tetralol 6 we unexpectedly encountered the formation of a bicyclo[3.2.2]nonane derivative 10. The natural sesquiterpenes[3] rotundene & rotundenol, the polycyclic toxin CBT[4] and Xanthoquinidins[5] possess the unique bicyclo[3.2.2]nonane nucleus. In view of the importance of the bicyclo[3.2.2]nonane skeleton in bicycloaromaticity[6], coupled with the difficulties involved with their preparation[7], prompted us to report our results in this paper.

Reaction of the diol 6 with phenol in the presence of anhydrous aluminium chloride in 1,2-dichloroethane gave the dibenzobicyclo[3.2.2]nonane derivative 10 in 70% yield.

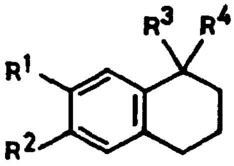


The diol 6 was prepared from the alcohol[8] 1 through the sequence of reactions indicated below. Thus the alcohol 1 was oxidized to the aldehyde 2, which was methylated to give the product 3. Reduction of 3 with sodium borohydride followed by acetylation afforded the acetate 4, which was oxidized with PDC-^{t}BuOOH to yield the ketone 5, which gave a diastereomeric mixture of diols 6 with sodium borohydride.

The mechanism of formation of 10 from 6 appears to involve the initial formation of the aryltetralin derivative 8 which undergoes an intramolecular Friedel-Crafts reaction probably through the dienone 9 to the compound 10. This mechanism is supported by the fact that while the aryl tetralin 8, synthesized separately, is smoothly transformed into the bicyclo[3.2.2]nonane derivative 10 in the presence of anhydrous $AlCl_3$ in 1,2-dichloroethane, the isomeric compound 7 is recovered unchanged under similar conditions. The exclusive formation of 8 in preference to 7 in this reaction, can be attributed to the steric hindrance exhibited by the methyl group to the incoming aryl group, thus disfavouring the formation of **7**. The hydroxymethyl group occupies the pseudoequatorial position.

Lithium/liq.ammonia/^{t}BuOH reduction of the methyl ether of **10** followed by hydrolysis with acid gave the unsaturated ketone **11**, thus confirming the structure of **10**.

To check the generality of the reaction, the diol **6** was reacted with different cresols and anisole, and in all these cases the corresponding bicyclo[3.2.2]nonane derivatives[9] were obtained in good yields as indicated in Table-1. Even the diol **17** synthesized from the alcohol **12**[8], through the intermediates **13** to **16**, employing the same sequence of reactions as in the case of the diol **6**, underwent smooth double Friedel-Crafts reaction yielding the bicyclo[3.2.2]nonane **21**, thus confirming the generality of the reaction (Table-1).



1. R^1=H ; R^2=OCH$_3$; R^3=H ; R^4=CH$_2$OH

2. R^1=H ; R^2=OCH$_3$; R^3=H ; R^4=CHO

3. R^1=H ; R^2=OCH$_3$; R^3=Me ; R^4=CHO

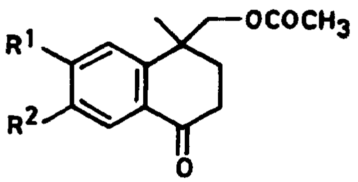
4. R^1=H ; R^2=OCH$_3$; R^3=Me ; R^4=CH$_2$OAc

12. R^1=OCH$_3$; R^2=H ; R^3=H ; R^4=CH$_2$OH

13. R^1=OCH$_3$; R^2=H ; R^3=H ; R^4=CHO

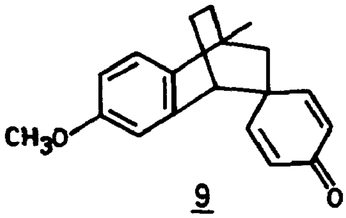
14. R^1=OCH$_3$; R^2=H ; R^3=Me ; R^4=CHO

15. R^1=OCH$_3$; R^2=H ; R^3=Me ; R^4=CH$_2$OAc



5. R^1=H ; R^2=OCH$_3$

16. R^1=OCH$_3$; R^2=H



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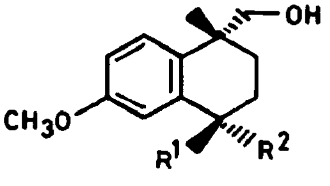
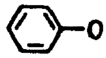
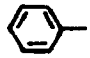
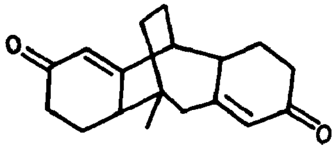


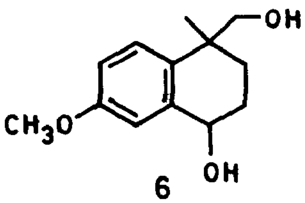
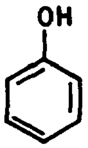
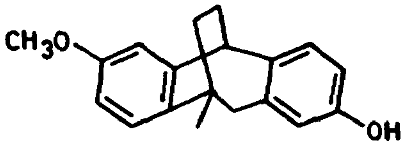
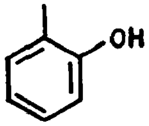
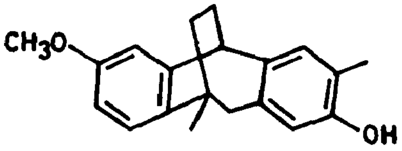
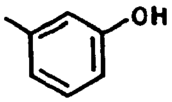
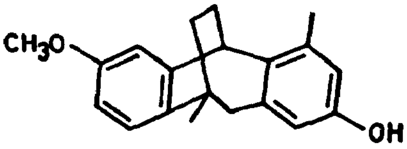
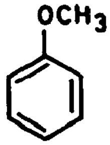
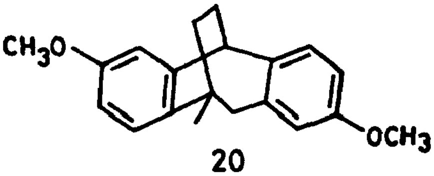
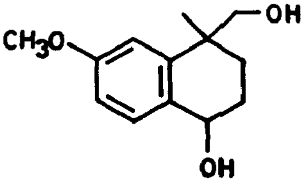
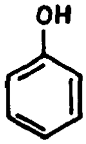
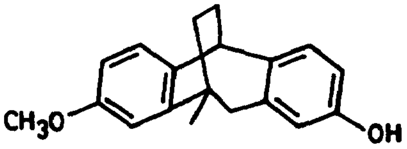
7. R^1 = OH ; R^2=H

8. R^1=H ; R^2 = OH



11

Table -1.

NO.	DIOL	ARYLATING AGENT	PRODUCT	YIELD* (%)
1.	 6		 10	70
2.	6		 18	58
3.	6		 19	51
4.	6		 20	75
5.	 17		 21	50

* Yields refer to pure isolated yields

In summary, we describe a simple and efficient method of synthesis of a bicyclo[3.2.2]nonane skeleton by a one pot double Friedel-Crafts reaction.

Acknowledgement: PB thanks the CSIR, New Delhi for a fellowship.

References:

1. Bijoy, P.; Subba Rao, G.S.R. *Synth. Commun.*, **1993**, 23, 2999.
2. Subba Rao, G.S.R.; Banerjee, D.K.; Umadevi, L.; Uma Sheriff. *Aust. J. Chem.*, **1992**, 45, 187.
3. Paknikar. S.K.; Motl, O.; Chakravarti, K.K. *Tetrahedron lett.*, **1977**, 2121.
4. Arrone, A.; Nasini, G.; Merlini, L.; Ragg, E.; Assante, G. J.Chem.Soc.Perkin Trans 1, **1993**, 145.
5. Tabata, N.; Tomoda, H.; Matsuzaki, K.; Omura, S. *J. Am. Chem. Soc.*, **1993**, 115, 8558.
6. Grutzner, J.B.; Winstein, S. *J. Am. Chem. Soc.*, **1972**, 94, 2200.
7. For the synthesis of bicyclo[3.2.2]nonanes, see: a) Cristol, S.J.; Noreen, A.L. *J. Org. Chem.*, **1976**, 41, 4016. b) Ciabattoni, J.; Crowley, J.E.; Kende, A.S. *J. Am. Chem. Soc.*, **1967**, 89, 2778. c) Schaefer, J.P.; Enders, L.S.; Moran, M.D. *J. Org. Chem.*, **1967**, 32, 3963. d) Hill, A.E.; Hoffmann, H.M.R. *J. Am. Chem. Soc.*, **1974**, 96, 4597. e) Berson, J.A.; Jones, M. *J. Am. Chem. Soc.*, **1964**, 86, 5017.
8. Bijoy, P.; Subba Rao, G.S.R. *Synth. Commun.*, **1993**, 23, 2701.
9. ^{1}H NMR(90MHz,CDCl$_3$) data for selected compounds:

   10. δ 1.45(s,3H,CH$_3$), 1.5-2.4(m,4H,CH$_2$), 2.91(d,J=3.64Hz,2H,ArCH$_2$), 3.76(s,3H,OCH$_3$), 4.65(s,1H,OH), 6.48-7.1(m,6H,ArH).

   18. δ 1.48(s,3H,CH$_3$), 1.4-2.4(m,4H,CH$_2$), 2.21(s,3H,ArCH$_3$), 2.93(d,J=5.4Hz,2H,ArCH$_2$), 3.8(s,3H,OCH$_3$), 4.6(bs,1H,OH), 6.56-7.0(m,5H,ArH).

   19. δ 1.52(s,3H,CH$_3$), 1.3-2.4(m,4H,CH$_2$), 2.34(s,3H,ArCH$_3$), 2.93(d,J=5.4Hz,2H,ArCH$_2$), 3.84(s,3H,OCH$_3$), 4.68(bs,1H,OH), 6.4-7.0(m,5H,ArH).

   20. δ 1.48(s,3H,CH$_3$), 1.4-2.4(m,4H,CH$_2$), 2.92(d,J=3.6Hz,2H,ArCH$_2$), 3.76(s,3H,OCH$_3$), 3.78(s,3H,OCH$_3$), 6.5-7.2(m,6H,ArH).

   21. δ 1.44(d,J=1Hz,3H,CH$_3$), 1.3-2.3(m,4H,CH$_2$), 2.92(d,J=3.6Hz,2H,ArCH$_2$), 3.7(s,3H,OCH$_3$), 4.6(bs,1H,OH), 6.4-7.16(m,6H,ArH).

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