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An expeditious total synthetic route to naturally occurring tricarbocyclic ring ring-*C*-aromatic diterpenoids: mechanisms of cyclialkylations

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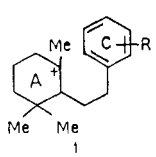
Abstract - The critical role of the nature of aromatic ring substituents in the open chain substrates in the acid-catalyzed cyclialkylation reaction through 2-2(arylethyl)-1,3,3-trimethylcyclohexyl cation is exemplified with a large number of easily accessible mono- and di-substituted 2-(2-arylethyl)-1,3,3-trimethylcyclohexanols and a few 2-(2-arylethyl)-3,3-dimethyl-1-methylenecyclohexanes in the distributions of the respective trans- and cis-podocarpatrienes. The cyclohexanol or the cyclohexylidene precursors having unactivated aromatic ring proceeds with high stereoselectivity leading to the respective trans-products, while the substrates with an electron donating substituent with respect to the site of electrophilic attack result in the corresponding cis- and the trans-product mixtures. Consistent mechanisms for these stereochemical results have been advanced. Based on these results simple syntheses of a few diterpenes have been realized.

INTRODUCTION

The acid-catalyzed intramolecular cyclialkylation reaction constitutes one of the simplest and most widely used methods for the synthesis of ring-C-aromatic resin acids (refs. 1-8) and various naturally occurring diterpenoids having gem-dimethyl group in a trans-octahydrophenanthrene structure (refs. 9-22). Despite the simplicity and converging nature of this method considerable confusion exists regarding the unpredictable stereochemical outcome of the cyclization products (refs. 5 and 19) which seems to depend upon the structure of the substrates including the nature and position of the electron donating substituent(s) in the aromatic ring in the open chain substrates. I would like to present in this paper the development of a consistent mechanism for the stereochemical results, particularly in the acid catalyzed cyclialkylation reaction (AC→ABC route) of 2-(2-arylethyl)-1,3,3-trimethylcyclohexyl cation **1**, generated from the easily accessible tertiary alcohols **2**, leading to an expeditious total synthetic route to naturally occurring diterpenoids having the basic skeletal structure **3**.



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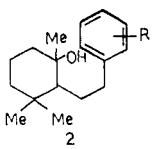

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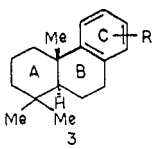

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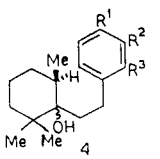

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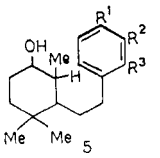


5

4 and 5 :

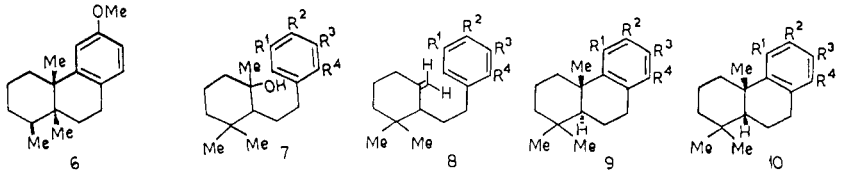
a, R^1=OMe; R^2=R^3=H

b, R^1=R^2=H; R^3=OMe

c, R^1=R^3=H; R^2=OMe

EARLIER STUDIES ON THE STEREOCHEMISTRY OF CYCLIALKYLATION PRODUCTS

As mentioned above, despite the simplicity of the AC→ABC route, in many cases it suffered from a lack of stereoselectivity (refs. 18-22). Attempts have been made (refs. 19-22) to rationalize the results of the various cyclialkylation reactions leading to diterpenoids and their congeners. From a detailed study Davis and his co-workers (refs. 23 and 24) have recently demonstrated that, under mild condition using $MeSO_3H$-P_2O_5 mixture as the cyclization reagent, p-methodoxyphenylethylcyclohexanols **4a** (trans-OH) **5a**, and the corresponding o-methoxy isomers **4b** (trans-OH) **5b** afford the respective trans-fused podocarpatriene derivatives **9a** and **9b** in good yields and stereochemical purity. In contrast, the m-methoxyphenylethyl substrates **4c** (trans-OH) **5c** under similar condition led to a mixture of trans and cis-cyclized products **9c** and **10c**, along with some other minor products, where the trans-compound predominates. It has also been shown that under the relatively harsh conditions of polyphosphoric acid induced cyclization, the alcohols **4a** or **5a** also give the rearranged cis-isomer **6** besides the trans-product **9c** (refs. 23-25). In all reported cyclialkylations leading to the tricyclic diterpenoids, having the general structure **3**, the carbocation **1** required for such reaction has been generated from the intermediate cyclohexanols, e.g. **4** and **5** (or the related cyclohexenes) involving hydride transfer steps. As a consequence it was desirable to study the cyclialkylation reactions of the tertiary cyclohexanols substrates, such as **2**, which in principle would lead to the cation **1**, mimizing the chance of rearrangement leading to the products of type **6**.

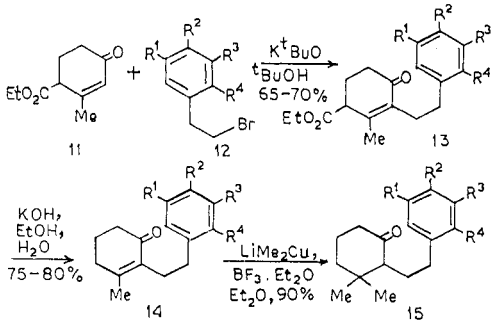


SYNTHESIS OF THE SUBSTRATES FOR CYCLIALKYLATIONS

The 2-arylethyl-3,3-dimethylcyclohexanones **(15a-k)**, key intermediates for the cyclohexanols **(7a-k)** or the cyclohexylidenes **(8a-d)**, were prepared in over 90% yield by a general method (refs. 26-28) involving conjugate addition (ref. 29) of a methyl group to the respective cyclohexenones **(14a-k)**. The cyclohexenones were obtained in good yields by alkylation of Hagemann's ester **(11)** with the appropriate phenylethyl bromides **(12a-k)** followed by alkaline hydrolytic decarboxylation of the corresponding C-3 alkylated products **13a-k**, produced in over 90-95% purity (Scheme-1).

The alcohols **(7a-k)** and the cyclohexylidenes **(8a-d)** were prepared by condensation of the ketones **15a-k** with MeMgI and Wittig reactions, respectively.

Scheme 1



7-10 and **12-15**

a, $R^1=R^3=R^4=H$; $R^2=OMe$
b, $R^1=R^2=R^3=H$; $R^4=OMe$
c, $R^1=R^2=R^4=H$; $R^3=OMe$
d, $R^1=R^2=R^3=R^4=H$
e, $R^1=R^2=R^4=H$; $R^3=Me$
f, $R^1=R^4=H$; $R^2=R^3=OMe$
g, $R^1=R^3=H$; $R^2=R^4=OMe$
h, $R^1=R^4=OMe$; $R^2=R^3=H$
i, $R^1=R^4=H$; $R^2=OMe$; $R^3=Me$
j, $R^1=R^3=R^4=H$, $R^2=i\text{-Pr}$
k, $R^1=R^2=R^4=H$; $R^3=i\text{-Pr}$

STEREOCHEMICAL DISTRIBUTION OF CYCLIZED PRODUCTS IN THE CYCLIALKYLATION REACTIONS OF 7 AND 8

To define the influence of the aromatic ring methoxy and methyl substituents in the phenylethylcyclohexanols **(7a-i)** and the olefins **(8a-d)** on stereoselectivity in the key cyclization step, these were subjected to cyclization with $MeSO_3H$-P_2O_5 (5:1) according to Axon et al (refs. 23 and 24). A part of the crude cyclization product isolated from each of the reactions (ref. 27) was filtered through a wide column of neutral alumina and subjected to analysis by GC and ^1H NMR (200 MHz). Quantitative evaluations of the trans- and cis-cyclized products are outlined in Table. Some of these results have already been reported (refs. 26 and 27). In most cases, the major trans- product from each of the cyclization reactions was identified by GC and ^1H NMR comparisons with purified samples and the minor cis-isomer was characterized specifically by the upfield signal (ref. 30) of the C-4 α-methyl group (δH 0.3-0.4).

MECHANISM OF CYCLIALKYLATION REACTIONS

Our results (Table) on the stereochemistry of cyclialkylation of the cyclohexanols **(7a-i)**, particularly under mild condition using $MeSO_3H$-P_2O_5 as reagent, provide with some important generalizations. These results are also consistent and qualitatively comparable with the observations by Davis and co-workers (refs. 23 and 24) on the cyclizations of the related methoxyphenylethylcyclohexanols **4a-c** and **5a-c**. Cyclizations of the cyclohexanol substrates **7(a,b,d,g,h)** with an unactivated aromatic nucleus lead cleanly to the respective trans-products **9(a,b,d,g,h)**. The exocyclic olefins **(8a,b,d)** also gave only the respective trans-products. In contrast, the cyclohexanols **7(c,e,f,i)** that incorporate an electron donating methoxy or methyl substituent, para to the site of electrophilic attack on the aromatic ring, including the disubstituted aromatic precursors (entries 10 and 13), generate (ref. 31) more diverse array of products (including ortho-cyclization) containing predominating or substantial amounts of the cis-isomers **10(c,e,f,i)** along with the trans-isomers **9(c,e,f,i)**. The cyclization of the olefin **8c** (entry 6) also gave the cis product **10c**. It is important to note that it is the location of the activating methoxy or methyl

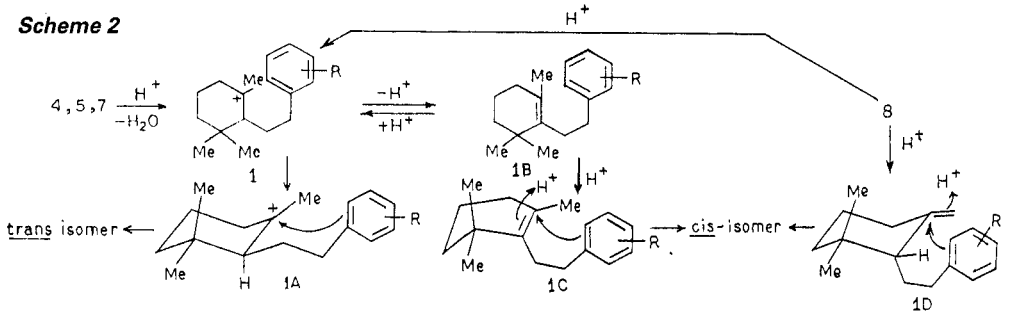
Table : Cyclization of Cyclohexanols **(7a-i)** and Cyclohexylidens **(8a-d)** with $MeSO_3H$-P_2O_5 (10:1) for 15 min at 20-25°C : Ratio of the trans and cis-podocarpatrienes.

Entry	Aocohol/ olefin	Yield[a] (%)	Products trans + cis	Ratio[b] of trans/cis
1	**7a**	93	**9a** + **10a**	99 : 1
2	**8a**	99	**9a** + **10a**	100 : 0
3	**7b**	95	**9b** + **10b**	100 : 0
4	**8b**	99	**9b** + **10b**	100 : 0
5	**7c**	83	**9c** + **10c**	42 : 58[c]
6	**8c**	95	**9c** + **10c**	34 : 66
			(contd.....)	
7	**7d**	93	**9d** + **10d**	99 : 1
8	**8d**	95	**9d** + **10d**	99 : 1
9	**7e**	80	**9e** + **10e**	70 : 30
10	**7f**	82	**9f** + **10f**	58 : 42
11	**7g**	92	**9g** + **10g**	97 : 3
12	**7h**	90	**9h** + **10h**	97 : 3
13	**7i**	81	**9i** + **10i**	60 : 40

[a]Yield of the trans and cis cyclized products in the isolated materials; [b]Determined by GC comparisons with pure trans- samples and integrated signal intensities of clearly separated peaks from ^1H NMR spectra in $CDCl_3$ at 200 MHz; [c]The ratio of **9c/10c** given in ref.27 was incorrect.

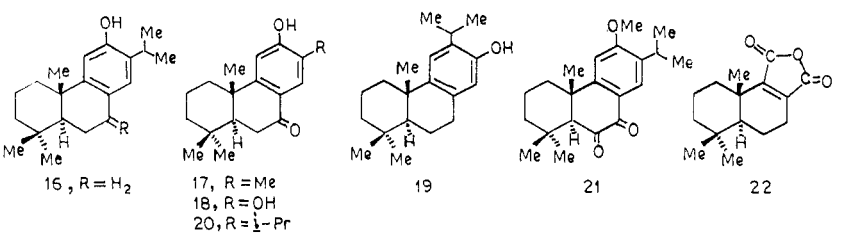
group with respect to the site of electrophilic attack that governs the reactivity of the aromatic ring. The stereochemical results of the present and the earlier works can be clearly explained by consideration that aromatic rings without the para activating group are not sufficiently nucleophilic to reaction through the concerted protonation cyclization pathways (refs. 5 and 31) **1C** or **1D** of the olefins **1B** or **8c** (Scheme-2), but require complete protonation to carbocation **1** which reacts with high stereoselectivity by pathway **1A** due to minimum steric effects (refs. 5 and 31) to give trans-products. With an activating para substituent, the pathways **1C** or **1D** competes with pathway **1A** to give a mixture of cis and trans-products. The exact ratio of products could vary significantly with small changes in reaction conditions or starting substrates.

Scheme 2



SYNTHESIS OF SOME NATURALLY OCCURRING DITERPENOIDS

As shown above, the easily accessible phenylethylcyclohexanol **(7a)** on cyclization under mild condition using $MeSO_3H$-P_2O_5 mixture affords practically pure trans product **9a** in excellent yield. In contrast, substrates **7g** and **7i** with an electron donating aromatic methoxy or a methyl group with respect to the site of electrophilic attack result in the corresponding trans- and cis mixtures **9g** and **10g**, and **9i** and **10i**. Based on these important informations remarkably simple stereoselective routes have been designed for synthesis of trans-A/B-ring-C-aromatic diterpenoids, for example, (±)-ferruginol **(16)**, (ref. 26), (±)-nimbiol **(17)** (ref. 27) and the first total synthesis of the recently isolated (ref. 33) (±)-nimbidiol **(18)** (refs. 27 and 32).



The stereochemical results of the cyclialkylation of 2-(2-p)-and-(2-m-isopropylphenethyl)-cyclohexanols **(7j)** and **(7k)** follow the general patterns observed with methyl or methoxy substituents, leading mainly to the trans-product **9j**, and the trans and cis-products mixture **9k** and **10k** in a ratio of ca 2:1, respectively (ref. 28). The hydrocarbon **9j** (ref. 34) was converted to (±)-sempervirol **(19)**. The trans and cis product mixture **(9k + 10k)** was transformed to (±)-sugiol **(20)** and (±)-xanthopherol **(21)**. Finally, the easily accessible trans-dimethoxy compound **(9h)** has been converted to the naturally occurring sesquiterpene (±)-winterin **(22)** by a known method (ref. 35).

CONCLUSION

In conclusion, we feel that operationally simple and efficient general convergent sequence developed during the present work certainly constitutes one of the shortest and highly stereocontrolled synthesis of the C-4-gem-dimethyl incorporating ring-C-aromatic diterpenoids and various other natural products. In addition, the present investigation has provided substantial evidence on the nature and stereochemistry of the cyclization of the cation of type **1** depending upon the position of aromatic substituents with rational mechanistic analysis which has been a matter of debate for many years (e.g. refs. 19,24 and 25).

Acknowledgements

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