Tetrahedron Letters, Vol.32, No.17, pp 1929-1932, 1991
Printed in Great Britain

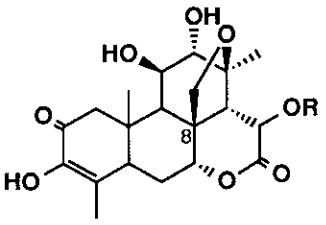
0040-4039/91 $3.00 + .00
Pergamon Press plc

THE REDUCTIVE ALKYLATION OF AROMATIC KETONES REVISITED. A NEW STEREOSELECTIVE ROUTE TO HIGHLY FUNCTIONALIZED 4a,8a-SUBSTITUTED 1,2,3,4,4a,6,8a,9,10,10a-DECAHYDROPHENANTHRENES.

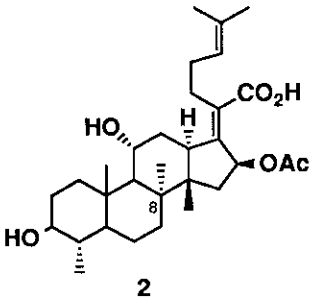
Alejandro J. Vila, Raquel M. Cravero and Manuel Gonzalez-Sierra*
Instituto de Quimica Organica de Sintesis (IQUIOS),
Facultad de Ciencias Bioquimicas y Farmaceuticas,
Suipacha 531, 2000 Rosario, ARGENTINA.

Abstract: A series of highly functionalized angularly substituted bicyclic and tricyclic ketones were obtained regio- and stereoseltively by means of a Birch reductive alkylation.

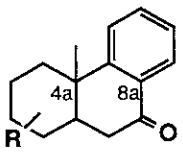
The structural diversity and biological importance of natural triterpenoids like bruceantin **1** and fusidic acid **2** have made them attractive synthetic targets.[1] In most cases, the control of the angular suibstituent stereochemistry has been a crucial step in their syntheses. For this reason, reactions providing a high stereoselectivity in the establishment of 8a configuration are of continuous interest.[2]



1



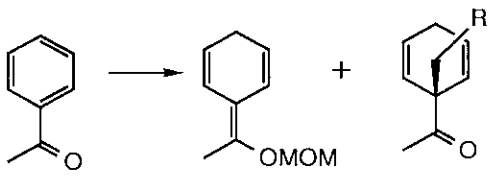
2



3

The metal-liquid ammonia reduction (Birch reaction) of alkyl and alkoxy benzenes has found wide application in organic syntheses over many years. More recently the reduction of aromatic ketones, traditionally regarded as unsuitable substrates, has been shown to be also possible.[3-5] we envisaged 4a-Methyl Octahydrophenanthrenes like **3** as logical substrates to carry on Birch reductive alkylations and study their stereochemical outcome.

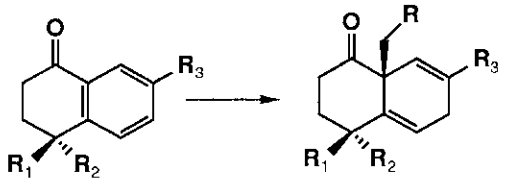
As we were particularly interested in attaining the introduction of oxygenated angular substituents, the best reaction conditions were initially set using acetophenone **4** as substrate. Following the techniques described[3,4] the alkylations proceeded satisfactorily except when using methoxy methyl chloride (ClMOM) as alkylating agent. In this case, a 1:1 mixture of the C- and O- alkylated products was obtained (compounds **5b** and **6**). It was necessary to eliminate the ammonia and to replace the organic cosolvent used in the reduction step (Et_2O or THF) by one with a lower cation- solvating ability[6] (benzene or toluene) to achieve only the dessired C- alkylated product.



4 **6** **5**

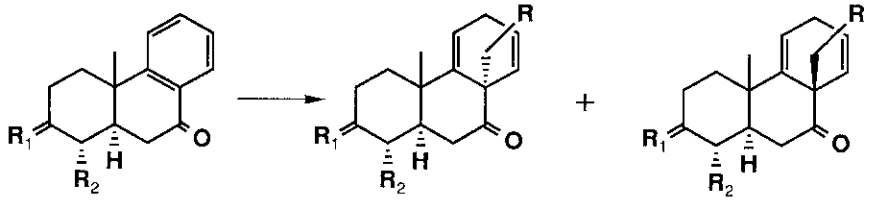
5a R=H
5b R=OMe
5c R=OBn

These model studies proved that this reaction was worthy of an assault in bi- and tricyclic systems. So we carried out a series of reactions on the substrates shown below.



8a $R=R_1=R_2=R_3=H$
8b $R=OMe$, $R_1=R_2=R_3=H$
8c $R=OBn$, $R_1=R_2=R_3=H$
9 $R=H$, $R_1=R_2=R_3=Me$
10a $R=R_3=H$, $R_1=CO_2H$, $R_2=Me$
10b $R=R_3=H$, $R_1=Me$, $R_2=CO_2H$

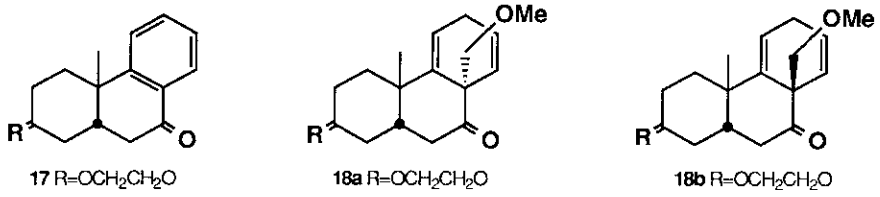
7a $R_1=R_2=R_3=H$
7b $R_1=R_2=R_3=Me$
7c $R_1=CO_2H$, $R_2=Me$, $R_3=H$



11a $R_1=R_2=H$
11b $R_1=OCH_2CH_2O$, $R_2=H$
11c $R_1=OCH_2CH_2O$, $R_2=Me$

12 $R=R_2=H$, $R=OMe$
14a $R_1=OCH_2CH_2O$, $R_2=R=H$
14b $R_1=OCH_2CH_2O$, $R_2=H$, $R=OMe$
16a $R_1=OCH_2CH_2O$, $R_2=Me$, $R=H$
16b $R_1=OCH_2CH_2O$, $R_2=Me$, $R=OMe$

13 $R_1=R_2=H$, $R=OMe$
15a $R_1=OCH_2CH_2O$, $R_2=R=H$



17 $R=OCH_2CH_2O$

18a $R=OCH_2CH_2O$

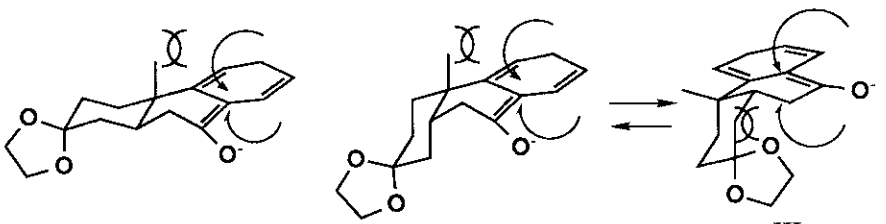
18b $R=OCH_2CH_2O$

19 R=OMOM

20a R=OMOM

20b R=OMOM

All these compounds are available in appreciable quantities through straightforward reactions[7,8] from low cost starting materials. Table 1 summarizes the results obtained, showing isolated yields [9] which range from good to



I II III

excellent (56-92%) and a high degree of stereoselection, which deserves a special comment. In the A/B trans fused compounds (**I**), the alkylations are shown to take place almost exclusively from the α face of the molecule. Meanwhile, for the cis fused compound **17**, which exists in a dynamic equilibrium between conformers **II** and **III**, no stereoselectivity was found (**18a/18b**, 1:1).
However, one can regain the stereocontrol by forcing the conformational equilibrium of the cis enolates toward one

Table 1: Birch reduction of benzylic ketones

Starting Material	Alkylation Reagent	Reaction Procedure	Products (% yiel)[b]
	MeI	A	**5a** (81)[c]
	ClMOM	A	**5b** (37) + **6** (35)
4	ClMOM	B	**5b** (88)
	ClBOM	A	**5c** (92)
	MeI	A	**8a** (82)[c]
7a	ClMOM	B	**8b** (86)
	ClBOM	A	**8c** (81)
7b	MeI	A	**9a** (86)
7c	MeI	A	**10a** (32) + **10b** (32)[c]
11a	ClMOM	B	**12** (64) + **13** (7)[d,e]
11b	MeI	A	**14a** (83) + **15a** (5)[d]
	ClMOM	B	**14b** (82)
11c	MeI	A	**16a** (92)
	ClMOM	B	**16b** (80)
17	ClMOM	B	**18a** (43) + **18b** (42)
19	ClMOM	B	**20a** (17) + **20b** (68)[d,e]
			20a (17) + **20b** (51)

[a] **Method A:** 1) 1 eq. ketone, 2.4 eq. K, 1.2 eq t-BuOH, Et2O or THF, NH_3 (l), -78°C, 20 min.; 2.4 eq. LiBr, 40 min.; 3) 3 eq. alkylating agent.
Method B: 1) 1 eq. Ketone, 2.4 eq. K, 1.2 eq t-BuOH, Et2O or THF, NH_3 (l), -78°C, 20 min.; 2) 2.4 eq. LiBr, 40 min.; 3) solvent removal under a N_2 stream; 4) residue taken up in toluene; 5) -78°C, 3 eq. alkylating agent.

[b] Pure compound isolated yield, except when indicated; [c] Taken from reference 4; [d] Estimated by ^1H NMR in the reaction mixture.; [e] Some of the 1-4 dienes with angular oxygenated substituens undergo partial decomposition upon column chromatography, and their stability seems to be related to the C-8a stereochemistry.

preferred conformation[10,11] through appropriate substitution, as shown by the 4:1 β/α ratio obtained in the alkylation of compound **19**, which is fixed in conformation **III**.[10,11] It is worthwhile to mention that in this case the alkilation proceeds mainly upon the β face of the molecule. Such manipulations allowed us to control the stereochemistry of the angular substituent.[12]

In conclusion, herein we have described the optimum conditions for the direct introduction of an angular -CH_2OR moiety through a reductive alkylation in mono-, bi- and tricyclic benzylic ketones. In the later, for the 4a-Methyl trans series, the reaction proceeds with high stereoselectivity producing an anti disposition of the angular substituents, as in the fusidanes. In addition, in the cis series the stereoselection can be manipulated toward the desired isomer through appropriate substitution The dienes obtained through this procedure may be seen as versatile intermediates in natural product synthesis, i.e., for the construction of polyfunctionalized decalins, tri- and tertracyclic di- and triterpenoids with stereochemically defined angular substituents. Additional work in this direction is in progress.

Acknowledgements: The authors wish to thank CONICET and the Universidad Nacional de Rosario for financial support. A.J.V. also thanks CONICET for a fellowship.

Refernces and Notes:

1. R. B. Boar, *Nat. Prod. Report*, 53 (1984).
2. L. Larsen and J. K. Sutherland, *J. Chem. Soc., Chem. Comm.*, 784 (1989).
3. For excellent updated reviews, see: a) P. W. Rabideau, *Tetrahedron*, 1579 (1989) b) J.M. Hook and L.N.Mander, *Nat. Prod. Report*, **3**, 35 (1986).
4. M. Narisada and F. Watanabe, *J.Org.Chem.*, **38**, 3887 (1973); J.M. Brown, T. M. Cresp and L.M. Mander, *J.Org.Chem.*, **42**, 3984 (1977).
5. R. McCague, C.J. Moody and C.W. Rees, *J.Chem.Soc., Perkin Trans 1*, 2399 (1983); Z. Lidert, R. McCague, C.J. Moody and C.W. Rees, *ibid.*, 383 (1985); C.J. Moody and C.W. Rees, *Ibid.*, 735 (1985); C.J. Moody and J. Toczek, *Tetrahedron Lett.*, 5253 (1986).
6. C. Reichardt, "Solvent effects in organic chemistry", 3rd Edition, Verlag-Chemie, N.Y., pp. 167-170.
7. M.T. Bogert, D. Davinson and M. Apfelbaum, *J.Am.Chem.Soc.*, **56**, 959 (1934); R.B. Miller and C.G. Gutierrez, *J.Org.Chem.*, **43**, 1569 (1978).
8. A.L. Campbell, H.N. Leader, C.L. Spencer and J.D, McChesney, *J.Org.Chem..*, **44**, 2746 (1979); M. Gonzalez-Sierra, H.M. Leader and J.D. McChesney, *J.Org.Chem.*, **50**, 4450 (1985);M. Gonzalez-Sierra, T.N. Thompson and J.D. McChesney, *J.Org.Chem.*, **50**, 4447 (1985).
9. All new compounds had satisfatory spectral and analytical data, including n.O.e. experiments and selective irradiations.
10. A.L. Campbell, H.N. Leader, M. Gonzalez-Sierra, C.L. Spencer and J.D. McChesney, *J.Org.Chem.*, **44**, 2755 (1979).
11. A.J. Vila, R.A. Spanevello, A.C. Olivieri, M. Gonzalez-Sierra and J.D. McChesney, *Tetrahedron*, 4951 (1989).
12. The relative estereochemistry of C-8a epimeric compounds was clearly established by ^{13}C NMR. The C-5 signal shows a substancial shielding (5 to 6 ppm) when the C_5-H bond is envolved in a compressing stem-to-stem interaction with the C-8a substituent, *i.e.*, those with an anti relationship in the trans series or a syn stereochemistry in the cis series. In this connection see: J.K. Saunders, H. Beierbeck, *Can.J.Chem.*, **55**, 2813 (1977); and compounds **16** and **17** in M. Nishizawa, H. Takenaka and Y. Hayashi, *J.Org.Chem.*, **51**, 806 (1986).

(Received in USA 4 January 1991)