New Access to Prostanoids Like from Easy Avaliable Starting Materials

Nicolas Brosse, Brigitte Jamart-Grégoire, and Paul Caubère*
Laboratoire de Chimie Organique I, URA CNRS 457, INCM FU CNRS 0008, Faculté des Sciences, Université H. Poincaré, Nancy I, BP 239, F-54506 Vandoeuvre-les-Nancy, France

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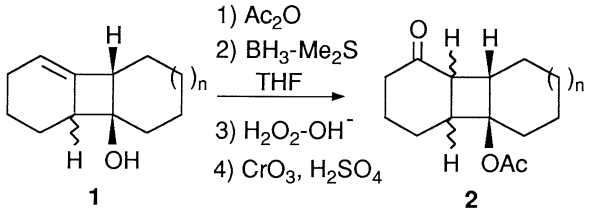
Methylene cyclobutanols resulting from one step elimination-additions were transformed into new prostanoid-like derivatives with potential biological activity.

Chemically stable analogs of prostaglandines have attracted widespread interests because of their varied and potential biological applications.[1]

As part of a program aiming at the synthesis of cyclopentanoid derivatives from commercial and inexpensive starting materials[2] we were interested in devising a new pathway to prostanoid-like compounds. The first results obtained in this way are reported in the present publication.

We previously established that methylene cyclobutanols **1** could be obtained on a large scale by condensation of ketone enolates on 1,2-cyclohexadiene easily generated from 1-chlorocyclohexene and a nucleophilic complex base.[3] The corresponding ketones **2** were then prepared in good yields according to Scheme 1 and reference 2a.

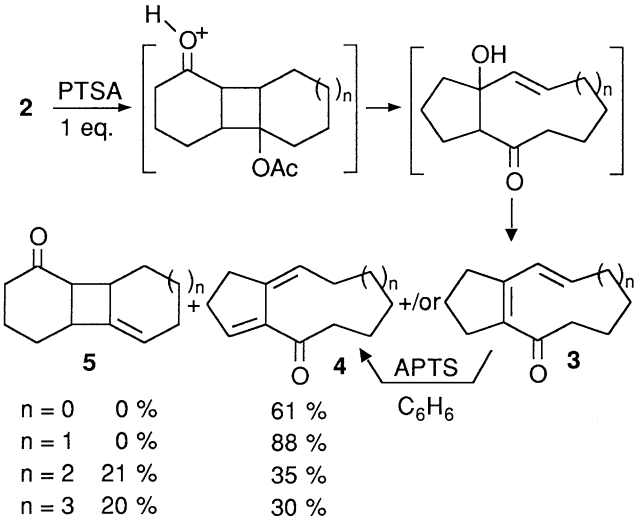


Scheme 1.

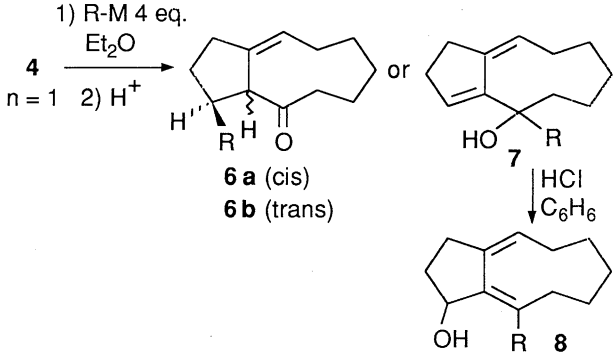
In the presence of PTSA (1 eq.) ketones **2** were transposed at 110°C according to Scheme 2. Dienones **3** were observed only with n = 0 and 1 and were easily transformed into **4** in fair to good yields.

In order to investigate the potential synthetic utility of the previously unknown ketones **4** we studied the condensation of organometallic derivatives with **4** n = 1.

The main interesting results are reported in Scheme 3 and Table 1.



Scheme 2.



Scheme 3.

In the presence of HCl in benzene, alcohols **7** were then easily transposed into alcohols **8** functionalized in the cyclopentane ring.

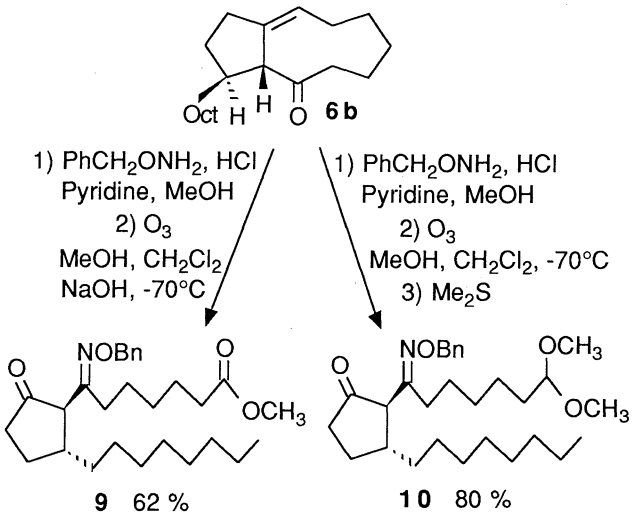
Alcohols **8** are interesting materials for further transformations in order to obtain "cycloprostanoid" compounds with the lateral chain replaced by a ring. Such transformations as well as the biological activity of alcohols **8** themselves are currently under investigation.

Another interesting application of the reaction products developed above is illustrated by the transformation of **6b** into **9** and **10** according to Scheme 4 using procedures described in the literature.[5]

Table 1.

R	M	T°C	t (h)	6a+6b %b	6b/6a	7 %b	8 %c
Me	Li	0	0.5			90	50
Ph	Li	20	3			55	62
Bu	Li	20	2			60	55
≡⟨	Li	20	2			62	73
Oct	MgBr+CuI	0	0.3	62	4/1		
Bu[a]	Cu(CN)Li2	0	0.3	80	4/1		
Me[a]	Cu(CN)Li2	0	0.3	64	4/1		
Ph[a]	Cu(CN)Li2	0	0.3	74	3/2		

[a]Reaction performed in the presence of 5 eq. of Me_3SiCl.[4] [b]Isolated yield based on **4** n = 1. [c]Isolated yield based on **7**.



Scheme 4.

Biological properties of **9** and **10** are also under investigation.

In the present note the first results dealing with a new pathway to prostanoid compounds were presented. It is noteworthy that the starting materials are commercial ketones. Thus compounds **4** n = 1 and **6** to **10** are derived from only cyclohexanone. Indeed they are obtained from the reaction of 1-chlorocyclohexene, prepared from cyclohexanone and PCl_5, with the nucleophilic complex base $NaNH_2$-cyclohexanone enolate.

References and Notes

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6 Data of some key compounds: paranitrobenzoate derivative of **8** R=Me: mp 81°C. Anal. Found: C, 70.26; H, 6.77; N, 4.42 %. Calcd for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79; N, 4.10. IR (KBr) ν 3112, 1721, 1609 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 7.8-8.3 (m, 4 H), 5.2-5.7 (m, 2 H), 1.0-2.3 (m, 17 H); ^{13}C NMR ($CDCl_3$) δ 231.8, 164.2, 150.2, 136.5, 134.8, 132.9, 130.5, 125.8, 123.3, 71.3, 31.1, 28.9, 28.4, 25.2, 22.8, 22.0, 20.5, 18.5. **10** mp 45°C. Anal. Found: C, 73.55; H, 10.28; N, 2.99 %. Calcd for $C_{29}H_{47}O_4N$: C, 73.53; H, 10.00; N, 2.96. IR (KBr) ν 3063, 3031, 1712, 1633 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.47 (m, 5 H), 7.07 (s, 2 H), 4.37 (t, 1 H), 3.33 (s, 6 H), 3.00 (d, $J_{CH\text{-}CH\text{-}Oct}$ = 6.7 Hz), 2.30-2.67 (m, 4 H), 1.10-1.17 (m, 25 H), 0.87 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.2, 158.6, 138.1, 128.3, 127.9, 127.6, 104.1, 75.2, 59.4, 52.4, 41.7, 37.0, 33.1, 32.2, 31.7, 29.5, 29.3, 29.1, 27.9, 26.6, 24.3, 24.0, 23.2, 22.5, 21.8, 14.0.