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SOME POSSIBILITIES OF PROSTANOID SYNTHESIS FROM BICYCLIC EPOXIDE SYNTHONS USING CUPRATE AND LITHIUM ALKYNYDE · BF₃ REAGENTS *

(Presented by Ü. Lille)

Bicyclic systems are highly attractive prostaglandin synthons because their inherent locked stereochemistry may be used to define the stereochemistry of prostanooids. To these bicyclic electrophiles belong also bicyclic epoxides. The main idea of this approach is as follows

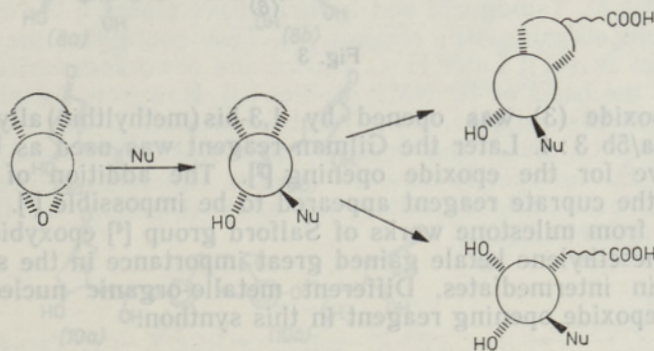


Fig. 1

The stereochemistry of hydroxy functions as well as the side chains are defined by the initial stereochemistry of bicyclic epoxide.

In this report I deal with some aspects and results obtained in the laboratory of prostanooid chemistry using cuprate and lithium alkynyde · BF₃ reagents in the synthesis of prostanooid intermediates from the following bicyclic epoxides

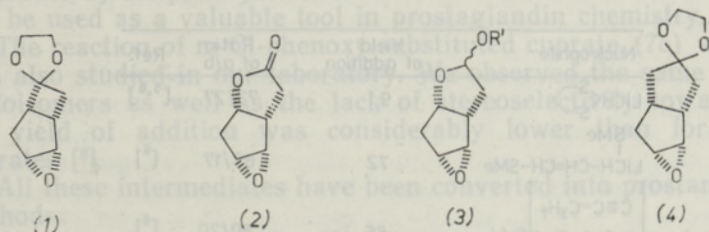


Fig. 2

Bicyclic epoxide was first used in prostaglandin synthesis by E. J. Corey and R. Noyori [1]. They have shown that bicyclic epoxide (3) is a useful prostaglandin synthon (Fig. 3).

* Lecture held at the symposium "Synthesis and Research of Prostaglandins". Tallinn, October, 1986.

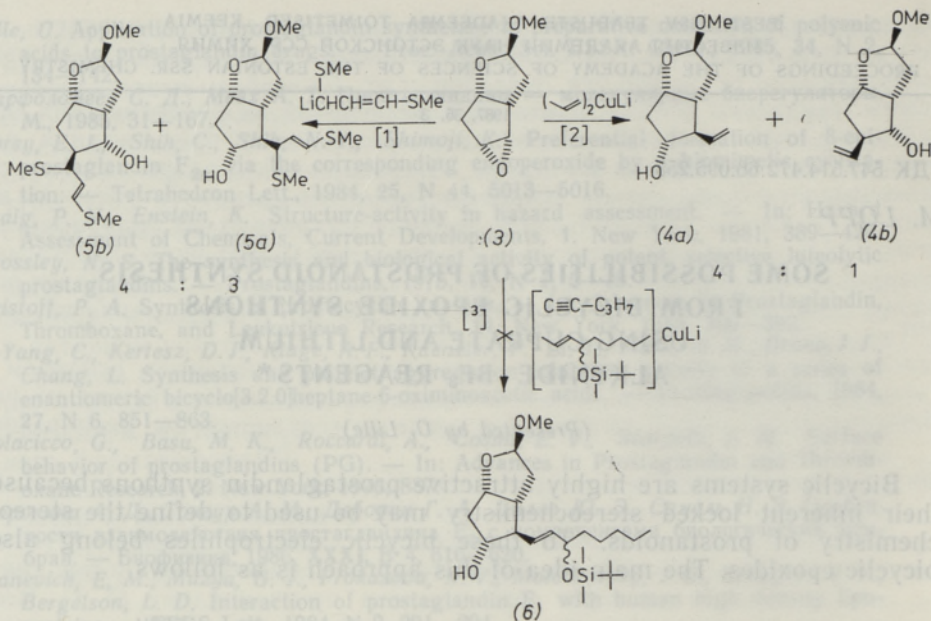
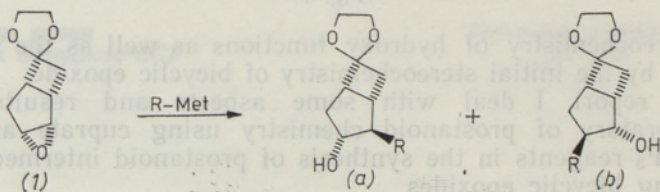


Fig. 3

Thus epoxide (3) was opened by 1,3-bis(methylthio)allyllithium at a ratio of 5a/5b 3:4. Later the Gilman reagent was used as being more regioselective for the epoxide opening [2]. The addition of the whole ω -chain by the cuprate reagent appeared to be impossible [3].

Starting from milestone works of Salford group [4] epoxybicyclo[3.2.0]-heptane-6-one ethylene ketale gained great importance in the synthesis of prostaglandin intermediates. Different metallo-organic nucleophiles are used as an epoxide opening reagent in this synthon.

Table 1


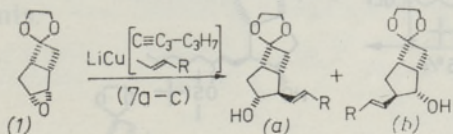

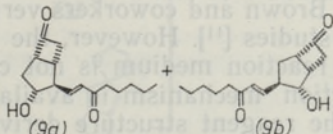
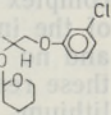
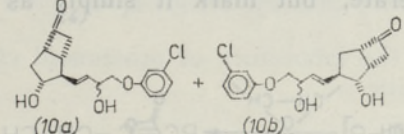


Nucleophile	Yield of addition	Ratio of a/b	Ref.
$\text{LiCH} \begin{array}{c} \text{S} \\ \diagup \quad \diagdown \\ \text{S} \end{array}$	91	73/27	[5,6]
$\text{LiCH} \begin{array}{c} \text{SMe} \\ \\ \text{CH=CH-SMe} \end{array}$	72	83/17	[6]
$\left[\begin{array}{c} \text{C}\equiv\text{C-C}_3\text{H}_7 \\ \\ \text{Si} \\ \\ \text{OSi} \end{array} \right] \text{CuLi}$	86	80/20	[6]
$\text{Me}_2\text{Al-C}\equiv\text{C-CH-C}_5\text{H}_{11}$ $\quad \quad \quad $ $\quad \quad \quad \text{OSiMe}_3$	97	67/33 41/59	[6] [7]
$\text{Me}_2\text{Al} \left[\text{C}\equiv\text{C-CH-C}_5\text{H}_{11} \right]_2 \text{Li}^+$ $\quad \quad \quad $ $\quad \quad \quad \text{OSiMe}_2\text{tBu}$		70/30	[7]

As can be seen from Table 1, the Corey reagent opens the epoxide function in synthon (1) more regioselectively than in lactolepoxide synthon (3) demonstrated above. From the point of view of the prostanoid synthesis, cuprate and alanate reagents are more perspective. The contradiction of the results in [6] and [7] is probably due to the complicity of alane/alanate reagents.

As a compliment to these well-known facts, some results of oxirane opening in epoxide (1) by cuprate reagents obtained in our laboratory are given in Table 2.

Table 2

Cuprate	Product after deblocking	Ratio of a/b	Total yield of addition, %	(7a) R = 
(7a)		4/1	59	(7b) R = 
(7b)		4/1	62	(7c) R = 
(7c)		4/1	25-32	

As is known, the epoxide opening with cuprate (7a) has a serious disadvantage: it completely lacks stereoselectivity towards the C15 hydroxyl function. This disadvantage can be overcome by using ketale cuprate (7b) which leads to ketoenones (9a) and (9b) at a 4/1 ratio. The ketoenone (9a) is easily oxidized into the corresponding lactone which can be reduced in a stereoselective manner into lactonediol by known methods. It should also be mentioned that (9a) and (9b) are easily separable by simple crystallization. For these reasons ketale cuprate (7b) can be used as a valuable tool in prostaglandin chemistry.

The reaction of m-Cl-phenoxy-substituted cuprate (7c) with epoxide (1) was also studied in our laboratory. We observed the same ratio, 4 : 1, for regioisomers as well as the lack of stereoselectivity towards C15. Only the yield of addition was considerably lower than for two previous cuprates [8].

All these intermediates have been converted into prostanoids by known methods.

As to lactone epoxide (2), its unreactivity towards cuprates was demonstrated by E. J. Corey. Surprisingly enough, the epoxide (4) was also unreactive towards cuprates under usual conditions [9]. Though being short and flexible, the cuprate synthesis suffers from several disadvantages. First, a large amount of ω -chain is required, the ω -chain precursor cannot be recovered from the unreacted cuprate. The second disadvantage is the long reaction time (usually 10–24 h) at uncomfortable temperature (-20 – -30°C). The most unfavourable disadvantage, from

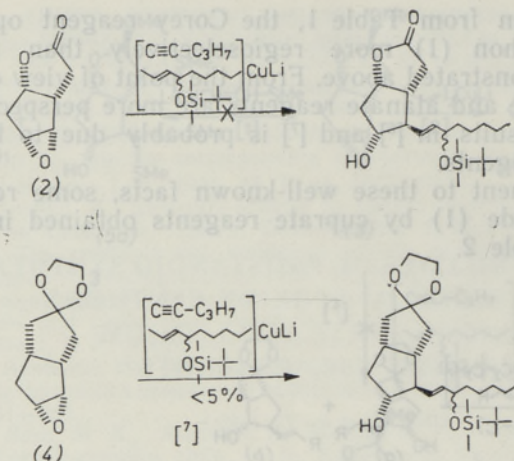


Fig. 4

our point of view, is its unreactivity towards epoxide (4). Therefore we searched for some other nucleophiles for the epoxide opening in prostanoid synthesis. Recently, M. Yamaguchi and I. Hirao have reported the epoxide opening by lithium alkynide \cdot BF₃ reagent [10]. They postulated the structure of the reagent as (11). Later H. C. Brown and coworkers verified the complex (12) on the basis of H¹ NMR studies [11]. However, the problem of the initial reactive substance in the reaction medium is not clear yet and no sufficient data about the reaction mechanism is available. For these reasons we do not specify here the reagent structure derived from lithium alkynide and BF₃ etherate, but mark it simply as lithium alkynide \cdot BF₃ reagent (12a).

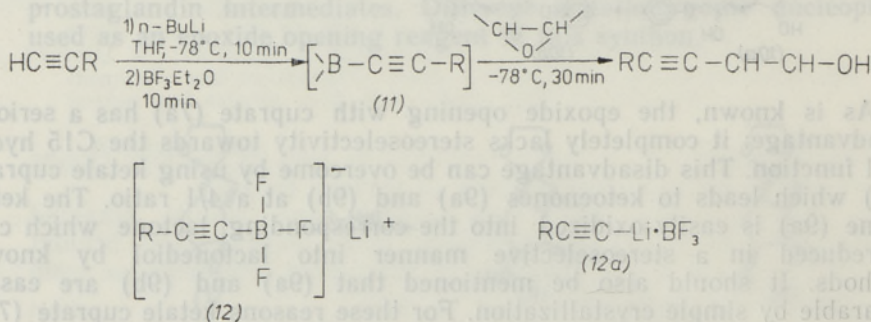


Fig. 5

In Fig. 6 there are presented some results of using lithium alkynide \cdot BF₃ reagent in the oxirane opening reaction with epoxides (1)–(4) in prostanoid synthesis [9, 12, 13].

Epoxide (1) reacts readily with lithium alkynide \cdot BF₃ reagent affording after deblocking ketone diols (13a) and (13b) in the ratio of 56:44. The reaction proceeds at -78°C in 10–30 minutes. This reaction shows a complete lack of stereoselectivity towards C15 hydroxyl function. These regioisomers are easily separable on silica gel but 15 α /15 β -isomers for compound (13a) are inseparable [14]. For regioisomers (13b), α / β -isomers are separable. The ratio of 15 α /15 β -isomers was separately determined by HPLC after the reduction of 13–14 triple bond yielding easily separable allylic alcohols [14]. Epoxide (3) reacts also with lithium alkynide \cdot BF₃ reagent, but in this case there is no regioselectivity as well as no stereoselectivity towards C15 hydroxyl function.

It can be stressed that epoxide (4) which is relatively unreactive towards cuprate reagent, readily reacts with lithium alkynide·BF₃ reagent affording lactonediods (15a) and (15b) at the ratio of 1:1. In this way, synthon (4) can be used in carbacyclin synthesis, giving one of the simplest and shortest way to carbacyclins [9].

Epoxide (2), which is unreactive towards cuprate reagents, reacts with lithium alkynide·BF₃ reagents yielding a complex mixture. Using the model lithium octynide·BF₃ reagent, we were able to establish that the addition reaction proceeds mainly in a 1,2-manner with a lactone carbonyl function. Enynol (16) was separated from the reaction mixture in 35% yield. The desired lactonol (17) was found to be present only in trace amounts.

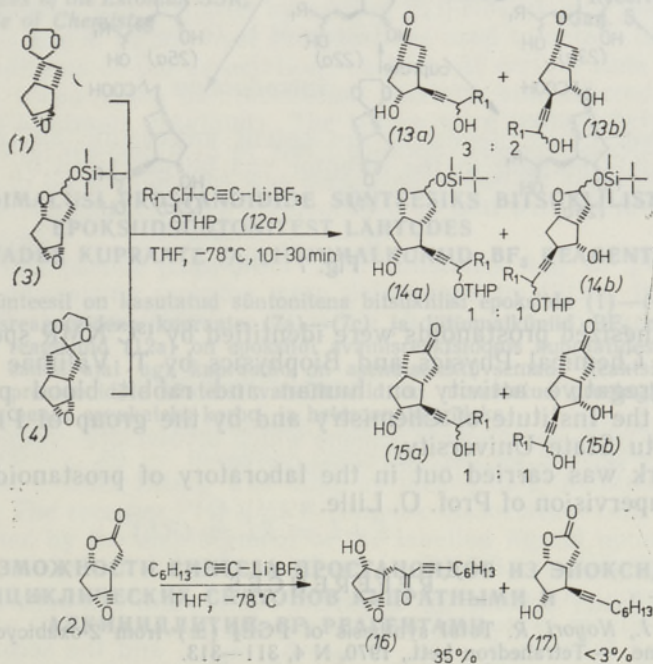


Fig. 6

Summarizing the results obtained by us using lithium alkynide·BF₃ reagents in the synthesis of prostanoic intermediates, it can be said that regardless of the low regioselectivity of the reagent towards epoxide (1) and of the lack of regioselectivity towards epoxides (3) and (4), the lithium alkynide·BF₃ reagent serves as a simple and convenient tool for the synthesis of several prostanoic intermediates. It can also be mentioned that lithium alkynide·BF₃ reagent is useful for the synthesis of both regioisomeric ketonediods. As is known, in some cases both isomers are valuable. Moreover, this approach enables us to recover unconsumed initial acetylene and use it repeatedly.

In Fig. 7 there are demonstrated some ways of converting the above-mentioned bicyclic intermediates into prostanoic [12].

As can be seen, the most universal intermediate is ketonediol (13a) from which all the other intermediates can be synthesized. In some cases, however, direct synthesis of the proper intermediate from the corresponding epoxide is more favourable, for example in the case of ketonediol (15a).

The same transformations shown in the present paper were also carried out starting from the corresponding regioisomers.

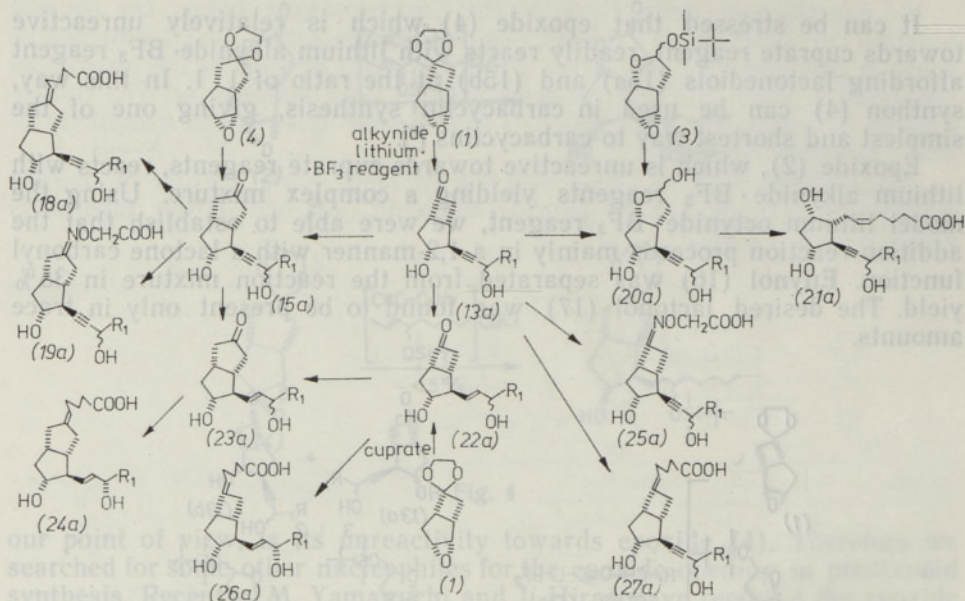


Fig. 7

The synthesized prostanooids were identified by ¹³C NMR spectra at the Institute of Chemical Physics and Biophysics by T. Välimäe and tested for antiaggregative activity on human and rabbit blood platelets by A. Lopp at the Institute of Chemistry and by the group of Prof. R. Teesalu at Tartu State University.

This work was carried out in the laboratory of prostanooid chemistry under the supervision of Prof. Ü. Lille.

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MÕNINGAID VÕIMALUSI PROSTANOIDIDE SÜNTEESIKS BITSÜKLILISTEST EPOKSIIDSÜNTHONITEST LÄHTUDES NING KASUTADES KUPRAATE JA LIITIUMALKÜNIID · BF_3 REAGENTE

Prostanoidide sünteesil on kasutatud süntonitena bitsüklilisi epoksiide (1)—(4) ning oksiraanringi avamisreagentidena kupraate (7a)—(7c) ja liitiumalküniid · BF_3 reagente (12a). On leitud, et reagentid (12a) on epoksiidi avamisreaktsioonis kupraatidest reaktsioonivõimelisemad, samal ajal aga kupraadid on asendiselektiivsemad. Reaktsioonides saadud bitsüklilised prostanoidide sünteesi vaheühendid on muundatud prostaglandiini-deks $\text{F}_{2\alpha}$ ja I_2 ning nende arvukateks karbo- ja heteroanaloogideks.

M. ЛОПП

НЕКОТОРЫЕ ВОЗМОЖНОСТИ СИНТЕЗА ПРОСТАНОИДОВ ИЗ ЭПОКСИДНЫХ БИЦИКЛИЧЕСКИХ СИНТОНОВ КУПРАТНЫМИ И АЛКИНИДЛИТИЙ · BF_3 -РЕАГЕНТАМИ

В синтезе простанойдов использованы в качестве синтонов бициклические эпоксиды (1)—(4), а в качестве реагентов раскрытия оксиранового кольца — купратные (7a)—(7c) и алкинидлтий · BF_3 -реагенты (12a). Установлено, что реакционная способность реагентов (12a) по отношению к эпоксидам выше, а региоселективность их при раскрытии оксиранов ниже, чем купратов (7a)—(7c). Полученные при раскрытии разные бициклические интермедиаты превращены в простагландины $\text{F}_{2\alpha}$, I_2 и их многочисленные карбо- и гетероаналоги.