Pergamon

Tetrahedron Letters 39 (1998) 3541–3542

TETRAHEDRON LETTERS

Stereoselective Chlorination of Steroidal 5,6-Olefin by an Electrochemical Method; A Convenient Synthesis of Blattelastanoside B

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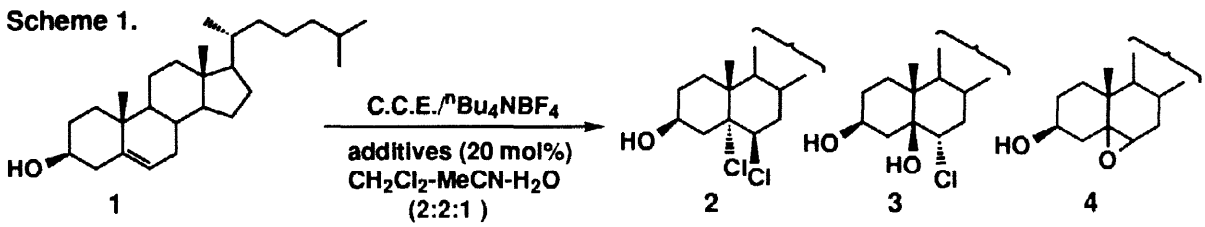
Received 12 January 1998; revised 18 February 1998; accepted 6 March 1998

Abstract: Stereoselective chlorination of cholesterol (**1**) was achieved by an electrochemical method to give a dichloride **2** and a cholohydrin **3**. Using this procedure, blattelastanoside B (**6**), an aggregation pheromone of the German cockroach, was synthesized from β-sitosterol (**5**) in short steps.

The oxidation of cholesterol (**1**), which includes the formation of the chlorides **2** and **3**, and an epoxide **4** (Scheme 1), has been extensively studied not only in organic synthesis[1] but also from the aspect of biological significance.[2] During our studies on oxidation of various substrates by an electrochemical method,[3] we found that **1** stereoselectively afforded **2** and **3**. Furthermore, this procedure was applied to β-sitosterol (**5**), resulting in a highly convenient synthesis of blattelastanoside B (**6**),[4] an aggregation pheromone of the German cockroach *Blattela germanica*. Reported herein are our findings.

Three products 5,6β-dichloro-5α-cholestan-3β-ol (**2**),[5] 6α-chloro-5β-cholestane-3β,5-diol (**3**)[5,6] and the epoxide **4**[7] (α:β=1:3) were obtained in 32, 31 and 7% yields, respectively, when the reaction was conducted under a constant current condition[8] (C. C. E. at -2.0 ~ -2.4 V *vs.* SCE, 25 mA/cm^2; 10 F/mol) with negative polarity in 2:2:1 CH_2Cl_2-MeCN-H_2O (20 mL) containing cholesterol (0.3 mmol), $FeCl_3$ and hematoporphyrin (HMP)[9] as additives (0.06 mmol) and $^nBu_4NBF_4$ as a supporting electrolyte (1.8 mmol) with continuous bubbling of O_2 gas using platinum plates both as an anode and a cathode, respectively (Entry 1, in Table1). It is noteworthy that the reaction proceeds stereoselectively to give a single isomer of the dichloride **2** or the chlorohydrin **3**. Similar conditions without O_2 bubbling afforded the chlorohydrin **3** as a major product in somewhat lower yield without forming any amount of the epoxide **4** (Entry 2). The yields of the chlorides were increased when only $FeCl_3$ was used as an additive (Entry 3),[10] whereas the use of excess $FeCl_3$ (5 eq) with accelerated the reaction rate (3 F/mol) decreased the yields (30-40%). Under the conditions with decelerated current density (20 mA/cm^2), the reactions did not go to completion (Entries 4 and 5). All the above reactions were sluggish under anodic oxidation conditions, resulting in much lower yield.

Scheme 1.



1 2 3 4

Table 1.

Entry	Additives	Current (mA/cm^{-2})	2 (%)	3 (%)	4 (%)	S.M.(%)
1	$FeCl_3$ - HMP/ O_2	25	32	31	7	trace
2	$FeCl_3$ - HMP	25	13	27	-	28
3	$FeCl_3$	25	20	43	-	trace
4	$FeCl_3$ - HMP/O_2	20	24	17	5	32
5	$FeCl_3$	20	17	38	-	21

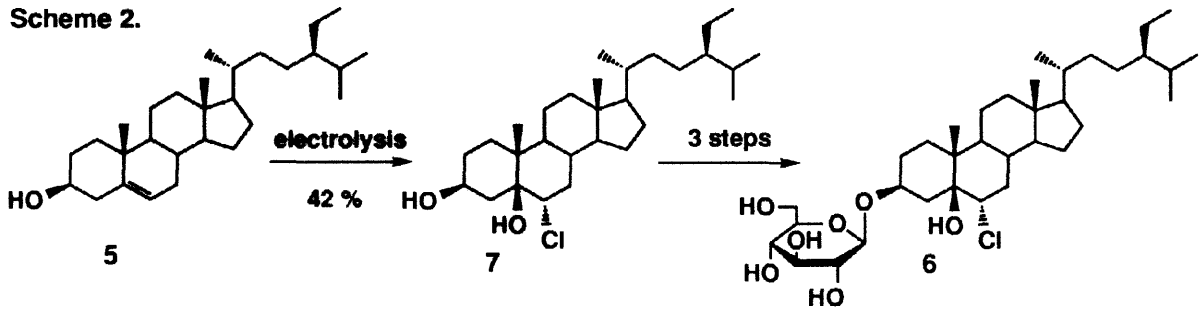
The mechanism in detail remains to be investigated, but some aspects related to the mechanism deserve comment. In all cases, using other organic solvents ($CHCl_3$, CCl_4 and CH_2ClCH_2Cl) instead of CH_2Cl_2 or 80% MeCNaq. resulted in a poor yield or a complex mixture. Other metal salts (KCl, $MnCl_2$, $CoCl_2$ and

PII: S0040-4039(98)00538-3

$ZnCl_2$) were also effective but to a much lesser extent. Without any additives, only a complex mixture was obtained. The reactions did not proceed at all by the use of H_2O_2 instead of electrolysis, which ruled out the possible involvement of electrochemically formed H_2O_2 from H_2O or O_2 under the conditions used. Furthermore, the epoxide **4** was not converted into either the dichloride **2** or the chlorohydrin **3** under these reaction conditions, implying the chlorides were not formed through an epoxide intermediate. Moreover, no reaction took place when using a divided cell. The stereoselectivity observed could be rationalized on the assumption that the reaction takes place in an electrical double layer,[11] where the substrate interacts with the active species in some sophisticated manner.

We have applied this chlorination reaction to an improved synthesis of blattelastanoside B (**6**), an aggregation pheromone of the German cockroach *Blattela germanica*. Treatment of β-sitosterol (**5**) under the same conditions as Entry 3 in Table 1 afforded the desired chlorohydrin **7**[12] in 42 % yield[13] (Scheme 2). The chlorohydrin **7**, the aglycon of **6**, has been previously synthesized from **5** in 21% overall yield in 11 steps and subsequently converted into **6** in 3 steps by Mori and co-workers.[4b] Accordingly, a highly convenient synthesis of **6** was completed by using our electrochemical procedure, demonstrating the usefulness of the electrochemical method for organic synthesis.

Scheme 2.



References and Notes

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5. Kimura, M.; Tohma, M.; Tomita, T. *Chem. Pharm. Bull.*, **1973**, *21*, 2521.
6. The structure of **8**, the monoacetate of **3**, was determined by X-ray crystallographic; Crystal data: $C_{29}H_{49}ClO_3$ (recrystallized from AcOEt-hexane), MW 481.16, orthorhombic, space group $P2_12_12_1$, a=12.978(3), b=32.719(5), c=6.729(4) Å, V=2857.3(19) Å^3, Z=4, Dx=1.119 Mg m^{-3}, μ(Mo Kα)=0.160 mm^{-1}, R=0.088 for 851 reflections.
7. Watabe, T.; Isobe, M.; Ozawa, N. *J. Biol. Chem.*, **1981**, *256*, 2900.
8. Electrolysis using a constant potential condition (C. P. E. at -2.4 V *vs.* SCE; 10 F/mol) gave the same results.
9. Hematoporphyrin was used based on the results previously reported in Ref. 3b, because we initially attempted to obtain hydroxylated product(s) at the 5,6-olefin site.
10. The chlorine atoms incorporated into the substrate should in part come from CH_2Cl_2 since the amount of chlorine in the products is larger than that of $FeCl_3$ used.
11. Bockris, J. O'M.; Devanathan, M. A. V.; Müller, K. *Proc. Roy. Soc. London*, **1963**, *A274*, 55.
12. All the spectral data of this compound were identical with those reported previously in Ref. 4b.
13. A dichloride corresponding to **2** was obtained together with **7** in 11% yield.