NEW METHOD OF PREPARATION OF BRASSINOSTEROIDS*

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Brassinosteroids with lactone B-ring (*II* and *IV*) were prepared by oxidation of the corresponding 6-keto derivatives *I* and *III* without protection of the hydroxyl groups against the action of the oxidation reagent.

In the synthesis of brassinolide, 24-epibrassinolide (24*R*-brassinolide), homobrassinolide, and other brassinolides with B-lactone ring, the last steps consist in the preparation of the lactone from the corresponding 6-keto derivative. According to the hitherto used reaction sequence[1 – 5], the vicinal diol grouping in the corresponding 6-keto derivative (in the A-ring, as e.g. in *Ia*, but also in the side-chain, as e.g. in *III*) is protected, usually as diacetate which is then subjected to Baeyer–Villiger oxidation to give the B-homo-lactone (e.g. *IIa*) with protected diol grouping(s). The deprotection is usually realized by alkaline hydrolysis whereupon the lactone ring has to be closed again in an acid medium.

In the course of our investigations on brassinosteroids we have found that no protection of the diol grouping is necessary and that the Baeyer–Villiger oxidation can be performed directly with the dihydroxy (*Ia* – *If*) or tetrahydroxy (*III*) 6-ketone, making thus the synthesis of brassinosteroids shorter. This method of preparation was already used by us in one of our previous studies[6]. In this paper we show that this reaction can be applied also to other 6-ketones (Scheme 1). We converted the corresponding 6-ketones *I* and *III* into lactone *II* and 24-epibrassinolide *IV* [(22*R*,23*R*,24*R*)-2α,3α,22,23-tetrahydroxy-24-methyl-B-homo-7-oxa-5α-cholestan-6-one]. As seen from Table I, this procedure not only shortens the synthetic pathway but also gives higher yields.

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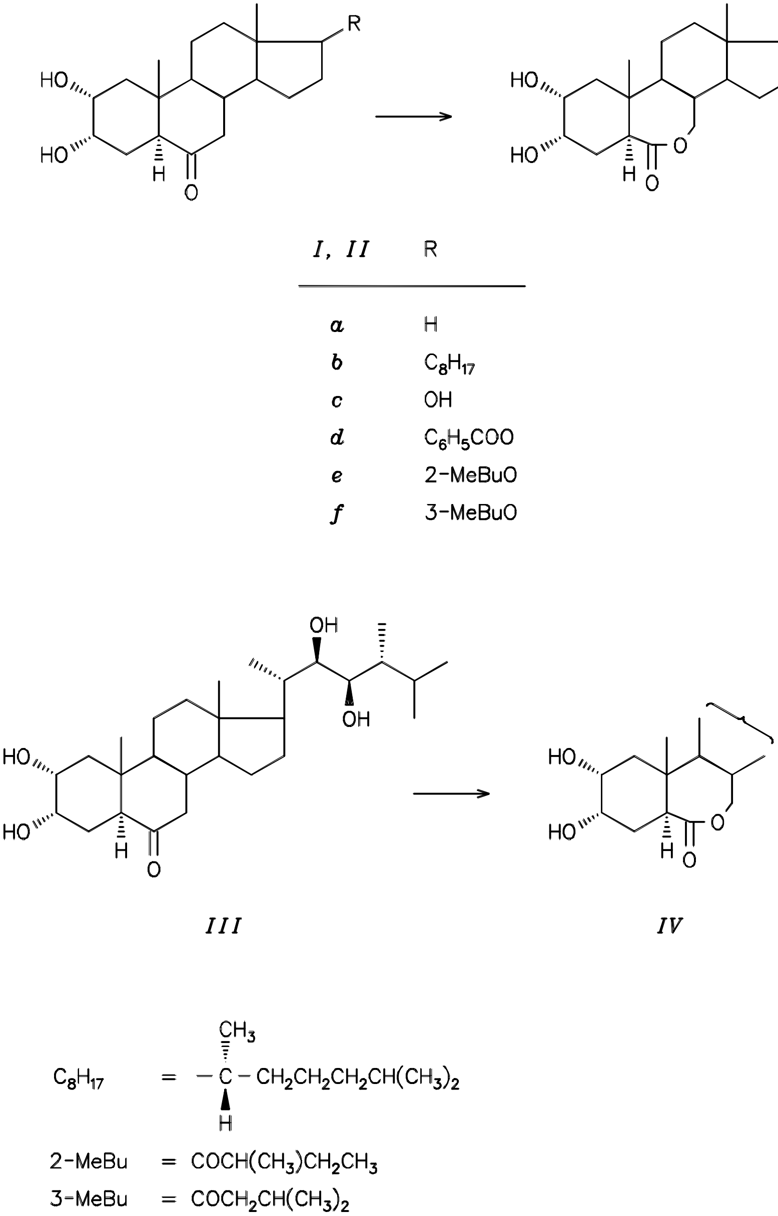

I, II	R
a	H
b	C_8H_{17}
c	OH
d	C_6H_5COO
e	2-MeBuO
f	3-MeBuO

III

IV

C_8H_{17} = $-\overset{CH_3}{\underset{H}{C}}-CH_2CH_2CH_2CH(CH_3)_2$

2-MeBu = $COCH(CH_3)CH_2CH_3$

3-MeBu = $COCH_2CH(CH_3)_2$

SCHEME 1

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Infrared spectra were recorded on a Zeiss UR 20 spectrometer in tetrachloromethane solution (unless stated otherwise), wavenumbers are given in cm^{-1}. Proton NMR spectra were taken in deuteriochloroform on a Varian XL-200 instrument (FT mode, 200 MHz) with tetramethylsilane as internal standard and the data were interpreted as the first-order spectra. ^1H NMR spectra and IR spectra of the prepared samples were identical with those given in the literature[1,7,10]. Preparative TLC was carried out on 200 × 200 mm plates coated with 0.7 mm thick layer of silica gel Woelm DC. The light petroleum was a fraction boiling at 40 – 62 °C.

Oxidation of 6-Ketones with Trifluoroperoxyacetic Acid

A solution of trifluoroperoxyacetic acid (prepared from trifluoroacetic anhydride (0.63 g, 3.0 mmol) and 50% hydrogen peroxide (0.10 g, 1.5 mmol) in dichloromethane (1.5 mm) immediately before use) was added to a solution of the 6-keto derivative (0.2 mmol) in dichloromethane (8 ml). The mixture was allowed to stand at room temperature for 24 h, the reaction course being monitored by TLC. The mixture was poured into water and the product was taken up in chloroform. The chloroform extract was washed with water, 5% aqueous solution of potassium hydrogen carbonate and water, dried and the solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography on silica gel in chloroform–isopropanol (9 : 1). Work-up of the appropriate fractions gave the desired lactone. For physical properties of the obtained lactones see Table I.

Oxidation of 6-Ketones with 3-Chloroperoxybenzoic Acid

A solution of the 6-keto derivative (0.2 mmol) in dichloromethane (10 ml) was mixed with solid 70% 3-chloroperoxybenzoic acid (0.74 g, 3 mmol) and the mixture was set aside at room temperature for 5 – 21 days, the reaction course being monitored by TLC. After the reaction had ended, the mixture was poured in water and worked up in the same manner as described in the preceding experiment.

TABLE I
Melting points and yields of the synthesized lactones (yields given for oxidation with trifluoroperoxyacetic acid; yields of oxidation with 3-chloroperoxybenzoic acid were about 10 – 15 % lower)

Ketone	Lactone	M.p., °C	Yield, %	Reported		
				M.p., °C	Yield, %	Ref.
Ia	*IIa*	185 – 188	85	186 – 188	15	7
Ib	*IIb*	136 – 138	67	oil	10	8
Ic	*IIc*	212 – 215	69	212 – 215	62	9
Id	*IId*	242 – 245	88	244 – 247	55	9
Ie	*IIe*	195 – 197	72	195 – 197	46	10
If	*IIf*	oil	78	oil	27	10
III	*IV*	255 – 257	53	256 – 258	<40	1

The residue, obtained after evaporation of chloroform, was purified by chromatography on thin layers of silica gel (elution with chloroform–isopropyl alcohol 9 : 1) or on a small column of silica gel (elution with chloroform–ether 1 : 1). Properties of the thus-obtained lactones agreed with those of lactones prepared according to the preceding procedure (oxidation with trifluoroperoxyacetic acid).

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REFERENCES

1. Thompson M. J., Mandava N., Flippen-Anderson J. L., Worley J. F., Dutky S. R., Robbins W. E., Lusby W.: J. Org. Chem. *44*, 5002 (1979).
2. Mori K., Sakakibara M., Ichikawa Y., Ueda H., Okada K., Umemura T., Zabuta G., Kuwahara S., Kondo M., Minobe M., Sogabe A.: Tetrahedron *38*, 2099 (1982).
3. Aburatani M., Takeuchi T., Mori K.: Agric. Biol. Chem. *51*, 1909 (1987).
4. Akhrem A. A., Lakhvich F. L., Khripach V. A., Kovganko N. V.: Dokl. Akad. Nauk SSSR *269*, 363 (1983).
5. Ishiguro M., Takatsuto S., Morisaki M., Ikekawa N.: J. Chem. Soc., Chem. Commun. *1980*, 962.
6. Kohout L., Strnad M.: Collect. Czech. Chem. Commun. *57*, 1731 (1992).
7. Kohout L., Strnad M.: Collect. Czech. Chem. Commun. *54*, 1019 (1989).
8. Kondo M., Mori K.: Agric. Biol. Chem. *47*, 97 (1983).
9. Kohout L., Cerny V., Strnad M.: Collect. Czech. Chem. Commun. *52*, 1027 (1987).
10. Kohout L.: Collect. Czech. Chem. Commun. *54*, 3348 (1989).

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