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# Submission of some Iodoformates to the Woodward–Prévost Conditions

Stefan Hamm,[a] Lothar Hennig,[a] Matthias Findeisen,[a] Dietrich Müller[b] and Peter Welzel[a,*]

[a]*Universität Leipzig, Fakultät für Chemie und Mineralogie, Johannisallee 29, D-04103 Leipzig, Germany*
[b]*Fakultät für Chemie der Ruhr-Universität, D-44780 Bochum, Germany*

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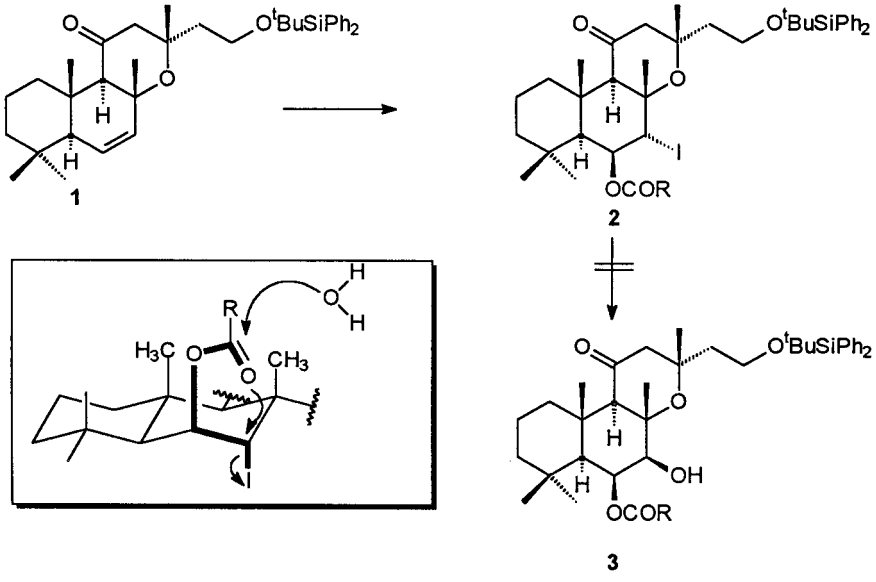
**Abstract**—The synthesis of two iodoformates is described. 3α-Iodo-5α-cholestane-2β-yl formate (**6**) reacts under the usual Woodward–Prévost conditions to provide the expected hydroxyformates **5** and **7**. Unfortunately, a 6β-formyloxy-7α-iodo-labdane derivative, prepared in the context of forskolin synthetic studies, could not be forced to react analogously. 

## Introduction

The Woodward–Prévost reaction[1,2] is a well-known procedure for the introduction of a *cis*-diol functionality at the sterically more hindered face of an olefin.

However, some examples were reported that did not proceed in the desired sense.[3–7] In the case of 5α-cholest-7-ene, a vicinal *trans*-diol (after ester cleavage), obviously the result of a classical Prévost reaction, was observed as the main product, even in the presence of water.[3] The reason for the non-participation of water was discussed in terms of sterical hindrance of flanking methyl groups preventing nucleophilic attack of water to the acetoxonium ion (Scheme 1).

Our synthetic approach towards forskolin and derivatives intended to introduce the 6,7-*cis*-diol moiety on the more sterically hindered face of **1** by a Woodward–Prévost reaction. The *trans*-iodoacetate **2** (R=$CH_3$), an intermediate of the reaction, was isolated in 75% yield and could not be induced to react to the desired *cis*-hydroxyacetate **3**




**Scheme 1.**

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* Corresponding author: Tel.: +49-341/97-36551; fax: +49-341/97-36599; e-mail: welzel@organik.chemie.uni-leipzig.de

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(R=$CH_3$).[8] Obviously, the neighbouring group effect of the acetate is not operating in this case, although an X-ray structure indicates that the requirements for the formation of the acetoxonium ion are probably met. An explanation could be that water participates in the nucleophilic substitution step and that the acetate carbonyl carbon has already some $sp^3$ character as the oxygen approaches C-7. Since the water must necessarily approach from the *exo*-direction this would position the acetate methyl group over ring B and lead to severe steric compression with the axial methyl groups at C-8 and C-10. It is interesting to note that the ortho esters formed from glycosyl halides with an ester group at C-2 have the alkyl group of the acid part mainly *endo* whereas the incoming alcohol is *exo*.[9]

We were interested to find out whether we could overcome the failure of the Woodward–Prévost reaction of 1 using a formate version, i.e. replace the acetate $CH_3$ by the less bulkier hydrogen.

In principle, two possibilities exist for this formate Woodward–Prévost reaction: One could treat the olefin with iodine and silver formate in formic acid–water, or prepare the *trans*-iodoformate independently and submit it to the usual Woodward–Prévost conditions.

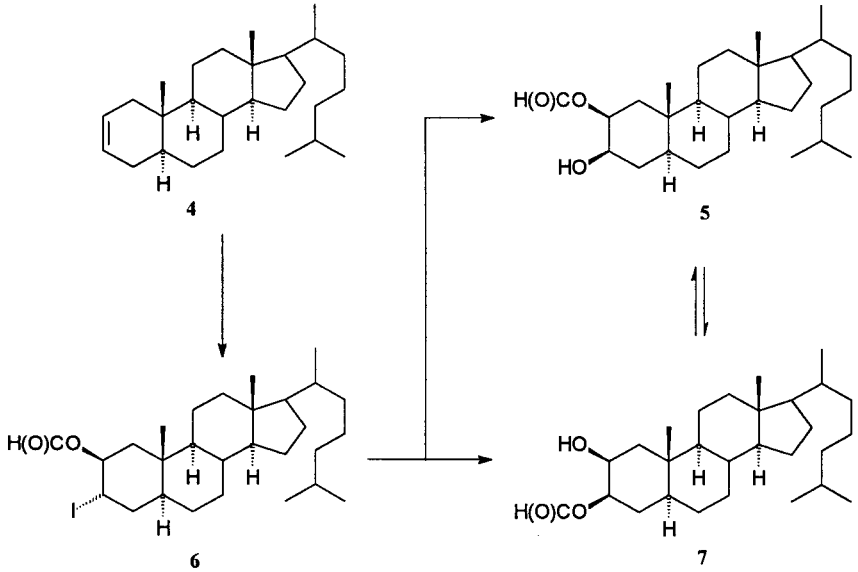
Unfortunately, **1** suffered extensive decomposition on treatment with iodine and silver formate[10] in formic acid at rt (Scheme 1).

Therefore, some methods for the preparation of *trans*-iodoformates[11–21] were tested and modified, with 5α-cholest-2-ene **4**, a well-known model compound for the Woodward–Prévost reaction (Scheme 2). Thus, **4** reacted with *N*-iodosuccinimide in DMF-chloroform in a slow (96 h) but mild reaction to give **6** (58% yield, 21% of 4 recovered).[11] The same product was obtained in a slow reaction (20 h) of **4** with *N*-iodosuccinimide and stoichiometric amounts of formic acid in chloroform at rt (54% yield, 29% recovered **4**).[20] At 40°C the reaction was complete after 2 h (58% yield of **6**). The most suitable procedure for the preparation of **6** consisted in the treatment of **4** with mercuric formate and iodine (72% yield, 15 min). Larger amounts of the reagents (2:2:1 molar ratio of olefin, $I_2$, $Hg(HCO_2)_2$) had to be used than in the previously reported examples.[21] The configuration of the iodoformate was determined by $^1$H NMR spectroscopy: The signals for 2-H and 3-H appeared as broad singlets with small vicinal coupling constants. Thus, the diaxial product was formed in agreement with the Fürst–Plattner rule.[22]

Iodoformate **6** was then submitted to the usual Woodward–Prévost conditions (AgOAc, stoichiometric $H_2O$, in HOAc). Two hydroxyformates **5** and **7** were isolated in a combined yield of 75% (3:2 ratio as determined by $^1$H NMR). The isomers could not be separated completely due to acyl migration even when the silica gel was treated with a base-containing eluent. The structural data of **5** and **7** were in accord with those of the corresponding hydroxyacetates.[23] The application of silver perchlorate monohydrate in THF at rt as an acid-free method led to the formation of **5** and **7** only in traces, besides numerous unidentified products.

For the formation of the iodoformate **2** (R=H) the reaction of **1** with *N*-iodosuccinimide in DMF, shown to be a mild method in the model case, was tried first. Rather extreme conditions (heating to 60°C for 6 d) were necessary. **2** (R=H) was isolated in a low yield of 11%. The method of choice was the reaction of **1** with mercuric formate and iodine giving **2** (R=H) in 87% yield. The attempt to convert **1** to **2** with NIS and stoichiometric amounts of formic acid in chloroform remained unsuccessful: No conversion could be detected after heating at 40°C for 48 h. The rise of temperature to 60°C caused complete decomposition of the starting material.

The structure of **2** (R=H) was in agreement with the NMR results. HMBC experiments confirmed the 6-iodo-7-formyloxy constitution. $J_{6,7}$ was 2.2 Hz.




**Scheme 2.**

Disappointingly, when **2** (R=H) was submitted to the usual Woodward–Prévost conditions, even heating at 80°C did not cause any conversion. The formate **2** seemed to be as unreactive as the corresponding acetate under these conditions.

In conclusion, we have shown that 3α-iodo-5α-cholestane-2β-yl formate (**6**) reacts nicely under the usual Woodward–Prévost conditions to provide the expected hydroxyformates. Unfortunately, the iodoformate 2 could not be forced to react analogously.

## Experimental

**3α-Iodo-5α-cholestane-2β-yl formate (6).** (a) To a solution of 5α-cholest-2-ene (**4**, 48 mg, 0.13 mmol) in chloroform (0.1 ml, filtered through basic alumina) a solution of *N*-iodosuccinimide (100 mg, 0.44 mmol) in *N*,*N*-dimethylformamide (1 ml) was added at room temperature, and the mixture was stirred for 96 h in the dark. After addition of water (2 ml) and stirring for 15 min the cognac-coloured mixture was washed with a saturated sodium thiosulfate solution (10 ml). Usual work-up (dichloromethane/sodium sulfate) and FC (petrolether–ethyl acetate 30:1) yielded **6** (41 mg, 58%). 10 mg of the starting material were recovered.

(b) To a stirred solution of 5α-cholest-2-ene (**4**, 30 mg, 82 μmol) in chloroform (0.5 ml) a solution of *N*-iodosuccinimide (67 mg, 300 μmol) in chloroform (1 ml) was added at room temperature. Formic acid (6 μl, 156 μmol) was added dropwise with rigorous stirring. After stirring for 20 h, the reaction mixture was diluted with chloroform, washed with an aqueous sodium thiosulfate solution (5 N) and neutralized with an aqueous sodium carbonate solution (2 N). After usual work-up (dichloromethane/sodium sulfate) and FC (petrolether–ethyl acetate 30:1) **6** (24 mg, 44 μmol, 54%) and recovered starting material **4** (9 mg, 24 μmol, 29%.) were isolated.

(c) To a stirred mixture of 5α-cholest-2-ene (**4**, 22 mg, 61 μmol) and mercury(II) formate (19 mg, 272 μmol) in dichloromethane (0.5 ml) a solution of iodine (133 mg, 524 μmol) in dichloromethane (4*0.5 ml) was added at room temperature. Initially, the reaction mixture discoloured the solution of iodine and became later yellow. After 15 min a quantitative conversion could be detected, and an orange precipitate occurred that was removed by filtration. The filtrate was washed with an aqueous sodium thiosulfate solution (10%) and with an aqueous potassium iodide solution (saturated). Usual work-up (dichloromethane/sodium sulfate) and FC (petrolether–ethyl acetate 20:1) yielded **6** (24 mg, 44 μmol, 72%). Mp: 109–110°C (petrolether), lit.110–111°C, ref. IR (KBr): 1721 (s, HC(O)O), 1181 (s, C–O). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=0.65 (s, 3H, $CH_3$), 0.86 (d, 1H, $CH_3$, $J$=6.6 Hz), 0.87 (d, 1H, $CH_3$, $J$=6.6 Hz), 0.91 (d, 5H, $CH_3$+$CH_2$, $J$=6.6 Hz), 0.94 (s, 1H, $CH_3$), 0.96–2.02 (mk, 27H, $10^*CH_2$, $7^*CH$), 4.56 ($s_{broad}$, 1H, 3β-H), 5.34 ($s_{broad}$, 1H, 2α-H), 7.91 (s, 1H, OC(O)–H). $C_{28}H_{47}O_2I$ (542.58, 542.26), FAB MS m/z=565.1 $[M+Na]^+$, 497.1 $[M+H-HCO_2H]^+$.

**Submitting 3α-iodo-5α-cholestane-2β-yl formate to Woodward–Prévost conditions**

To a suspension of **6** (44 mg, 81 μmol) in acetic acid (400 μl) water (15 μl, 830 μmol) and a suspension of silver acetate (19 mg, 116 μmol) in acetic acid (1 ml) were added. After stirring for 72 h at room temperature another portion of silver acetate (17 mg, 103 μmol) in acetic acid (0.5 ml) was added. The reaction was stopped after 96 h by adding an aqueous saturated sodium chloride solution (4 ml). The resulting yellowish precipitate was removed by filtration and washed with petrolether and ethyl acetate. The filtrate was evaporated, the residue dissolved in ethyl acetate and filtered again. The filtrate was neutralized with an aqueous saturated sodium hydrogencarbonate solution (5 ml) and worked up as usual. **5** and **7** were formed in a 3:2 ratio as determined by $^1$H NMR. FC (petrolether–ethyl acetate 8:1) gave **6** (4 mg, 7.9 μmol, 10%) besides a fraction rich in **5** (13 mg) and another one rich in **7** (14 mg). The combined yield was 75%. Subsequent FC (petrolether–ethyl acetate 8:1+0.1 vol.% triethylamine) of the **5**-rich fraction gave 3 mg of pure **5** and of **7**-rich fraction 2 mg of pure **7**.

**5α-Cholestane-2β,3β-diol 3-formate (7).** $^1$H NMR (200 MHz, $CDCl_3$): $\delta$=0.65 (s, $CH_3$), 0.50–2.20 (mk, 45H, $5^*CH_3$, $11^*CH_2$, $7^*CH$, $1^*OH$), 4.00–4.18 (m, H, $2_\alpha$-H), 4.87–4.94 (m, 1H, $3_\alpha$-H), 8.09 (d, 1H, OCHO, $J$=1 Hz). $C_{28}H_{48}O_3$ (432.69, 432.36), FAB-MS $m/z$=455.3 $[M+Na]^+$, 415.3 $[M+H-H_2O]^+$, 387.3 $[M+H-HCO_2H]^+$. HRMS: found 455.3501, calc for $C_{28}H_{48}O_3Na$ 455.3501.

**5α-Cholestane-2β,3β-diol 2-formate (5).** $^1$H NMR (200 MHz, $CDCl_3$): $\delta$=0.64 (s, 3H, $CH_3$), 0.70–2.20 (mk, 42H, $4^*CH_3$, $11^*CH_2$, $7^*CH$, $1^*OH$), 3.58–3.90 (m, 1H, $3_\alpha$-H), 5.10–5.22 (m, 1H, $2_\alpha$-H), 8.16 (s, 1H, OCHO). $C_{28}H_{48}O_3$ (432.69, 432.36), FAB-MS $m/z$=455.3 $[M+Na]^+$, 433.5 $[M+H]^+$, 415.3 $[M+H-H_2O]^+$, 387.3 $[M+H-HCO_2H]^+$. HRMS: found 433.3682, calc for $C_{28}H_{49}O_3$ 433.3681.

**(8*SR*, 13*SR*)-6β-Formyloxy-7α-iodo-8,13-epoxy-15-(*tert*-butyldiphenylsilanyloxy)-labd-11-one (*rac*-2, R=H)**

(a) To a stirred solution of *rac*-**1** (17 mg, 30 μmol) in chloroform (30 μl) a solution of *N*-iodosuccinimide (80 mg, 360 μmol) in DMF (300 μl) was added. After stirring for 67 h at room temperature no conversion could be detected. A second crop of NIS (47 mg, 209 μmol) in DMF (0.2 ml) was added and the mixture was stirred at 40°C for 18 h. Again, no conversion could be observed. A slow conversion took place at 60°C. The reaction was left at this temperature for 6 d. Then water (600 μl) was added. Work-up as described above and FC (petrolether–ethyl acetate 30:1) yielded *rac*-**2** (R=H, 3 mg, 3.4 μmol, 11%).

(b) *rac*-**1** (9 mg, 16 μmol) and mercury(II) formate (35 mg, 121 μmol) were dissolved in dichloromethane (0.25 ml) at room temperature. A solution of iodine (63 mg, 249 μmol) in dichloromethane (2 ml) was added. The reaction mixture initially discoloured the solution of iodine but turned yellow later. After 15 min quantitative conversion was observed.

Work-up as described above and FC (petrolether–ethylacetate 20:1) yielded *rac*-**2** (R=H, 10 mg, 14 μmol, 87%) as a colourless resin. IR ($CHCl_3$): 1719 (s, C=O). $^1$H NMR (400 MHz, $CDCl_3$, HH COSY): ($\delta$=0.76–0.81 (m, 1H, 1-H), 0.84 (s, 3H, $CH_3$-18), 0.96 (s, 3H, $CH_3$-19), 0.97 (s, 9H, $CH_3$-*tert*.-butyl), 1.04–1.13 (m, 1H, 3-H), 1.20 (s, 3H, $CH_3$-16), 1.27–1.35 (m, 1H, 3-H), 1.37 (s, 3H, $CH_3$-20), 1.54 (s, 3H, $CH_3$-17), 1.65–1.68 (m, 2H, $CH_2$-2), 1.84–1.88 (m, 2H, $CH_2$-14, $J_{14,15}$=6.8 Hz), 1.96 (s, 1H, 5-H), 2.19 (d, 1H, 1-H, $J_{1,1'}$=12.7 Hz), 2.22 (d, 1H, 12-H, $J_{12,12'}$=12.7 Hz), 2.59 (s, 1H, 9-H), 2.68 (d, 1H, 7H, $J$=2.2 Hz), 3.75–3.85 (m, 1H, 15-H), 3.90–3.96 (m, 1H, 15-H, $J_{14,15}$=6.8 Hz), 4.42 (d, 1H, 7-H, $J$=2.2 Hz), 5.76 (s, 1H, 6-H), 7.19–7.37 (m, 6H, Ar-H), 7.58–7.68 (m, 4H, Ar-H), 7.95 (s, 1H, 21-H). $^1$H NMR (600 MHz, $C_6D_6$): (=0.90 (s, 3H, $CH_3$-18), 0.92 (s, 3H, $CH_3$-19), 1.10 (s, 3H, $CH_3$-20), 1.24 (s, 9H, $CH_3$-*tert*-butyl), 1.35 (s, 3H, $CH_3$-16), 1.56 (s, 3H, $CH_3$-17), 1.90–1.95 (m, 1H, 14-H), 1.98–2.02 (m, 1H, 14-H, $^3J_{14,15}$=4.2 Hz), 2.07 ($s_{broad}$, 1H, 5-H), 2.21 (d, 1H, 12-H, $^2J_{12,12}$=9.4 Hz), 2.56 (d, 1H, 12-H, $^2J_{12,12'}$=9.4 Hz), 2.68 (s, 1H, 9-H), 4.05–4.08 (m, 1H, 15-H), 4.17–4.21 (m, 1H, 15-H, $^3J_{14,15}$=5.2 Hz), 4.41 (d, 1H, 7-H, $J$=1.7 Hz), 6.03 (s, 1H, 6-H), 7.27–7.33 (m, 6H, Ar-H), 7.86–7.88 (m, 5H, Ar-H, CHO). $^{13}$C NMR (100.6 MHz, $C_6D_6$, APT, HMQC, HMBC): ($\delta$=15.85 ($CH_3$-20), 17.15 ($CH_2$-2), 18.08 (Cq-*tert*-butyl), 22.10 ($CH_3$-19), 23.77 ($CH_3$-17), 25.89 ($CH_3$-*tert*-butyl), 27.88 ($CH_3$-16), 31.22 ($CH_3$-18), 32.65 (Cq-4), 36.48 (Cq-10), 39.74 ($CH_2$-1), 42.94 ($CH_2$-3), 45.18 (CH-7), 46.86 ($CH_2$-14), 47.10 (CH-5), 52.65 ($CH_2$-12), 59.75 ($CH_2$-15), 62.87 (CH-9), 74.68 (CH-6), 76.39 (Cq-8), 77.55 (Cq-13), 126.67/126.69 (CH-Ar), 128.62 (CH-Ar), 132.80 (Cq-Ar), 134.64/134.66 (CH-Ar), 158.89 (CH-21), 206.35 (Cq-11). $C_{37}H_{51}O_5SiI$ (730.79, 730.26), FAB MS: *m*/*z*=753.2 $[M+Na]^+$, 731.3 $[M+H]^+$, 603.5 $[M+H-HI]^+$. HRMS: found 731.2635, calc for $C_{37}H_{52}O_5SiI$ 731.2629.

### Submission of (13*S*)-6β-formyloxy-7α-iodo-8,13-epoxy-15-(*tert*-butyldiphenylsilanyloxy)-labd-11-one (*rac*-2, R=H) to Woodward–Prévost conditions

To a stirred solution of *rac*-**2** (R=H, 6 mg, 7.5 μmol) in acetic acid (96%, 100 μl) at room temperature a suspension of silver acetate (4.3 mg, 26 μmol) in acetic acid (3*100 μl) was given. After 7.5 h again a suspension of silver acetate (10 mg, 62 μmol) in acetic acid (2*100 μl) was added. After 24 h at 20°C the reaction mixture was warmed to 40°C for 3 h and then to 60°C. After 3 h at 60°C a further portion of silver acetate (17 mg, 102 μmol) in acetic acid (3*100 μl) was added and the mixture was stirred for 18 h. It was heated to 80°C and water (100 μl) was added. After cooling to room temperature no conversion of the starting material could be detected by TLC.

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