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Original Scientific Paper

Reaction of Cross-Conjugated Systems With Diisobutylaluminium-Hydride and Oxygen*

Milutin Stefanović and Bogdan Šolaja

Department of Chemistry, Faculty of Science, University of Belgrade, P.O. Box 550, 11001 Belgrade, Yugoslavia

and

Ivana Aljančić-Šolaja

Institute for Chemistry, Technology and Metallurgy, Njegoševa 12, 11000 Belgrade, Yugoslavia

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After discovering that conjugated ketones may be converted to *syn*-epoxy-alcohols by DIBAH and oxygen, the investigation was expanded to cross-conjugated dienone systems, *i. e.* α-santonin and adrosta-1,4-diene-3,17-dione. The addition of 1 M DIBAH in toluene converted these dienones to intermediate aluminoxy derivatives which, after passing oxygen through the reaction mixture and continuous addition of DIBAH, gave the corresponding *syn*-epoxy-alcohols. No formation of diepoxy and *anti*-epoxy--alcohols was observed.

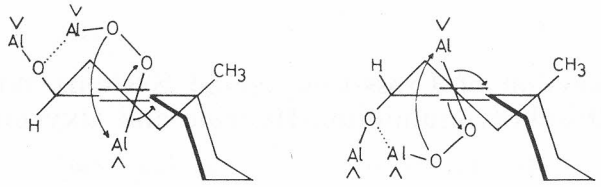
Diisobutylaluminium hydride (DIBAH) has been known as a versatile reducing agent for over 25 years.[1] Moreover, we established that steroidal 4-en-3-ones when treated with this reagent in toluene solution at —10 °C under argon, which was not liberated from traces of oxygen, gave the expected 3β-allylic alcohols and small amounts of 3β-hydroxy-4β,5β-epoxides.[2] By modifying the experimental conditions by passing molecular oxygen through the reaction mixture with simultaneous addition of DIBAH, we[3] increased the yields of *syn*-epoxy-alcohols to 45—90%.

We suggested[3] that the first stage of this one-pot reduction and epoxidation reaction is likely to involve attack of DIBAH on the ketone function to give an allylic aluminoxide, which undergoes subsequent epoxidation with tetraisobutyl-aluminiumperoxide (i-Bu_2AlO—$AOlBu_2^i$) formed as an interme-

* Dedicated to Professor Mihailo Lj. Mihailović on the occasion of his 60th birthday.

diate in the reaction of DIBAH and oxygen*. Also, in the epoxidation step the bulky tetraisobutylaluminium-peroxide molecule probably forms a donor--acceptor pair[3] (scheme 1) with the intermediate allylic aluminoxide, thus directing the formation of *syn*-epoxy-alcohol.

Scheme 1



Steroidal 5-en-3-ones, under the same epoxidation conditions, gave only homoallylic alcohols and none of the *syn*-epoxy-alcohols. Raising the reaction temperature to the boiling point of toluene containing the homallylic aluminoxide, and the passage of oxygen for several hours gave 4-en-3-ones in high yields.[4] The reaction mechanism was also established and the formation of 5-en-3β,4β-diols and 4-en-3β-ols as reaction intermediates was confirmed.

We also succeeded in transforming 5-en-3-ols to 4-en-3-ones using DIBAH and acetone. A simple treatment of steroidal 5-en-3-ols with DIBAH and the reflux of the aluminoxy intermediate in acetone gave 4-en-3-ones in high yields. In this way it was possible to obtain 17β-hydroxy-androsta-4-en-3-one and 20β-hydroxy-pregn-4-en-3-one for the first time in one operation starting from 3β-hydroxy-androsta-5-en-17-one and 3β-hydroxy-pregn-5-en-20-one, respectively.[3]

Now, we wish to report the results of the reduction, and also of the reduction with subsequent epoxidation of the cross-conjugated system of α-santonin and androsta-1,4-diene-3,17-dione, using DIBAH for the reduction and DIBAH/molecular oxygen for the epoxidation.

Thus, when α-santonin *I* (Fig. 1) was reduced with DIBAH at —10 °C, according to the general procedure (see Experimental), the main product was hemiacetal *II* in 14% yield**, the other product being hemiacetal *III* with the dienone ring unchanged (~1% yield).

Hemiacetal *II* was presumably derived from an intermediate of type II_i which underwent dienol-benzene rearrangement with migration of the angular methyl group to C-1. In solution, this compound exists in equilibrium with its aldehyde form *II'*, as indicated by ^{1}H NMR spectrum taken in deutero-

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* The proposed mechanism for the reaction of DIBAH and oxygen:

$$\underset{1}{i\text{-Bu}_2\text{AlH}} + \text{O}_2 \rightarrow \underset{2}{i\text{-Bu}_2\text{AlOOH}}$$

$$1 + 2 \rightarrow \underset{3}{i\text{-Bu}_2\text{AlOOAlBu}_2^i} + \text{H}_2$$

$$1 + 3 \rightarrow \underset{4}{i\text{-Bu}_2\text{AlOAlBu}_2^i} + \underset{5}{i\text{-Bu}_2\text{AlOH}}$$

$$1 + 5 \rightarrow 4 + \text{H}_2$$

** The disintegration of the products on SiO_2 column lowered the overall yield drastically, as indicated by TLC of the original reaction mixture.

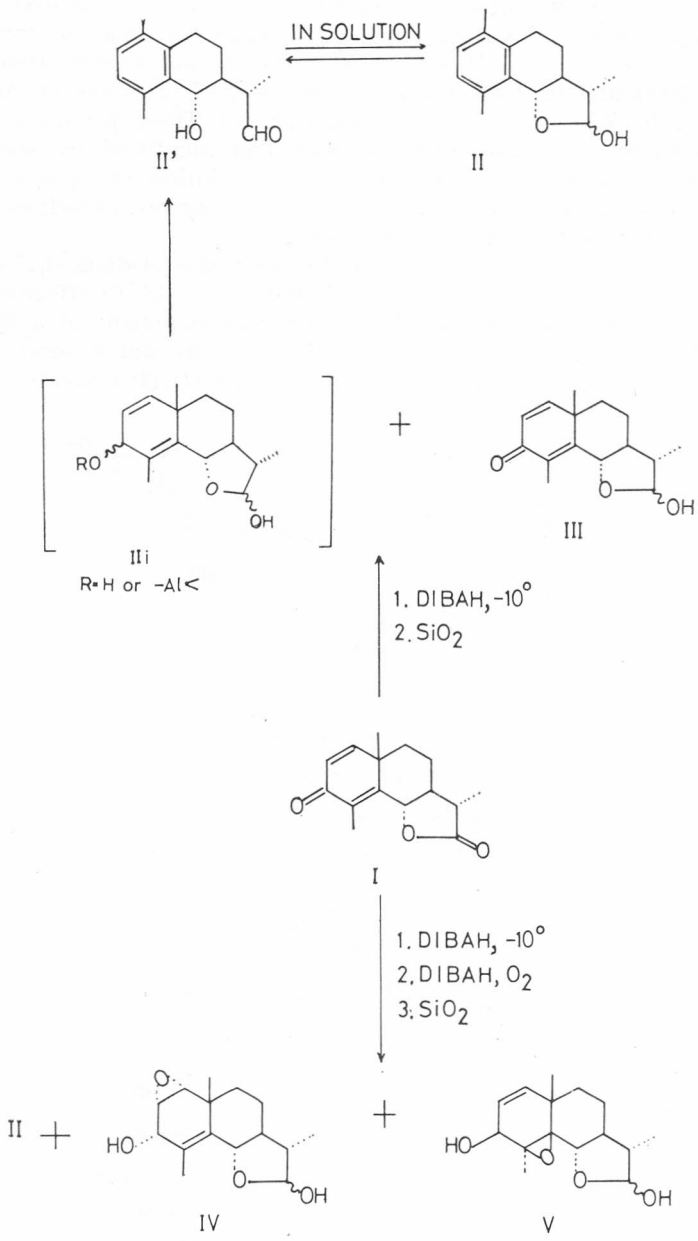


Figure 1.

pyridine solution*, and also by the appearance of the peak at 1740 cm^{-1} (for —CHO group) in IR spectrum taken in CCl_4 solution (absent when IR spectrum was taken in KBr pellets).*

However, when α-santonine was first reduced with DIBAH and subsequently epoxidized by passing oxygen through the reaction mixture with simultaneous addition of DIBAH, besides the dienol-benzene rearrangement product *II* (obtained in 2.5% yield), α- and β-epoxy-alcohols *IV* and *V* were formed as well (9% and 5% yields, respectively). These products were separated by column chromatography on SiO_2 and identified by spectral data. Relevant ^1H NMR data for the structure elucidation of epoxy-alcohols *IV* and *V* are given in Table I. It should be noted that no formation of diepoxy alcohols or *anti*-epoxy alcohols was observed.

Similar results were obtained with androsta-1,4-diene-3,17-dione, *i. e.* reduction of this dienone system with DIBAH at —10 °C afforded 4-methyl derivative *VII* (produced by dienol-benzene rearrangement of a species analogous to II_i) as the main product (in 52.6% yield) and a small amount of the 17-hydroxy compound with unchanged ring *VIII* (1% yield).

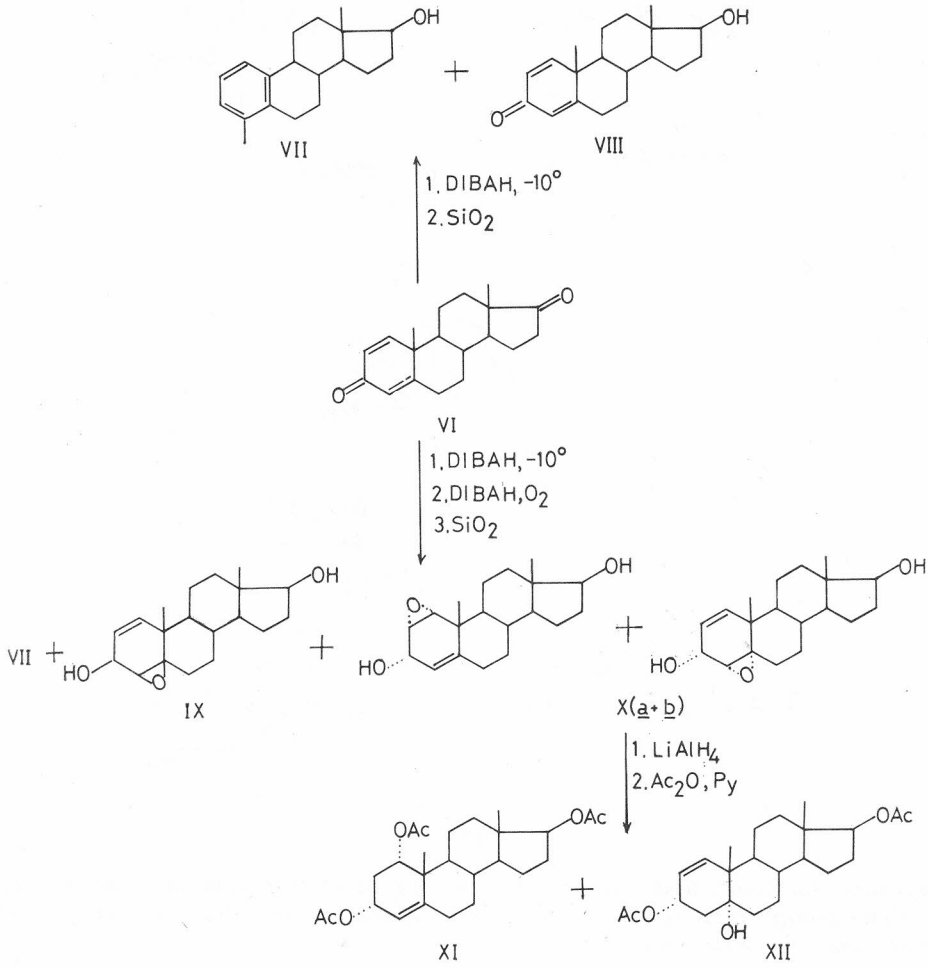
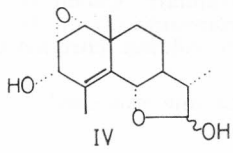
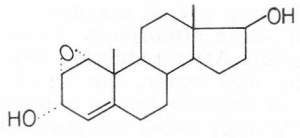
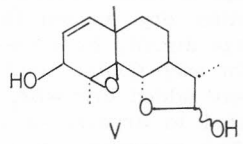
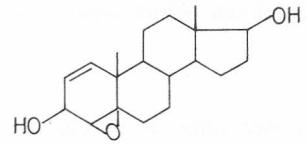
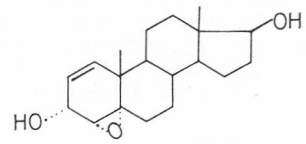


Figure 2.

On the other hand, reduction and further treatment of androsta-1,4-diene--3,17-dione *VI* with DIBAH and oxygen gave, in addition to 4-methyl derivative *VII* (45.4% yield), structurally and/or stereochemically different epoxy--alcohols *IX* (6% yield), and *Xa* and *Xb* (in overall yield 19.7%). Epoxy--alcohols *Xa* and *Xb* could not be separated by column chromatography with the mixture appearing as one spot on TLC in different developing systems. In ^{1}H NMR spectrum, it had two kinds of signals characteristic of structures X_a and X_b. These structures were determined indirectly by reductive cleavage of the epoxide ring with $LiAlH_4$ in boiling THF solution and acetylation of the corresponding alcohols thus obtained. In this way, epoxy-alcohol *Xa* was transformed to triacetate *XI*, while isomeric epoxy-alcohol *Xb* to diacetate

TABLE I

^{1}H NMR ($CDCl_3$, δ) Data of H-1 and H-2 of syn-*Epoxy-Alcohols*

Compound	H_1	H_2
 IV	3.03(d) $J = 4$ Hz	3.53(dd) $J = 4$ Hz $J = 5$ Hz
 a(from X)	3.25(d) $J = 4$ Hz	3.55(m)
 V	5.22(dd) $J = 10$ Hz $J = 2$ Hz	5.38(dd) $J = 10$ Hz $J = 2$ Hz
 IX	5.38(dd) $J = 11$ Hz $J = 2$ Hz	5.53(dd) $J = 11$ Hz $J = 2$ Hz
	5.30(ddd) $J = 10$ Hz $J = 2$ Hz $J = 2$ Hz	5.65(dd) $J = 10$ Hz $J = 2$ Hz

XII, which could be easily separated by column chromatography. The structure and stereochemistry of the santonin derivatives and the androstene compounds *IX*, *X* (*a*+*b*), *XI* and *XII* were elucidated by physical measurements, particularly ^{1}H NMR spectra. Thus, the coupling parameters observed for the resonance signals of the protons at C-2 in epoxy-alcohols (*IV*, *V IX*, *Xa* and *Xb*) (Table I) are in accordance with the proposed structures.[10] On the other hand, the chemical shifts of the methyl protons at C-18 and C-19, calculated according to the additivity rules for the substitution effects in steroid systems[11] for compounds *XI* (1.12 ppm and 0.85 ppm) and *XII* (0.92 ppm and 0.82 ppm) are in good agreement with the corresponding experimental values, *i. e.* *1.05* ppm and 0.78 ppm for *XI*, and 0.95 and 0.78 for *XII*.

EXPERIMENTAL

Melting points were taken on the Boetius PHMK apparatus and were not corrected. IR spectra were recorded (KBr pellets or $CHCl_3$ solution) on a Perkin-Elmer spectrophotometer, model 337. ^{1}H NMR spectra were recorded on a FT-80A spectrometer in $CDCl_3$ using tetramethylsilane as internal standard. Chemical shifts were expressed in terms of δ (ppm) values and coupling constants (J) in Hz. Thin-layer chromatography was performed on Silicagel G, and column chromatography on Silicagel for column chromatography (0.063—0.200 mm).

In all reactions the 1 M solution of DIBAH in hexane was used.

Reduction with DIBAH — General Procedure

Experiments were caried on a 2—3 g scale using a 1 M solution of DIBAH in hexane, in absolute toluene at —10 °C under an argon atmosphere. One mole equivalent of DIBAH was used for every carbonyl group. After reduction, the aluminoxy complex was destroyed by addition of methanol and water, the white precipitate was removed, and the filtrate was evaporated to dryness under reduced pressure. The products were isolated by column chromatography using benzene-ethyl acetate as eluent.

Reduction and Epoxidation with DIBAH and Oxygen-General

The reductions were performed as described above. After reduction, the obtained aluminoxy complex was oxidized by bubbling dry oxygen through the reaction mixture while adding DIBAH (with a syringe directly to the solution). At least two mole equivalents of DIBAH were added for each double bond. After the epoxidation was completed, methanol and water were added dropwise, the precipitate was removed, and the filtrate was evaporated to dryness *in vacuo*. The products were isolated by column chromatography. The exception was the mixture of epoxides *X* (*a* + *b*) which was reduced and acetylated before separation by column chromatography.

Reduction of α-Santonine

A solution of 2 g (8.13×10^{-3} mole) of α-santonine in absolute toluene was reduced with 17.9 ml of DIBAH at —10 °C, under an argon atmosphere. The usual work-up and column chromatography yielded:

II, 260 mg (14%), m. p. 97—100 °C (from acetone); $[\alpha]_D^{23}$ + 59.44° (c = 1, chl); IR (ν_{max}, CCl_4): 3620, 3420, 3080, 3030, 1740, 1490, 1470, 1050 cm^{-1}, IR (ν_{max}, KBr): 3400, 3070, 3040, 3020, 1490, 1470, 1050 cm^{-1}; ^{1}H NMR (ppm, pyridine-d_5): δ 1.02 and 1.08 (2 × d, J = 7 Hz, H-13), 2.05 (s, H-14), 2.55 and 2.65 (2 × s, H-15), 4.95 (m, H-6), 5.55 (d, J = 4 Hz, H-12, acetal), 6.95 and 7.00 (2 × s, H-2 and H-3), 9.68 (d, J = 2 Hz, aldehyde).

Anal. $C_{15}H_{20}O_2$ (232.29) calc'd.: C 77.55; H 8.68%
found: C 77.40; H 8.82%.

III, oil, IR (ν_{max}, film): 3395, 3030, 1660, 1620, 1600 cm^{-1}; ^1H NMR (ppm, $CDCl_3$): δ 1.12 (3 H, d, $J = 7$ Hz, H-13), 1.25 (3 H, d, $J = 7$ Hz, H-14), 2.17 (3 H, d, $J = 1.5$ Hz, H-15), 4.68 (1 H, d, $J = 10$ Hz, H-6), 5.18 (1 H, d, $J = 5$ Hz, H-12), 6.17 (1 H, d, $J =$ $= 10$ Hz, H-2), 6.65 (1 H, d, $J = 10$ Hz, H-1).

Reduction and Epoxidation of α-Santonine

A solution of 2 g (8.13×10^{-3} mole) of α-santonin in absolute toluene was reduced with 17.9 ml of 1 M DIBAH at —10 °C. When the reduction was completed (TLC), DIBAH (36 ml) under oxygen atmosphere was added. After the usual work--up, three products were obtained:

II, 50 mg (2.5%), m. p. 97—99 °C;

IV, 109 mg (9%), oil; $[\alpha]^{18}_D + 8.23°$ (c = 0.43, chl); IR (ν_{max}, CCl_4): 3410, 1730, 1685, 840 cm^{-1}; ^1H NMR (ppm, $CDCl_3$): δ 1.08 (3 H, s, H-14), 1.10 (3 H, d, $J = 8$ Hz, H-13), 1.98 (3 H, s, H-15), 3.03 (1 H, d, $J = 4$ Hz, H-1), 3.53 (1 H, dd, $J = 4$ Hz, $J =$ $= 5$ Hz, H-2), 4.10 (1 H, bd, $J = 8$ Hz, H-3), 4.38 (1 H, bd, $J = 10$ Hz, H-6), 5.06 (1 H, m, H-12);

V, 192 mg (5%), oil; $[\alpha]_D^{18} — 0.89°$ (c = 1.89, chl); IR (ν_{max}, CCl_4): 3420, 3020, 1660, 830 cm^{-1}; ^1H NMR (ppm, $CDCl_3$): δ 1.06 (3 H, s, H-14), 1.11 (3 H, d, $J = 8$ Hz, H-13), 1.78 (3 H, s, H-15), 4.12 (1 H, d, $J = 11$ Hz, H-3), 4.32 (1 H, d, $J = 10$ Hz, H-6), 5.12 (1 H, m, H-12), 5.22 (1 H, dd, $J = 10$ Hz, $J = 2$ Hz, H-1), 5.38 (1 H, dd, $J = 10$ Hz, $J = 2$ Hz, H-2).

Reduction of Androsta-1,4-diene-3,17-dione

A solution of 1.8 g (6.33×10^{-3} mole) of androsta-1,4-diene-3,17-dione in absolute toluene was reduced with 14 ml of DIBAH at —10 °C, in argon atmosphere. After work-up and column chromatography, products VII and VIII were obtained:

VII, 0.9 g (52.6%), m. p. 117—118 °C (from acetone-heptane), lit. m. p. 113— —114 °C[7]; IR (ν_{max}, KBr): 3320, 3060, 1580, 1470, 1140, 1080, 1060 cm^{-1}; ^1H NMR (ppm, $CDCl_3$): δ 0.75 (3 H, s, H-19), 2.20 (3 H, s, H-18), 3.70 (1 H, t, $J = 8$ Hz, H-17), 6.90— —7.15 (3 H, m, H-1, H-2 and H-3);

VIII[8], oil, IR (ν_{max}, KBr): 3460, 3030, 1680, 1615, 1595 cm^{-1}; ^1H NMR (ppm, $CDCl_3$): δ 0.80 (3 H, s, H-19), 1.23 (3 H, s, H-18), 3.63 (1 H, m, H-17), 6.03 (1 H, d, $J = 2$ Hz, H-4), 6.18 (1 H, dd, $J = 10$ Hz, $J = 2$ Hz, H-2), 7.03 (1 H, d, $J = 10$ Hz, H-1).

Reduction and Epoxidation of Androsta-1,4-diene-3,17-dione

A solution of 3 g (10.54×10^{-3} mole) of androsta-1,4-diene-3,17-dione in absolute toluene was reduced with 23.2 ml of DIBAH at —10 °C. When the reduction was complete (TLC), DIBAH (46.5 ml) was added under oxygen atmosphere. After the usual work-up products *VII*, *IX* and *X* (*a* + *b*) were obtained:

VII, 1.3 g (45.4%), m. p. 117—118 °C;

IX, 0.21 g (6%), m. p. 239 °C (from acetone); $[\alpha]_D^{24} + 57.46°$ (c = 0.56, chl); IR (ν_{max}, KBr): 3450, 3320, 3020, 1650, 1050, 840 cm^{-1}; ^1H NMR (ppm, $CDCl_3$): δ 0.75 (3 H, s, H-19), 1.12 (3 H, s, H-18), 3.25 (1 H, m, H-4), 3.70 (1 H, m, H-17), 4.45 (1 H, dd, $J = 11$ Hz, $J = 2$ Hz, H-3), 5.38 (1 H, dd, $J = 11$ Hz, $J = 2$ Hz, H-1), 5.53 (1 H, dd, $J = 11$ Hz, $J = 2$ Hz, H-2);

Anal. $C_{15}H_{28}O_3$ (304.21) calc'd.: C 74.96; H 9.27%
C 75.10; H 9.11%;

X (*a* + *b*), 0.63 g (19.7%); ^1H NMR (ppm, $CDCl_3$): δ 0.78 (s, H-19), *X* (*a* + *b*)), 1.03 and 1.08 (2 × s, H-18), *X* (*a* + *b*), 3.25 (d, $J = 4$ Hz, H-1, *Xa*), 3.33 (t, $J = 2$ Hz, H-4, *Xb*), 3.55 (m, H-2, *Xa*), 3.70 (m, H-17, *X* (*a* + *b*)), 4.32 (m, H-3, *X* (*a* + *b*)), 5.10 (d, $J = 2$ Hz, H-4, *Xa*), 5.30 (ddd, $J = 10$ Hz, $J = 2$ Hz, $J = 2$ Hz, H-1, *Xb*), 5.65 (dd, $J = 10$ Hz, $J = 2$ Hz, H-2, *Xb*).

Anal. $C_{19}H_{28}O_3$ (304.21) calc'd.: C 74.96; H 9.27%
found: C 74.90; H 9.05%.

Reductive Opening[9] *of Oxirane Ring and Acetylation*

A solution of *X* (*a* + *b*), 60 mg (1.97×10^{-4} mole) in THF was added dropwise to the suspension of 22 mg (5.91×10^{-4} mole) of $LiAlH_4$ in THF. The mixture refluxed for 2 hours, then a few drops of ethyl acetate and water were added, and the precipitate was removed and washed with methanol and chloroform. The filtrate was evaporated to dryness *in vacuo* and acetylated overnight with acetic anhydride in pyridine at room temperature. After work-up and column chromatography products *XI* and *XII* were obtained:

XI, 35.1 mg (41.16%), m. p. 142—145 °C (from acetone-hexane); $[\alpha]_D^{18} + 1.64°$ (c = 0.35, chl); IR (ν_{max}, CCl_4): 1725, 1650, 1355, 1245, 1040 cm^{-1}; ^1H NMR (ppm, $CDCl_3$): δ 0.78 (3 H, s, H-19), 1.05 (3 H, s, H-18), 2.00 (3H, s, —OAc), 2.03 (3 H, s, —OAc), 2.05 (3 H, s, —OAc), 4.58 (1 H, t, J = 8 Hz, H-17), 4.82 (1 H, m, H-1), 5.15 (1 H, m, H-3), 5.45 (1 H, d, J = 6 Hz, H-4).

Anal. $C_{25}H_{36}O_6$ (432.56) calc'd.: C 69.42; H 8.39%
found: C 69.12; H 8.24%;

XII, 23 mg (37.7%), m. p. 166—170 °C (from acetone hexane); $[\alpha]_D^{18} - 20.45°$ (c = 0.95, chl); IR (ν_{max}, CCl_4): 3580, 3030, 1730, 1355, 1235 cm^{-1}; ^1H NMR (ppm, $CDCl_3$): δ 0.78 (3 H, s, H-19), 0.95 (3 H, s, H-18), 2.00 (3 H, s, —OAc), 2.02 (3 H, s, —OAc), 4.58 (1 H, t, J = 6 Hz, H-17), 5.28 (1H, m, H-3), 5.65 (1 H, dd, J = 10 Hz, J = 2 Hz, H-1), 6.08 (1 H, dd, J = 10 Hz, J = 2 Hz, H-2);

Anal. $C_{23}H_{34}O_5$ (390.52) calc'd.: C 70.74; H 8.78%
found: C 70.78; H 8.62%.

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IZVOD

Reakcije dienona s diizobutilaluminij-hidridom i kiseonikom

M. Stefanović, B. Šolaja i I. Aljančić-Šolaja