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Dedicated to Full Member of the Russian Academy of Sciences B.A. Trofimov on the 65th Anniversary of His Birth

Trofimov Reaction with Oximes Derived from Ketosteroids: Steroid–Pyrrole Structures

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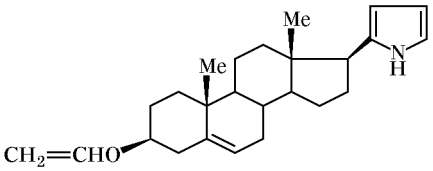
Abstract—Steroidal ketone oximes, namely pregnenolone oxime, Δ^5-cholesten-3-one oxime, and progesterone dioxime react with acetylene in superbasic systems (Trofimov reaction) to afford steroid–pyrrole assemblies. The process is accompanied by prototropic migration of double bonds in the steroid fragment and vinylation of hydroxy groups in sterols with acetylene. The *O*-vinyl group can readily be removed by methanolysis.

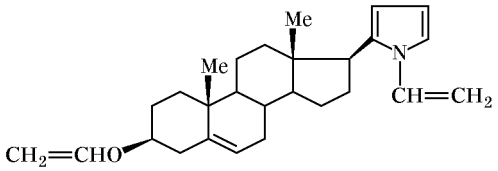
Steroid skeleton and pyrrole ring are components of many molecular structures responsible for fundamental biochemical processes. Structural variation of steroid molecules gives rise to a wide series of compounds which perform a diversity of functions, from structurization of cell membranes [1] and transport of nutrients to regulation of pregnancy and water–salt metabolism [2]. Pyrrole structures constitute a part of such physiologically important molecules as heme, chlorophyll, hemoglobin, alkaloids, vitamin B_{12}, etc. [3]. Therefore, combination of a pyrrole ring and steroid skeleton in a single molecule opens new prospects in the purposeful design of pharmacological agents. An illustrative example is extremely high biological activity of batrachotoxin whose structure includes both steroid and pyrrole fragments [4].

The goal of the present work was to elucidate the synthetic potential of the Trofimov reaction (synthesis of pyrroles from ketone oximes and acetylene in superbasic media) [5–8] as applied to formation of a bond between pyrrole ring and steroid skeleton.

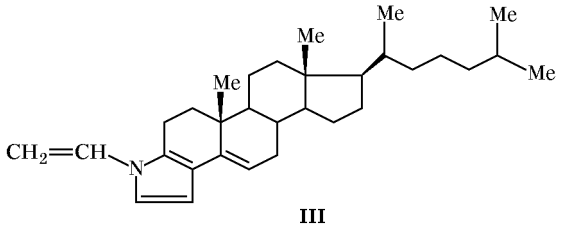
Previously, we briefly reported on the synthesis of pyrrole derivatives of steroids (compounds **I**–**III**) from pregnenolone oxime [9, 10] and Δ^5-cholesten-3-one oxime [11]. These results indicated the applicability of that approach to building up of a pyrrole ring both at the steroid chain and fused to the polycyclic framework [9–11].



I



II



III

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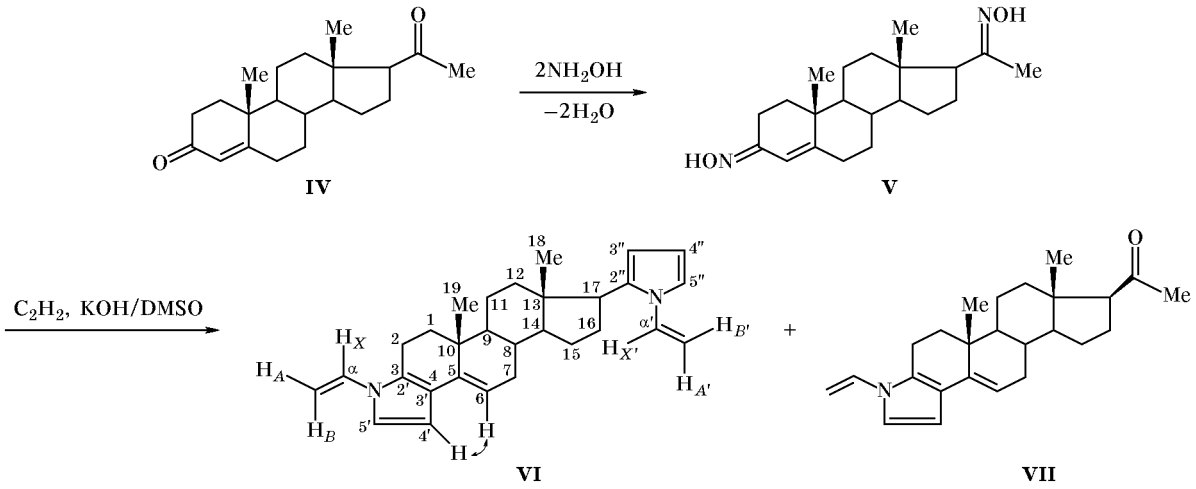
Scheme 1.



In the reaction with Δ^5-cholesten-3-one oxime (120°C, 30 min), the yield of steroid pyrrole **III** was considerably lower (25%) than the the yield of tetrahydroindoles from cyclohexanone oxime and its methyl derivatives (70–93%) [8, 12]. Nevertheless, the regioselectivity of this reaction (which involves only the methylene group in position *4*) is an indubitable synthetic advantage. The reactivity of the 1-hydroxyiminoethyl fragment of pregnenolone (100°C, 5 h, yield of **II** 63%) is comparable with that of alkyl methyl ketone oximes (100°C, 1 h, yield 70–80%) [6–8].

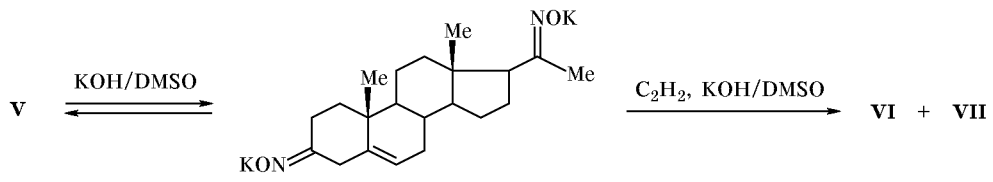
While continuing our studies on the Trofimov reaction with oximes derived from ketosteroids, we were the first to extend this approach to dioxime **V** obtained from progesterone (**IV**) (Scheme 1). The molecule of **IV** is an almost exact combination of structural fragments from pregnenolone and Δ^5-cholesten-3-one (except for the position of the double carbon–carbon bond). The reaction of dioxime **V** with acetylene in the system KOH–DMSO (120°C, 1 h) is accompanied by partial deoximation of the side-chain acetyl group, as it was observed with pregnenolone oxime [10]. The formation of pyrrole ring with participation of the oxime moiety in the steroid fragment follows the same pattern as in Δ^5-cholesten-3-one oxime [11]. It should be emphasized that up to now no examples of pyrrole synthesis by the Trofimov reaction have been reported for α,β-unsaturated ketone oximes.

Presumably, closure of the pyrrole ring is preceded by prototropic migration of the double carbon–carbon bond to give nonconjugated β,γ-unsaturated ketone oxime (Scheme 2). Taking into account that this process is unfavorable from the viewpoint of thermodynamics (for it involves rupture of conjugation), the yields of compounds **VI** and **VII** are low. An analogous double bond migration in the steroid series is known; for example, it was observed in the transformation of Δ^4-cholesten-3-one into Δ^5-cholesten-3-one ethylene acetal [13].

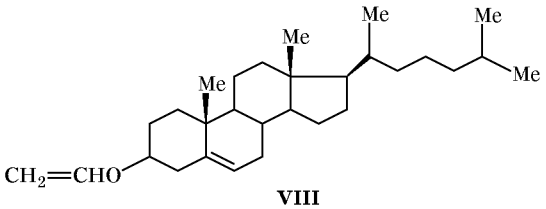
By varying the reaction conditions (100–140°C, 0.5–5 h), we have found that at 120°C in 1 h the overall yield of compounds **VI** and **VII** is about ~7%. Raising the temperature to 140°C, the reaction time being the same, results in strong tarring of the reaction mixture, which considerably complicates isolation of the target products. Almost no reaction with oxime **V** occurred at 100°C. It should be noted that even under relatively mild conditions (120°C, 1 h) a large amount of polymeric compounds is formed together with partially deoximated product **VII**.

In order to avoid undesirable deoximation process, we performed the reaction (120°C, 1 h) with dioxime **V** dicesium salt which was prepared from the corre-

Scheme 2.

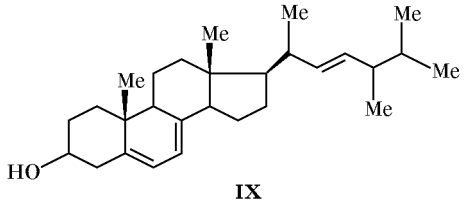


sponding dilithium derivative and CsF. In this case, we isolated only bis-pyrrole progesterone derivative **VI** (yield 8%), while deoximation product **VII** was not detected. This may be due to reduced concentration of water in the system (traces), which is necessary for the deoximation to occur. On the other hand, this procedure turned out to be inapplicable for selective synthesis of pyrrole derivative **II** from pregnenolone oxime. At 120°C (1 h), the reaction was accompanied by strong tarring, presumably because of formation of the corresponding vinyl ether which is unstable under the given conditions. In fact, in the reaction of pregnenolone oxime with acetylene in the system KOH–DMSO, the hydroxy group in position *3* undergoes complete vinylation [10]. We previously [14] developed a one-step procedure for the synthesis of cholesterol vinyl ether **VIII** via direct vinylation with acetylene under mild conditions (KOH–DMSO, 90°C, 1 h, yield 90%).



VIII

Our attempt to effect in such a way vinylation of structurally related ergosterol (**IX**, provitamin D_2) resulted in formation of a complex mixture of tars, whose ^{1}H NMR spectrum contained no signals assignable to *O*-vinyl group.

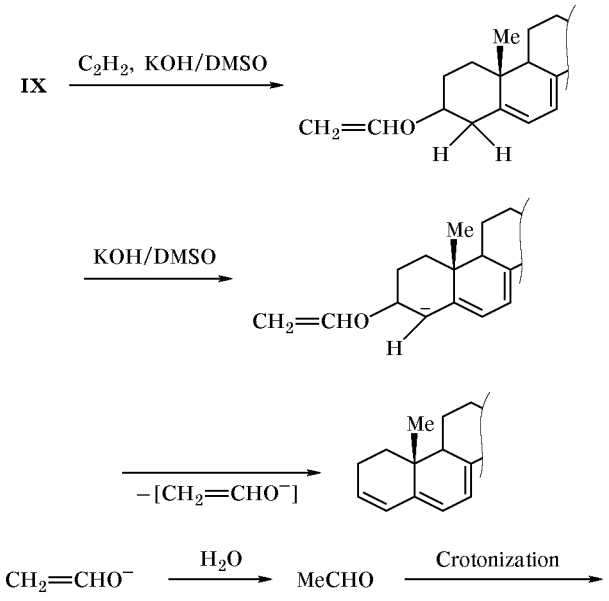


IX

The observed behavior of ergosterol (**IX**) may be interpreted in terms of the presence of a conjugated diene system in its molecule, which favors elimination of the vinyloxy group (Scheme 3). An analogous pattern was described in [15, 16] for the vinylation of 1,2-diols and polyols. Elimination of vinyloxy group may be facilitated by the energy gain due to formation of more extended conjugation chain in the product.

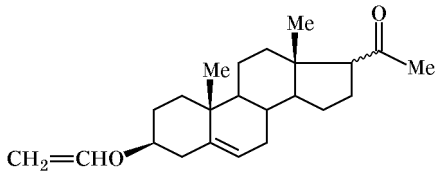
The vinylation of ergosterol (**IX**) in a superbasic medium (KOH–DMSO) can also be accompanied by multiposition prototropic migration of the side-chain double bond both toward terminal methyl groups

Scheme 3.



(with formation of thermodynamically more stable tetrasubstituted ethylene structure) and toward the steroid skeleton (up to formation of cyclopenetene fragment).

In the reaction of pregnenolone oxime with acetylene in the system KOH–DMSO, partial deoximation lead to formation of pregnenolone vinyl ether **X** [10], which indicated a relative stability of the acetyl group in the steroid molecule toward the given superbasic system. This fact is somewhat surprising, for ketones are known to readily react with KOH–DMSO, affording allyl alcohols and sulfoxides [17]. Presumably, the reactivity of the acetyl group in pregnenolone is reduced owing to shielding effect of the steroid fragment. Taking the above into account, we made an attempt to effect direct vinylation of pregnenolone in the system KOH–DMSO (100°C, 1 h).



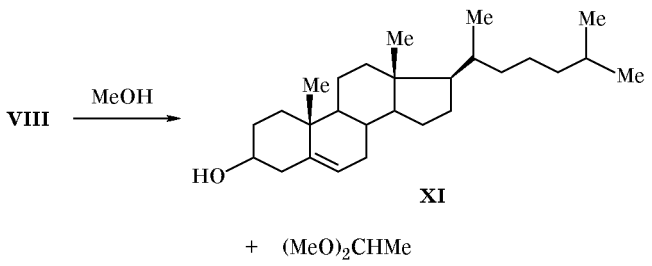
X

By extraction with diethyl ether we isolated from the reaction mixture ~50% of vinyl ether **X** (purity ~70%, a 4:1 mixture of 17β- and 17α-epimers, according to the ^{1}H NMR data).

O-Vinylation can be used to protect hydroxy group: The *O*-vinyl protection is readily removed by mild

acid-catalyzed alcoholysis. For example, heating of cholesterol *O*-vinyl ether (**VIII**) for 10 min in boiling methanol in the presence of trifluoroacetic acid regenerates 86% of cholesterol (**XI**) (Scheme 4).

Scheme 4.



The structure of bis-pyrrole progesterone derivative **VI** was proved by homonuclear ^1H–^1H 2M NMR spectroscopy (NOESY). Its NOESY spectrum contained a cross peak between the 4′-H and 6-H protons (see Scheme 1).

Thus the results of our study confirmed the possibility of using the Trofimov reaction for binding a steroid fragment to a pyrrole ring in one preparative step, via reaction of steroid ketone oximes with acetylene in superbasic catalytic systems; the process may be accompanied by quantitative vinylation of the existing hydroxy groups and emerging pyrrole NH groups. We also showed that O-vinylation may be used to protect hydroxy groups in steroid; the protection is stable in alkaline medium but can readily be removed by acid-catalyzed alcoholysis; this reaction may be useful for the chemistry of steroids.

Despite poor yields (in some cases) of the target products, the simplicity of the process and accessibility and low costs of the reagent make some of the above described reactions promising for the preparation of basic building blocks for combinatorial chemistry and for the development on this basis of representative libraries including challenging pharmacological agents which combine steroid and pyrrole fragments in a single molecule.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker 400-DPX spectrometer operating at 400.13 and 101.61 MHz, respectively; chloroform-*d* was used as solvent, and HMDS, as internal reference. The IR spectra were measured on a Bruker ISF25 instrument (in KBr). The molecular weights and elemental compositions were determined from the high-resolution mass spectra which were run on a Finnigan MAT 8200 mass spectrometer. The initial steroids were commercial products from ICN Pharmaceuticals; ergosterol was purchased from Fisher Biotech.

Progesterone dioxime (V). A mixture of 4.6 g (66 mmol) of hydroxylamine hydrochloride and 5.43 g (66 mmol) of sodium acetate in 30 ml of methanol was stirred for 10 min, and 50 ml of pyridine and 9.43 g (30.0 mmol) of progesterone (**IV**) were added. The mixture was stirred for 3 h and poured into 250 ml of cold water. The precipitate was filtered off, thoroughly washed with water, and dried under reduced pressure. Yield 9.89 g (96%), colorless powder. IR spectrum (KBr), ν, cm^{-1}: 3273 s, 2927 s, 2874 w, 2852 w, 1635 m, 1450 w, 1433 m, 1385 w, 1366 m, 1292 w, 1238 w, 1228 w, 1110 w, 1050 w, 1027 w, 991 w, 966 m, 954 m, 939 m, 909 m, 875 w, 861 m, 849 m, 750 w, 727 w, 707 w, 678 w, 635 w, 586 w. Found, %: C 73.01; H 9.55; N 7.73. $C_{21}H_{32}N_2O_2$. Calculated, %: C 73.22; H 9.36; N 8.13.

***N*,*N*′-Divinyl-17β-(2-pyrrolyl)pyrrolo[3,4-*b*]-androst-5-ene (VI).** A mixture of 0.48 g (20 mmol) of LiOH, 3.04 g (20 mmol) of CsF, and 10 ml of methanol was stirred for 10 min, 3.45 g (10 mmol) of progesterone dioxime and 30 ml of DMSO were added, the mixture was stirred for 20 min, and methanol was distilled off under reduced pressure at a temperature of about ~50°C (until distillation of DMSO started). To the resulting mixture which contained the corresponding dicesium salt we added 70 ml of DMSO, and the mixture was transferred into a 0.5-l high pressure reactor, saturated with acetylene at room temperature (initial acetylene pressure 14 atm), heated to 120°C, and kept for 1 h at that temperature (residual acetylene pressure 4 atm). The reactor was discharged, and the mixture was diluted with 150 ml of water and extracted with diethyl ether (4 × 50 ml). The extracts were combined, washed with water (3 × 50 ml), and dried over calcined potassium carbonate. The solvent was removed, and the residue was subjected to column chromatography on Al_2O_3 (weakly basic, deactivated with water) using diethyl ether as eluent. The product was additionally purified by recrystallization from acetone. Yield 0.32 g (8%), colorless transparent needles, mp 199–201°C. IR spectrum (KBr), ν, cm^{-1}: 3096 m (CH=CH_2); 2932 s, 2879 m, 2841 m (C–H); 1639 v.s (C=C); 1570 m (δCH, pyrrole ring); 1489 m (δCH, pyrrole ring); 1477 m (δCH); 1448 m (δCH); 1431 m (δCH_2); 1380 s (δCH, pyrrole ring); 1321 m (C–N); 1293 m (C–N); 1276, 1230, 959 m (δHC=CH); 848 m (δCH_2); 713 m (δCH, pyrrole ring). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.00 d.d (1H, $H_{X'}$, $^3J_{A',X'}$ = 8.7 Hz, $^3J_{B',X'}$ = 15.4 Hz), 6.96 d (1H, 5′′-H), 6.86 d

(1H, 5′-H), 6.77 d.d (1H, H_X, $^3J_{A,X}$ = 9.0 Hz, $^3J_{B,X}$ = 15.8 Hz), 6.26 d (1H, 4′-H), 6.18 t (1H, 4″-H), 6.04 d (1H, 3″-H), 5.70 q (1H, 6-H), 5.06 d (1H, $H_{B'}$-H), 5.00 d (1H, H_B), 4.63 d (1H, $H_{A'}$), 4.58 d (1H, H_A), 2.79 t (1H, 17-H, $^3J_{16,17}$ = 9.9 Hz), 0.98 s (3H, 19-Me), 0.59 s (3H, 18-Me). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 137.43 (C^5); 133.71 ($C^{2''}$); 131.40 (C^{α}); 130.31 ($C^{\alpha'}$); 126.69 (C^3); 120.37 (C^4); 116.75 ($C^{5''}$); 116.57 ($C^{5'}$); 115.06 (C^6); 109.09 ($C^{3''}$); 108.44 ($C^{4''}$); 105.54 ($C^{4'}$); 97.69 ($C^{\beta'}$); 96.53 (C^{β}); 56.70 (C^{14}); 48.43 and 47.23 (C^9, C^{17}); 44.37 (C^{13}); 38.65 (C^{12}); 36.25 (C^{10}); 34.73 (C^1); 32.56 (C^8); 31.72 (C^7); 28.44 (C^2); 24.28, 21.55, and 19.13 (C^{11}, C^{15}, C^{16}); 18.58 (C^{19}); 13.44 (C^{18}). Mass spectrum, *m*/*z* (I_{rel}, %): 412 (100) $[M]^+$, 397 (9) $[M - Me]^+$, 278 (42), 206 (20), 185 (45), 170 (25), 156 (12), 132 (19), 118 (49), 106 (23), 91 (13). Found, %: C 84.17; H 9.10; N 6.64. $C_{29}H_{36}N_2$. Calculated, %: C 84.42; H 8.79; N 6.79.

***N*,*N*′-Divinyl-17β-(2-pyrrolyl)pyrrolo[3,4-*b*]androst-5-ene (VI) and *N*-vinylpyrrolo[3,4-*b*]androst-5-ene (VII).** A mixture of 3.45 g (10 mmol) of progesterone dioxime and 1.12 g (17.2 mmol) of $KOH \cdot 0.5H_2O$ in 50 ml of DMSO was saturated with acetylene at room temperature (initial acetylene pressure 14 atm) in a 0.5-l high-pressure reactor. The mixture was then heated to 120°C and was kept at that temperature for 1 h (residual acetylene pressure 3 atm). The reactor was cooled and discharged, the reaction mixture was diluted with 150 ml of water, and 100 ml of diethyl ether was added. The mixture was shaken in a separatory funnel, and the undissolved material (polymeric products) was separated by filtration on a Büchner funnel and washed first with water and then with ether. After drying under reduced pressure we obtained 1.12 g of a light brown powder. IR spectrum (KBr), ν, cm^{-1}: 3424 br.s, 2935 br.s, 2878 w, 2847 w, 1639 s, 1574 w, 1491 w, 1445 m, 1380 m, 1232 w, 1166 w, 962 w, 849 w, 716 w. Found, %: C 78.87; H 9.08; N 4.78.

The ether extract was washed with water (3 × 50 ml) and dried over calcined potassium carbonate. The solvent was removed, and the residue was subjected to column chromatography on aluminum oxide (weakly basic, deactivated with water) using diethyl ether as eluent. We thus isolated 0.27 g of a mixture of bis- and monopyrrole progesterone derivatives **VI** and **VII** at a ratio of 1 : 5 (^{1}H NMR); overall yield ~7%.

Compound **VII**. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 6.83 d (1H, 5′-H), 6.75 d.d (1H, H_X, $^3J_{A,X}$ = 9.0 Hz, $^3J_{B,X}$ = 15.8 Hz), 6.21 d (1H, 4′-H), 5.65 q (1H, 6-H), 5.00 d.d (1H, H_B, $^2J_{A,B}$ = 1.1 Hz), 4.57 d.d (1H, H_A), 2.52 t (1H, 17-H, $^3J_{16,17}$ = 9.15 Hz), 2.11 s (3H, $C^{21}H_3$), 0.98 s (3H, $C^{19}H_3$), 0.66 s (3H, $C^{18}H_3$).

Pregnenolone vinyl ether (X). A mixture of 3 g (8.6 mmol) of pregnenolone and 1 g (15.4 mmol) of $KOH \cdot 0.5H_2O$ in 50 ml DMSO was saturated with acetylene at room temperature (initial acetylene pressure 14 atm) in a 0.5-l high-pressure reactor. The mixture was heated to 100°C and was kept for 1 h at that temperature (residual pressure 8 atm). The reactor was discharged, and the mixture was diluted with 150 ml of water and extracted with diethyl ether (4 × 50 ml). The combined extracts were washed with water (3 × 50 ml) and dried over calcined potassium carbonate. Removal of the solvent left 2.3 g of a tarry material which contained ~70% (^{1}H NMR data) of pregnenolone vinyl ether (yield ~50%). The ^{1}H NMR spectrum of **X** was given in [10].

Methanolysis of cholesterol vinyl ether (VIII). A mixture of 0.3 g (0.7 mmol) of cholesterol vinyl ether [14], 5 ml of methanol, and 0.01 g (0.09 mmol) of trifluoroacetic acid was heated for 10 min under reflux. The mixture was cooled, and the precipitate was filtered off, washed with cold methanol, and dried under reduced pressure. Yield of cholesterol (**XI**) 0.25 g (86%), colorless powder, mp 144–147°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.33 s (1H, 6-H), 3.50 m (1H, 3-H), 2.29 m (2H, 4β-H), 2.22 m (2H, 4-H), 2.01 d (2H, 7β-H), 1.01 s (3H, $C^{19}H_3$), 0.91 s (3H, $C^{21}H_3$), 0.86 s (3H, $C^{26}H_3$), 0.67 s (3H, $C^{18}H_3$).

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