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Chemoenzymatic Synthesis of (2*R*,6*R*,10*R*)-6,10,14-Trimethylpentadecan-2-ol, Sex Pheromone of Rice Moth (*Corcyra cephalonica*), and of Its (2*S*,6*R*,10*R*)-Diastereomer

R. V. Shafikov, A. Yu. Spivak, and V. N. Odinokov

Institute of Petrochemistry and Catalysis, Russian Academy of Sciences, Ufa, 450075 Russia
e-mail: ink@anrb.ru

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Abstract—Based on the catalyzed by lipase Amano PS kinetic separation of the two-component mixture of diastereomers of (2*RS*,6*R*,10*R*)-6,10,14-trimethylpentadecan-2-ol in the acylation with the succinic anhydride we obtained the (2*R*,6*R*,10*R*)-6,10,14-trimethylpentadecan-2-ol, the sex pheromone of rice moth (*Corcyra cephalonica*) and its (2*S*,6*R*,10*R*)-diastereomer.

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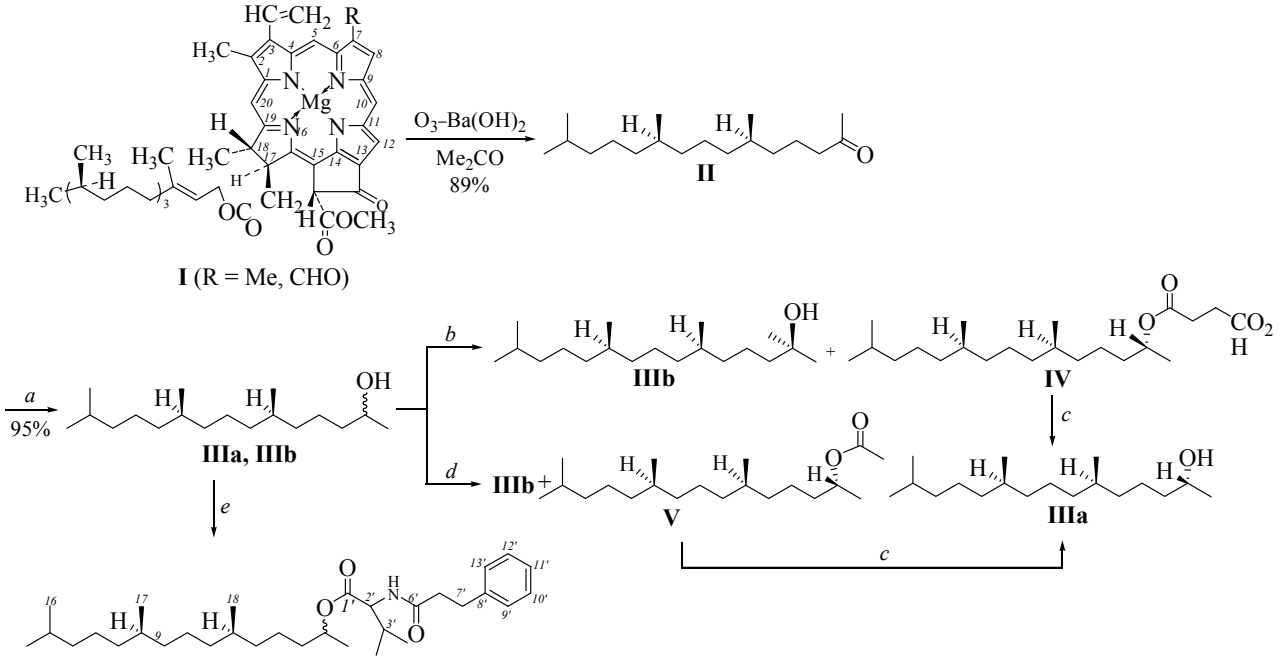
The natural pheromone of rice moth (*Corcyra cephalonica* Stainton), (2*R*,6*R*,10*R*)-6,10,14-trimethylpentadecane-2-ol (**IIIa**) and its 2*S*,6*R*,10*R*)-diastereomer **IIIb** were obtained by combining chiral block-synthons in multistage syntheses (11–12 stages) [1, 2]. An attractive approach to the synthesis of individual alcohols **IIIa** and **IIIb** consists in a kinetic separation of the two-component mixture of these diastereomers catalyzed by lipases. It was reported on the enzymatic preparation of (2*R*,6*R*,10*R*)-alcohol **IIIa** by the lipase PS catalyzed hydrolysis of acetates of the (2*RS*,6*R*,10*R*)-alcohols **IIIa** and **IIIb** [3], obtained from (*R*)-β-citronellol and methyl (*S*)-3-hydroxy-2-methylpropionate in a 13-stage synthesis [3].

We developed a short synthetic route to the diastereomeric mixture of the (2*RS*,6*R*,10*R*)-alcohols **IIIa** and **IIIb** by the hydride reduction of (6*R*,10*R*)-6,10,14-trimethylpentadecan-2-one (**II**) prepared by the previously elaborated method of the chlorophyll **I** ozonolysis obtained from common nettle (*Urtica dioica* L.) [4]. By the subsequent kinetic separation of the alcohols **IIIa** and **IIIb** mixture catalyzed by lipases we obtained optically pure diastereomers (2*R*,6*R*,10*R*)- **IIIa** and (2*S*,6*R*,10*R*)- **IIIb**.

The kinetic separation of the mixture of diastereomeric alcohols **IIIa** and **IIIb** was performed by their acylation with succinic anhydride or vinyl acetate in the presence of lipases *Amano PS* or *Candida cylindracea* in diisopropyl ether at 20°C. The unreacted alcohol **IIIb** and the acyl derivatives of alcohol **IIIa**, hemisuccinate **IV** or acetate **V**, were separated by column chromatography on silica gel. The alkaline hydrolysis of compounds **IV** and **V** yielded alcohol **IIIa**.

Aiming at the elucidation of the possibility of the estimation of the diastereomeric excess of alcohols **IIIa** and **IIIb** obtained by the enzymatic separation their diastereomers mixture by treating with N-benzyloxycarbonyl-L-valine (Cbz-L-valine) activated with *N,N'*-dicyclohexylcarbodiimide (DCC) and *N,N*-dimethylaminopyridine (DMAP) was converted into the corresponding mixture of O-(2*RS*-acyl)derivatives **VI**. The assignment of the signals in the ^{1}H and ^{13}C NMR spectra of compound **VI** was performed from the analysis of 1D and 2D spectra. In the ^{13}C NMR spectra of diastereomeric acylates **VI** a double set of signals is observed from the atoms C^{1}, C^{2}, $C^{2'}$, $C^{3'}$, $C^{4'}$, $C^{5'}$ contiguous to the chiral centers *2* and *2'*. However we failed to distinguish in the ^{1}H NMR spectra the signals suitable for the evaluation of the diastereomeric excess after the enzymatic separation of the mixture of alcohols **IIIa** and **IIIb**. Therefore the results of the separation of the mixture of diastereomers **IIIa** and **IIIb** cayalyzed by lipases were evaluated based on

Scheme.



a, $NaBH_4$–MeOH; *b*, succinic anhydride–Lipase–(*i*-PrO)$_2$O; *c*, MeONa–MeOH; *d*, AcOCH=CH_2–Lipase–(*i*-PrO)$_2$O; *e*, Cbz-L-valine–DCC–DMAP–CH_2Cl_2.

the optical rotation.

Alcohol (2*R*,6*R*,10*R*)- **IIIa** with a specific optical rotation $[\alpha]_D^{20}$ –6.3° (*c* 1.0, pentane) identical in the sign and the absolute value to the described in the literature optically pure (2*R*,6*R*,10*R*)-6,10,14-trimethylpentadecan-2-ol [1–3] was obtained by the hydrolysis of hemisuccinate **IV** formed at the 16% conversion of the alcohols mixture **IIIa** and **IIIb** after 2-hour reaction of the alcohols mixture with the equimolar amount of succinic anhydride in the diisopropyl ether in the presence of lipase *Amano PS* at 20°C. The hemisuccinate **IV** obtained in this experiment was also optically pure.

Acylation of the mixture of (2*RS*,6*R*,10*R*)-diastereomeric alcohols **IIIa** and **IIIb** with succinct anhydride (A) and vinyl acetate (B) in diisopropyl ether in the presence of lipases *Amano PS* (*PS-C*) and *Candida cylindracea* (*CCL*)[a]

Lipase	Acylating agent	Reaction time, h	Conversion, %	$[\alpha]_D^{20}$ in pentane (*ee*, %)	
				IIIa	**IIIb**
PS-C	A	2	16	–6.3 (99)	+0.7 (9)
PS-C	A	3	19	–5.0 (78)	+1.2 (15)
PS-C	A	4	22	–4.6 (72)	+1.6 (20)
PS-C	A	6	26	–3.7 (58)	+4.1 (51)
PS-C	A	24	48	–3.0 (47)	+8.1 (100)
PS-C[b]	A	7	18	–3.5 (55)	+1.6 (20)
CCL	A	24	51	+0.3	+5.0 (63)
PS-C	B	24	47	–1.4 (22)	+3.9 (49)

[a] The ratio of **IIIa** and **IIIb** to the acylating agent was equimolar, of **IIIa** and **IIIb** to lipase, 3 : 2 by weight; reaction temperature 20°C.
[b] Reaction temperature 8°C.

On reducing the acylation temperature to 8°C the same conversion of alcohols **IIIa** and **IIIb** was obtained in 7 h, and the optical purity of alcohol **IIIa** reduced therewith to 55% (see the table).

At increasing the conversion of the alcoxols mixture **IIIa** and **IIIb** the optical purity of (2*R*,6*R*,10*R*)-diastereomeric alcohol **IIIa** decreased (at the conversion 19, 22, and 26% the optical purity of obtained alcohol **IIIa** was 78, 72, and 58% respectively], but at the same time the optical purity of the residual alcohol **IIIb** increased (*ee* 15, 20, and 51%) (see the table). At the conversion ~50% attained at 20°C within 24 h alcohol (2*S*,6*R*,10*R*)-**IIIb** was obtained with a specific optical rotation $[\alpha]_D^{20}$ +8.1° (*c* 1.4, pentane) identical in the sign and the absolute value to the described in the literature optically pure (2*S*,6*R*,10*R*)-6,10,14-trimethylpentadecan-2-ol [1, 2].

The use as catalyst lipase CCL under the same conditions (20°C, 24 h, conversion ~50%) resulted in a decrease in the optical purity of alcohol **IIIb** to 63%, and the use of vinyl acetate as acylating agent (catalyst lipase *Amano PS*, 24 h, conversion ~50%) gave alcohol **IIIb** of the optical purity of 49% (see the table).

Thus the hydride reduction of (6*R*,10*R*)-6,10,14-trimethylpentadecan-2-one, the product of chlorophyll ozonolysis, made it possible to obtain by the shortest route the mixture of diastereomeric (2*RS*,6*R*,10*R*)-6,10,14-trimethylpentadecan-2-ols that at the catalysis with lipase *Amano PS* was kinetically separated into optically pure (2*R*,6*R*,10*R*)- and (2*S*,6*R*,10*R*)-6,10,14-trimethylpentadecan-2-ols **IIIa** and **IIIb**.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker Avance-400, operating frequencies 400.13 (H^1) and 100.62 (C^{13}) MHz, solvent $CDCl_3$. Homo- and heteronuclear experiments COSY, HSQC, HMBC were carried out on the spectrometer Bruker Avance-400 applying the standard programs of Bruker Co. The chemical shifts are reported with respect to TMS. The specific optical rotation was measured on a polarimeter Perkin Elmer-141. High resolution mass spectra were taken on an instrument MALDI TOF/TOF Autoflex-III Bruker. IR spectra were recorded on a spectrophotometer Carl Zeiss Jena Specord 75 IR from pellets with KBr. UV spectra were obtained on spectrophotometers Perkin Elmer Specord M-40 and Lambda-750. The TLC was performed on plates with SiO_2 (Silufol), development under the action of the ethanol solution of anise aldehyde acidified with sulfuric and acetic acids. The specific activity of the lipase from *Candida cylindracea* (CCL, Fluka) 3.85 units·mg^{-1}. The lipase *Amano Lipase PS* from *Burkholderia cepacia* was purchased from Aldrich.

(2*RS*,6*R*,10*R*)-6,10,14-Trimethylpentadecane-2-ols IIIa and IIIb. To a solution of 0.42 g (1.56 mmol) of (6*R*,10*R*)-6,10,14-trimethylpentadecan-2-one (**II**) ($[\alpha]_D^{25}$ +1.05°, prepared by procedure [4]) in 12 ml of MeOH at 0°C while stirring was added in one portion 0.12 g (3.20 mmol) of $NaBH_4$. The temperature was gradually raised to the ambient, and the mixture was stirred for 2 h. Then the reaction mixture was evaporated in air. To the residue 25 ml EtOAc was added, the solution was washed in succession with 3 N HCl (2 × 20 ml), with saturated solution of $NaHCO_3$, and with brine, and dried with $MgSO_4$. On evaporation of the solvent the yield of the mixture of alcohols **IIIa** and **IIIb** 0.40 g (95%). Colorless oily substance, R_f 0.56 (hexane–EtOAc, 3 : 1), $[\alpha]_D^{20}$ +0.8° (*c* 1.2, pentane), $[\alpha]_D^{20}$ 2.6° (*c* 2.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3600–3300, 1100 (OH). ^{1}H NMR spectrum, δ, ppm: 0.85 d, 0.87 d (12H, Me-C^6, Me-C^{10}, Me-C^{14}, H_3C^{15}, *J* 6.4 Hz), 1.06–1.57 m (24H, CH, CH_2), 1.19 d (3H, H_3C^1, *J* 6.4 Hz), 3.80 br.s (1H, OH), 3.79, 3.82 d.d (1H, HC^2, *J* 6.4 Hz). ^{13}C NMR spectrum, δ, ppm: 19.67 and 19.74 (Me-C^6, Me-C^{10}), 22.62 and 22.71 (Me-C^{14}, C^{15}), 23.24 (C^1), 24.48 (C^4), 24.46 and 24.79 (C^8, C^{12}), 27.97 (C^{14}), 32.78 (C^6, C^{10}), 37.02 (C^5), 37.28, 37.37 and 37.42 (C^7, C^9, C^{11}), 39.36 (C^{13}), 39.72 (C^3), 68.22 (C^2). Found, %: C 79.89; H 14.19. $C_{18}H_{38}O$. Calculated, %: C 79.93; H 14.16.

Hemisuccinate (2*R*,6*R*,10*R*)-6,10,14-trimethylpentadecane-2-ol (IV). To a solution of 0.14 g (0.52 mmol) of the mixture of alcohols **IIIa** and **IIIb** in 7 ml of diisopropyl ether was added 0.05 g (0.50 mmol) of succinic anhydride and 0.09 g of lipase *Amano PS*. The reaction mixture was stirred at 20°C monitoring the conversion of the substrate by TLC (eluent hexane–EtOAc, 3 : 1) and GLC (samples of the reaction mixture after treating with the ether solution of diazomethane). When the conversion attained 16% (2 h) the reaction mixture was filtered through a glass frit no. 3, the precipitate was washed with diisopropyl ether (3 × 10 ml), the combined filtrates were concentrated at the reduced pressure and 40°C. The residue was subjected to column chromatography on SiO_2 (5 g, eluent petroleum ether). We obtained 0.113 g (81%) of alcohol **IIIb** {R_f 0.56 (hexane–EtOAc, 3 : 1), $[\alpha]_D^{20}$ +2.1° (*c* 4.2, pentane), $[\alpha]_D^{20}$ +0.9° (*c* 3.1,

$CHCl_3$), *ee* 26%} and 0.025 g (13%) of hemisuccinate **IV**, R_f 0.08 (hexane–EtOAc, 3 : 1), $[\alpha]_D^{20}$ –2.1° (*c* 1.1, pentane), $[\alpha]_D^{20}$ –1.1° (*c* 0.9, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 0.85 and 0.87 d.d (12H, Me-C^6, Me-C^{10}, Me-C^{14}, H_3C^{15}, *J* 6.8 Hz), 1.08–1.57 m (21H, CH, CH_2), 1.28 d (3H, H_3C^1, *J* 6.8 Hz), 2.42 m (2H, $H_2C^{2'}$), 2.52 m (2H, $H_2C^{3'}$), 4.84 m (1H, HC^2). ^{13}C NMR spectrum, δ, ppm: 19.53 (C^1), 19.74 (Me-C^6, Me-C^{10}), 22.62 and 22.72 (Me-C^{14}, C^{15}), 24.51 and 24.81 (C^4, C^8 and C^{12}), 27.97 (C^{14}), 29.69 (C$^{2'}$ and C$^{3'}$), 32.69 and 32.82 (C^6, C^{10}), 36.18 (C^3), 37.01, 37.06, 37.31 and 37.50 (C^5, C^7, C^9, C^{11}), 39.37 (C^{13}), 71.38 (C^2), 174.28 (C$^{4'}$), 180.01 (C$^{1'}$). Found, %: C 71.36; H 11.37. $C_{22}H_{42}O_4$. Calculated, %: C 71.31; H 11.42.

(2*R*,6*R*,10*R*)-6,10,14-Trimethylpentadecane-2-ol (IIIa). To a solution of 0.025 g (0.068 mmol) of hemisuccinate **IV** in 3 ml of methanol was added 0.003 g (0.13 mmol) of sodium. The reaction mixture was stirred for 0.5 h, then 5% solution of HCl was added dropwise (till neutral reaction), the reaction product was extracted into EtOAc (3 × 6 ml), the extract was evaporated, the residue was subjected to column chromatography on SiO_2 (3 g, eluent petroleum ether). Yield 0.017 g (93%), R_f 0.56 (hexane–EtOAc, 3 : 1), $[\alpha]_D^{20}$ –6.3° (*c* 1.0, pentane) {$[\alpha]_D^{18}$ –6.4° (*c* 1.1, pentane) [1, 2], $[\alpha]_D^{20}$ –6.5° (*c* 4.9, pentane) [3]}, $[\alpha]_D^{20}$ –3.2° (*c* 1.2, $CHCl_3$). IR and ^{1}H NMR spectra are identical to those published in [1]. ^{13}C NMR spectrum was identical to the spectrum reported above for the mixture of alcohols **IIIa** and **IIIb**.

(2*S*,6*R*,10*R*)-6,10,14-Trimethylpentadecane-2-ol (IIIb). To a solution of 0.100 g (0.37 mmol) of the mixture of alcohols **IIIa** and **IIIb** in 5 ml of diisopropyl ether was added 0.037 g (0.37 mmol) of succinic anhydride and 0.066 g of lipase *Amano PS*. The reaction mixture was stirred at 20°C for 24 h (conversion 48%). Further workup was performed as described in the synthesis of compound **IV**. We obtained 0.052 g (52%) of alcohol **IIIb** {R_f 0.56 (hexane–EtOAc, 3 : 1), $[\alpha]_D^{20}$ +8.1° (*c* 1.4, pentane) ($[\alpha]_D^{18}$ +8.0° (*c* 1.1, pentane) [1, 2]), $[\alpha]_D^{20}$ +4.4° (*c* 2.2, $CHCl_3$); IR and ^{1}H NMR spectra are identical to those published in [1]} and 0.044 g (32%) of hemisuccinate **IV** {R_f 0.08 (hexane–EtOAc, 3 : 1), $[\alpha]_D^{20}$ –0.7° (*c* 1.6, $CHCl_3$)}.

(2*R*,6*R*,10*R*)-6,10,14-Trimethylpentadec-2-yl acetate (V). To a solution of 0.10 g (0.52 mmol) of the mixture of alcohols **IIIa** and **IIIb** in 5 ml of diisopropyl ether was added 0.03 g (0.50 mmol) of vinyl acetate and 0.07 g of lipase *Amano PS*. The reaction mixture was stirred at 20°C monitoring the conversion of the substrate as described above in the synthesis of compound **IV** at the acylation of the alcohols mixture with the succinic anhydride. Attaining the conversion of 47% the reaction mixture was worked up as described above. We obtained 0.053 g (53%) of alcohol **IIIb** {R_f 0.56 (hexane–EtOAc, 3 : 1), $[\alpha]_D^{20}$ +2.9° (*c* 2.7, $CHCl_3$)} and 0.039 g (34%) of acetate **V**, R_f 0.76 (hexane–EtOAc, 3 : 1), $[\alpha]_D^{20}$ +0.9° (*c* 2.1, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 0.85 and 0.87 d.d (12H, Me-C^6, Me-C^{10}, Me-C^{14}, H_3C^{15}, *J* 6.8 Hz), 1.05–1.61 m (21H, CH, CH_2), 1.21 d (3H, H_3C^1, *J* 6.0 Hz) 2.03 s (3H, MeCO), 4.90 m (1H, HC^2). ^{13}C NMR spectrum, δ, ppm: 19.61 (C^1), 19.72 and 19.96 (Me-C^6, Me-C^{10}), 21.34 (MeCO), 22.60 and 22.69 (Me-C^{14}, C^{15}), 22.85 (C^4), 24.44 and 24.78 (C^8, C^{12}), 27.96 (C^{14}), 32.66 and 32.77 (C^6, C^{10}), 36.22 (C^3), 36.76 (C^5), 37.27, 37.35 and 37.41 (C^7, C^9, C^{11}), 39.36 (C^{13}), 71.02 (C^2), 170.72 (CO). Found, %: C 76.91; H 12.84. $C_{20}H_{40}O_2$. Calculated, %: C 76.81; H 12.93.

(2*RS*,6*R*,10*R*)-6,10,14-Trimethylpentadec-2-yl-2-(*N*-benzyloxycarbonyl)-L-valinate (VI). To a solution of 0.06 g (0.22 mmol) of the mixture of alcohols **IIIa** and **IIIb** in 5 ml of freshly distilled CH_2Cl_2 was added at stirring 0.11 g (0.44 mmol) of Cbz-L-valine, 0.09 g (0.44 mmol) of DCC, and 0.004 g (0.03 mmol) of DMAP (a precipitate separated), the reaction mixture was stirred for 4 h till the complete consumption of the initial substrate (TLC monitoring). The reaction mixture was filtered through a folded paper filter, the filtrate was evaporated in a vacuum, the residue was subjected to column chromatography on SiO_2 (5 г, eluent petroleum ether). Yield 0.11 g (98%), colorless oily substance, R_f 0.69, (hexane–EtOAc, 3 : 1), $[\alpha]_D^{20}$ +5.1° (*c* 6.1, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3356 (NH), 2928 (O–CO), 1728 (C=O), 1536 and 1499 (Ph). UV spectrum ($CHCl_3$), $\lambda_{max.}$, nm (ε): 258 (272). ^{1}H NMR spectrum, δ, ppm: 0.88 d (12H, Me-C^6, Me-C^{10}, Me-C^{14}, H_3C^{15}, *J* 6.8 Hz), 0.99 and 1.00 d (6H, 4'-Me, 5'-Me, *J* 4.5 Hz), 1.08–1.62 m (21H, CH, CH_2), 1.24 d, 1.27 d (3H, H_3C^1, *J* 4.5 Hz), 2.20 m (1H, HC$^{3'}$), 4.31 m (1H, HC$^{2'}$), 4.97 m (1H, HC^2), 5.13 s (2H, $H_2C^{7'}$), 5.35 br.s (1H, NH), 7.27–7.38 m (5H, H$^{9'–13'}$). ^{13}C NMR spectrum, δ, ppm: 17.24 and 17.40 (C$^{5'}$), 18.93 and 19.10 (C$^{4'}$), 19.61 and 19.75 (Me-C^6, Me-C^{10}), 19.91 and 19.98 (C^1), 22.64, 22.74 and 22.84 (C^4, Me-C^{14}, C^{15}), 24.47 and 24.81 (C^8, C^{12}), 27.98 (C^{14}), 31.36 and 31.40 (C$^{3'}$), 32.66 (C^6), 32.80 (C^{10}), 36.15 (C^3),

36.72 (C^5), 37.29, 37.39 and 37.42 (C^7, C^9, C^{11}), 39.37 (C^{13}), 58.98 and 59.10 ($C^{2'}$), 66.95 ($C^{7'}$), 72.42 and 72.48 (C^2), 128.15 and 128.53 ($C^{9'}$–$C^{13'}$), 136.35 ($C^{8'}$), 156.22 ($C^{6'}$), 173.56 ($C^{1'}$). Found M^+ 526.860. $C_{31}H_{53}NNaO_4$. Calculated M 526.747.

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