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# Synthetic transformations of sesquiterpene lactones

## 9.* Synthesis of 13-(pyridinyl)eudesmanolides

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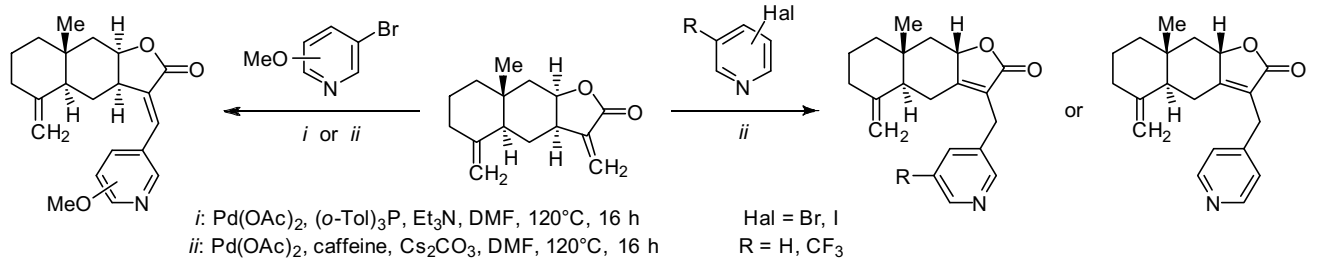



The reaction of isoalantolactone, a sesquiterpene α-methylidene-γ-lactone, with bromo(iodo)pyridines under the Heck reaction conditions gave 3-(pyridylmethylidene)-8a-methyldecahydronaphtho[2,3-*b*]furan-2(3*H*)-ones and 3-(pyridylmethyl)-8a-methyloctahydronaphtho[2,3-*b*]-furan-2(4*H*)-ones, products of double bond migration. The yield and product ratio depended on the reaction conditions and the nature of halopyridine. The effectiveness of $Pd(OAc)_2$–caffeine catalytic system was demonstrated in this reaction.

**Keywords**: bromopyridines, iodopyridines, isoalantolactone, Heck reaction.

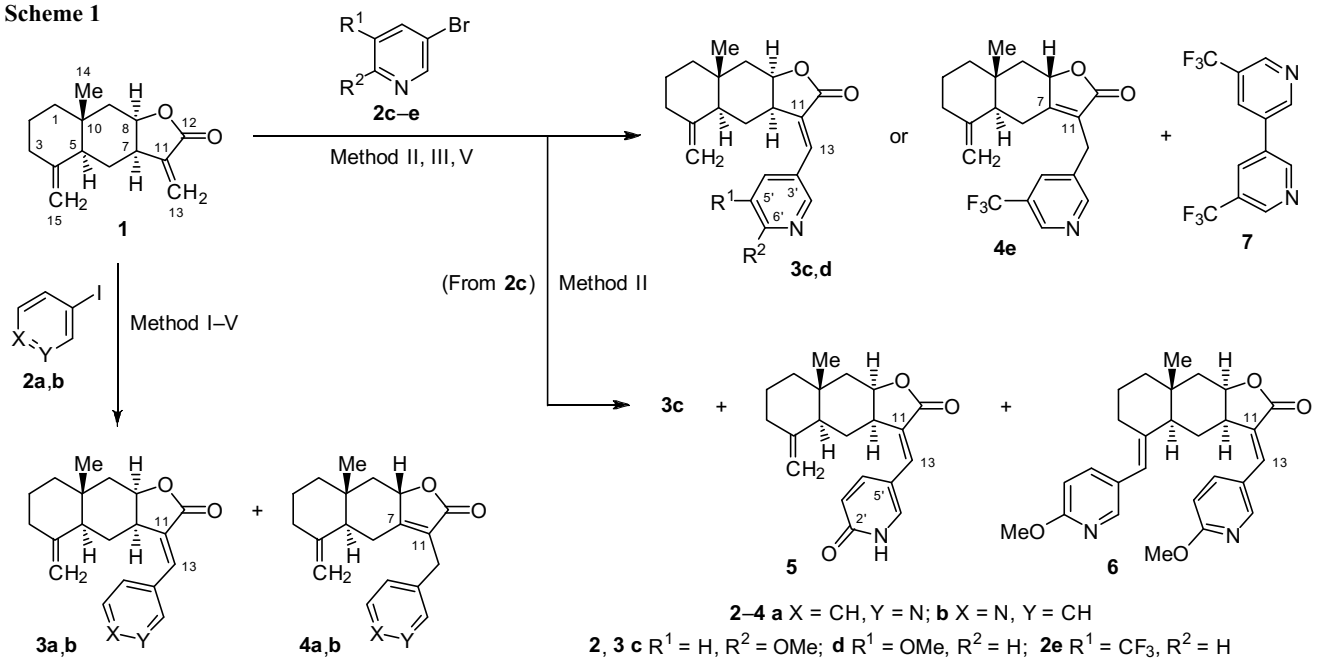
Sesquiterpene α-methylidene-γ-lactones are an important group of biologically active compounds, the synthetic modifications of which attract a significant interest.[1,2] Among the accessible methylidene lactones of eudesmane type are isoalantolactone (**1**), which has shown antibacterial, fungicidal, and antiproliferative activity.[3] Our studies of Heck reactions between the methylidene lactone **1** and aryl halides[4,5] or bromouracils[6] provide opportunities for the modification of lactone structure by introduction of aromatic or heteroaromatic substituents at position C-13 and preservation of α-methylidene-γ-lactone moiety in the molecule. This is a valuable modification of sesquiterpenoids, because the presence of an *exo*-methylidene double bond in the lactone ring has been associated with pharmacologically useful properties of the sesquiterpene lactones and their derivatives.[7]

The aim of this work was to study the possibility of introducing an additional pyridine substituent in the structure of methylidenelactone **1** by a cross-coupling reaction with bromo- or iodopyridine. It should be noted that compounds containing a pyridine ring in the structure are of major importance in the fields of organic and medicinal chemistry.[8]

We have previously shown that the reaction of isoalantolactone (**1**) with iodobenzenes, catalyzed by a $Pd(OAc)_2$–(*o*-Tol)$_3$P system (4:16 mol %) in the presence of $Et_3N$ as a base occurred upon heating in DMF (120°C, 16 h) and led to mixtures of the respective (*E*)-13-aryleudesma-4(15),11(13)-dien-8β,12-olides (50–85% yields) and 13-nor-11-arylmethyleudesma-4(15),7(11)-dien-8α,12-olides (3–25% yields).[4] Performing the reaction of isoalantolactone (**1**) with 3-iodopyridine (**2a**) under the indicated conditions (method I, Scheme 1) led to a mixture of (*E*)-13-(pyridin-3-yl)eudesma-4(15),11(13)-dien-8β,12-olide (**3a**) and 13-nor-11-[(pyridin-3-yl)methyl]eudesma-4(15),7(11)-dien-8α,12-olide (**4a**), isolated in 46 and 22% yields, respectively (Scheme 1). According to $^1$H NMR spectral data of the reaction mixture, conversion of the starting material reached 70%, the ratio of products **3a**:**4a** = 2:1. The same product ratio at a 65% conversion degree was obtained by performing the Pd-catalyzed reaction in the absence of ligand (method II) (the ratio was determined from $^1$H NMR spectral data of the reaction mixture, the products were not isolated preparatively). It was shown by specific experiments that maintaining 13-aryleudesmanolide **3a** under the reaction conditions according to method I ($Pd(OAc)_2$, (*o*-Tol)$_3$P, $Et_3N$, DMF, 120°C, 16 h) did not result in isomerization to compound **4a**. The

* For Communication 8, see[1].

**Scheme 1**




reaction of isoalantolactone (**1**) with 3-iodopyridine (**2a**) apparently had a lower selectivity for the formation of compounds with exocyclic methylidene double bond. The selectivity of Heck reaction is known to increase when carbonates of alkali metals are used as bases.[9,10] The reaction of lactone **1** with 3-iodopyridine (**2a**) in the presence of cesium carbonate (method III) resulted in the formation of compounds **3a** and **4a** in 5:1 ratio (80% conversion). When a cheaper base, potassium carbonate, was used under the same reaction conditions (method IV), an increase in the conversion was observed, reaching 88%, but the ratio of isomers **3a**:**4a** was 3:1 (the isolated yields were 63 and 21%, respectively). Thus, the variation of base allowed to modify the selectivity of reaction between the lactone **1** and 3-iodopyridine (**2a**).

Recent studies have considered xanthine derivatives, caffeine and theophylline, as effective ligands for Pd-catalyzed cross-coupling reactions, including the Heck reaction.[11–13] For example, a Heck reaction of 4-bromoacetophenone with methyl acrylate was successfully performed in the presence of bis(1,3,7,9-tetramethylxanthin-8-ylidene)palladium diiodide.[12] Some xanthines were also identified as effective ligands in the Suzuki–Miyaura reaction of halopyridines with phenylboronic acid.[13]

We assumed that the substitution of tris(*ortho*-tolyl)-phosphine ligand with caffeine should enhance the conversion and selectivity of Heck reaction between the methylidenelactone **1** and halopyridines. Indeed, the reaction of lactone **1** with 3-iodopyridine (**2a**), catalyzed by $Pd(OAc)_2$–caffeine system in the presence of $Cs_2CO_3$ in DMF and performed for 16 h at 120°C (method V), resulted in complete conversion and predominant formation of the exocyclic product (the ratio of isomers **3a**:**4a** was 10:1), isolated by column chromatography in 64% yield.

Thus, the nature of the base and ligand substantially affected the selectivity of reactions between isoalantolactone (**1**) and 3-iodopyridines (**2a**). The exocyclic adduct **3a** was formed more selectively when the base was cesium carbonate and the ligand was caffeine.

The reaction of isoalantolactone (**1**) with 4-iodopyridine (**2b**) catalyzed by $Pd(OAc)_2$–tris(*ortho*-tolyl)phosphine system (4:16 mol %) in DMF in the presence of triethylamine (method I) occurred even less selectively: the conversion of lactone **1** was 70%, the ratio of isomers **3b**:**4b** ~ 1:1 (Scheme 1). The conversion of lactone **1** was successfully improved by adding tetrabutylammonium bromide (TBAB) to the reaction mixture (method II).[6,14–16] According to literature data,[14a] this additive helps to stabilize the metallic colloids formed *in situ* and prevents their aggregation into larger, catalytically inactive particles. Another publication also considered the effects of tetraalkylammonium salts as phase-transfer catalysts.[16] The reaction proceeded with a full conversion of the starting lactone and formation of compounds **3b** and **4b** in a 1:1 ratio (the yields of compounds after column chromatography were 47 and 46%, respectively). It should be noted that the reaction of isoalantolactone (**1**) with 4-iodopyridine (**2b**) in the presence of cesium carbonate (method III) led to the formation of compounds **3b** and **4b** in a 1:2 ratio (89% conversion). Significant formation of 4,4'-bipyridine was observed under these conditions (up to ~30%, according to chromato-mass spectrometry analysis). Performing the reaction with palladium acetate catalyst in the presence of caffeine and cesium carbonate (method V) enabled a complete conversion of the starting lactone. The yield of double bond migration product **4b** was 53% (after column chromatography). Evidently, the ratio of isomeric products **3**, **4** substantially depends on the structure of iodopyridine.

**Table 1**. The conditions and product yields in reactions of isoalantolactone (**1**) with halopyridines **2a**–**e***

| Halo-pyridine | Method | Ligand (mol %) | Base (equiv) | TBAB, equiv | DMF, ml | Conversion, % | Product | Yield, % |
|---|---|---|---|---|---|---|---|---|
| **2a** | I | (*o*-Tol)$_3$P (16) | Et$_3$N (1.5) | – | 10 | 70 | **3a** | 46 |
| | | | | | | | **4a** | 22 |
| | III | (*o*-Tol)$_3$P (16) | $Cs_2CO_3$ (1.0) | – | 3 | 80 | **3a** | 62 |
| | | | | | | | **4a** | 13 |
| | IV | (*o*-Tol)$_3$P (16) | $K_2CO_3$ (1.0) | – | 3 | 88 | **3a** | 63 |
| | | | | | | | **4a** | 21 |
| | V | Caffeine (8) | $Cs_2CO_3$ (1.0) | – | 3 | 100 | **3a** | 64 |
| **2b** | I | (*o*-Tol)$_3$P (16) | Et$_3$N (1.5) | – | 10 | 70 | **3b** | 41 |
| | | | | | | | **4b** | 33 |
| | II | (*o*-Tol)$_3$P (16) | Et$_3$N (1.5) | 1.0 | 10 | 100 | **3b** | 47 |
| | | | | | | | **4b** | 46 |
| | III | (*o*-Tol)$_3$P (16) | $Cs_2CO_3$ (1.0) | – | 3 | 89 | **3b** | 29 |
| | | | | | | | **4b** | 56 |
| | V | Caffeine (8) | $Cs_2CO_3$ (1.0) | – | 3 | 100 | **4b** | 53 |
| **2c** | III | (*o*-Tol)$_3$P (16) | $Cs_2CO_3$ (1.0) | – | 3 | 23 | **3c** | 21 |
| | V | Caffeine (8) | $Cs_2CO_3$ (1.0) | – | 3 | 60 | **3c** | 51 |
| | II | (*o*-Tol)$_3$P (16) | Et$_3$N (1.5) | 1.0 | 10 | 100 | **3c** | 44 |
| | | | | | | | **5** | 16 |
| | | | | | | | **6** | 10 |
| **2d** | III | (*o*-Tol)$_3$P (16) | $Cs_2CO_3$ (1.0) | – | 3 | 15 | **3d** | 14 |
| | V | Caffeine (8) | $Cs_2CO_3$ (1.0) | – | 3 | 93 | **3d** | 89 |
| **2e** | III | (*o*-Tol)$_3$P (16) | $Cs_2CO_3$ (1.0) | – | 3 | – | **7** | 17 |
| | V | Caffeine (8) | $Cs_2CO_3$ (1.0) | – | 3 | 100 | **4e** | 72 |

* General conditions: 2.0 mmol (methods I, II) or 0.5 mmol (methods III–V) of lactone **1**, 1.2 equiv of halopyridine **2**, 4 mol % of $Pd(OAc)_2$, 120°C, 16 h.

The reactions of lactone **1** with 4-iodopyridine (**2b**) gave high yields of the double bond isomerization product **4b**, in contrast to the analogous reactions with 3-iodopyridine (**2a**).

The reaction of isoalantolactone (**1**) with 5-bromo-2-methoxypyridine (**2c**), 3-bromo-5-methoxypyridine (**2d**), or 3-bromo-5-(trifluoromethyl)pyridine (**2e**) was performed with $Pd(OAc)_2$–(*o*-Tol)$_3$P (method III) or $Pd(OAc)_2$–caffeine (method V) catalysts in DMF in the presence of $Cs_2CO_3$ (Table 1). The reaction of lactone **1** with bromopyridines **2c**,**d** according to method III resulted in a low degree of conversion and produced the exocyclic products **3c**,**d** with *E*-configuration (Scheme 1, Table 1). 3-Bromo-5-(trifluoromethyl)pyridine (**2e**) did not react with isoalantolactone (**1**) under the conditions of method III, giving instead the homocoupling product, 5,5'-bis-(trifluoromethyl)-3,3'-bipyridine (**7**) in 17% yield.

The reaction of lactone **1** with substituted 3-bromopyridines, catalyzed by $Pd(OAc)_2$–caffeine system in the presence of $Cs_2CO_3$ (method V), was more successful. The respective 13-(pyridin-3-yl)eudesmanolides **3c**,**d** or **4e** were isolated from this reaction in 51–89% yields. Characteristically, the reaction of isoalantolactone (**1**) with the methoxy-substituted bromopyridines **2c**,**d** produced the 13-(*E*)-(methoxypyridyl)eudesmanolides **3c**,**d** in 51 or 89% yields, while no formation of compounds with endocyclic structure was observed. The isomer **4e** with endocyclic structure was obtained by reacting isoalantolactone (**1**) with trifluoromethyl-substituted bromopyridine. Compound **3c** was isolated as the major product from a reaction of methylidenelactone **1** with bromide **2c**, catalyzed by $Pd(OAc)_2$–(*o*-Tol)$_3$P system in the presence of Et$_3$N and TBAB (120°C, 20 h) (method II, Table 1), along with 13(*E*)-(1*H*-2-oxopyridinon-5-yl)eudesmanolide (**5**) and 13,15-bis(pyridin-3-yl)eudesmanolide (**6**) as the minor products arising from cross coupling at both double bonds of isoalantolactone (**1**). Compound **5** apparently was formed under the reaction conditions as a result of 2-methoxypyridine ring transformation to a pyridine-2(1*H*)-one ring in compound **3c**. It can be assumed that *O*-demethylation was promoted by the presence of bromide anion in the system (introduced as tetrabutylammonium bromide), giving a 2-methoxypyridinium salt. Subsequent $S_N2$ substitution with elimination of methyl bromide under hydrolytic conditions led to the respective pyridin-2(1*H*)-one. Examples have been described in the literature where 2-methoxypyridines were converted to pyridin-2(1*H*)-ones by the action of such reagents as TMSI–$H_2O$, as well as aqueous HI[17a] or HBr.[17b]

The structures of the synthesized compounds were established based on the data set including elemental analysis and spectral features. The (*E*)-configuration of C(11)=C(13) double bond in lactones **3a**–**d**, **5**, and **6** was inferred from the presence of proton–carbon coupling constant corresponding to *cis* structure ($^3J \approx 6.6$ Hz) between the olefinic proton and lactone carbonyl carbon in $^{13}$C NMR spectrum (single resonant mode). A characteristic feature in $^1$H NMR spectra of (*E*)-isomers **3a**–**d**, **5** was the downfield shift of the H-7 proton (3.34–3.43 ppm) relative to the position of the respective proton in the spectrum of isoalantolactone (**1**) (2.93 ppm). The signal of the H-13 proton in $^1$H NMR spectra of (*E*)-isomers **3a**–**d**, **5**, **6** was located in the region of 7.11–7.38 ppm. The formation of 1*H*-pyridin-2-one ring in the structure of compound **5** was confirmed by the absence of methoxy group signal in $^1$H NMR spectrum and the presence of a carbonyl group signal (C-2') in $^{13}$C NMR spectrum at 163.7 ppm.

Characteristic features in $^1$H NMR spectra of compounds **4a**,**b**,**e** were the presence of proton signals due to the 13-$CH_2$ methylene group (for example, there were two doublets at 3.50 and 3.56 ppm ($J$ = 15.0 Hz) for compound **4a**), as well as a significant increase in the difference between the chemical shifts of 9-$CH_2$ protons (Δδ 1.2 ppm). One of the protons in the 9-$CH_2$ group, observed at higher field (1.07 ppm for compound **4a**), had an axial-axial coupling constant with the 8-CH proton ($J$ = 11.8 Hz). The 8(*S*)-configuration of compounds **4a**,**b**,**e** was confirmed from the NOESY spectra of compound **4a**, showing a cross peak between the proton signals of the 14-$CH_3$ methyl group and the 8-CH group.

Thus, a cross-coupling reaction catalyzed by palladium complexes was used to achieve the first synthesis of eudesmanolide derivatives with pyridine substituents at C-13 position from isoalantolactone and halopyridines. Variation of the catalytic system composition allowed to modify the selectivity of the cross-coupling reaction, increasing the yield of compounds with an exocyclic methylidene double bond, (*E*)-13-(pyridinyl)eudesma-4(15),11(13)-dien-8β,12-olides, or their endocyclic isomers, 13-nor-11-(pyridylmethyl)eudesma-4(15),7(11)-dien-8α,12-olides. The structure of halopyridine had a substantial effect on the yield and composition of the reaction products. For example, mostly compounds of exocyclic structure were formed in the reaction of isoalantolactone with 3-iodopyridine, as well as 3-bromopyridines containing an electron-donating substituent at positions 5 or 6. On the other hand, the main products in the reaction of isoalantolactone with 4-iodopyridine or 3-bromo-5-(trifluoromethyl)pyridine were compounds of endocyclic structure.

## Experimental

IR spectra were recorded for KBr pellets on a Vector-22 FT-IR spectrometer. UV absorption spectra were recorded for EtOH solutions ($10^{-4}$ mol/l) on an HP 8453 UV-Vis spectrometer. $^1$H, $^{13}$C, and $^{19}$F spectra of compound **4e** were acquired on a Bruker AV-300 spectrometer (300, 75, and 280 MHz, respectively). $^1$H and $^{13}$C NMR spectra of compound **6** were acquired on Bruker AV-400 (400 and 100 MHz, respectively), the rest compound spectra - on Bruker AV-600 (600 and 150 MHz, respectively) spectrometers. The solvents were $CDCl_3$ or 1:1 $CDCl_3$ + $CD_3OD$ (for compound **5**), TMS was used as internal standard. The multiplicity of $^{13}$C NMR signals was determined according to standard acquisition procedures in single resonant mode. The assignment of NMR signals was based on various types of proton–proton ($^1$H–$^1$H) and proton–carbon ($^1$H–$^{13}$C) correlation spectroscopy experiments (COSY, COLOC, COXH, NOESY – the mixing time was 1 s, pulse delay was 2 s). The atom numbering in the molecular backbone and substituents used for the description of $^1$H and $^{13}$C NMR spectra is given in the Scheme 1. High-resolution mass spectra were recorded on a DFS Thermo Scientific mass spectrometer (evaporator temperature 50–250°C, electrospray ionization). Elemental analysis was performed on a Carlo Erba 1106 CHN-analyzer. Melting points were determined on a Stuart SMF-38 hot stage and were not corrected. The specific optical rotation values were measured on a PolAAr 3005 polarimeter and were expressed in (deg·ml)/(g·dm), concentration – in grams per 100 ml of solution. The reaction products were isolated by column chromatography on silica gel (Acros, 0.035–0.240 mm), eluents $CHCl_3$–EtOH, 100:0→100:10; benzene–EtOAc, 10:1→1:10, TLC was performed on Silufol UV-254 plates (eluents 9:1 $CHCl_3$–EtOH; 3:1 benzene–EtOAc), visualization with iodine vapor or under UV light.

The solvents (benzene, DMF, $CHCl_3$, EtOAc), as well as $Et_3N$ were purified according to standard procedures and distilled under argon atmosphere immediately prior to the use in reactions. The reagents used in this study, 3-iodopyridine (**2a**), 4-iodopyridine (**2b**), 3-bromo-6-methoxypyridine (**2c**), 3-bromo-5-methoxypyridine (**2d**), 3-bromo-5-(trifluoromethyl)pyridine (**2e**), (*o*-Tol)$_3$P, caffeine, $Cs_2CO_3$, and TBAB were purchased from Alfa Aesar. $Pd(OAc)_2$ was synthesized according to a published procedure.[18] Isoalantolactone (**1**) used in this study was isolated by extraction from *Inula helenium* L., followed by separation of morpholine adducts according to a literature procedure.[19]

**Heck reaction of isoalantolactone (1) with halopyridines 2a–e** (General method). A glass ampoule was charged upon cooling to 0–5°C under argon flow with 3Å molecular sieves (10 mg), isoalantolactone (**1**) (117 mg, 0.5 mmol), halopyridine **2a**–**e** (0.6 mmol), $Pd(OAc)_2$ (4.5 mg, 4 mol %), the appropriate ligand, base, and DMF (3 ml), as well as 1 equiv of TBAB when needed. The ampoule was sealed and heated for 16 h at 120°C. When the reaction was complete, the ampoule was cooled, opened, the mixture was filtered, the filtrate was poured into a saturated NaCl solution (30 ml) and extracted with EtOAc (3×30 ml). The combined organic extracts were washed with saturated NaCl solution (1×30 ml), water (2×30 ml), dried over $MgSO_4$, and evaporated under reduced pressure provided by water aspirator. The oily residue was dissolved in a minimum amount of $CHCl_3$ and separated by silica gel column chromatography (eluent $CHCl_3$–EtOH, gradient 100:1→100:4). The starting lactone (**1**) was eluted first (in the case of incomplete conversion), followed by reaction products: compounds **3**, then compounds **4**, and homocoupling products: 3,3'-bipyridine,[20] 4,4'-bipyridine,[21] 3,3'-bis(5-methoxypyridine) (**7**).[22]

**(3a*R*,4a*S*,8a*R*,9a*R*,*E*)-8a-Methyl-5-methylidene-3-[(pyridin-3-yl)methylidene]decahydronaphtho[2,3-*b*]furan-2(3*H*)-one (3a)**. Colorless crystals. Mp 207–209°C (EtOH). $[\alpha]_{589}^{27}$ +291° (*c* 1.23, $CHCl_3$). IR spectrum, ν, cm$^{-1}$: 712, 889, 1000, 1172, 1215, 1423, 1657, 1737, 2830, 2911, 2929. UV spectrum, $\lambda_{max}$, nm (log ε): 274 (4.20). $^1$H NMR spectrum, δ, ppm ($J$, Hz): 0.85 (3H, s, $CH_3$); 1.26 (1H, ddd, $J$ = 13.0, $J$ = 12.7, $J$ = 3.0, 1-$CH_A$); 1.42 (1H, dd, $J$ = 13.9, $J$ = 12.4) and 1.95 (1H, ddd, $J$ = 13.9, $J$ = 6.6, $J$ = 2.1, 6-$CH_2$); 1.54 (1H, dd, $J$ = 15.8, $J$ = 4.8) and 2.25 (1H, dd, $J$ =15.8, $J$ = 1.6, 9-$CH_2$); 1.55–1.62 (3H, m, 1-$CH_B$, 2-$CH_2$); 1.91 (1H, d, $J$ = 12.4, 5-CH); 2.01 (1H, ddd, $J$ = 13.3, $J$ = 13.1, $J$ = 5.9) and 2.33 (1H, d, $J$ = 13.3, 3-$CH_B$); 3.40 (1H, ddd, $J$ = 12.4, $J$ = 6.2, $J$ = 5.1, 7-CH); 4.38 (1H, d, $J$ = 1.3) and 4.75 (1H, d, $J$ = 1.3, 15-$CH_B$);

4.51 (1H, ddd, *J* = 5.1, *J* = 4.8, *J* = 1.6, 8-CH); 7.36 (1H, dd, *J* = 8.0, *J* = 4.8, H-5'); 7.38 (1H, s, 13-CH); 7.80 (1H, ddd, *J* = 8.0, *J* = 1.9, *J* = 1.8, H-4'); 8.58 (1H, dd, *J* = 4.8, *J* = 1.6, H-6'); 8.78 (1H, d, *J* = 1.8, H-2'). $^{13}$C NMR spectrum, δ, ppm: 17.6 ($CH_3$); 22.6 (C-2); 24.6 (C-6); 34.4 (C-10); 36.7 (C-3); 39.6 (C-7); 41.2 (C-9); 42.1 (C-1); 46.3 (C-5); 76.9 (C-8); 106.7 (C-15); 123.8 (C-5'); 130.2 (C-11); 131.0 (C-13); 135.0 (C-3'); 136.2 (C-4'); 148.7 (C-4); 150.1 (C-6'); 150.3 (C-2'); 171.5 (C-12). Found, %: C 77.67; H 7.44; N 4.53. $C_{20}H_{23}NO_2$. Calculated, %: C 77.64; H 7.49; N 4.53.

**(4a*S*,8a*R*,9a*S*)-8a-Methyl-5-methylidene-3-[(pyridin-3-yl)methyl]-4a,5,6,7,8,8a,9,9a-octahydronaphtho[2,3-*b*]-furan-2(4*H*)-one (4a)**. Oily material. $[\alpha]_{589}^{26}$ +132° (*c* 0.40, $CHCl_3$). IR spectrum, ν, cm$^{-1}$: 714, 891, 1016, 1026, 1045, 1057, 1067, 1101, 1128, 1340, 1425, 1441, 1477, 1647, 1680, 1751, 2851, 2864, 2932. UV spectrum, $\lambda_{max}$, nm (log ε): 222 (4.14), 257 (3.57), 263 (3.60), 269 (3.52). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.82 (3H, s, $CH_3$); 1.07 (1H, dd, *J* = 12.1, *J* = 11.8) and 2.25 (1H, dd, *J* = 12.1, *J* = 6.3, 9-$CH_2$); 1.24 (1H, ddd, *J* = 14.7, *J* = 13.7, *J* = 4.4, 1-$CH_A$); 1.50–1.59 (3H, m, 1-$CH_B$, 2-$CH_2$); 1.76 (1H, d, *J* =13.0, 5-CH); 1.88 (1H, ddd, *J* = 14.5, *J* = 13.5, *J* = 4.6, 3-$CH_A$); 2.27–2.31 (2H, m, 3-$CH_B$, 6-$CH_A$); 2.71 (1H, dd, *J* = 14.0, *J* = 3.6, 6-$CH_B$); 3.50 (1H, d, *J* = 15.0) and 3.56 (1H, d, *J* = 15.0, 13-$CH_2$); 4.50 (1H, d, *J* = 1.5) and 4.79 (1H, d, *J* = 1.5, 15-$CH_2$); 4.81 (1H, dd, *J* = 11.8, *J* = 6.3, 8-CH); 7.15 (1H, dd, *J* = 7.8, *J* = 4.5, H-5'); 7.55 (1H, d, *J* = 7.8, H-4'); 8.38 (1H, d, *J* = 4.5, H-6'); 8.39 (1H, s, H-2'). $^{13}$C NMR spectrum, δ, ppm: 16.2 ($CH_3$); 22.0 (C-2); 25.6 (C-6); 26.3 (C-13); 35.9 (C-3); 36.7 (C-10); 40.4 (C-1); 47.3 (C-9); 49.8 (C-5); 77.9 (C-8); 106.8 (C-15); 122.4 (C-11); 123.4 (C-5'); 133.7 (C-3'); 135.9 (C-4'); 147.6 (C-6'); 147.8 (C-4); 149.3 (C-2'); 164.2 (C-7); 173.4 (C-12). Mass spectrum, *m*/*z* ($I_{rel}$, %): 310 (24), 309 $[M]^+$ (100), 308 (31), 294 (23), 264 (11), 130 (11), 93 (14), 92 (10), 91 (10), 77 (10). Found, *m*/*z*: 309.1722 $[M]^+$. $C_{20}H_{23}NO_2$. Calculated, *m*/*z*: 309.1723.

**(3a*R*,4a*S*,8a*R*,9a*R*,*E*)-8a-Methyl-5-methylidene-3-[(pyridin-4-yl)methylidene]decahydronaphtho[2,3-*b*]furan-2(3*H*)-one (3b)**. White crystals. Mp 164–166°C (EtOH). $[\alpha]_{589}^{31}$ +356° (*c* 0.50, $CHCl_3$). IR spectrum, ν, cm$^{-1}$: 540, 812, 889, 1001, 1171, 1223, 1416, 1591, 1746, 2930. UV spectrum, $\lambda_{max}$, nm (log ε): 269 (4.32). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.85 (3H, s, $CH_3$); 1.26 (1H, ddd, *J* = 13.2, *J* = 12.6, *J* = 3.0, 1-$CH_A$); 1.42 (1H, dd, *J* = 14.0, *J* = 12.7) and 1.93 (1H, ddd, *J* = 14.0, *J* = 6.0, *J* = 2.5, 6-$CH_2$); 1.54 (1H, dd, *J* = 15.8, *J* = 4.6) and 2.25 (1H, dd, *J* = 15.8, *J* = 1.4, 9-$CH_2$); 1.54–1.61 (3H, m, 1-$CH_B$, 2-$CH_2$); 1.92 (1H, d, *J* = 12.7, 5-CH); 2.01 (1H, ddd, *J* = 13.7, *J* = 13.2, *J* = 5.9) and 2.33 (1H, d, *J* = 13.0, 3-$CH_2$); 3.43 (1H, ddd, *J* = 12.7, *J* = 6.0, *J* = 5.1, 7-CH); 4.39 (1H, d, *J* = 1.1) and 4.76 (1H, d, *J* = 1.1, 15-$CH_2$); 4.52 (1H, ddd, *J* = 5.1, *J* = 4.6, *J* = 1.4, 8-CH); 7.32 (1H, s, 13-CH); 7.34 (2H, dd, *J* = 6.0, *J* = 1.3, H-3',5'); 8.66 (1H, dd, *J* = 6.0, *J* = 1.3, H-2',6'). $^{13}$C NMR spectrum, δ, ppm: 17.6 ($CH_3$); 22.6 (C-2); 24.6 (C-6); 34.3 (C-10); 36.7 (C-3); 39.6 (C-7); 41.1 (C-9); 42.0 (C-1); 46.2 (C-5); 77.0 (C-8); 106.8 (C-15); 123.1 (C-3',5'); 131.8 (C-13); 137.4 (C-11); 141.4 (C-4'); 148.7 (C-4); 150.6 (C-2',6'); 171.2 (C-12). Mass spectrum, *m*/*z* ($I_{rel}$, %): 310 (22), 309 $[M]^+$ (100), 294 (26), 267 (60), 174 (19), 173 (19), 121 (19), 117 (20), 93 (18), 79 (20). Found, *m*/*z*: 309.1721 $[M]^+$. $C_{20}H_{23}NO_2$. Calculated, *m*/*z*: 309.1723.

**(4a*S*,8a*R*,9a*S*)-8a-Methyl-5-methylidene-3-[(pyridin-4-yl)methyl]-4a,5,6,7,8,8a,9,9a-octahydronaphtho[2,3-*b*]-furan-2(4*H*)-one (4b)**. Oily material. $[\alpha]_{589}^{28}$ +126° (*c* 0.35, $CHCl_3$). IR spectrum, ν, cm$^{-1}$: 474, 791, 891, 1015, 1045, 1057, 1070, 1099, 1416, 1599, 1647, 1686, 1732, 1749, 2851, 2934. UV spectrum, $\lambda_{max}$, nm (log ε): 222 (4.23), 257 (3.48), 263 (3.41). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.87 (3H, s, $CH_3$); 1.13 (1H, dd, *J* =12.1, *J* = 11.9, 9-$CH_A$); 1.30 (1H, ddd, *J* = 14.2, *J* = 13.8, *J* = 4.9, 1-$CH_A$); 1.56–1.65 (3H, m, 1-$CH_B$, 2-$CH_2$); 1.79 (1H, d, *J* = 12.8, 5-CH); 1.94 (1H, ddd, *J* = 13.9, *J* = 13.3, *J* = 5.3, 3-$CH_A$); 2.30–2.36 (3H, m, 3-$CH_B$, 6-$CH_A$, 9-$CH_B$); 2.71 (1H, dd, *J* = 13.9, *J* = 3.7, 6-$CH_B$); 3.54 (1H, d, *J* = 15.0) and 3.61 (1H, d, *J* = 15.0, 13-$CH_2$); 4.54 (1H, d, *J* = 0.9) and 4.85 (1H, d, *J* = 0.9, 15-$CH_2$); 4.88 (1H, dd, *J* = 11.6, *J* = 6.4, 8-CH); 7.14 (2H, d, *J* = 6.0, H-3',5'); 8.48 (2H, d, *J* = 6.0, H-2',6'). $^{13}$C NMR spectrum, δ, ppm: 16.3 ($CH_3$); 22.1 (C-2); 25.9 (C-6); 28.5 (C-13); 36.1 (C-3); 36.8 (C-10); 40.6 (C-1); 47.5 (C-9); 50.0 (C-5); 78.1 (C-8); 107.0 (C-15); 121.9 (C-11); 123.6 (C-3',5'); 147.3 (C-4'); 148.0 (C-4); 149.8 (C-2',6'); 165.0 (C-7); 173.5 (C-12). Mass spectrum, *m*/*z* ($I_{rel}$, %): 310 (23), 309 $[M]^+$ (100), 201 (10), 130 (18), 94 (15), 93 (11), 91 (15), 79 (15), 77 (16). Found, *m*/*z*: 309.1725 $[M]^+$. $C_{20}H_{23}NO_2$. Calculated, *m*/*z*: 309.1723.

**(3a*R*,4a*S*,8a*R*,9a*R*,*E*)-3-[(6-Methoxypyridin-3-yl)methylidene]-8a-methyl-5-methylidenedecahydronaphtho-[2,3-*b*]furan-2(3*H*)-one (3c)**. Colorless crystals. Mp 161–162°C (EtOH). $[\alpha]_{589}^{27}$ +450° (*c* 0.33, $CHCl_3$). IR spectrum, ν, cm$^{-1}$: 829, 893, 937, 959, 1001, 1016, 1089, 1128, 1171, 1206, 1261, 1294, 1315, 1331, 1358, 1395, 1441, 1497, 1562, 1599, 1651, 1738, 1747, 2839, 2930. UV spectrum, $\lambda_{max}$, nm (log ε): 288 (4.29), 307 (4.32). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.85 (3H, s, 14-$CH_3$); 1.25 (1H, ddd, *J* = 13.2, *J* = 12.5, *J* = 3.0, 1-$CH_A$); 1.38 (1H, dd, *J* = 14.0, *J* = 12.4) and 1.96 (1H, ddd, *J* = 14.0, *J* = 6.6, *J* = 2.5, 6-$CH_2$); 1.52 (1H, dd, *J* = 15.7, *J* = 4.8) and 2.24 (1H, dd, *J* = 15.7, *J* = 1.4, 9-$CH_2$); 1.53–1.61 (3H, m, 1-$CH_B$, 2-$CH_2$); 1.89 (1H, d, *J* = 12.7, 5-CH); 2.00 (1H, ddd, *J* = 13.5, *J* = 13.2, *J* = 5.7) and 2.32 (1H, d, *J* = 13.5, 3-$CH_2$); 3.34 (1H, ddd, *J* = 12.4, *J* = 6.6, *J* = 5.3, 7-CH); 3.95 (3H, s, $OCH_3$); 4.38 (1H, d, *J* = 1.1) and 4.74 (1H, d, *J* = 1.1, 15-$CH_2$); 4.48 (1H, ddd, *J* = 5.3, *J* = 4.8, *J* = 1.4, 8-CH); 6.78 (1H, d, *J* = 8.7, H-5'); 7.33 (1H, s, 13-CH); 7.71 (1H, dd, *J* = 8.7, *J* = 2.5, H-4'); 8.34 (1H, d, *J* = 2.5, H-2'). $^{13}$C NMR spectrum, δ, ppm: 17.6 (14-$CH_3$); 22.6 (C-2); 24.5 (C-6); 34.4 (C-10); 36.7 (C-3); 39.5 (C-7); 41.2 (C-9); 42.1 (C-1); 46.3 (C-5); 53.7 ($OCH_3$); 76.8 (C-8); 106.7 (C-15); 111.5 (C-5'); 123.6 (C-3'); 131.3 (C-13); 131.4 (C-11); 138.6 (C-4'); 148.8 (C-4); 149.1 (C-2'); 164.5 (C-6'); 172.1 (C-12). Mass spectrum, *m*/*z* ($I_{rel}$, %): 340 (28), 339 $[M]^+$ (100), 338 (11), 204 (5), 203 (33), 175 (5), 146 (14), 91 (4), 81 (4), 79 (5). Found, *m*/*z*: 339.1831 $[M]^+$. $C_{21}H_{25}NO_3$. Calculated, *m*/*z*: 339.1829.

**5-(*E*)-[((3a*R*,4a*S*,8a*R*,9a*R*)-8a-Methyl-5-methylidene-2-oxodecahydronaphtho[2,3-*b*]furan-3(2*H*)-ylidene)-methyl]pyridin-2(1*H*)-one (5)**. Gray amorphous material.

$[\alpha]_{589}^{31}$ +556° (*c* 0.43, $CHCl_3$). IR spectrum, ν, $cm^{-1}$: 469, 528, 897, 999, 1128, 1175, 1207, 1223, 1240, 1317, 1433, 1543, 1584, 1609, 1655, 1744, 2839, 2866, 2909, 2928, 2965, 2984, 3069, 3142, 3169. UV spectrum, $\lambda_{max}$, nm (log ε): 225 (3.91), 308 (4.35). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.82 (3H, s, $CH_3$); 1.24 (1H, ddd, *J* = 13.4, *J* = 12.8, *J* = 2.8, 1-$CH_A$); 1.35 (1H, dd, *J* = 13.8, *J* = 12.5) and 1.85 (1H, ddd, *J* = 14.1, *J* = 6.6, *J* = 2.4, 6-$CH_2$); 1.51 (1H, dd, *J* = 15.7, *J* = 4.6) and 2.22 (1H, dd, *J* = 15.7, *J* = 1.3, 9-$CH_2$); 1.52–1.60 (3H, m, 1-$CH_B$, 2-$CH_2$); 1.89 (1H, d, *J* = 12.8, 5-CH); 1.98 (1H, ddd, *J* = 13.8, *J* = 12.9, *J* = 5.1) and 2.31 (1H, d, *J* = 13.6, 3-$CH_2$); 3.28 (1H, ddd, *J* = 12.5, *J* = 6.6, *J* = 5.3, 7-CH); 4.37 (1H, d, *J* = 0.9) and 4.74 (1H, d, *J* = 0.9, 15-$CH_2$); 4.47 (1H, ddd, *J* = 5.3, *J* = 4.6, *J* = 1.3, 8-CH); 6.62 (1H, d, *J* = 8.5, H-3'); 7.11 (1H, s, 13-CH); 7.58 (1H, d, *J* = 2.5, H-6'); 7.68 (1H, dd, *J* = 8.5, *J* = 2.5, H-4'). $^{13}$C NMR spectrum, δ, ppm: 17.5 ($CH_3$); 22.5 (C-2); 24.9 (C-6); 34.3 (C-10); 36.7 (C-3); 39.1 (C-7); 41.1 (C-9); 42.0 (C-1); 46.1 (C-5); 76.6 (C-8); 106.6 (C-15); 115.0 (C-5'); 120.9 (C-3'); 129.9 (C-13); 130.0 (C-11); 137.9 (C-4'); 140.3 (C-6'); 148.8 (C-4); 163.7 (C-2'); 172.2 (C-12). Mass spectrum, *m/z* ($I_{rel}$, %): 326 (22), 325 $[M]^+$ (100), 189 (73), 161 (26), 132 (35), 108 (17), 91 (26), 83 (17), 79 (17). Found, *m/z*: 325.1669 $[M]^+$. $C_{20}H_{23}NO_3$. Calculated, *m/z*: 325.1673.

**(3*E*,3a*R*,4a*R*,5*E*,8a*R*,9a*R*)-3,5-Bis[(6-methoxypyridin-3-yl)methylidene]-8a-methyldecahydronaphtho[2,3-*b*]-furan-2(3*H*)-one (6)**. Oily material. $[\alpha]_{589}^{28}$ +419° (*c* 0.54, $CHCl_3$). IR spectrum, ν, $cm^{-1}$: 752, 831, 993, 1026, 1099, 1128, 1144, 1161, 1184, 1200, 1217, 1254, 1265, 1288, 1346, 1360, 1371, 1394, 1444, 1460, 1493, 1564, 1599, 1655, 1751, 2929, 2941. UV spectrum, $\lambda_{max}$, nm (log ε): 247 (4.13), 288 (4.21), 303 (4.18). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.91 (3H, s, 14-$CH_3$); 1.32 (1H, ddd, *J* = 13.8, *J* = 13.5, *J* = 5.5, 1-$CH_A$); 1.48–1.63 (5H, m, 1-$CH_B$, 2-$CH_2$, 6-$CH_A$, 9-$CH_A$); 1.76 (1H, ddd, *J* = 14.0, *J* = 13.0, *J* = 3.9) and 2.84 (1H, d, *J* = 13.3, 3-$CH_2$); 2.01–2.07 (2H, m, 5-CH, 6-$CH_B$); 2.28 (1H, dd, *J* = 15.7, *J* = 1.2, 9-$CH_B$); 3.39 (1H, ddd, *J* = 12.2, *J* = 6.4, *J* = 5.5, 7-CH); 3.88 (3H, s, $OCH_3$); 3.94 (3H, s, $OCH_3$); 4.50 (1H, ddd, *J* = 5.3, *J* = 4.8, *J* = 1.2, 8-CH); 5.82 (1H, s, 15-CH); 6.65 (1H, d, *J* = 8.5, H-5"); 6.79 (1H, d, *J* = 8.7, H-5'); 7.32 (1H, dd, *J* = 8.6, *J* = 2.4, H-4"); 7.34 (1H, s, 13-CH); 7.73 (1H, dd, *J* = 8.7, *J* = 2.4, H-4'); 7.93 (1H, d, *J* = 2.3, H-2"); 8.37 (1H, d, *J* = 2.3, H-2'). $^{13}$C NMR spectrum, δ, ppm: 17.6 (14-$CH_3$); 22.3 (C-2); 24.3 (C-6); 30.1 (C-10); 34.9 (C-3); 39.4 (C-7); 41.1 (C-9); 42.0 (C-1); 46.9 (C-5); 53.0 ($OCH_3$); 53.5 ($OCH_3$); 77.7 (C-8); 109.8 (C-5"); 111.3 (C-5'); 117.4 (C-15); 123.3 (C-3"); 126.5 (C-3'); 131.0 (C-11); 131.2 (C-13); 138.5 (C-4"); 138.9 (C-4'); 143.0 (C-4); 146.0 (C-2"); 148.9 (C-2'); 162.0 (C-6"); 164.2 (C-6'); 171.9 (C-12). Mass spectrum, *m/z* ($I_{rel}$, %): 447 (24), 446 $[M]^+$ (79), 162 (37), 161 (9), 160 (6), 146 (9), 122 (17), 85 (36), 83 (100), 47 (8). Found, *m/z*: 446.2204 $[M]^+$. $C_{27}H_{30}N_2O_4$ Calculated, *m/z*: 446.2200.

**(3a*R*,4a*S*,8a*R*,9a*R*,*E*)-3-[(5-Methoxypyridin-3-yl)methylidene]-8a-methyl-5-methylidenedecahydronaphtho[2,3-*b*]-furan-2(3*H*)-one (3d)**. Colorless crystals. Mp 168–170°C (EtOH). $[\alpha]_{589}^{27}$ +380° (*c* 0.20, $CHCl_3$). IR spectrum, ν, $cm^{-1}$: 890, 1001, 1041, 1171, 1190, 1213, 1300, 1427, 1446, 1583, 1656, 1741, 2902, 2926. UV spectrum, $\lambda_{max}$, nm (log ε): 219 (4.13), 246 (4.12), 272 (4.11), 312 (3.97). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.84 (3H, s, 14-$CH_3$); 1.25 (1H, ddd, *J* = 13.1, *J* = 12.8, *J* = 4.7, 1-$CH_A$); 1.40 (1H, dd, *J* = 13.3, *J* = 12.5) and 1.94 (1H, ddd, *J* = 14.1, *J* = 6.6, *J* = 2.6, 6-$CH_2$); 1.52 (1H, dd, *J* = 15.7, *J* = 4.8) and 2.24 (1H, dd, *J* = 15.7, *J* = 1.6, 9-$CH_2$); 1.53–1.61 (3H, 1-$CH_B$, 2-$CH_2$); 1.89 (1H, d, *J* = 12.8, 5-CH); 2.00 (1H, ddd, *J* = 13.5, *J* = 13.2, *J* = 5.9) and 2.32 (1H, d, *J* = 13.5, 3-$CH_2$); 3.39 (1H, ddd, *J* = 12.1, *J* = 6.7, *J* = 5.3, 7-CH); 3.87 (3H, s, $OCH_3$); 4.37 (1H, d, *J* = 1.3) and 4.74 (1H, d, *J* = 1.3, 15-$CH_2$); 4.50 (1H, ddd, *J* = 6.0, *J* = 4.6, *J* = 1.3, 8-CH); 7.24 (1H, dd, *J* = 2.8, *J* = 2.2, H-4'); 7.35 (1H, s, 13-CH); 8.28 (1H, d, *J* = 2.8, H-6'); 8.40 (1H, d, *J* = 1.6, H-2'). $^{13}$C NMR spectrum, δ, ppm: 17.6 (14-$CH_3$); 22.5 (C-2); 24.6 (C-6); 34.3 (C-10); 36.7 (C-3); 39.6 (C-7); 41.1 (C-9); 42.0 (C-1); 46.2 (C-5); 55.6 ($OCH_3$); 76.9 (C-8); 106.7 (C-15); 120.9 (C-4'); 130.6 (C-11); 131.1 (C-13); 135.1 (C-3'); 137.7 (C-6'); 142.4 (C-2'); 148.6 (C-4); 155.5 (C-5'); 171.5 (C-12). Mass spectrum, *m/z* ($I_{rel}$, %): 340 (24), 339 $[M]^+$ (100), 324 (13), 298 (13), 204 (16), 203 (30), 175 (11), 147 (10), 146 (9), 79 (9). Found, *m/z*: 339.1832 $[M]^+$. $C_{21}H_{25}NO_3$. Calculated, *m/z*: 339.1829.

**(4a*S*,8a*R*,9a*S*)-8a-Methyl-5-methylidene-3-{[5-(trifluoromethyl)pyridin-3-yl]methyl}-4a,5,6,7,8,8a,9,9a-octahydronaphtho[2,3-*b*]furan-2(4*H*)-one (4e)**. Oily material. $[\alpha]_{589}^{28}$ +94° (*c* 0.50, $CHCl_3$). IR spectrum, ν, $cm^{-1}$: 715, 895, 1016, 1028, 1047, 1057, 1068, 1090, 1134, 1165, 1215, 1338, 1441, 1680, 1753, 2933. UV spectrum, $\lambda_{max}$, nm (log ε): 221 (4.13), 262 (3.42). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 0.87 (3H, s, $CH_3$); 1.13 (1H, dd, *J* = 12.7, *J* = 12.0) and 2.32 (1H, dd, *J* = 12.5, *J* = 6.5, 9-$CH_2$); 1.29 (1H, ddd, *J* = 13.5, *J* = 12.6, *J* = 4.8, 1-$CH_A$); 1.53–1.56 (3H, m, 1-$CH_B$, 2-$CH_2$); 1.81 (1H, d, *J* =12.7, 5-CH); 1.94 (1H, ddd, *J* = 13.8, *J* = 13.3, *J* = 5.8, 3-$CH_A$); 2.33–2.40 (2H, m, 3-$CH_B$, 6-$CH_A$); 2.72 (1H, dd, *J* = 13.8, *J* = 3.6, 6-$CH_B$); 3.62 (1H, d, *J* = 15.2) and 3.68 (1H, d, *J* = 15.2, 13-$CH_2$); 4.54 (1H, d, *J* = 0.8) and 4.85 (1H, d, *J* = 1.5, 15-$CH_2$); 4.88 (1H, dd, *J* = 11.4, *J* = 6.3, 8-CH); 7.80 (1H, s, H-4'); 8.64 (1H, d, *J* = 1.5, H-2'); 8.71 (1H, d, *J* = 1.0, H-6'). $^{13}$C NMR spectrum, δ, ppm: 16.3 ($CH_3$); 22.1 (C-2); 25.9 (C -6); 26.3 (C-13); 36.0 (C-3); 36.8 (C-10); 40.6 (C-1); 47.5 (C-9); 50.0 (C-5); 78.2 (C-8); 107.0 (C-15); 121.6 (C-11); 123.3 ($CF_3$); 126.5 (C-5'); 132.9 (C-4'); 134.0 (C-3'); 144.7 (C-6'); 147.8 (C-4); 152.7 (C-2'); 165.1 (C-7); 173.2 (C-12). $^{19}$F NMR spectrum, δ, ppm: 99.3 ($CF_3$). Mass spectrum, *m/z* ($I_{rel}$, %): 377 $[M]^+$ (100), 376 (11), 362 (12), 339 (7), 278 (21), 161 (9), 93 (8), 91 (8), 79 (8), 41 (7). Found, *m/z*: 377.1589 $[M]^+$. $C_{21}H_{22}F_3NO_2$. Calculated, *m/z*: 377.1597.

**5,5'-Bis(trifluoromethyl)-3,3'-bipyridine (7)**. Colorless crystals. Mp 167–169°C ($CHCl_3$). $^1$H NMR spectrum, δ, ppm (*J*, Hz): 8.12 (2H, s, H-4,4'); 8.94 (2H, s, H-2,2'); 9.01 (2H, d, *J* = 1.7, H-6,6'). $^{13}$C NMR spectrum, δ, ppm: 123.3 ($CF_3$); 126.5 (C-5'); 132.9 (C-4'); 134.0 (C-3'); 144.7 (C-6'); 152.7 (C-2'). $^{19}$F NMR spectrum, δ, ppm: 99.2 ($CF_3$). Mass spectrum, *m/z* ($I_{rel}$, %): 293 (14), 273 (15), 223 (20), 217 (7), 196 (5), 176 (4), 171 (4), 157 (8), 75 (6). Found, *m/z*: 292.0432. $C_{12}H_6F_6N_2$. Calculated, *m/z*: 292.0430.

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