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Studies on the Construction of the 2-Isooctyl Side Chain in 17-Azasteroids

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Summary. The transformations of (20*R*)- and (20*S*)-3β-hydroxy-16-oxo-24-nor-17-azachol-5-eno-23-nitriles towards the 17-aza analogue of cholesterol are described. Attempts of a direct addition of a four carbon atom fragment to nitriles were unsuccessful. Alternately, nitriles were transformed *via* carboxylic acids, methyl esters and primary alcohols into iodides. The coupling reaction of (20*S*)-iodide with $(i\text{-Bu})_2\text{CuLi}$ afforded the desired product in low yield but failed in the case of the 20*R* epimer.

Keywords. Azasteroids; 17-Azacholesterol; C(20)-Epimers of 17-Azasteroids; Side Chain Elaboration.

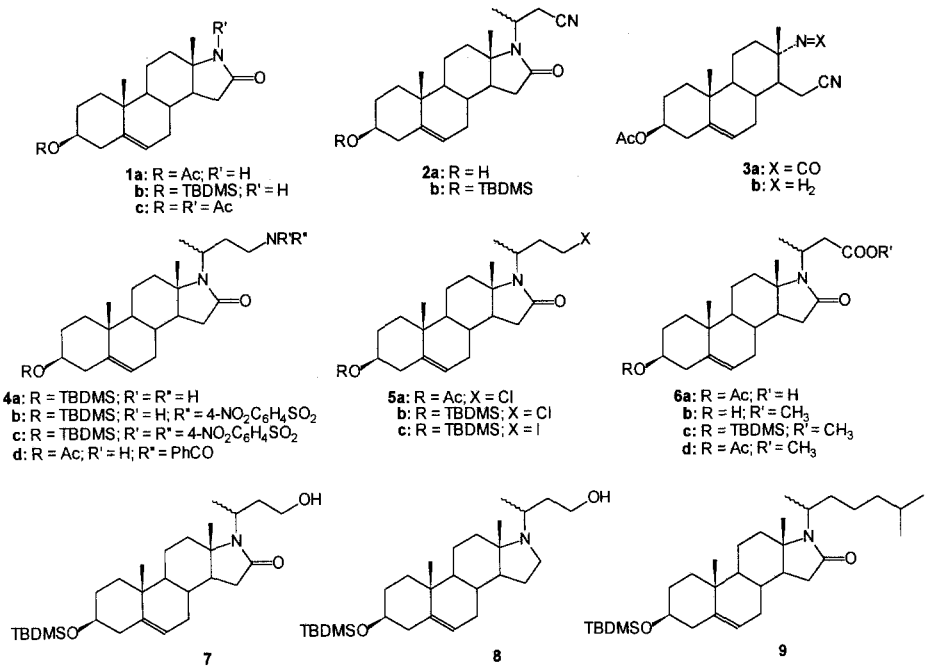
Untersuchungen zum Aufbau der 2-Isooctyl-Seitenkette in 17-Azasteroiden

Zusammenfassung. Die Umsetzungen von (20*R*)- und (20*S*)-3β-Hydroxy-16-oxo-24-nor-17-azachol-5-eno-23-nitril zum 17-aza-Analogon von Cholesterin werden beschrieben. Versuche einer direkten Addition eines 4-Atom-Fragments an Nitrile verliefen erfolglos. Als Ausweg wurden die Nitrile über Carbonsäuren, Methylester und primäre Alkohole zu den Iodiden umgesetzt. Die Kupplungsreaktion von (20*S*)-Iodid mit $(i\text{-Bu})_2\text{CuLi}$ ergab das gewünschte Produkt in niedriger Ausbeute; das (20*R*)-Epimere reagierte nicht.

Introduction

One of the most important challenges to the medicinal chemist is still the search for new hypocholesterolemic agents. Some aza analogues of cholesterol have been found to be potent inhibitors of cholesterol biosynthesis [1].

The aim of this work was to elaborate a method of side chain construction in 17-azasteroids. A convenient method of synthesis of 17-azasteroids with a normal five-membered D-ring was reported [2]. Direct alkylation at the nitrogen atom with secondary iodides (including 2-iodo-6-methylheptane) of either 17-aza steroid lactam **1** or the corresponding 17-aza steroid amine proved unsuccessful, probably due to steric hindrance. An alternative "step by step" method of side chain introduction was attempted. Recently, systematic studies on the alkylation of 17-aza steroid lactams by 1,4-addition to conjugated systems have been performed [3]. Among the conjugated systems studied, crotononitrile proved to be the only one that allowed to obtain 17-azasteroids with a side chain branched at the α position in satisfactory yield. This reaction seems to be the key transformation that may be used in the synthesis of 17-azacholesterol and other N-substituted 17-azasteroids.

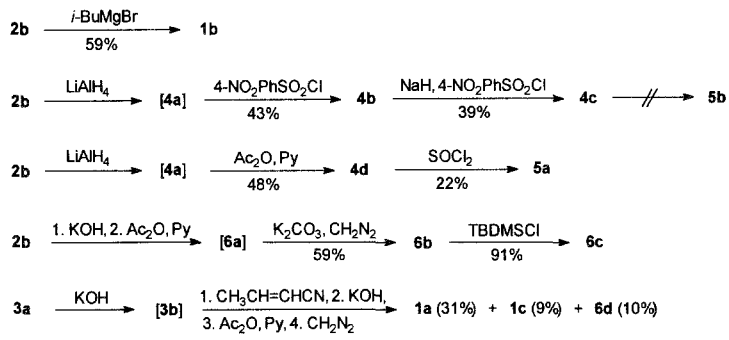


Scheme 1

Results and Discussion

The addition of lactam **1** to crotononitrile appeared to be non-stereoselective. The resulting mixture of epimers at C-20 (**2**) may be separated by column chromatography or by fractional crystallization. However, the separation at this stage of the synthesis is both difficult and unpractical. Therefore, the further construction of the side chain was performed with epimeric material. The epimeric mixture of nitriles with a 3β-hydroxyl group protected as *TBDMS* ether (**2b**) was subjected to a reaction with isobutylmagnesium bromide or isobutyllithium in order to extend the side chain [4]. However, in both cases dealkylation to the parent lactam **1b** took place instead. Less polar organometallic reagents (*e.g.* triisobutylaluminum) [5] did not cause this undesired process, but there was no reaction with the cyano group either. The side chain fragmentation was negligible during lithium aluminum hydride reduction of the nitrile **2b** to the primary amine **4a**. The more significant side process was the reduction of the lactam carbonyl group. Due to the over-reduction, the yield of amino-lactam **4a** was only 48%. The synthetic strategy included the conversion of $-NH_2$ into a good leaving group. This may be accomplished by a number of methods. The most attractive one seemed to be *Baumgarten's* two step procedure [6]. The primary amine was converted into the 4-nitrobenzenesulfonyl derivative **4b**. The 4-nitrobenzenesulfonamide anion was then treated with 4-nitrobenzenesulfonyl chloride in *DMF* to afford the corresponding imide **4c**. However, attempts to displace the *bis*[4-nitrobenzenesulfonyl]imide group with iodide were not successful.

Another method of transformation of primary amines into alkyl halides (usually chloride) consists in the reaction of the benzoyl derivative of the amine with thionyl



Scheme 2

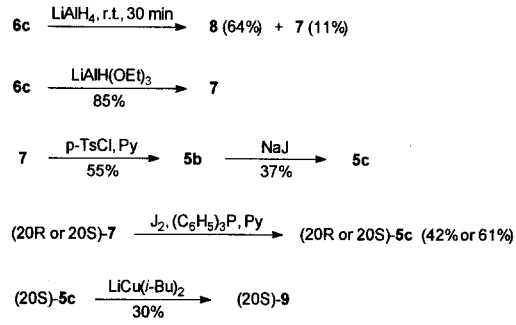
chloride. The initially formed benzimidoyl chloride undergoes fragmentation to benzonitrile and alkyl chloride on heating (*von Braun* reaction) [7]. In the reaction of benzamide **4d**, the corresponding chloride **5a** was formed in low yield only. Since other methods for $NH_2 \rightarrow X$ transformation seemed to be even less promising, further attempts were given up.

There are a number of methods for the preparation of aldehydes from nitriles [8, 9]. Some of them (*e.g.* reaction with *DIBAL*, $LiAlH(OEt)_3$, or Stephen reduction) were tried but did not proceed smoothly.

In contrary to the fragmentation occurring during the nitrile reactions with organometallic reagents, the alkaline hydrolysis of the nitrile **2a** proceeded without dealkylation. Apparently the less basic hydroxyl ion (in comparison with carbanion) does not abstract the α proton, and normal nucleophilic attack at the cyano group takes place. Drastic hydrolysis conditions (KOH, *n*-BuOH, at least 3 days reflux) were necessary. Shorter reaction time (16 h) led to the formation of large amounts of side chain amide. The transformation of –CN into –COOH was accompanied by hydrolysis of the D-ring lactam group. Thus, the primary reaction product required the subsequent recyclization of ring D with acetic anhydride. Although the yield of lactam acid **6a** (purified as methyl ester **6b**) was satisfactory, a different approach was also tried to avoid the necessity for a double cyclization of ring D. An intermediate in the synthesis of lactam **1**, isocyanate **3a** [2], was first hydrolyzed for a short time to the amino nitrile **3b**. This compound was then treated with crotononitrile and the crude product was subjected to prolonged hydrolysis followed by the ring D cyclization with acetic anhydride. Interestingly, lactam acid **6a** obtained in this reaction appeared to be a mixture of 20*R* and 20*S* epimers in the ratio 85:15 (by integration of the 21-H dublets in the ^1H NMR spectrum of the corresponding lactam ester **6d**) [10]. In spite of the favourable stereoselectivity (most natural steroids have 20*R* configuration) observed in this process, it does not seem to be of practical use due to its low yield.

The 3β-hydroxyl group in lactam ester **6b** was protected as *TBDMS* ether and the resulting compound **6c** (C-20 epimers) was subjected to lithium aluminum hydride reduction. The reaction appeared to be difficult to control. Under mild conditions (room temperature, 30 minutes, small excess of $LiAlH_4$), the reduction led predominantly to amino alcohols **8**. Silica gel column chromatography of the reaction products afforded consecutively lactam alcohol (20*S*)-**7** (about 11%), amino

alcohol (20*S*)-**8**, a mixture of both epimers **8** and amino alcohol (20*R*)-**8** (total yield of **8**: 64%) [11]. Thus, lactam alcohol (20*S*)-**7** seems to be more resistant to further reduction. The infrared spectra of both amino alcohols **8** showed an intramolecular hydrogen bond (a band at about 3350–3400 cm^{-1} remained unchanged in a dilute solution in CCl_4) which could slow down the inversion at the nitrogen atom. This may account for the observed changes in time in the ^1H NMR spectrum of amino alcohol (20*S*)-**8**. Most likely, the reduction of a lactam carbonyl group in **7** is particularly easy due to the binding of a reducing agent by the neighbouring hydroxyl group. It was found that the lactam carbonyl group reduction can be avoided by using lithium triethoxyaluminum hydride instead of $LiAlH_4$. The mixture of epimeric lactam alcohols **7** was obtained in excellent yield and separated by column chromatography. The separation of epimers should be preferably performed at this stage of the synthesis because it is relatively easy (much easier than in the case of nitriles **2**) – a single careful chromatography allowed a complete separation of epimers. To assign the stereochemistry at C-20, a sample of pure epimer of lactam ester (20*R*)-**6c** was also reduced and the more polar epimer of lactam alcohol (20*R*)-**7** was obtained which in turn yielded the more polar amino alcohol (20*R*)-**8** on further reduction.



Scheme 3

Both epimeric lactam alcohols **7** were treated with tosyl chloride in pyridine under normal conditions. However, instead of tosylates the corresponding chlorides **5b** were obtained as the only products. It is likely that the substitution of the intermediate tosylate was very easy as a result of an anchimeric assistance of the lactam carbonyl group. The chlorides **5b** were subjected to the reaction with lithium isobutylcuprate [12], but no reaction was detected in either case. Apparently, the chloro group was not a sufficiently good leaving group for this reaction and therefore its replacement by iodide was attempted [13]. The reaction of **5b** with sodium iodide in refluxing methyl ethyl ketone was only partially successful. The 23-iodo compound (20*S*)-**5c** was obtained from chloride (20*S*)-**5b** in a moderate yield while 23-chloride (20*R*)-**5b** failed to afford the corresponding iodide (a very polar material was formed which was not investigated further). Much better results were achieved when lactam alcohols **7** were subjected to direct transformation into iodides **5c**. Among many methods tried the best yield was obtained with iodine – triphenyl phosphine in pyridine/benzene [14]. Independently on the method of the OH → I transformation, the yield of (20*R*)-23-iodide **5c** was considerably lower than in 20*S*

series (61%) and amounted to max. 42%. The pure 23-iodide (20*R*)-**5c** appeared to be rather unstable, and its reaction with lithium isobutylcuprate was not successful (only traces of **9** could be detected). The same reaction with the 20*S* epimer afforded the desired product **9** in about 30% (the remaining material was the starting iodide **5c**). Compound (20*S*)-**9** was only slightly less polar than iodide **5c** and the separation was difficult.

Although the described synthesis does not seem to be a practical method of construction of a cholesterol 2-isooctyl side chain, some of the compounds described here may appear to be good intermediates for future syntheses of 17-azacholesterol. Further studies are in progress.

Experimental

Melting points were determined on a Kofler apparatus of Boetius type and are uncorrected. NMR spectra were recorded with a Bruker AC 200 F spectrometer using $CDCl_3$ solutions with *TMS* as an internal standard. Infrared spectra were recorded on a specord 75 IR as CCl_4 or $CHCl_3$ solutions unless otherwise stated. Mass spectra were obtained at 70 eV with an AMD-604 spectrometer. The reaction products were isolated by column chromatography performed on silica gel 70–230 or 230–400 mesh ASTM (Merck). Thin-layer chromatograms were developed on aluminum TLC sheets precoated with silica gel F_{254} and visualized with 50% sulfuric acid after heating. All solvents were dried and freshly distilled prior to use.

3β-Hydroxy-17-azaandrost-5-en-16-one tert-butyldimethylsilyl ether (**1b**) *by dealkylation of nitrile* **2b**

A stirred solution of nitrile **2b** (10 mg; 0.02 mmol; epimeric material) in 1 ml of anhydrous ether was treated with a freshly prepared 2.7 *M* solution of isobutylmagnesium bromide in ether (1 ml) and stirring was continued (1.5 h) at room temperature. To the reaction mixture a solution of NH_4Cl was added and the product was extracted with chloroform. After evaporation of the solvent from the dried ($MgSO_4$) extract the crude product was purified by column chromatography (elution with benzene-ethyl acetate 8:2). Yield: 5 mg (59%), m.p. 287–289 °C (benzene-hexane). A similar reaction of **2b** with isobutyllithium also resulted in dealkylation to **1b**.

(20ξ)-3β-Hydroxy-23-amino-24-nor-17-azachol-5-en-16-one tert-butyldimethylsilyl ether (**4a**) *and its mono- and di-4-nitrobenzenesulfonyl derivatives* **4b** *and* **4c**

To a stirred suspension of $LiAlH_4$ (18 mg; 0.47 mmol) in 2 ml of anhydrous ether nitrile **2b** (50 mg; 0.11 mmol) was added at 0 °C and stirring was continued for 2.5 h. The reaction was quenched with a drop of water, dried ($MgSO_4$), and all inorganic material was filtered off. The crude product of this reaction was used in the next step. In one experiment, amine **4a** was purified by flash chromatography; IR ($CHCl_3$), $\nu = 3360, 1657, 1373, 1249, 1085, 830\ cm^{-1}$; ^1H NMR, $\delta = 5.32$ (m, 1H, 6-H), 3.76 (m, 0.5H, 20-H), 3.48 (m, 1H, 3α-H), 3.30 (m, 0.5H, 20-H), 2.67 (bs, 2H, $-NH_2$), 1.39 (d, $J = 6.8$ Hz, 1.5H, 21-H), 1.32 (d, $J = 7.0$ Hz, 1.5H, 21-H), 1.14 (s, 1.5H, 18-H), 1.10 (s, 1.5H, 18-H), 1.02 (s, 3H, 19-H), 0.89 (s, 9H, *t*-Bu–Si), 0.06 (s, 6H, Me–Si).

The crude amine **4a** was treated with 4-nitrobenzenesulfonyl chloride (43 mg; 0.19 mmol) in anhydrous pyridine (1 ml) and allowed to stand overnight. The reaction mixture was poured into an aqueous solution of NH_4Cl and extracted with chloroform. The dried ($MgSO_4$) extract was evaporated *in vacuo* and the residue was subjected to silica gel column chromatography. The pure 4-nitrobenzenesulfonamide **4b** (30 mg; 43% calcd. from starting nitrile **2b**) was eluted with benzene-ether 8:2; IR ($CHCl_3$), $\nu = 3150, 1652, 1524, 1345, 1161, 1082, 831\ cm^{-1}$; ^1H NMR, $\delta = 8.35$ (m, 2H, arom-H), 8.06

(m, 2H, arom-H), 6.25 (dd, $J_1 = 8.9$ Hz, $J_2 = 3.6$ Hz, 0.5H, NH), 5.74 (t, $J = 5.8$ Hz, 0.5H, NH), 5.31 (m, 1H, 6-H), [4.09 (m, 0.5H), 3.46 (m, 1.5H), 3.15 (m, 0.5H), 2.99 (m, 1H), 2.69 (m, 0.5H) – 3α-H, 20-H and 23-H], 1.34 (d, $J = 7.1$ Hz, 1.5H, 21-H), 1.30 (d, $J = 7.3$ Hz, 1.5H, 21-H), 1.18 (s, 1.5H, 18-H), 1.08 (s, 1.5H, 18-H), 1.01 (s, 1.5H, 19-H), 1.00 (s, 1.5H, 19-H), 0.893 and 0.886 (2 × s, 9H, *t*-Bu–Si), 0.066 and 0.057 (2 × s, 6H, Me–Si).

A solution of compound **4b** (30 mg; 0.05 mmol) in 1 ml of anhydrous *DMF* was treated with sodium hydride (6 mg of 60% dispersion in mineral oil; 0.15 mmol) and 4-nitrobenzenesulfonyl chloride (20 mg; 0.09 mmol). The reaction was allowed to stand overnight and worked up in the usual manner. Sulfonimide **4c** (13 mg; 39%) was obtained in a pure state by column chromatography (elution with benzene-ether 9:1); IR ($CHCl_3$), $\nu = 1660$, 1530, 1348, 1167, 839 cm^{-1}; ^1H NMR, $\delta = 8.44$ (m, 4H, arom-H), 8.31 (m, 4H, arom-H), 5.33 (m, 1H, 6-H), [3.4–4.0 (m, 3.5H), 3.12 (m, 0.5H) – 3α-H, 20-H and 23-H], 1.38 (d, $J = 6.8$ Hz, 1.5H, 21-H), 1.32 (d, $J = 7.0$ Hz, 1.5H, 21-H), 1.106 and 1.096 (2 × s, 3H, 18-H), 1.02 (s, 3H, 19-H), 0.89 (s, 9H, *t*-Bu–Si), 0.06 (s, 6H, Me–Si).

The reaction of compound **4c** (13 mg) with potassium iodide (200 mg) in *DMF* (1 ml) at 100 °C for 2 h failed to afford the desired product **5c**.

(20ξ)-3β-Acetoxy-23-benzamino-24-nor-17-azachol-5-en-16-one (**4d**) *and von Braun reaction*

The reduction of nitrile **2b** (50 mg) with $LiAlH_4$ was carried out as described above. The reaction was quenched with a drop of water, 1 ml (8.5 mmol) of benzoyl chloride was added and the mixture was allowed to stand overnight at room temperature. After diluting with chloroform, the mixture was dried ($MgSO_4$) and the inorganic material was filtered off. The solvent was then removed *in vacuo*, the residue was dissolved in 2 ml of *THF*, and a few drops of concentrated HCl were added. After 0.5 h the reaction mixture was poured into water, neutralized with K_2CO_3 solution and extracted with chloroform. The dried ($MgSO_4$) extract was filtered through a short silica gel column and evaporated. The residue was dissolved in anhydrous pyridine (3 ml) and acetic anhydride (2 ml), and the reaction mixture was allowed to stand for 16 h. The crude acetylation product was isolated in the usual manner and purified by flash chromatography (elution with benzene-ethyl acetate 1:1). Yield: 26 mg (48%); ^1H NMR, $\delta = 7.86$ (m, 2H, arom-H), 7.45 (m, 2.5H, arom-H and N–H), 6.83 (m, 0.5H, N–H), 5.37 (m, 1H, 6-H), 4.60 (m, 1H, 3α-H), [4.24 (m, 0.5H), 3.91 (m, 0.5H), 3.45 (m, 1.5H), 2.92 (m, 0.5H) – 20-H and 23-H], 2.04 (s, 3H, CH_3COO-), 1.42 (d, $J = 6.8$ Hz, 1.5H, 21-H), 1.36 (d, $J = 6.8$ Hz, 1.5H, 21-H), 1.24 (s, 1.5H, 18-H), 1.12 (s, 1.5H, 18-H), 1.05 (s, 1.5H, 19-H), 1.03 (s, 1.5H, 19-H).

Compound **4d** (20 mg; 0.04 mmol) was dissolved in 1 ml of anhydrous nitromethane, three drops of thionyl chloride were added, and the reaction mixture was refluxed for 1.5 h. Volatile material was then removed *in vacuo*, water was added, and the products were extracted with chloroform. The solvent was evaporated from the dried ($MgSO_4$) extract and the residue was chromatographed on a silica gel column. The pure chloride **5a** (4 mg; 22%) was eluted with benzene-ether 8:2; IR ($CHCl_3$), $\nu = 1717$, 1660, 1248, 1030 cm^{-1}; ^1H NMR, $\delta = 5.38$ (m, 1H, 6-H), 4.60 (m, 1H, 3α-H), 3.3–3.7 (m, 3H, 20-H and 23-H), 2.68 (m, 0.5H, 22-H?), 2.04 (s, 3H, CH_3COO–), 1.41 (d, $J = 6.8$ Hz, 1.5H, 21-H), 1.34 (d, $J = 6.8$ Hz, 1.5H, 21-H), 1.14 and 1.12 (2 × s, 3H, 18-H), 1.05 (s, 3H, 19-H); MS, $m/z = 421$ (M^+, 2%), 406 (M^+ – Me, 66%), 386 (M^+ – Cl, 42%), 361 (M^+–HOAc; 20%), 346 (M^+ – HOAc–Me; 97%), 326 (M^+ – HOAc–Cl; 100%).

(20R)- and (20S)-3β-Hydroxy-24-nor-17-azachol-5-en-16-on-23-oic acid methyl ester (**6b**) *and its tert-butyldimethylsilyl ether* **6c**

A solution of nitrile **2a** (80 mg; 0.23 mmol; 20*R* or 20*S* or the epimeric mixture) in 20 ml of *n*-butanol was refluxed with a solution of KOH (1 g) in 10 ml of water for 5 days. *n*-Butanol and water were evaporated to dryness and the resulting solid was triturated with pyridine (50 ml) and acetic anhydride (40 ml). The obtained suspension was stirred overnight at room temperature. The reaction mixture was poured into ice water (500 ml) and extracted with chloroform. The extract was dried ($MgSO_4$) and

evaporated, the residue was dissolved in methanol (20 ml) and an aqueous solution of potassium carbonate was added. After 10 min reflux the mixture was carefully poured into cold 1% hydrochloric acid and extracted with chloroform. The crude hydroxy acid obtained by evaporation of the solvent was treated with an etheral solution of diazomethane. Hydroxy ester **6b** was purified by column chromatography (elution with benzene-ether 4:6; yield: 51 mg);

(20*R*)-**6b**: IR($CHCl_3$), $\nu = 3616, 3425, 1730, 1668, 1143, 1050\,cm^{-1}$; ^1H NMR, $\delta = 5.34$ (m, 1H, 6-H), 3.66 (s, 3H, CH_3–OCO–), 3.71 and 3.52 (2 × m, 2 × 1H, 3α-H and 20-H), 3.11 (dd, $J_{gem} = 15.8$ Hz, $J_{vic} = 8.7$ Hz, 1H, 22-H), 2.75 (dd, $J_{gem} = 15.8$ Hz, $J_{vic} = 5.2$ Hz, 1H, 22-H), 1.37 (d, $J = 6.8$ Hz, 3H, 21-H), 1.06 (s, 3H, 18-H), 1.02 (s, 3H, 19-H); ^{13}C NMR, $\delta = 175.2$ (C), 172.6 (C), 141.1 (C), 120.5 (CH), 71.3 (CH), 63.3 (C), 51.9 (CH), 51.5 (CH_3), 49.9 (CH), 45.2 (CH), 42.0 (CH_2), 39.0 (CH_2), 36.9 (CH_2), 36.6 (C), 35.5 (CH_2), 33.5 (CH_2), 31.3 (CH_2), 30.9 (CH_2), 30.4 (CH), 21.1 (CH_2), 20.0 (CH_3), 19.1 (CH_3), 16.8 (CH_3).

(20*S*)-**6b**: IR (CCl_4), $\nu = 3606, 3430, 1732, 1681, 1255, 1092, 1007\,cm^{-1}$; ^1H NMR, $\delta = 5.35$ (m, 1H, 6-H), 3.66 (s, 3H, CH_3–OCO–), 3.45–3.80 (m, 2H, 3α-H and 20-H), 3.11 (dd, $J_{gem} = 15.5$ Hz, $J_{vic} = 7.8$ Hz, 1H, 22-H), 2.71 (dd, $J_{gem} = 15.5$ Hz, $J_{vic} = 6.5$ Hz, 1H, 22-H), 1.43 (d, $J = 6.8$ Hz, 3H, 21-H), 1.10 (s, 3H, 18-H), 1.03 (s, 3H, 19-H); MS, $m/z = 389$ (M^+, 8%), 374 (M^+–Me, 100%), 358 (M^+–MeO, 5%), 342 (M^+–MeOH–Me, 18%), 300 (28%).

Compound **6b** (51 mg; 0.13 mmol, epimeric mixture), imidazole (27 mg; 0.4 mmol) and *tert*-butyldimethylsilyl chloride (30 mg; 0.2 mmol) were dissolved in 2 ml of anhydrous *DMF* and allowed to stand 16 h. The reaction mixture was poured into 200 ml of water and extracted with chloroform. Flash chromatography of the crude product (elution with benzene-ether 8:2) afforded 60 mg (91%) of compound **6c**; IR(CCl_4). $\nu = 1735, 1683, 1091, 832\,cm^{-1}$; ^1H NMR, $\delta = 5.31$ (m, 1H, 6-H), 3.67 and 3.66 (2 × s, 3H, CH_3–OCO–), 3.71 and 3.48 (2 × m, 2 × 1H, 3α-H and 20-H), 3.12 and 2.75 (2 × m, 2 × 1H, 22-H), 1.43 (d, $J = 6.8$ Hz, 1.5H, 21-H), 1.37 (d, $J = 6.8$ Hz, 1.5H, 21-H), 1.10 (s, 1.5H, 18-H), 1.06 (s, 1.5H, 18-H), 1.02 (s, 3H, 19-H), 0.89 (s, 9H, *t*-Bu–Si), 0.06 (s, 6H, Me–Si).

Pure 20*R* epimer of **6c** was also obtained (m.p. 143–146 °C from petroleum ether).

(20ξ)-3β-Acetoxy-24-nor-17-azachol-5-en-16-on-23-oic acid methyl ester (**6d**) *from isocyanate* **3a**

Isocyanate **3a** (850 mg; 2.39 mmol) was refluxed in *n*-butanol (25 ml) with water (2 drops) and KOH (1 g) for 25 min. The reaction mixture was then neutralized with conc. HCl, 15 ml of the solvent was distilled off, crotononitrile (2 ml; 24 mmol) was added and reflux was continued overnight. Next day, *n*-butanol (10 ml), water (20 ml) and KOH (5 g) were added and the mixture was heated under reflux for 72 h. All volatile material was removed *in vacuo* and the resulting solid was triturated with 30 ml of pyridine and 20 ml of acetic anhydride. After 16 h of stirring the reaction mixture was poured into ice water, acidified with hydrochloric acid and extracted with $CHCl_3$. Chloroform was evaporated and the residue was treated with etheral diazomethane. The products were separated by silica gel column chromatography and the following compounds were consecutively eluted: N-acetyl lactam **1c** [2] (elution with benzene-ether 8:2; 80 mg), methyl ester **6d** (a mixture of 20*R* and 20*S* epimers in the ratio 85:15; elution with benzene-ether 6:4; 104 mg), and lactam **1a** [2] (elution with benzene-ethyl acetate 1:9; 248 mg).

(20R)- and (20S)-3β,23-Dihydroxy-24-nor-17-azachol-5-en-16-one 3-tert-butyl-dimethylsilyl ether (**7**)

To a stirred suspension of $LiAlH_4$ (300 mg; 7.9 mmol) in 10 ml of anhydrous ether ethyl acetate (1.16 ml; 11.8 mmol) was added dropwise at 0 °C. After 15 min a solution of ester **6c** (340 mg; 0.68 mmol; epimeric mixture) in 5 ml of ether was added and 30 min later the reaction was quenched with a drop of water. The reaction mixture was dried with $MgSO_4$ and all inorganic material was filtered off. The crude product was carefully chromatographed on a silica gel column. With benzene-ether 1:1, 20*S* (139 mg) and 20*R* (101 mg) epimers of lactam alcohol **7** were eluted consecutively.

(20*R*)-**7**: m.p. 179–182 °C (CH_2Cl_2-hexane); IR(CCl_4), $\nu = 3440$, 1664, 1250, 1101, 841 cm^{-1}; ^1H NMR, $\delta = 5.32$ (m, 1H, 6-H), [4.09 (m, 1H) and 3.4–3.7 (m, 3H) – 3α-H, 20-H and 23-H], 2.88 (bs, 1H, HO–), 1.37 (d, $J = 7.1$ Hz, 21-H), 1.20 (s, 3H, 18-H), 1.02 (s, 3H, 19-H), 0.89 (s, 9H, *t*-Bu–Si), 0.06 (s, 6H, Me–Si); ^{13}C NMR, $\delta = 176.1$ (C), 141.8 (C), 120.2 (CH), 72.3 (CH), 63.8 (C), 59.3 (CH_2), 52.6 (CH), 49.9 (CH), 44.5 (CH), 42.7 (CH_2), 38.5 (CH_2), 37.0 (CH_2), 36.7 (C), 36.5 (CH_2), 33.3 (CH_2), 31.9 (CH_2), 31.0 (CH_2), 30.5 (CH), 25.9 (3 × CH_3), 21.2 (CH_2), 19.6 (CH_3), 19.2 (CH_3), 18.2 (CH_3 and C), −4.6 (2 × CH_3).

(20*S*)-**7**: m.p. 207–211 °C (benzene-hexane), IR(CCl_4), $\nu = 3405$, 1671, 1248, 1085, 832 cm^{-1}; ^1H NMR, $\delta = 5.32$ (m, 1H, 6-H), [3.64 (m, 2H) and 3.50 (m, 2H) – 3α-H, 20-H and 23-H], 1.42 (d, $J = 6.9$ Hz, 3H, 21-H), 1.11 (s, 3H, 18-H), 1.02 (s, 3H, 19-H), 0.89 (s, 9H, *t*-Bu–Si), 0.06 (s, 6H, Me–Si); ^{13}C NMR, $\delta = 175.9$ (C), 141.7 (C), 120.2 (CH), 72.3 (CH), 63.7 (C), 59.5 (CH_2), 51.4 (CH), 49.9 (CH), 45.3 (CH), 42.6 (CH_2), 37.5 (CH_2), 37.0 (CH_2), 36.6 (C), 36.0 (CH_2), 33.8 (CH_2), 31.8 (CH_2), 31.0 (CH_2), 30.4 (CH), 25.8 (3 × CH_3), 21.2 (CH_2), 19.2 (CH_3), 18.6 (CH_3), 18.1 (C), 17.3 (CH_3), −4.7 (2 × CH_3); MS, $m/z = 475$ (M^+, 6%), 460 (M^+–Me, 43%), 430 (M^+–CH_2CH_2OH, 12%), 418 (M^+–*t*-Bu, 100%), 326 (41%).

(20R)- and (20S)-24-Nor-17-azachol-5-en-3β,23-diol 3-tert-butyldimethylsilyl ether (**8**)

To a solution of ester **6c** (357 mg; 0.71 mmol) in 10 ml of ether $LiAlH_4$ (110 mg; 2.9 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched with water, dried ($MgSO_4$), and all inorganic material was filtered off. The solvent was removed *in vacuo* and the products were separated by column chromatography. With benzene-ether 1:1, lactam alcohol **7** was eluted (39 mg). Elution with chloroform-methanol 8:2 afforded consecutively amino alcohol (20*S*)-**8** (31 mg), a mixture of both epimers **8** (147 mg), and amino alcohol (20*R*)-**8** (32 mg).

(20*R*)-**8**: m.p. 141–144 °C (methanol), IR(CCl_4), $\nu = 3370$, 1249, 1085, 835 cm^{-1}; ^1H NMR, $\delta = 5.30$ (m, 1H, 6-H), [3.97 (m, 1H), 3.72 (m, 2H), 3.47 (m, 1H), 3.20 (m, 1H), 2.71 (m, 1H) – 3α-H, 16-H, 20-H, 23-H], 1.40 (d, $J = 6.6$ Hz, 3H, 21-H), 0.99 (s, 3H, 19-H), 0.98 (s, 3H, 18-H), 0.89 (s, 9H, *t*-Bu–Si), 0.06 (s, 6H, Me–Si); ^{13}C NMR, $\delta = 141.6$ (C), 120.7 (CH), 72.5 (CH), 62.7 (C), 60.7 (CH_2), 56.3 (CH), 55.2 (CH), 50.6 (CH_2), 49.7 (CH), 42.8 (CH_2), 39.4 (CH_2), 37.4 (CH_2), 36.5 (C), 34.7 (CH_2), 32.5 (CH), 32.0 (CH_2), 31.4 (CH_2), 25.9 (3 × CH_3), 24.2 (CH_2), 21.8 (CH_2), 19.4 (CH_3), 19.0 (CH_3), 18.3 (C), 11.1 (CH_3), −4.6 (2 × CH_3); MS, $m/z = 461$ (2%, M^+), 446 (M^+–Me; 100%), 416 (M^+–CH_2CH_2OH; 74%), 400 (17%).

(20*S*)-**8**: IR(CCl_4), $\nu = 3400$, 1242, 1078, 831 cm^{-1}; ^1H NMR, $\delta = 5.31$ (m, 1H, 6-H), [3.77 (m, 2H), 3.48 (m, 1H), 3.27 (m, 1H), 3.04 (m, 1H), 2.86 (m, 1H) – 3α-H, 16-H, 20-H, 23-H], 1.11 (d, $J = 6.5$ Hz, 3H, 21-H), 1.00 (s, 3H, 19-H), 0.89 (s, 9H, *t*-Bu–Si), 0.83 (s, 3H, 18-H), 0.06 (s, 6H, Me–Si); MS, $m/z = 461$ (M^+, 2%), 446 (M^+–Me; 100%), 416 (M^+–CH_2CH_2OH, 48%), 400 (27%).

(20R)- and (20S)-3β-Hydroxy-23-iodo-24-nor-17-azachol-5-en-16-one tert-butyl-dimethysilyl ether (**5c**)

To a solution of iodine (40 mg; 0.16 mmol) in 4 ml of benzene triphenylphosphine (40 mg; 0.16 mmol), pyridine (0.15 ml) and, 15 min later, (20*S*)-alcohol **7** (24 mg; 0.05 mmol) were added. The reaction mixture was stirred at room temperature for 2 h, volatile material was removed *in vacuo*, and the residue was chromatographed on a silica gel column. Pure (20*S*)-iodide **5c** (18 mg; 61%) was eluted with benzene-ethyl acetate 95:5. The analogous reaction of (20*R*)-alcohol **7** afforded (20*R*)-iodide **5c** in 42% yield.

(20*R*)-**5c**: IR($CHCl_3$), $\nu = 1668$, 1146, 1101, 842 cm^{-1}; ^1H NMR, $\delta = 5.32$ (m, 1H, 6-H), [3.35–3.65 (m, 3H), 3.21 (m, 1H) – 3α-H, 20-H and 23-H], 1.34 (d, $J = 6.8$ Hz, 3H, 21-H), 1.14 (s, 3H, 18-H), 1.02 (s, 3H, 19-H), 0.89 (s, 9H, *t*-Bu–Si), 0.06 (s, 6H, Me–Si).

(20*S*)-**5c**: m.p. 203–206 °C (benzene-hexane), IR($CHCl_3$), $\nu = 1665$, 1145, 1070, 839 cm^{-1}; ^1H NMR, $\delta = 5.32$ (m, 1H, 6-H), 3.48 (m, 1H, 3α-H), 3.05–3.35 (m, 3H, 20-H and 23-H), 2.65 (m, 1H, 22-H?), 1.39 (d, $J = 6.7$ Hz, 3H, 21-H), 1.12 (s, 3H, 18-H), 1.03 (s, 3H, 19-H), 0.89 (s, 9H, *t*-Bu–Si), 0.06 (s, 6H, Me–Si).

(20ξ)-3β-Hydroxy-23-chloro-24-nor-17-azachol-5-en-16-one tert-butyldimethylsilyl ether (**5b**) *and its transformation into iodide* **5c**

A solution of compound **7** (105 mg; 0.22 mmol; epimeric material) in 8 ml of anhydrous pyridine was treated with *p*-toluenesulfonyl chloride (344 mg; 1.8 mmol) and allowed to stand for 16 h. The extract was washed with water, dried ($MgSO_4$), and evaporated. The crude product was purified by column chromatography; 60 mg (55%) of chloride **5b** was eluted with benzene-ethyl acetate 9:1; ^{1}H NMR $\delta = 5.32$ (m, 1H, 6-H), 3.3–3.7 (m, 4H, 3α-H, 20-H and 23-H), 2.66 and 2.38 (2 × m, 2 × 0.5H, 22-H?), 1.41 (d, $J = 6.8$ Hz, 1.5H, 21-H), 1.34 (d, $J = 6.7$ Hz, 1.5 Hz, 21-H), 1.14 and 1.12 (2 × s, 3H, 18-H), 1.03 (s, 3H, 19-H), 0.89 (s, 9H, *t*-Bu–Si), 0.06 (s, 6H, Me–Si).

A solution of chloride **5b** (25 mg; epimeric material) in 8 ml of methyl ethyl ketone was refluxed for 16 h with sodium iodide (2 g). Benzene (10 ml) was added, a precipitate was filtered off and the solvent was removed *in vacuo*. The residue was purified by column chromatography. With benzene-ethyl acetate 19:1, iodide **5c** (20*S* epimer only) was eluted (11 mg).

(20S)-3β-Hydroxy-17-azacholest-5-en-16-one tert-butyldimethylsilyl ether (**9**)

To a suspension of Cu_2I_2 (412 mg; 1.08 mmol) in 4 ml of anhydrous ether 2.4 ml of 2 *M* solution of *iso*-butyllithium in ether was added dropwise under nitrogen at −30 °C. The reaction turned black and, after 10 min, a solution of (20*S*)-iodide **5c** (18 mg; 0.03 mmol) in ether was added. The reaction mixture was stirred at −30 °C to −10 °C for 2 h, quenched with water, dried ($MgSO_4$), and the solvent was removed *in vacuo*. Column chromatography of the residue afforded compound **9** (4 mg; 25%) eluted with benzene-ethyl acetate 97:3.

(20*S*)-**9**: m.p. 108–110 °C (hexane), IR($CHCl_3$), $\nu = 1667$, 1100, 843 cm^{-1}; ^{1}H NMR, δ 5.32 (m, 1H, 6-H), 3.48 (m, 1H, 3α-H), 3.13 (m, 1H, 20-H), 1.37 (d, $J = 6.8$ Hz, 3H, 21-H), 1.09 (s, 3H, 18-H), 1.02 (s, 3H, 19-H), 0.89 (s, 9H, *t*-Bu–Si), 0.86 (d, $J = 6.6$ Hz, 6H, 26-H and 27-H), 0.06 (s, 6H, Me–Si); ^{13}C NMR, $\delta = 175.3$ (C), 141.8 (C), 120.3 (CH), 72.4 (CH), 62.8 (C), 51.5 (CH), 50.0 (CH), 49.3 (CH), 42.7 (CH_2), 38.7 (CH_2), 37.1 (CH_2), 36.7 (C), 36.0 (CH_2), 33.8 (CH_2), 31.9 (CH_2), 31.1 (CH_2), 30.5 (CH), 29.7 (CH_2), 27.9 (CH), 25.9 (3 × CH_3), 25.3 (CH_2), 22.7 (CH_3), 22.6 (CH_3), 21.3 (CH_2), 19.3 (CH_3), 18.7 (CH_3), 18.2 (C), 17.3 (CH_3), −4.6 (2 × CH_3); MS, $m/z = 515$ (M^+, 4%), 500 (M^+–Me, 25%), 458 ($M^+ - t$-Bu, 100%), 430 (M^+–C_6H_{13}, 61%), 402 (M^+–C_8H_{17}, 25%).

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