Total Synthesis and Olfactory Evaluation of 5β,10-Dimethyl-*des*-A-18-*nor*-androstan-13β-ol: A Potential Human Pheromone?

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5β,10-Dimethyl-*des*-A-18-*nor*-androstan-13β-ol (Limdrostanol, **11**) was suspected to be the underlying parent steroid responsible for the interesting *urinous-animalic, woody* olfactory properties of the commercial odorant Timberol® (**6**–**9**), and the captives Norlimbanol® (**7**) and Limbanol® (**10**), and so could constitute a potential human pheromone. We report the first synthesis of **11**, starting with treatment of the bis-Grignard reagent of 1,4-dibromobutane (**15**) with γ-butyrolactone (**16**), Appel–Lee bromination of the resulting diol **17** with elimination of the tertiary hydroxy group, and transformation of the obtained bromo alkene **18** into the corresponding triphenylphosphonium salt **13**. This was subjected to a Schlosser–Wittig reaction with the γ,δ-unsaturated aldehyde **14**, prepared in turn by Grignard treatment of ethyl methacrylate (**19**) and subsequent Saucy–Marbet reaction of the resulting dimethyl carbinol **20** with ethyl vinyl ether (**21**). Cascade cyclization of the Schlosser–Wittig product **23** with methanesulfonic acid in dichloromethane at 0 °C afforded the tricyclic alkene **24**, which was transformed into the target structure **11** by epoxidation with 3-chloroperbenzoic acid and subsequent reduction with lithium triethylborohydride. In addition to **11**, the corresponding 14α-isomer **26** was obtained, and the olfactory properties of both are discussed. The high odor thresholds of **11** and **26**, as well as the distinct differences in odor with **6**–**10**, make it very unlikely that these *des*-A-18-*nor*-androstanols are the underlying odorous principle of **6**–**10**, or that they function as human pheromones. An alternative synthesis of **11** by cyclization of **23** at 0 °C with 0.8 equivalents of methanesulfonic acid in formic acid as terminating nucleophile is also discussed, but gave only unsatisfactory yields.

Introduction

Target and Retrosynthesis

Sex has turned out to be quite a successful strategy for evolution, even though, biochemically, cell division is less troublesome and more efficient than union. The necessary differentiation into male and female individuals is far from simple, as the underlying genetic information is too complex to be coded only in the sex-determining chromosomes. Hormones (Greek: ορμαν, to trigger) are therefore essential to switch on certain genes, not only in sexual differentiation but also in the regulation of reproductive cycles. Obviously, sex becomes more successful if information concerning presence and fertility is transferred between the sexes. The messenger substances that take on this role are called pheromones (Greek: φερειν, to transfer),[2] and are often chemically closely related to hormones. Probably the most prominent example of a pheromone in mammals is 5α-androst-16-en-3-one (**1**), which is secreted in the saliva of the boar and elicits the characteristic immobilization response (*lordosis*) of the estrous sow to the advance of her mate.[3] 5α-Androst-16-en-3-one (**1**), which emanates a *pronounced, persistent, and very intense urinous-animalic odor*,[4] has also been identified, together with the corresponding alcohols **2** and **3**, in human axillary sweat.[5] While the androsten-3α-ol **2** emanates a *strong, pleasant, and typical sandalwood odor*, its 3β-isomer **3** is weaker and possesses a more *animalic-urinous sandalwood note* (Figure 1).

The pleasant odor of **2** and the occurrence of **1**−**3** in human sweat and urine had resulted in speculations about the likelihood of them being human pheromones.[5] The first observation of the existence of human pheromones was the so-called McClintock effect. Martha McClintock[6a] noticed during her studies at Wellesley college in Massachusetts that the menstrual cycles of female room-mates living together became synchronized. This menstrual synchrony, the convergence of the onset date of the menstrual flow, has been experimentally replicated a number of times,[6b] and was recently shown to be at least partly mediated by the smell of 5α-androst-16-en-3α-ol (**2**).[7] The frequency of the pulsatile secretion of lutheinizing hormone (LH) in the follicular phase is significantly decreased by exposing women to **2**.[7] While one can debate about the biological use of this, it demonstrates the existence of substances with a pheromone effect on humans.

There may be more than one human pheromone. After a study by Jacob and McClintock[8a] on mood effects of ster-

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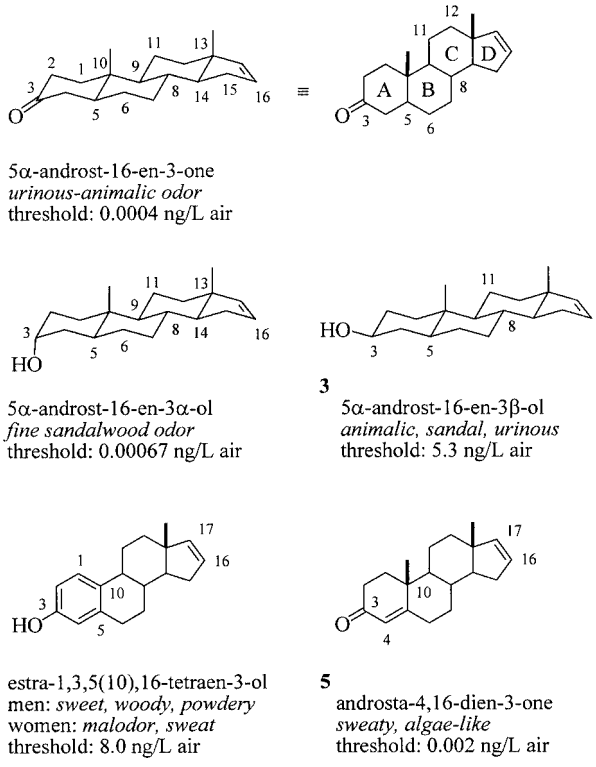


Figure 1. Steroids **1**−**5** with putative pheromone function in humans

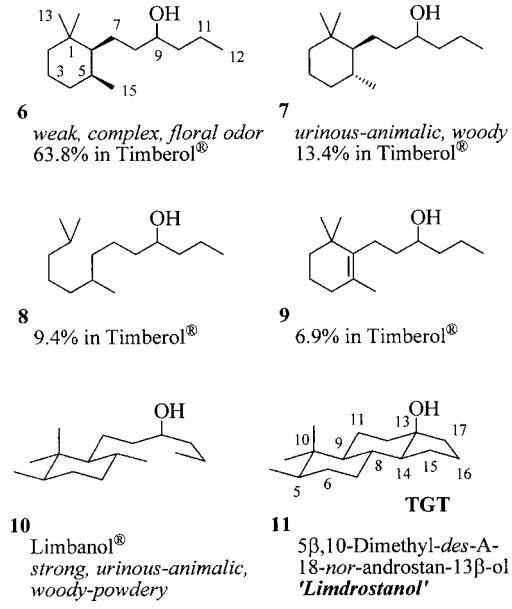


Figure 2. Timberol® components **6**−**9**, Limbanol® (**10**), and the *des*-A-18-*nor*-androstanol target molecule **11**, our so-called Limdrostanol, which was proposed to be the scaffold of **7** and **10**

oids on men and women, research is currently focusing on estra-1,3,5(10),16-tetraen-3-ol (**4**) as the prime putative pheromone of females and androsta-4,16-dien-3-one (**5**) as the prime putative pheromone of males.[8b] In our own experiments, we have indeed found that men described **4** as *sweet, woody, and powdery*, while women described it as a *malodorous note of sweaty, obnoxious character*. The odor threshold that we determined was not dependent on sex, however, and at 8.0 ng/L air was quite high. Androsta-4,16-dien-3-one (**5**) was described as *sweaty, algae-like* by both male and female subjects, and we determined an odor threshold of 0.002 ng/L air for both sexes. Lundström et al.[9] recently reported an absolute detection threshold of 211 μM in propylene glycol for **5**, but could not determine a threshold for **4**. Although **4** and **5** are already used in perfumes claimed to attract the opposite sex, such as "Realm" and "Realm Men" (Erox Corp., 1993),[10] sound evidence for such an effect is still lacking. Recently, Turner et al.[11] discovered in 5α-androst-16-en-7-one a new androstenone analogue that was reported also to smell *sandalwood-like*, as **3**, but much more weakly.

Astonishingly, Ohloff et al.[12] reported a *urinous-animalic note* reminiscent of the odor of steroids such as 5α-androst-16-en-3-one (**1**) to be present in the prominent perfumery raw material Timberol® (**6**−**9**, Figure 2). Timberol® (**6**−**9**) was discovered in 1979 by Klein and Rojahn of Dragoco (now Symrise),[13] and soon became a popular perfumery ingredient, especially in masculine fine fragrances. It can, for instance, be found at 1.5% in the woody chypre "Fahrenheit" (Dior, 1988) created by Jean-Louis Sieuzac, or at 1.7% in the woody fougère "Minotaure" (P. Picasso, 1992), although probably the most typical use was in "Basala" (Shiseido, 1993), which Dominique Preyssas built around a 5.7% content of Timberol® (**6**−**9**).

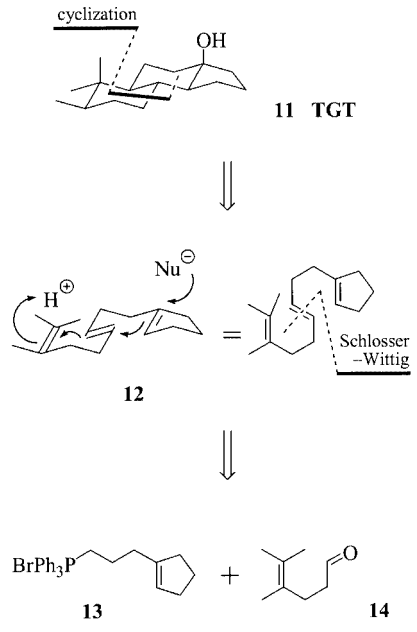
When Schulte-Elte and co-workers[14] at Firmenich investigated the commercial product, they discovered that the main *cis*-configured component **6** (63.8%) possesses only a *weak, rather complex odor of mainly floral tonality,* quite different from the overall *woody, animalic odor profile* of the mixture. This *woody, animalic* note was found to be mainly due to the *trans* isomer **7**, at 13.4% rather a minor constituent. In pure form, **7** also emanates quite strong urinous facets that to Schulte-Elte et al. recalled the odor of steroids. The other by-products of the industrial Timberol® synthesis, such as the open-chain alcohol **8** or 10-ethyl-7,8-dihydro-β-ionol (**9**), do not contribute much to the overall odor of the commercial material.

The interesting *steroid-type, urinous-animalic, woody characteristics* prompted the Firmenich researchers to develop an industrial synthesis[14] of the *trans* isomer **7**, which has been in captive use under the name of Norlimbanol® since the mid 1980s. The prefix "*nor*" in the name Norlimbanol® (**7**) refers to the finding that the irone analogue **10** had an even more *pronounced urinous-animalic odor of woody-powdery tonality.*[15] Compound **10** was thus considered by Ohloff et al.[12] to be the parent structure of this steroid-type woody odorant family, and was given the tradename of Limbanol® (**10**). Limbanol® (**10**) is also manufactured on an industrial scale and has been used as a captive in perfumery,[15] though to a lesser extent than Norlimbanol® (**7**). This, however, is only due to its more complex synthesis, and a correspondingly higher price.

The *superior steroid-type olfactory properties* of Limbanol® (**10**) were interpreted by Ohloff et al.[12] as originat-

ing from a steroid-type folding, which should be the result of an *all-equatorial* configuration of the substituents at C-3, C-5, and C-6 (ionone numbering, see Figure 2). In this conformation, depicted in Figure 2, the cyclohexyl ring corresponds to an androstane B ring with the additional 3-methyl substituents of **10** indicating an A ring fusion, while rings C and D should be formed by an appropriate folding of the hydroxyhexyl side chain, despite all the steric hindrance this would imply. Accordingly, 5β,10-dimethyl-*des*-A-18-*nor*-androstan-13β-ol (**11**) was proposed by Ohloff et al.[12] as the parent steroid responsible for the interesting olfactory properties of **7** and **10**, and likewise also of the commercial product Timberol® (**6**−**9**). However, this "Limdrostanol" (**11**), as we are going to call it below, was never synthesized, even though, if the chain of reasoning were correct, we might expect **11** to possess not only a *potent, highly interesting odor*, but *possibly also some pheromone-like impact*. To examine Ohloff et al.'s[12] speculations in greater detail we tackled the synthesis of Limdrostanol (**11**).

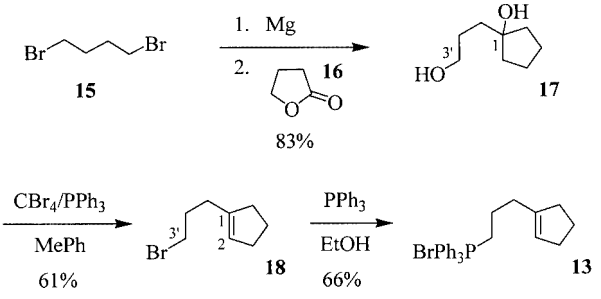
On reflection, "Limdrostanol" (**11**) appears to be quite a challenging target. As C-8 (steroid numbering, see Figure 2) is not quaternary-substituted, a topological retrosynthetic strategy through cationic cyclization initially appeared unfavorable to us, but this still seemed to be the shortest route and we decided to give it a try. Strategic disconnection of the fused ring system gives the triene **12**, which could undergo cationic cyclization with trapping of the positive charge by a nucleophile at the desired position C-13 (steroid numbering; see Figure 2). Schlosser−Wittig disconnection of the central *E*-configured double bond of **12** then reveals (3′-cyclopent-1-enylpropyl)triphenylphosphonium bromide (**13**) and 4,5-dimethylhex-4-enal (**14**) as the two building blocks for this convergent approach (Scheme 1).



Scheme 1. Retrosynthetic analysis of the target compound **11**

Results and Discussion

In the synthesis of the Wittig salt **13** (Scheme 2), we followed an efficient strategy that Schore and Knudsen[16] had applied in a synthesis of fused triquinanes by direct addition of α,ω-bis-Grignard reagents to lactones.[17] Thus, treatment of 1,4-dibromobutane (**15**) with an excess of magnesium in THF, followed by slow addition of a γ-butyrolactone (**16**) solution in THF at reflux provided 1-(3′-hydroxypropyl)cyclopentanol (**17**) in 83% yield after purification by flash chromatography (FC). Schore and Knudsen[16] also wanted to halogenate the primary hydroxy group of the diol **17** with concomitant elimination of the tertiary hydroxy group, but upon subjection of **17** to Appel−Lee chlorination[18] conditions with triphenylphosphane at reflux in carbon tetrachloride, the desired chloro alkene was obtained under the best conditions only in 36% yield,[16] while 1-oxaspiro[4.4]nonane was isolated in 39% yield as the major product of this reaction. We found, however, that the Appel−Lee bromination[19] of the diol **17** went smoothly and with selective elimination of the tertiary hydroxy group on treatment of **17** with two equivalents of triphenylphosphane and carbon tetrabromide in toluene at 60 °C, and the primary bromo alkene **18** was obtained in 61% yield after purification by flash chromatography on neutral aluminum oxide. An alternative synthesis of **18** starting from 1-allylcyclopentene had been reported by Brown and Salunkhe,[20] but without experimental details.

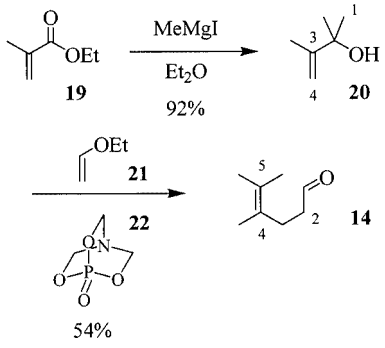


Scheme 2. Synthesis of the 3′-cyclopent-1-enylpropyl Wittig salt **13** from 1,4-dibromomethane (**15**) and γ-butyrolactone (**16**)

The transformation of **18** into the corresponding phosphonium salt **13** was less straightforward, and standard reaction conditions with triphenylphosphane at reflux in toluene or xylene afforded **13** in a maximum 20% yield. When the reaction was carried out in acetonitrile or nitromethane no phosphonium salt **13** was formed at all, but use of 2-propanol[21] as solvent began to improve the yields. The best results were obtained at reflux in ethanol, and after two days of heating of **18** with triphenylphosphane in ethanol, the Wittig salt **13** was isolated in 66% yield after recrystallization from toluene.

The synthesis of the second building block, the γ,δ-unsaturated aldehyde **14**, was achieved in two steps by making use of a Saucy−Marbet reaction (Scheme 3).[22] A standard Grignard reaction between ethyl methacrylate (**19**) and methylmagnesium iodide furnished the starting material **20** (92% yield) for this Claisen-type rearrangement. While in-

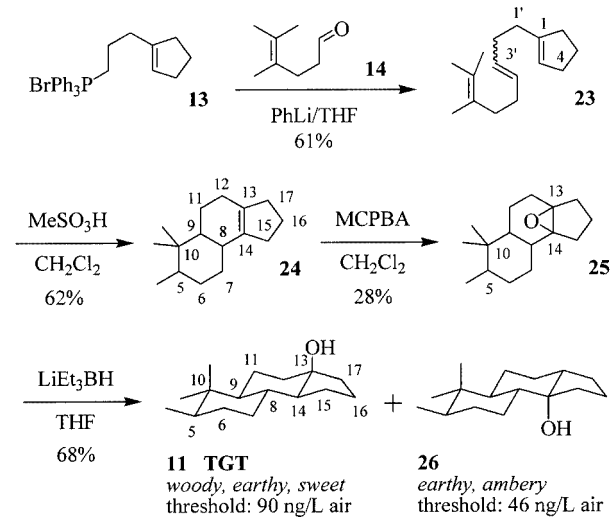
itial Saucy–Marbet reaction conditions[22] with the dimethyl carbinol **20** and ethyl vinyl ether (**21**) in the presence of phosphoric acid as catalyst resulted in yields around or below 20% (GC/MS), heating of **20** in ethyl vinyl ether (**21**) in an autoclave at 160 °C/17 bar in the presence of catalytic amounts of 2,6,7-trioxa-4-aza-1-phosphabicyclo[2.2.2]-octane 1-oxide (**22**),[23] provided our second building block **14** in 54% yield after chromatographic purification.



Scheme 3. Synthesis of 4,5-dimethylhex-4-enal (**14**) by Saucy–Marbet reaction

Next on the agenda was the central Wittig reaction between the phosphonium salt **13** and the γ,δ-unsaturated aldehyde **14**, in which a high *E* selectivity was hoped for (Scheme 4). Initial Wittig reactions between **13** and **14** under Fitjer–Quabeck conditions[24] with the use of potassium *tert*-butoxide as a base at reflux in tetrahydrofuran afforded, as suspected, exclusively *Z*-configured **23**, but in disappointingly moderate yields of only around 30%. The Schlosser modification[21,25] of the Wittig reaction should, however, permit the construction of *E*-disposed olefins from aldehydes and non-stabilized phosphorus ylides. By the general method of Bestmann et al.,[21] **13** was then transformed into its ylide by treatment with one equivalent of phenyllithium in THF, and then treated with **14** at −80 °C. Deprotonation of the obtained lithio betaine species with an additional equivalent of phenyllithium furnished, after quenching with methanol, 1-(7′,8′-dimethylnona-3′,7′-dienyl)cyclopent-1-ene (**23**), with an *E*/*Z* ratio of 8:2, in 61% yield.

The two building blocks **13** and **14** having been successfully stitched together, our effort was now directed towards the cascade cyclization of the triene **23** to provide the final ring system of our target molecule **11**, the most critical step of our synthetic plan (Scheme 1). First experiments were carried out in formic acid.[26] At room temperature, no conversion was discernible, but treatment of **23** with formic acid at 100 °C and hydrolysis with aqueous potassium hydroxide provided a complex mixture that could not be separated or further characterized, except that it also contained a secondary alcohol. Next, the triene **23** was treated with trifluoroacetic acid in dichloromethane at 0 °C,[27] but again a complex product mixture was obtained. This could not be characterized adequately to allow the identification of its components either after chromatographic fractionation



Scheme 4. Wittig–Schlosser olefination of **14**, acid-catalyzed cyclization of the resulting triene **23**, epoxidation, and subsequent reduction of **25** to the target structure **11**

or hydrolysis, but the target structure **11** was evidently not present in the fractionated mixtures.

Searching for more drastic conditions, we then applied fluorosulfonic acid in nitropropane according to a procedure used by Snowden et al.[28] for the synthesis of (±)-Ambrox from linear trienols or monocyclic dienols. Treatment of **23** with fluorosulfonic acid in 2-nitropropane at −90 °C afforded two new products with very similar chromatographic retentions and mass spectra resembling those of the starting material **23**. By repeated chromatography, one of these was enriched and tentatively assigned the structure of the tricycle **24** (Scheme 4), so apparently the fluorosulfonate group had eliminated under the reaction conditions with the formation of **24** and an isomeric compound. Although **24** was unintended, all that remained to convert it to the target structure **11** was the introduction of a hydroxy function at C-13.

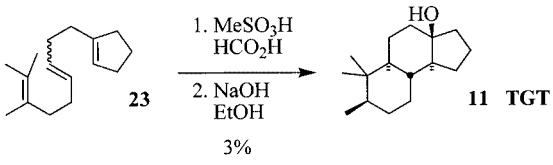
We decided to optimize this step, and found that treatment of **23** with an excess of methanesulfonic acid in dichloromethane at 0 °C increased the yield to 62%. Epoxidation of **24** with 3-chloroperbenzoic acid in dichloromethane at 0 °C then furnished, after workup and purification by flash chromatography, the corresponding epoxide **25**, albeit in a moderate yield of only 28%. Since all attempts to achieve reductive opening of **25** with lithium aluminum hydride were in vain, even at reflux in tetrahydrofuran or dioxane, we employed lithium triethylborohydride (Super-Hydride®) as the most powerful hydride nucleophile available to us. Treatment of the epoxide **25** with three equivalents of Super-Hydride® in tetrahydrofuran at reflux finally provided our molecular target Limdrostanol (**11**), accompanied by its regioisomer **26**. Despite similar chromatographic retentions, we were able to separate the two isomers by flash chromatography, and isolated **11** and **26** in 30% and 38% yields, respectively.

The structures and relative configurations of **11** and **26** were assigned by 2D NMR spectroscopy, including the use

of INADEQUATE experiments to establish all C−C connectivities. In the NOESY spectrum of **11**, a cross-peak between 10-Me_{ax} and 5-Me substantiated the β-*equatorial* orientation of the latter methyl group, while cross-peaks between 10-Me_{ax} and 6-H, as well as between 10-Me_{ax} and 8-H and between 8-H and 13-OH, established the β-*axial* configurations of all these substituents. Cross-peaks between 9-H_{ax} and 5-, 12- and 14-H then unambiguously established the α-axial configurations of these hydrogen atoms, since the *trans*fusion of rings B and C was apparent from a 1D slice extracted from the HSQC spectrum at δ = 36.2 ppm, which displayed a quadruplet with an *all-axial* coupling constant of 12.0 Hz for 8-H at δ = 1.38 ppm, thus determining the relative configurations of all stereocenters in 5β,10-dimethyl-*des*-A-18-*nor*-androstan-13β-ol (**11**).

The relative stereochemistry of the 14α-isomer **26** was determined similarly, with cross-peaks between 14-OH_{ax} and 9-H_{ax}, between 14-OH_{ax} and 7-H_{ax}, and between 14-OH_{ax} and 12-H_{ax} on the α-face, and cross-peaks between 10-Me_{ax} and 6-, 8- and 11-H in β-*axial* orientations. The β-*equatorial* configuration of 5-Me was again derived from a cross peak with 10-Me_{ax}. The high stereoselectivity, with *all-trans*-fusions of ring B, C and D in both **11** and **26**, reflects a concerted course of the cyclization of **25** to **26** according to the Stork−Eschenmoser hypothesis.[29]

Although we had reached our synthetic goal, we still wondered if the yield of **11** might be improved if formic acid were present as a terminating nucleophile in the cyclization reaction of **23** with methanesulfonic acid (Scheme 5). Subsequent alkaline hydrolysis of the crude products might then open up a direct route to our target molecule **11**, circumventing the formation of **26**. Thus, **23** was treated with 0.8 equivalents of methanesulfonic acid in formic acid at 0 °C, but Limdrostanol (**11**) was isolated by flash chromatography in a disappointingly low yield of only 3% after hydrolysis of the resulting product mixture with ethanolic sodium hydroxide. The circuitous route via the epoxide **25** was still superior to the direct conversion of **23** into the target molecule **11**, and in addition the olfactory evaluation of the 14α-isomer **26** in comparison with **11** was highly interesting.



Scheme 5. Direct synthesis of the target compound **11** from the triene **23**

Olfactory Evaluation and Conclusions

With both 5β,10-dimethyl-*des*-A-18-*nor*-androstan-13β-ol (Limdrostanol, **11**) and its 14α-isomer **26** to hand, we return to our initial starting point, of whether or not **11** is the odorous principle behind Limbanol® (**10**), Norlimbanol® (**7**), and Timberol® (**6**−**9**), and how likely it is that it constitutes a human pheromone. Neither Limdrostanol (**11**) nor its 14α-isomer **26** were reminiscent of Limbanol® (**10**), Norlimbanol® (**7**), or Timberol® (**6**−**9**), nor did they possess any typical *urinous-animalic woody odor*. 5β,10-Dimethyl-*des*-A-18-*nor*-androstan-13β-ol (**11**) was certainly *woody in smell, but in an earthy direction, reminding one of patchouli oil rather than of steroids*, and in addition it had some *sweet, almost chocolate-type character. Earthy aspects* were also present in the 14α-isomer **26**, which also emanated a *pleasant ambery note*. With an odor threshold of 46 ng/L air, **26** was somewhat more intense than the target compound **11**, for which we measured a threshold of 90 ng/L air. Both **11** and **26** are far weaker than Limbanol® (**10**), Norlimbanol® (**7**), or Timberol® (**6**−**9**), and they are even farther away from the thresholds of the putative human pheromones delineated in Figure 1. Neither the odor character nor the thresholds of **11** and **26** are gender-specific, and this altogether makes it highly improbable that they could function as human pheromones. Since both **11** and **26** differ distinctly from **6**−**10** in their odor profiles and are of weaker intensity, they do not even constitute appropriate templates for the design of new woody odorants.

So the dream of the fictitious fragrance chemist Henri Biotte in a short story by Roald Dahl has not come true: "What I intend to do," he said, "is to produce a perfume which will have the same electrifying effect upon a man as the scent of a bitch in heat has upon a dog! One whiff and that'll be it!"[30] Considering the consequences Henri Biotte suffers in this story, we should perhaps thank our lucky stars that **11** was not an active human pheromone.

Experimental Section

IR: Perkin−Elmer Spectrum One, Bruker VECTOR 22/Harrick SplitPea micro ATR, Si. NMR: Bruker ARX 300, Bruker AVANCE DPX 400, TMS int. (δ = 0 ppm). MS: Finnigan TSQ 700 (ESI), Finnigan SSQ 700 (CI: NH_3), Finnigan MAT 95 (EI: 70 eV), HP Chemstation 6890 GC/5973 Mass Sensitive Detector. FC: Merck Kieselgel 60 (40−63 μm). TLC: Merck Kieselgel 60 F_{254} (5 cm × 7.5 cm on aluminum); visualization reagent: PMA spray soln. for TLC, Merck 1.00480.0100. Melting points: Mettler FP5 melting point apparatus. Elemental analyses: Mikroanalytisches Laboratorium Ilse Beetz, 96301 Kronach, Germany. Unless otherwise stated, all reactions were performed under N_2 with reagents and solvents (puriss. or purum) from Fluka, used without further purification. The odor thresholds were determined by GC−olfactometry: Different dilutions of the sample substance are injected into a gas chromatograph in descending order of concentration until the panelist fails to detect the respective substance at the sniffing port. The panelist smells in blind and presses a button on perceiving an odor. If the recorded time matches the retention time, the sample is further diluted. The last concentration detected at the correct retention time is the individual odor threshold. The reported threshold values are the geometrical means of the individual odor thresholds of the different panelists.

1-(3′-Hydroxypropyl)cyclopentanol (17): A solution of 1,4-dibromobutane (**15**, 216 g, 1.00 mol) in dry THF (500 mL) was added dropwise over 3.5 h to magnesium turnings (72.9 g, 3.00 mol), the reaction being initiated by occasional heating with a heat gun. The

reaction mixture was stirred at reflux for an additional 3 h, and a solution of γ-butyrolactone (**16**, 94.6 g, 1.10 mol) in dry THF (1.3 L) was then added dropwise with stirring at reflux temp. over a period of 12 h. The reaction mixture was then cooled to room temp., and subsequently quenched with satd. aq. NH_4Cl solution (700 mL). The aqueous layer was extracted with Et_2O (3 × 600 mL), and the combined organic extracts were washed with brine (300 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel FC (Et_2O/MeOH, 98:2; R_f = 0.23) to afford the title compound **17** (120 g, 83%) as a slightly yellow oil. IR (film): $\tilde{\nu}$ = 3333 (s, ν O−H), 1058/981 (m, ν C−O), 1449 (m, δ C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.43−1.49 (m, 2 H, 2′-H_2), 1.52−1.58 (m, 2 H, 1′-H_2), 1.60−1.67 (m, 2 H, 2-, 5-H_b), 1.69−1.72 (m, 4 H, 3-,4-H_2), 1.78−1.83 (m, 2 H, 2-,5-H_a), 3.33 (s, 2 H, 1-,3′-OH), 3.64 (t, J = 6.0 Hz, 2 H, 3′-H_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.8 (2t, C-3,-4), 28.1 (t, C-2′), 38.5 (t, C-1′), 39.7 (t, C-2,-5), 63.0 (t, C-3′), 82.0 (s, C-1) ppm. MS (EI): *m/z* (%) = 144 (3) [M^+], 126 (5) [$M^+ - H_2O$], 97 (54) [$M^+ - C_2H_5OH$], 85 (76) [$C_6H_{13}^+$], 55 (100) [$C_4H_7^+$].

1-(3′-Bromopropyl)cyclopentene (18): Triphenylphosphane (432 g, 1.65 mol) was added portionwise at room temp. to a stirred suspension of Celite® (100 g), tetrabromomethane (547 g, 1.65 mol), and **17** (119 g, 825 mmol) in toluene (3 L), and stirring was continued for 3 h at 60 °C. The reaction mixture was cooled to room temp., and diluted with hexane (1 L). The precipitated triphenylphosphane oxide was filtered off and washed with hexane (200 mL), and the filtrate was concentrated on a rotary evaporator at reduced pressure. The crude product was purified by FC (hexane/Et_2O, 98:2; R_f = 0.54) on neutral aluminum oxide to furnish the title compound **18** (95.2 g, 61%). IR (film): $\tilde{\nu}$ = 657 (s, ν C−Br), 1436 (m, δ C−H), 3043 (w, ν C=C−H), 1650 (w, ν C=C−C) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.85 (dt, J = 7.0, 7.0 Hz, 2 H, 2′-H_2), 2.00 (dt, J = 7.0, 7.0 Hz, 2 H, 4-H_2), 2.19−2.24 (m, 4 H, 1′-,5-H_2), 2.27−2.32 (m, 2 H, 3-H_2), 3.39 (t, J = 6.5 Hz, 2 H, 3′-H_2), 5.37 (t, J = 2.0 Hz, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.4 (t, C-4), 29.5 (t, C-2′), 30.8 (t, C-3), 32.4 (t, C-3′), 33.5 (t, C-1′), 35.0 (t, C-5), 124.5 (d, C-2), 142.7 (s, C-1) ppm. MS (EI): *m/z* (%) = 190 (3) [M^+], 188 (3) [M^+], 109 (5) [$M^+ - Br$], 82 (18) [$C_6H_{10}^+$], 67 (100) [$C_5H_7^+$].

(3′-Cyclopent-1-enylpropyl)triphenylphosphonium Bromide (13): A solution of **18** (95.1 g, 502 mmol) in EtOH (200 mL) was added dropwise at room temp. over 20 min to a solution of triphenylphosphane (132 g, 502 mmol) in EtOH (800 mL). The reaction mixture was stirred at reflux for 2 days and was then cooled down to room temp., and the solvent was then evaporated on the rotary evaporator. The resulting residue was taken up in toluene (200 mL), and the phosphonium salt was precipitated by dropwise addition of Et_2O (150 mL). The precipitate was vacuum filtered, suspended at reflux in toluene (500 mL) for 1 h, and then stirred at room temp. for a further 2 h. The resulting crystals were filtered off under suction, washed with toluene (100 mL), and dried to constant weight at room temp./2 mbar to afford the title compound **13** (149 g, 66%). M.p. 208.1−210.2 °C. IR (KBr): $\tilde{\nu}$ = 1435/1113 (s, ν P−Ph), 693 (s, δ C−H oop, arom.), 1482 (m, δ C−H), 1586 (m, ν C=C, arom.), 3052 (m, ν C−H, arom.), 3043 (w, ν C=C−H) cm^{-1}. ^1H NMR (CD_3OD): δ = 1.82 (quint., J = 7.5 Hz, 4 H, 2′-,4-H_2), 2.10−2.14 (m, 2 H, 3-H_2), 2.27−2.33 (m, 4 H, 1′-,5-H_2), 3.39−3.45 (m, 2 H, 3′-H_2), 5.38 (br. s, 1 H, 2-H), 7.73−7.92 (m, 15 H, 2′′′-H−6′′′-H) ppm. ^{13}C NMR (CD_3OD): δ = 21.7/21.8 (2t, C-3′), 22.1 (t, C-1′), 24.3 (t, C-4), 32.3/32.5 (2t, C-1′), 33.2 (t, C-3), 35.0 (t, C-5), 119.2/120.4 (2s, C-1′′′), 126.5 (d, C-2), 131.4/131.5 (2d, C-3′′′,-5′′′), 134.6/134.8 (2d, C-2′′′, −6′′′), 136.2 (d, C-4′′′), 143.3 (s, C-1) ppm. MS (ESI): *m/z* (%) = 371 (100) [$M^+ - Br$] ppm. $C_{26}H_{28}BrP$ (451.39): calcd. C 69.18, H 6.25; found C 69.18, H 6.24.

2,3-Dimethylbut-3-en-2-ol (20): A solution of methyl iodide (284 g, 2.00 mol) in Et_2O (700 mL) was added dropwise over a period of 3 h to a stirred suspension of magnesium turnings (53.5 g, 2.20 mol) in Et_2O (80 mL), with the reaction being initiated by occasional heating with a heat gun. The reaction mixture was then stirred at reflux for an additional 3 h, and cooled to room temp. A solution of ethyl methacrylate (**19**, 114 g, 1.00 mol) in Et_2O (700 mL) was added dropwise over 2.5 h, and the mixture was stirred at reflux for an additional 16 h. After the reaction mixture had cooled down to room temp., it was quenched by addition of satd. aq. NH_4Cl solution (800 mL). The aqueous layer was extracted with Et_2O (3 × 500 mL), and the combined organic extracts were washed with brine (250 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was distilled over a 15-cm Vigreux column at 48−50 °C/20 mbar to provide the title compound **20** (92.3 g, 92%) as a colorless liquid. IR (film): $\tilde{\nu}$ = 3380 (s, ν O−H), 1449 (s, δ O−H), 1374 (s, δ CH_3), 1163 (s, ν C−O), 960/933 (s, ν C=C−H), 1449 (s, δ C−H), 3091 (m, ν C=C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.34 (s, 6 H, 1-H_3, 2-Me), 1.75 (s, 1 H, OH), 1.80 (s, 3 H, 3-Me), 4.75 (t, J = 1.5 Hz, 1 H, 4-$H_{(Z)}$), 4.99 (t, J = 1.5 Hz, 1 H, 4-$H_{(E)}$) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.1 (q, 3-Me), 28.8 (q, C-1, 2-Me), 73.1 (s, C-2), 108.4 (d, C-4), 152.0 (s, C-3) ppm. MS (EI): *m/z* (%) = 100 (8) [M^+], 85 (100) [$M^+ - CH_3$], 67 (11) [$M^+ - H_2O - CH_3$], 59 (64) [$C_3H_6O^+$].

4,5-Dimethylhex-4-enal (14): A mixture of **20** (72.1 g, 720 mmol) and 2,6,7-trioxa-4-aza-1-phosphabicyclo[2.2.2]octane 1-oxide (**22**, 1.09 g, 7.21 mmol) in ethyl vinyl ether (**21**, 114 g, 1.58 mol) was stirred for 3 h in an autoclave at 160 °C/17 bar. After the reaction mixture had cooled to room temp., it was diluted with Et_2O (500 mL), washed with HCl solution (0.5N, 100 mL), satd. aq. $NaHCO_3$ solution (2 × 100 mL), and brine (100 mL). The organic layer was dried (Na_2SO_4), and the solvent was evaporated on a rotary evaporator. The residue was purified by silica gel FC (pentane/Et_2O, 20:1; R_f = 0.34) to furnish the odoriferous title compound **14** (49.1 g, 54%). IR (film): $\tilde{\nu}$ = 1725 (s, ν C=O), 2719 (s, ν H−C=O), 1450 (s, δ C−H), 1375 (s, δ CH_3), 3043 (m, ν C=C−H), 844 (w, δ C=C−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.64 (s, 6 H, 5-Me_2), 1.66 (s, 3 H, 4-Me), 2.35 (t, J = 6.5 Hz, 2 H, 3-H_2), 2.44 (td, J = 6.5, 2.0 Hz, 2 H, 2-H_2), 9.77 (t, J = 2.0 Hz, 1 H, 1-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.4 (q, 4-Me), 20.2/20.6 (2q, C-6, 5-Me), 27.0 (t, C-3), 42.5 (t, C-2), 125.4 (s, C-5), 125.7 (s, C-4), 202.7 (s, C-1) ppm. MS (EI): *m/z* (%) = 126 (40) [M^+], 111 (25) [$M^+ - CH_3$], 108 (35) [$M^+ - H_2O$], 83 (29) [$C_6H_{11}^+$], 69 (35) [$C_5H_9^+$], 55 (100) [$C_4H_7^+$].

(3′*E*/*Z*)-1-(7′,8′-Dimethylnona-3′,7′-dienyl)cyclopent-1-ene (23): A phenyllithium solution in cyclohexane (2 M, 73.5 mL, 147 mol) was added dropwise over 20 min to a suspension of **13** (63.2 g, 140 mmol) in dry THF (600 mL). The resulting deep red solution was cooled to −80 °C, and a solution of **14** (17.7 g, 140 mmol) in dry Et_2O (200 mL) was added over a period of 20 min. After 15 min of stirring at −80 °C, the reaction mixture was warmed up to −30 °C and treated dropwise with additional phenyllithium solution (2 M, 73.5 mL, 147 mol). After 10 min of stirring at −30 °C, MeOH (21 mL) was added carefully, upon which a precipitate of triphenylphosphane oxide was formed. The resulting suspension was stirred for an additional 2 h at room temp., poured into water (300 mL), and extracted with Et_2O (3 × 400 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by silica gel FC (pentane/Et_2O, 98:2; R_f = 0.65) to furnish the title compound **23**

(18.7 g, 61%) as an isomeric mixture with an *E*/*Z* ratio of 8:2. IR (film): $\tilde{\nu}$ = 1445 (s, δ C−H), 965 (s, δ C=C−H), 1375 (s, δ CH_3), 1651 (m, ν C=C−C) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.63 (br. s, 9 H, 7′-Me, 8′-Me_2), 1.83 (quint., J = 7.0 Hz, 2 H, 4-H_2), 2.01−2.06 (m, 4 H, 2′-,5′-H_2), 2.03−7.09 (m, 2 H, 6′-H_2), 2.11−2.18 (m, 2 H, 3-H_2), 2.20−2.32 (m, 4 H, 5-,1′-H_2), 5.35−5.37 (m, 1 H, 2-H), 5.40−5.43 (m, 3′-,4′-H) ppm. **(3′*E*)-Isomer:** ^{13}C NMR ($CDCl_3$): δ = 18.3 (q, 7′-Me), 20.1 (q, 8′-Me), 20.5 (q, C-9′), 23.4 (t, C-4), 31.0 (t, C-2′), 31.2 (t, C-5′), 31.3 (t, C-3), 32.4 (t, C-6′), 34.7 (t, C-5), 35.2 (t, C-1′) 123.3 (d, C-2), 124.1 (s, C-8′), 127.4 (s, C-7′), 129.9 (d, C-3′), 130.3 (d, C-4′), 144.5 (s, C-1) ppm. **(3′*Z*)-Isomer:** ^{13}C NMR ($CDCl_3$): δ = 18.3 (q, 7′-Me), 20.1 (q, 8′-Me), 20.5 (q, C-9′), 23.4 (t, C-4), 25.7 (t, C-2′), 26.0 (t, C-5′), 31.3 (t, C-3), 32.4 (t, C-6′), 34.7 (t, C-5), 35.2 (t, C-1′) 123.3 (d, C-2), 124.1 (s, C-8′), 127.4 (s, C-7′), 129.5 (d, C-3′), 129.6 (d, C-4′), 144.4 (s, C-1) ppm. MS (EI): *m*/*z* (%) = 218 (2) [M^+], 203 (6) [$M^+ - CH_3$], 162 (9) [$M^+ - C_4H_8$], 83 (100) [$C_6H_{11}^+$]. $C_{16}H_{26}$ (218.4): calcd. C 88.00, H 12.00; found C 87.96, H 11.99.

5β,10-Dimethyl-*des*-*A*-18-*nor*-androst-13(14)-ene (24): A solution of methanesulfonic acid (8.65 g, 90.0 mmol) in CH_2Cl_2 (50 mL) was added at 0 °C over 30 min to a solution of **23** (3.93 g, 18.0 mmol) in CH_2Cl_2 (150 mL). After stirring for 1 h at 0 °C, the reaction mixture was poured into Et_2O (900 mL) and washed with water (2 × 150 mL), satd. aq. $NaHCO_3$ solution (2 × 200 mL), and brine (100 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated on a rotary evaporator. The resulting residue was purified by silica gel FC (hexane/Et_2O, 99:1; R_f = 0.66) to afford the title compound **24** (2.44 g, 62%) as a colorless oil. IR (film): $\tilde{\nu}$ = 1455 (s, δ C−H), 1372 (s, δ_s CH_3), 1651 (w, ν C=C) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.66 (br. s, 3 H, 10-Me_{ax}), 0.72 (s, 3 H, 5-Me), 0.86 (s, 3 H, 10-Me_{eq}), 1.12−1.19 (m, 1 H, 5-H), 1.32−1.38 (m, 4 H, 6-,7-H_2), 1.58−1.61 (m, 2 H, 11-H_2), 1.84−1.91 (m, 2 H, 16-H_2), 1.92−1.97 (m, 2 H, 12-H_2), 1.96−1.99 (m, 2 H, 8-,9-H), 2.09−2.17 (m, 4 H, 15-,17-H_2) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.8 (q, 10-Me_{ax}), 16.4 (q, 5-Me), 26.7 (q, 10-Me_{eq}), 22.3 (t, C-16), 23.6 (t, C-11), 27.1 (t, C-12), 31.3 (t, C-6), 32.6 (t, C-7), 36.0 (t, C-15), 37.1 (s, C-10), 37.7 (d, C-8), 38.3 (t, C-17), 42.2 (d, C-5), 51.1 (d, C-9), 133.9 (s, C-13), 138.5 (s, C-14) ppm. MS (EI): *m*/*z* (%) = 218 (45) [M^+], 203 (100) [$M^+ - CH_3$], 162 (34) [$M^+ - C_4H_8$], 109 (31) [$C_8H_{13}^+$]. $C_{16}H_{26}$ (218.4): calcd. C 88.00, H 12.00; found C 87.98, H 12.05.

5β,10-Dimethyl-13,14-epoxy-*des*-*A*-18-*nor*-androstane (25): A solution of 3-chloroperbenzoic acid (70%, 2.61 g, 10.6 mmol) in CH_2Cl_2 (40 mL) was added dropwise at 0 °C to a stirred solution of **24** (2.31 g, 10.6 mmol) in CH_2Cl_2 (50 mL), and the resulting suspension was stirred for an additional 4 h at 0 °C. The reaction mixture was then diluted with Et_2O (800 mL) and washed with aq. Na_2SO_3 solution (10%, 2 × 70 mL), satd. aq. $NaHCO_3$ (3 × 100 mL), and water (2 × 150 mL). The organic extract was dried (Na_2SO_4) and concentrated to dryness on a rotary evaporator. Repeated silica gel FC (hexane/Et_2O, 99:1) of the crude material furnished the title compound **25** (695 mg, 28%; R_f = 0.12). IR (film): $\tilde{\nu}$ = 1455 (s, δ C−H), 890/920 (s, ν C−O−C), 1372 (s, δ CH_3), 3050 (w, ν C−H, epoxide) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.61 (s, 3 H, 10-Me_{ax}), 0.77−0.80 (m, 1 H, 9-H), 0.81 (d, J = 6.0 Hz, 3 H, 5-Me), 0.88 (s, 3 H, 10-Me_{eq}), 1.12−1.19 (m, 1 H, 5-H), 1.31−1.37 (m, 2 H, 6-H_2), 1.38−1.43 (m, 2 H, 7-H_2), 1.57−1.58 (m, 4 H, 12-,17-H_2), 1.62−1.65 (m, 2 H, 11-H_2), 1.69−1.76 (m, 2 H, 16-H_2), 1.79−1.85 (m, 2 H, 15-H_2), 1.93−1.97 (m, 2 H, 8-,9-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.4 (q, 10-Me_{ax}), 16.5 (q, 5-Me), 19.7 (t, C-16), 22.9 (t, C-11), 26.7 (q, 10-Me_{eq}), 26.7 (t, C-15), 28.7 (t, C-12), 29.6 (t, C-17), 30.8 (t, C-6), 32.4 (t, C-7), 35.6 (s, C-10), 37.4 (d, C-8), 41.6 (d, C-5), 44.6 (d, C-9), 67.8 (s, C-14), 71.8 (s, C-13) ppm. MS (EI): *m*/*z* (%) = 234 (56) [M^+], 219 (57) [$M^+ - CH_3$], 216 (75) [$M^+ - H_2O$], 201 (100) [$M^+ - H_2O - CH_3$], 134 (67) [$C_{10}H_{14}^+$], 97 (78) [$C_7H_{14}^+$]. $C_{16}H_{26}O$ (234.4): calcd. C 81.99, H 11.18; found C 81.99, H 11.14.

5β,10-Dimethyl-*des*-A-18-*nor*-androstan-13β-ol (Limdrostanol, 11)/ 5β,10-Dimethyl-*des*-A-18-*nor*-androstan-14*α*-ol (26): A solution of **25** (610 mg, 2.60 mmol) in dry THF (12 mL) was added dropwise to a solution of lithium triethylborohydride (Super-Hydride®) in THF (1 M, 7.8 mL, 7.80 mmol), and the reaction mixture was stirred for 2 days under reflux. The reaction mixture was cooled to room temp., and then was taken up in Et_2O (800 mL) and washed with satd. aq. NH_4Cl solution (2 × 100 mL), water (100 mL), and brine (100 mL). The ethereal extract was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by silica gel FC (hexane/Et_2O, 99:1) to afford **11** (186 mg, 30%) and **26** (237 mg, 38%).

Data for **11**: R_f = 0.10 (hexane/Et_2O, 9:1). IR (Film): $\tilde{\nu}$ = 3474 (s, ν O−H), 1449 (s, δ C−H), 1389 (s, δ O−H), 1365 (m, δ CH_3), 1196 (m, ν C−O) cm^{-1}. ^1H NMR (C_6D_6): δ = 0.52 (br. s, 1 H, 13-OH_{ax}), 0.62 (dt, J = 10.5, 5.0 Hz, 1 H, 9-H_{ax}), 0.71 (s, 3 H, 10-Me_{ax}), 0.79 (2t, J = 11.0, 6.0, 1 H, 14-H_{ax}), 0.85 (d, J = 6.5 Hz, 3 H, 5-Me_{eq}), 0.88 (m_c, 1 H, 7-H_{ax}), 0.91 (s, 3 H, 10-Me_{eq}), 0.96 (2d, J = 6.0, 5.0 Hz, 1 H, 12-H_{ax}), 1.17 (m_c, 1 H, 5-H_{ax}), 1.20 (2d, J = 4.5 Hz, 1 H, 6-H_{ax}), 1.27 (tt, J = 7.5, 2.0 Hz, 1 H, 17-H_{ax}), 1.38 (q, J = 12.0 Hz, 1 H, 8-H_{ax}), 1.39 (m_c, 1 H, 6-H_{eq}), 1.42 (m_c, 1 H, 15-H_{ax}), 1.50 (m_c, 2 H, 16-H_{ax},17-H_{eq}), 1.55 (m_c, 2 H, 11-H_2), 1.62 (m_c, 1 H, 15-H_{eq}), 1.67 (q, J = 3.0 Hz, 1 H, 7-H_{eq}), 1.78 (quint., J = 3.5 Hz, 1 H, 16-H_{eq}), 1.80 (t, J = 3.0 Hz, 1 H, 12-H_{eq}) ppm. ^1H,^1H NOESY: 10-Me_{ax} × 5-Me_{eq}, 8-H_{ax} × 13-OH_{ax}, 10-Me_{ax} × 8-H_{ax}, 14-H_{ax} × 12-H_{ax}, 12-H_{ax} × 9-H_{ax}, 5-H_{ax} × 9-H_{ax}, 14-H_{ax} × 9-H_{ax}, 10-Me_{ax} × 6-H_{ax} ppm. ^{13}C NMR (C_6D_6): δ = 14.2 (q, 10-Me_{ax}), 16.8 (q, 5-Me_{eq}), 21.1 (t, C-16), 21.9 (t, C-11), 26.0 (t, C-15), 27.1 (q, 10-Me_{eq}), 31.1 (t, C-6), 32.6 (t, C-7), 36.1 (d, C-8), 36.2 (s, C-10), 36.9 (t, C-12), 39.4 (t, C-17), 42.8 (d, C-5), 52.8 (d, C-9), 54.4 (d, C-14), 77.8 (s, C-13) ppm. MS (EI): *m*/*z* (%) = 236 (10) [M^+], 218 (12) [$M^+ - H_2O$], 203 (22) [$M^+ - H_2O - CH_3$], 194 (100) [$C_{13}H_{22}O^+$]. $C_{16}H_{28}O$ (236.4): calcd. C 81.29, H 11.94; found C 81.12, H 11.96. Odor: Woody, earthy, sweet. Odor threshold: 90 ng/L air.

Data for 26: R_f = 0.12 (hexane/Et_2O, 9:1). M.p. 55.3−58.1 °C. IR (KBr): $\tilde{\nu}$ = 3505 (s, ν O−H), 1450 (s, δ C−H), 1389 (s, δ O−H), 1364 (s, δ CH_3), 1139 (m, ν C−O) cm^{-1}. ^1H NMR (C_6D_6): δ = 0.57 (br. s, 14-OH_{ax}), 0.66 (s, 3 H, 10-Me_{ax}), 0.85 (d, J = 6.5 Hz, 3 H, 5-Me_{eq}), 0.91 (s, 3 H, 10-Me_{eq}), 0.92 (dt, J = 4.0, 3.0 Hz, 1 H, 11-H_{ax}), 0.98 (quint., J = 4.0 Hz, 1 H, 13-H_{ax}), 1.10 (2d, J = 11.0 Hz, 1 H, 8-H_{ax}), 1.13 (m_c, 1 H, 5-H_{ax}), 1.17 (d, J = 4.0 Hz, 1 H, 9-H_{ax}), 1.18 (m_c, 1 H, 15-H_{ax}), 1.19 (m_c, 1 H, 6-H_{ax}), 1.38 (t, J = 4.0 Hz, 2 H, 7-H_{ax},12-H_{ax}), 1.40 (m_c, 1 H, 6-H_{eq}), 1.50 (m_c, 1 H, 7-H_{eq}), 1.51 (quint., J = 3.0, 1 H, 16-H_{ax}), 1.54 (m_c, 2 H, 12-H_{eq},15-H_{eq}), 1.57 (m_c, 2 H, 17-H_2), 1.72 (quint., J = 3.5 Hz, 1 H, 16-H_{eq}), 1.74 (m_c, 1 H, 11-H_{eq}) ppm. ^1H,^1H NOESY: 10-Me_{ax} × 8-H_{ax}, 10-Me_{ax} × 11-H_{ax}, 10-Me_{ax} × 5-Me_{eq}, 10-Me_{ax} × 6-H_{ax}, 9-H_{ax} × 14-OH_{ax}, 7-H_{ax} × 14-OH_{ax}, 12-H_{ax} × 14-OH_{ax}. ^{13}C NMR (C_6D_6): δ = 13.9 (q, 10-Me_{ax}), 16.8 (q, 5-Me_{eq}), 21.1 (t, C-16), 25.4 (t, C-12), 26.5 (t, C-11), 27.1 (q, 10-Me_{eq}), 27.2 (t, C-7), 28.2 (t, C-17), 30.8 (t, C-6), 36.2 (s, C-10), 37.3 (t, C-15), 42.4 (d, C-5), 45.7 (d, C-8), 46.4 (d, C-9), 48.8 (d, C-13), 80.6 (s, C-14) ppm. MS (EI): *m*/*z* (%) = 236 (25) [M^+], 218 (3) [$M^+ - H_2O$], 203 (9) [$M^+ - H_2O - CH_3$], 194 (100) [$C_{13}H_{22}O^+$]. $C_{16}H_{28}O$ (236.4): calcd. C 81.29, H 11.94; found C 81.26, H 11.92. Odor: earthy, ambery. Odor threshold: 46 ng/L air.

Direct Synthesis of 5β,10-Dimethyl-*des*-A-18-*nor*-androstan-13β-ol (Limdrostanol, 11) from (3′*E*/*Z*)-1-(7′,8′-Dimethylnona-3′,7′-dienyl)-cyclopent-1-ene (23): Methanesulfonic acid (892 mg, 9.28 mmol) was added dropwise at 0 °C to a stirred solution of **23** (2.54 g, 11.6 mmol) in HCOOH (20 mL), and the resulting slightly red solution was stirred for an additional 6 h at 0 °C. The reaction mixture was then diluted with Et_2O (1 L) and washed with water (2 × 200 mL), satd. aq. $NaHCO_3$ (3 × 150 mL), and brine (200 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was taken up in aq. NaOH/EtOH (1 M, 1:1, 60 mL), and the mixture was stirred at room temp. overnight. The reaction mixture was then poured into water (150 mL), and the product was extracted with Et_2O (3 × 300 mL). The ethereal extract was washed with brine (150 mL) and dried (Na_2SO_4), and the solvents were evaporated on a rotary evaporator. The resulting residue was purified by silica gel FC (hexane/Et_2O, 99:1) to afford **11** (84.9 mg, 3%) as a colorless oil. The spectroscopic data for the isolated compound were identical in all respects to those reported for **11** above.

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