Synthesis of Cephalostatin Analogues by Symmetrical and Non-Symmetrical Routes

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Received July 3, 1998

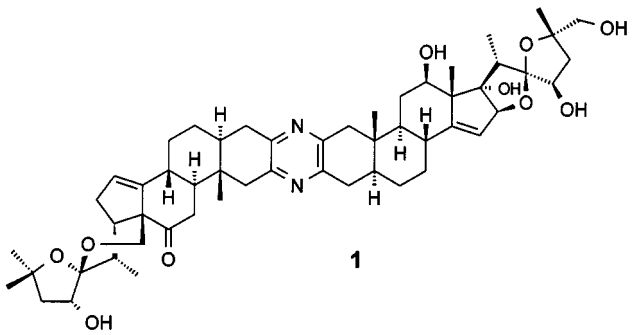
Keywords: Vinyl azides / Cephalostatins / Pyrazine formation / Desymmetrization / Enamino ketones

The synthesis of the cephalostatin-analogous bis-steroidal pyrazines **6**, **27a**/**b** and **41** by the transformation of the C_2-symmetrical diketone **6** as a central precursor, as well as the direct preparation of several non-symmetrical bis-steroidal pyrazines by coupling of enamino ketones (**5**, **40**) with vinyl azides (**17a**/**b**) is reported. Furthermore, an improved procedure for preparation of the diketone **6** described earlier is presented.

Introduction

Cephalostatin 1 (**1**) is the prototype of the cephalostatins and the ritterazines, a family of 30 tridecacyclic pyrazines, isolated by Pettit and co-workers since 1988 from the Indian Ocean marine worm *Cephalodiscus gilchristi*[1], and by the group of Fusetani from the tunicate *Ritterella tokioka*[2]. These compounds exhibit an extraordinarily strong cytostatic activity, with their most potent member Cephalostatin 1 (**1**)[3] being 400-fold more active in in vitro testing than Taxol[4], and therefore one of the most powerful cytostatics ever to be tested by the National Cancer Institute.

Scheme 1. Cephalostatin 1



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The availability of the cephalostatins from their only natural source, the marine worm *Cephalodiscus gilchristi* is still extremely limited. Pettit et al. reported the isolation of only 139 mg of Cephalostatin 1 (**1**) from 166 kg of "crude" marine worms and even less of the other cephalostatins[1][5]. Therefore, in vivo evaluations of the cephalostatins conducted to date have been rather limited[6].

The outstanding cytostatic activity together with the new and interesting structure and poor availability immediately led to synthetic activities in various laboratories, with different goals[7][8][9][10]. While other groups, after some preliminary studies, focused on the total synthesis of the cephalostatins[7], we ourselves embarked on a program to determine the essential biological substructures of the cephalostatins by synthesis and biological evaluation of appropriate analogues.

Systematic investigations in our laboratories led to two independent routes to easily accessible Cephalostatin analogues. The aim of one approach, named the *symmetrical route*, was the straightforward synthesis of symmetrical bis-steroidal pyrazines by dimerization of an α-amino ketone precursor such as an enamino ketone[11]. The C_2-symmetrical pyrazines of type **A** obtained this way then had to be desymmetrized and further functionalized at a later stage of the synthesis. The aim of the second approach, named the *non-symmetrical route*, was the direct synthesis of non-symmetrical bis-steroidal pyrazines of type **B** by chemo- and regioselectively controlled coupling of two different steroids (Scheme 2).

Results and Discussion

The Symmetrical Route – Easy Access to Simple Cephalostatin Analogues

Adopting inexpensive hecogenine acetate (**2**) as the starting point of our synthetic efforts, we first introduced the $\Delta^{14,15}$ double bond, a typical structural feature of the cephalostatins, which is quite unusual for other natural steroids, in an efficient two-step synthesis after substantial improvements of the Bladon procedure[12], to obtain homoallylic alcohol **3** (Scheme 3)[11][32].

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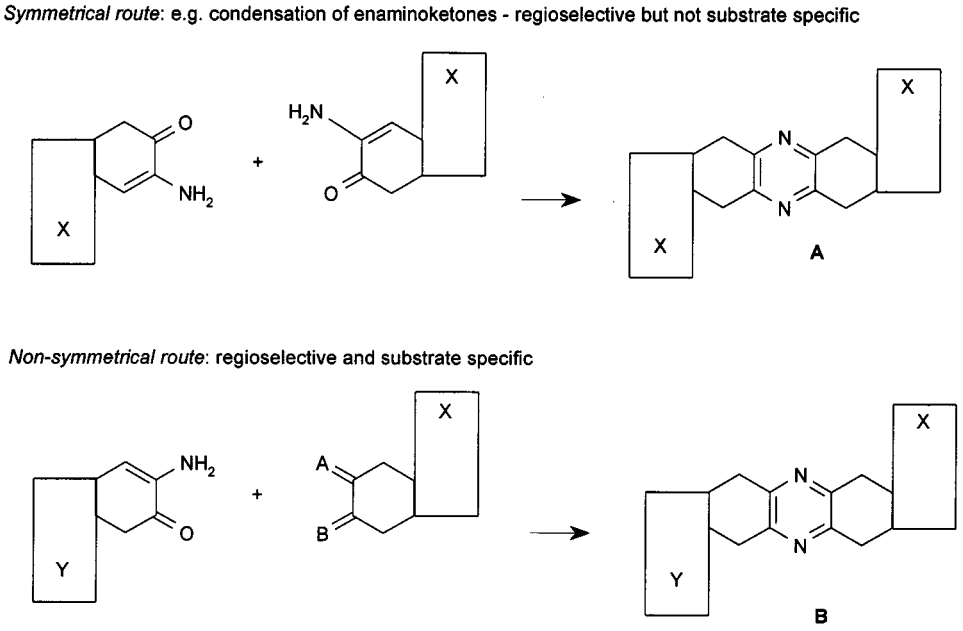
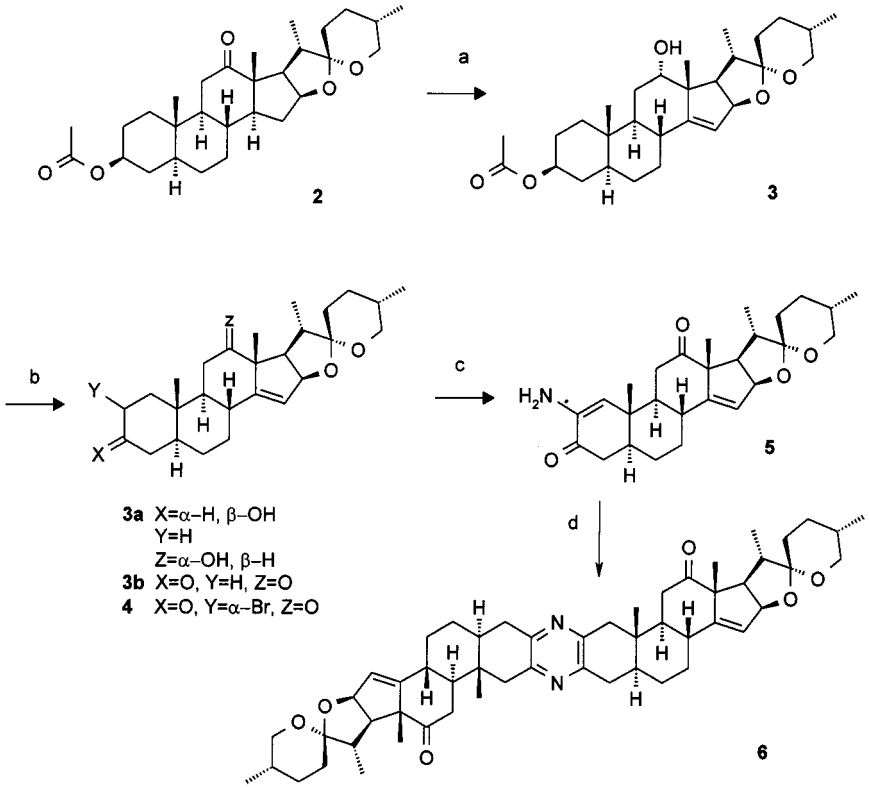
Scheme 2. Synthetic strategies leading to steroidal pyrazines



Scheme 3. The symmetrical approach

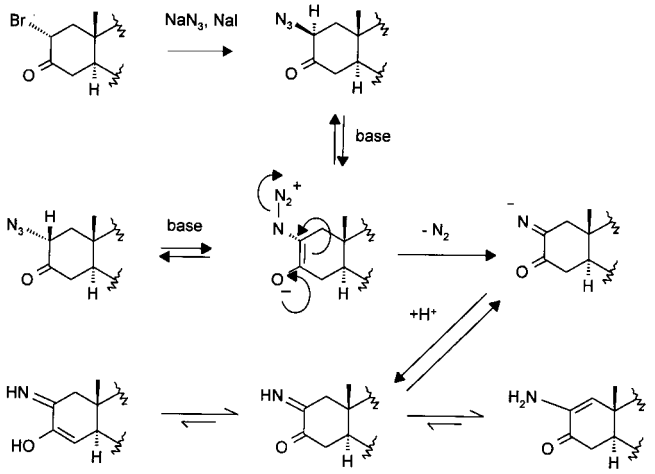


a) i. Dioxane, hν, 3 h; ii. $BF_3 \cdot Et_2O$, toluene, 40 min, 80% (steps i and ii). – b) i. KOH, MeOH, 70°C, 1 h; ii. PCC, SiO_2, NaOAc, CH_2Cl_2, 95% (steps i and ii); iii. PTAP, THF, r.t., 4.5 h, 81%. – c) NaN_3, NaI, DMF, 50°C, 1 h, 91%. – d) $Pd/BaSO_4$, H_2, MeOH, 4h, 73%.

Saponification of the C-3 acetate **3**, subsequent PCC oxidation, followed by chemo-, regio- and stereoselective bromination afforded the 2α-bromo-3,12-enedione **4**. Treatment of the bromo ketone **4** with sodium azide in DMF afforded the enamino ketone **5** with direct loss of nitrogen. We believe this reaction to proceed by initial bromide–azide exchange, followed by base-promoted loss of the acidic 2-proton with subsequent irreversible nitrogen loss (Scheme 4). Similar reactions have been reported in the literature for a number of α-azido ketones[13]. A further indication for

this base-catalyzed mechanism is the fact that α-azido ketones do not undergo nitrogen loss in neutral or acid media[14].

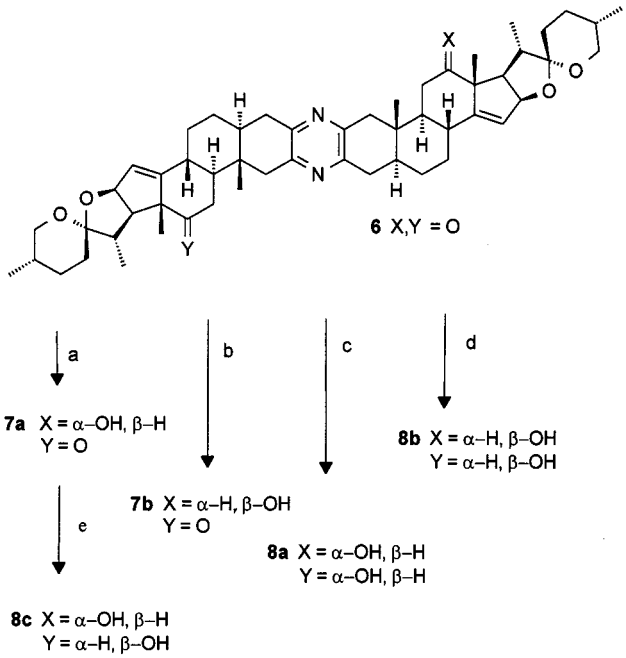
Scheme 4. Possible mechanism of enamino ketone formation



Finally, reductive dimerization of the enamino ketone **5** with palladium on charcoal/hydrogen afforded the C_2-symmetrical diketone **6** in seven steps, in an overall yield of 43% from hecogenine acetate **2**[15].

Desymmetrization of diketone **6** by diastereoselective reduction with lithium tris(*sec*-butyl)hydroborate afforded the α-hydroxy ketone **7a**, while sodium tetrahydroborate reduction provided the β-hydroxy ketone **7b** (Scheme 5). Under appropriate conditions, these reduction processes also gave rise to the symmetrical compounds α-diol **8a** and β-diol **8b**. Similarly, sodium tetrahydroborate reduction of the α-hydroxy ketone **6** furnished the non-symmetrical α,β-diol **8c**.

Scheme 5. Desymmetrization studies on diketone **6**



a) Lithium tris(*sec*-butyl)hydroborate, toluene (0.7 equiv.), −78°C, 1 h, 49% (based on recovered starting material: 82%). − b) $NaBH_4$ (0.7 equiv.), $MeOH/CH_2Cl_2$, (1:1), −78°C, 30 min., 47%, (based on recoverd starting material: 81%). − c) Lithium tris(*sec*-butyl)hydroborate (2.9 equiv.), toluene, −78°C, 1 h, 98%. − d) $NaBH_4$, $MeOH/CH_2Cl_2$, (1:1), −78°C, 4 h, 98%. − e) $NaBH_4$ (4 equiv.), $MeOH/CH_2Cl_2$, (1:1), −78°C, 2 h, 96%.

The Non-Symmetrical Route − Preparation of Vinyl Azides According to Zbiral's Procedure

Although the symmetrical route provided a fast eight-step access to non-symmetrical bis-steroidal pyrazines, its synthetic potential was still limited and a non-symmetrical approach was clearly desirable.

At the time when we started our first investigations on the directed non-symmetrical synthesis of bis-steroidal pyrazines, only one method, developed by Heathcock et al.[9] had been reported. In this example, a steroidal α-acetoxy ketone was coupled with an α-amino oxime ether at relatively high temperature (145°C). The conditions reported led to low yields, but nevertheless Fuchs et al. recently reported a substantial improvement of this methodology, which led to the first total synthesis of Cephalostatin 1 (**1**)[7]. Prior to these results, a new technique for the chemo- and regioselectively controlled coupling of two different steroids was developed in our laboratories[10].

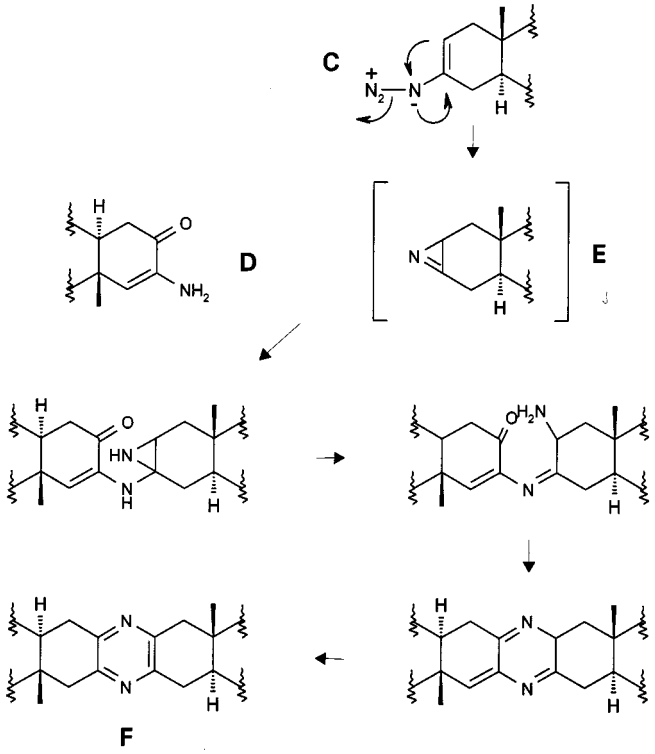
Since azirines may be considered as cyclic equivalents of α-amino ketones, we decided to combine vinyl azides of type **C**, which in turn are precursors of azirines, under thermal or photochemical conditions[16][17] with enamino ketones of type **D**. Having noticed that enamino ketones of type **D** are quite stable under thermal conditions and do not undergo dimerization, we anticipated the reaction of **D** with azirines of type **E** as similarly non-dimerizing analogues of α-amino ketones to constitute a facile route to non-symmetrical pyrazines **F** (Scheme 6).

As expected, treatment of the stable azirine **10**, easily prepared from *trans*-stilbene[18], with enamino ketone **9** and trifluoroacetic acid at 0°C in THF gave the steroidal pyrazine **11** in 63% yield (Scheme 7).

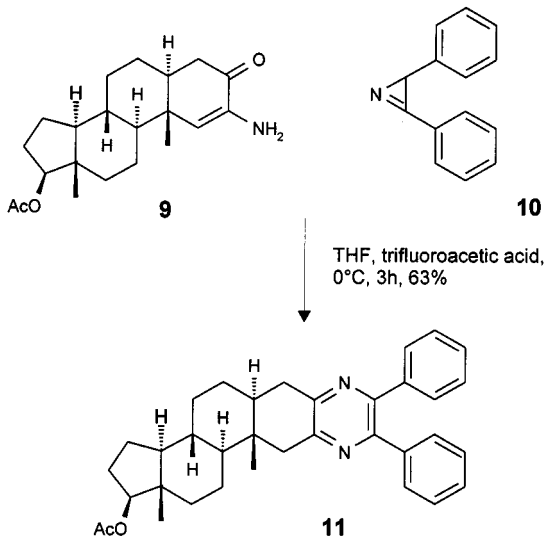
While the preparation of an A-ring enamino ketone of type **9** had been shown to be an easy process, the access to 2,3-vinyl azides as precursors of the 2,3-azirine proved to be more difficult. To obtain the first samples we utilized a modification of a synthetic pathway developed by Zbiral et al.[19] for simple steroids (Scheme 8).

Starting with homoallylic alcohol **3**, esterification with pivaloyl chloride and propionic anhydride, respectively, yielding **12a/b**, and selective saponification of the C-3 acetate afforded the 3β-alcohol **12c/d**. In our initial studies, we used the pivaloyl group instead of propionate to protect the 12-hydroxy functionality[10], but the pivalate compound proved to be absolutely stable towards saponification at a later stage of the synthesis. Nevertheless, deprotection could be achieved by reductive cleavage (DIBAL). Since this severely limits the choice of starting materials, we decided on the use of propionate as the alcohol protecting group. Tosylation of the 3β-alcohol **12c/d** and ALOX-B induced elimination led to the corresponding olefin **13c/d**[20]. After re-

Scheme 6. The non-symmetrical approach



Scheme 7. Preliminary studies on the non-symmetrical coupling strategy



gio- and diastereoselective epoxidation with dimethyldioxirane to give compound **14a/b** followed by a regio- and diastereoselective epoxide opening with triphenylphosphonium chloride[21], the 2β-chloro-3α-hydroxy compound **15a/b** was obtained. To introduce the azide under inversion of configuration at C-3, Zbiral and co-workers decided to use the Mitsunobu reaction. Unfortunately, this transformation turned out to be the bottleneck of the synthesis of 2,3-vinyl azides. Numerous experiments and systematic variations concerning the reagents, solvent and reaction procedure were undertaken. A representative sample of the attempted procedures is shown in Table 1. All reactions were run with 3 equiv. of diethyl azodicarboxylate (DEAD), except entry 1 (3.3 equiv.) and entry 5 (1.2 equiv.)

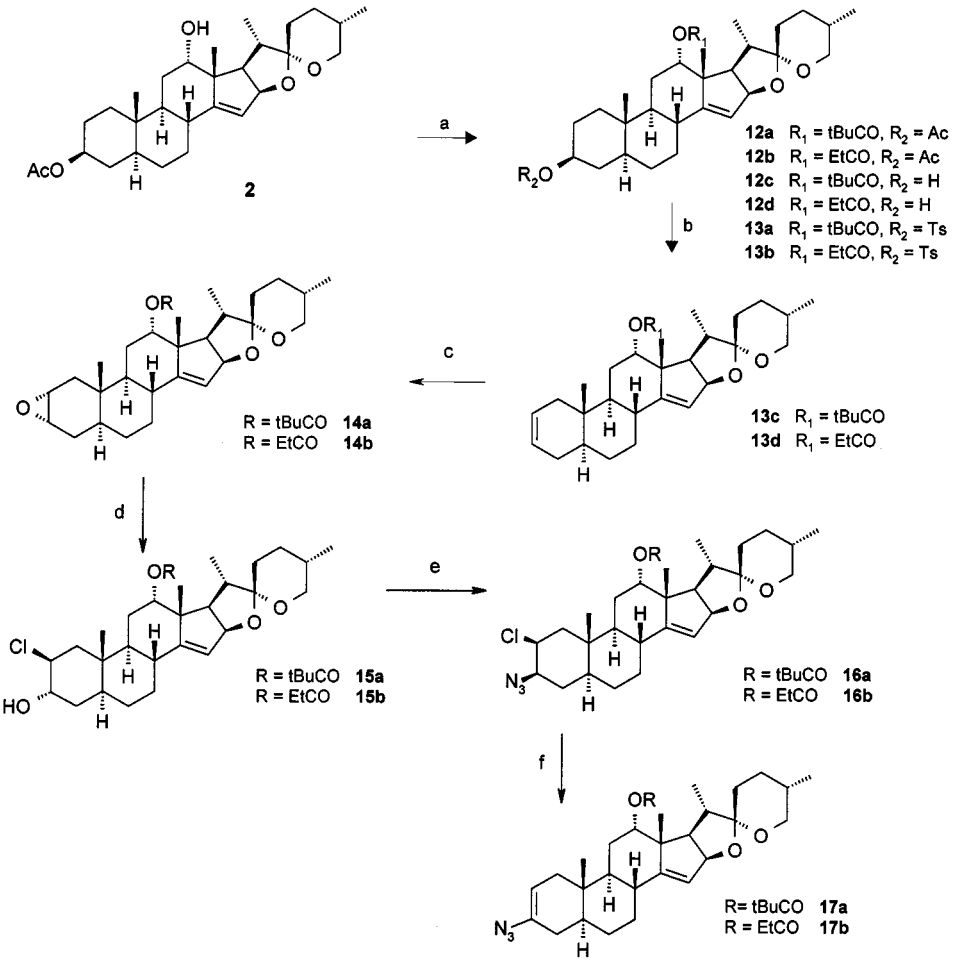
The best results were obtained using toluene as solvent and hydrazoic acid as the azide source (entries 1, 2, 6, and 9). The addition of sodium azide (entry 3) or of tetrabutylammonium azide (entry 4) to the hydrazoic acid did not increase the yields. In the latter case, the yield even decreased to below 10%. The use of diphenylphosphoryl azide (entry 5)[22] as the only azide source led to numerous byproducts and the yield of the desired product was below 20%. The change of the group R in the phosphane reagent from R = phenyl to R = butyl or R = *p*-methoxyphenyl necessary for the Mitsunobu reaction to take place did not generally increase the yields, so triphenylphosphane (3 equiv.) remained the best reagent. The amount of DEAD used in the reaction also should not differ from 3 equivalents. The yields dropped significantly if less was used. We also checked Barrett's conditions[23] (entry 10) where DEAD and PPh_3 are replaced by (chloromethylene)dimethylammonium chloride, a reagent that is easily prepared from dimethylformamide and oxalyl chloride. In this case, the only product we obtained was the formyl ester **18** in 49% yield (Scheme 9).

During our optimization studies, we made the noteworthy observation that it was possible to operate at low reaction temperatures ranging from room temperature to 40°C when using imidazole or α-pyridone as buffering agents (entries 6 and 9). In all other cases, when no buffers were used, a temperature of 80°C was necessary for the substitution to take place. This new temperature profile should become important if the synthesis requires thermally labile functional groups in the molecule. Nevertheless, the resulting yields using these conditions could not match those achieved under our standard conditions (PPh_3, DEAD, HN_3, toluene). The yields of 45% (40% for the propionate **16b**) given here were the best in which we could obtain the 3β-azido-2β-chloro-12α-pivalate (**16a**) and 3β-azido-2β-chloro-12α-propionate (**16b**), respectively. As the major byproduct (40−50%) under almost all the conditions listed, we obtained a mixture of allylic azides. Obviously, an elimination of the phosphorus complex yielding the allylic chloride takes place first, which is followed by S_N and S_N' reactions with azide anions (Scheme 10).

In order to study the effect of the C-2 substituent, we tried to replace the chlorine atom with bromine or fluorine (Scheme 11).

Epoxide opening of **14b** to form product **19a** was easily performed under the conditions known from the chlorine case. For the generation of the bromide **19a**, we prepared dibromotriphenylphosphane from bromine and triphenylphosphane in situ[21], and obtained the product in 76% yield. The introduction of a fluorine atom was more difficult, but we finally managed to perform the reaction in 56% yield using caesium fluoride as the fluorine source in a mixture of DMSO and pivalic acid. Both the bromohydroxy-steroid **19a** and the fluoro-hydroxy-steroid **19b** were exposed to the conditions of the Mitsunobu reaction

Scheme 8. Synthesis of steroidal vinyl azides



a) **13a**: i. PivCl, DMAP, pyridine, 100°C, 6 h; ii. KOH, MeOH, CH_2Cl_2, 70°C, 1 h, 94% (both steps); iii. TsCl, DMAP, CH_2Cl_2, r.t., 36 h; **13b**: i. $(C_3H_5O)_2O$, DMAP, pyridine, 100°C, 4 h; ii, KOH, MeOH, CH_2Cl_2, 70°C, 1 h, 89% (both steps); iii. TsCl, DMAP, CH_2Cl_2, r.t., 36 h. − b) ALOX B, toluene, 90°C, 4 h, **13c**: 87% (steps **12c** → **13a** → **13c**), **13d**: 75% (steps **12d** → **13b** → **13d**). − c) Dimethyldioxirane, CH_2Cl_2, 0°C, **14a**: 90 min, 93%, **14b**: 2 h, 88%. − d) PPh_3Cl_2, CH_2Cl_2, −15°C, 1 h, **15a**: 62%, **15b**: 73%, − e) DEAD, PPh_3, HN_3, PPTS, toluene, **16a**: 20 min 0°C, 10 min 70°C, 16 h r.t, 45%, **16b**: 20 min 0°C, 10 min 80°C, 1 h r.t., 40%, **16b**: DEAD, PPh_3, HN_3, imidazole, r.t., 24 h, 42%. − f) **17a**: KO*t*Bu, Et_2O, r.t., 1 h, 91%; **17b**: P_2-Et, Et_2O, r.t., 3 h, 98%.

Table 1. Modifications on the Mitsunobu reaction

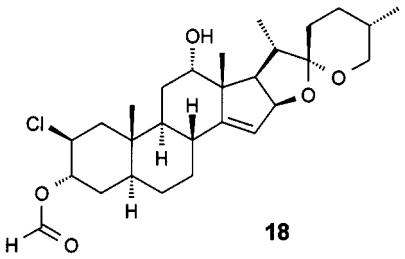
entry	conditions	phosphane	azide source	yield [%]
1[a]	toluene, 20 min 0°C, 10 min 70°C, 16 h r.t.	PPh_3	0.6 M HN_3, 3.9 equiv.	45
2	toluene, 20 min 0°C, 10 min 80°C, 1 h r.t.	PPh_3	1.4 M HN_3, 5 equiv.	40
3	toluene, 10 min 0°C, 10 min 80°C, 1 h r.t.	PPh_3	1.6 M HN_3, 1.5 equiv., 10 equiv. NaN_3	37
4	toluene, 10 min 0°C, 15 min 80°C, 1 h r.t.	PPh_3	1.6 M HN_3, 3 equiv., 10 equiv. $Bu_4N^+N_3^-$	< 10
5	THF, 3 d r.t.	PPh_3	$(PhO)_2P(O)N_3$	< 20
6	toluene, 24 h r.t., 5 equiv. imidazole	PPh_3	1.8 M HN_3, 5 equiv.	42
7	toluene, 0−80°C, 5 equiv. imidazole	PBu_3	1.8 M HN_3, 5 equiv.	< 10
8	toluene, 0−80°C, 5 equiv. imidazole	P(*p*-MeOPh)$_3$	1.8 M HN_3, 5 equiv.	< 10
9	toluene, 30 min 0°C, 10 min r.t., 90 min 40°C, 5 equiv. α-pyridone	PPh_3	1.8 M HN_3, 5 equiv.	39
10	THF, 45 min r.t. $(CHCl{=}N^+Me_2)Cl^-$, 2 equiv.	−	1.4 M HN_3, 3 equiv.	0 (**16b**), 49 (**18**)

[a] The starting material in entry 1 was the 12-pivaloyloxy compound **15a**.

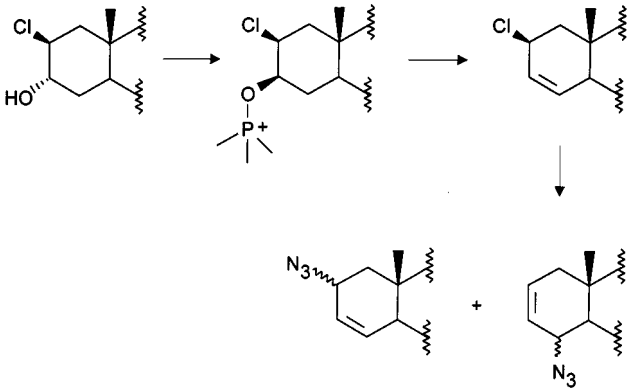
(PPh_3, DEAD, HN_3, toluene). The bromoazide **20a** seemed to be very unstable, as TLC revealed the conversion of the starting material into a new compound after just a few minutes which, however, decomposed to various elimination products upon work-up. On the other hand, the fluoroazide **20b** could be obtained in 49% yield, although the formation of allyl azides still could not be avoided.

We therefore assume that there is an effect of the 2-substituent, leading to elimination processes. The question remains as to whether this effect is caused by steric repulsion

Scheme 9

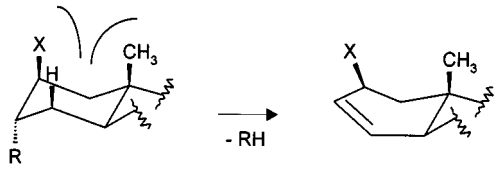


Scheme 10. Possible mode of by-product formation in Mitsunobu reaction



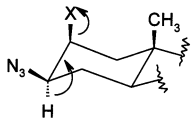
between the halogen and 19-methyl group (Scheme 12) or is due to electronic effects. Additionally, on the basis of our experiments (e.g. the Mitsunobu reaction resulting in **18**), we conclude that the trajectory of the incoming nucleophile leading to 3β-substituted compounds is blocked.

Scheme 12



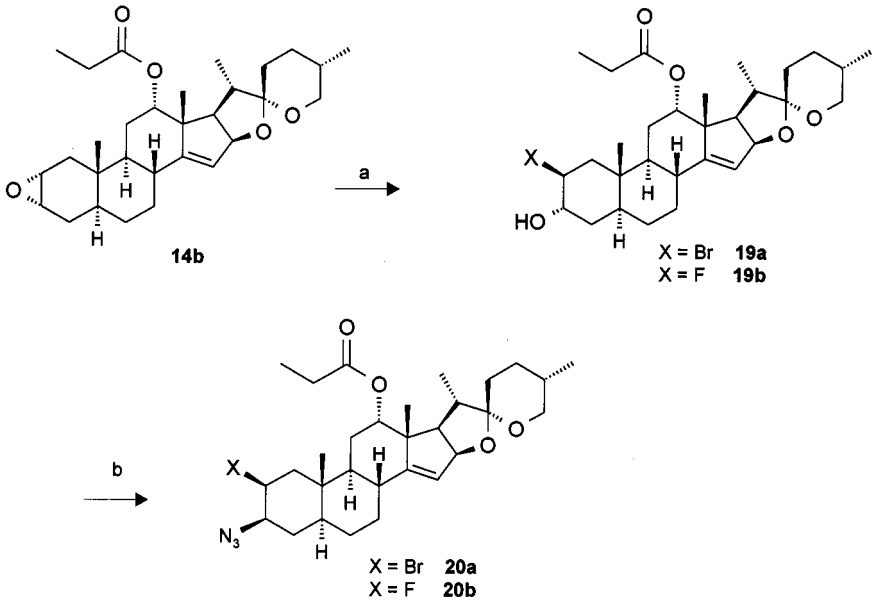
The 3β-azido-2β-chloro compounds **16a/b** provided the necessary anticoplanar orientation of the 2β-chloride and the 3α-proton required for E2 elimination (Scheme 13). This reaction did not present any problems in the case of the pivalate **16a**, whereas the propionate **16b** gave several by-products due to elimination of the protecting group with bases generally used for reactions of this kind, e.g. potassium butoxide or DBU. Using Schwesinger's phosphazene base P_2-Et[24] we were able to produce the 2,3-vinyl azide 12α-propionate **17b** in 98% yield. The overall yield starting from homoallylic alcohol **3** was 21% in the case of the pivalate (**17a**) and 18% in the case of the propionate (**17b**).

Scheme 13



The by-product resulting from the deprotection of the propionate cannot be used in the following coupling reaction, because the 12α-alcohol functionality leads to side reactions, resulting in low yields, by nucleophilic attack on the in situ generated azirine.

Scheme 11



a) **19a**: Br_2, PPh_3, CH_2Cl_2, r.t., 15 min, 76%; **19b**: CsF, LiF (cat.), pivalic acid, DMSO, 100°C, 6 h, 56%. − b) **20a**: DEAD, PPh_3, HN_3, toluene, 20 min 0°C, 10 min 80°C, 1 h r.t.; **20b**: DEAD, PPh_3, HN_3, toluene, 20 min 0°C, 10 min 80°C, 1 h r.t., 49%.

Attempted Preparation of Vinyl Azides by Different Approaches

Since this modified Zbiral technique was by no means completely satisfactory, we also tried to obtain a vinyl azide by using a *syn*-elimination process (Scheme 14).

Starting from 3-oxo-12-pivalate **21**, regio- and stereoselective bromination with $Py \cdot HBr_3$ provided compound **22**. We continued with a reduction of the bromo ketone **22** to bromo alcohol **23**, followed by an intramolecular S_N2 reaction furnishing the β-epoxide **24**. Subsequent treatment with sodium azide in dimethylacetanilide (DMAA) led to the α-azido alcohol **25** in 92% yield. To perform the *syn*-elimination process under mild conditions, we decided to use the Burgess reagent [methyl(carboxysulfamoyl)triethylammonium hydroxide inner salt][25]. The nucleophilic attack of the alcohol is believed to lead to a charged intermediate in the initial step (Scheme 15). Unfortunately, its subsequent *syn* elimination, which is supposed to proceed by a six-membered transition state, did not take place.

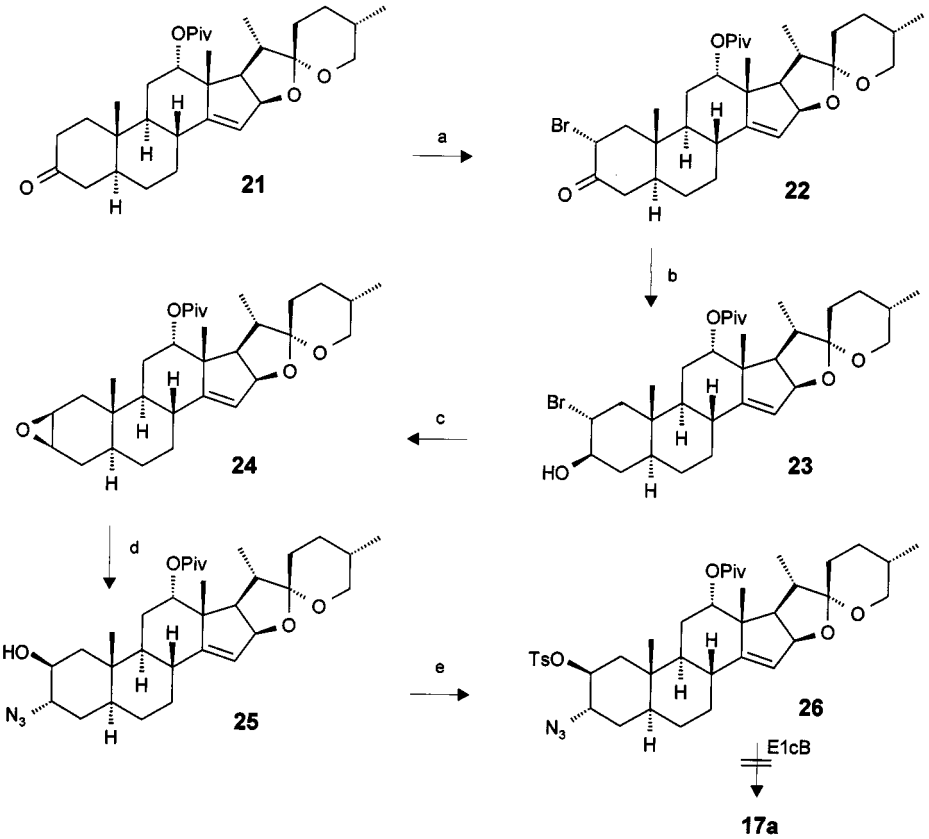
The reaction of the α-azido alcohol **25** with thionyl chloride[26], a method capable of providing both vinylic and chlorinated compounds, in this case led to chlorination under retention of configuration at position 2. The reaction with 1,1′-thiocarbonyldiimidazole produced the corresponding thioester which, however, did not undergo elimination upon heating[27]. We therefore treated the α-azido alcohol **25** with tosyl chloride and tried to achieve an E1cB elimination under various conditions (Table 2). Unfortunately, treatment of the azidotosylate **26** with selected bases again failed to yield the vinyl azide **17a**.

Pyrazine Coupling Reaction

The vinyl azide **17a/b** can be used for regio- and substrate-specific coupling, leading to bis-steroidal pyrazines (Scheme 16).

Presumably, vinyl azide **17a/b** is transferred in situ to an azirine by thermal or photochemical induction (see Scheme 6), which accounts for the selectivity of the reaction. The nucleophilic attack of the enamino ketone **5** can only take place at the 3-position of the azirine, generating an aziridine intermediate (cf. Scheme 6), which is opened by intramolecular proton shift. Condensation of the resulting amino group with the remaining keto group followed by isomerization is the final step that leads to the observed pyrazine **27a/b**[28]. The substrate specifity can be explained by the

Scheme 14



a) $Py \cdot HBr_3$, THF, r.t., 3 h, 66%. − b) $NaBH_4$, MeOH, CH_2Cl_2, 0°C, 90 min, 65%. − c) KOH, 2-propanol, *tert*-butyl methyl ether, 50°C, 1 h, 95%. − d) Dimethylacetamide, NaN_3, H_2O, 65°C, 18 h, 92%. − e) TsCl, DMAP, pyridine, 60°C, 24 h, 80%.

Scheme 15

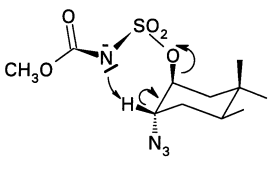


Table 2. Reaction conditions for E1cB reaction

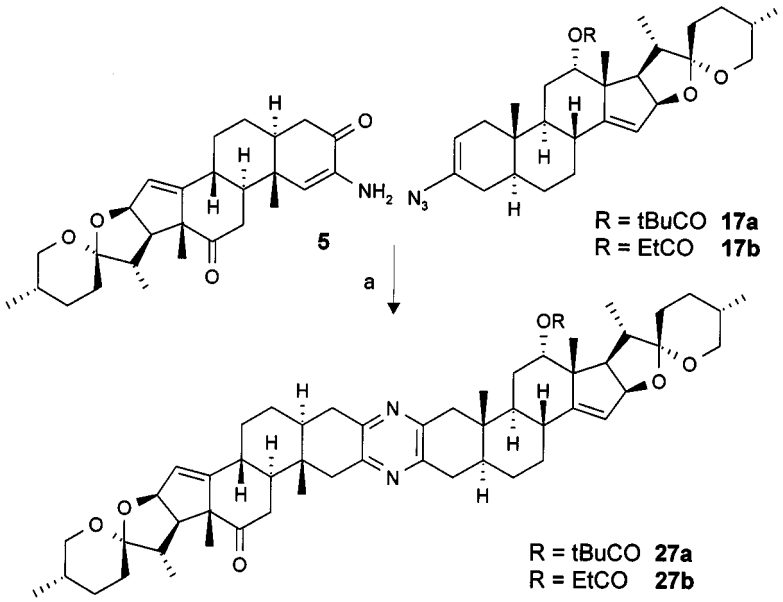
entry	base	solvent
1	KHMDS	toluene
2	KHMDS	THF
3	LiHMDS	THF
4	LDA	THF
5	KOH	MeOH
6	NaOEt	THF
7	KOtBu	THF
8	NaH	THF
9	P_2-Et	toluene

action to proceed best when the azirine is formed in a thermal process (Table 3).

The two pyrazines (**27a/b**) were compared with the corresponding products obtained by the symmetrical route, involving selective reduction to the α-hydroxy ketone **7a** (cf. Scheme 5), followed by esterification with pivaloyl chloride or propionic anhydride, respectively, and they proved to be identical.

With the thus established versatile method for the preparation of non-symmetrical bis-steroidal pyrazines at hand, we looked for alternative and highly functionalized natural materials as coupling compounds for the generation of simple Cephalostatin analogues. Since vinyl azide **17b** is easily

Scheme 16. Non-symmetric coupling reaction

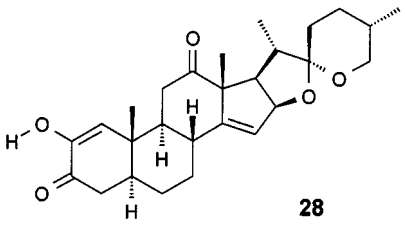


a) Δ or hν, solvent, water scavenger (see Table 3).

fact that the enamino ketone **5** as well as the vinyl azide **17a/b** are incapable of forming homodimers.

In order to obtain reproducible results in the pyrazine synthesis, the proper choice of the reaction conditions turned out to be crucial. If any water is present, the enamino ketone **5** can easily undergo hydrolysis to yield enol ketone **28** (Scheme 17)[42].

Scheme 17



The reaction system is also sensitive to both temperature and the vinyl azide/enamino ketone ratio. We found the re-

prepared, we decided to focus on the preparation of new enamino ketones bearing a double bond in the 14,15-position of the steroidal skeleton.

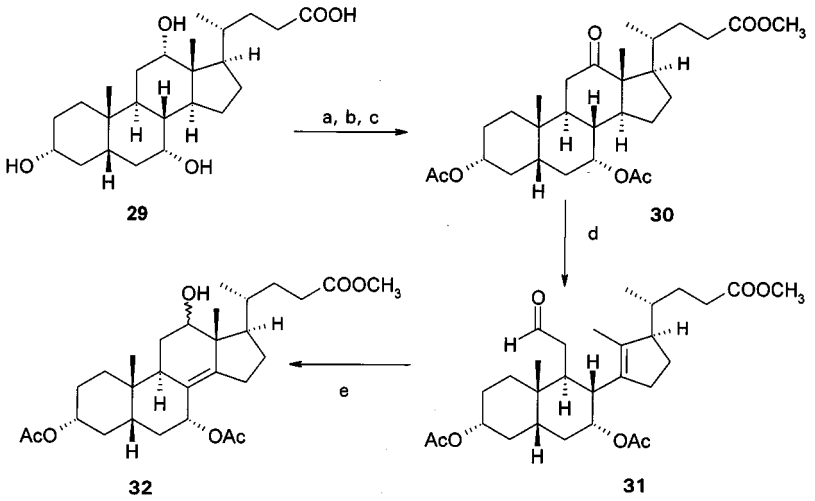
The family of the bile acids offers interesting functionalization, both due to their carboxylic acid side chains and their highly hydroxylated skeletons. This and the *cis* configuration of the rings A and B, which results in a different geometrical substructure, enables the bile acids to participate well in enterohepatic circulation in the body. For example, the complete bile acid pool of a human being of approx. 4 g is resorbed and resecreted up to 14 times every day. This has led to the pharmaceutical use of bile acid derivatives as liver targeting agents[29]. Moreover, with the crucial 12α-hydroxy group already being present, we were hoping for the easy introduction of the $\Delta^{14,15}$ double bond into the steroidal system using the Bladon procedure[12] (Scheme 18).

Esterification of the side chain of cholic acid (**29**) with the ion-exchange resin Amberlyst 15 in methanol quantita-

Table 3. Studies on the coupling reaction

entry	starting material	conditions	yield [%]
1	**16a**	dioxane, molecular sieves 3 Å, 1.0 equiv. **5**, 100°C, 90 min	51
2	**16b**	toluene, molecular sieves 3 Å, 1.2 equiv. **5**, 110°C, 2 h	36
3	**16b**	dioxane, DCCI, 1.2 equiv. **5**, 100°C, 2 h	13
4	**16b**	cyclohexane, molecular sieves 3 Å, 1.5 equiv. **5**, hν, 90 min	32
5	**16b**	pentane, dichloromethane, molecular sieves 3 Å, 1.8 equiv. **5**, hν, 90 min	29
6	**16b**	dioxane, molecular sieves 3 Å, 1.8 equiv. **5**, hν, 60 min	decomp.

Scheme 18



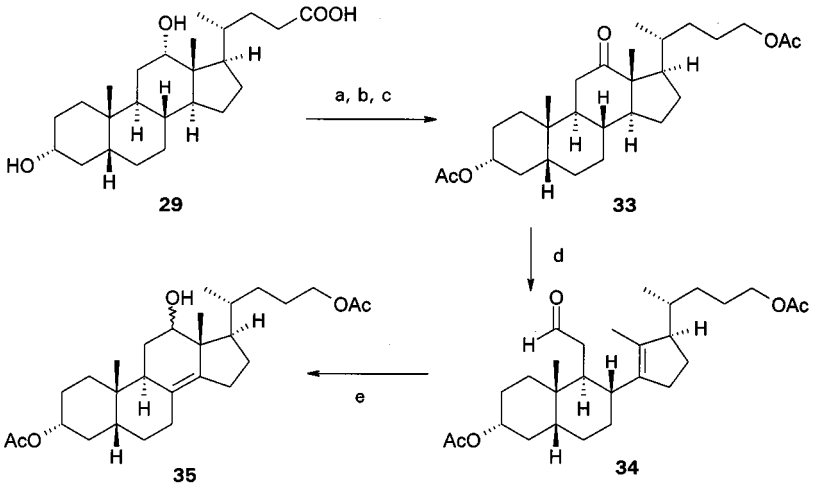
a) Amberlyst 15, methanol, r.t., 12 h, 99%. − b) Ac_2O, pyridine, toluene, r.t., 36 h, 70%. − c) PCC, silica gel, NaOAc, dichloromethane, r.t., 4 h, 95%. − d) hν, degassed dioxane, r.t., 90 min., 43%. − e) $BF_3 \cdot Et_2O$, toluene, 0°C, 30 min, 49%.

tively afforded methyl cholate[30]. Regioselective acylation at the 3- and 7-positions, followed by PCC oxidation of the remaining 12-alcohol function gave the 12-ketone **30** in a yield of 67% over the two steps. Exposure of a solution of **30** in absolute, degassed dioxane to UV light through a quartz glass filter gave a mixture of the expected aldehyde **31** and a second compound, which intrigued us owing to the appearance of signals of two olefinic carbon atoms in the ^{13}C-NMR spectrum, despite the fact that no olefinic hydrogen was seen in the ^{1}H-NMR spectrum. Moreover, exposure to UV light for longer periods of time, or treatment of aldehyde **31** with Lewis acids such as boron trifluoride−diethyl ether in toluene gave, besides decomposition products, exclusively this compound. The ^{13}C-DEPT spectrum showed the two olefinic carbon atoms to be quaternary, with the mass of the new compound being exactly in agreement with that of the expected $\Delta^{14,15}$ compound. This could only be explained in terms of the generation of the $\Delta^{8,14}$ or $\Delta^{8,9}$ isomers. A more comprehensive survey of the literature revealed that other groups had already obtained the corresponding $\Delta^{8,14}$ isomers of similar steroidal ketones derived from desoxycholic acid by irradiation with UV light through a Pyrex filter in dichloromethane for 4 h[31]. We therefore assigned this second compound as the $\Delta^{8,14}$ isomer **32**. Since we had explained the stereochemical outcome of the oxa-ene reaction leading to homoallylic alcohol **3** from hecogenine acetate (**2**) in terms of steric interactions with substituents on the β-face of the molecule[32], the 7α-acetate on aldehyde **31** could have been one reason for the different outcome of this reaction. We therefore resynthesized ketone **33** previously used by Habermehl and Hamann[31], and exposed it to UV light as before so as to generate aldehyde **34** (Scheme 19).

As this compound again gave rise to the $\Delta^{8,14}$ product upon treatment with a Lewis acid in toluene, we concluded that the different behavior of aldehydes **31** and **34** compared to the hecogenine case must be due to the A,B-*cis* configuration or the different substitution pattern on the D ring rather than to the 7-substituent.

Since we were unable to establish the $\Delta^{14,15}$ double bond using the Bladon procedure, we sought an alternative method for its introduction. Apocholic acid is known to undergo partial rearrangement to its $\Delta^{14,15}$ isomer upon exposure to dry hydrogen chloride in chloroform[33][34]. As apocholic acid methyl ester (**36**) can be prepared in good yield from cheap cholic acid (**29**) in two steps by treatment with a strong Lewis acid such as zinc(II) chloride[35], we expected to be able to produce synthetically useful amounts of the $\Delta^{14,15}$ isomer **37** (Scheme 20).

Scheme 19

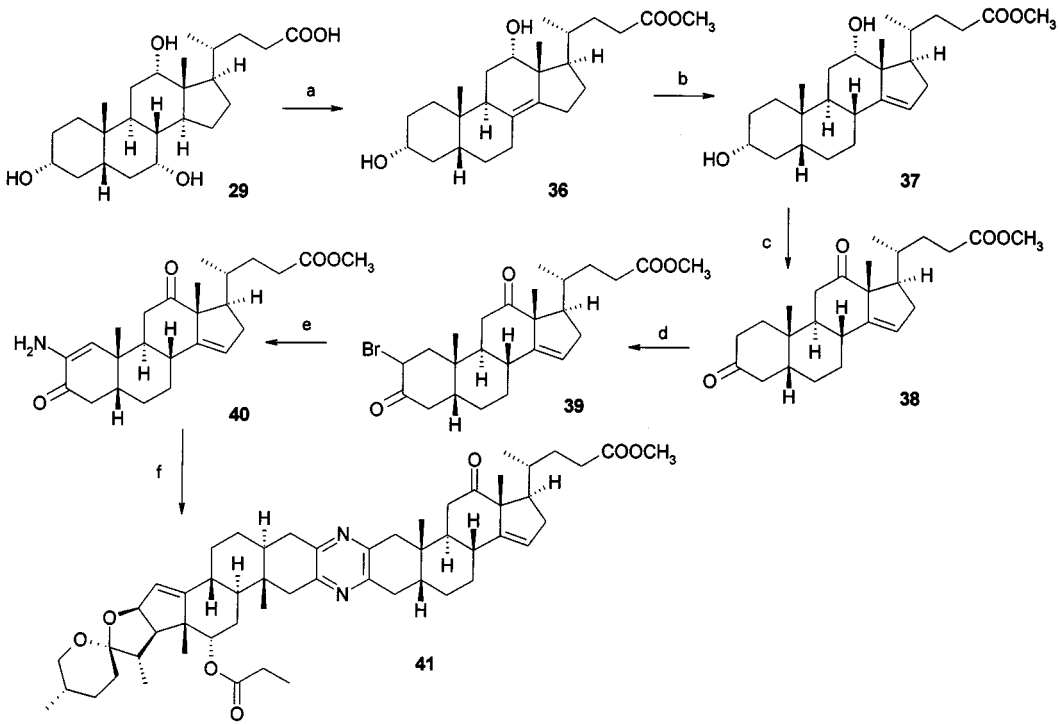


a) LAH, THF, reflux, 3 h, 70%. − b) Ac_2O, dioxane, pyridine, r.t., 24 h, 64%, − c) PCC, silica gel, NaOAc, dichloromethane, r.t., 3 h, 72%. − d) hν, degassed dioxane, r.t. 90 min., 40%. − e) $BF_3 \cdot Et_2O$, toluene, 0°C, 2 h, 42%.

The yield of the double bond rearrangement to diol **37** could be improved to 55% by conducting the reaction at low temperature. Diol **37** was oxidized using PCC to yield diketone **38**. However, the subsequent bromination could not be conducted as in the hecogenine case (cf. Scheme 3), since 3-oxo-5β-steroids are known to yield solely the 4-substituted product upon bromination due to the lower kinetic stability of the 2-enolate compared to the 4-enolate (Scheme 21).

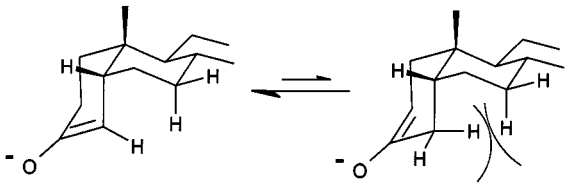
2-Bromo-3-oxo-5β-steroids are nevertheless available, either by thermodynamic bromination using phenylselenyl bromide over extended periods of time[36] or by 2,4-dibromination of the ketone and subsequent selective reduction using triphenylphosphane[37][38]. We chose the former

Scheme 20



a) i. $ZnCl_2$, acetone, 70°C, 3 h, 75%; ii. Amberlyst 15, methanol, r.t., 12 h, 99%. − b) HCl, chloroform, −78°C, 2 h, 55%. − c) PCC, silica gel, NaOAc, dichloromethane, r.t., 4 h, 81%. − d) PhSeBr, ethyl acetate, r.t., 9 d, 29% based on recovered starting material 50%). − e) NaN_3, NaI, DMF, 65°C, 2 h, 81%. − f) PPTs, 3-Å molecular sieves, dioxane, reflux, 2.5 h, 30%.

Scheme 21



method, which unfortunately yielded only a 1:1:1 mixture of starting material and the 2- and 4-bromides after 4 days in ethyl acetate at ambient temperature. Using the known procedure, the 2-bromo ketone **39** was transformed into the enamino ketone **40** in good yield and could be coupled with vinyl azide **17b** by the above method to give acceptable yields of dimer **41**. Finally, the biological evaluation of **41** as well as of the corresponding carboxylic acid showed, much to our disappointment, no significant activity[39]. We attribute this lack of biological activity to the tremendously altered three-dimensional molecular profile of dimer **41** (Figure 1)[40] compared to other analogues synthesized in our laboratories such as **7a** (Figure 2)[10].

This angular shape is mainly due to the characteristic *cis* relationship of the rings A and B of cholic acid, and the negative results in our activity tests indicate quite clearly the importance of a planar molecule as depicted in Figure 2.

Figure 1. Three-dimensional shape of dimer **41**

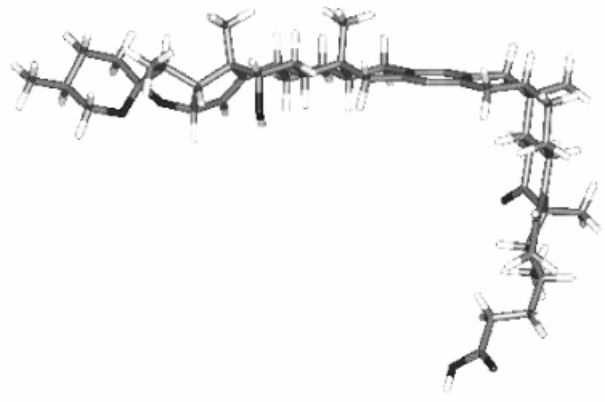
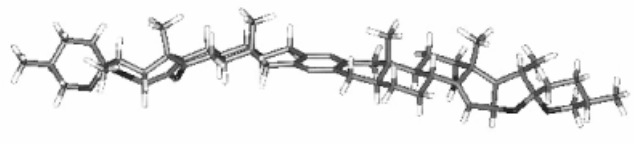


Figure 2. Three-dimensional shape of dimer **7a**



Fortunately, there are protocols in the literature for the AB-*cis*/AB-*trans* isomerization. This problem has been addressed in the meantime and we have made significant progress in the synthetic work on the corresponding *trans* isomers of cholic acid. Our results will be reported in due course.

We thank the *Deutsche Forschungsgemeinschaft* for two fellowships − "Graduiertenkolleg: Chemische und technische Grundlagen der Naturstofftransformation" (M. D., T. F.) −, the *Fonds der Chemischen Industrie* for a fellowship (R. J.), and Mr. *R. Christ* of the *Gesellschaft für Biotechnologische Forschung (GBF)*, Braunschweig, for support in obtaining the high-resolution FAB measurements.

Experimental Section

Melting points were determined with a Gallenkamp MPD 350 apparatus and are uncorrected. − NMR spectra were recorded with Bruker AM 400 or WP 200 instruments with Me_4Si or $CHCl_3$ (in $CDCl_3$) as internal standards: chemical shift signals (δ) are quoted as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quadruplet), m (multiplet), or br (broad). Methyl protons and all protons downfield of δ = 2.0 are reported. Other steroidal proton signals in the range δ = 0.7−2.0 are not reported since they are of no analytical value. ^{13}C-NMR data were recorded as DEPT or APT spectra. Carbon signals in DEPT spectra are reported as: s (C), d (CH), t (CH_2), q (CH_3), while carbon signals in APT spectra are reported as: + (C or CH_2) and − (CH or CH_3). Protons and carbon atoms are reported with position numbers according to standard steroid numbering. − IR spectra were recorded with Perkin-Elmer 580 and FT 1710 spectrometers and are reported as follows: s (strong), m (medium), w (weak) and br (broad). − UV spectra were obtained with a Beckman Model 3600 spectrophotometer and are reported as follows: s (strong) and sh (shoulder). − Mass spectra (MS) were recorded with a MAT 312 (Finnigan) at an ionization potential of 70 eV. High-resolution mass spectra (HRMS) were recorded using the peak-matching method with a VG Autospec spectrometer. Fast-atom bombardment mass spectra (FAB) were recorded with a VG Autospec spectrometer in an *m*-nitrobenzyl alcohol matrix. High-resolution fast-atom bombardment mass spectra (HRFAB) were recorded with an MAT 95 (Finnigan) instrument at the Gesellschaft für Biotechnologische Forschung (GBF, Braunschweig). − Elemental analyses (EA) were performed with CHN-Rapid (Heraeus) or varioEL (elementar Analysensysteme GmbH) instruments.

All reactions were monitored by thin-layer chromatography (TLC) carried out on DC-Alufolien Kieselgel $60F_{254}$ (Merck), with detection by UV light (λ = 254 nm) followed by treatment with cerium(IV) sulfate/phosphomolybdic acid and heating. Baker silica gel (particle size 0.03−0.06 mm) was used for flash column chromatography. Reagents were used as received. All reactions were carried out under argon in freshly distilled solvents under anhydrous conditions unless otherwise noted (no argon). Dry solvents were prepared by standard methods.

Enedione **3b**: For original preparation, see ref.[42]; we report herein a substantially improved procedure and complete spectroscopic data. A solution of homoallylic alcohol **2** (7.053 g, 14.92 mmol) and potassium hydroxide (2.511 g, 44.77 mmol) in methanol/dichloromethane (1:1) (70 ml) was refluxed for 40 min (no argon). After cooling to room temperature, the mixture was washed with water and brine and the combined aqueous layers were extracted with dichloromethane. The combined organic layers were dried with magnesium sulfate and concentrated to afford crude enediol **3a** as a white, crystalline solid. A sample of the crude material was recrystallized from petroleum ether/diethyl ether to afford pure material for characterization. − $C_{27}H_{42}O_4$; m.p. 175°C. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (d, $J_{27\text{-}25}$ = 6 Hz, 3 H, 27-H), 0.87 (s, 3 H, 19-H), 1.00 (d, $J_{21\text{-}20}$ = 6.5 Hz, 3 H, 21-H), 1.12 (s, 3 H, 18-H), 2.15 (m, 1 H, 8-H), 2.64 (dd, $J_{17\text{-}21}$ = 9.5 Hz, $J_{17\text{-}16}$ = 8 Hz, 1 H, 17-H), 3.43 (t, $J_{26a\text{-}25,26b}$ = 11 Hz, 1 H, 26a-H), 3.49 (br dd, $J_{26b\text{-}26a}$ = 11 Hz, $J_{26b\text{-}25}$ = 4.5 Hz, 1 H, 26b-H), 3.58 (tt,

$J_{3\text{-}2b,4b}$ = 10.5 Hz, $J_{3\text{-}2a,4a}$ = 5.5 Hz, 1 H, 3-H), 3.70 (m, 1 H, 12-H), 4.87 (dd, $J_{16\text{-}17}$ = 8 Hz, $J_{16\text{-}15}$ = 1.5 Hz, 1 H, 16-H), 5.54 (br s, 1 H, 15-H). − ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 11.8/14.1/17.1/18.3 (all −, 18/19/21/27-C), 28.1 (+), 28.4 (+), 28.7 (+), 29.4 (+), 30.0 (−), 30.8 (+), 31.2 (+), 33.9 (−), 35.3 (+, 10-C), 36.3 (+), 38.1 (+), 44.1 (−), 44.3 (−), 48.9 (−), 51.2 (+, 13-C), 52.8 (−), 66.1 (+, 26-C), 69.3 (−, 3-C), 74.7 (−, 12-C), 85.0 (−, 16-C), 105.5 (+, 22-C), 119.9 (−, 15-C), 153.1 (+, 14-C). − MS (160°C): *m/z* (%) = 430 [M$^+$] (57), 413 [M$^+$ − OH] (39), 315 (100), 297 (54), 286 (46), 126 (89). − IR (KBr): ν_{max} = 3436 cm^{-1} s br (O−H), 3058 w (alkene H), 2928 s (C−H), 2860 s (C−H), 1650 w (C=C), 1460 m (C−H), 1377 m (C−H), 1243 m (C−O). − HRMS: calcd. 430.3083; found 430.3071. − EA: calcd. C 75.31, H 9.83; found C 75.05, H 9.86. − Pyridinium chlorochromate (7.98 g, 37.03 mmol) and silica gel (8.0 g) were suspended in dichloromethane (100 ml) and stirred vigorously for 30 min. at room temperature (no argon). Sodium acetate (200 mg, 2.44 mmol) and crude enediol **3a** (7.389 g) were then added. After 16 h, the solid components were removed by filtration and the solvent was removed from the filtrate in vacuo. Short flash column chromatography (petroleum ether/ethyl acetate, 2:1) gave enedione **3b** (5.980 g, 95% from homoallylic alcohol **2**, 14.018 mmol). − $C_{27}H_{38}O_4$; m.p. 215°C (decomp.; after recrystallization from diethyl ether). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (d, $J_{27\text{-}25}$ = 6.5 Hz, 3 H, 27-H), 1.05 (d, $J_{21\text{-}20}$ = 7 Hz, 3 H, 21-H), 1.13 (s, 3 H, 19-H), 1.32 (s, 3 H, 18-H), 2.03 (m, 1 H, 7b-H), 2.18 (br dd, $J_{4a\text{-}4b}$ = 15 Hz, $J_{4a\text{-}5}$ = 4 Hz, 1 H, 4a-H), 2.28 (dd, $J_{4b\text{-}4a}$ = 15 Hz, $J_{4b\text{-}5}$ = 13.5 Hz, 1 H, 4b-H), 2.38 (dd, $J_{11a\text{-}11b}$ = 14.5 Hz, $J_{11a\text{-}9}$ = 5 Hz, 1 H, 11a-H), 2.34−2.43 (further 2 H, 2a/2b-H), 2.52 (br t, $J_{8\text{-}7a,9}$ = 10.5 Hz, 1 H, 8-H), 2.65 (dd, $J_{11b\text{-}11a}$ = 14.5 Hz, $J_{11b\text{-}9}$ = 13.5 Hz, 1 H, 11b-H), 3.34 (dd, $J_{17\text{-}20}$ = 9 Hz, $J_{17\text{-}16}$ = 8 Hz, 1 H, 17-H), 3.41 (t, $J_{26a\text{-}25,26b}$ = 11 Hz, 1 H, 26a-H), 3.52 (ddd, $J_{26b\text{-}26a}$ = 11 Hz, $J_{26b\text{-}25}$ = 4 Hz, $J_{26b\text{-}24x}$ = 2 Hz, 1 H, 26b-H), 4.77 (dd, $J_{16\text{-}17}$ = 8 Hz, $J_{16\text{-}15}$ = 2 Hz, 1 H, 16-H), 5.47 (br s, 1 H, 15-H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.0/13.7/17.1/20.9 (all −, 18/19/21/27-C), 28.2 (+), 28.7 (+), 29.1 (+), 30.2 (−), 31.2 (+), 34.0 (−), 36.3 (+), 37.3 (+), 37.76 (+), 37.72 (+), 44.1 (−), 44.3 (−), 45.7 (−), 49.7 (−), 53.0 (−), 62.2 (+, 13-C), 67.0 (+, 26-C), 83.8 (−, 16-C), 107.0 (+, 22-C), 121.3 (−, 15-C), 154.1 (+, 14-C), 210.4/210.6 (both +, 3/12-C). − MS (160°C): *m/z* (%) = 426 [M$^+$] (40), 408 (12), 356 (15), 311 (100), 297 (34), 148 (21), 126 (85). − IR (KBr): $\tilde{\nu}_{max}$ = 3070 cm^{-1} w (alkene H), 2929 s (C−H), 2872 m (C−H), 1713 s (C=O), 1645 w (C=C), 1459 m (C−H), 1376 m (C−H), 1243 m (C−O). − HRMS: calcd. 426.2770; found 426.2772. − EA: calcd. C 76.02, H 8.98; found C 76.02, H 8.93.

Bromo Ketone **4**: For original preparation see ref.[11]. We report here an improved procedure and completed spectroscopic data. A cold (0°C) solution of trimethyl(phenyl)ammonium perbromide (48.86 g, 126.08 mmol) in dry THF (400 ml) was added dropwise over a period of 3 h to a solution of enedione **3b** (51.224 g, 120.08 mmol) in dry THF (800 ml) also at 0°C. After a further 40 min, the reaction was quenched by the addition of 0.5 M sodium hydrogen carbonate solution (1000 ml). The aqueous layer was extracted with diethyl ether and the combined organic layers were washed with 0.5 M sodium hydrogen carbonate solution and brine, dried with sodium sulfate, and concentrated in vacuo to afford, after recrystallization from diethyl ether/petroleum ether, bromo ketone **4** (49.442 g, 81%, 97.81 mmol) as a white, crystalline product. − $C_{27}H_{37}O_4Br$; m.p. 189°C (after recrystallization from methanol). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (d, $J_{27\text{-}25}$ = 6 Hz, 3 H, 27-H), 1.04 (d, $J_{21\text{-}20}$ = 7 Hz, 3 H, 21-H), 1.21 (s, 3 H, 19-H), 1.31 (s, 3 H, 18-H), 2.04 (m, 1 H, 9-H), 2.38 (dd, $J_{11a\text{-}11b}$ = 14.5 Hz, $J_{11a\text{-}9}$ = 4.5 Hz, 1 H, 11a-H), 2.46−2.54 (m, 4 H, 1a/4a/4b/8-H), 2.65 (dd, $J_{11b\text{-}11a}$ = 14.5 Hz, $J_{11b\text{-}9}$ = 13.5 Hz, 1 H, 11b-H), 3.33 (dd, $J_{17\text{-}20}$ = 9 Hz, $J_{17\text{-}16}$ = 8 Hz, 1 H, 17-H), 3.40 (t, $J_{26a\text{-}25,26b}$ = 11 Hz, 1 H, 26a-H), 3.52 (ddd, $J_{26b\text{-}26a}$ = 11 Hz, $J_{26b\text{-}25}$ = 4 Hz, $J_{26b\text{-}24x}$ = 2 Hz, 1 H, 26b-H), 4.72 (dd, $J_{2\text{-}1a}$ = 13.5 Hz, $J_{2\text{-}1b}$ = 6 Hz, 1 H, 2-H), 4.76 (dd, $J_{16\text{-}17}$ = 8 Hz, $J_{16\text{-}15}$ = 2 Hz, 1 H, 16-H), 5.48 (br s, 1 H, 15-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8/13.8/17.1/20.9 (all q, 18/19/21/27-C), 27.7 (t), 28.7 (t), 28.9 (t), 30.3 (d), 31.2 (t), 33.6 (t), 37.3 (t), 39.3 (s, 10-C), 43.6 (t), 44.1 (d), 46.6 (d), 49.8 (d), 50.7 (t), 52.6 (d), 53.2 (d), 62.3 (s, 13-C), 67.1 (t, 26-C), 83.8 (d, 16-C), 107.1 (s, 22-C), 121.8 (d, 15-C), 153.5 (s, 14-C), 200.0 (s, 3-C), 211.5 (s, 12-C). − IR (KBr): $\tilde{\nu}_{max}$ = 3060 cm^{-1} w (alkene H), 2928 s (C−H), 2872 m (C−H), 1730 s (C=O), 1713 s (C=O), 1651 w (C=C), 1456 m (C−H), 1376 m (C−H), 1243 m (C−O). − MS (160°C): *m/z* (%) = 506 [M$^+$] [^{35}Br^{81}] (25), 504 [M$^+$] [^{35}Br^{79}] (27), 488/486 (14/15), 392/390 (69/64), 377/375 (21/23), 311 (28), 126 (100). − HRMS: calcd. 504.1875 for M$^+$ [^{35}Br^{79}]; found 504.1872.

Enamino Ketone **5**: For original preparation, see ref.[11]; we report here an improved procedure and complete spectroscopic data. Bromo ketone **4** (3.70 g, 7.32 mmol) was dissolved in 200 ml of dimethylformamide and then sodium azide (5.18 g, 79.7 mmol, 11 equiv.) and a few mg of sodium iodide were added. The suspension was stirred for 1 h at 50°C under argon. The reaction was then quenched by the addition of 100 ml of water and the mixture was extracted with methyl *tert*-butyl ether/hexanes (2:1). The combined extracts were washed with brine and dried with Na_2SO_4. The resulting 3.39 g of a yellow solid was recrystallized from diethyl ether/hexanes to yield 2.91 g (91%) of enamino ketone (**5**). − $C_{27}H_{37}NO_4$. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.86 (s, 1 H), 5.41 (t, *J* = 2 Hz, 1 H), 4.71 (dd, *J* = 2 Hz, *J* = 8 Hz, 1 H), 3.34 (m, 4 H), 2.50 (m, 5 H), 1.30 (s, 3 H), 1.10 (s, 3 H), 1.01 (d, *J* = 7 Hz, 3 H), 0.79 (d, *J* = 6 Hz, 3 H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.44 (q), 13.76 (q), 17.14 (q), 21.22 (q), 26.78 (t), 28.74 (t), 28.99 (t), 30.29 (d), 31.22 (t), 34.44 (d), 37.43 (t), 38.49 (s), 39.96 (t), 44.12 (d), 44.20 (d), 49.91 (d), 50.61 (d), 62.33 (s), 67.09 (t, 26-C), 83.83 (d, 16-C), 107.14 (s, 22-C), 121.33 (d, 15-C), 123.24 (d, 1-C), 138.33 (s, 2-C), 154.23 (s, 14-C), 194.95 (s, 3-C), 210.48 (s, 12-C). − IR (KBr): $\tilde{\nu}_{max}$ = 3452 cm^{-1} s, 3368 m, 3060 s, 1708 vs, 1676 s, 1628 m. − UV (MeOH): λ = 214, 290. − MS (210°C): *m/z* (%) = 439 [M$^+$] (25), 325 (35), 310 (19), 136 (25), 126 (19). − HRMS: calcd. 439.2723 for M$^+$; found 439.2708.

Enamino Ketone **9**: $C_{21}H_{31}NO_3$. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (s, 3 H), 0.99 (s, 3 H), 2.05 (s, 3 H), 0.60−2.55 (m, 19 H), 4.61 (dd, *J* = 9 Hz, *J* = 8 Hz, 1 H), 6.1 (s, 1 H). − IR (KBr): $\tilde{\nu}_{max}$ = 3460 cm^{-1}, 3370, 1720, 1670, 1630, 1580, 1440, 1370, 1250, 1040, 1032. − MS (EI, 160°C): *m/z* (%) = 346 (25), 344 (87), 329 (100), 316 (10), 288 (19), 270 (9), 176 (11), 136 (77), 122 (85). − HRMS: calcd. 344.2226; found 344.2225.

Diketone **6**: For original preparation see ref.[11]; we report here an improved procedure and complete spectroscopic data. A suspension of 5% palladium on barium sulfate (588 mg, 0.27 mmol Pd) in methanol (5 ml) was saturated with hydrogen. Then, a solution of enamino ketone **5** (1.381 g, 3.14 mmol) in methanol (22 ml) was added and hydrogenated under a slight positive hydrogen pressure for 4 h at room temperature. The catalyst was then removed by filtration through silica gel, eluting with dichloromethane/methanol (9:1). The eluate was concentrated and the residue was recrystallized from diethyl ether to afford diketone **6** (930 mg) as a white, crystalline solid. The mother liquor was concentrated and yielded after column chromatography a further 32 mg of the product, making a total yield of 962 mg of diketone **6** (73%, 1.14 mmol). − $C_{54}H_{72}N_2O_6$; m.p. >300°C (after recrystallization from ethyl acetate). − ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD, 5:1): δ = 0.82 (d,

$J_{27\text{-}25}$ = 6.5 Hz, 6 H, 27-H), 0.95 (s, 6 H, 19-H), 1.05 (d, $J_{21\text{-}20}$ = 7 Hz, 6 H, 21-H), 1.35 (s, 6 H, 18-H), 2.10 (m, 2 H), [2.46 (dd, J = 14.5 Hz, J = 4.5 Hz, 2 H), 2.51−2.55 (m, 4 H, 8-H), 2.65 (br dd, J = 18 Hz, J = 12.5 Hz, 2 H), 2.74−2.83 (m, 4 H), 2.88 (dd, J = 18 Hz, J = 5.5 Hz, 2 H); region 2.44−2.91 total 14 H, 8 × benzyl-H/2 × 8-H/4 × 11-H)], 3.36 (dd, $J_{17\text{-}20}$ = 9 Hz, $J_{17\text{-}16}$ = 8 Hz, 2 H, 17-H), 3.42 (t, $J_{26a\text{-}25,26b}$ = 11 Hz, 2 H, 26a-H), 3.53 (br d, $J_{26b\text{-}26a}$ = 11 Hz, 1 H, 26b-H), 4.79 (dd, $J_{16\text{-}17}$ = 8 Hz, $J_{16\text{-}15}$ = 2 Hz, 2 H, 16-H), 5.49 (br s, 2 H, 15-H). − ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$, 5:1): δ = 11.5/13.6/17.0/20.7 (all q, 18/19/21/27-C), 27.7 (t), 28.6 (t), 29.1 (t), 30.2 (d), 31.1 (t), 33.9 (d), 34.8 (t), 36.3 (s, 10-C), 37.2 (t), 41.0 (d), 44.1 (d), 44.8 (t), 49.7 (d), 53.1 (d), 62.3 (s, 13-C), 67.1 (t, 26-C), 84.0 (d, 16-C), 107.2 (s, 22-C), 121.5 (d , 15-C), 148.37/148.43 (s, 2/3-C), 154.2 (s, 14-C), 211.3 (s, 12-C). − IR (KBr): $\tilde{\nu}_{max}$ = 2928 cm^{-1} s (C−H), 2873 m (C−H), 1714 s (C=O), 1646 w (C=C), 1456 m (C−H), 1399 m (pyrazine), 1374 m (C−H), 1243 m (C−O). − UV (MeOH): λ = 288, 305 (sh). − FAB (monoisotopic mass 844.5390): *m/z* (%) = 846 [MH^+] (35), 732 (10), 391 (9), 154 (NBA matrix, 100%). − EA: calcd. C 76.74, H 8.59, N 3.31; found C 76.50, H 8.67, N 3.31.

β-Hydroxy Ketone **7b** *and β-Diol* **8b**: For original preparation see ref.[11]; we report here a different approach and complete spectroscopic data. To a cooled solution (−78°C) of diketone **6** (100 mg, 0.118 mmol) in dichloromethane/methanol 1:1 (3 ml) was added powdered sodium tetrahydroborate (20 mg, 0.53 mmol) under vigorous stirring. After 30 min, the reaction was quenched by slow addition of acetaldehyde (0.2 ml, 3.58 mmol). After warming to room temperature, the mixture was washed with saturated ammonium chloride solution and water, and the combined aqueous layers were extracted with dichloromethane. The combined organic layers were dried with sodium sulfate and concentrated in vacuo. Flash column chromatography (dichloromethane/methanol, 30:1) gave the starting diketone **6** (42 mg, 42%, 0.050 mmol), β-hydroxy ketone **7b** (47 mg, 47%, 0.055 mmol), and β-diol **8b** (7 mg, 7%, 0.008 mmol), all as white, crystalline solids.

7b: $C_{54}H_{74}N_2O_6$; m.p. >300°C (after recrystallization from ethyl acetate). − ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$, 5:1): δ = 0.82 (d, $J_{27'\text{-}25'}$ = 6 Hz, 3 H, 27′-H), 0.83 (d, $J_{27\text{-}25}$ = 6 Hz, 3 H, 27-H), 0.87 (s, 3 H, 19-H), 0.94 (s, 3 H, 19′-H), 1.03 (s, 3 H, 8-H), 1.05 (d, $J_{21\text{-}20}$ = 7 Hz, 3 H, 21-H), 1.06 (d, $J_{21'\text{-}20'}$ = 7 Hz, 3 H, 21′-H), 1.35 (s, 3 H, 18′-H), 2.04−2.11 (m, 2 H, 8-H and other H), [2.43−2.57 (m, 5 H), 2.59−2.68 (m, 2 H), 2.74−2.92 (m, 5 H); region 2.43−2.92 total 12 H, 8 × benzyl-H/8′-H/2 × 11′-H/17-H], 3.21 (dd, $J_{12\text{-}11b}$ = 11 Hz, $J_{12\text{-}11a}$ = 4.5 Hz, 1 H, 12-H), 3.34−3.54 (m, 5 H, 17′/26/26′-H), 4.79 (dd, $J_{16'\text{-}17'}$ = 8 Hz, $J_{16\text{-}15}$ = 2 Hz, 1 H, 16′-H), 4.88 (dd, $J_{16\text{-}17}$ = 8 Hz, $J_{16\text{-}15}$ = 2 Hz, 1 H, 16-H), 5.42 (br s, 1 H, 15-H), 5.49 (br s, 1 H, 15′-H). − ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$, 5:1): δ = 11.6/11.9/13.4/13.6/13.8/17.2 br/20.9 (all q, 18/18′/19/19′/21/21′/27/27′-C), 27.9 (t), 28.1 (t), 28.7 (t), 28.8 (t), 29.2 (t), 29.3 (t), 29.8 (t), 30.4 (d), 30.5 (d), 31.2 (t), 31.3 (t), 33.8 (d), 34.1 (d), 34.9 (t), 35.0 (t), 36.1/36.5 (both s, 10/10′-C), 37.4 (t), 41.2 (d), 41.5 (d), 44.3 (d), 44.6 (d), 44.9 (t), 45.3 (t), 49.8 (d), 52.3 (d), 53.0 (s, 13-C), 53.2 (d), 55.6 (d), 62.5 (s, 13′-C), 67.4/67.5 (both t, 26/26′-C), 78.6 (d, 12-C), 84.2/84.9 (both d, 16/16′-C), 107.2/107.4 (both s, 22/22′-C), 119.5 (d, 15-C), 121.7 (d, 15′-C), 148.3/148.4/149.1/149.2 (all s, pyrazine-C), 154.5 (s, 14′-C), 157.7 (s, 14-C), 211.6 (s, 12′-C). − IR (KBr): $\tilde{\nu}_{max}$ = 3444 cm^{-1} m br (O−H), 2928 s (C−H), 2875 m (C−H), 1715 m (C=O), 1645 w (C=C), 1456 m (C−H), 1399 s (pyrazine), 1376 m (C−H), 1243 m (C−O). − UV (MeOH): λ = 288 (s), 305 (sh). − FAB (monoisotopic mass 846.55469): *m/z* (%) = 848 [MH^+] (75), 830 [$MH^+ - H_2O$] (21), 734 (22), 391 (18), 154 (NBA matrix, 100%). − EA: calcd. C 76.56, H 8.80, N 3.31; found C 76.45, H 8.89, N 3.20.

8b: $C_{54}H_{76}N_2O_6$; m.p. >300°C (after recrystallization from ethyl acetate). − ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$, 5:1): δ = 0.82 (d, $J_{27\text{-}25}$ = 6.5 Hz, 6 H, 27-H), 0.88 (s, 6 H, 19-H), 1.03 (s, 6 H, 18-H), 1.05 (d, $J_{21\text{-}20}$ = 7 Hz, 6 H, 21-H), 2.08 (m, 2 H, 8-H), 2.49−2.66 (m, 6 H, 4 × benzyl-H/2 × 17-H), 2.79−2.93 (m, 4 H, benzyl-H), 3.21 (dd, $J_{12\text{-}11b}$ = 11 Hz, $J_{12\text{-}11a}$ = 4.5 Hz, 2 H, 12-H), 3.45 (t, $J_{26a\text{-}25,26b}$ = 11 Hz, 2 H, 26a-H), 3.52 (br d, $J_{26b\text{-}26a}$ = 11 Hz, 1 H, 26b-H), 4.88 (dd, $J_{16\text{-}17}$ = 8 Hz, $J_{16\text{-}15}$ = 1.5 Hz, 2 H, 16-H), 5.42 (br s, 2 H, 15-H). − ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$, 5:1): δ = 11.9/13.4/13.6/17.2 (all q, 18/19/21/27-C), 28.1 (t), 28.8 (t), 29.3 (t), 29.9 (t), 30.5 (d), 31.2 (t), 33.9 (d), 35.0 (t), 36.1 (s, 10-C), 41.5 (d), 44.7 (d), 45.3 (t), 52.3 (d), 52.9 (s, 13-C), 55.7 (d), 67.4 (t, 26-C), 78.6 (d, 12-C), 84.9 (d, 16-C), 107.1 (s, 22-C), 119.6 (d, 15-C), 148.8/149.0 (both s, pyrazine-C), 157.7 (s, 14-C). − IR (KBr): $\tilde{\nu}_{max}$ = 3448 cm^{-1} m br (O−H), 3056 w (alkene H), 2928 s (C−H), 2872 s (C−H), 1640 w (C=C), 1456 m (C−H), 1396 s (pyrazine), 1372 m (C−H), 1240 m (C−O). − UV (MeOH): λ = 288 (s), 305 (sh). − FAB (monoisotopic mass 848.57033): *m/z* (%) = 850 [MH^+] (100), 154 (34, NBA matrix). − EA: calcd. C 76.38, H 9.02, N 3.30; found C 76.30, H 9.29, N 3.04.

α-Hydroxy Ketone **7a** *and α-Diol* **8a**: To a cooled solution (−78°C) of diketone **6** (52 mg, 0.062 mmol) in dry toluene (5 ml), a 0.7 M solution of lithium hydrotris(isobutyl)borate in dry toluene (0.06 ml, 0.042 mmol) was added dropwise. After 1 h at −78°C, the reaction was quenched by the addition of saturated ammonium chloride solution (2 ml). After warming to room temperature, the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulfate, and concentrated, and afforded after flash column chromatography (petroleum ether/ethyl acetate, 3:2) the starting diketone **6** (20.8 mg, 40%, 0.025 mmol), α-hydroxy ketone **7a** (25.1 mg, 49%, 0.030 mmol) and α-diol **8a** (4.0 mg, 8%, 0.005 mmol), all as colorless, crystalline solids. The same procedure with 50 mg (0.059 mmol) of diketone **6** and 0.24 ml (0.168 mmol) of the 0.7 M solution of lithium hydrotris(isobutyl)borate in dry toluene gave only the α-diol **8a** (49 mg, 98%, 0.058 mmol).

7a: $C_{54}H_{74}N_2O_6$; m.p. >300°C (after recrystallization from ethyl acetate). − ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$, 5:1): δ = 0.82 (d, $J_{27\text{-}25}$ = 6 Hz, 6 H, 27/27′-H), 0.87 (s, 3 H, 19-H), 0.94 (s, 3 H, 19′-H), 1.02 (d, $J_{21\text{-}20}$ = 7 Hz, 3 H, 21-H), 1.06 (d, $J_{21'\text{-}20'}$ = 7 Hz, 3 H, 21′-H), 1.14 (s, 3 H, 18-H), 1.35 (s, 3 H, 18′-H), 2.11 (m, 1 H), 2.44−2.89 (m, 12 H, 8 × benzyl-H/8′/11′a/11′b/17-H), 3.36 (dd, $J_{17'\text{-}20'}$ = 9 Hz, $J_{17'\text{-}16'}$ = 8 Hz, 1 H, 17′-H), 3.42−3.55 (m, 4 H, 26/26′-H), 3.77 (br s, 1 H, 12-H), 4.79 (dd, $J_{16'\text{-}17'}$ = 8 Hz, $J_{16\text{-}15}$ = 2 Hz, 1 H, 16′-H), 4.91 (dd, $J_{16\text{-}17}$ = 8 Hz, $J_{16\text{-}15}$ = 2 Hz, 1 H, 16-H), 5.49 (br s, 1 H, 15′-H), 5.53 (br s, 1 H, 15-H). − ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$, 5:1): δ = 11.6/11.9/13.8/14.2/17.2 br/18.8/20.9 (all q, 18/18′/19/19′/21/21′/27/27′-C), 27.9 (t), 28.1 (t), 28.77 (t), 28.81 (t), 29.0 (t), 29.27 (t), 29.31 (t), 30.4 (d), 30.5 (d), 31.29 (t), 31.31 (t), 34.1 (d), 34.4 (d), 34.9 (t), 35.1 (t), 35.9 (s, 10-C), 36.4 (s, 10′-C), 37.3 (t), 41.2 (d), 41.6 (d), 44.3 (d), 44.89 (d), 44.94 (t), 45.2 (t), 49.2 (d), 49.9 (d), 52.2 (s, 13-C), 53.3 (d), 53.7 (d), 62.5 (s, 13′-C), 67.3 (br, both t, 26/26′-C), 75.8 (d, 12-C), 84.2 (d, 16′-C), 85.6 (d, 16-C), 107.0/107.4 (both s, 22/22′-C), 121.1 (d, 15′-C), 121.7 (d, 15-C), 148.2/148.3/149.2/149.3 (all s, pyrazine-C), 154.0 (s, 14-C), 154.4 (s, 14′-C), 211.5 (s, 12′-C). − IR (KBr): $\tilde{\nu}_{max}$ = 3460 cm^{-1} m br (O−H), 3056 w (alkene H), 2928 s (C−H), 2872 s (C−H), 1712 s (C=O), 1652 w (C=C), 1456 m (C−H), 1396 s (pyrazine), 1376 m (C−H), 1240 m (C−O). − UV (MeOH): λ = 288, 304 (sh). − FAB (monoisotopic mass 846.55469): *m/z* (%) = 848 [MH^+] (55), 733 (19), 136 (100%, NBA matrix). EA: calcd. C 76.56, H 8.80, N 3.31; found C 76.80, H 8.81, N 3.40.

8a: $C_{54}H_{76}N_2O_6$; m.p. >300°C (after recrystallization from ethyl acetate). − ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$, 5:1): δ = 0.82 (d, $J_{27\text{-}25}$ = 6.5 Hz, 6 H, 27-H), 0.87 (s, 6 H, 19-H), 1.02 (d, $J_{21\text{-}20}$ = 7 Hz, 6 H, 21-H), 1.14 (s, 6 H, 18-H), 2.18 (br t, $J_{8\text{-}7a,9}$ = 10.5 Hz, 2 H, 8-H), 2.47−2.70 (m, 6 H, 4 × benzyl-H/2 × 17-H), 2.79−2.85 (m, 4 H, benzyl-H), 3.42−3.52 (m, 4 H, 26-H), 3.77 (br s, 2 H, 12-H), 4.91 (br d, $J_{16\text{-}17}$ = 8 Hz, 2 H, 16-H), 5.53 (br s, 2 H, 15-H). − ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$, 5:1): δ = 11.9/14.2/17.2/18.8 (all q, 18/19/21/27-C), 28.2 (t), 28.8 (t), 29.0 (t), 29.3 (t), 30.5 (d), 31.3 (t), 34.4 (d), 35.1 (t), 35.9 (s, 10-C), 41.6 (d), 44.9 (d), 45.1 (t), 49.1 (d), 52.2 (s, 13-C), 53.7 (d), 67.3 (t, 26-C), 75.7 (d, 12-C), 85.6 (d, 16-C), 106.9 (s, 22-C), 121.1 (d, 15-C), 148.8/149.0 (both s, pyrazine-C), 154.0 (s, 14-C). − IR (KBr): $\tilde{\nu}_{max}$ = 3444 cm^{-1} m br (O−H), 3056 w (alkene H), 2928 s (C−H), 2872 s (C−H), 1644 w (C=C), 1456 m (C−H), 1400 s (pyrazine), 1370 m (C−H), 1240 m (C−O). − UV (MeOH): λ = 288 (s), 305 (sh). − FAB (monoisotopic mass 848.57033): *m/z* (%) = 850 [MH$^+$] (100), 154 (34, NBA matrix). − EA: calcd. C 76.38, H 9.02, N 3.30; found C 76.50, H 9.23, N 3.04.

α,β-Diol **8c**: To a cooled solution (−78°C) of α-hydroxy ketone **7a** (104 mg, 0.123 mmol) in dichloromethane/methanol (1:1) (2 ml) was added powdered sodium tetrahydroborate (18 mg, 0.48 mmol). After 2 h of vigorous stirring, the reaction was quenched by the addition of acetone (0.5 ml). After warming to room temperature and addition of dichloromethane (10 ml), the organic layer was washed with a 0.5 M sodium hydrogen carbonate solution and water. The combined aqueous layers were extracted with ethyl acetate. The combined organic layers were dried with sodium sulfate, concentrated, and afforded after recrystallization from ethyl acetate α,β-diol **8c** (100 mg, 96%, 0.118 mmol) as a white crystalline solid. − $C_{54}H_{76}N_2O_6$; m.p. > 300°C. − ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$, 5:1): δ = 0.82 (d, $J_{27'\text{-}25'}$ = 6 Hz, 3 H, 27′-H), 0.83 (d, $J_{27\text{-}25}$ = 6 Hz, 3 H, 27-H), 0.88 (s, 6 H, 19/19′-H), 1.02 (d, $J_{21'\text{-}20'}$ = 7 Hz, 3 H, 21′-H), 1.04 (s, 3 H, 18-H), 1.05 (d, $J_{21\text{-}20}$ = 7 Hz, 3 H, 21-H), 1.14 (s, 3 H, 18′-H), 2.08 (m, 1 H, 8-H), 2.19 (m, 1 H, 8′-H), [2.43−2.70 (m, 6 H), 2.81−2.91 (m, 4 H); region 2.43−2.91 total 10 H, 8 × benzyl-H/17/17′-H], 3.22 (dd, $J_{12\text{-}11b}$ = 11 Hz, $J_{12\text{-}11a}$ = 4.5 Hz, 1 H, 12-H), 3.42−3.52 (m, 4 H, 26/26′-H), 3.77 (br s, 1 H, 12′-H), 4.88 (dd, $J_{16\text{-}17}$ = 8 Hz, $J_{16\text{-}15}$ = 1.5 Hz, 1 H, 16-H), 4.91 (dd, $J_{16'\text{-}17'}$ = 8 Hz, $J_{16\text{-}15}$ = 1.5 Hz, 1 H, 16′-H), 5.42 (br s, 1 H, 15-H), 5.53 (br s, 1 H, 15′-H). − ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$, 5:1): δ = 11.90/11.91/13.4/13.6/14.2/17.16/17.17/18.8 (all −, 18/18′/19/19′/21/21′/27/27′-C), 28.1 (+), 28.2 (+), 28.8 (+), 29.1 (+), 29.3 (+), 29.9 (+), 30.45 (−), 30.50 (−), 31.2 (+), 31.3 (+), 33.8 (−), 34.4 (−), 35.0 (+), 35.1 (+), 35.9/36.1 (both +, 10/10′-C), 41.5 (−), 41.6 (−), 45.2 (+), 45.3 (+), 49.1 (−), 52.1 (+, 13-C), 52.3 (−), 52.9 (+, 13′-C), 53.7 (−), 55.7 (−), 67.27/67.33 (both +, 26/26′-C), 75.6 (−, 12-C), 78.5 (−, 12′-C), 84.9/85.6 (both −, 16/16′-C), 106.9/107.1 (both +, 22/22′-C), 119.5 (−, 15-C), 121.1 (−, 15′-C), 148.6/148.8/148.9/149.0 (all +, pyrazine-C), 153.9 (+, 14′-C), 157.7 (+, 14-C). − IR (KBr): $\tilde{\nu}_{max}$ = 3472 cm^{-1} m br (O−H), 3056 w (alkene H), 2928 s (C−H), 2872 s (C−H), 1648 w (C=C), 1456 m (C−H), 1396 s (pyrazine), 1372 m (C−H), 1240 m (C−O). − UV (MeOH): λ = 288 (s), 305 (sh). − FAB (monoisotopic mass 848.57033): *m/z* (%) = 850 [MH$^+$] (100), 832 [MH$^+$ − H_2O] (16), 717 (12), 154 (64, NBA matrix). − EA: calcd. C 76.38, H 9.02, N 3.30; found C 76.11, H 8.97, N 3.28.

Diphenylpyrazinoandrostane **11**: A solution of 100 mg (0.52 mmol) of azirine **10**, 150 mg (0.43 mmol) of enamino ketone **9**, and 50 µl of trifluoroacetic acid in degassed THF (10 ml) was stirred at 0°C for 3 h. After addition of 5 ml of satd. aq. NH_4Cl solution, the mixture was extracted twice with dichloromethane and the combined extracts were dried with $MgSO_4$. The solution was concentrated in vacuo and the residue was purified by flash chromatography to obtain 140 mg (63%) of diphenylpyrazinoandrostane **11**. − $C_{35}H_{42}N_2O_2$; m.p. 254°C. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.8−1.9 (m, 23 H), 2.05 (s, 3 H), 2.10−2.24 (m, 1 H), 2.48−3.18 (m, 4 H), 4.63 (dd, *J* = 8 Hz, *J* = 9 Hz, 1 H), 7.22−7.31 (m, 6 H), 7.37−7.43 (m, 4 H). − ^{13}C NMR ($CDCl_3$, APT, 50 MHz): δ = 12.07 (−), 12.11 (−), 20.78 (+), 21.18 (−), 23.55 (+), 27.50 (+), 28.30 (+), 31.15 (+), 35.17 (−), 35.62 (+), 35.86 (+), 36.87 (+), 41.89 (−), 42.56 (+), 46.06 (+), 50.63 (−), 53.64 (−), 82.76 (−), 128.19 (−), 129.65 (−), 138.98 (+), 139.02 (+), 149.65 (+), 149.82 (+), 149.86 (+), 171.23 (+). − IR (KBr): $\tilde{\nu}_{max}$ = 3060 cm^{-1}, 2923, 2928, 1734, 1448 w, 1393, 1247, 1029, 699. − UV (MeOH): λ = 320, 300 (sh), 248 nm. − MS (EI, 150°C): *m/z* (%) = 522 [M$^+$] (39), 521 (100), 260 (23). − HRMS: calcd. 522.3246; found 522.3108. − EA calcd. C 80.42, H 8.10, N 5.36; found C 80.24, H 7.78, N 5.82.

3β-Acetate 12α-Pivalate **12a**: A mixture of 15.3 g (32.4 mmol) of of homoallylic alcohol **3**, 160 ml of pyridine, 50 mg of DMAP and 7.2 ml (58 mmol) of pivaloyl chloride was heated at 100°C for 6 h. After cooling to room temperature, 30 ml of methanol was added. The solvents were evaporated in vacuo, the residue was dissolved in *tert*-butyl methyl ether, and 200 ml of 2 N aq. HCl was added. The aqueous layer was extracted with further *tert*-butyl methyl ether (100 ml), and the combined organic layers were washed with a saturated solution of $NaHCO_3$. After drying with $MgSO_4$, the solvent was evaporated in vacuo and the residue was purified on silica gel (hexane/ethyl acetate, 5:1). The product was obtained as a yellowish foam (16.9 g, 94%). − $C_{34}H_{52}O_6$. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.80 (d, *J* = 6.3 Hz, 27-H), 0.87 (s, 3 H, 19-H), 0.96 (d, *J* = 6.3 Hz, 3 H, 21-H), 1.00−1.91 (m, 32 H), 2.02 (s, 3 H, Ac-CH_3), 2.04−2.39 (m, 2 H), 3.35−3.52 (m, 2 H, 26-H), 4.77 (m, 1 H, 3-H), 4.86 (m, 2 H, 12/16-H), 5.47 (m, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, APT, 50 MHz): δ = 11.93, 14.14, 17.15, 18.86, 21.39, 25.91, 27.12, 28.10, 28.73, 29.55, 30.39, 31.08, 33.85, 34.39, 35.55, 36.60, 38.93, 44.47, 44.60, 49.90, 50.30, 53.54, 60.36, 67.05 (26-C), 73.28 (3-C), 77.94 (12-C), 85.04 (16-C), 106.61 (22-C), 120.17 (15-C), 154.26 (14-C), 170.60 (Ac-C=O), 177.85 (piv-C=O). − IR (KBr): $\tilde{\nu}$ = 2953 cm^{-1} (s), 2874 (m), 1712 (s), 1480 (m), 1367 (m), 1244 (m). − MS (EI, 120°C): *m/z* (%) = 556 [M$^+$] (14), 454 [M$^+$ − $C_5H_{10}O$] (22), 340 (20), 83 (100). − HRMS: calcd. 556.3764; found 556.3761. − EA: calcd. C 73.35, H 9.41; found C 73.62, H 9.29.

3β-Acetate 12α-Propionate **12b**: 40.18 g (84.95 mmol) of homoallylic alcohol **3** was dissolved in 500 ml of dry pyridine, and then 32.84 ml (254.84 mmol) of propionic anhydride and 200 mg of DMAP were added with stirring. The reaction mixture was heated at 100°C for 4 h. After cooling to room temperature and washing with 2 N aq. HCl (4 × 200 ml), the brown residue was diluted with 200 ml of methanol and washed with 100 ml of 2 N aq. HCl, a solution of satd. $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$ and the solvent was removed in vacuo. The residual brown oil (67 g) was filtered through silica gel and recrystallized from dichloromethane/methanol to yield a white foam (38.6 g, 86%). − $C_{32}H_{48}O_6$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.8 (d, *J* = 6.3 Hz, 3 H, 27-H), 0.87 (s, 3 H, 19-H), 0.96 (d, *J* = 6.8 Hz, 3 H, 21-H), 1.13 (s, 3 H, 18-H), 1.43 (m, 3 H, prop-CH_3), 0.77−1.88 (m, 35 H), 2.01 (s, 3 H, acetate), 2.16 (m, 1 H, 8-H), 2.27−2.35 (m, 3 H, 17-H, prop-CH_2), 3.38−3.53 (m, 2 H, 26-H), 4.66 (m, 1 H, 3-H), 4.83 (dd, *J* = 8.1, 1.8 Hz, 1 H, 16-H), 4.88 (t, *J* = 2.6 Hz, 1 H, 12-H), 5.45 (m, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.31 (q), 11.91 (q), 14.10 (q), 17.15 (q), 18.74 (q), 21.40 (q), 26.07 (t), 27.29 (t), 28.13 (t), 28.22 (t), 28.72 (t), 29.48 (t), 30.40 (d), 31.23 (t), 33.88 (t), 34.35 (d), 35.62 (s), 36.60 (t), 44.50 (d), 44.53 (d), 50.08 (s), 50.17 (d), 53.65 (d), 67.15 (t, 26-C), 73.33

(d, 3-C), 78.10 (d, 12-C), 85.19 (d, 16-C), 106.64 (s, 22-C), 120.60 (d, 15-C), 153.59 (s, 14-C), 170.60 (s, Ac-C=O), 173.99 (s, prop-C=O). − IR ($CHCl_3$): $\tilde{\nu}$ = 2980 cm^{-1} (m), 2952 (m), 2872 (m), 1724 (s), 1460 (w). − EA: calcd. C 72.69, H 9.15; found C 72.97, H 9.24.

3β-Alcohol 12α-Pivalate **12c**: A mixture of 18 g (32.3 mmol) of 3β-acetate 12α-pivalate **12a**, 4.2 g (39.6 mmol) of Na_2CO_3, 40 ml of dioxane, 30 ml of water, and 400 ml of methanol was heated for 4 h under reflux. After cooling to room temperature, 200 ml of water was added, and the mixture was extracted with two 200-ml portions of dichloromethane. The combined organic extracts were dried with $MgSO_4$ and the solvent was removed in vacuo. Filtration of the residue through silica gel yielded 15.9 g (96%) of a yellow crystalline product. − $C_{32}H_{50}O_5$; m.p. 110°C. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.80 (d, *J* = 6.2 Hz, 3 H, 27-H), 0.86 (s, 3 H, 19-H), 0.97 (d, *J* = 6.5 Hz, 3 H, 21-H), 1.03−1.89 (m, 32 H), 2.01−2.39 (m, 2 H), 2.90 (br s, 1 H, O−H), 3.35−3.64 (m, 3 H, 3/26-H), 4.87 (m, 2 H, 12/16-H), 5.45 (m, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, APT, 50 MHz): δ = 11.99, 14.16, 17.13, 18.80, 25.95, 27.08, 28.24, 28.66, 29.61, 30.31, 31.01, 31.13, 34.39, 35.55, 36.84, 37.83, 38.86, 44.42, 44.74, 49.85, 50.41, 53.48, 66.98 (26-C), 70.62 (3-C), 78.06 (12-C), 85.02 (16-C), 106.56 (22-C), 120.00 (15-C), 154.30 (14-C), 177.79 (C=O). − IR (KBr): $\tilde{\nu}$ = 3445 cm^{-1} (w), 2930 (s), 2873 (m), 1727 (s), 1480 (w), 1462 (m), 1285 (m). − MS (EI, 140°C): *m/z* (%) = 514 [M^+] (75), 412 [$M^+ - C_5H_{10}O_2$] (96), 340 (64), 297 (100), 126 (96). − HRMS: calcd. 514.3658; found 514.3657. − EA: calcd. C 74.67, H 9.79; found C 74.45, H 9.79.

3β-Alcohol 12α-Propionate **12d**: 43.3 g (81.85 mmol) of 3β-acetate-12α-propionate **12b** was dissolved in 350 ml of methanol and 20 ml of dichloromethane. A solution of 9.5 g (90 mmol) of Na_2CO_3 in 80 ml of water was added and the reaction mixture was stirred for 2 h. A further 10 g (94.7 mmol) of Na_2CO_3 in 80 ml of water was then added and stirring was continued for 20 h. After extraction with dichloromethane, the organic layer was dried with $MgSO_4$ and the solvent was removed in vacuo. Filtration of the residue through silica gel gave 36.6 g (92%) of a white, non-crystalline product. − $C_{30}H_{46}O_5$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.80 (d, *J* = 6.2 Hz, 3 H, 27-H), 0.85 (s, 3 H, 19-H), 0.97 (d, *J* = 6.8 Hz, 3 H, 21-H), 1.11 (t, *J* = 7.6 Hz, 3 H, prop-CH_3), 1.13 (s, 3 H, 18-H), 0.78−1.87 (m, 36 H), 2.16 (m, 1 H, 8-H), 2.26−2.35 (m, 3 H, α-C=O−H, 17-H), 3.38−3.52 (m, 2 H, 26-H), 3.57 (m, 1 H, 3-H), 4.82 (dd, *J* = 8.2, 1.9 Hz, 1 H, 16-H), 4.88 (t, *J* = 2.7 Hz, 1 H, 12-H), 5.45 (m, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.26 (q), 11.99 (q), 14.07 (q), 17.13 (q), 18.69 (q), 26.10 (t), 28.18 (t), 28.24 (t), 28.69 (t), 29.53 (t), 30.36 (d), 31.21 (t), 31.29 (t), 34.37 (d), 35.62 (s), 36.82 (t), 37.99 (t), 44.48 (d), 44.69 (d), 50.09 (s), 50.28 (d), 53.64 (d), 67.13 (t, 26-C), 71.02 (d, 3-C), 78.20 (d, 12-C), 85.20 (d, 16-C), 106.63 (s, 22-C), 120.46 (d, 15-C), 153.71 (s, 14-C), 173.95 (s, prop-C=O). − IR ($CHCl_3$): $\tilde{\nu}$ = 3608 cm^{-1} (w), 2980 (m), 2932 (s), 2860 (m), 1724 (s), 1652 (vw), 14.60 (m), 1376 (m), 1240 (m). − MS (EI, 110°C): *m/z* (%) = 486 (20), 412 (45). − HRMS: calcd. 486.3345; found 486.3351.

3β-Tosylate 12α-Pivalate **13a**: 51.22 g (99.5 mmol) of alcohol **12c**, 22.76 g (119.4 mmol) of *p*-tosyl chloride and 14.59 g (119.4 mmol) of DMAP were dissolved in 600 ml of dichloromethane. After 24 h, an additional portion of DMAP (1.22 g, 0.1 equiv.) was added to the reaction mixture. The mixture was poured into water after 5 d. The layers were allowed to separate and the aqueous phase was extracted with three portions of dichloromethane. The combined organic layers were washed with 2 N aq. HCl, satd. $NaHCO_3$ solution and brine. After drying with $MgSO_4$, the solvent was removed in vacuo. Purification on silica gel yielded 62.4 g (94%) of the desired product as a yellow foam. − $C_{39}H_{56}O_7S$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.79 (d, *J* = 6.3 Hz, 3 H, 27-H), 0.82 (s, 3 H, 19-H), 0.95 (d, *J* = 6.8 Hz, 3 H, 21-H), 1.12 (s, 3 H, 18-H), 1.15 (s, 9 H, *tert*-butyl), 2.13 (br t, *J* = 11 Hz, 1 H, 8-H), 2.31 (dd, *J* = 9.5, 8.2 Hz, 1 H, 17-H), 2.44 (s, 3 H, Ts-Me), 3.40 (t, *J* = 10.9 Hz, 1 H, 26-H), 3.47 (m, 1 H, 26-H), 4.41 (m, 1 H, 3-H), 4.82 (t, *J* = 2.4 Hz, 1 H, 12-H), 4.84 (dd, *J* = 8.0, 1.6 Hz, 1 H, 16-H), 5.44 (m, 1 H, 15-H), 7.32 (m, 2 H, Ts-H), 7.77 (m, 2 H, Ts-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 11.83 (q), 14.11 (q), 17.13 (q), 18.82 (q), 21.62 (q, Ts-CH_3), 25.92 (t), 27.13 (q, × 3, *tert*-butyl), 27.94 (t), 28.22 (t), 28.72 (t), 29.43 (t), 30.37 (d), 31.07 (t), 34.28 (d), 34.69 (t), 35.91 (s), 36.60 (t), 38.92 (s), 44.46 (d), 44.67 (d), 49.91 (s), 50.15 (d), 53.53 (d), 67.07 (t, 26-C), 77.87 (d, 12-C), 81.84 (d, 3-C), 85.01 (d, 16-C), 106.64 (s, 22-C), 120.25 (d, 15-C), 127.56 (d, × 2), 129.74 (d, × 2), 134.78 (s), 144.39 (s), 154.00 (s, 14-C), 177.82 (s, C=O). − IR (KBr): $\tilde{\nu}$ = 2952 cm^{-1} (m), 2928 (m), 2872 (m), 1724 (m), 1464 (m), 1456 (m), 1364 (m), 1284 (m), 1240 (s). − MS (EI, 180°C): *m/z* (%) = 668 (2), 567 (4), 497 (50), 394 (88), 281 (100). − HRMS: calcd. 668.3748; found 668.3761.

3-β-Tosylate 12α-Propionate **13b**: 35.5 g (73 mmol) of alcohol **12d**, 16.7 g (87.6 mmol) of *p*-tosyl chloride and 10.7 g (87.6 mmol) of DMAP were dissolved in 400 ml of dichloromethane. An additional portion of DMAP (7 g, 57.4 mmol) was added to the reaction mixture after 24 h. After 36 h, the mixture was poured into 200 ml of water. The layers were allowed to separate and the aqueous layer was extracted with three portions of dichloromethane. The combined organic layers were washed with 2 N aq. HCl, satd. $NaHCO_3$ solution and brine. After drying with $MgSO_4$, the solvent was removed in vacuo. Purification of the residue on silica gel yielded 33.7 g (72%) of the desired product as a yellow foam and 7.7 g (22%) of starting material **12d**. − $C_{37}H_{52}O_7S$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.80 (d, *J* = 6.3 Hz, 3 H, 27-H), 0.82 (s, 3 H, 19-H), 0.96 (d, *J* = 6.8 Hz, 3 H, 21-H), 1.10 (t, *J* = 7.5 Hz, 3 H, prop-CH_3), 1.11 (s, 3 H, 18-H), 0.78−1.84 (m, 35 H), 2.12 (m, 1 H, 8-H), 2.24−2.36 (m, 3 H, 17α-H, α-C=O), 2.44 (s, 3 H, Ts-CH_3), 3.38−3.52 (m, 2 H, 26-H), 4.38 (m, 1 H, 3-H), 4.81 (dd, *J* = 8.1, 1.8 Hz, 1 H, 16-H), 4.85 (t, *J* = 2.4 Hz, 1 H, 12-H), 5.43 (m, 1 H, 15-H), 7.30−7.34 (m, 2 H, Ts-H), 7.76−7.80 (m, 2 H, Ts-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.26 (q), 11.82 (q), 14.08 (q), 17.14 (q), 18.67 (q), 21.63 (q), 26.02 (t), 27.96 (t), 28.17 (t, × 2), 28.70 (t), 29.36 (t), 30.38 (d), 31.21 (t), 34.21 (d), 34.74 (t), 35.35 (s), 36.59 (t), 44.48 (d), 44.63 (d), 50.01 (d), 50.08 (s), 53.63 (d), 67.15 (t, 26-C), 78.03 (d, 12-C), 81.89 (d, 3-C), 85.15 (d, 16-C), 106.65 (s, 22-C), 120.68 (d, 15-C), 127.59 (d, × 2), 129.74 (d, × 2), 134.71 (s), 144.41 (s), 153.33 (s, 14-C), 173.90 (s, prop-C=O). − IR ($CHCl_3$): $\tilde{\nu}$ = 2980 cm^{-1} (m), 2952 (m), 2932 (m), 2876 (m), 1724 (m), 1460 (m), 1376 (m), 1240 (m), 1172 (s). − MS (EI, 220°C): *m/z* (%) = 641 (4), 567 (6). − HRMS: calcd. 640.3434; found 640.3448. − EA: calcd. C 69.34, H 8.18; found C 69.37, H 8.28.

2,14-Diene 12α-Pivalate **13c**: 62.02 g (92.7 mmol) of tosylate **13a** was dissolved in 600 ml of dry toluene and 1000 g of activated ALOX B was added to the solution. The reaction mixture was heated at 90°C for 29 h. The suspension was then allowed to cool to room temperature and filtered. The filtrate was concentrated in vacuo and the crude residue (58.7 g) was purified on silica gel to yield 42.89 g (93%) of a yellow foam. − $C_{32}H_{48}O_4$. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.80−2.22 (m, 40 H), 2.33 (dd, *J* = 8.9, 8.1 Hz, 1 H, 17-H), 3.37−3.56 (m, 2 H, 26-H), 4.88 (m, 2 H, 12/16-H), 5.49 (m, 1 H, 15-H), 5.57 (m, 2 H, 2/3-H). − ^{13}C NMR ($CDCl_3$, APT, 50 MHz): δ = 11.36, 14.10, 17.15, 18.74, 25.62, 27.11, 28.26, 28.73, 29.43, 30.06, 30.38, 31.07, 34.46, 34.67, 38.86, 39.52, 41.33, 44.48, 49.77, 50.17, 55.58, 66.99 (26-C), 78.03 (12-C),

85.01 (16-C), 106.50 (22-C), 120.73 (15-C), 125.34/125.77 (2/3-C), 154.31 (14-C), 177.65 (C=O). − IR (KBr): $\tilde{\nu}$ = 3022 cm^{-1}, 2954, 2928, 2874, 1727, 1654, 1480, 1461, 1283, 1155, 981, 902. − MS (EI, 130°C): *m/z* (%) = 496 [M^+] (30), 394 (68), 280 (100). − HRMS: calcd. 496.3553; found 496.3554.

2,14-Diene 12α-Propionate **13d**: 28.6 g (44.69 mmol) of tosylate **13b** was dissolved in 350 ml of dry toluene and 50 g of activated ALOX B was added to the solution. The reaction mixture was heated at 90°C. After 45 min, an additional portion (50 g) of ALOX B was added to the flask. The mixture was cooled after 3 h and filtered. The filtrate was concentrated in vacuo, and the residue was purified on silica gel and recrystallized from dichloromethane/methanol to give 17.8 g (85%) of white crystals (m.p. 105°C). − $C_{30}H_{44}O_4$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.79−0.81 (m, 6 H, 27-H, 19-H), 0.97 (d, *J* = 6.8 Hz, 3 H, 21-H), 1.11 (t, *J* = 7.5 Hz, 3 H, prop-CH_3), 1.15 (s, 3 H, 18-H), 0.79−2.08 (m, 33 H), 2.13 (m, 1 H, 8−H), 2.29 (q, *J* = 7.5 Hz, 2 H, α-C=O), 2.33 (m, 1 H, 17−H), 3.4−3.53 (m, 2 H, 26-H), 4.83 (dd, *J* = 8.1, 1.5 Hz, 1 H, 16−H), 4.89 (t, *J* = 2.6 Hz, 1 H, 12-H), 5.45 (m, 1 H, 15-H), 5.50−5.64 (m, 2 H, 2-H, 3-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.30 (q), 11.38 (q), 14.10 (q), 17.16 (q), 18.63 (q), 25.79 (t), 28.23 (t), 28.27 (t), 28.71 (t), 29.33 (t), 30.08 (t), 30.39 (d), 31.23 (t), 34.45 (d), 34.75 (s), 39.55 (t), 41.30 (d), 44.52 (d), 50.01 (s), 50.07 (d), 53.69 (d), 67.14 (t, 26-C), 78.27 (d, 12-C), 85.21 (d, 16-C), 106.63 (s, 22-C), 120.60 (d, 15-C), 125.40 (d), 125.85 (d), 153.83 (s, 14-C), 174.00 (s, prop-C=O). − IR ($CHCl_3$): $\tilde{\nu}$ = 2956 cm^{-1} (s), 2928 (s), 2876 (m), 1724 (s), 1652 (w), 1460 (m), 1380 (m), 1240 (m). − FAB-MS (NBA matrix): *m/z* (%) = 491 [M^+ + Na] (20), 469 [MH^+] (100). − EA: calcd. C 76.88, H 9.46; found C 76.68, H 9.48.

2,3-α-Epoxide 12α-Pivalate **14a**: 2.0 g (4.0 mmol) of the diene **13c** was dissolved in 10 ml of dichloromethane. At 0°C, 48 ml of a 0.09−0.1 M solution of dimethyldioxirane (DMDO) in acetone[41] was added dropwise. After 90 min, at this temperature, 50 ml of a satd. solution of $NaHSO_3$ was slowly poured into the reaction mixture. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried with $MgSO_4$. After evaporation of the solvent in vacuo, the residue was purified on silica gel to give 1.92 g (93%) of a yellow foam. − $C_{32}H_{48}O_5$. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.80−2.22 (m, 40 H), 2.31 (dd, *J* = 9.2, 8.4 Hz, 1 H, 17-H), 3.02−3.18 (m, 2 H, 2/3-H), 3.34−3.56 (m, 2 H, 26-H), 4.85 (m, 2 H, 12/16-H), 5.44 (s, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.62 (q),14.12 (q), 17.14 (q), 18.73 (q), 25.67 (t), 27.15 (q, × 3), 27.96 (t), 28.72 (t), 28.87 (t), 29.31 (t), 30.38 (d), 31.07 (t), 33.77 (s), 34.51 (d), 36.16 (d), 38.18 (t), 38.95 (s), 44.48 (d), 49.77 (s), 49.88 (d), 50.65 (d), 52.25 (d), 53.56 (d), 67.05 (t, 26-C), 77.85 (d, 12-C), 84.97 (d, 16-C), 106.59 (s, 22-C), 120.48 (d, 15-C), 153.95 (s, 14-C), 177.96 (s, C=O). − IR (KBr): $\tilde{\nu}$ = 2954 cm^{-1}, 2929, 2874, 1726, 1480, 1461, 1378, 1157, 1064, 981. − MS (EI, 150°C): *m/z* (%) = 512 [M^+] (30), 411 (62), 296 (100), 126 (71). − HRMS: calcd. 512.3502; found 512.3503. − EA: calcd. C 74.96, H 9.44; found C 74.85, H 9.50.

2,3-α-Epoxide 12α-Propionate **14b**: 4.8 g (10.26 mmol) of the diene **13d** was dissolved in 100 ml of dichloromethane. The solution was cooled to 0°C and 125 ml of a 0.09−0.1 M solution of dimethyldioxirane (DMDO) in acetone[41] was added dropwise. After 90 min at this temperature, 50 ml of a satd. solution of $NaHSO_3$ was slowly poured into the reaction mixture. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried with $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was purified on silica gel to give 4.38 g (88%) of a yellow foam. − $C_{30}H_{44}O_5$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.78−0.82 (m, 6 H, 19-H, 27-H), 0.97 (d, *J* = 6.8 Hz, 3 H, 21-H), 1.11 (t, *J* = 7.4 Hz, 3 H, prop-CH_3), 1.12 (s, 3 H, 18-H), 0.78−1.95 (m, 33 H), 2.01 (m, 1 H, 8-H), 2.25−2.35 (m, 3 H, 17-H, α-C=O), 3.09 (m, 1 H, 2-H), 3.16 (m, br, 1 H, 3-H), 3.38−3.52 (m, 2 H, 26-H), 4.81 (dd, *J* = 7.9, 1.5 Hz, 1 H, 16-H), 4.87 (t, *J* = 2.8 Hz, 1 H, 12-H), 5.44 (m, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.26 (q), 12.68 (q), 14.08 (q), 17.15 (q), 18.60 (q), 25.75 (t), 27.96 (t), 28.18 (t), 28.71 (t), 28.85 (t), 29.24 (t), 30.39 (d), 31.23 (t), 33.76 (s), 34.47 (d), 36.11 (d), 38.13 (t), 44.52 (d), 49.77 (d), 49.95 (s), 50.65 (d), 52.28 (d), 53.67 (d), 67.14 (t, 26-C), 78.04 (d, 12-C), 85.12 (d, 16-C), 106.63 (s, 22-C), 120.92 (d, 15-C), 153.29 (s, 14-C), 174.02 (s, prop-C=O). − IR ($CHCl_3$): $\tilde{\nu}$ = 2996 cm^{-1} (m), 2956 (s), 2876 (m), 1724 (s), 1460 (m). − MS (EI, 160°C): *m/z* (%) = 484 (39), 410 (71), 338 (40), 296 (100). − HRMS: calcd. 484.3189; found 484.3199. − EA: calcd. C 74.34, H 9.15; found C 74.27, H 9.47.

2β-Chloro-3α-hydroxy 12α-Pivalate **15a**: To a solution of 480 mg (0.94 mmol) of epoxide **14a** in 18 ml of dichloromethane, a solution of 374 mg (1.1 equiv.) of dichlorotriphenylphosphane in 4 ml of dichloromethane was added at −15°C. After stirring at this temperature for 1 h, the reaction was quenched with 30 ml of a satd. solution of $NaHSO_3$. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried with $MgSO_4$. Evaporation of the solvent in vacuo, purification of the residue on silica gel, and crystallization from dichloromethane/methanol yielded 318 mg (62%) of white crystals (m.p. 118°C). − $C_{32}H_{49}ClO_5$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.79 (d, *J* = 6.2 Hz, 3 H, 27-H), 0.96 (d, *J* = 6.8 Hz, 3 H, 31-H), 1.09 (s, 3 H), 1.14 (s, 3 H), 1.15 (s, 9 H), 2.22 (br t, *J* = 10.2 Hz, 1 H, 8-H), 2.32 (t, *J* = 8.8 Hz, 1 H, 17-H), 3.34−3.52 (m, 2 H, 26-H), 4.07 (m, 2 H, 2/3-H), 4.85 (m, 2 H, 12/16-H), 5.47 (m, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.13 (q), 14.36 (q), 17.14 (q), 18.91 (q), 25.70 (t), 27.16 (q, × 3), 27.57 (t), 28.72 (t), 29.36 (t), 30.38 (d), 30.71 (t), 31.06 (t), 33.82 (d), 36.21 (s), 38.41 (d), 38.95 (s), 40.09 (t), 44.45 (d), 49.96 (s), 51.26 (d), 53.50 (d), 59.14 (d), 67.07 (t, 26-C), 70.85 (d, 3-C), 77.97 (d, 12-C), 85.06 (d, 16-C), 106.66 (s, 22-C), 120.19 (d, 15-C), 154.28 (s, 14-C), 177.99 (s, C=O). − IR (KBr): $\tilde{\nu}$ = 3452 cm^{-1}, 2953, 2931, 2877, 1727, 1480, 1461, 1376, 1157, 1065, 1012, 980, 904. − MS (EI, 170°C): *m/z* (%) = 548 [M^+] (23), 512 (12), 446 (54), 332 (92), 296 (47), 126 (100). − HRMS: calcd. 548.3269; found 548.3267. − EA: calcd. C 69.99, H 8.99; found C 70.30, H 9.34.

2β-Chloro-3α-hydroxy 12α-Propionate **15b**: To a solution of 1.8 g (3.72 mmol) of epoxide **14b** in 20 ml of dichloromethane, a solution of 1.4 g (1.2 equiv.) of dichlorotriphenylphosphane in 10 ml of dichloromethane was added at −15°C. After stirring at this temperature for 1 h, the reaction was quenched with 30 ml of a satd. solution of $NaHSO_3$. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried with $MgSO_4$. Evaporation of the solvent in vacuo, purification of the residue on silica gel, and crystallization from dichloromethane/methanol yielded 1.42 g (73%) of white crystals (m.p. 198°C). − $C_{30}H_{45}ClO_5$. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.8 (d, *J* = 6.0 Hz, 3 H, 27-H), 0.97 (d, *J* = 6.7 Hz, 3 H, 21-H), 1.09 (s, 3 H, 19-H), 1.11 (t, *J* = 7.6 Hz, 3 H, prop-CH_3), 1.13 (s, 3 H, 18-H), 0.78−2.38 (m, 38 H), 3.38−3.53 (m, 2 H, 26-H), 4.04−4.13 (m, 2 H, 2/3-H), 4.82 (dd, *J* = 7.9, 1.7 Hz, 1 H, 16-H), 4.88 (m, 1 H, 12-H), 5.45 (m, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.23 (q), 14.10 (q), 14.37 (q), 17.15 (q), 18.74 (q), 25.79 (t), 27.57 (t), 28.14 (t), 28.70 (t), 29.31 (t), 30.38 (d), 30.73 (t), 31.20 (t), 33.74 (d), 36.23 (s), 38.38 (d), 40.14 (t), 44.47 (d), 50.13 (s), 51.08 (d), 53.60 (d), 59.15 (d), 67.15 (t, 26-C), 70.90 (d, 3-C), 78.08 (d, 12-C), 85.20 (d, 16-C), 106.66 (s, 22-C), 120.62 (d, 15-C), 153.58 (s, 14-C),

174.01 (s, C=O). − IR ($CHCl_3$): $\tilde{\nu}$ = 3608 cm^{-1} (w), 2980 (m), 2932 (s), 2880 (m), 1724 (s), 1460 (m). − MS (EI, 190°C): *m/z* (%) = 521 (10), 520 (29), 448 (27), 447 (23), 446 (63), 374 (37), 332 (100). − HRMS: calcd. 520.2956; found 520.2933. − EA: calcd. C 69.14, H 8.70; found C 69.13, H 8.70.

3β-Azido-2β-chloro 12α-Pivalate **16a**: 294 mg (0.54 mmol) of chloro alcohol **15a**, 464 mg (1.8 mmol) PPh_3 and 3 ml of a 0.6 M solution of HN_3 in toluene (1.8 mmol) were dissolved in 6 ml of dry toluene. After addition of 0.33 ml (2.1 mmol) of DEAD at 0°C by means of a syringe, the precipitation of a white solid was observed. After 20 min at this temperature, the reaction mixture was rapidly heated to 70°C for 10 min. The mixture was then allowed to cool and was subsequently stirred at room temperature for 16 h. After filtration through silica gel, the solvent was removed from the filtrate in vacuo and the residue was purified on silica gel to give 142 mg (45%) of the desired product as a yellow solid (m.p. 89°C). − $C_{32}H_{48}ClN_3O_4$. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.79−0.98 (m, 9 H), 1.00−2.44 (m, 32 H), 3.30−3.54 (m, 3 H), 4.43 (m, 1 H), 4.87 (m, 2 H, 12/16-H), 5.47 (d, *J* = 1.8 Hz, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, APT, 50 MHz): δ = 14.13, 15.23, 17.15, 18.91, 26.05, 27.14, 27.52, 28.19, 28.72, 29.30, 30.37, 31.04, 33.64, 36.08, 38.72, 44.44, 44.71, 46.63, 49.97, 51.38, 53.47, 60.46, 62.37, 67.07 (26-C), 77.08, 84.99 (16-C), 106.66 (22-C), 120.39 (15-C), 153.84 (14-C), 177.68 (C=O). − IR (KBr): $\tilde{\nu}$ = 2953 cm^{-1}, 2931, 2873, 2100, 1725, 1480, 1461, 1284, 1157, 981. − MS (EI, 180°C): *m/z* (%) = 575 (21), 574 ([M^+] (49), 538 (22), 471 (34), 357 (41), 126 (100). − HRMS: calcd. 573.3333; found 573.3335.

3β-Azido-2β-chloro 12α-Propionate **16b**: 675 mg (1.30 mmol) of chloro alcohol **15b** and 1.02 g (3.9 mmol) of PPh_3 were dissolved in 20 ml of dry toluene. At 0°C, 675 mg (3.9 mmol) of DEAD was added by means of a syringe, followed by 4.6 ml of a 1.4 M solution of HN_3 in toluene (6.5 mmol). After 15 min at this temperature, the reaction mixture was heated rapidly to 80°C for 10 min. The mixture was then allowed to cool and was subsequently stirred at room temperature for 90 min. The solvent was removed in vacuo and the residue was purified on silica gel to give 283 mg (40%) of the desired product and 264 mg (40%) of a mixture of regio- and diastereoisomeric allylic azides, both as yellow oils that foamed up in vacuo. − $C_{30}H_{44}ClN_3O_4$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.80 (d, *J* = 6.4 Hz, 3 H, 27-H), 0.97 (d, *J* = 6.6 Hz, 3 H, 21-H), 1.11 (t, *J* = 7.6 Hz, 3 H, prop-CH_3), 1.14 (s, 3 H), 1.15 (s, 3 H), 0.78−1.98 (m, 34 H), 2.15−2.36 (m, 4 H, 8-H, 17-H, α-C=O), 3.37−3.52 (m, 3 H, 3/26-H), 4.43 (m, 1 H, 2-H), 4.81 (dd, *J* = 8.1, 1.7 Hz, 1 H, 16-H), 4.88 (t, *J* = 2.8 Hz, 1 H, 12-H), 5.49 (m, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.28 (q), 14.10 (q), 15.20 (q), 17.15 (q), 18.77 (q), 26.16 (t), 27.55 (t), 28.15 (t), 28.20 (t), 28.71 (t), 29.25 (t), 30.38 (d), 31.21 (t), 33.60 (d), 36.14 (s), 44.47 (d), 44.73 (t), 46.60 (d), 50.17 (s), 51.20 (d), 53.60 (d), 60.54 (d), 62.45 (d), 67.18 (t, 26-C), 77.90 (d, 12-C), 85.14 (d, 16-C), 106.69 (s, 22-C), 120.85 (d, 15-C), 153.17 (s, 14-C), 173.83 (s, prop-C=O). − IR ($CHCl_3$): $\tilde{\nu}$ = 2980 (w), 2952 (m), 2880 (w), 2864 (w), 2104 (vs), 1724 (s), 1460 (m), 1240 (m). − MS (EI, 170°C): *m/z* (%) = 547 (34), 546 (75), 518 (43), 472 (50), 471 (76). − HRMS: calcd. 545.3020; found 545.3031. − EA: calcd. C 65.98, H 8.12, N 7.69; found C 66.44, H 8.33, N 7.24.

3-Azido-2-ene 12α-Pivalate **17a**: To a stirred solution of 338 mg (0.6 mmol) of chloroazide **16a** in 10 ml of dry diethyl ether, 123 mg (1.1 mmol) of sodium *tert*-butoxide (freshly sublimed) was added in three portions. After 1 h, the reaction mixture was poured into 20 ml of water. The aqueous layer was extracted with 50 ml of diethyl ether and the combined organic layers were dried with $MgSO_4$. The solvent was removed in vacuo to afford 288 mg (91%) of a red product. − $C_{32}H_{47}N_3O_4$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.79 (m, 6 H, 19/27-H), 0.97 (d, *J* = 6.8 Hz, 3 H, 21-H), 1.15 (s, 12 H), 2.14 (br t, *J* = 10.5 Hz, 1 H, 8-H), 2.33 (t, *J* = 8.6 Hz, 1 H, 17-H), 3.36−3.52 (m, 2 H, 26-H), 4.83−4.89 (m, 2 H, 12/16-H), 5.17 (d br, *J* = 5.5 Hz, 1 H, 2-H), 5.48 (m, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 11.49 (q), 14.12 (q), 17.15 (q), 18.77 (q), 25.87 (t), 27.13 (q, × 3), 27.93 (t), 28.73 (t), 29.21 (t), 30.28 (t), 30.39 (d), 31.09 (t), 34.37 (d), 34.64 (s), 38.84 (t), 39.23 (s), 41.51 (d), 44.50 (d), 49.81 (d), 49.86 (s), 53.60 (d), 67.09 (t, 26-C), 77.96 (d, 12-C), 85.00 (d, 17-C), 106.64 (s, 22-C), 110.21 (d, 2-C), 120.47 (d, 15-C), 133.79 (s, 3-C), 154.00 (s, 14-C), 177.87 (s, C=O). − IR (KBr): $\tilde{\nu}$ = 2954 cm^{-1}, 2928, 2875, 2099, 1726, 1668, 1480, 1461, 1283, 1157, 1065, 981. − MS (EI, 140°C): *m/z* (%) = 538 [M^+ + 1] (3), 537 [M^+], 509 [$M^+ - N_2$], 407 (9), 279 (20), 149 (100). − HRMS: calcd. 537.3567; found 537.3567.

3-Azido-2-ene 12α-Propionate **17b**: 358 mg (0.66 mmol) of chloro azide **16b** was dissolved in 3 ml of diethyl ether, and 262 µl (0.79 mmol) of the phosphazene base P_2-Et was slowly added at room temperature by means of a syringe. After 5 h, the solvent was evaporated in vacuo and the residue was purified on silica gel to give 307 mg (92%) of the vinyl azide **17b** as a white foam. − $C_{30}H_{43}N_3O_4$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.80 (d, *J* = 6.2 Hz, 3 H, 27-H), 0.80 (s, 3 H, 19-H), 0.98 (d, *J* = 6.8 Hz, 3 H, 21-H), 1.11 (t, *J* = 7.6 Hz, 3 H, prop-CH_3), 1.14 (s, 3 H, 18-H), 0.78−2.1 (m, 33 H), 2.13 (m, 1 H, 8-H), 2.26−2.36 (m, 3 H, 17-H, α-C=O), 3.39−3.53 (m, 2 H, 26-H), 4.83 (dd, *J* = 8.3, 1.8 Hz, 1 H, 16-H), 4.89 (t, *J* = 2.8 Hz, 1 H, 12-H), 5.17 (m, 1 H, 2-H), 5.46 (m, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.29 (q), 11.47 (q), 14.09 (q), 17.15 (q), 18.62 (q), 26.62 (t), 27.96 (t), 28.20 (t), 28.71 (t), 29.12 (t), 30.29 (t), 30.39 (d), 31.22 (t), 34.32 (d), 34.69 (s), 38.84 (t), 41.46 (d), 44.52 (d), 49.68 (d), 50.03 (s), 53.69 (d), 67.16 (t, 26-C), 78.10 (d, 12-C), 85.16 (d, 16-C), 106.66 (s, 22-C), 110.25 (d, 2-C), 120.89 (d, 15-C), 133.75 (s, 3-C), 153.31 (s, 14-C), 173.97 (s, prop-C=O). − IR ($CHCl_3$): $\tilde{\nu}$ = 3012 cm^{-1} (m), 2956 (s), 2928 (s), 2876 (m), 2100 (s), 1724 (s), 1460 (w), 1224 (s). − MS (EI, 160°C): 481 [$M^+ - N_2$] (13), 413 (13), 410 (11), 408 (12), 407 [$M^+ - C_5H_{10}O_2$] (17), 335 (12), 294 (15), 293 (28). − HRMS: calcd. 509.3254; found 509.3229. − EA: calcd. C 70.70, H 8.50; found C 70.47, H 8.43.

2β-Chloro-3α-formiato 12α-Propionate **18**: 126 mg (0.24 mmol) of chloro alcohol **15b** was dissolved in 4 ml of dry THF. A suspension of (chloromethylene)dimethylammonium chloride {[CHCl=N^+Me_2]Cl^-} in THF (0.84 ml, 2 equiv.) and 0.52 ml of a 1.4 M solution of HN_3 in toluene were added at room temperature. After 45 min, the solvents were evaporated in vacuo and the residue was purified on silica gel (hexanes/ethyl acetate, 10:1) furnishing 62 mg (49%) of **18** as a colorless oil. − $C_{31}H_{45}ClO_6$. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.75−2.38 (m, 37 H), 3.33−3.55 (m, 2 H, 26-H), 4.17 (m, 1 H, 2-H), 4.82 (dd, *J* = 8.1, 2.0 Hz, 1 H, 16-H), 4.89 (m, 1 H, 12-H), 5.21 (m, 1 H, 3-H), 5.47 (m, 1 H, 15-H), 8.03 (s, 1 H, formate). − IR ($CHCl_3$): $\tilde{\nu}$ = 2980 cm^{-1} (m), 2952 (s), 2880 (m), 1724 (s), 1460 (m), 1376 (m), 1240 (m), 1176 (m). − MS (EI, 160°C): *m/z* (%) = 551 (10), 549 [M^+] (20), 476 (18), 475 (17), 474 (35), 404 (21), 402 (34), 127 (100).

2β-Bromo-3α-hydroxy 12α-Propionate **19a**: 0.97 ml of a 1 M solution of bromine in dichloromethane was diluted with 15 ml of dichloromethane. After addition of 256 mg (0.98 mmol) of triphenylphosphane, the mixture turned yellow. Then, 430 mg (0.89 mmol) of epoxide **14b** in 5 ml of dichloromethane was added to the solution. After 15 min at room temperature, the reaction was quenched with aqueous $NaHCO_3$ and the mixture was washed with brine, dried with $MgSO_4$ and finally filtered through ALOX N.

After evaporation of the solvent from the filtrate in vacuo, 630 mg of crude product was obtained. Purification on silica gel gave 380 mg (76%) of **19a** as a white foam. − $C_{30}H_{45}BrO_5$. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.79 (d, *J* = 6 Hz, 3 H, 27-H), 0.97 (d, *J* = 6.8 Hz, 3 H, 21-H), 0.78−2.38 (m, 38 H), 3.34−3.54 (m, 2 H, 26-H), 4.21 (m, 2 H, 2/3-H), 4.81 (dd, *J* = 7.8, 1.9 Hz, 1 H, 16-H), 4.87 (m, 1 H, 12-H), 5.45 (s, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.23 (q), 14.10 (q), 14.54 (q), 17.15 (q), 18.74 (q), 21.06 (d), 25.80 (t), 27.55 (t), 28.13 (t), 28.69 (t), 29.28 (t), 30.37 (d), 30.82 (t), 31.20 (t), 33.72 (d), 36.54 (s), 38.25 (d), 40.64 (t), 44.47 (d), 50.13 (s), 51.24 (d), 53.58 (d), 67.15 (t, 26-C), 71.25 (d, 3-C), 78.06 (d, 12-C), 85.20 (d, 16-C), 106.67 (s, 22-C), 120.64 (d, 15-C), 153.54 (s, 14-C), 174.01 (s, C=O). − IR ($CHCl_3$): $\tilde{\nu}$ = 3608 (w), 2980 (m), 2952 (s), 2880 (m), 1724 (s), 1672 (w), 1652 (w), 1460 (m), 1240 (m), 1176 (m), 1060 (m). − MS (EI, 220°C): *m/z* (%) = 567 (19), 565 (17), 548 (22), 546 (24), 492 (34), 490 (34), 420 (35), 418 (34), 379 (37), 185 (35), 126 (46). − HRMS: calcd. 564.2450; found 564.2438.

2β-Fluoro-3α-hydroxy 12α-Propionate **19b**: 110 mg (0.23 mmol) of epoxide **14b**, 103 mg (0.69 mmol) of cesium fluoride and a catalytic amount of lithium fluoride were mixed in a 5-ml round-bottomed flask. Solid pivalic acid (2500 mg, 24.48 mmol) was dissolved in a small volume (0.5 ml) of dimethyl sulfoxide and 1.5 ml of this mixture was added to the flask as solvent. The reaction mixture was stirred for 6 h at 100°C and then poured into aqueous $NaHCO_3$. The resulting mixture was extracted with dichloromethane and the combined extracts were washed with brine and dried with $MgSO_4$. Evaporation of the solvent in vacuo and purification on silica gel (hexanes/ethyl acetate, 5:1) yielded 64 mg (56%) of **19b** as a colorless oil. − $C_{30}H_{45}FO_5$. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.79 (d, *J* = 6 Hz, 3 H, 27-H), 0.95 (s, 3 H), 0.97 (d, *J* = 6.7 Hz, 3 H, 21-H), 0.77−2.38 (m, 38 H), 3.35−3.53 (m, 2 H, 26-H), 3.80 (m, 1 H, 3-H), 4.78−4.92 (m, 3 H, 2/16/12-H), 5.46 (m, 1 H, 15-H). − MS (EI, 140°C): *m/z* (%) = 505 (18), 440 (20), 399 (21), 398 (49), 301 (17), 126 (100).

3β-Azido-2β-fluoro 12α-Propionate **20b**: 51 mg (0.1 mmol) of **19b** and 79 mg (0.3 mmol) of PPh_3 were dissolved in 1 ml of toluene, and then 53 mg (0.3 mmol) of DEAD and 310 µl of a 1.6 M solution of HN_3 in toluene were added. After 15 min at room temperature, the reaction mixture was rapidly heated to 80°C and maintained at this temperature for 10 min. The mixture was then allowed to cool and was subsequently stirred at room temperature for 90 min. The solvent was removed in vacuo and the residue was purified on silica gel to give 26 mg (49%) of the desired product as a colorless oil. − $C_{30}H_{44}FN_3O_4$. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.80 (d, *J* = 6.4 Hz, 3 H, 27-H), 0.96 (d, *J* = 6.8 Hz, 3 H, 21-H), 0.99 (s, 3 H), 3.37−3.53 (m, 2 H, 26-H), 4.81 (dd, *J* = 7.9, 1.9 Hz, 1 H, 16-H), 4.87 (m, 1 H, 12-H), 5.46 (m, 1 H, 15-H). − IR ($CHCl_3$): $\tilde{\nu}$ = 2956 cm^{-1} (m), 2882 (m), 2104 (s), 1724 (s). − FAB-MS: *m/z* (%) = 530 [MH^+] (14).

3-Oxo 12α-Pivalate **21**: 12.5 g (24.3 mmol) of alcohol **12c** was dissolved in 40 ml of dichloromethane and added to a suspension of 10.1 g (47 mmol) of pyridinium chlorochromate and 10 g of silica gel in 600 ml of dichloromethane. After 11 h at room temperature, half of the solvent was evaporated in vacuo. Et_2O (300 ml) was added and the resulting precipitate was filtered off. The filtrate was concentrated and the residue was purified on silica gel (hexanes/ethyl acetate, 5:1), affording 11.7 g (94%) of white crystals (m.p. 103°C). − $C_{32}H_{48}O_5$. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.78 (d, *J* = 6.6 Hz, 3 H, 27-H), 0.98 (d, *J* = 6.5 Hz, 3 H, 21-H), 1.03 (s, 3 H), 1.11−2.39 (m, 34-H), 3.35−3.55 (m, 2 H, 26-H), 4.88 (m, 2 H, 12/16-H), 5.49 (m, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, APT, 50 MHz): δ = 11.16, 14.08, 17.12, 18.80, 26.06, 27.05, 28.37, 28.65, 29.25, 30.30, 30.99, 34.21, 35.63, 37.84, 38.18, 38.84, 44.41, 46.41, 49.85, 49.88, 53.48, 66.98 (26-C), 77.70 (12-C), 84.90 (16-C), 106.52 (22-C), 120.49 (15-C), 153.62 (14-C), 177.67 (piv-C=O), 210.86 (3-C). − IR (KBr): $\tilde{\nu}$ = 2953 cm^{-1} (s), 2874 (m), 1723 (s), 1480 (m), 1460 (m), 1157 (m). − MS (EI, 160°C): *m/z* (%) = 513 (64), 410 (74), 337 (64), 295 (100), 126 (81). − HRMS: calcd. 512.3501; found 512.3311. − EA: calcd. C 74.96, H 9.44; found C 74.61, H 9.33.

2α-Bromo-3-oxo 12α-Pivalate **22**: 7.0 g (21.9 mmol) of pyridinium bromide perbromide in 30 ml of dry THF was added to a solution of 8.0 g (15.6 mmol) of **21** in 350 ml of THF at room temperature. After 1 h, the reaction mixture was poured into a satd. aq. $NaHCO_3$ solution. The aqueous layer was extracted twice with 150 ml of dichloromethane and the combined organic layers were dried with $MgSO_4$. After careful evaporation of the solvent in vacuo at room temperature, the residue was purified on silica gel (hexanes/ethyl acetate, 5:1) affording 6.1 g (66%) of the thermolabile product **22** as a colourless oil that foamed up in vacuo. − $C_{32}H_{47}BrO_5$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.79 (d, *J* = 6.1 Hz, 3 H, 27-H), 0.98 (d, *J* = 6.4 Hz, 3 H, 21-H), 1.01−2.51 (m, 35 H), 3.32−3.54 (m, 2 H, 26-H), 4.73 (dd, *J* = 13.6, 6.2 Hz, 1 H, 2-H), 4.88 (m, 2 H, 12/16-H), 5.59 (s, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, APT, 50 MHz): δ = 11.84 (−), 14.08 (−), 17.12 (−), 18.81 (−), 26.19 (+), 27.05 (−), 27.86 (+), 28.65 (−), 29.05 (+), 30.29 (−), 30.98 (+), 33.72 (−), 38.84 (+), 43.65 (+), 44.40 (−), 47.18 (−), 49.62 (−), 49.86 (+), 51.08 (+), 53.46 (−), 53.77 (−), 67.00 (+, 26-C), 77.36 (−, 12-C), 84.83 (−, 16-C), 106.56 (+, 22-C), 120.82 (−, 15-C), 153.02 (+, 14-C), 177.70 (+, piv-C=O), 200.41 (+, 3-C). − IR (KBr): $\tilde{\nu}$ = 2954 (m), 2874 (m), 1728 (s), 1480 (m), 1283 (m), 1156 (s), 1064 (m), 981 (m). − MS (EI, 140°C): *m/z* (%) = 592 [M^+] (19), 590 (19), 512 (9), 490 (28), 488 (28), 376 (62), 374 (63), 296 (37), 126 (100). − HRMS: calcd. 592.2587; found 592.2567. − EA: calcd. C 64.97, H 8.01; found C 64.43, H 7.81.

2α-Bromo-3β-hydroxy 12α-Pivalate **23**: 6.5 g (10.98 mmol) of bromo ketone **22** was dissolved in 50 ml of a 1:1 mixture of dichloromethane/methanol and the resulting solution was cooled to 0°C. Solid sodium tetrahydroborate (830 mg, 21.8 mmol) was then added in three portions. After 90 min, 2 N citric acid was added slowly. The mixture was extracted with dichloromethane. The combined organic layers were washed with a satd. solution of $NaHCO_3$ and brine, and dried with $MgSO_4$. Evaporation of the solvent and purification on silica gel gave 3.88 g (60%) of the β-alcohol **23** and 1.17 g (18%) of the corresponding α-alcohol. − $C_{32}H_{49}O_5Br$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.79 (d, *J* = 6.2 Hz, 3 H, 27-H), 0.89 (s, 3 H, 19-H), 0.96 (d, *J* = 6.6 Hz, 3 H, 21-H), 1.14 (s, 3 H, 18-H), 1.17 (s, 9 H, *tert*-butyl), 0.77−1.90 (m), 2.15 (br t, *J* = 10.5 Hz, 1 H, 8-H), 2.21 (dd, *J* = 12.8, 4.4 Hz, 1 H), 2.32 (dd, *J* = 9.2, 8.3 Hz, 1 H, 17-H), 3.40 (t, *J* = 10.9 Hz, 1 H, 26-H), 3.45−3.51 (m, 1 H, 26-H), 3.58−3.67 (m, 1 H, 3-H), 4.08 (ddd, 1 H, 2-H), 4.82−4.89 (m, 2 H, 12/16-H), 5.48 (s, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.39 (q, 19-C), 14.12 (q, 21-C), 17.14 (q, 27-C), 18.85 (q, 18-C), 26.09 (t), 27.13 (q, × 3, *tert*-butyl), 27.48 (t), 28.71 (t), 29.32 (t), 30.37 (d), 31.05 (t), 33.85 (d, 8-C), 35.88 (t), 38.95 (s), 39.29 (s), 44.46 (d), 44.57 (d), 48.11 (t), 49.90 (s), 50.04 (d), 53.52 (d, 17-C), 59.39 (d, 2-C), 67.08 (t, 26-C), 75.88 (d, 3-C), 77.64 (d, 12-C), 84.98 (d, 16-C), 106.65 (s, 22-C), 120.49 (d, 15-C), 153.70 (s, 14-C), 177.86 (s, C=O). − IR ($CHCl_3$): $\tilde{\nu}$ = 3560 cm^{-1} (w), 2956 (s), 2932 (s), 2872 (m), 1716 (s), 1480 (m), 1460 (m), 1376 (w), 1284 (m), 1240 (m), 1156 (s), 1056 (m). − MS (EI, 140°C): *m/z* (%) = 595 (3), 594 (2), 593 [M^+] (3), 493 (5), 491 [M^+ − pivOH] (4), 378 (6), 376 (6), 187 (8), 173 (12), 170 (12), 169 (90), 155 (100). − HRMS: calcd. 592.2763; found 592.2765.

2,3-β-Epoxide 12α-Pivalate **24**: 586 mg (0.99 mmol) of bromo alcohol **23** was dissolved in 5 ml of *tert*-butyl methyl ether, and then 45 ml of 2-propanol and 554 mg (9.87 mmol) of KOH were added. The reaction mixture was heated at 50°C for 3 h. After cooling to room temperature, the mixture was diluted with 100 ml of water and neutralized with 2 N citric acid. The aqueous layer was washed with *tert*-butyl methyl ether. The combined organic layers were successively washed with satd. aqueous $NaHCO_3$ solution and brine, and then dried with $MgSO_4$. The crude product (506 mg) was purified on silica gel (hexanes/ethyl acetate, 6:1), furnishing 481 mg (95%) of **24** as colorless crystals (m.p. 191−193°C). − $C_{32}H_{48}O_5$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.79 (d, *J* = 6.2 Hz, 3 H, 27-H), 0.89 (s, 3 H, 19-H), 0.96 (d, *J* = 6.8 Hz, 3 H, 21-H), 1.13 (s, 3 H, 18-H), 1.17 (s, 9 H, *tert*-butyl), 0.77−1.85 (m), 2.09 (m, 2 H), 2.32 (dd, *J* = 9.6, 8.3 Hz, 1 H, 17-H), 3.09 (br m, 1 H, 2-H), 3.17 (m, 1 H, 3-H), 3.40 (t, *J* = 10.9 Hz, 1 H, 26-H), 3.45−3.52 (m, 1 H, 26-H), 4.81−4.86 (m, 2 H, 12/16-H), 5.45 (m, 1 H, 15-H). − MS (EI, 120°C): *m/z* (%) = 512.6 [M^+] (58), 411 (35), 410 [M^+ − pivOH] (92), 398 (14), 338 (37), 298 (34), 297 (100). − HRMS: calcd. 512.3502; found 512.3503.

3α-Azido-2β-hydroxy 12α-Pivalate **25**: 2.4 g (4.68 mmol) of the epoxide **24** was dissolved in 30 ml of dimethylacetamide, and 1.5 g (23.4 mmol) of sodium azide and 3 ml of water were added. The reaction mixture was heated at 65°C for 18 h. After cooling to room temperature, 200 ml of water was added and the mixture was extracted with *tert*-butyl methyl ether. The combined organic layers were washed with brine and dried with $MgSO_4$. Purification on silica gel gave 2.4 g (92%) of the product as a white foam. − $C_{32}H_{49}N_3O_5$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.79 (d, *J* = 6.2 Hz, 3 H, 27-H), 0.96 (d, *J* = 6.6 Hz, 3 H, 21-H), 1.04 (s, 3 H), 1.14 (s, 3 H), 1.17 (s, 9 H, *tert*-butyl), 2.19 (m, 1 H, 8-H), 2.33 (dd, *J* = 9.3, 8.4 Hz, 1 H, 17-H), 3.37−3.52 (m, 2 H, 26-H), 3.74 (br s, 1 H, 3-H), 3.90 (br s, 1 H, 2-H), 4.81−4.91 (m, 2 H, 12/16-H), 5.48 (br s, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.07 (q), 14.14 (q), 17.14 (q), 18.90 (q), 25.66 (t), 27.18 (q, × 3, piv), 27.55 (t), 28.04 (t), 28.74 (t), 29.40 (t), 30.40 (d), 31.09 (t), 33.84 (d), 35.66 (s), 38.98 (s), 39.89 (d), 40.34 (t), 44.47 (d), 49.95 (s), 50.92 (d), 53.53 (d), 62.06 (d, 3-C), 67.08 (t, 26-C), 69.23 (d, 2-C), 77.97 (d, 12-C), 85.07 (d, 16-C), 106.64 (s, 22-C), 120.27 (d, 15-C), 154.22 (s, 14-C), 178.04 (s, C=O). − IR ($CHCl_3$): $\tilde{\nu}$ = 3612 (w), 2956 (s), 2932 (s), 2872 (m), 2096 (s), 1716 (s), 1652 (w), 1600 (w), 1480 (m), 1460 (m), 1376 (w), 1156 (s). − MS (EI, 170°C): *m/z* (%) = 556 (46), 453 [M^+ − $C_5H_{10}O_2$] (85), 339 (100), 126 (95). − HRMS: calcd. 555.3672; found 555.3662.

3α-Azido-2β-tosylato 12α-Pivalate **26**: 1.005 g (1.81 mmol) of azido alcohol **25** was dissolved in 10 ml of dry pyridine, and 690 mg (3.62 mmol) of *p*-toluenesulfonyl chloride and 20 mg of DMAP were added. The reaction mixture was heated at 60°C for 24 h. After pouring into 2 N aq. HCl, the aqueous layer was extracted with *tert*-butyl methyl ether. The combined organic layers were washed successively with 2 N aq. HCl (2 ×), satd. aqueous $NaHCO_3$ solution and brine, and finally dried with $MgSO_4$. After evaporation of the solvent, the residue was purified on silica gel to furnish 1030 mg (80%) of a colourless oil. − $C_{39}H_{55}N_3O_7S$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.79 (d, *J* = 6.2 Hz, 27-H), 0.95 (m, 6 H), 1.11 (s, 3 H), 1.14 (s, 9 H), 2.17 (m, 1 H, 8-H), 2.30 (m, 1 H, 17-H), 2.48 (s, 3 H, Ts-CH_3), 3.36−3.53 (m, 2 H, 26-H), 3.79 (br s, 1 H, 3-H), 4.41 (br s, 1 H, 2-H), 4.81 (m, 1 H, 12-H), 4.84 (m, 1 H, 16-H), 5.46 (m, 1 H, 15-H), 7.37 (m, 2 H, Ts), 7.77 (m, 2 H, Ts). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.51 (q), 14.13 (q), 17.14 (q), 18.83 (q), 21.71 (q, Ts-CH_3), 25.59 (t), 27.14 (q, × 3, *tert*-butyl), 27.29 (t), 28.01 (t), 28.70 (t), 29.23 (t), 30.37 (d), 31.04 (t), 33.76 (d, 8-C), 35.55 (s), 37.69 (t), 38.93 (s), 39.17 (d), 44.44 (d), 49.90 (s), 50.69 (d), 53.48 (d, 17-C), 59.49 (d, 3-C), 67.07 (t, 26-C), 77.69 (d, 12-C), 77.82 (d, 2-C), 85.00 (d, 16-C), 106.63 (s, 22-C), 120.38 (d, 15-C), 127.73 (d, Ts), 130.12 (d, Ts), 133.34 (s, Ts), 145.26 (s, Ts), 153.86 (s, 14-C), 177.89 (s, C=O). − IR ($CHCl_3$): $\tilde{\nu}$ = 2956 cm^{-1} (s), 2932 (s), 2872 (m), 2100 (s), 1716 (s), 1652 (w), 1596 (w), 1456 (m), 1368 (s), 1284 (m), 1176 (s), 1156 (s). − MS (EI, 200°C): *m/z* (%) = 709 [M^+] (28), 607 [M^+ − $C_5H_{10}O_2$] (61), 493 (65), 126 (93), 91 (100). − HRMS: calcd. 709.3761; found 709.3764.

12′-Oxo-12α-pivaloyloxy Dimer **27a**: 64 mg (0.12 mmol) of vinyl azide **17a**, 51 mg (0.12 mmol) of enamino ketone **5**, 30 mg of 4-Å molecular sieves (activated powder) and a catalytic amount (1 mg) of PPTS were mixed in a dried round-bottomed flask under argon. Then, 2 ml of dry dioxane was added and the reaction mixture was stirred for 2 h under reflux. The solvent was evaporated in vacuo and the residue was filtered through silica gel and then purified on silica gel (hexanes/ethyl acetate, 2:1) to give 55 mg (51%) of the dimer **27a**. − $C_{59}H_{82}N_2O_7$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.77−1.03 (m, 24 H), 1.18 (s, 9 H), 1.20−2.43 (m, 32 H), 2.47−2.92 (m, 8 H), 3.31−3.53 (m, 4 H, 26/26′-H), 4.78 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.90 (dd, *J* = 7.9, 2.0 Hz, 1 H), 4.93 (s, 1 H, 12′-H), 5.49 (s, 1 H), 5.52 (s, 1 H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 11.52, 11.75, 13.76, 14.10, 17.14, 18.79, 20.75, 26.08, 27.14, 27.85, 27.95, 28.74, 28.77, 30.31, 30.39, 31.09, 31.26, 33.95, 34.20, 35.15, 35.21, 35.68, 36.36, 37.20, 38.91, 41.24, 41.65, 44.21, 44.52, 45.17, 45.75, 49.75, 49.89, 49.92, 53.14, 53.60, 62.29, 67.09/67.12 (26/26′-C), 77.71 (12′-C), 83.93/85.00 (16/16′-C), 106.64/107.05 (22/22′-C), 120.67/121.56 (15/15′-C), 148.09/148.10/148.58/148.64 (1/1′/2/2′-C), 153.85/154.28 (14/14′-C), 177.60 (C=O), 210.73 (12-C). − IR (KBr): $\tilde{\nu}$ = 2956 cm^{-1}, 2932, 2872, 1716, 1400, 1376, 1192, 1156. − FAB-MS (NBA matrix): *m/z* (%) = 932 [MH^+] (100), 818 (27). − EA: calcd. C 76.09, H 8.87, N 3.01; found C 76.10, H 8.74, N 3.26.

12′-Oxo-12α-propanoyloxy Dimer **27b**: 49 mg (0.10 mmol) of vinyl azide **17b**, 50 mg (0.12 mmol) of enamino ketone **5**, 30 mg of 4-Å molecular sieves (activated powder) and a catalytic amount (1 mg) of PPTS were mixed in a dried round-bottomed flask under argon. Then, 2 ml of dry toluene was added and the reaction mixture was stirred for 2.5 h under reflux. The solvent was then evaporated in vacuo and the residue was purified on silica gel to give 31 mg (36%) of the dimer **27b**. − $C_{57}H_{78}N_2O_7$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.81 (d, *J* = 6.2 Hz, 6 H, 27/27′-H), 0.85 (s, 3 H), 0.92 (s, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 1.11 (t, *J* = 7.7 Hz, 3 H, prop-CH_3), 1.17 (s, 3 H, 18′-H), 1.33 (s, 3 H, 18-H), 2.18 (m, 1 H), 0.78−2.90 (m, 68 H), 3.34−3.56 (m, 5 H, 17/26/26′-H), 4.78 (dd, *J* = 8.1, 2.0 Hz, 1 H), 4.84 (dd, *J* = 7.9, 1.8 Hz, 1 H), 4.95 (m, 1 H, 12′-H), 5.48 (m, 1 H), 5.50 (m, 1 H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.25 (q), 11.51 (q), 11.73 (q), 13.76 (q), 14.08 (q), 17.15 (q, × 2), 18.69 (q), 20.75 (q), 26.25 (t), 27.85 (t), 27.92 (t), 28.14 (t), 28.71 (t), 28.77 (t), 29.09 (t), 29.13 (t), 30.31 (d), 30.38 (d), 31.23 (t), 31.26 (t), 33.95 (d), 34.20 (d), 35.17 (t), 35.21 (t), 35.65 (s), 36.35 (s), 37.20 (t), 41.21 (d), 41.59 (d), 44.20 (d), 44.53 (d), 45.19 (t), 45.77 (t), 49.75 (d), 49.82 (d), 50.03 (s), 53.14 (d), 53.66 (d), 62.28 (s), 67.12/67.17 (both t, 26/26′-C), 77.85 (d, 12′-C), 83.93/85.14 (both d, 16/16′-C), 106.66/107.04 (both s, 22/22′-C), 121.07/121.57 (both d, 15/15′-C), 148.06/148.10/148.56/148.66 (all s, 2/3/2′/3′-C), 153.21/154.28 (both s, 14/14′-C), 173. 71 (s, C=O), 210.70 (s, 12-C). − IR ($CHCl_3$): $\tilde{\nu}$ = 2956 cm^{-1} (s), 2932 (s), 2876 (m), 1712 (s), 1460 (m), 1400 (m). − FAB-MS (NBA matrix): *m/z* (%) = 904 [MH^+] (100). − HR-FAB: calcd. 903.5887; found 903.5999.

Enol Ketone **28**: Obtained as a by-product in reactions leading to **27a/b**. − $C_{27}H_{36}O_5$. − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.80

(d, J = 6 Hz, 3 H), 0.93−2.19 (m, 22 H), 2.49 (m, 3 H), 2.84 (t, J = 7.2 Hz, 1 H), 3.29−3.60 (m, 3 H), 4.77 (d, J = 4.2 Hz, 1 H, 16-H), 5.48 (s, 1 H, 15-H), 6.29 (s, 1 H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.90 (−), 13.95 (−), 17.15 (−), 20.96 (−), 26.99 (+), 28.91 (+), 29.01 (+), 30.34 (−), 31.29 (+), 34.46 (−), 37.75 (+), 39.92 (+), 39.95 (+), 43.41 (−), 44.23 (−), 50.00 (−), 51.03 (−), 62.51 (+), 67.13 (+, 26-C), 83.95 (−, 16-C), 107.14 (+, 22-C), 121.70 (−, 15-C), 124.57 (−), 134.43 (+), 153.97 (+, 14-C), 194.32 (+), 209.38 (+). − IR ($CHCl_3$): $\tilde{\nu}$ = 3424 cm^{-1} (w), 2929 (m), 2873 (m), 1714 (s), 1668 (m), 1460 (m), 1067 (m). − MS (EI, 190°C): *m/z* (%) = 440 [M^+] (5), 311 (10), 189 (33), 75 (100).

Methyl 3α,12α-Dihydroxy-5β,14α-chol-14(15)-en-24-oate (**37**): 30 g (73.4 mmol) of cholic acid and 30 g (220.6 mmol, 3 equiv.) of zinc(II) chloride were dissolved in 300 ml of freshly distilled acetone. The solution was heated at 80°C for 2 h and the solvent was slowly distilled off until TLC showed total conversion of the starting material. The solution was then cooled to room temperature and 300 ml of 0.5% aq. acetic acid was added. A white solid was deposited, which was collected by filtration and dried in vacuo. It was redissolved in methanol and the resulting solution was treated with 12 g of the ion-exchange resin Amberlyst 15. The mixture was then stirred for 12 h, the resin was separated by filtration, and the filtrate was concentrated in vacuo to afford a while solid. The solid was dissolved in 250 ml of freshly distilled chloroform and the solution was cooled to −78°C with dry ice/acetone. A dry stream of hydrogen chloride gas was passed through the solution for 2 h, followed by a stream of nitrogen to remove excess hydrogen chloride from the reaction vessel. Then, 100 ml of a 0.5 M solution of sodium hydrogen carbonate was added at low temperature and the mixture was allowed to warm to room temperature. The organic layer was separated, washed with water, dried with $MgSO_4$, and concentrated in vacuo to afford a yellow solid. Flash chromatography on 1 kg of silica gel with a solvent gradient of ethyl acetate/hexanes from 1:1 to 3:1 yielded 14.8 g (50%) of a white solid. − $C_{25}H_{40}O_4$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.88−0.96 (m, 9 H, 18-H, 19-H, 21-H), 1.0−2.4 (m, 25 H), 3.56 (m, 1 H, 3-H), 3.63 (s, 3 H, 25-H), 3.76 (t, J = 2 Hz, 1 H, 12-H), 5,25 (d, J = 2 Hz, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.8 (q), 17.8 (q), 23.0 (q), 24.0 (t), 26.9 (t), 29.3 (t), 30.6 (t), 30.9 (t), 31.2 (t), 32.0 (d), 33.6 (d), 34.3 (s), 34.8 (d), 35.0 (t), 35.1 (t), 36.3 (t), 42.0 (d), 47.0 (d), 51.6 (q), 51.8 (s), 71.7 (d, 12-C), 73.3 (d, 3-C), 120.2 (d, 15-C), 151.5 (s, 14-C), 174.9 (s, 24-C). − IR ($CHCl_3$): $\tilde{\nu}$ = 3420 cm^{-1} (w), 2928 (m), 2804 (m), 1740 (m), 1632 (m). − MS (EI): *m/z* (%) = 404 (5), 386 (100), 371 (95), 368 (22). − HRMS: calcd. 404.2929; found 404.2926.

Methyl 3,12-Dioxo-5β,14α-chol-14(15)-en-24-oate (**38**): 1.0 g (2.5 mmol) of the $\Delta^{14,15}$-diol **37** was dissolved in 30 ml of dichloromethane and a mixture of 2.13 g (9.9 mmol, 4 equiv.) of PCC, 2.13 g of silica gel and 176 mg (2.5 mmol, 1 equiv.) of sodium acetate was added. The suspension was stirred at room temperature for 4 h and then filtered through a plug of silica gel. The eluate was washed once with brine, dried with $MgSO_4$, and concentrated in vacuo to afford a yellow solid. Flash chromatography on 50 g of silica gel with a mixture of ethyl acetate/hexanes yielded 0.81 g (81%) of a white solid. − $C_{25}H_{36}O_4$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.90 (d, J = 7 Hz, 3 H, 21-H), 1.06 (s, 3 H, 18-H), 1.21 (s, 3 H, 19-H), 1.3−2.4 (m, 23 H), 3.63 (s, 3 H, 25-H), 5.28 (d, J = 2 Hz, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.6 (q), 19.2 (q), 22.0 (q), 23.5 (t), 26.1 (t), 30.6 (t), 31.4 (t), 33.6 (d), 34.4 (d), 34.9 (t), 35.5 (q), 36.5 (t), 37.1 (t), 38.5 (t), 41.0 (d), 42.1 (t), 43.7 (d), 47.1 (d), 51.6 (q), 62.8 (s), 120.9 (d, 15-C), 151.7 (s, 14-C), 174.7 (s, 24-C), 212.1 (s, 12-C), 213.3 (s, 3-C). − IR ($CHCl_3$): $\tilde{\nu}$ = 2936 cm^{-1} (m), 2872 (m), 1708 (m). − MS (EI): *m/z* (%) = 400 (10), 369 (3), 285 (100). − HRMS: calcd. 400.2600; found 400.2600. − EA: calcd: C 74.96, H 9.06; found C 74.75, H 9.06.

Methyl 2β-Bromo-3,12-dioxo-5β,14α-chol-14(15)-en-24-oate (**39**): 98 mg (0.24 mmol) of the diketone **38** and 69 mg (1.2 equiv., 0.3 mmol) of phenylselenyl bromide were dissolved in 2 ml of ethyl acetate and the solution was stirred at room temperature for 4 d. The solvent was then removed and the crude residue was purified by flash chromatography on 8 g of silica gel with a solvent mixture of ethyl acetate/hexanes to yield 34 mg (29%) of a yellow solid. − $C_{25}H_{35}BrO_4$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.95 (d, J = 6.6 Hz, 3 H, 21-H), 1.12 (s, 3 H, 18-H), 1.25 (s, 3 H, 19-H), 1.3−2.8 (m, 21 H), 3.68 (s, 3 H, 24-H), 4.65 (dd, J = 13.8, 5.6 Hz, 1 H, 2-H), 5.34 (m, 1 H, 15-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 17.7 (q), 19.2 (q), 21.7 (q), 23.4 (t), 26.0 (t), 30.7 (t), 31.7 (t), 33.6 (d), 34.5 (d), 34.9 (t), 38.5 (t), 39.1 (s), 41.3 (d), 41.6 (t), 44.5 (d), 47.3 (d), 48.8 (t), 51.6 (q), 52.3 (d, 3-C), 62.9 (s, 25-C), 121.5 (d, 15-C), 151.1 (s, 14-C), 176.7 (s, 24-C), 201.5 (s, 3-C), 212.6 (s, 12-C). − IR ($CHCl_3$): $\tilde{\nu}$ = 2932 cm^{-1} (m), 2872 (m), 1732 (m), 1708 (m), 1648 (m). − MS (EI): *m/z* (%) = 478 (5), 447 (5), 365 (100), 284 (69). − HRMS: calcd. 478.1719; found 478.1718.

Methyl 2-Amino-3,12-dioxo-5β,14α-chol-1(2),14(15)-dien-24-oate (**40**): 45 mg (0.10 mmol) of the 2-bromide **39** was dissolved in 2.5 ml of degassed DMF under argon. Then, 71.5 mg (11 equiv., 1.1 mmol) of sodium azide and one crystal of sodium iodide were added and the solution was heated to 65°C under argon for 2 h. The solution was then allowed to cool to room temperature and 1 ml of water was added. The mixture was extracted three times with a 2:1 mixture of *tert*-butyl methyl ether/hexanes, and the combined extracts were washed with brine and dried with $MgSO_4$. Removal of the solvent in vacuo yielded 34 mg (81%) of enamino ketone **40**. − $C_{25}H_{35}NO_4$. − ^{1}H NMR: δ = 0.92 (m, 3 H, 21-H), 1.21 (m, 6 H, 18-H and 19-H), 1.22−2.7 (m, 21-H), 3.64 (s, 3 H, 24-H), 5.28 (m, 1 H, 15-H), 5.60 (s, 1 H, 1 H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.4, 17.7, 19.2, 27.4, 29.5, 30.7, 31.7, 32.4, 33.6, 33.8, 34.6, 36.9, 35.4, 38.2, 38.8, 47.1, 53.0, 60.4, 121.8, 124.9, 150.0, 150.2, 174.29, 198.9, 212.5. − IR (KBr): $\tilde{\nu}$ = 3484 cm^{-1}, 3456, 1724, 1672, 1640. − MS (EI): *m/z* (%) = 413 (27), 298 (92), 283 (100). − HRMS: calcd. 413.2513; found 413.2512. − UV: λ = 209, 286 nm.

Dimer **41**: 40 mg of 2-enamino ketone **40** (0.10 mmol) and 51 mg of 3-vinyl azide **17b** (0.10 mmol) were dissolved in 1 ml of abs. dioxane and approx. 1 mg of PPTS was added. The solution was degassed with argon and 30 mg of 4-Å molecular sieves (activated powder) was added. The suspension was refluxed for 2.5 h under argon, allowed to cool to room temperature and filtered through a plug of silica gel with diethyl ether as eluent. The solvent was removed from the filtrate in vacuo and the crude residue was flash-chromatographed on 4 g of silica gel with a solvent mixture of ethyl acetate/hexanes to obtain 26 mg (30%) of dimer **41**. − $C_{55}H_{76}N_2O_7$. − ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.78−3.0 (m, 65 H), 3.45 (m, 2 H, 26′-H) 3.62 (s, 3 H, 24 H), 4.81 (d, 1 H, H-16′), 4.90 (s, 1 H, 12′-H), 5.28 (m, 1 H, 15-H), 5.60 (s, 1 H, 15′-H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.3 (q), 11.7 (q), 14.1 (q), 17.2 (q), 17.6 (q), 18.7 (q), 19.1 (q), 21.9 (q), 28.1 (t), 28.7 (t), 29.7 (t), 30.4 (d), 30.5 (t), 31.2 (t), 31.3 (t), 31.7 (t), 31.9 (t), 33.5 (d), 33.6 (t), 33.8 (t), 34.2 (d), 34.4 (d), 34.6 (t), 34.9 (t), 35.5 (s), 35.8 (s), 38.3 (t), 38.7 (s), 38.9 (d), 41.4 (d), 41.7 (d), 42.4 (t), 44.5 (d), 45.6 (t), 46.9 (d), 47.0 (d), 49.7 (d), 50.0 (s), 51.5 (q), 52.9 (d), 53.6 (d), 62.7 (s), 67.3 (t), 78.0 (d), 85.2 (d), 106.8 (s), 120.5 (d), 121.1 (d), 147.3 (s), 148.5 (s), 148.6 (s), 149.0 (s), 151.6 (s), 153.4 (s), 173.9 (s), 176.8 (s), 213.4 (s). − IR: $\tilde{\nu}$ = 1724 cm^{-1}, 1672, 1460, 1400. − FAB: *m/z* = 878 [MH^+] − HR-FAB: [MH^+] calcd: 877.5731; found 877.5838. − UV: λ = 305 (sh), 288 nm.

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