Selective Derivatization of the Ionophore X-206 at C(22) Maintaining Potassium Binding

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The insecticidal polyether antibiotic X-206 (**1**) complexes potassium ions using nearly all of its O-atoms either for binding to the metal ion or for participation in a H-bonding network which helps to hold X-206 in the ionophoric tertiary structure. The group OH–C(22) is not involved in these processes. It was supposed that derivatization of this group would not affect the ionophoric properties and would produce insecticidally active compounds. The chemistry leading to selective modification of OH–C(22) *via* the intermediate **6** was developed. The potassium-binding properties and insecticidal activities of the MeCOO–C(22) and MeO–C(22) compounds **3** and **11**, respectively, confirmed that derivatization of the peripheral OH–C(22) was a valid strategy for the synthesis of biologically active compounds.

Introduction. – The polyethers are a class of naturally occurring ionophore antibiotics [1a]. There are now more than 120 examples known [2]. The first ionophores of this kind were isolated in 1951 [3], but it was only much later in 1967 that the structure of one of these complicated molecules was solved by X-ray analysis [4]. The polyethers are best known for their activity as antibiotics and coccidiostatics, and several have found commercial use in these areas [5]. However, examples of insecticidal [6], acaricidal [7], and anthelmintic [8] properties of ionophores have been described. They exert their activity by complexing potassium, sodium, and hydron ions, thereby surrounding them in a lipophilic sheath and allowing their diffusion across biological membranes [1b][9]. The natural ionic gradients, which are vitally important for cells, are thus broken down. Fortunately, the toxicities of the compounds vary from organism to organism, which may be attributed more to their differing transport behaviour, rather than to intrinsic differences in ion-transport properties.

X-206 (**1**) was one of the first ionophores to be isolated [10], but it was only in 1975 that the X-ray structure was determined [11], after a first incorrect structural proposal had been made in 1971 [12]. X-206 was originally isolated by persuing its antibacterial activity, but in 1980, the *Chugai* pharmaceutical company patented its insecticidal and acaricidal activites [13]. More recently, *Gräfe* and *Schlegel* of the *Hans Knöll Institute* in Germany found a new organism which produced X-206 [14] and sent a sample to *Novartis* for routine screening. Its broad insecticidal and acaricidal activity were confirmed. Although this activity was patented by *Chugai*, and although an LD_{50} of 17 mg/kg in mouse was described [15], the insecticidal activity was so promising that a derivatization program was started in the hope that the insecticidal activity could be improved and the mammalian toxicity concomitantly reduced.

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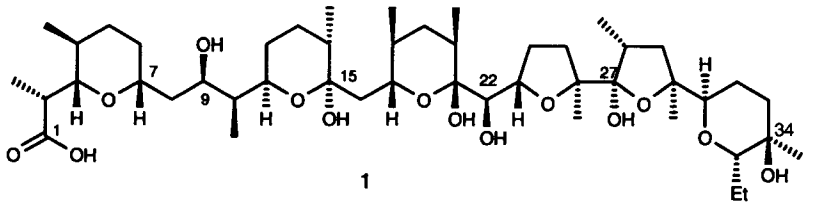


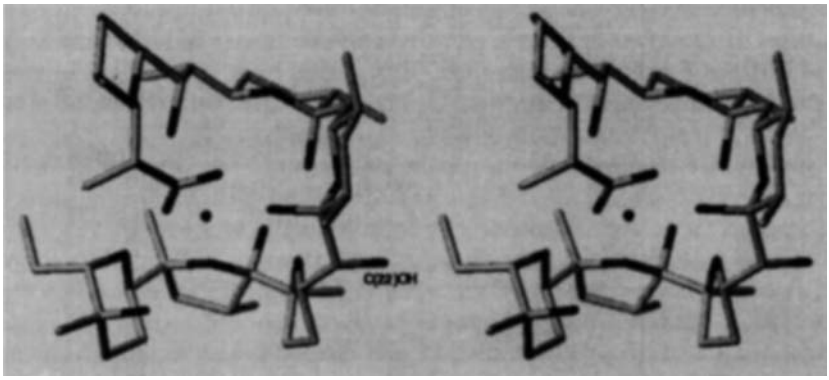


Figure. *Structure of X-206* (**1**) *and the X-ray structure of its* Na^+ *salt*

The derivatization of X-206 has not been intensively studied; this is also the case for polyether antibiotics in general. However, in 1988, *Evans et al.* described the total synthesis of X-206 [16]. Before starting the synthesis, the authors performed some derivatizations and degradations, and the observations they made are relevant to the present work, as described below.

Because of the ionophoric mode of action of X-206 [1a], the crystal structure [11] of the X-206 potassium salt can be regarded as the structure of the molecule bound to its biological target. Most of the O-atoms in the molecule bind to K^+. These and most of the rest of the oxy and hydroxy groups are involved in complex H-bonding networks which are partly responsible for holding the molecule in its tertiary structure. Although nearly all the O-atoms are on the inside of the tennis-ball seam-like tertiary structure [17], the group OH–C(22) is exposed on the periphery and is involved neither in binding to K^+ nor with the H-bonding network. We surmised that derivatization in this position would not affect the binding with K^+. Thus, derivatives obtained by modification at C(22) would have similar potassium-binding abilities, but otherwise differing physicochemical properties, and thus behave differently when released into the ecosystem relevant to insecticidal usage. This turned out to be the case. The target molecules, monoderivatized at C(22), all possessed approximately the same ability to complex K^+ [18], but they had greatly differing insecticidal activities [19]. Many were less active than X-206 itself, but fortunately, many were more active, thus validating our derivatization strategy. However, finally none of the compounds tested showed a suitable biological profile for development as a commercial insecticide.

This paper describes the preparation of suitably protected derivatives of X-206 which allowed the successful synthesis of the C(22)-derivatized targets.

Results and Discussion. – Most of the protecting-group strategies tried did not distinguish significantly between the several OH groups contained in X-206 [18]. However, by profiting from the natural complexing ability of X-206, the required selectivity was obtained.

Nearly all of the OH groups are bound in the interior of the potassium complex [11], but OH–C(22) is exposed. Thus, K^+ can exert a protecting template effect [20]. In fact acetylation of the potassium salt **2** of X-206 took place selectively at OH–C(22) to form **3** in high yield (*Scheme 1*). This template effect provided a useful route to other 22-*O*-acyl derivatives [21]. Conversion of **3** to its benzyl ester **4** was followed by alkylation of two OH groups with benzyloxymethyl chloride to give **5**. Mild basic hydrolysis of AcO–C(22) of **5** led to **6** in high yield. This proved to be a useful key intermediate which could be manipulated in a variety of ways, and furthermore, all of the protecting groups could be removed simultaneously by hydrogenolysis.

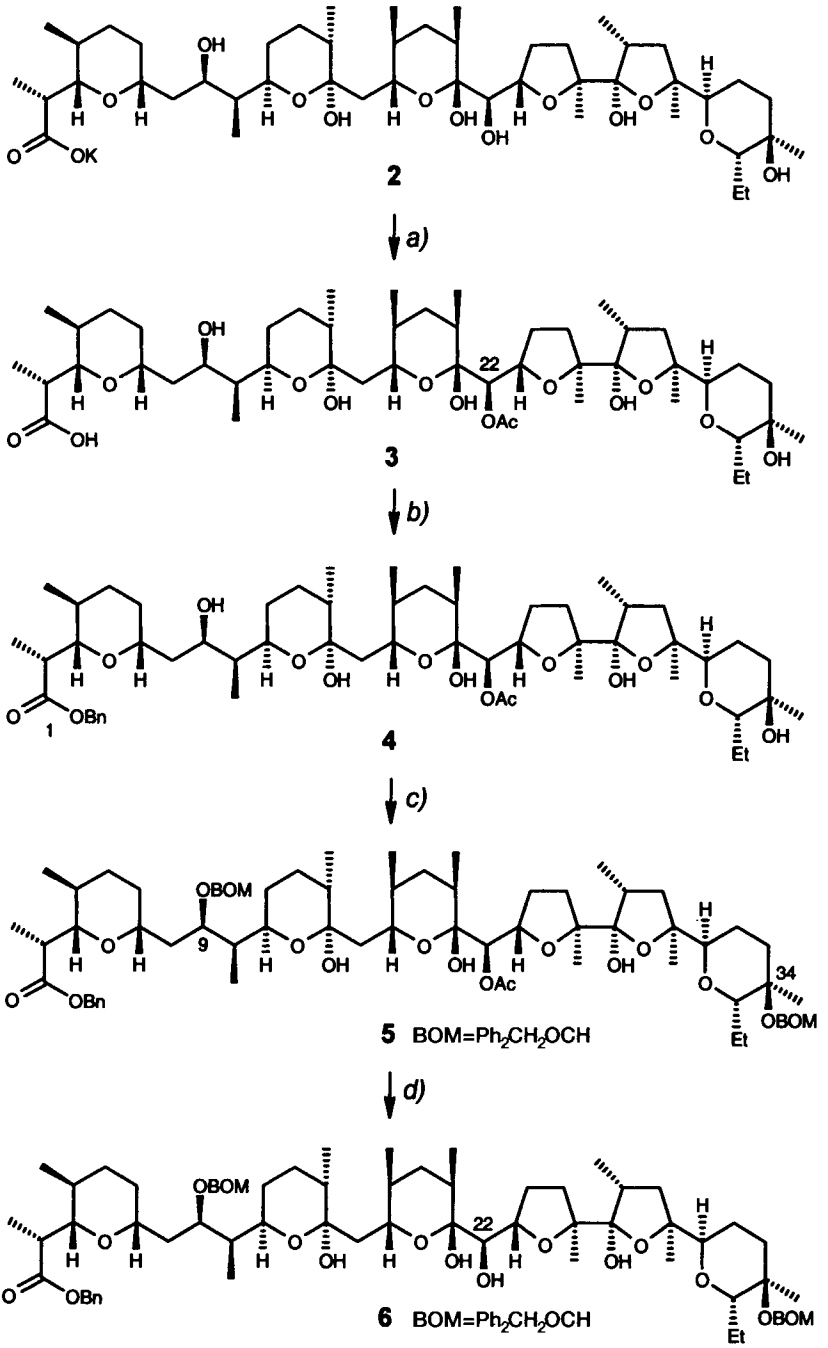
Alkylation of **6** required a powerful alkylating agent. *Meerwein*'s salt (trialkyloxonium tetrafluoroborate) [22] reacted well, and the methyl ether **7** and ethyl ether **8** were formed in good yields and deprotected by hydrogenolysis to **9** and **10**. Acylation of **6** again required a powerful acylating agent. A large excess of acyl chlorides in pyridine reacted slowly forming some esters, *e.g.*, **11** (→ **12** on deprotection), in good yields. Disappointingly, however, only mixtures of products were obtained in most cases.

Oxidation of **6** to the oxo derivative **13** was successful with tetrapropylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO) [23], after various other reagents such as pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), *Parikh-Doering*, and *Dess-Martin* periodinane yielded only mixtures of products. Hydrogenolytic cleavage of the protecting groups led to **14**. The oxo derivative **14** partially removed potassium and/or sodium ions from the silica gel during chromatography, yielding the product as a mixture of free acid and salt. However, simply shaking a solution of the chromatographed product mixture with dilute HCl solution yielded **14** as a pure free acid. Reduction of **13** with $NaBH_4$ led back to **6**. The C(22)-epimeric hydroxy compound was not observed. The *O*-methyl-oxime derivative **15** and the hydrazone derivative **16** were obtained in low yield, but their hydrogenolytic cleavage resulted only in complex product mixtures.

The benzophenone *O*-(oxalyloxime) (= 'benzophenone oxime oxalate') derivative **17** was of interest, because it was to serve as a radical precursor for the deoxygenation at C(22). The idea was to combine the advantages of the known procedures for decarboxylation of *N*-(oxalyloxy)carbothioamides (= '*O*-oxalylthiohydroxamates') [24] and 'benzophenone oxime oxalates' [25]. In the event, photolysis in the presence of *t*-BuSH led only to a single decarboxylation, and the formate **18**, was isolated (*Scheme 3*). Less effective H-donors and higher temperatures facilitate the decarboxylation of alkoxycarbonyl radicals [24][26]. However, when used in the decarboxylation of **17**, the less effective H-donors Bu_3SnH, $(Me_3Si)_3SiH$ and $(i\text{-}Pr)_3SiH$ still trapped the alkoxycarbonyl radical before the second decarboxylation step could take place, leading again either to **18** and/or decomposed material. Formation of a carbonothioate on treatment of **6** with carbonochloridothioates under various conditions failed.

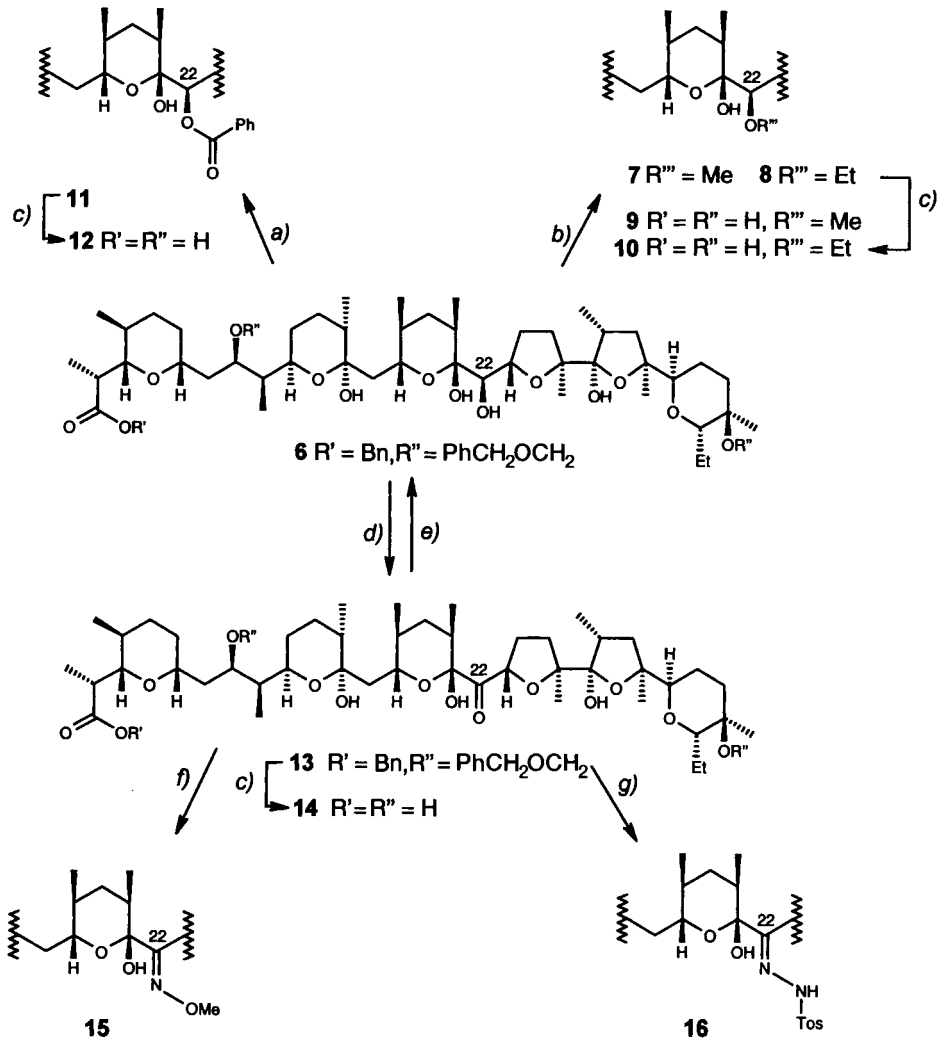
On attemped introduction of substituents of C(22) of **6** by nucleophilic attack on the corresponding tosylate **19**, an interesting and useful transformation occurred (*Scheme 4*). On treatment of **19** with $LiEt_3BH$ or NaSMe, the C(22)-epimeric hydroxy derivative **21**

Scheme 1. *Synthesis of Hemiacetal* **6**



a) Ac_2O, DMAP, C_6H_5N, r.t.; 80%. *b*) BnBr, $(i\text{-}Pr)_2EtN$, r.t.; 85%. *c*) $PhCH_2OCH_2Cl$, $(i\text{-}Pr)_2EtN$, CH_2Cl_2, 40°; 73%. *d*) K_2CO_3, MeOH, H_2O, THF, r.t.; 80%.

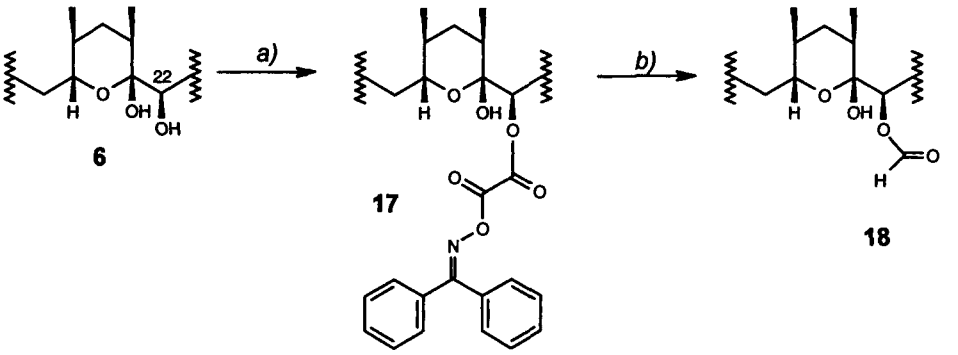
Scheme 2. *Derivatives Available from Compound* **6** *by Modification at C(22)*



a) PhCOCl, C_6H_5N, r.t.; 100%. *b*) R'''_3OBF_4, proton sponge, CH_2Cl_2, 0°, 81% **7**, 78% **8**. *c*) H_2, Pd/C, 0.05M $HClO_4$, THF r.t.; 7% **12**, 72% **9**, 71% **10**, 61% **14**. *d*) TPAP, NMO, CH_2Cl_2, MeCN, 4 Å molecular sieve, r.t.; 68%. *e*) $NaBH_4$, MeOH, r.t.; 45%. *f*) $H_2NOMe \cdot HCl$, C_6H_5N, r.t.; 16%. *g*) $H_2NNHTos$, AcOH, THF, r.t.; 31%.

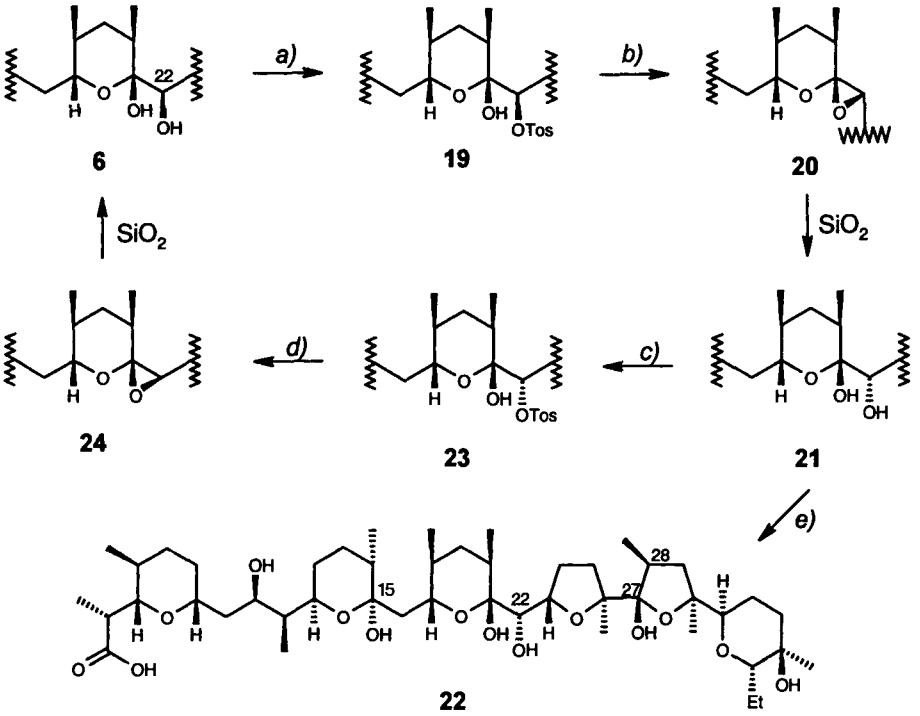
was isolated. Deprotection of **21** led to **22** which was obtained after silica-gel chromatography as a salt, as was the case for the oxo compound **14**. Again unusually, compound **22** was isolated as its C(27),C(28) epimer. This epimerization was also observed by *Evans et al.* in protected forms of X-206, but the bis-epimer was found to revert to the natural configuration on deprotection [16], a process which was understood to be driven by the stability of the tertiary structure of X-206. It thus appears that the tertiary structure of the native X-206 is destabilized in **22**. It is somewhat surprising that the derivatives with

Scheme 3. *Photoinitialized Decarboxylation of Benzophenone-(O-oxalyl oxime) Derivative* **17**



a) Benzophenone *O*-(chlorooxalyl)oxime, C_6H_5N, CH_2Cl_2, 0°. *b*) *t*-BuSH, i-PrOH, *hv*, r.t.; 39% (2 steps).

Scheme 4. *Epimerization via 1,4-Dioxaspiro[2.5]octane Derivatives* **20** *and* **24**



a) Tos_2O, DMAP, C_6H_5N, r.t.; 83%. *b*) DBU, THF, H_2O, r.t.; 76%. *c*) Tos_2O, DMAP, C_6H_5N, r.t.; 27%. *d*) LiOH, THF, H_2O, 10°; 34%. *e*) H_2, Pd/C, 0.05M $HClO_4$, THF, r.t.; 38%.

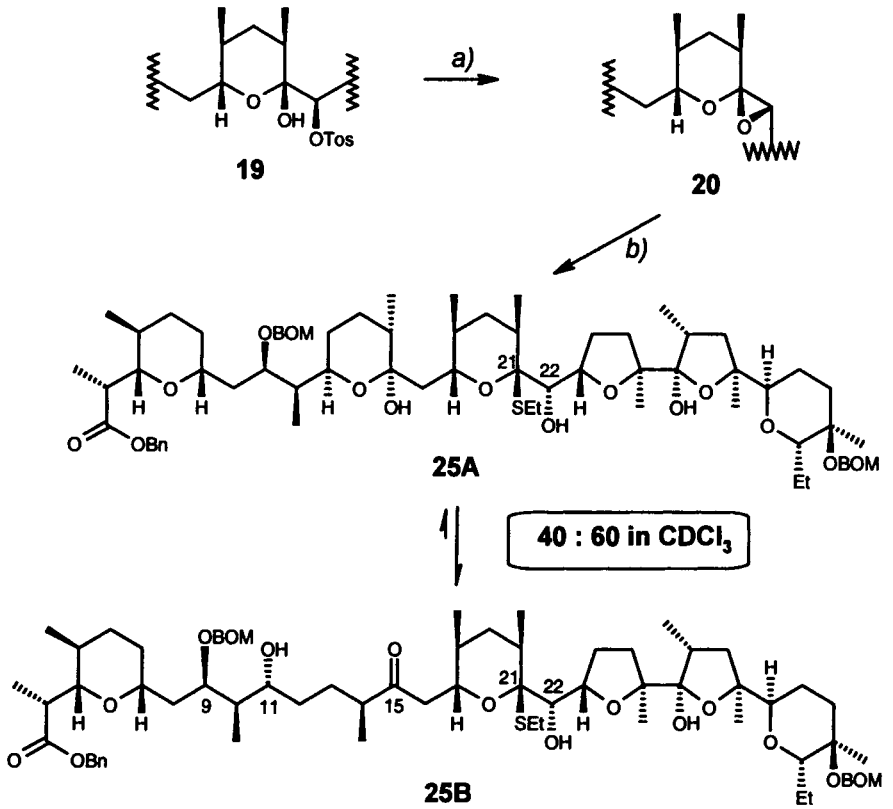
unchanged configuration, which bind well to K^+ and Na^+, do not extract these ions from the silica gel on chromatography, as seen with the **14** and **22**.

Some experiments were performed to establish the mechanism of formation of **21** in the expectation that this knowledge could be exploited for the preparation of new

derivatives. The C(22) centre in **19** is very hindered, so for the formation of **21**, we suspected intramolecular nucleophilic attack of OH–C(21) to form the spiro-oxirane **20** to be responsible, rather than an intermolecular nucleophilic attack of adventitious H_2O or OH^-. It is known that such spiro-oxiranes are reactive and can decompose on silica gel to diols [27]. The spiro-oxirane **20** was stable enough to be examined *in situ* by NMR after treating a solution of tosylate **19** in $CDCl_3$ with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The spiro-oxirane **20** existed as a mixture of two compounds which we suspect to be the hemiacetal and hydroxy ketone tautomers at C(15) (see below). This behaviour is thus similar to that seen by *Evans et al.* for the C(21) methyl acetal [16]. Through a very similar series of intermediates it was possible to convert the epimeric C(22) hydroxy derivative **21** *via* the tosylate **23** and presumably the spiro-oxirane **24** back into the original hydroxy compound **6**.

It was furthermore possible to trap the cation which is intermediate between the spiro-oxirane **20** and the hemiacetal form **21**. Thus, **20** was formed *in situ*, and treated with EtSH and Et_2AlCl at $-78°$ leading to the thioacetal **25** (*Scheme 5*). This compound also exists as a mixture of hemiacetal and hydroxy ketone tautomers at C(15), *i.e.*, **25A** and **25B**, respectively. According to TLC, it was possible to partially separate the

Scheme 5. *Trapping of the Cationic Intermediate of 1,4-Dioxospiro[2.5]octane Derivative* **20**



a) DBU, EtSH, THF, 4-Å molecular sieve, r.t.; *b*) Et_2AlCl, $-78°$; 39% of **25A**, 28% of **25B**.

tautomers by column chromatography (silica gel), but after evaporation of the eluates, each fraction showed the same tautomer composition. This behaviour now seems to be a general phenomenon for compounds monosubstituted at C(21).

Ionophoric and Biological Activity. – The K^+-binding ability of these compounds was determined [18][28] and their insecticidal activity screened [19] (see *Table*). The 22-*O*-acetyl derivative **3** and the 22-*O*-methyl derivative **11** both bind well to K^+, thus confirming our prognosis and validating our derivatization strategy. The log K_c values were close to that of X-206 [18]. We were unable to derive a log K_c value for the 22-oxo derivative **14**, which showed an unusual and complicated behaviour on titration with K^+.

Table. *Ionophoric and Insecticidal Activities of X-206 Derivatives*

			EC_{80} [ppm]		
	R at C(22)	log K_c (K^+)	*Heliothis*	*Plutella*	*Diabrotica*
1 (X-206)	OH	4.9	50	50	25
3	AcO	4.4	25	100	>100
11	MeO	4.8	25	>100	50

The insecticidal results (EC_{80}) varied considerably from compound to compound, again as expected, but the 22-*O*-acetyl derivative **3** and the 22-*O*-methyl compound **11** showed insecticidal activity comparable to, although somewhat weaker than that of X-206.

Conclusion. – Derivatization at C(22) of X-206 (**1**) became possible and straightforward through the use of **6**. Access to C(22)-epimeric compounds was achieved not by intermolecular S_N2 reactions, but by the intervention of the neighbouring OH–C(21), forming the strained 1,4-dioxaspiro[2.5]octane **20**, which is unprecedented in a molecule of this complexity [27]. From this unstable intermediate, nucleophiles could be selectively introduced at C(21).

Experimental Part

Biological Results. The tests for *Heliothis virescens* (larval stage 1), *Plutella xylostella* (larval stage 3), and *Diabrotica balteata* (larval stage 2) were performed in the insecticide screening facilities of *Novartis AG* [19] and are described in *Novartis* patents claiming such activites. A typical example is described in [29].

General. Solvents used were dried over molecular sieves. 1,2-Dimethoxyethane $(CH_2OMe)_2$ for chromatographic purposes was distilled and stored under Ar. Benzyl chloromethyl ether was purchased from *Sigma* and distilled under vacuum from $CaCl_2$. TLC and HPTLC: sheets from *Merck* (silica gel *60* F_{254}). Flash chromatography (FC): *Merck* silica gel *60* (0.040–0.063 mm). M.p.: *Büchi 535* apparatus; not corrected. IR Spectra: KBr pellets; *Bruker-IFS-55-FT-IR* or *Perkin-Elmer-1710-FT-IR* spectrophotometer. NMR Spectra: solvent as internal reference; *Varian Unity 500* or *Bruker DRX 500* (500 MHz for ^1H and 125.7 MHz for ^{13}C); chemical shifts in ppm; trivial skeleton numbering. Fast atom bombardment (FAB) MS: *Finnigan MAT 90*; 3-nitrobenzyl alcohol (NBA), thioglycerol (THG), or 2-nitrophenyl octyl ether (NPOE) matrix. Elemental analyses: *Perkin-Elmer-PE-240* (C, H, N), *Leco-RO-478* (O), and atomic-absorption spectrometer *Varian Spectra 400* (K).

6-{3-{6-{{6-{[5'-(6-Ethyltetrahydro-5-hydroxy-5-methyl-2H-pyran-2-yl)octahydro-2'-hydroxy-2,3',5'-trimethyl[2,2'-bifuran]-5-yl]hydroxymethyl}tetrahydro-6-hydroxy-3,5-dimethyl-2H-pyran-2-yl]methyl}tetrahydro-6-hydroxy-5-methyl-2H-pyran-2-yl}-2-hydroxybutyl}tetrahydro-α,3-dimethyl-2H-pyran-2-acetic Acid (*X-206*; **1**). Colourless solid. R_f 0.37 ($(CH_2OMe)_2$/hexane 3:7), 0.42 (MeCN/toluene 3:7). IR: 3393 (br.), 2937, 1738, 1460, 1381, 1040. ^{1}H-NMR (500 MHz, $CDCl_3$): see [17][30]: 6.45 (*d*, $J \approx 0.8$, OH–C(15)); 6.02 (*d*, $J = 1.1$, OH–C(27)); 4.48 (*dd*, $J = 11$, 5.2, H–C(23)); 4.41 (*d*, $J = 10$, H–C(9)); 4.15 (*t*, $J = 9.6$, H–C(17)); 3.63 (*td*, $J = 10.2$, H–C(11)); 3.58 (*dd*, $J = 9.6$, 3, H–C(3)); 3.51 (br. *t*, $J = 10$, H–C(7)); 3.48–3.37 (*m*, H–C(22), H–C(31), H–C(35)); 3.2–2.5 (*m*, OH–C(1), OH–C(9), OH–C(21), OH–C(34), H_2O); 2.76 (*qd*, $J = 7.3$, H–C(2)); 2.44 (*d*, $J = 12$, OH–C(22)); 2.31 (*dd*, $J = 12$, 8.6, H_A–C(29)); 2.28–2.12 (*m*, 3 H); 2.07 (*m*, H–C(28)); 1.88–1.0 (*m*, 27 H); 1.35, 1.20 (2*s*, 2 Me); 1.11 (*d*, $J = 7.0$, Me(47)); 1.07 (*s*, Me); 1.05 (*d*, $J = 6.6$, Me(44)); 0.98 (*t*, $J = 7.0$, Me(37)); 0.91 (2*d*, $J = 6.6$, 2 Me); 0.85 (2*d*, $J = 6.2$, 2 Me); 0.80 (*d*, $J = 6.6$, Me(45)). ^{13}C-NMR (125.7 MHz, $CDCl_3$; see [1c]): 176.39 (C(1)); 108.40 (C(27)); 99.62 (C(21)); 97.84 (C(15)); 89.44 (C(26)); 84.28 (C(3)); 83.84 (C(35)); 82.88 (C(30)); 81.10 (C(7)); 72.52 (C(17)); 71.87 (C(31)); 70.39 (C(22)); 70.09 (C(9)); 69.64 (C(34)); 68.85 (C(11)); 46.18 (C(10)); 42.32 (C(29)); 41.41 (C(8)); 40.73 (C(2)); 39.99 (C(16)); 39.23 (C(14)); 39.00 (C(28)); 36.04 (C(19)); 35.00 (C(18)); 33.44 (C(20)); 32.86 (C(25)); 32.63 (C(6)); 32.42 (C(5)); 31.33 (C(4)); 31.31 (C(12)); (C(33)); 29.13 (C(24)); 27.26 (C(13)); 25.59 (CMe); 25.02 (Me); 24.32 (Me); 21.62 (C(32)); 20.06 (C(36)); 18.37 (C(43)); 16.99 (C(46)); 16.81 (Me); 16.39 (Me); 14.82 (C(42)); 10.56 (C(37)); 8.99 (C(45)); 8.63 (C(47)). FAB-MS (THG): neg.: 869 ($[M - H_2O - H]$); pos.: 888 (M^+), 799. Anal. calc. for $C_{47}H_{82}O_{14} \cdot H_2O$ (889.17): C 63.49, H 9.52; found: C 63.51, H 9.56.

X-206 Potassium Salt (**2**). *a*) A soln. of **1** (20.0 g, 22.5 mmol) in 96% EtOH (500 ml) was treated with 0.1M KOH (200 ml) until the soln. reached pH 8.5 (pH meter). After standing for *ca.* 6 weeks, the long crystals which had grown were filtered off, washed with 10% EtOH, and dried under vacuum which caused the crystals to collapse to a white powder: 18.4 g (90%).

b) A soln. of **1** (15.0 g, 16.9 mmol) in THF (200 ml) was treated with 0.1M KOH (150 ml) (→ pH 8–9). H_2O (600 ml) was added, the soln. seeded with crystals, and the mixture stirred at 0° for 1 h. The product was filtered off, washed with 10% THF, and dried under vacuum. 12.3 g (80%) of **2**. R_f 0.37 ($(CH_2OMe)_2$/hexane 3:7), 0.42 (MeCN/toluene 3:7). M.p. 206–208° (dec.). IR: 3460, 3339 (br.), 2972, 2934, 1570 (COO^-), 1458, 1396, 1105, 1038; no $\tilde{\nu}$(C=O) of **1**; *cf.* [31]. ^{1}H-NMR (500 MHz, $CDCl_3$): 11.0 (br. *s*, OH); 6.84 (*s*, OH–C(15)); 5.55 (*s*, OH–C(27)); 4.56 (*dd*, $J = 11.6$, 5, H–C(23)); 4.39 (*s*, OH); 4.30 (*d*, $J = 9.6$, H–C(9)); 3.98 (*t*, $J = 10.0$, H–C(17)); 3.74 (br. *d*, $J = 12$, H–C(35)); 3.58 (*dd*, $J = 10$, 3, H–C(3)); 3.50 (*d*, $J = 12.0$, H–C(22)); 3.42 (br. *t*, $J = 10$, H–C(7)); 3.39 (*td*, $J = 10$, 2, H–C(11)); 3.31 (*dd*, $J = 12$, 2.4, H–C(31)); 2.59 (*qd*, $J = 7$, 3, H–C(2)); 2.34 (*d*, $J = 12.0$, OH–C(22)); 2.26–2.02 (*m*, 6 H); 1.90–1.0 (*m*, 27 H); 1.56, 1.16 (2*s*, 2 Me); 1.15 (*d*, $J = 6.4$, Me); 1.11 (*s*, Me); 1.0–0.94 (2*d*, *t*, 2 Me, Me(37)); 0.92 (*d*, $J = 6.4$, Me); 0.86, 0.84 (2*d*, $J = 6$, 2 Me); 0.80 (*d*, $J = 6.4$, Me). FAB-MS (THG): neg.: 907 ($[M - H]^-$), 889 ($[M - H_2O - H]^-$), 869 ($[M - K]^-$); pos.: 947 ($[M + K]^+$), 909 ($[M + H]^+$). Anal. calc. for $C_{47}H_{81}KO_{14}$ (909.25): C 62.09, H 8.98, K 4.30; found: C 61.77, H 8.85, K 4.18.

6-{3-{6-{{6-{(Acetyloxy)[5'-(6-ethyltetrahydro-5-hydroxy-5-methyl-2H-pyran-2-yl)octahydro-2'-hydroxy-2,3',5'-trimethyl[2,2'-bifuran]-5-yl]methyl}tetrahydro-6-hydroxy-3,5-dimethyl-2H-pyran-2-yl]methyl}tetrahydro-6-hydroxy-5-methyl-2H-pyran-2-yl}-2-hydroxybutyl}tetrahydro-α,3-dimethyl-2H-pyran-2-acetic Acid (*22-O-Acetyl-X-206*; **3**). A soln. of **2** (1.00 g, 1.10 mmol) and 4-(dimethylamino)pyridine (DMAP; 30 mg, 0.25 mmol) in pyridine (20 ml) and Ac_2O (2 ml) was left for 18 h and quenched with ice. After extracting with AcOEt/hexane 1:3 (3 ×), the extract was washed with 1M HCl and H_2O, dried ($MgSO_4$), and chromatographed ($(CH_2OMe)_2$/hexane 1:9 → 3:7) to yield 800 mg (80%) of **3**. White foam. R_f 0.34 ($(CH_2OMe)_2$/hexane 3:7), 0.32 (MeCN/toluene 2:8). IR: 3377 (br.), 2966, 2937, 1740, 1460, 1379, 1240, 1067. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.78 (*s*, OH–C(15)); 6.22 (*d*, $J = 1.6$, OH–C((27)); 4.99 (*s*, H–C(22)); 4.58 (*dd*, $J = 11$, 5, H–C(23)); 4.42 (*d*, $J = 10$, H–C(9)); 4.15 (*t*, $J = 10$, H–C(17)); 3.70–2.40 (*ca.* 8 OH, OH–C(1), OH–C(9), OH–C(21), OH–C(34), 2 H_2O); 3.65 (*td*, $J = 11$, 2, H–C(11)); 3.58 (*dd*, $J = 10$, 3, H–C(3)); 3.51 (br. *t*, $J = 11$, H–C(7)); 3.44 (br. *d*, $J \approx 10$, H–C(31)); 3.39 (*dd*, $J = 11.6$, 3.6, H–C(35)); 2.77 (*dd*, $J = 7$, 3, H–C(2)); 2.30 (*dd*, $J = 12$, 8, H_A–C(29)); 2.27–2.00 (*m*, 2 H); 2.18 (*s*, $MeCO_2$); 1.92 (*dd*, $J = 14$, 10, H_A–C(16)); 1.85–1.20 (*m*, *ca.* 30 H); 1.34, 1.15 (2*s*, 2 Me); 1.11 (*d*, $J = 6.8$, Me); 1.07 (*s*, Me); 1.04 (*d*, $J = 6.4$, Me); 0.97 (*t*, $J = 7$, Me(37)); 0.95, 0.92, 0.85, 0.84, 0.80 (5*d*, $J = 6.4$, 5 Me). FAB-MS (NBA): neg.: 911 ($[M - H]^-$); pos.: 935 ($[M + Na]^+$). Anal. calc. for $C_{49}H_{84}O_{15} \cdot 0.5\,H_2O$ (922.21): C 63.82, H 9.29; found: C 63.81, H 9.21.

22-O-Acetyl-X-206 Benzyl Ester (**4**). A soln. of **3** (3.51 g, 3.85 mmol), *N*-ethyldiisopropylamine (4 ml, 23.1 mmol), and benzyl bromide (2.3 ml, 19.2 mmol) in MeCN (40 ml) was left for 25 h and then worked up with AcOEt/hexane 1:3 and H_2O. The org. phase was washed with 2M HCl, H_2O, and brine. Drying ($MgSO_4$) and chromatography (AcOEt/hexane 1:9 → 35:65) yielded 3.27 g (85%) of **4**. Colourless foam. R_f 0.39 ($(CH_2OMe)_2$/

hexane 3:7), 0.29 (AcOEt/hexane 35:65). IR: 3387 (br.), 2996, 2935, 1740, 1458, 1377, 1240, 1163, 1042. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.40–7.28 (*m*, Ph); 6.59 (*s*, OH); 5.88 (*s*, 2 OH); 5.19, 5.16 (2 *d*, PhCH_2); 4.94 (*s*, H–C(22)); 4.54 (*dd*, *J* = 10, 5.6, H–C(23)); 4.35 (br. *d*, *J* = 10, H–C(9)); 4.17 (*t*, *J* = 9.4, H–C(17)); 3.78 (*td*, *J* = 10, 2, H–C(11)); 3.54 (*dd*, *J* = 10, 3.6, H–C(3)); 3.51 (*m*, H–C(7)); 3.37 (*dd*, *J* = 11.6, 3.6, H–C(35)); 3.31 (*m*, H–C(31)); 2.87 (*s*, 2 OH); 2.72 (*qd*, *J* = 7, 3.6, H–C(2)); 2.30 (*dd*, *J* = 12, 8.4, H_A–C(29)); 2.21 (*m*, 1 H); 2.18 (*s*, $MeCO_2$); 2.05 (*m*, H–C(28)); 1.90 (*dd*, *J* = 14, 11, 1 H); 1.84–1.10 (*m*, *ca.* 30 OH); 1.34, 1.17 (2*s*, 2 Me); 1.15, 1.05 (2*d*, *J* = 6.4, 2 Me); 1.03 (*s*, Me); 0.93, 0.90 (2 *d*, *J* = 6.4, 2 Me); 0.90 (*t*, *J* = 7.5, Me(37)); 0.84–0.79 (3*d*, 3 Me). FAB-MS (NBA): neg.: 1155 ([*M* + NBA]$^-$), 1001 ([*M* – H]$^-$), 911 ([*M* – Bn]$^-$). Anal. calc. for $C_{56}H_{90}O_{15} \cdot H_2O$ (1021.34): C 65.86, H 9.08; found: C 65.98, H 9.19.

*6-{3-{6-{{6-{(Acetyloxy){5'-{5-[(benzyloxy)methoxy]-6-ethyltetrahydro-5-methyl-2*H*-pyran-2-yl}octahydro-2'-hydroxy-2,3',5'-trimethyl[2,2'-bifuran]-5-yl}methyl}tetrahydro-6-hydroxy-3,5-dimethyl-2*H*-pyran-2-yl}-methyl}tetrahydro-6-hydroxy-5-methyl-2*H*-pyran-2-yl}-2-[(benzyloxy)methoxy]butyl}tetrahydro-α,3-dimethyl-2*H*-pyran-2-acetic Acid Benzyl Ester (22-O-Acetyl-9,34-bis-O-[(benzyloxy)methyl]-X-206 Benzyl Ester*; **5**) Benzyl chloromethyl ether (4.5 ml, 32 mmol) was added dropwise to a soln. of **4** (8 g, 8 mmol) and *N*-ethyldiisopropylamine (8.2 ml, 48 mmol) in CH_2Cl_2 (80 ml) under Ar, and the soln. was stirred at 40° for 4 d. The crude product was chromatographed (silica gel (192 g), AcOEt/CH_2Cl_2 7:93). The crude product (9 g) was rechromatographed (AcOEt/hexane 5:95 → 2:8): 7.25 g (73%) of **5**. Colourless foam. R_f 0.40 (AcOEt/hexane 1:3), 0.48 (MeCN/toluene 1:9, HPTLC). IR: 3398 (br.), 2935, 1742, 1456, 1379, 1236, 1163, 1040, 995. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.40–7.23 (*m*, 3 Ph); 6.48 (*s*, OH); 5.54 (*d*, *J* ≈ 0.9, OH); 5.30, 5.05 (2 *d*, *J* = 12.5, CO_2CH_2Ph); 5.01, 4.94 (2 *d*, *J* = 8.3, OCH_2O); 4.95, 4.90 (2 *d*, *J* = 7.5, OCH_2O); 4.77 (2 *s*, H–C(22), OH); 4.75, 4.64 (2 *d*, *J* = 12, OCH_2Ph); 4.72, 4.43 (2 *d*, *J* = 12, OCH_2Ph); 4.50 (*t*, *J* = 7.5, H–C(23)); 4.34 (*dd*, *J* = 10, 2.3, H–C(9)); 4.19 (*t*, *J* = 9.5, H–C(17)); 3.82 (*dd*, *J* = 11, 3, H–C(35)); 3.68 (*td*, *J* = 11, 2, H–C(11)); 3.34 (*dd*, *J* = 10, 3.3, H–C(3)); 3.33 (*m*, H–C(7)); 3.26 (*dd*, *J* = 11, 2.5, H–C(31)); 2.67 (*qd*, *J* = 7, 3.3, H–C(2)); 2.40 (*dd*, *J* = 12, 8, H_A–C(29)); 2.25 (*q*, *J* = 11, 1 H); 2.16 (*s*, $MeCO_2$); 2.02–0.86 (*m*, *ca.* 30 H); 1.30, 1.17, 1.14 (3*s*, 3 Me); 1.12 (*d*, *J* = 7.5, Me); 1.00, 0.93 (2*d*, *J* = 6, 2 Me); 0.92 (*t*, *J* = 7, Me(37)); 0.83 (2*d*, *J* = 6.4, 2 Me); 0.79 (*d*, *J* = 6, Me); 0.69 (*d*, *J* = 6.4, Me). FAB-MS (NBA): neg.: 1395 ([*M* + NBA]$^-$), 1241 ([*M* – H]$^-$), 1151 ([*M* – Bn]$^-$). Anal. calc. for $C_{72}H_{106}O_{17}$ (1243.62): C 69.54, H 8.59; found: C 69.41, H 8.54.

*6-{3-{6-{{6-{{5'-{5-[(Benzyloxy)methoxy]-6-ethyltetrahydro-5-methyl-2*H*-pyran-2-yl}octahydro-2'-hydroxy-2,3',5'-trimethyl[2,2'-bifuran]-5-yl}hydroxymethyl}tetrahydro-6-hydroxy-3,5-dimethyl-2*H*-pyran-2-yl}-methyl}tetrahydro-6-hydroxy-5-methyl-2*H*-pyron-2-yl}-2-[(benzyloxy)methoxy]butyl}tetrahydro-α,3-dimethyl-2*H*-pyran-2-acetic Acid Benzyl Ester (9,34-Bis-O-[(benzyloxy)methyl]-X-206 Benzyl Ester*; **6**). *a*) A soln. of **5** (8.26 g, 6.65 mmol) in THF (400 ml), 1% K_2CO_3 in MeOH (400 ml), and H_2O (400 ml) was stirred at r.t. After 24 h (TLC, acetone/hexane 1:4), the mixture was extracted with Et_2O/hexane 1:1 (4 ×), washed with H_2O and brine, dried ($MgSO_4$), and chromatographed (AcOEt/hexane 5:95 → 15:85): 6.36 g (80%) of **6**. Colourless foam.

b) $NaBH_4$ (2.4 mg, 63 μmol) was added to a soln. of **13** (25 mg, 21 μmol) in MeOH (250 μl). After 10 min (TLC, MeCN/toluene 1:9), the solvent was evaporated and the mixture dissolved in AcOEt/hexane 1:3, and washed with 0.5M HCl, H_2O, 0.5M $NaHCO_3$, H_2O, and brine. After drying ($MgSO_4$), the crude product was chromatographed (AcOEt/hexane 5:95 → 2:8): 11.3 mg (45%) of **6** after freeze-drying.

c) At 0° 1M LiOH (30 μl) was added dropwise to a soln. of **23** (20 mg, 14.8 μmol) in THF (400 μl). After 1 h at 10° (TLC, MeCN/toluene 1:9), the mixture was diluted with Et_2O/hexane 1:3 and washed with H_2O (3 ×), dried ($MgSO_4$), and chromatographed (AcOEt/hexane 5:95 → 2:8) to yield 6.1 mg (34%) of **6** after freeze-drying. R_f 0.48 (DME/hexane 1:4), 0.48 (acetone/toluene 5:95), 0.29 (AcOEt/hexane 1:4), 0.29 (acetone/hexane 1:4), 0.35 (MeCN/toluene 1:9). IR: 3408 (br.), 2935, 1744, 1456, 1379, 1163, 1043, 995, 698. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.40–7.23 (*m*, 3 Ph); 6.26 (*d*, *J* = 1, OH); 5.53 (*d*, *J* = 2, OH); 5.30, 5.06 (2 *d*, *J* = 12.4, CO_2CH_2Ph); 5.00, 4.94 (2 *d*, *J* = 8, OCH_2O); 4.96, 4.91 (2 *d*, *J* = 8, OCH_2O); 4.76, 4.65 (2 *d*, *J* = 12, OCH_2Ph); 4.74, 4.40 (2 *d*, *J* = 11.6, OCH_2Ph); 4.58 (*d*, *J* = 2, OH); 4.33 (*m*, H–C(9), H–C(23)); 4.19 (*t*, *J* = 10, H–C(17)); 3.84 (*dd*, *J* = 11, 3, H–C(35)); 3.68 (*td*, *J* = 11, 2, H–C(11)); 3.34 (*dd*, *J* = 10, 3.6, H–C(3)); 3.32 (*m*, H–C(7)); 3.30 (*dd*, *J* = 11, 2.4, H–C(31)); 3.23 (*d*, *J* = 12, H–C(22)); 2.68 (*qd*, *J* = 7, 3.6, H–C(2)); 2.48 (*d*, *J* = 12, OH–C(22)); 2.43 (*dd*, *J* = 12, 8.4, H_A–C(29)); 2.35 (*td*, *J* = 12, 8, 1 H); 2.18–1.00 (*m*, 30 H); 1.32, 1.22, 1.16 (3*s*, 3 Me); 1.13 (*d*, *J* = 7, Me); 1.01 (*d*, *J* = 6.4, Me); 0.93 (*t*, *J* = 7, Me(37)); 0.91, 0.85 (2*d*, *J* = 6.4, 2 Me); 0.82 (*d*, *J* = 7, Me); 0.80, 0.69 (2 *d*, *J* = 6.4, 2 Me). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 174.96, 138.33, 137.29, 136.77, 128.61, 128.45, 128.28, 128.22, 127.96, 127.93, 127.81, 127.74, 127.63, 107.86, 98.98, 97.63, 95.59, 90.83, 89.14, 83.25, 82.59, 79.30, 76.56, 75.33, 75.14, 73.59, 72.72, 72.46, 71.70 (C(22)), 69.98, 69.52, 65.89, 45.38, 42.44, 41.68, 41.33, 40.77, 39.77, 39.52, 35.98, 35.82, 34.02, 32.51, 32.23, 32.12, 31.17, 30.75, 30.21, 27.69, 25.86, 24.37, 23.75, 20.66, 18.33, 17.13, 16.89, 16.47, 14.94, 11.11, 9.17, 9.01. FAB-MS (NBA): neg.: 1353 ([*M* + NBA]$^-$), 1199 ([*M* – H]$^-$), 1109 ([*M* – Bn]$^-$). Anal. calc. for $C_{70}H_{104}O_{16}$ (1201.59): C 69.97, H 8.72; found: C 69.80, H 8.81.

6-{3-{6-{{6-{(Benzoyloxy)}5'-{5-[(benzyloxy)methoxy]-6-ethyltetrahydro-5-methyl-2H-pyran-2-yl}octahydro-2'-hydroxy-2,3',5'-trimethyl[2,2'-bifuran]-5-yl}methyl}tetrahydro-6-hydroxy-3,5-dimethyl-2H-pyran-2-yl}methyl}tetrahydro-6-hydroxy-5-methyl-2H-pyron-2-yl}-2-[(benzyloxy)methoxy]butyl}tetrahydro-α,3-dimethyl-2H-pyron-2-acetic Acid Benzyl Ester (*22-O-Benzoyl-X-206 Benzyl Ester*; **11**). Benzoyl chloride (0.2 ml, 240 mg, 1.71 mmol) was added to a soln. of **6** (170 mg, 141 μmol) in pyridine (0.5 ml). After 2 h, the mixture was cooled in ice and treated with H_2O. After 10 min, the mixture was partitioned between hexane, AcOEt, and H_2O, washed with 2M HCl, H_2O, and sat. $NaHCO_3$ soln., dried ($MgSO_4$), and chromatographed (MeCN/toluene 3:97): 75 mg (41%) of **11**. R_f 0.42 (MeCN/toluene 8:92, HPTLC). ^{1}H-NMR (500 MHz, $CDCl_3$, extract): 8.16, 7.59, 7.47 (*d*, *J* = 8, 2 H, *t*, *J* = 8, 1 H, *t*, *J* = 8, 2 H, PhCOO–C(22)); 5.04 (*s*, H–C(22)); 4.60 (*dd*, *J* = 9.5, 6.5, H–C(23)); spectrum very similar to that of **5**. FAB-MS (NBA; for $C_{77}H_{108}O_{17}$ (1305.69)): neg.: 1457 ($[M + NBA]^-$), 1303 ($[M - H]^-$), 1213 ($[M - Bn]^-$).

6-{3-{6-{{6-{(Benzoyloxy)[5'-(6-ethyltetrahydro-5-hydroxy-5-methyl-2H-pyran-2-yl)octahydro-2'-hydroxy-2,3',5'-trimethyl[2,2'-bifuran]-5-yl]methyl}tetrahydro-6-hydroxy-3,5-dimethyl-2H-pyran-2-yl}methyl}tetrahydro-6-hydroxy-5-methyl-2H-pyran-2-yl}-2-hydroxybutyl}tetrahydro-α,3-dimethyl-2H-pyran-2-acetic Acid (*22-O-Benzoyl-X-206*; **12**). A soln. of **11** (14 mg, 11 μmol) and 0.05M $HClO_4$ (0.5 ml) in THF (2 ml) was stirred with 5% Pd/C (5 mg) under H_2 for 2 days. The catalyst was filtered off over *Celite*, and the filtrate partitioned between AcOEt and H_2O. The org. phase was washed with H_2O (3×), dried, and chromatographed (AcOEt/hexane 1:9 → AcOEt): 3.1 mg (28%) of **12**. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.17 (*d*, *J* = 8), 7.59, 7.46 (2*t*, *J* = 8, Ph); 6.96 (*s*, OH–C(15)); 6.29 (*d*, *J* = 1.6, OH–C(27)); 5.23 (*s*, H–C(22)); 4.67 (*dd*, *J* = 11, 5, H–C(23)); 4.45 (*d*, *J* = 10, H–C(9)); 4.18 (*t*, *J* = 10, H–C(17)); 3.70–2.40 (*ca.* 8 OH, OH–C(1), OH–C(9), OH–C(21), OH–C(34), 2 H_2O), 3.69 (*td*, *J* = 11, 2, H–C(11)); 3.61 (*dd*, *J* = 10, 3, H–C(3)); 3.53 (br. *t*, *J* = 11, H–C(7)); 3.46 (br. *d*, *J* ≈ 10, H–C(31)); 3.39 (*dd*, *J* = 11.6, 3.6, H–C(35)); 2.77 (*dd*, *J* = 7, 3, H–C(2)); 2.30 (*dd*, *J* = 12, 8 H_A–C(29)); 1.93 (*dd*, *J* = 14, 10, H_A–C(16)); 1.85–1.20 (*m*, *ca.* 30 H); 1.37, 1.10, 1.07 (3*s*, 2 Me); 1.12 (*d*, *J* = 6.8, Me); 1.02 (*s*, Me); 0.98 (*d*, *J* = 6.4, Me); 0.85, 0.83, 0.82 (3*d*, *J* = 6.4, 5 Me). FAB-MS (NBA): neg.: 973 ($[M - H]^-$); pos.: 997 ($[M + Na]^+$).

6-{3-{6-{{6-{5'-{5-[(Benzoyloxy)methoxy]-6-ethyltetrahydro-5-methyl-2H-pyran-2-yl}octahydro-2'-hydroxy-2,3',5'-trimethyl[2,2'-bifuran]-5-yl}methoxymethyl}tetrahydro-6-hydroxy-3,5-dimethyl-2H-pyran-2-yl}methyl}tetrahydro-6-hydroxy-5-methyl-2H-pyran-2-yl}-2-[(benzyloxy)methoxy]butyl}tetrahydro-α,3-dimethyl-2H-pyran-2-acetic Acid Benzyl Ester (*9,34-Bis-O-[(benzyloxy)methyl]-22-O-methyl-X-206 Benzyl Ester*; **7**). To **6** (267 mg, 222.5 μmol) and *N,N,N',N'*-tetramethylnaphthalene-1,8-diamine (333 mg, 1.558 mmol), dried under vacuum, trimethyloxonium tetrafluoroborate (165 mg, 1.113 mmol) was added under Ar. After cooling to 0°, CH_2Cl_2 (3 ml) was slowly added with stirring. After 2.5 h, CH_2Cl_2 and MeOH were added, and the mixture was partitioned between half-sat. brine and AcOEt/hexane 1:3 (3×). The org. phase was washed with 0.5M HCl, H_2O, 0.5M $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$) and chromatographed (AcOEt/hexane 5:95 → 1:3): 218.6 mg (81%) of **7**. R_f 0.23 (AcOEt/hexane 1:4), 0.32 (MeCN/toluene 1:9). IR: 3389, 2935, 1744, 1456, 1379, 1163, 1128, 1042, 993, 698. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.40–7.23 (*m*, 3 Ph); 6.38 (*s*, OH); 5.49 (*d*, *J* = 1, OH); 5.29, 5.06 (2*d*, *J* = 12.4, CO_2CH_2Ph); 5.01, 4.95 (2*d*, *J* = 8, OCH_2O); 4.96, 4.91 (2*d*, *J* = 7.6, OCH_2O); 4.76, 4.65 (2*d*, *J* = 12, OCH_2Ph); 4.74, 4.40 (2*d*, *J* = 11.6, OCH_2Ph); 4.46 (*d*, *J* = 2, OH); 4.35 (*m*, H–C(9), H–C(23)); 4.23 (*t*, *J* = 10.5, H–C(17)); 3.84 (*dd*, *J* = 11, 3, H–C(35)); 3.70 (*td*, *J* = 10.6, 2, H–C(11)); 3.60 (*s*, MeO–C(22)); 3.33 (*dd*, *J* = 10, 3.4, H–C(3)); 3.32 (*m*, H–C(7)); 3.29 (*dd*, *J* = 11.6, 2.4, H–C(31)); 2.91 (*s*, H–C(22)); 2.67 (*qd*, *J* = 7, 3.4, H–C(2)); 2.40 (*dd*, *J* = 12, 8, H_A–C(29)); 2.30 (*td*, *J* = 11, 9, 1 H); 2.08–1.90 (*m*, 6 H); 1.81–0.80 (*m*, *ca.* 25 H); 1.30, 1.24, 1.16 (3*s*, 3 Me); 1.13 (*d*, *J* = 7, Me); 1.01 (*d*, *J* = 6.4, Me); 0.94 (*t*, *J* = 7.2, Me(37)); 0.89 (2*d*, *J* = 6.4, 2 Me); 0.83 (*d*, *J* = 7, Me); 0.78, 0.69 (2*d*, *J* = 6.4, 2 Me). FAB-MS (NBA): neg.: 1367 ($[M + NBA]^-$), 1213 ($[M - H]^-$), 1123 ($[M - Bn]^-$). Anal. calc. for $C_{71}H_{106}O_{16}$ (1215.61): C 70.15, H 8.79; found: C 70.26, H 8.93.

9,34-Bis-O-[(benzyloxy)methyl]-22-O-ethyl-X-206 Benzyl Ester (**8**). As described for **7**, with **6** (150 mg, 125 μmol), *N,N,N',N'*-tetramethylnaphthalene-1,8-diamine (187 mg, 875 μmol), triethyloxonium tetrafluoroborate (119 mg, 625 μmol), and CH_2Cl_2 (2 ml). Chromatography (MeCN/toluene 2:98 → 8:92) yielded 120 mg (78%) of **8**. Fine needles, after crystallization from Et_2O/hexane. R_f 0.38 (MeCN/toluene 1:9, HPTLC). M.p. 128°. IR: 3388, 2970, 2934, 1743, 1456, 1379, 1163, 1042, 993, 698. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.40–7.23 (*m*, 3 Ph); 6.29 (*s*, OH); 5.29, 5.06 (2*d*, *J* = 12.4, CO_2CH_2Ph); 5.22 (*s*, OH); 4.99, 4.87 (2*d*, *J* = 8.5, OCH_2O); 4.96, 4.90 (2*d*, *J* = 8.5, OCH_2O); 4.75, 4.64 (2*d*, *J* = 12, OCH_2Ph); 4.73, 4.23 (2*d*, *J* = 11, OCH_2Ph); 4.38–4.31 (*m*, H–C(9), H–C(23), OH); 4.22 (*t*, *J* = 10.5, H–C(17)); 3.86–3.79 (*m*, H–C(35), 1 H of $MeCH_2O$–C(22)); 3.70 (*td*, *J* = 10.6, 2, H–C(11)); 3.58 (*dq*, *J* = 9, 7, 1 H of $MeCH_2O$–C(22)); 3.35 (*dd*, *J* = 10, 3.4, H–C(3)); 3.34 (*m*, H–C(7)); 3.27 (*dd*, *J* = 11.6, 2.4, H–C(31)); 2.95 (*d*, *J* = 1, H–C(22)); 2.67 (*qd*, *J* = 7, 3.4, H–C(2)); 2.39 (*dd*, *J* = 12, 8, H_A–C(29)); 2.25 (*td*, *J* = 11, 9, 1 H); 2.08–0.80 (*m*, *ca.* 30 H); 1.29, 1.24 (2*s*, 2 Me); 1.22 (*t*, *J* = 7,

MeCH_2O–C(22)); 1.15 (*s*, Me); 1.13 (*d*, J = 7, Me); 1.00 (*d*, J = 6.4, Me); 0.94 (*t*, J = 7.2, Me(37)); 0.90, 0.87 (2*d*, J = 6.4, 2 Me); 0.82 (*d*, J = 7, Me); 0.78 (*d*, J = 6, Me), 0.70 (*d*, J = 6.4, Me). FAB-MS (NBA): neg.: 1381 ([M + NBA]$^-$), 1227 ([M – H]$^-$), 1137 ([M – Bn]). Anal. calc. for $C_{72}H_{108}O_{16} \cdot H_2O$ (1247.66): C 69.31, H 8.89; found: C 69.39, H 8.74.

*6-{3-{6-{{6-{[5'-(6-Ethyltetrahydro-5-hydroxy-5-methyl-2*H*-pyran-2-yl)octahydro-2'-hydroxy-2,3',5'-trimethyl[2,2'-bifuran]-5-yl]methoxymethyl}tetrahydro-6-hydroxy-3,5-dimethyl-2*H*-pyran-2-yl}methyl}tetrahydro-6-hydroxy-5-methyl-2*H*-pyron-2-yl}-2-hydroxybutyl}tetrahydro-α,3-dimethyl-2*H*-pyran-2-acetic Acid (22-*O*-Methyl-X-206*; **9**). A soln. of **7** (97 mg, 80 μmol) and 0.05M $HClO_4$ (2.5 ml) in THF (10 ml) was stirred with Pd/C (50 mg) under H_2 for 16 h. The catalyst was filtered off through *Celite*, and the filtrate diluted with Et_2O/hexane 1:1, washed with H_2O (3×), dried ($MgSO_4$), and chromatographed (($CH_2OMe)_2$/hexane 15:85 → 35:65): 51 mg (72%) of **9**. Solid after freeze-drying. R_f 0.39 (($CH_2OMe)_2$/hexane 4:6). IR: 3376 (br.), 2965, 2935, 1737, 1459, 1380, 1073, 1048, 991. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.70 (*s*, OH–C(15)); 6.24 (*d*, $J \approx 1$, OH–C(27)); 4.50 (*dd*, J = 11, 4.5, H–C(23)); 4.43 (*d*, J = 10, H–C(9)); 4.19 (*t*, J = 10, H–C(17)); 3.63 (*td*, J = 10, 2.5, H–C(11)); 3.60 (*s*, MeO–C(22)); 3.57 (*dd*, J = 10, 3, H–C(3)); 3.51 (*t*, J = 10, H–C(7)); 3.41 (*m*, H–C(31), H–C(35)); 3.16 (*s*, H–C(22)); 2.76 (*qd*, J = 7, 3, H–C(2)); 2.7–2.0 (OH–C(1), OH–C(9), OH–C(21), OH–C(34), H_2O); 2.29 (*dd*, J = 12, 8.3, H_A–(29)); 2.24 (*td*, J = 12, 7.5, 1 H); 2.19–2.00 (*m*, 4 H); 2.00 (*dd*, J = 14.3, 10, H_A–C(16)); 1.84–1.00 (*m*, *ca.* 30 H); 1.35, 1.23 (2*s*, 2 Me); 1.16 (*d*, J = 7, Me(47)); 1.07 (*s*, Me); 1.05 (*d*, J = 6.7, Me(44)); 0.98 (*t*, J = 7, Me(37)); 0.97, 0.91 (2*d*, J = 6.7, 2 Me); 0.85 (2*d*, $J \approx 7$, 2 Me); 0.80 (*d*, J = 6.7, Me(45)). FAB-MS (NBA): neg.: 883 ([M – H]$^-$); pos.: 907 ([M + Na]$^+$). Anal. calc. for $C_{48}H_{84}O_{14} \cdot H_2O$ (903.21): C 63.83, H 9.60; found: C 63.82, H 9.54.

22-O-Ethyl-X-206 (**10**). As described for **9**, with **8** (112 mg, 91.2 μmol), 0.05M $HClO_4$ (2.5 ml), THF (10 ml), and Pd/C (60 mg), for 2.5 d. Chromatography (($CH_2OMe)_2$/hexane 5:95 → 3:7) yielded 58 mg (71%) of **10**. Solid after freeze-drying. R_f 0.47 (($CH_2OMe)_2$/hexane 2:3). IR: 3377 (br.), 2968, 2935, 1737, 1459, 1380, 1158, 1127, 1101, 1072, 1045, 991. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.70 (*s*, OH–C(15)); 6.14 (*s*, OH–C(27)); 4.48 (*dd*, J = 11.3, 5, H–C(23)); 4.42 (*d*, J = 10, H–C(9)); 4.17 (*t*, J = 10, H–C(17)); 3.89 (*dq*, J = 9.5, 7, 1 H, MeCH_2O–C(22)); 3.70–3.61 (*m*, 2 H, H–C(11), MeCH_2O–C(22)); 3.6–2.8 OH–C(1), OH–C(9), OH–C(21), OH–C(34), H_2O); 3.57 (*dd*, J = 10, 3, H–C(3)); 3.51 (*t*, J = 10, H–C(7)); 3.41 (*m*, H–C(31), H–C(35)); 3.26 (*s*, H–C(22)); 2.75 (*qd*, J = 7, 3, H–C(2)); 2.29 (*dd*, J = 12, 8, H_A–C(29)); 2.22 (*td*, J = 12, 7.5, 1 H); 2.18–2.01 (*m*, 4 H); 1.98 (*dd*, J = 14.5, 10, H_A–C(16)); 1.84–1.00 (*m*, *ca.* 30 H); 1.35 (*s*, Me); 1.26 (*t*, J = 7, *Me*CH_2O–C(22)); 1.22 (*s*, Me); 1.12 (*d*, J = 7, Me(17)); 1.07 (*s*, Me); 1.05 (*d*, J = 6.6, Me(44)); 0.98 (*t*, J = 7, Me(37)); 0.94 (*d*, J = 7, Me); 0.91 (*d*, J = 6.8, Me); 0.85 (2*d*, $J \approx 7$, 2 Me); 0.80 (*d*, J = 6.7, Me(45)). FAB-MS (NBA): neg.: 897 ([M – H]$^-$); pos.: 921 ([M + Na]$^+$), 937 ([M + K]$^+$). Anal. calc. for $C_{49}H_{86}O_{14} \cdot 0.5\ H_2O$ (908.22): C 64.80, H 9.66; found: C 64.82, H 9.54.

*6-{3-{6-{{6-{{5'-{5-[(Benzyloxy)methoxy]-6-ethyltetrahydro-5-methyl-2*H*-pyran-2-yl}octahydro-2'-hydroxy-2,3',5'-trimethyl[2,2'-bifuran]-5-yl}oxomethyl}tetrahydro-6-hydroxy-3,5-dimethyl-2*H*-pyran-2-yl}methyl}tetrahydro-6-hydroxy-5-methyl-2*H*-pyran-2-yl}-2-[(benzyloxy)methoxy]butyl}tetrahydro-α,3-dimethyl-2*H*-pyran-2-acetic Acid Benzyl Ester (9,34-Bis-O-[(benzyloxy)methyl]-22,O-didehydro-X-206 Benzyl Ester*; **13**). A soln. of **6** (300 mg, 250 μmol) in CH_2Cl_2 (1.5 ml) and MeCN (0.3 ml) was treated with 4 Å powdered molecular sieves (150 mg), TPAP (8.8 mg, 25 μmol), and NMO (87.9 mg, 750 μmol) under Ar. After 18 h, the mixture was evaporated and the residue filtered with AcOEt/CH_2Cl_2 1:1 through a layer of silica gel. The crude product was rechromatographed (AcOEt/hexane 5:95 → 1:4): 205 mg (68%) of **13**. R_f 0.28 (AcOEt/hexane 1:3), 0.25 (MeCN/toluene 1:9). IR (CH_2Cl_2): 3473 (br.), 2936, 1736, 1456, 1380, 1163, 1103, 1037; 57% intensity increase for $\tilde{\nu}$ (C=O) (ester and ketone moieties) as compared to **6** and corresponding decrease for $\tilde{\nu}$ (OH) at *ca.* 3411 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.43–7.22 (*m*, 3 Ph); 5.71 (*d*, J = 1.4, OH); 5.34, 5.06 (2*d*, J = 12.6, CO_2CH_2Ph); 5.03 (*dd*, J = 8, 7, H–C(23)); 4.97, 4.92 (2*d*, J = 7.6, OCH_2O); 4.77, 4.66 (2*d*, J = 11.6, OCH_2Ph); 4.67, 4.55 (2*d*, J = 12, OCH_2Ph); 4.67, 4.60 (2*d*, J = 7.6, OCH_2O); 4.55 (*d*, J = 1.2, OH); 4.37 (*t*, J = 10, H–C(17)); 4.25 (*dd*, J = 9, 3.6, H–C(9)); 3.85 (*dd*, J = 11.5, 3.4, H–C(35)); 3.61 (*td*, J = 11, 2, H–C(11)); 3.42 (*dd*, J = 10, 3.4, H–C(3)); 3.36 (*m*, H–C(7)); 3.31 (*dd*, J = 11.6, 2.4, H–C(31)); 3.16 (*s*, OH); 2.71 (*qd*, J = 7, 3.4, H–C(2)); 2.46 (*dd*, J = 12.4, 8.4, H_A–C(29)); 2.38 (*dt*, J = 12, 8, 1 H); 2.28, 2.18 (2*m*, 2 H); 2.06 (2 *m*, 2 H); 1.92 (*ddd*, J = 13.6, 9, 3.6, 1 H); 1.89–0.70 (*m*, *ca.* 25 H); 1.33, 1.34, 1.16 (3*s*, 3 Me); 1.14 (*d*, J = 7, Me); 1.05 (*d*, J = 6.4, Me); 1.00 (*t*, J = 7.2, Me(37)); 0.91 (*d*, J = 6.4, Me); 0.84 (*d*, J = 6.0, Me); 0.81 (*d*, J = 7, Me); 0.77, 0.71 (2*d*, J = 6.4, 2 Me). FAB-MS (NBA): neg.: 1351 ([M + NBA]$^-$), 1198 (M^-), 1107 ([M – Bn]$^-$). Anal. calc. for $C_{70}H_{102}O_{16}$ (1199.57): C 70.09, H 8.57; found: C 70.31, H 8.43.

*6-{3-{6-{{6-{[5'-(6-Ethyltetrahydro-5-hydroxy-5-methyl-2*H*-pyran-2-yl)octahydro-2'-hydroxy-2,3',5'-trimethyl[2,2'-bifuran]-5-yl]oxomethyl}tetrahydro-6-hydroxy-3,5-dimethyl-2*H*-pyran-2-yl}methyl}tetrahydro-6-hydroxy-5-methyl-2*H*-pyran-2-yl}-2-hydroxybutyl}tetrahydro-α,3-dimethyl-2*H*-pyran-2-acetic Acid (22,O-Didehy-*

dro-X-206; **14**). *a*) As described for **13**, with **2** (500 mg, 551 μmol), CH_2Cl_2 (2.5 ml), MeCN (0.5 ml), 4-Å molecular sieves (250 mg), TPAP (29 mg, 83 μmol), and NMO (323 mg, 2.76 mmol), for 4 h. After filtration through silica gel, the product was shaken with 1M HCl and H_2O (2×), dried ($MgSO_4$), and chromatographed (($CH_2OMe)_2$/hexane 1:9 → 3:7) to yield a mixture of **14** and its salt (35–45% according to IR and NMR), which was treated with the acidic wash procedure described above. After drying ($MgSO_4$), 342 mg (72%) of **14** was isolated as the pure free acid.

b) As described for **9**, with **13** (25 mg, 20.9 μmol), 0.05M $HClO_4$ (0.6 ml), THF (2.5 ml), and 5% Pd/C (12 mg), for 4 h. After chromatography (($CH_2OMe)_2$/hexane 1:9 → 3:7), the product was shaken with acid, washed, and dried as described above: 11 mg (61%) of **14**. R_f 0.24 (($CH_2OMe)_2$/hexane 3:7). IR: 3473 (br.), 2965, 2935, 1734, 1460, 1381, 1159, 1104, 1048, 995. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.36 (*s*, OH); 5.13 (*t*, *J* = 8.4, H–C(23)); 4.82 (*s*, OH); 4.48 (*d*, *J* = 10.4, H–C(9)); 4.26 (*t*, *J* = 10, H–C(17)); 3.70 (*td*, *J* = 11, 2, H–C(11), OH); 3.58 (*dd*, *J* = 10, 3, H–C(3)); 3.57 (*t*, *J* = 10, H–C(7)); 3.44 (*dd*, *J* = 12, 3.6, 1 H); 3.35 (*dd*, *J* = 12, 2, 1 H); 3.32–2.80 (3 OH); 2.75 (*qd*, *J* = 7, 3, H–C(2)); 2.36–2.14 (*m*, 5 H); 2.09 (*m*, 1 H); 1.87 (*dd*, *J* = 14, 10, 1 H), 1.84–1.20 (*m*, *ca.* 25 H); 1.40, 1.26 (2*s*, 2 Me); 1.11 (*d*, *J* = 7, Me); 1.08 (*s*, Me); 1.07 (*d*, *J* = 6.4, Me); 0.98 (*t*, *J* = 7.4, Me(37)); 0.87, 0.86, 0.86 (3*d*, 3 Me), 0.82, 0.77 (2*d*, *J* = 6.4, 2 Me); signal shifts of up to 0.1 ppm were observed in the presence of H_2O, depending on workup (freeze-dried or foamed under vacuum); similar shifts were observed on D_2O exchange. FAB-MS (NBA): neg.: 867 ([*M* – H]$^-$). Anal. calc. for $C_{47}H_{80}O_{14}$ (869.14): C 64.95, H 9.28; found: C 65.22, H 9.56.

*6-{3-{6-{{6-{{5'-{5-[(Benzyloxy)methoxy]-6-ethyltetrahydro-5-methyl-2*H*-pyran-2-yl}octahydro-2'-hydroxy-2,3',5'-trimethyl[2,2'-bifuran]-5-yl}(methoxyimino)methyl}tetrahydro-6-hydroxy-3,5-dimethyl-2*H*-pyran-2-yl}methyl}tetrahydro-6-hydroxy-5-methyl-2*H*-pyran-2-yl}-2-[(benzyloxy)methoxy]butyl}tetrahydro-α,3-dimethyl-2*H*-pyran-2-acetic Acid Benzyl Ester (9,34-Bis-*O*-[(benzyloxy)methyl]-22-deoxy-22-(methoxyimino)-X-206 Benzyl Ester*; **15**). A soln. of **13** (20 mg, 16.7 μmol) and *O*-methylhydroxylammonium chloride (7 mg, 83.5 μmol) in pyridine (200 μl) was left 2 h, diluted with Et_2O/hexane 1:1, washed with 0.5M HCl and H_2O (3×), dried ($MgSO_4$), chromatographed (AcOEt/hexane 5:95 → 1:4), and freeze-dried: 3.3 mg (16%) of **15**. R_f 0.50 (AcOEt/hexane 3:7, HPTLC), 0.34 (MeCN/toluene 1:9, HPTLC). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.43–7.20 (*m*, 3 Ph); 5.50 (*d*, *J* = 1.4, OH); 5.34, 5.05 (2*d*, *J* = 12.4, CO_2CH_2Ph); 5.27 (*s*, OH); 4.97, 4.91 (2*d*, *J* = 8, OCH_2O); 4.87, 4.72 (2*d*, *J* = 7.4, OCH_2O); 4.81 (*dd*, *J* = 10, 6.4, H–C(23)); 4.77, 4.66 (2*d*, *J* = 11.8, OCH_2Ph); 4.70, 4.46 (2*d*, *J* = 12, OCH_2Ph); 4.35 (*t*, *J* = 10, H–C(17)); 4.26 (*dd*, *J* = 10, 2, H–C(9)); 3.85 (*dd*, *J* = 11, 3.8, H–C(35)); 3.71 (*s*, MeO–N); 3.65 (*td*, *J* = 11, 2, H–C(11)); 3.30 (*dd*, *J* = 12, 2.4, H–C(31)); 3.27 (*m*, H–C(7)); 3.23 (*dd*, *J* = 10, 3.4, H–C(3)); 3.15 (*s*, OH); 2.64 (*qd*, *J* = 7.2, 3.4, H–C(2)); 2.45 (*dd*, *J* = 12.4, 8.4, H_A–C(29)); 2.33 (*dt*, *J* = 12, 9, 1 H); 2.22–2.09 (*m*, 3 H); 2.06 (br. *d*, *J* = 13, 1 H); 1.94 (*ddd*, *J* = 13.6, 9, 3.6, 1 H); 1.84–0.70 (*m*, *ca.* 25 H); 1.30, 1.30, 1.15 (3*s*, 3 Me); 1.10 (*d*, *J* = 7.2, Me); 1.05 (*d*, *J* = 6.4, Me); 0.99 (*t*, *J* = 7.2, Me(37); 0.90 (*d*, *J* = 6.4, Me); 0.87 (*d*, *J* = 6.6, Me); 0.83 (*d*, *J* = 7, Me); 0.81 (*d*, *J* = 6.2, Me); 0.61 (*d*, *J* = 6.4, Me). FAB-MS (NBA): neg.: 1361 ([*M* + NBA – H_2O – H]$^-$), 1271 ([*M* + NBA – H_2O – Bn]$^-$), 1226 ([*M* – H]$^-$), 1135 ([*M* – Bn – H]$^-$).

*9,34-Bis-*O*-[(benzyloxy)methyl]-22-deoxy-22-(tosylhydrazono)-X-206 Benzyl Ester* (**16**). A soln. of **13** (1.00 g, 0.835 mmol), toluene-4-sulfonic acid hydrazide (467 mg, 2.51 mmol), and AcOH (100 μl) in THF (15 ml) was left 26 h, diluted with AcOEt/hexane 1:3, washed with 0.5M $NaHCO_3$ and H_2O, dried ($MgSO_4$), and chromatographed (AcOEt/hexane 15:85 → 1:3): 352 mg (31%) of **16**. Colourless foam. R_f 0.26 (AcOEt/hexane 1:3), 0.30 (MeCN/toluene 1:9). IR: 3456, 3188, 2933, 1742, 1456, 1379, 1171, 1095, 1041, 735, 698, 560, 549. ^{1}H-NMR (500 MHz, $CDCl_3$): 10.36 (*s*, NH); 7.48 (*d*, *J* = 9, 2 arom. H); 7.42–7.24 (*m*, 3 Ph); 7.07 (*d*, *J* = 9, 2 arom. H); 5.43 (*d*, *J* ≈ 0.8, OH); 5.31, 5.03 (2*d*, *J* = 12.4, CO_2CH_2Ph); 4.96, 4.91 (2*d*, *J* = 8, OCH_2O); 4.80–4.63 (*m*, OCH_2O, 2 OCH_2Ph, H–C(23), OH); 4.35 (*td*, *J* = 9, 3.6, H–C(17)); 4.23 (*dd*, *J* = 9.4, H–C(9)); 3.86 (*dd*, *J* = 12, 3, H–C(35)); 3.66 (*td*, *J* = 11, 2, H–C(11)); 3.29 (*dd*, *J* = 11, 2.4, H–C(31)); 3.27 (*m*, H–C(7)); 3.22 (*dd*, *J* = 9.6, 3, H–C(3)); 2.65 (*qd*, *J* = 7, 3, H–C(2)); 2.59 (*s*, OH); 2.48 (*dd*, *J* = 12, 9, H_A–C(29)); 2.38 (*m*, 1 H); 2.35 (*s*, MeC_6H_4); 2.26–2.08 (*m*, 3 H); 1.95–0.80 (*m*, *ca.* 30 H); 1.49, 1.27, 1.16 (3*s*, 3 Me); 1.10 (*d*, *J* = 6.6, Me); 1.04 (*d*, *J* = 6.3, Me); 0.99 (*t*, *J* = 7.4, Me(37)); 0.89 (*d*, *J* = 6.3, Me); 0.81 (*d*, *J* = 7, Me); 0.80 (*d*, *J* = 6.6, Me); 0.68, 0.30 (2*d*, *J* = 6.3, 2 Me). FAB-MS (NBA): neg.: 1365 ([*M* – H]$^-$). Anal. calc. for $C_{77}H_{110}N_2O_{17}S$ (1367.79): C 67.62, H 8.11, N 2.05; found: C 67.88, H 8.08, N 2.08.

*9,34-Bis-*O*-[(benzyloxy)methyl]-22-*O*-{2-[(diphenylmethylidene)aminooxy]-1,2-dioxoethyl}X-206 Benzyl Ester* (**17**). At 0°, 1M benzophenone *O*-(chlorooxalyl)oxime [32] in CH_2Cl_2 (249 μl, 249 μmol) was added to a soln. of **6** (100 mg, 83 μmol) and pyridine (134 μl, 1.66 mmol) in CH_2Cl_2 (1 ml) under Ar. After 5 min, the soln. was diluted with AcOEt/hexane 1:3, washed with 0.5M $NaHCO_3$, H_2O (2×), 0.5M HCl, H_2O, 0.5M $NaHCO_3$, H_2O (2×), and brine, and dried ($MgSO_4$). The crude product 148 mg (120 mg = 100%) showed some aromatic impurities according to NMR, but was otherwise pure. The material decomposed on attempted chromatography.

R_f 0.28 (AcOEt/hexane 1:3). ^{1}H-NMR (500 MHz, $CDCl_3$): 4.87 (*s*, H–C(22)); 4.50 (*t*, *J* = 8.5, H–C(23)) (extract). FAB-MS (NBA); for $C_{85}H_{113}NO_{19}$ (1452.83): neg.: 1360 ([*M* – Bn]$^-$), 1271 ([*M* – (N=CPh$_2$)]$^-$), 1253 ([1271 – H_2O]$^-$.

9,34-Bis-O-*[(benzyloxy)methyl]-22*-O-*formyl-X-206 Benzyl Ester* (**18**). A stirred soln. of crude **17** (20 mg) and *t*-BuSH (0.05 ml, 444 µmol) in dry i-PrOH (0.45 ml) was irradiated through borosilicate glass with a high-pressure Hg lamp (125 W), while a stream of Ar was passed over the soln. After 90 min, the solvent was evaporated and the crude product chromatographed (AcOEt/hexane 5:95 → 1:3): 5.4 mg (39% over 2 steps) of **18**. Solid compound after freeze-drying. R_f 0.40 (acetone/hexane 3:7), 0.44 (AcOEt/hexane 3:7). ^{1}H-NMR (500 MHz, $CDCl_3$): 8.32 (*s*, HCOO–C(22)); 7.42–7.24 (*m*, 3 Ph); 6.41, 5.59 (2*s*, 2 OH); 5.30, 5.06 (2*d*, *J* = 12.4, CO_2CH_2Ph); 5.03, 4.96 (2*d*, *J* = 8, OCH_2O); 4.96, 4.91 (2*d*, *J* = 8, OCH_2O); 4.91 (*s*, H–C(22)); 4.85 (*s*, OH); 4.76, 4.64 (2*d*, *J* = 12, OCH_2Ph); 4.74, 4.41 (2*d*, *J* = 11.6, OCH_2Ph); 4.51 (*dd*, *J* = 9, 7, H–C(23)); 4.35 (*dd*, *J* = 10, 3, H–C(9)); 4.22 (*t*, *J* = 10, H–C(17)); 3.84 (*dd*, *J* = 11, 3, H–C(35)); 3.69 (*td*, *J* = 11, 2, H–C(11)); 3.36 (*dd*, *J* = 10, 3.6, H–C(3)); 3.35 (*m*, H–C(7)); 3.28 (*dd*, *J* = 12, 2.2, H–C(31)); 2.68 (*qd*, *J* = 7, 3.6, H–C(2)); 2.41 (*dd*, *J* = 12, 8, H_A–C(29)); 2.30 (*td*, *J* = 11, 8, 1 H); 2.02–0.80 (*m*, *ca.* 30 H); 1.31, 1.17, 1.15 (3*s*, 3 Me); 1.15 (*d*, *J* = 7, Me); 1.00 (*d*, *J* = 6.4, Me); 0.93 (*t*, *J* = 7, *d*, *J* = 6.4, 2 Me); 0.83, 0.82 (2*d*, *J* = 6.8, 2 Me); 0.79 (*d*, *J* = 6, Me); 0.70 (*d*, *J* = 6.4, Me). FAB-MS (NBA; for $C_{71}H_{104}O_{17}$ (1229.60)): neg.: 1381 ([*M* + NBA]$^-$), 1227 ([*M* – H]$^-$), 1137 ([*M* – Bn]$^-$).

9,34-Bis-O-*[(benzyloxy)methyl]-22*-O-*tosyl-X-206 Benzyl Ester* (**19**). A soln. of **6** (800 mg, 0.667 mmol), *p*-toluenesulfonic anhydride (1.09 g, 3.34 mmol), and DMAP (16.3 mg, 0.133 mmol) in pyridine (8 ml) was stirred under Ar for 1 h, then treated with ice and acidified with 1M HCl. The mixture was extracted with AcOEt/hexane 1:3 (3×), washed with H_2O (2×), 0.5M $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and chromatographed (AcOEt/hexane 5:95 → 1:4): 751 mg (83%) of **19**. Colourless foam. R_f 0.37 (AcOEt/hexane 3:7). IR: 3403, 2967, 2935, 2879, 1743, 1456, 1380, 1362, 1176, 1097, 1040, 1001, 939, 870, 698. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.84 (*d*, *J* = 8, 2 arom. H); 7.40–7.25 (*m*, 2 arom. H, 3 Ph); 6.32, 5.45 (2 br. *s*, 2 OH); 5.31, 5.04 (2*d*, *J* = 12.3, CO_2CH_2Ph); 4.98, 4.94 (2*d*, *J* = 8, OCH_2O); 4.94, 4.90 (2*d*, *J* = 8, OCH_2O); 4.86 (*d*, *J* = 2.1, OH); 4.74, 4.63 (2*d*, *J* = 12, OCH_2Ph); 4.71, 4.44 (2*d*, *J* = 12, OCH_2Ph), 4.54 (*s*, H–C(22)); 4.51 (*t*, *J* = 8, H–C(23)); 4.30 (*dd*, *J* = 10.5, 3, H–C(9)); 4.12 (*t*, *J* = 10.5, H–C(17)); 3.82 (*dd*, *J* = 11, 3, H–C(35)); 3.65 (*td*, *J* = 11, 2, H–C(11)); 3.34 (*dd*, *J* = 10, 3, H–C(3)); 3.31 (*m*, H–C(7)); 3.25 (*dd*, *J* = 11, *ca.* 1.5, H–C(31)); 2.67 (*qd*, *J* = 7, 3, H–C(2)); 2.45 (*s*, MeC_6H_4); 2.39 (*dd*, *J* = 12, 8.5, H_A–C(29)); 2.18 (*td*, *J* = 12, 9, 1 H); 2.06–0.80 (*m*, *ca.* 30 H), 1.29, 1.15 (2*s*, 2 Me); 1.12 (*d*, *J* = 7, Me); 0.98 (*s*, Me); 0.96 (*d*, *J* = 6.4, Me); 0.93 (*t*, *J* = 7.2, Me(37)); 0.91 (*d*, *J* = 6.4, Me); 0.84, 0.82, (2*d*, *J* ≈ 7, 2 Me); 0.74 (*d*, *J* = 6.0, Me); 0.69 (*d*, *J* = 6.6, Me). FAB-MS (NBA): neg.: 1400, 1353 ([*M* – H]$^-$), 1263 ([*M* – Bn]$^-$). Anal. calc. for $C_{77}H_{110}O_{18}S$ (1355.78): C 68.22, H 8.18; found: C 68.20, H 8.19.

Intermediate 1,4-Dioxaspiro[2.5]octane Derivative **20**: *NMR Experiment*. DBU (1.1 µl, 7.4 µmol) was added to a soln. of **19** (5 mg, 3.7 µmol) in dry $CDCl_3$ (0.5 ml). After 5 d at r.t., two isomers (1:1) of **20** were observed by ^{1}H-NMR besides *ca.* 10% of starting material. TLC showed only **21** as well as a small amount of **19**. ^{1}H-NMR (500 MHz, $CDCl_3$): 2.97 (*d*, *J* = 5.5, H–C(22)); 2.84 (*d*, *J* = 7.5, H'–C(22)) (extract). ^{13}C-NMR Signals extracted from HSQC (500 MHz, $CDCl_3$): 62.5 (C(22)), 62.0 (C'(22)); δ(H) and δ(C) of the two spiroepoxide tautomers are consistent with those of known simple spiroepoxides [27b, c]. The same behaviour as for **25A** and **25B** (see below) is expected for the 21,22-epoxide.

9,34-Bis-O-*[(benzyloxy)methyl]-22-epi-X-206 Benzyl Ester* (**21**). *a*) At 0°, 1M lithium triethylborhydride in THF (11 µl) was added to a soln. of **19** (10 mg, 7.4 µmol) in THF (100 ml) under Ar. After 5 min, H_2O was added, the mixture extracted with AcOEt/hexane 1:1, washed with brine, dried ($MgSO_4$), and chromatographed (AcOEt/hexane 1:9 → 1:3): 2.7 mg (30%) of **21**.

b) DBU (110 µl, 739 µmol) was added dropwise to a soln. of **19** (500 mg, 369 µmol) in THF (5 ml) and H_2O (0.5 ml). After 1.5 h, the mixture was diluted with AcOEt/hexane 1:3, washed with 0.5M HCl and H_2O (3×), dried ($MgSO_4$), and chromatographed (AcOEt/hexane 1:9 → 3:7): 338 mg (76%) of **21**. R_f 0.30 (AcOEt/hexane 3:7), 0.14 (MeCN/toluene 1:9). IR (CH_2Cl_2): 3411, 2962, 2931, 1735, 1456, 1380, 1177, 1163, 1100, 1039, 1027; no hydroxy ketone absorptions. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.40–7.25 (*m*, 3 Ph); 5.77 (*d*, *J* = 1.2, OH); 5.30, 5.06 (2*d*, *J* = 12.4, CO_2CH_2Ph); 5.13 (*d*, *J* ≈ 2, OH); 4.97, 4.92 (2*d*, *J* = 8, OCH_2O); 4.95, 4.68 (2*d*, *J* = 9.6, OCH_2O); 4.76, 4.67 (2*d*, *J* = 11.6, OCH_2Ph); 4.71, 4.49 (2*d*, *J* = 12, OCH_2Ph); 4.29 (*dd*, *J* = 10, 3, H–C(9)); 4.24 (*td*, *J* = 10.5, 1.5, H–C(17)); 4.16 (*dd*, *J* = 10, 5, 3.4, H–C(23)); 3.85 (*dd*, *J* = 12, 3, H–C(35)); 3.81 (*t*, *J* = 3.4, H–C(22)); 3.70 (*td*, *J* = 11, 2, H–C(11)); 3.40 (*dd*, *J* = 10, 3.4, H–C(3)); 3.38 (*m*, H–C(7)); 3.32 (*dd*, *J* = 11.6, 2, H–C(31)); 2.96 (*s*, OH); 2.70 (*qd*, *J* = 7.4, 3.4, H–C(2)); 2.44 (*dd*, *J* = 12, 8.4, H_A–C(29)); 2.31 (*td*, *J* = 11.6, 8, 1 H); 2.18 (*m*, 1 H); 2.10 (br. *d*, *J* = 13, 1 H); 2.02 (*d*, *J* = 3.4, OH–C(22)); 2.00–0.80 (*m*, *ca.* 30 H); 1.31, 1.18, 1.16 (3*s*, 3 Me); 1.14 (*d*, *J* = 7.4, Me); 1.04 (*d*, *J* = 6.4, Me); 0.98 (*t*, *J* = 7.3, Me(37)); 0.92

(*d*, J = 6.6, Me); 0.88 (*d*, J = 6.4, Me); 0.82 (*d*, J = 7, Me); 0.79, 0.72 (2*d*, J = 6.4, 2 Me). ^{13}C-NMR Signal extracted from HSQC (500 MHz, $CDCl_3$): 73.6 (C(22)); δ similar to that of **6**, *i.e.* ring C in hemiacetal form; no evidence for hydroxy ketone forms. FAB-MS (NBA): neg.: 1353 ($[M + NBA]^-$), 1199 ($[M - H]^-$), 1109 ($[M - Bn]^-$). Anal. calc. for $C_{70}H_{104}O_{16}$ (1201.59): C 69.97, H 8.72; found: C 70.29, H 8.97.

22,27,28-Tri-epi-X-206 (**22**). As described for **9**, with **21** (100 mg, 83.3 µmol), 0.05M $HClO_4$ (2.5 ml), THF (10 ml), and 5% Pd/C (75 mg), for 24 h. After chromatography ($(CH_2OMe)_2$/hexane 15:85 → 45:55), the obtained salt (IR: 1565 cm^{-1}) was dissolved in AcOEt/hexane 1:1, shaken thoroughly with 1M HCl, washed with H_2O (3×), dried ($MgSO_4$), and freeze-dried; 27.2 mg (38%) of **22**. R_f 0.30 ($(CH_2OMe)_2$/hexane 1:1). IR: 3437 (br.), 2962, 2931, 2876, 1717, 1460, 1379, 1158, 1095, 1038, 1019, 973. ^{1}H-NMR ($CDCl_3$, 500 MHz): 5.44 (*s*, OH); 4.15 (*ddd*, J = 10.5, 6, 4, H–C(23)); 4.06 (*m*, H–C(11), H–C(17)); 4.05 (*d*, J = 12, H–C(9)); 4.00 (*d*, J = 4, H–C(22), *s*, OH); 3.65 (*m*, H–C(7)); 3.55 (*dd*, J = 9.6, 3, H–C(3)); 3.53 (*dd*, $J \approx$ 12, 3, H–C(35)); 3.38 (*dd*, J = 11, 3, H–C(31)); 2.74 (*qd*, J = 7, 3, H–C(2)); 2.59 (*m*, H–C(28), OH); 2.36 (*dt*, J = 11.5, 10.5, 1 H); 2.00–0.80 (*m*, *ca.* 35 H); 1.97 (*t*, J = 12, H_A–C(29)); 1.32, 1.15 (2*s*, 2 Me); 1.11 (*d*, J = 6.5, Me); 1.09 (*s*, Me); 1.08 (*d*, J = 6.5, Me); 1.02 (*t*, J = 7.5, Me(37)); 0.91, 0.90 (2*d*, $J \approx$ 6.5, 2 Me); 0.85 (*d*, J = 6.6, Me); 0.81, 0.80 (2*d*, $J \approx$ 7, 2 Me. The signals of H–C(28) and H_A–C(29) are consistent with epimerization at C(27) and C(28) [16]; signal shifts of up to 0.1 ppm were observed in the presence of H_2O, depending on workup (freeze-dried or foamed under vacuum); D_2O exchange led to similar shifts. FAB-MS (NBA; for $C_{47}H_{82}O_{14}$ (871.16)): neg.: 869 ($[M - H]^-$).

9,34-Bis-O-*[(benzyloxy)methyl]-22*-O-*tosyl-22-epi-X-206 Benzyl Ester* (**23**). A soln. of **21** (20 mg, 16.7 µmol), DMAP (0.4 mg, 3.3 µmol), and *p*-toluenesulfonic anhydride (27 mg, 83.3 µmol) in pyridine (200 µl) was stirred for 5 h, treated with ice, extracted with Et_2O/hexane 1:1, washed with 0.5M HCl, H_2O, 0.5M $NaHCO_3$, and H_2O, dried ($MgSO_4$), and chromatographed (toluene, MeCN/toluene 3:97 → 6:94): 6.1 mg (27%) of **23**. R_f 0.31 (AcOEt/hexane 3:7), 0.39 (MeCN/toluene 1:9). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.80 (*d*, J = 8.5, 2 arom. H); 7.42–7.20 (*m*, 2 arom. H, 3 Ph); 5.32, 5.05 (2*d*, J = 12, CO_2CH_2Ph); 4.96, 4.91 (2*d*, J = 8, OCH_2O); 4.93 (*d*, J = 3, H–C(22)); 4.91, 4.70 (2*d*, J = 8, OCH_2O); 4.90 (*s*, OH); 4.75, 4.65 (2*d*, J = 12, OCH_2Ph); 4.64, 4.56 (2*d*, J = 12, OCH_2Ph); 4.30 (*d*, J = 2, OH); 4.29 (*m*, H–C(23)); 4.20 (*m*, H–C(9), H–C(17)); 3.83 (*dd*, J = 11, 3, H–C(35)); 3.75 (*ddd*, J = 12, 9.2, H–C(11)); 3.30 (*m*, H–C(7)); 3.29 (*dd*, J = 10, 3.3, H–C(3)); 3.26 (*dd*, $J \approx$ 12, 2.5, H–C(31)); 2.90 (*s*, OH); 2.65 (*qd*, J = 7, 3.3, H–C(2)); 2.42 (*dd*, J = 12, 8.5, H_A–C(29)); 2.40 (*s*, MeC_6H_4); 2.18 (*dt*, J = 12, 9, 1 H); 2.07 (*m*, 1 H); 1.92 (*ddd*, J = 13.6, 9, 3.6, 1 H); 1.84–0.70 (*m*, *ca.* 30 H); 1.27, 1.15 (2*s*, 2 Me); 1.11 (*d*, J = 6.6, Me); 0.98 (*d*, J = 6.4, Me); 0.95 (*t*, $J \approx$ 7, Me(37)); 0.94 (*d*, $J \approx$ 6, Me); 0.88, 0.87 (2*d*, $J \approx$ 7, 2 Me); 0.80 (*s*, Me); 0.79 (*d*, $J \approx$ 6, Me); 0.65 (*d*, J = 6.4, Me). FAB-MS (NBA; for $C_{77}H_{110}O_{18}S$ (1355.78)): neg.: 1507 ($[M + NBA]^-$), 1353 ($[M - H]^-$), 1263 ($[M - Bn]^-$).

6-{3-{6-{{6-{{5'-{5-[(Benzyloxy)methoxy]-6-ethyltetrahydro-5-methyl-2H-pyran-2-yl}octahydro-2'-hydroxy-2,3',5'-trimethyl[2,2'-bifuran]-5-yl}hydroxymethyl}-6-(ethylthio)tetrahydro-3,5-dimethyl-2H-pyran-2-yl}methyl}tetrahydro-6-hydroxy-5-methyl-2H-pyran-2-yl}-2-[(benzyloxy)methoxy]butyl}tetrahydro-α,3-dimethyl-2H-pyran-2-acetic Acid Benzyl Ester (*9,34-Bis*-O-*[(benzyloxy)methyl]-21-deoxy-21-(ethylthio)-22-epi-X-206 Benzyl Ester*; **25A**). To a soln. of **19** (20 mg, 14.8 µmol) in THF (200 µl), powdered 4-Å molecular sieves (20 mg), ethanethiol (20 µl), and DBU (4.4 µl, 29.6 µmol) were added under stirring. After 3 h (TLC: complete conversion), the mixture was cooled to −78°, and 1M diethylaluminium chloride in hexane (37 µl, 370 µmol) was added dropwise. After 45 min, more DBU (5 µl, 33.6 µmol) was added and the mixture diluted with AcOEt/hexane 1:3, washed with 0.5M HCl, H_2O, 0.5M $NaHCO_3$, and H_2O (2×), dried ($MgSO_4$), and chromatographed ($(CH_2OMe)_2$/hexane 5:95 → 1:4): 7.2 mg (39%) of **25A** and 5.2 mg (28%) of **25B** after freeze-drying. These two isomers equilibrated after some time in soln. R_f ($(CH_2OMe)_2$/hexane 1:3) 0.35 (**25A**), 0.24 (**25B**). ^{1}H-NMR (500 MHz, $CDCl_3$; partial spectrum): 4.28–4.16 (*m*, 2 H (**25A**/**25B**)); 4.07 (*t*, J = 4.4, H–C(22) (**25B**)); 4.06–3.81 (*m*, 6 H (**25A**/**25B**)); 3.90 (*t*, J = 6, H–C(22) (**25A**)); 3.70 (*dt*, J = 7.5, 4.5, 1 H (**25A**)); 3.56–3.27 (*m*, 8 H (**25A**/**25B**)); 3.34 (*s*, 1 OH (**25B**)); 3.03 (*s*, OH (**25A**)); 3.01 (*dq*, J = 11.3, 7.5, H–C(14) (**25B**)); 2.78–2.67 (*m*, 4 H, 1 H of $MeCH_2S$ (**25A**/**25B**), H–C(2) (**25A**/**25B**)); 2.65 (*dd*, J = 16, 9, H_A–C(16) (**25B**)); 2.58–2.50 (*m*, 2 H, 1 H of $MeCH_2S$ (**25A**/**25B**)); 2.54 (*d*, J = 6, OH–C(22) (**25A**)); 2.53 (*d*, J = 4.4, OH–C(22) (**25B**)); 2.44 (*dd*, J = 12, 8.3, H_A–C(29) (**25B**)); 2.42 (*dd*, J = 12, 8.3, H_A–C(29) (**25A**)); 2.36–2.11 (*m*, 4 H (**25A**/**25B**)); the signals of H–C(14) and H_A–C(16) of **25B** indicate a hydroxy ketone form for ring B. FAB-MS (NBA; identical for **25A** and **25B**; for $C_{72}H_{108}O_{15}S$ (1245.71)): neg.: 1397 ($[M + NBA]^-$), 1181 ($[M - EtSH - H]^-$), 1153 ($[M - Bn]^-$).

In $CDCl_3$, both substances showed a ratio of 40% (**25A**) to 60% (**25B**). The behaviour of the two tautomers **25A** and **25B** is similar to that reported [16] for the acetal 21-*O*-methyl-X-206 methyl ester.

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