Use of the Potassium Ion as a Template for the Selective Derivatization of the Antibiotic X-206

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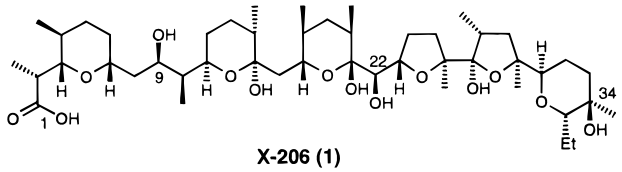
The templating effect of potassium ions on the ionophore antibiotic X-206 (**1**) ensured that most of the hydroxy, hemiacetal, and ether groups were involved in encapsulation of the metal atom, which allowed a selective derivatization at the unbound C(22) position. The mechanism of acylation at C(22) was investigated and the aquired knowledge used to achieve selective reactions on the benzyl ester **8** using a similar metal template protection.

Introduction

When metal ions complex with substrates, they can influence reactions in various ways. In a monodentate manner they can increase the rate of a reaction,[1] or through chelation they can hold a substrate in a conformation that encourages a particular stereoselectivity.[2] When the complexation is polydentate, the term template effect is often used. For example, corrins,[3] catenanes,[4] or peptides[5] can be prepared when several components are held together in a suitable arrangement by a templating cation. Similarly, polyfunctional long-chain molecules can be macrocyclized when suitably templated.[6] Here we describe the cationic complexation of most of the polar functionality of the polyether X-206, which protects it from reaction and allows a selective derivatization of the C(22) hydroxy group. This work was similar in concept to that of Isono et al.,[7] who described a related template effect in the reactions of cationomycin, which in turn was stimulated by the knowledge that the presence of cations can influence the reactivity of polyethers.[8] We describe here: first, the regioselectivity achieved using the template effect on X-206; second, the mixed anhydride **6**, which is probably an intermediate in the reaction and is in some cases isolable; and finally, the mechanism of lactone **7** formation. Knowing this mechanism, two measures were taken to avoid lactone formation and achieve clean C(22) derivatization: the use of acid fluorides rather than other acylating agents, which made a wide range of esters synthetically accessible, and the derivatization of the benzyl ester **8** in the presence of lipid-soluble potassium salts.

In addition to their anticoccidial and growth-promoting antibacterial properties, the polyether antibiotics possess other interesting activities.[9] One example is the ionophore X-206 (**1**), which has insecticidal and acaricidal activities in addition to being an antibiotic.[10] Unfortu-



X-206 (1)

nately, X-206 is a relative toxic compound, with an LD_{50} of 17 mg kg^{-1} in rodents.[11] However, we hoped that derivatization would lead to compounds with increased insecticidal activity and reduced toxicity.

The polyether antibiotics are ionophores, which complex cations, thus enabling them to diffuse across lipophilic cell membranes, thereby affecting the ion gradients that are vitally important for the cell.[9a] From the X-ray structure of X-206 (Figure 1), all of the interactions involved in its binding to cations are clearly evident.[12] Most of the oxygen atoms are in the center of the tertiary structure of X-206 and either bind to the metal ion or hydrogen bond to each other, but the C(22) OH is on the periphery of the tertiary structure and appears to be uninvolved in any aspect of cation binding. We therefore chose it as a position suitable for derivatization. Indeed, it transpired that derivatives at C(22) bound potassium well and were interesting insecticides, whereas derivatives at C(1), C(9), or C(34) were either very weak or inactive, either as insecticides or ionophores.[13]

Results and Discussion

The C(22) derivatives were originally prepared by a multistep procedure.[14] A useful intermediate (**2**), pro-

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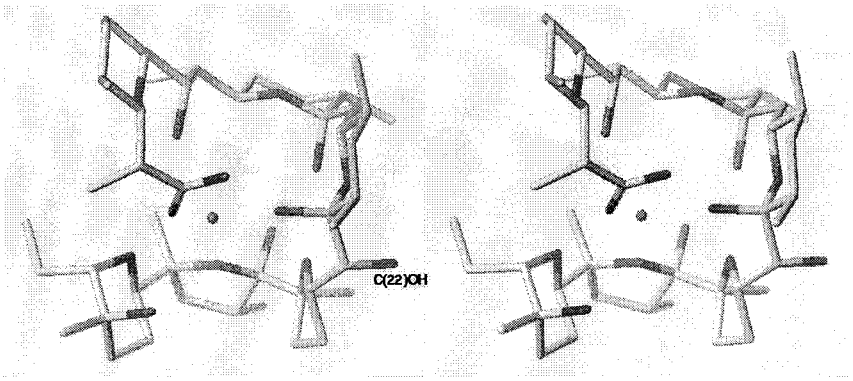
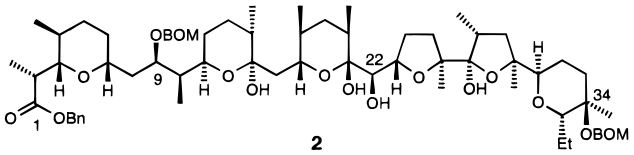


Figure 1. X-ray structure of X-206 sodium salt.



tected by hydrogenolytically cleavable groups, was used to synthesize a number of C(22) derivatives. These compounds turned out to be promising insecticides, particularly the C(22) esters, some of which were much better insecticides than X-206 itself.[13] As greater numbers and larger amounts of derivatives were required, a simpler route to their preparation was sought. This goal was achieved by exploiting the templating effect of potassium ions to prepare the desired C(22) esters in a single step as described below.

It was thought that potassium ion binding would protect the internal oxygen atoms from attack, allowing the C(22) OH group to be selectively derivatized. This turned out to be true, although the matter was more complex than we first imagined, as shown later. Thus, treatment of the potassium salt **3** with Ac_2O and pyridine led in a seemingly straighforward manner to **4a** in high yield, whereas a corresponding treatment of the free acid **1** gave a mixture of products from which **4a** was isolated in only 5% yield (Scheme 1). Isono et al. have described a similar acetylation of cationomycin at C(2) using the templating effect of sodium ions to achieve selectivity.[7]

Having demonstrated the effectiveness of the potassium ion as a protective template, **3** was treated with a variety of anhydrides, and indeed the straight chain aliphatic anhydrides yielded the desired esters (see Scheme 2 and Table 1). However, mixtures of compounds were obtained with other anhydrides, including benzoyl, phenyl acetyl, pivaloyl, chloroacetyl, and methacroyl anhydrides among others. As the anhydrides were only moderately successful, a number of other acylating agents were screened, using the benzoyl ester **4o** as a target. Treatment of **3** with BzCl in pyridine, Bz_2O in pyridine, or BzOH activated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride led to the lactone **7**, but fortunately benzoyl fluoride gave the desired ester **4o**, albeit in low yield. Pleasingly, however, when a series of other acid fluorides were examined under these conditions, the esters were formed in all cases, although again the yields were often only moderate. The acid fluorides **5** were prepared by simply treating the acids with 1 equiv of diethylaminosulfur trifluoride[15] and were used without further purification.

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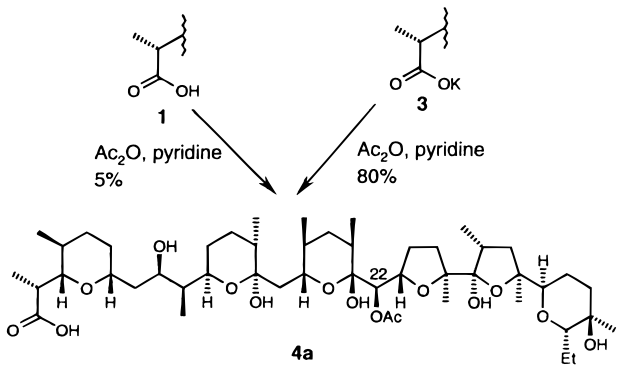
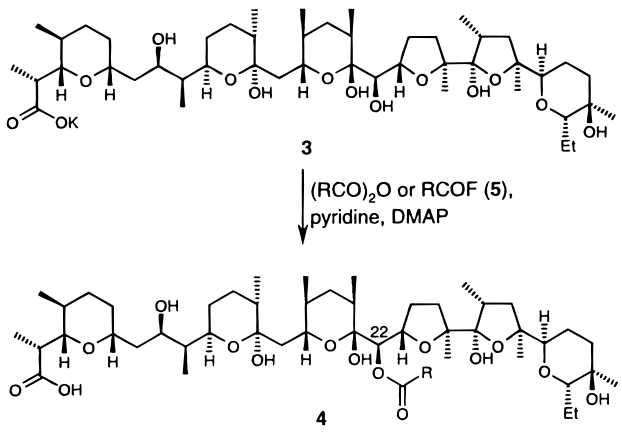
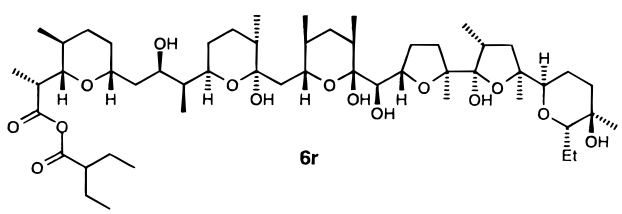
Scheme 1



Scheme 2



Several pieces of evidence indicated that the reaction proceeds via an intermediate mixed anhydride **6** (Scheme 3). First, an intermediate was seen during the reactions by TLC, which was isolated and characterized in the case of the mixed anhydride **6r**. Also, the lactone **7** is presum-



ably formed by cyclization of such a mixed anhydride. It is interesting that certain acylating agents yield the lactone **7**, whereas others form the desired C(22) esters selectively. Some information relating to this question

Table 1. Acylation of the Potassium Salt 3

R	method	product	yield (%)
CH_3	anhydride	**4a**	80
C_2H_5	anhydride	**4b**	79
$C_{11}H_{23}$	anhydride	**4c**	58
$C_{17}H_3$	anhydride	**4d**	51
$C_{17}H_{33}$ (oleate)	anhydride	**4e**	32
$C_{17}H_{31}$ (linolate)	anhydride	**4f**	45
$(CH_2)_2COOH$	anhydride	**4g**	77
$(CH_2)_3COOH$	anhydride	**4h**	45
i-Bu	anhydride	**4i**	50
n-Bu	anhydride	**4j**	55
n-Pr	anhydride	**4k**	82
i-Pr	anhydride	**4l**	59
n-pentyl	anhydride	**4m**	84
MeOCO	anhydride	**4n**	73
Ph	fluoride	**4o**	19
Bn	fluoride	**4p**	15
$PhOCH_2$	fluoride	**4q**	41
3-pentyl	fluoride	**4r**	19[a]
cyclopropyl	fluoride	**4s**	22
2-methyl cyclopropyl	fluoride	**4t**	54

[a] Plus 16% **7**.

can be obtained from the X-ray structure[12] of X-206 Na salt (Figure 1). As the C(22) OH is far away from C(1), the mixed anhydride **6** must conformationally twist away from its cation-binding tertiary structure for it to be able to cyclize to **7**. We assume, therefore, that cyclization takes place in uncomplexed **6**, which is more conformationally mobile. It then follows that fluoride as counterion serves to keep K^+ complexed to **6**, in a manner which we do not fully understand.

Implicit in the above mechanistic rationale is the ability of the mixed anhydride **6** to complex potassium ions, even though it is no longer anionic. We obtained evidence for this supposition by measuring calorimetrically the complexing ability of the benzyl ester **8**. It has a log K_c value of 2.8, which is less than that of X-206 (4.9) but is nevertheless significant, particularly when compared with derivatives at C(9) and C(34), which show no sign of cation binding.[16] The ion-binding abilites of **8** were further demonstrated by its selective acylation at the C(22) OH in the presence of potassium ions. This selectivity was not only of mechanistic interest, but it also opened a new route to C(22) derivatives, some of which were unattainable from other approaches. For K^+ ions to alter the course of the acylation of **8**, they have to be soluble in organic solvents, which is only the case when they are accompanied by large lipophilic anions. For example, potassium dodecyl sulfate was not soluble enough to alter the course of the acetylation of **8**, and therefore **10** was formed exclusively. However, addition of potassium tetrakis(4-chlorophenyl)-borate to the acetylation reaction led to the selective acetylation of **8** at C(22), yielding the ester **9** in 58% yield (Scheme 4).

The ionophoric properties of the 22-desoxy compound **13** illuminate the role of the C(22) O atom in cation binding. As our derivatization strategy rested wholly on the premise that this atom is uninvolved in binding, considerable effort was put into the synthesis of **13**. Only mixtures were obtained when **2** was treated with phenyl chlorothionoformate under various conditions**,** and only the lactone **7** was isolated from the K^+ salt of **3** under similar conditions. However, the desired thionocarbonate **11** was obtained when **8** was treated with phenyl chlorothionoformate in pyridine in the presence of potassium tetrakis(4-chlorophenyl)-borate, albeit in only 10% yield (Scheme 5). After radical reduction of **11** and deprotection, the deoxygenated compound **13** was formed, and its ionophoric properties were determined. From its log K_c value of 4.5, it is evident that the C(22) OH group does not contribute significantly to K^+ binding.

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Conclusion

The determination of C(22) in X-206 as a position that can be modified without loss of activity is important and useful for a number of reasons. First, it led to the synthesis of compounds with greatly improved insecticidal activity, although sadly their toxicological profile prohibited practical use.[13] Furthermore, with this methodology, a functionally active ionophoric X-206 may now be covalently attached to fluorescent or radioactive markers, photoaffinity labels, proteins, and solid phases. Because of the large number of functional groups in ionophores, the means of reacting selectively and extraperipherally is all important. Using the templating ability of metal ions, which is inherent to the natural function of ionophores, this goal was achieved.

Experimental Procedures

General. X-206 was obtained from Gräfe and Schlegel of the Hans Knöll Institute in Germany.[17] Most of the common procedures and instrumentation have been previously described, as has the preparation of **4a**.[14] The metal binding constants K_c were determined calorimetrically. Solutions of the derivatives in tetrabutylammonium hydroxide (1.2 mM) were titrated automatically with KCl or NaCl in MeOH at 25 °C.[16] The ^{1}H NMR signals were assigned mainly according to their appearance, which for most protons is very similar throughout the series of compounds described here. This is of course a subjective assignment based on our experience, so we relegate the NMR data to the Supporting Information.

X-206-22-Propionate (4b). A 100 mg (110 μmol) portion of **3** and 2.7 mg (22 μmol) of DMAP in 1 mL of pyridine were treated with 71 μL (550 μmol) of propionic anhydride. After 2.5 days the reaction mixture was treated dropwise with water to the point of turbidity. After 5 min the mixture was shaken between 1 M HCl and 50% EtOAc/hexane (3×). The organic phase was washed with water, dried with $MgSO_4$, and evaporated. The crude product was chromatographed with 5−10−15−20% MeCN/toluene to yield 80.2 mg (79%) of **4b** after freeze-drying. IR (KBr) 3389 (br), 2967, 2937, 1738, 1461, 1381, 1188, 1083, 1065, 1037, 992 cm^{-1}; *m/z* (Cs-FAB, NBA) neg. 925 $(M - H)^-$, pos. 949 $(M + Na)^+$, 799. Anal. Calcd for $C_{50}H_{86}O_{15}\cdot H_2O$: C, 63.53; H, 9.38. Found: C, 63.84; H, 9.24.

X-206-22-Methoxalate (4n). A solution of 200 mg (220 μmol) of **3** and 44 μL (550 μmol) of pyridine in 1 mL CH_2Cl_2 at 0 °C under argon was treated dropwise with 440 μL 1 M methoxalic anhydride[18] in CH_2Cl_2. After 30 min the mixture was diluted with CH_2Cl_2, washed with 0.5 M HCl (1×) and H_2O (3×), dried with $MgSO_4$, and evaporated. The crude product was chromatographed with 5−15−25−30−35% DME/hexane to yield 152.9 mg (73%) of **4n** after freeze-drying. IR (KBr) 3390 (br), 2966, 2937, 1772, 1744, 1459, 1381, 1313, 1202, 1166, 1102, 1037, 992 cm^{-1}; *m/z* (Xe-FAB, NBA) neg. 955 $(M - H)^-$, pos. 979 $(M + Na)^+$. Anal. Calcd for $C_{50}H_{84}O_{17}\cdot 0.5\ H_2O$: C, 62.15; H, 8.87. Found: C, 62.28; H, 8.82.

The other esters were prepared analogously to **4b** using either the anhydrides or the acid fluorides according to the Tables 2 and 3. Concentrated extracts of **4c** and **4d** were cooled in an ice bath before chromatography. The fatty acids that

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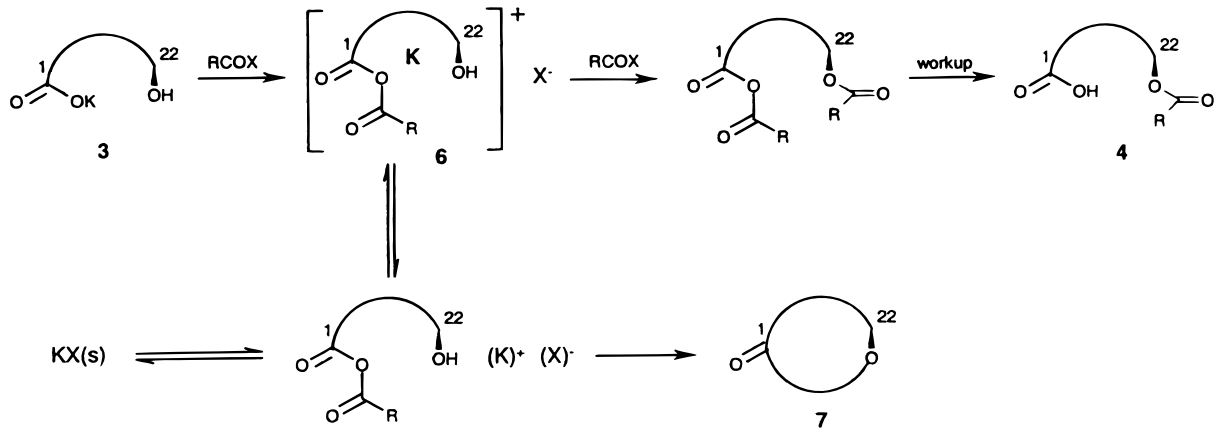
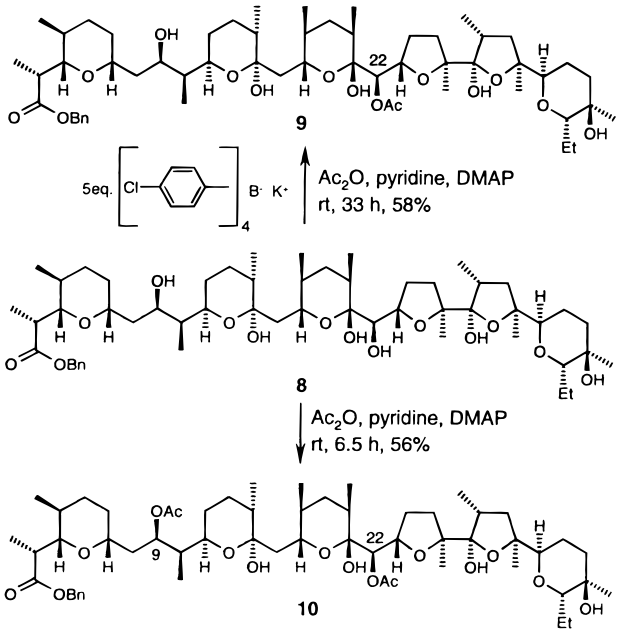
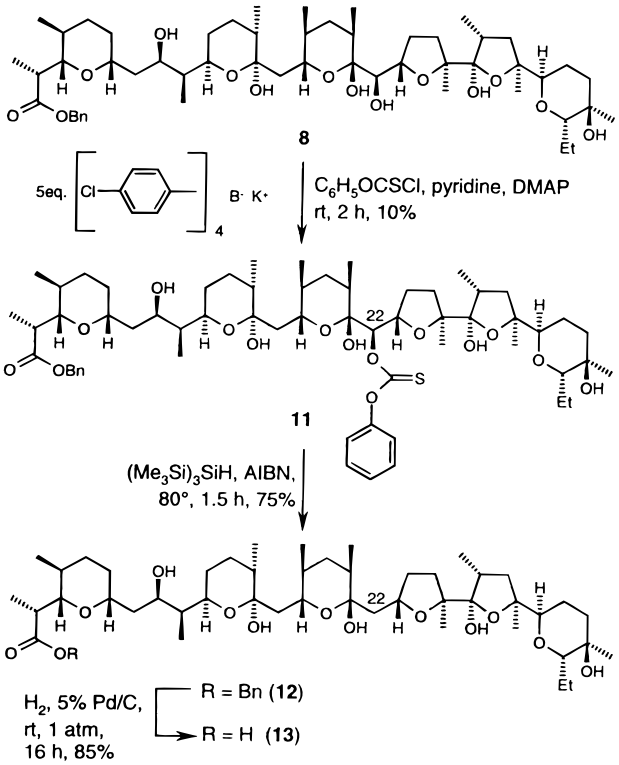
Scheme 3



Scheme 4



Scheme 5



crystallized were not applied to the column. The ^{1}H NMR spectra of the esters are almost superimposable with that of **4a**, with the exception of the ester peaks.

2-Ethyl-butyryl Fluoride (5r). A 2.2 mL (2.69 g, 16.7 mmol) portion of diethylaminosulfur trifluoride was added to a solution of 2 mL (1.84 g, 15.9 mmol) of 2-ethyl-butyric acid in 10 mL of CH_2Cl_2 at −60 °C. After stirring for 15 min at 0 °C, the mixture was shaken between pentane and water (2×). The pentane was dried with $MgSO_4$ and evaporated under water pump pressure to yield 1.65 g (88%) of 2-ethyl-butyryl fluoride, which according to ^{1}H NMR was pure apart from small amounts of CH_2Cl_2 and pentane. The other acid fluorides were prepared analogously according to a literature procedure[15] and used for the acylation of **3** without purification (Table 4).

X-206-22-Ethyl-butyryl anhydride (6r). A 100 mg (110 μmol) portion of **3** in 0.5 mL of pyridine was treated with 65 mg (550 μmol) of 2-ethyl-butyryl fluoride. After 3 days at room temperature the reaction mixture was worked up as usual. The crude mixture was chromatographed with 5−10−15−20% MeCN/toluene to yield 21 mg of crude **6r** and 47 mg of recovered X-206. The crude **6r** was rechromatographed under the same conditions to yield 5 mg (5%) of pure **6r**. *m/z* (Xe-FAB, NBA) neg. 1121 $(M + NBA)^-$, 967 $(M - H)^-$, pos. 991 $(M + Na)^+$.

X-206-22-Lactone (7). Benzoyl chloride (128 μL, 154 mg, 1.1 mmol) was added to a solution of **3** (100 mg, 110 μmol) in pyridine (0.5 mL). After 30 min at room temperature, the reaction mixture was worked up as usual to yield 379 mg of a crude mixture, which was chromatographed with 10−20−40% MeCN/toluene to yield 39 mg (36%) of the lactone **7** after freeze-drying from benzene. The lactone **7** was isolated in 37%

Table 2. Syntheses of X-206-22-Esters from Acid Anhydrides

compd	equiv anhydride	equiv DMAP	temp	time	yield (%)
4a	10	0.2	rt	18 h	80
4b	5	0.2	rt	2.5 d	79
4c	5	0.2	rt	3.5 d	58
4d	5	0.2	50 °C	3.5 d	51
4e	5	0.2	rt	5 d	32
4f	5	0.2	rt	5 d	45
4g	10	1	60 °C	4 d	77
4h	10	1	60 °C	4 d	45
4i	8	1	rt	4 h	50
4j	10	1	rt	4 h	55
4k	5	0.2	rt	5 d	82
4l	10	1	50 °C	5 d	59
4m	5	0.2	rt	5 d	84
4n	2.5	0	0 °C	30 min	73

Table 3. Syntheses of X-206-22-Esters from Acid Fluorides

compd	equiv RCOF	equiv DMAP	temp	time	yield (%)
4o	10	0	80 °C	30 min	19
4p	10	1	rt	15 min	15
4q	2.4	0	0 °C	15 min	41
4r	15	1	rt	16 h	19[a]
4s	20	1	rt	2 h	22
4t	18	1	rt	2 h	54

[a] Plus 16% lactone **7**. When 5 equiv of RCOF were used in pyridine without DMAP, **6r** (5%) was isolated.

Table 4. Syntheses of the Acid Fluorides RCOF (5)

compd	R	yield (%)
purchasable	Ph	
5p	Bn	79
5q	$PhOCH_2$	60
5r	3-pentyl	88
5s	cyclopropyl	45
5t	2-methyl	100

yield on treatment of **3** with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and benzoic acid in pyridine. It was also isolated in 71% yield on treatment of **3** with *p*-tolyl chlorothionoformate and DMAP in CH_2Cl_2. The confirmation of this structure through alternative synthesis is described in the Supporting Information. IR (KBr) 3501, 2935, 1742, 1458, 1379, 1162, 1101, 1057, 1009 cm^{-1}; *m/z* (Cs-FAB, THG) neg. 851 $(M - H)^-$. Anal. Calcd for $C_{47}H_{80}O_{13}$: C, 66.17; H, 9.45. Found: C, 66.19; H, 9.24.

X-206-Benzyl Ester (8). A 5.40 mL (45.3 mmol) portion of benzyl bromide was added dropwise to a solution of 10.0 g (11.3 mmol) of X-206 (**1**) and 9.60 mL (56.3 mmol) of *N*-ethyldiisopropylamine in 100 mL of acetonitrile. After 18 h the solvent was evaporated, and the residue was shaken between 75 mL of water and 250 mL of ether (3×). The combined etheral phase was washed with 0.5 M HCl (1×) and water (2×), dried with $MgSO_4$, and evaporated. Chromatography (35% EtOAc/hexane) afforded 9.56 g (88%) of the benzyl ester **8** as a white foam. IR (KBr) 3398 (br), 2964, 2935, 1740, 1458, 1381, 1065, 1042 cm^{-1}; *m/z* (Xe−FAB, THG) neg. 959 $(M - H_2O - H)^-$, 869 $(M - H_2O - Bn)^-$. Anal. Calcd for $C_{54}H_{88}O_{14}\cdot H_2O$: C, 66.23; H, 9.26. Found: C, 66.46; H, 9.34.

X-206-Benzyl Ester-9,22-diacetate (10). A 300 mg (0,312 mmol) portion of benzyl ester **8** and 7.5 mg of DMAP (62 μmol) were dissolved in 6 mL of pyridine and treated with 0.6 mL of acetic anhydride. HPTLC showed the formation of approximately equal amounts of the monoacetates, which did not accumulate but were further converted to the diacetate **10**, before **8** was consumed. After 6.5 h ice was added and after some time the mixture was shaken between H_2O and 75% EtOAc/hexane (3×). The organic phase was washed with 1 M HCl, H_2O, 0.5 M $NaHCO_3$, H_2O, and brine and dried with $MgSO_4$. The crude product was chromatographed (5−10−15−20% DME/hexane) to give 181 mg (56%) of **10** as a white foam. IR (KBr) 3412 (br), 2937, 1738, 1458, 1377, 1240, 1063 cm^{-1}; *m/z* (Cs-FAB, THG) neg. 1043 $(M - H)^-$, 953 $(M - Bn)^-$. Anal. Calcd for $C_{58}H_{92}O_{16}$: C, 66.64; H, 8.87. Found: C, 66.4; H, 8.8.

X-206-Benzyl Ester-22-acetate (9). A 0.2 mL portion of acetic anhydride was added to a solution of 100 mg (104 μmol) of **8**, 2.5 mg (21 μmol) of DMAP, and 258 mg (521 μmol) of potassium tetrakis(4-chlorophenyl)-borate in 2 mL of pyridine. After 33 h ice was added, and after a few minutes the mixture was shaken between H_2O and 25% EtOAc/hexane (3×). The organic phase was washed with 0.5 M HCl, H_2O, 0.5 M $NaHCO_3$, H_2O, and brine and dried with $MgSO_4$. Most of the borate salt was precipitated from a DME solution of the crude product by addition of hexane. The mother liquors were evaporated and chromatographed to yield 67 mg (64%) of **9**. According to 500 MHz ^1H NMR the material was identical to that prepared previously.[14] It contained approximately 10% of the diacetate **7** according to ^1H NMR.

X-206-Benzyl Ester-22-phenylthionocarbonate (11). A 1.8 mL (13.3 mmol) portion of phenyl chlorothionoformate was added dropwise to a solution of 1.00 g (1.04 mmol) of **8**, 4.13 g (8.32 mmol) of potassium tetrakis(4-chlorophenyl)-borate, and 26 mg (0.21 mmol) of DMAP in 10 mL of pyridine. After 2 h ice was added, and the mixture was extracted with 25% EtOAc/hexane (3×). The organic phase was washed with 1 M HCl, H_2O, 0.5 M $NaHCO_3$, H_2O, and brine and dried with $MgSO_4$. The crude material was chromatographed with 10−20−30% EtOAc/hexane, again with 10−15−20−25% EtOAc/hexane, and yet again with 10−20−25% DME/hexane to yield 108.4 mg (10%) of **11** as a white foam. IR (KBr) 3385 (br), 2965, 2936, 1739, 1457, 1381, 1278, 1201, 1064, 1038 cm^{-1}; *m/z* (Xe-FAB, NBA) neg. 1249 (M + NBA), 1095 $(M - H)^-$, 1005 $(M - Bn)^-$, 941 $(M - C(S)OPh - H_2O)^-$. Anal. Calcd for $C_{61}H_{92}O_{15}S\cdot 0.5H_2O$: C, 66.21; H, 8.47. Found: C, 66.20; H, 8.82.

22-Desoxy-X-206-benzyl Ester (12). A solution of 60 mg (54.7 μmol) of **11**, 84 μL (273.5 μmol) of tris(trimethylsilyl)-silane, and 9 mg (54.7 μmol) of α,α'-azoisobutyronitrile in 1.5 mL of toluene was heated under argon for 1.5 h at 80 °C. The solvent was evaporated, and the mixture was chromatopraphed (5−10−15−20% DME/hexane) to yield 38.5 mg of **12** (75%) as a white foam. IR (KBr) 3380 (br), 2933, 1739, 1457, 1380, 1166, 1088, 1050, 981 cm^{-1}; *m/z* (Xe-FAB, NBA) neg. 1097 (M + NBA), 1079 (M + NBA − H_2O), 943 $(M - H)^-$, 853 $(M - Bn)^-$. Anal. Calcd for $C_{54}H_{88}O_{13}$: C, 68.61; H, 9.38. Found: C, 68.23; H, 9.42.

22-Desoxy-X-206 (13). A solution of 38 mg (40.3 μmol) of **12** in 4 mL of THF containing 4 mg of Pd/C (5%) was hydrogenated at room temperature and normal pressure for 16 h. The catalyst was filtered off with Celite, and the crude product was chromatographed (15−25% DME/hexane) to yield 29.1 mg (85%) of **13** after freeze-drying. IR (KBr) 3368 (br), 2966, 2936, 1737, 1460, 1381, 1158, 1086, 1049, 979 cm^{-1}; *m/z* (Xe-FAB, NBA): neg. 853 $(M - H)^-$, pos. 877 $(M + Na)^+$, 893 $(M + K)^+$. Anal. Calcd for $C_{47}H_{82}O_{13}\cdot H_2O$: C, 64.65; H, 9.70. Found: C, 64.79; H, 9.76.

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Supporting Information Available: NMR data of the compounds and structure confirmation of the lactone **7** through alternative synthesis. This material is available free of charge via the Internet at http://pubs/acs/org.

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