Table 1. Inhibition of p38 MAP kinase, cytokine release, and cytochrome P450 isoforms by selected compounds.

Compound	$IC_{50} \pm SEM$ [μM][a] p38	TNF-α	IL-1β	Inhibition [%] of P450 isoforms[b] 2D6	3A4
SB 203580	0.29 ± 0.03 (7)	0.59 ± 0.09 (21)	0.037 ± 0.006 (20)	73.1	76.6
ML 3163	4.0 ± 1.0	1.1 ± 0.4 (4)	0.38 ± 0.13 (4)	71.8	87.1
4b	2.2 (1)	2.2 ± 0.9	0.45 ± 0.03	7.8	28.3
4c	0.50 (1)	0.51 ± 0.24 (4)	0.11 ± 0.03 (4)	13.4	16.5
4d	2.2 (1)	1.1 ± 0.3	0.38 ± 0.04	0.7	28.8

[a] Tests were carried out in duplicate, except where the number in brackets denotes otherwise. SEM = Standard error of measurement. [b] Results are from one experiment each, carried out at a test-compound concentration of 10 μM in phosphate buffer (pH 7.4) with DMSO (0.1%).

favorable cell-penetration properties. In the whole-blood assay, IC_{50} values (μM) for the most active derivatives **4b** (TNF-α: 5.6 ± 0.95, IL-1β: 1.5 ± 0.7), **4c** (TNF-α: 0.51 ± 0.24, IL-1β: 0.11 ± 0.03), and **4d** (TNF-α: 5.1 ± 0.4, IL-1β: 1.1 ± 0.7) were lower than those of lead compound ML 3163 (TNF-α: 20.3 ± 4.8, IL-1β: 2.78 ± 0.13), and close to the nanomolar range. Finally, the most promising results came from the toxicity screen, in which **4b–d** (Table 1) only moderately interacted with those P450 isoforms most important for drug metabolism.[9] This profile gives **4b–d** a clear advantage over both SB 203580 and ML 3163, and makes them strong candidates for further development as anti-inflammatory drugs.

Received: November 6, 2001 [Z18173]

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Tetrafunctional Photoaffinity Labels Based on Nakanishi's *m*-Nitroalkoxy-Substituted Phenyltrifluoromethyldiazirine**

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Photoaffinity labeling has been demonstrated to be a remarkably efficient method for studying the interactions of biologically significant compounds (ligands) with their target macromolecules.[1] The method allows the identification of the targets (for example, binding proteins) and, also the binding domain within the target protein. An appropriate photoaffinity-labeling compound should contain three structural elements:

a) a ligand which directs the label to the binding site on the protein,
b) a photolabile group for attaching to the protein,
c) an indicator that allows the identification of the labeled peptides after enzymatic digestion of the labeled protein.

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[**] We are grateful to Mrs. R. Herold and Mrs. R. Oehme for technical assistance. Financial support by the Deutsche Forschungsgemeinschaft, BC Biochemie GmbH, and the Fonds der Chemischen Industrie is gratefully acknowledged.

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Such an indicator may be a radioactive ligand or a nonradioactive tag such as a biotin group. The latter has the great advantage that it enables the labeling of the target protein and labeled protein fragments to be demonstrated by means of their interaction of biotin with avidin or streptavidin and isolating them by affinity chromatography.[2] Usually, the probes have the general appearance of **1**, that is, the photolabile group is attached to the ligand to which in turn the biotin tag is connected in a linear arrangement. Thus, the syntheses of these probes are linear and of limited efficiency.

1

We have now developed the two photoaffinity labeling reagents **7** (Scheme 1 A) and **18** (Scheme 3) which can accommodate the photophore, here an aryl trifluoromethyldiazirine (a carbene precursor first introduced by Brunner[3, 4]), the biotin tag, and the ligand attachment site independently.[5] Any desired ligand can be coupled to the free OH group of **7** and to the squaric ester function of **18** by an appropriate method. In addition, these compounds have two photolabile groupings, the diazirine moiety which generates the carbene intermediate on irradiation at 350 nm[6] and an alkyl *m*-nitrophenyl ether which undergoes a photosubstitution reaction to yield the corresponding *m*-nitrophenol on irradiation at the same wavelength in mildly basic solution.[7] As suggested by Nakanishi and co-workers,[8] the latter reaction can be used to remove both the ligand and the biotin tag from the peptide before mass spectrometric sequencing to avoid complications in its mass spectrometric analysis.

Amine **3** was prepared starting from dimethyl 5-hydroxyisophthalate (**2**) as described by Nakanishi and co-workers (Scheme 1 A).[8] The oxidation of **3** with dimethyldioxirane was already known to give the corresponding nitro compound **4a** in a reported yield of 66%. We found the reaction to be rather capricious. In our hands, the method of Krohn et al.[9] ($Zr(OtBu)_4$-mediated oxidation with *tert*-butyl hydroperoxide) gave far more reliable results. The yields of **4a** were uniformly in the range of 80%. Oxidative degradation of **4a**[10] provided aldehyde **4b**, and reduction of the latter with $NaBH_4$ furnished primary alcohol **4c** in 84% yield. Isocyanate **6** was obtained from (*R*)-malic acid (**5**) as described previously.[11] The coupling of **6** with primary alcohol **4c** gave urethane **9**, which reacted with the biotin derivative **8** (obtained from the corresponding, commercial diamine and biotin activated with *N*,*N*′-carbonyldiimidazole (CDI) in pyridine) to give **7** through amide formation and concomitant loss of the protecting group. The ^1H and ^{13}C NMR spectra of **7** were fully assigned by H,H COSY and ^{13}C,^1H COSY experiments. The ^{19}F NMR signal was found at $\delta = 12.65$ ppm ($CDCl_3$ solution, trifluoroacetic acid (TFA) $\delta = 0$ ppm). The ESI mass spectrum[12] showed the expected quasi molecular ion peaks.[13] Compound **7** can be regarded as a broadly applicable biotin-tagged photoaffinity label. We attached **7** to the moenomycin derivative **11b** (obtained from moenomycin A by the azo-coupling/Japp Klingemann route described previously[14]) to give **12** (Scheme 1 B), which was fully characterized by ^1H and ^{13}C NMR spectroscopy as well as mass spectrometry.[15]

The photochemistry of the system was studied with model compounds **4c** and **7**. Thus, experiments on an analytical scale (0.76 mmol L^{-1} in methanol, mercury high-pressure lamp, monochromator, 350 nm) indicate (see the isosbestic points in Figure 1) that **4c** is cleanly converted into the methoxy

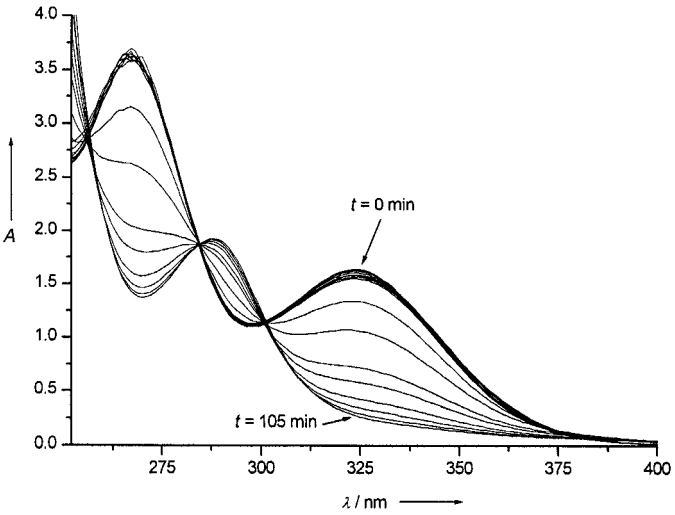

Figure 1. UV/Vis spectroscopic control of the conversion of **4c** into to **13**.

derivative **13** (Scheme 2). On a preparative scale, irradiation of **4c** (0.7 mM in methanol, 10 °C, argon atmosphere, 350 nm, Rayonet reactor) furnished the methoxy compound **13** in 70% yield (according to the ^{19}F NMR spectrum of the reaction mixture). After chromatographic purification, **13** was fully characterized by NMR spectroscopy and mass spectrometry.

The aromatic photosubstitution by which the *m*-nitroalkoxy derivatives are converted into the corresponding *m*-nitrophenols offers the very promising opportunity to assist mass spectrometric structural elucidation by simply executing the photosubstitution in a mixture of $H_2{}^{16}O$ and $H_2{}^{18}O$. We performed the cleavage reaction of **13** in 0.01 mol L^{-1} NaOH in a 4:1 mixture of $H_2{}^{16}O$ and $H_2{}^{18}O$. As Figure 2 shows the 4:1 ratio of $H_2{}^{16}O$ and $H_2{}^{18}O$ is nicely translated into a 4:1 ratio of the intensities of the molecular ions of the substitution products **14a** and **14b**. Thus, after a photoaffinity labeling experiment, all labeled peptides should be easily recognized by doublets with a mass difference of two in the mass spectra.

We also studied the photodegradation of photolabel **7** on an analytical scale (1.34 mM in methanol) under the conditions described above. The UV spectra are more complicated because of overlapping bands. The difference spectra ($A_{(t)} - A_{(t=0)}$) displayed in Figure 3 have been calculated to separate the absorptions of the reaction site. Figure 3 again nicely shows two isosbestic points indicative of a clean conversion of **7** into **15**.

A second broadly applicable photoaffinity reagent based on a *m*-nitroalkoxy-substituted phenyltrifluoromethyldiazirine (Nakanishi diazirine) was obtained from aldehyde **4b** and amino compound **16** by reductive amination to give secondary

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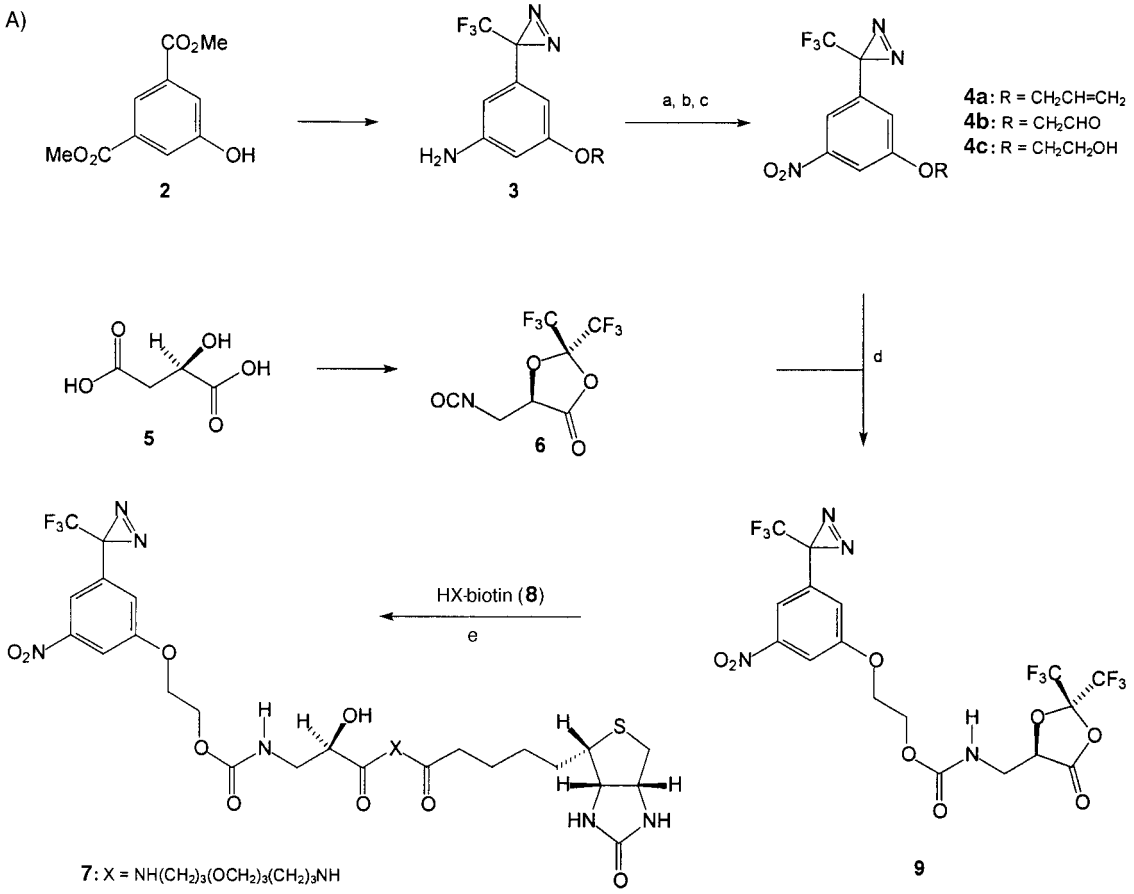

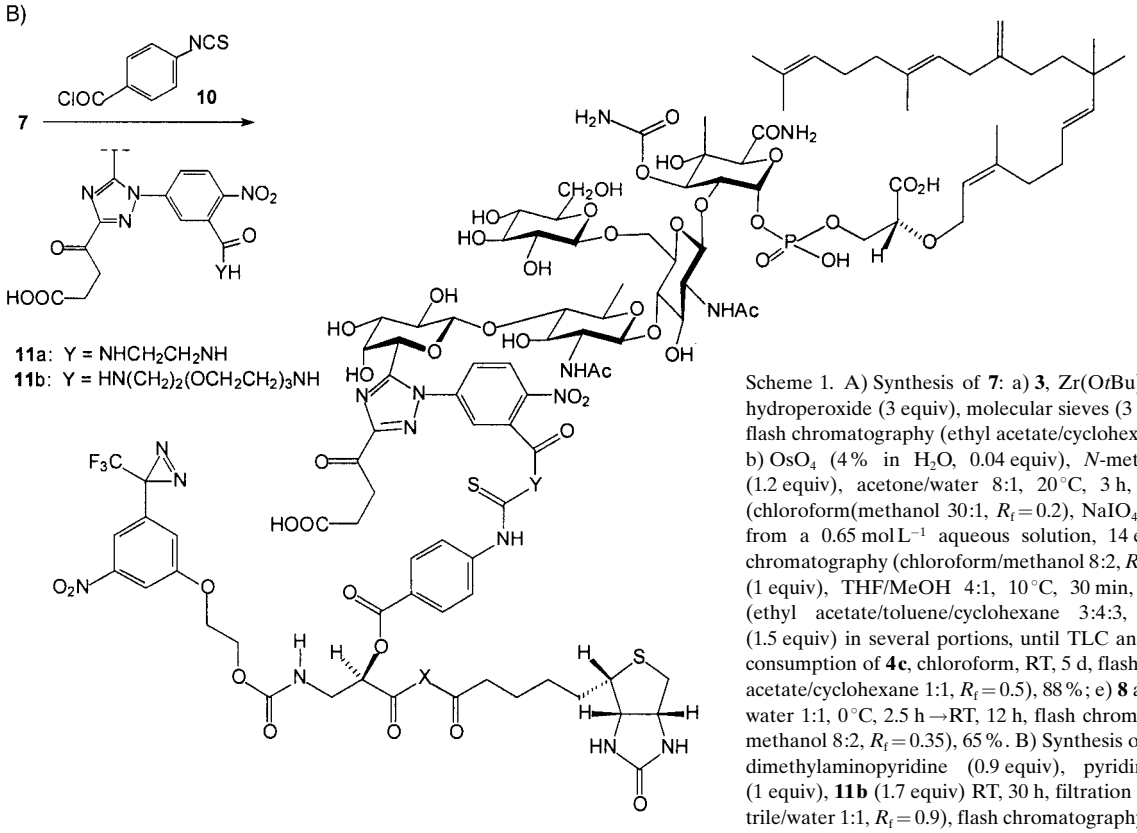

Scheme 1. A) Synthesis of **7**: a) **3**, $Zr(OtBu)_4$ (0.1 equiv), *tert*-butyl hydroperoxide (3 equiv), molecular sieves (3 Å), CH_2Cl_2, 20 °C, 19 h, flash chromatography (ethyl acetate/cyclohexane 2:8, $R_f = 0.7$), 80 %; b) OsO_4 (4 % in H_2O, 0.04 equiv), *N*-methylmorpholine-*N*-oxide (1.2 equiv), acetone/water 8:1, 20 °C, 3 h, flash chromatography (chloroform(methanol 30:1, $R_f = 0.2$), $NaIO_4$ on silica gel (obtained from a 0.65 mol L^{-1} aqueous solution, 14 equiv), RT, 24 h, flash chromatography (chloroform/methanol 8:2, $R_f = 0.8$), 74 %; c) $NaBH_4$ (1 equiv), THF/MeOH 4:1, 10 °C, 30 min, flash chromatography (ethyl acetate/toluene/cyclohexane 3:4:3, $R_f = 0.4$), 84 %; d) **6** (1.5 equiv) in several portions, until TLC analysis showed complete consumption of **4c**, chloroform, RT, 5 d, flash chromatography (ethyl acetate/cyclohexane 1:1, $R_f = 0.5$), 88 %; e) **8** and **9** (1.5 equiv), DME/water 1:1, 0 °C, 2.5 h → RT, 12 h, flash chromatography (chloroform/methanol 8:2, $R_f = 0.35$), 65 %. B) Synthesis of **12**: **7** and **10** (1 equiv), dimethylaminopyridine (0.9 equiv), pyridine, 0 °C, then water (1 equiv), **11b** (1.7 equiv) RT, 30 h, filtration through RP18 (acetonitrile/water 1:1, $R_f = 0.9$), flash chromatography (methanol/chloroform 2:8, $R_f = 0.1$, water/1-propanol 3:7, $R_f = 0.7$, RP18 (acetonitrile/water 3:7), 10 %.

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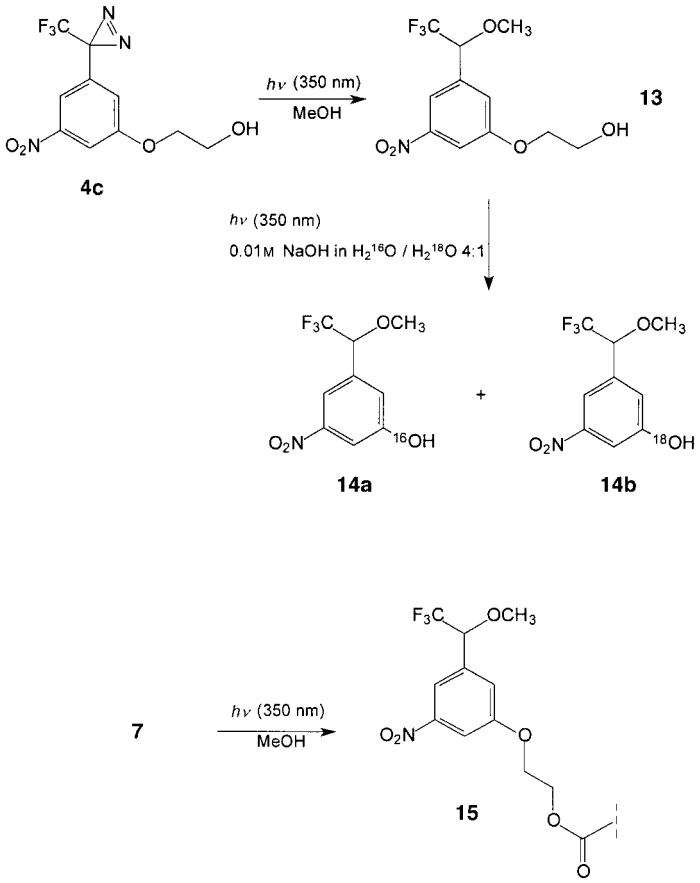

Scheme 2. Photochemical transformations.

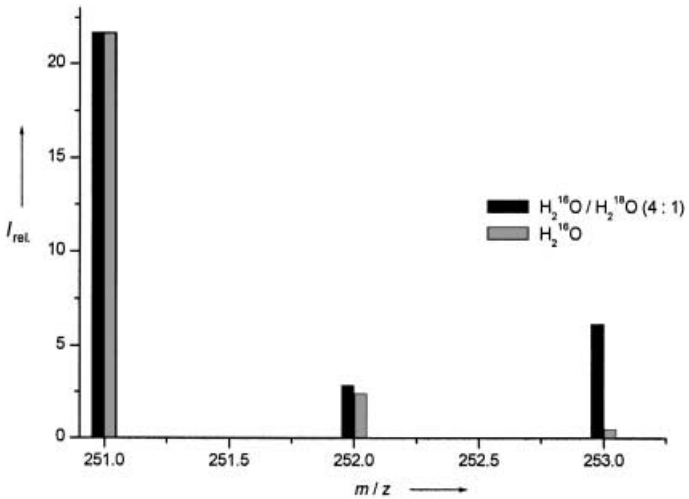

Figure 2. Molecular ions of the photo-substitution product(s) of **13**. Light gray: reaction in $H_2{}^{16}O$, black: reaction in 4:1 $H_2{}^{16}O/H_2{}^{18}O$.

amine **17** in 60% yield (Scheme 3). Reaction of **17** with diethyl squarate[16–18] provided squaric acid ester amide **18**.[19] As usual for squaric acid amides,[16] two ^{13}C NMR signals appeared for many carbon atoms, thus indicating the presence of two conformers. Compound **18** can be attached to any suitable ligand with a primary or secondary amino group. Thus, the reaction of **18** with the moenomycin derivative **11a** in a 1:1 mixture of water and methanol at pH 9 furnished

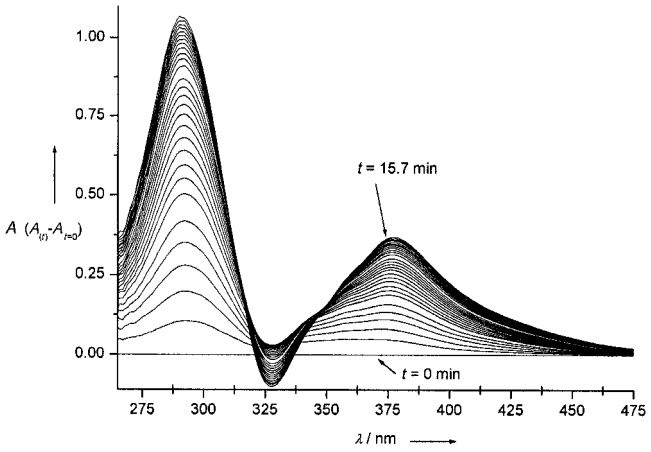

Figure 3. UV/VIS spectroscopic control of the conversion of **7** into **15**, difference spectra $A_{(t)} - A_{(t=0)}$.

compound **19**, which was characterized by NMR spectroscopy and mass spectrometry.[20]

Both **12** and **19** have been found to be antibiotically active against a number of *Staphylococcus aureus* strains (minimum inhibitory concentration (MIC): 4.8×10^{-7} and 3.2×10^{-7} mol L^{-1}, respectively)[21] although to a lower degree than moenomycin A itself.[22]

In conclusion, we have developed two biotinylated photoaffinity labels based on Nakanishi's diazirine that can be attached to any suitable ligand. The photochemical removal of the ligand and biotin from labeled peptides can be used to introduce a $^{16}O/^{18}O$ tag. This should greatly facilitate identification of cross-linked peptides by mass spectrometry. Compounds **12** and **19** are fully equipped for photoaffinity studies. In addition, they have been found to be antibiotically active, and their use in the photoaffinity labeling of their target protein, the transglycosylase domain of penicillin-binding protein 1b,[23] will be reported in due course.

Received: December 7, 2001 [Z18343]

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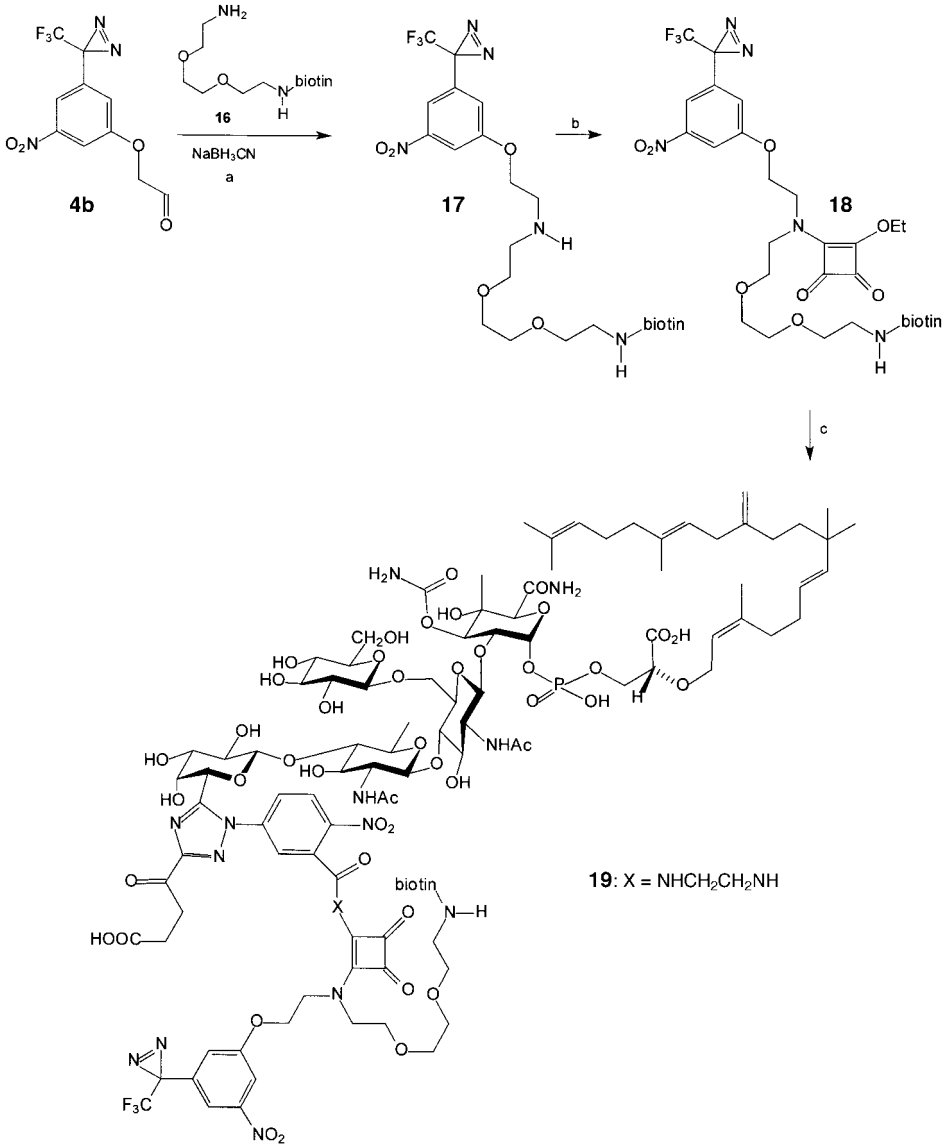

Scheme 3. Synthesis of **19**: a) **4b** and **16** (1.5 equiv), methanol, TFA (0.2 mol L^{-1} in methanol, adjusting the pH to 7.0), $NaCNBH_3$ (1 equiv), RT, 32 h, flash chromatography (methanol/chloroform 1:9, $R_f = 0.1$), 60 %; b) 3,4-diethoxy-3-cyclobutene-1,2-dione (2.7 equiv), ethanol, RT, 19 h, flash chromatography (methanol/chloroform 2:10, $R_f = 0.5$), 91 %; c) **11a**, water/methanol 1:1, Et_3N (adjusting the pH to 9), RT, 5 d, flash chromatography (1-propanol/water 7:2, $R_f = 0.5$), 32 %.

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[12] FT-ICR-MS (Apex II, Bruker Daltonics, water/methanol).

[13] $C_{34}H_{49}F_3N_8O_{12}S$ (850.86, 850.34), ESI MS: $m/z = 889.27644$ ($[M+K]^+$), calcd: 889.27743; 873.30178 ($[M+Na]^+$), calcd: 873.30350.

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[15] $C_{124}H_{177}F_3N_{19}O_{52}PS_2$ (2917.95, 2916.09), ESI MS: $m/z = 971.02420$ ($[M-3H]^{3-}$), calcd: 971.02343.

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[19] $C_{32}H_{40}F_3N_7O_{10}S$ (771.77, 771.25), ESI MS: $m/z = 772.25759$ $[M+H]^+$, calcd: 772.25822; 794.23993 $[M+Na]^+$, calcd: 794.24017.

[20] $C_{108}H_{151}F_3N_{17}O_{46}PS$ (2543.50, 2541.94), ESI MS: $m/z = 1269.96424$ ($[M-2H]^{2-}$), calcd: 1269.96320; 864.30686 ($[M-3H]^{3-}$), calcd: 864.30637.

[21] MIC values were determined by a serial twofold microdilution method (Iso-Sensitest medium, Oxoid). A series of decreasing concentrations of the compound under investigation was prepared in the medium. For inoculations, 1×10^5 cfu mL^{-1} were used. The MIC values were determined after 24 h at 37 °C (absence of visible turbidity).

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