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The Stereoselective Derivatisation of the *Re* or *Si* Faces of the $\Delta^{9,10}$-Double Bond of Soraphen A

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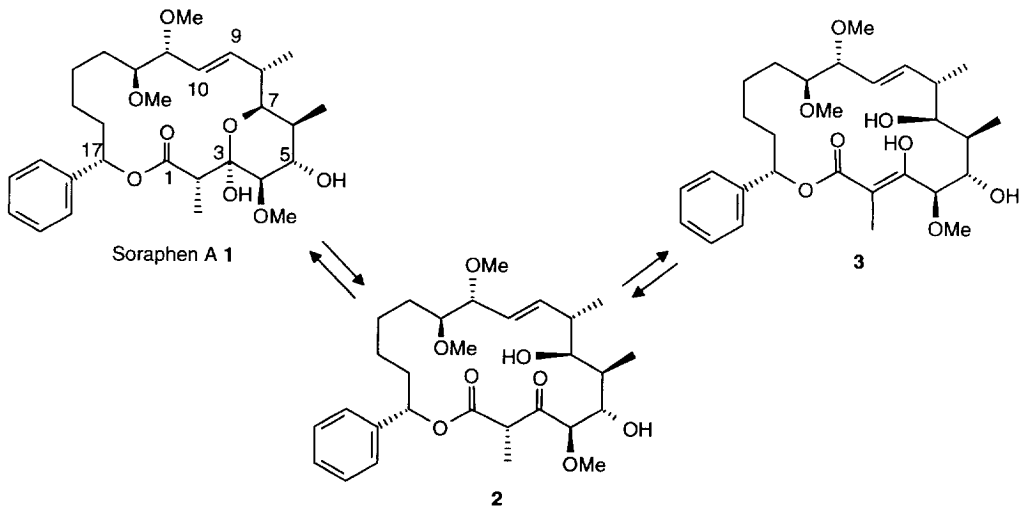
Abstract. The $\Delta^{9,10}$ double bond of soraphen A was found to react selectively on the *Si* face, whereas the same double bond in the hydroxy-ketone tautomer of soraphen A is attacked on the *Re* face. It became possible to prepare products of chosen stereochemistry by stabilising the requisite tautomer by use of the appropriate protecting groups. Attempts at S_N2 displacements on the soraphen molecule failed and electrophilic addition to the $\Delta^{9,10}$ double bond in our experiences never took place in a 1,2 manner. Based on these results and results with other macrolides, it is suggested that S_N1 reactions are more likely to succeed than S_N2 reactions in macrolide derivatisation.

Introduction. Soraphen A **1** was isolated recently from the myxobacterium *Sorangium cellulosum* by Höfle et al.[1] It was tested against a battery of pests in greenhouse trials, and was found to possess excellent activity against fungal pathogens on plants.[2] The fungicidal activity of **1** proved to be so interesting that the producing strain was reexamined and more than 20 congeneric metabolites were isolated, building a family of naturally occurring soraphen derivatives.[3] At the same time a collaborative derivatisation program was initiated starting from the major metabolite soraphen A.

1 belongs to the macrolide family of natural products, which were first isolated because of their antibacterial activity.[4] Later many further macrolides were discovered with other interesting and useful biological activities. In the agrochemical field the most notable compounds in this class are the anthelmintic, insecticidal and acaricidal milbemycins[5] and ivermectins.[6] Many macrolides have been derivatised usually with a view to optimising their biological activity. However, apart from the common macrocyclic lactone ring, the macrolides comprise such a diverse structural class, that results obtained from one macrolide cannot be directly applied to the derivatisation of others. We report here the reactions of electrophilic reagents on the $\Delta^{9,10}$ double bond of two tautomers of **1**, and suggest concepts which are of general relevance to macrolide derivatisation.

1 contains a hemiacetal group, which readily builds an equilibrium with its hydroxy-ketone tautomer **2** on dissolution in water.[7] This compound in turn is a β-keto ester which tautomerises readily to its enol form **3**. Due to the *E/Z* isomerism of the double bond of the enol **3** and epimerisation at C(2) in **1** and **2** a large number of tautomers are possible. We were able to prepare separately three of these tautomers **1**, **2**, and **3**, and to

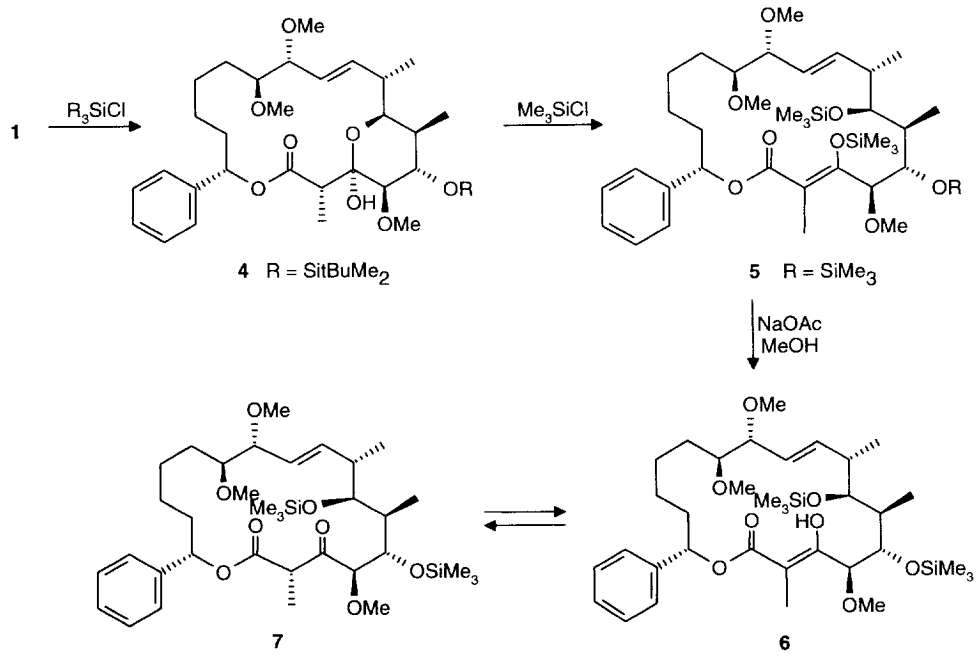
observe them interconvert in aqueous solution to build the same equilibrium mixture.[7] The hemiacetal **1** and hydroxy-ketone **2** tautomers are 16 and 18-membered macrolide rings respectively and may be expected to show different reactivity and stereoselectivity even at functionalities distant from the hemiacetal / hydroxy-ketone moiety. Furthermore the tautomerisation is so facile that it is often mobilised by the reaction conditions used during the derivatisation of **1**. In fact the success of the derivatisation program required an understanding of the reactivity of these tautomers and the stereoselectivity of their reactions. We describe here the reactivity of the $\Delta^{9,10}$ double bond in **1** and **2** towards electrophilic attack, and show that the hemiacetal tautomer **1** reacts *Si*-selectively and the hydroxy-ketone **2** *Re*-selectively.



Scheme 1

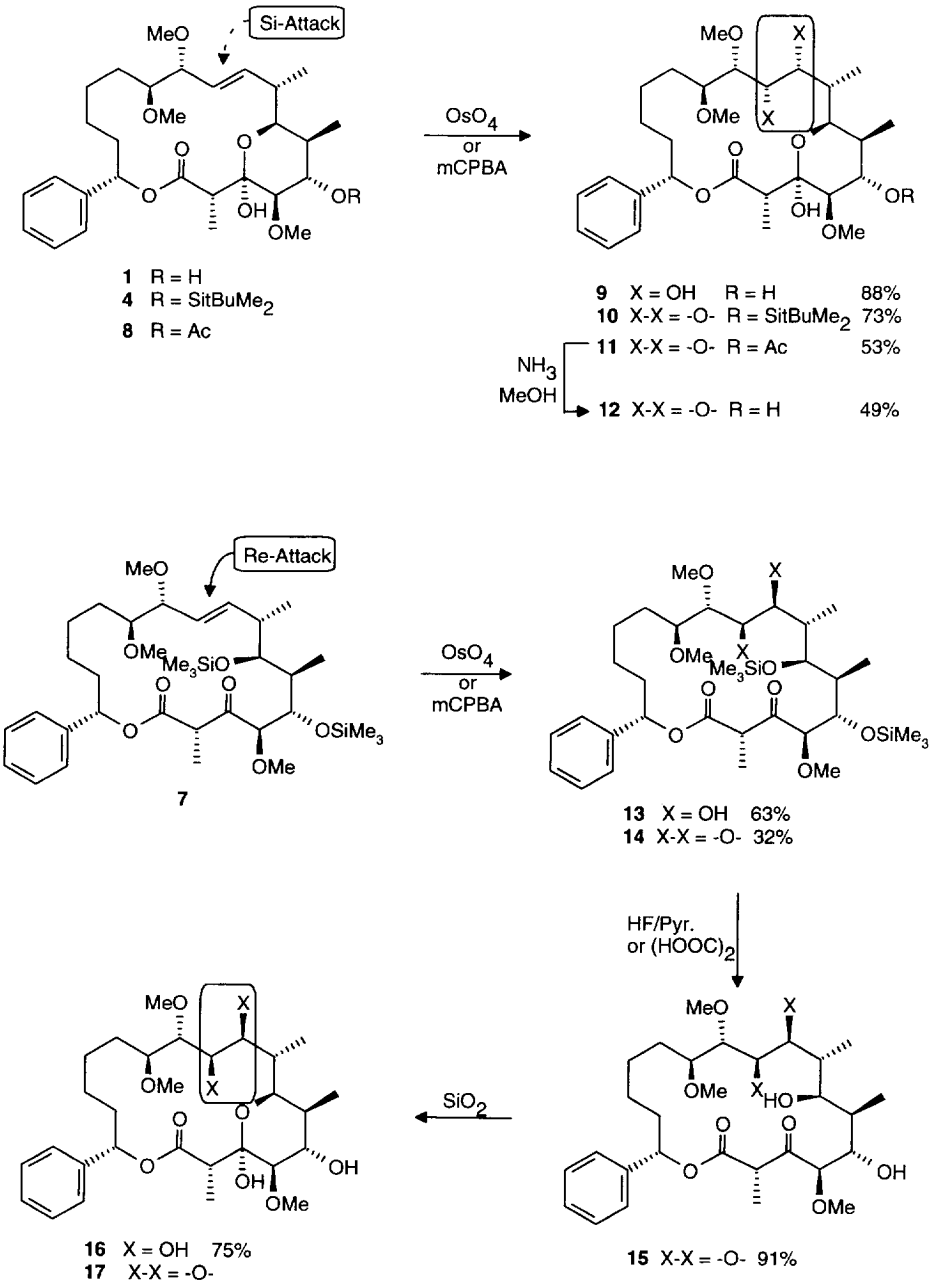
Results and Discussion. In non-polar organic solvents the opening of **1** to its hydroxyketone tautomer **2** was slow enough not to interfere with the attack of reactive electrophiles on the $\Delta^{9,10}$ double bond. However, the hydroxyketone tautomer **2** is less stable, closing to **1** slowly on standing or rapidly with mild acidic or basic catalysis. Therefore it was necessary to stabilise this tautomer by blocking the C(7)-OH group. Monosilylation of soraphen A with $tBuMe_2SiCl$ led to **4**, whereas persilylation with Me_3SiCl led to the trisilyl compound **5**. Selective cleavage of the C(3)-O-silyl group of **5** with mild base, initially produced the enol **6**, which subsequently entered into equilibrium with the ketone **7** under the reaction conditions. These two tautomers were separable by chromatography on silica and were then stable for long periods when stored at 4°C. They are more stable than the corresponding tautomers of open chain aliphatic β-ketoesters,[8] perhaps because of the limited number of conformations of the macrolide ring in which tautomerisation is possible. Other protecting group combinations were examined, but in most cases keto-enol interconvertion was fast, causing the tautomers to be less stable than **7** and **6** or often inseparable on chromatography. The C(5)-O, C(7)-O diacetate[9] of **2** existed solely in the keto form and reacted in a manner similar to **7** described below, but we were unable to remove the acetyl groups without destroying the molecule.[10] From the coupling constants and chemical shifts of the signals in the ^{1}HNMR spectrum of **7** it is apparent that its conformational behaviour is similar to that of **2**, indicating that it is a suitable substitute for **2** for the study of the

stereoselectivity of reactions at its $\Delta^{9,10}$ double bond.



Scheme 2

Treatment of **4** with m-chloroperbenzoic acid led to the 9*R*,10*S* epoxide **10** (73%) resulting from attack on the *Si* face of the double bond as indicated in Scheme 3. Similarly the acetate **8** was converted selectively to the corresponding epoxide **11** (53%). Without the C(5)-OH protecting group the double bond of soraphen A **1** is less reactive. It was recovered unchanged after treatment with MCPBA but reacted with CF_3COOOH, albeit less selectively, leading to a mixture of **12** (44%) and **17** (20%). The $\Delta^{9,10}$ double bond of soraphen A also reacted stereoselectively with OsO_4 on the *Si* face forming the triol **9** (88%). In contrast **7** reacted selectively on the *Re* face of the $\Delta^{9,10}$ double bond when treated with OsO_4 or m-chloroperbenzoic acid leading to **13** (63%) and **14** (32%) respectively. Removal of the silyl protecting groups from these compounds led to **16** (75%) and **15** (91%). **15** closed partially during chromatography to **17**. Although it was clear that **12** and **17** as well as **9** and **16** are diastereomeric pairs, it was not possible to assign the stereochemistry at C(9) and C(10) from the NMR data. Fortunately, crystals of **12** could be grown, which were subjected to X-ray analysis demonstrating the 9*R*,10*S* stereochemistry (Scheme 8, Exp. Part).

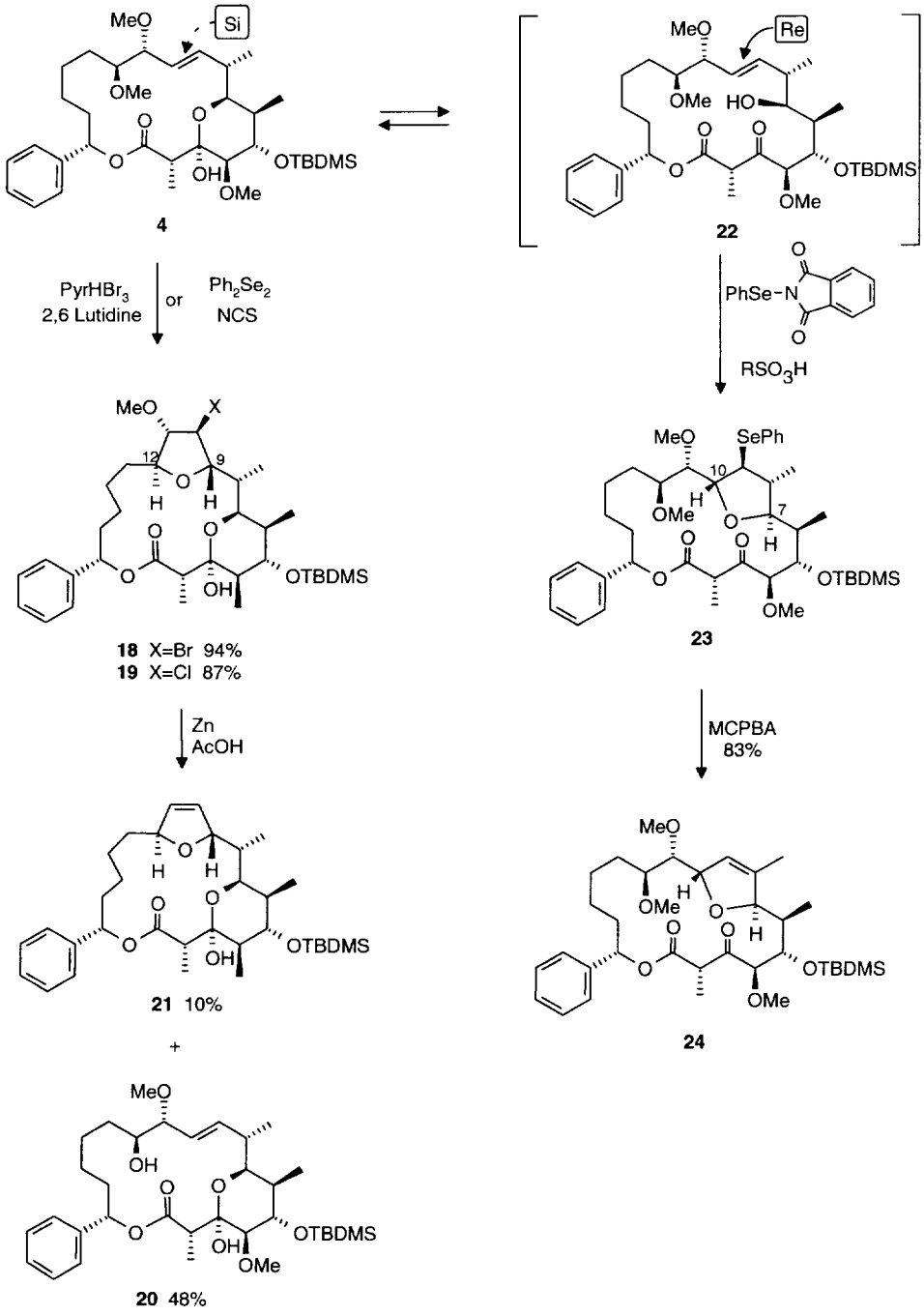

Si-Attack
MeO
OMe
O
O
O
OH
OMe
OR
OsO4
or
mCPBA
X
X
1 R = H
4 R = SitBuMe2
8 R = Ac
9 X = OH R = H 88%
10 X-X = -O- R = SitBuMe2 73%
11 X-X = -O- R = Ac 53%
NH3
MeOH
12 X-X = -O- R = H 49%
Re-Attack
Me3SiO
OSiMe3
7
13 X = OH 63%
14 X-X = -O- 32%
HF/Pyr.
or (HOOC)2
HO
SiO2
16 X = OH 75%
17 X-X = -O-
15 X-X = -O- 91%

Scheme 3

In the crystal structure[1] of **1** the *Re* face of the $\Delta^{9,10}$ double bond is directed inwards towards the rest of the macrolide ring, while the *Si* face is exposed to an incoming reagent in accord with the observed stereoselectivity. However, a systematic conformational search of **1** and its hydroxy-ketone tautomer **2** revealed that there were dozens of conformations of these rather flexible molecules with a ΔH_f less than 5 kcal above that of the lowest energy conformation.[11] These conformations are all kinetically viable and contribute to the reaction to different and unknown extents.[12] Consequently the stereoselectivity of the reactions of such flexible macrocyclic compounds cannot be reliably predicted from the analysis of their conformational populations. However it will be shown that the stereoselectivities determined empirically from the model reactions described above (Scheme 3) are of predictive value for the reactions of the tautomers of soraphen A with other electrophiles. By these means it is possible to produce products of desired stereochemistry through the choice of the appropriate substrate.

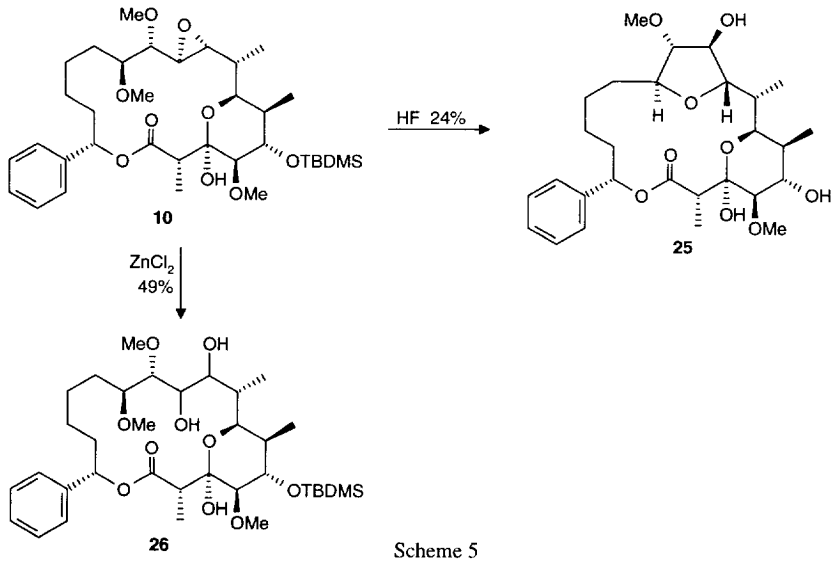
Having established that the two tautomers **1** and **2** react with peracids and OsO_4 on two different faces of their double bonds, their reaction with other electrophiles was examined. The stereochemistry of the products of treatment of **4** with pyridinium perbromide and phenyl selenyl phthalimide[13] is in accord with the stereoselectivities of the model reactions described above. However the products isolated arose not from 1,2 addition to the double bonds but were formed through the intervention of intramolecular oxygen nucleophiles. The bromination took several hours at room temperature to reach completion whereupon **18**, the product of a formal 5-endo-tetragonal[14] ring formation, was isolated. The stereochemistry of **18** at C(9) was determined by reductive elimination of the 11-methoxy group to **21**, which showed a 6.5 Hz coupling constant between H-C(12) and H-C(9) characteristic of a trans configuration.[15] The main product of the reductive elimination **20** is a protected form of the naturally occurring metabolite soraphen V, which was used as key intermediate for the synthesis of a series of fungicidally active derivatives.[16]

Chlorination of **4** with NCS led to **19** in a similar manner, but the selenation took another course. The reaction required longer reaction times at a higher temperature than described for disubstituted alkenes.[13] Again a product of intramolecular oxygen attack **23** rather than of 1,2 addition was isolated. The stereochemistry of **23** was proved through oxidation and selenoxide elimination to **24**. H-C(8) is cis to the selenyl group in **23**, and the 5.6 Hz coupling constant indicates the trans configuration[15] of H-C(7) and H-C(10) in **24**. It is thus evident that **23** results from attack of the selenylating agent on the *Re* face of the double bond of **4**. This result can be explained by assuming that the long reaction time, high temperature and acid catalysis mobilise an equilibrium of **4** with the hydroxy-ketone form **22**, which reacts on the *Re* face analogously to **7**. The C(7)-O in **22** is in the form of a hydroxy group, which can then attack C(10) forming the observed product **23**.

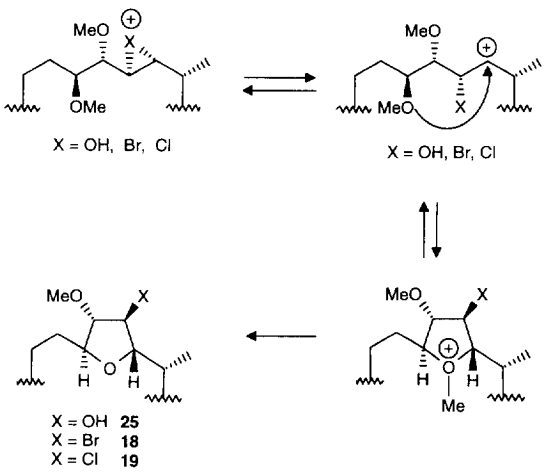

MeO
Si
OMe
OTBDMS
OH
OMe
4
PyrHBr3
2,6 Lutidine
or
Ph2Se2
NCS
MeO
X
OTBDMS
18 X=Br 94%
19 X=Cl 87%
Zn
AcOH
21 10%
+
MeO
OH
OTBDMS
OMe
20 48%
MeO
Re
OMe
HO
OTBDMS
OMe
22
PhSe-N
RSO3H
MeO
SePh
OMe
OTBDMS
OMe
23
MCPBA
83%
MeO
OMe
OTBDMS
OMe
24

Scheme 4

The reactions of the epoxide **10** (Scheme 5) mirrored those of the bromonium ion (Scheme 6). Attempts at opening the epoxide ring in **10** with nucleophiles such as mercaptans to form C(9),C(10) disubstituted compounds were unsuccessful. However treatment with mild protonic acids (HF/pyridine 24%; TsOH 24%) or Lewis acids (9-BBNOTf 30%) led to **25**. Analogously to the bromination, the mechanism involves a sequence of reversible steps culminating in the irreversible dealkylation of the oxonium salt (Scheme 6). It was apparent from their ^{1}HNMR spectra that **25** has the same configuration as **18** and **19**. The 9*S* stereochemistry was proved for **18**, and the 10S configuration of **25** is derived from **10**, the stereochemistry of which is clear from the crystal structure (Scheme 8). The diol **26** was formed when $ZnCl_2$ was used as Lewis acid. Here polyvalent zinc may bind to the C(12)-OMe group as well as to the epoxide oxygen preventing formation of **25** but encouraging the formation of a cation.

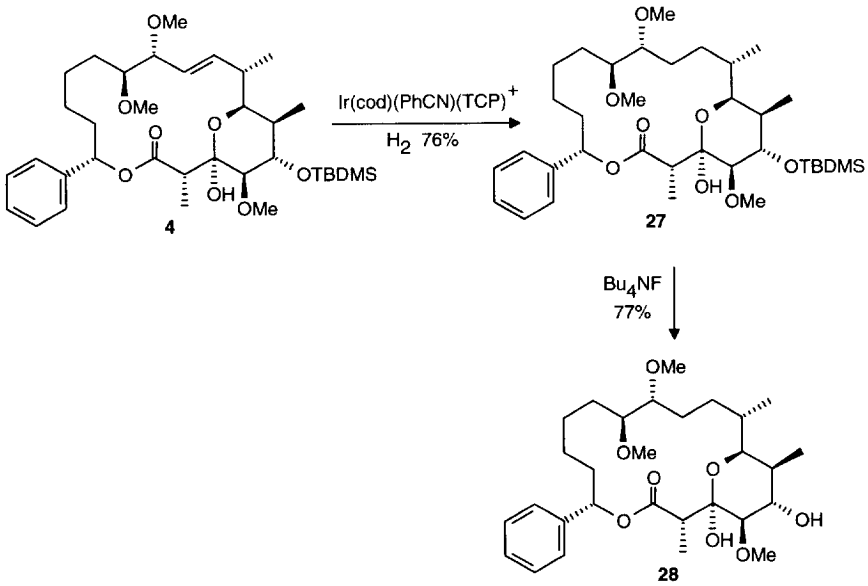


Scheme 5



Scheme 6

Hydrogenation of the double bond of soraphen A **1** required specific conditions. A variety of catalysts both hererogeneous (Pd/C; Pt/C; PtO_2) and homogeneous ($BrRh(PPh_3)_3$; $[Rh(nbd)dppb]BF_4$[17]) were slow and reduction of the double bond was preceded by hydrogenolysis of the benzylic C(17)-O bond. Also diimine caused no reaction. However hydrogenation of the C(5) protected compound **4** using $[Ir(cod)(PhCN)(tcp)]BF_4$[18] as catalyst met with success, and the product **27** was isolated in 76% yield. Deprotection afforded **28,** which was identical to the naturally occurring soraphen F.[3]



Scheme 7

Discussion and Conclusion.

It is clear from this work, that the presence of the macrolide ring has a profound effect on the reactivity of the $\Delta^{9,10}$ double bond of **1**. We suggest now that this effect is in accord with what is known about the reactivity of other macrolides, and also with the reactivity of large ring systems in general.

In the reactions shown in Scheme 4, no 1,2 addition took place. Similarly the epoxide **10** was resistant to nucleophilic attack, although it was opened by Lewis acids. The macrolide ring appears to be hindering an S_N2 attack on the epoxide or onium ions, which would lead to 1,2 addition products. The observation has been made that S_N2 reactions in the milbemycin / avermectin series of macrolides were either slow or more frequently unobserved, despite some effort to optimise the reaction conditions.[19] Furthermore recent reviews on macrolide derivatisation[4] cite only one report[20] of an S_N2 reaction. This effect in its most transparent form was measured in classical studies, where the rate of S_N2 attack on unsubstituted large-ring cycloalkyl halides was found to be lower than that of an open chain analog for every ring size tested.[21] For ring size 12 the rate was more than 100× lower than that of 6-bromo-undecane.[21] The presence of substituents in the rings of the macrolides serve to hinder the S_N2 reaction even further and thus it was suggested that the phenomenon of slow S_N2 reactions is general for macrocyclic compounds, and its avoidance can be recommended as a general rule of thumb for a successful macrolide derivatisation program.[19] In fact we have found both in the

milbemycin[19] series and in the soraphen[22] series that strategies based on S_N1 and radical substitution mechanisms are more successful than S_N2 strategies. It may be assumed that the macrolide ring interferes with the approach of a nucleophile to the reaction centre, whereas a dissociative S_N1[23] or radical[24] reaction suffers form no such handicap.

Not only does the macrolide ring have a dramatic effect on the reactivity of the double bond but also on the stereoselectivity of its reactions. Whereas it is possible to make mechanistic generalisations concerning reactivity as described above, the stereoselectivity is specific for each macrolide and furthermore in the case of **1** for each tautomer of this macrolide. The stereoselectivity of attack on the double bond of **1** and its hydroxy-ketone tautomer **2** arises from the conformational preferences of these macrolides. However, such large flexible structures have so many low energy conformers that a prediction of the stereochemical course of a reaction is unreliable.[12] Substructures containing particular functionalities have a preference for certain tortion angles.[25,26] In large flexible rings such substructures can dominate the conformational populations to the extent that an analysis of the local conformations allows a prediction of the stereoselectivity of the reactions at that part of the macrolide.[26,27] This approach is clearly not valid in the examples described here, as the surroundings of the C(9)-C(10) double bond are the same in both tautomers (**1** and **2**) but the stereoselectivity of the reactions are different. However by considering stereoselectivity as an empirical phenomenon it was possible to determine the facial preference of the double bond in two tautomers (**1** and **2**) of soraphen A. The more stable tautomer **1** reacted on the *Si* face and the hydroxy-ketones **7** and **22** reacted preferentially on the *Re* face. Having once established this pattern it was possible to tailor synthetic plans involving stereoselective reactions on either face of the $\Delta^{9,10}$ double bond of soraphen A.

The compounds described here were tested in greenhouse trials against a battery of plant pathogenic fungi. Where necessary of course the silyl protecting groups were removed. The compounds were all much weaker fungicides than soraphen A, with the exception of soraphen F (**28**) which was moderately less active.

EXPERIMENTAL

5,7-Di-O-trimethylsilyl-$\Delta^{2,3}$-soraphen A (**6**) and 5,7-bis-O-trimethylsilyl-soraphen A (**7**)

Compound **5**[9] (402 mg, 546 µmol) was dissolved in 1% NaOAc / MeOH (5 mL). After 60 min. at room temperature the reaction mixture was shaken between hexane, Et_2O, and water. The organic phase was dried over $MgSO_4$, the solvent evaporated and the residue chromatographed (10% EtOAc / hexane) to yield **6** (192 mg, 53%) and **7** (79 mg, 22%).

6:- ^{1}HNMR (300 MHz, $CDCl_3$): 0.11, 0.13 (2s, 2Me_3Si); 0.85, 1.10 (2d, 3H-C(20), 3H-C(21)); 1.19 - 1.83 (m, H-C(6), 2H-C(13), 2H-C(14), 2H- C(15), H-C(16)); 1.95 (s, 3H-C(18)); 2.06 (dd, J= 15 and 15, H-C(16)); 2.55 (m, H-C(8)); 3.06 (m, H-C(12)); 3.31, 3.32, 3.39 (3s, 3MeO); 3.44 (d, J=11, H-C(11)); 3.61 (dd, J=2 and 7, H-C(7)); 4.07 (d, J=8, H-C(5)); 4.11 (d, J=8, H-C(4)); 5.36 (dd, J=16 and 7, H-C(10)); 5.69 (dd, J=6 and 16, H-C(9)); 6.27 (dd, J=11 and 3, H-C(17)); 7.27 - 7.43 (m, Ph); 12.6 (s, OH). MS: (CI NH_3) +ve: 682$[M+NH_4]^+$ -ve: 664$[M]^{-\cdot}$.

7:- ^{1}HNMR (300 MHz, $CDCl_3$): 0.14 (s, 2Me_3Si); 0.96, 1.12 (2d, J=7, 3H-C(20), 3H-C(21)); 1.19 - 1.96 (m, H-C(6), 2H-C(13), 2H-C(14), 2H-C(15), 2H-C(16)); 1.29 (d, J=7, 3H-C(18)); 2.58 (m, H-C(8)); 3.24 (m, H-C(12)); 3.37, 3.42, 3.58 (3s, 3MeO); 3.56 (dd, J=8 and 2, H-C(11)); 3.83 (d, J=6, H-C(4)); 3.87 (d, J=8, H-

C(7)); 4.04 (q, J=7, H-C(2)); 4.13 (dd, J=6 and 2, H-C(5)); 3.43 (dd, J=15 and 6, H-C(9)); 5.77 (dd, J=10 and 5, H-C(17)); 5.82 (dd, J=15 and 7, H-C(10)); 7.25-7.40 (m, Ph).MS: (CI NH_3) +ve: 682$[M+NH_4]^+$ -ve: 664$[M]^-$.

9*R*,10*S*-Dihydroxy-soraphen A (**9**)

Osmium tetroxide (1.00g) was dissolved in diethyl ether (20 mL). A solution of **1** (500 mg 960 µmol) in pyridine (5 mL) was added and the mixture was let stand at room temperature for 18 days during which time a brownish solid was deposited. The mixture was filtered and washed with diethyl ether. The solid was dissolved in a mixture of 6% $NaHSO_4$ and pyridine (60:40) and stirred at room temperature for 40 min. The mixture was extracted with dichloromethane, dried over sodium sulfate, filtered and concentrated. Chromatography with ethyl acetate: hexane (1:1 → 5:1) gave 470 mg (88%) of **9**.

^{1}HNMR (250 MHz, CD_3COCD_3): 0.98 (d, J=7, 3H-C(21)); 1.06 (d, J=7, 3H-C(20)); 1.15 (d, J=7, 3H-C(18)); 1.22-2.12 (m, 10H, H-C(6), H-C(8), 2H-C(13)), 2H-C(14), 2H-C(15), 2H-C(16)); 3.05 (q, J=7, H-C(12)); 3.18 (dd, J=1 and 3, H-C(4)); 3.39, 3.42 and 3.46 (3s, 3OMe); 3.54-3.70 (m, 3H); 3.74-3.86 (m, 1H); 3.96-4.01 (m, 1H); 4.20-4.30 (m, 2H); 5.06 (t, J=5, 1H-OH); 5.59 (s, 1H-OH); 5.84 (dd, J=7, H-C(17)); 7.24-7.40 (m, 5H-Ph). MS: (CI NH_3) +ve: 572$[M+NH_4]^+$ -ve: 553$[M-H]^+$. FD: 555$[M+H]^+$.

5-t-Butyldimethylsilyl-9*R*,10*S*-epoxy-soraphen A. (**10**)

4 (1.500 g, 2.36 mmol) was dissolved in dichloromethane (20 mL). 3-Chloro-perbenzoic acid (2.50 g) was added and the suspension stirred at room temperature. After 18h the reaction mixture was diluted with ethyl acetate, washed with conc. sodium hydrogencarbonate, dried over sodium sulfate, filtered and concentrated. Chromatography with ethyl acetate: hexane (1:1) as eluant gave 1.114 g (73%) of **10**.

^{1}HNMR (360 MHz, CD_3COCD_3): 0.22 and 0.25 (2s, 2 Si-CH_3), 0.59 (d, J=7, 3H-C(21)); 0.96 (s, 9H, t-Bu); 1.10 (d, J=7, 3H-C(20)); 1.21 (d, J=7, 3H-C(18)); 1.26-2.23 (m, 10H, H-C(16), H-C(8), 2H-C(13), 2H-C(14), 2H-C(15), 2H-C(16)); 2.88 (dd, J=1 and 8, H-C(11)); 2.97 (q. J=7. H-C(2)); 3.08 (dd. J=1 and 8. H-C(10)); 3.17 (dd J=1 and 3, H-C(4)); 3.35-2.50 (m, 2H, H-C(9) and H-C(12)); 3.38, 3.43 and 3.46 (3s, 3 OCH_3); 4.08 (dd, J=3 and 11, H-C(7)); 4.45 (dd, J=3, H-C(5)); 5.55 (d, J=1, OH); 6.02 (dd, J=4 and 12, H-C(17)); 7.23 - 7.40 (m, 5H-Ph). MS (FD): 651$[M+H]^+$.

5-O-Acetyl-9*R*,10*S*-epoxy-soraphen A. (**11**)

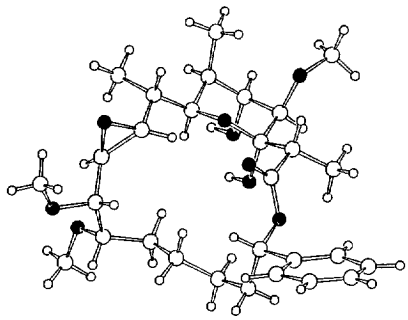
8[9] (100 mg 180 µmol) was dissolved in dichloromethane (2 mL). 3-chloro-perbenzoic acid (160 mg) was added and the suspension stirred for 18 h. at room temperature. The reaction mixture was then diluted with ethyl acetate, washed with sat. sodium bicarbonate solution, dried over sodium sulfate, filtered and concentrated. Chromatography with ethyl acetate: hexane (1:3) as eluent provided 54 mg (53%) of **11**.

^{1}HNMR (300 MHz, CD_3COCD_3): 0.59 (d, J=7, 3H-C(21)); 1.12 (d, J=7, 3H-C(20)); 1.17 (d, J=7, 3H-C(19)); 1.20-2.22 (m, 10H, H-C(6), H-C(8), 2H-C(13)); 2H-C(14), 2H-C(15), 2H-C(16)); 2.03 (s, 3H-OAc); 2.94-3.01 (m, 2H, H-C(11) and H-C(12)); 3.02 (q, J=7, H-C(2)); 3.21 (dd, J=1 and 3, H-C(4)); 3.28 (dd, J=2, H-C(9)); 3.43 (m, H-C(12)); 3.44, 3.45 and 3.47 (3s, 3 OCH_3), 3.95 (s, OH); 4.22 (dd, J=3 and 11, H-C(7)); 5.12 (dd, J=2, H-C(5)), 5.88 (dd, J=2 and 12, H-C(17)); 7.23-7.42 (m, 5H-Ph). MS (FD): 579 $[M+H]^+$.

9*R*,10*S*-Epoxy-soraphen A. (**12**)

11 (25 mg 43 µmol) was dissolved in methanol (1 mL). One drop of ammonia (25% in water) was added, and the solution stirred at room temperature for 4 h. The reaction mixture was taken up in ethyl acetate, washed with brine, dried over sodium sulfate, filtered and concentrated. Chromatography with ethyl acetate: hexane (1:3 → 1:1) as eluant yielded 11.4 mg (49%) of **12**.

^{1}HNMR (250 MHz, CD_3COCD_3): 0.58 (d, J=7, 3H-C(21)); 1.08 (d, J=7, 3H-C(20)); 1.20 (d, J=7, 3H-C(18)); 1.24-2.22 (m, 10H, H-C(6), H-C(8), 2H-C(13), 2H-C(14), 2H-C(15), 2H-C(16)); 2.87 (dd, J=1 and 8, H-C(11)); 2.97 (q, J=7, H-C(2)); 3.08 (dd, J=2 and 8, H-C(10)); 3.20 (dd, J=1 and 3, H-C(4)); 3.32-3.43 (m, 2H, H-C(9) and H-C(12)); 3.40, 3.41 and 3,42 (3s, 3OMe); 4.08 (dd, J=3 and 11, H-C(7)); 4.36 (dd, J=3, H-C(5)); 5.36 and 5.76 (2H, OH); 6.02 (dd, J=3 and 12, H-C(17)); 7.20-7.42 (m, 5H-Ph). MS (FD): 537$[M+H]^+$.



Scheme 8. X-Ray Structure of **12**[28]

5,7-Bis-O-trimethylsilyl-9,10-dihydro-9*S*,10*R*-dihydroxy-soraphen A (**13**)

Osmium tetroxide (333 mg, 1.310 mmol) was added to a solution of **7** (179 mg, 270 µmol) in toluene (2 mL) and pyridine (1 mL). After 5 min. the solution was diluted with MeOH (2 mL) and poured into a solution of $NaHSO_3$ (1.8 g) in water (30 mL) and pyridine (20 mL). After stirring for 30 min. the mixture was shaken between Et_2O and water and the ethereal layer washed with water (2x), HCl (2M, 2x), water again, and $NaHCO_3$ (1M). It was dried over $MgSO_4$ and the solvent evaporated. The crude product (192 mg) was chromatographed on silica with 50% EtOAc / hexane to yield 119 mg (63%) **13**.

^{1}HNMR (250 MHz, $CDCl_3$): 0.14, 0.19 (2s, 2Me-Si); 0.86, 0.93 (2d, J=7, 3H-C(20), 3H-C(21)); 1.47 (d, J=7, 3H-C(18)); 1.26, 1.52, 1.80, 2.22 (4m, H-C(6), H-C(8), 2H-C(13), 2H-C(14), 2H-C(15), 2H-C(16)); 3.22 (m, 1H), 3.50 (d, J=8, 1H), 3.80 (d, J=10, 1H), 3.90 (dd, J=10 and 2, 1H), 4.03 (d, J=8, 1H), 4.17 (m, 1H), 4.34 (m, 2H), 4.42 (m, 1H) (H-C(2), H-C(4), H-C(5), H-C(7), H-C(9), H-C(10), H-C(11), H-C(12), OH); 3.33, 3.56, 3.64 (3s, 3MeO); 5.99 (dd, J=7 and 7, H-C(17)); 7.27 (m, Ph).

5,7-Bis-O-trimethylsilyl-9*S*,10*R*-epoxy-soraphen A (**14**)

A solution of **7** (240 mg, 361 µmol) in CH_2Cl_2 (3 mL) was stirred rapidly with $NaHCO_3$ (1M, 5 mL) and treated with 3-chloroperbenzoic acid (55% pure, 250 mg, 796 µmol). After stirring for 2 h. at room temperature hexane (10 mL) was added and shaken. The hexane phase was separated, dried over $MgSO_4$, the solvent evaporated and the residue chromatographed on silica (16% EtOAc / hexane) to yield 78 mg (32%) **14**.

^{1}HNMR (250 MHz, $CDCl_3$): 0.13, 0.15 (2s, $2Me_3Si$); 0.79 - 2.04 (m, H-C(6), H-C(8), 2H-C(13), 2H-C(14), 2H-C(15), 2H-C(16)); 0.93, 1.21, 1.38 (3d, J=7, 3H-C(18), 3H-C(20), 3H-C(21)); 3.08 (m, H-C(9), H-C(10)); 3.37 - 3.57 (m, H-C(7), H-C(11), H-C(12)); 3.42, 3.47, 3.55 (3s, 3MeO); 3.83 (d, J=7, H-C(4)); 3.95 (d, J=7, H-C(5)); 4.10 (q, J=7, H-C(2)); 5.81 (dd, J=10 and 3, H-C(17)); 7.42 (m, Ph).

9,10-Dihydro-9*S*,10*R*-dihydroxy-soraphen A (**16**)

Compound **13** (44 mg, 63 µmol) was dissolved in HF/pyridine/THF (1 mL) and left at room temperature

for 60 min.. The mixture was shaken between Et_2O and water, and the ethereal layer washed with $NaHCO_3$ (1M). The solvent was evaporated and the crude product chromatographed on silica (80% EtOAc / hexane) to yield **16** (26 mg, 75%).

^{1}HNMR (500 MHz, $CDCl_3$): 0.89, 1.06, 1.11 (3d, J=7, 3H-C(18), 3H-C(20), 3H-C(21)); 0.78 - 2.16 (m, H-C(6), H-C(8), 2H-C(13), 2H-C(14), 2H-C(15), 2H-C(16)); 2.85 (br, OH); 3.18 (d, J=2, H-C(4)); 3.22 (q, J=7, H-C(2)); 3.37, 3.44, 3.50 (3s, 3MeO); 3.42 (m), 3.52 (m), 3.61 (dd, J=7 and 1), 3.68 (d,J=8), 3.92 (m), (H-C(9), H-C(10), H-C(11), H-C(12), OH); 4.00 (ddd, J=10, 2 and 2, H-C(5)); 4.06 (br, OH); 4.33 (dd, J=9 and 1, H-C(7)); 4.64 (s, HO-C(3)); 5.81 (d, J=9 and 6, H-C(17)); 7.26 - 7.37 (m, Ph). MS: (CI NH_3) +ve: 572[M+NH_4]$^+$ 554[M]$^+$ -ve: 634[M+Br]$^-$ 589[M+Cl]$^-$ 554[M]$^{-\cdot}$

9*S*,10*R*-Epoxy-soraphen A (**15**) and (**17**)

A solution of **14** (106 mg, 156 µmol) in 1% oxalic acid in methanol (3 mL) was left at room temperature for 60 min., then shaken between water and Et_2O. The ethereal phase was washed with $NaHCO_3$ (1M), dried over $MgSO_4$ and chromatographed on silica with 70% EtOAc / hexane to yield nearly pure **15** (76 mg, 91%). Chromatography with 10% acetone / CH_2Cl_2 gave a mixture of **17** and **15** (59 mg). Chromatography again with 70% EtOAc / hexane yielded **17** (10 mg, 12%) and **15** (10 mg, 12%). On standing in $CDCl_3$ solution, **15** slowly transformed into **17.**

15:- ^{1}HNMR (500 MHz, $CDCl_3$): 0.80 - 2.07 (m, H-C(6), H-C(8), 2H-C(13), 2H-C(14), 2H-C(15), 2H-C(16)); 1.03, 1.07 (2d, J=7, 3H-C(20), 3H-C(21)); 1.31 (d, J=7, 3H-C(18)); 1.92 (d, J=10, OH); 2.24 (d, J=6, OH); 2.91 (dd, J=8 and 2, H-C(10)); 3.00 (dd, J=5 and 1, H-C(9)); 3.29 (m, H-C(12)); 3.42, 3.46, 3.51 (3s, 3MeO); 3.50 (m, H-C(7)); 3.80 (q, J=7, H-C(2)); 3.86 (dd, J=2 and 2, H-C(11)); 4.08 (ddd, J=10, 9 and 2, H-C(5)); 4.36 (d, J=2, H-C(4)); 5.87 (dd, J=8 and 6, H-C(17)); 7.21 - 7.38 (m, Ph). MS: (CI NH_3) +ve: 554[M+NH_4]$^+$ 537[M+H]$^+$ -ve: 536[M]$^-$ 504[M-MeOH]$^-$.

17:- ^{1}HNMR (500 MHz, D_6-acetone): 0.63 (d, J=7, 3H-C(21)); 1.03, 1.07 (2d, J=7, 3H-C(18), 3H-C(20)); 0.85 - 1.99 (m, 2H-C(13), 2H-C(14), 2H-C(15), 2H-C(16)); 2.25 (m, H-C(8)); 2.32 (m, H-C(6)); 3.07 (q, J=7, H-C(2)); 3.13 (dd, J=7 and 2, H-C(10)); 3.19 (m, H-C(9)); 3.29 (m, H-C(12)); 3.40 (s, 3MeO); 3.42 (m, H-C(11)); 4.05 (m, H-C(5)); 4.11, (m, C(5)-OH); 4.18 (dd, J=7 and 2, H-C(7)); 4.75 (s, C(3)-OH); 5.61 (dd, J=6 and 2, H-C(17)); 7.25 - 7.42 (m, Ph). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.4 C(21); 10.5 C(20); 11.3 C(18); 21.6, 22.8 (C(14), C(15)); 26.6 C(13); 31.6 C(16); 32.0, 35.0 (C(6), C(8)); 45.7 C(2); 53.0 C(10); 57.7, 57.8 (3MeO); 57.8 (C(9); 69.0, 69.2 (C(5), C(7)); 76.1, 76.2 (C(4), C(17)); 81.5, 82.9 (C(11), C(12)); 99.6 C(3); 126.9 (C(2'), C(6')); 128.2 (C(4')); 128.5 (C(3'), C(5')); 139.9 C(1'); 171.2 C(1). MS: (CI NH_3) +ve: 554[M+NH_4]$^+$ 537 [M+H]$^+$ 519 [M-OH]$^+$.

5-O-t-Butyldimethylsilyl-9,10-dihydro-10*S*-bromo-12-desmethoxy-9*S*,12*S*-oxa-soraphen A (**18**)

Pyridinium perbromide (8.06 g, 25.2 mmol) was added with stirring to a solution of **4** (10.65 g, 16.8 mmol) and 2,6-lutidine (4.2 mL, 3.93 g, 33.6 mmol) in CH_2Cl_2 (46 mL). After 3.5 h. the reaction mixture was shaken between Et_2O (300 mL) and water (2 x 50 mL). The ethereal phase was washed with HCl (1M, 2 x 50 mL), water (2 x 50 mL), $Na_2S_2O_3$ (3%, 2 x 75 mL), and $NaCO_3$ (1M, 2 x 50 mL). After drying over $MgSO_4$ and evaporation of the solvent, the mixture was chromatographed on silica (800g) with 20% EtOAc / hexane to yield 11.02 g (94%) **18**.

^{1}HNMR (300 MHz, $CDCl_3$): 0.16 (s, 2Me-Si); 0.78, 1.03, 1.15 (3d, J=7, 3H-C(18), 3H-C(20), 3H-C(21)); 0.96 (s, tBu); 1.23 - 2.19 (H-C(6), H-C(8), 2H-C(13), 2H-C(14), 2H-C(15), 2H-C(16)); 3.02 (d, J=1, H-C(4)); 3.13 (dq, J_d=1, J_q=7, H-C(2)); 3.38, 3.62 (2s, 2MeO); 3.92 (m, H-C(12)); 3.98 (1H, dd, J=10 and 7),

4.05 (1H, m), 4.13 (2H, m), 4.58 (1H, dd, J=10 and 1) (H-C(5), H-C(7), H-C(9), H-C(10), H-C(11)); 4.99 (d, J=1, OH); 6.02 (dd, J=10 and 1, H-C(17)); 7.21 - 7.41 (m, Ph). MS: (CI NH_3) =ve: 716 and 718 $[M+NH_4]^+$ 698 and 700 $[M]^+$ -ve: 733 and 735 $[M+Cl]^-$ 697 and 699 $[M-H]^-$

5-O-t-Butyldimethylsilyl-9,10-dihydro-10*S*-chloro-12-desmethoxy-9*S*,12*S*-oxa-soraphen A (**19**)

A solution of **4** (206 mg, 325 µmol), diphenyl diselenide (15 mg, 48 µmol), and N-chlorosuccinimide (348 mg, 1.62 mmol) in CH_2Cl_2 (2 mL) was stirred for 7 h.. After evaporation of the solvent, the residue was chromatographed on silica (20-50% EtOAc / hexane) to yield 180 mg (87%) **19**.

^{1}HNMR (300 MHz, $CDCl_3$): 0.17 (s, 2Me-Si); 0.79, 1.02, 1,15 (3d, J=7, 3H-C(18), 3H-C(20), 3H-C(21)); 0.97 (s, tBu); 1.22 - 2.20 (m, H-C(6), H-C(8), 2H-C(13), 2H-C(14), 2H-C(15), 2H-C(16)); 2.98 (d, J=5 and 1, H-C(4)); 3.11 (dq, J_d=1, J_q=7, H-C(2)); 3.34, 3.58 (2s, 3H-C(19), 3H-C(22)); 3.97 (3H, m), 4.12 (2H, m), 4.47 (1H, m) (H-C(5), H-C(7), H-C(9), H-C(10), H-C(11), H-C(12)); 4.98 (d, J=1, OH); 6.02 (dd, J=10 and 1, H-C(17)); 7.21 - .40 (m, Ph). ^{13}C-NMR (75 MHz, $CDCl_3$): -4.7 (2Me-Si); 7.7 C(21); 10.6 C(20); 11.7 C(18); 18.4 ($Me_3\underline{C}$); 26.6 C(15); 31.3 C(13); 33.8 C(8); 35.4 C(6); 38.4 C(16); 46.0 C(2); 57.6, 58.9, 60.6 (C(10), 2MeO); 65.9, 71.0, 77.4, 80.5, 81.7 (C(4), C(5), C(7), C(9), C(12)); 73.6 C(17); 88.6 C(11); 99.1 C(3); 126.0 (C(2'), C(6')); 127.2 C(4'); 128.2 (C(3'), C(5')); 142.6 C(1'); 171.5 C(1). MS: (CI NH_3) +ve: 672$[M+NH_4]^+$ 654$[M]^+$ -ve: 689$[M+Cl]^-$ 653$[M-H]^+$

5-O-t-.Butyldimethylsilyl-soraphen V (**20**) and 5-O-t-butyldimethylsilyl-9,10-dihydro-10,11 dehydro-12-desmethoxy-9*S*,12*S*-oxa-soraphen A (**21**)

Zinc dust (104 g, 1.58 mol) was added with stirring and ice cooling to a solution of **18** (10.39g, 14.9 mmol) in acetic acid (200 mL). The mixture was stirred further at room temperature. When the mixture became thicker and difficult to stir more acetic acid (200 ml) was added. After 5 h. stirring Et_2O (200 mL) was added with stirring and the mixture filtered through Celite, washing with further Et_2O. The solvent was evaporated and the product redissolved in toluene and reevaporated to remove traces of acetic acid. The crude product was chromatographed on silica (800 g) with 20% - 50% EtOAc / hexane. **21** (886 mg, 10%) and **20** (4.43 g, 48%) were isolated.

20:- ^{1}HNMR (250 MHz, $CDCl_3$): 0.15, 0.16 (2s, 2Me-Si); 0.95 (s, tBu); 0.99, 1.09, 1.15 (3d, J=7, 3H-C(18), 3H-C(20), 3H-C(21)); 1.22 - 1.93 (m, H-C(6), 2H-C(13), 2H-C(14), 2H-C(15), H-C(16)); 2.07 (m, H-C(16)); 2.38 (d, J=1, HO-C(12)); 2.54 (m, H-C(8)); 3.01 (d, J=1.5, H-C(4)); 3.05 (dq, J_d=1, J_q=7, H-C(2)); 3.32, 3.38 (2s, 2MeO); 3.70 (dd, J=10 and 2, H-C(7)); 3.81 (dd, J=10 and 2, H-C(11)); 3.90 (d, J=10, H-C(12)); 4.17 (dd, J=2 and 2, H-C(5)); 5.23 (d, J=1, HO-C(3)); 5.39 (ddd, J=16, 8, and 1, H-C(10)); 6.10 (dd, J=11 and 1, H-C(17)); 6.42 (dd, J=16 and 5, H-C(9)); 7.22 - 7.39 (m, Ph). MS: (CI acetone) +ve: 621$[M+H]^+$ 603$[M+H-H_2O]^+$ -ve: 655$[M+Cl]^-$ 619$[M-H]^-$

21:- ^{1}HNMR (300 MHz, $CDCl_3$): 0.17 (s, 2Me-Si); 0.96 (s, tBu); 0.66, 0.99, 1.16 (3d, J=7, 3H-C(18), 3H-C(20), 3H-C(21)); 1.16 - 2.18 (m, H-C(6), H-C(8), 2H-C(13), 2H-C(14), 2H-C(15), 2H-C(16)); 2.98 (dd, J=2.5 and 1, H-C(4)); 3.17 (dq, J_d=1, J_q=7, H-C(2)); 3.37 (s, MeO); 4.08 (dd, J=2.5 and 2.5, H-C(5)); 4.25 (dd, J=11 and 3.5, H-C(7)); 4.73 (d, J=1, OH); 5.04 (m, H-C(12)); 5.27 (m, H-C(9)); 5.62 (ddd, J=6.2, 2.5, and 1.5, H-C(11)); 5.71 (m, H-C(10), H-C(17)); 7.18 - 7.38 (m, Ph). The H-C(9) - H-C(12) coupling constant of 6.5 Hz[15] was determined by double irradiation of the signals at 5.04, 5.27, and 5.62 ppm. MS: (CI NH_3) +ve: 588 $[M]^+$ 606 $[M+NH_4]^+$ -ve: 587 M^- 623 $[M+Cl]^+$.

5-O-t-Butyldimethylsilyl-9,10-dihydro-9*S*-phenylselenyl-7-desoxy-7*R*,10*R*-oxa-soraphen A. (**23**)

A solution of **4**[9] (124 mg, 195 µmol), phenylselenyl phthalimide (142mg, 468 µmol), and

camphersulfonic acid (28 mg, 120 µmol) in 1,2-dichloroethane (1 mL) was stirred at 60°C for 3 h.. The mixture was then shaken between Et_2O and $NaHCO_3$ (1M), and the ethereal phase dried over $MgSO_4$, and chromatographed on silica with 0-50% Et_2O/hexane to yield 83 mg (53%) **23**.

^{1}HNMR (300MHz, $CDCl_3$): 0.02, 0.04 (2s, 2Me-*Si*); 0.79 (s, tBu); 0.92 (d, J=7, 3H-C(20)); 1.10 (d, J=7, 3H-C(21)); 1.31 (d, J=7, 3H-C(18)); 1.25 - 1.82 (m, 2H-C(13), 2H-C(14), 2H-C(15), H-C(16)); 1,96 (m, H-C(6), H-C(8), H-C(16)); 2.93 (d, J=10, H-C(11)); 3.15 (dd, J=9 and 7, H-C(9)); 3.24, 3.37, 3.38 (3s, 3MeO); 3.33 (m, H-C(12)); 3.65 (dd, J=9 and 2, H-C(7)); 3.72 (q, J=7, H-C(2)); 4.15 (d, J=9, H-C(10)); 4.19 (dd, J=8 and 1, H-C(5)); 4.37 (d, J=1, H-C(4)); 5.78 (d, J=11, H-C(17)); 7.17 - 7.68 (m, 2Ph). A COSY spectrum was also performed. ^{13}C-NMR (75MHz, $CDCl_3$): -2.7, -2.4 (2Me-Si); 10.9 C(20); 13.0 C(18); 13.6 C(21); 18.8 $Me_3\underline{C}$; 29.4 C(13); 34.2 C(16); 37.2 C(6); 42.7 C(8); 47.2 C(2); 49.5 C(9); 58.1, 58.8, 61.5 (3MeO); 76.8 C(17); 77.4 C(5); 78.4 C(12); 83.5 C(10); 83.7 (C(7), C(11)); 88.0 C(4); 125.6 (C(2'), C(6')); 127.5 C(1''); 127.7 C(4'); 128.4 (C(3'), C(5'), C(4'')); 129.0 (C(3''), C(5'')); 136.3 (C(2''), C(6'')); 140.6 C(1'); 169.3 C(1); 203.6 C(3). MS (FD): 788 and 791 $[M]^+$.

5-O-t-Butyldimethylsilyl-8,9-dehydro-9,10-dihydro-7-desoxy-7*R*,10*R*-oxa-seco-soraphen A (**24**)

3-Chloroperbenzoic acid (210 mg, 1.22 mmol) was added to a solution of **23** (481 mg, 610 µmol) and pyridine (300 µL, 289 mg, 3.66 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was left overnight at room temperature, and then shaken between HCl (1M) and Et_2O. The ethereal phase was washed with water and $NaHCO_3$ (1M), dried over $MgSO_4$, and after evaporation of the solvent the product mixture was chromatographed on silica (30 g) with 20% EtOAc / hexane to yield 319 mg (83%) **24**.

^{1}HNMR (250 MHz, $CDCl_3$): -0.02, 0.07 (2s, 2Me-Si); 0.82 (s, tBu); 0.93 (d, J=7, 3H-C(20)); 1.16 - 2.03 (m, H-C(8), 2H-C(13), 2H-C(14), 2H-C(15), 2H-C(16)); 1.31 (d, J=7, 3H-C(18)); 1.70 (s, 3H-C(21)); 2.11 (m, H-C(6)); 2.98 (dd, J=7 and 2, H-C(11)); 3.35, 3.37, 3.44 (3s, 3MeO); 3.50 (m, H-C(12)); 3.87 (q, J=7, H-C(2)); 4.28 (dd, J=9 and 2, H-C(5)); 4.43 (d, J=2, H-C(4)); 4.76 (m, H-C(7)); 4.93 (m, H-C(10)); 5.52 (m, H-C(9)); 5.83 (dd, J=10 and 2, H-C(17)); 7.26 (m, Ph). Double irradiation of the signals at 2.11, 2.98, 3.50, and 5.52 ppm allowed the assignment of $J_{7,10}$ = 5.6 Hz.[15] MS (CI NH_3) +ve 650$[M+NH_4]^+$ -ve 632$[M]^-$ 600[M-MeOH]$^-$

9,10-Dihydro-10*S*-hydroxy-12-desmethoxy-9*S*,12*S*-oxa-soraphen A. (**25**)

HF (1.5 ml, 40% in water) was dissolved in acetonitrile (30 mL) and **10** (50 mg 77 µmol) was added. After stirring for 3 h. at room temperature, the reaction mixture was dissolved in ethyl acetate, washed with satd. sodium hydrogencarbonate solution, dried over sodium sulfate, filtered and concentrated. Chromatography with ethyl acetate: hexane (1:1) gave 9.7 mg (24%) of **25**.

^{1}HNMR (300 MHz, CD_3COCD_3): 0.80 (d, J=7, 3H-C(21)); 1.00 (d, J=7, 3H, C(20)); 1.15 (d, J=7, H-C(19)); 1,22-2.20 (m, 10H, H-C(6), H-C(8), 2H-C(13), 2H-C(14), 2H-C(15), 2H-C(16)); 3.03 (q, J=7, H-C(2)); 3.16 (dd, J=1 and 3), H-C(4)); 3,41 and 3.47 (2s, 2OMe), 3.77 (m, H-C(11)); 3.88 (m, H-C(12)); 4.04-4.13 (m, 2H, H-C(5) and H-C(10)); 4.18 (dd, J=2 and 8, H-C(9)); 4.23 (m, H-C(7)); 4.39 (d, J=5, OH); 5.85 (dd, J=2 and 10, H-C(17)); 7.23-7.44 (m, 5H-Ph). MS (FD) 504 $[M-H_2O]^+$.

5-t-Butyldimethylsilyl-9,10-dihydroxy-soraphen A. (**26**)

Compound **10** (52 mg 80 µmol) was dissolved in benzene (1 ml) and zinc bromide (560 mg, 2.5 mmol) was added. The suspension was stirred for 18 h. at room temperature, filtered, washed with ethyl acetate and concentrated. Chromatography with ethyl acetate: hexane (1:1) gave 28.3 mg (53%) of **26**.

^{1}HNMR (300 MHz; $CDCl_3$): 0.17 (s, 2$SiCH_3$), 0.78 (s, 9H, t-Bu), 1.05 (d, J=7, 3H-C(21)); 1.10 (d, J=7,

3H-C(20)); 1.17 (d, J=7, 3H-C(18)); 1.25-2.30 (m, 10H, H-C(6), H-C(8), 2H-C(13), 2H-C(14), 2H-C(15), 2H-C(16)); 3.01 (m, 2H, H-C(2) and H-C(4)); 3.38, 3.48 and 3.55 (3s, 3 OMe); 3.71 (s, OH); 3.73, 3.78 and 3.87 (3m, H-C(10), H-C(11) and H-C(12)); 4.13 (d, J=10, H-C(9)); 4.18 (s, OH); 4.22 (d, J=9, H-C(5)); 4.67 (dd, J=2 and 10, H-C(7)); 5.40 (d, J=1 OH-C(-3)); 6.18 (dd, J=2 and 12, H-C(17)); 7.22-7.40 (m, 5H-Ph).MS: (CI NH_3) +ve: 686$[M+NH_4]^+$ 668$[M-H_2O+NH_4]^+$ -ve: 703$[M+Cl]^-$ 668$[M]^-$.

5-O-t-Butyldimethylsilyl-soraphen F. (**27**)

Compound **4** (100 mg 16 µmol) and [Ir(1,5-cyclooctadiene)(C_6H_5CN)($P(C_6H_{11})_3$)] BF_4 (19.7 mg) was dissolved in dichloromethane (20 mL) and stirred for 80 min. at room temperature under an H_2 atmosphere. The reaction mixture was concentrated and chromatographed with ethyl acetate: hexane (1:5 → 1:2) yielding 76.3 mg (76%) of **27**.

^{1}HNMR (250 MHz, CD_3COCD_3): 0.20 and 0.23 (2s, 2 Si-CH_3); 0.82 (d, J=7, 3H-C(21)); 0.95 (s, 9H, t-Bu); 1.04 (d, J=7, 3H-C(20)); 1.14 (d, J=7,3H-C(18)); 1.18-2.09 (m, 14H, H-C(6), H-C(8), 2H-C(9), 2H-C(10), 2H-C(13), 2H-C(14), 2H-C(15), 2H-C(16)); 2.92 (q, J=8, H-C(2)); 3.08 (dd, J=1 and 3, H-C(4)): 3.29 (m, H-C(12)); 3.34, 3.36, 3.42 (3s, 3 OMe); 3.50 (m, H-C(11)); 3.98 (dd, J=2 and 11, H-C(7)); 4.36 (dd, J=2, H-C(5)); 5.22 (s, OH-C(3)); 5.86 (dd, J=4 and 10, H-C(17)); 7.21-7.43 (m, 5H-Ph). MS: (CI NH_3) +ve: 654 $[M+NH_4]^+$ -ve: 671$[M+Cl]^-$ 635$[M-H]^-$.

Soraphen F. (**28**)

27 (35 mg, 55 µmol) was dissolved in a solution of tetrabutylammonium fluoride in tetrahydrofuran (1.1 M, 2 mL) and stirred for 10 min. at room temperature. The reaction mixture was diluted with ethyl acetate, washed with brine, dried over sodium sulfate, filtered and concentrated. Chromatography with ethyl acetate: hexane (1:3 → 1:1) as eluant gave 22.1 mg (77%) soraphen F (**28**).

^{1}HNMR (250 MHz; CD_3COCD_3); 0.82 (d, J=7, 3H-C(21)); 1.02 (d, J=7, 3H-C(20)); 1.14 (d, J=7, 3H-C(18)); 1.16-2.09 (m, 14H, H-C(6), H-C(8). 2H-C(9), 2H-C(10), 2H-C(13), 2H-C(14), 2H-C(15), 2H-C(16)); 2.84 (q, J=8, H-C(2)); 3.12 (d, J=3, H-C(4)); 3.28 (m, H-C(12)); 3.33, 3.35, 3.38 (3s, 3 OMe); 3.48 (m, H-C(11)); 3.98 (dxd, J=2 and 11, H-C(7)), 4.24 (m, H-C(5)); 4.96 and 5.36 (2s, 2 OH); 4.84 (dd, J=5 and 9, H-C(17)); 7.20 - 7.42 (m, 5H-Ph). MS: (CI NH_3) +ve: 540$[M+NH_4]^+$ -ve: 557$[M+Cl]^-$ 521$[M-H]^-$.

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REFERENCES

1. Bedorf, N.; Schomberg, D.; Gerth, H.; Reichenbach, H.; Höfle, G. *Liebigs Ann. Chem.* **1993**, 1017. Gerth, K.; Bedorf, N.; Irschik, H.; Höfle, G.; Reichenbach, H. *J. Antibiotics* **1994**, *47*, 23-31.
2. Gesellschaft für Biotechnologische Forschung and Ciba-Geigy AG EP 2 824 55 A2.
3. Bedorf, N.; Böhlendorf, B.; Forche, E.; Gerth, K.; Höfle, G.; Irschik, H.; Jansen, R.; Kunze, B.; Reichenbach, H.; Sasse, F.; Steinmetz, H.; Trowitzch-Kienast, W.; Pachlatko, P. GBF and Ciba-Geigy EP 358606 (9 Sept. 1988) (Chem. Abs. 1990, 113, 41213s) and ref. 9.
4. Kirst, H. A. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G.; Ohno, M. Eds.;

Springer Verlag: Berlin, 1990, pp 39-63. Omura, S. *Macrolide Antibiotics: Chemistry, Biology and Practice*; Academic Press: Orlando, Florida, 1984.

5. Mishima. H.; Ide, J.; Muramatsu, S.; Ono, M. *J. Antibiot.* **1983**, *36*, 980-990.
6. Chabala, J. C.; Mrozik, H.; Tolman, R. L.; Eskola, P.; Lusi, A.; Peterson, L. H.; Woods, M. F.; Fischer, M. H. *J. Med. Chem.* **1980**, *23*, 1134-1136.
7. Höfle, G.; O'Sullivan, A. C.; Widmer, H-J. et al. unpublished results.
8. Rappoport, Z.; *The Chemistry of Enols*; Wiley: Chichester, 1990.
9. Böhlendorf, B. Ph. D. Thesis, Technische Universität Braunschweig, 1991.
10. Subsequently it was found that treatment with MeMgBr selectively removed the acetyl groups from this compound.
11. Heinrich Karfunkel and John Pearson (Ciba). Unpublished communication.
12. Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83-134.
13. Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A. *Tetrahedron*, **1985**, *41*, 4835-4842.
14. Kocovsky, P.; Pour, M. *J. Org. Chem.* **1990**, *55*, 5580-5588.
15. M. Barfield, M.; Spear, R. J.; Sternhell. S.; *J. Am. Chem. Soc.* **1975**, *97*, 5160-5167.
16. Höfle, G.; O'Sullivan, A. C.; Sutter. M. *Pest. Sci.* Submitted for publication.
17. Schrock, R. R.; Osborn, S. A. *J. Am. Chem. Soc.* **1971**, *93*, 3089-3091.
18. Cabeza, J. A.; Cativiela, C.; Diaz de Villegas, M. D.; Oro, L. A. *J. Chem. Soc. Perkin I*, **1988**, 1881-1884.
19. O'Sullivan, A. C.; Frei, B. In *Synthesis and Chemistry of Agrochemicals III, ACS Symposium Series 504*, Baker, D. R.; Fenyes, J. G.; Steffans, J. J. Eds; ACS: Washington DC, 1992, pp 239-257.
20. Hauske, J. R.; Guadliana, M.; Kostek, G. *J. Org. Chem.* **1983**, *48*, 5138-5140.
21. Van Straten, S. F.; Nicholls, R. V. V.; Winkler, C. A. *Can. J. Chem.* **1951**, *29*, 372-376. Schotsmans, L.; Fierens, P. J. C.; Verlie, T. *Bull. Soc. Chim. Belg.* **1959**, *68*, 580-598.
22. Unpublished results from these laboratories.
23. Brown, H. C.; Borkowsky, M. *J. Am. Chem. Soc.* **1952**, *74*, 1894-1902. Prelog. V.; Heck. R. *Helv. Chim. Acta.* **1955**, *38*, 1541-1545.
24. Overberger, C. G.; Biltech, H.; Finestone, A. B.; Lilker, J.; Herbert. J *J. Am. Chem. Soc.* **1953**, *73*, 2078-2082.
25. Frei, B.; Huxley, P.; Maienfisch, P.; Mereyala, H. B.; Rist, G.; O'Sullivan, A. C. *Helv. Chim. Acta.* **1990**, *73*, 1905-1917.
26. Lipkovitz, K. B.; Peterson, M. A. *Chem. Rev.* **1993**, *93*, 2463-2486.
27. Vedejs, E.; Gapinski. D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5058-5061.
28. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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