# Total Synthesis of Soraphen $A_{1\alpha}$

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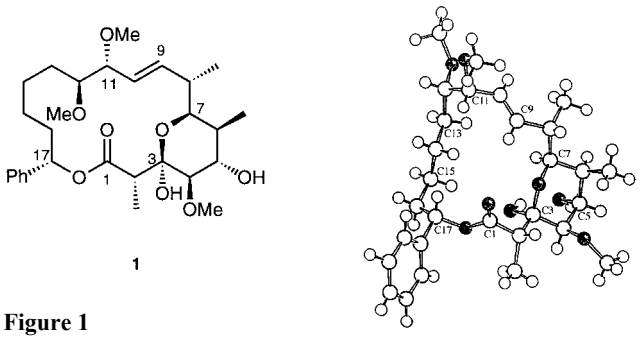
**Abstract:** The convergent synthesis of macrolide soraphen $A_{1\alpha}$ is described starting from glucose (western part) and mannose (eastern part). Mannose was converted into a 2-deoxyribohexopyranoside that could be methylated and reduced stereoselectively. Chain elongation at C–6 was carried out by stereoselective addition of a magnesium acetylide. The two fragments (western and eastern) were assembled by a Julia olefination followed by macrolactonization. The introduction of the methyl group at C–2 of norsoraphen occurred stereoselectively for thermodynamic reasons.

**Key words:** Soraphen $A_{1\alpha}$, macrolide, Julia olefination, chiral pool

Soraphen $A_{1\alpha}$ (**1**) is the parent compound of a family of macrolides which were isolated from *sorangum cellulosum* myxobacteria.[1] It is a highly potent fungicide which acts as a specific inhibitor of acetyl CoA carboxylase and thus disturbs the lipid synthesis in fungi.

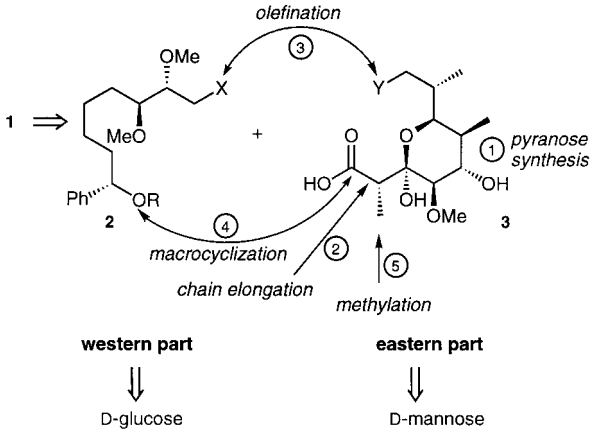



**1**

**Figure 1**

The structure as well as the absolute configuration of soraphen $A_{1\alpha}$ (**1**) was ascertained by X-ray crystallography (Figure 1).[1] It features an 18-membered lactone carrying a β-oxo group at C–3 which is present as a 6-membered hemiketal ring. All four substituents of this ring which adopts a chair conformation are axial whereas the *cis* ring fusion is equatorial. In addition, the macrolide possesses a C–9,C–10 *trans* double bond and an apolar hydrocarbon chain bearing a phenyl group at C–17. The crystal structure shows also that the methyl group at C–2 is equatorial and in the sterically favorable position. This was also demonstrated by Höfle and Böhlendorf by equilibration experiments.[2] Since it is the thermodynamically stable isomer, we decided to introduce this C–2 methyl group at the last step of the synthesis.

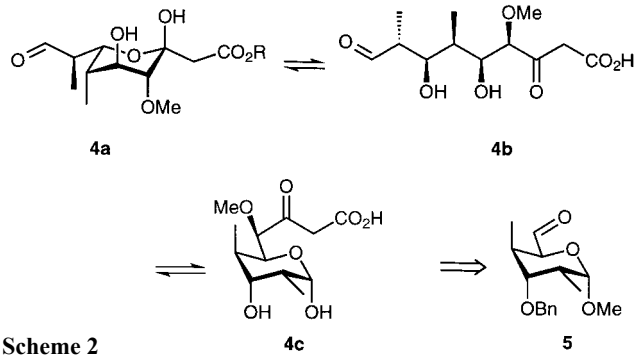
Two major disconnections result from the retrosynthetic analysis of soraphen $A_{1\alpha}$ (**1**). Cleaving the macrolide at the double bond and at the lactone function leads to the western and eastern fragments **2** and **3** (Scheme 1). The synthesis of **2a** (X: =O) starting from D-glucose will not be discussed further here since it was already described in a previous communication.[3] Fragment **3** should be obtained in two phases: synthesis of the pyranose skeleton and chain elongation. Coupling of the western (**2**) and the eastern (**3**) parts will be accomplished by an olefination reaction and a macrolactonization. In summary, five tasks proceed from our retrosynthetic scheme and will be discussed in this report: 1) Stereoselective synthesis of the pyranose ring, 2) Chain elongation, 3) Olefination, 4) Macrocyclization, 5) Stereoselective methylation at C–2.




**Scheme 1**

## 1 Synthesis of the Pyranose Ring 5

A close look at **4a** reveals that it is an L-ketose which, after a ring opening–ring closing sequence, should provide the D-aldose **4c** (Scheme 2). Compound **4c** should be obtained by stereoselective alkylation of the 6-aldehydo gulopyranoside **5**.




**Scheme 2**

The synthesis of the 1,5-dialdopyranose derivative **5** was already described by Hanessian et al.[4] in 17 steps starting from D-glucose. In this route, the equatorial methyl group

## Biographical Sketches

**Stephan Abel** was born in Eltville, Germany, in 1962. He studied at the Technische Hochschule Darmstadt and then moved to Basel where he completed his Ph.D. in 1993 in the group of Prof. B. Giese. In 1994, he joined the R&D Department of Sandoz Pharma AG and took the opportunity of a job rotation program to stay for one year (1995–1996) in the Chemical Development Center of the same company in Hanover, New Jersey. Since 1996, he is process research chemist at Novartis Pharma AG in Basel.

**Dominik Faber** was born in 1967 in Basel, Switzerland. He studied at the University of Basel and completed his Ph.D. work under the guidance of Prof. B. Giese in 1996. Subsequently, he joined the Department of Agricultural Chemistry at Sandoz (now Novartis Crop Protection) as a development chemist.

**Ottmar Hüter** was born in Mannheim, Germany, in 1962 and completed his Ph.D. work under the guidance of Prof. B. Giese at the University of Basel in 1993. From 1993 to 1995 he was a postdoctoral fellow in Prof. D. L. Boger's laboratory at the Scripps Research Institute, La Jolla. In 1995 he joined the Department of Agricultural Chemistry at Ciba-Geigy (now Novartis Crop Protection) as a research chemist.

**Bernd Giese** was born in Hamburg, Germany, in 1940. He studied chemistry at the Universities of Heidelberg, Hamburg and Munich where he completed his Ph.D. in 1969 under the direction of Prof. R. Huisgen. He then worked for two years on the synthesis of antidiabetics in the company BASF. Subsequently, he carried out his habilitation in the Universities of Münster and Freiburg. From 1978 to 1988 he was full professor at the Technische Hochschule Darmstadt and accepted his present position at the University of Basel in 1989.

at C–2 was introduced via ring opening of an epoxide (C–2) and subsequent epimerization. The axial methyl group at C–4 originated from catalytic hydrogenation of an exocyclic double bond. We designed a shorter synthesis beginning with D-mannose. The crucial intermediate in our synthesis of **5** is ketone **6**. This compound enabled us to bring in stereoselectively the two methyl groups (C–2, C–4) and the hydroxyl group at C–3. Subsequent oxidation at C–6 provided the aldehyde **5**.

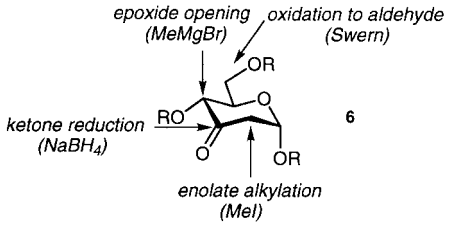
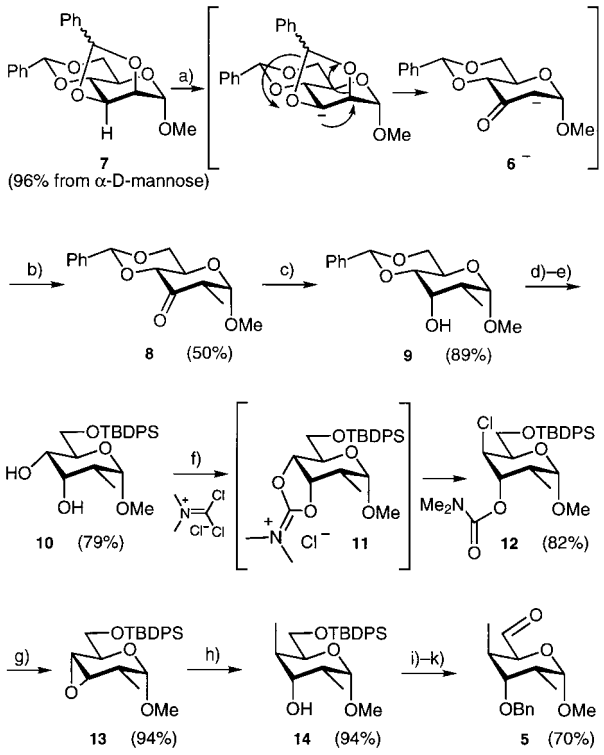



**Figure 2**

Ketone **6** was obtained by the Klemer–Horton rearrangement[5] from the protected mannose derivative **7**[5b] (Scheme 3). This strategy allowed us to introduce the methyl group at C–2: deprotonation of **7** followed by selective equatorial alkylation of the resulting enolate **6**$^-$ afforded exclusively the desired equatorial 2-methyl ribopyranose **8** in 50 % yield together with about 20 % of nonalkylated 2-deoxy compound. The mixture was used as such and the unmethylated product was separated after DIBAL reduction of the oxo group to **9** (89%). Deprotection of the 4,6-benzylidene group through catalytic hydrogenation on Pd/C, and subsequent silylation of the primary alcohol led to pyranoside **10**. The second methyl group (at C–4) was introduced by ring opening of an *allo*-configurated epoxide at (C–3,C–4).[6] In order to synthesize this epoxide it was necessary to convert the *cis* diol into a *trans* configurated product. This was carried out by submitting **10** to Viehe's salt in dichloroethane under reflux. In this reaction the phosgene iminium salt cyclizes with the *cis* diol to the cyclic intermediate **11** which is opened in a *trans* fashion by the chloride counterion. Thus, the 4-chloro-3-dimethylacetamido-*gulo* derivative **12** was obtained stereoselectively in 82% yield and was subsequently epoxidized with methyllithium in the presence of TMEDA (94 % yield). Cu(I)-catalyzed ring opening of epoxide **13** with methyl magnesium chloride was accomplished in 94% yield furnishing the *trans* diaxial isomer **14**. The last steps towards **5** consisted of benzylation of the remaining alcohol function at C–3 (89%), desilylation at C–6 with TBAF (87%) and Swern oxidation (91%). The 1,5-dialdopyranose derivative **5** was obtained in 10 steps from **6** in 20% overall yield and with complete control of the stereochemistry.

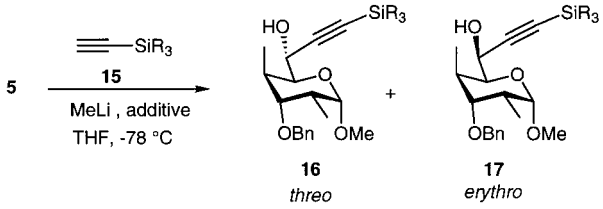



a) BuLi (2 equiv.), THF, –40 °C, 2h. b) MeI, HMPA, THF, –30 °C, 7 h, 50 % from **7**. c) DIBAL, toluene, 0 °C→ r.t., 45 min, 89%. d) $H_2$, 10% Pd–C, EtOAc:EtOH (1:1), r.t., 1h. e) TBDPSCl, DMAP, $NEt_3$, $CH_2Cl_2$, 2h, r.t., 89% over 2 steps. f) Dichloroethane, $NEt_3$, 100 °C, 30 min, 82%. g) MeLi, TMEDA, THF, –78 °C→ r.t., then reflux, 4h. h) MeMgCl, 4% CuBr, THF, r.t., 45 min, (94%). i) NaH, BnBr, $Bu_4NI$, THF, r.t., 6h, 89%. j) TBAF, THF, r.t., 2h, 87%. k) $(COCl)_2$, DMSO, $NEt_3$, $CH_2Cl_2$, –78 °C, 30 min, 91%.

**Scheme 3**

## 2 Chain Elongation: Synthesis of 4c

The next task consisted of elongating the chain by a stereoselective addition to the aldehyde function of **5**. We chose to use silyl acetylenes since it is known that their addition to sugar aldehydes occurs stereoselectively.[7] Moreover, silyl acetylides can be carboxylated easily (after desilylation), they are ketone equivalents and thus they should allow the introduction of the β-oxo ester group needed in **4c**. We added differently metallated silyl acetylenes to **5** (Scheme 4).



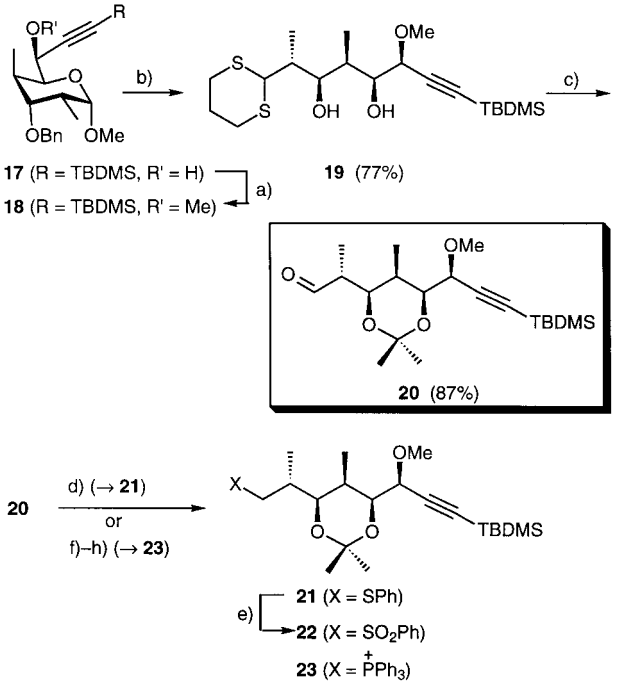

| $SiR_3$ | Metal | Yield (%) | **16 : 17** |
|---|---|---|---|
| TMS | Li | 89 | 1 : 2 |
| TBDMS | Li | 93 | 1 : 2.5 |
| TMS | MgBr | 85 | 1 : 20 |
| TBDMS | MgBr | 87 | 1 : >25 |
| TMS | $Li/TiCl_4–Ti(OPr^i)_4$ | 80 | 8 : 1 |

**Scheme 4**

The stereoselectivity of the addition follows the rules of chelate control with $Mg^{2+}$ salts and non-chelate control with mild Lewis acidic $Ti^{4+}$ salts.[8] Thus, the addition of

*tert*-butyldimethylsilyl acetylene to 1,5-dialdopyranose **5** led to the desired *erythro* derivative **17** in 87 % yield as sole diastereomer (**16:17**, 1:>25) at –35 °C.[9]

In the following, compound **17** ($SiR_3$ = TBDMS) was etherified with a large excess of methyl iodide and silver oxide under reflux in 89% yield.[10] The ring-opening reaction of methylglycoside **18** was then performed in order to obtain the various fragments necessary for an olefination with **2** either by a Julia or a Wittig reaction. Cleavage of the benzyl protecting group and ring opening were carried out in one step by treating **18** with 1,3-propanedithiol in the presence of boron trifluoride–diethyl ether complex at –20 °C→ 0 °C (keeping the temperature at –20 °C led only to thioacetalization). Thioacetal **19** was obtained in 77% yield, its diol function was protected as a dimethyl acetal and the thioacetal function subsequently hydrolyzed to aldehyde **20** (87% yield). Aldehyde **20** was the crucial intermediate from which the building blocks for the coupling reaction with **2** were obtained. Thus, reduction of **20** with sodium borohydride followed by reaction with diphenyl disulfide in the presence of tributylphosphine led to sulfide **21** (81% over 2 steps) which was further oxidized to the corresponding sulfone **22** (97%)[11] (Scheme 5). This building block would serve as a partner in a Julia reaction. On the other hand, we synthesized the phosphonium salt **23** necessary for a Wittig reaction by reduction of aldehyde **20** with $NaBH_4$, mesylation of the obtained alcohol, iodination, and substitution with triphenylphosphine.

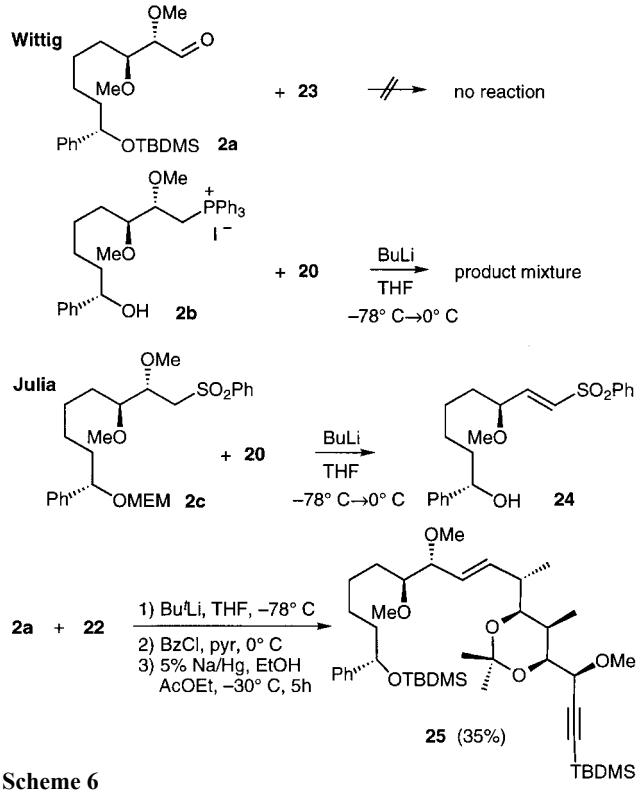



a) $Ag_2O$, MeI, reflux, 1–2h, 89%. b) Propanedithiol, $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, Ar, –20 °C → 0 °C, 1h, 77%. c) (i) Dimethoxypropane, acetone, Ar, CSA, r.t.; (ii) $CaCO_3$, MeI, $CH_3CN$, $H_2O$, r.t., 18 h, 87%. d) (i) $NaBH_4$, EtOH, Ar, 45 min; (ii) $(PhS)_2$, $PBu_3$, $CH_2Cl_2$, Ar, 0 °C, 3.5 h, 81%. e) MCPBA (55%), $NaHCO_3$, $CH_2Cl_2$, 0 °C → r.t., 45 min, 97%. f) (i) $NaBH_4$, EtOH, Ar, 0 °C, 45 min; (ii) MsCl, $Et_3N$, $CH_2Cl_2$, r.t., 90 min, 87%. g) NaI, acetone, reflux, 8h, 95%. h) $PPh_3$, $CH_3CN$, reflux, 4d, 93%

**Scheme 5**

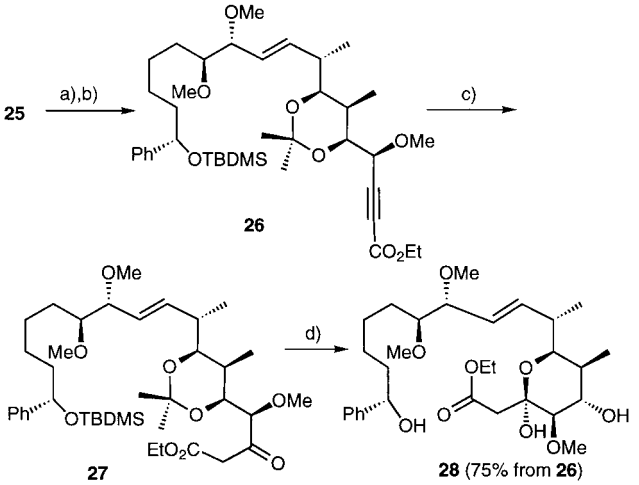
## 3 Olefination: Julia or Wittig?

The coupling of the eastern and western parts of soraphen was designed to follow either a Wittig or a Julia olefination. The Wittig pathway proved to be inefficient: no reaction was observed by treating aldehyde **2a** (X: =O) with phosphonium salt **23** whereas reaction of the phosphonium salt **2b** (X: $^+PPh_3$) with aldehyde **20** led to product mixtures. This failure was probably due to the easy elimination of the α-methoxy group in fragment **2b** under basic conditions. This was confirmed when we tried the Julia olefination of **2c** (X: $SO_2Ph$) with **20**. In the presence of BuLi at –78 °C, vinyl sulfone **24** was obtained as sole product together with unreacted aldehyde **20**. Successful olefination was achieved only by Julia coupling of the "eastern" sulfone **22** with the "western" aldehyde **2a**. The desired *trans* olefin **25** was obtained in 35% overall yield by reaction with *t*-BuLi in THF, subsequent benzoylation and reductive elimination with sodium amalgam (Scheme 6).




**Scheme 6**

At this point, the silyl acetylene moiety was converted into the β-oxo ester needed for the formation of the hemiketal **28** of soraphen. Thus, selective desilylation of the TBDMS group at alkyne **25** (with TBAF in THF at 0 °C) followed by carboxylation with ethyl chloroformate in the presence of BuLi yielded ethyl propiolate **26** in good yield. Reaction of the triple bond with morpholine gave the corresponding enamine which was hydrolyzed in situ with HCl to β-oxo ester **27**. The crude compound **27** was then treated with 60% acetic acid which opened the acetonide ring and induced intramolecular ketalization to yield **28** in 75% overall yield from **26**.



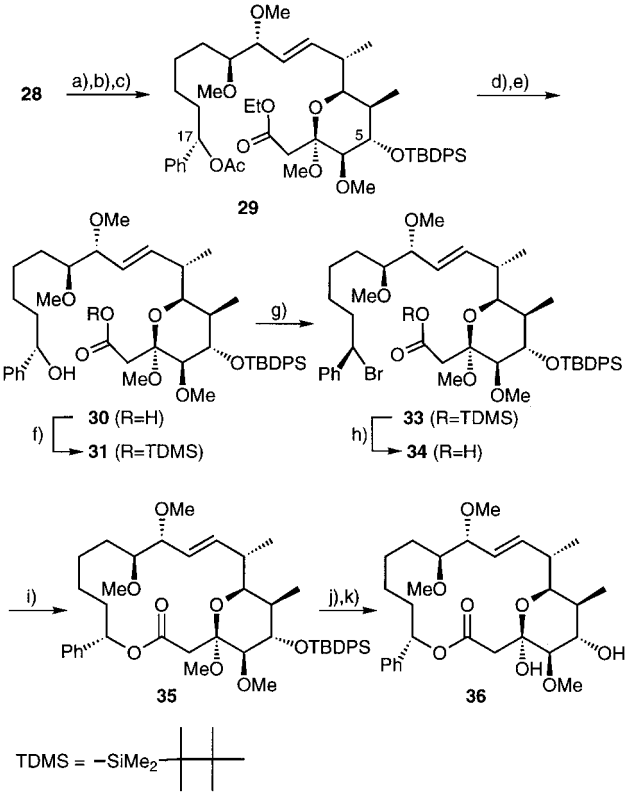

a) TBAF, THF, 0°C, 45 min, 85%. b) $ClCO_2Et$, BuLi, THF, –50°C→ 40°C, 1 h, 85%. c) (i) Morpholine, THF, reflux, 2 h. (ii) 2M HCl. d) 60% HOAc, 50°C, 2 h, 75%.

**Scheme 7**

## 4 Macrocyclization

The macrocyclization step could not be performed using the traditional addition/elimination sequence on the corresponding hydroxy carboxylic acid **30**.[12] To bring this step to completion, it was necessary to doubly activate both the benzylic alcohol and the acid. For this purpose, we followed the method of Kellogg[13] in which the alcohol is converted into the bromide with inversion of the configuration (**31**→**33**) and the carboxylate is used as its cesium salt. This salt is well dissociated[14] and facilitates the $S_N2$ reaction of the bromide (**34**→**35**) which should give back the desired configuration at the benzylic position of macrolide **35**.

The first tasks consisted of the saponification of the ethyl ester and bromination of the benzylic position of **28**. Before performing these steps, a few protections/deprotections at the various alcohol groups of **28** were required. Thus, silylation at O–5, followed by acetylation at the benzylic OH group and methylation of the anomeric hydroxyl group gave **29**. The ethyl ester of **29** was exchanged by a TMS-ethyl ester with Ti(*i*-OPr)$_4$ in 2-trimethylsilylethanol (90% yield).[15] This ester was then saponified together with the acetyl group at C–17 in the presence of cesium fluoride[16] in DMF and gave **30**. The carboxylic acid was esterified again to the thexyldimethylsilyl ester (TDMS) **31** in the presence of triethylamine[17] and bromination was carried out with $\alpha$-bromo enamine **32**[18] to give **33** in 91% overall yield from **30**. Compound **33** was ready for the macrocyclization which was carried out first by hydrolyzing the thexyl ester to acid **34** with $Et_3N$ in water and acetone and adding cesium carbonate to make the reactive cesium carboxylate. Macrolide **35** was obtained in 50% yield from **33**. This moderate yield of **35** originated probably from the facile elimination of bromide (benzylic position) in **34** yielding the corresponding styrene derivative. Two more deprotection steps on compound **35** (at the anomeric center and at C–5) led to norsoraphen **36**.

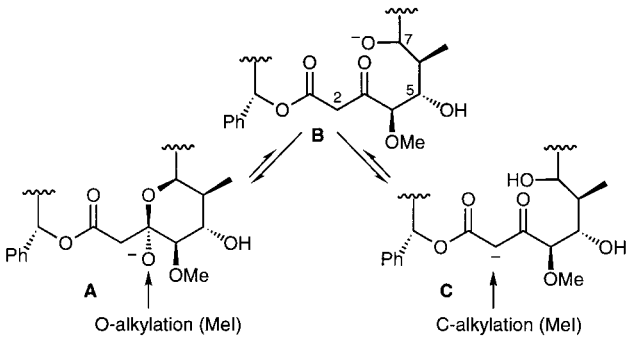



a) TBDPSCl, imidazole, DMF, –60°C, 7d, 96%. b) $Ac_2O$, pyridine, DMAP, r.t., 15 min, 98%. c) $HCOMe_3$:MeOH:$CH_2Cl_2$ (2:1:1), CSA, r.t., 4 d, 99%. d) $TMSCH_2CH_2OH$, Ti(*i*-OPr)$_4$, 100°C, 4 d, 90%. e) CsF, DMF, r.t., 1 d, 98%. f) TDMSCl, $NEt_3$, $CH_2Cl_2$, r.t., 20 min. g) $Me_2C$=C(Br)$NMe_2$ **32**, $NEt_3$, $CH_2Cl_2$, r.t., 1 h, 91% over 2 steps. h) $Et_3N$, $H_2O$, acetone, r.t., 15 min. i) $Cs_2CO_3$, DMF, r.t., 1 d, 50% over 2 steps. j) TBAF(1M), THF, 0°C, 4 h, 96%. k) HCl (1N), THF, r.t., 20 h, 99%.[12]

**Scheme 8**

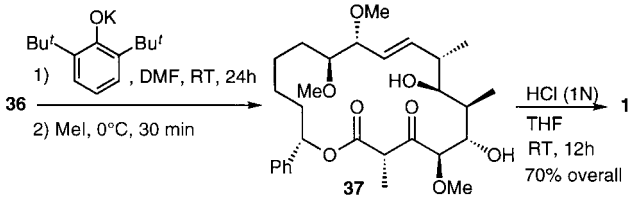
## 5 Stereoselective methylation at C–2

The last step of the synthesis consisted in the methylation of norsoraphen **36** at C–2. Höfle and Kiffe[19] had carried out studies on the methylation of soraphen $A_{1\alpha}$ (**1**) itself. They had shown that only the hemiketal form can be alkylated. Submitting the methyl ketal of soraphen to alkylation led to elimination of methanol yielding a C–2,C–3 double bond. On the other hand, the same studies[19] showed that it was necessary to use a sterically hindered base so that no methylation of the hemiketal function at C–3 takes place. Strong bases like NaH, BuLi or LDA did not lead to C-alkylation either. From these results, we concluded that under weak basic conditions, deprotonation occurs at the hemiketal and that a pH-dependent ring opening equilibrium (**A** ⇌ **B** ⇌ **C**) leads to enolate C via reprotonation of **B** by the conjugated acid and deprotonation of the β-oxo ester in **B**. Under strong basic conditions alcoholate **B** cannot be reprotonated by the conjugated acid anymore, thus it recyclizes towards A, which is thermodynamically favored, and no methylation is observed.




**Scheme 9**

Thus, the base should be very weak. It should just be strong enough to deprotonate the enol of the β-oxo ester in **B** so that *C*-methylation can occur. The alkylation step itself is very fast and has to take place quickly so that no dialkylation occurs. Another problem which arose in some cases was the alkylation at the hydroxyl group at C–5. Several bases and conditions were checked and the optimum conditions are summarized in Scheme 10.




**Scheme 10**

The best base was potassium 2,6-di-*tert*-butylphenolate. Indeed, when deprotonation was carried out in DMF at room temperature for 24 h, addition of methyl iodide at 0 °C for 30 min afforded the α-methylated β-oxo ester **37**. This product was directly cyclized under acidic conditions to give soraphen $A_{1\alpha}$ (**1**) in 70% overall yield from **36**. The physical and spectroscopic properties of the isolated product were identical with the reported data of the natural product.[1]

In conclusion, we have described here the first total synthesis of the fungicide soraphen $A_{1\alpha}$ (**1**) from glucose (via fragment **2**) and mannose (via fragment **3**).

**Methyl 4,6-*O*-Benzylidene-2-deoxy-2-*C*-methyl-α-D-ribohexopyranoside (8)**

In a flame-dried 1 L flask compound **7**[5b] (22.2 g, 60.0 mmol) was dissolved in anhyd THF (500 mL), the solution was purged with Ar for 15 min, then cooled to –40 °C. A 1.6 M solution of BuLi (60.0 mL, 96.0 mmol) was then added dropwise via syringe pump over 1 h. After addition of 25–30 mL BuLi, the solution turned bright red. At the end of the addition, stirring was continued for 30 min at –30 °C. At –35 °C, a mixture of anhyd HMPA (40.0 mL, 0.23 mol) and MeI (11.0 mL, 0.17 mol) was slowly added via syringe pump over 1 h, whereby the solution turned dark yellow. The mixture was stirred for 6 h at –30 °C then quenched by addition of sat. aq $NH_4Cl$ (150 mL) and diluted with $H_2O$ (200 mL). The organic phase was separated, the aqueous phase extracted with $Et_2O$ (3 × 200 mL), the combined organic phases washed with brine and dried ($Na_2SO_4$). The ethereal solution was concentrated in vacuo to a volume of ca. 100 mL and the flask was cooled (fridge). A white precipitate of **8** was formed, filtered, washed with pentane (3 × 100 mL), and dried under high vacuum. Compound **8** (8.40 g, 50 %) was obtained together with about 20% of the unmethylated sugar at C–2. The products could not be separated at this point because of their low solubility and the product mixture was used as it was in the next step. Data for pure **8**: mp: 198–200 °C. $R_f$ = 0.4 (pentane/$CH_2Cl_2$/$Et_2O$ = 3/1/1).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.07 (3H, d, *J* = 6.9 Hz), 2.82–2.86 (1H, m), 3.35 (3H, s), 3.91 (1H, dd, *J* = 10.2, 10.2 Hz), 4.08 (1H, ddd, *J* = 10.2, 9.8, 4.2 Hz), 4.26 (1H, dd, *J* = 9.8, 1.3 Hz), 4.34 (1H, dd, *J* = 10.2, 4.2 Hz), 4.94 (1H, d, *J* = 4.2 Hz), 5.55 (1H, s), 7.3–7.6 (5H, m).

$^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = 8.53, 48.69, 55.25, 65.71, 69.48, 82.90, 101.9, 104.5, 126.4–129.2 (3 × C) 136.6, 199,3.

Anal. Calcd. for $C_{15}H_{18}O_5$ (278.3): C, 64.74; H, 6.52. Found: C, 64.92; H, 6.43.

**Methyl 4,6-*O*-Benzylidene-2-deoxy-2-*C*-methyl-α-D-allopyranoside (9) by Reduction of 8 with DIBAL**

A mixture (11.9 g, 42.7 mmol) of compound **8** and its C–2 unmethylated isomer was suspended in anhyd toluene (300 mL) and the suspension purged with Ar for 15 min. At 0 °C a 1M solution of DIBAL (58.0 mL, 58.0 mmol) in toluene was slowly added, whereby the mixture became homogeneous. After the addition, the temperature was raised to r.t. and stirred for a further 45 min after which the reaction was completed. The excess of DIBAL was then destroyed at 0 °C with MeOH (15 mL). The mixture was washed with a solution of sodium potassium tartrate (3 × 100 mL), then with brine (100 mL), dried ($Na_2SO_4$), and concentrated in vacuo. The products were purified by flash chromatography on silica gel (pentane/EtOAc = 3/1) and alcohol **9** (8.50 g, 89 %) was obtained as white needles. Mp 122 °C. $R_f$ = 0.2 (pentane/EtOAc = 3:1).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.14 (3H, d, *J* = 7.3 Hz), 1.96–2.05 (1H, m),2.83 (1H, d, *J* = 7.8 Hz), 3.41 (3H, s), 3.57 (1H, dd, *J* = 9.7, 2.8 Hz), 3.78 (1H, dd, *J* = 10.2 Hz), 3.97 (1H, ddd, *J* = 7.8, 2.8 Hz), 4.13 (1H, ddd, *J* = 9.7, 5.0 Hz), 4.35 (1H, dd, *J* = 10.2, 5.0 Hz), 4.57 (1H, d, *J* = 3.5 Hz), 5.61 (1H, s), 7.30–7.50 (5H, m).

Anal. Calcd. for $C_{15}H_{20}O_5$ (280.3):C, 64.27; H, 7.19. Found: C, 64.30; H, 7.25. The other fractions obtained after chromatography contained the 2 isomeric alcohols coming from reduction of the unmethylated starting material.

**Methyl 6-*O*-*tert*-Butyldiphenylsilyl-4-chloro-3-*O*-(*N*,*N*-dimethylacetamido)-α-D-gulopyranoside (12)**

In a flame-dried 250 mL flask equipped with a condenser, diol **10** (5.50 g, 12.8 mmol) was dissolved in anhyd dichloroethane (90 mL) and in $Et_3N$ (27 mL) and the solution was purged with Ar for 10 min. Then, *N*,*N*-dimethylphosgeneiminium chloride (2.30 g, 20.0 mmol, the salt was previously dried for 2 h under high vacuum) was added rapidly in one portion. After 30 min, the mixture was hydrolyzed with sat. aq $NaHCO_3$ (100 mL) and $CH_2Cl_2$ (80 mL) was added. The organic phase was separated, the aqueous phase extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic phases were washed successively with 2M HCl (100 mL), sat. aq. $NaHCO_3$ (2 × 100 mL) and brine, dried ($Na_2SO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (pentane/EtOAc = 7:1→4:1) and **12** (5.43 g, 82 %) was obtained as a colorless oil. $R_f$ = 0.28 (pentane/EtOAc = 9:1).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.92 (3H, d, *J* = 7.1 Hz), 1.04 (9H, s), 2.45–2.53 (1H, m), 2.93, 2.96 (2 × 3H, broad s), 3.23 (3H, s), 3.73–3.83 (2H, m), 4.16 (1H, dd, *J* = 3.3, 1.6 Hz), 4.21 (1H, ddd, *J* = 1.6 Hz), 4.50 (1H, d, *J* = 3.8 Hz), 4.89 (1H, dd, *J* = 3.3, 3.3 Hz), 7.34–7.68 (10H, m).

Anal. Calcd. for $C_{27}H_{38}ClNO_5$ (520.14): C, 62.35; H, 7.36; N, 2.69. Found: C, 62.28; H, 7.49; N, 2.70. Its 3,4-diequatorial isomer (370 mg) was also isolated as a colorless oil. $R_f$ = 0.36 (pentane/EtOAc = 9:1).

$^{13}$C NMR of the corresponding 6-*O*-TBDMS ether of **12** (75.5 MHz, $CDCl_3$): δ = –5.74, –5.70, 11.52, 17.93, 25.50, 30.75, 35.38, 35.89, 55.07, 55.81, 62.65, 64.88, 72.87, 100.5, 155.3.

**Methyl 6-*O*-*tert*-Butyldiphenylsilyl-3,4-anhydro-2-deoxy-2-*C*-methyl-α-D-allopyranoside (13)**

In a flame-dried 250 mL flask, chlorocarbamate **12** (4.00 g, 7.77 mmol) was dissolved in anhyd THF (100 mL) under Ar and then treated with anhyd TMEDA (25 mL). The solution was purged with Ar for 10 min and then cooled to –78 °C. A 1.6 M solution of MeLi (11.2 mL, 17.9 mmol) in $Et_2O$ was added within 45 min via syringe pump. The mixture was stirred for a further 45 min at –78 °C then slowly warmed to r.t. The colorless solution obtained was then refluxed under Ar whereby it turned light brown. After 4 h, it was cooled to 0 °C and cautiously quenched with sat. aq $NH_4Cl$ (100 mL). The aqueous phase was separated and extracted with $Et_2O$ (3 × 50 mL). The combined organic phases were washed successively with sat. aq $NaHCO_3$ and brine, dried ($Na_2SO_4$), and concentrated in vacuo. Epoxide **13** was obtained (3.00 g, 94 %) as a colorless syrup which was pure enough to be used in the next step. A small portion was purified by flash chromatography on silica gel (pentane/$Et_2O$ = 5:1→3:1). $R_f$ = 0.43 (pentane/EtOAc = 9:1).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.07 (9H, s), 1.14 (3H, d, *J* = 7.2 Hz), 2.14–2.24 (1H, m), 3.15 (1H, dd, *J* = 4.1, 2.1 Hz), 3.29 (3H, s), 3.37 (1H, d, *J* = 4.1 Hz), 3.82–3.92 (2H, m), 4.00 (1H, dd, *J* = 5.8, 5.6 Hz), 4.48 (1H, d, *J* = 5.2 Hz), 7.36–7.70 (10H, m).

Anal. Calcd. for $C_{24}H_{32}O_4Si$ (412.6): C, 69.87; H, 7.82. Found: C, 69.60; H, 7.65.

$^{13}$C NMR of the corresponding 6-*O*-TBDMS ether of **13** (75.5 MHz, $CDCl_3$): δ = –5.52, –5.16, 12.40, 18.10, 25.68, 33.18, 52.77, 52.95, 56.33, 63.77, 67.83, 100.6.

**Methyl 6-*O*-*tert*-Butyldiphenylsilyl-2,4-dideoxy-2,4-*C*-dimethyl-α-D-gulopyranoside (14)**

CuBr (58 mg, 0.40 mmol) was introduced in a flame-dried 50 mL flask and epoxide **13** (3.20 g, 7.77 mmol) in anhyd THF (10 mL) was added with a syringe. At 0 °C and under rapid stirring, a 3M solution of MeMgBr (5.3 mL, 16 mmol) in $Et_2O$ was then added and the reaction was stirred for 45 min at r.t. The mixture was then hydrolyzed with sat. aq $NH_4Cl$ and the light blue aqueous phase extracted with $Et_2O$ (3 × 50 mL). The combined organic phases were washed with brine, dried ($Na_2SO_4$), and concentrated in vacuo. Compound **14** (3.1 g, 94 %) was obtained as a colorless syrup. $R_f$ = 0.55 (pentane/EtOAc = 8:1).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.79 (3H, d, *J* = 7.5 Hz), 1.01 (3H, d, *J* = 7.3 Hz), 1.03 (9H, s), 1.87–2.02 (2H, m), 3.34 (3H, s), 3.44 (1H, broad m), 3.58 (1H, dd, *J* = 10.5, 7.3 Hz), 3.73 (1H, dd, *J* = 10.5, 5.2 Hz), 4.13 (1H, ddd *J* = 7.3, 5.2, 2.5 Hz), 4.52 (1H, d, *J* = 3.2 Hz), 7.36–7.70 (10 H, m).

Anal. Calcd. for $C_{25}H_{36}O_4Si$ (428.62): C, 70.06; H, 8.47. Found: C, 69.89; H, 8.44.

$^{13}$C NMR of the corresponding 6-*O*-TBDMS ether of **14** (75.5 MHz, $CDCl_3$): δ = –5.44, –5.28, 10.73, 12.82, 18.26, 25.86, 32.46, 36.76, 52.77, 55.09, 64.01, 65.87, 74.99, 102.6.

**Conversion of compound 14 into aldehyde 5**

This conversion was performed in 3 standard steps: step 1, benzylation of OH group at C–4 of compound **14** (4-BnO-**14**); step 2, desilylation at C–6 (4-BnO-6-OH-**14**); step 3, oxidation to the aldehyde at C–6 to give the known compound **5**.[4] The spectroscopic data for the intermediates are given below:

**Methyl 3-Benzyl-6-*O*-*tert*-butyldiphenylsilyl-2,4-dideoxy-2,4-C-dimethyl-α-D-gulopyranoside (4-BnO-14)**

$R_f$ = 0.54 (pentane/$Et_2O$ = 5:1).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.81 (3H, d, *J* = 7.2 Hz), 0.96 (3H, d, *J* = 7.1 Hz), 1.07 (9H, s), 1.13–2.10 (2H, m), 3.20 (1H, dd, *J* = 3.1, 3.0 Hz), 3.40 (3H, s), 3.58 (1H, dd, *J* = 10.4, 7.0 Hz), 3.75 (1H, dd, *J* = 10.4, 6.0 Hz), 4.33 (1H, ddd, *J* = 7.0, 6.0, 2.5 Hz), 4.47 (2H, d, *J* = 12.9, 3.8 Hz), 4.74 (1H, d, *J* = 12.9 Hz), 7.28–7.75 (15 H, m).

Anal. Calcd. for $C_{32}H_{42}O_4Si$ (518.7): C, 74.09; H, 8.16. Found: C, 74.25; H, 8.30.

$^{13}$C NMR of the corresponding 6-*O*-TBDMS ether of 4-BnO-**14** (75.5 MHz, $CDCl_3$): δ = –5.41, –5.28, 10.57, 12.47, 18.24, 25.86, 31.11, 33.10, 55.54, 63.79, 65.99, 70.99, 79.94, 101.5, 126.0, 127.7, 128.5, 138.9.

**Methyl 3-*O*-Benzyl-2,4-dideoxy-2,4-C-dimethyl-α-D-gulopyranoside (4-BnO-6-OH-14)**

Mp 60–61 °C. $R_f$ = 0.20 (pentane/EtOAc = 3:2).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.87 (3H, d, *J* = 7.1 Hz), 0.95 (3H, d, *J* = 7.2 Hz), 1.80–2.00 (3H, m), 3.17 (1H, dd, *J* = 3.0, 3.0 Hz), 3.40 (3H, s), 3.52 (1H, br m), 3.70 (1H, dd, *J* = 10.4 Hz), 4.27 (1H, ddd, *J* = 2.5 Hz), 4.49 (2H, d, *J* = 12.8, 3.8 Hz), 4.71 (1H, d, *J* = 12.8 Hz), 7.27–7.37 (5 H, m).

$^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = 11.09, 12.51, 31.79, 33.08, 55.74, 64.03, 66.24, 71.20, 80.09, 101.6, 127.4, 127.8, 128.2, 138.8.

Anal. Calcd. for $C_{16}H_{24}O_4$ (280.4): C, 68.54; H, 8.63. Found: C, 68.34; H, 8.70.

**Methyl 3-Benzyl-8-*tert*-butyldimethylsilyl-2,4,7,8-tetradeoxy-2,4-*C*-dimethyl-L-*glycero*-α-D-*gulo*-oct-7-ynopyranoside (17) (*erythro* isomer)**

In a flame-dried 100 mL flask, magnesium chips (200 mg, 8.57 mmol) were covered with anhyd $Et_2O$ (10 mL). Dibromoethane (0.7 mL, 8.60 mmol) in anhyd $Et_2O$ (4 mL) was slowly added under cooling with an ice water bath. The white suspension obtained was then stirred for 30 min at r.t. This synthesis of $MgBr_2$ was repeated with the same amounts of Mg and dibromoethane in a smaller flask (50 mL) and stirred for 30 min at r.t. Then, in a flame-dried 25 mL flask, a 1.6 M MeLi solution (2.8 mL, 4.50 mmol) was dissolved in anhyd $Et_2O$ (5 mL). At 0 °C, a 90% solution of *tert*-butyldimethylsilyl acetylene[20] **15** ($SiR_3$=TBDMS, 750 mg, 4.81 mmol) in anhyd $Et_2O$ (4 mL) was slowly added dropwise to the MeLi solution. After the gas evolution, the mixture was stirred for further 15 min at r.t. The obtained lithium acetylide solution was then added by syringe (20 mL) in the 100 mL flask containing the $MgBr_2$ suspension and the syringe was rinsed with anhyd $Et_2O$ (5 mL). After stirring for 15 min at r.t., the white suspension of magnesium acetylide was cooled to –30 °C.

The second $MgBr_2$ suspension (in the 50 mL flask) was treated with a solution of compound **5** (334 mg, 1.20 mmol) in anhyd $Et_2O$ (2 mL). The solution was cooled to 0 °C, added slowly under an excess pressure of Ar via a double-sided cannula to the suspension of magnesium acetylide whereby the temperature was maintained under –30 °C. After rinsing with anhyd $Et_2O$ (2 × 5 mL) and 30 min stirring at –30 °C, the temperature was raised to 10 °C over 10 min and the reaction was quenched with sat. aq $NH_4Cl$ (20 mL). The aqueous phase was separated, diluted with more $H_2O$ (20 mL) and extracted with $Et_2O$ (3 × 30 mL). The combined organic phases were successively washed with $NaHCO_3$, $NH_4Cl$, and brine, dried ($Na_2SO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (pentane/$Et_2O$ = 2:1) and **17** (438 mg, 87%) was obtained as a white solid which was recrystallized from $Et_2O$ (white needles, mp: 76–77 °C). $R_f$ = 0.25 (pentane/$Et_2O$ = 2/1).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.12, 0.13 (2 × 3H, s), 0.92–0.96 (15H, d, *J* = 7.1 Hz), 1.90–2.11 (1H, m), 2.32–2.41 (2H, m), 3.18

(1H, dd, *J* = 3.0, 3.0 Hz), 3.41 (3H, s), 4.15 (1H, dd, *J* = 9.1, 2.2 Hz), 4.38 (1H, d, *J* = 12.6 Hz), 4.40 (1H, dd, *J* = 9.1, 3.2 Hz), 4.51 (1H, d, *J* = 4.3 Hz), 4.77 (1H, d, *J* = 12.6 Hz), 7.26–7.34 (5H, m).

$^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = –4.94, 10.42, 12.41, 16.21, 25.82, 31.03, 32.59, 55.51, 63.94, 69.20, 70.31, 79.29, 89.01, 101.5, 103.1, 127.5, 127.9, 128.2, 138.2.

Anal. Calcd. for $C_{24}H_{38}O_4Si$ (418.6): C, 68.86; H, 9.15. Found: C, 68.69; H, 9.08.

**Spectroscopic data of *threo* isomer 16**

$R_f$ = 0.52 (pentane/$Et_2O$ = 2/1).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.09, 0.10 (2 × 3H, s), 0.90–0.96 (15H, d, *J* = 7.1 Hz), 1.87 (1H, d, *J* = 5.8 Hz), 1.92–2.02 (1H, m), 2.28–2.38 (1H, m), 3.21 (1H, dd, *J* = 3.2, 3.1 Hz), 3.43 (3H, s), 4.16 (1H, dd, *J* = 8.6, 2.2 Hz), 4.35 (1H, dd, *J* = 8.6, 5.8 Hz), 4.44 (1H, d, *J* = 12.7 Hz), 4.51 (1H, d, *J* = 4.1 Hz), 4.75 (1H, d, *J* = 12.7 Hz), 7.26–7.38 (5H, m).

$^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = –4.69, 10.74, 12.59, 16.43, 25.63, 30.41, 32.90, 55.71, 62.98, 67.78, 70.87, 79.81, 88.41, 101.9, 106.3, 127.4, 127.9, 128.2, 138.8.

**(1*R*,2*R*,3*S*,4*S*)-6-*tert*-Butyldimethylsilyl-1-[(1*R*)-1-(1,3-dithian-2-yl)ethyl]-4-methoxy-2-methylhex-5-yne-1,3-diol (19)**

In a flame-dried 50 mL flask TBDMS-alkyne **18** (564 mg, 1.30 mmol) was dissolved under Ar in anhyd $CH_2Cl_2$ (12 mL), the solution was purged with Ar and cooled to –17 °C. The solution was then treated with propane-1,3-dithiol (2.1 mL, 21.0 mmol), then $BF_3$•$Et_2O$ (1.3 mL, 10.3 mmol) was slowly added so that the temperature of the mixture did not exceed –15 °C. After 10 min, the mixture was warmed up to 0 °C and stirred for further 45 min after which the temperature was raised again to r.t. and the mixture was hydrolyzed with $NaHCO_3$ (10 mL). Water and $CH_2Cl_2$ were added, the aqueous phase was extracted with $CH_2Cl_2$, (2 × 30 mL) the combined organic phases were washed with brine, dried ($Na_2SO_4$), and concentrated in vacuo. Flash chromatography on silica gel (pentane/$Et_2O$ = 3/2→1/2) gave dithioacetal **19** (420 mg, 77%) as a colorless syrup. $R_f$ = 0.28 (pentane/$Et_2O$ = 1/1).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.11 (6H, s), 0.91 (12H, m), 0.99 (3H, d, *J* = 7.1 Hz), 1.77–1.91 (1H, m), 1.98–2.07 (1H, m), 2.08–2.20 (2H, m), 2.85 (3H, m), 3.05 (2H, m), 3.46 (3H, s), 3.70 (1H, broad s), 3.88 (3H, m), 4.74 (1H, d, *J* = 2.4 Hz).

$^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = –4.87, 4.47, 12.40, 16.30, 25.87, 26.49, 30.60, 31.41, 34.38, 41.48, 51.76, 56.64, 74.14, 76.11, 78.92, 91.85, 100.9.

Anal. Calcd. for $C_{20}H_{38}O_3S_2Si$ (418.7): C, 57.37; H, 9.15. Found: C, 57.20; H, 9.03.

**(2*R*)-2-{(4*R*,5*R*,6*S*)-6-[(1*S*)-3-*tert*-Butyldimethylsilyl-1-methoxyprop-2-yn-1-yl]-2,2,5-trimethyl-1,3-dioxan-4-yl]propanal (20)**

Compound **19** (420 mg, 1.00 mmol) was dissolved in dimethoxypropane (2.0 mL) and acetone (5.0 mL) and the solution was purged with Ar. After addition of camphor-10-sulfonic acid (23.0 mg, 0.10 mmol) in acetone (0.2 mL), stirring was carried out for 10 h at r.t. The pale yellow solution was then hydrolyzed with sat. aq $NaHCO_3$ (10 mL) and $Et_2O$ added. The aqueous phase was extracted with $Et_2O$ (3 × 5 mL) and the combined organic phases washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. The acetonide (473 mg) was obtained and directly used in the next step without further purification.

The acetonide (460 mg, 1.00 mmol) was dissolved in $CH_3CN$ (7.0 mL) and $H_2O$ (3.5 mL). The solution was treated with $CaCO_3$ (374 mg) and with MeI (3.3 mL) under intense stirring. After 18 h at r.t., $CH_2Cl_2$ (5 mL) and $H_2O$ (10 mL) were added and after 10 min. stirring the solution became homogeneous. Extraction of the aqueous phase with $CH_2Cl_2$ (3 × 10 mL) was carried out and the combined organic phases were washed with brine, dried ($Na_2SO_4$), and concentrated in vacuo. Flash chromatography on silica gel (pentane/$Et_2O$ = 5:1→4:1) gave compound **20** (318 mg, 87 %) as a colorless oil. $R_f$ = 0.31 (pentane/ether 5:1).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.07, 0.08 (2 × 3H, s), 0.89 (15H, m), 1.37, 1.40 (2 × 3H, s), 1.82–1.92 (1H, m), 2.42–2.53 (1H, m), 3.42 (3H, s), 3.96 (2H, m), 4.03 (1H, dd, *J* = 10.2, 2.0 Hz), 9.69 (1H, d, *J* = 1.0 Hz).

$^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = –4.81, 5.09 , 8.80, 16.46, 19.41, 25.93, 29.52, 30.75, 47.08, 56.71, 73.66, 73.91, 75.51, 91.58, 99.66, 100.7, 204.5.

Anal. Calcd. for $C_{20}H_{36}O_4Si$ (368.6): C, 65.17; H, 9.84. Found: C, 65.50; H, 9.63.

**(2*R*)-2-{(4*R*,5*R*,6*S*)-6-[(1*S*)-3-*tert*-Butyldimethylsilyl-1-methoxyprop-2-yn-1-yl]-6-[(1*R*)-1-methyl-(2-phenylsulfanyl)ethyl]-2,2,5-trimethyl-1,3-dioxane (21)**

A solution of aldehyde **20** (308 mg, 0.83 mmol) in anhyd EtOH (6 mL) at 0 °C was purged with Ar, then treated with $NaBH_4$ (35 mg, 0.92 mmol) and stirred for 45 min. The reaction mixture was carefully hydrolyzed with sat. $NH_4Cl$ (10 mL) and the aqueous phase was extracted with $Et_2O$ (4 × 10 mL). The combined organic phases were washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. After drying the residue under high vacuum, the alcohol (304 mg) was obtained as a colorless oil which was pure enough to be directly used in the next step. The alcohol (295 mg, 0.80 mmol) was dissolved in $CH_2Cl_2$ (25 mL) and the mixture was purged with Ar and cooled to 0 °C. Subsequently, it was treated with diphenyl disulfide (698 mg, 3.20 mmol), then added dropwise with tributylphosphine (85%, 700 mg, 2.94 mmol) in $CH_2Cl_2$ (1.5 mL). After 3.5 h, the solvent was removed under vacuum and the residue was purified by flash chromatography on silica gel (pentane/$Et_2O$ = 9:1→3:1). Sulfide **21** (299 mg, 81% from **20**) was obtained as a colorless oil. $R_f$ = 0.33 (pentane/$Et_2O$ = 9:1).

$^1$H NMR ($CDCl_3$): δ = 0.11, 0.12 (2 × 3H, s), 0.86 (3H, d, *J* = 7.1 Hz), 0.93 (12 H, m, *J* = 6.9 Hz), 1.41, 1.45 (2 × 3H, s), 1.84–2.02 (2H, m), 2.72 (1H, dd, *J* = 12.8, 8.2 Hz), 3.40 (1H, dd, *J* = 12.8, 2.5 Hz), 3.46 (3H, s), 3.65 (1H, dd, *J* = 9.9, 1.9 Hz), 3.93 (1H, dd, *J* = 8.5, 2.0 Hz), 4.02 (1H, d, *J* = 8.5 Hz), 7.13–7.37 (5H, m).

$^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = –4.80, 5.02, 13.71, 16.44, 19.40, 25.93, 29.69, 31.20, 34.64, 36.68, 56.60, 73.76, 75.68, 75.79, 91.33, 99.48, 100.9, 125.1, 127.9, 128.7, 137.7.

Anal. Calcd. for $C_{26}H_{42}O_3SSi$ (462.8): C, 67.47; H, 9.15. Found: C, 67.15; H, 9.22.

**(4*S*,5*R*,6*R*)-4-[(1*S*)-3-*tert*-Butyldimethylsilyl-1-methoxyprop-2-yn-1-yl]-6-[(1*R*)-1-methyl-(2-phenylsulfonyl)ethyl]-2,2,5-trimethyl-1,3-dioxane (22)**

Sulfide **21** (130 mg, 0.28 mmol) in $CH_2Cl_2$ (8 mL) was treated with $NaHCO_3$ (168 mg, 2.00 mmol). Then, MCPBA (55%, 220 mg, 0.70 mmol) was added at 0 °C. After 5 min the ice bath was removed and the mixture left at r.t. for 45 min. After hydrolysis with sat. $NaHCO_3$ (10 mL) the mixture was partitioned between $H_2O$ and $CH_2Cl_2$ and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 25 mL). The organic phases were washed with brine, dried ($Na_2SO_4$), then concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (pentane/ $Et_2O$ 2:1→1:1). Sulfone **22** (134 mg, 97%) was obtained as a colorless oil. $R_f$ = 0.37 (pentane/$Et_2O$ = 1:1).

$^1$H NMR ($CDCl_3$): δ = 0.10, 0.11 (2 × 3H, s), 0.78 (3H, d, *J* = 6.8 Hz), 0.92 (9 H, m), 1.07 (3H, d, *J* = 6.7 Hz), 1.28, 1.34 (2 × 3H, s), 1.90–2.00 (1H, m, *J* = 2.2, 2.2 Hz), 2.06–2.18 (1H, m, *J* = 9.9, 6.7, 2.0 Hz), 2.83 (1H, dd, *J* = 14.1, 9.5 Hz), 3.43 (3H, s), 3.44 (1H, dd, *J* = 9.9, 2.2 Hz), 3.56 (1H, dd, *J* = 14.1, 2.0 Hz), 3.84 (1H, dd, *J* = 8.4, 2.2 Hz), 3.97 (1H, d, *J* = 8.4 Hz), 7.52–7.69, 7.88–7.95 (5H, m).

$^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = –4.80, 4.67, 14.21, 16.45, 19.43, 25.92, 29.55, 30.70, 30.72, 56.70, 58.38, 73.64, 75.37, 75.52, 91.60, 99.57, 100.7, 127.8, 129.1, 133.4, 140.1.

Anal. Calcd. for $C_{26}H_{42}O_5SSi$ (494.8): C, 63.11; H, 8.56. Found: C, 62.89; H, 8.33.

**Julia coupling between 2a and 22. Synthesis of product 25**

Sulfone **22** (120 mg, 0.24 mmol) was dissolved in anhyd THF (3 mL) and anhyd toluene (3 mL), the solution was purged with Ar and cooled to –78 °C. Then, a 1.6 M solution of *t*-BuLi (150 µL, 0.24 mmol) was added dropwise to the mixture which became yellow. After 20 min at –78 °C, a solution of aldehyde **2a**[3] (76.0 mg, 0.19 mmol) in THF (1 mL) and toluene (1 mL) was added and the mixture was stirred for further 70 min at –78 °C. Then, it was hydrolyzed with sat. aq $NH_4Cl$ (10 mL), warmed to r.t. and partitioned between $H_2O$ and $Et_2O$. The aqueous phase was extracted with $Et_2O$ (3 × 25 mL), the combined organic phases were washed with brine, dried ($Na_2SO_4$) and concentrated in vacuo. Unreacted **2a** was separated from the crude by flash chromatography on silica gel (pentane/$Et_2O$ = 5/2 → 1/1). The mixed fractions of **25** and remaining sulfone **22** were dissolved in pyridine (3 mL) and treated with benzoyl chloride (50 µL). After stirring overnight at r.t., the mixture was hydrolyzed with sat. aq $NaHCO_3$ and partitioned between $H_2O$ and $Et_2O$. The aqueous phase was extracted with $Et_2O$ (3 × 10 mL) the combined organic phases were washed with aq. $NaHCO_3$ (2 × 20 mL) and with brine and dried ($Na_2SO_4$). After concentration in vacuo the crude product was coevaporated 3 times with toluene and dried under high vacuum. Subsequently, the crude benzoylated product was dissolved in anhyd EtOAc (4 mL) and anhyd MeOH (2 mL) under Ar. The mixture was cooled to –30 °C and treated with 5% sodium amalgam (560 mg, 1.20 mmol), then stirred at –20 °C for 5 h. After hydrolysis with sat. aq $NH_4Cl$ (10 mL) at –20 °C, the temperature was raised to r.t., and the liquid phase decanted from mercury. Water and $Et_2O$ were added, the aqueous phase was extracted with $Et_2O$ (3 × 10 mL), the combined organic phases were washed with brine and dried ($Na_2SO_4$). After concentration in vacuo, the crude product was purified by flash chromatography on silica gel (pentane/EtOAc = 5/1). The *trans*-alkene **25** was obtained in 35% yield (34 mg). $R_f$ = 0.36 (pentane /$Et_2O$ = 3/1).

$^1$H NMR (300 MHz, $CDCl_3$): δ = –0.16, 0.01 (2 × 3H, s), 0.12, 0.13 (2 × 3H, s), 0.87 (9H, s), 0.90 (3H, d, *J* = 6.7 Hz), 0.94 (12H, m), 1.36, 1.38 (2 x 3H, s), 1.30–1.50 (5H, m), 1.55–1.80 (3H, m), 1.88–1.98 (1H, m), 2.28–2.40 (1H, m), 3.16 (1H, m), 3.24 (3H, s), 3.39 (3H, s), 3.46 (3H, s), 3.52 (2H, m), 3.90 (1H, dd, *J* = 8.6, 2.0 Hz), 4.01 (1H, d, *J* = 8.6 Hz), 4.60 (1H, dd, *J* = 5.3 Hz), 5.38 (1H, dd, *J* = 15.7, 8.4), 5.63 (1H, dd, *J* = 15.7, 7.2), 7.18–7.30 (5H, m).

$^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = –4.96, –4.83, –4.53, 5.05, 14.60, 18.21, 19.49, 25.73, 25.84, 25.87, 25.99, 29.79 (2C), 31.22, 37.32, 40.98, 55.94, 56.68, 58.54, 73.85, 75.01, 75.77, 77.01, 83.62, 84.74, 91.50, 99.39, 101.1, 125.8, 126.7, 127.9, 139.3, 145.8.

Anal. Calcd. for $C_{42}H_{74}O_6Si_2$ (731.2): C, 68.99; H, 10.20. Found: C, 69.13; H, 10.35.

**Thexyldimethylsilyl 5-*O*-(*tert*-Butyldiphenylsilyl)-2-desmethyl-17-hydroxy-3-*O*-methyl-1,17-secosoraphenic ester (31)**

In a 100 mL flask the acid **30** (622 mg, 800 µmol) was dissolved in anhyd $CH_2Cl_2$ (40 mL) under Ar and treated at 0 °C with $Et_3N$ (600 µL, 4.30 mmol) and thexyldimethylsilyl chloride (200 µL, 1.02 mmol). After 20 min at r.t. the crude product **31** was directly used without workup in the next step. $R_f$ = 0.62 ($CH_2Cl_2$/MeOH = 20/1).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.27, 0.31 (2 × 3H, 2 s), 0.76 (3H, d, *J* = 7.4 Hz), 0.83 (3H, d, *J* = 6.8 Hz), 0.87 (2 × 3H, d, *J* = 9.6 Hz), 0.88 (2 × 3H, s), 1.08 (9H, s), 1.10–1.85 (10 × 1H, m), 2.34 (1H, m), 2.57 (1H, d, *J* = 15.4 Hz), 2.92 (1H, d, *J* = 15.3 Hz), 2.92, 3.24, 3.28, 3.40 (4 × 3H, 4 s), 3.14 (1H, m), 3.42 (1H, s), 3.54 (1H, dd, *J* = 8.4, 3.7 Hz), 3.82 (1H, dd, *J* =10.3, 2.1 Hz), 3.87 (1H, d, *J* = 1.9 Hz), 4.67 (1H, dd, *J* = 7.3, 5.9 Hz), 5.39 (1H, dd, *J* = 15.4, 8.5 Hz), 5.76 (1H, dd, *J* = 15.4, 7.7 Hz), 7.24–7.73 (15 × 1H, m).

$^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = –2.70, –2.67, 10.08, 15.79, 18.34, 18.41, 19.96, 20.06, 19.33, 25.73, 25.89, 26.87, 30.76, 30.90, 33.85, 34.75, 38.04, 39.05, 39.31, 47.75, 56.23, 57.25, 58.64, 70.48, 70.56, 74.52, 78.48, 83.76, 84.78, 101.1, 125.9, 126.2, 127.45, 127.5, 128.4, 129.6, 133.9, 134.4, 135.8, 136.0, 139.9, 144.9, 169.6.

**Thexyldimethylsilyl 17-Bromo-5-*O*-(*tert*-butyldiphenylsilyl)-2-desmethyl-17-deoxy-17-epi-3-*O*-methyl-1,17-secosoraphenic ester (33)**

The crude TDMS ester **31** was treated with $NEt_3$ (600 µL, 4.30 mmol) and a 2.6 M solution of α-bromoenamine **32** (1.54 mL, 4.00 mmol) in dibromomethane. After 1 h at r.t. the mixture was hydrolyzed with $H_2O$ (60.0 µL, 3.33 mmol), dried ($Na_2SO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel ($CH_2Cl_2$/$Et_2O$ = 0/1 → 20/1). Bromide **33** (715 mg, 728 µmol, 91% from **30**) was isolated as a light yellow oil. $R_f$ = 0.80 ($CH_2Cl_2$/MeOH = 20/1).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.29, 0.31 (2 × 3H, 2 s), 0.76 (3H, d, *J* = 7.4 Hz), 0.84 (3H, d, *J* = 7.1 Hz), 0.87 (2 × 3H, d, *J* = 9.5 Hz), 0.88 (2 × 3H, s), 1.08 (9H, s), 1.20–1.70 (10 × 1H, m), 2.33 (1H, m), 2.57 (1H, d, *J* = 15.4 Hz), 2.92 (1H, d, *J* = 15.3 Hz), 2.92, 3.25, 3.28, 3.40 (4 × 3H, 4 s), 3.15 (1H, m), 3.26 (1H, s), 3.52 (1H, dd, *J* = 8.5, 3.6 Hz), 3.82 (1H, dd, *J* =10.4, 2.0 Hz), 3.86 (1H, d, *J* = 2.1 Hz), 4.95 (1H, dd, *J* = 7.7, 7.4 Hz), 5.39 (1H, dd, *J* = 15.5, 8.3 Hz), 5.77 (1H, dd, *J* = 15.4, 7.7 Hz), 7.24–7.73 (15 × 1H, m).

$^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = –2.71, 10.09, 15.76, 18.34, 18.42, 19.32, 19.95, 20.05, 24.62, 25.16, 26.87, 28.35, 30.72, 33.83, 34.73, 38.02, 39.27, 39.97, 47.74, 55.56, 56.23, 57.26, 58.74, 70.43, 70.55, 78.44, 83.62, 84.80, 101.1, 126.2, 127.2, 127.5, 128.3, 129.6, 135.8, 136.0, 133.8, 134.4, 140.1, 146, 169.5.

MS (FAB, NBA + KCl): *m/z* = 1019, 1021.

MS (FAB, NBA ): *m/z* = 663, 661, 325, 323, 255, 239, 213, 199, 197, 157, 135, 91, 73.

Anal. Calcd. for $C_{53}H_{81}BrO_8Si_2$ (982.31): C, 64.81; H, 8.31. Found C, 64.41; H, 8.57.

**17-Bromo-5-*O*-(*tert*-butyldiphenylsilyl)-2-desmethyl-17-deoxy-17-epi-3-*O*-methyl-1,17-secosoraphenic acid (34)**

In a 25 mL flask, the TDMS ester **33** (220 mg, 224 µmol) was stirred in a mixture of acetone (8.0 mL), $H_2O$ (2.0 mL), and $Et_3N$ (0.5 mL) at r.t. After 15 min, the mixture was treated with a 1M aq. solution of $NaH_2PO_4$ (50 mL, pH = 4) and the aqueous phase extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were dried ($Na_2SO_4$), and concentrated in vacuo at r.t. The crude carboxylic acid **34** (236 mg) was isolated as a very unstable product and was directly used in the next step without further purification. $R_f$ = 0.42 ($CH_2Cl_2$/MeOH = 20/1).

**5-*O*-(*tert*-Butyldiphenylsilyl)-2-desmethyl-3-*O*-methyl-soraphen (35)**

In a 500 mL flask, the crude carboxylic acid **34** (236 mg) was dissolved in anhyd DMF (200 mL) under Ar and treated with finely powdered anhyd $Cs_2CO_3$ (1.00 g, 3.07 mmol). After 1 day the mixture was treated with a 1M aq solution of $NaH_2PO_4$ (500 mL) and the aqueous phase extracted with $Et_2O$ (5 × 100 mL). The combined organic phases were washed with water (3 × 100 mL), dried ($Na_2SO_4$), and concentrated in vacuo. After evaporation of residual DMF under high vacuum, the crude product **35** was purified by flash chromatography on silica gel ($CH_2Cl_2$/$Et_2O$ = 25/1 → 10/1). The protected norsoraphen **35** (85.0 mg, 112 µmol, 50% from **33**) was obtained as a white foam. $R_f$ = 0.52 ($CH_2Cl_2$/$Et_2O$ = 9/1).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.74 (3H, d, *J* = 7.4 Hz), 0.81 (3H, d, *J* = 6.6 Hz), 1.11 (9H, s), 1.14–1.73 (9 × 1H, m), 2.39 (1H, m),

2.61 (1H, d, *J* = 12.6 Hz), 2.86 (1H, d, *J* = 12.7 Hz), 3.02, 3.30, 3.41, 3.49 (4 × 3H, 4 s), 3.12 (1H, d, *J* =1.9 Hz), 3.42 (1H, m), 3.77 (1H, dd, *J* = 8.8, 1.9 Hz), 3.95 (1H, d, *J* =1.9 Hz), 4.09 (1H, dd, *J* = 10.4, 2.5 Hz), 5.36 (1H, ddd, *J* = 16.2, 8.8, 1.0 Hz), 6.11 (1H, dd, *J* = 11.6, 1.6 Hz), 6.32 (1H, dd, *J* = 16.2, 4.4 Hz), 7.20–7.70 (15 × 1H, m).

$^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = 10.22, 12.68, 19.40, 24.15, 25.08, 27.11, 30.49, 34.92, 35.3, 36.44, 38.99, 52.42, 56.31, 57.97, 58.28, 72.16, 72.34, 72.47, 76.14, 83.72, 84.80, 101.1, 121.6, 126.3, 127.6, 127.6, 127.7, 128.35, 129.8, 139.9, 135.8, 135.9, 133.8, 133.9, 140.75, 141.9, 168.6.

MS (FAB, NBA + KCl): *m/z* = 797.

MS (FAB, NBA ): *m/z* = 727, 312, 255, 240, 239, 213, 197, 157, 135, 91.

Anal. Calcd. for $C_{45}H_{62}O_8Si$ (759.08): C, 71.21; H, 8.23. Found: C, 71.03; H, 8.32. The major byproduct of this reaction was the styrene derivative originating from elimination of HBr in **33**.

**Selective monomethylation of 2-norsoraphen (36). Synthesis of 3,7-secosoraphen (36)**

In a 10 mL flask norsoraphen **36** (10.0 mg, 19.7 μmol) and potassium 2,6-di-*tert*-butylphenolate (10.0 mg, 40.9 μmol) were dissolved in anhyd DMF (1 mL) under Ar. The mixture was stirred for 24 h at r.t., then it was poured on basic molecular sieves (4 Å, which had been previously treated with $Et_3N$) and diluted with anhyd DMF (2 mL). After cooling to 0 °C, MeI (1.00 mL, 16.0 mmol) was added and, after 30 min, hydrolysis with sat. aq $NH_4Cl$ (1 mL) was performed. After addition of $Et_2O$ (100 mL), the crude was washed with sat. aq $NH_4Cl$ (30 mL) and $H_2O$ (2 × 30 mL), dried ($Na_2SO_4$), and concentrated in vacuo . The crude secosoraphen **37** (10.5 mg) was used without further purification in the cyclization step to soraphen **1**. Note: when this reaction was carried out on a smaller scale, it was only reproducible when using a polyethylene flask because of the acidity of the glass surface.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.03 (3H, d, *J* = 6.6 Hz), 1.07 (3H, d, *J* = 6.8 Hz), 1.20–1.92 (8 × 1H, m), 1.28 (3H, d, *J* = 7.0 Hz), 1.92 (1H, m), 2.31 (1H, m), 3.15 (1H, m), 3.17 (1H, m), 3.35, 3.41, 3.49 (3 × 3H, 3 s), 3.71 (1H, q, *J* = 7.0 Hz), 3.90 (1H, dd, *J* = 6.0, 2.1 Hz), 3.99 (1H, dd, *J* = 10.0, 2.0 Hz), 4.50 (1H, d, *J* = 2.0 Hz), 5.50 (1H, dd, *J* = 16.0, 6.0 Hz), 5.70 (1H, dd, *J* = 6.9, 6.9 Hz), 5.87 (1H, dd, *J* = 16.0, 7.4 Hz), 7.30 (5 × 1H, m).

$^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = 8.5, 11.9, 14.7, 25.1, 25.2, 28.5, 34.7, 38.2, 39.5, 48.8, 57.3, 58.0, 58.8, 74.5, 76.1, 77.6, 82.2, 83.5, 85.1, 126.4, 127.3, 128.2, 128.5, 137.2, 139.1, 169.5, 203.1.

**Ring closure of secosoraphen 37 to soraphen $A_{1\alpha}$ (1)**

In a 25 mL flask the crude secosoraphen **37** (10.5 mg) was dissolved in THF (10 mL) and stirred with 1M HCl (5 mL) for 12 h at r.t. Then, $Et_2O$ (50 mL) was added and the two phases were separated. The organic phase was washed with $H_2O$ (2 × 20 mL), dried ($Na_2SO_4$), and concentrated in vacuo. The crude product was purified by HPLC (RP-18 column; gradient $CH_3CN/H_2O$ = 1/1→1/3). Soraphen $A_{1\alpha}$ (**1**) (7.21 mg, 13.8 μmol, 70% from norsoraphen **36**) was isolated as a white foam. $R_f$ = 0.37 (RP, $CH_3CN/H_2O$ = 2/1).

$^1$H NMR (300 MHz, $CDCl_3$): δ = 1.03 (3H, d, *J* = 6.9 Hz), 1.06 (3H, d, *J* = 7.6 Hz), 1.11 (3H, d, *J* = 7.1 Hz), 1.15–1.50 (5 × 1H, m), 1.66–1.74 (2 × 1H, m), 1.93 (1H, m), 2.10 (1H, m), 2.50 (1H, m), 3.14 (1H, q, *J* = 7.1 Hz), 3.18 (1H, d, *J* = 1.9 Hz), 3.29, 3.38, 3.44 (3 × 3H, 3 s), 3.42 (1H, m), 3.64 (1H, br s), 3.69 (1H, dd, *J* = 9.4, 2.2 Hz), 3.83 (1H, dd, *J* = 10.5, 2.7 Hz), 4.02 (1H, br s), 4.39 (1H, s), 5.48 (1H, ddd, *J* = 16.1, 9.5, 1.8 Hz), 5.86 (1H, dd, *J* = 11.0, 3.9 Hz), 6.19 (1H, dd, *J* = 16.1, 3.7 Hz), 7.26–7.37 (5 × 1H, m).

$^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = 10.3, 11.5, 12.4, 23.3, 25.7, 30.4, 35.4, 35.6, 35.7, 46.3, 56.1, 57.2, 58.0, 68.9, 72.4, 74.4, 76.3, 82.8, 85.0, 99.5, 122.8, 126.2, 128.2, 128.5, 139.6, 141.1, 170.8. These data were in full agreement with the data published in ref. 1.

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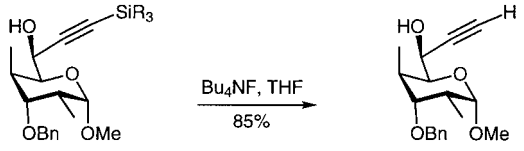
(9) Structure proof: A X-ray crystal structure analysis of **17** ($SiR_3$ = TBDMS) was obtained which confirmed the *erythro* configuration at C–6. The configuration of the other addition products was proved by comparing their NMR data with those of the desilylated compound obtained from **17** ($SiR_3$ = TBDMS).

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