10. The Enantioselective Synthesis of the 'Southern Part' of Soraphen A

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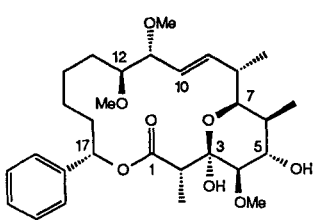
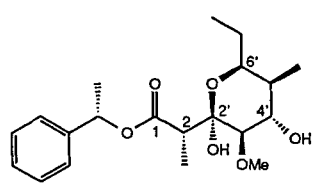
Using a series of enantioselective aldol condensations followed by an ester enolate addition, the cyclic hemiacetal **2** was prepared stereospecifically. Hemiacetal **2** represents the synthetically most challenging 'southern part' of the antifungal macrolide soraphen A (**1**). Spontaneous enolisation of **26**, the C(2) epimer of **2**, revealed that **2** is the most stable diastereoisomer at room temperature.

Introduction. – Soraphen A (**1**) is a macrolide isolated from the myxobacterial strain *Sorangium cellulosum* by *Höfle* and coworkers [1]. It was shown to exhibit potent fungicidal activity against a variety of plant pathogenic fungi [2]. In an attempt to mimic the fungicidal activity of soraphen A with a compound of simpler structure, we chose the model compound **2** representing the 'southern part' of the soraphen molecule. This compound comprises the Ph ring, the ester moiety, and the tetrahydropyran ring containing all the functionalities found in the natural product. One of the moieties found in this compound is the hemiacetal group, which in soraphen A (**1**) itself undergoes tautomerisation to the hydroxy-ketone form, and further to the enol of the resultant β-keto ester [3].



1 soraphen A



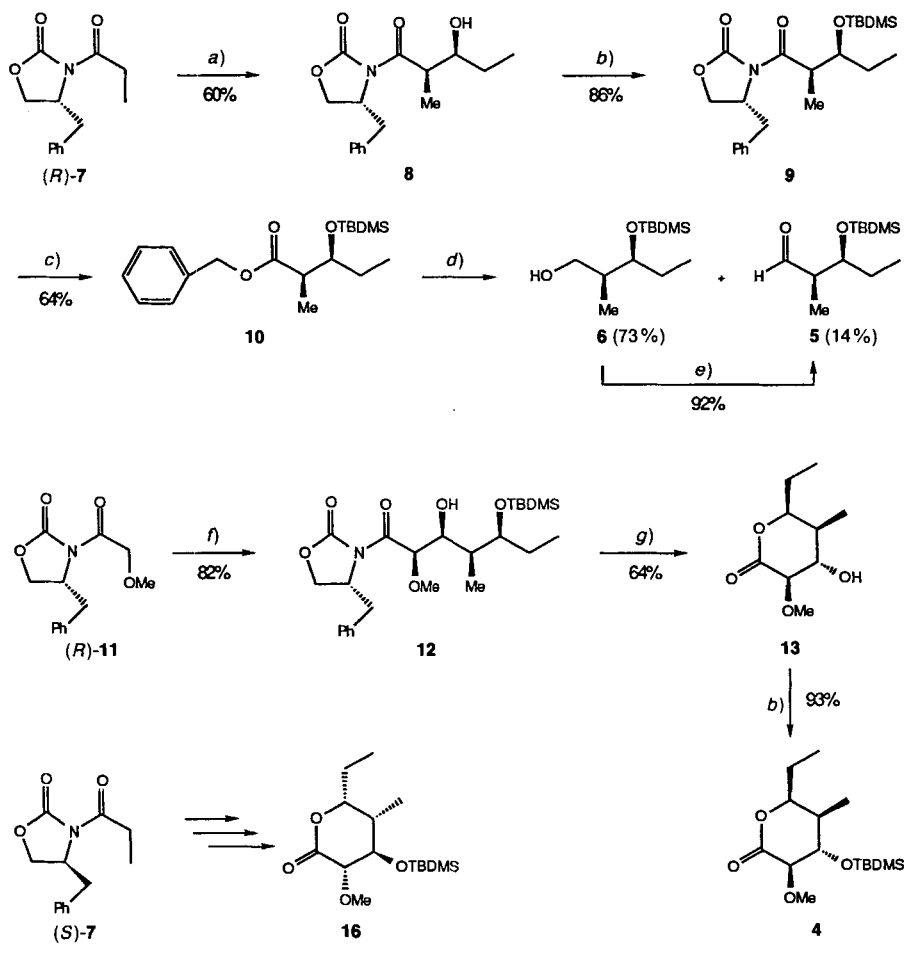
2 model compound

Results and Discussion. – In the synthesis of simpler analogs of the target molecule **2**, we observed that the addition of ester enolates to lactones [4] (*Meinwald* reaction) is a reaction which tolerates considerable variation [5]. Thus, it was chosen for the synthesis of the target compound **2** (see below, *Table*). The ester component **3** is trivial, but lactone **4** requires more careful consideration. This part of the soraphen A molecule itself is biosynthesized in the bacterium by a polyketide synthase [6]. It is, therefore, amenable to stereoselective synthesis using chiral aldol reagents [7], which have often served as build-

ing blocks for the synthesis of complex polyketide units. One class of these reagents which has found wide application stems from the chiral oxazolidinones introduced by *Evans* [8]. The chemistry of these compounds is well understood, and the direction and extent of the stereoselectivity is predictable.

For the synthesis of lactone **4** using this methodology, aldehyde **5** was required (*Scheme 1*). The corresponding alcohol **6** has been prepared previously by a stereoselective aldol reaction using a noncommercial camphor-derived sultam as a chiral auxiliary (96% ee) [9]. The enantiomer of **6** has been prepared by yet another stereoselective aldol synthesis from a noncommercial camphor-derived oxazolidinone (98% ee) [10]. The required aldehyde **5** has been obtained by degradation of a S-containing analog produced by bakers-yeast reduction of a β-keto-ester starting material (> 95% ee) [11]. The enan-

Scheme 1



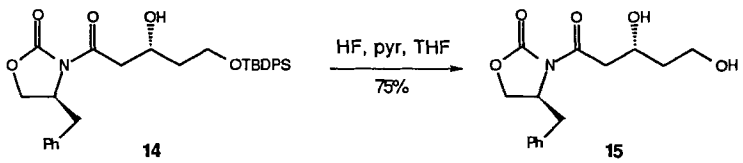
a) Et_3N, Bu_2BOTf, EtCHO, CH_2Cl_2. *b*) TBDMSCl, 1*H*-imidazole, DMF. *c*) $PhCH_2OLi$, THF. *d*) i-Bu_2AlH, CH_2Cl_2. *e*) SO_3·pyr, DMSO. *f*) Et_3N, Bu_2BOTf, **5**, CH_2Cl_2. *g*) HF, pyr, THF.

tiomer of **5**, finally has been prepared in several steps from levoglucusam [12], and very recently by a route similar to the one described here using the *Evans* oxazolidinone (*S*)-**7** [13].

Starting with the (4*R*)-oxazolidinone (*R*)-**7** [14], the aldol product **8** [13] was obtained from the enol boronate in 60% yield and protected with the (*t*-Bu)Me_2Si (TBDMS) group in high yield (*Scheme 2*). Reduction of **9** with $LiAlH_4$ [15] led to alcohol **6** [10] in only 33% yield[1]). The by-product isolated resulted from reductive opening of the oxazolidinone ring. The conversion of **9** to **6** was, therefore, performed in two steps. Replacement of the chiral auxiliary with benzyl alcoholate [16] led to **10**, and reduction of this ester with (i-Bu)$_2$AlH gave alcohol **6** in 73% yield. In addition, the desired aldehyde **5** was isolated in 14% yield. Alcohol **6** was then oxidised cleanly under *Doering*'s conditions [17] to the required aldehyde **5** [11] in excellent yield and complete diastereoisomeric purity as determined by ^{1}H-NMR. *Cane et al.* [13] used another sequence for removing the chiral auxiliary and forming aldehyde **5**. Transamidation of **8** with an aluminate of *N*,*O*-dimethyl-hydroxylamine, silylation of the OH group, and (i-Bu)$_2$AlH reduction afforded aldehyde **5** in 87% yield[1]).

Aldehyde **5** served as starting material for the next stereoselective aldol reaction. Treatment of the enol boronate of (*R*)-**11** [18] with **5** gave diastereoisomerically pure **12** in high yield. Removal of the silyl group under mild conditions [19] was accompanied by ring closure forming the desired lactone **13** in 64% yield. The same reaction conditions applied to the less substituted compound **14** led only to deprotection (→ **15**; *Scheme 2*) [5], and more severe conditions were subsequently required to invoke lactonisation. We

Scheme 2



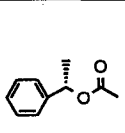
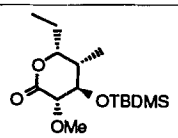
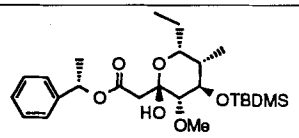
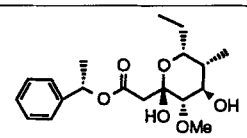
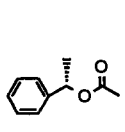
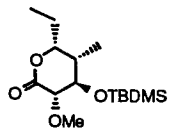
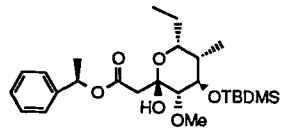
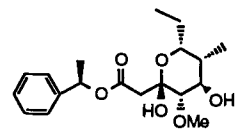
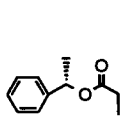
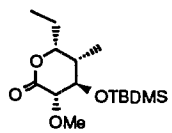
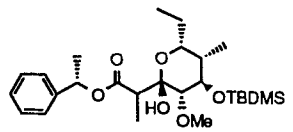
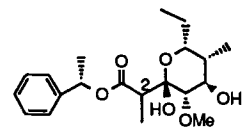
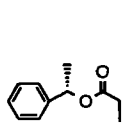
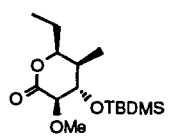
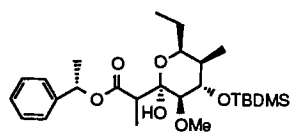
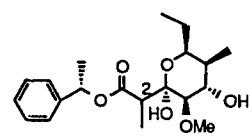
14 **15**

attribute the rapid ring closure of **12** to the presence of the various substituents which bias the conformational population towards ring closure in analogy with the gem-dimethyl effect [20] as originally observed by *Thorpe* and *Ingold* [21]. Silylation of **13** led to the required lactone **4** in high yield. The enantiomer **16** of lactone **4** was prepared by an identical series of steps in similar yields starting from (*S*)-**7**.

First attempts to use the unprotected lactone **13** for the *Meinwald* coupling with the enolates of the esters **3** and **17** gave disappointingly low yields. However, when the corresponding 4-{[(*tert*-butyl)dimethylsilyl]oxy}lactones **4** and **16** were employed, the additions were much cleaner, and the products **18**–**21** were obtained in better yields (*Table*). For example, **18**, the (*t*-Bu)Me_2Si ether of **22**, was isolated in 71% yield in comparison to 20% of **22** when the unprotected lactone was used as substrate. Lithium tetramethylpiperidine (LTMP) was used for the preparation of the enolates of the esters **3**, **17**, and *ent*-**17**, as we had previously shown that this base ensures high yields of enolates of benzylic esters [22]. Deprotection of the 4′-silyloxy group with Bu_4NF led to the desired products **2** and **22**–**26** in acceptable yields.

[1]) This experiment was performed in the enantiomeric series.

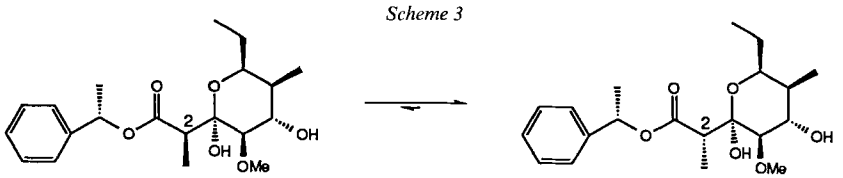
Table. *Condensation of Ester Enolates on Lactones* **16** *and* **4**

Ester	Lactone	Intermediate	Product
 **17**	 **16**	 **18** (71%)	 **22** (67%)
 *ent*-**17**	 **16**	 **19** (82%)	 **23** (89%)
 **3**	 **16**	 **20** (66%)	 **24/25** (49%)
 **3**	 **4**	 **21**	 **2/26** (31%)[a]

[a]) Yield over two steps.

When propionate **3** was used, mixtures of C(2) epimers were formed, *i.e.*, **24/25** from **16** and **2/26** from **4** (*Table*). On attempted separation of **2/26** by chromatography on silica gel, it became clear that **2** was the more stable epimer. Indeed, **2** was isolated in pure form, but **26** was continually obtained in a mixture with **2**. Even on standing in $CDCl_3$, **26** epimerized through a series of hydroxy ketone and enol tautomers completely to **2** within 3–4 weeks (*Scheme 3*). The natural product soraphen A (**1**) shows similar behaviour. Hydroxy ketone or enol tautomers of **1** are converted completely to diastereoisomerically pure **1** on equilibration. From the behaviour of the model compounds **2** and **26**, it is now apparent that the hemiacetal diastereoisomer of soraphen A is favoured over other tautomer/epimer combinations due to the spacial arrangement of substituents in the 'southern part' of **1** rather than to any influence of the macrocycle ring.

Scheme 3



Compounds **2** and **26** exhibited no fungicidal activity when tested against a series of plant pathogens in greenhouse trials[2]). Neither did they inhibit acetyl-coenzyme A carboxylase at concentrations up to 300 times the IC_{50} of soraphen A [25][3]). Thus our initial goal was not achieved. However, from a broader perspective, this work may serve as a guideline for a total synthesis of **1**.

Experimental Part

General. Solvents (*Fluka* or *Merck*, *puriss.*) were used without further distillation. THF was freshly distilled from Na/benzophenone under Ar. Glassware was dried with a flame and cooled under N_2. Flash chromatography (FC): *Merck* silica gel *60* (230–240 mesh). No attempts were made to isolate minor diastereoisomers; thus, no d.e.'s are given. All products isolated, however, were > 95% pure according to ^{1}H-NMR. M.p.: *Büchi-535* apparatus; not corrected. $[\alpha]_D$: *Perkin-Elmer 241* polarimeter; at 23 ± 2°. IR Spectra: *Perkin-Elmer-1420* spectrophotomer; in cm^{-1}. ^{1}H-NMR Spectra: *Varian-Unity-500* (500 MHz), *Bruker-ACF-250* (250 MHz), or *Bruker-AM-400* (400 MHz) spectrometer; δ in ppm rel. to $SiMe_4$ as internal standard, J in Hz. MS: electron impact (EI, 8 keV) or field desorption (FD); m/z (rel. %).

*(2′R,3′S,4R)-4-Benzyl-3-{[(3′-(*tert*-butyl)dimethylsilyloxy]-2′-methylpentanoyl}oxazolidin-2-one* (**9**). To a soln. of **8** (39 g, 133.8 mmol; prepared according to [13]) in DMF (260 ml) at 0° under Ar, 1*H*-imidazole (10.9 g, 160 mmol) and (*t*-Bu)Me_2SiCl (22.19 g, 147.2 mmol) were successively added. The mixture was stirred 24 h at r.t., then ice was added. The mixture was extracted with CH_2Cl_2, the extract washed with H_2O, dried (Na_2SO_4), and evaporated, and the residue submitted to FC (AcOEt/hexane 1:4): 46.3 g (86%) of **9**. M.p. 93–94°. $[\alpha]_D = -50.6$ ($c = 1.72$, $CHCl_3$). IR: 1700 (C=O), 1775 (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.00 (*s*, MeSi); 0.04 (*s*, MeSi); 0.9 (*s*, *t*-BuSi); 0.91 (*t*, $J = 7.5$, 3 H–C(5′)); 1.2 (*d*, $J = 7$, Me–C(2′)); 1.57 (*m*, 2 H–C(4′)); 2.76 (*dd*, $J = 13$, 9, 1 H, PhCH_2); 3.30 (*dd*, $J = 13$, 3.5, 1 H, PhCH_2); 3.88 (*dq*, $J = 7$, 7, H–C(2′)); 3.96 (*dt*, $J = 6$, 6, H–C(3′)); 4.17 (*m*, 2 H–C(5)); 4.60 (*m*, H–C(4)); 7.20–7.36 (*m*, arom. H). FD-MS: 406 ($[M + H]^+$), 348 ($[M - t\text{-Bu}]^+$). Anal. calc. for $C_{22}H_{35}NO_4Si$: C 65.15, H 8.70, N 3.45; found C 65.10, H 8.50, N 3.30.

*Benzyl (2R,3S)-3-[(*tert*-Butyl)dimethylsilyloxy]-2-methylpentanoate* (**10**). Under Ar, 1.6M BuLi in hexane (81.4 ml, 130.2 mmol) was slowly added to a soln. of benzyl alcohol (22.5 ml, 217 mmol) in dry THF (440 ml) at 0°. The mixture was stirred 30 min at 0°, then cooled to −10°, and a soln. of **9** (41 g, 101.1 mmol) in THF (120 ml) was added. The mixture was stirred 5 h at this temp., then sat. NH_4Cl soln. was added. The mixture was extracted with Et_2O, the extract washed with H_2O, dried (Na_2SO_4), and evaporated, and the residue submitted to FC (AcOEt/hexane 1:5): 21.60 g (64%) of **10**. IR: 1730 (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.00 (*s*, MeSi); 0.03 (*s*, MeSi); 0.84 (*t*, $J = 7.5$, 3 H–C(5)); 0.85 (*s*, *t*-BuSi); 1.15 (*d*, $J = 7$, Me–C(2)); 1.49 (*m*, 2 H–C(4)); 2.61 (*qd*, $J = 7$, 7, H–C(2)); 3.96 (*dt*, $J = 6$, 6, H–C(3)); 5.08 (*d*, $J = 12$, 1 H, PhCH_2); 5.14 (*d*, $J = 12$, 1 H, PhCH_2); 7.30–7.40 (*m*, arom. H).

*(2S,3S)-3-[(*tert*-Butyl)dimethylsilyloxy]-2-methylpentan-1-ol* (**6**). Under Ar, 1M (i-Bu)$_2$AlH in CH_2Cl_2 (44.1 ml, 44.1 mmol) was added to a soln. of **10** (13.5 g, 40.06 mmol) in toluene (70 ml) at −60°. The mixture was stirred 5 h at −60°, then more (i-Bu)$_2$AlH (16 ml, 16 mmol) was added and the mixture stirred again 2 h at −60°. The mixture was then poured into cold NH_4Cl soln. and acidified to pH 1 with 1M H_2SO_4. The product was extracted with toluene, the org. layer washed with aq. sat. $NaHCO_3$ and NaCl soln., dried (Na_2SO_4), and evaporated, and the residue submitted to FC (Et_2O/hexane 1:11): 1.3 g (14%) of **5** and 6.8 g (73%) of **6** [11]. $[\alpha]_D = -2.9$ ($c = 1.39$, $CHCl_3$; [11]: $[\alpha]_D = -3.1$ ($c = 2.1$, $CHCl_3$)).

*(2R,3S)-3-[(*tert*-Butyl)dimethylsilyloxy]-2-methylpentanal* (**5**). Under Ar, Et_3N (34.8 ml, 250 mmol) and a soln. of pyridine-sulfur trioxide (23.87 g, 150 mmol) in DMSO (90 ml) were successively added to a soln. of **6** (5.3 g, 22.8 mmol) in DMSO/CH_2Cl_2 1:1 (140 ml). The mixture was stirred 90 min at r.t. and then diluted with Et_2O and poured into ice-water. The product was extracted with Et_2O, the org. layer washed with H_2O and aq. sat. NaCl soln., dried ($MgSO_4$), and evaporated, and the residue submitted to FC (AcOEt/hexane 1:5): 4.81 g (92%) of **5** [11]. $[\alpha]_D = -53.3$ ($c = 1.01$, $CHCl_3$; [11]: $[\alpha]_D = -49.6$ ($c = 11.43$, $CHCl_3$); [13] and [12]: $[\alpha]_D = +22.7$ ($c = 2.4$, $CHCl_3$) and +62 ($c = 1$), resp. for enantiomer).

*(2′R,3′S,4R,4′S,5′S)-4-Benzyl-3-{[5′-(*tert*-Butyl)dimethylsilyloxy]-3′-hydroxy-2′-methoxy-4′-methylheptanoyl}oxazolidin-2-one* (**12**). Under Ar, Et_3N (5.34 ml, 38.32 mmol) and 1M dibutylboryl triflate in CH_2Cl_2 (35.37 ml, 35.37 mmol) were successively added to a soln. of (*R*)-**11** [18] (8.1 g, 32.62 mmol) in CH_2Cl_2 (80 ml) at −78°. The

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[2]) We thank Dr. *Roland Zeun* and his colleagues, *Ciba*, for screening these compounds.

[3]) The tests described here were performed by *Michelle Moreau*, *Susan Schenk*, and *Jacqueline Schmidt*, *Ciba*, Basel.

mixture was stirred 1 h at −78°, 15 min at 0°, and then cooled again to −78°. A soln. of **5** (6.78 g, 29.48 mmol) in CH_2Cl_2 (2 ml) was then added in 1 portion. The mixture was stirred 1 h at −78°, warmed to 0°, and stirred 1 h at 0°. Then 1M NaOAc in MeOH/H_2O 9:1 (210 ml) was added. After 5 min stirring, 30% H_2O_2 soln. (10 ml) was slowly added and the mixture stirred again 15 min at 10–15°. Then H_2O (400 ml) and hexane (400 ml) were added. The org. layer was washed with aq. sat. $NaHCO_3$ and NaCl soln., dried (Na_2SO_4), and evaporated, and the residue submitted to FC (AcOEt/hexane 1:4): 11.5 g (82%) of **12**. $[\alpha]_D = -18$ ($c = 1$, $CHCl_3$). IR: 1710 (C=O), 1780 (C=O), 3560 (OH). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.05 (*s*, MeSi); 0.06 (*s*, MeSi); 0.85 (*t*, $J = 7.5$, 3 H–C(7′)); 0.88 (*s*, *t*-BuSi); 0.98 (*d*, $J = 6$, Me–C(4′)); 1.55 (*dq*, $J = 7$, 2 H–C(6′)); 1.85 (*m*, H–C(5′)); 2.39 (*d*, $J = 6$, OH); 2.85 (*dd*, $J = 13$, 9, 1 H, PhCH_2); 3.40 (*dd*, $J = 13$, 3.5, 1 H, PhCH_2); 3.49 (*s*, MeO); 3.67 (*m*, H–C(3′)); 4.01 (*m*, H–C(4′)); 4.22 (*d*, $J = 4$, 2 H–C(5)); 4.71 (*m*, H–C(4)); 5.11 (*d*, $J = 4$, H–C(2′)); 7.22–7.38 (*m*, arom. H).

*(3*R*,4*S*,5*S*,6*S*)-6-Ethyltetrahydro-4-hydroxy-3-methoxy-5-methyl-2*H*-pyran-2-one* (**13**). Compound **12** (10.4 g, 21.7 mmol) was dissolved in HF/pyr/THF [19] (30 ml). The mixture was stirred 120 h at r.t., then diluted with AcOEt, washed with H_2O, 2M HCl, and H_2O, and dried (Na_2SO_4). FC (Et_2O/hexane 10:1) afforded 2.6 g (64%) of **13**. $[\alpha]_D = -5$ ($c = 1.18$, $CHCl_3$). IR: 1750 (C=O), 3580 (OH). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.01 (*t*, $J = 7$, *Me*CH_2); 1.02 (*d*, $J = 7$, Me–C(5)); 1.56, 1.77 (2*m*, MeCH_2); 2.07 (*m*, H–C(5)); 2.55 (*d*, $J = 2$, OH); 3.60 (*ddd*, $J = 7.5$, 7.5, 2, H–C(4)); 3.66 (*s*, MeO); 3.70 (*d*, $J = 7.5$, H–C(3)); 4.42 (*m*, H–C(6)). FD-MS: 189 ([M + H]$^+$).

*(3*R*,4*S*,5*R*,6*S*)-4-[(*tert*-Butyl)dimethylsilyloxy]-6-ethyltetrahydro-3-methoxy-5-methyl-2*H*-pyran-2-one* (**4**). A soln. of **13** (410 mg, 2.18 mmol) in DMF (2 ml) was added to a soln. of (*t*-Bu)Me_2SiCl (394.5 mg, 2.62 mmol) and 1*H*-imidazole (178.2 mg, 2.62 mmol) in DMF (5 ml). The mixture was stirred 18 h at r.t., then ice was added. The mixture was extracted with AcOEt, the org. layer washed with H_2O, 1M HCl, and H_2O, dried (Na_2SO_4), and evaporated, and the residue submitted to FC (AcOEt/hexane 1:5): 612 mg (93%) of **4**. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.10 (*d*, $J = 7$, Me_2Si); 0.90 (*s*, *t*-BuSi); 0.92 (*d*, $J = 7.5$, Me–C(5)); 1.02 (*t*, $J = 7.5$, *Me*CH_2); 1.52, 1.79 (2*m*, MeCH_2); 1.90 (*m*, H–C(5)); 3.57 (*dd*, $J = 1.5$, 6, H–C(4)); 3.60 (*s*, MeO); 3.79 (*d*, $J = 6$, H–C(3)); 4.45 (*ddd*, $J = 2.5$, 5, 8, H–C(6)).

*(3*S*,4*R*,5*S*,6*R*)-4-[(*tert*-Butyl)dimethylsilyloxy]-6-ethyltetrahydro-3-methoxy-5-methyl-2*H*-pyran-2-one* (**16**) was prepared using the same methodology as for **4**, but starting from (*S*)-**7** instead of (*R*)-**7**. ^{1}H-NMR: identical to those of the enantiomeric compounds described above.

*(1*S*)-1-Phenylethyl [(3′*S*,4′*R*,5′*R*,6′*R*)-6′-Ethyltetrahydro-2′,4′-dihydroxy-3′-methoxy-5′-methyl-2*H*-pyran-2′-yl]acetate* (**22**). *a*) Under Ar, 1.6M BuLi in hexane (149 µl, 0.238 mmol) was slowly added to a soln. of 2,2,6,6-tetramethylpiperidine (40 µl, 0.238 mmol) in dry THF (0.1 ml) at 0°. The mixture was stirred for 45 min and then cooled to −78°, and a soln. of **17** (39 mg, 0.238 mmol) in dry THF (0.15 ml) was slowly added. After 45 min at −78°, a soln. of **16** (60 mg, 0.198 mmol) in dry THF (0.1 ml) was slowly added. The mixture was stirred 4 h at −78° and 45 min at 0° and then quenched with aq. sat. NH_4Cl soln. (0.15 ml). The mixture was allowed to warm to r.t. and extracted with AcOEt. The org. layer was washed with H_2O, dried (Na_2SO_4), and evaporated. FC (AcOEt/hexane 1:3) yielded 65 mg (71%) of **18**. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.2 (*d*, $J = 3.8$, Me_2Si); 0.9 (*m*, *t*-BuSi, *Me*CH_2); 1.0 (*d*, $J = 7.5$, Me–C(5′)); 1.40 (*m*, MeCH_2); 1.55 (*d*, $J = 6.5$, Me); 1.60 (*m*, H–C(5′)); 2.68 (*d*, $J = 15$, 1 H–C(2)); 2.94 (*d*, $J = 15$, 1 H–C(2)); 3.30 (*s*, MeO); 3.39 (*m*, H–C(3′)); 4.05 (*m*, H–C(4′), H–C(6′)); 5.50 (*d*, $J = 2.5$, OH–C(2′)); 5.92 (*q*, $J = 6.5$, PhCH); 7.29–7.41 (*m*, arom. H).

b) A soln. of Bu_4NF (1M in THF, 131 µl, 0.131 mmol) was added to **18** (61 mg, 0.131 mmol) in THF (1 ml), and the mixture was stirred 45 min at r.t. AcOH (10 µl) was added and half of the solvent removed under vacuum. FC (AcOEt/hexane 1:3) afforded 31 mg (67%) of **22**. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.90 (*t*, $J = 7.5$, *Me*CH_2); 1.0 (*d*, $J = 7.5$, Me–C(5′)); 1.39, 1.55 (2*m*, MeCH_2); 1.56 (*d*, $J = 6.5$, Me); 1.78 (*m*, H–C(5′)); 2.51 (*d*, $J = 15$, 1 H–C(2)); 3.0 (*d*, $J = 15$, 1 H–C(2)); 3.14 (*dd*, $J = 1$, 2.5, H–C(3′)); 3.37 (*s*, MeO); 3.69 (*d*, $J = 10$, OH–C(4′)); 3.86 (*ddd*, $J = 2.5$, 2.5, 11, H–C(4′)); 4.14 (*ddd*, $J = 3$, 6, 8, H–C(6′)); 5.55 (*s*, OH–C(2′)); 5.94 (*q*, $J = 6.5$, PhCH); 7.28–7.38 (*m*, arom. H).

*(1*R*)-1-Phenylethyl [(3′*S*,4′*R*,5′*R*,6′*R*)-6′-Ethyltetrahydro-2′,4′-dihydroxy-3′-methoxy-5′-methyl-2*H*-pyran-2′-yl]acetate* (**23**). *a*) Using the procedure *a* described for **22**, but stirring for 2 h at −78° and 2 h at −10° before workup: 80 mg (82%) of **19**. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.11 (*d*, $J = 2$, Me_2Si); 0.9 (*t*, $J = 7.5$, *Me*CH_2); 0.92 (*s*, *t*-BuSi); 1.0 (*d*, $J = 7.5$, Me–C(5′)); 1.40 (*m*, MeCH_2); 1.55 (*d*, $J = 6.5$, Me); 1.60 (*m*, H–C(5′)); 2.67 (*d*, $J = 15$, 1 H–C(2)); 2.98 (*dd*, $J = 2$, 15, 1 H–C(2)); 3.35 (*dd*, $J = 1$, 2.5, H–C(3′)); 3.40 (*s*, MeO); 4.05 (*m*, H–C(4′), H–C(6′)); 5.46 (*d*, $J = 2.5$, OH–C(2′)); 5.92 (*q*, $J = 6.5$, PhCH); 7.21–7.40 (*m*, arom. H).

b) Treatment of **19** with Bu_4NF, using procedure *b* described for **22** yielded 50 mg (89%) of **23**. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.75 (*t*, $J = 7.5$, *Me*CH_2); 0.98 (*d*, $J = 7$, Me–C(5′)); 1.33, 1.43 (2*m*, MeCH_2); 1.57 (*d*, $J = 6.5$, Me); 1.75 (*m*, H–C(5′)); 2.58 (*d*, $J = 15$, 1 H–C(2)); 2.98 (*d*, $J = 15$, 1 H–C(2)); 3.18 (*dd*, $J = 1$, 2.5, H–C(3′)); 3.42 (*s*, MeO); 3.65 (*d*, $J = 10$, OH–C(4′)); 3.85 (*ddd*, $J = 2.5$, 2.5, 11, H–C(4′)); 4.08 (*ddd*, $J = 3$, 6, 8, H–C(6′)); 5.46 (*s*, OH–C(2′)); 5.95 (*q*, $J = 6.5$, PhCH); 7.27–7.39 (*m*, arom. H).

(1S)-1-Phenylethyl [(3'S,4'R,5'R,6'R)-6'-Ethyltetrahydro-2',4'-dihydroxy-3'-methoxy-5'-methyl-2H-pyran-2'-yl]propanoate (**24/25**). *a*) Using the procedure *a*) described for **22**, but stirring for 2 h at −80° and 4 h at −10°, then warming to r.t. before quenching with NH_4Cl afforded 158 mg (66%) of **20** (C(2) epimer mixture 1:1). ^{1}H-NMR (500 MHz, $CDCl_3$): 0.11 (*m*, 2 Me_2Si); 0.90 (*s*, *t*-BuSi); 0.93 (*s*, *t*-BuSi); 0.89–0.95 (*m*, 2 Me); 0.97 (*d*, *J* = 7.5, Me); 1.00 (*d*, *J* = 7.5, Me); 1.14 (*d*, *J* = 7.5, Me); 1.26 (*m*, MeCH_2); 1.33 (*d*, *J* = 7.5, Me); 1.53 (*d*, *J* = 7.5, Me); 1.56 (*d*, *J* = 7.5, Me); 1.60 (*m*, H–C(5')); 3.02 (*dd*, *J* = 1, 2.5, H–C(3')); 3.06 (*qd*, *J* = 1.5, 7, H–C(2)); 3.09 (*qd*, *J* = 1, 7, H–C(2)); 3.12 (*s*, MeO); 3.31 (*dd*, *J* = 1, 3, H–C(3')); 3.36 (*s*, MeO); 4.05 (*m*, H–C(4'), H–C(6')); 5.24 (*d*, *J* = 1, OH–C(2')); 5.42 (*d*, *J* = 2, OH–C(2')); 5.92 (*m*, PhC*H*); 7.28–7.40 (*m*, arom. H).

b) Treatment of **20** Bu_4NF, using the procedure *b* drescribed for **22** afforded 29.8 mg of pure **24** and 24.6 mg of **24/25** 5:8 (49%).

24: ^{1}H-NMR (500 MHz, $CDCl_3$): 0.90 (*t*, *J* = 7.5, *Me*CH_2); 1.01 (*d*, *J* = 7.5, Me–C(2)); 1.13 (*d*, *J* = 7.5, Me–C(5')); 1.39 (*m*, MeCH_2); 1.57 (*d*, *J* = 6.5, Me); 1.79 (*m*, H–C(5')); 3.10 (*q*, *J* = 7.5, H–C(2)); 3.18 (*dd*, *J* = 1, 2.5, H–C(3')); 3.40 (*s*, MeO); 3.58 (*m*, OH–C(4')); 3.94 (*m*, H–C(4')); 4.13 (*ddd*, *J* = 3, 6, 8, H–C(6')); 5.39 (*s*, OH–C(2')); 5.90 (*q*, *J* = 6.5, PhC*H*); 7.28–7.40 (*m*, arom. H).

25: ^{1}H-NMR (300 MHz, $CDCl_3$): 0.91 (*m*, *Me*CH_2); 1.30 (*d*, *J* = 7.5, Me–C(2)); 1.40 (*m*, MeCH_2); 1.59 (*d*, *J* = 6.5, Me); 1.75 (*m*, H–C(5')); 2.97 (*s*, MeO); 3.01 (*m*, H–C(3')); 3.10 (*q*, *J* = 7, H–C(2)); 3.82 (*m*, H–C(4')); 4.13 (*m*, H–C(6')); 4.71 (*s*, OH–C(2')); 5.94 (*q*, *J* = 6.5, PhC*H*); 7.28–7.40 (*m*, arom. H).

(1S)-1-Phenylethyl [(3'R,4'S,5'S,6'S)-6'-Ethyltetrahydro-2',4'-dihydroxy-3'-methoxy-5'-methyl-2H-pyran-2yl]propanoate (**2/26**). The procedure *a* described for **22** was used, but the mixture was stirred for 2.5 h at −78° and 1.5 h to r.t. before workup. Treatment of crude **21** with Bu_4NF using the procedure *b* described for **22** afforded 44 mg of pure **2** and 31 mg of **2/26** 2:3 (31%). **2**: ^{1}H-NMR (500 MHz, $CDCl_3$): 0.65 (*t*, *J* = 7.5, *Me*CH_2); 0.97 (*d*, *J* = 7.5, Me–C(2)); 1.22 (*d*, *J* = 7.5, Me–C(5')); 1.29, 1.36 (2*m*, MeCH_2); 1.56 (*d*, *J* = 6.5, Me); 1.75 (*m*, H–C(5')); 3.10 (*q*, *J* = 7.5, H–C(2)); 3.18 (*dd*, *J* = 1, 2.5, H–C(3')); 3.40 (*s*, MeO); 3.89 (*d*, *J* = 10, OH–C(4')); 3.95 (*ddd*, *J* = 2.5, 2.5, 11, H–C(4')); 4.07 (*ddd*, *J* = 3, 6, 8, H–C(6')); 5.32 (*s*, OH–C(2')); 5.91 (*q*, *J* = 6.5, PhC*H*); 7.28–7.39 (*m*, arom. H). ED-MS: 367 ([*M* + H]$^+$). Anal. calc. for $C_{20}H_{30}O_6$: C 65.55, H 8.25; found: C 65.6, H 8.4.

REFERENCES

[1] N. Bedorf, D. Schomburg, K. Gerth, H. Reichenbach, G. Höfle, *Liebigs Ann. Chem.* **1993,** 1017; K. Gerth, N. Bedorf, H. Irschik, G. Höfle, H. Reichenbach, *J. Antibiot.* **1994,** *47,* 23.

[2] *GBF mbH* and *Ciba-Geigy AG,* EP 282455 A2, 1993.

[3] B. Böhlendorf, Ph.D. Thesis, Braunschweig Technical University, Germany, 1991.

[4] A. J. Duggan, M. A. Adams, P. J. Brynes, J. Meinwald, *Tetrahedron Lett.* **1978,** *45,* 4323.

[5] B. Loubinoux, J-L. Sinnes, A.C. O'Sullivan, *J. Org. Chem.*, accepted; *iidem,* submitted to *Tetrahedron*; J-L. Sinnes, Ph.D. Thesis, University of Nancy, France, 1993.

[6] G. Höfle, *GBF mbH,* Braunschweig, Germany, personal communication.

[7] M. Braun, in 'Advances in Carbanion Chemistry', JAI Press, London, 1992, Vol. 1, p.177.

[8] D. A. Evans, *Aldrichim. Acta* **1982,** *15,* 23.

[9] W. Oppolzer, J. Blagg, I. Rodriguez, E. Walther, *J. Am. Chem. Soc.* **1990,** *112,* 2767.

[10] M. P. Bonner, E. R. Thornton, *J. Am. Chem. Soc.* **1991,** *113,* 1299.

[11] R. W. Hoffmann, W. Ladner, W. Helbig, *Liebigs Ann. Chem.* **1984,** 1170; R. W. Hoffmann, S. Dresely, B. Hildebrandt, *Chem. Ber.* **1988,** *121,* 2225.

[12] A. F. Sviridov, V. S. Borodkin, M. S. Ermolenko, D. V. Yashunsky, N. K. Kocetkov, *Tetrahedron* **1991,** *47,* 2291.

[13] D. E. Cane, W. Tan, W. R. Ott, *J. Am. Chem. Soc.* **1993,** *115,* 527.

[14] D. A. Evans, T. C. Britton, *J. Am. Chem. Soc.* **1987,** *109,* 6881.

[15] D. A. Evans, S. L. Bender, J. Morris, *J. Am. Chem. Soc.* **1988,** *110,* 2506.

[16] D. A. Evans, M. D. Ennis, D. J. Mathre, *J. Am. Chem. Soc.* **1982,** *104,* 1737.

[17] J. R. Parikh, W. von Doering, *J. Am. Chem. Soc.* **1967,** *89,* 5505; K. C. Nicolaou, R. A. Daines, J. Ueniski, W. S. Li, D. P. Papakathis, T. K. Chakraborty, *ibid.* **1988,** *110,* 4672.

[18] T. W. Ku, K. H. Konrad, J. G. Gleason, *J. Org. Chem.* **1989,** *54,* 3487.

[19] K. C. Nicolaou, S. P. Seitz, M. R. Pavia, N. A. Petasis, *J. Org. Chem.* **1979,** *44,* 4011.

[20] M. E. Jung, J. Gervay, *J. Am. Chem. Soc.* **1991,** *113,* 224; L. Mandolini, 'Advances in Physical Organic Chemistry', Academic, London, 1976, Vol. 22, p. 1–112; B. Capon, S. P. Mc Manus, 'Neighbouring Group Participation', Plenum, New York, 1976, p. 43.

[21] R. M. Beesley, C. K. Ingold, J. F. Thorpe, *J. Chem. Soc.* **1915,** *107,* 1080.

[22] B. Loubinoux, J-L. Sinnes, A. O'Sullivan, *J. Chem. Soc., Perkin Trans. 1*, accepted.

[23] H. F. Vahlensieck, L. Pridzun, H. Reichenbach, A. Hinnen, *Curr. Gen.* **1994,** *25,* 95.