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Enantioselective synthesis of the C11–C17 segment of soraphen $A_{1\alpha}$ via organoiron methodology

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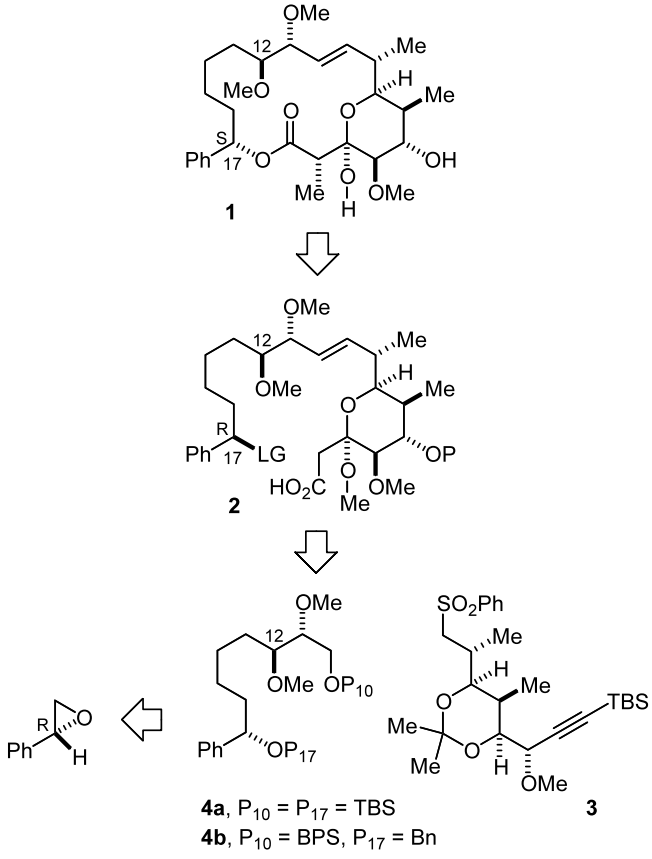
Abstract—The C11–C17 segment of the antifungal agent soraphen $A_{1\alpha}$ was prepared from glyceraldehyde acetonide in nine steps. The C12 stereocenter is derived from glyceraldehyde, while the C17 stereocenter as introduced by 1,6-asymmetric control via the coordinated $Fe(CO)_3$. © 2002 Published by Elsevier Science Ltd.

Soraphen $A_{1\alpha}$ (**1**) is a macrolide isolated from the myxobacteria *Sorangium cellulosum*.[1] This compound is a potent antifungal agent due to its inhibitory action against fungal acetyl-CoA carboxylase. Biological evaluations of semi-synthetic analogues of **1** reveal that their activity strongly depends on the configuration at C17, the nature of the C17 substituent, and the size of the macrocyclic ring.[2] This work also demonstrated that closure of the macrolactone ring was not possible by standard lactonization methods but could be accomplished via an S_N2 inversion at the C17 center (e.g. **2**). Thus, the ideal precursor for **1** has a C17 configuration *opposite to that present in the final product*.

Only a single synthesis of **1** has been reported.[3] Giese's retrosynthetic strategy depends on the Julia coupling of the C2–C9 segment **3** with a C10–C17 segment **4a** (Scheme 1). Won Lee's group has also reported the synthesis of a similar C10–C17 segment (**4b**).[4] Both of these routes derive the C17 stereochemistry from (*R*)-phenyloxirane. We herein report the preparation of a C11–C17 segment which utilizes organoiron methodology to establish the C12 and C17 stereocenters by 1,6-asymmetric induction.[5]

Complexation of the known[6] dienoate **5a** gave an essentially inseparable mixture of diastereomeric diene complexes **6a**/**7a** (70–90%, Scheme 2).[7] Solvolysis of **6a**/**7a** *in methanol* gave a *readily* separable mixture of methyl ether (+)-**8a** and the known[7] glycol (−)-**9a** (>90% ee). Analysis of the (*R*)- and (*S*)-Mosher's esters of **8a** indicated each to be >85% de. The absolute configuration of (+)-**8a**, at the diene–iron segment, was tentatively assigned as indicated in accord with the empirical relationship between the sign of the optical rotation and absolute configuration for (diene)$Fe(CO)_3$ com-



Scheme 1.

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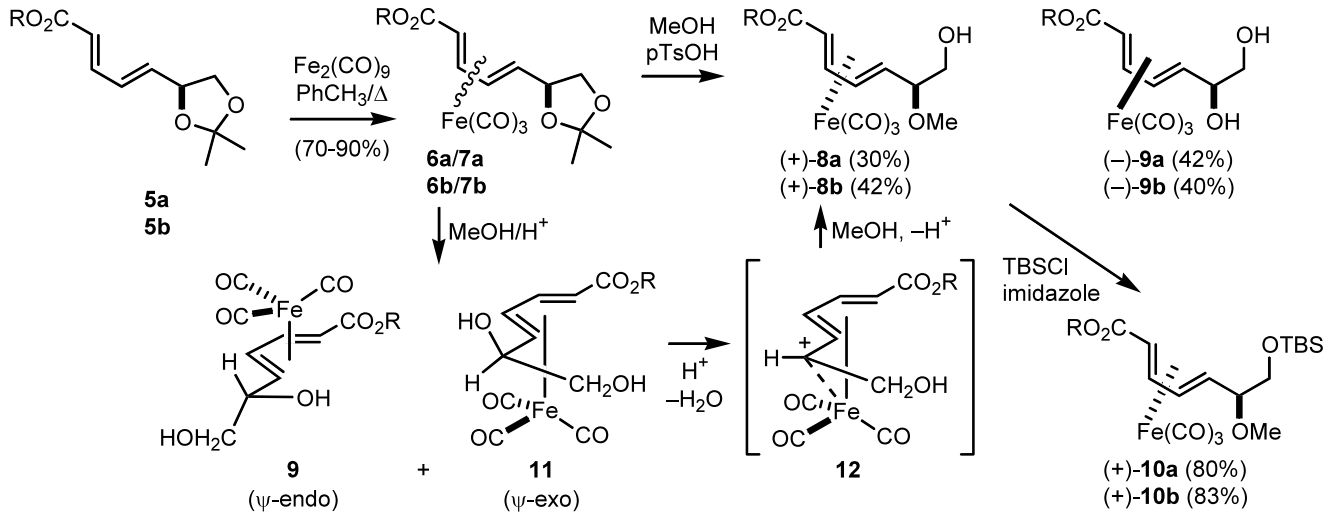
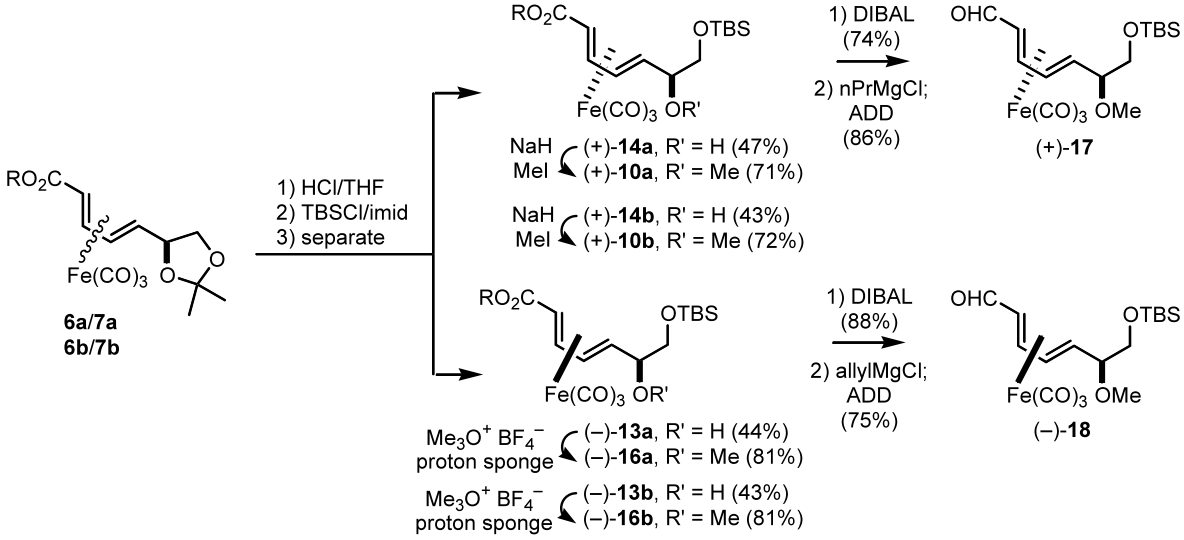


Scheme 2. (**a**, R = Me; **b**, R = Et).

plexes bearing electron-withdrawing groups.[8] In a similar fashion, ethyl ester **5b** gave (+)-**8b** and (–)-**9b**. Reaction of **8a** or **8b** with TBSCl/imidazole gave (+)-**10a** or (+)-**10b**, whose structural assignments were corroborated by independent synthesis (vide infra).

The formation of methyl ether **8** is rationalized in the following fashion (Scheme 2). Cleavage of the acetonide group gives the ψ-*endo* and ψ-*exo* diols **9** and **11**, respectively. Selective solvolysis of the ψ-*exo* dienol **11** proceeds via generation of the *trans* pentadienyl cation intermediate **12** which is captured by attack of the methanol solvent on the face opposite to iron to give **8**. Lillya et al. have previously demonstrated that solvolysis of ψ-*exo* dienyl dinitrobenzoate complexes occurs ca. 85–100 times faster than solvolysis of their ψ-*endo* diastereomers.[9]

The (diene)iron complexes **10a** or **10b** could be independently prepared in a different fashion (Scheme 3). We have previously reported[7] that the hydrolysis of **6a**/**7a** with HCl *in moist THF*, followed by protection of the primary alcohol group gave a readily separable mixture of (–)-**13a** and (+)-**14a** (of known configuration). Reaction of **14a** with NaH/MeI gave the ether (+)-**10a** which was identical with that prepared previously. In a similar fashion, hydrolysis of **6b**/**7b** gave a separable mixture of (–)-**13b** and (+)-**14b**, and methylation of (+)-**14b** gave (+)-**10b**. Surprisingly, attempted methylation of the diastereomeric alcohol (–)-**13a** or **b** under the Williamson conditions failed and resulted only in recovered starting material. One possible rationale for this lack of reactivity could be intramolecular stabilization of the alkoxide anion by attack on iron to afford the π-allyl species **15** (Fig. 1).[10] It was eventually found that the ψ-*endo* alcohol complexes **13a** or **b** could be methylated using Meerwein's salt,[11] to give the ethers (–)-**16a** or **b**. Reduction of (+)-**10a** or **b** followed by oxidation under Saigo–Mukaiyama conditions[12] gave the aldehyde complex (+)-**17**, while similar reaction of (–)-**16a** or **b** gave (–)-**18**.



Scheme 3. (**a**, R = Me; **b**, R = Et).

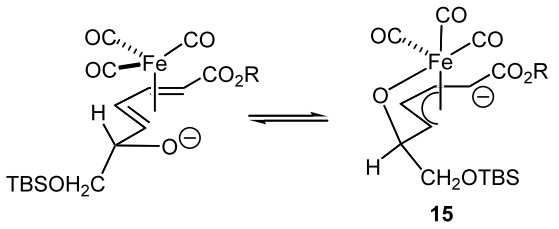
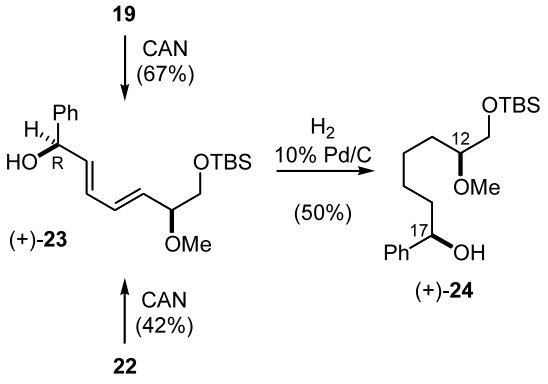


Figure 1.



Scheme 5.

Nucleophilic addition to (dienal)$Fe(CO)_3$ complexes proceeds with variable diastereoselectivity, depending on substituents present on the diene, the nucleophile, any Lewis acid additive as well as the reaction solvent.[13] Addition of phenyl magnesium bromide to (+)-**17**, using ether as solvent, gave a separable mixture of diastereomeric alcohols **19** and **20** (Scheme 4). The relative stereochemistries of **19** and **20** at C17 (soraphen numbering) were assigned as ψ-*exo* and ψ-*endo*, respectively, on the basis of their ^1H NMR spectral data[14] and their relative chromatographic mobility. In particular, the signals for H14 and H15 (soraphen numbering) of **19** appear at δ 5.32 and 5.50 ppm, respectively, while for **20** these signals appear overlapped at δ 5.30 ppm. The upfield shift for H15 of **20**, compared to **19**, is characteristic of ψ-*endo* (1-phenyl-2,4-dien-1-ol)iron complexes compared to their ψ-*exo* counterparts.[15] Additionally, **19** is more polar than **20**. It has been empirically found that ψ-*exo* dienol complexes are generally less mobile than their ψ-*endo* diastereomers.[16] In contrast to the reaction in ether, addition of PhMgBr to **17** in THF gave exclusively **19**, albeit in modest yield.

Addition of phenyl Grignard to (–)-**18**, in THF as solvent, gave a separable mixture of diastereomeric alcohols **21** and **22** (Scheme 4). The relative stereochemistries of **21** and **22** at C17 (soraphen numbering) were assigned as ψ-*exo* and ψ-*endo*, respectively, on the basis of their ^1H NMR spectral data[17] and their relative chromatographic mobility (**21** more polar than **22**). In comparison to these results, pre-mixing of **18** with $TiCl_4$ (CH_2Cl_2), followed by addition of PhMgBr gave only the ψ-*endo* alcohol **22**. It has been previously reported that formation of ψ-*endo* dienols are favored when Ti(IV) based reagents are used.[13] This has been rationalized on the basis that the titanium reagent favors the *s-trans* rotomer in solution due to linear coordination to the aldehyde carbonyl.

Complexes **19** and **22** are assigned the same configuration at C12 and C17, and differ only with respect to the coordination of the $Fe(CO)_3$ group. Oxidative removal of iron from either **19** or **22** with CAN gave the same free ligand (+)-**23** (Scheme 5).[18] Reduction of (+)-**23** (5% Pd/C) gave the saturated alcohol (+)-**24** which constitutes the C11–C17 segment of soraphen $A_{1\alpha}$.

In summary, the C11–C17 segment of soraphen $A_{1\alpha}$, with inverted stereochemistry at C17 as required for ring closure, was prepared in eight to nine steps from the optically active dienoate **5**. The C12 stereocenter is derived from glyceraldehyde, while the C17 stereocenter as introduced by 1,6-asymmetric control via the coordinated $Fe(CO)_3$.

Acknowledgements

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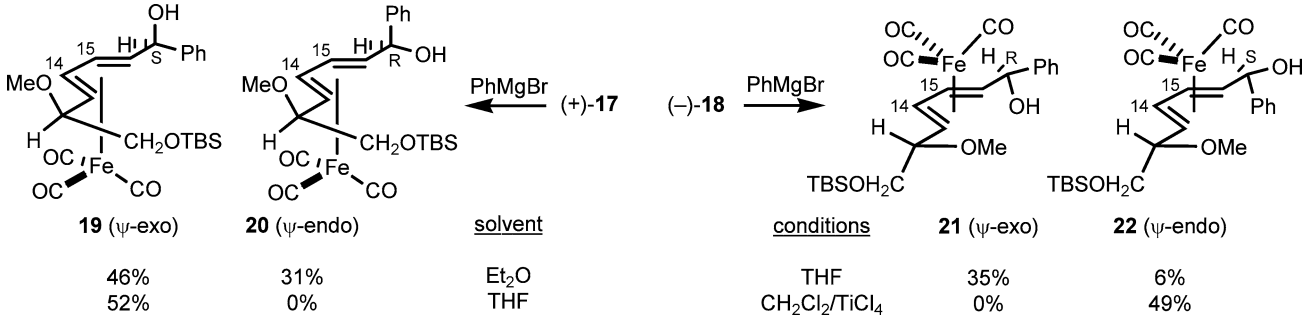

Scheme 4.

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14. Compound **19**: yellow fibers; mp 94.5–96°C; ^{1}H NMR ($CDCl_3$): δ 7.28–7.15 (m, 5H), 5.50 (dd, $J=5.0$, 9.1 Hz, 1H), 5.32 (dd, $J=5.0$, 9.2 Hz, 1H), 4.52 (dd, $J=2.2$, 7.8 Hz, 1H), 3.69 (dd, $J=3.7$, 10.9 Hz, 1H), 3.59 (dd, $J=5.8$, 11.0 Hz, 1H), 3.38 (s, 3H), 3.05 (ddd, $J=3.7$, 5.8, 6.7 Hz, 1H), 2.17 (d, $J=2.3$ Hz, OH), 1.25 (t, $J=8.0$ Hz, 1H), 1.01 (t, $J=8.3$ Hz, 1H), 0.88 (s, 9H), 0.05 (s, 6H).
Compound **20**: yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.28–7.15 (m, 5H), 5.25 (m, 2H), 4.51 (br d, $J=7.9$ Hz, 1H), 3.61 (dd, $J=3.7$, 11.0 Hz, 1H), 3.59 (dd, $J=5.8$, 11.0 Hz, 1H), 3.38 (s, 3H), 3.04 (m, 1H), 1.85 (br s, OH), 1.22 (m, 1H), 0.88 (m and s, 10H), 0.05 (s, 6H).
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17. Compound **21**: yellow oil; ^{1}H NMR ($CDCl_3$): δ 7.28–7.15 (m, 5H), 5.46 (dd, $J=4.9$, 8.3 Hz, 1H), 5.24 (dd, $J=4.9$, 8.8 Hz, 1H), 4.39 (dd, $J=3.1$, 8.0 Hz, 1H), 3.65 (dd, $J=6.0$, 10.2 Hz, 1H), 3.47–3.38 (m and s, 4H), 3.16 (q, $J=6.0$ Hz, 1H), 2.00 (d, $J=2.9$ Hz, OH), 1.16 (m, 1H), 0.99 (t, $J=7.6$ Hz, 1H), 0.88 (s, 9H), 0.03 (s, 6H).
Compound **22**: yellow solid; mp 85–89°C; ^{1}H NMR ($CDCl_3$): δ 7.37–7.20 (m, 5H), 5.25 (m, 2H), 4.51 (br d, $J=7.2$ Hz, 1H), 3.67 (dd, $J=6.6$, 10.5 Hz, 1H), 3.47 (s and m, 4H), 3.20 (m, 1H), 1.84 (br s, OH), 1.20 (m, 1H), 0.89 (m and s, 9H), 0.05 (s, 6H).
18. While removal of the $Fe(CO)_3$ group from **19** or **22** does not involve any change at C17, because of the rules for stereochemical prioritization the configurational designation changes from (*S*) to (*R*). Compound **23**: $[\alpha]_D=+13$ (*c* 0.28, MeOH); ^{1}H NMR ($CDCl_3$): δ 7.40–7.25 (m, 5H), 6.39–6.2 (m, 2H), 5.90 (dd, $J=6.4$, 14.5 Hz, 1H), 5.60 (dd, $J=7.0$, 14.3 Hz, 1H), 5.27 (d, $J=6.4$ Hz, 1H), 3.73–3.55 (m, 2H), 3.31 (s, 3H), 2.10 (s, OH), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 143.4, 136.1, 132.9, 132.6, 130.6, 129.2, 128.4, 126.9, 83.5, 75.4, 66.9, 57.6, 26.6, 19.1, –4.5.