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Total Synthesis of Alternaric Acid

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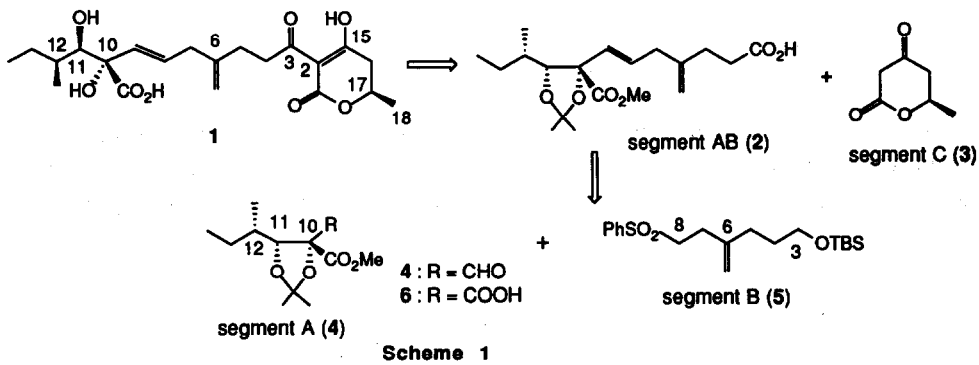
Abstract: A total synthesis of alternaric acid (1) has been achieved. Key reactions include the Julia olefination of tertiary aldehyde 4 and phenylsulfone 5, and novel one-pot construction of 3-acyl-4-hydroxy-5,6-dihydropyrone *via* Fries type rearrangement of *O*-enolacyl group of β-keto-δ-valerolactone toward α-position of the δ-lactone. The absolute configuration of alternaric acid has been shown to be that illustrated in structure 1.

Alternaric acid (**1**) was isolated in 1949 by Brian and co-workers from *Alternaria solani*, which is causal fungus of early blight disease on potato.[1a] This compound has phytotoxic and antifungal activities[1] similar to solanapyrones.[2] Recently, alternaric acid (**1**) was shown to delay the occurrence of hypersensitive death of potato cells infected by an incompatible race of *Phytophthora infestans*.[3] In the preceding communication, we disclosed the determination of complete stereochemistry of **1** through the synthesis of four possible diastereomers of the degradation product **6**, C(9)-C(14) fragment, of **1**.[4] Herein we would like to report a total synthesis of alternaric acid (**1**).

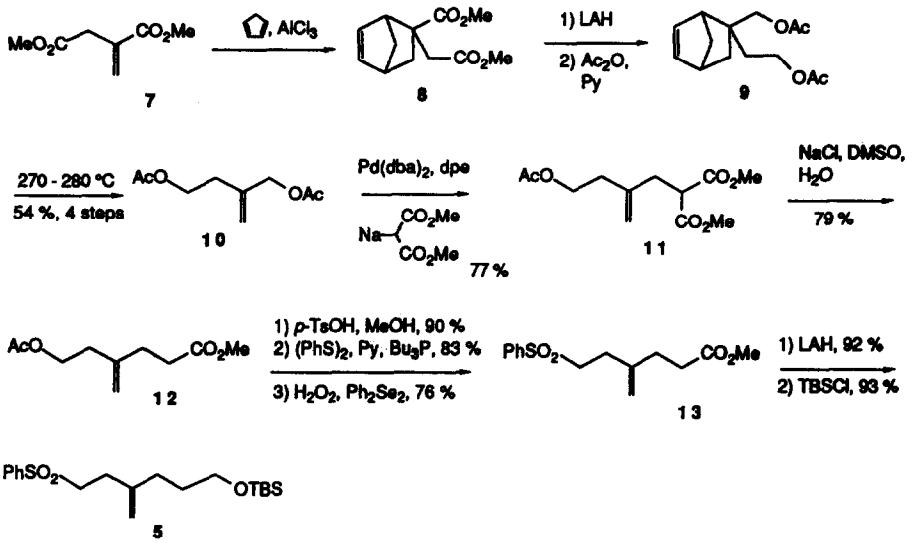


Scheme 1

Retrosynthetic analysis of **1** generated three building blocks : aldehyde **4** (segment A), phenylsulfone **5** (segment B) and β-keto-δ-valerolactone **3** (segment C) (Scheme 1), in which aldehyde **4** is considered to be combined with phenylsulfone **5** by Julia olefination.[5] Construction of 3-acyl-4-hydroxy-5,6-dihydropyrone from carboxylic acid **2** and β-keto-δ-valerolactone **3** *via* Fries type rearrangement of *O*-enolacyl group of β-keto-δ-valerolactone toward α-position of the δ-lactone was newly developed by utilizing dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP).

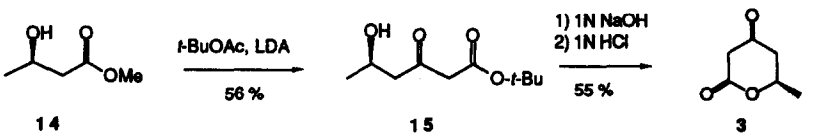
Since aldehyde **4** has already been prepared from (S)-(+)-2-methylbutanal in our previous paper,[4] phenylsulfone **5** and β-keto-δ-valerolactone **3** must be prepared. As shown in Scheme 2, segment B (**5**) was synthesized from dimethyl itaconate (**7**). Direct reduction of **7** failed to give the corresponding diol because of

its 1,4-reduction.We overcame this problem by protection of the olefin moiety according to retro-Diels-Alder procedure.[6] Diels-Alder reaction of **7** with cyclopentadiene gave a diastereomeric mixture of adduct **8**. Without isolation, reduction of **8** with lithium aluminum hydride and subsequent acetylation yielded diacetate **9**. Deprotection of **9** by heating (270~280 °C) furnished olefin **10** (54 % yield, 4 steps).[7] Palladium catalyzed allylic alkylation[8] of **10** with sodium dimethyl malonate gave dimethyl ester **11**, and decarboxylation of **11** by heating with sodium chloride in wet DMSO at 150 °C afforded the corresponding ester **12** without hydrolysis of methyl ester.[9] After the conversion of acetoxyl group of **12** into phenylsulfonyl group *via* three conventional reactions, reduction of methyl ester group of **13** with $LiAlH_4$ and following protection of primary alcohol with *t*-butyldimethylsilyl chloride provided C(3)-C(8) phenylsulfone **5** (segment B).



Scheme 2

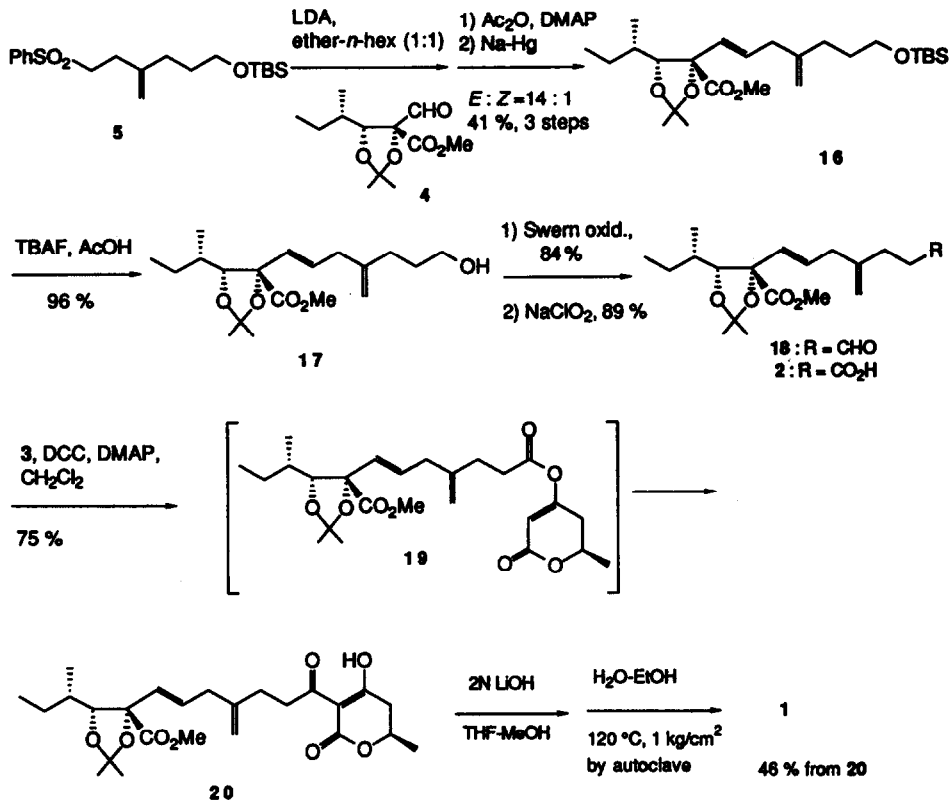
β-Keto-δ-valerolactone **3**, segment C, was prepared as following : Claisen condensation of **14** and lithium *t*-butyl acetate gave δ-hydroxy-β-keto ester **15** (56 % yield)[10] and hydrolysis of **15** with 1N sodium hydroxide and subsequent treatment of 1N hydrochloric acid afforded β-keto-δ-valerolactone **3** in 55 % yield (Scheme 3).



Scheme 3

Next steps to total synthesis involves Julia olefination[5] of aldehyde **4** (segment A)[4] and phenylsulfone **5** (segment B). In general, the addition of sulfone anions to aldehydes can be capricious process, and depends on base, solvent and auxiliary reagents.[11] In our case, following conditions gave good results ; treatment of phenylsulfone **5** with 1.5 equivalent lithium diisopropylamide at - 78 °C in ether-*n*-hexane (1 : 1) afforded the

corresponding sulfone anion, which reacted with aldehyde 4[4] to give the corresponding β-hydroxysulfones as a mixture of diastereomers. The mixture was acetylated, and subjected to elimination reaction with sodium amalgam.[5] The product **16** was obtained in 41 % overall yield, and it consisted of a 14 : 1 mixture of *E* and *Z* isomers. These were separated by MPLC to give the desired major isomer **16**. Removal of the silyl protecting group in *E*-olefin **16** yielded alcohol **17**. Swern oxidation[12] of the alcohol **17**, and followed sodium chlorite oxidation[13] of resultant aldehyde **18** furnished carboxylic acid **2** (segment AB).



Scheme 4

O-Enolacylation of β-keto-δ-valerolactone **3** (segment C) with carboxylic acid **2** in the presence of DCC and DMAP afforded 3-acyl-4-hydroxy-5,6-dihydropyrone **20**, $[\alpha]_D^{26}$ -3.8 ° (c=3.70, EtOH), {natural, $[\alpha]_D^{25}$ -5.2 ° (c=3.68, EtOH)},[1f] in good yield (75 %). This reaction involves simultaneously Fries type rearrangement of *O*-enolacyl group of β-keto-δ-valerolactone **19** toward α-position of the δ-lactone (Scheme 4). This newly developed method[14] is simple, mild and versatile compared with known procedure.[15]

The hydrolysis of **20** was not easy because of its instability to acid. The hydrolysis of acetonide of **20** with 1N hydrochloric acid in methanol-tetrahydrofuran gave the corresponding diol in only 21 % yield, but it was failed to obtain the target compound by further hydrolysis of methyl ester. Eventually, the problem was overcome by changing the order of hydrolysis reactions (Scheme 4). Thus, hydrolysis of methyl ester of **20** with 2N lithium hydroxide in methanol-tetrahydrofuran (1: 2) smoothly yielded the corresponding carboxylic

acid and following hydrolysis of acetonide by heating at 120 °C in autoclave provided alternaric acid (**1**), $[\alpha]_D^{24}$ 0 ° (c=1.00, acetone), {natural, optically inactive},[1d] in 45 % yield (2 steps). The spectroscopic data of synthetic **1** thus obtained was identical in all respects with those of natural **1**. This study not only confirms the absolute stereochemistry of alternaric acid but also has made possible to synthesize other analogs of alternaric acid for structure-activity relationship.[16]

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