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STEREO-DIVERGENT ASYMMETRIC TOTAL SYNTHESIS OF AVENACIOLIDE AND ISOAVENACIOLIDE. COMPLETE REVERSAL OF STEREOSELECTIVITY IN REDUCTION OF 2-VINYL ALDOLS WITH / WITHOUT TRIMETHYLSILYL DIRECTING GROUP

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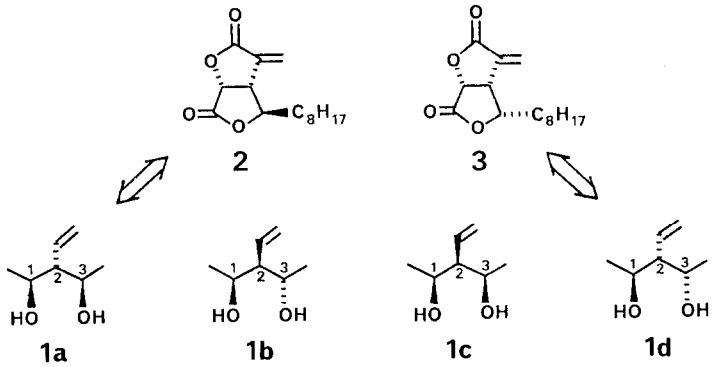
Summary: Stereo-divergent asymmetric total synthesis of avenaciolide and isoavenaciolide was achieved via 1,2-rearrangement of chiral epoxyalcohol derivatives, where complete reversal of stereoselectivity with / without the TMS-directing group in the reduction of 2-vinyl aldols was used as the key branching point.

2-Vinyl-1,3-diols (1a-d) are potentially versatile building blocks in natural product synthesis. We recently exploited a facile and efficient entry to these structures via the following two-stage process:

(1) stereospecific 1,2-rearrangement of epoxyalcohol derivatives,[1)]

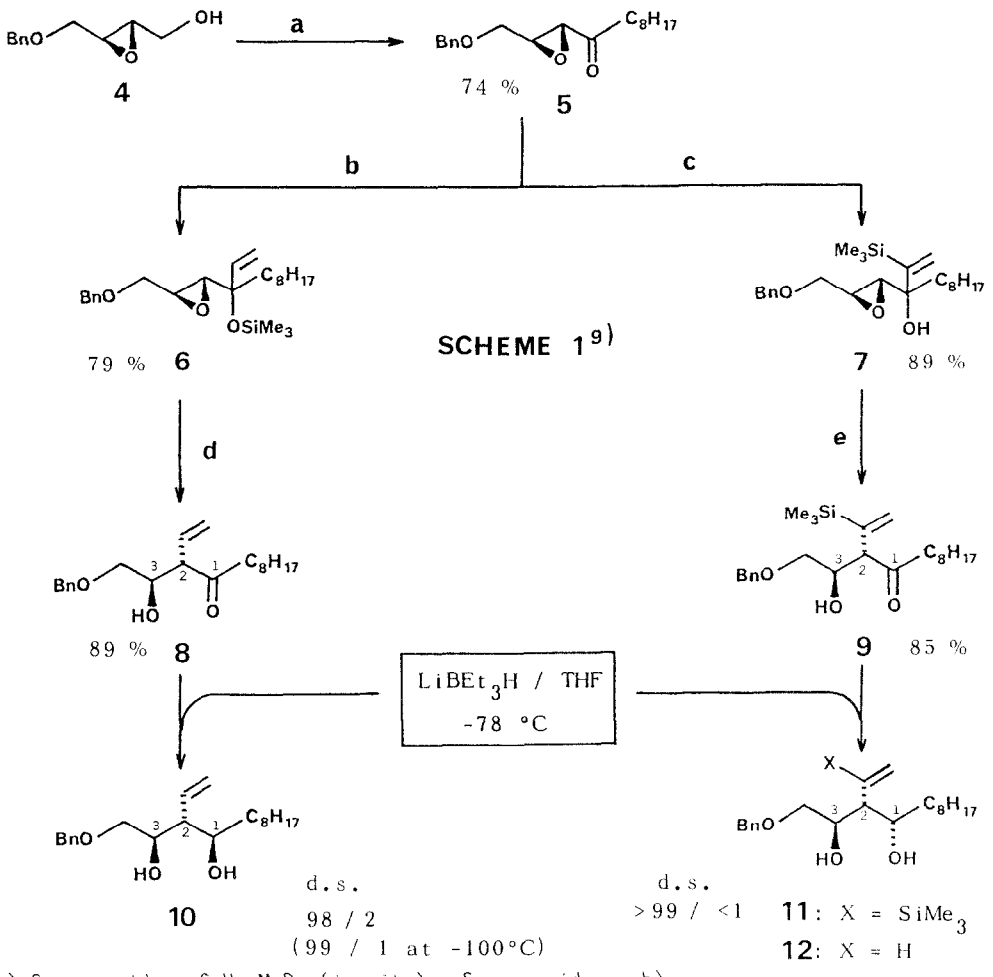
(2) stereoselective reduction of the resultant 2-vinyl aldols.[2)]

Based on the efficient stereo-directing effect by the TMS group in the latter step, the isomers possessing any *syn*-relationship(s) (1,2- and/or 2,3-*syn*: 1b-d) are now accessible in enantio- and diastereo-controlled manner, while the preparation of the *anti-anti* isomer 1a has been unresolved.



Avenaciolide (2) and isoavenaciolide (3) are the antifungal metabolites isolated from *Aspergillus avenaceus*, whose fascinating structures as well as the biological activities stimulated a number of studies on their total syntheses.[3,4)] As a part of application study, we planned the synthesis of these lactones with a hopeful challenge to the "*anti-anti* problem". We report here an intriguing solution by the complete reversal of the selectivity in the reduction of 2-vinyl aldols with / without the TMS-directing group, culminating in a stereo-divergent asymmetric total synthesis of these isomeric lactones.[5)]

To begin with, the known chiral epoxyalcohol 4 was prepared by the Sharpless

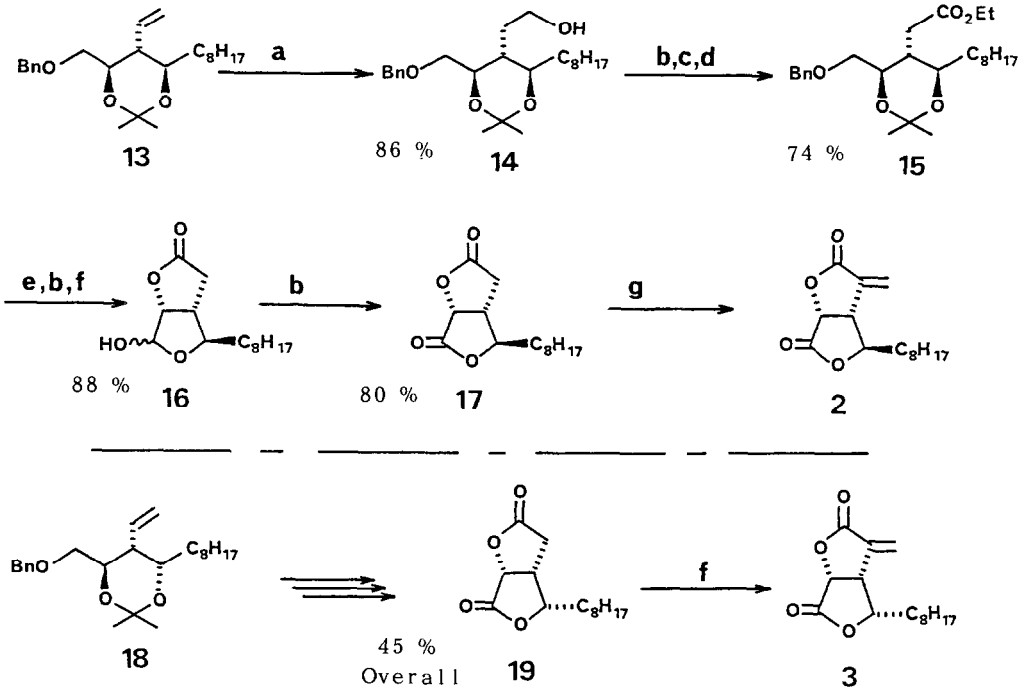


Keys: a) Swern oxidn., $C_8H_{17}MgBr$ (in situ); Swern oxidn., b) $H_2C{=}CHMgBr$ / THF; TMSCl, Imidazole / DMF, c) $H_2C{=}C(SiMe_3)Li$ / THF, d) $(i\text{-}PrO)_2TiCl_2$ / CH_2Cl_2, -78°C → -40°C, e) $BF_3{\cdot}OEt_2$ / CH_2Cl_2, -78°C → -40°C.

reaction[6], which in turn was converted to 6 and 7.[1] Subsequent 1,2-rearrangements of these epoxides were cleanly effected by the Lewis acids to give *threo* 2-vinyl aldols 8 and 9 as the single isomer in each case, which corresponds to the enantio- and diastereo-controlled synthesis of the 2-vinyl aldols.[7] Here, two points are notable: (i) the high migratory aptitude of the TMS-bearing vinyl group[8] made the conversion of 7 to its TMS ether unnecessary, (ii) $(i\text{-}PrO)_2TiCl_2$ gave better result in the rearrangement of 6 than $TiCl_4$, the Lewis acid in our original report.[1]

Attention was turned to the reduction of these *threo* aldols. Reduction of aldol 9 with $LiBEt_3H$ gave 1,2-syn isomer 11 as the single product,[9] efficiently directed by the TMS group as described.[2] In sharp contrast, reduction of the 2-vinyl aldol 8 lacking the TMS group under the same conditions furnished 1,2-*anti* isomer 10[9] with an excellent selectivity (1,2-*anti*/1,2-*syn*=98/2), which was further improved to 99/1 by carrying out the

SCHEME 2[9]



Keys: a) $(cyclo\text{-}C_6H_{11})_2BH$ / THF; H_2O_2, b) Swern oxidn., c) $NaClO_2$, pH 4, $Me_2C{=}CHMe$ / $tBuOH\text{-}H_2O$, d) $ClCO_2Et$, Et_3N; 4-DMAP, e) H_2, Pd-C, f) H^+ / dioxane-H_2O, g) Johnson's method (ref. 3d).

reduction at -100 °C. The ratio was unanimously determined by 400 MHz ^1H NMR and HPLC in comparison with the 1,2-*syn* isomer 12[9] which was obtained by desilylation of 11.[8] Thus, the impressive reversal of the diastereofacial selection with / without the TMS group enabled a dually selective preparation of the isomeric diols, *anti-anti* 10 and *syn-anti* 12.[10]

Elaboration of these 1,3-diols 10 and 12 led to the target bislactones. Scheme 2 illustrates the avenaciolide-series of the synthesis starting from 10: Diol 10 was protected as acetonide to give 13, which was subjected to hydroboration with $(c\text{-}C_6H_{11})_2BH$ followed by oxidative workup to afford alcohol 14.[11] Oxidation of alcohol 14 in two steps (Swern oxidation[12] followed by $NaClO_2$[13]) gave the corresponding carboxylic acid, which was directly esterified[14] to afford 15. After removal of the benzyl group and Swern oxidation, the resulting aldehyde was subjected to acid hydrolysis to give lactol 16. Finally, oxidation of 16 to bislactone 17[9] followed by the methylenation by the Johnson's procedure[3d] gave avenaciolide (2), which was indistinguishable from the authentic sample kindly provided by Dr. Aldridge.[15]

The same sequence of reactions was applied to the conversion of the isomeric alcohol 12 to the isomeric bislactone 19[9] which was methylenated[3d] to give isoavenaciolide (3), also fully superimposable with the natural sample.[15]

In summary, asymmetric total synthesis of the antifungal lactones, avenaciolide and isoavenaciolide, was accomplished in stereo-divergent manner.

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9) All new compounds were fully characterized by means of ^{1}H, ^{13}C NMR, IR, and high-resolution MS. Data of 100 MHz ^{13}C NMR (δ, $CDCl_3$) for selected compounds follow; 10: 14.1, 22.7, 25.1, 29.3, 29.6, 29.7, 31.9, 34.9, 53.3, 72.9, 73.3, 73.4, 73.7, 118.7, 127.8, 127.9, 128.5. 11: -1.1, 14.1, 22.7, 26.6, 29.3, 29.6, 29.7, 31.9, 33.0, 50.6, 71.5, 72.4, 73.27, 73.34, 127.8, 127.9, 128.1, 128.5, 137.8, 149.8. 12: 14.1, 22.7, 26.1, 29.3, 29.6, 29.7, 31.9, 34.6, 51.5, 71.0, 71.3, 73.0, 73.4, 118.8, 127.77, 127.84, 128.5, 134.5, 137.9.

10) Detailed study on this anti-selective reduction is in progress.

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15) 2: mp 52.5-54 °C (pentane-Et_2O)(lit.[3a] 49-50 °C, 54-56 °C); $[\alpha]_D^{28}$ -42°(c 0.54, EtOH) (lit.[3a] $[\alpha]_D^{26.5}$ -41.6° (c 1.2, EtOH)). 3: mp 129-130 °C (Et_2O)(lit.[4a] 129-130 °C), $[\alpha]_D^{32}$ -152°(c 0.38, EtOH)(lit.[4a] $[\alpha]_D^{27}$ -154° (c 1.1, EtOH)). The other spectroscopic data (^{1}H, ^{13}C NMR, IR and high-resolution MS) were in full agreement with those of the authentic samples by the direct comparison .

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