

Determination of the Relative and Absolute Configuration of Stigmatellin A by Chemical Correlation

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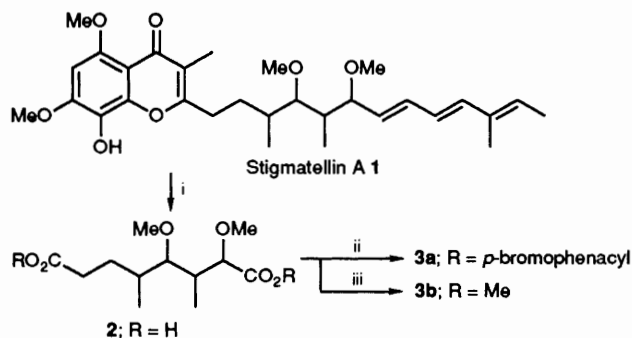
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The relative and absolute configuration of Stigmatellin A, isolated from the myxobacterium *Stigmatella aurantiaca* and a powerful inhibitor of electron transport, is determined through chemical correlation by employing a combination of our SAMP/RAMP hydrazone method and the Evans *syn*-aldol protocols.

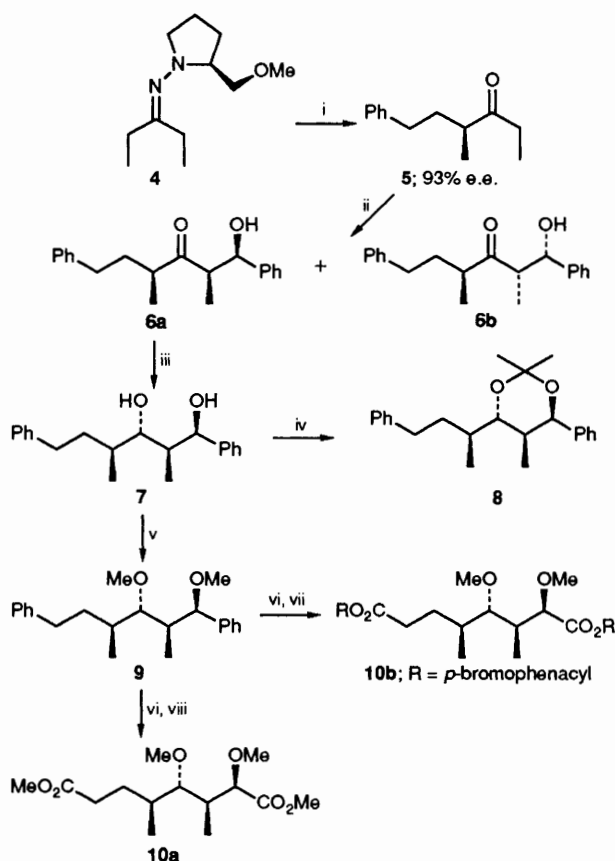
Stigmatellin A, **1**, first isolated by Höfle *et al.*¹ in 1983 from the gliding bacterium *Stigmatella aurantiaca*, has proved of great interest to the biological community to the extent that it is now commercially available (Fluka). As one of the most potent inhibitors known of the electron transport chain in both

chloroplasts^{2a} and mitochondria,^{2b} its use in elucidating the mode of action of these two vitally important processes has been considerable.^{2c}

As a necessary precursor to the first diastereo- and enantio-selective synthesis of this antibiotic, we required



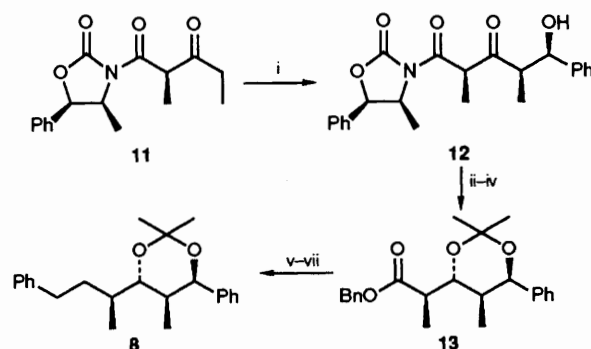
Scheme 1 Stigmatellin A and degradation studies.¹ *Reagents and conditions:* i, O₃, NaOH, H₂O₂; ii, 2,4'-dibromoacetophenone; iii, diazomethane.



Scheme 2 Synthesis of diesters **10a** and **10b**. *Reagents and conditions:* i, lithium diisopropylamine (LDA), THF, 0 °C, 5 h; PhCH₂CH₂Br, -80 to 25 °C, 16 h; O₃, CH₂Cl₂, -78 °C, 65%; ii, TiCl₄, Pr₂NEt, CH₂Cl₂, -78 °C, 1.5 h; PhCHO, -78 °C, 2 h, 70%; iii, Me₄NH-B(OAc)₃, MeCN-AcOH, 1:1, -25 °C, 48 h, 85%; iv, dimethoxypropane, *p*-MeC₆H₄SO₃H, CH₂Cl₂, 25 °C, 12 h, 96%; v, NaH, THF, 25 °C, 2 h; MeI, 25 °C, 12 h, 88%; vi, NaIO₄ (28 equiv.), RuCl₃·H₂O (cat.), MeCN-CCl₄-H₂O (3:2:2), 25 °C, 24 h; vii, CH₂N₂, 25 °C, 54% (2 steps); viii, Pr₂NEt, CH₂Cl₂, 2,4'-dibromoacetophenone, 25 °C, 12 h, 43% (2 steps).

detailed knowledge of the relative and absolute stereochemistry. Apart from one unsuccessful attempt to obtain crystals for X-ray analysis¹ (Scheme 1, compound **3a**), no further work had been previously directed towards this goal and thus the configuration remained unknown.

Our approach was to synthesise the eight possible diastereoisomeric degradation products **3a** and **3b** and correlate their data with that of natural product derived material. We now wish to report our initial studies leading to the diastereo- and enantio-selective synthesis of compounds **10a** and **10b**, identical to naturally derived **3a** and **3b**.



Scheme 3 Synthesis of acetonide **8** by an alternative route. *Reagents and conditions:* i, TiCl₄, Pr₂NEt, CH₂Cl₂, -78 °C, 1.5 h; PhCHO, CH₂Cl₂, -78 °C, 2 h, 81%; ii, Me₄NH-B(OAc)₃, MeCN-AcOH 1:1, -25 °C, 48 h, 92%; iii, dimethoxypropane, *p*-MeC₆H₄SO₃H, CH₂Cl₂, 12 h, 69%; iv, PhCH₂OLi, THF, 0 °C, 2 h, 94%; v, diisobutylaluminium hydride (DIBAL), Et₂O, -78 °C, 1 h; PhCH=PPh₃, THF, -78 °C to room temp., 4 h, 27%; vi, H₂-Pd/C, EtOH, 25 °C, 2 h, 63%.

We decided that the easiest way to carry the two diester functionalities through the synthesis would be as phenyl groups, which then allowed us to use readily available starting materials. As the key step to generate the first stereogenic centre we employed our SAMP/RAMP-hydrazone method.³

Therefore, alkylation of the lithium enolate of the known hydrazone **4a** [formed from (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP)^{4b} and diethyl ketone] in tetrahydrofuran (THF) with commercially available 2-phenyl-1-bromoethane followed without purification by oxidative cleavage of the C=N double bond with ozone gave ketone **5** in 65% overall yield. The absolute configuration was assigned as (*S*) in accordance with previous results^{4b} for SAMP hydrazone ketone alkylations. A titanium mediated aldol reaction⁵ then gave a mixture of the two *syn* isomers (assigned by the characteristic coupling constant between the vicinal protons across the new carbon-carbon bond) in a ratio of 3.1:1 and in 70% overall yield, these being easily separated by HPLC. It was interesting to note that the normally *syn* selective Bu₂BOTf⁶ (Tf = CF₃SO₂) reagent consistently gave an approximately 1:1 mixture of the two *anti* isomers. At the moment we have no explanation for this unusual discrepancy.

The enantiomeric excess (e.e.) of the major isomer (and hence the starting ketone) was determined by formation of the Mosher ester⁷ [(*R*)-MTPA-Cl (MTPA = α-methoxy-α-(trifluoromethyl)phenylacetic acid), Pr₂NEt, 4-dimethylamino-pyridine (DMAP; cat), CH₂Cl₂, 4 h, 25 °C]. Integration of the two signals corresponding to the proton α to the ester group in the ¹H NMR spectrum indicated an e.e. of 93%, which was confirmed by GC separation (column SE-54) of the two diastereoisomers.

The major isomer was assigned as **6a** by analogy to related results.^{4,8} This was also confirmed by an alternative synthesis of a later intermediate (see below).

anti Selective reduction⁹ with tetramethylammonium tri-acetoxyborohydride gave two diastereoisomeric diols in 85% yield and in 82% diastereoisomeric excess (d.e.); these were easily separated after conversion to either acetonide **8** [dimethoxypropane, *p*-MeC₆H₄SO₃H (cat.)] or diether **9** (NaH; MeI). In accordance with the results of Rychnovsky and Skalitzky¹⁰ and Evans *et al.*,¹¹ the major acetonide isomer was confirmed as *anti* due to the ¹³C NMR values of the two dioxolane methyl groups and the dioxolane quaternary carbon. (*anti*: methyl groups δ 23.63 and 25.72; quat. 100.70; *syn*: methyl groups δ 19.54 and 30.01; quat. 99.10).

The crucial oxidation of the two phenyl rings to the diacid was carried out using the modified Sharpless conditions¹² for RuO₄ oxidations. The diacid was not purified, but after a simple work-up (quench with propan-2-ol at 0 °C, dilute with diethyl ether, filter off the inorganic salts and removal of the

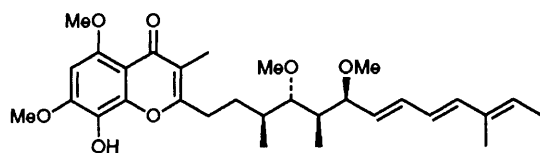


Fig. 1 Structure of Stigmatellin A 1

solvents *in vacuo*) was carried directly through to the diesters **10a** and **10b**. The former was found to be identical by ^1H and ^{13}C NMR to the natural product derived compound.¹ The latter was found to be identical by ^1H NMR, ^{13}C NMR and GC to a sample kindly provided by Professor Höfle. Natural product derived diester **10a** had $[\alpha]_{\text{D}}^{20} +8.2$ (*c* 20, MeOH);¹ synthetic $[\alpha]_{\text{D}}^{20} +4.6$ (*c* 0.8, MeOH); natural product derived diester **10b** had $[\alpha]_{\text{D}}^{20} +10.0$ (*c* 0.1, CHCl_3); synthetic $[\alpha]_{\text{D}}^{20} +9.85$ (*c* 0.655, CHCl_3). We believe that such agreement is sufficient to confirm that we have synthesised the correct enantiomer of the degradation product.

At this point, we decided that, as noted earlier, extra confirmation of the relative stereochemistry in the aldol reaction was required. To this effect, we resynthesised acetonide **8** by a completely independent route utilising the recently reported titanium mediated aldol reactions¹³ of diketone **11**. These are highly selective for the *syn* aldol isomer **12**. A series of straightforward transformations (Scheme 3) then gave the diphenyl acetonide **8**, which was found to be identical (^1H NMR, ^{13}C NMR, GC) to compound **8** synthesised by our original route (Scheme 2).

In conclusion, through a series of reactions of known selectivity (SAMP-hydrazone mediated alkylation, *syn* aldol reaction, *anti* reduction), we have synthesised the diesters **10a** and **10b**, which are indistinguishable from the diesters **3a** and **3b**, derived by degradation of Stigmatellin A. Therefore we conclude that the relative and absolute configuration of **1** is as shown in Fig. 1. Work is now in progress to apply these results to the total synthesis of Stigmatellin A.

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rally derived **3b** with spectra. This work was supported by the Fonds der Chemische Industrie. We thank Degussa AG, BASF AG, Bayer AG and Hoechst AG for providing us with chemicals.

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