

## Assignment of the Absolute Configuration to Winterstein's Acid, R-3-Dimethylamino-3-phenyl Propionic Acid, by the Asymmetric Synthesis of Homochiral (S)-(+)-Ethyl 3-Dimethylamino-3-phenyl Propionate

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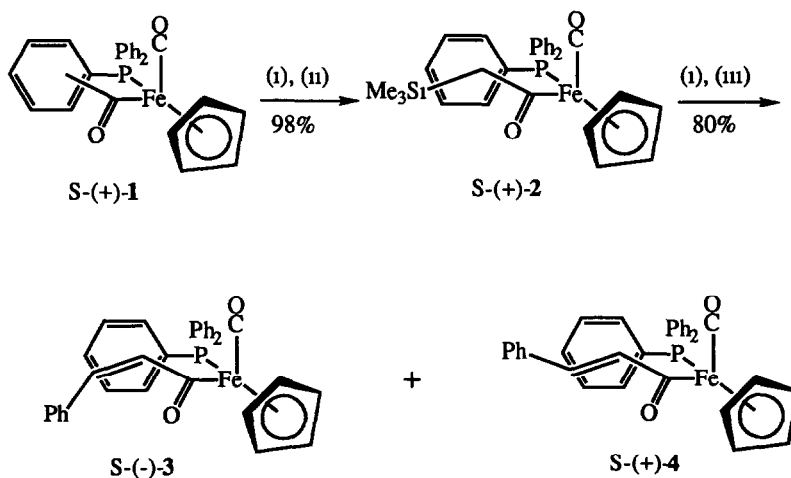
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**Abstract:** The asymmetric synthesis of homochiral (S)-(+)-ethyl 3-dimethylamino-3-phenyl propionate, via stereoselective Michael addition of lithium dimethylamide to (S)-Z-[( $\eta^5$ -C<sub>5</sub>H<sub>5</sub>)-Fe(CO)(PPh<sub>3</sub>)COCH=CHPh] and oxidative decomplexation, establishes the absolute configuration of Winterstein's acid, 3-dimethylamino-3-phenyl propionic acid, derived from Taxine B, as R

The diterpene Taxine B,<sup>1</sup> first isolated in 1856<sup>2</sup> from the Yew *Taxus baccata*, contains a carboxylate side chain which was isolated as Winterstein's acid from the initial hydrolysis of Taxine B.<sup>3</sup> The structure of Winterstein's acid was identified as 3-dimethylamino-3-phenyl propionic acid by independent synthesis.<sup>3</sup> Although synthetic homochiral Winterstein's acid has been obtained by resolution,<sup>3</sup> its absolute configuration has not been established.

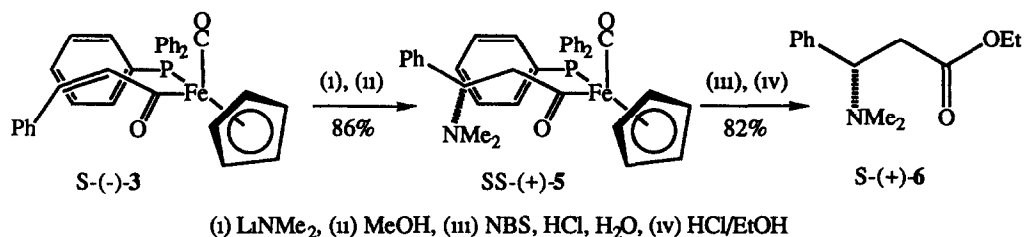
Deprotonation of the homochiral iron acetyl complex S-(+)-1 with butyllithium and quenching of the enolate with trimethylsilyl chloride gave the C-silylated derivative S-(+)-2, [ $\alpha$ ]<sub>D</sub><sup>20</sup><sub>546</sub> +301.1 (c 0.05, C<sub>6</sub>H<sub>6</sub>). Condensation of the lithium derived enolate of S-(+)-2 with benzaldehyde gave a mixture (40:60) of the Z- and E-cinnamoyl complexes 3 and 4.<sup>4</sup> Chromatographic separation (Al<sub>2</sub>O<sub>3</sub>, grade I) gave pure S-(-)-Z-3, [ $\alpha$ ]<sub>D</sub><sup>20</sup><sub>546</sub> -53.3 (c 0.05, C<sub>6</sub>H<sub>6</sub>) and S-(+)-E-4, [ $\alpha$ ]<sub>D</sub><sup>20</sup><sub>546</sub> +81.5 (c 0.05, C<sub>6</sub>H<sub>6</sub>).



(i) *n*-BuLi, (ii) Me<sub>3</sub>SiCl, (iii) PhCHO

Addition of lithium dimethylamide, generated by treatment of dimethylamine with butyllithium, to *S*-(-)-**3** at  $-100^{\circ}\text{C}$  followed by methanol quench gave the  $\beta$ -dimethylamino complex **5** (diastereomeric purity 75:1). Crystallisation from dichloromethane/hexane gave pure (*SS*)-(+)-**5**  $[\alpha]_{\text{D}}^{20} +356.9$  (c 0.05  $\text{C}_6\text{H}_6$ ). The configuration of the  $\beta$ -centre in **5** was assigned as *S* relative to the *S*-iron centre by analogy with addition to the corresponding *trans*-crotonyl complex<sup>5</sup> and by the characteristic shifts of the  $\alpha$ -protons<sup>5,6</sup>. The stereocontrol arises from lithium coordination to the acyl oxygen and delivery of the dimethylamide to the unhindered face of the *Z*-cinnamoyl ligand in the *cisoid* conformation with the acyl oxygen *anti* to the carbon monoxide ligand.<sup>5</sup>

Oxidative decomplexation of **5** with *N*-bromosuccinimide in tetrahydrofuran in the presence of 2.5 equivalents of 2.5 M aqueous hydrochloric acid gave, after purification by filtration through alumina and ion exchange chromatography (DOWEX 50X 8-100 resin), an aqueous solution of the HCl salt of 3-dimethylamino-3-phenyl propionic acid. This acid was converted to the ethyl ester *S*-(+)-**6** by evaporation of the water, and reaction with ethanol and hydrogen chloride gas. Basification and chromatography gave *S*-(+)-ethyl 3-dimethylamino-3-phenyl-propionate (**6**) as an oil, which could not be purified. Addition of 2.5 M HCl to **6** in tetrahydrofuran gave, after evaporation, the corresponding analytically pure crystalline (from  $\text{CHCl}_3$  :  $\text{EtOAc}$  1:1) HCl salt  $[\alpha]_{\text{D}}^{20} +10.2$ ,  $[\alpha]_{\text{D}}^{20} +23.1$  (c 0.5,  $\text{CHCl}_3$ ). The HCl salt of *S*-(+)-**6** was shown to be homochiral (>99.5% e.e.) by  $^1\text{H}$  n.m.r. spectroscopic analysis in the presence of (-)-2,2,2-trifluoro-1-(9-anthryl)ethanol in comparison with a racemic sample prepared from racemic **1**. This salt was used to regenerate pure *S*-(+)-ethyl 3-dimethylamino-3-phenyl-propionate (**6**)  $[\alpha]_{\text{D}}^{20} = +13.9$ ,  $[\alpha]_{\text{D}}^{20} +31.5$  (c 0.5,  $\text{CHCl}_3$ ).



Since the ethyl ester derived from natural 3-dimethylamino-3-phenylpropionic acid has  $[\alpha]_{\text{D}}^{18} = -15.5$  (neat),  $[\alpha]_{\text{D}}^{20} = -9.58$  (c 9.0,  $\text{CHCl}_3$ ),  $[\alpha]_{\text{D}}^{20} = -14.87$  (c 8.1,  $\text{Et}_2\text{O}$ ), and  $[\alpha]_{\text{D}}^{20} = -17.11$  (c 10.0,  $\text{MeOH}$ )<sup>3</sup> the above asymmetric synthesis establishes the absolute configuration of Winterstein's acid as *R*.

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#### References

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