The synthesis of (*S*)-(+)-gossypol *via* an asymmetric Ullmann coupling

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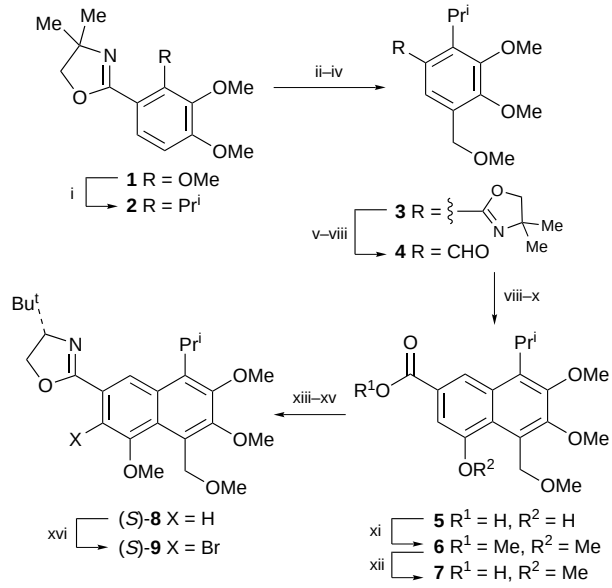
The first asymmetric total synthesis of (*S*)-(+)-gossypol is described using chiral oxazolines as the naphthyl substituent in a highly diastereoselective aryl–aryl coupling.

In 1886, racemic gossypol **13** was isolated[1] from cotton seeds and its structure elucidated in 1938 by Adams.[2] It is known to be active as an oral anti-spermatogenic agent[3] and has recently been tested on male subjects in China.[4] Additionally, (*R*)-gossypol was shown to be ten times more effective than its *S* antipode against tumour cells[5] and also showed inhibitory activity against HIV type 1.[6] The *S* antipode, on the other hand, has exhibited activity against herpes simplex virus,[7] and influenza[8] and parainfluenza virus.[7] The *S* enantiomer also induces DNA strand breaks in human leukocytes.[9]

Synthetic efforts to reach this axially chiral system have thus far only led to racemic gossypol, along with various analogues in the search for further biological activity.[10] The synthetic routes to gossypol feature mainly phenolic oxidative coupling, although in one instance an organolithium–$CoBr_2$ oxidative coupling was reported to proceed in poor (25%) yield.[10*c*]

Our approach to gossypol in enantiomerically pure form (either *R* or *S*) was based upon our earlier reports on asymmetric Ullmann couplings of 2-phenyl[11] or several naphthyl oxazolines.[12,13] In these earlier studies we showed that biaryl atropisomers could be accessed in high enantiomeric purity by either a thermodynamically controlled reaction[11] or a kinetically controlled process.[12,13] Due to the ample *ortho* substitution present in gossypol, restricted rotation about the symmetrically structural aryl–aryl bond showed relatively stable axially chiral enantiomers and indeed both have been isolated from natural sources.[14,15]

From the rich chemistry that has been developed[16] for the oxazoline moiety, both chiral and achiral, we felt this was a further opportunity to highlight a number of different reactions exhibited by the oxazolines. The route to (*S*)-**13** was initiated by transforming 2,3,4-trimethoxybenzene into the oxazoline **1** and displacing the 2-methoxy with isopropylmagnesium bromide as described previously (Scheme 1).[13] However, the route to gossypol required a pentasubstituted benzene **3** and, unlike the previous report, its preparation was not a trivial matter. We found that **2** could be metallated with ethoxyvinyllithium–HMPA[17] followed by addition of DMF to afford the intermediate formyl derivative. Reduction of the latter with $LiAlH_4$ and conversion to the methyl ether gave the tetrasubstituted phenyl oxazoline **3**. The oxazoline was removed, as described in previous studies,[16] to furnish the tetrasubstituted benzaldehyde **4** in 89% yield from **2**. A Stobbe condensation[18] followed by cyclization (Ac_2O–AcOH) and hydrolysis afforded the properly substituted naphthoic acid **5**. Our previous report on a model system[13] lacked the crucial substituent at C-5 in the naphthalene moiety. The naphthoic acid **5** was transformed, *via* its methyl ester **6**, to the tetramethoxynaphthoic acid **7** in 34% overall yield from starting oxazoline **1**. Conversion of **7** to the chiral oxazoline **8**[16*c*]† was performed with (*S*)-(+)-*tert*-leucinol[19] and then brominated in good yield to the bromonaphthalene **9**. This now represented the completely substituted precursor to gossypol and was subjected to the asymmetric Ullmann conditions. Heating a 40% solution of **9** in freshly distilled DMF and activated copper[20] (2 equiv.) at reflux for 1 h gave the



Scheme 1 *Reagents and conditions*: i, Pr^iMgCl, 96%; ii, EtOCH=CHLi, DMF; iii, $LiAlH_4$; iv, NaH, MeI, 72% over 3 steps; v, $MeOSO_2CF_3$; vi, $NaBH_4$; vii, H_2O^+, 89% from **2**; viii, NaH, dimethyl succinate; ix, AcOH, Ac_2O; x, KOH, 59% over 3 steps; xi, K_2CO_3, Me_2SO_4, 97%; xii, KOH, 98%; xiii, $(COCl)_2$; xiv, (*S*)-*tert*-leucine; xv, $SOCl_2$, 87% over 3 steps; xvi, Br_2, AcOH, 74%

binaphthyl system **10**‡ in 80% yield (Scheme 2) as a 17 : 1 diastereoisomeric mixture (NMR; *tert*-butyl singlets integrated between δ 0.50–0.55, ± 1% after several determinations). This is in contrast to the earlier report[13] where only a 11 : 1 diastereomeric ratio was obtained using a model system. After chromatography, the pure (a*S*,*S*)-**10** was relieved of its chiral auxiliary using previously described procedures[16*c*] to afford the diol (*S*)-**11**, which was immediately reduced to the requisite dimethyl derivative (*S*)-**12**.§ The *S* configuration assigned to **12** is based upon the previous transition state models[11,12] and had to await confirmation when gossypol was reached, since its X-ray structure and chiroptical properties have been reported.[21] The final approach to (*S*)-gossypol was accomplished by cleaving all eight methyl ethers with BBr_3 in CH_2Cl_2 at −78 °C for 24 h and immediatley transforming the polyhydroxy system to the bis(formyl) derivative using Swern conditions. The product (*S*)-**13**, reached in 9% overall yield from **1**, showed all The properties¶ for gossypol described in the literature[22,23] and was reached in only six steps from the bromonaphthyl oxazoline **9**. The enantiomeric purity of synthetic gossypol, as prepared above, was assessed as 99.2 : 0.8 by preparing the Schiff base from (*S*)-phenylalanine methyl ester and comparing it to racemic gossypol.[15]‖

Although the *S* enantiomer is known to be inactive as a male fertility agent,[3] simply carrying out the above syntheses using (*R*)-(−)-*tert*-leucinol would give the other gossypol antipode.

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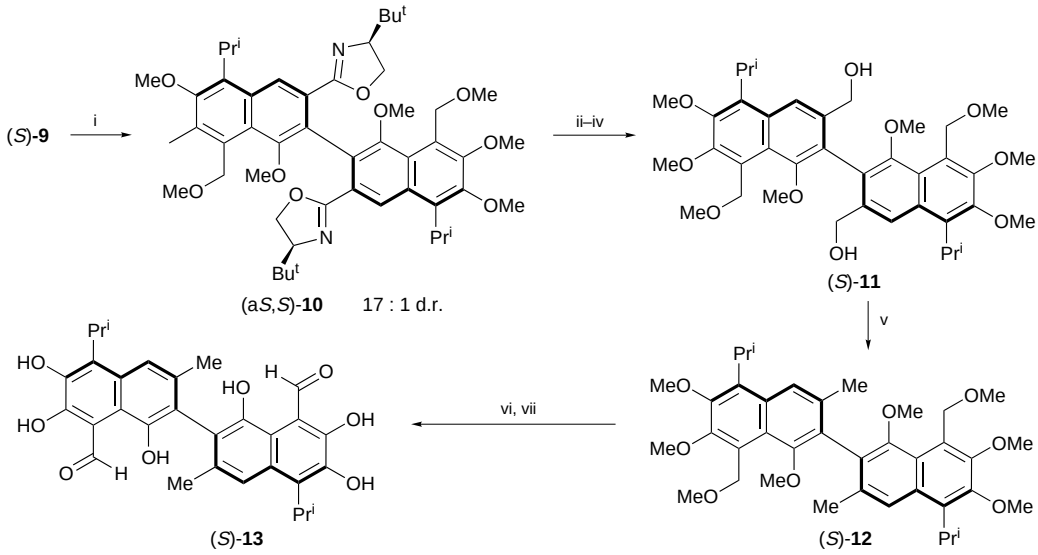

Scheme 2 *Reagents and conditions*: i, Cu^0, DMF, reflux, 80%; ii, TFA; iii, Ac_2O; iv, $LiAlH_4$, 72% over 3 steps; v, Pd/C, H_2, 84%; vi, BBr_3; vii, DMSO, $(COCl)_2$, 81% over 2 steps

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Footnotes and References

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† *Selected data* for (*S*)-**8**: light yellow oil $[\alpha]_D$ −61 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 9 H), 1.47 (d, 6 H, *J* 7.3), 3.40 (s, 3 H), 3.89 (s, 3 H), 3.99 (s, 3 H), 4.02–4.14 {m, 5 H [therein 4.07 (s, 3 H)]}, 4.23–4.34 (m, 2 H), 4.98 (s, 2 H), 7.49 (s, 1 H), 8.16 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.8, 32.5, 34.9, 32.0, 43.0, 57.6, 62.1, 78.4, 75.2, 85.2, 103.9, 105.0, 119.2, 124.0, 126.3, 128.4, 133.6, 143.3, 148.6, 149.8, 158.1; ν_{max}(thin film)/cm^{-1} 2952, 1655, 1450, 1263, 1183, 1042; HRMS: calc. for $C_{25}H_{35}NO_5$: 429.2515. Found: 429.2520.

‡ *Selected data* for (a*S*,*S*)-**10**: light yellow oil: $[\alpha]_D$ 228 (*c* 1.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.55 (s, 18 H), 1.48 (d, 12 H, *J* 7.4), 3.29 (s, 6 H), 3.85 (s, 6 H), 3.98–4.04 {m, 16 H [therein 3.98 (s, 6 H), 4.03 (s, 6 H)]}, 4.30–4.37 (m, 4 H), 5.16 (s, 4 H), 7.50 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 22.1, 24.9, 27.5, 47.3, 49.3, 52.4, 59.1, 67.1, 70.6, 81.4, 109.6, 119.2, 120.8, 123.1, 132.4, 145.2, 147.9, 146.0, 150.5, 151.9, 160.1; ν_{max} (thin film)/cm^{-1} 2957, 1644, 1594, 1463, 1341, 1242, 1030; calc. for $C_{50}H_{68}N_2O_{10}$: C, 70.07; H, 7.99. Found: C, 70.25; H, 7.89%.

§ *Selected data* for (*S*)-**12**: colorless oil: $[\alpha]_D$ 193 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (d, 12 H, *J* 7.3), 2.16 (s, 6 H), 3.13 (s, 6 H), 3.65 (s, 6 H), 4.08 {m, 14 H [therein 4.02 (s, 6 H), 4.11 (s, 6 H)]}, 5.35 (s, 4 H), 7.39 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2, 25.9, 29.1, 57.8, 62.0, 62.6, 68.4, 82.8, 103.3, 112.3, 117.2, 118.6, 120.5, 124.3, 125.9, 130.0, 134.1, 136.9; ν_{max}(thin film)/cm^{-1} 2957, 1654, 1602, 1459, 1290, 1246, 1034; calc. for $C_{38}H_{50}O_8$: C, 71.90; H, 7.94. Found: C, 71.95; H, 7.91%.

¶ *Selected data* for (*S*)-gossypol (*S*)-**13**: yellow powder: mp 186.1–186.9 °C (lit.,[2] 184 °C); $[\alpha]_D$ 371 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (d, 12 H, *J* 7.0), 2.14 (s, 6 H), 3.88 (septet, 2 H, *J* 6.9), 5.85 (s, 2 H), 6.39 (s, 2 H), 7.77 (s, 2 H), 11.11 (s, 2 H), 15.11 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 20.5, 28.1, 111.9, 114.9, 116.5, 118.2, 129.8, 134.0, 134.4, 143.4, 150.8, 156.0, 199.5; ν_{max}(KBr)/cm^{-1} 3377 (br), 1615, 1601, 1440, 1335, 1168 cm^{-1}; HRMS (LSIMS): calc. for $C_{30}H_{30}O_8$: 518.1941. Found: 518.1949.

‖ Racemic gossypol came from (i) a synthesis as above using achiral oxazolines, and (ii) purchased from Sigma. HPLC of the phenylalanine Schiff base from the Sigma material showed a 60 : 40 ratio of isomers, an indication that it originated from natural sources. The synthetic racemic material gave a 49 : 51 ± 1 ratio of diastereoisomers from (*S*)-phenylalanine. HPLC conditions: C_{18} reverse phase, 5 μm Hypersil®-ODS, gradient MeCN–KH_2PO_4 (0.01 M aq.) 91 : 9 to 82 : 18; monitored at 254 nm.

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