

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

A. I. Meyers* and Jeffrey J. Willemssen

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523-1872, USA

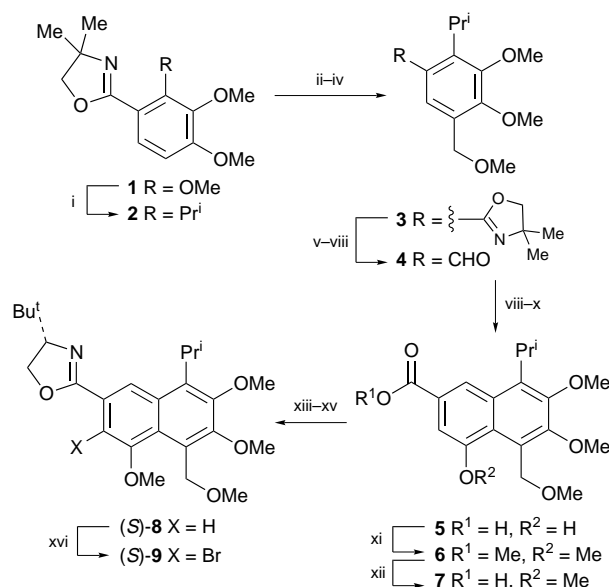
The first asymmetric total synthesis of (*S*)-(+)-gossypol is described using chiral oxazolines as the naphthyl substituent in a highly diastereoselective aryl–aryl coupling.

In 1886, racemic gossypol **13** was isolated¹ from cotton seeds and its structure elucidated in 1938 by Adams.² It is known to be active as an oral anti-spermatogenic agent³ 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 cells⁵ 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 influenza⁸ 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–CoBr₂ oxidative coupling was reported to proceed in poor (25%) yield.^{10c}

Our approach to gossypol in enantiomerically pure form (either *R* or *S*) was based upon our earlier reports on asymmetric Ullmann couplings of 2-phenyl¹¹ 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 reaction¹¹ 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 developed¹⁶ 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 ethoxyvinylolithium–HMPA¹⁷ followed by addition of DMF to afford the intermediate formyl derivative. Reduction of the latter with LiAlH₄ 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 condensation¹⁸ followed by cyclization (Ac₂O–AcOH) and hydrolysis afforded the properly substituted naphthoic acid **5**. Our previous report on a model system¹³ 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**^{16c†} was performed with (*S*)-(+)-*tert*-leucinol¹⁹ 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 copper²⁰ (2 equiv.) at reflux for 1 h gave the

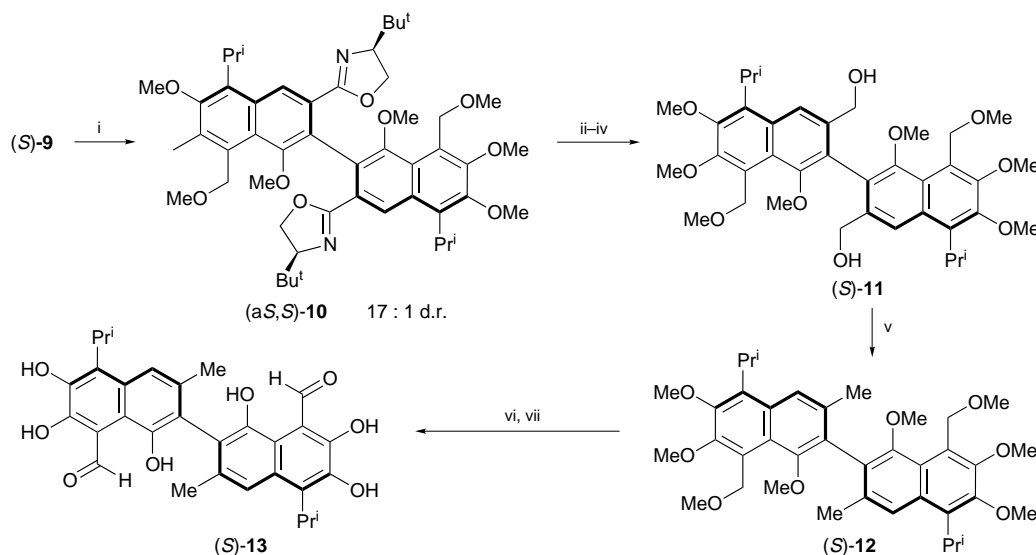


Scheme 1 Reagents and conditions: i, PrⁱMgCl, 96%; ii, EtOCH=CHLi, DMF; iii, LiAlH₄; iv, NaH, MeI, 72% over 3 steps; v, MeOSO₂CF₃; vi, NaBH₄; vii, H₂O⁺, 89% from **2**; viii, NaH, dimethyl succinate; ix, AcOH, Ac₂O; x, KOH, 59% over 3 steps; xi, K₂CO₃, Me₂SO₄, 97%; xii, KOH, 98%; xiii, (COCl)₂; xiv, (*S*)-*tert*-leucine; xv, SOCl₂, 87% over 3 steps; xvi, Br₂, 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 report¹³ where only a 11:1 diastereomeric ratio was obtained using a model system. After chromatography, the pure (*aS,S*)-**10** was relieved of its chiral auxiliary using previously described procedures^{16c} 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 BBr₃ in CH₂Cl₂ at –78 °C for 24 h and immediately 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.

The authors are grateful to the National Institutes of Health and the U.S. Department of Education for a fellowship



Scheme 2 Reagents and conditions: i, Cu⁰, DMF, reflux, 80%; ii, TFA; iii, Ac₂O; iv, LiAlH₄, 72% over 3 steps; v, Pd/C, H₂, 84%; vi, BBr₃; vii, DMSO, (COCl)₂, 81% over 2 steps

(J. W. W.). The authors also thank Dr K. Drauz of Degussa AG for generous samples of (*S*)-*tert*-leucine.

Footnotes and References

* E-mail: aimeyers@lamar.colostate.edu

† *Selected data for (S)-8*: light yellow oil [α]_D −61 (c 1.2, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₅H₃₅NO₅: 429.2515. Found: 429.2520.

‡ *Selected data for (aS,S)-10*: light yellow oil: [α]_D 228 (c 1.9, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₅₀H₆₈N₂O₁₀: C, 70.07; H, 7.99. Found: C, 70.25; H, 7.89%.

§ *Selected data for (S)-12*: colorless oil: [α]_D 193 (c 1.4, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₃₈H₅₀O₈: 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); [α]_D 371 (c 1.1, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₃₀H₃₀O₈: 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 \pm 1 ratio of diastereoisomers from (*S*)-phenylalanine. HPLC conditions: C₁₈ reverse phase, 5 μ m Hypersil®-ODS, gradient MeCN–KH₂PO₄ (0.01 M aq.) 91:9 to 82:18; monitored at 254 nm.

- 1 J. Longmore, *Indian J. Chem.*, 1986, **5**, 200.
- 2 R. Adams, R. C. Morris, D. J. Butterbaugh and E. C. Kirkpatrick, *J. Am. Chem. Soc.*, 1938, **60**, 2191 and earlier papers.
- 3 National Coordinating Group on Male Fertility Agents, *China's Med.*, 1978, **6**, 417.
- 4 S. Z. Qian and Z. G. Wang, *Annu. Rev. Pharmacol. Toxicol.*, 1984, **24**, 329.

- 5 A. E. A. Joseph, S. A. Martin and P. Knox, *Br. J. Cancer*, 1986, **54**, 511.
- 6 T. S. Lin, R. Schinazi, B. P. Griffith, E. M. August, B. H. F. Eriksson, D. K. Zheng and W. H. Prusoff, *Antimicrob. Agents Chemother.*, 1989, **33**, 2149.
- 7 P. H. Dorsett and E. E. Kerstine, *J. Pharm. Sci.*, 1975, **64**, 1073; R. J. Radloff, L. M. Deck, R. E. Royer and P. L. Vanderjagt, *Pharmacol. Res. Commun.*, 1986, **18**, 1063.
- 8 L. V. Goryunova and S. A. Vichkanova, *Farmakol. Toksikol.*, 1969, **32**, 615.
- 9 C. Yu, M. Sten, M. Nordenskjold, B. Lambert, S. A. Matlin and R. H. Zhou, *Mutat. Res.*, 1986, **164**, 71.
- 10 (a) J. D. Edwards and J. L. Cashaw, *J. Am. Chem. Soc.*, 1957, **79**, 2283; (b) M. C. Venati, *J. Org. Chem.*, 1981, **46**, 3124; (c) D. A. Shirley and W. L. Dean, *J. Am. Chem. Soc.*, 1957, **79**, 1205; (d) P. C. Meltzer, P. H. Bickford and G. H. Lambert, *J. Org. Chem.*, 1985, **50**, 3121; (e) V. I. Oguyonov, O. S. Petrov, E. P. Tiholov and N. M. Mollov, *Helv. Chim. Acta*, 1989, **72**, 353.
- 11 T. D. Nelson and A. I. Meyers, *Tetrahedron Lett.*, 1993, **34**, 3061.
- 12 T. D. Nelson and A. I. Meyers, *J. Org. Chem.*, 1994, **59**, 2577; A. I. Meyers and M. J. McKennon, *Tetrahedron Lett.*, 1995, **36**, 5869.
- 13 A brief report on the asymmetric Ullmann coupling leading to the (+)-apogossypol hexamethyl ether, a degradation product of **13**, has appeared: A. I. Meyers and J. J. Willemsen, *Tetrahedron Lett.*, 1996, **37**, 791.
- 14 S. A. Matlin, R. H. Zhou, G. Bialy, R. P. Bialy, R. H. Naqvi and M. C. Lindberg, *Contraception*, 1985, **31**, 141.
- 15 S. A. Matlin, A. G. Belengue, R. Tyson and R. G. Brooks, *J. High Resolut. Chromatogr.*, 1987, **10**, 86.
- 16 Three reviews on oxazolines and their synthetic utility have appeared (a) A. I. Meyers and E. D. Mihelich, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 270; (b) M. Reuman and A. I. Meyers, *Tetrahedron Reports*, 1985, 837; (c) T. G. Gant and A. I. Meyers, *Tetrahedron Reports*, 1994, 2297.
- 17 M. Shimano and A. I. Meyers, *J. Am. Chem. Soc.*, 1994, **116**, 10 815.
- 18 W. S. Johnson and G. H. Daub, *Org. React.*, Wiley, New York, 1950, vol. 1.
- 19 M. L. McKennon, A. I. Meyers, K. Drauz and M. Schwarm, *J. Org. Chem.*, 1993, **58**, 3568.
- 20 R. C. Fuson and E. A. Cleveland, *Org. Synth.*, 1955, **Coll. Vol. III**, 339.
- 21 L. Huang, S. Yi-Kang, G. Snatzke, D. K. Zheng and J. Zhou, *Collect. Czech. Chem. Commun.*, 1988, **53**, 2664.
- 22 J. W. Jarozewski, T. Strom-Hausen and L. L. Hansen, *Chirality*, 1992, **4**, 216; D. K. Zheng, Y. K. Si, J. K. Meng, L. Huang, *J. Chem. Soc., Chem. Commun.*, 1985, 168; D. S. Sampath and P. Balareem, *J. Chem. Soc., Chem. Commun.*, 1986, 649.
- 23 B. Brzezinski, J. Olejnik, S. Paszyc and T. F. Aripov, *J. Mol. Struct., Spectrosc. Lett.*, 1991, **24**, 509.

Received in Corvallis, OR, USA, 5th May 1997; 7/03043F