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An Asymmetric Synthesis of (+)-Apogossypol Hexamethyl Ether

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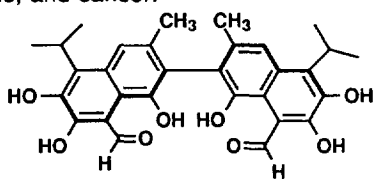
Summary: *The first asymmetric synthesis of the gossypol backbone via a stereocontrolled oxazoline mediated 2,2′ Ullmann coupling has been achieved.*

Gossypol (**1**), a polyphenolic binaphthyl isolated from cotton seed, has recently attracted considerable attention.[1] Pharmacologically this compound is known to be an oral antifertility agent in men and male animals, and shows activity for the potential treatment against HIV infections, diabetic complications, and cancer.[2]

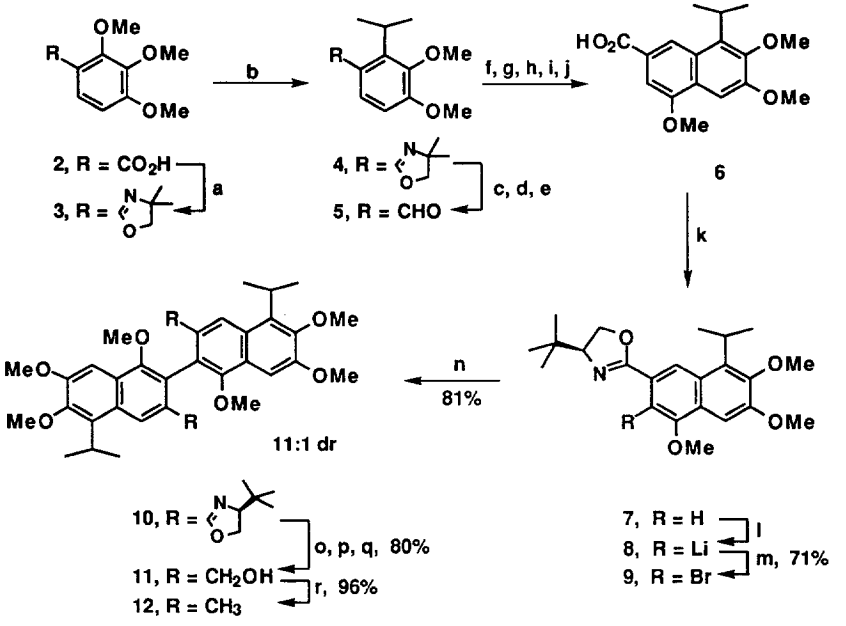


Gossypol (1)

Gossypol is a chiral molecule due to rotational restriction about the internaphthyl 2,2′ bond. Both atropisomers have been isolated from natural sources or resolved[3] but only the (-)-isomer exhibits oral antispermatogenic activity. Herein, we describe an efficient asymmetric synthesis of the gossypol backbone via a 2,2′-oxazoline mediated asymmetric Ullmann coupling, and the first asymmetric synthesis of apogossypol hexamethyl ether (**12**), a degradation derivative of **1**.[4]

Reaction of *o*-(methoxy)aryl oxazolines with alkyl lithiums or Grignard reagents to give the corresponding *o*-(alkyl)aryl oxazolines has been demonstrated previously in our laboratory.[5] This methodology was applied to the synthesis of the requisite pentasubstituted naphthyl oxazoline (**5**). Thus, treatment of the achiral oxazoline (**3**) with isopropylmagnesium chloride in THF[6], and subsequent hydrolysis of the oxazoline moiety gave the aldehyde (**5**).[7] The fully substituted naphthyl nucleus required for the Ullmann coupling was obtained using the Stobbe condensation[8] and simple methyl ester saponification led to the naphthoic acid (**6**). Chiral oxazoline (**7**) was prepared in a simple process from **6** and *tert*-leucinol.[9] *o*-Lithiation of **7** followed by reaction with tetrafluorodibromoethane gave the bromo oxazoline (**9**) in 71% yield.[10] Asymmetric Ullmann coupling[11] of the bromo oxazoline afforded an 81% yield of a 11:1 mixture of diastereoisomers (**10**) which could be separated by column chromatography (SiO_2, 8:1 Hex:EtOAc). The pure bis-naphthyloxazoline (**10**) was transformed in a three step process[12] to the chiral dicarbinol (**11**), $[\alpha]_D$ = 157.5 (CH_2Cl_2), which was enantiomerically pure by chiral HPLC assay.[13] Reduction of the chiral diol to apogossypol hexamethyl ether (**12**), m.p. 274-275°C (lit.[4]

273-274°C), $[\alpha]_D$ = 123.3 (CH_2Cl_2), occurred in 96% yield upon treatment of **11** with 10% Pd/C, a trace of HCl in ethanol, and H_2 at atmospheric pressure.[14,15] Based on previous asymmetric biaryl couplings from this group,[16] the S-absolute stereochemistry has been tentatively assigned to compounds **10-12**.



a) $(COCl)_2$; 2-Amino-2-methyl-1propanol; $SOCl_2$ b) *i*-PrMgCl c) Methyl triflate d) $NaBH_4$ e) Oxalic acid/H_2O f) Dimethyl succinate, *t*-BuOKg) AcOH,Ac_2O, AcONa; h) NaOH,MeOHi) K_2CO_3, $(CH_3O)_2SO_2$ j) NaOH, MeOH k) $(COCl)_2$; *tert*-Leucinol; $SOCl_2$ l) *n*-BuLi -78°-45° C m) $C_2F_4Br_2$ n) Cu°/ pyridine, reflux o) TFA, Na_2SO_4 p) Pyridine, Ac_2O q) $LiAlH_4$ r) 10% Pd/C, H_2, HCl, EtOH.

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