A Short Synthesis of (±)-Steganone and (±)-Steganacin

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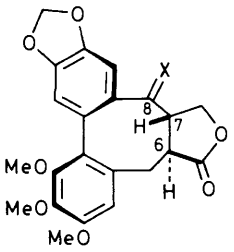
A short synthesis of (±)-steganone, using a stereoconvergent thallium trifluoroacetate-mediated biaryl coupling reaction, is described.

The antileukaemic bisbenzocyclo-octadiene lignans steganone (**1**) and steganacin (**2**)[1] have attracted considerable synthetic attention.[2] From a biosynthetic point of view the most interesting strategy has been the non-phenolic oxidation methodology which has resulted in the direct formation of the crucial biaryl bond, concomitant with the central eight-membered ring.[3] Unfortunately, the efficiency of the non-phenolic oxidation approach is curtailed by the apparent inability to carry out oxidative biaryl coupling in the presence of a benzylic oxygen substituent or masked equivalent.† Also, all the oxidative biaryl coupling approaches produce the wrong biaryl twist with respect to the stereochemistry of the lactone or ester substituents in the eight-membered ring. Subsequent thermal biaryl rotation rectifies this problem.

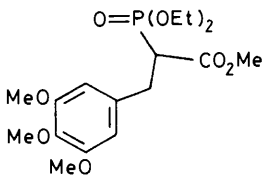
We report here a unique solution to these difficulties that involves an unprecedented stereoconvergent biaryl coupling reaction. Treatment of the phosphonate (**3**) with NaH–dimethoxyethane–piperonal (20 °C) gave the *E*-α,β-unsaturated ester (**4**) (91.5%) (containing <5% of the *Z*-isomer). When a solution of (**4**) in trifluoroacetic acid (TFA) at −18 °C was treated with $Tl(OCOCF_3)_3$‡ (1.15 equiv.) the biaryl (**6**) was isolated, after chromatography, in 81% yield. This yield is approximately twice that normally associated with non-phenolic oxidations in the steganone lignan area. In a separate series of experiments pure *E*-(**4**) was

† Many masked equivalents of the benzylic oxygen substituents at C-8 were tried ($-SO_2Ph$, $-CN$, $-SiMe_3$, *etc.*), and none successfully allowed oxidative biaryl coupling to take place.

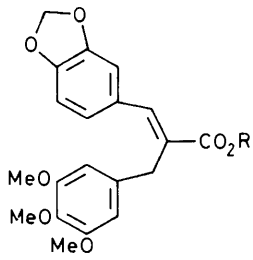
‡ $Tl(OCOCF_3)_3$ has been used for the oxidative dimerization of cinnamic acids (ref. 4).



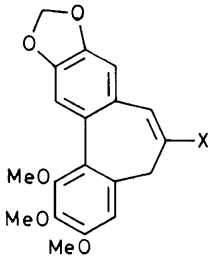
(1) X = O
(2) X = —OAc,---H



(3)



(4) R = Me
(5) R = H

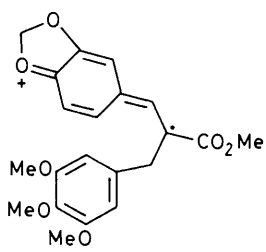


(6) X = CO_2Me
(7) X = CH_2OH

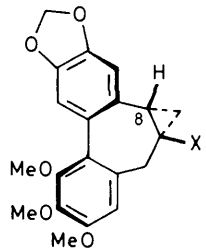
converted into (**6**) (70%) using the $Tl(OCOCF_3)_3$ procedure, and surprisingly, pure *Z*-(**4**) was also converted into (**6**) (28%). The stereoconvergent nature of the oxidative coupling reaction was shown to be the result of acid-catalysed (TFA) equilibration of *E*- and *Z* isomers, rather than oxidation of the cinnamate to a radical-cation (**4a**).

To complete the synthesis it is necessary to ring-expand the bisbenzocycloheptatriene (**6**) to an eight-membered ring, and establish the correct relative stereochemistry between the carboxylate substituent at C-6 and the biaryl twist. The cyclopropane (**8**) (available by an indirect route), did not undergo ring expansion using a variety of electrophilic and nucleophilic conditions, whereas the cyclopropylmethanol (**9**) [obtained by treatment of (**6**) with $LiAlH_4$ to give (**7**) (71% yield after recrystallization) followed by Simmons–Smith cyclopropanation (74%, as a single stereoisomer)] on exposure to AcOH–AcONa–$HClO_4$ at 45 °C for 3 h gave (**10**) (97%).[5] The stereochemistry depicted for both (**9**) and (**10**) is based respectively upon cyclopropanation from the most accessible face of the allylic double bond in (**7**), and solvolysis of (**9**) with inversion at C-8 to give (**10**). The correct relative configuration between C-6 and the biaryl twist was established by hydroboration (BH_3–tetrahydrofuran at 0 °C) followed by H_2O_2–NaOH and hydrolysis (K_2CO_3–H_2O–MeOH) to give the diol (**11**) (80%, m.p. 191—192 °C) as a single stereoisomer. To establish the relative stereochemistry of (**11**) unequivocally it was oxidized using Jones reagent at 20 °C to give the known oxo-acid (**12**) (80%), which on treatment with diazomethane gave the ester (**13**), m.p. 132.5—136 °C (from MeOH) (lit.[2] m.p. 133—134 °C). The oxo-acid (**12**) was converted into (±)-steganone using the standard conditions [KOH (5%)–CH_2O (37%), followed by Jones oxidation] and was identical to an authentic sample. In summary, this synthesis of (±)-steganone proceeds from piperonal in nine steps in an overall yield of 24% to the oxo-acid (**12**). This approach provides the requisite biaryl (**6**) in exceptionally high yield, and through solvolysis of (**9**) introduces the 8-oxygen substituent in a completely regiospecific reaction.§

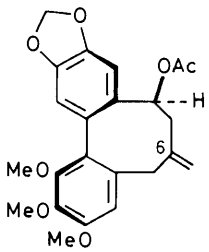
§ All new compounds gave satisfactory ^1H n.m.r., i.r., m.s. and/or microanalytical data in agreement with the proposed structures.



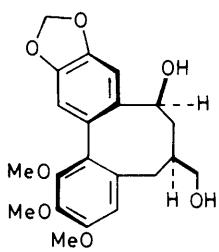
(4a)



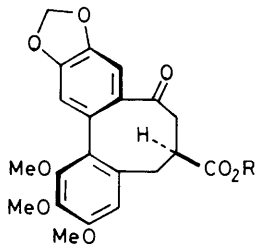
(8) X = CO_2Me
(9) X = CH_2OH



(10)



(11)



(12) R = H
(13) R = Me

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