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Asymmetric Total Synthesis of (+)-Pisatin, A Phytoalexin From Garden Peas (*Pisum sativum* L.)

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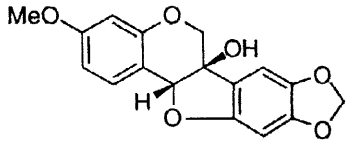
Abstract: A short asymmetric total synthesis of (+)-pisatin is described involving a Sharpless asymmetric dihydroxylation and an "hydrogenative cyclisation" as key steps.

In 1960, Perrin *et al.* isolated the pterocarpanol (+)-pisatin **1** from pods of garden peas (*pisum sativum* L.) which had been previously inoculated with fungal spores[1]. Interestingly, (+)-pisatin was able to inhibit the growth of the infecting fungus. Perrin *et al.* concluded that (+)-pisatin was a phytoalexin, a term coined earlier by Müller[2] and describing a defensive substance produced by plants in response to microbial attack. Despite this remarkable biological activity, only one synthesis of (+)-pisatin has been reported so far[3]. However, the described synthetic scheme is lengthy (16 steps) and the overall yield is low (0.08%). Furthermore, it involves a resolution step at a late stage in the synthesis.

Recently, we launched a biochemical program which aims at enhancing the natural defense of garden peas using structural analogues of (+)-pisatin **1**. A prerequisite to this study was to have at our disposal an efficient asymmetric route to **1** which could then be easily adapted to the preparation of optically pure analogues. Herein is described a short and enantioselective synthesis of (+)-pisatin **1**.



(+)-pisatin 1

After o-benzylation of sesamol, formylation took place with complete regioselectivity in the presence of the α,α-dichloromethyl methyl ether-$TiCl_4$ reagent[4] to provide aldehyde **3** (2 steps, 74%). Homologation of **3** into ester **5a** was achieved using a two step protocol. **3** was first exposed to methyl(methylthio)methyl sulfoxide (Tsuchihashi's reagent)[5] and powdered NaOH as a catalyst. This treatment furnished the ketenethioacetal **4** as a single stereoisomer [5c] (as seen by ^{1}H-NMR). Then, access to ester **5a** was best achieved

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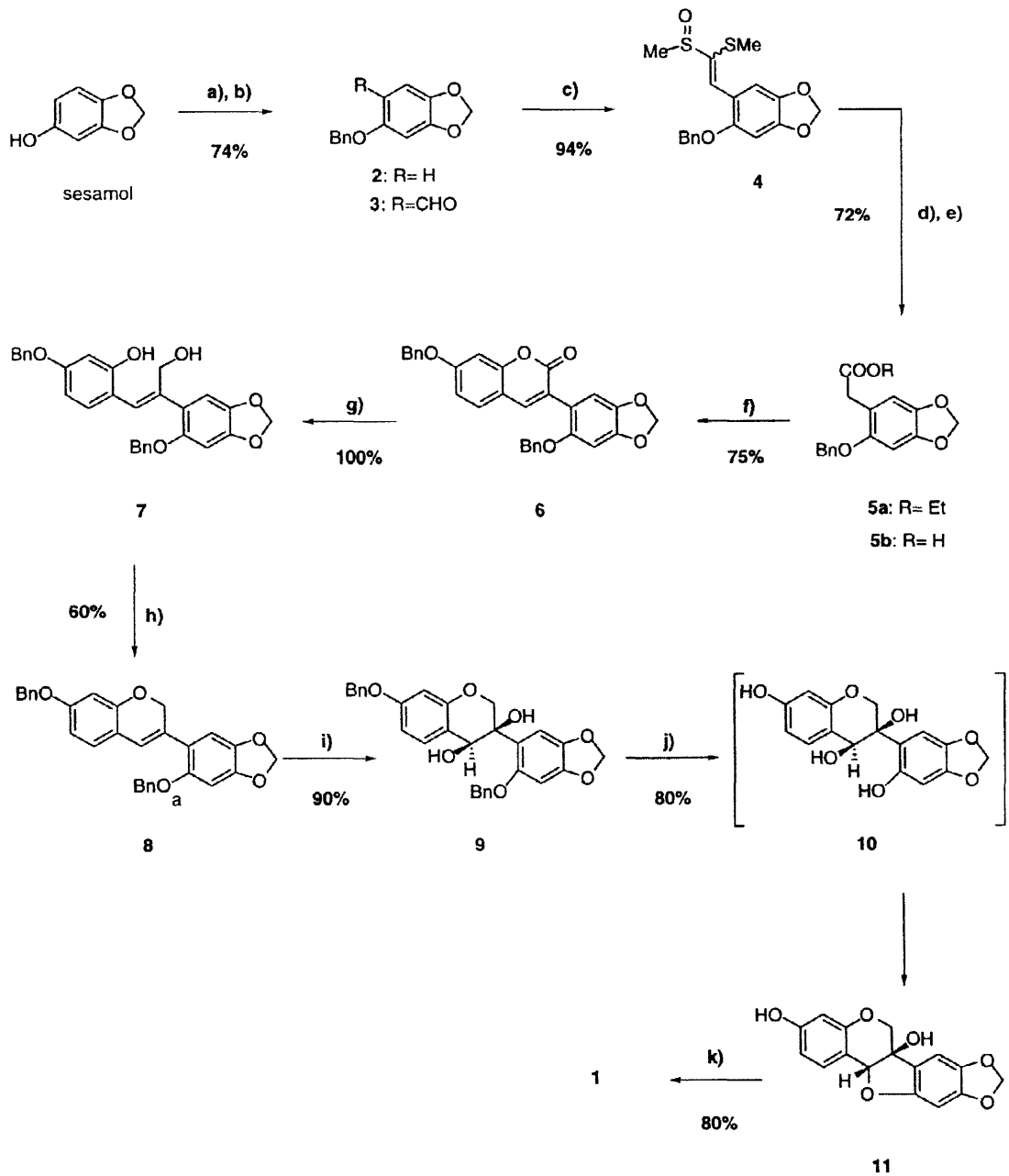
by treating **4** with an ethanolic solution of HCl and a catalytic amount of $CuCl_2$ according to a modification of Tsuchihashi's procedure[5] described recently by Schuda[6] (2 steps, 71%). Ester **5a** was then saponified and the resulting acid **5b** was coupled with 2-hydroxy-4-benzyloxybenzaldehyde[7] using phenyl dichlorophosphate as an acid activating agent[8] and DBU as the base to afford coumarin **6** (75%). After reduction of **6** in the presence of DIBAH[9] (100%), we attempted to cyclise diol **7** into *2H*-1-Benzopyran **8**. For this purpose, described methods recommend the use of either high temperature (mesitylene at reflux)[9] or strong acidic media (conc. HCl)[10]. Unfortunately, in our case, these conditions proved to be too harsh since only degradation of **7** was observed. Recourse to a much milder method was thus required.



a) BnBr, K_2CO_3, acetone, 60°C, 3 h.; **b)** Cl_2CHOCH_3, $TiCl_4$, CH_2Cl_2, 0 to 10°C, 5 min.; **c)** $CH_3SCH_2SOCH_3$, NaOH (0.34 eq.), 80°C, 1 h.; **d)** $CuCl_2.2H_2O$ (0.6 eq.), HCl in EtOH (0.25 M), reflux, 24 h.; **e)** powdered KOH, EtOH, R.T., 2 h.; **f)** 2-hydroxy-4-benzyloxybenzaldehyde, $PhOPOCl_2$, DBU, $ClCH_2CH_2Cl$, reflux, 48 h.; **g)** DIBAH, toluene, 0°C, overnight; **h)** PPh_3, DEAD, benzene, R.T., 12 h.; **i)** OsO_4 (1.2 eq.), dihydroquinine p-chlorobenzoate (1.2 eq.), CH_2Cl_2, -78°C, 24 h. then 20% $NaHSO_3$-20% Na_2SO_3, R.T., 30 min.; **j)** Pd/C (10%), MeOH, H_2 (1 atm.), R.T., 1.5 h.; **k)** Me_2SO_4, K_2CO_3, acetone, reflux, 30 min.

The Mitsunobu reaction[11a] which has been widely applied to the transformation of diol into cyclic ethers[11b] and which is well known to occur under practically neutral conditions seemed to be well suited for our problem. Indeed, treatment of **7** with the PPh_3-DEAD reagent provided smoothly *2H*-1-Benzopyran **8** with an acceptable 60% yield.

Arrival at **8** set the stage for the enantioselective elaboration of the two benzylic stereogenic centers. For this purpose, **8** was subjected to the catalytic Sharpless asymmetric dihydroxylation[12] using 0.5 eq. dihydroquinine p-chlorobenzoate, 1.25% OsO_4, 3 eq. K_3FeCN_6, 3 eq. K_2CO_3 in *t*BuOH-H_2O at room temperature. Surprisingly, under these conditions, **8** did not show any reactivity. However, treatment of **8** with a stoichiometric[13] amount of OsO_4 and dihydroquinine p-chlorobenzoate in toluene at room temperature, followed by a reductive work-up, furnished desired diol **9** in 80% ee[14]. Gratifyingly, when dihydroxylation was performed in CH_2Cl_2 at -78°C, the enantiomeric excess reached 94% and finally washing off the resulting solid with cold ether provided **9** optically pure, mp 140 °C, $[\alpha]_D^{20}$ +12 (c 0.17, abs. EtOH) in 90% yield. The lack of reactivity of **8** under catalytic conditions is unexpected. Strikingly, Dreiding models of the osmium (VI) ester obtained by addition of OsO_4 to **8** suggests that oxygen atom "a" (see **8** in scheme) could be positioned to chelate osmium (VI). If this chelation occurs, this would result in a significant increase in the osmium(VI) ester's stability and possibly in inhibition of hydrolysis. Thus, *in situ* recycling of the osmium and the chiral ligand would be prevented.

With optically pure diol **9** in hand, the next steps were to cleave protective groups and to construct the pterocarpanolic[15] framework. To our delight, it turned out that both transformations could actually be achieved in a single step in high yield. Indeed, treatment of a solution of diol **9** in MeOH with a large excess of Pd/C (10%)[16] under H_2 (1 atm.) furnished pterocarpanol **11**, mp 85°C, $[\alpha]_D^{20}$ +238 (c 0.15, EtOH) in 80% yield[17]. Monitoring the progress of the reaction by tlc showed rapid hydrogenolysis (≈5 min.) of the two benzyl ethers to provide the highly polar tetrol **10**. Then, **10** cyclises smoothly to **11**. Thus, this process of "hydrogenative cyclisation"[18] allows rapid and very efficient entry into pterocarpanolic systems. Finally, **11** was methylated in the presence of dimethylsulfate and K_2CO_3 to provide optically pure[19] (+)-pisatin **1**, mp 74°C, $[\alpha]_{578}^{20}$ +275 (c 0.15, abs. EtOH) in 80% yield. [natural (+)-pisatin: mp 61°C, $[\alpha]_{578}^{20}$ +280 (c 0.11, abs. EtOH][1,20].

In summary, we have developed a short (11 steps) and efficient (13% overall yield) asymmetric total synthesis of (+)-pisatin. Futhermore, the synthetic scheme should provide easy access to biologically interesting analogues. Progress on this work will be reported in due course.

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16. As much 10% Pd/C as diol **9** in weight was used.

17. Dehydration of **11** occurs easily under very mild acidic conditions. After filtration of the catalyst, the filtrate has to be neutralized with pyridine.

18. A similar "hydrogenative cyclisation" was observed by Kapil during the synthesis of the natural coumestan tuberostan: Prasad Krishna, A.V.; Kapil, R.S.; Popli, S.P. *J. Chem. Soc. Perkin Trans. I* **1986**, 1561-1563. Surprisingly, this type of cyclisation did not take place when the phenol located on the left side of diol **9** was protected as a methyl ether instead of a benzyl ether.

19. Optical purity of synthetic (+)-pisatin was checked by chiral phase HPLC (J.T. Backer Research products, 4.6x250mm, serial no 340085-17, product no RP-71130 Backerbond Chiral Phase DNBPG covalent 5μm); n-hexan/isopropanol 96.6/3.4; 2 ml/min.; detection at 308 nm: (+)-pisatin: R_t=12.7 min (single peak). (-)-pisatin[21]: R_t=11.6 min was not detected. Synthetic (+)-pisatin was thus optically pure.

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21. (-)-pisatin was prepared following the same synthetic scheme and by using dihydroquinidine p-chlorobenzoate as chiral ligand for the dihydroxylation step.