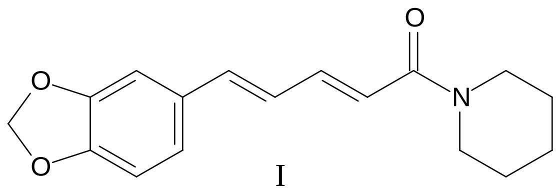
Experiment 3

Isolation of Piperine and Structural Confirmation by Synthesis

In the early days of organic chemistry, the structural elucidation of natural products required two components. The first was to perform known reactions on the natural product in order to degrade it into simpler, known materials, and then try to reconstruct what the original structure must have been in order to produce those simple materials. The second component was an attempt to synthesize the natural product by an unambiguous route. This would confirm the structure of the natural product - since the course of the reactions in the synthesis were known, the natural product must have the same structure as the synthesized material. A comparison of the physical properties of the natural and synthesized materials finished the confirmation. Even today, with the exotic spectroscopic and X-ray methods available, an unambiguous synthesis is still the best method of structural confirmation.

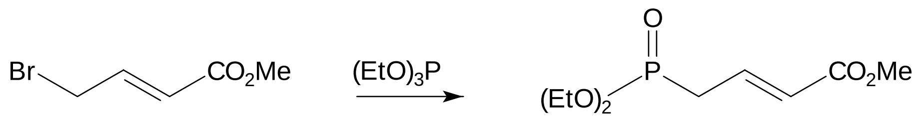
This experiment will model the isolation and confirmation of a proposed structure by synthesis. Piperine, an alkaloid, is relatively easily extracted from fresh peppercorns. It is reported to be responsible for the hot taste of black pepper.[1,2] The structure of piperine (**I**) is shown at right.



I

There are many structural features to piperine. There is an acetal, an aromatic ring, a *trans, trans* diene and an amide. The *trans, trans* diene is, synthetically, the most interesting feature of the molecule. Since the natural product has the *trans, trans* configuration, any reaction forming the diene must be stereospecific, and the diene must not isomerize after the reaction has occurred. With this requirement in mind, the most convenient synthesis of piperine involves a Wittig - Horner reaction of piperonal (**II**) with an appropriate phosphorane. The complete synthesis is shown below.[3,4]

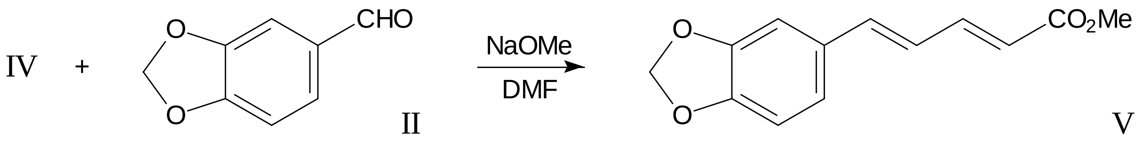
To begin, triethyl phosphite is added to the crotyl bromide (**III**) in an Arbusov reaction to provide the necessary phosphorane. The crotyl bromide already has one of the *trans* double bonds required for piperine, and this is retained in the phosphorane.



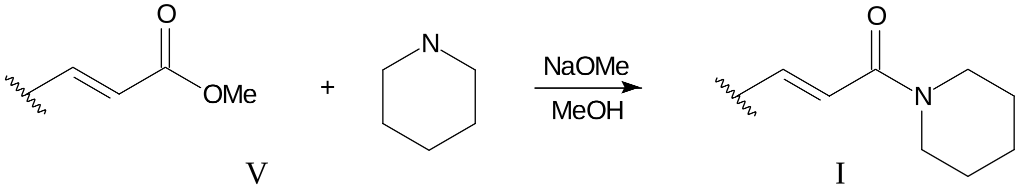
III

IV

A Wittig-Horner reaction of the phosphorane (**IV**) with piperonal (**II**) provides methyl piperate (**V**). The new double bond should be selectively formed as *trans*, and the double bond from the phosphorane should not isomerize



Finally, piperine is synthesized in a trans-amination reaction between **V** and piperidine. This reaction should also not isomerize either of the double bonds.



V I

Throughout this synthesis, the compounds and starting materials are analyzed by spectroscopic methods to confirm that the intermediates synthesized have the structures proposed. Comparison of the spectra of the synthetic piperine with the natural piperine will then confirm (or not) the structural proposal for piperine. In your report, you will have to justify your stereochemical conclusions.

Experimental

Isolation of Natural Piperine (I)

Grind fresh peppercorns (**25 g**) to a fine powder, place in a Soxhlet thimble, and extract with ethanol (**100 mL**) for 90 minutes. Cool the resulting solution, filter if necessary, and concentrate on the rotary evaporator. Keep the water bath below 60 °C during the concentration. Dissolve the residue in 10 % alcoholic potassium hydroxide (**25 mL**). Decant the solution if any residue remains. Cool the solution in an ice bath, and add water dropwise (about 30 ml will be required) to precipitate the piperine. Collect the piperine on a sintered glass funnel, and dry it on the vacuum pump. If time allows, a recrystallization from acetone:hexanes (3:2) will produce cleaner material. Record the mp, ir and ^{1}H nmr spectrum of piperine.

Methyl *E*-4-dimethylphosphonobut-2-enoate (IV)

In a fumehood, charge a 25 mL round bottom flask with methyl 4-bromocrotonate (**5.00 g**, 28.0 mmol). Add triethyl phosphite (**4.65 g**, 4.80 mL, 28 mmol, CAUTION - Stench!) *via* a syringe. Heat the reaction mixture at 150 °C using a controlled temperature oil bath for 90 minutes. Cool the reaction mixture, and Kugelrohr distil the reaction mixture at 70 °C for 20 minutes. This removes a by-product of the reaction. Continue to distil the bulk of the material at approximately 140 °C to obtain the phosphonate (**IV**). Record the ^{1}H nmr spectrum of the phosphonate. The nmr spectrum of the starting methyl 4-bromocrotonate will be provided.

Methyl piperate (V)

Mix the phosphonate **IV** (1 eq) and piperonal (**II**, 0.8 eq) in dry dimethylformamide (1.2 ml per mmole of **IV**). Sweep out the air atmosphere with nitrogen and cool the solution in an ice bath. Prepare a solution of sodium methoxide by dissolving sodium metal (1.5 eq) in dry methanol (2 x the volume of DMF). Add this solution to the DMF solution. Remove the ice bath and stir the reaction mixture at room temperature for 90 minutes. Pour the reaction mixture into water (10 mL per mmol **II**) and swirl for a few minutes. When possible, longer term cooling in the refrigerator will yield higher quantities of the product. Filter the resulting solid, rinse with a little cold methanol, and dry at the vacuum pump (heat may be required). Record the mp, ir and ^{1}H nmr spectrum of the ester **VI**. Also record a COSY spectrum of the ester. The nmr of piperonal will be provided.

Piperine (I)

Prepare a solution of sodium methoxide by dissolving sodium metal (**600 mg**, 26.1 g-atoms) in dry methanol (**25 mL**). To this solution, add methyl piperate (**1.00 g**, 4.3 mmol) and freshly distilled piperidine (**5 mL**, 50 mmol, available from your instructor). Heat the resulting mixture at reflux for at least 40 hours. Add the cooled reaction mixture to water (**100 mL**) and stir to obtain a yellow solid. Filter the precipitate, and dry on the vacuum pump. If time permits, this material may also be recrystallized. Record the mp, ir and ^{1}H nmr spectra of this material, and compare to the spectra of piperine obtained from black pepper.

Report

Use all of the spectra obtained to justify your structural conclusions about the compounds synthesized. This includes the provided spectra of the starting materials. Discuss the success of the synthesis. You may run ^{13}C nmr spectra if you wish, but they are not required for this experiment.

References

1. Grewe, R.; Freist, W.; Neumann, H.; Kersten, S. *Chem. Ber.* **1970**, *103*, 3752.
2. De Cleyn, R.; Verzele, M. *Bull. Soc. Chim. Belg.* **1975**, *84*, 435.
3. The synthesis is patterned after: Olsen, R.A.; Spessard, G.O. *J. Agric. Food Chem.* **1981**, *29*, 942.
4. Other reported syntheses of piperine: Dehmlow, E.V.; Shamout, A.R. *J. Chem. Research (S)* **1981**, 106. Also: Schulze, A.; Oediger, H. *Liebigs Ann. Chem.* **1981**, 1725.