The discovery of indoxacarb: oxadiazines as a new class of pyrazoline-type insecticides†

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Abstract: The evolution of the insecticidal pyrazoline moiety that was originally discovered in 1972 has led to the discovery of a new crop insecticide, indoxacarb, which is the first commercialized pyrazoline-type sodium-channel blocker. Both monocyclic and fused-tricyclic pyrazolines and pyridazines, as well as structurally related semicarbazones were examined prior to the discovery of analogous tricyclic oxadiazines which had similarly high activity as well as favorable environmental dissipation rates and low toxicity to non-target organisms. The eventual leading candidate, DPX-JW062, was originally obtained as a racemic molecule, but a chiral synthesis was developed which produces material that is 50% ee in the insecticidal (+)-*S*-enantiomer (DPX-MP062, indoxacarb).

Keywords: indoxacarb; oxadiazines; pyrazoline insecticides; sodium-channel blockers; asymmetric synthesis

1 INTRODUCTION

The discovery of insect-control compounds for crop protection with novel modes of action is vital towards managing pest strains that are resistant to existing compounds. The organophosphate and carbamate classes of cholinesterase-inhibiting insecticide, for example, have been in use for several decades and insect resistance to compounds with this mode of action has become a problem for growers. In addition, toxicity issues have placed restrictions on the use of many current compounds. Regulatory agencies worldwide have placed a premium on crop-protection chemistry having improved toxicological profiles towards non-target organisms. Also, new chemistries giving decreased environmental persistence and requiring lower use-rates (higher activities) are desired. The goal is to develop new insect-control compounds that are active against resistant pest strains, effective at low use-rates, and safe to people and to the environment.

The pyrazoline insecticides represent a class of chemistry which, until recently, had no commercial examples, despite being discovered nearly 30 years ago. The compounds were initially reported in patents from Philips–Duphar in 1973[1] as having high activity against Lepidopteran and Coleopteran pests (Fig 1). Subsequent patents[2,3] and publications[4–6] from Philips–Duphar on pyrazoline analogs with improved activity, along with the disclosure in 1982 that some pyrazolines showed activity against organophosphate-resistant insect species,[7] no doubt prompted work by other companies towards the identification of novel pyrazoline analogs.[8–12] The pyrazolines were reported by Salgado in 1990[13] to act by blocking the sodium channel of neurons, a novel insecticidal mode of

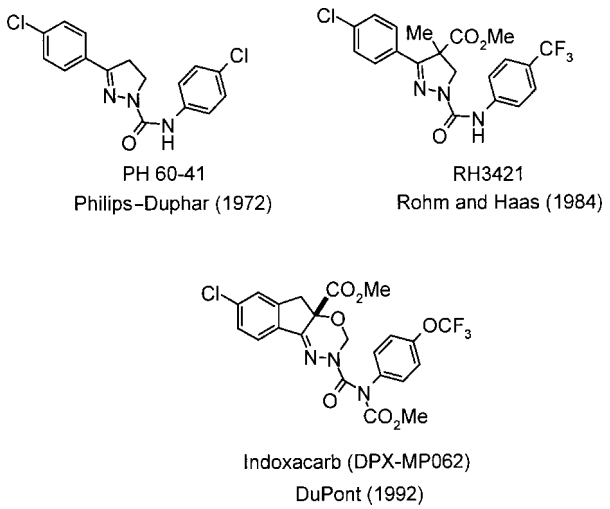

Figure 1. Early pyrazoline structures and indoxacarb.

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action. Synthesis efforts in the area focused on improving the toxicological[14] and environmental-fate properties[15] of the compounds while maintaining high insecticidal activity. A notable example is the Rohm and Haas compound RH3421, which was reported to have high insecticidal activity, low mammalian toxicity and a rapid rate of degradation in the environment.[16] The structure of this is similar to the Philips–Duphar compounds with the exception of having a methoxycarbonyl substituent at the 4-postion. Work at DuPont also focused on the discovery of novel pyrazoline-like insecticidal compounds with improved bio-efficacy along with favorable toxicological and environmental fate profiles.[17–24] The work involving the discovery of the oxadiazine analogs of the pyrazoline ring system which resulted in the new commercial insecticide indoxacarb (Steward™, Avaunt™) is described herein.[24,25]

2 STRUCTURAL MODIFICATIONS OF THE PYRAZOLINE NUCLEUS

DuPont research in the pyrazoline area, which began in the mid-1980s, was directed towards finding novel variations to the pyrazoline ring system that maintained high levels of insecticidal activity and favorable toxicological and environmental characteristics (Fig 2). For example, the semicarbazones represented a novel, ring-opened variation of the pyrazoline nucleus.[21] These compounds maintained high levels of insecticidal activity against a similar spectrum of pests (Lepidoptera and Coleoptera). Another variation was an inversion of the diazine nitrogens of the pyrazoline ring, resulting in 'upside-down' pyrazolines with high insecticidal activity.[18,19] Ring-expanded forms of the pyrazolines, known as pyridiazines, were found to be highly active.[22] Attachment of the pyrazoline ring at C-4 to the C-3 benzo substituent *via* a 1-, 2-, or 3-atom bridge resulted in 'tied-back' tricyclic pyrazolines (indazoles and oxyindazoles).[17,20] Similary, the pyridazines could be 'tied-back' into tricyclic forms. The tricyclic pyrazolines and pyridazines in many cases showed improved insecticidal activities over their monocyclic analogs.

The formation of the tricyclic analogs essentially fixes the conformation of the pyrazoline ring and forces the angular *R*-group into an axial orientation.[26] X-ray crystal structures have shown that substituents at the pyrazoline 4-position, and in analogous positions on the semicarbazones and tricyclic pyrazolines (oxyindazoles), typically adopt the axial orientation in the preferred conformers (Fig 3). Molecular modeling calculations also show a preference for axial orientations for the quasi-angular substituents for analogous pyridazines and 'upside-down' pyrazolines. Structure-activity relationships (SAR) in the pyrazoline area indicates the 4-substituent to be a key activity element in the structure. For example, lower alkyls, aryls and esters are preferred groups at this position for insecticidal activity.

3 TRICYCLIC PYRIDAZINE ANALOGS

The tricyclic pyridazine DPX-JP121 bearing a carbo-

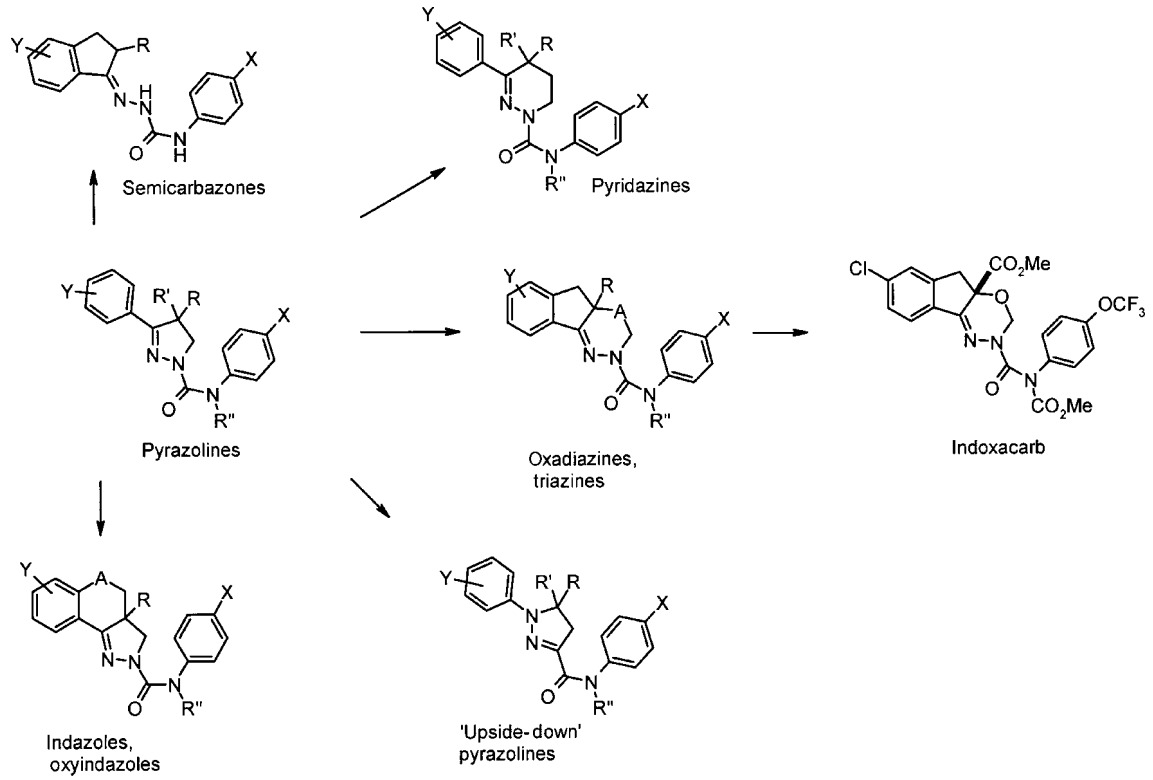


Figure 2. Modifications to the original pyrazoline structure.

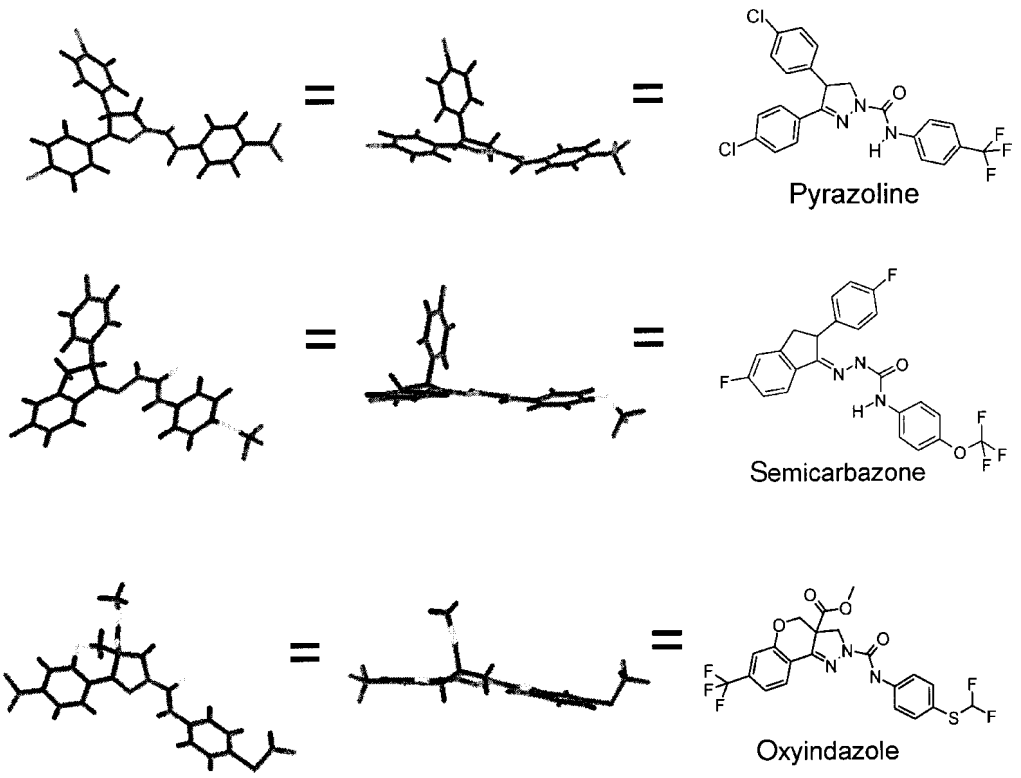


Figure 3. X-Ray crystal structure conformations of a representative pyrazoline, semicarbazone and oxyindazole.

methoxy substituent in the angular position was found to be highly active against *Spodoptera, Heliothis* and *Plutella* spp[22] In addition, DPX-JP121 showed low acute toxicity to mammals. Unfortunately, the compound showed less-than-ideal soil degradation rates, with a $t_{1/2}$ greater than 100 days. In addition, the synthesis of DPX-JP121 was complicated by the low yield conversion of the methoxycarbonylindanone (Fig 4; **1**) to the key intermediate 2-(2-bromoethyl)indanone **2**. The major product was formed as a result of *O*-alkylation, with the ratio of *O*-alkyl *vs C*-alkyl isomers being approximately 3:1. The separation of *O*-and *C*-bromoethylated products required careful flash chromatography, hindering efforts for preparative scale-up.

4 OXADIAZINES *VIA* O- FOR CH_2- SUBSTITUTION

We became interested in further potential modifications of the pyrazoline structure wherein one of the carbon atoms in the pyridazine ring of **3** was replaced by an oxygen atom (Fig 5).[24] The resulting oxadiazine **4** would be predicted to have similar structural morphology to the pyridazine (with a diazine ring-size intermediate between pyrazolines and pyridazines due to the slightly shorter C–O *vs* C–C bond distances) and, hence, was predicted to have similarly high levels of insecticidal activity. Additionally, the fact that the oxadiazine ring contains an *O,N*-acetal leads to the prediction that the oxadiazine ring may be susceptible to acidic hydrolysis, a factor which may contribute towards realizing shorter soil half-

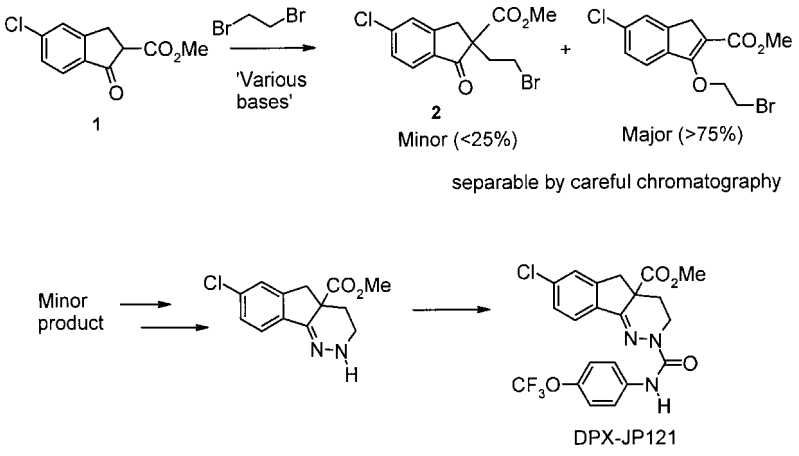


Figure 4. Preparation of tricyclic pyridazine DPX-JP121.

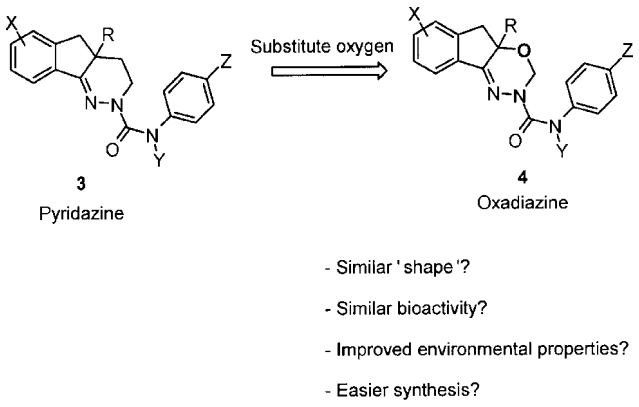


Figure 5. Pyridazine structure modification to form an oxadiazine.

lives. Moreover, the proposed synthetic route to these novel oxadiazines appeared fairly straightforward (Fig 6). The syntheses were envisaged to involve three key steps: (1) oxidative hydroxylation at the indanone 2-position, (2) formation of the indanone semicarbazone and (3) ring closure via *O,N*-acetal formation. These steps were readily accomplished and the desired tricyclic oxadiazines were obtained in good overall yields.

The first step, oxidative hydroxylation of indanones, was accomplished using a variety of conditions (Fig 7). In the cases where the 2-position was substituted by an electron-withdrawing ester group, the relatively high acidity of the 2-hydrogen allowed oxidation under

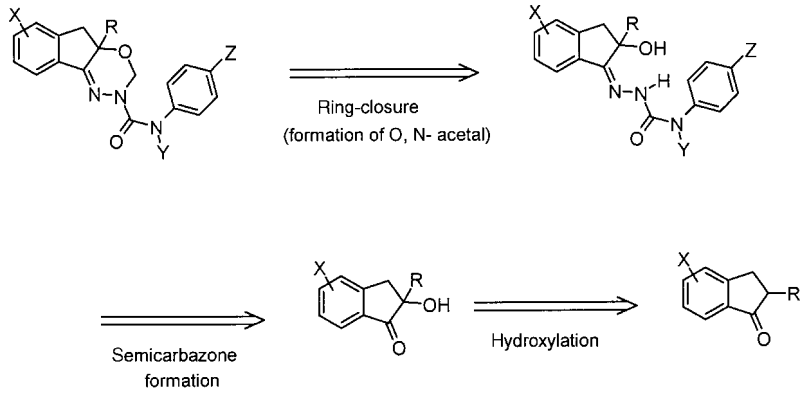


Figure 6. Retrosynthetic analysis of tricyclic oxadiazines.

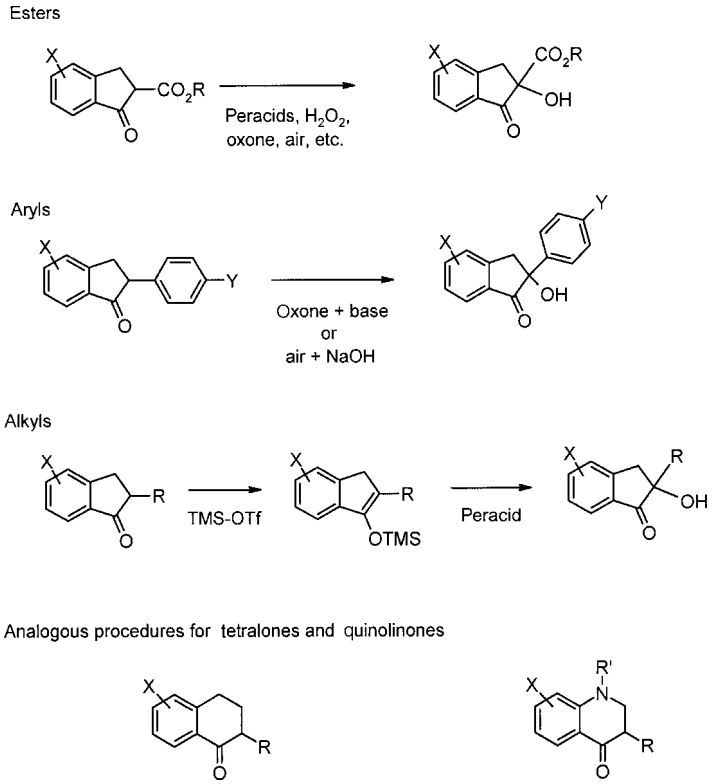


Figure 7. Hydroxylation reactions of indanones.

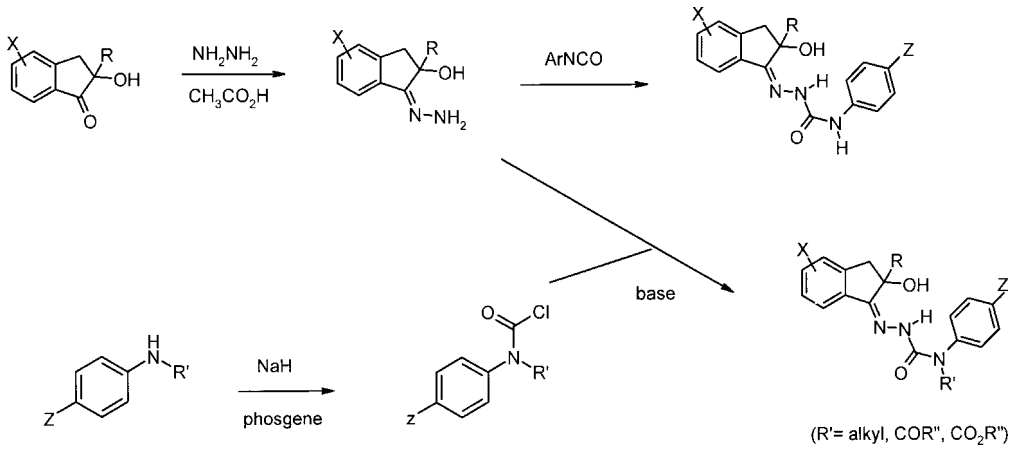


Figure 8. Semicarbazone formation from 2-hydroxyindanones.

mild conditions using, eg MCPBA[27] or hydrogen peroxide/sodium bicarbonate.[28] When the 2-substituent was an aromatic group, the use of more basic conditions (oxone with sodium hydroxide, air with sodium hydroxide and phase transfer catalyst[29]) became necessary for hydroxylation. With 2-alkyl substituted indanones, direct hydroxylation was not efficacious and the alternative two-step Rubottom procedure was used.[30] This method involved initial formation of the trimethylsilyl enol ether and subsequent treatment with an oxidizing agent (MCPBA). Tetralones and quinolinones, which are ring-expanded variants of indanones, were hydroxylated using analogous procedures.

The syntheses of the semicarbazone intermediates could be achieved using two complementary procedures (Fig 8). One procedure involved initial formation of the hydrazone followed by reaction with a phenyl isocyanate to give the semicarbazone precursors to the tricyclic oxadiazines.[21] In cases in which the desired oxadiazine product contained a substituent on the carboxanilide nitrogen, an alternative semicarbazone synthesis procedure, involving reaction of the hydrazone intermediate with a tertiary carbamoyl chloride, was a preferred option.[31] Both approaches gave high yields of the desired semicarbazone products.

The cyclization of the 2-hydroxy semicarbazones to give the target oxadiazine compounds involved formation of an *O,N*-acetal of formaldehyde (Fig 9).[32] In cases in which the carboxanilide nitrogen was unsubstituted, reactions of 2-hydroxy semicarbazones with paraformaldehyde in refluxing acetonitrile with an acid catalyst gave the desired tricyclic oxadiazines in good yields. In cases in which the carboxanilide nitrogen of the 2-hydroxy semicarbazones was substituted (with an alkyl, acyl or carbamoyl group), an alternative cyclization procedure using methylal and phosphorus pentoxide was preferred for best yields.[33] This procedure directly gave oxadiazines substituted at the carboxanilide nitrogen. Alternatively, these compounds could be obtained by *N*-alkylation or *N*-acylation of *N*-unsubstituted carboxanilides in the presence of a strong base (such as sodium hydride).

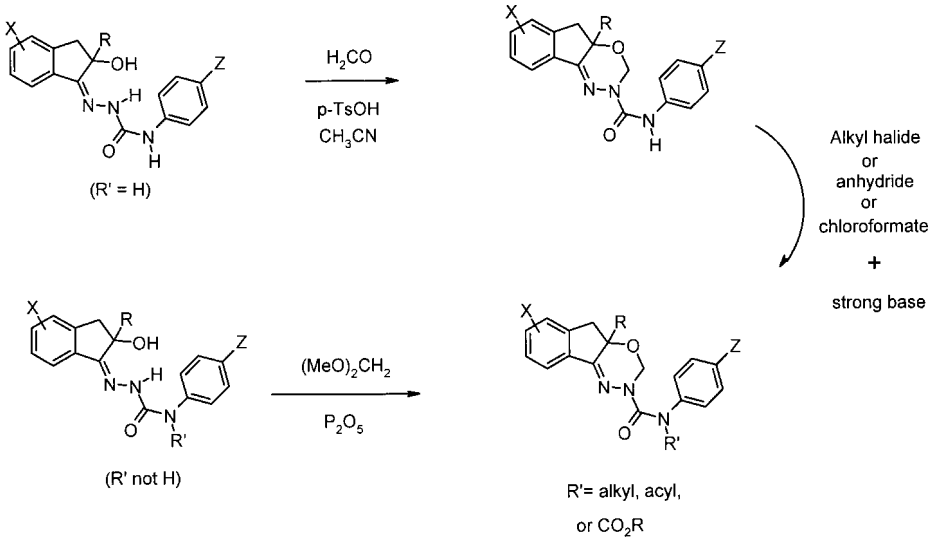


Figure 9. Oxadiazine-ring synthesis via *O,N*-acetal formation.

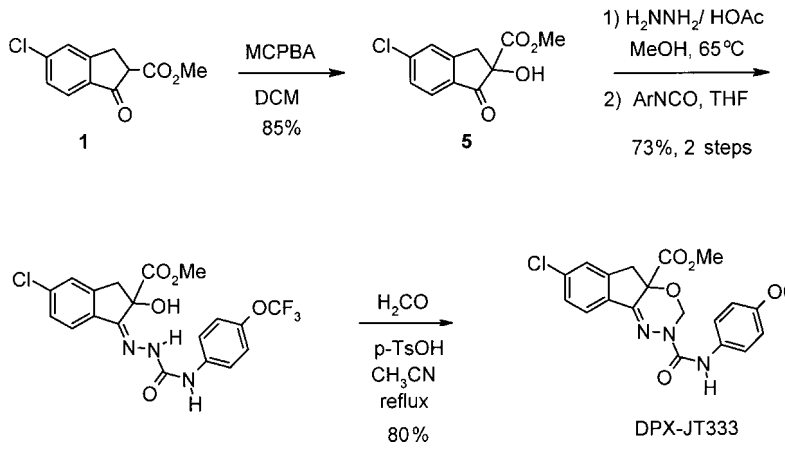


Figure 10. Synthesis of DPX-JT333.

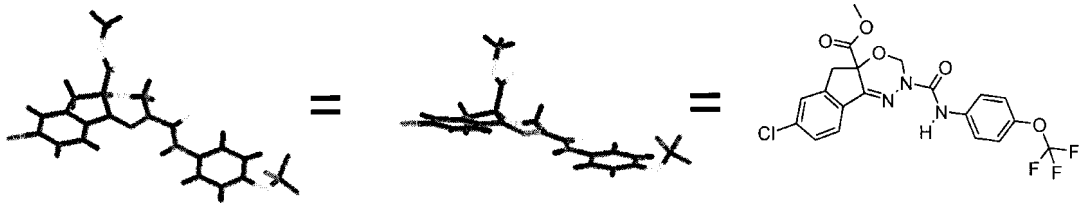


Figure 11. X-ray structure conformation of oxadiazine DPX-JT333.

The formation of DPX-JT333, which is the oxadiazine directly analogous to DPX-JP121, was achieved in good overall yield and required no chromatographic purifications of intermediates (Fig 10). X-ray crystallographic studies of DPX-JT333 showed a fairly planar conformation of most of the molecule with the angular carbomethoxy substituent residing outside the plane, analogous to the other pyrazoline analogs (Fig 11). DPX-JT333 was found to have insecticidal activity and an activity spectrum nearly identical to those of its pyridazine counterpart, DPX-JP121 (Fig 12). The rate of degradation in soil was clearly much enhanced in the case of DPX-JT333 (*vs* DPX-JP121) which showed a $t_{1/2}$ of less than 14 days (*vs* >100 days for DPX-JP121). It therefore appeared that the possible hydrolytic instability of the *O,N*-acetal resulted in compounds that degraded more rapidly in soil.

5 TRIAZINE ANALOGS

Triazines which are analogous to the oxadiazines could be prepared in a similar manner to the latter (Fig 13).[24] The first step involved amination of the indanone using cyclohexyl spiro-oxaziridine.[34] The resulting 2-amino indanone was isolated as the hydrochloride salt. Reaction with an aryl semicarbazide under acid catalysis gave the 2-amino semicarbazone

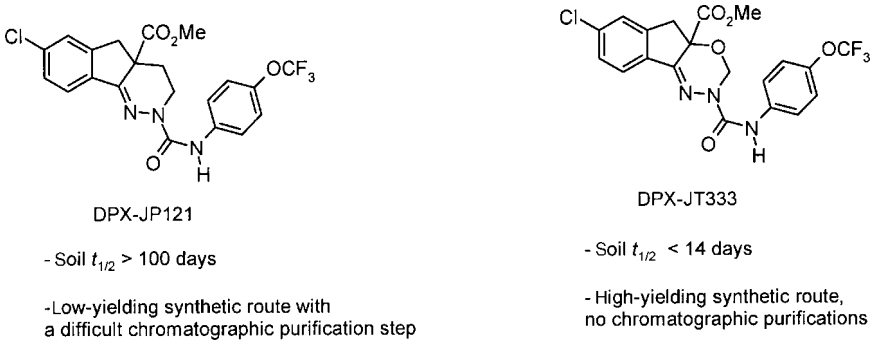


Figure 12. Comparison of DPX-JP121 *vs* DPX-JT333.

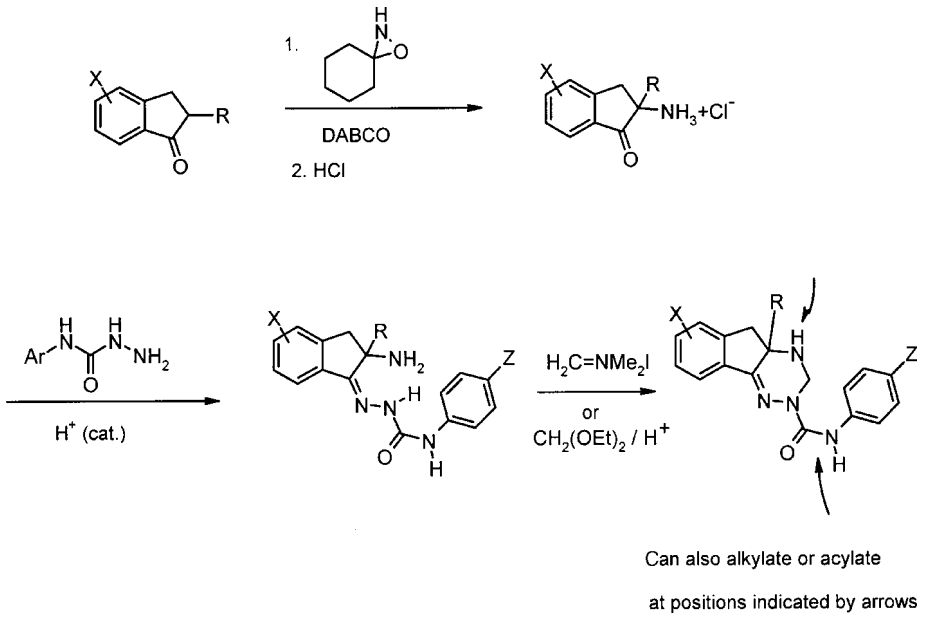


Figure 13. Synthesis of triazines.

(isolated as the free base) which was then cyclized to the tricyclic triazine using either Eschenmoser's salt or ethylal and acid catalysis. In the case of the triazines, further modifications were possible via functionalizations of either the triazine and/or the carboxanilide nitrogen atoms.

6 STRUCTURE–ACTIVITY RELATIONSHIPS (SAR)

The SAR for oxadiazines against fall armyworm, *Spodoptera frugiperda* (Smith) is summarized in Fig 14. It was found that substitution at the 4- or 5-positions of the benzo ring (X-substituents) gave analogs with the highest activity and, of those substituents, chlorine and bromine, along with trifluoroethoxy and trifluoromethyl, were the best. The angular R-group was either 4-halophenyl or methoxycarbonyl in the most active analogs, with alkyl substituents and higher esters giving lower levels of activity. The Z-substituent on the phenyl ring of the carboxanilide was typically *para* for the most active analogs, and the Z-substituent was usually trifluoromethoxy or trifluoromethyl. Finally, methoxycarbonyl or acetyl as Y-substituents gave the best activity for derivatives substituted at the carboxanilide nitrogen.

In the cases of ring-expanded tricyclic oxadiazines (derived from tetralones and quinolinones), SAR for the R-, X-, Y- and Z-substitutents was nearly analogous to the indanone-derived compounds in Fig 14 except for the position of the X-substituent on the benzo ring, which preferred 5-substitution for optimum activity (Fig 15). The triazine compounds had SAR and activities that were comparable to the analogous oxadiazines.

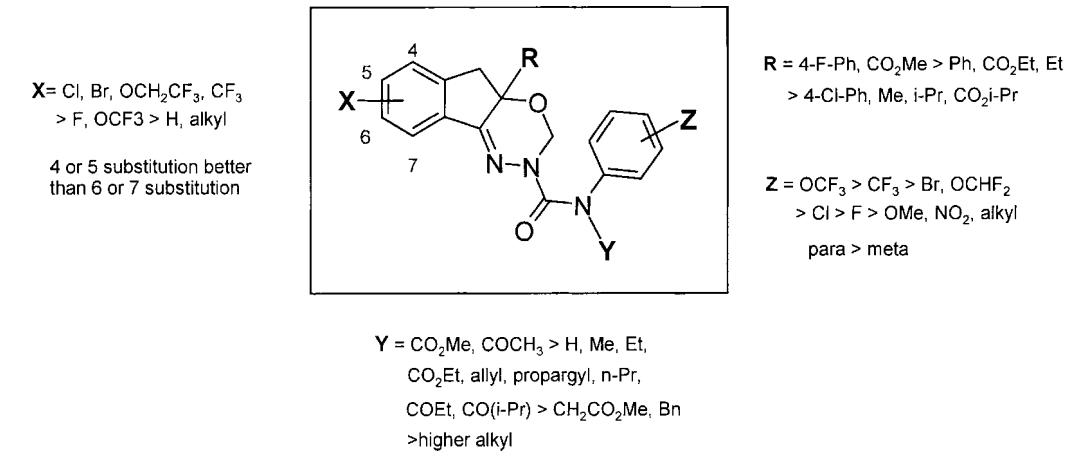


Figure 14. SAR for oxadiazines *vs Spodoptera frugiperda*. Note: substituents giving highest activities are listed first and relative activities are listed in descending order.

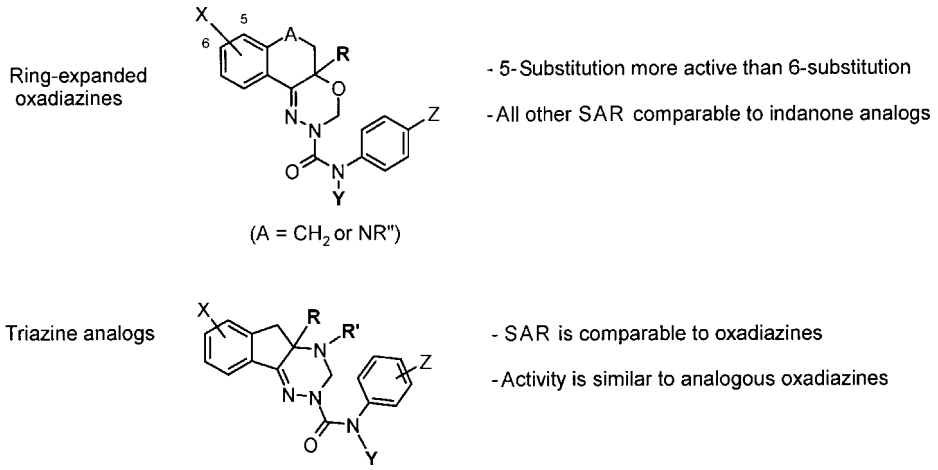
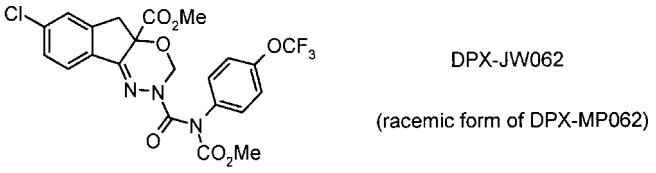


Figure 15. SAR summaries for ring-expanded tricyclic oxadiazines and for triazines.

7 SELECTION OF CANDIDATE COMPOUND DPX-JW062

Based on overall considerations of insecticidal efficacy, safety to non-target organisms (eg predatory insects, mammals, birds, fish), and rapid dissipation in the environment, the compound DPX-JW062 was selected for advanced pre-commercialization studies (Fig 16). DPX-JW062 was also found to be highly active against insect strains that had developed resistance to organophosphates, carbamates and pyrethroids.[25] The mode of action of DPX-JW062 was found to be through the blocking of the sodium channel in insects, the same as that previously reported for insecticidal pyrazolines.[35,36]

DPX-JW062 contains a chiral center and is a racemic molecule. Since the identity of the angular substituent at the chiral center of oxadiazines and other pyrazoline-type compounds had been found to be important in determining insecticidal activity,[37] we sought to prepare the individual enantiomers of DPX-JW062. The expectations were that one enantiomer would be more active than the other, possibly twice as active. The racemic mixture was separated by chiral HPLC and the resulting enantiomers were tested for insecticidal activity (Fig 17). The (+)-enantiomer, DPX-KN128 [(+)-DPX-JW062], was found to be twice as active as the racemic DPX-JW062, while the (−)-enantiomer was completely inactive. Thus, a chiral synthesis of (+)-DPX-JW062 became an important goal.



- Excellent control of *Spodoptera, Heliothis, Plutella, Trichoplusia, Cydia*
- Safe to beneficial insects
- Novel mode-of-action (blocks Na^+-channels)

Favorable toxicology:

- LC50 (rat) > 5000 mg kg^{-1}
- Not a skin or eye irritant
- Ames negative
- Quail LD50 > 2250 mg kg^{-1}

Safe to the environment:

- Soil $t_{1/2}$ = 5 days
- Bluegill LC50 > 1.0 mg $litre^{-1}$
- Rainbow trout LC50 > 0.5 mg $litre^{-1}$
- Rapidly hydrolyzes at pH > 7

Figure 16. Characteristics of DPX-JW062 (racemic indoxacarb).

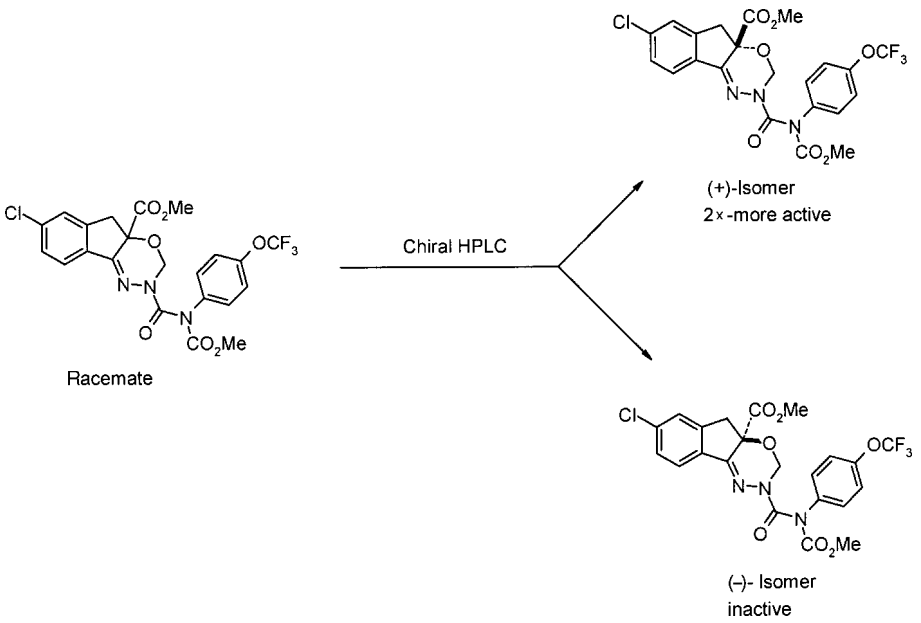


Figure 17. Separation of the active and inactive enantiomers of DPX-JW062.

8 ASYMMETRIC SYNTHESIS

In the synthesis of DPX-JW062, the introduction of chirality occurs in the hydroxylation of the 2-carbomethoxyindanone **1** to form **5** (Fig 18). An asymmetric approach to this oxidation was therefore sought.

We found that the use of the Sharpless asymmetric di-hydroxylation reagent (AD-mix)[38] effected the asymmetric hydroxylation of **1** directly (possibly via a di-hydroxylation of the enolic tautomer followed by hydrolysis). The AD-mix α and AD-mix β reagents gave 54% and 51% ee, respectively, of the (+)-and (−)-isomers of the chiral hydroxy-indanone intermediates **5** (see Fig 19). Each enantiomerically enriched intermediate was carried through the remainder of the synthesis to give the (+)-and (−)-isomers of DPX-JW062, each in approximately 50% ee. The use of the Sharpless asymmetric dihydroxylation procedure, however, was not ideal from the standpoint of scale-up since the AD-mix reagents contain osmium (which is both highly toxic and expensive). Alternative methods for asymmetric hydroxylation were therefore necessary for a commercial-scale synthesis of the enantiomerically enriched compound.

The chiral camphorsulfonyl–oxaziridine reagents developed by Davis *et al*[39] were found to effect asymmetric hydroxylation of **1** in the presence of catalytic sodium bicarbonate, albeit in only 35% ee (see Fig 20). A number of other procedures were also investigated (including use of Sharpless[40] and Jacobsen[41] asymmetric epoxidation procedures) without success. Finally, a novel procedure was discovered whereby a

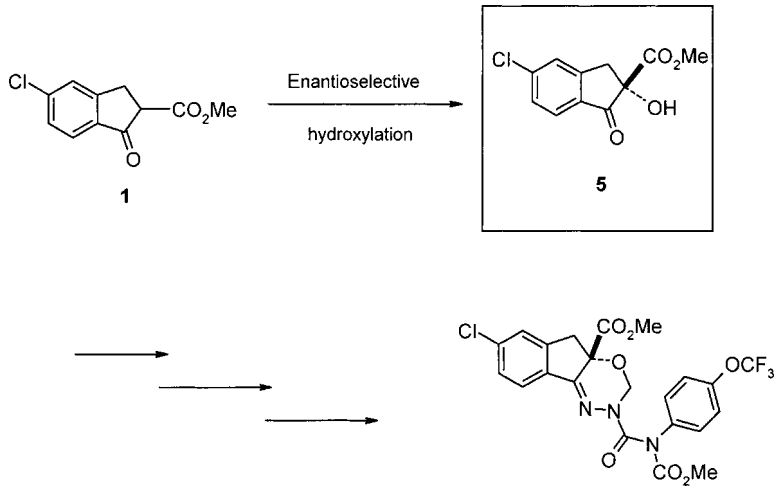


Figure 18. Asymmetric hydroxylation of **1**.

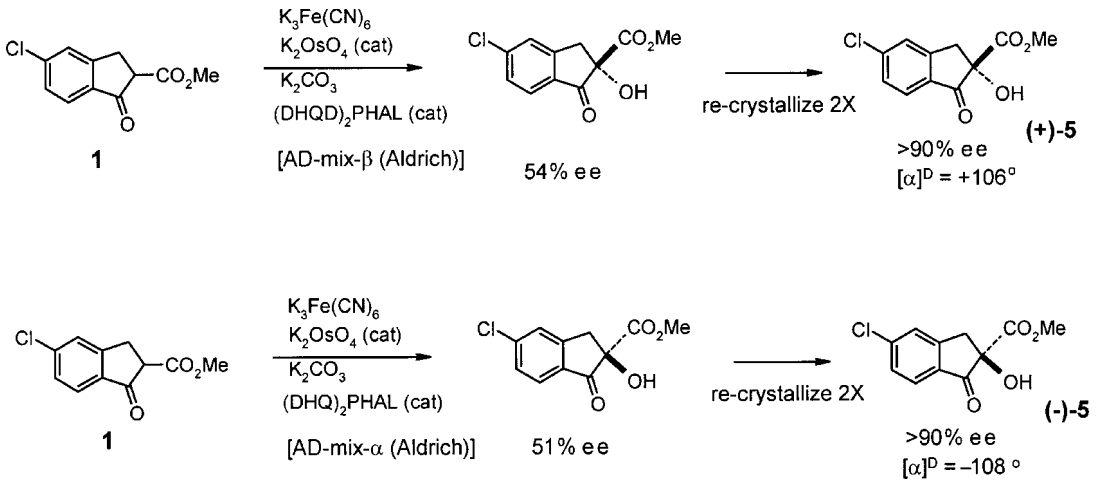


Figure 19. Asymmetric hydroxylation of **1** to form the individual enantiomers of **5**.

chiral base (cinchonine) catalyzed the reaction of **1** with *tert*-butyl hydroperoxide to give the (+)-hydroxy indanone **5** in 50% ee.[33] This reaction was amenable to commercial-scale synthesis. The remaining steps of carrying **5** through the synthesis to (+)-DPX-JW062 (50% ee) are shown in Fig 21. In the synthesis, the oxadiazine ring is formed as the benzyl carbamate (CBz)-protected form which is then de-protected to the somewhat unstable oxadiazine and coupled with the aniline carbamoyl chloride to yield the final product, (+)-DPX-JW062 (50% ee), which was renamed DPX-MP062. This compound was subsequently renamed indoxacarb.

9 CONCLUSIONS

Indoxacarb represents the first commercialized insecticide that acts by blocking the sodium channel in neurons, a mode of action first identified in pyrazolines. The discovery of indoxacarb was achieved by an extensive effort towards optimizing pyrazoline-type chemistry with regards to insecticidal efficacy, safety towards non-target organisms, and safety towards the environment. Variations to the pyrazoline nucleus led to the finding that structurally-related oxadiazines were also highly insecticidal. Optimization of the oxadiazines led to the identification of racemic indoxacarb (DPX-JW062) as a candidate for commercialization.

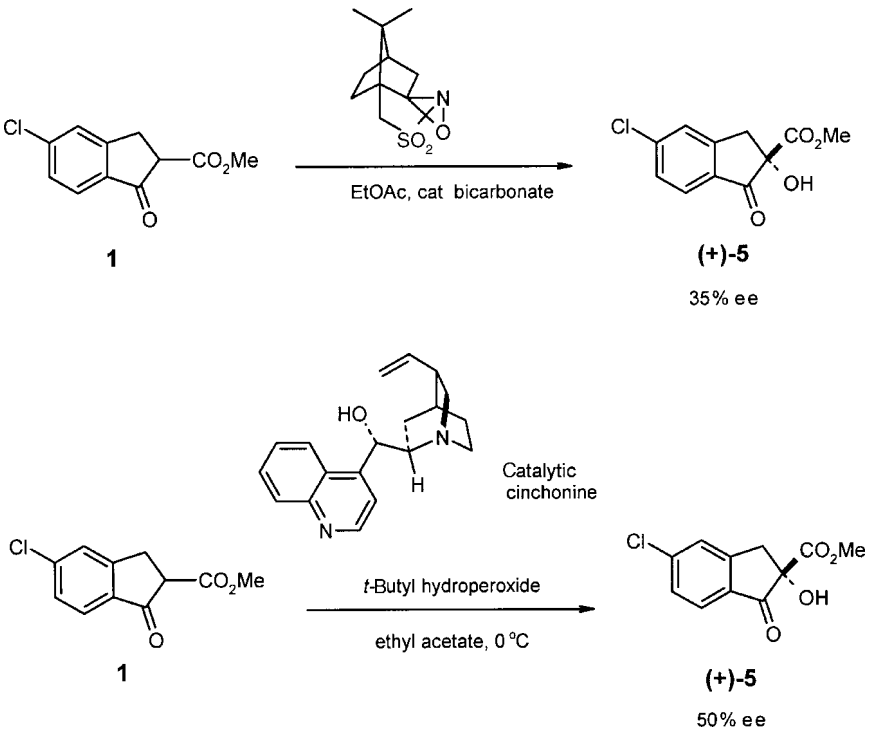


Figure 20. Other chiral syntheses of **5**.

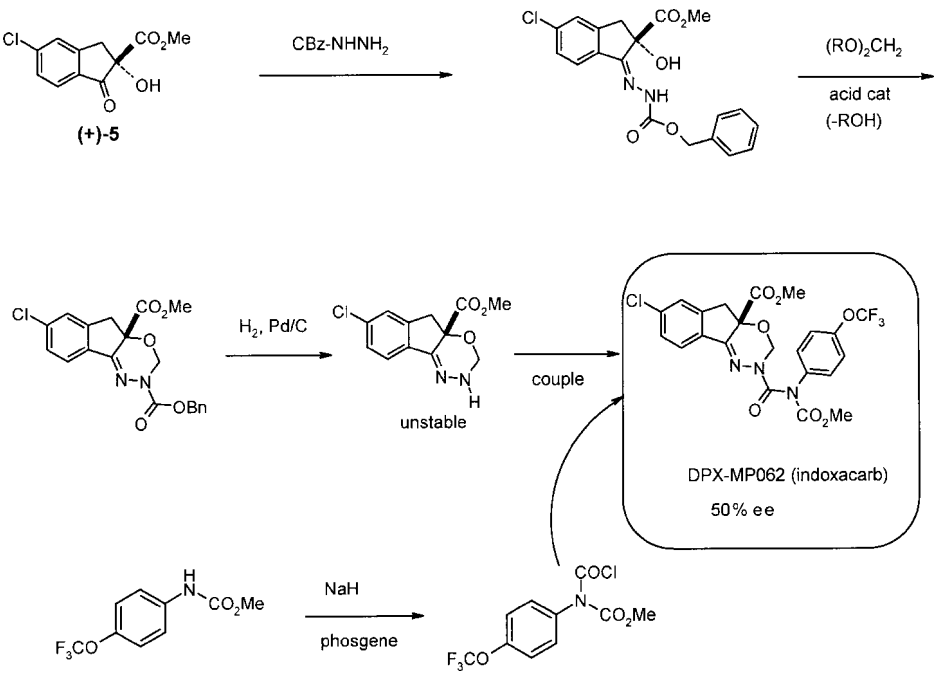


Figure 21. Synthesis of DPX-MP062 (indoxacarb).

Chiral synthesis provided a means of producing indoxacarb that is enantiomerically enriched in the active isomer.

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