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The Discovery of Bicyclopyrone

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Abstract: Two short topics were presented in the lecture titled *Some Highlights of an Agro Career* presented at the Fall Meeting Swiss Chemical Society, September 10th, 2021. The first of these topics discussed the discovery of the selective corn herbicide Bicyclopyrone. The second topic presented was concerned with host marking pheromones (HMPs), and described the HMP of the Mexican fruit fly *anastrepha ludens*, and its use in crop protection. The story concerning the host marking pheromones of the Mexican fruit fly has already been published in this journal[1] and thus this review will describe the discovery of Bicyclopyrone.

Keywords: Bicyclopyrone · Hydroxyphenylpyruvatedeoxygenase (HPPD) inhibitors · Selective herbicides

Born in Birmingham, England, ***Andy Edmunds*** received his PhD in Mechanistic Organic Photochemistry from the University of Warwick. He held post-doctorial positions at the Universities of Warwick and Oxford, before moving to Konstanz, Germany to work at Byk-Gulden. He began his career in Sandoz AG (now Syngenta) working in process chemistry in 1987. From 1988–1990 he carried out natural product research at the Sandoz Research institute in Vienna, Austria. He returned to Basel in 1990 where he has remained to this day with Syngenta crop protection in crop protection research, where he has made important contributions in herbicides, insecticides and fungicides in new active ingredient discovery.

1. Introduction

Herbicides are substances used to control undesired plants, also known as weeds. There are two types of herbicides; non-selective herbicides can be used to clear waste ground, industrial and construction sites, railways and railway embankments as they kill all plant material with which they come into contact. Examples of such non-selective herbicides are Paraquat and Glyphosate. Selective herbicides, on the other hand, control specific weed species, while leaving the desired crop relatively unharmed. Clearly, selective herbicides are useful in food production as they will prevent the weeds growing and competing with the desired crop for light, nutrients and water, as well as impeding the ease of harvesting of the desired crop. All of these factors will reduce the yield of the crop for the grower and add cost of the crop-derived products to the consumer. The requirements for selective herbicides are that they should control the weeds without damaging the crop, have low use rates (lower environmental load), be degradable (and thus leave no residues in the crop and subsequent products) and should not dissipate into ground water. Selective herbicides should also be produced sustainably at a cost which is beneficial for manufacturers, growers and consumers. This short review will discuss the discovery of a new selective herbicide, Bicyclopyrone, which exerts its herbicidal activity by inhibiting the enzyme hydoxyphenylpyruvatedeoxygenase (HPPD).

2. Discovery of HPPD Inhibitors

In 1977, scientists at Stauffer (a former legacy company of Syngenta) noticed that relatively few weeds grew under the bottle brush plant *Callistemon citrinus*. Analysis of soil samples where *C. citrinus* was growing revealed that the herbicide the plants were excreting was *leptospermone* (**1**, Fig. 1).[2] Pure samples of *leptospermone* (**1**) showed unique bleaching symptoms on several weed species albeit at relatively high rates (2 kg/Ha). This herbicidal activity was patented in 1980.[3] Independent of this discovery, in 1982 scientists from the same company were working on a project aimed at preparing novel acetyl-CoA carboxylase inhibitors, based upon the typical cyclohexanedione structure known for this class. The first targeted compound (**2**), prepared as shown in Fig. 1, showed some herbicidal activity and they thus attempted preparation of a phenyl analogue in a similar manner. This led not to the expected product (**3**), but to the triketone (**4**). This compound was devoid of herbicidal activity, but (luckily!) in safener screens the compound showed antidotal effects in soya for thiocarbamate herbicides. A further round of synthesis optimisation was undertaken and it was found that the compound (**5**) with an *ortho*-chloro substituent showed reasonable herbicidal activity. Furthermore, they noticed that it exhibited the same unique bleaching symptomology observed for *leptospermone* (**1**).[4] Further optimisation showed that removal of the methyl groups at the 5-position of the cyclohexanedione moiety (compound **6**) resulted in significantly enhanced herbicidal activity against a wide range of broad-leaved weeds, with good corn tolerance, when applied pre- and post-emergence at rates of about 2 kg/ha. The first patent was filed,[5] and the discovery of the benzoylcyclohexanedione herbicides had been made. These events are summarised in Fig. 1.

The generic structure of the HPPD herbicides is as shown in Fig. 1. The compounds contain a triketone moiety attached to an (het)aryl ring which is overall electron deficient and typically has a small *ortho* substituent. Triketones on the market are acidic with a pKa range of 2.7–3.3. Several triketone HPPD herbicides have reached the market place, such as Mesotrione, Tembotrione (selective corn herbicides) as well as Benzobicyclon, and Tefuryltrione (selective rice herbicides). These are shown in Fig. 2.

3. Mode of Action

Triketones exert their herbicidal activity by inhibition of the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD), which is an Fe(ɪɪ)-dependent, non-heme oxygenase that catalyses the oxidative decarboxylation and rearrangement of hydroxyl pyruvic acid (HPP) to homogentisate (HGA), the first committed step in tyrosine degradation.

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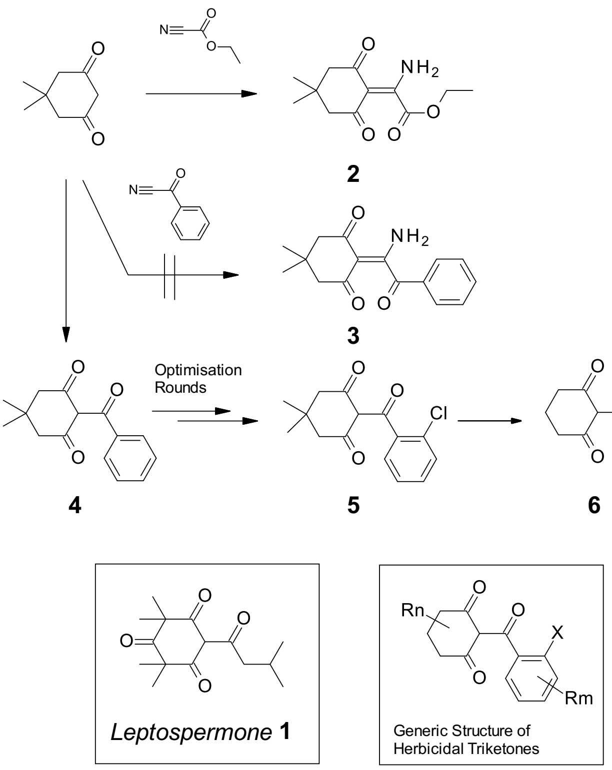


Fig. 1. Discovery of the triketone herbicides.

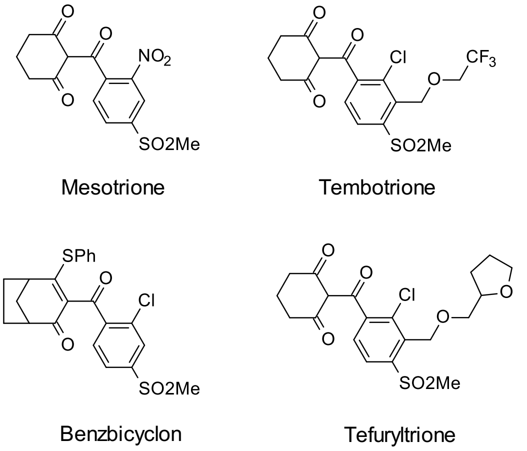
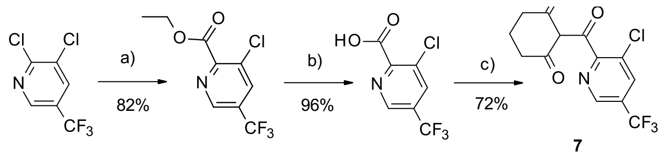


Fig. 2. Commercial HPPD compounds.

However, whereas HPPD-dependent tyrosine degradation is a process common across aerobic organisms, HPPD inhibitors are uniquely toxic to plants. In plants, the HGA product of the HPPD reaction is not only an intermediate in tyrosine degradation but also an essential intermediate in the pathways to the biosynthesis of tocopherols and plastoquinone (PQ). Depletion of carotenoids is associated with light-dependent generation of singlet oxygen which damages lipids and proteins and causes disassembly of the photosynthetic complex and release of free chlorophyll. Free chlorophyll is photodynamically photodestructive and itself generates further singlet oxygen eventually leading to the destruction of all leaf pigments and the characteristic white bleaching.[6]

4. Discovery of the Nicotinoyl Class of HPPD Herbicides

In the early-mid 1980s Ciba Geigy,[7] ICI,[8] and Stauffer[9] (all now Syngenta) had been interested in heterocyclic analogues of triketones, and each group had developed a specific emphasis on pyridines. In particular, chemists in Switzerland had developed access to such acids by selective carbonylation of the dichlorotrifluoromethyl pyridine intermediate in Scheme 1, left. Subsequent conversion to the triketone **7** afforded a compound that showed reasonable post-emergence herbicidal activity against broad-leaved weeds, albeit at relatively high rates (> 500 g ha^{-1}).



Reagents and conditions. a) 100°C under 50 bar CO in EtOH contg. Et_3N (3 eq.) and $(Ph_3P)_2PdCl_2$ (0.05eq); b) 2N NaOH, rt. c) DCC, CH_3CN, rt, 1hr, Cyclohexanedione then add Et_3N (2 eq.).

Scheme 1. Synthesis of picolinoyl HPPD inhibitors.

Isomeric nicotinic acids of the type **8** (Fig. 3) had not been synthesized as the pyridine *ortho*-substituent is a leaving group on an electron-deficient aromatic ring system, and thus intramolecular ring closure occurs leading to compounds **9** which are not active as herbicides (Fig. 3).

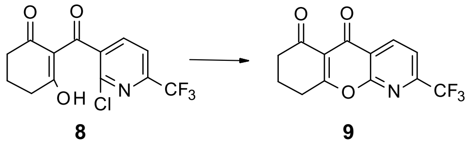
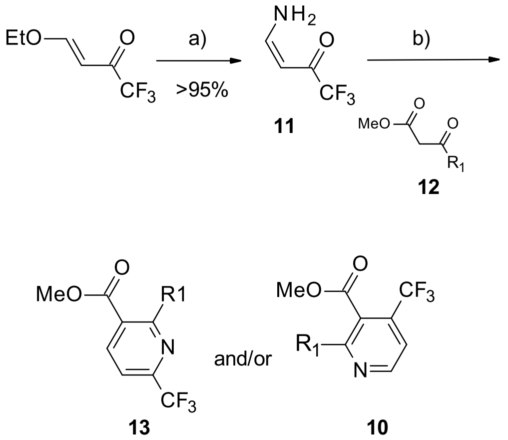


Fig. 3. Deactivation of pyridyl triketone herbicides by cyclisation.

We re-investigated this structural type by following up on an observation by Okada *et al.*, who had been trying to prepare 2,6-disubstituted trifluoromethyl nicotinoyl derivatives **10** by condensation of β-trifluoroacetylvinylamine **11** with active methylene compounds **12** (Scheme 2).[10]

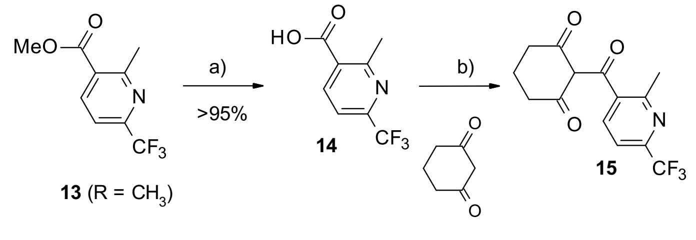
To their surprise, depending on the nature of the R^1 group, mixtures of the unexpected isomeric pyridine **13** as well as the expected isomer **10** were obtained. In the case of R^1 = methyl, the unexpected isomer **13**, in which the trifluoromethyl group attached to the carbon adjacent to the nitrogen in the starting mate-



Reagents and conditions: (a) NH_3 (aq.), CH_3CN, r.t.; b) CF_3CO_2H (0.1eq.), Toluene, Reflux.

Scheme 2. *De novo* pyridine synthesis.

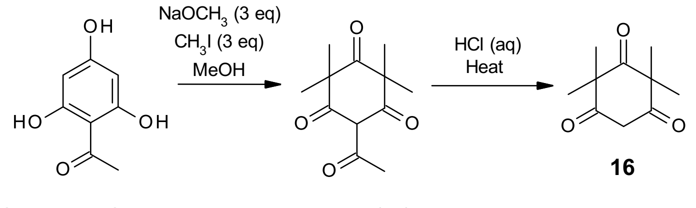
rial **11** is transposed from nitrogen by one carbon in the product, was the only compound obtained. We recognised the favourable 2,4-substitution pattern of the pyridine, containing a small non-leaving group at the 2-position, as a potentially novel building block for triketone chemistry. The hitherto unknown nicotinic acid **14** was readily prepared by hydrolysis of the ester, and after coupling to cyclohexane dione by O-acylation followed by O- to C-acyl rearrangement with cyanide catalysis afforded the first examples of the nicotinoyl subclass of triketone HPPD inhibitors bearing trifluoromethyl substituents (compound **15**, Scheme 3).[11]



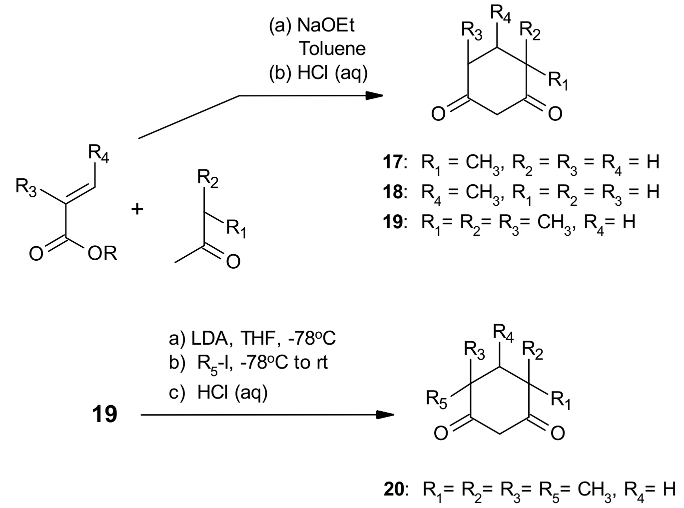
Reagents and conditions: (a) LiOH, H_2O/MeOH, r.t.; b) DCC, CH_3CN, rt, 1hr, then add Et_3N (2 eq.), acetonecyanohydrin (0.1 eq.).

Scheme 3. Synthesis of first nicotinoyl HPPD inhibitor.

In glasshouse tests, the unsubstituted cyclohexanedione **15** (Scheme 3) showed very good post-emergence control of key broad-leaved weeds and suppression of some of the key grass weeds in corn and cereals, whilst remaining selective to both crops. Pre-emergence herbicidal activity in corn was less impressive, which could at least in part be correlated to rapid degradation in soil (in model laboratory studies the compound had a measured half-life (DT_{50}) of 2 days). The effect of increasing methyl substitution on the cyclohexanedione ring was studied, as this was known to increase activity by blocking potential sites of metabolism.[6] The diones **16**, **17**, **18**, **19** and **20**, were synthesised as shown in Schemes 4 and 5, and then coupled with the nicotinoyl acid (Scheme 6).[11]



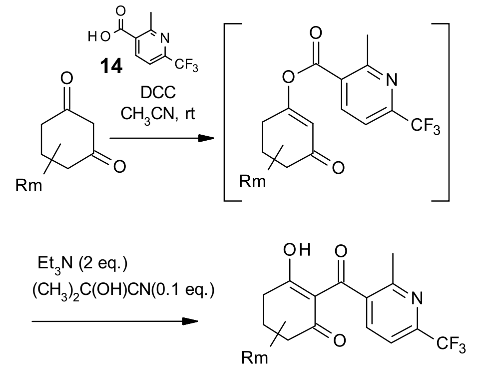
Scheme 4. Synthesis of syncarpic acid (**1b**).



17: $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$
18: $R_4 = CH_3$, $R_1 = R_2 = R_3 = H$
19: $R_1 = R_2 = R_3 = CH_3$, $R_4 = H$

20: $R_1 = R_2 = R_3 = R_5 = CH_3$, $R_4 = H$

Scheme 5. Synthesis of substituted cyclohexane diones.



Scheme 6. Synthesis of alkyl substiuted nicotinoyl HPPD inhibitors.

These were then coupled to 2-methyl-6-trifluoromethyl-nicotinic acid (**14**) to give monocyclic nicotinoyl cyclohexane diones (Scheme 6) using the chemistry previously described in Scheme 3. Although post-emergence broad-leaved weed control in glasshouse tests was not greatly affected, pre-emergence activity against these weeds increased dramatically, along with pre- and post-emergence activity against grass weeds. However, phytotoxicity to corn also tended to increase with increasing substitution. The order of activity of the compounds is qualitatively as shown in Fig. 4.

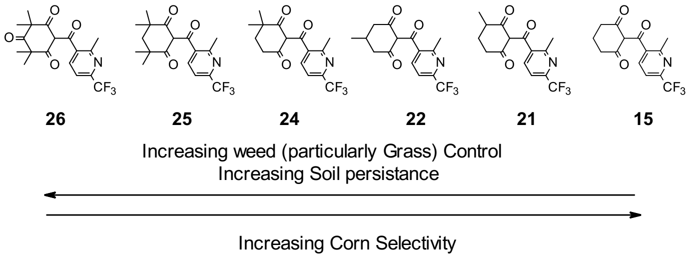


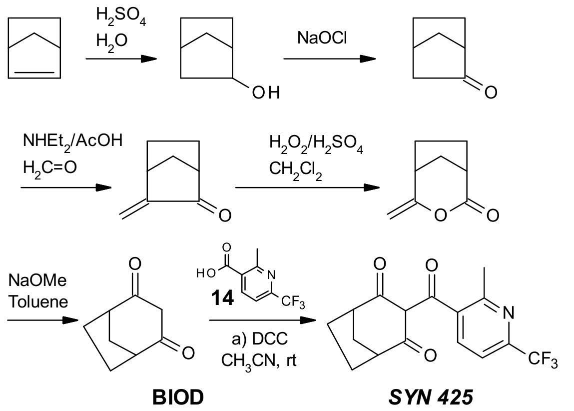
Fig. 4. Effect of increasing methyl substitution on the cyclohexane dione portions of nicotinoyl HPPD inhibitors.

A further price to pay in this strategy is the lack of soil metabolism (thus increasing soil persistence) with increasing methyl substitution. For example, compound **26** where oxidative metabolism in the dione ring is completely blocked, has measured soil half-life (DT_{50}) of >100 days in model laboratory studies.[6] As compounds **21**, **22**, and **24** showed the best selectivity to corn and good weed control, we chose to also synthesise bicyclo[3.2.1] octane-2,4-dione (BIOD) in a further round of optimization. This was synthesized according to Scheme 7.

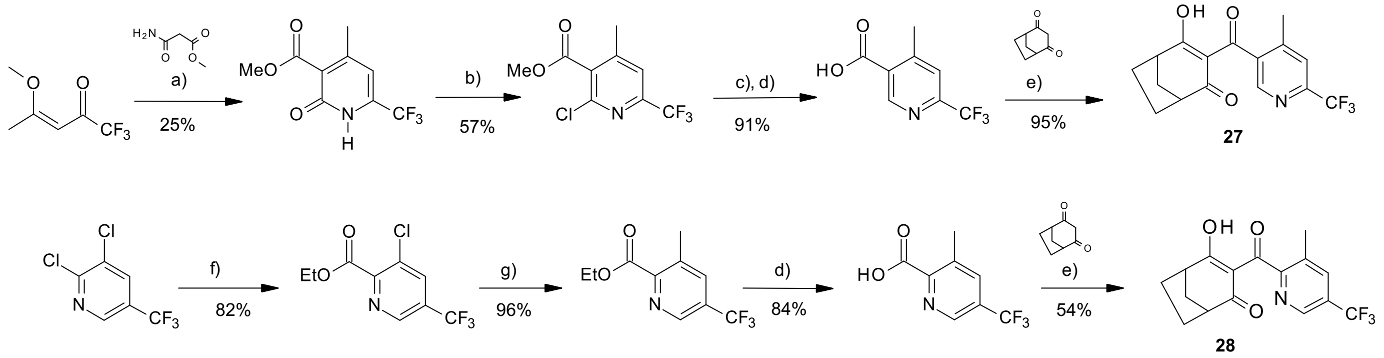
When BIOD was coupled to the nicotinic acid **14**, this gave the optimal compound (code name *SYN 425*) in terms of herbicidal pre- and post-emergent activity against grass and broad leaf weeds and selectivity of the diones studied.

As a next step in our optimization program, the effect of the position of the nitrogen atom in the heterocyclic ring on herbicidal activity was investigated. The isomeric pyridine analogues of *SYN 425* (**27** and **28**) were prepared as shown in Scheme 8.

The relative ranking of these pyridyl isomers against grass and broad leaf weeds is depicted in Fig. 5.



Scheme 7. Initial synthesis of BIOD.



Reagents and conditions. a) $NaOCH_3$, CH_3OH, reflux; (b) $PhOP(O)Cl_2$, 170°C; (c) $HC(O)O^-NH_4+$, 10% Pd/C, MeOH, r.t.; d) LiOH, H_2O/MeOH, r.t.; e) DCC, CH_3CN, rt, 1hr, then add Et_3N (2 eq.), acetone cyanohydrin (cat.). f) 100°C under 50 bar CO in EtOH contg. Et_3N (3 eq.) and $(Ph_3P)_2PdCl_2$ (0.05eq); g) $PdCl_2[P(Ph)_3]_2$ (5%), K_2CO_3 (3eq.), Trimethylboraxine, dioxane, reflux; (h) Neat, then heat to 100°C; i) NH_3 (aq.), CH_3CN, r.t.; j) CF_3CO_2H (0.1eq.), Toluene, Reflux.

Scheme 8. Synthesis of pyridyl regioisomers of *SYN 425*.

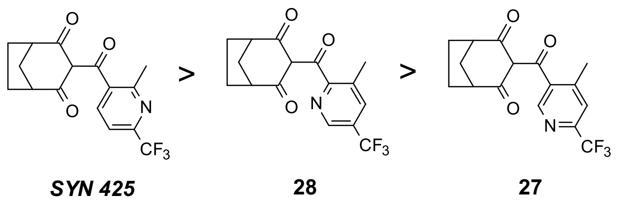


Fig. 5. Relative herbicidal potencies of isomeric pyridyl triketones.

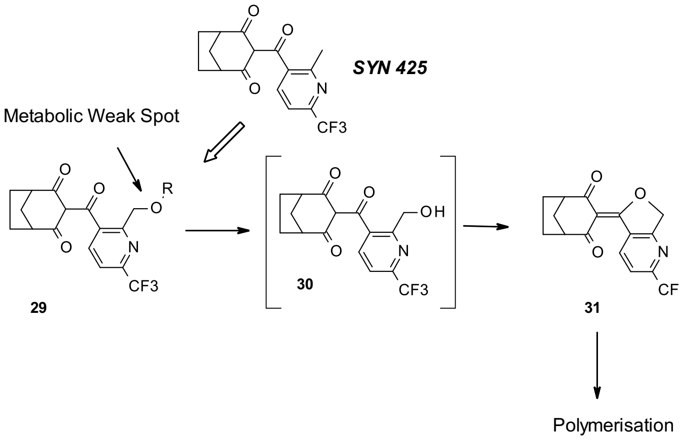


Fig. 6. Strategies for improving crop selectivity of *SYN 425* through enhanced metabolic degradation.

These studies enabled us to clearly define the first candidate for field trials in corn. The compound, with the code name *SYN 425* was prepared (Scheme 7) in multi-hundred gram quantities, and applied pre-emergent (application rate 100–150 g ai/ha) and post-emergent ((application rate 100–150 g ai/ha) in corn in the US and Europe to control grass and broad leaf weeds. *SYN 425* showed excellent control of important grass and broad leaf weeds at these rates but the balance between weed control and damage to the corn (*i.e.* the corn selectivity) was insufficient to warrant commercialization.

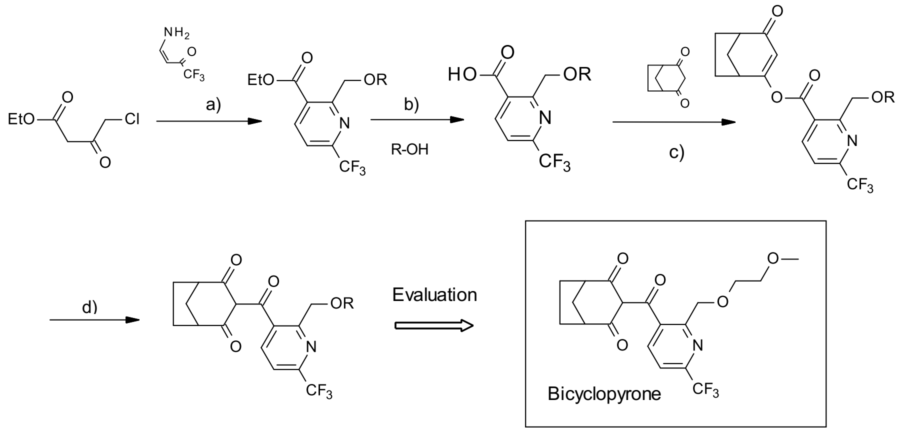
It was envisaged that it might be possible to improve crop selectivity in *SYN 425* by introducing metabolic 'weak points' into the pyridyl moiety, enabling faster corn metabolism to occur. To this aim, we chose to make derivatives of type **29** where the methyl of the nicotinic acid was substituted with alkoxy groups, as we further knew from laboratory studies that dealkylation of such alkoxymethyl compounds led to intermediates **30** that rapidly polymerized through intramolecular cylisation and then further degradation of the reactive Michael acceptor intermediate **31** *via* Michael addition (Fig. 6).

The alkoxymethyl compounds were readily prepared as shown in Scheme 9.

A range of alkoxymethyl derivatives were prepared and tested in the green house for their weed control against important corn weeds pre- and post-em, and for their selectivity against corn. This led us ultimately to choose the compound with a 2-methoxyethoxymethyl substituent on the nicotinic acid as the preferred compound for further development. The compound received the international standardization organization (ISO) name of Bicyclopyrone in 2009. Particularly interesting here is that Bicyclopyrone contains a larger *ortho* substituent than the usual HPPD types (*e.g.* Cl or Me), but is still tolerated at the enzyme site. As shown by an X-ray structure of Bicyclopyrone with *Arabidopsis thaliana,*[12] this is due to the fact that the methoxyethoxymethyl substituent folds into a compact *S*-gauche conformation. This is shown in Fig. 7.

Before commercialization, new syntheses were developed for BIOD, as it was reported that the BIOD synthesis used in Benzbicyclon synthesis was not cost-effective.[12] One of the syntheses that can be used to produce BIOD[13] is illustrated in Scheme 10.[13]

The key steps of the synthesis are; an ene-reaction of butadiene dimer (**32**), catalytic in di-isobutyl aluminum hydride (DIBAL-H) to give bicyclo[3.2.1]oct-3-ene (**33**). This is dissolved



Scheme 9. Preparation of alkoxymethyl nicotinoyl HPPD inhibitors.

in chlorobenzene and brominated under radical conditions to give the tribromo intermediate **34** as a solution in chlorobenzene. This solution is diluted with acetonitrile, and refluxed with 10% HCl to give BIOD in 68% yield after work-up.[13] This is coupled with the nicotinic acid chloride as previously described to give Bicyclopyrone.

Bicyclopyrone has subsequently been commercialized. There are several products containing this new active ingredient Bicyclopyrone. The products for use in corn are registered under the trade name of ACURON®[14] (mixture with S-Metolachlor, Atrazine, Mesotrione and Benoxacor) which uses four active ingredients including Bicyclopyrone, and three complementary modes of action (HPPD inhibition, inhibition of photosynthesis at PS II, and inhibition of VLCFAs) to target difficult broadleaf and grass weeds. ACURON® has been shown to control more than 70 weeds, including broadleaf and grass weeds like *Amaranthus sp.*, (Palmer amaranth, waterhemp), *Conyza Canadensis* (marestail), *Ambrosia sp.* (giant ragweed, common ragweed,), *kochia*, *Ipomoea* (morningglory), *Xanthium* (cocklebur), and *Salsola* (Russian thistle). Pre- and post-emergence crop safety enables ACURON® to be applied from 28 days pre-plant (including burndown) up to 12-inch corn.[14] ACURON® FLEXI (mixture with S-Metolachlor, Mesotrione and Benoxacor as safener) has a similar weed control profile and can be used without soil type restrictions where registered.[15] ACURON® UNO, in which Bicyclopyrone is the single active ingredient, is a selective herbicide registered in corn in South America for control of grasses and weeds during fallowing or at the pre-emerging stage of the corn.[16] It controls weeds such as *Digitaria sp.* (sourgrass, hairy crabgrass), *Echinochloa sp.* (barnyard grass), *Erigeron bonariensis* (Argentine fleabane), *Amaranthus sp.*, (Palmer amaranth, waterhemp), *Chloris sp.* (windmill grass or finger grass), and *Eleusine sp.* (goosegrass), amongst others. Bicyclopyrone use is not restricted to corn, and has also been commercialized as a cereal herbicide. Thus, TALINOR® herbicide is a post-emergence herbicide which controls broadleaf weeds in wheat and barley.[17] The product combines two active ingredients (Bicyclopyrone and Bromoxynil) and two modes of action (HPPD inhibition and PSII inhibition) to deliver standalone control of resistant and other difficult-to-control broadleaf weeds, including kochia, *Chenopodium album* (lambsquarters), *Tripleurospermum sp.* (mayweed chamomile), *Salsola* (Russian thistle) and Polvgonum convolvulus (wild buckwheat), and particularly those that have become resistant to ALS-inhibitor, synthetic auxin, and glyphosate herbicides.

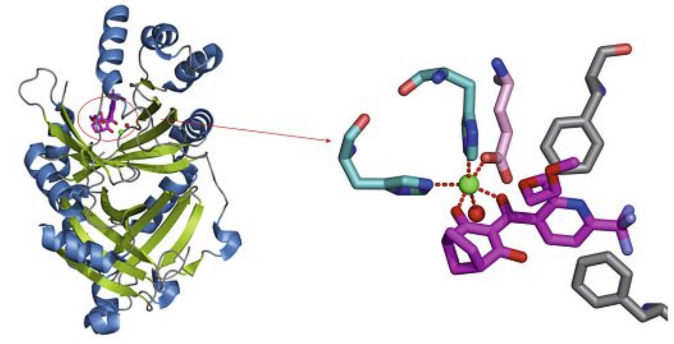
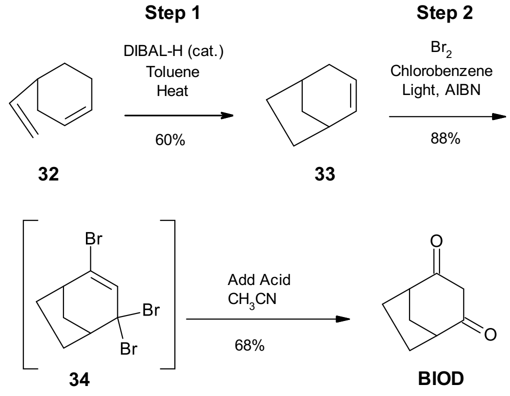


Fig. 7. X-ray structure of Bicyclopyrone bound to Arabidopsis HPPD (resolution 1.9Å). The inset shows the active site with Fe^{2+} liganded to three active site residues His226, His308, Glu394, a well-defined water and bidentate interaction with Bicyclopyrone, and the methoxyethoxymethyl side chain folded into an *S*-gauche conformation.



Scheme 10. Short synthesis of BIOD.

5. Conclusion

This short review has described some key aspects in the discovery of Syngenta's new selective herbicide, Bicyclopyrone. The key steps that led to the discovery of this molecule were firstly the serendipitous observation that compounds made to produce 2,6-disubstituted trifluoromethyl nicotinoyl derivatives led instead to 2,4-disubstituted trifluoromethyl nicotinoyl derivatives, which fulfilled the structural requirements to prepare HPPD derivatives with this moiety. The second key part of the story was the improvement in corn selectivity obtained by building metabolic handles into the nicotinoyl part of the molecule in the original lead, *SYN 425*. Finally, important improvements were achieved allowing more efficient preparation of the bicyclic dione moiety of the molecule.

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