Synthesis and Herbicidal Activity of Some Potent Bicyclic Ether Herbicides

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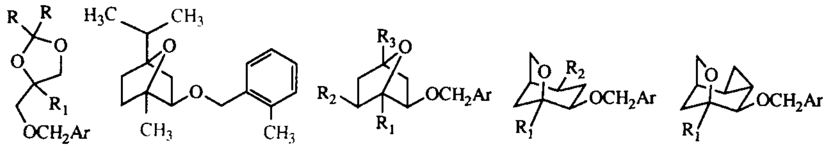
The glycol ether herbicides were discovered by Shell in the late 1960s.[1] Their initial glycol derivatives (**IV**; Fig. 1) were optimized by constricting the conformation with a more rigid bicyclic structure. Cinmethylin, the result of that optimization process,[2] provides pre-emergent control of many grass weeds in soybeans. Since the initial patent, a number of other companies (ICI, BASF, Bayer, FMC, Chevron, Du Pont, etc.) have filed patents related to these cyclic ethers. Compounds of Type **I**, **II** and **III** (Fig. 1) represent classes of potent, novel bicyclic ethers which were prepared from an initial Diels–Alder reaction from inexpensive starting materials.

Compound **Ia** (Fig. 2) can be prepared via the Diels–Alder adduct between acryloyl chloride and dimethylfuran. The resulting ester is isolated in a 2:1 ratio of *endo*:*exo* isomers. The *exo* isomer is reduced with lithium aluminum hydride (or treated with excess Grignard reagent) and the resulting alcohol is alkylated. Epoxidation occurs exclusively from the less hindered *exo* face.[3] Reductive opening of the epoxide gives mixtures of 2,5- and 2,6-substituted bicyclic ethers, which are benzylated to give **Ia**. Similar chemistry is used to prepare compounds of Type **Ib**. The Diels–Alder reaction of furan with acryloyl chloride occurs readily at room temperature to give a 2:1 mixture of *exo*:*endo* esters (Fig. 2).[4] Alternatively, structures **Ib** could be prepared from the Diels–Alder adduct of methyl vinyl ketone and furan using ZnI_2 as a catalyst.[5]

The [3.2.1] system is generated from the Diels–Alder adduct of maleic anhydride and alkyl-butadiene (Fig. 3). Reduction of the anhydride to the diol is followed by epoxidation with *m*-chloroperbenzoic acid to give a mixture of approximately 2:1 *trans*:*cis* epoxides[6] and in-situ cyclization to form the bicyclic diol. The presence of the *m*-chlorobenzoic acid provides sufficient acid catalysis to allow cyclization of the trans-epoxide. Selective alkylation of the primary alcohol is followed by Swern oxidation to the cyclic ketone. Reduction of this ketone gives only the *endo*-alcohol. Benzylation generates compound **IIa**. The intermediate bicyclic diol can also be converted to a mono-tosylate which reacts with a variety of nucleophiles (Fig. 4). The *exo*-alkyl isomer of **IIa** can be prepared using similar chemistry beginning with the *trans*-diester dienophile (**IIb** in Fig. 5).



IV Cinmethylin I II III

Fig. 1. Structures of compounds referred to in text.

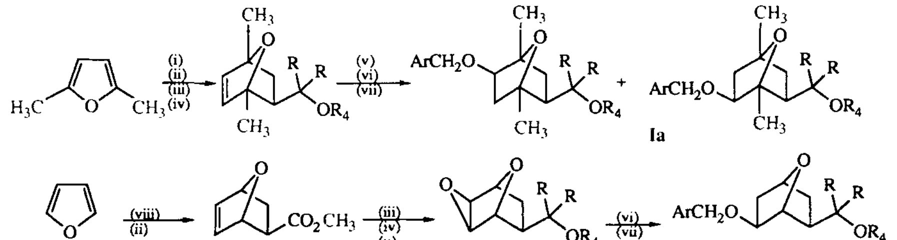


Fig. 2. Reagent conditions: (i) acryloyl chloride, $AlCl_3$, −40°C; (ii) methanol, pyridine; (iii) lithium aluminium hydride (LAH), tetrahydrofuran (THF) or alkylgrignard reagent, THF; (iv) NaH, alkyliodide, THF; (v) *m*-chloroperbenzoic acid (MCPBA), CH_2Cl_2; (vi) Superhyride®, THF; (vii) benzyl bromides, THF, NaH; (viii) acryloyl chloride, catalytic propylene oxide, 1–3 days.

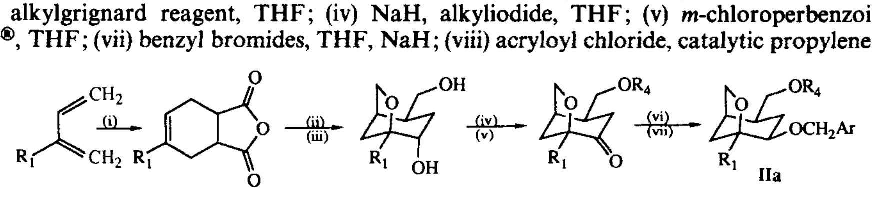


Fig. 3. Reagent conditions: (i) maleic anhydride; (ii) LAH, THF; (iii) MCPBA, CH_2Cl_2; (iv) NaH, alkyl iodide, THF; (v) oxalyl chloride, TEA, DMF, CH_2Cl_2, −78°C; (vi) benzyl bromides.

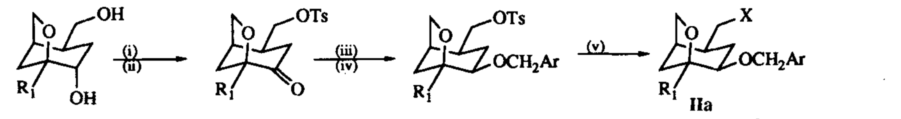


Fig. 4. Reagent conditions: (i) tosyl chloride, pyridine; (ii) Swern oxidation; (iii) Superhydride®, THF, −78°C; (iv) benzyl bromides, NaH; (v) nucleophiles.

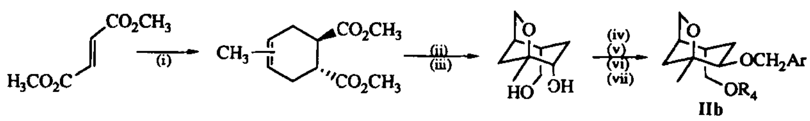


Fig. 5. Reagent conditions: (i) ZnI_2, 21 days; (ii) LAH, THF; (iii) MCPBA, CH_2Cl_2; (iv) alkyl iodides, NaH; (v) Swern oxidation; (vi) Superhydride®, THF, −78°C; (vii) benzyl bromides, NaH.

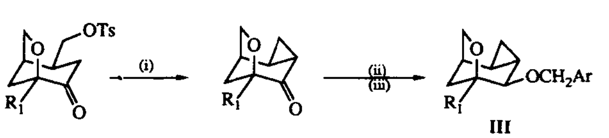


Fig. 6. Reagent conditions: (i) LDA, THF, −78°C to room temperature; (ii) Superhydride®, THF, −78°C; (iii) benzyl bromides.

Structures of Type **III** can be prepared by treatment of the ketone tosylate with lithium diisopropylamide (Fig. 6).

Compounds of Type **I** where R_1 is methyl show similar levels of activity when the R_2 group is in the 5- or the 6-position (compounds **1** & **2** in Table 1). The herbicidal activity decreases when the size of R_2 is increased (compounds **2** *vs* **3**). Structure–activity studies in similar systems have demonstrated that the R_1alkyl group is necessary for good activity (see compound **10** in Table 1 compared to cinmethylin). However, compounds of Type **I** where R_1=H are active when R_2 is a bulky group (compare compounds **4** & **7**). The optimal activity is seen when R_2 is $C(C_2H_5)_2OCH_3$ (compound **7**). Activity decreases when R_2 is either smaller (compound **4**) or larger (compounds **8**, **12** & **13**). A similar trend is seen when R_2 is unsaturated or contains a larger alkoxy group. When R_2 has unsymmetrical alkyl groups the order of increasing activity is $C(CH_3)(C_4H_9)OCH_3$ (compound **16**) < $C(CH_3)(C_3H_7)OCH_3$ (compound **15**) < $C(CH_3)(C_2H_5)OCH_3$ (compound **14**). It is possible that the bulky R_2 groups fill the space near the bridgehead position when R_1=H (see Fig. 7).

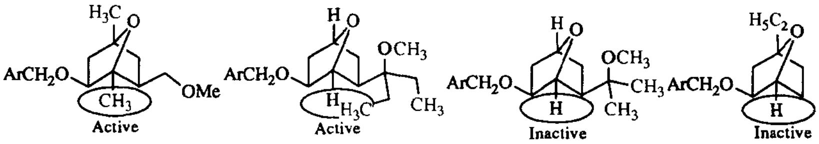


Fig. 7. Activity is possibly dependent upon the bridgehead position being filled spatially.

TABLE 1
Pre-emergent Activity of Compounds of Type I[a,b]

Compound	R_2	R_1	R_3	*Ar*	*Rate*[c] *(g ha^{-1})*	*Mean activity (% control)*
1	$CH_2OC_2H_5$	CH_3	CH_3	2-methylphenyl	100	25
2	$CH_2OC_2H_5$[d]	CH_3	CH_3	2-methylphenyl	100	25
3	$C(CH_3)_2OC_2H_5$	CH_3	CH_3	phenyl	50	0
4	$C(CH_3)_2OCH_3$	H	H	2-methylphenyl	50	0
5	$C(CH{=}CH_2)_2OCH_3$	H	H	2-fluorophenyl	50	40
6	$C(CH{=}CH_2)_2OC_2H_5$	H	H	2-fluorophenyl	50	13
7	$C(C_2H_5)_2OCH_3$	H	H	2-fluorophenyl	50	60
8	$C(C_3H_7)_2OCH_3$	H	H	2-fluorophenyl	100	60
9	$C(CH_2CH{=}CH_2)_2OC_2H_5$	H	H	2-fluorophenyl	50	0
10	H	H	C_2H_5	phenyl	50	0
11	$C(C_3H_7)_2OCH_2CH{=}CH_2$	H	H	2-fluorophenyl	50	0
12	$C(n\text{-}C_4H_9)_2OCH_3$	H	H	2-fluorophenyl	50	0
13	$C(i\text{-}C_4H_9)_2OCH_3$	H	H	2-fluorophenyl	50	0
14	$C(CH_3)C_2H_5)OCH_3$	H	H	2-methylphenyl	50	35
15	$C(CH_3)(C_3H_7)OCH_3$	H	H	2-methylphenyl	50	28
16	$C(CH_3)(C_4H_9)OCH_3$	H	H	2-methylphenyl	50	0
17	$C(CH_3)(C_4H_9)OCH_3$	H	H	2-fluorophenyl	50	28
18	$C(CH_3)(C_4H_9)OCH_3$	H	H	2,4-difluorophenyl	50	5
Cinmethylin	H	CH_3	$i\text{-}C_3H_7$	2-methylphenyl	50	80

[a] See Fig. 1.

[b] Data averaged over those for the four grass species *Setaria faberi* Herrm.; *Echinochloa crus-galli* (L.) Beauv.; *Bromus secalinus* (L.) and *Digitaria sanguinalis* (L.) Scop. 0 = zero and 100 = complete control.

[c] No injury to corn or soybean at these rates.

[d] 1 : 3 mixture of the 5-alkyl and 6-alkyl substitution.

TABLE 2
Pre-emergent Activity of Compounds of Type II[a]

Compound	R_1	R_2	*Ar*	*Mean activity*[b,c] (*% control*)
19	CH_3	CH_2Br	2-fluorophenyl	64
20	C_2H_5	CH_2N_3	2-fluorophenyl	74
21	CH_3	CH_2CN	2,6-dichlorophenyl	58
22	CH_3	CH_2CN	2,4,6-trimethylphenyl	0
23	CH_3	CH_2OH	phenyl	0
24	CH_3	CH_2N_3	2-fluorophenyl	76
25	C_2H_5	$CH_2S(O)CH_3$	phenyl	12
26	CH_3	CH_2I	2-bromophenyl	32
27	H	CH_2OCH_3	phenyl	1
28	CH_3	CH_2OCH_3	phenyl	95[d]
29	CH_3	*exo*-CH_2OCH_3	phenyl	16
30	CH_3	$CH_2N(CH_3)_2$	2-fluoro-6-chlorophenyl	0
31	CH_3	CH_2I	2-chlorophenyl	22
32	C_2H_5	CH_2SCH_3	phenyl	26
33	CH_3	$CH_2N(CH_3)_2$	2-methylphenol	0
34	C_2H_5	CH_2I	phenyl	54
35	CH_3	CH_2I	2-fluorophenyl	60
36	CH_3	CH_2SH	phenyl	0
37	CH_3	$CH_2C_2H_5$	2-fluoro-6-chlorophenyl	34
38	C_2H_5	CH_3	2-chlorophenyl	76
39	CH_3	CH_2CH_3	2-fluoro-6-chlorophenyl	76
40	C_2H_5	CH_2CH_3	2-fluoro-6-chlorophenyl	90
41	CH_3	CH_2OCH_3	*exo*-OCH_2aryl	0[e]

[a] See Fig. 1: Data averaged over those for the four grass species quoted in the footnote to Table 1: 0 = zero and 100 = complete control.

[b] At 50 g ha^{-1} (except for Compound **41**): control signifies untreated weeds.

[c] Little or no injury to corn and soybeans at these rates.

[d] Activity on four grass species.

[e] At 200 g ha^{-1}.

Meta or *para* substitution on the aromatic ring tends to decrease the herbicidal activity (compounds **17** and **18**).

The herbicidal activity of compounds of Type **II** is much greater when R_1=alkyl than when R_1=H (compounds **27** *vs* **28** in Table 2). The activity when R_1=methyl is similar to that when R_1=ethyl (compounds **20** & **24**). Compounds of Type **II** are active when R_2 consists of a halogen, nitrile, azide, hydrogen or alkyl group but little or no activity is displayed when R_2 is an alcohol, mercaptan or amine (compounds **23**, **33** & **36**). Compounds of Type **II** where R_2 is *endo* are more active than those of Type **II** where R_2 is *exo* (compounds **28** & **29**). Compounds of Type **II** are similar in activity to compounds of Type **III** and are generally more active than compounds of Type **I**. Some of the compounds of Type **II** were 3–4 times more potent than cinmethylin whereas compounds of Type **I** had activity equal to or less than that of this compound. As has been seen in other related systems, the gauche relationship between the ring oxygen and the benzyloxy group is essential for activity in related systems and is demonstrated by the lack of activity of compounds related to Compound **41** in Table 2.

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