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A Search for Biologically Active Compounds for Potential Pharmaceutic and Agronomic Applications

Alain De Mesmaeker*

Distinguished Senior Industrial Science Award 2023

Abstract: Summarized here are some aspects of my research activities in Ciba-Geigy Central Research Laboratories (1985–1996), in Novartis and Syngenta Crop Protection Research (1997–2020). I have followed the chronological order of these research activities covering only published data.

Keywords: Antisense · Keteneiminium salts · Radicals · Strigolactones

Alain De Mesmaeker obtained his PhD in Organic Chemistry from the Catholic University of Louvain, Belgium 1983. Following postdoctoral research at the Weizmann Institute, Israel, he joined in 1985 the Central Research Laboratories of Ciba-Geigy, Basel. In 1997 he moved to Novartis Crop Protection, then Syngenta where he was Head of Research Chemistry. He was Principal Syngenta Fellow and President of the Swiss Chemical Society.

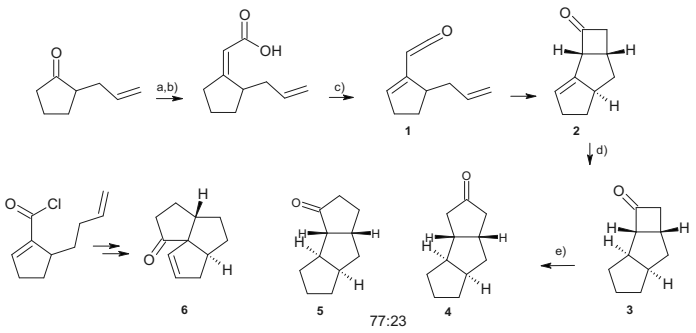
1. Synthesis of Triquinanes by Intramolecular 2+2 Cycloadditions of Vinyl Ketenes to Olefins

Intramolecular (2+2) cycloaddition of ketenes to olefins was used for the synthesis of various structures displaying potential broad applications to research projects. We described our approach using an intramolecular (2+2) cycloaddition of vinyl ketene **1** to olefin leading to a key intermediate **2**, which was converted into the desired triquinane skeleton **4/5** (Scheme 1).[1] Starting from allyl cyclopentanone, Peterson olefination furnished exclusively the desired vinyl ester with the exocyclic C=C bond. The corresponding acyl chloride reacted highly regioselectively (> 97%) with triethylamine at C-5 yielding the corresponding vinyl ketene **1**, which cyclized to the single isomer **2**. Catalytic hydrogenation of the cyclobutanone **2** proceeded stereoselectively from the less hindered face, furnishing the desired *cis*-anti-*cis* ring fusion **3**. The corresponding cyclopentanones **4/5** were readily separated after ring expansion and further derivatized.

A similar strategy was applied for the synthesis of angular annulated triquinanes as **6**.[1b] The use of vinyl ketenes (2+2) intramolecular cycloadditions to olefins has been further extensively applied to the synthesis of various derivatives displaying biological activities.

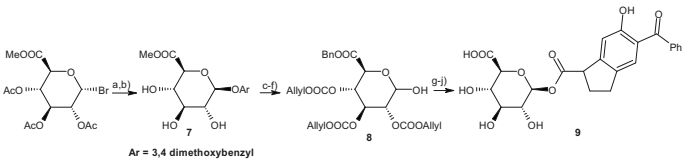
2. A Novel Protected Form of Glucuronic Acid for the Synthesis of Labile 1-O-acyl-β-D-Glucuronides

A major metabolic pathway in mammalians of carboxylic acid containing compounds (and of their precursors) is conjugation to glucuronic acid forming 1-O-acyl-β-D-glucuronides.[2] 1-O-acyl glucuronides are sensitive to electrophiles but extremely labile towards nucleophiles due to the activation of the anomeric ester.[3] 1-O-acyl glucuronides are very rapidly hydrolysed at pH > 8 and the 1-O-acyl group readily migrates to the hydroxylic functions at C-2, C-3 and C-4 in a dynamic equilibrium. They react readily with endogenous cellular nucleophiles (ROH, RSH, RNH_2), a process which could have biological implications and must be evaluated for drug candidates containing a carboxylic acid moiety despite the difficulty to isolate them in pure form from biological materials.[4] We designed a new protected form of glucuronic acid **8** which allowed, for example, the synthesis on gram scale of the 1-O-acyl-β-D-glucuronide **9** of oxindanac (Scheme 2).[5] The key features of this synthesis are the preparation of **7** on multigram scale (500g), the efficient introduction of the three allyl carbonate groups, the selective mild deprotection of the anomeric 3,4-dimethoxybenzyl group, the exchange of the methyl ester by benzyl without interference with the allyl carbonate groups, the stereoselective coupling of oxindanac to **8**, an improved deprotection procedure of the allyl carbonate groups with $Pd(PPh_3)_4$ in the presence of an excess of acetylacetone. The final cleavage of the benzyl ester allowed the isolation of glucuronide **9** requiring no further purification for biological evaluation. This procedure is applicable to various acyl glucuronides conjugates containing functional groups.



Scheme 1. Stereoselective synthesis of *cis-anti-cis* linear triquinanes using an intramolecular (2+2) cycloaddition of a vinyl ketene to an olefin. a) LiCA, THF, $Me_3SiCH_2COOtBu$, NH_4Cl *aq.*, 70%; b) CF_3COOH, CH_2Cl_2, 88%; c) $Me_2C{=}CNMe_2Cl$, $CHCl_3$, NEt_3, 62%; d) H_2, Pd/C, THF-AcOH, 77%; e) $N_2CHCOOEt$, $BF_3.Et_2O$, ether, HCl *aq.*, AcOH, 70%.

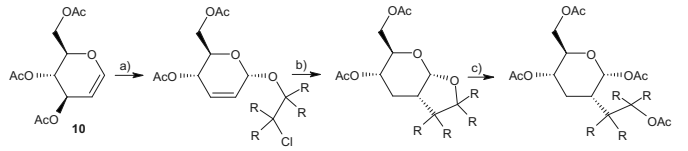
*Correspondence: Dr. A. De Mesmaeker, E-mail: alaindidier.demesmaeker@gmail.com



Scheme 2. Synthesis of the labile 1-O-acyl-β-D-glucuronide of oxindanac. a) Ag_2CO_3, 3,4-dimethoxybenzyl alcohol, PhH, 60%; b) MeONa, MeOH, 74%; c) Allyl chloroformate, pyridine, 87%; d) NaOH, THF; e) $Me_2C{=}CNMe_2Cl$, CH_2Cl_2; f) Benzyl alcohol, pyridine, CH_2Cl_2; 72% 3 steps; g) DDQ, CH_2Cl_2-H_2O, RT, 88%; h) PPh_3, diisopropyl azodicarboxylate, oxindanac, THF, 50%; i) $Pd(PPh_3)_4$, acetylacetone, THF, 35%; j) H_2, Pd/C, AcOEt-MeOH, > 90%.

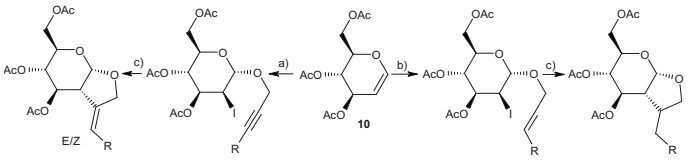
3. Stereoselective C-C Bond Formation in Carbohydrates by Radical Cyclization Reactions

The stereoselective C-C bond formation in carbohydrates to modify their biological properties has been actively investigated using various intermolecular reactions, including the addition of radicals to olefins.[6,7] Our strategy relies on radical cyclization reactions, which would increase its efficiency and stereoselectivity compared to intermolecular processes.[8] C-2-branched carbohydrates can be readily accessed by addition of an alcohol carrying a β-halogen atom as radical precursor to glycal **10** followed by treatment with nBu$_3$SnH leading to exclusive formation of *cis*-fused cyclized products in high yield (Scheme 3).[8] The cleavage of the bicyclic structure was efficiently achieved with acetyl chloride in the presence of $CoCl_2$.



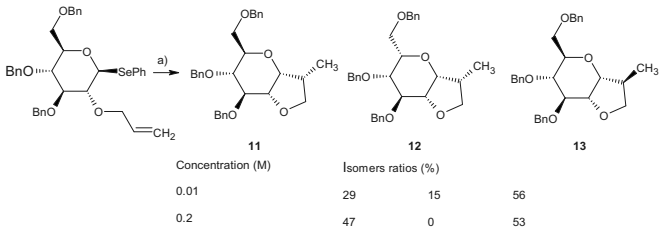
Scheme 3. Synthesis of C-2-branched carbohydrates by radical cyclization reaction. a) $ClCH_2$-CH_2-OH, $BF_3.Et_2O$ cat., PhH, 92% (α:β= 9:1); b) nBu$_3$SnH, AIBN cat., PhH, 96%; c) MeCOCl, $CoCl_2$ cat., MeCN, 92%.

Radical cyclization reactions can also be performed on the adduct of allylic and propargylic alcohols to glycal **10** in the presence of NIS (Scheme 4).[9]



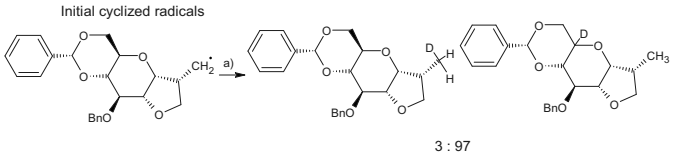
Scheme 4. Synthesis of C-2-branched carbohydrates by radical cyclization reaction. a) Propargylic alcohol, NIS, MeCN, 79–83%; b) Allylic alcohol, NIS, MeCN, 70–85%; c) nBu$_3$SnH, AIBN cat., PhH, 85–96%.

A similar strategy allowed the stereoselective formation of a new C-C bond at C-1 either from the α face or the β face depending on the orientation of the C-2 allylic or propargylic ether.[10] Unexpectedly, we observed in addition to the α- and β-C-8 epimers **11**, **13** the L-idose derivative **12**, which could be suppressed without reduction of the initial anomeric radical prior to cyclization under more concentrated conditions (0.2M) (Scheme 5).[10] The C-5 epimerization resulted from an intramolecular hydrogen atom transfer from C-5-H to the *endo*-cyclized radical having the α-configuration at C-8 followed by reduction of the C-5-centered radical by n-Bu$_3$SnH either from the β-face or from the α-face. The ease of the hydrogen atom transfer arises mainly from the favorable conformation in which the three atoms C-5-H C-9 adopt a close colinear arrangement. No epimerization occurred from D-mannose derivatives with the allylic ether side chain oriented on the β-face.[10] Prior to our work, there were only very few reports of hydrogen atom transfer reactions observed using nBu$_3$SnH as reducing agent.[11]



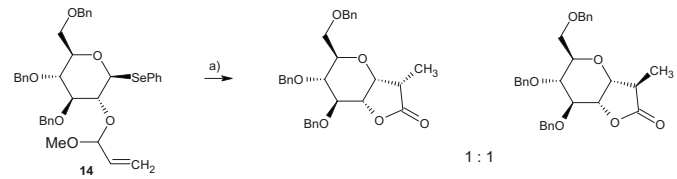
Scheme 5. 1-5 hydrogen atom transfer reaction during cyclization of anomeric radicals. a) nBu$_3$SnH, AIBN cat., PhH, combined isolated yields > 90%.

Using n-Bu$_3$SnD we demonstrated that the incorporation of deuterium at C-5 strongly depends on the nature and the stereochemistry of substituents and protective groups at C-4 and C-6 positions (Scheme 6).[10]



Scheme 6. Deuteration experiments for 1-5 hydrogen atom transfer reaction during cyclization of anomeric radicals. a) nBu$_3$SnD, AIBN cat., PhH, reflux, combined isolated yields > 92%.

The synthesis of C-1 C-branched carbohydrates required the introduction of a cleavable linker at C-7 (Scheme 7).[10e] Radical cyclization of **14** was performed at high concentration (0.3M) to prevent epimerization at C-5. After oxidation of ketals to the corresponding lactones the C-1 C-branched derivatives were obtained by ring cleavage.

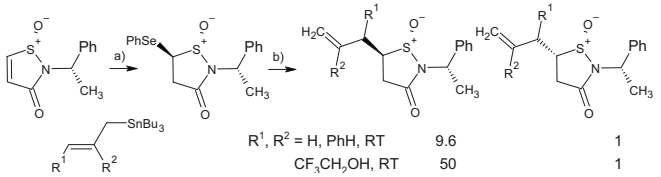


Scheme 7. Synthesis of C-1 C-branched carbohydrates by cyclization of anomeric radicals. a) nBu$_3$SnH, AIBN cat., PhH (0.3M), 89%; b) mCPBA, $BF_3.Et_2O$, CH_2Cl_2, 82%.

4. Stereoselective Addition Reactions of α-Sulfinyl Radicals to Olefins

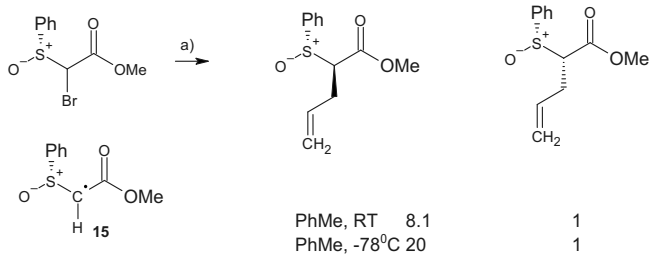
We applied radical addition reactions to various core structures beyond carbohydrates. We disclosed the first diastereoselective C-C bond formation by intermolecular addition of α-sulfinyl radical to C=C bond.[12] Although radical cyclization reaction of α-sulfinyl radicals was reported to lead to no or low selectivity with respect to the sulfinyl moiety,[13] we postulated that the steric

discrimination between the lone pair on sulphur and the S->O dipole would favour the approach of the allylic moiety from the less hindered face. This was observed in all cases with a 9:1 diastereoselectivity for allyl tributyltin at room temperature, which could be further increased by hydrogen bonding of the sulfoxide moiety to a protic solvent (isomers ratio in EtOH 18:1, in trifluoroethanol 50:1). Hydrogen bond formation between α-sulfinyl radical and protic solvent increases not only the electrophilicity of the radical but remarkably its stereochemical discrimination (Scheme 8).[12,14]



Scheme 8. Stereoselective addition of α-sulfinyl radicals to allyl tin derivatives. a) PhSeH, NEt_3 cat., > 90% single diastereomer; b) Allyltin derivatives, AIBN (1eq.), RT, irradiation.

The intra- and intermolecular additions of acyclic α-sulfinyl radicals to olefins were also investigated.[12] Steric discrimination between the faces of racemic α-sulfinyl radicals with an adjacent ester function adopting the preferred conformation **15** lead to high diastereoselectivity in intra- and intermolecular addition reactions at low temperature (Scheme 9).[12]



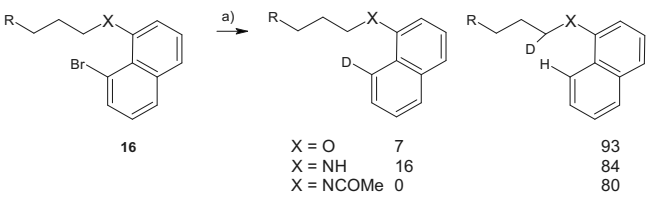
Scheme 9. Stereoselective inter- and intramolecular addition reactions of acyclic α-sulfinyl radicals. a) Allyl tributyltin, AIBN, > 90%, irradiation.

5. Regioselective Formation of C-Centred Radicals Using Intramolecular 1,5-Hydrogen Atom Transfer Reaction

The formation of a C-centred radical is frequently achieved by homolysis on a C-heteroatom bond with trialkyltin hydrides. The regioselective introduction of the radical precursor into a functionalized molecule might be challenging. We investigated the use of 1,5-hydrogen atom transfer reactions to generate efficiently and regioselectively C-centred radicals.[15,16] We used, for example, the naphthyl bromide **16** as a radical precursor to restrict the degree of conformational freedom to favour 1,5-hydrogen atom transfer (Scheme 10). Very high regioselective hydrogen atom translocation was achieved for protected alcohols and amines.[15b] The bromo naphthyl auxiliary to generate C-centred radicals adjacent to oxygen and nitrogen atoms was further developed with a *p*-OMe substituent removed under mild oxidative conditions after the radical reaction.

6. Design and Synthesis of Modified Oligonucleotides for their Use in Antisense Strategy

Antisense oligonucleotides with a base sequence complementary to targeted mRNA segment involved in a disease have been shown to be very attractive potential therapeutic agents.[17] Several properties of natural DNA oligonucleotides must be largely improved to allow their use in biological systems. Among them, resistance against nucleases, binding affinity to the complementary mRNA strand and cellular uptake must be increased.[17] Modification of the natural phosphodiester backbone of DNA by phosphorothioates significantly increases the resistance of the corresponding oligonucleotides towards nucleases, with a slight decrease of the affinity to complementary RNA. The additional stereogenic centre at phosphorus leads to oligonucleotides as a mixture of isomers.[18]



Scheme 10. Regioselective formation of C-centred radicals by 1,5-hydrogen atom transfer. a) nBu_3SnD, PhH, reflux.

We designed novel amides backbone replacements (Amides 1-5, Fig. 1) and incorporated them into oligonucleotides to evaluate their binding affinity to RNA and their resistance to nucleases.[19–21] These amide backbones reduce the overall charge of the corresponding oligonucleotides, improving their binding to RNA and their ability to enter cells.[22]

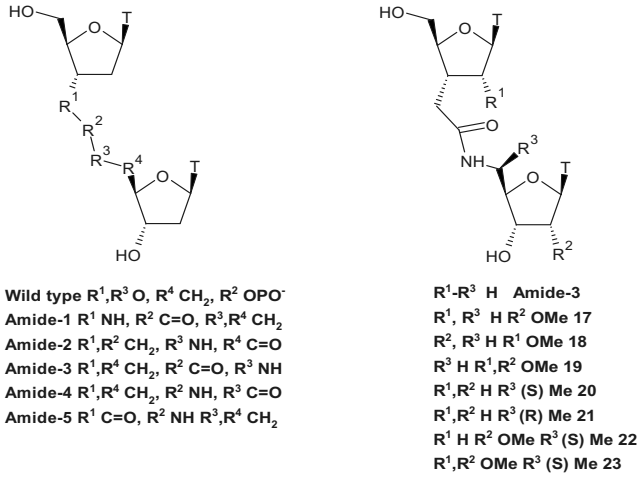


Fig. 1. Amides as backbone replacement of phosphodiester linkage for antisense oligonucleotides. .

Amide-1 dimer destabilized the duplex formed with complementary RNA strand (average ΔT_m/modification –2.9 °C).[19a] **Amide-2** was better tolerated, although with a decrease of thermal stability of the duplex with RNA (average ΔT_m/modification, N-H –1.6 °C).[19b] However, **Amide-3** replacement of phosphodiester backbone increased the thermodynamic stability of the duplex formed with RNA (average ΔT_m/modification, +0.4 °C).[20a] Substituents on the nitrogen atom of the amide are rather well tolerated, offering opportunities to modify the properties of oligonucleotides. Both rotamers present in *N*-substituted amides can fit into the duplexes.[20] Theoretical and NMR studies fully confirmed the good compatibility of **Amide-3** in oligonucleotides:RNA duplexes, the amide backbone favouring the required C-3' puckering of the upper furanose ring of the dimer.[20] **Amide-3** alternating with phosphodiesters increases thermal stability of the corresponding duplexes (average ΔT_m/modification N-H = +0.6 °C) with a very largely increased resistance towards nucleases. **Amides 3-4** adopt similar conformations, being mimics of the corresponding C=C double bond. (**Amide-4** average ΔT_m/modification = 0 °C).[21]

Amide-5, a structural isomer of **Amide-1**, lead to destabilization of the duplex with RNA (**Amide-5** average ΔT_m/modification = –3.5 °C).[20]

Amide-3 backbone replacement was further studied and 2'-OMe substituents were introduced on both 5-deoxyribose rings to favour C3'-*endo* puckering conformation and to further increase the resistance of the oligonucleotides to nucleases. The 2'-OMe substituent on the lower ring in **17** increased the thermodynamic stability of the corresponding duplex with RNA (average ΔT_m/modification = +2.5 °C). The 2'-OMe substituent on the upper ring in **18** slightly increased the duplex thermal stability compared to unsubstituted **Amide-3** (average ΔT_m/modification = +0.8 °C). The upper furanose ring adopts already a preferential 3'-*endo* conformation and is slightly affected by the additional 2'-OMe substituent.[20,23] However, the introduction of 2'-OMe substituents on both rings in **19** had a very positive effect on the thermal stability of the duplex with RNA (average ΔT_m/modification = +3.0 °C). A further preorganization of the amide backbone has been reached by the stereoselective introduction of a 5'-(*S*)-Me substituent in **20** leading to an increase in thermal stability (average ΔT_m/modification = +1.2 °C).[24] The 5'-(*R*)-Me substituent in **21** had a strong destabilizing effect on the duplex with RNA (average ΔT_m/modification = –4.3 °C) preventing a low energy conformation compatible with the helical structure.[24] Dramatic increase in melting temperature of the corresponding RNA duplexes were reached with both modifications (average ΔT_m/modification **22** = +3.5 °C; **23** = +3.7 °C). The formation of amide and of phosphodiester bonds in a single operation on solid phase greatly facilitated antisense oligonucleotides synthesis for biological evaluation.[25] In summary, **Amide-3** and **Amide-4** are optimal backbone replacements for antisense oligonucleotides, which can be further improved for their affinity towards RNA and resistance towards nucleases by 2'-OMe substitution on both furanose rings and by an additional 5'-(S)-Me substituent.

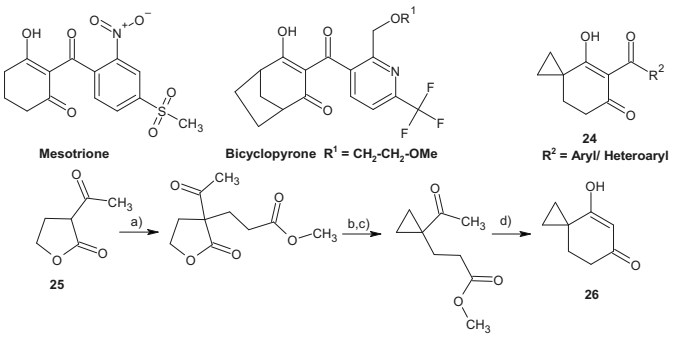
7. Design and Synthesis of Novel HPPD Inhibitors as Selective Herbicides

Mesotrione is a potent HPPD inhibitor used as selective herbicide in corn.[26] Bicylopyrone was recently introduced as selective corn herbicide with improved activity on grass weeds.[26b] We designed the novel spirocyclopropyl derivatives **24** displaying very good selectivity for corn and potent activity against broad leaves and grass weeds comparable to bicyclopyrone.[27] The spirocyclopropyl scaffold is more susceptible to glutathione *S*-transferase metabolism in corn than in grass weeds.[27] Spirocyclopropyl dione **26** was readily obtained from **25** in three steps and coupled with various aromatic acyl chlorides to furnish the corresponding triarylketones (Scheme 11).[27] Very rewardingly, among these derivatives selected for broad evaluation in field trials one displayed similar performance as selective herbicide in corn compared to the commercial bicyclopyrone.

8. Design and Synthesis of Strigolactones Derivatives for Applications to Sustainable Agriculture

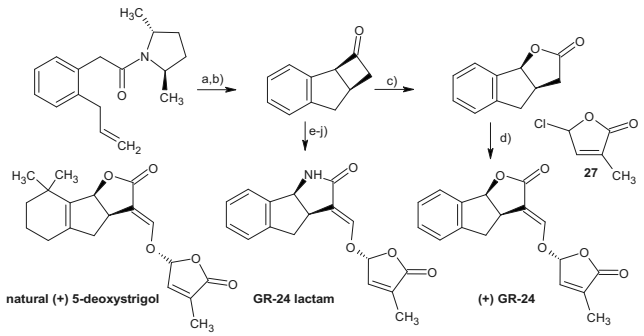
Strigolactones have been identified in root exudates as signalling molecules for parasitic weeds causing enormous damages to crops.[28] In 2005 the role of strigolactones as signalling molecules for the symbiotic association of plant roots with AM fungi (*arbuscular mycorrhizal fungi*) was uncovered.[29] The AM fungi due to their extended branched network facilitate extraction for the plant of minerals as phosphates, nitrates and of water. In 2008 the roles of strigolactones as phytohormones mediating root and plant architecture was uncovered.[30] Our research focused on the use strigolactone derivatives for sustainable agriculture.[31]

We accessed stereoselectively all four GR-24 isomers, a synthetic analogue of strigolactones used as standard in the field, by intramolecular (2+2) cycloaddition of keteneiminium salt carrying



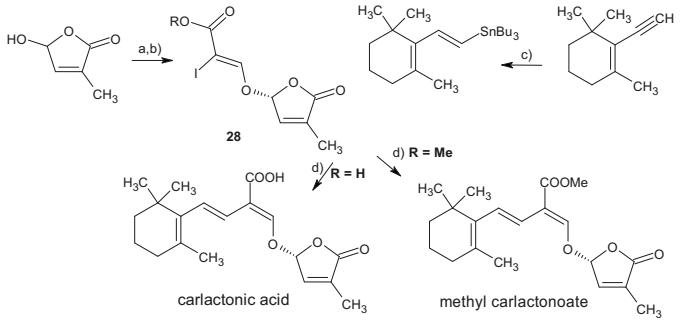
Scheme 11. Aryltriketones HPPD inhibitors as selective corn herbicides. a) NaH, methyl acrylate, *t*BuOH, 96%; b) NaI, NMP, 63%; c) NaH, DMF: THF, 50%; d) ArCOCl, acetone cyanohydrine cat., NEt_3, MeCN.

a chiral auxiliary on the nitrogen atom (Scheme 12).[32] Similarly, we achieved the stereoselective synthesis of the four isomers of 5-deoxystrigol, a key intermediate in the biosynthesis of strigolactones from β-carotene displaying potent biological activities.[32c]



Scheme 12. Stereoselective synthesis of strigolactones and strigolactams. a) Tf_2O, collidine, CH_2Cl_2; b) CCl_4, H_2O, 68%, *ee*= 92%; c) H_2O_2 *aq.*, AcOH, 92%; d) *t*BuOK, HCOOEt, THF, **27**, separation of diastereomers; e) O-mesitylenesulfonyl hydroxylamine, CH_2Cl_2, HCl *aq.*, 65%; f) Boc_2O, DMAP, Et_3N, CH_2Cl_2, 98%; g) *tert*-butoxybis(dimethylamino)methane; h) HCl *aq.*, THF, 80%; i) TFA, CH_2Cl_2, 86%; j) *t*BuOK, THF, **27**, 64%.

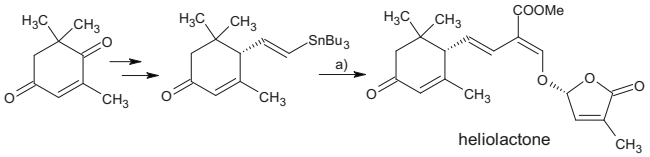
Strigolactones suffer from moderate stability in soil. To improve their potential use in the field, we designed the strigolactams displaying more favourable physicochemical properties, improved soil stability and biological performance.[33] Non-canonical strigolactones as methyl carlactonoate and carlactonic acid are key bio-



Scheme 13. Synthesis of methyl carlactonoate and carlactonic acid. a) Methyl propynoate, *N*-methylmorpholine, THF, 77%; b) NIS, AcOH, CH_2Cl_2, NEt_3, 86%, separation of enantiomers by chiral HPLC; c) nBu_3SnH, AIBN cat., PhH, 98%; d) $Pd_2(dba)_3$ cat., $AsPPh_3$, dioxane, 51-75%.

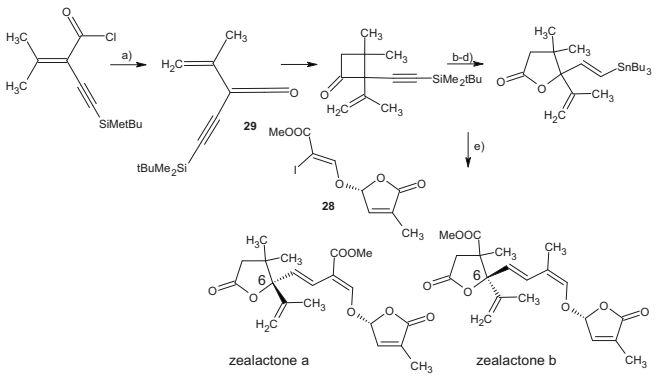
synthetic intermediates of strigolactones in plants. We studied their synthesis and their biological activity (Scheme 13).[34]

This strategy was applied to the synthesis of heliolactone, the major strigolactone isolated from sunflower root exudates (Scheme 14).[34b] Carlactonic acid, methyl carlactonoate and heliolactone display very promising activities as corn seed germination inducers and corn root growth promotors.[34]



Scheme 14. Synthesis of heliolactone. a) $Pd_2(dba)_3$ cat., P(furyl)$_3$, **28**, dioxane, 62%.

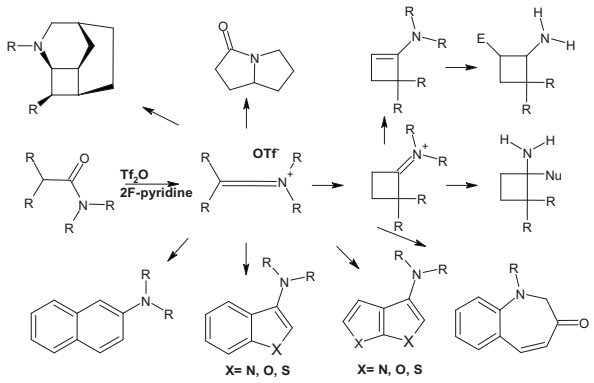
Zealactone is by far the major strigolactone isolated from corn root exudates.[35] The core structure of zealactone was established in a single step by (2+2) cycloaddition of the novel vinyl acetylenic ketene **29** to isobutene (Scheme 15).[36] Zealactone was isolated as a 1:1 mixture of epimers at C-6. The purified synthetic epimers did not interconvert under the conditions used for its isolation from corn confirming that zealactones a/b are formed in equal amounts during its biosynthesis.[35,36] Zealactone displayed spectacular biological results superior to most strigolactones and karrikines.[36,37]



Scheme 15. Synthesis of zealactone by (2+2) ketene cycloaddition to isobutene. a) NEt_3, isobutene, dichloroethane, 79%; b) *m*CPBA, *n*Bu_4OH, CH_2Cl_2, 61%; c) TBAF, THF, 96%; d) *n*Bu_3SnH, AIBN cat., toluene, 97%; e) $Pd_2(dba)_3$ cat., P(furyl)$_3$, **28**, dioxane, 80%.

9. Use of Keteneiminiums Salts for the Synthesis of Crop Protection Active Ingredients

The use of keteneiminiums salts was applied beyond strigolactones to the synthesis of various lead structures for crop protection projects. Few examples of structural modifications reached by treatment of an amide with triflic anhydride in the presence of 2-fluoropyridine followed by intra-or intermolecular reactions with double or triple bonds are summarized in Scheme 16.[38] Importantly, cyclobutyl amines were obtained from *N*-allyl amides by final treatment with $Pd(PPh_3)_4$.[38d–f] We reported the high reactivity of keteniminium salts in electrocyclization reactions leading to high yield synthesis of a variety of polyaromatic amines at room temperature.[33e,38j–q]



Scheme 16. Structural modifications by intra- and intermolecular reactions of keteneiminiums salts with double and triple bonds.

Conclusions

The described research underlines our interest and passion for organic synthesis for the search of biologically active compounds for pharmaceutic and agronomic applications. A central consideration was the elucidation of reaction mechanism and of the mode of action of our compounds in biological systems, which was only feasible with the support of talented scientists from other disciplines.

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