CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Gaining Insight Into Reactivity Differences Between Malonic Acid Half Thioester (MAHT) and Malonic Acid Half Oxyesters (MAHO)

Authors: Sean P. Bew, richard stephenson, jacques rouden, jeremy godemert, haseena seylani, and Luis A Martinez-lozano

To be cited as: *Chem. Eur. J.* 10.1002/chem.201605148

Link to VoR: http://dx.doi.org/10.1002/chem.201605148

Supported by
ACES

WILEY-VCH

10.1002/chem.201605148

WILEY-VCH

FULL PAPER

Gaining Insight Into Reactivity Differences Between Malonic Acid Half Thioester (MAHT) and Malonic Acid Half Oxyesters (MAHO)

Sean P. Bew,[a]* G. Richard Stephenson,[a]* Jacques Rouden,[b] Jeremey Godemert,[a] Haseena Seylani[a] and Luis A. Martinez-Lozano[a]

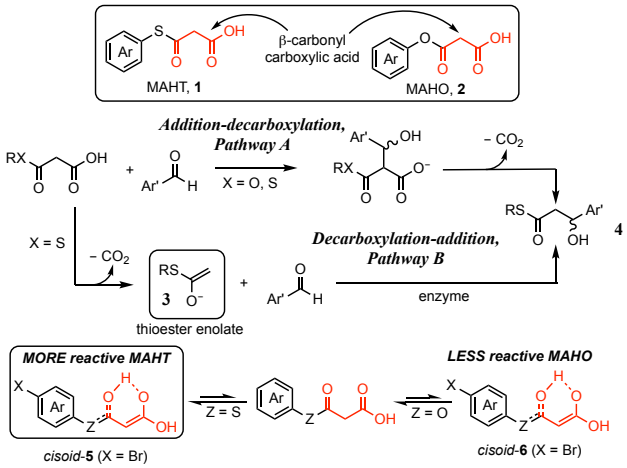
Abstract: An efficient two-step synthesis of structure- and function-diverse thiophenol- and (cyclo)alkyl-derived malonic acid half thioesters (MAHTs) and phenol-derived malonic acid half oxyesters (MAHOs) has been achieved using cheap, readily available and easily handled starting materials. The synthesis of the MAHTs and MAHOs (majority of which have not been previously reported) is readily scalable affording gram quantities of product. In a hydrogen → deuterium exchange, an interesting stereoelectronic effect was observed when different aryl groups were incorporated. Significant changes in the rates of hydrogen → deuterium exchange and levels of isotope incorporation were observed. By way of example, using [2H]methanol and 4-bromophenol-derived MAHO afforded only 14% [2H]-incorporation (9 minutes, k = 31) whereas the corresponding 4-bromothiophenol-derived MAHT afforded 97% [2H]-incorporation (9 minutes, k = 208). In a benchmarked procedure and comprehensive DFT study 54 ester and thioester configurations and conformations where characterised. This established in the MAHT series a sulfur-containing molecular orbital provides a path for increased delocalisation of electron-density into the enol which is unavailable in MAHOs, which facilitates keto-enol tautomerisation and consequently enhances the rate and percentage of hydrogen → deuterium exchange.

Introduction

Malonic acid half thioesters (MAHTs) and oxyesters (MAHOs) are frequently employed as key starting materials in C-C bond forming reactions *e.g.* Claisen couplings,[1] aldol[2], Mannich[3] and Michael[4] reactions.

The utility of MAHTs (**1**) and MAHOs (**2**, Scheme 1) in Nature and the 'reaction flask' resides in the reactivity associated with the β-carbonyl carboxylic acid group (red bonds in **1** and **2**) and its reaction with different electrophiles. Typical examples include aldehydes, *N*-tosylimines, *trans*-β-nitrostyrenes, azodicarboxylates and ketones. The reactions proceed *via* similar but 'inverted' mechanistic routes either 'addition-decarboxylation' pathway *i.e.* A (Scheme 1) or a 'decarboxylation-addition' pathway *i.e.* B. Depending on where the MAHO or MAHT reactions take place can influence which of these pathways is followed. For example, reacting a MAHO with a pyruvate ester in a 'reaction flask', current mechanistic understanding favors 'Pathway A'.[5] In contrast, utilizing a polyketide synthase (PKS) and a MAHT, the commonly accepted mechanism[6] involves decarboxylation, generating a thioester enolate (**3**, Scheme 1), with subsequent addition to an aldehyde affording a β-hydroxythioester *e.g.* **4**, 'Pathway B'. As a consequence of MAHT-enhanced reactivity, there is increasing interest in developing novel activation pathways for MAHTs; organocatalysis (*vida infra*) and metal-mediated catalysis are leading examples.[7]

Detailed studies on the reactivity differences of MAHTs and MAHOs have not been conducted. We propose these are related to their ease of keto-enol tautomerization. Probing the ability of MAHTs and MAHOs to tautomerization we report here insight into their reactivities using ^{1}H-NMR and a hydrogen → deuterium exchange protocol using structure- and function-diverse substrates based on **1** and **2**. A subsequent computational study afforded a better understanding of how changing the substituents on the aryl group in sulfur-stabilized MAHTs *e.g. cisoid*-**5** (Z = S, Scheme 1) and enol-stabilized MAHOs *e.g. cisoid*-**6** (Z = O) can enhance or decrease their reactivity.



Scheme 1. 'Addition-decarboxylation' and 'decarboxylation-addition' reaction pathways associated with MAHTs and MAHOs.

PKSs are large multi-domain enzymes that use MAHTs for the biosynthesis of fatty acids and biologically active secondary metabolites.[8] Examples of some important

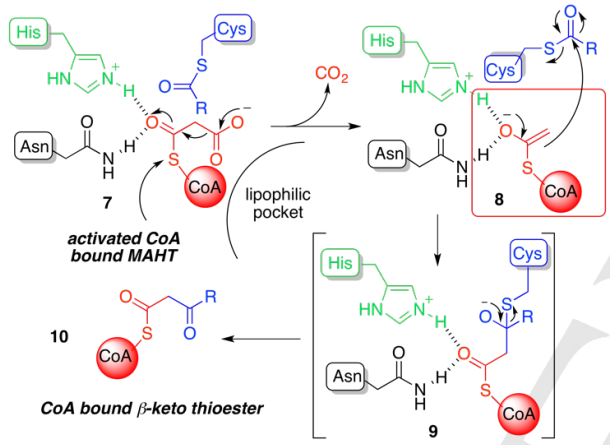
[a] Dr S. P. Bew, G. R. Stephenson, J. Godemert, H. Seylani, L. A. Martinez-Lozano
School of Chemistry
Norwich Research Park
University of East Anglia
NR4 7TJ, UK
E-mail: s.bew@uea.ac.uk or g.r.stephenson@uea.ac.uk
[b] Dr J. Rouden
Laboratoire de Chimie Moleculaire et thio-organique (LCMT)
UMR CNRS 6507, Ensicaen
6 Boulevard du Marechal Juin, 14050 Caen, France.

Supporting information for this article is given via a link at the end of the document.

10.1002/chem.201605148

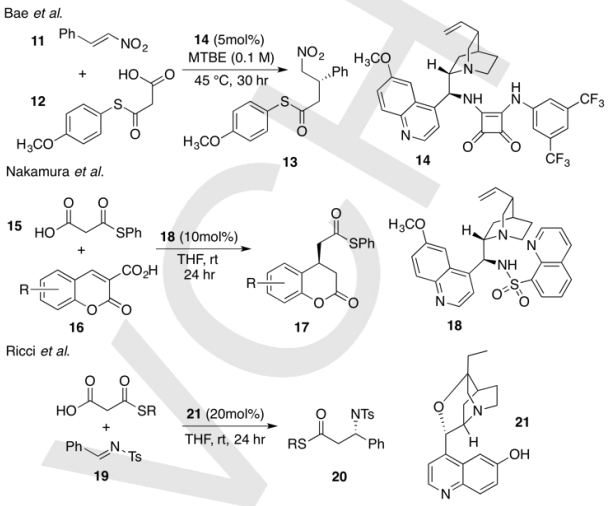
secondary metabolites include rifamycin (antibiotic), callystatin (anticancer), psymberin (anticancer), pridamicin (antifungal) and 6-deoxyerythrolide (antiviral). 'Activation' of the MAHTs in PKS is *via* an active site embedded histidine (His) and asparagine derived $CONH_2$ (Asn, Scheme 2). In this metal-free environment the CoA thioester malonic carboxylate anion is hydrogen-bonded (**7**) to protonated His and Asn. The activated MAHT eliminates CO_2 and generates reactive thioester enolate **8**. Due to its reactivity and close proximity to an electrophilic cysteine thioester it affords CoA bound β-keto thioester **10** *via* tetrahedral intermediate **9**.[9]

Efforts to build natural or artificial PKS constructs that mimic the capabilities of CoA-derived malonic thioesters *cf* **7** are held back by a lack of understanding of the reactivity, conformation and electronic 'communication' within **1** and **2**. Thus developing efficient, mild and sustainable protocols for structure- and function-diverse MAHO(T)s is important in their applications in biomimetic and synthetic processes.



Scheme 2. Biosynthetic acetyl-CoA derived MAHT 'activation', thioenolate formation and aldol condensation to generate acetyl-CoA bound β-ketothioester.

Increasing interest in the synthesis applications of MAHO(T)s can be attributed, in part, to their exploitation in asymmetric organocatalysis.[10] However, there are reports alluding to the difficulty in generating oxyester enolates of **1** that attribute this to the high p*K*a values of phenoxy esters *i.e.* ~18 (DMSO).[11] Therefore, increased emphasis has been placed on phenylthioesters which, generally, have lower p*K*a's ~16-17 (DMSO).[12] Substituting MAHTs for MAHOs, their application in organocatalytic protocols becomes viable. By way of example, Song *et al*. utilized **12** (Scheme 3) in conjunction with squaramide-derived organocatalyst **14** for the enantioselective Michael addition to *trans*-β-nitrostyrene **11** generating γ-amino acid precursors, based on **13** (88 - 99% *e.e.* and 15 - 96 yields).[13] Similarly, using cinchinone-derived catalyst **18** conjugate addition of **15** to coumarin **16** afforded thioester **17** in 95% - 99% yields and 84% - 92% *e.e.*'s.[14] Finally, Ricci *et al*. synthesised **20** *via* an enantioselective 'addition-decarboxylation' of aryl- or alkylthio-MAHTs to **19** using cinchona-derived catalyst **21**. The β-*N*-tosylamino thioesters (**20**) were produced in 21-79% *e.e.* and 42 - 84% yields.[15]



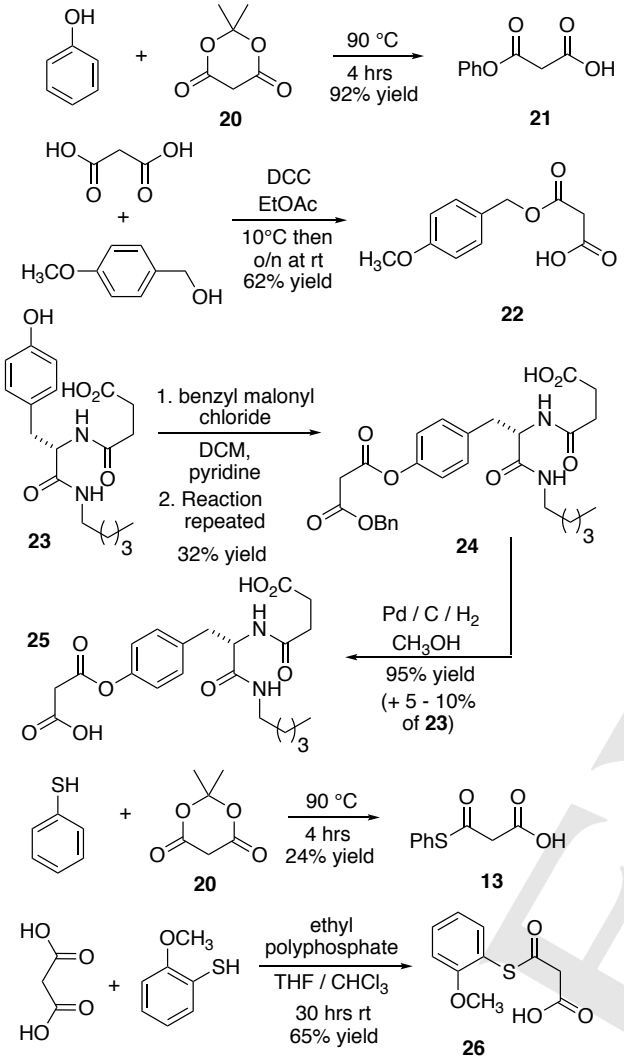
Scheme 3. Bae *et al*. Enantioselective biomimetic Michael addition of MAHT **12** to *trans*-β-nitrostyrene catalyzed by cinchona-based **14**. Nakamura *et al*. Enantioselective Michael addition reaction catalyzed by **18** generating thioester **17**. Ricci *et al*. Synthesis of β-*N*-tosylamino thioester **20** *via* 'addition-decarboxylative' reaction of a MAHT to **19** catalyzed by **21**.

Increasing applications of MAHOs and MAHTs reinforces the need for straightforward, efficient and scalable syntheses. Furthermore, there are relatively few syntheses of structure- and function-diverse aryloxy-derived MAHOs and arylthiol-derived MAHTs. The majority of MAHOs are generated using 2,2-dimethyl-1,3-dioxane-4,6-dione (**22**).[16] However, its thermal instability to elevated temperatures, requirement for cold storage and, unless freshly bought, recrystallization before use.[17] Kee *et al*. reacted phenol with **22** generating MAHO **23** (Scheme 4).[18] Mase *et al*. generated **25** (62% yield) from malonic acid and **24** using dicyclohexylcarbodiimide (DCC) as the coupling agent.[19] However, DCC is not particularly atom-efficient and although not commented on, removing trace amounts of dicyclohexylurea (DCU) from reaction products can be problematic.

Searching SciFinder for aryl thioester MAHTs generated 32 references, these contained 10 unique MAHTs. Further analysis revealed, rather surprisingly, only 2 different synthesis protocols had been utilized. Using Meldrum's acid, Kee *et al*. generated **15** in a 24% yield,[16] unfortunately it also generated difficult to remove dithiophenylmalonic ester by-product (not shown) afforded in a near equal percentage *i.e.* 21%. Imamoto *et al*. reported the synthesis of 8 MAHTs. The series comprised 5 alkyl and the 3 aryl thioesters *e.g.* **15**, **29** and 3-(2,4,6-trimethylphenylthio)-3-oxopropanoic acid (not shown) generated in 88%, 65% and 88% yields respectively. Potential problems and limitations reside in the use of 4 equivalents of malonic acid and not commercially available ethyl polyphosphate (also used in excess), and the long reaction time (30 hours). Imamoto probed the requirement for excess

10.1002/chem.201605148

malonic acid during the synthesis of **15**. However, 1 equivalent of malonic acid afforded a 40% yield, a 44% drop when compared with 4 equivalents.[20]



Scheme 4. Synthesis of MAHOs **23**, **25**, **28** and MAHTs **15** and **29**.

Results and Discussion

Our strategy had 3 components:

1. Part 1 - *Synthesis*. Our aim was to develop a simple, versatile, mild and efficient protocol for generating structure and function diverse thioaryl- and thioalkyl-derived MAHTs and aryl oxyester-derived MAHOs. It was important they were readily available from cheap 'off the shelf' reagents using an operationally straightforward protocol.[21] Furthermore, it was essential our protocol was applicable to the synthesis of sterically encumbered, electron-rich or electron-poor MAHO(T)s.
2. Part 2 - *Reactivity*. Exploring MAHO (**1**) and MAHT (**2**) reactivity, a comprehensive ^{1}H-NMR structure activity relationship (SAR) study sought to exploit their acidic α-CH_2's and probe the roles of the sulfur / oxygen in their ability to effect keto-enol tautomerisation in a hydrogen → deuterium exchange.
3. Part 3 - *Computation*. DFT studies were deployed to explain / determine the unusual reactivity displayed by some MAHTs in the hydrogen → deuterium exchange study (Part 2). Crucial differences in the delocalised molecular orbitals associated with the enol were identified and may account for their differing reactivities.

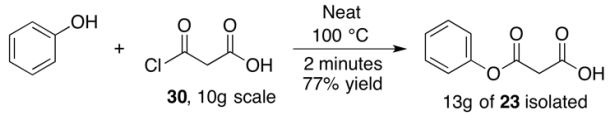
Initiating our work we developed a straightforward synthesis of malonyl mono-chloride[22] using readily available malonic acid and thionyl chloride. Stirring a mixture of the starting materials for 6 hours in ether at reflux, followed by removal of any volatile compounds (high vacuum), afforded a product suitable for use 'as is' in onward reactions. Without further purification 50 g batches of malonyl mono-chloride were readily synthesized and stored at ambient temperature, for at least 3 months, with no signs of decomposition.

Our next objective was to generate aryloxy-derived MAHOs. Currently, within the synthetic chemistry community, there is considerable interest in the development of solvent-free protocols.[23] Attempting the synthesis of **23** (Table 1), malonyl mono-chloride and phenol were mixed at ambient temperature. After a short period of time a slow coalescence towards a homogenous solution was observed which, if left for 2 hours, afforded complete dissolution. Stirring the reaction for a further 4 hours, a small aliquot was removed for analysis after dissolving in [2H]chloroform. Disappointingly, ^{1}H-NMR (400 MHz) indicated the majority of **30** (Scheme 5) was still present and only a small amount (~10%) of MAHO **23** had formed. Although it seemed this approach had merit, the reaction was incomplete and the time prohibitively long. The most straightforward way to increase the rate and hopefully generate **23** more efficiently was to raise the reaction temperature. At 100 °C the mixture quickly transformed into a homogeneous clear pale yellow solution. After 30-minutes it was cooled to room temperature and dichloromethane (DCM) added. The white precipitate was filtered, dried under vacuum and a small portion re-dissolved in [2H]chloroform. Gratifyingly ^{1}H-NMR analysis confirmed **23** had formed, with minimal decomposition in an unoptimized 75% yield.

Malonic acid derivatives are, generally, thermally unstable. For subsequent studies it was important to determine the rate of reaction between phenol and malonyl mono-chloride (no solvent) at 100 °C. Probing the synthesis of **23** it was analyzed at 4-, 9- and 19-minute intervals. ^{1}H-NMR spectrometry indicated consumption of phenol and, in all cases efficient formation of **23**. The reaction was repeated, again without solvent, in a preheated bath (100 °C) and rapidly cooled (ice-bath) after 2 minutes. **23** was isolated and purified *via* flash-column chromatography in a 77% yield. Thus, employing these conditions the synthesis of MAHO **23** was fast, efficient and high yielding. As previously noted, it was important our protocol was scalable affording, if desired, multi-gram quantities of MAHO(T)s. 10 g of malonyl mono-chloride was reacted with phenol (100 °C for 2 minutes) followed by

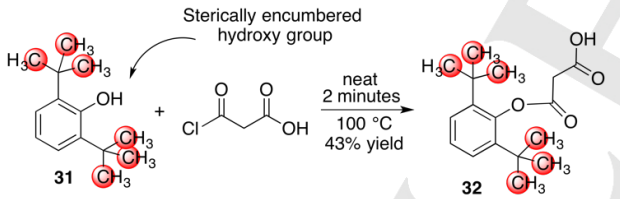
10.1002/chem.201605148

cooling and addition of DCM. Analysis of the precipitate confirmed **23** (13 g) had formed cleanly and efficiently in a 77% yield (Scheme 5).



Scheme 5. Efficient, multi-gram solvent-free synthesis of **23**

To facilitate 'take up' of our protocol it was important to demonstrate synthetic versatility. We probed the formation of sterically encumbered MAHOs by incorporating hindered 2,6-dimethylphenol, 2-*tert*-butylphenol as well as the extremely hindered 2,6-di-*tert*-butylphenol. Reacting 2,6-dimethylphenol and malonyl mono-chloride in our standard reaction conditions (*i.e.* 100 °C for 2 minutes) afforded after work up a white solid. Subsequent physicochemical analysis confirmed **41** (Table 1) had formed, in an unoptimized 66% yield. Increasing the steric bias further MAHOs derived from 2-*tert*-butylphenol and 2,6-di-*tert*-butylphenol were attempted. Using our standard reaction conditions afforded the previously unknown **42**, and **32** (Scheme 6). Both were isolated as easily handled, stable solids in 65% and 43% yields respectively. Although **32** was afforded in slightly lower isolated yield than **41** and **42**, the reaction seems fully amenable to generating highly sterically encumbered MAHOs. Changing tack, we sought to incorporate a sterically less challenging 2-allyphenol substituent. Employing standard conditions **43** (Table 1) was afforded with an embedded allyl group, a versatile chemical handle, in close proximity to the β-keto carboxylic acid in a pleasing 66% yield.



Scheme 6. Synthesis of sterically encumbered MAHO **32**

We turned our attention to the synthesis of MAHOs derived from electron-deficient substrates *e.g.* 2- and 4-nitrophenol, 2- and 4-cyanophenol as well as methyl 2- and 4-hydroxybenzoate. In the 4-substituted series, MAHOs **44** (4-nitrophenol), **45** (4-cyanophenol) and **47** (methyl 4-hydroxybenzoate) were all readily generated in good 66%, 60% and 51% isolated yields. Seemingly the known propensity of phenols to undergo *intermolecular* hydrogen-bond dimerization does not appear to hinder the formation of the MAHOs. In contrast, the incorporation of 2-nitrophenol or methyl 2-hydroxybenzoate resulted in poor isolated yields of **37** and **40** *i.e.* 25% and 21% respectively. Interestingly 2-cyanophenol afforded MAHO **46** with a restored and considerably higher (than **37** and **40**) 61% yield (Table 1).

Table 1. Examples of structure and function diverse MAHOs which are readily generated using a mild, efficient and straightforward reaction protocol.

No	Name	Yield[a]
23	3-oxo-3-(phenoxy)propanoic acid	77%
25	3-oxo-3-(4-methoxyphenoxy)propanoic acid	61%
32	3-oxo-3-(2,6-di-*tert*-butylphenoxy)propanoic acid	43%
37	3-oxo-3-(2-nitrophenoxy)propanoic acid	25%
40	3-oxo-3-((2-methoxycarbonyl)phenoxy)propanoic acid	21%
41	3-oxo-3-(2,6-dimethylphenoxy)propanoic acid	66%
42	3-oxo-3-(2-*tert*-butylphenoxy)propanoic acid	65%
43	3-oxo-3-(2-allylphenoxy)propanoic acid	66%
44	3-oxo-3-(4-nitrophenoxy)propanoic acid	66%
45	3-oxo-3-(4-cyanophenoxy)propanoic acid	60%
46	3-oxo-3-(2-cyanophenoxy)propanoic acid	61%
47	3-oxo-3-((4-methoxycarbonyl)phenoxy)propanoic acid	51%
48	3-oxo-3-(4-hydroxyphenoxy)propanoic acid	nd
49	3-oxo-3-(2-hydoxyphenoxy)propanoic acid	nd
50	3-oxo-3-(2-methoxyphenoxy)propanoic acid	45%
51	3-oxo-3-(4-chlorophenoxy)propanoic acid	64%
52	3-oxo-3-(4-bromophenoxy)propanoic acid	69%
53	3-oxo-3-(4-iodophenoxy)propanoic acid	77%
54	3-oxo-3-(2-chlorophenoxy)propanoic acid	68%
55	3-oxo-3-(2-bromophenoxy)propanoic acid	71%
56	3-oxo-3-(4-trifluoromethylphenoxy)propanoic acid	55%
57	3-oxo-3-(3-trifluoromethylphenoxy)propanoic acid	59%

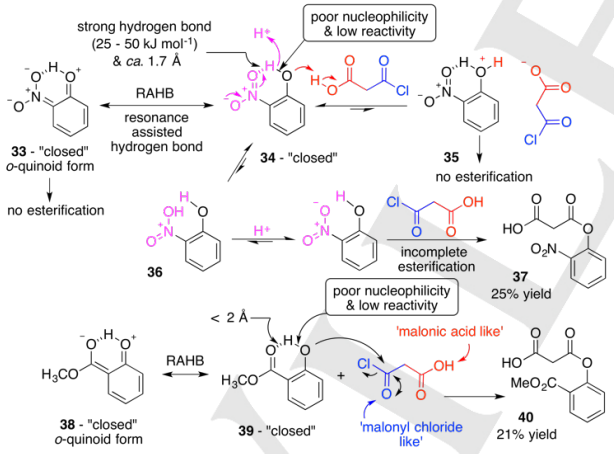
[a]. nd = not determined

We sought to rationalize the low yields for **37** and **40**. Here we propose an *intramolecular* hydrogen-bond in 2-nitrophenol and methyl 2-hydroxybenzoate perturbs, in a negative sense, their reaction with malonyl mono-chloride. A substantial body of evidence supports 2-nitrophenol's existence in a "closed" *i.e.* **34** (Scheme 7) or "open" (not shown) conformation. When "closed" the resulting resonance-assisted hydrogen bond (RAHB) generates non-esterifiable *o*-quinonoid **33**. Furthermore, in conformation **34** ("closed") its reactivity is significantly curtailed by a strong hydrogen-bond, which for 2-nitrophenol has been determined using different experimental techniques to be 25 - 35 kJ mol^{-1}.[24] Interestingly, *ab initio* studies predict a considerably higher 45 - 50 kJ mol^{-}

10.1002/chem.201605148

[1].[25] Needless to say which ever is considered, the strength of the hydrogen-bond is reflected in the short *ca*. 1.7 Å OH····O bond (based on X-ray diffraction[26]). The net result of the RAHB and the inductive effect (2-nitro group) is a reduction in the nucleophilicity of the phenolic hydroxyl of **34** affording it with poor reactivity towards acyl chloride **30**. A similar argument is proposed for **39**. Again, a *strong* intramolecular hydrogen bond *i.e*. OH····O (< 2.0 Å) combined with RAHB (**38**) and a strong inductive effect is highly effective at *reducing* the nucleophilicity of the phenolic hydroxyl group resulting in a low 21% yield of **40** (Table 1).

As a homogenous reaction it was prudent to consider the effect (if any) malonyl mono-chloride may have as a bifunctional hybrid-like and unconventional malonic acid-malonyl chloride 'solvent' on the poor yields of **37** and **40**. As a potential proton donor, we considered the possibility the 'malonic acid' (p*K*a 2.5) may protonate the phenolic oxygen of **34** generating malonate ion-pair **35** (Scheme 7) on route to **37**. However, the phenolic hydroxyl is poorly nucleophilic and as such it will be reluctant to undergo protonation by the weakly acidic carboxylic acid of **30**, furthermore once protonated **35** is no longer able to participate in the desired reaction pathway. It seems feasible **30** could protonate "closed" **34** *via* the pink arrows (Scheme 7) and disrupt the strong intramolecular hydrogen-bonded complex *i.e*. **34** → **36**. However, as a *major* reaction pathway this is unlikely because it requires breaking the strong OH····O=N(O)- bond. Applying similar RAHB arguments (*i.e*. formation of **38**) and reasoning, the low yield for *ortho*-ester **40** can be rationalized. Thus, it seems **37** and **40** are generated *via* an inefficient reaction of poorly nucleophilic **34** or **39** with malonyl mono-chloride *i.e*. **39** → **40** (Scheme 7).



Scheme 7. Poor reactivity of **34** and **39** is ascribed to RAHB and strong inductive effects associated with the 2-nitro and 2-carboxymethyl groups.

Reacting one equivalent of malonyl mono-chloride with electron-rich hydroquinone or catechol was at first promising. Although the isolation of the presumed mono-carboxylate **48** and **49** (Table 1) together with what appeared to be small quantities of the corresponding dicarboxylic acids (not shown) was straightforward (filtration), their insolubility in a wide range of solvents made further purification tedious, difficult and ultimately not possible. The synthesis of analytically pure, electron-rich aryl-derived MAHOs was, however, an important milestone. Incorporating the more lipophilic 4-methoxyphenol and 2-methoxyphenol the desired mono-carboxylic acids **25** and **50** were isolated as easily purified solids in 61% and 45% yields respectively (Table 1). Once again the 2-regioisomer (**50**) was afforded in a slightly lower than anticipated yield (*cf*. **37** and **40**). Presumably, 2-methoxyphenol generates a five-membered intermediate strength intramolecular hydrogen-bond (2.11 Å[27]), similar to **34** and **39**, that reduces its reactivity and results in a lower yield of product (**50**).

Synthesizing aryl halide derived MAHOs was important because of their applications as easily accessible starting materials capable of metal-catalyzed chemical manipulation and elaboration.[28] 4-Chloro, 4-bromo and 4-iodophenol reacted, without solvent, with malonyl mono-chloride (100 °C, 2 minutes) affording **51**, **52** and **53** in broadly similar 64%, 69% and 77% yields respectively. Furthermore, unlike the incorporation of strong EWGs at the 2-positions of **37** (nitro) and **40** (methyl ester) the 2-chloro- and 2-bromophenol adducts afforded 2-chlorophenyl-**54** and 2-bromophenyl-**55** in 68% and 71% yields respectively. Explaining the relatively weak '*ortho*-halo effect' it is known they form only moderately strong intramolecular X····HO bonds (X = Cl or Br).[29] Incorporating substrates equipped with more than one halogen was explored using the trifluoromethyl group. Both 4-(trifluoromethyl)phenol and 3-(trifluoromethyl)phenol afforded **56** (55% yield) and **57** (59% yield, Table 1). Clearly incorporting the trifluoromethyl moiety is not detrimental to a successful reaction outcome.

Confident our protocol was amenable to generating structure and function diverse aryloxy-derived MAHOs attention switched to the corresponding MAHTs. Utilizing the protocol for generating **23** *i.e*. neat, 100 °C, 2 minutes but with thiophenol we were surprised **15** was afforded in a poor 25% yield (*cf*. 77% yield for MAHO **23**, Table 1). Presumably the greater reactivity of **15** relative to MAHO **23** resulted in decomposition at the elevated reaction temperature. Attempting to mitigate this the rapid two-minute reaction time was maintained whilst the temperature was lowered to 65 °C.

Disappointingly **15** was afforded in a poor yield with the reaction comprising largely unreacted thiophenol and **30**. If, however, it was increased to two hours whilst maintaining the temperature at 65 °C **15** was isolated as a white solid after a simple work-up in a 59% yield. Our slightly modified protocol proved to be a convenient starting point for the incorporation of 16 commercially available thiophenols. Monocyclic 4-methylthiophenol, sterically encumbered 2,6-di-methylthiophenol and multicyclic 2-naphthalenethiol all reacted (individually) with malonyl mono-chloride. The desired MAHTs **58** - **60** were isolated in 59%, 43% and 52% yields respectively with the reaction appearing to be unaffected by steric bias, thus 2,6-dimethylthiophenol and 4-methylthiophenol afforded, within experimental error, identical yields. Similar to the

10.1002/chem.201605148

synthesis of electron-poor 4-nitrophenyl derived MAHO **44** (66% yield), 4-nitrothiophenol was readily transformed into the previously unknown **61** in a 52% yield. 2-Nitrothiophenol afforded the expected MAHT *i.e.* **62** in a 30% yield. Comparing **37** (25% yield) with the slightly higher yield of **62** can be accounted for in terms of the thiol group being more nucleophilic than the hydroxyl and within the 2-nitrothiophenol the intramolecular hydrogen-bond *i.e.* $-NO_2\cdots HS-$[30] (1.922 Å and 34.64 kJ mol^{-1}) being longer and weaker than the hydrogen-bond in **37**.

Incorporating electron-rich 4-methoxythiophenol and 2-methoxythiophenol the corresponding **12** and **29** (Scheme 4) were afforded in 61% and 51% yields respectively. The identical yields for 4-methoxyphenyl-MAHO **25** and 4-methoxythiophenyl-MAHT **12** (Table 2) verify the viability of incorporating EDGs on phenols or thiophenols and their suitability as starting materials for novel MAHO(T) synthesis.

Similar to the reasons outlined for aryl halide containing MAHOs **51** - **57** (Table 1), the incorporation of thioaryl halides and (trifluoromethyl)thiophenols in MAHTs was important. Employing our 'standard' MAHT reaction conditions malonyl mono-chloride was added, independently, to 4-chlorothiophenol, 3-chlorothiophenol, 2-chlorothiophenol, 4-bromothiophenol, 4-fluorothiophenol and 4-trifluoromethylphenol. The desired MAHTs **63** - **68** were isolated in 50% (4-chlorophenyl), 58% (3-chlorophenyl), 45% (2-chlorophenyl), 41% (4-bromophenyl), 65% (4-fluorophenyl) and 50% (4-trifluorophenyl) yields (Table 2). Reflecting on the slightly lower yield of **65** it is known, similar to 2-chlorophenol, an *ortho*-chlorine atom can generate a 5-membered intramolecular hydrogen bond (2.16 Å) with the adjacent thiol *i.e.* $-Cl\cdots HS-$[31] which *reduces* the nucleophilicity of the thiol, albeit not to the same extent as a 2-nitro group, and impedes its capacity to react efficiently with **30**. Similar to **56** and **57** 4-(trifluoromethyl)aryl substituted MAHT **68** was readily generated in a 50% yield and, within experimental error, an identical yield to 4-(trifluoromethyl)aryl substituted MAHO-**56** *i.e.* 55% yield. Disappointingly, all attempts at generating pentachlorophenyl-**69** failed with, at best, single figure yields returned. Presumably the five electron-withdrawing chlorine atoms reduce the nucleophilicity of the thiol to such an extent it is no longer able to react with acyl chloride **30**. Expanding the substrate scope, we sought to include representative examples of alkyl thiols. 3-Mercaptopropanoate methyl ester, benzyl mercaptan and cyclohexanethiol generated **70**, **71** and **72** in 30%, 55% and 44% yields respectively (Table 2).

Ultimately it is our intention to develop novel isotope derived MAHOs and MAHTs as multinuclear NMR[32] and mass spectrometric (MS) probes.[33] Therefore our focus switched to generating structure and electronically diverse isotopologues [2H]-MAHO (**73**) and [2H]-MAHT (**74**) (Scheme 8).

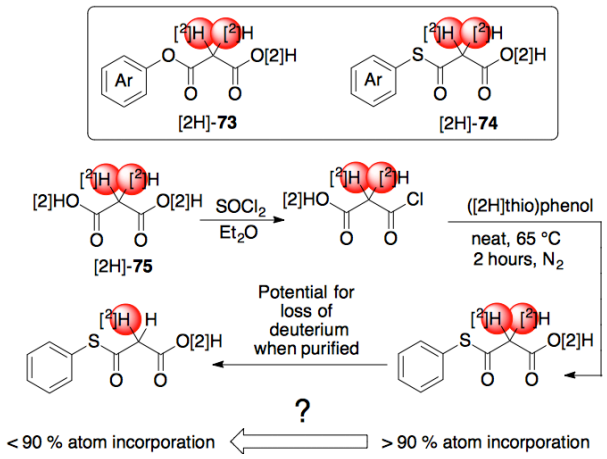
MAHOs and MAHTs are important motifs in synthetic and biological chemistry. (Scheme's 2 and 3). Similarly, stable isotopes, especially deuterium, are widely employed in many different research sectors *e.g.* pharmaceutical, agrochemical, biotech, medtech, materials and analytical chemistry. However, only a handful of deuterated MAHOs and MAHTs have been reported; apart from several recent examples from our own laboratory and Matille *et al*.[21] only two are known *i.e.* 2-methyl-3-oxo-3-(phenylthio)-[2H]propanoic acid and 2-([2H]methyl)-3-oxo-3-(phenylthio)propanoic acid.[34]

Table 2. Examples of structure and function diverse MAHTs which are readily generated using a mild, efficient and straightforward reaction protocol.

No	Name	Yield[a]
12	3-oxo-3-(4-methoxyphenylthio)propanoic acid	61%
15	3-oxo-3-(3-phenylthio)propanoic acid	59%
29	3-oxo-3-(2-methoxyphenythio)propanoic acid	51%
58	3-oxo-3-(4-methylphenylthio)propanoic acid	59%
59	3-oxo-3-(2,6-dimethylphenylthio)propanoic acid	43%
60	3-oxo-3-(2-napththylthio)propanoic acid	52%
61	3-oxo-3-(4-nitrophenylthio)propanoic acid	52%
62	3-oxo-3-(2-nitrophenylthio)propanoic acid	30%
63	3-oxo-3-(4-chlorophenylthio)propanoic acid	50%
64	3-oxo-3-(3-chlorophenylthio)propanoic acid	58%
65	3-oxo-3-(2-chlorophenylthio)propanoic acid	45%
66	3-oxo-3-(4-bromophenylthio)propanoic acid	41%
67	3-oxo-3-(4-fluorophenylthio)propanoic acid	65%
68	3-oxo-3-(4-trifluoromethylphenylthio)propanoic acid	50%
69	3-oxo-3-(pentachlorophenylthio)propanoic acid	2%
70	3-(2-methoxy-2-oxoethylthio)-3-oxopropanoic acid	30%
71	3-oxo-3-(benzylthio)propanoic acid	55%
72	3-oxo-3-(cyclohexylthio)propanoic acid	44%

We contemplated the synthesis of entities based on [2H]-**73** and [2H]-**74** using [2H]malonic acid ([2H]-**75**, Scheme 8). We had reservations however on progressing deuterated intermediates through multiple procedures and, potentially, drawn-out flash chromatography purifications using 'wet' and acidic silica gel. With our concerns focused on the product being produced with reduced levels of [2H]-incorporation resulting from deuterium → hydrogen exchange ('washout') at the acidic [2H]-methylenes. Opting for an alternative strategy we took advantage of the facile keto-enol tautomerisation properties of 'pre-assembled' MAHO(T)s and their potential for hydrogen → deuterium exchange. At the outset, it was important to establish a proof of principal using a simple MAHO and MAHT. Ester **23** and thioester **15** were dissolved in [2H]methanol and monitored by ^{1}H-NMR at 4-, 9-, 19- and 29-minutes. Table 3 outlines the rather surprising results with *significantly* divergent levels of [2H]-incorporation for these very similar compounds.

10.1002/chem.201605148



Scheme 8. Potential synthesis of MAHT [2H]-**77** from [2H]-**75**

Evidently after only 4 minutes the extent of deuterium exchange for thiophenol-derived MAHT **15** was significantly *faster* and more efficient than the corresponding phenol-derived **23**. Compare, for example, after only 4 minutes 72% incorporation for **15** with only 18% for **23**. Furthermore, after only 9 minutes **15** had incorporated 90% deuterium, 52% *more* than its chalcogen equivalent. After 29 minutes **23** still had not undergone complete isotope incorporation reaching a level equivalent to the same afforded by **15** in only 4 minutes! Clearly, switching phenol for thiophenol has a significant and positive effect on the *enol reactivity* of **15**. It was important to ascertain if the increased reactivity was an 'isolated' result specific to **15** or if it was a more general and if so more interesting, presumed, stereoelectronic effect. Using a selection of structure and function diverse MAHOs (17 examples) and MAHTs (7 examples) a comprehensive hydrogen → deuterium exchange study was undertaken. Employing a standard concentration of MAHO or MAHT (both 70 μM) in excess [2H]methanol (500 μL) the results are presented in Figure 1. What is immediately evident is high-levels of [2H]-incorporation can be readily achieved in the majority of substrates simply by stirring them at ambient temperature with a deuterated protic solvent.

Furthermore, there are *significant rate differences* between thioesters and esters [compare graphs (a) and (b)] but also within each of the two classes different aryl substituents have a significant influence on their reactivity and ability to undergo hydrogen → deuterium exchange. See, for example, the clear 'gap' between the majority of examples and the four electron-poor arenes (Figure 1). Our observation is further reinforced by comparing 4-bromothiophenol-derived MAHO **52** with 4-cyanophenol-derived MAHO **45**. Not only is there a noticeable difference in the rate of exchange but also a significant difference in the percentage of [2H]-incorporation. Compare 2,6-dimethylphenol-derived **59** which has nearly 50% [2H]-incorporation after only 9 minutes with 4-bromophenol-derived **52** which is less than 10%. Further highlighting the reactivity differences between almost identical MAHOs and MAHTs is the surprising observation with 4-bromothiophenol-derived **66** which afforded the *largest* percentage of [2H]-incorporation, after only 9 minutes (96%). This contrasts sharply with 4-bromophenol-derived **52** which, as already noted, afforded only 15% [2H]-incorporation - the only difference between them, a sulfur versus an oxygen atom.

Table 3. Percentage levels of [2H]-incorporation into MAHO **23** and MAHT **15** after 4-, 9-, 19- and 29-minute reaction times.

Time	Phenol MAHO 23
4	18% [2H]-incorporation
9	38% [2H]-incorporation
19	60% [2H]-incorporation
29	74% [2H]-incorporation
Time	**Thiophenol MAHO 15**
4	72% [2H]-incorporation
9	90% [2H]-incorporation
19	97% [2H]-incorporation
29	98% [2H]-incorporation

Dissecting the data generated from the hydrogen → deuterium study (Figure 1) several important observations and interpretations can be inferred:

1. Using easy to generate ^{1}H-NMR data on MAHOs and MAHTs it is possible to determine fundamental reaction rate differences between these two classes of compounds.
2. Integrating the remaining protons on the acidic α-methylenes of the MAHOs and MAHTs after 9 minutes afforded a convenient 'snap-shot' of the initial rate of hydrogen → deuterium exchange. Here we determined the percentage of [2H]-incorporation and the relative rates of reaction (*k*) associated with the exchange process.
3. The results (Table 4) clearly show MAHOs derived with 2- and 4-bromophenol undergo hydrogen → deuterium exchange at approximately the same rates *i.e.* *k* = ~31 ±2 and afford almost identical low levels of [2H]-incorporation *i.e.* 14% - 15%. In the same study, 4-methoxyphenol-derived **25** (*k* = 60), 4-trifluoromethylphenol-derived **56** (*k* = 67) and 4-chlorophenol derived **51** (*k* = 66) afforded, at similar rates of reaction, the [2H]-MAHOs with 27%, 30% and 31% [2H]-incorporation. Clearly, hydrogen → deuterium exchange in these MAHOs is faster and more efficient than the bromoaryl-substituted MAHOs.
4. Strong electron-withdrawing *para*- and *ortho*-substituted aryl groups on MAHOs *increase* (see Table 4) the rate of hydrogen → deuterium exchange, see for example **44** (4-nitrophenyl), **37** (2-nitrophenyl)

10.1002/chem.201605148

and **47** (4-carboxyphenyl methyl ester). For example, 4-cyanophenol-derived **45** affords 79% [2H]-incorporation with a rate *k* = 171 whereas phenol-derived **23** affords 38% [2H]-incorporation with a reduced rate *i.e*. *k* = 83.

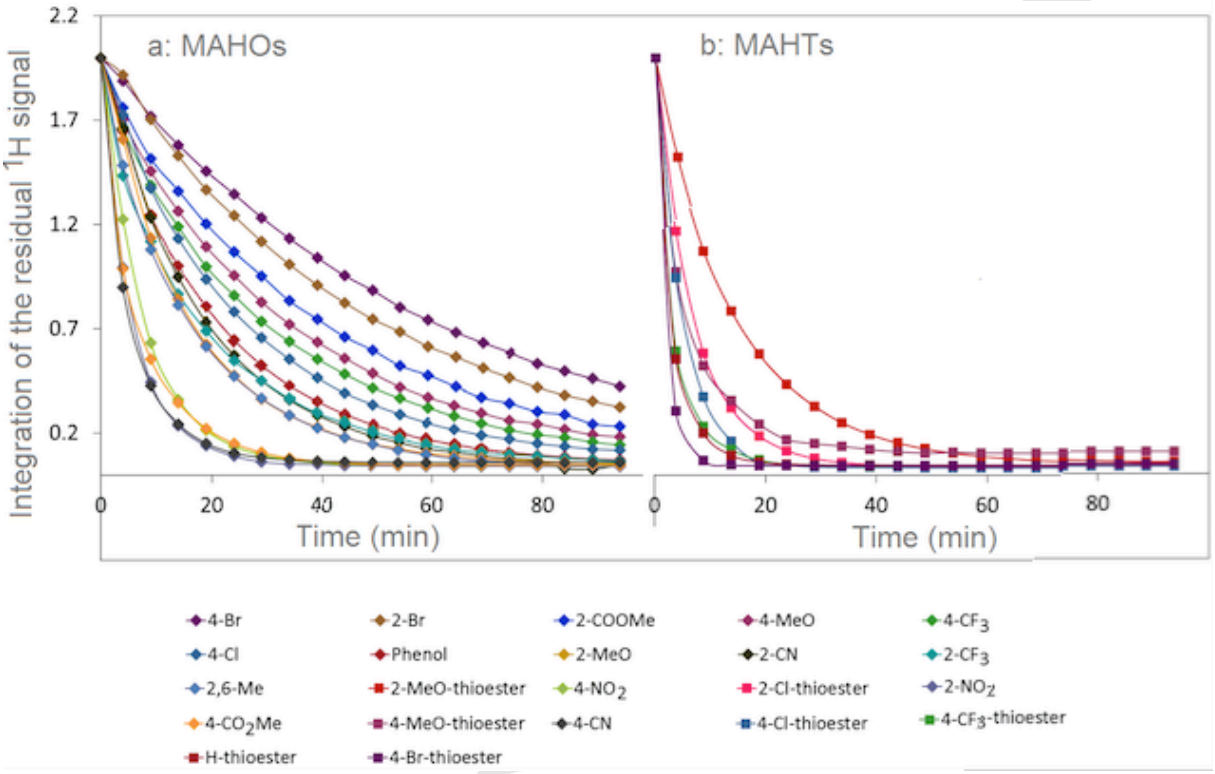


Figure 1. Rates of hydrogen → deuterium exchange for a variety of structure and function diverse MAHO and MAHOs.

5. Within the confines of our study the *overall* rate of hydrogen → deuterium exchange is significantly faster in the majority of MAHTs than MAHOs.
6. Increasing the *steric bulk* either side of the phenolic ester alcohol increases the *rate* of hydrogen → deuterium exchange but with only moderate increases (after 9 minutes) of [2H]-incorporation. Compare for example phenol-derived **23** (*k* = 83) with 2,6-dimethylphenol-derived **41** (*k* = 101).
7. In like-for-like comparisons incorporating specific *ortho*-substituents a *decrease* in the rate and percentage of [2H]-incorporation with respect a *para*-substituent was observed. For example, methyl *ortho*-ester-derived MAHO **40** returned 24% [2H]-incorporation (*k* = 53) and *ortho*-cyano-derived MAHO **46** 38% [2H]-incorporation (*k* = 85). Whilst the analogous *para*-methyl ester-derived **47** returned 72% [2H]-incorporation (*k* = 157) and *para*-cyano-derived **45** afforded 79% [2H]-incorporation (*k* = 171). Similarly, *ortho*-methoxythiophenol-derived **29** afforded lower [2H]-incorporation (46%) and at a slower rate (*k* = 102) than *para*-methoxythiophenol **12** with 74% [2H]-incorporation (k = 161). Differences in the levels of [2H]-incorporation in between *ortho*- and *para*-substituted MAHO(T)s seem dependent on steric congestion at the *ortho*-substituents.
8. The distributions of the hydrogen → deuterium exchange reaction rates are smaller, within the 9-minute window (see Table 4), for the MAHTs *i.e*. *k* = 102 → 208 than for the MAHOs *i.e*. *k* = 30 → 171. These results suggest, in general, the rate of exchange for MAHTs is less dependent on the aryl substitution than the MAHOs.
9. In nearly all examples the *initial rate* of hydrogen → deuterium exchange for the MAHTs were substantially *faster* than the majority of MAHOs. The only exceptions were when MAHOs were appended with strong electron-withdrawing groups *i.e*. **44** (4-nitrophenol), **37** (2-nitrophenol), **45** (4-cyanophenol) and **47** (4-carboxyphenyl methyl ester).
10. All the MAHTs afforded 95% [2H]-incorporation after less than 39 minutes. Indeed, excellent levels of deuterium were installed in many MAHTs in less than 20 minutes. Further highlighting the reactivity differences between MAHTs and MAHOs similar levels of [2H]-incorporation were only achieved for MAHOs **37**, **45** and **47** after stirring for 94 minutes (Figure 1). On the other hand MAHOs **23** (phenyl), **40** (2-carboxymethyl ester), **25** (4-methoxyphenyl), **51** (4-chlorophenyl), **52** (4-bromophenyl), **55** (2-

bromophenyl) and **56** (4-trifluoromethylphenyl) all afforded reduced levels of [2H]-incorporation *i.e*. 77% - 94% even after extended reaction times.

11. Further underlying the fundamental difference in reactivity between the oxygen- and sulfur-derived esters was the difference in the observed rates of exchange. In nearly all cases, the aryl thioester motifs underwent hydrogen → deuterium exchange at *significantly faster rates* than their oxygen counterparts when compared like-for-like *e.g.*

A. thiophenol derived **15** *faster* than phenol derived **23** *i.e*. k = 195 versus 83.

B. 4-bromothiophenol-derived **66** *faster* than 4-bromophenol-derived **52** *i.e*. k = 208 versus 31.

C. 4-trifluoromethylthiophenol-derived **68** *faster* than 4-trifluoromethylphenol-derived **56** *i.e*. k = 191 versus 67.

D. 4-chlorothiophenol **63** *faster* than 4-chlorophenol **51** *i.e*. k = 178 versus 66.

E. 4-methoxythiophenol **12** faster than 4-methoxyphenol **25** *i.e*. k = 161 versus 60.

Entry	Name / [2H]-incorporation	Rate
a	4-bromophenol / 14%	k = 31
b	2-bromophenol / 15%	k = 33
c	methyl-2-hydroxybenzoate / 24%	k = 53
d	4-methoxyphenol / 27%	k = 60
e	4-trifluoromethylphenol / 30%	k = 67
f	4-chlorophenol / 31%	k = 66
g	phenol / 38%	k = 83
h	2-methoxyphenol / 38%	k = 84
i	2-cyanophenol / 38%	k = 85
j	3-trifluoromethylphenol / 44%	k = 96
k	hexafluoroisopropanol / 43%	k = 96
l	2,6-dimethylphenol / 46%	k = 101
m	2-methoxythiophenol / 46%	k = 102
n	4-nitrophenol / 68%	k = 150
o	2-chlorothiophenol / 71%	k = 156
p	methyl-4-hydroxybenzoate / 72%	k = 157
q	4-methoxyphenol / 74%	k = 161
r	2-nitrophenol / 78%	k = 170
s	4-cyanophenol / 79%	k = 171
t	4-chlorothiophenol / 81%	k = 178
u	4-trifluoromethylthiophenol / 88%	k = 191
v	thiophenol / 90%	k = 195
w	4-bromothiophenol / 96%	k = 208

An explanation for the unusual MAHT reactivity enhancement was required. Initiating a computational study we sought to gain a comprehensive understanding of the reactivity differences. The electronic communication between the aryl ether and aryl thioether functionality and the enol was probed by DFT calculations. First, for the parent MAHO *i.e*. $PhOCH(OH)=CHCO_2H$, and MAHT *i.e*. $PhSCH(OH)=CHCO_2H$ the *E*- and *Z*-enols were compared in two representative conformations: (i) the enol-carboxylic acid section was close to co-planarity and (ii) the plane of the arene was orthogonal (~90°) to the enol-carboxylic acid section.[35]

In view of the similarity of the results obtained with the relatively rapid calculations possible with B3LYP/6-31G(d) or M06-2X/6-31+31G(d,p) compared with MO6-2X/def-QZVP we choose to employ B3LYP/6-31G(d) and M06-2X/6-31+31G(d,p) in the work described here as it would allow us to considerably extend our computational 'reach' examining the influence the substituents within the arene have on the conformations and molecular orbitals of the MAHO and MAHTs.[36] Initiating our study on MAHOs twenty-five distinct phenyl MAHO configurations / conformations were identified (see Table S3, SI) the most stable (–648.67222 Ha) retained the phenyl ring at about 92° (dihedral angle –92.14°) relative to the enol-carboxylic acid section which had an almost planar conformation. The enol was in the *E*-configuration, and the orientation of the carboxylic acid relative to the OPh group was *transoid*. The H-O-C-C, C-C-C-O and C-C-O-H sections of MAHO **23** and MAHT **15** were "e-z-z". A frequency calculation, however, indicated the –648.67222 Ha structure was a transition point not a true minimum. Further investigation identified two similar *more* stable forms (–648.67244 Ha), again corresponding to "*E-transoid-e-z-z"* structures, but now the phenyl ring was displaced from a perpendicular orientation to –62.3° (Figure 2) and –122.7° (Figure 3).

10.1002/chem.201605148

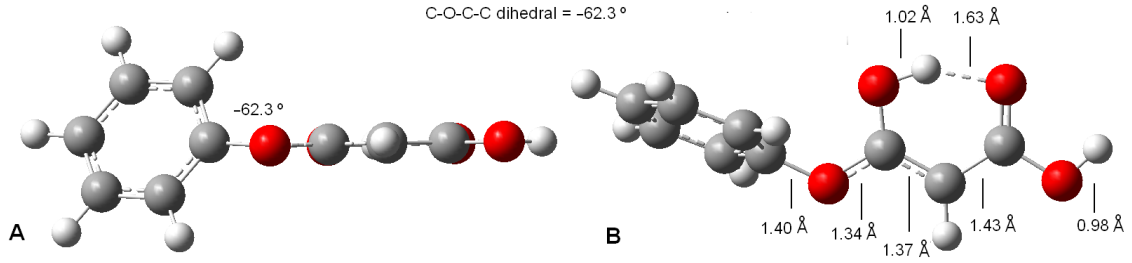


Figure 2. Minimum energy B3LYP/6-31G(d) structures for phenyl ester **23** in –62° dihedral angle form: (A): side view of the enol form of MAHO **23**; (B): top view of enol form of MAHO **2**

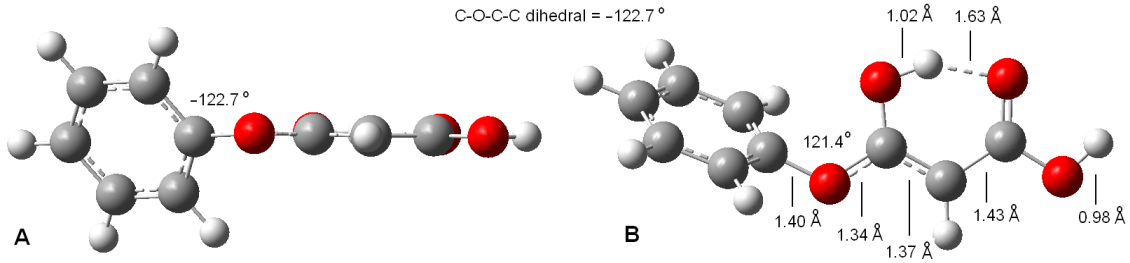


Figure 3. Minimum energy B3LYP/6-31G(d) structures for phenyl ester **23** in –123° dihedral angle form: (A): side view of the enol form of MAHO **23**; (B): top view of enol form of MAHO **2**

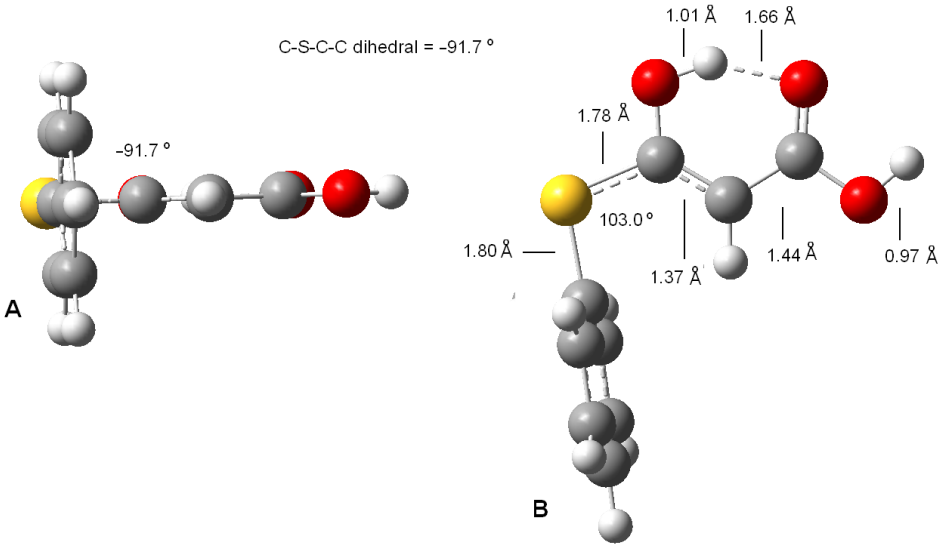


Figure 4. Minimum energy B3LYP/6-31G(d) structures for thioester **15** in –92° dihedral angle form: (A) side view of enol form of MAHT **15**; (B): top view of enol form of MAHT **15**

These two independently optimized structures had identical energies as well as almost identical bond lengths and angles. The structure at –648.67222 Ha corresponds to the transition between these conformers. As expected, the energy barrier for interconversion was very low *i.e.* 0.000215 Ha; <1 kJ mol^{-1}.[37] Applying the same computational procedure to the analogous MAHT (**15**) identified (Table S4, SI) a true minimum at –971.63728 Ha [B3LYP/6-31G(d) data] as the most stable form. In contrast to the data in Table S5 (SI), the *cisoid* form was observed, and although a minimum, it had a dihedral angle of –91.67° between PhS and -SC(OH)$CHCO_2H$ (Figure 4). An *E-transoid* MAHT conformation was identified (at –971.63648 Ha) and established to be a transition structure with –91.93° between the PhS and -SC(OH)=$CHCO_2H$. A true *E-transoid*

10.1002/chem.201605148

minimum was found at an almost identical energy with the PhS tilted at –103.3°. As expected, the central bond angle for the MAHTs (~ 103°, see Figure 4) was smaller than the MAHOs (~ 121°, see Figures 2 and 3) and the Ph-S and Ph-O bond lengths (1.80 Å and 1.40 Å respectively) were longer than the PhS-C and PhO-C bond lengths into the enol (1.78 Å and 1.34 Å). The preference for *cisoid* or *transoid* forms (for examples, see Figures 2 - 4) in these structures is finely balanced. The calculations were repeated with the highly recommended[38] M06-2X functional[39] using the 6-31+G(d,p) basis set[40] which has been identified[41] as one affording a good balance between performance and computing time for structures with non-covalent or H-bonding interactions. The *cisoid* conformation was the most stable in both MAHO and MAHT series.

In summary, with such finely balanced conformational preferences identified using B3LYP and MO6-2X and the small energy differences between both the *cisoid* and *transoid* series we have established both need to be considered when studying substituent effects on the aromatic ring and interpreting [2H]-incorporation results. In practice, the two conformers easily interconvert and both will be present in solution. It was decided to concentrate initially on the characterization of the more stable *E*-enols. The "*E-cisoid-e-z-z*" and "*E-transoid-e-z-z*" MAHO and MAHT structures (see the Tables S3 and S4 in SI) were now used as the basis to perform calculations on 4-methoxy, 4-chloro and 4-bromo aryl substituted MAHOs and MAHTs. In both the MAHO and MAHT series, *cisoid* and *transoid* minimum energy conformations were identified for the *E*-enols. Consistently in these structures (Table 7), in which hydrogen-bonding between the enol OH and the C=O of the carboxylic acid was apparent (illustrated in Figures 2 - 4 for the parent phenyl examples), the hydrogen bonding O···H separation was 1.63 - 1.66 Å. The O-H bond of the enol was lengthened to 1.01 - 1.02 Å compared to the carboxylic acid O-H at 0.98 Å and in all cases, the enol and carboxylic acid sections of the structure were essentially coplanar (dihedral angles +0.6 - –0.6°), and the C-C bond lengths within the C=CHCO_2H section shorter for C=CH than for CH-CO_2H (1.37 - 1.38 Å and 1.43 - 1.44 Å, respectively) but none-the-less these are both *significantly* shorter than a typical C-C bond, as expected because of the extended conjugation. The molecular orbitals of the gas phase optimised structures were examined from the LUMO down to the lowest π-orbital of the MAHO(T). Figures 5 - 10 illustrate well the flat delocalised π-systems associated with their structures. In general, the patterns of the orbitals were similar for all the MAHOs and MAHTs examined. The π-donation from the oxygen or sulfur atoms of the PhO / PhS groups[42] into the enol is clearly visible in the slightly higher energy *E-cisoid* HOMO-11[43] (ester, Figure 7) and *E-cisoid* HOMO-12 (thioester, Figure 8) molecular orbitals. Similarly, *E-transoid* HOMO-8 and *E-transoid* HOMO-10 show the delocalisation between the heteroatom link and the arene (Figure 9), especially in the thioester case. In Figures 5B, 7B and 9B, the tilted geometry of the MAHO distorts these orbitals.

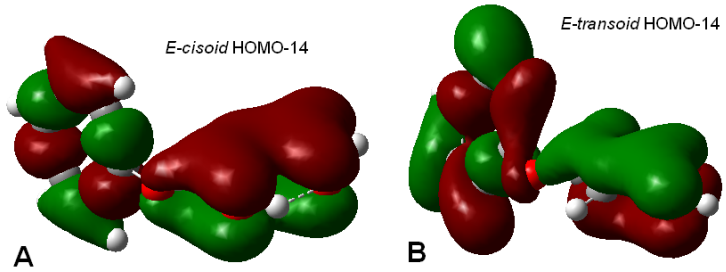
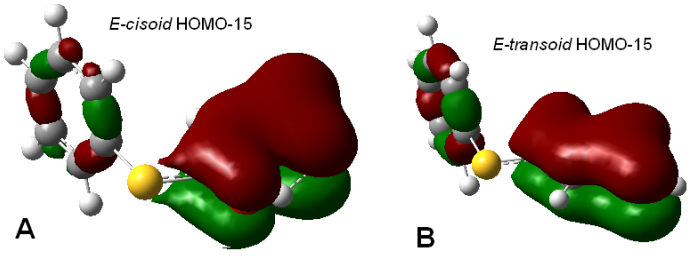


Figure 5. Low lying *E-cisoid* and *E-transoid* MOs in the ester structures with π-overlap across the enol and carboxylic acid (A: structure *cisoid*-**23**; B: structure *transoid*-**23**



10.1002/chem.201605148

Figure 6. Low lying *E-cisoid* and *E-transoid* MOs in the thioester structures with π-overlap across the enol and carboxylic acid (A: structure *cisoid*-**15**; B: structure *transoid*-**15**)

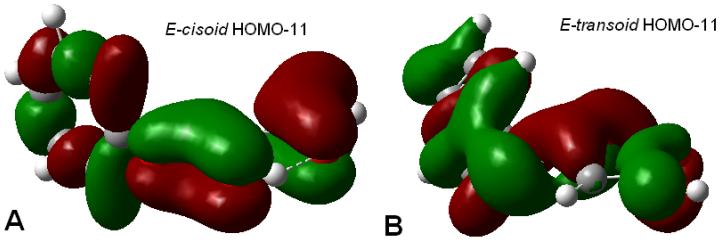


Figure 7. Typical examples of π-delocalisation in the parent MAHO **23** with π-overlap across the enol and carboxylic acid (A: structure *cisoid*-**23**; B: structure *transoid*-**23**)

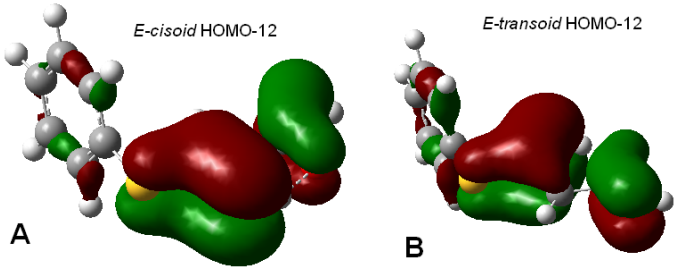


Figure 8. Typical examples of π-delocalisation in the parent MAHT **15** with π-overlap across the enol and carboxylic acid (A: structure *cisoid*-**15**; B: structure *transoid*-**15**).

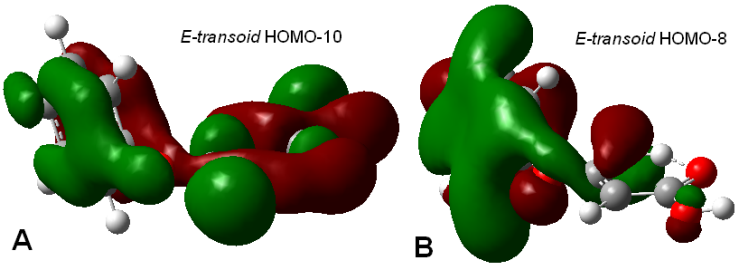


Figure 9. Orbitals illustrating π-overlap between the heteroatom and the arene (A: structure *cisoid*-**15**; B: structure *transoid*-**15**)

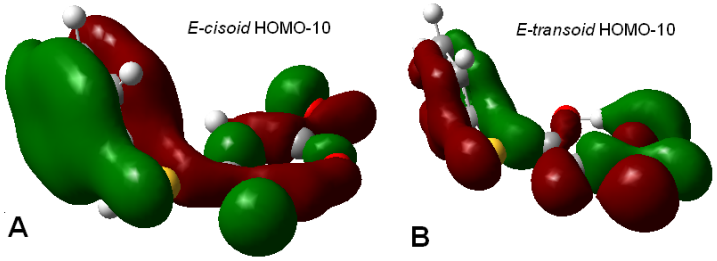


Figure 10. Orbitals illustrating π-overlap between the heteroatom and the arene (A: structure *cisoid*-**15**; B: structure *transoid*-**15**)

10.1002/chem.201605148

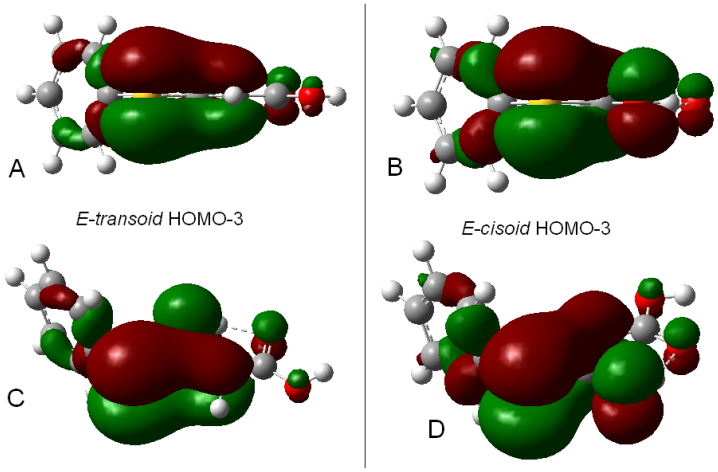


Figure 11. Orbitals illustrating p-overall between the heteroatom and the arene (A: structure *cisoid*-**15**; B: structure *transoid*-**15**)

These archetypal π-symmetry orbitals are observed across the whole series of MAHO and MAHT structures (see SI) with only minor variations in the sequence of relative energies. A significant difference between MAHOs and MAHTs, however, was identified from the presence of an *additional* frontier orbital (HOMO-3) in the thioesters (see Table 8, and Figure 11) which is delocalized between sulfur atom and the enol. In other aspects, the geometries and molecular orbitals of the MAHOs and MAHTs are very similar and consistently showing the same key features.[44] The significant HOMO-3 MAHT orbital, however, which was consistently present in all MAHT conformers examined in our study was not present in the MAHOs and provides for increased π-overlap in the MAHT series. This may account for the much easier enolisation and much faster deuterium incorporation observed in the NMR experiments for the parent phenol and thiophenol MAHO and MAHT structures.

Conclusions

In summary, we detail the synthesis of 39, mostly unknown, structure- and function-diverse MAHOs and MAHTs. All are easily prepared using a quick and efficient protocol. Whilst the yields in most cases are good, the inclusion of a strong EWG *i.e*. nitro or ester at the *ortho*-position on the aryl ring of the phenol or thiophenol starting materials affords the products, but with reduced yields. This is attributed to the formation of a strong *intramolecular* hydrogen-bond (*cf*. RAHB) between the hydroxyl or thiol group and the *ortho*-EWG. Overall, the formation of a resonance-assisted hydrogen bond and the inductive effect reduces nucleophilicity and reactivity towards the malonyl mono-chloride. Whilst probing the reactivity of the MAHO and MAHTs, as measured by hydrogen → deuterium exchange, we identified an unexpectedly rapid enolisation in the MAHT series. We ascribed the increased reactivity to the presence of an additional sulfur-centred frontier orbital which increases π-delocalisation between the heteroatom and the enol. The exceptional ease of enolisation in the MAHT series suggests these nucleophiles should offer new prospects for the efficient C-C bond formation under mild conditions. Ultimately, our work will help develop a better understanding of how Nature employs MAHTs for metabolite biosynthesis and with the two slightly different protocols now well established, we have the capability to synthesize either electron-rich, or electron-poor or sterically hindered aryl derived MAHOs or MAHTs.

Acknowledgements

The authors acknowledge the EPSRC, UEA, and INTERREG IVA (IS:CE chem project 4061) for financial support, the UEA high-performance cluster "Grace" for computational resources, and the EPSRC Mass Spectrometry Service for generating HRMS data.

Keywords: thioester • isotope exchange • DFT • reaction rate • hydrogen bond • π-delocalisation

[1] a) G. Zhou, D. Lim, D. M. Coltart, *Org. Lett*. **2008**, *10*, 3809 – 3812; b) A. I. Scott, C. J. Wiesner, S. Yoo, S. K. Chung, *J. Am. Chem. Soc.* **1975**, *97*, 6277 - 6278; c) Y. Kobuke, J.-I Yoshida, *Tetrahedron Lett*. **1978**, *19*, 367 - 370; d) M. W. Rathke, P. J. Cowan, *J. Org. Chem.* **1985**, *50*, 2622 - 2624; e) A. L. Gutman, A. Boltanski, *Tetrahedron Lett.* **1985**, *26*, 1573 - 1576; f) R. J. Clay, T. A. Collom, G. L. Karrick, J. Wemple, *Synthesis* **1993**, 290 - 292; g) X. Wang, W. T. Monte, J. J. Napier, A. Ghannam, *Tetrahedron Lett*. **1994**, *35*, 9323 - 9326; h) Y. Ryu, A. I. Scott, *Tetrahedron Lett.* **2003**, *44*, 7499 - 7502; i) N. Sakai, N. Sorde, S. Matile, *Molecules*, **2001**, *6*, 845-851.

[2] a) K. C. Fortner, M. D. Shair, *J. Am. Chem. Soc*. **2005**, *127*, 7284 – 7285; b) D. J. Schipper, S. Rousseaux, K. Fagnou, *Angew. Chem. Int. Ed*. **2009**, *48*, 8243 – 8246; c) S. Orlandi, M. Benaglia, F. Cozzi, *Tetrahedron Lett.* **2004**, *45*, 1747 - 1749; d) G. Lalic, A. D. Aloise, M. D. Shair, *J. Am. Chem. Soc*. **2003**, *125*, 2852 - 2853; e) N. Blaquiere, D. G. Shore, S. Rousseaux, K. Fagnou, *J. Org. Chem*. **2009**, *74*, 6190 – 6198; f) J. Baudoux, P. Lefevre, M.-C. Lasne, J. Rouden, *Green Chem.* **2010**, *12*, 252 - 259; g) K. Rohr, R. Mahrwald, *Org. Lett.* **2011**, *13*, 1878 - 1880; h) X.-J. Li, H.-Y. Xiong, M.-Q. Hua, J. Nie, Y. Zheng, J.-A. Ma, *Tetrahedron Lett.* **2012**, *53*, 2117 - 2120.

[3] a) L. Yin, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc*. **2009**, *131*, 9610 – 9611; b) Y. Umezawa, H. Morishima, S.-I. Saito, T. Takita, H. Umezawa, S. Kobayashi, M. Otsuka, M. Narita, M. Ohno, *J. Am. Chem. Soc.* **1980**, *102*, 6631 - 6633; c) M. Otsuka, M. Narita, M. Yoshida, S. Kobayashi, M. Ohno, Y. Umezawa, H. Morishila, S. Saito, T. Takita, H. Umezawa, *Chem. Pharm. Bull.* **1985**, *33*, 520 - 526; d) A. Ricci, D. Pettersen, L. Bernardi, F. Fini, M.-F. Fochi, R. Perez Herrera, V. Sgarzania, *Adv. Synth. Catal.* **2007**, *349*, 1037 - 1040; e) Y. Pan, C. Kee, Z. Jiang, T. Ma, Y. Zhao, Y. Yang, H. Xue, C.-H Tan, *Chem. Eur. J.* **2011**, *17*, 8363 - 8370; f) L. Yin, M. Kanai, M. Shibasaki, M. *Tetrahedron* **2012**, *68*, 3497 - 3506.

[4] a) J. Lubkoll, H. Wennemers, *Angew Chem. Int. Ed*. **2007**, *46*, 6841 – 6844; b) J. E. McMurry, W. A. Andrus, J. H. Musser, *Synth. Commun.* **1978**, *8*, 53 - 57; c) M. Banwell, D. Hockless, B. Jarrott, B. Kelly, A. Knill, R. Longmore, G. Simpson, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3555 - 3558; d) M. Makoto Furutachi, S. Mouri, S. Matsunaga, M. Shibasaki, *Chem. Asian J*. **2010**, *5*, 2351 - 2354; e) H. Y. Bae, S. Some, J. H. Lee, K.-Y. Kim, M. J. Song, S. Lee, Y. J. Zhang, C. E. Song, *Adv. Synth. Catal.* **2011**, *353*, 3196 - 3202.

[5] N. Blaquiere, D. G. Shore, S. Rousseaux, K. Fagnou, *J. Org. Chem*. **2009**, *74*, 6190 – 6198

[6] a) K. I. Arnstadt, G. Schindlbeck, F. Lynen, *Eur. J. Biochem*. **1975**, *55*, 561 – 571; b) M. J. S. Dewar, K. M. Dieter, *Biochemistry* **1988**, *27*, 3302 - 3308.

[7] K. C. Fortner, M. D. Shair, *J. Am. Chem. Soc*. **2007**, 129, 1032 - 1033

[8] a) C. Khosla, *Chem. Rev.* **1997**, *97*, 2577 – 2590; b) E. S. Sattely, M. A. Fischbach, C. T. Walsh, *Nat. Prod. Rep.* **2008**, *25*, 757 – 793; c) L. Van, G. Steven, B. Shen, *Current Opinion in Drug Discovery & Development* **2008**, *11*, 186 – 195; d) R. J. Cox, *Org. Biomol. Chem.* **2007**, *5*, 2010 – 2026; e) M. A. Fischbach, C. T. Walsh, *Chem. Rev*. **2006**, *106*, 3468 – 3496; f) K. J. Weissman, P. F. Leadlay, *Nature Reviews Microbiology* **2005**, *3*, 925 – 936; g) D. E. Cane, C. T. Walsh, C. Khosla, *Science* **1998**, *282*, 63 - 68.

[9] a) E. M. Musiol, T. Weber, *MedChemComm* **2012**, *3*, 871 – 886; b) F. Ishikawa, R. W. Haushalter, M. D. Burkart, *J. Am. Chem. Soc*. **2012**, *134*, 769 – 772; c) H. Morita, M. Yamashita, S.-P. Shi, T. Wakimoto, S. Kondo, R. Kato, S. Sugio, T. Kohno, I. Abe, *PNAS* **2011**, *108*, 13504 -13509; d) J. J. Gehret, L. Gu, W. H. Gerwick, P. Wipf, D. H. Sherman, J. L. Smith, *J. Bio. Chem*. **2011**, *286*, 14445 – 14454; e) D. H. Kwan, P. F. Leadlay, *ACS Chem. Biol.* **2010**, *5*, 829 - 838.

[10] A) Z.-L. Wang, *Adv. Synth. Catal.* **2013**, *355*, 2745 – 2755; b) S. Nakamura, *Org. Biomol. Chem*. **2014**, *12*, 394- 405; c) Y. Pan, C.-H. Tan, *Synthesis*, **2011**, 2044 – 2053; d) H. Y. Bae, J. H. Sim, J.-W. Lee, B. List, C. E. Song, *Angew Chem. Int. Ed*. **2013**, *52*, 12143 – 12147; e) H.-N. Yuan, S. Wang, J. Nie, Q. Yao, J.-A. Ma, *Angew Chem. Int. Ed*. **2013**, *52*, 3869 – 3873; f) N. Hara, S. Nakamura, M. Sano, R. Tamura, Y. Funahashi, N. Shibata, *Chem. Eur. J*. **2012**, *18*, 9276 – 9280; g) S. Nakamura, M. Sano, A. Toda, D. Nakane, H. Masuda, *Chem. Eur. J*. **2015**, *21*, 3929 – 3932; h) H. Y. Bae, *Synlett*, **2015**, *26*, 705 – 706; i) H. Y. Bae, C. E. Song, *Bull. Korean. Chem Soc*., **2014**, *35*, 1590 – 1600; j) L. Bernardi, A. Ricci, M. C. Franchini, *Curr. Org. Chem*., **2011**, *15*, 2210 – 2226; k) Y. Cotelle, V. Lebrun, N. Sakai, T. R. Ward, S. Matile, *ACS Central Science*, **2016**, *2*, 388 – 393; l) J. Saadi, H. Wennemers, *Nat. Chem*. **2016**, *8*, 276 – 280; m) Q. Ren, T. Gao, W. Li, H. Wan, P. Yimin, S. Yanhong, S. Sun, L. Hu, M. Wu, H. Guo, *New J. Chem*., **2015**, *39*, 5100 – 5103.

[11] N. Utsumi, S. Kitagaki, C. F. Barbas, III, *Org. Lett*. **2008**, *10*, 3405 - 3408.

[12] Y. Pan, C. W. Kee, Z. Jiang, T. Ma, Y. Zhao, Y. Yang, H. Xue, C.-H. Tan, *Chem. Eur. J*. **2011**, *17*, 8363 - 8370.

[13] H. Y. Bae, S. Some, J. H. Lee, J.-Y. Kim, M. J. Song, M. J. Lee, Z. Sungyul, C. E. Song, *Adv. Synth. Catal.* **2011**, *353*, 3196 - 3202.

[14] S. Nakamura, M. Sano, A. Toda, D. Nakane, H. Masuda, *Chem. Eur. J.* **2015**, *21*, 3929-3932.

[15] A. Ricci, D. Pettersen, L. Bernardi, F. Fini, M. Fochi, R. P. Herra, V. Sgarzani, *Adv. Syn. Cat*. **2007**, *349*, 1037 – 1040.

[16] A. S. Ivanov, *Chem. Soc. Rev*. **2008**, *37*, 789 - 811.

[17] Eds.: W. L. F. Armarego and D. D. Perrin, *Purification of Laboratory Chemicals* 6th Edition, Butterworth-Heinemann, Oxford, **2009**.

[18] S.-J. Park, J.-C. Lee, K. I. Lee, *Bull. Korean Chem. Soc*. **2007**, *28*, 1203 - 1205.

[19] T. Mase, H. Arima, K. Tomioka, T. Yamada, K. Murase, *Eur. J. Med. Chem*. **1988**, *23*, 335 – 339.

[20] T. Imamoto, M. Kodera, M. Yokoyama, *Bull. Chem. Soc. Jpn*. **1982**, *55*, 2303-2304.

[21] a) S. P. Bew, G. R. Stephenson, J. Rouden, L. A. Martinez-Lozano, H. Seylani, *Org. Lett.* **2013**, *15*, 3805-3807; b) F. N. Miros, Y. Zhao, G. Sargsyan, M. Pupier, C. Besnard, C. Beuchat, J. Mareda, N. Sakai, S. Matile, *Chem. Eur. J.* **2016**, *22*, 2648 - 2657

[22] Monomalonyl chloride is commercially available from Akos (http://www.akosgmbh.eu/), Aurora Fine Chemicals (http://www.aurorafinechemicals.com/) and FCH Group (http://www.fchgroup.net).

[23] a) M. S. Singh, S. Chowdhury, *RSC Advances* **2012**, *2*, 4547 – 4592; b) J. G. Hernandez, E. Juaristi, *Chem. Comm.* **2012**, *48*, 5396 – 5409; c) H. M. Marvaniya, K. N. Modi, D. J. Sen, *Int. J. Drug Dev. & Res.* **2011**, *3*, 34 – 43; d) V. P. Shevchenko, I. Y. Nagaev, N. F. Myasoedov, *J. Labelled Comp. and Radiopharmaceuticals* **2010**, *53*, 693 – 703; e) W. C. Shearouse, D. C. Waddell, J. Mack, *Current Opinion in Drug Discovery & Development* **2009**, *12*, 772 – 783; f) M. A. P. Martins, C. P. Frizzo, D. N. Moreira, L. Buriol, P. Machado, *Chem. Rev.* **2009**, *109*, 4140 - 4182.

[24] A. Heintz, S. Kaptenia, S. P. Verekin, *J. Phys. Chem. A.* **2007**, *111*, 6552 - 6562

[25] K. B. Borisenko, C. W. Bock, I. Hargittai, *J. Phys. Chem.,* **1994**, *98*, 1442 – 1448.

[26] F. Iwasaki, Y Kawano, *Acta. Cryst. B* **1978**, *38*, 1286 -1288.

[27] J. Zheng, K. Kwak, X. Chen, J. B. Asbury, Ma. D. Fayer, *J. Am. Chem. Soc*. **2006**, *128*, 2977 – 2987.

[28] a) B. Rigo, D. Fasseur, P. Cauliez, D. Couturier, *Tetrahedron Lett*, **1989**, *30*, 3073 – 3076; b) X.-J. Li, H.-Y. Xiong, M.-Q. Hua, J. Nie, Y. Zheng, J.-A. Ma, *Tetrahedron Lett.* **2012**, *53*, 2117 - 2120.

[29] M. H. Abraham, R. J. Abraham, A. E. Aliev, C. F. Tormena, *Physical Chemistry Chemical Physics* **2015**, *17*, 25151-25159.

[30] H. Heydari, H Raissi, F. Mollania, *Struct. Chem*. **2015**, *26*, 971 – 987.

[31] T. Kobayashi, A. Yamashita, Y. Furuya, R. Horie, M. Hirota *Bull. Chem. Soc. Jpn*. **1972**, *45*, 1493-1498.

[32] a) G. Hilt, F. Pünner, J. Möbus, V. Naseri, M. A. Bohn, *Eur. J. Org. Chem.* **2011**, *30*, 5962 - 5966; b) D. Sheppard, D.-W. Li, R. Brüschweiler, V. Tugarinov, *J. Am. Chem. Soc.* **2009**, *131*, 15853 - 15865; c) N. F. Breen, T. Weidner, K. Li, D. G. Castner, G. P. Drobny, *J. Am. Chem. Soc.* **2009**, *131*, 14148 - 14148; d) Y. Liu, R. Warmuth, *Org. Lett.* **2007**, *9*, 2883 - 2886; e) B. Reif, Y. Xue, V. Agarwal, M. S. Pavlova, M. Hologne, A. Diehl, Y. E. Ryabov, N. R. Skrynnikov, *J. Am. Chem. Soc.* **2006**, *128*, 12354 - 12355; f) Y.-L. Zhao K. N. Houk, R. Dalit, A. Scarso, J. Rebek, Jr., *J. Am. Chem. Soc.* **2004**, *126*, 11428 - 11429; g) S. Bolvig, E. P. Hansen, *Mag. Res. Chem.* **1996**, *34,* 467-478; h) K. L. Servis, R. L. Domenick, *J. Am. Chem. Soc.* **1985**, *107*, 7186 - 7189; i) D. Bal, A. Kraska-Dziadecka, A. Gryff-Keller, *J. Org. Chem.* **2009**, *74,* 8604 - 8608; j) P. E. Hansen, *J. Labelled Compds. Radiopharm.,* **2007**, *50,* 967-981; k) R. M. Claramunt, C. Lopez, M. D. Santa Maria, D. Sanz, J. Elguero, *Prog Nuc. Mag. Res. Spect.* **2006**, *49*, 169 - 206; l) S. Bolvig, F. Duus, E. P. Hansen, Erik, *Mag. Res. Chem*. **1998**, *36*, 315 - 384.

[33] a) H. R. Lu, M.-G. Gu, Q. Huang, J. J. Huang, W.-Y. Lu, H. Lu, Q.-S. Huang, *Antimicrobial Agents and Chemotherapy*, **2013**, *57,* 1872 - 1881; b) S. Mehmood, C. Domene, E. Forest, J.-M. Jault, *PNAS*, **2012**, *109*, 10832 -

10.1002/chem.201605148

10836; c) K.-Y. Chung, S. G. F. Rasmussen, T. Liu, S. Li, B. T. DeVree, P.-S Chae, D. Calinski, B. K. Kobilka, V. L. Woods Jr.; R. K. Sunahara, *Nature*, **2011**, *477*, 611 - 615; d) F. Ito, S. Ando, M. Luchi, T. Ukari, M. Takasaki, K. Yamaguchi, *Tetrahedron*, **2011**, *67*, 8009 - 8013; e) D. Houde, S. A. Berkowitz, *Pharmaceutical Technology*, **2010**, *s12*, s14; f) E. V. Kudrik, A. B. Sorokin, *Chem. Eur. J,* **2008**, *14*, 7123-7126; g) M. Chen, K. D. Cook, I. Kheterpal, R. Wetzel, *J. Am. Soc. Mass Spec.* **2007**, *18*, 208 - 217; h) S. Y. Dai, M. C. Fitzgerald, *Biochemistry*, **2006**, *45*, 12890 - 12897; i) T. J. D. Jorgensen, H. Grdsvoll, M. Ploug, P. Roepstorff, *J. Am. Chem. Soc*. **2005**, *127*, 2785 - 2793; j) V. L. Woods, Jr.; Y. Hamuro, *J. Cell Biochem*., **2001**, *37*, 89-98; k) I. D. Figueroa, D. H. Russell, *J. Am. Soc. Mass Spect*., **1999**, *10*, 719.

[34] S. Taoka, R. Padmakumar, C. B. Grissom, R. Banerjee, *Bioelectromagnetics* **1997**, *18*, 506 - 513.

[35] a) Each was optimized using Gausian09 [35b] with the B3LYP functional[35c] and the 6-31G(d) basis set [35d] in gas phase calculations. The choice of functional and basis set for the first stage of our work has been firmly established *i.e*. benchmarked in our preliminary calculations[21] with the parent thiophenyl-derived MAHT (**15**) in which very similar results were obtained with both B3LYP and MO6-2X functionals and the 6-31G(d), 6-31+G(d,p) and def-QZVP basis sets; b) Gaussian 09, Revision – M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09, revision A.1*; Gaussian, Inc.: Wallingford, CT, 2009; c) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648−5652; d) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785−789; e) R. Ditchfield, W. J. Hehre, J. A. Pople, *J. Chem. Phys*. **1971**, *54*, 724 - 726; f) The MO6-2X/def-QZVP level of theory has been validated by Fogueri *et al*. in a full benchmarked study incorporating 52 melatonin conformers see U. M. Fogueri, S. Kozuch, A. Karton, J. M. L. Martin, *J. Phys. Chem. A* **2013**, *117*, 2269 - 2277. A computational study on dimethyl monothiocarbonate by Vedova *et al*. invoked an anomeric and mesomeric effects and natural bond order to explain the conformational preferences, see M. F. Erben, R. Boese, C. O. D. Vedova, H. Oberhammer, H. Willner *J. Org. Chem*. **2006**, *71*, 616-622.

[36] Of relevance to our computational work on MAHOs and MAHTs was a successful study on *cis-trans* amide bond rotamers in peptoids this included examples with thioamide bonds see J. S. Laursen, J. Engel-Andreasen, P. Fristrup, P. Harris, C. A. Olsen, *J. Am. Chem. Soc.* **2013**, *135*, 2835−2844.

[37] Very similar results for the MAHO series were obtained from calculations using MO6-2X/6-31+G(d,p) with energies ranging from –648.33202 to –648.31256 Ha [*cf*. –648.67243 to –648.64890 Ha, B3LYP/6-31G(d) data].

[38] E. G. Hohenstein, S. T. Chill, C. D. Sherrill, *J. Chem. Theory Comput.* **2008**, *4*, 1996–2000.

[39] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215–241.

[40] I. D. Mackie, G. A. DiLabio, *J. Phys. Chem. A* **2008**, *112*, 10968–10976.

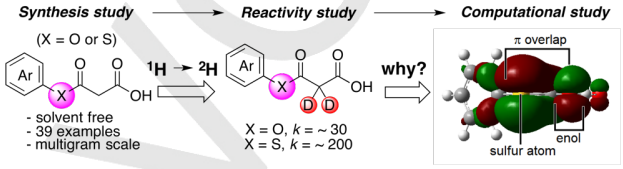
[41] S. O. Nilsson Lill, *J. Phys. Chem. A* **2009**, *113*, 10321–10326.

[42] a) S. Nagata, T. Yamabe, K. Fukui *J. Phys. Chem.* **1975**, *79*, 2335–2340; b) M. Geronés, A. J. Downs, M. F. Erben, M. Ge, R. M. Romano, L. Yao, C. O. D. Védova, *J. Phys. Chem. A* **2008**, *112*, 5947 – 5953; c) A. Rai-Chaudhuri, W. Shong Chin, D. Kaur, C. Y. Mok, Hsing H. Huang *J. Chem. Soc., Perkin Trans. 2*, **1993**, 1249-1250; d) N. Y. Dugarte, M. F. Erben, R. M. Romano, M.-F. Ge, Y. Li and C. O. D. Védova *J. Phys. Chem. A*, **2010**, *114*, 9462–9470.

[43] The notation HOMO–n indicates the sequence of molecular orbitals in descending order of energy, starting from the HOMO, then HOMO–1, HOMO–2, *etc*.

[44] For example see a) Figure 5 (MAHO) and Figure 6 (MAHT) with π-overlap across the S-enol-CO_2H section of the structure; b) Figure 7 (MAHO) and Figure 8 (MAHT) π-overlap with one additional vertical node; c) Figure 5 (MAHO) and Figure 6 (MAHT) additional delocalisation of electron density through the heteroatom.

[45] G. E. Wilson Jr., A. Hess, *J. Org. Chem.* **1974**, *39*, 3170 - 3170.



MAHTS are the best. Three comprehensive studies on the synthesis, reactivity ([2H]-exchange) and conformational properties of aryl (thio)ester-derived MAHOs and MAHTs are reported. Using 'off the shelf' starting materials and a solvent-free protocol 39 structure and function diverse MAHOs and MAHTs are readily generated. These are the fastest, easiest and most environmentally friendly routes to MAHO(T)s. The synthetically valuable ease of enolisation of the MAHTs is accounted for by the computationally established presence of an additional frontier orbital unique to the MAHT series which provides enhanced π-delocalisation between the sulfur and the enol.