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SYNTHESIS OF ANALOGUES OF MONIC ACIDS A AND C: POTENTIAL HERBICIDES AND INHIBITORS OF ISOLEUCYL tRNA SYNTHETASE

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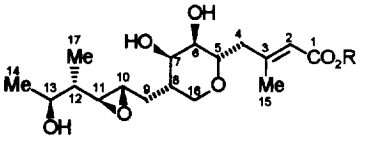
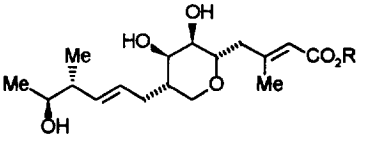
Abstract. The *m*-substituted benzene compounds **16-21** and biphenyl derivatives **25-27** have been synthesised as simplified analogues of monic acids A **3** and C **4**. In addition the disubstituted 1,3-dioxanes **41-43** have been prepared and all compounds tested as herbicides and for their ability to inhibit spinach chloroplast isoleucyl tRNA synthetase.

Pseudomonic acids A **1** and C **2** are antimicrobial substances produced by *Pseudomonas fluorescens* which interfere with bacterial protein biosynthesis by competitively inhibiting isoleucyl tRNA synthetase (ITRS).[2] It has further been suggested that **1** acts as a bifunctional inhibitor with the *C*-8 and *C*-5 side chain interacting with an isoleucine and ATP binding site, respectively.[3] The corresponding hydrolysis products of **1** and **2** are monic acids A **3**[4] and C **4**[5], respectively, and we have recently reported that ester and amide derivatives of **3** and **4** are herbicidal.[6]



1 R = $(CH_2)_8CO_2H$
3 R = H



2 R = $(CH_2)_8CO_2H$
4 R = H
5 R = Et

In order to prepare simplified derivatives that could potentially be used as agrochemicals we looked first at replacing the pyran ring in monic acid with a simple benzene ring spacer group. Using the SYBYL software package,[7] Figure 1 shows that an orthogonally oriented *m*-substituted benzene ring (thin line, partial structure only) overlays with the structure of ethyl monate C **5** (thick line) taken from the Cambridge Crystallographic Database.[5]

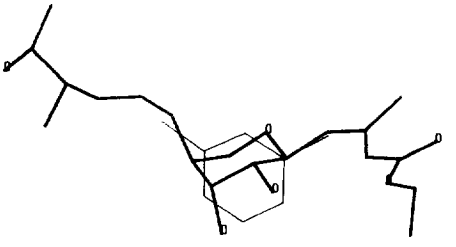
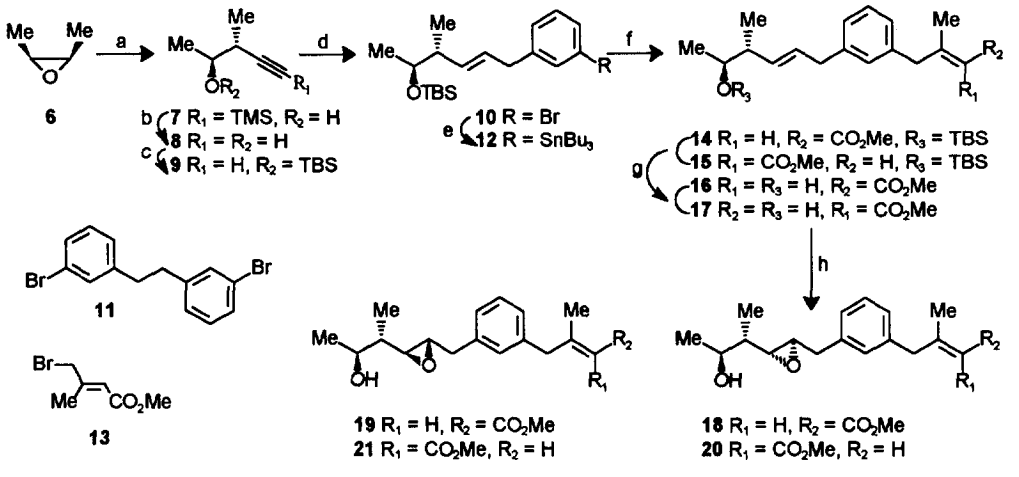


Figure 1

Whilst there have been several syntheses of the pseudomonic acid family[8] we chose the chemistry described below as being the most appropriate for our modified structures. Commercially available *meso*-epoxide **6**[9,10] was reacted with lithium (trimethylsilyl)acetylide in the presence of $BF_3{\cdot}Et_2O$[11] to give racemic **7** which was desilylated with NaOMe/MeOH to afford acetylenic alcohol **8** in 44% overall yield (Scheme 1). Compound **8** was identical (^1H NMR, GC) to a sample prepared from reaction of **6** with lithium acetylide ethylenediamine complex,[12] but we found the two step process(**6**→**7**→**8**) more convenient. Protection of the alcohol group in **8** as its TBS ether gave **9** (69%), which was hydroborated with dicyclohexylborane[13] and the intermediate vinyl borane reacted with 3-bromobenzyl bromide in the presence of $Pd(PPh_3)_4$ under Suzuki's conditions[14] to give the bromo-olefin **10** in 49% yield. A small amount of the homocoupled product **11** was also formed. Addition of **10** to a cold (-78°C) solution of Bu_3SnLi[15] afforded **12** in 32% yield inseparable from the by-products[16] Bu_4Sn, $Bu_3SnSnBu_3$ and Bu_3SnH as estimated by comparison to standard GC samples. Crude **12** underwent a Stille coupling[17] with the (E)-bromoacrylate **13**[18] in the presence of $(CH_3CN)_2PdCl_2$ to afford a 1:1 mixture of (E)- and (Z)-acrylates **14** and **15** in 91% yield (based on the GC estimate of **12**) which were separated by HPLC (Sorbsil C30 5μ SiO_2) and desilylated with an AcOH/H_2O/THF mixture (TBAF gave complex products) to give products **16** (96%) (δ_H5.69, dt, 1H; δ_H5.42, dd, 1H, J_{trans}CH=CH = 15.5Hz; δ_H2.13, s, 3H, acrylate C-CH_3) and **17** (85%) (δ_H5.70, dt, 1H; δ_H5.40, dd, 1H, J_{trans} CH=CH = 15.7Hz; δ_H1.79, s, 3H, acrylate C-CH_3). Treatment of **16** with *m*-chloroperoxybenzoic acid (MCPBA) gave two separable (HPLC) diastereomeric epoxides arbitrarily assigned **18** (34%) and **19** (33%).[19,21] Similarly, epoxidation of **17** with MCPBA afforded two separable products **20** (33%) and **21** (43%), again arbitrarily assigned.[20,21]

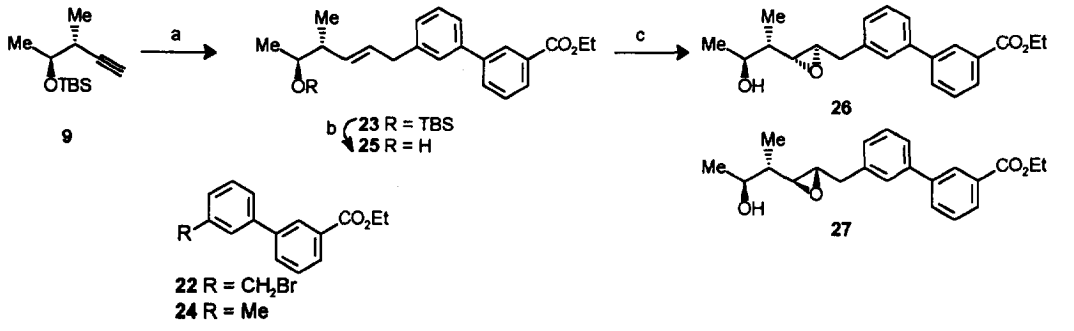
Scheme 1



a) TMS acetylene (1.5eq), *n*BuLi (1.5eq), $BF_3{\cdot}Et_2O$ (1.6eq), THF, -78°C, 30 mins.; b) NaOMe/MeOH, RT, 2 hrs. then Amberlite IRC 50 (H^+) resin; c) TBSOTf (1eq), 2,6-lutidine (1.3eq), CH_2Cl_2, 0°C→RT, 3 hrs.; d) dicyclohexylborane (1.2eq), Et_2O, 0°C, 45 mins then evaporate, add toluene, 3-bromobenzyl bromide (1eq), $Pd(Ph_3P)_4$ (3 mol %), 2M NaOH (2eq), 80°C, 2 hrs→RT then 30% H_2O_2, 3M NaOH (0.75eq), 1hr.; e) $Bu_3SnSnBu_3$ (1.1eq), *n*BuLi (1eq), THF, -78°C, 15 mins.; f) **13**, (1.5eq), $(CH_3CN)_2PdCl_2$ (3 mol %), THF, 50°C, 3 hrs., then add more **13** (0.5eq), 4 hrs., then more **13** (0.5 eq), 2 days; g) AcOH/THF/H_2O (3:2:1), RT, 3 days. h) MCPBA (1eq), CH_2Cl_2, RT, 16hrs.

Replacement of both the pyran ring and acrylate group with a biphenyl ring was also achieved using similar chemistry. Thus, the vinyl borane produced from **9** as described above underwent a Suzuki coupling with the bromomethyl-biphenyl ester **22**[22] to afford the olefin **23** in 45% yield (Scheme 2). A small amount of the toluene **24** was also produced during the reaction. Desilylation with TBAF in THF was quite sluggish affording alcohol **25** in 64% yield which was further converted with MCPBA into the separable (HPLC) and arbitrarily assigned epoxides **26**(or **27**) (46%) (δ_H3.19, dt, 1H, J = 5.9, 2.4Hz; δ_H3.03, dd, 1H, J = 14.3, 5.9Hz; δ_H2.91, m, 2H; δ_H1.18, d, 3H, J = 6.2Hz; δ_H1.00, d, 3H, J = 7.1Hz) (δ_C58.4)[21]and **27**(or **26**) (38%) (δ_H3.01, m, 2H, δ_H2.89, m, 2H; δ_H1.22, d, 3H, J = 6.2Hz; δ_H0.92, d, 3H, J = 7.1Hz) (δ_C57.2)[21](4% of the alternative diastereomer is also present).

Scheme 2



a) Dicyclohexylborane (1.2eq), Et_2O, 0°C, 45 min, then evaporate and add toluene, **22**, $Pd(PPh_3)_4$ (3 mol %), 2M NaOH (2eq), 80°C, 2 hrs then 3M NaOH (0.75eq), 30% H_2O_2, RT, 1hr.; b) TBAF (1eq), THF, RT, 16 hrs., then more TBAF (0.5eq), 16hrs., then more TBAF (0.5eq), 28 hrs.; c) MCPBA, CH_2Cl_2, RT, 16 hrs.

A simpler replacement for the pyran ring of monic acid was also sought which still retained the ability to accept H-bonds. Using the SYBYL software, Figure 2 shows that a *cis*-2,5-disubstituted-1,3-dioxane structure (thin line) (**43**), overlays well with ethyl monate C **5** (thick line).

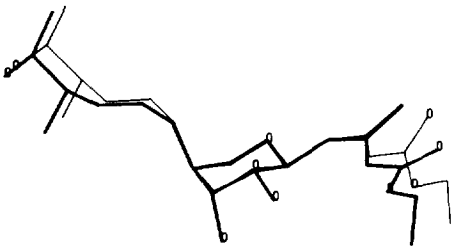
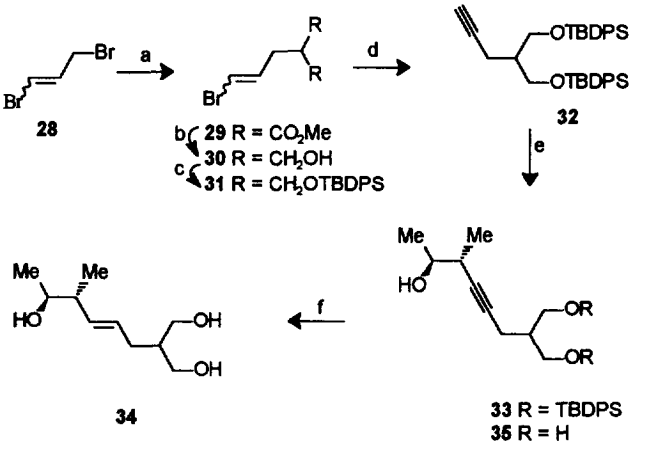


Figure 2

Commercially available dibromide **28**[9] as an approximate 1:3 mixture of E:Z isomers was reacted with sodio dimethylmalonate to give diester **29** (50%) which was reduced with $LiAlH_4$ to diol **30** (34%) then further protected as its bis TBDPS ether **31** (49%) (Scheme 3). Reaction of **31** with *n*BuLi gave acetylene **32** (quant.) which was reacted with epoxide **6** in the presence of BF_3•Et_2O to produce the acetylenic alcohol **33** in 59% yield. The acetylenic

group in **33** was reduced with $LiAlH_4$ in hot diglyme with concomitant loss of the silyl protecting groups to afford key diol **34** (δ_H5.54, dt, 1H; δ_H5.38, dd, 1H, J_{trans}CH=CH = 15.4Hz) contaminated with an inseparable amount (7%, as estimated by ^{1}H NMR) of acetylenic diol **35**.

Scheme 3

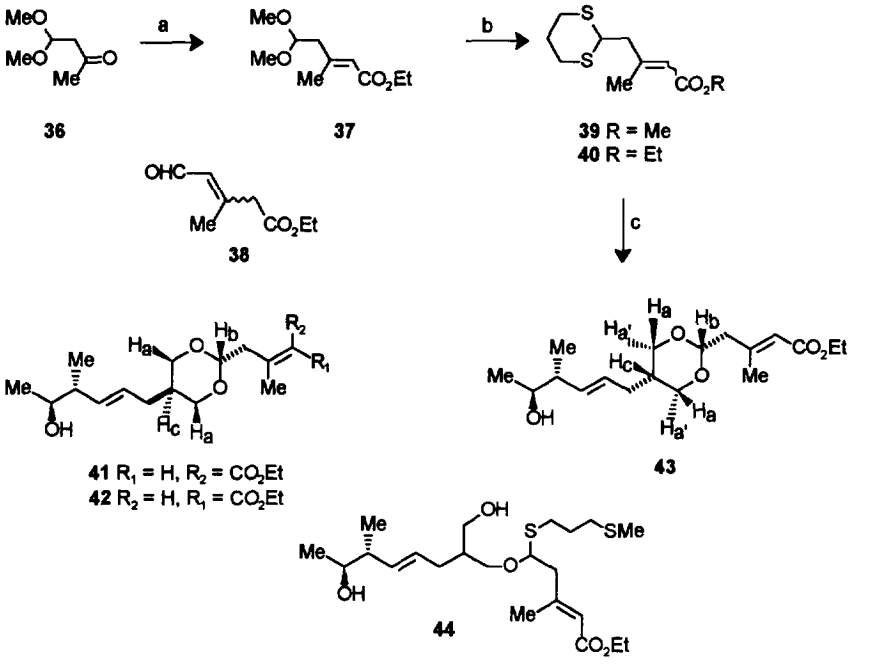


a) Dimethyl malonate, NaH, THF, -78°C→RT, 1 hr., b) $LiAlH_4$ (2.5eq), Et_2O, 0°C→RT, 4 hrs.; c) TBDPSCl (2.5eq), Imidazole (5eq), DMF, RT, 2 days; d) *n*BuLi (2eq), THF, -35°C, 2 hrs.; e) **6** (2eq), *n*BuLi (1eq), BF_3•Et_2O (1eq), THF, -78°C, 1.25 hrs., f) $LiAlH_4$, (3eq), diglyme, 100°C, 16hrs.

In order to form the 1,3-dioxane ring it was initially envisaged that diol **34** would react with the (E)-acetal **37** (prepared from the commercially available ketone **36**[9]) but this proved difficult to accomplish under the conditions we tried (catalysis with protic acids or BF_3•Et_2O) (Scheme 4). All attempts to hydrolyse the dimethyl acetal group of **37**, under acidic conditions, in order to unmask the aldehyde, led to migration of the double bond to produce **38** as a mixture of geometrical isomers. However, thioacetals have been prepared in order to overcome this type of problem.[23,24] Therefore a 3:1 mixture of E:Z isomers of **37** was transacetalated with propane-1,3-thiol in the presence of BF_3•Et_2O to afford a mixture of ethyl esters **40** and the transesterified methyl esters **39**, from which pure (E)-**40** (stereochemistry confirmed by NOE) was obtained in 23% yield by HPLC. A trial coupling of diol **34** and thioacetal (E)-**40** under activation from $Me_3O^+BF_4^-$ (2eq) led to the formation of a 1,3-dioxane ring but it was observed that some E to Z isomerization of the acrylate moiety had occurred. Suspecting that this may be due to the released tetrafluoroboric acid, Et_3N was added in an attempt to prevent this, and this gave the presumed intermediate hemithioacetal[23] **44** (tentatively assigned) in 22% yield which on treatment with Hg^{2+} afforded the 1,3-dioxanes **41-43**; however this modification did not suppress the E to Z isomerisation of the acrylate group. Compounds **41-43**, present in a 1:2:1 ratio, respectively, and in 24% yield from **44**, were difficult to separate from each other, but careful HPLC gave products of 85 - 95 % purity. The *cis* and *trans* disposition of the dioxane ring in **41-43** were indicated by NOE experiments. Irradiation of methine protons H_a (δ_H3.30, br.t) in **41** causes an enhancement of proton H_b (δ_H

4.65, t). A large coupling constant for J_{Ha-Hc} of 11.7Hz is also observed. Irradiation of the methylene multiplet $H_{aa'}$ (δ_H3.89) of **43** caused enhancements of both H_b and H_c.

Scheme 4



a) Triethyl phosphonoacetate (1.1 eq), NaH, (1.2 eq), DMF, 0°C→RT, 16 hrs., then 60°C, 1hr; b) $HS(CH_2)_3SH$ (1.2 eq), $BF_3{\bullet}Et_2O$ (1 eq), CH_2Cl_2, 0°C, 4 hrs.; c) $Me_3O^+BF_4^-$ (2 eq), CH_2Cl_2, RT, 4 hrs., then add Et_3N (2 eq), **34** (1 eq), RT, 5 days, SiO_2 (ethyl acetate/hexane, 1:1) then HgO, (2 eq), $HgCl_2$ (2 eq), CH_3CN, RT, 1.5 hrs.

Compounds **16-21**, **25-27** and **41-43**, obtained as oils, were tested for their herbicidal activity against a range of broadleaved and grass weeds commonly found in commercially important crops, but no significant effect was observed. The ability for the same compounds to inhibit spinach chloroplast ITRS was also investigated. Monic acid A **3** as a standard gave 75% inhibition of the enzyme at a concentration of 1μM. At this rate none of the compounds described above displayed significant enzyme inhibition.

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19. **Data for 18 (or 19)**. ^{1}H NMR (270MHz, $CDCl_3$): δppm 7.26 (t, 1H, J = 7.8Hz), 7.14 (d, 1H, J = 7.8Hz), 7.04 (m, 2H), 5.66 (s, 1H), 3.68 (s, 3H), 3.63 (m, 1H), 3.42 (s, 2H), 3.13, (dt, 1H, J = 5.7, 2.4Hz), 2.93 (dd, 1H, J = 14.3, 5.7Hz), 2.78 (m, 2H), 2.13 (s, 3H), 2.10 (br.s, 1H), 1.53 (m, 1H), 1.14 (d, 3H, J = 6.2Hz), 0.96 (d, 3H, J = 6.9Hz). ^{13}C NMR (67.8MHz, $CDCl_3$): δppm 167.2 (s), 158.7 (s), 138.0 (s), 137.5 (s), 129.8 (d), 128.8 (d), 127.6 (d) 127.4 (d), 116.8 (d), 69.9 (d), 61.5 (d), 58.1 (d)*, 51.0 (q), 46.9 (t), 41.9 (d), 38.5 (t), 21.1 (q), 18.8 (q), 13.28 (q). EIMS m/z 318 (M^+).
Data for 19 (or 18). ^{1}H NMR (270MHz, $CDCl_3$): δppm 7.26 (t, 1H, J = 7.8Hz), 7.12 (d, 1H, J = 7.8Hz), 7.05 (m, 2H), 5.67 (s, 1H), 3.82 (m, 1H), 3.69 (s, 3H), 3.41 (s, 2H), 2.92 (m, 2H), 2.78 (m, 2H), 2.39 (br.s, 1H), 2.12 (s, 3H), 1.32 (m, 1H), 1.20 (d, 3H, J = 6.2Hz), 0.89 (d, 3H, J = 7.1Hz). ^{13}C NMR (67.8MHz, $CDCl_3$): δppm 167.1 (s), 158.7 (s), 138.0 (s), 137.5 (s), 129.7 (d), 128.8 (d), 127.6 (d), 127.3 (d), 116.8 (d), 71.4 (d), 61.6 (d), 57.2 (d)*, 50.9 (q), 46.9 (t), 42.9 (d), 38.3 (t), 20.6 (q), 18.7 (q), 12.7 (q). EIMS m/z 318 (M^+). Also present is 5% of the alternative diastereomer.
20. **Data for 20 (or 21)**. ^{1}H NMR (270MHz, $CDCl_3$): δppm 7.24 (t, 1H, J = 7.8Hz), 7.10 (m, 3H), 5.79 (br.s, 1H), 4.08-3.94 (ABsystem, 2H, J = 13.6Hz), 3.74 (s, 3H), 3.63 (m, 1H), 3.12 (dt, 1H, J = 5.8, 2.4Hz), 2.94 (dd, 1H, J = 14.3, 5.8Hz), 2.80 (dd, 1H, J = 6.7, 2.4Hz), 2.75 (dd, 1H, J = 14.3, 5.8Hz), 2.23 (br.s, 1H), 1.80 (d, 3H, J = 1.5Hz), 1.52 (m, 1H) 1.13 (d, 3H, J = 6.4Hz), 0.96 (d, 3H, J = 6.9Hz). ^{13}C NMR (67.8MHz, $CDCl_3$): δppm 167.0 (s), 158.1 (s), 139.1 (s), 137.3 (s), 129.57 (d), 128.7 (d), 127.4 (d), 127.0 (d), 116.7 (d), 69.9 (d), 61.6 (d), 58.2 (d)*, 51.1 (q), 42.0 (d), 38.8 (t), 38.6 (t), 24.6 (q), 21.0 (q), 13.3 (q). EIMS m/z 318 (M^+).
Data for 21 (or 20). ^{1}H NMR (270MHz, $CDCl_3$): δppm 7.23 (t, 1H, J = 7.8Hz), 7.10 (m, 3H), 5.78 (br.s, 1H), 4.08-3.96 (ABsystem, 2H, J = 13.6Hz), 3.82 (m, 1H), 3.74 (s, 3H), 2.92 (m, 2H), 2.76 (m, 2H), 2.43 (br.s, 1H), 1.80 (d, 3H, J = 1.5Hz), 1.31 (m, 1H), 1.20 (d, 3H, J = 6.2Hz), 0.89 (d, 3H, J = 7.1Hz). ^{13}C NMR (67.8MHz, $CDCl_3$): δppm 166.9 (s), 158.0 (s), 139.1 (s), 137.4 (s), 129.5 (d), 128.7 (d), 127.4 (d), 126.9 (d), 116.7 (d), 71.5 (d), 61.8 (d), 57.3 (d)*, 51.1 (q), 42.9 (d), 38.7 (t), 38.4 (t), 24.6 (q), 20.62 (q), 12.66 (q). EIMS m/z 318 (M^+). Also present is 7% of the alternative diastereomer.
21. References 4 and 9 (supplementary material) report ^{13}C NMR data for C-10 of the diastereomeric epoxides formed from the MCPBA oxidation of derivatives of monic acid C, pseudomonic acid C and an intermediate keto-olefin used in the preparation of methyl pseudomonate C. In all cases the lower frequency resonance corresponds to that found in natural pseudomonic acid derivatives. One might therefore, with caution, assign the structures **18-21** (equivalent carbon asterisked) and **26-27** as shown in the Schemes.
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